Digital Subtraction Angiography (DSA) of transplanted kidney - Ovine heterotypic kidney transplantation

Bron Lott - University of Adelaide
Raj Perumal - Large Animal Research & Imaging Facility (LARIF) node, SAHMRI PIRL
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NISA, STEM, Innovation, Data Tsunami, these are the terms that are changing the way we think about science and research. This change has been so dramatic that, this week, an episode of Q&A was devoted to the topic, and yes, infrastructure was identified as a critical component of the landscape. So, is NIF active in this space? This issue of our quarterly newsletter demonstrates that NIF is engaged across the spectrum of these changes.

Data has always been important to NIF, and we are providing the tools to empower our users to best practice in data management. Read about ImageTrove, developed because we recognize data as something to be treasured. And yes, it provides the map, so your treasure is not destined to be lost.

Innovation, making research relevant in today’s changing world. NIF is not only thinking about industry engagement and translation, we are active. The Bionic Spine, science fiction not so long ago, is becoming a reality, in Australia, at the University of Melbourne. And whether it be beginning of life (Monash), or understanding degenerative diseases (LARIF), imaging is playing a role. In all these projects, you can read how NIF is working alongside industry partners. Whist at UQ, new contrast agents, for investigating efficacy of prostate cancer therapy, are being developed, with a view to translation.

If research infrastructure is to make a difference, the economic reality require agility and efficiency. In an international collaboration, NIF scientists at ANSTO/University of Sydney also improving the technology and the workflows, whilst maintaining data integrity.

And STEM – where are the future scientists? NIF is helping to create that spark in the minds of young people, as they consider their future role in society, and encourage them to pursue a career in science, technology and maths.

I hope that you enjoy reading about the research that is enabled through NCRIS-funded research infrastructure, and that it might spark your innovative thoughts as to how you could use the National Imaging Facility capability.

Professor Graham Galloway
Director of Operations
Committed to best practice data management, National Imaging Facility (NIF) partnered with Australian National Data Service (ANDS) through a grant, funded in 2014, to develop an informatics tool for ingesting and archiving imaging data sets. This tool, which was first developed by Dr. Andrew Janke from Centre for Advanced Imaging (CAI), The University of Queensland (UQ) node, is called “ImageTrove” and makes use of Research Data Storage Infrastructure (RDSI) storage allocations and the National eResearch Collaboration Tools and Resources (NeCTAR) for compute resources.

ImageTrove provides a very low resistance path for NIF users’ data to be ingested into well curated and managed data systems such as OMERO, Mediaflux LiveArc, DaRIS and myTARDIS. This path directly feeds into existing national efforts such as the CVL (Characterisation Virtual Laboratory) and presents an AAF (Australian Access Federation) authenticated glue layer between the geographically distributed NIF instruments and RDSI based national level storage allocations. This process is promoted within NIF as the primary pathway for all data to enable users to gain the benefits of data provenance and availability to CVL and provides a more transparent pathway for metadata to RDA (Research Data Australia).

Over the past few years, UQ’s Research Computing Centre (RCC) and CAI have been working closely to deploy ImageTrove, which has recently paid off with another institution of UQ, Centre for Microscopy and Microanalysis (CMM), adopting the software for managing data sets from microscopes, MRI and CT machines.

“These imaging facilities can generate large amounts of data very quickly. This data must be stored somewhere reliable and accessible, since in many cases the data must be made available to collaborators or made discoverable when the research is published. The ImageTrove software, connected to RDS infrastructure, helps CMM and other groups around Australia to provide secure, robust and consistent data management processes for researchers”, said RCC eResearch Analyst, Dr Edan Scriven.

RCC’s involvement is part of the RDS Image Publishing Data Services project, which aims to enable imaging instruments to be data publishers to ensure data are accessible and ready for research use.

For more information on ImageTrove, please contact Dr. Andrew Janke (andrew.janke@cai.uq.edu.au).
Early February this year, a research breakthrough was published in Nature Biotechnology, which brings hope to patients, paralyzed by injury or illness. This breakthrough, which is a revolutionary bionic spine made by Melbourne researchers, could mean that patients with spinal cord injuries can potentially control a robotic limb using the power of thoughts and get back on their feet again.

