Institution: University of Glasgow (UofG)		
Unit of Assessment: UoA 5 (Biological Sciences)		
Title of case study: Deciphering the underlying immunopathology of Guillain–Barré syndrome to drive advances in targeted treatment		
Period when the underpinning research was undertaken: 2000–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:**
(1) Prof Hugh Willison **(2)** Dr Susan Halstead **(3)** Dr Rhona McGonigal **(4)** Mr John Goodfellow	**(1)** Professor of Neurology **(2)** Research Associate **(3)** Research Associate **(4)** Clinical Lecturer in Neurology; Hon Clinical Senior Lecturer	**(1)** 1990–present **(2)** 2003–2008; 2012–present **(3)** 2006–present **(4)** 2009–2019; 2019–present
Period when the claimed impact occurred: August 2013–present		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

The autoimmune disease Guillain–Barré syndrome (GBS) is the most frequent cause of acute flaccid paralysis worldwide yet treatment options are limited. UofG research on the immunopathology of GBS has stimulated commercial investment by global pharmaceutical companies for preclinical and early phase clinical trials to develop and/or repurpose complement inhibitors and other drugs as targeted therapies; for example, eculizumab (Alexion Pharmaceuticals), ANX005 (Annexon Biosciences), and ARGX-117 (argenx). In addition, UofG work with the International GBS Outcome Study (IGOS) Consortium has supported a phase 2 trial of imlifidase (Hansa Biopharma) as a novel treatment for GBS.

2. Underpinning research

With a research portfolio spanning over 30 years, UofG neurologist **Prof Hugh Willison** is one of the foremost international experts on the immunopathogenesis of autoimmune neuropathies, particularly GBS.

Creation of mouse model identifies complement factors in immunopathogenesis of GBS

GBS is a rare disease that develops as an immune response to a prior infection—typically gastroenteritis caused by *Campylobacter jejuni*—which generates anti-ganglioside autoantibodies that cross-react with components of the peripheral nervous system, leading to paralysis. Although GBS has been under investigation since it was first described in 1916, current treatment options remain limited. Lack of a suitable mouse model for GBS posed a major hurdle to advances in both understanding the immunopathology of this disease and assessment of candidate therapeutic agents. UofG research has been instrumental in addressing this gap.

In 2005, UofG researchers reported the use of anti-ganglioside autoantibodies to develop the first definitive human-equivalent mouse model of GBS (**Mr John Goodfellow**, **Dr Susan Halstead**, **Willison**) [3.1]. This model subsequently demonstrated that the complement system is critical for driving development of GBS (**Dr Rhona McGonigal**, **Halstead**, **Willison**) [3.2]. The complement system is a key component of the immune response; it comprises a large number of circulating factors, which become activated via a proteolytic cascade in response to immune challenge. The UofG team found that treatment of *ex vivo* muscle preparations with an inhibitor of complement factor C5 (eculizumab; Alexion Pharmaceuticals, New Haven, USA) provided neuroprotection from antibody-mediated injury [3.2]. Together, these findings indicated that blocking components of the complement system might offer a novel treatment option for patients with GBS.

Preclinical and early phase clinical trials of complement inhibitors as treatment for GBS

Eculizumab

Eculizumab (marketed as Soliris) is a humanised monoclonal antibody licensed for use in autoimmune conditions such as atypical haemolytic uraemic syndrome. To determine the efficacy of this drug as a potential treatment for GBS, UofG researchers conducted a preclinical study that showed eculizumab completely protected the GBS mouse model from developing

neurological symptoms (2008; **Halstead**, **Willison**) [3.3]. During 2009–2010, **Willison** conducted the first clinical study of a complement inhibitor for autoimmune neuropathy, a safety study of eculizumab administered concurrently with intravenous immunoglobulin, among 13 patients with multifocal motor neuropathy [3.4]. This study was funded by Alexion and confirmed that the combination therapy was safe. In addition, the trial revealed a small treatment effect of eculizumab that was independent of the co-administered immunoglobulin [3.4]. **Halstead**, **Goodfellow** and **Willison** subsequently undertook the first clinical trial of eculizumab for GBS in combination with intravenous immunoglobulin (ICA-GBS; NCT02029378). With funding from Alexion, this phase 2 randomised double-blind placebo-controlled trial enrolled eight GBS patients and was conducted during 2014–2016 [3.5]. The findings demonstrated that eculizumab could be used safely for this novel indication.

