BIOGRAPHICAL SKETCH

NAME:	Kotenko, Sergei V.
eRA COMMONS USER NAME:	SKOTENKO
POSITION TITLE:	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 Engineering Physics Institute, Moscow, USSR	MS	1985	Physics
Institute for Genetics of Microorganisms, Moscow, USSR	PhD	1990	Molecular Biology

A. Personal Statement

My strongest expertise lies in molecular biology and molecular immunology; and my laboratory has a long-standing interest in unraveling molecular mechanisms of cytokine action and advancing our knowledge of the complex role played by cytokines in the regulation of immune and inflammatory responses. Through database mining, cloning efforts and studies of ligand-receptor interactions, my group contributed to the discovery of several novel cytokines such as cytomegalovirus-encoded interleukin 10 (cmvIL-10), IL-19 and interferon lambdas (IFN-λs), as well as the identification and characterization of functional receptor complexes for these and other cytokines including IL-10, IL-22, IL-26, and IFN-λs. Type III IFNs, or IFN-λs, were co-discovered and described in 2003 by our research team and scientists from Zymogenetics. Since that time, research in my laboratory has focused on understanding why two distinct antiviral systems, the type I and type III IFN antiviral systems, have evolved in mammals, and how this knowledge can be translated into the clinic. In addition to studying roles of type I and type III IFNs in antiviral responses, we are also actively exploring functions of these IFNs and other cytokines, particularly those from the family of IL-10-related cytokines, in the regulation of immune and inflammatory responses, and their potential application for cancer immunotherapies. Animal models are also being used in the lab to develop and test novel IFN-based biologics as broad spectrum immune-modulatory agents and to explore their therapeutic potential for the treatment of infections and cancer. My lab has developed many unique reagents, learned, adapted and aced various research techniques, has excellent research facilities, and a track record of successful collaborations with other laboratories and pharmaceutical companies that are important assets for the proposed work.

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

ACTIVE

R01 CA-260137-01A1 (MPI: Birge/Kotenko) 02/01/22-01/31/27
National Institutes of Health
Targeting a phosphatidylserine/TAM receptor/PD-L1 axis as a vulnerability in cancer
The goal of this project is to investigate the role of phosphatidylserine-activated receptor tyrosine kinase Mertk as a driver of immune evasion in breast cancer.

Research Bridge Grant COCR21RBG011 (MPI: Birge, Kotenko) 05/01/21-04/30/23
New Jersey Commission on Cancer Research
Targeting a phosphatidylserine/TAM receptor/PD-L1 axis as a vulnerability in cancer
The goal of this bridge project is to develop a knock-in mouse model expressing human Mertk in the C57BL/6 background and assess Mertk expression in human archived breast cancer tissues.

ROI U01HL150852 (MPI: Birge, Kotenko) 11/15/22-05/15/24
National Institutes of Health REACH program
Development of Interferon fusion proteins as broad-spectrum antivirals
The goal of this project is to develop and characterize novel IFN-based biologics targetable to the sites of virus infection as potential antivirals for acute respiratory diseases involving influenza virus and SARS-CoV-2.

COMPLETED

Research Grant (MPI: Birge, Durbin, Kotenko, Parker, Rivera) 07/01/20-06/30/22
Rutgers Center for COVID-19 Response and Pandemic Preparedness
IFN-based antivirals for the treatment of SARS-CoV-2
The goal of this proposal is to establish novel approaches and tools to dissect the roles of type I and III IFNs in defense against SARS-CoV-2.

5R01AI104669 (MPI: Durbin, Kotenko) 01/18/13-12/31/18
National Institutes of Health
Development of IFN-λ3 for the prevention and treatment of virus infection
In these studies, we examine the role of IFN-λ3 in immunity to mucosal viral pathogens, comparing the effects of type I and type III IFNs, test antiviral properties of IFN-λ3 in several mouse models of virus infection, and explore the development of IFN-λ3 for clinical applications as a broad-spectrum antiviral.

