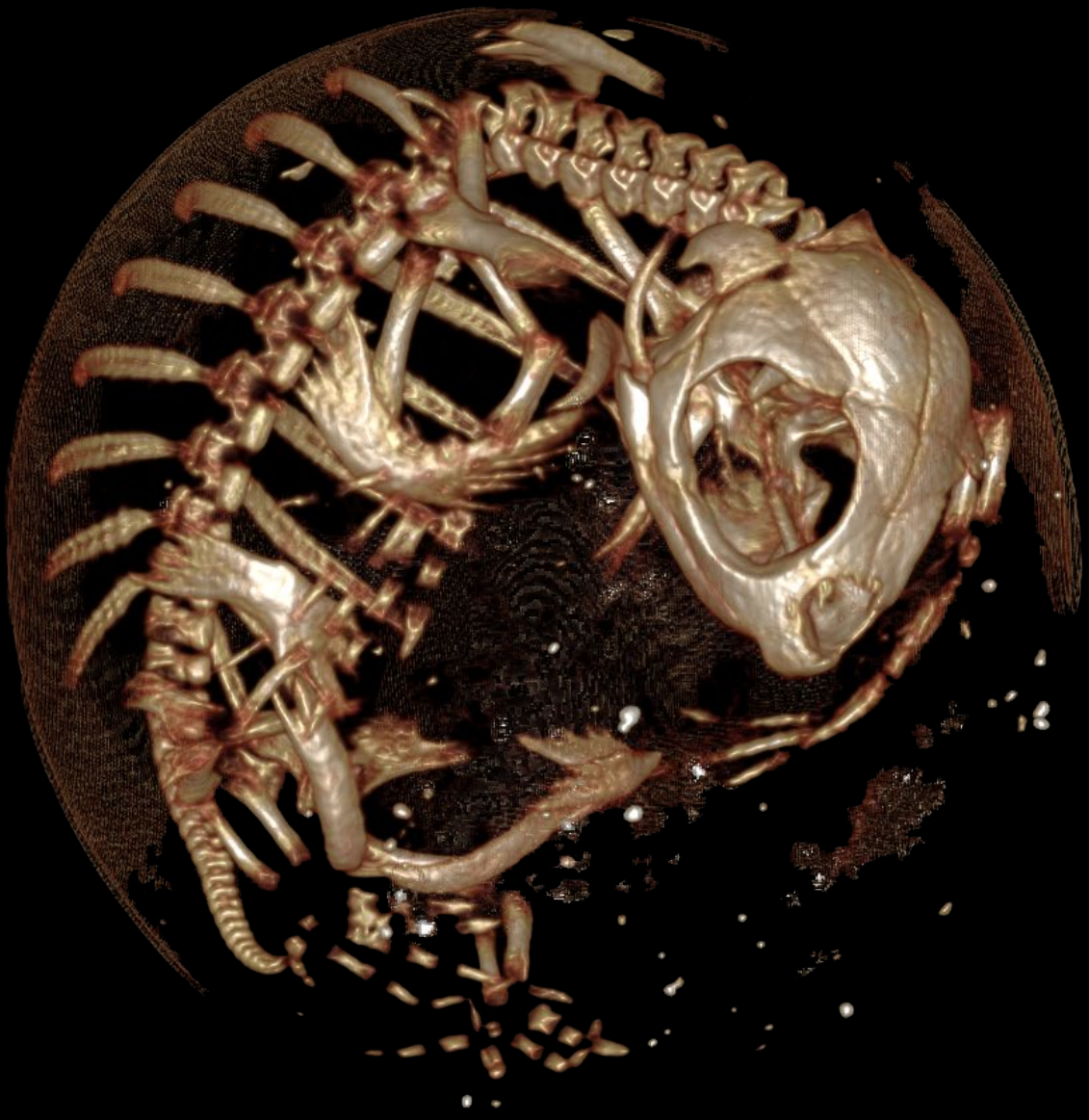
National Imaging Facility

National Imaging Facility Quarterly Newsletter Issue Two 2018



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IN THIS ISSUE

On the cover: CT scan of a turtle embryo in its egg, collected from Monte Bello nuclear test site in Western Australia. CT scans were used to identify eggs with turtles for further analysis. The project was led by ANSTO Environment, with contributions from Ms Emma Davis and Mr David Zahra (image acquisition and reconstruction). Image courtesy of ANSTO and Dr Mitra Safavi-Naeini.

