Institution: University of Strathclyde		
Unit of Assessment: B8 - Chemistry		
Title of case study: Accelerating drug development through novel iridium catalysts for enhanced hydrogen isotope exchange labelling		
Period when the underpinning research was undertaken: 2008-2017		
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:**
William Kerr	Professor	01/10/1989 – present
Tell Tuttle	Professor	01/01/2007 – present
Period when the claimed impact occurred: August 2013 – July 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Iridium catalysts developed by Kerr have been adopted by the global pharmaceutical industry to achieve faster and more efficacious incorporation of radioactive and non-radioactive isotopes of hydrogen into a wider range of drug candidates. The catalysts enable key pharmacological tests to be carried out earlier and more effectively. These efficiencies have resulted in considerable time and money savings, a reduction in the amount of radioactive waste produced, and increased process safety. Wide and rapid adoption across the pharmaceutical industry has been facilitated further by Strem Chemicals, Inc., which has added three new Kerr catalysts to the existing range, and expanded sales through the relevant review period.

2. Underpinning research

Context

Designing effective yet safe drugs poses a major challenge to pharmaceutical companies, with around 90% of candidate molecules failing due to the strict criteria associated with marketable medicines. These failures drive up the cost of developing a new chemical entity into a marketed drug, which on average costs in excess of USD3,700,000,000 [**S1**]. Costs increase as candidates progress to later development stages, so it is vital to acquire as much pharmacological information relating to the potential drugs as early as possible within any drug discovery programme. Efforts to improve the efficiency of drug development are therefore of extreme importance to the pharmaceutical industry.

This drive for efficiency has heightened the strategic importance of absorption, distribution, metabolism and excretion (ADME) studies. Key approaches within ADME studies crucially require access to isotopically labelled compounds [**S2**]. These labelled molecules are most conveniently made by using a catalyst able to replace hydrogen atoms in a potential drug compound with a heavier isotope, deuterium or tritium. This method of labelling, known as hydrogen isotope exchange (HIE), is widely used within the pharmaceutical industry. Before Kerr's research, the industry standard for this operation was an iridium complex known as Crabtree's catalyst, which exchanges the hydrogen atoms adjacent to Lewis basic groups in the molecule in a process known as directed HIE. However, Crabtree's catalyst has several significant disadvantages. Large quantities of it are needed to label compounds, reducing efficiency and generating appreciable quantities of waste, both radioactive and non-radioactive. Moreover, only a narrow range of solvents can be used, and with a limited selection of substrates, significantly lowering its applicability.

Kerr's research on improved catalysts for HIE began in 2004. Initial results with a Strathclyde-funded PhD student led to interest from scientists at AstraZeneca in 2005, who then collaborated with Kerr, funding two additional research projects at Strathclyde to support further developments.

Key findings

The seminal advance by Kerr et al., published in 2008, reported the development of practical and convenient methods for the preparation of novel iridium complexes, with the key attribute that they possessed both bulky N-heterocyclic carbene (NHC) and encumbered phosphine ligands [R1]. Kerr then demonstrated that, as predicted, these complexes showed exceptional activity in HIE processes, with low relative levels of catalyst loading and mild reaction conditions delivering remarkably high percentage levels of deuterium labelling across a range of substrates. The research also demonstrated applicability to tritium, a radioactive hydrogen isotope [R2], facilitating drug candidate metabolism studies of key importance within the pharmaceutical industry. Understanding of catalyst reactivity and selectivity was also advanced through a range of mechanistic investigations, alongside theoretical studies in collaboration with Tuttle [R2].

By 2013, three NHC/phosphine iridium catalysts had been created for isotope labelling via directed HIE. Since then, Kerr has expanded the applicability of these catalysts to include a range of new substrates, including non-aryl sp^2 systems and sp^3 centres, as well as pharmaceutically important motifs such as indoles and other nitrogen-based heterocycles [R3].

Since 2014, additional effective catalysts have also been established through a combination of preparative and theoretical studies. Specifically, the Kerr group found that modification of the counter-ion resulted in catalysts with elevated activity and, importantly, solubility in a much broader range of solvents than the initial Kerr catalysts [R4]. Not only does this mean that labelling requires a smaller amount of catalyst, but it allows for the labelling of a wider scope of drug-like molecules which are often not soluble in the restricted selection of (e.g. chlorinated) solvents compatible with Crabtree's catalyst.

