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Application Number: 16418889 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-1111CON6
	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.

PARSE EX.1007.003

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.

PARSE EX.1007.004

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.

PARSE EX.1007.005

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.

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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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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-1111CON6

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-1111CON6

	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	

PARSE EX.1007.009

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-1111CON6

	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.	

PARSE EX.1007.010

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-1111CON6

	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.	

PARSE EX.1007.011

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-1111CON6

	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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FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	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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	Application Number	
	Filing Date	
	First Named Inventor	Paul Giresi
	Art Unit	
	Examiner Name	
	Attorney Docket Number	STAN-1111CON6

	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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NON-PATENT LITERATURE DOCUMENTS Remove

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	
	First Named Inventor	Paul Giresi
	Art Unit	
	Examiner Name	
	Attorney Docket Number	STAN-1111CON6

	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	

PARSE EX.1007.014

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-1111CON6

	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-1111CON6

CERTIFICATION STATEMENT

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

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

OR

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

See attached certification statement.

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

☒ A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/James S. Keddie/	Date (YYYY-MM-DD)	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.**

PARSE EX.1007.016

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.

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Electronically Filed

INFORMATION DISCLOSURE STATEMENT Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450		
	Attorney Docket	STAN-1111CON6
	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-1111CON6

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:	36078106
Application Number:	16418889
International Application Number:	
Confirmation Number:	2173
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-1111CON6
Receipt Date:	21-MAY-2019
Filing Date:	
Time Stamp:	19:38:32
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	052219INTEFSW19390100
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-1111CON6_Track-I-Request.pdf	153028 b356a0598e825a44348b3072088aed5aa614faca	no	2
Warnings:					
Information:					
2	Application Data Sheet	STAN-1111CON6_ADS.pdf	1562113 d3e02766291e3a4b9b162db8aa9c95bc8aa7c0a4	no	8
Warnings:					
Information:					
3	Oath or Declaration filed	STAN-1111_Declaration.pdf	2631268 33851ffd2e22ea833687b722be9a9e464b6a3655	no	4
Warnings:					
Information:					
4	Power of Attorney	STAN-1111CON6_GPOA.pdf	344481 965c1d010e1ea668444d5503f3deed731e5c262b	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-1111CON6_Prelim_Amendment.pdf	66424 c9340f117e2bc0dc090aeaf266ea2bd21844a92f	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-1111CON6_IDS.pdf	1037598 525e77acbc158f20b0ab6089faaa8a852a673dc5	no	10
Warnings:					
Information:					
8	Transmittal Letter	STAN-1111CON6_IDS-Transmittal.pdf	30746 e0494e73dc76697d9ffb9907a781a146f8c1a92b	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	40161 c1fa282f0790a2167f50ed06ea8645e5bb2d8720	no	2
Warnings:					

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Information:	
Total Files Size (in bytes):	6954022

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.

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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-1111CON6
	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	State/Province	Country of Residence
Palo Alto	CA	US

Mailing Address of Inventor:

Address 1	264 Durand Way
Address 2	

City	State/Province	Postal Code	Country
Palo Alto	CA	94304	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	State/Province	Country of Residence
Redwood City	CA	US

Mailing Address of Inventor:

Address 1	3523 Altamont Way
Address 2	

City	State/Province	Postal Code	Country
Redwood City	CA	94062	US

Inventor 3 Remove

Legal Name

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

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

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	STAN-1111CON6
	Application Number	
Title of Invention	Transposition of Native Chromatin for Personal Epigenomics	

City	Stanford	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

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

Mailing Address of Inventor:

Address 1	765A Live Oak		
Address 2			
City	Menlo Park	State/Province	CA
Postal Code	94025	Country	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-1111CON6	Small Entity Status Claimed	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	24	Suggested Figure for Publication (if any)	

Filing By Reference :

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	STAN-1111CON6
	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

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	STAN-1111CON6
	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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	STAN-1111CON6
	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

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	STAN-1111CON6
	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

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	STAN-1111CON6
	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.

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VIII-4-1-1-4	Inventor's Signature: (The signature must be that of the inventor, not that of the agent)	
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VIII-4-1-2-1	Name (LAST, First)	BUENROSTRO, Jason D.
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VIII-4-1-1-3	Mailing Address:	264 Durand Way Palo Alto, CA 94304 United States of America
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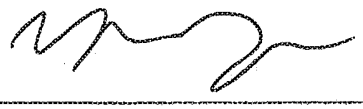
VIII-4-1-3-4	Inventor's Signature: (The signature must be that of the inventor, not that of the agent)	
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Application Number	
Filing Date	
First Named Inventor	Paul GIRESI
Title	TRANSPOSITION OF NATIVE CHROMATIN FOR PERSONAL EPIGENOMICS
Art Unit	
Examiner Name	
Attorney Docket Number	STAN-1111CON6

SIGNATURE of Applicant or Patent Practitioner

Signature	/James S. Keddie/	Date (Optional)	May 21, 2019
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Title	Executive Director, Office of Technology Licensing Stanford University		

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(54) **Title**: TRANSPOSITION INTO NATIVE CHROMATIN FOR PERSONAL EPIGENOMICS

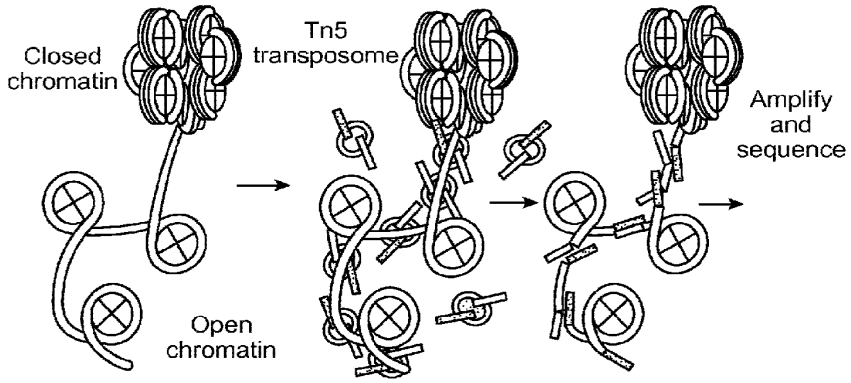

FIG. 1A

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

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TRANSPOSITION INTO NATIVE CHROMATIN FOR PERSONAL EPIGENOMICS

GOVERNMENT SUPPORT

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

CROSS-REFERENCING

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

BACKGROUND

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

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SUMMARY

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

INCORPORATION BY REFERENCE

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

BRIEF DESCRIPTION OF THE FIGURES

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DEFINITIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Other definitions of terms may appear throughout the specification.

DESCRIPTION OF EXEMPLARY EMBODIMENTS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Compositions

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

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

Kits

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

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

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

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

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

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Embodiments

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

EXAMPLES

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

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

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

Materials and Methods

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

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

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

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

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

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

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

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

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

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

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

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

Data Analysis

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

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

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

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

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

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

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

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

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

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

Results

ATAC-seq probes chromatin accessibility with transposons

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

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

ATAC-seq insert sizes disclose nucleosome positions

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

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

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

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ATAC-seq reveals patterns of nucleosome-TF spacing

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

ATAC-seq footprints infer factor occupancy genome-wide

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

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allowing reconstruction of regulatory networks.

ATAC-seq enables epigenomic analysis on clinical timescales

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

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

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

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

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

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autoimmunity, and neuropsychiatric disorders are viable applications.

Example 2. Single-Cell ATAC-seq

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

Transposases can serve as an open-chromatin stain

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

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

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

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Example 3. Quality control

Assay for 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.

PARSE EX.1007.089

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.

PARSE EX.1007.090

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.

PARSE EX.1007.091

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:

PARSE EX.1007.092

(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.

PARSE EX.1007.094

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.

PARSE EX.1007.095

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.

PARSE EX.1007.096

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.

