
BIOGRAPHICAL SKETCH

NAME: Bukreyev, Alexander A.

eRA COMMONS USER NAME: ABUKREYE

POSITION TITLE: Professor with Tenure
Senior Scientist, Sealy Center for Vaccine Development

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
M.S., Pharmacy, Pyatigorsk Pharmaceutical Institute, Pyatigorsk, Russia	M.S.	06/1984	Pharmacy
State Research Center of Virology and Biotechnology "Vector", Novosibirsk, Russia	Ph.D.	05/1993	Molecular biology
The Foundation for Advanced Education in the Sciences, Bethesda, Maryland	N/A	10/1996	Molecular and Cellular Mechanisms of Immunity
The Foundation for Advanced Education in the Sciences, Bethesda, Maryland	N/A	10/1997	Cell Biology of Immunity and Inflammation
National Institute of Allergy and Infectious Diseases, NIH, Bethesda, Maryland	Postdoc	08/1998	Virology

A. Personal Statement

At the Laboratory of Infectious Diseases (LID) at NIAID, NIH, in 1995, my research focused on molecular and immunological studies of respiratory syncytial virus (RSV), which like Ebola and Marburg filoviruses is a non-segmented negative strand virus. At LID, I also worked on the development of vectored vaccines against emerging and respiratory viruses, including RSV, human parainfluenza virus type 3 (HPIV3), SARS coronavirus, the highly pathogenic H5N1 avian influenza virus, and most extensively, Ebola virus. Currently my group at the University of Texas Medical Branch at Galveston focuses on the following directions:

- 1) Characterization of antibody responses to filovirus infections in humans, in collaboration with Dr. James Crowe, Jr.,
- 2) Development of therapeutic human monoclonal antibody treatments for filoviruses,
- 3) Development of mucosal respiratory tract vaccines against filoviruses based on human and non-human paramyxovirus vectors,
- 4) Investigation of mechanisms of "immune paralysis" caused by filoviruses,
- 5) Development of therapeutics targeting filoviral replication and interferon-antagonist functions (in collaboration with Dr. Sergei Nekhai and Dr. Chris Basler),
- 6) Comparative immunology of bats as a reservoir of filoviruses (in collaboration with Dr. Chris Basler).

To get insight into these scientific topics, we are using molecular tools, including reverse genetics (i.e. development of genetically modified filoviruses from the DNA-copies of their genomes and use of mini-genomes), immunological tools such as multi-parameter flow cytometry, human immune cells and animal models. Our research includes experiments in BSL-2 and BSL-4 labs in the Galveston National Laboratory. During my career, I have acquired extensive experience in molecular virology of non-segmented negative-strand viruses, including the use or development of reverse genetic systems of five such viruses, including filoviruses. I have also acquired extensive experience in viral immunology and in vaccinology, including pre-clinical testing of vaccine candidates in rodents and non-human primates. My studies resulted in 90 publications, including 50 first or senior/co-senior authorship publications, in *Science*, *Cell*, *Journal of Clinical Investigation*, *PNAS*, *PLOS Pathogens*, *The Lancet*, *Journal of Virology*, *Vaccine* and other high-quality journals. I am a current member of NIH Vaccines Against Microbial Diseases (VMD) Study Section. I have experience directing and working in multi-investigator groups on vaccine development and immune responses to virus infections or vaccines. I completed the UTMB Foundational Management Training Program and I am well qualified to run large collaborative studies.

B. Positions and Honors

Positions and Employment

- 1986-1989 **Engineer-researcher**, Laboratory of Molecular Biology of RNA viruses, Institute of Molecular Biology, State Research Center of Virology and Biotechnology, Novosibirsk, Russia "Vector".
- 1989-1990 **Junior Researcher**, Laboratory of Molecular Biology of RNA viruses, Institute of Molecular Biology, State Research Center of Virology and Biotechnology, Novosibirsk, Russia "Vector".
- 1990-1994 **Researcher**, Laboratory of Molecular Biology of RNA viruses, Institute of Molecular Biology, State Research Center of Virology and Biotechnology "Vector", Novosibirsk, Russia.
- 1994-1995 **Senior Researcher, Group Leader**, Laboratory of Molecular Biology of RNA viruses, Institute of Molecular Biology, State Research Center of Virology and Biotechnology "Vector", Novosibirsk, Russia.
- 1995 -1998 **Visiting Fellow**. Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, Maryland.
- 1998 - 2000 **Research Fellow**. Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, Maryland.
- 2000 - 2010 **Staff Scientist**. RNA Viruses Section, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, Maryland.
- 2010- **Professor**. Departments of Pathology and Microbiology & Immunology, University of Texas Medical Branch, Galveston, Texas.
Full member of the Microbiology & Immunology Graduate Program and Associate Member of the Experimental Pathology of the University of Texas Graduate School of Biomedical Services.

