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| **Institution:** The University of Manchester | | |
| **Unit of Assessment:** 8 (Chemistry) | | |
| **Title of case study:** C4X Discovery: generating market-leading drug candidates from cutting-edge technology | | |
| **Period when the underpinning research was undertaken:** 2005 – 2013 | | |
| **Details of staff conducting the underpinning research from the submitting unit:** | | |
| **Name(s):** | **Role(s) (*e.g.* job title):** | **Period(s) employed by submitting HEI:** |
| Andrew Almond | Reader (2016 – present)<br>Lecturer (2005 – 2016) | 2005 – present |
| Charles Blundell | Postdoctoral Research Associate | 2005 – 2008 |
| **Period when the claimed impact occurred:** August 2013 – July 2020 | | |
| **Is this case study continued from a case study submitted in 2014?** N | | |

## 1. Summary of the impact

Researchers at The University of Manchester invented technology that expedites drug discovery by measuring the bioactive shapes of small molecules with unprecedented accuracy using nuclear magnetic resonance. The technology, assigned to spin-out C4XDiscovery, was used to successfully initiate several novel drug programmes, which led to the company raising GBP31,000,000 *via* a floatation on the London Stock Exchange.

Its lead programme aims to treat addiction across a broad range of substance use disorders – which are areas of unmet need costing the United States USD1,000,000,000,000 annually – by targeting the craving process itself. The technology delivered drug candidates for this programme significantly quicker than traditional pharmaceutical methodologies, with substantially lower toxicity and side-effects and saving 90% of the typical pre-clinical cost, which averages around USD1,000,000,000. The programme entered clinical development in 2018 *via* a USD294,000,000 licencing deal with Indivior PLC.

## 2. Underpinning research

### Background

The impact is underpinned by research at The University of Manchester (UoM) from 2005–2008 conducted by Dr Andrew Almond and Dr Charles Blundell. The researchers invented new methods for determining small molecule 3D-shapes, and in particular, techniques that could be applied to complex sugars, which pose a unique set of research problems given their high flexibility. One strand of research led to determination of 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 **[1-3]**.

### Discovery and patent application

During their research on hyaluronan (2005–2008), funded by a BBSRC David Phillips Research Fellowship, Almond and Blundell developed a quantitative theory that enabled raw nuclear magnetic resonance (NMR) experimental data to be used to calculate a quantified flexible structure of a hyaluronan hexasaccharide **[4]**. 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. Furthermore, this nascent technological breakthrough was applicable to virtually any small flexible molecule, including drugs and peptides **[4]**.

Using proof-of-concept funding from UoM and two BBSRC Follow-on-Fund research grants, the dynamic 3D-structures of several important molecules were resolved and the research became more applied and directed towards the pharmaceutical sector. Importantly, the resultant models were established to be predictive of bioactive shape, *i.e.* the bound molecular shape required for ligand-based drug discovery processes such as virtual screening, chemical scaffold hopping and pharmacophore identification **[4]**. A patent to protect the technology was filed in 2007, which has been granted in the USA **[5]** and Japan as of November 2019. In 2008, Conformetrix Ltd (now C4X Discovery Ltd) was spun out of UoM to commercially license the technology.

## 3. References to the research

This research is published in top Medicinal Chemistry journals **[4]**, and high-quality Chemistry journals **[1-3]**, including in the *Journal of the American Chemical Society*. These publications also describe some of the other methods that are used by C4XDiscovery to expedite drug discovery**.** The underlying research was presented at prestigious international meetings, including the 223rd American Chemical Society National Meeting in Florida (USA) in 2002. The research was twice a finalist in the BBSRC Innovator of the Year competition (2009 and 2016), runner up in BBSRC Activating Impact Awards (2013) and shortlisted for the Thomas Kuhn Paradigm Shift Award with the invited prize seminar "Molecular key cutting" at the 2010 ACS Spring National Meeting & Exposition in San Francisco.

**Peer-reviewed journal publications and patents**


[1] **Almond A**, DeAngelis PL, **Blundell CD**. Dynamics of hyaluronan oligosaccharides revealed by 15N 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**, 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

[5] **Blundell CD** and **Almond A**. Method for determining three dimensional structures of dynamic molecules. US patent number US20100191517A1 (filed 2007, granted 2019).