Citations:

Kotenko SV (2002) The Family of IL-10-Related Cytokines and Their Receptors: Related, But to What Extent? *Cytokine Growth Factor Rev.* **13**, 223-240; PMID: 12486876

Kotenko SV (2011) IFN-λs. *Curr. Opin. Immunol.*, **23**, 583-590; PMID: 21840693

Kotenko SV, Durbin JE (2017) Contribution of type III interferons to antiviral immunity: location, location, location. *J. Biol. Chem.* **592**, 7295-7303; PMID: 28289095

Kotenko SV, Rivera A, Parker D, Durbin JE (2019) Type III IFNs: Beyond antiviral protection. *Semin. Immunol.* **43**:101303; PMID: 31771761

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2014-date	Professor, Department of Microbiology, Biochemistry & Molecular Genetics, Rutgers New Jersey Medical School, Newark, NJ
2013	Centers of Excellence for Translational Research (CETR) (U19), NIAID/NIH, stage 1 reviewer
2009-2010	Alliance for Lupus Research Peer Review Committee: Target Identification in Lupus, reviewer
2006-date	Member of the "*Journal of Interferon and Cytokine Research*" Editorial Board
2004-date	Nomenclature Committee; International Society for Interferon and Cytokine Research
2005-2014	Associate Professor, Department of Biochemistry & Molecular Biology, UMDNJ New Jersey Medical School, Newark, NJ
2001-2005	Assistant Professor, Department of Biochemistry & Molecular Biology, UMDNJ New Jersey Medical School, Newark, NJ
2000-date	Member of the "*Genes and Immunity*" Editorial Board
1996-2001	Adjunct Assistant Professor, Department of Molecular Genetics & Microbiology, UMDNJ Robert Wood Johnson Medical School, Piscataway, NJ
1992-1996	Research Associate, Department of Molecular Genetics & Microbiology, UMDNJ Robert Wood Johnson Medical School, Piscataway, NJ
1992-date	Member, International Society for Interferon and Cytokine Research
1990-1992	Senior Research Fellow, Department of Biotechnology, Institute for Genetics of Microorganisms, Moscow, USSR
1983-1990	M.S. Trainee, Research Fellow, Lab. Eukaryotic Gene Structure, Institute for Genetics of Microorganisms, Moscow, USSR

Honors

2013	The Foundation of UMDNJ's Excellence in Research Award
2010	Milstein Award, International Society for Interferon and Cytokine Research
2001	Award from the Arthritis National Research Foundation for the presentation at the 2001 Cytokine Odyssey Meeting
1999	Milstein Young Investigator Award, International Society for Interferon and Cytokine Research
1998-2001	American Heart Association, Career Development Award
1997	First place, International Cytokine Society Young Investigator Award
1985	M.S. Diploma with honor, Moscow Engineering Physics Institute, Department of Theoretical and Experimental Physics, Moscow, USSR

C. Contributions to Science

1. My interest in cytokine biology started with the discovery and characterization of IFN-γR2, the second receptor chain of the IFN-γ receptor complex, at the time when the concept for multi-subunit receptor complexes just started to emerge. My further studies delineated ligand:receptor interactions, receptor architecture and downstream signal transduction pathways for type I and type II IFNs. We showed that ligand binding causes oligomerization of receptor subunits, which initiates signal transduction events: activation of receptor associated Jak tyrosine kinases, phosphorylation of receptor intracellular domains, followed by phosphorylation and activation of transcriptional factors of the STAT family. We demonstrated that Jak2 interacts with the intracellular domain of IFN-γR2, that other Jak kinases can functionally substitute for Jak2, and that STATs are exclusively recruited through the IFN-αR2 subunit. These studies helped to shape our understanding of the cascade of events triggered by cytokines signaling through multi-subunit receptor complexes.

