BIOGRAPHICAL SKETCH

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NAME: Korennykh, Alexei

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

POSITION TITLE: Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Moscow State University, Moscow, RUSSIA	Doctorate	06/1997	Enzymology and Chemistry
The University of Chicago, Chicago, IL	M.S.	06/2000	Physical Sciences
The University of Chicago, Chicago, IL	Ph.D.	06/2005	Protein and RNA Biochemistry
UCSF (San Francisco, CA, USA)	Postdoctoral	06/2011	Structural Biology, Biophysics, Cell Biology

A. Personal Statement

Our laboratory is focused on and passionate about structural, biochemical and cell biology understanding of RNA regulation and immune recognition in human cells. The key innovative aspects of our work are (i) emphasis on mechanistic and structural understanding in areas that lack a detailed molecular knowledge, and (ii) development of new RNA-seq methods and new research tools (inhibitors as mechanistic probes; biosensors). Our work seeded multiple collaborations and contributed fundamental knowledge about processes underlying immune, metabolic and neoplastic human diseases. We combine X-ray crystallography, cryo-EM, biochemistry, biophysics, proteomics and transcriptomics to build accurate views of cellular mechanisms. My areas of training include protein and RNA biochemistry, biophysics, structural biology and molecular biology. My research experience is in the areas of unfolded protein response, protein kinases, interferon response, dsRNA sensing, RNA decay, and metabolism.

We value and promote the culture of inclusivity and safe working environment, where lab members are required to have up to date safety trainings and to use safe techniques. We emphasize the importance of unbiased experimentation and presentation of results. My lab has a standard that cell biology and biochemical data have to be reproduced multiple times in independent experiments, while effects that we consider interesting have to be strong: ideally, orders-of magnitude for quantitative results or “all-or-nothing” for qualitative results. We support individual development of scientists according to their motivation and interests, such that all graduate students in my laboratory obtained their PhD degrees based on major biological findings. Following PhD defense, my former students continue biomedical work at top universities in the USA and in biomedical industry.

Ongoing and recently completed projects that I would like to highlight include:

R01GM110161
Korennykh (PI)
5/1/20-5/1/24
Structure and Function of Kinase Family Receptors Regulating Translation

The Vallee Foundation Award
Korennykh (PI)
8/1/16-8/1/22

Self-RNA Cleavage as an Arm of Innate Immunity

Intellectual Property Accelerator Fund program
Korennykh (PI)
1/30/20-12/30/21
Inhibitors of Nocturnin as Novel Drugs against Metabolic Syndrome

Burroughs Wellcome Fund Award 1013579
Korennykh (PI)
7/1/14-6/30/19
Systems analysis of pathogen defense mediated by 2',5'-linked isoRNA

Citations:

1. ***Korennykh, A.V.***, Egea, P.F., Korostelev, A.A., Finer-Moore, J., Zhang, C., Shokat, K.M., Stroud, R.M., and Walter, P. (2009) The unfolded protein response signals through high-order assembly of Ire1. *Nature* 457(7230); 687-93. PMCID: PMC2846394
2. Han, Y., Whitney, G., Donovan, J. and ***Korennykh, A.*** (2012) Innate Immune Messenger 2-5A Tethers Human RNase L into Active High-Order Complexes. *Cell Reports* 2 (4); 902-13. PMID: 23084743
3. Han, Y., Donovan, J., Rath, S., Whitney, G., Chitrakar, A. and **Korennykh, A.** (2014). Structure of human RNase L reveals the basis for regulated RNA decay in the IFN response. *Science* 343; 1244. PMCID: PMC4731867.
4. Chitrakar, A., Rath, S., Donovan, J., Demarest, K., Li, Y., Sridhar, R. R., Weiss, S. R., Kotenko, S. V., Wingreen, N. S., **Korennykh, A**. (2019). Real-time 2-5A kinetics suggest that interferons beta and lambda evade global arrest of translation by RNase L. *PNAS*. PMCID: PMC6754276

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2016-present	Associate Professor of Molecular Biology, Princeton University
2016-2020	Member, RNA society
2012	MRC ad hoc grant reviewer
2011-present	Peer reviewer for eLife, PNAS, JCB, JMB, BBA - Proteins and Proteomics, EMBO J., Science, Science Signaling, Nature Communications, Nature Chemical Biology, Cell Reports, Cell Research, Oncotarget, Nucleic Acids Research, PLoS Pathogens, etc.
2011-2016	Assistant Professor of Molecular Biology, Princeton University
2006-2011	Postdoctoral Fellow, University of California, San Francisco (UCSF), Peter Walter, advisor
1999-2005	Graduate Fellow, Department of Chemistry, The University of Chicago

