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Application Number: 16418796 Document Date: 05/21/2019

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Form Revision Date: March 1, 2019

Electronically Filed

PRELIMINARY AMENDMENT AND CERTIFICATION REGARDING SEQUENCE LISTING	Attorney Docket No.	STAN-1111CON5
	Confirmation No.	TBD
	First Named Inventor	Paul Giresi
	Application Number	TBD
	Filing Date	HEREWITH
	Group Art Unit	TBD
	Examiner Name	TBD
Address to: Mail Stop Amendment 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 SPECIFICATION

Please amend the paragraph starting on line 10 of page 1 as shown below:

This application is a continuation of U.S. Patent Application No. 16/160,719, filed on October 15, 2018, which is a continuation of U.S. Patent Application No. 16/043,874, filed on July 24, 2018, which is a continuation of U.S. Patent Application No. 14/784,250, filed on October 13, 2015, which application is a § 371 national phase filing of International Application No. PCT/US2014/038825, filed on May 20, 2014, which ~~This~~ application claims the benefit of U.S. Provisional application serial no. 61/826,728, filed on May 23, 2013, which **applications are** ~~application is~~ incorporated by reference herein in **their** ~~its~~ entirety.

10x Genomics, Inc. Exhibit 2010
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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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. (New) A method for determining accessibility of a site of a polynucleotide to an insertional enzyme complex, comprising:

(a) contacting said polynucleotide with an insertional enzyme complex to produce at least one tagged fragment of said polynucleotide;

(b) performing a nucleic acid assay on said at least one tagged fragment or a derivative thereof to provide insertion data; and

(c) analyzing said insertion data to determine accessibility of said site of said polynucleotide to said insertional enzyme complex.

79. (New) The method of claim 78, wherein (b) comprises sequencing said at least one tagged fragment or a derivative thereof to provide said insertion data, wherein said insertion data comprises sequence information comprising a sequence read.

80. (New) The method of claim 79, wherein (c) comprises mapping said sequence information to a sequence of said polynucleotide.

81. (New) The method of claim 78, further comprising using said determined accessibility to identify one or more proteins that are bound to said polynucleotide at said site.

82. (New) The method of claim 81, wherein at least one of said proteins is a transcription factor.

83. (New) The method of claim 78, wherein said polynucleotide is from or derived from a cell.

10x Genomics, Inc. Exhibit 2010
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01033
Page 00004

84. (New) The method of claim 78, wherein said polynucleotide is present in a cell sample.

85. (New) The method of claim 84, wherein said cell sample is a cell or a cell nucleus.

86. (New) The method of claim 85, wherein said cell or said cell nucleus is not fixed.

87. (New) The method of claim 85, wherein prior to (a), said cell or said cell nucleus is permeabilized, allowing said insertional enzyme complex to contact said polynucleotide.

88. (New) The method of claim 87, wherein said cell or cell nucleus is minimally perturbed during said permeabilization.

89. (New) The method of claim 87, wherein said permeabilization comprises contacting said cell or said cell nucleus with a permeabilization agent.

90. (New) The method of claim 12, wherein said permeabilization agent is selected from the group consisting of NP40, digitonin, tween, streptolysin, and a cationic lipid.

91. (New) The method of claim 89, wherein said permeabilization comprises subjecting said cell or cell nucleus to a hypotonic shock or sonication.

92. (New) The method of claim 85, further comprising, prior to (b), lysing said cell or cell nucleus.

93. (New) The method of claim 78, wherein said insertional enzyme complex does not comprise an antibody specific to a protein that is part of said polynucleotide.

94. (New) The method of claim 78, wherein said insertional enzyme comprises a transposase.

95. (New) The method of claim 94, 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, ISS, IS6, IS10, IS21, IS30, IS50, IS51, IS150, IS256, IS407, IS427, IS630, IS903, IS911, IS982, IS1031, ISL2, L1, Mariner, P element, Tam3, Tel, Tc3, Tel, THE-1, Tn/0, TnA, Tn3, Tn7, Tn10, Tn552, Tn903, Toll, Tol2, TnlO, and Tyl.

96. (New) The method of claim 94, wherein said transposase is a Tn5 transposase or derived from a Tn5 transposase.

97. (New) The method of claim 94, wherein said transposase is a hyperactive Tn5 transposase.

Remarks Under 37 CFR § 1.115

Formal Matters

Claims 78-97 are pending.

Claims 1-77 are canceled. Claims 78-97 are added.

No new matter has been added.

Certification Regarding Sequence Listing

Applicant submits herewith the attached Sequence Listing in .txt format. As set out in MPEP §2422.03(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 §2422.03(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 Patent In version 3.5, 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.
Applicant respectfully submits that the present patent application is now in compliance with 37 CFR §§ 1.821-1.825.

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.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: May 21, 2019

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

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IPR2023-01033
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PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
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 contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	
Filing Date	
First Named Inventor	Paul Giresi
Art Unit	
Examiner Name	
Attorney Docket Number	STAN-1111CON5

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	5137829		1992-08-11	Nag et al.	
	2	5965443		1999-10-12	Reznikoff et al.	
	3	6159717		2000-12-12	Savakis et al.	
	4	6207384		2001-03-27	Mekalanos et al.	
	5	6258571		2001-07-10	Chumakov et al.	
	6	6291243		2001-09-18	Fogarty et al.	
	7	6294385		2001-09-25	Goryshin et al.	
	8	6593113		2003-07-15	Tenkanen et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	
	Filing Date	
	First Named Inventor	Paul Giresi
	Art Unit	
	Examiner Name	
	Attorney Docket Number	STAN-1111CON5

	9	6613752		2003-09-02	Kay et al.	
	10	7608451		2009-10-27	Cooper et al.	
	11	7745218		2010-06-29	Kim et al.	
	12	7608434		2009-10-27	Reznikoff et al.	
	13	7138267		2006-11-21	Jendrisak et al.	
	14	8124404		2012-02-28	Alphey	
	15	8420386		2013-04-16	Ivics et al.	
	16	8598328		2013-12-03	Koga et al.	
	17	8829171		2014-09-09	Steemers et al.	
	18	8927218		2015-01-06	Forsyth	
	19	9005935		2015-04-14	Belyaev	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	
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	20	9074251		2015-07-07	Steemers et al.	
	21	9080211		2015-07-14	Grunenwald et al.	
	22	9150916		2015-10-06	Christen et al.	
	23	9175295		2015-11-03	Kaminaka et al.	
	24	9238671		2016-01-19	Goryshin et al.	
	25	9328382		2016-05-03	Drmanac et al.	
	26	9574226		2017-02-21	Gormley et al.	

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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	20030032141		2003-02-13	Nguyen	
	2	20040101880		2004-05-27	Rozwadowski 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	Paul Giresi
	Art Unit	
	Examiner Name	
	Attorney Docket Number	STAN-1111CON5

	3	20100120098		2010-05-13	GRUNENWALD, et al.	
	4	20120297493		2012-11-22	Cooper et al.	
	5	20130203605		2013-08-08	Shendure et al.	
	6	20150111788		2015-04-23	Fernandez et al.	
	7	20150337298		2015-11-26	Xi et al.	
	8	20150368638		2015-12-24	Steemers et al.	
	9	20150376608		2015-12-31	Kaper et al.	
	10	20160060691		2016-03-03	Giresi et al.	
	11	20160115474		2016-04-28	Jelinek et al.	
	12	20160122753		2016-05-05	Mikkelsen et al.	
	13	20160160235		2016-06-09	Solodushko et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	
	Filing Date	
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	Examiner Name	
	Attorney Docket Number	STAN-1111CON5

	14	20160177359		2016-06-23	Ukanis et al.	
	15	20160208323		2016-07-21	Bernstein et al.	
	16	20160376663		2016-12-29	Brown	
	17	20140274740		2014-09-18	Srinivasan et al.	
	18	20160115474		2016-04-28	Jelinek et al.	
	19	20130079251		2013-03-28	Boles	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	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	WO 2007/093819	WO		2007-08-23	ISIS INNOVATION LIMITED		
	2	WO 2009/147386	WO		2009-12-10	OXFORD BIODYNAMICS LIMITED		
	3	WO 2010/048605	WO		2010-04-29	EPICENTRE TECHNOLOGIES CORPORATION		

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	Attorney Docket Number	STAN-1111CON5

	4	WO 2014/108810	WO		2014-07-17	ILLUMINA CAMBRIDGE LTD		
	5	WO 2016/191618	WO		2016-12-01	ZHENG JIANBIAO et al.		
	6	WO 2016/207647	WO		2016-12-29	OXFORD BIODYNAMICS LIMITED		
	7	WO 2016/207653	WO		2016-12-29	OXFORD BIODYNAMICS LIMITED		
	8	WO 2016/207661	WO		2016-12-29	OXFORD BIODYNAMICS LIMITED		
	9	WO 2017/015075	WO		2017-01-26	HARVARD COLLEGE		
	10	WO 2017/025594	WO		2017-02-16	CHEM FORSCHUNGSZENTRUM FÜR MOLEKULARE MEDIZIN GMBM		
	11	WO2012106546	WO		2012-08-09	SHENDURE et al.		
	12	CN102292455	CN		2011-12-21	Bio-Rad Laboratories, Inc.		

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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]

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	1	ADEY, et al., "Ultra-low-input, tagmentation-based whole-genome bisulfite sequencing", Genome Research, 2012, 22 (6): 1139-1143.	
	2	ASON et al., "DNA Sequence Bias During Tn5 Transposition", J. Mol. Biol., 2004, 335: 1213-1255.	
	3	BJORNSSON et al., "Intra-individiual change over time in DNA methylation with familial clustering, JAMA, June 25, 2008, Vol. 299 No. 24, pages 2877-2883	
	4	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	
	5	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	
	6	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.	
	7	GREEN et al., "Insertion site preference of Mu, Tn5, and Tn7 transposons", Mobile DNA, 2012, 3:3, 6 pages.	
	8	Parks et al., "ChIP-Seq: advantages and challenges of a maturing technology", Nature, vol. 10, pages 669-680, October (Year: 2009)	
	9	Haring et al., "Chromatin immunoprecipitation: optimization, quantitative analysis and data normalization", Plant Methods, 3 (11): 1-25 (Year: 2007)	
	10	SIMON, et al., "Using formaldehyde-assisted isolation of regulatory elements (FAIRE) to isolate active regulatory DNA", Nature Protocols, 2012, 7(2): 256-267.	
	11	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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	Attorney Docket Number	STAN-1111CON5

	12	ZENTNER et al., "Surveying the epigenomic landscape, one base at a time", Genome Biology, 2012, 13:250, 8 pages.	
	13	Epicentre., "EZ-Tn5TM Custom Transposome Construction Kits", www.epicentre.com, pages 1-17, 2012.	
	14	AHERN, "TOOLS & TECHNOLOGY, Biochemical, Reagent Kits Offer Scientists Good Return On Investment", THE SCIENTIST, 1995, vol. 20, pages 20 and 22.	

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	
	Filing Date	
	First Named Inventor	Paul Giresi
	Art Unit	
	Examiner Name	
	Attorney Docket Number	STAN-1111CON5

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.

X 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)	2019-05-21
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.**

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.

Electronically Filed

INFORMATION DISCLOSURE STATEMENT Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket	STAN-1111CON5
	First Named Inventor	Paul GIRESI
	Application Number	TBD
	Confirmation No.	TBD
	Filing Date	HEREWITH
	Group Art Unit	TBD
	Examiner Name	TBD
	Title: *"Transposition of Native Chromatin for Personal Epigenomics"*	

Sir:

Applicant submits 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.

Applicant 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.

All of the references identified herein were disclosed in parent application serial number 16/160,719, and as such, copies thereof are not included pursuant to the provisions of 37 CFR § 1.98(d).

Statements

☒ **No 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.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: May 21, 2019

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 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/Sherry Long
Attorney Docket Number:	STAN-1111CON5

Filed as Small Entity

Filing Fees for Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY FILING FEE (ELECTRONIC FILING)	4011	1	75	75
UTILITY SEARCH FEE	2111	1	330	330
UTILITY EXAMINATION FEE	2311	1	380	380
REQUEST FOR PRIORITIZED EXAMINATION	2817	1	2000	2000
Pages:				
Claims:				
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
PROCESSING FEE, EXCEPT PROV. APPLS.	2830	1	70	70
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**2855**

Electronic Acknowledgement Receipt	
EFS ID:	36077515
Application Number:	16418796
International Application Number:	
Confirmation Number:	6413
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-1111CON5
Receipt Date:	21-MAY-2019
Filing Date:	
Time Stamp:	18:37:25
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$2855
RAM confirmation Number	052219INTEFSW18375600
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	TrackOne Request	STAN-1111CON5_Track-I-Request.pdf	153028 b356a0598e825a44348b3072088aed5aa614faca	no	2
Warnings:					
Information:					
2	Application Data Sheet	STAN-1111CON5_ADS.pdf	1562105 44362eb6bd4e23763a1f44fbf3e08d45b87a096c	no	8
Warnings:					
Information:					
3	Oath or Declaration filed	STAN-1111_Declaration.pdf	2631268 33851ffd2e22ea833687b722be9a9e464b6a3655	no	4
Warnings:					
Information:					
4	Power of Attorney	STAN-1111CON5_GPOA.pdf	339993 ca7a1ce71ed3ba39a36e93aec4311bcaaf74759d	no	2
Warnings:					
Information:					
5		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:					
6		STAN-1111CON5_Prelim_Amendment.pdf	66423 7c7cefbfa143ccb16b26e071bfb3c08dd3b1e12a	yes	6
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Preliminary Amendment		1	1	
	Specification		2	2	
	Claims		3	5	
	Applicant Arguments/Remarks Made in an Amendment		6	6	
Warnings:					
Information:					
7	Information Disclosure Statement (IDS) Form (SB08)	STAN-1111CON5_IDS.pdf	1037586 5595dd6ef14e27518575ff478355e0bf68678949	no	10
Warnings:					
Information:					
8	Transmittal Letter	STAN-1111CON5_IDS-Transmittal.pdf	30754 065cca6188cf5310a01a797ba16cb7593931b0a7	no	2
Warnings:					
Information:					
9	Sequence Listing (Text File)	STAN-1111_Seq_Listing.txt	5239	no	-
Warnings:					
Information:					
10	Fee Worksheet (SB06)	fee-info.pdf	40055 768470b0d2be6e9f9da510c526f6da6485f6a019	no	2
Warnings:					

Information:	
Total Files Size (in bytes):	6949415

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: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Paul Giresi	Nonprovisional Application Number (if known):	
Title of Invention:	TRANSPOSITION OF NATIVE CHROMATIN FOR PERSONAL EPIGENOMICS		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.
2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.
3. The applicable box is checked below:

I. ☑ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /James S. Keddie/	Date May 21, 2019
Name (Print/Typed) James S. Keddie	Practitioner Registration Number 48920

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☑ *Total of 1 forms are submitted.

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.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	STAN-1111CON5
	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

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	STAN-1111CON5
	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-1111CON5	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 :

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	STAN-1111CON5
	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)
	Continuation of	16160719	2018-10-15
Prior Application Status	Patented		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16160719	Continuation of	16043874	2018-07-24	10150995	2018-12-11
Prior Application Status	Patented				Remove

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	STAN-1111CON5
	Application Number	
Title of Invention	Transposition of Native Chromatin for Personal Epigenomics	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16043874	Continuation of	14784250	2015-10-13	10059989	2018-08-28
Prior Application Status	Expired			Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)		
14784250	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	

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.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	STAN-1111CON5
	Application Number	
Title of Invention	Transposition of Native Chromatin for Personal Epigenomics	

Authorization to Permit Access:

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

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 o f 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

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	STAN-1111CON5
	Application Number	
Title of Invention	Transposition of Native Chromatin for Personal Epigenomics	

Mailing Address Information For Applicant:			
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	
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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	STAN-1111CON5
	Application Number	
Title of Invention	Transposition of Native Chromatin for Personal Epigenomics	

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/			Date (YYYY-MM-DD)	2019-05-21
First Name	James S.	Last Name	Keddie	Registration Number	48920

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

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.**

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 C o o p eration 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.

PCT

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
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Application Number	
Filing Date	
First Named Inventor	Paul GIRESI
Title	TRANSPOSITION OF NATIVE CHROMATIN FOR PERSONAL EPIGENOMICS
Art Unit	
Examiner Name	
Attorney Docket Number	STAN-1111CON5

SIGNATURE of Applicant or Patent Practitioner

Signature	/James S. Keddie/	Date (Optional)	May 21, 2019
Name	James S. Keddie	Registration Number	48,920
Title (if Applicant is a juristic entity)			
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Name	Karin Hope Immergluck		
Title	Executive Director, Office of Technology Licensing Stanford University		

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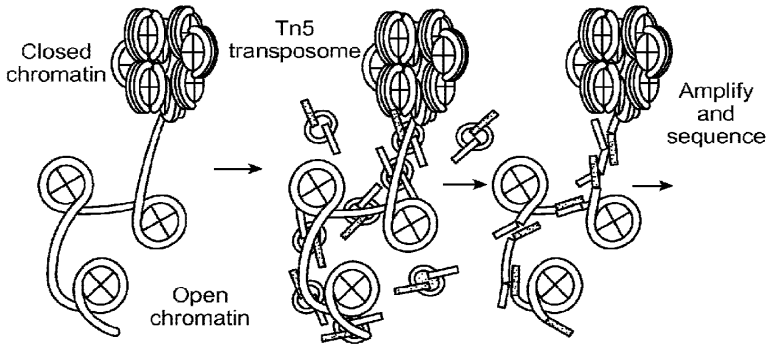

FIG. 1A

(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
5 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
10 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
15 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:**
20 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
25 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
30 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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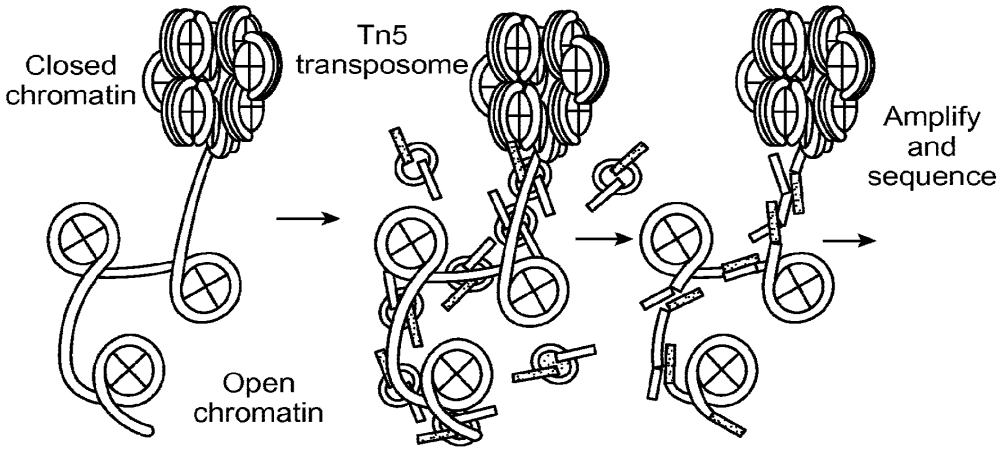

FIG. 1A

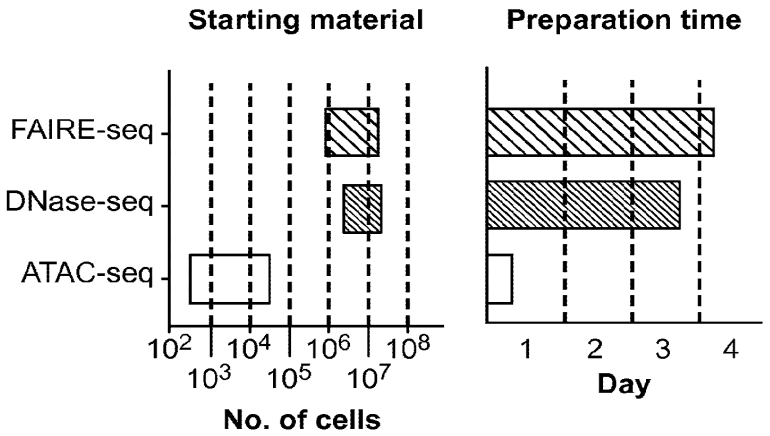

FIG. 1B

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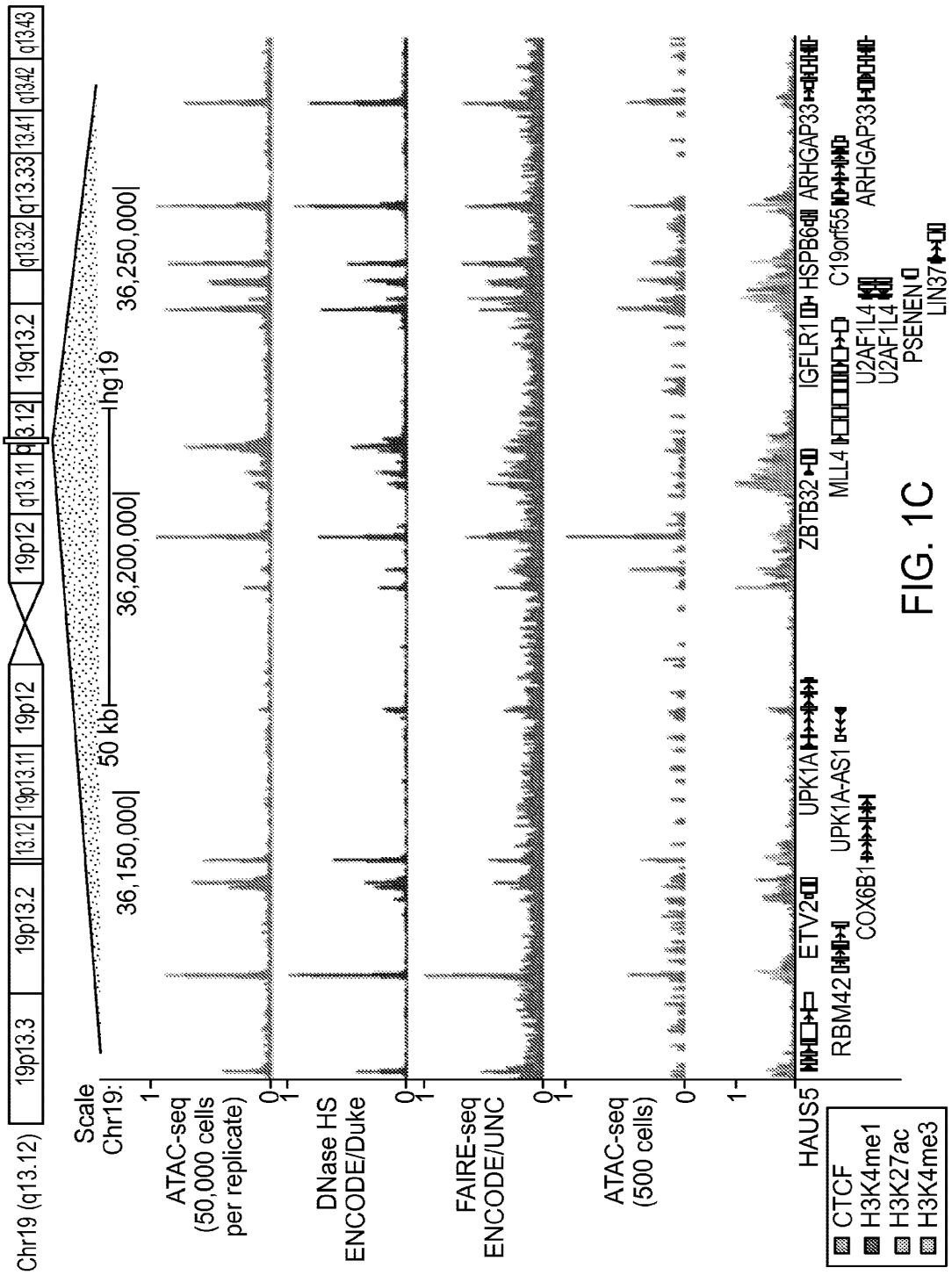

FIG. 1C

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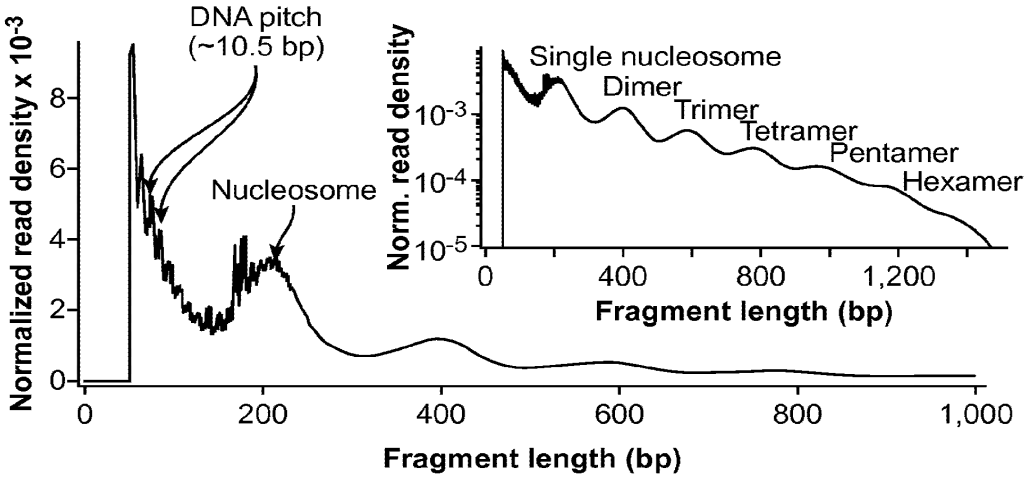

