CURRICULUM VITAE

Name: Sergei M. Mirkin

Position Title: Professor and Department Chair
White Family Chair in Biology

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Education:

1978	M.S. in Genetics	Moscow State University, Moscow, USSR
1983	Ph.D. in Molecular Biology	Institute of Molecular Genetics, Russian Academy of Sciences, Moscow, USSR Advisor - Prof. Roman B. Khesin

Employment History:

1978-1983	Graduate Student	Institute of Molecular Genetics, Russian Academy of Sciences, Moscow, USSR Advisor - Prof. Roman B. Khesin
1983-1988	Postdoctoral Fellow	Institute of Molecular Genetics, Russian Academy of Sciences, Moscow, USSR Advisor - Prof. Maxim Frank-Kamenetskii
1988-1989	Group Leader	Institute of Molecular Genetics, Russian Academy of Sciences, Moscow, USSR
1989-1990	Fogarty International Fellow	La Jolla Cancer Research Foundation, La Jolla, CA, U.S.A. Advisor - Dr. Terumi Kohwi-Shigematsu
1990-1996	Assistant Professor	Department of Genetics, University of Illinois at Chicago, Chicago, IL, U.S.A.
1996-2002	Associate Professor	Department of Molecular Genetics, University of Illinois at Chicago, Chicago,

		IL, U.S.A.
2002-2003	Professor	Department of Molecular Genetics, University of Illinois at Chicago, Chicago, IL, U.S.A.
2003-2006	Professor	Department of Biochemistry and Molecular Genetics, University of Illinois at Chicago, Chicago, IL, U.S.A.
2007-Present	Professor, White Family Chair in Biology	Department of Biology, Tufts University, Medford, MA, U.S.A.
2013-Present	Department Chair	Department of Biology, Tufts University, Medford, MA, U.S.A.

Honors, Awards, Professional Activities:

Highest Honors Master of Sciences Thesis, Moscow State University, 1978.

Honorary Diploma for the Best Work in Physical-Chemical Biology, USSR Academy of Sciences, 1985.

Research Committee, USSR Academy of Medical Sciences, 1988 -1989

Research Committee, American Cancer Society, Illinois Division, 1993 -1996

Editorial board, *Gene Therapy and Molecular Biology* 1997- 2010

Member of the NIH/NICHD Special Emphasis Panel (2001), ad hoc member of the Neuroscience II study section (1999), ad hoc member of the NIH Biochemistry Study Section (2000, 2002), ad hoc member of the NIH Molecular Genetics C study section (2005), ad hoc member of the NIH Molecular Genetics B study section (2007)

American Society for Biochemistry and Molecular Biology, 2002 - present

American Society for Microbiology, 2003 – present

Associate Editor of the *GENE*, 2003 – 2011

Guest Editor for *ChemTracts - Biochemistry and Molecular Biology* theme issues "Unstable Microsatellites in the Human Genome", Part 1 – December 2004, Part 2 – March 2005

Session Chair at *14th Conversations in Biomolecular Dynamics*, Albany, 2005

International Advisory Board for *Molecular Biology (Mosk)*, 2005 – present

Managing Editor of the *Frontiers in Bioscience*, 2005 – present

Organizer, 6th International Conference on Unstable Microsatellites and Human Disease, Costa Rica, 2009

Session Chair at *16h Conversations in Biomolecular Dynamics*, Albany, USA, 2009

Session Chair, FASEB Summer Research Conference "Biological Consequences of Structured DNA", Steamboat Springs, USA, 2010

Session Chair at "Mutagenesis" Gordon Research Conference, Colby College, USA, 2010

Senior Organizing Committee, Conversations in Biomolecular Structure and Dynamics, Albany, USA, 2010-present

Full Member, Molecular Genetics B Study Section, NIH, 2010-2016

Editor-in-Chief of the *Current Opinions in Genetics and Development*, 2010-2013

Vice Chair, FASEB Summer Research Conference "Dynamic DNA Structures in Biology", Steamboat Springs, USA, 2012

Session Chair, 18th Conversations in Biomolecular Dynamics, Albany, USA, 2013

Vice Chair, Gordon Research Conference "DNA Damage, Mutation & Cancer", Ventura, USA, 2014

Convener, "DNA Dynamics" Symposium, 114 ASM General Meeting, Boston, 2014

Session Chair, Gordon Research Conference "Mutagenesis", Girona, Spain, 2014

Chair, FASEB Summer Research Conference "Dynamic DNA Structures in Biology", Itasca, USA, 2014

Session Chair, Cold Spring Harbor Meeting "DNA Replication and Genome Integrity", Cold Spring Harbor Laboratory, USA, 2015

Chair, Gordon Research Conference "DNA Damage, Mutation & Cancer", Ventura, USA, 2016

Keynote Speaker at FASEB Summer Research Conference “Dynamic DNA Structures in Biology”, Saxon River, USA, 2016

Keynote Speaker, 19th Annual Midwest DNA Repair Symposium, Dayton, USA, 2017

Invited Speaker at Scientific Meetings and Conferences:

International Conference "Recognition Studies in Nucleic Acids", 1989, Sheffield, U. K.

