Institution: EaStCHEM School of Chemistry

Unit of Assessment: UoA 8: Chemistry

Title of case study: New companies formed to develop therapies that control immune system response as a result of research on protein factor H

Period when the underpinning research was undertaken: 2008 – 2016

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:
Paul Barlow	Professor of Structural Biology	May 1994 to present
Andrew Herbert	Postdoctoral Fellow	Nov 2004 – Dec 2009 & Aug 2011 – Mar 2018
Eliza Makou	Research Fellow	April 2014 – July 2019
Dušan Uhrín	Professor of NMR Spectroscopy	July 1995 to present

Period when the claimed impact occurred: 2015 – 31 December 2020

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

1. Summary of the impact

Research by EaStCHEM Professor Paul Barlow and colleagues has provided atomic resolution insights into the structure, function, and interactions of factor H (FH), a key human blood protein that stops the immune system from attacking self-cells. These advances, along with the group's novel recombinant method for production of FH in large quantities, have underpinned the creation of, and the technology behind, two new companies, *Gemini Therapeutics* and *Invizius*. Each company has developed unique interventions that harness FH to reduce damage to human cells caused by immune system attack: *Gemini* with its precision medicine approach to prevent blindness caused by age-related macular degeneration; and *Invizius* with its *H-Guard*® technology to suppress, at source, the immune system reaction to the dialysis filter as a foreign body and the resulting cardiovascular damage.

In only five years, *Gemini* has raised investment of USD42,000,000 (with a further USD216,000,000 committed as of 12-2020) and has created 40 jobs. It has succeeded in manufacturing recombinant FH for clinical use, which is currently progressing through Phase II clinical trials. *Invizius*, since 2015, has created 9 jobs and raised investment of GBP3,855,500, with offers for a further GBP4,200,000 secured as of 12-2020 to fund full clinical trials of *H-Guard*®.

2. Underpinning research

The challenge: understanding the complement system for development of new therapies

As part of the human immune system, the 30 blood-borne proteins that comprise the complement system work together to defend the body against invading microbes and to clear debris arising from damaged or dying human cells. Inappropriate or disproportionate activation of the complement system causes numerous autoimmune, degenerative and inflammatory diseases, as well as undesirable inflammatory responses to medical interventions. Factor H (FH) is a key human complement-regulating protein that protects healthy "self" tissue from attack by the complement system. The ability to control complement attack through harnessing the regulatory action of FH presents exciting opportunities for the development of therapies. Rational design of such therapeutic strategies requires an in-depth knowledge of the structure and mode of action of complement proteins, including FH; however, advances in understanding how complement proteins function have been held back by a lack of detailed structural insight. Difficulty in producing FH in sufficient quantities has also been a barrier to its therapeutic use.

A multidisciplinary approach to understanding regulation of the complement system

EaStCHEM Professor Paul Barlow performs world-leading research on the human complement system and has published nearly 100 papers on the topic. Following deployment of synthetic biology approaches to recombinant production and glycoengineering of complement proteins, he uses techniques including NMR spectroscopy, X-ray crystallography, mass spectrometry, surface plasmon resonance (on custom-made biomimetic sensor chips) and fluorescence resonance energy transfer to study these proteins on an atomic level. This research has brought major progress towards an understanding of the structure and function of complement proteins, which serves as the basis for their therapeutic application.

Structure and function of FH at atomic-level resolution

With EaStCHEM colleagues Dr Andrew Herbert and Professor Dušan Uhrín, Barlow's research since 2008 has revealed how FH interacts with key molecular partners that are crucial to its protective function. These include the complement protein fragment C3b, which initiates complement-mediated attack and is FH's primary target when protecting self-cells, as well as the carbohydrates that act as markers of self-cell surfaces. The team mapped key functional sites of FH and proposed a model, now widely accepted, in which the central domains of FH act in a hinge-like fashion to bring together the C3b-interacting domains at either end of the FH protein, thus initiating a cooperative binding modality that inhibits complement attack **[R1]**. By revealing the functional importance of all 20 domains within FH, Barlow's model makes clear that the full-length molecule, despite the challenges associated with its synthesis, is likely to be the best candidate for developing therapeutic approaches for complement suppression. The group has also studied genetic mutations that compromise FH's ability to bind C3b and carbohydrates markers, thus weakening its ability to protect cells in two human organs, the kidney and eye **[R2]**. In the eye, this leads to the creation of extracellular deposits in the macula, signalling the early stages of age-related macular degeneration (AMD).

