

Impact case study (REF3b)

Institution: Heriot Watt University
Unit of Assessment: 8 Chemistry
Title of case study: Inhibitors for respiratory disease
1. Summary of the impact <p>Phosphodiesterase (PDE) research by Prof. David Adams of Heriot-Watt University (HWU) has discovered compounds with potent combined anti-inflammatory and bronchorelaxant activity, relevant to asthma and chronic obstructive pulmonary disease (COPD). This fuelled a major therapeutic development programme by the Japanese company, Kyorin Pharmaceutical Co. Ltd, resulting in 22 patents (18 published since 2008) with a direct link to the foundational work at HWU. The work was a key factor in Kyorin's continued commissioning of projects with Scottish Biomedical (SB) up to £14.9M, a technology management company founded by Scottish Universities, enabling SB's transition into a fully independent drug-discovery services company, [Text removed for publication].</p>
2. Underpinning research <p>Cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) are key messenger molecules that are vital to cell function. The intracellular levels of these species are regulated by as many as 11 phosphodiesterase gene families (PDE1-11). Prof. David Adams has worked on phosphodiesterase at HWU for >13 years and has collaborated with internationally leading molecular biology groups to unravel key aspects of PDE regulation and subcellular targeting. Work on mapping protein-binding interfaces on PDE4 for key signalling complexes has been funded by MRC, EU and Scottish Enterprise and has been carried out in collaboration with the Houslay group (Glasgow and Strathclyde Universities).</p> <p>PDE4 inhibitors have long been known to exhibit good anti-inflammatory activity and modest bronchodilatory activity, and this prompted interest in their development as a treatment option for respiratory disease. In the 1980s Kyorin developed ibudilast for use in asthma therapy and stroke in Japan, the drug's pharmacological activity issuing, in part, from it being a non-selective PDE inhibitor. Kyorin further developed the drug in the 1990s by coupling the ibudilast pyrazolopyridine core to a pyridazinone to provide a new prototype compound, KCA-965. However, it remained unclear what overall PDE-inhibitory profile was optimal for achieving dual anti-inflammatory and bronchodilatory action in a single compound. The company therefore sought partnerships and as part of this between 2000 and 2006 they awarded ca. £1.8M to Adams, allowing him to establish a medicinal chemistry programme to develop PDE inhibitors from KCA-965.</p> <p>Having developed appropriate synthetic methodology,¹ Adams brought a hypothesis-driven medicinal chemistry approach to develop a series of novel pyrazolopyridine-pyridazinone inhibitors for enzymes of the PDE3 and PDE4 families. By undertaking a structure-activity relationship survey and employing conformationally constrained molecular probes, the Adams group discovered that compounds within the series bind to the catalytic pocket of PDE3 and PDE4 enzymes in a fundamentally distinct manner, and that optimisation required structural reorganisation of the pyrazolopyridine-pyridazinone core.² This discovery allowed the activity of compounds to be fine-tuned so as to provide either potent selective PDE4 inhibitors or dual PDE3/4-selective inhibitors with promising biological activity.</p> <p>An important feature of the programme at HWU was that it provided the molecular tools to investigate the pharmacological benefit from targeting both PDE3 and PDE4. At the outset of the work PDE4 inhibitors were already known to exhibit modest bronchodilatory activity in addition to possessing good anti-inflammatory activity. The bronchodilatory activity arises because PDE inhibition leads to elevated cAMP levels in the airway smooth muscle and so promotes relaxation. Both PDE4 and PDE3 mediate cAMP hydrolysis, however, and inhibition of PDE3 is more effective than inhibition of PDE4 for inducing airway smooth muscle relaxation. By unlocking the structural</p>

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determinants that control PDE3- and PDE4-inhibitory selectivity in the HWU chemical series it was possible to develop compounds with promising dual anti-inflammatory and bronchorelaxant activity.²⁻⁶

Biological assessment of the compounds developed from the Adams group medicinal chemistry programme was undertaken by the Kyorin-Scotland Research Laboratory (KSRL), a facility set up in 2000 between Scottish Biomedical (SB) and Kyorin with an initial £5.2M investment.

