Institution: Canterbury Christ Church University (CCCU)

Unit of Assessment: 5 – Biological Sciences

Title of case study: ICS5.02 Development of novel therapeutics from animal venom

Period when the underpinning research was undertaken: 2015-2020

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:**
Dr Carol Trim	Senior Lecturer	06/01/2014 – date

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

Efficient and timely drug discovery relies on the rapid identification of candidate compounds, referred to as "lead compounds." One novel source of lead compounds, which can subsequently be developed into new therapeutics, is animal venoms. Canterbury Christ Church University (CCCU) research, undertaken in collaboration with the local biotechnology company Venomtech Ltd., has provided novel evidence for the effects of venom and venom fractions on cancer cells, and on bacteria and fungi. This has allowed revision and extension of Venomtech Ltd.'s product lines, providing new and improved compound libraries, and has improved Venomtech Ltd.'s production processes. With CCCU work forming a key part of Venomtech Ltd.'s advertising material, this research is directly linked to sales, revenue increases and to investment in the company. CCCU research has therefore delivered impact on commerce and the economy via its effects on a local company with a global reach.

2. Underpinning research

Increasing the pace of drug discovery is a key global goal, both to increase treatment options (*e.g.,* for cancer) and to provide alternative therapeutics in situations where resistance is an issue (*e.g.,* bacterial antibiotic resistance). This requires there to be appropriate libraries of potentially active compounds from which lead compounds can be identified. Animal venom components derived from both vertebrates (*e.g.,* snakes) and from invertebrates (*e.g.,* spiders and scorpions) represent an under-exploited source for such libraries of potential therapeutics, as the venom of any given species may contain hundreds of different active components. Given the complexity of venoms, their exploitation in the development of therapeutics requires characterisation and fractionation in order to identify active components. In order to achieve this, the animals concerned must also be safely and humanely handled and housed. It is also critical that those working in drug discovery recognise that venoms are important sources of lead compounds. Working with a local biotechnology company, Venomtech Ltd., CCCU research has addressed each of these challenges. This collaboration therefore exemplifies both the Unit of Assessment's (UoA's) approach of undertaking research that addresses the specific needs of stakeholders via coordinated and sustained activity, and the University's approach of seeking to deliver deep local and regional impact that has focussed wider influence.

Research led by Dr Carol Trim has focussed on the potential of venom components for the development of cancer therapeutics, with a specific aim of identifying factors that block the Epidermal Growth Factor Receptor (EGFR). This receptor is present on the surface of many cell types but is overexpressed in a large number of cancers, and is important in cancer cell growth. Dr Trim's work has shown, in cell culture assays, that venom and venom components from multiple species of snakes, scorpions and spiders lowers the growth and viability of many cancer cell lines, and has identified both line-specific and venom-specific effects. Subsequent analysis of the effects of these venoms on EGFR and related receptor tyrosine kinase family members – highly conserved and functionally important druggable targets for cancer therapy – has identified widespread changes in protein phosphorylation **[R1]**. Further characterisation of these anti-

cancer effects has shown that some are mediated via interactions with EGFR, whilst others have different mechanisms of action **[R1].** This work has therefore identified multiple candidate venoms and venom fractions that represent candidates for therapeutics targeting EGFR, and for characterising novel pathways that can block cancer cell growth. The work also clearly shows that there are many potentially valuable biologically active components present in these venoms. Foundational work that allowed this research to be performed has also identified ways to optimise the processing and storage of venoms, and has identified ways to extract venom from novel sources **[R2]**. These elements of the work have therefore increased the venom yield per animal, allowed venom extraction from novel species, and extended the product shelf life of extracted venom and venom components.
A similar strategy has been used to identify venoms and venom components that have antimicrobial and antifungal effects. Here, assays treating multiple microbial species with venom and venom components from different species have shown effects on survival and growth. This indicates that venoms also represent a rich source of lead compounds for the identification of anti-microbial drugs. Research conducted in collaboration with Dr Sterghios Moschos at Northumbria University has also characterised the oral and venom microbiome of snakes, spiders and scorpions **[R3]**. That viable microorganisms are found in venoms challenges the dogma of venom sterility, and explains why venoms have evolved antimicrobial peptides. This aspect of the CCCU research therefore provides the essential theoretical framework that justifies venoms as a source of antimicrobial drug candidates.

In combination, this body of research has therefore identified and validated venoms as sources of lead compounds for work seeking to develop antimicrobials, antifungals and cancer treatments. Elements of this work are ongoing and aim to characterise specific venom components and to understand their mode of action, *i.e.,* to generate further impact by defining specific candidate therapeutics. The completed work to date has however already had significant impact on Venomtech Ltd., by supporting revenue increases and company expansion.

