Institution: University of Sussex

Unit of Assessment: 8 – Chemistry

Title of case study: The impact of novel photochemistry and automated chemistry methods in the search for new medicines

Period when the underpinning research was undertaken: 2014 – 2020

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:
Professor Brian Cox	Professor of Pharmaceutical Chemistry	01/11/2014 – 18/12/2020
Dr Victor Zdorichenko	Research Fellow	01/12/2015 – 30/11/2017

Period when the claimed impact occurred: 2016 – 2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Research in the Cox group at Sussex uses modern techniques in photochemistry and automated chemistry to create novel patentable compounds for the pharmaceutical and biotechnology industry. The products have highly desirable drug-like properties, a higher chance of providing marketable drugs, and are less likely to fail in the R&D process, ultimately benefitting patients with better therapies. The start-up company Photodiversity Ltd was formed to develop this research, [text removed for publication] with customers including major international pharmaceutical and biotechnology companies such as [text removed for publication]. Photodiversity Ltd was shortlisted for the Royal Society of Chemistry's 2019 Emerging Technologies Competition. The not-for-profit partnership Medicines for Malaria Venture (MMV) is using compounds donated by Photodiversity Ltd in its search for new malaria medicines in Africa.

2. Underpinning research

The degree of three-dimensionality of molecules made for drug discovery is a crucial consideration: "flatness" increases the risk of failure in the research and development optimisation process. Failure is very expensive and also deprives patients of a new medicine.

Since 2015, Sussex research, led by Cox, has set out to design and prepare new libraries of molecules with increased three-dimensionality using photochemistry and automated chemistry methods. Collections of chemical compounds (libraries) are the fundamental starting point for the majority of drug discovery projects. The diversity and uniqueness of a collection is key to the success of a drug discovery project with regards to decreasing attrition and increasing novelty to secure intellectual property. The design of each set of compounds is based on the alignment of the desired molecular structural features, which are defined by the biological target, and the potential chemical accessibility of such molecules. A key goal is to produce intermediate scaffolds (building blocks) that have all the desired structural features as well as multiple points of diversification, given that an essential requirement for drug optimisation in the discovery process is the ability to modify the properties of molecules to produce a medicine [R1].

Photochemistry is a branch of chemistry concerned with chemical reactions induced by light. Light induces molecules to achieve an "excited state" and undergo reactions that are impossible or very difficult using conventional chemistry which operates in the "ground state". Photochemistry is unparalleled in its ability to convert simple planar molecules into complex, novel, diverse, three-dimensional multi-functionalised molecules with just the addition of

photons. Photocycloadditions in particular can give rise to complex polycyclic systems under "reagentless" and "green" conditions with 100% atom economy, which also has enormous attraction from an economic and environmental impact perspective. It is this science that the Cox group set out to research [R1].

In one project, Cox led an investigation into the potential of photochemistry to increase three-dimensionality by investigating bridged pyrrolidine molecules. Computational analysis clearly demonstrated that overall the percentage of three-dimensional character (using two independent 3D descriptors (PMI and PBF Score)) of the bridged pyrrolidines prepared was found to be significantly higher (by 91%) than that of pharmaceutical company [text removed for publication] reference compound collection. Also reported was that the degree of shape and 3D character may be prospectively designed and biased toward fragments with enhanced 3D character. The 3D motifs within these molecules were also found to reside in distinct and different regions of molecular space compared to the space largely occupied by conventional screening libraries. This enables a clear direction that can be followed by those making new molecules to enhance screening collections [R2].

In a second project, photochemistry techniques were used to design and synthesise a small library of 234 molecules, again based on a bridged pyrrolidine scaffold. These molecules were then evaluated as a starting point for antimalarial drugs, in conjunction with the charity Medicines for Malaria Venture (MMV). Using a standard screening approach a number of active antimalarial compounds were discovered. Three compounds were found to be active antimalarials at a level of less than 2 micromolar, a hit rate of 1.28%. This compared extremely favourably with the previous two screens performed by MMV that had hit rates of 0.07-0.09%. One compound underwent further profiling and was shown to have similar activity against a resistant strain of malaria and good metabolic stability in microsomal systems. Critically the active compounds had excellent drug-like properties and multiple points of potential variation [R3].

