ACRF IMAGE X INSTITUTE

AUSTRALIAN CANCER RESEARCH FOUNDATION

THE UNIVERSITY OF SYDNEY

ACRF GRANT AWARDED 2014

The $2.5 million funding from the Australian Cancer Research Foundation supported three unique cancer imaging and targeted radiotherapy devices. These include an MRI-Linac , a real-time cancer imaging and targeted therapy system; the Nano-X, a smarter, smaller cancer radiotherapy system and a robotic imaging machine to advance patient connected imaging.

MRI Linac, a powerful experimental cancer radiation therapy system based at Liverpool Hospital

ABOUT ACRF IMAGE X INSTITUTE

The ACRF Image X Institute, based in Sydney, is a world- leading research centre for basic and translational medical innovation. The work focuses on radiation oncology imaging, and targeted radiotherapy systems.

What is the purpose?

To create, share and apply scientific knowledge to improve health by building new technology for cancer imaging and targeted radiation therapy

How would this be achieved?

- Invent and explore new ideas that lead to scientific discoveries.
- Apply key discoveries for real-world benefit through first-in-human clinical trials.
- Translate successful clinical trial outcomes into widespread clinical practice to improve global health.

2019 OUTCOMES

In 2019, key outcomes reported by the ACRF Image X Institute include:

- Clinical studies - 8 studies have been completed; 8 studies are currently recruiting subjects & 9 studies are under development. A total of 14 sites are involved in Australia and NZ.
- 24 Scientific publications
- Intellectual Property: 9 Patents filed with 13 license agreements.

2 articles were published by the popular science Physics World:

The first article is based around the question. How can we reduce the size, reliability and the room and equipment cost of radiotherapy? Gently rotate the patient rather than a 3-tonne complex and sensitive radiation source. This idea has led to the development of the Nano-X cancer radiotherapy system in partnership with the Prince of Wales Hospital. Dr Paul Liu, who is leading the development and research program for the Nano-X, was interviewed about this project. See https://physicsworld.com/a/patient-rotation-enables-fixed-beam-radiotherapy-system/

The prototype radiotherapy system combines a fixed vertical radiation beam with horizontal patient rotation. (Courtesy: Paul Liu)

In addition, Tess Reynolds' Best in Physics work on her patient connected imaging project 'ACROBEAT' was highlighted by Physics World. See: https://physicsworld.com/a/aapm-showcases-the-best-in-physics/

A UNIQUE CAPABILITY: ARTIS pheno training and installation of real-time control:

The ARTIS pheno C-Arm is an advanced robotic imaging system, purchased with funding from the ACRF grant, and situated in the Hybrid Theatre of Sydney Imaging. Through a research agreement with Siemens Healthineers Image X is the only research group provided with real-time control of the operation of this imaging system. Two scientists from Siemens Healthineers in Germany visited to install the control addition and provide training. This installation will allow the experimental validation of methods developed by A/Prof Ricky O'Brien and Dr Tess Reynolds to adapt image acquisition to the patients' cardiac and respiratory signals.

THANK YOU TO ACRF SUPPORTERS

I would especially like to thank the ACRF for its funding and support going forward, which is instrumental in enabling us to carry out our ground-breaking research and ensures we can work towards better outcomes for cancer patients.

Sincerely

Paul Keall, Ph.D, DABR, DABMP, FInstP, FACPSEM, FAAPM, GAICD
Professor and NHMRC Senior Principal Research Fellow Director,
ACRF Image X Institute

NOTE FROM ACRF:
Congratulations Paul on your induction as a Fellow of the American Society for Radiation Oncology and Oncology (ASTRO), at the 2019 annual meeting in Chicago. This award is based upon service to ASTRO and contributions to the field of Radiation Oncology.
We think you are amazing!

PAUL KEALL CONGRATULATES RESEARCHERS FOR ACHIEVEMENTS IN 2019

In 2019 we were able to congratulate two of our Higher Degree Research students on their awards. Ben Cooper whose PhD thesis is entitled, "The investigation of novel x-ray imaging technique in radiation oncology". It was fantastic that Dr Ben Cooper won the 2019 Australasian College of Physical Scientists and Engineers in Medicine (ACPSEM) Better Healthcare Technology Foundation PhD award for his PhD thesis. Ben's award in 2019 follows Brendan Whelan's award in 2018 and Sean Pollock's in 2017. Ben did his PhD part-time, whilst working full time – he is now Chief Physicist at Canberra Hospital. I am also very proud of Fiona Hegi-Johnson who also graduated in 2019. Fiona Hegi-Johnson whose PhD thesis "Let there be light: Harnessing the Power of New Imaging Technologies to Improve Outcomes for Lung Cancer Radiotherapy Patients", has subsequently obtained a Peter MacCallum Cancer Centre Clinician Researcher Fellowship, a wonderful recognition of Fiona's achievements and will enable her to carry out further research to improve cancer imaging, biology understanding and targeted treatments.

