Evgeny Nudler, Ph.D.

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Education

Year	Degree	Field	Institution
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

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

Academic Appointments

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
2024- Founding Director, Center for Unified Structural Proteomics (CUSP)

Awards/Honors

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
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

2018 Glenn Award for Research in Biological Mechanisms of Aging
2025 Blavatnik Family Foundation Award
2026 The Carl Nathan MD Lectureship

Research Statement

Our most significant contributions include:

1. RNA polymerase (RNAP) *backtracking* and *ratcheting*: In 1997 we described back-and-forth sliding of RNAP along DNA and RNA (Nudler et al., *Cell* 1997). Our group then showed that this universal phenomenon, which we called "backtracking", plays a key role in controlling gene expression (e.g. Proshkin et al., *Science* 2010), genome instability (e.g. Dutta et al., *Cell* 2011), and DNA repair (e.g. Epshtein et al., *Nature* 2014). We were also first to demonstrate that RNAP is a *Brownian ratchet* machine (Bar-Nahum et al., *Cell* 2005). Our findings explained in mechanistical detail how RNAP translocates and responds to regulatory signals and elongation factors. More recently, we have shown that RNAP II exhibits persistent backtracking over distances exceeding 20nt in human cells. This prolonged backtracking phenomenon frequently manifests near promoters and splicing junctions, exerting significant influence over the expression of a multitude of genes. Notably, histone genes emerge as particularly susceptible to persistent backtracking, underscoring the necessity for resolving such events promptly to ensure timely expression during cell division (Yang et al., *Mol Cell* 2024).

2. Transcription termination and antitermination: We have uncovered the mechanistical principles of the termination process in bacteria and formulated models explaining the molecular pathways leading to both intrinsic and Rho-dependent transcription termination (Gusarov and Nudler, *Mol Cell* 1999; Epshtein et al., *Mol Cell* 2007; Epshtein et al., *Nature* 2010; Hao et al., *Mol Cell* 2021). We also studied how these processes are regulated in the cell and formulated mechanistical models of factor-dependent (Gusarov and Nudler, *Cell* 2001) and factor-independent (Mironov et al., *Cell* 2002; Sedlyarova et al., *Mol Cell* 2017) modes of regulation. Our studies uncovered novel functions of Rho, such as silencing of horizontally transferred genes (Cardinal et al., *Science* 2008) and preserving genomic integrity (Dutta et al., *Cell* 2011). We also found that Rho functions as a global regulator of transcription, acting at 5'UTRs of numerous genes, and that sRNAs control Rho termination genome-wide, thus establishing sRNAs as transcription elongation factors (Sedlyarova et al., *Cell* 2016).

3. Transcription-driven DNA repair: In 2014 we found that the key DNA repair helicase UvrD binds RNAP during elongation and forces it to slide backward along DNA (Epshtein et al., *Nature* 2014). By inducing backtracking, UvrD exposes DNA lesions shielded by RNAP, allowing the repair enzymes to access the damage sites. We also showed that bacterial alarmone ppGpp contributes to UvrD-mediated TCR by rendering RNAP backtracking-prone (Kamarthapu et al., *Science* 2016; Weaver et al., *NSMB* 2023). Because backtracking is a shared feature of all cellular RNAPs, this mechanism enables RNAP to function as a global DNA damage scanner in bacteria and eukaryotes. More recently we showed that RNAP serves as a platform for the assembly of functional nucleotide excision repair (NER) complexes (Bharati et al., *Nature* 2022). Contrary to the conventional dogma, we show that TCR accounts for most chromosomal NER events and is largely independent of Mfd (Bharati et al., *Nature* 2022; Martinez et al., *Nat Commun* 2022) – a DNA translocase thought to be necessary and sufficient for TCR. We also discovered that ribonucleotide excision repair (RER) is driven by transcription in *E. coli* (Hao et al., *Cell* 2023).

4. *Riboswitches*: In 2002, we discovered the first ligand-sensing mRNAs that regulate biosynthetic genes in *B. subtilis* (Mironov et al., *Cell* 2002). Simultaneously, Breaker and colleagues 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, translation initiation, and modulating alternative splicing and mRNA stability (reviewed in Serganov and Nudler *Cell* 2013).

5. 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 (Shamovsky et al., *Nature* 2006). We have shown that HSR1 serves as a molecular thermosensor. We also showed that eEF1A1 orchestrates the whole process of heat shock response, from transcription activation to mRNA stabilization, transport, and translation (Vera et al., *eLife* 2014). These findings provide a new paradigm of cellular adaptation to stress, with far-reaching clinical implications in neurodegeneration and cancer.

6. *Gas-defense system* in bacteria: We showed that endogenously produced gases NO and H_2S protect bacteria from oxidative stress, immune attack, and many antibiotics (Gusarov et al., *Science* 2009; Shatalin et al., *Science* 2011). These results support the emerging concept of antibiotic killing, which relies in part on oxidative damage, and establish NO- and H_2S-producing enzymes as promising targets for antimicrobial therapy. We also discovered the critical role of endogenous H_2S in bacterial tolerance, including the formation of persister cells and biofilms, and developed small molecule inhibitors targeting this defense system to potentiate standard-of-care antibiotics (Shatalin et al., *Science* 2021). In a separate line of investigation, we showed that NO produced by bacteria inside their host diffuses into animal tissues where it activates a defined set of genes that protect the host from environmental stress and extend its lifespan (Gusarov et al., *Cell* 2013).

7. **Aging and metabolism**: We demonstrated that excessive dietary thiols—whether from food or produced by commensal bacteria—accelerate aging in model organisms such as *C. elegans* (Gusarov et al., *Nat Commun* 2021). Together with our earlier work (Gusarov et al., *Nat Commun* 2017), these findings support the emerging view that excessive antioxidants can impair physiological redox signaling and homeostasis and blunt the beneficial effects of exercise. In mice, conditional cysteine restriction causes rapid fat loss through activation of the integrated stress response and the oxidative stress response; these pathways amplify one another, driving induction of GDF15 and FGF21. We also observed unexpectedly low tissue levels of coenzyme A—previously considered highly stable—resulting in reduced mitochondrial function and metabolic rewiring (Varghese et al., *Nature* 2025). These results point to potential strategies for treating metabolic diseases and addressing the obesity epidemic. In a separate line of research, we found that extracellular GAPDH promotes Alzheimer's disease progression by enhancing amyloid-β aggregation and cytotoxicity (Lazarev et al., *Aging Dis* 2021). We further showed that toxic amyloid-β oligomerization is zinc-dependent and that selected small molecules, including the tetrapeptide HAEE, can disrupt this process and therefore have potential as anti-amyloid therapeutics (Mitkevitch et al., *Aging Dis* 2021).

Bibliography (172 peer-reviewed publications):

https://pubmed.ncbi.nlm.nih.gov/?term=nudler+e&sort=date

https://scholar.google.com/citations?user=a7g38iwAAAAJ&hl=en