

# KEYSTONE SYMPOSIA

on Molecular and Cellular Biology

## Cerebral Fluid Flow and Function: Lymphatics, Glymphatics and the Choroid Plexus (Q4)

Scientific Organizers: Edwin S. Monuki, Maria Lehtinen and Maiken Nedergaard

Supported by the Directors' Fund

## Brain Therapeutics: Disruptive Technologies and Opportunities (Q3)

Scientific Organizers: Maria-Jesus Blanco, Kalpana M. Merchant and Mabel Loza

February 16-19, 2020 • Eldorado Hotel & Spa • Santa Fe, NM, USA

Supported by the Directors' Fund

Discounted Abstract & Scholarship Deadline: October 29, 2019 / Abstract Deadline: November 19, 2019 / Discounted Registration Deadline: December 17, 2019

### SUNDAY, FEBRUARY 16

#### Arrival and Registration

### MONDAY, FEBRUARY 17

#### Welcome and Keynote Address (Q4)

- \***Edwin S. Monuki**, University of California, Irvine, USA
- \***Maiken Nedergaard**, University of Copenhagen, Denmark
- \***Maria Lehtinen**, Harvard Medical School, USA
- Kari K. Alitalo**, University of Helsinki, Finland  
*Role of Lymphangiogenic Factors in Cerebral Fluid Flow and Neuropathological Processes in the CNS*

#### Welcome and Keynote Address (Q3)

- \***Maria-Jesus Blanco**, Sage Therapeutics, USA
- Darryle Schoepp**, USA  
*Neuroscience Therapeutics: Current Pipeline Challenges and Lessons Along the Way*

#### Choroid Plexus and CSF Regulation of Stem Cells (Q4)

- \***Edwin S. Monuki**, University of California, Irvine, USA
- Norman Ruthven Saunders**, University of Melbourne, Australia  
*The Choroid Plexus: Mechanisms that Limit Drug Entry into the Developing Brain*
- Nanna MacAulay**, University of Copenhagen, Denmark  
*Mechanism of CSF Secretion – Conventional Osmosis versus Active Water Transport*
- Maria Lehtinen**, Harvard Medical School, USA  
*Illuminating the Choroid Plexus*
- Neil Dani**, Boston Children's Hospital, USA  
*Short Talk: A Cellular and Spatial Map of the Choroid Plexus across Ventricles and Ages*
- Annarita Patrizi**, German Cancer Research Center, Germany  
*Short Talk: Rescuing Cortical Features in Rett Syndrome through the Choroid Plexus*

#### Challenges and Opportunities for Brain Therapeutics: Preclinical to Clinical Translation (Q3)

- \***Maria-Jesus Blanco**, Sage Therapeutics, USA
- Kalpana M. Merchant**, Vincere Biosciences, Inc., USA  
*De-Risking Approaches for Disease-Modifying Therapies for Parkinson's Disease: Opportunities and Challenges Exemplified by the Parkin Activator Program*
- Chas Bountra**, University of Oxford, UK  
*New Technologies, Collaborations and Processes, to Accelerate the De-Risking of Pioneer Drug Targets, for Neuro-Psychiatric Conditions*

**Shoichiro Ando**, Niigata University, Japan

*Short Talk: Gene Therapy for DRPLA Model Mice by AAV-Delivered CRISPR / Cas9*

**Trevor John Gonzalez**, Duke University, USA

*Short Talk: Engineering Synthetic Circular RNAs for AAV Mediated Expression in the Brain*

**Chao-Hsien Chen**, University of Texas MD Anderson Cancer Center, USA

*Short Talk: Reversal of Neurodegeneration through Clearance of pTau by Engineered Monocytes*

**Andrea Crotti**, Astellas Pharma, USA

*Short Talk: BIN1 Favors the Spreading of Tau via Extracellular Vesicles*

#### Workshop 1 (Q4)

- \***Julie Siegenthaler**, University of Colorado Denver, USA
- Alexandra E. Hochstetler**, Indiana University Purdue University Indianapolis, USA  
*Functional Studies of Ion Transport in Choroid Plexus Epithelial Cells*
- Engin Deniz**, Yale University, USA  
*Building Xenopus as a Model System for Hydrocephaly and Ependymal Ciliogenesis*
- Eri Iwasawa**, Cincinnati Children's Hospital Medical Center, USA  
*Neuroinflammation and Impaired Neural Differentiation in a Novel Rat Model of Neonatal Hydrocephalus Lacking Motile Cilia-mediated CSF Flow*
- Huixin Xu**, Boston Children's Hospital, USA  
*Developmental Control of Cerebral Fluid Distribution and CSF-K<sup>+</sup> by Choroid Plexus*
- Jo Stratton**, McGill University, Canada  
*Ependymal Cells: Their Transcriptional Landscape and Role in Brain Injury*
- Jessie Newville**, University of New Mexico School of Medicine, USA  
*Disruption and Rescue of Ependymal Motile Cilia Function in a Model of Posthemorrhagic Hydrocephalus of Prematurity*
- Haley Masters**, University of California, Irvine, USA  
*Single Cell Transcriptomic and Cell Biological Analysis of Human Choroid Plexus Epithelial Cells Derived from Pluripotent Stem Cells*
- Michael Neel**, University of California, Irvine, USA  
*Characterization of an Aging-Related Amyloid of the Human Choroid Plexus*

