Institution: University of Warwick

Unit of Assessment: B8 Chemistry

Title of case study: An anti-inflammatory molecule for the pharmaceutical industry

1. Summary of the impact

A new anti-inflammatory molecule FX125L was developed by David Fox at Warwick, in collaboration with David Grainger (Department of Medicine, Cambridge) and Funxional Therapeutics Ltd (FXT). Research in lead optimization, mechanistic preclinical chemistry, synthetic route development (for scale-up), and CMC (chemistry, manufacturing and controls) was conducted at Warwick. As a result FX125L completed Phase 1 and entered Phase 2 clinical trials in humans for the treatment of asthma or other inflammatory diseases. Its sale to Boehringer Ingelheim generated a multi-million pound return for FXT and its investors.

2. Underpinning research

Warwick research has underpinned the development of a potent anti-inflammatory drug for oral administration in a disease area where, according Transparency Market Research (2013) the market will reach $27Bn in 2017. This includes a wide range of disorders including asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, inflammatory bowel disease, psoriasis and acne.

Beginning in 2006, Dr David Fox (Assistant then Associate Professor at Warwick) worked with 'biotech' SME Funxional Therapeutics Ltd to identify and develop a lead clinical candidate from a *ca* 150 molecule library of Broad-Spectrum Chemokine Inhibitors (BSCIs) for the treatment of inflammatory disease. Fox had previously synthesised these compounds in Cambridge (Fox *et al., J. Med. Chem*. **2009**, *52*, 3591). Significant funding to support the Warwick work (£411K) came from FXT, supporting four PhD students (alongside university funding) and two research assistants. On the basis of biological data from the research group of David Grainger (Department of Medicine, Cambridge and FXT), an analysis of the IP position and an assessment of synthetic tractability, Fox created a short list of compounds. Fox and his research team determined structure activity relationships within the library and added a further *ca* 150 pure compounds made at Warwick, evaluating the particular advantages and disadvantages of various substructures (e.g. lactam ring size and side chain branching) [1]. The short-listed molecules were tested in collaboration with Funxional Therapeutics in a range of preclinical experiments to determine their ADMET (absorption, distribution, metabolism, excretion and toxicity) properties and *in vitro* and *in vivo* efficacy. Fox and Grainger analysed these results and two potential candidates were selected; FX97L and FX125L. While both compounds contained the same 2,2-dimethylpropionylamino sidechain, Fox developed at Warwick a new and highly efficient one-pot, three step synthesis of the piperidinone FX125L as a single enantiomer. This was a far easier process than that required for the synthesis of the enantiomerically pure seven-membered ring of FX97L and was subsequently taken forward. The results of all this research were published as a highly detailed patent incorporating extensive data [1]. While the structure of the chemical compound that is FX125L has thus been published, it has not been explicitly labelled as such for reasons of commercial sensitivity and in accord to the wishes of Funxional Therapeutics Ltd.

The identification of FX125L as a potential anti-inflammatory clinical candidate prompted Fox and group to design and synthesise new classes of both arylcarbonylamino- and arylsulfonylamino-lactams as back-up drug candidates. Various arene substitution patterns were investigated including fluoro and trifluoromethyl substitutions, and various of the compounds were found to have potencies in an *in vitro* cell migration assay equivalent or better than FX125L (in collaboration with Grainger). Two patent applications concerning the use of these compounds as anti-inflammatory agents have been published [2,3].

The proposal from Grainger that the biological target of BSCIs is the somatostatin G protein coupled receptor SSTR2, prompted Fox and group to design and synthesise hybrid lactam containing compounds and traditional non-lactam SSTR2 agonists and antagonists [4]. This resulted in development of a 'split binding' or allosteric model for the active site of SSTR2 (i.e. that both somatostatin and FX125L can induce receptor signalling). It was also determined that some non-lactam derivatives can act as cell migration inhibitors [4]. This research suggests that the biochemistry of somatostain is far more complex than previously thought. The activity of these peptide analogues (i.e. that both series act as BSCIs) strongly supported the first-in-class status of FX125L, boosting investor confidence (Section 4).

