Institution: University of Bristol		
Unit of Assessment: 4) Psychology, Psychiatry and Neuroscience		
Title of case study: Novel implantable drug delivery system for neurological conditions creates jobs and improves quality of life		
Period when the underpinning research was undertaken: 2009 - 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:**
Alison Bienemann	Clinical Research Fellow	05/1997 - present
Steven Gill	Honorary Professor of Neurosurgery	2006 - present
Alan Whone	Consultant Senior Lecturer in Movement Disorder	10/2012 - present
Neil Barua	Clinical Lecturer	02/2010 - 08/2016
Will Singleton	Clinical Research Fellow	08/2015 - 08/2017
Period when the claimed impact occurred: 1st August 2013 - 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

University of Bristol research developed a novel, in-house drug delivery system for the safe and reproducible use of Convection Enhanced Delivery (CED) in the treatment of Parkinson's disease and end-of-life neuro-oncology patients. In collaboration with industrial partner Renishaw plc, who have invested tens of millions and employed 70 staff, the drug delivery system has been successfully implanted in 300 patients. The system improves quality of life in Parkinson's disease and neuro-oncology patients, reducing the need for repeat surgical intervention, decreasing medication requirements, allowing care in an outpatient setting and extending median survival.

2. Underpinning research

A major obstacle to the effective treatment of neurological disorders is the blood-brain barrier, which regulates the passage of molecules from the circulation into the central nervous system. Convection Enhanced Delivery (CED) is a method of pressure mediated drug delivery to the brain, through intraparenchymal microcatheters, overcoming the problem of the blood-brain barrier, and enabling widespread distribution of therapeutic agents throughout the target tissue region.

Glial cell line-derived neurotrophic factor (GDNF) is a potent neurotrophic factor with restorative effects in a wide variety of rodent and primate models of Parkinson's disease, but penetration into brain tissue from either the blood or the cerebro-spinal fluid is limited. In 2003, a trial to deliver GDNF directly to the putamen of Parkinson's disease patients showed some signals of efficacy but failed to demonstrate drug delivery more than a few millimetres beyond the catheter tip by a diffusion-dependent approach. The trial identified the need for alterations to the design of drug-delivery methodology, and in 2005 Professor Gill was awarded an MRC grant [i] to undertake research utilising CED for intraparenchymal drug delivery. The research was conducted from 2005 with Prof Gill joining the University of Bristol in an Honorary position from 2008.

The in-house drug delivery system developed consisted of an implantable microcatheter technology and a skull-mounted port which enabled intermittent rather than continuous infusions, and therefore permitting higher flow rates facilitating target-area penetration through convection rather than diffusion. The body of research included designing and evaluating indwelling recess-

stepped catheters [2] and a transcutaneous port, and it involved the assessment of the system in a large animal model [1]. This in-house drug delivery system has since been used in clinician-led studies involving human patients in the UK [3-5].

Initial research was completed under a collaboration with the licence holders for GDNF (MedGenesis), with early pre-clinical research informing the next step that the company took in their approach to required toxicity studies. In 2012, funding from Parkinson's UK and The Cure Parkinson's Trust [ii] supported a single-centre, placebo-controlled, randomised controlled trial of intermittent infusions of GDNF administered via an implanted CED system. Dr Alan Whone was the Chief Investigator leading both the double blind and open label clinical trials. The study showed increased uptake of 18F-dopa on positron emission tomography (PET) throughout the putamen, demonstrating region of interest drug-delivery and target tissue engagement and thus overcoming earlier delivery limitations [4, 5].

3. References to the research

1) **Bienemann A**, **White E**, Woolley M, Castrique E, Johnson DE, Wyatt M, Murray G, Taylor H, **Barua N**, **Gill SS**. (2012). The development of an implantable catheter system for chronic or intermittent convection-enhanced delivery. *Journal of Neuroscience Methods,* 203(2): 284-291. DOI:10.1016/j.jneumeth.2011.10.002

2) **White E, Bienemann A**, Taylor H, Hopkins K, Cameron A, **Gill S**. (2012). A phase I trial of carboplatin administered by convection-enhanced delivery to patients with recurrent/progressive glioblastoma multiforme. *Contemporary Clinical Trials,* 33(2), 320-331. DOI:10.1016/j.cct.2011.10.010

3) **Barua NU,** Hopkins K, Woolley M, O'Sullivan S, Harrison R, Edwards RJ, **Bienemann AS**, Wyatt MJ, Arshad A, **Gill SS**. (2016). A novel implantable catheter system with transcutaneous port for intermittent convection-enhanced delivery of carboplatin for recurrent glioblastoma. *Drug Delivery,* 23(1): 167-173. DOI:10.3109/10717544.2014.908248

4) **Whone A** *et al.* (29 co-authors, **Gill SS** corresponding author). (2019). Randomized trial of intermittent intraputamenal glial cell line-derived neurotrophic factor in Parkinson's disease. *Brain,* 142(3): 512-525. DOI:10.1093/brain/awz023

