Institution:
University of Cambridge

Unit of Assessment:
UoA1

Title of case study:
Establishing an evidence-based therapeutic approach to ANCA-associated vasculitis

1. Summary of the impact (indicative maximum 100 words)

Jayne's team have co-ordinated a sequence of randomised clinical trials, that have defined the standard of care for ANCA vasculitis treatment and shaped national and international guideline statements, NHS national commissioning guidance and an on-going NICE assessment. Together with Ken Smith his group have pioneered the use of the B cell-depleting agent rituximab, in vasculitis, contributing key evidence that led to its licence approval (USA and EU) for this indication. Ken Smith's group supported by Jayne's clinical team have discovered novel therapeutic biomarkers, patented and being assessed in Phase II clinical studies, that promise to deliver "personalised medicine" in this and related conditions. These activities have harmonised the management of vasculitis, are improving patient outcomes, and have provided a resource for on-going scientific and clinical studies.

2. Underpinning research (indicative maximum 500 words)

Over the last decade Professor Ken Smith, Chair of Medicine and Dr David Jayne, University Reader in Vasculitis (both tenured appointments in the Department of Medicine, respectively from 1996 and September 2013; Jayne was previously Associate Lecturer through the office of the School of Clinical Medicine from March 2013 and NHS Consultant, Renal Unit, Addenbrooke's Hospital since 2001), have built up a translational programme focussed on biomarker identification and delivering improved therapy for Anti-neutrophil cytoplasmic antibody (ANCA) - associated vasculitis (AAV). AAV is a severe systemic inflammatory condition, with 20 new cases per million in the UK each year. It commonly causes renal failure or pulmonary haemorrhage and has a fatality rate of up to 30% at 5 years, while causing substantial long – term morbidity in survivors. David Jayne co-ordinates an expanding international vasculitis network supporting clinical trials and biomarker studies (1).

Bringing a novel therapeutic approach into the clinic: B cell depletion in AAV

Rituximab is a depleting monoclonal antibody against the B cell-specific surface antigen CD20, previously developed for the treatment of B cell lymphoma. Following basic research in Cambridge defining the humoral contribution to pathogenesis of AAV, Smith and Jayne commenced the first pilot study of B cell depletion as a potential induction therapy in 2001. This demonstrated a high remission rate for patients with disease refractory to the standard of care and suggested rituximab might provide an effective alternative to the relatively toxic cyclophosphamide and inspired a subsequent international trial, RITUXVAS, led by Jayne (2). The response permitted withdrawal of immunosuppressives and glucocorticoids, improvement in quality of life, reduced hospitalisations and protection of vital organ function.

Defining new biomarkers and targets for future therapy

Personalised therapy, that would allow those with mild disease to receive reduced therapy, (with reduced toxicity), and those with an aggressive disease course to benefit from intensified therapy (with increased efficacy), is a major goal in AAV as in other autoimmune diseases. The Smith group have identified polymorphisms underlying disease susceptibility (3). Such an approach also requires prognostic biomarkers - Smith and colleagues, using a transcriptomic approach studying pre-sorted circulating leucocytes, have identified phenotypic differences in an immune activation pathway of use both as a biomarker and for the study of disease pathogenesis, this CD8-T cell transcriptional signature predicts long-term prognosis in those presenting with AAV (4), and is likely to have widespread application as it also effective in SLE, Crohn's Disease and Inflammatory Bowel Disease (5).

An additional approach to define novel therapeutic pathways has involved a genetic study of AAV. Building on a number of candidate gene studies performed in Cambridge and elsewhere, the first Genome-Wide Association Study of the disease performed in 2012 by a European Consortium led

by Ken Smith and funded by the British Heart Foundation and NIHR Cambridge Biomedical Research Centre. This compared DNA samples 2,500 AAV patients with those from healthy controls. This has demonstrated conclusively that Wegener's Granulomatosis and Microscopic Polyangiitis are genetically distinct diseases, raising the possibility that they may respond to different therapeutic approaches rather than to the identical ones currently used. It has also shown that the primary disease causing factor and genetic abnormality in Wegener's Granulomatosis is the response to a single autoantigen, as the MHC, alpha1-antitrypsin, and its substrate the autoantigen proteinase 3, are all risk factors for disease. That a single antigenic response lies at the core of disease susceptibility suggests novel future approaches to therapy (6).

