Funded by:	Australia Rheumatology Association Research Fund
Recipient:	Dr Thomas Khoo
Intended Department	Southern Adelaide Local Health Network
Project:	Identifying predictors for the development of severe statinrelated muscle disease and optimising its treatment through exploring the role of the anti-HMGCR antibody

Scientific summary: ARA Ken Muirden Overseas Training Fellowship

Overview:

I am very grateful for the support of the Ken Muirden overseas training fellowship in completing a year with the Manchester Myositis Research Group, University of Manchester, and Salford Royal NHS Foundation Trust, in the United Kingdom.

This fellowship combined both research and clinical training with leading experts in the field of muscle diseases. The opportunity to immerse myself in this sub-specialty interest has allowed me to benefit from a wealth of knowledge, resources and collaborations, which I hope to apply to my ongoing PhD studies, as well as future clinical practice and research endeavours, in Australia.

From a research perspective, this fellowship year progressed from outlining the epidemiology of the idiopathic inflammatory myopathies (IIM), to identifying the areas of need in a unique subset of IIM, anti-HMGCR positive immune-mediated necrotising myopathy (IMNM), to establishing a multi-site clinical collaboration and submitting a proposal for an international genetic collaborative investigation.

Clinically, I joined the Rheumatology department at Salford Royal Hospital, a quaternary referral centre of excellence for muscle diseases. Participating in the weekly neuromuscular clinic, interacting with the multidisciplinary team, and assisting with quality improvement projects, I benefited from a broad exposure to complex muscle pathology spanning inflammatory, autoimmune, and genetic aetiologies.

Finally, the support of the Ken Muirden ARA Fellowship has been invaluable in enabling me to attend multiple international scientific meetings, connect with worldwide IIM experts for future collaborations, interact with patient-partners from different countries, and contribute to the forefront of myositis research as an investigator on various phase 2 and 3 clinical trials.

Research outputs/publications:

The following research publications and associated presentations have occurred during my Ken Muirden Fellowship year.

Khoo T, Lilleker JB, Thong BY, Leclair V, Lamb JA, Chinoy H. <u>Epidemiology of the idiopathic</u> <u>inflammatory myopathies</u>. Nat Rev Rheumatol. 2023 Oct 6. doi:10.1038/s41584-023-01033-0

Khoo T, Lilleker JB, Thong BY, Leclair V, Lamb JA, Chinoy H. <u>Reply to: Current classification</u> <u>criteria underestimate the incidence of idiopathic inflammatory myopathies by ignoring</u> <u>subgroups</u>. Nat Rev Rheumatol 2024.

- This review article, published in the leading Rheumatology journal, Nature Reviews Rheumatology, was a collaboration between international authors summarising the global epidemiology of IIM and areas that need representation in the future IIM research agenda. This article, and the figures that were designed specifically to accompany this publication, has generated significant interest since publication and been cited at international conference presentations on IIM.

Khoo T, Chinoy H. <u>Anti-HMGCR immune-mediated necrotising myopathy: Addressing the</u> <u>remaining issues</u>. Autoimm Rev. 2023, doi:10.1016/j.autrev.2023.103468

- Anti-HMGCR IMNM is a rare sub-type of IIM which can cause profound weakness and is often refractory to treatment. Research is limited for anti-HMGCR IMNM due to the rare incidence of this unique side effect of statin medications, lack of awareness, and difficulty accessing reliable testing for the anti-HMGCR antibody. However, given the close relationship with statin use, there are potentially key learnings to be derived from anti-HMGCR IMNM that can be generalised to our understanding of the genetic-environmental interactions culminating in IIM. This review article summarises the research that has been performed in this area so far and highlights the wide-reaching issues that still need to be investigated to inform how anti-HMGCR arises and how this unique myopathy can best be treated, or potentially even prevented.
- **Presentation:** "Anti-HMGCR: Past, Present and Future", UK myositis network (MYONET) meeting (London, UK)

Khoo T, Lyu X, Lilleker J, Lamb J, Limaye V, Chinoy H. <u>Anti-HMGCR Immune-mediated</u> <u>Necrotising Myopathy: Calculation of Incidence and Confirmation of Low Malignancy Risk in</u> <u>Two Independent Cohorts. A Retrospective Case Review</u>. *Arthritis Rheumatol*. 2023; 75 (suppl 9).

- This research is an international collaboration (UK and Australia) involving three specialist myositis centres contributing detailed clinical data on patients with anti-HMGCR IMNM. Given the rarity of anti-HMGCR IMNM, the method of this research enabled the analysis of a unique cohort; multi-national data of this sample size has not been previously assembled.
- This research has been presented at national and international meetings, and is in the process of being reviewed for anticipated journal publication.

- **Presentation**: "Anti-HMGCR Immune-mediated Necrotising Myopathy: Calculation of Incidence and Confirmation of Low Malignancy Risk in Two Independent Cohorts. A Retrospective Case Review", American College of Rheumatology (ACR) Annual Convergence (San Diego, USA)
- **Presentation**: "Anti-HMGCR myopathy a retrospective multi-site case series", South Australian branch of the Australian Rheumatology Association (SA ARA) Annual Meeting (Adelaide, Australia)

Ongoing research projects:

These projects commenced during the period of my overseas fellowship and are in various stages of completion.

