Institution: Newcastle University

Unit of Assessment: UoA-1

Title of case study: Uncovering the genetic basis of atypical haemolytic uraemic syndrome leads to improved treatment.

1. Summary of the impact

Research conducted by Professor Tim Goodship and co-workers at Newcastle has had a profound effect on the prognosis for patients with atypical haemolytic uraemic syndrome (aHUS). By engaging in research on the genetic factors underlying the disease they developed an understanding of the molecular mechanisms responsible. Identifying that the majority of patients with aHUS have either acquired or inherited abnormalities of the regulation of complement (part of the immune system) led to the establishment of a UK national service for genetic screening and treatment with the complement inhibitor eculizumab. As eculizumab is now available to patients in England, the progression to end-stage renal failure can be prevented and patients already on dialysis will soon be successfully transplanted.

2. Underpinning research

Researchers and funding

Professor Tim Goodship led this research. Co-investigators at Newcastle University were: Professor Judith Goodship and Dr David Kavanagh. Funding of around £1.3M was obtained from a number of charitable sources and the Medical Research Council.

Background

Haemolytic uraemic syndrome is a condition in which small blood vessels are blocked by blood clots. It predominantly affects children and is the most common cause of acute kidney failure in children. The overall incidence of the condition is estimated at 2.1 cases per 100,000 persons per year and it is usually associated with infection by the bacterium *E. coli* O157. However, there is also a rare, chronic, severe form known as atypical haemolytic uraemic syndrome (aHUS), which can be either inherited or arise spontaneously and again predominantly affects children. aHUS represents 5-10% of haemolytic uraemic syndrome cases at presentation, which equates to around 200 people being affected in the UK. The prognosis for affected individuals is poor: there is 8% mortality around the time of presentation and 50% of survivors will require long-term dialysis within two years. The outcome of kidney transplantation in aHUS affected individuals is poor, with a high risk of disease recurrence and subsequent transplant loss. The overall five year transplant survival for aHUS patients is only 51% and outcome is even worse (30% five year survival) in patients known to have an underlying genetic abnormality (Le Quintrec et al. 2013, PubMed ID: 23356914). For all patients undergoing kidney transplant for any indication, the five year survival is ~77% (Gondos et al. 2013 PubMed ID: 23060279).

Research

In the early 1990s Goodship began caring for an individual from a family in the North East of England within which multiple generations had been affected by aHUS. At this time nothing was known about the cause of the disease but help from this family offered an opportunity to identify the underlying molecular mechanisms of the disease. In 1998 Goodship and colleagues at Newcastle University were the first (R1) to establish linkage of aHUS to a specific region on chromosome 1 that includes the gene for complement regulator factor H (CFH) and identified two mutations. (Complement is a group of proteins that play a pivotal role in the immune system, allowing the body to distinguish between host and foreign cells or pathogens). Subsequently, the Newcastle group demonstrated the clustering of such mutations in the C terminal exons (regions important for host recognition), identified other genes associated with aHUS (such as complement factor I (CFI) and membrane cofactor protein CD46) and were the first to identify factor H autoantibodies in association with complement gene mutations (R2, R3). They demonstrated that inherited or acquired abnormalities affecting components of the alternative complement pathway were present in ~70% of aHUS patients.

Building on this research, Goodship collaborated with Professor Giuseppe Remuzzi (Mario Negri

Institute, Bergamo, Italy) to show that the underlying mutation in aHUS was a strong predictor of kidney transplant outcome. In aHUS patients with a factor H mutation there is an 80% risk of losing a transplanted kidney within two years (R4). Further research demonstrated that combined liver and kidney transplantation was associated with better outcomes in such cases (R5). Genetic testing is therefore clearly an essential tool to facilitate the appropriate treatment of aHUS patients.

As complement plays a central role in the pathogenesis of aHUS, further research has been conducted on complement inhibitors as potentially effective treatments for the disease. Two clinical trials (37 patients) of the anti-C5 humanised monoclonal antibody *eculizumab* (brand name *Soliris*) have been undertaken, with substantial contributions provided by Goodship. The results of these trials (R6) showed that treatment with eculizumab resulted in improved kidney function: in one trial patient improvement was such that dialysis was discontinued in 4 of the 5 patients in the trial on dialysis and earlier intervention with the drug was associated with greater patient improvement.

3. References to the research

R1. Warwicker P, **Goodship THJ**, Donne RL, Pirson Y, Nicholls A, Ward RM, **Goodship JA**. Genetic studies into inherited and sporadic haemolytic uraemic syndrome. *Kidney Int*. 1998;53:836-844. doi**:** 10.1111/j.1523-1755.1998.00824.x **Cited by 267**.

