



Organic and inorganic research hand in hand: Veronique Gouverneur and Jon Dilworth work closely in radiolabeling biologically active molecules for imaging and therapeutic applications.

The UK takes to PET

The new molecular imaging laboratory at the University of Oxford marks the first stage in establishing a national PET research center in the United Kingdom.

By Linda Brookes



The Siemens Oxford Molecular Imaging Laboratory is located in the university's inorganic chemistry building.

Positron emission tomography (PET) imaging is beginning a period of major expansion in the United Kingdom. In October 2005, the UK government announced its plan to invest approximately €29 million over two years to expand the provision of PET facilities nationwide in an effort to become a global player in providing PET services. A specially commissioned report recommended the establishment of up to 16 new PET centers. This includes six centers with a PET scanner and a cyclotron located on the same site, where basic, translational, and clinical research into new applications of radiopharmaceuticals could take place. Oxford is one of these centers, and the new facilities are currently being set up at the university and city hospitals.

As part of a collaboration between government and industry to fund research in this field, a grant of approximately €2.9 million was awarded to the University of Oxford by the Department of Trade and Industry (DTI), the Engineering and Physical Sciences Research Council (EPSRC), and Siemens, to support a project entitled 'Chemistry and Image Analysis for Assessment of Radiation Therapy using PET.' The project involves Professor Jon Dilworth, MA, DPhil, DSc, FRSC; Veronique Gouverneur, MA, PhD (Department of Chemistry); and Sir Michael Brady, FRS FEng (Department of Engineering). Central to this project is a new laboratory containing state-of-the-art instrumentation for the handling of positron-emitting radioisotopes used for PET imaging. "Once we had the funding from the government and the connection with Siemens, we were able to persuade the university to invest in the infrastructure of the laboratory," says Dilworth. The Siemens Oxford Molecular Imaging Laboratory (SOMIL), located in

the university's inorganic chemistry building, was formally inaugurated at the end of January 2007 by Michael Reitermann, President of Siemens Medical Solutions Molecular Imaging Division. The facility will be used for radiolabeling biologically active molecules for imaging and therapeutic applications. Additionally, Siemens and the Oxford University's team work closely to develop software for image post-processing (for integration and analysis in the Inveon Research Workplace). Inveon is a preclinical Siemens scanner capable of PET, single photon emission-computed tomography (SPECT), and computed tomography (CT) studies.

Hypoxia Study for Expanded Knowledge

The goal of the project is to identify new agents for imaging tumor hypoxia – a characteristic of solid tumors that increases their resistance to radiotherapy and chemotherapy, as well as triggering angiogenesis. Patients who show a higher degree of hypoxia in a tumor have a worse prognosis. By detecting and quantifying tumor hypoxia, treatment can be targeted more specifically and its effects can be monitored.

Ideally, radiation therapy should be matched exactly with the profile of the tumor. It is believed that a high percentage of patients are currently being unnecessarily treated with radiotherapy because the clinician is unaware that hypoxic tissue is being irradiated. These patients experience the side effects of radiation without gaining any therapeutic benefit.

PET enables noninvasive detection and quantification of tumor hypoxia. A number of radionuclide-labeled hypoxia markers have been developed for PET, but

in general, although they show preferential uptake in hypoxic tumor cells, they are not ideal. New agents are needed that can better differentiate between hypoxia and normoxia or anoxia, and that are more selective for different levels of hypoxia. Professor Dilworth and Dr. Gouverneur are attempting to synthesize such agents based on compounds that have already been shown to be hypoxic selective. They identify these compounds from the scientific literature, and then manipulate the chemistry so that the same compounds can be produced by an improved process or so that they can produce variants with superior properties. The radioisotopes are introduced into the compounds at the latest possible stage in the synthesis, depending on the half-life of the isotope. "The chemistry of these compounds is then manipulated so that they can be synthesized by improved routes or show enhanced biological properties," Dilworth says. "It is impossible to control the chemistry of these compounds without understanding the fundamental radiochemistry first. That is the spinoff that comes from a project like this; while we are focused on hypoxia, we generate methodologies and knowledge that is then expandable."

Dilworth's primary focus in this project is on copper(II)bis(thiosemicarbazones). The radioisotope of copper used for labeling these compounds is cyclotron-generated ⁶⁴Cu, a relatively long-lived positron emitter. The resulting complexes are highly selective for hypoxic cells. To further understand the chemical reasons for this process, he is studying the fundamental