Soh[#] J, Donnelly[#] RJ, **Kotenko[#] SV**, Mariano[#] TM, Cook[#] JR, Wang N, Emanuel SL, Schwartz B, Miki T, Pestka, S (1994) Identification and Sequence of an Accessory Factor Required for Activation of the Human Interferon Gamma Receptor. *Cell* **76**, 793-802 ([#]equal contribution) PMID: 8124716

Kotenko SV, Izotova LS, Pollack BP, Mariano TM, Donnelly RJ, Muthukumaran G, Cook JR, Garotta G, Silvennoinen O, Ihle JN, Pestka S (1995) Interaction between the Components of the Interferon γ Receptor Complex. *J. Biol. Chem.* **270**, 20915-20921; PMID: 7673114

Kotenko SV, Izotova LS, Pollack BP, Muthukumaran G, Paukku K, Silvennoinen O, Ihle, JN, Pestka S (1996) Other Kinases Can Substitute for Jak2 in Signal Transduction by Interferon-γ. *J. Biol. Chem.* **271**, 17174-17182; PMID: 8663414

Kotenko SV, Izotova LS, Mirochnitchenko OV, Lee C, Pestka S (1999) The Intracellular Domain of IFN-αR2c Chain is Responsible for Stat Activation. *Proc. Natl. Acad. Sci. USA* **96**, 5007-5012; PMID: 10220409

2. I have also made significant contributions to the discovery and characterization of IL-10-related cytokines and their receptor complexes. First, I identified IL-10R2, a long sought second chain of the IL-10 receptor complex (International Cytokine Society Young Investigator Award, 1997). Then, I demonstrated that the same receptor, IL-10R2, is also required for the formation of functional receptor complexes for IL-10-related cytokines, IL-22 and IL-26, as well as for type III IFNs, IFN-λ. I also discovered and characterized an IL-22 binding protein (IL-22BP), a naturally occurring IL-22 antagonist. I was also involved in characterization of receptor complexes for other IL-10 related cytokines, IL-19, IL-20 and IL-24, as well as in cloning and initial characterization of IL-19. Sharing of the common IL-10R2 chain between established a novel paradigm for IL-10-related cytokines similar to the well-known case of shared use of the γ_c chain by others cytokines.

Kotenko SV, Krause CD, Izotova LS, Pollack BP, Wu W, Pestka S (1997) Identification and Functional Characterization of a Second Chain of the Interleukin-10 Receptor Complex. *EMBO J.* **16,** 5894-5903; PMID: 9312047

Kotenko* SV, Izotova LS, Mirochnitchenko OV, Esterova E, Dickensheets H, Donnelly RP, and Pestka* S (2001) Identification of the Functional Interleukin-22 (IL-22) Receptor Complex: the IL-10R2 Chain (IL-10Rb) Is a Common Chain of Both the IL-10 and IL-22 (IL-10-Related T Cell-Derived Inducible Factor, IL-TIF) Receptor Complexes. *J. Biol. Chem.* **276,** 2725-2732 (*corresponding authors); PMID: 11035029

Kotenko* SV, Izotova LS, Mirochnitchenko OV, Esterova E, Dickensheets H, Donnelly RP, Pestka* S (2001) Identification, Cloning and Characterization of a Novel Soluble Receptor That Binds IL-22 and Neutralizes Its Activity. *J. Immunol.* **166**, 7096-7103 (*corresponding authors); PMID: 11390454

Sheikh F, Baurin VV, Lewis-Antes A, Shah NK, Smirnov SV, Anantha S, Dickensheets H, Dumoutier L, Renauld JC, Zdanov A, Donnelly RP, **Kotenko SV** (2004) IL-26 Signals Through a Novel Receptor Complex Composed of IL-20R1 and IL-10R2. *J. Immunol.* **172,** 2006-2010; PMID: 14764663

3. I also discovered several viral proteins that are involved in immune evasion, and studied mechanisms of their actions. I discovered that cytomegalovirus (CMV) encodes its own unique IL-10 homolog (cmvIL-10), which is involved in immune regulation of virus-host interaction (Milstein Young Investigator Award, International Society for Interferon and Cytokine Research, 1999). I demonstrated that despite the fact that human IL-10 and cmvIL-10 proteins are only 27% identical, cmvIL-10 requires both subunits of the human IL-10 receptor complex to induce signal transduction events and biological activities. My lab also discovered the first virus defense mechanism that directly targets type III IFNs. A yatapoxvirus-encoded secreted Y136 glycoprotein was characterized as a potent pan-IFN antagonist, that inhibits all members of the type I and type III IFN families. These studies expanded the arsenal of countermeasures used by viruses to counteract host antiviral defenses.