PARSE EX.1007.097

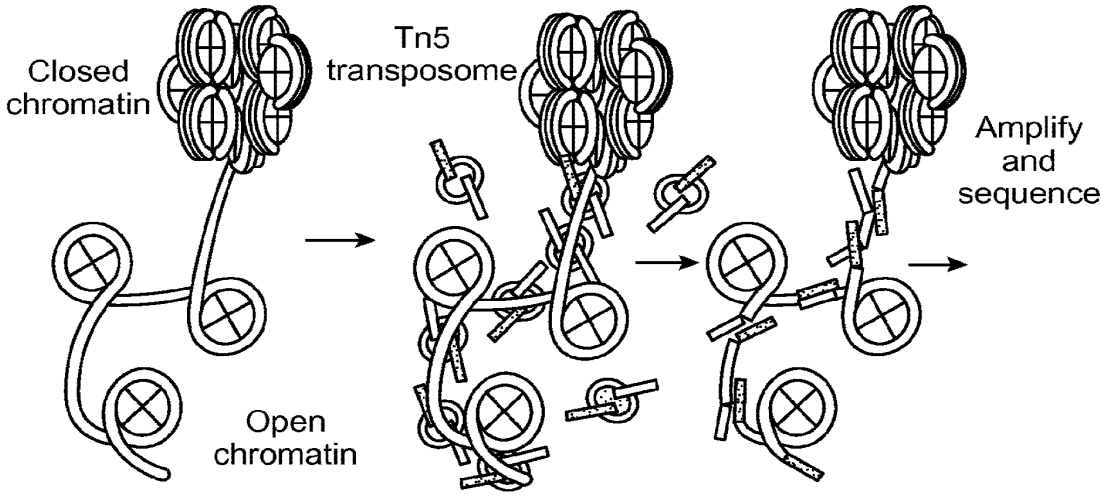

FIG. 1A

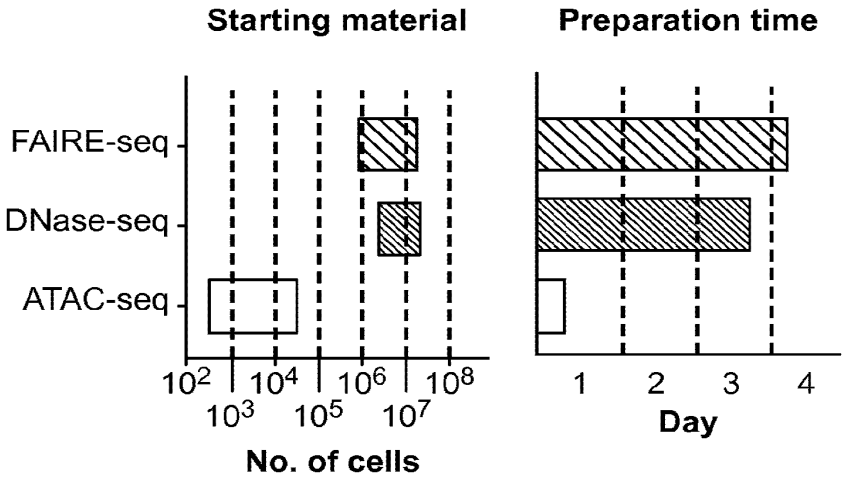

FIG. 1B

PARSE EX.1007.098

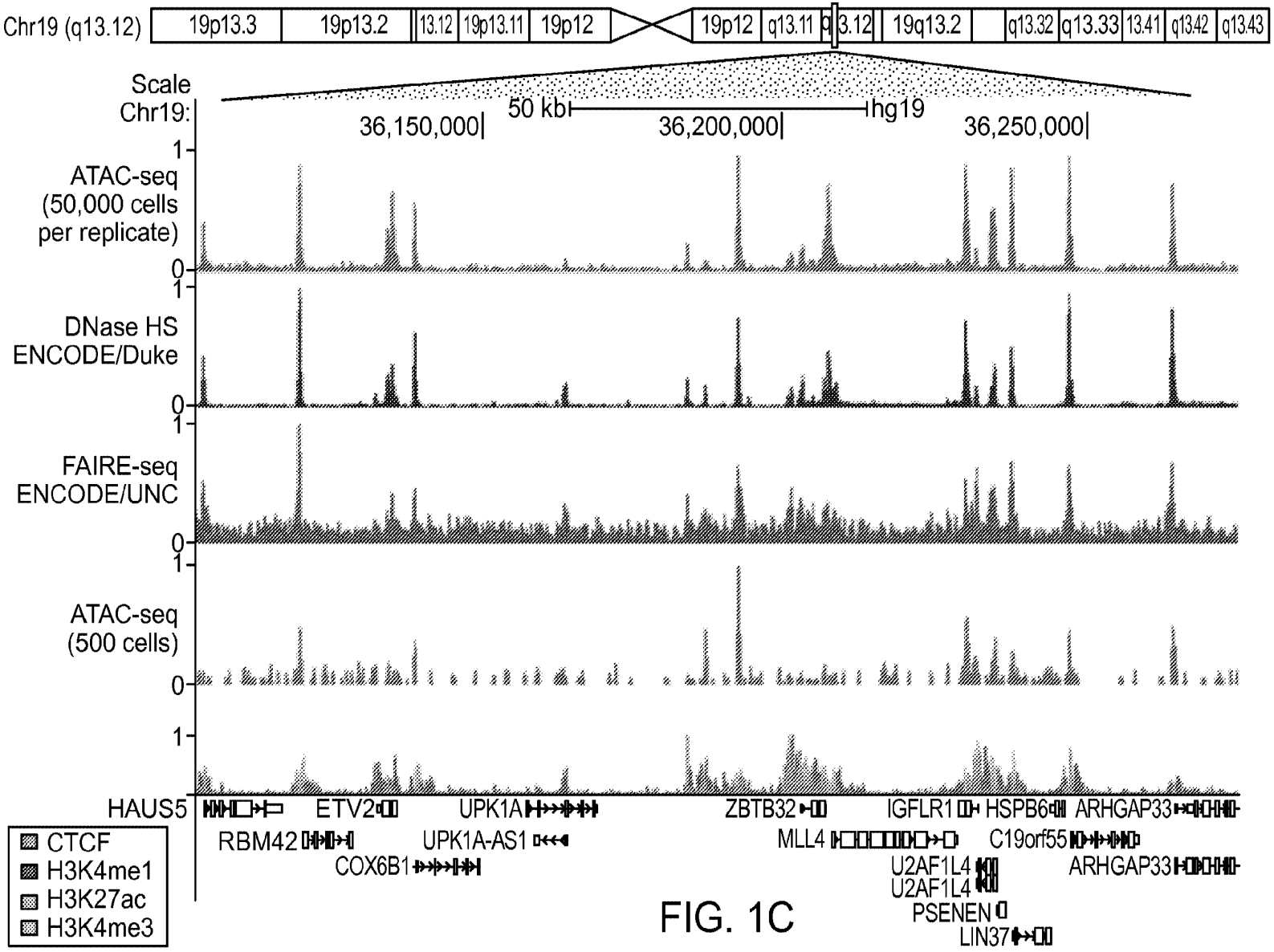

FIG. 1C

PARSE EX.1007.099

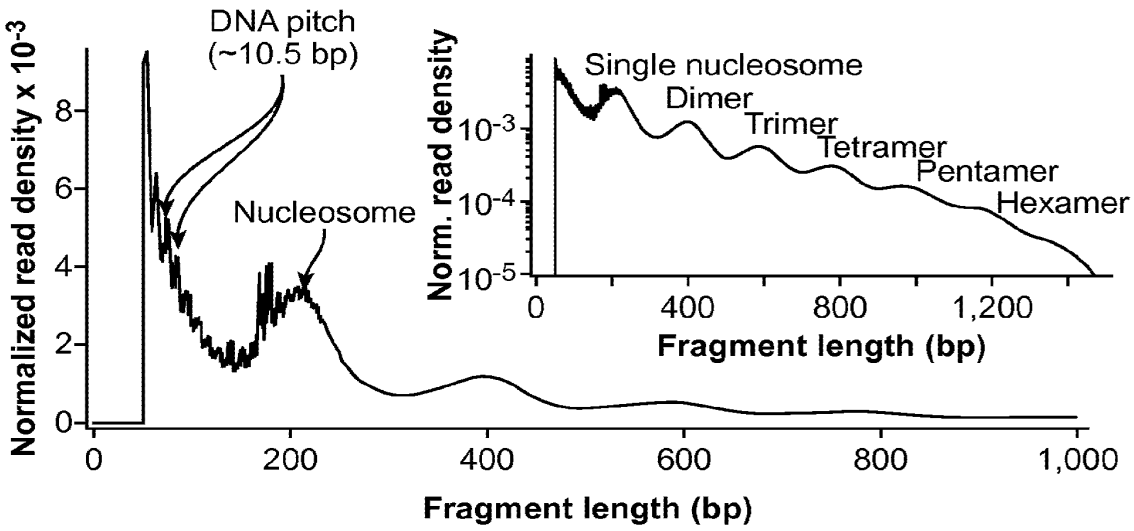

FIG. 2A

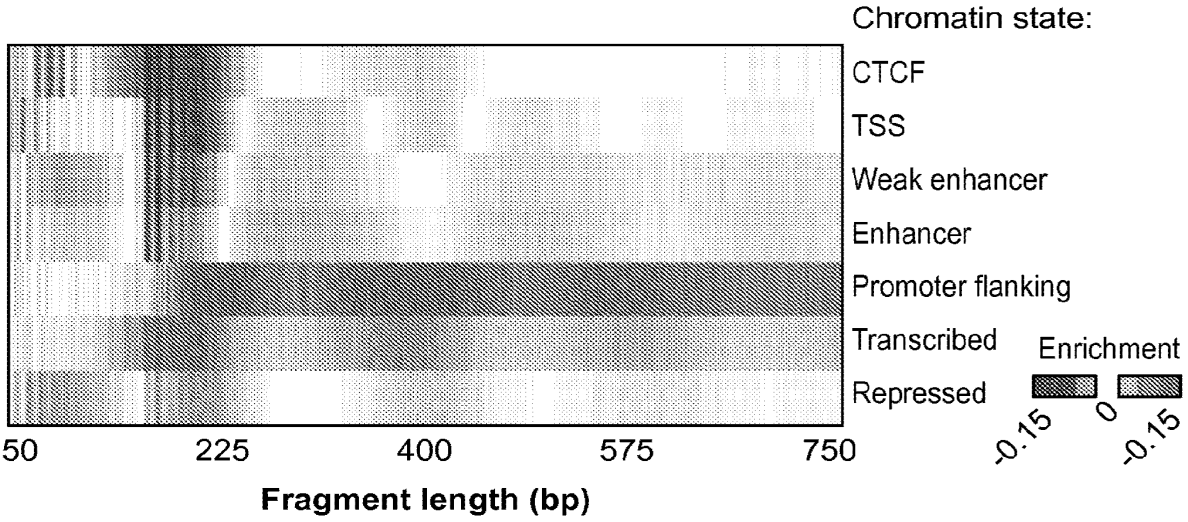

FIG. 2B

PARSE EX.1007.100

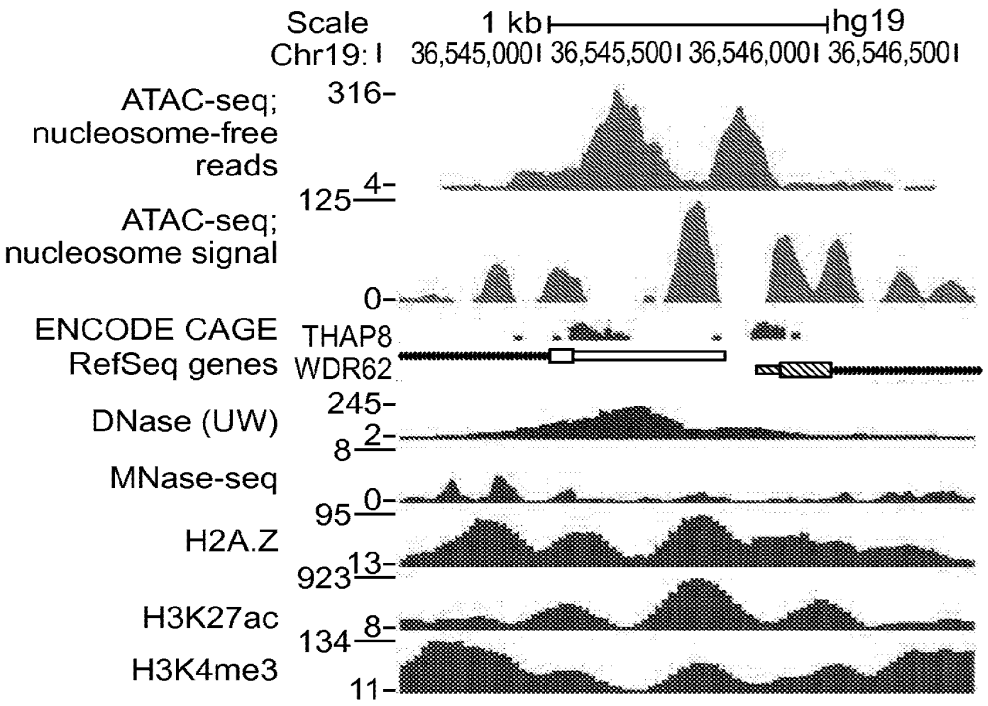

FIG. 3A

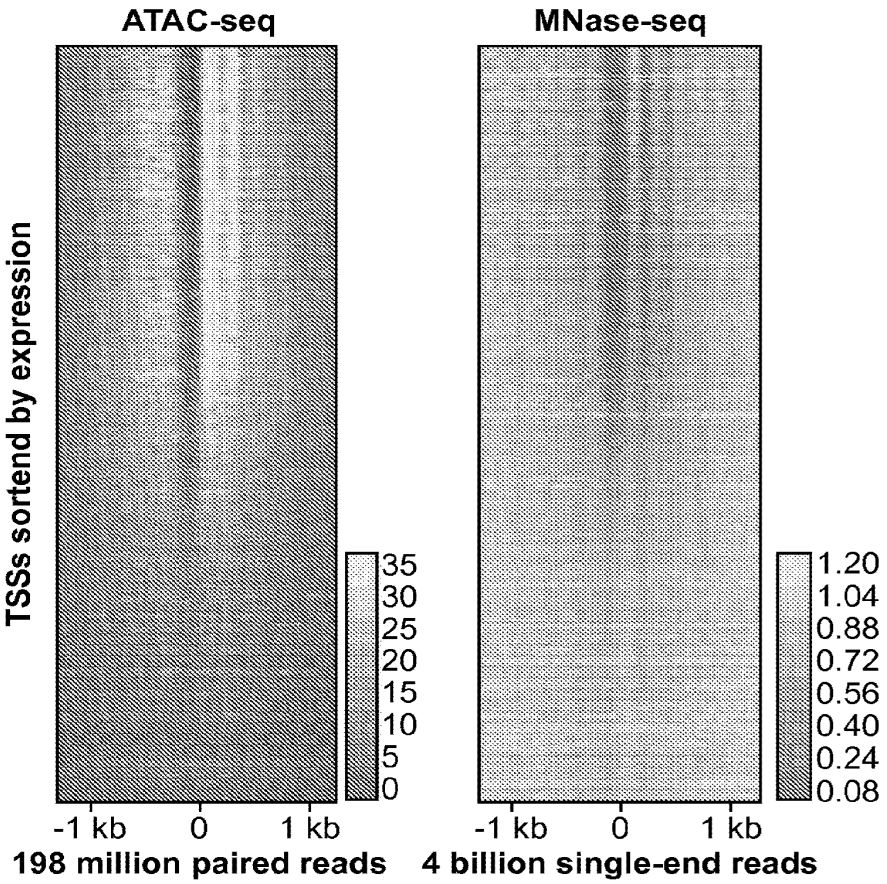

FIG. 3B

PARSE EX.1007.101

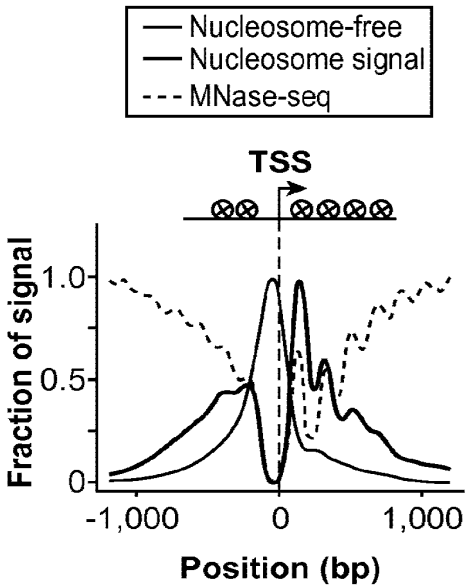

FIG. 3C

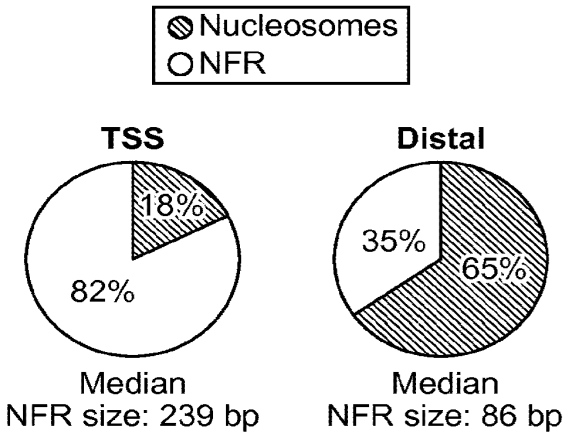

FIG. 3D

PARSE EX.1007.102

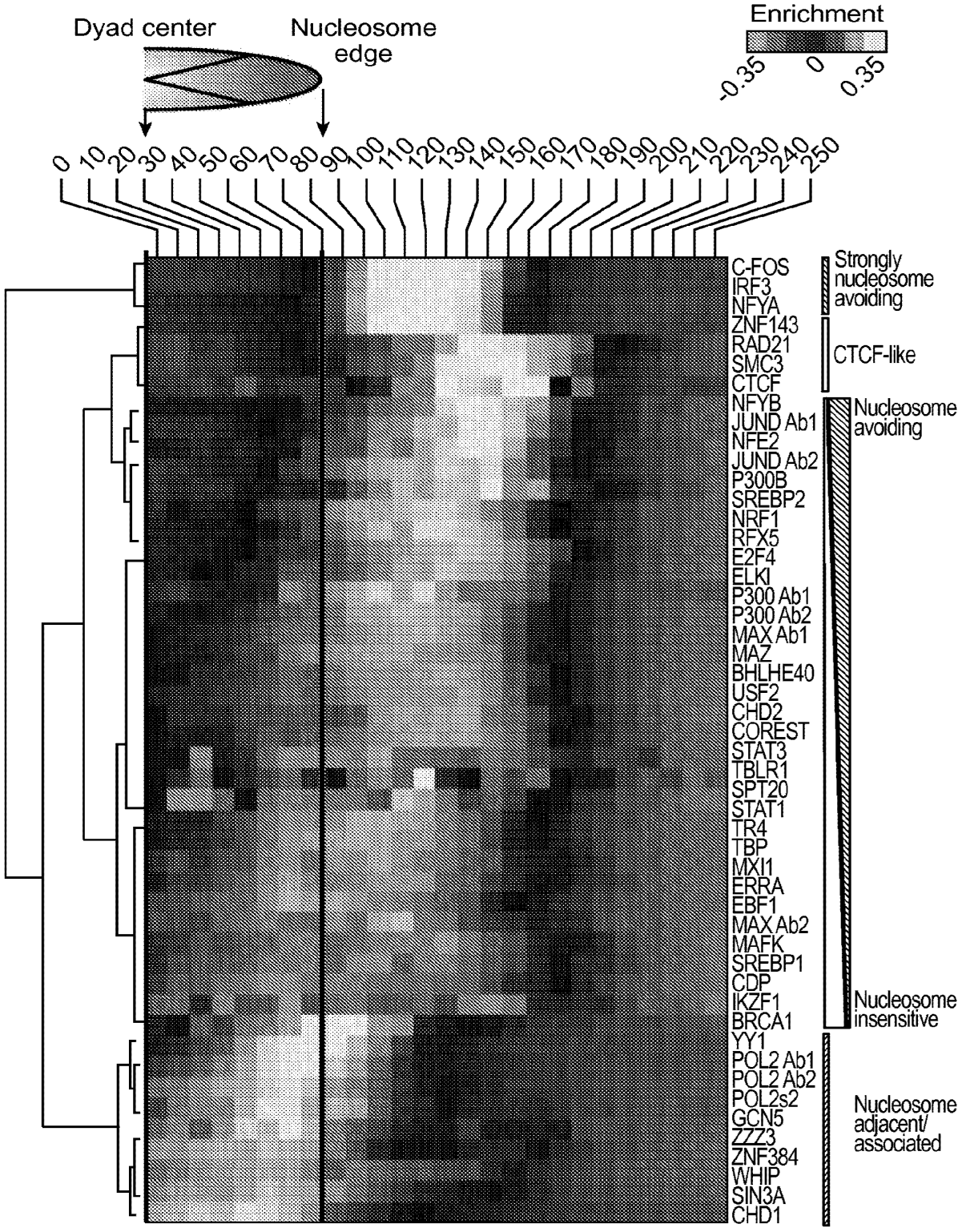

FIG. 3E

PARSE EX.1007.103

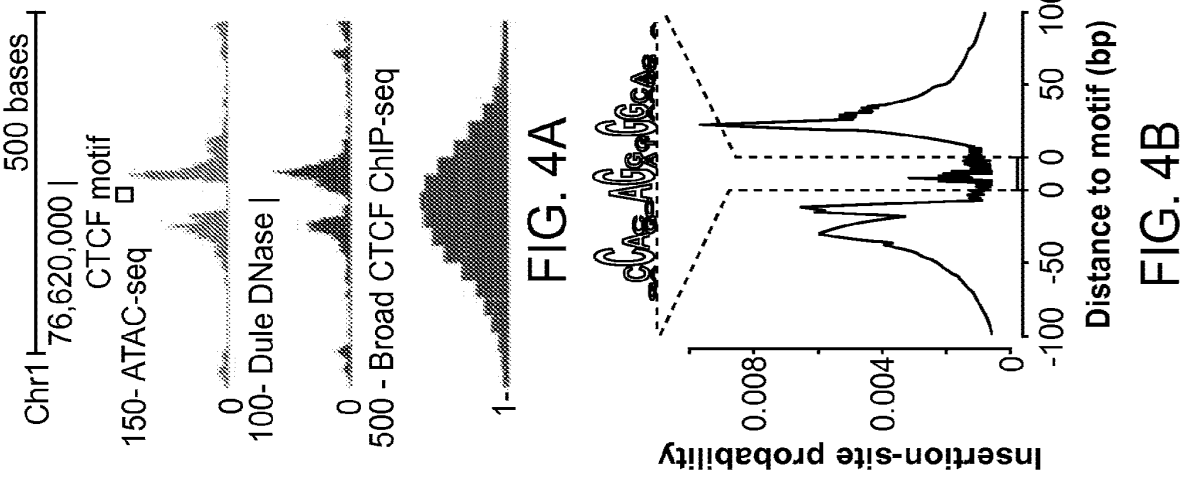

FIG. 4A

FIG. 4B

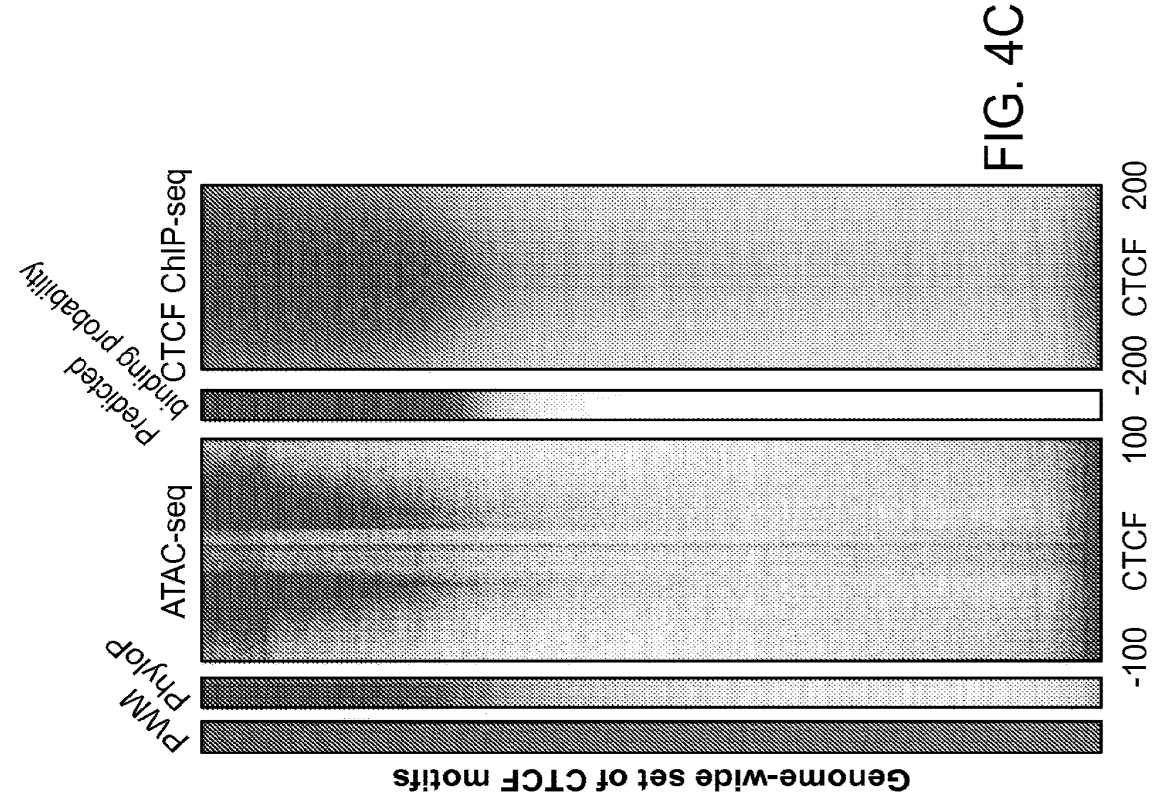

FIG. 4C

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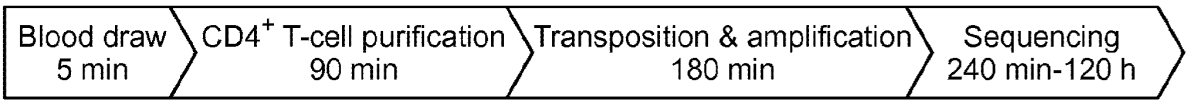

