PTO-1390 (06-13)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A SUBMISSION UNDER 35 U.S.C. 371

Attorney Docket No.	
STAN-1111	
U.S. Application No. (if known, see 37 CFR 1.5)	

International Application No.	International Filing Date	Priority Date Claimed
PCT/US2014/038825	May 20, 2014	May 23, 2013

Title of Invention
Transposition of Native Chromatin for Personal Epigenomics

First Named Inventor
Giresi, Paul

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. ☑ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). NOTE: The express request under 35 U.S.C. 371(f) will not be effective unless the requirements under 35 U.S.C. 371(c)(1), (2), and (4) for payment of the basic national fee, copy of the International Application and English translation thereof (if required), and the oath or declaration of the inventor(s) have been received.
2. ☑ A copy of the International Application (35 U.S.C. 371(c)(2)) is attached hereto (not required if the International Application was previously communicated by the International Bureau or was filed in the United States Receiving Office (RO/US)).
3. An English language translation of the International Application (35 U.S.C. 371(c)(2))
   a. ☑ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
4. An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4))
   a. ☑ is attached.
   b. ☐ was previously filed in the international phase under PCT Rule 4.17(iv).

Items 5 to 8 below concern amendments made in the international phase.

PCT Article 19 and 34 amendments

5. ☐ Amendments to the claims under PCT Article 19 are attached (not required if communicated by the International Bureau) (35 U.S.C. 371(c)(3)).
6. ☐ English translation of the PCT Article 19 amendment is attached (35 U.S.C. 371(c)(3)).
7. ☐ English translation of annexes (Article 19 and/or 34 amendments only) of the International Preliminary Examination Report is attached (35 U.S.C. 371(c)(5)).

Cancellation of amendments made in the international phase

8a. ☐ Do not enter the amendment made in the international phase under PCT Article 19.

8b. ☐ Do not enter the amendment made in the international phase under PCT Article 34.

NOTE: A proper amendment made in English under Article 19 or 34 will be entered in the U.S. national phase application absent a clear instruction from applicant not to enter the amendment(s).

The following items 9 to 17 concern a document(s) or information included.

9. ☑ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
10. ☐ A preliminary amendment.
11. ☑ An Application Data Sheet under 37 CFR 1.76.
12. ☐ A substitute specification. NOTE: A substitute specification cannot include claims. See 37 CFR 1.125(b).
13. ☑ A power of attorney and/or change of address letter.
14. ☑ A computer-readable form of the sequence listing in accordance with PCT Rule 13*ter*.3 and 37 CFR 1.821-1.825.
15. ☑ Assignment papers *(cover sheet and document(s))*. Name of Assignee: The Board of Trustees of the Leland Stanford Junior University
16. ☑ 37 CFR 3.73(c) Statement *(when there is an Assignee)*.

This collection of information is required by 37 CFR 1.414 and 1.491-1.492. The information is required to obtain or retain a benefit by the public, which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 15 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

U.S. APPLN. No. (if known – see 37 CFR 1.5)	INTERNATIONAL APPLICATION No.	ATTORNEY DOCKET No.
	PCT/US2014/038825	STAN-1111

17. ☐ Other items or information:

The following fees have been submitted.	CALCULATIONS	PTO USE ONLY
18. ☑ Basic national fee (37 CFR 1.492(a)) **$280**	$ 140	
19. ☑ Examination fee (37 CFR 1.492(c)) If the written opinion prepared by ISA/US or the international preliminary examination report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4) ..... **$0** All other situations **$720**	$ 360	
20. ☑ Search fee (37 CFR 1.492(b)) If the written opinion prepared by ISA/US or the international preliminary examination report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4) ..... **$0** Search fee (37 CFR 1.445(a)(2)) has been paid on the international application to the USPTO as an International Searching Authority ..... **$120** International Search Report prepared by an ISA other than the US and provided to the Office or previously communicated to the US by the IB ..... **$480** All other situations **$600**	$ 60	
TOTAL OF 18, 19, and 20 =	$ 560	
☐ Additional fee for specification and drawings filed in paper over 100 sheets (excluding sequence listing in compliance with 37 CFR 1.821(c) or (e) in an electronic medium or computer program listing in an electronic medium) (37 CFR 1.492(j)). Fee for each additional 50 sheets of paper or fraction thereof **$400**		

Total Sheets	Extra Sheets	Number of each addition 50 or fraction thereof (round **up** to a whole number)	RATE	
- 100 =	/ 50 =		x **$400**	$

Surcharge of **$140.00** for furnishing any of the search fee, examination fee, or the oath or declaration after the date of commencement of the national stage (37 CFR 1.492(h)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	- 20 =		x **$80**	$	
Independent claims	- 3 =		x **$420**	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$780**	$	
Processing fee of **$140.00** for furnishing the English translation later than 30 months from the earliest claimed priority date (37 CFR 1.492(i)). +				$	
TOTAL OF ABOVE CALCULATIONS =				$ 560	
☑ **Applicant asserts small entity status.** See 37 CFR 1.27. Fees above are reduced by ½.					
☐ **Applicant certifies micro entity status.** See 37 CFR 1.29. Fees above are reduced by ¾. Applicant must attach form PTO/SB/15A or B or equivalent.					
TOTAL NATIONAL FEE =				$ 560	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property. +				$	
TOTAL FEES ENCLOSED =				$ 560	
				Amount to be refunded:	$
				Amount to be charged:	$

a. ☐ A check in the amount of $_____ to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees.

c. ☑ The Director is hereby authorized to charge additional fees which may be required, or credit any overpayment, to Deposit Account No. 50-0815 as follows:

i. ☐ any required fee.

ii. ☑ any required fee except for excess claims fees required under 37 CFR 1.492(d) and (e) and multiple dependent claim fee required under 37 CFR 1.492(f).

d. ☑ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038. The PTO-2038 should only be mailed or faxed to the USPTO. However, when paying the basic national fee, the PTO-2038 may NOT be faxed to the USPTO.

ADVISORY: If filing by EFS-Web, do **NOT** attach the PTO-2038 form as a PDF along with your EFS-Web submission. Please be advised that this is **not** recommended and by doing so your **credit card information may be displayed via PAIR**. To protect your information, it is recommended to pay fees online by using the electronic payment method.

NOTE: Where an appropriate time limit under 37 CFR 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the International Application to pending status.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File)Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013, and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

NOTE 1: By providing this statement under 37 CFR 1.55 or 1.78, **this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA**.

NOTE 2: A U.S. national stage application may not claim priority to the international application of which it is the national phase. The filing date of a U.S. national stage application is the international filing date. See 35 U.S.C. 363.

Correspondence Address

☑ The address associated with Customer Number: 77974 **OR** ☐ Correspondence address below

Name					
Address					
City		State		Zip Code	
Country			Telephone		
Email					

Signature	/James S. Keddie/	Date	October 13, 2015
Name (Print/Type)	James S. Keddie	Registration No. (Attorney/Agent)	36,677

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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Original (for SUBMISSION)

VIII-4-1	**Declaration: Inventorship (only for the purposes of the designation of the United States of America)** Declaration of Inventorship (Rules 4.17(iv) and 51bis.1(a)(iv)) for the purposes of the designation of the United States of America:	I hereby declare that I believe I am the original inventor or an original joint inventor of a claimed invention in the application. This declaration is directed to international application No. PCT/US2014/038825. I hereby declare that the above-identified international application was made or authorized to be made by me. I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.
VIII-4-1-1-1	Name (LAST, First)	GIRESI, Paul
VIII-4-1-1-2	Residence: (city and either US state, if applicable, or country)	Palo Alto, California
VIII-4-1-1-3	Mailing Address:	264 Durand Way Palo Alto, CA 94304 United States of America
VIII-4-1-1-4	Inventor's Signature: (The signature must be that of the inventor, not that of the agent)	
VIII-4-1-1-5	Date:	6/19/14
VIII-4-1-2-1	Name (LAST, First)	BUENROSTRO, Jason D.
VIII-4-1-2-2	Residence: (city and either US state, if applicable, or country)	Redwood City, California
VIII-4-1-2-3	Mailing Address:	3523 Altamont Way Redwood City, CA 94062 United States of America
VIII-4-1-2-4	Inventor's Signature: (The signature must be that of the inventor, not that of the agent)	
VIII-4-1-2-5	Date:	
VIII-4-1-3-1	Name (LAST, First)	CHANG, Howard Y.
VIII-4-1-3-2	Residence: (city and either US state, if applicable, or country)	Stanford, California
VIII-4-1-3-3	Mailing Address:	946 Casanueva Place Stanford, CA 94305 United States of America
VIII-4-1-3-4	Inventor's Signature: (The signature must be that of the inventor, not that of the agent)	
VIII-4-1-3-5	Date:	

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Original (for **SUBMISSION**)

VIII-4-1	**Declaration: Inventorship (only for the purposes of the designation of the United States of America)** Declaration of Inventorship (Rules 4.17(iv) and 51bis.1(a)(iv)) for the purposes of the designation of the United States of America:	I hereby declare that I believe I am the original inventor or an original joint inventor of a claimed invention in the application. This declaration is directed to international application No. PCT/US2014/038825. I hereby declare that the above-identified international application was made or authorized to be made by me. I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.
VIII-4-1-1-1	Name (LAST, First)	GIRESI, Paul
VIII-4-1-1-2	Residence: (city and either US state, if applicable, or country)	Palo Alto, California
VIII-4-1-1-3	Mailing Address:	264 Durand Way Palo Alto, CA 94304 United States of America
VIII-4-1-1-4	Inventor's Signature: (The signature must be that of the inventor, not that of the agent)	
VIII-4-1-1-5	Date:	
VIII-4-1-2-1	Name (LAST, First)	BUENROSTRO, Jason D.
VIII-4-1-2-2	Residence: (city and either US state, if applicable, or country)	Redwood City, California
VIII-4-1-2-3	Mailing Address:	3523 Altamont Way Redwood City, CA 94062 United States of America
VIII-4-1-2-4	Inventor's Signature: (The signature must be that of the inventor, not that of the agent)	Jason Buenrostro 9/18/2014
VIII-4-1-2-5	Date:	
VIII-4-1-3-1	Name (LAST, First)	CHANG, Howard Y.
VIII-4-1-3-2	Residence: (city and either US state, if applicable, or country)	Stanford, California
VIII-4-1-3-3	Mailing Address:	946 Casanueva Place Stanford, CA 94305 United States of America
VIII-4-1-3-4	Inventor's Signature: (The signature must be that of the inventor, not that of the agent)	
VIII-4-1-3-5	Date:	

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Original (for SUBMISSION)

VIII-4-1	**Declaration: Inventorship (only for the purposes of the designation of the United States of America)** Declaration of Inventorship (Rules 4.17(iv) and 51bis.1(a)(iv)) for the purposes of the designation of the United States of America:	I hereby declare that I believe I am the original inventor or an original joint inventor of a claimed invention in the application. This declaration is directed to international application No. PCT/US2014/038825. I hereby declare that the above-identified international application was made or authorized to be made by me. I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.
VIII-4-1-1-1	Name (LAST, First)	GIRESI, Paul
VIII-4-1-1-2	Residence: (city and either US state, if applicable, or country)	Palo Alto, California
VIII-4-1-1-3	Mailing Address:	264 Durand Way Palo Alto, CA 94304 United States of America
VIII-4-1-1-4	Inventor's Signature: (The signature must be that of the inventor, not that of the agent)	
VIII-4-1-1-5	Date:	
VIII-4-1-2-1	Name (LAST, First)	BUENROSTRO, Jason D.
VIII-4-1-2-2	Residence: (city and either US state, if applicable, or country)	Redwood City, California
VIII-4-1-2-3	Mailing Address:	3523 Altamont Way Redwood City, CA 94062 United States of America
VIII-4-1-2-4	Inventor's Signature: (The signature must be that of the inventor, not that of the agent)	
VIII-4-1-2-5	Date:	
VIII-4-1-3-1	Name (LAST, First)	CHANG, Howard Y.
VIII-4-1-3-2	Residence: (city and either US state, if applicable, or country)	Stanford, California
VIII-4-1-3-3	Mailing Address:	946 Casanueva Place Stanford, CA 94305 United States of America
VIII-4-1-3-4	Inventor's Signature: (The signature must be that of the inventor, not that of the agent)	
VIII-4-1-3-5	Date: 7/11/14	

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Original (for **SUBMISSION**)

VIII-4-1-4-1	Name (LAST, First)	GREENLEAF, William J.
VIII-4-1-4-2	Residence: (city and either US state, if applicable, or country)	Menlo Park, California
VIII-4-1-4-3	Mailing Address:	2372 Branner Drive Menlo Park, CA 94025 United States of America
VIII-4-1-4-4	Inventor's Signature: (The signature must be that of the inventor, not that of the agent)	
VIII-4-1-4-5	Date:	18 Aug 2014

PTO/AIA/80 (07-12)
Approved for use through 11/30/2014. OMB 0651-0035
U.S. Patent and Trademark Office; U.S DEPARTMENT OF COMMERCE
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POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

■ Practitioners associated with Customer Number: 77974

OR

☐ Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignments documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:

■ The address associated with Customer Number: 77974

OR

☐	Firm or Individual Name			
	Address			
	City		State	Zip
	Country			
	Telephone		Email	

Assignee Name and Address: THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY
Office of the General Counsel, Building 170
3rd Floor, Main Quad, P.O. Box 20386
Stanford, CA 94305-2038

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent) is required to be Filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of The practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature	Katharine Ku	Date	May 27, 2015
Name	Katharine Ku	Telephone	(650) 723-0651
Title	Director, Office of Technology Licensing		

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Electronically Filed

CERTIFICATION REGARDING SEQUENCE LISTING Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket	STAN-1111
	First Named Inventor	Buenrostro, Jason D.
	Application Number	Not Yet Assigned
	Filing Date	Concurrently Herewith
	Confirmation Number	Not Yet Assigned
	Group Art Unit	Not Yet Assigned
	Examiner Name	Not Yet Assigned
	Title: "TRANSPOSITION OF NATIVE CHROMATIN FOR PERSONAL EPIGENOMICS"	

Sir:

Applicants submit herewith the attached Sequence Listing in .txt format. As set out in MPEP §502.05, IX(A), the Office has advised that if the sequence listing text file submitted via EFS-Web complies with the requirements of 37 CFR 1.824(a)(2)-(6) and (b) (i.e., is a compliant sequence listing ASCII text file), the text file will serve as both the paper copy required by 37 CFR 1.821(c) and the computer readable form (CRF) required by 37 CFR 1.821(e). Further, per MPEP §502.05, IX(A), neither (1) a second copy of the sequence listing in a PDF file; nor (2) a statement under 37 CFR 1.821(f) (indicating that the paper copy and CRF copy of the sequence listing are identical) should be submitted.

The Sequence Listing was prepared with the software PatentIn, and conforms to the Patent Office guidelines. Applicant respectfully submits that the subject application is in adherence to 37 CFR §§ 1.821-1.825. I hereby certify that the enclosed submission includes no new matter.

Applicants respectfully submit that the present patent application is now in compliance with 37 CFR §§ 1.821 - 1.825. The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-1111.

Respectfully submitted,

BOZICEVIC, FIELD & FRANCIS LLP

Dated: October 13, 2015

By: /James S. Keddie, Reg. No. 48,920/
James S. Keddie

Docket No. STAN-1111
USSN: Not Yet Assigned

Registration No. 48,920

BOZICEVIC, FIELD & FRANCIS LLP
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East Palo Alto, California 94303
Telephone: (650) 327-3400
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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 November 2014 (27.11.2014)

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(10) International Publication Number
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20 May 2014 (20.05.2014)

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(26) Publication Language: English

(30) Priority Data:
61/826,728 23 May 2013 (23.05.2013) US

(71) Applicant: **THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY** [US/US]; 1705 El Camino Real, Palo Alto, California 94306-1106 (US).

(72) Inventors: **GIRESI, Paul**; 264 Durand Way, Palo Alto, California 94304 (US). **BUENROSTRO, Jason D.**; 3523 Altamont Way, Redwood City, California 94062 (US). **CHANG, Howard Y.**; 946 Casanueva Place, Stanford, California 94305 (US). **GREENLEAF, William J.**; 2372 Branner Drive, Menlo Park, California 94025 (US).

(74) Agent: **KEDDIE, James S.**; Bozicevic, Field & Francis LLP, 1900 University Avenue, Suite 200, East Palo Alto, California 94303 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

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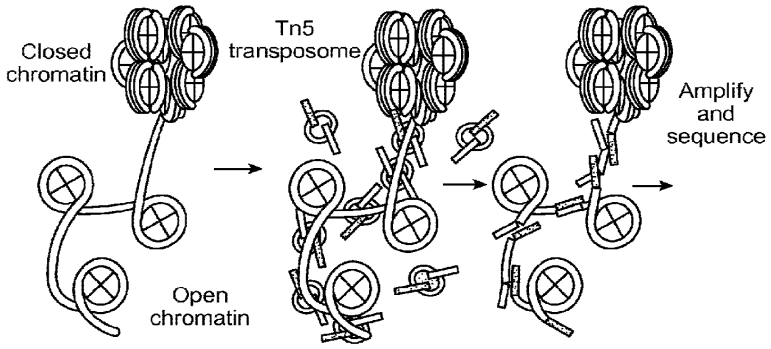


FIG. 1A

(57) Abstract: Provided herein is a method for analyzing polynucleotides such as genomic DNA. In certain embodiments, the method comprises: (a) treating chromatin isolated from a population of cells with an insertional enzyme complex to produce tagged fragments of genomic DNA; (b) sequencing a portion of the tagged fragments to produce a plurality of sequence reads; and (c) making an epigenetic map of a region of the genome of the cells by mapping information obtained from the sequence reads to the region. A kit for performing the method is also provided.

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TRANSPOSITION INTO NATIVE CHROMATIN FOR PERSONAL EPIGENOMICS

GOVERNMENT SUPPORT

This invention was made with Government support under contracts AI057229, HG000044, and NS073015 awarded by the National Institutes of Health. The Government has certain rights in the invention.

CROSS-REFERENCING

This application claims the benefit of U.S. Provisional application serial no. 61/826,728, filed on May 23, 2013, which application is incorporated by reference herein in its entirety.

BACKGROUND

Eukaryotic genomes are hierarchically packaged into chromatin, and the nature of this packaging plays a central role in gene regulation. Major insights into the epigenetic information encoded within the nucleoprotein structure of chromatin have come from high-throughput, genome-wide methods for separately assaying the chromatin accessibility ("open chromatin"), nucleosome positioning, and transcription factor (TF) occupancy. While published protocols exist, those methods require millions of cells as starting material, complex and time-consuming sample preparations, and cannot simultaneously probe the interplay of nucleosome positioning, chromatin accessibility, and TF binding. These limitations are problematic in three major ways: First, current methods can average over and "drown out" heterogeneity in cellular populations. Second, cells must often be grown *ex vivo* to obtain sufficient biomaterials, perturbing the *in vivo* context and modulating the epigenetic state in unknown ways. Third, input requirements often prevent application of these assays to well-defined clinical samples, precluding generation of "personal epigenomes" in diagnostic timescales. Provided herein are methods for analyzing polynucleotides, including their accessibility and their structure, that can overcome these limitation(s). Also provided are single-cell methods that can provide higher sensitivity and further information on chromatin accessibility, including cell-to-cell variability, to potentially enable its use as a biomarker.

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SUMMARY

Provided herein is a method for analyzing polynucleotides such as genomic DNA. In certain embodiments, the method comprises: (a) treating chromatin isolated from a population of cells with a transposase and molecular tags to produce tagged fragments of polynucleotides; (b) sequencing a portion of the tagged fragments to produce a plurality of sequence reads; and (c) making an epigenetic map of a region of the genome of the cells by mapping information obtained from the sequence reads to the region.

In some cases, the information is obtained using the nucleotide sequences at the beginning and, optionally, the end of a sequence read. In some cases, the information mapped in (c) is selected from one or more of: (i) cleavage sites for the transposase; (ii) the sizes of the fragments produced in step (a); (iii) sequence read length; (iii) the positions of sequence reads of a defined range in length; and (iv) sequence read abundance. In some instances, the fragments of a defined size range are nucleosome-free fragments.

In some instances, the epigenetic map shows one or more of: (i) a profile of chromatin accessibility along the region; (ii) DNA binding protein occupancy for a binding site in the region; (iii) nucleosome-free DNA in the region; (iv) positioning of nucleosomes along the region; and/or (v) chromatin states. In some cases, the method can further comprise measuring global occupancy of a binding site for the DNA binding protein. The DNA binding protein can, for example, be a transcription factor.

In some cases, the population of cells can be composed of about 500 to 100,000 cells. The cells can be isolated from an individual, such as from the blood of the individual. In some examples, the cells can be of the same cell type. In some examples, the cells can be FACS–selected cells.

In some instances, the treating step (a) can comprise: isolating nuclei from the population of cells; and combining the isolated nuclei with the insertional enzyme complex, wherein the combining results in both lysis of the nuclei to release the chromatin and production of the tagged fragments of genomic DNA. In some examples, the transposase can be derived from Tn5 transposase. In other examples, the transposase can be derived from MuA transposase. In further examples, the transposase can be derived from Vibhar transposase (e.g. from *Vibrio harveyi*).

The present disclosure also provides a method for comparing two samples comprising: (a) analyzing a first population of cells to produce a first epigenetic map; and (b) analyzing a second population of cells to produce a second epigenetic map; and (c) comparing the first epigenetic map to the second epigenetic map. For example, the first

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population of cells and the second population of cells can be collected from the same individual at different times. Alternatively, the first population of cells and the second population of cells can be different populations of cells collected from different individuals.

The present disclosure further provides a diagnostic method, comprising: analyzing chromatin from a patient to produce an epigenetic map; and providing a diagnosis or prognosis based on the epigenetic map.

The present disclosure provides a method for determining accessibility of a polynucleotide at a site, wherein the polynucleotide is from a cell sample, comprising: (a) inserting a plurality of molecular tags with an insertional enzyme into the polynucleotide; and (b) using the molecular tags to determine accessibility at the site. The method can further comprise using the determined accessibility to identify one or more proteins that are bound to the polynucleotide at the site. In some cases, at least one of the proteins is a transcription factor. The method can also comprise using the molecular tags to generate an accessibility map of the polynucleotide.

The present disclosure also provides a method for analyzing the three-dimensional structure of a polynucleotide from a cell sample, comprising: (a) inserting a plurality of molecular tags with an insertional enzyme into the polynucleotide; and (b) using the molecular tags to analyze the three-dimensional structure of the polynucleotide. In some cases, the insertional enzyme can comprise two or more enzymatic moieties wherein each of the enzymatic moieties inserts a common sequence into the polynucleotide. The enzymatic moieties can be linked together. The common sequence can comprise a common barcode. The enzymatic moieties can comprise transposases. The polynucleotide can fragmented into a plurality of fragments during step (a), wherein the fragments comprising the common barcode are determined to be in proximity in the three-dimensional structure of the polynucleotide.

The polynucleotide can be fragmented into a plurality of fragments during the insertion. The method can further comprise amplifying the fragments. The accessibility can be determined by sequencing the fragments and thereby generating a plurality of sequencing reads. The fragments can, for example, be sequenced by a high-throughput sequencing technique. The method can further comprise normalizing the sequencing reads based on the sequence insertion preference of the insertional enzyme. The length of the sequenced reads can also be used to determine a chromatin state annotation.

The cell sample can be permeabilized to allow access for the insertional enzyme. In some cases, the nuclei in the cell sample can be minimally perturbed during the

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permeabilization. The cell sample can be permeabilized using a permeabilization agent including, but not limited to, NP40, digitonin, tween, streptolysin, and/or cationic lipids. The cell sample can also be permeabilized using hypotonic shock and/or ultrasonication.

The method can further comprise analyzing a disease state in a subject based on the accessibility of the specific site, wherein the cell sample is obtained from the subject. The cell sample and/or the polynucleotides can also be divided into a plurality of portions, which may be optionally divided based on the molecular tags. The method can further comprise analyzing a phenotype of the cell sample. In some cases, the phenotype can be correlated to the accessibility of the site.

The insertion can be facilitated by addition of one or more divalent cations. In some cases, the one or more divalent cations can comprise magnesium. In some cases, the one or more divalent cations can comprise manganese.

The cell sample can be obtained from a primary source. The cell sample can consist of less than about 500,000 cells, or even a single cell. The polynucleotide can be bound to a plurality of association molecules. The association molecules can comprise proteins, such as histones. The insertional enzyme can be a transposase. In some cases, the transposase can be derived from a Tn5 transposase. In other cases, the transposase can be derived from a MuA transposase. In further cases, the transposase can be derived from a Vibhar transposase (e.g. from *Vibrio harveyi*). In some cases, the molecular tags can comprise sequencing adaptors, which may further comprise a barcode label. The barcode label can comprise a unique sequence. In other cases, the molecular tags can comprise fluorescence tags. The insertional enzyme can further comprise an affinity tag, which may optionally be an antibody that binds to a transcription factor, a modified nucleosome, and/or a modified nucleic acid. The modified nucleic acid can, for example be a methylated or hydroxymethylated DNA. The affinity tag can also be a single-stranded nucleic acid, which may optionally bind to a target nucleic acid. The insertional enzyme can further comprise a nuclear localization signal.

The present disclosure also provides compositions. The composition can comprise a polynucleotide, an insertional enzyme and an insert element, wherein: the insert element comprises a nucleic acid comprising a predetermined sequence; and the insertional enzyme further comprises an affinity tag. The composition can also comprise a polynucleotide, an insertional enzyme and an insert element, wherein: the insertional enzyme comprises two or more enzymatic moieties; and the enzymatic moieties are linked together. The affinity tag can be an antibody, which may optionally be bound to a transcription factor, a modified nucleosome, and/or a modified nucleic acid. The modified nucleic acid can be, for example,

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a methylated or hydroxymethylated DNA. The affinity tag can also be a single-stranded nucleic acid, which may be optionally bound to a target nucleic acid. The insert element can be bound to the insertional enzyme and the insertional enzyme is bound to the polynucleotide. The polynucleotide can be further bound to a plurality of association molecules. The association molecules can comprise proteins such as, for example, histones.

The present disclosure further provides kits. The kit can comprise: (a) reagents for isolating nuclei from a population of cells; (b) an insertional enzyme complex, and (c) transposase reaction buffer. In some cases, the components of the kit can be configured such that, combining the reaction buffer, transposon tags and adaptors with nuclei *in vitro* results in both lysis of the nuclei to release chromatin and production of tagged fragments of genomic DNA. The kit can also comprise: a cell lysis buffer; an insertional enzyme comprising an affinity tag; and an insert element comprising a nucleic acid, wherein the nucleic acid comprises a predetermined sequence. The kit can further comprise: a cell lysis buffer; an insertional enzyme comprising two or more enzymatic moieties, wherein the enzymatic moieties are linked together; and (c) an insert element. The affinity tag can be an antibody, which can optionally bind to a transcription factor, a modified nucleosome, and/or a modified nucleic acid. The modified nucleic acid can be, for example, a methylated or hydroxymethylated DNA. The affinity can also be a single-stranded nucleic acid, which may be optionally bound to a target nucleic acid.

These and other features of the present teachings are set forth herein.

INCORPORATION BY REFERENCE

All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE FIGURES

The skilled artisan will understand that the drawings, described below, are for illustration purposes only. The drawings are not intended to limit the scope of the present teachings in any way.

FIGS. 1A-1C: ATAC-seq is a sensitive, accurate probe of open chromatin state. **(a)** ATAC-seq reaction schematic. Transposase (green), loaded with sequencing adapters (red

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and blue), inserts only in regions of open chromatin (nucleosomes in grey) and generates sequencing library fragments that can be PCR amplified. (**b**) Approximate reported input material and sample preparation time requirements for genome-wide methods of open chromatin analysis. (**c**) A comparison of ATAC-seq to other open chromatin assays at a locus in GM12878 lymphoblastoid cells displaying high concordance. Lower ATAC-seq track was generated from 500 FACS-sorted cells.

FIGS. 2A-2B: ATAC-seq provides genome-wide information on chromatin compaction. (**a**) ATAC-seq fragment sizes generated from GM12878 nuclei (red) indicate chromatin-dependent periodicity with a spatial frequency consistent with nucleosomes, as well as a high frequency periodicity consistent with the pitch of the DNA helix for fragments less than 200 bp. (Inset) log-transformed histogram shows clear periodicity persists to 6 nucleosomes. (**b**) Normalized read enrichments for 7 classes of chromatin state previously defined.

FIGS. 3A-3E: ATAC-seq provides genome-wide information on nucleosome positioning in regulatory regions. (**a**) An example locus containing two transcription start sites (TSSs) showing nucleosome free read track, calculated nucleosome track (Methods), as well as DNase, MNase, and H3K27ac, H3K4me3, and H2A.Z tracks for comparison. (**b**) ATAC-seq (198 million paired reads) and MNase-seq (4 billion single-end reads from ref 23) nucleosome signal shown for all active TSSs (n=64,836), TSSs are sorted by CAGE expression. (**c**) TSSs are enriched for nucleosome free fragments, and show phased nucleosomes similar to those seen by MNase-seq at the -2, -1, +1, +2, +3 and +4 positions. (**d**) Relative fraction of nucleosome associated vs. nucleosome free (NFR) bases in TSS and distal sites (see Methods). (**e**) Hierarchical clustering of DNA binding factor position with respect to the nearest nucleosome dyad within accessible chromatin reveals distinct classes of DNA binding factors. Factors strongly associated with nucleosomes are enriched for chromatin remodelers.

FIGS 4A-4C: ATAC-seq assays genome-wide factor occupancy. (**a**) CTCF footprints observed in ATAC-seq and DNase-seq data, at a specific locus on chr1. (**b**) Aggregate ATAC-seq footprint for CTCF (motif shown) generated over binding sites within the genome (**c**) CTCF predicted binding probability inferred from ATAC-seq data, position weight matrix (PWM) scores for the CTCF motif, and evolutionary conservation (PhyloP). Right-most column is the CTCF ChIP-seq data (ENCODE) for this GM12878 cell line, demonstrating high concordance with predicted binding probability.

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FIGS. 5A-5D: ATAC-seq enables real-time personal epigenomics. (**a**) Work flow from standard blood draws. (**b**) Serial ATAC-seq data from proband T-cells over three days. (**c**) Example of application of ATAC-seq data (green track) to prioritize candidate TF drug targets. Among identified TF binding sites proximal to cytokine gene *IL2* that can be targeted by FDA-approved drugs, only NFAT is engaged in proband T-cells. ATAC-seq footprint prediction is confirmed by alignment with published NFAT ChIP-seq data (blue track, data from ref [35]). (**d**) Cell type-specific regulatory network from proband T cells compared with GM12878 B-cell line. Each row or column is the footprint profile of a TF versus that of all other TFs in the same cell type. Color indicates relative similarity (yellow) or distinctiveness (blue) in T versus B cells. NFAT is one of the most highly differentially regulated TFs (red box) whereas canonical CTCF binding is essentially similar in T and B cells.

FIG. 6: ATAC-seq peak intensity correlates well with DNase-seq peak intensity. Peaks in Duke DNase-seq (down sampled to 60 x 10^6 reads), UW DNase-seq (40 x 10^6 reads), and ATAC-seq data (60 x 10^6 paired-end reads) were called using ZINBA (Rashid et al Genome Biol. 2011 12: R67). Because each data set has different read lengths we chose to filter for peaks within mappable regions (Duke DNase-seq = 20 bp reads, UW DNase-Seq = 36bp reads and ATAC-Seq = paired-end 50 bp reads). The log10(read intensity) was compared for (A) Duke DNase-seq and ATAC-seq, (B) UW DNase-seq and ATAC-seq, and (C) UW DNAse-seq and Duke DNase-seq. Technical reproducibility of ATAC-seq data is shown in D.

FIG. 7: ATAC-seq captures a large fraction of DNase identified peaks. Peaks were called for all data sets using ZINBA. The venn-diagram shows overlap of the peak calls between each method. Below: The majority of ATAC-seq reads are in intense peaks that intersect with Duke and UW DNase-seq peaks. The total fraction of reads within peaks called from ATAC-seq, UW DNase-seq, and Duke DNase-seq, as well as the intersections of these data are shown. More than 65% of reads from all three methods are found in the intersection of the three methods' peaks, suggesting that strong well-stereotyped peaks are detected by all methods. Table cell color is proportional to fraction of reads.

FIG. 8: Graphs of the number of reads overlapping the set of open chromatin regions identified by Duke DNase, UW DNase and FAIRE in GM12878 cells compared to a set of background regions, wherein to determine the read depth required for detecting open chromatin sites sensitivity and specificity was assessed at varying read depths, including

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50k, 100k, 500k, 10 million and 50 million reads. The bottom graph shows the performance of ATAC-seq in GM12878 cells was assessed using 500, 5,000 or 50,000 cells as starting material.

FIG. 9: Tn5 insertion preferences in genomic DNA and chromatin. Nucleotide frequency scores represent the observed nucleotide frequency of each base, nucleotide frequencies are normalized to 1. The x=0 position represents the read start, and the dotted line represents the symmetry axis of the Tn5 dimer. We see no substantial differences between Tn5 insertion preferences between purified genomic DNA and human chromatin, suggesting that the local insertion preference into chromatin is identical to that found in naked genomic DNA. These reported sequence preferences are similar to those previously reported (main text ref. 11).

FIG. 10: Graph of the average intensity per base of each feature at every ATAC-seq peak; all ENCODE ChIP data was normalized to input; data has been processed using a sliding window of 200 peaks.

FIG. 11: ATAC-seq of various cell numbers. A representative UCSC genome browser track of data from different starting numbers of cells for ATAC-seq. This same locus is also shown in Fig. 1b of the main text. In order: 500 cells were isolated using FACS and two replicates of 500 cells and 5,000 cells were done by a simple dilution from cell culture. For comparison, the bottom track represents 50,000 cells, also show in Fig. 1b. This figure demonstrates that we are able to capture open chromatin sites from as few as 500 cells.

FIG. 12: Fitting nucleosome peaks in ATAC-seq fragment size distribution to enable nucleosome occupancy measurements. The observed fragment distribution was partitioned into four populations of reads – reads expected to originate from open DNA, and reads that span 1, 2 or 3 putative nucleosomes. To enable this partitioning of the data, the ATAC-seq fragment distribution was fit to the sum of 1) an exponential function for fragment distribution pattern at insert sizes below one nucleosome, and 2) 5 Gaussians to the distributions arising from protection from one, two, three, four and five nucleosomes. The sum of these fits is shown (black dotted line) is similar to the observed fragment distribution (blue line). Vertical dotted lines are boundaries for identification of fragments as originating from the nucleosome-free (<100bps), 1-nucleosome, 2-nucleosome and 3-nucleosome regions. Dotted lines were set to ensure that <10% of fragments originate from neighboring, as defined by our fit.

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FIG. 13: Select set of transcription factor footprints detected by ATAC-seq in GM12878 cells. For the indicated transcription factors the aggregate signal of ATAC-seq reads were computed using CENTIPEDE on the genome-wide sets of sites matching the corresponding motif. Reads were calculated in the region +/-100 bp of the motif boundary. The vertical dashed lines indicate the boundaries of the motifs.

FIG. 14: Prediction of CTCF binding sites using ATAC-seq and DNase footprinting with CENTIPEDE. Prediction of CTCF binding sites was assessed using the genome-wide set of CTCF motifs sorted by the posterior probability reported by CENTIPEDE. Those overlapping CTCF ChIP-seq peaks were used as the positive set and all others were considered as the negative set. This yielded an area under the curve (AUC) of 0.92, which suggests specific and sensitive binding inference for CTCF. Duke DNase and UW DNase data were used with the same settings of CENTIPEDE, and ROC plots are shown. ATAC-seq data consisted of 198 x 10^6 paired reads, Duke DNase-comprised 245 x 10^6 reads, and UW DNase comprised 48 x 10^6 reads.

FIG. 15: T-cell specific NFAT regulation: Examples of T-cell-specific NFAT target genes predicted by ATAC-seq and confirmed by alignment with NFAT ChIP-seq (data from main text ref 35).

FIG. 16: ATAC-seq of FACS-purified cell populations from human blood. (A) From a standard blood draw, we used Fluorescence-Activated Cell Sorting (FACS) to purify CD4+ T-cells, CD8+ T-cells, and CD14+ monocytes. Each population generated successful ATAC-seq data (B) and revealed cell-type specific open chromatin sites at known lineage-specific genes.

FIG. 17: Detection of allele specific open chromatin in GM12878 cells with ATAC-seq. Using publicly available variant data, we measured the allele frequency in open chromatin regions at putative heterozygous loci. Because of potential for spurious heterozygous sites, we required more than two reads to validate the heterozygosity of the allele. Red points (n=167) are candidate allele specific open chromatin sites at $p<10^{-5}$, while grey (n=900) represent candidates at $p<0.01$. P-values were calculated using a Bayesian model developed by Audic et al (Genome Research 1997 7, 986–995).

FIG. 18: Transposases can serve as an open-chromatin stain. By loading Tn5 transposes with fluorescently labeled DNA adapters, transposition events, shown in green, are primarily localized to the nucleus, and exhibit a punctate pattern consistent with higher order organization.

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FIG. 19: Single-cell ATAC-seq data from a single nucleus (blue) show clear peak at the expected positions of open-chromatin genome wide compared to 50,000 cells.

FIG. 20: Single cell insert length distribution matches that from 50,000 cells showing periodicity due to the presence of nucleosomes.

DEFINITIONS

Unless defined otherwise herein, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described.

All patents and publications, including all sequences disclosed within such patents and publications, referred to herein are expressly incorporated by reference.

Numeric ranges are inclusive of the numbers defining the range. Unless otherwise indicated, nucleic acids are written left to right in 5' to 3' orientation; amino acid sequences are written left to right in amino to carboxy orientation, respectively.

The headings provided herein are not limitations of the various aspects or embodiments of the invention. Accordingly, the terms defined immediately below are more fully defined by reference to the specification as a whole.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Singleton, et al., DICTIONARY OF MICROBIOLOGY AND MOLECULAR BIOLOGY, 2D ED., John Wiley and Sons, New York (1994), and Hale & Markham, THE HARPER COLLINS DICTIONARY OF BIOLOGY, Harper Perennial, N.Y. (1991) provide one of skill with the general meaning of many of the terms used herein. Still, certain terms are defined below for the sake of clarity and ease of reference.

The term "sample" as used herein relates to a material or mixture of materials, typically containing one or more analytes of interest. In one embodiment, the term as used in its broadest sense, refers to any plant, animal or viral material containing DNA or RNA, such as, for example, tissue or fluid isolated from an individual (including without limitation plasma, serum, cerebrospinal fluid, lymph, tears, saliva and tissue sections) or from in vitro cell culture constituents, as well as samples from the environment.

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The term "nucleic acid sample," as used herein, denotes a sample containing nucleic acids. Nucleic acid samples used herein may be complex in that they contain multiple different molecules that contain sequences. Genomic DNA samples from a mammal (e.g., mouse or human) are types of complex samples. Complex samples may have more than about 10^4, 10^5, 10^6 or 10^7, 10^8, 10^9 or 10^{10} different nucleic acid molecules. A DNA target may originate from any source such as genomic DNA, or an artificial DNA construct. Any sample containing nucleic acid, e.g., genomic DNA from tissue culture cells or a sample of tissue, may be employed herein.

The term "mixture," as used herein, refers to a combination of elements, that are interspersed and not in any particular order. A mixture is heterogeneous and not spatially separable into its different constituents. Examples of mixtures of elements include a number of different elements that are dissolved in the same aqueous solution and a number of different elements attached to a solid support at random positions (i.e., in no particular order). A mixture is not addressable. To illustrate by example, an array of spatially separated surface-bound polynucleotides, as is commonly known in the art, is not a mixture of surface-bound polynucleotides because the species of surface-bound polynucleotides are spatially distinct and the array is addressable.

The term "nucleotide" is intended to include those moieties that contain not only the known purine and pyrimidine bases, but also other heterocyclic bases that have been modified. Such modifications include methylated purines or pyrimidines, acylated purines or pyrimidines, alkylated riboses or other heterocycles. In addition, the term "nucleotide" includes those moieties that contain hapten or fluorescent labels and may contain not only conventional ribose and deoxyribose sugars, but other sugars as well. Modified nucleosides or nucleotides also include modifications on the sugar moiety, e.g., wherein one or more of the hydroxyl groups are replaced with halogen atoms or aliphatic groups, or are functionalized as ethers, amines, or the like.

The term "nucleic acid" and "polynucleotide" are used interchangeably herein to describe a polymer of any length, e.g., greater than about 2 bases, greater than about 10 bases, greater than about 100 bases, greater than about 500 bases, greater than 1000 bases, greater than 10,000 bases, greater than 100,000 bases, greater than about 1,000,000, up to about 10^{10} or more bases composed of nucleotides, e.g., deoxyribonucleotides or ribonucleotides, and may be produced enzymatically or synthetically (e.g., PNA as described in U.S. Patent No. 5,948,902 and the references cited therein) which can hybridize with naturally occurring nucleic acids in a sequence specific manner analogous to that of two

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naturally occurring nucleic acids, e.g., can participate in Watson-Crick base pairing interactions. Naturally-occurring nucleotides include guanine, cytosine, adenine, thymine, uracil (G, C, A, T and U respectively). DNA and RNA have a deoxyribose and ribose sugar backbone, respectively, whereas PNA's backbone is composed of repeating N-(2-aminoethyl)-glycine units linked by peptide bonds. In PNA various purine and pyrimidine bases are linked to the backbone by methylenecarbonyl bonds. A locked nucleic acid (LNA), often referred to as inaccessible RNA, is a modified RNA nucleotide. The ribose moiety of an LNA nucleotide is modified with an extra bridge connecting the 2' oxygen and 4' carbon. The bridge "locks" the ribose in the 3'-endo (North) conformation, which is often found in the A-form duplexes. LNA nucleotides can be mixed with DNA or RNA residues in the oligonucleotide whenever desired. The term "unstructured nucleic acid," or "UNA," is a nucleic acid containing non-natural nucleotides that bind to each other with reduced stability. For example, an unstructured nucleic acid may contain a G' residue and a C' residue, where these residues correspond to non-naturally occurring forms, i.e., analogs, of G and C that base pair with each other with reduced stability, but retain an ability to base pair with naturally occurring C and G residues, respectively. Unstructured nucleic acid is described in US20050233340, which is incorporated by reference herein for disclosure of UNA.

The term "oligonucleotide" as used herein denotes a single-stranded multimer of nucleotide of from about 2 to 200 nucleotides, up to 500 nucleotides in length. Oligonucleotides may be synthetic or may be made enzymatically, and, in some embodiments, are 30 to 150 nucleotides in length. Oligonucleotides may contain ribonucleotide monomers (i.e., may be oligoribonucleotides) or deoxyribonucleotide monomers, or both ribonucleotide monomers and deoxyribonucleotide monomers. An oligonucleotide may be 10 to 20, 21 to 30, 31 to 40, 41 to 50, 51 to 60, 61 to 70, 71 to 80, 80 to 100, 100 to 150 or 150 to 200 nucleotides in length, for example.

"Primer" means an oligonucleotide, either natural or synthetic, that is capable, upon forming a duplex with a polynucleotide template, of acting as a point of initiation of nucleic acid synthesis and being extended from its 3' end along the template so that an extended duplex is formed. The sequence of nucleotides added during the extension process is determined by the sequence of the template polynucleotide. Usually primers are extended by a DNA polymerase. Primers are generally of a length compatible with their use in synthesis of primer extension products, and are usually in the range of between 8 to 100 nucleotides in length, such as 10 to 75, 15 to 60, 15 to 40, 18 to 30, 20 to 40, 21 to 50, 22 to 45, 25 to 40, and so on. Typical primers can be in the range of between 10-50 nucleotides long, such as

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15-45, 18-40, 20-30, 21-25 and so on, and any length between the stated ranges. In some embodiments, the primers are usually not more than about 10, 12, 15, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, or 70 nucleotides in length.

Primers are usually single-stranded for maximum efficiency in amplification, but may alternatively be double-stranded. If double-stranded, the primer is usually first treated to separate its strands before being used to prepare extension products. This denaturation step is typically effected by heat, but may alternatively be carried out using alkali, followed by neutralization. Thus, a "primer" is complementary to a template, and complexes by hydrogen bonding or hybridization with the template to give a primer/template complex for initiation of synthesis by a polymerase, which is extended by the addition of covalently bonded bases linked at its 3' end complementary to the template in the process of DNA synthesis.

The term "hybridization" or "hybridizes" refers to a process in which a region of nucleic acid strand anneals to and forms a stable duplex, either a homoduplex or a heteroduplex, under normal hybridization conditions with a second complementary nucleic acid strand, and does not form a stable duplex with unrelated nucleic acid molecules under the same normal hybridization conditions. The formation of a duplex is accomplished by annealing two complementary nucleic acid strand region in a hybridization reaction. The hybridization reaction can be made to be highly specific by adjustment of the hybridization conditions (often referred to as hybridization stringency) under which the hybridization reaction takes place, such that two nucleic acid strands will not form a stable duplex, e.g., a duplex that retains a region of double-strandedness under normal stringency conditions, unless the two nucleic acid strands contain a certain number of nucleotides in specific sequences which are substantially or completely complementary. "Normal hybridization or normal stringency conditions" are readily determined for any given hybridization reaction. See, for example, Ausubel et al., Current Protocols in Molecular Biology, John Wiley & Sons, Inc., New York, or Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press. As used herein, the term "hybridizing" or "hybridization" refers to any process by which a strand of nucleic acid binds with a complementary strand through base pairing.

A nucleic acid is considered to be "selectively hybridizable" to a reference nucleic acid sequence if the two sequences specifically hybridize to one another under moderate to high stringency hybridization and wash conditions. Moderate and high stringency hybridization conditions are known (see, e.g., Ausubel, et al., Short Protocols in Molecular Biology, 3rd ed., Wiley & Sons 1995 and Sambrook et al., Molecular Cloning: A

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Laboratory Manual, Third Edition, 2001 Cold Spring Harbor, N.Y.). One example of high stringency conditions include hybridization at about 42 °C in 50% formamide, 5X SSC, 5X Denhardt's solution, 0.5% SDS and 100 μg/ml denatured carrier DNA followed by washing two times in 2X SSC and 0.5% SDS at room temperature and two additional times in 0.1 X SSC and 0.5% SDS at 42 °C.

The term "duplex," or "duplexed," as used herein, describes two complementary polynucleotide region that are base-paired, i.e., hybridized together.

The term "amplifying" as used herein refers to the process of synthesizing nucleic acid molecules that are complementary to one or both strands of a template nucleic acid. Amplifying a nucleic acid molecule may include denaturing the template nucleic acid, annealing primers to the template nucleic acid at a temperature that is below the melting temperatures of the primers, and enzymatically elongating from the primers to generate an amplification product. The denaturing, annealing and elongating steps each can be performed one or more times. In certain cases, the denaturing, annealing and elongating steps are performed multiple times such that the amount of amplification product is increasing, often times exponentially, although exponential amplification is not required by the present methods. Amplification typically requires the presence of deoxyribonucleoside triphosphates, a DNA polymerase enzyme and an appropriate buffer and/or co-factors for optimal activity of the polymerase enzyme. The term "amplification product" refers to the nucleic acids, which are produced from the amplifying process as defined herein.

The terms "determining," "measuring," "evaluating," "assessing," "assaying," and "analyzing" are used interchangeably herein to refer to any form of measurement, and include determining if an element is present or not. These terms include both quantitative and/or qualitative determinations. Assessing may be relative or absolute. "Assessing the presence of" includes determining the amount of something present, as well as determining whether it is present or absent.

The term "using" has its conventional meaning, and, as such, means employing, e.g., putting into service, a method or composition to attain an end. For example, if a program is used to create a file, a program is executed to make a file, the file usually being the output of the program. In another example, if a computer file is used, it is usually accessed, read, and the information stored in the file employed to attain an end. Similarly if a unique identifier, e.g., a barcode is used, the unique identifier is usually read to identify, for example, an object or file associated with the unique identifier.

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The term "ligating," as used herein, refers to the enzymatically catalyzed joining of the terminal nucleotide at the 5' end of a first DNA molecule to the terminal nucleotide at the 3' end of a second DNA molecule.

A "plurality" contains at least 2 members. In certain cases, a plurality may have at least 2, at least 5, at least 10, at least 100, at least 100, at least 10,000, at least 100,000, at least 10^6, at least 10^7, at least 10^8 or at least 10^9 or more members.

If two nucleic acids are "complementary," they hybridize with one another under high stringency conditions. The term "perfectly complementary" is used to describe a duplex in which each base of one of the nucleic acids base pairs with a complementary nucleotide in the other nucleic acid. In many cases, two sequences that are complementary have at least 10, e.g., at least 12 or 15 nucleotides of complementarity.

An "oligonucleotide binding site" refers to a site to which an oligonucleotide hybridizes in a target polynucleotide. If an oligonucleotide "provides" a binding site for a primer, then the primer may hybridize to that oligonucleotide or its complement.

The term "strand" as used herein refers to a nucleic acid made up of nucleotides covalently linked together by covalent bonds, e.g., phosphodiester bonds. In a cell, DNA usually exists in a double-stranded form, and as such, has two complementary strands of nucleic acid referred to herein as the "top" and "bottom" strands. In certain cases, complementary strands of a chromosomal region may be referred to as "plus" and "minus" strands, the "first" and "second" strands, the "coding" and "noncoding" strands, the "Watson" and "Crick" strands or the "sense" and "antisense" strands. The assignment of a strand as being a top or bottom strand is arbitrary and does not imply any particular orientation, function or structure. The nucleotide sequences of the first strand of several exemplary mammalian chromosomal regions (e.g., BACs, assemblies, chromosomes, etc.) is known, and may be found in NCBI's Genbank database, for example.

The term "top strand," as used herein, refers to either strand of a nucleic acid but not both strands of a nucleic acid. When an oligonucleotide or a primer binds or anneals "only to a top strand," it binds to only one strand but not the other. The term "bottom strand," as used herein, refers to the strand that is complementary to the "top strand." When an oligonucleotide binds or anneals "only to one strand," it binds to only one strand, e.g., the first or second strand, but not the other strand.

The term "sequencing," as used herein, refers to a method by which the identity of at least 10 consecutive nucleotides (e.g., the identity of at least 20, at least 50, at least 100 or at least 200 or more consecutive nucleotides) of a polynucleotide is obtained.

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The terms "next-generation sequencing" or "high-throughput sequencing" refer to the so-called parallelized sequencing-by-synthesis or sequencing-by-ligation platforms currently employed by Illumina, Life Technologies, and Roche, etc. Next-generation sequencing methods may also include nanopore sequencing methods or electronic-detection based methods such as Ion Torrent technology commercialized by Life Technologies or single-molecule fluorescence-based method commercialized by Pacific Biosciences.

The term "barcode sequence" or "molecular barcode," as used herein, refers to a unique sequence of nucleotides used to a) identify and/or track the source of a polynucleotide in a reaction and/or b) count how many times an initial molecule is sequenced (e.g., in cases where substantially every molecule in a sample is tagged with a different sequence, and then the sample is amplified). A barcode sequence may be at the 5′-end, the 3'-end or in the middle of an oligonucleotide. Barcode sequences may vary widely in size and composition; the following references provide guidance for selecting sets of barcode sequences appropriate for particular embodiments: Brenner, U.S. Pat. No. 5,635,400; Brenner et al, Proc. Natl. Acad. Sci., 97: 1665-1670 (2000); Shoemaker et al, Nature Genetics, 14: 450-456 (1996); Morris et al, European patent publication 0799897A1; Wallace, U.S. Pat. No. 5,981,179; and the like. In particular embodiments, a barcode sequence may have a length in range of from 4 to 36 nucleotides, or from 6 to 30 nucleotides, or from 8 to 20 nucleotides.

The term "in vitro" refers to a reaction that occurs in a vessel with isolated components, not in cells.

The term "distributed" in the context of cleavage sites that are distributed along the length of a target nucleic acid molecule, refers to insertions that are spaced from another along the length of the target nucleic acid molecule. There is no requirement that all of the insertions are spaced by the same amount. Rather, spacing between insertions may be random, semi-random, or not random.

The term "chromatin," as used herein, refers to a complex of molecules including proteins and polynucleotides (e.g. DNA, RNA), as found in a nucleus of a eukaryotic cell. Chromatin is composed in part of histone proteins that form nucleosomes, genomic DNA, and other DNA binding proteins (e.g., transcription factors) that are generally bound to the genomic DNA.

The term "treating," as used herein, refers to combining under conditions (e.g., a suitable temperature, time and conditions) that result in a reaction, e.g., cleavage.

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The term "chromatin isolated from a population of cells," as used herein, refers to a source of chromatin that is caused to be made available. Isolated nuclei (which can be lysed to produce chromatin) as well as isolated chromatin (i.e., the product of lysed nuclei) are both considered types of chromatin isolated from a population of cells.

The term "transcription factor", as used herein, refers to any polypeptide that may act by itself or in combination with at least one other polypeptide to regulate gene expression levels. The term includes, but is not limited to, polypeptides that directly bind DNA sequences. Transcription factors can either increases or suppress expression levels. Examples of transcription factors include, but are not limited to Myc/Max, AP-1 (Jun, Fos, ATF), CREB, SMAD, HIF, ETS, ERG, ELK, STAT, estrogen receptor (ER), androgen receptor (AR), glucocorticoid receptor (GR), progesterone receptor (PR), NFκB, p53, OCT, SOX and PAX. The transcription factor may be a transcription factor identified by sequence analysis or a naturally-occurring reading frame sequence that has not been previously characterized as a transcription factor. The polypeptide may also be an artificially generated or chemically or enzymatically modified polypeptide.

The term "insertional enzyme complex," as used herein, refers to a complex comprising an insertional enzyme and two adaptor molecules (the "transposon tags") that are combined with polynucleotides to fragment and add adaptors to the polynucleotides. Such a system is described in a variety of publications, including Caruccio (Methods Mol. Biol. 2011 733: 241-55) and US20100120098, which are incorporated by reference herein.

The term "tagged fragments," as used herein, refers to polynucleotide fragments that are attached to tags.

The term "region," as used herein, refers to a contiguous length of nucleotides in a genome of an organism. A chromosomal region may be in the range of 1 bp to the length of an entire chromosome. In some instances, a region may have a length of at least 200 bp, at least 500 bp, at least 1 kb, at least 10 kb or at least 100 kb or more (e.g., up to 1 Mb or 10 Mb or more). The genome may be from any eukaryotic organism, e.g., an animal or plant genome such as the genome of a human, monkey, rat, fish or insect.

The term "epigenetic map," as used herein, refers to any representation of epigenetic features, e.g., sites of nucleosomes, nucleosome-free regions, binding sites for transcription factors, etc. A map can be physically displayed, e.g., on a computer monitor. Exemplary epigenetic maps are shown in Fig. 1C, 3A, 4A, 4B, 5B and 5C.

The term "mapping information," as used herein, refers to assembling experimentally-obtained information about an area to a physical map of the area.

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The term "sequence read abundance," as used herein, refers to the number of times a particular sequence or nucleotide is observed in a collection of sequence reads.

The term "nucleosome-free fragments," as used herein, refers to fragments of genomic DNA that are relatively depleted or devoid of nucleosomes, i.e., between nucleosomes.

The term "chromatin accessibility," as used herein, refers to how accessible a nucleic acid site is within a polynucleotide, such as in genomic DNA, i.e., how "open" the chromatin is. A nucleic acid site associated with a polypeptide, such as with genomic DNA in nucleosomes, is usually inaccessible. A nucleic acid site not complexed with a polypeptide is generally accessible, such as with genomic DNA between nucleosomes (with the exception of nucleic acid sites complexed with transcription factors and other DNA binding proteins).

The term "DNA binding protein occupancy," as used herein, refers to whether a binding site for a sequence specific DNA binding protein (e.g., a binding site for a transcription factor) is occupied by the DNA binding protein. DNA binding protein occupancy can be measured quantitatively or qualitatively.

The term "global occupancy," as used herein, refers to whether a plurality of different binding sites for a DNA binding protein that are distributed throughout the genome (e.g., a binding sites for a transcription factor) are bound by the DNA binding protein . DNA binding protein occupancy can be measured quantitatively or qualitatively.

The term "diagnosis," as used herein, refers to a determination of whether a subject has a particular disease or condition.

The term "prognosis," as used herein, refers to prediction of a clinical outcome, e.g., disease recurrence, recovery from a disease, death, as well as a prediction of how a subject that has a particular disease or condition will respond to a particular treatment.

Other definitions of terms may appear throughout the specification.

DESCRIPTION OF EXEMPLARY EMBODIMENTS

In one aspect, a method for analyzing chromatin is provided. In certain embodiments, the method comprises: (a) treating chromatin isolated from a population of cells with an insertional enzyme complex to produce tagged fragments of genomic DNA. In this step, the chromatin is tagmented (i.e., cleaved and tagged in the same reaction) using an insertional enzyme such as Tn5 or MuA that cleaves the genomic DNA in open regions in the chromatin and adds adaptors to both ends of the fragments. Methods for tagmenting isolated genomic DNA are known in the art (see, e.g., Caruccio Methods Mol. Biol. 2011 733: 241-

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55; Kaper et al, Proc. Natl. Acad. Sci. 2013 110: 5552-7; Marine et al, Appl. Environ. Microbiol. 2011 77: 8071-9 and US20100120098) and are commercially available from Illumina (San Diego, CA) and other vendors. Such systems may be readily adapted for use herein. In some cases, the conditions may be adjusted to obtain a desirable level of insertion in the chromatin (e.g., an insertion that occurs, on average, every 50 to 200 base pairs in open regions). The chromatin used in the method may be made by any suitable method. In some embodiments, nuclei may be isolated, lysed, and the chromatin may be further purified, e.g., from the nuclear envelope. In other embodiments, the chromatin may be isolated by contacting isolated nuclei with the reaction buffer. In these embodiments, the isolated nuclei may lyse when it makes contact with the reaction buffer (which comprises insertional enzyme complexes and other necessary reagents), which allows the insertional enzyme complexes access to the chromatin. In these embodiments, the method may comprise isolating nuclei from a population of cells; and combining the isolated nuclei with the transposase and adaptors, wherein the combining results in both lysis of the nuclei to release said chromatin and production of the adaptor-tagged fragments of genomic DNA. The chromatin does not require cross-linking as in other methods (e.g., ChIP-SEQ methods).

After the chromatin has been fragmented and tagged to produce tagged fragments of genomic DNA, at least some of the adaptor tagged fragments are sequenced to produce a plurality of sequence reads. The fragments may be sequenced using any convenient method. For example, the fragments may be sequenced using Illumina's reversible terminator method, Roche's pyrosequencing method (454), Life Technologies' sequencing by ligation (the SOLiD platform) or Life Technologies' Ion Torrent platform. Examples of such methods are described in the following references: Margulies et al (Nature 2005 437: 376–80); Ronaghi et al (Analytical Biochemistry 1996 242: 84–9); Shendure et al (Science 2005 309: 1728-32); Imelfort et al (Brief Bioinform. 2009 10:609-18); Fox et al (Methods Mol Biol. 2009;553:79-108); Appleby et al (Methods Mol Biol. 2009;513:19-39) and Morozova et al (Genomics. 2008 92:255-64), which are incorporated by reference for the general descriptions of the methods and the particular steps of the methods, including all starting products, methods for library preparation, reagents, and final products for each of the steps. As would be apparent, forward and reverse sequencing primer sites that are compatible with a selected next generation sequencing platform can be added to the ends of the fragments during the amplification step. In certain embodiments, the fragments may be amplified using PCR primers that hybridize to the tags that have been added to the fragments, where the primer used for PCR have 5' tails that are compatible with a particular sequencing platform.

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In certain cases, the primers used may contain a molecular barcode (an "index") so that different pools can be pooled together before sequencing, and the sequence reads can be traced to a particular sample using the barcode sequence.

In another aspect, the present disclosure provides a method for determining accessibility of a polynucleotide at a site, wherein the polynucleotide is from a cell sample, said method comprising: inserting a plurality of molecular tags with an insertional enzyme into the polynucleotide and using the molecular tags to determine accessibility at the site. The cell sample can be from a primary source. The cell sample may consist of a single cell. The cell sample may consist of a finite number of cells (e.g. less than about 500,000 cells).

The method can further comprise using the determined accessibility to identify one or more proteins that are bound to the polynucleotide at the site. In some instances, at least one of the proteins is a transcription factor. Additionally, the method can comprise using the molecular tags to generate an accessibility map of the polynucleotide.

The polynucleotide may be fragmented into a plurality of fragments during the insertion of the molecular tags. In some cases, the fragments may be amplified. In some cases, the fragments can be sequenced to generate a plurality of sequencing reads. This may be used to determine the accessibility of the polynucleotide at any given site. The fragments may be sequenced using a high-throughput sequencing technique. In some cases, the sequencing reads can be normalized based on the sequence insertion preference of the insertional enzyme. The length of the sequenced reads can be used to determine a chromatin state annotation.

The polynucleotide can be bound to a plurality of association molecules. The association molecules can be, for example, proteins, nucleic acids or saccharides. In some cases, the association molecules can comprise histones. In other cases, the association molecules can comprise aptamers.

The insertional enzyme can be any enzyme capable of inserting a nucleic acid sequence into a polynucleotide. In some cases, the insertional enzyme can insert the nucleic acid sequence into the polynucleotide in a substantially sequence-independent manner. The insertional enzyme can be prokaryotic or eukaryotic. Examples of insertional enzymes include, but are not limited to, transposases, HERMES, and HIV integrase. The transposase can be a Tn transposase (e.g. Tn3, Tn5, Tn7, Tn10, Tn552, Tn903), a MuA transposase, a Vibhar transposase (e.g. from *Vibrio harveyi*), Ac-Ds, Ascot-1, Bs1, Cin4, Copia, En/Spm, F element, hobo, Hsmar1, Hsmar2, IN (HIV), IS1, IS2, IS3, IS4, IS5, IS6, IS10, IS21, IS30, IS50, IS51, IS150, IS256, IS407, IS427, IS630, IS903, IS911, IS982, IS1031, ISL2, L1,

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Mariner, P element, Tam3, Tc1, Tc3, Tel, THE-1, Tn/O, TnA, Tn3, Tn5, Tn7, Tn10, Tn552, Tn903, Tol1, Tol2, TnlO, Tyl, any prokaryotic transposase, or any transposase related to and/or derived from those listed above. In certain instances, a transposase related to and/or derived from a parent transposase can comprise a peptide fragment with at least about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% amino acid sequence homology to a corresponding peptide fragment of the parent transposase. The peptide fragment can be at least about 10, about 15, about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 60, about 70, about 80, about 90, about 100, about 150, about 200, about 250, about 300, about 400, or about 500 amino acids in length. For example, a transposase derived from Tn5 can comprise a peptide fragment that is 50 amino acids in length and about 80% homologous to a corresponding fragment in a parent Tn5 transposase. In some cases, the insertion can be facilitated and/or triggered by addition of one or more cations. The cations can be divalent cations such as, for example, Ca^{2+}, Mg^{2+} and Mn^{2+}.

The molecular tags can comprise sequencing adaptors, locked nucleic acids (LNAs), zip nucleic acids (ZNAs), RNAs, affinity reactive molecules (e.g. biotin, dig), self-complementary molecules, phosphorothioate modifications, azide or alkyne groups. In some cases, the sequencing adaptors can further comprise a barcode label. Further, the barcode labels can comprises a unique sequence. The unique sequences can be used to identify the individual insertion events. Any of the tags can further comprise fluorescence tags (e.g. fluorescein, rhodamine, Cy3, Cy5, thiazole orange, etc.).

Additionally, the insertional enzyme can further comprise an affinity tag. In some cases, the affinity tag can be an antibody. The antibody can bind to, for example, a transcription factor, a modified nucleosome or a modified nucleic acid. Examples of modified nucleic acids include, but are not limited to, methylated or hydroxymethylated DNA. In other cases, the affinity tag can be a single-stranded nucleic acid (e.g. ssDNA, ssRNA). In some examples, the single-stranded nucleic acid can bind to a target nucleic acid. In further cases, the insertional enzyme can further comprise a nuclear localization signal.

In some cases, the cell sample can be permeabilized to allow access for the insertional enzyme. The permeabilization can be performed in a way to minimally perturb the nuclei in the cell sample. In some instances, the cell sample can be permeabilized using a permeabilization agent. Examples of permeabilization agents include, but are not limited to, NP40, digitonin, tween, streptolysin, and cationic lipids. In other instances, the cell sample

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can be permeabilized using hypotonic shock and/or ultrasonication. In other cases, the insertional enzyme can be highly charged, which may allow it to permeabilize through cell membranes.

In yet another aspect, the present disclosure provides a method for analyzing the three-dimensional structure of a polynucleotide from a cell sample, comprising: inserting a plurality of molecular tags with an insertional enzyme into the polynucleotide; and using the molecular tags to analyze the three-dimensional structure of the polynucleotide. The insertional enzyme can comprise two or more enzymatic moieties, which may be optionally linked together. The enzymatic moieties can be linked by using any suitable chemical synthesis or bioconjugation methods. For example, the enzymatic moieties can be linked via an ester/amide bond, a thiol addition into a maleimide, Native Chemical Ligation (NCL) techniques, Click Chemistry (i.e. an alkyne-azide pair), or a biotin-streptavidin pair. In some cases, each of the enzymatic moieties can insert a common sequence into the polynucleotide. The common sequence can comprise a common barcode. The enzymatic moieties can comprise transposases or derivatives thereof. In some embodiments, the polynucleotide may be fragmented into a plurality of fragments during the insertion. The fragments comprising the common barcode can be determined to be in proximity in the three-dimensional structure of the polynucleotide.

The polynucleotide can be genomic DNA. The polynucleotide can be further bound to proteins, such as histones, and may be optionally packaged in the form of chromatin. In particular cases, DNA fragments corresponding to one or more regions of a genome (e.g., 2 or more, 10 or more, 50 or more, 100 or more, up to 1,000 or more regions) may be enriched, i.e., selected, by hybridization prior to sequencing. In these embodiments, the entire library does not need to be sequenced. Depending on the desired result and length of the selected region (if a selection step has been performed), this step of the method may result in at least 1,000 sequencing (e.g., at least 10,000, at least 100,000, at least 500,000, at least 10^6, at least $5x10^6$, up to 10^7 or more sequencing reads). The sequence reads are generally stored in computer memory.

Some embodiments of the methods involve making an epigenetic map of a region of the genome of the cells. This step may be done by mapping information obtained from the sequence reads to the region. In these embodiments, the sequence reads are analyzed computationally to produce a number of numerical outputs that are mapped to a representation (e.g., a graphical representation) of a region of interest. As will be explained in greater detail below, many types of information may be mapped, including, but not

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limited to: (i) cleavage sites for the transposase; (ii) the sizes of the fragments produced in step a); (iii) fragment length; (iii) the positions of sequence reads of a defined range in length; and (iv) sequence read abundance.

For example, the sequence reads may be analyzed computationally to identify the ends of the fragments (from which the transposon cleavage sites can be inferred). In these embodiments, one end of a fragment can be defined by sequence that is at the beginning of a sequencing read and the other end of the fragment can be defined by sequence that is at the beginning of a second sequencing read, where the first and second sequencing reads were obtained by paired end sequencing (e.g., using Illumina's sequencing platform). The same information can be obtained from examining the beginning and end of longer sequence reads (which should, in theory, have the sequence of both adaptors; one at one end and the other at the other end). In these embodiments, a single sequence read may contain both adaptor sequences, in which case both ends of a fragment (which correspond to two cleavage sites for the two separate transposases) can be inferred from a single sequence read. The lengths of the fragments can be calculated by, e.g., mapping the fragment ends onto the nucleotide sequence of the region of interest, and counting the number of base pairs between those positions. The information used may be obtained using the nucleotide sequences at the beginning and/or the end of a sequence read.

In certain cases, the sequence reads can be placed into groups by length. In some embodiments, some sequences can be annotated as being a nucleosome-free sequence (i.e., a sequence from a fragment that is predicted to be between nucleosomes) based on its size. Reads that are associated with mononucleosomes, dinucleosomes and trinucleosomes can also be identified. These cutoffs can be determined using the data shown in **Fig. 12**. Fragment lengths (which provide the same information as sequence read lengths) can also be processed in the same way. In certain cases, sequence read abundance, i.e., the number of times a particular sequence in a genomic region is represented in the sequence reads, may be calculated.

The resultant epigenetic map can provide an analysis of the chromatin in the region of interest. For example, depending on which information is mapped, the map can show one or more of the following: a profile of chromatin accessibility along the region; DNA binding protein (e.g., transcription factor) occupancy for a site in the region; nucleosome-free DNA in the region; positioning of nucleosomes along the region; and a profile of chromatin states along the region. In some embodiments, the method may further comprise measuring global occupancy of a binding site for the DNA binding protein by, e.g., aggregating data for one

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DNA binding protein over a plurality of sites to which that protein binds. In certain instances, the map can also be annotated with sequence information, and information about the sequence (e.g., the positions of promoters, introns, exons, known enhancers, transcriptional start sites, untranslated regions, terminators, etc.) so that the epigenetic information can be viewed in context with the annotation.

In certain embodiments, the epigenetic map can provide information regarding active regulatory regions and/or the transcription factors that are bound to the regulatory regions. For example, nucleosome positions can be inferred from the lengths of sequencing reads generated. Alternatively, transcription factor binding sites can be inferred from the size, distribution and/or position of the sequencing reads generated. In some cases, novel transcription factor binding sites can be inferred from sequencing reads generated. In other cases, novel transcription factors can be inferred from sequencing reads generated.

The population of cells used in the assay may be composed of any number of cells, e.g., about 500 to about 10^6 or more cells, about 500 to about 100,000 cells, about 500 to about 50,000 cells, about 500 to about 10,000 cells, about 50 to 1000 cells, about 1 to 500 cells, about 1 to 100 cells, about 1 to 50 cells, or a single cell. In some cases, the cell sample can consist of less than about 1000, about 2000, about 3000, about 4000, about 5000, about 6000, about 7000, about 8000, about 9000, about 10,000, about 15,000, about 20,000, about 25,000, about 30,000, about 40,000, about 50,000, about 60,000, about 70,000, about 80,000, about 90,000, about 100,000, about 120,000, about 140,000, about 160,000, about 180,000, about 200,000, about 250,000, about 300,000, about 350,000, about 400,000, about 450,000, about 500,000, about 600,000, about 700,000, about 800,000, about 900,000, or about 1,000,000 cells. In other cases, the cell sample can consist of more than about 1000, about 2000, about 3000, about 4000, about 5000, about 6000, about 7000, about 8000, about 9000, about 10,000, about 15,000, about 20,000, about 25,000, about 30,000, about 40,000, about 50,000, about 60,000, about 70,000, about 80,000, about 90,000, about 100,000, about 120,000, about 140,000, about 160,000, about 180,000, about 200,000, about 250,000, about 300,000, about 350,000, about 400,000, about 450,000, about 500,000, about 600,000, about 700,000, about 800,000, about 900,000, or about 1,000,000 cells.

The cells can be from any source. In certain cases, the cells may be obtained from a culture of cells, e.g., a cell line. In other cases, the cells may be isolated from an individual (e.g., a patient or the like). The cells may be isolated from a soft tissue or from a bodily fluid, or from a cell culture that is grown *in vitro*. In particular embodiments, the chromatin may be isolated from a soft tissue such as brain, adrenal gland, skin, lung, spleen, kidney,

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liver, spleen, lymph node, bone marrow, bladder stomach, small intestine, large intestine or muscle, etc. Bodily fluids include blood, plasma, saliva, mucous, phlegm, cerebral spinal fluid, pleural fluid, tears, lactal duct fluid, lymph, sputum, cerebrospinal fluid, synovial fluid, urine, amniotic fluid, and semen, etc.

In some embodiments, the polynucleotide (e.g. genomic DNA, chromosomal DNA) used in the method may be from blood cells, wherein blood cells refers to a sample of whole blood or a sub-population of cells in whole blood. Sub-populations of cells in whole blood include platelets, red blood cells (erythrocytes), platelets and white blood cells (i.e., peripheral blood leukocytes, which are made up of neutrophils, lymphocytes, eosinophils, basophils and monocytes). These five types of white blood cells can be further divided into two groups, granulocytes (which are also known as polymorphonuclear leukocytes and include neutrophils, eosinophils and basophils) and mononuclear leukocytes (which include monocytes and lymphocytes). Lymphocytes can be further divided into T cells, B cells and NK cells. Peripheral blood cells are found in the circulating pool of blood and not sequestered within the lymphatic system, spleen, liver, or bone marrow. Other cells are present in blood that can be isolated. If blood is first contacted with an agent and then a sample of the blood is used in an assay, then a portion or all of the contacted blood may be used in the assay.

In certain embodiments, the cell sample can be isolated directly from a primary source. For example, the cell sample can be isolated directly from fresh tissues. In other cases, the cell sample can be isolated directly from frozen tissues. In yet other cases, the cell sample can be isolated directly from fixed tissues. Further examples of primary sources of cell samples include, but are not limited to, cells dissociated from tissues, blood cells, FFPE tissues, bacterial, viral, mitochondria, chloroplast, *in vitro* assembled protein DNA complexes, neutrophil extracellular traps.

Using the methods provided in the present disclosure, the disease state in a subject can be analyzed based on the accessibility of a polynucleotide site in a cell sample obtained from the subject. For example, transcription factor occupancy at any given site can result in the lack of accessibility at the site. Based on the transcription factor occupancy, the subject can then be treated with a suitable agent (e.g. a transcription factor inhibitor).

In certain cases, the cell samples can be further analyzed phenotypically. For example, the cell samples can be analyzed using fluorescence activated cell sorting (FACS) and/or laser capture microdissection (LCM). In some cases, the cell sample and/or polynucleotides may be divided into a plurality of portions. The portions can be divided

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based on the molecular tags (e.g. fluorescence tags). In some cases, the cell sample and/or polynucleotides can be sorted. The sorting can be performed after the molecular tags are inserted into the polynucleotide. The sorting can be performed before the fragments are sequenced. The gene transcription of the cell samples can also be analyzed using techniques such as fluorescence *in situ* hybridization (FISH). The chromatin accessibility can be correlated with the phenotypical, transcriptional or translational analysis.

In some embodiments, the cells are of the same cell type. In these embodiments, the population of cells may be selected by MACS or FACS from a heterogeneous population of cells, e.g., blood, by known methods using labeled antibodies to cells surface markers. A wide variety of cells can be isolated using these methods, including stem cells, cancer stem cells and subsets of blood cells. In particular embodiments the following cells may be isolated from blood by FACS or MACS; T cells ($CD3^+$ $CD4^+$ $CD8^+$), B cells ($CD19^+$ $CD20^+$), dendritic cells ($CD11c^+$ $CD20^+$), NK Cell ($CD56^+$), stem cells/precursor cells ($CD34^+$; hematopoietic stem cells only), macrophage/monocytes ($CD14^+$ $CD33^+$), granulocytes ($CD66b^+$), platelet ($CD41^+$ $CD61^+$ $CD62^+$), erythrocytes ($CD235a^+$), endothelial cells ($CD146^+$) and epithelial cells ($CD326^+$). Subsets of these cells can be isolated using antibodies to further cell surface markers.

In some embodiments, the method can be used to compare two samples. In these embodiments, the method may comprise analyzing a first population of cells using the above-described method to produce a first epigenetic map; and analyzing a second population of cells using the above-described method to produce a second epigenetic map; and comparing the first epigenetic map to the second epigenetic map, e.g., to see if there are any changes in chromatin openness or transcription factor occupancy, for example.

In some embodiments, the first population of cells and the second population of cells are collected from the same individual at different times. In other embodiments, the first population of cells and the second population of cells are different populations of cells collected from tissues or different individuals.

Exemplary cell types that can be used in the method include, for example, cells isolated from a tissue biopsy (e.g., from a tissue having a disease such as colon, breast, prostate, lung, skin cancer, or infected with a pathogen etc.) and normal cells from the same tissue, e.g., from the same patient; cells grown in tissue culture that are immortal (e.g., cells with a proliferative mutation or an immortalizing transgene), infected with a pathogen, or treated (e.g., with environmental or chemical agents such as peptides, hormones, altered temperature, growth condition, physical stress, cellular transformation, etc.), and normal

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cells (e.g., cells that are otherwise identical to the experimental cells except that they are not immortalized, infected, or treated, etc.); cells isolated from a mammal with a cancer, a disease, a geriatric mammal, or a mammal exposed to a condition, and cells from a mammal of the same species, e.g., from the same family, that is healthy or young; and differentiated cells and non-differentiated cells from the same mammal (e.g., one cell being the progenitor of the other in a mammal, for example). In one embodiment, cells of different types, e.g., neuronal and non-neuronal cells, or cells of different status (e.g., before and after a stimulus on the cells) may be compared. In another embodiment, the experimental material is cells susceptible to infection by a pathogen such as a virus, e.g., human immunodeficiency virus (HIV), etc., and the control material is cells resistant to infection by the pathogen. In another embodiment of the invention, the sample pair is represented by undifferentiated cells, e.g., stem cells, and differentiated cells. Cells from yeast, plants and animals, such as fish, birds, reptiles, amphibians and mammals may be used in the subject methods. In certain embodiments, mammalian cells, i.e., cells from mice, rabbits, primates, or humans, or cultured derivatives thereof, may be used.

In some exemplary embodiments, the method may be used to identify the effect of a test agent, e.g., a drug, or to determine if there are differences in the effect of two or more different test agents. In these embodiments, two or more identical populations of cells may be prepared and, depending on how the experiment is to be performed, one or more of the populations of cells may be incubated with the test agent for a defined period of time. After incubation with the test agent, the chromatin of the populations of cells can be analyzed using the methods set forth above, and the results can be compared. In a particular embodiment, the cells may be blood cells, and the cells can be incubated with the test agent ex vivo. These methods can be used to determine the mode of action of a test agent, to identify changes in chromatin structure or transcription factor occupancy in response to the drug, for example.

The method described above may also be used as a diagnostic (which term is intended to include methods that provide a diagnosis as well as methods that provide a prognosis). These methods may comprise, e.g., analyzing chromatin from a patient using the method described above to produce an epigenetic map; and providing a diagnosis or prognosis based on the epigenetic map.

The method set forth herein may be used to provide a reliable diagnostic to any condition associated with altered chromatin or DNA binding protein occupancy. The method can be applied to the characterization, classification, differentiation, grading, staging,

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diagnosis, or prognosis of a condition characterized by an epigenetic pattern (e.g., a pattern of chromatin accessibility or DNA binding protein occupancy). For example, the method can be used to determine whether the epigenetic map of a sample from an individual suspected of being affected by a disease or condition is the same or different compared to a sample that is considered "normal" with respect to the disease or condition. In particular embodiments, the method can be directed to diagnosing an individual with a condition that is characterized by an epigenetic pattern at a particular locus in a test sample, where the pattern is correlated with the condition. The methods can also be used for predicting the susceptibility of an individual to a condition.

Exemplary conditions that are suitable for analysis using the methods set forth herein can be, for example, cell proliferative disorder or predisposition to cell proliferative disorder; metabolic malfunction or disorder; immune malfunction, damage or disorder; CNS malfunction, damage or disease; symptoms of aggression or behavioral disturbance; clinical, psychological and social consequences of brain damage; psychotic disturbance and personality disorder; dementia or associated syndrome; cardiovascular disease, malfunction and damage; malfunction, damage or disease of the gastrointestinal tract; malfunction, damage or disease of the respiratory system; lesion, inflammation, infection, immunity and/or convalescence; malfunction, damage or disease of the body as an abnormality in the development process; malfunction, damage or disease of the skin, the muscles, the connective tissue or the bones; endocrine and metabolic malfunction, damage or disease; headache or sexual malfunction, and combinations thereof.

In some embodiments, the method can provide a prognosis, e.g., to determine if a patient is at risk for recurrence. Cancer recurrence is a concern relating to a variety of types of cancer. The prognostic method can be used to identify surgically treated patients likely to experience cancer recurrence so that they can be offered additional therapeutic options, including preoperative or postoperative adjuncts such as chemotherapy, radiation, biological modifiers and other suitable therapies. The methods are especially effective for determining the risk of metastasis in patients who demonstrate no measurable metastasis at the time of examination or surgery.

The method can also be used to determining a proper course of treatment for a patient having a disease or condition, e.g., a patient that has cancer. A course of treatment refers to the therapeutic measures taken for a patient after diagnosis or after treatment. For example, a determination of the likelihood for recurrence, spread, or patient survival, can assist in determining whether a more conservative or more radical approach to therapy should be

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taken, or whether treatment modalities should be combined. For example, when cancer recurrence is likely, it can be advantageous to precede or follow surgical treatment with chemotherapy, radiation, immunotherapy, biological modifier therapy, gene therapy, vaccines, and the like, or adjust the span of time during which the patient is treated.

In a particular embodiment, a lab will receive a sample (e.g., blood) from a remote location (e.g., a physician's office or hospital), the lab will analyze cells in the sample as described above to produce data, and the data may be forwarded to the remote location for analysis.

Compositions

In one aspect, the present disclosure provides compositions related to the methods provided herein. The composition can comprise a polynucleotide, an insertional enzyme and an insert element, wherein: the insert element can comprise a nucleic acid comprising a predetermined sequence and the insertional enzyme can further comprise an affinity tag. The polynucleotide can be further bound to a plurality of association molecules. The association molecules can be proteins (e.g. histones) or nucleic acids (e.g. aptamers). The affinity tag can be an antibody. In some cases, the antibody can be bound to a transcription factor. In other cases, the antibody can be bound to a modified nucleosome. In further cases, the antibody can be bound to a modified nucleic acid. Examples of modified nucleic acids include, but are not limited to, methylated or hydroxymethylated DNA. The affinity tag can also be a single-stranded nucleic acid (e.g. ssDNA, ssRNA). In some cases, the single-stranded nucleic acid can be bound to a target nucleic acid. In some instances, the insertional enzyme can further comprise a nuclear localization signal.

