**Institution:** Imperial College London

**Unit of Assessment:** 5 Biological Sciences

**Title of case study**: 4 - Overcoming a major bottleneck in structural biology: the development and commercialization of innovative membrane protein crystallization screens

**1. Summary of the impact** (indicative maximum 100 words)

Research carried out within Imperial's Life Sciences department led to a collection of new kit solutions to screen the crystallisation conditions of various membrane proteins. These screens were exclusively commercialized by Molecular Dimensions, a UK company, in 2002, 2003 and 2008 under license from Imperial College London. They are the primary screening kit in membrane protein crystallization that is commercially available. These screens have helped to screen the crystallization conditions of a wide range of membrane proteins, leading to many new structures. Molecular Dimensions has sold [text removed for publication] screens, worth more than [text removed for publication], to both academia and industry all over the world.

**2. Underpinning research** (indicative maximum 500 words)

The results of genome sequencing projects have shown that up to 30% of human proteins occur in cell membranes. Membrane proteins play crucial roles in many biological functions, including the capture of energy from sunlight by plants, the use of energy in cells, and the movement of molecules across cell membranes. They are particularly important in medicine, since over 50% of commercially available drugs (such as antihistamines, beta blockers, antipsychotic drugs, morphine) target membrane proteins. We need to understand membrane protein structures to provide a basic understanding of life at the molecular level and for computer-aided rational design of new drugs, which could reduce the number of animal experiments and unwanted side effects. X-ray crystallography is currently the most successful method for determining the three-dimensional structure of membrane proteins. To determine medically relevant membrane protein structures more efficiently, we have established the Membrane Protein Laboratory at the UK synchrotron radiation facility, the Diamond Light Source, as an Imperial College outstation by combining recently developed high throughput technologies for protein crystallisation and the state-of-the-art X-ray diffraction data collection system. Nevertheless, growing the crystals required for this technique remains as one of the major bottlenecks in this area of structural biology. This is especially true for membrane proteins that are of particular interest due to their medical relevance.

To address this problem, a team of Imperial scientists, Dr. Simon Newstead, Dr. Sebastian Ferrandon and Dr. Elizabeth Carpenter, under the supervision of Prof. Iwata, has undertaken a detailed analysis of the crystallization conditions from all membrane protein structures deposited in the Protein Data Bank (PDB). The PDB contains the information, including crystallization conditions, for all published protein-structures. Recent research successes have significantly increased the numbers of high-resolution membrane protein structures using X-ray crystallography. A sufficient amount of data is now available in the PDB on successful membrane protein crystallization to allow the rational design of a more specific crystallization screen. With this aim in mind, we constructed a database of crystallization information of membrane proteins that were crystallized using the vapor diffusion technique, the most commonly used method for initial crystal screening. This information has been analyzed so that the success of different parameters can be easily compared for different membrane protein families. Main parameters, which we found critical for successful crystallisation, are detergent selection, types of precipitant, types of buffers and pH ranges, types and concentrations of salts and additives. Based on this analysis, we created a

series of new screening solution kits for membrane protein crystallization [1,2].

Imperial College and Molecular Dimensions collaborated closely to commercialize the screens MemStart (2002), MemSys (2003), MemGold (2008) and MemPlus (2008) under license from Imperial College. Dr Jeanette Hobbs and Mrs Davina Jordan from Molecular Dimensions also played a crucial role for the commercialization of these products. Today, these screens are widely used in membrane protein crystallization. Many membrane protein structures have now been solved using these products (for example, [3-6]).