FIG. 5A

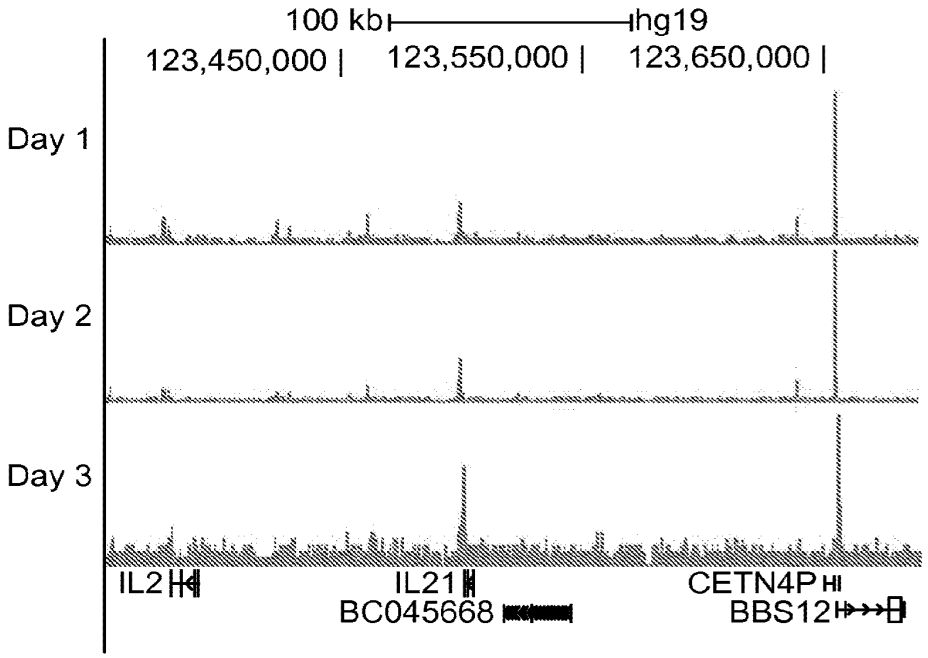

FIG. 5B

PARSE EX.1007.105

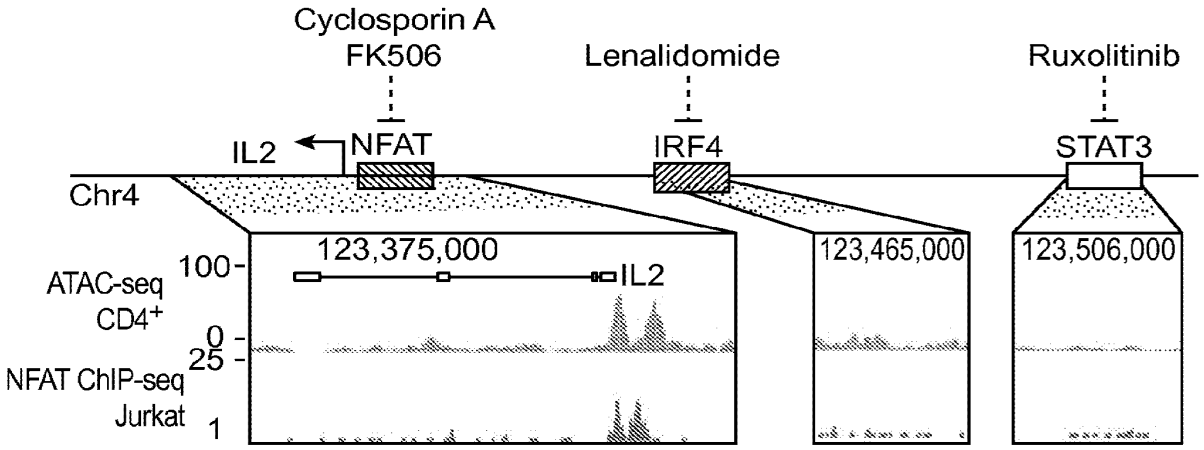

FIG. 5C

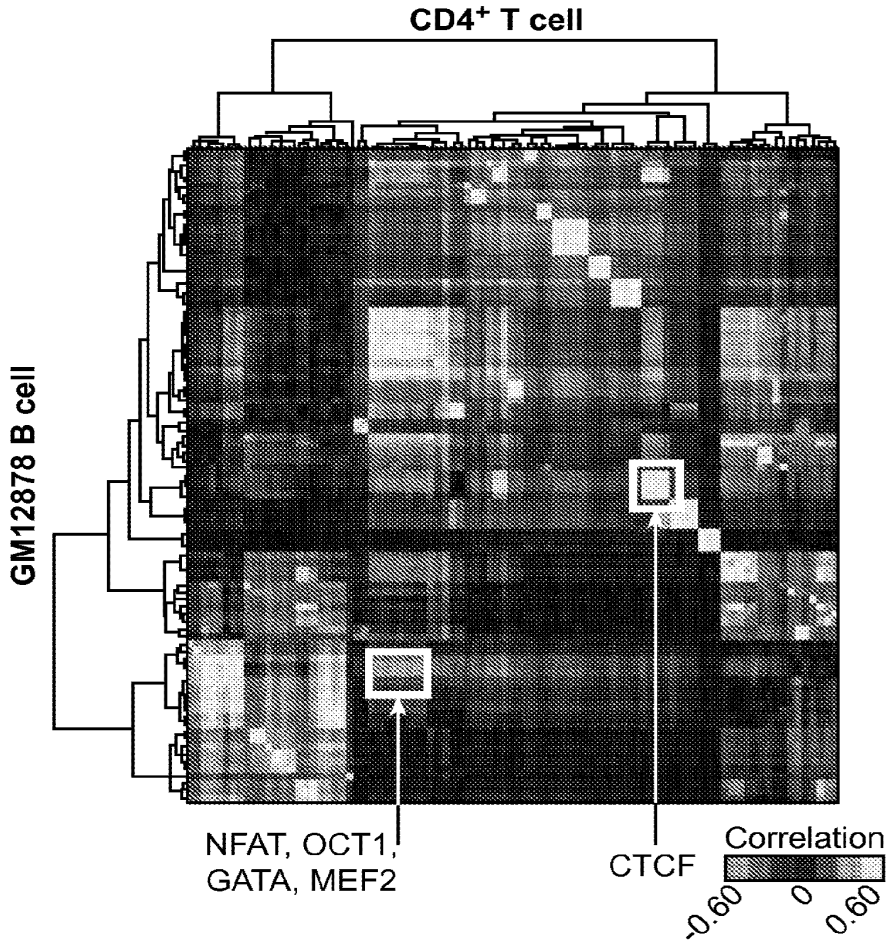

FIG. 5D

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PARSE EX.1007.107

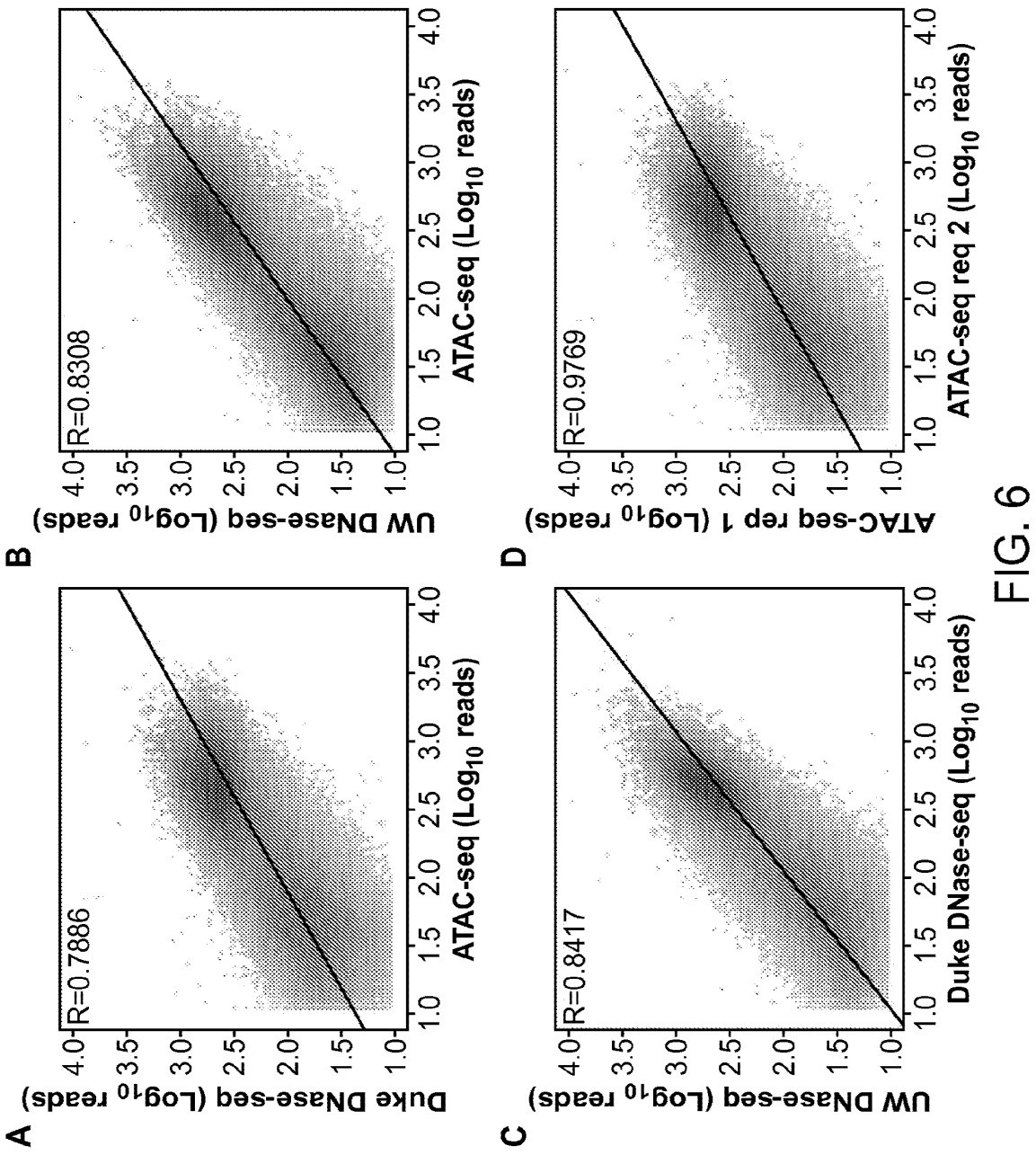
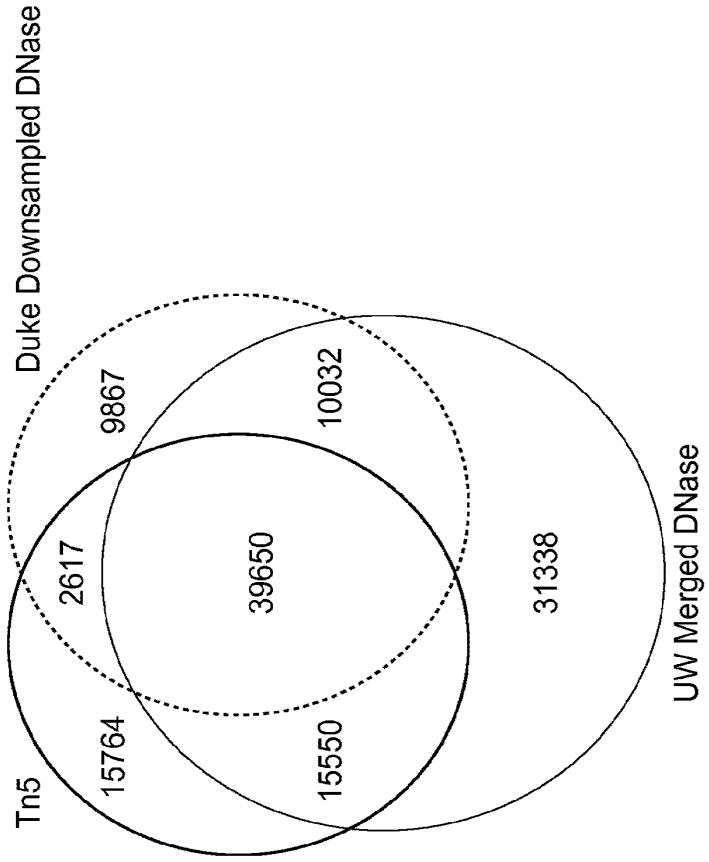


FIG. 6



	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

PARSE EX.1007.108

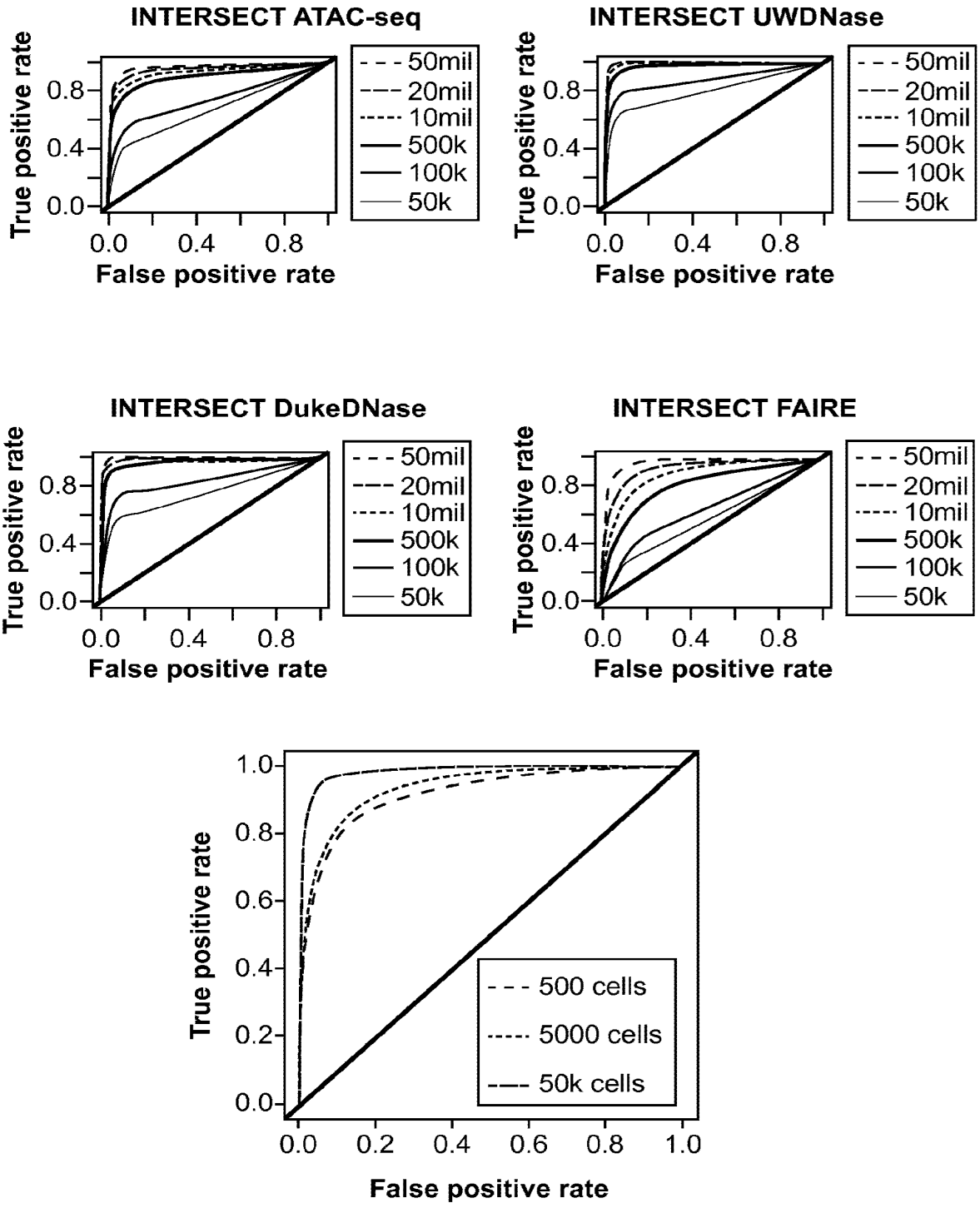


FIG. 8

PARSE EX.1007.109

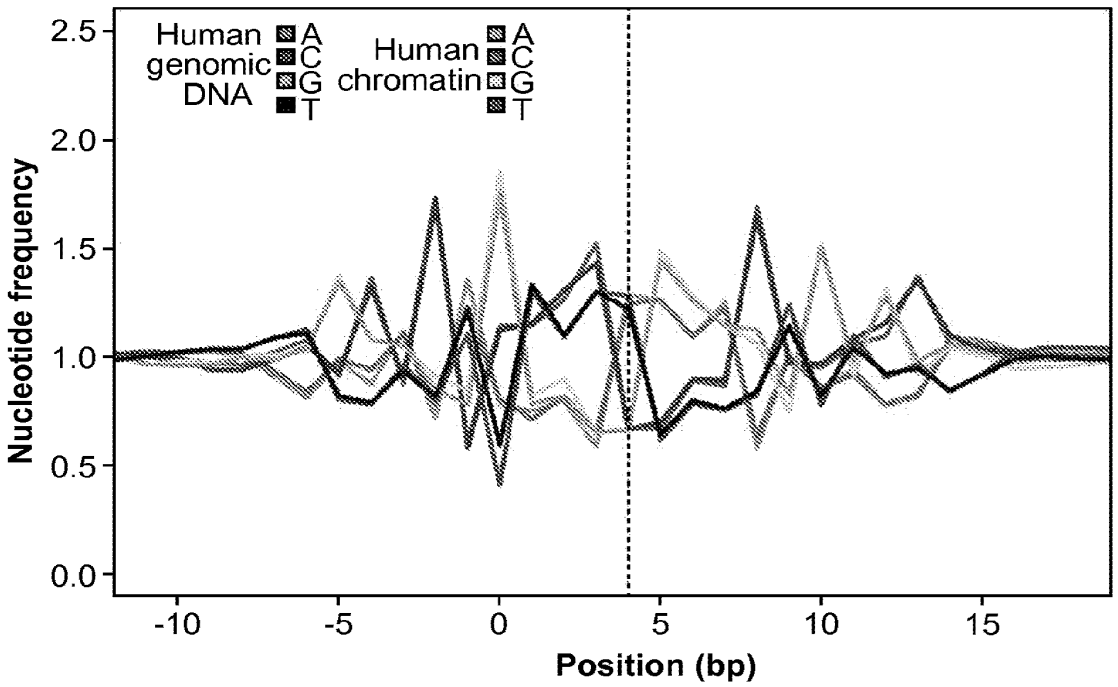


FIG. 9

PARSE EX.1007.110

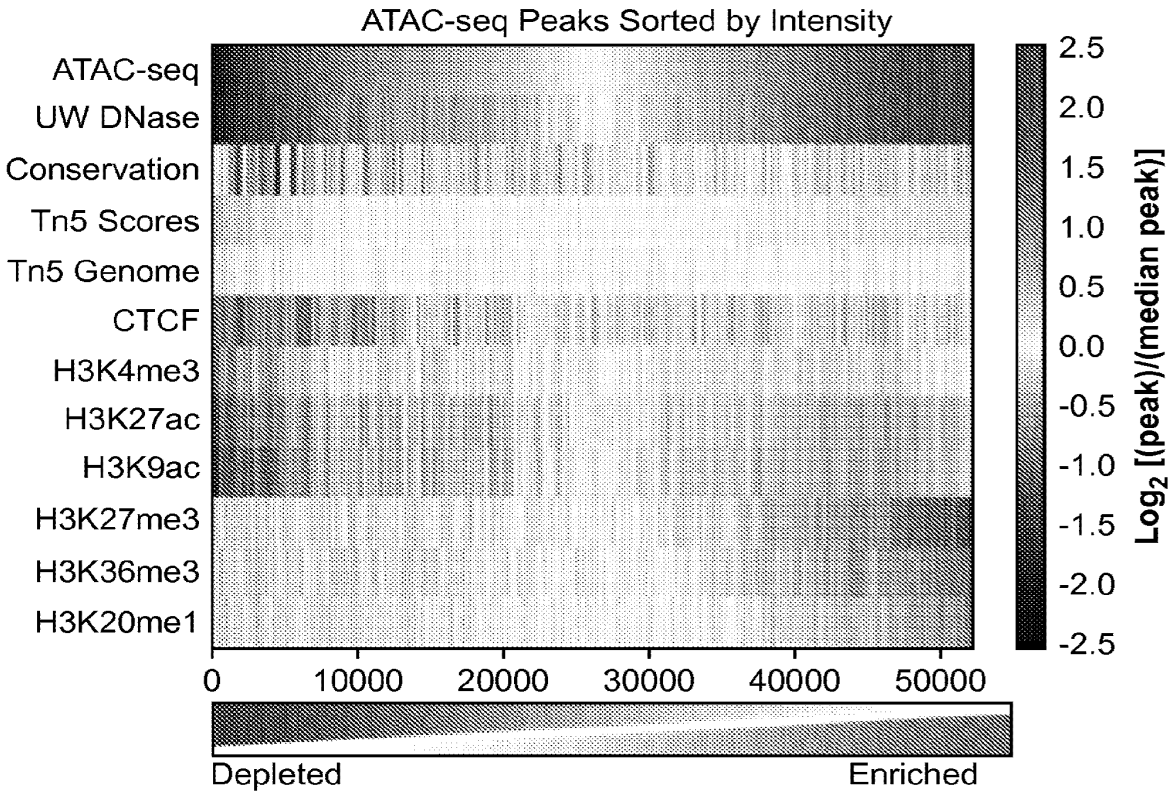


FIG. 10

PARSE EX.1007.111

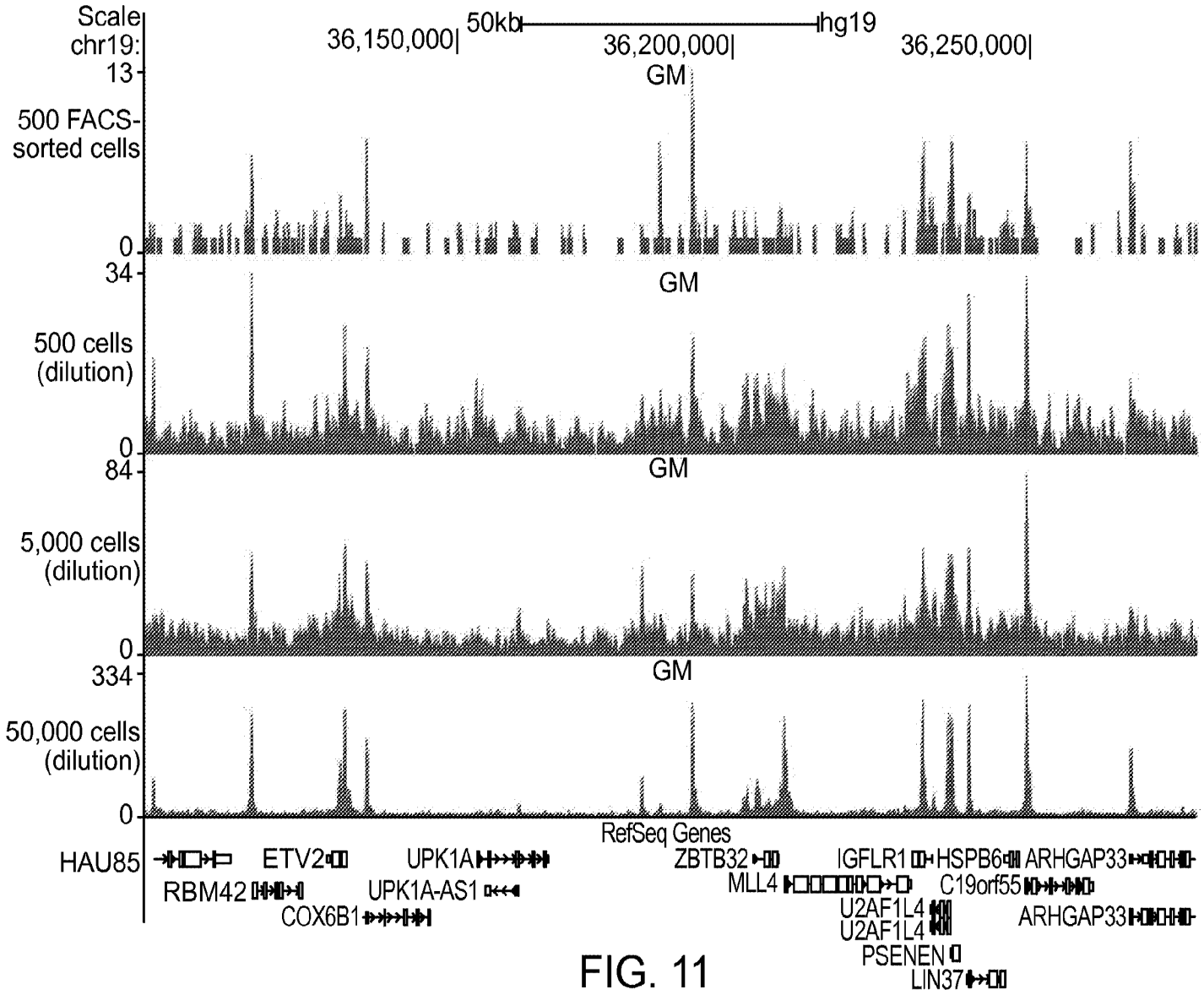


FIG. 11

SUBSTITUTE SHEET (RULE 26)

PARSE EX.1007.112

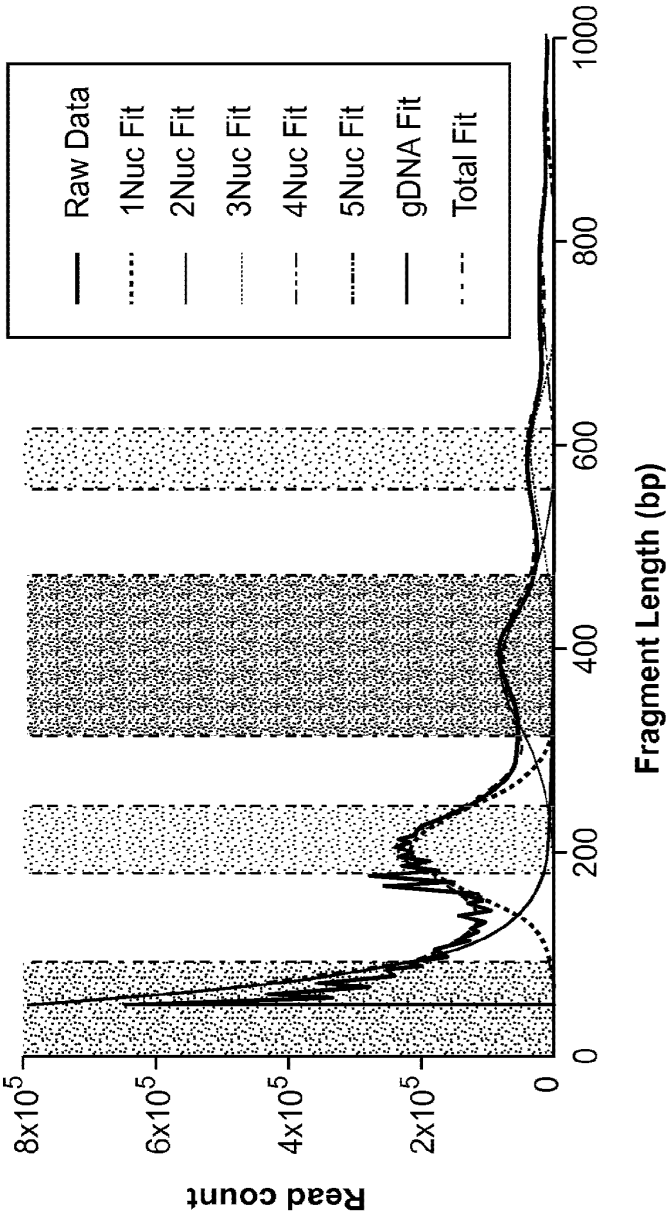


FIG. 12

PARSE EX.1007.113

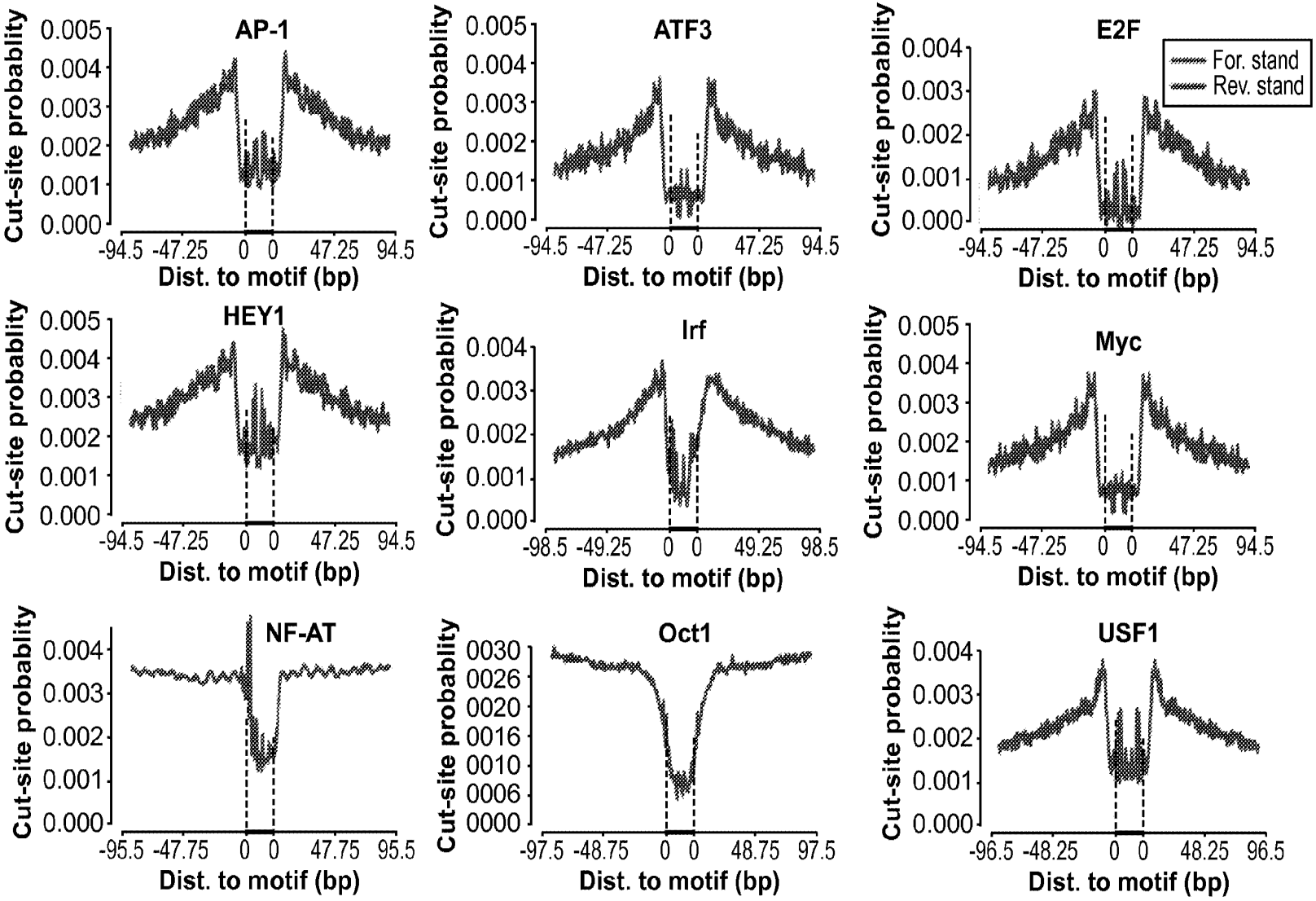


FIG. 13

SUBSTITUTE SHEET (RULE 26)