FEBS Conference on Bioorganic Chemistry, 1989, Moscow, USSR.

XI West Coast Chromatin and Chromosomes Meeting, 1989, Assilomar, U.S.A.

XIII West Coast Chromatin and Chromosomes Meeting, 1991, Assilomar, U.S.A.

INSERM-NIH Conference "Antisence Oligonucleotides and Ribonucleases-H, 1992, Arcachon, France.

XIV West Coast Chromatin and Chromosomes Meeting, 1992, Assilomar, U.S.A.

International Symposium "Analysis of Structures of Biomacromolecules and Their Interactions with Environmental Cytotoxic Agents", 1993, Brno, Czech Republic.

International Symposium "Pharmaceutical Design: Anti-sense, Triple Helix, Nucleic Acids Binding Drugs", 1994, Palo Alto, U.S.A.

First International Antisense Conference of Japan, 1994, Kyoto, Japan.

XVII West Coast Chromatin and Chromosomes Meeting, 1995, Assilomar, U.S.A.

Gene Therapy and Molecular Biology International Conference, 1997, Crete, Greece

DNA Replication and Transcription International Conference, 1998, Crete, Greece

Banbury Conference "The Role of DNA Topology, Conformation and Associated Factors in Gene Expression", 1999, Cold Spring Harbor, U.S.A.

2nd International Conference on "Unstable Microsatellites and Human Disease", 1999, Chapel Hill, U.S.A.

4th International Conference on "Unstable Microsatellites and Human Disease", 2004, Banff, Canada.

International Symposium “DNA Structure, Genomic Rearrangements and Human Disease”, 2006, Houston, U.S.A.

5th International Conference on "Unstable Microsatellites and Human Disease", 2006, Granada, Spain.

28th Asilomar Chromatin and Chromosome Conference, 2006, Asilomar, U.S.A.

15th Conversations in Biomolecular Dynamics, 2007, Albany, U.S.A.

Chromosome Dynamics Gordon Conference, 2007, Biddeford, U.S.A.

FASEB Summer Research Conference “DNA Palindromes”, 2008, Saxon River, USA

Mutagenesis Gordon Conference, 2008, Oxford, UK

6th International Conference "Unstable Microsatellites and Human Disease", 2009, Guanacaste, Costa Rica

Chromosome Dynamics Gordon Conference, 2009, Barga, Italy (declined)

FASEB Summer Research Conference “Biological Consequences of Structured DNA”, 2010, Steamboat Springs, USA

Mutagenesis, Gordon Research Conference, 2010, Colby College, USA

Environmental Mutagen Society, 41 Annual Meeting, 2010, Fort Worth, USA

Genomic Disorders 2011 - The Genomics of Rare Diseases, 2011, Cambridge, UK

17th Conversations in Biomolecular Dynamics, 2011, Albany, USA

International Congress on Research of Rare and Orphan Diseases, 2012, Basel, Switzerland

DNA Damage, Mutation & Cancer, Gordon Research Conference, 2012, Ventura Beach, USA

FASEB Summer Research Conference “Dynamic DNA Structures in Biology”, Steamboat Springs, USA, 2012

Genome Instability, Evolution and Human Diseases, 2013, St. Petersburg, Russia

Jubilee Scientific Conference, Institute of Molecular Genetics, Russian Academy of Science, Moscow, Russia, June 19-20, 2013.

Gordon Research Conference “DNA Damage, Mutation & Cancer”, Ventura, USA, 2014

Gordon Research Conference “Mutagenesis”, Girona, Spain, 2014

Cold Spring Harbor Meeting “DNA Replication and Genome Integrity”, Cold Spring Harbor Laboratory, USA, 2015

International Meeting “"At the Intersection of DNA Replication and Genome Maintenance: from Mechanisms to Therapy", Trieste, Italy 2016

Invited Scientific Seminars:

Department of Molecular Biology, Princeton University, 1991

Laboratory of Oncogenesis, NCI, Frederick, 1991

Basic Sciences Division, Fred Hutchinson Cancer research Center, 1991

Museum d’Histoire Naturelle, Paris, France, 1992

SRI International, Menlo Park, 1992

Department of Biochemistry, Northwestern University, 1992

Department of Biochemistry, University of Alberta, Edmonton, Canada, 1993

Department of Pharmacology, Mayo Clinic, Rochester, 1993

Laboratory of Molecular Genetics, NIEHS, NIH, Research Triangle Park, 1993

Department of Pharmacology, UMDNJ-Robert Wood Johnson Medical School, Piscataway, 1993

Genetics and Biochemistry Branch, NIDDK, NIH, Bethesda, 1993

Department of Biology, Iowa State University, 1994

Nuclear Medicine Department, NIH, Bethesda, 1995

Department of Biochemistry, Oklahoma State University, 1997

Basic Science Division, Fred Hutchinson Cancer research Center, 1997

Department of Molecular Biology, Max Planck Institute for Biophysical Chemistry, Goettingen, Germany, 1997