ANX005

UofG expertise in complement inhibition as a potential targeted therapy for GBS led to a collaboration with Annexon Biosciences (San Francisco, USA). In 2013, **McGonigal** and **Willison** tested this company's complement factor C1q inhibitor (ANX005; also known as M1) in an updated transgenic version of the UofG mouse model of GBS [3.6]. This research showed that ANX005 attenuated injury and conferred a neuroprotective effect, positioning C1q as an additional target in the complement system for treating GBS patients.

3. References to the research

1. **Goodfellow JA**, Bowes T, Sheikh K, Odaka M, **Halstead SK**, Humphreys PD, Wagner ER, Yuki N, Furukawa K, Furukawa K, Plomp JJ, **Willison HJ** (2005) Overexpression of GD1a ganglioside sensitizes motor nerve terminals to anti-GD1a antibody-mediated injury in a model of acute motor axonal neuropathy. J Neurosci;25(7):1620–1628 (doi:10.1523/JNEUROSCI.4279-04.2005).
2. **McGonigal R**, Rowan EG, Greenshields KN, **Halstead SK**, Humphreys PD, Rother RP, Furukawa K, **Willison HJ** (2010) Anti-GD1a antibodies activate complement and calpain to injure distal motor nodes of Ranvier in mice. Brain;133:1944–1960 (doi:10.1093/brain/awq119). *[Alexion co-author: Rother]*
3. **Halstead SK**, Zitman FMP, Humphreys PD, Greenshields K, Verschuuren JJ, Jacobs BC, Rother RP, Plomp JJ, **Willison HJ**. (2008) Eculizumab prevents anti-ganglioside antibody-mediated neuropathy in a murine model. Brain;131:1197–1208 (doi:10.1093/brain/awm316). *[Alexion co-author: Rother]*
4. Fitzpatrick AM, Mann CA, Barry S, Brennan K, Overell JR, **Willison HJ** (2011) An open label clinical trial of complement inhibition in multifocal motor neuropathy. J Peripher Nerv Syst;16(2):84–91 (doi:10.1111/j.1529-8027.2011.00328.x). *[Study funded by Alexion]*
5. Davidson AI, **Halstead SK**, **Goodfellow JA**, Chavada G, Mallik A, Overell J, Lunn MP, McConnachie A, van Doorn P, **Willison HJ** (2017) Inhibition of complement in Guillain–Barré syndrome: the ICA-GBS study. J Peripher Nerv Syst;22(1):4–12 (doi:10.1111/jns.12194). *[Study funded by Alexion]*
6. **McGonigal R**, Cunningham ME, Yao D, Barrie JA, Sankaranarayanan S, Fewou SN, Furukawa K, Yednock TA, **Willison HJ** (2016). C1q-targeted inhibition of the classical complement pathway prevents injury in a novel mouse model of acute motor axonal neuropathy. Acta Neuropathol Commun; 4:23 (doi:10.1186/s40478-016-0291-x). *[Annexon co-authors: Sankaranarayanan and Yednock]*

Research funding

Willison's research on GBS has been continuously funded by the Wellcome Trust for the past 25 years, most recently through an Investigator Award of GBP2,000,000 (2016–2021).

4. Details of the impact

Context

GBS has an annual incidence of 1.1–1.8 cases per 100,000 people (equivalent to 600–1,000 cases in the UK each year). Although rare, this condition is associated with high healthcare costs, as approximately 20% of patients experience persistent and substantial morbidity that limits their mobility and quality of life, with an additional 15% reporting residual pain and tiredness. GBS is also the most frequent cause of acute flaccid paralysis worldwide; however, therapeutic options for affected individuals are limited.

Willison's pioneering research on GBS has been widely recognised by his peers; for example, in 2015, he was awarded the Alan J Gebhart Prize by the Peripheral Nerve Society, the highest honour that this organisation can bestow [5.A]. Expertise in the immunopathogenesis of GBS has enabled Willison and his team to make major contributions to the field, including advances in targeted treatment options that provide commercial benefits for the pharmaceutical industry.

Development of targeted therapies for GBS

Rare disease is a difficult area of investment for pharmaceutical companies, with research and development of new treatments facing issues such as high level of complexity within disease groups; difficulty in recruiting sufficient numbers of patients for clinical trials; and low financial return. The UofG mouse model of GBS [3.1], which mimics human disease by recapitulating the relevant immunological pathways, has been pivotal in driving the development of targeted therapies for this rare condition.