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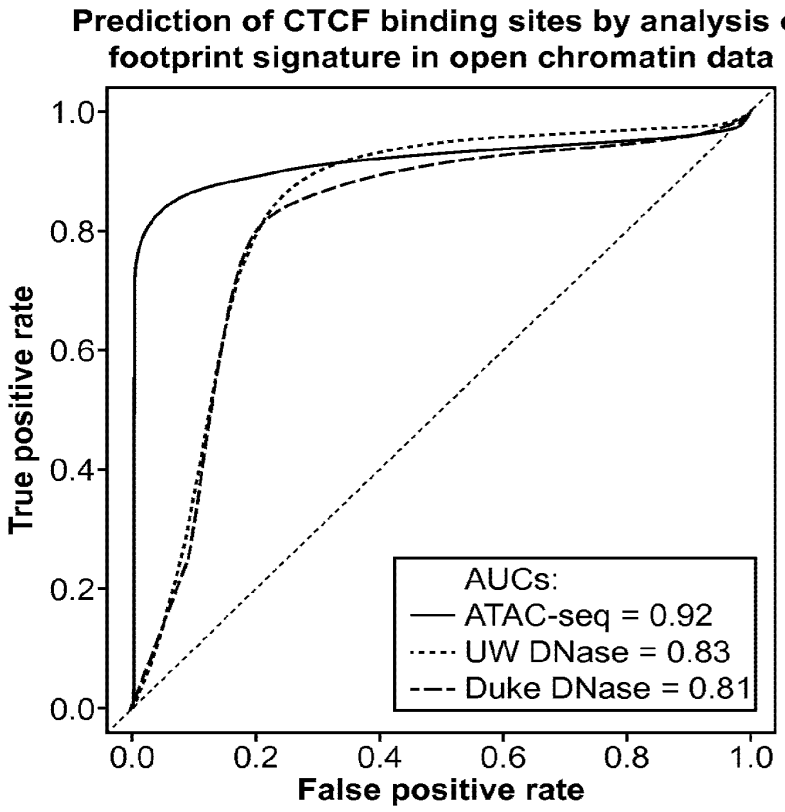

FIG. 14

PARSE EX.1007.115

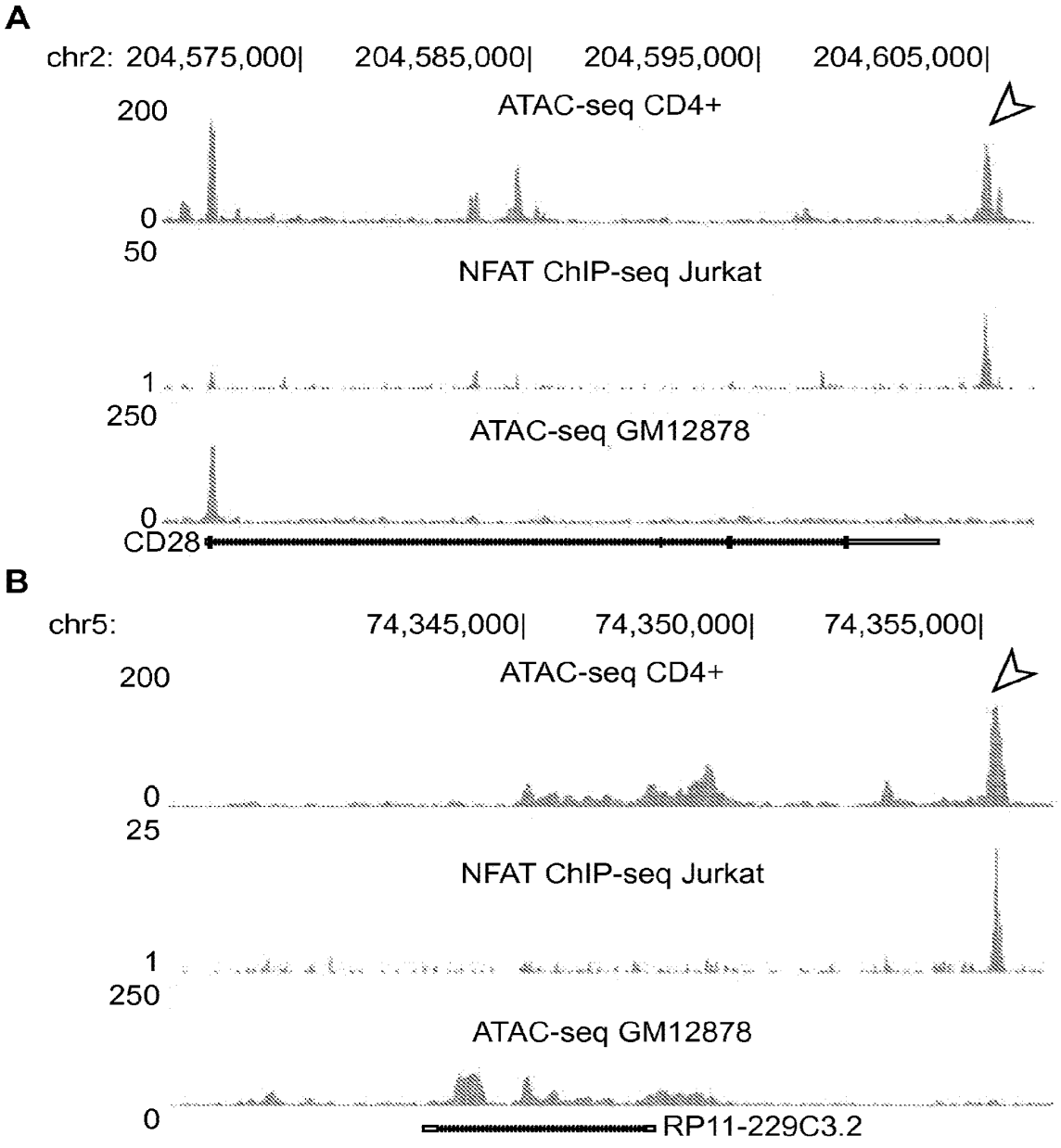

FIG. 15

PARSE EX.1007.116

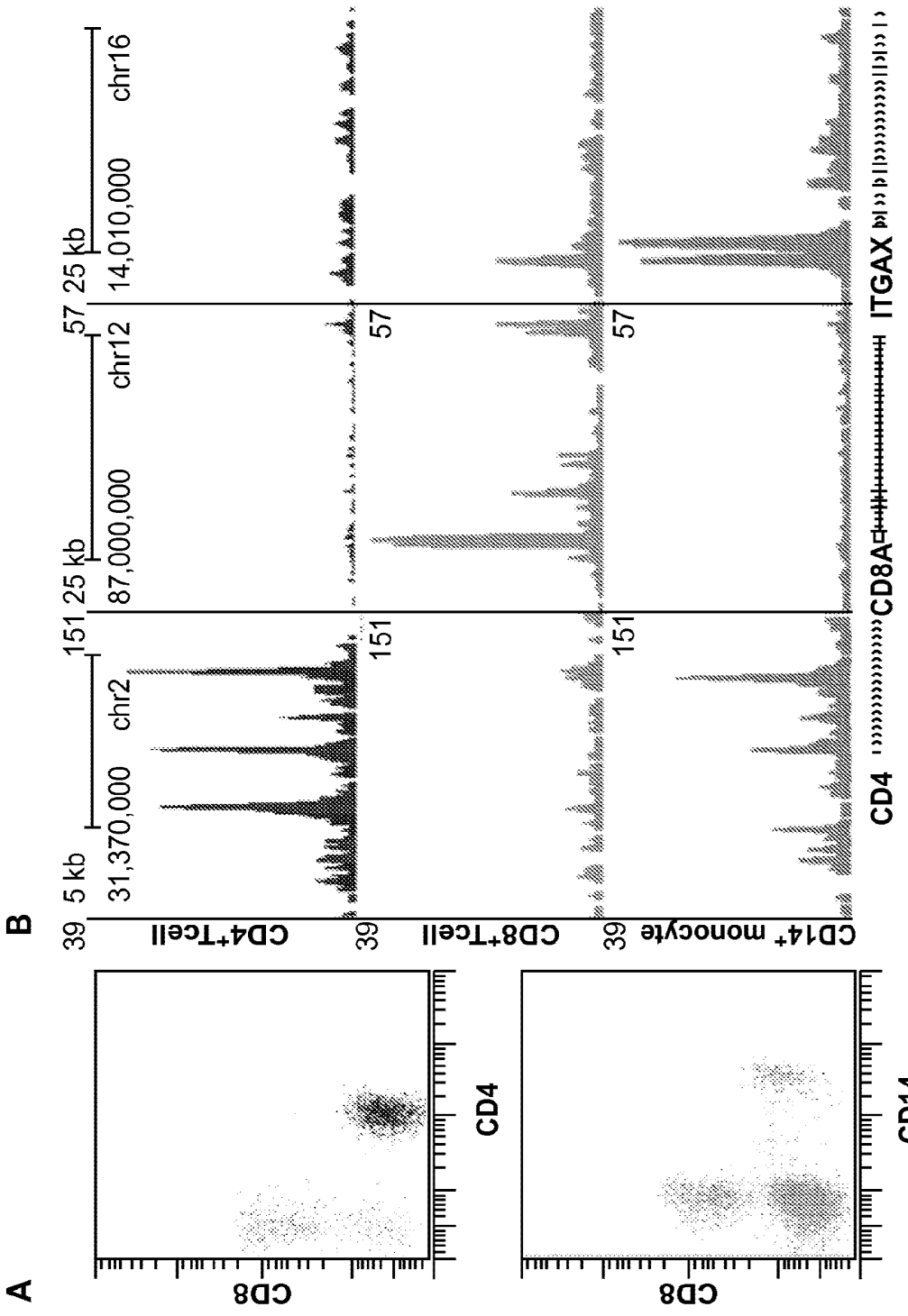

FIG. 16

PARSE EX.1007.117

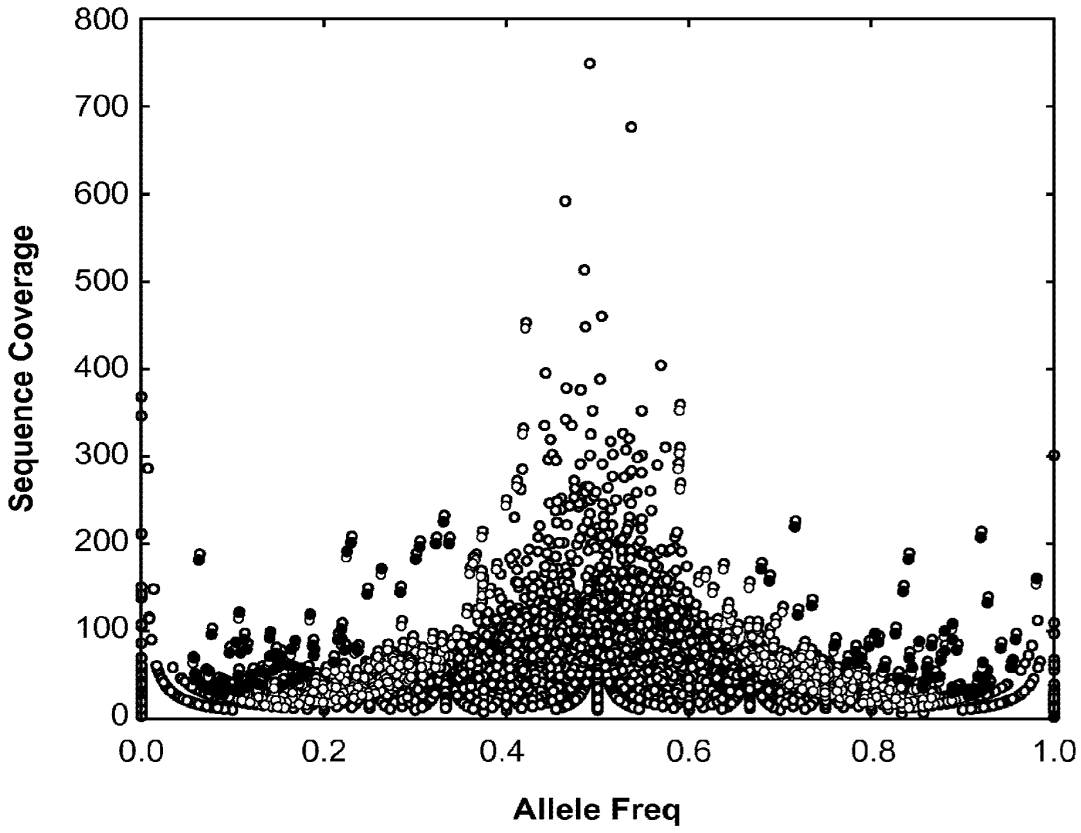

FIG. 17

PARSE EX.1007.118

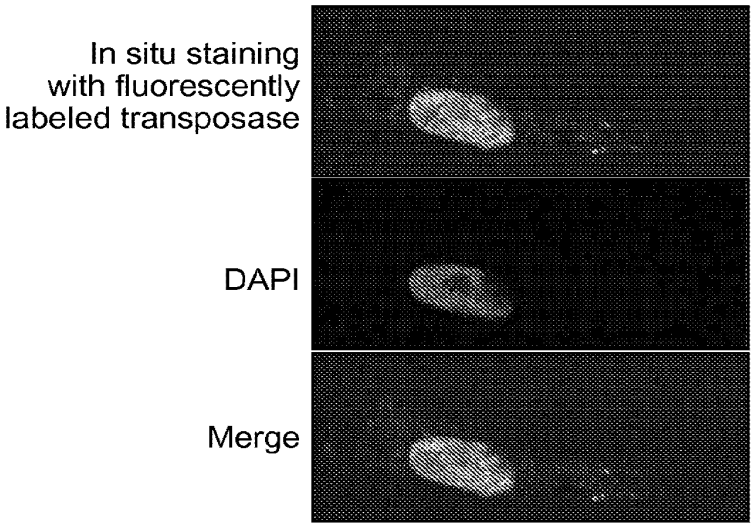

FIG. 18

PARSE EX.1007.119

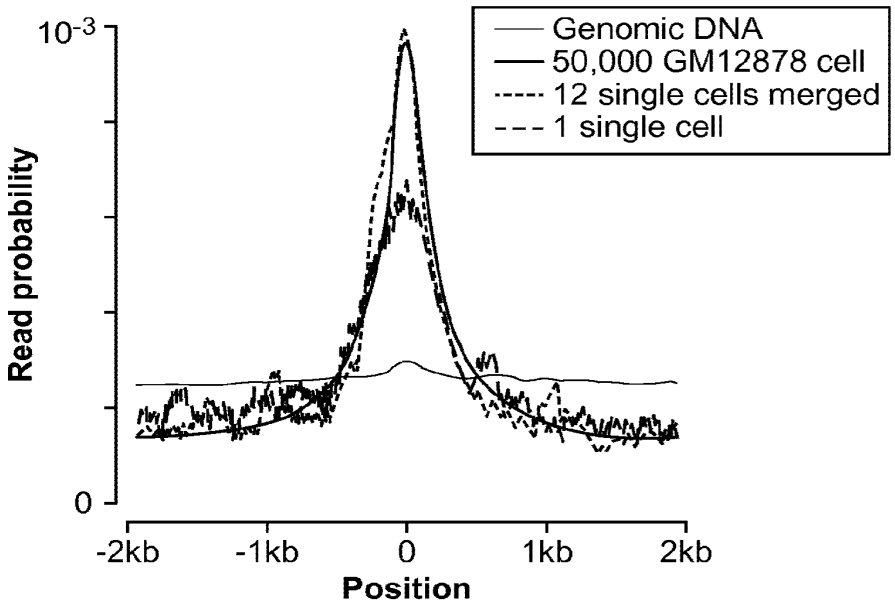

FIG. 19

PARSE EX.1007.120

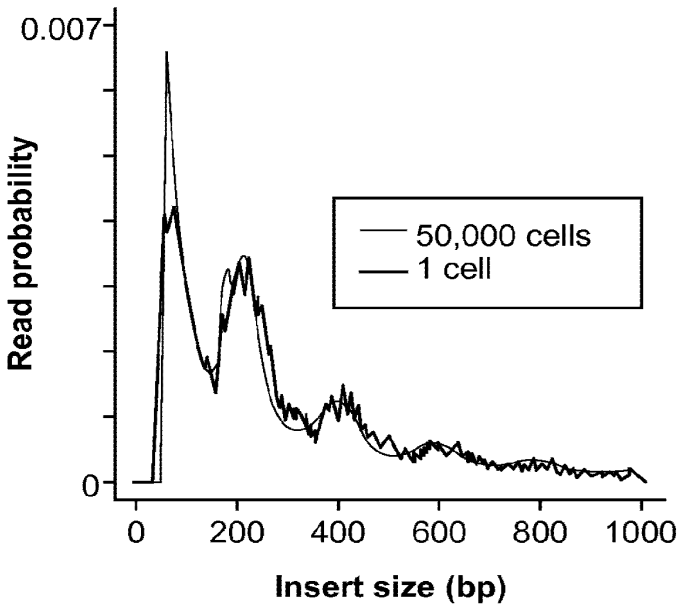

FIG. 20

PARSE EX.1007.121

==========
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=42; sec=21; ms=615;]
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Validated By CRFValidator v 1.0.5

Application No: 16418889 Version No: 1.0

Input Set:

Output Set:

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Finished: 2019-05-21 19:39:32.324
Elapsed: 0 hr(s) 0 min(s) 0 sec(s) 564 ms
Total Warnings: 25
Total Errors: 0
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Actual SeqID Count: 25

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Input Set:

Output Set:

Started: 2019-05-21 19:39:31.760
Finished: 2019-05-21 19:39:32.324
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Total Errors: 0
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Error code	Error Description
	This error has occured more than 20 times, will not be displayed

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Chang, Howard Y
Greenleaf, William J
Giresi, Paul

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/418,889	05/21/2019	1636	785	STAN-1111CON6	20	1

CONFIRMATION NO. 2173

FILING RECEIPT

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

Date Mailed: 07/05/2019

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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: The patent practitioners associated with Customer Number 77974

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

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Permission to Access Search Results: No

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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 16/418,889**
Projected Publication Date: 10/10/2019
Non-Publication Request: No
Early Publication Request: No
** **SMALL ENTITY** **
Title

Transposition of Native Chromatin for Personal Epigenomics

Preliminary Class

435

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

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this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 37, Code of Federal Regulations, 5.11 & 5.15

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/418,889

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 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(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 B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

Substitute for Form PTO-1360
(For use with Form PTO/SB/06)

Application Number	Filing Date
16418889	

Applicant(s) Paul Giresi

* May be used for additional claims or amendments

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT			*		*		*	
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Total Depend	19	↵	0	↵	0	↵							
Total Claims	20		0		0								

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/418,889	05/21/2019	Paul Giresi	STAN-1111CON6	2173

77974 7590 07/09/2019

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

EXAMINER	
ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
07/09/2019	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

PARSE EX.1007.137

Decision Granting Request for Prioritized Examination (Track I)	**Application No.** 16/418,889	**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	

PARSE EX.1007.138

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
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.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/418,889	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))	* 29	Minus	** 20	= 9		x $50 =	450
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $230 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	450

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:	16418889
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-1111CON6

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	9	50	450
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**450**

Electronic Acknowledgement Receipt

EFS ID:	36616726
Application Number:	16418889
International Application Number:	
Confirmation Number:	2173
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-1111CON6
Receipt Date:	17-JUL-2019
Filing Date:	21-MAY-2019
Time Stamp:	18:46:48
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$450
RAM confirmation Number	071819INTEFSW18471700
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-1111CON6_PrelimAmend.pdf	41676 6deb6bf24f6151509858a45d1ef33ad73766f87d	no	6
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30246 4b02d393694b106d9ea02bdcdecdbfe925b9bd28	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	71922		

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.

