



Customer Insights

- Multi-modal molecular imaging driving pre-clinical research & pharmaceutical development

Multi-Modal Molecular Imaging Driving Pre-Clinical Research & Pharmaceutical Development

Multi-modal molecular imaging at Massachusetts General Hospital – driving pre-clinical research and patient pathways and accelerating pharmaceutical development .



Peter Caravan, PhD, Director of the Caravan Lab in the Athinoula A. Martinos Center for Biomedical Imaging and co-director of the Institute for Innovation in Imaging (I³), both at Massachusetts General Hospital. Dr Caravan has recently been appointed Professor of Radiology at Harvard Medical School.

“Give creative people like my colleagues here at Massachusetts General Hospital the tools and they will do groundbreaking work.”

Massachusetts General Hospital (MGH) was established to provide care to Boston’s sick in 1811. It subsequently became the first teaching hospital for Harvard University’s new medical school. Today, MGH has the broadest hospital-based research program in the United States, with an annual research budget in excess of \$900 million and research programs that span more than 30 clinical departments and centers of excellence across the hospital. Approximately 1,200 clinical trials take place at MGH at any given time.

The Department of Radiology at MGH is currently the largest in the US and, in addition to the significant workload of routine patient imaging, a series of special interest research centers are housed under its umbrella.

Innovative imaging at MGH

Within the scope of this research work, there has been a long-standing interest in magnetic resonance imaging (MRI) at MGH, starting in the 1980s in what was then called the NMR Center. This group was involved at the dawn of molecular imaging: imaging molecules of medical interest within living patients. Several important innovations came out of the center: it

was the birthplace of fMRI (functional MRI), and pioneering work in perfusion, angiography and functional brain imaging all emerged.

Dr Caravan picks up the story: “The department grew over the years. It broadened out to include, for example, optics, magnetoencephalography, and computational cores for complex, quantitative multimodal imaging. Then, with the growth of positron emission tomography (PET), especially simultaneous PET/MR imaging, the leadership team was very interested to expand the work of the Center further – but this required, for the first time, a chemistry commitment to prepare radiolabeled tracers on site. That was my background, and what brought me to MGH. I joined the team in 2007 to help establish a new molecular imaging facility to take advantage of PET technology.”

A year later, in 2008, a commercial prototype PET/MRI called BrainPET (Siemens) was installed and the first patient imaging programs began. This was followed by establishment of a state-of-the-art PET radiotracer effort, including a cyclotron and radiochemistry production facility to enable researchers to prepare PET radiotracers for human research studies.

Imaging modalities that are now dedicated to research (separate from the clinical service provision) at the various institutes within MGH

include: 8 large-bore MRI scanners for human studies including two simultaneous PET/MRI systems, 3 small-bore MRI systems for animal work, micro-PET, micro-SPECT (Single Photon Emission Computed Tomography), micro-CT (Micro Computed Tomography), optical imaging such as fNIR (functional Near-Infrared) spectroscopy, and magnetic particle imaging (MPI).

The program has continued to flourish and now, 10 years on and housed in the Athinoula A. Martinos Center for Biomedical Imaging, a faculty of around 80 staff, plus students and post-doctoral researchers, make up one of the world's premier research centers devoted to the development of advanced biomedical imaging technologies and tools, and their application to solve challenges in neuroscience, oncology, cardiology and many other clinical pathologies.

Dr Caravan explains how the center operates today: "We have a very horizontal structure in the center, with a large number of principle investigators who have a broad range of research interests. It's a great mix of groups – some are concentrated on hardware, others on tracer development, many are working on preclinical models, several focus on monitoring active disease in patients. All enjoy the collaborative nature of the center and the flow of ideas and technology into their diverse projects. It means that my colleagues can take advantage of the latest advances where normally they would be working with an 'off-the-shelf' solution."

Towards the end of 2018, the center celebrated its 10-year molecular imaging program with a symposium to highlight some of the research its investigators were pursuing at that time.

Presentations covered optical, PET, MRI, MPI and molecular imaging, as well as image-guided therapy. The range of application areas was equally varied, with talks about the use of molecular imaging in immunotherapy and other cancer applications, Alzheimer's and other neurodegenerative diseases, neuropathic pain, fundamental neuroscience, cardiovascular disease, chronic liver disease, and idiopathic pulmonary fibrosis. The lectures also emphasized the many innovations in radiochemistry, including molecular probe development, hardware, and image analysis and data modelling techniques, to have come out of the Center over the past decade.

Collaboration with Bruker

"We have recently secured two grants that would not have been awarded if we did not have the Bruker system for simultaneous animal analysis."