5) **Whone A** *et al.* (29 co-authors, **Gill SS** corresponding author). (2019). Extended Treatment with Glial Cell Line-Derived Neurotrophic Factor in Parkinson's Disease, *Journal of Parkinson's Disease,* 9(2), 301-313. DOI:10.3233/JPD-191576

6) **Gill SS** (Inventor), Renishaw plc (Assignee). (2019). US 2019/0314605 A1: Neurosurgical apparatus and method

Grant Information:

i) **Gill SS.** The development of innovative techniques for the controlled delivery of novel drugs into the brain of patients with Parkinson's disease, MRC, 2006-2009, GBP338,901

ii) **Whone A.** A trial to assess the safety and efficacy of intermittent putaminal GDNF infusions administered via convection enhanced delivery in Parkinson's disease. Parkinson's UK and The Cure Parkinson's Trust (Grant J-1102), 2012-2017, GBP3.5 million (including further extension to study funding)

4. Details of the impact

Research by the University of Bristol (UoB) Functional Neurosurgery Research Group has cumulated in the development of an in-house drug delivery system (iHM-DDS) for the predictable and reproducible use of CED in the experimental treatment of Parkinson's disease and for the last option for neuro-oncology patients on compassionate grounds when the standard treatment regime has failed. The current protocol has not changed for over ten years and there is an unmet clinical need for more targeted treatment.

Product development and industrial collaboration

UoB led trials of the novel in-house drug delivery system [4, 5], were carried out in collaboration with precision engineering specialists Renishaw plc [A]. In 2019, the system was patented [6], and trademarked by Renishaw as neuroinfuse™ [B]. The General Manager of Renishaw plc reports the investment of 'tens of millions' including the employment of over 70 staff working specifically on the CED system and notes that the research [1-5] '*has been essential in development of [Renishaw's] devices'* [A]. This is currently the only device offering an intermittent implantable system. The device was awarded the TCT Healthcare Application Award 2019 and has received considerable industry media coverage. Renishaw have also invested in a new Lab2Clinic programme, a joint initiative developed from UoB's extensive experience and research, to use the iHM-DDS, and to create efficient translational pathways for novel neurological drug delivery [C]. This marks a paradigm shift in direct-target delivery of future novel therapies as they become available, for a host of neurological conditions.

In addition, phase 1-2 clinical study has been carried out using the Renishaw technology with Finnish biopharmaceutical company Herantis Pharma plc, which utilised the neuroinfuse™ drug delivery device to investigate the safety and performance/tolerability of both the device and cerebral dopamine neurotrophic factor (CDNF), as a treatment for Parkinson's disease in Finland and Sweden. During this trial, 17 Parkinson's disease patients were implanted with the device for delivery of CDNF, in a phase I first in human drug and device safety study, which reached its primary endpoint [D].

At the end of 2020, 90 devices have been implanted in patients including 43 from the GDNF trial [4, 5]. Cumulative clinical experience has achieved close to 300 catheter implantations and more than 2,000 infusion cycles safely completed. This is equivalent to approximately 8,000 individual catheter infusions.

Impact on quality of life

The UoB developed drug delivery system [1-6] allows therapeutics to be delivered to clinically meaningful brain targets with spatial accuracy to deliver therapy when required over the lifetime of the patient, as well as enabling experimental approaches to treating patients facing life-limiting conditions.

i) Neuro-oncology

Glioblastoma multiforme (GBM) and Diffuse Intrinsic Pontine Glioma (DIPG), are both highly aggressive brain tumours and are usually rapidly fatal. Incidence of DIPG is 1 to 2 cases per 100,000 population with a peak incidence of 6-9 years. Five-year survival rate is less than 1% and half of patients die within nine months of diagnosis. Treatment for DIPG, is an ongoing unmet clinical need.

Pre-clinical DIPG research has led to clinical translation of a drug combination, which has been used on a compassionate use basis via the iHM-DDS [Ei, Eii]. The results have shown increased median overall survival from 9 to 15.5 months [Eii]. This study also demonstrated that CED infusions can be performed on an outpatient basis and are tolerated by these patient groups. Some patients were able to return to school in between treatment cycles as the normal negative side effects from standard care were not seen [E]. [text removed for publication] [F]. In total, 28 children with DIPG have received intermittent infusions of chemotherapy to the pons within the UK [E, F]. This treatment took place within The Harley Street Clinic, London and formerly in Bristol Children's hospital using the Renishaw iHM-DDS [J].

In addition, four adults with recurrent GBM have been treated on compassionate grounds with intermittent infusions of carboplatin here in Bristol and a clinical protocol is in place to impact the prognosis of patients. One patient who underwent CED extended her overall survival to 30 months with another clear reduction of tumour following one cycle of carboplatin [2].

ii) Parkinson's disease

Parkinson's disease is the fastest growing neurological condition in the world. A 2015 Global Burden of Disease study estimated the prevalence of Parkinson's to be approximately 6.2 million people worldwide. As the incidence of Parkinson's rises significantly with age, and people are living longer, this is expected to increase to nearly 13 million by 2040.

