Institution: Newcastle University		
Unit of Assessment: UoA5		
Title of case study: Fibrofind, a stable human alternative for testing anti-fibrotic drugs		
Period when the underpinning research was undertaken: 2019-2020		
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:**
Prof Jelena Mann	Professor of Epigenetics	1/9/06 to present
Prof Fiona Oakley	Professor of Fibrosis Biology	1/9/06 to present
Prof Derek Mann	Professor of Hepatology	1/9/06 to present
Dr Lee Borthwick	Senior Lecturer	5/9/05 to present
Miss Hannah Paish	Research Technician	1/8/16 to present
Mr Lee Reed	Senior Laboratory Technician	26/7/10 to present
Mrs Helen Brown	Research Technician	9/9/13 to 9/10/15
Dr Clive Griffiths	Strategic Research Adviser	1/7/16 to 17/9/19
Dr Michael Drinnan	Honorary Reader	1/7/03 to present
Mr Mark Bryan	Research Technician	1/7/16 to 30/6/18
Dr Jack Leslie	Senior Research Associate	1/1/18 to present
Mr Ben Barksby	Research Technician	1/8/17 to present
Miss Abigail Watson	Research Technician	28/11/16 to 31/8/19
Dr Julia Whitehall	PhD student	2016 to 2019
Dr Marco Zaki	PhD student	Nov 2015 to Dec 2019
	2 research associates, 1 Newcastle University Research Fellow and 1 technician also assisted the research	
Period when the claimed impact occurred: 2019–present		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Fibrosis is the thickening and scarring of organ tissue and has a large associated health burden. Current models of fibrosis are poor predictors for anti-fibrotic drug interactions in the human body and as a consequence many drugs fail when tested in human trials. Precision cut slices (PCSs) of human tissues offer better predictive abilities. Newcastle has developed a novel bioreactor for keeping PCSs viable, developing the platform and the protocol for inducing fibrosis, to improve the predictability of drug action on fibrotic tissue *ex vivo*. This led to the spin-out company FibroFind, which tests anti-fibrotic drugs using the PCSs bioreactor and fibrosis protocol. FibroFind has generated approximately £1.6M in revenue since 2019 from 25 large pharmaceutical/SME contracts and created jobs. Companies using FibroFind technology have experienced increased share prices of up to 48% following successful completion of drug candidate testing.

2. Underpinning research

Fibrosis

Fibrosis is a pathological state occurring in any soft tissue where an imbalance exists between fibrogenesis, the synthesis and deposition of extracellular matrix (ECM), and fibrolysis, the breakdown and clearance of ECM. Fibrosis is common to all forms of chronic diseases of respiratory, renal, CNS, cardiovascular, GI/pancreatic and musculoskeletal systems. Fibrosis therefore represents a massive world-wide healthcare burden and is a significant cause of mortality. It is estimated to underlie 45% of all diseases and deaths in the western world[1].

Challenges of current fibrosis models

Potential anti-fibrotic compounds or drugs need to be validated through lengthy and expensive pipelines of preclinical cell-based assays, animal models of disease and eventually clinical trials.

[1] Wynn TA. (2008) Cellular and molecular mechanisms of fibrosis. *Journal of Pathology*. 214(2):199–210. DOI: 10.1002/path.2277

However, while cell assays and animal models are useful for drug discovery, drugs often fail when advanced to clinical trials because of unforeseen complications due to fundamental differences between the human body versus cell culture or animal systems (R1). The process of identifying candidate drugs to take further in clinical trials can take decades and cost billions of pounds while still being subject to an immensely high failure rate[2]. There is therefore an unmet need to develop more biologically representative and accurate pre-clinical models of human fibrosis. This area is of significant interest to the pharmaceutical and biotechnology industries as such models would allow for preclinical testing of multiple therapeutic solutions and provide a resource for identifying potential treatment pathways.

Development of a novel bioreactor

Precision cut slices (PCSs) generated from a variety of human organs provide a solution to many disease modelling issues (R1). Current technology can only maintain PCS viability for around 24 hours. Newcastle research led to the development of a bioreactor which maintains PCS viability and function for 7 to 14 days (R2).

Newcastle's bioreactor gently rocks PCSs in specially constructed plates with channels between sets of two wells of the plate. Movement of the plate provides bidirectional flow of the media between wells (R3). The resulting set up surrounds the PCSs in a normoxic environment and maintains viability. Fibrosis is induced by culturing PCSs with profibrogenic stimuli for 72 hours. Histological staining, changes in fibrogenic gene expression and tissue collagen confirm stable fibrosis. During development, fibrosis can be significantly attenuated by an Alk5 inhibitor, a potent inhibitor of fibrosis, providing a reliable benchmarking control for anti-fibrotic drugs trialled using this technology (R2).

