MISI
Molecular Imaging Society of India

DRISHTI

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FROM THE EDITORIAL DESK...

by Jyotsna Rao and Uma Krishnan

Welcome back everyone to our second newsletter, which is based on molecular imaging in neurology. We were encouraged by your response to our first newsletter based on infectious diseases. Bringing out the first newsletter taught us many things and we hope to streamline and fine tune future newsletters based on those experiences. Hope you receive this latest one as you did our first.

We share our grief with you for losing the imaging pioneer, leader, mentor, and guiding force behind MISI, Dr. Sam Gambhir. The best tribute we could pay to him would be to continue striving to build MISI to contribute not only to the Indian imaging community, but also internationally. We seek your inputs and co-operation in this endeavour. We have a special article about his contributions to molecular imaging.

We are proud to announce that our team has grown and have been joined by Dr. Deepak Behera as Director, Executive Strategy and Alliance, Abhinay Joshi as Treasurer and Dr. Shreya Goel as Scientific Program Manager and Academic Liaison. We are sure we will be able to achieve greater success with their expertise.

Neurology is an area where molecular imaging has been playing a role both in diagnosis and drug development. We have included wide ranging topics with contributions from both academia and industry. We hope this edition stimulates ideas and discussions in this challenging field where there is so much more to do. We look forward to your suggestions, so we can keep improving ourselves.

ANNOUNCEMENTS!

FASMI council meeting

MISI delegation with present at the FASMI council meeting on Nov 20, 2020. Drs. Jyotsna Rao and Uma Krishnan will attend the FASMI council meeting to present the society's current state of affairs and discuss strategic partnerships. The Council meeting is to be held during FASMI-2020.

FASMI-2020

MISI members have been extended complimentary access to attend the virtual conference. Please reach out to us for information on ho wto get you free access to FASMI-2020. More information on the conference: https://www.fasmi2020.com/

Educational Webinars

MISI is launching a monthly educational webinar series beginning in November 2020. Our first webinar will explore Artificial Intelligence applications in Clinical Imaging, particularly Molecular Imaging on November 4, 8:30 pm IST/10 am EST/4 pm CET. Please sign up for our future newsletters and webinars at our website: https://mis-i.org. If you would like to speak at a MISI webinar or propose a speaker, please email info@mis-i.org.

Upcoming Newsletters

MISI's upcoming newsletters will focus on the following topics.

January 2021: Immunoimaging

April 2021: Artificial Intelligence in Molecular Imaging

MISI invites contributions from members and non-members alike towards future newsletters. Non-member contributors will receive one-year complimentary membership to MISI.

3D PRINTING IN NEUROINTERVENTIONAL RADIOLOGY: CHARACTERIZATION OF CEREBROVASCULAR DISORDERS WITH VENOUS ETIOLOGY

by Keerthi Valluru, David Saloner, Matthew Amans

Reduced costs, increased access, and improved awareness of 3D printing software and hardware has led to steep increases in the application of 3D printing to a variety of applications in medicine from the manufacturing of custom prosthetics, creation of tissue constructs and organoids, visualization of 3D anatomy, and printing patient-specific models for surgical planning. In neurointerventional radiology, 3D printing can aid in the creation of patient-specific vascular flow models to characterize and investigate the underlying sources of cerebrovascular anomalies such as intracranial aneurysms, arteriovenous malformations, idiopathic intracranial hypertension (IIH), pulsatile tinnitus, etc. Pulsatile tinnitus (PT) is the perception of a rhythmic sound synchronous to the heartbeat heard without an external source, affecting 3-5 million Americans. PT is frequently associated with aberrant blood flow in cerebral venous vasculature near the cochlea. Our experience suggests that patient-specific 3D printed cerebrovascular flow models can help identify anatomical and flow features that may cause venous pulsatile tinnitus (PT), validate new imaging techniques that can improve the standard of care diagnostic tests for PT diagnosis, and aid in the development and testing of new intravascular device prototypes to objectively diagnose PT.

Identify the source of PT using patient-specific vascular flow models:

Venous PT often relates to flow irregularities in the transverse sinus, sigmoid sinus and high-cervical internal jugular vein. Over the years, we have built a library of 3D printed vascular flow models that are exact geometric replicas of venous sinuses found in normal subjects and in subjects with PTI. Typically, the creation of a flow model begins by extracting segmented surface contours from high-resolution CE-MRA studies and exporting as a mesh file. Using CAD software, the mesh file is modified by adding flow extensions at the inlet and the outlet to allow tubing connections to a rotary pump simulating cardiac cycle. The luminal anatomy is then printed in wax with a 3D printer. Lastly, the wax lumen is embedded in silastic and melted out once the silastic has set. Fig. 1 illustrates one such model corresponding to a patient's venous anatomy with high-riding jugular bulb. Injection of dye through this model visually confirmed a vortex core, also identified on 4D MR flow to be the likely source of PT.

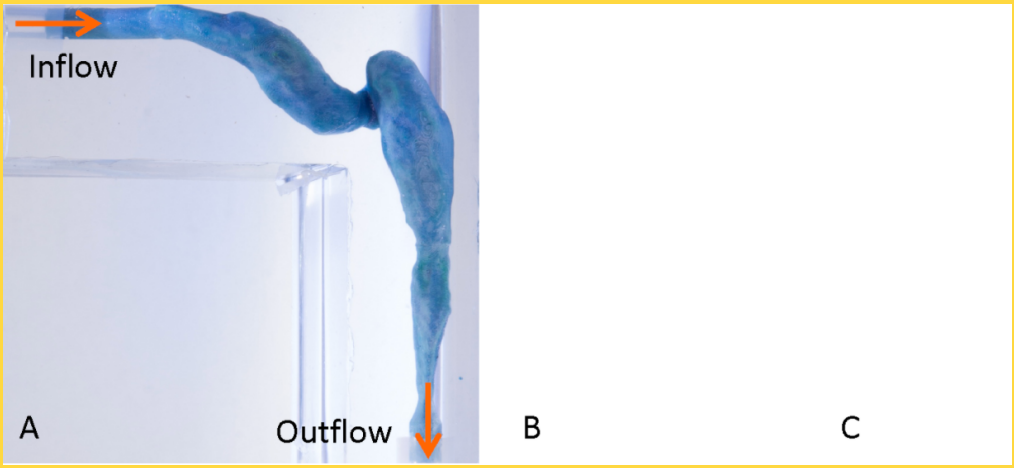


Figure 1. 3D printed exact replica of patient-specific venous anatomy. Wax replica (A) prior to melting out from the silastic. Dye dilution experiment (B) performed in this wax replica confirmed the vortex pattern of flow seen on 4D flow MRI (C) which is suspected to be the source of PT.

Develop new diagnostic and therapeutic devices for cerebrovascular venous disorders:

Oftentimes, diagnosing the cause of PT can be very challenging for clinicians and patients. We developed an intravascular device prototype named “Phonocatheter” that can measure and record PT sounds as well as replay them in real time2. The Phonocatheter is a 6Fr catheter able to record intravascular sounds through an embedded microphone. By using 3D printed patient-specific flow models of a patient with PT caused by idiopathic intracranial hypertension, we performed proof-of-concept experiments to test the utility of Phonocatheter (Fig. 2). In this patient, PT was resolved by cerebrospinal fluid removal via lumbar puncture (LP). Prior to and almost immediately after the LP, she underwent MR imaging consisting of anatomic and flow evaluation sequences (Fig. 3). The Phonocatheter was inserted in these models through a 9Fr access port and was navigated into the transverse sinus stenosis region. An electronic stethoscope was placed externally over the same stenosis region to record PT transluminally and validate the sound measurements recorded by Phonocatheter (n=10). The Phonocather was in good agreement with the electronic stethoscope demonstrating that the peak-to-rms (mean ± standard deviation) sound amplitude was significantly louder ($p<0.0001$) in the stenosis region in pre-LP model (Stethoscope: 9.03 ± 1.61; Phonocatheter: 6.62 ± 1.55) compared to the same region in post-LP model (Stethoscope: 4.20 ± 0.86; Phonocatheter: 3.62 ± 0.88; Fig. 2).