**Grants funding the research and pathway to impact**


**Almond, A.** PI. Five-year David Phillips Fellowship grant. The role of molecular dynamics in extracellular matrix organisation. Investigations of hyaluronan, free and bound to proteins. BBSRC. Grant reference: JF191032. Dates: 10/2002-10/2007. GBP405,000.

**Almond, A.** PI. BBSRC Follow-on-fund. A graphical user interface for novel software that expedites drug-discovery by providing experimentally-determined 3D structures of natural ligands. Grant reference: BB/F528006/1. Dates: 11/2007-11/2008. GBP109,000.

**Almond, A.** PI. BBSRC Follow-on-fund grant. Customisation of our 3D drug-discovery software to the pharmaceutical sector: product analysis and development. Grant reference: BB/F528081/1 Dates: 1/2008-1/2009. GBP116,000.

**Almond, A.** PI. Royal Society of Edinburgh / BBSRC Enterprise personal Fellowship to develop a business plan for spinning the technology out of the UoM. Dates: 10/2008-10/2009. GBP50,000.


## 4. Details of the impact

**Context**

Ligand-based drug design is a contemporary and exciting area of pharmaceutical R&D that aims to predict the affinity and selectivity of small molecules (candidate drugs) in the absence of the receptor 3D information. It relies on chemical and physical knowledge exclusively from small molecules that bind to the biological target of interest, such as small molecules 3D shape and flexibility. However, current methods of determining small molecule 3D shape and flexibility have limitations: protein co-crystallography is very expensive and time-consuming, small molecule crystallography suffers from non-physiological packing artefacts, computational modelling predictions of the 3D-shapes of small molecules and proteins needed to predict binding is inaccurate, and neither NMR methods nor crystallography can quantify small molecule flexibility.

The technology invented at UoM, Conformetrix (hereinafter referred to as "UoM Technology") overcomes these shortcomings, producing accurate, experimentally determined 3D shapes in solution. Its accuracy and novelty stems from the fact that it can quantify the flexible (rather than time-averaged) shapes of small molecules in solution (*i.e.*, to effectively reproduce the Boltzmann distribution of conformations for a given molecule) to the atomic resolution needed for

drug design **[4]**. These can then be used in traditional computer-aided drug design workflows, such as virtual screening, molecular docking, pharmacophore mapping and structure activity relationship models to improve the speed and accuracy of drug hit identification and lead optimization. C4XD have stated that, "*The patented [UoM] technology platform* […] *is at the heart of the C4XD drug discovery engine enabling rapid progress in developing new and better drugs at a fraction of the cost compared to best industry practice.*" **[A]**

**Pathways to impact**

The UoM Technology was taken from the laboratory to a spin-out company by Almond and Blundell (*via* research, translational and proof-of-concept funding and a secondment of Almond from the University to C4XD). A demonstration prototype was developed using BBSRC Follow-on-Funding and the drafting of a business plan was enabled by a BBSRC/RSE Enterprise Fellowship. C4XDiscovery was assigned IP from The University of Manchester and incorporated in 2007 (it was originally named Conformetrix Limited), hereinafter referred to as "C4XD." Since 2013, C4XD has achieved significant growth and expansion into new technologies and therapeutic areas, by development and application of the UoM Technology. The appointment of Dr Clive Dix as CEO is particularly significant given his experience as a leading UK pharmaceutical R&D executive.

The impact of the UoM Technology falls into three categories: (i) accelerating drug discovery for C4XD and the associated benefits; (ii) economic impacts for C4XD; and (iii) creating new partnerships between C4XD and other pharmaceutical companies to take advantage of the UoM Technology.

**Reach and significance of impact**

**(i) Accelerating drug discovery for C4XD**

An example of the UoM Technology enhancing drug discovery at C4XD is its impact on their anti-addiction and substance abuse programmes. Abuse of tobacco, alcohol and illicit drugs costs the US alone over USD740,000,000,000 annually in healthcare, crime and lost productivity (according to the US National Institute on Drug Abuse, NIDA) and represents a substantial area of unmet medical need, forecast to be worth an estimated USD13,000,000,000 *per annum* in 2018 **[B]**. The UoM Technology enabled rational identification of multiple drug candidates that are highly specific to the Orexin G-protein coupled receptor (Orexin-1). C4XD estimates the development of their molecules, including the lead pre-clinical candidate drug C4X3256, has been achieved at less than 10% of the typical industry cost, and been delivered in a fraction of the time normally required **[B, C(p15)]**. Development of a drug candidate up until clinical studies costs industry on average circa USD1,000,000,000, and C4XD achieved this milestone using investment and revenues that totalled less than GBP100,000,000, while also progressing its other preclinical drug programmes. These candidates are substantially safer and have improved pharmacokinetic and pharmacodynamic properties compared to competitor best-in-class alternatives, which were discovered using traditional pharmaceutical methodologies.