3. References to the research (indicative maximum of six references)

1. Hiemstra TF, Walsh M, Mahr A, Savage CO, de Groot K, Harper L, Hauser T, Neumann I, Tesar V, Wissing KM, Pagnoux C, Schmitt W, Jayne DR; European Vasculitis Study Group (EUVAS). Mycophenolate mofetil vs. azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. **JAMA**. 2010;304:2381-2388.
2. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, Savage CO, Segelmark M, Tesar V, van Paassen P, Walsh D, Walsh M, Westman K, Jayne DR; European Vasculitis Study Group. "Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis." **N Engl J Med**. 2010;363:211-220
3. Willcocks LC, Lyons PA, Clatworthy MR, Robinson JI, Yang W, Newland SA, Plagnol V, McGovern NN, Condliffe AM, Chilvers ER, Adu D, Jolly EC, Watts R, Lau YL, Morgan AW, Nash G, Smith KGC. Copy number of FCGR3B, which is associated with systemic lupus erythematosus, correlates with protein expression and immune complex uptake. **J Exp Med**. 2008;205:1573-1582.
4. McKinney EF, Lyons PA, Carr EJ, Hollis JL, Jayne DRW, Willcocks LC, Koukoulaki M, Hatton A, MacAry PA, Brazma A, Chaudhry AN and Smith KGC. "A CD8 memory T cell transcription signature predicts prognosis in autoimmune diseases." **Nature Medicine,** 2010;16:586-589.
5. Lee JC, Lyons PA, McKinney EF, Carr EJ, Bredin F, Rickman HR, Ratlamwala H, Hatton A, Rayner TF, Parkes M, Smith KGC. "Gene expression profiling in CD8 T-cells predicts disease course in Crohn's disease and ulcerative colitis." **Journal of Clinical Investigation**, 2011;121:4170-9.
6. Lyons PA, Rayner TF, Trivedi S, Holle JU, Watts RA, Jayne DRW, Baslund B, Brenchley P, Bruchfeld A, Chaudhry AN, Cohen Tervaert JW, Deloukas P, Feighery C, Gross WL, Guillevin L,Gunnarsson I, Harper L, Hrušková Z, Little MA, Martorana D, Neumann T, Ohlsson S, Padmanabhan S, Pusey CD, Salama AD, Sanders J-S F, Savage CO, Segelmark M, Stegeman CA, Tesař V, Vaglio A, Wieczorek S, Wilde B, Zwerina J, Rees AJ, Clayton DG and **Smith KGC**. "Genetically Distinct Subsets within ANCA-Associated Vasculitis" **New England Journal of Medicine,** 2012;367:214-223.

4. Details of the impact (indicative maximum 750 words)

A. Clinical studies and Guidelines

Jayne has co-ordinated the European vasculitis network since 2001 and founded the European Vasculitis Society (EUVAS) in 2011. EUVAS has taken a strategic and collaborative approach to the development of an evidence base to drive therapeutic advances in vasculitis

Studies via the EUVAS collaboration led by Jayne have informed changes in the classification of disease, the 2012 Chapel Hill consensus statement, on clinical (1), epidemiological (2), histological (3) and genetic (4) grounds, allowing recommendations to be made to enhance clinical trial design and have provided a framework for personalised medicine in vasculitis (1).

Such trials have improved patient outcomes by optimising the balance of current therapies between efficacy and toxicity. They have also stratified treatment according to severity and resulted in the publication of 5 consensus treatment recommendations, between 2006 and 2012, sponsored by the European League against Rheumatism (EULAR) and the British Society of Rheumatology, now used widely through Europe (5-8). Uptake of EUVAS methodology and guidance has extended beyond the EU, with collaborative studies in USA, Canada, Japan and Australia. NICE is conducting its first Health Technology Appraisal (HTA) in vasculitis this year

based, in part, on work from this group.

The RITUXVAS trial (NCT 00748644, Jayne was PI) and other studies contributed to the licensing of Rituximab for ANCA associated vasculitis by the FDA in 2011 and EMA in 2013, and used in consultation in a NICE HTA 'Further Appraisal Consultation Document' (released September 2013) (9, 10). On-going studies by Jayne's group are defining pharmacogenomic markers to guide dosing and patient stratification, which it is hoped will provide long-term control of disease with a reduction in morbidity and mortality and improve the cost-effectiveness and safety of this therapy.