Electronically Filed

PRELIMINARY AMENDMENT Under 37 CFR § 1.115		
	Attorney Docket No.	STAN-1111CON6
	Confirmation No.	2173
	First Named Inventor	Paul Giresi
	Application Number	16/418,889
	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	WILDER, CYNTHIA B
	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

1-97. (Cancelled)

98. (New) A method for generating a sequencing library from a plurality of cells, comprising:

a) lysing a plurality of cells to provide a plurality of cell nuclei, wherein the plurality of cell nuclei comprises chromatin;

b) contacting a cell nucleus of the plurality of cell nuclei with a transposase complex such that polynucleotides of the cell nucleus are tagmented at regions of open chromatin to produce a plurality of tagged fragments; and

c) performing one or more nucleic acid reactions on the tagged fragment to produce a sequencing library.

99. (New) The method of claim 98, further comprising sequencing the sequencing library.

100. (New) The method of claim 98, wherein the one or more nucleic acid reactions comprise a nucleic acid amplification reaction.

101. (New) The method of claim 100, wherein said nucleic acid amplification reaction is configured to add one or more functional sequences to said tagged nucleic acid molecules or derivatives thereof, wherein said one or more functional sequences are compatible with a selected next generation sequencing platform.

102. (New) The method of claim 98, wherein a tagged fragment of the plurality of tagged fragments comprises a nucleotide sequence corresponding to the tagged fragment.

103. (New) The method of claim 102, wherein the tagged fragment further comprises a primer sequence.

104. (New) The method of claim 98, wherein the transposase complex comprises a Tn5 transposase or a transposase derived from a Tn5 transposase.

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105. (New) The method of claim 104, wherein said Tn5 transposase is a hyperactive Tn5 transposase.

106. (New) The method of claim 98, wherein said transposase complex comprises a first nucleic acid insert element comprising a first adapter sequence.

107. (New) The method of claim 106, wherein said first adapter sequence comprises a first sequencing adapter sequence.

108. (New) The method of claim 106, wherein said first adapter sequence comprises a barcode sequence.

109. (New) The method of claim 106, wherein said first adapter sequence comprises a first primer sequence.

110. (New) The method of claim 98, wherein said transposase complex comprises a second nucleic acid insert element comprising a second adapter sequence.

111. (New) The method of claim 110, wherein said second adapter sequence comprises a comprises a second sequencing adapter sequence.

112. (New) The method of claim 110, wherein said second adapter sequence comprises a barcode sequence.

113. (New) The method of claim 110, wherein said first adapter sequence comprises a second primer sequence.

114. (New) The method of claim 98, further comprising using the sequencing library to determine chromatin accessibility of the polynucleotides of the cell nuclei.

115. (New) The method of claim 98, further comprising using the sequencing library to identify transcriptionally active sites on the polynucleotides of the cell nuclei.

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116. (New) The method of claim 98, further comprising using the sequencing library to determine epigenetic features of the polynucleotides of the cell nuclei.

117. (New) The method of claim 98, further comprising using the sequencing library to determine transcription start sites.

118. (New) The method of claim 98, further comprising using the sequencing library to determine positioning of nucleosomes in the chromatin.

119. (New) The method of claim 98, wherein the transposase complex does not comprise an antibody specific to a protein that is part of chromatin.

120. (New) A method for generating a sequencing library from a plurality of cells, comprising:

a) lysing a plurality of cells to isolate a plurality of cell nuclei, wherein the plurality of cell nuclei comprise chromatin;

b) contacting a cell nucleus of the plurality of cell nuclei with a Tn5 transposase complex such that polynucleotides of the cell nucleus are tagmented at regions of open chromatin to produce a plurality of tagged fragments,

wherein the Tn5 transposase complex comprises a first sequencing adapter sequence and a second sequencing adapter sequence,

wherein the Tn5 transposase complex does not comprise an antibody specific to a protein that is part of chromatin,

wherein a tagged fragment of the plurality of tagged fragment comprises

i. a nucleotide sequence corresponding to a region of open chromatin,

ii. the first sequencing adapter sequence, and

iii. the second sequencing adapter sequence; and

c) performing one or more nucleic acid reactions on the tagged fragment to produce a sequencing library.

121. (New) The method of claim 120, further comprising sequencing the sequencing library.

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122. (New) The method of claim 120, further comprising using the sequencing library to determine chromatin accessibility of the polynucleotides of the cell nuclei.

123. (New) The method of claim 120, further comprising using the sequencing library to identify transcriptionally active sites on the polynucleotides of the cell nuclei.

124. (New) The method of claim 120, further comprising using the sequencing library to determine epigenetic features of the polynucleotides of the cell nuclei.

125. (New) The method of claim 120, further comprising using the sequencing library to determine transcription start sites (TSSs).

126. (New) The method of claim 120, further comprising using the sequencing library to determine positioning of nucleosomes in the chromatin.

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REMARKS UNDER 37 CFR § 1.115

Formal Matters

Claims 98-126 are pending after entry of the amendments set forth herein.

Claims 1-97 are canceled without prejudice.

Claims 98-126 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-1111CON6.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: July 17, 2019

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

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Facsimile: (650) 327-3231

PARSE EX.1007.149

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/418,889	05/21/2019	Paul Giresi	STAN-1111CON6	2173

77974 7590 08/09/2019

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
08/09/2019	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):

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PARSE EX.1007.150

Office Action Summary	Application No. 16/418,889	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) 98-126 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) 98-126 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 7/17/2017 is acknowledged. Claims 1-97 have been canceled. Claims 98-126 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.

Double Patenting

3. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process... may obtain a patent therefor..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the claims that are directed to the same invention so they are no

longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

4. Claims 98-126 of this application is patentably indistinct from claims 101-129 of Application No. 16/160576. Pursuant to 37 CFR 1.78(f), when two or more applications filed by the same applicant or assignee contain patentably indistinct claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the patentably indistinct claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

Claim Rejections - 35 USC § 112

6. 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.

7. Claims 114-118 and 122-126 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

(a) Claims 114-118 and 122-126 are indefinite because they appear to recite “intended use” limitations of the claims but do not actually recite how the claimed limitations are intended to be carried out. The limitations do not appear to further limit

the method steps of the independent claims 98 and 120 from which they depend. Further the recitation of "using"….."to determine" as recited therein is not active and positive language and thus one cannot determine how to achieve these results using only the method steps recited therein.

Prior art

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Boles (US 20130079251, effective filing date August 2011) teach a reagent system and method for generating DNA sequencing libraries. The system can include a transposase reagent complexed with a linear DNA reagent, the DNA reagent having transposase recognition sequences and sequencing adapter sequences at each end of the DNA reagent, whereby on reaction with a DNA molecule targeted for sequencing, the transposase inserts the adapter-bearing linear DNA reagent into the sequencing target to form a cointegrate structure, wherein the sequencing target is cleaved at a single position, and the ends of the cleaved target are joined to the ends of the adapter-bearing linear DNA reagent [0020]. Boles teaches at paragraph [0073], FIG. 8A is a schematic diagram illustrating a transposition-mediated library generation system 800 that can be optimized for use in automated bump array instrument. Transposase enzymes can be loaded with linear recombinant transposon substrates. Lines 802 and 804 represent dsDNA substrates. Transposition reactions can insert the linear transposon substrates into the HMW DNA targets. The co-integrate product DNA can remain high in molecular weight after transposition, and therefore it can be bumped away from the transposon reagent stream after reaction. FIG. 8B is a schematic diagram depicting the

structure of transposition cointegrates. NGS adapter sequences can be located adjacent to the transposon ends and allow sequencing into the insert from either end. The final library can be cleaved out of the HMW co-integrate by cleavage at engineered restriction enzyme sites that release the adapter-terminated sequencing library from the rest of the co-integrate (final cleavage not shown).

Fernandez et al teach (US 20150111788; effective filing date November 22, 2011) teach a method for tagging chromatin comprising: a. providing chromatin from a sample; b. adding to the provided chromatin, an antibody-oligonucleotide complex comprising an antibody covalently conjugated to a transposase:transposon complex containing a transposase complexed with a transposon cassette, to create a reaction mixture, wherein: (i) the antibody binds to a target protein in the chromatin; and (ii) the transposon cassette comprises: (1) transposase recognition sequences required for catalysis of a DNA integration reaction; (2) one or more oligonucleotide bar code sequences to uniquely identify the conjugated antibody; and (3) an extraction moiety; c. allowing said antibody from step (b) to bind its target in said chromatin in said reaction mixture; d. activating transposase-mediated transposition of the transposon cassette into DNA of the chromatin to tag the chromatin; and e. extracting the tagged DNA from step d using the extraction moiety of step b (see claims).

While the art teaches various aspect of the instant invention, the prior art does not teach contacting the cell nucleus of the plurality of cell nuclei with a transposase complex such that polynucleotides of the cell nucleus are tagmented at regions of open chromatin to produce a plurality of tag fragments in combination with the additional steps.

Conclusion

9. No claims are allowed. However, the claims have not been rejected under prior art. 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. 16/418,889	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-20130079251-A1	03-2013	Boles; T. Christian	C12M45/09	506/26
*	B	US-20150111788-A1	04-2015	Fernandez; Joseph	C12N15/1093	506/26
	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	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/418,889	Giresi et al.
	Examiner	Art Unit
	CYNTHIA B WILDER	1637

CPC - Searched*		
Symbol	Date	Examiner
C07K14/47	08/03/2019	CW
C07K7/08	08/03/2019	CW
G01N27/3335	08/03/2019	CW
C12Q1/6806	08/03/2019	CW

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
Inventor search on PALM, text search on WEST, review of IDS, review of related applications and documents cited therein , review of ISR documents cite in PCR application PCT/CN2016/108940, text search on google	08/03/2019	CW

/CYNTHIA B WILDER/ Primary Examiner, Art Unit 1637	

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/418,889	Giresi et al.
	Examiner	Art Unit
	CYNTHIA B WILDER	1637

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
G01N27/3335		08/03/2019	CW
C12Q1/6806		08/03/2019	CW
C07K7/08		08/03/2019	CW
C07K14/47		08/03/2019	CW

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Google sequencing library and nuclei and chromatin and transposase and open chr Sign in

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[PDF] Assessing chromatin accessibility in maize using ATAC-seq - bioRxiv
https://www.biorxiv.org/content/biorxiv/early/2019/01/22/526079.full.pdf
by YJ Lee - 2019 - Related articles
Jan 22, 2019 - The resulting NGS reads are characterized as DNase I hypersensitive sites (DHSs), which represent accessible regions of chromatin (7). ... This method takes advantage of the engineered prokaryotic transposase Tn5 that cleaves DNA in open chromatin regions and simultaneously integrates adapters into cleavage sites in vivo.

People also ask

What is ATAC seq used for?

What is chromatin accessibility?

What is chip analysis?

What is Mnase seq?

Feedback

Single Cell ATAC - 10x Genomics
https://www.10xgenomics.com/solutions/single-cell-atac/
Identify open chromatin regions by using a transposase enzyme to preferentially insert and tag accessible DNA fragments with adaptors, to get sequencing ...

Epigenetics applications - ATAC-seq | Abcam
https://www.abcam.com/epigenetics/epigenetics-application-spotlight-atac-seq
A rapid and sensitive technique to assess genome-wide chromatin accessibility. Assay for transposase-accessible chromatin sequencing (ATAC-seq) builds on a process called tagmentation: the simultaneous fragmentation and tagging of a genome with sequencing adaptors1.

Assessing chromatin accessibility in maize with ATAC-seq - NCBI - NIH
https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE120491
Jan 23, 2019 - The isolated nuclei were treated with a transposase that fragments and tags ... subjected to two rounds of PCR to generate the ATAC-seq library. In the first round of PCR, these fragments were amplified with 5 cycles and sequencing ... is effective in identifying open chromatin regions of the maize genome.

Assay for Transposase-Accessible Chromatin-Sequencing Using ...
cshprotocols.cshlp.org/cgi/reprint/pdb.prot098327v1.pdf?ijkey...keytype=finite
genomic locations of "open" chromatin, footprints of DNA-binding proteins, and ... DNA in accessible chromatin and tags the sites with sequencing adaptors. ... Nextera DNA Library Preparation Kit (including 2× TD Buffer and Tn5 Transposase) (Illumina ... Clipped pipette tips help to prevent shearing of nuclei and chromatin.

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 ... tagging of DNA performed by Tn5 transposase pre-loaded with sequencing ... After library preparation, the DNA is sequenced with NGS technology, and ...

Computational Methods for Assessing Chromatin Hierarchy ...
https://www.sciencedirect.com/science/article/pii/S2001037017300934
by P Chang - 2018 - Cited by 3 - Related articles
Ligation junctions are detected in conventional 3C libraries via PCR followed by gel ... inside the nuclei instead of "in solution," thereby decreasing the probability of false .... -Java-based tool for identification of optimal extension of sequence tags. .... The Tn5 transposase cleaves DNA fragments from open chromatin regions.

PARSE EX.1007.161

CUT&Tag for efficient epigenomic profiling of small samples and ...

https://www.nature.com › nature communications › articles

by HS Kaya-Okur - 2019 - Cited by 6 - Related articles

Apr 29, 2019 - Article | Open | Published: 29 April 2019 ... In CUT&Tag, a chromatin protein is bound in situ by a specific ... Activation of the transposase efficiently generates fragment libraries ... All steps from live cells to sequencing-ready libraries can be ... Unfixed cells or nuclei (blue) are permeabilized and mixed with ...

Identification of Open Chromatin Regions in Plant Genomes Using ...

europepmc.org/articles/pmc5693289

by M Bajic - 2018 - Cited by 17 - Related articles

We provide detailed instructions for transposase treatment of nuclei isolated ... Sequencing adapters are inserted into open chromatin regions, and the ... This generates a library of DNA fragments in which each end represents an insertion site. ... In addition, we describe the Isolation of Nuclei TAgged in specific Cell Types ...

Characterization of chromatin accessibility with a transposome ...

https://genomebiology.biomedcentral.com/articles/10.1186/s13059-016-0882-7

by BC Sos - 2016 - Cited by 25 - Related articles

Feb 4, 2016 - Chromatin accessibility captures in vivo protein-chromosome binding ... For DNase-Seq millions of cells are required for nuclei isolation, DNase I ... release DNA fragments and then to generate sequencing libraries, PCR ..... in the transposition reaction for tagging open chromatin was used for this reaction.

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Searches related to sequencing library and nuclei and chromatin and transposase and open chromatin and tagged fragment

atac seq protocol	**atac seq vs rna seq**
single cell atac-seq	**single cell atac-seq cost**
atac-seq cost	**single cell atac-seq 10x**
atac seq 10x	**10x atac-seq protocol**

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Transposition of native **chromatin** for fast and sensitive epigenomic profiling of **open chromatin**, DNA-binding proteins and nucleosome position

JD Buenrostro, PG Giresi, LC Zaba, HY Chang... - Nature ..., 2013 - nature.com

... Amplify and **sequence** ... (a) ATAC-**seq** reaction schematic. **Transposase** (green), loaded with **sequencing** adaptors (red and blue), inserts only in regions of **open chromatin** (between nucleosomes in gray) and generates **sequencing-library** fragments that can be PCR-amplified ...

☆ 99 Cited by 1792 Related articles All 12 versions

Transposition of native **chromatin** for multimodal regulatory analysis and personal epigenomics

JD Buenrostro, PG Giresi, LC Zaba, HY Chang... - Nature ..., 2013 - ncbi.nlm.nih.gov

... blue), inserts only in regions of **open chromatin** (nucleosomes in grey) and generates **sequencing library** fragments that ... peak intensities correlate well with markers of active **chromatin** and not with **transposase sequence** preference (Supplementary ... (a) ATAC-**seq** fragment sizes ...

☆ 99 Cited by 16 Related articles All 2 versions

Technical considerations for functional **sequencing** assays

W Zeng, A Mortazavi - Nature immunology, 2012 - nature.com

... the most easily understood dis- ease-related mutations are those in the coding **sequence** of expressed ... in medium to highly expressed genes that match or exceeds coverage attained with exome **sequencing**. For example, a gene expressed at 10 RPKM in a RNA-**seq** sam- ple ...

☆ 99 Cited by 36 Related articles All 12 versions

Genome-scale mapping of DNase I hypersensitivity

S John, PJ Sabo, TK Canfield, K Lee ... - Current protocols in ..., 2013 - Wiley Online Library

... genome-wide level readouts of regulatory elements across any cell or tissue type in any **sequenced** species ... (D) High-throughput **sequencing** of DHS libraries and (E) validation of DNase I-**seq** obtained data with ... Quality control: checkpoint prior to high-throughput **sequencing** ...

☆ 99 Cited by 69 Related articles All 6 versions »

... of 3D nuclear architecture: 3D structured illumination microscopy of defined chromosomal structures visualized by 3D (immuno)-FISH **opens** new perspectives for ...

Y Markaki, D Smeets, S Fiedler, VJ Schmid... - ..., 2012 - Wiley Online Library

... I have read and accept the Wiley Online **Library** Terms and Conditions of Use ... preservation of the nuclear morphology and **chromatin** ultrastructure, and (ii) sufficient DNA-probe accessibility to the target DNA **sequence** to secure ... DAPI has a high affinity to AT-rich **sequences** ...

☆ 99 Cited by 108 Related articles All 10 versions »

Genomes of replicatively senescent cells undergo global epigenetic changes leading to gene silencing and activation of transposable elements

M De Cecco, SW Criscione, EJ Peckham... - Aging cell, 2013 - Wiley Online Library

... We applied recently developed software (Day et al., 2010) for assessing repeat **sequence** coverage from high-throughput **sequencing** data ... In the FAIRE-**seq** data sets, satellite **sequences** were depleted in FAIRE and became prominently enriched in senescent cells (Fig ...

☆ 99 Cited by 186 Related articles All 5 versions »

The piggyBac transposon displays local and distant reintegration preferences and can cause mutations at noncanonical integration sites

MA Li, SJ Pettitt, S Eckert, Z Ning, S Rice... - ... and cellular biology, 2013 - Am Soc Microbiol

☆ 99 Cited by 50 Related articles All 10 versions »

Migraine genetics--a review: part I

S Silberstein, D Dodick - Headache: The Journal of Head and ..., 2013 - Wiley Online Library

... causal, but can lead to the identification of the precise DNA **sequence** that is ... Disease-associated SNP variants perturb transcription factor recognition **sequences**, alter allelic **chromatin** states ... The companion paper to follow DNA **sequencing** will summarize the advances in our ...

☆ 99 Cited by 16 Related articles All 8 versions »

PARSE EX.1007.163

Methods for identifying higher-order **chromatin** structure

SA Sajan, RD Hawkins - Annual review of genomics and human ..., 2012 - annualreviews.org

... probe, which in turn required a prior knowledge of the DNA **sequence** being examined ... of DNase-chip and DNase-**seq** by employing Illumina and Roche/454 **sequencing** to generate a ... More recently, DNase-**seq** was used to characterize DHSs in five embryonic stages of fruit fly ...

☆ 99 Cited by 76 Related articles All 9 versions »

High-throughput **sequencing** of a single chromosome: a moth W chromosome

W Traut, H Vogel, G Glöckner, E Hartmann ... - Chromosome ..., 2013 - Springer

... 36.5 %. We tested three TEs by PCR, cloning and Sanger **sequencing** for correctness of the assembly and W-specificity, one each from LTR ... W reads and contigs containing stretches of >50 nt with >90 identity to mtDNA and those with >15 nt flanking **sequence** ... 15 nt flanking **seq** ...