FIG. 2A

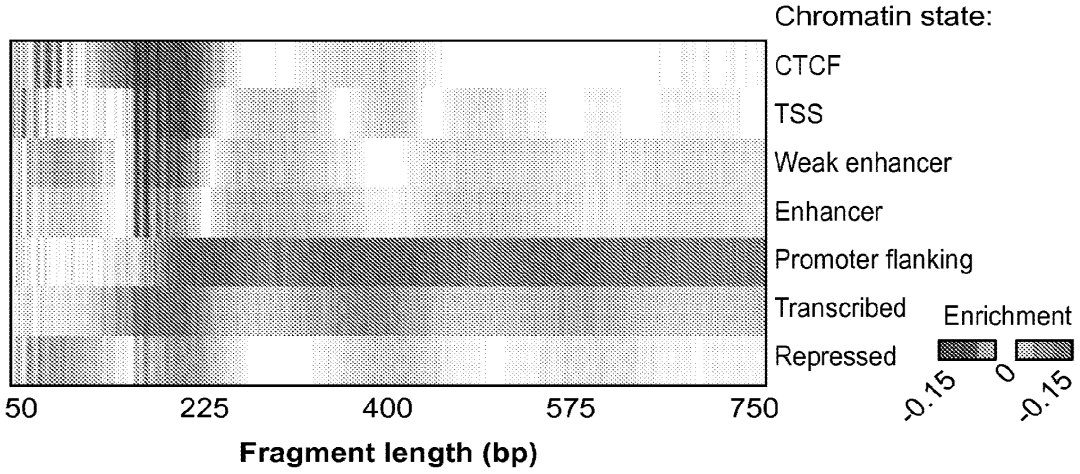

FIG. 2B

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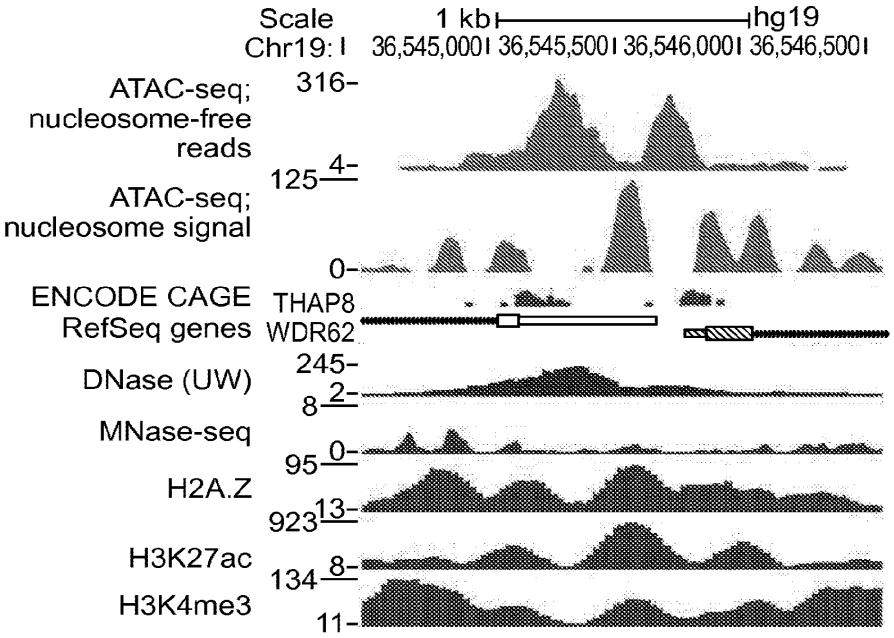

FIG. 3A

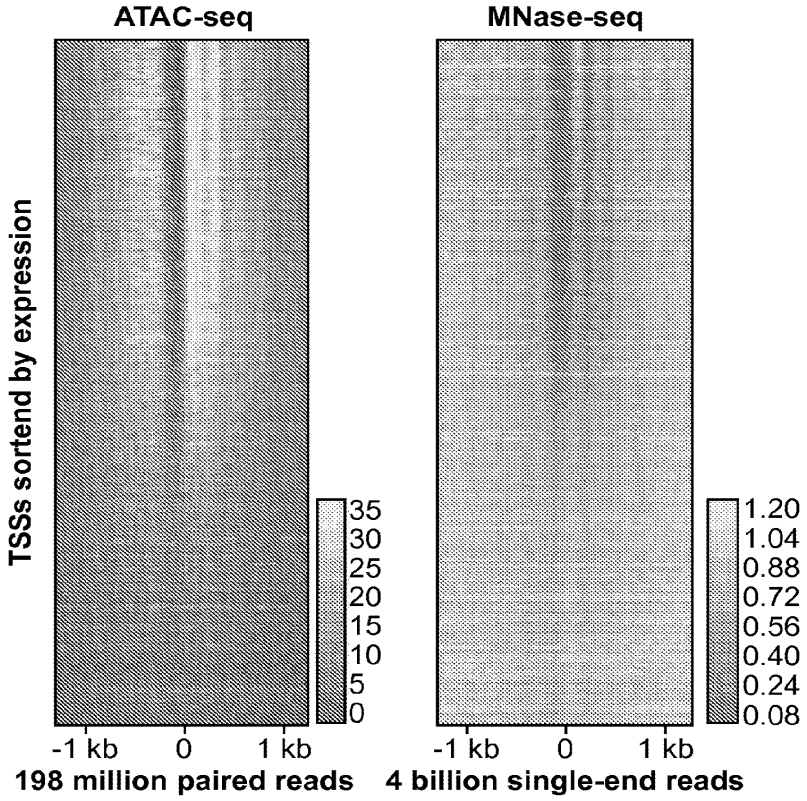

FIG. 3B

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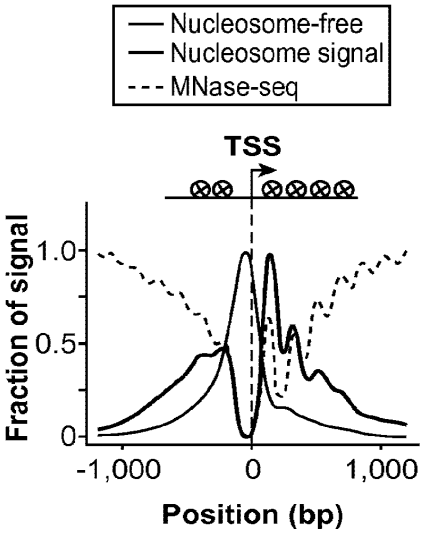

FIG. 3C

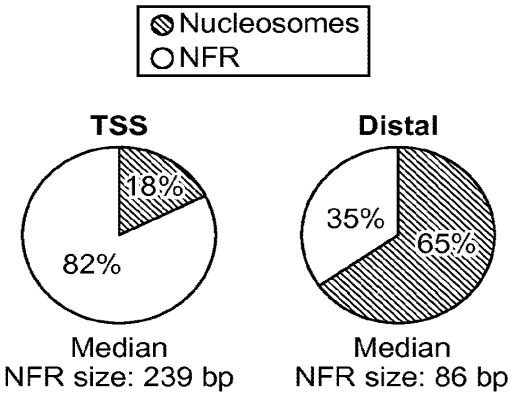

FIG. 3D

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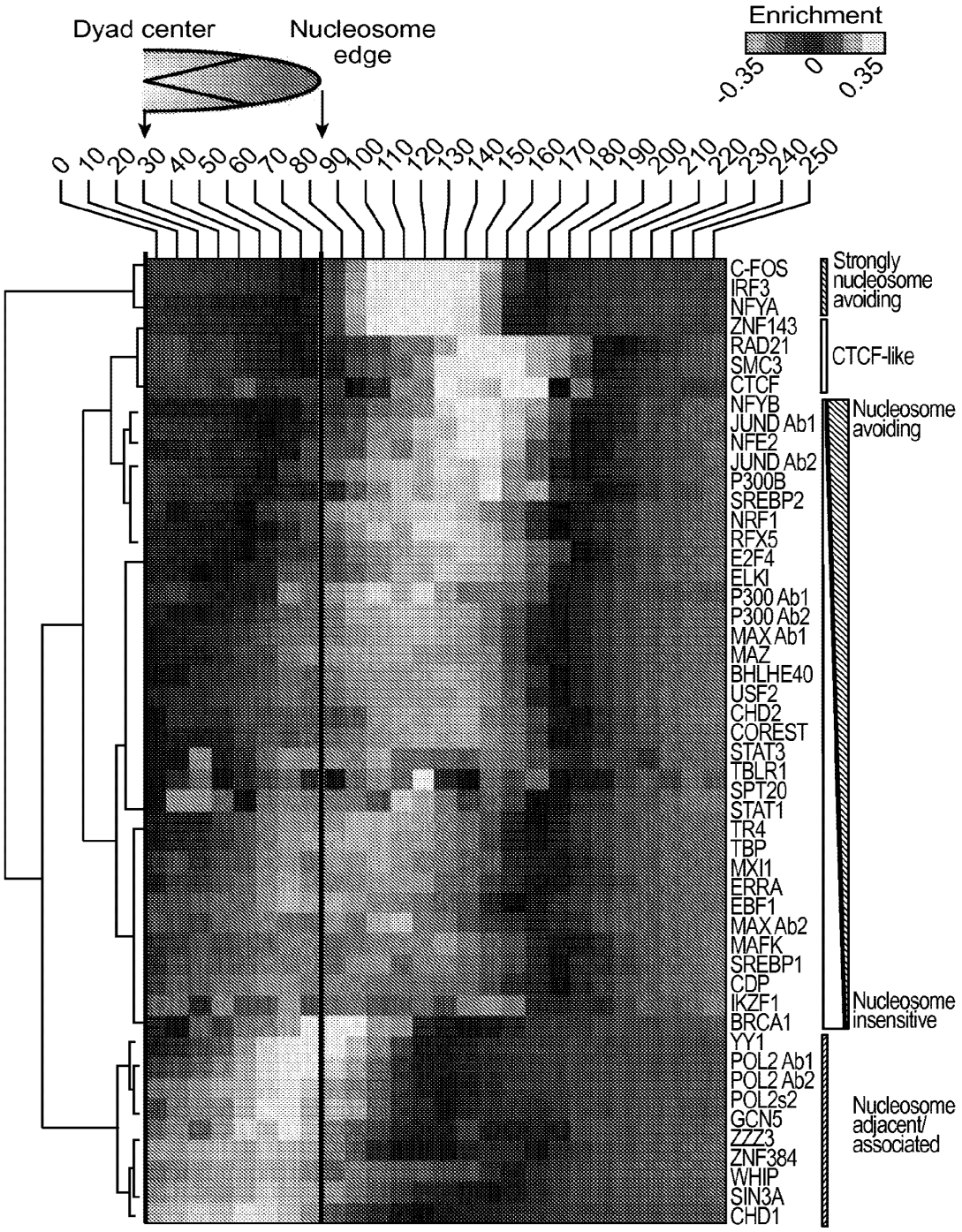

FIG. 3E

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FIG. 4A

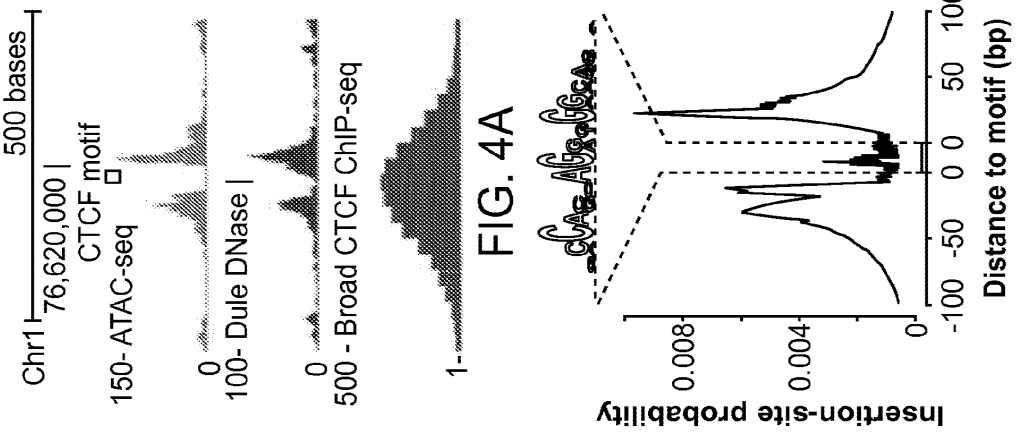

FIG. 4B

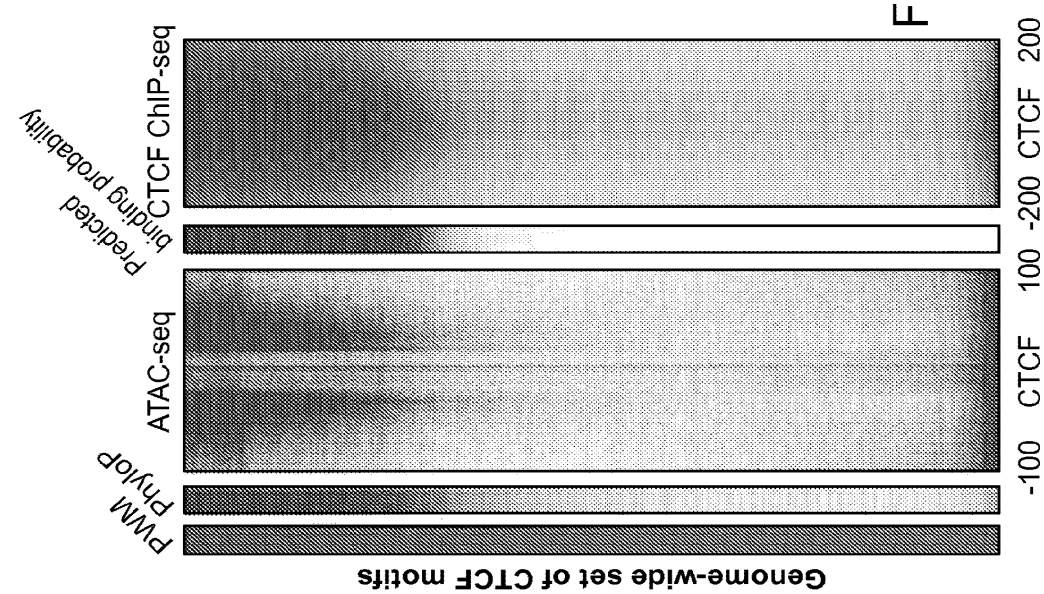

FIG. 4C

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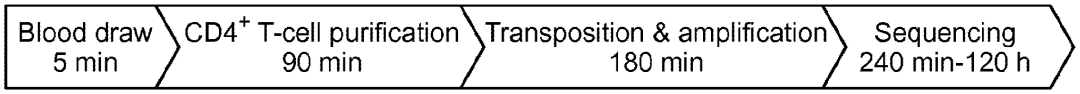

FIG. 5A

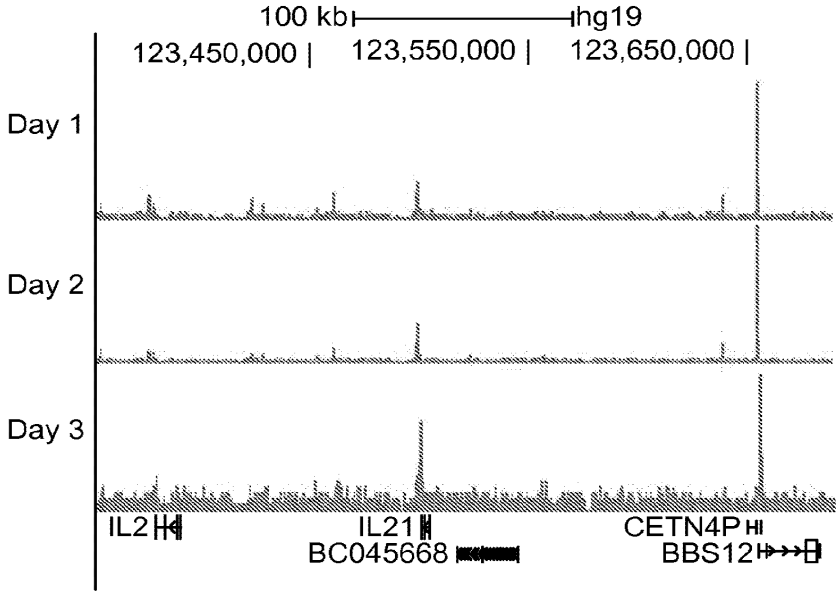

FIG. 5B

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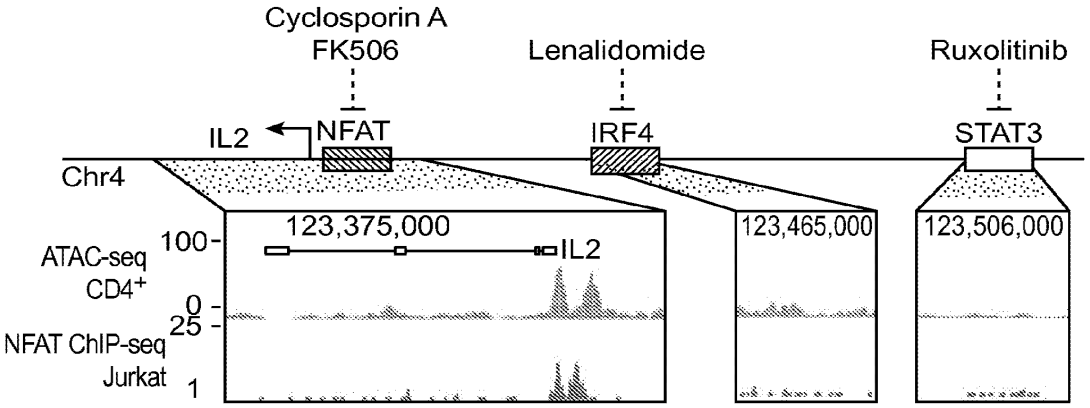

FIG. 5C

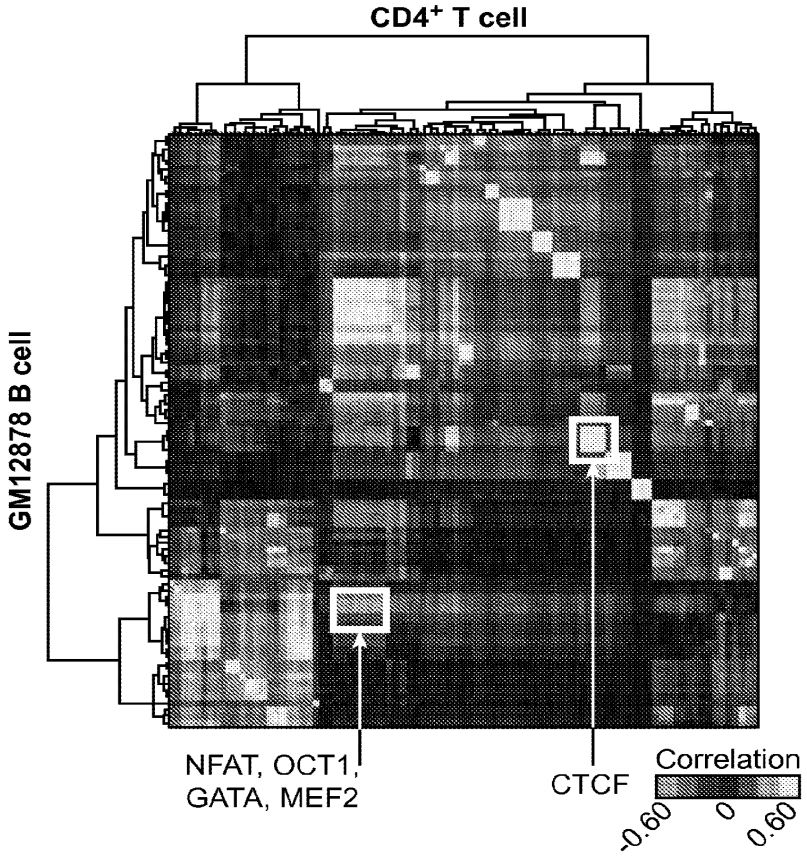

FIG. 5D

10x Genomics, Inc. Exhibit 2010
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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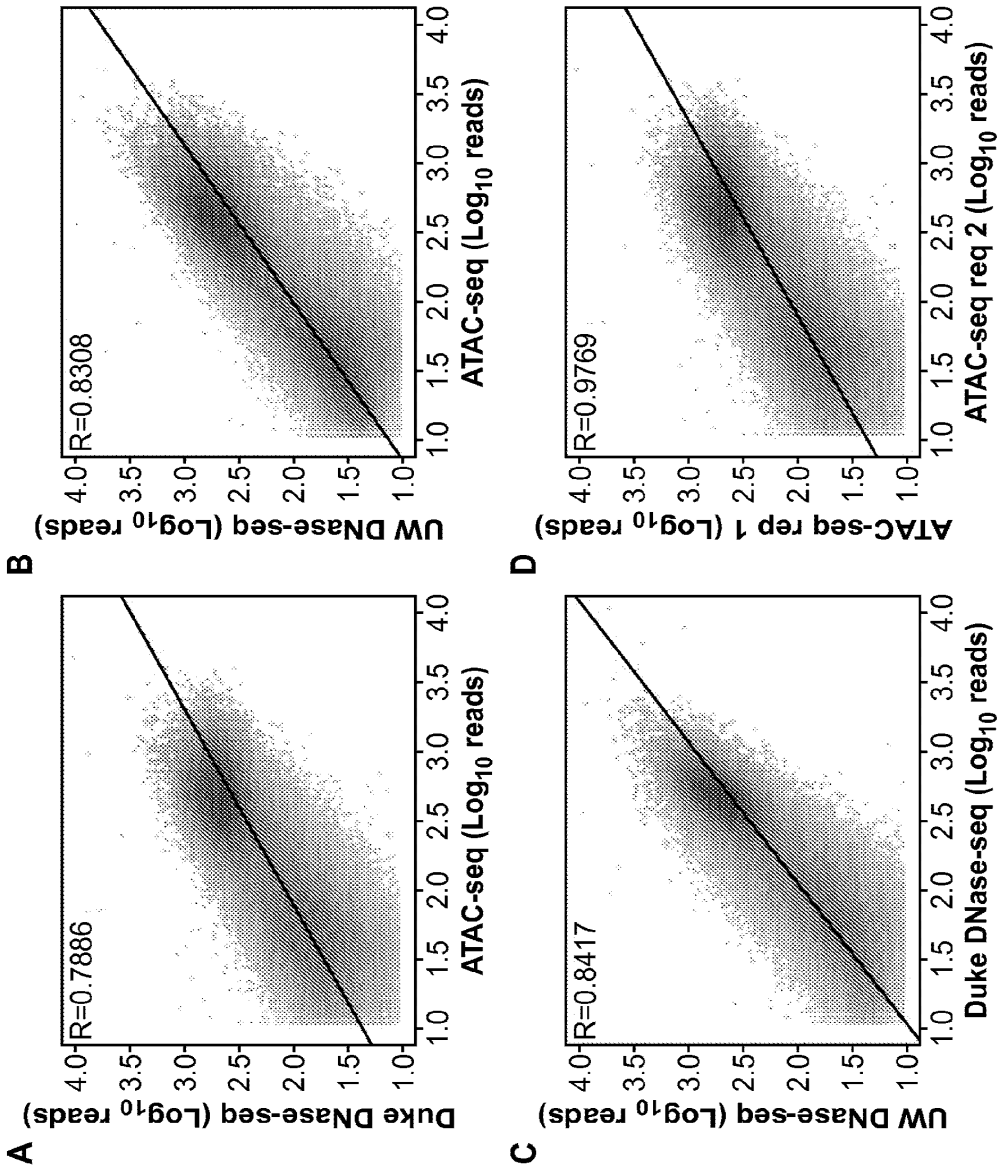

FIG. 6

10x Genomics, Inc. Exhibit 2010
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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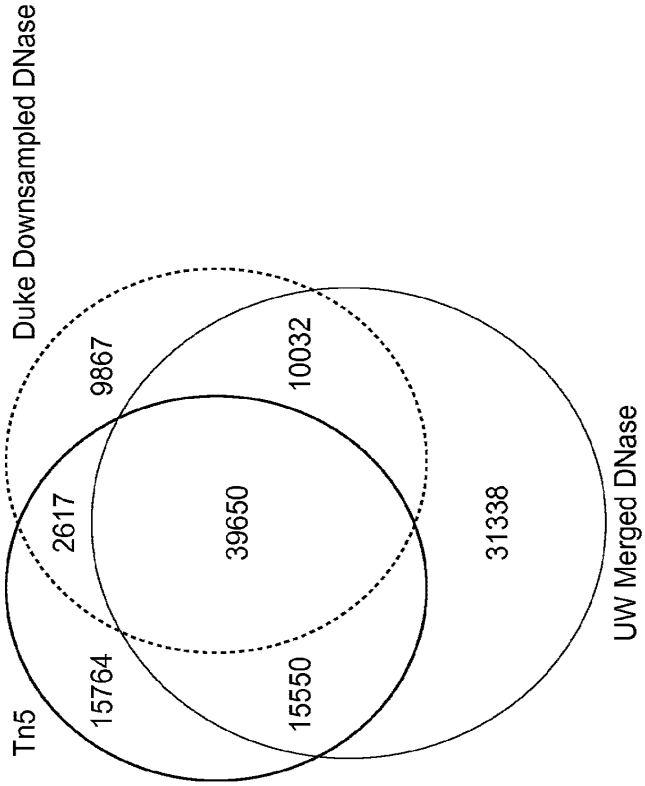

	ATAC Unique	UW Unique	Duke Unique	ATAC and UW	ATAC and Duke	UW and Duke	Intersect
ATAC-Seq	6.30%	4.36%	1.08%	10.83%	1.53%	2.09%	73.80%
UW DNase	1.32%	8.13%	0.68%	7.57%	0.33%	4.34%	77.62%
Duke DNase	2.10%	5.27%	14.80%	4.02%	1.44%	6.91%	65.46%

