Trans-Agency Blood Brain Interface Workshop 2016

Exploring key challenges and opportunities associated with blood, brain, and their interface

June 7-8, 2016
Neuroscience Center Building (NSC)
6001 Executive Boulevard
Bethesda, Maryland

Participating Agencies/Institutes/Programs:

National Heart, Lung, and Blood Institute, NIH
National Cancer Institute, NIH
National Center for Advancing Translational Sciences, NIH
Extracellular RNA Communication Program, NIH Common Fund
Combat Casualty Care Research Program, DoD

Sponsored by:

National Heart, Lung, and Blood Institute
National Cancer Institute
Combat Casualty Care Research Program, DoD

Table of Contents

INTRODUCTION

The goal of this workshop is to bring together experts to examine key challenges and proposed recommendations associated with the interface between the circulatory system and the brain. The workshop will include experts from across the spectrum of the blood-brain interface, not just the blood-brain barrier, to highlight the promise and potential of technologies for diagnostics and therapy development. The event will encourage collaborations across the various groups represented at the meeting. Additionally, attendees will have the opportunity to generate a set of recommendations that could facilitate development in this promising field.

PRIMARY WORKSHOP QUESTIONS

1. What technology is closest to clinical translation and why?
2. What is the most prevalent brain disease/injury state that requires significant push in BBB delivery strategies?
3. What is the potential harm after BBB is altered? Can post-BBB disruption recovery be an issue?
4. When keeping the end goal in mind in terms of human applications, are there any technologies available that more closely model the human condition that could either complement or replace animal models?
5. How can current clinical practice best inform translational developments in this space? What about early clinical trials and the concept of reverse translation?
6. In this era of team science, can collaborations across fields stimulate therapeutic development in this space? If so, how can this process be facilitated and accomplished?

ACKNOWLEDGEMENTS

The workshop organizers would like to thank the following people for their work and contributions to the meeting program:

WORKSHOP CHAIRS

Berislav Zlokovic, MD, PhD | Workshop Chair, University of Southern California

Peter Searson, PhD | Workshop Co-Chair, Johns Hopkins School of Medicine

Richard Kraig, MD, PhD | Session Chair, University of Chicago Medical Center

Julia Ljubimova, MD, PhD | Session Chair, Cedars-Sinai Medical Center

A Tamara Crowder, PhD | Session Chair, Combat Casualty Care Research Program, DoD

WORKSHOP STEERING COMMITTEE

A Tamara Crowder, PhD | Combat Casualty Care Research Program, DoD

Kristin Fabre, PhD | NCATS, NIH

Andrei Kindzelski, MD, PhD | NHLBI, NIH

Lillian Kuo, PhD | NIAID, NIH

Xiao Lei, PhD | NHLBI, NIH

Christina Liu, PhD | NCI, NIH

Tania Lombo, PhD | NCATS, NIH

Martha Lundberg, PhD | NHLBI, NIH

Anthony Pusateri, PhD | Combat Casualty Care Research Program, DoD

Pothur Srinivas, PhD | NHLBI, NIH

Danilo Tagle, PhD | NCATS, NIH

William Timmer, PhD | NCI, NIH

Michel Twery, PhD | NHLBI, NIH

Ronald Warren, PhD | NHLBI, NIH

NIH WORKSHOP ORGANIZERS

Margaret Ochocinska, PhD | Program Director, DBDR, NHLBI, NIH

Christina Liu, PhD | Program Director, NCI, NIH

Andrei Kindzelski, MD, PhD | Program Director, DBDR, NHLBI, NIH

Traci Mondoro, PhD | Branch Chief, DBDR, NHLBI, NIH

Naomi Clarke | Extramural Support Assistant, DBDR, NHLBI, NIH

Della Claiborne | Program Specialist, DBDR, NHLBI, NIH

Terrie Squadere | Administrative Supervisor, DBDR, NHLBI, NIH

Chris Miller | Program Specialist, DBDR, NHLBI, NIH

AGENDA, Tuesday, June 7

7:30 AM ***Welcome and Registration***

General Session I (Conference Room C/D, 1st Floor)

8:00 AM ***Welcome***
Gary Gibbons, MD, Director, NHLBI

8:10 AM ***Workshop Introduction***
Keith Hoots, MD, Director, DBDR

Goals and Objectives
Margaret Ochocinska, PhD, Program Director, DBDR

8:20 AM ***Keynote: Initial Experience in a Pilot Study of Blood-Brain Barrier Opening for Chemo-Drug Delivery to Brain Tumors by MR-Guided Focused Ultrasound***
Todd Mainprize, MD, Sunnybrook Health Sciences Center

Blood Sciences Session I (Conference Room C/D, 1st Floor)
Session Chair: Berislav Zlokovic, MD, PhD, University of Southern California

8:40 AM ***Session Introduction***
Berislav Zlokovic, MD, PhD, University of Southern California

8:45 AM ***The Blood-Brain Barrier and Neurodegeneration***
Berislav Zlokovic, MD, PhD, University of Southern California

9:05 AM ***Microfluidics for Blood Research: from disease simulation to patient-specific phenotyping to diagnostics***
Scott Diamond, PhD, Penn Center for Molecular Discovery

9:25 AM ***Microparticles Impact Coagulation after Traumatic Brain Injury***
Michael Goodman, MD, University of Cincinnati

9:45 AM ***Fibrinogen in Neurological Diseases: mechanisms, imaging, therapeutics***
Katerina Akassoglou, PhD, UCSF School of Medicine

10:05 AM ***Exosomes in Glioma: their potential as carriers of information between the tumor and immune cells***
Theresa Whiteside, PhD, University of Pittsburgh

10:25 AM ***Break***

Blood Sciences Session II (Conference Room C/D, 1st Floor)
Session Chair: A Tamara Crowder, PhD, Combat Casualty Care Research Program, DoD

10:40 AM ***Session Introduction***
A Tamara Crowder, PhD, Combat Casualty Care Research Program, DoD

10:50 AM ***Monitoring the Central Nervous System through Peripheral Biofluids***
Kendall Jensen, PhD, TGen Center for Noninvasive Diagnostics

11:10 AM ***Studying the Blood-Brain Barrier: perspectives from understanding the biokinetics of biomarkers of brain injury***
Alex Valadka, PhD, Virginia Commonwealth University

11:30 AM ***Post-traumatic Cerebral Blood Flow, Autoregulation, and the Neurovascular Unit***
Donald Marion, MD, Defense and Veterans Brain Injury Center

11:50 AM ***Employing Transporters at Blood-Brain Interfaces to Regulate the Brain's Metabolomic and Pharmacologic Microenvironment***
Robert Clark, MD, University of Pittsburgh

12:10 PM ***Lunch***
Pre-ordered boxed lunches for presenters are available in Conference Room E

Exosome Therapeutics Session (Conference Room C/D, 1st Floor)
Session Chair: Richard Kraig, MD, PhD, University of Chicago Medical Center

1:10 PM ***Session Introduction***
Richard Kraig, MD, PhD, University of Chicago Medical Center

1:15 PM ***In Vivo Tracking of Dendritic Cell Exosomes Delivered to Brain***
Richard Kraig, MD, PhD, University of Chicago Medical Center

1:35 PM ***High Content Proteomics/Lipidomics Analysis: on a path toward understanding the mechanisms of exosome-mediated cellular uptake and blood-brain barrier crossing***
Anastasia Khvorova, PhD, University of Massachusetts Medical School

1:55 PM ***Exosome-like Nanoparticles Delivering Therapeutic Agents through an Intranasal Route Inhibit Brain Tumor Progression***
Huang-Ge Zhang, PhD, University of Louisville

2:15 PM ***Plasma Exosomes Enriched for Neuronal Origin: a source of biomarkers for neurodegenerative and neuroinflammatory diseases***
Dimitrios Kapogiannis, MD, National Institute of Aging, NIH

2:35 PM ***HER2-targeted Extracellular Vesicles Delivery of Therapeutic mRNA for Enzyme Prodrug Therapy***
A.C. Matin, PhD, Stanford University

2:55 PM ***Break***

Discussion Session

3:10 PM ***Open Microphone Discussion and Panel - Blood Brain Interface I***
***(*Conference Room C/D, 1st Floor)**
Moderator: Andrei Kindzelski, MD, PhD, Program Director, DBDR

4:45 PM ***Wrap-up***
Margaret Ochocinska, PhD

5:00 PM **Adjourn**

6:30 PM **Informal Dinner**
Democracy Grille

Wednesday, June 8

7:30 AM ***Welcome and Registration***

8:00 AM ***Keynote: From Blood–Brain Barrier to Blood–Brain Interface: new opportunities for CNS drug delivery***
William Banks, MD, FACE, University of Washington

Next Generation *in vitro* BBB Models Session (Conference Room C/D, 1st Floor)
Session Chair: Peter Searson, PhD, Johns Hopkins School of Medicine

8:20 AM ***Session Introduction***
Peter Searson, PhD, Johns Hopkins School of Medicine

8:25 AM ***Assessing the Feasibility of an in vitro Neurovascular Unit***
Peter Searson, PhD, Johns Hopkins School of Medicine

8:45 AM ***NeuroVascular Unit (NVU) on a Chip: new direction in blood-brain barrier modeling and perfusion***
Jacquelyn Brown, PhD, Vanderbilt University

9:05 AM ***Modeling and Targeting the Blood-Brain Barrier in Health and Disease***
Eric Shusta, PhD, University of Wisconsin - Madison

9:25 AM ***Developing Tridimensional Models of the Human Cerebral Cortex in vitro***
Sergiu Pasca, MD, Stanford University

9:45 AM ***Revealing the Transport Mechanisms, Kinetics, and Energetics of Drugs Diffusing through Membranes of the Blood-Brain Barrier***
Martin Ulmschneider, PhD, Johns Hopkins University

10:05 AM ***Break***

Blood-Brain Barrier Delivery and Targeting Session (Conference Room C/D, 1st Floor)
Session Chair: Julia Ljubimova, MD, PhD, Cedars-Sinai Medical Center

10:20 AM ***Session Introduction***
Julia Ljubimova, MD, PhD, Cedars-Sinai Medical Center

10:25 AM ***Overcoming Blood-Brain Barrier for Precise Diagnosis, Targeting and Treatment of Primary and Metastatic Brain Tumors***
Julia Ljubimova, MD, PhD, Cedars-Sinai Medical Center

10:45 AM ***Nanotechnology Takes Aim at the Blood-Brain Barrier***
Efstathios (Stathis) Karathanasis, PhD, Case Western Reserve University

11:05 AM ***Spherical Nucleic Acids for the Precision Treatment of Malignant Glioma***
Alexander Stegh, PhD, Northwestern University

11:25 AM ***Three Areas Where Studies of the Blood-Brain Barrier Change Patient Care***
Edward Neuwelt, MD, Oregon Health & Science University and the Portland Veterans Affairs Medical Center

11:45 AM ***Drug and Nucleic Acid Delivery to the Brain***
Justin Hanes, PhD, Johns Hopkins University

12:05 AM ***Break***
Pre-ordered boxed lunches for presenters are available in Conference Room E for the working lunch

Discussion Session

12:15 PM ***Open Microphone Discussion and Panel - Blood Brain Interface II***
Working Lunch
***(*Conference Room C/D, 1st Floor)**
Moderator: Christina Liu, PhD, Program Director, NCI

1:15 PM ***Wrap Up and Next Steps***
Margaret Ochocinska, PhD

1:30 PM **Adjourn Workshop**

BIOGRAPHIES

Dr. Katerina Akassoglou is a Senior Investigator at the Gladstone Institute of Neurological Disease, and a Professor in the Department of Neurology at the University of California, San Francisco. Dr. Akassoglou has pioneered studies in the investigation of the role of the blood clotting factor fibrinogen in CNS autoimmunity, trauma, and neurodegeneration. Her aim is to understand the mechanisms that control the communication between the brain, immune, and vascular systems with the goal to design novel therapies for neurologic diseases—and in particular, multiple sclerosis and neurodegenerative diseases. Her lab employs a multifaceted approach to her research, incorporating animal modeling, in vivo two-photon microscopy, drug discovery and pre-clinical translational research, and clinical biomarker studies. Dr. Akassoglou was awarded by the White House the Presidential Early Career Award for Scientists and Engineers, the Abel Award from ASPET, the Dana Foundation Award in Brain and Immunoimaging, a EUREKA award from NINDS, and The Marilyn Hilton Award for Innovation in Multiple Sclerosis Research by the Conrad N. Hilton Foundation.

Dr. William Banks is ACOS–R&D at the Seattle VA and Professor of Medicine at the University of Washington. His work has focused on brain-body communication as mediated by interactions between the blood-brain barrier (BBB) and peptides, regulatory proteins, and other informational molecules. Dr. Banks and his mentor Abba Kastin were the first to show that peptides crossed the BBB, later extending this work to regulatory proteins (e.g., cytokines, leptin, and ghrelin), showing that such transport is altered by neuroinflammation and in disease models for obesity, Alzheimer's, and diabetes. He has also applied these concepts to the development of CNS drugs.

Dr. Jacquelyn A. Brown received the B.A. degree in biology and chemistry from Alfred University and the Ph.D. in neuroscience from Washington University in St. Louis working in Dr. Paul Bridgman's lab studying growth cone guidance. Following postdoctoral appointments in cancer biology, psychiatry and biomedical engineering, Dr. Brown was appointed as Staff Scientist of the Vanderbilt Institute for Integrative Biosystems Research and Education. She is leading the development of the NeuroVascular Unit and its application as a cellular model of the human blood-brain barrier in multiple studies supported by the NIH NCATS Tissue Chip program.

Dr. Robert S.B. Clark is Chief of the Division of Pediatric Critical Care Medicine and provides clinical service for both the general and pediatric neurocritical care services. Broadly speaking, his current research interests include mechanisms of cell death and neurological dysfunction after traumatic and ischemic brain injury, particularly in the developing brain. Laboratory efforts encompass in vitro and in vivo models of brain trauma and ischemia, and translational studies in patients suffering from these injuries. He has a strong interest in pediatric neurocritical care. He has established an infrastructure for the successful training of young investigators, and has served as the primary research mentor for over 25 clinical fellows, post-doctoral fellows, graduate students, and/or medical students. He has enjoyed continuous NIH funding since 1996, served as primary sponsor for multiple K-funded trainees and serves as Co-PI on the T32 grant "Training in Pediatric Neurointensive Care and Resuscitation Research", and has served on over 60 NIH study sections since 2001. He has over 200 publications including over 150 peer-reviewed research manuscripts. In a recent report by Thomas Reuters Web of Science's **SCIENCE**WATCH he was listed as one of the top 25 most prolific authors of papers on traumatic brain injury in the world from 2001-2014 (http://sciencewatch.com/articles/special-topic-traumatic-brain-injury). His publications have been highlighted in *Science*, *Nature*, *Scientific American*, *Science & Vie* (Paris), and *The Wall Street Journal*.

Dr. Tammy Crowder is a native of Virginia and received her undergraduate degree in Biological Sciences from the University of Maryland. She earned her Master's degree in Medical Microbiology and Doctorate in Neuroscience at the Uniformed Services University of the Health Sciences in Bethesda, MD. Dr. Crowder completed a post-doctoral fellowship at the National Institutes of Health and then transitioned to the Congressionally Directed Medical Research Program as the lead Traumatic Brain Injury Science (TBI) Officer providing scientific/technical support/guidance and overseeing TBI research in excess of $150 million dollars. In 2009 she took over as Chief of Staff for the Defense and Veterans Brain Injury Center, the DoD TBI Center of Excellence, providing overall direction and execution of its program management functions. Dr. Crowder is currently the Neurotrauma portfolio manager for the Combat Casually Care Research Program and is responsible for the planning programming, budgeting and execution of Defense Health Program dollars allocated for traumatic brain injury and related neurotrauma. Dr. Crowder's awards include the Commander's Award for Civilian Service and the Department of the Army's Superior Civilian Service Award.

Dr. Scott L. Diamond is the Arthur E. Humphrey Professor of Chemical and Biomolecular Engineering at the University of Pennsylvania. Dr. Diamond researches *Cardiovascular Therapeutic Technologies* in several key areas: microfluidics, blood systems biology, drug discovery, and gene delivery. He has produced over 200 publications and patents. He has trained over 50 PhD students and postdoctoral fellows. He is the recipient of the NSF National Young Investigator Award, the NIH FIRST Award, the AHA Established Investigator Award, and the AIChE Colburn Award. He is an elected fellow of the American Institute for Medical and Biological Engineering and Biomedical Engineering Society (BMES).