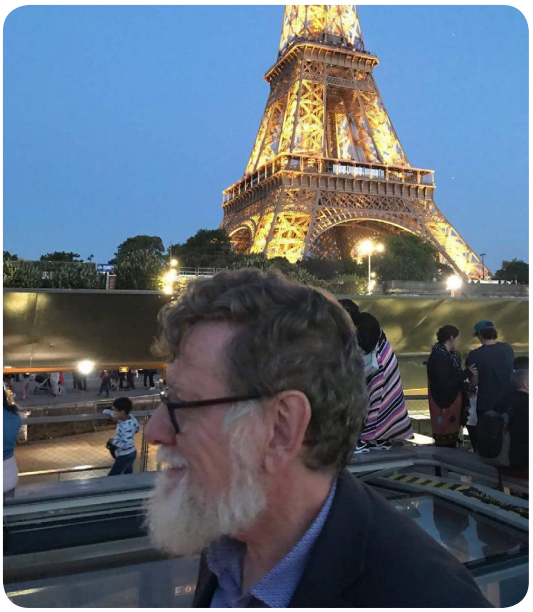
CEO'S MESSAGE

The recent federal budget brought very welcome news for NIF, with new NCRIS funding of $53M over the next five years. This will provide much needed capital renewal, addressing the needs identified in the National Research Infrastructure Roadmap. NIF continues to emphasise the critical importance of the human capital, and this has been recognized with an additional $10M for NIF Fellows, who support your research through provision of expertise in imaging technology and in data management and analysis. The value of our staff is exemplified through the awards and recognition that they have received from their peers, and we congratulate Lindy and Mitra for the awards. Further identifying the importance of people, through our training workshops, NIF is committed to supporting their career development, so that they can better serve your needs.

In this newsletter, we highlight two neuroscience projects, designed to understand the changes in the chemistry and structure of the brain during disease processes. NIF also invests in technology, whether it be identifying artefacts introduced by identification markers, or developing and deploying better data curation tools.

This is our last Newsletter in this format. Going forward, we have decided that a monthly e-zine will be accessible to more people, and give us the opportunity to share news with you more frequently. Be assured, whilst there is a change in format, the same enthusiasm and commitment to excellence will continue. We hope that you will continue to derive pleasure through the stories we share.

NIF is part of the National Research Infrastructure, a community of like-minded capabilities, who are passionate in their common goal to underpin Australian science with world-class infrastructure. Like any community, there are times of joy and times of sadness. NIF joins with the rest of the infrastructure community in grieving the loss of John La Salle, who, as Executive Director of the Atlas of Living Australia, was a passionate supporter for the whole of NCRIS. Taken suddenly and too early, we remember John fondly, as a gifted scientist, a powerful advocate and a great friend.



Professor Graham Galloway
NIF Chief Executive Officer

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RESEARCH PROJECT

Uncoupling N-acetylaspertate from brain pathology: implication for Canavan disease gene therapy

N-Acetylaspartate (NAA) is the second most abundant organic metabolite in the brain, but its physiological significance remains puzzling. Toxic NAA accumulation appears to be the key factor for neurological decline in Canavan disease—a fatal neurometabolic disorder caused by deficiency in the NAA-degrading enzyme aspartoacylase.

To date, clinical outcome of gene replacement therapy for this spongiform leukodystrophy has not met expectations. To identify the target tissue and cells for maximum anticipated treatment benefit, we employed comprehensive phenotyping of novel mouse models to assess cell type-specific consequences of NAA depletion or elevation. We show that NAA deficiency causes neurological deficits affecting unconscious defensive reactions aimed at protecting the body from external threat. This finding suggests, while NAA reduction is pivotal to treat Canavan disease, revoking NAA synthesis should be avoided. At the other end of the spectrum, while predicting pathological severity in Canavan diseased mice, increased brain NAA levels are not neurotoxic per se. In fact, in transgenic mice overexpressing the NAA synthesizing enzyme Nat8l in neurons, supra-physiological NAA levels were uncoupled from neurological deficits. In contrast, elimination of aspartoacylase expression exclusively in oligodendrocytes elicited Canavan disease like pathology. Although conditional aspartoacylase deletion in oligodendrocytes abolished expression in the entire Central Nervous System (CNS), the remaining aspartoacylase in peripheral organs was sufficient to lower NAA levels, delay disease onset and ameliorate histopathology.