The lead pre-clinical candidate drug, C4X3256, has highly desirable properties that had not previously been achieved through conventional drug discovery methodologies **[B]**. In particular, the compound has negligible off-target effects to a homologous receptor (Orexin-2), which causes insomnia, allowing rapid development into a therapy to tackle the craving associated with addictions to substances such as tobacco, opioid analgesics, and alcohol. Using the UoM Technology to study ligands that bind with varying affinities to the two receptor homologues, C4X3256 was able to be identified as having crucial specificity of C4X3256 for Orexin-1 over Orexin-2 **[B]**. C4XD had previously announced efficacy data of its lead compound, C4X3256, in *in vivo* models of addiction **[D]** and the pivotal pre-clinical and toxicology studies were completed successfully. In 2018 C4XD was awarded a grant of USD480,000 from the NIDA to support the pre-clinical development of C4X3256 in cocaine use disorder **[B]**.

Alongside C4XD's Orexin-1 antagonist programme, the UoM Technology has driven several other promising drug discovery programmes. For example, it was used to identify multiple drug leads that activate Nuclear factor erythroid 2-related factor 2 (NRF2), a human transcription factor associated with the cardiovascular diseases Pulmonary Arterial Hypertension (PAH) and Sickle Cell Disease, both of which are orphan indications **[B]**. In pre-clinical evaluation, several

lead compounds identified using the UoM Technology show prolonged duration of action following low oral dosing, including in blood **[B]**.

Another successful application of the UoM Technology at C4XD has been in targeting the signalling protein Interleukin-17 (IL-17), a high-value clinical target for inflammatory and auto-immune diseases with a ~USD13,000,000,000 *p/a* market **[B]**. The only clinically-approved drugs for IL-17 are injectable monoclonal antibodies. A goal of many companies is to identify orally-administered drugs for IL-17, in part because patients find oral pills preferable to injections. Using the UoM technology, C4XD has identified selective molecular inhibitors of IL-17, which maintain the pharmacokinetics properties of small, drug-like molecules **[B]**. C4XD say they "[continue] *to receive strong interest from potential partners for this oral IL-17 inhibitor approach*" **[B]**.

**(ii) Economic impacts from successful commercialisation and formation of C4XD**
C4XD was the first BBSRC part-funded spin-out to be listed on the London Stock Exchange, following admission to AIM (Alternative Investment Market) in 2014 with a market capitalisation of GBP31,000,000 **[E]**. C4XD subsequently raised over GBP33,000,000 from public investors enabling the UoM Technology to be applied across strategic and opportunistic therapeutic areas to build a balanced pre-clinical portfolio of 11 discovery programmes, spanning immunology, inflammation, neurology, neurodegeneration and cancer. In 2016, C4XD acquired Adorial Limited for GBP1,700,000 using revenue and investment proceeds from the UoM Technology platform. The acquired technology, Taxonomy 3, is used to drive forward the search for novel gene targets and then the UoM Technology is used in tandem to enable hit identification, further enabling and expediting early-stage drug discovery.

The UoM Technology has resulted in significant new R&D growth in Manchester, and created high quality graduate and PhD jobs, as evidenced by C4XD's financial results. **FY2017**: Revenue GBP143,000, R&D expenditure GBP6,100,000 (+16% YOY), employees 42. **FY2018**: Revenue GBP7,064,000, R&D expenses GBP6,992,000 (+15% year on year: YOY), employees 47 (+12% YOY) **[F]**. **FY2019**: In 2018, C4XD changed its business model to move away from service contracts and towards its own pharmaceutical development, and as such generated no revenue in FY2019 – however, it successfully raised GBP17,700,000 in funding from external investment, and spent GBP10,585,000 on R&D **[F]**. **FY2020**: R&D spend of GBP6,900,000, and raised a further GBP9,200,000 from external investment in two tranches **[F]**.