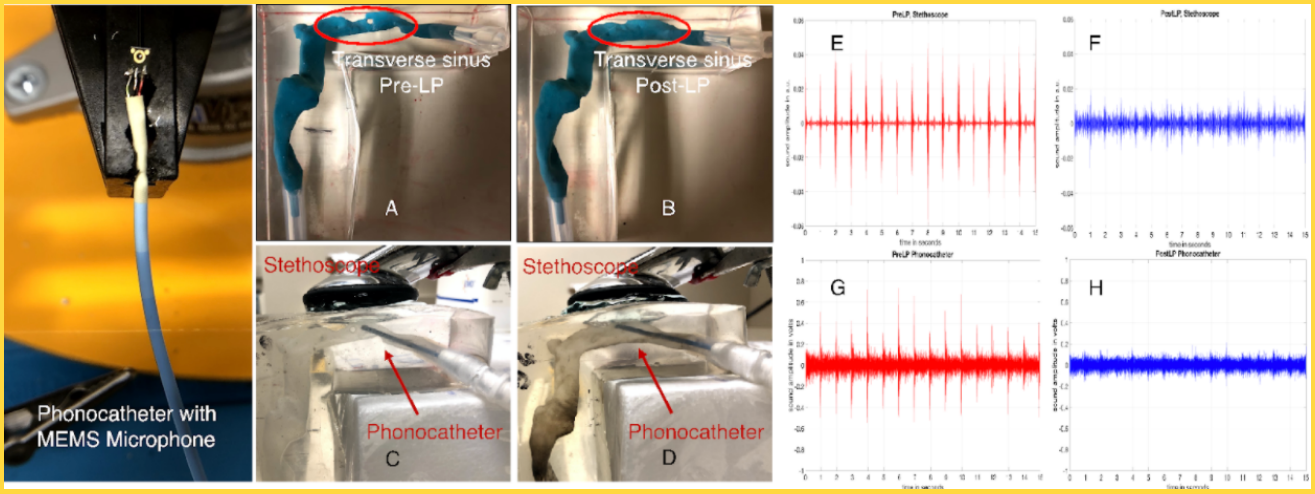


Figure 2. Prototype of MEMS based microphone-enabled catheter (Phonocatheter) shown on the left. 3D printed venous segment showing transverse sinus, sigmoid sinus, and internal jugular vein derived from a patient's CE-MRA dataset acquired: (A) before lumbar puncture, and (B) after lumbar puncture. The wax was melted resulting in translucent pre-LP and post-LP patent flow models as seen in (C) and (D). In both these models, sound measurements from transverse sinus region were recorded by an electronic stethoscope and Phonocatheter. (E, F) Sound amplitude (a.u.) recorded transluminally with stethoscope from pre-LP model and post-LP model respectively. (G, H) Corresponding sound amplitude (volts) recorded intraluminally with Phonocatheter from pre-LP model and post-LP model suggesting that the Phonocatheter measurements agree with those of stethoscope.

Develop imaging techniques to replace invasive venous manometry:

To determine if PT patients may benefit from advanced treatment techniques such as venous sinus stenting (VSS), they often undergo venous manometry, which is a painful procedure that exposes them to the risks of arrhythmia, intracranial hemorrhage, and exposure to ionizing radiation. To offer a better triage to these patients, our team has developed a robust, MR-based, noninvasive set of tools (4D Flow MRI with ICOSA6) that can determine the flow velocity field and distribution of turbulent kinetic energy (TKE) to analyze the patient anatomy and flow conditions before and after treatment3. Using the 3D printed pre-LP and post-LP patient-specific flow models described above, we validated our MR tools to characterize the flow parameters

responsible for PT. 4D Flow MRI of the models revealed qualitative similarity of flow patterns to in vivo results (Fig. 3), revealing high velocity jets in the transverse sinus region pre-LP with jet reduction post-LP. TKE was most pronounced in the region immediately distal to the stenosis in the pre-LP model, and greatly reduced in the post-LP model. Very similar features were seen both in vitro and in vivo in the pre-LP (PT) state that were absent in the post-LP (no PT) state validating the utility of 3D printed patient-specific flow models as in vitro surrogates for venous causes of PT that could enable concrete determination of the links between geometry, blood flow, and sound generation.

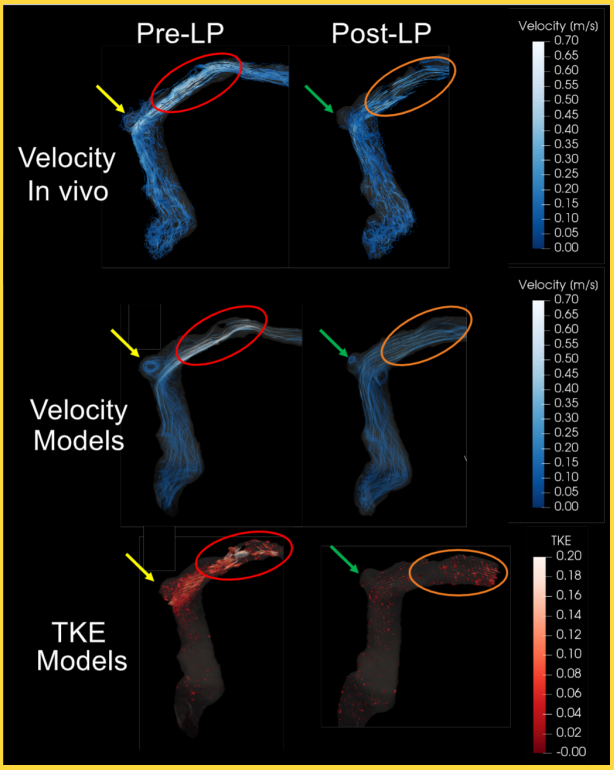


Figure 3. 4D-Flow MRI of the patient-specific benchtop flow models revealed qualitative similarity of flow patterns to in vivo results shown in the top row. High velocity jets were seen in the transverse sinus region pre-lumbar puncture with jet reduction in the corresponding region post-lumbar puncture (middle row). Turbulent kinetic energy (TKE) was most pronounced in the region immediately distal to the transverse sinus stenosis in the pre-LP model, and greatly reduced in the post-LP model (bottom row).

In summary, our experience suggests that 3D printed patient-specific models are invaluable to characterize neurovascular disorders such as PT. These models are useful to reproduce sounds very similar to those appreciated by patients and examiners in the cases of objective PT with high reliability. Our work with patient-specific benchtop venous flow models shows that these models can reliably produce sounds and help identify flow features that may cause PT. These models also allow for device testing and further investigation into the exact mechanistic link between patient geometry, blood flow, and sound.

References:

1. Valluru K, Parkhill J, Gautam A, et al. Sound Measurement in Patient-Specific 3D Printed Bench Models of Venous Pulsatile Tinnitus. Otol Neurotol. Published online 2020. doi:10.1097/MAO.0000000000002452

2. Amans M, Valluru K, Kondapavulur S, et al. E-132 Microphone enabled catheter to quantify venous pulsatile tinnitus in patient-specific flow models. In: ; 2020. doi:10.1136/neurintsurg-2020-snis.164

3. Haraldsson H, Leach JR, Kao EI, et al. Reduced jet velocity in venous flow after CSF drainage: Assessing hemodynamic causes of pulsatile tinnitus. Am J Neuroradiol. Published online 2019. doi:10.3174/ajnr.A6043