Comparable endpoints of the conditional and complete aspartoacylase knockout indicate that optimal Canavan disease gene replacement therapies should restore aspartoacylase expression in oligodendrocytes. On the basis of these findings we executed an ASPA gene replacement therapy targeting oligodendrocytes in Canavan diseased mice resulting in reversal of pre-existing CNS pathology and lasting neurological benefits.

This finding signifies the first successful post-symptomatic treatment of a white matter disorder using an adeno-associated virus vector tailored towards oligodendroglial-restricted transgene expression.

The full publication can be found with DOI 10.1007/s00401-017-1784-9

Authors: Georg von Jonquieres, Ziggy H.T. Spencer, Benjamin D. Rowlands, Claudia B. Klugmann, Andre Bongers, Anne E. Harasta, Kristina E. Parley, Jennie Cederholm, Orla Teahan, Russell Pickford, Fabien Delerue, Lars M. Ittner, DOminik Frohlich, Catriona A. McLean, Anthony S. Don, Miriam Schneider, Gary D. Housley, Caroline D. Rae, Matthias Klugmann

Dr Caroline Rae is the NIF Node Director at the UNSW-NeuRA node and Dr Andre Bongers is a Facility Fellow at the UNSW-BRIL node.

Every two years, the Australia and New Zealand Society for Magnetic Resonance (ANZMAG) awards two medals to recognize the exceptional contributions of a senior and junior member of the community. Beyond research, this award also recognizes contributions to teaching and service to the discipline. Prof Caroline (Lindy) Rae received this year's ANZMAG medal for her outstanding contributions to magnetic resonance. Indeed, Prof Rae's impact in the discipline is evident. One of her students, Lavanya Anchata, also received a poster award and travel grant at the conference.

Congratulations, Prof Rae!

