Preclinical MR Fingerprinting studies being conducted on a Bruker Biospec 9.4T MRI scanner by CWRU graduate students Christina MacAskill (Chris Flask lab) and Yuran Zhu (Xin Yu lab).

MRI

Imaging Serves as a Scientific Hub to Unite Preclinical and Clinical Research

Innovation with Integrity

The Case Center for Imaging Research (CCIR) in the Department of Radiology at Case Western Reserve University (CWRU) and University Hospitals – Cleveland Medical Center (UHCMC) in Cleveland, Ohio, focuses on the use of advanced imaging technologies to conduct medical and scientific studies. The unique position of the CCIR housed within University Hospitals of Cleveland enables the collaborative environment that brings together experts in imaging, mathematics, chemistry, physics, biomedical engineering, and radiology, to make ground-breaking contributions to medical science. The Imaging Research Core is the functional arm of the CCIR at CWRU with the primary goal of bringing novel imaging methods to all investigators in Northeast Ohio.

As a tenured professor in the CCIR, Professor Chris Flask works with magnetic resonance imaging (MRI) to explore the mechanisms of disease, understand what the results mean, determine what methodology works best, and most importantly, determine what the limitations of those imaging methods are. His research interests include the development of new, fast, and reproducible quantitative MRI methods, such as magnetic resonance fingerprinting methods, and their application for a variety of genetic diseases including cystic fibrosis, autosomal recessive and dominant polycystic kidney disease, and sickle cell disease.

In his work, Prof. Flask collaborates closely with with radiologists and clinicians within the hospital, to allow this research to eventually impact many patients whose diagnoses and/or treatments will become more accurate, more comfortable, safer, and/or less expensive because of these imaging advancements.

"We have experts from multiple fields bringing all their knowledge together to determine how to approach these medical problems from an imaging perspective, and answer questions in unique and profound ways," Prof. Flask explains. *"Collaboration has become the gold standard in biomedical research because you can't answer these questions alone. We're looking at how we can work together and apply imaging techniques with the goal of helping patients."*

Working with cutting-edge technology from Bruker, Prof. Flask and his colleagues are breaking new ground in MRI and imaging technology to find new ways to apply preclinical animal research and translate those capabilities into a clinical setting.

Where the CCIR began

In 1999, the National Cancer Institute identified medical imaging, particularly cellular and molecular imaging, as an opportunity in the fight against cancer. Based on its strong imaging program in the School of Medicine and the Case School of Engineering, CWRU faculty members Jeffrey Duerk, PhD, Jonathan Lewin, MD, and David Wilson, PhD, began to envision the creation of the CCIR. In 2001, construction of the center began after a $12 million commitment from the university for faculty startup, renovations, staff, and pilot funding.

Prof. Flask, still a graduate student at the time and working on his own research, was given a key role in coordinating the design and construction of the new facility, which opened in 2005.

"That's also when I started working closely with Bruker on site planning enabling MRI experiments tailored to CCIR's speciifc needs." he explains. The relationships Prof. Flask developed in those early years served as the foundation of the collaborative nature of the CCIR, which continues to this day.

"Preclinical research was really exploding at the time," he reveals. *"My job was to help figure out how to get the lab built and make it operational. It was a blessing in many ways because I've sat down with almost every person at CWRU and University Hospitals – Cleveland Medical Center to ask for help, and that enabled me to establish relationships. Those interactions were the very beginning of the highly collaborative environment that we've built here in the CCIR, so we were able to hit the ground running and grow rapidly when the center opened."*

Uniting preclinical and clinical research

From the outset, the CCIR team has deemed that collaborations between preclinical and clinical researchers and across disciplines can foster a more holistic approach to solving complex medical challenges. The combination of preclinical and clinical research accelerates the translation of scientific discoveries from the laboratory to real-world applications, providing new opportunities for improving patient care and medical advancements.