Other Experience and Professional Memberships

- 1996- American Society for Virology, Full Member.
- 1997-2010 NIH Virology Interest Group.
- 2009 Convener of the Vaccine and Viral Vectors III Workshop, 28th Annual Meeting of American Society for Virology, University of British Columbia, Vancouver, Canada.
- 2010 Convener of the Filoviruses Workshop, 29th Annual Meeting of American Society for Virology, Montana State University, Bozeman, Montana.
- 2010- Expert Review in Vaccines. Member of Editorial Board.
- 2011 Convener of the Filoviruses Workshop, 30th Annual Meeting of American Society for Virology, University of Minnesota, Minneapolis, Minnesota.
- 2011-2013 American Society for Virology Program Planning Committee.
- 2012-2017 Member of the *Filoviridae* Study Group of the International Committee on Taxonomy of Viruses.
- 2012 Convener of the Emerging Viruses Workshop, 31th Annual Meeting of American Society for Virology, University of Wisconsin, Madison, Wisconsin (invited).
- 2013 Convener of the Viral Epidemiology Workshop, 32th Annual Meeting of American Society for Virology, The Pennsylvania State University, University Park, Pennsylvania. July 20-24, 2013.
- 2014 Member of the Organizing Committee of the 6th International Symposium on Filoviruses, Galveston, Texas.
- 2013 Member of NIAID/NIH review panel for the Partnership for Biodefense program RFA-AI-13-013.
- 2014, 2015 *Ad hoc* member of the NIH Vaccines against Microbial Diseases (VMD) Study Section.
- 2014- *Vaccine*. Member of Editorial Board (Council of 100).
- 2015- Journal of Virology. Member of Editorial Board.
- 2016 Member of NIAID/NIH Special Emphasis ZRG1 IMM-U(90) Study Section, June 29-30, 2016.
- 2017-2020 Member of NIH Vaccines Against Microbial Diseases (VMD) Study Section.

Ad hoc reviewer for: PLOS Pathogens; PLOS Neglected Tropical Diseases; The Lancet; Journal of Clinical Investigation; Scientific Reports (NPG); Journal of Infectious Diseases; Emerging Microbes & Infections (NPG); Cellular and Molecular Life Sciences; Journal of Infection; Cellular Microbiology; Molecular Therapy; FEBS Letters; Clinical and Vaccine Immunology; Gene Therapy; Human Immunology; Expert Review of Vaccines; European Cytokine Network; DNA and Cell Biology; Applied Microbiology and Biotechnology; Current Medical Chemistry; Journal of General Virology; Archives of Virology.

Honors

- 1994 Personal Russian State Scholarship for Young Outstanding Scientists. Awarded by the Presidium of the Russian Academy of Sciences.

- 1999 Special Act of Service Award, National Institute of Allergy and Infectious Diseases in Recognition and Appreciation of Special Achievement.
- 2000 The National Institute of Health Fellows Award for Research Excellence (competitive).
- 2001, 2002, 2003, 2004, 2005 National Institute of Allergy and Infectious Diseases Staff Recognition Awards in Recognition and Appreciation of Special Achievement.
- 2005 The National Institutes of Health Merit Award.
- 2006, 2007, 2008 (two awards), 2009 (two awards) Performance Award in Recognition of Special Achievement in Support of the Mission of the National Institute of Allergy and Infectious Diseases.
- 2015 Researcher of the Year, Department of Pathology, University of Texas Medical Branch.

C. Contribution to Science

1. At the Laboratory of Infectious Diseases, NIAID, NIH, my research focused on molecular and immunological studies of RSV. I demonstrated that the virus can express a foreign protein from an added gene and that certain genes can be deleted. I next focused on characterization of the effects of certain immunomodulating proteins of the virus on the adaptive response using animal models and human immune cells. I demonstrated that the domains aimed at inhibition of the interferon response have also a profound effect on the adaptive response, which was not totally expected at the time. I also demonstrated that the secreted form of RSV G protein reduces the efficiency of antibody neutralization of the virus.