The composition can comprise a polynucleotide, an insertional enzyme and an insert element, wherein: the insertional enzyme comprises two or more enzymatic moieties and the enzymatic moieties are linked together. The insert element can be bound to the insertional enzyme. The insertional enzyme can also be bound to the polynucleotide. In some cases, the polynucleotide can be further bound to a plurality of association molecules. The association molecules can be proteins (e.g. histones) or nucleic acids (e.g. aptamers).

Kits

In yet another aspect, the present disclosure provides kits that contain reagents for practicing the subject methods, as described above. The subject kits can comprise: (a) reagents for isolating nuclei from a population of cells; (b) transposase and transposon tags,

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and (c) transposase reaction buffer, wherein the components of the kit are configured such that, combining the reaction buffer, transposase and adaptors with nuclei *in vitro* results in both lysis of the nuclei to release chromatin and production of adaptor-tagged fragments of genomic DNA.

In some cases, the kit can comprise: (a) a cell lysis buffer; (b) an insertional enzyme comprising an affinity tag; and (c) an insert element comprising a nucleic acid, wherein said nucleic acid comprises a predetermined sequence. The insertional enzyme can be, for example, a transposase. The insertional enzyme can also comprise two or more enzymatic moieties that are linked together. In some cases, the affinity tag can be an antibody. The antibody can bind to a transcription factor, a modified nucleosome, or a modified nucleic acid. Examples of modified nucleic acids include, but are not limited to, methylated or hydroxymethylated DNA. In other cases, the affinity tag can be a single-stranded nucleic acid (e.g. ssDNA, ssRNA).

The kit may optionally contain other components, for example: PCR primers, PCR reagents such as polymerase, buffer, nucleotides etc., as described above. The various components of the kit may be present in separate containers or certain compatible components may be precombined into a single container, as desired.

In addition to above-mentioned components, the subject kits may further include instructions for using the components of the kit to practice the subject methods, i.e., instructions for sample analysis. The instructions for practicing the subject methods are generally recorded on a suitable recording medium. For example, the instructions may be printed on a substrate, such as paper or plastic, etc. As such, the instructions may be present in the kits as a package insert, in the labeling of the container of the kit or components thereof (i.e., associated with the packaging or subpackaging) etc. In other embodiments, the instructions are present as an electronic storage data file present on a suitable computer readable storage medium, e.g., CD-ROM, diskette, etc. In yet other embodiments, the actual instructions are not present in the kit, but means for obtaining the instructions from a remote source, e.g., via the internet, are provided. An example of this embodiment is a kit that includes a web address where the instructions can be viewed and/or from which the instructions can be downloaded. As with the instructions, this means for obtaining the instructions is recorded on a suitable substrate.

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Embodiments

A method of mapping chromatin is provided. In some embodiments, this method comprises the steps of: fragmenting the chromatin of rare or abundant cells with a transposase which inserts sequencing adapters into the polynucleotides within the chromatin, and amplifying and sequencing the fragments to generate a cell-specific map.

In certain embodiments, the cell-specific map provides information regarding active regulatory regions and the transcription factors that are bound to said regulatory regions.

In certain embodiments, the number of said rare cells is between 1 and 100,000.

In certain embodiments, the transposase is derived from Tn5 transposase.

In certain embodiments, the transposase is derived from MuA transposase.

In certain embodiments, nucleosome positions are inferred from the lengths of sequencing reads generated.

In certain embodiments, transcription factor binding sites are inferred from sequencing reads generated.

In certain embodiments, chromatin is isolated directly from fresh tissues.

In certain embodiments, chromatin is isolated directly from frozen tissues.

In certain embodiments, chromatin is isolated directly from fixed tissues.

In certain embodiments, sequences are added to the sequencing adapter to uniquely identify the fragments for multiplexing (barcoding).

In certain embodiments, an affinity tag is used to target the transposase to a specific macromolecule of interest.

In certain embodiments, sequences are added to the sequencing adapter to uniquely identify the fragments for multiplexing (barcoding), and an affinity tag is used to target the transposase to a specific macromolecule of interest.

In certain embodiments the affinity tag is an antibody targeted to a transcription factor.

In certain embodiments the affinity tag is an antibody targeted to a modified nucleosome.

In certain embodiments, the insert size distribution at a specific genomic locus is used to infer chromatin openness.

In certain embodiments, the insert size distribution and positions of insertion are used to infer transcription factor binding.

In certain embodiments, the number of sequencing reads obtained is normalized by measured sequence insertion preference of the transposase.

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In certain embodiments, novel transcription factor binding sites are inferred from sequencing reads generated.

In certain embodiments, novel transcription factors are inferred from sequencing reads generated.

In certain embodiments, causal variants can be inferred by looking at allele specific generation of sequencing reads.

In certain embodiments, chromatin state annotations are inferred from the distribution of lengths of sequencing reads.

EXAMPLES

Aspects of the present teachings can be further understood in light of the following examples, which should not be construed as limiting the scope of the present teachings in any way.

Example 1. Assay for Transposase Accessible Chromatin using sequencing (ATAC-seq)

Described herein is an Assay for Transposase Accessible Chromatin using sequencing (ATAC-seq) - based on direct *in vitro* transposition of sequencing adapters into native chromatin – as a rapid and sensitive method for integrative epigenomic analysis. ATAC-seq captures open chromatin sites using a simple 2-step protocol from 500 to 50,000 cells, and reveals the interplay between genomic locations of open chromatin, DNA binding proteins, individual nucleosomes, and higher-order compaction at regulatory regions with nucleotide resolution. Classes of DNA binding factor that strictly avoid, can tolerate, or tend to overlap with nucleosomes have been discovered. Using ATAC-seq, the serial daily epigenomes of resting human T cells was measured and evaluated from a proband via standard blood draws, demonstrating the feasibility of reading personal epigenomes in clinical timescales for monitoring health and disease.

Materials and Methods

An exemplary implementation of ATAC-seq protocol has three major steps:

1) Prepare nuclei: To prepare nuclei, 50,000 cells were spun at 500 x g for 5 minutes, followed by a wash using 50 μL of cold 1x PBS and centrifugation at 500 x g for 5 minutes. Cells were lysed using cold lysis buffer (10 mM Tris-Cl, pH 7.4, 10 mM NaCl, 3 mM $MgCl_2$ and 0.1% IGEPAL CA-630). Immediately after lysis, nuclei were spun at 500 x g for 10 minutes using a refrigerated centrifuge. To avoid losing cells during the nuclei

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prep, a fixed angle centrifuge was used and they were carefully pipetted away from the pellet after centrifugations.

2) Transpose and purify: Immediately following the nuclei prep, the pellet was resuspended in the transposase reaction mix (25 μL 2x TD buffer, 2.5 μL Transposase (Illumina) and 22.5 μL of nuclease free water). The transposition reaction was carried out for 30 minutes at 37 °C. Directly following transposition the sample was purified using a Qiagen Minelute kit.

3) PCR: Following purification, we amplified library fragments using 1x NEBnext PCR master mix and 1.25 μM of custom Nextera PCR primers 1 and 2 (see table below), using the following PCR conditions: 72°C for 5 minutes, 98°C for 30 seconds, followed by thermocycling at 98°C for 10 seconds, 63°C for 30 seconds and 72°C for 1 minute. To reduce GC and size bias in PCR, the PCR reactions were monitored using qPCR in order to stop amplification prior to saturation. To do this, the full libraries were amplified for 5 cycles, after 5 cycles an aliquot of the PCR reaction was taken and added to 10 μl of the PCR cocktail with Sybr Green at a final concentration of 0.6x. We ran this reaction for 20 cycles, to determine the additional number of cycles needed for the remaining 45 μL reaction. The libraries were purified using a Qiagen PCR cleanup kit yielding a final library concentration of ~30 nM in 20 μL. Libraries were amplified for a total of 10-12 cycles.

Ad1_noMX:	AATGATACGGCGACCACCGAGATCTACACTCGTCGGCAGCGTCAGATGTG (SEQ ID NO:1)
Ad2.1_TAAGGCGA	CAAGCAGAAGACGGCATACGAGATTCGCCTTAGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:2)
Ad2.2_CGTACTAG	CAAGCAGAAGACGGCATACGAGATCTAGTACGGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:3)
Ad2.3_AGGCAGAA	CAAGCAGAAGACGGCATACGAGATTTCTGCCTGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:4)
Ad2.4_TCCTGAGC	CAAGCAGAAGACGGCATACGAGATGCTCAGGAGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:5)
Ad2.5_GGACTCCT	CAAGCAGAAGACGGCATACGAGATAGGAGTCCGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:6)
Ad2.6_TAGGCATG	CAAGCAGAAGACGGCATACGAGATCATGCCTAGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:7)
Ad2.7_CTCTCTAC	CAAGCAGAAGACGGCATACGAGATGTAGAGAGGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:8)
Ad2.8_CAGAGAGG	CAAGCAGAAGACGGCATACGAGATCCTCTCTGGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:9)
Ad2.9_GCTACGCT	CAAGCAGAAGACGGCATACGAGATAGCGTAGCGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:10)
Ad2.10_CGAGGCTG	CAAGCAGAAGACGGCATACGAGATCAGCCTCGGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:11)
Ad2.11_AAGAGGCA	CAAGCAGAAGACGGCATACGAGATTGCCTCTTGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:12)
Ad2.12_GTAGAGGA	CAAGCAGAAGACGGCATACGAGATTCCTCTACGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:13)

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Ad2.13_GTCGTGAT	CAAGCAGAAGACGGCATACGAGATATCACGACGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:14)
Ad2.14_ACCACTGT	CAAGCAGAAGACGGCATACGAGATACAGTGGTGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:15)
Ad2.15_TGGATCTG	CAAGCAGAAGACGGCATACGAGATCAGATCCAGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:16)
Ad2.16_CCGTTTGT	CAAGCAGAAGACGGCATACGAGATACAAACGGGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:17)
Ad2.17_TGCTGGGT	CAAGCAGAAGACGGCATACGAGATACCCAGCAGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:18)
Ad2.18_GAGGGGTT	CAAGCAGAAGACGGCATACGAGATAACCCCTCGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:19)
Ad2.19_AGGTTGGG	CAAGCAGAAGACGGCATACGAGATCCCAACCTGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:20)
Ad2.20_GTGTGGTG	CAAGCAGAAGACGGCATACGAGATCACCACACGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:21)
Ad2.21_TGGGTTTC	CAAGCAGAAGACGGCATACGAGATGAAACCCAGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:22)
Ad2.22_TGGTCACA	CAAGCAGAAGACGGCATACGAGATTGTGACCAGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:23)
Ad2.23_TTGACCCT	CAAGCAGAAGACGGCATACGAGATAGGGTCAAGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:24)
Ad2.24_CCACTCCT	CAAGCAGAAGACGGCATACGAGATAGGAGTGGGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:25)

Low cell number protocol: To prepare the 500 and 5,000 cell reactions the same protocol was used with some notable exceptions: The transposition reaction was done in a 5 μL instead of 50 μL reaction. Also, the Qiagen Minelute purification was eliminated prior to PCR and instead took the 5 μL reaction immediately after transposition directly into the 50 μL PCR.

Library QC and quantitation: During the ATAC-seq protocol, the size selection step was avoided to maximize the library complexity. The sequenced insert size is a distribution between 40 bp to 1 kb with a mean of ~120 bps. From bioanalyzer and gels we observed fragments >2 kb, which would make Qubit and other mass-based quantitation methods hard to interpret. For this reason we quantified our libraries using qPCR based methods.

$CD4^+$ enrichment from peripheral blood: One green-top tube of whole blood was obtained from 1 normal volunteer three times over a 72-hour period, under a Stanford University IRB-approved protocol. Informed consent was obtained. 5mL of blood at each timepoint was negatively selected for CD4+ cells, using RosetteSep Human $CD4^+$ T Cell Enrichment Cocktail (StemCell Technology). RosetteSep cocktail was incubated with the blood at 50μL/mL for 20 min, diluted in an equal volume of PBS with 2% FBS, and underlayed with 15 mL Ficol-Paque Plus (GE). Blood was centrifuged for 20 minutes at

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1200 x g without break, negatively selected cells were removed from the density medium: plasma interface, and cells were washed X2 in PBS with 2% FBS.

FACS sorting peripheral blood leukocytes and GM cells: GM 12878 cells were stained with DAPI NucBlue Fixed Cell Stain (molecular probes) and live cells were sorted using a FACSAria (BD Biosciences) using a 100 μm nozzle. One peripheral blood sample (buffy coat) was stained with BD Bioscience antibodies CD14-A-488 (M5E2, 1:20), CD3-PE-Cy7 (SK7, 1:20), CD4-APC-Cy7 (RPA-T4, 1:20), and CD8 (RPA-T8, 1:20) for 20 minutes in the dark at RT. Cells were lysed using BDpharmLyse 1:10 dil in diH20 (BD) for 15 min, centrifuged for 5 minutes, washed with PBS 2% FBS X 2, and resuspended in PBS with 2% FBS. 50,000 $CD3^+CD8^+$, $CD3^+CD4^+$, and $CD14^+$ cell populations were sorted into PBS with 10% FBS.

Data Analysis

Primary data processing: Data was collected using either 34 x 8 x 34 reads from a MiSeq or 50 x 8 x 50 reads on a HiSeq. Reads were aligned to hg19 using BOWTIE (Langmead et al *Genome Biol.* 2009 **10,** R25) using the parameters –X2000 and –m1. These parameters ensured that fragments up to 2 kb were allowed to align (-X2000) and that only unique aligning reads were collected (-m1). For all data files duplicates were removed using Picard.

For peak calling and footprinting, the read start sites were adjusted to represent the center of the transposon binding event. Previous descriptions of the Tn5 transposase show that the transposon binds as a dimer and inserts two adapters separated by 9 bps (Adey, A. *et al. Genome Biol* 2010 **11:** R119). Therefore, all reads aligning to the + strand were offset by +4 bps, and all reads aligning to the – strand were offset -5 bps.

ATAC-seq peak calling: We used ZINBA to call all reported ATAC-seq peaks in this manuscript. ZINBA was run using a window size of 300 bp and an offset 75 bp. Alignability was used to model the zero-inflated component and the ATAC-seq read count for the background and enriched components. Enriched regions were identified as those with a posterior probability >0.8.

ATAC-seq insertion size enrichment analysis within chromatin annotations: First, the distribution of paired-end sequencing fragment sizes overlapping each chromatin state (see the ensemble.org website) were computed. The distributions were then normalized to the percent maximal within each state and enrichment was computed relative to the genome-wide set of fragment sizes.

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Nucleosome positioning: To generate the nucleosome position data track, we chose to split reads into various bins. Reads below 100 bps were considered nucleosome free, reads between 180 and 247 bps were considered to be mononucleosomes, reads between 315 and 473 bps were considered to be dinucleosomes and reads between 558 and 615 were considered to be trinucleosomes (for determining cutoffs see Fig. 12). Dinucleosome reads were split into two reads and Trinucleosome reads were split into three reads. Reads were analyzed using Danpos and Dantools using the parameters -p 1, -a 1, -d 20, -clonalcut 0. The background used was nucleosome free reads (reads less than 100 bps), allowing an effective negative weighting of these reads. This analysis allows calling multiple overlapping nucleosomes. Although generating nucleosome tracks using simple insert size cutoffs may yield false positives due to other nucleosome sized features, i.e. enhanaceosomes, we observed that we faithfully recapitulated global features on nucleosome position genome-wide (**Fig 2c,d** main text).

ChIP-seq peak calling and clustering: ChIP-seq data was downloaded from the UCSC ENCODE repository. Peaks where called using GEM (Guo et al, *PLoS Comput. Biol.* 2012 **8:** e1002638), the parameters used where -k_min 6 -k_max 20. Inputs where used as a control for peak calling. Binding events were annotated by distance to the nearest dyad in bins of 10 bps. Factors were then hierarchically clustered using Euclidean distance and normalized by gene and centered by mean. (Eisen et al. *Proc. Natl. Acad. Sci.* 1998 **95:** 14863–14868).

Footprinting using CENTIPEDE: The genome-wide set of motifs were obtained from the ENCODE motif repository (at the website of broadinstitute.org). The input for CENTIPEDE included the PWM score, conservation (PhyloP) and ATAC-seq counts within +/-100bp of each genomic region matching a motif. ChIP-seq data was obtained from the UCSC ENCODE repository.

Comparison of transcription factor regulatory networks: Transcription factor regulatory networks were constructed by comparing the GENCODE v14 genes with the genome-wide set of posterior probabilities estimated by CENTIPEDE for the respective cell-types. The extent of a transcription factor regulating each gene was determined by taking the sum of the weighed posterior probabilities for a given transcription factor mapping to the same chromosome. For each mapped motif the posterior probability was weighted based on the distance to the transcription start site for each gene. Comparison of transcription factor regulatory networks was computed as the correlation of each transcription factor in a given

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cell type with all transcription factors in the other cell type. The resulting correlation matrix was hierarchically clustered using the Pearson correlation coefficient and complete linkage.

Candidate IL2 enhancer analysis: ENCODE data on the UCSC genome browser was inspected to identify putative IL2 enhancers in one or more cell types that may be responsive to FDA approved immomodulatory drugs. We scanned the intergenic region upstream of IL2 in hg19 for (i) enhancer-associated histone marks (H3K4me1 and H3K27ac), (ii) binding by one or more TFs as confirmed by ChIP-seq, and (iii) the TF pathway can be targeted by a human therapeutic. This analysis identified IRF4 and STAT3 binding sites in addition to the known NFAT-responsive elements.

Results

ATAC-seq probes chromatin accessibility with transposons

Hyperactive Tn5 transposase (Goryshin, J Biol Chem. 1998 **273:** 7367–7374; Adey, A. *et al. Genome Biol* 2010 **11:** R119, loaded *in vitro* with adapters for high-throughput DNA sequencing, can simultaneously fragment and tag a genome with sequencing adapters (previously described as "tagmentation"). It was hypothesized that transposition by purified Tn5, a prokaryotic transposase, on small numbers of unfixed eukaryotic nuclei would interrogate regions of accessible chromatin. An Assay for Transposase Accessible Chromatin followed by high-throughput sequencing (ATAC-seq) is described. ATAC-seq uses Tn5 transposase to integrate its adapter payload into regions of accessible chromatin, whereas steric hindrance less accessible chromatin makes transposition less probable. Therefore, amplifiable DNA fragments suitable for high-throughput sequencing are preferentially generated at locations of open chromatin (**Fig 1a**). The entire assay and library construction can be carried out in a simple two-step process involving Tn5 insertion and PCR. In contrast, published DNase- and FAIRE-seq protocols for assaying chromatin accessibility involve multi-step protocols and many potentially loss-prone steps, such as adapter ligation, gel purification, and crosslink reversal. For instance, a published DNase-seq protocol calls for approximately 44 steps, and two overnight incubations, while published FAIRE-seq protocols require two overnight incubations carried out over at least 3 days. Furthermore, these protocols require 1-50 million cells (FAIRE) or 50 million cells (DNase-seq), perhaps because of these complex workflows (**Fig 1b**). In comparison to established methods, ATAC-seq enables rapid and efficient library generation because assay and library preparation are carried out in a single enzymatic step.

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Extensive analyses show that ATAC-seq provides accurate and sensitive measure of chromatin accessibility genome-wide. ATAC-seq was carried out on 50,000 and 500 unfixed nuclei isolated from GM12878 lymphoblastoid cell line (ENCODE Tier 1) for comparison and validation with chromatin accessibility data sets, including DNase-seq and FAIRE-seq. At a locus previously highlighted by others, (**Fig. 1c**), ATAC-seq has a signal-to-noise ratio similar to DNase-seq, which was generated from approximately 3 to 5 orders-of-magnitude more cells. Peak intensities were highly reproducible between technical replicates (R=0.98), and highly correlated between ATAC-seq and DNase-seq (R=0.79 and R=0.83, **Fig. 6**), and it is noted that the majority of reads within peaks come from intersections of DNase and ATAC-seq peaks (**Fig. 7**). Comparing our data to DHSs identified in ENCODE DNase-seq data, receiver operating characteristic (ROC) curves demonstrate a similar sensitivity and specificity as DNase-seq (**Fig. 8**). It is also noted that ATAC-seq peak intensities correlate well with markers of active chromatin and not with transposase sequence preference (**Figs. 9** and **10**). Highly sensitive open chromatin detection is maintained even when using 5,000 or 500 human nuclei as starting material (**Figs. 8** and **11**), although, under the conditions used, sensitivity is diminished for smaller numbers of input material, as can be seen in Fig 1c.

ATAC-seq insert sizes disclose nucleosome positions

It was found that ATAC-seq paired-end reads produce detailed information about nucleosome packing and positioning. The insert size distribution of sequenced fragments from human chromatin has clear periodicity of approximately 200 base pairs, suggesting many fragments are protected by integer multiples of nucleosomes (**Fig 2a**). This fragment size distribution also shows clear periodicity equal to the helical pitch of DNA. By partitioning insert size distribution according to functional classes of chromatin as defined by previous models (Hoffman et al. Nucleic Acids Res. 2013 41: 827–841), and normalizing to the global insert distribution we observe clear class-specific enrichments across this insert size distribution (**Fig. 2b**), demonstrating that these functional states of chromatin have an accessibility "fingerprint" that can be read out with ATAC-seq. These differential fragmentation patterns are consistent with the putative functional state of these classes, as CTCF-bound regions are enriched for short fragments of DNA, while transcription start sites are differentially depleted for mono-, di- and tri-nucleosome associated fragments. Transcribed and promoter flanking regions are enriched for longer multi-nucleosomal fragments, suggesting they may represent more compacted forms of chromatin. Finally, prior studies have shown that certain DNA sequences are refractory to nuclease digestion and

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released as large, multi-nucleosome-sized fragments; subsequent studies showed that such fragments are condensed heterochromatin. Indeed repressed regions were found to be depleted for short fragments and enriched for phased multi-nucleosomal inserts, consistent with their expected inaccessible state. These data suggest that ATAC-seq reveals differentially accessible forms of chromatin, which have been long hypothesized to exist *in vivo*.

To explore nucleosome positioning within accessible chromatin in the GM12878 cell line, data was partitioned into reads generated from putative nucleosome free regions of DNA, and reads likely derived from nucleosome associated DNA (see **Fig. 12**). Using a simple heuristic that positively weights nucleosome associated fragments and negatively weights nucleosome free fragments (see Methods), we calculated a data track used to call nucleosome positions within regions of accessible chromatin (Chen, K. et al. Genome Research 2013 23, 341–351). An example locus (**Fig. 3a**) contains a putative bidirectional promoter with CAGE data showing two transcription start sites (TSS) separated by ~700bps. ATAC-seq reveals in fact two distinct nucleosome free regions, separated by a single well-positioned mononucleosome (**Fig. 3a**). Compared to MNase-seq, ATAC-seq data is more amenable to detecting nucleosomes within putative regulatory regions, as the majority of reads are concentrated within accessible regions of chromatin (**Fig. 3b**). By averaging signal across all active TSSs, it is noted that nucleosome-free fragments are enriched at a canonical nucleosome-free promoter region overlapping the TSS, while the nucleosome signal is enriched both upstream and downstream of the active TSS, and displays characteristic phasing of upstream and downstream nucleosomes (**Fig. 3c**). Because ATAC-seq reads are concentrated at regions of open chromatin, a strong nucleosome signal is seen at the +1 nucleosome, which decreases at the +2, +3 and +4 nucleosomes, in contrast, MNase-seq nucleosome signal increases at larger distances from the TSS likely due to over digestion of more accessible nucleosomes. Additionally, MNase-seq (4 billion reads) assays all nucleosomes, whereas reads generated from ATAC-seq (198 million paired reads) are concentrated at regulatory nucleosomes (**Fig. 3b,c**). Using the nucleosome calls, putative distal regulatory regions and TSSs were further partititioned into regions that were nucleosome free and regions that were predicted to be nucleosome bound. It is noted that TSSs were enriched for nucleosome free regions when compared to distal elements, which tend to remain nucleosome rich (**Fig. 3d**). These data suggest ATAC-seq can provide high-resolution readout of nucleosome associated and nucleosome free regions in regulatory elements genome wide.

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ATAC-seq reveals patterns of nucleosome-TF spacing

ATAC-seq high-resolution regulatory nucleosome maps can be used to understand the relationship between nucleosomes and DNA binding factors. Using ChIP-seq data, we plotted the position of a variety of DNA binding factors with respect to the dyad of the nearest nucleosome. Unsupervised hierarchical clustering (**Figure 3e**) revealed major classes of binding with respect to the proximal nucleosome, including 1) a strongly nucleosome avoiding group of factors with binding events stereotyped at ~180 bases from the nearest nucleosome dyad (comprising C-FOS, NFYA and IRF3), 2) a class of factors that "nestle up" precisely to the expected end of nucleosome DNA contacts, which notably includes chromatin looping factors CTCF and cohesion complex subunits RAD21 and SMC3; 3) a large class of primarily TFs that have gradations of nucleosome avoiding or nucleosome-overlapping binding behavior, and 4) a class whose binding sites tend to overlap nucleosome-associated DNA. Interestingly, this final class includes chromatin remodeling factors such as CHD1 and SIN3A as well as RNA polymerase II, which appears to be enriched at the nucleosome boundary. The interplay between precise nucleosome positioning and locations of DNA binding factor immediately suggests specific hypotheses for mechanistic studies, a potential advantage of ATAC-seq.

ATAC-seq footprints infer factor occupancy genome-wide

ATAC-seq enables accurate inference of DNA binding factor occupancy genome-wide. DNA sequences directly occupied by DNA-binding proteins should be protected from transposition; the resulting sequence "footprint" reveals the presence of the DNA-binding protein at each site, analogous to DNase digestion footprints. At a specific CTCF binding site on chromosome 1, we observed a clear footprint (a deep notch of ATAC-seq signal), similar to footprints seen by DNase-seq, at the precise location of the CTCF motif that coincides with the summit of the CTCF ChIP-seq signal in GM12878 cells (**Fig 4a**). The ATAC-seq signal was averaged over all expected locations of CTCF within the genome and observed a well-stereotyped "footprint" (**Fig. 4b**). Similar results were obtained for a variety of common TFs (for examples see **Fig. 13**). We inferred the CTCF binding probability from motif consensus score, evolutionary conservation, and ATAC-seq insertion data to generate a posterior probability of CTCF binding at all loci (**Fig. 4c**) (Pique-Regi et al. Genome Research 2011 21 447–455). Results using ATAC-seq closely recapitulate ChIP-seq binding data in this cell line and compare favorably to DNase-based factor occupancy inference (see **Fig. 14**), suggesting that factor occupancy data can be extracted from these ATAC-seq data

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allowing reconstruction of regulatory networks.

ATAC-seq enables epigenomic analysis on clinical timescales

ATAC-seq is rapid, information rich, and compatible with small numbers of cells and may serve as a powerful tool for personalized epigenomics in the clinic. Specifically, one can envision "personal epigenomics" as genome-scale information about chromatin generated from an individual from a standard clinical sample in a clinical timescale. ATAC-seq was applised to assay the personal T-cell epigenome of a healthy volunteer via standard serial blood draws, to demonstrate a workflow capable of generating ATAC-seq libraries in clinical timescales. Using rapid T-cell enrichment and sample handling protocols, the total required time from blood draw to sequencing was approximately 275 minutes (**Fig. 5a**). When coupled with ongoing improvements to sequencing and analysis turn-around times, ATAC-seq can offer the possibility of a daily turn-around time for a personal epigenomic map. To explore this possibility, ATAC-seq was performed on three consecutive days via standard blood draws from a single individual (**Fig. 5b**). As an exercise to consider how personal epigenomic maps may contain personalized regulatory information, we investigated ATAC-seq profile at the *IL2* locus. IL-2 is a key cytokine that drives T-cell growth and functions in inflammatory and autoimmune diseases. Furthermore, distinct drugs inhibit the activities of different transcription factors that bind putative *IL2* enhancers in a context-dependent manner. In principle, one might wish to identify the causal transcription factor pathway in order to rationally target inhibition without exposing the patient to drugs unlikely to serve the therapeutic goal of IL-2 blockade. ATAC-seq shows that in the proband's T-cells, only NFAT, but not two other drug targets, is engaging *IL2* (**Fig. 5c**), providing clinically relevant information on the regulatory state of this individual.

Using ATAC-seq footprints the occupancy profiles of 89 transcription factors in proband T-cells were generated, enabling systematic reconstruction of regulatory networks. With this personalized regulatory map, we compared the genomic distribution of the same 89 transcription factors between GM12878 and proband CD4+ T-cells. Transcription factors that exhibit large variation in distribution between T-cells and B-cells are enriched for T-cell specific factors (**Fig. 5d**). This analysis shows NFAT is differentially regulating, while canonical CTCF occupancy is highly correlated within these two cell types (**Fig. 5d**). Supporting this interpretation, it is noted that specific loci where NFAT is localized nearby to known T-cell specific genes such as CD28 and a novel lincRNA RP11-229C3.2 (**Fig. 15**). Additionally, ATAC-seq of $CD4^+$ and $CD8^+$ T-cells, and monocytes isolated by

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fluorescence-activated cell sorting (FACS) from a single blood draw created an interpretative framework for the personal epigenomes, and demonstrated that ATAC-seq is compatible with cellular enrichment using surface markers (**Fig. 16**). Separately, allele-specific chromatin accessibility has been shown to be particularly relevant to our understanding of human disease. As a proof of principle we also used ATAC-seq to identify candidate allele-specific open chromatin regions within the GM12878 cell line (**Fig. 17**). These results demonstrate the feasibility of generating detailed personalized gene regulatory networks from clinical samples, opening the door for future diagnostic applications.

Epigenomic studies of chromatin accessibility have yielded tremendous biological insights, but are currently limited in application by their complex workflows and large cell number requirements. While, improvements of existing methods may enable them to reach the similar performance, ATAC-seq in certain cases can offer substantial advantages over existing technologies due to its speed, simplicity, and low input cell number requirement. ATAC-seq is an information rich assay, allowing simultaneous interrogation of factor occupancy, nucleosome positions in regulatory sites, and chromatin accessibility genome-wide. These insights are derived from both the position of insertion and the distribution of insert lengths captured during the transposition reaction. While extant methods such as DNase- and MNase-seq can provide some subsets of the information in ATAC-seq, they each require separate assays with large cell numbers, which increases the time, cost, and limits applicability to many systems. ATAC-seq also provides insert size "fingerprints" of biologically relevant genomic regions, suggesting that it capture information on chromatin compaction. ATAC-seq may have broad applicability, significantly add to the genomics toolkit, and improve our understanding of gene regulation, particularly when integrated with other powerful rare cell techniques, such as FACS, laser capture microdissection (LCM) and recent advancements in RNA-seq.

ATAC-seq may be used to generate "personal epigenomic" profiles on a timescale compatible with clinical decision-making. Optimized procedures can transform a clinical blood sample to completed sequencing library in 275 minutes. The reduced input requirements and rapid workflows, when coupled with the recent introduction of rapid-turnaround high-throughput sequencing instruments, such as the MiSeq and HiSeq2500, should enable investigation of personalized epigenetic landscapes of selected tissues both in the lab and the clinic. ATAC-seq is compatible with FACS, enabling studies on carefully sorted and rare subpopulations from primary tissues. Cellular subpopulations selected at different points in development and aging, and human diseases, including cancer,

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autoimmunity, and neuropsychiatric disorders are viable applications.

Example 2. Single-Cell ATAC-seq

Single-cell chromatin accessibility datasets were obtained using the ATAC-seq protocol. To ensure that the ratio of transposase molecules to open chromatin sites was kept nearly constant, the single-cell ATAC-seq assay was carried out by manipulating individual cells after an initial transposition reaction.

Transposases can serve as an open-chromatin stain

It was observed that after *in vitro* insertion of sequencing adapter, the Tn5 transposase remained tightly bound to the DNA and formed a high-affinity macromolecular complex that prevented dissociation of the generated ATAC-seq DNA fragments. To support this observation, Tn5 transposase was loaded with fluorescently labeled DNA adapters, and allowed for visualization of regions of open chromatin within the nucleus of individual cells (**Fig. 18**). Additional electrophoretic mobility shift assays also indicated that the transposase remained associated to DNA after transposition.

Single-Cell ATAC-seq provides unique reads characteristic of chromosomal DNA

Since this fluorescence signal localized to the nucleus and was detectable even after transposition, the single-cell ATAC-seq experiment was performed by keeping the transposed fragments in the nucleus during subsequent sorting and cell selection steps. A group of cells were permeabilized, and the chromosomal DNA was transposed with Tn5 transposase. The cells were kept under conditions that prevented the resulting ATAC-seq fragments from leaving the cell nucleus, (i.e. divalent cation was not chelated), and the individual cells were sorted into independent PCR reactions for library preparation, as described above. This workflow significantly simplified the workflow for single-cell analysis and provided two additional advantages. First, this abrogated any effect of the sorting process on the chromatin state because transposition preceded sorting. Second, it provided more robust ATAC-seq signal, as cells were sorted directly into a PCR master mix and amplified. Using this workflow, ~2,000-5,000 unique ATAC-seq reads per cell were generated. These reads were enriched for known open chromatin sites in GM12878 cells (**Fig. 19**) and displayed characteristic periodic enrichments indicative of nucleosomes (**Fig. 20**).

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Example 3. Quality control

Assay for **T**ransposase **A**ccessible **C**hromatin (ATAC-seq) has been shown to be compatible with many methods for cell collection and has also worked effectively across many cell types and species. However, the following protocol has been optimized for human lymphoblastoid cells. Minor variations (i.e. cell number, centrifugation speeds, and lysis conditions) may optimized for particular applications.

I. Cell Preparation

1. Harvest cells (no fixation), protocol to be defined by the user.
2. Spin down 50,000 cells at 500 ×g for 5 min, 4°C.
3. Wash once with 50 μL of cold 1x PBS buffer. Spin down at 500 ×g for 5 min, 4°C.
4. Gently pipette to resuspend the cell pellet in 50 μL of cold lysis buffer (10 mM Tris-HCl, pH 7.4, 10 mM NaCl, 3 mM $MgCl_2$, 0.1% IGEPAL CA-630). Spin down immediately at 500 ×g for 10 min, 4°C.
5. Discard the supernatant, and immediately continue to transposition reaction.

II. Transposition Reaction and Purification

1. Make sure the cell pellet is set on ice.
2. To make the transposition reaction mix, combine the following:

   25 μL 2x TD Buffer (Illumina Cat #FC-121-1030)
   2.5 μL Tn5 Transposes (Illumina Cat #FC-121-1030)
   22.5 μL Nuclease Free H_2O
   50 μl Total

3. Gently pipette to resuspend nuclei in the transposition reaction mix.
4. Incubate the transposition reaction at 37°C for 30 min.
5. Immediately following transposition, purify using a Qiagen MinElute Kit.
6. Elute transposed DNA in 10 μL Elution Buffer (10mM Tris buffer, pH 8).
7. Purified DNA can be stored at -20°C.

III. PCR Amplification

1. To amplify transposed DNA fragments, combine the following in a PCR tube:

   10 μL Transposed DNA
   9.7 μL Nuclease Free H_2O
   2.5 μL 25μM Customized Nextera PCR Primer 1*

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2.5 µL 25µM Customized Nextera PCR Primer 2* [Barcode]
0.3 µL 100x SYBR Green I** (Invitrogen Cat #S-7563)
25 µL NEBNext High-Fidelity 2x PCR Master Mix (New England Labs Cat #M0541)
50 µL Total

* Complete list of primers are shown above.

**10,000x SYBR Green I is diluted in 10mM Tris buffer, pH 8 to make a 100x working solution.

2. Cycle as follows:

(1) 72°C, 5 min
(2) 98°C, 30 sec
(3) 98°C, 10 sec
(4) 63°C, 30 sec
(5) 72°C, 1 min
(6) Repeat steps 3-5, 4x
(7) Hold at 4°C

3. In order to reduce GC and size bias in PCR, the PCR reaction is monitored using qPCR to stop amplification prior to saturation. To run a qPCR side reaction, combine the following:

5 µL 5 cycles PCR amplified DNA
4.44 µL Nuclease Free H_2O
0.25 µL 25µM Customized Nextera PCR Primer 1*
0.25 µL 25µM Customized Nextera PCR Primer 2*
0.06 µL 100x SYBR Green I
5 µL NEBNext High-Fidelity 2x PCR Master Mix
15 µL Total

* Complete list of primers available in Section VI of this protocol

4. qPCR cycle as follows:

(1) 98°C, 30 sec
(2) 98°C, 10 sec
(3) 63°C, 30 sec
(4) 72°C, 1 min
(5) Repeat steps 2-4, 19x
(6) Hold at 4°C

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5. The additional number of cycles needed for the remaining 45 μL PCR reaction is determined as following:

(1) Plot linear Rn vs. Cycle
(2) Set 5000 RF threshold
(3) Calculate the # of cycle that is corresponded to ¼ of maximum fluorescent intensity

If the # of cycle to be added lies in between two cycles, the # is determined by taking the smaller integer as the # of cycle to be added (i.e., blue and pink samples)
If two samples have similar Ct values but differs in the fluorescent intensities, calculate the # of cycle using the sample with lower fluorescent intensity (i.e., red and blue samples)

6. Run the remaining 45 μL PCR reaction to the correct # of cycle. Cycle as follows:

(1) 98°C, 30 sec (2) 98°C, 10 sec (3) 63°C, 30 sec (4) 72°C, 1 min
(5) Repeat steps 2-4, x times
(6) Hold at 4°C

7. Purify amplified library using Qiagen PCR Cleanup Kit. Elute the purified library in 20 μL Elution Buffer (10mM Tris Buffer, pH 8). Be sure to dry the column before adding elution buffer.

IV. Library QC using Gel Electrophoresis

1. Dilute 1:20 100bp NEB DNA ladder with 10mM Tris Buffer, pH 8.
2. Add 0.6 μL 10x SYBR Green I to every 5 μL of diluted ladder.
3. Mix 1:1 of the diluted ladder with 2x DNA loading dye.
4. Mix 1:1 of amplified library with 2x DNA loading dye.
5. Run amplified library on 5% Bio-Rad Mini-Protean TBE Precast Gel (stored at 4°C). Load 5 μL diluted ladder/DNA loading dye mixture. Load 10 μL amplified library/DNA loading dye mixture.
6. Run at ~100 mV for 45 min.

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7. SYBR Green I dye has an excitation maximum at ~488 nm and has an emission maximum at ~520 nm. DNA stained with SYBR Green I dye can be visualized using a blue-light source or imaging systems equipped with laser that emits at 488 nm. We typically use Typhoon TRIO Variable Mode Imager from Amersham Biosciences for visualization. Images are best obtained by digitizing at 100 microns pixel size resolution with a 520 nm band-pass emission filter to screen out reflected and scattered excitation light and background fluorescence.

V. Library Quantitation

We use qPCR based methods to quantify our ATAC-seq libraries. We have found that other methods, such as Bioanalyzer and Qubit, can give misleading and inaccurate results due to the large distribution of insert sizes. We recommend quantifying libraries using the KAPA Library Quant Kit for Illumina Sequencing Platforms (KAPABiosystems).

Although the foregoing embodiments have been described in some detail by way of illustration and example for purposes of clarity of understanding, it is readily apparent to those of ordinary skill in the art in light of the above teachings that certain changes and modifications can be made thereto without departing from the spirit or scope of the appended claims.

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CLAIMS

What is claimed is:

1. A method for analyzing chromatin, comprising:

(a) treating chromatin isolated from a population of cells with an insertional enzyme complex to produce tagged fragments of genomic DNA;

(b) sequencing at least some of the tagged fragments to produce a plurality of sequence reads; and

(c) making an epigenetic map of a region of the genome of said cells by mapping information obtained from the sequence reads to the region.

2. The method of claim 1, wherein the information is obtained using the nucleotide sequences at the beginning and, optionally, the end of a sequence read.

3. The method of any of claims 1-2, wherein the information mapped in (c) is selected from one or more of:

(i) cleavage sites for the transposase;

(ii) the sizes of the fragments produced in step (a);

(iii) sequence read length;

(iii) the positions of sequence reads of a defined range in length; and

(iv) sequence read abundance.

4. The method of claim 3, wherein the fragments of a defined size range are nucleosome-free fragments.

5. The method of any of claims 1-4, wherein the epigenetic map shows one or more of:

(i) a profile of chromatin accessibility along the region;

(ii) DNA binding protein occupancy for a binding site in the region;

(iii) nucleosome-free DNA in the region;

(iv) positioning of nucleosomes along the region;

(v) chromatin states.

6. The method of claim 5, further comprising measuring global occupancy of a binding site for said DNA binding protein.

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7. The method of claim 5, wherein the DNA binding protein is a transcription factor.

8. The method of any of claims 1-7, wherein the population of cells is composed of 500 to 100,000 cells.

9. The method of any of claims 1-8, wherein the cells are isolated from an individual.

10. The method of any of claims 1-9, wherein the cells are isolated from blood of said individual.

11. The method of claims 1-10, wherein the cells are of the same cell type.

12. The method of claim 11, wherein the cells are FACS–selected cells.

13. The method of any of claims 1-12, wherein the treating step (a) comprises:

isolating nuclei from the a population of cells; and

combining the isolated nuclei with said insertional enzyme complex, wherein the combining results in both lysis of the nuclei to release said chromatin and production of said tagged fragments of genomic DNA.

14. The method of any of claims 1-13, wherein the transposase is derived from Tn5 transposase.

15. The method of any of claims 1-14, wherein the transposase is derived from MuA transposase.

16. A method for comparing two samples comprising:

(a) analyzing a first population of cells using the method of claim 1 to produce a first epigenetic map; and

(b) analyzing a second population of cells using the method of claim 1 to produce a second epigenetic map; and

(c) comparing the first epigenetic map to the second epigenetic map.

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17. The method of claim 16, wherein the first population of cells and the second population of cells are collected from the same individual at different times.

18. The method of claim 16, wherein the first population of cells and the second population of cells are different populations of cells collected from different individuals.

19. A diagnostic method, comprising:

analyzing chromatin from a patient using the method of claim 1, to produce an epigenetic map; and

providing a diagnosis or prognosis based on the epigenetic map.

20. A kit comprising:

(a) reagents for isolating nuclei from a population of cells;

(b) an insertional enzyme complex, and

(c) transposase reaction buffer,

wherein the components of the kit are configured such that, combining the reaction buffer, transposon tags and adaptors with nuclei *in vitro* results in both lysis of the nuclei to release chromatin and production of tagged fragments of genomic DNA.

21. A method for determining accessibility of a polynucleotide at a site, wherein said polynucleotide is from a cell sample, comprising:

(a) inserting a plurality of molecular tags with an insertional enzyme into said polynucleotide; and

(b) using said molecular tags to determine accessibility at said site.

22. The method of claim 21, further comprising using said determined accessibility to identify one or more proteins that are bound to said polynucleotide at said site.

23. The method of claim 22, wherein at least one of said proteins is a transcription factor.

24. The method of claim 21, further comprising using said molecular tags to generate an accessibility map of said polynucleotide.

25. A method for analyzing the three-dimensional structure of a polynucleotide from a cell sample, comprising:

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(a) inserting a plurality of molecular tags with an insertional enzyme into said polynucleotide; and

(b) using said molecular tags to analyze the three-dimensional structure of said polynucleotide.

26. The method of claim 21 or 25, wherein said cell sample is obtained from a primary source.

27. The method of claim 21 or 25, wherein said cell sample consists of less than about 500,000 cells.

28. The method of claim 27, wherein said cell sample is a single cell.

29. The method of claim 21 or 25, wherein said polynucleotide is fragmented into a plurality of fragments during step (a).

30. The method of claim 29, further comprising amplifying said fragments.

31. The method of claim 29, wherein said accessibility is determined or said three-dimensional structure is analyzed by sequencing said fragments and thereby generating a plurality of sequencing reads.

32. The method of claim 31, wherein said fragments are sequenced by a high-throughput sequencing technique.

33. The method of claim 31, further comprising normalizing said sequencing reads based on the sequence insertion preference of said insertional enzyme.

34. The method of claim 31, wherein the length of said sequenced reads is used to determine a chromatin state annotation.

35. The method of claim 21 or 25, further comprising permeabilizing said cell sample to allow access for said insertional enzyme.

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36. The method of claim 35, wherein the nuclei in said cell sample is minimally perturbed during said permeabilization.

37. The method of claim 35, wherein said cell sample is permeabilized using a permeabilization agent.

38. The method of claim 37, wherein said permeabilization agent is selected from the group consisting of NP40, digitonin, tween, streptolysin, and cationic lipids.

39. The method of claim 35, wherein said cell sample is permeabilized using hypotonic shock and/or ultrasonication.

40. The method of claim 21 or 25, wherein said insertional enzyme further comprises a nuclear localization signal.

41. The method of claim 21 or 25, wherein said insertion is facilitated by addition of one or more divalent cations.

42. The method of claim 41, wherein said one or more divalent cations comprises magnesium.

43. The method of claim 41, wherein said one or more divalent cations comprises manganese.

44. The method of claim 21 or 25, further comprising analyzing a disease state in a subject based on said accessibility of said specific site or said three-dimensional structure of said polynucleotide, wherein said cell sample is obtained from said subject.

45. The method of claim 21 or 25, further comprising dividing said cell sample or said polynucleotides into a plurality of portions.

46. The method of claim 45, wherein said portions are divided based on said molecular tags.

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47. The method of claim 21 or 25, further comprising analyzing a phenotype of said cell sample.

48. The method of claim 47, wherein said phenotype is correlated to said accessibility of said site or said three-dimensional structure of said polynucleotide.

49. The method of claim 21 or 25, wherein said insertional enzyme comprises two or more enzymatic moieties.

50. The method of claim 49, wherein each of said enzymatic moieties inserts a common sequence into said polynucleotide.

51. The method of claim 50, wherein said common sequence comprises a common barcode.

52. The method of claim 49, wherein said enzymatic moieties are linked together.

53. The method of claim 49, wherein said enzymatic moieties comprise transposases.

54. The method of claim 21 or 25, wherein said polynucleotide is fragmented into a plurality of fragments during step (a), and wherein said fragments comprising said common barcode are determined to be in proximity in the three-dimensional structure of said polynucleotide.

55. The method of claim 21 or 25, wherein said molecular tags comprise sequencing adaptors.

56. The method of claim 55, wherein said sequencing adaptors further comprise a barcode label.

57. The method of claim 55, wherein said barcode labels comprises a unique sequence.

58. The method of claim 21 or 25, wherein said molecular tags comprise fluorescence tags.

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59. A composition comprising a polynucleotide, an insertional enzyme and an insert element, wherein:

(a) said insert element comprises a nucleic acid comprising a predetermined sequence; and

(b) said insertional enzyme further comprises an affinity tag.

60. A composition comprising a polynucleotide, an insertional enzyme and an insert element, wherein:

(a) said insertional enzyme comprises two or more enzymatic moieties; and

(b) said enzymatic moieties are linked together.

61. A kit comprising:

(a) a cell lysis buffer;

(b) an insertional enzyme comprising an affinity tag; and

(c) an insert element comprising a nucleic acid, wherein said nucleic acid comprises a predetermined sequence.

62. A kit comprising:

(a) a cell lysis buffer;

(b) an insertional enzyme comprising two or more enzymatic moieties, wherein said enzymatic moieties are linked together; and

(c) an insert element.

63. The method, composition or kit of claim 21, 25, 59, 60, 61 or 62, wherein said polynucleotide is bound to a plurality of association molecules.

64. The method, composition or kit of claim 63, wherein said association molecules are proteins.

65. The method, composition or kit of claim 64, wherein said proteins comprise histones.

66. The method, composition or kit of claim 21, 25, 59, 60, 61 or 62, wherein said insertional enzyme is a transposase.

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67. The method, composition or kit of claim 66, wherein said transposase is derived from a Tn5 transposase.

68. The method, composition or kit of claim 66, wherein said transposase is derived from a MuA transposase.

69. The method, composition or kit of claim 66, wherein said transposase is derived from a Vibhar transposase.

70. The method, composition or kit of claim 21, 25, 59, 60, 61 or 62, wherein said insertional enzyme further comprises an affinity tag.

71. The method, composition or kit of claim 70, wherein said affinity tag is an antibody.

72. The method, composition or kit of claim 71, wherein said antibody binds to a transcription factor.

73. The method, composition or kit of claim 71, wherein said antibody binds to a modified nucleosome.

74. The method, composition or kit of claim 71, wherein said antibody binds to a modified nucleic acid.

75. The method, composition or kit of claim 74, wherein said modified nucleic acid is a methylated or hydroxymethylated DNA.

76. The method, composition or kit of claim 70, wherein said affinity tag is a single-stranded nucleic acid.

77. The method, composition or kit of claim 76, wherein said single-stranded nucleic acid binds to a target nucleic acid.

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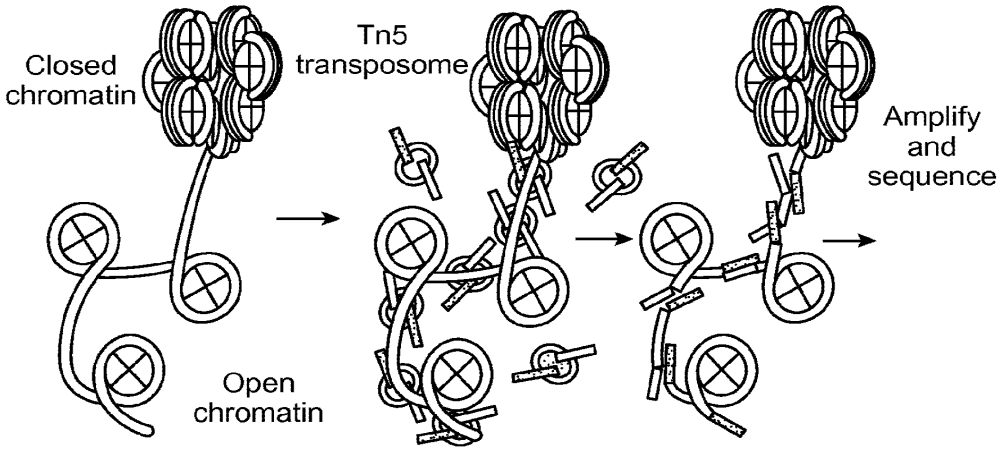


FIG. 1A

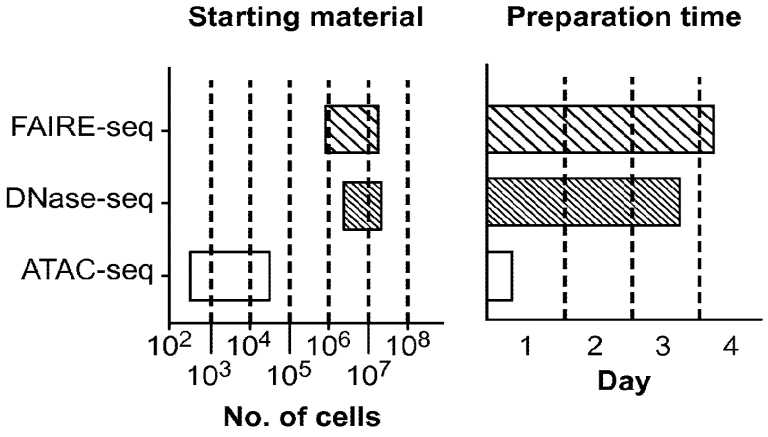


FIG. 1B

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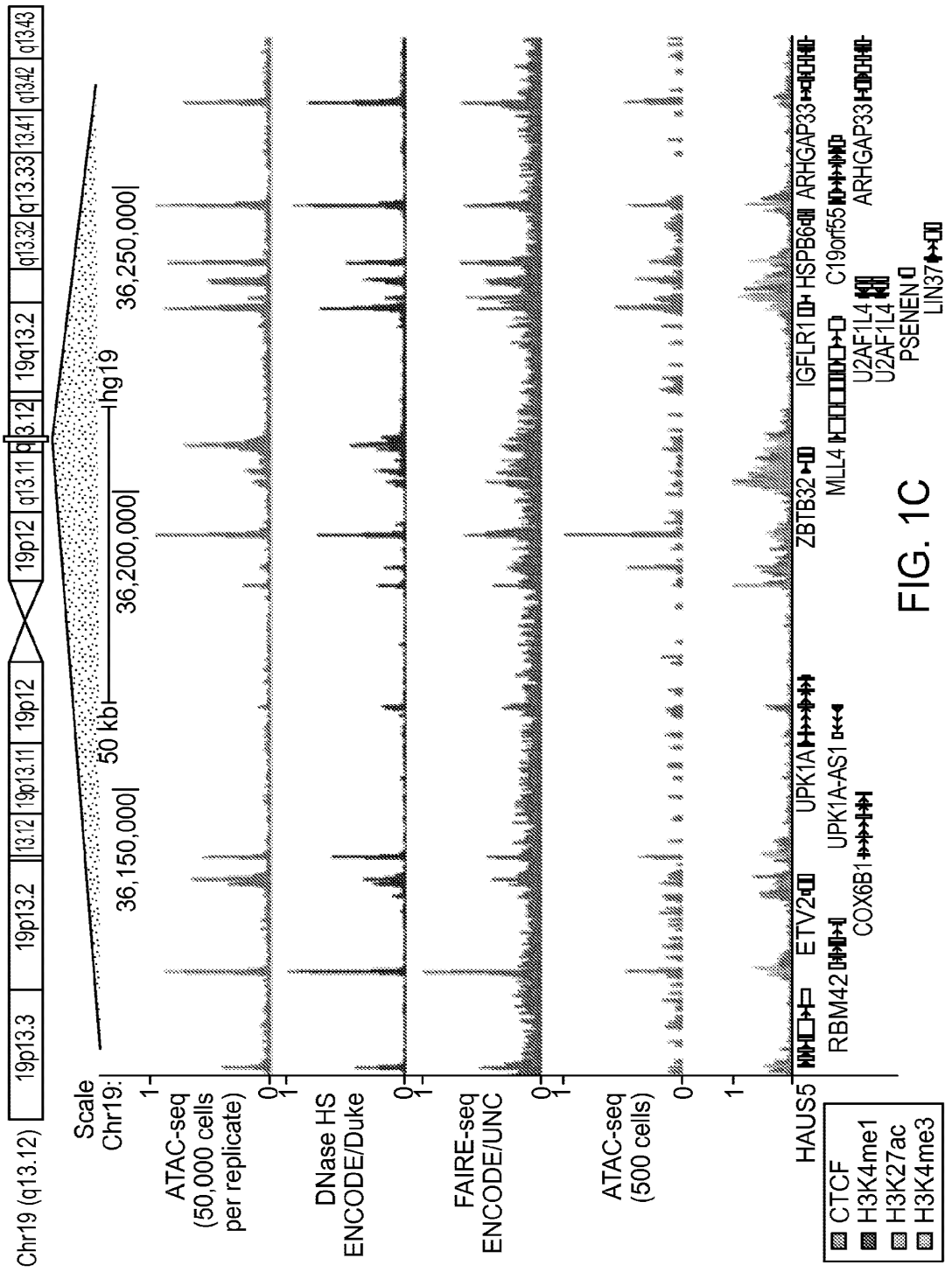


FIG. 1C

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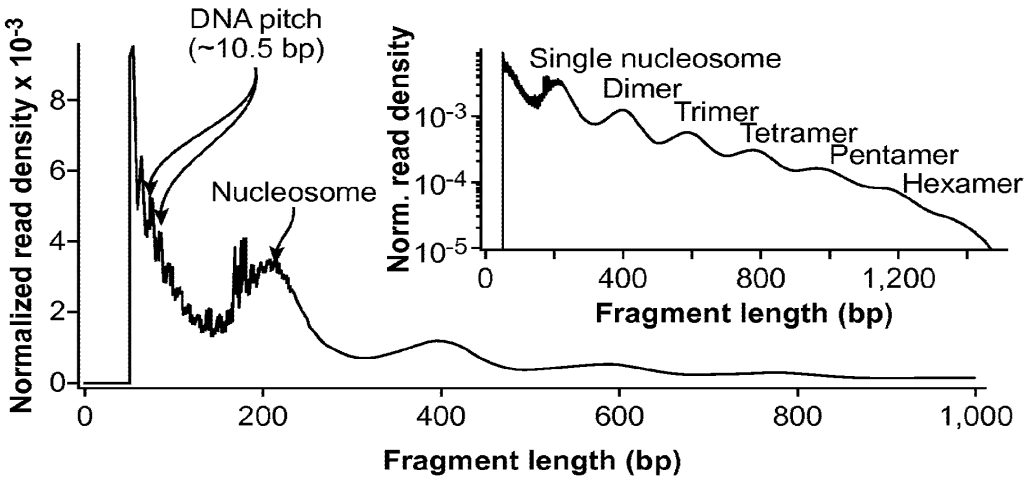


FIG. 2A

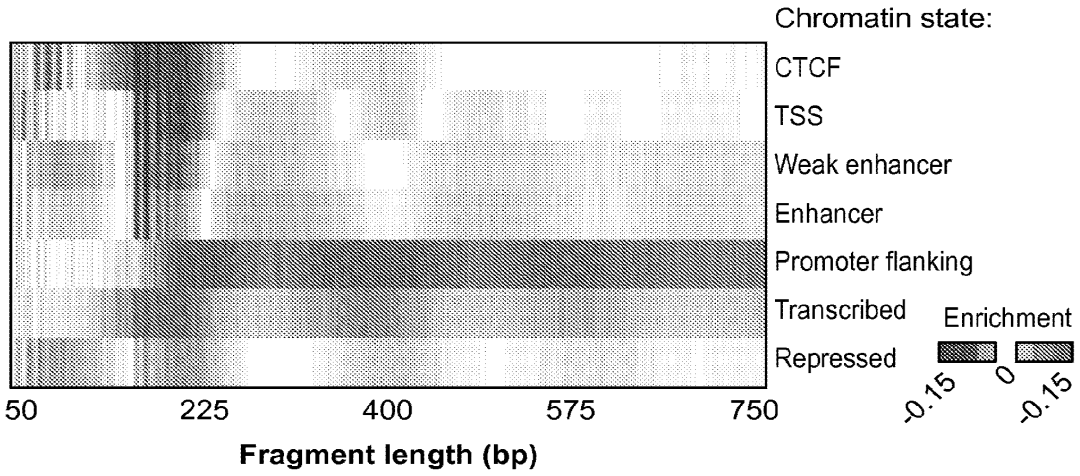


FIG. 2B

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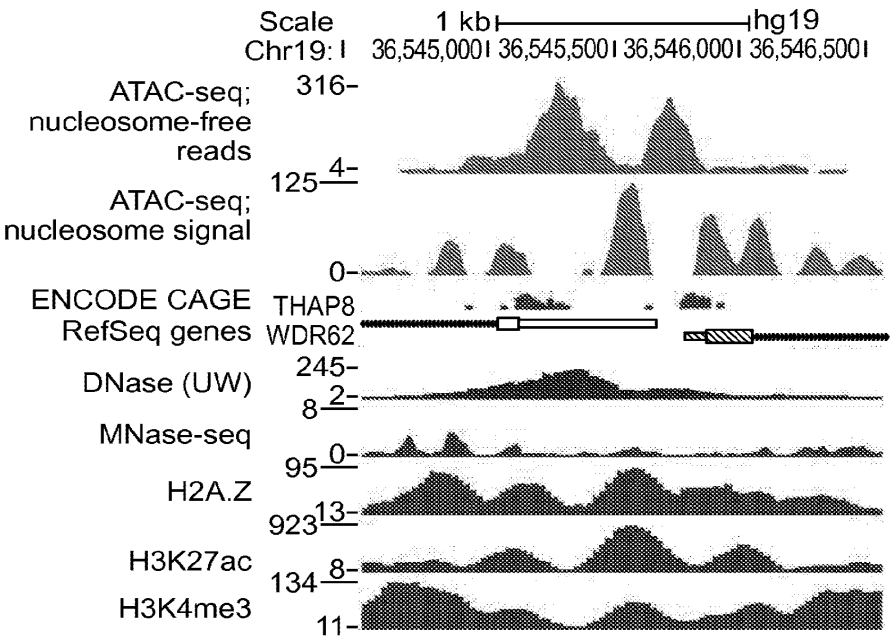


FIG. 3A

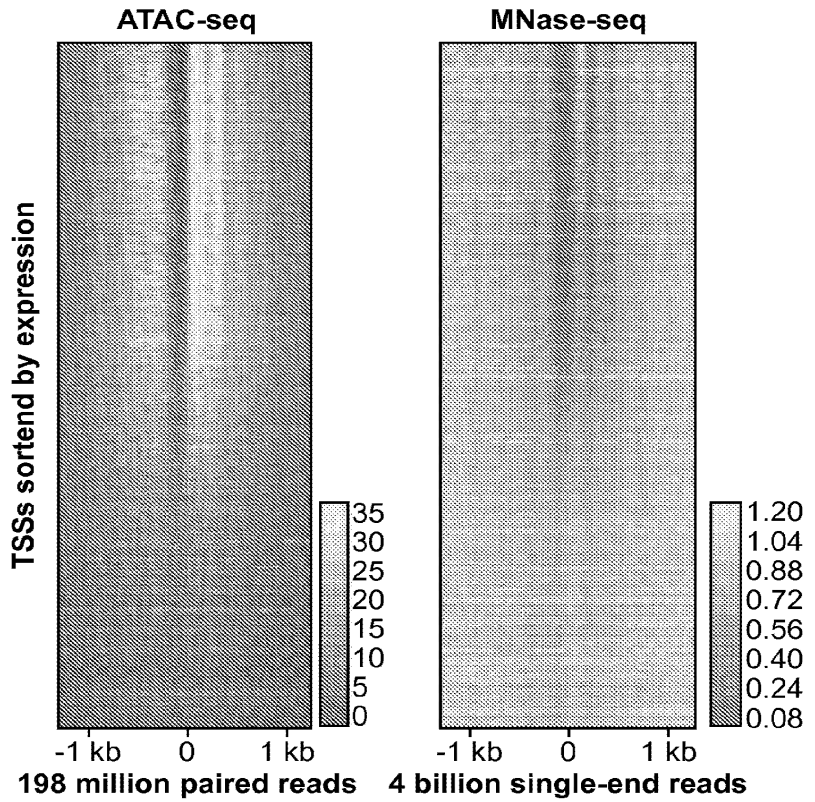


FIG. 3B

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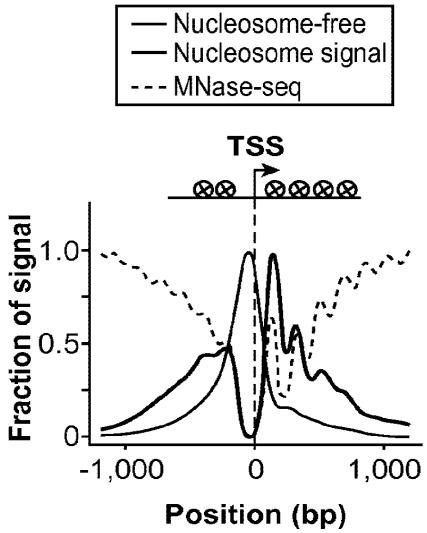


FIG. 3C

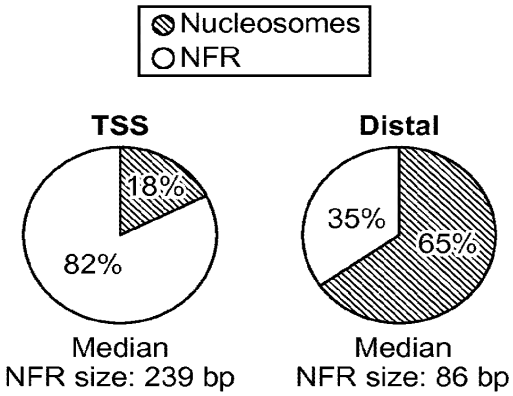


FIG. 3D

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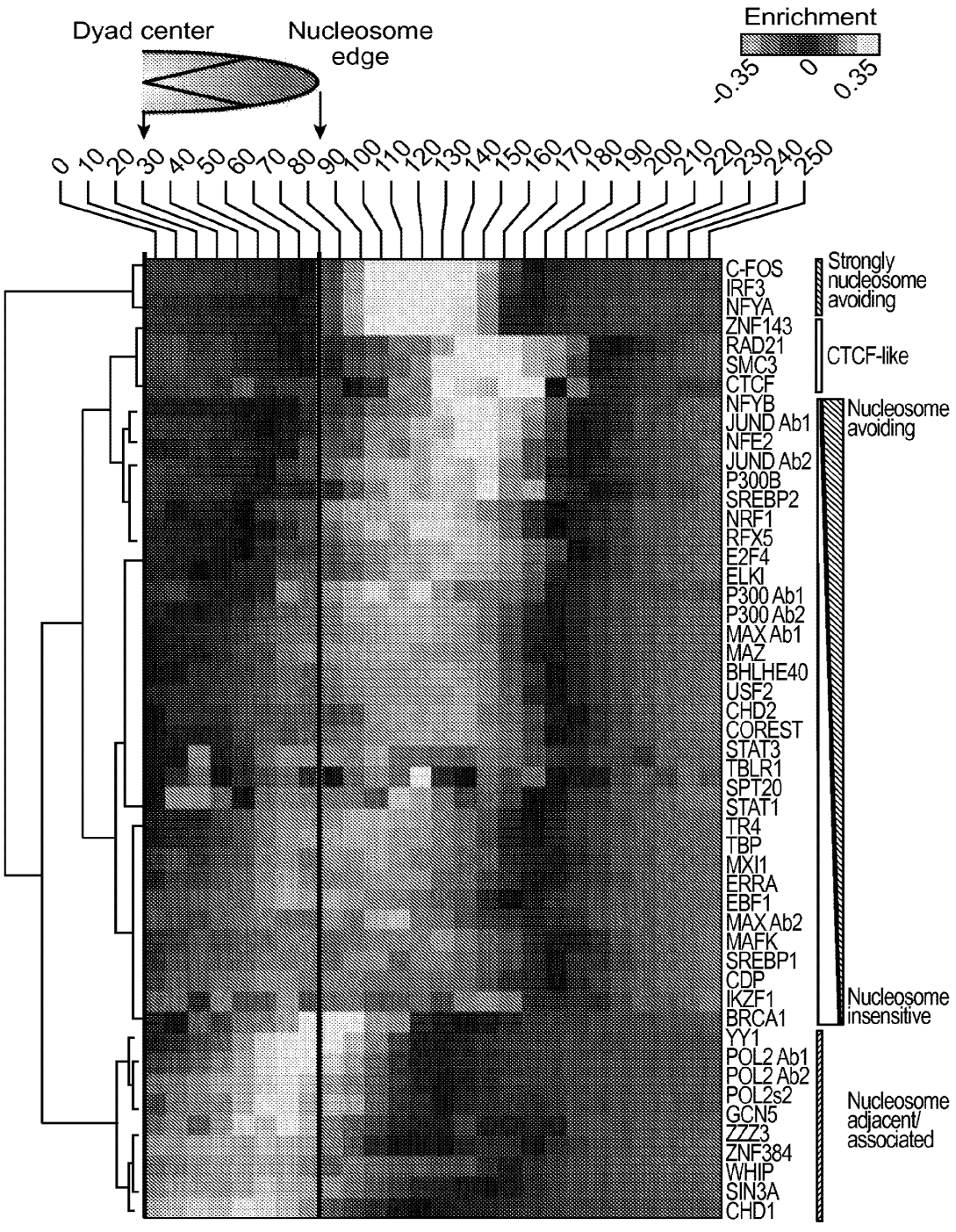


FIG. 3E

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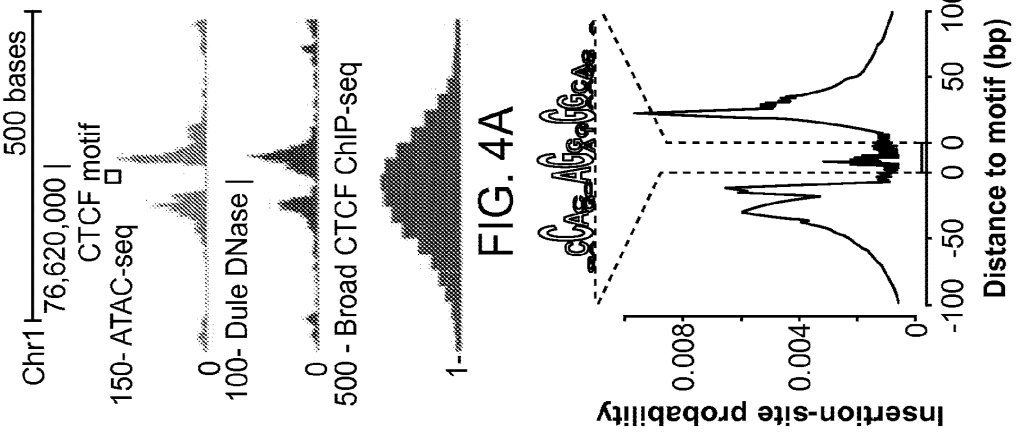


FIG. 4A

FIG. 4B

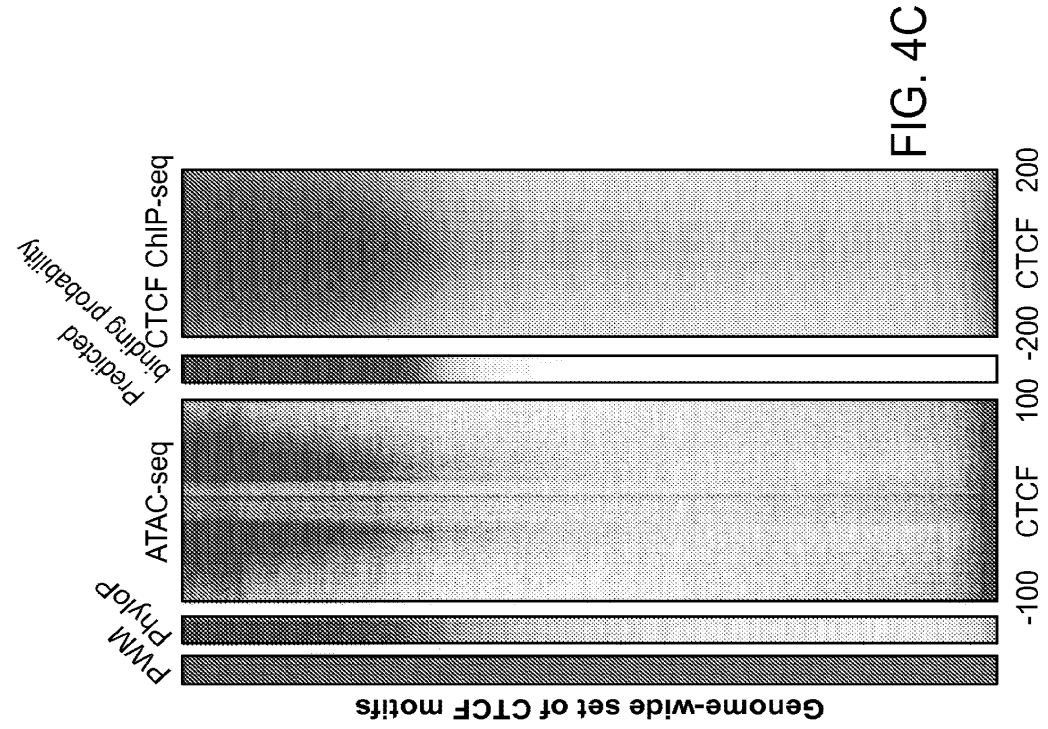


FIG. 4C

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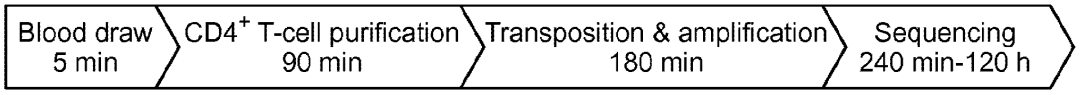


FIG. 5A

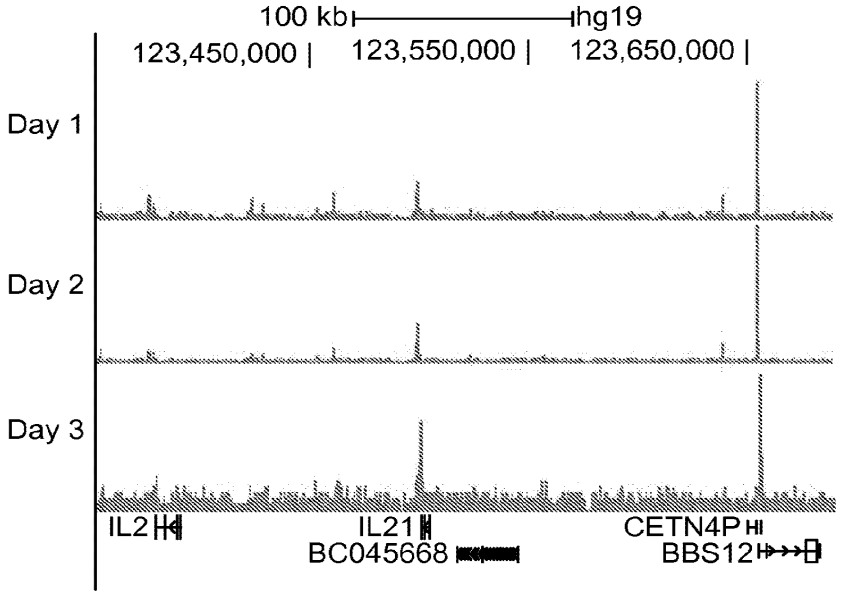


FIG. 5B

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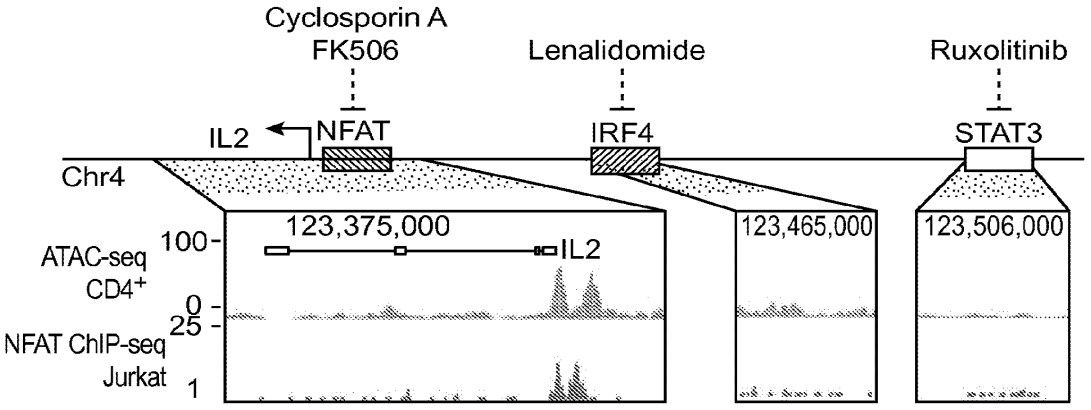


FIG. 5C

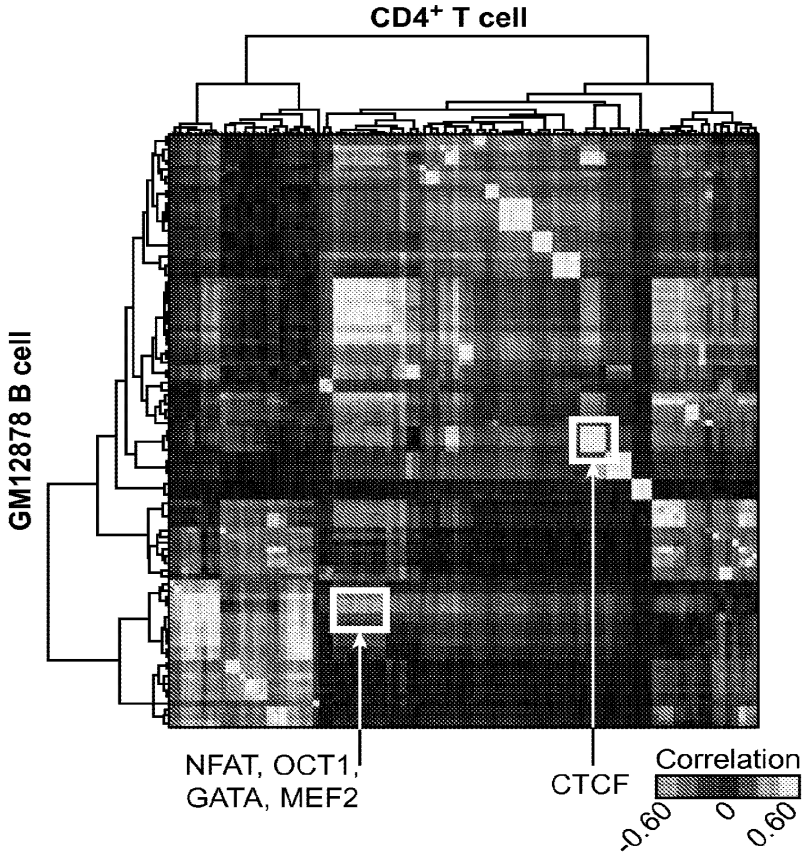


FIG. 5D

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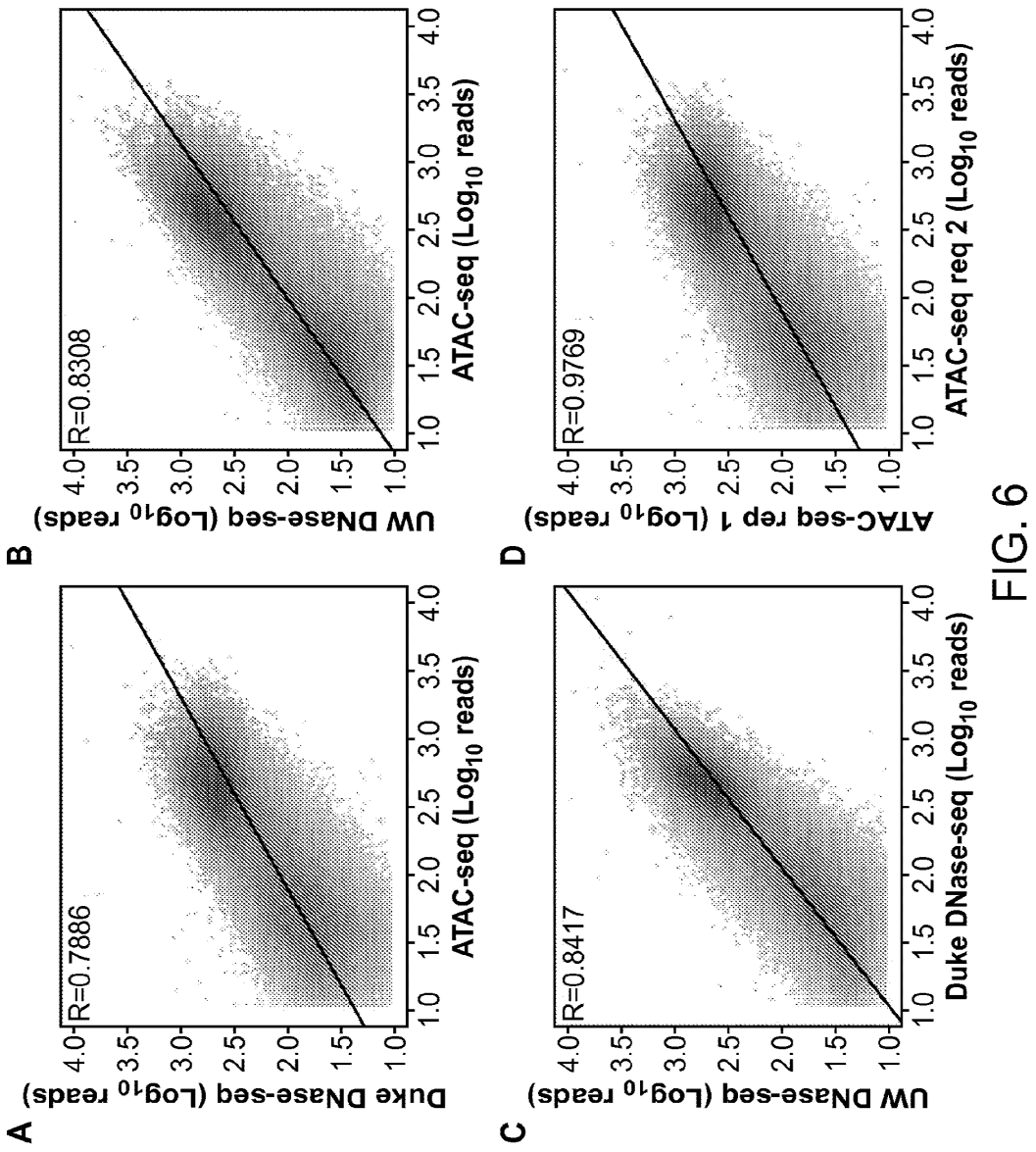
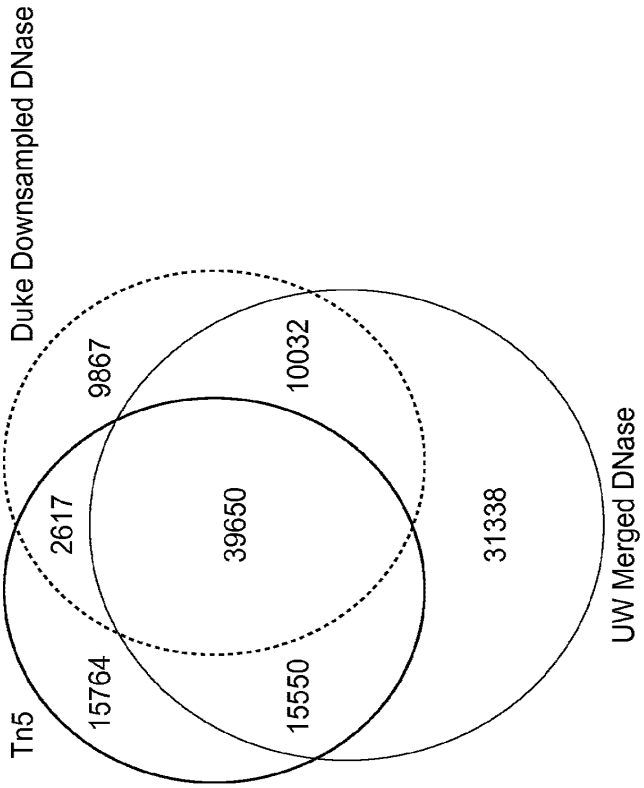