FIG. 7

10x Genomics, Inc. Exhibit 2010
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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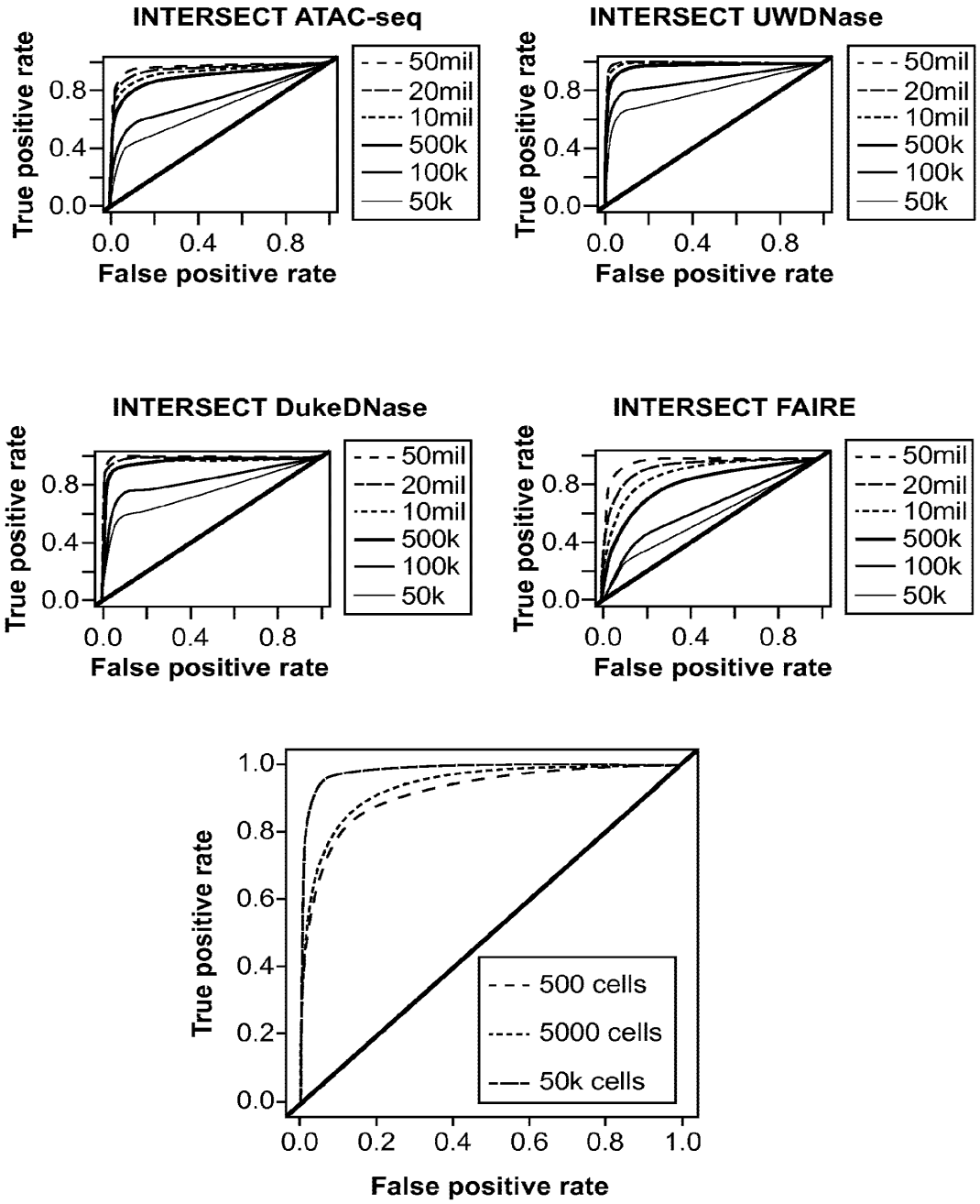

FIG. 8

10x Genomics, Inc. Exhibit 2010
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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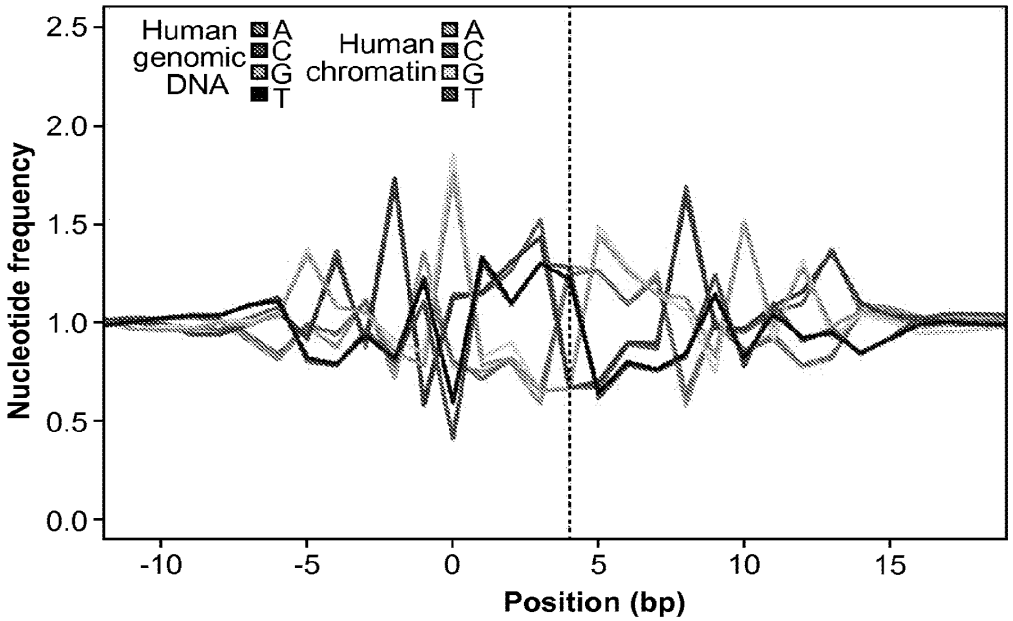

FIG. 9

10x Genomics, Inc. Exhibit 2010
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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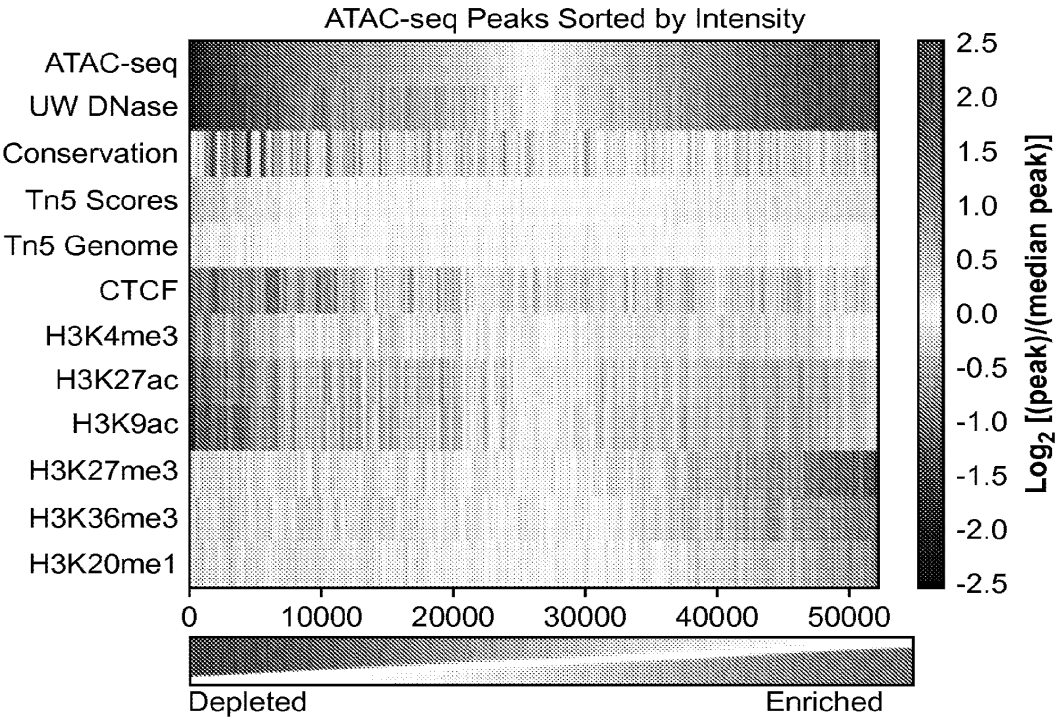

FIG. 10

10x Genomics, Inc. Exhibit 2010
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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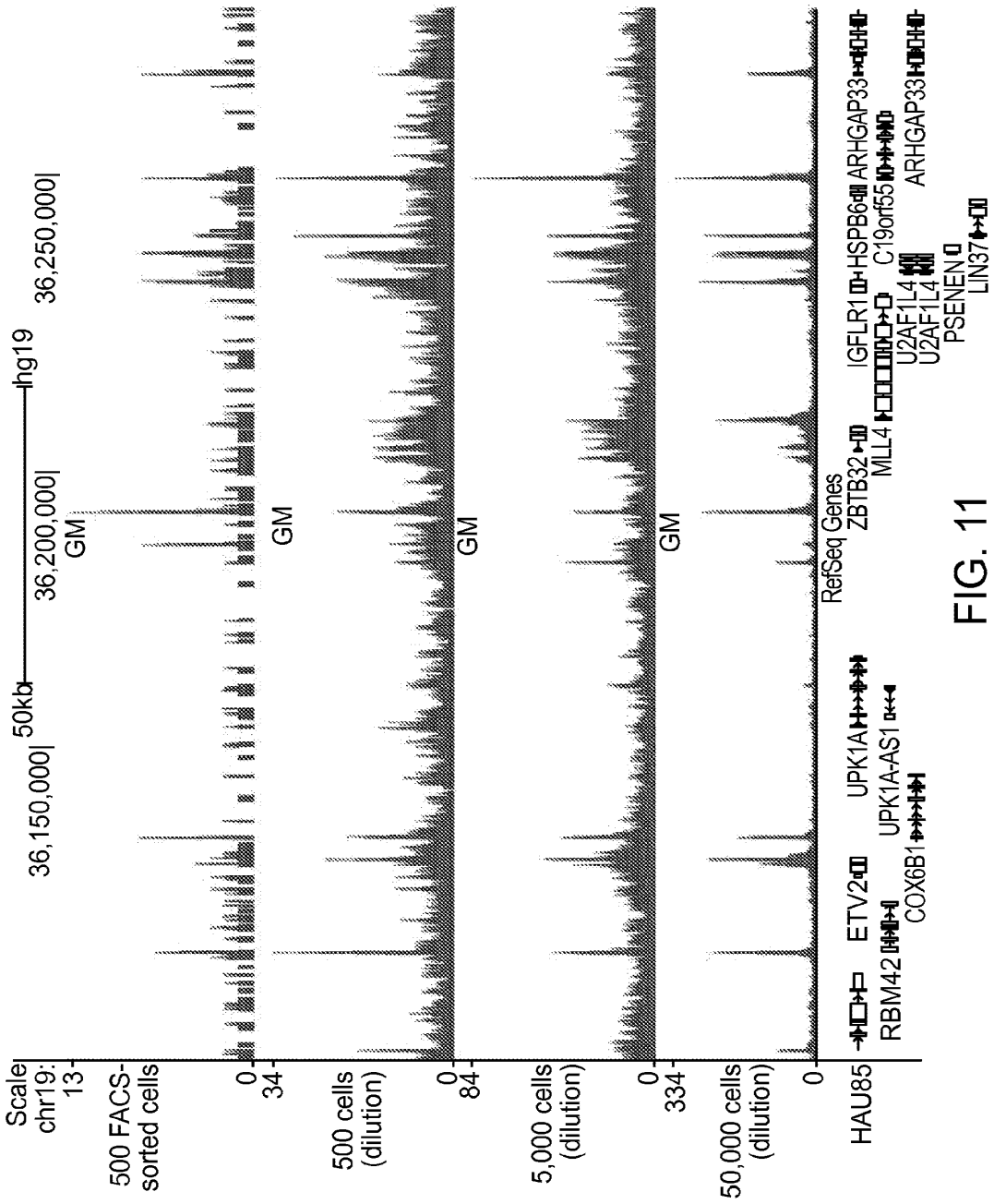

FIG. 11

10x Genomics, Inc. Exhibit 2010
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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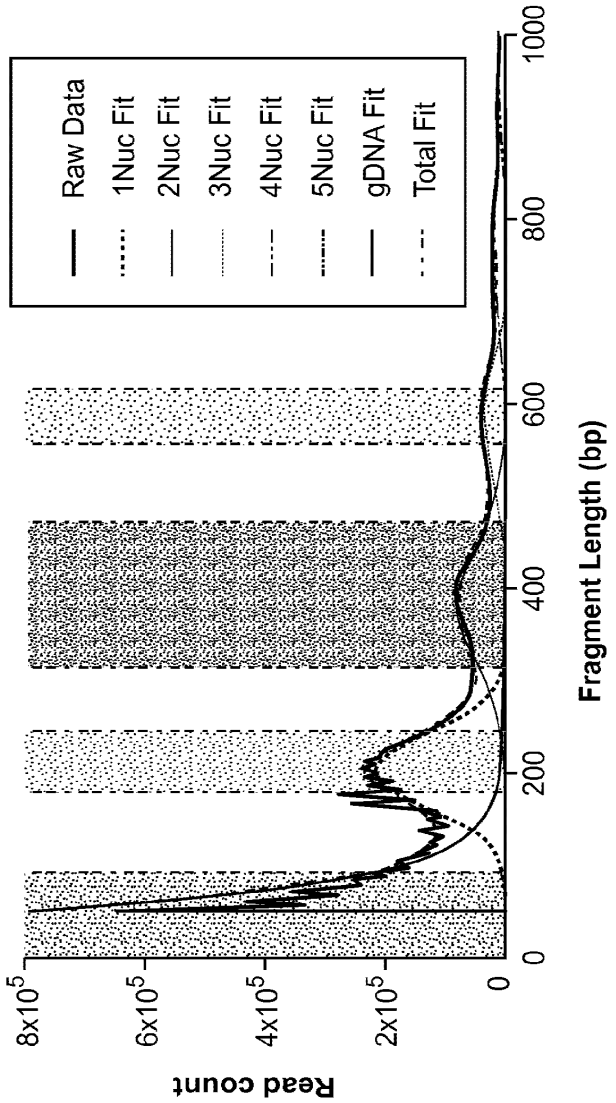

FIG. 12

10x Genomics, Inc. Exhibit 2010
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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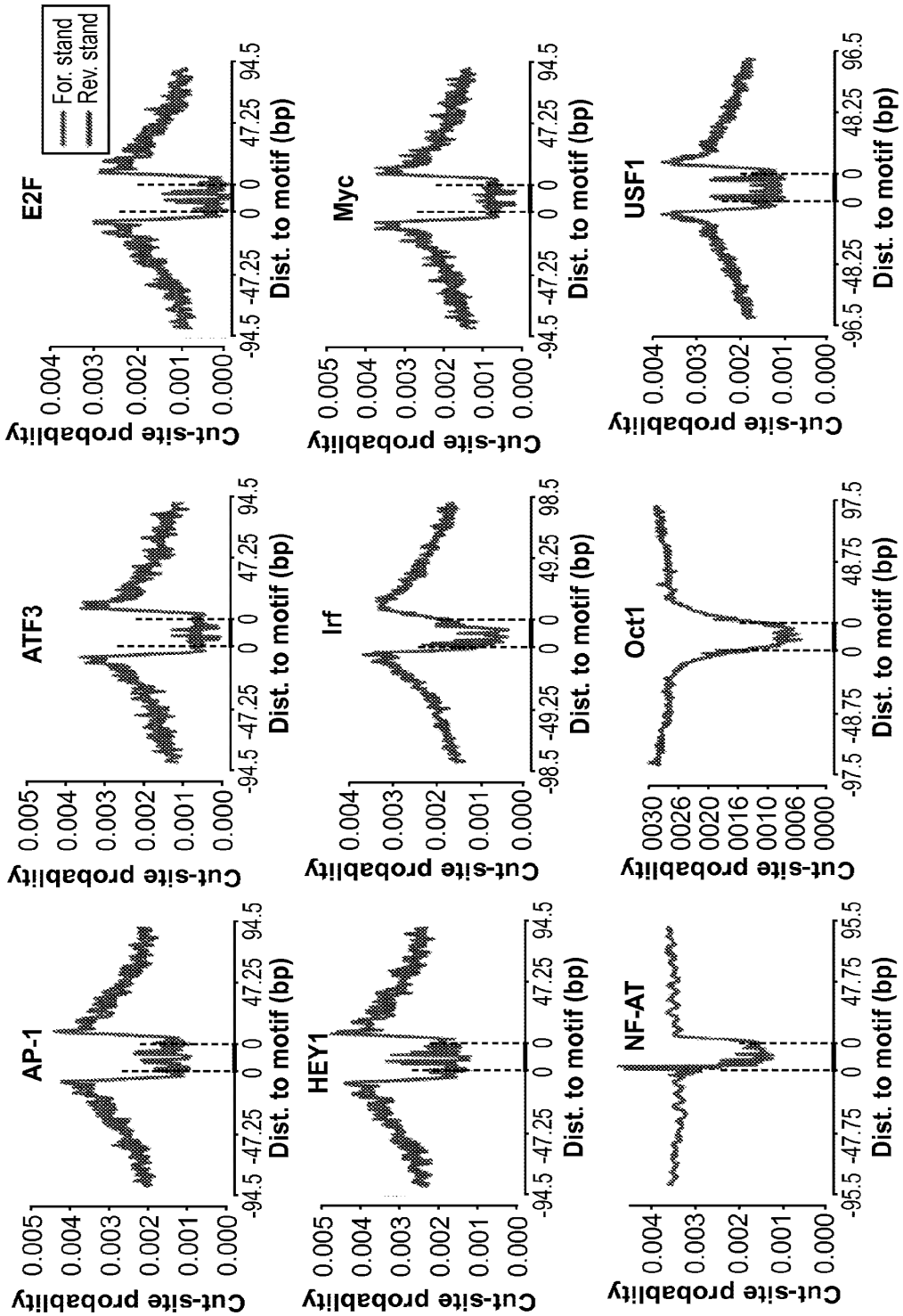

FIG. 13

10x Genomics, Inc. Exhibit 2010
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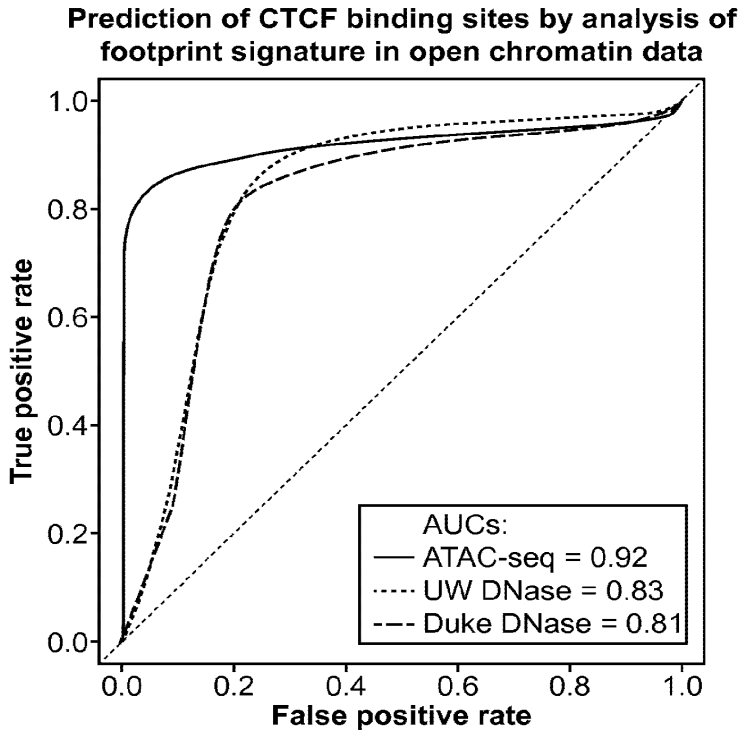

FIG. 14

10x Genomics, Inc. Exhibit 2010
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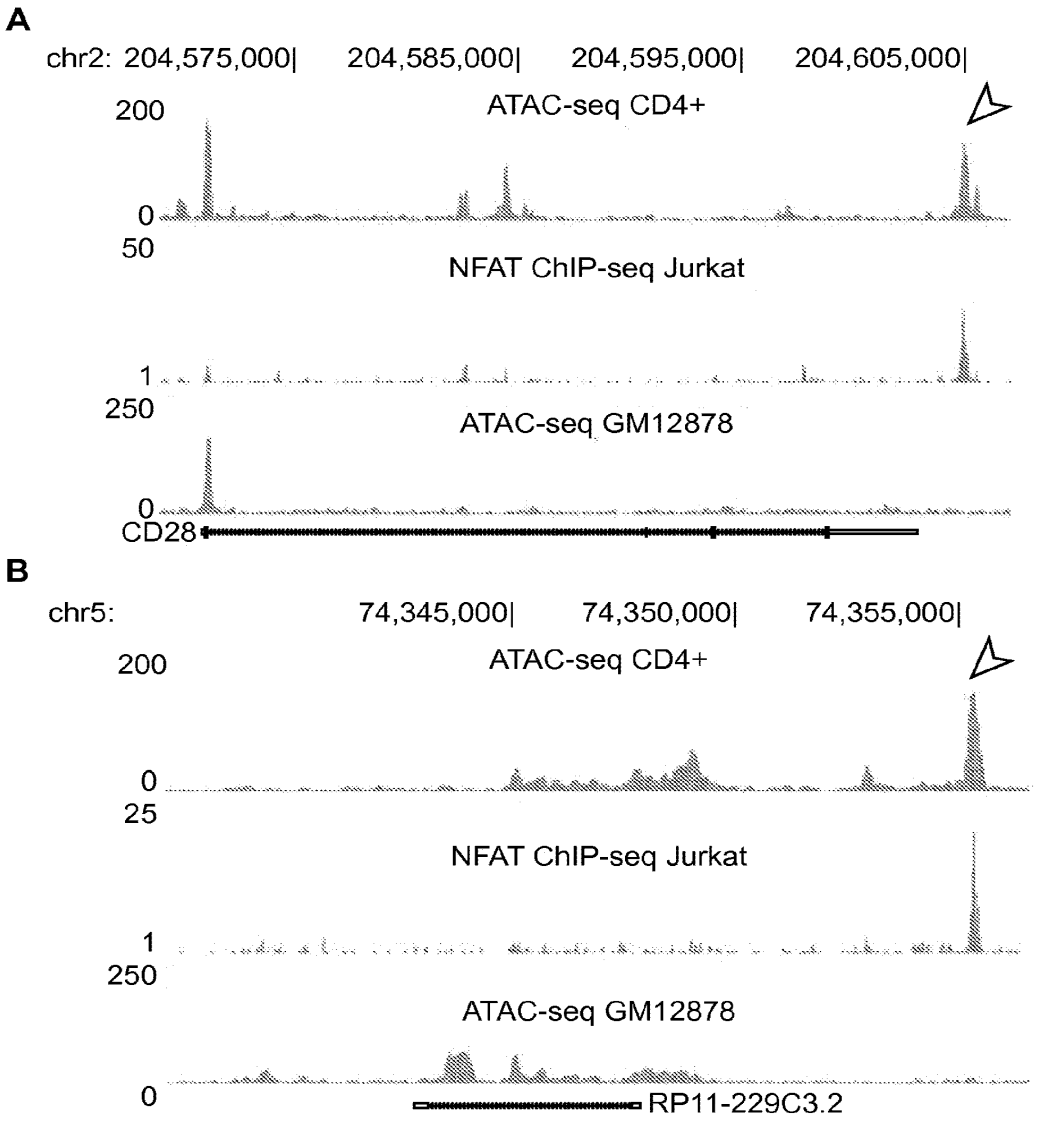

FIG. 15

10x Genomics, Inc. Exhibit 2010
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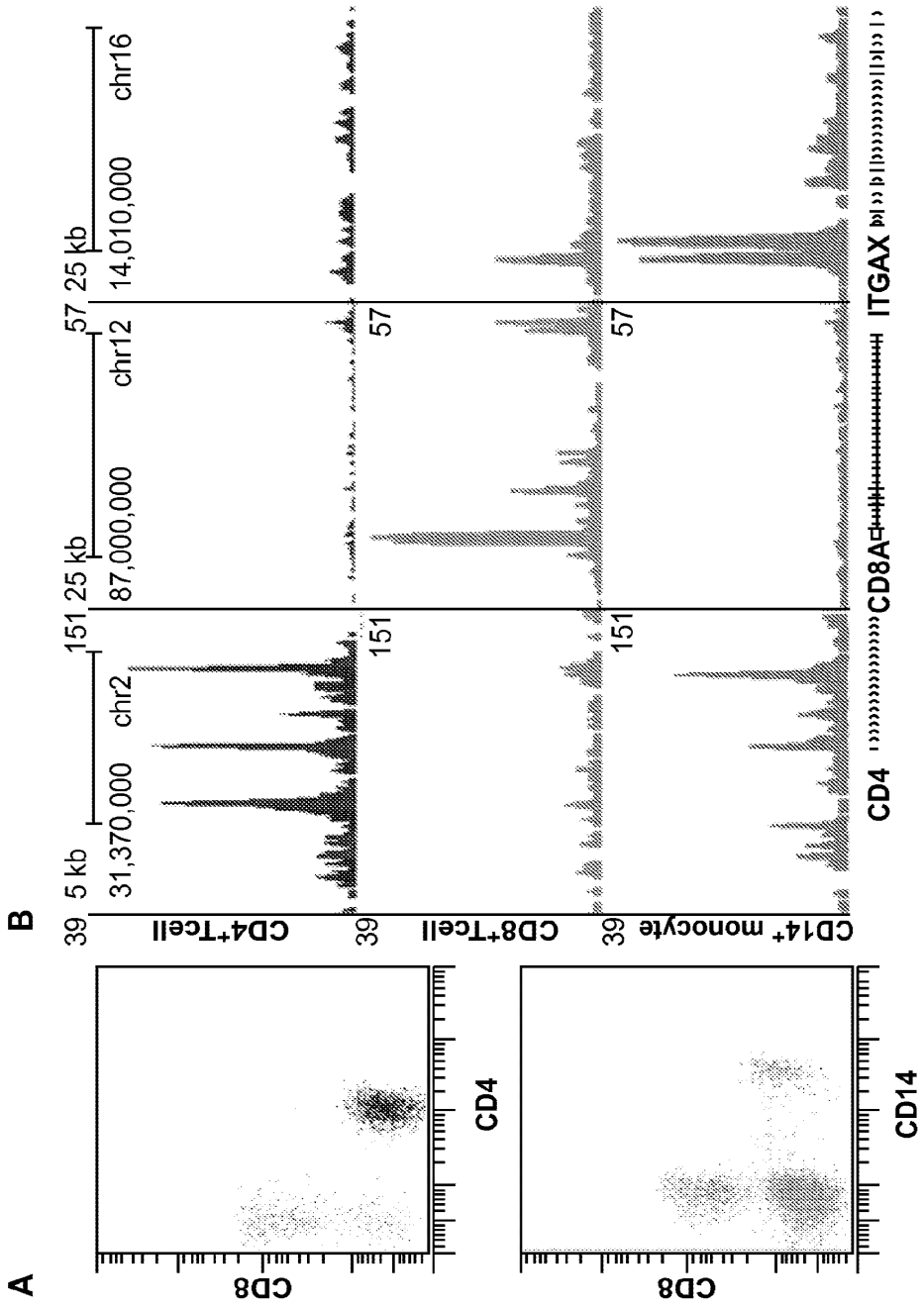