- Kotelkin, A., Belyakov, I.M., Yang, L., Berzofsky, J.A., Collins, P.L. & **Bukreyev, A.** (2006). The NS2 protein of human respiratory syncytial virus suppresses the cytotoxic T cell response as a consequence of suppressing the type I interferon response. *J. Virol* 80 (21), 5958-5967. PMID: PMID16731934.
- Munir, S., Hillyer, P., Le Nouën, C., Buchholz, U.J., Rabin, R., Collins, P. & **Bukreyev, A.** (2011). Respiratory syncytial virus interferon antagonist NS1 protein suppresses and skews the T lymphocyte response. *PLoS Pathogens* 7(4): e1001336. PMID: PMC3080852
- Bukreyev, A.**, Yang, L., Fricke, J., Cheng, L., Ward, J. M., Murphy, B. R. & Collins, P. L. (2008). The secreted form of the G glycoprotein of respiratory syncytial virus helps the virus evade antibody-mediated restriction of replication by acting as an antigen decoy and through effects of Fc receptor-bearing leucocytes. *J. Virol.* 82 (24):12191-12204. PMID: PMC2593351.

2. At NIH, I also worked on the development of vaccines against various respiratory pathogens, including RSV, parainfluenza viruses, SARS coronavirus, and the H5N1 highly pathogenic influenza virus, and also on development of ways to modulate the immune response by co-expression of cytokines by recombinant viruses. We found that co-expression of interferon gamma by a recombinant RSV strongly attenuates its replication in the respiratory tract while maintaining the immune response at the level induced by the non-attenuated virus.

- Bukreyev, A.** Skiadopoulos, M. H., McAuliffe, J., Murphy, B. R., Collins P. L. & Schmidt, A. C. (2002). More antibody with less antigen: Can immunogenicity of attenuated live virus vaccines be improved? *Proc. Natl. Acad. Sci. USA* 99:16987-16991. The article was chosen for PNAS press release on 12/09/02. PMID: PMC12482928.
- Bukreyev, A.** Lamirande, E. W., Buchholz, U. J., Vogel, L. N., Elkins, W. R., St. Clair, M., Murphy, B. R., Subbarao K. & Collins P. L. (2004). Mucosal immunization protects monkeys against SARS coronavirus infection. *Lancet.* 363(9427):2122-2127. The article was chosen for *Lancet* press release on 06/23/04 and a NIH press release on 06/24/04. PMID15220033.
- Bukreyev, A.**, Belyakov, I. M., Prince, G. A., Yim, K. C., Harris, K. K., Berzofsky J. A. & Collins P. L. (2005). Expression of interleukin-4 by recombinant respiratory syncytial virus is associated with accelerated inflammation and a non-functional cytotoxic T lymphocyte response following primary infection but not following challenge with wild-type virus. *J. Virol.* 79:9515-9526. The article was chosen for *J. Virol.* spotlight. PMID: PMC1181599.

3. I pioneered development of needle-free vaccines against Ebola virus based on human and non-human respiratory paramyxovirus vectors. Our latest study demonstrated that a single dose of our respiratory vaccine delivered to the respiratory tract of non-human primates completely protects animals from death and a severe disease caused by a lethal challenge with Ebola virus. We also performed an in-depth analysis of cell-mediated response in the peripheral blood, spleen and lung tissues of immunized macaques, resulting in identification of unusually highly activated Ebola-specific T cells in lungs.

- a. **Bukreyev, A.**, Yang, L, Zaki, S. R., Shieh, W-J, Rollin, P. E., Murphy, B. R., Collins, P. L. & Sanchez, A. (2006). A single intranasal inoculation with a paramyxovirus-vectored vaccine protects guinea pigs against a lethal dose Ebola virus challenge. *J. Virol.* 80(5), 2267-2279. PMID: PMC1395378
- b. **Bukreyev, A.**, Rollin, P.E., Tate, M. Yang, L., Zaki, S.R., Shieh, W.-J., Murphy, B. R. , Collins, P. L. & Sanchez, A. (2007). Intranasal vaccination with a paramyxovirus-vectored vaccine protect primates against challenge with Ebola virus. *J. Virol.* 81(12), 6379-6388. PMID: PMC1900097.
- c. Meyer, M., Garron, T., Lubaki, N. M., Mire, C. E., Fenton, K. A., Klages, C., Olinger, G. G., Geisbert, T. W., Collins P. L., & **Bukreyev, A.** (2015) Aerosolized Ebola vaccine protects primates and elicits lung-resident T-cell responses. *J. Clin. Invest.* 125(8): 3241-55. The article was chosen for UTMB press release and NIH press release on 07/13/2015. PMID: PMC4563760.

