Institution: University of Bradford

Unit of Assessment: A3 - Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: Incanthera Plc, a successful spin-out company from the University of Bradford, has attracted a £9 million external investment and created high quality technical jobs in northern England.

Period when the underpinning research was undertaken: 2008– 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:
Prof Robert A Falconer	Professor of Medicinal Chemistry	2005 – present
Prof Paul M Loadman	Professor of Pharmacokinetics and Drug Metabolism	1996 – present
Dr Klaus Pors	Senior Lecturer in Chemical Biology	2005 - present

Period when the claimed impact occurred: 1 August 2013 – present

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

1. Summary of the impact (indicative maximum 100 words)

The development of ICT2588, a novel tumour-targeted anti-cancer prodrug, and associated molecules, has directly resulted in the commercialisation of research, investment in the biotech industry, and created high-skill employment in the North of England. The research has generated IP that has been commercialised through Incanthera plc. Over GBP4,000,000 private Venture Capital funding was raised to progress ICT2588 through preclinical evaluation. Ellipses Pharma recently acquired the technology, injecting GBP4,900,000 into the programme to enable a Phase I clinical trial and associated studies. This led directly to an increase in employment within Incanthera from 2 to 5 FTE, attracted VC funding to the region, and led to flotation of the company on the NEX (AQSE) stock exchange.

2. Underpinning research (indicative maximum 500 words)

Despite major advances in the clinic there is still a significant unsolved problem in treating cancer with chemotherapy without causing debilitating side effects to the patient. One approach is to selectively target a potent anti-cancer agent directly to the tumour microenvironment, protecting normal tissues from exposure to the drug. The tumour-expressed matrix metalloproteinases (MMPs) have been shown by University of Bradford (UoB) researchers to have ideal characteristics for development of tumour-activated therapeutics [1].

A series of therapeutics were developed by the UoB team, which utilise MMPs localised within the tumour microenvironment to safely trigger release of a potent anticancer agent (azademethylcolchicine) selectively in the tumour. The research was funded by Cancer Research UK/Yorkshire Cancer Research. Azademethylcolchicine is a vascular disrupting agent (VDA), a class of therapeutic that has attracted considerable attention in recent decades but has yet to realise a clinically useful drug due to toxicity caused by a lack of selective targeting in patients (specifically cardiotoxicity) [2].

ICT2588, our lead agent, has been shown to be selectively activated by MMPs in the tumour, with minimal active agent released in normal tissue, and a lack of cardiotoxicity in preclinical models [2]. Administration of ICT2588 to tumour-bearing mice resulted in significant anti-tumour efficacy in a range of tumour models (including prostate, breast, lung, colon), and tumour cures

in combination with standard chemotherapy [1]. Advanced animal toxicology studies have thus far not revealed toxicity.

UoB spin-out company Incanthera Ltd. (www.incanthera.com) was founded in 2010 by researchers at UoB to act as the commercial development vehicle for ICT2588. To progress the initial new drug candidate, Incanthera initially secured GBP375,000 funding in Jan 2012 from SPARK Impact, manager of the North West Biomedical Venture Capital Fund, to progress towards a Phase I clinical trial with ICT2588. Positive results from the initial toxicology studies helped to attract funding from outside of North of England and to establish 2 permanent staff at Incanthera (headcount: 2; FTEs: 2).

A collaboration with Stanford University's world-leading imaging specialists, has realised a nanoparticle-tethered 'theranostic' version of ICT2588 (ICT-CLIO). This novel construct has demonstrated significant added value: further improved tumour penetration, blood-brain-barrier penetration, and efficacy in glioblastoma (GBM, a deadly brain tumour) in preclinical models, superior to temozolomide (the standard of care) with simultaneous utility as an MRI contrast agent [4,5]. Synergy in combination with radiotherapy, central to treatment of brain cancer, has also been demonstrated, providing a clear path to clinical use [5].

In addition, the UoB team embarked on the development of a targeted-taxane version of ICT2588 (paclitaxel prodrug, ICT3205) [6]. Taxanes are central to prostate cancer chemotherapy and many other cancers, and the commercial market for a targeted taxane is thus huge. Taxanes lack selective toxicity (producing significant side effects, which limits the dose that can be given, and thus potential efficacy) and lack solubility in aqueous media, necessitating use of injection vehicles (i.e. Kolliphor, polysorbate 80, ethanol) which cause toxicity and irritation *per se*. Preclinical data demonstrated the selective release, enhanced tumour concentrations and a lack of selective toxicity following administration of ICT3205 in animal models of prostate cancer [6]. ICT3205 importantly demonstrates the utility of the prodrug concept as a platform technology.

In parallel, the UoB team has developed prodrug technology focused on utilising the metabolic activity of tumour-expressed cytochromes P450 enzymes to activate prodrugs. Work has focused on delivery of the ultra-potent duocarmycin family of natural products and has resulted in demonstration of efficacy in preclinical models [7]. This research led to a project to deliver duocarmycins using an MMP-targeted approach, currently funded by Breast Cancer Now, bringing together the two complementary technologies.

