Institution: The Institute of Cancer Research

Unit of Assessment: UoA5

Title of case study: Establishing the spin out company Domainex to exploit novel protein expression technology

1. Summary of the impact

The Institute of Cancer Research (ICR) founded the spin out company Domainex in 2002 in collaboration with UCL and Birkbeck. The company was set up on the basis of novel research into the expression of soluble protein domains to provide services to a range of bioscience-based companies. Within the period 2008-2013, Domainex has established profitability and positioned itself as a successful company employing over 30 scientists at its laboratories in Cambridge. It has established programmes and contracts with over 20 international clients in medicinal chemistry, drug discovery, monoclonal antibody development and agrochemical science, making a major commercial impact in all these fields.

2. Underpinning research

Early in 1999, Professor Laurence Pearl, who was then at UCL, initiated a research project to identify and express soluble protein domains derived from full-length protein macromolecules in order to facilitate drug discovery and other applications. In July 1999, following the appointment of Pearl (ICR Faculty, 1999-2010) and his UCL colleague Dr Chris Prodromou (ICR Senior Staff Scientist, 1999-2010) to the ICR, their research team took the lead in progressing the protein domain project in collaboration with Professor Paul Driscoll of UCL and Dr Renos Savva of Birkbeck. Throughout, Pearl led the project and most of the research work was conducted at the ICR.

The exploitation of potential new protein targets – for drug and vaccine development, for the development of novel agrochemicals and for the generation of new monoclonal antibodies – usually requires sizeable quantities of soluble proteins for high-throughput screening and structure-based development. However, in many cases, recombinant expression of full-length proteins is problematic, and identification of soluble subconstructs is a slow trial and error process that is often unsuccessful.

The Pearl team developed a fast and effective, high-throughput approach for the identification of soluble protein domains, which they named combinatorial domain hunting (CDH) (Ref 1). In essence, CDH combines a method for the production of unbiased, finely-sampled gene-fragment libraries with a screening protocol that provides 'holistic' readouts of solubility, ligand binding and yield for thousands of protein fragments.

To further the technological development and commercial exploitation of CDH, the ICR founded a spin out company, Domainex, in 2002, in partnership with UCL and Birkbeck and with Pearl as Chief Scientific Officer of the company. Under the leadership of Pearl, the academic research teams continued to work with Domainex to develop the technology further and to facilitate service contracts.

The first CDH proof of principle study was carried out using a multidomain protein, the p85α subunit of class I PI3 kinase. Research over many years by a number of international teams had empirically defined the domain architecture of this protein. In contrast, with CDH it took less than twelve months to successfully identify stable, soluble and highly expressed protein segments encapsulating the known domains (Ref 2). Similarly, using the CDH approach, the Pearl team was able to study another target which was historically difficult to express, human MEK-1. They identified a fragment which covers the kinase domain of MEK-1 and expresses and crystallises significantly better than designed expression constructs. The crystal structure of this fragment was reported, explaining some of its superior properties (Ref 3).

The CDH technology has been developed further by the Pearl team working with their Domainex

partners, resulting in the publication of the 'CDH squared' method. This method addresses the additional structural complexity of protein-protein interactions, enabling the rapid elucidation of stable protein-protein core complexes. The HSP90/CDC37 complex was used as a first proof of principle of this new technique (Ref 4). The research began at ICR, but was completed after Pearl and Prodromou had relocated to the University of Sussex.

3. References to the research

All ICR authors are in bold and ICR team leaders/Faculty are in bold and underlined.

1. Patent: Publication No: WO/2003/040391. 2003, International application No: PCT/GB2002/005075. Method for producing and identifying soluble protein domains. Inventors: McAlister, Savva, **Pearl, Prodromou,** Driscoll. Applicants: ICR, UCL, Birkbeck, and the inventors. Granted in Europe, Japan and Canada. (http://patentscope.wipo.int/search/en/WO2003040391)
2. Reich S, Puckey LH, Cheetham CL, Harris R, Ali AAE, Bhattacharyya U, Maclagan K, Powell KA, **Prodromou C, Pearl LH**, Driscoll PC, Savva R. 2006, Combinatorial Domain Hunting: An effective approach for the identification of soluble protein domains adaptable to high-throughput applications. Protein Sci. 15 (10), 2356-2365. (http://dx.doi.org/10.1110/ps.062082606)
3. Meier C, Brookings DC, Ceska TA, Doyle C, Gong H, McMillan D, Saville GP, Mushtaq A, Knight D, Reich S, **Pearl LH**, Powell KA, Savva R, Allen RA. 2012, Engineering human MEK-1 for structural studies: A case study of combinatorial domain hunting. J Struct Biol. 177 (2), 329-334. (http://dx.doi.org/10.1016/j.jsb.2012.01.002)
4. Maclagan K, Tommasi R, Laurine E, **Prodromou C**, Driscoll PC, **Pearl LH**, Reich S, Savva R. 2011, A combinatorial method to enable detailed investigation of protein-protein interactions. Future Med Chem. 3 (3), 271-282. (http://dx.doi.org/10.4155/fmc.10.289)

4. Details of the impact

The formation of Domainex has had a strong commercial impact worldwide across a number areas, including drug discovery, monoclonal antibody production and agrochemical development.