Our PhD students are carefully selected on their outstanding capabilities and it is rewarding Nicholas Hindley, a PhD student won a very highly competed and prestigious Fulbright Foreign Student Program and will spend part of next year at Massachusetts General Hospital/Harvard Medical School, in addition to visiting other sites where machine learning and image reconstruction are strong themes. Nicholas was successful in receiving a $2K Cancer Research Network Postgraduate Conference Travel Grant. Nicholas also received the Most Outstanding Presentation Award at the MedPhys19 annual NSW/ACT medical physics conference, along with Natasha Morton who received the Postgraduate Award. It was great that Emily Hewson was selected for a Sydney Vital Scholar Award, a $10k award.

It is always gratifying when our staff are recognised and rewarded for their outstanding work and several early career researchers have established their leadership in their fields. Paul Liu was awarded a 3-year Early Career Fellowship for "Upright radiotherapy for improved lung cancer treatment outcomes" David Waddington was also awarded a 3-year early career fellowship "Personalising cancer radiation therapy via dynamic MRI-based adaptation to changing tumour anatomy and biology". Paul and David were two of only four Cancer Institute NSW Early Career Fellowships awarded in 2019.

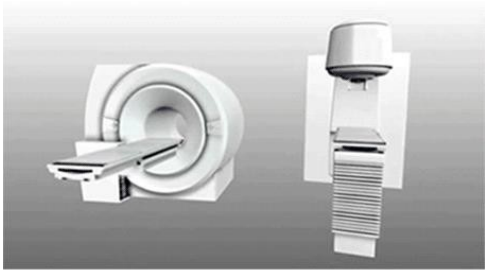
Our work at the Institute has be internationally recognised at the American Association of Physicists in Medicine (AAPM) with three invited talks (Paul Liu and myself), four oral presentations – all from PhD students Emily Hewson (x2), Nicholas Hindley and Natasha Morton, seven snap orals Andy Shieh, Marco Mueller, Paul Liu, Praise Lim, Owen Dillon, Tess Reynolds and Trang Nguyen. In addition, we had three e-posters, Samuel Blake, Kehuan Shi and Elisabeth Steiner.

ACRF IMAGE X INSTITUTE

CURRENT AND ONGOING PROJECTS.

PROJECTS GEARED TOWARDS CREATING NOVEL CANCER RADIOTHERAPY SYSTEMS:

- **The Australian MRI-LINAC Program**
  This project aims to improve the accuracy of radiation delivery in cancer treatment by integrating radiotherapy with real-time MR imaging of tumours.

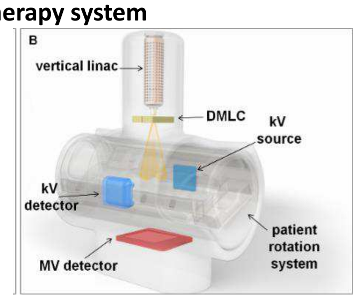


The basic problem we are trying to solve with this project is one of the most fundamental problems in radiation oncology; anatomy changes throughout the course of treatment due to a wide variety of physiological processes. Although there a wide variety of tools to compensate for this motion, most of them cannot be utilised when they're most needed: when the treatment beam is on. In addition, all existing approaches have several limitations. X-ray based techniques deposit unwanted imaging dose in the patient, very few techniques can directly visualise the tumour meaning some assumption of correlation between surrogate motion and tumour motion must be made, and finally many techniques require the use of surgically implanted markers. In addition, no current techniques provide adequate description of the nearby organs at risk.

Our solution to these problems is to utilise the most flexible medical imaging modality in the world: MRI. MRI enables direct tumour visualisation with exquisite soft tissue contrast, requires no implanted markers, and imparts no imaging dose. MRI also enables visualisation of the surrounding anatomy, which enables plan adaption not just based on the tumour position but also on the position of surrounding organs. Finally, MRI can be used to perform functional imaging such as diffusion weighted MRI or Dynamic Contrast Enhanced MRI. These techniques can be used to predict treatment outcomes and adapt the treatment accordingly.