FIG. 16

10x Genomics, Inc. Exhibit 2010
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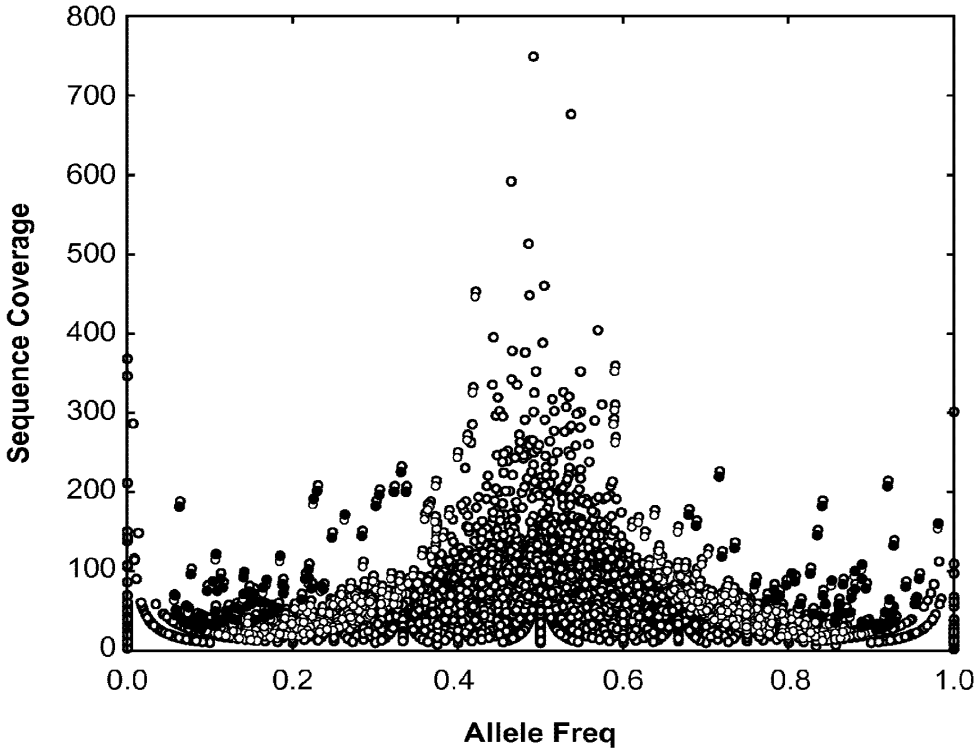

FIG. 17

10x Genomics, Inc. Exhibit 2010
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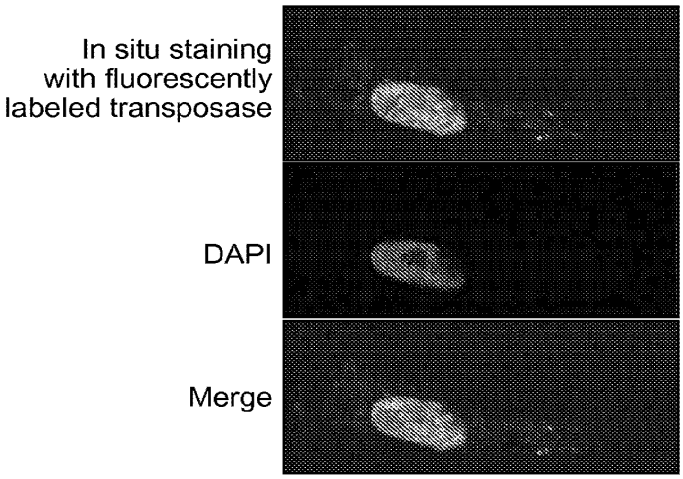

FIG. 18

10x Genomics, Inc. Exhibit 2010
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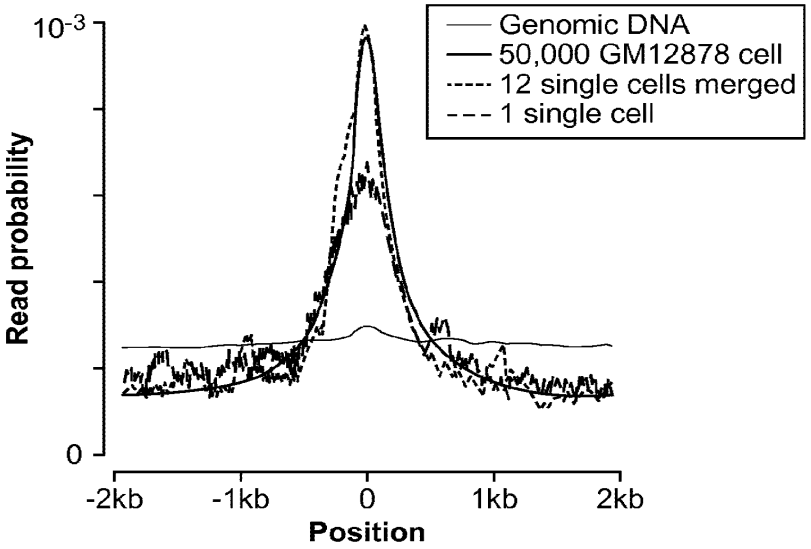

FIG. 19

10x Genomics, Inc. Exhibit 2010
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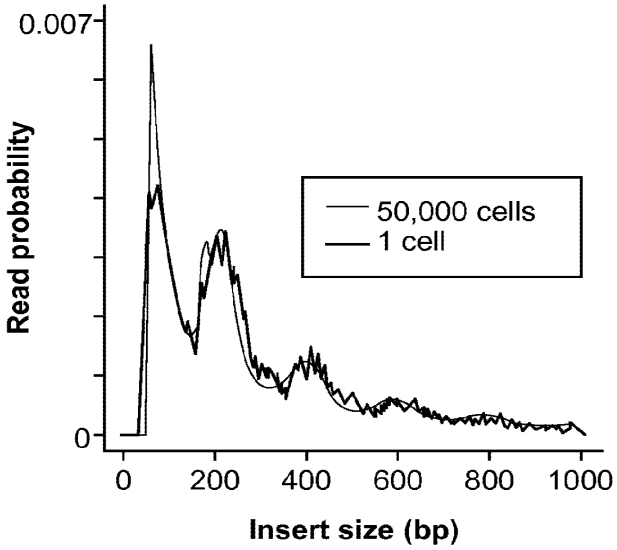

FIG. 20

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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
Timestamp: [year=2019; month=5; day=23; hr=14; min=39; sec=23; ms=637;]
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Validated By CRFValidator v 1.0.5

Application No: 16418796 Version No: 1.0

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Output Set:

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Finished: 2019-05-21 18:38:24.254
Elapsed: 0 hr(s) 0 min(s) 0 sec(s) 673 ms
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Total Errors: 0
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Actual SeqID Count: 25

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Input Set:

Output Set:

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Finished: 2019-05-21 18:38:24.254
Elapsed: 0 hr(s) 0 min(s) 0 sec(s) 673 ms
Total Warnings: 25
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Error code	Error Description
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Chang, Howard Y
Greenleaf, William J
Giresi, Paul

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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/418,796	05/21/2019	2676	785	STAN-1111CON5	20	1

CONFIRMATION NO. 6413

FILING RECEIPT

OC000000109353907

77974
Stanford University Office of Technology Licensing
Bozicevic, Field & Francis LLP
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

Date Mailed: 07/09/2019

Receipt is acknowledged of this non-provisional utility 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 FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

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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: None

Domestic Priority data as claimed by applicant

This application is a CON of 16/160,719 10/15/2018 PAT 10337062
which is a CON of 16/043,874 07/24/2018 PAT 10150995
which is a CON of 14/784,250 10/13/2015 PAT 10059989
which is a 371 of PCT/US2014/038825 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.

If Required, Foreign Filing License Granted: 07/02/2019
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/418,796**
Projected Publication Date: 10/17/2019
Non-Publication Request: No
Early Publication Request: No
**** SMALL ENTITY ****
Title

Transposition of Native Chromatin for Personal Epigenomics

Preliminary Class

358

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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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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Title 37, Code of Federal Regulations, 5.11 & 5.15

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The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

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NOT GRANTED

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IPR2023-01033
Page 00134

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/418,796

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	75		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	330		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	380		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	20 minus 20 =	*	x 50 =	0.00	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*	x 230 =	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	785		TOTAL	

APPLICATION AS AMENDED - PART II

		(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($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
AMENDMENT A	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
AMENDMENT A	Application Size Fee (37 CFR 1.16(s))									
AMENDMENT A	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
AMENDMENT B	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
AMENDMENT B	Application Size Fee (37 CFR 1.16(s))									
AMENDMENT B	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.

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/418,796	05/21/2019	Paul Giresi	STAN-1111CON5	6413

77974 7590 07/11/2019
Stanford University Office of Technology Licensing
Bozicevic, Field & Francis LLP
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER
BERTAGNA, ANGELA MARIE

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
07/11/2019	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

PTOL-90A (Rev. 04/07)

Decision Granting Request for Prioritized Examination (Track I)	**Application No.** 16/418,796	**Applicant(s)** Giresi et al.	
	Examiner BRIAN W BROWN	**Art Unit** OPET	**AIA (FITF) Status** Yes

1. THE REQUEST FILED 21 May 2019 IS **GRANTED** .

   The above-identified application has met the requirements for prioritized examination
   A. ☑ for an original nonprovisional application (Track I).
   B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination**. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

   A. filing a **petition for extension of time** to extend the time period for filing a reply;

   B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims** , or a multiple dependent claim;

   C. filing a **request for continued examination** ;

   D. filing a notice of appeal;

   E. filing a request for suspension of action;

   F. mailing of a notice of allowance;

   G. mailing of a final Office action;

   H. completion of examination as defined in 37 CFR 41.102; or

   I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to BRIAN BROWN at (571)272-5338.

In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/BRIAN W BROWN/ Petitions Examiner, OPET	

U.S. Patent and Trademark Office
PTO-2298 (Rev. 02-2012)

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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 16/418,796	Filing Date 05/21/2019	☐ 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 $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $230 =	
☐ 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	07/17/2019	(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))	* 30	Minus	** 20	= 10		x $50 =	500
	Independent (37 CFR 1.16(h))	* 4	Minus	*** 3	= 1		x $230 =	230
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	730

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.

Electronic Patent Application Fee Transmittal

Application Number:	16418796
Filing Date:	21-May-2019
Title of Invention:	Transposition of Native Chromatin for Personal Epigenomics
First Named Inventor/Applicant Name:	Paul Giresi
Filer:	James Samuel Keddie/Priscilla Lam
Attorney Docket Number:	STAN-1111CON5

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
CLAIMS IN EXCESS OF 20	2202	10	50	500
INDEPENDENT CLAIMS IN EXCESS OF 3	2201	1	230	230
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**730**

Electronic Acknowledgement Receipt	
EFS ID:	36616589
Application Number:	16418796
International Application Number:	
Confirmation Number:	6413
Title of Invention:	Transposition of Native Chromatin for Personal Epigenomics
First Named Inventor/Applicant Name:	Paul Giresi
Customer Number:	77974
Filer:	James Samuel Keddie/Priscilla Lam
Filer Authorized By:	James Samuel Keddie
Attorney Docket Number:	STAN-1111CON5
Receipt Date:	17-JUL-2019
Filing Date:	21-MAY-2019
Time Stamp:	18:36:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$730
RAM confirmation Number	071819INTEFSW18412400
Deposit Account	500815
Authorized User	Priscilla Lam
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.16 (National application filing, search, and examination fees) 37 CFR 1.17 (Patent application and reexamination processing fees)	

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 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	Preliminary Amendment	STAN-1111CON5_PrelimAmend.pdf	40415 3b56de1c53c54607f0aa92e89af72723c5795702	no	6
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	31917 4efbdea4b2c0b295a772e284e20e7b65afc24b93	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	72332		

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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.

Electronically Filed

PRELIMINARY AMENDMENT Under 37 CFR § 1.115	Attorney Docket No.	STAN-1111CON5
	Confirmation No.	6413
	First Named Inventor	Paul Giresi
	Application Number	16/418,796
	Filing Date	May 21, 2019
Address to: Mail Stop Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Group Art Unit	1637
	Examiner Name	BERTAGNA, ANGELA MARIE
	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, including their current status identifiers, is set forth below.

1-97. (Cancelled)

98. (New) A composition comprising:

a permeabilized cell nucleus comprising a plurality of polynucleotide molecules;

an insertional enzyme complex; and

an insert element comprising at least one nucleic acid comprising a predetermined sequence.

99. (New) The composition of claim 98, further comprising a permeabilization agent selected from the group consisting of: NP40, digitonin, tween, steptolysin, cationic lipids, and any combination thereof.

100. (New) A composition comprising:

a permeabilized cell nucleus comprising a plurality of polynucleotide molecules, wherein the plurality of polynucleotide molecules comprises genomic DNA comprising a plurality of open chromatin regions;

an insertional enzyme complex; and

an insert element comprising at least one nucleic acid comprising a predetermined sequence.

101. (New) The composition of claim 100, wherein the insertional enzyme complex comprises one or more enzymatic moieties.

102. (New) The composition of claim 101, wherein the insertional enzyme complex comprises two or more enzymatic moieties.

103. (New) The composition of claim 102, wherein the two or more enzymatic moieties are linked together.

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Parse Biosciences, Inc. v. 10x Genomics, Inc.
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104. (New) The composition of claim 100, wherein the insertional enzyme complex comprises a nuclear localization signal.

105. (New) The composition of claim 100, wherein the insertional enzyme complex is configured to insert a nucleic acid sequence into at least one of the polynucleotide molecules.

106. (New) The composition of claim 105, wherein the insertional enzyme complex is configured to insert the nucleic acid sequence into at least one of the polynucleotide molecules in a substantially sequence independent manner.

107. (New) The composition of claim 100, wherein the insertional enzyme complex comprises an enzyme selected from the group consisting of: transposases, HERMES, and HIV integrases.

108. (New) The composition of claim 107, wherein the insertional enzyme complex comprises a transposase.

109. (New) The composition of claim 108, wherein the transposase is a Tn transposase.

110. (New) The composition of claim 109, wherein the Tn transposase is selected from the group consisting of: Tn3, Tn5, Tn7, Tn10, Tn552 and Tn903.

111. (New) The composition of claim 110, wherein the transposase is a Tn5 transposase.

112. (New) The composition of claim 100, wherein the insert element comprises one or more molecular tags.

113. (New) The composition of claim 112, wherein one or more of the molecular tags comprises a sequencing adaptor.

114. (New) The composition of claim 113, wherein one or more of the sequencing adaptors comprises a barcode label.

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115. (New) A composition comprising:

a permeabilized cell nucleus;

an insertional enzyme complex comprising a transposase enzyme; and

a plurality of tagged nucleic acid fragments, wherein each tagged nucleic acid fragment comprises a first sequencing adapter and a second sequencing adapter;

wherein each tagged nucleic acid fragment is derived from a region of open chromatin.

116. (New) The composition of claim 115, wherein the plurality of tagged nucleic acid fragments correspond to two or more regions of a genome.

117. (New) The composition of claim 115, wherein the plurality of tagged nucleic acid fragments correspond to at least 1,000 regions of a genome.

118. (New) The composition of claim 117, wherein the plurality of tagged nucleic acid fragments correspond to genome-wide regions of open chromatin.

119. (New) The composition of claim 117, wherein the transposase is a Tn transposase.

120. (New) The composition of claim 119, wherein the Tn transposase is a Tn5 transposase.

121. (New) A composition comprising:

a permeabilized cell nucleus;

an insertional enzyme complex comprising a transposase enzyme; and

a plurality of tagged nucleic acid fragments, wherein each tagged nucleic acid fragment comprises a first sequencing adapter and a second sequencing adapter;

wherein the insertional enzyme complex and the tagged nucleic acid fragments are bound to one or more regions of open chromatin within the cell nucleus in a substantially sequence independent manner to form a high affinity macromolecule complex.

122. (New) The composition of claim 121, further comprising a plurality of divalent cations.

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123. (New) The composition of claim 122, wherein the divalent cations are not chelated.

124. (New) The composition of claim 122, wherein the divalent cations are selected from the group consisting of: magnesium, manganese, or any combination thereof.

125. (New) The composition of claim 121, wherein the transposase is a Tn transposase.

126. (New) The composition of claim 125, wherein the Tn transposase is selected from the group consisting of: Tn3, Tn5, Tn7, Tn10, Tn552 and Tn903.

127. (New) The composition of claim 126, wherein the transposase is a Tn5 transposase.

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REMARKS UNDER 37 CFR § 1.115

Formal Matters

Claims 98-127 are pending after entry of the amendments set forth herein.

Claims 1-97 are canceled without prejudice.

Claims 98-127 are new. Support for the new claims can be found throughout the application as filed.

No new matter has been added.

Applicant(s) submit(s) 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-1111CON5.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: July 17, 2019

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

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/418,796	05/21/2019	Paul Giresi	STAN-1111CON5	6413

77974 7590 08/30/2019
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
08/30/2019	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

PTOL-90A (Rev. 04/07)

Office Action Summary	Application No. 16/418,796	Applicant(s) Giresi et al.	
	Examiner CYNTHIA B WILDER	Art Unit 1637	AIA (FITF) 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 7/17/2019.

☐ 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) 98-127 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) 98-127 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 _____ 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 5/21/2019.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

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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 preliminary amendment filed 7/17/2019 is acknowledged. Claims 1-97 have been canceled. Claims 98-127 have been added and are pending.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on 5/21/2019 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.

Drawings

3. The drawings were received on 5/21/2019. These drawings are found acceptable by the examiner.

Claim Rejections - 35 USC § 112

4. 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.

5. Claim 107 is 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) Claim 107 is indefinite at the recitation of the abbreviations "HERMES" and "HIV" because abbreviations often have more than one meaning in the art. It is suggested inserting the full name of the abbreviation into the claims.

Claim Rejections - 35 USC § 103

6. 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.

7. 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.

8. Claim 98-127 is/are rejected under 35 U.S.C. 103 as being unpatentable over Grunewald et al (US 20100120098, May 2010) in view of Jouvenot (US 20110206042, December 2011) and further in view of Audit et al (Nucleic Acid Research, 37 (18), 6064-6075, 2009).

Regarding claims 98-100, Grunewald et al teach a composition comprising target DNA with a transposase and a transposon end or transposon end comprising a

transferred strand that has a tag domain in its 5' portion, under conditions wherein a transposition reaction is catalyzed by the transposase and wherein the target DNA is fragmented to generate a plurality of target DNA fragments and a transferred strand of the transposon end or transposon end composition is joined the 5' ends of each of a plurality of the target DNA fragments (e.g., [0017], [0018], [0042], [0045], [0050] see also [0098-[0099]). The references teaches that the composition may be in the form of a reaction mixture comprising double stranded target DNA and any of the tagged transposon end nucleic acid molecules and/or transposase complex composition [0048] and further comprise transposase, [0045], and non-ionic detergent such as Nonidet P-40 and/or Tween 20 [0045].

Regarding claims 101-103, Grunenwald et al wherein the insertional enzyme complex comprises one or more enzymatic moieties (e.g., [0045]-[0048], [0052], [0094], [0098], [0099]) and [0224]).

Regarding claim 104, the limitation "wherein the insertional enzyme complex comprising a nuclear localization signal" is deemed an inherent property of the insertional complex of Grunenwald which comprise of elements synonymous with the teachings of the instant invention (see citations above and throughout the entire teachings of Grunenwald).

Regarding 105, Grunenwald et al teach wherein the insertional enzyme complex is configured to insert a nucleic acid sequence into at least one of the polynucleotide molecules {(e.g., [0093], [0094]).

Regarding claim 106, Grunenwald et al teach wherein the insertional enzyme complex is configured to insert the nucleic acid sequence into at least one of the polynucleotide molecules in a substantially sequence independent manner.

Regarding claim 107-108, Grunenwald et al teach wherein the insertional enzyme complex comprises an enzyme selected transposases or integrases ([0045] – [0052], [0094]).

Regarding claims 109 -111, Grunenwald et al teach wherein the transposase is a Tn transposase, wherein said Tn transposase is Tn5 transposase ([0045]).

Regarding claims 112-113, Grunenwald et al teach wherein the insert element comprises one or more molecular tags (e.g., [0009], [0018], [0021], [0039], [0508])

Regarding claim 114, Grunenwald et al teach, wherein one or more of the sequencing adaptors comprises a barcode label (e.g.,[0068], [0480], [0508]).

Regarding claims 98-114, Grunenwald et al do not expressly teach wherein the composition comprise of a permeabilized cell nucleus, but notes that composition may comprise of genomic DNA, subgenomic DNA, or chromosomal DNA such as isolated from chromosome or a portion of a chromosome ([0146]).

Regarding claim 115, 116, and 121, Grunenwald et al teach a composition comprising:; an insertional enzyme complex comprising a transposase enzyme; and a plurality of tagged nucleic acid fragments, wherein each tagged nucleic acid fragment comprises a first multiple sequencing adapter ((e.g., [0017], [0018], [0042], [0045], [0050] see also [0098-[0099]; see also [0009], [0079], [0162], [0164], [0201], [0263], [0273], [0296], [0403] – [0404] which teaches BP1 and BP2 which corresponds to Illumina bPCR adaptor tags comprising barcoded sequences).

Regarding claims 116-117, Grunenwald teach wherein the plurality of tagged nucleic acid fragments correspond to multiple genomic DNA fragments or a library of tagged DNA fragments ([0121], [0147]) and further wherein target DNA comprises of a whole genome of a cell or organism ([0273]). Thus the limitations of claims recited therein falls within the teachings of the limitations of teachings of Grunenwald.

Regarding claims 119-120, Grunenwald et al teach wherein the transposase is a Tn transposase and wherein the Tn transposase is a Tn5 transposase ([0045])

Regarding claims 122-124, Grunenwald et al teach wherein the composition further comprising a plurality of divalent cations, wherein said divalent cations are selected from the group consisting of: magnesium, manganese, or any combination thereof ([0081], [0338], [0339) and [0340]).

Regarding claim 125, Grunenwald et al teach wherein the transposase is a Tn transposase and wherein the transposase is a Tn5 transposas ([0045]).

Regarding claims 98-125, especially the claims 98, 100, 115, 118 and 121, Grunenwald differs from the instant invention in that the reference does not expressly teach wherein the composition or reaction mixture of the methods disclosed therein comprise of a permeabilized cell nucleus. Grunenwald also do not expressly teach wherein the tagged nucleic acid fragments are derived from regions of open chromatin.

Regarding the claims 98-125, Jouvenot teaches a method and reaction mixture for analyzing chromatin structure and/or epigenetic status in chromosomal DNA of a cell wherein the composition comprises permeabilzing nucleus of a cell to all for entry of an insertional enzyme [0008], (0012], [0022], [0023], [0030], [0032]). Jouvenot teaches that permeabilizing of the cell membrane occurs in such a way such that it will not disrupt the

structure of the genomic DNA of the cell such that nucleosomal or chromatin structure is not destroyed [0055]. Jouvenot teaches wherein such agents used to permeabilize the cells comprise of NP40, Tween 20 or Triton X-100 [0055]-[0057]). Jouvenot teaches wherein the composition or reaction mixture further comprise the use of a nicking polypeptide which may allow analysis of "open" versus "closed" closed chromatin regions [0048].

Grunenwald et al and Jouvenot do not expressly teach plurality of DNA or fragments derived from open chromatin regions as recited in the claims 100-127.

In a general teaching, Audit provides motivation as to why one of ordinary skill in the art would want to incorporate nucleic acids from open chromatin regions into a composition as instantly claimed for analysis. Audit et al teach that genome wide investigation of chromatin architecture have revealed that at large scales, regions enriched in open chromatin fibers correlate with region of high gene density; whereas, at small scales DNA accessibility, nucleosome distribution and modifications are important determinant for transcriptional activity (page 6066, col. 1, lines 2-9).

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 modify the composition of Grunenwald to encompass permeabilized cell nucleus as taught by Jouvenot for the obvious benefit of allowing for entry of endonuclease into the nuclease and additionally for the benefit of allowing for chromatin structure analysis and/or epigenetic events in DNA regions of interest to detected.

The ordinary artisan would have been motivated at the time of the effective filing date of the claimed invention to obtain nucleic acids from open chromatin regions as noted

by Jouvenot and Audit et al into the composition of Grunenwald based on the advantages taught by Audit et al that genome-wide investigation of chromatin architecture have revealed that at large scales, regions enriched in open chromatin fibers correlate with region of high gene density; whereas, at small scales DNA accessibility, nucleosome distribution and modifications are important determinant for transcriptional activity (page 6066, col. 1, lines 2-9).