The invention of combinatorial domain hunting (CDH) by the Pearl team at the ICR, involving collaborating scientists from UCL and Birkbeck, represents a major breakthrough in protein biology. Before this it was extremely difficult, if not sometimes impossible, to produce soluble quantities of many natural proteins. Drug discovery, vaccine development, monoclonal antibody production and agrochemical development depend on high throughput screening combined with structural biology, and these approaches are not possible without large quantities of soluble protein. The three founding institutions decided that the best way to make an impact with CDH would be to form a start up company to exploit CDH commercially as a service to science-based companies worldwide. On this premise, the company Domainex was established in 2002 with Pearl as Chief Scientific Officer and a non-executive directorship was held by the ICR, representing the three founding institutions.

On the basis of the underpinning research studies by teams led by Pearl, proof of concept of the application of CDH to intractable proteins of commercial biotechnological interest has subsequently been established. Domainex has made significant advances, particularly in the impact period, 2008 onwards. Domainex has raised around £5 million in investment finance (£4 million post 2008) and has expanded such that it now employs over 30 people at its premises in Cambridge [1]. In 2008, Domainex' services business became profitable and it continues to do so today.

Domainex uses its CDH technology on projects paid for by a wide range of international clients, and since 2008 over 20 collaborations have been successfully completed. Drug discovery is the usual objective of these collaborative projects, but there have also been monoclonal antibody development and agrochemical projects. At least one of the CDH drug discovery projects that

Domainex has serviced reached the clinical trials stage of development by 2013 [2]. Most of these collaborations are not in the public domain for reasons of commercial confidentiality. Collaborators Domainex has worked with since 2008 that can be publically disclosed are UCB Pharma Ltd (UCB), Ark and Pharmidex. Domainex' clients come from the US, Europe and Japan.

Domainex' collaboration with UCB was one of its early commercial CDH projects. This led to successful engineering of human MEK-1 and the work has now been published (Research Ref 3 above).

Domainex now offers medicinal chemistry services as well as CDH. Three medicinal chemistry programmes in which Domainex has been engaged have resulted in compounds that are now in clinical trial and two other programmes are at the pre-clinical stage. Published examples of the work of Domainex using its innovative chemistry are Robinson et al. [3] and Jarvis et al. [4].

Domainex has its own in-house drug discovery programmes based around the CDH discovery and its long term objective is to grow this aspect to add value to the company. Currently, Domainex has support from the government through the Technology Strategy Board (TSB) for these programmes [5]. One in-house drug discovery programme that has used CDH is the collaboration with the ICR on developing inhibitors of IKKε [6]. The current status is that the lead chemical series is in the late lead optimisation phase and work is progressing towards identifying a pre-clinical candidate. Domainex is also collaborating with the ICR and the University of Sussex on a programme to develop inhibitors of tankyrase [7, 8]. This programme has been the successful recipient of two Wellcome Trust Seeding Drug Discovery awards totalling nearly £8 million. Pre-clinical candidates have now been developed and are being actively commercialised [9].

Domainex' success has merited a number of awards, including the Innovation in Enabling Biotechnology Prize at the UKTI Bioentrepreneurial Company of the Year Awards (2009) and the 2010 Genesis Life Science Innovation and Enterprise Programme of the Year Award.

5. Sources to corroborate the impact

[1]. http://www.domainex.co.uk/news_article_070311.asp

[2]. CEO of Domainex (Identifier 1)

[3]. Robinson C et al. 2011, Future Med Chem 3 (13), 1567-1570 (http://dx.doi.org/10.4155/fmc.11.107)

[4]. Jarvis et al. 2010, J Med Chem 53 (5), 2215-2226 (http://dx.doi.org/10.1021/jm901755g).

[5]. http://www.obn.org.uk/obn_/news_item.php?r=PKICV2429901

[6]. Patent WO/2013/024282. Filing date: 14 Aug 2012. Inventors Newton, G, Perrior, T. **Ashworth, A**. and **Lord, C**. Inhibitor or down-regulator of the expression of one or both of TBK1 IKK-epsilon for use in the treatment of PI3kinase dependent cancer. (http://patentscope.wipo.int/search/en/WO2013024282)

[7]. http://www.domainex.co.uk/news2009.asp

[8]. Patent: Publication No: WO/2013/132253. 3-aryl-5-substituted-isoquinoline-1-one compounds and their therapeutic use. Applicant: ICR. Inventors: **Ashworth**, **Lord**, **Elliott**, **Niculescu-Duvaz**, Porter, Boffey, Bayford, Firth-Clark, Jarvis, Perrior, Key. (http://patentscope.wipo.int/search/en/WO2013132253)

[9]. http://www.icr.ac.uk/enterprise/opportunities_navon/index.shtml