3. References to the research (* = best indicates the quality of the underpinning research)

[1]* K. A. Johnston, R. W. Allcock, Z. Jiang, I. D. Collier, H. Blakli, G. M. Rosair, P. D. Bailey, K. M. Morgan, Y. Kohno and D. R. Adams "Concise routes to pyrazolo[1,5-a]pyridin-3-yl pyridazin-3-ones." *Org. Biomol. Chem.* 2008, 6, 175–186. [doi: <http://dx.doi.org/10.1039/b713638b>]

[2]* R. W. Allcock, H. Blakli, Z. Jiang, K. A. Johnston, K. M. Morgan, G. M. Rosair, K. Iwase, Y. Kohno and D. R. Adams "Phosphodiesterase inhibitors. Part 1: Synthesis and structure-activity relationships of pyrazolopyridine-pyridazinone PDE inhibitors developed from ibudilast." *Bioorg. Med. Chem. Lett.* 2011, 21, 3307–12. [doi: <http://dx.doi.org/10.1016/j.bmcl.2011.04.021>]

[3]* K. Ochiai, N. Ando, K. Iwase, T. Kishi, K. Fukuchi, A. Ohinata, H. Zushi, T. Yasue, D. R. Adams, and Y. Kohno "Phosphodiesterase inhibitors. 2: Design, synthesis and structure-activity relationships of dual PDE3/4-inhibitory pyrazolo [1,5-a]pyridines with anti-inflammatory and bronchodilatory activity." *Bioorg. Med. Chem. Lett.* 2011, 21, 5451–46. [doi: <http://dx.doi.org/10.1016/j.bmcl.2011.06.118>]

[4] K. Ochiai, S. Takita, T. Eiraku, A. Kojima, K. Iwase, T. Kishi, K. Fukuchi, T. Yasue, D. R. Adams, R. W. Allcock, Z. Jiang and Y. Kohno "Phosphodiesterase inhibitors. Part 3: Design, synthesis and structure-activity relationships of dual PDE3/4-inhibitory fused bicyclic heteroaromatic-dihydropyridazinones with anti-inflammatory and bronchodilatory activity." *Bioorg. Med. Chem.* 2012, 20, 1644–58. [doi: <http://dx.doi.org/10.1016/j.bmc.2012.01.033>].

[5] K. Ochiai, S. Takita, A. Kojima, T. Eiraku, N. Ando, K. Iwase, T. Kishi, A. Ohinata, Y. Yageta, T. Yasue, D. R. Adams and Y. Kohno "Phosphodiesterase inhibitors. Part 4: Design, synthesis and structure-activity relationships of dual PDE3/4-inhibitory fused bicyclic heteroaromatic-4,4-dimethylpyrazolones." *Bioorg. Med. Chem. Lett.* 2012, 22, 5833–38. [<http://dx.doi.org/10.1016/j.bmcl.2012.07.088>]

[6] K. Ochiai, S. Takita, A. Kojima, T. Eiraku, K. Iwase, T. Kishi, A. Ohinata, Y. Yageta, T. Yasue, D. R. Adams and Y. Kohno "Phosphodiesterase inhibitors. Part 5: Hybrid PDE3/4 inhibitors as dual bronchorelaxant/anti-inflammatory agents for inhaled administration." *Bioorg. Med. Chem. Lett.* 2012, 22, 375–81. [<http://dx.doi.org/10.1016/j.bmcl.2012.08.121>].

Grants

Medical Research Council MRC/G0400053, £1.9m, 1/10/2006, 48 months; Exploration of PDE4 structure and function (PI Houslay, with Adams a named collaborator)

Thera-cAMP (EU FP6/037189), 1/10/2006 – 30/9/2009; Identification of therapeutic molecules to target compartmentalised cAMP signalling networks in human disease (PI Houslay, with Adams a named collaborator)

4. Details of the impact

Current practices for therapeutic management of asthma and chronic obstructive pulmonary disease (COPD) rely heavily on treatment with corticosteroids and β_2 -agonists, the former to control underlying inflammatory dysfunction and the latter to afford symptomatic relief for airway constriction. However, long-term use of corticosteroids can produce adverse side effects, and the safety of long-acting β_2 -agonists is also currently under scrutiny. New safer and effective options for the treatment of respiratory disease are therefore highly significant in their potential societal and economic impact.