Additionally, Kerr and co-workers showed that a further and related series of NHC/chloride complexes were also active catalysts. Crucially, tuning of the distinct electronic and steric properties of these NHC/chloride complexes has further broadened the applicability of this catalyst series. For example, this has allowed, for the first time, the efficient labelling of the pharmaceutically important primary sulfonamide group [R5]. Computational studies revealed the unique binding mode between the substrate and the newly developed iridium catalysts. This more detailed understanding then led to the unprecedented formyl-selective labelling of aldehydes with the same general catalyst class [R6].

3. References to the research (Strathclyde affiliated authors in **bold**; FWCI at 02/02/2021)

R1 **J.A. Brown**, **S. Irvine**, **A.R. Kennedy**, **W.J. Kerr**, S. Andersson, G.N. Nilsson (2008) Highly active iridium(I) complexes for catalytic hydrogen isotope exchange, *Chemical Communications*, 1115-1117. https://doi.org/10.1039/B715938B [FWCI: 2.79]

R2 **J.A. Brown**, **A.R. Cochrane**, **S. Irvine**, **W.J. Kerr**, **B. Mondal**, **J.A. Parkinson**, **L.C. Paterson**, **M. Reid**, **T. Tuttle**, S. Andersson, G.N. Nilsson (2014) The synthesis of highly active iridium(I) complexes and their application in catalytic hydrogen isotope exchange, *Advanced Synthesis Catalysis*, 356(17): 3551-3562 https://doi.org/10.1002/adsc.201400730 [FWCI: 1.47; REF2]

R3 **W.J. Kerr**, **D.M. Lindsay**, **P.K. Owens**, **M. Reid**, **T. Tuttle**, S. Campos (2017) Site-selective deuteration of *N*-heterocycles via iridium-catalyzed hydrogen isotope exchange, *ACS Catalysis*, 7(10): 7182-7186 https://doi.org/10.1021/acscatal.7b02682 [FWCI: 1.83]

R4 **A.R. Kennedy**, **W.J. Kerr**, **R. Moir**, **M. Reid** (2014) Anion effects to deliver enhanced Iridium Catalysts for hydrogen isotope exchange processes, *Organic & Biomolecular Chemistry*, 12**:** 7927-7931. https://doi.org/10.1039/C4OB01570C [FWCI: 1.43]

R5 **W.J. Kerr**, **M. Reid**, **T. Tuttle** (2015) Iridium-catalyzed C-H activation and deuteration of primary sulfonamides: an experimental and computational study, *ACS Catalysis*, 5: 402-410. https://doi.org/10.1021/cs5015755 [FWCI: 2.69; REF2]

R6 **W.J. Kerr**, **M. Reid**, **T. Tuttle** (2017) Iridium-catalyzed formyl-selective deuteration of aldehydes, *Angewandte Chemie International Edition*, 56: 7808-7812. https://doi.org/10.1002/anie.201702997 [FWCI: 1.88; REF2]

Notes on the quality of research: In 2015, Kerr was awarded the Melvin Calvin Award of the International Isotope Society (IIS) for outstanding contributions to the science of isotopes and isotopically labelled compounds. All the listed references were published in peer-reviewed international journals. The research work was underpinned by funding awards and EPSRC Knowledge Transfer Grants, including:

I. Kerr. AstraZeneca Research Award (03/10/2005-31/01/2009). Improved Homogeneous Iridium Catalyst for Efficient and Selective Hydrogen-Isotope Exchange. Total Awarded: GBP64,923.

II. Kerr. AstraZeneca Research Award (01/10/2008-30/09/2012). Enhanced Homogeneous Iridium Complexes for Widespread Application in Hydogen Isotope Exchange and as New Catalysts in an Array of Organic Synthetic Procedures. Total Awarded: GBP75,000.

