Institution: King's College London

Unit of Assessment: 12 Engineering

Title of case study: Galliprost - Democratisation of PET imaging technology for prostate cancer patients through smart radiochemistry

Period when the underpinning research was undertaken: 2007-2020

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:
Philip Blower	Professor of Imaging Chemistry	From 01/01/2006
Robert Hider	Professor of Pharmacy (Emeritus Staff)	From 01/10/1987
Greg Mullen	Senior Lecturer, Imaging Biology/Radiopharmaceutics	From 02/01/2007
Vincenzo Abbate	Senior Lecturer, Analytical, Environmental & Forensic Sciences	From 20/10/2008
James Ballinger	Honorary Lecturer, Imaging Chemistry & Biology	From 01/04/2007
Michelle Ma	Senior Lecturer, Imaging Chemistry & Biology	From 01/03/2013
Gary Cook	Professor of PET Imaging	From 28/03/2011

Period when the claimed impact occurred: 2017-2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact (indicative maximum 100 words)

Prostate cancer kills over 10,000 men annually in the United Kingdom alone. Positron Emission Tomography (PET) imaging is central to managing prostate cancer. Synthesis of radiotracers for PET imaging is usually complex and time-consuming, limiting availability for patients.

At the School of Biomedical Engineering and Imaging Sciences of King's College London (King's) we engineered tris-hydroxypyridinone (THP), a patented chelator for gallium-68 which helped synthesise a PET tracer using a simple and quick single-vial kit, named Galliprost. This kit has improved treatment decisions in over 1,500 patients globally till date, allowing more appropriate and effective treatment and provided cost savings of GBP600- GBP1,500 per patient.

King's licensed the intellectual property relating to THP to Theragnostics Ltd, which commercialised the Galliprost kit. In October 2019, GE Healthcare and Theragnostics Limited announced a global commercial partnership for worldwide rollout of Galliprost based on a US market estimate of USD500,000,000 (10-2019).

2. Underpinning research (indicative maximum 500 words)

Prostate cancer kills over 10,000 men annually in the UK. Positron Emission Tomography (PET) imaging, central to managing prostate cancer, relies on radiotracers such as gallium-68 to identify cancer cells. However, traditional methods of synthesising gallium-68 radiotracers are complex, requiring time-consuming, costly preparation. This significantly limits the availability of PET imaging to patients.

The key to this problem lies in the engineering of the chelating agents, which bind the gallium-68 to a biomolecule vector. Previous chelators used in this area were not explicitly engineered for this purpose. These were macrocyclic to achieve long-term in vivo stability, which imposed barriers to synthesis that required complex synthesis steps that hospitals were ill-equipped to carry

out. To overcome this, we reasoned that (i) because of the short half-life of ^{68}Ga, long-term in vivo stability (and hence macrocyclic structure) was unnecessary and (ii) the chemical similarities between iron and gallium provided a way forward by adapting known chelating agents for iron.

A suitable template for their design emerged from an earlier body of work by Hider and co-workers (also at King's) on engineering hydroxypyridinone ligands which had been developed for treatment of diseases involving iron overload. A collaboration between Hider and Blower was begun to evaluate a tris-hydroxypyridinone (THP) ligand, and found it would complex gallium very rapidly, at room temperature, in quantitative yield, without extremes of pH, highly selectively so as not to be affected by contaminating trace metals, and free of isomerism. Thus, THP enabled fast and efficient gallium-68 radiolabelling using a simple, single-vial kit achieving a preparation time of just 5 minutes, instead of the several hours required for previous methods.

This formulation allows the tracer to be produced on site, in a manner suitable for frontline healthcare staff, without complex procedures or costly infrastructure.

We showed that it could be conjugated to targeting molecules without inducing new isomerism. We showed between 2007 and 2010 that THP uniquely fulfilled the criteria for a suitable bifunctional chelator to address the unmet need [R1, R2].

We then developed chemistry to incorporate the THP into targeting molecules including proteins [R3], small peptides [R4] and other molecules (unpublished) and demonstrated that they could be readily radiolabelled in a couple of minutes with minimal manipulation by operatives and no need for automated synthesis machinery.

All of these were successfully shown in animal models to be suitable for PET imaging. We developed a specific conjugate that would target prostate cancer by binding with high affinity and selectivity to the PSMA expressed by prostate cancer cells and validated it biologically in animals by PET imaging of human prostate cancers in mice [R5].