The MRI-Linac program is funded by the NHMRC through to 2022, and a prototype system has been constructed at Liverpool hospital. In other MRI-Linac designs the magnetic field is orientated perpendicular to the treatment beam, which causes unwanted dose perturbations and hot spots. Our in-line design, in which the magnetic field is in the same direction as the treatment beam, minimises or even exploits these effects. Our design is the only high field in-line system in the world. We have a large and expanding intellectual property portfolio and are currently moving towards our first patient treatment. We are actively seeking partners to aid in commercialisation of our product.

- **Nano-X: A new class of cancer radiotherapy system**



This project aims to develop a low-cost radiotherapy system based on a stationary radiation beam and patient rotation. A stationary radiation beam eliminates the need to rotate heavy expensive equipment and could result in a treatment system that is more robust and more reliable. The rotation of the patient rather than the rotation of the equipment may provide the next generation of radiotherapy systems.

PROJECTS GEARED TOWARDS CREATING BETTER CANCER IMAGING TECHNOLOGY:

- **Patient Connected Imaging (Clearer patient imaging with less dose)**
  Respiratory Adaptive Computed Tomography (REACT)--> formerly RMG4DCT

Current 4DCT does not account for changes to a patient's breathing during imaging. This leads to errors in the resulting image, for example, the tumour can look a different shape, larger or smaller than it actually is. These errors can propagate throughout the radiotherapy treatment process.
REACT aims to reduce both the number and size of these imaging errors, by accounting for changes to a patient's breathing and gating the CT beam automatically during the imaging process. This project will later be extended to include dual respiratory and cardiac motion. Both projects use patient signals to adapt the imaging machine to the patient. The project will use the Respiratory Gating Platform for future experiments.

- **Patient Connected Imaging (CBCT) retrospective**
  Improved 4D CBCT Image Acquisition RMG-4DCBCT

To overcome the problem of first generation 4D CBCT, our goal is to develop and investigate a second generation respiratory modulated (RM) 4D CBCT system. The innovation is the respiratory signal actively controls image acquisition resulting in improved image quality and / or reduced imaging dose from in-room CBCT image guidance, at the time of treatment. This project will eventually be extended to include dual respiratory and cardiac motion.

- **Patient Connected Imaging (CBCT) real-time ACROBEAT**
  (Adaptive CaRdiac cOne BEAm computed Tomography)
  By monitoring tumour motion and adapting the hardware to patient.
  During Radiotherapy: Adjust gantry rotation speed and kV frequency.

Currently, cardiac motion is not accounted for during pre-treatment imaging for central lung tumours. This can result in positioning errors due to cardiac motion and induce blurring in the acquired images. Here, we aim to produce 3D thoracic CBCT images that reduce the effect of both cardiac and respiratory motion on image quality under free-breathing conditions on a Linac for applications in radiotherapy and a robotic C-arm for applications in interventional radiology

- **CT Ventilation Imaging**
  (a novel software- based solution that can map out the healthy areas of the lung simultaneously while routine pre-treatment scans are carried out.)

CT Ventilation is an open source software program which uses CT imaging data to show where healthy lung tissue is, so that healthy tissue can be spared during radiotherapy treatment planning. If we can detect where the healthy tissue is, we can optimize the treatment plan to ensure the radiation beam is passing through in the best possible position and angle, sparing as much healthy tissue as possible. This is achieved by acquiring CT-images of the lung at exhale and inhale states, using breath-hold CT, or 4D-CT (CT imaging which is in 3D and captures the image over time, to show movement). Then applying deformable image registration (DIR) software to determine a spatial mapping ("deformation map") between the exhale and inhale CT images. Through quantitative analysis based on the information from the DIR software a ventilation metric image is obtained.

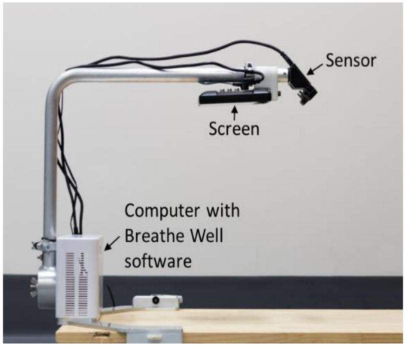
The resulting ventilation image can be superimposed directly onto the anatomic image, providing an added dimension of functional information which is easy to understand and can be of direct benefit in planning a radiotherapy treatment.

PROJECTS GEARED TOWARDS CREATING BETTER CANCER TARGETING TECHNOLOGY (TUMOUR ACQUISITION, TUMOUR TRACKING AND BEAM ADAPTATION)

- **Improving Cancer Imaging and Targeted Radiotherapy with Audiovisual Biofeedback AVIATOR** (lung)
  (Breath guidance to optimise radiation delivery to tumour and reduce healthy tissue damage)

  There is a clear link between irregular breathing and errors in medical imaging and radiation treatment for lung radiotherapy. We assume that irregular respiration is a surrogate for clinical outcomes in lung cancer radiotherapy and that AV biofeedback helps to improve breathing regularity. In a prospective multi-institutional randomised clinical trial, we will test the impact of AV biofeedback on clinical outcomes.

