Institution: University of Hull

Unit of Assessment: 08 - Chemistry

Title of case study: Integrated radiotracer synthesis and scanning to improve patient access to state-of-the-art diagnostic PET-CT scans for cancer treatment and other healthcare advances

Period when the underpinning research was undertaken: 2004 – to date

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Prof Steve Archibald	Project leader, Molecular Imaging	2000 – to date
Prof Nicole Pamme	Lab-on-a-chip Chemist	2005 – to date
Prof Carl Redshaw	Inorganic Chemist	2012 – to date
Prof Ross Boyle	Professor in Organic Chemistry	2000 – to date
Dr Benjamin Burke	Fellow in Translational PET	2015 – 2019
Dr Nikos Efthimiou	Fellow in Imaging Sciences	2016 – 2019
Dr Alex Iles	Experimental Officer: Lab on a Chip	2005 – to date

Period when the claimed impact occurred: 2014-2020

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact

Research in radiochemistry and biomolecular processes from the Chemistry Department at Hull has developed advances in molecular imaging science that have substantially improved diagnostic scanning capabilities for patients. Through a unique partnership with a local charity (Daisy Appeal) and Hull University Teaching Hospitals (HUTH) NHS Trust, this consortium has attracted >£15 million investment to build a bespoke centre where research and clinical services are integrated. The research has impacted upon the health of patients by providing much-improved infrastructure for cancer diagnosis (>12,500 patients scanned in the unit, equating to a 3-fold increase in patient numbers). The research and business communities have benefited with specialist training (of >80 research and healthcare professionals, see 4.4) and intellectual property (see 3).

2. Underpinning research

Chemistry research underpinned the partnership between The University of Hull (UoH) and Daisy Appeal that built a £3.5 million radiochemistry research centre (on UoH campus, completed 2014), a £2.5 million clinical scanning centre (HUTH, completed 2014) and a £9.5 million Molecular-Imaging Research facility (HUTH, completed 2021). The Positron Emission Tomography (PET) research group at UoH has conducted radiochemistry research since 2004. It develops microfluidic methods for radiopharmaceutical synthesis, nanoparticles for theranostics and new radiometal chelators.[1] Currently 40 researchers and postgraduate students are involved in this research across the University and NHS. The key research activities underpinning this impact have been: optimising radioactive tracer synthesis (2.1), delivering dose-on-demand imaging drugs using compact cyclotrons (2.2), miniaturised radiodetector technology (2.3) and managing the successful implementation of interdisciplinary projects linking chemistry research to clinical developments that improve NHS practice (2.4).

2.1 Optimised clinical radiotracer isotope production

UoH research pioneered the use of flow synthesis radiochemistry labelling processes with microfluidic chips (bespoke and fabricated in house) or capillary reactors to optimise isotope-processing technologies by the highly efficient removal of metal ion contaminants.[2] These chemical reactions are performed in yields that are comparable to leading clinical standards. They have been achieved with faster turnaround rates and greater potential for scalability to improve availability and supply to patients, to allow improved access to the best standard of diagnostic care.[3] Two patents were granted on this technology that, alongside other patents (see below), underpinned a current Medical Research Council Developmental Pathway Funding Scheme (MRC DPFS) project to translate this method to clinical good manufacturing practice (GMP) standards with an aim of commercialisation through a new spinout company in 2022 on completion of the MRC project.

2.2 Developing dose on demand for next generation PET radiopharmacy

The new radiosynthesis processes developed at the UoH form an integrated production technology that minimises operator input and de-skills production through automation. This has lower infrastructure requirements and reduces production cost by >30%. Synthesis of radiotracers had been demonstrated in microfluidic flow systems previously but the essential analytical chemistry for quality control (QC) testing was largely ignored by other researchers. The Hull team has developed an integrated microfluidic QC platform, compatible with compact cyclotrons, for the rapid, low volume (10-100 µL) QC of radiotracers that tackles one of the biggest regulatory challenges to widespread use of this technology.[4] In the devices and processes developed at UoH, QC was fully integrated to ensure that the regulatory compliance needed in tracer production for patient administration was achieved.[5] Three patents have been granted, with one application pending (see above for the commercialisation plan).