"We had a unique opportunity because the CCIR is part of the Department of Radiology at CWRU and University Hospitals," Prof. Flask explains. *"It's not typical. Our approach is about bringing basic scientists and clinicians together and using imaging as a scientific hub. The people and the collaborations make the difference."*

The CCIR provides access to imaging technology, as well as a gateway to imaging techniques developed in-house by faculty and opportunities to develop novel imaging techniques that suit a researcher's needs. Current imaging applications include imaging for disease detection and visualization, drug delivery, biodistribution, and pharmacokinetic modelling, gene expression imaging, imaging of cancer and early assessments of cancer therapies, cardiovascular imaging, metabolism, nanotechnology development, imaging physics, and hardware and software engineering.

"The CCIR really draws all of these diverse researchers to the table to enable a broader discussion on biomedical imaging applications," Prof. Flask says. *"We have 30-40 researchers here at any given moment, as well as a critical mass of expertise across multiple disciplines. Research is not for the faint of heart. Your grant funding is based on building a good team, and it requires the ability to dialogue. It comes down to people with the skills, but also the willingness. We want people who want to work together – and Bruker as a partner also fits that profile."*

Chris A. Flask, PhD, is a Professor in the Departments of Radiology, Pediatrics, and Biomedical Engineering and the Director of the Imaging Research Core at the CWRU School of Medicine. After starting out as a chemical engineer in the petroleum additives industry, Prof. Flask received his graduate degree in Biomedical Engineering with a focus on MRI physics. Now, Dr. Flask's research focuses on the translation of imaging technologies from preclinical animal models to clinical studies in patients. Using his extensive experience in both basic science and translational imaging, Prof. Flask's work has played a key role in advanced MRI acquisition design, optical imaging, image processing, and life sciences with over 100 peer-reviewed publications and numerous NIH and foundation grants.

Involved with CCIR since its inception, Prof. Flask has worked extensively with Bruker for almost 20 years, particularly in the initial implementation of imaging technology, as well as through a recent upgrade process.

"Bruker has been a great partner," Prof. Flask says. *"The Bruker team has collaborated with us by understanding our work and have provided exactly what we needed. We're not a conventional academic research facility, and we appreciate how they acknowledge our distinct requirements."*

The work of Prof. Flask and his team focuses on using insights from preclinical research conducted on animal models using Bruker instruments to explore the underlying mechanisms of diseases, treatments, and interventions – which can then guide the design of clinical trials by providing a foundation of knowledge about how a particular treatment or approach might work. By comparing preclinical data to pathological data, CCIR researchers can better understand the translational relevance of preclinical findings to human diseases.

"I always need validation of what our imaging data is showing us, so we're comparing our preclinical quantitative MRI results with what we're seeing in pathology," Prof. Flask explains. *"We're constantly asking researchers if they really know what they are measuring. The advantage of combining pre-clinical and clinical MRI methods is having the confidence to know exactly what the data is showing us by scanning both animals and patients and being able to compare those results. It's an iterative process that has proven to be very successful."*

Accelerating new treatments for rare diseases

Prof. Flask's collaborations include some of the most challenging diseases in modern medicine, including cystic fibrosis[1–3] and polycystic kidney disease.[4,5] In particular, his recent work with Dr. Katherine Dell, MD, a pediatric nephrologist at CWRU and the Cleveland Clinic, has shown promise in providing a basis for applying quantitative MRI techniques to stage and monitor progression in children and young adults with autosomal recessive polycystic kidney disease (ARPKD). The team is particularly excited because ARPKD is a genetic disease associated with significant mortality and morbidity in babies and young children, and currently there are no disease-specific treatments available for patients.

"It's one of my proudest moments, because our imaging work will likely directly enable some of the first clinical trials for kids with ARPKD," Prof. Flask says. *"It's a disease that not many people know about because it's rare, but it's also quite lethal. Approximately one third of the kids with ARPKD don't make it out of the neonate phase. Of the kids that do survive, another 50 percent have significant and sometimes life-threatening clinical issues by 15 years of age."*

It's also an example of the strong personal motivation of Prof. Flask and the CCIR team to make a positive impact on society. This type of collaborative research holds great potential to create meaningful change to improve patients' lives.