Dr. Michael Goodman After attending Duke University as an undergraduate, Dr. Goodman enrolled in Albany Medical College as a medical student then transferred to University of Cincinnati College of Medicine to complete medical school and remained at Cincinnati to complete his General Surgery residency, which included two years of basic science research in intracellular signaling for cardioprotection and post-traumatic inflammatory responses. During his subsequent fellowship in Surgical Critical Care at the University of Texas Health Science Center at Houston Dr. Goodman developed a clinical interest in the dynamic changes of coagulation following injury after gaining experience with thromboelastography and platelet aggregation. Dr. Goodman returned to the University of Cincinnati as an Assistant Professor of Surgery in the Division of Trauma and Critical Care to pursue a career in trauma, surgical critical care, general surgery, and surgical research with a focus on the relationship of coagulation to post-traumatic inflammation and microparticle generation. Since joining the faculty, Dr. Goodman have been awarded several military surgical research grants and become an Associate Program Director for the General Surgery residency program.

Dr. Justin Hanes is the Lewis J. Ort Endowed Professor of Ophthalmology and Director of the Center for Nanomedicine at the Johns Hopkins University, where he also holds faculty appointments in the departments of Biomedical Engineering, Chemical & Biomolecular Engineering, Environmental Health Sciences, Neurosurgery, Oncology, and Pharmacology & Molecular Sciences. He is an inventor on more than 125 patents and patent applications focused in the area of advanced delivery systems that make drugs safer and more effective. Companies launched based on these patents include Advanced Inhalation Research (acquired by Alkermes), Civitas Therapeutics (acquired by Acorda Therapeutics), Kala Pharmaceuticals, and GrayBug Vision. He is also a founder of Theraly Pharmaceuticals and Ashvattha Therapeutics. Dr. Hanes is known for developing new methods of targeted and sustained drug and gene delivery to specific sites in the body. He has served on the scientific advisory boards for several companies, including Genentech in the Drug Delivery Division, and he is the most recent past chair of the Gene and Drug Delivery Study Section of the National Institutes of Health. He serves on the Editorial Boards of ten scientific journals focused on biomaterials, pharmaceutical science, medicine, and controlled drug delivery. Dr. Hanes has delivered more than 170 invited lectures, is a fellow of four scientific societies, and has won prestigious awards, including being named among "The World's Top 100 Young Innovators and Leaders in Technology and Business" by the *MIT Technology Review*, "The World's Most Influential Scientific Minds: 2014" by Thompson Reuters (based on the high number of his papers ranked in the top 1% in their field based on citations over the past 10 years), and an Edward C. Nagy Investigator by the National Institute of Biomedical Imaging and Bioengineering of the NIH. He has been named a "Global Young Leader" by the US National Academy of Sciences, and he was elected to the Global Young Academy based upon a recommendation by the US National Academy of Sciences. He was inducted into the National Academy of Inventors in 2014. His degrees are in Chemical Engineering from UCLA (B.S. 1991) and MIT (Ph.D. 1996), and he completed a postdoctoral fellowship in Oncology and Neurosurgery at Johns Hopkins prior to beginning his faculty position in 1998.

Dr. Dimitrios Kapogiannis is a neurologist sub-specialized in Behavioral Neurology. He was trained as MD in the National University of Athens, Greece, and completed his neurology residency training at the Harvard Medical School/ Massachusetts General Hospital, followed by a clinical fellowship at the National Institute of Neurological Disorders and Stroke. Currently, he works as a tenure-track Clinical Investigator at the Laboratory of Neurosciences of the National Institute on Aging and Assistant Professor at the Department of Neurology at Johns Hopkins University. Dr. Kapogiannis conducts translational, biomarker and clinical interventional studies on cognitive aging and various neurodegenerative diseases, in particular, Alzheimer's disease. His lab has been a pioneer in deriving neural exosomes from plasma and using them as a source of biomarkers for Alzheimer's disease.

Professor Efstathios (Stathis) Karathanasis is the Director of the Cancer Nanotechnology research program at Case Western Reserve University and a member of the Case Comprehensive Cancer Center, where he serves as the Co-Leader of the Nanotechnology Focus Group. The overarching goal of his research program is to develop impactful nanomedicines for the most hard-to-treat and lethal forms of cancer. He joined the School of Medicine at Case Western Reserve University in 2009, where he has a joint appointment in the Department of Biomedical Engineering and the Department of Radiology. A native of Greece, Dr. Karathanasis grew up in Thessaloniki and graduated from Aristotle University in 1999 with a B.S. in chemical engineering. In 2001, he moved to the United States, where he completed his doctoral degree at the University of Houston (2005) and postdoctoral training at Georgia Institute of Technology (2009).

Dr. Anastasia Khvorova is Professor in the RNA Therapeutics Institute and the Program in Molecular Medicine at the University of Massachusetts Medical School (UMMS) in Worcester, Massachusetts. Before joining the UMMS faculty, she held leadership positions in industry, including Vice President of Research & Development and Chief Science Officer of Dharmacon, Founder and Scientific Advisor of Advirna, and Chief Science Officer and Senior Vice President of RXi Pharmaceuticals. Dr. Khvorova's industry experience in drug discovery and development collaborations with pharmaceutical companies along with her expertise in chemistry and cell biology allowed her to establish a lab at UMMS that brings together organic chemists and RNA biologists to develop novel approaches and solutions to understanding natural and therapeutic RNA trafficking and delivery.

Dr. Richard Kraig is a professor in the Department of Neurology at The University of Chicago and the William D. Mabie Professor in the Neurosciences. Dr. Kraig's research centers on deciphering the immune signaling by which environmental enrichment (i.e., increased intellectual, social, and physical activity) improves brain health. Dr. Kraig and his colleagues, Drs. Aya D. Pusic and Kae M. Pusic discovered that environmental enrichment prompts release of microRNA containing exosomes from blood that promote myelination and oxidative tolerance within normal or damaged brain without toxic effects. Analogous nutritive exosomes can be harvested from stimulated dendritic cells grown *in vitro* and delivered to the CNS. Thus, the Kraig group is working to develop microRNA containing exosomes that emulate environmental enrichment as scalable therapeutics for neurological diseases involving demyelination and oxidative stress.

Dr. Julia Ljubimova is Professor and Director of Nanomedicine Research Center at the Department of Neurosurgery, Cedars-Sinai Medical Center. She has been working in clinical and basic cancer research during her entire career. Her major interests are cancer biomarkers as tools for developing new nanomedicine imaging agents and drugs against primary and metastatic brain and breast tumor and targets for precise non-invasive diagnostics. One of the novel markers, a structural tumor vessel wall protein laminin-411, is currently in a clinical trial as a prognostic and diagnostic marker for human glial tumor progression. These discoveries led to the development of new technologies for drug delivery and engineering of new class of tumor-targeted anti-cancer nanomedicine drugs. Nano immunology and nano toxicology are novel important subjects of the fight against tumors and inflammation, which are currently studied in the Nanomedicine Research Center. Dr. Ljubimova's research is supported by NIH/NCI, private and industry grants. She is the author of over 80 research publications, reviews and book chapters as well as an inventor on twelve issued patents, and patent applications.

Dr. Todd Mainprize is currently the Head of the Division of Neurosurgery at Sunnybrook Health Science Centre. He completed his medical school training in Saskatoon Saskatchewan in 1996. His neurosurgical training was done in Toronto where he did 5 years of post-graduate research in the medical genetics and cellular biology of brain tumors. After finishing neurosurgical and research training, he started his career in neuro-oncology and skull base surgery at Sunnybrook Health Science Centre in 2008. His research interest is the translation of MRI guided Focused Ultrasound to treat brain tumors. Sunnybrook has the seventh largest cancer center in North America and is the busiest trauma center in Canada. Todd is married to his wife of 12 years with three children, Graham age 11, Thomas age 8 and Victoria age 6.

Dr. Donald W. Marion is an academic neurosurgeon who currently serves as Senior Traumatic Brain Injury Consultant for the Defense and Veterans Brain Injury Center, Dept. of Defense. He has focused on the clinical pathophysiology and treatment of traumatic brain injury (TBI) for more than 30 years. He is a charter author of the Brain Trauma Foundation's Guidelines for the Management of Severe Traumatic Brain Injury, and published the first clinical report to show benefit of therapeutic moderate hypothermia for TBI (*The New England Journal of Medicine, 1997*). He is the editor of a book entitled Traumatic Brain Injury, and has authored or co-authored more than 200 journal articles and book chapters, most related to TBI. Dr. Marion's previous positions have included Professor and Chair of the Department of Neurosurgery, The Boston University School of Medicine; Professor and Vice-Chair, Department of Neurosurgery, The University of Pittsburgh School of Medicine; and Director of the Brain Trauma Research Center at the University of Pittsburgh. He is past Chair of the Joint Section on Neurotrauma and Critical Care of the American Association of Neurological Surgeons and Congress of Neurological Surgeons; past President of the National Association of Injury Control and Research Centers; and past Chair of the Neurosurgery Subsection, the Committee on Trauma of the American College of Surgeons. Dr. Marion sits on the Editorial Boards of *Neurosurgery*, *The Journal of Trauma*, and *The Journal of Neurocritical Care*. He has served as the Science Officer of the Children's Neurobiological Solutions Foundation (CNS), Santa Barbara, CA, and managed the Foundation's stem cell grant portfolio.

Dr. AC Matin received his PhD from UCLA, and then moved to the State University of Groningen (Netherlands), returning to the US as a faculty member in Stanford University Medical School. He has contributed to several areas in microbial molecular biology. To detoxify heavy metal carcinogens, Dr. Matin discovered and improved a new enzyme ChrR. The latter proved useful also in activating prodrugs including a new one CNOB that Dr. Matin discovered. He has made human dendritic cell exosomes that can specifically confer CNOB activating capacity on HER2+ve cells; these also appear capable of crossing the blood-brain barrier and treating brain metastasized cancer.

Dr. Edward Neuwelt has made distinguished contributions to the field of blood-brain barrier science for over three decades. The overall focus of his career has been to improve the understanding and treatment of central nervous system (CNS) malignancies. His research focuses on neuroimaging brain tumor vasculature in preclinical models, the clinical use of ferumoxytol to image brain tumors, blood-brain barrier disruption chemotherapy in primary CNS lymphoma, targeting adhesion molecules in brain tumors, and chemoprotection and chemo-enhancement for brain tumor therapy.

Dr. Sergiu Pasca is an Assistant Professor in the Department of Psychiatry and Behavioral Sciences at Stanford University. He is also part of the Stanford Neurosciences Institute, the Institute for Stem Cell Biology and Regenerative Medicine and a fellow of the ChEM-H Institute. His laboratory is primarily focused on the development of in vitro human cellular models for studying human brain development and for identifying neuronal phenotypes for neuropsychiatric disorders. His lab is also developing methods for the differentiation of human pluripotent stem cells and novel functional assays for studying patient-derived neural cells. Dr. Pasca is a recipient of a NARSAD Young Investigator Award, the MQ Award for Transforming Mental Health, the NIMH Director's BRAINS award, and he is the Baxter Endowed Faculty Scholar at Stanford.

Dr. Peter Searson is the Reynolds Professor of Engineering and the Director of the Johns Hopkins Institute for Nanobiotechnology. He received his PhD from the University of Manchester in England and was a post-doctoral associate at MIT. His research focus is on *in vitro* microvessel models of the tumor microenvironment and the blood-brain barrier.

Dr. Eric V. Shusta received his Ph.D. in 1999 from the University of Illinois where, under the guidance of Dr. Dane Wittrup, he studied the production and engineering of antibodies and T-cell receptors using yeast. He followed this with postdoctoral training at the University of California-Los Angeles in the laboratory of Dr. William Pardridge where he helped pioneer molecular level analyses of the blood-brain barrier. Currently, Dr. Shusta is the Howard Curler Distinguished Professor in the Department of Chemical and Biological Engineering at the University of Wisconsin-Madison. His research focuses on antibody-based brain drug delivery and the development of molecular, cellular and protein engineering tools that can help gain a better understanding of blood-brain barrier transport and function. He has been recognized by the Dreyfus New Faculty Award, an NSF Career award, the ACS BIOT division young investigator award, among others, and was recently elected fellow in the American Institute for Medical and Biological Engineering.

Dr. Alexander Stegh obtained his PhD from the University of Chicago, and the Leibniz University of Hannover, and did his postdoctoral studies at the Dana-Farber Cancer Institute/Harvard Medical School. His research program is aimed at understanding the genetic program that underlies the pathogenesis of Glioblastoma (GBM), the most prevalent and malignant form of brain cancer, and to drive these basic discoveries toward pharmaceutical opportunities using nanotechnology and high-throughput medicinal chemistry. He is an Assistant Professor at Northwestern University. His work has been awarded with the prestigious Sidney Kimmel, James S. McDonnell 21st century science and ACS scholar awards.

Dr. Martin Ulmschneider graduated with a BA in Physics from Oxford University. He stayed at Oxford for his graduate studies on membrane protein simulations at the Laboratory of Biophysics. He subsequently obtained a Wellcome Trust international traveling fellowship to work on membrane protein folding at the Indian Institute of Science in Bangalore, the University of Rome La Sapienza, and Oxford University. After a brief stint at the University of Utrecht, he obtained a Marie Curie International Fellowship to work at the Universities of California, Irvine and London on membrane active peptides. He is currently an Assistant Professor at Johns Hopkins University working on a range of membrane related phenomena.

Dr. Alex Valadka attended medical school at the University of Chicago. His interest in neurotrauma and critical care led him to pursue his neurosurgical residency at the Medical College of Virginia. He then joined the faculty of Baylor College of Medicine and subsequently worked at other institutions in Texas. He returned to Richmond in 2015 to become Chair of Neurosurgery at Virginia Commonwealth University. Dr. Valadka maintains a strong clinical and research interest in neurotrauma and critical care. He is also active in organized neurosurgery. He currently serves as President-elect of the American Association of Neurological Surgeons and as a Director of the American Board of Neurological Surgery.

Dr. Kendall Van Keuren-Jensen has been at TGen in Phoenix, AZ, for 8 years where she is an Associate Professor in Neurogenomics and is Co-Director of the TGen Center for Noninvasive Diagnostics. Dr. Keuren-Jensen is Co-Director for the NIH Extracellular RNA Communication Consortium RNAseq Working Group. Her current work focuses on identifying ways to monitor central nervous system injury and disease through noninvasive means. She did her PhD thesis at Cold Spring Harbor Laboratory with Stony Brook University, focusing on the role of activity in shaping dendritic morphology and synaptic maturation. Prior to that, she received a Master Degree in Pharmacology and Toxicology from the University of Kansas.

Dr. Theresa L. Whiteside received both her MA and PhD degree in Microbiology from Columbia University, New York, NY. She is a Diplomate of the American Board of Medical Laboratory Immunology (1979). She was a Fogarty Senior International Fellow at the Ludwig Institute for Cancer Research in Lausanne, Switzerland (1984-85). At the University of Pittsburgh, Dr. Whiteside rose through the faculty ranks to become Professor of Pathology with secondary appointments as Professor of Immunology and Otolaryngology (1989-present). She served as Director of the Immunologic Monitoring and Diagnostic Laboratory at the University of Pittsburgh Cancer Institute for over 20 years. She has authored 570 peer-reviewed papers and 125 chapters and review articles. She received a *Honoris causa* degree in Medicine from The Poznan Medical University in Poland in 2011 and was awarded a Richard V. Smalley Memorial Award by the Society of Immunotherapy of Cancer in 2012.