**(iii) Benefits for partnering organisations through use of the UoM Technology**
By 2018 C4XD's Orexin-1 antagonist drug discovery programme had met preclinical endpoints and entered clinical development as a novel addiction therapy *via* a license agreement with US-based Indivior (which markets Subutex and Suboxone, both substitution products for opioid addiction) **[G]**. C4XD received an upfront payment of USD10,000,000 (3/2018) and up to USD284,000,000 of development, regulatory and commercialisation milestones in addition to royalties **[B]**. Indivior has a global and exclusive license to C4X3256 and all other compounds in the same patent family and is responsible for the cost and execution of all further development. In September 2019, Indivior received a significant grant from the US National Institutes of Health to advance C4X3256 through clinical evaluation in the treatment of Opioid Use Disorder, which in 2018 affected some 10.3 million people over the age of 12 in the USA **[B]**. This grant is allowing C4X3256 to progress through Phase 1 clinical evaluation, and fund toxicological and metabolism studies to enable Phase 2 clinical evaluation **[B]**.

In 2014, C4XD signed a research collaboration agreement to apply the UoM Technology across therapeutic projects at Takeda Pharmaceutical Company (Asia's largest pharmaceutical company: ~30,000 employees, revenue USD16,200,000,000) to enhance lead discovery and hit identification **[B, H]**. The Senior Director of Chemistry at Takeda commented: "*We are pleased to partner with C4XD and are excited about the potential of this collaboration. C4XD has a highly innovative platform technology [UoM Technology] which complements our strong research base to accelerate product development*." **[H]** No financial terms have been disclosed.

In 2016, C4XD entered a collaboration with Hamburg-based Evotec AG (~2,000 employees, revenue EUR258,000,000) to apply the UoM Technology to co-develop new small molecule drugs across a range of targets, therapeutic areas and stages of development **[B, I]**. No financial

terms were disclosed but Evotec indicated that the collaboration was beneficial because it would reduce near-term costs while increasing the potential output of C4XD's drug discovery engine. Evotec's Chief Operating Officer commented: "*We are very pleased to continue and expand the broad-based drug discovery collaboration with C4XD. This integrated drug discovery deal showcases our broad target class expertise coupled with our industry leading platform, which perfectly complements C4XD's technology and expertise…*" **[I]**.

Recently, C4XD has entered into partnerships with e-Therapeutics (05/2018), Horizon Discovery (12/2018) and PhoreMost (7/2019) to use the UoM Technology to accelerate co-development of therapies for Parkinson's disease and cancer. The CEO of PhoreMost said, "*We are thrilled to be joining forces with C4XD within this neurodegeneration collaboration, a therapeutic area that has a pressing need for new and better targets… C4XD's [UoM Technology] is ideally suited to use the 3D biological shape information derived from SITESEEKER targets and convert this into small molecules starting points that will lead to the next generation of therapeutics*" **[A]**. While the terms of the agreement were not disclosed, it is reasonable to expect that both companies agreed to share revenues on validated targets produced by the collaboration.

In 2017, C4XD collaborated with videogame developed Epic Games, developing their 4Sight virtual reality (VR) platform using the Unreal Engine **[B]**. This incorporates the UoM Technology, as well as C4XD's Taxonomy3, to allow teams of drug developers to engage in "multiplayer", real-time 3D molecular design in a VR environment **[B]**.

**5. Sources to corroborate the impact**


[A] C4X press release (June 2019) C4X Discovery and PhoreMost collaboration to accelerate Parkinson's Disease drug discovery pipeline. Available at: https://bit.ly/3a4LPF8

[B] Letter from Chief Scientific Officer of C4X Discovery, received 5 February 2020

[C] London Stock Exchange admission document. Available at: https://bit.ly/3cUEauO

[D] C4X press release (November 2017) C4XD presents data on its lead addiction programme: Orexin-1 antagonist. Available at: https://bit.ly/3e5Ts0B

[E] C4X press release (October 2014) C4X Discovery: First Day of Dealings on AIM following £11m Placing. Available at: https://bit.ly/2MGpqFv

[F] C4XD annual reports and accounts for years ending 31 July 2017, 31 July 2018, 31 July 2019 and 31 July 2020

[G] C4X press release (March 2018) C4X Discovery signs licensing agreement with Indivior for addiction programme worth up to USD294M. Available at: https://bit.ly/38d2iWC

[H] C4X press release (August 2014) C4X Discovery enters collaboration with Takeda Cambridge Limited. Available at: https://bit.ly/2MGP6lm

[I] C4X press release (September 2016) C4X Discovery Enters New Strategic Collaboration with Evotec. Available at: https://bit.ly/2YXSWbZ