Institution: University of Nottingham

Unit of Assessment: UoA5

Title of case study: Spin out Exonate generates investment and job creation through the development of a revolutionary eye drop treatment for neovascular eye disease.

Period when the underpinning research was undertaken: 2013 - present

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:
David Bates	Professor of Oncology	2013 - present
Jennifer Batson	Hermes Fellow	October 2013 – April 2015

Period when the claimed impact occurred: 2014 - present

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact

Innovative research conducted by Professor Bates and Dr Batson at the University of Nottingham (UoN) led to the development of a revolutionary new treatment for neovascular eye disease *via* eye drops. The company Exonate was spun out to develop this eye drop treatment in December 2013 and licensed a UoN patent for the use of the novel compounds in neovascular eye disease in April 2014. As of December 2020, Exonate employs 18 people, has raised approximately GBP9,000,000 in investment and has secured a collaboration deal with Janssen Pharmaceuticals, part of Johnson & Johnson [redacted text].The first in human clinical trials of the eye drop commenced in November 2020 in Australia.

2. Underpinning research

Neovascular eye disease is the leading cause of sight loss in developed countries, of which Age-related Macular Degeneration (AMD) and Diabetic Macular Oedema (DMO) are the most common. AMD is the UK's leading cause of sight loss affecting over 600,000 people, with 70,000 new cases diagnosed each year. In 2016, the Macular Society projected that the number of people with AMD is expected to double by 2050 to 1,300,000 – equivalent to 400 new cases every day.

There are two types of AMD, wet and dry. Wet AMD is the more severe form and occurs when abnormal blood vessels grow under the macula and retina. DMO is the leading cause of blindness in the working population and is also caused by increased blood vessel growth into the retina, driven by excess of the angiogenic protein VEGF.

Angiogenesis, or blood vessel growth, is normally regulated by VEGF, which naturally exists in both pro- and anti-angiogenic variants. The pro-angiogenic isoforms are known to promote angiogenesis in many conditions, including wet AMD and DMO. Current treatments for wet AMD and DMO are antibody-based and do not differentiate between pro- and anti-angiogenic VEGF isoforms and so inhibit both. Consequently, there could be potential side effects from long-term treatments that deplete both forms of VEGF. Current antibody-based treatments are delivered as monthly intraocular injections, which are uncomfortable, carry an infection risk, and require administration by medical staff. Consequently, there is a need to develop a cheaper, safer, and more precise treatment that can be self-administered.

Previous work undertaken by Professor Bates while at the University of Bristol working in collaboration with Professor Steven Harper demonstrated that Serine/Arginine protein Kinase 1 (SRPK1) inhibition led to reduced expression of specifically pro-angiogenic VEGF-A isoforms, restoring the balance of pro and anti-angiogenic isoforms to normal physiological levels. This downstream splicing of VEGF as the target for inhibitors was patented by the University of Bristol and an initial class of inhibitors was patented by Professor Bates at the University of Bristol with Professor Jonathan Morris from University of New South Wales (UNSW) and further licensed to the University of Nottingham (UoN). Professors Bates and

Harper and Professor Lucy Donaldson at UoN had shown that SRPK1 inhibitors were capable of modifying VEGF signalling in ocular diseases, but also in pain, cancer, and kidney diseases.

In April 2013, Professor Bates joined the UoN and set up an in-house screening assay for selective SPRK1 inhibitors. Professor Bates (UoN) and co-inventor Professor Morris (UNSW) designed novel compounds (piperazine derivatives), which were subsequently synthesised in Professor Morris' laboratory. An initial screening of 23 of these compounds conducted between April and December 2013 at UoN produced initial data on four compounds that demonstrated for the first time that there were potent compounds that inhibited SRPK1 selectively **[1]**. The promising results from this initial screening led to Professor Bates gaining a GBP50,000 Hermes Enterprise Fellowship **[4]** for Dr Batson to join the team in November 2013. The positive results provided the motivation for Professors Bates (UoN), Donaldson (UoN) and Harper (University of Bristol) to spin out Exonate Ltd in 2013.

From November 2013 to April 2014, Dr Batson continued to work at UoN to screen the piperazine derivatives and identified Sphinx31, which showed high selectivity and efficacy for inhibiting SRPK1 and thereby selectively inhibiting pro-angiogenic VEGF **[1]**. Further analysis using a novel porcine eye-permeability assay developed by Professor Bates and Dr Batson demonstrated that these compounds had scleral permeability, which revealed clinical potential for these compounds to be delivered in the form of eye drops **[2]**. This data was submitted in Patent Application WO 2015/159103 A1 in April 2014, published in October 2015 and granted in 2018 **[3]**. This composition of matter patent covered the novel chemistry of the compound, its mode of delivery and its function to alter splicing of VEGF, acknowledging the novelty of targeting SRPK1.

