

Impact case study (REF3b)

Institution: WestCHEM
Unit of Assessment: Sub-panel 8 – Chemistry
Title of case study: Improved drug discovery and development through use of novel iridium catalysts
1. Summary of the impact

Labelled compounds form an essential part of drug discovery and development within the pharmaceutical industry. Novel iridium catalysts, developed by Kerr at WestCHEM since 2008, have introduced a step-change in the ability to label pharmaceutical candidate compounds with radioactive (tritium) or non-radioactive (deuterium) isotopes.

The catalysts are applicable to specific types of compounds that comprise approximately one-third of all drug candidates. Advantages of the catalysts include greater efficacy (less catalyst needed and higher yield of labelled product, giving cost savings), greater speed (efficiency savings), and a significant decrease in radioactive waste compared with previous methods (environmental and safety benefits).

Even since 2008, their adoption within the pharmaceutical industry has been extremely rapid; e.g., the multinational pharmaceutical company AstraZeneca now applies the Kerr methodology to 90% of their relevant candidate compounds. Additional impact has been achieved by Strem Chemicals who have been manufacturing and marketing the catalysts worldwide since October 2012. Even in that very short period, multiple sales have been made on three continents providing economic benefit to the company.

2. Underpinning research

Context

The design of drugs, with optimal potency and pharmacokinetic properties, as well as increased safety profile, poses a major challenge for pharmaceutical laboratories. Attrition, or high failure rate, has emerged as a central problem in modern drug development. This contributes to an average cost of \$1.7 billion for developing a new chemical entity (NCE) into a marketable drug. The really expensive failures are those that fail late in the testing process and so it is vital to get as much information about candidate medicines as early as possible. Efforts to improve efficiency are of high interest to the pharma industry with gains of 10% in the study of the pharmacokinetics of candidate drugs resulting in savings of the order of \$100M per drug. This has heightened the importance of absorption, distribution, metabolism, excretion, and toxicology (ADMET) studies. ADMET studies require the use of radiolabelled compounds. These labelled compounds are most conveniently made by taking the unlabelled drug candidate and introducing the label in a single step by hydrogen isotope exchange (HIE) through C-H activation on an aromatic ring *ortho*- to a substituent that can interact with a suitable catalyst. This method of labelling applies to one-third of all drug candidates.

Prior to the WestCHEM research, the industry standard for this operation was Crabtree's catalyst, also an iridium complex. This catalyst has a number of significant disadvantages:

1. Dichloromethane is usually the only solvent tolerated by this catalyst, but many drug candidates are insoluble in that solvent,
2. Bulky substituents near the site of the hydrogen to be exchanged inhibit the process,
3. Inactive iridium dimers and trimers form from Crabtree's complex, compromising its longevity,
4. Many substituents on the drug candidate do not deliver any appreciable degree of labelling,
5. Although nominally a catalyst, high loadings of Crabtree's complex (in many cases, more than 100 mole%) are often required, and
6. These high loadings normally lead to a lack of labelling regioselectivity.

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Key findings

In the original WestCHEM paper published in 2008 [1], practical and convenient methods were developed for the preparation of novel iridium complexes, with the key attribute that they possessed both bulky *N*-heterocyclic carbene and bulky phosphine ligands. Kerr (Professor, WestCHEM) predicted and then demonstrated that these complexes show exceptional activity in hydrogen isotope exchange processes. Previous efforts by other research teams to prepare similar compounds had failed, but through two PhD projects at WestCHEM, Kerr discovered an approach that was successful and convenient. The research for the initial publication was carried out with deuterium (non-radioactive isotope of hydrogen) but with clear applicability to tritium (radioactive isotope of hydrogen) and with the stated aim of addressing important studies of metabolism of drug candidates within the pharmaceutical industry.