Honors

2019	Biomedical/Healthcare/Life Sciences Accelerator Award, Princeton University
2019	Molecular Biology Innovation Award, Princeton University
2016	The Vallee Foundation Award Fellow
2015	James A. Elkins, Jr. '41 Preceptorship, Princeton University
2014	Burroughs Wellcome Research Award
2014	Kimmel Foundation for Cancer Research Award
2011	General Biology Research Award BioMed Central, 6th Annual Awards, London, UK
2010	2010 UCSF Dean's Postdoctoral Research Prize
2007	Jane Coffin Childs Postdoctoral Fellow
2007	Cancer Research Institute (CRI) Postdoctoral Fellowship (awarded)
2004	1st Graduate Prize in Organic & Bioorganic Chemistry, The University of Chicago
2001	Burroughs Wellcome Graduate Fellow
1995	George Soros International Scholar (ISSEP)

C. Contributions to Science

1. My early work was on ribosome recognition by proteins. The central question was to understand how ribosome-inactivating proteins can find the specific rRNA site on the extensive surface of the ribosome. We found that these proteins use the negative electrostatic field of the ribosome. First, they collide with the ribosome randomly, then they diffuse in 2D space over the ribosomal surface, using the long-range electrostatic guidance to stay in the vicinity of the ribosome. This allows them to rapidly find and cleave the single cognate chemical bond in 28S rRNA, blocking protein synthesis. Some of the enzymes we studied perfected this mechanism to cleave the ribosomes faster ($k_{cat}/K_m > 10^{10}$ $M^{-1}s^{-1}$) than the "literature perfect enzyme", superoxide dismutase. We observed reaction rate constants that match the Smoluchowski-Einstein limit for perfect encounters. This work uncovered a fundamental mechanism for rapid protein-ribosome recognition.
    a. ***Korennykh, A.V.***, Piccirilli, J.A., and Correll, C.C. (2006) The electrostatic character of the ribosomal surface enables extraordinarily rapid target location by ribotoxins. *Nature Structural & Molecular Biology* 13(5); 436-43. PMCID: PMC1847776
    b. ***Korennykh, A.V.***, Correll, C.C., and Piccirilli, J.A. (2007) Evidence for the importance of electrostatics in the function of two distinct families of ribosome inactivating toxins. *RNA* 13(9); 1391-6. PMCID: PMC1950761
    c. ***Korennykh, A.V.***, Plantinga, M.J., Correll, C.C., and Piccirilli, J.A. (2007) Linkage Between Substrate Recognition and Catalysis During Cleavage of Sarcin/Ricin Loop RNA by Restrictocin. *Biochemistry* 46(44); 12744-56. DOI: 10.1021/bi700931y
2. My following work focused on structural mechanisms in the unfolded protein response (UPR). The UPR is an essential mechanism of cell homeostasis and stress response associated with protein misfolding. I carried out extensive biochemical and biophysical characterization of the central receptor in the UPR, kinase/RNase Ire1, and discovered that Ire1 is activated by forming a high-order assembly. I developed small molecule modulators (inhibitors and activators) of Ire1 described in peer reviewed publications and patent applications. Additionally, I determined the crystal structure of the high-order assembly of Ire1 in complex with a small-molecule Ire1 activator. This work explained how Ire1 is activated during the UPR and provided the tools for developing Ire1-targeting therapies.
    a. ***Korennykh, A.V.***, Egea, P.F., Korostelev, A.A., Finer-Moore, J., Zhang, C., Shokat, K.M., Stroud, R.M., and Walter, P. (2009) The unfolded protein response signals through high-order assembly of Ire1. *Nature* 457(7230); 687-93. PMCID: PMC2846394
    b. Aragón, T., van Anken, E., Pincus, D., Serafimova, I.M., ***Korennykh, A.V.***, Rubio, C.A., and Walter, P. (2009) Messenger RNA targeting to endoplasmic reticulum stress signaling sites. *Nature* 457(7230); 736-40. PMCID: PMC2768538
    c. Mendez AS, Alfaro J, Morales-Soto MA, Dar AC, McCullagh E, Gotthardt K, Li H, Acosta-Alvear D, Sidrauski C, **Korennykh AV**, Bernales S, Shokat KM, Walter P. (2015) Endoplasmic reticulum stress-independent activation of unfolded protein response kinases by a small molecule ATP-mimic. Elife, May 19;4. PMCID: PMC4436593
    d. Patents : Methods of Inhibiting IRE1 US8980899B2 (2015)
3. My independent research focused on structural mechanisms and physiology of dsRNA sensing in the interferon response. DsRNA is a dangerous molecule arising from viruses as well as from genomic defects that develop in cancer cells. DsRNA is a potent trigger for the interferon response, and a broad activator of the innate immune system. My laboratory solved the crystal structure of the dsRNA-activated kinase-RNase RNase L. We also determined the structural mechanisms of the dsRNA receptors OAS1 and OAS3 (OASs), which activate RNase L. Our structural and biochemical analyses explained how the OASs recognize dsRNA and how these sensors employ dsRNA binding for regulated synthesis of the second messenger 2-5A, which bind and activate RNase L. Our work demonstrated that RNase L is activated cooperatively by assembling high-order complexes templated by the bound 2-5A molecules. Our studies advanced the structural, biochemical and biophysical understanding of the OAS/RNase L pathway, and the dsRNA sensing overall. We complemented our structural and mechanistic studies by cell biology and high-throughput transcriptomics work. Our most recent contribution to the field is the crystal structure-based design of a 2-5A biosensor. The use of this biosensor revealed an unanticipated global change in cells sensing dsRNA: these cells switch off basal translation and activate prioritized synthesis of interferons (reference d).

