Advances in Molecular Imaging
A One-Day Symposium

Australian Institute for Bioengineering and Nanotechnology
The University of Queensland
Thursday 7th May 2015

Organised by:
ARC Centre of Excellence in Convergent Bio-Nano Science and Technology (COE CBNS)

and

Australian Institute for Bioengineering and Nanotechnology
# Program Outline

<table>
<thead>
<tr>
<th>Time</th>
<th>Session Title</th>
<th>Thursday 7th May</th>
<th>Affiliation</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.00am</td>
<td>Conference Opening Prof Andrew Whittaker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.10am</td>
<td>Plenary Session 1</td>
<td>Prof Jason Lewis</td>
<td>Memorial Sloan Kettering Cancer Center</td>
<td>Molecular imaging in precision medicine</td>
</tr>
<tr>
<td>10.00am</td>
<td>Morning Tea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.30am</td>
<td>Session 2 - Keynote 1</td>
<td>Assoc Prof Stephen Rose</td>
<td>The Australian e-Health Research Centre, CSIRO</td>
<td>The challenges to make glioma a chronic disease: Progress from a molecular imaging viewpoint</td>
</tr>
<tr>
<td>11.00am</td>
<td>Invited 1</td>
<td>Assoc Prof Paul Thomas</td>
<td>Specialised PET Services Queensland, Metro North Hospital and Health Service</td>
<td>Challenges and opportunities in clinical molecular imaging</td>
</tr>
<tr>
<td>11.30am</td>
<td>Invited 2</td>
<td>Assoc Prof Rajiv Bhalla</td>
<td>Centre for Advanced Imaging, University of Queensland</td>
<td>The application of group 13 metals in the development of radiopharmaceuticals</td>
</tr>
<tr>
<td>11.50am</td>
<td>Invited 3</td>
<td>Prof Pamela Russell</td>
<td>Australian Prostate Cancer Research Centre, Queensland University of Technology</td>
<td>Improving imaging of prostate cancer by targeting prostate-specific membrane antigen</td>
</tr>
<tr>
<td>12.10am</td>
<td>Lunch</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13.10pm</td>
<td>Session 3 - Keynote 2</td>
<td>Prof Gary Egan</td>
<td>ARC Centre of Excellence for Integrative Brain Function, Monash University</td>
<td>Deciphering brain function using next generation brain imaging technologies</td>
</tr>
<tr>
<td>13.50pm</td>
<td>Invited 4</td>
<td>Dr Nick Ariotti</td>
<td>Institute for Molecular Biosciences and Centre for Microscopy and Microanalysis, University of Queensland</td>
<td>Electron microscopy and Apex – a new tool for answering complex biological questions at high-resolution</td>
</tr>
<tr>
<td>14.00pm</td>
<td>Invited 5</td>
<td>Dr Angus Johnston</td>
<td>Monash Institute of Pharmaceutical Sciences, Monash University</td>
<td>Using nanotechnology to understand biological interactions</td>
</tr>
<tr>
<td>14.30pm</td>
<td>Keynote 3</td>
<td>Prof Mark Hutchinson</td>
<td>ARC Centre of Excellence for Nanoscale BioPhotonics</td>
<td>Centre for Nanoscale BioPhotonics: creating windows into the body</td>
</tr>
<tr>
<td>15.10pm</td>
<td>Afternoon Tea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15.40pm</td>
<td>Session 4 - Invited 6</td>
<td>Dr Kris Thurecht</td>
<td>Centre for Advanced Imaging, University of Queensland</td>
<td>Multimodal molecular imaging with polymer nanoparticles</td>
</tr>
<tr>
<td>16.00pm</td>
<td>Invited 7</td>
<td>Prof Tom Davis</td>
<td>ARC Centre of Excellence in Convergent Bio-Nano Science &amp; Technology, Monash University</td>
<td>Theranostic hybrid polymer nanoparticles</td>
</tr>
<tr>
<td>16.20pm</td>
<td>Invited 8</td>
<td>Prof Thomas Nann</td>
<td>Ian Wark Research Institute, University of South Australia</td>
<td>From mono disperse nanoparticles to multi-modal contrast agents</td>
</tr>
<tr>
<td>16.40 pm</td>
<td>Plenary Session 5</td>
<td>Prof John McGhee</td>
<td>3D Visualisation Aesthetics Laboratory, UNSW</td>
<td>3D computer arts-led approaches in MRI and CT</td>
</tr>
<tr>
<td>17.30pm</td>
<td>Conference Close Prof Tom Davis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Detailed Program and Abstracts