2.3: Miniaturised radiodetector technology

The UoH group worked closely with colleagues in nuclear physics at the University of York to develop miniaturised radio-HPLC detectors for the QC analysis of PET radiotracer molecules, based on a microfluidic device fabricated out of plastic scintillator and a small footprint, low-cost silicon photomultiplier (SiPM) light sensor[5]. The platform enables real-time detection of the radioisotope with low analysis volume to minimise sample waste and clinically-relevant levels of activity (10MBq to 5GBq), while offering a far smaller and more versatile unit compared to conventional detectors.[6] This collaboration established the first positron detector available that can be integrated into miniaturised devices (that are compatible with compact cyclotron technology), for radiochemistry in tracer production. The patent application has been granted (see 3).

2.4: Integrating research and clinical settings

The chemistry research was central to underpin the healthcare advances. Archibald's team synthesised radiotracers, provided radiopharmaceuticals and gave biomolecular process input for projects in clinical translation involving national and international collaborators. Archibald's team *optimised scanning protocols for drug delivery* (collaboration with Hull York Medical School (HYMS), HUTH NHS and Chiesi Farmaceutici, Italy) through radiolabelling chemistry, providing chemical basis for new tracers in *analysed clinical data* (collaboration with HUTH NHS and Jaber Alahmad Center for Molecular Imaging, Kuwait) and *informed protocols* for administering radiopharmaceuticals to patients (HUTH clinical cardiology team). The chemistry capability in the PETRC on UoH campus was used to test and inform the clinical processes and planning. These projects range from optimising the amount of drug given to patients, through improving the understanding of the biochemical processes, to determining the timing of scans to maximise the potential of a successful clinical outcome. Archibald and Burke synthesised radiotracers to carry out preclinical studies with Nuclear Cardiology at Castle Hill Hospital to develop new 99mTc-sestamibi scanning protocols used at the HUTH NHS Trust. The teams used the radiotracers to determine the impact of biochemical washout on mitochondrial function reporting to improve understanding of heart tissue viability in cardiac perfusion scans and improve patient treatment.

3. References to the research

(1) **Burke B.P.**, Grantham W., Burke, M.J., Nichol, G.S., Roberts, D., Renard, I., Hargreaves, R., Cawthorne, C.J., **Archibald, S.J.,** Lusby, P.J. Visualizing Kinetically Robust (Co4L6)-L-III Assemblies in Vivo: SPECT Imaging of the Encapsulated Tc-99m TcO4- Anion. *J Am Chem Soc.* 2018;140:16877-16881.

(2) Positron detection in silica monoliths for miniaturised quality control of PET radiotracers M. D. Tarn, D. Maneuski, R. Alexander, N. J. Brown, V. O'Shea, S. L. Pimlott, **N. Pamme** and **S. J. Archibald** *Chemical Communications,* 2016, 52, 7221 – 7224

(3) Aliyu, S.A., Avery, G., Cawthorne, C., **Archibald, S.J.,** Kadir, T., Willaime, J. M. Y., Morice, A. H., Hart, S.P., Crooks, M.G. Textural analysis demonstrates heterogeneous F-18 - fluorodeoxyglucose uptake in radiologically normal lung in patients with idiopathic pulmonary fibrosis. *Eur Respir J.* 2018;52.

(4) Granted patent. **S. J. Archibald,** P. He, M. D. Tarn, M. M. N. Esfahani, N. J. Brown, **N. Pamme**, S. J. Haswell, R. Alexander "System for radiopharmaceutical production" EP3209628B, granted and published 4th December 2019

(5) **Burke, B. P.;** Miranda, C. S.; Lee, R. E.; Renard, I.; Nigam, S.; Clemente, G. S.; D'Huys, T.; Ruest, T.; Domarkas, J.; Thompson, J. A.; Hubin, T. J.; Schols, D.; Cawthorne, C. J.; **Archibald, S. J.,** 64Cu PET imaging of the CXCR4 chemokine receptor using a cross-bridged cyclam bis-tetraazamacrocyclic antagonist. *Journal of Nuclear Medicine* 2020, *61* (1), 123-128.