Eculizumab

Alexion specialises in exploiting complement biology for the discovery, development and commercialisation of therapies for rare diseases. **Willison** first engaged with this company in 2003, when it agreed to supply eculizumab for his preclinical work in the UofG mouse model of GBS [5.A]. The positive response reported by the UofG team [3.2, 3.3] convinced Alexion to invest in further investigation of eculizumab as a treatment for GBS, with UofG researchers demonstrating a clinical benefit among patients with autoimmune neuropathy in two early phase clinical trials [3.4, 3.5]. This work led to a joint patent between UofG and Alexion (**Willison** and **Halstead** listed as co-inventors), describing the methods and compositions for treatment with eculizumab repurposed for GBS [5.B]. The patent was granted novelty in Japan and Korea (2015), as well as in the USA and Europe (2016).

Demyelinating GBS is the predominant subtype detected in Europe and North America; by contrast, 30%–65% of GBS patients in East Asia, Central America and South America are diagnosed with the axonal subtype. Given this regional difference, a phase 2b randomised double-blind placebo-controlled trial was conducted in Japan during 2015–2016 (JET-GBS; NCT02493725) to inform Alexion's global development plans for eculizumab as a treatment for GBS [5.C]. The design of JET-GBS was influenced by the ICA-GBS trial protocol [3.5, 5.A]. JET-GBS enrolled 35 patients who were unable to walk independently. An improvement in functional grade (ability to run) was recorded at 24 weeks post-intervention among 74% of patients in the eculizumab group versus 18% in the placebo group. These findings encouraged Alexion to seek regulatory approval for eculizumab in Japan. On 19 June 2020, the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) granted SAKIGAKE designation for eculizumab in GBS [5.C]. SAKIGAKE is analogous to the European Medicines Agency PRIME programme and the US Food and Drug Administration (FDA) Breakthrough Therapy designation. It provides enhanced support for companies developing innovative treatments for diseases with unmet clinical need, and confers several advantages, including prioritised consultation and expedited review. This was the first SAKIGAKE designation received by Alexion; consequently, the company focused its GBS development pipeline for eculizumab on the Japanese market, with plans to initiate a phase 3 study in 2021, pending regulatory feedback from the PMDA [5.C].

In December 2020, Alexion announced that it had been acquired by AstraZeneca. According to the press release [5.C], this deal benefits AstraZeneca through "*Greater scientific presence in immunology by adding Alexion's innovative complement-technology platforms and strong pipeline … the company will further globalise Alexion's portfolio*". In addition, AstraZeneca will establish a dedicated rare disease unit, to be headquartered in Boston.

ANX005

Annexon develops disease-modifying therapies for patients with autoimmune diseases that involve the complement pathway. Given his expertise regarding the role of complement in GBS, Annexon reached out to **Willison** in 2012 and invited him to sit on the Scientific Advisory Board [5.D]. In this role, Willison has provided insight regarding the classical complement

pathway in GBS; enabled preclinical research on Annexon's anti-C1q antibody ANX005 using the UofG GBS mouse model [3.6]; advised on the design of proof-of-concept clinical trials for ANX005; and brokered introductions between Annexon and physicians around the world who have contributed to both preclinical and clinical studies by providing samples from patients with GBS [5.D]. Annexon's Chief Scientific Officer highlighted that the preclinical findings [3.6] have *"proven to be critical for obtaining both financial investor and clinical investigator interest in our clinical studies. As a result, we have initiated GBS clinical studies in Bangladesh, have obtained Fast Track and Orphan Drug Status designations for our studies in GBS by the US FDA and will begin early phase clinical studies in the EU and USA"* [5.D]. This approach to GBS treatment led to a joint UofG–Annexon patent, with **Willison** and **McGonigal** listed as co-inventors (2016) [5.B].

Annexon conducted the first clinical trial of ANX005 for GBS at the National Institute of Neurosciences and Hospital in Dhaka, Bangladesh, primarily on the advice of **Willison** owing to the increased incidence of GBS in this country (3.25 cases per 100,000 people). He was also able to broker introductions to key staff; for example, at the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) [5.E]. This phase 1b placebo-controlled dose-escalation trial was conducted during 2017–2019. It was the first clinical trial of a novel interventional drug of this nature to take place in Bangladesh, providing a valuable developmental opportunity such as the employment of more than 40 study personnel (physicians, laboratory staff, support staff) [5.E]. The preliminary data were released by Annexon in September 2019 [5.E]. ANX005 was well-tolerated at all dose levels among 31 patients with GBS, and no drug-related serious adverse events or discontinuations were recorded. Patients treated with ANX005 had reduced levels of a biomarker for nerve damage in neurodegenerative disease and exhibited positive trends across key GBS outcome measures such as muscle strength. These findings were sufficiently promising to warrant additional clinical trials for this indication.