9.00am  Conference Opening Prof Andrew Whittaker

Session 1 Plenary Session One
Chair Andrew Whittaker

9:10 am  Plenary lecture Prof Jason Lewis, Memorial Sloan Kettering Cancer Center
“Molecular imaging in precision medicine”
Jason Lewis
The use of Molecular Imaging (MI) for the delineation of disease is well-established and widely used in clinical and research settings. With a recent emphasis on Precision Medicine – MI is uniquely situated to aid and guide the undertaking of PM as it offers the ability to quantitatively measure biological and receptor-based processes using a wide spectrum of specifically designed probes. These probes can be designed using small molecule-, peptide-, antibody- and nanoparticle-based platforms and can be utilized in any number of imaging technologies (PET, MRI, CT, Raman, US). This presentation will review the current state-of-the-art in the use of molecular imaging agents in the context of precision medicine and companion diagnostics.

10:00 am  Break for Morning Tea

Session 2 Clinical Aspects of PET and MRI
Chair Kris Thurecht

10:30 am  Keynote lecture Assoc Prof Stephen Rose, The Australian e-Health Research Centre, CSIRO
“The challenges to make glioma a chronic disease: Progress from a molecular imaging viewpoint”
Stephen Rose, Simon Puttick, Nick Dowson, Andrew Whittaker, Mike Fay, Paul Thomas, Lindy Jeffree, Bryan Day, Brett Stringer, Andrew Boyd
Despite the recent advances in resection techniques and delivery of adjuvant therapies, the prognosis of high-grade glioma is poor, with a median survival of 12-18 months. Two key factors contribute to this dilemma: (i) the limitation of current diagnostic imaging technology (e.g. MRI), for providing clinically relevant information about tumour pathology and behaviour; (ii) overcoming the limited effectiveness of current therapies to target invasive proliferating tumour cells. A paradigm shift in treatment strategy is urgently required. In this presentation, I will outline our research program based around the use of F18-DOPA PET imaging for optimising image-guided therapy for patients with glioma. I will also highlight our progress in the development of innovative theranostic imaging technology for direct delivery of antibody drug conjugates or radioimmunoconjugates as a personalized approach for treating patients with glioma.

11:10 am  Invited lecture Assoc Prof Paul Thomas Specialised PET Services Queensland, Metro North Hospital and Health Service
“Challenges and opportunities in clinical molecular imaging”
Paul Thomas

11:30 am  Invited lecture Assoc Prof Rajiv Bhalla, Centre for Advanced Imaging, University of Queensland
“The application of group 13 metals in the development of radiopharmaceuticals”
Rajiv Bhalla
The increasing need to label peptides and macromolecules efficiently with F-18 has meant there is a growing demand to develop simpler and faster methods for radionuclide labelling this class of compounds. McBride and others have reported the use of Al-18F complexes based upon functionalised bis-carboxylate derivatives of 1,4,7-triazacyclononane for imaging a wide range of peptides rapidly in a single step. However, the need for elevated temperatures (100°C) for fluorination in this ‘one-pot’ approach provides limitations on its broader utility due to the thermal instability of some important biomolecules. In order to further extend the scope of this approach, an increased understanding of the chemistry and properties of fluoride complexes of the Group 13 elements is required. This presentation reports the development of novel metal complexes of aluminium, gallium and indium halides and reports their fast 18F and 19F incorporation via halide exchange at room temperature in aqueous solution.

11.50 am Invited lecture Prof Pamela Russell, Australian Prostate Cancer Research Centre, QUT
“Improving imaging of prostate cancer by targeting prostate-specific membrane antigen”
Brian Tse, Benjamin Thierry, Gary Cowin, Kristofer Thurecht, Adrian Fuchs, Amanda Pearce, Mei-Chun Yeh, Warren D Heston, Stephen Huang, Andrew Whittaker, Pamela J Russell
Prostate cancer is most commonly diagnosed as a visceral cancer in men and is the second leading cause of cancer death. With its long natural history, this disease results in a highly significant burden on the healthcare system. We have developed ferromagnetic nanoparticles and hyperbranched polymers targeted to prostate cancer via prostate specific membrane antigen, which is expressed in early and advanced stage disease. These have led to improved targeted imaging in preclinical studies, and show promise for enhancing imaging via MRI and PET. Attachment of chemotherapeutic agents to these targeted agents may lead to increased efficacy avoiding the side effects that accompany systemic therapy.

