Institution: University of Bath		
Unit of Assessment: A3 Allied Health Professions, Dentistry, Nursing and Pharmacy		
Title of case study: Advances in autoantibody detection lead to improved management of autoimmune rheumatic disease.		
Period when the underpinning research was undertaken: 2005-2019		
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:**
Professor Neil McHugh	Professor of Pharmacoepidemiology and consultant Rheumatologist, previously Senior Lecturer	2013 - present; 1991 - 2002
	Consultant Rheumatologist and Category C in the UOA	2002 - 2013
Dr Zoe Betteridge	Research Fellow, former Research Associate and Officer	2005 – 2018
Dr Sarah Tansley	Lecturer, former NIHR Academic Clinical Lecturer in Rheumatology, NIHR Academic Clinical Fellow in Rheumatology and Category C in the UoA	2016 to June 2020; July 2020 - present
Period when the claimed impact occurred: August 2013 – July 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Myositis (inflammation of the muscles) is a rare autoimmune disease affecting around 15,000 individuals in the UK and more than 1,000,000 world-wide. The University of Bath autoimmune serology group has identified autoantibodies in this condition which can be used to rapidly diagnose the disease using a small sample of blood as well as monitor effective therapies. Commercially available tests based on the work at University of Bath are used world-wide (217,284 tests with EuroImmun kit alone in 2019). We estimate at least 5% of new cases of myositis per year are diagnosed with a Bath-discovered autoantibody and so benefit from earlier diagnosis and intervention.

2. Underpinning research

Autoantibodies are a hallmark of autoimmune rheumatic diseases, such as myositis, a rare debilitating condition (affecting approximately 15,000 individuals in the UK and approximately 1,100,000 worldwide) that causes substantial morbidity and mortality and requires aggressive treatment and careful management. As with many autoimmune conditions, myositis is difficult to diagnose, most often needing intrusive muscle biopsies and MRI scans (which in children typically necessitates a general anaesthetic).

The research community was first alerted to the presence of specific autoantibodies in the blood of myositis patients, with the discovery of anti-Mi2 in 1976. Since then, a further 16 autoantibody targets have been characterised in myositis (of which 3 were discovered by the Bath serology group) [**1,2,3**]. Although the role of autoantibodies in myositis is still unclear, they are valuable diagnostic biomarkers present in approximately 60% of cases [**4,5,6**], avoiding the need for invasive investigations and also providing important prognostic information. The presence of a myositis-specific autoantibody (MSA) in patient serum not only leads to a more rapid diagnosis but also predicts whether that individual is likely to respond to a given treatment.

Immunoprecipitation (IPP), a technique employed to test for the presence of autoantibodies in patient serum, is highly sensitive and accurate, but time-consuming, labour intensive, and requires a high degree of expertise to perform. The University of Bath autoimmune serology group has established a world-leading diagnostic service for clinical use, developing and optimising IPP to identify MSAs some of which cannot be detected by other means.

Between 2005 and 2019, the Bath autoimmune serology group used their expertise in IPP to discover the myositis-specific autoantibodies anti-SAE [**1**], anti-Zo [**2**], and anti-EIF3 [**3**], and for the first time describe the associated disease phenotypes. The team further determined the prevalence of all known myositis autoantibodies, and associated clinical features, in a large European cohort of 1,637 patients [**4**]. This study represents the largest of its kind, using prospectively collected data. The following novel autoantibody frequencies were reported: anti-SAE 2.6% (8% dermatomyositis, 1% juvenile dermatomyositis; JDM), anti-Zo 0.3%, anti-EIF3 0.44%. Using a conservative estimate of myositis incidence of 1 per 1,000,000 per year in the general population, and a prevalence of 14 per 100,000 (Scandinavian data), Bath-identified MSAs are present in 310 of the UK population (and 36,000 people world-wide). Importantly, Bath research has shown that anti-SAE typically identifies myositis cases at an early stage in patients who present with skin rashes before later developing inflamed muscles, hence offering a much earlier opportunity for diagnosis and therapeutic intervention [**5**].

Myositis is rare in children with an incidence of 3 per 1,000,000 per year. In contrast to adults very few affected children were believed to have autoantibodies. Bath researchers have analysed the serum of approximately 400 patients aged under 16 years with myositis. The IPP technique allowed the detection of more newly discovered MSAs (anti-MDA5, anti-NXP2, and anti-TIF1g) in 40% of the juvenile population that would otherwise not be detected by other means [**6**]. They demonstrated that MSA were important biomarkers for defined disease phenotypes (e.g., anti-NXP2 calcinosis, anti-HMGCR severe disease, anti-MDA5 lung involvement). Importantly, the group have shown that in both adult and juvenile disease, MSA have an increasingly important role in early diagnosis and clinical management.