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Professor Jon Dilworth,
Head of Radiochemistry,
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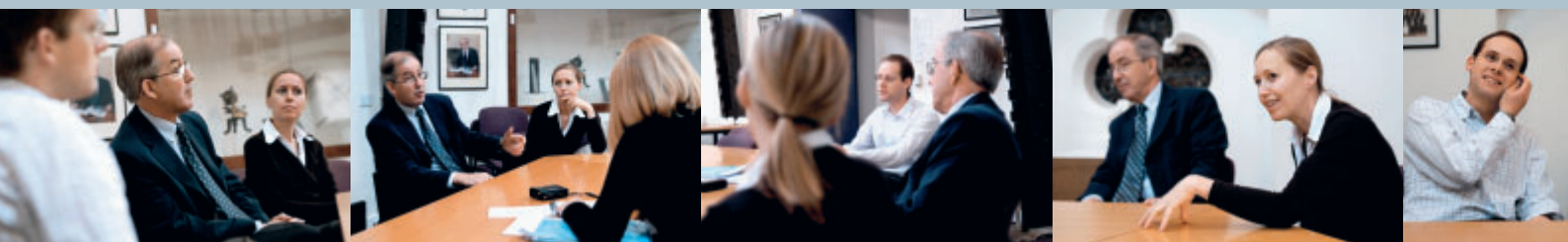
properties of the complexes using techniques such as electrochemistry and density functional theory (DFT). Several new classes of copper(II) complexes have been synthesized based on their redox and chemical properties and are being tested for hypoxic selectivity.

Gouverneur is working on the synthesis of radiolabeled fluorinated compounds based on the glucose analogue F-18 fluorodeoxyglucose (F18-FDG), currently the best-known and most widely used PET radiotracer for imaging tumor hypoxia. Imaging with FDG is based on the increased glucose meta-bolism that occurs in tumor tissue. Gouverneur is also investigating com-plexes based on F-18 fluoromisonidazole (F18-FMISO) – the first nitroimidazole developed for use in PET scanning.

Exploring the Potential of Various Compounds

The group is also looking at hybridizing different types of hypoxia markers, combining nitroimidazoles and the

Oxford University's Biomarker Research Team



The interdisciplinary team tries to identify new agents for imaging tumor hypoxia, a characteristic of solid tumors that increases their resistance to radiotherapy and chemotherapy, as well as triggering angiogenesis.

Jon Dilworth, DPhil, DSc, is Professor of Inorganic Chemistry and a Fellow of St Anne's College, University of Oxford. He received his graduate degree from Jesus College, Oxford, and gained his DPhil and DSc at the University of Sussex in Brighton, UK. In 1985, he took the Chair of Chemistry at the University of Essex, UK, and in 1997 moved to his current position at Oxford.

Veronique Gouverneur, PhD, is Reader in Chemistry at the University of Oxford and a Fellow of Merton College. She graduated and received her PhD from the Université Catholique de Louvain (Belgium). She moved to The Scripps Research Insti-

tute (La Jolla, CA, USA) in 1992, then to the Université Louis Pasteur (Strasbourg, France), and arrived in Oxford in 1998.

Simon Bayly, PhD, is Senior Postdoctoral Research Scientist in the Department of Chemistry at the University of Oxford.

Sir Michael Brady, (who was not present at the interview), is BP Professor of Information Engineering in the Department of Engineering Science and a Fellow of Keble College at the University of Oxford. He came to Oxford in 1985 from MIT, where he had been Senior Research Scientist in the Artificial Intelligence Laboratory. Recently, his research interests have been focused on medical image analysis and

minimally invasive surgery. He also co-founded the Wolfson Medical Vision Laboratory. Brady founded Mirada Solutions Ltd., which was eventually acquired to later become part of Siemens Medical Solutions Molecular Imaging. He also works on oncologic image analysis with GlaxoSmithKline.



Sir Michael Brady

copper(II)bis(thiosemicarbazones), to investigate whether any extra benefit can be obtained by linking them. It is difficult to predict, Dilworth admits, because the mechanisms by which they work are subtly different and not yet fully understood. Consequently, when these functionalities are combined, they could produce an additive effect, a lesser effect, or even a completely different effect.

"What we are hoping to end up with is complementary information from different compounds," Dilworth says. "One compound may image hypoxia by direct response to oxygen concentration; another may act by binding to a specific site within the tumor. They both produce an image, but by different mechanisms. The information and the time course would be slightly different, giving com-

plementary views of hypoxia from different perspectives."

After the complexes have been synthesized and radiolabeled, the next step in the project is to generate images that can be sent to Professor Brady's group so that they can extract the data using proprietary medical image analysis software.

Research Soon Under One Roof

Typically, a complex is sent to the Gray Cancer Institute in London for animal imaging. From that image, the biodistribution of the compound is examined. One must then decide as to whether the molecule needs to be modified, in which case the synthesis or the chemistry may be revised and the complex sent for imaging again. This is a gradual process,

which evolves toward a compound with all the optimal characteristics, Dilworth explains. In vitro testing is also done on different cancer cell lines using fluorescent analogues of the compounds under investigation. If a compound is not fluorescent, fluorophores are attached so that as the cell becomes hypoxic, changes in the cellular distribution of the complex can be followed using a fluorescence microscope.