The IP for ICT3205 [6], duocarmycin prodrugs [7] and ICT-CLIO [8] have been additionally assigned to Incanthera. This research was led by Falconer and Loadman. Pors led the duocarmycin prodrug-related research, each at the Institute of Cancer Therapeutics, University of Bradford (www.bradford.ac.uk/ict) (between 2005 and present).

3. References to the research (indicative maximum of six references)

1. Atkinson, J.M.; et al (2010). "Development of a tumor-targeted vascular disrupting agent activated by Membrane-type Matrix Metalloproteinases (MT-MMPs)." *Cancer Research*, 70: 6902-6912. DOI: 10.1158/0008-5472.CAN-10-1440
2. Gill, J.H. et al. (2014) "The Tumor-Targeted Prodrug ICT2588 Demonstrates Therapeutic Activity Against Solid Tumors and Reduced Potential for Cardiovascular Toxicity." *Molecular Pharmaceutics*, 2014, *11,* 1294−1300.DOI: 10.1021/mp400760b

3. Falconer, R.A. et al (2015) "Preparation of peptidyl compounds for the treatment of cancer" Patent No: WO 2010046628 (2010); CN 102143762 (2014); JP 5820272 (2015); US20110275554A1 (2011), US 8927486 https://patents.google.com/patent/US20110275554

4. Mohanty, S. et al. (2017) "A novel theranostic strategy for MMP-14 expressing glioblastomas impacts survival." *Molecular Cancer Therapeutics*,16: 1909-1921. DOI: 10.1158/1535-7163.MCT-17-0022

5. Wu, W. et al. (2019). "Radiation plus theranostic combination therapy for targeting glioblastomas." *Nanotheranostics*, 3: 299-310. DOI: 10.7150/ntno.35342

6. Loadman, P.M. et al. (2015). "MMP-sensitive taxane prodrug" GB, EU Patent Applications; GB1521215.2A, EP3383437A1 (Filed Dec 2015, 2018). https://patents.google.com/patent/EP3383437A1/en

7. Travica, S. et al. (2013) "Colon Cancer–Specific Cytochrome P450 2W1 Converts Duocarmycin Analogues into Potent Tumor Cytotoxins." *Clinical Cancer Research*, 2013, *19*, 2952-2961. DOI: 10.1158/1078-0432.CCR-13-0238

8. Loadman, P.M. et al (2016). "Tumour-targeted Theranostic." Patent No: GB 2516882 (2015); WO 2015014756 (2015); EP 3027217 https://patents.google.com/patent/WO2015014756A1/en

Grants

1. Falconer, R.A. (P.I.); Loadman, P.M.; Pors, K.; Shnyder S.D.; Twelves, C.J. Breast Cancer Now. "Development of a novel, targeted cytotoxic treatment for breast cancer." Jan 2019; 2.5 years; GBP191,037.

2. Falconer, R.A. (co-P.I.); Loadman, P.M. (co-P.I.); Shnyder S.D. University of Bradford Collaboration Development Grant. " *In vivo* evaluation of a novel prodrug of AZD-6738." Jan 2018; 4 months; GBP18,295.

3. Falconer, R.A. (P.I.), Loadman, P.M., Adams, K. Yorkshire Innovation Fund. March 2014; 1 year; GBP27,038.

4. Falconer, R.A. (P.I.); Loadman, P.M. Guangzhou Healthtech Open Innovation Proof of Concept Fund. "Development of a rapid, highly sensitive and selective detection system for cancer." Dec 2012; 2 years; GBP200,000.

5. Patterson, L.H. (P.I.), Afarinkia, K.; Sutton, C.W.; Falconer, R.A.; Pors, K.; Loadman, P.M.; Gill, J.H.; Shnyder S.D. Yorkshire Cancer Research. "Cancer Medicines Discovery" Programme grant extension. Grant Ref: B209PG. October 2012; 1 year; GBP330,552.

6. Gill, J.H.; Loadman, P.M. (P.I.); Falconer, R.A.; Shnyder, S.D.; Prostate Cancer UK. "Development of tumour-selective therapeutics for advanced prostate cancer" Grant Ref: PG10-05. October 2011; 3 years; GBP257,816.

7. Patterson, L.H. (P.I.), Afarinkia, K.; Sutton, C.W.; Falconer, R.A.; Pors, K.; Loadman, P.M.; Gill, J.H.; Shnyder S.D. Yorkshire Cancer Research. "Cancer Medicines Discovery" Grant Ref: B209PA. October 2008; 4 years; GBP1,373,685.

8. Gill, J.H. (P.I.); Loadman, P.M.; Falconer R.A.; Patterson, L.H. Modern Biosciences. "MMP-activated prodrugs" June 2008; 1 year; GBP75,000.

4. Details of the impact (indicative maximum 750 words)

The underpinning research and intellectual property associated with MMP-activated prodrug ICT2588 and related anti-cancer molecules has been the driving force for the development of Incanthera from a small university spin-out company (established in 2010), through a major

successful licencing deal, to a public limited company (2020), and as such has provided significant impact. Since 2013, positive impact has been achieved in the following areas: research commercialisation, biotech industry, high-skill employment, and economic success.