Dr. Huang-Ge Zhang's research largely explores the underlying physiologic questions regarding endogenous exosomes (referred to as mammalian cell derived exosomes) and exogenous exosomes (plan cell derived exosomes) and their promising role as therapeutic vehicles in delivering treatment for a diverse range of medical conditions, including malignancies including brain tumor, diabetes, and autoimmune diseases. Dr. Zhang's on-going effort to translate his basic science findings to the clinical field has led to patents on a number of his discoveries. Dr. Zhang's group has found that nanoparticles released from the flesh of fruits could be of particular usefulness as a therapeutic delivery vehicle based on data generated from ongoing clinical trials for treatment of colon cancer and colitis mouse models. His published data also suggest that fruit nanoparticles are preferentially taken up by monocytes and macrophages. Therefore, in principal, this strategy could be applied to any disease in which activation of macrophages and monocytes play a role in the disease process

Dr. Berislav V. Zlokovic is the director of the Zilkha Neurogenetic Institute, Professor and Chair of the Department of Physiology & Biophysics at the Keck School of Medicine, and a Professor of Biological Sciences at the Dornsife College of Letters, Arts and Sciences of University of Southern California. Dr. Zlokovic has a life-long career in studying the role of blood vessels in the pathogenesis and treatment of neurological disorders such as Alzheimer's disease, related disorders and stroke. Using animal models and studying human brain, his laboratory has shown that dysfunction in the blood-brain barrier and brain microcirculation can accumulate before neuronal dysfunction and contribute to the onset and progression of neurodegeneration, neurological disorder and cognitive impairment. Findings of his research team contributed to Phase 2 and 3 clinical studies in Alzheimer's patients based on clearance of amyloid-beta and/or blockade of its re-entry into the brain, and Phase 2 studies in stroke patients based on APC treatment as a neuroprotective agent. Thomson Reuters listed Dr. Zlokovic as one of "The World's Most Influential Scientific Minds" in 2014 for ranking in 1% of the most-cited authors in the field of neurosciences (2002 – 2012). He is the recipient of many awards, including the MetLife Award for Medical Research, the Potamkin Prize from the American Academy of Neurology, the Javits Award from NINDS, and the MERIT Award from the NIA. He is a fellow of the AAAS and a member of The Dana Alliance for Brain Initiative, the Serbian Academy of Sciences and Arts and The European Academy of Sciences (Academia Europeae).

ABSTRACTS

Initial Experience in a Pilot Study of Blood-Brain Barrier Opening for Chemo-Drug Delivery to Brain Tumors by MR-Guided Focused Ultrasound

Todd Mainprize, MD

Sunnybrook Health Sciences Center

Introduction

Magnetic resonance-guided focused ultrasound (MRgFUS) can be used to reversibly open the blood-brain barrier (BBB) for targeted drug delivery (1). Research on animal models, including non-human primates (2), has been conducted to investigate the effectiveness and characteristics of BBB openings. Here we describe our initial experience in a pilot clinical study to establish the feasibility, safety and preliminary efficacy of focused ultrasound to temporarily open the BBB to deliver chemotherapy to brain tumors.

Methods

This phase-one clinical trial of BBB opening by focused ultrasound was approved by Health Canada. A modified clinical MRgFUS brain system (ExAblate 4000, 230 kHz, Insightec, Tirat Carmel, Israel) was used with a 3T MR scanner (Signa MR750, GE Healthcare, Milwaukee, WI, USA). Two hours before the procedure, liposomal doxorubicin Caelyx (Janssen, Toronto, Canada) was intravenously infused over 1 hour at a dose of 30 mg/m^2. The patient's head was then shaved and positioned in the FUS array with a stereotactic frame. Two targets close to the posterior margin of the glial tumor were chosen based on T2 images (Fig.1). Each target consisted of a 3x3 grid of 9 spots at 3 mm spacing. For each spot, 2.6 ms on, 30.4 ms off FUS pulses were repeated for 300ms before steering to the next spot. The pattern was repeated periodically resulting in an overall pulse repetition frequency (PRF) for each spot of 0.9%. A bolus injection of 4 ul/kg of Definity microbubbles (Lantheus Medical Imaging, N. Billerica, MA, USA) was applied simultaneously with each sonication (1/5th of the clinical dose for ultrasound imaging). With the first injection of microbubbles, 10s short sonications at 5W, 7W and 9W acoustic power were applied to find the appropriate power level based on feedback of cavitation signals. Cavitation signals were detected by two receivers and sampled at a rate of 2 MHz. Spectrum integration from 75 kHz to 155 kHz was calculated and two threshold levels of the spectrum integration were defined as a safety mechanism based on pre-clinical studies on a trans-human skull pig model (3). 9W was found to be adequate for these targets. 50 s sonications at 9W were then applied at each target, with a separate bolus injection of microbubbles for each. Post sonication, Gd (Gadovist, Bayer)-enhanced 3D FSPGR images were acquired to verify the BBB openings, and T2*-weighted GRE images (TE=15ms) were collected to detect potential hemorrhage. After the treatment, the patient was released from the head frame and MR scans were repeated with an 8-channel head coil for better quality images. The patient underwent routine tumor resection the next day and tissue samples at the two BBB opening targets were collected for quantification of chemotherapy drug concentration.

Results

BBB opening was successfully achieved at both locations with clear Gd enhancement of the 3x3 grid patterns (Fig.2). Despite using the same power level, the actual acoustic pressure at the 2nd target was lower than the first due to steering of the FUS beam. Small dark signals within individual sonicated spots in the T2* image (Fig.3) indicated low-level extravasation of red blood cells. The quantification of drug concentration is pending further analysis.

Discussion

The 3mm spacing of the 9 spots was intentionally designed to form a grid pattern of Gd enhancement for easier confirmation in heterogeneous tumors for the initial cases. We do not expect an impact on other parameters if the spacing needs to be reduced for an more uniform drug distribution within the BBB opening volume. The level of extravastion of RBC was low and not a concern in the tumor environment. Our animal experiments have shown that the cavitation signal can be used during the sonications to control the power level for eliminating the RBC exravasations (4). The current system did not use this method during sonications.

The tumor in this patient was in the right temporal lobe adjacent to the skull. The two targets were ~4 cm lateral from the midline of the brain, and the 2nd target was also ~2.5 cm posterior. Thermal ablations by FUS at these off-centre locations are technically challenging due to excessive skull heating. However, successful BBB openings at these locations were demonstrated at low powers at 230 kHz. If these results can be repeated in other patients without complications, then the method may provide a new way to deliver therapeutic agents into brain for the treatment of tumors and other brain diseases.

Acknowledgements

The authors thank the Focused Ultrasound Foundation for funding this trial and InSightec for technical supports of the ExAblate system. The development of this method was funded by NIH grant no. EB003268.

References

1.Hynynen K et al. Radiology 2001;220:640-6.
2.McDannold N et al. Cancer Research 2012;72:3652-63.
3.Huang Y et al. ISMRM 2015, abstract 37.
4.O'Reilly MA et al. Radiology 2012;263:96-106.

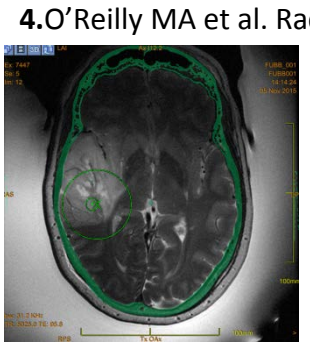
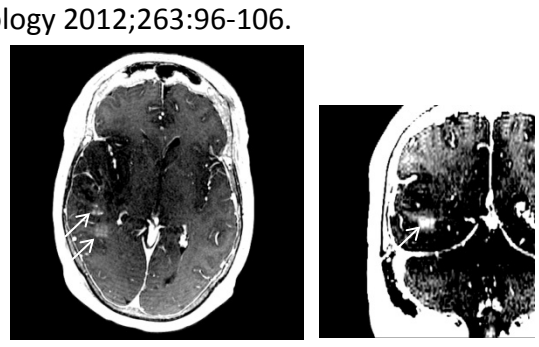


Fig.1 Intraoperative T2w MR image showing the tumor and the first BBB target.



a b

Fig.2 a) Axial Gd-enhanced T1w MR images showing the first (top arrow) and second (bottom) BBB openings. B) Coronal view across the second target.

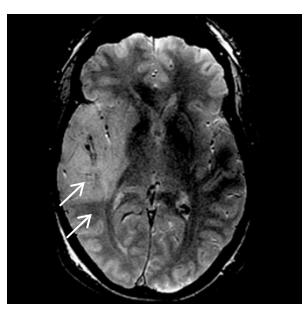


Fig.3 T2*w image shows low level of RBC extravasation (small dark spots) within the two target volumes.

The Blood-Brain Barrier and Neurodegeneration

Berislav V. Zlokovic, MD, PhD

University of Southern California

Blood vessels in the brain are organized with surprising precision, patterned in parallel with the major brain circuits tasked with sensation, memory and motion. This tight interrelationship may reflect key functional roles in neuronal normal function, disease and brain aging. I will briefly discuss i) cellular and molecular mechanisms and genetic defects in blood vessels and the neurovascular unit (e.g., pericytes, endothelial cells, astrocyte, etc.) that can lead to blood-brain barrier (BBB) breakdown and neurodegeneration in rare monogenic human diseases and animal models; ii) the effects of Alzheimer's-associated risk genes (e.g., APOE4) on blood vessels and BBB; and iii) new neurovascular BBB imaging and molecular biomarkers in the living human brain in relation to cognitive impairment. Finally, I will examine potential therapeutic targets at the BBB and treatments directed at the neurovascular unit in Alzheimer's disease (AD) and stroke, such as iv) inhibition of the receptor for advanced glycation end products (RAGE) at the BBB in AD, and v) protection of the BBB and the neurovascular unit by blood-derived protease activated protein C (APC) in stroke, that have advanced from bench to bedside - Phase 3 and Phase 2 clinical studies in AD patients and stroke patients, respectively.

Microfluidics for Blood Research: From disease simulation to patient-specific phenotyping to diagnostics

Scott L. Diamond, PhD

University of Pennsylvania

Blood is a multicellular tissue that functions in a hemodynamic context. The biophysics of blood flow can dictate the function of molecules and cells in the vasculature with consequent effects on haemostasis, thrombosis, embolism, inflammation, and fibrinolysis. Flow and transport dynamics are very distinct for: (1) haemostasis vs. thrombosis and (2) venous vs. arterial episodes. Intraclot transport changes dramatically the moment hemostasis is achieved or the moment a thrombus becomes fully occlusive. With platelet concentrations that are 50 to 200-fold greater than platelet rich plasma, clots formed under flow have very different composition and structure compared to blood clotted statically in a tube.

Our laboratory has developed a number of microfluidic devices to create precisely controlled reactive blood flows. This allows various reaction, transport, and cell biology issues to be studied with controlled hemodynamics. Venous and arterial thrombotic conditions can be mimicked using small volumes of human blood (or mouse blood). Both conditions of bleeding and conditions of thrombosis can be created with microfluidic devices. To date, we have investigated numerous therapeutic modalities such as: (1) anti-platelet agents targeting COX1, P2Y1, P2Y12, guanylate cyclase, and IP-receptor (2) NSAID-aspirin interactions, (3) recombinant FVIIa, (4) antibodies and antagonists against contact pathway factors FXIIa, FXIa, and platelet polyphosphate, (4) thrombolytic agents, and (5) plasmin inhibitors. Additionally, small volume patient-specific samples from cardiovascular patients, trauma patients, neonates, and hemophiliacs have been evaluated by microfluidics. For example, we have detected a remarkable platelet dysfunction under flow in trauma patients. In a model of bleeding, a side-view device allows clotting on a porous collagen/TF plug at constant pressure differential across the developing hemostatic clot. The core-shell architecture of clots made in injured mouse vessels is fully replicated in this device using human blood.

The *in microfluidico* research methodology has become particularly critical to blood research and to Blood Systems Biology research. Significant progress has been made in linking platelet and coagulation cascade models to multiscale simulations of thrombosis under flow, as measured in microfluidic devices. Combining micropatterning with microfluidics has provided a means to measure platelet function and coagulation under flow in a combinatorial manner that approaches that of well-plate formats. Most recently, the use of endothelial cells cultured within microfluidic devices followed by exposure to flowing whole blood are revealing new rheological- and transport-dependent mechanisms which may be highly relevant to the blood-brain interface.

Microparticles Impact Coagulation after Traumatic Brain Injury

Michael Goodman, MD

University of Cincinnati

Background The pathophysiology that drives the subacute hypercoagulable state commonly seen after traumatic brain injury (TBI) is not well understood. Alterations caused by TBI in platelet and microparticle (MP) numbers and function have been suggested as possible causes; however, the contributions of platelets and MPs are currently unknown.

Methods A weight-drop technique of TBI using a murine model of moderate head injury was used. Blood was collected at intervals after injury. MP enumeration and characterization were performed using Nanoparticle Tracking Analysis, and platelet counts and coagulation parameters were determined using thromboelastometry. A MP procoagulant assay was used to compare activity between injured and sham mice.

Results At 24 h after injury, there were no changes in circulating platelet numbers. However, there was a decrease in platelet contribution to clot formation. In contrast, there was a decline in circulating total MP numbers. When MPs from sham mice were added to the blood from head-injured animals, there was a normalization of platelet contribution to clot formation. Conversely, when MPs from TBI mice were added to sham blood, there was a significant decrease in platelet contribution to clot formation. Notably, there was an increase in MP procoagulant activity in head-injured mice.

Conclusions MPs generated after TBI likely contribute to altered coagulation after head injury and may play a key role in the development of a posttraumatic hypercoagulable state in TBI patients.

Fibrinogen in Neurological Diseases: mechanisms, imaging, therapeutics

Katerina Akassoglou, PhD

Gladstone Institute of Neurological Disease, Department of Neurology at the University of California, San Francisco, CA

Protection of the CNS from leakage of plasma proteins by the blood-brain barrier (BBB) is lifted in a wide range of neuroimmune and neurodegenerative diseases, as well as after traumatic injury. However, whether blood proteins contribute to neuroinflammation and neuronal damage remains poorly understood. Our laboratory has discovered unanticipated functions for the blood coagulation factor fibrinogen in the activation of CNS innate immunity, induction of astrocyte scar formation, and inhibition of remyelination. Such diverse functions have mechanistic underpinnings on the unique structure of fibrinogen, which contains multiple binding sites for cellular receptors and proteins expressed in the nervous system[1]. Fibrinogen is abundantly deposited in the brain in human neurological diseases, including multiple sclerosis (MS) and Alzheimers disease[1]. We showed that fibrinogen is a potent pro-inflammatory mediator in the nervous system by activating the CD11b/CD18 integrin receptor (also known as Mac-1 and complement receptor 3) in microglial cells[2]. Fibrinogen stimulates a unique transcriptional signature in microglia inducing chemokine release and the recruitment of peripheral immune cells into the CNS[3]. Using in vivo two-photon imaging, we showed in Experimental Autoimmune Encephalomyelitis (EAE), an animal model of MS that microglia perform constant surveillance of blood vessel walls and specifically cluster around blood vessels with fibrin deposition[4]. Genetic disruption of the fibrinogen/CD11b interaction suppresses microglial cluster formation, neurologic symptoms, inflammation, demyelination, and axonal damage in EAE[2,4]. Furthermore, by developing a molecular probe to detect thrombin activation in the CNS, we demonstrated that activation of the coagulation cascade preceded onset of neurological signs, increased at disease peak, and correlated with fibrin deposition, microglial activation, demyelination, axonal damage, and clinical severity in EAE[5]. These studies identified the blood coagulation factor fibrinogen as a novel molecular link between BBB disruption, activation of CNS innate immunity, and neurodegeneration. Our drug discovery approach based on a novel fibrin-directed immunotherapy that selectively targets the proinflammatory functions of fibrin without affecting its beneficial effects in hemostasis will be discussed.

1. Davalos & Akassoglou, **Semin Immunopathol**. 2012. 34:43-62
2. Adams et al., **J Exp Med**. 2007. 204:571-82
3. Ryu et al., **Nat Commun** 2015, 6:8164.
4. Davalos et al., **Nat Commun**. 2012; 3:1227
5. Davalos et al., **Ann Neurol** 2014, 75:303-308

Exosomes in Glioma: their potential as biomarkers of prognosis and as carriers of information between the tumor and immune cells

Theresa Whiteside, PhD

University of Pittsburgh

Exosomes in plasma of glioma patients hold promise as biomarkers of prognosis. In this study, an attempt was made to determine whether changes in total exosomal protein and in expression levels of mRNA in exosomes could serve as surrogate markers of immunological and clinical responses in glioma patients receiving anti-tumor vaccines. Exosomes were isolated from pre/post-vaccine plasma specimens in 20/22 patients enrolled in a phase I/II trial with the anti-tumor vaccine. Protein content of exosomal fractions isolated from patients' plasma was analyzed, and mRNA expression levels for 24 immunoregulatory genes were studied by multiplex qRT-PCR. Pre- to post-vaccination changes in exosomal protein and ΔCt values were correlated with immunological and clinical responses and survival using Spearman rank statistics and hazard ratios. Exosomal protein levels positively correlated ($p<0.0043$) with the WHO tumor grade at diagnosis. Protein levels were lower in post- vs. pre-vaccination exosome fractions. Post-therapy increases in tumor size were associated with elevations in exosome proteins in glioblastoma but not always in anaplastic astrocytoma (AA). Only exosomal ΔCt values for IL-8, TIMP-1, TGF-β and ZAP70 were significant ($p<0.04$ to $p<0.001$). The ΔCt for IL-8 and TGF-β mRNA positively correlated with post-vaccine immunologic responses to glioma antigens, while ΔCt for TIMP-1 mRNA was negatively correlated to ΔCt for IL-8 and TGF-β. Only ΔCt for IL-8 weakly correlated with OS and TTP. In post-vaccine exosomes of the longest surviving patient with AA, mRNA for PD-1 was persistently elevated. In this study we showed that protein and mRNA expression levels for immune-related genes in plasma exosomes were useful in evaluating glioma patients' response to vaccination therapy.