Department of Biochemistry, Mayo Clinic, Rochester, 1998

Department of Biochemistry, Northwestern University, Evanston, 1998

Cancer Center, Northwestern University, Chicago, 1998

Children Memorial Institute for Education and Research, 1998

Department of Molecular Biology, Princeton University, 1999

Division of Biology, Lawrence Berkeley National Laboratory, Berkeley, 1999

Department of Biochemistry, University of Illinois at Urbana, 1999

Laboratory of Molecular Genetics, NIEHS, NIH, Research Triangle Park, 1999

Department of Microbiology, Wayne State University, 2000

Institute des Hautes Etudes Scientifiques, Bures Sur Yvette, France, 2000

Laboratory of Immunopathology, NIAID, NIH, Bethesda, 2001

Jackson Laboratory, Bar Harbor 2001

Institute of Biosciences and Technology, Texas A&M University, Houston 2002

Pharmacology Seminar Series, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Piscataway, 2003

Genetics and Biochemistry Branch, National Institutes of Health, Bethesda 2003

Gene Regulation and Chromosome Biology Laboratory, National Cancer Institute, Frederick 2004

Genetic Task Force of Illinois, Chicago 2004

Department of Molecular Biology, University of California, Berkeley 2004

Joint Seminars in Molecular Biology, University of California, Davis 2004

Department of Biochemistry & Molecular Biology, Wright State University, Dayton 2004

Department of Biochemistry and Molecular Biology, University of Arkansas for Medical Sciences, Little Rock 2004

Department of Biochemistry and Molecular Genetics, University of Alabama, Birmingham 2004

Department of Biology, Tufts University, Medford 2005

Department of Biochemistry, University of Illinois, Urbana 2005

Eppley Institute for Cancer Research, University of Nebraska, Omaha 2006

Institute of Molecular Genetics, Russian Academy of Sciences, Moscow 2006

School of Biology, Georgia Institute of Technology, Atlanta, 2006

Department of Molecular Genetics & Microbiology, University of Florida, Gainesville, 2006

Centro de Investigaciones Biológicas, Madrid, Spain, 2006

UT MD Anderson Cancer Center, Science Park, 2006

Lutheran General Cancer Research Center, Chicago, 2007

National Cancer Institute, Bethesda, 2007

Marine Biological Laboratory, Woods Hole, 2007

Program for Bioinformatics, Boston University, Boston, 2008

Department of Microbiology, University of Illinois, Urbana, 2010

Department of Biology, Stanford University, 2011

Department of Biology, Northeastern University, Boston, 2011

Department of Microbiology, University of Georgia, Athens, 2013

Program in Genetics and Genomics, Duke University, Durham, 2013

Massachusetts General Hospital Cancer Center, Charlestown, 2014

Biomolecular Sciences Institute, Florida State University, Miami, 2014

Biochemistry and Molecular Pharmacology, New York University, 2014

Biochemistry & Molecular Genetics, University of Virginia School of Medicine, 2016

PhD Genetics Seminar, University of Iowa, 2017

Current Grant Support:

"Replication of Simple DNA Repeats" Agency: National Institutes of Health, National Institute of General Medical Sciences. Type: 5R01GM060987. Principal Investigator: Sergei M. Mirkin, Ph.D. Years: 13-to-16. TDC - $873,631; TC - $1,335,525. Period: February 1, 2001 to January 31, 2018.

Expansions of simple DNA repeats are implicated in nearly thirty hereditary disorders in humans. They include debilitating neurological disorders, such as Huntington's disease, fragile X mental retardation, myotonic dystrophy, Friedreich's ataxia and others. This proposal concentrates on molecular mechanisms responsible for repeat expansions in yeast and mammalian cells.

"Mechanisms of inherent genome instability" Agency: National Institutes of Health, National Institute of General Medical Sciences. Type: 5P01GM105473_Project 3. Principal Investigator: Sergei M. Mirkin, Ph.D. Period: April 1, 2014 to March 31, 2019. TDC - $1,125,000; TC - $1,715,142.

This proposal is devoted to the mechanisms of inherent genome instability, which occurs without external DNA damage and leads to numerous hereditary diseases in humans, as well as to genome rearrangements in cancer. Specifically, it concentrates on genome instability caused by transcription-replication collisions, or mediated by interstitial telomeric sequences.

Completed Grant Support:

American Cancer Society Illinois Division, "The mechanism of DNA modification by chloroacetaldehyde", Principal Investigator, 9/28/90 - 9/27/92

American Cancer Society, MG-25 "Triple-helical DNA in oncogene promoters", Principal Investigator, 01/01/92 - 12/31/93

National Institutes of Health, R55GM46405-01A1 "Triple-helical DNA in the TATA-less oncogene promoters", Principal Investigator, 10/1/92 - 9/30/94

National Science Foundation, MCB723924 "DNA triplexes and replication", Principal Investigator, 09/01/94 - 08/31/01

National Institutes of Health, 1RO1GM60987 "Transcriptionally-dependent rearrangements in DNA", Principal Investigator, 05/01/96 - 04/30/00

Council for Tobacco Research, #4468 "Trinucleotide repeats and replication", Principal Investigator, 01/01/97 – 12/31/99

National Institutes of Health, 3R01CA093729-08S1 "Repair of Genome Destabilizing DNA Structures", Co-PI, 8/1/09 – 7/31/2013

Teaching:

1986-1989 Instructor of the Undergraduate Course "Enzymology of Genetic Processes" at the Moscow Physical Technical Institute.

