Institution: University of Glasgow

Unit of Assessment: Unit 5, Biological Sciences

Title of case study: Towards a new, safe, oral treatment for psoriasis and psoriatic arthritis

1. Summary of the impact

Psoriasis is a chronic inflammatory skin disorder affecting up to 2.5% of the world's population, approximately 30% of whom eventually develop psoriatic arthritis, which can lead to debilitating long-term health problems. Current therapies are limited owing to side effects or reductions in efficacy. Prof Miles Houslay, University of Glasgow has performed internationally recognised research on drug targets to alleviate the symptoms of inflammatory skin conditions. Working with Celgene, Houslay identified lead compounds and assays to screen promising early compounds for the treatment of psoriasis and psoriatic arthritis for clinical development. This identified the lead compound (apremilast), which was subsequently developed by Celgene. Between 2010 and 2013, phase III trials on apremilast have validated it as a safe, clinically effective oral drug, on the basis of which apremilast was submitted for regulatory approval of its use in patients with psoriatic arthritis to the health authorities of the USA and Canada in March 2013.

2. Underpinning research

Developing therapeutic drugs that target the cause of disease, rather than its symptoms, requires a comprehensive understanding of the mechanisms of disease development. Over the past 25 years, Professor Miles Houslay has established an internationally recognised centre of research expertise in cell signalling at the University of Glasgow. The work of his group focuses on the identification of new targets in cAMP signalling. cAMP is a messenger molecule that enables cells to communicate and effective targeting of cAMP signalling can lead to the development of anti-inflammatory and anti-cancer therapeutics.

Houslay's group has particular expertise focused on the PDE4 family of cAMP phosphodiesterases (PDE4), which are key regulators of cell signalling and are predominantly expressed in pro-inflammatory and other immune cells.[1] As such, PDE4 proteins play a role in controlling the production of key mediators of inflammation. Selective inhibitors of PDE4 have been shown to have an anti-inflammatory therapeutic effect on diseases such as asthma, psoriasis, rheumatoid arthritis and chronic obstructive pulmonary disease.

Establishing molecular and cellular tools to explore PDE4-targeting drugs

There are four PDE4 genes, *PDE4A*, *PDE4B*, *PDE4C* and *PDE4D*, each of which can produce multiple protein products (isoforms). Houslay was among the first to identify and characterise many of these different isoforms and their occurrence in different cell types.[2,3] Until the early 1990s, PDE4 research had been hampered by the relatively low PDE4 protein levels in human cells and the sensitivity of these proteins to degradation. Between 1994 and 1997, Houslay's team established optimised molecular toolkits to enable the biochemical and pharmacological study of PDE4. This involved collaboration with Graeme Bolger (University of Utah) who worked with the Glasgow team on the molecular cloning and mutagenesis of PDE4 isoforms. This work led to the identification and characterization of new PDE4 isoforms in cell lines[2,3] and the generation of antibodies that could be used to specifically detect and quantify the different PDE4 isoforms in cells.[3]

By applying these techniques, Houslay's team showed that the physiological function of isoforms encoded by the *PDE4A* and *PDE4D* genes is linked to their ability to form complexes with other signalling proteins and move to specific locations within a cell. This established that PDE4-inhibitors have different functional outcomes depending on where in the cell the targeted PDE4 isoforms are located.[2,4,5] By 1996, the Houslay lab had for the first time identified the specific part of any PDE4 isoform that defines its location and activity within a cell, and by determining the structure of this targeting domain revealed how this isoform interacts specifically with its binding partners. A subsequent collaboration with Professor Robert Lefkowitz (Duke University, USA), led to the first demonstration that recruitment to a specific part of the cell by such binding-complexes,

altered the function of a single PDE4D isoform.[5] The research explains why PDE4 selective inhibitors may exhibit different effects, depending on whether they discriminate towards particular PDE4 isoforms; thus the work highlights the therapeutic potential of disrupting the ability of an isoform to move within cells to the particular location that is associated with disease.[1]

Application of molecular tools in research collaboration with industry

In 1997, the University of Glasgow was invited to provide pre-clinical testing and evaluation of drug compounds that were within Celgene's 'Selective Cytokine Inhibitory Drug' (SelCID^{TM}) programme. This research agreement was initiated by the then Chief Scientific Officer at Celgene, who approached Houslay after Celgene had observed that key compounds that had been tested as anti-cancer drugs showed a PDE4-inhibitory activity and had anti-inflammatory potential.