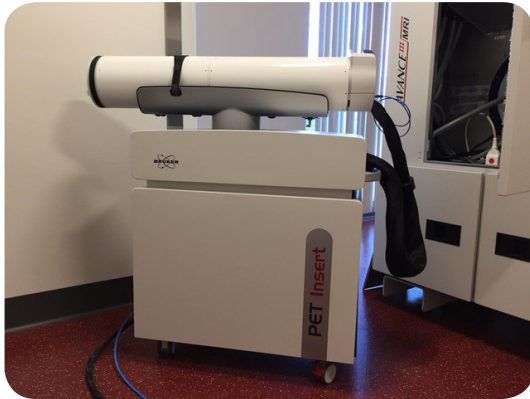
The Martino's Center team's experience with PET/MR over 10 years generated potential ideas to explore, many of which were not able to be realized with traditional large-bore systems, or human subjects.

Dr Caravan explains: *"We wanted to be more active, imaging tissues and organs and then perhaps taking them out for further analysis. We needed to get down to animal models and utilize smaller scale systems that were tailored to this work. This is when we made a great connection with Bruker and started some very profitable discussions."*

"Bruker comes from a background in MRI before adding PET and other modalities to the portfolio. So, unlike others who came from PET and didn't have the depth of knowledge about the benefits MRI could bring, Bruker knew instinctively that the symbiosis of the modalities could bring much more than just the co-location of the signals."

Bruker and MGH initiated a research agreement that Dr Caravan describes as being very fruitful. Dr Caravan continues, *"I believe Bruker has learned a lot about how we look at problems. And, from our side, I can say that they have been tremendous – in terms of applications and hardware support. The whole partnership has been very collaborative, for example, our joint work in solving problems of data analysis where isotopes have energies that make quantification difficult."*

Dr Caravan continues: "At the time of the symposium, four novel PET tracers had been invented and had first-in-human studies performed at the Martinos Center. During 2019 we added three more."



End-to-end application

In many hospital settings, the focus for molecular imaging is with 'large-bore' systems for human imaging, be it whole body, or targeted to a single organ – the brain, for example. The goal is most often diagnosis – or staging – or therapeutic monitoring of a patient. As noted above, MGH utilizes a range of advanced technologies to achieve this goal.

Importantly, scaling these same imaging technologies down to a 'small-bore' format enables a key part of preclinical research – the construction and testing of small animal models that allow scientists to gain a deeper understanding of human disease development and the effect and safety of potential treatments.

Importantly, the concurrent development of novel PET probes is an essential support to both of these applications.

Dr Caravan explains how these principles are applied at MGH: "Our mission can be summed up as the translation of innovations from across

PET insert

The most recent hardware addition to MGH is the Bruker PET insert, installed in 2019. A critical factor in choosing the system was the ability to image multiple mice at the same time. Working with isotopes of carbon that have a short 20-minute half-life is expedited greatly by the ability to image six animals simultaneously.

Dr. Caravan adds, *"The system has really been the right choice. It was easy to install, is very easy to use, and has the wide field of view and flexibility that has allowed us to, for example, fabricate specific carriers and cradles that meet the needs of our research."*

"It's also important to say that the system has not just supported our efforts to secure grants to expand our work, it has enabled us to plan projects that just could not have been conceived without it. We have recently secured two grants that would not have been awarded if we did not have the Bruker system for simultaneous PET/MRI."

the center into a commercial framework. We look to develop models and novel tracers for first-in-human studies and, whilst we use all imaging modalities where appropriate, much of our work is designed to take advantage of the benefits of PET. Most important is the fact that PET molecular imaging probes offer a shorter and more economical path to clinical translation when compared to MRI probes. The low microgram mass dose required for PET allows for an abbreviated preclinical safety and toxicology package to be submitted to regulators to initiate human studies."

Recent work – fibrosis, thrombosis and more

Turning to Dr Caravan's personal research focus, and the current work of his team, he explains that there is an ongoing interest in the wide range of clinical pathologies where fibrosis plays a key role: *"More than half of all deaths are caused by diseases that have some fibrotic component. Most chronic diseases of the heart (cardiomyopathies, myocardial infarction, atrial fibrillation), liver (hepatitis B, C, steatohepatitis), kidney (diabetic nephropathy), lung (pulmonary fibrosis), arteries (atherosclerosis), and many cancers, all result in fibrosis or scarring of the tissue."*

Against this broad background, the Caravan lab is developing imaging-based molecular methods and tools to detect and stage fibrosis in different organs and monitor response to drug treatments. Dr Caravan expands: "Often we don't have particularly good tools to look at tissue fibrosis – especially at early stages of the disease – or the ability to distinguish ongoing injury vs historic scarring. With our work we strive to better understand fibrosis biology and how it is intertwined with inflammation and immune responses."