1992-2002 Director of the Graduate Course GENE 514 "Structure and Function of Nucleic Acids" at the University of Illinois at Chicago, College of Medicine.

2003-2006 Director of the Graduate Course GCLS 502 “Molecular Biology” at the University of Illinois at Chicago, College of Medicine.

2007-present Co-director of the Advanced Undergraduate/Graduate Course Bio188, “Seminar in Molecular Biology and Genetics.”

2008-present Director, Advanced Undergraduate/Graduate Course Bio190, “DNA: From Structure to Function”

University Service:

2007-2008 Chair, Faculty Recruitment Committee, Biology, Tufts University

1992-2006 Graduate Admission Committee at the Department of Molecular Genetics, UIC

1995-1997 Seminar Committee for the Molecular and Cellular Biology Training Program, College of Medicine, UIC

1999-2004 MD/Ph.D. Admission Committee, College of Medicine, UIC

1999-2006 Chair, Campus Research Board Life Sciences Sub-Committee.

2000-2002 Recruitment Committee for the Head of the merged Biochemistry/Molecular Biology Department, College of Medicine, UIC

2002-2005 UIC Senate, Chair of Research Committee

2008-2009 Chair, Faculty Recruitment Committee, Department of Biology, Tufts University

2010-2011 Chair, Faculty Recruitment Committee, Department of Biology, Tufts University

2012-2014 Planning Group and Steering Committee, Tufts Innovation Institute

2013-present Chair, Biology Department

2014-2016 Member, Steering Committee, Tufts Innovation Institute

Graduate Students Advised:

		Current position
George M. Samadashwily	Ph.D., 1996	Physician in Georgia
Randal Cox	Ph.D., 1997	Chief Scientist at Rippleshot
Gordana Raca	Ph.D., 2001	Assistant Professor, University of Chicago
Gerald Buldak	Ph.D., 2004	Lecturer, Loyola University, Chicago
Ekaterina V. Mirkin	Ph.D., 2006	Lecturer, Tufts University
Irina Voineagu	Ph.D., 2008	Senior Lecturer, University of New South Wales
Christine Surka	M.S., 2010	Scientist, Caltech
Vera Egorova	M.S., 2011	Sales Representative, Oracle
Kartik Shah	Ph.D., 2013	Scientist, Amgen Inc.
Ryan McGinty	2012–present	Tufts University
Alexander Neil	2014–present	Tufts University
Ekaterina Spivakovsky-Gonzalez	2014–present	Tufts University

Postoctoral Fellows Advised:

		Current position
Andrew Dayn, Ph.D.	1990 – 1993	Vice-President, Exigen Inc.
Ganapathirama Raghu, Ph.D.	1992 – 1994	Biotechnology Consultant and Contractor
Alexey Danilkovich, Ph.D.	1993 – 1994	Senior Scientist, Russian Academy of Sciences
Andrey Krasilnikov, Ph.D.	1996 – 2000	Associate Professor, Pennsylvania State University

Elena Siyanova, Ph.D.	1996 – 2000	Deceased
Maria Krasilnikova, Ph.D.	1996 – 2005	Research Assistant Professor, Pennsylvania State University
Alexander Shishkin, Ph.D.	2005 – 2011	Senior Scientist, Illumina Inc.
Sylwia Szwarocka, Ph.D.	2007 – 2007	Scientist, Polish Academy of Sciences
Anna Aksenova, Ph.D.	2009 – 2013	Senior Scientist, St. Petersburg State University
Thomas Ebersole, Ph.D.	2009 – 2013	Self-employed
Jane Christina Kim, Ph.D.	2010–2016	Assistant Professor, UC San Marcos
Artem Kononenko, Ph.D.	2014–present	Tufts University
Elina Radchenko, Ph.D.	2015–present	Tufts University
Jessica Wilks, Ph.D.	2015–2016	Broad Institute
Jorge Cebrian Castillo, Ph.D.	2016–present	Tufts University

Publications

Book Chapters (reverse chronological order):

Mirkin S. (2006) "Replication of Expandable Repeats". In: *Genetic Instabilities and Neurological Diseases*, 2nd ed., R.D. Wells and T. Ashizawa eds., pp. 637-644.

Krasilnikova, M.M., **Mirkin, S.M**. (2004) Analysis of triplet repeat replication by 2 dimensional gel-electrophoresis. In: *Methods in Molecular Biology, vol. 277: Trinucleotide Repeat Protocols.* Edited by: Y. Kohwi © Humana Press Inc., Totowa, NJ, pp.19-28.