☆ 99 Cited by 26 Related articles All 15 versions »

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WEST Search History for Application 16418889

Creation Date: 2019080516:14

Prior Art Searches

Query	DB	Hits	Op.	Plur.	Thes.	Date
sequencing library same cell	PGPB, USPT, USOC, EPAB, DWPI	1472	ADJ	YES		08-03-2019
sequencing library same cells	PGPB, USPT, USOC, EPAB, DWPI	1472	ADJ	YES		08-03-2019
sequencing library same cells	PGPB, USPT, USOC, EPAB, DWPI	1472	ADJ	YES		08-03-2019
(sequencing library same cells) same (lys$ same nuclei)	PGPB, USPT, USOC, EPAB, DWPI	22	ADJ	YES		08-03-2019
(sequencing library same cells same (lys$ same nuclei)) same chromatin	PGPB, USPT, USOC, EPAB, DWPI	3	ADJ	YES		08-03-2019
(sequencing library same cells same (lys$ same nuclei)) and chromatin	PGPB, USPT, USOC, EPAB, DWPI	15	ADJ	YES		08-03-2019
(sequencing library same cells same (lys$ same nuclei) and chromatin) and (transposase complex or Tn5 transposase)	PGPB, USPT, USOC, EPAB, DWPI	6	ADJ	YES		08-03-2019
		10	ADJ	YES		08-03-2019

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(sequencing library same cells same (lys$ same nuclei)) and (transposase complex or Tn5 transposase)	PGPB, USPT, USOC, EPAB, DWPI					
(sequencing library same cells same (lys$ same nuclei) and (transposase complex or Tn5 transposase)) and chromatin	PGPB, USPT, USOC, EPAB, DWPI	6	ADJ	YES		08-03-2019
(sequencing library same cells same (lys$ same nuclei) and (transposase complex or Tn5 transposase) and chromatin) and ((tagged same fragment) or tag$)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-03-2019
(sequencing library same cells same (lys$ same nuclei) and (transposase complex or Tn5 transposase) and chromatin) and (amplification or sequencing)	PGPB, USPT, USOC, EPAB, DWPI	6	ADJ	YES		08-03-2019
(sequencing library same cells same (lys$ same nuclei) and (transposase complex or Tn5 transposase) and chromatin and (amplification or sequencing)) and (tag$)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-03-2019
(sequencing library same cells same (lys$ same nuclei) and (transposase complex or Tn5 transposase) and chromatin and (amplification or sequencing)) and (tag$ or barcod$)	PGPB, USPT, USOC, EPAB, DWPI	4	ADJ	YES		08-03-2019
(sequencing library same cells same (lys$ same nuclei) and (transposase complex or Tn5 transposase) and chromatin and (amplification or sequencing) and (tag$ or barcod$)) and (adapter or adaptor)	PGPB, USPT, USOC, EPAB, DWPI	3	ADJ	YES		08-03-2019
20130079251	PGPB, USPT, USOC, EPAB, DWPI	8	ADJ	YES		08-03-2019
20130079251.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-03-2019

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20130079251.pn. and (nuclei or nucleus)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-03-2019
(20130079251.pn. and (nuclei or nucleus)) and (chromatin or open$ chromatin)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-03-2019
(20130079251.pn. and (nuclei or nucleus)) and (chromatin)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-03-2019
generat$ same sequencing library	PGPB, USPT, USOC, EPAB, DWPI	2274	ADJ	YES		08-03-2019
(generat$ same sequencing library) same cells	PGPB, USPT, USOC, EPAB, DWPI	678	ADJ	YES		08-03-2019
(generat$ same sequencing library same cells) same (nuclei or nucleus)	PGPB, USPT, USOC, EPAB, DWPI	33	ADJ	YES		08-03-2019
(generat$ same sequencing library same cells same (nuclei or nucleus)) same chromatin	PGPB, USPT, USOC, EPAB, DWPI	9	ADJ	YES		08-03-2019
(generat$ same sequencing library same cells same (nuclei or nucleus) same chromatin) and transposase	PGPB, USPT, USOC, EPAB, DWPI	8	ADJ	YES		08-03-2019
(generat$ same sequencing library same cells same (nuclei or nucleus) same chromatin and transposase) and (sequencing or amplification)	PGPB, USPT, USOC, EPAB, DWPI	8	ADJ	YES		08-03-2019

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(generat$ same sequencing library same cells same (nuclei or nucleus) same chromatin and transposase and (sequencing or amplification)) and (adapter or adaptor)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-03-2019
(generat$ same sequencing library same cells same (nuclei or nucleus) same chromatin and transposase and (sequencing or amplification) and (adapter or adaptor)) and transposase	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-03-2019
WO 2014190214	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-03-2019
16/418889 or 16/160719 or 160/43874 or 14/78425 or 61/826728	PGPB, USPT, USOC, EPAB, DWPI	17	ADJ	YES		08-03-2019
(16/418889 or 16/160719 or 160/43874 or 14/78425 or 61/826728) and (generat$ same sequencing library)	PGPB, USPT, USOC, EPAB, DWPI	17	ADJ	YES		08-03-2019
(16/418889 or 16/160719 or 160/43874 or 14/78425 or 61/826728 and (generat$ same sequencing library)) and (lys$ same cells)	PGPB, USPT, USOC, EPAB, DWPI	17	ADJ	YES		08-03-2019
(16/418889 or 16/160719 or 160/43874 or 14/78425 or 61/826728 and (generat$ same sequencing library) and (lys$ same cells)) and chromatin	PGPB, USPT, USOC, EPAB, DWPI	17	ADJ	YES		08-03-2019
(16/418889 or 16/160719 or 160/43874 or 14/78425 or 61/826728 and (generat$ same sequencing library) and (lys$ same cells) and chromatin) and transposase	PGPB, USPT, USOC, EPAB, DWPI	14	ADJ	YES		08-03-2019
(16/418889 or 16/160719 or 160/43874 or 14/78425 or 61/826728 and (generat$ same sequencing library) and (lys$ same cells) and chromatin and transposase) and tag$	PGPB, USPT, USOC, EPAB, DWPI	14	ADJ	YES		08-03-2019

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(16/418889 or 16/160719 or 160/43874 or 14/78425 or 61/826728 and (generat$ same sequencing library) and (lys$ same cells) and chromatin and transposase and tag$) and sequencing library	PGPB, USPT, USOC, EPAB, DWPI	14	ADJ	YES		08-03-2019
(16/418889 or 16/160719 or 160/43874 or 14/78425 or 61/826728 and (generat$ same sequencing library) and (lys$ same cells) and chromatin and transposase and tag$ and sequencing library) and open chromatin	PGPB, USPT, USOC, EPAB, DWPI	14	ADJ	YES		08-03-2019
(20130079251) and chromatin	PGPB, USPT, USOC, EPAB, DWPI	6	ADJ	YES		08-03-2019
16/418889	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-03-2019
16/160719	PGPB, USPT, USOC, EPAB, DWPI	11	ADJ	YES		08-03-2019
10/344329	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-03-2019
(10/344329) and ((C07K14/47 | C07K7/08 | G01N27/3335).CPC.)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-03-2019
20090117573	PGPB, USPT, USOC, EPAB, DWPI	12	ADJ	YES		08-03-2019
(20090117573) and chromatin	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-03-2019

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(20090117573) and tagment$	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-03-2019
(20090117573) and transposase	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-03-2019
20130079251 and tagmen$	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-03-2019
tagment$ same open chromatin	PGPB, USPT, USOC, EPAB, DWPI	19	ADJ	YES		08-03-2019
(tagment$ same open chromatin) and nuclei	PGPB, USPT, USOC, EPAB, DWPI	14	ADJ	YES		08-03-2019
(tagment$ same open chromatin and nuclei) and transposase	PGPB, USPT, USOC, EPAB, DWPI	14	ADJ	YES		08-03-2019
(tagment$ same open chromatin and nuclei and transposase) and (sequencing library)	PGPB, USPT, USOC, EPAB, DWPI	13	ADJ	YES		08-03-2019
(tagment$ same open chromatin and nuclei and transposase and (sequencing library)) and (plurality same cell)	PGPB, USPT, USOC, EPAB, DWPI	10	ADJ	YES		08-03-2019
(tagment$ same open chromatin and nuclei and transposase and (sequencing library) and (plurality same cell)) and (adapter or adaptor)	PGPB, USPT, USOC, EPAB, DWPI	10	ADJ	YES		08-03-2019

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(tagment$ same open chromatin and nuclei and transposase and (sequencing library) and (plurality same cell) and (adapter or adaptor)) and (amplification)	PGPB, USPT, USOC, EPAB, DWPI	10	ADJ	YES		08-03-2019
(tagment$ same open chromatin and nuclei and transposase and (sequencing library) and (plurality same cell) and (adapter or adaptor) and (amplification)) and tn5 transposase	PGPB, USPT, USOC, EPAB, DWPI	10	ADJ	YES		08-03-2019
8583380.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-03-2019
(8583380.pn.)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-03-2019
chromatin and (8583380.pn.)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-03-2019
sequencing library same adaptor ligation products	PGPB, USPT, USOC, EPAB, DWPI	7	ADJ	YES		08-05-2019
(sequencing library same adaptor ligation products) and fluorophore	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-05-2019
((sequencing same library) and (adaptor same ligation products))	PGPB, USPT, USOC, EPAB, DWPI	515	ADJ	YES		08-05-2019
((sequencing same library) and (adaptor same ligation products))	PGPB, USPT, USOC, EPAB, DWPI	515	ADJ	YES		08-05-2019

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(((sequencing same library) and (adaptor same ligation products))) and intercalating dye	PGPB, USPT, USOC, EPAB, DWPI	79	ADJ	YES		08-05-2019
(((sequencing same library) and (adaptor same ligation products)) and intercalating dye) and real-time PCR	PGPB, USPT, USOC, EPAB, DWPI	78	ADJ	YES		08-05-2019
(((sequencing same library) and (adaptor same ligation products)) and intercalating dye and real-time PCR) and (fluorophore same probe)	PGPB, USPT, USOC, EPAB, DWPI	71	ADJ	YES		08-05-2019
(((sequencing same library) and (adaptor same ligation products)) and intercalating dye and real-time PCR and (fluorophore same probe)) and fluoescence	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-05-2019
(((sequencing same library) and (adaptor same ligation products)) and intercalating dye and real-time PCR and (fluorophore same probe)) and fluorescence	PGPB, USPT, USOC, EPAB, DWPI	71	ADJ	YES		08-05-2019
(((sequencing same library) and (adaptor same ligation products)) and intercalating dye and real-time PCR and (fluorophore same probe) and fluorescence) and percentage	PGPB, USPT, USOC, EPAB, DWPI	38	ADJ	YES		08-05-2019
(((sequencing same library) and (adaptor same ligation products)) and intercalating dye and real-time PCR and (fluorophore same probe) and fluorescence and percentage) and affinity	PGPB, USPT, USOC, EPAB, DWPI	25	ADJ	YES		08-05-2019
(((sequencing same library) and (adaptor same ligation products)) and intercalating dye and real-time PCR and (fluorophore same probe) and fluorescence and percentage and affinity) and DNA polymerase	PGPB, USPT, USOC, EPAB, DWPI	25	ADJ	YES		08-05-2019
(((sequencing same library) and (adaptor same ligation products)) and intercalating dye and real-time PCR and (fluorophore same probe) and fluorescence and percentage and affinity and DNA polymerase) and quencher	PGPB, USPT, USOC, EPAB, DWPI	15	ADJ	YES		08-05-2019

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US-20160298182-A1.did.	PGPB	n/a	ADJ	YES		08-05-2019
US-20160298182-A1.did.	PGPB	1	ADJ	YES		08-05-2019
sequencing library adaptor ligation product	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-05-2019
sequencing library same adaptor ligation product	PGPB, USPT, USOC, EPAB, DWPI	7	ADJ	YES		08-05-2019
sequencing library same adaptor ligation product	PGPB, USPT, USOC, EPAB, DWPI	n/a	ADJ	YES		08-05-2019
20130079251	PGPB, USPT, USOC, EPAB, DWPI	8	ADJ	YES		08-05-2019
20150111788	PGPB, USPT, USOC, EPAB, DWPI	3	ADJ	YES		08-05-2019
(20150111788) and (sequencing same library)	PGPB, USPT, USOC, EPAB, DWPI	3	ADJ	YES		08-05-2019
(20150111788 and (sequencing same library)) and (blood and (nuclei or nucleus) and chromatin)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-05-2019
(20150111788 and (sequencing same library)) and blood	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-05-2019
(20150111788 and (sequencing same library)) and (nuclei or nucleus)	PGPB, USPT,	0	ADJ	YES		08-05-2019

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	USOC, EPAB, DWPI					
20150111788 and (chromatin and (nuclei or nucleus))	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-05-2019
201501117812 and (chromatin)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-05-2019
20150111788 and chromati$	PGPB, USPT, USOC, EPAB, DWPI	3	ADJ	YES		08-05-2019
(20130079251) and histon$	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-05-2019
((20130079251) or (20150111788)) and primer	PGPB, USPT, USOC, EPAB, DWPI	10	ADJ	YES		08-05-2019
20150111788.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-05-2019
20150111788.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-05-2019
20130079251.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-05-2019
((20150111788.pn.) or (20130079251.pn.))	PGPB,	4	ADJ	YES		08-05-2019

PARSE EX.1007.174

and (sequencing or amplification)	USPT, USOC, EPAB, DWPI					
((20150111788.pn.) or (20130079251.pn.)) and (open$ same chromatin)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-05-2019
((20150111788.pn.) or (20130079251.pn.)) and (open$ same chromatin)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-05-2019
(20150111788) and (open$)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-05-2019
(20150111788) and accessibility	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-05-2019
(20150111788) and access$	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-05-2019
(20150111788) and (open$ or access$ or chromatin or cleav$ or stain$)	PGPB, USPT, USOC, EPAB, DWPI	3	ADJ	YES		08-05-2019
(20150111788) and (open$ or clos$)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-05-2019
(20150111788) and (sequencing library)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-05-2019

PARSE EX.1007.175

(20150111788 and (sequencing library)) and (cells)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-05-2019
(20150111788 and (sequencing library) and (cells)) and open chromatin	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-05-2019
open chromatin same transposases	PGPB, USPT, USOC, EPAB, DWPI	66	ADJ	YES		08-05-2019
(open chromatin same transposases) same tag$	PGPB, USPT, USOC, EPAB, DWPI	12	ADJ	YES		08-05-2019

PARSE EX.1007.176

Bibliographic Data

Application No: 16/418,889

Foreign Priority claimed: ○ Yes ◉ No

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

Verified and Acknowledged: /CYNTHIA B WILDER/ (Examiner's Signature) /CBW/ (Initials)

Title: Transposition of Native Chromatin for Personal Epigenomics

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
05/21/2019	435	1637	STAN-1111CON6
RULE			

APPLICANTS

The Board of Trustees of the Leland Stanford Junior University, Stanford, CA,

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Howard Y. Chang Stanford, CA, UNITED STATES

William J. Greenleaf Menlo Park, CA, UNITED STATES

CONTINUING DATA

This application is a 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

PCT/US2014/038825 has PRO of 61826728 05/23/2013

FOREIGN APPLICATIONS

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Doc description: Information Disclosure Statement (IDS) Filed

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	
Filing Date	
First Named Inventor	Paul Giresi
Art Unit	
Examiner Name	
Attorney Docket Number	STAN-1111CON6

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.	

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Application Number	
Filing Date	
First Named Inventor	Paul Giresi
Art Unit	
Examiner Name	
Attorney Docket Number	STAN-1111CON6

	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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	Application Number	
	Filing Date	
	First Named Inventor	Paul Giresi
	Art Unit	
	Examiner Name	
	Attorney Docket Number	STAN-1111CON6

	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.	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.B.W/

/CYNTHIA B WILDER/ (08/03/2019) 08/03/2019

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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-1111CON6

	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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Application Number	
Filing Date	
First Named Inventor	Paul Giresi
Art Unit	
Examiner Name	
Attorney Docket Number	STAN-1111CON6

	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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/CYNTHIA B WILDER/ (08/03/2019) 08/03/2019

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-1111CON6

	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.		

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

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

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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-1111CON6

	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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/CYNTHIA B WILDER/ (08/03/2019) 08/03/2019

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-1111CON6

	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/ (08/03/2019)	Date Considered	08/03/2019

*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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.B.W/

Transposition of native **chromatin** for fast and sensitive epigenomic profiling of open **chromatin**, DNA-binding proteins and nucleosome position

JD Buenrostro, PG Giresi, LC Zaba, HY Chang... - Nature ..., 2013 - nature.com

... First, current methods can average over and 'drown out' hetero- geneity in **cellular** populations ... Second, **cells** must often be grown ex vivo to obtain sufficient material, and such conditions perturb the ... and infer the positions of DNA-binding proteins using 'footprinting' in a B-**cell** line ...

☆ 99 Cited by 1800 Related articles All 12 versions

Transcriptional silencing of **transposons** by Piwi and maelstrom and its impact on **chromatin** state and gene expression

G Sienski, D Dönertas, J Brennecke - Cell, 2012 - Elsevier

... The third family member Piwi, however, is enriched in the **nucleus**, and its silencing mode is much less understood ... Importantly, a stable **cell** line derived from ovarian somatic **cells** (these cultured **cells** are called OSSs or OSCs) has been established (Niki et al., 2006; Saito ...

☆ 99 Cited by 381 Related articles All 11 versions

Piwi induces piRNA-guided transcriptional silencing and establishment of a repressive **chromatin** state

A Le Thomas, AK Rogers, A Webster... - Genes & ..., 2013 - genesdev.cshlp.org

... the resulting repression of host gene transcription were observed in an ovarian somatic **cell** (OSC) culture ... genes should be eliminated from the fly population but can be detected in cultured **cells** ... Dissected ovaries were lysed in **lysis** buffer (20 mM HEPES at pH 7.0, 150 mM KCl ...

☆ 99 Cited by 288 Related articles All 8 versions »

Multiple roles for Piwi in silencing Drosophila **transposons**

NV Rozhkov, M Hammell, GJ Hannon - Genes & development, 2013 - genesdev.cshlp.org

... Considered together, our data suggest that we achieved strong, **cell** type-specific depletion of ... mechanisms by which Piwi contributes to **transposon** silencing in somatic, follicle **cells**, we generated ... We isolated **nuclei** from ovaries of piwi knockdown and control flies and allowed ...

☆ 99 Cited by 179 Related articles All 13 versions »

Transposable elements become active and mobile in the genomes of aging mammalian somatic tissues

M De Cecco, SW Criscione, AL Peterson... - Aging (Albany ..., 2013 - ncbi.nlm.nih.gov

... Hence, the age-associated “loosening” of RTEs appears to be conserved and can be found in several postmitotic **cell** types. Another interpretation is that postmitotic **cells** can acquire some phenotypes typically associated with **cellular** senescence [43] ...

☆ 99 Cited by 153 Related articles All 7 versions »

DmGTSF1 is necessary for Piwi–piRISC-mediated transcriptional **transposon** silencing in the Drosophila ovary

H Ohtani, YW Iwasaki, A Shibuya, H Siomi... - Genes & ..., 2013 - genesdev.cshlp.org

... This variegation may be due to subtle unexpected differences in knockdown and/or **cell** manipulation conditions ... **Cells** (2 × 10 8) were cross-linked with 1% formaldehyde for 10 min at room ... The DNA–protein complexes were lysed with 1% **lysis** buffer (50 mM HEPES-KOH at pH ...

☆ 99 Cited by 79 Related articles All 9 versions »

Measuring Arabidopsis **chromatin** accessibility using DNase I-polymerase chain reaction and DNase I-chip assays

H Shu, W Gruissem, L Hennig - Plant physiology, 2013 - Am Soc Plant Biol

... The Plant **Cell**; Plant Direct; The Arabidopsis Book; Plant **Cell** Teaching Tools; ASPB; Plantae. User menu ... Search for this keyword. Advanced search. Plant Physiology. Other Publications: Plant Physiology; The Plant **Cell**; Plant Direct; The Arabidopsis Book; Plant **Cell** Teaching Tools ...

☆ 99 Cited by 23 Related articles All 13 versions »

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Transposition of native **chromatin** for multimodal regulatory analysis and personal epigenomics

JD Buenrostro, PG Giresi, LC Zaba, HY Chang... - Nature ..., 2013 - ncbi.nlm.nih.gov

... Immediately after **lysis**, **nuclei** were spun at 500 × g for 10 minutes using a refrigerated centrifuge ... **Cells** were lysed using BDpharmLyse 1:10 dil in diH20 (BD) for 15 min, centrifuged ... 50,000 CD3 + CD8 + , CD3 + CD4 + , and CD14 + **cell** populations were sorted into PBS with 10 ...

☆ 99 Cited by 16 Related articles All 2 versions

Target gene analysis by microarrays and **chromatin** immunoprecipitation identifies HEY proteins as highly redundant bHLH repressors

J Heisig, D Weber, E Englberger, A Winkler... - PLoS ..., 2012 - journals.plos.org

... patterns and expression levels determine the final outcome of HEY induced **cellular** responses ... due to longer induction, differential potency of the bHLH protein or **cell**-intrinsic mechanisms ... of down- and upregulated genes from microarray analysis of HEK293 **cells** after induction ...

☆ 99 Cited by 47 Related articles All 17 versions »

UAP56 couples piRNA clusters to the perinuclear **transposon** silencing machinery

F Zhang, J Wang, J Xu, Z Zhang, BS Koppetsch... - Cell, 2012 - Elsevier

... 2 of the germarium, where meiotic breaks form, and in later nurse **cell nuclei** undergoing endoreduplication ... In uap56 sz15′ /uap56 28 mutants, γH2Av foci persist in oocyte **nuclei** and appear to be ... However, UAP56 is expressed in both the germline and somatic follicle **cells** ...

☆ 99 Cited by 158 Related articles All 13 versions

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/418,889	Filing Date 05/21/2019	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

	(Column 1)	(Column 2)			
FOR	NUMBER FILED	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	09/13/2019	(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))	* 29	Minus	** 29	= 0		x $50 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $230 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	SLIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/APRIL L. WALKER/
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	Confirmation No.	2173
	First Named Inventor	Paul Giresi
	Application Number	16/418,889
	Filing Date	May 21, 2019
Address to: Mail Stop AMENDMENT Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Group Art Unit	1637
	Examiner Name	CYNTHIA B. WILDER
	Title: "*Transposition of Native Chromatin for Personal Epigenomics*"	

Sir:

This amendment is responsive to the Office Action dated August 9, 2019, for which a three-month period for response was given, making this response due on November 9, 2019. Accordingly, this response is timely filed.

In view of the remarks put forth below, reconsideration and allowance are respectfully requested.