Monitoring the Central Nervous System through Extracellular RNA in Peripheral Biofluids

Kendall Van Keuren-Jensen, PhD

TGen Center for Noninvasive Diagnostics

The discovery and reliable detection of markers for central nervous system (CNS) disorders and injuries is complicated by the inaccessibility of the diseased tissue. The inability to easily or directly test the brain and spinal cord has hindered the collection of informative samples and reduced our ability to monitor changes in the CNS. Frequent, longitudinal assessment of disease progression and therapeutic efficacy would provide invaluable feedback to clinicians and researchers regarding molecular changes underlying injury, disease, and response to therapy. Investigators have, and continue to, examine protein and metabolomic changes in circulating biofluids, searching for molecular information that will improve diagnostic accuracy and CNS monitoring. Molecular information found in biofluids provides a less invasive opportunity for more frequent sampling and monitoring of the CNS. Recently, there has been a focus on RNAs that have the potential to get from the CNS to the periphery where they can be detected. Extracellular vesicles and protein complexes, such as Argonaute and HDL, have been found to carry RNA from cells in the CNS into peripheral circulation. There is currently no way to determine where the RNA in a biofluid sample originates. RNA isolated from a plasma sample is a mixture of RNAs from liver, kidney, heart - presumably all tissues in the body. Each tissue may have a different contribution to the plasma sample; more active tissues, larger tissues, or more vascular tissues might contribute more extracellular material - this is currently unknown. It is also not known how information from the CNS gets into peripheral circulation across the blood-brain interface, by an active or passive process? How do disease and injury change the rate and number of extracellular RNAs that get into circulation? We wanted to assess the number and types of extracellular RNA from the CNS that could be detected in biofluids; cerebrospinal fluid, plasma, saliva, and urine. We sequenced the extracellular RNA in 100s of biofluid samples. We used several analytical tools to look at the representation of tissue-enriched transcripts in different biofluids. We found that CNS-specific transcripts were detectable in every biofluid, cerebrospinal fluid contained the largest amount of brain-enriched transcripts. We will continue to improve the way we collect, enrich, and sequence biofluid samples to advance the detection of CNS-derived RNAs in biofluids. Our ability to understand how the blood-brain interface contributes to the variability in detecting and accurately measuring CNS biomarkers in the periphery, would be a significant advance to the field.

Studying the Blood-Brain Barrier: perspectives from understanding the biokinetics of biomarkers of brain injury

Alex Valadka[1], Ronald Hayes[1,2], Olena Glushakova[1,2]

[1]Virginia Commonwealth University, Richmond, Virginia
[2]Banyan Biomarkers, San Diego, California

BARRIERS:

1) Failure of investigators to discriminate between movement of analytes from blood to brain (blood-brain barrier) and from brain to blood (brain-blood barrier).

2) Assumption that BBB opening is evidence of a pathological event rather than appreciating that the BBB can be dynamically regulated in response to a number of frequently occurring environmental events such as exercise and stress.

3) A large literature on BBB alterations employing uncritical use of non-physiological agents such as HRP or Evans blue that assume these changes accurately reflect changes in physiological analytes.

4) Failure to appreciate the complexity of BBB (e.g., recent characterization of the potential role of the brain glymphatic system).

5) There is no single "Gold Standard" for BBB opening. Investigators have generally failed to recognize that the BBB characteristics of each analyte will probably have to be described individually in specific clinical contexts (e.g., TBI vs. exercise).

6) The frequent invocation of the BBB as a mechanism underlying the biokinetic properties of analytes without providing any evidence.

7) The absence of funding initiatives effectively identifying and supporting studies to advance understanding of BBB function.

8) The absence of recurring venues and sustained special interest groups to facilitate collaborations and exchanges of information between basic science and clinical investigators studying the BBB.

CHALLENGES/RESPONSES TO BARRIERS:

(1) The development of broadly accepted experimental paradigms that can systematically compare and (ideally) quantify changes in Blood-Brain Barrier and Brain-Blood Barrier functions in rigorously defined contexts (disease vs. environmental) using physiologically relevant analytes.

These paradigms should:

a) Include integration of *in vitro, in vivo* and human studies.

b) Emphasize the use and development of non-invasive technologies to facilitate preclinical-clinical comparisons.

c) Distinguish between research goals that address mechanistic questions vs. studies seeking to change clinical practice.

(2) The establishment of a DoD (potentially inter-agency?) "Blood-Brain Interface Special Interest Group" tasked with systematic responses to the barriers identified by this conference and associated with a jointly authored peer-reviewed publication.

Post-traumatic Cerebral Blood Flow, Autoregulation, and the Neurovascular Unit

Donald Marion, MD

Defense and Veterans Brain Injury Center

Cerebral blood flow (CBF), and particularly blood flow in brain regions adjacent to contusions or underlying post-traumatic hematomas, is variable and likely effected by the inflammatory response as well as neurotransmitters. Immediately following a severe traumatic brain injury (TBI) there is a significant decrease in CBF immediately after the trauma, and local disruption of pressure and chemical CBF autoregulation. The impact of post-traumatic inflammation and excessive release of neurotransmitters on vascular smooth muscle may be enhanced by disruption of the BBB, though this is not necessarily the case. Murine studies of blast injury, a common mechanism in the Military, have found alterations of the vascular extracellular matrix, sustained microglial and astroglial reaction, and sustained inflammatory responses. Ischemia is common in the penumbra of tissue surrounding contusions, and, in murine studies, reductions in rCBF during hypoxia closely relate to areas with compromised BBB. Two separate clinical xenon/CT CBF trials have described that actual CBF changes that occur in patients with severe TBI during the first few days after their injury. Additional xenon/CT CBF studies show the significant variability in chemical autoregulation. In summary, post-traumatic CBF and autoregulatory changes are complex and likely related to hypoxia/ischemia early after the injury, disruption of the BBB due to mechanical and physiologic injury, and the cellular and molecular inflammatory response.

Employing Transporters at Blood-Brain Interfaces to Regulate the Brain's Metabolomic and Pharmacologic Microenvironment

Robert Clark, MD

University of Pittsburgh

An underappreciated barrier to effective drug delivery are membrane transporters at blood-brain interfaces. These include solute carriers (SLC) and ATP-binding cassette (ABC) transporters at the blood-brain and brain-CSF barriers (BBB and BCSFB). Transporter substrates include endogenous molecules as well as drugs (xenobiotics). Strategies to capitalize on these xenobiotic transporters at blood-brain interfaces to optimize brain bioavailability of potentially neuroprotective compounds include targeted use of transporter inhibitors. Several promising FDA-approved substrates and inhibitors repurposed for use in combination are readily available, and may be efficacious for a number of neurological diseases including traumatic brain injury (TBI). The roadmap for clinical development of a prototype combinational strategy, N-acetylcysteine (substrate) and probenecid (inhibitor), for treatment of severe TBI in children will be discussed in detail.

In Vivo Tracking of Dendritic Cell Exosomes Delivered to Brain

Richard P. Kraig, MD, PhD

The University of Chicago

We have shown that interferon gamma-stimulated dendritic cells (SDCs) release exosomes (SDC-Exos) containing specific miRNAs which promote myelination and reduce oxidative stress. The SDC-Exos administered to brain slice cultures preferentially enter oligodendrocytes, and to a lesser extent microglia. These effects emulate those seen after exposure to exosomes derived from the serum of animals that experienced environmental enrichment (i.e., increased physical, intellectual and social activity). SDC-Exo not only increase myelin levels days after nasal administration to naïve animals but also increase remyelination *in vivo* after lysolecithin-induced exposure, a chemical model of multiple sclerosis.

Other work from our laboratory showed that spreading depression, the likely underlying cause of migraine with aura, and a well-established model of migraine in experimental animals, triggers transient oxidative stress and demyelination. SDC-Exos reduce oxidative stress after nasal administration and also increase the threshold for spreading depression, consistent with that seen after environmental enrichment. These three animal models demonstrate that SDC-Exos can effectively improve brain function after nasal administration. However, little is known about the route, time course, and destination of nasally delivered SD-Exos. Here, we report our initial results involving tracking of SDC-Exos to brain after nasal administration.

We used mCLING (membrane-binding fluorophore-cysteine-lysine-palmitoyl group) to label exosomes. mCLING labels plasma membranes and is taken up by endocytosis. Thus, it is ideally suited for organelle tracking. Importantly, the dye remains labelled to membranes after fixation. mCLING also “flickers” with application of ground state depletion microscopy, which makes the dye well-suited for super resolution microscopy that provides 20 nm resolution. The use of this dye will allow subcellular tracking of exosome uptake (and perhaps release).

We first used mCLING to label SDC-Exos that were then transfected with a fluorescently labeled inhibitor for miR-219. While the details of this procedure are not completely worked out, we feel this double-labeling strategy, when coupled to super resolution microscopy, will prove to be an efficient and accurate means to determine relative exosome transfection efficiency. The labeled exosomes can also be sized and counted via this staining/imaging approach. We next labelled SDC-Exos with mCLING and tracked their entry into brain after nasal administration compared to normal controls. Our results using wide field, confocal and super resolution microscopy showed that the exosomes easily enter brain and are widely distributed. They appear to follow CSF flow pathways. Further work will confirm this and begin to show their subcellular movement within brain cells. Measurements after intravenous delivery of mCLING SDC-Exos are ongoing.

Our results provide functional and now anatomical evidence that SDC-Exos enter brain and show wide spread impact and distribution. Collectively, these results support the use of SD-Exos as a novel cell-based therapeutic to mitigate the impact of neurodegenerative disorders.

High Content Proteomics/Lipidomics Analysis: on a path toward understanding the mechanisms of exosome-mediated cellular uptake and blood-brain barrier crossing

Anastasia Khvorova, PhD

RNA Therapeutics Institute, University of Massachusetts Medical School, Worcester, MA

Extracellular vesicles (EVs) have received much interest for clinical use as vehicles for oligonucleotide therapeutic (ONT) delivery as well as endogenous carriers of disease biomarkers for diagnostic purposes. Currently, efficient and non-toxic ONT delivery to the central nervous system represents a significant barrier to their use in the treatment of neurological disorders, such as Huntington's disease. Exosomes have the potential to act as "native" ONT delivery vehicles, but robust and scalable methods for loading therapeutic RNA cargo into exosomes are lacking. We show that hydrophobically modified siRNAs (hsiRNAs) efficiently load into exosomes upon co-incubation, without altering vesicle size, distribution, or integrity, and promote efficient neuronal internalization and *Huntingtin* mRNA silencing both *in vitro* and *in vivo*.

Exosomes are highly efficient in the functional intracellular transfer of small endogenous RNAs and have the potential to cross the blood-brain barrier. The RNA content of exosomes is under thorough investigation as a fingerprint for disease diagnosis. There is limited information available on the protein and lipid composition of EV membranes, despite the importance of this information for understanding EV biogenesis, biomarker trafficking, and blood-brain barrier crossing. We will present recent data from a high resolution proteomics and lipidomics analysis of exosomes from different cell sources and discuss their functional contributing components.

Exosomes-like Nanoparticles Delivering Therapeutic Agents through an Intranasal Route Inhibit Brain Tumor Progression

Huang-Ge Zhang, PhD

University of Louisville

A large number of drugs with therapeutic potential for treatment of brain related diseases are never pursued due to their inability to be delivered across the BBB in therapeutic concentrations. Although intranasal delivery provides a practical, noninvasive method for delivering therapeutic agents to the brain, the quantities of drug administered nasally that have been shown to be transported directly from nose-to-brain are very low. Although our results previously published suggest that intranasal delivery of an anti-inflammatory agent such as curcumin, and the anti-Stat3 agent, JSI-124, provides a promising noninvasive approach for the treatment of brain inflammatory related diseases such as malignant gliomas, biosafety considerations and large scale production of mammalian cell-derived exosomes has been challenging. To meet this challenge, we recently developed fruit-based nanovectors made of lipids extracted from edible plant exosomes. Exosome-like nanoparticles from grapefruit naturally encapsulate small RNAs, and proteins. We have shown that grapefruit derived nanovectors (GNVs) are highly efficient for delivering a variety of therapeutic agents including drugs, DNA expression. In this study, we demonstrate the capability of a grapefruit-derived nano vector (GNVs) to carry miR17 for therapeutic treatment of mouse brain tumor. We show that GNVs coated with folic acid (FA-GNVs) are enhanced for targeting the GNVs to a folate receptor positive GL26 brain tumor. Additionally, FA-GNVs coated polyethylenimine (FA-pGNVs) not only enhance the capacity to carry RNA, but the toxicity of the polyethylenimine is eliminated by the GNVs. Intranasal administration of miR17 carried by FA-pGNVs led to rapid delivery of miR17 to the brain that was selectively taken up by GL-26 tumor cells. Mice treated intranasally with FA-pGNV/miR17 had delayed brain tumor growth. Our results demonstrate that this strategy may provide a noninvasive therapeutic approach for treating brain related disease through intranasal delivery.

Plasma Exosomes Enriched for Neuronal Origin: a source of biomarkers for neurodegenerative and neuroinflammatory diseases

Dimitrios Kapogiannis, MD

National Institute of Aging/NIH

All cells shed several types of membranous vesicles to the extracellular space, as part of their normal function. Exosomes are extracellular vesicles (EVs) with a 30-150 nm range of diameters that originate from the endosomal/multivesicular body/lysosomal system, express various surface markers and contain RNA and peptides reflecting their cell of origin. EVs circulate in all body fluids, including blood and CSF. Brain EVs cross the blood-brain barrier via a variety of mechanisms. We developed a methodology for enriching peripheral blood EVs for neuronal origin based on immunoprecipitation with antibodies against neuronal cell adhesion molecules, NCAM and L1CAM. To date, we have performed a series of case-control studies to examine whether a priori hypothesized proteins differ in L1CAM+ enriched exosomes in patients with Alzheimer's disease (AD), Frontotemporal Dementia (FTD), Parkinson disease (PD), Multiple Sclerosis (MS), and Traumatic Brain Injury (TBI) vs. controls. Regarding AD, we found that patients have much higher p-T181-tau, p-S396-tau, and Ab42 (pathogenic proteins implicated in the tangle and plaque pathology of AD). In addition, we found that L1CAM+ EVs from AD patients contain higher levels of Ser-phosphorylated insulin receptor substrate-1 (IRS-1), a tissue biomarker of (brain) insulin resistance, and consistent alterations in downstream signaling molecules; altered levels of endosomal-lysosomal proteins, which may relate to abnormal clearance of misfiled proteins; decreased levels of intracellular factors that promote cell resistance to stressors; and decreased levels of synaptic proteins. Certain differences appear large enough to discriminate between patients and controls. Ongoing large-scale replication studies are based on samples from longitudinal studies, such as the Baltimore Longitudinal Study on Aging. A profile of exosomal peptides may serve as a blood test for AD (and other neurological diseases). Moreover, some of the alterations were already present up to 10 years prior to AD diagnosis raising the possibility of preclinical diagnosis for enrollment in secondary prevention clinical trials. A final possibility is that these peptides may respond to experimental treatments and be used as theramarkers in clinical trials. EV-based biomarkers have the potential of revolutionizing AD clinical practice and research.

HER2-targeted extracellular vesicles delivery of therapeutic mRNA for enzyme prodrug therapy

AC Matin, PhD

Stanford University

Wang JH[1], Harada M[1], Delcayre A[2], Antes TJ[3], Gupta A[3], Kanada M[4], Jeffrey S[5], Pegram M[6], Wilson C[7], Grant G[7], Contag C[1,4], Matin AC[1]

[1]Microbiology & Immunology, Stanford School of Medicine, [2]ExoThera LLC, [3]System Biosciences Inc., [4]Pediatrics, Stanford School of Medicine, [5]Surgery, Stanford School of Medicine, [6]Med/Oncology, [7]Neurosurgery

Background: HER2 is overexpressed in aggressive breast cancers. We are using extracellular vesicles (EVs) the 'body's antigen delivery system', for targeting our novel prodrug (CNOB/ChrR6) regimen specifically to HER2 positive cancer; the cytotoxic product of this regimen, MCHB, can be visualized noninvasively in living mice. EVs are thought to possess the capacity to deliver genetic material effectively. Although our preferred approach is to deliver targeted EV-mediated therapeutic mRNA, which would bypass problems of using DNA for this purpose (e.g., ineffective transcription), we have also used DNA for gene delivery (Kanada, Ronald, Kim, Paulmurugan, Ge, Bachmann, Hardy, Gambhir, Matin, Contag; abstract submitted). Whether EVs can cross the blood-brain barrier (BBB) was also investigated. The EV-based therapy holds the promise of personalized medicine using patient's own dendritic cell (DC) EVs; these have the further advantage of harboring functional MHC-peptide complexes and various immunity-stimulating factors.