A GENTLE INTRODUCTION TO THE MR PERFUSION IMAGING IN THE BRAIN

by Sandeep Ganji

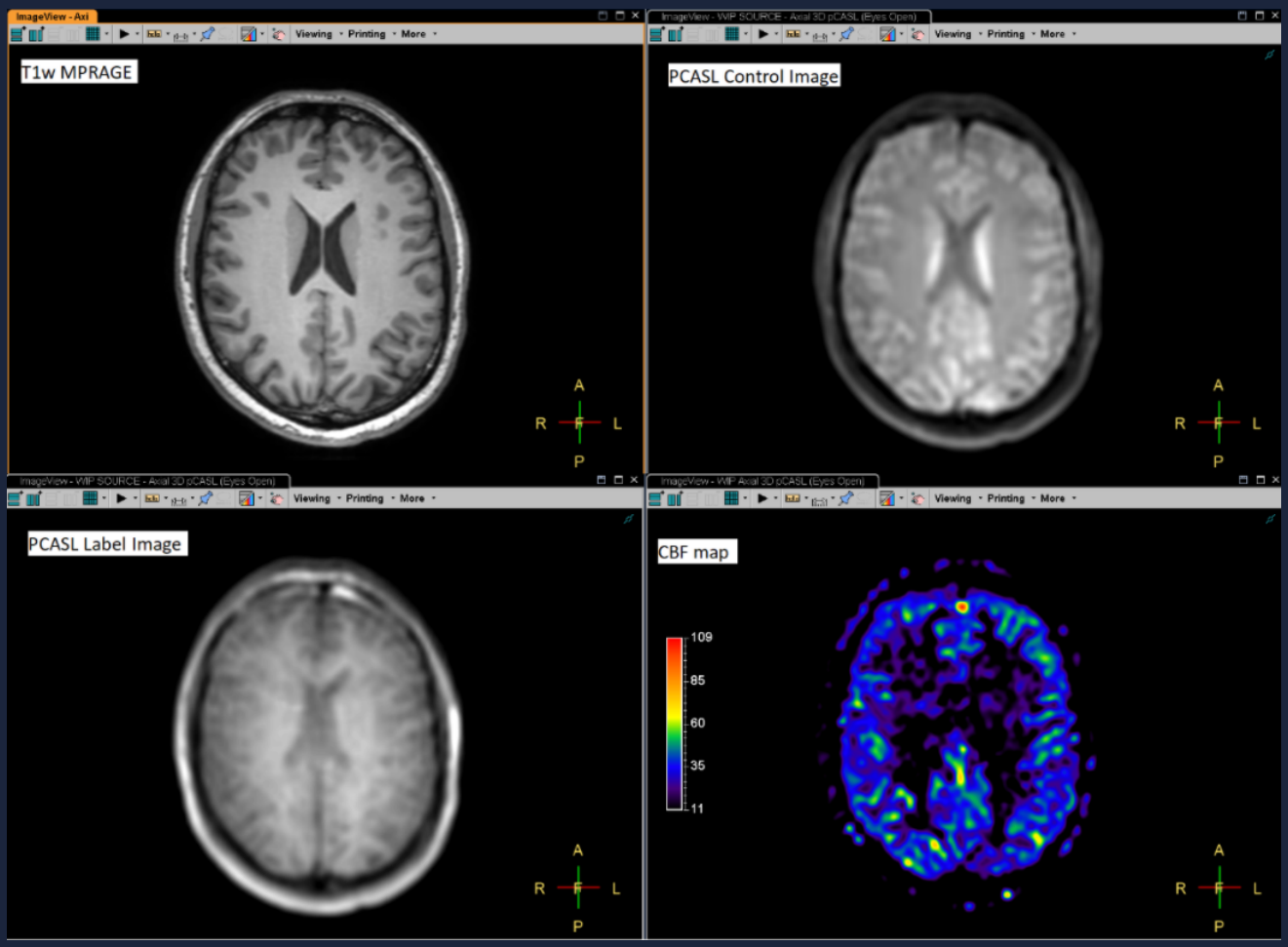
Cerebral perfusion is an important process by which oxygen, substrates, and nutrients are delivered to the brain tissue by means of blood flow and cerebral blood flow, (CBF) indicating the rate of delivery of arterial blood to a capillary bed in the brain tissue [1-3]. CBF is an important part of the brain hemodynamics. Clinically perfusion imaging can be done by a variety of imaging techniques and they basically fall into 2 categories: those who use the exogenous (e.g. gadolinium contrast agents, Positron emission tomography (PET) agents, stable xenon for CT, single photon emission computed tomography agents) and those who use endogenous (e.g. water)[3]. These in turn can be further classified as diffusible and non-diffusible tracers, depending on their ability to enter the tissue from capillary vessels. The non-diffusible tracers in some cases do reach the tissue if the blood brain barrier is broken.

Traditionally radioactively labeled water (H215O) was used for measuring the dynamic and nondynamic information of cerebral blood flow (CBF), such as for studying the effects of drug administration, functional activation, and tumor metabolism [4, 5]. With advancements in the field of computed tomography (CT) and magnetic resonance imaging (MRI), new methods for obtaining quantitative brain CBF have emerged. Dynamic contrast enhanced (DCE) imaging with iodinated contrast (for CT) and gadolinium chelate (for MRI) are also used to measure the cerebral perfusion. Xenon-enhanced computed tomography

(Xe/CT) is specially regarded as the gold-standard technique for brain perfusion imaging [3, 6-8]. Over the last decade, arterial spin labeled (ASL) perfusion MRI has gained a wide acceptance for noninvasively measuring the CBF using magnetically labeled arterial spins as an endogenous diffusive tracer. Unlike PET, Xe/CT, and DCE-MRI, ASL MRI is a completely noninvasive imaging, using water as the contrast agent (endogenous) and offers the advantage over traditional contrast bolus techniques by not requiring a gadolinium-based tracer contrast agent. ASL also allows for a more accurate quantification of CBF, including arterial transit time (time taken for blood to travel from the labeling region to tissue voxel). Hence in the recent years ASL has become a safe, and cost-effective alternative for PET, Xe-CT and DCE-MRI based CBF measurement. However, one major challenge of ASL imaging is the relatively low signal-to-noise ratio (SNR) of about 1% compared to the static tissue signal [9]. Often the utility of ASL is reduced due to larger prevalence of dynamic susceptibility contrast-MRI or CT.

ASL uses arterial blood water as an endogenous diffusible tracer. It essentially contains three components: labeling, post-labeling delay (PLD), and image acquisition (readout approaches). During labeling the magnetization of the blood is inverted the using radiofrequency (RF) pulses and after a delay time that allows for the labeled blood to reach the brain tissue and then the desired plane is acquired. A separate set of control images without the labeling of arterial spins are acquired as a reference. And finally, the difference between controled and labeled images gives the measure of labeled blood delivered to the brain tissue by way of perfusion. The ASL

labeling techniques can be classified into three groups: 1) continuous ASL, 2) pulsed ASL (PASL) and 3) velocity selective labeling ASL (VSASL) [10]. Within the continuous ASL, there are two sub-types of ASL techniques: continuous ASL (CASL), and pseudo-continuous ASL (PCASL) [10]. Currently, PCASL is the preferred implementation of CASL [11], where a train of slice-selective RF pulses are applied at the labeling plane, along with a train of gradient pulses that have a small but non-zero mean value [10]. The below figure shows the PCASL, CBF, and corresponding T1w image from a healthy volunteer. As for the labeling delay, it depends on the labeling type, for example, for PCASL and single PLD method, PLD is set just longer than the longest value of arterial transit time, which is the transport time from the labeling position to the tissue [10]. Typically, ATT is empirically calculated and used for a given study population. One can also measure the ATT using the multiple PLD acquisition where ASL data is acquired with varying PLD times. For ASL image acquisition, there are several readout approaches such as multislice single-shot 2D echo-planar imaging (EPI), spiral readout, 3D segmented methods like 3D multiecho stack of spirals [12, 13] or 3D GRASE [14, 15]. One of the most important features of MR based perfusion imaging is its ability to quantify CBF. For more details about the CBF models and assumptions of it, the ASL consensus paper by the ISMRM Perfusion Study Group goes through the details about the models and assumptions [10]. For quantification of ASL, there are several perfusion imaging softwares that take the source ASL images (control and label) and imaging parameters to generate quantitative CBF maps. Some example softwares are cloud based BASIL (FSL) [16], tool MRICLoud [17], ExploreASL, [18], and ASLtbx [19].



Perfusion, especially quantified CBF using noninvasive of ASL MRI, is very useful in various diseases, both hyperperfusion and hypoperfusion changes can reflect different underlying mechanisms of the disease. Perfusion is extensively used in cardiovascular imaging for understanding the vascular disease, acute, and Chronic ischaemic processes. There are several clinical applications of ASL for neuroscience and neurology. For example, CBF can be used in the acute stroke (intra-arterial and intravenous), collateral flow,lacunar stroke and microangiopathy, hemorrhage, occlusive intracranial vessels, transient ischemic attack, and congenital Disease. There is significant research that shows the use of ASL MRI for detecting patterns of regional hypoperfusion in Alzheimer's dementia, correlating well with metabolic imaging using fluorodeoxyglucose PET [5, 9, 10, 20]. CBF changes are also better localized both spatially and

temporally, arising primarily from the arterial side, compared to BOLD, which is a more venous oxygenation signal. This makes CBF a good candidate for functional imaging. There is a great potential for ASL MR imaging to transform the field of neuroscience and the Knowledge of the brain perfusion may provide unique physiological information, which is difficult to obtain using typical anatomical imaging. This may eventually lead to better patient management in a wide range of disease states.