The ordinary artisan would have been motivated at the time of the effective filing date to provide a composition comprising the elements as taught by Grunenwald in view of Jouvenot and further in view of Audit et al for the obvious goal of providing improved method for generating libraries of DNA fragments from desired target molecules as suggested from Grunenwald.

Conclusion

9. No claims are allowed. 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. 16/418,796	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-20100120098-A1	05-2010	Grunenwald; Haiying Li	C12N15/10	435/91.2
*	B	US-20110306042-A1	12-2011	Jouvenot; Yann	C12Q1/68	435/6.1
	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	Audit et al., Nucleic Acids Research, 37(18):6064-6075, August (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.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/418,796	Giresi et al.
	Examiner	Art Unit
	CYNTHIA B WILDER	1637

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* 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

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

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WEST Search History for Application 16418796

Creation Date: 2019082711:12

Prior Art Searches

Query	DB	Hits	Op.	Plur.	Thes.	Date
(composition or mixture or reaction) and (permeabiliz$ same cell same nucleus)	PGPB, USPT, USOC, EPAB, DWPI	4883	ADJ	YES		08-24-2019
((composition or mixture or reaction) and (permeabiliz$ same cell same nucleus)) same (polynucleotide or DNA)	PGPB, USPT, USOC, EPAB, DWPI	4883	ADJ	YES		08-24-2019
(composition or mixture or reaction) same (permeabiliz$ same cell same nucleus)	PGPB, USPT, USOC, EPAB, DWPI	552	ADJ	YES		08-24-2019
16/418796	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-24-2019
L3l2 same (Transposase or HIV integrases or HERMES)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-24-2019
((composition or mixture or reaction) same (permeabiliz$ same cell same nucleus)) same (Transposase or HIV integrases or HERMES)	PGPB, USPT, USOC, EPAB, DWPI	14	ADJ	YES		08-24-2019
((composition or mixture or reaction) same (permeabiliz$ same cell same nucleus) same (Transposase or HIV integrases or HERMES)) same (adapter or tag$ or linker$)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-24-2019
20100120098.pn.		2	ADJ	YES		08-24-2019

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	PGPB, USPT, USOC, EPAB, DWPI					
((composition or mixture or reaction) same (permeabiliz$ same cell same nucleus) same (Transposase or HIV integrases or HERMES)) and chromatin	PGPB, USPT, USOC, EPAB, DWPI	14	ADJ	YES		08-24-2019
open chromatin	PGPB, USPT, USOC, EPAB, DWPI	1021	ADJ	YES		08-24-2019
(open chromatin) and ((composition or mixture or reaction) same (permeabiliz$ same cell same nucleus))	PGPB, USPT, USOC, EPAB, DWPI	20	ADJ	YES		08-24-2019
(open chromatin and (composition or mixture or reaction) same (permeabiliz$ same cell same nucleus)) and (Transposase or HIV integrases or HERMES)	PGPB, USPT, USOC, EPAB, DWPI	18	ADJ	YES		08-24-2019
(open chromatin) same (permeabiliz$ same cell same nucleus)	PGPB, USPT, USOC, EPAB, DWPI	11	ADJ	YES		08-24-2019
(20100120098.pn.) and (open same chromatin)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-24-2019
(20100120098.pn.) and (chromatin)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-24-2019
(open chromatin) and (Transposase or HIV integrases or HERMES)	PGPB, USPT, USOC, EPAB, DWPI	169	ADJ	YES		08-24-2019

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(open chromatin and (Transposase or HIV integrases or HERMES)) and (adaptor$ or adapter$ or linker$ or tag$ or barcod$)	PGPB, USPT, USOC, EPAB, DWPI	163	ADJ	YES		08-24-2019
(open chromatin and (Transposase or HIV integrases or HERMES) and (adaptor$ or adapter$ or linker$ or tag$ or barcod$)) and (permeabiliz$ same cell same nucleus)	PGPB, USPT, USOC, EPAB, DWPI	32	ADJ	YES		08-24-2019
(open chromatin and (Transposase or HIV integrases or HERMES) and (adaptor$ or adapter$ or linker$ or tag$ or barcod$)) and (permeabiliz$ same nucleus)	PGPB, USPT, USOC, EPAB, DWPI	32	ADJ	YES		08-24-2019
(open chromatin and (Transposase or HIV integrases or HERMES) and (adaptor$ or adapter$ or linker$ or tag$ or barcod$)) and (composition or reaction mixture or mixture or kit)	PGPB, USPT, USOC, EPAB, DWPI	159	ADJ	YES		08-24-2019
(open chromatin and (Transposase or HIV integrases or HERMES) and (adaptor$ or adapter$ or linker$ or tag$ or barcod$) and (composition or reaction mixture or mixture or kit)) and (NP40 or digitonin or tween or steptolysin or lipid)	PGPB, USPT, USOC, EPAB, DWPI	121	ADJ	YES		08-24-2019
(open chromatin and (Transposase or HIV integrases or HERMES) and (adaptor$ or adapter$ or linker$ or tag$ or barcod$) and (composition or reaction mixture or mixture or kit) and (NP40 or digitonin or tween or steptolysin or lipid)) and complex	PGPB, USPT, USOC, EPAB, DWPI	111	ADJ	YES		08-24-2019
(open chromatin and (Transposase or HIV integrases or HERMES) and (adaptor$ or adapter$ or linker$ or tag$ or barcod$) and (composition or reaction mixture or mixture or kit) and (NP40 or digitonin or tween or steptolysin or lipid) and complex) and Tn5 transposase	PGPB, USPT, USOC, EPAB, DWPI	46	ADJ	YES		08-24-2019
(open chromatin and (Transposase or HIV integrases or HERMES) and (adaptor$ or adapter$ or linker$ or tag$ or barcod$) and (composition or reaction mixture or mixture or kit) and (NP40 or digitonin or tween or steptolysin or lipid) and complex) and Tn5	PGPB, USPT, USOC, EPAB, DWPI	57	ADJ	YES		08-24-2019

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(open chromatin and (Transposase or HIV integrases or HERMES) and (adaptor$ or adapter$ or linker$ or tag$ or barcod$) and (composition or reaction mixture or mixture or kit) and (NP40 or digitonin or tween or steptolysin or lipid) and complex and Tn5) and (magnesium or manganese)	PGPB, USPT, USOC, EPAB, DWPI	31	ADJ	YES		08-24-2019
2015111788	PGPB, USPT, USOC, EPAB, DWPI	3	ADJ	YES		08-24-2019
20150111788	PGPB, USPT, USOC, EPAB, DWPI	3	ADJ	YES		08-24-2019
((composition or mixture or reaction) same (permeabiliz$ same cell same nucleus) same (Transposase or HIV integrases or HERMES) same (adapter or tag$ or linker$)) and ((C12Q1/6806 | C12Q2521/507 | C12Q2525/191 | C12Q2535/122 | C07K1/13 | C07K2319/60 | C12N15/90 | C12N9/22).CPC.)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-24-2019
20100120098.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(20100120098.pn.) and chromatin	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
(20100120098.pn.) and chroma$	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
(20100120098.pn.) and chromatin	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
20100120098.pn.		2	ADJ	YES		08-26-2019

	PGPB, USPT, USOC, EPAB, DWPI					
(20100120098.pn.) and (cell same nucle$ or nucleus or nuclei or peameabil$)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20100120098.pn.) and predetermin$	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
(20100120098.pn.) and (adapter or adaptor)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
20140111788.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(20140111788.pn.) and chromatin	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
(20140111788.pn.) and (premeabil$ same (cell or nucle$))	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
premeabiliz$ cell nucle$	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
(20100120098.pn.) and (cell same nucle$ or nucleus or nuclei or permeabil$)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019

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(20140111788.pn.) and (cell same nucle$ or nucleus or nuclei or permeabil$)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
permeabiliz$ cell nucle$	PGPB, USPT, USOC, EPAB, DWPI	55	ADJ	YES		08-26-2019
(20140111788.pn.) and (cell or nucle$ or nucleus or nuclei or permeabil$ or chromatin)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
(permeabiliz$ cell nucle$) and transpos$	PGPB, USPT, USOC, EPAB, DWPI	11	ADJ	YES		08-26-2019
(permeabiliz$ cell nucle$) same (Mixture or composition or kit)	PGPB, USPT, USOC, EPAB, DWPI	8	ADJ	YES		08-26-2019
(permeabiliz$ cell nucle$) same (transpos$ or adapter or adaptor or sequencing tag$ or tag$ or barcod$ or nuclear localization signal)	PGPB, USPT, USOC, EPAB, DWPI	5	ADJ	YES		08-26-2019
US-20190211404-A1.did.	PGPB	1	ADJ	YES		08-26-2019
2011306042.pn.	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
20113006042.pn.	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
20110306042.pn.	PGPB, USPT, USOC,	2	ADJ	YES		08-26-2019

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	EPAB, DWPI					
(20110306042.pn.) and (cell or nucle$ or nucleus or nuclei or permeabil$ or chromatin)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(20110306042.pn. and (cell or nucle$ or nucleus or nuclei or permeabil$ or chromatin)) and (open$)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20110306042.pn. and (cell or nucle$ or nucleus or nuclei or permeabil$ or chromatin) and (open$)) and (chromat$ or chromatin or transpos$ or Tn5)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20110306042.pn. and (cell or nucle$ or nucleus or nuclei or permeabil$ or chromatin) and (open$)) and (transpos$ or Tn5)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
(20110306042.pn. and (cell or nucle$ or nucleus or nuclei or permeabil$ or chromatin) and (open$)) and (transpos$ or Tn5 or adapter or adaptor or sequencing tag$ or barcode)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
(20110306042.pn. and (cell or nucle$ or nucleus or nuclei or permeabil$ or chromatin) and (open$)) and (transpos$ or Tn5 or adapter or adaptor or sequencing tag$ or barcode or recombina$)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20110306042.pn. and (cell or nucle$ or nucleus or nuclei or permeabil$ or chromatin) and (open$) and (transpos$ or Tn5 or adapter or adaptor or sequencing tag$ or barcode or recombina$)) and sequencing	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
(20110306042.pn. and (cell or nucle$ or nucleus or nuclei or permeabil$ or chromatin) and (open$) and (transpos$ or Tn5 or adapter or adaptor or sequencing tag$ or barcode or recombina$)) and sequenc$	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
WO 2011050147	PGPB, USPT,	1	ADJ	YES		08-26-2019

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	USOC, EPAB, DWPI					
(20100120098.pn.) and (cell$ same transpo$)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20100120098.pn.) and (Mixture or composition or kit)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(20100120098.pn.) and ((Mixture or composition or kit) same NP40 digitonin or tween or steptolysin or cationic lipids)	PGPB, USPT, USOC, EPAB, DWPI	n/a	ADJ	YES		08-26-2019
(20100120098.pn.) and ((Mixture or composition or kit) same (digitonin or tween or NP40 or steptolysin or cationic lipid))	PGPB, USPT, USOC, EPAB, DWPI	n/a	ADJ	YES		08-26-2019
(20100120098.pn. and (Mixture or composition or kit)) and (NP40 or digitonin or tween or steptolysin or cationic lipid)	PGPB, USPT, USOC, EPAB, DWPI	n/a	ADJ	YES		08-26-2019
(20100120098.pn.) and (NP40 or digitonin or tween or streptolysin or captionic lipid)	PGPB, USPT, USOC, EPAB, DWPI	n/a	ADJ	YES		08-26-2019
(NP40 or digitonin or tween or streptolysin or captionic lipid)	PGPB, USPT, USOC, EPAB, DWPI	n/a	ADJ	YES		08-26-2019
20100120098	PGPB, USPT, USOC, EPAB, DWPI	14	ADJ	YES		08-26-2019
20100120098.pn.	PGPB,	2	ADJ	YES		08-26-2019

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	USPT, USOC, EPAB, DWPI					
(20100120098.pn.) and (NP40 or digitonin or tween or steptolysin or cationic lipids)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20100120098.pn.) and (NP40 or digitonin or tween or steptolysin or cationic lipids)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
((20110306042.pn. and (cell or nucle$ or nucleus or nuclei or permeabil$ or chromatin) and (open$) and (transpos$ or Tn5 or adapter or adaptor or sequencing tag$ or barcode or recombina$)) and sequenc$)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
((20100120098.pn.) and (Mixture or composition or kit))	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(((20100120098.pn.) and (Mixture or composition or kit))) and two	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(20100120098.pn.) and moiet$	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20100120098.pn.) and transposase	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(20100120098.pn.) and (nuclear localization signal)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019

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(nuclear localization signal)	PGPB, USPT, USOC, EPAB, DWPI	15167	ADJ	YES		08-26-2019
((nuclear localization signal)) and ((20100120098) or (20100120098.pn.))	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
20110306042.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(20110306042.pn.) and (nuclear same localization same signal)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
(20110306042.pn.) and (nuclear or localization or signal$)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(20110306042.pn.) and (nucl$ or local$ or signal$)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(20100120098) and (insert$)	PGPB, USPT, USOC, EPAB, DWPI	13	ADJ	YES		08-26-2019
(20100120098.pn.) and (insert$)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20100120098.pn.) and (transposases or integrase)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019

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(20100120098.pn.) and (molecular tag$ or tag$ or adapter or adaptor)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(20100120098.pn.) and (barcod$)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20100120098.pn.) and (regions or multiple or plurality or genome)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20100120098.pn. and (regions or multiple or plurality or genome)) and tagged nucleic acid	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20100120098) and (cell or nucle$ or nucleus or nuclei or permeabil$ or chromatin or genome)	PGPB, USPT, USOC, EPAB, DWPI	14	ADJ	YES		08-26-2019
(20100120098.pn.) and (cell or nucle$ or nucleus or nuclei or permeabil$ or chromatin or genome)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(20100120098) and ((adapter or adaptor) and (first and second))	PGPB, USPT, USOC, EPAB, DWPI	13	ADJ	YES		08-26-2019
(20100120098.pn.) and ((adapter or adaptor) and (first and second))	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20100120098.pn. and ((adapter or adaptor) and (first and second))) and (genom$ same region)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019

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(20100120098.pn.) and (genom$ same region)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20100120098.pn.) and ((genom$ same region) or ((plurality or multiple) same region))	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20100120098.pn.) and tagged nucleic acid	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20100120098.pn.) and tagged same (nucleic acid or region or fragment)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(20100120098.pn. and tagged same (nucleic acid or region or fragment)) and (whole genome or (multiple or region))	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20100120098.pn.) and (magnesium or manganese or Mg or Mn or cation or divalent)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(20110306042.pn.) and (open$ or heterochromatin)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20100120098.pn.) and heterochromatin	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
20150111788.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019

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(20150111788.pn.) and (open$ or heterochromatin)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(open$ same chromatin)	PGPB, USPT, USOC, EPAB, DWPI	3210	ADJ	YES		08-26-2019
((open$ same chromatin)) and transposase	PGPB, USPT, USOC, EPAB, DWPI	304	ADJ	YES		08-26-2019
((open$ same chromatin) and transposase) and permeabilized	PGPB, USPT, USOC, EPAB, DWPI	66	ADJ	YES		08-26-2019
((open$ same chromatin) and transposase and permeabilized) and tagged nucleic acid	PGPB, USPT, USOC, EPAB, DWPI	6	ADJ	YES		08-26-2019
open chromatin	PGPB, USPT, USOC, EPAB, DWPI	1021	ADJ	YES		08-26-2019
(open chromatin) same access$	PGPB, USPT, USOC, EPAB, DWPI	223	ADJ	YES		08-26-2019
(open chromatin same access$) and transpos$	PGPB, USPT, USOC, EPAB, DWPI	98	ADJ	YES		08-26-2019
(open chromatin same access$ and transpos$) and (sequencing or adaptor or tagging)	PGPB, USPT, USOC, EPAB, DWPI	84	ADJ	YES		08-26-2019

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(20160145685.pn. or 20160145685.pn. or 20110185442.pn. or 2015111788.pn.) and (sequencing or adaptor or tagging)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
((20160145685.pn. or 20160145685.pn. or 20110185442.pn. or 2015111788.pn.) and (sequencing or adaptor or tagging)) and (open chromatin)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
((20160145685.pn. or 20160145685.pn. or 20110185442.pn. or 2015111788.pn.) and (sequencing or adaptor or tagging) and open chromatin) and transpo$	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(open chromatin region$) or (open chromatin same regions) or (open chromatin same fragments)	PGPB, USPT, USOC, EPAB, DWPI	509	ADJ	YES		08-26-2019
(open chromatin region$) or (open chromatin same regions) or (open chromatin same fragments) or (open chromatin near region)	PGPB, USPT, USOC, EPAB, DWPI	509	ADJ	YES		08-26-2019
((open chromatin region$) or (open chromatin same regions) or (open chromatin same fragments) or (open chromatin near region)) and (transpo$)	PGPB, USPT, USOC, EPAB, DWPI	313	ADJ	YES		08-26-2019
((open chromatin region$) or (open chromatin same regions) or (open chromatin same fragments) or (open chromatin near region) and (transpo$)) and permeabiliz$	PGPB, USPT, USOC, EPAB, DWPI	79	ADJ	YES		08-26-2019
((open chromatin region$) or (open chromatin same regions) or (open chromatin same fragments) or (open chromatin near region) and (transpo$) and permeabiliz$) and (adaptor or adapter)	PGPB, USPT, USOC, EPAB, DWPI	32	ADJ	YES		08-26-2019
20120064517.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019

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(20120064517.pn.) and (composition or mixture)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20120064517.pn.) and (transposition or transposase or transposon)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
(20120064517.pn.) and (sequencing)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(20120064517.pn. and (composition or mixture)) and (sequencing)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
open chromatin regions	PGPB, USPT, USOC, EPAB, DWPI	109	ADJ	YES		08-26-2019
(open chromatin regions) and transposition	PGPB, USPT, USOC, EPAB, DWPI	35	ADJ	YES		08-26-2019
14/892911	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
14/359877	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(14/359877) and (open$ chromatin)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019

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(14/892911) and (open$ chromatin)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
61/629555	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(61/629555) and (open$ chromatin)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(open$ chromatin regions)	PGPB, USPT, USOC, EPAB, DWPI	109	ADJ	YES		08-26-2019
((open$ chromatin regions)) same (genomic or DNA)	PGPB, USPT, USOC, EPAB, DWPI	84	ADJ	YES		08-26-2019
((open$ chromatin regions) same (genomic or DNA)) and (composition or kit or mixture)	PGPB, USPT, USOC, EPAB, DWPI	78	ADJ	YES		08-26-2019
((open$ chromatin regions) same (genomic or DNA) and (composition or kit or mixture)) and sequencing	PGPB, USPT, USOC, EPAB, DWPI	71	ADJ	YES		08-26-2019
((open$ chromatin regions) same (genomic or DNA) and (composition or kit or mixture)) and transpos$	PGPB, USPT, USOC, EPAB, DWPI	45	ADJ	YES		08-26-2019

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... and sensitive epigenomic profiling of **open chromatin**, ... - Buenrostro - Cited by 1830

... cell profiling of **chromatin** accessibility by combinatorial ... - Cusanovich - Cited by 338

... epigenetic marks for **open chromatin** across the maize ... - Liu - Cited by 169

ATAC-seq - Wikipedia

https://en.wikipedia.org › wiki › ATAC-seq

ATAC-seq is a technique used in molecular biology to assess genome-wide chromatin ... ATAC-seq identifies accessible DNA regions by probing **open chromatin** with hyperactive mutant Tn5 **transposase** that inserts ... fragmentation and tagging of DNA performed by Tn5 **transposase** pre-loaded with sequencing **adaptors**.

Description · Applications · Single-cell ATAC-seq · Efficiency and specifications

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Epigenetics applications - ATAC-seq | Abcam

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Assay for **transposase**-accessible chromatin sequencing (ATAC-seq) builds on a ... mutant Tn5 **transposases**, preloaded with DNA **adapters**, tag genomic DNA for ... Methods to assess **open chromatin** via NGS have been in use for a number of ...

ATAC-Seq - Illumina

https://www.illumina.com › sequencing-method-explorer › kits-and-arrays

In this method, gDNA is incubated with Tn5 transposomes, which fragments it and adds **adapters** simultaneously, in **open chromatin** regions. Deep sequencing ...

ATAC-seq Guidelines - Harvard FAS Informatics

https://informatics.fas.harvard.edu › atac-seq-guidelines

Jan 18, 2019 - ATAC-seq (Assay for **Transposase**-Accessible **Chromatin** with high-throughput sequencing) is a method for determining **chromatin** accessibility across the genome. It utilizes a hyperactive Tn5 **transposase** to insert sequencing **adapters** into **open chromatin** regions (Fig. 1).

Experimental design · Sequence reads · Quality control · Alignment

ATAC-seq: A Method for Assaying Chromatin Accessibility Genom...

https://www.ncbi.nlm.nih.gov › pmc › articles › PMC4374986

by J Buenrostro - 2015 - Cited by 569 - Related articles

Jan 5, 2015 - The assay of **transposase** accessible chromatin (Buenrostro et al., 2013) ... et al., 2010) to simultaneously cut and ligate **adapters** for high-throughput ... of **open chromatin**, DNA-binding proteins and nucleosome position.

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ATAC-see reveals the accessible genome by transposase-mediate...

https://www.ncbi.nlm.nih.gov › pmc › articles › PMC5509561

by X Chen - 2016 - Cited by 46 - Related articles

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Oct 17, 2016 - After imaging the spatial organization of the accessible genome in 3D, the inserted **adaptors** allow deep sequencing to map **open chromatin** ...

I-ATAC: Interfacing Assay for Transposase-Accessible Chromatin ...

https://www.jax.org › research-and-faculty › resources › i-atac

ATAC-seq is a new protocol to capture **open chromatin** sites by performing **adaptor** ligation and fragmentation of **open chromatin** regions. Due to its efficiency in ...

transposition of native chromatin for fast and sensitive ... - Nature

https://www.nature.com › articles › nmeth.2688.pdf

by JD Buenrostro - 2013 - Cited by 1826 - Related articles

Oct 6, 2013 - AtAc-seq captures **open chromatin** sites using a simple two-step protocol ... **transposase** integrates its **adaptor** payload into regions of accessi-.

Interactive Quality and Pre-Processing Pipeline for ATAC ... - Fronti...

https://www.frontiersin.org › conf.fninf.2016.20.00020 › event_abstract

by Z AHMED - Cited by 1 - Related articles

Jul 18, 2016 - **Transposase**-accessible chromatin is of importance to better understand ... by performing **adaptor** ligation and fragmentation of **open chromatin** ...

[PDF]

"ATAC-seq: A Method for Assaying Chromatin Accessibility Geno...

https://www.umassmed.edu › globalassets › lawson-lab › images

by JD Buenrostro - 2015 - Cited by 569 - Related articles

Tn5 **transposase**, which inserts sequencing **adapters** into accessible regions of .... **adapter** 2 barcode closed **chromatin** amplify and sequence **open chromatin**.

Searches related to open chromatin and transposase and adaptor

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atac-seq cost

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Bibliographic Data

Application No: 16/418,796

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☐ No ☐ Met After Allowance

Verified and Acknowledged: /Cynthia Wilder/ /CW/

Examiner's Signature Initials

Title: Transposition of Native Chromatin for Personal Epigenomics

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05/21/2019 **RULE**	435	1637	STAN-1111CON5

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William J. Greenleaf Menlo Park, CA, UNITED STATES

CONTINUING DATA

This application is a CON of 16160719 10/15/2018 PAT 10337062

16160719 is a CON of 16043874 07/24/2018 PAT 10150995

16043874 is a CON of 14784250 10/13/2015 PAT 10059989

14784250 is a 371 of PCT/US2014/038825 05/20/2014

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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	5137829		1992-08-11	Nag et al.	
	2	5965443		1999-10-12	Reznikoff et al.	
	3	6159717		2000-12-12	Savakis et al.	
	4	6207384		2001-03-27	Mekalanos et al.	
	5	6258571		2001-07-10	Chumakov et al.	
	6	6291243		2001-09-18	Fogarty et al.	
	7	6294385		2001-09-25	Goryshin et al.	
	8	6593113		2003-07-15	Tenkanen et al.	

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	9	6613752		2003-09-02	Kay et al.	
	10	7608451		2009-10-27	Cooper et al.	
	11	7745218		2010-06-29	Kim et al.	
	12	7608434		2009-10-27	Reznikoff et al.	
	13	7138267		2006-11-21	Jendrisak et al.	
	14	8124404		2012-02-28	Alphey	
	15	8420386		2013-04-16	Ivics et al.	
	16	8598328		2013-12-03	Koga et al.	
	17	8829171		2014-09-09	Steemers et al.	
	18	8927218		2015-01-06	Forsyth	
	19	9005935		2015-04-14	Belyaev	

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	20	9074251		2015-07-07	Steemers et al.	
	21	9080211		2015-07-14	Grunenwald et al.	
	22	9150916		2015-10-06	Christen et al.	
	23	9175295		2015-11-03	Kaminaka et al.	
	24	9238671		2016-01-19	Goryshin et al.	
	25	9328382		2016-05-03	Drmanac et al.	
	26	9574226		2017-02-21	Gormley et al.	

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	1	20030032141		2003-02-13	Nguyen	
	2	20040101880		2004-05-27	Rozwadowski et al.	

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	3	20100120098		2010-05-13	GRUNENWALD, et al.	
	4	20120297493		2012-11-22	Cooper et al.	
	5	20130203605		2013-08-08	Shendure et al.	
	6	20150111788		2015-04-23	Fernandez et al.	
	7	20150337298		2015-11-26	Xi et al.	
	8	20150368638		2015-12-24	Steemers et al.	
	9	20150376608		2015-12-31	Kaper et al.	
	10	20160060691		2016-03-03	Giresi et al.	
	11	20160115474		2016-04-28	Jelinek et al.	
	12	20160122753		2016-05-05	Mikkelsen et al.	
	13	20160160235		2016-06-09	Solodushko et al.	

