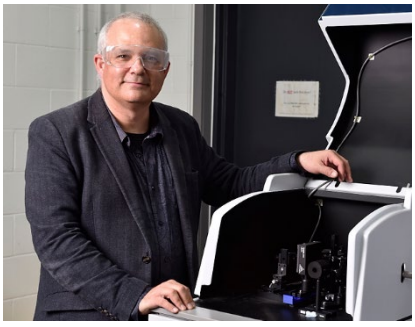
INVITED SPEAKERS AND OTHER CONTRIBUTORS

Kristine Glunde, PhD
Professor of Radiology, Oncology & Biological Chemistry
Director, Applied Imaging Mass Spectrometry (AIMS)
The Johns Hopkins University School of Medicine

Biomedical MALDI Imaging Applications: Tissue Mapping of Drug Metabolism and Biomarker Discovery

Biography: Dr. Glunde is Professor of Radiology, Oncology and Biological Chemistry at The Johns Hopkins University School of Medicine, and the founding Director of the Applied Imaging Mass Spectrometry (AIMS) Core. Her research program focuses on cancer biology and molecular imaging of cancer. Her lab combines molecular and cancer biology approaches with multi-scale imaging to investigate and visualize molecular events that drive cancer growth, invasion, and metastasis. Imaging technologies used in Dr. Glunde's lab span magnetic resonance spectroscopic imaging, mass spectrometry imaging, and optical and fluorescence imaging. Since joining the Faculty of the Johns Hopkins School of Medicine in 2003, Dr. Glunde has been involved in numerous research studies on cancer metabolism and molecular imaging of cancer as Principal Investigator and Co-Investigator. Throughout this time, she has mentored more than 45 students, post-doctoral fellows, and junior faculty. She has published over 100 publications in the field of cancer metabolism and molecular imaging of cancer. Since 2019, Dr. Glunde is the inaugural director of the AIMS Core at the Johns Hopkins Medical Institutions (JHMI), making available this highly multiplexed, high throughput tissue imaging technology to faculty at Johns Hopkins and outside institutions. She has built a quickly expanding mass spectrometry imaging program, where her team interacts with a diverse group of over 55 users, spanning multiple departments at Johns Hopkins and several institutions nationwide.

Abstract: Reprogramming of molecular and metabolic pathways is a hallmark of cancer, enabling cancer cells to rapidly proliferate, invade, and metastasize. My lab team is investigating such altered key metabolic pathways in cancer, including their specific roles in migration, invasion, and metastasis. An integral part of our methodological approach is matrix-assisted laser desorption/ionization (MALDI) mass spectrometry imaging, as it allows us to spatially map a plethora of different biomolecules in tissue sections of primary tumors and corresponding metastases. MALDI imaging allows for histology-integrated visualization of various classes of biomolecules, including metabolites, lipids, proteins, N-glycans, drugs, and neurotransmitters at microscopic spatial resolution. This presentation will (1) briefly introduce MALDI imaging, (2) showcase examples of innovative MALDI imaging applications in cancer and neuroscience research, and (3) close with a brief discussion of current technology developments in the field.



Peter B. O'Connor, PhD
Professor of Chemistry
Director, Warwick Ion Cyclotron Resonance Laboratory
The University of Warwick

2-Dimensional Mass Spectrometry, a New Tool for Proteomics

Biography: Dr. O'Connor is Professor of Chemistry at The University of Warwick, and the founding Director of the Ion Cyclotron Resonance Laboratory and national FTICR mass spectrometry facility. His expertise and research revolves around advances in mass spectrometry instrumentation, techniques, methods, and applications. The Warwick ICR laboratory has a 15 tesla and 2x 12 tesla FTICR mass spectrometers, a TIMS-TOF, and two other small TOF mass spectrometers. The lab routinely runs LC-MS, LC-MS/MS, and GC-MS experiments and has many fragmentation methods including CID, ExD, IRMPD, and UVPD running routinely. MS^n experiments are possible as well with this instrumentation. This laboratory is available on a collaborative or fee-for-service basis depending on the difficulty of the experiment.

Dr. O'Connor has about 200 publications with an h-index of about 45. He has graduated 22 PhD students and mentored a far larger number of postdoctoral fellows, MSc students, and undergraduates. The general focus is on any type of (bio)chemistry that needs advanced mass spectrometry tools and techniques to solve a problem. Typical, interesting mass spectrometry experiments include complex lipidomics, small molecule metabolite structural analysis, proteomics instrumentation and methods developments, top-down proteomics, post-translational modification

analysis, and more recently native mass spectrometry analysis. Collaborative studies involve analysis of metalloorganic drug binding and structural modifications in proteins, characterization of metal bound proteins in the brain, biofuel characterization, polymeric excipient and drug delivery formulations, glycosylations in the spike protein, lipidomics relevant in placental tissue, etcetera.

Abstract: Proteomics, as it is currently implemented worldwide, primarily uses liquid chromatography (LC) along with tandem mass spectrometry (MS/MS) to identify peptides and proteins as well as to determine higher-order information like population and distributions of post-translational modifications (phosphorylation, deamidation, glycation, glycosylation etc.) and information about folding structures of proteins. Most of these methods generate complex mixtures of closely related molecules, commonly with 10's of thousands of more components in the mixtures. LC, and other chromatography methods like GC, IMS, and CE, are used to simplify that mixture so that the mass spectrometer is not overwhelmed. Furthermore, if too many mixture components are detected at once, or if they happen to overlap closely in m/z space, then the mass spectrometer will struggle to isolate a single component for fragmentation, which is a problem as having multiple precursors prior to fragmentation results in a chimeric spectrum where it is challenging or impossible to determine which particular fragment is from which precursor.

The new technique of 2-dimensional mass spectrometry solves this problem. Borrowing a trick from the NMR community, instead of isolating individual components, it is possible to modulate the ions radially inside the instrument through a fragmentation zone, and correlate fragments to precursors through their modulation frequencies using the Fourier transform. This approach creates large-scale images of all fragments from all mixtures, even in a complex mixture. We will show how to generate these tandem mass spectrometry images for proteins and peptides with a variety of MS/MS techniques.

Nina Ogrinc, PhD

Postdoctoral Researcher at PRISM Laboratory, ULille, France

Robot-Assisted for SpiderMass in vivo real-time topography mass spectrometry imaging

Biography: Nina Ogrinc finished her PhD at the University of Ljubljana, and the Department of Low and Medium energy Physics, at Jozef Stefan Institute, Slovenia. In 2014, she joined the group of Prof. Ron Heeren (M4I) in Maastricht, Netherlands as a postdoctoral researcher. During this time, she was involved in the Marie Curie BRAINPATH consortium and actively engaged in a variety of projects developing and applying new mass spectrometry imaging tools for biomarker discovery (lipids, metabolites, peptides) in neurodegenerative diseases. Since October 2018 she is working at laboratory PRISM (Inserm U1192, University of Lille), on a highly innovative SpiderMass project, an instrument designed for guided surgery and real-time diagnosis in the surgical operating room. She is currently developing a multimodal platform for mass spectrometry and imaging techniques which will enable complex, low cost, rapid, molecular profiling for faster cancer diagnostics and biomarker discovery during surgery. She is also participating in several outreach activities such as the Labroots Webinar on Clinical Uses of Mass Spectrometry and is a mentor for Females in Mass Spectrometry. In the last three years she was also a chair of the Mass Spectrometry Imaging study group of the European Molecular Imaging Society.

Abstract: Surgery is a key approach for treatment and diagnosis of solid tumours. Despite several image guidance techniques and intraoperative assessment, clear surgical margins and debulking efficiency remain scarce. To reduce the risk of re-sections there is an urgent for rapid and sensitive intraoperative imaging tools. The SpiderMass, based on water-assisted laser desorption-ionization (WALDI), is an ambient MS technique which retrieves molecular information directly in-vivo and in real-time. Through robotic assistance, the SpiderMass, has recently paved its way to topographical molecular imaging of biological samples and could provide images of defined areas within the body and help with the precise discrimination of tumour and peritumoral regions. The system was already applied to several biological samples starting with model tissues including beef liver, apple core with seeds and then translated to skin biopsies. The system was further applied inside of the body of the mouse to demonstrate the potential of future in vivo imaging of organs. The first in vivo experiments were performed on a volunteer finger and organs of a mussel. These examples of SpiderMass topographical MSI is a stepping stone into next generation in vivo molecular image guidance during surgery.

Matteo Spinelli, PhD
Assistant Professor of Physiology,
Department of Neuroscience
Università Cattolica del Sacro Cuore, Rome

Neural stem cell-derived extracellular vesicles: a new potential therapeutic approach to counteract cognitive decline

Biography: Dr. Spinelli is an Assistant Professor of Physiology at the Università Cattolica del Sacro Cuore (Department of Neuroscience) in Rome. He got a master's degree in Neurobiology (2012) at Sapienza University of Rome, and he got a PhD in Neuroscience at University Cattolica in Rome (2017). During his PhD, under the supervision of Prof. Claudio Grassi, he investigated the role of metabolic signals in the regulation of brain plasticity focusing on the study of both epigenetic and post-translational mechanisms underlying the impact of nutrients on adult neurogenesis and synaptic functions. During his postdoctoral studies, he discovered the critical role of aberrant protein S-palmitoylation in the brain insulin resistance-dependent impairment of synaptic plasticity, learning and memory. Moreover, he studied the epigenetic mechanisms underlying the transgenerational transmission of maternal insulin resistance- dependent cognitive dysfunction to the next generations. From 2019 to 2020, he also took part to a scientific project in the Prof. Antonella Riccio lab at the University College of London, where he investigated the role of protein S-nitrosylation as novel epigenetic mechanism regulating chromatin remodeling. Recently, his research activity has been focalized on the ability of stem cell-derived exosomes to preserve the neurogenic niche and to counteract the memory deficits in animal models of cognitive decline.

Abstract: Overnutrition and metabolic disorders induce cognitive deficits by affecting both neural stem cell (NSCs) niche and mature neurons. Type 2 diabetes-related cognitive impairment is correlated with decreased adult neurogenesis in the hippocampus due to defective proliferation, differentiation, and cell survival. In physiological conditions, adult NSC release extracellular vesicles (exo-NSC) contributing to intercellular communication and regulating brain cell activity. Recent studies revealed the capability of exo-NSC to improve brain functions and counteract cognitive decline occurring in experimental models of neurological diseases, but the underlying molecular mechanisms are still poorly understood. We investigated the effects of intranasal administration of exo-NSC on brain plasticity in a well-established experimental model of brain insulin resistance (i.e. mice fed with a high fat diet). Our results demonstrated that intranasal administration of exo-NSC was able to deliver the vesicles into the hippocampus of mice restoring the HFD-dependent proliferation/senescence unbalance of the neurogenic niche and preventing HFD-induced memory impairment. Interestingly, exo-NSCs seem to differently modulate intracellular molecular cascades in mature neurons and NSCs. Precisely, exo-NSC prevented the inhibition of BDNF/TrKB/CREB signaling in differentiated neurons, whereas they rescued IRS1/FoxOs-mediated transcription of pro-proliferative genes in NSCs. Collectively, our findings highlight the role of extracellular vesicle cargo in the regulation of brain plasticity and provide evidence of the potential therapeutic effect of these vesicles against metabolic disease-related cognitive deficits.

Paulo Henrique Rosado-de-Castro, MD, PhD
Vice-Chair, Department of Nuclear Medicine, Clementino Fraga Filho University Hospital
Adjunct Professor, Department of Anatomy, Institute of Biomedical Sciences
Federal University of Rio de Janeiro

Stem Cell Imaging

Biography: Dr. Rosado-de-Castro received his MD/PhD from the Federal University of Rio de Janeiro (UFRJ), through the Medical Scientist Training Program. He specialized in Radiology and Diagnostic Imaging at the Federal Hospital of Ipanema and in Nuclear Medicine at the National Institute of Cancer of Brazil. He is currently the Vice-Chair at the Department of Nuclear Medicine, Clementino Fraga Filho University Hospital, and an Adjunct Professor at the Department of Anatomy, Institute of Biomedical Sciences, UFRJ. He is a researcher at the Lab for Experimental Neuropathology and at the National Center for Bioimaging and Structural Biology. Coordinator of the Medical Residency Program in Nuclear Medicine at UFRJ and of the Fellow in Hybrid Imaging and Radionuclide Therapies at the D'Or Institute for Research and Education (IDOR). Permanent Professor at the PhD Program in Medicine (Radiology) at the UFRJ School of

Medicine and at the PhD Program in Medical Sciences at the D'Or Institute for Research and Education. Young Medical Leadership of the National Academy of Medicine of Brazil. Young Scientist of the Carlos Chagas Filho Foundation for Research Support of the State of Rio de Janeiro (2018 and 2022).

Abstract: Cell therapies, originally developed for the treatment of hematologic ailments, are presently being explored in preclinical and clinical studies for different diseases, including of the central nervous system. In this scenario, noninvasive imaging techniques lead to greater comprehension of these therapies, including by evaluating the distribution, safety and efficacy of the cells. Our group has used techniques such as SPECT, CT and MRI in clinical studies of cell therapies for ischemic stroke and in preclinical models of ischemic and hemorrhagic stroke, global brain ischemia, Huntington's disease, amyotrophic lateral sclerosis and optic nerve diseases. The presentation will focus on the results of some of these studies, and also in the future possibilities for research.