Discovery of enhanced FH action to stop complement attack

The group, with key input from Herbert, then examined the ability of some bacteria to hijack FH to protect themselves against complement system attack **[R3]**. They found that a domain of *Streptococcus pneumoniae* protein PspC (a PspC truncate, PspCN) not only binds the full-length of FH extraordinarily tightly (K_D in the picomolar range) but also enhances the regulatory functions of FH by binding to its central hinge-like region and stabilising its active structure **[R3]**. Binding to PspCN doubles FH affinity for C3b and increases fivefold its ability to suppress complement activation. This inspired the group to exploit these bacterial FH-binding proteins to stop complement activation and the resulting damage triggered when blood comes into contact with foreign surfaces such as dialysis filters, medical devices such as stents and catheters, or transplanted organs. Patent protection for the invention was granted in 2015 **[R4]**.

First recombinant production of FH

The development of FH-based therapies had been constrained by difficulties in scaling up its production, with sources restricted to human blood plasma or inadequate quantities generated by expression in cultured plant, mammalian or insect cells. In 2011, the Barlow group developed a novel method to make significant quantities of FH recombinantly by transforming cells of the yeast *Pichia pastoris* with a proprietary designer FH gene **[R5]**. With subsequent improvements, this method produces hundreds of milligrams of protein per litre of culture, far more than other technologies can currently produce. Patent protection for the method was granted in 2011 **[R6]**.

3. References to the research

The underpinning research was supported by peer-reviewed grants (BB/I007946/1, BB/L024403/1, WT 081179/z/06/z), published as peer-reviewed outputs in well-regarded journals, and has resulted in granted patents.

R1. H.P. Morgan, C.Q. Schmidt, M. Guariento, B.S. Blaum, D. Gillespie, **A.P. Herbert**, D. Kavanagh, H.D. Mertens, D.I. Svergun, C.M. Johansson, **D. Uhrín**, **P.N. Barlow** and J.P. Hannan, "Structural basis for engagement by complement Factor H of C3b on a self-surface", *Nat. Struct. Mol. Biol.*, **2011**, *18*, 463-470. DOI: 10.1038/nsmb.2018.

R2. **A.P. Herbert**, **D. Uhrín**, M. Lyon, M.K. Pangbourne and **P.N. Barlow**, "Disease-associated Sequence Variations Congregate in a Polyanion Recognition Patch on Human Factor H Revealed in Three-dimensional Structure". *J. Biol. Chem.*, **2006**, *281*, 16512-16520. DOI: 10.1074/jbc.M513611200.

R3. **A.P. Herbert**, **E. Makou**, Z.A. Chen, H. Kerr, A. Richards, J. Rappsilber and **P.N. Barlow**, "Complement Evasion Mediated by Enhancement of Captured Factor H: Implications for Protection of Self-Surfaces from Complement". *J. Immunol.*, **2015**, *195*, 4986-4998. DOI: 10.4049/jimmunol.1501388.

R4. **A. Herbert**, **P. Barlow** and **E. Makou**, "Proteins with diagnostic and therapeutic uses", *Granted patent* WO 2015/055991 A1 **2015**.

R5. C.Q. Schmidt, F.C. Slingsby, A. Richards and **P.N. Barlow**, "Production of biologically active complement Factor H in therapeutically useful quantities", *Protein Expression Purif.*, **2011**, *76*, 254-263. DOI: 10.1016/j.pep.2010.12.002.

R6. C. Schmidt, **P.N. Barlow** and A. Richards, "Recombinant Factor H and variants and conjugates thereof", *Granted patent* WO 2011/077102 A1 **2011**.

4. Details of the impact

Two new companies have been formed to develop unique clinical interventions that exploit the ability of the complement-control protein FH to protect our own cells from damage. The intellectual property of these companies stems directly from insights into the structure-function relationships of FH, and recombinant technology for its bioproduction, provided by EaStCHEM Professor Paul Barlow and colleagues. In the five years since its co-founding by Barlow and Dr Andrew Herbert, in 2015, *Gemini* has raised investment of USD42,000,000 (with a further USD216,000,000 committed as of 12-2020) and created 40 jobs. *Invizius*, since 2015, has raised investment of GBP3,855,500 (with offers for a further GBP4,200,000 secured as of 12-2020) and created 9 jobs (headcount: 9; FTEs: 9).

Formation of *Gemini Therapeutics* to target a cure for dry age-related macular degeneration (AMD)

Gemini Therapeutics is a precision medicine company focused on the development of new therapies for dry AMD, the leading cause of irreversible blindness amongst people over 50 in the developed world. In many patients, dry AMD results from mutations in FH that reduce its protective action on self-cells and allow the immune system, over time, to damage cells in the eye. According to a 2014 study published in *The Lancet* (DOI: 10.1016/ S2214-109X(13)70145-1), 2,500,000 patients globally would benefit from a therapy that restores FH functionality. The company has raised over USD42,000,000 in seed and Series A funding since 2016 and created employment for over 40 staff, mainly PhD-level scientists **[S1]**.