Aims: To use HER2-targeting EVs for specific and effective delivery of prodrug therapy to HER2 cancer.

Methodology: Using exosome-display technology employing p6mLSC1C2 plasmid, we have described before, we constructed a chimeric protein, anti-HER2 (ML39) scFv conjugated to the lactadherin C1C2 domain. After 4-day incubation of transiently transfected HEK293 cells, EVs were harvested (conditioned medium; ultra-centrifugation), and pure chimeric protein was isolated using His-tag columns. Naïve HEK293 or DC EVs were reconstituted with the chimeric protein. ELISA quantified the specificity of the resulting HER2 targeting-EVs. For cell binding assays, CFSE-labeled targeted EVs were incubated with BT474 (strongly HER2+ve) or MCF7 cells (little HER2 expression), and visualized by fluorescence microscopy. To determine mRNA transfer capability, the directed EVs were loaded with ChrR6 mRNA by Xport-based technology, and incubated with BT474 cells followed by CNOB treatment. MCHB production was quantified by fluorescence at 584/612nm. DNA was introduced into the EVs using minicircle (MC) transfected cells. A cranial window model was used to visualize the mouse brain vasculature.

Results: Transfected HEK293 cells produced EVs expressing the anti-HER2 scFv/C1C2 chimeric protein. DCs lack lactadherin and generate naïve EVs. These were incubated with the chimeric protein. The resulting directed DC EVs showed 10 times greater targeting capacity than EVs from the transfected HEK293 cells (ELISA). They also displayed greater targeting activity to BT474 than to MCF7 cells (fluorescence microscopy). Directed, loaded EVs specifically conferred transcription-independent (actinomycin D-resistant, cyclohexamide sensitive) capacity on BT474 cells to activate CNOB (generation of MCHB fluorescence), showing successful delivery of translationally-competent ChrR6 mRNA. Use of EVs from MC-transfected 4T1 cells showed improved EV-mediated DNA delivery and expression. EVs had a short circulation time but were visible in the vasculature *in vivo* but did not cross the normal BBB; they did appear to attach to the tumor vasculature.

Conclusions: We have successfully engineered EVs capable of high level HER2 binding with capacity for functional delivery of therapeutic nucleic acids including mRNA. The directed loaded EVs are being tested in mice with implanted orthotopic BT474 tumors as well as in xenograft models with patient-derived HER2+ve cancer cells in mice.

From Blood–Brain Barrier to Blood–Brain Interface: new opportunities for CNS drug delivery

William A Banks, MD, FACE

Research & Development, Veterans Affairs Puget Sound Health Care System; Division of Gerontology and Geriatric Medicine, Department of Medicine, University of Washington, Seattle WA USA

The blood-brain barrier (BBB) acts as a complex interface, regulating the exchange of nutrients, informational molecules, and other substances between the CNS and blood. The significant barrier properties of the BBB occur primarily at the level of the brain endothelial cell (BEC) and include the physical aspects of the cellular barrier often reinforced by enzymatic activity and brain-to-blood transport systems. The BBB is permeable to selected substances, transporting them in the blood-to-brain or brain-to-blood directions. Our lab has shown that these substances include informational molecules, such as gastrointestinal peptides and regulatory proteins, cytokines, and chemokines as well as oligophosphorothiolate molecules and exosomes. Thus, the BBB is pivotal to the formation of the gut-brain axis, neuroimmune axes, and other communication pathways between the CNS and peripheral tissues. The BEC communicates with pericytes, astrocytes, and other cells forming the neurovascular unit by secreting and responding to substances such as nitric oxide, chemokines, cytokines, and prostaglandins. This communication induces the barrier function at the BEC and dictates other BBB characteristics such as the type and robustness of transport and enzymatic activities. Thus the BBB is able to adapt to changing physiologic needs during development, fasting, or sleep. Similarly the BBB also adapts to disease conditions, but can also be a target of disease and has been postulated to play a primary role in the development or progression of several conditions, including multiple sclerosis, Alzheimer's disease, traumatic brain injury, and obesity. The complexity of the BBB and the neurovascular unit makes a single, universal approach to CNS drug development problematic, but also provides a wealth of special opportunities and approaches that can be targeted to specific disease situations. For example, a BBB transporter that recognizes phosphorothiolate oligonucleotides can be used to deliver antisense molecules that are effective in reversing the oxidative stress, BBB dysfunctions, and memory impairments in mouse models of Alzheimer's disease or to increase the CNS delivery of a therapeutic by selectively inhibiting the therapeutic's brain-to-blood transporter; alpha-adrenergics can induce mannose 6-phosphate receptor-dependent transport of lysosomal enzymes across the BBB; pegylated blockers of the BBB transport of leptin can induce feeding, possibly treating anorexia; exosomes can be used to deliver neurotrophins or other therapeutic agents across the BBB as treatments for neurodegenerative diseases. Finally, circulating levels of alpha-synuclein packaged in exosomes presumably derived from the CNS have been proposed as a biomarker in Parkinson's disease. Thus, the multiple roles that the BBB plays as a CNS/peripheral tissue interface are important in the normal physiological functioning of the brain and peripheral tissues, the treatment and diagnosis of disease states, and the development of CNS drugs.

Assessing the Feasibility of an in vitro Neurovascular Unit

Peter Searson, PhD

Johns Hopkins School of Medicine

The blood-brain barrier, or neurovascular unit, comprises 600 km of capillaries formed by highly specialized endothelial cells, and supported by pericytes that modulate contractility, and astrocytes that regulate capillary dilation. Together, these cells regulate the supply of nutrients and other essential molecules to the brain while maintaining tight control of the microenvironment in which neurons and other brain cells function. Advances in stem cell biology and tissue engineering, coupled with the limitations of animal models, have led to rapid advances in the development of *in vitro* models. These span microfluidic variations of the transwell assay for high throughput drug screening to perfusable microvessels in an extracellular matrix. We are using a reverse engineering approach to develop an *in vitro* model of the human blood-brain barrier that includes a perfusable microvessel embedded in extracellular matrix and captures the important physical and biological characteristics in a physiologically relevant geometry. Reverse engineering is particularly well suited for the blood-brain barrier, which is inherently complex and involves multiple cell types. In particular it allows us to elucidate the underlying physical and biochemical processes that regulate the blood-brain barrier phenotype of brain capillaries and microvessels, while simultaneously allowing us to systematically increase the complexity of the model. Here we discuss the use of stem cell technology as a source of human brain microvascular endothelial cells and pericytes, and the incorporation of human astrocytes into 3D models of the blood-brain barrier. We also discuss the current progress and challenges in developing an *in vitro* model of the neurovascular unit.

NeuroVascular Unit (NVU) on a Chip: new direction in blood-brain barrier modeling and perfusion

Jacquelyn A. Brown[1,2], Mingjian Shi[3], Simona G. Codreanu[4,5], Stacy D. Sherrod[2,4,5,6], Dmitry A. Markov[1,2], M. Diana Neely[7,8,9,10], Clayton M. Britt[2,11], Ronald S. Reiserer[2,11], Monika G. Everheart[2], Philip C. Samson[2,11], Lisa J. McCawley[1,2,12], Donna J. Webb[2,3], Aaron B. Bowman[7,8,9,10,13], John A. McLean[2,4,5,6], John P. Wikswo[1,2,11,14]

[1]Department of Biomedical Engineering, Vanderbilt University, Nashville, TN 37235, USA; [2]Vanderbilt Institute for Integrative Biosystems Research and Education, Vanderbilt University, Nashville, TN 37235, USA;[3]Department of Biological Sciences, Vanderbilt University, Nashville, TN 37235, USA; [4]Department of Chemistry, Vanderbilt University, Nashville, TN 37235, USA; [5]Center for Innovative Technology, Vanderbilt University, Nashville, TN 37235, USA; [6]Vanderbilt Institute of Chemical Biology, Vanderbilt University Medical Center, Nashville, TN 37232, USA; [7]Departments of Neurology and Pediatrics, Vanderbilt University Medical Center, Nashville, TN 37232, USA; [8]Vanderbilt Kennedy Center, Vanderbilt University, Nashville, TN 37203, USA; [9]Vanderbilt Brain Institute, Vanderbilt University Medical Center, Nashville, TN 37232, USA; [10]Vanderbilt Center in Molecular Toxicology, Vanderbilt University Medical Center, Nashville, TN 37232, USA;[11]Department of Physics and Astronomy, Vanderbilt University, Nashville, TN 37235, USA; [12]Department of Cancer Biology, Vanderbilt University Medical Center, Nashville, TN 37232, USA; [13]Department of Biochemistry, Vanderbilt University Medical Center, Nashville, TN 37232, USA; [14]Department of Molecular Physiology and Biophysics, Vanderbilt University Medical Center, Nashville, TN 37232, USA

The blood-brain barrier (BBB) is a highly dynamic structure that provides both protection and support for the central nervous system and insulates it from the rest of the body, including the immune system and other organ systems. The BBB must facilitate the entry of required nutrients into the brain while simultaneously excluding potentially harmful compounds. This unique vascular structure is also responsible for providing or preventing access to the brain for drug treatment options. Given its critical role in brain function, drug access, and cancer metastasis, tractable and faithful *in vitro* models are needed for investigating how the BBB responds to and recovers from various assaults, as well as for evaluating drug and toxin penetration across the barrier. To make inroads on achieving this goal, we have developed a model of the BBB containing multiple cell types, with 3D organization of those cells in relation to one another, and differential serum exposure. Our microfluidic device, which we call the NeuroVascular Unit (NVU), is comprised of both a vascular chamber and a brain chamber separated by a porous membrane. This design allows cell-to-cell communication between endothelial cells, astrocytes, and pericytes and independent perfusion of both compartments separated by the membrane. This dual-chamber device also provides the high shear forces created by flow for mature tight junction formation in the vascular chamber, while keeping shear stress low in the brain chamber. The NVU represents approximately one millionth of the human brain, and hence has sufficient cell mass to support a breadth of analytical measurements, including ELISA, IM-MS, and QPCR to list a few. Integrity of the NVU's BBB can be assessed by using either FITC-dextran diffusion or transendothelial electrical resistance or both to look at barrier function. The Vanderbilt NVU allows for both real-time and endpoint analysis of BBB function as it responds over time, as well as providing a window into the neuronal consequence of BBB alterations.

Modeling and Targeting the Blood-Brain Barrier in Health and Disease

Eric Shusta, PhD

University of Wisconsin

Millions of people worldwide are afflicted with neurological diseases such as Parkinson's disease, Alzheimer's disease, brain cancer, and cerebral AIDS. Although many new drugs are being developed to combat these and other brain diseases, few new treatments have made it to the clinic. The impermeable nature of the brain vasculature, also known as the blood-brain barrier (BBB), is at least partially responsible for the paucity of new brain therapeutics. As examples, approximately 98% of small molecule pharmaceuticals do not enter the brain after intravenous administration, and the BBB prevents nearly all protein and gene medicines from entering the brain. Our research group is therefore focused on developing tools for the analysis of the brain drug delivery process and identifying novel strategies for circumventing this transport barrier. This presentation will detail our recent work regarding the development of human pluripotent cell-based in vitro experimental models that accurately mimic the BBB characteristics observed in vivo. Such models are amenable to drug permeability screening and human disease modeling. In addition, I will discuss our efforts to overcome BBB restrictions on brain drug delivery. To this end, we are mining large antibody libraries to identify antibodies that can target and act as artificial substrates for endogenous receptor-mediated BBB nutrient transport systems. After conjugation to drug payloads that can include small molecules, proteins, or DNA therapeutics, these antibodies could have the potential to deliver medicines across the BBB noninvasively.

Developing Tridimensional Models of the Human Cerebral Cortex in vitro

Sergiu Pasca, MD

Stanford University

In this talk I will describe our work on developing methods for generating functional forebrain cultures starting from human induced pluripotent stem cells. Specifically, I will describe our work on developing neural spherical structures resembling the human cerebral cortex, which we call human cortical spheroids. These floating spheroids grow up to 5 mm in diameter, and include deep and superficial layer pyramidal neurons of the cortex, as well as astrocytes. After developing in culture for ~10 weeks, cortical spheroids display transcriptional characteristics of late mid-fetal human cortex. Neurons display spontaneous electrical activity and form functional synapses, and the emerging neural network activity can be probed in preparations similar to slice recordings of the animal brain. Neural spheroids cultures allow a detailed interrogation of human cortical development, function and disease, and represent a versatile platform for generating other neuronal and glial subtypes *in vitro*.

Revealing the Transport Mechanisms, Kinetics, and Energetics of Drugs Diffusing through Membranes of the Blood-Brain Barrier

Yukun Wang[1], Peter C. Searson[1,2], & Martin B. Ulmschneider[1,2,*]

[1]Department of Engineering and Materials Science, Johns Hopkins University, Baltimore, MD 21218, USA
[2]Institute of NanoBioTechnology, Johns Hopkins University, Baltimore, MD 21218, USA
**Correspondence to: martin@ulmschneider.com*

Abstract:

Molecular transport into the brain is limited and controlled by the blood-brain barrier (BBB). This barrier is maintained by a combination of tight junctions between endothelial cells, which suppress paracellular transport from the vasculature into the brain extracellular fluid, and efflux pumps located in the basolateral membrane that regulate transcellular transport. This architecture restricts transport from the vasculature into the brain to molecules that efficiently diffuse through both the basolateral and apical plasma membranes of human brain endothelial cells, and are not substrates for efflux pumps, which transport molecules from the cytoplasm back into the vasculature.

To study transcellular transport through the BBB we have developed computational models of both the basolateral and apical endothelial cell membranes from experimentally known lipid compositions. These models are used to simulate spontaneous transmembrane diffusion of molecules using unbiased long timescale atomic detail molecular dynamics (MD) techniques. The key advantage of this approach compared to other simulation techniques is that it does not only provide the free energy barrier profile for molecular diffusion across both membrane types, but that it also reveals the molecular transport mechanisms, and allows direct determination of the transport kinetics, which in turn can be validated experimentally.

Overcoming Blood-Brain Barrier for Precise Diagnosis, Targeting and Treatment of Primary and Metastatic Brain Tumors

Julia Ljubimova, Eggehard Holler, Keith Black

Cedars-Sinai Medical Center

Clinical problems in glioma treatment: Little progress in pharmacological brain cancer treatment is due to the inability of many drugs to cross the blood-brain barrier (BBB) mostly formed by brain vascular endothelium. The BBB was discovered by Edwin E. Goldman more than 100 years ago. It protects the brain from environmental "noise", but, when the pharmacological treatment is needed, the same barrier prevents the brain influx of most drugs useful for the brain cancer treatment. For over a century, scientific effort to circumvent the BBB still has not answered many questions about the drug delivery through the most powerful biological barrier in the body.

Nanomedicine advances in overcoming the blood-brain barrier: An obstacle in brain tumor treatment is a limited ability for delivery of a number of therapeutic and immunoregulatory molecules. For instance, therapeutic monoclonal antibodies, such as trastuzumab for breast and ovarian cancer, cetuximab for lung and breast cancer, and rituximab for lymphoma are effective for primary tumor treatment but cannot penetrate the BBB to reach brain tumors, and fail to treat brain metastases. Nanotechnology can master these problems by developing nanomedicines able to cross the BBB and deliver drugs and immunostimulatory agents directly to the brain tumors and to the immune cells in its microenvironment.

Using systemically administered novel nanobiopolymers based on polymalic acid platform (Polycefin^{TM} family of nano agents), we have delivered through the BBB nano drugs and imaging agents, which dramatically reduced glioblastoma size and normalized brain cancer vasculature (Ding et al. *PNAS,* 2010). Inhibition of tumor specific proteins decreased the tumor size by 90%. Such nano drug treatments also significantly protected the brain from edema development.