Mirkin, S.M. (2001) DNA topology: Fundamentals. In: *Encylopedia of Life Sciences*, http://www.els.net, London: Nature Publishing Group

Mirkin, S.M. (1999) Structure and biology of H DNA. In: *Triple Helix Forming Oligonucleotides*, Kluwer Academic Publishers (Norwell, MA) C. Malvy and A. Harel-Bellan eds., pp. 193-222.

Pati, S., **Mirkin, S.M.**, Feuerstein, B., Zarling, D. (1997) Sequence-specific DNA targeting. In: *Encyclopedia of Cancer* **v. III**, pp. 1601-1625, Academic Press, Inc., San Diego, CA.

Invited Reviews (reverse chronological order):

Shah, K.A., **Mirkin, S.M.** (2015) The hidden side of unstable DNA repeats: Mutagenesis at a distance. *DNA Repair* **32**: 106-112.

Mirkin, E.V., **Mirkin, S.M.** (2014) To switch or not to switch: at the origin of repeat expansion disease. *Mol. Cell* **53**: 1-3.

Belotserkovskii, B.P., **Mirkin, S.M**., Hanawalt, P.C. (2013) DNA sequences that interfere with transcription: implications for genome function and stability. *Chem. Rev.* **113**: 8620-8637.

Kim, J.C., **Mirkin, S.M.** (2013) The balancing act of DNA repeat expansions. *Curr. Opin. Genet. Dev.* 23, 280-288.

Mirkin, S.M. (2013) DNA replication: driving past four-stranded snags. *Nature* 497, 449-450.

Mirkin, S.M. (2010) Getting to the core of repeat expansions by cell reprogramming. *Cell Stem Cell* **7**, 545-546.

Voineagu, I., Freudenreich, C.F., **Mirkin, S.M.** (2009) Checkpoint Responses to Unusual Structures Formed by DNA Repeats. *Mol. Carcinogen*. **48**, 309-318.

Mirkin, S.M. (2008) Discovery of alternative DNA structures: a heroic decade (1979-1989) Front. Biosci. **13**, 1064-1071.

Mirkin, S.M. (2007) Expandable DNA Repeats and Human Disease. *Nature*, **447**, 932-940.

Mirkin, E.V., **Mirkin, S.M.** (2007) Replication fork stalling and natural impediments. *Microbiol Mol Biol Rev.* **71**, 13-35.

Mirkin, S.M. (2006) DNA structures, repeat expansions and human hereditary disorders. *Curr. Opin. Struct. Biol.*, **16**, 1–8.

Mirkin, S.M. (2005) Toward the unified theory for repeat expansions. *Nature Struct. Mol. Biol.* **12**, 635-637.

Mirkin, S.M. (2004) Molecular models for repeat expansions. *Chemtracts - Biochem. Mol. Biol*.**17**, 639-662.

Mirkin, S.M., Smirnova, E.V. (2002) Positioned to expand. *Nature Genet*., **31**, 5-6.

Siyanova, E. Y., **Mirkin, S.M.** (2001) Expansion of trinucleotide repeats. *Mol. Biol (Mosk.)* **35**, 168-182.

Krasilnikova, M.M., Samadashwily, G.M., **Mirkin, S.M.** (1999) Replication of simple DNA repeats. *Gene Ther. Mol. Biol.* **3**, 397-412.

Mirkin, S.M. (1997) Everything you always wanted to know about triplexes (but were afraid to ask). *J. Am. Chem. Soc.* **119**, 6692.

Frank-Kamenetskii, M.D., **Mirkin, S.M.** (1995) Triplex DNA structures. *Annu. Rev. Biochem.* **64**, 65-95.

Mirkin, S.M., Frank-Kamenetskii, M.D. (1994) H-DNA and related structures. *Annu. Rev. Biophys. Biomol. Struct.* **23**, 541-576.

Gragerov, A.I., **Mirkin, S.M.** (1980) Influence of DNA superhelicity on the major genetic processes in prokaryotes. *Mol. Biol (Mosk.)* **14**, 8-34.

Essays (reverse chronological order):

Mirkin S. M. (2011) A Renaissance Man: In Memoriam of Jon Widom (1955-2011). J. Biomol. Struct. Dynam. **29**, 253-255

Mirkin S. M. (2008) A Tribute to Evgenii V. Ananiev (1947-2008). *PLoS Genet.* **4:**e1000122.

Mirkin, S.M. (2002) Thinking of R. B. Khesin. *Mol. Biol. (Mosk.)*, **36**, 347-360.

Experimental Papers (reverse chronological order):

Kim, J.C., Harris, S.T., Dinter. T., Shah, K.A., **Mirkin S.M.** (2017) The role of break-induced replication in large-scale expansions of $(CAG)_n/(CTG)_n$ repeats. *Nat Struct Mol Biol* **24**: 55-60.

Aksenova, A.Y., Han, G., Shishkin, A.A., Volkov, K.V., **Mirkin, S.M.** (2015) Expansion of interstitial telomeric sequences in yeast. *Cell Rep.* **13**: 1545-1551.

Pandey, S., Ogloblina, A.M., Belotserkovskii, B.P., Dolinnaya, N.G., Yakubovskaya, M.G., Mirkin, S.M., Hanawalt, P.C. (2015) Transcription blockage by stable H-DNA analogs in vitro. *Nucleic Acids Res.* 43: 6994-7004.