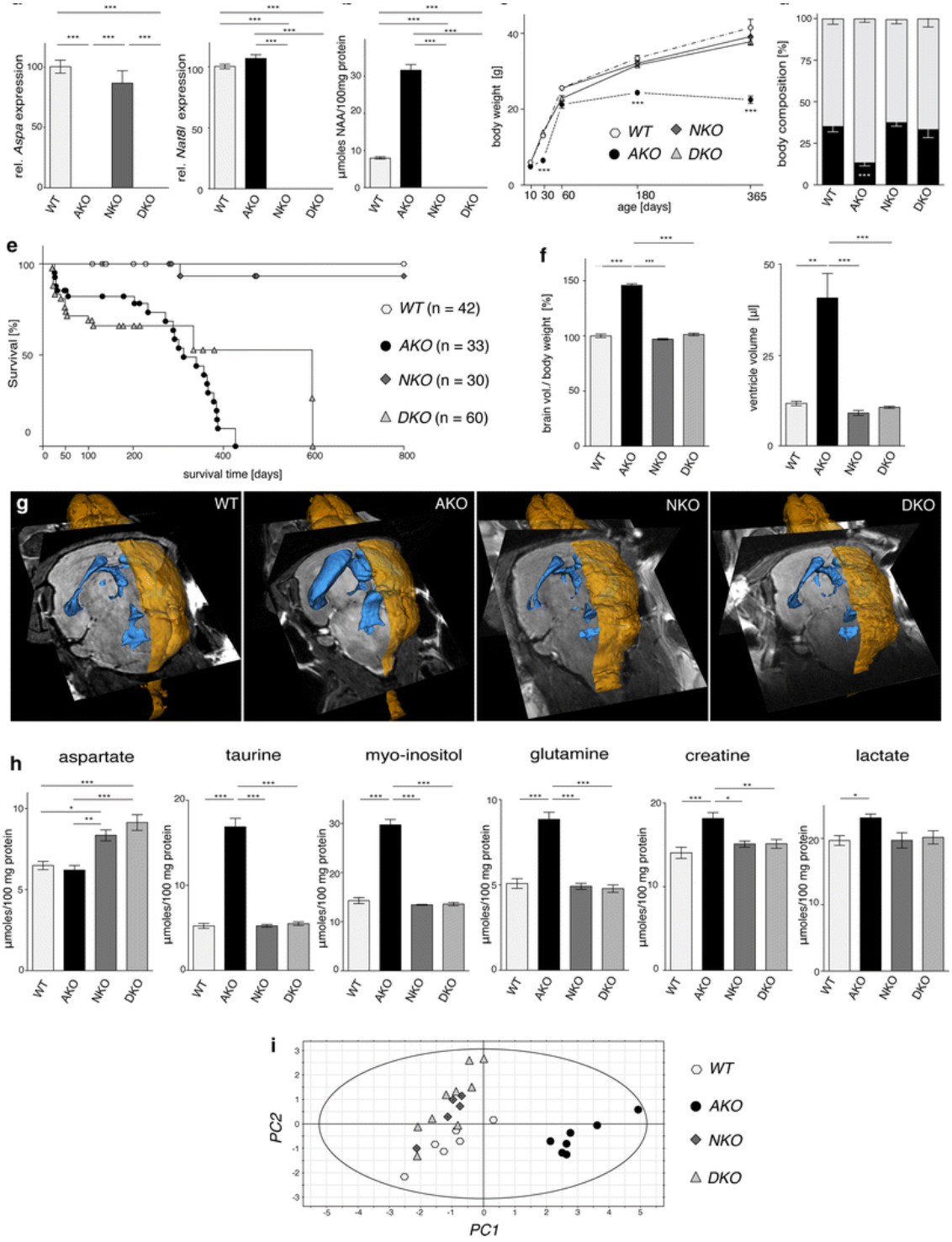
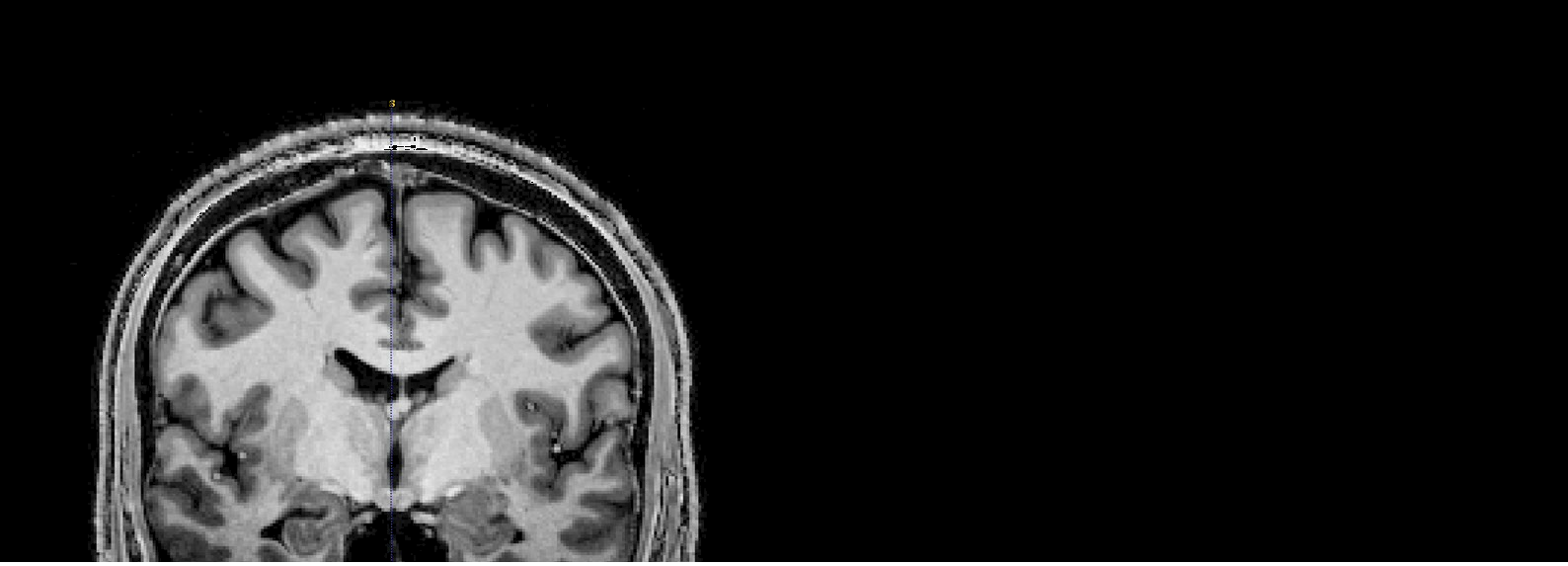


Figure 1: Pathological consequences of manipulation of NAA metabolism. See online article for full length description



NATIONAL COLLABORATION

Installation of the first human ultra-high field MRI systems in the southern hemisphere brought Australia to the forefront of ultra-high field research and opened up the possibility to probe the human brain with an unprecedented level of detail.