R2. Richards A, Buddles MR, Donne RL, Kaplan BS, Kirk E, Venning MC, Tielemans CL, **Goodship JA, Goodship THJ**. Factor H mutations in hemolytic uremic syndrome cluster in exons 18-20, a domain important for host cell recognition. Am. J. Hum. Genet. 2001;68(2):485-490. doi**:** 10.1086/318203 **Cited by 181.**

R3. **Kavanagh D**, Kemp EJ, Mayland E, Winney RJ, Duffield JS, Warwick G, Richards A, Ward R, **Goodship JA, Goodship TH**. Mutations in complement factor I predispose to development of atypical hemolytic uremic syndrome. J. Am. Soc. Nephrol. 2005;16(7):2150-5. doi**:** 10.1681/ASN.2005010103 **Cited by 132.**

R4. Bresin E, Daina E, Noris M, Castelletti F, Stefanov R, Hill P, **Goodship THJ**, Remuzzi G. Outcome of renal transplantation in patients with non-shiga toxin-associated hemolytic uremic syndrome: Prognostic significance of genetic background. Clin. J. Am. Soc. Nephrol. 2006;1(1):88-99. doi**:** 10.2215/CJN.00050505 **Cited by 75.**

R5. Saland JM, Emre SH, Shneider BL, Benchimol C, Ames S, Bromberg JS, Remuzzi G, Strain L, **Goodship THJ**. Favorable long-term outcome after liver-kidney transplant for recurrent hemolytic uremic syndrome associated with a factor H mutation. Am. J. Transplant 2006;6(8):1948-52. doi**:** 10.1111/j.1600-6143.2006.01375.x **Cited by 65.**

R6. Legendre CM, Licht C, Muus P, Greenbaum LA, Babu S, Bedrosian C, Bingham C, Cohen DJ, Delmas Y, Douglas K, Eitner F, Feldkamp T, Fouque D, Furman RR, Gaber O, Herthelius M, Hourmant M, Karpman D, Lebranchu Y, Mariat C, Menne J, Moulin B, Nürnberger J, Ogawa M, Remuzzi G, Richard T, Sberro-Soussan R, Severino B, Sheerin NS, Trivelli A, Zimmerhackl LB, **Goodship T** and Loirat C. Terminal Complement Inhibitor Eculizumab in Atypical Hemolytic–Uremic Syndrome. *The New England Journal of Medicine* 2013; 368: 2169-81. DOI:10.1056/NEJMoa1208981 (***Drs. Legendre, Licht, Muus, Goodship, and Loirat contributed equally to this article as joint senior authors.***)

Research funding	£
Charitable foundations	503,449 (around half from AMRC charities)
MRC	655,975
Northern Counties Kidney Research Fund	193,992
Total	1,353,416

4. Details of the impact

While the cause of aHUS was unknown, Newcastle researchers realised that an effective treatment was more likely to be developed if the underlying molecular mechanisms of the condition were understood. Treatment for aHUS was limited, with patients reaching end stage kidney failure

and requiring lifelong dialysis while living with the risk of early death. Newcastle research established that abnormalities in complement (a key component of the immune system that allows the body to distinguish between itself and foreign cells) were found in the majority of aHUS patients and that some of the mutations affected products of the liver.

Genetic testing

As most of the abnormalities were shown to have a genetic basis, an NHS diagnostic service was established within the Northern Molecular Genetics Laboratory at the Centre for Life in Newcastle in 2002 (Ev a). All aHUS mutation screening for the UK is provided by the Newcastle laboratory. Between 2002 and 2007 16 samples were tested for three genes, CFH, CFI and CD46; genes being tested sequentially. From 2008, 612 samples were tested for these three genes with analysis being simultaneous and in 2011 testing extended to five genes simultaneously, adding another 337 samples by July 2013 (Ev b).

Best practice: diagnosis and treatment of aHUS

In 2009 Goodship, on behalf of the Renal Association, the British Committee for Standards in Haematology and the British Transplantation Society, led the development of national clinical practice guidelines for the management of aHUS in the UK (Ev c).

Genetic testing. Initial diagnosis and management of aHUS includes the recommendation that screening for the genes identified by Newcastle-led research be conducted in order to determine the best treatment for the patient. The value of genetic testing to the patient is that by identifying the exact abnormalities they carry, treatment options can be directed to their particular manifestation of the disease.

Kidney transplant. Accurate genetic testing can now identify those patients who would benefit from a kidney transplant and those who would not.