FIG. 6

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	ATAC Unique	UW Unique	Duke Unique	ATAC and UW	ATAC and Duke	UW and Duke	Intersect
ATAC-Seq	6.30%	4.36%	1.08%	10.83%	1.53%	2.09%	73.80%
UW DNase	1.32%	8.13%	0.68%	7.57%	0.33%	4.34%	77.62%
Duke DNase	2.10%	5.27%	14.80%	4.02%	1.44%	6.91%	65.46%

FIG. 7

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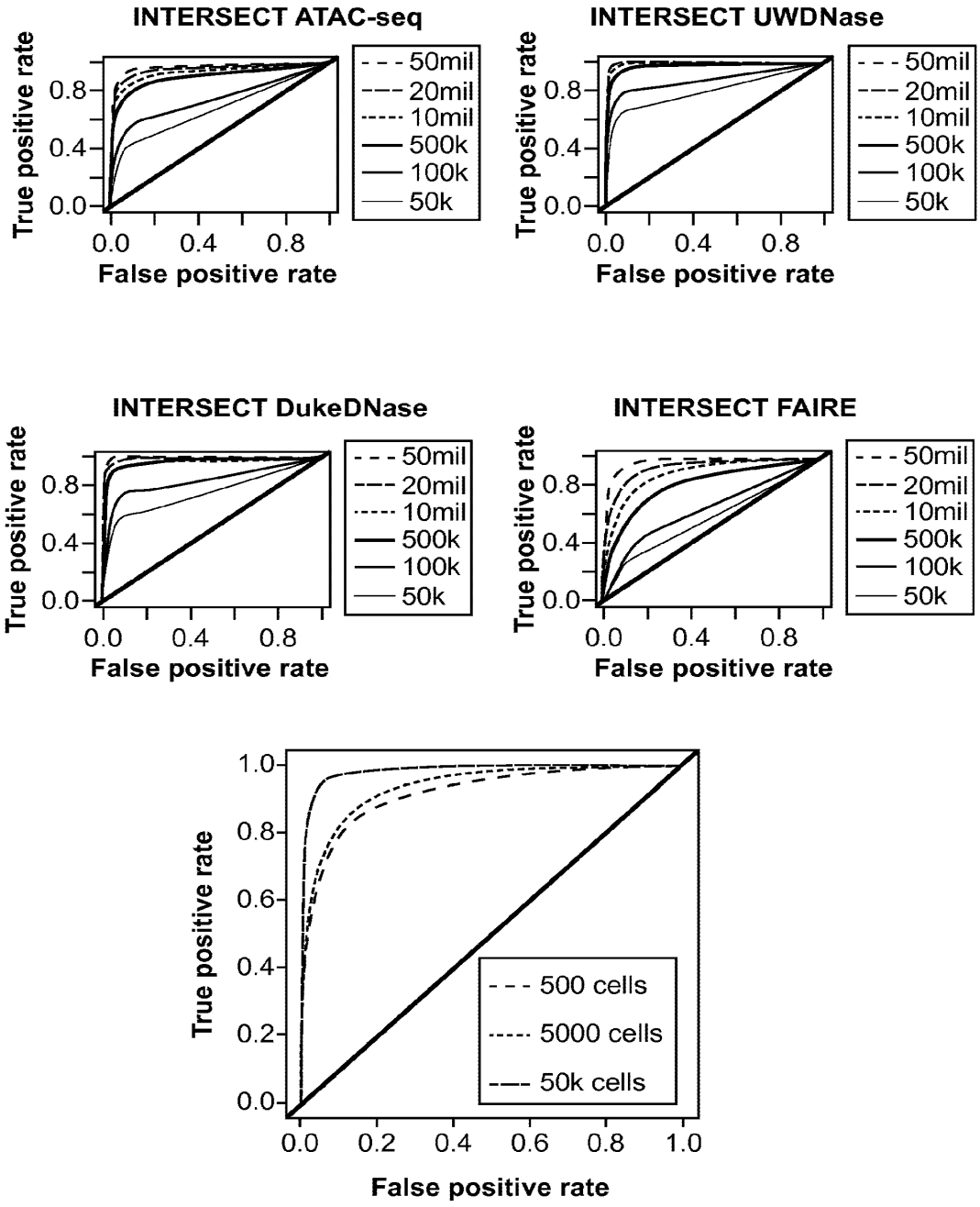


FIG. 8

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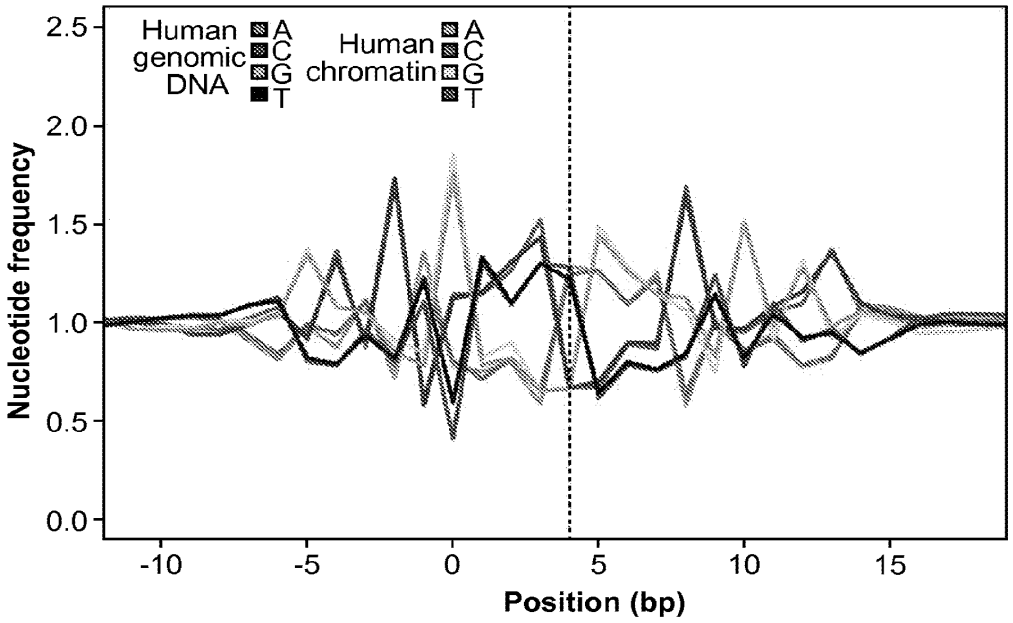


FIG. 9

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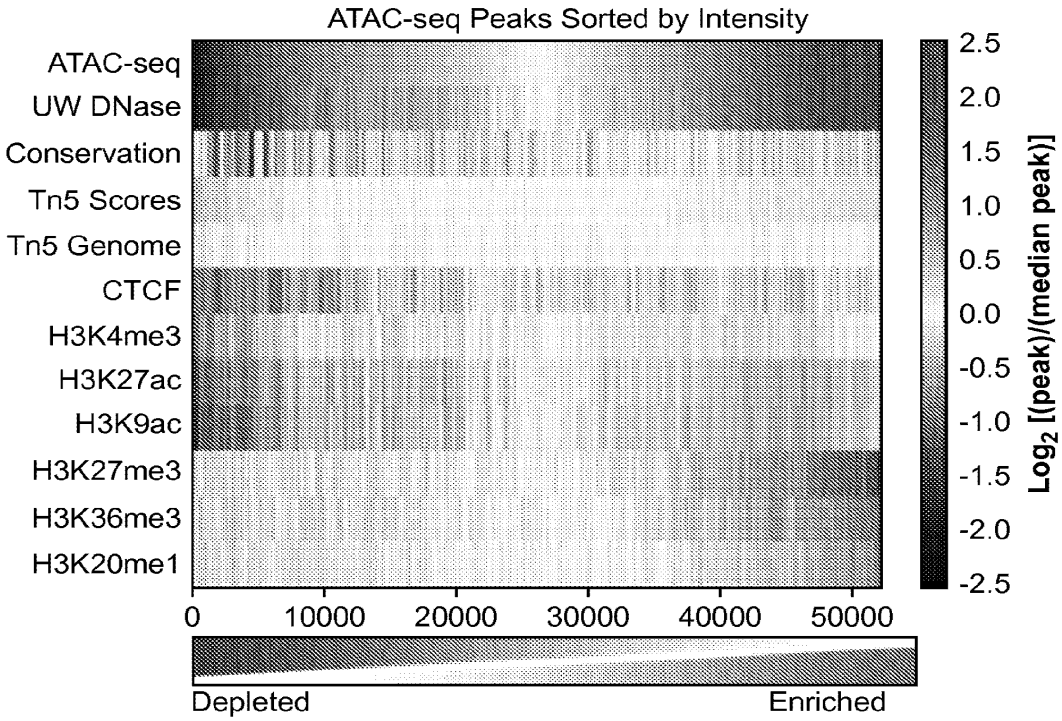


FIG. 10

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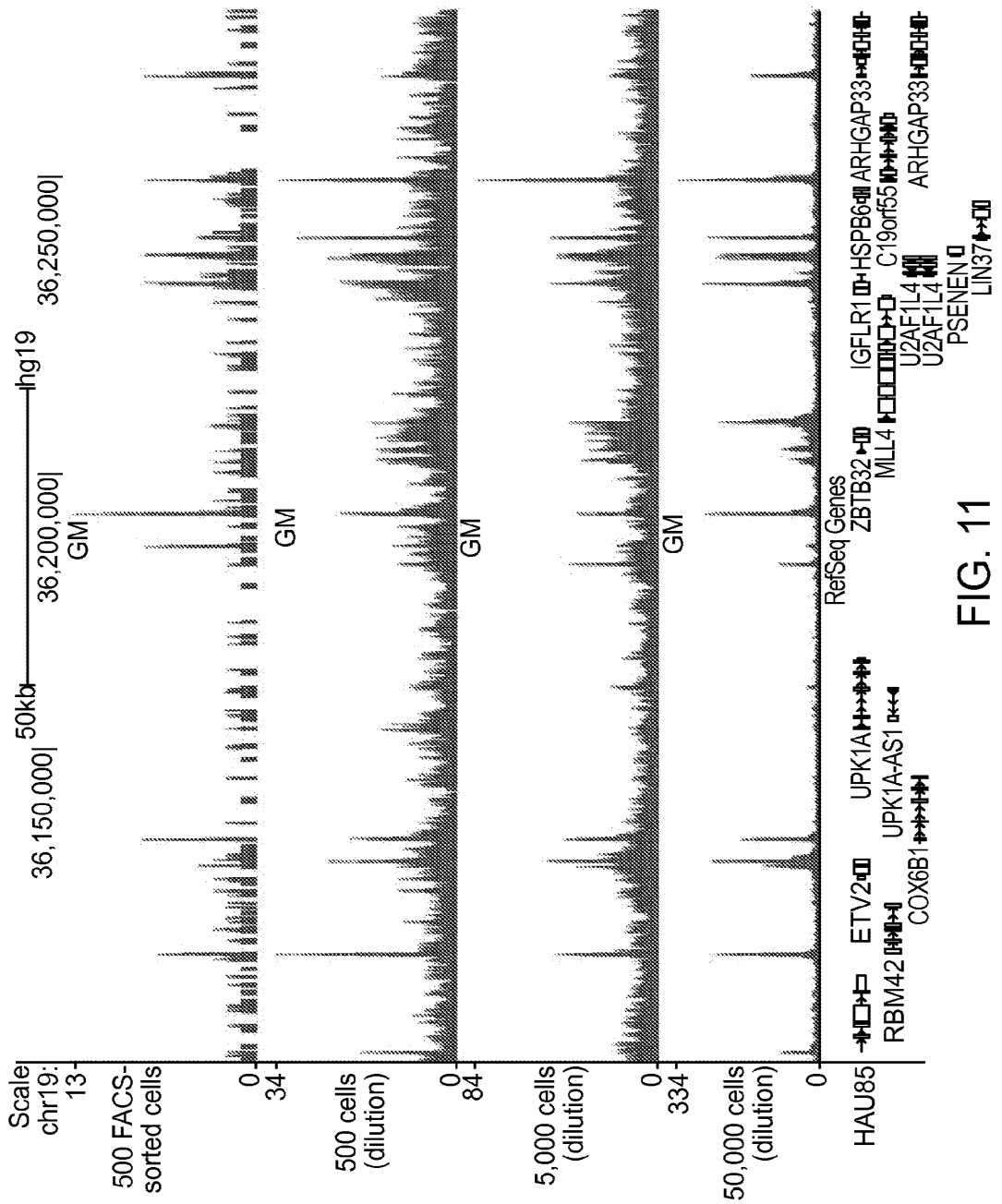


FIG. 11

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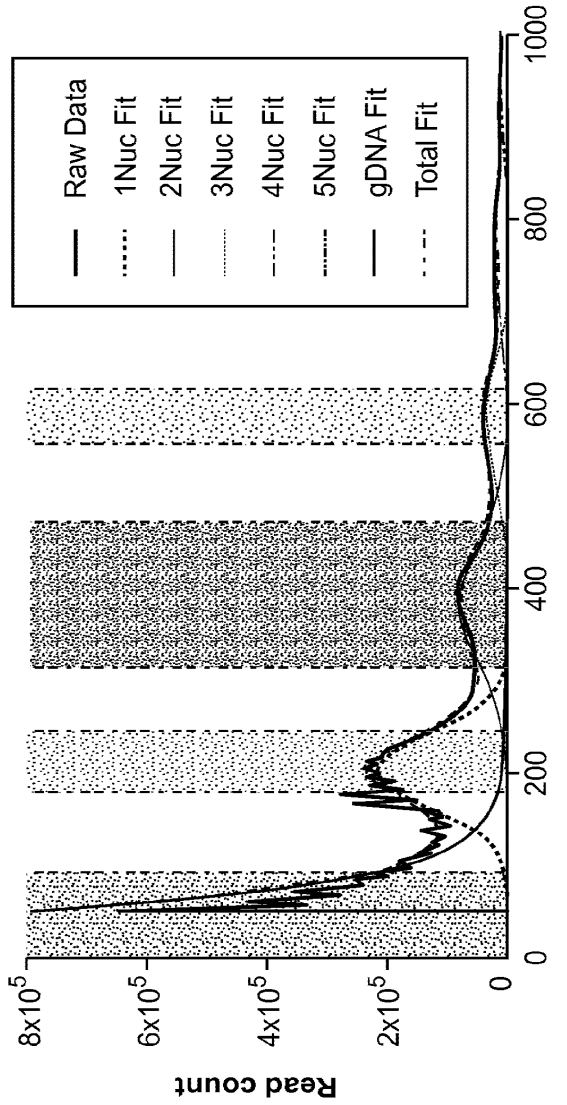


FIG. 12

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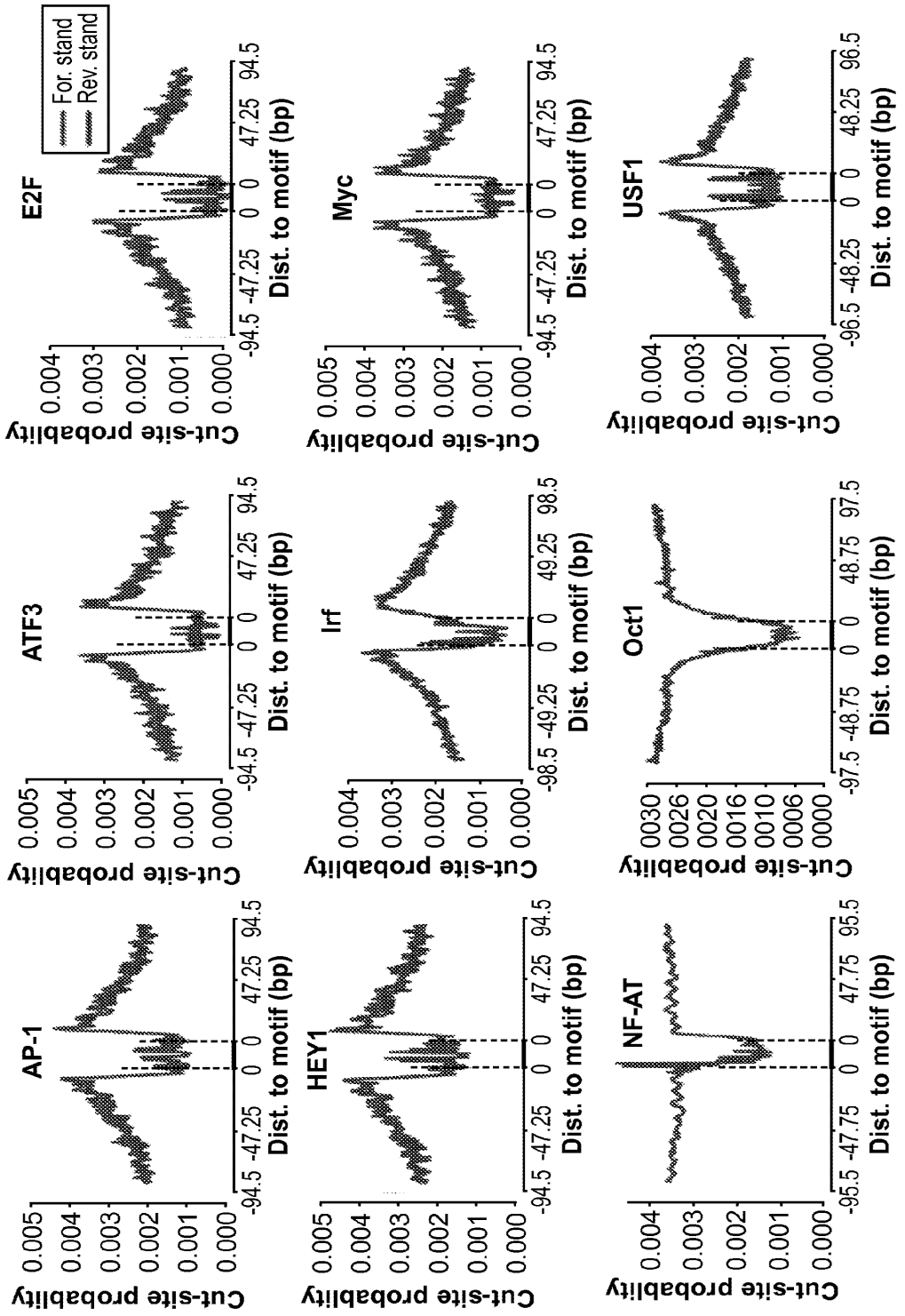


FIG. 13

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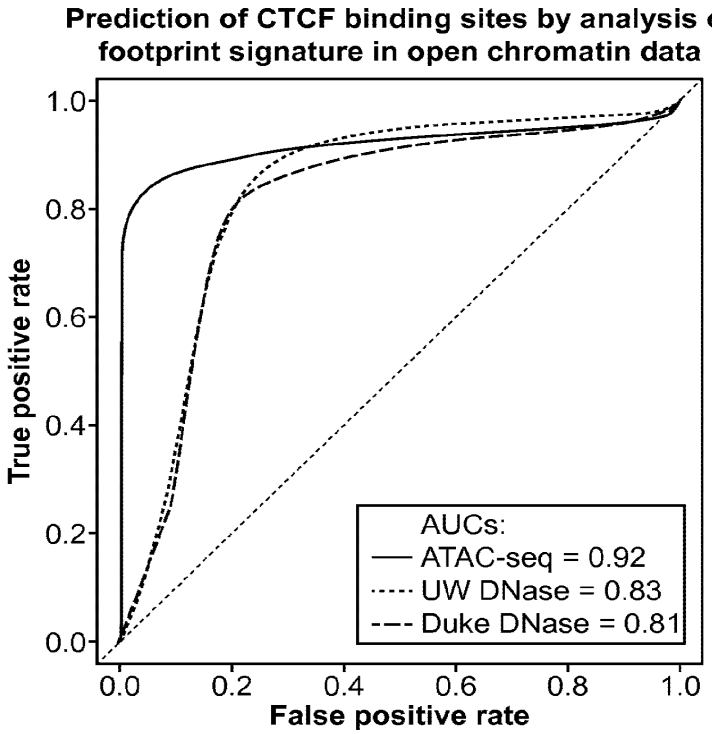


FIG. 14

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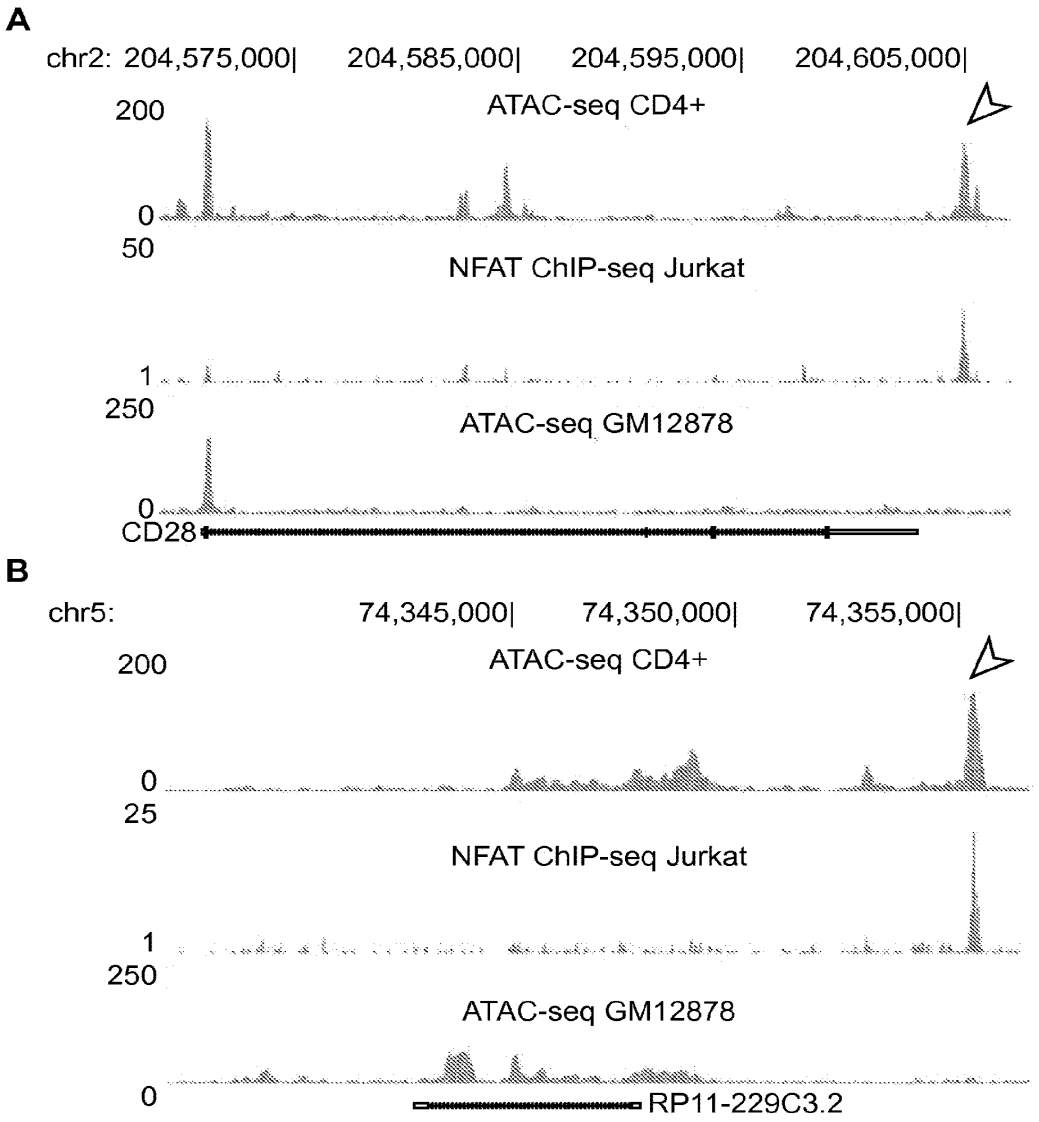


FIG. 15

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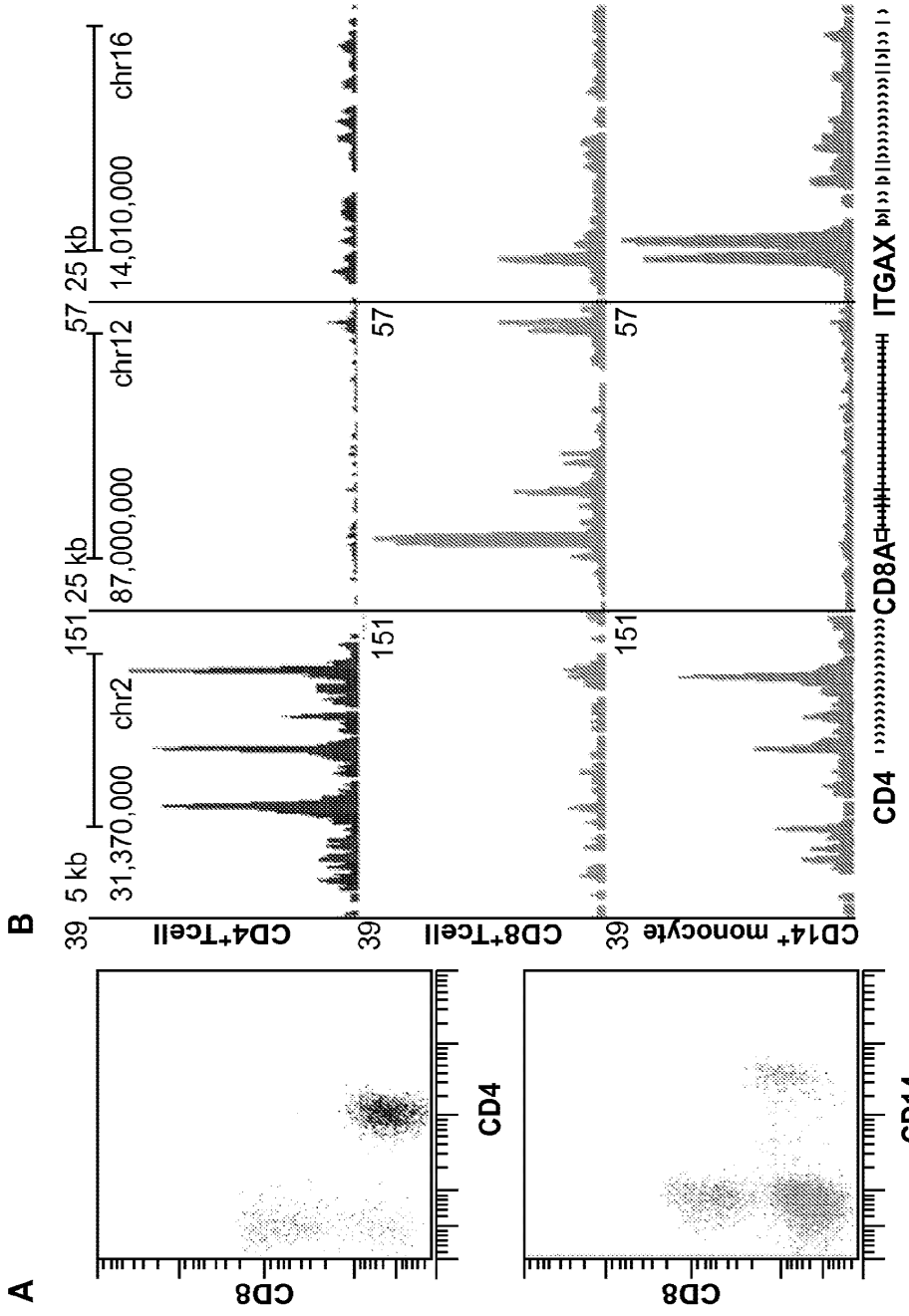


FIG. 16

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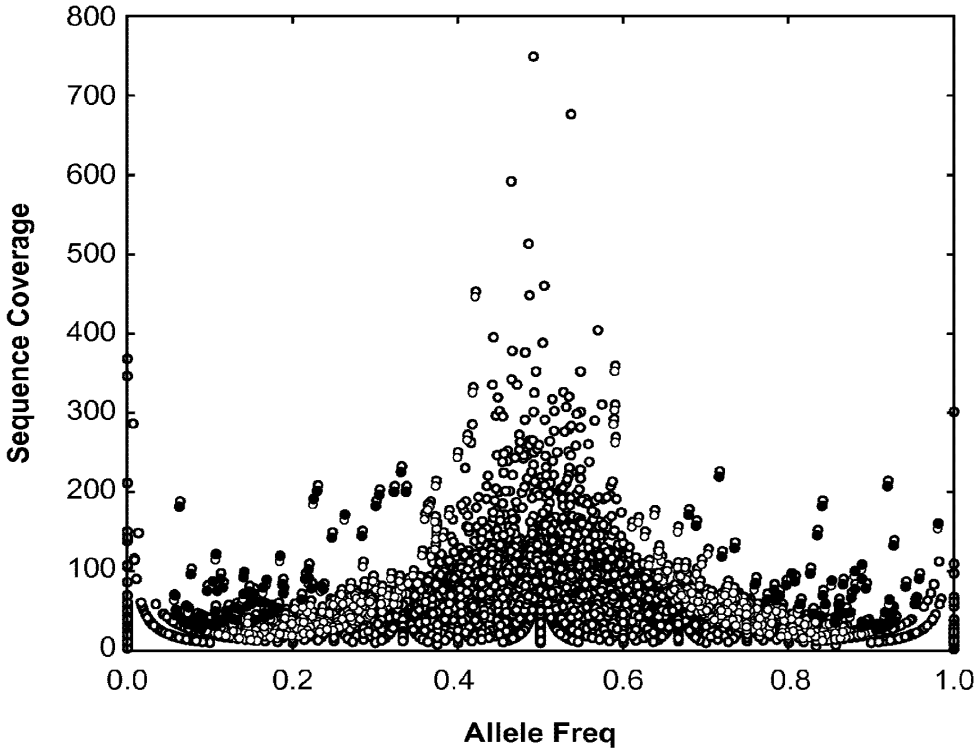


FIG. 17

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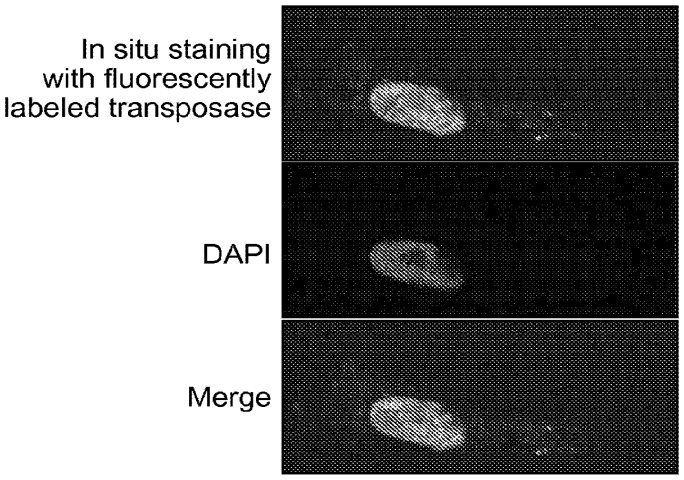


FIG. 18

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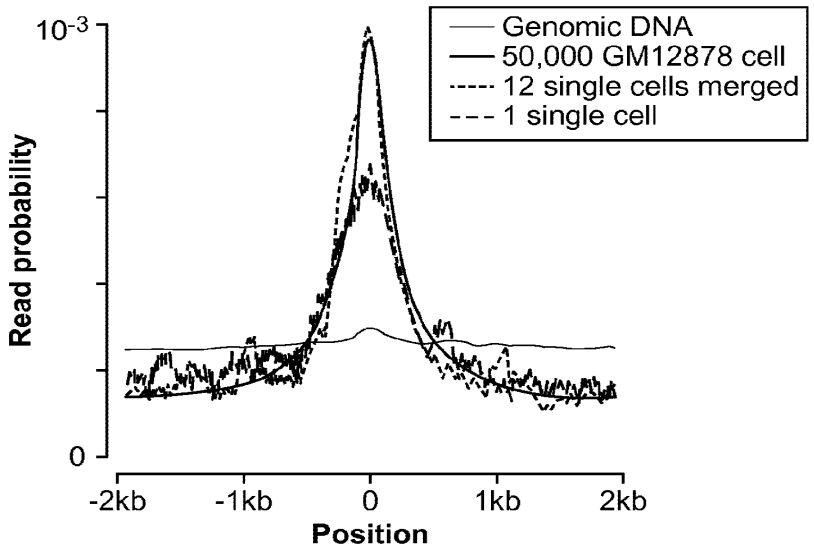


FIG. 19

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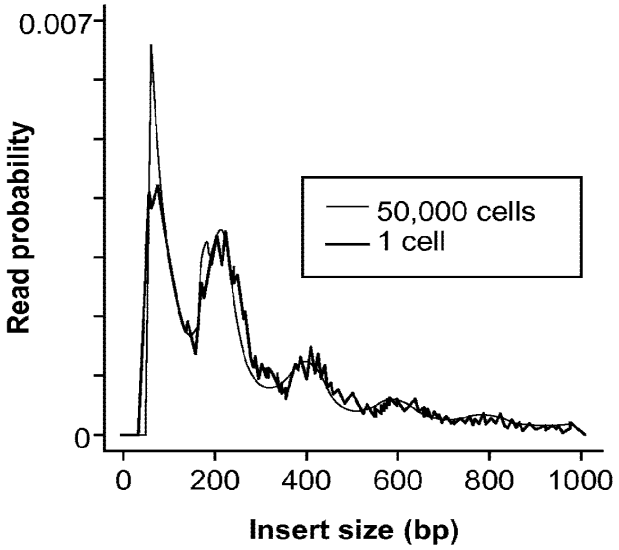


FIG. 20

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

AUGUST 29, 2014

PTAS

JAMES S. KEDDIE
1900 UNIVERSITY AVENUE
SUITE 200
EAST PALO ALTO, CA 94306

502955092

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NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

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RECORDATION DATE: 08/28/2014

REEL/FRAME: 033632/0143
NUMBER OF PAGES: 8

BRIEF: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

DOCKET NUMBER: STAN-1111WO

ASSIGNOR:
GIRESI, PAUL — DOC DATE: 06/19/2014

ASSIGNOR:
CHANG, HOWARD Y. — DOC DATE: 07/11/2014

ASSIGNOR:
BUENROSTRO, JASON D. — DOC DATE: 08/20/2014

ASSIGNOR:
GREENLEAF, WILLIAM J. — DOC DATE: 08/20/2014

ASSIGNEE:
THE BOARD OF TRUSTEES OF THE LELAND
STANFORD JUNIOR UNIVERSITY
1705 EL CAMINO REAL
PALO ALTO, CALIFORNIA 94306-1106

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APPLICATION NUMBER: FILING DATE:
PATENT NUMBER: ISSUE DATE:
PCT NUMBER: US2014038825
TITLE:

ASSIGNMENT RECORDATION BRANCH
PUBLIC RECORDS DIVISION

ASSIGNMENT OF APPLICATION

THIS ASSIGNMENT, by **Giresi, Paul** residing in Palo Alto, California, **Buenrostro, Jason D.** residing in Redwood City, California, **CHANG, HOWARD Y.** residing in Stanford, California, **Greenleaf, William J.** residing in Menlo Park, California, (hereinafter referred to as the assignors), witnesseth:

WHEREAS, the said assignors have invented certain new and useful improvements in:

"Transposition into Native Chromatin for Personal Epigenomics"

X filed on 20 March 2014 as PCT International Application No. PCT/US2014/038825 designating the United States.

____ for which an application for a United States Patent was executed on ____, and

WHEREAS, **The Board of Trustees of the Leland Stanford Junior University**, a non-profit organization duly organized under and pursuant to the laws of California, and having its principal place of business at 1705 El Camino Real, Palo Alto, California 94306-1106 (hereinafter referred to as the assignee), is desirous of acquiring their right, title and interest in and to said invention and said application for Letters Patent of the United States, and in and to any Letters Patent or Patents, United States or foreign, to be obtained therefor and thereon:

NOW THEREFORE, for good and sufficient considerations, the receipt of which is hereby acknowledged, said assignors have sold, assigned, transferred and set over, and by these presents do sell, assign, transfer and set over, unto the assignee, its successors, legal representatives and assigns, all of their right, title and interest in and to the above-mentioned invention, application for Letters Patent, and any and all Letters Patent or Patents in the United States of America and all foreign countries which may be granted therefor and thereon, and in and to any and all divisions, continuations, and continuations-in-part of said application, or reissues or extensions of said Letters Patent or Patents, and all rights under the International Convention for the Protection of Industrial Property, the same to be held and enjoyed by said assignee, for its own use and behalf and the use and behalf of its successors, legal representatives and assigns, to the full end of the term or terms for which Letters Patent or Patents may be granted, as fully and entirely as the same would have been held and enjoyed by the assignors, had this sale and assignment not been made.

AND for the same consideration, said assignors hereby covenant and agree to and with said assignee, its successors, legal representatives and assigns, that, at the time of execution and delivery of these presents, no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment and that said assignors have good and full right and lawful authority to sell and convey the same in the manner herein set forth.

AND for the same consideration, said assignors hereby covenant and agree to and with said assignee, its successors, legal representatives and assigns, that said assignors will, whenever counsel of said assignee, or the counsel of its successors, legal representatives and assigns, shall advise that any proceeding in connection with said invention, or said application for Letters Patent, or any proceeding in connection with Letters Patent for said invention in any country, including interference proceedings, is lawful and desirable, or that any division, continuation or continuation-in-part of any application for Letters Patent or any reissue or extension of any Letters Patent, to be obtained thereon, is lawful and desirable, sign all papers and documents, take all lawful oaths, and do all acts necessary or required to be done for the procurement, maintenance, enforcement and defense of Letters Patent for said invention, without charge to said assignee, its successors, legal representatives and assigns, but at the cost and expense of said assignee, its successors, legal representatives and assigns.

AND said assignors hereby request the Commissioner of Patents to issue said Letters Patent of the United States to said assignee as the assignee of said invention and the Letters Patent to be issued thereon for the use and behalf of said assignee, its successors, legal representatives and assigns.

Date 6/19/14 Name of Inventor _____

Giresi, Paul

Date _____ Name of Inventor _____

Buenrostro, Jason D.

ASSIGNMENT OF APPLICATION

Date July 11, 2018 Name of Inventor CHANG, HOWARD Y.

Date _____ Name of Inventor Greenleaf, William J.

ASSIGNMENT OF APPLICATION

THIS ASSIGNMENT, by **Giresi, Paul** residing in Palo Alto, California, **Buenrostro, Jason D.** residing in Redwood City, California, **CHANG, HOWARD Y.** residing in Stanford, California, **Greenleaf, William J.** residing in Menlo Park, California, (hereinafter referred to as the assignors), witnesseth:

WHEREAS, the said assignors have invented certain new and useful improvements in:

"Transposition into Native Chromatin for Personal Epigenomics"

X filed on 20 March 2014 as PCT International Application No. PCT/US2014/038825 designating the United States.

___ for which an application for a United States Patent was executed on ___, and

WHEREAS, **The Board of Trustees of the Leland Stanford Junior University**, a non-profit organization duly organized under and pursuant to the laws of California, and having its principal place of business at 1705 El Camino Real, Palo Alto, California 94306-1106 (hereinafter referred to as the assignee), is desirous of acquiring their right, title and interest in and to said invention and said application for Letters Patent of the United States, and in and to any Letters Patent or Patents, United States or foreign, to be obtained therefor and thereon:

NOW THEREFORE, for good and sufficient considerations, the receipt of which is hereby acknowledged, said assignors have sold, assigned, transferred and set over, and by these presents do sell, assign, transfer and set over, unto the assignee, its successors, legal representatives and assigns, all of their right, title and interest in and to the above-mentioned invention, application for Letters Patent, and any and all Letters Patent or Patents in the United States of America and all foreign countries which may be granted therefor and thereon, and in and to any and all divisions, continuations, and continuations-in-part of said application, or reissues or extensions of said Letters Patent or Patents, and all rights under the International Convention for the Protection of Industrial Property, the same to be held and enjoyed by said assignee, for its own use and behalf and the use and behalf of its successors, legal representatives and assigns, to the full end of the term or terms for which Letters Patent or Patents may be granted, as fully and entirely as the same would have been held and enjoyed by the assignors, had this sale and assignment not been made.

AND for the same consideration, said assignors hereby covenant and agree to and with said assignee, its successors, legal representatives and assigns, that, at the time of execution and delivery of these presents, no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment and that said assignors have good and full right and lawful authority to sell and convey the same in the manner herein set forth.

AND for the same consideration, said assignors hereby covenant and agree to and with said assignee, its successors, legal representatives and assigns, that said assignors will, whenever counsel of said assignee, or the counsel of its successors, legal representatives and assigns, shall advise that any proceeding in connection with said invention, or said application for Letters Patent, or any proceeding in connection with Letters Patent for said invention in any country, including interference proceedings, is lawful and desirable, or that any division, continuation or continuation-in-part of any application for Letters Patent or any reissue or extension of any Letters Patent, to be obtained thereon, is lawful and desirable, sign all papers and documents, take all lawful oaths, and do all acts necessary or required to be done for the procurement, maintenance, enforcement and defense of Letters Patent for said invention, without charge to said assignee, its successors, legal representatives and assigns, but at the cost and expense of said assignee, its successors, legal representatives and assigns.

AND said assignors hereby request the Commissioner of Patents to issue said Letters Patent of the United States to said assignee as the assignee of said invention and the Letters Patent to be issued thereon for the use and behalf of said assignee, its successors, legal representatives and assigns.

Date _____ Name of Inventor _____

Giresi, Paul

Date 8/20/2014 Name of Inventor _____

Buenrostro, Jason D.

ASSIGNMENT OF APPLICATION

Date _____ Name of Inventor _____
CHANG, HOWARD Y.

Date 20 Aug 2014 Name of Inventor _____
Greenleaf, William J.

ASSIGNMENT OF APPLICATION

Hereby accepted on behalf of the assignee

James S Keddie

Signature

8-25-14 James S. Keddie

Date Name (print)

Senior Patent Agent, Bozicevic, Field & Francis LLP

Title and Company

PTO/AIA/96 (08-12)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: The Board of Trustees of the Leland Stanford Junior University

Application No./Patent No.: Not Yet Assigned Filed/Issue Date: Concurrently Herewith

Titled: Transposition of Native Chromatin for Personal Epigenomics

The Board of Trustees of the Leland Stanford Junior University, a non-profit organization

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☑ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☑ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 033632, Frame 0143, or for which a copy thereof is attached.

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

   1. From: _____ To: _____

      The document was recorded in the United States Patent and Trademark Office at

      Reel _____, Frame _____, or for which a copy thereof is attached.

   2. From: _____ To: _____

      The document was recorded in the United States Patent and Trademark Office at

      Reel _____, Frame _____, or for which a copy thereof is attached.

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450**.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/96 (08-12)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☑ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/James S. Keddie /	October 13, 2015
Signature	Date
James S. Keddie	48,920
Printed or Typed Name	Title or Registration Number

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	Transposition of Native Chromatin for Personal Epigenomics
First Named Inventor/Applicant Name:	Paul Giresi
Filer:	James Samuel Keddie
Attorney Docket Number:	STAN-1111
Filed as Small Entity	

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Basic National Stage Fee	2631	1	140	140
Natl Stage Search Fee - U.S. was the ISA	2641	1	60	60
Natl Stage Exam Fee - all other cases	2633	1	360	360
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**560**

Electronic Acknowledgement Receipt	
EFS ID:	23759425
Application Number:	14784250
International Application Number:	PCT/US2014/038825
Confirmation Number:	6877
Title of Invention:	Transposition of Native Chromatin for Personal Epigenomics
First Named Inventor/Applicant Name:	Paul Giresi
Customer Number:	77974
Filer:	James Samuel Keddie/Kym Moore
Filer Authorized By:	James Samuel Keddie
Attorney Docket Number:	STAN-1111
Receipt Date:	13-OCT-2015
Filing Date:	
Time Stamp:	17:24:54
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$560
RAM confirmation Number	4877
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal of New Application	STAN-1111_transmittal.pdf	139980 46dca113319abb03579a38c601f3ac2015007c33	no	4
Warnings:					
Information:					
2	Oath or Declaration filed	STAN-1111_declaration.pdf	2631268 33851ffd2e22ea833687b722be9a9e464b6a3655	no	4
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Form (SB08)	STAN-1111_ids.pdf	612149 d2bb9f8564f36a20ebab4aa6b613d14fffea5e03	no	4
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
4	Non Patent Literature	BJORNSSON_reference.pdf	11261754 d9e181778a45a69a7506e8d2fa13f7f14eb15514	no	11
Warnings:					
Information:					
5	Non Patent Literature	GANGADHARAN_reference.pdf	19233323 06d0a44f25a2f19a1233b1ca9c0ba6f2ff881d84	no	13
Warnings:					
Information:					
6	Application Data Sheet	STAN-1111_efs_ads.pdf	1561591 3b0ab9f2018fd06d71b9fabeb85ac4a86a222a16	no	8
Warnings:					
Information:					
7	Power of Attorney	STAN-1111_POA.pdf	2204695 264ef2845886af6d89f090eedbb1dc7fac526e0d	no	1

Warnings:					
Information:					
8	Sequence Listing (Text File)	STAN-1111_Seq_Listing.txt	5239	no	0
Warnings:					
Information:					
9	Sequence Listing	STAN-1111_Cert_Seq_Listing.pdf	81479 a6a4bfcdb6a8deb1b8c929379505b6fcbec71e31	no	2
Warnings:					
Information:					
10		STAN-1111_application.pdf	1082964 70826ecaba8df38dd90ea0f9af077a77e1361580	yes	80
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Abstract		1	1	
	Specification		2	48	
	Claims		49	56	
	Drawings-only black and white line drawings		57	80	
Warnings:					
Information:					
11	Documents submitted with 371 Applications	STAN-1111_assignment_papers.pdf	817971 449f7f8e96e6ec52085c63d2ca1ccaa4c9120198	no	7
Warnings:					
Information:					
12	Assignee showing of ownership per 37 CFR 3.73	STAN-1111_statement_373c.pdf	80900 5171f185023b0741dbb5f8226a89939ea0582ccc	no	3
Warnings:					
Information:					
13	Fee Worksheet (SB06)	fee-info.pdf	34771 613f2dc581967888855ac170434d31d0640005745	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	39748084		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/08a (01-10)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	
	Filing Date	
	First Named Inventor	Buenrostro, Jason D.
	Art Unit	
	Examiner Name	
	Attorney Docket Number	STAN-1111

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2012/106546	WO	A2	2012-08-09	Shendure et al.		☐
If you wish to add additional Foreign Patent Document citation information please click the Add button								Add

NON-PATENT LITERATURE DOCUMENTS			Remove
Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	
	Filing Date	
	First Named Inventor	Buenrostro, Jason D.
	Art Unit	
	Examiner Name	
	Attorney Docket Number	STAN-1111

	1	GANGADHARAN et al., DNA transposon Hermes insert into DNA in nucleosome-free regions in vivo, Proc nat Ad Sci, December 21, 2010, Vol. 107, No. 51, pages 1966-1972.	☐
	2	BJORNSSON et al., Intra-individual change over time in DNA methylation with familial clustering, JAMA, June 25, 2008, Vol. 299 No. 24, pages 2877-2883.	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01030
Page 00109

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	
	Filing Date	
	First Named Inventor	Buenrostro, Jason D.
	Art Unit	
	Examiner Name	
	Attorney Docket Number	STAN-1111

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/James S. Keddie/	Date (YYYY-MM-DD)	2015-10-13
Name/Print	James S. Keddie	Registration Number	48920

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01030
Page 00110

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01030
Page 00111

PTO/AIA/14 (12-13)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	STAN-1111
	Application Number	
Title of Invention	Transposition of Native Chromatin for Personal Epigenomics	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Paul		Giresi	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Palo Alto	State/Province	CA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	264 Durand Way		
Address 2			
City	Palo Alto	State/Province	CA
Postal Code	94304	Country i	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Jason	D.	Buenrostro	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Redwood City	State/Province	CA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	3523 Altamont Way		
Address 2			
City	Redwood City	State/Province	CA
Postal Code	94062	Country i	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Howard	Y.	Chang	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	STAN-1111
	Application Number	
Title of Invention	Transposition of Native Chromatin for Personal Epigenomics	

City	Stanford	**State/Province**	CA	**Country of Residence** i	US

Mailing Address of Inventor:

Address 1	946 Casanueva Place		
Address 2			
City	Stanford	**State/Province**	CA
Postal Code	94305	**Country** i	US

Inventor 4 Remove

Legal Name

Prefix	**Given Name**	**Middle Name**	**Family Name**	**Suffix**
	William	J.	Greenleaf	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Menlo Park	**State/Province**	CA	**Country of Residence** i	US

Mailing Address of Inventor:

Address 1	765A Live Oak		
Address 2			
City	Menlo Park	**State/Province**	CA
Postal Code	94025	**Country** i	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	77974		
Email Address	docket@bozpat.com	Add Email	Remove Email

Application Information:

Title of the Invention	Transposition of Native Chromatin for Personal Epigenomics		
Attorney Docket Number	STAN-1111	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	24	**Suggested Figure for Publication (if any)**	

Filing By Reference :

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	STAN-1111
	Application Number	
Title of Invention	Transposition of Native Chromatin for Personal Epigenomics	

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	77974		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the application number blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	a 371 of international	PCT/US2014/038825	2014-05-20
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/US2014/038825	Claims benefit of provisional	61826728	2013-05-23

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	STAN-1111
	Application Number	
Title of Invention	Transposition of Native Chromatin for Personal Epigenomics	

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(d). When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX) [i]the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(h)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country [i]	Filing Date (YYYY-MM-DD)	Access Code [i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Authorization to Permit Access:

☒ Authorization to Permit Access to the Instant Application by the Participating Offices

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	STAN-1111
	Application Number	
Title of Invention	Transposition of Native Chromatin for Personal Epigenomics	

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :

If the Applicant is an Organization check here. ☒

Organization Name	The Board of Trustees of the Leland Stanford Junior University		
Mailing Address Information:			
Address 1	Office of the General Counsel, Building 170		
Address 2	3rd Floor, Main Quad, P.O. Box 20386		
City	Stanford	**State/Province**	CA
Country [i]	US	Postal Code	94305-2038
Phone Number		Fax Number	

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	STAN-1111
	Application Number	
Title of Invention	Transposition of Native Chromatin for Personal Epigenomics	

Email Address	

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not subsitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication . An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications

Signature	/James S. Keddie, Reg. No. 48,920/			Date (YYYY-MM-DD)	2015-10-13
First Name	James	Last Name	Keddie	Registration Number	48920

Additional Signature may be generated within this form by selecting the Add button. Add

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	STAN-1111
	Application Number	
Title of Invention	Transposition of Native Chromatin for Personal Epigenomics	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01030
Page 00119

DocCode – SEQ.TXT

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Application Number: 14784250 Document Date: 10/13/2015

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Form Revision Date: August 26, 2013

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Original (for SUBMISSION)

VIII-4-1	**Declaration: Inventorship (only for the purposes of the designation of the United States of America)** Declaration of Inventorship (Rules 4.17(iv) and 51bis.1(a)(iv)) for the purposes of the designation of the United States of America:	I hereby declare that I believe I am the original inventor or an original joint inventor of a claimed invention in the application. This declaration is directed to international application No. PCT/US2014/038825. I hereby declare that the above-identified international application was made or authorized to be made by me. I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.
VIII-4-1-1-1	Name (LAST, First)	GIRESI, Paul
VIII-4-1-1-2	Residence: (city and either US state, if applicable, or country)	Palo Alto, California
VIII-4-1-1-3	Mailing Address:	264 Durand Way Palo Alto, CA 94304 United States of America
VIII-4-1-1-4	Inventor's Signature: (The signature must be that of the inventor, not that of the agent)	
VIII-4-1-1-5	Date: 6/19/14	
VIII-4-1-2-1	Name (LAST, First)	BUENROSTRO, Jason D.
VIII-4-1-2-2	Residence: (city and either US state, if applicable, or country)	Redwood City, California
VIII-4-1-2-3	Mailing Address:	3523 Altamont Way Redwood City, CA 94062 United States of America
VIII-4-1-2-4	Inventor's Signature: (The signature must be that of the inventor, not that of the agent)	
VIII-4-1-2-5	Date:	
VIII-4-1-3-1	Name (LAST, First)	CHANG, Howard Y.
VIII-4-1-3-2	Residence: (city and either US state, if applicable, or country)	Stanford, California
VIII-4-1-3-3	Mailing Address:	946 Casanueva Place Stanford, CA 94305 United States of America
VIII-4-1-3-4	Inventor's Signature: (The signature must be that of the inventor, not that of the agent)	
VIII-4-1-3-5	Date:	

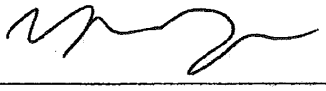
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Original (for SUBMISSION)

VIII-4-1	**Declaration: Inventorship (only for the purposes of the designation of the United States of America)** Declaration of Inventorship (Rules 4.17(iv) and 51bis.1(a)(iv)) for the purposes of the designation of the United States of America:	I hereby declare that I believe I am the original inventor or an original joint inventor of a claimed invention in the application. This declaration is directed to international application No. PCT/US2014/038825. I hereby declare that the above-identified international application was made or authorized to be made by me. I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.
VIII-4-1-1-1	Name (LAST, First)	GIRESI, Paul
VIII-4-1-1-2	Residence: (city and either US state, if applicable, or country)	Palo Alto, California
VIII-4-1-1-3	Mailing Address:	264 Durand Way Palo Alto, CA 94304 United States of America
VIII-4-1-1-4	Inventor's Signature: (The signature must be that of the inventor, not that of the agent)	
VIII-4-1-1-5	Date:	
VIII-4-1-2-1	Name (LAST, First)	BUENROSTRO, Jason D.
VIII-4-1-2-2	Residence: (city and either US state, if applicable, or country)	Redwood City, California
VIII-4-1-2-3	Mailing Address:	3523 Altamont Way Redwood City, CA 94062 United States of America
VIII-4-1-2-4	Inventor's Signature: (The signature must be that of the inventor, not that of the agent)	Jason Buenrostro
VIII-4-1-2-5	Date:	9/18/2014
VIII-4-1-3-1	Name (LAST, First)	CHANG, Howard Y.
VIII-4-1-3-2	Residence: (city and either US state, if applicable, or country)	Stanford, California
VIII-4-1-3-3	Mailing Address:	946 Casanueva Place Stanford, CA 94305 United States of America
VIII-4-1-3-4	Inventor's Signature: (The signature must be that of the inventor, not that of the agent)	
VIII-4-1-3-5	Date:	

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Original (for SUBMISSION)

VIII-4-1	**Declaration: Inventorship (only for the purposes of the designation of the United States of America)** Declaration of Inventorship (Rules 4.17(iv) and 51bis.1(a)(iv)) for the purposes of the designation of the United States of America:	I hereby declare that I believe I am the original inventor or an original joint inventor of a claimed invention in the application. This declaration is directed to international application No. PCT/US2014/038825. I hereby declare that the above-identified international application was made or authorized to be made by me. I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.
VIII-4-1-1-1	Name (LAST, First)	GIRESI, Paul
VIII-4-1-1-2	Residence: (city and either US state, if applicable, or country)	Palo Alto, California
VIII-4-1-1-3	Mailing Address:	264 Durand Way Palo Alto, CA 94304 United States of America
VIII-4-1-1-4	Inventor's Signature: (The signature must be that of the inventor, not that of the agent)	
VIII-4-1-1-5	Date:	
VIII-4-1-2-1	Name (LAST, First)	BUENROSTRO, Jason D.
VIII-4-1-2-2	Residence: (city and either US state, if applicable, or country)	Redwood City, California
VIII-4-1-2-3	Mailing Address:	3523 Altamont Way Redwood City, CA 94062 United States of America
VIII-4-1-2-4	Inventor's Signature: (The signature must be that of the inventor, not that of the agent)	
VIII-4-1-2-5	Date:	
VIII-4-1-3-1	Name (LAST, First)	CHANG, Howard Y.
VIII-4-1-3-2	Residence: (city and either US state, if applicable, or country)	Stanford, California
VIII-4-1-3-3	Mailing Address:	946 Casanueva Place Stanford, CA 94305 United States of America
VIII-4-1-3-4	Inventor's Signature: (The signature must be that of the inventor, not that of the agent)	
VIII-4-1-3-5	Date: 7/11/14	

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Original (for **SUBMISSION**)

VIII-4-1-4-1	Name (LAST, First)	GREENLEAF, William J.
VIII-4-1-4-2	Residence: (city and either US state, if applicable, or country)	Menlo Park, California
VIII-4-1-4-3	Mailing Address:	2372 Branner Drive Menlo Park, CA 94025 United States of America
VIII-4-1-4-4	Inventor's Signature: (The signature must be that of the inventor, not that of the agent)	
VIII-4-1-4-5	Date:	18 Aug 2014

632584

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

June 15, 2014

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: *61/826,728*
FILING DATE: *May 23, 2013*
RELATED PCT APPLICATION NUMBER: *PCT/US14/38825*

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS *US61/826,728*

Certified by

David J. Kappos

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

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Application Number: 61826728 Document Date: 05/23/2013

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Form Revision Date: February 8, 2006

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01030
Page 00126

TRANSPOSITION OF NATIVE CHROMATIN FOR PERSONAL EPIGENOMICS

Inventors: Jason D. Buenrostro, Paul G. Giresi,
Howard Y. Chang, and William J. Greenleaf

Background of the Invention

[0001] The present invention relates generally to epigenomic profiling and, more specifically, to a method for the rapid profiling of an epigenome by direct transposition of sequencing adapters into native chromatin.

[0002] Eukaryotic genomes are hierarchically packaged into chromatin (*1*), and the nature of this packaging plays a central role in gene regulation (*2*). The regulatory landscape on chromatin is highly dynamic, cell type-specific, and varies by individual genomes—challenging technologies to capture and highlight these features. Major insights into the epigenetic information encoded within the nucleoprotein structure of chromatin have come from high-throughput, genome-wide methods for assaying chromatin "openness" – the accessibility of DNA to the machinery of gene expression (*3*, *4*). The identification of DNase I hypersensitivity sites (DHS) with high-throughput sequencing, in particular, has proven an information-rich, genome-wide analysis tool, defining locations of transcription factor binding, active transcription start sites, enhancers, and insulators in a wide variety of cell lines and tissue samples (*4*, *5*). Genome-wide DNase-seq, as read out with base-specific sensitivity, can also be used to footprint transcription factor binding sites within open chromatin regions, allowing *de novo* derivation of transcription factor regulatory networks in health (*6*, *7*) and disease (*8*). Despite these successes, current methods for assaying chromatin accessibility employ multiple biochemical steps that require individual calibration and typically require ~10^7 cells as input material (*9*, *10*). These limitations are problematic in three major ways: 1) the methods "average out" and "drown out" heterogeneity in cellular populations; 2) cells must often be expanded *ex vivo* to obtain sufficient biomaterials, altering the epigenetic state in unknown ways; finally, 3) input requirements often prevent application of these assays to well-defined clinical samples, precluding generation of "personal epigenomes" in diagnostic timescales.

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Summary of the Invention

[0003] Epigenomic studies of chromatin accessibility have yielded tremendous biological insights, but are currently limited in application by their complex workflows and large cell number requirements. Here we report a robust technology for rapid profiling of an epigenome by direct transposition of sequencing adapters into native chromatin. The method enables rapid (~30 minutes) capture of open chromatin sites from ~1,000 to 100,000-fold fewer cells than conventional methods. Upon deep-sequencing, genomic locations of open chromatin, DNA binding proteins, and nucleosome phasing are read out comprehensively at nucleotide-resolution. We measured and interpreted the serial daily epigenomes of resting human T cells from a proband via standard blood draws, demonstrating the feasibility of reading personal epigenomes in real time for monitoring health and disease. We refer to this method as assay of transposase accessible chromatin, abbreviated as ATAC-seq.

Brief Description of the Figures

[0004] Fig. 1A is a schematic representation of the ATAC-seq reaction; Fig. 1B are graphs of the approximate input material and sample preparation time requirements for genome-wide methods of chromatin analysis; and Fig. 1C is a composite graph that shows a comparison of the ATAC-seq to other open chromatin assays at a locus in GM12878 lymphoblastoid cells displaying high concordance.

[0005] Fig. 2A shows CTCF footprints ovserved in ATAC-seq and DNase-seq data at a specific locus on chr1; Fig. 2B is a graph of the aggregate ATAC-seq footprint for CTCF (motif green) generated over binding sites within the genome; and Fig. 2C is a chart of the CTCF predicted binding probability inferred from ATAC-seq data, position weight matrix (PWM) scores for the CTCF motif, evolutionary conservation (PhyloP), and wherein the right-most column is the CTCF ChiP-seq data (Encyclopedia of DNA Elements, or "ENCODE") for the cell line.

[0006] Fig. 3A is a chart of the ATAC-seq fragment sizes generated from GM12878 cell line nuclei (red) and the pitch of the DNA helix for fragments less than 200 bp together with a log-transformed histogram showing that clear periodicity persists to 6 nucleosomes (inset); Fig. 3B is a V-plot of H2A.Z-bound loci in *S. cerevisiae* and shows periodicity indicative of well-positioned upstream and downstream nucleosomes; and Fig. 3C is a graph of the averaged read

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center positions obtained from fragments expected to come from nucleosome-free regions (red) and a synthetic signal describing nucleosome positions (blue) in human GM12878 cells.

[0007] Fig. 4A is a schematic representation of the work flow from standard blood draws; Fig. 4B is a graph showing the serial ATAC-seq data from proband T-cells over three days; Fig. 4C is an example of the application of ATAC-seq data to prioritize candidate transcription factor (TF) drug targets; Fig. 4D is a graphical representation of the cell type-specific regulatory network from proband T-cells; and Figs. 4E and 4F are examples of T-cell-specific NFAT target genes predicted by ATAC-seq and confirmed by alignment with NFAT ChIP-seq.

[0008] Figs. 5A-C are graphical representations of peaks in the Duke DNase-seq (down sampled to 60 x 10^6 reads), UW DNase-seq (40 x 10^6 reads), and ATAC-seq data (60 x 10^6 paired-end reads) were called using ZINBA; Fig. 5D is a graph showing the technical reproducibility of the ATAC-seq data.

[0009] Fig. 6 is a Venn-diagram showing the overlap of the peak calls for the data set of Fig. 5.

[0010] Figs. 7A-D are graphs of the number of reads overlapping the set of open chromatin regions identified by Duke DNase, UW DNase and FAIRE in GM12878 cells compared to a set of background regions, wherein to determine the read depth required for detecting open chromatin sites sensitivity and specificity was assessed at varying read depths, including 50k, 100k, 500k, 10 million and 50 million reads; Fig. 7E is a graph showing the performance of ATAC-seq in GM12878 cells was assessed using 500, 5,000 or 50,000 cells as starting material.

[0011] Fig. 8 is a graph of the nucleotide frequency scores representing the observed nucleotide frequency of each base; nucleotide frequencies are normalized to 1; the x=0 position represents the read start, and the dotted line represents the symmetry axis of the Tn5 dimer.

[0012] Fig. 9 is graph of the average intensity per base of each feature at every ATAC-seq peak; all ENCODE ChIP data was normalized to input; data has been processed using a sliding window of 200 peaks.

[0013] Fig. 10 are charts of representative UCSC genome browser track of data from different starting numbers of cells for ATAC-seq.

[0014] Fig. 11 shows graphs of a select set of transcription factor footprints detected by ATAC-seq in GM12878 cells; for the indicated transcription factors the aggregate signal of ATAC-seq reads were computed using CENTIPEDE on the genome-wide sets of sites matching

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the corresponding motif; reads were calculated in the region +/-100 bp of the motif boundary; the vertical dashed lines indicate the boundaries of the motifs.

[0015] Fig. 12 is a chart showing the prediction of CTCF binding cites using ATAC-seq footprinting with CENTIPEDE; prediction of CTCF binding sites was assessed using the genome-wide set of CTCF motifs sorted by the posterior probability reported by CENTIPEDE; those overlapping CTCF ChIP-seq peaks were used as the positive set and all others were considered as the negative set; this yielded an area under the curve (AUC) of 0.92, which suggests specific and sensitive binding inference for CTCF.

[0016] Fig. 13 is a chart fitting nucleosome peaks in ATAC-seq fragment size distribution to enable nucleosome occupancy measurements.

[0017] Figs. 14A are charts of ATAC-seq of FACS-purified cell populations from human blood; Figs. 14B are charts showing cell-type specific open chromatin sites at known lineage-specific genes.

[0018] Fig. 15 is a chart of the allele frequency in open chromatin regions in GM12878 cells with ATAC-seq.

[0019] Fig. 16A represents the normalized read enrichments for 7 classes of chromatin state. 16B displays an example locus containing two TSSs showing nucleosome free read track, calculated nucleosome track (Methods), as well as DNase, MNase, and H3K27ac, H3K4me3, and H2A.Z tracks for comparison; Fig. 16F displays hierarchical clustering of DNA binding factor position with respect to the nearest nucleosome dyad within accessible chromatin reveals distinct classes of DNA binding factors; factors strongly associated with nucleosomes are enriched for chromatin remodelers.

Description of the Invention

Example 1

[0020] We have developed a novel open-chromatin assay based on direct transposition of sequencing adapters into regions of accessible chromatin. Hyperactive Tn5 transposase (*11*, *12*), loaded with adapters for high-throughput sequencing, can simultaneously tag genomic samples with sequencing adapters and fragment the genome (previously described as "tagmentation" (*12*)). In our method, Tn5 transposase integrates its adapter payload into regions of accessible chromatin, whereas compaction and sequestration of the chromatin make transposition

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improbable due to steric clashes with the transposase (Fig 1A). Therefore, amplifiable DNA fragments suitable for high-throughput sequencing are generated at locations of open chromatin, and the entire assay and library construction can be carried out in a single enzymatic step, significantly diminishing the time required to assay open chromatin, and radically reducing the input requirements (*9*, *10*) (Fig 1B).

[0021] Extensive analyses show that ATAC-seq provides accurate and sensitive measurement of open chromatin sites. We carried out the transposition reaction on 50,000 or 500 unfixed nuclei isolated from GM12878 limphoblastoid cell line (ENCODE Tier 1 (*14*)) for comparison and validation with other open chromatin data sets, including DNase-hypersensitivity (*9*) and FAIRE-seq (*3*). At a locus of interest, previously highlighted by others (*5*), (Fig. 1C), ATAC-seq signal has signal-to-noise similar to DNase-seq signals generated from approximately 3 to 5 orders-of-magnitude more cells (*9*, *10*). Peaks were called genome-wide on the ATAC-seq datasets using ZINBA (*15*) (Methods). Because each data set has different read lengths, we chose to filter for peaks within mappable regions (Duke Dnase-seq = 20 bp reads, UW DNase-seq = 35 bp reads, and ATAC-seq = paired-end 50 bp reads). Peak intensities were highly reproducible between technical replicates (R=0.98; Fig. 5D). We also observe a high correlation coefficient of peak intensities between ATAC-seq and DNase-seq (R=0.79 and R=0.83, Figs. 5A and 5B, respectively) and note that the majority of reads within peaks come from intersections of DNase and ATAC-seq peaks (Fig. 6). More than 65% of reads from all three methods are found in the intersection of the three methods' peaks, suggesting that strong well-stereotyped peaks are detected by all three methods (Table 1; cell color strength is proportional to the fraction of reads).

Table 1

	ATAC Unique	UW Unique	Duke Unique	ATAC and UW	ATAC and Duke	UW and Duke	Intersect
ATAC-Seq	6.30%	4.36%	1.08%	10.83%	1.53%	2.09%	73.80%
UW DNase	1.32%	8.13%	0.68%	7.57%	0.33%	4.34%	77.62%
Duke DNase	2.10%	5.27%	14.80%	4.02%	1.44%	6.91%	65.46%

[0022] Comparing our data to DHSs identified in ENCODE DNase-seq data, receiver operating characteristic (ROC) curves demonstrate a similar sensitivity and specificity as DNase-seq (Fig. 7). The ATAC-seq peak intensity correlates well with markers of active chromatin (Fig. 8). Indeed, we see no substantial differences between Tn5 insertion preferences between purified

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genomic DNA and human chromatin, suggesting that the local insertion preference into chromatin is identical to that found in naked genomic DNA. We also note that the ATAC-seq peak intensity does not correlate with transposase sequence preference (Fig. 9). We observed that ATAC-seq peak intensity was most strongly correlated with DNase hypersensitivity (see Fig. 5 for more information) and CTCF (see Fig. 2). ATAC-Seq is only moderately correlated with Tn5 sequence preference. Tn5 scores represents a theoretical insertion bias derived using the PWM (see Fig. S4), Tn5 genome is derived from data produced from Adey et al. (*12*). Briefly, data was trimmed and processed identically to what was described in the analysis. We also saw that ATAC-seq was correlated with histone marks associated with active chromatin (H3K4me3, H4K27ac and H3k9ac), and anti-correlated with histone marks associated with inactive chromatin (H3K27me3) and gene bodies (H3K36me3 and H4K20me1). We also note a moderate enrichment for conserved bases at higher intensity peaks. These reported sequence preferences are similar to those previously reported (*27*). Highly sensitive open chromatin detection is maintained even when using 5,000 or 500 human nuclei as starting material (Figs. 7, 10, respectively). With respect to Fig. 10, this same locus is also shown in Figure 1B of the main text. In order: 500 cells were isolated using FACS and two replicates of 500 cells and 5,000 cells were done by a simple dilution from cell culture. For comparison, the bottom track represents 50,000 cells, also show in Fig. 1B. This figure demonstrates that we are able to capture open chromatin sites from as few as 500 cells.

[0023] ATAC-seq revealed multiple aspects of gene regulatory events and chromatin structure in a single rapid assay. DNA sequences directly occupied by DNA-binding proteins are protected from transposition; the resulting sequence "footprint" reveals the identity of the DNA-binding protein at each site, analogous to DNase digestion footprints (*16*). At a specific CTCF binding site on chromosome 1, we observed a clear footprint (a deep notch of ATAC-seq signal), similar to footprints seen by DNase-seq (*17*), at the precise location of the CTCF motif that coincides with the summit of the CTCF ChIP-seq signal in GM12878 cells (Fig 2A). We averaged ATAC-seq signal over all expected locations CTCF within the genome and observed clear evidence of a well-stereotyped "footprint" (Fig. 2B). Similar results were obtained for a variety of other common TFs (for examples see Fig. 11). We inferred the CTCF binding probability from motif consensus score, evolutionary conservation, and ATAC-seq footprinting data to generate a posterior probability of CTCF binding at all loci (Fig. 2C) (*18*). Results using ATAC-seq closely

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recapitulate ChIP-seq binding data in this cell line (see Fig. 12) suggesting that factor occupancy data can be extracted from these ATAC-seq datasets, allowing reconstruction of regulatory networks.

[0024] ATAC-seq paired-end reads produce information about nucleosome packing and positioning. The insert size distribution of sequenced fragments from human chromatin has clear periodicity at approximately 200 base pairs, suggesting many fragments are protected by integer multiples of nucleosomes (Fig 3A). This fragment size distribution also shows clear periodicity equal to the helical pitch of DNA (*12*). To explore nucleosome phasing in depth, we performed ATAC-seq in *S. cerevisae*, where gold standard datasets of nucleosome positioning were created (*19*). Displaying read fragment size versus read center in a "V-plot"(*20*) recapitulates the known positioning of H2A.Z nucleosomes and reveals periodicity of positioned upstream and downstream nucleosomes (Fig. 3B).

[0025] ATAC-seq paired-end reads produce also produce detailed information about nucleosome packing and positioning. By partitioning insert size distribution according to functional classes of chromatin as defined by previous models, and normalizing to the global insert distribution (Methods) we observe clear class-specific enrichments across this insert distribution (Fig. 16A), demonstrating that these functional states of chromatin have an accessibility "fingerprint" that can be read out with ATAC-seq. These differential fragmentation patterns are consistent with the putative functional state of these classes, as insulator regions are enriched for short fragments of DNA, while transcription start sites are depleted for mono-, di- and tri-nucleosome associated fragments. Transcribed and promoter flanking regions are enriched for longer multi-nucleosomal fragments, suggesting they are more compacted than other states that require access to DNA by regulatory factors. Finally, repressed regions are highly depleted for short fragments, consistent with their expected compacted state. ATAC-seq reveals these differentially compacted forms of chromatin, which have been long hypothesized to exist *in vivo*.

[0026] To explore nucleosome positioning around active transcription start sites (TSSs) in the GM12878 cell line, we partitioned our data into reads generated from putative nucleosome-free regions of DNA, and reads likely derived from nucleosome-associated fragments (Methods and Fig. 13). The observed fragment distribution was partitioned into six populations of reads – reads expected to originate from open DNA, and reads that span 1, 2 or 3 putative nucleosomes. To enable this partitioning of the data, the ATAC-seq fragment distribution was fit to the sum of 1)

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an exponential function for fragment distribution pattern at insert sizes below one nucleosome, and 2) 5 Gaussians to the distributions arising from protection from one, two, three, four and five nucleosomes. The sum of these fits is shown (black dotted line) is similar to the observed fragment distribution (blue line). Vertical dotted lines are boundaries for identification of fragments as originating from the nucleosome-free (<100bps), 1-nucleosome, 2-nucleosome and 3-nucleosome regions. Dotted lines were set to ensure that <10% of fragments originate from neighboring peaks, as defined by our fit. Using a simple heuristic that positively weights nucleosome associated fragments and negatively weights nucleosome free fragments (see Methods), we calculated a data track used to call nucleosome positions within regions of accessible chromatin[20]. An example locus (Fig. 16B) contains a putative bidirectional promoter with CAGE data showing two transcription start sites separated by ~700bps. ATAC-seq reveals in fact two distinct nucleosome free regions, separated by a single well-positioned mononucleosome (Fig. 16C). Compared to MNase-seq, ATAC-seq data is especially amenable to detecting nucleosomes within putative regulatory regions to improve genome annotation, as the majority of reads are concentrated within accessible regions of chromatin. By averaging signal over all transcription start sites (TSSs), we note nucleosome free fragments are enriched at a canonical nucleosome free promoter region overlapping the TSS, while our nucleosome signal is enriched both upstream and downstream of the active TSS, and displays characteristic phasing of upstream and downstream nucleosomes[6,7] (Fig. 3C). Thus, ATAC-seq can simultaneously read out chromatin structure and regulatory transactions with DNA binding proteins genome-wide.

[0027] Investigation of the distance between DNA binding factors and nucleosomes revealed distinct classes of factor-nucleosome spacing. Using ChIP-seq data, we plotted the position of a variety of DNA binding factors with respect to the dyad of the nearest nucleosome. Unsupervised hierarchical clustering (Figure 16C) revealed major classes of binding with respect to the proximal nucleosome, including 1) a strongly nucleosome avoiding group of factors with binding events stereotyped at ~170 bases from the nearest nucleosome (comprising C-FOS, NFYA and IRF3), 2) a highly constrained class that binds proximal to the expected end of nucleosome DNA contacts (comprising CTCF, RAD21, SMC3, and ZNF143), 3) a large class of primarily transcription factors that have gradations of nucleosome avoiding or nucleosome-overlapping binding behavior, and 4) a class whose binding sites tend to overlap nucleosome

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associated DNA. Interestingly, this final class includes chromatin remodeling factors such as CHD1 and SIN3A as well as RNA polymerase II, which appears to be enriched at the nucleosome boundary[8] These data suggest ATAC-seq can provide high-resolution readout of nucleosome associated and nucleosome free regions in regulatory elements genome wide.

[0028] Because ATAC-seq allows rapid open-chromatin assays from small numbers of cells, we applied the method to assay the personal T-cell epigenomes of a healthy volunteer via standard blood draws. The rapidity of this assay makes it feasible for guiding clinical decisions in real time. Using rapid T-cell enrichment and sample handling protocols (Methods), the total required time from blood draw to sequencing was approximately 275 minutes, enabling the possibility of daily turn-around time for open chromatin maps (Fig. 4A). We performed ATAC-seq on three consecutive days via standard blood draw from a single individual (Fig. 4B). We explore ATAC-seq profile at the *IL2* locus as an exercise to consider how personal epigenomic maps may contain clinically actionable information. IL-2 is a key cytokine that drives T-cell growth and function in inflammatory and autoimmune diseases (*22*). Distinct drugs (*23-25*) inhibit the activities of different transcription factors that bind putative *IL2* enhancers in a context-dependent manner, raising the conundrum of choosing one or more optimal drugs. In principle, we wish to antagonize the causal transcription factor pathway without exposing the patient to drugs that are unlikely to serve the therapeutic goal of IL-2 blockade. ATAC-seq shows that in the proband's T-cells, only NFAT, but not two other drug targets, is engaging *IL2* (Fig. 4C), which rationally nominates a precise treatment plan.

[0029] Conversely, we are able to consider the global consequences of inhibiting NFAT or other transcription factors. ATAC-seq footprints generated the occupancy profiles of transcription factors in proband T-cells, enabling systematic reconstruction of regulatory networks. With this personalized regulatory map, we compared the genomic distribution of 89 transcription factors between GM12878 and proband CD4+ T-cells. Transcription factors that exhibit large variation in distribution between T-cells and B-cells are enriched for T-cell specific factors (Fig. 4D). This analysis showed NFAT as a major T-cell specific regulator, as can be seen at specific loci where NFAT is localized nearby to known T-cell specific genes such as CD28 (Fig. 4E) and a novel lincRNA RP11-229C3.2 (Fig. 4F). In contrast, canonical CTCF occupancy is highly correlated in different cell types (Fig. 4D). These results demonstrate the feasibility of generating detailed

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personalized gene regulatory networks from clinical samples, opening the door for future diagnostic applications.

[0030] Separately, ATAC-seq of $CD4^+$ and $CD8^+$ T-cells, and monocytes isolated by fluorescence-activated cell sorting (FACS) from a single blood draw created an interpretative framework for the personal epigenomes, and demonstrated that ATAC-seq is compatible with cellular enrichment using surface markers (Fig. 14). ATAC-seq can also identify candidate allele specific open chromatin regions (Fig. 15). Using publicly available variant data, we measured the allele frequency in open chromatin regions at putative heterozygous loci. Because of potential for spurious heterozygous sites, we required more than two reads to validate the heterozygosity of the allele. Red points (n=167) are candidate allele specific open chromatin sites at $p<10^{-5}$, while grey (n=900) represent candidates at $p<0.01$. P-values were calculated using a Bayesian model developed by Audic et al. (*28*). These allele-specific effects are especially relevant to human disease (*8*).

[0031] ATAC-seq is a robust, rapid open chromatin assay that will enable the interrogation of the epigenetic landscape of rare biological samples with newfound precision and speed. Because the assay is compatible with FACS, investigation of separable subpopulations of cells based on surface markers will be enabled. For example, cellular subpopulations selected at different points of development, and in human diseases, such as cancer, autoimmunity, and neuropsychiatric disorders are viable applications. The reduced input requirements and rapid workflows, when coupled with the recent introduction of rapid-turnaround high-throughput sequencing instruments, will enable investigation of personalized epigenetic landscapes of selected tissues both in the lab and the clinic.

METHODS

[0032] The ATAC-seq protocol has three major steps:

Prepare nuclei:

[0033] To prepare nuclei, we spun 50,000 cells at 500 x g for 5 minutes, followed by a wash using 50 µL of cold 1x PBS and centrifugation at 500 x g for 5 minutes. Cells were lysed using cold lysis buffer (10 mM Tris-Cl, pH 7.4, 10 mM NaCl, 3 mM $MgCl_2$ and 0.1% IGEPAL CA-630). Immediately after lysis, nuclei were spun at 500 x g for 10 minutes using a refrigerated

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centrifuge. To avoid losing cells during the nuclei prep, we used a fixed angle centrifuge and carefully pipetted away from the pellet after centrifugations.

Transpose and purify:

[0034] Immediately following the nuclei prep, the pellet was resuspended in the transposase reaction mix (25 µL 2x TD buffer, 2.5 µL Transposase (Illumina) and 22.5 µL of nuclease free water). The transposition reaction was carried out for 30 minutes at 37 °C. Directly following transposition the sample was purified using a Qiagen Minelute kit.

PCR:

[0035] Following purification, we amplified library fragments using 1x NEBnext® PCR master mix and 1.25 µM of custom Nextera PCR primers 1 and 2 (see Table 2), using the following PCR conditions: 72 °C for 5 minutes, 98 °C for 30 seconds, followed by thermocycling at 98 °C for 10 seconds, 63 °C for 30 seconds and 72 °C for 1 minute. To reduce GC and size bias in our PCR we monitored the PCR reaction using qPCR in order to stop amplification prior to saturation. To do this, we amplified the full libraries for 5 cycles, after 5 cycles we took an aliquot of the PCR reaction and added 10 µl of the PCR cocktail with Sybr® Green at a final concentration of 0.6x. We ran this reaction for 20 cycles, to determine the additional number of cycles needed for the remaining 45 µL reaction. The libraries were purified using a Qiagen PCR cleanup kit yielding a final library concentration of ~30 nM in 20 µL. Libraries were amplified for a total of 10-12 cycles.