Although the phase 1 trial of GDNF did not meet the success criteria, it was deemed a crucial step towards future use of the drug and was a seen as a success for the iHM-DDS [4, 5]. Planned future trials led by the UoB team will investigate dose and exposure to improve clinical outcomes. However, the trial also demonstrated an improved quality of life to those participants. The use of an implantable drug delivery system reduces the need for repeat surgery, as well as reducing medication requirements. In addition to the primary success of CED in delivering large volumes of a drug throughout a target structure, the system also enables repeat infusions and flexible/custom administration regimes, which can be delivered in a simple out-patient setting [4, 5].

Trial participant Tom Phipps, 63, from Bristol, was the first person to undergo the pioneering surgery. He said: '*During the trial I noticed an improvement in my mobility and energy levels, and I was even able to reduce my medication. Since it ended, I have slowly increased my medication but I still ride my bike, dig my allotment and chair the local branch of Parkinson's UK'* [Hii].

Impact on Parkinson's community and public awareness

Publication of the GDNF trial results in early 2019 [4, 5], attracted substantial interest across the Parkinson's disease community and was reported extensively in national and international newspapers. An evaluation revealed 274 pieces of coverage across international, national and regional (print, broadcast and online) media, and generating over a million hits [G, H, I]. The GDNF trial was also the subject of a two-part fly-on-the-wall documentary for the BBC that followed the study for more than 5 years – The Parkinson's Drug Trial: A Miracle Cure? These programmes received the prestigious Grierson Award for 'Best Science Documentary' 2019 [I].

Company Creation

As a direct result of the underpinning research, two companies have been created, Renishaw Neuro Solutions Ltd in 2016 and Neurochase Ltd, both with the intention of moving forward with enhancing clinical outcomes for future generations. Renishaw Neuro Solutions is a wholly owned subsidiary of Renishaw plc, which aims to market the intraparenchymal drug delivery system, neuroinfuse™ through their commitment of staff and funds as noted above [A-D].

Neurochase, founded by Professor Gill in January 2020, aims to accelerate the development and commercialisation of innovative therapeutics for the central nervous system by building the next generation of universally accessible interventional engineering tools for functional neurosurgery. Neurochase are already committed to work involving Motor Neuron Disease (MND) (Funding Neuro Charity), Frontal lobe dementia (NeuroGenUs) and Epilepsy (CombiGene) in the future.

5. Sources to corroborate the impact

A) i) Renishaw (2020). Corroborating statement – General Manager, Renishaw Neuro Solutions
ii) Renishaw (2019). Engineering innovation brings hope for a Parkinson's cure
iii) Renishaw (2016). Adding to survival chances - pioneering treatment relies on 3D printing

B) Renishaw (2020). Products: neuroinfuse™ drug delivery system

C) Renishaw (2020). Lab2Clinic™ – central nervous system (CNS) drug delivery service

D) i) ClinicalTrials.gov (2017). NCT03295786: Clinical Study to Test the Safety of CDNF by Brain Infusion in Patients With Parkinson's Disease
ii) ClinicalTrials.gov (2018). NCT03775538: Safety of CDNF by Brain Infusion in Patients With Parkinson's Disease. Extension to HP-CD-CL-2002 Clinical Study

E) i) Szychot E, Walker D, Collins P, Hyare H, Shankar A, **Bienemann A,** Hollingworth M, **Gill S.** (2020). DIPG-82. Clinical experience of convection enhanced delivery (CED) of carboplatin and sodium valproate into the pons for the treatment of diffuse intrinsic pontine glioma (dipg) in children and young adults after radiotherapy. *Neuro-Oncology,* 22, iii303–iii303. DOI:10.1093/neuonc/noaa222.123
ii) Singleton WGB, Barua NU, Morgan J, **Bienemann AS**, Killick-Cole CL, Asby DJ, Edwards RJ, Lowis SP, **Gill SS.** (2016). NS-21 Multi-Catheter Intermittent Convection-Enhanced Delivery Of Carboplatin As A Treatment For Diffuse Intrinsic Pontine Glioma (DIPG): Pre-Clinical Rationale And Early Clinical Experience. *Neuro-Oncology,* 18, iii131. DOI:10.1093/neuonc/now078.21

F) Walker D (2019). Investigators brochure – Protocol Number CED-DIPG-001

G Parkinson's UK (2019). News: GDNF clinical trial offers hope for restoring brain cells damaged in Parkinson's

H) The Cure Parkinson's Trust (2019). i) The GDNF Trial - the facts and ii) The GDNF Trial – Tom's story

I i) BBC Two (2019). Documentary - The Parkinson's Drug Trial: A Miracle Cure?
Two-part documentary filmed over 6 years following patients in the Phase II GDNF trial [4,5].
ii) The Grierson Trust (2019). The Grierson Awards – *Sargent Disc* Best Science Documentary

J) ecancer (2016). Video: Convection enhanced delivery of chemotherapy to paediatric brain stem tumours