As of next year, all the facilities for the research done by Professor Dilworth and his group will be in Oxford. Up to now, he and his colleagues have faced challenges, especially using and transporting the radiolabeled compounds, because the different facilities are located outside of Oxford. Without a PET scanner in the Oxford area, imaging of the group's

Further Biomarker Research

Siemens Medical Solutions is the world's first full-service diagnostics company, integrating in vivo and in vitro imaging diagnostic capabilities.

New research facility in the USA: Siemens has also opened a new state-of-the-art research facility in Culver City, CA. The facility is dedicated exclusively to the development of molecular imaging biomarkers, which will become in vivo diagnostic tools for identifying diseases such as cancer and neurological diseases, even at their earliest stages. Once the imaging biomarkers bind to the diseased cells or tissues, they cause them to 'light up' when scanned using PET-CT (positron emission tomography-computed tomography) or SPECT-CT (single photon emission-computed tomography). In addition to continued work on a new research imaging agent to aid in Alzheimer's detection, the future research will branch out into the areas of neurology and cardiovascular disease. The new Alzheimer's imaging agent is already used by Wyeth Pharmaceuticals in clinical studies of new therapies in development for Alzheimer's disease.

Latest Studies: Recent imaging biomarker studies on diseases such as Alzheimer's or tumors have shown that these biomarkers are highly accurate in identifying disease indicators. A December 2006 study published in the *New England Journal of Medicine* reported that researchers at the University of California, Los Angeles (UCLA) were 98 percent accurate in identifying Alzheimer's disease among a group of volunteers who presented mild cognitive impairment. The researchers were using a specific

biomarker in conjunction with PET scanning. The study brought forth a new diagnostic technique developed by UCLA researchers, which combines the new imaging biomarker and PET. The technique was first reported in the January 2002 issue of the *American Journal of Geriatric Psychiatry*.

According to Jorge R. Barrio, Professor of Medical and Molecular Pharmacology, the use of this biomarker technology may provide physicians with an early diagnostic tool and a backup in identifying susceptible individuals. This also allows an early start of a treatment plan before symptoms appear. PET in combination with the currently approved imaging agent F-18 fluorodeoxyglucose (F18-FDG) has been traditionally used to measure the metabolic function in cells. FDG-PET has been used for years in aiding diagnosis of various neurological conditions including Alzheimer's and Parkinson's disease. However, FDG cannot identify the abnormal brain protein deposits – amyloid plaques and tangles – that may cause Alzheimer's. Current antidementia drug development is focusing on treatment and prevention of the accumulation of those deposits. After the first phase, the study protocol will focus on the use of the biomarker in patient populations and its potential to seek out tangles and plaques in the brain of living Alzheimer's disease patients. Using PET imaging, biomarker molecules are considered to have the potential to 'light up' the parts of the brain with high concentrations of the imaging biomarker. Through the analysis of the PET data, researchers can identify the disease specifically, and do so in advance of the onset of symptoms.

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radiopharmaceuticals has been done in London – 65 kilometers away. However, the half-lives of the radioisotopes used in the Oxford research are relatively short, especially the half-life of F18-FDG, which is just under two hours – not long enough to do fluorine radiolabeling in Oxford and then transport the compound to London for imaging. This situation will soon change when a PET scanner is set up on the site of the new Oxford Cancer Centre at Churchill Hospital. The Centre will also have a cyclotron for production of radioisotopes. In the future, biological testing of the research compounds will be carried out by the Department of Radiation, Oncology, and Biology at Churchill Hospital. “Hopefully, the new imaging agents will go into clinical trials and eventually make their way into the patients in the

hospital community there,” says Dilworth. The project to identify new hypoxia selective agents will run for up to four years. In addition to Professor Dilworth and Dr. Gouverneur, it will involve two post-doctoral researchers, two students, and a technician working in the university’s department of chemistry. It represents a collaboration not only between researchers in organic and inorganic chemistry, but also with researchers in engineering and in the clinical setting. “Everything must be synchronized across all these disciplines to complete the project,” Dilworth stresses. “Molecular imaging is almost the prime example of a multidisciplinary collaboration right across the board, and that is what makes it so difficult to manage, but very interesting to be involved with,” he says. “The

University of Oxford now recognizes that for a long-term future, it must drive the association between the medical sciences and the physical sciences. It sees molecular imaging as one of the best bridges across this divide. This has all come together at a critical time in the expansion of PET imaging in the UK.” The aim of Professor Dilworth and his colleagues is to make Oxford an international center for molecular imaging in both clinical and fundamental research. They believe that it has the potential to become one of the leading centers worldwide for molecular imaging research.

Linda Brookes is a freelance medical writer and editor, who commutes between London and New York, working for a variety of clients in the healthcare and pharmaceutical fields.



The laboratory was formally inaugurated at the end of January 2007. Oxford University’s biomarker research team is setting up special radiochemical facilities and systems which need to operate under strictly regulated conditions.