4. Details of the impact

The novel iridium catalysts emerging from the underpinning research (as detailed in Section 2) demonstrated a clear superiority over the industry-standard species. Further testing and refinement of the methodology at Strathclyde was followed by ready transfer of the technology into AstraZeneca, in the first instance, where the new catalysts were applied to a range of current drug candidates. As the research programme expanded, the links with AstraZeneca grew, and between 2012 and 2016 collaborations also developed with other pharmaceutical companies. Accordingly, the impacts achieved from the research during the current period have been:

- Appreciable uptake by global pharmaceutical companies, owing to the improved performance of the catalysts.
- More effective pharmacological assessment of a broader range of drug candidates, rapidly and directly labelled using the developed Kerr catalysts.
- Significant environmental, time and cost benefits to pharma companies.
- Enhanced availability of the catalysts, including new product ranges for Strem.

Process improvements, escalated pharmaceutical applications, and global uptake

In the period following their discovery, the new catalyst technology has significantly impacted the way pharmaceutical companies prosecute ADME studies on their pipeline of candidates. As described by the Head of Isotope Chemistry at Sanofi, *'The catalysts developed by the Kerr group in Strathclyde are the gold standard in iridium-catalysed HIE reactions used in the pharma industry'* [**S3**].

The Global Head of Isotope Chemistry at AstraZeneca explicitly indicates [**S4**] the quantitative difference that these catalysts have made and continue to make within their drug discovery and development programmes. For example, in the period since 2014 of all the drug candidates that were subjected to HIE within AstraZeneca laboratories globally, 72% were labelled using Kerr catalysts [**S4**]. Since these labelling studies underpin the development and delivery of all AstraZeneca drug candidates, the new catalysts have a clear, pervasive and significant positive impact on the development of new medicines within this multinational company. The benefits of the Kerr catalysts for tritium labelling were also made clear by AstraZeneca's Global Head of Isotope Chemistry: *'[Alternative] routes would have been longer and/or would have generated more waste, with a negative impact on time, cost, and efficiency as a result'* [**S4**]. The reduced environmental impact of the catalysts has also been demonstrated within AstraZeneca, who have made a commitment to the Swedish Nuclear Regulatory Agency to reduce gaseous emissions of

tritium-labelled compounds. Including use of the Kerr catalysts, efforts to date towards this goal within AstraZeneca have resulted in a ~40% reduction in gaseous tritiated waste [**S4**].

Global uptake of the Kerr catalysts has expanded significantly, with many of the world's top pharmaceutical companies, including Merck, Sanofi, Research Triangle Institute (RTI), Roche, Janssen, and Bayer, now using the catalysts for more effective drug labelling. The broad applicability and impact of Kerr catalysts has been widely communicated by a number of these pharmaceutical companies, including within journal publications (e.g. *Å. Lindelöf, et al., J. Label. Compd. Radiopharm., 2016, 59: 340-345; K. T. Neumann, et al., J. Label. Compd. Radiopharm., 2017, 60: 30–35; P. Allen, et al., J. Label. Compd. Radiopharm., 2017, 60: 124-129*). At Roche, where around 50% of HIE-dependent tritium labelling now relies on Kerr catalysts, the Heads of Isotope Synthesis describe Kerr catalysts as *'internationally leading in the way that they appreciably extend the toolbox for HIE*', and added that '*Kerr catalysts are also notably employed in key screening campaigns with new substrates*' [**S5**]. The improved solubility of the second-generation Kerr catalysts allows them to be used for a significantly greater number of ADME applications than previously, and Sanofi's Head of Isotope Chemistry credits the catalysts with reducing the time needed to tritiate compounds from four weeks to just one [**S3**]. This reduction in time for labelling studies also translates into significant financial savings. For example, the Director of Radiochemistry at RTI, and formerly of Merck and Schering-Plough, estimates that use of the Kerr catalysts '*saved 3-8 weeks synthesis time for each compound accessed with the Kerr catalysts, alongside the removal of concomitant safety concerns with more lengthy routes involving radiolabelled materials. Such time savings equate to approximate average cost savings of around USD36,000 (07-2020) per compound, a figure which includes the labour hours, materials, instrumentation and projected waste costs'* [**S6**].

In addition to that detailed above, the catalysts have also been used specifically to label marketed pharmaceuticals. For example, at RTI a Kerr catalyst provided direct access to labelled drug molecules required as part of the National Institute on Drug Abuse (NIDA) programme [**S6**]. Additionally, the catalysts were employed by Sanofi in the labelling of marketed Sanofi drug compounds, such as Zolpidem and Glibenclamide, in order to allow key pharmaceutical studies not previously performed on these products [**S3**].

