Institution: King's College London		
Unit of Assessment: 8 (Chemistry)		
Title of case study: Delivering the therapeutic impact of hydroxypyridinone chelators		
Period when the underpinning research was undertaken: 2005 - 2019		
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 Robert Hider	Emeritus Professor	1987 – 2008
Dr Jane Preston	Senior Lecturer	1995 – present
Prof Phil Blower	Professor of Imaging Chemistry Interim Head of Chemistry Department (25%)	2006 – present 2012 – 2013
Dr Greg Mullen	Senior Lecturer	2007 – 2014
Dr Vincenzo Abbate	Senior Lecturer	2008 – present
Prof Gary Cook	Professor of PET Imaging	2011 – 2020
Dr Michelle Ma	Senior Lecturer	2013 – present
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 (indicative maximum 100 words)

King's research has helped deliver the wide-ranging therapeutic potential of metal-chelating hydroxypyridinones (HOPOs).

Building on our development of *Deferiprone* as a standard treatment for β-thalassemia, research on iron-chelating HOPOs has created next generation HOPO therapeutics with improved efficiency and reduced toxicity, now in commercialization by Zede Pharma-Tech Ltd. Beyond β-thalassemia, our work has also established HOPOs as a potential therapy for free radical-based neurotoxicity, and HOPO compounds for Parkinson's and Alzheimer's diseases have entered Phase 2 trials, with reported improved patient outcomes.

We have similarly developed and patented HOPO ^{68}Ga chelators as new tools for radiopharmaceutical delivery. Working with Theragnostics Ltd, a kit for simple on-site radiotracer production for prostate cancer PET imaging was established. This kit has improved the accessibility of prostate cancer screening, leading to reduced screening delays (from several months to weeks), improved treatment decisions in over 1,500 patients to date, and cost savings of GBP600 to GBP1,500 per patient**.** Phase 3 trials are currently underway, and in 2019 GE Healthcare and Theragnostics entered a commercial partnership for a worldwide rollout of *Galliprost.*

2. Underpinning research (indicative maximum 500 words)

The 'hard' metal binding properties, simple derivatization, and biocompatibility of HOPO chelators make them attractive as potential therapeutics - both in the direct treatment of metal ion dysfunction, and as metallodrug components. In a coordinated strategy, chemists in the Institute for Pharmaceutical Sciences and the Department for Imaging Chemistry & Biology have worked to develop HOPOs as future therapeutics in a number of important disease areas:

King's researchers discovered a new class of HOPOs that avoids agranulocytosis - the most significant side effect in their current use to treat β-thalassemia. Earlier research by Prof Robert Hider on iron-chelating HOPOs led to the creation of *Deferiprone*, now a standard treatment for β-thalassemia patients worldwide. As part of our campaign to develop improved HOPOs, a range of novel R_2 substituted, multidentate, and dendritic chelators were developed (e.g. [**1**,**2**]). Building on this framework, synthesis with collaborators at Zhejiang University produced a library of next-generation HOPO analogues for screening. Lead compounds show

metal selectivity comparable to *Deferiprone*, but with significantly improved iron scavenging ability. A patent was granted in 2014 (EP2692724A1), with underpinning work published in 2020 [**3**].

King's researchers demonstrated that HOPO iron-chelators can also be used to address free radical-based neurotoxicity. In response to the discovery that Parkinson's disease is associated with the concentration of iron in the brain, and that iron also promotes the toxicity of amyloid β-peptide, we sought to apply HOPOs to the treatment of neurodegenerative diseases. Our research has established a protective effect from HOPOs on neurons under a range of Alzheimer's and Parkinson's disease relevant insults [**4**].

We transformed iron-capturing HOPOs into gallium-capturing molecules. Based on the chemical similarities between iron and gallium, collaboration between Profs Hider (Institute for Pharmaceutical Sciences) and Blower (Department for Imaging Chemistry & Biology, and Head of Department of Chemistry 2012 – 2013) led to the development of new bifunctional tris-hydroxypyridinone chelators, able to simply and selectivity capture ^{68}Ga at room temperature, neutral pH, and micromolar concentrations of ligand (e.g. [**5**]). We modified HOPO gallium chelators with targeting epitopes including proteins and small peptides to create a new class of radiotracer agents for cancer screening. We demonstrated that the resulting compounds fulfilled the therapeutic requirements for simple production, rapid radiolabelling, and high contrast imaging in animal models (e.g., [**6**]).