3. References to the research

Key publications (University of Nottingham UoA5 researchers, at the time of publication, are highlighted in bold)

1 **Batson J**, Toop HD, Redondo C, **Babaei-Jadidi R**, Chaikuad A, Wearmouth SF, Gibbons B, **Allen C**, Tallant C, Zhang J, Du C, Hancox JC, Hawtrey T, Da Rocha J, Griffith R, Knapp S, **Bates DO**, Morris JC (2017). Development of potent selective SRPK1 inhibitors as potential topical therapeutics for neovascular eye disease. *ACS Chem. Biol.* 12, 3, 825-832. doi: 10.1021/acschembio.6b01048

2 **Batson J**, Toop H, **Rowlinson J**, **Allen CL**, **Brian G**, Morris J, **Bates DO** (2016). Development of novel angiogenesis inhibitors with scleral permeability required for therapeutic exposure as eye drop. *Conference proceedings in Investigative Ophthalmology & Visual Science, September 2016, Vol.57, 774. Presented at the Association for Research in Vision and Ophthalmology (ARVO) 2016 Annual Meeting, May 1-5 2016, Seattle, Washington, USA.*

Patents

3 University of Nottingham, Newsouth Innovations Pty Limited, "*Piperazine derivatives for treating disorders".* Inventors **David Bates** and Jonathan Morris, International Patent Application WO 2015/159103 A1, 22.10.2015. Licenced to Exonate in 2018, web link

Grants

4 2013-2014, Hermes Fellowship, "SPHINX: Development of AMD Therapeutic", **Bates** PI, GBP50,000

4. Details of the impact

DMO and wet AMD are progressive eye diseases that create difficulties in carrying out everyday tasks like reading, recognising faces and driving, and thus represent a substantial impairment to people's independence and quality of life. The potential to revolutionise treatment for a healthcare issue that affects hundreds of millions of people globally has made Exonate a highly investable opportunity. Exonate received investment of over **GBP9,000,000** between 2014 and 2019. It also secured a collaboration deal with the international pharmaceutical company Janssen Pharmaceuticals to develop an eye drop for

the treatment of wet AMD and DMO [redacted text]. This successful international investment into a UK company has created employment for **18 employees** at Exonate **[S1]**.

Incorporation of Exonate linked to compound early development

Early screening data generated by Professor Bates and Dr Batson (April-December 2013) demonstrated efficacy at low concentrations of SRPK1 inhibitors **[1]**. This efficacy was a strong indicator of high potential for clinical use and alongside the patent and existing know-how from the University of Bristol consequently provided the impetus to spin out Exonate **[S1]**. Exonate Ltd was spun out of the UoN in 2013 by Professors Bates and Donaldson (UoN) and Professor Steven Harper (University of Bristol) based on their intellectual property, along with that of Professor Jonathan Morris (University of New South Wales) who designed, synthesised and provided the compounds **[S1]**.

In April 2014 a licence and pipeline agreement between the UoN and Exonate meant UoN knowhow was shared with Exonate and continued to contribute to the development of the company. Sphinx31 was the primary candidate compound used in the drug discovery process and led to the nomination of the final optimised clinical candidate – EXN407. Dr Batson left the UoN in 2015 to join Exonate as the company's principal scientist. Professor Bates remained at UoN and also serves as Exonate's Chief Scientific Officer.

In 2018, the piperazines, including Sphinx31, led Exonate researchers to identify that a heterocyclic substituent was important for potency and permeability, and optimisation led to compounds like the drug nominated as the preferred compound. Patent WO2015/159103 A1 was formally licenced to Exonate in 2018 **[3]**. Further specific patents, owned by the company, have been developed to protect three elements: the compound's efficacy against the target; permeability properties that allow the compound to get to the retina through the eyeball; and the way it is engineered to disintegrate in the bloodstream in order to avoid systemic off-target effects **[S2,** WO2019063996A1, GB202010829D0**]**.