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### Roundtable: Collaboration & Knowledge Integration Models for Successful Brain Therapeutics (Q3)

\***Mabel Loza**, BioFarma Research Group, University of Santiago de Compostela, Spain

**James E. Audia**, Chicago Biomedical Consortium, USA  
*Drug Discovery in the Academic and Not-For-Profit Community*

**Sohini Chowdhury**, Michael J. Fox Foundation, USA

**Suzana Petanceska**, NIA, National Institutes of Health, USA

### Glymphatics (Q4)

\***Christopher Moore**, Brown University, USA

**Maiken Nedergaard**, University of Copenhagen, Denmark  
*Sleep Regulation and Disease Roles of the Glymphatic System*

**Jeffrey J. Iliff**, Oregon Health and Science University, USA  
*Molecular and Cellular Regulation of the Glymphatic System*

**Helene Benveniste**, Yale School of Medicine, USA  
*Glymphatic Flow, Regulation and Function*

**Iben Lundgaard**, University of Lund, Sweden  
*Short Talk: Cerebral Blood Flow Drives Efflux of CSF from the Ventricular System*

**Judith de Vos**, Amsterdam University Medical Center, Netherlands  
*The Imaging Cryomicrotome: A Setup for Large Volume 3D Mesoscopic Visualization*

### Advances in Technologies to Garner Insights into Disease Biology (Q3)

\***Chas Bountra**, University of Oxford, UK

**Edoardo Marcora**, Icahn School of Medicine at Mount Sinai, USA  
*From Human Genetics to Causal Biology in Alzheimer's Disease*

**Lena F. Burbulla**, Northwestern University, Feinberg School of Medicine, USA  
*Modeling Pathogenesis of Parkinson's Disease Using iPSC*

**Damian G. Wheeler**, Translucence Biosystems, Inc, USA  
*Short Talk: Brain-Wide Cellular Resolution Measurement of Neuronal Activity and Neuroinflammation*

**Xiaoqing Li**, University of Texas at Dallas, USA  
*Short Talk: Optical Opening of the Blood-Brain Barrier by Laser Excitation of Vasculature-Targeting Plasmonic Nanoparticles*

**Daniela Lecca**, National Institute on Aging, National Institutes of Health, USA  
*Short Talk: Neuroinflammation as a Therapeutic Target in Neurodegenerative Diseases*

### Poster Session 1

**TUESDAY, FEBRUARY 18**

### Lymphatics and CSF Dynamics (Q4)

\***Maiken Nedergaard**, University of Copenhagen, Denmark

**Jonathan Kipnis**, University of Virginia, USA  
*Lymphatic-Glymphatic Roles in Aging and Disease*

**Erik N.T.P. Bakker**, University of Amsterdam, Netherlands  
*The Impact of High Blood Pressure on the Brain: Studies in Spontaneously Hypertensive Rats*

**Steffi Dreha-Kulaczewski**, University Medical Center Göttingen, Germany  
*Breathe to Drive CSF Flow*

**Julie Siegenthaler**, University of Colorado Denver, USA  
*Short Talk: Origins, Development and Function of the Arachnoid Barrier Layer, a Key Component of the Blood-CSF Barrier*

**Ji Hoon Ahn**, Korea Advanced Institute of Science and Technology, South Korea  
*Short Talk: Meningeal Lymphatic Vessels at the Skull Base Drain Cerebrospinal Fluid*

**Fengfei Ding**, Huazhong University of Science and Technology, China  
*Short Talk: Chronic Sleep Fragmentation Alters the Brain Glymphatic Function*

**Humberto Mestre**, University of Rochester Medical Center, USA  
*Short Talk: Cerebrospinal Fluid Influx Drives Acute Ischemic Tissue Swelling*

**John R. Cirrito**, Washington University, School of Medicine, USA  
*Short Talk: Using Micro-Immunoelectrodes to Study Rapid Mechanisms of A $\beta$  Clearance from the Brain Interstitial Fluid of Mice*

### Integrating Novel Medicinal Chemistry Approaches Targeting the Brain (Q3)

\***James E. Audia**, Chicago Biomedical Consortium, USA

**Anastasia Khvorova**, University of Massachusetts Medical School, USA  
*RNAi-Based Modulation of Gene Expression in Central Nervous System*