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	14	20160177359		2016-06-23	Ukanis et al.	
	15	20160208323		2016-07-21	Bernstein et al.	
	16	20160376663		2016-12-29	Brown	
	17	20140274740		2014-09-18	Srinivasan et al.	
	18	20160115474		2016-04-28	Jelinek et al.	
	19	20130079251		2013-03-28	Boles	

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	1	WO 2007/093819	WO		2007-08-23	ISIS INNOVATION LIMITED		
	2	WO 2009/147386	WO		2009-12-10	OXFORD BIODYNAMICS LIMITED		
	3	WO 2010/048605	WO		2010-04-29	EPICENTRE TECHNOLOGIES CORPORATION		

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	Examiner Name	
	Attorney Docket Number	STAN-1111CON5

	4	WO 2014/108810	WO		2014-07-17	ILLUMINA CAMBRIDGE LTD		
	5	WO 2016/191618	WO		2016-12-01	ZHENG JIANBIAO et al.		
	6	WO 2016/207647	WO		2016-12-29	OXFORD BIODYNAMICS LIMITED		
	7	WO 2016/207653	WO		2016-12-29	OXFORD BIODYNAMICS LIMITED		
	8	WO 2016/207661	WO		2016-12-29	OXFORD BIODYNAMICS LIMITED		
	9	WO 2017/015075	WO		2017-01-26	HARVARD COLLEGE		
	10	WO 2017/025594	WO		2017-02-16	CHEM FORSCHUNGSZENTRUM FÜR MOLEKULARE MEDIZIN GMBM		
	11	WO2012106546	WO		2012-08-09	SHENDURE et al.		
	12	CN102292455	CN		2011-12-21	Bio-Rad Laboratories, Inc.		

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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]

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/CYNTHIA B WILDER/ (08/24/2019) 08/24/2019

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	
	First Named Inventor	Paul Giresi
	Art Unit	
	Examiner Name	
	Attorney Docket Number	STAN-1111CON5

	1	ADEY, et al., "Ultra-low-input, tagmentation-based whole-genome bisulfite sequencing", Genome Research, 2012, 22 (6): 1139-1143.	
	2	ASON et al., "DNA Sequence Bias During Tn5 Transposition", J. Mol. Biol., 2004, 335: 1213-1255.	
	3	BJORNSSON et al., "Intra-individiual change over time in DNA methylation with familial clustering, JAMA, June 25, 2008, Vol. 299 No. 24, pages 2877-2883	
	4	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	
	5	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	
	6	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.	
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	8	Parks et al., "ChIP-Seq: advantages and challenges of a maturing technology", Nature, vol. 10, pages 669-680, October (Year: 2009)	
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/CYNTHIA B WILDER/ (08/24/2019) 08/24/2019

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
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	Art Unit	
	Examiner Name	
	Attorney Docket Number	STAN-1111CON5

	12	ZENTNER et al., "Surveying the epigenomic landscape, one base at a time", Genome Biology, 2012, 13:250, 8 pages.	
	13	Epicentre., "EZ-Tn5TM Custom Transposome Construction Kits", www.epicentre.com, pages 1-17, 2012.	
	14	AHERN, "TOOLS & TECHNOLOGY, Biochemical, Reagent Kits Offer Scientists Good Return On Investment", THE SCIENTIST, 1995, vol. 20, pages 20 and 22.	

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EXAMINER SIGNATURE

Examiner Signature	/CYNTHIA B WILDER/ (08/24/2019)	Date Considered	08/24/2019

*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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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/418,796	05/21/2019	Paul Giresi	STAN-1111CON5

CONFIRMATION NO. 6413

PUBLICATION NOTICE

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STANFORD UNIVERSITY OFFICE OF TECHNOLOGY LECENSING
BOZICEVIC, FIELD & FRANCIS LLP
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

Title: Transposition of Native Chromatin for Personal Epigenomics

Publication No.US-2019-0316196-A1
Publication Date:10/17/2019

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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.

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/418,796	Filing Date 05/21/2019	☐ 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 $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $230 =	
☐ 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	12/02/2019	(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))	* 30	Minus	** 30	= 0		x $50 =	0
	Independent (37 CFR 1.16(h))	* 4	Minus	*** 4	= 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".	/MOLIKI I MAY/
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Examiner: Cynthia B. Wilder
	)	
Paul Giresi et al.	)	Art Unit: 1637
	)	
Application No. 16/418,796	)	Confirmation No. 6413
	)	
Filed: May 21, 2019	)	Attorney Ref. STAN-1111CON5
	)	
For: **TRANSPOSITION OF NATIVE CHROMATIN FOR PERSONAL EPIGENOMICS**	)	**Customer No. 77974**

FILED VIA EFS ON: December 2, 2019

RESPONSE TO OFFICE ACTION

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Commissioner:

This communication is responsive to the non-final Office Action mailed on August 30, 2019, setting a 3-month period for reply. This application is also under Track 1 Examination. Therefore, this communication is timely filed. In view of the amendments to the claims and the remarks set forth herein, reconsideration and allowance are respectfully requested.

Amendment to the claims begin on page **2** of this communication.

Remarks/Arguments begin on page **6** of this communication.

In the Claims:

The following listing of claims will replace all previous versions:

1.-97. (Cancelled)

98. (**Currently amended**) A composition comprising:

a permeabilized cell nucleus comprising**:**

(a) a plurality of polynucleotide molecules;

(b) an insertional enzyme complex; and

(c) an insert element comprising at least one nucleic acid comprising a predetermined sequence.

99. (Previously presented) The composition of claim 98, further comprising a permeabilization agent selected from the group consisting of: NP40, digitonin, tween, steptolysin, cationic lipids, and any combination thereof.

100. (**Currently amended**) A composition comprising:

a permeabilized cell nucleus comprising**:**

(a) a plurality of polynucleotide molecules, wherein the plurality of polynucleotide molecules comprises genomic DNA comprising a plurality of open chromatin regions;

(b) an insertional enzyme complex; and

(c) an insert element comprising at least one nucleic acid comprising a predetermined sequence.

101. (Previously presented) The composition of claim 100, wherein the insertional enzyme complex comprises one or more enzymatic moieties.

102. (Previously presented) The composition of claim 101, wherein the insertional enzyme complex comprises two or more enzymatic moieties.

103. (Previously presented) The composition of claim 102, wherein the two or more enzymatic moieties are linked together.

104. (Previously presented) The composition of claim 100, wherein the insertional enzyme complex comprises a nuclear localization signal.

105. (Previously presented) The composition of claim 100, wherein the insertional enzyme complex is configured to insert a nucleic acid sequence into at least one of the polynucleotide molecules.

106. (Previously presented) The composition of claim 105, wherein the insertional enzyme complex is configured to insert the nucleic acid sequence into at least one of the polynucleotide molecules in a substantially sequence independent manner.

107. (**Currently amended**) The composition of claim 100, wherein the insertional enzyme complex comprises an enzyme selected from the group consisting of: transposases, ~~HERMES~~ **Hermes transposase**, and **human immunodeficiency virus (**HIV**)** integrases.

108. (Previously presented) The composition of claim 107, wherein the insertional enzyme complex comprises a transposase.

109. (Previously presented) The composition of claim 108, wherein the transposase is a Tn transposase.

110. (Previously presented) The composition of claim 109, wherein the Tn transposase is selected from the group consisting of: Tn3, Tn5, Tn7, Tn10, Tn552 and Tn903.

111. (Previously presented) The composition of claim 110, wherein the transposase is a Tn5 transposase.

112. (Previously presented) The composition of claim 100, wherein the insert element comprises one or more molecular tags.

113. (Previously presented) The composition of claim 112, wherein one or more of the molecular tags comprises a sequencing adaptor.

114. (Previously presented) The composition of claim 113, wherein one or more of the sequencing adaptors comprises a barcode label.

115. (**Currently amended**) A composition comprising:

a permeabilized cell nucleus[[;]] **comprising:**

(a) an insertional enzyme complex comprising a transposase enzyme; and

(b) a plurality of tagged nucleic acid fragments, wherein each tagged nucleic acid fragment comprises a first sequencing adapter and a second sequencing adapter; wherein each tagged nucleic acid fragment is derived from a region of open chromatin.

116. (Previously presented) The composition of claim 115, wherein the plurality of tagged nucleic acid fragments correspond to two or more regions of a genome.

117. (Previously presented) The composition of claim 115, wherein the plurality of tagged nucleic acid fragments correspond to at least 1,000 regions of a genome.

118. (Previously presented) The composition of claim 117, wherein the plurality of tagged nucleic acid fragments correspond to genome-wide regions of open chromatin.

119. (Previously presented) The composition of claim 117, wherein the transposase is a Tn transposase.

120. (Previously presented) The composition of claim 119, wherein the Tn transposase is a Tn5 transposase.

121. (**Currently amended**) A composition comprising:

a permeabilized cell nucleus[[;]] **comprising:**

(a) an insertional enzyme complex comprising a transposase enzyme; and

(b) a plurality of tagged nucleic acid fragments, wherein each tagged nucleic acid fragment comprises a first sequencing adapter and a second sequencing adapter;

wherein the insertional enzyme complex and the tagged nucleic acid fragments are bound to one or more regions of open chromatin within the cell nucleus in a substantially sequence independent manner to form a high affinity macromolecule complex.

122. (Previously presented) The composition of claim 121, further comprising a plurality of divalent cations.

123. (Previously presented) The composition of claim 122, wherein the divalent cations are not chelated.

124. (Previously presented) The composition of claim 122, wherein the divalent cations are selected from the group consisting of: magnesium, manganese, or any combination thereof.

125. (Previously presented) The composition of claim 121, wherein the transposase is a Tn transposase.

126. (Previously presented) The composition of claim 125, wherein the Tn transposase is selected from the group consisting of: Tn3, Tn5, Tn7, Tn10, Tn552 and Tn903.

127. (Previously presented) The composition of claim 126, wherein the transposase is a Tn5 transposase.

REMARKS

Prior to the present amendment, claims 98-127 were pending and rejected on various grounds.

Claims 1-97 are cancelled without prejudice or disclaimer.

Claims 98, 100, 107, 115, and 121 are amended herein.

Claims 98, 100, 115 and 121 are amended to clarify that the permeabilized cell nucleus comprises the listed elements.

Claim 107 is amended to clarify the abbreviated names of two transposase enzymes.

No new matter is added.

Claim Rejections - 35 USC § 112

Claim 107 stands rejected under 35 § USC 112(b) or 35 USC § 112 (pre-AIA), second paragraph, as allegedly being indefinite for failing to distinctly and particularly claim the subject matter regarded as the invention. According to the rejection, recitation of the abbreviations "HERMES" and "HIV" allegedly renders claim 107 indefinite.

Without acquiescing to the rejection and solely in an effort to expedite an allowance, the claims have been amended, thus rendering the instant rejection moot. Applicant notes that "Hermes" is not an abbreviation, but the name of a specific transposase.

In light of the above, Applicant requests that the rejections under 35 USC § 112 be withdrawn.

Claim Rejections - 35 USC § 103

Claims 98-127 are rejected under 35 USC § 103 as being unpatentable over *Grunenwald* et al. (US 20100120098) in view of *Jouvenot* (US 20110306042), and further in view of *Audit* et al (Nucleic Acid Research, 37(18):6064-6075, 2009). For the reasons provided below, Applicant disagrees and requests that the rejection be withdrawn.

In order to meet its burden in establishing a rejection under 35 USC § 103, the Office must first demonstrate that a prior art reference, or references when combined, teach or suggest all claim elements. *Süd-Chemie v. Multisorb Technologies,* 554 F.3d 1001 (Fed. Cir. 2009).

Furthermore, the Supreme Court in *KSR v. Teleflex* stated that "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions." *See, e.g.*, *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007) at 1740. As such, in addition to showing that all elements of a claim were known in the prior art, and that one of ordinary skill in the art had a reason to combine them, the Office must also provide evidence that the combination would be a **predicted success**. *See Crocs, Inc.* v. *U.S. International Trade Commission,* 598 F.3d 1294 (Fed. Cir. 2010) (emphasis added).

Without agreeing with the rejection, and solely to advance prosecution, Applicant has amended the pending claims to clarify that the compositions comprise a permeabilized cell nucleus, which in turn comprises the elements listed in the claims.

Applicant asserts that the Examiner has failed to establish a *prima facie* case of obviousness for the rejected claims because the Examiner has failed to demonstrate that the cited art references, either alone or in combination, teach or suggest all elements of the claimed compositions. Furthermore, the Examiner has failed to demonstrate that one of ordinary skill in the art would have had a reasonable expectation of success in combining the various elements of the cited art in the manner suggested to arrive at the compositions recited in the pending claims.

For example, in formulating the rejection, the Examiner alleges that:

> Grunewald et al teach a composition comprising target DNA with a transposase and a transposon end or transposon end comprising a transferred strand that has a tag domain in its 5' portion, under conditions wherein a transposition reaction is catalyzed by the transposase and wherein the target DNA is fragmented to generate a plurality of target DNA fragments and a transferred strand of the transposon end or transposon end composition is joined [sic] the 5' ends of each of a plurality of the target DNA fragments.

Office Action, pages 3-4. The Examiner admits that *Grunenwald* fails to "expressly teach wherein the composition or reaction mixture of the methods disclosed therein comprise of a permeabilized cell nucleus…and wherein the tagged nucleic acid fragments are derived from regions of open chromatin." *Id.* at 6.

To remedy this deficiency, the Examiner relies on *Jouvenot* for allegedly teaching "a method and reaction mixture for analyzing chromatin structure and/or epigenetic status in chromosomal DNA of a cell wherein the composition comprises permeabilizing nucleus of a cell to all [sic] for entry of an insertional enzyme." *Id.* The Examiner further admits that neither *Grunenwald* nor *Jouvenot* "expressly teach plurality of DNA or fragments derived from open chromatin regions as recited in the claims 100-127 [sic]," but then relies on *Audit* for allegedly teaching that "genome wide investigation of chromatin architecture have revealed that at large scales, regions enriched in open chromatin fibers correlate with region of high gene density…" *Id.* at 7.

The Examiner then concludes that "[i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time of the effective filing date of the invention to have been motivated to modify the composition of Grunenwald to encompass permeabilized cell nucleus as taught by Jouvenot for the obvious benefit of allowing for entry of endonuclease into the nuclease [sic] and additionally for the benefit of allowing for chromatin structure analysis and/or epigenetic events in DNA regions of interest to detected [sic]." *Id.*

The deficiency in the *prima facie* case is that *none of the cited references teach or suggest a composition comprising* ***a permeabilized cell nucleus****, in addition to the other elements listed in the claims*. For example, the Examiner admits that *Grunenwald* does not teach a permeabilized cell nucleus, or that the tagged nucleic acid fragments are derived from regions of open chromatin. But the Examiner's reliance on *Jouvenot* for this element is incorrect in that *Jouvenot* does not teach a composition comprising a permeabilized cell nucleus comprising the elements recited in the pending claims. To the contrary, *Jouvenot* teaches a **multi-step approach** that involves contacting nuclear DNA with a first DNA endonuclease to introduce single-stranded nicks, labeling those nicks, ligating the labeled nicks, then introducing a second DNA endonuclease to introduce additional single-stranded nicks, labeling the additional nicks, ligating the additional nicks, and then comparing the nicks resulting from the first and second DNA endonucleases to analyze chromatin structure or epigenetic status of the nuclear DNA. At no point does *Jouvenot's* approach result in a composition comprising a permeabilized cell nucleus

comprising the elements recited in the pending claims, e.g., an insertional enzyme complex and an insert element comprising at least one nucleic acid comprising a predetermined sequence. Nor does *Jouvenot* suggest creating such a composition, as *Jouvenot* teaches the criticality of labeling nicks with a detectable label, and then subsequently analyzing the labeled nicks to analyze chromatin structure and/or epigenetic information.

Jouvenot's prosecution history further confirms its deficiencies in teaching or suggesting each and every element of the pending claims. For example, *Jouvenot's* claims 1-23 were rejected for not being supported by an enabling disclosure. USSN: 13/152,012, Office Action dated Dec. 7, 2012, pages 5-7. Notably, the Examiner stated:

> As to the instant application, the examiner finds no evidence in the prior art or the disclosure itself that the claimed process can be used to analyze chromatin structure and/or the epigenetic status of chromosomal DNA. The specification lacks one or more working examples wherein the applicant shows that the claimed invention can in fact be used to analyze chromatin structure and/or the epigenetic status of chromosomal DNA and how this analysis could occur. In the absence of evidence to the contrary, the examiner can only conclude that the invention is merely an idea and/or a proposal for future research.

Id. at page 7.

In response to this rejection, *Jouvenot* cancelled claims 1-23 and focused on claims 24-30, which recited kits, and which had initially been indicated as allowable. However, upon further examination of these claims, the Examiner located prior art that rendered the kit claims obvious, and *Jouvenot* was not able to point to any unexpected results that would rebut this determination. *Jouvenot's* application was then abandoned, and no continuing applications were filed.

Accordingly, *Jouvenot's* disclosure does not remedy the deficiencies of *Grunenwald* because *Jouvenot* does not teach or suggest compositions comprising each and every element of the pending claims. Additionally, *Jouvenot's* prosecution history provides additional evidence that it is not an enabling disclosure, and therefore would not provide one of ordinary skill in the art with a motivation to combine the references, or a reasonable expectation of success in doing

so, to arrive at the pending claims. There is simply no guidance or teaching in *Jouvenot* that would lead one of ordinary skill in the art to apply *Grunenwald's* teaching to a cell nucleus with a reasonable expectation of success in creating a composition as recited in the pending claims.

Regarding the third cited reference, the Examiner's cursory reliance on *Audit* for the general teaching that "one of ordinary skill in the art would want to incorporate nucleic acids from open regions of chromatin into a composition as instantly claimed for analysis" is also insufficient. *Audit* makes no mention of compositions comprising the elements recited in the pending claims, and therefore fails to remedy the above-identified deficiencies of *Jouvenot*.

In addition to the deficiencies noted above, Applicant also respectfully notes that the obviousness rejection utilizes hindsight to construct a recognition of the problem being solved, rather than recognizing the solution being presented.

It is well established that an obviousness rejection must demonstrate that the problem was known in the art or that the asserted formulation of the problem was derived directly from the prior art, rather than from the challenged claims, and that defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness. *Insite Vision Inc. v. Sandoz, Inc.,* 783 F.3d 853, 859 (Fed. Cir. 2015).

Applicant respectfully asserts that it is not sufficient to rely solely on interrelated teachings of cited references without more than conclusory statements that one of ordinary skill in the art would be motivated to combine the elements as taught. Obviousness jurisprudence has made it clear that the sole reason for making a proposed combination of prior art elements cannot be a problem defined in terms of its solution. Rather, the problem to be solved must be gleaned from something *other than the Applicant's own specification*.

The present rejection takes this unavailing approach by merely identifying elements of the pending claims in the cited art, and linking them together with conclusory statements regarding their benefits, without first identifying the problem to be solved in the prior art. As such, the rejection amounts to impermissible hindsight reconstruction.

For the reasons provided above, Applicant asserts that the rejection of claims 98-127 under § 103 as being unpatentable over *Grunenwald* in view of *Jouvenot* and *Audit* should be withdrawn.

CONCLUSION

Applicant submits that the pending claims are in condition for allowance, and an action to that end is respectfully requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

All required fees have been submitted herewith, and the Commissioner is not authorized to charge any additional fees.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: December 2, 2019

By: /James S. Keddie/
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EFS ID:	37903346
Application Number:	16418796
International Application Number:	
Confirmation Number:	6413
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-1111CON5
Receipt Date:	02-DEC-2019
Filing Date:	21-MAY-2019
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1		STAN-1111CON5_RespOA.pdf	68998 e59346974d0599b8686522e1639f3e1554604ed8	yes	11

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	5
	Applicant Arguments/Remarks Made in an Amendment	6	11
Warnings:			
Information:			
	Total Files Size (in bytes):	68998	

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.

<u>New Applications Under 35 U.S.C. 111</u>
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.
<u>National Stage of an International Application under 35 U.S.C. 371</u>
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.
<u>New International Application Filed with the USPTO as a Receiving Office</u>
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)
Approved for use through 1/31/2014. OMB 0651-0032
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 16/418,796	Filing Date 05/21/2019	☐ 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 $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $230 =	
☐ 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	12/13/2019	(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))	* 30	Minus	** 30	= 0		x $50 =	0
	Independent (37 CFR 1.16(h))	* 4	Minus	*** 4	= 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.	SLIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/SHARONE R MOORE/
*** 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.**

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/418,796	05/21/2019	Paul Giresi	STAN-1111CON5	6413

77974 7590 12/13/2019
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
12/13/2019	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

PTOL-90A (Rev. 04/07)

Applicant-Initiated Interview Summary	**Application No.** 16/418,796	**Applicant(s)** Giresi et al.	
	Examiner CYNTHIA B WILDER	**Art Unit** 1637	**AIA (FITF) Status** Yes

All participants (applicant, applicants representative, PTO personnel):

(1) Cynthia Wilder, Patent Examiner.

(2) James Keddie, Applicant's Representative.

(3) Benjamin Pelletier, Applicant's Representative.

(4) Alissa Faris, Applicant's Representative.

Date of Interview: 04 December 2019.

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: 98-127.

Identification of prior art discussed: _____.

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...)

Applicant's representatives and the examiner discussed claim interpretations in light of the cited prior art and differences between the claimed invention and the cited prior art. The examiner noted that she would consider Applicant's representatives comments when reviewing their response. The examiner noted that she would telephone applicant's representative if deemed necessary to expedite towards allowance. No final agreement was reached..

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	

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Parse Biosciences, Inc. v. 10x Genomics, Inc.
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Page 00206

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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Examiner: Cynthia B. Wilder
	)	
Paul Giresi et al.	)	Art Unit: 1637
	)	
Application No. 16/418,796	)	Confirmation No. 6413
	)	
Filed: May 21, 2019	)	Attorney Ref. STAN-1111CON5
	)	
For: **TRANSPOSITION OF NATIVE CHROMATIN FOR PERSONAL EPIGENOMICS**	)	**Customer No. 77974**

FILED VIA EFS ON: December 13, 2019

SUPPLEMENTAL AMENDMENT AND REPLY

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Commissioner:

This communication is supplemental to the Amendment filed on December 2, 2019, and follows an Examiner interview, conducted on December 4, 2019.

In view of the amendments to the claims and the remarks set forth herein, reconsideration and allowance are respectfully requested.

Amendment to the claims begin on page **2** of this communication.

A Summary of the Interview appears on page **7** of this communication.

Remarks begin on page **8** of this communication.

Electronic Acknowledgement Receipt

EFS ID:	38030815
Application Number:	16418796
International Application Number:	
Confirmation Number:	6413
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-1111CON5
Receipt Date:	13-DEC-2019
Filing Date:	21-MAY-2019
Time Stamp:	18:31:27
Application Type:	Utility under 35 USC 111(a)

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-1111CON5_RespOA_Supplemental.pdf	42521 e74b84d4db581f376ac7445b2c02b1df7e589ec0	yes	9

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Applicant Arguments/Remarks Made in an Amendment	8	9
	Applicant summary of interview with examiner	7	7
	Claims	2	6
	Supplemental Response or Supplemental Amendment	1	1
Warnings:			
Information:			
	Total Files Size (in bytes):	42521	

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<u>New Applications Under 35 U.S.C. 111</u>
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.
<u>National Stage of an International Application under 35 U.S.C. 371</u>
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.
<u>New International Application Filed with the USPTO as a Receiving Office</u>
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.

REMARKS

Prior to the present amendment, claims 98-127 were pending.

Claims 99, 110, and 126 are cancelled without prejudice or disclaimer.

Claims 98, 100, 101, 102, 104-106, 111, and 127 are amended herein.

New claims 128-130 are presented.

Upon entry of this amendment, claims 98, 100-109, 111-125, and 127-130 will be pending in the present application. Reconsideration is respectfully requested.

Claims 98, 101, 102, and 104-106 are amended to clarify claim terms and/or correct typographical errors. Claim 100 is amended to clarify the claimed aspect with respect to the Examiner's suggestion during the Interview, and new claims 128-130 have similarly been presented. Support for amended claim 100 can be found at least, for example, at page 43, lines 10-15, of the specification as originally filed. Claims 111 and 127 are amended in view of the cancellation of claims 110 and 126.

No new matter is added.

Applicant restates the arguments presented in the Response to Office Action submitted on December 2, 2019, as those arguments apply to the pending claims presented herein.

Any instance herein where Applicant has addressed certain comments of the Office shall not be construed as a concession to other comments or arguments advanced by the Office. Any circumstance in which Applicant has amended or cancelled a claim also does not mean that Applicant concedes to the arguments or positions advanced by the Office with respect to that claim or other claims pending herein.

CONCLUSION

Applicant submits that the pending claims are in condition for allowance, and an action to that end is respectfully requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

All required fees have been submitted herewith, and the Commissioner is not authorized to charge any additional fees.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: December 13, 2019

By: /James S. Keddie/
James S. Keddie
Registration No. 48920

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shore Parkway, Suite 200
Redwood , California 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

SUMMARY OF THE INTERVIEW

Applicant thanks Primary Examiner Wilder for extending the courtesy of a telephonic interview to Applicant's representatives James Keddie, Ben Pelletier, and Alissa Faris, on December 4, 2019. During the interview, amendments and arguments consistent with those detailed herein and in the Response to Office Action filed on December 2, 2019, were discussed.

In the Claims:

The following listing of claims will replace all previous versions:

1.-97. (Cancelled)

98. (**Currently amended**) A composition comprising:

a permeabilized cell nucleus comprising:

(a) a plurality of polynucleotide molecules; **and**

(b) an insertional enzyme complex~~; and~~ **comprising an insertional enzyme and**

~~(c)~~ an insert element comprising ~~at least one nucleic acid comprising~~ a predetermined sequence.