4. Currently my lab is working on isolation and characterization of human monoclonal antibodies from filovirus (Ebola and Marburg) survivors and characterization of mechanisms of antibody neutralization of filoviruses using the isolated antibodies. The study is being performed in collaboration with Dr. James Crowe, Jr. (Vanderbilt University). We identify and characterize the most potent neutralizing and cross-neutralizing human mAbs, identify protective epitopes, and test and optimize protection of human mAbs in rodents and NHP.

- a. Flyak, A. I., Ilinykh, P. A., Murin, C. D., Garron, T., Shen, X., Fusco, M. L., Hashiguchi, T., Bornholdt, Z. A., Slaughter, J. C., Sapparapu, G., Ksiazek, T. G., Ward A. B., Saphire, E. O., **Bukreyev A.*** & Crowe, J. E., Jr.* (2015). Mechanism of human antibody-mediated neutralization of Marburg virus. *Cell* 160(5) 893-903. *Co-senior authors. PMID: PMC4344968. The article was chosen for UTMB and the Vanderbilt University press releases on February 26, 2015. PMID: PMC4344968.
- b. Ilinykh P. A., Shen, X., Flyak, A. I., Kuzmina, N., Ksiazek T. G., Crowe, J. E., Jr., Jr. & **Bukreyev A.** (2016) Chimeric filoviruses for identification and characterization of monoclonal antibodies. *J. Virol.* 90(8): 3890-901. PMID: PMC4810552.
- c. Flyak A. I., Shen X., Murin C. D., Turner, H. L., Fusco, M. L., Lampley, R., Kose, N., Ilinykh, P. A., Kuzmina, N., Branchizio, A., King, H., Brown, L., Bryan, C., Davidson, E., Doranz, B. J., Slaughter, J. C., Sapparapu, G., Klages, C., Ksiazek, T. G., Saphire, E. O., Ward, A. B., **Bukreyev, A.,*** and Crowe J. E., Jr.* (2016) Cross-reactive and potent neutralizing antibody responses in human survivors of natural Ebolavirus infection. *Cell* 164(3): 392-405. * Co-corresponding authors. The article was chosen for UTMB and the Vanderbilt University press releases on 1/21/2016, and was highlighted in *Nature* 529, 440. PMID: PMC4733404.

5. My lab also works on identification of mechanisms of the high pathogenicity of Ebola virus. We found that interferon inhibiting domains of the virus prevent maturation of dendritic cells that results in a deficient stimulation of T cells. We also found that Ebola virus glycoprotein directly triggers T lymphocyte death through interaction with TLR4 despite of the lack of infection of these cells, and inhibition of TLR4 reduces death Ebola infected animals. Furthermore, in collaboration with Ivan Marazzi (Mount Sinai School of Medicine) we identified the role of topoisomerase 1 in pathogenesis of Ebola infection.

- a. N. M. Lubaki, P. Younan, R. I. Santos, M. Meyer, M. Iampietro, R. A. Koup, **A. Bukreyev.** (2016). The Ebola interferon inhibiting domains attenuate and dysregulate cell-mediated immune responses. *PLOS Pathogens* 21(12):e1006031. The article was chosen for UTMB press releases on 12/01/2016.
- b. M. Iampietro, P. Younan, A. Nishida, M. Dutta, N. M. Lubaki, R. I. Santos, R. A. Koup, M. G. Katze, and **A. Bukreyev.** (2017). Ebola virus glycoprotein directly triggers T lymphocyte death despite of the lack of infection. *PLOS Pathogens* 13(5):e1006397. PMID: 28542576.
- c. P. Younan, P. Ramanathan, J. Graber, F. Gusovsky, and **A. Bukreyev.** (2017). The TLR4 antagonist Eritoran protects mice from lethal filovirus challenge. *mBio* 8(2) e00226-17. PMID: 28442605.
- d. Rialdi, A., Campisi, L., Zhao, N., Lagda, A. C., Pietzsch, C., Ho, J. S., Martinez-Gil, L., Fenouil, R., Chen, X., Edwards, M., Metreveli, G., Jordan, S., Peralta, Z., Muniz-Fontela, C., Bouvier, N., Merad, M., Jin, J., Weirauch, M., Heinz, S., Benner, C., van Bakel, H., Basler, C., Garcia-Sastre, A., **Bukreyev, A.** & Marazzi I. (2016) Topoisomerase 1 inhibition suppresses inflammatory genes and protects from death by inflammation. *Science*. Epub on Apr 28, 2016. The article was chosen for Icahn School of Medicine at Mount Sinai press release on 4/28/2016. PMID: 27127234.