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

1. Liu, Z. D., Kayyali, R., **Hider, R. C.**, Porter, J. B., and Theobald, A. E. (2002). Design, synthesis, and evaluation of novel 2-substituted 3-hydroxypyridin-4-ones: structure-activity investigation of metalloenzyme inhibition by iron chelators. *J. Med. Chem.,* 45(3):631-639. doi.org/10.1021/jm010817i
2. Zhou, T., **Hider, R. C.**, Liu, Z. D., and Neubert, H. (2004). Iron(iii)-selective dendritic chelators. *Tetrahedron Letters*, 45(51):9393–9396. doi.org/10.1016/j.tetlet.2004.10.110
3. Chen, W., Yuan, X., Li, Z., Lu, Z., Kong, S., Jiang, H., Du, H., Pan, X., Nandi, M., Kong, X., Brown, K., Liu, Z., Zhang, G., **Hider, R. C.**, and Yu, Y. (2020). CN128: A new orally active hydroxypyridinone iron chelator. *J. Med. Chem.*, 63(8):4215-4226. doi.org/10.1021/acs.jmedchem.0c00137
4. Molina-Holgado, F., Gaeta, A., Francis, P. T., Williams, R. J., and **Hider, R. C.** (2008). Neuroprotective actions of deferiprone in cultured cortical neurones and SHSY-5y cells. *J. Neurochem.*, 105(6):2466-2476. doi.org/10.1111/j.1471-4159.2008.05332.x
5. Berry, D. J., Ma, Y., Ballinger, J. R., Tavaré, R., Koers, A., Sunassee, K., Zhou, T., Nawaz, S., **Mullen, G. E. D**., **Hider, R. C.**, and **Blower, P. J.** (2011). Efficient bifunctional gallium-68 chelators for positron emission tomography: tris(hydroxypyridinone) ligands. *Chem. Comm.*, 47(25):7068. doi.org/10.1039/c1cc12123e
6. **Ma, M. T.**, Cullinane, C., Imberti, C., Torres, J. B., Terry, S. Y. A., Roselt, P., Hicks, R. J., and **Blower, P. J.** (2015). New tris(hydroxypyridinone) bifunctional chelators containing isothiocyanate groups provide a versatile platform for rapid one-step labeling and PET imaging with ^{68}Ga. Biocanj Chem., 27(2):309-318. doi.org/10.1021/acs.bioconjchem.5b00335

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

Our work to improve HOPO iron-chelators has led to a next generation of therapy for β-thalassemia resulting in improved patient outcomes and the founding of the company Zede Pharma Tech. β-thalassemia major is the world's most common genetic blood disorder, affecting 330,000 infants per year globally. Children only survive with transfusion of normal red blood cells**;** but frequent transfusions lead to a toxic build-up of iron and without treatment to remove excess iron they die by age ~25.

The iron-chelating HOPO *Deferiprone* is a standard treatment for β-thalassemia; developed as a result of our earlier work in this area. Over 50,000 people are now treated with *Deferiprone* each

year, providing each with a lifespan extension of 45 years on average. In 2015 *Deferiprone* was approved by the Canadian Agency for Drugs and Technologies in Health, marking the effective conclusion of a sequence of regulatory approvals in 65 countries, including the EU, USA, and China.

In August 2013, our collaboration with researchers at Zhejiang University led to *CN128*, a compound with improved chelation efficiency and reduced side effects for β-thalassemia [**3**]. Based on this discovery Zede Pharma Tech was established. Prof Hider is a board member of Zede Pharma Tech. In 2020, the company had a registered capital of RMB12,110,000 (GBP1,350,000 02/2021) [**A**]. Zede Pharma Tech has successfully completed Phase 1 clinical trials on *CN128* (NCT03673085, NCT03935633), and a GBP5,000,000 Phase 2 clinical trial (NCT04614779) is currently underway at Guangxi University Hospital. To date, these preclinical results showed that the commercialised compounds derived from our research are 4 times more efficient than *Deferiprone* at removing toxic iron, with no indications, to date, of agranulocytosis in either primates or humans.

HOPO iron-chelators have entered Phase 2 trials for the treatment of neurodegenerative diseases with improved patient outcomes. Beyond β-thalassemia, our research [**4**] demonstrated that HOPOs can address free radical-based neurotoxicity. Phase 1 (NCT00943748) and 2 (NCT01539837, NCT02728843) clinical trials of *Deferiprone* in Parkinson's Disease patients show reduced severity of symptoms and slower disease progression. In February 2016, a larger trial (NCT02655315) began, recruiting 372 Parkinson's patients at 25 sites across eight European countries; the trial is expected to finish in spring 2021. A Phase 2 trial to investigating the potential for *Deferiprone* to treat Alzheimer's disease is underway (NCT03234686).