12.10 pm Break for Lunch

---

Session 3 Materials and Microscopy
Chair Tom Davis

13:10 pm Keynote lecture Prof Gary Egan Director, ARC Centre of Excellence for Integrative Brain Function, Monash University
“Deciphering brain function using next generation brain imaging technologies”
Gary Egan
The ARC Centre of Excellence for Integrative Brain Function was established in 2014 to undertake multi-scale brain research to understand how the brain integrates information in large-scale networks to yield complex behaviours including attention, prediction and decision making. Novel in vivo brain imaging technologies and applications, with a particular emphasis on simultaneous MR-PET brain imaging applications using multi-contrast agents, will be presented. The presentation will include a brief overview of the Centre’s knowledge sharing program, the Brain Dialogue, that is actively disseminating and communicating the Centre’s research findings through public activities.

13.50 pm Invited lecture Dr Nick Ariotti, Institute for Molecular Biosciences and Centre for Microscopy and Microanalysis, University of Queensland
“Electron microscopy and Apex – a new tool for answering complex biological questions at high-resolution”
Nicholas Ariotti, Thomas Hall and Robert G. Parton
Transmission electron microscopy allows for high-resolution analysis of cellular morphologies but has traditionally been viewed as a technically demanding, slow and non-quantifiable technique. As GFP revolutionized the detection of proteins by light microscopy, similarly new genetic tags for electron microscopy (EM) have great potential for EM visualization of proteins in cells. This talk will discuss the recent advances in three-dimensional imaging techniques and focus on a new system that allows for EM detection of GFP-tagged protein libraries for reliable and accurate subcellular protein distribution. We have developed a new modular system that allows for simplified and faster analysis of protein localisations and improved sampling of time courses/treatments for EM. The technique is compatible with three-dimensional electron microscopy techniques, correlative light and electron microscopy and we also demonstrate that we can readily apply this method to the localization of GFP-tagged proteins to EM-resolution in a zebrafish model system. The utility of this technique will be revealed with several cell biological questions.

14.10pm Invited lecture Dr Angus Johnston, Monash Institute of Pharmaceutical Sciences, Monash University
“Using nanotechnology to understand biological interactions”
Angus PR Johnston, Haiyin Liu
To engineer ‘smart’, responsive materials for drug delivery it is essential to understand how nanoparticles interact with cells. Targeted delivery of drugs to specific cells in the body by immobilising therapeutics inside antibody functionalised nanoparticles has the potential to revolutionise the treatment of many diseases. However, our understanding of how these nanoengineered materials interact with cells is limited. We are developing tools to understanding how these materials interact with cells, so we can engineer materials that respond better to the biological conditions they encounter. In particular, we are interested in understanding the internalisation, processing and trafficking of nanoparticles in cells. We have developed a simple, high throughput method for determining the cellular uptake and using this technique, we have demonstrated that the antibodies used to target polymer nanoparticles to cells plays an important role in internalisation.

14.30pm Keynote lecture Prof Mark Hutchinson, Centre for Nanoscale BioPhotonics, University of Adelaide
“Centre for Nanoscale BioPhotonics: creating windows into the body”
Mark R Hutchinson, Martin Gosnell, Jeremy Thompson, Ewa Goldys
The Centre for Nanoscale BioPhotonics (CNBP) brings together physics, material science, chemistry, biochemistry, embryology, neuroscience and cardiovascular scientists to create new tools so that biologists can ask new questions about living systems. This presentation will provide an overview of the current scientific activities of the CNBP together with our preclinical, and clinical translational aspirations. Additionally, a specific highlight will be provided of the innovative hyperspectral technology and analysis techniques that are being employed in the CNBP to characterise and provide label free imaging of endogenous fluorophores in developing embryos. The broader ramifications of this technology and others like it that are being developed in the CNBP will be discussed.