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Table 2 - Oligos

Ad1_noMX:	AATGATACGGCGACCACCGAGATCTACACTCGTCGGCAGCGTCAGATGTG
Ad2.1_TAAGGCGA	CAAGCAGAAGACGGCATACGAGATTCGCCTTAGTCTCGTGGGCTCGGAGATGT
Ad2.2_CGTACTAG	CAAGCAGAAGACGGCATACGAGATCTAGTACGGTCTCGTGGGCTCGGAGATGT
Ad2.3_AGGCAGAA	CAAGCAGAAGACGGCATACGAGATTTCTGCCTGTCTCGTGGGCTCGGAGATGT
Ad2.4_TCCTGAGC	CAAGCAGAAGACGGCATACGAGATGCTCAGGAGTCTCGTGGGCTCGGAGATGT
Ad2.5_GGACTCCT	CAAGCAGAAGACGGCATACGAGATAGGAGTCCGTCTCGTGGGCTCGGAGATGT
Ad2.6_TAGGCATG	CAAGCAGAAGACGGCATACGAGATCATGCCTAGTCTCGTGGGCTCGGAGATGT
Ad2.7_CTCTCTAC	CAAGCAGAAGACGGCATACGAGATGTAGAGAGGTCTCGTGGGCTCGGAGATGT
Ad2.8_CAGAGAGG	CAAGCAGAAGACGGCATACGAGATCCTCTCTGGTCTCGTGGGCTCGGAGATGT
Ad2.9_GCTACGCT	CAAGCAGAAGACGGCATACGAGATAGCGTAGCGTCTCGTGGGCTCGGAGATGT
Ad2.10_CGAGGCTG	CAAGCAGAAGACGGCATACGAGATCAGCCTCGGTCTCGTGGGCTCGGAGATGT
Ad2.11_AAGAGGCA	CAAGCAGAAGACGGCATACGAGATTGCCTCTTGTCTCGTGGGCTCGGAGATGT
Ad2.12_GTAGAGGA	CAAGCAGAAGACGGCATACGAGATTCCTCTACGTCTCGTGGGCTCGGAGATGT
Ad2.13_GTCGTGAT	CAAGCAGAAGACGGCATACGAGATATCACGACGTCTCGTGGGCTCGGAGATGT
Ad2.14_ACCACTGT	CAAGCAGAAGACGGCATACGAGATACAGTGGTGTCTCGTGGGCTCGGAGATGT
Ad2.15_TGGATCTG	CAAGCAGAAGACGGCATACGAGATCAGATCCAGTCTCGTGGGCTCGGAGATGT
Ad2.16_CCGTTTGT	CAAGCAGAAGACGGCATACGAGATACAAACGGGTCTCGTGGGCTCGGAGATGT
Ad2.17_TGCTGGGT	CAAGCAGAAGACGGCATACGAGATACCCAGCAGTCTCGTGGGCTCGGAGATGT
Ad2.18_GAGGGGTT	CAAGCAGAAGACGGCATACGAGATAACCCCTCGTCTCGTGGGCTCGGAGATGT
Ad2.19_AGGTTGGG	CAAGCAGAAGACGGCATACGAGATCCCAACCTGTCTCGTGGGCTCGGAGATGT
Ad2.20_GTGTGGTG	CAAGCAGAAGACGGCATACGAGATCACCACACGTCTCGTGGGCTCGGAGATGT
Ad2.21_TGGGTTTC	CAAGCAGAAGACGGCATACGAGATGAAACCCAGTCTCGTGGGCTCGGAGATGT
Ad2.22_TGGTCACA	CAAGCAGAAGACGGCATACGAGATTGTGACCAGTCTCGTGGGCTCGGAGATGT
Ad2.23_TTGACCCT	CAAGCAGAAGACGGCATACGAGATAGGGTCAAGTCTCGTGGGCTCGGAGATGT
Ad2.24_CCACTCCT	CAAGCAGAAGACGGCATACGAGATAGGAGTGGGTCTCGTGGGCTCGGAGATGT

Low cell number protocol:

[0036] To prepare the 500 and 5,000 cell reactions we used the same protocol with some notable exceptions: The transposition reaction was done in a 5 μL instead of 50 μL reaction. Also, we eliminated the Qiagen Minelute purification prior to PCR, instead we took the 5 μL reaction immediately after transposition directly into the 50 μL PCR. We have also demonstrated low cell number library construction using purification (using the Minelute purification system) both with and without carrier DNA to prevent loss of sample. In cases where carrier DNA was used, we have used PCR primer for subsequent amplification as carrier DNA. In general, purification gives data that is cleaner and higher quality.

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Library QC and quantitation:

[0037] During the ATAC-seq protocol, we chose to avoid a size selection step to maximize the library complexity. The sequenced insert size is a distribution between 40 to 1 kb with a mean of ~120 bps. From bioanalyzer and gels we observed fragments >2 kb, which would make Qubit and other mass-based quantitation methods hard to interpret. For this reason, we chose to quantify our libraries using qPCR based methods.

$CD4^+$ enrichment from peripheral blood.

[0038] One green-top tube of whole blood was obtained from 1 normal volunteer three times over a 72-hour period, under a Stanford University IRB-approved protocol. Informed consent was obtained. 5mL of blood at each timepoint was negatively selected for $CD4^+$ cells, using RosetteSep Human $CD4^+$ T Cell Enrichment Cocktail (StemCell Technology). RosetteSep cocktail was incubated with the blood at 50μL/mL for 20 min, diluted in an equal volume of PBS with 2% FBS, and underlayed with 15 mL Ficol-Paque Plus (GE). Blood was centrifuged for 20 minutes at 1200 x g without break, negatively selected cells were removed from the density medium: plasma interface, and cells were washed X2 in PBS with 2% FBS.

FACS sorting peripheral blood leukocytes and GM cells.

[0039] GM 12878 cells were stained with DAPI NucBlue Fixed Cell Stain (molecular probes) and live cells were sorted using a FACSAria (BD Biosciences) using a 100 μm nozzle. One peripheral blood sample (buffy coat) was stained with BD Bioscience antibodies CD14-A-488 (M5E2, 1:20), CD3-PE-Cy7 (SK7, 1:20), CD4-APC-Cy7 (RPA-T4, 1:20), and CD8 (RPA-T8, 1:20) for 20 minutes in the dark at RT. Cells were lysed using BDpharmLyse 1:10 dil in diH20 (BD) for 15 min, centrifuged for 5 minutes, washed with PBS 2% FBS X 2, and resuspended in PBS with 2% FBS. 50,000 $CD3^+CD8^+$, $CD3^+CD4^+$, and $CD14^+$ cell populations were sorted into PBS with 10%FBS.

Analysis:

Primary data processing:

[0040] Data was collected using either 34 x 8 x 34 reads from a MiSeq or 50 x 8 x 50 reads on a HiSeq. Adapter sequences were trimmed from the FASTQ files. Reads were aligned to hg19

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using BOWTIE (*26*) using the parameters –X2000 and –m1. These parameters ensured that fragments up to 2 kb were allowed to align (-X2000) and that only unique aligning reads were collected (-m1). For all files duplicates were removed using Picard.

[0041] For peak calling and footprinting, we adjusted the read start sites to represent the center of the transposition binding event. Previous descriptions of the Tn5 transposase show that the transposome binds as a dimer and inserts two adapters separated by 9 base pairs (*12*). Therefore, all reads aligning to the + strand were offset by 4 bp to the right, and all reads aligning to the – strand were offset 5 bp to the left.

Peak calling

[0042] We used ZINBA to call all reported peaks in this manuscript. ZINBA was run using a window size of 300 bp and an offset 75 bp. Alignability was used to model the zero-inflated component and the ATAC-seq read count for the background and enriched components. Enriched regions were identified as those with a posterior probability >0.8.

ChIP-seq peak calling and clustering

[0043] : ChIP-seq data was downloaded form the UCSC ENCODE repository, for a complete list of data use see supplementary table 2. Peaks where called using GEM[4], the parameters used where -k_min 6 -k_max 20. Inputs where used as a control for peak calling. Binding events where annotated by distance to the nearest dyad in binds of 10 bps. Factors were then hierarchically clustered using Euclidean distance and normalized by gene and centered by mean[5].

[0044]

Footprinting using CENTIPEDE:

[0045] The genome-wide set of motifs were obtained from the ENCODE motif repository (http://www.broadinstitute.org/~pouyak/encode-motif-disc/). The input for CENTIPEDE (*18*) included the PWM score, conservation (PhyloP) and ATAC-seq counts within +/-100bp of each genomic region matching a motif. ChIP-seq data was obtained from the UCSC ENCODE repository.

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Nucleosome positioning:

To phase nucleosome positions at transcription start sites, we split reads into bins. Reads below 100bps were considered nucleosome free, reads between 180 and 247 bps were considered to be mononucleosomes, reads between 315 and 473 bps were considered to be dinucleosomes and reads between 558 and 615 were considered to be trinucleosomes (for determining cutoffs see Fig. 13). Dinucleosome reads were split into two reads and Trinucleosome reads were split into three reads. Reads were analyzed using Danpos and Dantools (*27*) using the parameters –p1, --clonalcut 0. The background was defined by nucleosome free reads (reads less than 100 bps).

Analysis of fragment size as a function of chromatin annotation:

[0046] First the distribution of paired-end sequencing fragment sizes overlapping each chromatin state (http://www.ensembl.org/info/docs/funcgen/regulatory_segmentation.html) were computed. The distributions were then normalized to the percent maximal within each state and enrichment was computed relative to the genome-wide set of fragment sizes.

Comparison of transcription factor regulatory networks:

[0047] Transcription factor regulatory networks were constructed by comparing the GENCODE v14 genes with the genome-wide set of posterior probabilities estimated by CENTIPEDE for the respective cell-types. The extent of a transcription factor regulating each gene was determined by taking the sum of the weighed posterior probabilities for a given transcription factor mapping to the same chromosome. For each mapped motif the posterior probability was weighted based on the distance to the transcription start site for each gene. Comparison of transcription factor regulatory networks was computed as the correlation of each transcription factor in a given cell type with all transcription factors in the other cell type. The resulting correlation matrix was hierarchically clustered using the Pearson correlation coefficient and complete linkage.

Candidate IL2 enhancer analysis:

[0048] We inspected ENCODE data on UCSC genome browser to identify putative IL2 enhancers in one or more cell types that may be responsive to FDA approved immomodulatory drugs. We scanned the intergenic region upstream of IL2 in hg19 for (i) enhancer-associated histone marks (H3K4me1 and H3K27ac), (ii) binding by one or more TFs as confirmed by ChIP-

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seq, and (iii) the TF pathway can be targeted by a human therapeutic. This analysis identified IRF4 and STAT3 binding sites in addition to the known NFAT-responsive (*22*).

[0049] The foregoing description and drawings comprise illustrative embodiments of the present inventions. The foregoing embodiments and the methods described herein may vary based on the ability, experience, and preference of those skilled in the art. Merely listing the steps of the method in a certain order does not constitute any limitation on the order of the steps of the method. The foregoing description and drawings merely explain and illustrate the invention, and the invention is not limited thereto, except insofar as the claims are so limited. Those skilled in the art that have the disclosure before them will be able to make modifications and variations therein without departing from the scope of the invention.

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We claim:

1. A method of mapping chromatin, comprising the steps of:
   (a) fragmenting the chromatin of rare or abundant cells with transposase which inserts sequencing adapters into the fragments, and
   (b. amplifying and sequencing the fragments to generate a cell-specific map.

2. A method as defined in claim 1, wherein the cell-specific map provides information regarding active regulatory regions and the transcription factors that are bound to said regulatory regions.

3. A method as defined in claim 1, wherein the number of said rare cells is between 1 and 100,000.

4. A method as defined in claim 1, wherein the transposase is derived from Tn5 transposase.

5. A method as defined in claim 1, wherein the transposase is derived from MuA transposase.

6. A method as defined in claim 1, wherein nucleosome positions are inferred from the lengths of sequencing reads generated.

7. A method as defined in claim 1, wherein transcription factor binding sites are inferred from sequencing reads generated.

8. A method as defined in claim 1, wherein chromatin is isolated directly from fresh tissues.

9. A method as defined in claim 1, wherein chromatin is isolated directly from frozen tissues.

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10. A method as defined in claim 1, wherein chromatin is isolated directly from fixed tissues.

10. A method as defined in claim 1, wherein sequences are added to the sequencing adapter to uniquely identify the fragments for multiplexing (barcoding).

11. A method as defined in claim 1, wherein an affinity tag is used to target the transposase to a specific macromolecule of interest.

12. A method as defined in claim 1, wherein sequences are added to the sequencing adapter to uniquely identify the fragments for multiplexing (barcoding), and an affinity tag that is match to unique sequence is used to target the transposase to a specific macromolecule of interest.

13. A method of claim 14 wherein the affinity tag is an antibody targeted to a transcription factor.

14. A method of claim 14 wherein the affinity tag is an antibody targeted to a modified nucleosome.

15. A method as defined in claim 1, wherein the insert size distribution at a specific genomic locus is used to infer chromatin openness.

16. A method as defined in claim 1, wherein the insert size distribution and positions of insertion are used to infer transcription factor binding.

17. A method as defined in claim 1, wherein the number of sequencing reads obtained is normalized by measured sequence insertion preference of the transposase.

18. A method as defined in claim 1 wherein novel transcription factor binding sites are inferred from sequencing reads generated.

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19. A method as defined in claim 1 wherein novel transcription factors are inferred from sequencing reads generated.

20. A method as defined in claim 1 wherein causal variants can be inferred by looking at allele specific generation of sequencing reads.

21. A method as defined in claim 1 wherein chromatin state annotations are inferred from the distribution of lengths of sequencing reads.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	8968129/3
	Application Number	
Title of Invention	Transposition of Native Chromatin for Personal Epigenomics	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
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☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

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Title of the Invention	Transposition of Native Chromatin for Personal Epigenomics		
Attorney Docket Number	8968129/3	Small Entity Status Claimed	☒
Application Type	Provisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)		Suggested Figure for Publication (if any)	

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Prior Application Status			Remove
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Title of Invention	Transposition of Native Chromatin for Personal Epigenomics	

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	8968129/3
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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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Abstract

A method for fast and efficient chromatin hypersensitivity mapping in small cell numbers using direct transposition. Chromatin of rare or abundant cells is fragmented with transponase which inserts sequencing adapters into the fragments. The fragments are amplified and sequenced to generate a cell-specific map which provides information regarding active regulatory regions and the transcription factors that are bound to the regulatory regions. Maps can be generated from as few as about 50 cells.

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Page 00156

Electronic Acknowledgement Receipt	
EFS ID:	15857403
Application Number:	61826728
International Application Number:	
Confirmation Number:	4465
Title of Invention:	Transposition of Native Chromatin for Personal Epigenomics
First Named Inventor/Applicant Name:	Jason Buenrostro
Customer Number:	26386
Filer:	Kent A. Herink/Patty Law
Filer Authorized By:	Kent A. Herink
Attorney Docket Number:	8968129/3
Receipt Date:	23-MAY-2013
Filing Date:	
Time Stamp:	16:15:03
Application Type:	Provisional

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$130
RAM confirmation Number	3138
Deposit Account	122250
Authorized User	LAW, PATTY
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)					
File Listing:					
Document Number	**Document Description**	**File Name**	**File Size(Bytes)/ Message Digest**	**Multi Part /.zip**	**Pages (if appl.)**
1	Application Data Sheet	AppDataSheet.pdf	1507911 c9671cde777968e7764e6d602ec0d0572c964f7a	no	7
Warnings:					
Information:					
2		ProvisionalApp_ASFILED_23May2013.pdf	5302827 8068f3aaf8da01f3d7b38223a2d0b13017990bc6	yes	35
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Specification		1	19	
	Claims		20	22	
	Abstract		23	23	
	Drawings-other than black and white line drawings		24	35	
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	29548 ee65b9c8e1aeed249e174325653f3755c15b99ff	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	6840286		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

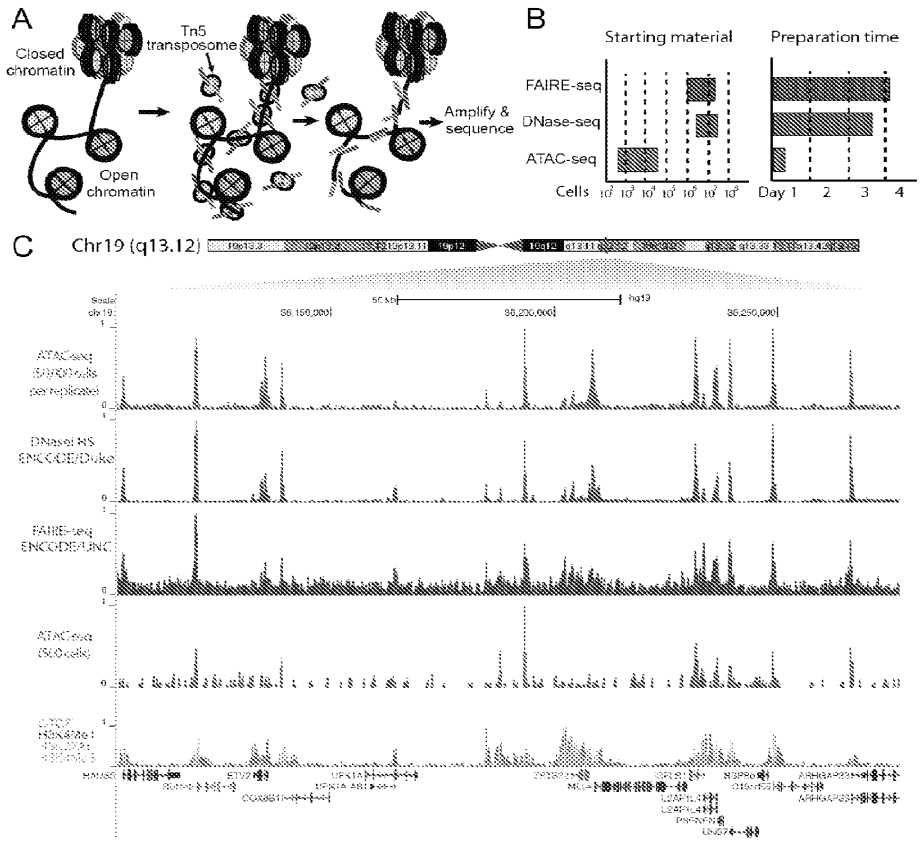


FIG. 1

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01030
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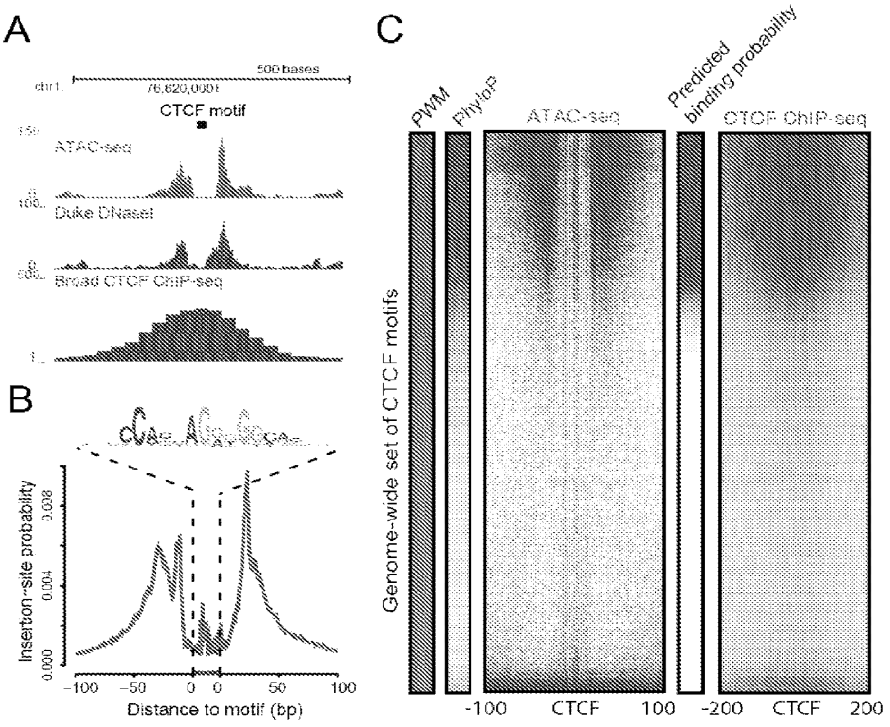


FIG. 2

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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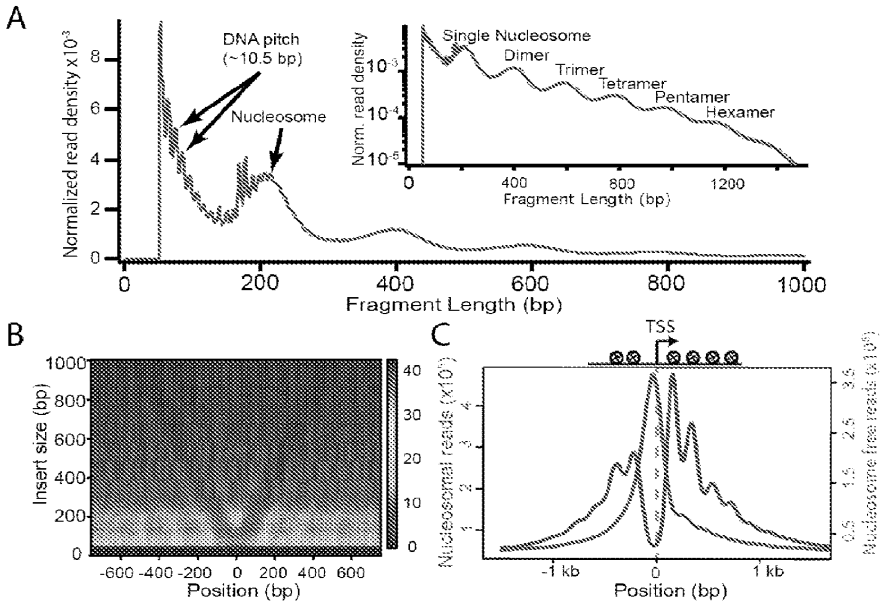


FIG. 3

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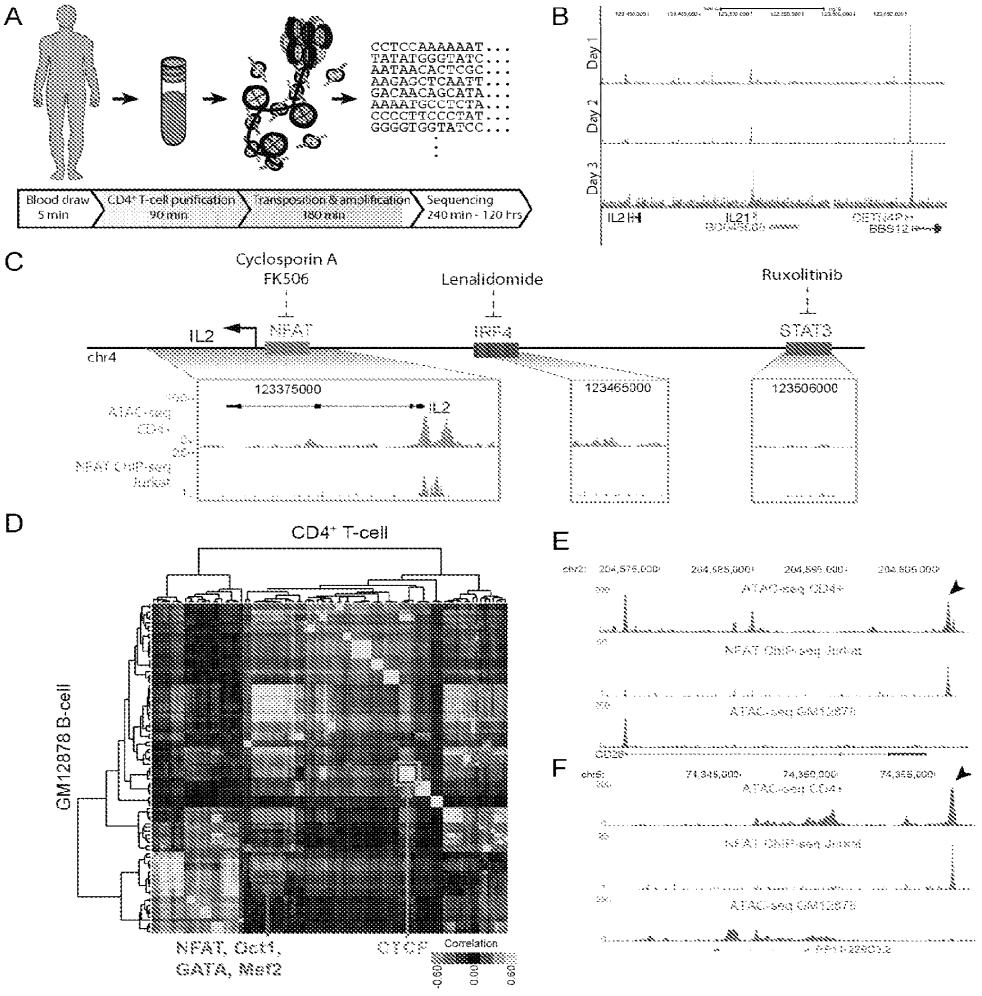


FIG. 4

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Parse Biosciences, Inc. v. 10x Genomics, Inc.
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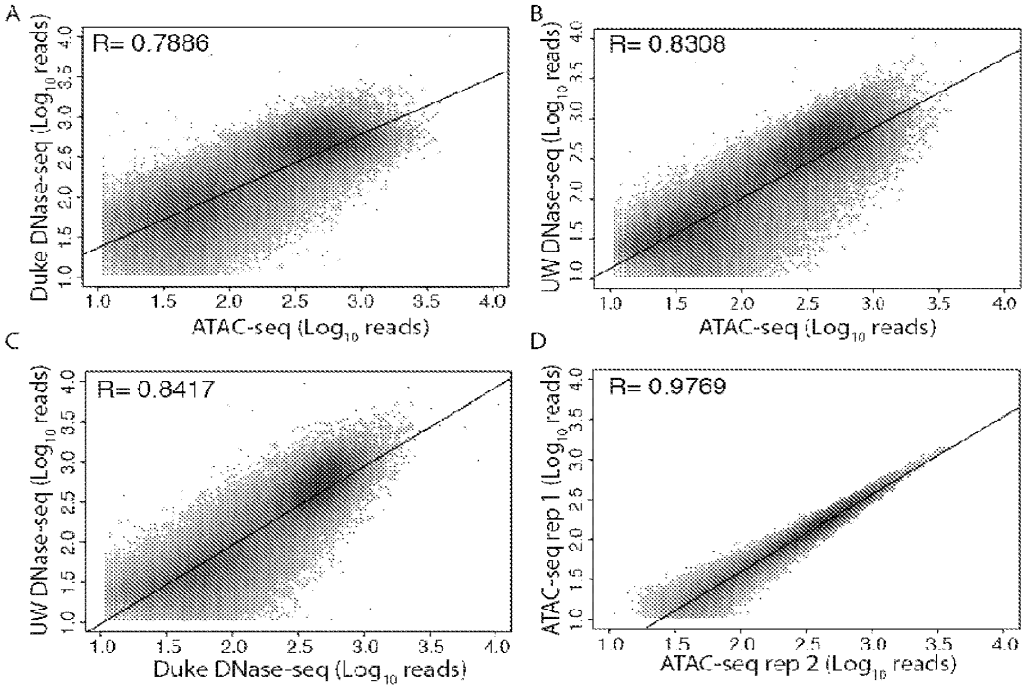


FIG. 5

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Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01030
Page 00164

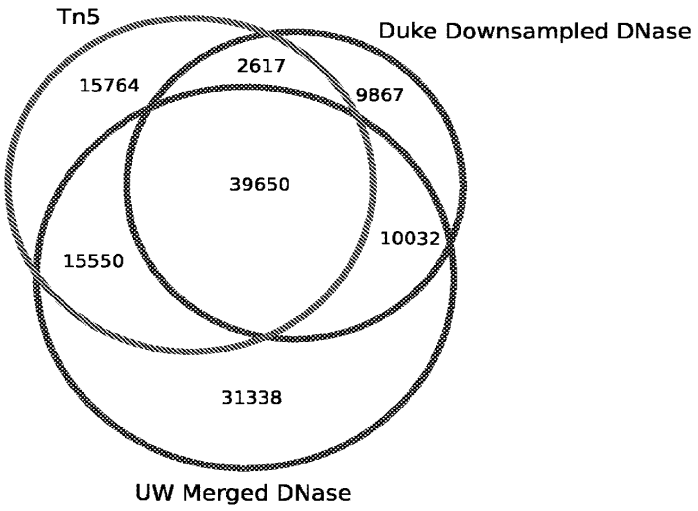


FIG. 6

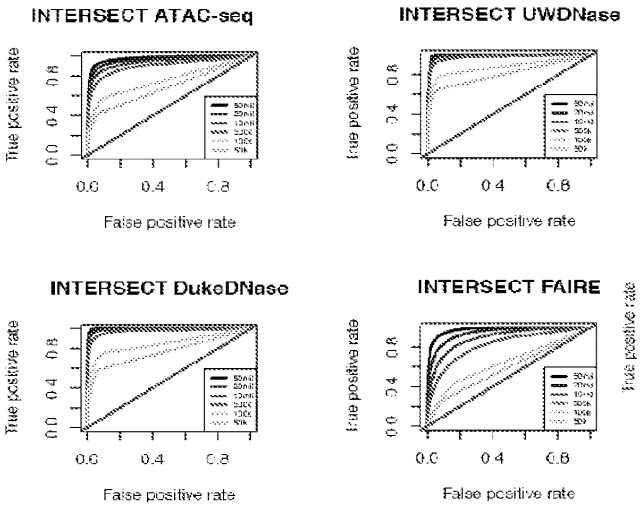


FIG. 7A-D

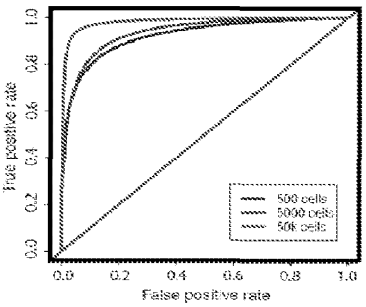


FIG. 7E

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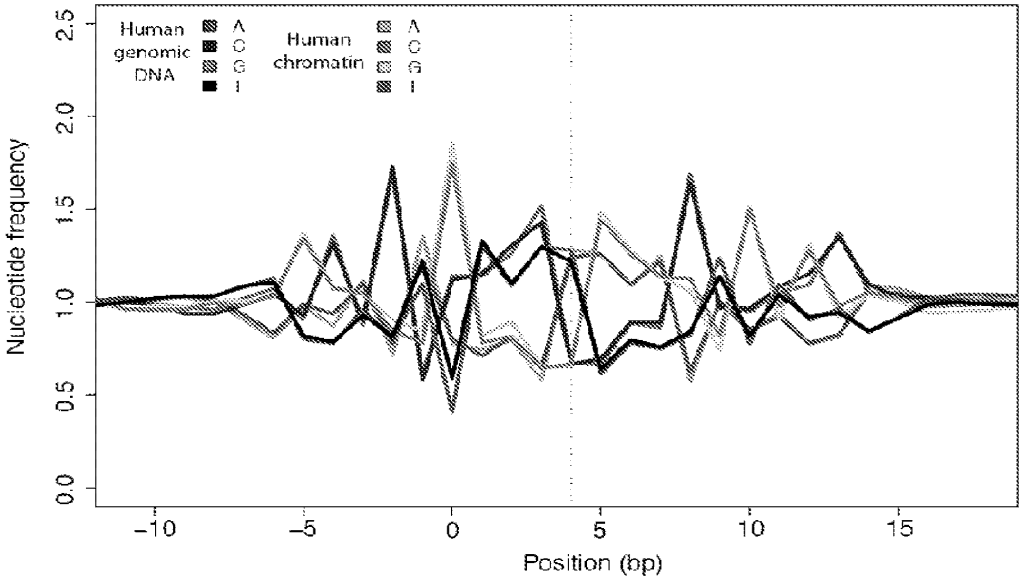


FIG. 8

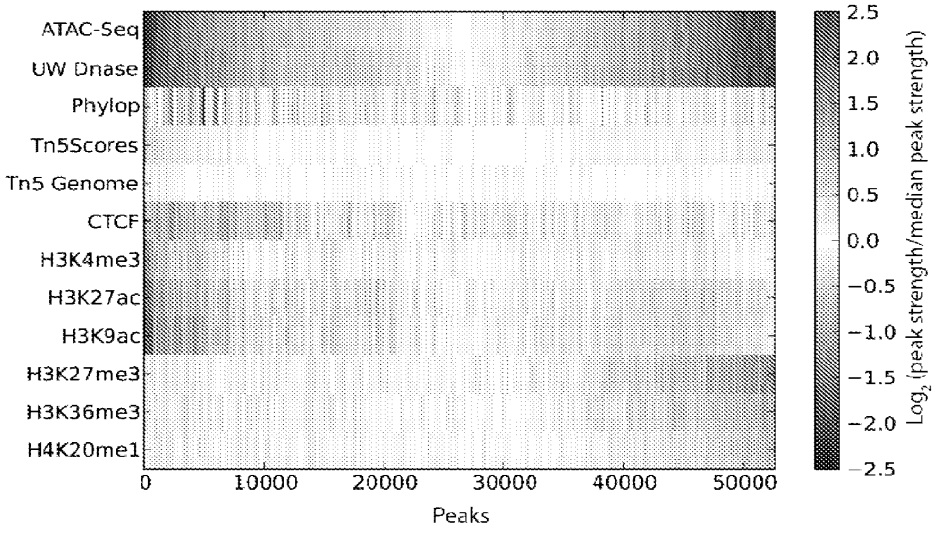


FIG. 9

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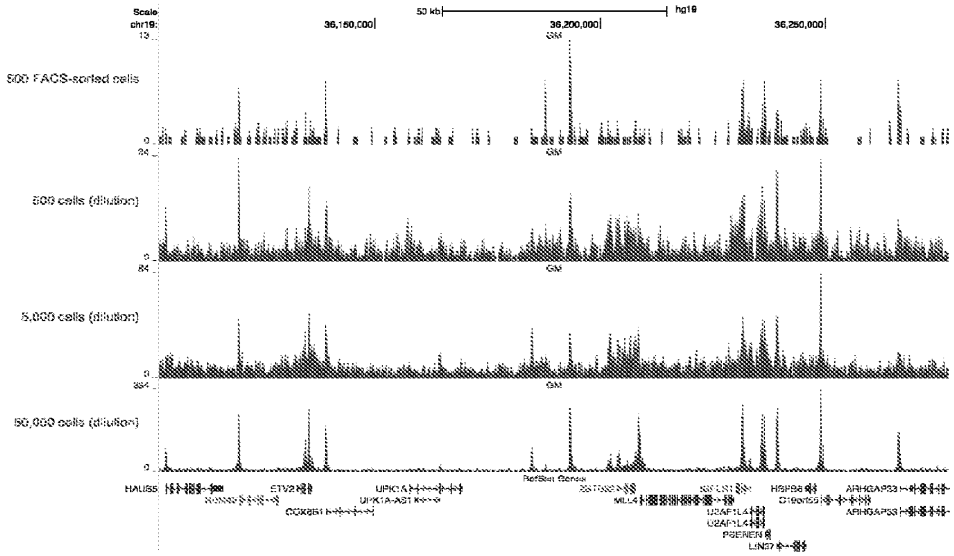


FIG. 10

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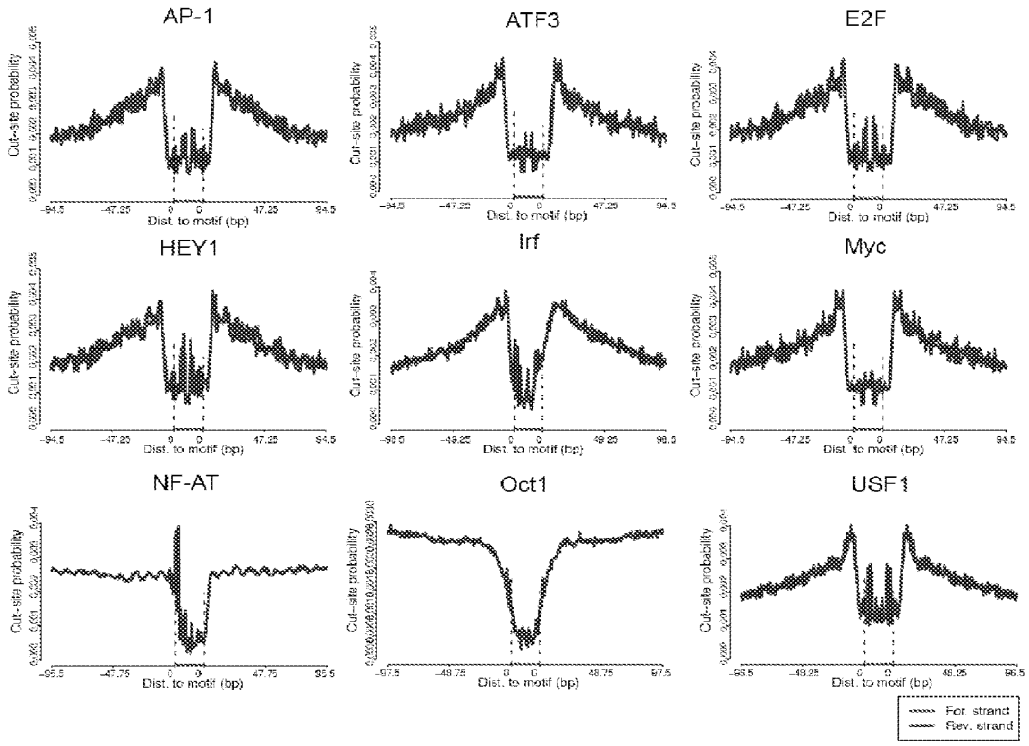


FIG. 11

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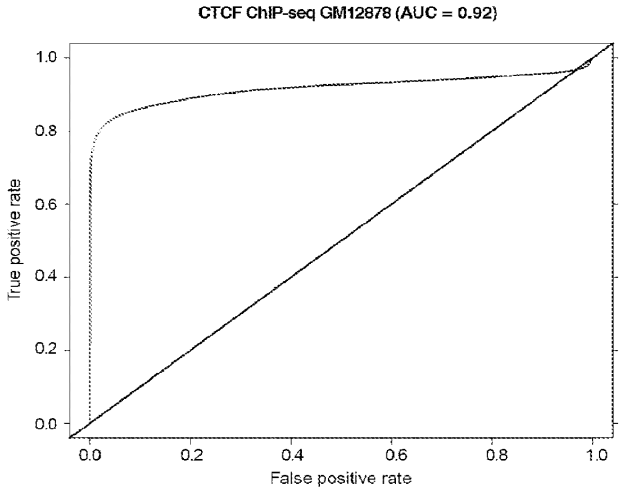


FIG. 12

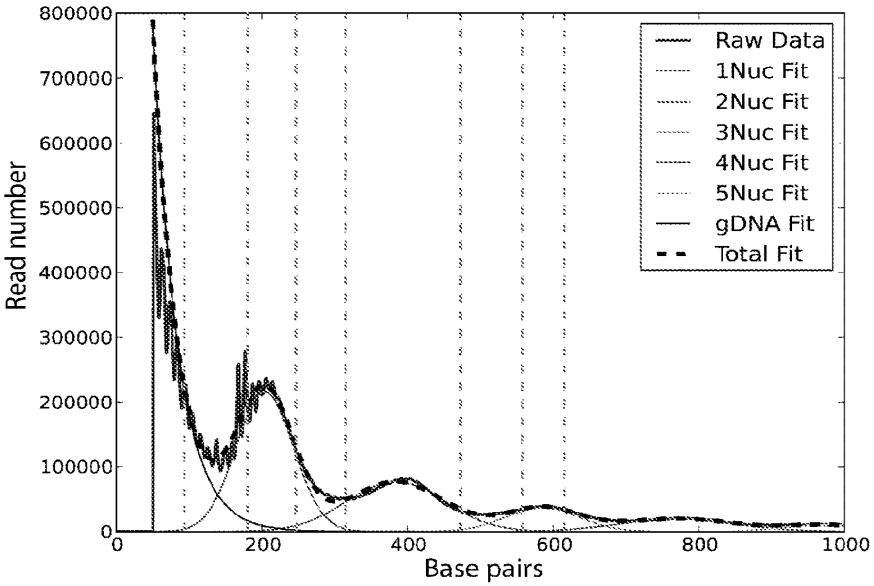


FIG. 13

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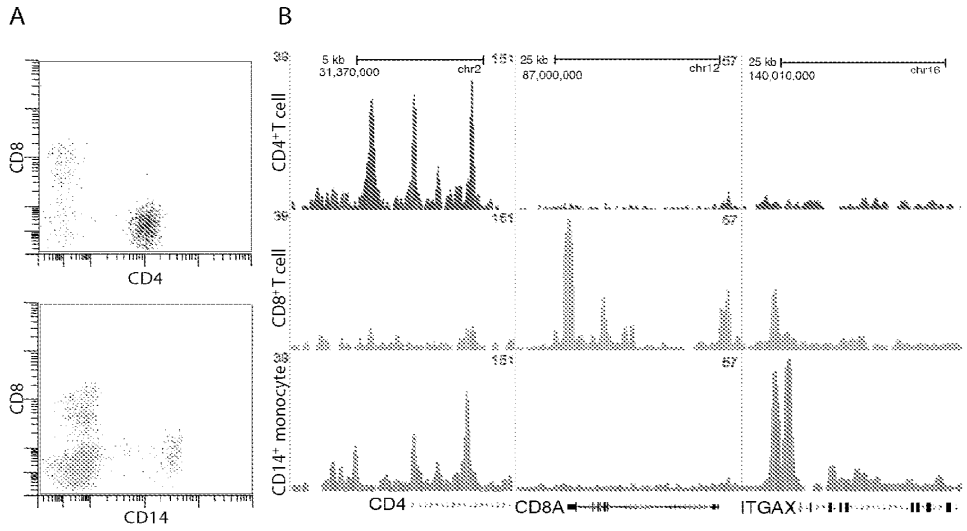


FIG. 14

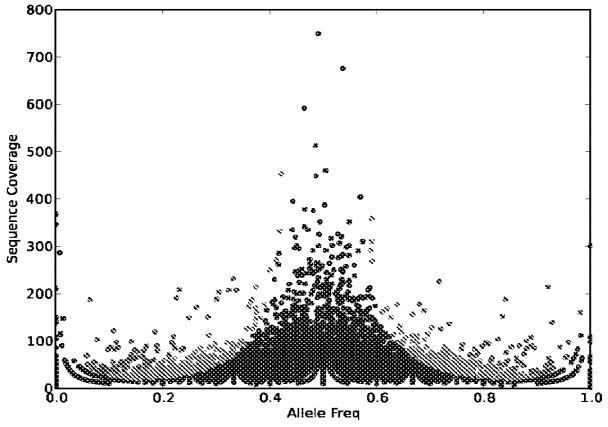


FIG. 15

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Parse Biosciences, Inc. v. 10x Genomics, Inc.
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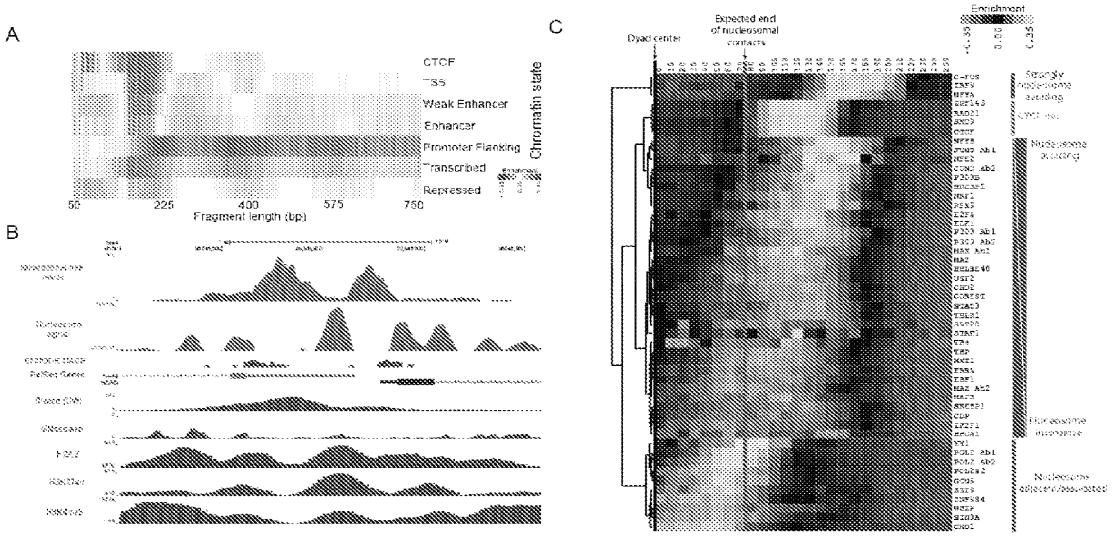


FIG. 16

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WIPO
WORLD
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DOCUMENT MADE AVAILABLE UNDER THE PATENT COOPERATION TREATY (PCT)

International application number:		**PCT/US2014/038825**
International filing date:		**20 May 2014 (20.05.2014)**
Document type:		**Certified copy of priority document**
Document details:	Country/Office:	**US**
	Number:	**61/826,728**
	Filing date:	**23 May 2013 (23.05.2013)**
Date of receipt at the International Bureau:		**16 June 2014 (16.06.2014)**

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a),(b) or (b-*bis*)

34, chemin des Colombettes
1211 Geneva 20, Switzerland
www.wipo.int

PCT REQUEST

Original (for **SUBMISSION**)

0	**For receiving Office use only**	
0-1	International Application No.	PCT/US14/38825
0-2	International Filing Date	20-05-2014 20 MAY 2014
0-3	Name of receiving Office and "PCT International Application"	PCT INTERNATIONAL APPLICATION RO/US

0-4	**Form PCT/RO/101 PCT Request**	
0-4-1	Prepared Using	PCT-SAFE [EASY/EFS-Web mode] Version 3.51.061.237 MT/FOP 20140401/0.20.5.21
0-5	**Petition** The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	**Receiving Office (specified by the applicant)**	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	**Applicant's or agent's file reference**	STAN-1111WO
I	**Title of Invention**	TRANSPOSITION INTO NATIVE CHROMATIN FOR PERSONAL EPIGENOMICS
II	**Applicant**	
II-1	This person is	Applicant only
II-2	Applicant for	All designated States
II-4	Name	THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY
II-5	Address	1705 El Camino Real Palo Alto, California 94306-1106 United States of America
II-6	State of nationality	US
II-7	State of residence	US
III-1	**Applicant and/or inventor**	
III-1-1	This person is	Inventor only
III-1-3	Inventor for	
III-1-4	Name (LAST, First)	GIRESI, Paul
III-1-5	Address	264 Durand Way Palo Alto, California 94304 United States of America

PCT REQUEST

Original (for **SUBMISSION**)

III-2	**Applicant and/or inventor**	
III-2-1	This person is	Inventor only
III-2-3	Inventor for	
III-2-4	Name (LAST, First)	BUENROSTRO, Jason D.
III-2-5	Address	3523 Altamont Way Redwood City, California 94062 United States of America
III-3	**Applicant and/or inventor**	
III-3-1	This person is	Inventor only
III-3-3	Inventor for	
III-3-4	Name (LAST, First)	CHANG, Howard Y.
III-3-5	Address	946 Casanueva Place Stanford, California 94305 United States of America
III-4	**Applicant and/or inventor**	
III-4-1	This person is	Inventor only
III-4-3	Inventor for	
III-4-4	Name (LAST, First)	GREENLEAF, William J.
III-4-5	Address	2372 Branner Drive Menlo Park, California 94025 United States of America
IV-1	**Agent or common representative; or address for correspondence**	
	The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	Agent
IV-1-1	Name (LAST, First)	KEDDIE, James S.
IV-1-2	Address	BOZICEVIC, FIELD & FRANCIS LLP 1900 University Avenue, Suite 200 East Palo Alto, California 94303 United States of America
IV-1-3	Telephone No.	650.327.3400
IV-1-4	Facsimile No.	650.327.3231
IV-1-5	e-mail	docket@bozpat.com
IV-1-5(a)	E-mail authorization The receiving Office, the International Searching Authority, the International Bureau and the International Preliminary Examining Authority are authorized to use this e-mail address, if the Office or Authority so wishes, to send notifications issued in respect of this international application:	exclusively in electronic form (no paper notifications will be sent)
IV-1-6	Agent's registration No.	48,920

PCT REQUEST

Original (for **SUBMISSION**)

V	DESIGNATIONS		
V-1	**The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.**		
VI-1	**Priority claim of earlier national application**		
VI-1-1	Filing date	23 May 2013 (23.05.2013)	
VI-1-2	Number	61/826,728	
VI-1-3	Country	US	
VI-2	**Priority document request**		
	The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1	
VI-3	**Incorporation by reference :**		
	where an element of the international application referred to in Article 11(1)(iii)(d) or (e) or a part of the description, claims or drawings referred to in Rule 20.5(a) is not otherwise contained in this international application but is completely contained in an earlier application whose priority is claimed on the date on which one or more elements referred to in Article 11(1)(iii) were first received by the receiving Office, that element or part is, subject to confirmation under Rule 20.6, incorporated by reference in this international application for the purposes of Rule 20.6.		
VII-1	**International Searching Authority Chosen**	United States Patent and Trademark Office (USPTO) (ISA/US)	
VIII	**Declarations**	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	–	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	–	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	–	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	–	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	–	

PCT REQUEST

Original (for **SUBMISSION**)

IX	Check list	Number of sheets	Electronic file(s) attached
IX-1	Request (including declaration sheets)	4	✓
IX-2	Description	47	–
IX-3	Claims	8	–
IX-4	Abstract	1	✓
IX-5	Drawings	23	–
IX-6a	Sequence listing part of the description (also to be used for the purposes of international search)	–	✓
IX-7	TOTAL	83	
	Accompanying Items	Paper document(s) attached	Electronic file(s) attached
IX-8	Fee calculation sheet	✓	–
IX-20	**Figure of the drawings which should accompany the abstract**	1A	
IX-21	**Language of filing of the international application**	English	
X-1	**Signature of applicant, agent or common representative**	/James S. Keddie, Reg.No. 48,920/	
X-1-1	Name (LAST, First)	KEDDIE, James S.	
X-1-2	Name of signatory		
X-1-3	Capacity (if such capacity is not obvious from reading the request)		

FOR RECEIVING OFFICE USE ONLY

10-1	**Date of actual receipt of the purported international application**	20 MAY 2014 (20.05.14)
10-2	**Drawings:**	
10-2-1	Received	
10-2-2	Not received	
10-3	**Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application**	
10-4	**Date of timely receipt of the required corrections under PCT Article 11(2)**	
10-5	**International Searching Authority**	ISA/US
10-6	**Transmittal of search copy delayed until search fee is paid**	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	**Date of receipt of the record copy by the International Bureau**	

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

KEDDIE, James S.
Bozicevic, Field & Francis LLP
1900 University Avenue, Suite 200
East Palo Alto, California 94303
ÉTATS-UNIS D'AMÉRIQUE

Date of mailing *(day/month/year)*
08 September 2015 (08.09.2015)

Applicant's or agent's file reference
STAN-1111WO

IMPORTANT NOTIFICATION

International application No.
PCT/US2014/038825

International filing date *(day/month/year)*
20 May 2014 (20.05.2014)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address
THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY
1705 El Camino Real
Palo Alto, California 94306-1106
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY
Office of the General Counsel
Building 170, 3rd Floor, Main Quad
P.O. Box 20386
Stanford, CA 94305-2038
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:
☐ Notifications by e-mail authorized

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 89 75

Authorized officer
Wagner Nathalie
e-mail pt05.pct@wipo.int
Telephone No. +41 22 338 74 05

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Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01030
Page 00177

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 November 2014 (27.11.2014)

WIPO | PCT

(10) International Publication Number
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(51) International Patent Classification:
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(21) International Application Number:
PCT/US2014/038825

(22) International Filing Date:
20 May 2014 (20.05.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/826,728 23 May 2013 (23.05.2013) US

(71) Applicant: **THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY** [US/US]; 1705 El Camino Real, Palo Alto, California 94306-1106 (US).

(72) Inventors: **GIRESI, Paul**; 264 Durand Way, Palo Alto, California 94304 (US). **BUENROSTRO, Jason D.**; 3523 Altamont Way, Redwood City, California 94062 (US). **CHANG, Howard Y.**; 946 Casanueva Place, Stanford, California 94305 (US). **GREENLEAF, William J.**; 2372 Branner Drive, Menlo Park, California 94025 (US).

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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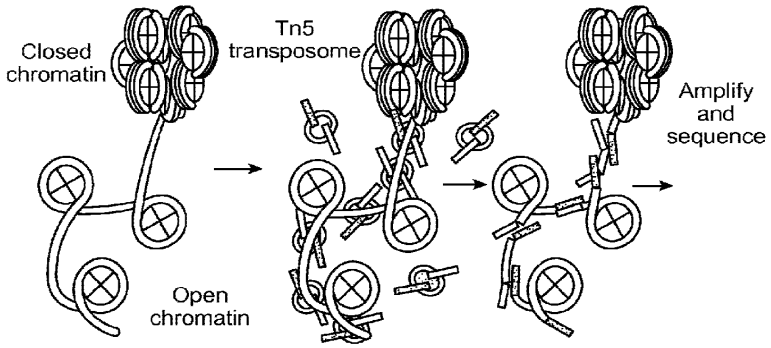


FIG. 1A

(57) Abstract: Provided herein is a method for analyzing polynucleotides such as genomic DNA. In certain embodiments, the method comprises: (a) treating chromatin isolated from a population of cells with an insertional enzyme complex to produce tagged fragments of genomic DNA; (b) sequencing a portion of the tagged fragments to produce a plurality of sequence reads; and (c) making an epigenetic map of a region of the genome of the cells by mapping information obtained from the sequence reads to the region. A kit for performing the method is also provided.

WO 2014/189957 A2

TRANSPOSITION INTO NATIVE CHROMATIN FOR PERSONAL EPIGENOMICS

GOVERNMENT SUPPORT

This invention was made with Government support under contracts AI057229, HG000044, and NS073015 awarded by the National Institutes of Health. The Government has certain rights in the invention.

CROSS-REFERENCING

This application claims the benefit of U.S. Provisional application serial no. 61/826,728, filed on May 23, 2013, which application is incorporated by reference herein in its entirety.

BACKGROUND

Eukaryotic genomes are hierarchically packaged into chromatin, and the nature of this packaging plays a central role in gene regulation. Major insights into the epigenetic information encoded within the nucleoprotein structure of chromatin have come from high-throughput, genome-wide methods for separately assaying the chromatin accessibility ("open chromatin"), nucleosome positioning, and transcription factor (TF) occupancy. While published protocols exist, those methods require millions of cells as starting material, complex and time-consuming sample preparations, and cannot simultaneously probe the interplay of nucleosome positioning, chromatin accessibility, and TF binding. These limitations are problematic in three major ways: First, current methods can average over and "drown out" heterogeneity in cellular populations. Second, cells must often be grown *ex vivo* to obtain sufficient biomaterials, perturbing the *in vivo* context and modulating the epigenetic state in unknown ways. Third, input requirements often prevent application of these assays to well-defined clinical samples, precluding generation of "personal epigenomes" in diagnostic timescales. Provided herein are methods for analyzing polynucleotides, including their accessibility and their structure, that can overcome these limitation(s). Also provided are single-cell methods that can provide higher sensitivity and further information on chromatin accessibility, including cell-to-cell variability, to potentially enable its use as a biomarker.

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SUMMARY

Provided herein is a method for analyzing polynucleotides such as genomic DNA. In certain embodiments, the method comprises: (a) treating chromatin isolated from a population of cells with a transposase and molecular tags to produce tagged fragments of polynucleotides; (b) sequencing a portion of the tagged fragments to produce a plurality of sequence reads; and (c) making an epigenetic map of a region of the genome of the cells by mapping information obtained from the sequence reads to the region.

In some cases, the information is obtained using the nucleotide sequences at the beginning and, optionally, the end of a sequence read. In some cases, the information mapped in (c) is selected from one or more of: (i) cleavage sites for the transposase; (ii) the sizes of the fragments produced in step (a); (iii) sequence read length; (iii) the positions of sequence reads of a defined range in length; and (iv) sequence read abundance. In some instances, the fragments of a defined size range are nucleosome-free fragments.

In some instances, the epigenetic map shows one or more of: (i) a profile of chromatin accessibility along the region; (ii) DNA binding protein occupancy for a binding site in the region; (iii) nucleosome-free DNA in the region; (iv) positioning of nucleosomes along the region; and/or (v) chromatin states. In some cases, the method can further comprise measuring global occupancy of a binding site for the DNA binding protein. The DNA binding protein can, for example, be a transcription factor.

In some cases, the population of cells can be composed of about 500 to 100,000 cells. The cells can be isolated from an individual, such as from the blood of the individual. In some examples, the cells can be of the same cell type. In some examples, the cells can be FACS–selected cells.

In some instances, the treating step (a) can comprise: isolating nuclei from the population of cells; and combining the isolated nuclei with the insertional enzyme complex, wherein the combining results in both lysis of the nuclei to release the chromatin and production of the tagged fragments of genomic DNA. In some examples, the transposase can be derived from Tn5 transposase. In other examples, the transposase can be derived from MuA transposase. In further examples, the transposase can be derived from Vibhar transposase (e.g. from *Vibrio harveyi*).

The present disclosure also provides a method for comparing two samples comprising: (a) analyzing a first population of cells to produce a first epigenetic map; and (b) analyzing a second population of cells to produce a second epigenetic map; and (c) comparing the first epigenetic map to the second epigenetic map. For example, the first

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population of cells and the second population of cells can be collected from the same individual at different times. Alternatively, the first population of cells and the second population of cells can be different populations of cells collected from different individuals.

The present disclosure further provides a diagnostic method, comprising: analyzing chromatin from a patient to produce an epigenetic map; and providing a diagnosis or prognosis based on the epigenetic map.

The present disclosure provides a method for determining accessibility of a polynucleotide at a site, wherein the polynucleotide is from a cell sample, comprising: (a) inserting a plurality of molecular tags with an insertional enzyme into the polynucleotide; and (b) using the molecular tags to determine accessibility at the site. The method can further comprise using the determined accessibility to identify one or more proteins that are bound to the polynucleotide at the site. In some cases, at least one of the proteins is a transcription factor. The method can also comprise using the molecular tags to generate an accessibility map of the polynucleotide.

The present disclosure also provides a method for analyzing the three-dimensional structure of a polynucleotide from a cell sample, comprising: (a) inserting a plurality of molecular tags with an insertional enzyme into the polynucleotide; and (b) using the molecular tags to analyze the three-dimensional structure of the polynucleotide. In some cases, the insertional enzyme can comprise two or more enzymatic moieties wherein each of the enzymatic moieties inserts a common sequence into the polynucleotide. The enzymatic moieties can be linked together. The common sequence can comprise a common barcode. The enzymatic moieties can comprise transposases. The polynucleotide can fragmented into a plurality of fragments during step (a), wherein the fragments comprising the common barcode are determined to be in proximity in the three-dimensional structure of the polynucleotide.

The polynucleotide can be fragmented into a plurality of fragments during the insertion. The method can further comprise amplifying the fragments. The accessibility can be determined by sequencing the fragments and thereby generating a plurality of sequencing reads. The fragments can, for example, be sequenced by a high-throughput sequencing technique. The method can further comprise normalizing the sequencing reads based on the sequence insertion preference of the insertional enzyme. The length of the sequenced reads can also be used to determine a chromatin state annotation.

The cell sample can be permeabilized to allow access for the insertional enzyme. In some cases, the nuclei in the cell sample can be minimally perturbed during the

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permeabilization. The cell sample can be permeabilized using a permeabilization agent including, but not limited to, NP40, digitonin, tween, streptolysin, and/or cationic lipids. The cell sample can also be permeabilized using hypotonic shock and/or ultrasonication.

The method can further comprise analyzing a disease state in a subject based on the accessibility of the specific site, wherein the cell sample is obtained from the subject. The cell sample and/or the polynucleotides can also be divided into a plurality of portions, which may be optionally divided based on the molecular tags. The method can further comprise analyzing a phenotype of the cell sample. In some cases, the phenotype can be correlated to the accessibility of the site.

The insertion can be facilitated by addition of one or more divalent cations. In some cases, the one or more divalent cations can comprise magnesium. In some cases, the one or more divalent cations can comprise manganese.

The cell sample can be obtained from a primary source. The cell sample can consist of less than about 500,000 cells, or even a single cell. The polynucleotide can be bound to a plurality of association molecules. The association molecules can comprise proteins, such as histones. The insertional enzyme can be a transposase. In some cases, the transposase can be derived from a Tn5 transposase. In other cases, the transposase can be derived from a MuA transposase. In further cases, the transposase can be derived from a Vibhar transposase (e.g. from *Vibrio harveyi*). In some cases, the molecular tags can comprise sequencing adaptors, which may further comprise a barcode label. The barcode label can comprise a unique sequence. In other cases, the molecular tags can comprise fluorescence tags. The insertional enzyme can further comprise an affinity tag, which may optionally be an antibody that binds to a transcription factor, a modified nucleosome, and/or a modified nucleic acid. The modified nucleic acid can, for example be a methylated or hydroxymethylated DNA. The affinity tag can also be a single-stranded nucleic acid, which may optionally bind to a target nucleic acid. The insertional enzyme can further comprise a nuclear localization signal.

The present disclosure also provides compositions. The composition can comprise a polynucleotide, an insertional enzyme and an insert element, wherein: the insert element comprises a nucleic acid comprising a predetermined sequence; and the insertional enzyme further comprises an affinity tag. The composition can also comprise a polynucleotide, an insertional enzyme and an insert element, wherein: the insertional enzyme comprises two or more enzymatic moieties; and the enzymatic moieties are linked together. The affinity tag can be an antibody, which may optionally be bound to a transcription factor, a modified nucleosome, and/or a modified nucleic acid. The modified nucleic acid can be, for example,

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a methylated or hydroxymethylated DNA. The affinity tag can also be a single-stranded nucleic acid, which may be optionally bound to a target nucleic acid. The insert element can be bound to the insertional enzyme and the insertional enzyme is bound to the polynucleotide. The polynucleotide can be further bound to a plurality of association molecules. The association molecules can comprise proteins such as, for example, histones.

The present disclosure further provides kits. The kit can comprise: (a) reagents for isolating nuclei from a population of cells; (b) an insertional enzyme complex, and (c) transposase reaction buffer. In some cases, the components of the kit can be configured such that, combining the reaction buffer, transposon tags and adaptors with nuclei *in vitro* results in both lysis of the nuclei to release chromatin and production of tagged fragments of genomic DNA. The kit can also comprise: a cell lysis buffer; an insertional enzyme comprising an affinity tag; and an insert element comprising a nucleic acid, wherein the nucleic acid comprises a predetermined sequence. The kit can further comprise: a cell lysis buffer; an insertional enzyme comprising two or more enzymatic moieties, wherein the enzymatic moieties are linked together; and (c) an insert element. The affinity tag can be an antibody, which can optionally bind to a transcription factor, a modified nucleosome, and/or a modified nucleic acid. The modified nucleic acid can be, for example, a methylated or hydroxymethylated DNA. The affinity can also be a single-stranded nucleic acid, which may be optionally bound to a target nucleic acid.

These and other features of the present teachings are set forth herein.

INCORPORATION BY REFERENCE

All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE FIGURES

The skilled artisan will understand that the drawings, described below, are for illustration purposes only. The drawings are not intended to limit the scope of the present teachings in any way.

FIGS. 1A-1C: ATAC-seq is a sensitive, accurate probe of open chromatin state. **(a)** ATAC-seq reaction schematic. Transposase (green), loaded with sequencing adapters (red

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and blue), inserts only in regions of open chromatin (nucleosomes in grey) and generates sequencing library fragments that can be PCR amplified. (**b**) Approximate reported input material and sample preparation time requirements for genome-wide methods of open chromatin analysis. (**c**) A comparison of ATAC-seq to other open chromatin assays at a locus in GM12878 lymphoblastoid cells displaying high concordance. Lower ATAC-seq track was generated from 500 FACS-sorted cells.

FIGS. 2A-2B: ATAC-seq provides genome-wide information on chromatin compaction. (**a**) ATAC-seq fragment sizes generated from GM12878 nuclei (red) indicate chromatin-dependent periodicity with a spatial frequency consistent with nucleosomes, as well as a high frequency periodicity consistent with the pitch of the DNA helix for fragments less than 200 bp. (Inset) log-transformed histogram shows clear periodicity persists to 6 nucleosomes. (**b**) Normalized read enrichments for 7 classes of chromatin state previously defined.

FIGS. 3A-3E: ATAC-seq provides genome-wide information on nucleosome positioning in regulatory regions. (**a**) An example locus containing two transcription start sites (TSSs) showing nucleosome free read track, calculated nucleosome track (Methods), as well as DNase, MNase, and H3K27ac, H3K4me3, and H2A.Z tracks for comparison. (**b**) ATAC-seq (198 million paired reads) and MNase-seq (4 billion single-end reads from ref 23) nucleosome signal shown for all active TSSs (n=64,836), TSSs are sorted by CAGE expression. (**c**) TSSs are enriched for nucleosome free fragments, and show phased nucleosomes similar to those seen by MNase-seq at the -2, -1, +1, +2, +3 and +4 positions. (**d**) Relative fraction of nucleosome associated vs. nucleosome free (NFR) bases in TSS and distal sites (see Methods). (**e**) Hierarchical clustering of DNA binding factor position with respect to the nearest nucleosome dyad within accessible chromatin reveals distinct classes of DNA binding factors. Factors strongly associated with nucleosomes are enriched for chromatin remodelers.

FIGS 4A-4C: ATAC-seq assays genome-wide factor occupancy. (**a**) CTCF footprints observed in ATAC-seq and DNase-seq data, at a specific locus on chr1. (**b**) Aggregate ATAC-seq footprint for CTCF (motif shown) generated over binding sites within the genome (**c**) CTCF predicted binding probability inferred from ATAC-seq data, position weight matrix (PWM) scores for the CTCF motif, and evolutionary conservation (PhyloP). Right-most column is the CTCF ChIP-seq data (ENCODE) for this GM12878 cell line, demonstrating high concordance with predicted binding probability.

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FIGS. 5A-5D: ATAC-seq enables real-time personal epigenomics. (**a**) Work flow from standard blood draws. (**b**) Serial ATAC-seq data from proband T-cells over three days. (**c**) Example of application of ATAC-seq data (green track) to prioritize candidate TF drug targets. Among identified TF binding sites proximal to cytokine gene *IL2* that can be targeted by FDA-approved drugs, only NFAT is engaged in proband T-cells. ATAC-seq footprint prediction is confirmed by alignment with published NFAT ChIP-seq data (blue track, data from ref [35]). (**d**) Cell type-specific regulatory network from proband T cells compared with GM12878 B-cell line. Each row or column is the footprint profile of a TF versus that of all other TFs in the same cell type. Color indicates relative similarity (yellow) or distinctiveness (blue) in T versus B cells. NFAT is one of the most highly differentially regulated TFs (red box) whereas canonical CTCF binding is essentially similar in T and B cells.

FIG. 6: ATAC-seq peak intensity correlates well with DNase-seq peak intensity. Peaks in Duke DNase-seq (down sampled to 60 x 10^6 reads), UW DNase-seq (40 x 10^6 reads), and ATAC-seq data (60 x 10^6 paired-end reads) were called using ZINBA (Rashid et al Genome Biol. 2011 12: R67). Because each data set has different read lengths we chose to filter for peaks within mappable regions (Duke DNase-seq = 20 bp reads, UW DNase-Seq = 36bp reads and ATAC-Seq = paired-end 50 bp reads). The log10(read intensity) was compared for (A) Duke DNase-seq and ATAC-seq, (B) UW DNase-seq and ATAC-seq, and (C) UW DNAse-seq and Duke DNase-seq. Technical reproducibility of ATAC-seq data is shown in D.

FIG. 7: ATAC-seq captures a large fraction of DNase identified peaks. Peaks were called for all data sets using ZINBA. The venn-diagram shows overlap of the peak calls between each method. Below: The majority of ATAC-seq reads are in intense peaks that intersect with Duke and UW DNase-seq peaks. The total fraction of reads within peaks called from ATAC-seq, UW DNase-seq, and Duke DNase-seq, as well as the intersections of these data are shown. More than 65% of reads from all three methods are found in the intersection of the three methods' peaks, suggesting that strong well-stereotyped peaks are detected by all methods. Table cell color is proportional to fraction of reads.

FIG. 8: Graphs of the number of reads overlapping the set of open chromatin regions identified by Duke DNase, UW DNase and FAIRE in GM12878 cells compared to a set of background regions, wherein to determine the read depth required for detecting open chromatin sites sensitivity and specificity was assessed at varying read depths, including

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50k, 100k, 500k, 10 million and 50 million reads. The bottom graph shows the performance of ATAC-seq in GM12878 cells was assessed using 500, 5,000 or 50,000 cells as starting material.

FIG. 9: Tn5 insertion preferences in genomic DNA and chromatin. Nucleotide frequency scores represent the observed nucleotide frequency of each base, nucleotide frequencies are normalized to 1. The x=0 position represents the read start, and the dotted line represents the symmetry axis of the Tn5 dimer. We see no substantial differences between Tn5 insertion preferences between purified genomic DNA and human chromatin, suggesting that the local insertion preference into chromatin is identical to that found in naked genomic DNA. These reported sequence preferences are similar to those previously reported (main text ref. 11).

FIG. 10: Graph of the average intensity per base of each feature at every ATAC-seq peak; all ENCODE ChIP data was normalized to input; data has been processed using a sliding window of 200 peaks.

FIG. 11: ATAC-seq of various cell numbers. A representative UCSC genome browser track of data from different starting numbers of cells for ATAC-seq. This same locus is also shown in Fig. 1b of the main text. In order: 500 cells were isolated using FACS and two replicates of 500 cells and 5,000 cells were done by a simple dilution from cell culture. For comparison, the bottom track represents 50,000 cells, also show in Fig. 1b. This figure demonstrates that we are able to capture open chromatin sites from as few as 500 cells.

FIG. 12: Fitting nucleosome peaks in ATAC-seq fragment size distribution to enable nucleosome occupancy measurements. The observed fragment distribution was partitioned into four populations of reads – reads expected to originate from open DNA, and reads that span 1, 2 or 3 putative nucleosomes. To enable this partitioning of the data, the ATAC-seq fragment distribution was fit to the sum of 1) an exponential function for fragment distribution pattern at insert sizes below one nucleosome, and 2) 5 Gaussians to the distributions arising from protection from one, two, three, four and five nucleosomes. The sum of these fits is shown (black dotted line) is similar to the observed fragment distribution (blue line). Vertical dotted lines are boundaries for identification of fragments as originating from the nucleosome-free (<100bps), 1-nucleosome, 2-nucleosome and 3-nucleosome regions. Dotted lines were set to ensure that <10% of fragments originate from neighboring, as defined by our fit.

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FIG. 13: Select set of transcription factor footprints detected by ATAC-seq in GM12878 cells. For the indicated transcription factors the aggregate signal of ATAC-seq reads were computed using CENTIPEDE on the genome-wide sets of sites matching the corresponding motif. Reads were calculated in the region +/-100 bp of the motif boundary. The vertical dashed lines indicate the boundaries of the motifs.

FIG. 14: Prediction of CTCF binding sites using ATAC-seq and DNase footprinting with CENTIPEDE. Prediction of CTCF binding sites was assessed using the genome-wide set of CTCF motifs sorted by the posterior probability reported by CENTIPEDE. Those overlapping CTCF ChIP-seq peaks were used as the positive set and all others were considered as the negative set. This yielded an area under the curve (AUC) of 0.92, which suggests specific and sensitive binding inference for CTCF. Duke DNase and UW DNase data were used with the same settings of CENTIPEDE, and ROC plots are shown. ATAC-seq data consisted of 198 x 10^6 paired reads, Duke DNase-comprised 245 x 10^6 reads, and UW DNase comprised 48 x 10^6 reads.

FIG. 15: T-cell specific NFAT regulation: Examples of T-cell-specific NFAT target genes predicted by ATAC-seq and confirmed by alignment with NFAT ChIP-seq (data from main text ref 35).

FIG. 16: ATAC-seq of FACS-purified cell populations from human blood. (A) From a standard blood draw, we used Fluorescence-Activated Cell Sorting (FACS) to purify CD4+ T-cells, CD8+ T-cells, and CD14+ monocytes. Each population generated successful ATAC-seq data (B) and revealed cell-type specific open chromatin sites at known lineage-specific genes.

FIG. 17: Detection of allele specific open chromatin in GM12878 cells with ATAC-seq. Using publicly available variant data, we measured the allele frequency in open chromatin regions at putative heterozygous loci. Because of potential for spurious heterozygous sites, we required more than two reads to validate the heterozygosity of the allele. Red points (n=167) are candidate allele specific open chromatin sites at $p<10^{-5}$, while grey (n=900) represent candidates at $p<0.01$. P-values were calculated using a Bayesian model developed by Audic et al (Genome Research 1997 7, 986–995).

FIG. 18: Transposases can serve as an open-chromatin stain. By loading Tn5 transposes with fluorescently labeled DNA adapters, transposition events, shown in green, are primarily localized to the nucleus, and exhibit a punctate pattern consistent with higher order organization.

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FIG. 19: Single-cell ATAC-seq data from a single nucleus (blue) show clear peak at the expected positions of open-chromatin genome wide compared to 50,000 cells.

FIG. 20: Single cell insert length distribution matches that from 50,000 cells showing periodicity due to the presence of nucleosomes.

DEFINITIONS

Unless defined otherwise herein, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described.

All patents and publications, including all sequences disclosed within such patents and publications, referred to herein are expressly incorporated by reference.

Numeric ranges are inclusive of the numbers defining the range. Unless otherwise indicated, nucleic acids are written left to right in 5' to 3' orientation; amino acid sequences are written left to right in amino to carboxy orientation, respectively.

The headings provided herein are not limitations of the various aspects or embodiments of the invention. Accordingly, the terms defined immediately below are more fully defined by reference to the specification as a whole.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Singleton, et al., DICTIONARY OF MICROBIOLOGY AND MOLECULAR BIOLOGY, 2D ED., John Wiley and Sons, New York (1994), and Hale & Markham, THE HARPER COLLINS DICTIONARY OF BIOLOGY, Harper Perennial, N.Y. (1991) provide one of skill with the general meaning of many of the terms used herein. Still, certain terms are defined below for the sake of clarity and ease of reference.

The term "sample" as used herein relates to a material or mixture of materials, typically containing one or more analytes of interest. In one embodiment, the term as used in its broadest sense, refers to any plant, animal or viral material containing DNA or RNA, such as, for example, tissue or fluid isolated from an individual (including without limitation plasma, serum, cerebrospinal fluid, lymph, tears, saliva and tissue sections) or from in vitro cell culture constituents, as well as samples from the environment.

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The term "nucleic acid sample," as used herein, denotes a sample containing nucleic acids. Nucleic acid samples used herein may be complex in that they contain multiple different molecules that contain sequences. Genomic DNA samples from a mammal (e.g., mouse or human) are types of complex samples. Complex samples may have more than about 10^4, 10^5, 10^6 or 10^7, 10^8, 10^9 or 10^{10} different nucleic acid molecules. A DNA target may originate from any source such as genomic DNA, or an artificial DNA construct. Any sample containing nucleic acid, e.g., genomic DNA from tissue culture cells or a sample of tissue, may be employed herein.

The term "mixture," as used herein, refers to a combination of elements, that are interspersed and not in any particular order. A mixture is heterogeneous and not spatially separable into its different constituents. Examples of mixtures of elements include a number of different elements that are dissolved in the same aqueous solution and a number of different elements attached to a solid support at random positions (i.e., in no particular order). A mixture is not addressable. To illustrate by example, an array of spatially separated surface-bound polynucleotides, as is commonly known in the art, is not a mixture of surface-bound polynucleotides because the species of surface-bound polynucleotides are spatially distinct and the array is addressable.

The term "nucleotide" is intended to include those moieties that contain not only the known purine and pyrimidine bases, but also other heterocyclic bases that have been modified. Such modifications include methylated purines or pyrimidines, acylated purines or pyrimidines, alkylated riboses or other heterocycles. In addition, the term "nucleotide" includes those moieties that contain hapten or fluorescent labels and may contain not only conventional ribose and deoxyribose sugars, but other sugars as well. Modified nucleosides or nucleotides also include modifications on the sugar moiety, e.g., wherein one or more of the hydroxyl groups are replaced with halogen atoms or aliphatic groups, or are functionalized as ethers, amines, or the like.

The term "nucleic acid" and "polynucleotide" are used interchangeably herein to describe a polymer of any length, e.g., greater than about 2 bases, greater than about 10 bases, greater than about 100 bases, greater than about 500 bases, greater than 1000 bases, greater than 10,000 bases, greater than 100,000 bases, greater than about 1,000,000, up to about 10^{10} or more bases composed of nucleotides, e.g., deoxyribonucleotides or ribonucleotides, and may be produced enzymatically or synthetically (e.g., PNA as described in U.S. Patent No. 5,948,902 and the references cited therein) which can hybridize with naturally occurring nucleic acids in a sequence specific manner analogous to that of two

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naturally occurring nucleic acids, e.g., can participate in Watson-Crick base pairing interactions. Naturally-occurring nucleotides include guanine, cytosine, adenine, thymine, uracil (G, C, A, T and U respectively). DNA and RNA have a deoxyribose and ribose sugar backbone, respectively, whereas PNA's backbone is composed of repeating N-(2-aminoethyl)-glycine units linked by peptide bonds. In PNA various purine and pyrimidine bases are linked to the backbone by methylenecarbonyl bonds. A locked nucleic acid (LNA), often referred to as inaccessible RNA, is a modified RNA nucleotide. The ribose moiety of an LNA nucleotide is modified with an extra bridge connecting the 2' oxygen and 4' carbon. The bridge "locks" the ribose in the 3'-endo (North) conformation, which is often found in the A-form duplexes. LNA nucleotides can be mixed with DNA or RNA residues in the oligonucleotide whenever desired. The term "unstructured nucleic acid," or "UNA," is a nucleic acid containing non-natural nucleotides that bind to each other with reduced stability. For example, an unstructured nucleic acid may contain a G' residue and a C' residue, where these residues correspond to non-naturally occurring forms, i.e., analogs, of G and C that base pair with each other with reduced stability, but retain an ability to base pair with naturally occurring C and G residues, respectively. Unstructured nucleic acid is described in US20050233340, which is incorporated by reference herein for disclosure of UNA.

The term "oligonucleotide" as used herein denotes a single-stranded multimer of nucleotide of from about 2 to 200 nucleotides, up to 500 nucleotides in length. Oligonucleotides may be synthetic or may be made enzymatically, and, in some embodiments, are 30 to 150 nucleotides in length. Oligonucleotides may contain ribonucleotide monomers (i.e., may be oligoribonucleotides) or deoxyribonucleotide monomers, or both ribonucleotide monomers and deoxyribonucleotide monomers. An oligonucleotide may be 10 to 20, 21 to 30, 31 to 40, 41 to 50, 51 to 60, 61 to 70, 71 to 80, 80 to 100, 100 to 150 or 150 to 200 nucleotides in length, for example.

"Primer" means an oligonucleotide, either natural or synthetic, that is capable, upon forming a duplex with a polynucleotide template, of acting as a point of initiation of nucleic acid synthesis and being extended from its 3' end along the template so that an extended duplex is formed. The sequence of nucleotides added during the extension process is determined by the sequence of the template polynucleotide. Usually primers are extended by a DNA polymerase. Primers are generally of a length compatible with their use in synthesis of primer extension products, and are usually in the range of between 8 to 100 nucleotides in length, such as 10 to 75, 15 to 60, 15 to 40, 18 to 30, 20 to 40, 21 to 50, 22 to 45, 25 to 40, and so on. Typical primers can be in the range of between 10-50 nucleotides long, such as

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15-45, 18-40, 20-30, 21-25 and so on, and any length between the stated ranges. In some embodiments, the primers are usually not more than about 10, 12, 15, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, or 70 nucleotides in length.

Primers are usually single-stranded for maximum efficiency in amplification, but may alternatively be double-stranded. If double-stranded, the primer is usually first treated to separate its strands before being used to prepare extension products. This denaturation step is typically effected by heat, but may alternatively be carried out using alkali, followed by neutralization. Thus, a "primer" is complementary to a template, and complexes by hydrogen bonding or hybridization with the template to give a primer/template complex for initiation of synthesis by a polymerase, which is extended by the addition of covalently bonded bases linked at its 3' end complementary to the template in the process of DNA synthesis.

The term "hybridization" or "hybridizes" refers to a process in which a region of nucleic acid strand anneals to and forms a stable duplex, either a homoduplex or a heteroduplex, under normal hybridization conditions with a second complementary nucleic acid strand, and does not form a stable duplex with unrelated nucleic acid molecules under the same normal hybridization conditions. The formation of a duplex is accomplished by annealing two complementary nucleic acid strand region in a hybridization reaction. The hybridization reaction can be made to be highly specific by adjustment of the hybridization conditions (often referred to as hybridization stringency) under which the hybridization reaction takes place, such that two nucleic acid strands will not form a stable duplex, e.g., a duplex that retains a region of double-strandedness under normal stringency conditions, unless the two nucleic acid strands contain a certain number of nucleotides in specific sequences which are substantially or completely complementary. "Normal hybridization or normal stringency conditions" are readily determined for any given hybridization reaction. See, for example, Ausubel et al., Current Protocols in Molecular Biology, John Wiley & Sons, Inc., New York, or Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press. As used herein, the term "hybridizing" or "hybridization" refers to any process by which a strand of nucleic acid binds with a complementary strand through base pairing.