3. References to the research

[1] D. J. Grainger (Cambridge) and D. J. Fox (Coventry), *Anti-inflammatory composition comprising 3-(2',2'-dimethylpropanoylamino)-tetrahydropyridin-2-one* US200900364862009, priority date 02 Aug 2007, http://www.google.com/patents/US20090036486.
This compound selection patent presents a great deal of detailed information as required by patent granting bodies (here the USPTO) in order to allow protection of a specific compound that was included within a previous patent application without being synthesised. This class of patent application comes under extremely close scrutiny as it effectively extends the patent coverage for the compound. It was granted because the specific named compound *3-(2',2'-dimethylpropanoylamino)-tetrahydropyridin-2-one* possesses unexpected and non-obviously-predictable, highly desirable pharmaceutical properties that other members of the general class do not. This work will be re-published in a journal once the structure can be revealed.

[2] D. J. Grainger (Cambridge) and D. J. Fox (Coventry), *Anti-inflammatory agents* WO 2011154696 2011, priority date 08 June 2010. http://www.google.com/patents/WO2011154696A1.
This patent describes the use of arenecarbonylamino-lactams as 'back-up' compounds for FX125L some of which are even more potent than FX125L but are further behind in clinical development.

[3] D. J. Grainger (Cambridge) and D. J. Fox (Coventry), *Anti-inflammatory agents* WO 2011154695 2011, priority date 08 Jun 2010, http://www.google.com/patents/WO2011154695A1.
This patent describes the use of arenesulfonylamino-lactams as 'back-up' compounds for FX125L some of which are even more potent than FX125L but are further behind in clinical development.

[4] Royall, Sophie C. (**2012**) *Anti-inflammatory SSTR2 ligands*. PhD thesis, University of Warwick. http://wrap.warwick.ac.uk/51776/.
Once necessary IP restrictions are lifted – see ref [1] – publications will follow.

4. Details of the impact

During the EPSRC's 2009 Chemistry International Review, a senior officer of the Index Ventures-backed company Funxional Therapeutics Ltd with a substantial track record in the 'biotech' industry described the company's interaction with Fox at Warwick as "the life-blood of FXT" [5]. In the period 2006-13 the Fox group at Warwick has been the *de facto* chemistry group for FXT and was involved in all aspects of medicinal chemistry and biological investigation; exploratory synthesis, lead-optimisation, compound selection and preclinical chemical development [6]. The identification of FX125L as the lead candidate, underpinned by the continuing confidence borne of the medicinal and biological mechanism research at Warwick [1-4] led to FXT's decision to push FX125L into clinical trials [5,7] and, "made the key chemistry contribution to the success of this programme" [6].

In 2008 Fox acted on behalf of FXT as lead chemistry consultant for the synthesis of multiple kilograms of FX125L. The synthetic route developed at Warwick (see Section 2) was transferred to a contract research organisation employed by FXT. Fox subsequently provided the scientific direction and substantial new experimental input, and, "convincingly solved several problems that emerged during scale-up" [6] including unwanted racemisation and the suspected crystallisation of

FX125L as different polymorphs. As part of the consultancy, analytical standards were also developed at Warwick to test the long-term chemical and stereochemical stability of FX125L [5].
A second Funxional Therapeutics senior officer states that, "the underpinning work commissioned by FXT at Warwick was used in the initiation of clinical trials," and following the FDA approved Investigational New Drug (IND) application of FX125L for the treatment of asthma (January 2009) and access to large quantities of pure FX125L from the Warwick route, Phase 1 trials were started [8]. Studies in an animal model of allergic asthma quickly showed that FX125L exhibits a superior efficacy profile to dexamethasone or montelucast [9].