References:

1. Detre, J.A., et al., Perfusion imaging. Magn Reson Med, 1992. 23(1): p. 37-45.

2. Lassen, N.A., Cerebral blood flow and oxygen consumption in man. Physiol Rev, 1959. 39(2): p. 183-238.

3. Bammer, R., MR and CT Perfusion and Pharmacokinetic Imaging: Clinical Applications and Theoretical Principles. 2016, [N.p.]: Wolters Kluwer Health.

4. Firestone, L.L., et al., Human brain activity response to fentanyl imaged by positron emission tomography. Anesth Analg, 1996. 82(6): p. 1247-51.

5. Jenkins, B.G., Pharmacologic magnetic resonance imaging (phMRI): imaging drug action in the brain. Neuroimage, 2012. 62(2): p. 1072-85.

6. Bews, J., et al., A simplified method for measuring cerebral

blood flow with xenon-enhanced computed tomography. Clin Phys Physiol Meas, 1991. 12(3): p. 279-87.

7. Suzuki, R., T. Nariai, and K. Hirakawa, [Measurement of cerebral blood flow by stable xenon-enhanced computed tomography (series 3)]. No Shinkei Geka, 1993. 21(3): p. 197-203.

8. Rubin, G., et al., Xenon-enhanced computed tomography cerebral blood flow measurements in acute cerebral ischemia: Review of 56 cases. J Stroke Cerebrovasc Dis, 1999. 8(6): p. 404-11.

9. Grade, M., et al., A neuroradiologist's guide to arterial spin labeling MRI in clinical practice. Neuroradiology, 2015. 57(12): p. 1181-202.

10. Alsop, D.C., et al., Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: A consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia. Magn Reson Med, 2015. 73(1): p. 102-16.

11. Dai, W., et al., Continuous flow-driven inversion for arterial spin labeling using pulsed radio frequency and gradient fields. Magn Reson Med, 2008. 60(6): p. 1488-97.

12. Ye, F.Q., et al., Noise reduction in 3D perfusion imaging by attenuating the static signal in arterial spin tagging (ASSIST). Magn Reson Med, 2000. 44(1): p. 92-100.

13. Vidorreta, M., et al., Comparison of 2D and 3D single-shot ASL perfusion fMRI sequences. Neuroimage, 2013. 66: p. 662-71.

14. Gunther, M., K. Oshio, and D.A. Feinberg, Single-shot 3D imaging techniques improve arterial spin labeling perfusion measurements. Magn Reson Med, 2005. 54(2): p. 491-8.

15. Fernandez-Seara, M.A., et al., Continuous arterial spin labeling perfusion measurements using single shot 3D GRASE at 3 T. Magn Reson Med, 2005. 54(5): p. 1241-7.

16. Castellaro, M., et al., A Variational Bayesian inference method for parametric imaging of PET data. Neuroimage, 2017. 150: p. 136-149.

17. Li, Y., et al., ASL-MRICloud: An online tool for the processing of ASL MRI data. NMR Biomed, 2019. 32(2): p. e4051.

18. Mutsaerts, H., et al., ExploreASL: An image processing pipeline for multi-center ASL perfusion MRI studies. Neuroimage, 2020. 219: p. 117031.

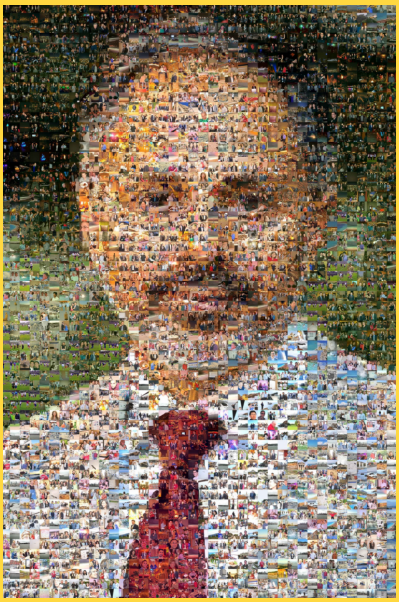
19. Wang, Z., et al., Empirical optimization of ASL data analysis using an ASL data processing toolbox: ASLtbx. Magn Reson Imaging, 2008. 26(2): p. 261-9.

20. Baig, M.W., Pharmacologic perfusion imaging. Who needs it and why? Postgrad Med, 1992. 91(1): p. 185-7, 190-2.

DR. SANJIV SAM GAMBHIR: A TRIBUTE

by Jyotsna Rao

In Loving Memory



Sanjiv Sam Gambhir, MD, PhD

November 23, 1962 - July 18, 2020

Dr Sanjiv Sam Gambhir left us on July 18th this year after losing a valiant battle to cancer. We wish to pay tribute to this molecular imaging colossus who changed the way we look at cancer.

After graduating with a degree in physics from the Arizona State University, Sam joined the UCLA MD PhD program. Armed with degrees in biomathematics and medicine, he started his academic career at UCLA and moved to Stanford University where he was the Virginia and DK Ludwig professor of cancer research, director of the molecular imaging program, and chairman of the department of radiology.

Sam guided around 150 graduate and postdoctoral students who went on to have brilliant careers. Work in his lab included bioluminescence, fluorescence optical imaging, ultrasound and photo-acoustics, among many other areas. He revolutionized

cancer imaging through various techniques like reporter gene PET, and micro-bubble and immunodiagnostics techniques. When the role of FDG PET was still evolving, he was one of the pioneers who ensured cancer indications were reimbursed by insurance, which led to universal acceptance of PET as an indispensable tool in cancer management.

Sam authored over 650 peer reviewed scientific articles, was on the editorial board of prestigious journals, was on the advisory Council of NIBIB and advisor to NCI, was honored with several prestigious awards by RSNA, ESMI, SNMMI, and Imperial College of London to name a few, he co-edited a text book titled Nuclear Medicine in Clinical Diagnosis and Treatment with Peter Ell, was the author of Molecular Imaging Principles and Practice, and was the sole author of Molecular Imaging: A Primer. His interpretation of scans was widely appreciated by clinicians. He had over 40 patents and started 3 biotechnology companies.

A walking encyclopedia, Sam had a wide range of interests including politics, sports, and arts. When struck with the personal tragedy of losing his only teenage son to cancer it only spurred him on to deeper research into personalized and early cancer diagnosis. His latest contribution was the smart toilet for day to day monitoring of a person's cellular function derangement. Dr. Gambhir was fittingly awarded the Dean's Medal by Stanford University for excellence along with the announcement of the Sanjiv Sam Gambhir Professorship of Translational Medicine on the eve of his death. Professionally, I first connected with Sam when I had the opportunity to collaborate with him in writing about the clinical utility of FDG

PET in cancer along with my mentor Dr Peter Valk when Sam was at UCLA. I first met him in person in 2002, at an IASNM dinner reception.

Shortly thereafter, I moved to India where, being in corporate clinical practice, there was very little scope for academic endeavors. With scant resources and support, I had significant self doubt regarding pursuing my love for research and contributions to the field of Molecular Imaging. However, Sam and I met in Hawaii at a WMIC briefly, which started our collaborations and publications and led to a long distance friendship. He entered my life as a beacon, showed me the path to realizing my dreams and potential by not only connecting me to the right resources but also by prodding and encouraging me continuously along the way, thereby giving me the confidence that I sorely needed to do what I love.

I consider myself fortunate to have connected with him at a personal level. We even shared our problems - he supported me when I was going through a life threatening illness, and also shared his grief over losing his son, Milan, with me. Sam had great faith and belief in me. I could not have achieved what I have without his unstinting support. His passing away is an irreparable personal loss to me.

Above all, the entire Molecular Imaging community and beyond will miss him as a friend, mentor, guide, and someone we could look up to for inspiration and guidance who worked tirelessly until the last moment. We will miss his compassion and sense of humor. MISI will be indebted to him for being the guiding force behind its formation.

THE CIRCLE OF ALZHEIMER'S DISEASE MOLECULAR IMAGING

by Amol Takalkar

Molecular imaging is a new paradigm that includes the visualization, characterization, and measurement of biological processes at the molecular and cellular levels in humans and other living systems. Recent advances in scanner technology as well as in specific targeted radiopharmaceuticals have the potential to make it an important diagnostic tool in the early assessment, risk stratification, evaluation, and follow-up of patients with many chronic conditions including cancer, cardiac, and neurological diseases. It is expected to play an increasingly significant role in neurological conditions such as brain tumors, dementias (Alzheimer's and others), movement disorders, seizure disorders, traumatic brain injuries, and psychiatric disorders.