Complete List of Published Work in NCBI My Bibliography:

<http://www.ncbi.nlm.nih.gov/sites/myncbi/1p7HsBTax7xQ9/bibliography/47809246/public/?sort=date&direction=ascending>

D. Research Support

Ongoing Research Support

HTDRA1-15-1-0034 Crowe (PI) 04/01/13-03/31/18
Human Monoclonal Antibodies Against Ebola and Marburg Viruses.
The goal of this project is to perform basic science research experiments to determine the molecular basis for antibody neutralization of filoviruses Ebola and Marburg.
Role: co-I

R01AI10288 Bukreyev (PI) 06/01/13-05/31/18
Broadly Specific Needle-free Vaccines Against Emerging and Biothreat Viruses
The goal of this project is to develop needle-free vaccine against multiple species of Ebola virus and against Marburg virus. The vaccine will be based on human and/or non-human respiratory paramyxovirus vectors.
Role: PI

U19AI109664 Project 3 Basler (PI) 03/01/14-02/28/19
Project 3 - Therapeutics Targeting Filoviral Interferon-antagonist and Replication Functions: Small Molecules Disabling Dephosphorylation of Ebola and Marburg.
The goal of this project is development of a drug against the Ebola and Marburg viruses based on a molecule targeting protein phosphatase 1 and preventing dephosphorylation of the viral VP30 protein.
Role: PI of Project 3

U19AI109664 Core B Bukreyev (PI) 03/01/14-02/28/19
Core B - Therapeutics Targeting Filoviral Interferon-antagonist and Replication Function: BSL-4 Core
The goal of this project is to develop and test small molecule anti-filoviral therapeutics that target filoviral interferon (IFN) antagonist functions and VP30 function.
Role: PI of Core B

U19AI109711 Geisbert (PI) 03/01/14-02/28/19
Advancement of Treatments for Ebola and Marburg Virus Infections Project Title: Project 3: Therapeutic Human Monoclonal Antibody Treatments for Filoviruses.
The goals of this project are: to isolate large panels of human mAbs to EBOV and MARV from the B cells of humans following natural infection, to identify and characterize the most potent neutralizing and cross-neutralizing human mAbs, and to test and optimize protection of human mAbs in rodents and NHP.
Role: co-I

U19AI109945 Basler (PI) 03/01/14-02/28/19
Mechanisms of Evasion of the Innate and Adaptive Immune Responses to Filoviruses: Mechanisms of "Immune Paralysis" Caused by Filoviruses - Project 2.
The goal of this project is to investigate the fundamental mechanisms of the unusually rapid disabling of the adaptive immune system by the Ebola and Marburg viruses.
Role: PI of Project 2

HDTRA1-14-1-0013 Basler (PI) 05/01/14-04/30/19
Comparative Immunology of Rousettus Aegyptiacus Reservoir with Filoviruses.
The goal of this project is to use massively parallel sequencing to catalog the Egyptian fruit bat transcriptome (mRNAs and miRNAs) and to use these sequence data to develop assays for comparative immunology.
Role: co-I and PI of UTMB sub-contract

Completed Research Support

U54AI057156 Walker (PI) 03/01/11-02/28/14
Western Regional Center of Excellence for Biodefense and Emerging Infectious Diseases Research (WRCE) Subproject: DP007: Aerosol Vaccination against Ebola Virus.
The goal of this project is to test aerosol delivery of the respiratory vaccine against Ebola virus in a non-human primate model of Ebola virus and to characterize the immune responses to vaccination.
Role: PI of the project