99. (**Cancelled**)

100. (**Currently amended**) A composition comprising:

a permeabilized cell nucleus comprising:

(a) **chromatin comprising genomic DNA and a plurality of DNA binding proteins, wherein the chromatin comprises a plurality of open chromatin regions** ~~a plurality of polynucleotide molecules, wherein the plurality of polynucleotide molecules comprises genomic DNA comprising a plurality of open chromatin regions~~; **and**

(b) an insertional enzyme complex~~; and~~ **comprising an insertional enzyme and**

~~(c)~~ an insert element comprising ~~at least one nucleic acid comprising~~ a predetermined sequence**, wherein the insertional enzyme complex is bound to one of said open chromatin regions**.

101. (**Currently amended**) The composition of claim 100, wherein the insertional enzyme ~~complex~~ comprises one or more enzymatic moieties.

10x Genomics, Inc. Exhibit 2010
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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Page 00214

102. (**Currently amended**) The composition of claim 101, wherein the insertional enzyme ~~complex~~ comprises two or more enzymatic moieties.

103. (Previously presented) The composition of claim 102, wherein the two or more enzymatic moieties are linked together.

104. (**Currently amended**) The composition of claim 100, wherein the insertional enzyme ~~complex~~ comprises a nuclear localization signal.

105. (**Currently amended**) The composition of claim 100, wherein the insertional enzyme complex is configured to insert ~~a nucleic acid sequence~~**the insert element** into ~~at least one of the polynucleotide molecules~~**the genomic DNA at an open chromatin region**.

106. (**Currently amended**) The composition of claim 105, wherein the insertional enzyme complex is configured to insert the ~~nucleic acid sequence~~**insert element** into ~~at least one of the polynucleotide molecules~~**the genomic DNA** in a substantially sequence independent manner.

107. (Previously presented) The composition of claim 100, wherein the insertional enzyme complex comprises an enzyme selected from the group consisting of: transposases, Hermes transposase, and human immunodeficiency virus (HIV) integrases.

108. (Previously presented) The composition of claim 107, wherein the insertional enzyme complex comprises a transposase.

109. (Previously presented) The composition of claim 108, wherein the transposase is a Tn transposase.

110. (**Cancelled**)

111. (**Currently amended**) The composition of claim ~~110~~**109**, wherein the **Tn** transposase is a Tn5 transposase.

112. (Previously presented) The composition of claim 100, wherein the insert element comprises one or more molecular tags.

113. (Previously presented) The composition of claim 112, wherein one or more of the molecular tags comprises a sequencing adaptor.

114. (Previously presented) The composition of claim 113, wherein one or more of the sequencing adaptors comprises a barcode label.

115. (Previously presented) A composition comprising:

a permeabilized cell nucleus comprising:

(a) an insertional enzyme complex comprising a transposase enzyme; and

(b) a plurality of tagged nucleic acid fragments, wherein each tagged nucleic acid fragment comprises a first sequencing adapter and a second sequencing adapter; wherein each tagged nucleic acid fragment is derived from a region of open chromatin.

116. (Previously presented) The composition of claim 115, wherein the plurality of tagged nucleic acid fragments correspond to two or more regions of a genome.

117. (Previously presented) The composition of claim 115, wherein the plurality of tagged nucleic acid fragments correspond to at least 1,000 regions of a genome.

118. (Previously presented) The composition of claim 117, wherein the plurality of tagged nucleic acid fragments correspond to genome-wide regions of open chromatin.

119. (Previously presented) The composition of claim 117, wherein the transposase is a Tn transposase.

120. (Previously presented) The composition of claim 119, wherein the Tn transposase is a Tn5 transposase.

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Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01033
Page 00216

121. (Previously presented) A composition comprising:

a permeabilized cell nucleus comprising:

(a) an insertional enzyme complex comprising a transposase enzyme; and

(b) a plurality of tagged nucleic acid fragments, wherein each tagged nucleic acid fragment comprises a first sequencing adapter and a second sequencing adapter;

wherein the insertional enzyme complex and the tagged nucleic acid fragments are bound to one or more regions of open chromatin within the cell nucleus in a substantially sequence independent manner to form a high affinity macromolecule complex.

122. (Previously presented) The composition of claim 121, further comprising a plurality of divalent cations.

123. (Previously presented) The composition of claim 122, wherein the divalent cations are not chelated.

124. (Previously presented) The composition of claim 122, wherein the divalent cations are selected from the group consisting of: magnesium, manganese, or any combination thereof.

125. (Previously presented) The composition of claim 121, wherein the transposase is a Tn transposase.

126. (**Cancelled**)

127. (**Currently amended**) The composition of claim ~~126~~**125**, wherein the **Tn** transposase is a Tn5 transposase.

128. **(New)** The composition of claim 100, wherein (a) and (b) are contained within the permeabilized cell nucleus.

129. **(New)** The composition of claim 100, wherein the permeabilized cell nucleus is isolated from a cell.

130. **(New)** The composition of claim 100, wherein the permeabilized cell nucleus is contained within a cell.

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IPR2023-01033
Page 00218

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NOTICE OF ALLOWANCE AND FEE(S) DUE

77974 7590 04/03/2020
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BOZICEVIC, FIELD & FRANCIS LLP
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER
WILDER, CYNTHIA B

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 04/03/2020

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/418,796	05/21/2019	Paul Giresi	STAN-1111CON5	6413

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	07/06/2020

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: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PTOL-85 (Rev. 02/11)

10x Genomics, Inc. Exhibit 2010
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (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 04/03/2020
STANFORD UNIVERSITY OFFICE OF TECHNOLOGY LICENSING
BOZICEVIC, FIELD & FRANCIS LLP
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

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 transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/418,796	05/21/2019	Paul Giresi	STAN-1111CON5	6413

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	07/06/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
WILDER, CYNTHIA B	1637	435-006120

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 03-09 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 must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). 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. Fees submitted: ❑Issue Fee ❑Publication Fee (if required) ❑Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

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. _____

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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.
16/418,796	05/21/2019	Paul Giresi	STAN-1111CON5	6413

77974 7590 04/03/2020
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	

DATE MAILED: 04/03/2020

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.

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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 30 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. 16/418,796	Applicant(s) Giresi et al.	
	Examiner CYNTHIA B WILDER	Art Unit 1637	AIA (FITF) 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 12/13/2010.
   ☐ 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 98,100-109,111-125 and 127-130 . 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 a reply 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 _____.
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

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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 12/13/2019 is acknowledged. Claims 98, 100, 101, 1-2, 105, 106, 111 and 127 have been amended. Claims 1-97, 99, 110 and 126 have been canceled. All of the arguments and amendments have been thoroughly reviewed and considered. Applicant's arguments were found persuasive to obviate the rejections of the prior Office action. Accordingly, the rejections of the prior Office action are withdrawn.

2. The following is an examiner's statement of reasons for allowance: Applicant's amendment and arguments were found persuasive to obviate the rejections of the prior Office action. The closest prior art has already been made of record. While the teaching of Jouvenot (US 20110306042; citation previously made or record) discloses a permeabilizing cell membrane such that the structure of genomic DNA of the cells including nucleosomal or chromatic structure are not disrupt [0055], the prior art either alone or in combination, do not teach or suggest a composition comprising a cell nucleus comprising a plurality of polynucleotide molecules and an insertional enzyme complex comprising an insertion enzyme and an insert element comprising a predetermine sequence. No prior art either alone or in combination teach the composition further comprising open chromatin regions. Thus, the claimed invention comprising the combination of components which make up the composition is deemed to be novel and non-obvious over the teachings of 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 https://ppair-my.uspto.gov/pair/PrivatePair. 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

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/418,796	Giresi et al.
	Examiner	**Art Unit**
	CYNTHIA B WILDER	1637

CPC - Searched*		
Symbol	**Date**	**Examiner**
C12Q2521/301	03/31/2020	CW
C12Q1/6806	03/31/2020	CW
C12Q1/6869	03/31/2020	CW
C12Q2537/164	03/31/2020	CW
C12Q2521/507	03/31/2020	CW
C12Q2525/191	03/31/2020	CW
C12Q2535/122	03/31/2020	CW
C12Q1/6874	03/31/2020	CW
G16B20/00	03/31/2020	CW
G16B30/00	03/31/2020	CW
G16H50/20	03/31/2020	CW

CPC Combination Sets - Searched*		
Symbol	**Date**	**Examiner**

US Classification - Searched*			
Class	**Subclass**	**Date**	**Examiner**
435	91.2	03/31/2020	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	

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/418,796	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, review of related application and documents filed therein, search on global dossier, review of IDS, search on pubmed, citation search in post-dated art	03/31/2020	CW

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
C12Q2521/301		03/31/2020	CWCW
C12Q1/6806		03/31/2020	CW
C12Q1/6869		03/31/2020	CW
C12Q2537/164		03/31/2020	CW
C12Q2521/507		03/31/2020	CW
C12Q2525/191		03/31/2020	CW
C12Q2535/122		03/31/2020	CW
C12Q1/6874		03/31/2020	CW
G16B20/00		03/31/2020	CW
G16B30/00		03/31/2020	CW
G16H50/20		03/31/2020	CW

/CYNTHIA B WILDER/ Primary Examiner, Art Unit 1637	

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	CYNTHIA B WILDER	1637

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	03/31/2020								
-	1	-								
-	2	-								
-	3	-								
-	4	-								
-	5	-								
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-	42	-								

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
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	Examiner	**Art Unit**
	CYNTHIA B WILDER	1637

CLAIM		DATE								
Final	Original	03/31/2020								
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-	44	-								
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CLAIM		DATE								
Final	Original	03/31/2020								
-	95	-								
-	96	-								
-	97	-								
1	98	=								
-	99	-								
2	100	=								
3	101	=								
4	102	=								
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21	120	=								
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24	123	=								
25	124	=								
26	125	=								
-	126	-								
27	127	=								
28	128	=								
29	129	=								
30	130	=								

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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
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	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
G16B	/	30	/	00	I	2019-02-01
C12Q	/	1	/	6806	I	2013-01-01
G16H	/	50	/	20	I	2018-01-01
G16B	/	20	/	00	I	2019-02-01
C12Q	/	2521	/	301	A	2013-01-01
C12Q	/	2537	/	164	A	2013-01-01

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
C12Q	/	1	/	6869	I	1	1	2013-01-01
C12Q	/	2521	/	301	I	1	2	2013-01-01
C12Q	/	2537	/	164	I	1	3	2013-01-01
C12Q	/	1	/	6806	I	2	1	2013-01-01
C12Q	/	2521	/	301	I	2	2	2013-01-01
C12Q	/	2521	/	507	I	2	3	2013-01-01
C12Q	/	2525	/	191	I	2	4	2013-01-01
C12Q	/	2535	/	122	I	2	5	2013-01-01

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	30	
/CYNTHIA B WILDER/ Primary Examiner, Art Unit 1637	31 March 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office

Part of Paper No.: 20200331

10x Genomics, Inc. Exhibit 2010
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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/418,796	Giresi et al.
	Examiner	**Art Unit**
	CYNTHIA B WILDER	1637

INTERNATIONAL CLASSIFICATION				
CLAIMED				
C12P	/	19	/	34

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 30	
/CYNTHIA B WILDER/ Primary Examiner, Art Unit 1637 (Primary Examiner)	31 March 2020 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/418,796	Giresi et al.
	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
-	1	-	18	-	35	-	52	-	69	-	86	5	103	21	120
-	2	-	19	-	36	-	53	-	70	-	87	6	104	22	121
-	3	-	20	-	37	-	54	-	71	-	88	7	105	23	122
-	4	-	21	-	38	-	55	-	72	-	89	8	106	24	123
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-	12	-	29	-	46	-	63	-	80	-	97	15	114		
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-	16	-	33	-	50	-	67	-	84	3	101	19	118		
-	17	-	34	-	51	-	68	-	85	4	102	20	119		

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 30	
/CYNTHIA B WILDER/ Primary Examiner, Art Unit 1637 (Primary Examiner)	31 March 2020 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

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permeabilized nuclease and chromatin and (tag or adaptor or adapter)

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Page 2 of about 46,900 results (0.67 seconds)

www.protocols.io › view › bench-top-cut-amp-tag-z6hf9b6

Bench top CUT&Tag - Protocols.io

Apr 21, 2019 - Anneal each of Mosaic end - adapter A (ME-A) and Mosaic end - adapter B (ME-B) ... chromatin in the absence of magnesium, which activates nucleases. ... Dear Cut&Run/Tag team, ... CRITICAL STEP:All steps prior to the cell permeabilization are ... would you be able to share your 96 adaptor sequences?

www.epicypher.com › Blog

Still Using ChIP? Try CUT&RUN for Enhanced Chromatin ...

Jul 23, 2019 - ChIP-seq is the standard approach for chromatin mapping, but is impeded ... In ChIC, the protein of interested is first tagged by an antibody. ... Release Under Nuclease (CUT&RUN) approach evolved from ChIC, adapting ... In CUT&RUN, unfixed cells are immobilized on magnetic beads and permeabilized.
Missing: adaptor adapter)

bmcgenomics.biomedcentral.com › articles

Unbiased chromatin accessibility profiling by RED-seq ...

by PB Chen - 2014 - Cited by 12 - Related articles
Dec 15, 2014 - Conversely, micrococcal nuclease digestion of chromatin followed by deep ... First, we performed RE digestion on permeabilized cells without nuclear ... RSs are shown in red, yellow boxes (Step 3) represent RS-proximal adaptors, ... Poisson p-value threshold relative to local tag count, default: 0.0001 3.

www.freepatentsonline.com › ...

TRANSPOSITION OF NATIVE CHROMATIN FOR PERSONAL ...

The method of claim 82, wherein said cell or said nucleus is permeabilized with ... In some cases, the molecular tags can comprise sequencing adaptors, which ...

www.freepatentsonline.com › ...

In Situ ATAC Sequencing - Massachusetts Institute of ...

Jan 31, 2019 - The method according to claim 14, where the tagged genomic DNA fragment is sequenced. ... comprise sequencing adaptors, which may further comprise a barcode label. ... (B) A single HeLa nucleus, demonstrating that spatial information ... HeLa cells were permeabilized in swellable polymer, digested, ...

patents.google.com › patent

US20160060691A1 - Transposition of Native Chromatin for ...

The cell sample can be permeabilized to allow access for the insertional enzyme. ... In some cases, the molecular tags can comprise sequencing adaptors, which ... (a) CTCF footprints observed in ATAC-seq and DNase-seq data, at a specific ...

www.karger.com › Article › Fulltext

Open Chromatin in Plant Genomes - FullText - Cytogenetic ...

by W Zhang - 2014 - Cited by 13 - Related articles
Jun 6, 2014 - Open chromatin exhibits high sensitivity to DNase I cleavage. ... high molecular weight DNA, sequential ligation with 2 different adaptors, ... and ChIA-PET (chromatin interaction analysis by paired-end tag ... revealed by genomic footprinting of permeabilized cells using DNase I and ligation-mediated PCR.

www.cell.com › cell-systems › pdfExtended

Permanganate/S1 Nuclease Footprinting Reveals Non-B DNA ...

by F Kouzine - 2017 - Cited by 61 - Related articles
Feb 22, 2017 - Density of ssDNA-seq tags normalized as reads per kilobase per million (RPKM). ... cubations with permeabilized cells, isolated nuclei, or genomic ... Illumina adaptors were

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ligated with T4 DNA ligase, and the reaction was ...

journals.plos.org › plosone › article › journal.pone.0070994

The Innate Immunity Adaptor SARM Translocates to the ...

by CR Sethman - 2013 - Cited by 14 - Related articles

Jul 29, 2013 - Here, we report that SARM translocates to the nucleus of human ... to the Nucleus to Stabilize Lamins and Prevent DNA Fragmentation in ... Toll-like receptor adaptors, plays an important role in innate immunity signaling and apoptosis. ... An AU1 tag was added at the NH2 terminus to facilitate immunoblot ...

academic.oup.com › nar › article › doi › nar › gkz799

Unique and assay specific features of NOMe-, ATAC- and ...

by KJV Nordström - Cited by 1 - Related articles

Oct 4, 2019 - After the tagmentation of chromatin (fragmentation and tagging by ... Following the incubation of permeabilized cells or nuclei with M.CviPI, the extracted DNA is ... DNase I and inclusion of adapters with the transposase in ATAC puts ... by the transposase-assisted incorporation of NGS adaptors into open ...

Searches related to permeabilized nuclease and chromatin and (tag or adaptor or adapter)

cut and tag **henikoff**

cut and **run nature protocol**

pa-mnase

cut and tag **protocol**

cut and **run kit**

henikoff cut and **run**

cut and **run protocol**

a streamlined protocol and **analysis pipeline for cut&run** chromatin **profiling**

protein a-mnase

protein a-micrococcal nuclease

an efficient targeted nuclease **strategy for high-resolution mapping of dna binding sites**

cut&tag

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permeabilized nuclei and plurality of polynucleotide molecules

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www.brooklyn.cuny.edu › ahp › SDPS › SD.PS.polynuc.html

Polynucleotides - Science at a Distance

The Giant Molecules of Life. Polynucleotides. Nucleotides, Nucleotides are the building blocks of polymers called polynucleotides. Each nucleotide monomer ...
Missing: permeabilized nuclei plurality

People also ask

- Is a polynucleotide the same as a nucleic acid?
- Is ATP a polynucleotide?
- Which is a polynucleotide?
- What is polynucleotide synthesis?

Feedback

www.khanacademy.org › ... › Central dogma and the genetic code

Nucleic acids (article) | Khan Academy

In eukaryotes, such as plants and animals, DNA is found in the nucleus, ... The sugar molecule has a central position in the nucleotide, with the base attached to ...
Missing: permeabilized plurality

www.freepatentsonline.com › ...

SINGLE-CELL RNA SEQUENCING USING CLICK-CHEMISTRY

Dec 26, 2019 - A method for analyzing RNAs in a permeabilized cell or nucleus ... The method of claim 45, wherein the transferring is catalyzed by: (i) polynucleotide kinase; or (ii) ... with non-coding RNA molecules, long interspersed nuclear elements ... RNA is sequenced from a plurality of permeabilized cells or nuclei.

www.ncbi.nlm.nih.gov › books › NBK21644

Nucleic Acid Synthesis - Molecular Cell Biology - NCBI ...

Here we consider a few general principles governing the formation of polynucleotide chains in cells and briefly discuss some properties of the enzymes that ...
Missing: permeabilized plurality

patents.google.com › patent

US20110296556A1 - Polynucleotide molecules for gene ...

As used herein, "polynucleotide" refers to a nucleic acid molecule containing multiple nucleotides and generally refers both to "oligonucleotides" (a polynucleotide ...

www.google.com › patents

EP1579005A1 - Methods and compositions for analysis of ...

... the method comprising: (a) isolating a plurality of polynucleotide sequences from the ... The practice of conventional techniques in molecular biology, biochemistry, ... The terms "nucleic acid," "polynucleotide," and "oligonucleotide" are used ... For example, isolated chromatin or permeabilized nuclei are exposed to low ...

www.google.com › patents

Method for Generating A Three-Dimensional Nucleic Acid ...

Current methods involve extracting nucleic acid molecules from their native ... acid matrix is provided where a plurality of nucleic acid molecules, such as DNA or RNA, ... They are then

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treated with Proteinase K to **permeabilized** the tissue. ... As used herein, the term "**polynucleotide**" refers to a strand of nucleic acids that can ...

patentimages.storage.googleapis.com › ... PDF

US 2016/0060691 A1

May 20, 2014 - Provided herein is a method for analyzing **polynucleotides**. Such as genomic DNA ... prise: isolating **nuclei** from the population of cells; and com bining the isolated ... ing a **plurality** of **molecular** tags with an insertional enzyme into the ... 0015 The cell sample can be **permeabilized** to allow access for the ...

patents.justia.com › patent

US Patent Application for HIGH THROUGHPUT MULTIOMICS ...

Nov 7, 2019 - **Nucleic acid** fragments comprising a capture sequence (or a ... a **nucleus** to generate a **permeabilized nucleus**, for example using a detergent such as Triton X-100. ... (RNA) **molecules**, and wherein barcoding the **plurality** of **nucleic acid** ... A universal sequence can be a region of **nucleotide** sequence that is ...

google.com › patents

Patent US20060075523 - Abiotic stress responsive ... - Google

An isolated **nucleic acid molecule** comprising a **polynucleotide** selected from the ... determining the **nucleotide** sequence of a **plurality** of isolated **polynucleotides** to ... protoplast transformation, electroporation of partially **permeabilized** cells, ...

In order to show you the most relevant results, we have omitted some entries very similar to the 10 already displayed.
If you like, you can repeat the search with the omitted results included.

Searches related to permeabilized nuclei and plurality of polynucleotide molecules

nucleic acids function	**phosphodiester bond**
polynucleotide **structure**	polynucleotide **chain** of **dna contains**
polynucleotide **strand**	**number** of polynucleotide **strands in mrna**
nucleic acid synthesis	**nucleic acid structure**
dna structure	**nucleic acid biochemistry**
polynucleotide **synthesis**	polynucleotide **bond**

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permeabilized nuclease and chromatin and (tag or adaptor or adapter)

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research.fhcrc.org › henikoff › methods

HENIKOFF LAB -- Methods - Fred Hutch

Chromatin fractions extracted with low salt after micrococcal nuclease ... INTACT (Isolation of Nuclei TAgged in specific Cell Types) ... permeabilized and subjected to "Click" chemistry to attach a biotin tag to the incorporated base analog. ... DNA end polishing and direct ligation of adaptors permits sample-to-Illumina library ...

research.fhcrc.org › henikoff › recent-research › research-chromatin

HENIKOFF LAB -- Chromatin immunoprecipitation revisited

Micrococcal nuclease (MNase) cleaves double stranded DNA, and then "nibbles" on the ... Here intact permeabilized cells are incubated with an antibody against a ... Terri Bryson constructed a 6xHis and HA-tagged protein A-protein G-MNase ... Activation of the transposase within K562 cells ligates adaptors to chromatin ...

People also search for

cut&run reagent	epicypher cut and run
henikoff jg	cut&tag qpcr
mnase-seq protocol	cut and run peak calling

www.ncbi.nlm.nih.gov › pmc › articles › PMC5518929

Chromatin immunoprecipitation and an open chromatin assay ...

by S Yang - 2016 - Cited by 3 - Related articles

Jun 20, 2016 - It functions similarly to assays of DNase I hypersensitivity coupled with ... For ATAC-seq, cells are permeabilized to allow the modified bacterial Tn5 ... The "tagged" DNA fragments are then purified from their interacting proteins ... ends within open chromatin regions with unique Illumina library adaptors.

www.ncbi.nlm.nih.gov › pmc › articles › PMC5755553

Generation of Native Chromatin Immunoprecipitation ... - NCBI

by A Lorzadeh - 2017 - Cited by 3 - Related articles

Dec 12, 2017 - Cover the plate with a plastic seal, label "A-tail + BC", quick spin, and place it on ice. Proceed to step 4.5. Adaptor ligation. Retrieve from the -20 ° ...

en.wikipedia.org › wiki › Adapter_(genetics)

Adapter (genetics) - Wikipedia

An adapter or adaptor, or a linker in genetic engineering is a short, chemically synthesized, single-stranded or double-stranded oligonucleotide that can be ligated to the ends of other DNA ...

Missing: permeabilized nuclease (tag

www.biorxiv.org › content PDF

A streamlined protocol and analysis pipeline for ... - bioRxiv

by MP Meers - Cited by 3 - Related articles

Release Using Nuclease (CUT&RUN) (1), which is based on the chromatin ... To improve the purification protocol, we added a 6-His tag (32) into the pK19-pA-MN ... a Branson Sonifier blunt-end adapter at output level 4, 45 seconds intervals for ... In some experiments, cells were permeabilized and antibody was added and.

Missing: adaptor | Must include: adaptor

www.biorxiv.org › content PDF

CUT&Tag for efficient epigenomic profiling of small ... - bioRxiv

by HS Kaya-Okur - Cited by 49 - Related articles

Nuclease (pA-MNase) fusion protein in permeabilized cells without cross-linking9. ... it must be followed by DNA end polishing and adapter li- gation to prepare ...

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www.nature.com › nature protocols › protocols

GRID-seq for comprehensive analysis of global RNA ... - Nature

Jun 7, 2019 - **Chromatin** in higher eukaryotic nuclei is extensively bound by various RNA species. ... **DNA** by deep sequencing (GRID-seq) of fixed **permeabilized** nuclei that allows ... Next, Y-shaped **adaptors** are ligated to the paired-end **tags** for ... and displacement capability but lacks the 3' to 5' **exonuclease** activity.

www.illumina.com › dam › documents › products › research_reviews PDF

DNA Sequencing Methods Collection - Illumina

109 MNase-Seq: Micrococcal **Nuclease** Sequencing MAINE-Seq: ... 119 CATCH-IT: Covalent Attachment of **Tags** to Capture Histones and Identify Turnover ... sequence contains cell-identifying barcodes, 5' Illumina **adaptors**, and a T7 promoter. ... the **DNase** I digestion are carried out in vivo, within **permeabilized** cells.242.

www.protocols.io › view › bench-top-cut-amp-tag-z8hf9b6

Bench top CUT&Tag - Protocols.io

Apr 21, 2019 - Anneal each of Mosaic end - **adapter** A (ME-A) and Mosaic end - **adapter** B (ME-B) ... **chromatin** in the absence of magnesium, which activates **nucleases**. ... Dear Cut&Run/Tag team, ... CRITICAL STEP:All steps prior to the cell **permeabilization** are ... would you be able to share your 96 **adaptor** sequences?

