

CURRICULUM VITAE

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Education

| <u>Year</u> | <u>Degree</u> | <u>Field</u> | <u>Institution</u> |
|-------------|---------------|--------------|--|
| 1989 | B.A. | Biology | Division of Biology, Moscow State University, Moscow, USSR |
| 1992 | M.S. | Genetics | Department of Genetics, Moscow State University, Russia |
| 1995 | Ph.D. | Biochemistry | Institute of Molecular Genetics, Russian Academy of Sciences |

Postdoctoral Training

| <u>Dates</u> | <u>Specialty</u> | <u>Mentor</u> | <u>Place of Training</u> |
|--------------|-------------------|-----------------|--|
| 1995-1997 | Molecular Biology | Dr. A. Goldfarb | Public Health Research Institute, New York |

Academic Appointments

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| 1997-2003 | Assistant Professor, New York University School of Medicine, New York, NY |
| 2003-2005 | Associate Professor (tenured), New York University School of Medicine |
| 2005-2008 | Professor, Dept. of Biochemistry, NYU School of Medicine |
| 2008- | Julie Wilson Anderson Professor, NYU School of Medicine |
| 2013- | Investigator, Howard Hughes Medical Institute |

Awards/Honors

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| 1997 | The Helen Hay Whitney Foundation research fellowship (declined) |
| 1998 | The Searle Scholar Award |
| 2001 | The Irma T. Hirschl Career Scientist Award |
| 2002 | The Edward Mallinckrodt, Jr. Foundation Research Award |
| 2002 | Fogarty International Research Collaboration Award |
| 2004 | Keynote Lecture: The RNA Biochemistry Symposia. Blaubeuren, Germany |
| 2004 | United States-Israel Bi-national Science Foundation Award |
| 2006 | The Dynasty Foundation Award |
| 2006 | NIH Director's Pioneer Award |
| 2008 | Crain's "40 Under 40" Alumni |
| 2008 | Julie Wilson Anderson Professorship (endowment chair) |
| 2009 | The Vilcek Foundation Finalist Prize |
| 2010 | Keynote Lecture: The Harden Conference on Transcription. Cambridge, UK |
| 2010 | The Blavatnik Award, New York Academy of Science |
| 2011 | The Robertson Foundation Award |
| 2012 | Biogerontology Research Foundation Award |

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| 2012 | Blavatnik Family Foundation Award |
| 2013 | Investigator, Howard Hughes Medical Institute |
| 2013 | Honorary Professor, Moscow Institute of Physics and Technology |
| 2013 | Master Scientist, NYU Langone Medical Center |
| 2014 | Dean's Honor Lecture, NYU School of Medicine |
| 2016 | The Neil Welker Memorial Award |
| 2016 | Engelhardt Memorial Lecture, IMB, Russian Academy of Science |
| 2016 | Elected Foreign Member, Russian Academy of Sciences |
| 2017 | Elected Fellow, American Academy of Arts and Sciences |

Research Statement

Our most significant contributions to science include:

1. Discovery and implications of RNA polymerase (RNAP) “backtracking” and “ratcheting”:

In 1997 we described back-and-forth sliding of RNAP along DNA and RNA. Our group then showed that this phenomenon, which we called “*backtracking*”, plays the key role in regulating gene expression (via pausing and termination), in transcriptional fidelity, in genome instability, and in coupling transcription to DNA repair. We were also the first to demonstrate that RNAP is a Brownian ratchet machine. Our findings explained in mechanistical details how RNAP translocates, how it responds to regulatory signals and factors, and how it terminates transcription.

2. Mechanisms of transcription termination and antitermination. We have uncovered the general mechanistical principles of the termination process in bacteria and formulated models explaining the intricate molecular pathways leading to both intrinsic and Rho-dependent transcription termination. We also studied how these processes are regulated in the cell and formulated the mechanistical models of factor-dependent (antitermination) and factor-independent (riboswitches) modes of regulation. Our studies uncovered novel functions of Rho, such as its role in silencing of horizontally transferred (and potentially toxic) genes and in preserving genomic integrity. We found that Rho functions as the global regulator of transcription acting at the 5'UTRs of hundreds of bacterial genes, and that sRNAs control Rho-dependent termination genome-wide, thus establishing sRNAs as transcription elongation factors.