Shah, K.A., McGinty, R.J., Egorova, V.I., **Mirkin, S.M.** (2014) Coupling transcriptional state to large-scale repeat expansions in yeast. *Cell Rep.* 9: 1594-1602.

Polak, P., Lawrence, M.S., Haugen, E., Stoletzki, N., Stojanov, P., Thurman, R.E., Garraway, L.A., **Mirkin, S.**, Getz, G., Stamatoyannopoulos, J.A., Sunyaev, S.R. (2014) Reduced local mutation density in regulatory DNA of cancer genomes is linked to DNA repair. *Nat. Biotechnol*. **32**, 71-75.

Aksenova, A.Y., Greenwell, P.W., Dominska, M., Shishkin, A.A., Kim, J.C., Petes, T.D., **Mirkin, S.M.** (2013) Genome rearrangements caused by interstitial telomeric sequences in yeast. *Proc. Natl. Acad. Sci. USA* **110**, 19866-19871.

Belotserkovskii, B.P., Neil, A.J., Saleh, S.S., Shin, J.H., **Mirkin, S.M.**, Hanawalt, P.C. (2013) Transcription blockage by homopurine DNA sequences: role of sequence composition and single-strand breaks. *Nucleic Acids Res.* 41, 1817-1828.

Shah, K.A., Shishkin, A.A., Voineagu, I., Pavlov, Y.I., Shcherbakova, P.V., **Mirkin SM**. (2012) Role of DNA polymerases in repeat-mediated genome instability. *Cell Rep.* 2, 1088-1095.

Zhang, Y., Shishkin, A.A., Nishida, Y., Narayanan, V., Marcinkowski-Desmond, D., Saini, N., Volkov, K.V., **Mirkin, S.M.**, Lobachev, K.S. (2012) Genome-wide screen identifies pathways that govern GAA/TTC repeat fragility and expansion in dividing and non-dividing yeast cells. *Mol. Cell* 48, 254-265.

Chandok GS, Patel MP, **Mirkin SM**, Krasilnikova MM. (2012) Effects of Friedreich's ataxia GAA repeats on DNA replication in mammalian cells. *Nucleic Acids Res.* **40**, 3964-3974.

Anand, R.P., Shah, K.A., Niu, H., Sung, P., **Mirkin, S.M.**, Freudenreich, C.H. (2012) Overcoming natural replication barriers: differential helicase requirements. *Nucleic Acids Res* **40**, 1091-105.

Tang, W., Dominska, M., Greenwell, P.W., Harvanek, Z., Lobachev, K.S., Kim, H.M., Narayanan, V., **Mirkin, S.M.**, Petes, T.D. (2011) Friedreich's ataxia (GAA)n•(TTC)n repeats strongly stimulate mitotic crossovers in Saccharomyces cerevisae. *PLoS Genet.* **7**, e1001270.

Cherng, N., Shishkin, A.A., Schlager, L.I., Tuck, R.H., Sloan, L., Matera, R., Sarkar, P.S., Ashizawa, T., Freudenreich, C.H., **Mirkin, S.M.** (2011) Expansions, contractions, and fragility of the spinocerebellar ataxia type 10 pentanucleotide repeat in yeast. *Proc. Natl. Acad. Sci. USA* **108**, 2843-2848.

Belotserkovskii B.P., Liu R., Tornaletti S., Krasilnikova M.M., **Mirkin S.M.**, Hanawalt P.C. (2010) Mechanims and implications of transcription blockage by guanine-rich DNA sequences. *Proc. Natl. Acad. Sci. USA*, **107**,12816-12821.

Shishkin, A.A., Voineagu, I., Matera, R., Cherng, N., Chernet, B.T., Krasilnikova, M.M., Narayanan, V., Lobachev, K.S., **Mirkin, S.M.** (2009) Large-scale expansions of Friedreich's ataxia GAA repeats in yeast. *Mol. Cell* **35**, 82-92.

Stamatoyannopoulos, J.A., Adzhubei, I., Thurman, R.E., Kryukov, G.V. **Mirkin, S.M.**, Sunyaev, S.R. (2009) Time of human DNA replication predicts mutation rate. *Nat. Genet.*, **41**, 393-395.

Voineagu, I., Surka, C.F., Shishkin, A.A., Krasilnikova, M.M., **Mirkin, S.M.** (2009) Replisome stalling and stabilization at CGG repeats, which are responsible for chromosomal fragility. *Nat. Struct. Mol. Biol.* **16**, 226-228.

Kim HM, Narayanan V, Mieczkowski PA, Petes TD, Krasilnikova MM, **Mirkin SM,** Lobachev KS. (2008) Chromosome fragility at GAA tracts in yeast depends on repeat orientation and requires mismatch repair. *EMBO J.* **27,** 2896-2906.

Voineagu, I., Narayanan V., Lobachev, K.S., **Mirkin, S.M.** (2008) Replication stalling at unstable inverted repeats: Interplay between DNA hairpins and fork stabilizing proteins. *Proc. Natl. Acad. Sci. USA*, **105**, 9936-9941.