Commercialisation of HOPO ^{68}Ga chelators has provided improved accessibility of prostate cancer screening, leading to reduced screening delays (from months to weeks) and improved treatment decisions in over 1500 patients. Prostate cancer kills over 10,000 men annually in the UK. Positron Emission Tomography (PET) imaging, central to managing prostate cancer, relies on radiotracers to identify cancer cells. However, traditional methods of radiotracer synthesis are complex, needing an on-site cyclotron and time-consuming costly preparation. This significantly limits the availability of PET imaging.

We developed tris-hydroxypyridinone (THP), a patented (WO2012063028A1, WO2017076879A1) chelator engineered for fast and efficient ^{68}Ga radiolabelling. We also formulated a simple single-vial sterile kit for producing the tracer quickly under clinical, "good manufacturing practice" (GMP) conditions [**B**]. *Galliprost* preparation takes just 15 minutes (compared to several hours for conventional tracers) [**C**] and provides a 'heatmap' image of Prostate-Specific Membrane Antigen in PET/CT scans. This formulation allows the tracer to be produced on site, in a manner suitable for frontline healthcare staff, without complex procedures or infrastructure.

The impact of this work is evidence by the screening service established in partnership with Guy's and St Thomas' Hospitals. Dr Gibson, Head of Radiopharmacy emphasised *"The development of Galliprost kit formulation has had a massive impact on the Clinical service…."* Notably, this service was set up much more quickly (from several months to just 4 weeks for initial validation; and from typically 6 hours to 15 minutes for daily production) compared to what could be done previously. To date, this service has benefited over 1,000 patients at Guy's and St Thomas' Hospitals alone and provides significant cost savings of GBP600 to GBP1,500 per patient [**C**]. More widely, *Galliprost* is now used in routinely in 12 hospitals across Europe [**C, D, E**], and by July 2020 an estimated total of 1,500+ patients had benefited from the use of *Galliprost* [**C, D, E, F**]. A phase 2 clinical study demonstrated 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 [**G**].

***Galliprost* has 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 GDP13,000,000 in investment capital, ~90% directed towards *Galliprost* development. Phase 2 trials (NCT03617588) were completed in 2020, with Phase 3 prostate cancer trials now underway, with FDA/MHRA approval targeted for 2021. Theragnostics has recently launched a USD45,000,000 Series A financing round to take *Galliprost* to market [**I**].

Since 2016, Theragnostics has appointed 6 staff in the UK and 4 in USA as a result of *Galliprost*. The investment and progress through clinical trials has led to milestone payments and accrued royalties [**H**], and to new research scientist and PhD student appointments at King's funded by Theragnostics; totalling GBP500,000, with a future additional commitment of GBP530,000 [**G**].

Further economic impact has also occurred via sub-licensing. Theragnostics commissioned CheMatech (France, 2016) 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 [**I**].

***Our work has resulted in the worldwide distribution of Galliprost*.** In 2019, Theragnostics entered a commercial partnership with GE Healthcare to provide global distribution, preparation, and further development of *Galliprost* [**J**]. The US market estimate for this treatment is USD500,000,000.

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

[A] Zede Pharma Tech:

(a) Company information

(b) Company finances (2020)

[B] 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.org/10.2967/jnumed.117.191882

[C] Guy's and St Thomas' NHS Trust clinical service impact testimonial. Victoria Gibson. Head of Radiopharmacy. (2020)

[D] ^{68}Ga-PSMA uro-oncology at Guys & St Thomas' NHS Trust. Simon Hughes, Consultant Clinical Oncologist. (2020)

[E] Thorsten, D., Schmuck, S., Juhl, C.,Teichert, S., Zörgiebel, J., Wester, H-J., Schneefeld, S. M., Walte, A. C. A., Thackeray, J. T., Ross, T. L., and Bengel, F. M. (2018). Imaging Characteristics and First Experience of [68Ga]THP-PSMA, a Novel Probe for Rapid Kit-Based Ga-68 Labeling and PET Imaging: Comparative Analysis with [68Ga]PSMA I&T. *Mol Im. & Biol.*, 20(4):650–658. doi.org/10.1007/s11307-018-1160-8

[F] 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, V. S., Cook, G. J. R. (2020) The Management Impact of 68Gallium-Tris(Hydroxypyridinone) Prostate Specific Membrane Antigen PET-CT Imaging for High-Risk and Biochemically Recurrent Prostate Cancer. *Eur. J. Nucl. Med. Mol. Imaging* 47:674-686. doi.org/10.1007/s00259-019-04643-7

[G] Galliprost testimonial. Gregory Mullen. CEO, Theragnostics Ltd. (2019)

[H] Summary of royalty income to KCL and grant awarding bodies. Ceri Matthews, KCL IP and licensing manager. (2020)

[I] Chematech catalogue of THP compounds. (2020)

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