Syed Shadab Raza, PhD
Associate Professor of Biotechnology
Era's Lucknow Medical College and Hospital
Era University, Lucknow

Overcoming the hurdles of stem cell homing and survival in a stressful environment: Implications for neurotransplantations

Biography: Dr. Raza is an Associate Professor and the Head of the Stem Cells and Regenerative Medicine programme at Era's Lucknow Medical College and Hospital, Era University, Lucknow, India. Additionally, he serves as the Assistant Dean of the Faculty of Basic Medical Sciences at Era University. He is the PI of the Laboratory for Stem Cell Biology and Regenerative Medicine, where he directs a multidisciplinary team specialized in stem cell therapy for neurodegenerative disorders, especially ischemic stroke. Specifically, he is interested in exploring the fate of stem cells in an ischemic microenvironment. He has received various prestigious awards and honours for his contributions in the fields of neuroscience and regenerative medicine, notably, the International Brain Research Organization Fellowship, the Japan Neuroscience Society Award, the Indian Academy of Biomedical Sciences Neuroscience Award, and the IBRO-APRC Fellowship, to name a few. He has the honour of being an elected member of three of India's four science academies, like the National Academy of Science India, the National Academy of Medical Sciences, and the Indian Science Congress Association. His recent work has been published in prestigious scientific journals such as Stem Cells, Stem Cell Research and Therapy, Stem Cell Reviews and Reports, Chemical Engineering Journal, etc.

Abstract: Stem cell therapy is at the forefront of the treatment of ischemic stroke. However, until now, it has largely failed at the clinics. The two most important reasons for the failure are: i). the lack of target homing; and ii). the low survival of the transplanted cells. To find a solution for an effective stem cell therapy, it is imperative to understand the migration, behavior, and function of these cells. Thus far, no *in* ovo model has been reported for studying the ischemia-reperfusion (I/R) and stem cell homing mechanisms. In this context, we created a model of I/R by occluding and releasing the right vitelline artery of a 3-day old developing chick embryo to study the mechanism beneath the homing of the transplanted cells. While on the issue of cell survival after transplantation in the stroke brain, we investigate the impact of oxidative and inflammatory stress, which is typically present in ischemically challenged tissue, on human stem cells. We employ oxygen-glucose deprivation to induce oxidative and inflammatory stress in stem cells in vitro, while the middle cerebral artery occlusion method is employed to understand the migratory and functional behaviour of endogenous as well as exogenous stem cells in ischemic brains. Overall, our findings contribute to developing strategies to minimize therapeutic stem cell loss under ischemic stress. This presentation will lead to a better understanding of post-transplantation stem cell homing and survival strategies, along with the pathways involved.

Kendell Pawelec, PhD
Assistant Professor
Michigan State University, Lansing, USA

Using nanoparticle contrast agents for long-term monitoring of neural implants

Biography: Dr. Pawelec trained as a materials scientist engineer and is an Assistant Professor at Michigan State University, in the Radiology department. A major focus of her research is on the interface between biology and materials, including understanding how materials properties can be utilized to direct fundamental cellular responses and characterizing novel materials for medical devices. She also has a strong interest on clinical translation, including the scalability and manufacturability of devices that promote tissue regeneration.

Abstract: Implantable medical devices for nerve repair, produced from polymeric materials, have gained widespread clinical use. However, after implantation, it remains difficult to evaluate the devices for proper positioning and to determine subsequent device damage. Thus, radiologists often cannot diagnose device failure before catastrophic consequences to the patient occur. Incorporation of nanoparticle contrast agents allow radiologists to successfully monitor devices over time. For radiopaque nanoparticles (tantalum oxide, TaOx), the addition of contrast agents into a polymer matrix modifies the mechanical properties of the substrate and significantly impacts the biological response of glia cultured on the surface, including attachment and protein marker expression. The features of biomedical devices that can be tracked over time are dependent on the amount of contrast agent incorporated. At 5wt%, overall dimensions of a porous biomedical implant can be tracked, but no information is available on fine features like wall thickness. An upper range of 20wt% TaOx was defined, as this allowed for significantly higher x-ray intensity above background, without detrimental effects on tissue repair. This highlights the need to balance imaging, materials properties and biological response when designing implants for long-term monitoring.

Ruman Rahman, PhD
Associate Professor of Molecular Neuro-Oncology
School of Medicine, University of Nottingham

Polymer-based neurosurgically-applied interstitial drug delivery for malignant glioma

Biography: After graduating with a BSc in Genetics from the University of Edinburgh, Dr. Ruman Rahman completed a PhD in Molecular Biology at the Roslin Institute, University of Edinburgh. He joined the Children's Brain Tumour Research Centre, University of Nottingham, as a Post-Doctoral Research Associate in 2007. After receiving the Nottingham Advanced Research Fellowship for the Faculty of Medicine in 2011, Dr. Rahman was appointed Assistant Professor in October 2013 and awarded the British Neuro-Oncology Society Young Investigator of the Year in 2014. He is currently an Associate Professor of Molecular Neuro-Oncology at the University of Nottingham's new flagship Biodiscovery Institute.

His research team focuses on intra-tumour genomic heterogeneity and interstitial drug delivery for childhood and adult brain cancers, with a particular emphasis on infiltrative disease, with a grant portfolio of £4.5M over the past 5 years. His affiliation to professional bodies includes membership on the Grant Evaluation Committee for the French National Institute of Health and Medical Research (INSERM) and Society for Neuro-Oncology Conference Scientific Review Committee. Ruman is Chair of the international Children's Brain Tumour Drug Delivery Consortium which spans leading institutions across Europe and North America, and co-Chair of the British Neuro-Oncology Society Research Subcommittee.

Abstract: Surgical resection is the mainstay standard-of-care for isocitrate dehydrogenase wild-type glioblastoma; yet despite removal of macroscopically visible tumour followed by adjuvant chemo- and radiotherapy, tumour recurrence manifesting from residual disease has resulted in a persistent median survival of 15 months.

We have developed a localised interstitial drug delivery system using polymer microparticles made from poly(*DL*-lactic-co-glycolic acid) (PLGA) and poly(ethylene glycol) (PEG). PLGA/PEG loaded with chemotherapeutics forms a paste at room temperature upon mixing with saline and only sinters at body temperature, retaining close apposition to the surgical resection cavity lining. Combined delivery of Temozolomide and Etoposide via PLGA/PEG confers a

long-term survival benefit associated with disease-free brain in an orthotopic high-grade glioma model, and delivery of Olaparib sensitises orthotopic tumours to radiotherapy, similarly conferring a significant survival advantage. As a direct corollary, we have recently developed methodology to detect and discriminate combinations of label-free chemotherapeutic compounds which have penetrated brain parenchyma, using 3D-orbitrap secondary ion mass spectrometry (3D-orbiSIMS). Our work encourages the neuro-oncology community to consider mass spectrometry imaging modalities to complement *in vivo* efficacy studies, as an analytical tool to assess brain distribution of systemically administered drugs, or localised brain penetration of drugs released from micro- or nano-scale biomaterials.

Neil R. Thomas
Professor of Medicinal & Biological Chemistry
The Biodiscovery Institute
School of Chemistry
University of Nottingham, University Park, Nottingham, NG7 2RD, UK

Protein Nanocage-Based Theranostics and Drug Delivery

Biography: Professor Thomas is Head of the Biological Chemistry Theme (Division) in the School of Chemistry and Deputy Director of the Biodiscovery Institute (housing 800+ researchers from 5 Schools) at the University of Nottingham (UoN). He has a BSc(Hons) Chemistry 1st Class from the University of Southampton (1987) and a PhD in mechanistic enzymology with Prof. David Gani also at Southampton, with the final stages being completed at the University of St Andrews (1990). He then held a NATO/SERC postdoctoral fellowship at The Pennsylvania State University in the laboratory of Prof. Steve Benkovic (1990-92) before taking up a Royal Society University Research Fellowship and proleptic lectureship at the University of Bath (1992-95). He transferred the RS URF to Nottingham in 1995 and has subsequently been promoted to Associate (2003) and Full Professor (2008). He has undertaken several sabbaticals at the Molecular Foundry, Berkeley Lab. His current research is focused on the development of new peptide and protein-based drug delivery vehicles and imaging agents for use against cancer and bacterial infections as well as developing new spider silk derived materials for regenerative medicine applications. He has served on several Royal Society, Royal Society of Chemistry and BBSRC committees.

Abstract: Nanoparticles are increasingly being used as drug carriers, for imaging and combining both roles as theranostics. A multidisciplinary team at Nottingham has focused on harnessing and modifying the natural properties of the ubiquitous protein nanocage, apoferritin for use in targeted anticancer drug delivery. Apoferritin is composed of 24 subunits that self-assemble into a 12 nm diameter spherical capsule. Apoferritin's biochemical function is to safely store iron ions and to release these as required. Consequently, it transits cells using the transferrin receptor (Trf1) and once in the endosome releases iron ions (~pH 5.6) and then disassembles (<pH 4) in the late endosome/lysosome. We have exploited horse spleen and human forms of apoferritin to deliver near-infrared fluorescent PbS quantum dots and MRI active Mn(II) nanoparticles into cells for imaging. We have also encapsulated anticancer drugs such as gefitinib, temozolomide and some benzothiazoles (up to 500 drugs per capsule) and determined their activity on breast cancer and glioma cells. Through protein engineering of the exterior of the apoferritin nanocage, we have redirected the apoferritin nanocage to target other biomarkers such as EGFR and HER2 that are expressed at elevated levels on some cancer cell surfaces. Data on these studies will be presented.

Anna Jablonska, PhD
Assistant Professor
Diagnostic Radiology and Nuclear Medicine
University of Maryland, Baltimore

Radiolabeling of biological drugs.

Biography: Dr. Anna Jablonska is an Assistant Professor in the Department of Diagnostic Radiology and Nuclear Medicine at the University of Maryland, Baltimore. She joined the UMB in 2020 as a part of Program in Image Guided Neurointerventions (PIGN), which provides a platform to exploit the synergies of therapeutic agents, neurointerventions and rapidly evolving imaging capabilities. As a part of this program

Dr. Jablonska focuses on radiolabeling of therapeutics agents to help combat the challenge of drug targeting, particularly in disorders of the CNS.

Abstract: Imaging plays a very important role in the progress of the drug development and delivery field. Multiple studies and clinical trials showed that effectiveness of drug can be strongly compromised unless it is delivered to its site of action at a dosage needed for maximize therapeutic effects. This is especially visible in attempts of delivering treatment into the brain. Because of its excellent sensitivity and quantitative images PET is highly feasible for imaging of drug delivery and pharmacokinetics and allows to answer the important questions of "Where is it going, is it reaching the target, how long it stays there and how is it cleared?". Part of the focus of our group is the optimize radiolabeling of the multiple therapeutic agents, including cells, EVs, antibodies and LNPs with protecting their activity and function. Our selection of 89Zr with half-life of 78h as prefer radionuclides allows for imaging of delivered drug not only during the intervention but also longitudinally, what is essential to guide the administration of therapeutics to the brain.

Wojciech Lesniak, Ph.D.
Instructor and Director of Radiometabolite Laboratory
Department of Radiology, Division of Nuclear Medicine and Molecular Imaging
Johns Hopkins School of Medicine

Radiosynthesis PET tracers and their application in imaging of neurogenerative disorders

Biography: Dr. Wojciech Lesniak earned a M.Sc. in Chemistry (1997) and a Ph.D. in Bioinorganic Biomedical Chemistry (2001) at the University of Wroclaw (Wroclaw, Poland). Afterwards, Dr. Lesniak completed post-doctoral training at the University of Michigan in the Department of Chemistry and the Center of Nanotechnology for Medicine (2004). He then worked as an Oncology Instructor at the Roswell Park Cancer Institute (2005-2010) and a Research Associate at the Wayne State University (2010-2011). Since 2012, he has been working at the Johns Hopkins School Medicine a in the Department of Radiology. Currently, he holds position of an instructor and director of the radio-metabolite laboratory at the Johns Hopkins School Medicine. His research focuses on development and evaluation of variety of agents for numerous biomedical applications, mainly targeted cancer imaging and therapy. He authored number of peer-rewired scientific papers, book chapter and a few patents.

Abstract: Positron imaging tomography (PET) is increasingly utilized in clinical trials of neurological disorders due to recent advance in radiochemistry. Various radionuclides including 18F, 11C, 15O, 13N, 124I, 68Ga and 64Cu are used for radiolabeling of different chemical scaffolds. Among them 18F, 11C are the most frequently utilized owing to their short half-life time and energy window. Radiotracers for PET imaging of amyloid β and tau tangles have revolutionized clinical trials in Alzheimer's disease permitting longitudinal imaging in patients. Efforts are underway to develop radiotracers for other targets. Here, we present synthesis of PET radiotracers for imaging of α7-nicotinic cholinergic receptor, α4β2 nicotinic acetylcholine receptor, soluble epoxide hydrolase and macrophage colony-stimulating factor 1 receptor (CSF1R) that are associated with wide range of neurogenerative disorders. Detailed initial PET imaging evaluation of [11C)]CPPC radiotracer for CSF1R associated with activated microglia cells will also be presented.

Jesús Ruiz-Cabello, PhD
Ikerbasque Research Professor
Deputy Director of Research of the Spanish Network of Pulmonary Research
Research Center in biomaterials, CIC biomaGUNE
San Sebastian, Spain

Nanotechnology for drug delivery to the brain

Biography: Dr. Ruiz-Cabello is an Ikerbasque Research Professor at the Center for Cooperative Research in Biomaterials, CIC biomaGUNE, in San Sebastián, where he leads the Molecular and Functional biomarker group and is the coordinator of the molecular imaging resources of the center, including MRI, nuclear imaging, radiochemistry, and animal services. He is deputy director of the Spanish lung disease research network and has been head of the Advanced Imaging Unit of the Spanish Center for Cardiovascular Research (CNIC). Since this period at CNIC, his line of research has mainly focused on pulmonary and systemic vascular diseases such as pulmonary hypertension and arteriosclerosis. His laboratory combines molecular biology, nanotechnology, and multimodal and multiscale imaging approaches to investigate and visualize molecular events that influence the

development of these pathologies, such as the discovery of diagnostic biomarkers and therapeutic monitoring. Imaging technologies used in Dr. Ruiz-Cabello's lab include magnetic resonance imaging, positron emission imaging, and optical and fluorescence imaging. Since he joined the CIC biomaGUNE faculty in 2018, Dr. Ruiz-Cabello has also started developing new molecular tracers for PET imaging. He has mentored 35 Ph.D. students, postdocs, and young professors throughout this time. He has published over 200 publications in different fields, mainly using different imaging approaches and techniques. He was a founder of a technology-based company that is still active and pioneered the use and control of gases for pulmonary respiration imaging. After joining CIC biomaGUNE, I have initiated collaborations in other fields (mainly cancer, aging, and brain) with researchers from different institutions.