- **Breathe Well: Improving Cancer Imaging and Targeted Radiotherapy with Audiovisual Biofeedback BRAVEHeart** (breast)**– empowering breast cancer radiotherapy patients to save their hearts**

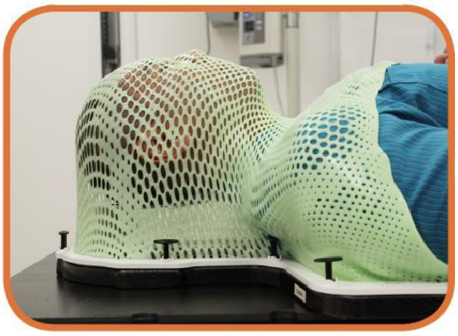


  Left-sided breast cancer radiotherapy leads to an increased risk for cardiac diseases compared to right sided breast cancer. The risk from radiotherapy on the left side can be reduced by the deep inspiration breath hold technique that moves the heart away from the incident radiation. The Breathe Well device monitors the central chest of patients and provides them with visual guidance to achieve reproducible breath holds. In a randomised clinical trial, we will test Breathe Well compared to the clinically used Real-Time Position Management (RPM) system for its ability to guide the patients into reproducible and stable breath holds. The RPM system involves placing a marking block on the upper abdomen of the patient. This block then acts as a surrogate for tracking chest motion. We have developed a new audiovisual biofeedback device called Breathe Well to help the patients normalise their breathing and help regulate their breath holds. Breathe Well tracks chest motion directly and does not involve the use of any surrogate markers.

- **Breathe Well: Improving Cancer Imaging and Targeted Radiotherapy with Audiovisual Biofeedback LAVA** (liver)

  Inadequate respiratory-related tumour motion management, especially for irregular respiratory- related tumour motion negatively affects the clinical outcome for liver stereotactic body radiotherapy. We assume that irregular respiration is a surrogate for clinical outcomes in liver cancer radiotherapy and that AV biofeedback helps to improve breathing regularity. We evaluate the improvement in reproducibility of respiratory-related tumour motion (via fiducial maker surrogacy) for liver cancer patients with the AV biofeedback respiratory guidance system.

- **Remove the Mask – (Head and Neck Cancer (HNC))**
  Immobilisation Mask

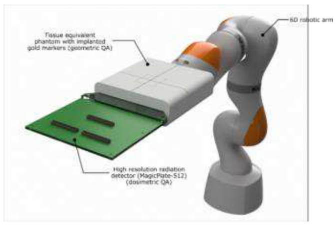


Head and Neck cancer radiotherapy requires immobilisation masks. For up to 50% of HNC patients these masks cause anxiety, distress and potentially reduced treatment adherence. We will develop surface guidance technology with X-ray imaging to enable mask-free HNC radiotherapy. In the first stage mask-free surface guided radiotherapy will be tested in mock treatments, in the second stage with integrated internal imaging in HNC radiotherapy and in the third stage integrated with internal imaging and real-time treatment adaptation in HNC radiotherapy. This project will build on the developments from the Breathe Well project (AV biofeedback) and involve KIM for internal motion monitoring and MLC tracking for treatment adaptation. The NHMRC project proposal submitted to Cancer Australia in 2018 will be resubmitted for reconsideration in 2019.

- **Kilovoltage Intrafraction Monitoring (KIM) (Detecting tumour positions in real-time)**

Kilovoltage intrafraction monitoring is a novel intrafraction real-time tumour tracking modality. It involves a single gantry-mounted kV X-ray imager (widely available on most Linacs) acquiring 2D projections of implanted fiducial markers. 3D positions are then reconstructed by maximum likelihood estimation of a 3D probability density function.