Key to the bionic spine is a passive stent-electrode recording array (stentrode) that is deployed via minimally invasive catheter angiography in a cerebral vein to achieve chronic recordings. The stent is inserted into the jugular vein in the neck using a catheter and pushed up the vein until it reaches the motor cortex. It avoids the brain trauma which may be caused by direct implantation of traditional arrays into the brain via open craniotomy. The stentrode was trialled in freely moving sheep for 190 days with the recorded brain signals getting stronger once tissue grew around the stent. "Containing 12-electrodes, the stent is like a recording device which collects the electrical activity from neurons in the patient’s motor cortex before translating the activity into commands. The commands are carried via 12 wires to a transmitter implanted just under the skin on the chest. The transmitter then sends the commands wirelessly to an exoskeleton - or to a wheelchair", reported The Sydney Morning Herald1.

The stentrode may facilitate a range of clinical applications in the future including applications in neural stimulation which opens the possibility of achieving deep and superficial brain stimulation therapies without the requirement for craniotomy. Multiple deep brain stimulation targets have been identified as being accessible via arteries and veins, with targets for Parkinson’s disease and obsessive-compulsive disorder being particularly suitable2.

National Imaging Facility contributed to this breakthrough by the facilities and scientific & technical assistance provided at the Melbourne Brain Centre Imaging Unit. For further information on this breakthrough, please contact Dr. Thomas J Oxley (thomas.oxley@unimelb.edu.au) and Dr. Bradford Moffat (bmoffat@unimelb.edu.au) for more information on the available facilities and expertise at the Melbourne Brain Centre Imaging Unit.

Industry Partners
Victorian start-up SmartStent and Medtronic

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Vascular electrocorticography: somatosensory evoked potentials. a) Representative example of peak-to-peak amplitude over post-implant time (S4). Scale bars, 30 ms and 100 μV. b) Peak-to-peak amplitudes over time (linear regression, P = 0.42, n = 703 peaks; 5 sheep). c) Detection of SSEPs over early implantation period (box and whisker plot, n = 5 sheep). d-g) Electrode positions in four sheep implanted with stentrode, demonstrated with co-registered MRI-CT reconstructions to limb motor (red) and sensory (yellow) areas. Scale bar, 2 cm. h,j) Three-dimensional reconstructed electrodes within co-registered SSS. Scale bar, 3 mm. Representative variable SSEP morphology with phase reversal dipole (blue dashed line). Scale bars, 30 ms and 50 μV.
Osteoporosis models in animals are required to investigate the efficacy of pharmaceutical and physical treatments, and the regulatory bodies such as the United States Food and Drug Administration (FDA) require that any treatment be tested in two distinct animal species demonstrating modeling and remodeling of bone. The well established ovariectomised rodent is to be used as the modeling system of bone, whilst the second species should be a large animal model with remodeling of bone similar to humans.

An appropriate model should allow for: “1) appropriateness as an analog, 2) transferability of information, 3) genetic uniformity of organisms where applicable, 4) background knowledge of biological properties, 5) cost and availability, 6) generalizability of the results, 7) ease and adaptability to experimental manipulation, 8) ecological considerations, and 9) ethical and societal implications” 2. Nonhuman primates are the ideal model with respect to bone metabolism, but are expensive, must be of a suitable age for osteoporosis investigation and difficult to maintain. The Sheep is establishing itself as an appropriate model for bone research due to the similarity of bone size, bone metabolism, bone strength, ease of handling, cost, and bone physiology.

Knowledge of the age and trajectory of skeletal maturity is important in designing animal models of bone strength, remodeling and metabolism, particularly if younger animals are used.

A project1 carried out at the Large Animal Research and Imaging Facility (LARIF) aimed to follow the changes in bone mass and tissue composition in sheep from 4 months to 4 years of age and to determine the rate of change and the time to reach maturity of body composition.

A cohort of 14 female Merino lambs, selected randomly, had dual energy x-ray absorptiometric (DXA) measurements of the lumbar spine and total body performed at approximately 6 month intervals from 4 months of age to 24 months of age. “Principles of laboratory animal care” (NIH publication No. 85-23, revised 1985) and specific national laws were followed and all experiments were examined and approved by the IMVS Animal Ethics committee.

The project presented DXA estimations on body composition including bone density at 4 time points in the first two years of the 14 developing lambs, as well as measurements in comparable adult sheep. It was concluded that adult levels of bone density are reached by 18 months and lean body mass by 2 years. Therefore, studies requiring maximum average bone density should use sheep at least 18 months old, whilst maximum lean mass requires sheep at least 24 months old.