a. Han, Y., Whitney, G., Donovan, J. and ***Korennykh, A.*** (2012) Innate Immune Messenger 2-5A Tethers Human RNase L into Active High-Order Complexes. *Cell Reports* 2 (4); 902-13. PMID: 23084743.
b. Donovan, J., Dufner, M., and ***Korennykh, A.*** (2013) Structural basis for cytosolic double-stranded RNA surveillance by human oligoadenylate synthetase 1. *PNAS* 110(5), 652-1657. PMCID: PMC3562804
c. Han, Y., Donovan, J., Rath, S., Whitney, G., Chitrakar, A. and ***Korennykh, A.*** (2014) Structure of human RNase L reveals the basis for regulated RNA decay in the IFN response. *Science* 343; 1244. PMCID: PMC4731867
d. Chitrakar, A., Rath, S., Donovan, J., Demarest, K., Li, Y., Sridhar, R. R., Weiss, S. R., Kotenko, S. V., Wingreen, N. S., **Korennykh, A**. (2019). Real-time 2-5A kinetics suggest that interferons beta and lambda evade global arrest of translation by RNase L. *PNAS*. PMCID: PMC6754276

4. My recent work on structural biology in circadian clock and metabolism. Some 15 years ago it has been found that expression of the protein Nocturnin is controlled by the circadian clock, increasing by two orders of magnitude in the mouse liver in early evening. During our studies of mRNA deadenylation (poly-A tail removal), we serendipitously discovered that Nocturnin lacks deadenylase activity (reference a). A similar paradoxical conclusion was simultaneously reported by Abshire et al. (*Nucleic Acids Research*, 2018). We determined the crystal structure of Nocturnin, which lead us to the conclusion that Nocturnin may not be a deadenylase. Our findings prompted a search for the true biologic substrate of Nocturnin. In collaboration with the metabolomics expert at Princeton, Joshua Rabinowitz, we found that Nocturnin indeed has a novel activity and cleaves NADP(H). The involvement of Nocturnin in metabolism has been widely recognized, but it had not been expected that the enzyme directly targets the central cofactor in redox metabolism and ROS control: NADP(H). This result reveals a fundamentally novel mechanism of metabolism regulation.
    a. Estrella M., Du J., **Korennykh A.**, Crystal structure of human Nocturnin catalytic domain. *Scientific Reports - Nature* 8(1) 2018 p. 16294 (2018) PMCID: PMC6214945
    b. Estrella M., Du J., Chen L., Rath S., Prangley E., Chitrakar A., Aoki T., Schedl P., Rabinowitz J., **Korennykh A.** (2019). The metabolites $NADP^+$ and NADPH are the targets of the circadian protein Nocturnin (Curled) BioRxiv 534560 [**Preprint**]. January 30, 2019 [cited 2019 Jan 31] Available from: https://doi.org/10.1101/534560

Complete list of my publications:
https://pubmed.ncbi.nlm.nih.gov/?term=korennykh