We have also engineered Polycefin nano drug variants to treat human EGFR-positive lung, triple negative breast cancer, and HER-2/*neu* positive breast tumors in nude mice. The same nano drugs were used to precisely diagnose and then treat brain metastases from lung, triple negative and HER2/*neu* positive breast cancer (Inoue et al. *Cancer Res,* 2011; Patil et al. *ACS Nano,* 2015). Further, we have successfully treated primary HER2/*neu* positive breast cancer with a combination nanodrug that blocked HER2/*neu* synthesis and provided an immune system boost by tumor-targeted IL-2 at the same time. IL-2 was delivered as part of fusion monoclonal antibody against HER2/*neu* positive breast cancer (Ding et al. *J Control Release,* 2013). Overall, the development of versatile biodegradable and non-toxic nanobioconjugates based on naturally derived polymalic acid (Ljubimova et al. *J Vis Exp,* 2014) with their ability of targeting brain, lung, and breast human tumors in preclinical cancer models resulted in significantly increased survival of tumor-bearing animals.

Future scientific and clinical developments: 1. Brain metastasis. Its treatment becomes a major issue for brain cancer management; 2. Personalized nanomedicine. Cancer immunology is currently coming back and may soon provide new mainstream cancer therapies; 3. Diagnostic and targeting. Current targeting strategies of nano drugs and imaging agents are based on monoclonal antibodies that will be substituted by peptides in the future to reduce immunogenicity and production costs. 4. Significant advances of nanotechnology in cancer treatment give hope for the use of its achievements to treat a variety of neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases, which are on the rise due to the aging of the world population.

Nanotechnology Takes Aim at the Blood-Brain Barrier

Efstathios (Stathis) Karathanasis, PhD

Case Western Reserve University

Unmet clinical need: Today, physicians have access to an ever increasing number of highly potent drugs. For example, despite advancements in surgery and radiotherapy, the aggressive forms of brain tumors, such as gliomas, are still uniformly lethal with current therapies offering only palliation complicated by significant toxicities. Gliomas are characteristically diffuse with infiltrating edges and nearly inaccessible to systemic therapies due to the brain-tumor barrier. Currently, aggressive efforts are underway to further understand brain-tumor's microenvironment and identify brain tumor cell-specific regulators amenable to pharmacologic interventions. While new potent agents are continuously becoming available, efficient drug delivery to brain tumors remains a limiting factor. This stems from the fact that drug molecules are not specifically designed to consider the microenvironment of hard-to-treat cancers. While drugs are selected based on their potency to kill cancer cells, the ability of these molecules to navigate and gain access into hard-to-reach brain regions is not carefully considered.

The Nanochain solution: To effectively seek and destroy brain tumors, we developed a new class of multicomponent chain-like nanoparticles, termed nanochains. The efficacy of nanochains has been demonstrated in several preclinical rodent models of aggressive brain tumors. The nanochains facilitated effective delivery of drugs into hard-to-reach tumors using a safe and low dose, which has the potential to unfold the field and allow significant expansion of therapies to diseases in the brain where success is currently very limited.

How does it work? A nanochain particle is comprised of three iron oxide nanospheres and a drug-loaded liposome chemically linked into a 100-nm linear, chain-like assembly with high precision. The nanochain possesses a unique ability to scavenge diseased endothelium. By utilizing effective vascular targeting, the nanochains achieve rapid deposition on the vascular bed of glioma sites establishing well-distributed drug reservoirs on the endothelium of brain tumors. Notably, our animal studies showed that a remarkable 4.7% of the injected dose of nanochains accumulated in glioma tumors. This represented an 18.6-fold higher dose when compared to today's chemotherapies. A few hours later, after nanochains slip from the blood stream and congregate in tumors, a radiofrequency coil is placed outside near the body. The coil creates a "mild" radiofrequency field (similar to the frequencies of FM radio). The field causes the magnetic tails of the nanochain to vibrate, breaking open the liposome spheres. Given the relatively low RF frequencies and power used in our system compared to clinical MRI, these RF fields are well understood, and thus the cost and clinical deployment of such system present a low degree of difficulty. The application of radiofrequency facilitates on-command rapid release of high amounts of free drug specifically at the tumor site, which is then capable of spreading to deep regions of gliomas, which are otherwise inaccessible by today's drug molecules. While the majority of our efficacy studies have used cancer drugs as model drug candidates, the versatile nature of the nanochain platform can be adapted to a wide variety of cancer drugs.

Spherical Nucleic Acids for the Precision Treatment of Malignant Glioma

Alexander Stegh, PhD

Northwestern University

Malignant brain tumors are aggressive and neurologically debilitating tumors considered as one of the deadliest of human cancers. Treatment options are limited and at best offer temporary relief from progressive tumor growth. Brain tumors are composed of rapidly growing, stem cell-like, and therapy-evading cells. These characteristics are conferred by a complex landscape of genetic and epigenetic changes that distinguish cancerous from normal brain tissue. Informed by the tumor's genetic and epigenetic makeup, several 'targeted' pharmacologicals have been approved for treatment of brain cancers, foremost inhibitors of known cancer-associated enzymatic activities. It has become apparent, however, that the majority of cancer genes represent unprecedented, non-enzymatic targets with unknown function that cooperate to drive cancer progression and therapy resistance. This observation begs the question, how can multiple, 'undruggable', and uncharacterized genes be therapeutically targeted? This challenge has galvanized chemists, biologists, geneticists and medical doctors alike, and has led to the development of gene silencing approaches that rely on the introduction of small RNA molecules into cancer cells to specifically deactivate cancer genes. The robust delivery of RNA and associated protein factors into brain tumor tissue, however, remains a significant bottleneck in the development of *in vivo* gene silencing therapeutics. Nanotechnology continues to provide fundamentally different approaches to the treatment of genetic disease. In particular, spherical nucleic acids (SNAs) represent one of the most prominent, promising and scalable gene regulation platforms. SNAs consist of nanoparticle cores densely functionalized with shells of radially oriented oligonucleotides. SNAs, unlike conventional nucleic acids, are able to transverse cellular membranes, including the blood-brain-barrier, effectively accumulate, and pervasively infiltrate intracerebral brain tumors upon systemic intravenous delivery, reduce tumor burden and increase survival of brain tumor-bearing mice. Importantly, at Northwestern University, first-generation SNAs are entering early phase clinical testing in patients diagnosed with glioblastoma (GBM), the most aggressive and prevalent form of malignant brain tumors in adults. Using these significant accomplishments as a springboard, efforts in my laboratory center on the advanced development and characterization, and development of SNA constructs for the treatment of malignant brain cancers.

Three Areas Where Studies of the Blood-Brain Barrier Change Patient Care

Edward Neuwelt, MD

Oregon Health & Science University and the Portland Veterans Affairs Medical Center

Blood-brain barrier (BBB) research by our group has had a positive impact on improving survival and long-term outcomes in patients with primary and metastatic brain tumors in three areas: 1) brain tumor therapy, 2) neuroimaging, and 3) the prevention of platinum-induced ototoxicity.

1) **BBB disruption (BBBD) chemotherapy: long-term outcomes in primary CNS lymphoma (PCNSL)**. Intra-arterial (IA) infusion of hyperosmotic mannitol reversibly opens the BBB by shrinking cerebrovascular endothelial cells and opening tight junctions between the cells. This approach transiently increases delivery of chemotherapy, antibodies, and nanoparticles to brain. Preclinical studies in normal rats and numerous brain tumor models have optimized the BBBD technique. Multiple clinical trials have shown its safety and efficacy. In a multi-institutional clinical trial in 149 patients newly diagnosed with PCNSL we showed that methotrexate-based chemotherapy in conjunction with BBBD results in successful and durable tumor control and outcomes that are comparable or superior to other PCNSL treatment regimens (Angelov JCO 2009). Prospective evaluation of PCNSL survivors who were treated with BBBD chemotherapy showed stable or improved cognitive status at a median follow-up of 12 years (range: 2 to 26 years) after diagnosis (Doolittle, J Clin Oncol 2013). Patients receiving BBBD chemotherapy in our series showed equivalent cognition and neuroimaging outcomes compared to patients treated with high dose methotrexate without BBBD (Doolittle, Neurology 2013). Current studies are evaluating immunotherapy with monoclonal antibodies (mAb) targeting B-lymphoma antigens as a mechanism to further improve the complete response rate and overall survival.

2) **Novel magnetic resonance imaging (MRI) techniques for measuring changes in brain tumor vasculature and inflammation**. *F*erumoxytol, a super paramagnetic iron oxide nanoparticle that is FDA approved for iron replacement therapy, is a new MRI contrast agent that improves several aspects of brain neuroimaging. At early time points, less than 2 h after intravenous infusion, the ferumoxytol nanoparticles are trapped in the vasculature as a blood pool agent and allow accurate perfusion measurements of blood volume. In preclinical brain tumor studies, ferumoxytol improves the consistency of relative cerebral blood volume (rCBV) measurements in rats before and after treatment with anti-angiogenic and therapeutic mAbs (Gahramonov, Radiology 2011). At later time points, >24 h, ferumoxytol crosses the BBB in intracerebral lesions where it is taken up by activated microglia, astrocytes, and tumor-associated macrophages (McConnell, *Nanomedicine: Nanotech Biol Med 2016)*

In patients with malignant brain tumors, radiographic worsening after radiation therapy can be caused by true tumor progression or by BBB leakage of contrast due to an inflammatory response called pseudoprogression. Unlike true tumor progression, MRI signal changes in pseudoprogression stabilize spontaneously and are associated with a favorable prognosis. Neuroimaging with ferumoxytol provides a mechanism to differentiate tumor progression from pseudoprogression, which can resolve the clinical dilemma of continuation of effective therapy or transferring non-responders to novel therapies.

3) **Chemoprotection and chemo-enhancement for brain tumor therapy.**

Platinum-based chemotherapy is used to treat a variety of childhood malignancies, but is associated with progressive and irreversible toxicities, in particular ototoxicity (**Neuwelt 2010**). Research from our lab has shown that the thiols N-acetylcysteine (NAC) and sodium thiosulfate (STS) can protect against cisplatin-induced ototoxicity, and NAC is also protective against bone marrow and kidney toxicity. These chemoprotective agents do no cross the BBB, so we can separate brain tumor therapy from chemoprotection in time and space. In patients with brain tumors treated with carboplatin based chemotherapy in conjunction with BBBD, we have shown that STS protects against carboplatin-based hearing loss and may also protect against carboplatin-induced severe thrombocytopenia (Doolittle, Adv Pharmacol. 2014). Our preclinical and clinical studies of STS chemoprotection led to Phase III cooperative group trials at the Children's Oncology Group (COG) and the International Society of Paediatric Oncology (SIOP), of STS for protection against cisplatin-induced hearing loss in children. To date, STS has been shown to be protective against cisplatin-induced hearing loss in children, and has not shown any evidence of tumor protection in children with localized disease.

Drug and Nucleic Acid Delivery to the Brain

Justin Hanes, PhD

Center for Nanomedicine at the Wilmer Eye Institute, Departments of Biomedical Engineering, Chemical & Biomolecular Engineering, Neurosurgery, Oncology, Ophthalmology, and Pharmacology & Molecular Sciences, the Johns Hopkins University, Baltimore, USA

Nanoparticle-based drug and nucleic acid therapies hold promise to improve treatments for a variety of brain disorders, including brain tumors and neurodegenerative diseases. However, it is difficult to achieve widespread drug and gene delivery in the brain due to the blood-brain barrier and the nanoporous and highly adhesive extracellular matrix that minimizes distribution of nanoparticles once they reach the brain parenchyma. We recently demonstrated that sub-114 nm nanoparticles rapidly penetrated healthy brain tissue and brain tumor tissue, but only if they possessed an extremely high surface coverage of hydrophilic and neutrally charged polyethylene glycol (PEG). We used this knowledge to create drug and nucleic acid loaded nanoparticle formulations that more effectively spread within the brain parenchyma following local injection or infusion ("brain penetrating nanoparticles" or "BPN"). We showed that paclitaxel loaded BPN were more effective in treating rats with brain tumors than similar nanoparticles that do not penetrate as efficiently. Also, unlike DNA nanoparticles with standard PEG coatings, DNA nanoparticles with dense PEG coatings were highly stable in cerebrospinal fluid and rapidly diffused in freshly excised healthy and tumor rodent brain tissues *ex vivo*. Consistent with *ex vivo* transport behavior, these "DNA BPN" rapidly penetrated within the brain following administration by convection enhanced delivery, leading to markedly improved distribution and overall level of transgene expression compared to DNA nanoparticles with standard PEG coating densities. With our collaborators, led by Dr. Richard Price at the University of Virginia and Jung Soo Suk at the Johns Hopkins School of Medicine, we found that systemically-administered BPN can be delivered into desired regions of the brain using image-guided focused ultrasound with microbubbles that temporarily disrupt the BBB. We are working with Dr. Price, Dr. Suk and colleagues to test these particles in the treatment of brain cancer, Parkinson's disease and other disorders that affect the CNS.

References

[1] Nance EA, Woodworth GF, Sailor KA, Shih T-Y, Xu Q, Swaminathan G, Xiang D, Eberhart C, Hanes J. (2012) A dense poly(ethylene glycol) coating improves penetration of large polymeric nanoparticles within brain tissue, ***Sci Transl Med***, 4:149ra119.
[2] Nance E*, Timbie K*, Miller GW, Song J, Louttit C, Burke C, Klibanov AL, Shih T-Y, Swaminathan G, Tamargo RJ, Woodworth GF, Hanes J, Price R. (2014) Non-invasive delivery of stealth, brain-penetrating nanoparticles across the blood-brain barrier using MRI-guided focused ultrasound, ***J Control Release***, 189:123-32.
[3] Kim AJ, Woodworth GF, Boylan NJ, Suk JS, Hanes J. (2014) Highly compacted pH-responsive DNA nanoparticles mediate transgene silencing in experimental glioma, ***J Mater Chem B Mater Biol Med.*** 2(46):8165-8173.
[4] Nance E, Zhang C, Shih T-Y, Hanes J. (2014) Brain penetrating nanoparticles improve paclitaxel efficacy against malignant glioma, ***ACS Nano***, 8(10):10655-64.
[5] Mastorakos P, Zhang C, Berry S, Oh Y, Lee S, Eberhart CG, Woodworth GF, Suk JS, Hanes J. (2015) Highly PEGylated DNA Nanoparticles Provide Uniform and Widespread Gene Transfer in the Brain, ***Adv Healthc Mater***, doi: 10.1002/adhm.201400800.