Research from the Barlow group underpinned the development and viability of *Gemini*'s lead therapeutic approach and was key to initial fund-raising and company set up **[S1]**. Barlow's research provides a deep understanding of the structure-function relationships of FH that underlie disease mechanisms. It established the feasibility and desirability of treating AMD by administering FH **[R2]** and showed the full-length protein to be the best therapeutic candidate **[R1]**. The full-length FH-replacement strategy attracted the attention of the biotechnology entrepreneur who would become *Gemini*'s first CEO and became the new company's lead approach. Recognizing that FH had been "*notoriously difficult to produce in quantities sufficient to support clinical use*" **[S1]**, he initiated contact with the Barlow lab in 2015. He concluded that their novel recombinant method for production of FH **[R6]** was "*clearly superior to known alternatives*", and that partnership with the Barlow group presented "*a unique opportunity to very rapidly get the company he envisaged off the ground*" **[S1]**. Barlow and Herbert were scientific co-founders of *Gemini* **[S2]**, and the Barlow lab continues to provide guidance on the FH-replacement approach and on progressing the protein product towards clinical use **[S1]**. These contributions shaped *Gemini*'s plans and enabled the founders to convince investors that the company would be in "*a uniquely strong position to get products to market within a compressed timeframe*" **[S1]**. Licensing options of the Barlow patents also proved to be a crucial component of *Gemini*'s IP portfolio during fund raising.

The creation of *Gemini Therapeutics* presents a unique opportunity to work towards a therapy for AMD. They are the first company to apply a precision medicine approach, targeted to the specific genetics of patients, to ocular diseases, and the only company that has succeeded in manufacturing recombinant FH (called *GEM-103*) for use in the clinic **[S1]**.

Progress of *Gemini Therapeutics*

Phase 1 clinical trials of *GEM-103*, completed in 2020, met all safety endpoints and, importantly, provided evidence of the desired therapeutic effect: injection of *GEM-103* to the eye produced a prolonged increased in levels of FH that supports the desired mechanism of action **[S3]**. The Phase 2a ReGAtta study commenced enrolment in 09-2020 **[S3]**. A proposal for Fast Track designation was submitted and positively reviewed by the FDA in late 2020 (approval announced 09-01-2021). In parallel, *Gemini* began optimising their precision medicine approach through *CLARITY*, a major genetic profiling study designed to provide unprecedented insight into the role of genetic risk in retinal diseases (launched 01-2019) **[S1, S4]**.

The strength of *Gemini's* precision medicine approach, together with positive Phase 1 clinical trial results, have attracted a "blank-cheque" "*Special Purpose Acquisition Company*" (SPAC), providing a route to take the company public. In 10-2020, *Gemini Therapeutics* and *FS Development Corp.* announced a merger agreement creating "*Gemini Therapeutics, Inc."* and providing funding of USD121,000,000 to advance *Gemini*'s pipeline, plus a further USD95,000,000 of private investment **[S5]**. The combined company's common stock is expected to be listed on Nasdaq in early 2021 **[S5]**. This provides a solid foundation for future progress.

Formation of *Invizius* to target cardiovascular damage caused by dialysis

Invizius spun out from the University of Edinburgh in 04-2018 to develop a breakthrough technology to reduce cardiovascular damage caused by dialysis **[S6]**, which currently kills almost half of all dialysis patients worldwide and reduces life expectancy to just one third of normal **[S6]**. The *Invizius* technology is underpinned by Herbert and Barlow's research **[R6]** that discovered the possibility of exploiting pathogenic bacteria PspCN to recruit and enhance the action of FH to prevent immune system attack on medical devices, and the inflammation and cardiovascular damage that results **[S6]**. The initial focus of *Invizius* has been the incorporation of this technology through a priming solution, *H-Guard*®, which coats the dialysis filter and very tightly sequesters FH from the patient's blood to render the device invisible to the immune system (Figure 1). The *Invizius* approach is unique in preventing, at source, the blood's reaction to the foreign body, rather than treating the consequences, which presents the first major innovation in dialysis filter haemocompatibility since the 1980s **[S6]**.