AMENDMENTS TO THE CLAIMS

Please amend the claims as shown below. A complete listing of the claims, including their current status identifiers, is set forth below.

1-97. (Cancelled)

98. (Previously presented) A method for generating a sequencing library from a plurality of cells, comprising:

a) lysing a plurality of cells to provide a plurality of cell nuclei, wherein the plurality of cell nuclei comprises chromatin;

b) contacting a cell nucleus of the plurality of cell nuclei with a transposase complex such that polynucleotides of the cell nucleus are tagmented at regions of open chromatin to produce a plurality of tagged fragments; and

c) performing one or more nucleic acid reactions on the tagged fragment to produce a sequencing library.

99. (**Currently amended**) The method of claim 98, further comprising sequencing the sequencing library **to produce a plurality of sequence reads**.

100. (Previously presented) The method of claim 98, wherein the one or more nucleic acid reactions comprise a nucleic acid amplification reaction.

101. (Previously presented) The method of claim 100, wherein said nucleic acid amplification reaction is configured to add one or more functional sequences to said tagged nucleic acid molecules or derivatives thereof, wherein said one or more functional sequences are compatible with a selected next generation sequencing platform.

102. (Previously presented) The method of claim 98, wherein a tagged fragment of the plurality of tagged fragments comprises a nucleotide sequence corresponding to the tagged fragment.

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103. (Previously presented) The method of claim 102, wherein the tagged fragment further comprises a primer sequence.

104. (Previously presented) The method of claim 98, wherein the transposase complex comprises a Tn5 transposase or a transposase derived from a Tn5 transposase.

105. (Previously presented) The method of claim 104, wherein said Tn5 transposase is a hyperactive Tn5 transposase.

106. (Previously presented) The method of claim 98, wherein said transposase complex comprises a first nucleic acid insert element comprising a first adapter sequence.

107. (Previously presented) The method of claim 106, wherein said first adapter sequence comprises a first sequencing adapter sequence.

108. (Previously presented) The method of claim 106, wherein said first adapter sequence comprises a barcode sequence.

109. (Previously presented) The method of claim 106, wherein said first adapter sequence comprises a first primer sequence.

110. (Previously presented) The method of claim 98, wherein said transposase complex comprises a second nucleic acid insert element comprising a second adapter sequence.

111. (**Currently amended**) The method of claim 110, wherein said second adapter sequence comprises a ~~comprises a~~ second sequencing adapter sequence.

112. (Previously presented) The method of claim 110, wherein said second adapter sequence comprises a barcode sequence.

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113. (Previously presented) The method of claim 110, wherein said first adapter sequence comprises a second primer sequence.

114. (**Currently amended**) The method of claim [[98]]**99**, further comprising ~~using the sequencing library to determine chromatin accessibility of the polynucleotides of the cell nuclei~~**analyzing the sequence reads to generate a profile of chromatin accessibility along the polynucleotides of the cell nuclei**.

115. (**Currently amended**) The method of claim [[98]]**99**, further comprising ~~using the sequencing library to identify transcriptionally active sites on the polynucleotides of the cell nuclei~~**analyzing the sequence reads to determine a DNA binding protein occupancy for one or more DNA binding protein binding sites in the polynucleotides of the cell nuclei**.

116. (**Currently amended**) The method of claim [[98]]**99**, further comprising ~~using the sequencing library to determine epigenetic features of the polynucleotides of the cell nuclei~~**analyzing the sequence reads to generate an epigenetic map representing one or more epigenetic features of the polynucleotides of the cell nuclei**.

117. (**Currently amended**) The method of claim [[98]]**99**, further comprising ~~using the sequencing library to determine transcription start sites~~**analyzing the sequence reads to determine a position of one or more transcription start sites (TSSs) in the polynucleotides of the cell nuclei**.

118. (**Currently amended**) The method of claim [[98]]**99**, further comprising ~~using the sequencing library to determine positioning of nucleosomes in the chromatin~~**analyzing the sequence reads to determine a position of one or more nucleosomes in the polynucleotides of the cell nuclei**.

119. (Previously presented) The method of claim 98, wherein the transposase complex does not comprise an antibody specific to a protein that is part of chromatin.

120. (Previously presented) A method for generating a sequencing library from a plurality of cells, comprising:

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a) lysing a plurality of cells to isolate a plurality of cell nuclei, wherein the plurality of cell nuclei comprise chromatin;

b) contacting a cell nucleus of the plurality of cell nuclei with a Tn5 transposase complex such that polynucleotides of the cell nucleus are tagmented at regions of open chromatin to produce a plurality of tagged fragments,

wherein the Tn5 transposase complex comprises a first sequencing adapter sequence and a second sequencing adapter sequence,

wherein the Tn5 transposase complex does not comprise an antibody specific to a protein that is part of chromatin,

wherein a tagged fragment of the plurality of tagged fragment comprises

i. a nucleotide sequence corresponding to a region of open chromatin,

ii. the first sequencing adapter sequence, and

iii. the second sequencing adapter sequence; and

c) performing one or more nucleic acid reactions on the tagged fragment to produce a sequencing library.

121. (**Currently amended**) The method of claim 120, further comprising sequencing the sequencing library **to produce a plurality of sequence reads**.

122. (**Currently amended**) The method of claim [[120]]**121**, further comprising ~~using the sequencing library to determine chromatin accessibility of the polynucleotides of the cell nuclei~~**analyzing the sequence reads to generate a profile of chromatin accessibility along the polynucleotides of the cell nuclei**.

123. (**Currently amended**) The method of claim [[120]]**121**, further comprising ~~using the sequencing library to identify transcriptionally active sites on the polynucleotides of the cell nuclei~~**analyzing the sequence reads to determine a DNA binding protein occupancy for one or more DNA binding protein binding sites in the polynucleotides of the cell nuclei**.

124. (**Currently amended**) The method of claim [[120]]**121**, further comprising ~~using the sequencing library to determine epigenetic features of the polynucleotides of the cell nuclei~~**analyzing the sequence**

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reads to generate an epigenetic map representing one or more epigenetic features of the polynucleotides of the cell nuclei.

125. (**Currently amended**) The method of claim [[120]]**121**, further comprising ~~using the sequencing library to determine transcription start sites (TSSs)~~**analyzing the sequence reads to determine a position of one or more transcription start sites (TSSs) in the polynucleotides of the cell nuclei**.

126. (**Currently amended**) The method of claim [[120]]**121**, further comprising ~~using the sequencing library to determine positioning of nucleosomes in the chromatin~~**analyzing the sequence reads to determine a position of one or more nucleosomes in the polynucleotides of the cell nuclei**.

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REMARKS

Formal Matters

Claims 98-126 are pending after entry of the amendments set forth herein.

Claims 98-126 were examined and were rejected.

Claims 99, 111, 114-118, and 121-126 are amended. The amendments to the claims were made solely in the interest of expediting prosecution and are not to be construed as acquiescence to any objection or rejection of any claim. Support for the amendments to claim 99 is found at page 19, lines 18-19; amendments to claim 114 is found at page 23, line 30; amendments to claim 115 is found at page 23, lines 30-31; amendments to claim 116 is found at page 17, lines 29-30, page 23, line 28 through page 24, line 5; amendments to claim 117 is found at page 24, lines 1-5; amendments to claim 118 is found at page 24, lines 6-9; amendments to claim 121 is found at page 19, lines 18-19; amendments to claim 122 is found at page 23, line 30; amendments to claim 123 is found at page 23, lines 30-31; amendments to claim 124 is found at page 17, lines 29-30, page 23, line 28 through page 24, line 5; amendments to claim 125 is found at page 24, lines 1-5; amendments to claim 126 is found at page 24, lines 6-9. Accordingly, no new matter is added.

Applicant respectfully requests reconsideration of the application in view of the remarks made herein.

Double Patenting

Claims 98-126 were allegedly patentably indistinct from claims 101-129 of Application No. 16/160,576. Applicant was required to either cancel the patentably indistinct claims from all but one application or maintain a clear line of demarcation between the applications.

Claims 101-129 of Application No. 16/160,576 have been amended in a manner that renders them patentably distinct from the claims of the present application, and as such, the double patenting rejection can be withdrawn.

Withdrawal of this rejection is requested.

Claim Rejections – 35 USC § 112

Claims 114-118 and 122-126 were rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

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In making this rejection, the Examiner argues that claims 114-118 and 122-126 are indefinite because they appear to recite "intended use" limitations, and for not reciting active and positive language.

The Applicant submits that claims 99 and 121 have been amended to clarify that the sequencing library is sequenced **to produce a plurality of sequence reads**. Rejected claims 114-118 and 122-126 are amended to depend from claims 99 or 121, and their language is made more active by reciting "analyzing the sequence reads to determine" the recited element(s). In light of the amendments, the rejections under 35 USC 112 can be withdrawn.

Claim 111 is amended to correct a minor typographical error.

The Applicant submits that this rejection has been addressed. Withdrawal of this rejection is respectfully requested.

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, the Examiner is invited to 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-1111CON6.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: September 13, 2019

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

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PARSE EX.1007.197

Electronic Acknowledgement Receipt

EFS ID:	37165038
Application Number:	16418889
International Application Number:	
Confirmation Number:	2173
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-1111CON6
Receipt Date:	13-SEP-2019
Filing Date:	21-MAY-2019
Time Stamp:	18:28:11
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-1111CON6_RespOA.pdf	49757 dc0d77d3fb5daf4faf4878e81054efdff0c39dc8	yes	8

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	6
	Applicant Arguments/Remarks Made in an Amendment	7	8
Warnings:			
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	Total Files Size (in bytes):	49757	

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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.

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (03-15)
Approved for use through 07/31/2016. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16418889
Filing Date	2019-05-21
First Named Inventor	Paul Giresi
Art Unit	1637
Examiner Name	Cynthia B. Wilder
Attorney Docket Number	STAN-1111CON6

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16418889
	Filing Date	2019-05-21
	First Named Inventor	Paul Giresi
	Art Unit	1637
	Examiner Name	Cynthia B. Wilder
	Attorney Docket Number	STAN-1111CON6

	1	AUDIT et al., "Open chromatin encoded in DNA sequence is the signature of 'master' replication origins in human cells", Nucleic Acids Research, 2009, 37(18): 6064-6075.	

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.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16418889
Filing Date	2019-05-21
First Named Inventor	Paul Giresi
Art Unit	1637
Examiner Name	Cynthia B. Wilder
Attorney Docket Number	STAN-1111CON6

CERTIFICATION STATEMENT

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

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

OR

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

See attached certification statement.

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

A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/James S. Keddie/	Date (YYYY-MM-DD)	2019-09-13
Name/Print	James S. Keddie	Registration Number	48920

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

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

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

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

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

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

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

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

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

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

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

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

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Electronic Patent Application Fee Transmittal

Application Number:	16418889
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-1111CON6

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:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	2806	1	120	120
		Total in USD ($)		**120**

Electronic Acknowledgement Receipt

EFS ID:	37165983
Application Number:	16418889
International Application Number:	
Confirmation Number:	2173
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-1111CON6
Receipt Date:	13-SEP-2019
Filing Date:	21-MAY-2019
Time Stamp:	19:59:23
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$120
RAM confirmation Number	E20199CJ59420454
Deposit Account	
Authorized User	
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	STAN-1111CON6_IDS.pdf	1035212 f049b4baa7636759a3c7d15e9a3a528b11ff977e	no	4
Warnings:					
Information:					
2	Non Patent Literature	Audit.pdf	1624838 2f9a7e63244bc1e4bf63d61e73b7f4e2b120c8fe	no	12
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30435 8e10c087ddd7fed8ac67933febe9ee65bd9c380d	no	2
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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.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/418,889	05/21/2019	Paul Giresi	STAN-1111CON6

CONFIRMATION NO. 2173

77974
STANFORD UNIVERSITY OFFICE OF TECHNOLOGY LECENSING
BOZICEVIC, FIELD & FRANCIS LLP
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

PUBLICATION NOTICE

Title: Transposition of Native Chromatin for Personal Epigenomics

Publication No.US-2019-0309362-A1
Publication Date:10/10/2019

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

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NOTICE OF ALLOWANCE AND FEE(S) DUE

77974 7590 12/10/2019

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REDWOOD CITY, CA 94065

EXAMINER
WILDER, CYNTHIA B

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 12/10/2019

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/418,889	05/21/2019	Paul Giresi	STAN-1111CON6	2173

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	03/10/2020

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.

PARSE EX.1007.209

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 12/10/2019

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.
16/418,889	05/21/2019	Paul Giresi	STAN-1111CON6	2173

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	03/10/2020

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. _____

PARSE EX.1007.210

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.
16/418,889	05/21/2019	Paul Giresi	STAN-1111CON6	2173

77974 7590 12/10/2019

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	

DATE MAILED: 12/10/2019

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.

PARSE EX.1007.211

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. 16/418,889	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 9/13/2019.
   ☐ 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 98-126 . 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 9/13/2019.
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

PARSE EX.1007.213

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/418,889	Giresi et al.
	Examiner	Art Unit
	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	12/02/2019									
-	1	-									
-	2	-									
-	3	-									
-	4	-									
-	5	-									
-	6	-									
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-	40	-									
-	41	-									
-	42	-									

PARSE EX.1007.214

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/418,889	Giresi et al.
	Examiner	Art Unit
	CYNTHIA B WILDER	1637

CLAIM		DATE								
Final	Original	12/02/2019								
-	43	-								
-	44	-								
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-	46	-								
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-	94	-								

PARSE EX.1007.215

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/418,889	Giresi et al.
	Examiner	**Art Unit**
	CYNTHIA B WILDER	1637

CLAIM		DATE								
Final	Original	12/02/2019								
-	95	-								
-	96	-								
-	97	-								
1	98	=								
2	99	=								
3	100	=								
4	101	=								
5	102	=								
6	103	=								
7	104	=								
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21	118	=								
22	119	=								
23	120	=								
24	121	=								
25	122	=								
26	123	=								
27	124	=								
28	125	=								
29	126	=								

PARSE EX.1007.216

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/418,889	Giresi et al.
	Examiner	Art Unit
	CYNTHIA B WILDER	1637

CPC - Searched*		
Symbol	**Date**	**Examiner**
C07K14/47	12/02/2019	CW
C07K7/08	12/02/2019	CW
G01N27/3335	12/02/2019	CW
C12Q1/6806	12/02/2019	CW

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

US Classification - Searched*			
Class	**Subclass**	**Date**	**Examiner**
435	91.2	12/02/2019	CW

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	**Date**	**Examiner**
Inventor search on PALM, text search on WEST, review of IDS, review of related applications and documents cited therein , review of ISR documents cite in PCR application PCT/CN2016/108940, text search on google	08/03/2019	CW
UPDATED cursory search on WEST, review of IDS, review of related application for double patenting issues	12/02/2019	CW

/CYNTHIA B WILDER/ Primary Examiner, Art Unit 1637	

PARSE EX.1007.217

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/418,889	Giresi et al.
	Examiner	Art Unit
	CYNTHIA B WILDER	1637

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
G01N27/3335		12/02/2019	CW
C12Q1/6806		12/02/2019	CW
C07K7/08		12/02/2019	CW
C07K14/47		12/02/2019	CW

/CYNTHIA B WILDER/ Primary Examiner, Art Unit 1637	

PARSE EX.1007.218

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/418,889	Giresi et al.
	Examiner	**Art Unit**
	CYNTHIA B WILDER	1637

CPC						
Symbol					**Type**	**Version**
C12Q	/	1	/	6874	F	2013-01-01
C12Q	/	1	/	6869	I	2013-01-01
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)	29	
/CYNTHIA B WILDER/ Primary Examiner, Art Unit 1637	02 December 2019	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20191202

PARSE EX.1007.219

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/418,889	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		Total Claims Allowed:	
(Assistant Examiner)	(Date)	29	
/CYNTHIA B WILDER/ Primary Examiner, Art Unit 1637	02 December 2019	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

PARSE EX.1007.220

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/418,889	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	-	17	-	33	-	49	-	65	-	81	-	97	16	113
-	2	-	18	-	34	-	50	-	66	-	82	1	98	17	114
-	3	-	19	-	35	-	51	-	67	-	83	2	99	18	115
-	4	-	20	-	36	-	52	-	68	-	84	3	100	19	116
-	5	-	21	-	37	-	53	-	69	-	85	4	101	20	117
-	6	-	22	-	38	-	54	-	70	-	86	5	102	21	118
-	7	-	23	-	39	-	55	-	71	-	87	6	103	22	119
-	8	-	24	-	40	-	56	-	72	-	88	7	104	23	120
-	9	-	25	-	41	-	57	-	73	-	89	8	105	24	121
-	10	-	26	-	42	-	58	-	74	-	90	9	106	25	122
-	11	-	27	-	43	-	59	-	75	-	91	10	107	26	123
-	12	-	28	-	44	-	60	-	76	-	92	11	108	27	124
-	13	-	29	-	45	-	61	-	77	-	93	12	109	28	125
-	14	-	30	-	46	-	62	-	78	-	94	13	110	29	126
-	15	-	31	-	47	-	63	-	79	-	95	14	111		
-	16	-	32	-	48	-	64	-	80	-	96	15	112		

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 29	
/CYNTHIA B WILDER/ Primary Examiner, Art Unit 1637 (Primary Examiner)	02 December 2019 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (03-15)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16418889
Filing Date	2019-05-21
First Named Inventor	Paul Giresi
Art Unit	1637
Examiner Name	Cynthia B. Wilder
Attorney Docket Number	STAN-1111CON6

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	1	20110306042		2011-12-15	Jouvenot	

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/CYNTHIA B WILDER/ (12/02/2019) 12/02/2019

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Examiner Name	Cynthia B. Wilder
Attorney Docket Number	STAN-1111CON6

	1	AUDIT et al., "Open chromatin encoded in DNA sequence is the signature of 'master' replication origins in human cells", Nucleic Acids Research, 2009, 37(18): 6064-6075.

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EXAMINER SIGNATURE

Examiner Signature	/CYNTHIA B WILDER/ (12/02/2019)	Date Considered	12/02/2019

*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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WEST Search History for Application 16418889

Creation Date: 2019120213:47

Prior Art Searches

Query	DB	Hits	Op.	Plur.	Thes.	Date
sequencing library same cell	PGPB, USPT, USOC, EPAB, DWPI	1472	ADJ	YES		08-03-2019
sequencing library same cells	PGPB, USPT, USOC, EPAB, DWPI	1472	ADJ	YES		08-03-2019
sequencing library same cells	PGPB, USPT, USOC, EPAB, DWPI	1472	ADJ	YES		08-03-2019
(sequencing library same cells) same (lys$ same nuclei)	PGPB, USPT, USOC, EPAB, DWPI	22	ADJ	YES		08-03-2019
(sequencing library same cells same (lys$ same nuclei)) same chromatin	PGPB, USPT, USOC, EPAB, DWPI	3	ADJ	YES		08-03-2019
(sequencing library same cells same (lys$ same nuclei)) and chromatin	PGPB, USPT, USOC, EPAB, DWPI	15	ADJ	YES		08-03-2019
(sequencing library same cells same (lys$ same nuclei) and chromatin) and (transposase complex or Tn5 transposase)	PGPB, USPT, USOC, EPAB, DWPI	6	ADJ	YES		08-03-2019
		10	ADJ	YES		08-03-2019

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(sequencing library same cells same (lys$ same nuclei)) and (transposase complex or Tn5 transposase)	PGPB, USPT, USOC, EPAB, DWPI					
(sequencing library same cells same (lys$ same nuclei) and (transposase complex or Tn5 transposase)) and chromatin	PGPB, USPT, USOC, EPAB, DWPI	6	ADJ	YES		08-03-2019
(sequencing library same cells same (lys$ same nuclei) and (transposase complex or Tn5 transposase) and chromatin) and ((tagged same fragment) or tag$)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-03-2019
(sequencing library same cells same (lys$ same nuclei) and (transposase complex or Tn5 transposase) and chromatin) and (amplification or sequencing)	PGPB, USPT, USOC, EPAB, DWPI	6	ADJ	YES		08-03-2019
(sequencing library same cells same (lys$ same nuclei) and (transposase complex or Tn5 transposase) and chromatin and (amplification or sequencing)) and (tag$)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-03-2019
(sequencing library same cells same (lys$ same nuclei) and (transposase complex or Tn5 transposase) and chromatin and (amplification or sequencing)) and (tag$ or barcod$)	PGPB, USPT, USOC, EPAB, DWPI	4	ADJ	YES		08-03-2019
(sequencing library same cells same (lys$ same nuclei) and (transposase complex or Tn5 transposase) and chromatin and (amplification or sequencing) and (tag$ or barcod$)) and (adapter or adaptor)	PGPB, USPT, USOC, EPAB, DWPI	3	ADJ	YES		08-03-2019
20130079251	PGPB, USPT, USOC, EPAB, DWPI	8	ADJ	YES		08-03-2019
20130079251.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-03-2019