Krasilnikova, M.M., Kireeva, M.L., Petrovic, V., Knijnikova, N., Kashlev, M., **Mirkin, S.M.** (2007) Effects of Friedreich's ataxia (GAA)n·(TTC)n repeats on RNA synthesis and stability. *Nucleic Acids Res.* **35**, 1075-1084.

Mirkin, E. V., Castro Roa, D., Nudler E., **Mirkin, S.M.** (2006) Transcription regulatory elements are punctuation marks for DNA replication. *Proc. Natl. Acad. Sci. USA*, **103**, 7276-7281.

Mirkin, E. V., **Mirkin, S.M.** (2005) Mechanisms of transcription-replication collisions in bacteria. *Mol. Cell. Biol*. **25**, 888-895.

Krasilnikova, M.M., **Mirkin, S.M.** (2004) Replication stalling at Friedreich's ataxia (GAA)n repeats in vivo. *Mol. Cell. Biol*. **24**, 2286-2295.

Buldak, G.L., **Mirkin , S.M.** (2003) Unusual chemical hypersensitivity of the d(GA)n·d(TC)n repeat in vivo dependent on functional lactose repressor. *Gene Ther. Mol. Biol*. **7**, 291-298.

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Research Interests:

The field of my research, broadly defined, is DNA structure and functioning. I am primarily interested in the role of various DNA repeats in genome maintenance and their effects on major genetic transactions in health and disease. Secondly, my lab studies complex interplays between genetic machineries, operating simultaneously at a given genomic segment, such as replication and transcription. Finally, I have been fascinated by DNA conformations that differ from the canonical B-DNA since my postdoctoral years. Thus, a significant part of my research is devoted to unusual DNA structures and their biological roles. These three directions of my research are principally intertwined, building the framework for better understanding of genome structure, evolution and functioning.

Replication and expansion of simple DNA repeats.

Uncontrollable expansions of trinucleotide repeats lead to more than two dozens of human hereditary neurological disorders, including Fragile X mental retardation, Huntington's disease, myotonic dystrophy, Friedreich's ataxia, *etc*. The molecular mechanisms of repeat expansions have, therefore, attracted a very broad attention. My lab is pursuing a hypothesis that abnormal replication of expandable repeats could be in charge of this phenomenon. Using two-dimensional electrophoretic analysis of the replication intermediates, we were the first ones to demonstrate that replication fork is indeed stalled within those repetitive runs in a length and orientation-dependent manner *in vivo*. While our original observations were made in a model bacterial system, we have subsequently extended them into eukaryotic cells, including yeast and mammals. In all three systems, expandable repeats attenuated DNA replication. There was a good agreement between the repeats' lengths, causing replication blockage in our systems, and their expansion thresholds in human pedigrees. Furthermore, there was a clear-cut correlation

between the strength of the replication stalling and the repeat's propensity to expand/contract in our experimental system. Finally, specific mutations in the replication proteins drastically increased the frequency of repeat expansions. Based on these observations and many supporting data from other labs, we have proposed a replication model for repeat expansions. It implies that the replication fork stalling at expandable repeats is caused by their ability to form stable DNA structures in the lagging strand template. Expansions and contractions supposedly occur during the imprecise replication fork restart within those repetitive runs.

We are currently pursuing these studies in several directions. We analyze the replication of other structure-prone repeats, differing from trinucleotide repeats, to affirm that replication stalling is the universal phenomenon for this class of DNA sequences. We have developed an experimental system, which allows us to select for the large-scale expansions and/or contractions of various repeats in yeast. We plan to develop a principally similar selection system in mammalian cells. These systems should help us to unravel the role of cis- and trans-acting factors in repeat expansions. In the long run, they could also help searching for drugs that affect the rates of expansions or contractions, which could be useful for treatment of the debilitating disorders, caused by expandable repeats.

Mechanisms of genome instability caused by interstitial telomeric repeats.

In addition to their location at chromosomal termini, telomeric repeats also are present at internal sites of the chromosomes in many organisms. Two types of interstitial telomeric sequences (ITSs) were detected in mammalian genomes: heterochromatic ITSs (het-ITSs) and short ITSs (s-ITSs). Het-ITSs are believed to be the remnants of ancestral chromosomal fusions; they often colocalize with sites of spontaneous or induced chromosome breakage sites. S-ITSs are believed to represent insertions of telomeric repeats that occur during

the repair of double-stranded DNA breaks. In primates and rodents, s-ITSs co-localize with certain chromosomal fragile sites, map to chromosome breakpoints in cancer cells, and present at sites of jumping translocations in patients with Prader-Willi syndrome.

The mechanisms of genome instability caused by ITSs remain unknown. We have developed a yeast system to investigate the effects of various ITSs, including human ITSs, on genome stability. We found that these repeats are enormously polymorphic in length and trigger gross chromosomal rearrangements, including deletions, duplications inversions and translocations, as well as a formation of acentric minichromosomes. We are carrying out various genetic and biochemical screens to unravel molecular mechanisms of these phenomena.