Industry Partners
The Royal Adelaide Hospital
Institute of Medical and Veterinary Science
The Adelaide Centre for Spinal Research, S.A. Pathology

For more information on this project, please contact Dr. Barry Chatterton (barry.chatterton@gmail.com) and to have more information on available facilities at LARIF node, please contact Dr. Tim Kuchel (Tim.Kuchel@sahealth.sa.gov.au).

Positioning of animal for scanning. Left) Masking tape was used to secure the animal to maintain correct orientation. The Hologic body composition phantom is adjacent to the animal. Right) lumbar spine analysis. Human software has been adapted for the analysis and labels are not correct with regard to vertebral level, representative spinal images during sheep growth are shown.

Lung development and maturation are relatively late events in fetal development of many mammals including humans. Consequently, preterm birth presents a physiological challenge for the neonate as the poorly developed lungs are unable to provide the oxygen requirements of the newborn.

Preterm birth, defined as birth prior to 37 completed weeks of gestation, affects 7–12% of births worldwide. Many of these babies, as explained above, have impaired lung function, rendering them unable to survive without assistance. In Australia, 28% of all infants required some form of respiratory support in the delivery room, with suction and oxygen support encompassing the majority of this support. Respiratory support is the cornerstone of successful neonatal resuscitation; it allows appropriate transition from fetal to neonatal circulation as well as aiding in lung liquid clearance and functional residual capacity establishment. However, it is now well established that assisted ventilation increases inflammation and injury to the preterm lungs. Therefore, although mechanical ventilation at birth is life-saving for many preterm babies, the lungs are easily injured. Moreover, the birth transition is also a period of unstable blood flow in the neonate as it is removed from the large supply of blood within the placenta.

Fluctuations in cerebral blood flow in the immature preterm baby have now been shown to cause ischemia and microbleeds in the more vulnerable brain regions. In the intensive care units preterm babies are not routinely scanned like adults who present with suspected neurological damage. Hence, the extent of brain injury and long term consequences of such injuries in preterm babies has largely gone unnoticed.

Dr. Graeme Polglase of the Ritchie Centre at the Hudson Institute of Medical Research is leading a multidisciplinary team that investigates the impact of haemodynamic changes on the development of brain injury in lamb models of preterm delivery. His team of perinatal physiologists is working with Dr. James Pearson and Dr. Qizhu Wu of the Monash Biomedical Imaging (MBI) preclinical team and jointly supervised PhD student Dhafer Alahmari to investigate the impact of injurious ventilation and inflammation on brain function with MRI and MR spectroscopy protocols in sedated lambs following preterm delivery. Furthermore, in these studies this team is now investigating the efficacy of routine and novel interventions, including stem cell therapy, that have the potential to reduce brain injury.

Utilising the preclinical capabilities at MBI node of National Imaging Facility (NIF), Graeme’s team is investigating how chronic inflammation worsens brain injury in preterm lambs. Their approach examines the occurrence of microbleeds (Figure 1. T1 angiography sequence) and changes in metabolites and neuronal activity through spectroscopy and diffusion tensor imaging shortly after birth in animals with or without ventilation procedures, which until recently were the standard resuscitation procedure for very preterm babies. The ability to investigate which factors drive brain injury in preterm babies and evaluate novel therapies using clinical MR scanners is an important research translation at this node of the NIF consortium.

Industry Partner
Hudson Institute of Medical Research

For more details about this project, please contact Dr. Graeme Polglase (graeme.polglase@hudson.org.au) or Dr. Qizhu Wu (qi.wu@monash.edu). For more details about the facilities and access to the MBI Node at Clayton, please contact Dr. Charles Hardy (charles.hardy@monash.edu).

Figure 1. T1-weighted angiography images (upper panel) and susceptibility-weighted imaging (bottom panel) reveal internal bleeding at the ventral surface of the brain of a preterm lamb after a brief 15 min period of injurious mechanical ventilation.
In preclinical Positron Emission Tomography (PET) imaging, several research groups have recently proposed different experimental set ups allowing multiple animals to be simultaneously imaged in a scanner in order to reduce the costs and increase the throughput. Simultaneous scanning of several animals also ensures injections with the same specific activity, which may be otherwise subject to significant variations when animals are injected at different time and possibly with tracers from different productions.

In addition, it is well known that the performance of a PET system, in terms of spatial resolution and sensitivity, is optimal at the center of the field of view (FOV) and degrades quickly with increasing distance from the center. In previous studies, the technical feasibility has been demonstrated and the signal degradation caused by additional mice in the FOV characterized, however, the impact of the signal degradation on the outcome of a PET study has not yet been studied.