(6) Tarn, M.D., Kizilyer, N.Y., Esfahani, M.M.N., Joshi, P., Brown, N.J., **Pamme, N.,** Jenkins, D.G., **Archibald, S.J.** Plastic Scintillator-Based Microfluidic Devices for Miniaturized Detection of Positron Emission Tomography Radiopharmaceuticals. *Chemistry-a European Journal*. 2018;24:13749-13753.

Research grants (total of £3.5 million to the University of Hull researchers since 2012)

I. Daisy Appeal Charity £580,000 (2012-2017) 'Integrated microfluidic devices for per patient dose synthesis and validation.'
II. EU FP7 'iTERM: imaging for tissue engineering ITN' total value €3,575,729 (6 universities and 4 companies) Project Co-I. Lead site for PET imaging.
III. Higher Education Innovation Fund £269,000 (2014-2016) 'Positron emission tomography in drug development'
IV. Cardiac Trust £278,000 (2018-2020) 'Radiochemistry facilities for cardiac tracer production'
V. Medical Research Council £520,000 (2019-2022) 'New technology to improve capability for clinical radiopharmaceutical production'

Research prizes

a) Steve Archibald, SNMMI scientific highlight Baltimore USA (microfluidics) June 2015
b) Ben Burke, Preclinical Nuclear Imaging Meeting, Overall best presentation Award Nov 2018
c) Nikos Efthimiou, European Society for Molecular Imaging, Poster presentation prize (Nuclear Imaging | Technology) March 2019 http://www.e-smi.eu/index.php?id=emim-2019-looking-back
d) Isaline Renard European Society for Molecular Imaging Poster presentation prize (PET/SPECT, Radionuclide, X-ray, CT | New Probes) March 2019 http://www.e-smi.eu/index.php?id=emim-2019-looking-back

Patents (1-6 granted and 7 under examination)

1. RADIOACTIVITY DETECTION ***WO2017153722A1*** 14/09/2017
2. MONOLITHIC BODY ***WO2016063070A1*** 28/04/2016
3. METHOD AND APPARATUS FOR THE ANALYSIS OF COMPOUNDS ***EP3209418A2*** 30/08/2017
4. SYSTEM FOR RADIOPHARMACEUTICAL PRODUCTION ***EP3209628A1*** 30/08/2017
5. RADIOISOTOPE RECOVERY ***EP3210211A1*** 30/08/2017
6. Compositions comprising macrocycle derivatives incorporating bridged macrocycles and methods of producing and using same ***US10927108B2*** 23/02/21
7. INERT NANOCAPSULES ***WO2020016561A1*** patent application under examination

4. Details of the impact

Our impact derives from research innovations in Chemistry, and from partnership with a local charity (Daisy Appeal) and HUTH NHS. It improves patient care facilities and increases clinical trial opportunities at Castle Hill Hospital (that serves Hull and the East Riding of Yorkshire). Our research into radiopharmaceutical synthesis, molecular imaging processes and next generation NHS radiopharmacy facility design has resulted in multifaceted impacts. UoH's innovative medical imaging technologies have impacted on patient health (4.1), NHS services (4.2) and research environment (4.3), facilitating international research interactions and attracting skilled workers to the region. These impacts underpinned the vision and strategy for the combined facility that was built on a needs analysis