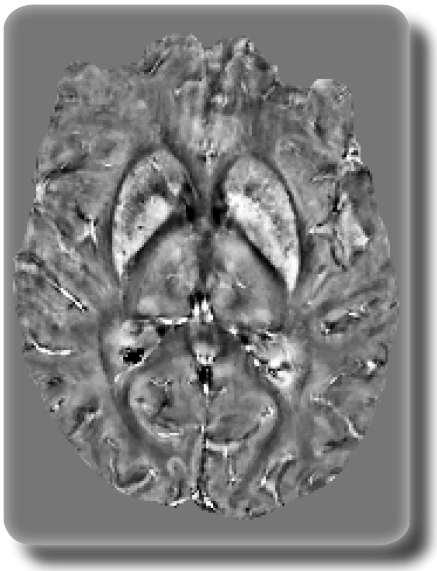
Australia has been at the forefront of dementia research with world leading studies such as the Australian Imaging and Lifestyle study of Ageing (AIBL) led by a consortium of Australia's leading Dementia centres, or the recently started Prospective Study of Ageing (PISA) led by the QIMR Berghofer.

The installation of the first human ultra-high field MRI systems on the southern hemisphere in 2014 opened up a new era of research within Australia's National Imaging Facility. In 2014, a 7T whole-body research scanner (Siemens Healthcare, Erlangen, Germany) with a 32-channel head coil (Nova Medical, Wilmington, USA) was installed in Brisbane at the Centre for Advanced Imaging, now under the leadership of Ian Brereton and Markus Barth. A few months later an identical machine was installed at the University of Melbourne under the leadership of Roger Ordidge and Brad Moffat. This brought Australia to the forefront of ultra-high field research and opened up the possibility to probe the human brain with an unprecedented level of detail.

With this new 7T MRI capability available came the question of whether ultra-high field MRI could improve imaging biomarkers for neurodegeneration diagnosis. A new project was established, led by the CSIRO and co-funded by the CRC for Mental Health.

A large team of experts was assembled, led by Dr Olivier Salvado, involving the two MRI 7T teams, the QIMR Berghofer, the Florey Institute of Neuroscience, various investigators from the AIBL study, and the Siemens Australia team. The aims were to characterise imaging biomarkers at 7T, especially compared to 3T, and to identify a suitable imaging protocol for a clinical elderly population. Several candidate sequences were identified which could benefit from the increased field strength and provide clinical information for neurodegeneration. Testing on volunteers was performed to evaluate each sequence and optimise parameters. The timing target was a maximum imaging time of 40 minutes, which could fit within a 1 hour time slot.

For more information on the AIBL-related study on Alzheimer's Disease, please see the NIF Quarterly Newsletter Issue Two, 2017.



(Above) 3D MP2RAGE 0.9mm isotropic showing exceptional tissue contrast. (Right) Example of a Quantitative susceptibility mapping (QSM), a mechanism useful for chemical identification and quantification of specific biomarkers.

The first multi-centre study of Dementia at 7T ultra-high field MRI in Australia

After careful review and testing, the final imaging protocol included a list of core sequences done at both sites:

- T1W MP2RAGE (0.9 min isotropic, 6 min),
- Multi echo GRE (0.75mm isotropic, 8 min)
- T2W TSE coronal for hippocampus subfields (0.5x0.5x0.6mm^3, using 3 blocks of 4min40)
- 2D FLAIR TSE (1x1x3 mm^3, 3 min)

Both Melbourne and Brisbane also had the opportunity to add additional sequences as exploratory aims should the subjects be comfortable extending the scanning time. These included MRI spectroscopy, resting state fMRI, and MRI diffusion imaging.

Much consideration was given in selecting a cohort that would allow establishment of normative data and provide preliminary results for expending the study. The project team identified the following cohort: 40 healthy subjects ranging from 50 to 70 were recruited in Brisbane (ageing study), supplemented by up to 20 patients with fronto-temporal dementia (FTD); 40 subjects from the AIBL study (Alzheimer's) were recruited in Melbourne selecting for healthy control with (15) and without (15) Amyloid burden as detected by PET, enriched by 10 Amyloid positive MCI and AD patients to act as a positive control group. The recruitment of FTD subjects, led by Christine Guo at the QIMR, is still active in Brisbane.

It has been a large project to setup as it was one of the first large scale (100+ subjects) studies in Australia aimed at a challenging population of elderlies, many with neurodegenerative disorders, and thus subject to motion and feeling uncomfortable in the scanners.