New catalyst product ranges via Strem Chemicals, Inc.

Commercial impact and significant worldwide uptake of the iridium catalysts have been driven through the adoption of the recently developed Kerr catalysts as commercial products by Strem Chemicals, Inc. Between October 2012 and October 2017, 3 NHC/phosphine iridium catalysts were commercialised by Strem Chemicals, Inc. As a result of Kerr's further research, 2 of the new counter-ion complexes and 1 NHC/Cl catalyst were also commercialised by Strem Chemicals, Inc. in November 2017. Sales of the compounds have provided an economic benefit to this SME company [**S7**], and the ready commercial availability of the catalysts has significantly lowered the barrier to adoption and widespread use of this new technology by international pharmaceutical companies, as described above.

Between August 2013 and July 2020, Strem made sales to more than 50 different customers in more than 10 countries. The purchasers of the Kerr catalysts include pharmaceutical companies, fine chemical companies, other industrial organisations and academic labs [**S7**].

The Chief Executive Officer of Strem Chemicals, Inc. states that:

> *'sales to pharmaceutical companies of the 3 catalysts first commercialised in 2012 have continued to grow and now represent a highly popular line of products within our portfolio. The addition of 3 of Kerr's new complexes continues to expand this product line and have a positive impact on the pharmaceutical industry. These 3 new catalysts, added to our catalogue in 2017, have appreciably broadened the scope of the iridium(I)-catalysed hydrogen isotope exchange process, resulting in new users*

employing these catalysts, as well as existing users broadening the palette of catalysts they routinely employ.' [**S7**]

The impact of the suite of novel iridium catalysts developed by Kerr continues to expand. By shortening the time for pharmacological evaluation of a wider range of drug candidate molecules, those with a poor pharmacological profile are eliminated earlier, while more promising candidates can be accelerated through the drug discovery process. The increased efficiency and effectiveness of hydrogen isotope exchange afforded by the Kerr catalysts is making an important contribution to faster development of new drug products in the pharmaceutical industry.

5. Sources to corroborate the impact

S1 Sources to corroborate contextual information:

(a) Hardman & Co. (2019) Global Pharmaceuticals: 2018 Industry Statistics. Accessed 01/09/2020: https://bit.ly/3q449nt (Gives the value of the global pharmaceutical prescription drug market as US$865bn in 2018);

(b) Forbes (2012) The Truly Staggering Cost of Inventing New Drugs. Accessed 01/09/2020: https://bit.ly/3cYTQgG (Provides the research spend per drug per pharmaceutical company);

(c) DiMasi, J. A., Grabowski, H. G. and Hansen, R. W (2016). Innovation in the pharmaceutical industry: New estimates of R&D costs. Journal of Health Economics, 47: 20-33. DOI: 10.1016/j.jhealeco.2016.01.012.

S2 For overviews of the importance of labelled compounds in ADME/drug metabolism and pharmacokinetic (DMPK) studies, and communication of the increased drivers and demands for radiolabelled drug candidates earlier in the drug development process, see:

(a) Isin, E. M., Elmore, C. S., Nilsson, G. N., Thompson, R. A. and Weidolf, L. (2012). Use of radiolabeled compounds in drug metabolism and pharmacokinetic studies, Chem. Res. Toxicol., 25: 532−542. DOI: 10.1021/tx2005212;

(b) Lockley, W. J. S., McEwen, A. and Cooke, R. (2012). Tritium: a coming of age for drug discovery and development ADME studies, J. Label. Compd. Radiopharm., 55: 235-257. DOI: 10.1002/jlcr.2928.

S3 Corroborating statement from the Head of Isotope Chemistry, Sanofi, dated 31 July 2020.

S4 Corroborating statement from the Head of Isotope Chemistry, Pharmaceutical Sciences, BioPharmaceuticals R&D, AstraZeneca, dated 31 July 2020.

S5 Corroborating statement from the Laboratory Head of Isotope Synthesis and the Section Head of Isotope Synthesis, Roche, dated 31 July 2020.

S6 Corroborating statement from the Director of Radiochemistry, Research Triangle Institute (RTI), and formerly of Merck and Schering-Plough, dated 31 July 2020.

S7 Corroborating statement from the Chief Executive Officer, Strem Chemicals, Inc., dated 31 August 2020.