Combined liver-kidney transplant. Two of the genes associated with aHUS (*CFH* and *CFI*), identified by Newcastle-led research, encode complement regulators produced by the liver. Finding mutations in these genes in a particular patient indicates that the patient is at high risk of a kidney transplant failing. For such patients a combined liver/kidney transplant might be a treatment option. This procedure has been undertaken successfully and to date 25 such double transplants have been performed worldwide, including three in the UK (Ev d).

Eculizumab: optimal treatment for aHUS

There is, however, a significant question of patient benefit in combined liver-kidney transplant. With a one year mortality rate of 25% it is, understandably, not an option chosen by many patients. This very high risk meant that the researchers continued exploring other treatment options. Goodship and colleagues identified a complement inhibitor, the drug eculizumab (an anti-C5 humanised monoclonal antibody made by Alexion Pharmaceuticals (Ev e)) as a good candidate for repurposing to treat aHUS patients.

Two clinical trials, for which Goodship was the UK Chief Investigator, were conducted (results in R6, Goodship joint senior author). Based on the results, eculizumab was approved in 2011 by both the FDA (Ev f) in the USA and the European Medicines Agency (Ev g) for the treatment of aHUS. There are no other approved treatments for the disease.

Funding treatment. Evidence of the efficacy of eculizumab in treating aHUS led to the submission of an application for the establishment of a National Specialised Service for aHUS in Newcastle with funding for the drug. This was reviewed by the Advisory Group for National Specialised Services (AGNSS) in June 2012.

> *AGNSS considered that Eculizumab for aHUS was a life-saving and life-transforming product that despite the very high cost should be available in England to patients with aHUS. … With the exception of a single member, AGNSS agreed that the combination of the factors* [detailed earlier in the document] *justified recommending this high-cost product. (Ev h)*

The annual cost per aHUS patient, per year of eculizumab, has been calculated as £327,600 for an

adult and £163,800 for a child (Ev i).

This high cost led to Government concerns about its affordability and so the *National Institute for Health and Care Excellence* (NICE) were asked to report. However, in 2013 NHS England implemented an interim policy whereby eculizumab will be funded for aHUS patients. The Public Health Adviser, Specialised Services Team, NHS England has confirmed,

> *As a consequence of the findings from recent clinical trials of the terminal complement inhibitor eculizumab, on 1st April 2013 NHS England adopted an interim policy of funding this drug for those patients who had received it in the clinical trial and any new patient who would benefit from it. (Ev j)*

In practice this means that around 20 patients per year will receive the drug and the interim policy is expected to be extended to aHUS patients who receive kidney transplants in September 2013. The significance of this decision is that no child or adult in the UK should now progress to end stage kidney failure caused by aHUS.

5. Sources to corroborate the impact

Ev a. UK Genetic Testing Network. aHUS associated gene dossier. http://www.ukgtn.nhs.uk/ukgtn/LabFileDownload.do?uniqueIdentifier=3343B60250578360016F7C9E263999CF

Ev b. The Associate Director of the Northern Molecular Genetics Service can be contacted to corroborate the information regarding genetic tests for aHUS.

Ev c. Taylor CM, Machin S, Wigmore SJ, Goodship TH. Clinical Practice Guidelines for the management of atypical Haemolytic Uraemic Syndrome in the United Kingdom. Br. J. Haematol. 2010;148(1):37-47

Ev d. Information about transplants can be found in Journal of the American Society of Nephrology 2009, 20(5): 940-9. http://jasn.asnjournals.org/content/20/5/940 DOI: 10.1681/ASN.2008080906. (Citations = 59)

Ev e. Soliris product information (includes results of clinical trials). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000791/WC500054208.pdf

Ev f. FDA approves Soliris for rare paediatric blood disorder: Orphan drug receives second approval for rare disease http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2011/ucm272990.htm

Ev g. EMA approval. Soliris (eculizumab) changes since initial authorisation of medicine http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/000791/WC500112852.pdf

Ev h. AGNSS; Meeting minutes. April 2011. www.specialisedservices.nhs.uk%2Flibrary%2F34%2FAGNSS_minutes_of_meeting___1st_Aprill_2011.pdf

Ev i. The Independent: article on aHUS and eculizumab, including an interview with a Newcastle based patient. http://www.independent.co.uk/life-style/health-and-families/health-news/at-what-cost-lifesaving-drug-withheld-8632371.html

Ev j. Correspondence from the Public Health Adviser, Specialised Services Team, NHS England, who has agreed to be contacted to corroborate the impact of Newcastle-led research on the interim funding policy for eculizumab, is available on request.