Subsequent treatment with the test drug thus provides measurement of the drug efficacy in supressing fibrosis in the human organ (R2). First developed for liver slices (R2, R4) the bioreactor can now also maintain PCSs from kidney and lung tissue[3]. The bioreactor in combination with PCSs provides an experimental model that closely replicates what happens in the human body. This increases the likelihood that the therapeutic effects observed in the model will translate to human disease and provides a pre-clinical window in which to test drugs in intact human tissue.

Establishment of FibroFind

A Newcastle University-based commercial service providing access to this bioreactor and PCS models began operating in 2016[4], generating a pre-spinout turnover of £2.3 million. This success led to the spin-out of the small biotechnology company FibroFind Ltd from the University in May 2019. The bioreactor technology was invented and patented by the Newcastle Fibrosis Research Group, (https://patents.justia.com/patent/20190002809, R3) and has now been signed over to FibroFind Ltd.

3. References to the research

SciVal field-weighted citation impact (FWCI) as of December 2020. Newcastle researchers in **bold.**

R1. **Oakley F**, **Gee LM**, **Sheerin NS**, **Borthwick LA**. (2019) Implementation of pre-clinical methodologies to study fibrosis and test anti-fibrotic therapy. *Current Opinion in Pharmacology.* 49:95-101. DOI: doi.org/10.1016/j.coph.2019.10.004. FWCI: 0.26.

R2. **Paish HL**, **Reed LH**, **Brown H**, **Bryan MC**, **Govaere O**, **Leslie J**, **Barksby BS**, **Garcia Macia M**, **Watson A**, **Xu X**, **Zaki MYW**, **Greaves L**, **Whitehall J**, French J, White SA, Manas DM, Robinson SM, Spoletini G, **Griffiths C**, **Mann DA**, **Borthwick LA**, **Drinnan**

[2] DiMasi JA, Grabowski HG, Hansen RW. (2016) Innovation in the pharmaceutical industry: New estimates of R&D costs. *Journal of Health Economics*. 47:20-33. DOI: http://dx.doi.org/10.1016/j.jhealeco.2016.01.012

[3] Human tissue precision-cut slices, A FibroFind Patented Technology. FibroFind webpage https://www.fibrofind.com/solutions-and-technology/human-tissue-precision-cut-slices/

[4] FibroFind are cited as the contract research organisation (CRO) that carried out PCS investigation in Widjaja et al. (2019) Inhibiting Interleukin 11 Signaling Reduces Hepatocyte Death and Liver Fibrosis, Inflammation, and Steatosis in Mouse Models of Non-Alcoholic Steatohepatitis. *Gastroenterology*. 157(3):777-792. DOI: https://doi.org/10.1053/j.gastro.2019.05.002

MJ, **Mann J**, **Oakley F**. (2019) A Bioreactor Technology for Modeling Fibrosis in Human and Rodent Precision-Cut Liver Slices. *Hepatology*. 70(4):1377-1391. DOI: 10.1002/hep.30651. FWCI: 2.81.

R3. **Oakley F**, **Borthwick L**, **Griffiths C**, **Drinnan M.** (2017) Cell Culture. World Intellectual Property Organization. PCT/GB2016/0533l0. Patent available at https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2017068376

R4. De Chiara F, Thomsen KL, Habtesion A, Jones H, Davies N, Gracia-Sancho J, Manicardi N, Hall A, Andreola F, **Paish HL**, **Reed LH**, **Watson AA**, **Leslie J**, **Oakley F**, Rombouts K, Mookerjee RP, **Mann J**, Jalan R. (2020) Ammonia scavenging prevents progression of fibrosis in experimental non-alcoholic fatty liver disease. *Hepatology*, 71(3):874-892. DOI: 10.1002/hep.30890. FWCI: 2.15.

4. Details of the impact

Economic impacts resulting from the development of the patented bioreactor and fibrosis models have been experienced by both FibroFind and the companies that have used the technology.

Impacts on FibroFind

FibroFind Ltd offers pharmaceutical and biotechnology companies preclinical fibrosis models in human liver, kidney and lung tissues in order to identify fibrosis pathways, test drug efficacy and advise on the optimal research solutions to test anti-fibrotic compounds. Between May 2019 and 31st July 2020, FibroFind has grown rapidly. A small biotechnology company, their workforce has expanded from 2 to 10 employees, benefitting the local economy. FibroFind has also signed contracts worth approximately £1.6M with 25 other biotechnology companies; 9 large pharmaceutical companies and 16 SMEs. These client companies are based internationally with 12 in the USA, 4 in Canada, 4 in Europe and 5 in the UK (EV1).

Impact on large pharmaceutical companies using FibroFind

The bioreactor technology and fibrosis model allow companies who contract FibroFind greater predictive ability when testing new therapeutic agents ahead of clinical trials. For example, [Company X] have been using the FibroFind model in a series of studies [redacted for publication] (EV2).