Alzheimer's Disease (AD), the most common cause for dementia globally, is a gradually progressive neurodegenerative brain disease that slowly destroys memory and other important cognitive abilities and mental functions to such an extent that even the ability to carry out simple tasks is severely impaired, making it serious enough to interfere with daily life. Currently, it is considered irreversible with no proven effective treatment to halt or reverse course once it has set in. In addition to lack of proper definitive treatment, accurately diagnosing AD remains challenging as well. The current clinical approach to diagnose AD with a thorough neuropsychological evaluation, blood and CSF analysis, and brain imaging to exclude other, reversible forms of cognitive impairment have significant limitations to

correctly diagnose AD, especially in the early phase or when patients first present with some concerning symptoms, since they lack specificity and coexisting brain pathologies exist with increasing frequency in this age group, further confounding the clinical dilemma. Neuropathologic examination of the brain is still considered the gold standard for diagnosis of AD, but very few patients undergo invasive brain tissue sampling ante-mortem. The neuropathologic diagnosis of AD requires the presence of extracellular beta-amyloid plaques and intracellular tau protein neurofibrillary tangles. Although this has been known to us for over a 100 years, definitive pathologic diagnosis of AD remains problematic even today. The original set of neuropathologic criteria to diagnose Alzheimer's Disease (AD), the most common cause for dementia globally, is a gradually progressive neurodegenerative brain disease that slowly destroys memory and other important cognitive abilities and mental functions to such an extent that even the ability to carry out simple tasks is severely impaired, making it serious enough to interfere with daily life. Currently, it is considered irreversible with no proven effective treatment to halt or reverse course once it has set in. In addition to lack of proper definitive treatment, accurately diagnosing AD remains challenging as well. The current clinical approach to diagnose AD with a thorough neuropsychological evaluation, blood and CSF analysis, and brain imaging to exclude other, reversible forms of cognitive impairment have significant limitations to correctly diagnose AD, especially in the early phase or when patients first present with some concerning symptoms, since they lack specificity and coexisting brain pathologies exist with increasing frequency in this age group, further confounding the clinical dilemma. Neuropathologic examination of the brain is

still considered the gold standard for diagnosis of AD, but very few patients undergo invasive brain tissue sampling ante-mortem. The neuropathologic diagnosis of AD requires the presence of extracellular beta-amyloid plaques and intracellular tau protein neurofibrillary tangles. Although this has been known to us for over a 100 years, definitive pathologic diagnosis of AD remains problematic even today. The original set of neuropathologic criteria to diagnose AD by the National Institute on Aging (NIA) in 1985 were based on age-related amyloid plaque density. In 1991, he Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria emphasized the neuritic plaques in the frontal, temporal, and parietal cortices and required the presence of dementia clinically to render a neuropathologic diagnosis of definite, probable, or possible AD. To incorporate neurofibrillary tangles in the diagnosis of AD, NIA and Reagan Institute combined the CERAD neuritic plaque scoring with the Braak staging (a measure of neurofibrillary tau burden) in 1997 to determine a high, intermediate or low probability for AD in patients with dementia. The most current set of neuropathologic criteria to diagnose AD were revised in 2012 by NIA and Alzheimer's Association (AA) as it became more universally acknowledged that AD pathology can be present in the absence of clinical symptoms. These 2012 NIA-AA Guidelines use an ABC scoring system based on the semi-quantitative measure of Thal Aβ amyloid phase (A score), Braak NFT stage (B score), and CERAD neuritic plaque score (C score) to describe the amount of AD neuropathological change ranging from none to low to intermediate to high amounts of change, and they are applicable to patients with or without dementia.

AD is now considered as a patho-clinical continuum with the neuropathological changes of AD starting to occur years or even decades before clinical symptoms develop, with overt dementia being the last stage of the continuum. It is now known that AD associated amyloid deposition and tauopathy precedes structural and even functional changes in the brain by decades. The traditional brain imaging techniques (such as brain CT or MRI) pick up structural changes that lack specificity akin to clinical symptoms and occur much more downstream in the AD continuum. Functional changes precede structural changes in the brain and functional brain imaging has the ability to detect AD earlier but had been largely restricted to Positron Emission Tomography (PET) of the brain with a fluorinated glucose analogue, f-18 fluorodeoxyglucose (FDG) for decades. However, more recently, specific PET probes for beta-amyloid plaque imaging of the brain as well as tauopathy have been developed and hold promise for AD patients.

FDG PET provides a map of glucose metabolism and can detect the functional loss of synapses and neurons due to neuropathological changes of AD. Vulnerable regions of the brain start showing deficits in the form of decreased FDG uptake and this can detect AD or potential AD in the very early clinical presentation (mild cognitive impairment or MCI) or sometimes, even before the patients meet clinical criteria for MCI. Typically, deficits are first noted in the posterior cingulate gyrus region and extend to the posterior parietal and temporal regions. The initial findings may be unilateral, and the deficits become bilateral as the disease advances with the involvement of frontal lobes in severe cases of AD. Figure 1 shows the typical parieto-temporal deficits on FDG Brain PET Imaging in a

patient with advanced AD. As FDG PET imaging became more routine in clinical practice for oncology, functional/metabolic brain imaging with FDG PET also became more prevalent.

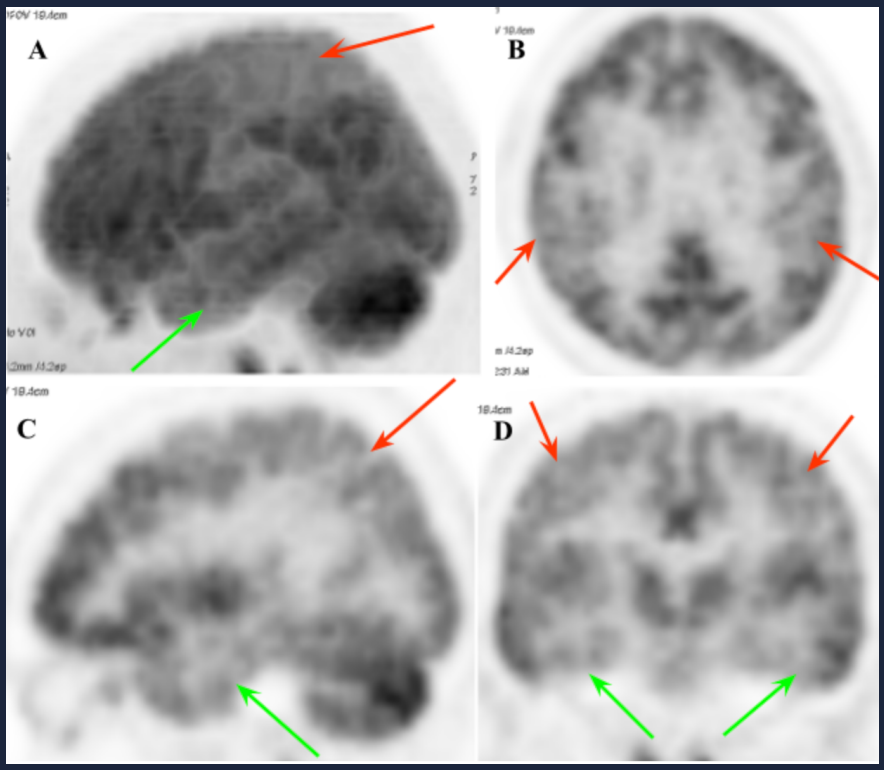


Figure 1. Selected images of FDG Brain PET Imaging in a patient with AD with a Maximal Intensity Projection (MIP) image in the sagittal projection (A) and selected transaxial (B), sagittal (C) and Coronal (D) slices showing hypometabolic deficits in the form of decreased FDG uptake in the bilateral parietal (red arrows) and temporal (green arrows) regions.