Abstract: Imaging techniques are ideal for diagnosing almost all pathologies and organs early. Still, they also serve to monitor the target of a given treatment directly and to measure the efficiency of a given therapy. Nanotechnology is a perfect complement to this mission because it introduces novel formulations that increase efficiency, diminish the toxicity of treatments, or as a simple accompaniment to provide the necessary image signal for said purpose. Different biocompatible nanomaterials have been used or can be used for imaging applications. Within the wide range of possibilities, in this presentation, we will limit to two widely used in imaging, such as lipid nanoparticles and those based on iron oxide. The essential aspects we have introduced over the last few years will also be highlighted, such as the possibility of making rapid and efficient modifications to improve its function and targetability and the scalability of its production for possible clinical applications. Finally, results in collaboration with two of these nanosystems will be presented for their potential application in the brain through MRI or PET-guided imaging.

Erik M. Shapiro, PhD
Professor of Radiology, Physiology, Biomedical Engineering, and Chemical Engineering & Material Science
Associate Chair, Department of Radiology and Division Director, Biomedical Imaging
Michigan State University

Simultaneous PET/MRI with orthogonal and parallel PET/MRI contrast agents

Biography: Dr. Shapiro is currently Professor of Radiology, Physiology, Biomedical Engineering and Chemical Engineering at Michigan State University. He also serves as Associate Chair for Research for the Radiology Department and Division Director for Biomedical Imaging in the MSU Institute for Quantitative Health Sciences and Engineering (IQ). Over the course of a >15-year academic career, Dr. Shapiro has made innovative and impactful advancements in multi-modal molecular imaging. In MRI, Dr. Shapiro pioneered methods for in vivo single cell detection, a feat for which he was awarded an NIH Director's New Innovator Award. In CT, Dr. Shapiro has led important efforts to visualize biomaterial implants by doping with radiopaque materials. In PET, Dr. Shapiro is now pioneering the concept of multimodal paired PET/MRI agents to probe orthogonal and parallel modes of experimental imaging investigations.

Abstract: PET/MRI is a maturing imaging discipline capable of either sequentially or simultaneously acquiring both PET and MRI of the same subject with near perfect anatomical and temporal registration. While PET/MRI typically performs 'molecular imaging' by PET with MRI anatomy, PET/MRI is fully capable of performing simultaneous molecular imaging in both modalities. We characterize orthogonal PET/MRI as simultaneously delivering two molecular imaging agents – 1 for PET and 1 for MRI (think 18F-FDG for PET and Gd-based agents for MRI) and interrogating cancer physiology and metabolism from two different angles or approaches. We characterize parallel PET/MRI as two contrast agents, at least one in each modality, that are essentially the same molecule, and act on the same target or perform same action, except the two molecules harbor different imaging moieties (think Gd-EOB-DTPA for MRI, 86Y-EOB-DTPA for PET to measure liver function or OATP reporter gene). Parallel PET/MRI yields complementary imaging information about a single biological phenomenon, and the combined use solves a deficiency in the other imaging modality. Examples in each paradigm will be discussed.

Johannes Boltze, MD, PhD
Professor of Neuroscience
The University of Warwick

Interindividual differences in infarct kinetics and acute penumbera protection

Biography: Dr. Boltze has been trained as physician and neurobiologist, holding doctoral degrees in both disciplines. He is currently a Full Professor of Neuroscience and Director of Biomedical Science degree stream at the School of Life Sciences, University of Warwick, United Kingdom. His research is focused on cerebrovascular diseases such as stroke and cerebral small vessel disease with cognitive decline. Dr. Boltze's group is particularly interested in translational research, for instance the impact of frequent comorbidities such as hypertension on disease progress, severity, and the impact of established as well as novel therapeutics. Current research activities comprise acute metabolic support as an option for transient neuroprotection helping to keep the time window for recanalization open for a longer time, as well as translational work using large animal stroke models.
Dr. Boltze has published more than 170 peer-reviewed scientific articles and book chapters he also listed as an inventor on 7 patents (h-factor of 45, >7100 citations; Google Scholar). He serves as the Co-Editor in Chief for the newly founded journal Neuroprotection and is an Associate Editor for Basic and Translational Science in Stroke. He also serves on editorial boards of several leading journals in his field including CNS Neuroscience & Therapeutics, JCBFM, and Translational Stroke research. Next to his engagement in SIGN, Dr. Boltze is also the president of the International Symposium on Neuroprotection & Neurorepair.
Abstract: Mechanical recanalization procedures have revolutionized acute stroke therapy. I patients presenting with a penumbra, time recanalization clearly improves functional outcome. However, the number of patients benefitting from recanalization remains limited for tow major reasons. First, in patients with cerebral collateralization, the penumbra is short-lived and may not be present anymore once the patients reach a hospital capable of performing recanalization. Second, the time patients require to reach these hospitals is still too long even for many patients who exhibit an initially sufficient cerebral collateralization. A potential solution for both problems would be a protocol for acute penumbra protection extending the time window for recanalization.
The inter-individual differences in cerebral collateralization are not well mimicked by current inbred rodent models of ischemic stroke with recanalization such as the filament model. We therefore investigated stroke evolution in an outbred canine model of ischemic stroke. We found that animals can be allocated to two groups, i.e., fast and slow progressors. In the latter, infarct maturation takes significantly longer (4.5+ h), well mimicking the situation observed in human stroke patients. Second, an artificial protein with massively increase oxygen binding capacity and specifically releasing oxygen in hypoxic tissues was tested for its potential to temporally preserve the penumbra. The study confirmed substantial inter-individual differences in infarct growth, again well resembling the situation in human patients. The experimental intervention was able to slow infarct evolution in slow but not fast progressors with overall modest effects.
Overall results were encouraging and may validate further refinement of the approach, but effect sizes observed were relatively small and much closer to what is routinely observed in human clinical trials staying behind of what is usually observed in rodent models. This may, however, indicate a high translational value of large animal stroke models in late stage-experimental research.

Berta Puig, PhD
Associate Professor (PD) of Experimental Neurology
University Medical Center Hamburg-Eppendorf (UKE)

Extracellular Vesicles in Ischemic Stroke

Biography: Dr. Berta Puig is a principal investigator in the 'Experimental Research in Stroke and Inflammation' (ERSI) lab, Neurology Department at the University Medical Center Eppendorf (UKE) in Hamburg, Germany. For her work on neurodegenerative diseases, she earned her Ph.D. in Neuroscience with the highest honors in 2003 at the University of Barcelona where she continued as a postdoctoral researcher. In 2008 she moved to the Institute of Neuropathology at the UKE in Hamburg, focussing on prion biology and prion diseases. Since 2016 she is a group leader working in the ERSI lab (led by Prof. Magnus) at the Neurology Department and since then, her main focus is on the EVs in brain tissue. She has a strong background in cell and molecular biology and a publication record with numerous studies related to

neurodegeneration, signaling cascades, and extracellular vesicles in neurological disorders, leading to over 60 peer-reviewed publications in internationally renowned journals. She has also mentored several BSc, MSc, MD, and Ph.D. students and is a member of the Editorial Board of the 'Journal of Extracellular Vesicles' (JEV) and other life science journals.

Abstract: In the last 25 years, extracellular vesicles (EVs), which are membrane-enclosed particles released by nearly all types of cells, have evolved from being considered trash bags to important messengers in intercellular communication, potentially reliable markers of (brain) diseases, and promising drug delivery tools. In our lab, we are investigating their role in the pathophysiology of stroke by directly isolating EVs from brain tissue of a mouse model of stroke (transient Middle Cerebral Artery Occlusion, tMCAO). By using proteomic and transcriptomic approaches we could assess that the protein and mRNA content of EVs is changing at different time points after stroke. Likewise, the EV release by different brain cells, especially astrocytes and microglia, is altered upon stroke, indicating differential temporal regulation. We are also currently investigating mechanisms of neuronal rescue by EVs loaded with therapeutic compounds.

Francisco Pan-Montojo, MD, PhD
Neurologist
Leader of a Clinician Scientist Group at the University Hospital LMU

Treating brain ischemia mimicking worm survival strategies

Biography: Dr. Francisco Pan-Montojo is a Leader of a Clinician Scientist at the Psychiatry and Psychotherapy Department from the LMU University Hospital combining his work as clinician with basic research in his lab. Dr. Pan-Montojo´s research focuses on the pathophysiology of neurological diseases, especially Parkinson´s disease (PD), and the development of neuroprotective drug candidates. As a Clinician Scientist Group focused on translational research, his lab combines the use of a broad spectrum of techniques ranging from in vitro approaches such as: neuronal culture models of several neurological diseases or microscopy-based calcium imaging, molecular biology to several in vivo C. elegans and mouse models for neurological diseases such as ALS, PD or psychiatric diseases such as PTSD and depression or experimental treatment on patients. Since joining the LMU University Hospital in 2014, Dr. Pan-Montojo has been involved in numerous studies on PD, ALS and stroke as Principal Investigator and Co-Investigator.

Abstract: Stroke is the second leading cause of death and disability worldwide. Current treatments, such as pharmacological thrombolysis or mechanical thrombectomy, reopen occluded arteries but do not protect against ischemia-induced damage that occurs before reperfusion or neuronal damage induced by ischemia/reperfusion. It has been shown that disrupting the conversion of glyoxal to glycolic acid (GA) results in a decreased tolerance to anhydrobiosis in Caenorhabditis elegans dauer larva and that GA itself can rescue this phenotype. During the process of desiccation/rehydration, a metabolic stop/start similar to the one observed during ischemia/reperfusion occurs. In this study, the protective effect of GA is tested in different ischemia models, i.e., in commonly used stroke models in mice and swine. The results show that GA, given during reperfusion, strongly protects against ischemic damage and improves functional outcome. Evidence that GA exerts its effect by counteracting the glutamate-dependent increase in intracellular calcium during excitotoxicity is provided. These results suggest that GA treatment has the potential to reduce mortality and disability in stroke patients.

Abass Alavi, M.D., Ph.D. (Hon), D.Sc. (Hon),
Professor of Radiology and Neurology, Pearlman School of Medicine, University of Pennsylvania

Unique and Unparalleled Impact of Modern Imaging Techniques on Research and Day to Day Practice of Medicine

Biography: Dr. Abass Alavi is a Professor of Radiology and Associate Director at the Institute on Aging at the University of Pennsylvania Perelman School of Medicine. Dr. Alavi is recognized as a pioneer in molecular and nuclear imaging, having contributed to the development of positron emission tomography (PET), in particular utilizing the radiotracer 18F fluorodeoxyglucose (FDG) in PET imaging, and later using 18F-FDG-PET in conjunction with computed tomography (CT) and magnetic resonance imaging (MRI) to understand diseases. Working under the guidance of Dr. David Kuhl, Dr. Alavi and colleagues were pioneers in performing modern tomographic imaging by utilizing single gamma emitting radionuclides--single photon emission computer tomography (SPECT). Dr. Alavi received his medical degree from University of Tehran School of Medicine in 1964. He did his post-graduate training as an intern (1966-1967) and first year resident (1967-1968) at Albert Einstein Medical Center in Philadelphia, a second year residency in medicine (1968-1969) at Veterans Administration Hospital in Philadelphia, a fellowship in hematology (1969-1970) at the Hospital of the University of Pennsylvania, a residency in radiology (1970-1971) at Beth Israel Hospital in Boston, and a fellowship in nuclear medicine (1971-1973) at the Hospital of the University of Pennsylvania.
Dr. Alavi's over 1,500 journal articles have been cited over 75,000 times according to Google Scholar and he has received numerous awards, including the Georg Charles de Hevesy Nuclear Pioneer Award in 2004 and the Benedict Cassen Prize for Research in Nuclear Medicine of Society of Nuclear Medicine and Molecular Imaging (SNMMI) in 2012.

Abstract: The introduction of X-Ray by Roentgen in 1895 started a major revolution in medicine and still continues to have an impact on its current practice on a daily basis. However, no major, physics-based invention was initiated until the 1960s when David Kuhl at the University of Pennsylvania (Penn) introduced the concept of tomography as we know today. He and his colleagues were first to design an instrument that allowed radiation-based imaging of brain tumors by a technique that was called "emission tomography" at the time. The invention of Computed Tomography (CT) by Hounsfield in 1971 added a major dimension to modern imaging armamentarium. While prototype CT imaging was somewhat complicated and limited in scope, over the past 5 decades, this very powerful imaging modality has matured significantly and is nowadays the workhorse of clinical practice of medicine. The introduction of the concept of MRI in 1970s by Lauterbur added a major dimension to medical imaging and its role in complicated diseases and disorders.
Initial applications of emission tomography were primarily focused on assessing blood-brain barrier abnormalities by conventional radiotracers. However, the significant superiority of contrast enhanced CT over emission tomography propelled investigators at Penn to introduce the concept of assessing brain glucose metabolism by radiolabeled deoxyglucose. Efforts at Penn soon led to synthesizing 18F-Fluorodeoxyglucose (FDG) and the first human studies were performed in August 1976. The success of this effort was a major stimulus to mobilizing forces for practical applications of positron emitting radiopharmaceuticals for both research and clinical purposes. Investigators at Washington University, led by Michael Ter-Pegossian, designed and built prototype positron emission tomography (PET) instruments that further enhanced the role of the modality in many settings. Over the years, significant advances have been made in designing CT, MRI, and PET imaging which has improved practical applications of such instruments. In 2000, the first hybrid PET/CT instrument was introduced by investigators at the University of Pittsburgh, and this allowed combining molecular images acquired by PET with those of CT. During the past 10 years, PET/MRI instruments have further enhanced our ability to combine the advantages of these two powerful modalities as a single powerful unit.
During the past several years, investigators at University of California, Davis and United Imaging in Shanghai have designed and built total body PET/CT instruments for simultaneous imaging of the entire body with a single acquisition. Similar approaches have been adopted by investigates at Penn, the University of Kraków, and Siemens which is further enhancing the role of this approach worldwide. Over the past few decades, molecular imaging with PET has made a major impact in many domains in medicine. While initial interests were focused on brain imaging

because of the limitations of available instruments during the early years of PET technology, the introduction of body imaging has expanded interests into imaging various malignancies, cardiovascular disorders, and many infectious/inflammatory diseases. The application of PET to the day-to-day practice of medicine has substantially improved patient care in many disciplines including neurology, oncology, orthopedics, and other disorders of mankind.

