Institution: University of Manchester

Unit of Assessment: UoA5

Title of case study: Opening the door to ligand-based drug discovery: a rapid and accurate technology for determining bioactive 3D molecular shapes

1. Summary of the impact

A critical step in drug discovery is accurate determination of bioactive 3-dimensional structures of biologically-relevant molecules. Almond and Blundell's proprietary method for analysing Nuclear Magnetic Resonance (NMR) data has led to a world-first capability and establishment of the company Conformetrix (renamed C4X Discovery in 2013). The platform technology ('MolGyrate') is used to determine the dynamic 3-dimensional-conformation of biologically relevant molecules directly from NMR data within weeks, compared with months to years for traditional methods. C4X Discovery has secured substantial private investment (the company has not disclosed the amount). In 2012 AstraZeneca began to apply the technology across their entire pre-clinical therapeutic pipeline to enhance lead discovery and hit identification.

2. Underpinning research

Background

The impact is based on research at the University of Manchester (UoM) from 2005-2008. The key researchers were:

Dr Andrew Almond (Lecturer, 2005-date; co-founder of Conformetrix / C4X Discovery Ltd.)

Dr Charles Blundell (Post-Doctoral Research Associate, 2005-2008; co-founder of C4X Discovery Ltd.; Chief Scientist C4X Discovery Ltd, 2008-date)

The researchers worked on carbohydrate 3D-conformation, which poses a unique set of research problems given the high carbohydrate flexibility. One strand of their research determined the molecular 3D-shape of the flexible polysaccharide hyaluronan, which is distributed widely throughout mammalian connective, epithelial, and neural tissues. Almond and Blundell achieved this by performing computer simulations of the molecule in the presence of aqueous solvent, preparing pure samples in the laboratory and performing detailed experiments to validate the computational results [1-5]. Prior hypotheses relating to assembly of hyaluronan (and hence connective tissue) were based on a plastic space-filling molecular model; the discovery of hyaluronan's accurate 3-dimensional shape and flexibility has dramatically altered the understanding of extracellular matrix biology.

Discovery and patent application

During their research on hyaluronan (2005-2008), Almond and Blundell developed a quantitative theory that enabled raw NMR experimental data to be used to calculate a quantified flexible structure of a hyaluronan hexasaccharide without the need for inaccurate computer simulations. The molecular 3D-shape of this molecule was resolved for the first time, validating the new methodology on an inherently flexible biomolecule; a world first. At this time it was realised that the nascent technological breakthrough could be applied to any small flexible molecule [6], drugs and peptides in particular. Using proof-of-concept funding from UoM, the dynamic 3D-structures of several important molecules were resolved. A UK-patent entitled, "Method for determining three-dimensional structures of dynamic molecules," was filed in 2007 (applicants: Blundell CD and Almond A; UK patent application number 0718027.6). The patent has reached the National phase and applications have been filed in all major territories.

3. References to the research

The research on hyaluronan has been published in international biochemistry and chemistry journals.

1. **Almond A**, DeAngelis PL, **Blundell CD**. Dynamics of hyaluronan oligosaccharides revealed by ^{15}N relaxation. *J. Am. Chem. Soc.* 2005; 127: 1086-1087. DOI:10.1021/ja043526i

2. **Almond A**, DeAngelis PL, **Blundell CD**. Hyaluronan: the local solution conformation

determined by NMR and computer modelling is close to a contracted left-handed four-fold helix. *J. Mol. Biol.* 2006; 358: 1256-1269. DOI:10.1016/j.jmb.2006.02.077

3. **Blundell CD**, DeAngelis PL, **Almond A**. Hyaluronan: the absence of amide-carboxylate hydrogen bonds and the chain conformation in aqueous solution are incompatible with stable secondary and tertiary structure models. *Biochem. J.* 2006; 396: 487-498. DOI:10.1042/BJ20060085
4. **Blundell CD**, Reed MA, **Almond A**. Complete assignment of hyaluronan oligosaccharides up to hexasaccharides. *Carbohydr. Res.* 2006; 341: 2803-2815. DOI:10.1016/j.carres.2006.09.023
5. **Blundell CD, Almond A.** Enzymatic and chemical methods for the generation of pure hyaluronan oligosaccharides with both odd and even numbers of monosaccharide units. *Anal. Biochem.* 2006; 353: 236-247. DOI:10.1016/j.ab.2006.03.013
6. **Blundell CD**, Packer MJ, **Almond A**. Quantification of free ligand conformational preferences by NMR and their relationship to the bioactive conformation. *Bioorg. Med. Chem.* 2013; 21: 4976–4987. DOI:10.1016/j.bmc.2013.06.056

4. Details of the impact

Context

Methods of determining small biological molecule 3D-conformation for use in structure-based design have numerous limitations:

- protein co-crystallography for a novel target is very expensive and can take years of trial and error
- the anhydrous packing environment in small molecule crystals leads to non-physiological conformations
- the theoretical nature of computational modelling leads to unreliable 3D-predictions
- NMR methods cannot account for flexibility without resorting to inaccurate computational chemistry