The desire to intervene early in the development of a disease is a clear focus, as is the idea that appropriate monitoring of disease in an individual patient can help meet the goals of personalized treatment. Dr Caravan comments: *"You can easily imagine that with this approach we are collaborating with colleagues exploring fundamental biology, clinicians treating patients, and the pharmaceutical companies who are working on better treatment options. It's a very diverse outlook."*

Currently, early detection and quantitative staging, as well as assessing how much fibrosis is present, often relies on using biopsy tissue. In many cases, this is a one-off process, making tracking therapy or disease activity difficult. In many cases the process of taking a biopsy carries significant risk to the patient. Imaging can alleviate the need for biopsy but, as Dr Caravan explains, moving to molecular imaging with instruments such as Bruker's PET and simultaneous PET/MR systems come into their own: *"The effects of advanced disease, such as cirrhosis in the liver, are easy to see with established imaging techniques. But these morphological methods do not work so well at early stage, and they are not really sensitive to small changes or dynamic development of disease."*

Initially, Dr Caravan developed a probe that targets type 1 collagen, the overexpression of which is a hallmark of organ fibrosis. Initial work was for MRI but this has now been translated to PET, where it is being used in a number of clinical trials. Dr Caravan describes the project: *"We set out to provide a new tool for non-invasive PET imaging of human pulmonary fibrosis. Starting with a cyclic peptide that we had identified by phage display and had confirmed could recognize and bind to type 1 human collagen, our initial work functionalized the molecule to provide magnetic resonance signal enhancement."*

The resulting MRI probe showed excellent ability to detect and stage disease in preclinical models of cardiac, hepatic, and pulmonary fibrosis¹. The next stage built on this success to take advantage of PET's capability to be quantitative and readily translatable to clinical research. The peptide probe was modified for PET and then evaluated in two established mouse models of pulmonary fibrosis. The probe (⁶⁸Ga-CPB8) showed high specificity,

and high target/background ratios in diseased animals. The PET signal and lung uptake correlated with the amount of lung collagen in mice with fibrosis. Furthermore, it was demonstrated that ^{68}Ga -CPB8 could be used to monitor response to treatment. In all cases, ex vivo analysis of lung tissues from patients with pulmonary fibrosis supported the animal model findings.

Dr Caravan concludes:

“With ^{68}Ga -CPB8, we have a very promising candidate for non-invasive imaging of human pulmonary fibrosis.”

The group has also built technology sensitive to active fibrosis as opposed to older injury. This is still at preclinical stage, but they have collected data in lung, liver and kidney applications and are working now to translate this into clinical programs.

In addition, the team is working in the related area of thrombosis (blood clot). Thrombosis is a critical event in cardiovascular diseases such as myocardial infarction, stroke, and pulmonary embolism (PE), all leading causes of death and morbidity. Currently detection often requires multiple diagnostic techniques that depend on the location of the thrombus. For example, ultrasound is needed for detection of deep vein

thrombosis (DVT), invasive transesophageal echocardiography (TEE) and MRI for cardiac chamber clots, and CT pulmonary angiography for PE. Despite the success of these techniques, there is a need for imaging tests that can identify thrombus anywhere in the body and can be used to image multiple vascular territories. Moreover, current techniques do not provide information on thrombus or embolus composition, data which may prove invaluable in guiding treatment decisions.

As with their work on fibrosis, Dr. Caravan's group started with a successful MRI probe, and looked to transition to PET imaging. In this case, a driving factor was that, with MRI, two scans are required, one pre- and one post-injection of the probe, whereas only a single scan, post-injection, is required with PET.

Dr Caravan outlines the research²: *“There are fibrin-specific peptides that enable the development of thrombus specific probes for different imaging modalities – MR, optical, PET, or SPECT imaging – for example. The MR probe EP-2104R has been shown to be effective in detection of thrombi in humans so we took this as our starting point. We optimized a ^{64}Cu -labeled probe that revealed fast renal blood clearance, low background signal, and persistent uptake in thrombus”* (Figure 1).

Dr. Caravan sums up: *“Given the favorable properties of ^{64}Cu -FBP8 in animal models, data with ^{64}Cu -FBP8 in humans will certainly be forthcoming. For clinical applications with ^{64}Cu -FBP8, an imaging paradigm where the patient is imaged one to three hours after administration*