Raphael Guzman, MD
Professor of Neurosurgery and Neurosciences
Chair Dept. of Neurosurgery
University Hospital Basel
Switzerland

Intraoperative Imaging in Neurosurgery

Biography: Prof. Raphael Guzman is a Professor of Neurosurgery and Neurosciences at the University Hospital of Basel in Switzerland and Chair of the Department of Neurosurgery. After residency in neurosurgery at the University Hospital in Bern, Switzerland he completed a postdoctoral research fellowship, a cerebrovascular fellowship and a pediatric neurosurgery fellowship at Stanford University. After five years as an Assistant Professor of neurosurgery at Stanford he was elected Vice-Chair of the Department of Neurosurgery at the University Hospital in Basel and in 2021 elected to the Co-Chair position. Within the Department of Biomedicine, he is a principal investigator in a research group on brain ischemia and regeneration. Dr Guzman's research for the past 20 years has been in the area of regenerative medicine with a focus on stroke and spinal cord injury. He is interested in image guided delivery of stem cells in brain ischemia. Currently his lab investigates the role of neuroinflammation and its effect on endogenous neurogenesis after ischemic brain injury. His clinical research is investigating intraoperative imaging and the use of virtual reality in surgical planning.

Abstract: Intraoperative imaging in neurosurgery has become more ubiquitous over the past decade including intraoperative computed tomography (CT), magnetic resonance imaging (MRI), Ultrasound (US) and cerebral digital subtraction angiography (DSA). In addition, surgical microscopy has advanced from mere optical imaging to digital augmented reality using fluorescent dyes to image malignant brain tumors and cerebrovascular pathologies. In this lecture we will discuss the evidence of benefit for patient's outcome behind these imaging technologies. We will also review some current trials using intraoperative imaging.

Michael Lim, MD, PhD
Professor
Chair of Neurosurgery Department
Stanford University, USA

Immunotherapy for Brain Tumors

Biography: Dr. Michael Lim is a Professor and Chair of Neurosurgery at Stanford University. Dr. Lim obtained his MD from the Johns Hopkins University School of Medicine. He then completed his residency in Neurosurgery at Stanford University Hospital and went on to become a Professor of Neurosurgery, Oncology and Radiation Oncology at Johns Hopkins before returning to Stanford as Chair. Dr. Lim's surgical interest is in both benign and malignant brain tumors, with a particular interest in gliomas (including ependymoma), meningioma, pituitary tumors and skull base tumors. He has extensive experience in new and innovative neurosurgical techniques including image guided surgery, microsurgery, minimally invasive procedures and endoscopic surgery. Dr. Lim's primary research interest is developing immune-based therapies against brain tumors. His research laboratory is focused on understanding the mechanisms of immune evasion by primary brain tumors. Findings from his laboratory are directed towards translation to novel therapies against brain tumors. In addition to running a laboratory, he currently serves as the principal investigator of several large brain tumor immunotherapy clinical trials based on findings from his laboratory.

Abstract: Despite success in improving survival for patients with systemic cancers with immunotherapy, results have thus far been disappointing for GBM. Resistance mechanisms include global immunosuppression, suppressive myeloid cells, and exhausted immune cells. Surveillance of multiple T-cell populations in GBM has shown that exhausted immune cells are very common. We will discuss mechanisms of exhaustion, questions on where exhaustion occurs, and if exhaustion of immune cells is permanent.

Graeme Woodworth, MD, PhD
University of Maryland, Baltimore

MRI-guided Focused Ultrasound and the coming era of Neurosonics in Neurosurgery

Biography: Graeme Woodworth, MD, FACS is Professor and Chair of the Department of Neurosurgery at the University of Maryland School of Medicine. He also serves as the Director of the Brain Tumor Program and the Translational Therapeutics Research Group in the Greenebaum Comprehensive Cancer Center at the University of Maryland. Dr. Woodworth completed medical school and neurosurgical residency training at Johns Hopkins. He also completed fellowships in cancer nanomedicine at Johns Hopkins and cranial endoscopy at Cornell with Dr. Ted Schwartz. His clinical subspecialty areas of interest are Neurosurgical Oncology and Skull base and Stereotactic surgery. Dr. Woodworth's research focuses on developing new therapeutic strategies to improve the treatments and outcomes for patients with malignant brain tumors. These efforts include (1) leveraging the diverse interstitial effects of transcranial focused ultrasound and hyperthermia, (2) developing advanced nano-therapeutics to improve treatment efficacy, and (3) expanding the suite of patient-derived and genetically engineered models of human brain tumors to improve predictive therapeutic testing. A core component of the research has been centered on the concept of using the operating room as a portal for discovery and opportunity to improve our understanding of and therapeutic delivery to brain cancers. Dr. Woodworth's team is leading the first-in-human clinical trials of MRI-guided focused ultrasound (FUS) and Laser Interstitial Thermal Therapy (LITT) combined with radiation in the United States. Dr. Woodworth will provide insights into the emerging role and impact of image-guided focused ultrasound in neurosurgery.

Abstract: MRI guided focused ultrasound is emerging as a clinical tool for multiple brain diseases. The work described in this presentation will review current uses of transcranial image guided focused ultrasound as well as ongoing clinical trials and future uses. Specifically, the work related to microbubble-enhanced focused ultrasound for blood brain barrier opening currently ongoing at the University of Maryland will be discussed.

Teresa Gasull, PhD
Neuroscience Senior Researcher at Germans Trias i Pujol Research Institute (IGTP)
Leader of the Cellular & Molecular Neurobiology (CMN) Research Group - Barcelona Bio Hub

Neurointerventionism to overcome old barriers to model stroke in swine

Biography: Dr. Gasull holds a Master degree in Neuroscience and a PhD in Biology. She was appointed a Ramón y Cajal position at the CSIC, and since 2006 she leads the Cellular and Molecular Neurobiology (CMN) Research Group at the Germans Trias i Pujol Research Institute. Her research aims at the study of stroke with a strong translational focus to generate scientific knowledge of neurovascular disorders, cerebral iron dysregulation in stroke, and multimodal imaging of the pathophysiological hallmarks of the ischemic or hemorrhagic stroke. The research done at the CMN research group using proofs-of-concept in in vivo preclinical models of stroke has been applied to the development of healthcare innovations in the fields of therapy, biomarkers of stratification, classification and prediction, and machine/deep learning neurobehavioral assessment. Dr. Gasull is a member of the Spanish Thematic Network of Stroke Research RICORS STROKE, which has more than 100 associated scientists, and of the AGAUR group of Research in Neurosciences of the IGTP, she has been awarded with innovation programs Bioemprendedor XXI and CaixaImpulse and has received funding as PI for 13 competitive research projects and agreements with companies in the pharmaceutical/biotechnology field. She has published 40 articles and is author of 2 patents in the field of stroke. She is member and reviewer for the Society for Redox Biology & Medicine, Topic Editor for Cells, Guest Editor for IJMS, member of the monitoring committee of the doctoral program in Neurosciences at the Institut de Neurociències of the UAB, and member of the external commitee of the IGTP/HGTP Biobanc and of the Gender Dimension in Research Working Group of IGTP.

Abstract: The still insufficient advances in the management/treatment options for ischemic stroke patients recommend that upcoming preclinical research used animals with more human-like brain characteristics. The swine brain is considered appropriate although the presence of the rete mirabile (RM) prevents direct catheterization of the intracranial arteries to produce focal cerebral ischemia. To overcome this barrier we have used a catheter+guide navigated up to the RM entry and the pressure cooker technique to deposit Squid-12 embolization material to fill,

overflow and occlude the left RM, the left internal carotid artery and left circle of Willis wing up to the middle cerebral arteries' (MCAs) origins. This occlusion mimics that produced in the filament model in rodents, probably the most used model in preclinical stroke studies. The technique successfully occluded up to the MCAs origins as stated with a multimodal MRI scanning study, and induced early damage 90 min post-occlusion that later evolved to a large cerebral infarction with no mortality during the intervention. This minimally invasive ischemic stroke model in swine is reproducible and shows translational features, including changes in blood biomarkers previously reported in human stroke.

Franklin D. West
Professor of Regenerative Biosciences
Regenerative Bioscience Center
University of Georgia, USA

Magnetic Resonance Imaging to Evaluate Therapeutics in Porcine Stroke and Traumatic Brain Injury Models.

Biography: Dr. Franklin West is a leading expert in stem cell biology with a focus on stem cell reprogramming and stem cell therapies for neural injury and diseases including stroke and traumatic brain injury. He was named one of the nation's top scholars under 40 by Georgia Trends and Diverse: Issues in Higher Education magazines and has been featured on NPR, CNN, and FOX News. He did his Bachelor's of Science in Biology at Morehouse College and his PhD in Stem Cell Biology at the University of Georgia, where he currently serves as an Associate Professor of Regenerative Biosciences. Dr. West's work at UGA has led to the production of the first live chimeric pigs from induced pluripotent stem cells and the development of novel stem cell to germ cell culture systems. Recently, his work has focused on the development of translational swine models of neural injury, swine specific assessment tools, and the evaluation of novel therapeutics including neural stem cells and neural stem cell extracellular vesicles in the swine system.

Abstract: Stroke and traumatic brain injury (TBI) are global leading causes of long term disability and death. Despite decades of research and 100s of human clinical trials, there are few or no approved therapeutics for stroke and TBI, respectively. This has led to significant interest in evaluating novel therapeutics in translational animal models, such as the pig, that have higher predictive value and using clinically relevant assessment modalities such as magnetic resonance imaging (MRI). In this talk, we will explore how neural stem cells and microbiome transplantation effect stroke and traumatic brain injury recovery in porcine models utilizing MRI. We will evaluate how these treatments alter key clinical MRI parameters including intracerebral lesioning, swelling, and hemorrhage and their relationship to functional outcomes such as changes in neurological severity scores and motor function.

Maria Sady DVM
Reaserch Assistant,
Center for Translational Medicine
Warsaw University of Life Sciences, Warsaw, Poland

PET/MR integrated with AngioSuite and operating room as an ultimate solution for neurointerventions

Biography: M. Sady is an assistant and doctoral student at the Center for Translational Medicine at the Warsaw University of Life Sciences in Poland who graduated from the Faculty of Veterinary Medicine in 2018.
She completed research internships in Poland and abroad, including at the McGowan Institute for Regenerative Medicine at the University of Pittsburgh in USA. Since starting to collaborate with Centers M. Sady has been involved in many projects and grants on biomedical research as investigator and co-investigator.
M. Sady is particularly interested in advanced imaging diagnostics, physiology and pathology of reproduction and translational medicine. *She is* competent at both laboratory *research* and the *clinical* practice, especially in developing preclinical animal model and *related biological materials*.
Maria Sady, DVM is a graduate of the Faculty of Veterinary Medicine, Warsaw University of Life Sciences. Apart from her studies, M. Sady gained knowledge on additional clinical internships at farms and studs and in clinics and clinics for animals. Dr M. Sady clinical internships at farms and studs, also in clinics she took active part in many medical procedures and treatments performed in animals. She completed an internship at the Institute of

Experimental and Clinical Medicine of the Polish Academy of Sciences in Olsztyn, learning the procedures for working with laboratory animals (including handling of laboratory animals, genotyping).

Abstract: Introducing PET/MRI imaging combining full magnetic resonance imaging and positron emission tomography is a challenge in practice. The feasibility of integrated PET/MRI has been demonstrated for many clinical and preclinical imaging applications demanding multiparametric imaging capabilities, high soft tissue contrast and lower radiation.

Promising results have been obtained in whole-body cancer staging, multiparametric tumor imaging, assessment of metastases, in cardiac (i.e., myocardial viability, cardiac sarcoidosis) and brain imaging (i.e., glioma grading, Alzheimer's disease) and in the imaging of young patients with potentially curable diseases. Hybrid imaging opened the numerous possibilities in clinical practice, but as usual innovations generate new dilemmas. For PET/MRI further clinical studies and technical innovation on scanner hard- and software are crucial including optimizing imaging protocols and their appropriate applications. The current data in this field is incomplete due to (among other reasons) lack of fully adapted facilities for conducting groundbreaking translational research. The strategy of bench to bedside is consistent with general trend towards the personalized medicine approach and will help meet commitments to support innovative project and international research cooperation. Also, the translation of new PET tracers from pre-clinical evaluation into clinical applications and agreements on adequate refunding of PET/MRI examinations are needed. The future of advanced imaging diagnostic is part of a general trend towards the animal model research. In conclusion, PET/MRI seems to be a promising diagnostic imaging tool with potential for further development in clinical indications and technical efficiency improvements.