A nucleic acid is considered to be "selectively hybridizable" to a reference nucleic acid sequence if the two sequences specifically hybridize to one another under moderate to high stringency hybridization and wash conditions. Moderate and high stringency hybridization conditions are known (see, e.g., Ausubel, et al., Short Protocols in Molecular Biology, 3rd ed., Wiley & Sons 1995 and Sambrook et al., Molecular Cloning: A

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Laboratory Manual, Third Edition, 2001 Cold Spring Harbor, N.Y.). One example of high stringency conditions include hybridization at about 42 °C in 50% formamide, 5X SSC, 5X Denhardt's solution, 0.5% SDS and 100 μg/ml denatured carrier DNA followed by washing two times in 2X SSC and 0.5% SDS at room temperature and two additional times in 0.1 X SSC and 0.5% SDS at 42 °C.

The term "duplex," or "duplexed," as used herein, describes two complementary polynucleotide region that are base-paired, i.e., hybridized together.

The term "amplifying" as used herein refers to the process of synthesizing nucleic acid molecules that are complementary to one or both strands of a template nucleic acid. Amplifying a nucleic acid molecule may include denaturing the template nucleic acid, annealing primers to the template nucleic acid at a temperature that is below the melting temperatures of the primers, and enzymatically elongating from the primers to generate an amplification product. The denaturing, annealing and elongating steps each can be performed one or more times. In certain cases, the denaturing, annealing and elongating steps are performed multiple times such that the amount of amplification product is increasing, often times exponentially, although exponential amplification is not required by the present methods. Amplification typically requires the presence of deoxyribonucleoside triphosphates, a DNA polymerase enzyme and an appropriate buffer and/or co-factors for optimal activity of the polymerase enzyme. The term "amplification product" refers to the nucleic acids, which are produced from the amplifying process as defined herein.

The terms "determining," "measuring," "evaluating," "assessing," "assaying," and "analyzing" are used interchangeably herein to refer to any form of measurement, and include determining if an element is present or not. These terms include both quantitative and/or qualitative determinations. Assessing may be relative or absolute. "Assessing the presence of" includes determining the amount of something present, as well as determining whether it is present or absent.

The term "using" has its conventional meaning, and, as such, means employing, e.g., putting into service, a method or composition to attain an end. For example, if a program is used to create a file, a program is executed to make a file, the file usually being the output of the program. In another example, if a computer file is used, it is usually accessed, read, and the information stored in the file employed to attain an end. Similarly if a unique identifier, e.g., a barcode is used, the unique identifier is usually read to identify, for example, an object or file associated with the unique identifier.

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The term "ligating," as used herein, refers to the enzymatically catalyzed joining of the terminal nucleotide at the 5' end of a first DNA molecule to the terminal nucleotide at the 3' end of a second DNA molecule.

A "plurality" contains at least 2 members. In certain cases, a plurality may have at least 2, at least 5, at least 10, at least 100, at least 100, at least 10,000, at least 100,000, at least 10^6, at least 10^7, at least 10^8 or at least 10^9 or more members.

If two nucleic acids are "complementary," they hybridize with one another under high stringency conditions. The term "perfectly complementary" is used to describe a duplex in which each base of one of the nucleic acids base pairs with a complementary nucleotide in the other nucleic acid. In many cases, two sequences that are complementary have at least 10, e.g., at least 12 or 15 nucleotides of complementarity.

An "oligonucleotide binding site" refers to a site to which an oligonucleotide hybridizes in a target polynucleotide. If an oligonucleotide "provides" a binding site for a primer, then the primer may hybridize to that oligonucleotide or its complement.

The term "strand" as used herein refers to a nucleic acid made up of nucleotides covalently linked together by covalent bonds, e.g., phosphodiester bonds. In a cell, DNA usually exists in a double-stranded form, and as such, has two complementary strands of nucleic acid referred to herein as the "top" and "bottom" strands. In certain cases, complementary strands of a chromosomal region may be referred to as "plus" and "minus" strands, the "first" and "second" strands, the "coding" and "noncoding" strands, the "Watson" and "Crick" strands or the "sense" and "antisense" strands. The assignment of a strand as being a top or bottom strand is arbitrary and does not imply any particular orientation, function or structure. The nucleotide sequences of the first strand of several exemplary mammalian chromosomal regions (e.g., BACs, assemblies, chromosomes, etc.) is known, and may be found in NCBI's Genbank database, for example.

The term "top strand," as used herein, refers to either strand of a nucleic acid but not both strands of a nucleic acid. When an oligonucleotide or a primer binds or anneals "only to a top strand," it binds to only one strand but not the other. The term "bottom strand," as used herein, refers to the strand that is complementary to the "top strand." When an oligonucleotide binds or anneals "only to one strand," it binds to only one strand, e.g., the first or second strand, but not the other strand.

The term "sequencing," as used herein, refers to a method by which the identity of at least 10 consecutive nucleotides (e.g., the identity of at least 20, at least 50, at least 100 or at least 200 or more consecutive nucleotides) of a polynucleotide is obtained.

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The terms "next-generation sequencing" or "high-throughput sequencing" refer to the so-called parallelized sequencing-by-synthesis or sequencing-by-ligation platforms currently employed by Illumina, Life Technologies, and Roche, etc. Next-generation sequencing methods may also include nanopore sequencing methods or electronic-detection based methods such as Ion Torrent technology commercialized by Life Technologies or single-molecule fluorescence-based method commercialized by Pacific Biosciences.

The term "barcode sequence" or "molecular barcode," as used herein, refers to a unique sequence of nucleotides used to a) identify and/or track the source of a polynucleotide in a reaction and/or b) count how many times an initial molecule is sequenced (e.g., in cases where substantially every molecule in a sample is tagged with a different sequence, and then the sample is amplified). A barcode sequence may be at the 5′-end, the 3'-end or in the middle of an oligonucleotide. Barcode sequences may vary widely in size and composition; the following references provide guidance for selecting sets of barcode sequences appropriate for particular embodiments: Brenner, U.S. Pat. No. 5,635,400; Brenner et al, Proc. Natl. Acad. Sci., 97: 1665-1670 (2000); Shoemaker et al, Nature Genetics, 14: 450-456 (1996); Morris et al, European patent publication 0799897A1; Wallace, U.S. Pat. No. 5,981,179; and the like. In particular embodiments, a barcode sequence may have a length in range of from 4 to 36 nucleotides, or from 6 to 30 nucleotides, or from 8 to 20 nucleotides.

The term "in vitro" refers to a reaction that occurs in a vessel with isolated components, not in cells.

The term "distributed" in the context of cleavage sites that are distributed along the length of a target nucleic acid molecule, refers to insertions that are spaced from another along the length of the target nucleic acid molecule. There is no requirement that all of the insertions are spaced by the same amount. Rather, spacing between insertions may be random, semi-random, or not random.

The term "chromatin," as used herein, refers to a complex of molecules including proteins and polynucleotides (e.g. DNA, RNA), as found in a nucleus of a eukaryotic cell. Chromatin is composed in part of histone proteins that form nucleosomes, genomic DNA, and other DNA binding proteins (e.g., transcription factors) that are generally bound to the genomic DNA.

The term "treating," as used herein, refers to combining under conditions (e.g., a suitable temperature, time and conditions) that result in a reaction, e.g., cleavage.

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The term "chromatin isolated from a population of cells," as used herein, refers to a source of chromatin that is caused to be made available. Isolated nuclei (which can be lysed to produce chromatin) as well as isolated chromatin (i.e., the product of lysed nuclei) are both considered types of chromatin isolated from a population of cells.

The term "transcription factor", as used herein, refers to any polypeptide that may act by itself or in combination with at least one other polypeptide to regulate gene expression levels. The term includes, but is not limited to, polypeptides that directly bind DNA sequences. Transcription factors can either increases or suppress expression levels. Examples of transcription factors include, but are not limited to Myc/Max, AP-1 (Jun, Fos, ATF), CREB, SMAD, HIF, ETS, ERG, ELK, STAT, estrogen receptor (ER), androgen receptor (AR), glucocorticoid receptor (GR), progesterone receptor (PR), NFκB, p53, OCT, SOX and PAX. The transcription factor may be a transcription factor identified by sequence analysis or a naturally-occurring reading frame sequence that has not been previously characterized as a transcription factor. The polypeptide may also be an artificially generated or chemically or enzymatically modified polypeptide.

The term "insertional enzyme complex," as used herein, refers to a complex comprising an insertional enzyme and two adaptor molecules (the "transposon tags") that are combined with polynucleotides to fragment and add adaptors to the polynucleotides. Such a system is described in a variety of publications, including Caruccio (Methods Mol. Biol. 2011 733: 241-55) and US20100120098, which are incorporated by reference herein.

The term "tagged fragments," as used herein, refers to polynucleotide fragments that are attached to tags.

The term "region," as used herein, refers to a contiguous length of nucleotides in a genome of an organism. A chromosomal region may be in the range of 1 bp to the length of an entire chromosome. In some instances, a region may have a length of at least 200 bp, at least 500 bp, at least 1 kb, at least 10 kb or at least 100 kb or more (e.g., up to 1 Mb or 10 Mb or more). The genome may be from any eukaryotic organism, e.g., an animal or plant genome such as the genome of a human, monkey, rat, fish or insect.

The term "epigenetic map," as used herein, refers to any representation of epigenetic features, e.g., sites of nucleosomes, nucleosome-free regions, binding sites for transcription factors, etc. A map can be physically displayed, e.g., on a computer monitor. Exemplary epigenetic maps are shown in Fig. 1C, 3A, 4A, 4B, 5B and 5C.

The term "mapping information," as used herein, refers to assembling experimentally-obtained information about an area to a physical map of the area.

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The term "sequence read abundance," as used herein, refers to the number of times a particular sequence or nucleotide is observed in a collection of sequence reads.

The term "nucleosome-free fragments," as used herein, refers to fragments of genomic DNA that are relatively depleted or devoid of nucleosomes, i.e., between nucleosomes.

The term "chromatin accessibility," as used herein, refers to how accessible a nucleic acid site is within a polynucleotide, such as in genomic DNA, i.e., how "open" the chromatin is. A nucleic acid site associated with a polypeptide, such as with genomic DNA in nucleosomes, is usually inaccessible. A nucleic acid site not complexed with a polypeptide is generally accessible, such as with genomic DNA between nucleosomes (with the exception of nucleic acid sites complexed with transcription factors and other DNA binding proteins).

The term "DNA binding protein occupancy," as used herein, refers to whether a binding site for a sequence specific DNA binding protein (e.g., a binding site for a transcription factor) is occupied by the DNA binding protein. DNA binding protein occupancy can be measured quantitatively or qualitatively.

The term "global occupancy," as used herein, refers to whether a plurality of different binding sites for a DNA binding protein that are distributed throughout the genome (e.g., a binding sites for a transcription factor) are bound by the DNA binding protein . DNA binding protein occupancy can be measured quantitatively or qualitatively.

The term "diagnosis," as used herein, refers to a determination of whether a subject has a particular disease or condition.

The term "prognosis," as used herein, refers to prediction of a clinical outcome, e.g., disease recurrence, recovery from a disease, death, as well as a prediction of how a subject that has a particular disease or condition will respond to a particular treatment.

Other definitions of terms may appear throughout the specification.

DESCRIPTION OF EXEMPLARY EMBODIMENTS

In one aspect, a method for analyzing chromatin is provided. In certain embodiments, the method comprises: (a) treating chromatin isolated from a population of cells with an insertional enzyme complex to produce tagged fragments of genomic DNA. In this step, the chromatin is tagmented (i.e., cleaved and tagged in the same reaction) using an insertional enzyme such as Tn5 or MuA that cleaves the genomic DNA in open regions in the chromatin and adds adaptors to both ends of the fragments. Methods for tagmenting isolated genomic DNA are known in the art (see, e.g., Caruccio Methods Mol. Biol. 2011 733: 241-

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55; Kaper et al, Proc. Natl. Acad. Sci. 2013 110: 5552-7; Marine et al, Appl. Environ. Microbiol. 2011 77: 8071-9 and US20100120098) and are commercially available from Illumina (San Diego, CA) and other vendors. Such systems may be readily adapted for use herein. In some cases, the conditions may be adjusted to obtain a desirable level of insertion in the chromatin (e.g., an insertion that occurs, on average, every 50 to 200 base pairs in open regions). The chromatin used in the method may be made by any suitable method. In some embodiments, nuclei may be isolated, lysed, and the chromatin may be further purified, e.g., from the nuclear envelope. In other embodiments, the chromatin may be isolated by contacting isolated nuclei with the reaction buffer. In these embodiments, the isolated nuclei may lyse when it makes contact with the reaction buffer (which comprises insertional enzyme complexes and other necessary reagents), which allows the insertional enzyme complexes access to the chromatin. In these embodiments, the method may comprise isolating nuclei from a population of cells; and combining the isolated nuclei with the transposase and adaptors, wherein the combining results in both lysis of the nuclei to release said chromatin and production of the adaptor-tagged fragments of genomic DNA. The chromatin does not require cross-linking as in other methods (e.g., ChIP-SEQ methods).

After the chromatin has been fragmented and tagged to produce tagged fragments of genomic DNA, at least some of the adaptor tagged fragments are sequenced to produce a plurality of sequence reads. The fragments may be sequenced using any convenient method. For example, the fragments may be sequenced using Illumina's reversible terminator method, Roche's pyrosequencing method (454), Life Technologies' sequencing by ligation (the SOLiD platform) or Life Technologies' Ion Torrent platform. Examples of such methods are described in the following references: Margulies et al (Nature 2005 437: 376–80); Ronaghi et al (Analytical Biochemistry 1996 242: 84–9); Shendure et al (Science 2005 309: 1728-32); Imelfort et al (Brief Bioinform. 2009 10:609-18); Fox et al (Methods Mol Biol. 2009;553:79-108); Appleby et al (Methods Mol Biol. 2009;513:19-39) and Morozova et al (Genomics. 2008 92:255-64), which are incorporated by reference for the general descriptions of the methods and the particular steps of the methods, including all starting products, methods for library preparation, reagents, and final products for each of the steps. As would be apparent, forward and reverse sequencing primer sites that are compatible with a selected next generation sequencing platform can be added to the ends of the fragments during the amplification step. In certain embodiments, the fragments may be amplified using PCR primers that hybridize to the tags that have been added to the fragments, where the primer used for PCR have 5' tails that are compatible with a particular sequencing platform.

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In certain cases, the primers used may contain a molecular barcode (an "index") so that different pools can be pooled together before sequencing, and the sequence reads can be traced to a particular sample using the barcode sequence.

In another aspect, the present disclosure provides a method for determining accessibility of a polynucleotide at a site, wherein the polynucleotide is from a cell sample, said method comprising: inserting a plurality of molecular tags with an insertional enzyme into the polynucleotide and using the molecular tags to determine accessibility at the site. The cell sample can be from a primary source. The cell sample may consist of a single cell. The cell sample may consist of a finite number of cells (e.g. less than about 500,000 cells).

The method can further comprise using the determined accessibility to identify one or more proteins that are bound to the polynucleotide at the site. In some instances, at least one of the proteins is a transcription factor. Additionally, the method can comprise using the molecular tags to generate an accessibility map of the polynucleotide.

The polynucleotide may be fragmented into a plurality of fragments during the insertion of the molecular tags. In some cases, the fragments may be amplified. In some cases, the fragments can be sequenced to generate a plurality of sequencing reads. This may be used to determine the accessibility of the polynucleotide at any given site. The fragments may be sequenced using a high-throughput sequencing technique. In some cases, the sequencing reads can be normalized based on the sequence insertion preference of the insertional enzyme. The length of the sequenced reads can be used to determine a chromatin state annotation.

The polynucleotide can be bound to a plurality of association molecules. The association molecules can be, for example, proteins, nucleic acids or saccharides. In some cases, the association molecules can comprise histones. In other cases, the association molecules can comprise aptamers.

The insertional enzyme can be any enzyme capable of inserting a nucleic acid sequence into a polynucleotide. In some cases, the insertional enzyme can insert the nucleic acid sequence into the polynucleotide in a substantially sequence-independent manner. The insertional enzyme can be prokaryotic or eukaryotic. Examples of insertional enzymes include, but are not limited to, transposases, HERMES, and HIV integrase. The transposase can be a Tn transposase (e.g. Tn3, Tn5, Tn7, Tn10, Tn552, Tn903), a MuA transposase, a Vibhar transposase (e.g. from *Vibrio harveyi*), Ac-Ds, Ascot-1, Bs1, Cin4, Copia, En/Spm, F element, hobo, Hsmar1, Hsmar2, IN (HIV), IS1, IS2, IS3, IS4, IS5, IS6, IS10, IS21, IS30, IS50, IS51, IS150, IS256, IS407, IS427, IS630, IS903, IS911, IS982, IS1031, ISL2, L1,

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Mariner, P element, Tam3, Tc1, Tc3, Tel, THE-1, Tn/O, TnA, Tn3, Tn5, Tn7, Tn10, Tn552, Tn903, Tol1, Tol2, TnlO, Tyl, any prokaryotic transposase, or any transposase related to and/or derived from those listed above. In certain instances, a transposase related to and/or derived from a parent transposase can comprise a peptide fragment with at least about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% amino acid sequence homology to a corresponding peptide fragment of the parent transposase. The peptide fragment can be at least about 10, about 15, about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 60, about 70, about 80, about 90, about 100, about 150, about 200, about 250, about 300, about 400, or about 500 amino acids in length. For example, a transposase derived from Tn5 can comprise a peptide fragment that is 50 amino acids in length and about 80% homologous to a corresponding fragment in a parent Tn5 transposase. In some cases, the insertion can be facilitated and/or triggered by addition of one or more cations. The cations can be divalent cations such as, for example, Ca^{2+}, Mg^{2+} and Mn^{2+}.

The molecular tags can comprise sequencing adaptors, locked nucleic acids (LNAs), zip nucleic acids (ZNAs), RNAs, affinity reactive molecules (e.g. biotin, dig), self-complementary molecules, phosphorothioate modifications, azide or alkyne groups. In some cases, the sequencing adaptors can further comprise a barcode label. Further, the barcode labels can comprises a unique sequence. The unique sequences can be used to identify the individual insertion events. Any of the tags can further comprise fluorescence tags (e.g. fluorescein, rhodamine, Cy3, Cy5, thiazole orange, etc.).

Additionally, the insertional enzyme can further comprise an affinity tag. In some cases, the affinity tag can be an antibody. The antibody can bind to, for example, a transcription factor, a modified nucleosome or a modified nucleic acid. Examples of modified nucleic acids include, but are not limited to, methylated or hydroxymethylated DNA. In other cases, the affinity tag can be a single-stranded nucleic acid (e.g. ssDNA, ssRNA). In some examples, the single-stranded nucleic acid can bind to a target nucleic acid. In further cases, the insertional enzyme can further comprise a nuclear localization signal.

In some cases, the cell sample can be permeabilized to allow access for the insertional enzyme. The permeabilization can be performed in a way to minimally perturb the nuclei in the cell sample. In some instances, the cell sample can be permeabilized using a permeabilization agent. Examples of permeabilization agents include, but are not limited to, NP40, digitonin, tween, streptolysin, and cationic lipids. In other instances, the cell sample

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can be permeabilized using hypotonic shock and/or ultrasonication. In other cases, the insertional enzyme can be highly charged, which may allow it to permeabilize through cell membranes.

In yet another aspect, the present disclosure provides a method for analyzing the three-dimensional structure of a polynucleotide from a cell sample, comprising: inserting a plurality of molecular tags with an insertional enzyme into the polynucleotide; and using the molecular tags to analyze the three-dimensional structure of the polynucleotide. The insertional enzyme can comprise two or more enzymatic moieties, which may be optionally linked together. The enzymatic moieties can be linked by using any suitable chemical synthesis or bioconjugation methods. For example, the enzymatic moieties can be linked via an ester/amide bond, a thiol addition into a maleimide, Native Chemical Ligation (NCL) techniques, Click Chemistry (i.e. an alkyne-azide pair), or a biotin-streptavidin pair. In some cases, each of the enzymatic moieties can insert a common sequence into the polynucleotide. The common sequence can comprise a common barcode. The enzymatic moieties can comprise transposases or derivatives thereof. In some embodiments, the polynucleotide may be fragmented into a plurality of fragments during the insertion. The fragments comprising the common barcode can be determined to be in proximity in the three-dimensional structure of the polynucleotide.

The polynucleotide can be genomic DNA. The polynucleotide can be further bound to proteins, such as histones, and may be optionally packaged in the form of chromatin. In particular cases, DNA fragments corresponding to one or more regions of a genome (e.g., 2 or more, 10 or more, 50 or more, 100 or more, up to 1,000 or more regions) may be enriched, i.e., selected, by hybridization prior to sequencing. In these embodiments, the entire library does not need to be sequenced. Depending on the desired result and length of the selected region (if a selection step has been performed), this step of the method may result in at least 1,000 sequencing (e.g., at least 10,000, at least 100,000, at least 500,000, at least 10^6, at least $5x10^6$, up to 10^7 or more sequencing reads). The sequence reads are generally stored in computer memory.

Some embodiments of the methods involve making an epigenetic map of a region of the genome of the cells. This step may be done by mapping information obtained from the sequence reads to the region. In these embodiments, the sequence reads are analyzed computationally to produce a number of numerical outputs that are mapped to a representation (e.g., a graphical representation) of a region of interest. As will be explained in greater detail below, many types of information may be mapped, including, but not

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limited to: (i) cleavage sites for the transposase; (ii) the sizes of the fragments produced in step a); (iii) fragment length; (iii) the positions of sequence reads of a defined range in length; and (iv) sequence read abundance.

For example, the sequence reads may be analyzed computationally to identify the ends of the fragments (from which the transposon cleavage sites can be inferred). In these embodiments, one end of a fragment can be defined by sequence that is at the beginning of a sequencing read and the other end of the fragment can be defined by sequence that is at the beginning of a second sequencing read, where the first and second sequencing reads were obtained by paired end sequencing (e.g., using Illumina's sequencing platform). The same information can be obtained from examining the beginning and end of longer sequence reads (which should, in theory, have the sequence of both adaptors; one at one end and the other at the other end). In these embodiments, a single sequence read may contain both adaptor sequences, in which case both ends of a fragment (which correspond to two cleavage sites for the two separate transposases) can be inferred from a single sequence read. The lengths of the fragments can be calculated by, e.g., mapping the fragment ends onto the nucleotide sequence of the region of interest, and counting the number of base pairs between those positions. The information used may be obtained using the nucleotide sequences at the beginning and/or the end of a sequence read.

In certain cases, the sequence reads can be placed into groups by length. In some embodiments, some sequences can be annotated as being a nucleosome-free sequence (i.e., a sequence from a fragment that is predicted to be between nucleosomes) based on its size. Reads that are associated with mononucleosomes, dinucleosomes and trinucleosomes can also be identified. These cutoffs can be determined using the data shown in **Fig. 12**. Fragment lengths (which provide the same information as sequence read lengths) can also be processed in the same way. In certain cases, sequence read abundance, i.e., the number of times a particular sequence in a genomic region is represented in the sequence reads, may be calculated.

The resultant epigenetic map can provide an analysis of the chromatin in the region of interest. For example, depending on which information is mapped, the map can show one or more of the following: a profile of chromatin accessibility along the region; DNA binding protein (e.g., transcription factor) occupancy for a site in the region; nucleosome-free DNA in the region; positioning of nucleosomes along the region; and a profile of chromatin states along the region. In some embodiments, the method may further comprise measuring global occupancy of a binding site for the DNA binding protein by, e.g., aggregating data for one

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DNA binding protein over a plurality of sites to which that protein binds. In certain instances, the map can also be annotated with sequence information, and information about the sequence (e.g., the positions of promoters, introns, exons, known enhancers, transcriptional start sites, untranslated regions, terminators, etc.) so that the epigenetic information can be viewed in context with the annotation.

In certain embodiments, the epigenetic map can provide information regarding active regulatory regions and/or the transcription factors that are bound to the regulatory regions. For example, nucleosome positions can be inferred from the lengths of sequencing reads generated. Alternatively, transcription factor binding sites can be inferred from the size, distribution and/or position of the sequencing reads generated. In some cases, novel transcription factor binding sites can be inferred from sequencing reads generated. In other cases, novel transcription factors can be inferred from sequencing reads generated.

The population of cells used in the assay may be composed of any number of cells, e.g., about 500 to about 10^6 or more cells, about 500 to about 100,000 cells, about 500 to about 50,000 cells, about 500 to about 10,000 cells, about 50 to 1000 cells, about 1 to 500 cells, about 1 to 100 cells, about 1 to 50 cells, or a single cell. In some cases, the cell sample can consist of less than about 1000, about 2000, about 3000, about 4000, about 5000, about 6000, about 7000, about 8000, about 9000, about 10,000, about 15,000, about 20,000, about 25,000, about 30,000, about 40,000, about 50,000, about 60,000, about 70,000, about 80,000, about 90,000, about 100,000, about 120,000, about 140,000, about 160,000, about 180,000, about 200,000, about 250,000, about 300,000, about 350,000, about 400,000, about 450,000, about 500,000, about 600,000, about 700,000, about 800,000, about 900,000, or about 1,000,000 cells. In other cases, the cell sample can consist of more than about 1000, about 2000, about 3000, about 4000, about 5000, about 6000, about 7000, about 8000, about 9000, about 10,000, about 15,000, about 20,000, about 25,000, about 30,000, about 40,000, about 50,000, about 60,000, about 70,000, about 80,000, about 90,000, about 100,000, about 120,000, about 140,000, about 160,000, about 180,000, about 200,000, about 250,000, about 300,000, about 350,000, about 400,000, about 450,000, about 500,000, about 600,000, about 700,000, about 800,000, about 900,000, or about 1,000,000 cells.

The cells can be from any source. In certain cases, the cells may be obtained from a culture of cells, e.g., a cell line. In other cases, the cells may be isolated from an individual (e.g., a patient or the like). The cells may be isolated from a soft tissue or from a bodily fluid, or from a cell culture that is grown *in vitro*. In particular embodiments, the chromatin may be isolated from a soft tissue such as brain, adrenal gland, skin, lung, spleen, kidney,

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liver, spleen, lymph node, bone marrow, bladder stomach, small intestine, large intestine or muscle, etc. Bodily fluids include blood, plasma, saliva, mucous, phlegm, cerebral spinal fluid, pleural fluid, tears, lactal duct fluid, lymph, sputum, cerebrospinal fluid, synovial fluid, urine, amniotic fluid, and semen, etc.

In some embodiments, the polynucleotide (e.g. genomic DNA, chromosomal DNA) used in the method may be from blood cells, wherein blood cells refers to a sample of whole blood or a sub-population of cells in whole blood. Sub-populations of cells in whole blood include platelets, red blood cells (erythrocytes), platelets and white blood cells (i.e., peripheral blood leukocytes, which are made up of neutrophils, lymphocytes, eosinophils, basophils and monocytes). These five types of white blood cells can be further divided into two groups, granulocytes (which are also known as polymorphonuclear leukocytes and include neutrophils, eosinophils and basophils) and mononuclear leukocytes (which include monocytes and lymphocytes). Lymphocytes can be further divided into T cells, B cells and NK cells. Peripheral blood cells are found in the circulating pool of blood and not sequestered within the lymphatic system, spleen, liver, or bone marrow. Other cells are present in blood that can be isolated. If blood is first contacted with an agent and then a sample of the blood is used in an assay, then a portion or all of the contacted blood may be used in the assay.

In certain embodiments, the cell sample can be isolated directly from a primary source. For example, the cell sample can be isolated directly from fresh tissues. In other cases, the cell sample can be isolated directly from frozen tissues. In yet other cases, the cell sample can be isolated directly from fixed tissues. Further examples of primary sources of cell samples include, but are not limited to, cells dissociated from tissues, blood cells, FFPE tissues, bacterial, viral, mitochondria, chloroplast, *in vitro* assembled protein DNA complexes, neutrophil extracellular traps.

Using the methods provided in the present disclosure, the disease state in a subject can be analyzed based on the accessibility of a polynucleotide site in a cell sample obtained from the subject. For example, transcription factor occupancy at any given site can result in the lack of accessibility at the site. Based on the transcription factor occupancy, the subject can then be treated with a suitable agent (e.g. a transcription factor inhibitor).

In certain cases, the cell samples can be further analyzed phenotypically. For example, the cell samples can be analyzed using fluorescence activated cell sorting (FACS) and/or laser capture microdissection (LCM). In some cases, the cell sample and/or polynucleotides may be divided into a plurality of portions. The portions can be divided

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based on the molecular tags (e.g. fluorescence tags). In some cases, the cell sample and/or polynucleotides can be sorted. The sorting can be performed after the molecular tags are inserted into the polynucleotide. The sorting can be performed before the fragments are sequenced. The gene transcription of the cell samples can also be analyzed using techniques such as fluorescence *in situ* hybridization (FISH). The chromatin accessibility can be correlated with the phenotypical, transcriptional or translational analysis.

In some embodiments, the cells are of the same cell type. In these embodiments, the population of cells may be selected by MACS or FACS from a heterogeneous population of cells, e.g., blood, by known methods using labeled antibodies to cells surface markers. A wide variety of cells can be isolated using these methods, including stem cells, cancer stem cells and subsets of blood cells. In particular embodiments the following cells may be isolated from blood by FACS or MACS; T cells ($CD3^+$ $CD4^+$ $CD8^+$), B cells ($CD19^+$ $CD20^+$), dendritic cells ($CD11c^+$ $CD20^+$), NK Cell ($CD56^+$), stem cells/precursor cells ($CD34^+$; hematopoietic stem cells only), macrophage/monocytes ($CD14^+$ $CD33^+$), granulocytes ($CD66b^+$), platelet ($CD41^+$ $CD61^+$ $CD62^+$), erythrocytes ($CD235a^+$), endothelial cells ($CD146^+$) and epithelial cells ($CD326^+$). Subsets of these cells can be isolated using antibodies to further cell surface markers.

In some embodiments, the method can be used to compare two samples. In these embodiments, the method may comprise analyzing a first population of cells using the above-described method to produce a first epigenetic map; and analyzing a second population of cells using the above-described method to produce a second epigenetic map; and comparing the first epigenetic map to the second epigenetic map, e.g., to see if there are any changes in chromatin openness or transcription factor occupancy, for example.

In some embodiments, the first population of cells and the second population of cells are collected from the same individual at different times. In other embodiments, the first population of cells and the second population of cells are different populations of cells collected from tissues or different individuals.

Exemplary cell types that can be used in the method include, for example, cells isolated from a tissue biopsy (e.g., from a tissue having a disease such as colon, breast, prostate, lung, skin cancer, or infected with a pathogen etc.) and normal cells from the same tissue, e.g., from the same patient; cells grown in tissue culture that are immortal (e.g., cells with a proliferative mutation or an immortalizing transgene), infected with a pathogen, or treated (e.g., with environmental or chemical agents such as peptides, hormones, altered temperature, growth condition, physical stress, cellular transformation, etc.), and normal

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cells (e.g., cells that are otherwise identical to the experimental cells except that they are not immortalized, infected, or treated, etc.); cells isolated from a mammal with a cancer, a disease, a geriatric mammal, or a mammal exposed to a condition, and cells from a mammal of the same species, e.g., from the same family, that is healthy or young; and differentiated cells and non-differentiated cells from the same mammal (e.g., one cell being the progenitor of the other in a mammal, for example). In one embodiment, cells of different types, e.g., neuronal and non-neuronal cells, or cells of different status (e.g., before and after a stimulus on the cells) may be compared. In another embodiment, the experimental material is cells susceptible to infection by a pathogen such as a virus, e.g., human immunodeficiency virus (HIV), etc., and the control material is cells resistant to infection by the pathogen. In another embodiment of the invention, the sample pair is represented by undifferentiated cells, e.g., stem cells, and differentiated cells. Cells from yeast, plants and animals, such as fish, birds, reptiles, amphibians and mammals may be used in the subject methods. In certain embodiments, mammalian cells, i.e., cells from mice, rabbits, primates, or humans, or cultured derivatives thereof, may be used.

In some exemplary embodiments, the method may be used to identify the effect of a test agent, e.g., a drug, or to determine if there are differences in the effect of two or more different test agents. In these embodiments, two or more identical populations of cells may be prepared and, depending on how the experiment is to be performed, one or more of the populations of cells may be incubated with the test agent for a defined period of time. After incubation with the test agent, the chromatin of the populations of cells can be analyzed using the methods set forth above, and the results can be compared. In a particular embodiment, the cells may be blood cells, and the cells can be incubated with the test agent ex vivo. These methods can be used to determine the mode of action of a test agent, to identify changes in chromatin structure or transcription factor occupancy in response to the drug, for example.

The method described above may also be used as a diagnostic (which term is intended to include methods that provide a diagnosis as well as methods that provide a prognosis). These methods may comprise, e.g., analyzing chromatin from a patient using the method described above to produce an epigenetic map; and providing a diagnosis or prognosis based on the epigenetic map.

The method set forth herein may be used to provide a reliable diagnostic to any condition associated with altered chromatin or DNA binding protein occupancy. The method can be applied to the characterization, classification, differentiation, grading, staging,

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diagnosis, or prognosis of a condition characterized by an epigenetic pattern (e.g., a pattern of chromatin accessibility or DNA binding protein occupancy). For example, the method can be used to determine whether the epigenetic map of a sample from an individual suspected of being affected by a disease or condition is the same or different compared to a sample that is considered "normal" with respect to the disease or condition. In particular embodiments, the method can be directed to diagnosing an individual with a condition that is characterized by an epigenetic pattern at a particular locus in a test sample, where the pattern is correlated with the condition. The methods can also be used for predicting the susceptibility of an individual to a condition.

Exemplary conditions that are suitable for analysis using the methods set forth herein can be, for example, cell proliferative disorder or predisposition to cell proliferative disorder; metabolic malfunction or disorder; immune malfunction, damage or disorder; CNS malfunction, damage or disease; symptoms of aggression or behavioral disturbance; clinical, psychological and social consequences of brain damage; psychotic disturbance and personality disorder; dementia or associated syndrome; cardiovascular disease, malfunction and damage; malfunction, damage or disease of the gastrointestinal tract; malfunction, damage or disease of the respiratory system; lesion, inflammation, infection, immunity and/or convalescence; malfunction, damage or disease of the body as an abnormality in the development process; malfunction, damage or disease of the skin, the muscles, the connective tissue or the bones; endocrine and metabolic malfunction, damage or disease; headache or sexual malfunction, and combinations thereof.

In some embodiments, the method can provide a prognosis, e.g., to determine if a patient is at risk for recurrence. Cancer recurrence is a concern relating to a variety of types of cancer. The prognostic method can be used to identify surgically treated patients likely to experience cancer recurrence so that they can be offered additional therapeutic options, including preoperative or postoperative adjuncts such as chemotherapy, radiation, biological modifiers and other suitable therapies. The methods are especially effective for determining the risk of metastasis in patients who demonstrate no measurable metastasis at the time of examination or surgery.

The method can also be used to determining a proper course of treatment for a patient having a disease or condition, e.g., a patient that has cancer. A course of treatment refers to the therapeutic measures taken for a patient after diagnosis or after treatment. For example, a determination of the likelihood for recurrence, spread, or patient survival, can assist in determining whether a more conservative or more radical approach to therapy should be

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taken, or whether treatment modalities should be combined. For example, when cancer recurrence is likely, it can be advantageous to precede or follow surgical treatment with chemotherapy, radiation, immunotherapy, biological modifier therapy, gene therapy, vaccines, and the like, or adjust the span of time during which the patient is treated.

In a particular embodiment, a lab will receive a sample (e.g., blood) from a remote location (e.g., a physician's office or hospital), the lab will analyze cells in the sample as described above to produce data, and the data may be forwarded to the remote location for analysis.

Compositions

In one aspect, the present disclosure provides compositions related to the methods provided herein. The composition can comprise a polynucleotide, an insertional enzyme and an insert element, wherein: the insert element can comprise a nucleic acid comprising a predetermined sequence and the insertional enzyme can further comprise an affinity tag. The polynucleotide can be further bound to a plurality of association molecules. The association molecules can be proteins (e.g. histones) or nucleic acids (e.g. aptamers). The affinity tag can be an antibody. In some cases, the antibody can be bound to a transcription factor. In other cases, the antibody can be bound to a modified nucleosome. In further cases, the antibody can be bound to a modified nucleic acid. Examples of modified nucleic acids include, but are not limited to, methylated or hydroxymethylated DNA. The affinity tag can also be a single-stranded nucleic acid (e.g. ssDNA, ssRNA). In some cases, the single-stranded nucleic acid can be bound to a target nucleic acid. In some instances, the insertional enzyme can further comprise a nuclear localization signal.

The composition can comprise a polynucleotide, an insertional enzyme and an insert element, wherein: the insertional enzyme comprises two or more enzymatic moieties and the enzymatic moieties are linked together. The insert element can be bound to the insertional enzyme. The insertional enzyme can also be bound to the polynucleotide. In some cases, the polynucleotide can be further bound to a plurality of association molecules. The association molecules can be proteins (e.g. histones) or nucleic acids (e.g. aptamers).

Kits

In yet another aspect, the present disclosure provides kits that contain reagents for practicing the subject methods, as described above. The subject kits can comprise: (a) reagents for isolating nuclei from a population of cells; (b) transposase and transposon tags,

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and (c) transposase reaction buffer, wherein the components of the kit are configured such that, combining the reaction buffer, transposase and adaptors with nuclei *in vitro* results in both lysis of the nuclei to release chromatin and production of adaptor-tagged fragments of genomic DNA.

In some cases, the kit can comprise: (a) a cell lysis buffer; (b) an insertional enzyme comprising an affinity tag; and (c) an insert element comprising a nucleic acid, wherein said nucleic acid comprises a predetermined sequence. The insertional enzyme can be, for example, a transposase. The insertional enzyme can also comprise two or more enzymatic moieties that are linked together. In some cases, the affinity tag can be an antibody. The antibody can bind to a transcription factor, a modified nucleosome, or a modified nucleic acid. Examples of modified nucleic acids include, but are not limited to, methylated or hydroxymethylated DNA. In other cases, the affinity tag can be a single-stranded nucleic acid (e.g. ssDNA, ssRNA).

The kit may optionally contain other components, for example: PCR primers, PCR reagents such as polymerase, buffer, nucleotides etc., as described above. The various components of the kit may be present in separate containers or certain compatible components may be precombined into a single container, as desired.

In addition to above-mentioned components, the subject kits may further include instructions for using the components of the kit to practice the subject methods, i.e., instructions for sample analysis. The instructions for practicing the subject methods are generally recorded on a suitable recording medium. For example, the instructions may be printed on a substrate, such as paper or plastic, etc. As such, the instructions may be present in the kits as a package insert, in the labeling of the container of the kit or components thereof (i.e., associated with the packaging or subpackaging) etc. In other embodiments, the instructions are present as an electronic storage data file present on a suitable computer readable storage medium, e.g., CD-ROM, diskette, etc. In yet other embodiments, the actual instructions are not present in the kit, but means for obtaining the instructions from a remote source, e.g., via the internet, are provided. An example of this embodiment is a kit that includes a web address where the instructions can be viewed and/or from which the instructions can be downloaded. As with the instructions, this means for obtaining the instructions is recorded on a suitable substrate.

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Embodiments

A method of mapping chromatin is provided. In some embodiments, this method comprises the steps of: fragmenting the chromatin of rare or abundant cells with a transposase which inserts sequencing adapters into the polynucleotides within the chromatin, and amplifying and sequencing the fragments to generate a cell-specific map.

In certain embodiments, the cell-specific map provides information regarding active regulatory regions and the transcription factors that are bound to said regulatory regions.

In certain embodiments, the number of said rare cells is between 1 and 100,000.

In certain embodiments, the transposase is derived from Tn5 transposase.

In certain embodiments, the transposase is derived from MuA transposase.

In certain embodiments, nucleosome positions are inferred from the lengths of sequencing reads generated.

In certain embodiments, transcription factor binding sites are inferred from sequencing reads generated.

In certain embodiments, chromatin is isolated directly from fresh tissues.

In certain embodiments, chromatin is isolated directly from frozen tissues.

In certain embodiments, chromatin is isolated directly from fixed tissues.

In certain embodiments, sequences are added to the sequencing adapter to uniquely identify the fragments for multiplexing (barcoding).

In certain embodiments, an affinity tag is used to target the transposase to a specific macromolecule of interest.

In certain embodiments, sequences are added to the sequencing adapter to uniquely identify the fragments for multiplexing (barcoding), and an affinity tag is used to target the transposase to a specific macromolecule of interest.

In certain embodiments the affinity tag is an antibody targeted to a transcription factor.

In certain embodiments the affinity tag is an antibody targeted to a modified nucleosome.

In certain embodiments, the insert size distribution at a specific genomic locus is used to infer chromatin openness.

In certain embodiments, the insert size distribution and positions of insertion are used to infer transcription factor binding.

In certain embodiments, the number of sequencing reads obtained is normalized by measured sequence insertion preference of the transposase.

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In certain embodiments, novel transcription factor binding sites are inferred from sequencing reads generated.

In certain embodiments, novel transcription factors are inferred from sequencing reads generated.

In certain embodiments, causal variants can be inferred by looking at allele specific generation of sequencing reads.

In certain embodiments, chromatin state annotations are inferred from the distribution of lengths of sequencing reads.

EXAMPLES

Aspects of the present teachings can be further understood in light of the following examples, which should not be construed as limiting the scope of the present teachings in any way.

Example 1. Assay for Transposase Accessible Chromatin using sequencing (ATAC-seq)

Described herein is an Assay for Transposase Accessible Chromatin using sequencing (ATAC-seq) - based on direct *in vitro* transposition of sequencing adapters into native chromatin – as a rapid and sensitive method for integrative epigenomic analysis. ATAC-seq captures open chromatin sites using a simple 2-step protocol from 500 to 50,000 cells, and reveals the interplay between genomic locations of open chromatin, DNA binding proteins, individual nucleosomes, and higher-order compaction at regulatory regions with nucleotide resolution. Classes of DNA binding factor that strictly avoid, can tolerate, or tend to overlap with nucleosomes have been discovered. Using ATAC-seq, the serial daily epigenomes of resting human T cells was measured and evaluated from a proband via standard blood draws, demonstrating the feasibility of reading personal epigenomes in clinical timescales for monitoring health and disease.

Materials and Methods

An exemplary implementation of ATAC-seq protocol has three major steps:

1) Prepare nuclei: To prepare nuclei, 50,000 cells were spun at 500 x g for 5 minutes, followed by a wash using 50 μL of cold 1x PBS and centrifugation at 500 x g for 5 minutes. Cells were lysed using cold lysis buffer (10 mM Tris-Cl, pH 7.4, 10 mM NaCl, 3 mM $MgCl_2$ and 0.1% IGEPAL CA-630). Immediately after lysis, nuclei were spun at 500 x g for 10 minutes using a refrigerated centrifuge. To avoid losing cells during the nuclei

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prep, a fixed angle centrifuge was used and they were carefully pipetted away from the pellet after centrifugations.

2) Transpose and purify: Immediately following the nuclei prep, the pellet was resuspended in the transposase reaction mix (25 μL 2x TD buffer, 2.5 μL Transposase (Illumina) and 22.5 μL of nuclease free water). The transposition reaction was carried out for 30 minutes at 37 °C. Directly following transposition the sample was purified using a Qiagen Minelute kit.

3) PCR: Following purification, we amplified library fragments using 1x NEBnext PCR master mix and 1.25 μM of custom Nextera PCR primers 1 and 2 (see table below), using the following PCR conditions: 72°C for 5 minutes, 98°C for 30 seconds, followed by thermocycling at 98°C for 10 seconds, 63°C for 30 seconds and 72°C for 1 minute. To reduce GC and size bias in PCR, the PCR reactions were monitored using qPCR in order to stop amplification prior to saturation. To do this, the full libraries were amplified for 5 cycles, after 5 cycles an aliquot of the PCR reaction was taken and added to 10 μl of the PCR cocktail with Sybr Green at a final concentration of 0.6x. We ran this reaction for 20 cycles, to determine the additional number of cycles needed for the remaining 45 μL reaction. The libraries were purified using a Qiagen PCR cleanup kit yielding a final library concentration of ~30 nM in 20 μL. Libraries were amplified for a total of 10-12 cycles.

Ad1_noMX:	AATGATACGGCGACCACCGAGATCTACACTCGTCGGCAGCGTCAGATGTG (SEQ ID NO:1)
Ad2.1_TAAGGCGA	CAAGCAGAAGACGGCATACGAGATTCGCCTTAGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:2)
Ad2.2_CGTACTAG	CAAGCAGAAGACGGCATACGAGATCTAGTACGGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:3)
Ad2.3_AGGCAGAA	CAAGCAGAAGACGGCATACGAGATTTCTGCCTGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:4)
Ad2.4_TCCTGAGC	CAAGCAGAAGACGGCATACGAGATGCTCAGGAGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:5)
Ad2.5_GGACTCCT	CAAGCAGAAGACGGCATACGAGATAGGAGTCCGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:6)
Ad2.6_TAGGCATG	CAAGCAGAAGACGGCATACGAGATCATGCCTAGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:7)
Ad2.7_CTCTCTAC	CAAGCAGAAGACGGCATACGAGATGTAGAGAGGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:8)
Ad2.8_CAGAGAGG	CAAGCAGAAGACGGCATACGAGATCCTCTCTGGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:9)
Ad2.9_GCTACGCT	CAAGCAGAAGACGGCATACGAGATAGCGTAGCGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:10)
Ad2.10_CGAGGCTG	CAAGCAGAAGACGGCATACGAGATCAGCCTCGGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:11)
Ad2.11_AAGAGGCA	CAAGCAGAAGACGGCATACGAGATTGCCTCTTGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:12)
Ad2.12_GTAGAGGA	CAAGCAGAAGACGGCATACGAGATTCCTCTACGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:13)

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Ad2.13_GTCGTGAT	CAAGCAGAAGACGGCATACGAGATATCACGACGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:14)
Ad2.14_ACCACTGT	CAAGCAGAAGACGGCATACGAGATACAGTGGTGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:15)
Ad2.15_TGGATCTG	CAAGCAGAAGACGGCATACGAGATCAGATCCAGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:16)
Ad2.16_CCGTTTGT	CAAGCAGAAGACGGCATACGAGATACAAACGGGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:17)
Ad2.17_TGCTGGGT	CAAGCAGAAGACGGCATACGAGATACCCAGCAGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:18)
Ad2.18_GAGGGGTT	CAAGCAGAAGACGGCATACGAGATAACCCCTCGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:19)
Ad2.19_AGGTTGGG	CAAGCAGAAGACGGCATACGAGATCCCAACCTGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:20)
Ad2.20_GTGTGGTG	CAAGCAGAAGACGGCATACGAGATCACCACACGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:21)
Ad2.21_TGGGTTTC	CAAGCAGAAGACGGCATACGAGATGAAACCCAGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:22)
Ad2.22_TGGTCACA	CAAGCAGAAGACGGCATACGAGATTGTGACCAGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:23)
Ad2.23_TTGACCCT	CAAGCAGAAGACGGCATACGAGATAGGGTCAAGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:24)
Ad2.24_CCACTCCT	CAAGCAGAAGACGGCATACGAGATAGGAGTGGGTCTCGTGGGCTCGGAGATGT (SEQ ID NO:25)

Low cell number protocol: To prepare the 500 and 5,000 cell reactions the same protocol was used with some notable exceptions: The transposition reaction was done in a 5 μL instead of 50 μL reaction. Also, the Qiagen Minelute purification was eliminated prior to PCR and instead took the 5 μL reaction immediately after transposition directly into the 50 μL PCR.

Library QC and quantitation: During the ATAC-seq protocol, the size selection step was avoided to maximize the library complexity. The sequenced insert size is a distribution between 40 bp to 1 kb with a mean of ~120 bps. From bioanalyzer and gels we observed fragments >2 kb, which would make Qubit and other mass-based quantitation methods hard to interpret. For this reason we quantified our libraries using qPCR based methods.

$CD4^+$ enrichment from peripheral blood: One green-top tube of whole blood was obtained from 1 normal volunteer three times over a 72-hour period, under a Stanford University IRB-approved protocol. Informed consent was obtained. 5mL of blood at each timepoint was negatively selected for CD4+ cells, using RosetteSep Human $CD4^+$ T Cell Enrichment Cocktail (StemCell Technology). RosetteSep cocktail was incubated with the blood at 50μL/mL for 20 min, diluted in an equal volume of PBS with 2% FBS, and underlayed with 15 mL Ficol-Paque Plus (GE). Blood was centrifuged for 20 minutes at

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1200 x g without break, negatively selected cells were removed from the density medium: plasma interface, and cells were washed X2 in PBS with 2% FBS.

FACS sorting peripheral blood leukocytes and GM cells: GM 12878 cells were stained with DAPI NucBlue Fixed Cell Stain (molecular probes) and live cells were sorted using a FACSAria (BD Biosciences) using a 100 μm nozzle. One peripheral blood sample (buffy coat) was stained with BD Bioscience antibodies CD14-A-488 (M5E2, 1:20), CD3-PE-Cy7 (SK7, 1:20), CD4-APC-Cy7 (RPA-T4, 1:20), and CD8 (RPA-T8, 1:20) for 20 minutes in the dark at RT. Cells were lysed using BDpharmLyse 1:10 dil in diH20 (BD) for 15 min, centrifuged for 5 minutes, washed with PBS 2% FBS X 2, and resuspended in PBS with 2% FBS. 50,000 $CD3^+CD8^+$, $CD3^+CD4^+$, and $CD14^+$ cell populations were sorted into PBS with 10% FBS.

Data Analysis

Primary data processing: Data was collected using either 34 x 8 x 34 reads from a MiSeq or 50 x 8 x 50 reads on a HiSeq. Reads were aligned to hg19 using BOWTIE (Langmead et al *Genome Biol.* 2009 **10,** R25) using the parameters –X2000 and –m1. These parameters ensured that fragments up to 2 kb were allowed to align (-X2000) and that only unique aligning reads were collected (-m1). For all data files duplicates were removed using Picard.

For peak calling and footprinting, the read start sites were adjusted to represent the center of the transposon binding event. Previous descriptions of the Tn5 transposase show that the transposon binds as a dimer and inserts two adapters separated by 9 bps (Adey, A. *et al. Genome Biol* 2010 **11:** R119). Therefore, all reads aligning to the + strand were offset by +4 bps, and all reads aligning to the – strand were offset -5 bps.

ATAC-seq peak calling: We used ZINBA to call all reported ATAC-seq peaks in this manuscript. ZINBA was run using a window size of 300 bp and an offset 75 bp. Alignability was used to model the zero-inflated component and the ATAC-seq read count for the background and enriched components. Enriched regions were identified as those with a posterior probability >0.8.

ATAC-seq insertion size enrichment analysis within chromatin annotations: First, the distribution of paired-end sequencing fragment sizes overlapping each chromatin state (see the ensemble.org website) were computed. The distributions were then normalized to the percent maximal within each state and enrichment was computed relative to the genome-wide set of fragment sizes.

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Nucleosome positioning: To generate the nucleosome position data track, we chose to split reads into various bins. Reads below 100 bps were considered nucleosome free, reads between 180 and 247 bps were considered to be mononucleosomes, reads between 315 and 473 bps were considered to be dinucleosomes and reads between 558 and 615 were considered to be trinucleosomes (for determining cutoffs see Fig. 12). Dinucleosome reads were split into two reads and Trinucleosome reads were split into three reads. Reads were analyzed using Danpos and Dantools using the parameters -p 1, -a 1, -d 20, -clonalcut 0. The background used was nucleosome free reads (reads less than 100 bps), allowing an effective negative weighting of these reads. This analysis allows calling multiple overlapping nucleosomes. Although generating nucleosome tracks using simple insert size cutoffs may yield false positives due to other nucleosome sized features, i.e. enhanaceosomes, we observed that we faithfully recapitulated global features on nucleosome position genome-wide (**Fig 2c,d** main text).

ChIP-seq peak calling and clustering: ChIP-seq data was downloaded from the UCSC ENCODE repository. Peaks where called using GEM (Guo et al, *PLoS Comput. Biol.* 2012 **8:** e1002638), the parameters used where -k_min 6 -k_max 20. Inputs where used as a control for peak calling. Binding events were annotated by distance to the nearest dyad in bins of 10 bps. Factors were then hierarchically clustered using Euclidean distance and normalized by gene and centered by mean. (Eisen et al. *Proc. Natl. Acad. Sci.* 1998 **95:** 14863–14868).

Footprinting using CENTIPEDE: The genome-wide set of motifs were obtained from the ENCODE motif repository (at the website of broadinstitute.org). The input for CENTIPEDE included the PWM score, conservation (PhyloP) and ATAC-seq counts within +/-100bp of each genomic region matching a motif. ChIP-seq data was obtained from the UCSC ENCODE repository.

Comparison of transcription factor regulatory networks: Transcription factor regulatory networks were constructed by comparing the GENCODE v14 genes with the genome-wide set of posterior probabilities estimated by CENTIPEDE for the respective cell-types. The extent of a transcription factor regulating each gene was determined by taking the sum of the weighed posterior probabilities for a given transcription factor mapping to the same chromosome. For each mapped motif the posterior probability was weighted based on the distance to the transcription start site for each gene. Comparison of transcription factor regulatory networks was computed as the correlation of each transcription factor in a given

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cell type with all transcription factors in the other cell type. The resulting correlation matrix was hierarchically clustered using the Pearson correlation coefficient and complete linkage.

Candidate IL2 enhancer analysis: ENCODE data on the UCSC genome browser was inspected to identify putative IL2 enhancers in one or more cell types that may be responsive to FDA approved immomodulatory drugs. We scanned the intergenic region upstream of IL2 in hg19 for (i) enhancer-associated histone marks (H3K4me1 and H3K27ac), (ii) binding by one or more TFs as confirmed by ChIP-seq, and (iii) the TF pathway can be targeted by a human therapeutic. This analysis identified IRF4 and STAT3 binding sites in addition to the known NFAT-responsive elements.

Results

ATAC-seq probes chromatin accessibility with transposons

Hyperactive Tn5 transposase (Goryshin, J Biol Chem. 1998 **273:** 7367–7374; Adey, A. *et al. Genome Biol* 2010 **11:** R119, loaded *in vitro* with adapters for high-throughput DNA sequencing, can simultaneously fragment and tag a genome with sequencing adapters (previously described as "tagmentation"). It was hypothesized that transposition by purified Tn5, a prokaryotic transposase, on small numbers of unfixed eukaryotic nuclei would interrogate regions of accessible chromatin. An Assay for Transposase Accessible Chromatin followed by high-throughput sequencing (ATAC-seq) is described. ATAC-seq uses Tn5 transposase to integrate its adapter payload into regions of accessible chromatin, whereas steric hindrance less accessible chromatin makes transposition less probable. Therefore, amplifiable DNA fragments suitable for high-throughput sequencing are preferentially generated at locations of open chromatin (**Fig 1a**). The entire assay and library construction can be carried out in a simple two-step process involving Tn5 insertion and PCR. In contrast, published DNase- and FAIRE-seq protocols for assaying chromatin accessibility involve multi-step protocols and many potentially loss-prone steps, such as adapter ligation, gel purification, and crosslink reversal. For instance, a published DNase-seq protocol calls for approximately 44 steps, and two overnight incubations, while published FAIRE-seq protocols require two overnight incubations carried out over at least 3 days. Furthermore, these protocols require 1-50 million cells (FAIRE) or 50 million cells (DNase-seq), perhaps because of these complex workflows (**Fig 1b**). In comparison to established methods, ATAC-seq enables rapid and efficient library generation because assay and library preparation are carried out in a single enzymatic step.

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Extensive analyses show that ATAC-seq provides accurate and sensitive measure of chromatin accessibility genome-wide. ATAC-seq was carried out on 50,000 and 500 unfixed nuclei isolated from GM12878 lymphoblastoid cell line (ENCODE Tier 1) for comparison and validation with chromatin accessibility data sets, including DNase-seq and FAIRE-seq. At a locus previously highlighted by others, (**Fig. 1c**), ATAC-seq has a signal-to-noise ratio similar to DNase-seq, which was generated from approximately 3 to 5 orders-of-magnitude more cells. Peak intensities were highly reproducible between technical replicates (R=0.98), and highly correlated between ATAC-seq and DNase-seq (R=0.79 and R=0.83, **Fig. 6**), and it is noted that the majority of reads within peaks come from intersections of DNase and ATAC-seq peaks (**Fig. 7**). Comparing our data to DHSs identified in ENCODE DNase-seq data, receiver operating characteristic (ROC) curves demonstrate a similar sensitivity and specificity as DNase-seq (**Fig. 8**). It is also noted that ATAC-seq peak intensities correlate well with markers of active chromatin and not with transposase sequence preference (**Figs. 9** and **10**). Highly sensitive open chromatin detection is maintained even when using 5,000 or 500 human nuclei as starting material (**Figs. 8** and **11**), although, under the conditions used, sensitivity is diminished for smaller numbers of input material, as can be seen in Fig 1c.

ATAC-seq insert sizes disclose nucleosome positions

It was found that ATAC-seq paired-end reads produce detailed information about nucleosome packing and positioning. The insert size distribution of sequenced fragments from human chromatin has clear periodicity of approximately 200 base pairs, suggesting many fragments are protected by integer multiples of nucleosomes (**Fig 2a**). This fragment size distribution also shows clear periodicity equal to the helical pitch of DNA. By partitioning insert size distribution according to functional classes of chromatin as defined by previous models (Hoffman et al. Nucleic Acids Res. 2013 41: 827–841), and normalizing to the global insert distribution we observe clear class-specific enrichments across this insert size distribution (**Fig. 2b**), demonstrating that these functional states of chromatin have an accessibility "fingerprint" that can be read out with ATAC-seq. These differential fragmentation patterns are consistent with the putative functional state of these classes, as CTCF-bound regions are enriched for short fragments of DNA, while transcription start sites are differentially depleted for mono-, di- and tri-nucleosome associated fragments. Transcribed and promoter flanking regions are enriched for longer multi-nucleosomal fragments, suggesting they may represent more compacted forms of chromatin. Finally, prior studies have shown that certain DNA sequences are refractory to nuclease digestion and

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released as large, multi-nucleosome-sized fragments; subsequent studies showed that such fragments are condensed heterochromatin. Indeed repressed regions were found to be depleted for short fragments and enriched for phased multi-nucleosomal inserts, consistent with their expected inaccessible state. These data suggest that ATAC-seq reveals differentially accessible forms of chromatin, which have been long hypothesized to exist *in vivo*.

To explore nucleosome positioning within accessible chromatin in the GM12878 cell line, data was partitioned into reads generated from putative nucleosome free regions of DNA, and reads likely derived from nucleosome associated DNA (see **Fig. 12**). Using a simple heuristic that positively weights nucleosome associated fragments and negatively weights nucleosome free fragments (see Methods), we calculated a data track used to call nucleosome positions within regions of accessible chromatin (Chen, K. et al. Genome Research 2013 23, 341–351). An example locus (**Fig. 3a**) contains a putative bidirectional promoter with CAGE data showing two transcription start sites (TSS) separated by ~700bps. ATAC-seq reveals in fact two distinct nucleosome free regions, separated by a single well-positioned mononucleosome (**Fig. 3a**). Compared to MNase-seq, ATAC-seq data is more amenable to detecting nucleosomes within putative regulatory regions, as the majority of reads are concentrated within accessible regions of chromatin (**Fig. 3b**). By averaging signal across all active TSSs, it is noted that nucleosome-free fragments are enriched at a canonical nucleosome-free promoter region overlapping the TSS, while the nucleosome signal is enriched both upstream and downstream of the active TSS, and displays characteristic phasing of upstream and downstream nucleosomes (**Fig. 3c**). Because ATAC-seq reads are concentrated at regions of open chromatin, a strong nucleosome signal is seen at the +1 nucleosome, which decreases at the +2, +3 and +4 nucleosomes, in contrast, MNase-seq nucleosome signal increases at larger distances from the TSS likely due to over digestion of more accessible nucleosomes. Additionally, MNase-seq (4 billion reads) assays all nucleosomes, whereas reads generated from ATAC-seq (198 million paired reads) are concentrated at regulatory nucleosomes (**Fig. 3b,c**). Using the nucleosome calls, putative distal regulatory regions and TSSs were further partititioned into regions that were nucleosome free and regions that were predicted to be nucleosome bound. It is noted that TSSs were enriched for nucleosome free regions when compared to distal elements, which tend to remain nucleosome rich (**Fig. 3d**). These data suggest ATAC-seq can provide high-resolution readout of nucleosome associated and nucleosome free regions in regulatory elements genome wide.

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ATAC-seq reveals patterns of nucleosome-TF spacing

ATAC-seq high-resolution regulatory nucleosome maps can be used to understand the relationship between nucleosomes and DNA binding factors. Using ChIP-seq data, we plotted the position of a variety of DNA binding factors with respect to the dyad of the nearest nucleosome. Unsupervised hierarchical clustering (**Figure 3e**) revealed major classes of binding with respect to the proximal nucleosome, including 1) a strongly nucleosome avoiding group of factors with binding events stereotyped at ~180 bases from the nearest nucleosome dyad (comprising C-FOS, NFYA and IRF3), 2) a class of factors that "nestle up" precisely to the expected end of nucleosome DNA contacts, which notably includes chromatin looping factors CTCF and cohesion complex subunits RAD21 and SMC3; 3) a large class of primarily TFs that have gradations of nucleosome avoiding or nucleosome-overlapping binding behavior, and 4) a class whose binding sites tend to overlap nucleosome-associated DNA. Interestingly, this final class includes chromatin remodeling factors such as CHD1 and SIN3A as well as RNA polymerase II, which appears to be enriched at the nucleosome boundary. The interplay between precise nucleosome positioning and locations of DNA binding factor immediately suggests specific hypotheses for mechanistic studies, a potential advantage of ATAC-seq.

ATAC-seq footprints infer factor occupancy genome-wide

ATAC-seq enables accurate inference of DNA binding factor occupancy genome-wide. DNA sequences directly occupied by DNA-binding proteins should be protected from transposition; the resulting sequence "footprint" reveals the presence of the DNA-binding protein at each site, analogous to DNase digestion footprints. At a specific CTCF binding site on chromosome 1, we observed a clear footprint (a deep notch of ATAC-seq signal), similar to footprints seen by DNase-seq, at the precise location of the CTCF motif that coincides with the summit of the CTCF ChIP-seq signal in GM12878 cells (**Fig 4a**). The ATAC-seq signal was averaged over all expected locations of CTCF within the genome and observed a well-stereotyped "footprint" (**Fig. 4b**). Similar results were obtained for a variety of common TFs (for examples see **Fig. 13**). We inferred the CTCF binding probability from motif consensus score, evolutionary conservation, and ATAC-seq insertion data to generate a posterior probability of CTCF binding at all loci (**Fig. 4c**) (Pique-Regi et al. Genome Research 2011 21 447–455). Results using ATAC-seq closely recapitulate ChIP-seq binding data in this cell line and compare favorably to DNase-based factor occupancy inference (see **Fig. 14**), suggesting that factor occupancy data can be extracted from these ATAC-seq data

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allowing reconstruction of regulatory networks.

ATAC-seq enables epigenomic analysis on clinical timescales

ATAC-seq is rapid, information rich, and compatible with small numbers of cells and may serve as a powerful tool for personalized epigenomics in the clinic. Specifically, one can envision "personal epigenomics" as genome-scale information about chromatin generated from an individual from a standard clinical sample in a clinical timescale. ATAC-seq was applised to assay the personal T-cell epigenome of a healthy volunteer via standard serial blood draws, to demonstrate a workflow capable of generating ATAC-seq libraries in clinical timescales. Using rapid T-cell enrichment and sample handling protocols, the total required time from blood draw to sequencing was approximately 275 minutes (**Fig. 5a**). When coupled with ongoing improvements to sequencing and analysis turn-around times, ATAC-seq can offer the possibility of a daily turn-around time for a personal epigenomic map. To explore this possibility, ATAC-seq was performed on three consecutive days via standard blood draws from a single individual (**Fig. 5b**). As an exercise to consider how personal epigenomic maps may contain personalized regulatory information, we investigated ATAC-seq profile at the *IL2* locus. IL-2 is a key cytokine that drives T-cell growth and functions in inflammatory and autoimmune diseases. Furthermore, distinct drugs inhibit the activities of different transcription factors that bind putative *IL2* enhancers in a context-dependent manner. In principle, one might wish to identify the causal transcription factor pathway in order to rationally target inhibition without exposing the patient to drugs unlikely to serve the therapeutic goal of IL-2 blockade. ATAC-seq shows that in the proband's T-cells, only NFAT, but not two other drug targets, is engaging *IL2* (**Fig. 5c**), providing clinically relevant information on the regulatory state of this individual.

Using ATAC-seq footprints the occupancy profiles of 89 transcription factors in proband T-cells were generated, enabling systematic reconstruction of regulatory networks. With this personalized regulatory map, we compared the genomic distribution of the same 89 transcription factors between GM12878 and proband CD4+ T-cells. Transcription factors that exhibit large variation in distribution between T-cells and B-cells are enriched for T-cell specific factors (**Fig. 5d**). This analysis shows NFAT is differentially regulating, while canonical CTCF occupancy is highly correlated within these two cell types (**Fig. 5d**). Supporting this interpretation, it is noted that specific loci where NFAT is localized nearby to known T-cell specific genes such as CD28 and a novel lincRNA RP11-229C3.2 (**Fig. 15**). Additionally, ATAC-seq of $CD4^+$ and $CD8^+$ T-cells, and monocytes isolated by

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fluorescence-activated cell sorting (FACS) from a single blood draw created an interpretative framework for the personal epigenomes, and demonstrated that ATAC-seq is compatible with cellular enrichment using surface markers (**Fig. 16**). Separately, allele-specific chromatin accessibility has been shown to be particularly relevant to our understanding of human disease. As a proof of principle we also used ATAC-seq to identify candidate allele-specific open chromatin regions within the GM12878 cell line (**Fig. 17**). These results demonstrate the feasibility of generating detailed personalized gene regulatory networks from clinical samples, opening the door for future diagnostic applications.

Epigenomic studies of chromatin accessibility have yielded tremendous biological insights, but are currently limited in application by their complex workflows and large cell number requirements. While, improvements of existing methods may enable them to reach the similar performance, ATAC-seq in certain cases can offer substantial advantages over existing technologies due to its speed, simplicity, and low input cell number requirement. ATAC-seq is an information rich assay, allowing simultaneous interrogation of factor occupancy, nucleosome positions in regulatory sites, and chromatin accessibility genome-wide. These insights are derived from both the position of insertion and the distribution of insert lengths captured during the transposition reaction. While extant methods such as DNase- and MNase-seq can provide some subsets of the information in ATAC-seq, they each require separate assays with large cell numbers, which increases the time, cost, and limits applicability to many systems. ATAC-seq also provides insert size "fingerprints" of biologically relevant genomic regions, suggesting that it capture information on chromatin compaction. ATAC-seq may have broad applicability, significantly add to the genomics toolkit, and improve our understanding of gene regulation, particularly when integrated with other powerful rare cell techniques, such as FACS, laser capture microdissection (LCM) and recent advancements in RNA-seq.

ATAC-seq may be used to generate "personal epigenomic" profiles on a timescale compatible with clinical decision-making. Optimized procedures can transform a clinical blood sample to completed sequencing library in 275 minutes. The reduced input requirements and rapid workflows, when coupled with the recent introduction of rapid-turnaround high-throughput sequencing instruments, such as the MiSeq and HiSeq2500, should enable investigation of personalized epigenetic landscapes of selected tissues both in the lab and the clinic. ATAC-seq is compatible with FACS, enabling studies on carefully sorted and rare subpopulations from primary tissues. Cellular subpopulations selected at different points in development and aging, and human diseases, including cancer,

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autoimmunity, and neuropsychiatric disorders are viable applications.

Example 2. Single-Cell ATAC-seq

Single-cell chromatin accessibility datasets were obtained using the ATAC-seq protocol. To ensure that the ratio of transposase molecules to open chromatin sites was kept nearly constant, the single-cell ATAC-seq assay was carried out by manipulating individual cells after an initial transposition reaction.

Transposases can serve as an open-chromatin stain

It was observed that after *in vitro* insertion of sequencing adapter, the Tn5 transposase remained tightly bound to the DNA and formed a high-affinity macromolecular complex that prevented dissociation of the generated ATAC-seq DNA fragments. To support this observation, Tn5 transposase was loaded with fluorescently labeled DNA adapters, and allowed for visualization of regions of open chromatin within the nucleus of individual cells (**Fig. 18**). Additional electrophoretic mobility shift assays also indicated that the transposase remained associated to DNA after transposition.

Single-Cell ATAC-seq provides unique reads characteristic of chromosomal DNA

Since this fluorescence signal localized to the nucleus and was detectable even after transposition, the single-cell ATAC-seq experiment was performed by keeping the transposed fragments in the nucleus during subsequent sorting and cell selection steps. A group of cells were permeabilized, and the chromosomal DNA was transposed with Tn5 transposase. The cells were kept under conditions that prevented the resulting ATAC-seq fragments from leaving the cell nucleus, (i.e. divalent cation was not chelated), and the individual cells were sorted into independent PCR reactions for library preparation, as described above. This workflow significantly simplified the workflow for single-cell analysis and provided two additional advantages. First, this abrogated any effect of the sorting process on the chromatin state because transposition preceded sorting. Second, it provided more robust ATAC-seq signal, as cells were sorted directly into a PCR master mix and amplified. Using this workflow, ~2,000-5,000 unique ATAC-seq reads per cell were generated. These reads were enriched for known open chromatin sites in GM12878 cells (**Fig. 19**) and displayed characteristic periodic enrichments indicative of nucleosomes (**Fig. 20**).

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Example 3. Quality control

Assay for Transposase Accessible Chromatin (ATAC-seq) has been shown to be compatible with many methods for cell collection and has also worked effectively across many cell types and species. However, the following protocol has been optimized for human lymphoblastoid cells. Minor variations (i.e. cell number, centrifugation speeds, and lysis conditions) may optimized for particular applications.

I. Cell Preparation

1. Harvest cells (no fixation), protocol to be defined by the user.
2. Spin down 50,000 cells at 500 ×g for 5 min, 4°C.
3. Wash once with 50 µL of cold 1x PBS buffer. Spin down at 500 ×g for 5 min, 4°C.
4. Gently pipette to resuspend the cell pellet in 50 µL of cold lysis buffer (10 mM Tris-HCl, pH 7.4, 10 mM NaCl, 3 mM $MgCl_2$, 0.1% IGEPAL CA-630). Spin down immediately at 500 ×g for 10 min, 4°C.
5. Discard the supernatant, and immediately continue to transposition reaction.

II. Transposition Reaction and Purification

1. Make sure the cell pellet is set on ice.
2. To make the transposition reaction mix, combine the following:

   25 µL 2x TD Buffer (Illumina Cat #FC-121-1030)
   2.5 µL Tn5 Transposes (Illumina Cat #FC-121-1030)
   22.5 µL Nuclease Free H_2O
   50 µl Total

3. Gently pipette to resuspend nuclei in the transposition reaction mix.
4. Incubate the transposition reaction at 37°C for 30 min.
5. Immediately following transposition, purify using a Qiagen MinElute Kit.
6. Elute transposed DNA in 10 µL Elution Buffer (10mM Tris buffer, pH 8).
7. Purified DNA can be stored at -20°C.

III. PCR Amplification

1. To amplify transposed DNA fragments, combine the following in a PCR tube:

   10 µL Transposed DNA
   9.7 µL Nuclease Free H_2O
   2.5 µL 25µM Customized Nextera PCR Primer 1*

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2.5 µL 25µM Customized Nextera PCR Primer 2* [Barcode]
0.3 µL 100x SYBR Green I** (Invitrogen Cat #S-7563)
25 µL NEBNext High-Fidelity 2x PCR Master Mix (New England Labs Cat #M0541)
50 µL Total

* Complete list of primers are shown above.

**10,000x SYBR Green I is diluted in 10mM Tris buffer, pH 8 to make a 100x working solution.

2. Cycle as follows:

(1) 72°C, 5 min
(2) 98°C, 30 sec
(3) 98°C, 10 sec
(4) 63°C, 30 sec
(5) 72°C, 1 min
(6) Repeat steps 3-5, 4x
(7) Hold at 4°C

3. In order to reduce GC and size bias in PCR, the PCR reaction is monitored using qPCR to stop amplification prior to saturation. To run a qPCR side reaction, combine the following:

5 µL 5 cycles PCR amplified DNA
4.44 µL Nuclease Free H_2O
0.25 µL 25µM Customized Nextera PCR Primer 1*
0.25 µL 25µM Customized Nextera PCR Primer 2*
0.06 µL 100x SYBR Green I
5 µL NEBNext High-Fidelity 2x PCR Master Mix
15 µL Total

* Complete list of primers available in Section VI of this protocol

4. qPCR cycle as follows:

(1) 98°C, 30 sec
(2) 98°C, 10 sec
(3) 63°C, 30 sec
(4) 72°C, 1 min
(5) Repeat steps 2-4, 19x
(6) Hold at 4°C

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5. The additional number of cycles needed for the remaining 45 μL PCR reaction is determined as following:

(1) Plot linear Rn vs. Cycle
(2) Set 5000 RF threshold
(3) Calculate the # of cycle that is corresponded to ¼ of maximum fluorescent intensity

If the # of cycle to be added lies in between two cycles, the # is determined by taking the smaller integer as the # of cycle to be added (i.e., blue and pink samples)
If two samples have similar Ct values but differs in the fluorescent intensities, calculate the # of cycle using the sample with lower fluorescent intensity (i.e., red and blue samples)

6. Run the remaining 45 μL PCR reaction to the correct # of cycle. Cycle as follows:

(1) 98°C, 30 sec (2) 98°C, 10 sec (3) 63°C, 30 sec (4) 72°C, 1 min
(5) Repeat steps 2-4, x times
(6) Hold at 4°C

7. Purify amplified library using Qiagen PCR Cleanup Kit. Elute the purified library in 20 μL Elution Buffer (10mM Tris Buffer, pH 8). Be sure to dry the column before adding elution buffer.

IV. Library QC using Gel Electrophoresis

1. Dilute 1:20 100bp NEB DNA ladder with 10mM Tris Buffer, pH 8.
2. Add 0.6 μL 10x SYBR Green I to every 5 μL of diluted ladder.
3. Mix 1:1 of the diluted ladder with 2x DNA loading dye.
4. Mix 1:1 of amplified library with 2x DNA loading dye.
5. Run amplified library on 5% Bio-Rad Mini-Protean TBE Precast Gel (stored at 4°C). Load 5 μL diluted ladder/DNA loading dye mixture. Load 10 μL amplified library/DNA loading dye mixture.
6. Run at ~100 mV for 45 min.

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7. SYBR Green I dye has an excitation maximum at ~488 nm and has an emission maximum at ~520 nm. DNA stained with SYBR Green I dye can be visualized using a blue-light source or imaging systems equipped with laser that emits at 488 nm. We typically use Typhoon TRIO Variable Mode Imager from Amersham Biosciences for visualization. Images are best obtained by digitizing at 100 microns pixel size resolution with a 520 nm band-pass emission filter to screen out reflected and scattered excitation light and background fluorescence.

V. Library Quantitation

We use qPCR based methods to quantify our ATAC-seq libraries. We have found that other methods, such as Bioanalyzer and Qubit, can give misleading and inaccurate results due to the large distribution of insert sizes. We recommend quantifying libraries using the KAPA Library Quant Kit for Illumina Sequencing Platforms (KAPABiosystems).

Although the foregoing embodiments have been described in some detail by way of illustration and example for purposes of clarity of understanding, it is readily apparent to those of ordinary skill in the art in light of the above teachings that certain changes and modifications can be made thereto without departing from the spirit or scope of the appended claims.

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CLAIMS

What is claimed is:

1. A method for analyzing chromatin, comprising:

(a) treating chromatin isolated from a population of cells with an insertional enzyme complex to produce tagged fragments of genomic DNA;

(b) sequencing at least some of the tagged fragments to produce a plurality of sequence reads; and

(c) making an epigenetic map of a region of the genome of said cells by mapping information obtained from the sequence reads to the region.

2. The method of claim 1, wherein the information is obtained using the nucleotide sequences at the beginning and, optionally, the end of a sequence read.

3. The method of any of claims 1-2, wherein the information mapped in (c) is selected from one or more of:

(i) cleavage sites for the transposase;

(ii) the sizes of the fragments produced in step (a);

(iii) sequence read length;

(iii) the positions of sequence reads of a defined range in length; and

(iv) sequence read abundance.

4. The method of claim 3, wherein the fragments of a defined size range are nucleosome-free fragments.

5. The method of any of claims 1-4, wherein the epigenetic map shows one or more of:

(i) a profile of chromatin accessibility along the region;

(ii) DNA binding protein occupancy for a binding site in the region;

(iii) nucleosome-free DNA in the region;

(iv) positioning of nucleosomes along the region;

(v) chromatin states.

6. The method of claim 5, further comprising measuring global occupancy of a binding site for said DNA binding protein.

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7. The method of claim 5, wherein the DNA binding protein is a transcription factor.

8. The method of any of claims 1-7, wherein the population of cells is composed of 500 to 100,000 cells.

9. The method of any of claims 1-8, wherein the cells are isolated from an individual.

10. The method of any of claims 1-9, wherein the cells are isolated from blood of said individual.

11. The method of claims 1-10, wherein the cells are of the same cell type.

12. The method of claim 11, wherein the cells are FACS–selected cells.

13. The method of any of claims 1-12, wherein the treating step (a) comprises:

isolating nuclei from the a population of cells; and

combining the isolated nuclei with said insertional enzyme complex, wherein the combining results in both lysis of the nuclei to release said chromatin and production of said tagged fragments of genomic DNA.

14. The method of any of claims 1-13, wherein the transposase is derived from Tn5 transposase.

15. The method of any of claims 1-14, wherein the transposase is derived from MuA transposase.

16. A method for comparing two samples comprising:

(a) analyzing a first population of cells using the method of claim 1 to produce a first epigenetic map; and

(b) analyzing a second population of cells using the method of claim 1 to produce a second epigenetic map; and

(c) comparing the first epigenetic map to the second epigenetic map.

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17. The method of claim 16, wherein the first population of cells and the second population of cells are collected from the same individual at different times.

18. The method of claim 16, wherein the first population of cells and the second population of cells are different populations of cells collected from different individuals.

19. A diagnostic method, comprising:

analyzing chromatin from a patient using the method of claim 1, to produce an epigenetic map; and

providing a diagnosis or prognosis based on the epigenetic map.

20. A kit comprising:

(a) reagents for isolating nuclei from a population of cells;

(b) an insertional enzyme complex, and

(c) transposase reaction buffer,

wherein the components of the kit are configured such that, combining the reaction buffer, transposon tags and adaptors with nuclei *in vitro* results in both lysis of the nuclei to release chromatin and production of tagged fragments of genomic DNA.

21. A method for determining accessibility of a polynucleotide at a site, wherein said polynucleotide is from a cell sample, comprising:

(a) inserting a plurality of molecular tags with an insertional enzyme into said polynucleotide; and

(b) using said molecular tags to determine accessibility at said site.

22. The method of claim 21, further comprising using said determined accessibility to identify one or more proteins that are bound to said polynucleotide at said site.

23. The method of claim 22, wherein at least one of said proteins is a transcription factor.

24. The method of claim 21, further comprising using said molecular tags to generate an accessibility map of said polynucleotide.

25. A method for analyzing the three-dimensional structure of a polynucleotide from a cell sample, comprising:

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(a) inserting a plurality of molecular tags with an insertional enzyme into said polynucleotide; and

(b) using said molecular tags to analyze the three-dimensional structure of said polynucleotide.

26. The method of claim 21 or 25, wherein said cell sample is obtained from a primary source.

27. The method of claim 21 or 25, wherein said cell sample consists of less than about 500,000 cells.

28. The method of claim 27, wherein said cell sample is a single cell.

29. The method of claim 21 or 25, wherein said polynucleotide is fragmented into a plurality of fragments during step (a).

30. The method of claim 29, further comprising amplifying said fragments.

31. The method of claim 29, wherein said accessibility is determined or said three-dimensional structure is analyzed by sequencing said fragments and thereby generating a plurality of sequencing reads.

32. The method of claim 31, wherein said fragments are sequenced by a high-throughput sequencing technique.

33. The method of claim 31, further comprising normalizing said sequencing reads based on the sequence insertion preference of said insertional enzyme.

34. The method of claim 31, wherein the length of said sequenced reads is used to determine a chromatin state annotation.

35. The method of claim 21 or 25, further comprising permeabilizing said cell sample to allow access for said insertional enzyme.

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36. The method of claim 35, wherein the nuclei in said cell sample is minimally perturbed during said permeabilization.

37. The method of claim 35, wherein said cell sample is permeabilized using a permeabilization agent.

38. The method of claim 37, wherein said permeabilization agent is selected from the group consisting of NP40, digitonin, tween, streptolysin, and cationic lipids.

39. The method of claim 35, wherein said cell sample is permeabilized using hypotonic shock and/or ultrasonication.

40. The method of claim 21 or 25, wherein said insertional enzyme further comprises a nuclear localization signal.

41. The method of claim 21 or 25, wherein said insertion is facilitated by addition of one or more divalent cations.

42. The method of claim 41, wherein said one or more divalent cations comprises magnesium.

43. The method of claim 41, wherein said one or more divalent cations comprises manganese.

44. The method of claim 21 or 25, further comprising analyzing a disease state in a subject based on said accessibility of said specific site or said three-dimensional structure of said polynucleotide, wherein said cell sample is obtained from said subject.

45. The method of claim 21 or 25, further comprising dividing said cell sample or said polynucleotides into a plurality of portions.

46. The method of claim 45, wherein said portions are divided based on said molecular tags.

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47. The method of claim 21 or 25, further comprising analyzing a phenotype of said cell sample.

48. The method of claim 47, wherein said phenotype is correlated to said accessibility of said site or said three-dimensional structure of said polynucleotide.