In a project1 collaborated by the ANSTO/University of Sydney node of the National Imaging Facility, the collaborators thoroughly investigated, using Monte Carlo simulated [18F]FDG and [11C]Raclopride PET studies, different experimental designs for whole-body and brain acquisitions of two mice and assessed the actual impact on the detection of biological variations as compared to a single-mouse setting.

First, the validation of the PET-SORTEO Monte Carlo simulation platform for the simultaneous simulation of two animals was extended. Then, [18F]FDG and [11C]Raclopride input mouse models for the simulation of realistic animal distance as well as the use of reconstruction methods with resolution modeling should be preferred. Dual mode acquisition did not have a major impact on ROI-based analysis except in situations where uptake values in organs from the same subject were compared. The simulated [11C]Raclopride study however showed that dual-mice imaging strongly reduced the sensitivity to variations when mice were positioned side-by-side while no sensitivity reduction was observed when they were facing each other.

In the simulated [18F]FDG whole-body study showed that the resolution loss due to the off-center positioning of the mice was the biggest contributing factor in signal degradation at the pixel level and a minimal inter-

This is the first study showing the impact of different experimental designs for whole-body and brain acquisitions of two mice on the quality of the results using Monte Carlo simulated [18F]FDG and [11C]Raclopride PET studies. This study validates unique experimental capabilities, which enable researchers to make the most of the radiotracers production and scanners availability.

Collaborators
ANSTO/University of Sydney Node
CERMEP - Imagerie du vivant, Lyon, France
Institut Pluridisciplinaire Hubert Curien, Université de Strasbourg, France
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World Cancer Day - Enhanced MRI of Preclinical Prostate Cancer

National Imaging Facility (NIF) scientists take part in beating cancer by their powerful weapon of knowledge, skills, and experience. They pursue a range of research and development projects from new approaches for early detection to developing potential treatments of cancer and anything in between. They collaborate and assist various research community groups as well as industry partners with optimal use of the state-of-the-art imaging technologies, widely available across mainland Australia. This year, on World Cancer Day - February 4th - NIF participated in raising awareness on cancer and supporting cancer research studies and developments. Below, is a summary of some of the research projects carried out at NIF nodes that contribute to a better understanding of cancer.


MRI is a useful imaging tool in prostate cancer management. It provides excellent soft tissue contrast and multidimensional information, does not involve exposure to ionizing radiation, and is non-invasive. However, like other imaging modalities such as computed tomography (CT), transurethral ultrasound (TRUS) and nuclear imaging, MRI cannot adequately detect small tumors.

The ability to accurately detect and locate small tumors is necessary for early detection of disease and for assessment of response to therapy in cancer patients. In recent years, the use of biomarker-targeted probes linked with nanoparticle-based contrast agents to enhance these imaging modalities has been a major area of research. Iron oxide magnetic nanoparticles (MNPs) are powerful contrast agents for MRI. Their superparamagnetic properties make them effective at reducing transverse (spin-spin) T2-relaxation time, causing negative contrast in magnetic resonance (MR) images. MNP-assisted MRI has the potential to improve the assessment of cell surface receptor expression on tumors, liver function (macrophage content and activity), inflammation, degenerative diseases, angiogenesis, perfusion and apoptosis.

A project1 conducted at the University of Queensland node evaluated the potential of newly-developed, biocompatible iron oxide magnetic nanoparticles conjugated with J591, an antibody to an extracellular epitope of PSMA, to enhance MRI of prostate cancer. This was done by performing MRI on mice with preestablished orthotopic LNCaP-luc tumors and intravenously injected with either MNPs alone or J591-MNPs. MR images of tumors from mice that received the J591-MNP conjugates show significant darkening at the prostate region, at the 2- and 24-h post-injection time points, as shown in the image, below. The study provided proof-of-concept that PSMA-targeted MNPs can effectively enhance MRI of prostate cancer in a preclinical model of the disease.

Based on its biocompatibility, stability, together with its ability to enhance MRI, PSMA-targeting MNPs have promise to be translated into the clinic to improve the management of prostate cancer.

Collaborators
Australian Prostate Cancer Research Centre, Ceramisphere Pty Ltd, and Ian Wark Institute.

For more information, please contact Dr. Gary Cowin (gary.cowin@cai.uq.edu.au).

