BIOGRAPHICAL SKETCH

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NAME: Gordenin, Dmitry, A

eRA COMMONS USER NAME (credential, e.g., agency login): GORDENINDA

POSITION TITLE: Principal Investigator, Mechanisms of Genome Dynamics group, National Institute of Environmental Health Sciences (NIH)

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
St. Petersburg State University, St. Petersburg, Russia	BS/Master	1973	Biology/Genetics
St. Petersburg State University, St. Petersburg, Russia	Ph.D.	1978	Genetics
St. Petersburg State University, St. Petersburg, Russia	Post-doctoral	1981	Genetics

A. Positions and Honors

Positions and Employment

1981-1988 St. Petersburg State University, St. Petersburg, Russia, Senior Research Fellow/Group Leader
1988-1997 St. Petersburg State University, St. Petersburg, Russia, Supervising Research Fellow/Research Group Leader
1997-present - National Institute of Environmental Health Sciences (NIEHS, NIH)
1997 – 2001 -Visiting Scientist
2001 – 2010 - Staff Scientist
2010 – 2015 - Senior Associate Scientist
2015 – present – Principal Investigator, Mechanisms of Genome Dynamics Group

Other Experience and Professional Memberships

SPECIALTY BOARDS

1980 - 1997 Faculty Board for the Department of Genetics, St. Petersburg State University
1993-1994 Board of Experts for the Russian Program Frontiers in Genetics
1994 Board of Scientific Counselors for the School of Biological Sciences, St. Petersburg State University
1996 - present Editorial Board of Mutation Research, Fundamental and Molecular Mechanisms of Mutagenesis section
2013 – National Consortium for Data Science, invited participant of the 2013 Summit (Chapel Hill, NC)
2016 – present Associate Editor, PLoS Genetics

SERVICE ON NIH/NIEHS COMMITTEES

1996 - DIR Discussion Group for the NIEHS Environmental Genome Project
1998 - present Environmental Genomics Faculty
2009 – 2014 NIEHS Committee on Next Generation Sequencing Technology
2012 - Knowledge and Data Management Working Group for the implementation of the NIEHS strategic plan
2012-2013 Ad hoc advisor to NIH Patient Protection and Data Management Group for facilitating of controlled access data sharing.
2014-2015 Co-chair of NIEHS Genome Data Sharing Committee.
2015-2016 NIEHS Genome Data Sharing Committee Advisory to NIEHS Genome Policy Administrator
2015-present Voting Member of dbGaP Data Access Committee for NIEHS
2015 – 2016, 2018-2019 Member of Genetics/Genomics Search Committee for NIH Stadtman Investigator program
2016 Member of Search Committee for NIEHS Biostatistics and Computational Biology Branch
2016-present NIEHS DIR Genome Policy Administrator
2018-present Chair of NIEHS Distinguished Lecture Series and Conference Support Committee

HONORS

2003. NIEHS Award "Paper of the Year" (For a paper published in the year 2002.--Lobachev K.S., Gordenin D.A., Resnick M.A. 2002. The Mre11 complex is required for repair of hairpin-capped double-strand breaks and prevention of chromosome rearrangements. Cell v. 108, 183-193).
2004. NIEHS Award "Paper of the Year" (For a paper published in the year 2003.--Jin Y.H., Clark A.B., Slebos R.J., Al-Refai H., Taylor J.A., Kunkel T.A., Resnick M.A., and Gordenin D.A. 2003. Cadmium is a mutagen that acts by inhibiting mismatch repair. Nature Genetics, v. 34, 326-329)

2008. NIEHS Award "Paper of the Year" (For a paper published in the year 2007 -- Storici F, Bebenek K., Kunkel T.A., Gordenin D.A. and Resnick M.A. 2007. RNA-Templated DNA Repair. Nature, v. 447, 338-341.)
2009 NIEHS Outstanding Staff Scientist Award
2009 NIEHS Award "Paper of the Year" (For a paper published in the year 2008 -- Nick McElhinny SA, Gordenin D.A., Stith C.M., Burgers P.M., and Kunkel T.A. 2008. Division of labor at the eukaryotic replication fork. Mol. Cell. v. 30, 137-144.)

B. Contribution to Science

1. ***Distinct outcomes from defects in eukaryotic replicative DNA polymerase delta and epsilon for genome instability***.

This finding published in *PNAS* in 1992 was the first *in vivo* demonstration of the distinct roles of eukaryotic replicative DNA polymerase delta and epsilon in DNA maintenance. It provided *in vivo* support for the hypothesis based on biochemical experiments that DNA polymerase delta is primarily responsible for lagging strand replication, while DNA polymerase epsilon mainly operates in leading strand synthesis.

Gordenin DA, Malkova AL, Peterzen A, Kulikov VN, Pavlov YI, Perkins E, Resnick MA. Transposon Tn5 excision in yeast: influence of DNA polymerases alpha, delta, and epsilon and repair genes. *Proc Natl Acad Sci U S A*. 1992;89(9):3785-9. PubMed PMID: 1315039; PMCID: PMC525575. **(*D. Gordenin – corresponding author*)**.