The interaction with AstraZeneca (at Mölndal in Sweden) triggered through the funding of the second PhD project mentioned above, led to easy further development and transfer of the technology between WestCHEM and Mölndal. Specifically, application to the use of tritium labelling could be more conveniently carried out at the industrial site, which had appropriate safety measures to routinely produce radioactively labelled compounds. In 2010, an overview was published by Nilsson (AstraZeneca) and Kerr [2] showing the development of the collaboration. By 2010, three novel air-stable complexes showed great promise, providing effective labelling in short times (hours rather than days) at low loading (usually 0.5 % catalyst loading) to an extended list of substituents with tolerance of a wider list of solvents than could be used for Crabtree's complex, and with excellent selectivity in the site of labelling (through 5-membered metallacycle intermediates over slower labelling through 6-membered metallacycle intermediates). Labelling of typical complex drug molecules bearing multiple substituents was demonstrated. Most impressively, the clean reactions seen with the new complexes averted the serious problems of radioactively labelled waste that had arisen with the Crabtree complex. A representative assay in the 2010 overview paper showed that at least 16 radiolabelled products were formed on a particular drug candidate using Crabtree's catalyst, compared with just the single desired product using the new catalyst regime.

Key researchers

William J Kerr (appointed as Lecturer, WestCHEM, October 1989, Senior Lecturer from April 1997 and Professor of Organic Chemistry from April 2002).

3. References to the research

References 1, 2 and 5 best illustrate the quality of the research. Paper 1 is submitted as part of REF2.

- [1] Highly active iridium(I) complexes for catalytic hydrogen isotope exchange, J. A. Brown, S. Irvine, A. R. Kennedy, W. J. Kerr, S. Andersson and G. N. Nilsson, *Chem. Commun.*, **2008**, 1115-1117. DOI: **10.1039/B715938B**
- [2] The development and use of novel iridium complexes as catalysts for ortho-directed hydrogen isotope exchange reactions, G. N. Nilsson and W. J. Kerr, *J. Label. Compd. Radiopharm.*, **2010**, 53, 662-667. DOI: **10.1002/jlcr.1817**
- [3] Highly Active Iridium(I) Complexes for Catalytic Hydrogen Isotope Exchange, (conference abstract at major international meeting) W. J. Kerr, S. Irvine, J. A. Brown, S. Andersson & G. N. Nilsson. *Abstracts of Papers of the American Chemical Society*, **2007**, 234, 79-ORGN; IDS Number: V12JA; ISSN: 0065-7727
- [4] Highly Active Iridium(I) Complexes for Catalytic Hydrogen Isotope Exchange and Selective Hydrogenation, J. A. Brown, S. Irvine, A. R. Kennedy, W. J. Kerr, S. Andersson and G. Nilsson, *J. Label. Compd. Radiopharm.*, **2009**, 52, 210-211. DOI: **10.1002/jlcr.1590**

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[5] Application of neutral iridium(I) N-heterocyclic carbene complexes in ortho-directed hydrogen isotope exchange, A. R. Cochrane, S. Irvine, W. J. Kerr, M. Reid, S. Andersson and G. N. Nilsson, *J. Label. Compd. Radiopharm.* **2013**, *56*, 451-454. DOI: [10.1002/jlcr.3084](https://doi.org/10.1002/jlcr.3084)

4. Details of the impact**Process from research to impact**

The original idea and research arose from Kerr at WestCHEM. Initial results with a WestCHEM-funded PhD student led to interest from AstraZeneca who then decided to collaborate with Kerr, through funding an additional PhD student to work on the project at WestCHEM. The success of those two students' research and frequent interactions between the Kerr group and AstraZeneca then led to immediate and extensive testing of the methodology at WestCHEM and also within the company on many of its drug candidate compounds.

Type(s) of impact**Process improvements**

The Global Head of Isotope Chemistry at AstraZeneca explicitly indicates the quantitative difference that these catalysts are making within their drug discovery and development programmes. In drug candidate compounds that are susceptible to HIE reactions (about one-third of all their drug candidates), 90% now use the Kerr catalysts while 10% still use the older Crabtree catalysts. Since these studies underpin the development of all of the AstraZeneca drug candidates, it is clear that the new catalysts have a pervasive and significant influence on the development of new medicines within this multinational company. Of course, since AstraZeneca were parties in the original collaboration first published in 2008, it is to be expected that they would still have a lead in applying it to their work.

New product ranges

An extension of the impact has been the adoption of the new catalysts as commercial products by Strem Chemicals. They have marketed and sold the catalysts since October 2012 and in the 9 months since launch, [text removed for publication.]