49. The method of claim 21 or 25, wherein said insertional enzyme comprises two or more enzymatic moieties.

50. The method of claim 49, wherein each of said enzymatic moieties inserts a common sequence into said polynucleotide.

51. The method of claim 50, wherein said common sequence comprises a common barcode.

52. The method of claim 49, wherein said enzymatic moieties are linked together.

53. The method of claim 49, wherein said enzymatic moieties comprise transposases.

54. The method of claim 21 or 25, wherein said polynucleotide is fragmented into a plurality of fragments during step (a), and wherein said fragments comprising said common barcode are determined to be in proximity in the three-dimensional structure of said polynucleotide.

55. The method of claim 21 or 25, wherein said molecular tags comprise sequencing adaptors.

56. The method of claim 55, wherein said sequencing adaptors further comprise a barcode label.

57. The method of claim 55, wherein said barcode labels comprises a unique sequence.

58. The method of claim 21 or 25, wherein said molecular tags comprise fluorescence tags.

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59. A composition comprising a polynucleotide, an insertional enzyme and an insert element, wherein:

(a) said insert element comprises a nucleic acid comprising a predetermined sequence; and

(b) said insertional enzyme further comprises an affinity tag.

60. A composition comprising a polynucleotide, an insertional enzyme and an insert element, wherein:

(a) said insertional enzyme comprises two or more enzymatic moieties; and

(b) said enzymatic moieties are linked together.

61. A kit comprising:

(a) a cell lysis buffer;

(b) an insertional enzyme comprising an affinity tag; and

(c) an insert element comprising a nucleic acid, wherein said nucleic acid comprises a predetermined sequence.

62. A kit comprising:

(a) a cell lysis buffer;

(b) an insertional enzyme comprising two or more enzymatic moieties, wherein said enzymatic moieties are linked together; and

(c) an insert element.

63. The method, composition or kit of claim 21, 25, 59, 60, 61 or 62, wherein said polynucleotide is bound to a plurality of association molecules.

64. The method, composition or kit of claim 63, wherein said association molecules are proteins.

65. The method, composition or kit of claim 64, wherein said proteins comprise histones.

66. The method, composition or kit of claim 21, 25, 59, 60, 61 or 62, wherein said insertional enzyme is a transposase.

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67. The method, composition or kit of claim 66, wherein said transposase is derived from a Tn5 transposase.

68. The method, composition or kit of claim 66, wherein said transposase is derived from a MuA transposase.

69. The method, composition or kit of claim 66, wherein said transposase is derived from a Vibhar transposase.

70. The method, composition or kit of claim 21, 25, 59, 60, 61 or 62, wherein said insertional enzyme further comprises an affinity tag.

71. The method, composition or kit of claim 70, wherein said affinity tag is an antibody.

72. The method, composition or kit of claim 71, wherein said antibody binds to a transcription factor.

73. The method, composition or kit of claim 71, wherein said antibody binds to a modified nucleosome.

74. The method, composition or kit of claim 71, wherein said antibody binds to a modified nucleic acid.

75. The method, composition or kit of claim 74, wherein said modified nucleic acid is a methylated or hydroxymethylated DNA.

76. The method, composition or kit of claim 70, wherein said affinity tag is a single-stranded nucleic acid.

77. The method, composition or kit of claim 76, wherein said single-stranded nucleic acid binds to a target nucleic acid.

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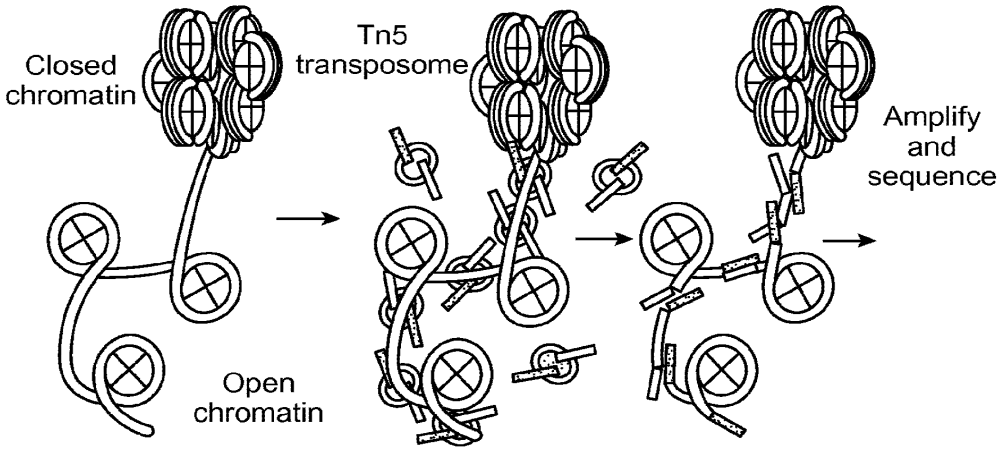


FIG. 1A

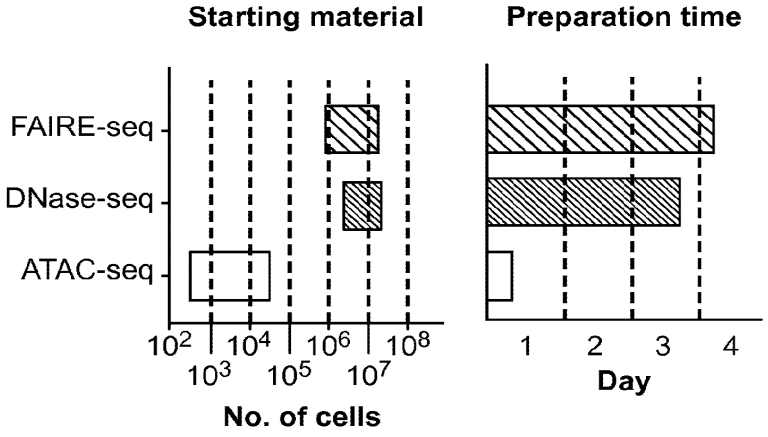


FIG. 1B

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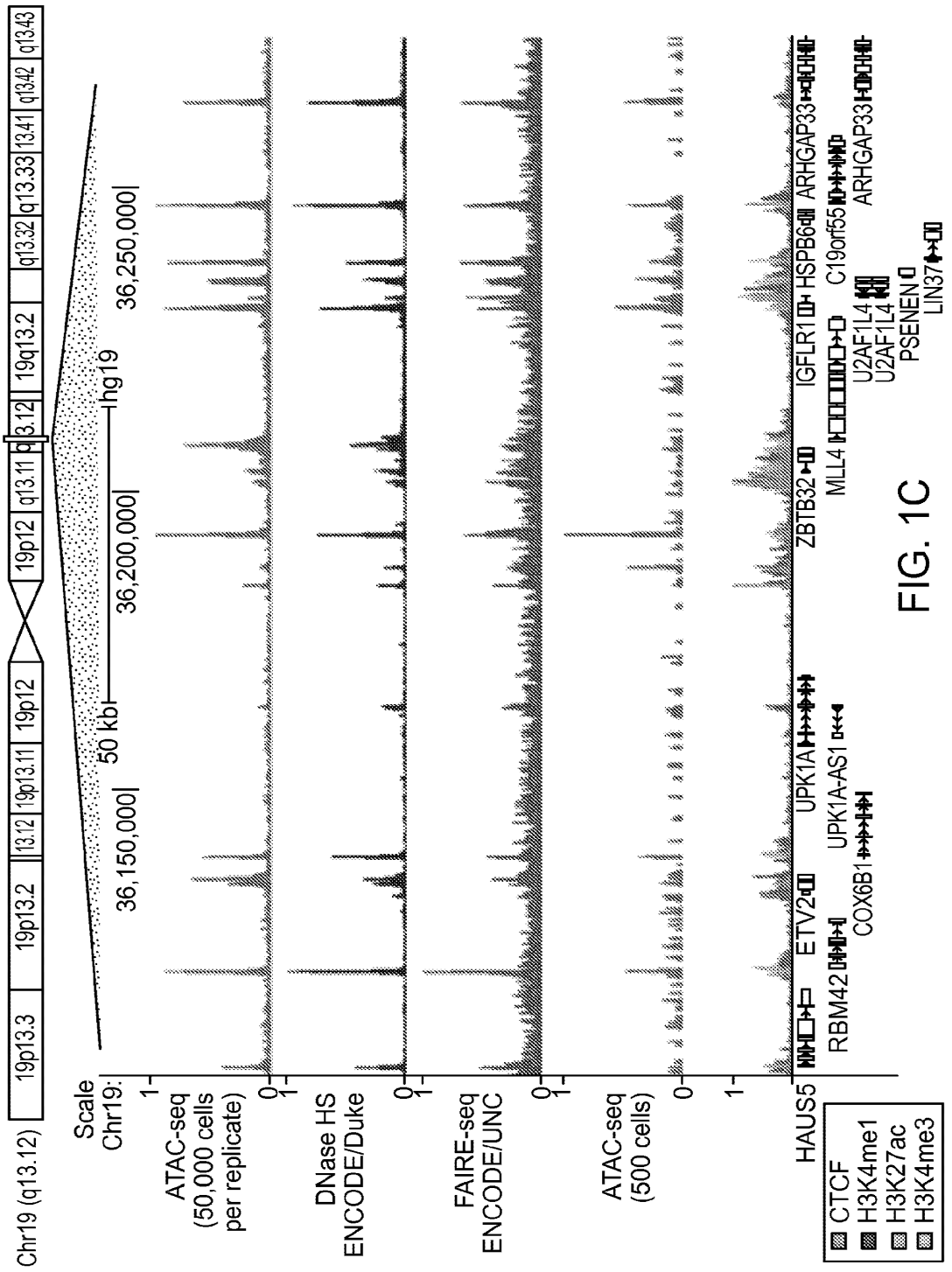


FIG. 1C

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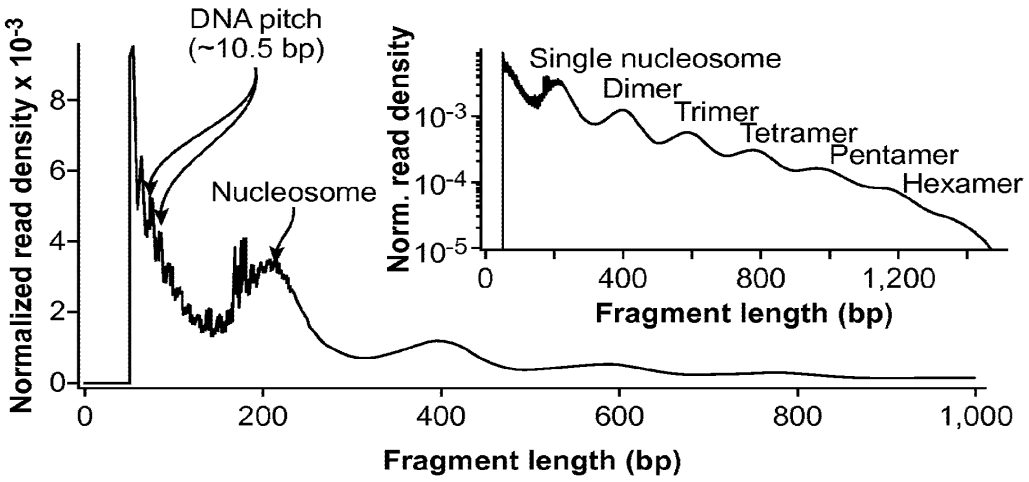


FIG. 2A

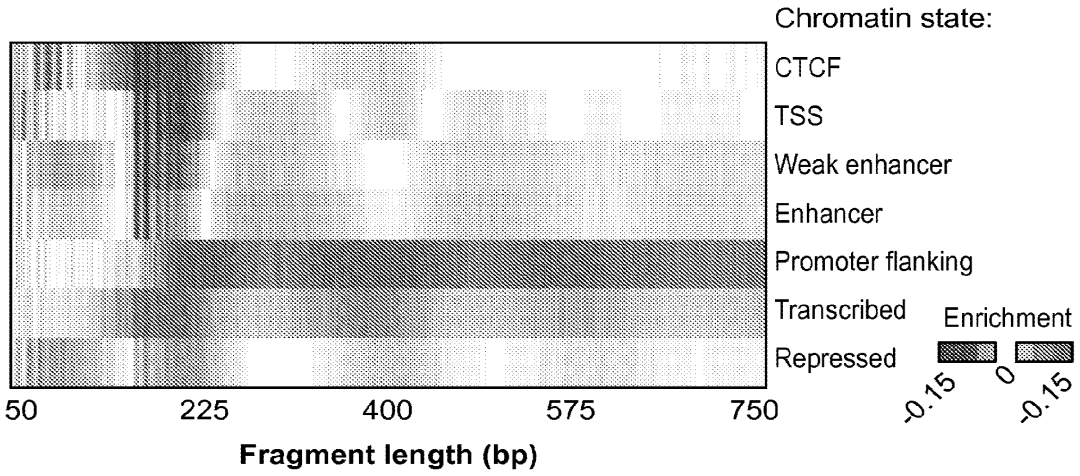


FIG. 2B

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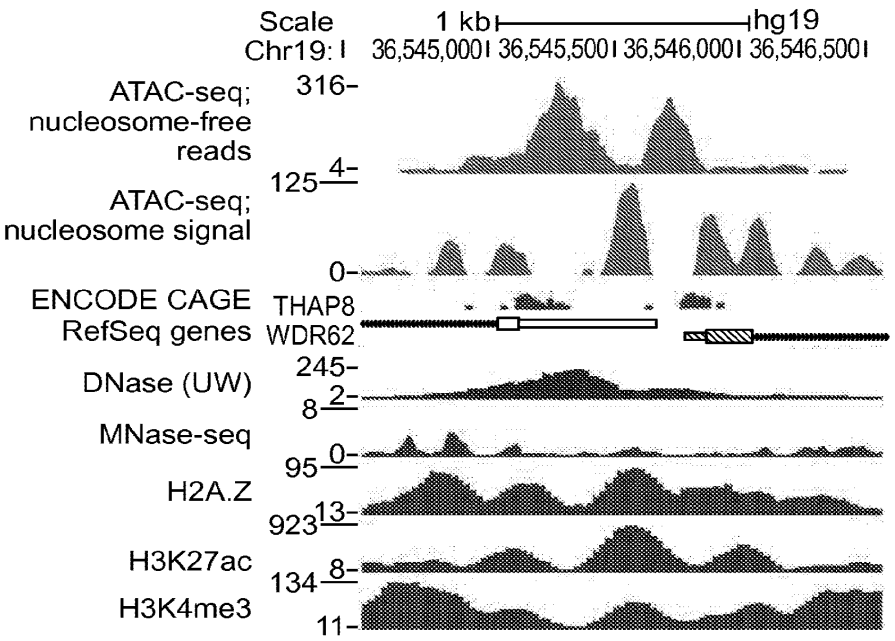


FIG. 3A

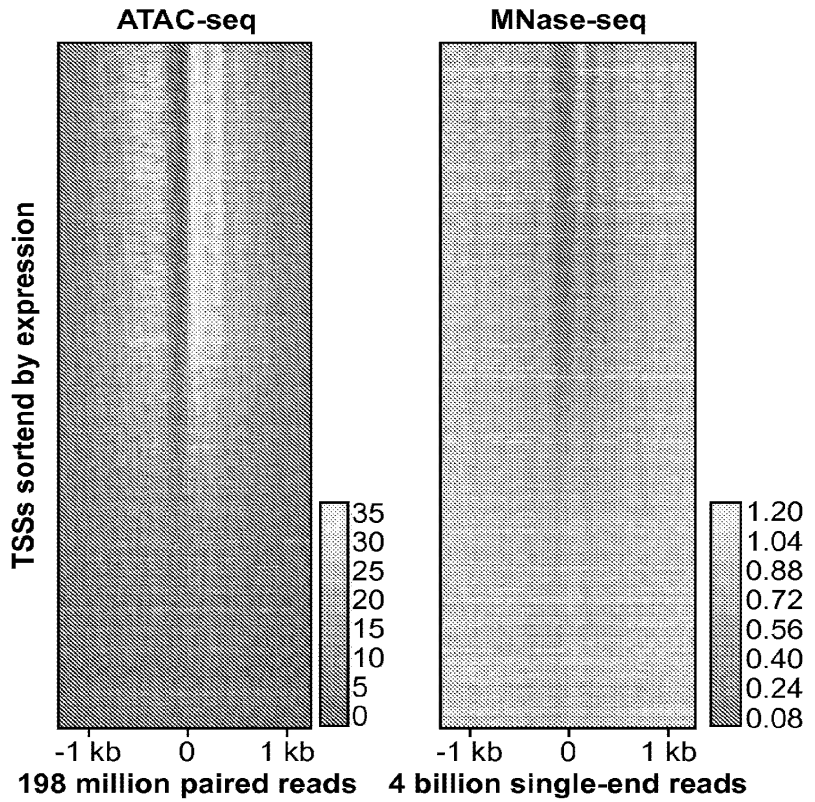


FIG. 3B

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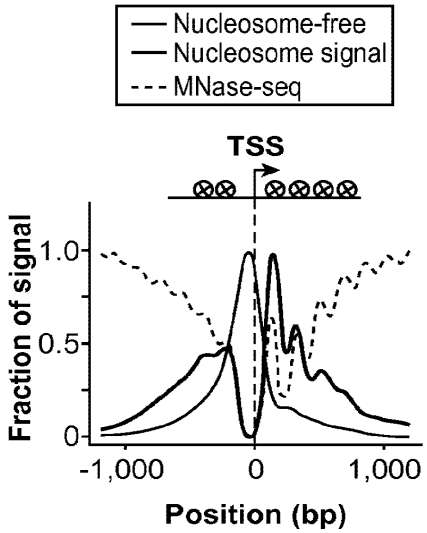


FIG. 3C

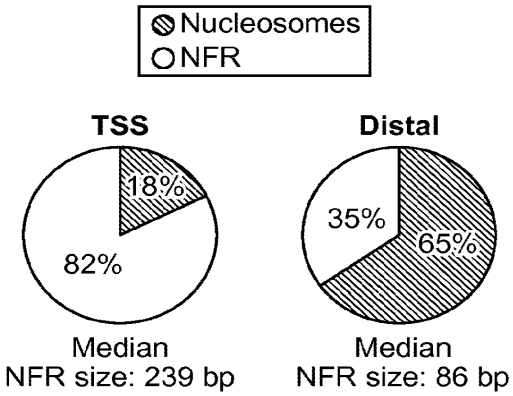


FIG. 3D

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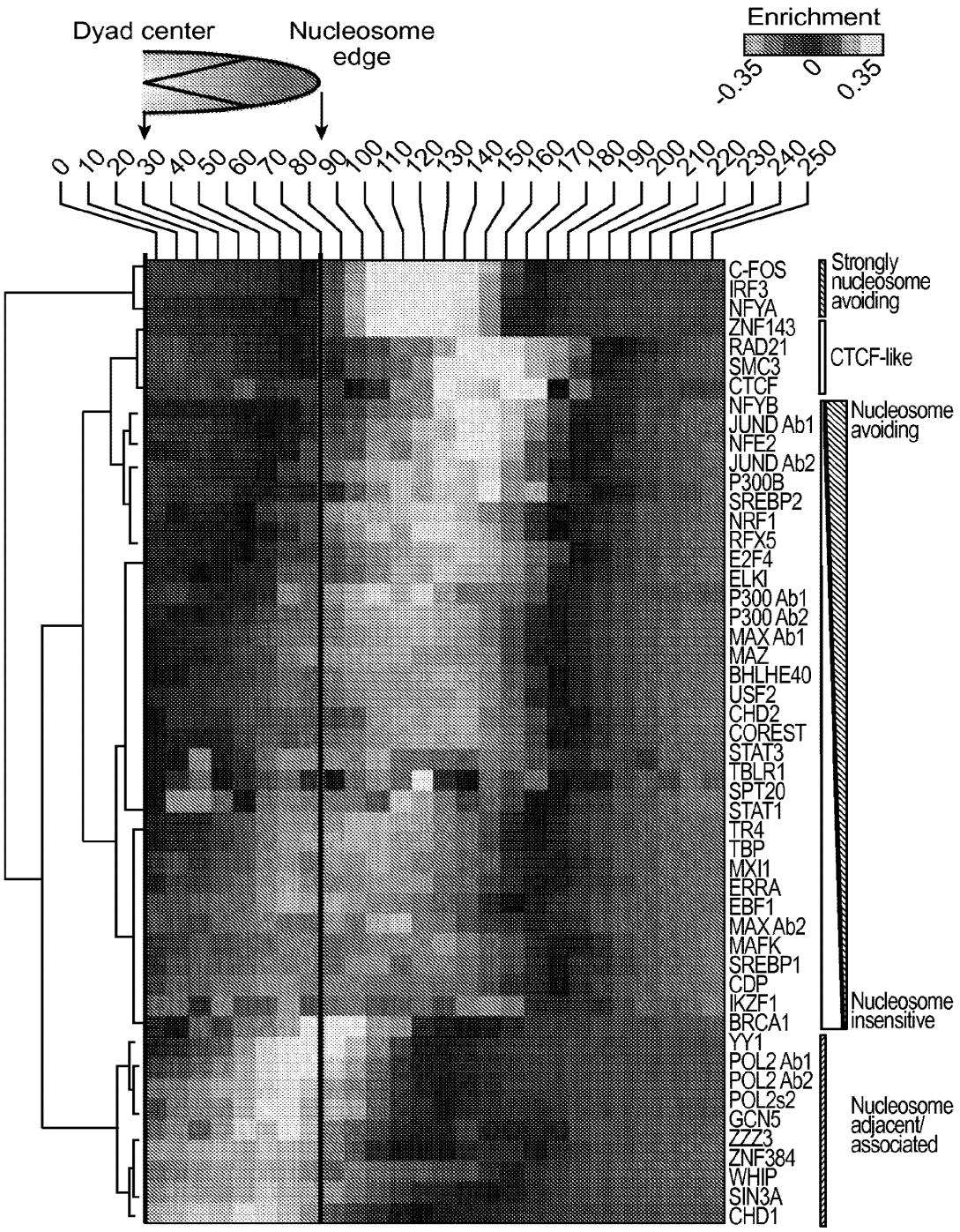


FIG. 3E

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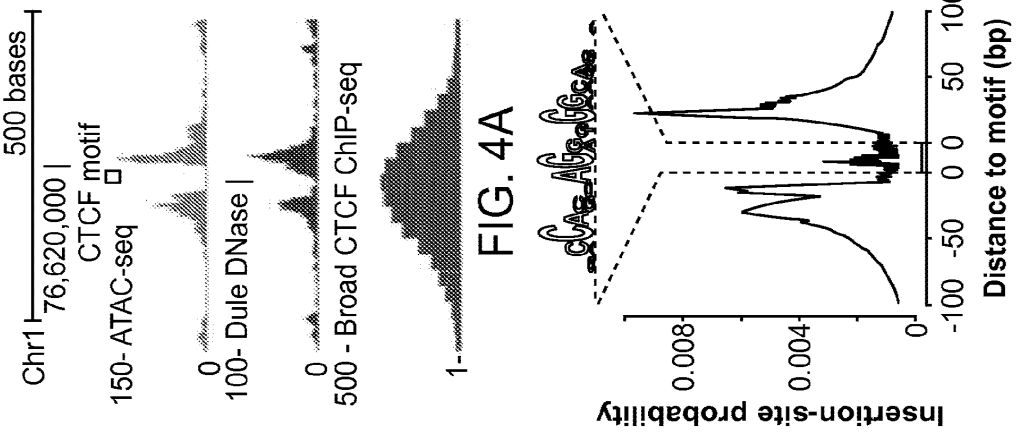


FIG. 4A

FIG. 4B

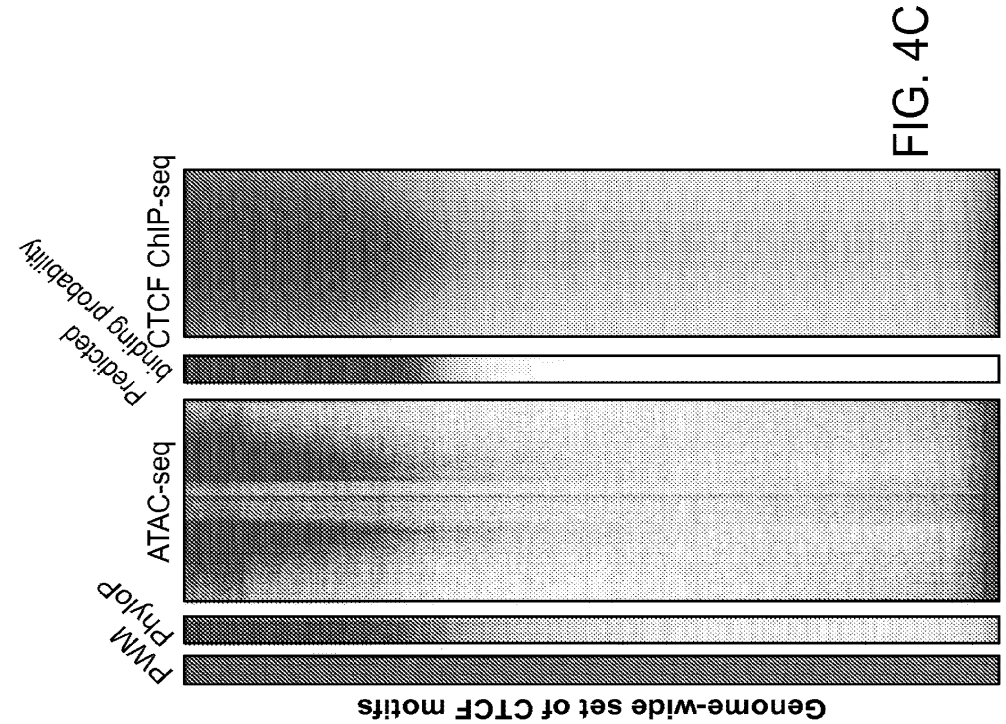


FIG. 4C

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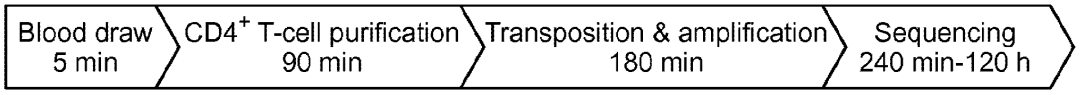


FIG. 5A

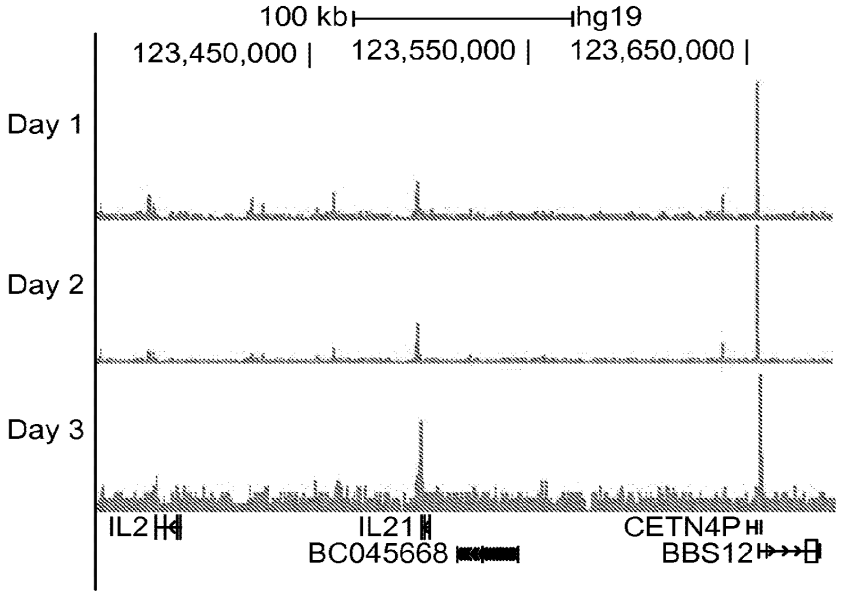


FIG. 5B

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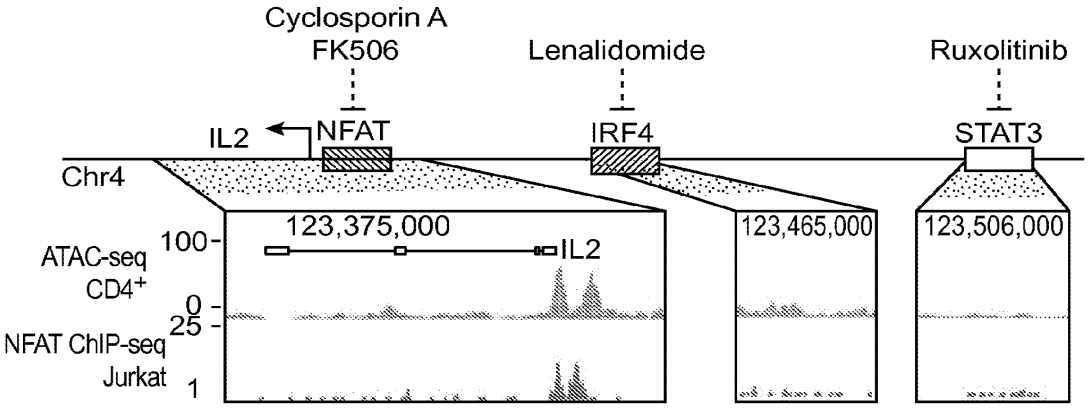


FIG. 5C

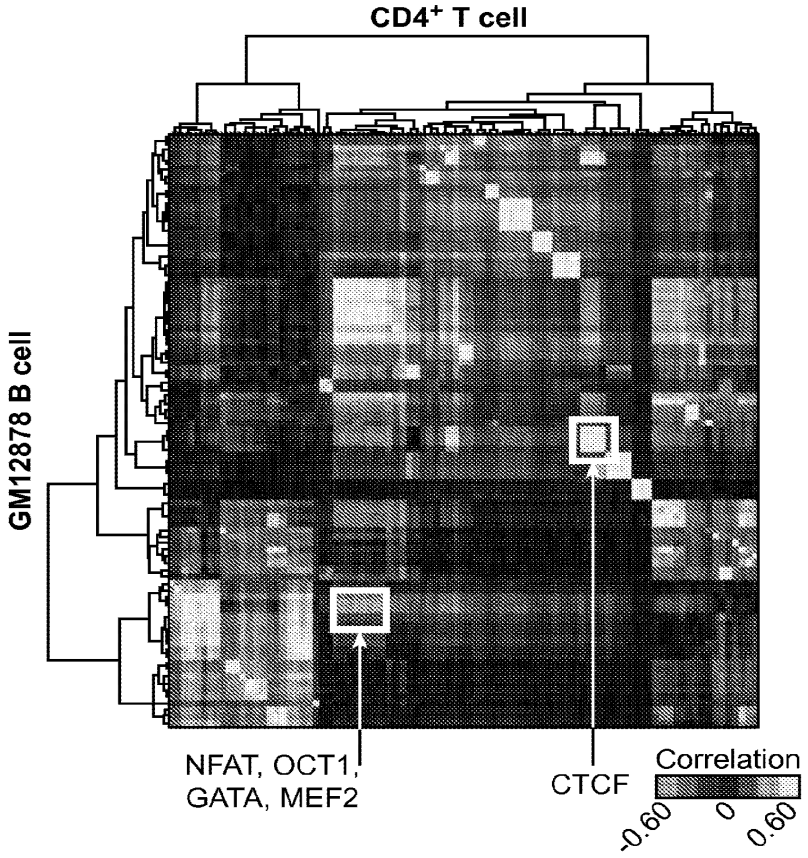


FIG. 5D

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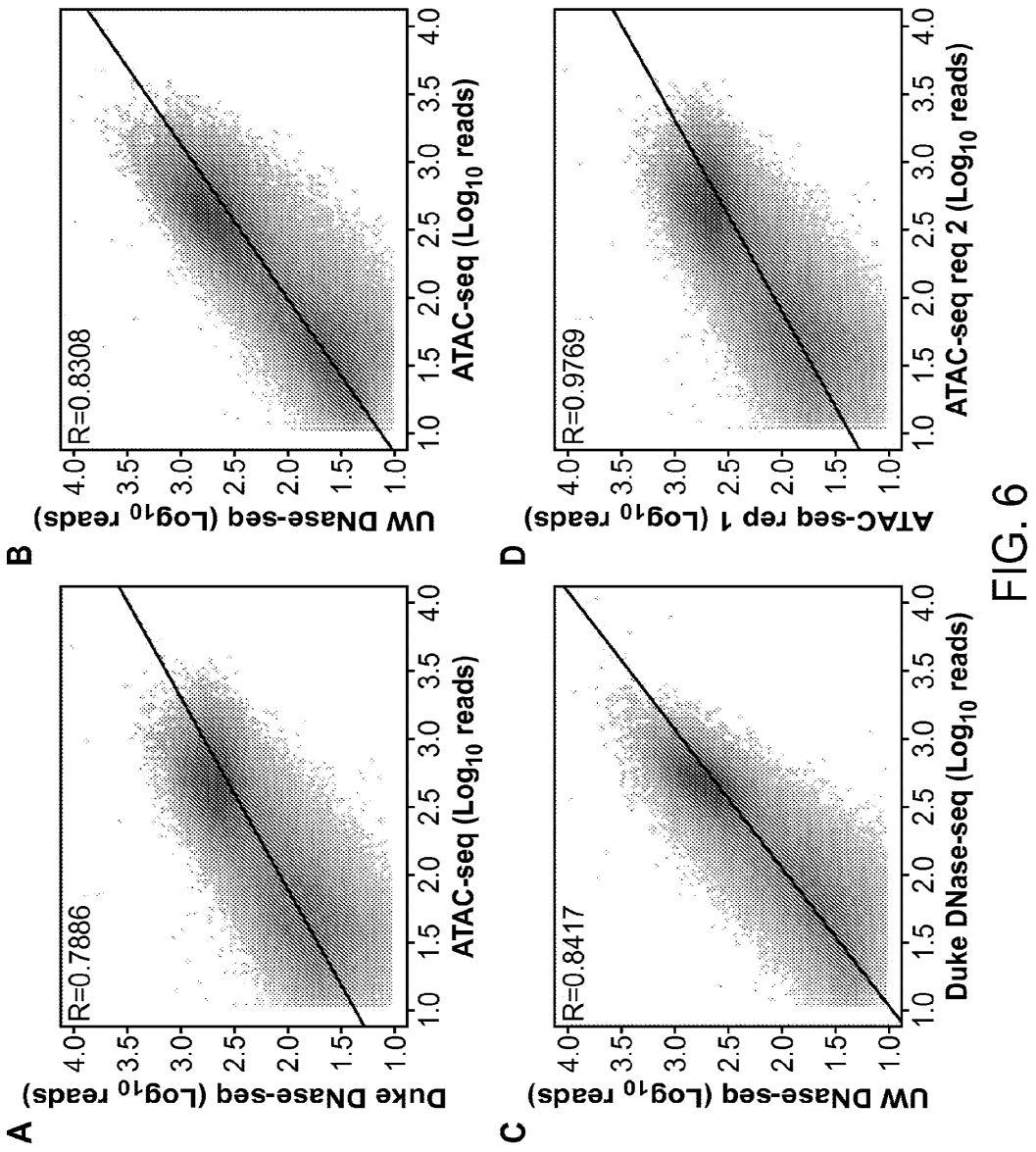
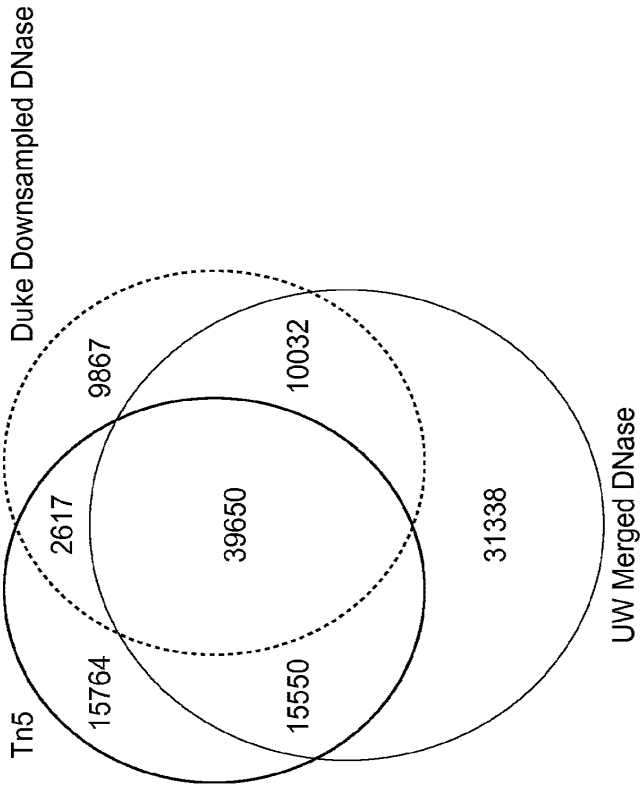


FIG. 6

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	ATAC Unique	UW Unique	Duke Unique	ATAC and UW	ATAC and Duke	UW and Duke	Intersect
ATAC-Seq	6.30%	4.36%	1.08%	10.83%	1.53%	2.09%	73.80%
UW DNase	1.32%	8.13%	0.68%	7.57%	0.33%	4.34%	77.62%
Duke DNase	2.10%	5.27%	14.80%	4.02%	1.44%	6.91%	65.46%

FIG. 7

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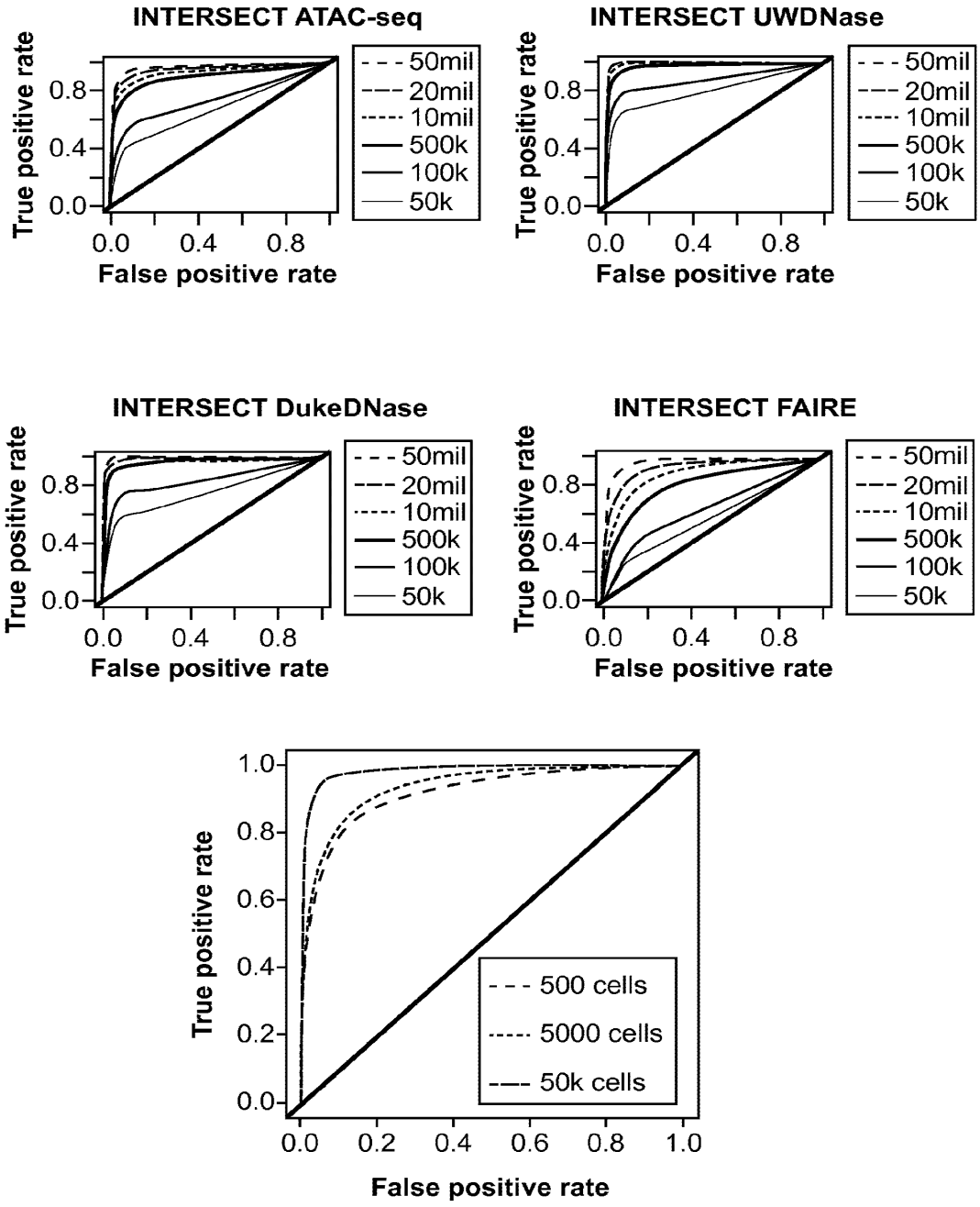


FIG. 8

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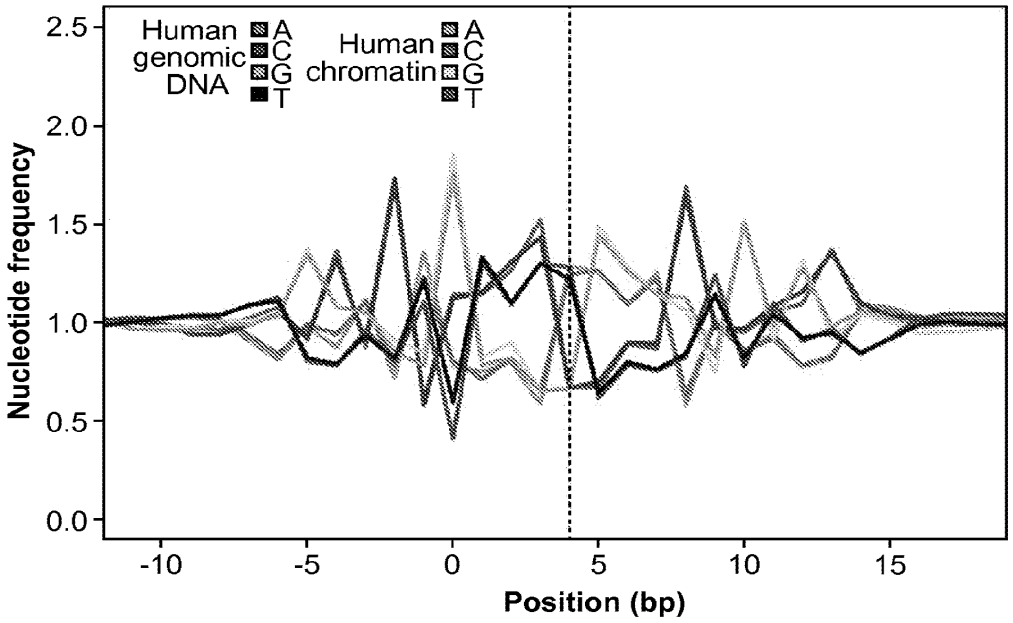


FIG. 9

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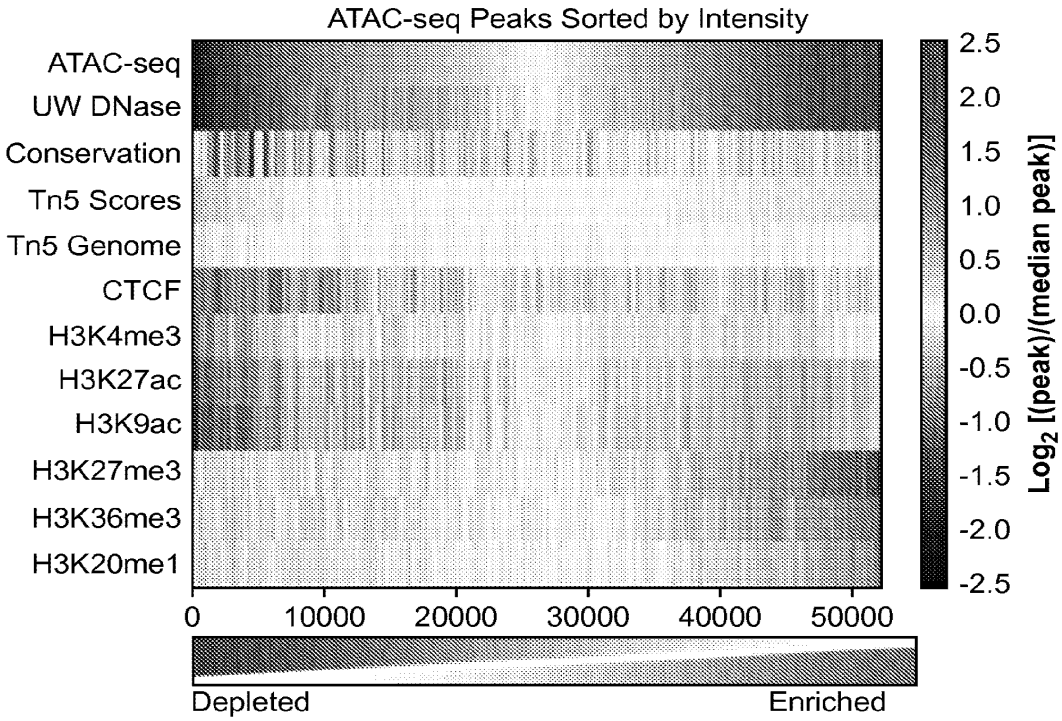


FIG. 10

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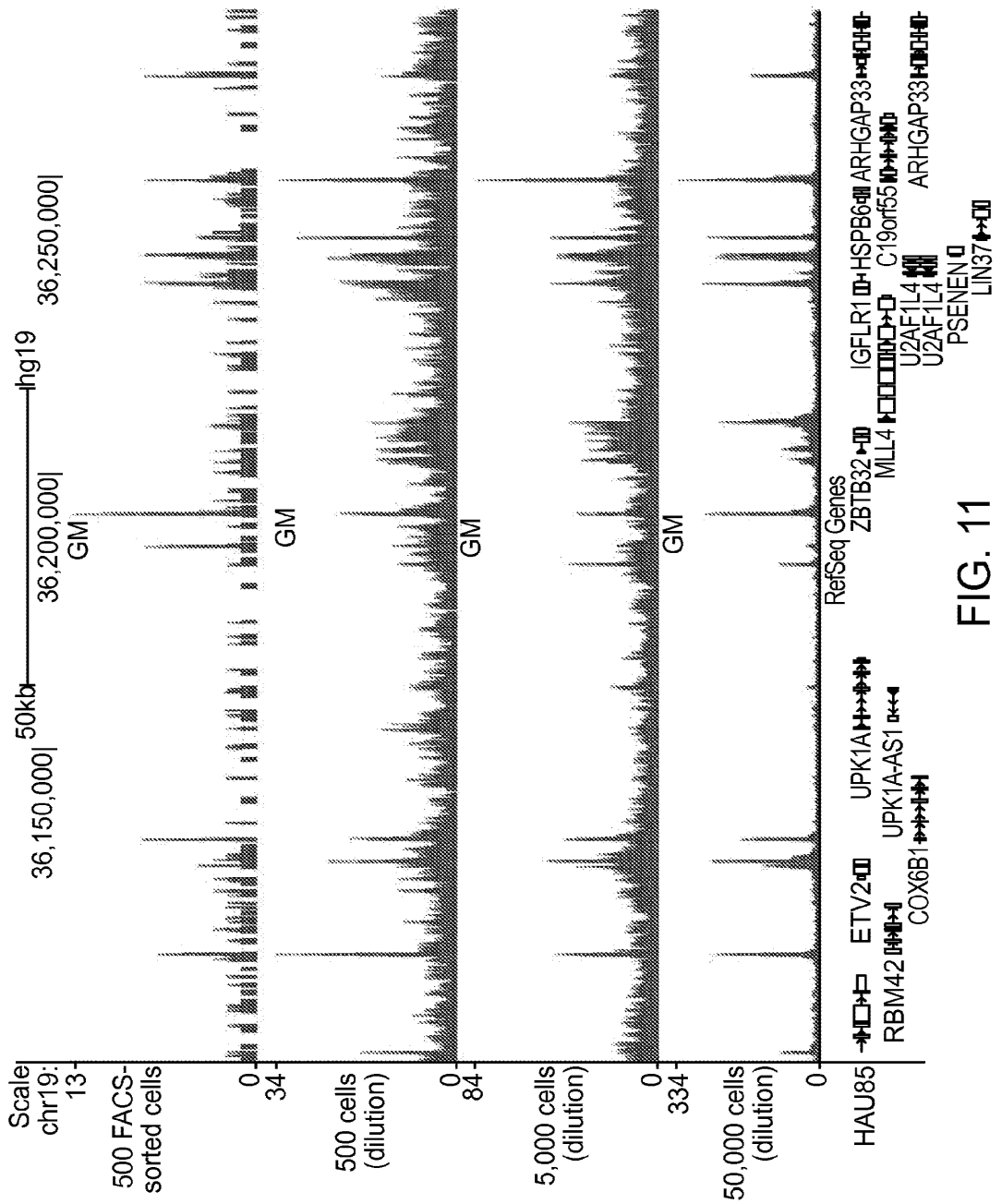


FIG. 11

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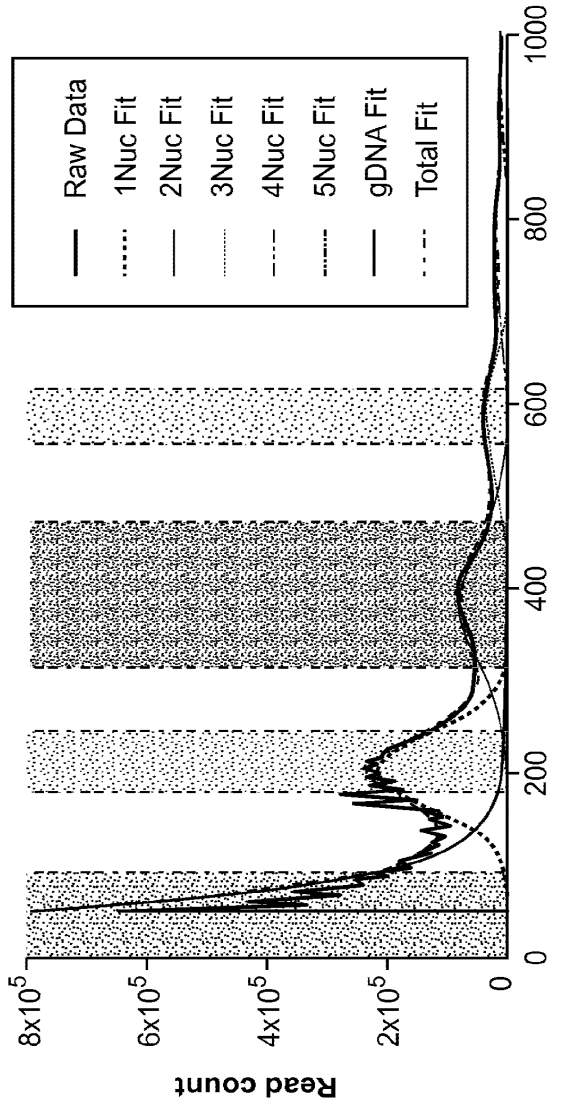


FIG. 12

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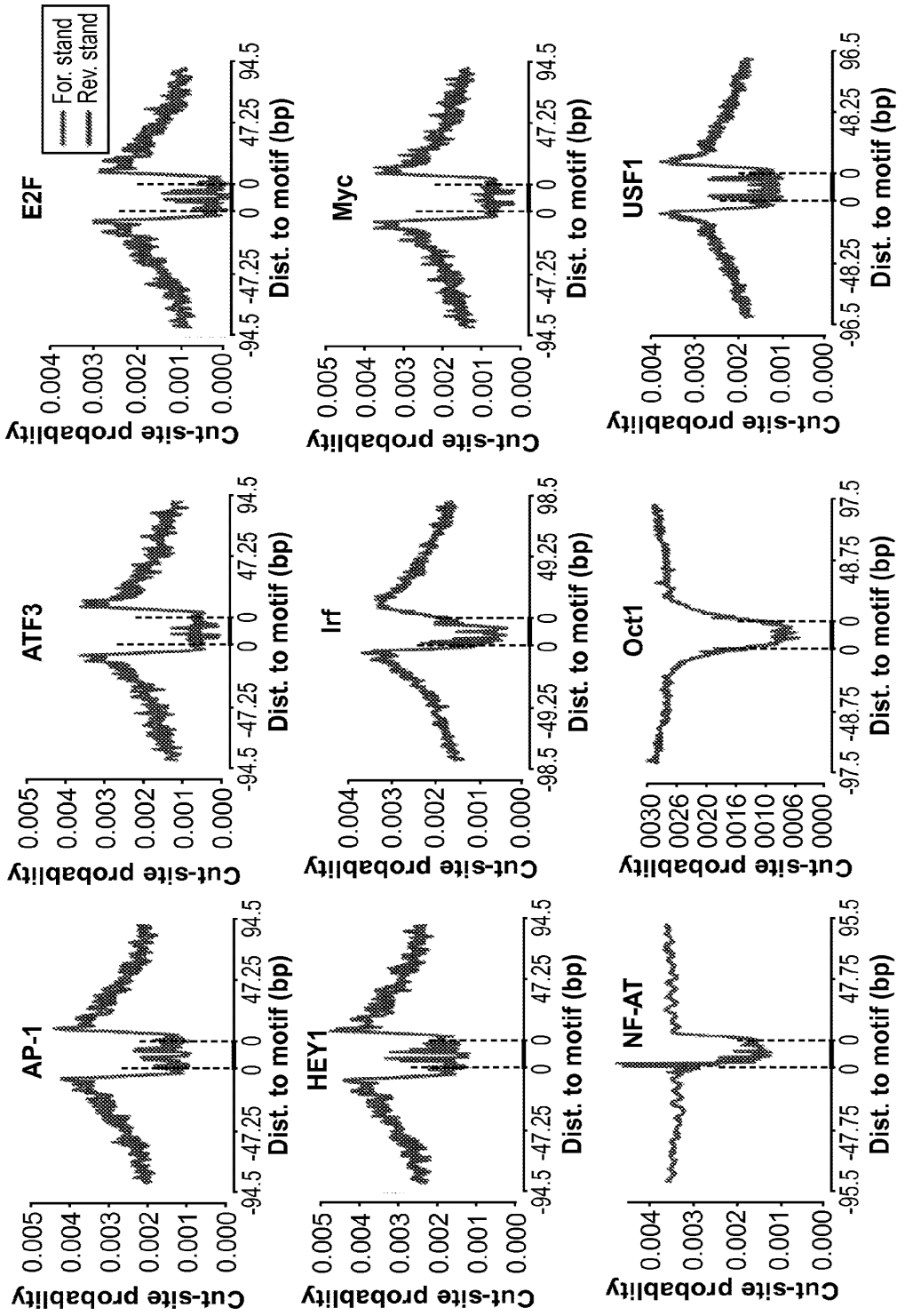


FIG. 13

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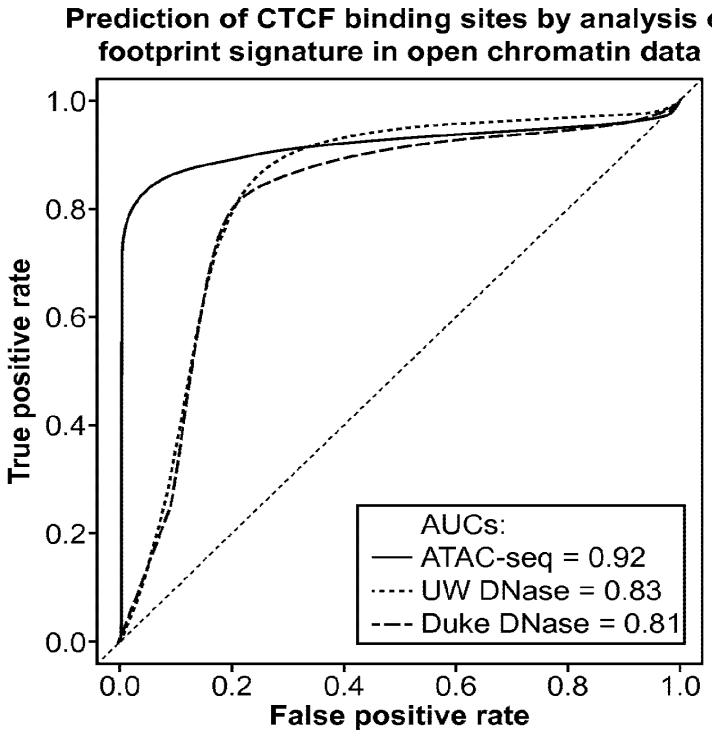


FIG. 14

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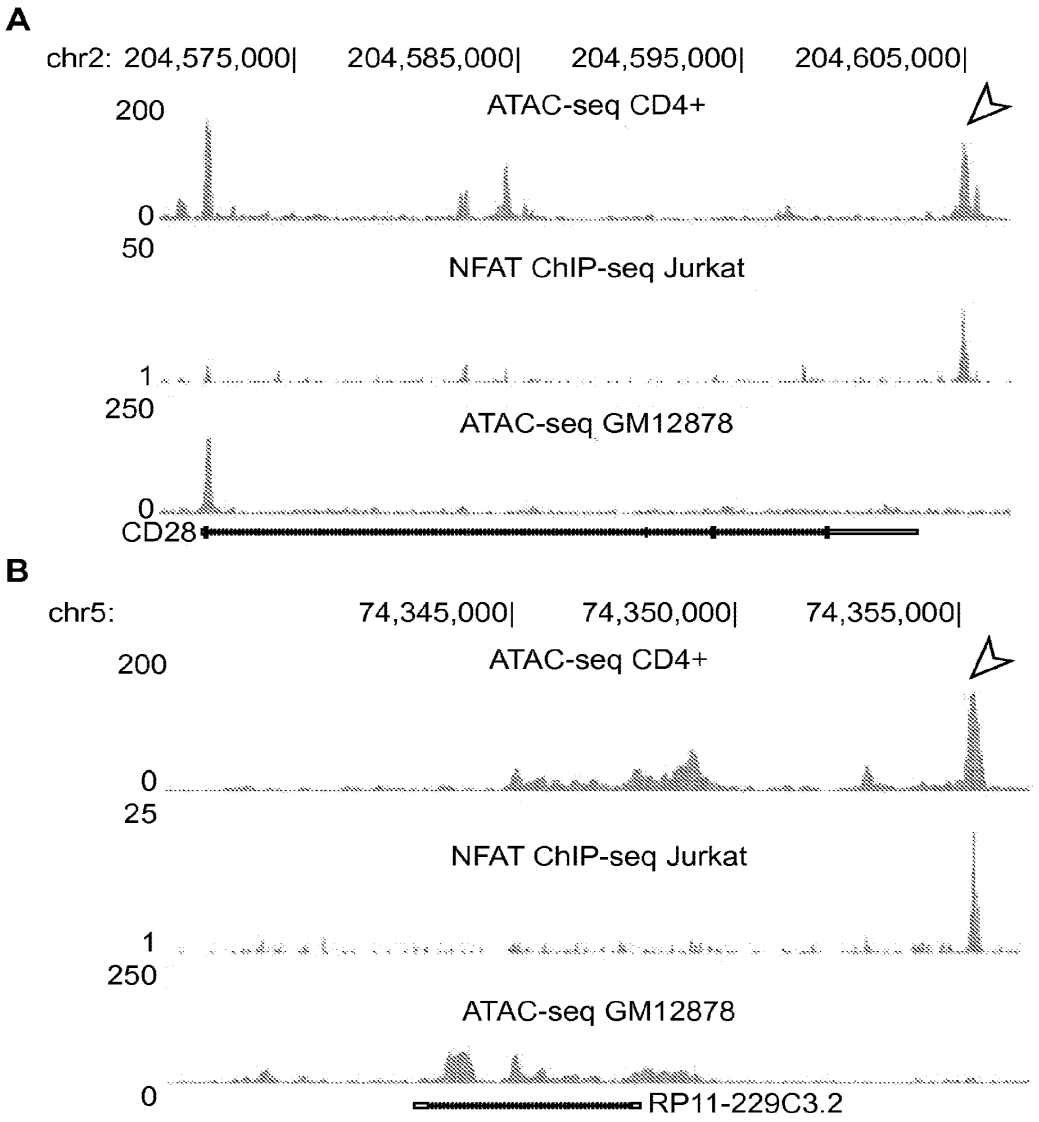


FIG. 15

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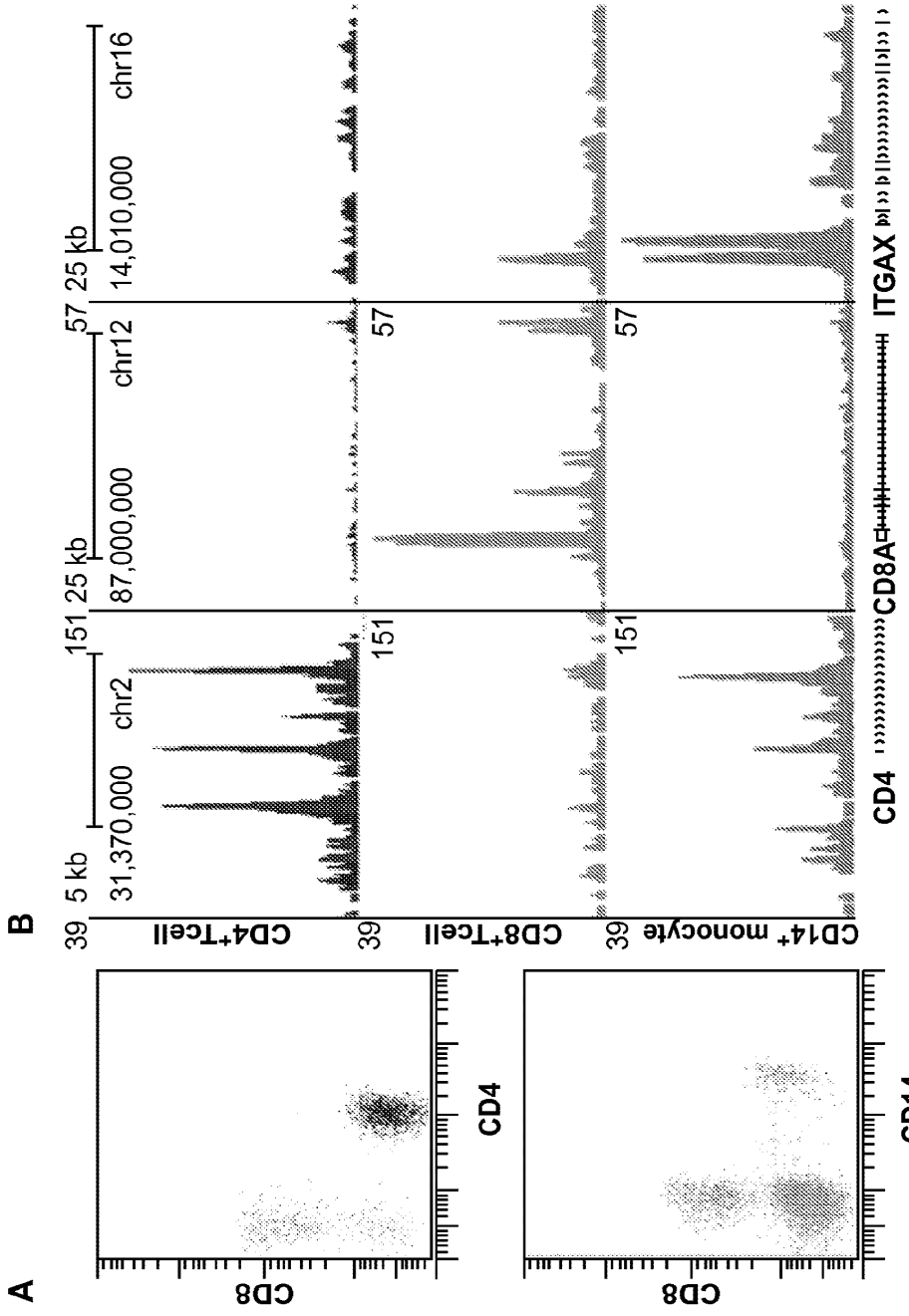


FIG. 16

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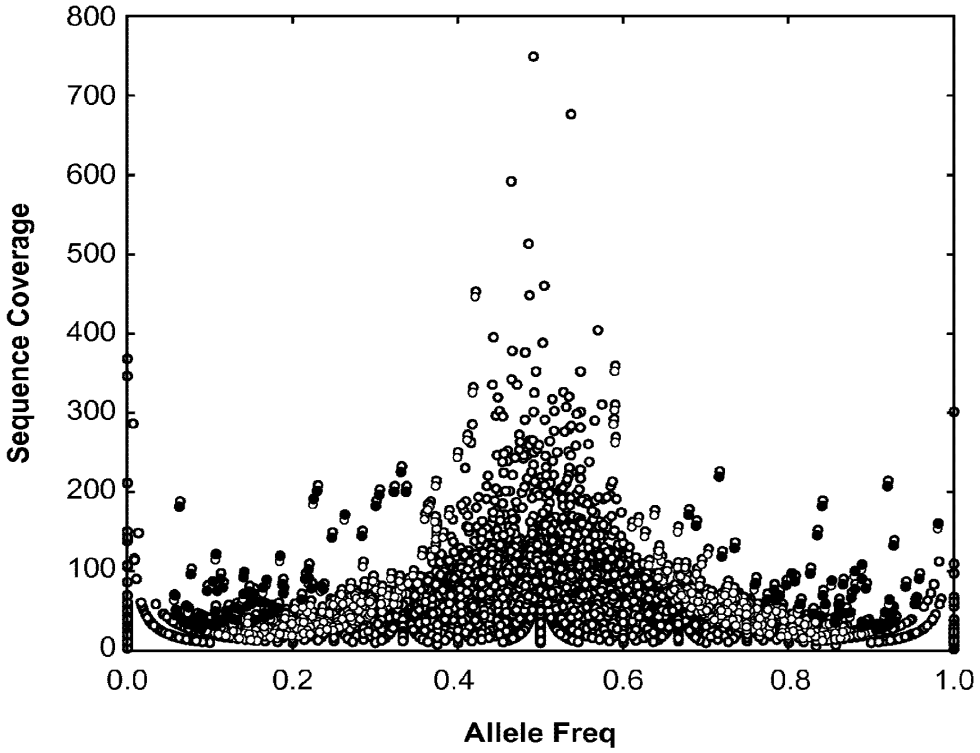


FIG. 17

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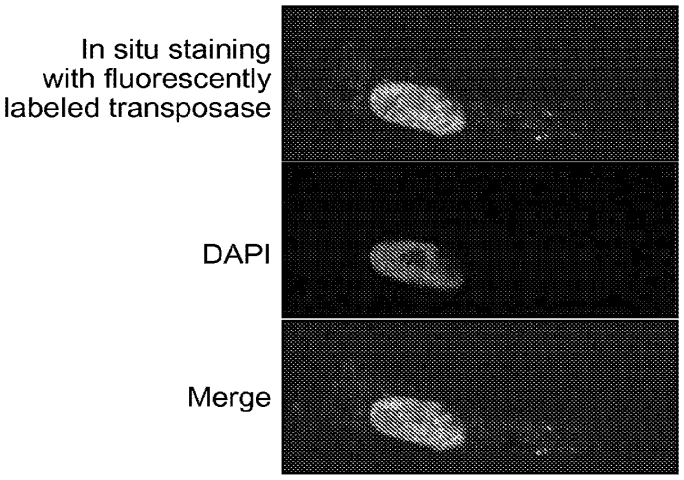


FIG. 18

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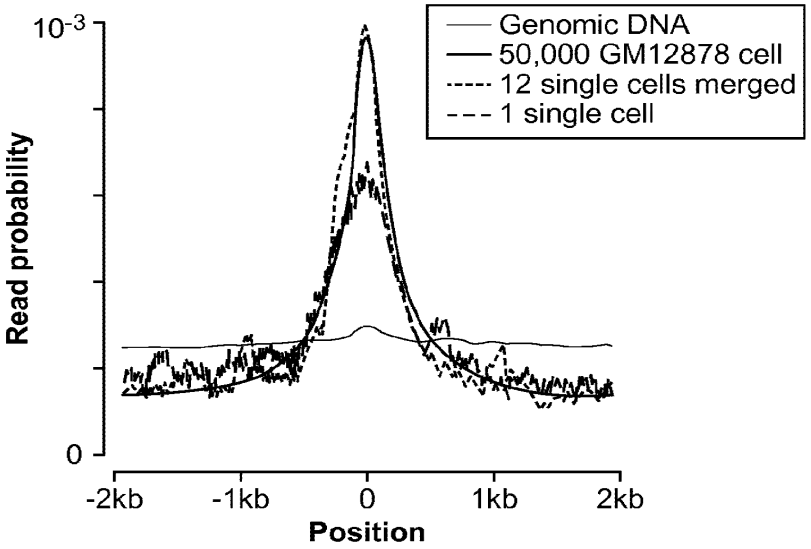


FIG. 19

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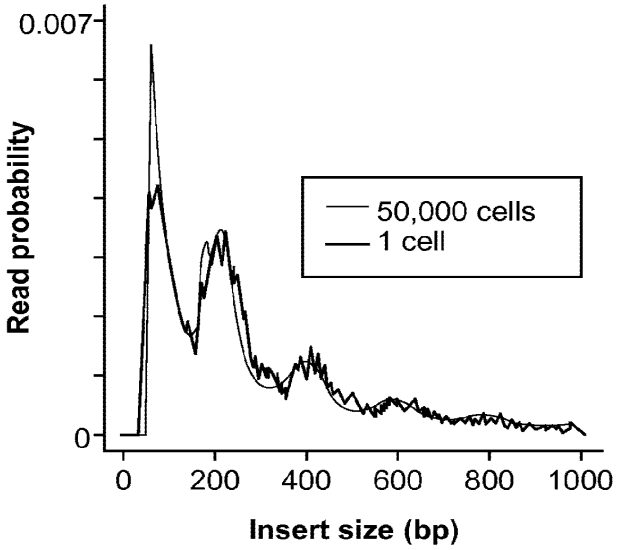


FIG. 20

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(74) Agent: **KEDDIE, James S.**; Bozicevic, Field & Francis LLP, 1900 University Avenue, Suite 200, East Palo Alto, California 94303 (US).

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(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

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8 January 2015

(54) Title: TRANSPOSITION INTO NATIVE CHROMATIN FOR PERSONAL EPIGENOMICS

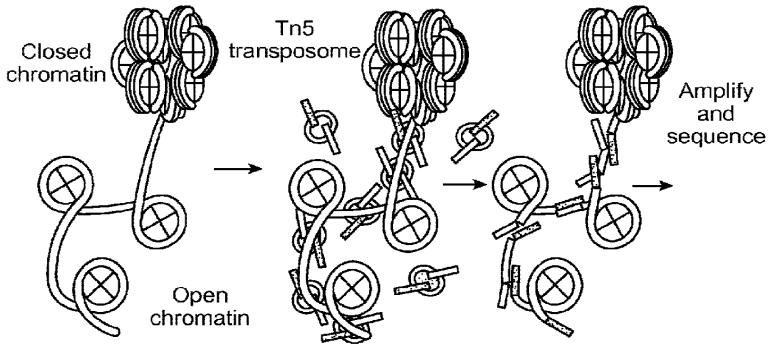


FIG. 1A

(57) Abstract: Provided herein is a method for analyzing polynucleotides such as genomic DNA. In certain embodiments, the method comprises: (a) treating chromatin isolated from a population of cells with an insertional enzyme complex to produce tagged fragments of genomic DNA; (b) sequencing a portion of the tagged fragments to produce a plurality of sequence reads; and (c) making an epigenetic map of a region of the genome of the cells by mapping information obtained from the sequence reads to the region. A kit for performing the method is also provided.

WO 2014/189957 A3

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Sequence Listing was accepted.
If you need help call the Patent Electronic Business Center at (866) 217-9197 (toll free).
Reviewer: Anjum, Durreshwar (CGI Federal)
Timestamp: [year=2015; month=10; day=20; hr=9; min=0; sec=35; ms=295;]
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Validated By CRFValidator v 1.0.4

Application No: 14784250 Version No: 1.0

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UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/784,250	10/13/2015		560	STAN-1111	77	8

CONFIRMATION NO. 6877

FILING RECEIPT

77974
Stanford University Office of Technology Licensing
Bozicevic, Field & Francis LLP
1900 University Avenue
Suite 200
East Palo Alto, CA 94303

OC000000078776805

Date Mailed: 11/23/2015

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Paul Giresi, Palo Alto, CA;
Jason D. Buenrostro, Redwood City, CA;
Howard Y. Chang, Stanford, CA;
William J. Greenleaf, Menlo Park, CA;

Applicant(s)

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, Stanford, CA;

Power of Attorney: The patent practitioners associated with Customer Number 77974

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/US14/38825 05/20/2014
which claims benefit of 61/826,728 05/23/2013

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

If Required, Foreign Filing License Granted: 11/19/2015
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/784,250**

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01030
Page 00268

Projected Publication Date: 03/03/2016

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

Transposition of Native Chromatin for Personal Epigenomics

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

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10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01030
Page 00269

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01030
Page 00270

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www.uspto.gov

U.S. APPLICATION NUMBER NO.	FIRST NAMED INVENTOR	ATTY. DOCKET NO.
14/784,250	Paul Giresi	STAN-1111

77974
Stanford University Office of Technology Licensing
Bozicevic, Field & Francis LLP
1900 University Avenue
Suite 200
East Palo Alto, CA 94303

INTERNATIONAL APPLICATION NO.	
PCT/US14/38825	
I.A. FILING DATE	PRIORITY DATE
05/20/2014	05/23/2013

CONFIRMATION NO. 6877
371 FORMALITIES LETTER

OC000000078776606

Date Mailed: 11/23/2015

Notification of Insufficiency Under 37 CFR 1.492 and/or 1.495 (DO/EO/US)

The following items have been submitted by the applicant or the International Bureau to the United States Patent and Trademark Office as a Designated / Elected Office (37 CFR 1.495).

- Indication of Small Entity Status
- Priority Document
- Copy of the International Application filed on 10/13/2015
- Copy of the International Search Report filed on 10/13/2015
- Preliminary Amendments filed on 10/13/2015
- Information Disclosure Statements filed on 10/13/2015
- Sequence Listing txt file (EFS or physical medium) filed on 10/13/2015
- Inventor's Oath or Declaration filed on 10/13/2015
- Request for Immediate Examination filed on 10/13/2015
- U.S. Basic National Fees filed on 10/13/2015
- Priority Documents filed on 10/13/2015
- Power of Attorney filed on 10/13/2015
- Authorization to Permit Access filed on 10/13/2015
- Application Data Sheet (37 CFR 1.76) filed on 10/13/2015

The following items **MUST** be furnished within the period set forth below:

- Additional claim fees of $**6800** as a small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.

SUMMARY OF FEES DUE:

Total additional fees required for this application is $**6800** for a Small Entity:

Total additional claim fee(s) for this application is $**6800**
- $**1050** for **5** independent claims over 3.
- $**5360** for **134** total claims over 20.
- $**390** for multiple dependent claim surcharge.

ALL OF THE ITEMS SET FORTH ABOVE MUST BE SUBMITTED WITHIN TWO (2) MONTHS FROM THE DATE OF THIS NOTICE. FAILURE TO PROPERLY RESPOND WILL RESULT IN ABANDONMENT.

The time period set above may be extended by filing a petition and fee for extension of time under the provisions of 37 CFR 1.136(a).

FORM PCT/DO/EO/923 (371 Formalities Notice)

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

MARIAN E DAY

Telephone: (703) 756-1142

FORM PCT/DO/EO/923 (371 Formalities Notice)

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01030
Page 00272

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 14/784,250

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	140		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	60		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	360		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	154 minus 20 =	* 134	x 40 =	5360	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	8 minus 3 =	* 5	x 210 =	1050			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				390			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	7360		TOTAL	

APPLICATION AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
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FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
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FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

Substitute for Form PTO-1360
(For use with Form PTO/SB/06)

Application Number	Filing Date
14784250	

Applicant(s) Paul Giresi

* May be used for additional claims or amendments

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
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FILED ELECTRONICALLY

PRELIMINARY AMENDMENT Under CFR 1.115	Attorney Docket No.	STAN-1111
	Confirmation No.	6877
	First Named Inventor	Giresi, Paul
	Application Number	14/784,250
	Filing Date	October 13, 2015
	Group Art Unit	TBA
	Examiner Name	TBA
Address to: Mail Stop Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Title: *"Transposition of Native Chromatin for Personal Epigenomics"*	

Sir:

Prior to the examination of the above-referenced application on the merits, please enter the amendments below.

AMENDMENTS TO THE CLAIMS

Please amend the claims as shown below. A complete listing of the claims in this case, with their status identifiers, is set forth below.

1-77. (Cancelled)

78. (New) A method for analyzing chromatin, comprising:

(a) contacting chromatin from a nucleus of at least one cell with an insertional enzyme complex to produce a plurality of tagged fragments of genomic DNA,

(b) performing a nucleic acid assay on a tagged fragment of said plurality to provide fragment information, and

(c) generating, with the aid of a computer processor, a representation of epigenetic features of a genome region of said at least one cell by mapping said fragment information to said genome region.

79. (New) The method of claim 78, wherein said chromatin is contacted with said insertional enzyme complex within said nucleus of said cell.

80. (New) The method of claim 78, wherein said fragment information comprises one or more of: size of said tagged fragment, position of said tagged fragment in said genome region, cleavage site of said tagged fragment, length of said tagged fragment, and position of a tagged fragment of a defined range in length in said genome region.

81. (New) The method of claim 78, wherein performing said nucleic acid assay on said tagged fragment comprises sequencing said tagged fragment to provide said fragment information, wherein said fragment information comprises a sequence read.

82. (New) The method of claim 78, wherein said epigenetic features include one or more of: a profile of chromatin accessibility along said genome region, DNA binding protein occupancy at a binding site in said genome region, nucleosome-free DNA in said genome region, positioning of nucleosomes along said genome region, and a profile of chromatin states along said genome region.

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83. (New) The method of claim 81, wherein said fragment information comprises one or more of:

(i) a cleavage site for said insertional enzyme complex,

(ii) read length of said sequence read,

(iii) position of a sequence read of a defined range in length in said genome region, and

(iv) sequence read abundance.

84. (New) The method of claim 83, wherein said cleavage site is within a nucleosome-free region of said chromatin.

85. (New) The method of claim 78, wherein said at least one cell is a plurality of cells.

86. (New) The method of claim 85, wherein said plurality of cells comprises fewer than 500,000 cells.

87. (New) The method of claim 82, wherein said DNA binding protein is a transcription factor.

88. (New) The method of claim 82, wherein said chromatin states include one or more of: CTCF-associated, transcription start site, weak enhancer, enhancer, promoter flanking, transcribed, and repressed.

89. (New) The method of claim 78, wherein said genome region comprises a regulatory region.

90. (New) The method of claim 78, wherein said insertional enzyme complex comprises a transposase or an HIV integrase.

91. (New) The method of claim 90, wherein said transposase is selected from a prokaryotic transposase, a Tn transposase, a MuA transposase, a Vibhar transposase, HERMES, Ac-Ds, Ascot-1, Bsl, Cin4, Copia, En/Spm, F element, hobo, Hsmar1, Hsmar2, IN (HIV), IS1, IS2, IS3, IS4, IS5, IS6,

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IS10, IS21, IS30, IS50, IS51, IS150, IS256, IS407, IS427, IS630, IS903, IS911, IS982, IS1031, ISL2, L1, Mariner, P element, Tam3, Tc1, Tc3, Tel, THE-1, Tn/O, TnA, Tn3, Tn5, Tn7, Tn10, Tn552, Tn903, Tol1, Tol2, TnlO, and Tyl.

92. (New) The method of claim 78, wherein said insertional enzyme complex comprises two or more enzymatic moieties.

93. (New) The method of claim 78, wherein said at least one cell is from a blood sample.

94. (New) The method of claim 83, further comprising normalizing said sequence read abundance based on a sequence insertion preference of said insertional enzyme complex.

95. (New) The method of claim 78, further comprising the step of permeabilizing said at least one cell prior to step (a).

96. (New) A kit for generating a representation of epigenetic features of a genome region comprising:

(a) at least one reagent for permeabilizing or lysing a cell,

(b) an insertional enzyme complex, and

(c) instructions for generating a representation of epigenetic features comprising the steps of (1) combining components of said kit with a cell to produce a plurality of tagged fragments of genomic DNA and (2) analyzing said tagged fragments to generate said representation.

97. (New) The kit of claim 96, wherein components of said kit are configured such that combining said at least one reagent and said insertional enzyme complex with a cell results in both (1) permeabilization or lysis of said cell and (2) production of a plurality of tagged fragments of genomic DNA.

98. (New) The kit of claim 96, further comprising computer readable medium comprising codes that, upon execution by one or more processors, generates said representation.

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99. (New) The kit of claim 96, wherein analyzing said tagged fragments comprises performing a nucleic acid assay on at least one tagged fragment of said plurality.

100. (New) The kit of claim 96, wherein said insertional enzyme complex comprises a transposase or an HIV integrase.

101. (New) The kit of claim 100, wherein said transposase is selected from a prokaryotic transposase, a Tn transposase, a MuA transposase, a Vibhar transposase, HERMES, Ac-Ds, Ascot-1, Bsl, Cin4, Copia, En/Spm, F element, hobo, Hsmar1, Hsmar2, IN (HIV), IS1, IS2, IS3, IS4, IS5, IS6, IS10, IS21, IS30, IS50, IS51, IS150, IS256, IS407, IS427, IS630, IS903, IS911, IS982, IS1031, ISL2, L1, Mariner, P element, Tam3, Tc1, Tc3, Tel, THE-1, Tn/O, TnA, Tn3, Tn5, Tn7, Tn10, Tn552, Tn903, Tol1, Tol2, TnlO, and Tyl.

102. (New) The kit of claim 96, further comprising a transposase reaction buffer.