Pete Harvey, PhD
Assistant Professor of Molecular Imaging
School of Medicine & School of Chemistry
University of Nottingham
UK

MRI contrast agent approaches for studying drug delivery to the brain

Biography: Dr Peter Harvey, Assistant Professor of Molecular Imaging, School of Medicine & School of Chemistry, University of Nottingham

Abstract: Treatments and diagnoses are severely limited by our inability to visualise the biochemical processes underlying disease. Nowhere is this issue more limited than in the brain, due to the high level of complexity and presence of the blood-brain barrier. Our ability to disease processes is often limited to fluorescence or histological methods, largely limited to in vitro models that struggle to replicate the complex environment found in the body or ex vivo snapshots that capture a single moment of time. New approaches are needed that combine biochemically specific in vivo real-time imaging with in vitro and ex vivo approaches. Here, I will present our ongoing work on preclinical development of molecular imaging tools for studying drug delivery to the brain.

James Choi, PhD
Imperial College London, UK

Drug delivery across the blood-brain barrier using short ultrasound pulses

Biography: Dr James J Choi leads the Noninvasive Surgery & Biopsy Laboratory at Imperial College London, United Kingdom. He has contributed significantly to the development of ultrasound methods for delivering drugs across the blood-brain barrier. For this work and other contributions to the therapeutic ultrasound field, he was awarded the Frederick V Hunt Postdoctoral Research Fellowship in Acoustics from the Acoustical Society of America in 2011; and the Frederic Lizzi Award from the International Society for Therapeutic Ultrasound in 2022, the top early career award in the field of therapeutic ultrasound.He has published 44 journal articles with more than 3,100 citations. His articles have been published in PNAS, Journal of the National Cancer Institute, Applied Physics Letters, and Radiology. 13 of his articles have been cited over 100 times. He has had two of his patents licensed (US 2011/0295105 A1, US 2009/0005711 A1), and his PhD work at Columbia University has gone on to clinical trials in treating patients with Alzheimer's disease and paediatric brain cancer.He obtained a BS in Computer Engineering at the University of Michigan, Ann Arbor (USA) in 2004, and a PhD in Biomedical Engineering at Columbia University (USA) in 2010. He was a post-doctoral research assistant and Frederick V Hunt Postdoctoral

Research Fellow at the University of Oxford (UK) from 2010. In 2013, Dr Choi founded the Noninvasive Surgery & Biopsy Laboratory at Imperial College London, United Kingdom.

Abstract: In this talk, I will describe a short-pulse ultrasound method for delivering drugs across the blood-brain barrier. I will start by describing how long pulses of ultrasound and microbubbles are used to alter the permeability of the blood-brain barrier. I will include a broad review of methods currently being used both in animal models and on human patients, pointing out the benefits and concerns. I will then describe the work conducted in my laboratory, which has primarily focused on using short pulses of ultrasound to safely and reversibly alter the blood-brain barrier permeability. I will finish my talk with a description of our latest work on delivering drugs to diffuse midline gliomas and plans to translate this clinically.

Tao L. Lowe, PhD
Frederick G. Smith, MS, DDS and Venice K. Paterakis, DDS Professor of Oral and Maxillofacial Surgery
Professor of Bioengineering
University of Maryland

Polysaccharide-based Nanoparticles for Sustained Drug Delivery Across the Blood Brain Barrier

Biography: Dr. Lowe is the Frederick G. Smith, MS, DDS, and Venice K. Paterakis, DDS Professor of Oral and Maxillofacial Surgery and Professor of Bioengineering at the University of Maryland. She received her Ph.D. with an Eximia Cum Laude from the University of Helsinki, Finland. She conducted two years' postdoctoral research in the Chemical Engineering Department at University of Wisconsin, Madison. Dr. Lowe's research interests include the design and development of multifunctional biomaterials for targeted and sustained drug, gene, and stem cell delivery for tissue engineering and disease therapy. Her work has focused on nanotechnology to overcome biological barriers; sustained drug delivery to treat neurological diseases, cancers and diabetes in the brain, eye, ear, face and blood; and regeneration of nerve, bone and cartilage. Dr. Lowe has published many high impact peer-reviewed papers in leading biomaterial related journals including Biomaterials, Tissue Engineering, and Advanced Drug Delivery Review, etc. She currently holds 8 issued and 4 pending U.S. and international patents. Her biomaterials for translational research program has been supported by NIH, DoD, Coulter Foundation, and JDRF, etc, and recognized in the RSC's Chemistry in Britain, Press Release of ARVO, and Feature Research in the "EURETINA-Brief" of European Association of Retina Specialists, etc. Dr. Lowe has given over 90 invited talks around the world. She has served in leadership roles in a variety of professional societies including AAPS, BMES, SFB, ARVO, AIChE, ACS, and CRS. She was the Chair of the Biomaterials Area of AIChE in 2010 and Chair of the AAPS Nanotechnology Focus Group during 2015-2017. In her lab, she has trained more than 150 individuals who have become successful scientists, engineers, physician-scientists, dentist-scientists, pharmacists, and educators. Dr. Lowe has achieved numerous honors and awards including Early Career Award in Translational Research from the Coulter Foundation, and AAPS Fellow.

Abstract: Blood brain and retinal barriers (BBB) are selective and protective barriers preventing adverse components from entering the brain/eye from the blood stream, but also formidable obstacles to overcome when trying to deliver therapeutic agents to the brain. In this talk, I will discuss our research activities in developments of polysaccharide-based nanoparticles for targeted and sustained delivery of drugs across the BBB for the treatments of neurological disorders in the brain. The main focus will be the in vitro and in vivo evaluations of the effects of the developed nanoparticles on the permeability of drugs across the BBB and the integrity of the BBB barriers after penetrations.

Ying Meng, PhD
Sunnybrook Research Institute, Toronto, Canada

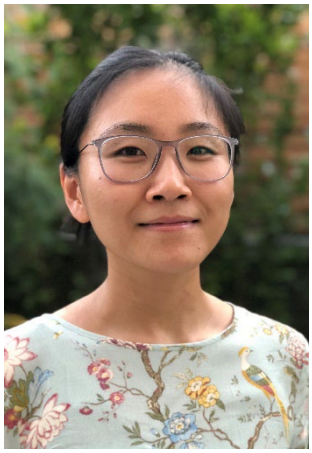


Image-guided brain delivery of trastuzumab using MR-guided focused ultrasound

Biography: Dr Ying Meng is a clinician scientist with research interest in image-guided and minimally-invasive neurosurgery. Her PhD research, supervised by Dr Nir Lipsman, was centered on focused ultrasound, particularly in the application of blood-brain barrier disruption and drug delivery. She is currently the chief resident, completing neurosurgery training, at the University of Toronto

Abstract: Drug delivery to the brain is hampered by the presence of the blood-brain barrier (BBB). MR-guided focused ultrasound (MRgFUS) has shown promising results in increasing drug delivery into the brain parenchyma in animal models. Results in patients are lacking. Our study used radiopharmaceuticals to demonstrate MRgFUS successfully and safely increased monoclonal antibody trastuzumab concentration in the targeted versus non-targeted lesions in four patients with Her2-positive brain metastasis. This first-in-human trial suggests that MRgFUS is a safe and effective method to deliver treatments across the BBB and paves the way for the use of this method for other neurological conditions.

Dheeraj Gandhi MD, FACR
Professor and Vice Chair of Radiology
Professor of Neurology and Neurosurgery
Director, Interventional Neuroradiology
Director of CMIT Center
University of Maryland School of Medicine

MR guided FUS: Next frontier in image guided (non-surgical) Neurosurgery

Biography: Dheeraj Gandhi is Professor of Radiology, Neurology and Neurosurgery and Vice Chair of Radiology. His clinical and research interests are in minimally invasive endovascular therapies of cerebrovascular disorders and MR guided FUS. He has authored five books and over 220 manuscripts including numerous articles in high impact journals like NEJM, Lancet and JAMA. He has received numerous accolades inclusive of Magna Cum Laude and Summa Cum Laude awards from ASNR, Certificate of Merit from RSNA, Bruce-Line prize for clinical research, RSNA roentgen research award, Award for editorial excellence from Radiology, Shock Trauma Hero Award and Fellow of American College of Radiology. He is the Director of Interventional Neuroradiology and serves on the executive committee of a Gold plus Comprehensive stroke center. His provides oversight as a clinical director of Center of Metabolic Imaging and Therapeutics (CMIT center) that has a designation of MR Guided focused ultrasound center of excellence. He is particularly proud of numerous cutting-edge research studies and clinical trials that have been performed and underway at the CMIT Center due to an outstanding multidisciplinary collaboration between Neurosurgery, Neurology and Interventional Neuroradiology programs.

Abstract: Rapid developments in MRI-guided focused ultrasound (MRgFUS) technology have significant implications for treating focal CNS pathologies including but not limited to neurodegenerative, and malignant processes. MRgFUS is currently employed in the clinical setting for treating essential tremor and Parkinson's Disease by producing precise, incisionless, transcranial lesions. Additional trials are underway that are investigating it's use in conditions such as Neuropathic pain, Trigeminal Neuralgia, Obsessive compulsive disorder and Epilepsy amongst others. This non-invasive technology can also be modified for non-destructive applications to safely and transiently open the blood-brain barrier (BBB) to deliver a range of therapeutics, including antibodies and cells. This review is meant to provide an overview of current status of MR Guided FUS and areas of potential future translation.

Gabe Kwong, PhD
Associate Professor of Biomedical Engineering
Wallace H. Coulter Distinguished Faculty Fellow
Georgia Tech and Emory School of Medicine

Thermogenetic Control of CAR T Cells to Potentiate Therapy Against Brain Tumors

Biography: Dr. Kwong is an Associate Professor and Wallace H. Coulter Distinguished Faculty Fellow in the Department of Biomedical Engineering at Georgia Tech and Emory. He earned his B.S. in Bioengineering with Highest Honors from University of California at Berkeley, his Ph.D. from Caltech, and conducted postdoctoral studies at MIT. Dr. Kwong directs the Laboratory for Synthetic Immunity where he leads a multidisciplinary team focused on engineering cell therapies and immune sensors for early detection. His research impacts broad arenas in biomedicine including cancer, transplantation medicine, and infectious diseases. His work is published in leading scientific journals and profiled broadly including coverage in The Economist, NPR, BBC, and WGBH-2, Boston's PBS station. In recognition of his work, Dr. Kwong was named a "Future Leader in Cancer Research and Translational Medicine" by the Massachusetts General Hospital, and selected by the National Academy of Engineering to the US Frontiers of Engineering. His list of distinctions include the Burroughs Wellcome Fund Career Award at the Scientific Interface, NIH Director's New Innovator Award, TEDMED Hive Innovator Award, and the SBUR Don Coffey Lectureship. Dr. Kwong is co-founder of Glympse Bio and Port Therapeutics that have combined to raise over $85+ million in capital with several products undergoing clinical evaluation. He holds over 25 issued or pending patents in biotechnology.

Abstract: In the wake of the clinical success of CAR T cells against hematological cancers, treatment of solid tumors continues to be met with poor responses owing to challenges such as tumor suppression and heterogeneity. We are developing a new class of thermal responsive CAR T cells that can potentiate solid tumor therapy by the localized production of therapeutic transgenes in response to tumor-localized hyperthermia. This category of CAR T cells are engineered with thermal gene switches that are inactive at body temperature (37°C) but switch ON in response to small and transient changes in temperature (~42°C) to drive transgene expression to levels 50–200 fold above basal levels. We recently showed that tumor-localized expression of potent immunomodulators – such as cytokine superagonists and bi-specific T cell engagers – by CAR T cells can potentiate therapy against solid tumors and mitigate antigen escape to reduce relapse rates in mouse models. Working with the Arvanitis lab at Georgia Tech, these advances are now being applied in the context of difficult-to-treat brain tumors, using MRI guided Focused Ultrasound (MRgFUS) for the safe and targeted hyperthermia of intracranial tumors to enhance their treatment.

Raag Airan, MD, PhD
Assistant Professor of Radiology
University of Stanford, USA

Focused Ultrasound Strategies for Targeted Drug Delivery to the Central Nervous System

Biography: Raag Airan MD, PhD is a neuroradiologist and an Assistant Professor of Radiology (Neuroradiology) and, by courtesy, of Materials Science & Engineering and Psychiatry & Behavioral Sciences at Stanford University. He studies Physics and Math at MIT before completing his PhD in Bioengineering at Stanford University, followed by residency and fellowship in Radiology/Neuroradiology at Johns Hopkins. After fellowship he returned to Stanford in 2016 where he has since remained and started up a laboratory developing focused ultrasound based interventions for the nervous system, principally to enable targeted drug delivery.

Abstract: Much of neurologic and psychiatric care is based on pharmacologic interventions. However, the functional anatomy and connectivity of the brain is highly heterogenous, changing substantially across every several millimeters of brain. This warrants the development of techniques that enable targeted delivery of compounds that have known therapeutic potential selectively to the critical brain regions of interest. In principle, doins so would maximize their therapeutic efficacy versus their side effects due to action at off-target brain regions and in the rest of

the body. In this talk we will discuss different ultrasound-based strategies for enabling targeted delivery of pharmacologic agents including blood-brain barrier opening, ultrasonic drug uncaging, and ultrasound glymphatic enhancement.