It was a great team effort with much help and support provided by the MRI 7T facility in terms of expertise but also scanning time for testing the protocol on volunteers. Safety of the subjects was the highest priority and conservative guidelines in terms of suitability for high magnetic field were used. This resulted in stringent exclusion criteria for any suspected metallic implants, which was a challenge for recruitment. Overall, the project has been successfully completed with superb image quality obtained using state of the art sequences. A significant effort is now underway to analyse this wealth of data.

Acknowledgments:
Many thanks to Olivier Salvado, Jurgen Fripp, Steffen Bollmann, Brad Moffat, Saskia Bollmann, Markus Barth and Amir Fazlollahi for their contributions to this article and for providing the images used.

People involved in the study:

CSIRO: Dr Parnesh Raniga, Dr Jurgen Fripp, Dr Pierrick Bourgeat, Dr Amir Fazlollahi, Dr Olivier Salvado

Florey Institute of Neuroscience: Dr Alan Connelly, Dr Shawna Farquharson, Dr. Tia Cummins and Prof. Chris Rowe

University of Melbourne: Prof. Roger Ordidge, A/Prof Bradford Moffat (NIF Fellow) Drs Amanda Ng, Scott Kolbe, Jon Cleary, Rebecca Glarin and Mr Robert Williams (NIF Fellow)

QIMR: Christine Guo

UQ: Dr Markus Bath, Saskia Bollmann, Dr Steffen Bollmann (NIF Fellow) , Aiman Al-Najjar, Nicole Atcheson

Siemens: Dr Kieran O'Brien, Dr Benjamin Schmitt, Dr Sonal Josan

Royal Melbourne Hospital: Dr Patricia Desmond

Funding: CRC for Mental Health, QIMR Berghofer, CSIRO

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Creating a smart-lab: automating the preclinical research process

INDUSTRY COLLABORATION

Unique and permanent identification of laboratory animals is important to ensure the quality and integrity of preclinical laboratory studies.

At the beginning of last year, SAHMRI started a large collaboration with Somark to test their new technology platform. The Somark product suite is built using micro radio frequency identification (microRFID) technology to create a 'smart-lab', consequently automating much of the preclinical research process. The solution implements a digital link between research animals, their environment and the equipment in the lab. By integrating tagged animals via tag readers, the Somark software platform and integrated lab equipment, such as scales and MRI machines, enables much of the preclinical data collection process to be automated. As the solution assimilates with the Somark software platform we will use analytics and artificial intelligence methods to deliver powerful insights on that data in real-time.

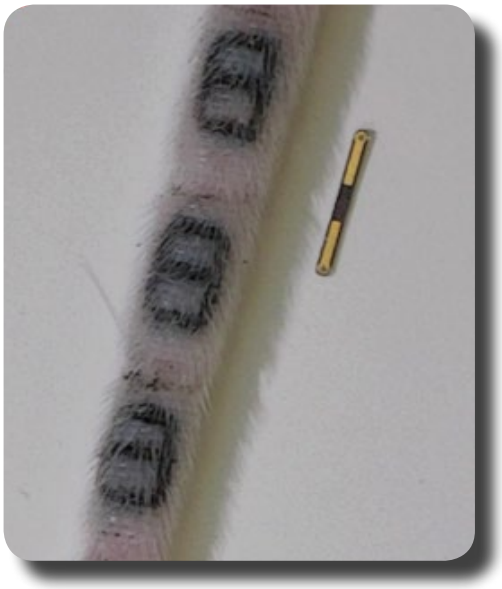
The Somark product suite includes the microRFID Tag and a range of its supporting components including the Handheld Injector, an automated tag injecting device (Ai.Tag), tag readers (Ai.Read) and a Data Hub (Ai.Connect). The details of each product are as follows:

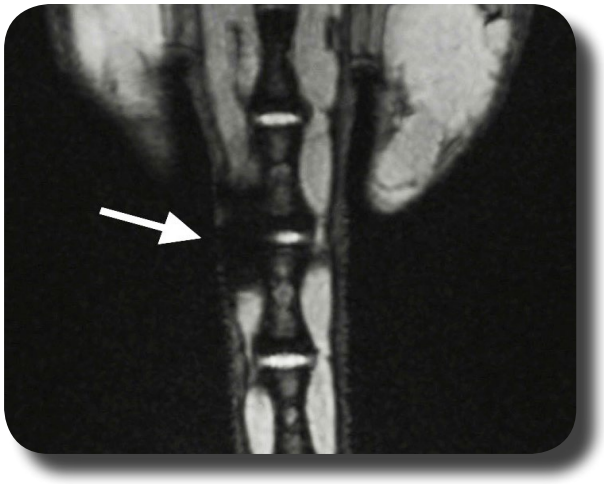
The Somark microRFID Tag is the world's only fully functional microRFID tag specifically designed for rodents. It is implanted via non-surgical means using the Handheld Injector or the Ai.Tag automated tag injection garage, both of which are created by Somark. The microRFID Tag integrates with tag readers (Ai.Tag), the Data Hub (Ai.Connect) and the Somark software (Ai. Cloud), to automate data collection relating to the animal and the preclinical research process in real-time.

LARIF decided to test these microRFID tags in their scanner to see if they create artefacts and if the tags are still useful after scanning at 3T. We also wanted to check for burns in the area.

The T1 weighted 3D turbo spin echo sequence gave us the outline of the microchip and also the needle canal. The volume of the microchip is 4.55 mm³. While avoiding segmentation of the needle canal, some of this volume might have been air.

Then we ran the T2* weighted gradient sequence. In the resulting image, you can see that the microchip and any trapped air caused a blooming artefact. The blooming artefact volume was 71.77 mm³. This artefact might be larger in a scanner with a bigger field strength.





In the literature burns have been reported when imaging tattoos using haste sequences. We ran a T2* haste sequence with TR=1650.0 ms, TE=96 ms, Flip angle=150 deg, 27 slices of 1.5mm slice thickness. FoV=130 mm, five averages and a voxel size of 0.4×0.4×1.5 mm. After we imaged the rat, we necropsied the tail. Under gross inspection we could not see any changes of the tissue around the injection area.

The microchip was fully operational after this experiment.

community pages

the people, tools and activities that form the building blocks of the NIF community

Enhancing Characterisation Tools

NIF is committed to not only ensuring Australian researchers have access to state of the art imaging equipment, but also providing better access to data processing, analysis and management tools. Thanks to a new project part-funded by the Australian Research Data Commons (ARDC, formerly ANDS-Nectar-RDS), NIF is a partner of the Characterisation Data Enhanced Virtual Laboratory, which among other outcomes will:

- Federate the existing Characterisation Virtual Laboratory across Australia and expand on the available tools,
- Make Characterisation digital objects more Findable, Accessible, Interoperable, Reusable (FAIR) though community outreach
- Upskill the research workforce and train the next generation of experts through a domain specific training program, and
- Develop a nationally coordinated network of informatics experts.

Recognizing the need for a more robust program to spread knowledge and underpin change, the partners have made FAIR data and training a priority under this project. NIF will lead the FAIR Data and Training component and will build on other projects which aim to make data more trusted and valuable for future use.

For more information on the CVL and DEVL project, visit: www.clv.org.au

Project Partners include:
Monash University (Lead Agent), Microscopy Australia (formerly AMMRF), Australian Nuclear Science and Technology Organisation (ANSTO), University of Sydney, University of Queensland, University of Western Australia and University of Wollongong

Celebrating our community's achievements

As a national infrastructure, NIF is fortunate to work with many outstanding researchers from different disciplines. Dr Mitra Safavi-Naeini is among those in the NIF community being recognized for her work, specifically on the development of Neutron Capture Enhanced Particle Therapy (NCEPT). This approach aims to exploit thermal neutrons produced inside patients as a by-product of particle therapy. Outcomes from this research could result in more effective treatment and reduce patient complications.

Dr Safavi-Naeini was one of three awardees of the Yamagiwa-Yoshida Memorial International Study Grant, which enables investigators to carry out 3-month bilateral research projects abroad. She will be travelling to the National Institute of Radiological Sciences in Japan to obtain experimental proof of concept for the newly developed approach.

Earlier in April, she was also chosen for a placement in the Fraunhofer-Gelleschaft Innovation Tour 2018. Awarded for their innovative proposals, 23 Australians, including Dr Safavi-Naeini, will participate in a week-long Innovation tour through Germany in November. They will be given the opportunity to network, visit universities, institutions and companies to lay the foundation of on-going project development

Beyond these awards, Dr Safavi-Naeini and her team at ANSTO were successful with their entry into CSIRO's ON Prime Sydney program, which assists researcher teams in taking their concept to market delivery. The ANSTO team is now half-way through the course.