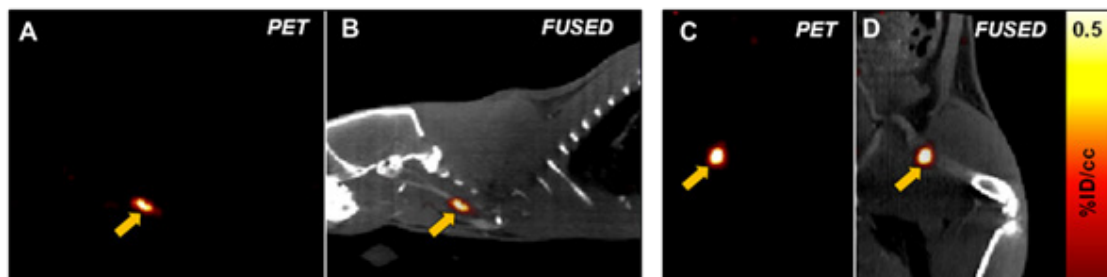


Figure 1: **A)** ^{64}Cu -FBP8 PET of the head and thorax of a rat with a region of focal PET signal (arrow) and **B)** fused PET with CT angiogram showing thrombus localized to common carotid artery (arrow). **C)** ^{64}Cu -FBP8 PET of the pelvis and thighs of a rat with a region of focal PET signal (arrow) and **D)** fused PET with CT angiogram showing thrombus localized to the femoral vein (arrow).

of the probe, allowing ample time for blood clearance, may become a standard approach. Furthermore, given the extent of structure-activity data available, it is clear that other probes using a different isotope or imaging reporter could also be developed for human use."

Looking ahead

A mindset of continuous improvement is embedded in the Caravan Laboratory philosophy. The team is constantly looking to improve and reimagine better probes. Recently published work³ on developing an alternative to Gadolinium-based contrast agents (GBCAs) is a case in point.

Dr Caravan explains their approach: "GBCAs have been used in combination with MRI for many years and are considered extremely safe. However, trace amounts of gadolinium (Gd) have been detected in the skin and central nervous system of patients with normal renal function, months to years after administration."

Neither the biodistribution and clearance of GBCAs, nor the chemical form of the retained gadolinium species is fully understood. Yttrium(III) and Gd(III) have very similar ionic radii, leading to very similar chemical behavior, so Dr Caravan's colleagues wanted to determine if it could serve as a PET imaging reporter for Gd in GBCAs. The results led the team to the clear conclusion that Y³⁺ can indeed be used as a surrogate for Gd³⁺ in GBCAs. Dr Caravan confirms: "We believe that Yttrium-86 labelled GBCAs represent a useful new tool to study the whole-body distribution and elimination of GBCAs."

Interest has also been shown recently in the role of fibrin in neuroinflammatory conditions like multiple sclerosis and Alzheimer's disease, and Dr Caravan's team has studies in progress in this area too.

And with COVID-19, both the fibrosis and the thrombosis probes are proving useful. For example, many patients with COVID-19 have exhibited blood clotting disorders, so the ⁶⁴Cu-FBP8 probe is being used to look for thromboemboli in the body. In addition, the ⁶⁸Ga-CPB8 probe is being used to look at the condition of the lung in recovered patients, aiming to assess how susceptible they might be to pulmonary fibrosis in the future. These studies are ongoing at MGH.

Dr Caravan sums up his work, saying:

"Imaging read-outs can be interpreted very broadly, and our experience highlights that the opportunity afforded by PET technology is much wider than what many think of as the traditional application areas of oncology and neurology. Furthermore, using PET in addition to MRI and other modalities has proven that we can generate far more robust models of disease."

Further reading and a bibliography of publications from Dr Caravan and his colleagues at MGH can be accessed at:

<https://www.ncbi.nlm.nih.gov/myncbi/peter.caravan.1/bibliography/public/?sortby=pubDate&sdirection=descending>

For more information on small PET imaging, visit:

https://www.bruker.com/products/preclinical-imaging/nuclear-molecular-imaging.html?gclid=CjwKCAjwxev3BRBBEiwAiB_PWP_tzhLhvNs4yWr0eaVqnegfUY1ZX28l6vq06K2Jn-YnBW7bCUew_oRoCEfgQAvD_BwE

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- [3] Le Fur M et al., Angew Chem Int Ed. 2020;59(4):1474-8.

About Peter Caravan

Dr Caravan is an NIH funded investigator based at MGH since 2007, whose research focuses broadly in the areas of fibrosis, thrombosis, and probe (MRI, PET, CT, optical) technology development. Dr Caravan received his BSc (Honors) at Acadia University, his PhD in chemistry from the University of British Columbia, followed by an NSERC postdoctoral fellowship at the Université de Lausanne. Prior to joining the team at MGH, he spent 9 years in industry, developing tissue-specific (e.g. gadofosveset) and responsive MRI contrast agents. He is co-inventor of EP-2104R, a fibrin-specific contrast agent for thrombus detection, that was the first molecular MR imaging agent to enter into human clinical trials. He holds investigational new drug applications for two novel PET tracers invented in his lab and currently being evaluated in 8 clinical trials. Dr Caravan has contributed twelve book chapters on the chemistry, properties, and uses of imaging. He has published more than 160 peer-reviewed papers on the chemistry of imaging probes, the biophysics of the interactions of these probes with proteins, and their application in animal models of disease and in patients. Dr Caravan is co-inventor on 25 granted or pending patents related to new imaging agents and methods for their use.

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