3. References to the research

R1. **Cox, B**.; Booker-Milburn, K. I.; Elliot, L.; Robertson-Ralph, M.; **Zdorichenko, V**. Escaping from Flatland: [2 + 2] Photocycloaddition; Conformationally Constrained sp^3-rich Scaffolds for Lead Generation**.** *ACS Medicinal Chemistry Letters.* (2019), *10*, 1512-1517. (https://doi.org/10.1021/acsmedchemlett.9b00409) 13 citations (Google Scholar)

R2. **Cox, B**.; **Zdorichenko, V**.; Cox, P. B.; Booker-Milburn, K. I.; Paumier, R.; Elliott, L. D.; Robertson-Ralph, M.; Bloomfield, G. Escaping from Flatland: Substituted Bridged Pyrrolidine Fragments with Inherent Three-Dimensional Character. *ACS Medicinal Chemistry Letters*. (2020), *11*, 1185-1190. (https://doi.org/10.1021/acsmedchemlett.0c00039) 7 citations (Google Scholar)

R3. **Cox, B**.; Duffy, J.; **Zdorichenko, V**.; Bellanger, C.; Hurcum, J.; Laleu, B.; Booker-Milburn, K. I.; Elliott, L.; Robertson-Ralph, M.; Swain, C.; Bishop, S.; Hallyburton, I.; Anderson, M. Escaping from Flatland: Antimalarial Activity of sp^3-Rich Bridged Pyrrolidine derivatives. *ACS Medicinal Chemistry Letters*. (2020), *11*, 2497-2503. (https://doi.org/10.1021/acsmedchemlett.0c00486)

R1-3 are published in ACS Medicinal Chemistry Letters, which is an internationally-recognised journal published by the American Chemical Society.

4. Details of the impact

Lovering *et al* showed in 2009 that more complex, three-dimensional molecules are significantly more likely to progress from the discovery process, through clinical trials, into marketed drugs without failure. This positive impact on attrition has tremendous value financially and therapeutically. With the average cost of developing a new drug being around USD1,300,000,000, the failure of a drug candidate, particularly in later stages of clinical trials, is extremely costly and even jeopardises the whole model of drug discovery. The clinical impact of failure is also acute, with patients deprived of life-saving and life-changing medicines.

Accordingly, Photodiversity's underpinning research was concerned with designing and preparing new libraries of molecules with increased three-dimensionality using photochemistry and automated chemistry methods, and has led to the following impacts.

Commercial impact

Photodiversity Ltd (www.photodiversity.uk.com) was founded in March 2015 with support from the Universities of Sussex and Bristol and the Sussex Innovation Centre. The goal was to realise the potential of Cox et al's expertise in state-of-the-art photochemistry and automated chemistry research to make molecules for sale to pharmaceutical and biotech companies and non-profit organisations, for use in drug development. A key activity of Photodiversity is the production of libraries of compounds and intermediate scaffolds (building blocks) that are both novel, 3D-rich and have multiple points of diversification, which are both essential requirements for drug discovery.

Since it was established in 2015, Photodiversity [text removed for publication]. Its customers are major pharmaceutical companies including [text removed for publication], cutting-edge biotech companies such as Polyphor, Vipergen and Bicyle Therapeutics and its products are instrumental in the work of not-for-profit groups such as Medicines for Malaria Venture. These are all discussed further below. Thus the impact of Photodiversity Ltd is on the global drug discovery process, with higher quality compound libraries leading to decreased failure rates which will save money and ultimately ensure more medicines get to patients.

Photodiversity has attained a global reputation with the excitement around its work shown by its shortlisting in the "enabling technologies" section of the Royal Society of Chemistry's 2019 Emerging Technologies Competition. This is "an annual innovation competition that seeks to identify the most novel, innovative and promising chemistry in the UK and Europe" with judges noting that Photodiversity's work showed "strong evidence of relevance to the market … clearly it could have a significant impact" [S2].

Impact on pharmaceutical industry

Research with two of Photodiversity's collaborators – [text removed for publication] and the Swiss charity Medicines for Malaria Venture – detail the unique structural nature of Photodiversity's photochemically derived libraries [R2, R3].