PARTICIPANTS

Natalie Abrams, PhD
Program Officer
NCI, NIH
Phone: 301-435-0728
Email: natalie.abrams@nih.gov

Neeraj Agarwal, PhD
HSA
NEI, NIH
Phone: 301-451-2020
Email: agarwalnee@nei.nih.gov

Felipe Aguel, PhD
Program Director
NINDS
Phone: 301-496-1447
Email: Felipe.Aguel@nih.gov

Katerina Akassoglou, PhD
Professor
UCSF School of Medicine
Phone: 415-734-2512
Email: kakassoglou@gladstone.ucsf.edu

Syed Ali, PhD
SBRS
NCTR/FDA
Phone: 870-543-7123
Email: Syed.ali@fda.hhs.gov

Julia Arnold, PhD
Program Director - Brain SPORES
NIH- NCI - Translational Research Program
Phone: 240-275-5691
Email: jarnold@mail.nih.gov

Victor A. Arrieta
MD PhD Student
National Cancer Institute
Phone: 301-443-2767
Email: victor.arrieta@nih.gov

Tatjana Atanasijevic, PhD
Research Fellow
NINDS
Phone: 301-435-4362
Email: atanasijevict@mail.nih.gov

Rolanda Bailey, BS
Research Associate
NOB
Phone: 301-443-2492
Email: baiileyro@mail.nih.gov

Praveen Balimane, PhD
Reviewer
FDA
Phone: 240-402-5230
Email: praveen.balimane@fda.hhs.gov

William Banks, MD, FACE
Professor
University of Washington
Phone: 206-764-2701
Email: wabanks1@uw.edu

Tony Beck, MS, PhD
Director OSE/SEPA
NIH
Phone: 301-435-0805
Email: beckl@mail.nih.gov

Jessica Beck, DVM
CBSTP Fellow
NCI, NIH
Phone: 301-594-9682
Email: jessica.beck@nih.gov

Eric Bernhard, PhD
Chief, Radiotherapy Development Branch
NCI
Phone: 240-276-5704
Email: bernhardej@mail.nih.gov

Michelle Berny-Lang, PhD
Program Director
National Cancer Institute
Phone: 301-480-4890
Email: michelle.berny-lang@nih.gov

Julia Berzhanskaya, PhD
Program Analyst
NIH/NCCIH
Phone: 301-451-2569
Email: Julia.Berzhanskaya@nih.gov

Seetha Bhagavan, PhD
Health Scientist Administrator
National Institutes of Health/Center for Scientific Review
Phone: 301-237-9838
Email: bhagavas@csr.nih.gov

Simona Bianconi, MD
Staff Clinician
NICHD
Phone: 301-496-8597
Email: simona.bianconi@nih.gov

Keith Black, MD
Chair, Dept of Neurosurgery
Cedars-Sinai Medical Center
Phone: 310-423-1773
Email: black@cshs.org

Chris Boshoff, PhD
Scientific Project Manager
NINDS
Phone: 301-496-0664
Email: chris.boshoff@nih.gov

Kasia Bourcier, PhD
Program Officer
NIAID
Phone: 240-627-3482
Email: bourcierkd@niaid.nih.gov

Cheryl Anne Boyce, PhD
Chief
Implementation Science Branch, CTRIS, NHLBI, NIH
Phone: 301-496-1051
Email: cboyce@mail.nih.gov

Brenda Brooks, MA, BA
Program Analyst
FDA
Phone: 301-796-2555
Email: brenda.brooks@fda.hhs.gov

Claudette Brooks, MD
Supv Medical Officer
ORWH OD/DPCPSI NIH
Phone: 301-435-0971
Email: claudette.brooks@nih.gov

Pim Brouwers, PhD
Deputy Division Director
NIMH
Phone: 240-627-3863
Email: pb56u@nih.gov

Jacquelyn Brown, BA, PhD
Staff Scientist
Vanderbilt University
Phone: 615-322-2569
Email: jacquelyn.a.brown@vanderbilt.edu

John Butman, MD, PhD
Staff Clinician
NIH/CC
Phone: 301-402-5827
Email: jbutman@nih.gov

Karim Calis, PharmD, MPH
Adjunct Senior Clinical Investigator
NICHD/NIH
Phone: 301-928-2413
Email: kcalis@nih.gov

Niamh Cawley, PhD
Staff Scientist
NICHD
Phone: 301-435-8920
Email: cawleyn@mail.nih.gov

Naresh Chand, DVM, MS, MVSc, PhD
Program Officer
NIH
Phone: 301-443-8895
Email: nchand@mail.nih.gov

Marc Charette, PhD
Program Director
NHLBI
Phone: 301-435-0560
Email: marc.charette@nih.gov

YungChia Chen, BS, MS, PhD
ASEE Post-Doctoral Fellow
NRL
Phone: 202-404-2360
Email: chen.yungc3@gmail.com

Daofen Chen, PhD
Program Director
NINDS/NIH
Phone: 301-451-6858
Email: daofen.chen@nih.gov

Prashant Chittiboina, MD, MPH
Assistant Clinical Investigator
NINDS
Phone: 301-496-5728
Email: prashant.chittiboina@nih.gov

Peter Choyke, MD
Senior Investigator
NCI
Phone: 301-402-8409
Email: pchoyke@nih.gov

Robert Clark, MD
Professor
University of Pittsburgh School of Medicine
Phone: 412-692-5164
Email: clarkrs@upmc.edu

Deborah Colosi, PhD
Program Officer
NIMH
Phone: 301-605-2275
Email: Deborah.Colosi@nih.gov

Richard Conroy, PhD
Program Director
National Institutes of Health
Phone: 301-402-1486
Email: conroyri@mail.nih.gov

Tomer Cooks
Visiting Fellow
NCI
Phone: 301-402-8773
Email: tomer.cooks@nih.gov

Roderick Corriveau, PhD
Program Director
NINDS
Phone: 301-496-5680
Email: roderick.corriveau@nih.gov

Tammy Crowder, PhD
Neurotrauma Portfolio Manager
Combat Casualty Care Research Program
Phone: 301-619-3341
Email: alicia.t.crowder.civ@mail.mil

Elvis Cuevas, PhD
Research Fellow
NCTR/FDA
Phone: 870-543-7285
Email: elvis-yane.cuevas-martinez@fda.hhs.gov

Michael Dandenault, PhD, BS Biology
Assistant Portfolio Manager, Neurotrauma
Combat Casualty Care Research Program
Phone: 301-619-2427
Email: michael.dandenault@gmail.com

Alexia Daoust, PhD
Visiting Fellow
NIH
Phone: 301-594-7314
Email: daoustalexia@hotmail.fr

Nancy Desmond, PhD
Office Director
NIMH
Phone: 301-443-3107
Email: ndesmond@nih.gov

Scott Diamond, PhD
Professor
University of Pennsylvania
Phone: 215-573-5702
Email: sld@seas.upenn.edu

Ramon Diaz-Arrastia, MD, PhD
Professor of Neurology and Director of Clinical Research
Uniformed Services University of the Health Sciences
Phone: 301-295-5537
Email: Ramon.Diaz-Arrastia@usuhs.edu

Donna DiMichele, MD
Deputy Director
NIH/NHLBI/DBDR
Phone: 301-435-0080
Email: donna.dimichele@nih.gov

Lester R Drewes, PhD
Professor
University of Minnesota Medical School Duluth
Phone: 218-726-7925
Email: ldrewes@d.umn.edu

Jamie Driscoll, BA
Chief, Molecular Pharmacology
NIMH
Phone: 301-443-5288
Email: jdrisco1@mail.nih.gov

Michael Ellenbogen
Dementia Advocate
Phone: 215-343-9395
Email: authorellenbogen@gmail.com

Mehdi Farokhnia, MD
Postdoc Fellow
NIAAA and NIDA
Phone: 301-827-1488
Email: mehdi.farokhnia@nih.gov

Joseph Frank, MD, MS
Chief
NIH- Frank Lab
Phone: 301-402-4314
Email: jf5z@nih.gov

Aniruddha Ganguly, PhD
Program Director
NIH/National Cancer Institute
Phone: 240-276-5905
Email: gangulya@mail.nih.gov

Gallya Gannot, DMD,PhD
HSA
NIDCR/NIH
Phone: 301-451-5096
Email: gallya.gannot@nih.gov

Holly Garriock, PhD
Health Scientist Administrator
NIMH
Phone: 301-443-9230
Email: holly.garriock@nih.gov

Aarti Gautam, PhD
Molecular Biologist
US Army center for Environmental Health Research
Phone: 301-619-7683
Email: aarti.gautam.civ@mail.mil

Gary Gibbons, MD
Director
National Heart, Lung, and Blood Institute
Phone: 301-496-5166
Email: gary.gibbons@nih.gov

Michael Goodman, MD
Assistant Professor of Surgery
University of Cincinnati
Phone: 513-558-6524
Email: michael.goodman@uc.edu

Rashmi Gopal-Srivastava, PhD
Director, Extramural Research Program, ORDR
Office of Rare Diseases Research (ORDR), NCATS
Phone: 301-402-4336
Email: gopalr@mail.nih.gov

Martin Green, PhD
Supervisory Toxicologist
FDA
Phone: 201-796-2640
Email: martin.green@fda.hhs.gov

John Griffin, BS, PhD
Professor
Scripps Research Institute
Phone: 858-784-8220
Email: jgriffin@scripps.edu

Brunilde Gril, PhD
Staff Scientist
NCI
Phone: 301-451-6445
Email: grilbrun@mail.nih.gov

Andrea Gropman, MD
Chief,
Neurodevelopmental Pediatrics and Neurogene
Children's National Medical Center
Phone: 202-476-3511
Email: agropman@childrensnational.org

Liliana Guedez, PhD
Senior Clinical Scientist
NEI, NIH
Phone: 301-435-4562
Email: liliana.guedez@nih.gov

Matthew Hall, PhD
Group Leader
NCGC, NCATS
Phone: 301-217-5727
Email: hallma@mail.nih.gov

Sewoon Han, PhD
Postdoctoral Scholar
University of California, Berkley
Phone: 267-663-1898
Email: eomsteom@berkley.edu

Justin Hanes, PhD
Director
Johns Hopkins University
Phone: 443-287-7921
Email: hanes-cnm@jhmi.edu

Manjit Hanspal, PhD
Program Director
NHLBI/NIH
Phone: 301-435-0050
Email: hanspalm@nhlbi.nih.gov

Shuyu Hao, MD
Volunteer
NCI
Phone: 301-451-9052
Email: shuyu.hao@nih.gov

Curtis C. Harris, MD
Chief, Laboratory of Human Carcinogenesis
NCI
Phone: 301-496-2048
Email: harrisc@mail.nih.gov

Chris Hartshorn, PhD
Program Director
NIH/NCI
Phone: 301-435-3941
Email: christopher.hartshorn@nih.gov

Brandon Harvey, PhD
Core Director/Staff Scientist
NIDA
Phone: 443-740-2590
Email: bharvey@mail.nih.gov

Sharie Haugabook, PhD
Sr. Project manager
NIH/NCATS
Phone: 301-217-6038
Email: sharie.haugabook@nih.gov

Miles Herkenham, PhD
Senior Investigator
NIMH/NIH
Phone: 302-496-8288
Email: herkenh@mail.nih.gov

Meena Hiremath, PhD,PMP
Director, Office of Extramural Policy & Training
Division of Extramural Research Activities
Phone: 301- 435-0569
Email: hirematm@mail.nih.gov

Craig Hooper, PhD
Director Division of Blood Disorders
CDC
Phone: 404-639-3750
Email: chooper@cdc.gov

Keith Hoots, MD
Director
NIH/NHLBI/DBDR
Phone: 301-435-0080
Email: hootswk@nhlbi.nih.gov

Jun Hua, PhD
Assistant Professor
JHMI
Phone: 4439230000
Email: huajun78@hotmail.com

Sadhana Jackson, MD
Asst clinical investigator
NCI
Phone: 301-496-6620
Email: sadhana.jackson@nih.gov

Laura Jaeger, PhD
Science Policy Analyst
FDA/CDER
Phone: 301-796-5937
Email: Laura.Jaeger@fda.hhs.gov

Jeymohan Joseph, PhD
Chief,
HIV Neuropathogenesis and Therapeutics Bran
National Institute of Mental Health
Phone: 240-627-3869
Email: jjeymoha@mail.nih.gov

Yashar Kalani, MD, PhD
Assistant Professor
Barrow Neurological Institute
Phone: 602-746-0768
Email: stemcelldoctor@kalanimed.com

Dimitrios Kapogiannis, MD
Clinical Investigator
NIA, NIH
Phone: 410-350-3953
Email: kapogiannisd@mail.nih.gov

Efstathios (Stathis) Karathanasis, PhD
Assistant Professor
Case Western Reserve University
Phone: 216-844-5281
Email: stathis@case.edu

Johan Karlsson, PhD
Postdoc
Johns Hopkins University
Phone: 667-207-1668
Email: jkarlss1@jhu.edu

LeeAnn Keener, BSN
Clinical Research Nurse
NIH
Phone: 301-594-2005
Email: leeann.keener@nih.gov

John Kehne, PhD
Program Director, ETSP
NIH/NINDS/OTR
Phone: 301-402-6833
Email: john.kehne@nih.gov

Kimbra Kenney, MD
Associate Professor, Neurology
USUHS & NICoE, WRNMMC
Phone: 301-295-6420
Email: kimbra.kenney@usuhs.edu

Anastasia Khvorova, PhD
Professor
RNA Therapeutics Institute, UMass Medical School
Phone: 774-455-3638
Email: Anastasia.Khvorova@umassmed.edu

Min-Jeong Kim, MD, PhD
Post-doc visiting fellow
NIH/NIMH
Phone: 301-451-8894
Email: min-jeong.kim@nih.gov

Andrei Kindzelski, MD, PhD
Medical Officer, Program Director
NIH/NHLBI/DBDR
Phone: 301-435-0050
Email: kindzelski@nhlbi.nih.gov

Natalia Komissarova, PhD
SRO
CSR
Phone: 301-435-1206
Email: komissar@mail.nih.gov

Zsofia Kovacs, PhD
Visiting Fellow
NIH
Phone: 301-435-4635
Email: zsofia.kovacs@nih.gov

Richard Kraig, MD, PhD
Professor
University of Chicago Medical Center
Phone: 773-702-0802
Email: rkraig@neurology.bsd.uchicago.edu

Lillian Kuo, PhD
Program Officer
NIAID
Phone: 240-292-4621
Email: lillian.kuo@nih.gov

Jennifer Kwan, PhD
Mathematical Statistician
NIAID
Phone: 301-402-7887
Email: jennifer.kwan@nih.gov

Pascal Laeng, PhD
Scientific Project Manager
NINDS
Phone: 301-496-7416
Email: pascal.laeng@nih.gov

Lalitha Lalitha, MD, PhD
Chief, Diagnostic Imaging Branch
National Cancer Institute
Phone: 240-276-6510
Email: shankarl@mail.nih.gov

Susan Lantz, MS
Biologist
FDA/NCTR
Phone: 870-543-7021
Email: susan.lantz@fda.hhs.gov

Lawrence Latour, PhD
Staff Scientist
NINDS-NIH
Phone: 301-496-0463
Email: latourl@ninds.nih.gov

Mary Lee, MD
Physician
NIAAA
Phone: 301-845-0545
Email: leemary@mail.nih.gov

Michael Lehmann, PhD
Staff Scientist
NIH
Phone: 301-402-3243
Email: michael.lehmann@nih.gov

Emily Leibovitch,
Research Associate
NINDS, NIH
Phone: 301-496-0519
Email: emily.leibovitch@nih.gov

Margaret Lentz, PhD
Imaging Physicist
NIH/NIAID
Phone: 617-953-5298
Email: margaret.lentz@nih.gov

Zhiyong Li, MD
Volunteer Scientist
NINDS
Phone: 301-480-1798
Email: li.zhiyong@nih.gov

Jan Li, MD. PhD.
SRO
CSR
Phone: 301-402-9607
Email: Jan.Li@nih.gov

Ti Lin, PhD
Program Analyst
NIH
Phone: 301-594-5367
Email: linti@mail.nih.gov

Yuehe Lin, PhD
Professor
Washington State University
Phone: 509-335-8523
Email: yuehe.lin@wsu.edu

Adrian Lita, PhD
Special Volunteer
NIH/CRI/NOB
Phone: 301-435-3016
Email: adrian.lita@nih.gov

Christina Liu, PhD, PE
Program Director
NCI/NIH
Phone: 301-451-2408
Email: christina.liu@nih.gov

Julia Ljubimova, MD, PhD
Director of the Nanomedicine Research Center
Cedars-Sinai Medical Center
Phone: 310-423-0834
Email: julia.ljubimova@cshs.org

Tania Lombo, PhD
Sc. Program Manager
NCATS
Phone: 301-451-1467
Email: tania.lombo@nih.gov

Lucie Low, PhD
Research Fellow
NIH
Phone: 301-594-7609
Email: lucie.low@nih.gov

Jie Lu, MD, PhD
Scientist
NINDS
Phone: 301-480-1798
Email: jie.lu@nih.gov

Shuiyu Lu, PhD
Staff Scientist
NIH/NIMH
Phone: 301-451-3904
Email: shuiyu.lu@gmail.com

Nadya Lumelsky, PhD
Branch Chief
NIH
Phone: 301-594-7703
Email: nadyal@nidcr.nih.gov

Martha Lundberg, PhD
Program Director
NIH-NHLBI-DCVS
Phone: 301-435-0513
Email: lundberm@nhlbi.nih.gov

Nicholas Lyssenko, PhD
Research Associate
University of Pennsylvania
Phone: 215-746-6403
Email: nilys@upenn.edu

Linda MacArthur, PhD
Scientific Review Officer
Center for Scientific Review
Phone: 301-537-9986
Email: linda.macarthur@nih.gov

Linda Maguire, MHS, MA-CBN
PhD Candidate, GTA
George Mason University
Phone: 703-895-3450
Email: maguire.usa@gmail.com

Todd Mainprize, MD
Neurosurgeon
Sunnybrook Health Science Centre
Phone: 416-480-4739
Email: todd.mainprize@sunnybrook.ca

Monica Manglani
Graduate Student
NIH
Phone: 301-443-7984
Email: monica.manglani@nih.gov

Kathy Mann Koepke, PhD
Program Director
NIH/NICHD
Phone: 301-435-6855
Email: kmk@nih.gov

Donald Marion, MD
Senior Clinical Consultant
Defense and Veterans Brain Injury Center/GDIT
Phone: 240-485-6591
Email: Donald.W.Marion.CTR@Mail.mil