However, this typical "posterior pattern" on FDG PET was not easy to be discerned in very early cases, especially MCI and that led to the advent of digital era in brain PET with objective analysis of FDG brain PET images using various statistical parametric mapping software to augment the visual analysis of PET images with voxel-based statistical image analysis and comparison to a statistical map of a normal database, frequently coregistered to MRI. Various software packages such as Neurostat, Statistical Parametric Mapping (SPM), Cortex ID (GE), Scenium (Siemens), MIMneuro (MIMVista), PALZ (PMOD), and NeuroQ (Syntermed) provided robust objective evaluation

of the FDG Brain PET data and were deemed useful in early stages of AD or MCI related to AD. Figure 2 depicts SPM analysis of FDG Brain PET Imaging for 4 cases of AD ranging from MCI to early AD to progressively more advanced AD. It ably demonstrates the power of these software to detect subtle changes/deficits that are very hard to be analyzed visually by the naked eye.

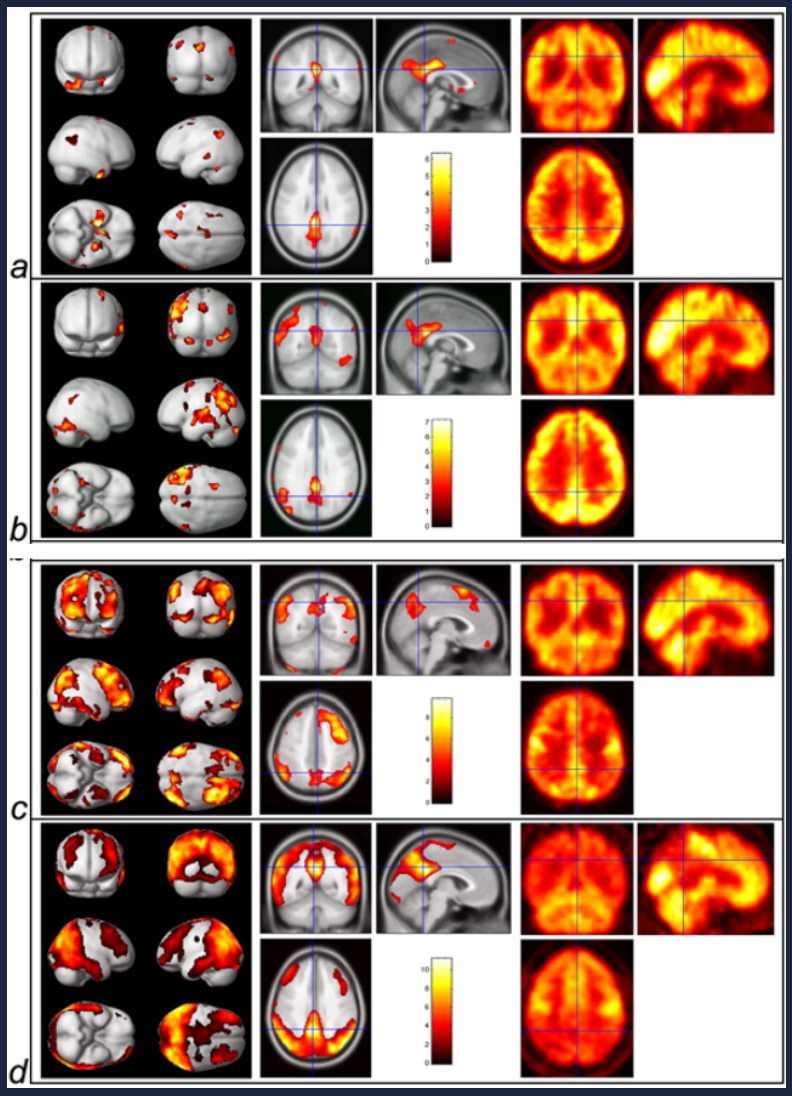


Figure 2. SPM Analysis of FDG PET Imaging in various stages of AD with MCI (a), early AD (b), and progressively more advanced AD (c and d). The left column is the surface rendered view of regions of decreased metabolism, the middle column is the cross-sectional view, and the right column shows three orthogonal slices of the actual PET brain image for each patient. In the left and middle columns, the colored blobs represent the SPM(Z) statistic for each and every voxel, at a threshold of Z=2, extent of 100 voxels. Thus, only regions with a size of 100 voxels and with an intensity peak height greater than Z=2 are shown.

In spite of the robust evaluation of functional/metabolic brain imaging with FDG PET Brain Imaging augmented with objective statistical analysis, the sensitivity and specificity of the typical hypometabolic deficits is approximately 80% and 60% respectively. There remained a need for better imaging tools to non-invasively diagnose AD with high accuracy to help in the workup of AD. Beta Amyloid Plaque Brain PET Imaging allows us to non-invasively assess the presence or absence of the beta-amyloid neuritic plaques in the brain with high accuracy. Since these plaques are a hallmark of AD and are required for the diagnosis of AD, the absence of these plaques on imaging is not consistent with a neuropathological diagnosis of AD, while the presence of these plaques on imaging indicate a high probability of AD. The hallmarks of a negative or normal beta amyloid plaque brain PET scan are a predominantly white matter pattern of uptake with minimal to no grey matter uptake and preserved grey-white interface/differentiation throughout the cerebral cortex. When there is increased grey matter uptake (more than the white matter uptake) with loss of grey-white differentiation/interface, it is considered abnormal or a positive scan. There are three FDA approved agents available in the US for beta amyloid plaque imaging of the brain with PET: F-18 Florbetapir (Amyvid®, FDA approved in 2012), F-18 Flutemetamol (Vizamyl®, FDA approved in 2013), and F-18 Florbetaben (Neuraceq®, FDA approved in 2014). Figure 3 depicts a positive/abnormal and negative/normal beta-amyloid brain PET scan. Although FDA approved, the clinical utilization of these scans in the workup of AD has remained very limited as insurance companies do not provide reimbursement for these scans with the rationale that since there are no effective treatments for AD, accurately diagnosing AD with these scans

does not change patient outcomes. However, these specific imaging probes have the potential to accurately exclude non-Alzheimer's patients while enrolling patients in trials to develop treatment for AD.

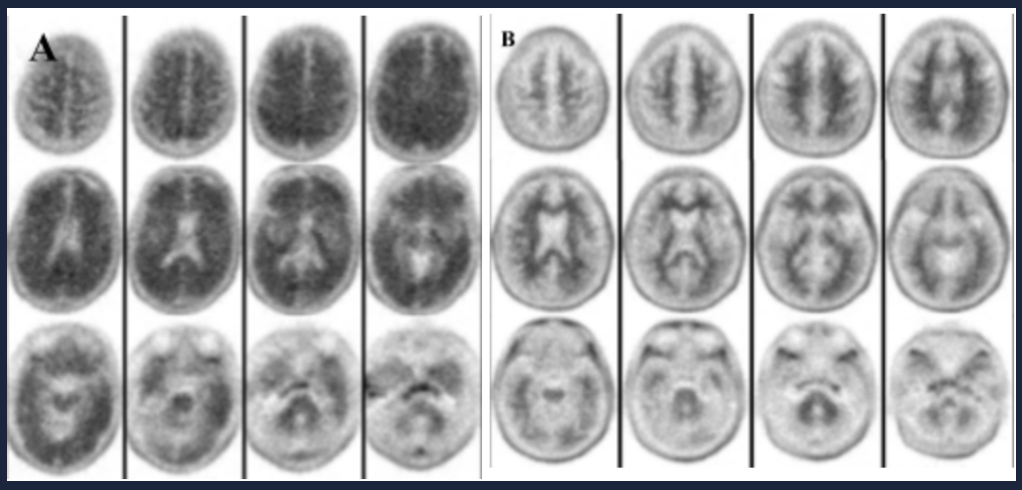


Figure 3. Beta-amyloid plaque brain PET imaging with F-18 Florbetapir (Amyvid®) showing an abnormal or positive scan (A) with diffusely increased grey matter uptake and loss of grey-white differentiation throughout the cerebral cortex, and a normal or negative scan (B) with predominantly white-matter uptake and preserved grey-white differentiation throughout the cerebral cortex.