Steven W. Hetts, MD
Professor of Radiology & Biomedical Imaging
Co-Director of HHT Center of Excellence
Chief of Interventional Neuroradiology, Mission Bay
UCSF School of Medicine
Kazim H. Narsinh, MD
Assistant Professor of Radiology & Biomedical Imaging
Neuro-oncology Lead, Focused Ultrasound in Neuroscience Program
UCSF School of Medicine

Multimodality Imaging in Endovascular Stroke & Tumor Treatment

Biography: Dr. Hetts is Chief of Interventional Neuroradiology at the UCSF Mission Bay Hospitals, where he provides minimally invasive endovascular therapy for children and adults with stroke, cerebrovascular disease and tumors. Dr. Hetts received his MD from Harvard Medical School and his undergraduate degree from Harvard College. He completed his medical internship at Stanford and his diagnostic radiology residency, diagnostic neuroradiology fellowship, and interventional neuroradiology fellowship at UCSF. As Co-Director of the Interventional Radiology Research Laboratory, Dr. Hetts is involved in translating basic science and engineering research into clinical applicability. The main theme of his research is development of novel image-guided endovascular devices and techniques for the treatment of stroke, tumors, vascular malformations, and other conditions accessible through the blood vessels or skin. He has been the principal investigator on an NIH-sponsored project to develop remote-controlled endovascular catheters for use in interventional MRI. **Dr. Narsinh** is the Neuro-Oncology Lead Physician in the Focused Ultrasound in Neuroscience program at UCSF Health. Dr. Narsinh earned his medical degree from the University of California, San Diego, during which time he completed a research fellowship at the Howard Hughes Medical Institute. He completed a radiology residency at UC San Diego, followed by an interventional radiology fellowship at the University of Pennsylvania. At UCSF, he completed fellowships in neuroradiology and neurointerventional radiology. At UCSF, he provides minimally invasive therapies for children and adults with stroke, cerebrovascular disease, tumors, and vascular anomalies. Recently, he has focused on the development and execution of clinical trial protocols implementing MR-guided focused ultrasound for temporary disruption of the blood-brain barrier and delivery of sonodynamic therapy in pediatric and adult patients with brain tumors such as diffuse midline glioma and glioblastoma.

Abstract: Image-guided endovascular interventions have been increasing in prevalence over the years, as minimally invasive procedures continue to replace invasive surgical procedures. Endovascular interventions are almost exclusively performed under x-ray fluoroscopy, which has exquisite spatial and temporal resolution. However, magnetic resonance imaging (MRI) offers unique benefits over x-ray fluoroscopy, including superior soft-tissue contrast, lack of ionizing radiation, and ability to measure quantitative imaging biomarkers during the procedure. During ischemic stroke or neuro-oncologic interventions, the ability to identify infarcted or neoplastic tissue during the procedure could improve outcomes. Although MRI guidance could be an attractive alternative to conventional x-ray guidance in this regard, it brings with it distinctive challenges. Our lab has been developing novel methods for MRI guidance and MRI-safe equipment for use during neurointerventional procedures to treat stroke and cancer

Imad Derraz, MD, MSc
Interventional Neuroradiologist
Montpellier University Hospital

Multimodal Approach for ExtraAxial Tumor Treatment: A First Experience of Transcranial Embolization and Transcranial Cryotherapy

Biography: Dr. Derraz received his medical training and certificates at University of Montpellier and Nancy, France. He then joined the University Hospital of Montpellier as a Consultant Interventional Neuroradiologist. His clinical and research interests focus on the treatment of cerebrovascular disorders including ischemic stroke, cerebral small vessel disease, carotid disease, intracranial aneurysms and vascular malformations. He is also investigating the added value of MR perfusion measurements, acquired immediately after acute reperfusion therapy, in determining secondary stroke injury and predicting early and late neurological outcomes in stroke patients.

He is the Principle Investigator (PI) for the ongoing OTEMACS trial (Onyx™ Trial For The Embolization Of The Middle Meningeal Artery For Chronic Subdural Hematoma), designed to demonstrate that middle meningeal artery embolization via a minimally invasive endovascular approach combined with standard (surgical/conservative) management is superior to standard management alone, in reducing the rate of chronic subdural hematoma (CSDH)-related surgical interventions and the recurrence rate in patient with CSDH. His is also co-PI for several international multicentre studies (LASTE, MOSTE, TITAN).

Abstract: Despite recent advances in the molecular biology understanding of malignant brain tumors, CNS chemotherapy remains challenging because of the impermeable blood-brain barrier (BBB). Interventional imaging-guided brain cryotherapy is technique that creates a tissue lesion by making a severe targeted hypothermia and possibly a BBB disruption. The future immunomodulatory approaches might be combined with brain tumors cryoablation to increase the cryoimmune response.

This presentation will showcase an example of our first experience of extraaxial tumor cryotherapy CT-guided coupled with transcranial Onyx™ injection Angio-guided and briefly discuss the current technology developments in the field.

Michał Zawadzki, MD, PhD
Head of the Division of Interventional Neuroadiology,
Central Clinical Hospital of Ministry of Interior and Administration in Warsaw

Real-time MRI-guided neurointerventions: from animals to patient

Bioigraphy: Dr. Zawadzki is Interventional Neuroradiologist working as a Head of the Division of Interventional Radiology at the Central Clinical Hospital of Ministry of Interior and Administration in Warsaw. His main clinical activities include brain aneurysms treatment with complex remodeling techniques, vascular malformations embolizations with both - arterial and venous approach as well as ischemic stroke treatment. His research now is focused on interventional MRI - together with the SIGN society funding members he performed first-in-human endovascular neurointervention under real-time MRI guidance - intraarterial drug delivery to brain tumor. Now he is developing other applications of iMRI.

Another field of his interest is radiation protection during x-ray endovascular neurointerventions using advanced shielding and artificial intelligence applications thus providing “RayFree” environment for operators.

Abstract: X- ray based fluoroscopy, biplane digital subtraction angiography (DSA) and 3D reconstructions of rotational angiograms are fundamental tools for practicing neurointeventions. Real-time MRI is a new modality for guidance of endovascular procedures in brain diseases, adding physiological and anatomical data unavailable in x-ray based techniques. It is especially useful during intra-arterial infusions of drugs, stem cells, treatment of brain tumors or in experimental models of various diseases, including stroke. My presentation will describe our experience with this technique in animal models,
first-in-human applications and potential future directions.

Dileep R. Yavagal, MD, MBBS
Clinical Professor of Neurology and Neurosurgery
Director, Interventional Neurology, Co-Director Neuroendovascular Surgery
Director, Neurological Platform, Interdisciplinary Stem Cell Institute
University of Miami Miller School of Medicine
Miami, FL

Progress in Translation of Intra-arterial Mesenchymal Stem Cells for Acute Stroke Recovery: Studies in the Canine Endovascular Stroke Model.

Biography: Dr. Yavagal is a Clinical Professor of Neurology and Neurosurgery at the University of Miami Miller School of Medicine. He combines clinical neurointerventional & stroke practice with laboratory and clinical investigations of novel acute stroke therapies. His translational laboratory has been funded since 2008 to study intra-arterial mesenchymal stem cell therapy in small and large animal models.
He has been part of the leadership of several landmark stroke thrombectomy trials and co-led the first randomized controlled trial of IA autologous cell therapy for subacute ischemic stroke, RECOVER-Stroke. He has mentored more than 35 students, post-doctoral fellows, and junior faculty. He has published over 200 publications in the field of stroke and neurointervention. Since 2018, Dr. Yavagal is the inaugural director of the Neurological Platform at the Interdisciplinary Stem Cell Institute at the University of Miami.

Abstract: Despite major advances in reperfusion therapies (RT) for acute ischemic stroke, currently, over 50% of such treated AIS patients remain disabled or die. Importantly, the time-sensitive eligibility for RT, and limited 24-hour time treatment window exclude a large proportion of AIS patients from this treatment. Pre-clinical studies of mesenchymal stem cell (MSC) therapy administered in the acute time window in rodent models of AIS have shown consistent promise for the last two decades in extending the time window and benefit in stroke treatment. Among them, the intra-arterial (IA) route of delivery is highly attractive for clinical translation. However, the progress toward large clinical trials of IA MSCs have been hindered by the inability to reliably extrapolate safe and efficacious IA dosing of MSCs solely based on results in rodent studies. My laboratory has studied IA delivery of MSCs in a canine endovascular middle cerebral artery reperfusion model to find a range of escalating safe of IA MSCs applicable to clinical trials as well as define a toxic dose. We have also shown dose-dependent efficacy in functional improvement, infarct size-reduction, and diffusion tensor imaging improvement. Our studies have also shown mechanistic findings underlying the efficacy in a large animal brain.
This presentation will (1) discuss the techniques of IA cell delivery in endovascular canine rMCAO model , (2) the safety and dose-dependent efficacy of IA MSC doses in this model (3) the immunohistochemistry findings pointing to the mechanisms of action of IA MSCs in rMCAO acute recovery.

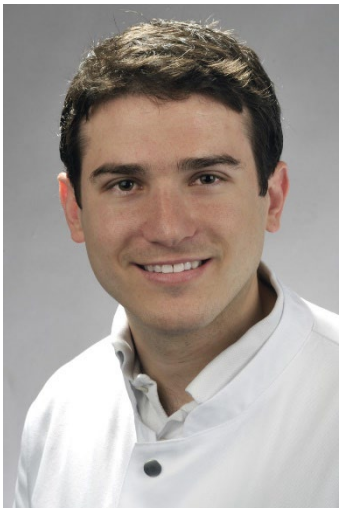
Webster Kadzatsa MD
MMed Rad Onco
Program Coordinator - Radiation Oncology
Department of Oncology
Faculty of Medicine and Health Sciences
University of Zimbabwe

Bench to Bedside and backwards (BBB), what are we dropping on the way?

Biography: Dr Kadzatsa is a clinical oncologist and lecturer at the University of Zimbabwe Faculty of Health sciences in the Department of Oncology. He is the program coordinator of the radiation oncology training program and has mentored a number of students training in oncology and radiation sciences related postgraduate programs. He has co- authored over 20 publication in clinical oncology. He is interested in the application of the lost sciences.

Abstract: The brain can be a sanctuary site for metastatic cancers. Development of brain metastatic disease confers poor quality of life and poor prognosis of cancer patients. The drug levels needed to sterilize subclinical tumours may be relatively low making the sterilization of micrometastatic disease highly possible if these levels are achieved. The blood brain barrier reduces our ability to achieve tumoricidal drug levels. Steroids are noted to increase the barrier effect of the BBB meaning they may further lower the brain parenchymal antitumor drug concentration.

Most anti cancer drugs are emetogenic and controlling emesis is essential in anti cancer treatment. Fortunately or unfortunately steroids are part of most of the adjuvant chemotherapy drug regimes mostly for their antiemetic and antihypersensitivity potential.
Our quest for new knowledge and evidence may make us blind to the unused, old, existing good and solid science. Our bag of tools (drugs, science and evidence) for managing cancers is now getting too full that access to the right tools may be made more difficult by the pouring in of new tools. We may be dropping much more good science from the bench to the bedside and back, losing our efficiency to achieve cure. The blood brain barrier will work against us if we do not pay attention. There is plenty of evidence for this.



Peter Ludewig, PhD
University of Hamburg, Germany

Future Technologies for Point-of-Care Stroke Imaging

Biography: Peter Ludewig is a clinician scientist at the department of neurology at the University Medical Center Hamburg-Eppendorf in Germany.
Besides his clinical activities focusing on the acute care of stroke patients, he works in the research group "Experimental Research in Stroke and Inflammation" of Prof. Tim Magnus in Hamburg. His work centers on understanding the blood-brain barrier in stroke, how immune cells enter the ischemic brain, and the role of angiogenesis in stroke and post-stroke regeneration. Additional interests include improving the care of stroke patients through new imaging technologies. Together with the group of Prof. Tobias Knopp, he is working on developing the new technology Magnetic Particle Imaging from bench to bedside.

Abstract: Stroke is one of the leading worldwide causes of death and sustained disability. Rapid and accurate assessment of cerebral perfusion is essential to diagnose and successfully treat stroke patients. Magnetic Particle Imaging (MPI) is a new technology with the potential to overcome some limitations of established imaging modalities. It is an innovative and radiation-free imaging technique with high sensitivity, specificity, and superior temporal resolution. MPI enables imaging and diagnosis of stroke and other neurological pathologies such as hemorrhage, tumors, and inflammatory processes. MPI scanners also offer the potential for targeted therapies of these diseases. Due to lower field requirements, MPI scanners can be designed as resistive magnets and employed as mobile devices for bedside imaging. With these advantages, MPI could accelerate and improve the diagnosis and treatment of neurological disorders.

Gregory Bix, MD, PhD, FAHA
Tulane University, New Orleans, USA

It's all in your head? Acute and chronic neuropathology with SARS-CoV-2 infection

Biography: Dr. Greg Bix is the Director of the Clinical Neuroscience Research Center, the Vada Odom Reynolds Chair in Stroke Research, and Professor and Vice Chair of Clinical and Translational Research and academic affairs in the Departments of Neurosurgery and Neurology at Tulane University School of Medicine. He is a Fellow of the American Heart Association and also has many prestigious international positions including Clinical Senior Lecturer at the University of Glasgow (Scotland), Adjunct Professor at Queensland University of Technology (Australia), and Professor at the University of Manchester (England). He is a productive (> 70 publications) NIH-funded principal investigator with a research focus on the role of extracellular matrix and its receptors in stroke, vascular dementia and long COVID. Dr. Bix is the inventor on several U.S. and Global patents on novel therapeutics for cerebrovascular injury and disease. In November, 2021, Dr. Bix received the Spirit of Tulane Award for his work on COVID-19 and long-COVID.

Abstract: SARS-CoV-2, the respiratory virus responsible for the current COVID-19 pandemic, can significantly impact vascular integrity and function throughout the body. For these reasons, infection can impact many organs (e.g. heart, brain) outside of the respiratory system regardless of whether the virus actually enters those organs. This may explain, in part, the overlap in vascular risk factors (e.g. diabetes, hypertension, obesity, vascular dementia) and severity of acute and chronic COVID-19 disease, AND why the virus may impact tissues devoid of its putative ACE2 receptor. Indeed, we were the first to provide direct experimental evidence that SARS-CoV-2 can employ vascular integrins

such as alpha5beta1 as alternative receptors to infect endothelial cells. As alpha5beta1 integrin plays a critical role in blood-brain barrier integrity, and acute and chronic neurologic complaints (e.g. brain fog, migraines, focal neurologic deficits) are not uncommon with COVID-19, we investigated the potential for SARS-CoV-2 to cause acute and chronic (long-COVID) neuropathology in nonhuman primates and normal laboratory mice with the goal of defining these changes and to develop novel therapeutic approaches to prevent or improve COVID neuropathology.