Adriana Marques, MD
Head, Clinical Studies Unit
NIAID
Phone: 301-435-7668
Email: amarques@niaid.nih.gov

Leslie J Marshall, PhD
Program Officer/FAC-COR
DAIDS/NIAID
Phone: 240-292-4782
Email: marshalllj@niaid.nih.gov

Padma Maruvada, PhD
Program Director
NIDDK/NIH
Phone: 301-594-8884
Email: padma.maruvada@nih.gov

AC Matin, BSc, MSc, PhD
Professor
Stanford University School of Medicine
Phone: 650-725-4745
Email: a.matin@stanford.edu

Joseph Mattapallil, PhD
Associate Professor
Uniformed Services University
Phone: 301-295-3737
Email: joseph.mattapallil@usuhs.edu

Patrick McNeely, PhD
Graduate Student
University of Delaware
Phone: 304-761-6593

Jurij Mojsiak, MS
Pharmacologist
NIH/NIDA
Phone: 301-443-9804
Email: jm200p@nih.gov

Traci Mondoro, PhD
Branch Chief
NIH/NHLBI/DBDR
Phone: 301-435-0050
Email: mondorot@nhlbi.nih.gov

Manuel Moro, DVM, PhD
Program OfficialNIH/
NIH/ORIP
Phone: 301-435-0960
Email: manuel.moro@nih.gov

Seid Muhie, PhD
Research Scientist
Geneva/Usacehr
Phone: 301-619-7449
Email: smuhie@genevausa.org

Yoh-suke Mukouyama, PhD
Senior Investigator
NHLBI
Phone: 301-451-1663
Email: mukoyamay@mail.nih.gov

Christian Mustroph, BS
MRSP Fellow
NIH
Phone: 301-435-6308
Email: christian.mustroph@nih.gov

Pushpanathan Muthuirulan, PhD
Postdoctoral Visiting Fellow
NICHD/NIH
Phone: 301-451-6570
Email: pushpanathan.muthuirulan@nih.gov

Kuniyuki Nakamura, MD, PhD
Visiting Fellow
NIH
Phone: 301-451-9783
Email: kuniyuki.nakamura@nih.gov

Edjah Nduom, MD
Staff Clinician
National Institutes of Health
Phone: 301-480-0284
Email: edjah.nduom@nih.gov

Andrea Naranjo, PhD
Postdoctoral Fellow
NIH
Phone: 301-761-6593
Email: andrea.naranjo-erazo@nih.gov

Edward Neuwelt, MD
Director of the Blood Brain Barrier Program
OHSU
Phone: 503-494-5626
Email: neuwelte@ohsu.edu

Thomas O'Brien, MD, MPH
Senior Investigator
National Cancer Institute
Phone: 240-276-7104
Email: obrient@mail.nih.gov

Margaret Ochocinska, PhD
Program Director
NIH/NHLBI/DBDR
Phone: 301-435-0050
Email: ochocinm@nhlbi.nih.gov

Crystal Okorie, BA
CEO
Body Whisper NYC
Email: crystal.okorie@gmail.com

Ekaterine Orjonikidze, MD
President
Women 4 Woman
Phone: 995-599-302708
Email: orjonikidzeeka@yahoo.com

Elizabeth Ottinger, PhD
Senior Project Manager Drug Development
NIH/NCATS
Phone: 301-217-5478
Email: ottingerea@mail.nih.gov

Anurag Paranjape, PhD
Visiting postdoctoral fellow
NCI/NIH
Phone: 301-594-0701
Email: anurag.paranjape@nih.gov

Sergiu Pasca, MD
Assistant Professor
Stanford University
Phone: 650- 497-5922
Email: spasca@stanford.edu

Shyama Patel, PhD
Research Fellow
FDA
Phone: 301.796.2880
Email: shyama.patel@fda.hhs.edu

Aaron Pawlyk, PhD
Senior Advisor
NIDDK
Phone: 301-451-7299
Email: pawlykac@mail.nih.gov

Michele Pearson, BA
Program Specialist
NIMH
Phone: 301-443-9263
Email: pearsonmi@mail.nih.gov

Susan Pierce, PhD
Chief, Laboratory of Immunogenetics
NIAID, NIH
Phone: 301-496-9589
Email: spierce@nih.gov

Larry Pinkus, PhD
Sceintific Review Officer
CSR/NIH
Phone: 301-435-1214
Email: PinkusL@csr.nih.gov

Karl H. Plate, MD
Director
Frankfurt University Medical School
Phone: +49/69-630184146
Email: karl-heinz.plate@kgu.de

Nikorn Pothayee, PhD
NIH Reseach Fellow
NIH/NINDS
Phone: 301-402-9709
Email: pothayeen@ninds.nih.gov

Bill Potter, MD, PhD
Sr Advisor
NIMH
Phone: 301-640-0726
Email: bill.potter@nih.gov

Rich Price, BS, MS, PhD
Professor
University of Virginia
Phone: 434-924-0020
Email: rprice@virginia.edu

Shamsi Raeissi, PhD
Scientific Project Manager
NIH/NINDS/OTR
Phone: 301-496-5870
Email: shamsi.raeissi@nih.gov

Nishadi Rajapakse, PhD, MHS
Program Director
NIH/NIMHD
Phone: 919-345-5413
Email: chandima.rajapakse@nih.gov

Vasudev Ramachandra Rao, MD, MS
Program Officer
NIMH
Phone: 301-825-3259
Email: vasudev.ramachandrarao@nih.gov

Stanley Rapoport, MD
Scientific Advisor
National Institute on Aginh
Phone: 301-496-1765
Email: sir@mail.nih.gov

Sonia Razaqyar, BS
Associate Clinical Investigator
NINR
Phone: 202-210-7374
Email: razaqyarms@od.nih.gov

Bruce Reed, PhD
Director, Div of Neuroscience, Development & Aging
CSR/NIH
Phone: 301-402-4160
Email: bruce.reed@nih.gov

Renee Ren-Patterson, MD, PhD
Senior Research Scientist
NIMH
Phone: 202-386-1962
Email: renpatr@mail.nih.gov

Robert Robey, PhD
Chemist
NIH/NCI
Phone: 301-496-0796
Email: robeyr@mail.nih.gov

Denise Russo, MS, PhD
Deputy Branch Chief
NIH/NICHD
Phone: 301-435-6871
Email: Drusso1@mail.nih.gov

Joseph Santoro, PhD
Audience Development
Startup Grind
Phone: 202-730-9885
Email: jos.a.santoro@gmail.com

John Satterlee, PhD
Health Science Administrator
NIDA
Phone: 301-435-1020
Email: satterleej@nida.nih.gov

Brittany Schuck, BS, PhD,
Postdoctoral Research Fellow
NCATS/NIH
Phone: 301-217-4020
Email: brittany.wright@nih.gov

Peter Searson, PhD
Professor
Johns Hopkins School of Medicine
Phone: 410-516-8774
Email: searson@jhu.edu

Natasha Sheybani, BS
PhD Student
University of Virginia
Phone: 804-919-0507
Email: nds3sa@virginia.edu

Haiwen Shi, PhD
Mathematical Statistician
FDA/CDRH
Phone: 301-796-4204
Email: Haiwen.Shi@fda.hhs.gov

Ming Shih, PhD
Chemist
NIDA
Phone: 301-443-8422
Email: mshih@mail.nih.gov

Eric Shusta, PhD
Professor
University of Wisconsin - Madison
Phone: 608-262-1092
Email: eshusta@wisc.edu

Alexis Simpkins, MD PhD
Vascular Neurology Fellow
NIH
Phone: 301-435-9321
Email: alexis.simpkins@nih.gov

DeeDee Smart, MD, PhD
Tenure-Track Investigator
ROB/CCR/NCI/NIH
Phone: 301-496-5457
Email: smartd@mail.nih.gov

James Smirniotopoulos, BS, MD
Special Volunteer
NLM
Phone: 301-435-3192
Email: medpixman@gmail.com

Betsy Smith, MD
Medical Officer
NIH
Phone: 240-292-4788
Email: bs161v@nih.gov

Ariane Soldatos, MD, MPH
Pediatric Neurologist
National Institutes of Health
Phone: 301-496-1562
Email: ariane.soldatos@nih.gov

Pothur Srinivas, PhD, MPH
Program Director
NIH
Phone: 301-402-3712
Email: srinivap@mail.nih.gov

Patricia Steeg, PhD
Deputy Chief, Women's Malignancies Branch
NCI
Phone: 301-402-2732
Email: steegp@mail.nih.gov

Alexander Stegh, PhD
Assistant Professor
Northwestern University
Phone: 312-503-2879
Email: a-stegh@northwestern.edu

Daniel Stimson, PhD, JD
Chief, Science Policy, Outreach and Reporting
NHLBI
Phone: 202-744-7533
Email: daniel.stimson@nih.gov

Luke Stoeckel, PhD
Program Director
NIH-NIDDK
Phone: 301-741-9223
Email: luke.stoeckel@nih.gov

Clare Stroud, PhD
Senior Program Officer
National Academies of Sciences, Engineering, & Medicine
Phone: 202-334-1847
Email: cstroud@nas.edu

Christine Swanson-Fischer, PhD
Program Analyst
NIH-NINDS
Phone: 301-496-5680
Email: christine.swanson-fischer@nih.gov

Danilo Tagle, PhD
Associate Director for Special Initiatives
NCATS, NIH
Phone: 301-594-8064
Email: danilo.tagle@nih.gov

Aileen Tartanian, BS
Post-Baccalaureate IRTA
National Human Genome Research Institute, NIH
Phone: 301-496-5649
Email: aileen.tartanian@nih.gov

Sean Taylor, MBA, BA
CEO
Jaroop
Phone: 860-357-2060 ext 300
Email: sean@jaroop.com

Christine Taylor, MS, BS, BA
Biology Teacher
Wolcott High School
Phone: 860-357-2060 ext 300
Email: sean@jaroop.com

John Thomas, PhD
Program Director
NHLBI
Phone: 301-435-0065
Email: thomasj@nhlbi.nih.gov

Xenia Tigno, PhD, MS
Program Officer
ABDB, DLD, NHLBI, NIH
Phone: 301-443-4027
Email: xenia.tigno@nih.gov

Kelsie Timbie, BS
Scientific Programs Manager
Focused Ultrasound Foundation
Phone: 904-891-6548
Email: ktimbie@fusfoundation.org

William Tu, PhD
Postdoc
NIH/CC
Phone: 301-435-4488
Email: tut@cc.nih.gov

Illarion Turko, PhD
Research Chemist
National Institute of Standards and Technology
Phone: 240-314-6257
Email: iturko@umd.edu

Casmir Turnquist, PhD, MSc, BA
Postdoctoral Fellow
NCI
Phone: 301-496-7313
Email: casmir.turnquist@nih.gov

Martin Ulmschneider, BA, DPhil
Assistant Professor
Johns Hopkins University
Phone: 443-449-3867
Email: mulmsch1@jhu.edu

Alex Valadka, MD
Professor and Chair
VCU Neurosurgery
Phone: 814.828.9165
Email: avaladka@gmail.com

Yolanda Vallejo-Estrada, PhD
Program Director
NIDCR
Phone: 301-594-8926
Email: yolanda.vallejo-estrada@nih.gov

Kendall Van Keuren-Jensen, PhD
Associate Professor
TGen Center for Noninvasive Diagnostics
Phone: 602-343-8400
Email: kjensen@tgen.org

Bhadrasain Vikram, MD
Branch Chief
NCI/NIH
Phone: 240-276-5690
Email: vikramb@mail.nih.gov

Mohan Viswanathan, PhD
Acting Director, OSR
NCATS
Phone: 301-312-3745
Email: mv10f@nih.gov

Nora Volkow, MD
IC Director
NIH/NIDA
Phone: 301-443-6480
Email: nvolkow@nida.nih.gov

Tongguang Wang, MD, PhD
Staff Scientist
NINDS/NIH
Phone: 301-827-4083
Email: david.wang@nih.gov

Ronald Warren, PhD
Program Officer
NHLBI
Phone: 301-435-0499
Email: ronald.warren@nih.gov

Cathy Wedeen, PhD
Scientific Review Officer
NIH, NICHD
Phone: 301-435-6878
Email: wedeenc@mail.nih.gov

Lora Weidner, BS
Student
NIMH, NIH
Phone: 301-594-5721
Email: lora.deuitch@nih.gov

Kent Werner, MD, PhD
Resident
Johns Hopkins Neurology Department
Phone: 301-346-2696
Email: kent@jhmi.edu

Keith Whitaker, PhD
Biologist
US Army Research Laboratory
Phone: 410-278-5599
Email: keith.w.whitaker1.civ@mail.mil

Theresa Whiteside, PhD
Professor of Pathology, Immunology and Otolaryngol
University of Pittsburgh
Phone: 412-624-0096
Email: whitesidetl@upmc.edu

Vicky Whittemore, PhD
Program Director
NINDS/NIH
Phone: 301-496-1917
Email: vicky.whittemore@nih.gov

Lois Winsky, PhD
Branch Chief
Division of Neuroscience, NIMH
Phone: 301-443-5288
Email: lwinsky@mail.nih.gov

Xin Xu, PhD
Sr. Scientist
NIH
Phone: 301-217-4673
Email: Xin.xu3@nih.gov

Ye Yan, PhD
Research Fellow
NHLBI
Phone: 310-594-6194
Email: ye.yan@nih.gov

Dan Yang, MD, PhD
Staff Scientist
NHLBI
Phone: 301-496-1690
Email: yangd4@mail.nih.gov

Nora Yang, PhD
Dir Portfolio Management
NIH
Phone: 301-217-6036
Email: nora.yang@nih.gov

Meijun Ye, PhD
Staff Fellow
FDA
Phone: 301-796-5197
Email: meijun.ye@fda.hhs.gov

Cecil Yen, PhD
Postdoc
NINDS
Phone: 301-594-3031
Email: cecilyen@gmail.com

Ottavia Zattra, BS
Student
UNC-Chapel Hill
Phone: 919-308-2926
Email: zattra@live.unc.edu

Gary Zhang, PhD, MPH
Scientific Review Officer
NIH/NIDCR
Phone: 301-594-4864
Email: Zhanggu@mail.nih.gov

Hongen Zhang, PhD
Bioinformatics Scientist
NCI
Phone: 301-402-9788
Email: hzhang@mail.nih.gov

Huang-Ge Zhang, PhD
Professor
University of Louisville
Phone: 502-852-8623
Email: huangge.zhang@louisville.edu

Jun Zhu, PhD
Core Director
NHLBI
Phone: 301-443-7927
Email: jun.zhu@nih.gov

Alexandra Zimmer, MD, MSc
Staff Clinician
CCR/Women's Malignancies Branch
Phone: 301-496-8915
Email: alexandra.zimmer@nih.gov

Berislav Zlokovic, MD, PhD
Director
Zilkha Neurogenetic Institute
Phone: 323-442-2722
Email: zlokovic@usc.edu

LOGISTICS

Lunch and Refreshments | The following food options have been made available for your convenience:

Boxed lunches: If you pre-ordered a boxed lunch, you can collect it in Conference Room E (where you checked in) during the lunch break.

Lunch information: Workshop attendees may purchase light refreshments in the NSC snack shop located on the lobby level (open hours from 7:30 AM to 3:30 PM). Additional restaurants near the Neuroscience Center Building are located in the Pike & Rose shopping center next door.

Workshop Dinner | A dinner will take place Tuesday night, 6:30 PM, at Democracy Grille, located in the Bethesda Marriott Suites at 6711 Democracy Boulevard, Bethesda Maryland 20817 USA.

NSC Parking | If you wish to request a parking pass and were not provided one at check-in, please inform a staff member at the Welcome Desk.

Return to Airport | Staff at the Welcome Desk will be available to assist you in booking any necessary return transportation to the airport.

Shuttle Service between Hotel and Meeting Venue | For participants staying at the Bethesda Marriott Suites, there will be a shuttle to take you from the hotel to the meeting site each day. Please note that the shuttles will depart promptly to allow enough time to arrive at the meeting venue and go through NIH security and registration prior to the start of the workshop. The shuttle schedule is as follows:

Day 1, June 7:

7:00 AM – Shuttle from Bethesda Marriott Suites to NSC

5:30 PM – Shuttle from NSC to Bethesda Marriott Suites

Day 2, June 8:

7:00 AM – Shuttle from Bethesda Marriott Suites to NSC

There will be no return shuttle to the hotel on the second day, so please remember to bring your luggage to the meeting. We will watch your bags at the Welcome Desk in Conference Room E.