Beta amyloid brain PET imaging is definitely a significant leap in imaging AD. However, there are several limitations to amyloid plaque imaging. Amyloid is believed to accumulate very early in the disease process and the plaque burden has plateaued by the time the patient has clinical dementia. Also, it may be present in other diseases or in clinically normal elderly subjects (although the most recent NIA-AA guidelines also take into consideration that neuropathological changes of AD can occur in the absence of clinical symptoms of dementia). Amyloid plaques accumulate prior to the onset of dementia and the density or distribution of plaques is not well correlated with the severity of symptoms in patients as the disease progresses. Amyloid plaque imaging has not been established to predict the rate of future deterioration or as a

tool to predict or monitor response to therapy. Hence, there still remains an unmet need in AD imaging: an imaging probe that would accurately assess disease severity and also assess response to successful therapeutic intervention. The presence and severity of tau pathology may be able to address both of these unmet needs. Abundant neocortical neurofibrillary tangles are not observed in cognitively normal individuals and the density and distribution of phosphorylated tau, aggregated in neurofibrillary tangles, increases with AD-related cognitive impairment and correlates with neurodegeneration and cognitive impairment. CSF tau assays do not identify the location or extent of tau deposits in the brain and have limited utility as a longitudinal biomarker. F-18 flortaucipir (Tauvid ®) is a recently FDA approved (May 28, 2020) PET imaging agent that binds to phosphorylated tau aggregates (but not normal, monomeric tau) in human brain tissue. Normal patients show no significant uptake with just nonspecific background activity in the brain. However, in AD patients it shows regionally-specific increased grey matter uptake. This changes with disease severity with more prominent uptake in more severe/advanced cases. Thus, it can potentially serve as a biomarker for disease severity/neurodegeneration with potential applications for selecting AD patients for therapy, serving as a baseline and subsequent monitoring of disease progression in therapeutic trials. Figure 4 shows two serial flortaucipir brain PET scans showing increasing uptake on subsequent imaging indicating disease progression. The uptake on tau brain PET imaging appears to be temporo-parietal regions, analogous to the hypometabolic deficits seen on FDG brain PET imaging, philosophically making us come a full circle in the functional imaging workup of AD!

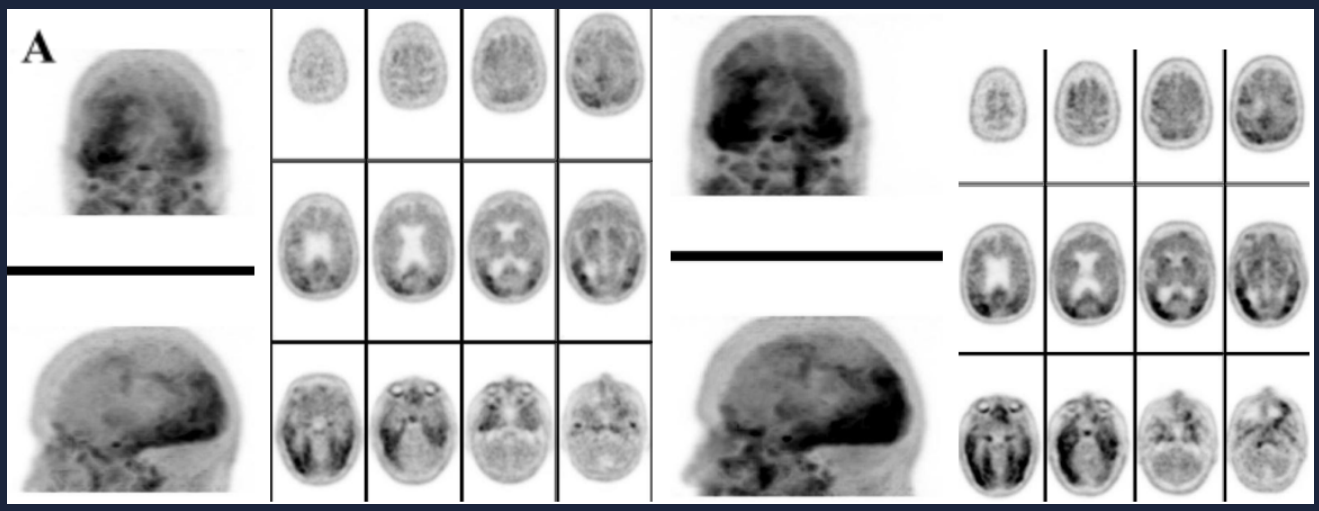
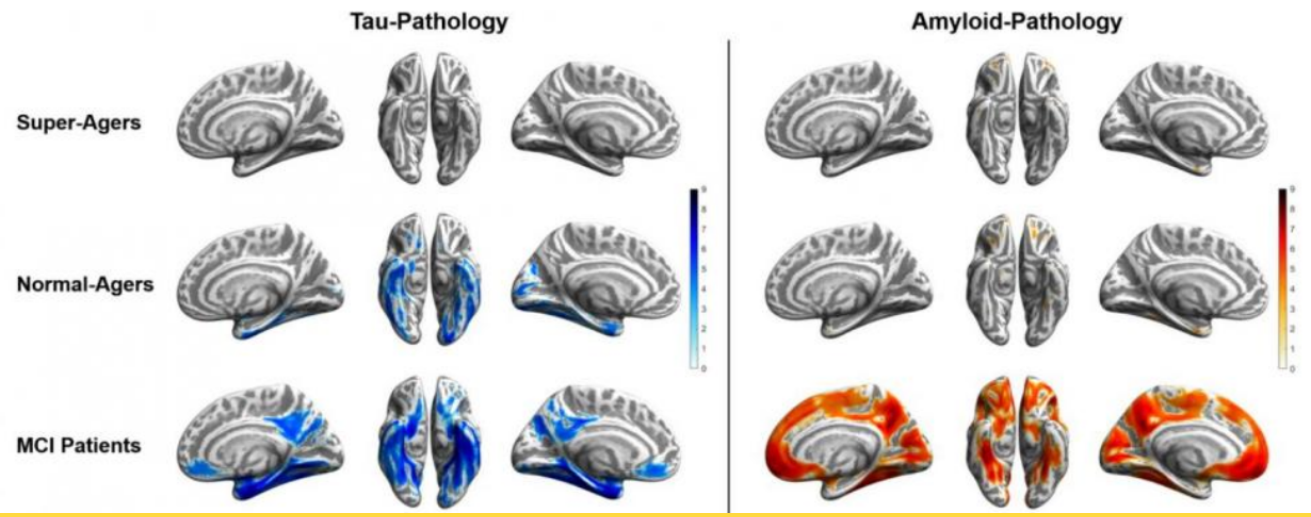


Figure 4. Tau pathology brain PET imaging with F-18 Flortaucipir (Tauvid®) in an AD patient with positive/abnormal beta amyloid brain PET scan (not shown) showing increased uptake in the parieto-temporal regions (A) at baseline prior to initiation of therapy; with further increased and more prominent as well as more extensive uptake in the bilateral parieto-temporal regions (B) a year later after treatment with an investigational agent, indicating disease progression. The left column shows coronal (top) and sagittal (bottom) MIP images with the series of transaxial slices of PET images on the right.

DRISHTI NEUROIMAGE HIGHLIGHT

by Abhinay Joshi



MISI highlights the 2020 SNMMI image of the year as Drishti NeuroImage. The image shows tau (left) and amyloid (right) distribution patterns for super-agers (top row), normal-agers (middle row) and patients with mild cognitive impairment (MCI) (bottom row).

As we age, many of us lose cognitive abilities at various rates - even at the same age, some seem to become cognitively impaired, while others appear to retain full cognitive abilities quite late in life!

Researchers in Germany attempted to unravel this mystery by using molecular imaging of brains in three groups of age- and education-matched patients who were all more than 80 years old. They targeted two brain proteins commonly associated with loss of cognitive function. Using 18F-AV-45 for tau PET and 18F-AV-1451 for amyloid PET they compared images of the brain in the three test groups with those from a control group of younger cognitively normal and amyloid-negative individuals.

The tau and amyloid scans of super-agers were similar to those of the younger control group. The normal-agers showed increased tau burden in inferior temporal and precuneal areas, but no significant difference in amyloid burden when compared to controls. Both amyloid and tau burdens were increased in MCI patients.

The researchers concluded that the phenomenon of selected individuals cognitively performing above the norm even at advanced age (super-agers) appears to be associated with resistance to tau and amyloid pathology, which likely permits maintenance of cognitive performance. Difference between normal aging and MCI appears to be driven by amyloid burden.

These results drive the need to determine responsible resistance factors, which may lead to new options and pathways in the management of cognitive impairment.