Some of the NCRIS community members who attended the March 2018 Forum in Canberra. Included in this photo was our colleague, Dr John La Salle of Atlas of Living Australia. Vale John La Salle.

Photo provided by the Department of Education and Training

bridges and pathways: building research ecosystems

This past May, NIF held its Annual Meeting at the Melbourne Brain Centre in Parkville. This three-day event brought together members of the NIF community, from Governing Board Members and Node Directors to Facility and Informatics Fellows, around a vision of creating a new chapter for the program.

Directors and Fellows alike were challenged with how to build on NIF's previous achievements and take the national capability to the next level. Within their thematic groups, Fellows were presented with a grand challenge – identify a national initiative. Over a day and a half, the thematic groups underwent a series of activities and developed a detailed impact pathway for their initiatives.

Integral to the success of these projects will be collaboration with external groups, including industry. MTPConnect's Michelle Burke and Telix Pharmaceutical's CEO, Christian Behrenbruch , also attended the Fellows Workshop to share their valuable insights into fostering better engagement with universities and research institutions.

national initiatives

In late 2017, the members of the NCRIS community, including NIF, participated in an impact planning workshop to better understand how to identify, measure and evaluate the impact of infrastructure. In a program-wide effort to share and apply these learnings, the Fellows workshop focused on the application of the impact pathway to the identified national initiatives.

Human Imaging

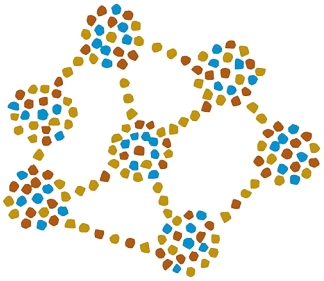
An unprecedented amount of research data is being acquired on a daily basis. This theme's initiative will leverage existing MRI data to create a new database. Among the different dimensions of this project, the theme will need to navigate the challenges presented by ethics and find a coordinated approach to data reuse for the future.

Molecular Imaging

In order to improve reproducibility and enable the standardization of protocols, one of the theme's activities will be focused on sending a pre-clinical phantom to sites to collect node data. The project is currently underway to gather QA data for PET instruments and review protocols for potential multi-node animal studies.

Animals Plants & Materials

NIF has identified growing engagement with museums at many nodes to image Australia's flora and fauna. Recognizing the existing work of other capabilities such as Atlas of Living Australia and Bioplatform Australia's Oz Mammal Genome initiative to capture genomic information, the theme will look to developing a data delivery model to integrate genomic and phenomic data.



Over the last 12 years, NIF has worked to build a research ecosystem that goes beyond provision of imaging infrastructure. The capability has delivered $150m of state-of-art equipment and properly designed laboratories that are fit for purpose. NIF has contributed to and developed policies and procedures, and continues to lead in the data management space, building new tools in collaboration with the Australian Research Data Commons (ARDC). Facility and Informatics Fellows have made significant contributions to imaging and continue to support the needs of the user community.

In 2016, the Roadmap identified future needs and gaps in the research community. With those and the needs of the existing and future imaging users in mind, NIF underwent a data collection exercise last August which informed the National Infrastructure Investment Plan. We are pleased to share that NIF was successful in receiving an additional $53m funding for the next five years.

NIF will be able to maintain its portfolio of imaging capability as world-class in structural, functional and molecular imaging. The network will continue to support publicly funded research and will provide essential tools for MRFF and BFT, including pre-clinical and clinical imaging technology and new radiochemistry capability essential for understanding molecular interactions and fuelling new therapy management technologies. In response to concerns raised in the Roadmap, a network of radiochemistry capability will be coordinated, which ensures researchers have access to a comprehensive range of radiotracers. NIF will also deliver new world-leading technology with total-body PET and Connectome Gradients.

NIF will continue to implement technology and processes for best practice in data management, including promoting the FAIR Data Principles and its domain-specific applications. NIF is also working to connect disparate datatypes, connecting genomic data to phenomic data.

We are confident that the success NIF has achieved thus far is due to the engagement and input of the communities we work with. NIF proposed a nationally coordinated approach to the future of imaging in Australia and we remain committed to engaging with you, our colleagues, users, institutions and across government bodies to ensure that the implementation of the investment entrusted to us remains in the best interest of Australia.

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An Australian Government Initiative

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