Compounds designed and prepared in collaboration with [text removed for publication] for the purpose of compound archive enhancement had increased three-dimensionality of molecules. Such screening collections in [text removed for publication] and in wider drug discovery will reduce the risk of failure in the research and development optimisation process. [text removed for publication]

Libraries of compounds have been sold to other major global pharmaceutical companies as starting points for their drug discovery projects. [text removed for publication] chose Photodiversity's compounds specifically because they recognise the importance of increased three-dimensionality of molecules in their screening programmes [S4].

Photodiversity has also sold compounds to research and development customers who use them as a basis to develop their own libraries. These include Polyphor (Switzerland), a world-leader in peptide-based therapeutics who said: "We utilised the compounds to synthesise new macrocycles for our collection. The new macrocycles were shown to have a unique shape… and provided biologically active compounds for our on-going research" [S5]. Other R&D customers are Vipergen (Denmark), a major producer of DNA-encoded libraries with cutting-edge technology enabling screening on unprecedented scale [S6] and Bicycle Therapeutics (UK), another company with a novel library platform technology [S7].

Photodiversity's building blocks are being used as alternative structural motifs by the Queensland Emory Drug Discovery Initiative (Australia) in "our ongoing drug optimisation programs" [S8]. Key Organics Ltd used Photodiversity's unique technology platform to provide bulk commercial chemicals for a customer [S9].

Impact on the search for new malaria drugs

In another ongoing relationship, Photodiversity designed and produced libraries of compounds for Medicines for Malaria Venture (MMV), an organisation devoted to the development of new antimalarials. There is increased prevalence and mounting resistance to existing medicines, with 228,000,000 cases of malaria worldwide and 405,000 deaths (2018).

Libraries supplied to MMV produced significant activity: the hit rate and level of activity described in section 2 and reference [R3] is rarely encountered in antimalarial screening, normally only achieved after significant optimisation. As MMV corroborates: "The hit rate found for this library of compounds was enhanced by 10-fold compared to our previous two screens of compounds derived from other sources … the failure rate is predicted to be lower which has enormous positive cost implications" [S10].

This makes Photodiversity's library an excellent starting point for optimisation into potent antimalarial drugs and proves that increasing the content of 3D character, relative to compounds from commercial sources, increases the chance of finding an active hit and will lead ultimately to a reduced chance of failure in the research and development process. This open literature publication ensured a patent-free opportunity for worldwide researchers to optimise these molecules into a commercially unencumbered antimalarial medicine.

Photodiversity and MMV have agreed to work with antimalarial specialists at the UCT Drug Discovery and Development Centre (H3D) (University of Cape Town), on a new drug discovery project. The H3D research centre at the University of Cape Town is Africa's first integrated drug discovery and development centre whose work on malaria has produced the first clinical candidate to come out of Africa. H3D are "very pleased to confirm that we will start work on a new project to optimize molecules recently published by Photodiversity in collaboration with MMV" [S11]. Ultimately, malaria patients will not only benefit from drugs developed from Photodiversity's molecular starting points, but also more broadly from the use of photochemistry and other chemistries that move the field of design, production and screening towards molecules with increased 3D character.

5. Sources to corroborate the impact

S1. [text removed for publication]
S2. Letter of support: Emily Vipond, Programme Manager – Enterprise, Royal Society of Chemistry, UK, November 2020. [PDF]
S3. [text removed for publication]
S4. [text removed for publication]
S5. Letter of support: Dr Daniel Obrecht, Chief Scientific Officer, Polyphor Ltd, Switzerland, December 2020. [PDF]
S6. Letter of support: Dr Nils Jakob Vest Hansen, Chief Executive Officer, Vipergen ApS, Denmark, December 2020. [PDF]
S7. Letter of support: Dr Paul Beswick, Director of UK Chemistry & IP, Bicycle Therapeutics Ltd, UK, December 2020. [PDF]
S8. Letter of support: Dr Mark Ashton, Executive Director, IP Commercialisation, UNIQUEST, Austrailia, December 2020. [PDF]
S9. Letter of support: Steve Brough, Commercial Manager, Key Organics Ltd, UK, December 2020. [PDF]
S10. Letter of support: Dr James Duffy, Director, Drug Discovery, Medicines for Malaria (MMV), Switzerland, December 2020. [PDF]
S11. Letter of support: Kelly Chibale, Director UCT Drug Discovery and Development Centre (H3D), South Africa, Janaury 2021. [PDF]