3. References to the research

1. **Betteridge, Z**, Gunawardena, H, North, J, Slinn, J & **McHugh, NJ** 2007, 'Identification of a novel autoantibody directed against small ubiquitin-like modifier activating enzyme in dermatomyositis', *Arthritis & Rheumatism*, vol. 56, no. 9, pp. 3132-3137. https://doi.org/10.1002/art.22862

2. **Betteridge, Z**, Gunawardena, H, North, J, Slinn, J & **McHugh, NJ** 2007, 'Anti-synthetase syndrome: a new autoantibody to phenylalanyl transfer RNA synthetase (anti-Zo) associated with polymyositis and interstitial pneumonia', *Rheumatology*, vol. 46, no. 6, pp. 1005-1008. https://doi.org/10.1093/rheumatology/kem045

3. **Betteridge, Z**, Chinoy, H, Vencovsky, J, Winer, J, Putchakayala, K, Ho, P, Lundberg, I, Danko, K, Cooper, R & **McHugh, N** 2020, 'Identification of a novel autoantigen eukaryotic initiation factor 3 associated with polymyositis', *Rheumatology (Oxford, England)*, vol. 59, no. 5, pp. 1026–1030. https://doi.org/10.1093/rheumatology/kez406

4. **Betteridge, Z**, Tansley, S, Shaddick, G, Chinoy, H, Cooper, RG, New, RP, Lilleker, JB, Vencovsky, J, Chazarain, L, Danko, K, Nagy-Vincze, M, Bodoki, L, Dastmalchi, M, Ekholm, L, Lundberg, IE, **McHugh, N** and UKMyonet contributors 2019, 'Frequency, mutual exclusivity and clinical associations of myositis autoantibodies in a combined European cohort of idiopathic inflammatory myopathy patients', *Journal of Autoimmunity*, 101, pp. 48-55. https://doi.org/10.1016/j.jaut.2019.04.001

5. **Betteridge, ZE**, Gunawardena, H, Chinoy, H, North, J, Ollier, WER, Cooper, RG & **McHugh, NJ** 2009, 'Clinical and human leucocyte antigen class II haplotype associations of autoantibodies to small ubiquitin-like modifier enzyme, a dermatomyositis-specific autoantigen target, in UK Caucasian adult-onset myositis', *Annals of the Rheumatic Diseases*, vol. 68, no. 10, pp. 1621-1625. https://doi.org/10.1136/ard.2008.097162

6. Tansley, SL, Simou, S, Shaddick, G, **Betteridge, ZE**, Almeida, B, Gunawardena, H, Thomson, W, Beresford, MW, Midgley, A, Muntoni, F, Wedderburn, LR and **McHugh, NJ** 2017, 'Autoantibodies in juvenile-onset myositis: Their diagnostic value and associated clinical phenotype in a large UK cohort', *Journal of Autoimmunity*, 84, pp. 55-64. https://doi.org/10.1016/j.jaut.2017.06.007

4. Details of the impact

The discovery of novel myositis-specific autoantibody (MSAs) by the Bath group and studies highlighting their clinical utility in patient stratification have transformed the clinical approach to investigation and treatment of adults and children with myositis. This has benefited both Industry and patients, particularly those patients with anti-SAE, anti-Zo and anti-EIF3 who would otherwise be considered autoantibody negative.

Impact on industry

The anti-SAE and anti-Zo autoantibodies, discovered by the Bath serology team, have to-date been incorporated into diagnostic kits (e.g. ELISA, line blot) sold by the following manufacturers: EUROIMMUN, D-Tek, Alphadia, Inova, RDL, and ARUP [**A**]. In contrast to the traditional Immunoprecipitation (IPP) technique, these kits offer faster, cheaper autoantibody characterisation, without the need for specialist expertise, meaning that more patient samples can now be tested for these biomarkers. A 2019 survey, conducted by the Bath serology group, of 111 clinical experts (based at 65 institutions across 6 continents and belonging to the International Myositis Assessment and Clinical Studies (IMACS) Group) revealed the widespread accessibility of these diagnostic tools:

"ELISA was reported to be the most widely used MSA detection technique worldwide, used by 46% of respondents' local laboratories. This was followed by the line blot, used by 37% of respondents' laboratories. In Europe, the market was dominated by the EUROIMMUN line blot; 74% of European respondents' local laboratories used a line blot and 48% the EUROIMMUN line blot" [**B**].

The IMACS survey also showed that, of the nine most popular commercial assay manufacturers, two thirds include anti-SAE and 1 in 9 anti-Zo, discovered at Bath [**A** and **B**].

As the primary European manufacturer of assay kits [**c**], EUROIMMUN report that, since the inclusion of anti-SAE on their line blot in 2013, there has been a 50 fold increase in its use, with 217,281 strips being tested worldwide in 2019, generating an estimated revenue of GBP5,700,000 (based on UK price of GBP26.50 per strip) [**C, D**].