"My personal experience as a father of a child with a chronic disease, who spent considerable time in a hospital undergoing tests and treatment, has profoundly impacted my research," he says. *"It's beyond just diagnosing a child with a disease. It's determining the status of the disease, how well the child is responding to therapy and the physiological effects. We want to make medicine better, more rigorous, and more objective to help patients."*

Working with Bruker

Currently the CCIR has both the 7.0 T and 9.4 T Bruker BioSpec preclinical MRI instruments, which were chosen to help the team with their most challenging applications. Designed for the emerging market of preclinical imaging and molecular MRI, the innovative modular concept of the Bruker BioSpec enables small animal MRI application in life science, biomedical, and preclinical research.

"Bruker provides us with state-of-the-art instrumentation. In my mind, there is no real competitor," Prof. Flask says. *"It's a very stable system, which is important because we are conducting some very challenging MRI experiments. We push the preclinical scanners very hard as our goal is to have imaging data on a mouse model in 10 seconds, not every hour or two, so we can see the dynamics of the physiology and organ-based function. Most of the other preclinical MRI systems on the market cannot meet these technical demands."*

Next steps

Based on these accomplishments, Prof. Flask and his team plan to expand the collaborative environment of CCIR to include multimodal imaging techniques, including positron emission tomography (PET) and PET-MRI, which can support even more comprehensive research. One part of this plan includes adding PET to the center's human MRI system, which would provide the opportunity to do large animal as well as human studies.

"We have enough of a critical mass of people to show that this preclinical and clinical partnership really does work," Prof. Flask explains. *"We want more people to understand how it all fits, so the integration becomes even bigger. We're bringing the same approach to multimodal imaging because these techniques are very complementary and have much more potential. For example, you can take some of our quantitative MRI methods and MR fingerprinting methods that provide information on tissue composition and function, and then couple it with PET imaging capabilities to provide complementary mechanistic and molecular information. That's where our program is headed."*

By integrating information from various imaging methods, researchers and professionals can gather a more complete picture, enhancing their ability to diagnose, analyze, and interpret complex phenomena. That expansion includes more opportunities for collaboration, as well as research on other diseases.

"By taking the successful model that we've already established and expanding into a multimodal platform, we're adding knowledge as well as bringing more people on board. It also enables us to tackle other diseases like Alzheimer's with neurotransmitter assessments, brain architecture and connectivity. It's a whole new area with great potential to help patients that I'm excited about seeing grow significantly in the next few years."

References:

1. Dasenbrook EC, Lu L, Donnola S, et al. Normalized T1 magnetic resonance imaging for assessment of regional lung function in adult cystic fibrosis patients--a cross-sectional study. PLoS One. 2013;8(9):e73286. doi:10.1371/journal.pone.0073286
2. Donnola SB, Dasenbrook EC, Weaver D, et al. Preliminary comparison of normalized T1 and non-contrast perfusion MRI assessments of regional lung disease in cystic fibrosis patients. J Cyst Fibros. 2017;16(2):283-290. doi:10.1016/j.jcf.2015.11.009
3. McBennett K, MacAskill CJ, Keshock E, et al. Magnetic resonance imaging of cystic fibrosis: Multi-organ imaging in the age of CFTR modulator therapies. J Cyst Fibros. 2022;21(2):e148-e157. doi:10.1016/j.jcf.2021.11.006
4. MacAskill CJ, Erokwu BO, Markley M, et al. Multi-parametric MRI of kidney disease progression for autosomal recessive polycystic kidney disease: mouse model and initial patient results. Pediatr Res. 2021;89(1):157-162. doi:10.1038/s41390-020-0883-9
5. MacAskill CJ, Markley M, Farr S, et al. Rapid B1-Insensitive MR Fingerprinting for Quantitative Kidney Imaging. Radiology. 2021;300(2):380-387. doi:10.1148/radiol.2021202302

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info@bruker.com

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