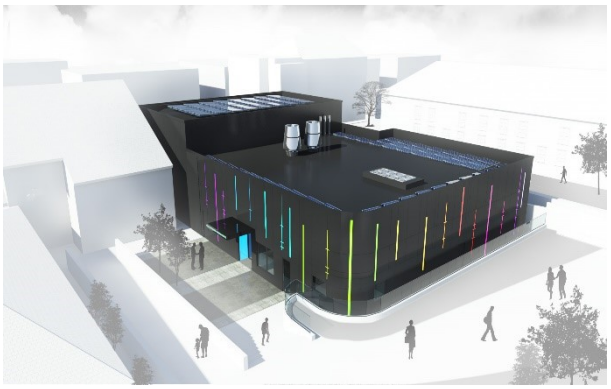

Fig. 1: New MIRC building due for completion in July 2021: an impact of the research success within the REF

for the region's medical imaging (4.4). A partnership with the NHS and Daisy Appeal charity was established to deliver >£15 million of new facilities that would improve patient care and allow commercial radiosynthesis opportunities to be developed from new technologies and UoH research (see Fig. 1).

4.1. Impact on patient health

Research by the UoH team underpinned the investment in the next generation of tracers and technologies, and the building of a new clinical facility in Hull. The impact on patient health is facilitated by improved, advanced services for patient care in HUTH NHS. This is delivered through equipment and facilities purchased by Daisy Medical Research Ltd: a non-profit company with turnover of >£0.5 million that was set up by the consortium. All funds are reinvested in the development of, and research opportunities for, medical imaging, Archibald has been a Director since the company was set up in 2014, contributing scientific expertise and the research strategy.

Fig. 2: New clinical scanner allowing 3-fold increase in patient numbers scanned and clinical research scanning.

The Jack Brignall PET-CT centre, built by Daisy Medical Research, offers a huge improvement in patient care. It replaced a limited capacity mobile scanner that was only based at the hospital for two days a week. This permanent fixture increased the number of scans three-fold, and its state-of-the-art equipment has improved the healthcare and experience of >12,500 patients who have been scanned within the REF period (see Fig. 2). The availability of new types of scans tested in the University PET Research Centre has also improved the capabilities of Nuclear Cardiology at Castle Hill Hospital. For example, their research has resulted in changes to 99mTc-sestamibi scanning protocols at the hospital to improve cardiac ischemia characterisation in >200 seriously ill patients per annum. Other patient groups have similarly benefited due the introduction of innovative scanning programmes/protocols. These include patients with amyloid scans; sarcoidosis and drug delivery to the lung with more than 50 patients benefitting per annum.

4.2. Impact on the NHS

The research relationship with HUTH NHS has led to the development of integrated research facilities at the hospital site and to major change in the practice and delivery of NHS radiopharmacy in Hull. These changes have improved the facilities for delivery of radiopharmacy and reduced the risk of patient service failure to ensure that all patients can receive their diagnosis as rapidly as possible. Three new buildings have been constructed for preclinical research (including radiochemistry), clinical scanning and clinical radiotracer production (at a cost of >£15 million). A collaborative team has been developed for molecular imaging research across multiple NHS departments and University disciplines. This ensures that service delivery for HUTH NHS is of the highest standard. The ongoing clinical trials have already upskilled the local workforce and enhanced their ability to handle an increased range of patient conditions. NHS staff have been integrated into the University teams with 25 new jobs created by the development so far.

4.3. Impact on the cross-sector research environment

As one of five company directors for the not-for-profit, Daisy Medical Research Ltd, Archibald has worked with clinical colleagues to ensure the Siemens Biograph PET-CT flow (owned by the company) facilitates research and routine clinical studies. All funds are reinvested into the development of new facilities in the region and the expansion of research capability at UoH and HUTH NHS. Seven patent applications (six granted) filed in the REF period and led by the UoH focussed on radiosynthesis and analytical methods. They attracted MRC DPFS funding to bridge from invention to spinout company formation on completion of the MRC project in 2022.