The approach underpinning the MMP-targeted prodrug technology (exemplified by ICT2588) is to improve the therapeutic index of agents currently used in the clinic, or resurrect agents deemed too toxic for use in patients. This is achieved by targeting the drug selectively to cancer tissue (where it is activated and released) and preventing exposure of normal tissues to drug.

Following the early investment to progress ICT2588, Incanthera acquired additional IP generated by the Bradford group (2015) which extended the ICT2588 delivery mechanism to other drugs, specifically in this case to deliver taxanes (e.g., paclitaxel, docetaxel). This provided another generation of potential therapeutics and was key to demonstrating the wider utility of the MMP prodrug concept as a platform technology. The market for paclitaxel and docetaxel is large, given their use in multiple cancer types globally. Subsequent licencing deals followed for the UoB-Stanford University invention ICT-CLIO (2015), and IP underpinning the Cytochromes P450-activated duocarmycin prodrugs developed at UoB (2015, S1]. Each was licenced to Incanthera, had a direct impact on the relative commercial value of the company, and was crucial to attracting a further investment of GBP2,000,000 [S2], including from SPARK Impact, and increasing the number of jobs within the company by 2, to a total of 5 posts (FTEs: 5). Total investment in the company over the 2013-20 period is approx. GBP10,000,000 [S3].

Incanthera's development of ICT2588 was the focus of employment within the company (plus expert consultants in drug development/clinical trials, commercial contracts supporting staff at UoB) as well as support of CRO investigators conducting the scale-up manufacture, preclinical toxicology evaluation and design of a clinical trial protocol for a Phase I clinical trial of ICT2588 in cancer patients. The IP for ICT2588 was protected in multiple territories globally [S4].

In 2017, Ellipses Pharma (https://ellipses.life), acquired the ICT2588 technology, injecting GBP4,900,000 into Incanthera, to enable a clinical trial in cancer patients (currently scheduled for 2022) [S5]. This was a significant milestone for the Incanthera, and has informed their business model of acquiring IP, de-risking and adding value prior to seeking a licencing deal for a clinic-ready asset. This licencing deal provided external endorsement of the research, and the company, its first major licencing deal, and provided the platform to acquire further drug technologies (including IP independent of UoB). Incanthera acquired Onco-NX Ltd [S6] and its lead agent ES5 (a bioreductive prodrug), and IP for a cancer-preventing sun cream (Sol).

Having proven the business model of adding value to IP prior to licencing (demonstrated with ICT2588/ICT3205/ICT-CLIO) and with new acquisition Sol, Incanthera succeeded with an initial public offering (IPO), generating a further GBP1,200,000 (gross), and successful listing on the NEX stock exchange (now Aquis Stock Exchange, AQSE Growth Market) in Feb 2020 [S7, S8, S9]. This is a significant achievement, given the current financial climate and Brexit uncertainty. The company now trades as Incanthera plc. Shares in Incanthera were initially offered at GBP0.095, increasing by more than 100% to GBP0.20 (Nov 2020) [S8]. The University of Bradford is a major shareholder in Incanthera.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[S1] Successful Fundraising, Acquisition of New Drug Programme, Acquisition of Spear Therapeutics Limited (January 2015)
Incanthera news release detailing the licencing deal for the duocarmycin prodrug family of prodrugs ('novel targeted chemotoxin selective for colorectal cancer').

[S2] City news: Incanthera
Daily Express news article detailing Incanthera securing VC funding

[S3] Testimonial letter – Incanthera plc (February 2021)

[S4] Incanthera strategic IP review

"The results of the IP portfolio review have resulted in the decision to maintain European patent protection across 21 European countries, effectively 99% of the European marketplace, for the Company's lead asset, ICT01-2588, whilst progressing worldwide patent protection, to enhance existing markets including the United States and Japan. This strategic decision enhances ICT01-2588's commercial value in the world's second largest oncology market, estimated at US$30bn in 2018".

[S5] Announcement of Commercial Deal for innovative cancer therapeutic (July 2017)
Incanthera news release detailing the licencing deal with Ellipses Pharma, who acquired the MMP prodrug technology

[S6] Incanthera buys Salford spin-out Onco-NX
News article describing Incanthera's acquisition of Onco-NX

[S7] Admission to trading on the NEX Exchange Growth Market (February 2020)

"Incanthera has built an exciting portfolio of innovative oncology technologies and we believe we have an excellent opportunity, led by an experienced and committed management team, to deliver a real difference in the global fight against cancer.

This public listing on NEX will provide an excellent platform for further growth, through awareness and further progression of our existing technologies"

[S8] Aquis Stock Exchange | Incanthera plc | IPO
Link to the company profile on the AQUIS exchange, providing share price profile, and stock transaction summary

[S9] Incanthera Ltd | Hardman & Co (hardmanandco.com)
Company summary and financial information