15.10pm Break for Afternoon Tea
Invited lecture Dr Kris Thurecht, Centre for Advanced Imaging, University of Queensland
“Multimodal molecular imaging with polymer nanoparticles”
Kristofer J Thurecht
Molecular imaging follows biological processes in living subjects by utilising one of a variety of available techniques. Molecular imaging agents can be designed for various functions: to diagnose and differentiate diseased tissue from normal tissue; to provide information on a disease state (prognosis); and ultimately to monitor the effect of a treatment. Polymeric molecular imaging agents have become increasingly popular due to the inherent advantages of using large molecules in vivo, including enhanced circulation times (due to slower excretion as a result of particle size and chemistry), uptake and accumulation in tumours via the Enhanced Permeation and Retention (EPR) effect, the ability for multivalent attachment of targeting ligands and the ability to carry a large concentration of image-detectable molecules. These properties allow for an increase in local concentration of imaging molecules, which leads to an increased signal-to-noise ratio (SNR) and potentially higher quality images. In this presentation we describe the development of molecular imaging probes that utilise multiple modalities, utilise a variety of targeting mechanisms and ultimately provide a means to deliver a therapeutic payload. In this way, maximum information about a disease can be extracted from a particular imaging session, often informing on the complicated biology of diseases. Molecular imaging modalities such as optical imaging, PET and MRI will be discussed.

Invited lecture Prof Tom Davis Director, ARC Centre of Excellence in Convergent Bio-Nano Science & Technology, Monash University
“Theranostic hybrid polymer nanoparticles”
Tom Davis
1. Iron oxide nanoparticles
I will describe the synthesis of iron oxide nanoparticles IONPs (diameters around 60 nm) with excellent colloidal stability in both water and serum, imparted by carefully designed grafted polymer shells. The aim was to design nanoparticles that act as responsive MRI contrast agents and allow signalling on drug release. The IONPs were stabilised with polymer shells were built with attached aldehyde functionality to enable the reversible attachment of doxorubicin (DOX) via imine bonds, providing a controlled release mechanism for DOX in acidic environments, as typically observed in tumours or within the lysosome in cells. The IONPs were shown to be readily taken up by cell lines (MCF7 breast cancer cells and H1299 lung cancer cells) and intracellular release of DOX was proven using in-vitro fluorescence lifetime microscopy (FLIM) measurements in MCF7. The IONPs were also assessed as MRI contrast agents. We observed a significant change in the transverse relaxivity properties of the IONPs, going from 220 to 390 mM⁻¹ s⁻¹, in the presence or absence of conjugated DOX. This dependence of MRI signal on DOX/IONP/water interactions may be exploited in future theranostic applications.
2. Gadolinium –containing star polymers
Dual-functional star polymers (diameters 15 nm) were synthesized producing nanoparticles with excellent colloidal stability in both water and serum. The nanoparticles were built with aldehyde groups in the core and activated esters in the arms. We exploited the different reactivity of the two functional groups to sequentially react with different amino compounds; doxorubicin (DOX) and DO3A-tBu-NH₂ - a chelating agent effective for the complexation of gadolinium ions (Gd). The activated ester group was employed to attach the DO3A chelating agent, while the aldehyde groups were exploited for DOX conjugation, providing a controlled release mechanism for DOX in acidic environments. DOX/Gd loaded nanoparticles were rapidly taken up by MCF-7 breast cancer cells, subsequently releasing DOX as demonstrated using in vitro fluorescence lifetime imaging microscopy (FLIM). Endosomal, DOX release was observed, using a phasor plot representation of the fluorescence lifetime data, showing an increase of
native DOX with time. The MRI properties of the stars were assessed and the relaxivity of Gd loaded in stars was three times higher than conventional organic Gd/DO3A complexes.