2. Transcription coupled DNA repair (TCR): In 2014 we uncovered a general mechanism of TCR that relies on active RNAP backtracking. We found that in bacteria, UvrD binds RNAP during transcription elongation and, using its helicase activity, forces RNAP to slide backward along DNA. By inducing backtracking, UvrD exposes DNA lesions shielded by blocked RNAP, allowing the repair enzymes to gain access to sites of damage. The small molecule alarmone ppGpp and general elongation factor NusA contribute to UvrD-mediated TCR. Because backtracking is a shared feature of all cellular RNAP, this mechanism enables RNAPs to function as global DNA damage scanners in bacteria and eukaryotes.

3. Discovery and characterization of riboswitches: In 2002 we described the first ligand-sensing mRNAs that regulate biosynthetic genes in *B. subtilis*. Simultaneously, Ron Breaker reported similar findings in *E. coli*. Since then dozens of riboswitches have been described in bacteria and eukaryotes where they control numerous genes. We have shown that riboswitches can activate and suppress gene expression acting at the level of transcription termination (both intrinsic and Rho-dependent), translation initiation, and also modulating alternative splicing and mRNA stability (in plants).

4. Discovery of the eukaryotic RNA thermosensor: In 2006 we isolated a complex composed of the translation elongation factor eEF1A1 and a novel non-coding RNA (**HSR1**) that is required for activation of heat shock genes in mammals. We have accumulated evidence demonstrating that HSR1 serves as a *bona fide* molecular *thermosensor*, which is set for different temperatures

in different organisms. We also showed that eEF1A1 orchestrates the whole process of heat shock response, from transcription activation to mRNA stabilization, transport, and translation. These findings provide a new paradigm of cellular adaptation to stress, with far-reaching clinical implications.

5. Bacterial gasotransmitters: We have shown that endogenously produced gases NO and H₂S protect bacteria from oxidative stress, immune attack, and numerous antibiotics. These results support the emerging concept of antibiotic killing, which relies in part on oxidative damage, and establish NO- and H₂S-producing enzymes as promising new targets for antimicrobial therapy. We further showed that NO produced by bacteria inside *C. elegans* diffuses into animal's tissues where it activates a defined set of genes that protect nematodes from environmental stress and extend their lifespan.

Bibliography:

1. Gragerov A., Nudler E., Komissarova N., Gaitanaris G. A., Gottesman M. E., Nikiforov V. (1992) Cooperation of GroEL/GroES and DnaK/DnaJ heat shock proteins in preventing protein misfolding in *Escherichia coli*. **Proc Natl Acad Sci USA** **89**, 10341-10344.
2. Kashlev M., Nudler E., Goldfarb A., White T., Kutter E. (1993) Bacteriophage T4 Alc protein: a transcription termination factor sensing local modification of DNA. **Cell** **75**, 147-154.
3. Bezanilla M., Drake B., Nudler E., Kashlev M., Hansma P. K., Hansma H. G. (1994) Motion and enzymatic degradation of DNA in the atomic force microscope. **Biophysical J** **67**, 2454-2459.
4. Nudler E., Goldfarb A., Kashlev M. (1994) Discontinuous mechanism of transcription elongation. **Science** **265**, 793-796.
5. Nudler E., Kashlev M., Nikiforov V., Goldfarb A. (1995) Coupling between transcription termination and RNA polymerase inchworming. **Cell** **81**, 351-357.
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7. Kashlev M., Nudler E., Severinov K., Borukhov S., Komissarova N., Goldfarb A. (1996) His-tagged RNA polymerase and transcription in solid phase. **Methods Enzymol** **274**, 326-334.
8. Nudler E., Mustaev A., Lukhtanov E. and Goldfarb A. (1997). The RNA/DNA hybrid maintains the register of transcription by preventing backtracking of RNA polymerase. **Cell** **89**, 33-41.
9. Korzhova N, Mustaev A, Nudler E, Nikiforov V, and Goldfarb A. (1998) Mechanistic model of the elongation complex of *Escherichia coli* RNA polymerase. **Cold Spring Harb Symp Quant Biol** **63**, 337-345
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