Transcription-replication interplay and its effect on the genome organization and stability.

Since transcription and replication share the same template, occasional collisions between the two machineries are inevitable and can interfere with both processes. We have recently found that the head-on collisions with elongating RNA polymerase is much more detrimental for the replication fork progression *in vivo* than the co-directional collisions. Furthermore, we have proven that these collisions are caused by the direct, physical impact of the two machineries, rather than the long-range alterations of the DNA template. These results, combined with the data on the preferred co-directional alignment of transcription units with the direction of replication in prokaryotes, have led us to suggest that the main disadvantage of the head-on collisions could be in their inhibitory effect on DNA replication.

Besides collisions with elongating RNA polymerases, we study the effects of the transcription initiation or termination complexes on the replication fork progression. This could be even more important direction, since most genes are not actively transcribed during DNA replication. We have recently found that the steadfast transcription initiation complexes inhibit

the replication fork progression in an orientation-dependent manner, during head-on collisions. Transcription terminators also appeared to attenuate DNA replication, but in the opposite, co-directional orientation. Notably in both instances, the replication fork is stalled immediately after passing the coding region. Transcription regulatory signals, thus, serve as "punctuation marks" for DNA replication *in vivo* by attenuating the replication fork progression, as it has traversed the coding areas. This attenuation could provide an extra time for the repair or recombination machineries to clear the coding areas off the newly acquired mutations.

This project is now developing in several directions. First, we are expanding our collision studies from the *E. coli* into yeast *S. cerevisiae* and, eventually, mammals. Second, we plan to experimentally determine mutation rates in the transcribed areas that are replicated head-on or co-directionally. This study will be carried out in yeast, using selectable genes driven by the S-phase-specific promoters. Finally, we are starting a major bioinformatics project, aimed at estimating the sequence divergence between genes in numerous bacterial genomes depending on their positioning relative to the direction of the replication.

Unusual DNA structures, including DNA triplexes.

More than a decade ago, we have characterized an unusual three-stranded DNA structure, H-DNA, formed by homopurine-homopyrimidine mirror repeats. Little did we know at a time that one of those repeats, $(GAA)_n \cdot (TTC)_n$, will be eventually implicated in the development of the hereditary human disorder, Friedreich's ataxia. We have since found that formation of unusual DNA structures by H motifs during the DNA synthesis *in vitro* could block various DNA polymerases. Remarkably, the polymerase itself triggered the formation of an unusual DNA structure that subsequently inhibited it. Simple DNA repeats including, but not limited to H motifs were, thus, called "suicidal sequences" for the DNA polymerization. It has now become

apparent that various DNA repeats could serve as suicidal motifs for the RNA polymerase, as well. Considerable efforts are currently being devoted to the detection of DNA triplexes and other unusual DNA structures inside living cells and elucidating their biological roles in norm and disease.

Achievements as Department Chair

I became Chair of Biology Department at Tufts in 2013. Department currently consists of twenty-six full-time faculty members, whose interests center on understanding life at the molecular, cellular, organismal, population and community levels. Below are some milestones reached on my watch.

In 2014, our Department was ranked 3rd nationwide among all undergraduate Biology departments by College factual (USA Today). Biology is currently the second biggest major at Tufts, with ~150 seniors graduated in 2015. A major factor contributing to this popularity is the great opportunity our students have to participate in cutting-edge research. More than 100 undergraduates conducted independent research projects in Biology in 2014-2015 academic year including 14 exceptional senior honors theses. On the teaching front, we are working hard to maintain the highest standards for which Tufts is famous. A striking affirmation of the department's continuing efforts to enhance student learning was Senior Lecturer Susan Koegel's being chosen as the 2015 TCU Professor of the Year.

We were privileged to attract several outstanding new faculty members during the last three years, including Dr. Elizabeth Crone, who joined us from Harvard Forest, as Associate Professor in Population Ecology and Dynamics, Dr. Benjamin Wolfe, who joined us from Harvard to become Assistant Professor in Microbiology, Dr. Kate Mirkin, also from Harvard, who became our new lecturer in Genetics, and Dr. Mimi Kao from University of California, San Francisco, who just started as Assistant Professor in Physiology.

Our Department maintains an active and productive research enterprise led by faculty members who enjoy wide recognition in the scientific community. More than eighty papers in high-impact journals came out of the Department during the past year alone. Our research endeavors are well supported by external grants, including new research initiatives supported by several Program Project Grants. Currently, the total amount of our external funding is ~$35 million with annuakl annual grants exceeding $8 million. As a result, Biology has become the best-funded Department of the School of Arts and Sciences in 2015!

All of this would not have been possible without enormous talent and hard work of our students, postdoctoral fellows and staff. Our graduate program grew significantly during the last three years: forty-five students are currently enrolled in the program. The success with funding also allowed us to build post-graduate population: twenty-two excellent postdoctoral fellows are now working in the Department. Last but not the least, we have a truly outstanding departmental staff, who has just won Tufts “Extraordinary Colleague Award” Distinction.