**Dates of when the research was carried out:** 2007-2008

**Key researchers and their positions held:**

- Dr Simon Newstead - Imperial College London, Research Associate (2004-2009)
- Sebastian Ferrandon - Imperial College London, Research Associate (2004-2006)
- Dr. Elizabeth Carpenter - Imperial College London, X-Ray Facility Manager (2002-2005), CSB Structural Biology Facilities Manager (2005-2007), Facility coordinator at Diamond-MPL (2007-2009).
- Prof. So Iwata - Imperial College London, Chair of Membrane Protein Crystallography (2000-2007), David Blow Chair of Biophysics (2007-present)
- Dr Jeanette Hobbs – Molecular Dimensions, Sales Director/ Research Investigator (2007-present)
- Davina Jordan – Molecular Dimensions, Sales/Research Investigator (2005-2008)

**3. References to the research** (* References that best indicate quality of underpinning research)


[1] *Newstead S., Ferrandon S,. Iwata S., '*Rationalizing α-helical membrane protein crystallization'*, Protein Sci., 17:466-472 (2008). DOI, **Times cited: 35** (WoS, 20/6/13)

[2] *Newstead S, Hobbs J., Jordan D.,Carpenter E., Iwata S., '*Insights into outer membrane protein crystallisation*', Molecular Membrane Biology, 25(8) :631-638 (2008). DOI, **Times cited: 4** (WoS, 23/4/13)

[3] *Newstead, S., Drew, D., Cameron, A.D., Postis, V.L., Xia, X., Fowler, P.W., Ingram, J.C., Carpenter, E.P., Sansom, M.S., McPherson, M.J., Baldwin, S.A., Iwata, S., '*Crystal structure of a prokaryotic homologue of the mammalian oligopeptide-proton symporters, PepT1 and PepT2'*, EMBO Journal, 30: 417 - 426 (2011). DOI, **Times cited: 36** (WoS, 20/6/13)

[4] Hino, T., Matsumoto, Y., Nagano, S., Sugimoto, H., Fukumori, Y., Murata, T., Iwata, S., Shiro, Y. '*Structural Basis of Biological $N_2O$ Generation by Bacterial Nitric Oxide Reductase*', Science, 330:1666-1670 (2010). DOI, **Times cited: 44** (WoS 20/6/13)

[5] Hino, T., Arakawa, T, Iwanari, H., Yurugi-Kobayashi, T., Ikeda-Suno, C., Nakada-Nakura, Y., Kusano-Arai, O., Weyand, S., Shimamura, T., Nomura, N., Cameron, A.D., Kobayashi, T., Hamakubo, T., Iwata, S., Murata, T., '*G-protein-coupled receptor inactivation by an allosteric inverse-agonist antibody*', Nature 482: 237-240 (2012). DOI, **Times cited: 30** (WoS 20/6/13).

[6] Weyand, S., Shimamura, T., Yajima, S., Suzuki, S., Mirza, O., Krusong, K., Carpenter, E.P., Rutherford, N.G., Hadden, J.M., O'Reilly, J., Ma, P., Saidijam, M., Patching, S.G., Hope, R.J., Norbertczak, H.T., Roach, P.C.J., Iwata, S., Henderson, P.J.F., Cameron, A.D., '*Structure and Molecular Mechanism of a Nucleobase–Cation–Symport-1 Family Transporter'*, Science 322:709-713 (2008). DOI, **Times cited: 132** (WoS, 24/6/13)



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- BBSRC, BBS/B/14418, "The Membrane Protein Structure Initiative (Mpsi)", £504,122, 01/07/2004-30/04/10, (via University of Glasgow) PI: Prof NW Isaacs

- Wellcome Trust, 079209/Z06/Z, "Membrane Protein Laboratory at Diamond", £1,665,063, 01/04/2006-28/02/2010, PI: Prof S Iwata.
- European Commission PF6 "European Membrane Protein Consortium (E-MEP)", £530,834 (£109,663 to Dept. of Medicine), 01/03/2004-31/10/2009, PI: Prof S Iwata (Coordinated by Aston University), CoI: N Chayen (Dept. of Medicine).