A statement from the Chairman of the Executive Board for EUROIMMUN, leader in autoimmune serology diagnostics [**B, C**], reads as follows:

"The inclusion of this marker [anti-SAE1] was instrumental to EUROIMMUN's quest to cover all relevant antibodies specific to, and associated with, myositis...The [Bath] group also identified anti-Zo autoantibodies in myositis patients. EUROIMMUN will implement this new important marker into their new myositis profiles" [**C**].

Impact on patient wellbeing and clinical practice/policy

A Consultant Paediatric Rheumatologist at the Leeds Teaching Hospitals NHS Trust described how testing for anti-HMG CoA autoantibody, identified by the Bath serology group as a biomarker of JDM, after several years of difficulties in understanding the condition of his patient, finally enabled a definitive diagnosis to be made:

"[W]e were really struggling to understand her diagnosis in 2015. She had presented around 5 years earlier with rashes and weakness. [T]he result of positive HMG CoA antibodies was very helpful and contributed significantly to a confident diagnosis of HMG CoA antibody associated autoimmune myopathy. This has helped the young person psychologically to a large extent and has allowed more directed treatment, which I am confident has allowed a

better outcome than if we had continued to follow standard pathways, with the uncertainty of diagnosis 'hanging over us" [**E**].

At present there are no guidelines for the investigation or treatment of patients with myositis. Guidelines for the management of patients with myositis are currently under development by the British Society of Rheumatology (Neil McHugh and Sarah Tansley are both contributing to this project). Despite a lack of guidelines, it is clear that the Bath serology group has contributed to a substantial change in the overall diagnostic approach, by highlighting the importance of autoantibody testing. In the IMACS group survey:

"…the majority of participants reported that MSA testing influenced their diagnostic confidence (83%), the information they relayed to their patients on prognosis (86%), further investigations planned (81%), and even their recommended treatment (73%)" [**B**].

A renowned Manchester-based Professor and Consultant Rheumatologist, who oversees the collection of adult myositis samples for the clinical and scientific UK Myositis Network (UKMYONET), gave the following statement:

"The Bath serology group have changed the pattern of practice in the work-up and management of myositis cases here in the UK and elsewhere, through the discovery of new autoantibodies, and their ability to measure those not detectable by other means. Certainly, their work has helped reduce diagnostic delay and other unnecessary investigations. They have helped shape NHS England clinical commissioning policy for treatment of myositis and by demonstrating the presence of myositis autoantibodies have allowed more patients access to effective treatment such as Rituximab" [**F**].

NHS England Rituximab Clinical Commissioning Policy 2018 concluded that there was sufficient evidence to support the routine commissioning of rituximab in the treatment of adult myositis patients who have autoantibodies relevant to myositis [**G**]. This includes those autoantibodies discovered by the Bath group meaning that approximately 60 myositis patients a year are able to receive rituximab, which they would otherwise be denied.

5. Sources to corroborate the impact

A. EUROIMMUN line blot https://www.euroimmun.com/products/autoimmune-diagnostics/pd/rheumatology/connective-tissue-diseases/1530-4/3/78808/

   D-Tek BlueDiver dot kits (for SAE1 and SAE2) http://www.d-tek.be/en/products/kit/151-myos12div-24.html (and for Zo) http://www.d-tek.be/en/products/kit/134-syn10div-24.html

   Alphadia http://www.alphadia.be/en/immunodot.html

   Inova Diagnostics (currently under development) https://www.frontiersin.org/articles/10.3389/fimmu.2019.00848/full

   RDL https://www.labcorp.com/tests/520011/anti-sae1-ab-igg-rdl

   ARUP https://arupconsult.com/ati/idiopathic-inflammatory-myopathies?_ga=2.166743806.1327898515.1580822224-1486978201.1576596124

B. International Myositis Assessment and Clinical Studies (IMACS) Group Myositis Autoantibody Scientific Interest Group 2020, 'The promise, perceptions, and pitfalls of immunoassays for autoantibody testing in myositis', *Arthritis Research & Therapy*, vol. 22, no. 1, 117. https://doi.org/10.1186/s13075-020-02210-2. IMACS survey commentary (and raw data available on request). Publication of data collected from a survey designed by the Bath serology group and performed within the IMACS scientific interest group (of which Prof. McHugh is current Chair), in order to evidence/quantify the impact of using autoantibody assay kits (which include autoantibodies discovered in Bath) in clinical practice worldwide.

C. EUROIMMUN Chief Executive of the Board testimonial, 04/02/20.

D. EUROIMMUN line blot sales figures (email correspondence with EUROIMMUN), 13/02/20.

E. Clinician testimonial (anti-HMG CoA in JDM), 10/01/20.

F. Clinician/UK MYONET Chair testimonial (evidencing a change in practice), 29/12/20.

G. Rituximab Clinical Commissioning Policy, 15/07/16. https://www.england.nhs.uk/wp-content/uploads/2018/07/Rituximab-for-the-treatment-of-dermatomyositis-and-polymyositis-adults.pdf