Myositis Genetics Consortium (MYOGEN)/International Myositis Assessment and Clinical Studies Group (IMACS) project: Exploring the genetic architecture of patients with anti-HMGCR immune-mediated necrotising myopathy

- This project will involve the largest international analysis of genetic associations of anti-HMGCR with the aim of proposing a genetic risk score of HLA and non-HLA interactions that predispose to this rare side effect of statin exposure.

Editorial: Is there a role for complementary medicine in the management of fatigue in rheumatic diseases?

- The concept of this editorial came from the anecdote that many patients reviewed for rheumatological issues try, and sometimes derive benefit from, complementary and alternative medicine (CAM) options for symptoms that are difficult to treat, such as fatigue. This editorial aims to summarise the concepts behind CAM use, what role CAM may have in treating rheumatic conditions, and how we, as physicians, may need to adapt our everyday practice to deal with a world where social media is increasingly being used to promote CAM.

Other presentations:

"Myositis – current treatments, clinical trials and future possibilities", Myositis UK Patient Meet up (national webinar, UK)

"Diagnosis and management of myositis-related interstitial lung disease", North-West Respiratory Meets Rheumatology Conference (Warrington, UK)

"The skin as a snapshot of systemic inflammation", British Society of Rheumatology Case-Based Conference (Liverpool, UK) – awarded best oral presentation

"Tissue is the Issue", North-West Rheumatology Club Winter Meeting (Warrington, UK) – awarded best case presentation

"A case of VEXAS: enough to tick the boxes?", North-West Rheumatology Club Spring Meeting (Knutsford, UK) – awarded best case presentation

Salford Royal Hospital Peer-Review Education Meetings:

"Anti-SAE antibody positive myositis" "Unifying diagnosis or overlap syndrome: paediatric autoinflammation?"

"Anti-GBM in a patient with diffuse systemic sclerosis"

"How to besiege a Castle: IL-6 antagonism in Castleman's Disease"

"Hypervitaminosis – an emerging concern?"

Clinical skills:

In 2023, I also had the opportunity to join the clinical Rheumatology team at Salford Royal Foundation NHS Trust. These clinical activities allowed me to continue developing my skills as a clinician, lead a team of junior doctors, experience another country's healthcare system with different merits and challenges to Australia, and participate in regular departmental educational events.

My clinical activities included:

- Conducting a weekly specialised Rheumatology neuromuscular clinic with a national referral base
- Participating in a weekly multidisciplinary neuromuscular meeting
- Participating as an investigator on multiple Phase 2 and 3 clinical trials in myositis
- Contributing to the on-call roster and holding the consultant-connect Rheumatology referral phone
- Supervising junior doctors on the Rheumatology unit
- Fortnightly teaching sessions with medical students from the University of Manchester
- Coordination of a weekly journal club/clinical case discussion

Summary:

The past year has been full of incredible opportunities. The research and clinical exposures, international collaborations and conference presentations have been invaluable. I am confident that this plethora of varied experiences has improved my skills as a clinician and researcher. I am very thankful to Arthritis Australia and the Ken Muirden ARA Fellowship for enabling me to participate in an overseas fellowship of such high calibre, and I am enthusiastic to translate my new skills and experiences to ongoing clinical work and research endeavours back home in Australia.

Lay summary: ARA Ken Muirden Overseas Training Fellowship

I am very grateful for the support of Arthritis Australia and the Ken Muirden ARA Fellowship in completing a year overseas with the Manchester Myositis Research Group and Salford Royal NHS Foundation Trust.

My clinical and research work overseas has mainly focused on myositis, a condition which causes muscle weakness, and can also affect the skin, lungs, heart and gut. Although rare, myositis can be debilitating and, in some cases, life-threatening. I have had the opportunity to work with leading experts on myositis and have published research in highly acclaimed journals during my time overseas. In particular, I have formed an international collaboration researching a particular type of myositis called anti-HMGCR myopathy, which can happen as a side effect of statin medications. Statins are the most common medication prescribed globally, used to lower cholesterol, but can rarely result in myositis.

There is still a great deal to learn about how statins cause myositis, why the muscles are affected in some people but not others, and how we can best treat people who develop this side effect.

My year overseas has been invaluable in producing a research output of international significance, and planning ongoing collaborations which aim to significantly progress our understanding of myositis.

Additionally, I have had the opportunity to experience clinical work in a myositis centre of excellence. This level of clinical exposure has allowed me to gain knowledge, experience and familiarity with the approach to diagnosing and treating myositis, especially in situations of unusual, complex and challenging symptoms. I have also had the chance to interact with patients, their families and advocacy organisations, helping me to develop a deeper appreciation of the patient perspective on healthcare journeys with muscle problems.

The support of Arthritis Australia and the Ken Muirden ARA Fellowship has equipped me with a broad spectrum of research and clinical experiences which I look forward to bringing home, to benefit Australians with rheumatic conditions.