16.20pm Invited lecture Prof Thomas Nann, Ian Wark Research Institute, University of South Australia
“From mono disperse nanoparticles to multi-modal contrast agents”
Melissa Dewi, Renee Goreham, Anna Cifuentes Rius, Kathryn Schroeder, Valentina Milanova, Thomas Nann
Imaging techniques such as magnetic resonance imaging (MRI), X-ray computed tomography (XCT) or positron emission tomography (PET) are clinical standard methods to detect and locate tumour tissue. However, none of these techniques offer a universal solution. For instance, they do not allow for visualisation of malignant tissue under surgery. Similarly, available contrast agents are very different in terms of specificity (targeting), toxicity, clearance and signal. We have synthesised multi-modal contrast agents by combining individual nanoparticles to more sophisticated nano-architectures. Our strategy follows the idea to first fabricate mono-disperse nanoparticles with optimised properties and then combining these particles to more complex systems. In this presentation, we will show selected examples of the assembly of highly sophisticated, multi-modal contrast agents.

Session 5 Plenary Session Two
Chair Tom Davis

16.40 pm Plenary Lecture Prof John McGhee, 3D Visualisation Aesthetics Laboratory, University of New South Wales
3D computer arts-led approaches in MRI and CT
John McGhee
Contemporary clinical imaging modalities such as Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) capture cross-sectional image slices of any given subject. The subsequent 3D data visualisation can provide additional scientific or clinical insight. However, if we widen access to lay or naïve users what visual aesthetic should we adopt? Also, how should we experience or navigate through that data? In this research work, carried out at the 3D Visualisation Aesthetics lab at UNSW, arts-led modes of data enhancement is discussed. Two case studies are cited, firstly the Med-i Virtual Reality (VR) project where Oculus Rift headsets and 3D data visualisation are used as an aide in stroke rehabilitation and communication. A second project in the field of vascular disease takes renal angiography data acquired on MR and deploys 3D pre-rendered approaches to visualise and animate blood flow.

17.30pm Conference Close Prof Tom Davis
About the CBNS

The ARC Centre of Excellence in Convergent Bio-Nano Science and Technology (CBNS: www.bionano.org.au) was established in mid-2014 as a national innovator in bio-nano sciences, bringing together a diverse team of Australia’s leading scientists to develop next generation bio-responsive nanostructured materials.

The key science that underpins all the activities of the centre is to fully understand and then exploit the bio-nano interface. The four broad application areas that ensue from the fundamental understanding and that are the core research areas of the CBNS are: 1) Drug delivery systems, including gene therapy delivery; 2) Vaccine delivery systems; 3) Bio-imaging technologies – both cellular and whole body imaging; 4) Sensors and diagnostics. In addition the Centre research is fully integrated with unifying themes including the social dimensions of bio-nanotechnology and a systems biology approach to fully describing the complex interactions that dictate success or failure of nanotechnology for therapeutic applications.

To succeed in this bio-nano area requires an integrated team of researchers coming from diverse backgrounds and we have assembled a remarkable team of highly distinguished scientists and engineers covering nanotechnology, polymer science, cell biology, cancer biology, systems biology, chemical engineering, immunology, chemistry and social science. The centre is constituted of five primary nodes: Monash University, Melbourne University, University of NSW, University of Queensland and the University of South Australia in addition to eight overseas partners and the Australian Nuclear Science and Technology Organisation. We currently have more than 100 staff members and 90 PhD, masters and honours students working on core Centre research.

About the AIBN

The University of Queensland’s Australian Institute for Bioengineering and Nanotechnology (AIBN: www.aibn.uq.edu.au), established in 2004, is an integrated multi-disciplinary research institute bringing together the skills of world-class researchers in the areas of bioengineering and nanotechnology.

The AIBN is home to 18 research groups working at the interface of the biological, chemical and physical sciences to alleviate current problems in human health and environmental issues. The Institute has three key areas that collectively distinguish it from other institutes in the country, namely AIBN’s:

- Research excellence;
- Industry focus; and
- Dynamic research environment.

These characteristics focus AIBN research efforts on developing new products, processes and devices for improving human health and quality of life. In this way the Institute goes beyond basic research to promote and develop the growth of innovative industries, which will benefit the Queensland and Australian economies.

Acknowledgements

Symposium Chairs
- Prof Andrew Whittaker, University of Queensland
- Prof Tom Davis, Monash University

Registration and Administrative Support
- Dr Wei Zhao, University of Queensland
- Ms Petrina Gilmore, University of Queensland
- Ms Julia Cianci, Monash University

Financial Support
- Australian Research Council
- ARC Centre of Excellence in Convergent Bio-Nano Science and Technology (COE CBNS)
- Australian Institute for Bioengineering and Nanotechnology