Invizius has raised investment of GBP3,855,500 to support development of the technology **[S6]**. Commercial and technology development between 06-2015 and 03-2018 was funded with support totalling GBP605,500 from Scottish Enterprise's High-Growth Spinout Programme (HGSP). The success of translational activities under the HGSP funding paved the way for the spin out of *Invizius*, with Herbert as founder and Chief Technology Officer and Barlow as scientific advisor **[S7]**. *Mercia Technologies* invested GBP500,000 of seed funding in 04-2018. A further GBP2,750,000 raised in 10-2019 has supported the company as it conducts pre-clinical testing and manufacturing, and preparation for its therapy to enter clinical trials **[S8]**. The company has created employment for 9 staff (headcount: 9; FTEs: 9) **[S6]**. Approximately 40% of development spend is outsourced to contract research and contract manufacturing organisations in the UK and Europe, supporting this valuable sector of the economy more widely **[S6]**.

***Figure 1**: Dialysis filter coated with H-Guard® priming solution to hide the device from immune system attack. Image credit: Invizius.*

Progress of *Invizius*

By 12-2020, *Invizius* had demonstrated success in key areas, confirming the promise of the technology and paving the way for First-in-Human studies **[S6]**. *Ex vivo* testing in rigs that model the dialysis blood circuit has shown a marked reduction in complement activation when the dialysis filter circuit is coated with *H-Guard*®, providing confidence in the efficacy of the priming solution. Importantly, this reduction occurs in the crucial first hour of contact with the filter, which is known to trigger the maximum immune response. Results also indicate that *H-Guard*® is effective in bringing complement activation down to a baseline level, even in cases where it otherwise would be high.

Other major achievements include successful completion of acute toxicology studies in animals, full development of the protein manufacturing process, and demonstration of the production yields necessary to produce *H-Guard*® at a cost that is commercially viable in the dialysis market **[S6]**. Success in these areas has underpinned *Invizius*'s next round of investment: as of 12-2020 the company has secured Series A offers amounting to GBP4,200,000 **[S6]**, to fund the development of the *H-Guard*® technology to and through first-in-human studies.

In recognition of their innovative solution to a major health need, *Invizius* have been named one of the "*Fierce 15*" Med Tech Companies of 2018, as well as '*Best Innovative MedTech'* at the 2018 OBN Awards **[S9]**.

5. Sources to corroborate the impact

S1. Letter from CTO of *Gemini Therapeutics*. Confirms the role of the research in underpinning company set up and lead approach, and resulting economic benefit and success.

S2. "Scientific Founders". Page from Gemini Therapeutics website confirming Barlow and Herbert as scientific co-founders. https://geminitherapeutics.com/about/scientific-founders/

S3. "Gemini Therapeutics Announces GEM103 Meets All Endpoints in Phase 1 Clinical Study." Web news article from *Gemini Therapeutics*, 13-11-2020. Confirms success of Phase I clinical trials. https://investors.geminitherapeutics.com/news/news-details/2020/Gemini-Therapeutics-Announces-GEM103-Meets-All-Endpoints-in-Phase-1-Clinical-Study/default.aspx

S4. "Gemini Therapeutics Announces the Initiation of CLARITY, a Disease Registry and Natural History Study of Subjects with Dry AMD and High-Risk Genotypes." Web news article from *Gemini Therapeutics*, 07-01-2019. Confirms initiation of major CLARITY genetic profiling studies to support *Gemini*'s precision medicine approach. https://investors.geminitherapeutics.com/news/news-details/2019/Gemini-Therapeutics-Announces-the-Initiation-of-CLARITY-a-Disease-Registry-and-Natural-History-Study-of-Subjects-with-Dry-AMD-and-High-Risk-Genotypes/default.aspx

S5. "Foresite pulls Gemini Therapeutics to Nasdaq in a quick $216M SPAC flip." Web news article from Endpoint News, 15-10-2020. Confirms merger agreement with *FS Development Corps* and committed funding. https://endpts.com/foresite-pulls-gemini-therapeutics-to-nasdaq-in-a-quick-216m-spac-flip/

S6. Letters from CEO of *Invizius*. Confirm the role of the research in underpinning company set up and technology, and resulting economic benefit and success.

S7. "Our team". Page from Invizius website confirming Herbert as CTO and Barlow as scientific advisor. https://www.invizius.com/team/

S8. "Invizius attracts £2.75m investment." News article from Invizius website, 10-2019. Confirms £2.75M of funding raised. https://www.invizius.com/news/2-75m-investment-1/

S9. Web articles from FierceBiotech and OBN confirming awards to Invizius.

a) "FierceMedTech's 2018 Fierce 15", 11-02-2019, https://www.fiercebiotech.com/special-report/fiercemedtech-s-2018-fierce-15

b) "OBN Awards 2018 – Winners Recognised at Industry Leading Event", 12-10-2018, https://obn.org.uk/News/Latest-News/entryid/1578