In September 2019, ANX005 received FDA Fast Track designation for the treatment of GBS [5.E]. This designation expedites the development, review and approval of investigational product candidates that are intended to treat serious conditions with unmet medical need. A phase 1b multicentre study to evaluate the safety, tolerability and drug–drug interactions of ANX005 and intravenous immunoglobulin (NCT04035135) started recruitment in February 2020. Recruiting centres are located in Bangladesh, Denmark, the Netherlands, the UK (UofG Biomedical Research Centre) and the USA. Study completion is expected by September 2021. In addition, patient dosing has started in a phase 2/3 clinical study of ANX-005. On announcing this development in December 2020, the President and Chief Executive Officer of Annexon stated: "*We are pleased to advance our GBS program into later-stage clinical development, bringing us closer to potentially delivering a much-needed treatment option to patients combatting this debilitating disease. The advancement of ANX005 also continues to inform our ongoing clinical development across a host of additional complement-mediated autoimmune and neurodegenerative diseases*" [5.E].

Imlifidase

The International GBS Outcome Study (IGOS) Consortium aims to identify clinical and biological determinants and predictors of disease course in a large international cohort (>1,500 patients). **Willison** is a member of the IGOS Consortium Steering Committee; he also runs the UK arm of this programme, and chairs the Biomarkers Subgroup. UofG involvement is instrumental for the development of GBS clinical trial platforms, where it provides a means for recruitment and assessment of cases. One example of IGOS-supported research is a phase 2 study of imlifidase conducted by Hansa Biopharma (Lund, Sweden). This potential intervention for GBS is a bacterial immunoglobulin G-degrading enzyme derived from *Streptococcus pyogenes*. The clinical trial (NCT03943589) will assess the safety, tolerability, efficacy, pharmacodynamics and pharmacokinetics of imlifidase among 30 patients with GBS. Recruitment began in June 2019, with study completion expected by December 2022. Recruiting centres are based in France, the Netherlands and the UK (Queen Elizabeth University Hospital, Glasgow; **Goodfellow**).

Supporting preclinical drug development
In August 2019, **Willison** signed research agreements with argenx (Breda, the Netherlands) and Polyneuron Pharmaceuticals (Basel, Switzerland) to conduct preclinical work using the UofG mouse model of GBS [3.1]. Argenx takes a strategic academic–industry collaborative approach to developing antibody-based therapies for autoimmune diseases. Willison is supporting development of the argenx complement factor c2 inhibitor (ARGX-117) [5.F], which has already entered a phase 1 trial to test route of administration among healthy volunteers (data expected by mid-2021) [5.F]. Polyneuron Pharmaceuticals is a biotechnology start-up company focussing on rare autoimmune diseases of the nervous system with unmet clinical need. Willison is investigating a molecule (PN-1018) developed by this company to target a novel therapeutic pathway in GBS [5.F].

5. Sources to corroborate the impact
PDFs uploaded for all listed items.

A. **Testimonial** from the Chair of the ICA-GBS independent data monitoring committee to substantiate Willison's expertise and leadership in developing eculizumab for GBS.
B. **Examples of patents:** (1) US9388235B2 (eculizumab, Alexion 2016). Willison and Halstead listed as co-inventors; (2) US2016/0326237 (ANX005, Annexon 2016). Willison and McGonigal listed as co-inventors.
C. **Clinical development of eculizumab for GBS:** (1) The JET-GBS study findings: Misawa S *et al*. (2018) *Lancet Neurol.*;17(6):519–529 (doi:10.1016/S1474-4422(18)30114-5). Halstead *et al.* [3.3] and Davidson *et al*. [3.5] cited as refs 27 and 28, respectively; (2) Letter from the Alexion Head of R&D announcing SAKIGAKE designation (June 2020); (3) Alexion pipeline (listed as Soliris) (4) Alexion press release announcing acquisition by AstraZeneca (December 2020).
D. **Testimonial** from the Chief Scientific Officer of Annexon to substantiate Willison's expertise and leadership in developing ANX005 for GBS.
E. **Clinical development of ANX005 for GBS:** (1) Testimonial from icddr,b outlining the institutional value of the phase 1b clinical trials being conducted in Bangladesh; (2) Annexon press release outlining phase 1b trial results (September 2019); (3) Annexon press release confirming FDA Fast Track designation (September 2019); (4) Annexon press release announcing the phase 2/3 clinical trial (December 2020); (5) Annexon pipeline.
F. **Preclinical development of novel GBS therapies:** (1) Research agreement with argenx (August 2019); (2) ARGX-117 pipeline; (3) Press release highlighting ARGX-117 phase 1 trial (October 2020); (4) Research agreement with Polyneuron Pharmaceuticals (2019); (5) Polyneuron Pharmaceuticals pipeline.