103. (New) The kit of claim 96, wherein said insertional enzyme complex comprises two or more enzymatic moieties.

104. (New) The kit of claim 96, wherein said insertional enzyme complex comprises an affinity tag.

105. (New) The kit of claim 96, wherein said at least one reagent is selected from NP40, digitonin, tween, streptolysin, and a cationic lipid.

106. (New) A method for determining accessibility of a site of a polynucleotide to an insertional enzyme complex, comprising:

(a) contacting a polynucleotide with an insertional enzyme complex to produce at least one fragment tagged with a molecular tag,

(b) performing a nucleic acid assay on said at least one fragment to obtain insertion data, and

(c) analyzing said insertion data to determine accessibility of a site of said polynucleotide to said insertional enzyme complex.

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107. (New) The method of claim 106, wherein said insertion data comprises one or more of:

(i) molecular tag insertion position in said polynucleotide, and

(ii) size of said fragment tagged with a molecular tag.

108. (New) The method of claim 106, wherein said molecular tag comprises a sequencing adaptor.

109. (New) The method of claim 106, wherein said polynucleotide is bound to a plurality of association molecules.

110. (New) The method of claim 106, wherein said insertional enzyme comprises a transposase.

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REMARKS

Formal Matters

Claims 1-77 are cancelled.

Claims 78 to 110 are new.

Support for newly added clams 78-110 is set forth in the following table:

Claim No.	Support (from US 14/784,250 Specification as Filed)
78	Page 18, Line 28 – Page 19, Line 34; Page 23, Lines 4-18
79	Page 43, Lines 9-25
80	Page 22, Line 29 – Page 23, Line 3
81	Page 19, Lines 17-34
82	Page 23, Line 28 – Page 24, Line 5
83	Page 22, Line 29 – Page 23, Line 3
84	Page 23, Lines 4 - 27
85	Page 20, Lines 4-9
86	Page 20, Lines 4-9
87	Page 23, Lines 28-34
88	Figure 2B
89	Page 24, Lines 6-12
90	Page 20, Lines 26-34
91	Page 20, Line 26 - Page 21, Line 15
92	Page 22, Lines 4-18
93	Page 25, Lines 5-18
94	Page 3, Lines 26-32
95	Page 3, Line 33 – Page 4, Line 3
96	Page 29, Line 31 – Page 30, Line 31
97	Page 29, Line 31 – Page 30, Line 31
98	Page 30, Lines 18-31
99	Page 29, Line 31 – Page 30, Line 31
100	Page 20, Lines 26-34

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101	Page 20, Line 26 – Page 21, Line 15
102	Page 29, Line 32 – Page 30, Line 4
103	Page 30, Lines 5-13
104	Page 30, Lines 5-13
105	Page 21, Line 30 – Page 22, Line 3
106	Page 20, Lines 4-21
107	Page 37, Line 12 – Page 41, Line 1
108	Page 21, Lines 16-22
109	Page 20, Lines 22-25
110	Page 20, Line 26 - Page 21, Line 3

No new matter has been added.

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number STAN-1111.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: February 22, 2016

By: /James S. Keddie, Reg. No. 48,920/
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Electronic Patent Application Fee Transmittal

Application Number:	14784250
Filing Date:	13-Oct-2015
Title of Invention:	Transposition of Native Chromatin for Personal Epigenomics
First Named Inventor/Applicant Name:	Paul Giresi
Filer:	James Samuel Keddie/Tiffany Turner
Attorney Docket Number:	STAN-1111

Filed as Small Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Claims in excess of 20	2615	13	40	520
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Extension - 1 month with $0 paid	2251	1	100	100
Miscellaneous:				
		Total in USD ($)		**620**

Electronic Acknowledgement Receipt	
EFS ID:	24983702
Application Number:	14784250
International Application Number:	
Confirmation Number:	6877
Title of Invention:	Transposition of Native Chromatin for Personal Epigenomics
First Named Inventor/Applicant Name:	Paul Giresi
Customer Number:	77974
Filer:	James Samuel Keddie
Filer Authorized By:	
Attorney Docket Number:	STAN-1111
Receipt Date:	22-FEB-2016
Filing Date:	13-OCT-2015
Time Stamp:	19:56:05
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$620
RAM confirmation Number	6563
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		STAN-1111-Prelim_Amend.pdf	44473 24005aaf23d41f64910db955d73448fe1dcf5c26	yes	8

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Preliminary Amendment	1	1
Claims	2	6
Applicant Arguments/Remarks Made in an Amendment	7	8

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	32106 1ae47c8bec2c676ae11f1716cee03dab97a1732f	no	2

Warnings:

Information:

Total Files Size (in bytes):	76579

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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/784,250	Filing Date 10/13/2015	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	02/22/2016						
	Total (37 CFR 1.16(i))	* 33	Minus	** 154	= 0	X $40 =	0
	Independent (37 CFR 1.16(h))	* 3	Minus	***8	= 0	X $210 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**0**

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

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/MONIQUE BRUNSON/

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/784,250	10/13/2015	Paul Giresi	STAN-1111

CONFIRMATION NO. 6877

77974
Stanford University Office of Technology Licensing
Bozicevic, Field & Francis LLP
1900 University Avenue
Suite 200
East Palo Alto, CA 94303

PUBLICATION NOTICE

OC000000081128148

Title: Transposition of Native Chromatin for Personal Epigenomics

Publication No.US-2016-0060691-A1
Publication Date:03/03/2016

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The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

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In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

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Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/784,250	10/13/2015	1639	1080	STAN-1111	33	3

CONFIRMATION NO. 6877

UPDATED FILING RECEIPT

77974
Stanford University Office of Technology Licensing
Bozicevic, Field & Francis LLP
1900 University Avenue
Suite 200
East Palo Alto, CA 94303

OC000000081213720

Date Mailed: 03/08/2016

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Paul Giresi, Palo Alto, CA;
Jason D. Buenrostro, Redwood City, CA;
Howard Y. Chang, Stanford, CA;
William J. Greenleaf, Menlo Park, CA;

Applicant(s)

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, Stanford, CA;

Power of Attorney: The patent practitioners associated with Customer Number 77974

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/US14/38825 05/20/2014
which claims benefit of 61/826,728 05/23/2013

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: No

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

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Page 00289

If Required, Foreign Filing License Granted: 11/19/2015

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/784,250**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

Transposition of Native Chromatin for Personal Epigenomics

Preliminary Class

506

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 14/784,250

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	140		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	60		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	360		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	33 minus 20 =	* 13	x 40 =	520	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*	x 210 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	1080		TOTAL	

APPLICATION AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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U.S. APPLICATION NUMBER NO.	FIRST NAMED INVENTOR	ATTY. DOCKET NO.
14/784,250	Paul Giresi	STAN-1111

77974
Stanford University Office of Technology Licensing
Bozicevic, Field & Francis LLP
1900 University Avenue
Suite 200
East Palo Alto, CA 94303

INTERNATIONAL APPLICATION NO.	
PCT/US14/38825	
I.A. FILING DATE	PRIORITY DATE
05/20/2014	05/23/2013

CONFIRMATION NO. 6877
371 ACCEPTANCE LETTER

OC000000081215721

Date Mailed: 03/08/2016

NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C 371 AND 37 CFR 1.495

The applicant is hereby advised that the United States Patent and Trademark Office, in its capacity as a Designated / Elected Office (37 CFR 1.495), has ACCEPTED the above identified international application for national patentability examination in the United States Patent and Trademark Office.

The United States Application Number assigned to the application is shown above. A Filing Receipt will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE "FILING DATE or 371(c) DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371 (c)(1) and (c)(2) REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN BELOW.** The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363)

10/13/2015
DATE OF RECEIPT OF 35 U.S.C.
371(c)(1) and (c)(2) REQUIREMENTS

The following items have been received:

- Indication of Small Entity Status
- Copy of the International Application filed on 10/13/2015
- Copy of the International Search Report filed on 10/13/2015
- Preliminary Amendments filed on 10/13/2015
- Information Disclosure Statements filed on 10/13/2015
- Sequence Listing txt file (EFS or physical medium) filed on 10/13/2015
- Inventor's Oath or Declaration filed on 10/13/2015
- Request for Immediate Examination filed on 10/13/2015
- U.S. Basic National Fees filed on 10/13/2015
- Priority Documents filed on 10/13/2015
- Power of Attorney filed on 10/13/2015
- Authorization to Permit Access filed on 10/13/2015
- Application Data Sheet (37 CFR 1.76) filed on 10/13/2015

FORM PCT/DO/EO/903 (371 Acceptance Notice)

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01030
Page 00293

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

MARIAN E DAY

Telephone: (703) 756-1142

FORM PCT/DO/EO/903 (371 Acceptance Notice)

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01030
Page 00294

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (03-15)
Approved for use through 07/31/2016. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	14784250
	Filing Date	2015-10-13
	First Named Inventor	Giresi, Paul
	Art Unit	1639
	Examiner Name	
	Attorney Docket Number	STAN-1111

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20100120098		2010-05-13	GRUNENWALD, et al.	
	2	20130203605		2013-08-08	SCHENDURE, et al.	

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	1	WO2010048605	WO		2010-04-29	EPICENTRE TECHNOLOGIES CORPORATION		

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14784250
	Filing Date	2015-10-13
	First Named Inventor	Giresi, Paul
	Art Unit	1639
	Examiner Name	
	Attorney Docket Number	STAN-1111

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	BOYLE, et al. "High-resolution genome-wide in vivo footprinting of diverse transcription factors in human cells", Genome Res. 2011 Mar;21(3):456-64.	
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01030
Page 00296

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14784250
	Filing Date	2015-10-13
	First Named Inventor	Giresi, Paul
	Art Unit	1639
	Examiner Name	
	Attorney Docket Number	STAN-1111

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/James S. Keddie, Reg. No. 48,920/	Date (YYYY-MM-DD)	2016-04-14
Name/Print	James S. Keddie	Registration Number	48,920

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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IPR2023-01030
Page 00297

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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IPR2023-01030
Page 00298

Electronic Acknowledgement Receipt

EFS ID:	25495272
Application Number:	14784250
International Application Number:	
Confirmation Number:	6877
Title of Invention:	Transposition of Native Chromatin for Personal Epigenomics
First Named Inventor/Applicant Name:	Paul Giresi
Customer Number:	77974
Filer:	James Samuel Keddie
Filer Authorized By:	
Attorney Docket Number:	STAN-1111
Receipt Date:	14-APR-2016
Filing Date:	13-OCT-2015
Time Stamp:	18:05:03
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	STAN-1111-IDS-1449.pdf	1035346 a4a96396f73460868ebeb68e385f0abf873c7324	no	4
Warnings:					
Information:					

2	Non Patent Literature	BOYLE.pdf	3874551 cd1091815fa968451d69e383cdf05d2174033ec9	no	10
Warnings:					
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3	Foreign Reference	WO2010048605.pdf	25086460 b1e26132d840eeb1d4a8c44a746524cf1ea6bb75	no	210
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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
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Third-Party Submission Under § 37 CFR 1.290

Concise Description of Relevance

U.S. Serial No. 14/892,911 (U.S. Publication No. 2016/0115474), filed November 20, 2015, is a U.S. national stage filing under 35 U.S.C. § 371 of PCT patent application No. PCT/US2014/039250, filed May 22, 2014, which claims the benefit of priority under 35 U.S.C. § 119(e) to U.S. Provisional Application Ser. No. 61/826,481, filed May 22, 2013.

Claim Language- US Serial No. 14/784,250 (U.S. Publication No. 2016/0060691 Giresi et al.)	U.S. Serial No. 14/892,911 (U.S. Publication No. US 2016/0115474)
78. A method for analyzing chromatin, comprising: (a) contacting chromatin from a nucleus of at least one cell with an insertional enzyme complex to produce a plurality of tagged fragments of genomic DNA,	Abstract- Disclosed herein are compositions, methods and kits useful for epigenetic analysis based on the use of transposons that are targeted to specific regions of chromatin based on DNADNA interactions, protein-protein interactions, RNA-RNA interactions, and nucleic acid-protein interactions.
(b) performing a nucleic acid assay on a tagged fragment of said plurality to provide fragment information, and	[0018] Another aspect of the invention concerns methods and reagents for making a nucleic acid sequence library or libraries. Such methods involve extracting and optionally fragmenting chromatin from a prepared sample, adding at least one oligonucleotide-transposome construct comprising an extraction moiety, allowing said oligonucleotide-transposome construct to locate at its/their DNA and/or noncoding RNA-binding sites in said chromatin, tagging the nucleic acid in said chromatin fragments with said construct by inducing an intermolecular

	reaction between said oligonucleotide and said nucleic acid, extracting the nucleic acid so tagged using the extraction moiety. In a related embodiment, the oligonucleotide contains peptide nucleic acid that targets G-quadruplex structures. In other aspects, the extracted taggednucleic acid is sequenced.
(c) generating, with the aid of a computer processor, a representation of epigenetic features of a genome region of said at least one cell by mapping said fragment information to said genome region.	[0170] Sequencing and 50-nt reads were generated on a HiSeq sequencer and aligned to the human genome (hgl 9). Only uniquely aligning reads were kept and duplicate reads were removed, resulting in 545,182 alignments for the TAMChIP sample. A control standard ChIP-Seq data set (traditional ChIP-seq on MCF7 chromatin using the H3K4me3 antibody) was down-sampled to the same number of alignments and analyzed in parallel. Signal maps were generated and the fragment densities in32-nt bins along the genome was determined. The resulting histograms were visualized in the Integrated Genome Browser (IGB). Peak calling was performed using SICER (Zang et al., Bioinformatics 25, 1952- 1958, 2009) at a standard cutoff of E-value=l. SICER identified 10,897 peaks for TAM-ChIP and 12,526 peaks for traditional ChIP, which are within expectations for this histone mark if compared to numerous previous assays and 91.5% of the TAM-ChIP peaks overlapped with the traditional ChIP peaks (FIG. 15)
80. The method of claim 78, wherein said fragment information comprises one or more of: size of	[0040] FIG. 10— shows Tn5 Transposase activity on Hela DNA and chromatin. Illumina Tagment DNA buffer and Tn5 (A) or TS-Tn5 (B) transposase, ranging

said tagged fragment, position of said tagged fragment in said genome region, cleavage site of said tagged fragment, length of said tagged fragment, and position of a tagged fragment of a defined range in length in said genome region.	from 5 to 20 Units, were added to HeLa DNA.The samples were incubated at 55°C. for 5 minutes and allowed to cool to 10° C. One fourth of the tagmented DNA was analyzed on a 1.5% agarose gel. C-,DNA with no transposase added. C. Tagmentation of Hela chromatin DNA. 25 Units of Tn5 transposome was added to 10 µg of crosslinked HeLa chromatin sonicated to varying extents. Tagmented chromatin was treated with RnaseA and Protein K and crosslinks reversed followed by purification. For the lane marked 20F, tagmentation products were first passed through a size exclusion spin column to remove low molecular weight DNA fragments and primers as well as salts and other impurities that could impede with the downstream PCR reaction. 100 ng of tagmented DNA was subjected to 15 cycles of PCR and one fifth of the PCR reaction volume was analyzed on a 1.5% agarose gel. gDNA=Naked genomic DNA subjected to tagmentation, purification and 100 ng of the purified product subjected to subsequent PCR amplification. MW markers: lowest band in M100=100 bp; Lowest band on Ml kb=0.5 kB. next band=l. Arrow denotes position of input, untagemented DNA. Bracket denotes migration smear of randomly tagmented DNA fragments of varying sizes.
81. The method of claim 78, wherein performing said nucleic acid assay on said tagged fragment comprises sequencing said tagged	Figure 15- shows new generation sequencing profile of TAM-ChIP library. Example 4-The DNA libraries produced by the optimized method in developed in the preceding

fragment to provide said fragment information, wherein said fragment information comprises a sequence read.	experiments with IgG, RNA polymerase II, and H3K4tm antibody-transposome conjugates are compared with the libraries produced via traditional ChIP-Seq performed with the same unconjugated antibodies. For traditional ChIP-Seq, Hela chromatin extracts generated for the above set of experiments are incubated with 5 µg antibody for 16 hours at 4° C. 1 µg are left unprocessed and serve as the input control. Antibody-chromatin complexes are captured using protein A coated magnetic beads, washed, eluted, and DNA purified following established procedures. ChIP with 5 µg of non-immune rabbit IgG is performed in parallel as an antibody specificity control. The ChIP-enriched and the untreated sonicated gDNA are processed according standard protocols for library preparation for sequencing in the Illumina Genome Analyzer GA11. This consists of end-repair, adaptor ligation, size-selection and PCR amplification, and all these steps are done and sequencing performed according to standard methods. The generated data from both TAM-ChIP and traditional ChIP from two independent experiments is analyzed. Reads mapped to the human genome (alignments) are analyzed to find genomic regions with significant enrichments (" peaks") over alignments obtained from either
82. (New) The method of claim 78, wherein said epigenetic features include one or more of: a profile of chromatin accessibility along said	[0171] When annotated with genes, it was found that 83.6% of the TAM-ChIP peaks and 84.2% of the traditional ChIP peaks were located in promoters (defined as -7500 to +2500 relative to TSS). In

genome region, DNA binding protein occupancy at a binding site in said genome region, nucleosome-free DNA in said genome region, positioning of nucleosomes along said genome region, and a profile of chromatin states along said genome region.	conclusion, the correlation between the TAM-ChIP and traditional ChIP data is extremely high. In both assay, highest signals were seen at the transcriptional start site (TSS), as shown in the promoter profile (-5000 to +5000) generated by seqMINER in FIG. 35, which is consistent with published results (Ye et ah, 2011). The typical seqMINERS promoter profiles for H3K4me3 ChIP-seq datashow double peaks as can be seen for the traditional ChIP-seqin pink. The profile for the generated TAM-ChIP library on the other hand does not show the exact same pattern. These data indicate that although the generated library was strikingly similar (91.5%) to the traditional ChIP additional optimization of the current TAM-ChIP library generation is required to achieve the optimal TAM-ChIP protocol for multi-analyte purposes
87. (New) The method of claim 82, wherein said DNA binding protein is a transcription factor.	[0078] TAM-ChIP enables rapid (<24 hour elapsed time) and streamlined analysis of one or several protein-chromatin interactions for analysis of a single gene all the way through to genome-wide interrogation. To achieve this, proteins, such antibodies specific for the protein(s) of interest, transcription factors, or chromodomains, such as in HP1 and Polycomb proteins are first conjugated to a transposase:transposon complex (Transposome) charged with synthetic oligonucleotide(s) that features comprise a transposon cassette containing the following features: :

88. The method of claim 82, wherein said chromatin states include one or more of: CTCF-associated, transcription start site, weak enhancer, enhancer, promoter flanking, transcribed, and repressed.	[0171] When annotated with genes, it was found that 83.6% of the TAM-ChIP peaks and 84.2% of the traditional ChIP peaks were located in promoters (defined as -7500 to +2500 relative to TSS). In conclusion, the correlation between the TAM-ChIP and traditional ChIP data is extremely high. In both assay, highest signals were seen at the transcriptional start site (TSS), as shown in the promoter profile (-5000 to +5000) generated by seqMINER in FIG. 35, which is consistent with published results (Ye et al., 2011). The typical seqMINERS promoter profiles for H3K4me3 ChIP-seq data show double peaks as can be seen for the traditional ChIP-seqin pink. The profile for the generated TAM-ChIP library on the other hand does not show the exact same pattern. These data indicate that although the generated library was strikingly similar (91.5%) to the traditional ChIP additional optimization of the current TAM-ChIP library generation is required to achieve the optimal TAM-ChIP protocol for multi-analyte purposes [0172] These results indicate that the TS-Tn5 transposase can be directed in a specific manner to chromatin via an antibody specific for a chromatin associated protein— in this case, a post-translational histone modification that is associated with transcriptionally active regions of the genome.

90. The method of claim 78, wherein said insertional enzyme complex comprises a transposase or an HIV integrase.	Abstract-Disclosed herein are compositions, methods and kits useful for epigenetic analysis based on the use of transposons that are targeted to specific regions of chromatin based on DNA-DNA interactions, protein-protein interactions, RNA-RNA interactions, and nucleic acid-protein interactions.
91. The method of claim 90, wherein said transposase is selected from a prokaryotic transposase, a Tn transposase, a MuA transposase, a Vibhar transposase, HERMES, Ac-Ds, Ascot-1, Bsl, Cin4, Copia, En/Spm, F element, hobo, Hsmarl, Hsmar2, IN (HIV), IS1, IS2, IS3, IS4, IS5, IS6 IS10, IS21, IS30, IS50, IS51, IS150, IS256, IS407, IS427, IS630, IS903, IS911, IS982, IS1031, ISL2, LI, Mariner, P element, Tam3, Tel, Tc3, Tel, THE-1, Tn/O, TnA, Tn3, Tn5, Tn7, TnlO, Tn552, Tn903, Toll, Tol2, TnlO, and Tyl.	Figure 6- shows Tn5 transposase-antibody conjugates Figure 10- shows Tn5 transposase activity on Hela DNA and chromatin. Figure 11- shows Tn5 constructs for secondary and primary conjugation scheme
96. A kit for generating a representation of epigenetic features of a genome region comprising: (a) at least one reagent for permeabilizing or lysing a cell, (b) an insertional enzyme complex, and (c) instructions for generating a	[0026] An embodiment disclosed herein are kits including reagents, protein-transposome complex(s) and/or oligonucleotide-transposome construct(s), and instructions for their use

representation of epigenetic features comprising the steps of (1) combining components of said kit with a cell to produce a plurality of tagged fragments of genomic DNA and (2) analyzing said tagged fragments to generate said representation.	
106. A method for determining accessibility of a site of a polynucleotide to an insertional enzyme complex, comprising: (a) contacting a polynucleotide with an insertional enzyme complex to produce at least one fragment tagged with a molecular tag, (b) performing a nucleic acid assay on said at least one fragment to obtain insertion data, and (c) analyzing said insertion data to determine accessibility of a site of said polynucleotide to said insertional enzyme complex.	Figure 15- shows new generation sequencing profile of TAM-ChIP library. [0097] Data disclosed herein shows that the antibody-transposome construct could be directed to chromatin in a specific manner through a primary antibody that binds trimethyllysine at residue 4 of Histone H3 (H3K4me3), a post translation modification found in the promoter regions of transcriptionally active genes. FIG. 14 shows that, in the presence of 10 μg of chromatin, but not 0.1 μg, the TS-Tn5 transposome complex but not the Tn5 transposome complex effectively tagmented chromatin regions bound by the primary antibody. Further, the untranslated regions on chromosome 12 and 20, showed no enrichment, indicating no tagmentation by the transposase, confirming that the primary antibody was directing the transposase to chromatin fragments associated with antibody. Control reactions, lacking either the primary antibody or lacking the secondary transposome conjugate, showed no tagmentation in any of the regions analyzed. The no primary antibody control

	reaction confirms that tagmentation is driven solely by primary antibody binding events. The secondary antibody alone is unable to direct tagmentation of chromatin.
107. The method of claim 106, wherein said insertion data comprises one or more of: molecular tag insertion position in said polynucleotide, and size of said fragment tagged with a molecular tag.	Figure 15- shows new generation sequencing profile of TAM-ChIP library. Example 4-The DNA libraries produced by the optimized method in developed in the preceding experiments with IgG, RNA polymerase II, and H3K4tm antibody-transposome conjugates are compared with the libraries produced via traditional ChIP-Seq performed with the same unconjugated antibodies. For traditional ChIP-Seq, Hela chromatin extracts generated for the above set of experiments are incubated with 5 µg antibody for 16 hours at 4° C. 1 µg are left unprocessed and serve as the input control. Antibody-chromatin complexes are captured using protein A coated magnetic beads, washed, eluted, and DNA purified following established procedures. ChIP with 5 µg of non-immune rabbit IgG is performed in parallel as an antibody specificity control. The ChIP-enriched and the untreated sonicated gDNA are processed according standard protocols for library preparation for sequencing in the Ulumina Genome Analyzer GA11. This consists of end-repair, adaptor ligation, size-selection and PCR amplification, and all these steps are done and sequencing performed according to standard methods. The generated data from both TAM-ChIP and traditional ChIP from two

	independent experiments is analyzed. Reads mapped to the human genome (alignments) are analyzed to find genomic regions with significant enrichments (“ peaks”) over alignments obtained from either

Third-Party Submission Under § 37 CFR 1.290
Concise Description of Relevance

U.S. Serial No. 14/359,877 (U.S. Publication No. 2015/0111788 A1), entitled Multiplex Isolation of Protein-Associated Nucleic Acids, filed May 21, 2014, is a § 371 of International Application No. PCT/US2012/066472, filed November 23, 2012 which claims the benefit of priority of U.S. Serial No. 61/629,555, filed November 22, 2011.

Claim Language- US Serial No. 14/784,250 (U.S. Publication No. 2016/0060691 Giresi et al.)	U.S. Publication No. 2015/0111788
1. A method for analyzing chromatin, comprising: (a) contacting chromatin from a nucleus of at least one cell with an insertional enzyme complex to produce a plurality of tagged fragments of genomic DNA,	Abstract-discusses multiplex isolation of protein-associated nucleic acids using transposon-assisted TAM-ChIP Figure 1- shows TAM-ChIP method [0019]-TAM-ChIP, enables rapid (<24 hour elapsed time) and streamlined analysis of one or several protein-chromatin interactions for analysis of either a single gene all the way through to genome-wide interrogation.
(b) performing a nucleic acid assay on a tagged fragment of said plurality to provide fragment information, and	Figure 1- shows TAM-ChIP, including making of sequence library [0028]-Following DNA purification to remove proteins, PCR amplification (or another suitable amplification process) with primers complementary to the oligonucleotides can be performed to generate NGS compatible libraries for sequencing.
(c) generating, with the aid of a computer processor, a	From Example 4-Reads mapped to the human genome (alignments) are analyzed to find genomic regions with

representation of epigenetic features of a genome region of said at least one cell by mapping said fragment information to said genome region.	significant enrichments (“ peaks”) over alignments obtained from either Input or IgG control DNA. Dozens of H3K4tm and RNA Polymerase II ChIP-Seq assays are performed and analyzed, and very similar results are obtained with the peak calling algorithms MACS [32], SICER [33], or CCAT [34]. In addition, software is used to extend the read alignments to the actual length of the DNA fragments (-200-250 bp), and to generate a “ signal map” showing alignment (“ tag”) densities in 32-bp bins across the genome and reproducibility between replicates is typically -80%. Peaks and signal maps are entered into gene annotation and sample comparison software, returning concise Excel tables showing peak metrics and location of peaks relative to genes. These are used to compare the representation of genomic sequences in the DNA libraries prepared by two methods and show concordance of genomic coverage.
80. The method of claim 78, wherein said fragment information comprises one or more of: size of said tagged fragment, position of said tagged fragment in said genome region, cleavage site of said tagged fragment, length of said tagged fragment, and position of a tagged fragment of a defined range in length in said genome region.	From Example 6-Proximity-mediated ligation is performed, resulting in ligation of the antibody delivered oligos to the target-associated free genomic DNA ends (FIG. 9). Digestion of the cross-linked chromatin and the proximity ligation strategy using sonicated or restriction enzyme digested cross-linked chromatin is well established, and these methods build upon and inventively improve on those used in the 5C and Hi-C technologies (Dostie and Dekker, 2007; Lieberman-Aiden et al., 2009). The key to the ligation is to perform this step under diluted

	conditions which favor the interaction of DNA molecules held in close proximity. Following ligation, cross-links can be reversed by heating to 65°C overnight, and proteins can be removed with proteinase K treatment. The regions of interest (e.g., the regions bound by the protein of interest and targeted by the antibody) can be enriched by PCR using primers that anneal to regions within the ligated oligonucleotide sequence, and the resulting amplified DNA can be sequenced using, for example, the Illumina platform, resulting in a genome wide protein binding profile.
81. The method of claim 78, wherein performing said nucleic acid assay on said tagged fragment comprises sequencing said tagged fragment to provide said fragment information, wherein said fragment information comprises a sequence read.	Figure 1- shows TAM-ChIP, including making of sequence library From Example 6- The regions of interest (e.g., the regions bound by the protein of interest and targeted by the antibody) can be enriched by PCR using primers that anneal to regions within the ligated oligonucleotide sequence, and the resulting amplified DNA can be sequenced using, for example, the Illumina platform, resulting in a genome wide protein binding profile.
82. (New) The method of claim 78, wherein said epigenetic features include one or more of: a profile of chromatin accessibility along said genome region, DNA binding	Figure 4 Figure 9 From Example 6- These methods use cross-linked and sonicated (or restriction digested) chromatin as a starting material. Instead of conjugation to

protein occupancy at a binding site in said genome region, nucleosome-free DNA in said genome region, positioning of nucleosomes along said genome region, and a profile of chromatin states along said genome region.	transposase, this approach uses conjugation of an antibody to short double-stranded DNA oligonucleotides of known sequence. The conjugate is incubated with cross-linked chromatin that has been either restriction enzyme digested or sonicated, resulting in antibody binding at the intended target. Proximity-mediated ligation is performed, resulting in ligation of the antibody delivered oligos to the target-associated free genomic DNA ends (FIG. 9). Digestion of the cross-linked chromatin and the proximity ligation strategy using sonicated or restriction enzyme digested cross-linked chromatin is well established, and these methods build upon and inventively improve on those used in the 5C and Hi-C technologies (Dostie and Dekker, 2007; Lieberman-Aiden et al., 2009). The key to the ligation is to perform this step under diluted conditions which favor the interaction of DNA molecules held in close proximity. Following ligation, cross-links can be reversed by heating to 65°C. overnight, and proteins can be removed with proteinase K treatment. The regions of interest (e.g., the regions bound by the protein of interest and targeted by the antibody) can be enriched by PCR using primers that anneal to regions within the ligated oligonucleotide sequence, and the resulting amplified DNA can be sequenced using, for example, the Illumina platform, resulting in a genome wide

	protein binding profile. In addition, this approach is well suited to generate binding profiles of multiple factors in the same sample. This is achieved by designing multiple oligonucleotides, each containing a unique bar code sequence, and conjugating these unique oligos to different antibodies. Multiple antibody conjugates can be added to the same sample at the same time. After sequencing, the data for the multiple targets can be sorted based on the bar code sequence.
87. (New) The method of claim 82, wherein said DNA binding protein is a transcription factor.	An extensive number of ChIP-validated antibodies are commercially available or can be developed using conventional antibody production techniques. Here, antibodies to a chromatin associated protein (RNA polymerase II) and a structural chromatin protein, a histone (anti-histone H3 trimethyl-lysine 4 (H3K4tm) mark associated with transcriptionally active chromatin), are conjugated to the EZ-Tn5 transposome using any suitable approach, two of which are described below [0043]
88. The method of claim 82, wherein said chromatin states include one or more of: CTCF-associated, transcription start site, weak enhancer, enhancer, promoter flanking, transcribed, and	An extensive number of ChIP-validated antibodies are commercially available or can be developed using conventional antibody production techniques. Here, antibodies to a chromatin associated protein (RNA polymerase II) and a structural chromatin protein, a histone (anti-histone H3 trimethyl-lysine 4 (H3K4tm)

repressed.	mark associated with transcriptionally active chromatin), are conjugated to the EZ-Tn5 transposome using any suitable approach, two of which are described below [0043]
90. The method of claim 78, wherein said insertional enzyme complex comprises a transposase or an HIV integrase.	Figure 1, Figure 3, - all show methods and constructs involving tagmentation using transposon construct Figure 7- shows transposase-antibody conjugates.
91. The method of claim 90, wherein said transposase is selected from a prokaryotic transposase, a Tn transposase, a MuA transposase, a Vibhar transposase, HERMES, Ac-Ds, Ascot-1, Bsl, Cin4, Copia, En/Spm, F element, hobo, Hsmarl, Hsmar2, IN (HIV), IS1, IS2, IS3, IS4, IS5, IS6 IS10, IS21, IS30, IS50, IS51, IS150, IS256, IS407, IS427, IS630, IS903, IS911, IS982, IS1031, ISL2, LI, Mariner, P element, Tam3, Tel, Tc3, Tel, THE-1, Tn/O, TnA, Tn3, Tn5, Tn7, TnlO, Tn552, Tn903, Toll, Tol2, TnlO, and Tyl.	Figure 3- shows Tn5 transposase

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290
CONCISE DESCRIPTION OF RELEVANCE

Application Number	14784250

U.S. PATENTS

Cite No	Patent Number	Concise Description of Relevance

U.S. PATENT APPLICATION PUBLICATION

Cite No	Publication Number	Concise Description of Relevance
1	20150111788	See Attached

2	20160115474	See Attached

FOREIGN PATENT DOCUMENTS		
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U.S. PATENT APPLICATION PUBLICATIONS				
Cite No	Publication Number	Kind Code [1]	Publication Date (YYYY-MM-DD)	First Named Inventor
1	20160115474		2016-04-28	Mary Anne Jelinek
2	20150111788		2015-04-23	Joseph Fernandez

FOREIGN PATENTS AND PUBLISHED FOREIGN PATENT APPLICATIONS						
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THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	14784250

		☐	☐

STATEMENTS

The party making the submission is not an individual who has a duty to disclose information with respect to the above-identified application under 37 CFR 1.56.

This submission complies with the requirements of 35 U.S.C. 122(e) and 37 CFR 1.290.

☐ The fee set forth in 37 CFR 1.290(f) has been submitted herewith.

☒ The fee set forth in 37 CFR 1.290(f) is not required because this submission lists three or fewer total items and, to the knowledge of the person signing the statement after making reasonable inquiry, this submission is the first and the only submission under 35 U.S.C 122(e) filed in the above-identified application by the party making the submission or by a party in privity with the party.

☐ This resubmission is being made responsive to a notification of non-compliance issued for an earlier filed third-party submission. The corrections in this resubmission are limited to addressing the non-compliance. As such, the party making this resubmission: (1) requests that the Office apply the previously-paid fee set forth in 37 CFR 1.290(f), or (2) states that no fee is required to accompany this resubmission as the undersigned is again making the fee exemption statement set forth in 37 CFR 1.290(g).

Signature	/Robert Prince/		
Name/Print	Robert Prince	Registration Number (if applicable)	38583

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IPR2023-01030
Page 00321

Electronic Acknowledgement Receipt	
EFS ID:	28029730
Application Number:	14784250
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First Named Inventor/Applicant Name:	
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/784,250	10/13/2015	Paul Giresi	STAN-1111	6877

77974 7590 01/18/2017

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WILDER, CYNTHIA B	

ART UNIT	PAPER NUMBER
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14/784,250	13 October, 2015	GIRESI ET AL.	STAN-1111

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A third-party submission under 37 CFR 1.290 has been filed on 1/12/17, and is being entered in the above-identified application. Please allow a few days for the submission to be visible in the Patent Application Information Retrieval (PAIR) system.

/Marianne Seidel/
QAS, TC 1600

PTO-90C (Rev.04-03)

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Application Number	14784250
Filing Date	2015-10-13
First Named Inventor	Giresi, Paul
Art Unit	1637
Examiner Name	WILDER, CYNTHIA B.
Attorney Docket Number	STAN-1111

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	Application Number	14784250
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	First Named Inventor	Giresi, Paul
	Art Unit	1637
	Examiner Name	WILDER, CYNTHIA B.
	Attorney Docket Number	STAN-1111

	1	ADEY, et al., "Ultra-low-input, tagmentation-based whole-genome bisulfite sequencing", Genome Research, 2012, 22 (6): 1139-1143.	
	2	BUENROSTRO, et al., "Tranposition of native chromatin for fast and sensitive epigenomic profiling of open chromatin, DNA-binding proteins and nucleosome position", Nature Methods, 2013, 10(12): 1213-1218.	
	3	SIMON, et al., "Using formaldehyde-assisted isolation of regulatory elements (FAIRE) to isolate active regulatory DNA", Nature Protocols, 2012, 7(2): 256-267.	
	4	SONG, et al., "DNase-seq: A High-Resolution Technique for Mapping Active Gene Regulatory Elements across the Genome from Mammalian Cells", Cold Spring Harbor Laboratory Press, 2010, 2010(2), doi:10.1101/pdb.prot5384.	

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Page 00328

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	Application Number	14784250
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	First Named Inventor	Giresi, Paul
	Art Unit	1637
	Examiner Name	WILDER, CYNTHIA B.
	Attorney Docket Number	STAN-1111

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OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/James S. Keddie/	Date (YYYY-MM-DD)	2017-02-16
Name/Print	James S. Keddie	Registration Number	48920

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

10x Genomics, Inc. Exhibit 2001
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Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01030
Page 00330

Electronic Acknowledgement Receipt

EFS ID:	28384113
Application Number:	14784250
International Application Number:	
Confirmation Number:	6877
Title of Invention:	Transposition of Native Chromatin for Personal Epigenomics
First Named Inventor/Applicant Name:	Paul Giresi
Customer Number:	77974
Filer:	James Samuel Keddie/Sherry Long
Filer Authorized By:	James Samuel Keddie
Attorney Docket Number:	STAN-1111
Receipt Date:	16-FEB-2017
Filing Date:	13-OCT-2015
Time Stamp:	19:25:15
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	STAN-1111_IDS.pdf	1035643 21150a40e6de11a679e0ee35c787f9001d939b8d	no	4

Warnings:

Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
2	Non Patent Literature	ADEY.pdf	587158 5646eaf1fe73f4ee8d7567ba2e3fd8f93b3609e2	no	6
Warnings:					
Information:					
3	Non Patent Literature	BUENROSTRO.pdf	718217 e91620d4824bcd207cdb4203ce0f7c088b77d7d1	no	8
Warnings:					
Information:					
4	Non Patent Literature	SIMON.pdf	2477012 f9acef4b6410ec3c3324a175f606e7b7d9b64abd	no	15
Warnings:					
Information:					
5	Non Patent Literature	SONG.pdf	3565055 b3adb7bea036633d171471d25c3be528653def9a	no	12
Warnings:					
Information:					
			Total Files Size (in bytes):	8383085	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/784,250	10/13/2015	Paul Giresi	STAN-1111	6877

77974 7590 08/25/2017

Stanford University Office of Technology Licensing
Bozicevic, Field & Francis LLP
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER	
WILDER, CYNTHIA B	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
08/25/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@bozpat.com

10x Genomics, Inc. Exhibit 2001
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Office Action Summary	Application No. 14/784,250	Applicant(s) GIRESI ET AL.	
	Examiner CYNTHIA B. WILDER	Art Unit 1637	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/16/2017*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *78-110* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☐ Claim(s) _____ is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☒ Claim(s) *78-110* are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

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DETAILED ACTION

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

REQUIREMENT FOR UNITY OF INVENTION

As provided in 37 CFR 1.475(a), a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention"). Where a group of inventions is claimed in a national stage application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

The determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim. See 37 CFR 1.475(e).

WHEN CLAIMS ARE DIRECTED TO MULTIPLE CATEGORIES OF INVENTIONS

As provided in 37 CFR 1.475(b), a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:

(1) A product and a process specially adapted for the manufacture of said product; or

(2) A product and process of use of said product; or

(3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or

(4) A process and an apparatus or means specifically designed for carrying out the said process; or

(5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.

Otherwise, unity of invention might not be present. See 37 CFR 1.475(c).

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 78-95, drawn to a method for analyzing chromatin.

Group II, claim(s) 96-105, drawn to a kit.

Group III, claim(s) 106-110, drawn to a method for determining accessibility of a site of a polynucleotide to an insertional enzyme complex.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follow: (a) Transposase selected from the following:

prokaryotic transposase,	Hsmar2,
a Tn transposase,	IN (HIV),
a MuA transposase,	IS 1,
a Vibhar transposase,	IS2,
HERMES,	IS3,
Ac-Ds,	IS4
Ascot-1,	IS5,
Bsl,	IS6,
Cin4,	IS 10,
Copia,	IS21,
En/Spm,	IS30,
F element,	IS50,
hobo,	IS51,
	IS 150,
	IS256,
Hsmarl,	IS407,

IS427, THE-1,

IS630, Tn/O,

IS903, TnA,

IS911, Tn3,

IS982, Tn5,

IS 1031, Tn7,

ISL2, TnlO,

LI, Tn552,

Mariner, Tn903,

P element, Toll,

Tam3, Tol2,

Tel, TnlO,

Tc3, and Tyl.

Tel,

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise require all the limitations of an allowed generic claim.

The groups of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The common technical feature shared by the groups I-III are an insertion enzyme complex (e.g., transposase). However, the broadest first invention, namely the kit of claim 96, comprising a permeabilizing or lysing reagent and an insertional enzyme is sufficiently broad and distinct such that it is not limited only to the method of the group I for a method of analyzing a chromatin or a method for determining accessibility of a site of a polynucleotide and thus can be utilized in methods not technically related to the assays of Group I and II. Likewise, the common technical feature, the insertional enzyme complex (.e.g, transposase) is not special and does not represent a contribution over the prior art. For example, Nguyen et al (US 20030032141) teach a kit comprising an insertional enzyme complex (e.g., transposase) and a cell lysis reagent (e.g.0105) and Shendure et al (citation made of record on ISR (international search report) which teaches lysis reagent and insertional enzyme complex (see citation on ISR made of record and additionally pages 13 and 14). Accordingly, unity is lacking.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does

not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention or species.

Should applicant traverse on the ground that the inventions have unity of invention (37 CFR 1.475(a)), applicant must provide reasons in support thereof. Applicant may submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. Where such evidence or admission is provided by applicant, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be corrected in compliance with 37 CFR 1.48(a) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. A request to correct inventorship under 37 CFR 1.48(a) must be accompanied by an application data sheet in accordance with 37 CFR 1.76 that identifies each inventor by his or her legal name and by the processing fee required under 37 CFR 1.17(i).

The examiner has required restriction between product or apparatus claims and process claims. Where applicant elects claims directed to the product/apparatus, and all

product/apparatus claims are subsequently found allowable, withdrawn process claims that include all the limitations of the allowable product/apparatus claims should be considered for rejoinder. All claims directed to a nonelected process invention must include all the limitations of an allowable product/apparatus claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product/apparatus claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product/apparatus are found allowable, an otherwise proper restriction requirement between product/apparatus claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product/apparatus claim will not be rejoined. See MPEP § 821.04. Additionally, in order for rejoinder to occur, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product/apparatus claims. **Failure to do so may result in no rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CYNTHIA B. WILDER whose telephone number is (571)272-0791. The examiner can normally be reached on a flexible schedule.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CYNTHIA B WILDER/
Primary Examiner, Art Unit 1637

Notice of References Cited	Application/Control No. 14/784,250	Applicant(s)/Patent Under Reexamination GIRESI ET AL.	
	Examiner CYNTHIA B. WILDER	Art Unit 1637	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-2003/0032141 A1	02-2003	Nguyen, Hiep-Hoa T.	C07K14/195	435/69.1
	B	US-				
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01030
Page 00344

PATENT
Attorney Docket No. STAN-1111

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application	)	
	)	
Inventors: Paul Giresi, et al.	)	Examiner: Cynthia B. Wilder
	)	
Application No.: 14/784,250	)	Art Unit: 1637
	)	
Filed: October 13, 2015	)	Confirmation No.: 6877
	)	
Title: TRANSPOSITION OF NATIVE CHROMATIN FOR PERSONAL EPIGENOMICS	)	
	)	

ELECTRONICALLY FILED ON: October 3, 2017

M/S Amendment
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO RESTRICTION REQUIREMENT

Sir:

This communication is in response to the Restriction Requirement dated August 25, 2017. The shortened statutory period for response expires on October 25, 2017. This response is submitted prior to shortened statutory period for reply, therefore, no extension fee is required to enter this response.

Applicant respectfully requests reconsideration of the above-referenced application in view of the following remarks.

Remarks begin on page **2** of this paper.

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REMARKS

Claims 78-110 are pending.

Reconsideration of the Application is respectfully requested in light of the following remarks.

Election of Invention

The Office has requested election of an invention from the following groups:

Group I (claims 78-95), drawn to a method for analyzing chromatin.

Group II (claims 96-105), drawn to a kit.

Group III (claims 106-110), drawn to a method for determining accessibility of a site of a polynucleotide to an insertional enzyme complex.

Applicant elects Group I, without traverse. Claims 78-95 encompass the elected group.

Applicant reserves the right pursuant to 35 U.S.C. §121 to file one or more divisional applications directed to the non-elected invention during the pendency of the present application.

Election of Species

The Office has also requested an election of a species of transposase.

Applicant elects the species "Tn transposase," without traverse. Claims 78-95 encompass the elected species.

Upon allowance of the elected species, the Examiner is required to conduct searches for other species within the genus.

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CONCLUSION

Applicant submits that this paper fully addresses the Restriction Requirement mailed August 25, 2017. Should the Examiner have any questions, the Examiner is encouraged to contact the undersigned at the telephone number provided.

The Commissioner is authorized to charge any additional fees which may be required, including petition fees and extension of time fees, to Deposit Account No. 50-0815 (Docket No. STAN-1111).

Respectfully submitted,

BOZICEVIC, FIELD & FRANCIS LLP

Dated: October 3, 2017

By: /James S. Keddie/
James S. Keddie
Reg. No. 48,920

Bozicevic, Field & Francis LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, California 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

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Page 00347

Electronic Acknowledgement Receipt	
EFS ID:	30551997
Application Number:	14784250
International Application Number:	
Confirmation Number:	6877
Title of Invention:	Transposition of Native Chromatin for Personal Epigenomics
First Named Inventor/Applicant Name:	Paul Giresi
Customer Number:	77974
Filer:	James Samuel Keddie/Sherry Long
Filer Authorized By:	James Samuel Keddie
Attorney Docket Number:	STAN-1111
Receipt Date:	03-OCT-2017
Filing Date:	13-OCT-2015
Time Stamp:	17:46:52
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		STAN-1111_Resp_RR.pdf	25322 54ac825d2d90a20cfa9a5c37484b6ef5a0518ccd	yes	3

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Response to Election / Restriction Filed	1	1
	Applicant Arguments/Remarks Made in an Amendment	2	3
Warnings:			
Information:			
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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
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If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
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PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/784,250	Filing Date 10/13/2015	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	10/03/2017	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 33	Minus	** 33	= 0	X $40 =	0
	Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $210 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
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This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	14784250
Filing Date	2015-10-13
First Named Inventor	Giresi, Paul
Art Unit	1637
Examiner Name	WILDER, CYNTHIA B.
Attorney Docket Number	STAN-1111

U.S.PATENTS Remove

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	1	WO2009147386	WO		2009-12-10	OXFORD BIODYNAMICS LIMITED		
	2	WO2016207647	WO		2016-12-29	OXFORD BIODYNAMICS LIMITED		
	3	WO2016207653	WO		2016-12-29	OXFORD BIODYNAMICS LIMITED		

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14784250
	Filing Date	2015-10-13
	First Named Inventor	Giresi, Paul
	Art Unit	1637
	Examiner Name	WILDER, CYNTHIA B.
	Attorney Docket Number	STAN-1111

	4	WO2016207661	WO		2016-12-29	OXFORD BIODYNAMICS LIMITED		
	5	WO2007093819	WO		2007-08-23	ISIS INNOVATION LIMITED		

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NON-PATENT LITERATURE DOCUMENTS [Remove]

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14784250
	Filing Date	2015-10-13
	First Named Inventor	Giresi, Paul
	Art Unit	1637
	Examiner Name	WILDER, CYNTHIA B.
	Attorney Docket Number	STAN-1111

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/James S. Keddie/	Date (YYYY-MM-DD)	2017-11-01
Name/Print	James S. Keddie	Registration Number	48920

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IPR2023-01030
Page 00353

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Page 00354

Electronic Acknowledgement Receipt

EFS ID:	30830772
Application Number:	14784250
International Application Number:	
Confirmation Number:	6877
Title of Invention:	Transposition of Native Chromatin for Personal Epigenomics
First Named Inventor/Applicant Name:	Paul Giresi
Customer Number:	77974
Filer:	James Samuel Keddie/Sherry Long
Filer Authorized By:	James Samuel Keddie
Attorney Docket Number:	STAN-1111
Receipt Date:	01-NOV-2017
Filing Date:	13-OCT-2015
Time Stamp:	20:24:33
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	STAN-1111_IDS.pdf	1035306 36a464740048f39991837b6ce8a23740349aa8b0	no	4

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Warnings:					
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3	Foreign Reference	WO2009147386.pdf	3464581 9db8d1f6cb9d77a502be9bd269eee90979c76ae4	no	78
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Warnings:					
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5	Foreign Reference	WO2016207653.pdf	22967177 faa1fb9226adb910cc4233aaf568e041c601210a	no	298
Warnings:					
Information:					
6	Foreign Reference	WO2016207661.pdf	9132953 bb5d89aa333b238661c741ba965fbab7c162741f	no	339
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New Applications Under 35 U.S.C. 111

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ATAC-seq protocol

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ATAC-seq: A Method for Assaying Chromatin Accessibility ...

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UNIT 21.29 ATAC-seq: A Method for Assaying Chromatin Accessibility Genome-Wide

Authors: Jason D Buenrostro · Beijing Wu · Howard Y Chang · William J Greenleaf

Affiliation: Stanford University · Howard Hughes Medical Institute

About: Transposase

ATAC-seq: A Method for Assaying Chromatin Accessibility ...

www.ncbi.nlm.nih.gov › Journal List › HHS Author Manuscripts

ATAC-seq was designed with speed in mind; we have optimized the **protocol** to require a total time of 3 hours. The above **protocol** for nuclei extraction requires 30 minutes. Transposition and purification requires 45 minutes.

[PDF] ATAC-seq Penn State University – Hardison Lab 03-14-16 ...

https://www.encodeproject.org/.../**ATACseq**_PSUHardison_Mar2016.pdf

protocol and synthesized by IDT for the use in the Hardison lab. Cell collection: Use approximately 50,000 cells. Cell lysis: Collect cells and transfer to 1.7 ml microcentrifuge tube. Spin down cells at 600 xg for 10 min at 4°C. Gently remove and discard SN. Wash once ...

Epigenetics applications - ATAC-seq | Abcam

www.abcam.com/epigenetics/**epigenetics-application-spotlight-atac-seq** ▾

Though ATAC-seq is not optimized for low cell numbers, modification to the **protocol** have been made to accommodate this: microfluidics can be used to separate single ...

[PDF] ATAC-seq: A Method for Assaying Chromatin Accessibility ...

greenleaf.stanford.edu/...2015_current_**protocols**_molecular_biology.pdf

Chromatin Accessibility Genome-Wide ... ATAC-seq data sets can also be bioinformatically separated into ... following **protocol** has been optimized for human ...

Authors: Jason D Buenrostro · Beijing Wu · Howard Y Chang · William J Greenleaf

Affiliation: Stanford University · Howard Hughes Medical Institute

About: Transposase

Protocol ATAC Seq | Polymerase Chain Reaction - Scribd

https://www.scribd.com/document/260319675/**Protocol-ATAC-Seq** ▾

Protocol ATAC Seq - Download as PDF File (.pdf), Text File (.txt) or read online.

ATAC-seq - Wikipedia

https://**en.wikipedia.org**/wiki/**ATAC-seq** ▾

ATAC-seq (Assay for Transposase-Accessible Chromatin using sequencing) is a technique used in molecular biology to study chromatin accessibility. The technique was first described in 2013, as an

Related searches

atac seq kit

atac sequencing

atac seq data analysis

atac seq nature methods

mnase seq

faire seq

open chromatin

attack seq

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IPR2023-01030
Page 00358

alternative or complementary method to MNase-seq (sequencing of micrococcal nuclease sensitive sites), FAIRE-seq and DNAse-seq.

Description · Usage and ... · Advantages · External source

ATAC-seq protocol - SEQanswers

seqanswers.com/forums/showthread.php?t=45636 ▾

Jun 30, 2015 · Hi everyone, I am planning to use ATAC-seq with my samples. But I can not find a detailed **protocol** in their nature method paper. Also there is no response in ATAC forum.

[PDF] ATAC-seq: from experimental design to computational ...

https://gencore.bio.nyu.edu/wp-content/uploads/2015/10/NYU-HiTS...

ATAC-seq **protocol** • Isolation of intact nuclei (Day 1) • Fragment and tag chromatin (Day 1) • Amplify library (Day 2)

Omni-ATAC-seq: Improved ATAC-seq protocol : Protocol Exchange

www.nature.com/**protocolexchange**/**protocols**/6107

We present Omni-ATAC, an improved ATAC-seq **protocol** for chromatin accessibility profiling that works universally across multiple cell types and cell contexts with ...

Greenleaf: ATAC-seq

greenleaf.stanford.edu/portfolio_details_buenrostro_2013_nature... ▾

ATAC-seq captures open chromatin sites using a simple two-step protocol with 500-50,000 cells and reveals the interplay between genomic locations of open chromatin, DNA-binding proteins, individual nucleosomes and chromatin compaction at nucleotide resolution.

[PDF] Assay for Transposase Accessible Chromatin using ...

neurolincs.org/pdf/**ATAC-Seq-Protocol**.pdf

Pamela Milani (Fraenkel Lab) – pmilani@mit.edu Jan 2016 Assay for **Transposase Accessible Chromatin using Sequencing (ATAC-Seq) Protocol** modified from:

Related searches for ATAC-seq protocol

atac seq **kit**	**mnase** seq
atac **sequencing**	**faire** seq
atac seq **data analysis**	**open chromatin**
atac seq **nature methods**	**attack** seq

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Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01030
Page 00359

Doc Code:IDS.3P
Document Description: Third-Party Submission Under 37 CFR 1.290

PTO/SB/429(08-12)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	14784250

U.S. PATENTS

Cite No	Patent Number	Kind Code [1]	Issue Date (YYYY-MM-DD)	First Named Inventor

U.S. PATENT APPLICATION PUBLICATIONS

Cite No	Publication Number	Kind Code [1]	Publication Date (YYYY-MM-DD)	First Named Inventor
1	20160115474		2016-04-28	Mary Anne Jelinek
2	20150111788		2015-04-23	Joseph Fernandez

FOREIGN PATENTS AND PUBLISHED FOREIGN PATENT APPLICATIONS

Cite No	Foreign Document Number [3]	Country Code [2]	Kind Code [1]	Publication Date (YYYY-MM-DD)	Applicant, Patentee or First Named Inventor	T [5]
						☐

NON-PATENT PUBLICATIONS (e.g., journal article, Office action)

Cite No	Author (if any), title of the publication, page(s) being submitted, publication date, publisher (where available), place of publication (where available).	T [5]	E [6]

EFS Web 2.1.17

/CYNTHIA B WILDER/ (12/05/2017) 12/05/2017

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.B.W/

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	14784250

		☐	☐

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.B.W/

STATEMENTS

The party making the submission is not an individual who has a duty to disclose information with respect to the above-identified application under 37 CFR 1.56.

This submission complies with the requirements of 35 U.S.C. 122(e) and 37 CFR 1.290.

☐ The fee set forth in 37 CFR 1.290(f) has been submitted herewith.

☒ The fee set forth in 37 CFR 1.290(f) is not required because this submission lists three or fewer total items and, to the knowledge of the person signing the statement after making reasonable inquiry, this submission is the first and the only submission under 35 U.S.C 122(e) filed in the above-identified application by the party making the submission or by a party in privity with the party.

☐ This resubmission is being made responsive to a notification of non-compliance issued for an earlier filed third-party submission. The corrections in this resubmission are limited to addressing the non-compliance. As such, the party making this resubmission: (1) requests that the Office apply the previously-paid fee set forth in 37 CFR 1.290(f), or (2) states that no fee is required to accompany this resubmission as the undersigned is again making the fee exemption statement set forth in 37 CFR 1.290(g).

Signature	/Robert Prince/		
Name/Print	Robert Prince	Registration Number (if applicable)	38583

Examiner Signature	/CYNTHIA B WILDER/ (12/05/2017)	Date Considered	12/05/2017

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/784,250	Giresi et al.
	Examiner	Art Unit
	CYNTHIA B WILDER	1637

CPC - Searched*		
Symbol	Date	Examiner
C12Q1/6869	12/08/2017	CW
C12Q2521/301	12/08/2017	CW
C12Q2537/164	12/08/2017	CW
C12Q1/6874	12/08/2017	CW

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
435	6.1	12/08/2017	CW
435	91.2	12/08/2017	CW

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Inventor search on PALM, text search on WEST and google (search terms attached, review of IDS and third party submission, review of AIA statutory framework	12/08/2017	CW

/CYNTHIA B WILDER/ Primary Examiner, Art Unit 1637	

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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Page 00362

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/784,250	Giresi et al.
	Examiner	Art Unit
	CYNTHIA B WILDER	1637

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
C12Q2521/301		12/08/2017	CW
C12Q1/6869		12/08/2017	CW
C12Q2537/164		12/08/2017	CW
C12Q2537/164		12/08/2017	CW

/CYNTHIA B WILDER/ Primary Examiner, Art Unit 1637	

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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Page 00363

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (03-15)
Approved for use through 07/31/2016. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	14784250
Filing Date	2015-10-13
First Named Inventor	Giresi, Paul
Art Unit	1637
Examiner Name	WILDER, CYNTHIA B.
Attorney Docket Number	STAN-1111

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	WO2009147386	WO		2009-12-10	OXFORD BIODYNAMICS LIMITED		
	2	WO2016207647	WO		2016-12-29	OXFORD BIODYNAMICS LIMITED		
	3	WO2016207653	WO		2016-12-29	OXFORD BIODYNAMICS LIMITED		

/CYNTHIA B WILDER/ (12/06/2017) 12/06/2017

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14784250
	Filing Date	2015-10-13
	First Named Inventor	Giresi, Paul
	Art Unit	1637
	Examiner Name	WILDER, CYNTHIA B.
	Attorney Docket Number	STAN-1111

	4	WO2016207661	WO		2016-12-29	OXFORD BIODYNAMICS LIMITED		
	5	WO2007093819	WO		2007-08-23	ISIS INNOVATION LIMITED		

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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	
	Filing Date	
	First Named Inventor	Buenrostro, Jason D.
	Art Unit	
	Examiner Name	
	Attorney Docket Number	STAN-1111

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2012/106546	WO	A2	2012-08-09	Shendure et al.		☐
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	
	First Named Inventor	Buenrostro, Jason D.
	Art Unit	
	Examiner Name	
	Attorney Docket Number	STAN-1111

	1	GANGADHARAN et al., DNA transposon Hermes insert into DNA in nucleosome-free regions in vivo, Proc nat Ad Sci, December 21, 2010, Vol. 107, No. 51, pages 1966-1972.	☐
	2	BJORNSSON et al., Intra-individual change over time in DNA methylation with familial clustering, JAMA, June 25, 2008, Vol. 299 No. 24, pages 2877-2883.	☐

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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WEST Search History for Application 14784250

Creation Date: 2017120616:05

Prior Art Searches

Query	DB	Hits	Op.	Plur.	Thes.	Date
20160115474 or 20150111788	PGPB, USPT, USOC, EPAB, DWPI	4	ADJ	YES		12-05-2017
(20100120098 or 20130203605).PN.	PGPB, USPT, USOC, EPAB, DWPI	4	ADJ	YES		12-05-2017
("20030032141").PN.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		12-05-2017
wo 2012106546	PGPB, USPT, USOC, EPAB, DWPI	4	ADJ	YES		12-05-2017
14/784250	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-05-2017
(14/784250) and ((C12Q1/6869 | C12Q2521/301 | C12Q2537/164 | C12Q1/6874).CPC.)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-05-2017
chromatin same (tn transposase)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		12-06-2017
chromatin same (transposase)	PGPB, USPT, USOC, EPAB, DWPI	220	ADJ	YES		12-06-2017
(chromatin same (transposase)) same tag$	PGPB, USPT, USOC, EPAB, DWPI	12	ADJ	YES		12-06-2017
(chromatin same (transposase) same tag$) and (mapping or epigenetic feature)	PGPB, USPT, USOC, EPAB, DWPI	6	ADJ	YES		12-06-2017
(chromatin same (transposase) same tag$ and (mapping or epigenetic feature)) and (nucleus same cell)	PGPB, USPT, USOC, EPAB, DWPI	4	ADJ	YES		12-06-2017

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WO 20100048605 or 20050130161	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		12-06-2017
WO 2010048605	PGPB, USPT, USOC, EPAB, DWPI	8	ADJ	YES		12-06-2017
14/900217	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-06-2017
WO 2013078470	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		12-06-2017
20120258892	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		12-06-2017
(20120258892) and chromatin	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-06-2017
(20120258892 and chromatin) and transposase	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-06-2017
(20120258892 and chromatin and transposase) and nucleus	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		12-06-2017
(20120258892 and chromatin and transposase) and cell	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-06-2017
transposase same nucleus	PGPB, USPT, USOC, EPAB, DWPI	154	ADJ	YES		12-06-2017
(transposase same nucleus) same cell	PGPB, USPT, USOC, EPAB, DWPI	133	ADJ	YES		12-06-2017
(transposase same nucleus same cell) same chromatin	PGPB, USPT, USOC, EPAB, DWPI	22	ADJ	YES		12-06-2017
14/784250	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-06-2017
(14/784250) and ((C12Q1/6869 | C12Q2521/301 | C12Q2537/164 | C12Q1/6874).CPC.)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-06-2017

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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Notice of References Cited	Application/Control No. 14/784,250	Applicant(s)/Patent Under Reexamination Giresi et al.	
	Examiner CYNTHIA B WILDER	Art Unit 1637	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-20150111788-A1	04-2015	Fernandez; Joseph	C12N15/1093	506/26
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

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*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Plants Methods, 3 (11): 1-25 (Year: 2007)
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01030
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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (03-15)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	14784250
Filing Date	2015-10-13
First Named Inventor	Giresi, Paul
Art Unit	1639
Examiner Name	
Attorney Docket Number	STAN-1111

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20100120098		2010-05-13	GRUNENWALD, et al.	
	2	20130203605		2013-08-08	SCHENDURE, et al.	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	WO2010048605	WO		2010-04-29	EPICENTRE TECHNOLOGIES CORPORATION		

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14784250
	Filing Date	2015-10-13
	First Named Inventor	Giresi, Paul
	Art Unit	1639
	Examiner Name	
	Attorney Docket Number	STAN-1111

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	BOYLE, et al. "High-resolution genome-wide in vivo footprinting of diverse transcription factors in human cells", Genome Res. 2011 Mar;21(3):456-64.	
	2		

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EXAMINER SIGNATURE

Examiner Signature	/CYNTHIA B WILDER/ (12/05/2017)	Date Considered	12/05/2017

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

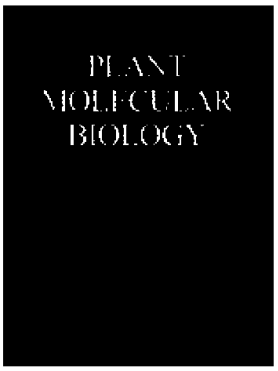
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Volume 50, Issue 1, September 2002

ISSN: 0167-4412 (Print) 1573-5028 (Online)



In this issue (12 articles)

OriginalPaper

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Hyun Uk Kim, Robyn Cotter, Sheila Johnson, Mineo Senda...

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OriginalPaper

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Marina Malatrasi, Timothy J. Close, Nelson Marmiroli

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Erratum Structural and functional organization of the `1S0.8 gene-rich region' in the Triticeae

Devinder Sandhu, Kulvinder S. Gill

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/784,250	10/13/2015	Paul Giresi	STAN-1111	6877

77974 7590 12/13/2017

Stanford University Office of Technology Licensing
Bozicevic, Field & Francis LLP
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER	
WILDER, CYNTHIA B	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
12/13/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01030
Page 00376

Office Action Summary	Application No. 14/784,250	Applicant(s) Giresi et al.	
	Examiner CYNTHIA B WILDER	Art Unit 1637	AIA Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 11/1/2017 .

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____ .

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 78-110 is/are pending in the application.

5a) Of the above claim(s) 96-110 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 78-95 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 13 October 2015 is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☑ Notice of References Cited (PTO-892)

2)☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 11/1/2017, 2/16/2017, 1/12/2017, 4/14/2016 and 10/13/2015.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01030
Page 00377

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Election/Restrictions

2. Applicant's election without traverse of Group I, claims 78-95 and species, Tn transposase, in the reply filed on 10/3/2017 is acknowledged. Accordingly, the claims 96-110 are withdrawn from consideration as being drawn to a non-elected invention.

Drawings

3. The drawings were received on 10/13/2015. These drawings are found acceptable by the examiner.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on 11/1/2017, 2/16/2016, 4/14/2016, 10/13/2015 and third-party submission 1/12/2017 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112

5. The following is a quotation of 35 U.S.C. 112(b):

> (b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 80, 82, 83, 88 and 94 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

(a) The claims 80, 82, 83, 88 are indefinite because they recite improper Markush language. Specifically, the limitations recited in the claims do not share a common use or is known in the art to be functionally equivalent. It is suggested amending the claims to recite ---one or more selected from the group consisting of--- instead of "one or more:"

(b) The claim 88 is indefinite at the recitation of "CTCF" because abbreviations often have more than one meaning in the art. It is suggested amending the claim to recite the full name of the abbreviation.

(c) Claim 88 is indefinite and confusing at the recitation of "chromatin states include one or more of: CTCF-associated, transcription start site, weak enhancer, enhancer, promoter flanking, transcribed and repressed" because it is unclear as to what is intended to be gleaned from the disclosure or how these limitations relates to the chromatin. For example is applicant suggesting that the chromatin is transcribed or is located at the transcription start site or associated with an enhancer or something entirely different? A clear interpretation cannot be ascertained.

(d) Claim 94 is indefinite at "sequence insertion preference" because it is unclear as to what applicant is making reference to. The limitation is not defined in the specification and one cannot ascertain what is intended to be encompassed by the limitation in regards to the insertional enzyme.

(e) Claim 95 lacks proper antecedent basis for "the step of permeabilizing". It is suggested amending the claim to recite ---a step…".

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a)(2) the claimed invention was described in a patent issued under section 151, or in an application for patent published or deemed published under section 122(b), in which the patent or application, as the case may be, names another inventor and was effectively filed before the effective filing date of the claimed invention.

8. Note: The claims as currently written are sufficiently broad. Therefore, for the purpose of application of prior art, the claims are being given the broadest reasonable interpretation by the examiner.

Claim(s) 78-83, 85, 87-92 is/are rejected under 35 U.S.C. 102(a)(2) as being anticipated by Fernandez et al {Fernandez, used interchangeably herein} (US 20150111788, effective filing date November 22, 2011).

Regarding claim 78, Fernandez et al teach a method for analyzing chromatin, comprising: (a) contacting chromatin from a nucleus of at least one cell with an insertional enzyme complex to produce a plurality of tagged fragments of genomic DNA, (b) performing a nucleic acid assay on a tagged fragment of said plurality to provide fragment information (Figure 1, para. [0017], [0025], [0028], Example 1—[0031] - [0036]); see also para. [0040]-[0041]; see also example 3 and 4). Regarding the step (c) of generating, with the aid of a computer processor, a representation of epigenetic features of a genome region of said at least one cell by mapping said fragment information to said genome region Fernandez teaches in the Examples 3 and Example 4 wherein software is used to

extend the sequence read alignments and generate signal maps. Fernandez et al teach that peaks and signal maps are entered into gene annotation and sample comparison. These are used to compare the representation of genomic sequences in the DNA libraries (col. 7, ex. 4). Fernandez et al also teaches after sequencing, the data for multiple targets can be sorted based on the bar code sequence (last two lines of example 6). Thus these limitation meets the claim as broadly written.

Regarding claim 79, Fernandez et al teach wherein said chromatin is contacted with said insertional enzyme complex within said nucleus of said cell ([0025], [0027], Figure 1 and [0036]-[0037]).

Regarding claim 80, Fernandez et al teach wherein said fragment information comprises one or more of: size of said tagged fragment ([0036], [0039]).

Regarding claim 81, Fernandez et al teach wherein performing said nucleic acid assay on said tagged fragment comprises sequencing said tagged fragment to provide said fragment information, wherein said fragment information comprises a sequence read (para. [0036] and [0039]).

Regarding claim 82, Fernandez et al teach wherein said epigenetic features include one or more of: DNA binding protein occupancy at a binding site in said genome region (see e.g., [0033] which teaches analysis of the sequence specific binding protein, p53 binding site using ChIP).

Regarding claim 83, Fernandez et al teach wherein said fragment information comprises one or more of: read length of said sequence read ([0036], [0039], [0041]).

84. (New) The method of claim 83, wherein said cleavage site is within a nucleosome-free region of said chromatin.

Regarding claim 85, Fernandez teach wherein said at least one cell is a plurality of cell ([0024] and [0039]).

Regarding claim 87, Fernandez et al teach wherein said DNA binding protein is a transcription factor, e.g., p53 ([0033]) .

Regarding claim 88, Fernandez et al teach wherein said chromatin states include transcription (See table 1, [0036], [0043], [0052]).

Regarding claim 89, Fernandez et al teach wherein said genome region comprises a regulatory region (see examples).

Regarding claims 90 and 91, Fernandez et al teach wherein said insertional enzyme complex comprises a transposase, wherein said transposase is Tn5 transposase ([0025], [0027], and Example 1).

Regarding claim 92, Fernandez et al teach wherein said insertional enzyme complex comprises two or more enzymatic moieties ([0045 teaches two transposase molecules per antibody molecule which is used in the TAM-Chip assay). Thus, Fernandez teaches the limitations of the claims recited above.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

9. Claim 86 is/are rejected under 35 U.S.C. 103 as being unpatentable over Fernandez et al as recited above. Regarding claim 86, Fernandez et al teach that improvements in CHIP assay the use of magnetic beads which has allowed a ten-fold reduction in sample size requirements from 2-10 million cells to 0.1 million (100 000 cells) to 1 million cells (0007). Fernandez further teaches that the number of cells required is thus directly proportional to the number of proteins to be analyzed. (0007). Fernandez et al additionally teach that method of the recited invention have the potential to significantly reduce the amount of samples needed compared to traditional ChIP methods (0008). Thus it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the effective filing date of the claimed invention that a reduce sample size of less than 500 000 cells are within the scope of the claim invention. One of ordinary skill in the art at the time of the effective filing date of the invention could have expected a reasonable expectation of success in performing the chromatin based assay.

10. Claim 94 is/are rejected under 35 U.S.C. 103 as being unpatentable over Fernandez et al as previously applied above in view of Haring et al. (Plant Methods., (2007) 3: 11, pages 1-25). Regarding claim 94, Fernandez teaches a method for analyzing chromatin as previously disclosed above. Fernandez teaches wherein software programs are utilized to obtain sequence reads and analyze data and to compare the representation of genomic sequences in the DNA libraries prepared by the method and to show concordance of genomic coverage. Fernandez et al do not expressly teach normalization of the data. However, normalizing the data of Fernandez is within the ordinary artisan capabilities and commonly known and applied in the technical field for improving data quality and interpretation.

In a general teaching, Haring et al discuss quantitative analysis and normalization of data obtained from ChIP (chromatin immunoprecipitation) based protocols. Haring teaches that Chip procedures consist of many steps that can influence the final results. The reference teaches that before the obtained data can be interpreted, the variation caused by all of the steps must be taken into account (page 14, section (5) Data Normalization). Haring teaches that normalization serves to correct for this technical variation. (See section 5, data normalization and conclusions). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of the effective filing date of the claimed invention to have been motivated to have normalized the data of Fernandez et al with a reasonable expectation of success to reduce data variation for improved data interpretation. Such methodologies are within the ordinary artisan's capabilities as suggested by Haring. Accordingly, one of ordinary skill in the art at the

time of the effective filing date of the claimed invention could expect a reasonable expectation of success in obtaining the claimed invention.

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Jendrisak et al., WO 2010048605 (citation made of record on IDS filed 4/14/16) teach a method of contacting chromatin with an insertional enzyme complex to produce a plurality of tagged fragments and performing a nucleic acid assay to provide fragment information (see abstract and claims at pages 167-184).

Conclusion

12. Claims 78-92, 94 and 95 have been rejected. The claims 93 and 95 have not been rejected under prior art. The claim 93 is objected. Amending the claims to clearly recite a step of performing the assay on a blood sample and permeabilizing the cell prior to the step (a) might obviate the prior art rejection currently made of record. Any inquiry concerning this communication or earlier communications from the examiner should be directed to CYNTHIA B WILDER whose telephone number is (571)272-0791. The examiner can normally be reached on Flexible.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, GARY BENZION can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CYNTHIA B WILDER/
Primary Examiner, Art Unit 1637

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14784250
Filing Date	2015-10-13
First Named Inventor	Giresi, Paul
Art Unit	1637
Examiner Name	WILDER, CYNTHIA B.
Attorney Docket Number	STAN-1111

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	Filing Date	2015-10-13
	First Named Inventor	Giresi, Paul
	Art Unit	1637
	Examiner Name	WILDER, CYNTHIA B.
	Attorney Docket Number	STAN-1111

	1	ADEY, et al., "Ultra-low-input, tagmentation-based whole-genome bisulfite sequencing", Genome Research, 2012, 22 (6): 1139-1143.	
	2	BUENROSTRO, et al., "Tranposition of native chromatin for fast and sensitive epigenomic profiling of open chromatin, DNA-binding proteins and nucleosome position", Nature Methods, 2013, 10(12): 1213-1218.	
	3	SIMON, et al., "Using formaldehyde-assisted isolation of regulatory elements (FAIRE) to isolate active regulatory DNA", Nature Protocols, 2012, 7(2): 256-267.	
	4	SONG, et al., "DNase-seq: A High-Resolution Technique for Mapping Active Gene Regulatory Elements across the Genome from Mammalian Cells", Cold Spring Harbor Laboratory Press, 2010, 2010(2), doi:10.1101/pdb.prot5384.	

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Methods for Shearing and Tagging DNA for Chromatin ...

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domesticated **transposase** pogZ, another ... LEDGF/p75-**integrase** complex onto the **chromatin** via its PWWP domain (75-fold increase in affinity).

Published in: **Journal of Biological Chemistry** · 2014

Authors: Jelle Hendrix · Bart Van Heertum · Els Vanstreels · Dirk Daelemans · Jan De Rijck

Affiliation: Katholieke Universiteit Leuven · Rega Institute For Medical Research

About: **Transposase** · Kinetics · Binding site · Repressor · **Chromatin** · Plasma protein binding

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Tagging chromatin with retrotransposons: target ...
genesdev.cshlp.org/content/13/20/2738.full.html
Tagging chromatin with retrotransposons: target specificity of the Saccharomyces Ty5 retrotransposon changes ... This suggests that **integrase** is the **chromatin** sensor.

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Published in: **Journal of Biological Chemistry** · 2009
Authors: Koen Bartholomeeusen · Frauke Christ · Jelle Hendrix · Jeanchristophe Rain · Stepha...
Affiliation: Katholieke Universiteit Leuven · French Institute of Health and Medical Research · Pari...
About: **Integrase** · **Transposase** · Peptide sequence · Recombinant DNA

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AMENDMENT UNDER 37 C.F.R. §1.111 Address to: Mail Stop Amendment Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket No.	STAN-1111
	Confirmation No.	6877
	First Named Inventor	Giresi, Paul
	Application Number	14/784,250
	Filing Date	October 13, 2015
	Group Art Unit	1637
	Examiner Name	WILDER, CYNTHIA B
	Title: "*Transposition of Native Chromatin for Personal Epigenomics*"	

Sir:

This amendment is responsive to the Office Action dated December 13, 2017 for which a three-month period for response was given making this response due by March 13, 2018. This response is filed with a request for a one month time extension and, as such, this response is timely filed. In view of the amendments to the claims and the remarks put forth below, reconsideration and allowance are respectfully requested.

Electronic Patent Application Fee Transmittal

Application Number:	14784250
Filing Date:	13-Oct-2015
Title of Invention:	Transposition of Native Chromatin for Personal Epigenomics
First Named Inventor/Applicant Name:	Paul Giresi
Filer:	James Samuel Keddie/Sherry Long
Attorney Docket Number:	STAN-1111

Filed as Small Entity

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Electronic Acknowledgement Receipt	
EFS ID:	32261640
Application Number:	14784250
International Application Number:	
Confirmation Number:	6877
Title of Invention:	Transposition of Native Chromatin for Personal Epigenomics
First Named Inventor/Applicant Name:	Paul Giresi
Customer Number:	77974
Filer:	James Samuel Keddie/Sherry Long
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Attorney Docket Number:	STAN-1111
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	STAN-1111_IDS.pdf	1036873 37831d07695ad6ba542ee6536c2a684163da084e	no	8
Warnings:					
Information:					
2	Foreign Reference	WO2014108810A2.pdf	3458525 4578a2ce4371331b6800b99fcfa4a85f26b1c900	no	74
Warnings:					
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3	Foreign Reference	WO2016191618A1.pdf	6301072 d2b6a0025dc2fac7e416f88586bd0fd75c147ba0	no	105
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4	Foreign Reference	WO2017015075A1.pdf	6513554 78b03f915fb13adb886f634cc9d75b446ac4e3d1	no	80
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5	Foreign Reference	WO2017025594A1.pdf	7616504 4e90f79d65267c32f8c498006741b6a279ccee362	no	141
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6	Non Patent Literature	Ason.pdf	8489278 a37117a26dd2a1a00241a8b54871315da82014d9	no	13
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7	Non Patent Literature	Green.pdf	2253611 2f6b7186022b99e77db230761eff8bd0d48320b3	no	6
Warnings:					
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8		STAN-1111_RespOA.pdf	62091 dea86dfa9acae905285690e847d5aacc.bf2f072d	yes	9
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Applicant Arguments/Remarks Made in an Amendment		6	9	
	Claims		2	5	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
Warnings:					
Information:					
9	Fee Worksheet (SB06)	fee-info.pdf	32524 147dfc2354c0032c091391106eb2a54eeb93b01d	no	2
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	14784250
Filing Date	2015-10-13
First Named Inventor	Giresi, Paul
Art Unit	1637
Examiner Name	WILDER, CYNTHIA B.
Attorney Docket Number	STAN-1111

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	9328382		2016-05-03	Drmanac et al.	
	2	6294385		2001-09-25	Goryshin et al.	
	3	6593113		2003-07-15	Tenkanen et al.	
	4	8829171		2014-09-09	Steemers et al.	
	5	9238671		2016-01-19	Goryshin et al.	
	6	9074251		2015-07-07	Steemers et al.	
	7	8420386		2013-04-16	Ivics et al.	
	8	9080211		2015-07-14	Grunenwald et al.	

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	9	9150916		2015-10-06	Christen et al.	
	10	8927218		2015-01-06	Forsyth	
	11	9005935		2015-04-14	Belyaev	
	12	8124404		2012-02-28	Alphey	
	13	9574226		2017-02-21	Gormley et al.	
	14	7138267		2006-11-21	Jendrisak et al.	
	15	7608434		2009-10-27	Reznikoff et al.	
	16	9175295		2015-11-03	Kaminaka et al.	
	17	8598328		2013-12-03	Koga et al.	
	18	6613752		2003-09-02	Kay et al.	
	19	7608451		2009-10-27	Cooper et al.	

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	Art Unit	1637
	Examiner Name	WILDER, CYNTHIA B.
	Attorney Docket Number	STAN-1111

	20	5137829		1992-08-11	Nag et al.	
	21	5965443		1999-10-12	Reznikoff et al.	
	22	6258571		2001-07-10	Chumakov et al.	
	23	6207384		2001-03-27	Mekalanos et al.	
	24	7745218		2010-06-29	Kim et al.	
	25	6159717		2000-12-12	Savakis et al.	
	26	6291243		2001-09-18	Fogarty et al.	

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	1	20160122753		2016-05-05	Mikkelsen et al.	
	2	20160060691		2016-03-03	Giresi et al.	

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	3	20160115474		2016-04-28	Jelinek et al.	
	4	20150376608		2015-12-31	Kaper et al.	
	5	20150368638		2015-12-24	Steemers et al.	
	6	20130203605		2013-08-08	Shendure et al.	
	7	20150111788		2015-04-23	Fernandez et al.	
	8	20160208323		2016-07-21	Bernstein et al.	
	9	20160177359		2016-06-23	Ukanis et al.	
	10	20160376663		2016-12-29	Brown	
	11	20150337298		2015-11-26	Xi et al.	
	12	20160160235		2016-06-09	Solodushko et al.	
	13	20040101880		2004-05-27	Rozwadowski et al.	

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	Art Unit	1637
	Examiner Name	WILDER, CYNTHIA B.
	Attorney Docket Number	STAN-1111

	14	20120297493		2012-11-22	Cooper et al.			

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	1	WO 2017/025594	WO		2017-02-16	CEMM FORSCHUNGSZENTRUM FÜR MOLEKULARE MEDIZIN GMBH		
	2	WO 2016/191618	WO		2016-12-01	ZHENG JIANBIAO et al.		
	3	WO 2017/015075	WO		2017-01-26	HARVARD COLLEGE		
	4	WO 2014/108810	WO		2014-07-17	ILLUMINA CAMBRIDGE LTD		

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	ASON et al., "DNA Sequence Bias During Tn5 Transposition", J. Mol. Biol., 2004, 335: 1213-1225.	
	2	GREEN et al., "Insertion site preference of Mu, Tn5, and Tn7 transposons", Mobile DNA, 2012, 3:3, 6 pages.	

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	Art Unit	1637
	Examiner Name	WILDER, CYNTHIA B.
	Attorney Docket Number	STAN-1111

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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	Art Unit	1637
	Examiner Name	WILDER, CYNTHIA B.
	Attorney Docket Number	STAN-1111

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/James S. Keddie/	Date (YYYY-MM-DD)	2018-04-05
Name/Print	James S. Keddie	Registration Number	48920

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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REMARKS

FORMAL MATTERS:

Claims 78-95 and 111-116 are pending after entry of the amendments set forth herein.

Claims 78-95 were examined and rejected.

Claims 96-110 are canceled without prejudice.

Claims 78, 80, 82, 83, 88, 94 and 95 are amended. Support for the amendment to claim 78 is found at, e.g., page 4, lines 21-23 (invoking *In re Johnson* to exclude elements that are positively recited in the specification from the claims (see *In re Johnson* 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) and MPEP § 2173.05.I)) and page 33, lines 3-7. The remainder of the claims is amended for clarity.