4.4 Driving translational interactions and attracting skilled workers to Hull

Our facility has collaboration agreements for research with other institutions. We have supplied radiotracers synthesised in Hull for preclinical imaging to the University of Leeds and the

Medicines Discovery Catapult, and we have delivered Cancer Research UK funded collaborative research studies (with Imperial College) to inform a planned clinical trial. Agreements are in progress to supply tracers to the Universities of Liverpool and Sheffield, making our centre a focus for translational medical imaging research in the North of England. The UoH has hosted placement students, internships, PhD studentships and visiting scientists from countries including Uganda, Saudi Arabia, Iraq, France, Turkey and Thailand,. We have provided expert training in radiochemistry technology training for researchers and healthcare professionals in the specialised area of positron emission tomography radiochemistry which has been taken back to the home countries. This has facilitated international capabilities for radiochemistry/ radiotracer production. In the REF period there have been 5 externally funded MSc and PhD studentships to explicitly gain radiochemistry skills for international researchers and >20 secondments and PhD student exchanges with staff trained in radiochemistry and radiopharmacy. These researchers have moved back to skilled radiochemistry positions in their home countries (in many cases the specialised training was part of the funded recruitment process and a strategic expansion of expertise in the home country with UoH identified as a leading global centre for radiochemistry training).

4.5 Researchers' design input into shared research-healthcare facilities

The chemistry research team worked hand-in-hand with the NHS radiopharmacy and nuclear medicine staff to design an integrated facility for the production of clinical radiopharmaceuticals (see Fig. 3). Archibald and Burke were essential members of the planning group, working with medical staff, the project managers and architects to design an integrated healthcare facility where research and healthcare would develop side by side. Archibald and Burke designed layouts, specified equipment and operational strategy (staffing requirements), and decisions on equipment procurement were made by a group led by Archibald. This integration benefits the University as translational studies into healthcare delivery are now possible; it also improved facilities at the Castle Hill Hospital site for radiopharmaceutical production dramatically. This process also upskilled NHS staff with the latest technology for future patient benefit (eight NHS staff are affiliated to the UoH and five received additional hands-on training on campus in the new radiochemistry technology). This process therefore benefits our collective research capacity as well as healthcare delivery.

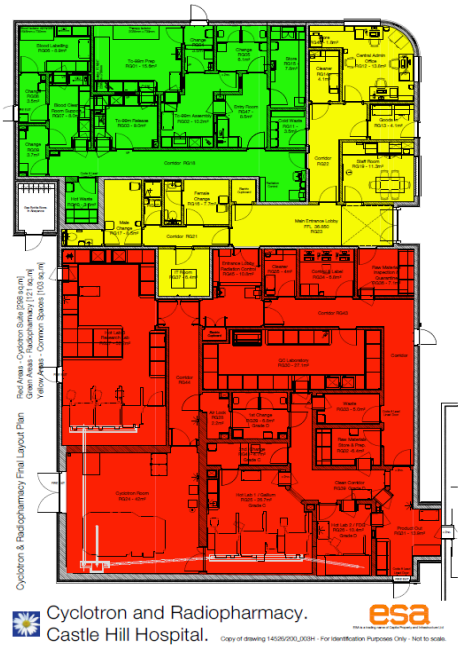

Fig. 3: New building designed with University Chemistry Department staff to integrate NHS production with research

5. Sources to corroborate the impact

1. Testimonial from Chairman of the Daisy Appeal
2. Testimonial from NHS management (patients scanned and benefits).
3. Testimonial from NHS Nuclear Medicine Specialist
4. Testimonial from trained scientist in Thailand
5. Testimonial from NHS Radiopharmacy Production manager (building design)
6. Intellectual property (see section 3)
7. Yorkshire Post article 2010 https://www.yorkshirepost.co.uk/news/fund-raising-charity-launching-fresh-medical-research-appeal-1949439
8. Invest Hull News 2020 https://investhull.co.uk/latest-news/daisy-appeal-sets-target-for-launch-of-space-age-weapon-in-fight-against-killer-diseases
9. Hull Daily Mail https://www.hulldailymail.co.uk/news/hull-east-yorkshire-news/east-yorkshire-life-saving-medical-4209071
10. UK PET Network website https://www.petnetwork.org.uk/who-we-are