3. References to the research

[R1] Output published in 2020 in an internationally recognised journal that has a rigorous peer-review process that demonstrates widespread changes in receptor tyrosine kinase phosphorylation in response to venom from six species – McCullough, D., Atofanei, C., Knight, E., Trim, S.A. and Trim, C.M., 2020. Kinome scale profiling of venom effects on cancer cells reveals potential new venom activities. Toxicon, 185, pp.129-146.

[R2] Output published in 2019 in an internationally recognised journal that has a rigorous peer-review process that reports the development and validation of a method for extracting non-destructively extracting venom from jellyfish. Robinson, P., Trim, S. and Trim, C., 2019. Non-invasive extraction of Cnidarian venom through the use of autotomised tentacles. Animal Technology and Welfare, 18(3), pp.167-173.

[R3] Working paper deposited as a preprint in 2018 that challenges the dogma of venom sterility, indicates that venomous animal bite wounds present an increased primary infection risk, and that has been cited 5 times to date – Esmaeilishirazifard, E., Usher, L., Trim, C., Denise, H., Sangal, V., Tyson, G.H., Barlow, A., Redway, K.F., Taylor, J.D., Kremyda-Vlachou, M. and Loftus, T.D., Lock, M.M.G., Wright, K., Dalby, A., Snyder, L.A.S., Wuster, W., Trim, S. and Moschos, S.A., 2018. Microbial adaptation to venom is common in snakes and spiders. bioRxiv, p.348433.

The key funders of this research are Kent Cancer Trust, and Venomtech Ltd.

4. Details of the impact

Venomtech Ltd. is a biotechnology company established in 2010 and based at the Discovery Park Enterprise Zone (Sandwich, Kent). The company was founded with the aim of helping to solve one of the key problems in drug discovery; that of finding adequate new drug leads. With

the UK's largest venomous animal library, and one of the largest such collections globally, Venomtech Ltd. focusses on supplying arrayed libraries of both venoms and venom fractions, and offers a range of venom-related contract research services. With customers around the world and major markets in the UK, Europe and the US, Venomtech Ltd. is globally important in this area of drug discovery.

As one of the first of the industrial collaborations stemming from CCCU's Life Sciences Industry Liaison Lab – the UoA's industry hub at the Discovery Park site where research is embedded with local industry partners – CCCU researchers have been working with Venomtech Ltd. since its opening in March 2016. In line with the UoA's approach to maximising impact, the research outlined in this case study was undertaken in close collaboration with Venomtech Ltd. and specifically sought to meet the company's key challenges of: demonstrating the action of venoms against specific targets; obtaining sufficient quantities of venom at the quality required; and developing new product lines. CCCU research has had impact on Venomtech Ltd. by addressing all of these challenges, delivering revenue increases and supporting company expansion, with much of the impact to date focussed on Venomtech Ltd. as a direct research user.

CCCU research has demonstrated that venoms and venom fractions are active against specific targets such as particular cancer cell lines or specific bacteria or fungi (*e.g.,* **[R1]**). CCCU research has also enabled Venomtech Ltd. to progress projects much faster than they could have on their own **[S1]**, facilitating their entry into, and expansion within, the market for contract research services. Research has also allowed a new species group to be added to the company's portfolio **[R2]**, and has optimised the processes involved in venom extraction, fractionization and storage. This process optimisation has produced an 80% reduction in time for Venomtech Ltd.'s initial hit to lead service and improvements in product stability across all the company's products **[S1]**.

Results of CCCU research are now present in the majority of Venomtech Ltd.'s product marketing material and white papers, with approximately 60% of this material referencing or presenting the results of CCCU research and evidencing the effect of venoms **[S1]**. CCCU research has therefore impacted Venomtech Ltd.'s sales and, in the period from 2016-2020, an estimated GBP70,000 of sales revenue can be directly linked to CCCU work, with, for example, sales of approximately GBP30,000 attributed to the use of these data in 2019 **[S1]**. CCCU was also the dominant partner in the data presented to investors as part of Venomtech Ltd.'s most recent successful round of investment in 2020 **[S1-2]**, with the CCCU work demonstrating that the company's concept works, and that people buy into it. This investment in Venomtech Ltd. has facilitated team expansion and the acquisition of new instrumentation, further increasing the scale of venom arrays that can be delivered, and enhancing the company's ability to undertake contracted research **[S1, S3]**.

In combination, this means that through the direct effects of CCCU research on Venomtech Ltd., there has been significant impact, both on commerce and the economy. A broader impact of this research is also evidenced by the engagement of new companies and customers with Venomtech, indicating that the use of venoms and venom components is becoming a more established part of early-stage drug discovery.

5. Sources to corroborate the impact

S1 CEO of Venomtech Ltd.
S2 https://discovery-park.co.uk/venomtech-announce-closure-of-angel-investment-and-relocation-to-new-lab-space/
S3 https://venomtech.co.uk/news/2020/09/venomtech-announces-new-investment/