Searches related to permeabilized nuclease and chromatin and (tag or adaptor or adapter)

cut and tag **henikoff**

henikoff cut and **run**

pa-mnase

cut and **run kit**

cut and **run nature protocol**

cut and **run protocol**

a streamlined protocol and **analysis pipeline for cut&run** chromatin **profiling**

protein a mnase

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WEST Search History for Application 16418796

Creation Date: 2020033116:27

Prior Art Searches

Query	DB	Hits	Op.	Plur.	Thes.	Date
(composition or mixture or reaction) and (permeabiliz$ same cell same nucleus)	PGPB, USPT, USOC, EPAB, DWPI	4883	ADJ	YES		08-24-2019
((composition or mixture or reaction) and (permeabiliz$ same cell same nucleus)) same (polynucleotide or DNA)	PGPB, USPT, USOC, EPAB, DWPI	4883	ADJ	YES		08-24-2019
(composition or mixture or reaction) same (permeabiliz$ same cell same nucleus)	PGPB, USPT, USOC, EPAB, DWPI	552	ADJ	YES		08-24-2019
16/418796	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-24-2019
L3l2 same (Transposase or HIV integrases or HERMES)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-24-2019
((composition or mixture or reaction) same (permeabiliz$ same cell same nucleus)) same (Transposase or HIV integrases or HERMES)	PGPB, USPT, USOC, EPAB, DWPI	14	ADJ	YES		08-24-2019
((composition or mixture or reaction) same (permeabiliz$ same cell same nucleus) same (Transposase or HIV integrases or HERMES)) same (adapter or tag$ or linker$)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-24-2019
20100120098.pn.		2	ADJ	YES		08-24-2019

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	PGPB, USPT, USOC, EPAB, DWPI					
((composition or mixture or reaction) same (permeabiliz$ same cell same nucleus) same (Transposase or HIV integrases or HERMES)) and chromatin	PGPB, USPT, USOC, EPAB, DWPI	14	ADJ	YES		08-24-2019
open chromatin	PGPB, USPT, USOC, EPAB, DWPI	1021	ADJ	YES		08-24-2019
(open chromatin) and ((composition or mixture or reaction) same (permeabiliz$ same cell same nucleus))	PGPB, USPT, USOC, EPAB, DWPI	20	ADJ	YES		08-24-2019
(open chromatin and (composition or mixture or reaction) same (permeabiliz$ same cell same nucleus)) and (Transposase or HIV integrases or HERMES)	PGPB, USPT, USOC, EPAB, DWPI	18	ADJ	YES		08-24-2019
(open chromatin) same (permeabiliz$ same cell same nucleus)	PGPB, USPT, USOC, EPAB, DWPI	11	ADJ	YES		08-24-2019
(20100120098.pn.) and (open same chromatin)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-24-2019
(20100120098.pn.) and (chromatin)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-24-2019
(open chromatin) and (Transposase or HIV integrases or HERMES)	PGPB, USPT, USOC, EPAB, DWPI	169	ADJ	YES		08-24-2019

(open chromatin and (Transposase or HIV integrases or HERMES)) and (adaptor$ or adapter$ or linker$ or tag$ or barcod$)	PGPB, USPT, USOC, EPAB, DWPI	163	ADJ	YES		08-24-2019
(open chromatin and (Transposase or HIV integrases or HERMES) and (adaptor$ or adapter$ or linker$ or tag$ or barcod$)) and (permeabiliz$ same cell same nucleus)	PGPB, USPT, USOC, EPAB, DWPI	32	ADJ	YES		08-24-2019
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(open chromatin and (Transposase or HIV integrases or HERMES) and (adaptor$ or adapter$ or linker$ or tag$ or barcod$)) and (composition or reaction mixture or mixture or kit)	PGPB, USPT, USOC, EPAB, DWPI	159	ADJ	YES		08-24-2019
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(open chromatin and (Transposase or HIV integrases or HERMES) and (adaptor$ or adapter$ or linker$ or tag$ or barcod$) and (composition or reaction mixture or mixture or kit) and (NP40 or digitonin or tween or steptolysin or lipid)) and complex	PGPB, USPT, USOC, EPAB, DWPI	111	ADJ	YES		08-24-2019
(open chromatin and (Transposase or HIV integrases or HERMES) and (adaptor$ or adapter$ or linker$ or tag$ or barcod$) and (composition or reaction mixture or mixture or kit) and (NP40 or digitonin or tween or steptolysin or lipid) and complex) and Tn5 transposase	PGPB, USPT, USOC, EPAB, DWPI	46	ADJ	YES		08-24-2019
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(open chromatin and (Transposase or HIV integrases or HERMES) and (adaptor$ or adapter$ or linker$ or tag$ or barcod$) and (composition or reaction mixture or mixture or kit) and (NP40 or digitonin or tween or steptolysin or lipid) and complex and Tn5) and (magnesium or manganese)	PGPB, USPT, USOC, EPAB, DWPI	31	ADJ	YES		08-24-2019
2015111788	PGPB, USPT, USOC, EPAB, DWPI	3	ADJ	YES		08-24-2019
20150111788	PGPB, USPT, USOC, EPAB, DWPI	3	ADJ	YES		08-24-2019
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20100120098.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
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(20100120098.pn.) and chromatin	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019

20100120098.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(20100120098.pn.) and (cell same nucle$ or nucleus or nuclei or peameabil$)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20100120098.pn.) and predetermin$	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
(20100120098.pn.) and (adapter or adaptor)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
20140111788.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(20140111788.pn.) and chromatin	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
(20140111788.pn.) and (premeabil$ same (cell or nucle$))	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
premeabiliz$ cell nucle$	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
(20100120098.pn.) and (cell same nucle$ or nucleus or nuclei or permeabil$)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019

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(20140111788.pn.) and (cell same nucle$ or nucleus or nuclei or permeabil$)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
permeabiliz$ cell nucle$	PGPB, USPT, USOC, EPAB, DWPI	55	ADJ	YES		08-26-2019
(20140111788.pn.) and (cell or nucle$ or nucleus or nuclei or permeabil$ or chromatin)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
(permeabiliz$ cell nucle$) and transpos$	PGPB, USPT, USOC, EPAB, DWPI	11	ADJ	YES		08-26-2019
(permeabiliz$ cell nucle$) same (Mixture or composition or kit)	PGPB, USPT, USOC, EPAB, DWPI	8	ADJ	YES		08-26-2019
(permeabiliz$ cell nucle$) same (transpos$ or adapter or adaptor or sequencing tag$ or tag$ or barcod$ or nuclear localization signal)	PGPB, USPT, USOC, EPAB, DWPI	5	ADJ	YES		08-26-2019
US-20190211404-A1.did.	PGPB	1	ADJ	YES		08-26-2019
2011306042.pn.	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
20113006042.pn.	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
20110306042.pn.	PGPB, USPT, USOC,	2	ADJ	YES		08-26-2019

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	EPAB, DWPI					
(20110306042.pn.) and (cell or nucle$ or nucleus or nuclei or permeabil$ or chromatin)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(20110306042.pn. and (cell or nucle$ or nucleus or nuclei or permeabil$ or chromatin)) and (open$)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20110306042.pn. and (cell or nucle$ or nucleus or nuclei or permeabil$ or chromatin) and (open$)) and (chromat$ or chromatin or transpos$ or Tn5)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20110306042.pn. and (cell or nucle$ or nucleus or nuclei or permeabil$ or chromatin) and (open$)) and (transpos$ or Tn5)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
(20110306042.pn. and (cell or nucle$ or nucleus or nuclei or permeabil$ or chromatin) and (open$)) and (transpos$ or Tn5 or adapter or adaptor or sequencing tag$ or barcode)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
(20110306042.pn. and (cell or nucle$ or nucleus or nuclei or permeabil$ or chromatin) and (open$)) and (transpos$ or Tn5 or adapter or adaptor or sequencing tag$ or barcode or recombina$)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20110306042.pn. and (cell or nucle$ or nucleus or nuclei or permeabil$ or chromatin) and (open$) and (transpos$ or Tn5 or adapter or adaptor or sequencing tag$ or barcode or recombina$)) and sequencing	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
(20110306042.pn. and (cell or nucle$ or nucleus or nuclei or permeabil$ or chromatin) and (open$) and (transpos$ or Tn5 or adapter or adaptor or sequencing tag$ or barcode or recombina$)) and sequenc$	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
WO 2011050147	PGPB, USPT,	1	ADJ	YES		08-26-2019

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	USOC, EPAB, DWPI					
(20100120098.pn.) and (cell$ same transpo$)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20100120098.pn.) and (Mixture or composition or kit)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(20100120098.pn.) and ((Mixture or composition or kit) same NP40 digitonin or tween or steptolysin or cationic lipids)	PGPB, USPT, USOC, EPAB, DWPI	n/a	ADJ	YES		08-26-2019
(20100120098.pn.) and ((Mixture or composition or kit) same (digitonin or tween or NP40 or steptolysin or cationic lipid))	PGPB, USPT, USOC, EPAB, DWPI	n/a	ADJ	YES		08-26-2019
(20100120098.pn. and (Mixture or composition or kit)) and (NP40 or digitonin or tween or steptolysin or cationic lipid)	PGPB, USPT, USOC, EPAB, DWPI	n/a	ADJ	YES		08-26-2019
(20100120098.pn.) and (NP40 or digitonin or tween or streptolysin or captionic lipid)	PGPB, USPT, USOC, EPAB, DWPI	n/a	ADJ	YES		08-26-2019
(NP40 or digitonin or tween or streptolysin or captionic lipid)	PGPB, USPT, USOC, EPAB, DWPI	n/a	ADJ	YES		08-26-2019
20100120098	PGPB, USPT, USOC, EPAB, DWPI	14	ADJ	YES		08-26-2019
20100120098.pn.	PGPB,	2	ADJ	YES		08-26-2019

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	USPT, USOC, EPAB, DWPI					
(20100120098.pn.) and (NP40 or digitonin or tween or steptolysin or cationic lipids)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20100120098.pn.) and (NP40 or digitonin or tween or steptolysin or cationic lipids)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
((20110306042.pn. and (cell or nucle$ or nucleus or nuclei or permeabil$ or chromatin) and (open$) and (transpos$ or Tn5 or adapter or adaptor or sequencing tag$ or barcode or recombina$)) and sequenc$)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
((20100120098.pn.) and (Mixture or composition or kit))	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(((20100120098.pn.) and (Mixture or composition or kit))) and two	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(20100120098.pn.) and moiet$	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20100120098.pn.) and transposase	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(20100120098.pn.) and (nuclear localization signal)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019

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(nuclear localization signal)	PGPB, USPT, USOC, EPAB, DWPI	15167	ADJ	YES		08-26-2019
((nuclear localization signal)) and ((20100120098) or (20100120098.pn.))	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
20110306042.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(20110306042.pn.) and (nuclear same localization same signal)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
(20110306042.pn.) and (nuclear or localization or signal$)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(20110306042.pn.) and (nucl$ or local$ or signal$)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(20100120098) and (insert$)	PGPB, USPT, USOC, EPAB, DWPI	13	ADJ	YES		08-26-2019
(20100120098.pn.) and (insert$)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20100120098.pn.) and (transposases or integrase)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019

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(20100120098.pn.) and (molecular tag$ or tag$ or adapter or adaptor)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(20100120098.pn.) and (barcod$)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20100120098.pn.) and (regions or multiple or plurality or genome)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20100120098.pn. and (regions or multiple or plurality or genome)) and tagged nucleic acid	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20100120098) and (cell or nucle$ or nucleus or nuclei or permeabil$ or chromatin or genome)	PGPB, USPT, USOC, EPAB, DWPI	14	ADJ	YES		08-26-2019
(20100120098.pn.) and (cell or nucle$ or nucleus or nuclei or permeabil$ or chromatin or genome)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(20100120098) and ((adapter or adaptor) and (first and second))	PGPB, USPT, USOC, EPAB, DWPI	13	ADJ	YES		08-26-2019
(20100120098.pn.) and ((adapter or adaptor) and (first and second))	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20100120098.pn. and ((adapter or adaptor) and (first and second))) and (genom$ same region)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019

(20100120098.pn.) and (genom$ same region)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20100120098.pn.) and ((genom$ same region) or ((plurality or multiple) same region))	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20100120098.pn.) and tagged nucleic acid	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20100120098.pn.) and tagged same (nucleic acid or region or fragment)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(20100120098.pn. and tagged same (nucleic acid or region or fragment)) and (whole genome or (multiple or region))	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20100120098.pn.) and (magnesium or manganese or Mg or Mn or cation or divalent)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(20110306042.pn.) and (open$ or heterochromatin)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20100120098.pn.) and heterochromatin	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
20150111788.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019

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(20150111788.pn.) and (open$ or heterochromatin)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(open$ same chromatin)	PGPB, USPT, USOC, EPAB, DWPI	3210	ADJ	YES		08-26-2019
((open$ same chromatin)) and transposase	PGPB, USPT, USOC, EPAB, DWPI	304	ADJ	YES		08-26-2019
((open$ same chromatin) and transposase) and permeabilized	PGPB, USPT, USOC, EPAB, DWPI	66	ADJ	YES		08-26-2019
((open$ same chromatin) and transposase and permeabilized) and tagged nucleic acid	PGPB, USPT, USOC, EPAB, DWPI	6	ADJ	YES		08-26-2019
open chromatin	PGPB, USPT, USOC, EPAB, DWPI	1021	ADJ	YES		08-26-2019
(open chromatin) same access$	PGPB, USPT, USOC, EPAB, DWPI	223	ADJ	YES		08-26-2019
(open chromatin same access$) and transpos$	PGPB, USPT, USOC, EPAB, DWPI	98	ADJ	YES		08-26-2019
(open chromatin same access$ and transpos$) and (sequencing or adaptor or tagging)	PGPB, USPT, USOC, EPAB, DWPI	84	ADJ	YES		08-26-2019

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(20160145685.pn. or 20160145685.pn. or 20110185442.pn. or 2015111788.pn.) and (sequencing or adaptor or tagging)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
((20160145685.pn. or 20160145685.pn. or 20110185442.pn. or 2015111788.pn.) and (sequencing or adaptor or tagging)) and (open chromatin)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
((20160145685.pn. or 20160145685.pn. or 20110185442.pn. or 2015111788.pn.) and (sequencing or adaptor or tagging) and open chromatin) and transpo$	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(open chromatin region$) or (open chromatin same regions) or (open chromatin same fragments)	PGPB, USPT, USOC, EPAB, DWPI	509	ADJ	YES		08-26-2019
(open chromatin region$) or (open chromatin same regions) or (open chromatin same fragments) or (open chromatin near region)	PGPB, USPT, USOC, EPAB, DWPI	509	ADJ	YES		08-26-2019
((open chromatin region$) or (open chromatin same regions) or (open chromatin same fragments) or (open chromatin near region)) and (transpo$)	PGPB, USPT, USOC, EPAB, DWPI	313	ADJ	YES		08-26-2019
((open chromatin region$) or (open chromatin same regions) or (open chromatin same fragments) or (open chromatin near region) and (transpo$)) and permeabiliz$	PGPB, USPT, USOC, EPAB, DWPI	79	ADJ	YES		08-26-2019
((open chromatin region$) or (open chromatin same regions) or (open chromatin same fragments) or (open chromatin near region) and (transpo$) and permeabiliz$) and (adaptor or adapter)	PGPB, USPT, USOC, EPAB, DWPI	32	ADJ	YES		08-26-2019
20120064517.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019

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(20120064517.pn.) and (composition or mixture)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(20120064517.pn.) and (transposition or transposase or transposon)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-26-2019
(20120064517.pn.) and (sequencing)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(20120064517.pn. and (composition or mixture)) and (sequencing)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
open chromatin regions	PGPB, USPT, USOC, EPAB, DWPI	109	ADJ	YES		08-26-2019
(open chromatin regions) and transposition	PGPB, USPT, USOC, EPAB, DWPI	35	ADJ	YES		08-26-2019
14/892911	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
14/359877	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
(14/359877) and (open$ chromatin)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019

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(14/892911) and (open$ chromatin)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-26-2019
61/629555	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(61/629555) and (open$ chromatin)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-26-2019
(open$ chromatin regions)	PGPB, USPT, USOC, EPAB, DWPI	109	ADJ	YES		08-26-2019
((open$ chromatin regions)) same (genomic or DNA)	PGPB, USPT, USOC, EPAB, DWPI	84	ADJ	YES		08-26-2019
((open$ chromatin regions) same (genomic or DNA)) and (composition or kit or mixture)	PGPB, USPT, USOC, EPAB, DWPI	78	ADJ	YES		08-26-2019
((open$ chromatin regions) same (genomic or DNA) and (composition or kit or mixture)) and sequencing	PGPB, USPT, USOC, EPAB, DWPI	71	ADJ	YES		08-26-2019
((open$ chromatin regions) same (genomic or DNA) and (composition or kit or mixture)) and transpos$	PGPB, USPT, USOC, EPAB, DWPI	45	ADJ	YES		08-26-2019
PERMEABILIZED CELL NUCLEUS	PGPB, USPT, USOC, EPAB, DWPI	25	ADJ	YES		03-30-2020

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14/784250	PGPB, USPT, USOC, EPAB, DWPI	4	ADJ	YES		03-30-2020
permeabilized cell nucleus same polynucleotide	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		03-30-2020
permeabilized nucleus	PGPB, USPT, USOC, EPAB, DWPI	73	ADJ	YES		03-30-2020
(permeabilized nucleus) same polynucleotide	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		03-30-2020
(permeabilized nucleus) and polynucleotide	PGPB, USPT, USOC, EPAB, DWPI	51	ADJ	YES		03-30-2020
(permeabilized nucleus and polynucleotide) and chromatin	PGPB, USPT, USOC, EPAB, DWPI	45	ADJ	YES		03-30-2020
(permeabilized nucleus and polynucleotide and chromatin) and tagged fragment	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		03-30-2020
(permeabilized nucleus and polynucleotide and chromatin) and polynucleotide	PGPB, USPT, USOC, EPAB, DWPI	45	ADJ	YES		03-30-2020
(permeabilized nucleus and polynucleotide and chromatin and polynucleotide) and transposase	PGPB, USPT, USOC, EPAB, DWPI	20	ADJ	YES		03-30-2020

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permeabilized same (nuclei or nucleus)	PGPB, USPT, USOC, EPAB, DWPI	4666	ADJ	YES		03-30-2020
permeabilized same (nuclei or nucleus)	PGPB, USPT, USOC, EPAB, DWPI	4666	ADJ	YES		03-30-2020
(permeabilized same (nuclei or nucleus)) same (polynucleotides or DNA or fragments or oligonucleotide or nucleic acid)	PGPB, USPT, USOC, EPAB, DWPI	1016	ADJ	YES		03-30-2020
(permeabilized same (nuclei or nucleus) same (polynucleotides or DNA or fragments or oligonucleotide or nucleic acid)) same (insertional enzyme or transposase or Tn5 or MuA or Vibhar)	PGPB, USPT, USOC, EPAB, DWPI	29	ADJ	YES		03-30-2020
(permeabilized same (nuclei or nucleus) same (polynucleotides or DNA or fragments or oligonucleotide or nucleic acid) same (insertional enzyme or transposase or Tn5 or MuA or Vibhar)) same (tag$ or antibody or adaptor or adapter or affinity tag)	PGPB, USPT, USOC, EPAB, DWPI	18	ADJ	YES		03-30-2020
permeabilized same (nuclei or nucleus)	PGPB, USPT, USOC, EPAB, DWPI	4668	ADJ	YES		03-31-2020
permeabilized same (nuclei or nucleus)	PGPB, USPT, USOC, EPAB, DWPI	4668	ADJ	YES		03-31-2020
(permeabilized same (nuclei or nucleus)) same (polynucleotides or DNA or fragments or oligonucleotide or nucleic acid)	PGPB, USPT, USOC, EPAB, DWPI	1016	ADJ	YES		03-31-2020
(permeabilized same (nuclei or nucleus) same (polynucleotides or DNA or fragments or oligonucleotide or nucleic acid)) same (insertional enzyme or transposase or Tn5 or	PGPB, USPT, USOC, EPAB,	29	ADJ	YES		03-31-2020

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MuA or Vibhar)	DWPI					
(permeabilized same (nuclei or nucleus) same (polynucleotides or DNA or fragments or oligonucleotide or nucleic acid) same (insertional enzyme or transposase or Tn5 or MuA or Vibhar)) same (tag$ or antibody or adaptor or adapter or affinity tag)	PGPB, USPT, USOC, EPAB, DWPI	18	ADJ	YES		03-31-2020
20160053253 or 20140235506	PGPB, USPT, USOC, EPAB, DWPI	4	ADJ	YES		03-31-2020
(20160053253 or 20140235506) and (nuclei or nucleus)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		03-31-2020
(20160053253 or 20140235506 and (nuclei or nucleus)) and (permeab$)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		03-31-2020
permeabil$ same (cell or nuclei or nucleus)	PGPB, USPT, USOC, EPAB, DWPI	135371	ADJ	YES		03-31-2020
(permeabil$ same (cell or nuclei or nucleus))	PGPB, USPT, USOC, EPAB, DWPI	135371	ADJ	YES		03-31-2020
(permeabil$ same (cell or nuclei or nucleus)) same chromatin	PGPB, USPT, USOC, EPAB, DWPI	1085	ADJ	YES		03-31-2020
(permeabil$ same (cell or nuclei or nucleus) same chromatin) same tag$	PGPB, USPT, USOC, EPAB, DWPI	24	ADJ	YES		03-31-2020
(permeabil$ same (cell or nuclei or nucleus) same chromatin same tag$) same (fragment	PGPB, USPT,	17	ADJ	YES		03-31-2020

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or polynucleotide or DNA or nucleic acid)	USOC, EPAB, DWPI					
2011306042 or WO 2011050147	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		03-31-2020
2011306042 or WO 2011050147	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		03-31-2020
20110306042 or WO 2011050147	PGPB, USPT, USOC, EPAB, DWPI	3	ADJ	YES		03-31-2020
20100120098.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		03-31-2020
(20100120098.pn.) and (nuclei or nucleus or membrane)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		03-31-2020
16/418796	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		03-31-2020
(16/418796) and (insert element same predetermined sequence)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		03-31-2020

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PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (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.

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STANFORD UNIVERSITY OFFICE OF TECHNOLOGY LICENSING
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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 transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/418,796	05/21/2019	Paul Giresi	STAN-1111CON5	6413

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~~ UNDISCOUNTED	~~$500~~ $1000	$0.00	$0.00	~~$500~~ $1000	07/06/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
WILDER, CYNTHIA B	1637	435-006120

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 03-09 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 must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). 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. Fees submitted: ☒ Issue Fee ☒ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

☒ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 50-0815

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 1, 2020

Typed or printed name James S. Keddie Registration No. 48920

PTOL-85 Part B (08-18) Approved for use through 01/31/2020 OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

10x Genomics, Inc. Exhibit 2010
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-01033
Page 00260

Electronic Patent Application Fee Transmittal

Application Number:	16418796
Filing Date:	21-May-2019
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-1111CON5

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

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:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
UTILITY APPL ISSUE FEE	1501	1	1000	1000
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1000**

Electronic Acknowledgement Receipt	
EFS ID:	39890560
Application Number:	16418796
International Application Number:	
Confirmation Number:	6413
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-1111CON5
Receipt Date:	01-JUL-2020
Filing Date:	21-MAY-2019
Time Stamp:	18:57:05
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$1000
RAM confirmation Number	E202071I57212393
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-1111CON5_IssueFeeTransmittal.pdf	1243391 57105d64729657be75cf5c41620ddb153cd4f7e0	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	31865 e0e19717cd85d1bd19ad3ca48a52dc6e10cc317d	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1275256		

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.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/418,796	08/11/2020	10738357	STAN-1111CON5	6413

77974 7590 07/22/2020
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 0 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.

IR103 (Rev. 10/09)

AO 120 (Rev. 08/10)

TO:	Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED 8/24/2022	U.S. DISTRICT COURT for the District of Delaware
PLAINTIFF 10X GENOMICS, INC.		DEFENDANT PARSE BIOSCIENCES, INC. and THE BOARD OF TRUSTEES OF LELAND STANFORD JUNIOR UNIVERSITY

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	10,155,981	12/18/2018	10x Genomics, Inc.
2	10,697,013	6/30/2020	10x Genomics, Inc.
3	10,240,197	3/26/2019	10x Genomics, Inc.
4	10,150,995	12/11/2018	The Board of Trustees of the Leland Stanford Junior University
5	10,619,207	4/14/2020	The Board of Trustees of the Leland Stanford Junior University

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

ADDENDUM TO AO 120 (ADDITIONAL PATENTS)

DOCKET NO.	DATE FILED 8/24/2022	U.S. DISTRICT COURT for the District of Delaware
PLAINTIFF 10X GENOMICS, INC.		DEFENDANT PARSE BIOSCIENCES, INC. and THE BOARD OF TRUSTEES OF LELAND STANFORD JUNIOR UNIVERSITY

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
6	10,738,357	August 11, 2020	The Board of Trustees of the Leland Stanford Junior University
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading		
	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
21			
22			
23			
24			
25			

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
16/418,796	2019-May-21

(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		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 #
16/418,796	**10/26/2022 03:26:49 PM ET**	**STAN-1111CON5**

Title of Invention

TRANSPOSITION OF NATIVE CHROMATIN FOR PERSONAL EPIGENOMICS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	10738357
CONFIRMATION #	6413	FILED BY	Maureen Fugate
PATENT CENTER #	61107140	FILING DATE	05/21/2019
CUSTOMER #	77974	FIRST NAMED INVENTOR	Paul Giresi
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	David Casimir

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
S12-404 41398.308 Signed POA.pdf	2	Power of Attorney	1447 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
S12-404 41398.308 Signed POA.pdf	67272095C98B46AB19208F9C0CA37CA3F42B6AC00F4D2F601F1497B6A4D568BBB73B0042B891220712DCB132AFFD64C24EBD4CABEDE8D6BCB7270A86C4E5393C

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.

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
16/418,796	05/21/2019	Paul Giresi	STAN-1111CON5

CONFIRMATION NO. 6413

166677
Casimir Jones, S.C.
2275 Deming Way Ste 310
Middleton, WI 53562

POA ACCEPTANCE LETTER

OC000000136783183

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**.

/ctuazon/