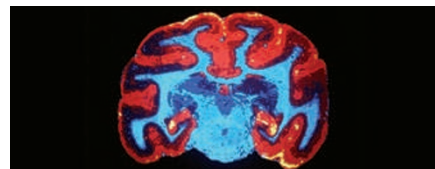


# Imaging

Imaging technologies are increasingly being applied to aid translational research — for example, by allowing drug–target interactions to be monitored in clinical trials. Our two interviewees this month describe their careers in this field.



**Richard Hargreaves, Ph.D.** Vice President, Worldwide Head of Discovery Neuroscience, Merck Research Laboratories, West Point, Pennsylvania, USA.

Until recently, many approaches to drug discovery in neuroscience have been largely empirical, with programmes advancing to proof-of-concept clinical trials without clear evidence on important factors such as drug pharmacodynamics in the central nervous system (CNS). To address this issue, in the last decade, Richard Hargreaves has established and led a worldwide imaging group to support drug discovery and development across all of Merck's therapeutic areas.

"A key attraction of this assignment was the challenge of establishing molecular and functional imaging techniques to aid translational research in our neuroscience programmes by providing evidence of CNS target engagement by drug candidates and monitoring their pharmacodynamic effects on relevant neural pathways," explains Hargreaves.

Hargreaves first became involved in research that led to his interest in using imaging in neuroscience while studying for his Ph.D. in the physiology department at King's College London, UK, with Michael Bradbury and Jill Cremer. During this time, he also worked in the pharmacology department of the British Industrial Biological Research Association, London. "My studies focused on blood–brain barrier glucose transfer, cerebral blood flow and glucose metabolism," he says. "This, together with my fascination with neuropharmacology, led me to CNS drug discovery and then to applying the rapid advances that were being made in non-invasive imaging technologies to study the action of drugs on the brain."

Following this path, he joined Les Iversen and Sue Iversen at Merck's newly established neuroscience research centre in Harlow, UK, in 1988. He subsequently led the discovery biology teams that contributed to the development of various drugs, including the pioneering neurokinin 1 receptor antagonist aprepitant, which is used to prevent nausea and vomiting following chemotherapy. The important role of positron emission tomography (PET) imaging in the registration of aprepitant led to an increased appreciation of the value that imaging could provide, and encouraged Hargreaves to take on

the role of establishing a global imaging group in the USA as part of an initiative from Peter Kim, President of Merck Research Laboratories, known as 'Target-through-Phase2B innovation'.

In 2008, he became Vice President and Worldwide Head of Discovery Neuroscience. and together with the Neuroscience franchise head Darryle Schoepp, he has overall responsibility for the strategic and scientific direction across the neuroscience drug discovery process. "This move has allowed me to use the imaging capabilities that we built as platforms to improve decision-making in our neuroscience programmes," he says. "Now, although our understanding of neural pathways in health and disease is still developing, we can at least increase our probability of therapeutic success by focusing only on the best molecules that have imaging biomarkers that allow us to confidently test our clinical hypotheses."

The opportunity to combine drug discovery with imaging to have a better understanding of CNS disease and drug actions is one aspect he finds particularly rewarding. "There are few jobs where every day you get to follow your scientific passions, see something new and have a chance to discover something that could make a profound difference to the lives of many people," he concludes.



**Eugenii A. Rabiner, FCPsych (SA)** Director, Clinical Imaging Applications, GlaxoSmithKline Clinical Imaging Centre, Hammersmith Hospital, London, UK.

When the GlaxoSmithKline (GSK) Clinical Imaging Centre (CIC) was established in 2005, it was the first CIC owned and managed by a pharmaceutical company. The Clinical Imaging Applications (CIA) group at the CIC interacts with clinical and preclinical drug development teams at GSK to ensure the optimal application of imaging techniques in drug development. "We assess whether imaging approaches are well placed to address challenges arising in drug development, and if so, design specific studies," says Eugenii Rabiner, Director of CIA. The CIC has extensive expertise in neuropsychiatric molecular imaging, and is rapidly expanding its capabilities in the fields of oncology, inflammatory and metabolic diseases.

Rabiner's research interests in imaging developed during his training as a psychiatrist at the University of Cape Town, South Africa. "I was interested in doing some research and did a 5-year fellowship applying PET imaging at the MRC [Medical Research Council] Cyclotron Unit at Hammersmith Hospital in London and the Psychopharmacology Research Unit at the University of Oxford. My work focused on 5-HT<sub>1A</sub> receptor function in mood disorders, and investigated the binding of a number of novel and established compounds to brain 5-HT<sub>1A</sub> receptors," he says.

Following his fellowship, Rabiner was keen to stay at the cutting edge of imaging research. "As my research interests are in exploring the interactions of pharmaceuticals with their *in vivo* targets, it was a logical step to move to a pharmaceutical company." He joined GSK in December 2001 as a psychiatrist responsible for the PET programme supporting the Psychiatry and Neurology Centres for Excellence in Drug Discovery. "The idea of working in a large well-resourced organisation which focused on *in vivo* psychopharmacology was very appealing," he adds.

In July 2005, GSK established the CIC and Rabiner took the role of Head of the CIA

group. He leads a team of imaging scientists who support GSK's drug development teams. "Imaging applications require a thorough understanding of the biology specific to the question being asked, the drug development process, and of the technical and practical aspects of various imaging techniques, so the main challenge is in bringing a wide range of specialists into a single study team and leading them through an effective study," he explains.

Although leading a variety of specialists may be challenging, Rabiner also considers it to be an advantage. "Being part a large pharmaceutical company provides me with access to a variety of gifted scientists. This means that I can get valuable input into my work from a wide range of sources." His team also collaborates with many academic PET units, such as the Columbia University PET group in New York, USA, and the Yale University PET Centre in New Haven, USA. Given these extensive opportunities for external input, Rabiner notes that another challenge is to be able to understand and keep enough focus on the details without losing the big picture. "It is essential to keep an open mind and be willing to critically accept input wherever it may come from."