Enhancement of MRI with J591-MNP (pilot study). Once the pre-established LNCaP-luc tumors had reached the desired size (based on bioluminescence signal; inset), which occurred approximately 4-weeks post tumor cell injection, the mice were injected intravenously with MNPs alone (n = 2) or J591-MNP (n = 3). Administration of J591-MNP conjugates resulted in significant darkening of magnetic resonance images of the prostate region, at 2- and 24-h post-injection. No darkening effect occurred in mice given MNPs alone. Red arrows: orthotopic LNCaP-luc tumors. Magnetic resonance images of representative mice from each group are shown. MNP: Magnetic nanoparticle. Figure was reproduced with permission from Nanomachine as agreed by Future Medicine Ltd.


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First SAHMRI Placement Scheme

The South Australian Health and Medical Research Institute (SAHMRI), part of the LARIF node of the National Imaging Facility, has recently opened fourth year placement positions for Nuclear Medicine students. The placements are held within the Molecular Imaging and Therapy Research Unit (MITRU) and the rodent imaging facility is managed by National Imaging Facility’s Fellow, Dr. Marianne Keller.

Judy Duong, one of the first students to attend the placement, describes her experience at SAHMRI an interesting & valuable one. “My time in the Animal Scanning facility has taught me more about the clinical trial phases. It was really interesting to learn how important preclinical imaging is in the spectrum of research developments and innovations. I was given practical sessions on how to use the micro-PET/SPECT scanner and how to manipulate the collected data in various processing applications. After these sessions, I was able to observe rodent imaging from radiopharmaceutical injection to post-processing image displays. I really enjoyed learning about the similarities and differences between the Nuclear Medicine aspect of animal and human imaging”, said Judy.

Judy further explained, “apart from the weekly seminars, I was also given the opportunity to attend the ‘Molecular Imaging Symposium’ and the ‘Research Imaging Snapshot’ held at SAHMRI. This gave me insight into the research and developments that are currently occurring interstate and overseas. From my perspective, the most intriguing aspect of this placement for Nuclear Medicine students is the chance to observe the process of how a PET tracer goes from a cyclotron to a Nuclear Medicine department. After the PET tracer is produced, quality control (QC) testing is performed. A number of QC tests must pass before a release form is issued to a department to allow the tracer to be injected into patients. I observed and assisted in the numerous steps involved in the Production and QC processes and also performed experiments on various compounds.”

The placement has proved to develop the students’ knowledge and understanding of different aspects of Nuclear Medicine. Judy acknowledged the effectiveness of such opportunity in her learning process and recommended it to all her peers: “My appreciation has grown, now knowing that there are many other components involved in performing a PET scan in both animal and human imaging. My time in MITRU and the Animal Scanning facility has been such a positive experience and I believe this placement will benefit all up-and-coming Nuclear Medicine graduates!”

CSIRO’s ‘Scientist in Schools’

Scientists in Schools is a national volunteer program, which brings real science into the classroom and teaches critical thinking to students – a life skill that is beyond the classroom. It provides skilled volunteers the opportunity to have a positive impact and make a difference to science and technology education in primary and secondary Australian schools.

As part of this program, Centre for Advanced Imaging (CAI) in the University of Queensland node invited year 11 physics students of Cavendish Road State High School to tour CAI’s world-leading facilities and learn first-hand about the instrumentation and research from the scientists themselves.

Students visited the cyclotron (a particle accelerator for making radioisotopes), used the robotic arms that scientists use to handle radioactive materials, and saw several other imaging facilities. They also learnt about the use of PET-scanners, a commonly used diagnostic tool in cancer studies.

“Aside from the impressive nature of the facilities and research happening at CAI, it was enlightening to note that ‘real’ scientific research is multidisciplinary - the team at CAI includes physicists, chemists and computer scientists, just to name a few. Students with an interest in science can study many varied disciplines to be involved in such exciting careers”, said the head of department - science - at Cavendish Road State High School.
The higher education conference, organized by Universities Australia and held on 9-11 March this year, was the annual signature event for the sector attracting over 800 delegates including Vice-Chancellors, Chancellors, senior university representatives, Government representatives, industry representatives, members of research community, international education specialists, media and those with an interest in higher education.

The conference highlighted the 2016 theme of “transforming Australia: universities and their communities” and featured an exceptional line up of speakers including Senator The Hon Simon Birmingham and Senator The Hon Kim Carr.

National Imaging Facility and other NCRIS capabilities that had the opportunity to exhibit at the conference presented the infrastructure and expertise that are available to Australian universities’ research communities, research institutes, and industries, encouraging visitors to engage and learn more.