The MolGyrate technology overcomes these limitations, bringing accurate, experimentally-determined solution structures (which relate directly to the bioactive conformation [6]) to the market. This method has proven capable of producing accurate bioactive structures for natural ligands, performing rapid hit identification and removing bottlenecks in lead optimisation, accelerating medicinal chemistry, reducing costs and increasing productivity. To illustrate:

- C4X Discovery determined the flexible structure of carazolol in a week, validating it to have the same shape as in the β2-adrenergic receptor co-crystal.
- The company also solved an antagonist of the Class B GPCR corticotropin-releasing factor receptor in the same time frame. It is successfully using this approach to develop novel selective inhibitors of the orexin-1 receptor, with potential to treat anxiety and addiction.

Pathways to impact

The technology was taken from the laboratory to a spin-out company through research by Almond and Blundell (via research, translational and proof-of-concept funding and a secondment from UoM). A prototype was developed using BBSRC Follow-on funding (for demonstration to investors and pharmaceutical clients). The drafting of a business plan was enabled by a BBSRC/RSE Enterprise Fellowship awarded to Almond in 2007. Conformetrix was assigned IP from the UoM and incorporated in 2007 (its name changed to C4X Discovery in 2013).

Reach and significance of the impact

During the impact period the success of C4X Discovery and the underpinning research, which includes a research collaboration with AstraZeneca (AZ) across its pre-clinical therapeutic pipeline, have been recognised through a series of awards: Bionow Start Up Company of the Year (2008), NorthWest Development Agency GRAND award for Innovative R&D (2009), and Bionow Emerging Biomedical Technology Project of the Year (2011). Almond was also a finalist in the BBSRC Innovator of the Year competition (2009) [A], and the company is profiled in a BBSRC Impact

Evidence Report (2012) [B]. More recently, the UoM and UoM IP were joint runners-up in the 2013 BBSRC Fostering Innovation 'Activating Impact' Awards (with C4X Discovery being one of two examples).

Formation of a successful spin-out company:
Since 2008 C4X Discovery has raised several £million in venture capital funding (specific amount not disclosed due to commercial confidentiality), through a series of investments from Aquarius Equity Partners [C], a fund focussed on UK life science technology.

In September 2012, Aquarius Equity Partners announced the release of a third tranche of investment, triggered by significant progress of the company against milestones. [Text removed for publication].

Industry investment in R&D through in-house evaluation studies:
C4X Discovery has provided paid services to the world's largest pharmaceutical and biotech companies (not disclosed due to commercial confidentiality). [Text removed for publication].

Collaborative agreement with AstraZeneca to enhance drug discovery and optimisation:
In 2012 C4X Discovery announced a two-year research collaboration agreement with AZ, under which MolGyrate will be applied across AZ's entire pre-clinical therapeutic pipeline to enhance lead discovery and hit identification. The VP and Head of Discovery Sciences at AZ said:

"*We are excited to be working with Conformetrix. We believe their technology will provide a powerful addition to our hit identification and lead optimisation approaches, supporting our strategic objectives to improve the quality and choice of candidate compounds for our early pipeline*" [D].

Also in *BioCentury*, a US-based biotech business newsletter, he said:

"*As we've done due diligence, we've been looking to see if there is anything else out there that competes with Conformetrix's technology, and we feel it is truly unique*" [E].

The collaborative agreement with Conformetrix forms part of a revamped business development strategy for AZ [F]. The research collaboration is one of only two involving companies/groups in Europe (and the only UK deal, the majority being US-based ventures) and involves a team drawn from both companies to manage the research strategy [G]. C4X Discovery received an undisclosed upfront payment and research funding, and is eligible for funding milestones as certain targets are met.

5. Sources to corroborate the impact

A. BBSRC Innovator of the Year 2009: Andrew Almond (finalist): http://www.bbsrc.ac.uk/web/FILES/Publications/innovator_2009.pdf

B. BBSRC Impact Evidence Reports 2012: Conformetrix

C. http://www.bbsrc.ac.uk/publications/impact/conformetrix-impact.aspxLetter of support from a Director at Aquarius Equity Partners, *confirming investments into C4X Discovery*.

D. Conformetrix and AstraZeneca sign collaborative agreement. AstraZeneca Global, 16 April 2012: http://www.astrazeneca.com/Research/news/Article/16042012--conformetrix-and-astrazeneca http://www.c4xdiscovery.com/news/press-releases/conformetrix-astrazenica-collaborate.html

E. Confirming conformations. BioCentury: The Bernstein Report on BioBusiness, 30 April 2012.

F. Racing to rebuild AZ. BioCentury: The Bernstein Report on BioBusiness, 5 November 2012.

G. AstraZeneca boosts structure-activity R&D with Conformetrix's new NMR-based approach. "The Pink Sheet" Daily, 16 April 2012.