New claims 111-116 have been added. Support for the new claims is found at, e.g., page 17, lines 29-33, page 23, line 28 to page 24, line 1, and page 37, line 13.

No new matter is added.

INTERVIEW SUMMARY

Examiner Wilder is thanked for a productive interview with the undersigned, Ali Alemozafar (Reg. No. 68,180), Jason Schultz (Reg. No. 74,740), Amy Lam (Reg. No. 75,223) on April 3, 2018. The teachings of Fernandez (US20150111788) and the present method were discussed.

Applicants proposed to amend claim 78 to require that the insertional enzyme complex does not comprise an antibody specific to a protein that is part of said chromatin. Exr. Wilder indicated that such an amendment, if entered, would result in withdrawal of the rejections over Fernandez.

REJECTIONS UNDER §112, ¶2

Claims 80, 82, 83, 88, 94 and 95 were rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claims 80, 82, 83 and 88

Claims 80, 82, 83 and 88 have been amended to recite "selected from the group consisting of", which addresses part of this rejection.

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Claim 88 has been amended to recite the official full name of CTCF: "CCCTC-binding factor" and to clarify the chromatin states. These amendments address the other part of this rejection.

Withdrawal of this rejection of claims 80, 82, 83, and 88 is requested.

Claim 94

Claim 94 is rejected for reciting the phrase "sequence insertion preference". Without any intention to acquiesce to the correctness of this rejection, and solely to expedite the prosecution of this application, Applicant has amended claim 94 to clarify the claimed subject matter. Claim 94 has been amended to recite an "insertion sequence preference." One of ordinary skill in the art would know the meaning of the term "insertion sequence preference" (see, e.g., Green et al, Mob. DNA 2012 3:3 and Ason et al, J. Mol. Biol. 2004 335: 1213-1225, submitted herewith in an Information Disclosure Statement).

Withdrawal of this rejection of claim 94 is therefore requested.

Claim 95

Claim 95 has been amended in a way that addresses this rejection.

Withdrawal of this rejection of claim 95 is therefore requested.

REJECTIONS UNDER §102

Claims 78-83, 85, 87-92 were rejected under 35 U.S.C. 102(a)(2) as being anticipated by Fernandez (US 20150111788). The Applicants respectfully traverse this rejection.

Without any intention to acquiesce to the correctness of this rejection, and solely to expedite the prosecution of this application, claim 78 has been amended to recite an insertional enzyme complex that "does not comprise an antibody specific to a protein that is part of said chromatin".

As discussed in the aforementioned interview, Fernandez's method relies on antibody-transposase conjugates that are ***specific*** for proteins in the chromatin (see the entirety of Fernandez's disclosure, e.g., Fig. 1). Such conjugates are excluded from the present claims and, as such, Fernandez cannot anticipate the present claims.

Withdrawal of this rejection is therefore requested.

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REJECTIONS UNDER §103(A)

Claim 86 was rejected under 35 U.S.C. 103 as being unpatentable over Fernandez, *supra*.

Claim 94 was rejected under 35 U.S.C. 103 as being unpatentable over Fernandez, *supra*, in view of Haring et al. (Plant Methods 2007 3:1-25).

Without any intention to acquiesce to the correctness of this rejection, and solely to expedite the prosecution of this application, claim 78 has been amended to recite an insertional enzyme complex that "does not comprise an antibody specific to a protein that is part of said chromatin".

As discussed in the aforementioned interview, Fernandez's method relies on antibody-transposase conjugates that are ***specific*** for proteins in the chromatin (see the entirety of Fernandez's disclosure, e.g., Fig. 1). Fernandez does not teach or suggest any method that uses an insertional enzyme complex that "does not comprise an antibody specific to a protein that is part of said chromatin", as claimed. Haring does not cure such deficiency of Fernandez.

Withdrawal of this rejection is therefore requested.

NEW CLAIMS

New claims 111-116 are believed to be patent for at least the reasons as set forth above.

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Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number STAN-1111.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: April 5, 2018

By: /James S. Keddie/
James S. Keddie
Registration No. 48920

Enclosure(s): IDS to cite Green et al, Mob. DNA 2012 3:3 and Ason et al, J. Mol. Biol. 2004 335: 1213-1225.

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AMENDMENTS TO THE CLAIMS

Please amend the claims as shown below. A complete listing of the claims, including their current status identifiers, is set forth below.

1-77. (Cancelled)

78. (Currently amended) A method for analyzing chromatin, comprising:

(a) contacting chromatin from a nucleus of at least one cell with an insertional enzyme complex to produce a plurality of tagged fragments of genomic DNA**, wherein said insertional enzyme complex does not comprise an antibody specific to a protein that is part of said chromatin**,

(b) performing a nucleic acid assay on a tagged fragment of said plurality to provide fragment information, and

(c) generating, with the aid of a computer processor, a representation of epigenetic features of a genome region of said at least one cell by mapping said fragment information to said genome region.

79. (Previously presented) The method of claim 78, wherein said chromatin is contacted with said insertional enzyme complex within said nucleus of said cell.

80. (Currently amended) The method of claim 78, wherein said fragment information comprises one or more **members selected from the group consisting** of: size of said tagged fragment, position of said tagged fragment in said genome region, cleavage site of said tagged fragment, length of said tagged fragment, and position of a tagged fragment of a defined range in length in said genome region.

81. (Previously presented) The method of claim 78, wherein performing said nucleic acid assay on said tagged fragment comprises sequencing said tagged fragment to provide said fragment information, wherein said fragment information comprises a sequence read.

82. (Currently amended) The method of claim 78, wherein said epigenetic features include

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~~one or more~~ **a plurality of members selected from the group consisting** of: ~~a profile of~~ chromatin accessibility along said genome region, DNA binding protein occupancy along said genome region, nucleosome-free DNA [[in]] **along** said genome region, positioning of nucleosomes along said genome region, and ~~a profile of~~ chromatin states along said genome region.

83. (Currently amended) The method of claim 81, wherein said fragment information comprises one or more **members selected from the group consisting** of:

(i) a cleavage site for said insertional enzyme complex,

(ii) read length of said sequence read,

(iii) position of a sequence read of a defined range in length in said genome region, and

(iv) sequence read abundance.

84. (Previously presented) The method of claim 83, wherein said cleavage site is within a nucleosome-free region of said chromatin.

85. (Previously presented) The method of claim 78, wherein said at least one cell is a plurality of cells.

86. (Previously presented) The method of claim 85, wherein said plurality of cells comprises fewer than 500,000 cells.

87. (Previously presented) The method of claim 82, wherein said DNA binding protein is a transcription factor.

88. (Currently amended) The method of claim 82, wherein said chromatin states include one or more **members selected from the group consisting** of: **chromatin that is associated with CCCTC-binding factor** ~~CTCF associated~~, **chromatin that has a** transcription start site, **chromatin that has a** weak enhancer, **chromatin that has an** enhancer, **chromatin that is flanking a** promoter ~~flanking~~, **chromatin that is** transcribed, and **chromatin that is transcriptionally** repressed.

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89. (Previously presented) The method of claim 78, wherein said genome region comprises a regulatory region.

90. (Previously presented) The method of claim 78, wherein said insertional enzyme complex comprises a transposase or an HIV integrase.

91. (Previously presented) The method of claim 90, wherein said transposase is selected from a prokaryotic transposase, a Tn transposase, a MuA transposase, a Vibhar transposase, HERMES, Ac-Ds, Ascot-1, Bsl, Cin4, Copia, En/Spm, F element, hobo, Hsmar1, Hsmar2, IN (HIV), IS1, IS2, IS3, IS4, IS5, IS6, IS10, IS21, IS30, IS50, IS51, IS150, IS256, IS407, IS427, IS630, IS903, IS911, IS982, IS1031, ISL2, L1, Mariner, P element, Tam3, Tc1, Tc3, Tel, THE-1, Tn/O, TnA, Tn3, Tn5, Tn7, Tn10, Tn552, Tn903, Tol1, Tol2, TnlO, and Tyl.

92. (Previously presented) The method of claim 78, wherein said insertional enzyme complex comprises two or more enzymatic moieties.

93. (Previously presented) The method of claim 78, wherein said at least one cell is from a blood sample.

94. (Currently amended) The method of claim 83, further comprising normalizing said sequence read abundance based on a**n** **insertion** sequence ~~insertion~~ preference of said insertional enzyme complex.

95. (Currently amended) The method of claim 78, further comprising ~~the step of~~ permeabilizing said at least one cell prior to step (a).

96.-110. (Cancelled)

111. (New) The method of claim 78, wherein said epigenetic features include chromatin accessibility along said genome region.

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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112. (New) The method of claim 78, wherein said epigenetic features include DNA binding protein occupancy along said genome region.

113. (New) The method of claim 78, wherein said epigenetic features include nucleosome-free DNA along said genome region.

114. (New) The method of claim 78, wherein said epigenetic features include positioning of nucleosomes along said genome region.

115. (New) The method of claim 78, wherein said epigenetic features include chromatin states along said genome region.

116. (New) The method of claim 91, wherein said Tn5 is a hyperactive Tn5 transposase.

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PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/784,250	Filing Date 10/13/2015	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $40 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $210 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

AMENDMENT	04/05/2018	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 24	Minus	** 33	= 0		x $50 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $230 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	tina J barden
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/784,250	10/13/2015	Paul Giresi	STAN-1111	6877

77974 7590 04/12/2018

Stanford University Office of Technology Licensing
Bozicevic, Field & Francis LLP
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CALIFORNIA 94065
UNITED STATES OF AMERICA

EXAMINER
WILDER, CYNTHIA B

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
04/12/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@bozpat.com

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01030
Page 00418

Applicant-Initiated Interview Summary	**Application No.** 14/784,250	**Applicant(s)** Giresi et al.	
	Examiner CYNTHIA B WILDER	**Art Unit** 1637	**AIA Status** Yes

All participants (applicant, applicants representative, PTO personnel):

(1) James Keddie, Applicant's representative.

(2) Ali Alemozafar, Applicant's representative.

(3) Amy Lam, Applicant's Representative.

(4) Cynthia Wilder, Patent Examiner.

Date of Interview: 03 April 2018.

Type: ☑ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☑112 ☑102 ☑103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 78,88 and 93-94.

Identification of prior art discussed: Fernandez et al.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

See Continuation Sheet.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/CYNTHIA B WILDER/ Primary Examiner, Art Unit 1637	

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01030
Page 00419

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicants correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,-
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicants record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiners version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, Interview Record OK on the paper recording the substance of the interview along with the date and the examiners initials.

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: Applicants representatives presented a summary of the instant invention. Applicants representatives discussed claimed differences of the instant invention over the prior art and proposed draft amendments to obviate the prior art rejection made of record. The examiner agreed that the proposed draft amendment potentially obviate the prior art rejection made of record. Applicant's representatives also discussed claimed rejections under 35 USC 112 second paragraph directed to the claim 94. Applicants representatives noted that the limitation was a standard term in the related art and that the specification provided adequate support for the limitation. The examiner acknowledged Applicants comments and agreed that the limitation was definite. The claim 93 was discussed and the Examiner acknowledged that the claim was not rejected but that a cursory search on the claim 93 was performed and it was deemed not to be free of the prior art as previously indicated. The examiner acknowledged however that since the claim depended from the claim 78, if the claim 78 is allowable the claim 93 would also be allowable. The examiner noted that an updated searched would be performed. It was agreed that if any additional issues were to be raised that the examiner would contact Applicant prior to issuing an Office action.

From: James S. Keddie
To: Wilder, Cynthia
Subject: RE: 14/784,250 (STAN-1111)
Date: Saturday, March 31, 2018 10:56:34 AM

Dear Exr. Wilder,

I have attached a proposed amendment and agenda for Monday's interview. I'll give you a quick call at around 11am your time on Monday to confirm that you got it.

Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with the undersigned and practitioners in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application by video conferencing, instant messaging, or electronic mail. I understand that a copy of these communications will be made of record in the application file.

Please call me on (650) 833 7723 if you have any questions.

Warm regards,

James
48,920

From: James S. Keddie
Sent: Wednesday, March 21, 2018 9:28 AM
To: cynthia.wilder@uspto.gov
Subject: 14/784,250 (STAN-1111)

Dear Exr. Wilder,

Could you give me a call on (650) 833 7723, about setting up an interview for 14/784,250?

Thanks,

James

James Keddie Ph.D.
Senior Patent Agent
BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Main: (650) 327-3400; Fax: (650) 327-3231
Direct: (650) 833-7723; Email: keddie@bozpat.com

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Francis LLP can arrange for proper delivery, and then please delete the message from your system. Thank you.

****FOR DISCUSSION PURPOSES ONLY****
****PLEASE DO NOT ENTER****

Application No:	14/784,250
Title:	Transposition of Native Chromatin for Personal Epigenomics
Examiner:	WILDER, CYNTHIA B.
Attorney Docket No:	STAN-1111

Interview on Monday April 2, 2018 at 2 PM EST

Planned attendees: James Keddie (Reg. No. 48,920), Ali Alemozafar (Reg. No. 68,180), Jason Schultz (Reg. No. 74,740), Amy Lam (Reg. No. 75,223)

Proposed amendment

78. (Proposed) A method for analyzing chromatin, comprising:

(a) contacting chromatin from a nucleus of at least one cell with an insertional enzyme complex to produce a plurality of tagged fragments of genomic DNA**, wherein said insertional enzyme complex does not comprise an antibody specific to a protein that is part of said chromatin**,

(b) performing a nucleic acid assay on a tagged fragment of said plurality to provide fragment information, and

(c) generating, with the aid of a computer processor, a representation of epigenetic features of a genome region of said at least one cell by mapping said fragment information to said genome region. (see, e.g., paragraph [0074] and [0157] of the publication)

Agenda

- Discuss USC 102 rejection of claim 78
- Discuss USC 112 rejections of:
  - Claim 88
  - Claim 94
- Discuss basis of objection to claim 93

From: James S. Keddie
To: Wilder, Cynthia
Subject: Re: 14/784,250 (STAN-1111)
Date: Monday, April 2, 2018 9:53:59 AM

I'll check as soon as I get in. I expect that it will be okay. James

On Apr 2, 2018, at 5:06 AM, Wilder, Cynthia <Cynthia.Wilder@USPTO.GOV> wrote:

> Good Morning Mr. Keddie,
> Is it possible for us reschedule the interview for tomorrow or Wednesday? I have a scheduling conflict that I had completely forgot about. If we can reschedule I would truly appreciate it. If we cannot reschedule, is it possible to change the time from 2 PM to 5:30 or 6 PM eastern standard time?
>
> Regards,
>
> Cynthia
>
> ---
>
> **From:** James S. Keddie [mailto:keddie@bozpat.com]
> **Sent:** Saturday, March 31, 2018 10:56 AM
> **To:** Wilder, Cynthia <Cynthia.Wilder@USPTO.GOV>
> **Subject:** RE: 14/784,250 (STAN-1111)
>
> Dear Exr. Wilder,
>
> I have attached a proposed amendment and agenda for Monday's interview. I'll give you a quick call at around 11am your time on Monday to confirm that you got it.
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> Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with the undersigned and practitioners in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application by video conferencing, instant messaging, or electronic mail. I understand that a copy of these communications will be made of record in the application file.
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> Please call me on (650) 833 7723 if you have any questions.
>
> Warm regards,
>
> James
> 48,920
>
> ---
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> **From:** James S. Keddie
> **Sent:** Wednesday, March 21, 2018 9:28 AM
> **To:** cynthia.wilder@uspto.gov
> **Subject:** 14/784,250 (STAN-1111)

Dear Exr. Wilder,

Could you give me a call on (650) 833 7723, about setting up an interview for 14/784,250?

Thanks,

James

James Keddie Ph.D.
Senior Patent Agent
BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Main: (650) 327-3400; Fax: (650) 327-3231
Direct: (650) 833-7723; Email: keddie@bozpat.com

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	14/784,250
				Filing Date	2015-10-13
				First Named Inventor	Paul Giresi
				Art Unit	1637
				Examiner Name	CYNTHIA B WILDER
Sheet	1	of	1	Attorney Docket Number	STAN-1111

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				
	2				

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				
	2				

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1					
	2					

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	ZENTNER et al., "Surveying the epigenomic landscape, one base at a time", Genome Biology, 2012, 13:250, 8 pages.	
	2		

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Electronically Filed

INFORMATION DISCLOSURE STATEMENT	Attorney Docket No.	STAN-1111
	Confirmation No.	6877
	First Named Inventor	Paul Giresi
	Application Number	14/784,250
	Filing Date	October 13, 2015
	Group Art Unit	1637
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	CYNTHIA B WILDER
	Title: "*Transposition of Native Chromatin for Personal Epigenomics*"	

Sir:

Applicants submit herewith documents which may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 C.F.R. § 1.56. This submission is not intended to constitute an admission that any document referred to therein is "prior art" for this invention unless specifically designated as such. A listing of the documents is shown on enclosed Form PTO/SB/08A and copies of the foreign patents and non-patent literature are also enclosed.

The Examiner is requested to make the documents listed on the enclosed PTO/SB/08A of record in this application. Applicants would appreciate the Examiner initialing and returning the initialed copy of form PTO/SB/08A, indicating the documents cited therein have been considered and made of record herein.

Statements

☐ **No statement**

☒ **PTA Statement under 37 CFR § 1.704(d)(1):** Each item of information contained in the information disclosure statement filed herewith:

(i) Was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement; or

(ii) Is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

☒ **IDS Statement under 37 CFR § 1.97(e)(1):** Each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement; or

☐ **IDS Statement under 37 CFR § 1.97(e)(2):** No item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of the information disclosure statement.

Fees

☒ No fee is believed to be due.

☐ The appropriate fee set forth in 37 C.F.R. §1.17(p) accompanies this information disclosure statement.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number STAN-1111.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: June 7, 2018

By: /James S. Keddie/
James S. Keddie
Reg. No. 48,920

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

Electronic Acknowledgement Receipt	
EFS ID:	32839440
Application Number:	14784250
International Application Number:	
Confirmation Number:	6877
Title of Invention:	Transposition of Native Chromatin for Personal Epigenomics
First Named Inventor/Applicant Name:	Paul Giresi
Customer Number:	77974
Filer:	James Samuel Keddie/Sherry Long
Filer Authorized By:	James Samuel Keddie
Attorney Docket Number:	STAN-1111
Receipt Date:	07-JUN-2018
Filing Date:	13-OCT-2015
Time Stamp:	21:13:07
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	STAN-1111_IDS.pdf	22839 1c272095a368563578914c574bfac7a914b8b3fe	no	1

Warnings:

Information:					
This is not an USPTO supplied IDS fillable form					
2	Transmittal Letter	STAN-1111_IDS-Transmittal.pdf	48969 a28a479681ac3af7c4ac16b6a43b2f4348705790	no	2
Warnings:					
Information:					
3	Non Patent Literature	Zentner.pdf	809082 1d07361f22b02f6327948648e056823f940deda1	no	8
Warnings:					
Information:					
			Total Files Size (in bytes):	880890	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

77974 7590 06/27/2018

Stanford University Office of Technology Licensing
Bozicevic, Field & Francis LLP
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CALIFORNIA 94065
UNITED STATES OF AMERICA

EXAMINER
WILDER, CYNTHIA B

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 06/27/2018

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/784,250	10/13/2015	Paul Giresi	STAN-1111	6877

TITLE OF INVENTION: Transposition of Native Chromatin for Personal Epigenomics

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$500	$0.00	$0.00	$500	09/27/2018

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 02/11)

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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Page 00432

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

77974 7590 06/27/2018

Stanford University Office of Technology Licensing
Bozicevic, Field & Francis LLP
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CALIFORNIA 94065
UNITED STATES OF AMERICA

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/784,250	10/13/2015	Paul Giresi	STAN-1111	6877

TITLE OF INVENTION: Transposition of Native Chromatin for Personal Epigenomics

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$500	$0.00	$0.00	$500	09/27/2018

EXAMINER	ART UNIT	CLASS-SUBCLASS
WILDER, CYNTHIA B	1637	435-006000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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Page 00433

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/784,250	10/13/2015	Paul Giresi	STAN-1111	6877

77974 7590 06/27/2018

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SUITE 200
REDWOOD CITY, CALIFORNIA 94065
UNITED STATES OF AMERICA

EXAMINER	
WILDER, CYNTHIA B	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 06/27/2018

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 02/11)

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 14/784,250	Applicant(s) Giresi et al.	
	Examiner CYNTHIA B WILDER	Art Unit 1637	AIA Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 6/7/2018.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 78-95 and 111-116 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information , please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file areply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☑ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 6/7/2018, 4/5/2018.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/CYNTHIA B WILDER/
Primary Examiner, Art Unit 1637

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA. Applicant's amendment filed 4/5/2018 is acknowledged. Claims 1-77 and 96-110 have been canceled. Claim 78, 80, 82, 83, 88, 94, 95 have been amended. Claims 111-116 have been added. Claims 78-95 and 111-116 are pending. All of the arguments have been thoroughly reviewed and considered. Applicant's amendment were found persuasive to obviate the rejections of the prior Office action. Accordingly, the rejections are withdrawn.

Reasons for Allowance

2. The following is an examiner's statement of reasons for allowance: Applicant amendments of the claims 78-95 and 111-116 were found persuasive to obviate the rejections of the prior Office action. Applicant's amendments of the claims were found sufficient to overcome the prior art of Fernandez et al made of record in the prior Office action. No prior art was found teaching or suggesting a method for analyzing chromatin comprising contacting chromatin from a nucleus of at least one cell with an insertional enzyme complex to produce a plurality of tagged fragments of genomic DNA, wherein said insertion al enzyme complex does not comprise an antibody specific to a protein that is part of said chromatin, performing a nucleic acid assay on a tagged fragment of said plurality to provide fragment information and generating with the aid of a computer processor, a representation of epigenetic features of a genomic region of said at least one cell by mapping said fragment information to said genome region. An updated search did not reveal any prior art against the claimed invention. In fact, the prior art

teaches away from chromatin analysis as instantly clamed to obtain epigenetic information. Rather the art supports chromatin immunoprecipitation, which involves the use of an insertional complex that comprises an antibody specific to a protein that is part of the chromatin, as a main tool for investigating epigenetic marks (see e.g., Parks et al., Nature, 10: 669-680, 2009; entire reference, especially Figure 1). Accordingly, the instant invention is deemed novel and non-obvious over the prior art.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

3. Any inquiry concerning this communication or earlier communications from the examiner should be directed to CYNTHIA B WILDER whose telephone number is (571)272-0791. The examiner can normally be reached on Flexible.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, GARY BENZION can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information

for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CYNTHIA B WILDER/
Primary Examiner, Art Unit 1637

Notice of References Cited	Application/Control No. 14/784,250	Applicant(s)/Patent Under Reexamination Giresi et al.	
	Examiner CYNTHIA B WILDER	Art Unit 1637	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A					
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Parks et al. Nature, vol. 10, pages 669-680, October (Year: 2009)
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01030
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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/784,250	Giresi et al.
	Examiner	Art Unit
	CYNTHIA B WILDER	1637

CPC - Searched*		
Symbol	Date	Examiner
C12Q1/6869	12/08/2017	CW
C12Q2521/301	12/08/2017	CW
C12Q2537/164	12/08/2017	CW
C12Q1/6874	12/08/2017	CW
C12Q1/6869	06/20/2018	CW
C12Q2521/301	06/20/2018	CW
C12Q1/6874	06/20/2018	CW
C12Q2537/164	06/20/2018	CW

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
435	6.1	12/08/2017	CW
435	91.2	12/08/2017	CW
435	91.2	06/20/2018	CW

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

/CYNTHIA B WILDER/ Primary Examiner, Art Unit 1637	

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01030
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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/784,250	Giresi et al.
	Examiner	Art Unit
	CYNTHIA B WILDER	1637

Search Notes		
Search Notes	**Date**	**Examiner**
Inventor search on PALM, text search on WEST and google (search terms attached, review of IDS and third party submission, review of AIA statutory framework	12/08/2017	CW
Updated search on WEST, review of IDS, updated search on google, text search on pubmed, review of citations of post-dated art which supports the invention. Review of published art by Applicants.	06/20/2018	CW

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
C12Q2521/301		12/08/2017	CW
C12Q1/6869		12/08/2017	CW
C12Q2537/164		12/08/2017	CW
C12Q2537/164		12/08/2017	CW

/CYNTHIA B WILDER/ Primary Examiner, Art Unit 1637	

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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/784,250	Giresi et al.
	Examiner	**Art Unit**
	CYNTHIA B WILDER	1637

CPC								
Symbol							**Type**	**Version**
C12Q	/	1	/	6874			F	2013-01-01
C12Q	/	1	/	6869			I	2013-01-01

CPC Combination Sets									
Symbol							**Type**	**Set**	**Ranking**	**Version**
C12Q	/	1	/	6869			I	1	1	2013-01-01
C12Q	/	2521	/	301			A	1	2	2013-01-01
C12Q	/	2537	/	164			A	1	3	2013-01-01

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	24	
/CYNTHIA B WILDER/ Primary Examiner, Art Unit 1637	20 June 2018	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

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10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/784,250	Giresi et al.
	Examiner	**Art Unit**
	CYNTHIA B WILDER	1637

INTERNATIONAL CLASSIFICATION				
CLAIMED				
C12P	/	19	/	34

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**
435	91.2

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	24	
/CYNTHIA B WILDER/ Primary Examiner, Art Unit 1637	20 June 2018	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

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	Examiner	**Art Unit**
	CYNTHIA B WILDER	1637

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
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(Assistant Examiner)	(Date)	24	
/CYNTHIA B WILDER/ Primary Examiner, Art Unit 1637	20 June 2018	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

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	CYNTHIA B WILDER	1637

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
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	Examiner	Art Unit
	CYNTHIA B WILDER	1637

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... co-localize with **epigenetic** marks for open **chromatin** ... - Liu - Cited by 150
Heritable **epigenetic** mutation of a **transposon**-flanked ... - Saze - Cited by 157

Transposition of native chromatin for fast and sensitive epigenomic ...

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by JD Buenrostro - 2013 - Cited by 1065 - Related articles
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Transposase-Accessible Chromatin Assay for Fast and Sensitive ...

https://www.whatisepigenetics.com/transposase-accessible-chromatin-assay-for-fast-an...
Nov 18, 2013 - For a Better Understanding of Open **Chromatin**, DNA-Binding ... JD et al., **Transposition** of native **chromatin** for fast and sensitive **epigenomic** ...

Transposition of Native Chromatin for Personal Epigenomics - THE ...

www.freepatentsonline.com/y2016/0060691.html
Mar 3, 2016 - Provided herein is a method for analyzing polynucleotides such as genomic DNA. In certain embodiments, the method comprises: (a) treating ...

Transposition of native chromatin for fast and sensitive epigenomic ...

search.ebscohost.com/login.aspx?direct=true&profile=ehost...site...
Abstract: We describe an assay for transposase-accessible **chromatin** using sequencing (ATAC-seq), based on direct in vitro **transposition** of sequencing ...

US20160060691A1 - Transposition of Native Chromatin for Personal ...

https://patents.google.com/patent/US20160060691A1/en
Major insights into the **epigenetic** information encoded within the nucleoprotein structure of **chromatin** have come from high-throughput, genome-wide methods ...

Transposition of native chromatin for fast and sensitive epigenomic ...

https://scinapse.io/papers/2117757143
ATAC-seq queries the location of open **chromatin**, t | Jason D. Buenrostro, Paul G. Giresi, Lisa C. Zaba, | | sci-napse.

An epigenetic switch ensures transposon repression upon dynamic ...

https://elifesciences.org/articles/11418
by M Walter - 2016 - Cited by 49 - Related articles
The various **transposon** families of the mammalian genome can adopt different types of repressive **chromatin** responses upon DNA methylation loss.

Searches related to transposition and chromatin and epigenomic

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transposition of native chromatin for multimodal regulatory analysis and personal epigenomics

atac-seq nature methods

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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	14784250
Filing Date	2015-10-13
First Named Inventor	Giresi, Paul
Art Unit	1637
Examiner Name	WILDER, CYNTHIA B.
Attorney Docket Number	STAN-1111

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	9328382		2016-05-03	Drmanac et al.	
	2	6294385		2001-09-25	Goryshin et al.	
	3	6593113		2003-07-15	Tenkanen et al.	
	4	8829171		2014-09-09	Steemers et al.	
	5	9238671		2016-01-19	Goryshin et al.	
	6	9074251		2015-07-07	Steemers et al.	
	7	8420386		2013-04-16	Ivics et al.	
	8	9080211		2015-07-14	Grunenwald et al.	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
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Filing Date	2015-10-13
First Named Inventor	Giresi, Paul
Art Unit	1637
Examiner Name	WILDER, CYNTHIA B.
Attorney Docket Number	STAN-1111

	9	9150916		2015-10-06	Christen et al.	
	10	8927218		2015-01-06	Forsyth	
	11	9005935		2015-04-14	Belyaev	
	12	8124404		2012-02-28	Alphey	
	13	9574226		2017-02-21	Gormley et al.	
	14	7138267		2006-11-21	Jendrisak et al.	
	15	7608434		2009-10-27	Reznikoff et al.	
	16	9175295		2015-11-03	Kaminaka et al.	
	17	8598328		2013-12-03	Koga et al.	
	18	6613752		2003-09-02	Kay et al.	
	19	7608451		2009-10-27	Cooper et al.	

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	First Named Inventor	Giresi, Paul
	Art Unit	1637
	Examiner Name	WILDER, CYNTHIA B.
	Attorney Docket Number	STAN-1111

	20	5137829		1992-08-11	Nag et al.	
	21	5965443		1999-10-12	Reznikoff et al.	
	22	6258571		2001-07-10	Chumakov et al.	
	23	6207384		2001-03-27	Mekalanos et al.	
	24	7745218		2010-06-29	Kim et al.	
	25	6159717		2000-12-12	Savakis et al.	
	26	6291243		2001-09-18	Fogarty et al.	

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	1	20160122753		2016-05-05	Mikkelsen et al.	
	2	20160060691		2016-03-03	Giresi et al.	

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	First Named Inventor	Giresi, Paul
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	Examiner Name	WILDER, CYNTHIA B.
	Attorney Docket Number	STAN-1111

	3	20160115474		2016-04-28	Jelinek et al.	
	4	20150376608		2015-12-31	Kaper et al.	
	5	20150368638		2015-12-24	Steemers et al.	
	6	20130203605		2013-08-08	Shendure et al.	
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	8	20160208323		2016-07-21	Bernstein et al.	
	9	20160177359		2016-06-23	Ukanis et al.	
	10	20160376663		2016-12-29	Brown	
	11	20150337298		2015-11-26	Xi et al.	
	12	20160160235		2016-06-09	Solodushko et al.	
	13	20040101880		2004-05-27	Rozwadowski et al.	

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	14	20120297493		2012-11-22	Cooper et al.	

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	1	WO 2017/025594	WO		2017-02-16	CEMM FORSCHUNGSZENTRUM FÜR MOLEKULARE MEDIZIN GMBH		
	2	WO 2016/191618	WO		2016-12-01	ZHENG JIANBIAO et al.		
	3	WO 2017/015075	WO		2017-01-26	HARVARD COLLEGE		
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	1	ASON et al., "DNA Sequence Bias During Tn5 Transposition", J. Mol. Biol., 2004, 335: 1213-1225.	
	2	GREEN et al., "Insertion site preference of Mu, Tn5, and Tn7 transposons", Mobile DNA, 2012, 3:3, 6 pages.	

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	Attorney Docket Number	STAN-1111

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Robertson's Mutator **transposons** in A. thaliana are ... - Singer - Cited by 313
Transcriptional silencing of **transposons** by Piwi and ... - Sienski - Cited by 306
Transposition of native **chromatin** for fast and sensitive ... - Buenrostro - Cited by 1065

Chromatin structure and transposable elements in organismal aging

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3849598/
by JG Wood - 2013 - Cited by 53 - Related articles
Dec 4, 2013 - Keywords: **chromatin**, heterochromatin, **transposable** elements, retrotransposons, RNAi, histone modifications, epigenetics of aging, silencing.

Chromatin Landscapes of Retroviral and Transposon Integration Profiles

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3983033/
by J de Jong - 2014 - Cited by 38 - Related articles
Apr 10, 2014 - The ability of retroviruses and **transposons** to insert their genetic material into host **DNA** makes them widely used tools in molecular biology, ...

Transposable elements and the epigenetic regulation of the genome ...

https://www.nature.com/.../transposable-elements-and-the-epigenetic-regulation-of-2651...
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Chromatin Structure, Heterochromatin, and Transposable Genetic ...

https://link.springer.com/article/10.1023/A:1015309720404
by BA Leibovitch - 2002 - Cited by 1 - Related articles
A higher content of several important chromosomal proteins was recently revealed in **chromatin** of **transposable** genetic elements (TGE). The possible role of ...

DNA methylation restrains transposons from adopting a chromatin ...

genesdev.cshlp.org/content/29/12/1256.full
by N Zamudio - 2015 - Cited by 49 - Related articles
Abstract. **DNA** methylation is essential for protecting the mammalian germline against **transposons**. When **DNA** methylation-based **transposon** control is ...

Chromatin-modifying genetic interventions suppress age ... - PNAS

www.pnas.org/content/pnas/113/40/11277.full.pdf
by JG Wood - 2016 - Cited by 30 - Related articles
Oct 4, 2016 - aging | heterochromatin | **transposable** elements | dietary restriction | ... epigenetic **chromatin** marks are seen with age, and age-related.

Chromatin and Transposons in Senescent Cells -- Fight Aging!

https://www.fightaging.org/archives/.../chromatin-and-transposons-in-senescent-cells/
Feb 5, 2013 - Senescent cells have removed themselves from normal operation and really should be destroyed, either by their own programmed cell death ...

Chromatin variation associated with liver metabolism is mediated by ...

https://epigeneticsandchromatin.biomedcentral.com/articles/10.../s13072-016-0078-0
by J Du - 2016 - Cited by 5 - Related articles
Chromatin variation associated with liver metabolism is mediated by **transposable** elements. Juan Du,; Amy Leung,; Candi Trac,; Michael Lee,; Brian W. Parks, ...

Chromatin structure and transposable elements in organismal aging ...

https://europepmc.org/abstract/med/24363663
by JG Wood - 2013 - Cited by 53 - Related articles
Abstract: Epigenetic regulatory mechanisms are increasingly appreciated as central to a diverse array of biological processes, including aging. An...

Searches related to chromatin and (transposon or transposase)

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define transposon	transposable elements human genome
types of transposons	transposable elements are dna sequences that
transposon silencing	role of transposable elements in genetic regulation

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				Filing Date	2015-10-13
				First Named Inventor	Paul Giresi
				Art Unit	1637
				Examiner Name	CYNTHIA B WILDER
Sheet	1	of	1	Attorney Docket Number	STAN-1111

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	2				

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1					
	2					

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
/C.B.W/	1	ZENTNER et al., "Surveying the epigenomic landscape, one base at a time", Genome Biology, 2012, 13:250, 8 pages.	
	2		

Examiner Signature	/CYNTHIA B WILDER/ (06/12/2018)	Date Considered	06/12/2018

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

WEST Search History for Application 14784250

Creation Date: 2018052016:30

Prior Art Searches

Query	DB	Hits	Op.	Plur.	Thes.	Date
20160115474 or 20150111788	PGPB, USPT, USOC, EPAB, DWPI	4	ADJ	YES		12-05-2017
(20100120098 or 20130203605).PN.	PGPB, USPT, USOC, EPAB, DWPI	4	ADJ	YES		12-05-2017
("20030032141").PN.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		12-05-2017
wo 2012106546	PGPB, USPT, USOC, EPAB, DWPI	4	ADJ	YES		12-05-2017
14/784250	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-05-2017
(14/784250) and ((C12Q1/6869 | C12Q2521/301 | C12Q2537/164 | C12Q1/6874).CPC.)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-05-2017
chromatin same (tn transposase)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		12-06-2017
chromatin same (transposase)	PGPB, USPT, USOC, EPAB, DWPI	220	ADJ	YES		12-06-2017
(chromatin same (transposase)) same tag$	PGPB, USPT, USOC, EPAB, DWPI	12	ADJ	YES		12-06-2017
(chromatin same (transposase) same tag$) and (mapping or epigenetic feature)	PGPB, USPT, USOC, EPAB, DWPI	6	ADJ	YES		12-06-2017
(chromatin same (transposase) same tag$ and (mapping or epigenetic feature)) and (nucleus same cell)	PGPB, USPT, USOC, EPAB, DWPI	4	ADJ	YES		12-06-2017

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WO 20100048605 or 20050130161	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		12-06-2017
WO 2010048605	PGPB, USPT, USOC, EPAB, DWPI	8	ADJ	YES		12-06-2017
14/900217	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-06-2017
WO 2013078470	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		12-06-2017
20120258892	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		12-06-2017
(20120258892) and chromatin	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-06-2017
(20120258892 and chromatin) and transposase	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-06-2017
(20120258892 and chromatin and transposase) and nucleus	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		12-06-2017
(20120258892 and chromatin and transposase) and cell	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-06-2017
transposase same nucleus	PGPB, USPT, USOC, EPAB, DWPI	154	ADJ	YES		12-06-2017
(transposase same nucleus) same cell	PGPB, USPT, USOC, EPAB, DWPI	133	ADJ	YES		12-06-2017
(transposase same nucleus same cell) same chromatin	PGPB, USPT, USOC, EPAB, DWPI	22	ADJ	YES		12-06-2017
14/784250	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-06-2017
(14/784250) and ((C12Q1/6869 | C12Q2521/301 | C12Q2537/164 | C12Q1/6874).CPC.)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-06-2017

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14/784250	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		05-20-2018
(14/784250) and (insertional enzyme sane antibody)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		05-20-2018
(14/784250) and (insertional enzyme same antibody)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		05-20-2018
20150111788	PGPB, USPT, USOC, EPAB, DWPI	3	ADJ	YES		05-20-2018
insertional enzyme complex	PGPB, USPT, USOC, EPAB, DWPI	3	ADJ	YES		05-20-2018
chromatin same tag$	PGPB, USPT, USOC, EPAB, DWPI	668	ADJ	YES		05-20-2018
(chromatin same tag$) same (transposase or HIV integrase)	PGPB, USPT, USOC, EPAB, DWPI	15	ADJ	YES		05-20-2018
chromatin same (transposase or HIV integrase)	PGPB, USPT, USOC, EPAB, DWPI	254	ADJ	YES		05-20-2018
(chromatin same (transposase or HIV integrase)) same (tag$ or label$ or reporter)	PGPB, USPT, USOC, EPAB, DWPI	31	ADJ	YES		05-20-2018
(14/784250) and ((C12Q1/6869 | C12Q2521/301 | C12Q2537/164 | C12Q1/6874).CPC.)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		05-20-2018

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Page 00462

Bibliographic Data

Application No: 14/784,250

Foreign Priority claimed: (•) Yes ( ) No

35 USC 119 (a-d) conditions met: [✓] Yes [ ] No [ ] Met After Allowance

Verified and Acknowledged: /Cynthia Wilder/ (Examiner's Signature) /CW/ (Initials)

Title: Transposition of Native Chromatin for Personal Epigenomics

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/13/2015	435	1637	STAN-1111
RULE			

APPLICANTS

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, Stanford, CA, UNITED STATES

INVENTORS

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Howard Y. Chang Stanford, CA, UNITED STATES

William J. Greenleaf Menlo Park, CA, UNITED STATES

CONTINUING DATA

This application is a 371 of PCT/US14/38825 05/20/2014

PCT/US14/38825 has PRO of 61826728 05/23/2013

FOREIGN APPLICATIONS

IF REQUIRED, FOREIGN LICENSE GRANTED**

11/19/2015

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Scholarly articles for **atac-seq protocol**

ATAC-seq: A method for assaying chromatin ... - Buenrostro - Cited by 234
Transposition of native chromatin for fast and sensitive ... - Buenrostro - Cited by 1065
... vivo tumor development by **ATAC-seq** and FAIRE-seq ... - Davie - Cited by 56

ATAC-seq: A Method for Assaying Chromatin Accessibility Genome ...

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4374986/
by J Buenrostro - 2015 - Cited by 234 - Related articles
Jan 5, 2015 - Keywords: **ATAC-seq**, Transposase, Chromatin Accessibility ... regulatory landscape of chromatin with a relatively simple **protocol** that can be ...
Abstract · Introduction · COMMENTARY

[DOC] ATAC-seq Protocol

https://www.med.upenn.edu/.../ATAC-seq%20Protocol%20-%20Kaestner%20Lab%20...
ATAC-seq Protocol. Kaestner Lab. Reagents. 1X PBS. Nuclease-free H20. NP-40 10%. Nextera DNA Library Prep Kit (Illumina, catalog # FC-121-1030).

An improved ATAC-seq protocol reduces background and enables ...

https://www.nature.com/articles/nmeth.4396
by MR Corces - 2017 - Cited by 10 - Related articles
Aug 28, 2017 - We present Omni-ATAC, an improved **ATAC-seq protocol** for chromatin accessibility profiling that works across multiple applications with ...
Abstract · Main · Methods · References

ATAC-Seq - Illumina

https://www.illumina.com/science/sequencing-method-explorer/kits.../atac-seq.html
ATAC-Seq uses the Tn5 transposome to detect nucleosome-free regions of the genome. The method is commonly used, and optimized **protocols** are available ...

Epigenetics applications - ATAC-seq | Abcam

www.abcam.com/epigenetics/epigenetics-application-spotlight-atac-seq
The main advantage of **ATAC-seq** over these existing methods is the simplicity of the library preparation **protocol**: Tn5 insertion followed by two rounds of PCR.

ATAC-seq Guidelines - Harvard FAS Informatics

https://informatics.fas.harvard.edu/atac-seq-guidelines.html
Nov 1, 2017 - The developers of the **ATAC-seq** method have published a detailed **protocol** for the laboratory procedure (Buenrostro et al., 2015). Here are a ...

[PDF] Garber Lab ATAC-seq protocol - ENCODE

https://www.encodeproject.org/documents/...fdc4.../ATAC_garberlab_protocol.pdf
Garber Lab **ATAC-seq protocol**. University of Massachusetts Medical School Program in Bioinformatics and Integrative Biology. 368 Plantation Street. Worcester ...

[PDF] ATAC---seq - Blueprint Epigenome

www.blueprint-epigenome.eu/UserFiles/File/Protocols/ATAC_Seq_Protocol.pdf
Blueprint: Assay for Transposase Accessible Chromatin (**ATAC---seq**). To obtain ... Harvest cells (no fixation), **protocol** to be defined by the user. 2. Spin down ...

ATAC-seq Protocol - Creative Biogene

https://www.creative-biogene.com/support/atac-seq-protocol.html
ATAC-seq Protocol. Cellpreparation 1. 50,000 cells ... When sequencing ATAC-seq libraries, sequencing primers and reagents must be used. For nucleosome ...

Searches related to atac-seq protocol

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atac-seq kit

atac-seq review

atac-seq troubleshooting

atac-seq nature methods

an improved atac-seq protocol **reduces background and enables interrogation of frozen tissues**

atac-seq illumina

atac-seq service

atac-seq analysis

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Electronically Filed

AMENDMENT UNDER 37 C.F.R. §1.312	Attorney Docket No.	STAN-1111
	Confirmation No.	6877
	First Named Inventor	Giresi, Paul
	Application Number	14/784,250
	Filing Date	October 13, 2015
	Group Art Unit	1637
Address to: Mail Stop Issue Fee Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	WILDER, CYNTHIA B
	Title: "*Transposition of Native Chromatin for Personal Epigenomics*"	

Sir:

This amendment is responsive to the Notice of Allowance and Fees Due dated June 27, 2018. Applicants submit that the amendments set forth below raise no new issues. Entry of these amendments is thus respectfully requested.

AMENDMENTS TO THE CLAIMS

Please amend the claims as shown below. A complete listing of the claims, including their current status identifiers, is set forth below.

1-77. (Cancelled)

78. (Currently amended) A method for analyzing chromatin, comprising:

(a) contacting chromatin from a nucleus of at least one cell with an insertional enzyme complex to produce a plurality of tagged fragments of genomic **deoxyribonucleic acid (**DNA**)**, wherein said insertional enzyme complex does not comprise an antibody specific to a protein that is part of said chromatin,

(b) performing a nucleic acid assay on a tagged fragment of said plurality **of tagged fragments** to provide fragment information, and

(c) generating, with the aid of a computer processor, a representation of epigenetic features of a genome region of said at least one cell by mapping said fragment information to said genome region.

79. (Currently amended) The method of claim 78, wherein said chromatin is contacted with said insertional enzyme complex within said nucleus of said **at least one** cell.

80. (Currently amended) The method of claim 78, wherein said fragment information comprises one or more members selected from the group consisting of: **a** size of said tagged fragment, **a** position of said tagged fragment in said genome region, **a** cleavage site of said tagged fragment, **a** length of said tagged fragment, and **a** position of **said** [[a]] tagged fragment [[of]] **in** a defined range [[in]] **of** length in said genome region.

81. (Previously presented) The method of claim 78, wherein performing said nucleic acid assay on said tagged fragment comprises sequencing said tagged fragment to provide said fragment information, wherein said fragment information comprises a sequence read.

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82. (Previously presented) The method of claim 78, wherein said epigenetic features include a plurality of members selected from the group consisting of: chromatin accessibility along said genome region, DNA binding protein occupancy along said genome region, nucleosome-free DNA along said genome region, positioning of nucleosomes along said genome region, and chromatin states along said genome region.

83. (Currently amended) The method of claim 81, wherein said fragment information comprises one or more members selected from the group consisting of:

(i) **information regarding** a cleavage site for said insertional enzyme complex,

(ii) **a** read length of said sequence read,

(iii) **a** position of **said** [[a]] sequence read [[of]] **in** a defined range [[in]] **of** length in said genome region, and

(iv) **a** sequence read abundance.

84. (Previously presented) The method of claim 83, wherein said cleavage site is within a nucleosome-free region of said chromatin.

85. (Previously presented) The method of claim 78, wherein said at least one cell is a plurality of cells.

86. (Previously presented) The method of claim 85, wherein said plurality of cells comprises fewer than 500,000 cells.

87. (Previously presented) The method of claim 82, wherein said DNA binding protein is a transcription factor.

88. (Currently amended) The method of claim 82, wherein said chromatin states include one or more members selected from the group consisting of: chromatin that is associated with CCCTC-

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binding factor, chromatin that has a transcription start site, ~~chromatin that has a weak enhancer,~~ chromatin that has an enhancer, chromatin that is flanking a promoter, chromatin that is transcribed, and chromatin that is transcriptionally repressed.

89. (Previously presented) The method of claim 78, wherein said genome region comprises a regulatory region.

90. (Currently amended) The method of claim 78, wherein said insertional enzyme complex comprises a transposase or **a** ~~an~~ **human immunodeficiency virus (**HIV**)** integrase.

91. (Currently amended) The method of claim 90, wherein said transposase is selected from **the group consisting of** a prokaryotic transposase, a Tn transposase, a MuA transposase, a Vibhar transposase, HERMES, Ac-Ds, Ascot-1, Bsl, Cin4, Copia, En/Spm, F element, hobo, Hsmar1, Hsmar2, IN (HIV), IS1, IS2, IS3, IS4, IS5, IS6, IS10, IS21, IS30, IS50, IS51, IS150, IS256, IS407, IS427, IS630, IS903, IS911, IS982, IS1031, ISL2, L1, Mariner, P element, Tam3, Tc1, Tc3, Tel, THE-1, Tn/O, TnA, Tn3, Tn5, Tn7, Tn10, Tn552, Tn903, Tol1, Tol2, TnlO, and Tyl.

92. (Previously presented) The method of claim 78, wherein said insertional enzyme complex comprises two or more enzymatic moieties.

93. (Previously presented) The method of claim 78, wherein said at least one cell is from a blood sample.

94. (Currently amended) The method of claim 83, **wherein said fragment information comprises said sequence read abundance and said method** further ~~comprising~~ **comprises** normalizing said sequence read abundance based on an insertion sequence preference of said insertional enzyme complex.

95. (Currently amended) The method of claim 78, further comprising permeabilizing said at

least one cell prior to ~~step~~ (a).

96.-110. (Cancelled)

111. (Previously presented) The method of claim 78, wherein said epigenetic features include chromatin accessibility along said genome region.

112. (Previously presented) The method of claim 78, wherein said epigenetic features include DNA binding protein occupancy along said genome region.

113. (Previously presented) The method of claim 78, wherein said epigenetic features include nucleosome-free DNA along said genome region.

114. (Previously presented) The method of claim 78, wherein said epigenetic features include positioning of nucleosomes along said genome region.

115. (Previously presented) The method of claim 78, wherein said epigenetic features include chromatin states along said genome region.

116. (Previously presented) The method of claim 91, wherein said Tn5 is a hyperactive Tn5 transposase.

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The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number STAN-1111.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: July 10, 2018

By: /James S. Keddie/
James S. Keddie
Registration No. 48920

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Electronic Patent Application Fee Transmittal

Application Number:	14784250
Filing Date:	13-Oct-2015
Title of Invention:	Transposition of Native Chromatin for Personal Epigenomics
First Named Inventor/Applicant Name:	Paul Giresi
Filer:	James Samuel Keddie/Tammy Hu
Attorney Docket Number:	STAN-1111

Filed as Small Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	2501	1	500	500

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**500**

Electronic Acknowledgement Receipt	
EFS ID:	33138763
Application Number:	14784250
International Application Number:	
Confirmation Number:	6877
Title of Invention:	Transposition of Native Chromatin for Personal Epigenomics
First Named Inventor/Applicant Name:	Paul Giresi
Customer Number:	77974
Filer:	James Samuel Keddie/Tammy Hu
Filer Authorized By:	James Samuel Keddie
Attorney Docket Number:	STAN-1111
Receipt Date:	10-JUL-2018
Filing Date:	13-OCT-2015
Time Stamp:	20:03:33
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$500
RAM confirmation Number	071118INTEFSW00006166500815
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	STAN-1111_IssueFree_Transmittal_cute.pdf	194164 2b9872d59e442b3eafa3bfb615388c22f7f2c912	no	1
Warnings:					
Information:					
2		STAN-1111_312_amendment.pdf	40021 b500a92a6c89365fbc726f3d51450d9df0715b84	yes	6
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment after Notice of Allowance (Rule 312)		1	1	
	Claims		2	5	
	Applicant Arguments/Remarks Made in an Amendment		6	6	
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30092 5186784b88af2ccf05446605aecc417c0dfdec26	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	264277		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PART B - FEE(S) TRANSMITTAL

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(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/784,250	10/13/2015	Paul Giresi	STAN-1111	6877

TITLE OF INVENTION: Transposition of Native Chromatin for Personal Epigenomics

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$500	$0.00	$0.00	$500	09/27/2018

EXAMINER	ART UNIT	CLASS-SUBCLASS
WILDER, CYNTHIA B	1637	435-006000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 James S. Keddie
2 Bozicevic, Field & Francis LLP
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: The Board of Trustees of the Leland Stanford Junior University
(B) RESIDENCE: (CITY and STATE OR COUNTRY): Stanford, California

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

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☐ Publication Fee (No small entity discount permitted)

☐ Advance Order - # of Copies _____

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☐ A check is enclosed.

☒ Payment by credit card. ~~Form PTO-2038 is attached.~~

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5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /James S. Keddie/ Date July 10, 2018

Typed or printed name James S. Keddie Registration No. 48920

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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Page 00478

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/784,250	10/13/2015	Paul Giresi	STAN-1111	6877

77974 7590 07/24/2018

Stanford University Office of Technology Licensing
Bozicevic, Field & Francis LLP
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CALIFORNIA 94065
UNITED STATES OF AMERICA

EXAMINER
WILDER, CYNTHIA B

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
07/24/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@bozpat.com

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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Response to Rule 312 Communication	Application No.	Applicant(s)	
	14/784,250	Giresi et al.	
	Examiner	Art Unit	AIA Status
	CYNTHIA B WILDER	1637	Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

1. ☑ The amendment filed on 10 July 2018 under 37 CFR 1.312 has been considered, and has been:
   a) ☐ entered.
   b) ☑ entered as directed to matters of form not affecting the scope of the invention.
   c) ☐ disapproved because the amendment was filed after the payment of the issue fee.
      Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.
   d) ☐ disapproved. See explanation below.
   e) ☐ entered in part. See explanation below.

/CYNTHIA B WILDER/
Primary Examiner, Art Unit 1637

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01030
Page 00480

OK TO ENTER: /C.B.W/

Electronically Filed

AMENDMENT UNDER 37 C.F.R. §1.312	Attorney Docket No.	STAN-1111
	Confirmation No.	6877
	First Named Inventor	Giresi, Paul
	Application Number	14/784,250
	Filing Date	October 13, 2015
	Group Art Unit	1637
Address to: Mail Stop Issue Fee Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	WILDER, CYNTHIA B
	Title: "*Transposition of Native Chromatin for Personal Epigenomics*"	

Sir:

This amendment is responsive to the Notice of Allowance and Fees Due dated June 27, 2018. Applicants submit that the amendments set forth below raise no new issues. Entry of these amendments is thus respectfully requested.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/784,250	08/28/2018	10059989	STAN-1111	6877

77974 7590 08/08/2018

Stanford University Office of Technology Licensing
Bozicevic, Field & Francis LLP
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 125 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Paul Giresi, Palo Alto, CA;
THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, Stanford, CA;
Jason D. Buenrostro, Redwood City, CA;
Howard Y. Chang, Stanford, CA;
William J. Greenleaf, Menlo Park, CA;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

Electronically Filed

REQUEST FOR RECONSIDERATION OF PATENT TERM ADJUSTMENT UNDER 37 C.F.R. § 1.705(d) Address to: Mail Stop: PETITIONS Commissioner for Patents PO Box 1450 Alexandria, VA 22313	Attorney Docket	STAN-1111
	First Named Inventor	Paul Giresi
	Patent Number	10,059,989
	Confirmation Number	6877
	Filing/371(c) Date	October 13, 2015
	Group Art Unit	1637
	Examiner Name	Cynthia B. Wilder
	Title: "*Transposition of Native Chromatin for Personal Epigenomics*"	

Sir:

Under 37 C.F.R. § 1.705(d), the patentee respectfully requests reconsideration of the Patent Term Adjustment (PTA) determined for the above-referenced patent, which issued on August 28, 2018, making this Request due by October 28, 2018. Accordingly, this Request is timely filed.

Provided herewith is: (1) the fee of $200.00 as set forth in 37 C.F.R. § 1.18(e); and (2) a statement of the facts involved.

STATEMENT OF FACTS

According to 37 C.F.R. § 1.704(d), a paper containing only an Information Disclosure Statement (IDS) in compliance with §§ 1.97 and 1.98 will not be considered a failure to engage in reasonable efforts to conclude prosecution (processing or examination) of the application under paragraphs (c)(6), (c)(8), (c)(9), or (c)(10) of this section if it is accompanied by a statement that each item of information contained in the IDS was first cited in any communication from a foreign patent office in a counterpart application and that this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the IDS.

The IDS filed on June 7, 2018 was in compliance with §§ 1.97 and 1.98 and was accompanied by the appropriate statement under Rule 704(d), as described above. As such, no Applicant delay should have been incurred in association with the filing of this IDS.

Accordingly, the total delay for circumstances constituting a failure by the Applicant to engage in reasonable efforts to conclude processing or examination as set forth in 37 C.F.R. § 1.704 (Applicant delay) should be 74 days, not 130 days, as was calculated by the Office.

The patentee agrees that USPTO delay under 35 U.S.C. § 154(b)(1)(A) (type A delay) is **255 days**, as indicated on the enclosed PTA calculation from the USPTO.

The patentee agrees that USPTO delay under 35 U.S.C. § 154(b)(1)(B) (type B delay) is **0 days**, as indicated on the enclosed PTA calculation from the USPTO.

The patentee agrees that USPTO delay under 35 U.S.C. § 154(b)(1)(C) (type C delay) is **0 days**, as indicated on the enclosed PTA calculation from the USPTO.

The patentee agrees that overlap between type A delay and type B delay or between type A delay and type C delay is **0 days**, as indicated on the enclosed PTA calculation from the USPTO.

In view of the above, the patentee submits that the total PTA for the above-referenced patent should be **181 days** (255 days of A delay + 0 days of B delay + 0 days of C delay – 0 days of overlap between type A delay and type B delay – 74 days of Applicant delay), *not 125 days*, as was calculated by the Office. The patentee respectfully requests that the PTA calculation be reconsidered in light of the above.

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Page 00484

CONCLUSION

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-1111.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: September 7, 2018

By: /James S. Keddie, Reg. No. 48,920/
James S. Keddie
Registration No. 48,920

Enclosure:

- The Office's PTA calculation for USPN 10,059,989 (3 pages)

BOZICEVIC, FIELD & FRANCIS LLP
210 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01030
Page 00485

14/784,250	Transposition of Native Chromatin for Personal Epigenomics	STAN-1111	08-26-2018:19:21:41

Patent Term Adjustments

Patent Term Adjustment (PTA) for Application Number: 14/784,250

Filing or 371(c) Date:	10-13-2015	Overlapping Days Between {A and B} or {A and C}:	0
Issue Date of Patent:	-	Non-Overlapping USPTO Delays:	255
A Delays:	255	PTO Manual Adjustments:	0
B Delays:	0	Applicant Delays:	130
C Delays:	0	Total PTA Adjustments:	125

Patent Term Adjustment History Explanation Of Calculations

Number	Date	Contents Description	PTO(Days)	APPL(Days)	Start
104.5	08-28-2018	PTA 36 Months			104.4
104.4	10-13-2015	Commencement Date			0
104	08-28-2018	Patent Issue Date Used in PTA Calculation			0
103	07-25-2018	Export to Final Data Capture			0
102	07-24-2018	Dispatch to FDC			0
101	07-24-2018	Email Notification			0
100	07-24-2018	Printer Rush- No mailing			0
99	07-24-2018	Mail Response to 312 Amendment (PTO-271)		15	93
98	07-19-2018	Office Action Review			0
97	07-18-2018	Application Is Considered Ready for Issue			0
96	07-18-2018	Response to Amendment under Rule 312			0
95	07-10-2018	Finished Initial Data Capture			0
94	07-13-2018	Pubs Case Remand to TC			0
93	07-10-2018	Amendment after Notice of Allowance (Rule 312)			0
92	07-10-2018	Issue Fee Payment Verified			0
91	07-03-2018	Sequence Forwarded to Pubs on Tape			0
90	07-10-2018	Issue Fee Payment Received			0
89	06-26-2018	Export to Initial Data Capture			0
88	06-27-2018	Electronic Review			0
87	06-27-2018	Email Notification			0
86	06-27-2018	Mail Notice of Allowance			0
85	06-25-2018	Office Action Review			0
84	06-25-2018	Office Action Review			0
83	06-21-2018	Office Action Review			0
82	06-21-2018	Office Action Review			0
81	06-21-2018	Notice of Allowance Data Verification Completed			0
80	06-21-2018	Issue Revision Completed			0
79	06-21-2018	Document Verification			0
78	06-20-2018	Reasons for Allowance			0
77	06-20-2018	Allowability Notice			0
74	06-12-2018	Information Disclosure Statement considered			0
73	06-07-2018	Information Disclosure Statement (IDS) Filed		56	64
67	04-30-2018	Information Disclosure Statement considered			0
66	04-05-2018	Electronic Information Disclosure Statement			0
65	04-17-2018	Date Forwarded to Examiner			0
64	04-12-2018	Response after Non-Final Action		30	54
63	04-17-2018	Request for Extension of Time - Granted			0
62	04-12-2018	Email Notification			0
61	04-12-2018	Mail Applicant Initiated Interview Summary			0

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60	04-09-2018	Interview Summary - Applicant Initiated - Telephonic			0
59	04-09-2018	Interview Summary- Applicant Initiated			0
58	04-05-2018	Information Disclosure Statement (IDS) Filed			0
57	11-01-2017	Electronic Information Disclosure Statement		29	46
56	12-13-2017	Electronic Review			0
55	12-13-2017	Email Notification			0
54	12-13-2017	Mail Non-Final Rejection			0
53	12-08-2017	Non-Final Rejection			0
52	12-06-2017	Information Disclosure Statement considered			0
51	12-05-2017	Information Disclosure Statement considered			0
50	12-05-2017	Information Disclosure Statement considered			0
49	12-05-2017	Information Disclosure Statement considered			0
48	11-01-2017	Information Disclosure Statement (IDS) Filed			0
47	10-17-2017	Date Forwarded to Examiner			0
46	10-03-2017	Response to Election / Restriction Filed			0
45	08-25-2017	Electronic Review			0
44	08-25-2017	Email Notification			0
43	08-25-2017	Mail Restriction Requirement	255		104.4
42	08-22-2017	Office Action Review			0
41	08-22-2017	Restriction/Election Requirement			0
40	02-16-2017	Electronic Information Disclosure Statement			0
39	02-16-2017	Information Disclosure Statement (IDS) Filed			0
38	01-19-2017	Email Notification			0
37	01-18-2017	Mail Third Party IDS communication			0
36	01-17-2017	Office Action Review			0
35	01-17-2017	Third Party IDS communication			0
34	04-14-2016	Electronic Information Disclosure Statement			0
33	04-14-2016	Information Disclosure Statement (IDS) Filed			0
32	04-03-2016	Case Docketed to Examiner in GAU			0
31	02-22-2016	Preliminary Amendment			0
30	10-13-2015	Request for Foreign Priority (Priority Papers May Be Included)			0
29	10-13-2015	Electronic Information Disclosure Statement			0
28	03-08-2016	Email Notification			0
27	03-08-2016	Email Notification			0
26	10-13-2015	371 Completion Date			0
25	03-07-2016	Application Is Now Complete			0
24	03-07-2016	Application Dispatched from OIPE			0
23	03-07-2016	FITF set to YES - revise initial setting			0
22	10-13-2015	Patent Term Adjustment - Ready for Examination			0
21	03-08-2016	Notice of DO/EO Acceptance Mailed			0
20	03-08-2016	Filing Receipt - Updated			0
19	02-22-2016	Additional Application Filing Fees			0
17	10-13-2015	Copy of the International Application			0
16	03-04-2016	Email Notification			0
15	03-03-2016	Application ready for PDX access by participating foreign offices			0
14	03-03-2016	PG-Pub Issue Notification			0
13	11-23-2015	Electronic Review			0
12	11-23-2015	Email Notification			0
11	11-23-2015	Email Notification			0
10	11-23-2015	371 Supplemental Fees Missing - Form M923			0

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9	11-23-2015	Filing Receipt	0
8	10-13-2015	Applicants have given acceptable permission for participating foreign	0
7	10-13-2015	CRF Disk Has Been Received by Preexam / Group / PCT	0
6	10-20-2015	CRF Is Good Technically / Entered into Database	0
5	10-20-2015	Applicant Has Filed a Verified Statement of Small Entity Status in Compliance with 37 CFR 1.27	0
4	10-13-2015	Information Disclosure Statement (IDS) Filed	0
3	10-13-2015	Cleared by OIPE CSR	0
2	10-13-2015	ENTITY STATUS SET TO UNDISCOUNTED (INITIAL DEFAULT SETTING OR STATUS CHANGE)	0
1	10-13-2015	Initial Exam Team nn	0
0.5	05-20-2014	International Filing date	0

Close Window

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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Page 00488

Electronic Patent Application Fee Transmittal

Application Number:	14784250
Filing Date:	13-Oct-2015
Title of Invention:	Transposition of Native Chromatin for Personal Epigenomics
First Named Inventor/Applicant Name:	Paul Giresi
Filer:	James Samuel Keddie/Sherry Long
Attorney Docket Number:	STAN-1111

Filed as Small Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
APPLICATION FOR PATENT TERM ADJUSTMENT	2455	1	200	200
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**200**

Electronic Acknowledgement Receipt	
EFS ID:	33657225
Application Number:	14784250
International Application Number:	
Confirmation Number:	6877
Title of Invention:	Transposition of Native Chromatin for Personal Epigenomics
First Named Inventor/Applicant Name:	Paul Giresi
Customer Number:	77974
Filer:	James Samuel Keddie/Sherry Long
Filer Authorized By:	James Samuel Keddie
Attorney Docket Number:	STAN-1111
Receipt Date:	07-SEP-2018
Filing Date:	13-OCT-2015
Time Stamp:	19:08:53
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$200
RAM confirmation Number	091018INTEFSW19091600
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Patent Term Adjustment Petition	STAN-1111_PTA_Request.pdf	32996 b49198464ba41da7890229114d752f486b5f0450	no	3
Warnings:					
Information:					
2	Patent Term Adjustment Petition	USPN10059989-PTA_Calculation_USPTO.pdf	71357 dc450ef898f21ef294202d124ef1d138bea061c0	no	3
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30399 1aafde5888649a5338546c404f419da10113faa7	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	134752		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/784,250	10/13/2015	Paul Giresi	STAN-1111	6877

77974 7590 01/17/2019

Stanford University Office of Technology Licensing
Bozicevic, Field & Francis LLP
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER	
WILDER, CYNTHIA B	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
01/17/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@bozpat.com

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

In re Patent No. 10,059,989	: DECISION ON REQUEST FOR
Giresi et al.	: RECONSIDERATION OF
Issue Date: August 28, 2018	: PATENT TERM ADJUSTMENT
Application No. 14/784,250	: and
Filed: October 13, 2015	: NOTICE OF INTENT TO ISSUE
Atty Docket No.: STAN-1111	: CERTIFICATE OF CORRECTION

This is a decision on Patentee's request for reconsideration pursuant to 37 C.F.R. § 1.705(b) filed September 7, 2018, requesting that the Office adjust the patent term adjustment from one hundred and twenty-five (125) days to one hundred and eighty-one (181) days.

The petition to correct the patent term adjustment indicated on the above-identified patent to indicate that the term of the above-identified patent is extended or adjusted by one hundred and eighty-one (181) days is **GRANTED**.

The Office acknowledges the submission of the $200.00 fee set forth in 37 C.F.R. § 1.18(e). No additional fees are required. A review of Office records shows this patent is not subject to a terminal disclaimer.

The application is being forwarded to the Certificates of Correction Branch for issuance of a certificate of correction. The Office will issue a certificate of correction indicating that the term of the above-identified patent is extended or adjusted by **one hundred and eighty-one (181) days.**

Telephone inquiries specific to this matter should be directed to the undersigned at (571) 272-3225.

/Paul Shanoski/
Paul Shanoski
Attorney Advisor
Office of Petitions

Encl: Adjusted PTA calculation
DRAFT Certificate of Correction

DRAFT COPY

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT : 10,059,989 B2

DATED : **Aug. 28, 2018** **DRAFT**

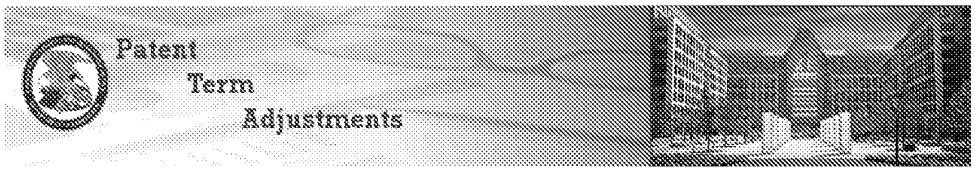
INVENTOR(S) : **Giresi et al.**

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the cover page,

[*] Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 USC 154(b) by 125 days

Delete the phrase "by 125 days" and insert – by 181 days --



PTA/PTE Information | Patent Term Adjustment | Patent Term Extension | Calculation Explanation

Application Number*: 14784250 | Open | Explanation of PTA Calculation | Explanation of PTE Calculation

Print

PTA Calculations for Application: 14784250

Application Filing Date	10/13/2015	**OverLapping Days Between (A and B) or (A and C)**	0
Issue Date of Patent	08/28/2018	**Non-Overlapping USPTO Delays**	255
A Delays	255	**PTO Manual Adjustment**	56
B Delays	0	**Applicant Delay (APPL)**	130
C Delays	0	**Total PTA (days)**	181

* - Sorted Column

File Contents History

Action Number	Action Recorded Date	Action Due Date	Action Code	Action Description	Duration PTO	Duration APPL	Patent Action Number
110	01/10/2019		P028	Adjustment of PTA Calculation by PTO	56		0
104.5	08/28/2018	10/13/2018	PTA36M	PTA 36 Months			104.4
104	08/28/2018		PTAC	Patent Issue Date Used in PTA Calculation			0
103	07/25/2018		EFDC	Export to Final Data Capture			0
102	07/24/2018		D1935	Dispatch to FDC			0
101	07/24/2018		EML_NTR	Email Notification			0
100	07/24/2018		TCPB	Printer Rush- No mailing			0
99	07/24/2018	07/10/2018	MN271	Mail Response to 312 Amendment (PTO-271)		15	93
98	07/19/2018		OAR	Office Action Review			0
97	07/18/2018		PILS	Application Is Considered Ready for Issue			0
96	07/18/2018		N271	Response to Amendment under Rule 312			0
94	07/13/2018		PUBTC	Pubs Case Remand to TC			0
95	07/10/2018		FIDC	Finished Initial Data Capture			0
93	07/10/2018		A.NA	Amendment after Notice of Allowance (Rule 312)			0
92	07/10/2018		N084	Issue Fee Payment Verified			0
90	07/10/2018		IFEE	Issue Fee Payment Received			0
91	07/03/2018		CRFT	Sequence Forwarded to Pubs on Tape			0
88	06/27/2018		ELC_RVW	Electronic Review			0
87	06/27/2018		EML_NTF	Email Notification			0
86	06/27/2018		MN/=.	Mail Notice of Allowance			0
89	06/26/2018		EIDC	Export to Initial Data Capture			0
85	06/25/2018		OAR	Office Action Review			0
84	06/25/2018		OAR	Office Action Review			0
83	06/21/2018		OAR	Office Action Review			0
82	06/21/2018		OAR	Office Action Review			0
81	06/21/2018		N/=.	Notice of Allowance Data Verification Completed			0
80	06/21/2018		IREV	Issue Revision Completed			0
79	06/21/2018		DVER	Document Verification			0
78	06/20/2018		EX.R	Reasons for Allowance			0
77	06/20/2018		CNTA	Allowability Notice			0
74	06/12/2018		IDSC	Information Disclosure Statement considered			0
73	06/07/2018	04/12/2018	WIDS	Information Disclosure Statement (IDS) Filed		56	64
67	04/30/2018		IDSC	Information Disclosure Statement considered			0
65	04/17/2018		FWDX	Date Forwarded to Examiner			0
63	04/17/2018		XT/G	Request for Extension of Time - Granted			0
64	04/12/2018	03/13/2018	A...	Response after Non-Final Action		30	54
62	04/12/2018		EML_NTR	Email Notification			0
61	04/12/2018		MEXIA	Mail Applicant Initiated Interview Summary			0
60	04/09/2018		EXAT	Interview Summary - Applicant Initiated - Telephonic			0

Action Number	Action Recorded Date	Action Due Date	Action Code	Action Description	Duration PTO	Duration APPL	Parent Action Number
59	04/09/2018		EXIA	Interview Summary- Applicant Initiated			0
66	04/05/2018		EIDS.	Electronic Information Disclosure Statement			0
58	04/05/2018		WIDS	Information Disclosure Statement (IDS) Filed			0
56	12/13/2017		ELC_RVW	Electronic Review			0
55	12/13/2017		EML_NTF	Email Notification			0
54	12/13/2017		MCTNF	Mail Non-Final Rejection			0
53	12/08/2017		CTNF	Non-Final Rejection			0
52	12/06/2017		IDSC	Information Disclosure Statement considered			0
51	12/05/2017		IDSC	Information Disclosure Statement considered			0
50	12/05/2017		IDSC	Information Disclosure Statement considered			0
49	12/05/2017		IDSC	Information Disclosure Statement considered			0
57	11/01/2017	10/03/2017	EIDS.	Electronic Information Disclosure Statement		28	46
48	11/01/2017		WIDS	Information Disclosure Statement (IDS) Filed			0
47	10/17/2017		FWDX	Date Forwarded to Examiner			0
46	10/03/2017		ELC.	Response to Election / Restriction Filed			0
45	08/25/2017		ELC_RVW	Electronic Review			0
44	08/25/2017		EML_NTF	Email Notification			0
43	08/25/2017	12/13/2016	MCTRS	Mail Restriction Requirement	255		104.4
42	08/22/2017		OAR	Office Action Review			0
41	08/22/2017		CTRS	Restriction/Election Requirement			0
40	02/16/2017		EIDS.	Electronic Information Disclosure Statement			0
39	02/16/2017		WIDS	Information Disclosure Statement (IDS) Filed			0
38	01/19/2017		EML_NTR	Email Notification			0
37	01/18/2017		MP3DS	Mail Third Party IDS communication			0
36	01/17/2017		OAR	Office Action Review			0
35	01/17/2017		P3DS	Third Party IDS communication			0
34	04/14/2016		EIDS.	Electronic Information Disclosure Statement			0
33	04/14/2016		WIDS	Information Disclosure Statement (IDS) Filed			0
32	04/03/2016		DOCK	Case Docketed to Examiner in GAU			0
28	03/08/2016		EML_NTR	Email Notification			0
27	03/08/2016		EML_NTR	Email Notification			0
21	03/08/2016		M903	Notice of DO/EO Acceptance Mailed			0
20	03/08/2016		FLRCPT.U	Filing Receipt - Updated			0
25	03/07/2016		COMP	Application Is Now Complete			0
24	03/07/2016		OIPE	Application Dispatched from OIPE			0
23	03/07/2016		FTFS	FITF set to YES - revise initial setting			0
16	03/04/2016		EML_NTR	Email Notification			0
15	03/03/2016		CCRDY	Application ready for PDX access by participating foreign offices			0
14	03/03/2016		PG-ISSUE	PG-Pub Issue Notification			0
31	02/22/2016		A.PE	Preliminary Amendment			0
19	02/22/2016		ADDFLFEE	Additional Application Filing Fees			0
13	11/23/2015		ELC_RVW	Electronic Review			0
12	11/23/2015		EML_NTF	Email Notification			0
11	11/23/2015		EML_NTR	Email Notification			0
10	11/23/2015		M923	371 Supplemental Fees Missing - Form M923			0
9	11/23/2015		FLRCPT.O	Filing Receipt			0
6	10/20/2015		CRFE	CRF Is Good Technically / Entered into Database			0
5	10/20/2015		SMAL	Applicant Has Filed a Verified Statement of Small Entity Status in Compliance with 37 CFR 1.27			0
104.4	10/13/2015		COMMN	Commencement Date			0
30	10/13/2015		RQPR	Request for Foreign Priority (Priority Papers May Be Included)			0
29	10/13/2015		EIDS.	Electronic Information Disclosure Statement			0
26	10/13/2015		371COMP	371 Completion Date			0
22	10/13/2015		PTA.RFE	Patent Term Adjustment - Ready for Examination			0
17	10/13/2015		CPYIA	Copy of the International Application			0
8	10/13/2015		APPERMS	Applicants have given acceptable permission for participating foreign			0
7	10/13/2015		CRFL	CRF Disk Has Been Received by Preexam / Group / PCT			0
4	10/13/2015		WIDS	Information Disclosure Statement (IDS) Filed			0
3	10/13/2015		L194	Cleared by OIPE CSR			0
2	10/13/2015		BIG.	ENTITY STATUS SET TO UNDISCOUNTED (INITIAL DEFAULT SETTING OR STATUS CHANGE)			0
1	10/13/2015		IEXX	Initial Exam Team nn			0
0.5	05/20/2014		NEFILE	International Filing date			0

Export to: Excel

Office of Petitions: Routing Sheet

4700

Application No. 14784250

This application is being forwarded to your office for further processing. A decision has been rendered on a petition filed in this application, as indicated below. For details of this decision, please see the document PET.OP.DEC filed on the same date as this document.

- [X] **GRANTED**
- [ ] **DISMISSED**
- [ ] **DENIED**

Office of Petitions: Decision Count Sheet

Mailing Month: 1

Application No.: 14784250

14784250

For US serial numbers: enter number only, no slashes or commas. Ex: 10123456
For PCT: enter "51+single digit of year of filing+last 5 numbers", Ex. for PCT/US05/12345, enter 51512345

Deciding Official: Paul Shanoski

Count (1) - Palm Credit 14784250

Decision: GRANT

FINANCE WORK NEEDED
☐ Select Check Box for YES

GRANT

Decision Type: 551 - 37 CFR 1.705(d) - PATENT TERM ADJUSTMENT AF

551

Notes:

Count (2)

Decision: n/a

FINANCE WORK NEEDED
☐ Select Check Box for YES

Decision Type: NONE

Notes:

Count (3)

Decision: n/a

FINANCE WORK NEEDED
☐ Select Check Box for YES

Decision Type: NONE

Notes:

Initials of Approving Official (if required)

If more than 3 decisions, attach 2nd count sheet & mark this box ☐

Printed on: 1/10/2019

Office of Petitions Internal Document - Ver. 5.0

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY.DOCKET NO./TITLE	REQUEST ID
14/784,250	10/13/2015	Paul Giresi	STAN-1111	176450

Acknowledgement of Loss of Entitlement to Entity Status Discount

The entity status change request below filed through Private PAIR on 10/18/2022 has been accepted.

CERTIFICATIONS:

Change of Entity Status:

X Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be notification of loss of entitlement to small or micro entity status, as applicable.

This portion must be completed by the signatory or signatories making the entity status change in accordance with 37 CFR 1.4(d)(4).

Signature:	/James S. Keddie/
Name:	James S. Keddie
Registration Number:	48920

Correction of Entity Status And Payment of Fee Deficiency		
	Attorney Docket	STAN-1111
	Applicant	The Board of Trustees of the Leland Stanford Junior University
	Serial Number	14/784,250
	Patent No.	10,059,989
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Issue Date	August 28, 2018
	Title:	*"Transposition of Native Chromatin for Personal Epigenomics"*

Sir:

Patentee respectfully submits that the entity status of the above-identified application has been corrected from small to large.

Patentee for the above-identified patent was erroneously indicated as small entity when the first maintenance fee (3.5 Year) was submitted on January 27, 2022. The total deficient fee owed for this patent is itemized in the table below.

Fee description	Fee(s) paid	Fee(s) Due	Fee deficiency
First maintenance Fee	$1000 (fee code 2551)	$2000 (fee code 1551)	**$1000**

Therefore, the total deficient fee owed for this application is **$1000**.

The Commissioner is hereby authorized to charge the deficient fee of $1000 to Deposit Account No. 50-0815.

Should any unresolved issues remain, a telephone call to the undersigned agent would be appreciated.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: October 18, 2022

By: /James S. Keddie/
James S. Keddie
Registration No. 48,920

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

Electronic Acknowledgement Receipt

EFS ID:	46845339
Application Number:	14784250
International Application Number:	
Confirmation Number:	6877
Title of Invention:	Transposition of Native Chromatin for Personal Epigenomics
First Named Inventor/Applicant Name:	Paul Giresi
Customer Number:	77974
Filer:	James Samuel Keddie/Sherry Long
Filer Authorized By:	James Samuel Keddie
Attorney Docket Number:	STAN-1111
Receipt Date:	18-OCT-2022
Filing Date:	13-OCT-2015
Time Stamp:	21:52:39
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	STAN-1111_CorrectEntityStatus_FeeDef.pdf	22540 328c5d88330c795ed0f4fef36884e2e98836 1fa6	no	1

Warnings:

Information:	
Total Files Size (in bytes):	22540

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82B (07-13)
Approved for use through 03/31/2021. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number

POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date
14/784,250	2015-Oct-13

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. 166677

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☑ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature	/Justin Zahrt/	Date (Optional)	October 25, 2022
Name	Justin Zahrt		
Title	Assistant Director of Intellectual Property at The Board of Trustees of the Leland Stanford Junior University		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
14/784,250	**10/26/2022 03:22:46 PM ET**	**STAN-1111**

Title of Invention

Transposition of Native Chromatin for Personal Epigenomics

Application Information

APPLICATION TYPE	Utility - U.S. National Stage under 35 USC 371	PATENT #	10059989
CONFIRMATION #	6877	FILED BY	Maureen Fugate
PATENT CENTER #	61107246	FILING DATE	10/13/2015
CUSTOMER #	77974	FIRST NAMED INVENTOR	Paul Giresi
INTL. APPLICATION #	-	INTL. FILING DATE	-
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	David Casimir

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
S12-404 41398.252 Signed POA.pdf	2	Power of Attorney	1466 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
S12-404 41398.252 Signed POA.pdf	A5008BD14A466D9FD9C011B3FF2C1C0753485E4BC77AE3A6 CD0B0E80263E50EC76AB8DA65C22A4CB22EC1F5D55ECC21 E5F7A12C00D78CD9B1294F5702D3F2C8A

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/784,250	10/13/2015	Paul Giresi	STAN-1111

CONFIRMATION NO. 6877

166677
Casimir Jones, S.C.
2275 Deming Way Ste 310
Middleton, WI 53562

POA ACCEPTANCE LETTER

OC000000136783627

Date Mailed: 11/14/2022

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 10/26/2022.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/mnguyen/

10x Genomics, Inc. Exhibit 2001
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01030
Page 00508

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/784,250	10/13/2015	Paul Giresi	STAN-1111

CONFIRMATION NO. 6877

77974
STANFORD UNIVERSITY OFFICE OF TECHNOLOGY LICENSING
BOZICEVIC, FIELD & FRANCIS LLP
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

POWER OF ATTORNEY NOTICE

OC000000136783626

Date Mailed: 11/14/2022

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 10/26/2022.

- The Power of Attorney to you in this application has been revoked by the applicant. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/mnguyen/

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.	: 10,059,989 B2
APPLICATION NO.	: 14/784250
DATED	: August 28, 2018
INVENTOR(S)	: Giresi et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

The first or sole Notice should read --

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 181 days.

Signed and Sealed this
Third Day of January, 2023

Katherine Kelly Vidal

Katherine Kelly Vidal
Director of the United States Patent and Trademark Office