Matt Brookes, Professor
University of Nottingham, UK

Next generation brain imaging: mapping electrophysiological function using quantum technology

Biography: Matt Brookes is a Professor of Physics at the University of Nottingham, UK. Following undergraduate training in Physics he undertook a Ph.D. in the field of multi-modal functional neuroimaging, working with magnetoencephalography (MEG) and magnetic resonance imaging (MRI). Following this he undertook postdoctoral studies working on the development of ultra-high field MRI, mathematical modelling for MEG, and combined EEG/MRI. Brookes now leads MEG research at the University of Nottingham. His research spans the gamut of neuroimaging science from development of hardware to clinical application. His group undertook many of the key studies that led to the introduction of quantum technology to the acquisition of MEG data, and the subsequent deployment and commercialisation of wearable MEG technology. Their work on mathematical modelling in MEG led to many of the (now standard) techniques for brain network mapping, and clinical research areas of interest include schizophrenia, multiple sclerosis, mild traumatic brain injury and epilepsy. In a career spanning 17 years, Brookes has published over 140 papers, he currently leads a ~£6m research programme, and accolades include the Blavatnik awards for young scientists in the UK, where he was selected as the 2022 laureate in physical sciences and engineering.

Abstract: Magnetoencephalography (MEG) is an imaging technology which measures human brain function. Specifically it maps, with high spatio-temporal accuracy, the formation and dissolution of electrophysiological brain networks as they respond to ongoing cognitive demand. MEG is an exceptionally powerful tool for neuroscientific research, and has significant clinical utility, particularly in areas such as epilepsy. However, conventional MEG scanners are based on large, cumbersome and extremely expensive instrumentation which make them difficult to deploy in practice. In this talk, I will describe a new generation of MEG system which offers a step change in the field of clinical neurophysiology. I will demonstrate how this new “quantum enabled” technology enables measurement of brain electrophysiology with unprecedented precision; I will show how it can be used to scan people whilst they move freely, and how it can be adapted to fit any patient – enabling high fidelity data capture in subjects from newborn to the elderly. I will demonstrate how this novel instrumentation is being developed and deployed in children with intractable epilepsy, and in adults with mild traumatic brain injury.

Ciprian Ionita
University of Buffalo, USA

New AI applications for management and endovascular treatment of stroke patients

Biography: Ciprian N. Ionita is an Assistant Professor with the main appointment in the Biomedical Engineering Department and secondary appointments in the Neurosurgery and Radiology departments at University at Buffalo. He is the director of the Endovascular Devices and Imaging lab at Canon (former Toshiba) Stroke and Vascular Research Center. I am the CEO and co-founder of the QAS.AI Inc. His research focuses on improvement of endovascular image guided interventions and encompasses three major components: medical imaging, computer programming and endovascular device development.

Abstract: The increasing use of quantitative imaging to determine the severity, and guide treatment, of neurovascular disease has created a prolific environment for the development and implementation of advanced, AI-driven diagnostic models. This talk will focus on latest AI developments which combines quantitative angiographic

imaging of neurovascular disease with data-driven methods to improve triaging, clinical workflow and real-time guidance of endovascular surgeries of stroke patients.

Marcin Możejko
Computational Biology Group,
University of Warsaw

Deep Learning for Healthcare: Opportunities, Challenges, and Solutions

Biography: Marcin Możejko is an experienced deep learning engineer, and researcher with over 7 years of professional, and academic experience. He has been working on projects including natural language processing, computer vision, and generative modeling. His models were deployed on millions of devices, and served as a part of solutions of companies like Microsoft, Novartis and PwC. In his latest project he developed a generative modeling for a peptide generation that resulted in generation of 10 new antimicrobial peptides. Currently he is pursuing the PhD at the Computational Biology Group at the University of Warsaw, where he cooperates with the Immucan Consortium on a generative modeling of human cells using Image Mass Spectrometry data. Another field of his work is creating AI algorithms for prediction of x-ray scatter radiation during endovascular neurointerventions, enabling creating a “RayFree” environment for medical personnel.

Abstract: Recent progress in deep learning techniques introduced a plethora of new possibilities for modeling data, and solving health challenges. However, contrary to popular belief, deep learning is not a magic technique that would easily solve any problem once it is applied. In my talk I will explain what problems are suitable for deep learning, and present examples of successful applications in healthcare. Later I will describe why these solutions succeeded, and what are potential pitfalls for successful AI applications. I will present a few potential solutions for these pitfalls, and a short guideline for successful deep learning projects.

David Dreizin, PhD
University of Maryland, Baltimore, USA

Toward Explainable Artificial Intelligence for Trauma Computer Tomography

Biography: Dr. Dreizin is Associate Professor in the Department of Diagnostic Radiology and Nuclear Medicine at University of Maryland and has practiced in the section of Trauma and Emergency Radiology and R. Adams Cowley Shock Trauma Center (among the world’s busiest trauma centers) for the past 10 years. An Ithaca New York “townie”, he went on the graduate Magna cum Laude from Cornell University and attended medical school at Weill Cornell Medical College in New York City. Dr. Dreizin completed a residency in diagnostic radiology at the University of Miami and Jackson Memorial Hospital where he developed an interest in the nascent field of trauma radiology while rotating through Ryder Trauma Center. Since then, he has published 60 articles, over half as first author, primarily on trauma CT. A number of his educational papers are now considered required reading for radiology trainees. His scientific work focuses on artificial intelligence and computer vision for quantifying torso hemorrhage on CT and he is recognized as the primary driver of research in this area worldwide. His group was the first to segment and quantify traumatic pelvic hematoma, hemoperitoneum, hemothorax, and active bleeding in the torso using deep learning methods, and he is developing deployable tools to quantify hemorrhage burden and organ injury at the point of care. His work is currently supported by a National Institute of Biomedical Imaging and Bioengineering (NIBIB) NIH K08 career development award. Dr. Dreizin is also interested in diffuse axonal brain injury (DAI). At present, early diagnosis and treatment of this common injury type remains elusive and he seeks to develop algorithms to assay the severity of diffuse axonal injury from admission CT scans using synthetic MRI. Dr. Dreizin will present his perspective on developing explainable artificial intelligence (XAI) tools for torso trauma and describe potential avenues for this technology for early detection and personalized objective outcome prediction after TBI.

Abstract: Objectives: After listening to this presentation, audience members will be able to:

1. Discuss the basic elements of responsible, ethical artificial intelligence in medical imaging.
2. Explain the steps involved in the development of robust, accessible, and interpretable tools in the field.
3. Describe regulatory pathways for computer aided detection (CADt, CADe, and CADx) tools.

Miroslaw Janowski, M.D., Ph.D.
Associate Professor, Department of Diagnostic Radiology and Nuclear Medicine
Co-Director, Program on Image Guided Neurointerventions
University of Maryland, Baltimore

Biography: Miroslaw Janowski, MD, PhD, is an Associate Professor in the Department of Diagnostic Radiology and Nuclear Medicine at the University of Maryland, Baltimore, and Co-Director of the Program on Image-Guided Neurointerventions (PIGN). After completing a residency in neurosurgery at the Medical University of Warsaw, Poland, and obtaining PhD in neuroscience and neurotransplantations at the Mossakowski Medical Research Center, Polish Academy of Sciences, dr Janowski pursued his academic career at Johns Hopkins University. Next, he moved to the University of Maryland, Baltimore, to co-direct the Program in Image Guided Neurointerventions (PIGN). He has been continuously funded by NIH, DoD, and the State of Maryland since 2012. His research led to over 120 peer-reviewed papers and several patents, which served as a basis for entrepreneurial efforts. He is also a frequent, high-quality reviewer recognized by the STROKE and NEUROCRITICAL CARE journals as an outstanding and top reviewer, respectively. He is also reviewing grant applications to the European Innovation Council (EIC) – one of the top funding agencies.

Piotr Walczak, M.D., Ph.D.
Professor Department of Diagnostic Radiology and Nuclear Medicine
Co-Director, Program on Image Guided Neurointerventions
University of Maryland, Baltimore

Biography: Piotr Walczak, MD/PhD, Professor at the Department of Diagnostic Radiology and Nuclear Medicine University of Maryland Baltimore, Co-Director of the Program on Image-Guided Neurointerventions (PIGN). He received training in regenerative medicine at the University of South Florida and in molecular and cellular imaging from the Johns Hopkins University. His research program focuses on using multi-modality imaging to improve the delivery of therapeutic agents to the brain in the treatment of stroke, myelin diseases and brain cancer. He has published over 200 articles with a significant impact on his field of research, as evidenced by citation index upwards of 8,000.

Zdzislaw Gajewski, Prof. Dr Sci. PhD, DVM, Msc.
Professor of animal reproduction and experimental medicine
Director, Center for Translational Medicine
Warsaw University of Life Sciences, Warsaw, Poland

Biography: Dr Sc. Z. Gajewski is tenure Professor and Director of Center for Translational Medicine at Warsaw University of Life Sciences in Warsaw, Poland. His research and teaching area is reproduction of animals and translational medicine. He has secured significant funding and received many research grants as principal investigator and contributed to additional grants as co-investigator. He went through the entire career path from residency to a full professorship in Poland at WULS in Warsaw but also at various institutions abroad in many European countries, in USA, Israel, Canada and ultimately at the Center for Translational Medicine at WULS which he created, he secured the significant many millions of funding and where he is the Director. For this paradigm, he coined the phrase "One World, One Life, One Health," which is an excellent response to a much-needed gap in translational research.
Center for Translational Medicine in Warsaw, which is a culmination of Prof. Gajewski's efforts through extremely effective fundraising, is a truly unique initiative in many aspects, including access to modern equipment for investigators, a well-trained and committed team of scientists and modern training programs for undergraduate and graduate students. The center has the latest and most advanced imaging infrastructure, and the jewel in the crown is the angiography / neurosurgery suite integrated with the PET / MR scanner. It is one of the few installations of its kind in the world and is used by clinical researchers at many institutions around the world. It raises the profile of Warsaw veterinary medicine and the experimental capabilities of the veterinary school, building significant bridges with medical science. His vision of forging an alliance between veterinary and human medicine is very clear, and the driving force he provides promises to create a unique research resource that is sure to contribute to both public health and animal welfare. The professor's dedication to this vision and his considerable energy are evident in the construction that continues to this day. Imaging technologies used in Prof. Z. Gajewski's laboratory include magnetic resonance imaging, positron emission tomography (PET)/magnetic resonance (MR), spectroscopic imaging, mass spectrometry, and optical and fluorescence imaging. His laboratory

combines molecular biology and cancer biology approaches with multi-scale imaging to study and visualize the molecular events that drive cancer growth, invasion and metastasis. He has published more than 100 papers on animal reproduction, tumorigenesis, electrophysiology, biochemistry, metabolism, and the use of diagnostic imaging for therapy and diagnosis in small and large animal models.

EARLY STAGE INVESTIGATOR ABSTRACTS

Luiza Stanaszek[1],Piotr Rogujski[1], Agnieszka Graczyk-Jarzynka[2], Barbara Lukomska[1]
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Overexpression of neuregulin-1 as an approach to increase the therapeutic potential of glial restricted progenitors (GRPs)

Background: Glia dysfunction is a pathological characteristic of different neurodegenerative and demyelinating diseases, thus the replacement of damaged glia seems to be a reasonable therapeutic approach. Therefore exogenous glial restricted progenitors (GRPs) seem to be promising candidates for transplantation therapy. Previously it was shown that mice GRPs (mGRPs) transplanted into shiverer mice (demyelination model) revealed some therapeutic potential in terms of lifespan prolongation however their myelination ability was limited. Neuregulin-1 (Nrg-1) has been shown to play an essential role in the proliferation, migration and differentiation of myelinating cells in the peripheral nervous system. In this consent, a strategy to overexpress Nrg-1 to increase the therapeutic abilities of GRPs before their transplantation is justified. Aim: To evaluate if transduction of mGRPs with lentiviral vectors overexpressing Nrg-1, will have an impact on the therapeutic abilities of mGRP. Materials and Methods: Fetal mGRPs were transduced with a lentiviral vector encoding neuregulin-1. Overexpression of Nrg-1 in transfected mGRPs was verified by qRT-PCR and Western-blotting analyses. The phenotype of mGRPs-Nrg-1 was assessed using immunocytochemical and Flow Cytometry techniques. The migratory potential of mGRPs-Nrg-1 was checked using scratch assay, and their myelinating ability was studied in a co-culture of modified mGRPs with mice dorsal root ganglion neurons. Results/Conclusions: The results of our studies showed that overexpression of Nrg-1 in mGRPs decreases their proliferating ability however at the same time it increases its differentiation towards mature oligodendrocytes compared to non-engineered mGRPs. The analyses of migratory and myelinating potentials of mGRPs-Nrg-1 are in progress. Funding: SONATA 2017/26/D/NZ3/00721,
DISCLOSURES
None

Anna Andrzejewska[1], Renata Grzela[2,3], Anna Stankiewicz Drogon[3], Piotr Rogujski[1], Siranjeevi Nagaraj[2], Edward Darzynkiewicz[2,3], Barbara Lukomska[1] and Mirosław Janowski[4,5]
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5 Tumor Immunology and Immunotherapy Program, University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center, University of Maryland, Baltimore, MD, USA

Clinically applicable mRNA-based bioengineering of human mesenchymal stem cells

INTRODUCTION: Mesenchymal stem cells (MSCs) are known for their universal supportive role in reparative processes, however their action after transplantation is often insufficient to obtain a clinical effect. Therefore, a

strategy to modify MSC before transplantation is necessary to support their activity through the use of clinically applicable engineering methods. Thus, the goal of our research was to develop a robust, low-immunogenic and well-tolerated by cells method of human MSC engineering using mRNA-based cell modification. METHODS: Human bone marrow-derived MSCs were transfected with luciferase-coding mRNA with different cap analogs: m27,3'-OGpppG (ARCA), β-S-ARCA D1 and β-S-ARCA D2. Two methods of mRNA purification and several transfection protocols were compared. The efficiency of mRNA-based MSC transfection was analysed by luminescence measurement. In addition, MSC metabolic activity was assessed in CCK-8 assay. Finally, the expression of genes encoding proteins involved in mRNA decapping and immune-response of cells was evaluated by qRT-PCR. RESULTS AND CONCLUSIONS: In our studies ARCA-capped mRNA purified by HPLC was crucial to obtain a robust level of luciferase-coding mRNA translation in MSC. The highest level of luciferase expression was observed 8-12 hours after MSC transfection using β-S-ARCA D1-capped mRNA. HPLC-purified ARCA-capped mRNA-based approach of MSC modification was well tolerated by cells in terms of their metabolic activity. Moreover, this technique did not affect the expression of genes encoding proteins involved in decapping and cellular immune response in transfected MSCs. Thus, our study demonstrated that ARCA-capped mRNA-based engineering is an efficient and safe modification strategy for MSCs.