To pursue this goal, in 2000 Kyorin entered into an agreement with Scottish Biomedical (SB), a technology management company founded jointly by Scottish Universities in 1994, to set up a PDE biology research facility, the Kyorin-Scotland Research Laboratory (KSRL), with an initial project of £5.2M. Consultancy oversight came from Prof. Miles Houslay (University of Glasgow), one of the foremost authorities in the global PDE biology community, while the medicinal chemistry direction was provided by Adams. KSRL functioned to screen compounds initially provided largely by Adams' medicinal chemistry group and the promising activity of emerging compounds was central to the success of this initial programme, which cemented the Kyorin-SB partnership. According to a senior manager of Scottish Biomedical:

“Prof Adams’ group provided compound series and informed advice on all aspects of the medicinal chemistry associated with the SB/Kyorin project. Prof Adams was one of the academic advisors employed for the original project. His role allowed Kyorin to be confident that the chemistry element of the project was being managed well and that informed advice for the critical decision stages was available. Prof Adams continued to play a vital role in the success of the first PDE project which allowed a follow up project 3 years later. Prof Adams contribution was essential to the success of the PDE programme (that)... helped cement the partnership between Kyorin and SB.”

In July 2002 a second £5.2M project by Kyorin was agreed to extend the KSRL portfolio to development of therapeutics for type 2 diabetes, and the respiratory disease programme was extended for 3 years with a further tranche of funding (£4.5M) from 2003. Adams contributed medicinal chemistry support throughout the period to 2006, eventually assisting SB with the appointment of their own medicinal chemistry team. This completed the transition of SB to a fully independent preclinical drug discovery services company [Text removed for publication].

The Adams group played an important role in establishing the PDE medicinal chemistry research direction for Kyorin, and the success of the work provided the basis for a major PDE drug development programme at Kyorin's central Discovery Research Laboratories from 2004 and through the current REF assessment period, employing 3 chemists and 6 biologists to develop the work begun at HWU. The programme has generated 22 patents (18 published within the current REF assessment period) with a direct link to the foundational work and direction contributed by HWU. A senior manager at Kyorin's Discovery Research Laboratory in Japan stated that:

“The work undertaken at Heriot-Watt University provided a substantive benefit to Kyorin's PDE programme.”

Throughout the current REF period Adams has continued to work with Kyorin, developing a multi-part series of papers to disclose details of the PDE programme and raise the company profile.¹⁻⁶ These papers evince the impact of the work performed in the Adams group in shaping the direction of Kyorin's PDE programme. The success of the PDE programme and establishment of a partnership with SB was also strategically important to Kyorin in establishing a research network and presence in Europe.

There is still considerable scope for bringing new best-in-class PDE4 inhibitors to the market as drugs with improved efficacy and reduced side effect profiles for a range of inflammatory conditions in the respiratory field and beyond. The first PDE4-selective inhibitor to reach the market, roflumilast, was developed by the competitor company, Nycomed. Roflumilast is indicated as a

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treatment for a subset of severe COPD cases and was approved in the EU only in June 2010. It was subsequently also approved by the FDA for use in the US (March 2011). A second PDE4 inhibitor, apremilast from Celgene, will be launched in the near future as treatment for psoriatic arthritis, with predicted annual sales of \$1.5-2bn by 2017. The global market for asthma/COPD drugs, \$38bn pa in 2012, is set to rise to \$47bn pa by 2017 [BCC Research]. Kyorin's own PDE programme therefore remains an important asset in its portfolio of inflammatory and respiratory disease research.

5. Sources to corroborate the impact

A senior manager, SB Drug Discovery

A senior manager, Discovery Research Laboratories, Kyorin Pharmaceutical Co., Ltd.

Press releases from The Scotland Office (09/07/01) and Kyorin Pharmaceutical Co., Ltd (31/07/02).

Newspaper articles from The Sunday Herald (12/11/00 and 01/07/0), The Scotsman (01/08/2002 and 27/11/03) and The Herald (01/08/02).