2. ***In vivo demonstration of the escape of long microsatellites from DNA polymerase proofreading***.

As a result of such an escape, all the burden of preventing replication errors from becoming mutations falls on mismatch repair. This finding along with *in vitro* studies from the Kunkel lab at NIEHS provided a mechanistic explanation for hypermutation of microsatellites in mismatch repair deficient cells, a distinct feature of mismatch repair deficient human cancers.

Tran HT, Keen JD, Kricker M, Resnick MA, **Gordenin DA**. Hypermutability of homonucleotide runs in mismatch repair and DNA polymerase proofreading yeast mutants. *Mol Cell Biol*. 1997;17(5):2859-65. PubMed PMID: 9111358; PMCID: PMC232138. ***(featured in ASM News as a journal highlight for May, 1997)***).

3. ***Phenomenon of strong mutagenesis mediated by environmental inhibition of mismatch repair by low levels (similar to environmental levels) of a known human carcinogen, cadmium***.

Jin YH, Clark AB, Slebos RJ, Al-Refai H, Taylor JA, Kunkel TA, Resnick MA, **Gordenin DA**. Cadmium is a mutagen that acts by inhibiting mismatch repair. *Nat Genet*. 2003;34(3):326-9. doi: 10.1038/ng1172. PubMed PMID: 12796780; PMCID: PMC2662193. (***NIEHS Paper of the Year Award, 2004***)

4. ***New biological roles of 3'→5' exonuclease activity of eukaryotic replicase -DNA polymerase delta***.

Demonstrated important roles of DNA polymerase 3'→5' exonuclease in mismatch repair and Okazaki fragment maturation in the lagging strand in addition to generally known 'textbook function' of this activity in proofreading of replication errors.

a. Jin YH, Obert R, Burgers PM, Kunkel TA, Resnick MA, **Gordenin DA**. The 3'-->5' exonuclease of DNA polymerase delta can substitute for the 5' flap endonuclease Rad27/Fen1 in processing Okazaki fragments and preventing genome instability. *Proc Natl Acad Sci U S A*. 2001;98(9):5122-7. doi: 10.1073/pnas.091095198. PubMed PMID: 11309502; PMCID: PMC33174

b. Jin YH, Ayyagari R, Resnick MA, **Gordenin DA**, Burgers PM. Okazaki fragment maturation in yeast. II. Cooperation between the polymerase and 3'-5'-exonuclease activities of Pol delta in the creation of a ligatable nick. *J Biol Chem*. 2003;278(3):1626-33. doi: 10.1074/jbc.M209803200. PubMed PMID: 12424237.

c. Jin YH, Garg P, Stith CM, Al-Refai H, Sterling JF, Murray LJ, Kunkel TA, Resnick MA, Burgers PM, **Gordenin DA**. The multiple biological roles of the 3'-->5' exonuclease of Saccharomyces cerevisiae DNA polymerase delta require switching between the polymerase and exonuclease domains. *Mol Cell Biol*. 2005;25(1):461-71. doi: 10.1128/MCB.25.1.461-471.2005. PubMed PMID: 15601866; PMCID: PMC538786.

5. ***Hypermutation in damaged single-stranded DNA and APOBEC mutagenesis in human cancers***.

I found that single-strand DNA (ssDNA) can be an at-risk situation for the genome. The genetic information of cellular organisms is encoded within double-stranded DNA (dsDNA) genomes. Yet during routine DNA transactions, such as replication, transcription, or recombination the DNA must exist

transiently in ssDNA form, which is especially vulnerable to chemical modification. Since most DNA repair mechanisms function specifically on double-strand DNA (dsDNA), ssDNA could be a very sensitive target for genome instability. The ssDNA genome instability studies are targeted to developing high-throughput systems as well as to identifying special mechanisms of mutagenesis and health-related consequences of mutagenesis in ssDNA. As a result of this series of studies we developed a set of sensitized reporters of environmentally induced genome instability and identified ssDNA specific APOBEC cytidine deaminases, normally operating within the innate immunity system, to be the strongest source of mutations in many human cancers

a. Yang Y, Sterling J, Storici F, Resnick MA, **Gordenin DA**. Hypermutability of damaged single-strand DNA formed at double-strand breaks and uncapped telomeres in yeast Saccharomyces cerevisiae. *Plos Genet*. 2008;4(11):e1000264. doi: 10.1371/journal.pgen.1000264. PubMed PMID: 19023402; PMCID: PMC2577886

b. Roberts SA, Sterling J, Thompson C, Harris S, Mav D, Shah R, Klimczak LJ, Kryukov GV, Malc E, Mieczkowski PA, Resnick MA, **Gordenin DA**. Clustered mutations in yeast and in human cancers can arise from damaged long single-strand DNA regions. *Mol Cell*. 2012;46(4):424-35. doi: 10.1016/j.molcel.2012.03.030. PubMed PMID: 22607975; PMCID: PMC3361558. **(*previewed by Cell the Leading Edge category*)**