**Jacob M. Hooker**, Harvard Medical School, USA  
*Integrating PET Tracers into CNS Drug Discovery: Impact on the Discovery of Novel HDAC Ligands*

**Maria-Jesus Blanco**, Sage Therapeutics, USA  
*Discovery of Novel Clinical Compounds for CNS Disorders*

### Speaker to be Announced

**Paula Perez Pardo**, Utrecht University, Netherlands  
*Short Talk: Positive Effects of Small Molecule Tryptophan-2,3-Dioxygenase Inhibitors on Motor and Non-Motor Symptoms in a Mouse Model of Parkinson's Disease*

**Xavier Barril**, Gain Therapeutics, Spain  
*Short Talk: Correcting Protein Misfolding with Structurally Targeted Allosteric Regulators (STAR): Applications in Rare Diseases and Brain Therapeutics*

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### Integrating Brain-Body Signaling (Q4)

\***Maria Lehtinen**, Harvard Medical School, USA

**Fiona Doetsch**, University of Basel, Switzerland  
*Choroid Plexus Regulation of Adult Neural Stem Cells*

**Claire Wyart**, Institut du Cerveau et de la Moelle Epinière, France  
*Origin and Role of the Cerebrospinal Fluid Bidirectional Flow in the Central Canal*

**Craig Ferris**, Northeastern University, USA  
*Imaging the Effect of the Circadian Light-Dark Cycle on the Glymphatic System in Awake Rats*

**Laura Lewis**, Boston University, USA  
*Coordinated Neural, Vascular, and Cerebrospinal Fluid Dynamics in Human Sleep*

### Diagnostic and/or Disease-State Biomarkers (Q3)

\***Kalpana M. Merchant**, Vincere Biosciences, Inc., USA

**Gwenn A. Garden**, University of Washington, USA  
*Emerging Glial Biomarkers of CNS Disease*

**Steffany A.L. Bennett**, University of Ottawa, Canada  
*Lipidomic-Based Insights into Disease Mechanisms: A Targeted Lipidomics Discovery Pipeline for Network and Flux Analysis*

**David Nguyen**, Sage Therapeutics, USA  
*Novel Digital Technologies towards CNS Translational Insights*

**Jagan A. Pillai**, Cleveland Clinic, USA  
*Short Talk: Pathway Based Analysis to Evaluate Inflammatory Analytes of Significance for Therapeutic Targeting in Alzheimer's Disease*

**Sang Bin Hong**, Seoul National University Hospital, South Korea  
*Short Talk: Initial Oligoclonal Band Positivity as a Disease-State Biomarker in Anti-NMDA Receptor Encephalitis*

### Poster Session 2

#### WEDNESDAY, FEBRUARY 19

### Choroid Plexus and CSF Regulation of Neuroimmune Responses (Q4)

\***Fiona Doetsch**, University of Basel, Switzerland

**Adam Chodobski**, Alpert Medical School of Brown University, USA  
*Choroid Plexus in Brain Injury and Neuroinflammation*

**Jean-François Ghersi-Egea**, Lyon Neurosciences Research Center, France  
*Antioxidant Defence at the Choroid Plexus Influences CSF Inflammation during Systemic Perinatal Injuries*

**Michal Schwartz**, Weizmann Institute of Science, Israel  
*Choroid Plexus Regulation of the Neuroimmune Response*

**Jan Remsik**, Memorial Sloan Kettering Cancer Center, USA  
*Short Talk: Immunological Determinants of Leptomeningeal Metastasis*

**Frederick B. Shipley**, Harvard University, USA

*Short Talk: Tracking Calcium Dynamics and Immune Surveillance at the Choroid Plexus*

**Marcus Stoodley**, Macquarie University, Australia  
*Short Talk: Physiological Drivers of Fluid Flow in the Spinal Subarachnoid Space and Spinal Cord*

**Gabriel Jensen**, University of Maine, USA  
*Short Talk: The Meninges and Choroid Plexus are Prominent Telomerase Reverse Transcriptase-Expressing Adult Stem Cell Niches in the Mouse Brain*

**June Goto**, Cincinnati Children's Hospital, USA  
*Short Talk: Impaired Glymphatic Flow and The Delayed Neural Differentiation in CCDC39-Deficient Rat Model of Neonatal Hydrocephalus*

### Ensuring Target Engagement: Innovative Approaches Towards Neuroimaging and Brain Delivery (Q3)

\***Jacob M. Hooker**, Harvard Medical School, USA

**Tetsuya Suhara**, National Institutes for Quantum and Radiological Science and Technology, Japan  
*Strategies for Utilizing Neuroimaging Biomarkers in CNS Drug Discovery and Development*