Kotenko SV, Saccani S, Izotova LS, Mirochnitchenko OV, Pestka S (2000) Human Cytomegalovirus Harbors Its Own Unique Interleukin-10 Homolog (cmvIL-10). *Proc. Natl. Acad. Sci. USA* **97,** 1695-1700; PMID: 10677520

Bartlett NW, Renauld JC, Dumoutier L, **Kotenko SV**, McVey C, Lee HJ, Smith JL (2004) A New Member of the Interleukin 10-Related Cytokine Family Encoded by a Poxvirus. *J. Gen. Virol.* **85**, 1401-1412; PMID: 15166422

Huang J, Smirnov SV, Lewis-Antes A, Balan M, Li W, Tang S, Silke GV, Pütz MM, Smith GL, **Kotenko SV** (2007) Inhibition of type I and type III interferons by a secreted glycoprotein from Yaba-like disease virus. *Proc. Natl. Acad. Sci. USA* **104**, 9822-9827; PMID: 17517620

4. The most recent and significant contribution to the field of cytokine research is the discovery and characterization of type III IFNs, or IFN-λs (Milstein Award, International Society for Interferon and Cytokine Research). This group of cytokines was co-discovered and described in 2003 by our research team and scientists from Zymogenetics. We cloned three highly homologous IFN-λ proteins, distinct from type I IFNs, which signal through a unique receptor complex composed of IFN-λR1 and IL-10R2 chains and trigger signal transduction pathways similar to those induced by type I IFNs, including formation of the IFN-stimulated gene factor 3 (ISGF3) transcriptional complex. Thus, we identified a novel ligand-receptor system that, upon engagement, leads to the establishment of an antiviral state by a mechanism similar to, but independent from type I IFNs. This discovery opened a new direction in antiviral research, and led to better understanding of a complex nature of viral-host interactions and the development of novel antiviral therapeutics. Since the discovery of IFN-λs, research in my laboratory has focused on obtaining more information about the IFN-λ antiviral system with the ultimate goal to understand why two distinct antiviral systems, the type I and type III IFN antiviral systems, have evolved in mammals, and how this knowledge can be translated into clinic. In addition, immunomodulatory activities of IFN-λs remain poorly characterized and are the subject of ongoing studies with the use of conditional IFN-λR1 deficient animals that were generated in the lab. Our studies of gastrointestinal (GI) rotavirus infection revealed a well-orchestrated spatial and temporal tuning of innate antiviral responses in the intestinal tract where two types of IFNs through distinct patterns of their expression and distinct but overlapping sets of target cells coordinately regulate antiviral defenses against heterologous or homologous rotaviruses with substantially different effectiveness. These studies also revealed an unexpected age-dependent change in specific contribution of type I versus type III IFNs to antiviral defenses in the gastrointestinal tract. Using mouse model of intestinal injury we recently demonstrated that type I and type III IFNs support epithelial regeneration following acute colonic injury through the up-regulation of amphiregulin expression in either epithelial or hematopoietic compartment by IFN-λ or IFN-α/β, respectively. Together, these data underscore the pleiotropic functions of these critical antiviral cytokines. Although the work from our and other groups significantly extended our understanding of the biology of type III IFNs, we just started to scratch the surface of the biological significance and potential clinical use of IFN-λs.

Kotenko* SV, Gallagher* G, Baurin VV, Lewis-Antes A, Shen M, Shah NK, Langer JA, Sheikh F, Dickensheets H, Donnelly RP (2003) Interferon-λs mediate antiviral protection through a unique class II cytokine receptor complex. *Nat. Immunol.* **4**, 69-77 (*corresponding authors); PMID: 12483210

Lin, J-D, Feng, N, Sen, A, Balan, M, Tseng, H-C, McElrath, C, Smirnov, SV, Peng, J, Yasukawa, LL, Durbin, RK, Durbin, JE, Greenberg*, HB, and **Kotenko*, SV** (2016) Distinct roles of type I and type III interferons in intestinal immunity to homologous and heterologous rotavirus infection. *PloS Path.* **12**(4): e1005600. doi:10.1371 (*corresponding authors); PMID: 27128797