Investment of GBP9,000,000 raised by Exonate through four funding rounds and a Wellcome Trust award (2014 – 2019)

i. First funding round closed in April 2014 and raised GBP400,000 **[S3]**: early data generated by Professor Bates and Dr Batson at UoN, alongside data on pain generated by Professor Lucy Donaldson at UoN, was presented to potential investors during the first funding round. Investors included IPGroup, Fusion IP (now part of IPGroup), University of Nottingham, Nottingham Angels and private investors. The first funding round was used to set the company up, to invest in an initial prototype project to test feasibility of the approach for developing permeable SRPK1 inhibitors and to fund the patents on the first compounds **[S2,** WO2017064512A1**]**.
ii. Second funding round closed in October 2015 and raised just under GBP800,000 **[S4]**: investors included the Angel CoFund. This funding round allowed Exonate to enable *in vivo* testing and expand the chemistry studies to identify new clinically promising candidates with better potency, permeability, solubility and distribution in the retina and less toxicity.
iii. Third funding round closed in November 2016 and raised just under GBP1,500,000 **[S5]**: investors included the Angel CoFund and new investment from the Australian venture fund Uniseed, the University of Bristol Enterprise Fund (managed by Parkwalk), Martlet of Cambridge, Wren Capital, as well as further Angel Investors and O2h Ventures. This investment allowed Exonate to develop business partnerships that could lead to licensing deals, to employ a clinical advisory team to aid the planning and design of a clinical trial, and to undertake *in vivo* proof-of-concept studies in relevant species to further guide research towards a lead candidate.
iv. The Wellcome Trust Seeding Drug Discovery Award in February 2017 secured GBP4,900,000 **[S6]**: the award funded the continued development of an eye drop treatment, allowing Exonate to move from a lead candidate to an optimised compound that became the clinical candidate compound, and to undertake safety pharmacology and chemical manufacturing and testing. Uniseed Chief Executive Officer said: *"the Wellcome*

Trust award further validates the decision to invest into Exonate as it has provided a unique opportunity for Uniseed to get in at the "ground floor" of a drug development program that has been de-risked by being supported by the world's largest pre-eminent medical research charity funding research into human health" **[S7]**. In July 2017, Exonate secured the *'One to Watch'* award at the UK Business Angels Association Investment Awards, with the judges stating that *'Exonate is showing promise in developing revolutionary approaches to treatments for eye conditions, and has been backed by investors with deep industry knowledge'* **[S8]**.

v. Fourth funding round closed in January 2019 and raised GBP1,500,000: investors included the Angel CoFund, the Australian venture fund Uniseed, the University of Bristol Enterprise Fund (managed by Parkwalk), Martlet of Cambridge, Wren Capital, O2h Ventures, as well as further Angel investors. Funds were used to undertake business development and complete crucial critical path experiments (e.g. reactive metabolite and other safety tests) to secure a commercial deal with the global pharmaceutical company Johnson & Johnson **[S9]**.

Exonate secured a treatment development deal with Janssen Pharmaceuticals [redacted text]:

In December 2019, Exonate Ltd secured a major collaboration agreement with Janssen Pharmaceuticals Inc, a pharmaceutical company based in New Jersey (USA) and part of the Johnson & Johnson family of companies **[S10]**. The collaborative programme aims to develop a new eye drop treatment for retinal vascular diseases such as wet AMD and DMO and is organised in development milestones [redacted text]:

i. First milestone: signing of the collaboration agreement in December 2019
ii. Second milestone: pre-clinical safety approval in December 2019
iii. Third milestone: Clinical Trial Notification Approval in September 2020 **[S11]**
iv. Fourth milestone: first patient enrolment in the clinical trial in November 2020
v. Fifth milestone: clinical trial conclusion with the last visit of the last of 48 patients is planned for December 2021

[redacted text]

5. Sources to corroborate the impact (websites were last accessed on 18/01/2021)

S1 Corroborating statement from CEO of Exonate
S2 Exonate patents:
WO2019063996A1 'SRPK1 inhibitors', web link
GB202010829D0 'Compounds for treatment of neovascular diseases', web link
WO2017064512A1 'Compounds', web link
S3 Exonate press release on successful first funding round (April 2014), web link
S4 'Exonate closes second successful funding round' (15 Oct 2015), web link
S5 'Exonate closes successful funding round' (30 Nov 2016), web link
S6 2017-2020, Wellcome Trust Seeding Drug Discovery Award: Optimisation and preclinical development of small molecule inhibitors of SRPK1 for topical application in the treatment of wet Age Related Macular Degeneration (wAMD) through modulation of VEGF splicing, (202673/Z/16/Z) web link
S7 'Exonate receives Wellcome Trust funding to develop eye drop treatment' (6 Feb 2017), web link
S8 Exonate is the 'One to Watch' in the Best Investment in Life Sciences (7 July 2017), web link
S9 'Exonate closes successful £1.5 million fundraising' (3 Jan 2019), web link
S10 'Healio News announces Exonate deal with Janssen Pharmaceuticals, web link
S11 Clinical Trial Notification (Pdf document) and ClinicalTrials.gov website showing the Status as 'Recruiting' as of December 2020, web link