As part of Phase 1 trials, 66 healthy participants in the USA received a wide range of doses (0.03 mg to 3 g of FX125L), and the study was completed in July 2009. FX125L was safe and well tolerated at all dose levels. No serious adverse events or patient withdrawal were observed [10]. The pharmacokinetic profile of FX125L was linear over the wide range of doses studied, which led to the development of a convenient once-daily oral dosing regimen. "The results in humans are consistent with the preclinical data, suggesting that FX125L has a very wide safety margin, and confirmed the excellent drug-like profile of FX125L" [8].

In January 2010 a second Phase 1 study in which US patients received multiple ascending doses was completed and the results were "entirely consistent with those of the single dose study and confirmed the excellent drug-like profile of FX125L" [11].

Phase 2 clinical trials studying the effects of FX125L on asthma, COPD, rheumatoid arthritis and psoriasis were announced [11] and in May 2010, FXT reported that it had raised €10M in a private Series B financing round to fund these initial Phase 2 clinical studies in inflammatory disease [12].

FXT have stated that as a result of the underpinning Warwick research "FX125L has optimal CMC (chemistry, manufacturing and controls) characteristics and is obtained by a straightforward 3-step chemical synthesis with an extremely low cost of goods" [5,7]. In addition FX125L was described as an "ideal pharmaceutical" by potential large pharmaceutical firm investors [5]. The collaboration with Warwick was therefore vital for the success of Phase 1 clinical trials and the continuing funding and progress of Phase 2 trials [5,6].

In July 2012 Boehringer Ingelheim and Funxional Therapeutics announced acquisition by the former of FX125L and the somatotaxin portfolio to treat inflammation. This sale generated an undisclosed multi-million pound return for FXT and its investors [13]. "The confidence that Funxional was thereby able to create in the synthetic route and analytical standards, alongside the novel and highly favourable performance of the drug, underpinned BI's decision to acquire FX125L and the somatotaxin portfolio" [6].

The Warwick research thus provided the synthetic and medicinal chemistry that allowed phase 1 and phase 2 clinical trials in humans and underpinned investor confidence. This led to substantial economic impact in the pharmaceutical industry and will lead to important health impacts in a disease area that affects the majority of families. The success of FX125L and the identification of the SSTR2 as its molecular target has led to Index Ventures employment of Fox as their lead medicinal chemist in their new biotech companies E3Bio Ltd and Purple Pharmaceuticals Ltd [5].

5. Sources to corroborate the impact

[5] Senior officer #1, Funxional Therapeutics Ltd; statement 23 Sept 2013.

[6] Senior officer #2, Funxional Therapeutics Ltd; statement 25 Sept 2013.

[7] Funxional Therapeutics Ltd website on FX125L, web link, retrieved 20 June 2013.

[8] Funxional Therapeutics Ltd press release 08 July 2009, web link.

[9] *FX125L, a novel small molecule chemokine inhibitor, attenuates neutrophil accumulation in a model of allergic asthma and exhibits a superior efficacy profile to dexamethasone or monteleukast*, J. Reckless, V. Piercy, K. Langley, I. Purvis, D. Fox, D. Grainger, *Allergy*, 64 (s90), 539-550, DOI: 10.1111/j.1398-9995.2009.02077.x.

[10] *First clinical experience with FX125L, an anti-inflammatory oral small molecule with an entirely novel mechanism of action*, P. Wieser, R. Cooper, L. Wang-Smith, J. Reckless, K.J. Champion, V. Petrolese, D. Grainger, *Ann. Allergy Asthma Immunol.* 2009; 103[5] [suppl 3]: abstract 5] http://dx.doi.org/10.1016/S1081-1206(10)60675-8

[11] Funxional Therapeutics Ltd press release 08 Jan 2010, web link.

[12] Funxional Therapeutics Ltd press release 26 May 2010, web link.

[13] Funxional Therapeutics Ltd/Boehringer Ingelheim press release 23 July 2012, web link.