**4. Details of the impact** (indicative maximum 750 words)

**Dissemination of the impact**

From the research highlighted in section 2, Prof. Iwata's team was able to present a collection of new crystallization screening kits; MemStart, MemSys, MemGold and MemPlus. These kits were exclusively commercialized by UK company Molecular Dimensions between 2002 and 2008, via Imperial Innovations, under license from Imperial College [A]. They were some of the first screens available to the research community and are now *"widely acknowledged as the gold standard as the starting point for membrane protein crystal growth*" [A].

**The nature of the impact**

The current screens sold by Molecular Dimensions, underpinned by Imperial research, are MemStart, MemSys, MemGold, and MemPlus, which range from between £75 to £300 per unit [B, C]. [text removed for publication]. Managing Director of Molecular Dimensions, Tony Savill, stated that "*the impact [of the solution kits] is not only manifested in sales but also in our ability to attract other collaborators with methods that can be commercialised and thus serve to continually build on the range of products we can offer for membrane protein research*" [B].

These products have been sold to many industrial organisations and academic institutions across the world (see the beneficiaries section for the names). This research has benefited the whole scientific community in the field of membrane protein structural biology at worldwide scale, and Molecular Dimensions benefitted financially with the exclusive commercialization of the screens. Savill adds that "*the research carried out by So Iwata's group and the successes they have achieved is followed in the literature all over the world and other membrane protein research scientists are eager to use their successful methods. It has led to Molecular Dimensions being recognised as the leading company in providing new products for this challenging sector*" [B].

**Beneficiaries**

Molecular Dimensions is the main disseminator of the product, and consequently the first beneficiary. With the exclusive commercialization of the screens, Molecular Dimensions is being recognised as the leading company in providing new products for this challenging sector. The products are sold all over the world with 52% sold in North America, 26% in Europe and 21% in Asia to both world-leading academic institutions and the pharmaceutical industry. [text removed for publication], who are working on membrane protein drug targets [B].

**The significance**

Membrane proteins perform a variety of functions in our body and more than 50% of commercially available drugs target these membrane proteins. Therefore, structural information of membrane proteins plays a vital role in medicine and in pharmaceutical drug discovery programs. The field of structure-based drug design is a rapidly growing area in which many successes have occurred in recent years. The explosion of genomic, proteomic, and structural information of membrane proteins has provided hundreds of new targets and opportunities for future drug discovery. The method is now routinely used in the pharmaceutical industry. It is difficult to evaluate the economic impact of the particular screens because they are used in a complicated drug discovery cycle. It is,

however, certain that our products strengthen the UK pharmaceutical industry (see the list of the companies using the kits above), which contributed £8.4 billion to the UK's GDP and invested a total of £3.9 billion in research and development in 2007.

**Date of the impact**

The impacts occurred from 2008 onwards, when the screens were exclusively commercialized by Molecular Dimensions, under license from Imperial College.

Today, with the increasing number of membrane protein structures, updated information has been used to design new solution kits that should prove useful for both initial crystallization scouting and subsequent crystal optimization. These new screens are also commercialized by Molecular Dimensions under the license of Oxford University [D, E].

**5. Sources to corroborate the impact** (indicative maximum of 10 references)

[A] 'Innovative Products for Membrane Protein Crystallography' page stating the products are under license from Imperial http://www.moleculardimensions.com/applications/upload/Membrane%20crystallography%20products.pdf (Archived here)

[B] Letter from Managing Director, Molecular Dimensions, 16/5/13 (letter available from Imperial College on request)

[C] Molecular Dimensions 'Membrane Protein Crystal Growth Screens' catalogue page http://www.moleculardimensions.com/shopdisplayproducts.asp?id=20&cat=Membrane+Protein+Crystal+Growth+Screens+ (Archived at https://www.imperial.ac.uk/ref/webarchive/shf on 24/4/13)

[D] Parker, J. and Newstead, S., *'Current trends in alpha helical membrane protein crystallization: an update*', Protein Science, 21:1358-1365 (2012).

Individuals who can corroborate impact:

[E] Dr Simon Newstead, University of Oxford