Espinosa V, Dutta O, McElrath C, Du P, Chang YJ, Cicciarelli B, Pitler A, Whitehead I, Obar JJ, Durbin JE, **Kotenko SV**, Rivera A (2017) Type III interferon is a critical regulator of innate antifungal immunity. *Sci. Immunol.* **2**(16). pii: eaan5357; PMID: 28986419

McElrath C, Espinosa V, Lin J-D, Peng J, Sridhar R, Dutta O, Tseng H-C, Smirnov SV, Risman H, Sandoval MJ, Davra V, Chang Y-J, Pollack BP, Birge RB, Galan M, Rivera A, Durbin JE, **Kotenko SV** (2021) Critical Role of Interferons in Gastrointestinal Injury Repair. *Nat. Commun.*, **12**(1), 2624, doi.org/10.1038/s41467-021-22928-0; PMID: 33976143

5. My lab is also interested in tumor immunology. We were first to describe pro-apoptotic and antitumor properties of IFN-λs. We demonstrated that similar to classical type I IFNs (IFN-α/β), type III IFNs also possess anti-tumor activities in mouse models of melanoma or hepatoma tumor growth. However, different effects on immune cells suggested that type I and type III IFNs engaged overlapping but distinct antitumor mechanisms. Recently, we also started to explore the role of TAM receptor tyrosine kinases, Tyro3, Axl, and Mertk, in cancer development and progression. TAMs interact with endogenous ligands, protein S (Pros1) and growth arrest-

specific gene 6 (Gas6), which, in turn, opsonize phosphatidylserine (PS) on apoptotic cells (ACs) and serve as bridging molecules between ACs and TAMs. TAMs are overexpressed in a variety of cancers; and abnormal expression and activation of TAMs have been implicated in promoting proliferation and survival of cancer cells, as well as in suppressing anti-tumor immunity. Our studies revealed a previously unappreciated functional diversity of TAM receptors, and demonstrated that despite their similarity, TAMs perform distinct functions in both immunoregulation and the recognition and removal of ACs.

Lasfar A, Lewis-Antes A, Smirnov SV, Anantha S, Abushahba W, Tian B, Reuhl K, Dickensheets H, Donnelly RP, Raveche E, **Kotenko SV** (2006) Characterization of the Mouse IFN-λ Ligand-Receptor System: IFN-λs Exhibit Anti-Tumor Activity against B16 Melanoma. *Cancer Res.* **66**, 4468-4477; PMID: 16618774

Tsou W-I, Nguyen K-Q, Calarese DA, Garforth SJ, Antes AL, Smirnov SV, Almo SC, Birge* RB, **Kotenko* SV** (2014) Receptor Tyrosine Kinases, TYRO3, AXL and MER, Demonstrate Distinct Patterns and Complex Regulation of Ligand-Induced Activation. *J. Biol. Chem.* **289**, 25750-25763 (*corresponding authors); PMID: 25074926

Kasikara C, Davra V, Calianese D, Geng K, Spires TE, Quigley M, Wichroski M, Sriram G, Suarez-Lopez L, Yaffe MB, **Kotenko SV**, De Lorenzo MS, Birge RB (2019) Pan-TAM tyrosine kinase inhibitor BMS-777607 enhances anti-PD-1 mAb efficacy in a murine model of triple-negative breast cancer. *Cancer Res.* **79**, 2669-2683; PMID: 30877108

Davra V, Kumar S, Geng K, Calianese D, Mehta D, Gadiyar V, Kasikara C, Lahey KC, Chang Y, Wichroski M, Gao C, De Lorenzo MS, **Kotenko SV**, Bergsbaken T, Mishra PK, Gause WC, Quigley M, Spires TE, Birge RB (2021) Axl and Mertk receptors cooperate to promote breast cancer progression by combined oncogenic signaling and evasion of host anti-tumor immunity. *Cancer Res.* **81**, 698 712; PMID: 33239426

Complete list of my publications can be found at:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/41156091/?sort=date&direction=ascending