Between 1997 and 2004, Celgene provided Houslay with £747,300 in research funding for the testing of Celgene's patented compounds. The programme exploited a key set of assays that Houslay's laboratory had developed. This enabled Houslay's team to evaluate inhibitor activity in a broad range of PDE4 isoforms, each having distinct cellular location and interactions (and thus functions), and in several pro-inflammatory immune cells, which are core to inflammatory responses in the body.[6] By the end of 2004, these assays had led to the identification by Houslay and Celgene of a compound (CC-10004, also known as apremilast) that met requirements of a strong potential lead drug for development. The specific assays that were developed by Houslay and were crucial for the success of this screening are unpublished owing to commercial confidentiality and cannot be described in detail here. However, among the assays that were developed by the University of Glasgow were those that Celgene published in retrospect to justify the early development of apremilast based on its PDE4-dependent activities.[7]

Key University of Glasgow researchers: Miles Houslay (Gardiner Chair of Biochemistry, University of Glasgow 1984-2011); Dr Ian McPhee (Postdoctoral Research Associate, 1994-2001); Dr Elaine Huston (Research Fellow, 1995-present); Dr George Baillie (Postdoctoral Research Assistant, 1995-2007); Dr Malcolm Shepherd (Clinical Lecturer, 2002-2008). ***Key external collaborators:*** Dr Graeme Bolger (Assistant Professor, University of Utah, USA)[2,3]; Professor Robert Lefkowitz (Professor of Biochemistry and Chemistry, Duke University Medical Centre, USA)[5]; Dr Peter Schafer (Senior Principle Investigator, Celgene Corporation, USA) – the collaborating industrial partner within Celgene[7].

3. References to the research

1. Houslay, M.D., Schafer, P. & Zhang, K. (2005). Keynote Review: Phosphodiesterase-4 as a therapeutic target. *Drug Discov Today* **10**, 1503-1519 [doi: 10.1016/S1359-6446(05)03622-6]
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7. Schafer, P.H., Parton, A., Gandhi, A.K., Capone, L., Adams, M., Wu, L., Bartlett, J.B., Loveland, M.A., Gilhar, A., Cheung, Y.F., Baillie, G.S., Houslay, M.D., Man, H.W., Muller, G.W., Stirling, D.I. (2010) Apremilast, a cAMP phosphodiesterase-4 inhibitor, demonstrates anti-inflammatory activity *in vitro* and in a model of psoriasis. *Br. J. Pharmacol*. **159**, 842-855 [doi: 10.1111/j.1476-5381.2009.00559.x.]

Grant funding:
Analysis of novel inhibitors of cyclic AMP phosphodiesterases. (1997-2002) Celgene Corp. £747,300 to Miles Houslay (#23184/1-5)

4. Details of the impact

In 2010, the market for psoriasis treatments alone was valued at $3.9 billion. Current first-line treatments, including analgesics, oral non-steroidal anti-inflammatory drugs and topical steroid creams, are aimed at symptomatic relief of pain or swelling, but these are often short-term measures. As management of psoriasis and psoriatic arthritis is a long-term issue, several disease-modifying anti-rheumatic drugs that suppress either growth of new skin cells or inflammation have been developed. However, these are often associated with organ toxicity and other side effects. Many last resort drugs for patients who don't respond to the above therapies require weekly injections and are associated with partial response or non-response in half of all patients.