**Mickael Tanter**, Physics for Medicine, France  
*Functional Ultrasound Imaging of the Brain Activity: A Fast Growing Neuroimaging Modality with Unique Features for Preclinical and Clinical Studies*

**Maria José Alonso**, University of Santiago de Compostela, Spain  
*Nanotechnology-Based Strategies for the Delivery of Biological Drugs to the Brain*

**Lisa L. Shafer**, Cerebral Therapeutics, Inc., USA  
*Emerging Strategies for Brain Drug Delivery: Case Study Applications*

**Robert G. Thorne**, Denali Therapeutics, USA  
*Characterizing Fusion Protein Transport Across CNS Barriers: Leveraging Imaging and Other Novel Methods to Assess Brain Delivery*

**Frances G. Ghinger†**, University of Maryland, Baltimore County, USA  
*Short Talk: Optical Imaging of Ventromedial Prefrontal Cortex Activity Following Chronic Stress*

### Workshop 2 (Q4)

\***Iben Lundgaard**, University of Lund, Sweden

**Jin Cui**, Boston Children's Hospital, USA  
*Choroid Plexus as a Site of Immune Activation in a Model of Autism Spectrum Disorders*

**Marco Fanous**, Duke University, USA  
*Aquaporin 4 Regulates Adeno-Associated Viral (AAV) Transport across the Blood Brain Barrier*

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**Juchen Li**, Fudan University, China

*Investigation of the Glymphatic System using Awake and Anesthetized Mouse MRI*

**Darshan Sapkota**, Washington University School of Medicine, USA

*Stop Codon Readthrough of Aqp4 Generates a Novel AQP4 Isoform with Pathophysiological Significance*

**Hannah Elizabeth Jones**, University of Colorado Anschutz Medical Campus, USA

*Developmental Timing and Origins of Perivascular Brain Fibroblasts*

**Daphne M.P. Naessens**, Amsterdam UMC, Netherlands

*Elucidating Brain Water Management in Spontaneously Hypertensive Rats*

**Dakota E R DeFreitas**<sup>†</sup>, Washington University in St. Louis, USA

*Evaluation of CSF Distribution in Post-Hemorrhagic Hydrocephalus Rat Brain using Gold Nanoparticle Enhanced X-ray Nanotomography*

**Cameron Sadegh**, Harvard University, USA

*Choroid Plexus Epithelia Respond Rapidly to Hemorrhage to Minimize Ventriculomegaly Prior to Global Compensatory Increases in CSF Reabsorption*

**Jordan C. Xu**, UC Irvine, USA

*Dural Lymphatic Changes in Normal Pressure Hydrocephalus*

**Andrew T. Hale**, Vanderbilt University School of Medicine, USA

*Integration of Human Genetics and Multi-Omics Data Implicates Novel Pathways in Hydrocephalus*

### Diagnostics and Therapies (Q4)

\***Jeffrey J. Iliff**, Oregon Health and Science University, USA

**Edwin S. Monuki**, University of California, Irvine, USA

*Towards a Choroid Plexus-Based Regenerative Medicine*

**Kristopher T. Kahle**, Yale School of Medicine, USA

*A Role for Inflammation: TLR-4-mediated Cerebrospinal Fluid*

*Hypersecretion in Post-hemorrhagic and Post-infectious Hydrocephalus*

**Christopher Moore**, Brown University, USA

*A Systems Approach to the Choroid Plexus*

**Patricia I. Dickson**, Washington University, USA

*CSF Delivery of Therapeutics*

### Innovative Therapeutic Approaches Targeting the Brain (Q3)

**Aletta D. Kraneveld**, University of Utrecht, Netherlands

*Parkinson's Disease: No Guts No Glory*

**Giorgia Quadrato**, University of Southern California - USC Stem Cell, USA

*Modeling Human Brain Development and Disease at Single Cell Resolution with Organoids*

**Shun Mitsui**, Tokai University School of Medicine, Japan

*Short Talk: Neural Cell-Specific SQSTM1 Deficiency Accelerates the Onset of Disease in an ALS Mouse Model*

**Nicholas T. Hertz**, Mitokinin Inc., USA

*Short Talk: Small Molecule Activators of PINK1 Activity Rescue Sporadic PD Associated alpha-Synuclein Pathology*

**Taotao Lao**, Massachusetts General Hospital/ Harvard Medical School, USA

*Short Talk: TREML2 Regulates Microglia Functions in an Alzheimer's Disease Model*

### Meeting Wrap-Up: Outcomes and Future Directions (Q4)

**Edwin S. Monuki**, University of California, Irvine, USA

**Maria Lehtinen**, Harvard Medical School, USA

### Meeting Wrap-Up: Outcomes and Future Directions (Organizers) (Q3)

**THURSDAY, FEBRUARY 20**

**Departure**