Establishing an evidence base for conventional therapy of AAV

David Jayne has extended the EUVAS group to include vasculitis networks in Japan, North America, Australia and New Zealand permitting large scale clinical trials and parallel biomarker and epidemiologic studies. The Cambridge team has lead an international consortium since 2001, that firstly developed and validated clinical assessment tools and a methodology for performing large scale interventional clinical trials, then co-ordinated eleven randomised controlled trials that now define the standard of care in ANCA vasculitis (6,7). The team are leading on a study examining the applicability of plasma exchange (funded by government agencies in the UK, USA, Canada, Australia and Japan; PEXIVAS NCT00987389, Jayne is PI, commenced 2010). They have also shown the efficacy of maintenance therapy in preventing relapse in AAV, and are leading an international trial RITAZAREM (NCT01697267, Jayne is PI, commenced April 2013), contributing to a stratification approach for individual patient care.

B. Novel Therapeutics; B cell depletion with Rituximab in vasculitis

The outcome of the initial use of rituximab in vasculitis in Cambridge has been the completion of two phase 3 studies of its use as induction therapy, one was Jayne-led, which were published together in the New England Journal of Medicine. The introduction of rituximab since 2005 for ANCA associated vasculitis has been hailed by patient groups and the medical press alike (9, 10), and resulting in immediate widespread changes to clinical practice.

C. Personalised Medicine in vasculitis

Prognostic biomarker discovery by the Cambridge group has led to great interest in the clinical and scientific community, successful patent protection (11), and the development of on-going clinical studies prior to commercialisation. These biomarkers are now undergoing clinical validation for their utility in patient stratification and personalised medicine (12). Validation of this biomarker in a prospective study in AAV (ARC grant funded) and Crohn's Disease (Wellcome Trust Translational Award funded) is about to commence led by the Smith team.

5. Sources to corroborate the impact (indicative maximum of 10 references)

A. Clinical studies via the EUVAS collaboration

1. Hellmich B, Flossmann O, Gross WL et al. EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis. Ann Rheum Dis. 2007;66:605-617.
2. Watts RA, Scott DG, Jayne DR et al. Renal vasculitis in Japan and the UK--are there differences in epidemiology and clinical phenotype? Nephrol Dial Transplant. 2008;23:3928-3931.
3. Berden AE, Ferrario F, Hagen EC et al. Histopathologic Classification of ANCA-Associated Glomerulonephritis. J Am Soc Nephrol. 2010 21(10):1628-36
4. Lyons PA, Rayner TF, Trivedi S et al. Genetically distinct subsets within ANCA-Associated Vasculitis. N Engl J Med. 2012;367: 214-223.
5. Lapraik C, Watts R, Bacon P et al. BSR and BHPR guidelines for the management of adults with ANCA associated vasculitis. Rheumatology (Oxford). 2007;46:1615-1616.
6. Mukhtyar C, Guillevin L, Cid MC et al. EULAR Recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis. 2009;68:310-317.
7. Mukhtyar C, Guillevin L, Cid MC et al. EULAR Recommendations for the management of large vessel vasculitis. Ann Rheum Dis. 2009;68:318-323.
8. Guerry MJ, D'Cruz D, Brogan P, et al. Recommendations for the use of rituximab in ANCA vasculitis. Rheumatology 2012 Apr;51(4):634-43.

B. B cell depletion with Rituximab in vasculitis

9. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm251946.htm - Patient Organisations such as the Vasculitis Foundatiion
http://guidance.nice.org.uk/TAG/334/Consultation/DraftGuidance

C. Personalised Medicine in vasculitis

10. US Provisional patent application number 61/145,824 – priority date: 20 January 2009. Title: Methods for classifying subjects (1). US Provisional patent application number 61/145,831 – priority date 20 January 2009. Title: Methods for classifying subjects (2)
11. McKinney EF, Lyons PA, Carr EJ et al. “A CD8 memory T cell transcription signature predicts prognosis in autoimmune diseases.” Nature Medicine, 2010;16:586-591.