Reach and significance

Labelled compounds form an essential part of drug discovery and development within the pharmaceutical industry, allowing a rapid understanding of the metabolism of candidate drugs, and discrimination between candidates that can be progressed and those that must be rejected. Efforts to improve the efficiency are important; efficiency gains of 10% in the study of the pharmacokinetics of candidate drugs would bring savings of the order of \$100M per drug. (Source 6).

The pharmaceutical industry is now applying the new technology directly to its pipeline of pharmaceutical candidates, with AstraZeneca in the lead, but with uptake gathering pace globally. At present, the principal impact is on operational efficiencies and cost reductions for the pharmaceutical companies, but the impact passes to the population at large through the provision of safer, more effective medicines at lower cost and with less environmental impact.

The Global Head of Isotope Chemistry, AstraZeneca (Source 1) notes:

'The Kerr catalysts are now 'state of the art' in this area of labelling. Indeed, on analysing our internal data for the past 15 months (Jan. 2012 – March, 2013), within our global drug discovery programmes at AstraZeneca, of the tritiation by isotope exchange, 90% of all compounds investigated were labelled with the Kerr-type catalysts. I would predict that this level of impact will continue within our company and will be replicated within similar organisations internationally.'

The former Associate Director of Isotope Chemistry, AstraZeneca, Mölndal, Sweden, currently an independent consultant, (Source 2) says:

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'These new catalysts have changed the map for the isotope chemist world-wide and especially in the pharma business. The Kerr catalysts have been transformational in that they have delivered notable efficiency savings, with tritiation cycle times down from approximately 3 weeks to less than 1 week; as well as these time savings, the use of these catalysts at such low loadings has significantly reduced (radioactive) waste. These catalysts are now available from a commercial supplier and all chemists can use them very easily. Moreover, they are shelf stable and, based on the confidence delivered by their efficiencies, D tests are now often discarded in drug projects, with the experimentation going directly to the 'hot' process on the T manifold.' (D = deuterium; T = tritium).

Further impact has arisen and continues to increase from the business of Strem Chemicals who now manufacture and sell the catalysts. The Chief Operating Officer, Strem Chemicals (Source 3) reports:

'The commercial availability of Prof. Kerr's novel iridium complex technology for the R&D community is significantly increasing the adoption, and future potential use, of his associated catalysis methods in industry in the widest sense and especially within pharmaceutical companies. We have already seen interest and direct purchases from a series of drug companies and others in evaluating the technology in their direct business-aligned applications.'

Within the first year, Strem Chemicals' products were purchased by [text removed for publication] thereby extending the beneficial reach of Kerr's catalysts.

The application of the new catalysts within the pharmaceutical industry ultimately impacts on mankind, since we are dependent on the development of safe and effective medicines at reasonable cost and without detrimental effect on safety or the environment. Use of the Kerr catalysts is helping to speed up drug discovery and development, allowing a rapid understanding of the metabolism of candidate drugs, and discrimination between candidates that can be progressed and those that must be rejected.

5. Sources to corroborate the impact

- [1] Letter from *Global Head of Isotope Chemistry, AstraZeneca R&D* corroborates the impact within *AstraZeneca*.
- [2] The *Chief Operating Officer, Strem Chemicals* can be contacted to provide information on sales of the iridium catalysts.
- [3] Statement from the former *Associate Director of Isotope Chemistry, AstraZeneca, Mölndal, Sweden* (currently an independent consultant) corroborates the impact of the catalysts in isotope chemistry in the pharmaceutical business.
- [4] Publications mentioned under section 3 above.
- [5] www.pharmaceutical-drug-manufactures.com (access date: October 2010) gives the value of the global pharmaceutical market in 2010 and estimates it for 2013.
- [6] High Clinical Trials Attrition Rate Is Boosting Drug Development Costs, Lang, L. *Gastroenterology* **2004**, *127*, 1026, reports the savings of \$100 Million per drug that could be achieved with a 10% efficiency gain in the study of pharmacokinetic studies; (DOI:10.1053/j.gastro.2004.08.066)
- [7] Synthesis of ximelagatran, melagatran, hydroxymelagatran, and ethylmelagatran in H-3 labeled form, R. Simonsson, G. Stenhagen, C. Ericsson, and C. S. Elmore, *J. Label. Compd. Radiopharm.*, **2013**, *56*, 334-337, shows a real industrial example of the use of one of the Kerr catalysts within an AZ drug discovery programme (DOI: 10.1002/jlcr.3028)