- **6DoF Robot**
  A Quality Assurance (QA) Device



The 6DoF Robot was designed to be used with KIM to ensure that the geometric tracking was accurate so providing geometric quality assurance and validation of the KIM tracking technology. KIM delivers the radiation by tracking 3 fiducial gold markers.
The 6 degrees of freedom robot device (6DoF Robot) is a kit, which consists of, Image X software to control the motion of the off-the-shelve robot arm, mechanical fixings to allow the robot to be mounted and fixed onto the treatment couch and a phantom, which is a sensor device held in the robot hand. The robot holds a phantom, which is representative of a patient. The phantom consists of an acrylic plate, which represents human tissue, being of similar density when irradiated and so provides a similar image under X-ray radiation. Ideally the device would use a material, which would have identical properties to human tissue. There are 3 gold fiducial markers, embedded in the acrylic phantom, that provide a means of geometrical tracking, as they would do with KIM technology. The robot arm utilises mathematical algorithms that mimic the tumour motion, which arises from multiple sources. Thus, the robot arm closely simulates the tumour motion through small horizontal, vertical and rotational movements of the acrylic phantom. Thus, if the KIM technology is correctly tracking the motion of the markers, this will be evident through the comparison of the known simulated robot/ phantom and hence marker positions with the KIM tracking data. Hence

the kit provides the geometric quality assurance (QA).
The 3 gold markers can be replaced by EM markers, i.e. rf tags, as used and tracked by the Varian Calypso system, an approved system. The robot kit is versatile and can also be used with other radiation therapy systems such as Cyber Knife, by replacing the types of markers. It is planned that the QA device will later also include a means of measuring dose delivered to the site.

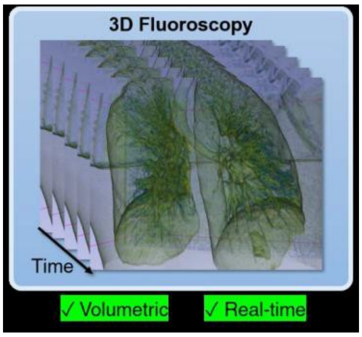
❖ **Beam Adaptation (Multi Leaf Collimator - MLC)**
(MLC: Targeting / reshaping the beam to match the respective tumour position through the collimator leaf configurations)

This project uses Multi Leaf Collimator reconfiguration in conjunction with passive transponder devices (referred to as chips, beacons or rf tags) embedded in the patients to triangulate on the tumour position. The MLC changes the shape of the beam to match the tumour as the radiation deliver system rotates around the patient. There are three (8mm) beacons per patient, each beacon operating at a different frequency. The beacons have a dual purpose, firstly the three beacons act like a GPS system- so can triangulate on the tumour and so is used to track the tumour motion. Secondly the arrangement of the beacons inside the patient help to identify the individual. When the beacons receive an electromagnetic pulse, they respond with a return signal at the designed frequency.

❖ **Beam Adaptation (MLC)**
Multi-target tracking

When treating patients with locally advanced cancer, we are often required to treat multiple targets with large independent motion. The goal of this project is to be able to adapt treatment to the motion of these targets to maximise radiation coverage to the cancer target and minimise dose to healthy tissue. This is done by dividing the MLC aperture into segments assigned to each target and translating the MLC aperture to correspond to each targets' motion, constantly adapting the beam in real-time throughout treatment. KIM will be used in conjunction with MLC tracking to locate the target positions.

❖ **Markerless Tumour Tracking (Lung – higher contrast images)**
Real-time volumetric imaging for high precision radiotherapy: 3D fluoroscopy



This project aims to accurately predict 3D thoracic motion in real-time. The purpose of this work is to enable precise beam adaptation during image-guided radiotherapy. This will be achieved by, firstly, developing robust diaphragm and heart tracking algorithms; and secondly, utilising dual respiratory-cardiac tracking to construct patient-specific motion models. As the project aims to achieve direct diaphragm tracking and relate it to tumour motion, it is useful in improving 4DCT and respiratory gating. Insofar as the project seeks to achieve dual respiratory-cardiac tracking it has important implications for patient-connected imaging. Furthermore, as the project is geared toward achieving precise beam adaptation there are important links with MLC tracking and since real-time diaphragm and heart tracking is achieved using intrafraction imaging, there are also significant ties with the KIM project.

❖ **Markerless Tumour Tracking Lung – higher contrast images**

Lung tumour motion can be large and unpredictable, which needs to be monitored and adapted to. The goal of this project is to enable direct tumour motion monitoring during lung cancer radiotherapy on a standard Linac without the need for marker implantation. The innovation is the combination of pre-treatment patient modelling using the 4DCT and image processing of real-time kV images in which tumours with inferior/low visibility can be tracked.

- **Markerless Tumour Tracking Markerless liver tumour tracking**

  Liver tumour experiences clinically significant motion but is difficult to track due to the lack of soft tissue image contrast. The goal is to overcome this challenge and enable real-time monitoring of liver tumour motion on a standard Linac without the need for marker implantation. Due to the high correlation between diaphragm and liver motion, the diaphragm is tracked on kV images, the position of which is used to infer the location of the liver tumour.