SPOTLIGHT MEMBER OF THE QUARTER: DR. ANIL KUMAR MISHRA

by Uma Krishnan

Dr. Anil Kumar Mishra is the Head and Additional Director of the Institute of Nuclear Medicine and Allied Sciences (INMAS). His research career spans over 35 years and is primarily focused on Radiopharmaceutical Chemistry, Nuclear Chemistry, and Bio-conjugate Chemistry. He completed his M.Sc. in Chemistry from Gorakhpur University and followed it up with a Ph.D. in Organometallic Chemistry from the Benaras Hindu University (BHU). Dr. Mishra worked on development of magnetic resonance contrast agents and synthesis of polyazamacrocycles for gas separation applications as part of Professor Roger Guillard's group at the Université de Bourgogne, Dijon, France. He then moved to Professor C. F Meares's research team at University of California, Davis, USA where he focused on the development of metal based imaging agents and C-functionalized macrocycles. He carried out his

third post-doctoral stint with Professor Chatal at INSERM, Nantes, France where he worked on bioconjugates for targeted imaging.

Dr. Mishra returned to India in 1997 where he joined as Scientist D and Head of Radiopharmaceutics at INMAS, a premier research arm of the Defence Research & Development Organization (DRDO). He is currently Scientist G and the Head of the Division of Cyclotron and Radiopharmaceutical Sciences. He served as a Visiting Professor at the Max Planck Institute of Cybernetics, Tubingen Germany during 2002-2003 where he was involved in the development of responsive MR contrast agents for neuroscience. He also is a Visiting Professor at University of Bordeaux, France and a Honorary Professor at Deakin University, Australia. As a project leader, Dr. Mishra developed novel SPECT imaging agents (Met-SPECT& CDTMP) ready for technology transfer to BRIT and Industries. He was instrumental in establishing the Molecular Imaging and Research Centre (MIRC) at INMAS with excellent Radiopharmaceutical Chemistry facilities and demonstrated its capability throughout the country for the first time in the field of Imaging sciences through the development of specific PET-pharmaceuticals based on C-11, F-18, F2-18(g) and N-13 amide. As a scientist, the Mishra Peptide method developed by him for the synthesis of C-substituted macrocycles has been successfully employed for a diverse set of applications that include development of metal-based imaging agents, labelling biological vectors for biomedical applications, trapping toxic metals and heavy isotopes from nuclear waste, and in the development of specific MR contrast agents and fluorine-based imaging agents. His research team had also developed a

bifunctional bone imaging agent and a novel synthetic route for DO3A to label trivalent metal ions for chemical and biological applications. He has a rich publication track record with over 290 publications in peer-reviewed high impact international journals and six patents granted. He has handled several high profile projects at the National and International levels. He is currently associated with the use of Nuclear Energy for Oncology and Neurology (NEON) for early detection, staging, and functional mapping.

Dr. Mishra is the recipient of several awards, the most notable being the DRDO young scientist Award from the Prime Minister of India in 1999 and the Award from British Nuclear Medicine Society Harrogate, UK in 2014. He is an active member of several associations including the American Chemical Society, the European Association of Nuclear Medicine, Society of Nuclear Medicine, Society of Nuclear Medicine, N. Chapter, Society of Magnetic Resonance Imaging, International Society of Radiation Biology (I), World Molecular Imaging Society (WMIS), and the Molecular Imaging Society of India (MISI). He is a core member of Radiopharmaceuticals of India (DCGI) and an expert member in the task forces constituted by the Department of Biotechnology and Department of Science & Technology.

His rich scientific experience and forward-thinking approach for realizing self-reliance continues to inspire and motivate numerous scientists. We are positive that his valuable inputs and scientific contributions will continue to guide MISI and its members for long-term success and sustainability.

DR. SANDEEP GANJI...

received a bachelor's degree in Biomedical Engineering from Osmania University, Hyderabad, India and got his doctoral and post-doctoral degree from The University of Texas Southwestern Medical Center (UTSW), Dallas, Texas, USA. His doctoral research focused on developing novel in vivo MR methods for fast and reliable imaging of brain neurochemicals under various disease conditions. His research work is internationally recognized by other scientists in the field for its novelty and value. His research has led to the detection and measurement of the first onco-metabolite 2-hydroxyglutarate (2HG) in human brain tumors. Dr. Ganji is continuing his research work in the field of medical imaging as a Clinical Scientist at Philips Healthcare, working on site at Mayo Clinic at Rochester, MN, USA. He is responsible for managing and participating in the collaborative clinical research at the academic sites to co-develop and implement novel imaging technologies for unmet clinical applications. His current work is focused on bringing advanced imaging analysis pipelines, such as ASL quantification, segmentation, and machine learning models, to clinics.

DR. AMOL TAKALKAR...

is a board certified Nuclear Medicine and Molecular Imaging Specialist with significant experience and expertise in PET/CT imaging including the novel Molecular Imaging PET probes as well as the upcoming paradigm of theranostics combining specific PET radiopharmaceuticals with complementary radionuclide therapies for targeted internal radiation. His research Interests include Molecular Imaging and Therapy using FDG and other PET probes in oncology, neurology, cardiology, inflammation, infection and other pathophysiologic processes as well as novel radionuclide therapies. He is frequently invited to give talks nationally and internationally. He is very involved in various professional societies related to Molecular Imaging and has served in leadership positions in various councils and committees at the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the American College of Nuclear Medicine (ACNM). He has also served as the President of the Southwest Chapter of SNMMI (that included Texas, Louisiana, Arkansas, Oklahoma and New Mexico) and currently serves as the President of the Indo-American Society of Nuclear Medicine (IASNM). Before joining Emory, he was the "go-to" person for Molecular Imaging in Shreveport, Louisiana for 15 years where he served as the Medical Director at Center for Molecular Imaging & Therapy (CMIT) at the Biomedical Research Foundation of Northwest Louisiana (BRF) as well as Professor of Radiology and Associate Director of Research in the Department of Radiology at Louisiana State University Health Sciences Center in Shreveport, Louisiana.

DR. UMA KRISHNAN...

is a Ph.D. in Chemistry and has post-doctoral experience at UT Southwestern Medical Centre, Dallas, USA. She works with nanostructures and carries out surface modification to tailor their properties for appropriate applications in therapy and diagnosis. Development of stimuli-responsive intelligent therapeutics and point-of-care devices for diagnosis of clinically relevant markers is a major focus of her research lab. Her group uses silico, in vitro, 3D spheroids and in vivo studies to establish the efficacy of these nanomaterials for the intended application. Understanding molecular mechanisms of these nano-interventions and assessment of safety and efficacy using a combination of molecular, biochemical, electrophysiological, imaging and spectroscopic techniques, is also a component of the group's research activities. She has over 200 publications in this area. She is currently the Secretary of MISI. She can be reached at umakrishnan@sastra.edu

DR. JYOTSNA RAO...

graduated in medicine from Osmania Medical College, Hyderabad, India. She trained in nuclear medicine at Christ Hospital, Cincinnati, Ohio and received her clinical PET fellowship from Northern California PET Imaging Center, Sacramento, California. After several years of clinical practice in the US, Dr. Rao came back to India and has been with Apollo Gleneagles PET-CT Centre in Hyderabad, practicing general Nuclear Medicine and PET. Dr. Rao enjoys teaching and mentoring and has been teaching post-graduate students in nuclear medicine, guiding medical students and mentoring students from non-medical backgrounds with cross-functional training and interests. Dr. Rao has presented at national and international conferences, co-authored papers including collaborative ones with Stanford University, and has been a peer-reviewer for various journals. She is the current President of MISI.

DR. KEERTHI VALLURU...

is a Research and Development Engineer in Neurointerventional Radiology at the University of California San Francisco, where he strategizes and innovates new approaches to address cerebrovascular disorders, including using imaging and 3D printing. He has previously provided application support for iThera's multispectral optoacoustic tomography imaging technologies and developed a multimodality imaging platform integrating PET/MRI/13C hyperpolarized MRS imaging and ultrasound and translated into human trials at Stanford University. Keerthi is well published with more than 30 peer-reviewed publications to his credit and is also experienced in device development and technology validation.

DR. ABHINAY JOSHI...

is a molecular imaging industry veteran with almost 15 years of experience in bringing radiopharmaceuticals and medical imaging devices from development to the clinic, including amyloid and tau PET tracers. With an education in instrumentation engineering, biomedical engineering, business foundations, and technology management, Abhinay brings together a well-rounded perspective on molecular imaging technologies. Academically, he has authored more than 35 papers and presented at several national and international conferences. Abhinay also promotes nuclear medicine & molecular imaging by active involvement in various societies, including his current position as the Treasurer of MISI.

CREDITS TO...

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