We then engineered a sterile kit (Galliprost) for producing the tracer quickly under clinical, good manufacturing practice (GMP) conditions, and validated it. The Galliprost tracer has been clinically evaluated at King's and its partner NHS Trust in over 1,000 patients, showing that it meets both its key aims of impacting patient management (about one third of patients had treatment decision changed as a result of the scan) and being very easily synthesised in the hospital setting [R6].

3. References to the research (indicative maximum of six references)

R1. Berry DJ, Ma Y, Ballinger JR, Tavaré R, Koers A, Sunassee K, Zhou T, Nawaz S, Mullen GED, Hider RC, Blower PJ (2011). Efficient bifunctional gallium-68 chelators for positron emission tomography: tripodal tris(hydroxypyridone) ligands. *Chem Commun*;47:7068 - 7070. PMC3929899. DOI: 10.1039/c1cc12123e

R2. Tsionou MI, Knapp CE, Foley CA, Munteanu CR, Cakebread A, Imberti C, Eykyn TR, Young JD, Paterson BM, Blower PJ, Ma MT (2017). Comparison of macrocyclic and acyclic chelators for gallium-68 radiolabelling. *RSC Adv,*7:49586–49599. PMC5708347. DOI: 10.1039/C7RA09076E

R3. Nawaz S, Mullen GED, Sunassee K, Bordoloi J, Blower PJ, Ballinger JR (2017). Simple, mild, one-step labelling of proteins with gallium-68 using a tris(hydroxypyridinone) bifunctional chelator: a ^{68}Ga-THP-scFv targeting the prostate specific membrane antigen. *Eur J Nucl Med Mol Imaging Res,* 7:86. PMC5655379 DOI: 10.1186/s13550-017-0336-6

R4. Ma MT, Cullinane C, Waldeck K, Roselt P, Hicks RJ, Blower PJ (2015). Rapid kit-based ^{68}Ga labelling and PET imaging with THP-Tyr^3-octreotate: a preliminary comparison with DOTA-Tyr^3-octreotate. *Eur J Nucl Med Mol Imaging Res,* 5:52. PMC4600075. DOI: 10.1186/s13550-015-0131-1

R5. Young JD, Abbate V, Imberti C, Meszaros LK, Ma MT, Terry SYA, Hider RC, Mullen GE, Blower PJ (2017). ^{68}Ga-THP-PSMA: a PET imaging agent for prostate cancer offering rapid, room temperature, one-step kit-based radiolabeling. *J Nucl Med,* 58:1270-1277. DOI: 10.2967/jnumed.117.191882

R6. Kulkarni M, Hughes S, Mallia A, Gibson V, Young J, Aggarwal A, Morris S, Challacombe B, Popert R, Brown C, Cathcart P, Dasgupta P, Warby VS, Cook GJR (2020). The Management Impact of ^{68}Gallium-Tris(Hydroxypyridinone) Prostate Specific Membrane Antigen (^{68}Ga- THP-PSMA) PET-CT Imaging for High-Risk and Biochemically Recurrent Prostate Cancer. Eur. J. Nucl. Med. Mol. Imaging, 47:674-686. DOI: 10.1007/s00259-019-04643-7

4. Details of the impact (indicative maximum 750 words)

Galliprost addresses the unmet need for a generic radiolabelling technology that is quick, simple, and cost-effective to use, with minimal infrastructure or expertise. By providing an affordable and easily deployable technology it is democratising the access, availability, and usability of a vital radiolabelling technology. It has now been taken up by GE Healthcare which has primed it for a global rollout and impact.

Improved accessibility of prostate cancer screening:

The impact of this simplicity of production is illustrated by the screening service established in partnership with Guy's and St Thomas' Hospitals, beginning in 2017. This service was set up much more quickly (from typically 6 months to a few days in initial validation; and from typically 6 hours to a few minutes in daily production) than could be done previously [S1]. This has now benefited over 1,000 patients at Guy's and St Thomas' Hospitals alone, allowing the most appropriate primary treatment in patients with a new diagnosis and earlier and potentially more curative treatment in those with recurrence [S2], and provided significant cost savings of GBP600 to GBP1,500 per patient [S1]. In words of the Head of Radiopharmacy, Guy's Hospital, *"The development of Galliprost (THP-PSMA) kit formulation has had a massive impact on the clinical service at Guy's & St Thomas' NHS Foundation Trust"* [S1].