Houslay's research established a detailed understanding of molecular components of PDE4-dependent cell signalling, which enabled the identification of highly resolved molecular targets by drug development programmes aimed at anti-inflammatory therapeutics. This was recognised by Celgene, who engaged Houslay as a consultant at the outset of their PDE4 inhibitor programme. Houslay's major contribution was recognized by a Senior Principal Investigator overseeing apremilast at Celgene Corporation:

> *"Because of his laboratory's capabilities at U. Glasgow at that time, and his technical expertise in the area of PDE4 molecular biology, Miles was able to help us evaluate the biochemical and pharmacological properties of our leading compounds. His findings and advice helped us to select CC-10004 (apremilast) for preclinical development."* [a]

With this crucial contribution of Houslay, Celgene was able to proceed to clinical studies of apremilast as an oral anti-inflammatory therapy for psoriatic arthritis and psoriasis. These have been taken from early phase I trials in 2003 through to phase III clinical trials between 2010 and 2013. The phase III trials PALACE 1–PALACE 4 (2010-2013) involved patients with psoriatic arthritis, whereas the phase III trials ESTEEM 1 and ESTEEM 2 (2010-2012) focused on patients with psoriasis.

The four phase III clinical trials that involved patients with psoriatic arthritis (more than 2,000 patients in total) aimed to meet a primary clinical endpoint of a 20% improvement of tender or swollen joints, as assessed by both the patient and the physician.[b,c,d] In July 2012, it was reported that up to 50.8% of the 495 patients that had been treated with apremilast in PALACE 1 achieved the primary endpoint by 16 weeks (and maintained at week 24), compared with 19% for those taking a placebo.[b] In June 2013, the 52 week long-term data showed continued improvement in signs and symptoms in about 60% of patients.[e] The primary clinical endpoint has also been met by the trials ESTEEM 1 and ESTEEM 2, which involved 1,250 patients with psoriasis[f]. In ESTEEM 1, psoriasis area and severity were reduced by 75% over 16 weeks in 33.1% of Apremilast-treated patients compared with 5.3% of placebo patients.[g] Crucially, the side-effects of apremilast were mild to moderate, with no serious adverse events.

Based on the combined data from PALACE 1, PALACE 2 and PALACE 3, applications for the approval of apremilast as a treatment in psoriatic arthritis were submitted to health regulatory authorities in the USA and Canada in March 2013.[g] By the end of 2013, further submissions to health authorities in the USA, and in Europe are expected to seek regulatory approval of apremilast for moderate-to-severe plaque psoriasis and for psoriatic arthritis and psoriasis,

respectively.[h]

Without Houslay's research at the University of Glasgow, it would not have been possible to select apremilast as an initial hit compound, and thus develop into a potential oral drug for psoriasis and psoriatic arthritis. This fact was formally recognised by Celgene in January 2013, when Houslay was inducted into Celgene's Joshua Lederberg Society:

> *'Membership to the Society is extended to external collaborators who have had a relationship with Celgene for greater than five years and whose work has changed the practice of medicine...Because of Miles' invaluable contributions to the field of understanding PDE4 inhibition at the molecular and cellular level, and his key advisory role in the selection and preclinical development of Apremilast, he was honored as one of the few external inductees into the Society.'*[a]

5. Sources to corroborate the impact

a. Statement provided by the Senior Principal Investigator, Translational Development, Celgene Corporation; available on request.
b. Oral Apremilast Achieves Statistical Significance for the Primary Endpoint of ACR20 in the First Phase III Study (PALACE-1) in Patients with Psoriatic Arthritis. Press release by Celgene Corporation.
c. Apremilast Palace Program Demonstrates Robust and Consistent Statistically Significant Clinical Benefit Across Three Pivotal Phase III Studies (PALACE 1, PALACE 2 and PALACE 3). Press release by Celgene Corporation.
d. Apremilast Achieves Statistical Significance for the Primary and Major Secondary Endpoints in Fourth Pivotal Phase III Study (PALACE 4). Press release by Celgene Corporation.
e. Signs and Symptoms of Psoriatic Arthritis Significantly Improved in Patients Receiving Long-Term Oral Apremilast Treatment in Phase III Study (PALACE 1). Press release by Celgene Corporation.
f. Apremilast ESTEEM Program Meets Primary and Major Secondary Endpoint in Pivotal Phase III Psoriasis Trials. Press release by Celgene Corporation.
g. Oral Apremilast Achieves Statistical Significance for the Primary Endpoint of PASI-75 in the First Phase III Study (ESTEEM 1) in Patients with Psoriasis. Press release by Celgene Corporation.
h. Celgene Reports First Quarter 2013 Operating and Financial Results. Press release by Celgene Corporation.