c. Chan K, Sterling JF, Roberts SA, Bhagwat AS, Resnick MA, **Gordenin DA**. Base damage within single-strand DNA underlies in vivo hypermutability induced by a ubiquitous environmental agent. *Plos Genet*. 2012;8(12):e1003149. doi: 10.1371/journal.pgen.1003149. PubMed PMID: 23271983; PMCID: PMC3521656

d. Roberts SA, Lawrence MS, Klimczak LJ, Grimm SA, Fargo D, Stojanov P, Kiezun A, Kryukov GV, Carter SL, Saksena G, Harris S, Shah RR, Resnick MA, Getz G, **Gordenin DA**. An APOBEC cytidine deaminase mutagenesis pattern is widespread in human cancers. *Nat Genet*. 2013;45(9):970-6. doi: 10.1038/ng.2702. PubMed PMID: 23852170; PMCID: PMC3789062.

e. Chan K, Roberts SA, Klimczak LJ, Sterling JF, Saini N, Malc EP, Kim J, Kwiatkowski DJ, Fargo DC, Mieczkowski PA, Getz G, **Gordenin DA**. An APOBEC3A hypermutation signature is distinguishable from the signature of background mutagenesis by APOBEC3B in human cancers. *Nat Genet*. 2015;47(9):1067-72. doi: 10.1038/ng.3378. PubMed PMID: 26258849; PMCID: PMC4594173

f. Sakofsky CJ, Saini N, Klimczak LJ, Chan K, Malc EP, Mieczkowski PA, Burkholder AB, Fargo D, **Gordenin DA**. Repair of multiple simultaneous double-strand breaks causes bursts of genome-wide clustered hypermutation. PLoS biology. 2019;17(9):e3000464. Epub 2019/10/01. doi: 10.1371/journal.pbio.3000464. PubMed PMID: 31568516; PMCID: PMC6786661

g. Saini N, Sterling JF, Sakofsky CJ, Giacobone CK, Klimczak LJ, Burkholder AB, Malc EP, Mieczkowski PA, **Gordenin DA**. Mutation signatures specific to DNA alkylating agents in yeast and cancers. *Nucleic Acids Res*. 2020;48(7):3692-707. Epub 2020/03/07. doi: 10.1093/nar/gkaa150. PubMed PMID: 32133535; PMCID: PMC7144945.

h. Hudson KM, Klimczak LJ, Sterling JF, Burkholder AB, Kazanov MD, Saini N, Mieczkowski, PA, **Gordenin, DA**. Glycidamide-induced hypermutation in yeast single-stranded DNA reveals a ubiquitous clock-like mutational motif in humans. Nucleic Acids Res. 2023;51(17):9075-100. Epub 20230720. doi: 10.1093/nar/gkad611. PubMed PMID: 37471042; PubMed Central PMCID: PMCPMC10516655

6. ***Lifetime mutation load accumulated by human non-cancerous somatic cells***

Somatic genomes are constantly accumulating changes caused by endogenous lesions, errors in DNA replication and repair, as well as environmental insults, however accurate measurements of mutation load in healthy cells was missing. In this study, we developed an experimental approach to accurately determine the somatic genome changes accrued in cell lineages over the lifetime of healthy humans. The amounts and types of mutations in skin cells resembled many cancers. Moreover, sun-exposed skin cells had a higher mutation load attributable to ultraviolet radiation (UV) unlike cells from hips that were

protected by clothing. Our work provided precise measurements of the mutation loads in single cells in human skin. Furthermore, our data allowed defining the mutagenic impacts of environmental and endogenous processes within the same individual and led to conclusion that these processes have a comparable impact on the somatic mutation load.

a. Saini N, Roberts SA, Klimczak LJ, Chan K, Grimm SA, Dai S, Fargo DC, Boyer JC, Kaufmann WK, Taylor JA, Lee E, Cortes-Ciriano I, Park PJ, Schurman SH, Malc EP, Mieczkowski PA, **Gordenin DA**. The Impact of Environmental and Endogenous Damage on Somatic Mutation Load in Human Skin Fibroblasts. *Plos Genet*. 2016;12(10):e1006385. Epub 2016/10/28. doi: 10.1371/journal.pgen.1006385. PubMed PMID: 27788131; PMCID: PMC5082821.

b. Saini N, Giacobone CK, Klimczak LJ, Papas BN, Burkholder AB, Li JL, Fargo DC, Bai R, Gerrish K, Innes CL, Schurman SH, **Gordenin DA**. UV-exposure, endogenous DNA damage, and DNA replication errors shape the spectra of genome changes in human skin. *Plos Genet*. 2021;17(1):e1009302. Epub 2021/01/15. doi: 10.1371/journal.pgen.1009302. PubMed PMID: 33444353; PMCID: PMC7808690.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/dimitry.gordenin.1/bibliography/42199239/public/?sort=date&direction=descending