Galliprost has been used routinely in >10 hospitals world-wide (including St Thomas' Hospital London; Royal Marsden Hospital, London; University College Hospital, London; Addenbrookes Hospital, Cambridge; Medizinische Hochschule Hannover, Germany; Shanghai Cancer Centre, Shanghai, China; Peter MacCallum Cancer Centre, Melbourne, Australia; Moorabbin Hospital, Melbourne, Australia; and private hospitals in the London area) providing improved accessibility of prostate cancer screening, leading to reduced service implementation lead times (from 6 months to 3 days) and improved treatment decisions.

Better treatment plan for patients of prostate cancer:

By December 2020, an estimated 1,500 patients globally have benefited from the use of Galliprost, [S1, S2, S3, S4]. 34% of patients have their management or treatment changed from the adoption of this scan [S3]. Theragnostics has also reported data from a phase two clinical study which met its primary and secondary endpoints, demonstrating that one third of newly diagnosed prostate cancer patients - and over 50% of patients with biochemically recurrent disease - had their treatment plans modified as a result of a Galliprost scan. The change in patient management increased to 75% in a post-radical radiotherapy setting [S7]. In words of Dr Simon Hughes, Consultant Clinical Oncologist at Guy's and St. Thomas' NHS foundation Trusts, *"As uro-oncologists we continue to see the benefit of the greater reliability and accuracy of ^{68}Ga-PSMA PET/CT in our patients, allowing the most appropriate primary treatment in patients with a new diagnosis and earlier and potentially more curative treatment in those with recurrence"* [S2].

Galliprost has also created direct economic benefit:

We licensed our intellectual property to Theragnostics Ltd (formally Imaging Equipment Research Ltd.), who commercialised the kit formulation. Prof Blower is a Scientific Advisory Board Member of Theragnostics. Theragnostics has accrued GBP13,000,000 in investment capital [S4], ~90% directed towards Galliprost development.

Phase 2 trials were completed in 2020 with Phase 3 prostate cancer trials scheduled to start late 2020 with FDA/MHRA approval targeted for 2021. Theragnostics has recently launched a USD45,000,000 Series A financing round to take Galliprost to market [S4].

Since 2016, Theragnostics has appointed 6 staff in UK and 4 in USA as a result of Galliprost [S4]. The investment and progress through clinical trials has led to milestone payments and accrued

royalties [S5], and to new research scientist and PhD student appointments funded by Theragnostics; totalling GBP500,000 with a future commitment of GBP530,000 [S4].

Further economic impact has also occurred via sub-licensing. Theragnostics commissioned ChemaTech to synthesise THP derivatives for sales to researchers for development of their own radiopharmaceuticals, and to supply the THP-PSMA conjugate for Galliprost kit production [S4, S6].

In addition, King's has received GBP157,360 in the REF reporting period between August 2013 to December 2020 as licensing fees, royalties on sales and reimbursement of patenting expenses [S5].

Uptake by Global Medical Technology leader GE Heathcare:

In 2019, Theragnostics entered a commercial partnership with GE Healthcare to provide global distribution, preparation and further development of Galliprost [S7]. *"We are excited to partner with Theragnostics on Galliprost to give vital insights into prostate cancer"* said Sanka Thiru, Global Product Leader, Molecular Imaging Oncology in GE Healthcare's Pharmaceutical Diagnostics business. *"We believe that this partnership enables both parties to leverage each other's key areas of expertise in order to accelerate the development of Galliprost and ultimately improve patient care"* [S7]. GE Healthcare is the healthcare division of GE and has operations in over 160 countries globally with a reported revenue of USD18,000,000,000 in 2020 [S8].

5. Sources to corroborate the impact (indicative maximum of 10 references)

S1. Testimonial from Victoria Gibson, Head of Radiopharmacy, Guy's hospital, Guy's and St Thomas' NHS Trust clinical service, 24th June 2020

S2. Testimonial from Simon Hughes, Consultant Clinical Oncologist, uro-oncology, Guy's hospital, Guy's and St Thomas' NHS Trust clinical service, ^{68}Ga-PSMA, 26th June 2020

S3. Publication: Kulkarni M et al., (2020). The Management Impact of ^{68}Gallium-Tris(Hydroxypyridinone) Prostate Specific Membrane Antigen PET-CT Imaging for High-Risk and Biochemically Recurrent Prostate Cancer. *Eur. J. Nucl. Med. Mol. Imaging*

S4. Testimonial from: Gregory Mullen, CEO, Theragnostics Ltd., 16th August 2019

S5. Summary of royalty income to King's and grant awarding bodies

S6. Chematech catalogue of THP compounds (2020)

S7. GE Healthcare and Theragnostics announce global commercial partnership for late stage PSMA diagnostic for prostate cancer (2019)

S8. About GE Healthcare Systems