Impacts on SMEs using FibroFind

Contracted work with SMEs has been promoted through press releases and state that the bioreactor technology provided by FibroFind was pivotal in generating positive results and continuing the development of anti-fibrotic drugs. In May 2017 the CEO of Nuformix Plc said about pre-clinical development work for their drug NXP002 "*We're extremely lucky to have had the chance to work with **FibroFind** since its inception – the quality of its people, knowledge and expertise make it a unique place to study fibrosis. The first phase of our programme has concluded positively in multiple fibrotic conditions and we're very excited by the results we've seen*" (EV3). In January 2018 Nuformix Plc released a Regulatory News Service (RNS) release describing the positive results from their NXP002 Pilot Study in Lung and Liver Fibrosis (EV4). In this statement the CEO once again stated "*Traditional pre-clinical fibrosis models offer limited utility as they don't recreate the disease in a genetically or physiologically relevant way, meaning success doesn't always translate into patients. In contrast, the studies conducted at Newcastle University and **FibroFind** put the Nuformix NXP002 programme as close to patient as possible. The results … give us great confidence in what will happen when NXP002 reaches patients and robustly support entry to patient proof-of-concept studies immediately after completion of our pharmacokinetic studies.*"

Other companies have experienced an increase in share price following publication of positive data obtained using FibroFind technology. In June 2019 Hepion Pharmaceuticals (previously called Contravir Pharmaceuticals Inc.) released positive results of their drug trial targeting liver fibrosis. This trial directly involved FibroFind technology (EV5, EV6) and in a statement the CEO of Hepion Pharmaceuticals said "*the results from this study are highly meaningful because they come from fully intact samples of human livers. The closer that experimental models are to replicating what happens in the human body, the greater the likelihood that the therapeutic effects*

observed in the models will translate to human diseases." Further adding that "*precision cut liver slices adds to the growing list of experiments where CRV431 has demonstrated effectiveness and gives us great confidence in developing CRV431 for NASH and other liver diseases*" (EV6). Following the release of these positive results Hepion's stock increased 48% (EV5 and EV7) and Hepion announced a public offering of approximately $15.6 million (EV5 and EV8). The following year in June 2020, Hepion stock again rose 46% (EV9) following the release of positive results from an expanded clinical study of CRV431, again utilising FibroFind's technology (EV5, EV10).

Summary
FibroFind is a successful spin out company formed from Newcastle development of patented improved bioreactor technology combined with protocols for fibrosis induction in PCSs. Both large pharmaceutical companies and SMEs have benefitted from testing their drugs using this technology, including increased share prices and increased confidence of candidate drugs.

5. Sources to corroborate the impact

EV1. Letter of support from Chief Financial Officer of FibroFind Ltd. PDF
EV2. [Company X evidence. Redacted for publication]
EV3. Nuformix announces fibrosis programme with FibroFind. 2nd May 2017. PDF. https://nuformix.com/news/nuformix-announces-fibrosis-programme-with-fibrofind/
EV4. Release from Nuformix Plc about their NXP002 Pilot Study in Lung and Liver Fibrosis. 31st January 2018. PDF. https://www.proactiveinvestors.co.uk/LON:NFX/Nuformix-Plc/rns/LSE20180131070005_13515393
EV5. Letter of support from Chief Executive Officer of Hepion Pharmaceuticals. PDF available on request.
EV6. Compelling positive results reported from Human Liver Experiments with ContraVir (Hepion) Pharmaceuticals' NASH Drug Candidate. 17th June 2019. PDF. https://www.globenewswire.com/news-release/2019/06/17/1869573/0/en/Compelling-Positive-Results-Reported-from-Human-Liver-Experiments-with-ContraVir-Pharmaceuticals-NASH-Drug-Candidate.html
EV7. Investors cheer ContraVir's (Hepion) positive results from a human-liver experiment using its CRV431 drug candidate. 17th June 2019. PDF. https://www.proactiveinvestors.com/companies/news/222263/investors-cheer-contravir-s-positive-results-from-a-human-liver-experiment-using-its-crv431-drug-candidate-222263.html
EV8. ContraVir (Hepion) Pharmaceuticals, Inc. announces pricing of $15.6 million public offering. 18th June 2019. PDF. https://www.globenewswire.com/news-release/2019/06/18/1870316/0/en/ContraVir-Pharmaceuticals-Inc-Announces-Pricing-of-15-6-Million-Public-Offering.html
EV9. Hepion Pharmaceuticals +46% on positive NASH data. 28th January 2020. PDF. https://seekingalpha.com/news/3535512-hepion-pharmaplus-46-on-positive-nash-data
EV10. Hepion's NASH drug candidate, CRV431, demonstrates superior antifibrotic efficacy in expanded human liver study. 28th January 2020. PDF. https://www.accesswire.com/574373/Hepions-NASH-Drug-Candidate-CRV431-Demonstrates-Superior-Antifibrotic-Efficacy-in-Expanded-Human-Liver-Study