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20130079251.pn. and (nuclei or nucleus)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-03-2019
(20130079251.pn. and (nuclei or nucleus)) and (chromatin or open$ chromatin)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-03-2019
(20130079251.pn. and (nuclei or nucleus)) and (chromatin)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-03-2019
generat$ same sequencing library	PGPB, USPT, USOC, EPAB, DWPI	2274	ADJ	YES		08-03-2019
(generat$ same sequencing library) same cells	PGPB, USPT, USOC, EPAB, DWPI	678	ADJ	YES		08-03-2019
(generat$ same sequencing library same cells) same (nuclei or nucleus)	PGPB, USPT, USOC, EPAB, DWPI	33	ADJ	YES		08-03-2019
(generat$ same sequencing library same cells same (nuclei or nucleus)) same chromatin	PGPB, USPT, USOC, EPAB, DWPI	9	ADJ	YES		08-03-2019
(generat$ same sequencing library same cells same (nuclei or nucleus) same chromatin) and transposase	PGPB, USPT, USOC, EPAB, DWPI	8	ADJ	YES		08-03-2019
(generat$ same sequencing library same cells same (nuclei or nucleus) same chromatin and transposase) and (sequencing or amplification)	PGPB, USPT, USOC, EPAB, DWPI	8	ADJ	YES		08-03-2019

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(generat$ same sequencing library same cells same (nuclei or nucleus) same chromatin and transposase and (sequencing or amplification)) and (adapter or adaptor)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-03-2019
(generat$ same sequencing library same cells same (nuclei or nucleus) same chromatin and transposase and (sequencing or amplification) and (adapter or adaptor)) and transposase	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-03-2019
WO 2014190214	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-03-2019
16/418889 or 16/160719 or 160/43874 or 14/78425 or 61/826728	PGPB, USPT, USOC, EPAB, DWPI	17	ADJ	YES		08-03-2019
(16/418889 or 16/160719 or 160/43874 or 14/78425 or 61/826728) and (generat$ same sequencing library)	PGPB, USPT, USOC, EPAB, DWPI	17	ADJ	YES		08-03-2019
(16/418889 or 16/160719 or 160/43874 or 14/78425 or 61/826728 and (generat$ same sequencing library)) and (lys$ same cells)	PGPB, USPT, USOC, EPAB, DWPI	17	ADJ	YES		08-03-2019
(16/418889 or 16/160719 or 160/43874 or 14/78425 or 61/826728 and (generat$ same sequencing library) and (lys$ same cells)) and chromatin	PGPB, USPT, USOC, EPAB, DWPI	17	ADJ	YES		08-03-2019
(16/418889 or 16/160719 or 160/43874 or 14/78425 or 61/826728 and (generat$ same sequencing library) and (lys$ same cells) and chromatin) and transposase	PGPB, USPT, USOC, EPAB, DWPI	14	ADJ	YES		08-03-2019
(16/418889 or 16/160719 or 160/43874 or 14/78425 or 61/826728 and (generat$ same sequencing library) and (lys$ same cells) and chromatin and transposase) and tag$	PGPB, USPT, USOC, EPAB, DWPI	14	ADJ	YES		08-03-2019

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(16/418889 or 16/160719 or 160/43874 or 14/78425 or 61/826728 and (generat$ same sequencing library) and (lys$ same cells) and chromatin and transposase and tag$) and sequencing library	PGPB, USPT, USOC, EPAB, DWPI	14	ADJ	YES		08-03-2019
(16/418889 or 16/160719 or 160/43874 or 14/78425 or 61/826728 and (generat$ same sequencing library) and (lys$ same cells) and chromatin and transposase and tag$ and sequencing library) and open chromatin	PGPB, USPT, USOC, EPAB, DWPI	14	ADJ	YES		08-03-2019
(20130079251) and chromatin	PGPB, USPT, USOC, EPAB, DWPI	6	ADJ	YES		08-03-2019
16/418889	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-03-2019
16/160719	PGPB, USPT, USOC, EPAB, DWPI	11	ADJ	YES		08-03-2019
10/344329	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-03-2019
(10/344329) and ((C07K14/47 | C07K7/08 | G01N27/3335).CPC.)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-03-2019
20090117573	PGPB, USPT, USOC, EPAB, DWPI	12	ADJ	YES		08-03-2019
(20090117573) and chromatin	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-03-2019

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(20090117573) and tagment$	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-03-2019
(20090117573) and transposase	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-03-2019
20130079251 and tagmen$	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-03-2019
tagment$ same open chromatin	PGPB, USPT, USOC, EPAB, DWPI	19	ADJ	YES		08-03-2019
(tagment$ same open chromatin) and nuclei	PGPB, USPT, USOC, EPAB, DWPI	14	ADJ	YES		08-03-2019
(tagment$ same open chromatin and nuclei) and transposase	PGPB, USPT, USOC, EPAB, DWPI	14	ADJ	YES		08-03-2019
(tagment$ same open chromatin and nuclei and transposase) and (sequencing library)	PGPB, USPT, USOC, EPAB, DWPI	13	ADJ	YES		08-03-2019
(tagment$ same open chromatin and nuclei and transposase and (sequencing library)) and (plurality same cell)	PGPB, USPT, USOC, EPAB, DWPI	10	ADJ	YES		08-03-2019
(tagment$ same open chromatin and nuclei and transposase and (sequencing library) and (plurality same cell)) and (adapter or adaptor)	PGPB, USPT, USOC, EPAB, DWPI	10	ADJ	YES		08-03-2019

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(tagment$ same open chromatin and nuclei and transposase and (sequencing library) and (plurality same cell) and (adapter or adaptor)) and (amplification)	PGPB, USPT, USOC, EPAB, DWPI	10	ADJ	YES		08-03-2019
(tagment$ same open chromatin and nuclei and transposase and (sequencing library) and (plurality same cell) and (adapter or adaptor) and (amplification)) and tn5 transposase	PGPB, USPT, USOC, EPAB, DWPI	10	ADJ	YES		08-03-2019
8583380.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-03-2019
(8583380.pn.)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-03-2019
chromatin and (8583380.pn.)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-03-2019
sequencing library same adaptor ligation products	PGPB, USPT, USOC, EPAB, DWPI	7	ADJ	YES		08-05-2019
(sequencing library same adaptor ligation products) and fluorophore	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-05-2019
((sequencing same library) and (adaptor same ligation products))	PGPB, USPT, USOC, EPAB, DWPI	515	ADJ	YES		08-05-2019
((sequencing same library) and (adaptor same ligation products))	PGPB, USPT, USOC, EPAB, DWPI	515	ADJ	YES		08-05-2019

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(((sequencing same library) and (adaptor same ligation products))) and intercalating dye	PGPB, USPT, USOC, EPAB, DWPI	79	ADJ	YES		08-05-2019
(((sequencing same library) and (adaptor same ligation products)) and intercalating dye) and real-time PCR	PGPB, USPT, USOC, EPAB, DWPI	78	ADJ	YES		08-05-2019
(((sequencing same library) and (adaptor same ligation products)) and intercalating dye and real-time PCR) and (fluorophore same probe)	PGPB, USPT, USOC, EPAB, DWPI	71	ADJ	YES		08-05-2019
(((sequencing same library) and (adaptor same ligation products)) and intercalating dye and real-time PCR and (fluorophore same probe)) and fluoescence	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-05-2019
(((sequencing same library) and (adaptor same ligation products)) and intercalating dye and real-time PCR and (fluorophore same probe)) and fluorescence	PGPB, USPT, USOC, EPAB, DWPI	71	ADJ	YES		08-05-2019
(((sequencing same library) and (adaptor same ligation products)) and intercalating dye and real-time PCR and (fluorophore same probe) and fluorescence) and percentage	PGPB, USPT, USOC, EPAB, DWPI	38	ADJ	YES		08-05-2019
(((sequencing same library) and (adaptor same ligation products)) and intercalating dye and real-time PCR and (fluorophore same probe) and fluorescence and percentage) and affinity	PGPB, USPT, USOC, EPAB, DWPI	25	ADJ	YES		08-05-2019
(((sequencing same library) and (adaptor same ligation products)) and intercalating dye and real-time PCR and (fluorophore same probe) and fluorescence and percentage and affinity) and DNA polymerase	PGPB, USPT, USOC, EPAB, DWPI	25	ADJ	YES		08-05-2019
(((sequencing same library) and (adaptor same ligation products)) and intercalating dye and real-time PCR and (fluorophore same probe) and fluorescence and percentage and affinity and DNA polymerase) and quencher	PGPB, USPT, USOC, EPAB, DWPI	15	ADJ	YES		08-05-2019

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US-20160298182-A1.did.	PGPB	n/a	ADJ	YES		08-05-2019
US-20160298182-A1.did.	PGPB	1	ADJ	YES		08-05-2019
sequencing library adaptor ligation product	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-05-2019
sequencing library same adaptor ligation product	PGPB, USPT, USOC, EPAB, DWPI	7	ADJ	YES		08-05-2019
sequencing library same adaptor ligation product	PGPB, USPT, USOC, EPAB, DWPI	n/a	ADJ	YES		08-05-2019
20130079251	PGPB, USPT, USOC, EPAB, DWPI	8	ADJ	YES		08-05-2019
20150111788	PGPB, USPT, USOC, EPAB, DWPI	3	ADJ	YES		08-05-2019
(20150111788) and (sequencing same library)	PGPB, USPT, USOC, EPAB, DWPI	3	ADJ	YES		08-05-2019
(20150111788 and (sequencing same library)) and (blood and (nuclei or nucleus) and chromatin)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-05-2019
(20150111788 and (sequencing same library)) and blood	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-05-2019
(20150111788 and (sequencing same library)) and (nuclei or nucleus)	PGPB, USPT,	0	ADJ	YES		08-05-2019

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	USOC, EPAB, DWPI					
20150111788 and (chromatin and (nuclei or nucleus))	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-05-2019
2015011178l2 and (chromatin)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-05-2019
20150111788 and chromati$	PGPB, USPT, USOC, EPAB, DWPI	3	ADJ	YES		08-05-2019
(20130079251) and histon$	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-05-2019
((20130079251) or (20150111788)) and primer	PGPB, USPT, USOC, EPAB, DWPI	10	ADJ	YES		08-05-2019
20150111788.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-05-2019
20150111788.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-05-2019
20130079251.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-05-2019
((20150111788.pn.) or (20130079251.pn.)) and	PGPB,	4	ADJ	YES		08-05-2019

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(sequencing or amplification)	USPT, USOC, EPAB, DWPI					
((20150111788.pn.) or (20130079251.pn.)) and (open$ same chromatin)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-05-2019
((20150111788.pn.) or (20130079251.pn.)) and (open$ same chromatin)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-05-2019
(20150111788) and (open$)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-05-2019
(20150111788) and accessibility	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		08-05-2019
(20150111788) and access$	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-05-2019
(20150111788) and (open$ or access$ or chromatin or cleav$ or stain$)	PGPB, USPT, USOC, EPAB, DWPI	3	ADJ	YES		08-05-2019
(20150111788) and (open$ or clos$)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-05-2019
(20150111788) and (sequencing library)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-05-2019

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(20150111788 and (sequencing library)) and (cells)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		08-05-2019
(20150111788 and (sequencing library) and (cells)) and open chromatin	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		08-05-2019
open chromatin same transposases	PGPB, USPT, USOC, EPAB, DWPI	66	ADJ	YES		08-05-2019
(open chromatin same transposases) same tag$	PGPB, USPT, USOC, EPAB, DWPI	12	ADJ	YES		08-05-2019
20110306042.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		12-02-2019
20110306042.pn. and (open same chromatin)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-02-2019
(20110306042.pn.) and (nuclei)	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		12-02-2019
(20110306042.pn. and (nuclei)) and tagment$	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		12-02-2019
20170037453.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		12-02-2019

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(20170037453.pn.) and (open same chromatin)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-02-2019
(20170037453.pn. and (open same chromatin)) and (nucleus or nuclei)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-02-2019
(20170037453.pn. and (open same chromatin) and (nucleus or nuclei)) and (tag$ or tagment$)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-02-2019
(20170037453.pn. and (open same chromatin) and (nucleus or nuclei) and (tag$ or tagment$)) and (sequencing same library)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-02-2019
(20170037453.pn. and (open same chromatin) and (nucleus or nuclei) and (tag$ or tagment$) and (sequencing same library)) and amplification	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-02-2019
(20110306042.pn. and (open same chromatin)) and (nucleus or nuclei)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-02-2019
(20110306042.pn. and (open same chromatin) and (nucleus or nuclei)) and transposa$	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		12-02-2019
(20110306042.pn. and (open same chromatin) and (nucleus or nuclei)) and transpos$	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		12-02-2019
(20110306042.pn. and (open same chromatin) and (nucleus or nuclei)) and (sequenc$ same library)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-02-2019

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(20110306042.pn. and (open same chromatin) and (nucleus or nuclei) and (sequenc$ same library)) and (transposase or transpo$)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-02-2019
20130079251	PGPB, USPT, USOC, EPAB, DWPI	8	ADJ	YES		12-02-2019
20150111788	PGPB, USPT, USOC, EPAB, DWPI	3	ADJ	YES		12-02-2019
(20150111788) and (sequencing same library)	PGPB, USPT, USOC, EPAB, DWPI	3	ADJ	YES		12-02-2019
(20150111788 and (sequencing same library)) and (blood and (nuclei or nucleus) and chromatin)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		12-02-2019
(20150111788 and (sequencing same library)) and blood	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		12-02-2019
(20150111788 and (sequencing same library)) and (nuclei or nucleus)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		12-02-2019
20150111788 and (chromatin and (nuclei or nucleus))	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		12-02-2019
2015011178l2 and (chromatin)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		12-02-2019

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20150111788 and chromati$	PGPB, USPT, USOC, EPAB, DWPI	3	ADJ	YES		12-02-2019
(20130079251) and histon$	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		12-02-2019
((20130079251) or (20150111788)) and primer	PGPB, USPT, USOC, EPAB, DWPI	10	ADJ	YES		12-02-2019
20150111788.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		12-02-2019
20150111788.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		12-02-2019
20130079251.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		12-02-2019
((20150111788.pn.) or (20130079251.pn.)) and (sequencing or amplification)	PGPB, USPT, USOC, EPAB, DWPI	4	ADJ	YES		12-02-2019
((20150111788.pn.) or (20130079251.pn.)) and (open$ same chromatin)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		12-02-2019
15/675234	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-02-2019

PARSE EX.1007.238

sequencing library same cell	PGPB, USPT, USOC, EPAB, DWPI	1679	ADJ	YES		12-02-2019
sequencing library same cells	PGPB, USPT, USOC, EPAB, DWPI	1679	ADJ	YES		12-02-2019
sequencing library same cells	PGPB, USPT, USOC, EPAB, DWPI	1679	ADJ	YES		12-02-2019
(sequencing library same cells) same (lys$ same nuclei)	PGPB, USPT, USOC, EPAB, DWPI	25	ADJ	YES		12-02-2019
(sequencing library same cells) same chromatin	PGPB, USPT, USOC, EPAB, DWPI	98	ADJ	YES		12-02-2019
(sequencing library same cells) and chromatin	PGPB, USPT, USOC, EPAB, DWPI	573	ADJ	YES		12-02-2019
(sequencing library same cells same chromatin) and (transposase complex or Tn5 transposase)	PGPB, USPT, USOC, EPAB, DWPI	36	ADJ	YES		12-02-2019
(sequencing library same cells) and (transposase complex or Tn5 transposase)	PGPB, USPT, USOC, EPAB, DWPI	135	ADJ	YES		12-02-2019
(sequencing library same cells same chromatin and (transposase complex or Tn5 transposase)) and chromatin	PGPB, USPT, USOC, EPAB, DWPI	36	ADJ	YES		12-02-2019

PARSE EX.1007.239

(sequencing library same cells and (transposase complex or Tn5 transposase)) and ((tagged same fragment) or tag$)	PGPB, USPT, USOC, EPAB, DWPI	112	ADJ	YES		12-02-2019
(sequencing library same cells and (transposase complex or Tn5 transposase)) and (amplification or sequencing)	PGPB, USPT, USOC, EPAB, DWPI	135	ADJ	YES		12-02-2019
(sequencing library same cells and (transposase complex or Tn5 transposase) and ((tagged same fragment) or tag$)) and (tag$)	PGPB, USPT, USOC, EPAB, DWPI	112	ADJ	YES		12-02-2019
(sequencing library same cells and (transposase complex or Tn5 transposase) and ((tagged same fragment) or tag$)) and (tag$ or barcod$)	PGPB, USPT, USOC, EPAB, DWPI	112	ADJ	YES		12-02-2019
(sequencing library same cells and (transposase complex or Tn5 transposase) and ((tagged same fragment) or tag$) and (tag$)) and (adapter or adaptor)	PGPB, USPT, USOC, EPAB, DWPI	107	ADJ	YES		12-02-2019
20130079251	PGPB, USPT, USOC, EPAB, DWPI	8	ADJ	YES		12-02-2019
20130079251.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		12-02-2019
20130079251.pn. and (nuclei or nucleus)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-02-2019
(20130079251.pn.) and (chromatin or open$ chromatin)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		12-02-2019

PARSE EX.1007.240

(20130079251.pn.) and (chromatin)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		12-02-2019
generat$ same sequencing library	PGPB, USPT, USOC, EPAB, DWPI	2589	ADJ	YES		12-02-2019
20130079251	PGPB, USPT, USOC, EPAB, DWPI	8	ADJ	YES		12-02-2019
20150111788	PGPB, USPT, USOC, EPAB, DWPI	3	ADJ	YES		12-02-2019
(sequencing library same cell) and (sequencing same library)	PGPB, USPT, USOC, EPAB, DWPI	1679	ADJ	YES		12-02-2019
(sequencing library same cells) and (blood and (nuclei or nucleus) and chromatin)	PGPB, USPT, USOC, EPAB, DWPI	265	ADJ	YES		12-02-2019
(sequencing library same cells) and blood	PGPB, USPT, USOC, EPAB, DWPI	1280	ADJ	YES		12-02-2019
(sequencing library same cells) and (nuclei or nucleus)	PGPB, USPT, USOC, EPAB, DWPI	544	ADJ	YES		12-02-2019
20150111788 and (chromatin and (nuclei or nucleus))	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		12-02-2019

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20150111781l2 and (chromatin)	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		12-02-2019
20150111788 and chromati$	PGPB, USPT, USOC, EPAB, DWPI	3	ADJ	YES		12-02-2019
(15/675234) and histon$	PGPB, USPT, USOC, EPAB, DWPI	0	ADJ	YES		12-02-2019
((15/675234) or (sequencing library same cell)) and primer	PGPB, USPT, USOC, EPAB, DWPI	1468	ADJ	YES		12-02-2019
20150111788.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		12-02-2019
20150111788.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		12-02-2019
20130079251.pn.	PGPB, USPT, USOC, EPAB, DWPI	2	ADJ	YES		12-02-2019
((sequencing library same cells and (transposase complex or Tn5 transposase) and ((tagged same fragment) or tag$) and (tag$)) or (sequencing library same cells and (transposase complex or Tn5 transposase) and ((tagged same fragment) or tag$) and (tag$ or barcod$))) and (sequencing or amplification)	PGPB, USPT, USOC, EPAB, DWPI	112	ADJ	YES		12-02-2019
((sequencing library same cells and (transposase complex or Tn5 transposase) and ((tagged same fragment) or tag$) and (tag$)) or	PGPB, USPT, USOC,	44	ADJ	YES		12-02-2019

PARSE EX.1007.242

(sequencing library same cells and (transposase complex or Tn5 transposase) and ((tagged same fragment) or tag$) and (tag$ or barcod$))) and (open$ same chromatin)	EPAB, DWPI					
open chromatin	PGPB, USPT, USOC, EPAB, DWPI	1072	ADJ	YES		12-02-2019
(open chromatin) same transposase	PGPB, USPT, USOC, EPAB, DWPI	82	ADJ	YES		12-02-2019
(open chromatin same transposase) same (nucleus or nuclei)	PGPB, USPT, USOC, EPAB, DWPI	39	ADJ	YES		12-02-2019
(open chromatin same transposase same (nucleus or nuclei)) and (tagment$ or tag$)	PGPB, USPT, USOC, EPAB, DWPI	32	ADJ	YES		12-02-2019
16/418889	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-02-2019
(16/418889) and ((C12Q2521/301 | C12Q1/6806 | C12Q1/6869 | C12Q2537/164 | C12Q2521/507 | C12Q2525/191 | C12Q2535/122 | C12Q1/6874 | G16B20/00 | G16B30/00 | G16H50/20).CPC.)	PGPB, USPT, USOC, EPAB, DWPI	1	ADJ	YES		12-02-2019

PARSE EX.1007.243

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 12/10/2019

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.
16/418,889	05/21/2019	Paul Giresi	STAN-1111CON6	2173

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	~~$560~~ $1000	$0.00	$0.00	~~$560~~ $1000	03/10/2020

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 March 3, 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

PARSE EX.1007.244

Electronic Patent Application Fee Transmittal

Application Number:	16418889
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-1111CON6

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:	38760339
Application Number:	16418889
International Application Number:	
Confirmation Number:	2173
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-1111CON6
Receipt Date:	03-MAR-2020
Filing Date:	21-MAY-2019
Time Stamp:	19:50:22
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	E202033J50371027
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-1111CON6_IssueFeeTransmittal.pdf	1334502 9934c92682a86925c4e625f6839bbdce94d7c610	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	32073 1699549ced418dd0ee841bee605ca6b6ad0bc671	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1366575		

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.
16/418,889	04/14/2020	10619207	STAN-1111CON6	2173

77974 7590 03/25/2020

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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.

PARSE EX.1007.249

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	U.S. DISTRICT COURT
	8/24/2022	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			
2			
3			
4			
5			

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	U.S. DISTRICT COURT
	8/24/2022	for the District of Delaware

PLAINTIFF	DEFENDANT
10X GENOMICS, INC.	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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16			
17			
18			
19			
20			

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			