DISCLOSURES

This work was supported by grant NCR&D STRATEGMED1/235773/19/NCBR/2016; MMRI statutory grant no. 6, and ESF (POWR.03.02.00-00-I028/17-00).

Błażej Nowak [a,b], Piotr Rogujski[a], Barbara Lukomska[a], Miroslaw Janowski[c,d], Anna Andrzejewska[a]

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Heterogenous interactions of glioblastoma with mesenchymal stem cells

Objective and Hypothesis: Mesenchymal stem cells (MSCs) due to their strong tropism toward cancer cells, have been used as vectors delivering therapeutic agents in neurooncology. However, the ambiguous effect of MSCs on glioblastoma (GBM) growth was reported. In our study, we tested the hypothesis that MSCs' impact on tumor cells may depend on the GBM molecular subtype (classical, proneural, or mesenchymal). Methods:Human GBM samples were obtained from 7 patients during surgical resection, and primary cultures of tumor cells were established. Each GBM subtype was determined by flow cytometry analysis of discriminating antigen expression (CD44, EGFR, MERKT, p53, Olig2). Further, GBM cells were co-cultured with human bone marrow MSCs (ratio GBM: MSC 1:1 or 2:1) or cultured in MSC-conditioned media (MSC-CM) for 7 days. Findings: As indicated by surface antigens analysis, we obtained in vitro culture of 5 mesenchymal (cultures: 1,2,4,5,7) and 2 classical (culture 3 and 6) subtypes of GBM. In 3 of 7 co-cultures (1,3,7), MSCs did not affect GBM growth. In 2 of 7 co-cultures (4,6), MSCs promoted GBM growth. In co-culture no. 5, MSCs inhibited GBM growth, and in co-culture no. 2, the MSC effect depended on GBM cells ratio to MSC (progression or inhibition). When cultured with MSC-CM, GBM cells underwent morphology transformation and increased N-cadherin expression, indicating an epithelial-mesenchymal transition. Conclusion: We have not observed any uniform and repetitive trend of GBM cell behavior in and between molecular subtypes. GBM cells exposed to MSCs present high heterogeneity even in the same GBM molecular subtype. In contrast, MSC-CM promotes epithelial-mesenchymal transition indicating tumor progression. The limit of the study is the small sample size, which will be expanded in future experiments.

DISCLOSURES

This work was supported by NSC grant no. 2020/04/X/NZ3/00008; MMRI statutory grant no. 6, and ESF (POWR.03.02.00-00-I028/17-00).

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Towards a novel method for custom cranial augmentation to expand the therapeutic window of transcranial focused ultrasound

Introduction: Skull density ratio (SDR) is a cranial metric that is currently used to qualify patients for transcranial focused ultrasound (tcFUS) treatments. While an SDR threshold of >0.4 has been used historically for this purpose, some patients with SDR values above this threshold may still experience treatment limitations and/or off-target effects. Accordingly, we are developing methods beyond SDR to enable faster, safer, and more precise tcFUS treatments. In this study, we explore components of this new approach using clinically relevant biomaterials. Methods: We tested a variety of available biomaterials that have been developed for human implantation and cranial reconstruction. Cadaveric skulls were imaged using computed tomography (CT) and the CT data was used to analyze and model tcFUS treatments at various clinical target locations. These skulls were then filled with brain tissue-mimicking gel and baseline tcFUS treatments were performed using the clinical MRI-guided FUS system (Insighec, Exablate Neuro Type 1). Results: The acoustic impedance/attenuation of the selected biomaterials was determined across a frequency range (150 kHz - 1 MHz). As predicted by the analytical platform and validated by the experimental tcFUS data, the implantation of one and two sonolucent windows led to an increase in the temperature range at the target sites of 1.2-2°C and 1.9-4.2°C, respectively. Conclusions: This study explored a new method to model, predict, and augment tcFUS treatments. This approach offers the potential to improve the safety, efficiency, and efficacy of tcFUS treatment while also providing an option for patients who would otherwise experience tcFUS treatment failure.

DISCLOSURES
None

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Focused ultrasound inducible ‘synthetic antigens’ for heterogenous brain tumor therapy by universal CAR T cells

Objectives and Hypothesis Chimeric Antigen Receptor (CAR) T cell treatment of brain tumors, including glioblastoma, remains challenging due to tumor heterogeneity and lack of tumor-associated antigens (TAAs). Here, we develop focused ultrasound (FUS) inducible synthetic antigens to sensitize solid tumors for recognition and elimination by CAR T cells. Unlike TAAs, we designed synthetic antigens that are orthogonal to endogenous proteins to eliminate off-tumor targeting. Using the RSV-F camelid single-domain antibody (VHH) as a synthetic antigen, we can preferentially target tumors with universal αVHH CARs, circumventing the need for TAA discovery. We hypothesize that local induction of VHH expression on brain tumors by FUS will enable CAR-mediated killing of heterogenous brain tumors while mitigating off-tumor toxicities. Methods and findings We designed a thermal gene switch (TS) responsive to increases in temperature (~42°C) to drive VHH expression on the surface of tumor cells when heated and observed a pronounced increase in VHH+ tumor cells upon heating in vitro. Using FUS to deposit heat intracranially, we observed a 40-fold increase in luminescent activity compared to unheated mice. For in vivo therapy studies, mice bearing triple-negative E0771 mammary tumors with constitutive VHH expression were treated with control or αVHH CARs which led to a reduction in tumor burden and protection against tumor rechallenge, indicating epitope spread. Conclusions We demonstrated an approach to render untargetable tumors vulnerable to CAR recognition. Looking forward, we will deposit mild hyperthermia intracranially by FUS to activate TS circuits and locally induce VHH expression in brain tumors for CAR-mediated targeting.

DISCLOSURES
G.A.K. is co-founder of Glympse Bio and Port Therapeutics, and consults for Glympse Bio, Port Therapeutics, and Satellite Bio. This study could affect his personal financial status. The terms of this arrangement have been

reviewed and approved by Georgia Tech in accordance with its conflict-of-interest policies. L.G., A.Z., D.V., P.J.S. and G.A.K. are listed as inventors on a patent application pertaining to the results of the paper. The patent applicant is the Georgia Tech Research Corporation. The application number is PCT/US21/54972.

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Improve efficacy of image-guided endovascular neuro-interventions: focus on spatial precision of the blood brain barrier opening in a mouse model

Objective It was to test the hypothesis that fully occlusive catheterization of the CCA and resulting re-routing of cerebral circulation restricts brain volume perfused by the catheter to deep brain structures. In contrast, less disruptive catheterization by accessing the external carotid artery (ECA) results in broader perfusion. Methods. Male C57BL6 mice (10-12 weaks) were subjected to catheterization of ECA or CCA for injection into the ICA. Mice with IA catheter were placed in 9.4T MRI (Bruker) for image-guided neurointervention. IA gadolinium (0.001M) was administered using infusion pump at the rate ranging between 150-500ul/min). DCE and GE-EPI sequences were used to dynamically assess brain perfusion territory. Mannitol (25%) was injected IA over 30s at pre-determined speed to open the BBB and DCE with IV bolus of Gd (0.1mmol/kg) was used to determine BBB integrity. Results. IA delivery via CCA resulted in perfusion of restricted brain territory, (hippocampus and thalamus) (Fig.1A). When catheter was placed in the ECA trans-catheter perfusion was directed to nearly entire hemisphere with significantly larger brain territory (Fig.1B, quantified in Fig.1E; $p \leq 0.05$). Importantly ipsilateral cortex was consistently perfused. This spatially selective perfusion territory was in good agreement with brain region with open BBB following Mannitol injection (Fig.1 C, D). We did not observe hemorrhages or lasting neurological deficits. Conclusions. We have shown that by selecting ECA vs. CCA it is possible to achieve some degree of spatial selectivity in mice and that for targeting cerebral cortex ECA catheterization is a method of choice.
DISCLOSURES
Nothing to disclose

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The impact of a pandemic on the self-perception of depressive behaviors among academic youth

Introduction: The COVID-19 pandemic has hit the entire world in ways unknown to those living today. The consequences were multifaceted and manifested themselves on many layers of life across the entire cross section of society. The academic youth is a particularly sensitive and, at the same time, very important population for ensuring the proper future of our entire society. Depressive behavior and depression are one of the most disabling conditions, thus they warrant an attention. Methods: Kutcher Depression Adolescent Scale (KDAS) has been used to measure of self-perception of depressive behaviors among academic youth. Prior to pandemic we have subjected 404 students to KDAS (range 18-30 years, mean 21.58, SD 2.14, including 63.4 % females and 36.4 males). During COVID-19 pandemic, the another cohort of 273 students were subjected to KDAS (range 18-29 years, mean 21.62, SD 2.19, including 83.2 % females and 16.8 males). Results: Our studies revealed that prior to pandemic only 6.9% of participants demonstrated depressive behavior, while this number dramatically jumped to 48.4% during the pandemic (test t Student: $p<0.05$). Discussion, limitations and future outlook: Our result indicate rapid growth of depressive behavior in academic youth, which is very troubling to the well-being of society in the years to come. Lack of information on the SARS-CoV-2 seroconversion is a serious limitation, so we cannot differentiate between purely psychological effects, and potential consequences of SARS-CoV-2 on individual self-perception. Testing of academic youth with KDAS in post-pandemic era will be vital to better understand long-term consequences of COVID-19.
DISCLOSURES
None

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Local EAE- a precise model of autoimmune demyelination

ABSTRACT CONTENT (1500 CHARACTERS/ 250 WORDS MAXIMUM)
Multiple sclerosis (MS) is a devastating, demyelinating and autoimmune disease of unknown origin. Animal models of MS are important to study the pathomechanisms and develop cures; however, currently available ones are lacking reproducibility and clinical relevance. To accelerate the therapeutic research, a priority is to develop better models that are cost effective, highly reproducible and with excellent clinical relevance. So far, experimental autoimmune encephalomyelitis (EAE) is by far the most prevalent model of MS and that mimic the autoimmune demyelination throughout the entire central nervous system (CNS). However, the model is lacking spatial control over lesion distribution with most lesions localized in the spinal cord. On the other hand, the second most popular in vivo models, toxin-based demyelination, is using the chemicals to induce demyelination at desirable site. While precision of lesion placement is excellent in this model this is not a flawless method, because direct chemical injury is lacking clinical relevance. To enhance the discovery of the effective treatment, we propose a hybrid system taking advantage from toxin models (lesion placement) with the advantages of the EAE, ultimately providing a local autoimmune encephalomyelitis (LAE) in the rat brain. We immunized the rats against myelin, to develop a subclinical autoimmunity. This step was followed by blood-brain barrier opening with stereotactic VEGF injection. We confirmed the autoimmunity and minor neurological impairment. Histological assessment confirmed the lesion development after both 3- and 7 days post-injection. With our approach we were successful in developing a demyelinating lesion with high reproducibility and low morbidity.
EARLY STAGE INVESTIGATOR AWARD ELIGIBLE
Yes
DISCLOSURES
None

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Endovascular stroke model in swine with reperfusion capability – a new platform for testing therapeutics in acute stroke.

Background and aims: Despite successful reperfusion many patients still do not achieve good outcome, challenging the search for a new generation of adjuvant therapy that could be administered immediately after thrombectomy. Testing new drug interventions requires the use of animal models, and with the limited clinical relevance of rodents, we focused on developing a suitable stroke model in pigs. Our aim was to develop endovascular, minimally invasive ischemic stroke in a pig with the possibility of reperfusion, suitable for testing the efficacy of intraarterial drugs. **Methods**:IA catheter was navigated under x-ray to pharyngeal ascendant artery and pigs were transferred to 3T MRI for image-guided IA injection of procoagulant (thrombin). MRI protocol included dynamic GE-EPI for assessment of trans-catheter perfusion and monitoring thrombin-mediated clotting. IA tPA was administered after 2hrs. Lesion evolution was monitored with ADC, T2w and T1w+C and correlated with behavioral and histological readouts. **Results:** Infusion of procoagulant resulted in blockage of cerebral arteries visualized on DSC and perfusion scans. Ischemic damage was detected within 15 minutes on ADC maps. Interestingly, longitudinal MRI of lesion evolution within 2 hours with ADC showed reversibility of ischemic changes in regions undergoing spontaneous reperfusion. IA tPA resulted in reperfusion to near baseline levels. T2 lesions were observed in the cortex and subcortical white matter 7 days and then 30 days after stroke. **Conclusions:** Our endovascular ischemic stroke in pigs enables reperfusion and as such is an excellent, clinically relevant setting for testing the therapeutic efficacy of post-thrombectomy therapeutic strategies.
DISCLOSURES
D.G., P.W., and M.J. are co-owners of Ti-com sp. z o.o. All other authors declare no competing interests