Warren Haynes Research Fellowship

Doctor Vivien Li | Progress Report

Projects and preliminary results

Advancing clinical translation of tolerogenic dendritic cells for treatment of MS

Multiple sclerosis (MS) is a disease resulting from damage to the fatty insulating covering around nerve cells in the brain and spinal cord called 'myelin'. It occurs when the body's own immune system starts to attack the myelin, leading to inflammation, cell damage and neurological symptoms.

In this project, I am aiming to develop a new approach to treat MS based on using patients' own blood immune cells, in particular dendritic cells which are central to orchestrating immune responses. These cells are isolated and grown from the blood of patients, treated with anti-inflammatory signals in the laboratory in combination with disease-causing proteins (autoantigens). They are then re-administered to the patient, where they selectively target and dampen down the disease-causing immune cells that promote inflammation and cause nerve cell damage in MS. This approach has advantages over existing therapies as it targets key initiating events in MS by retraining the disease-causing immune cells to tolerate the autoantigens. It avoids the risks of suppressing the immune system broadly such as infections and can be individualised for patients based on their genetics, which determines the types of autoantigens that could be a trigger for their disease.

This project advances my existing work towards clinical translation. I have already developed techniques to grow these immune cells from patient blood samples and defined culture conditions that can modify their behaviour to assume protective/anti-inflammatory rather than disease-inducing/pro-inflammatory characteristics. I have identified a novel autoantigen involved in MS that enables selective targeting of the disease-causing immune cells.

The next steps focus on clinical translation:

1. Identifying patient populations who may be suitable candidates for this therapy, stratified by risk genes for MS. To date, I have analysed the characteristics of dendritic cells generated from the blood cells of over half of the planned cohort of 42 patients.

2. Testing this treatment approach in a mouse model of MS, prior to taking this to human clinical trials. I have begun establishing a mouse model of MS, experimental autoimmune encephalomyelitis, in our laboratory in order to the test the effect of the novel autoantigen on disease severity and the effectiveness of tolerogenic dendritic cells as a potential therapy.

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PRIMeS (Progression in Multiple Sclerosis)

I have been a co-lead investigator on the PRIMeS (Progression in Multiple Sclerosis) cohort research study, which commenced recruitment in early 2024 through the Royal Melbourne Hospital Neuroimmunology Centre. This study aims to quantify and develop markers of latent progression of disability in MS occurring in the absence of relapses, which is responsible for over 30% of disability accrual in relapsing forms of MS and inadequately targeted by current disease-modifying therapies. 300 participants, who are at key periods in their MS disease course when latent disability progression may occur, will be recruited and undergo deep phenotyping to provide detailed clinical, paraclinical and radiological data and contribute biospecimens for neuroimmunological phenotyping and biobanking.

To date, we have recruited approximately 30% of the target 300 participants with MS. I have been predominantly involved in the laboratory and MRI aspects of this project. My role has included overseeing the recruitment of, training and supervising a laboratory assistant in processing biological specimens collected from participants, appropriately biobanking these samples and developing clear standard operating procedures for these processes. I have also helped develop the protocol, worked through ethics submissions and amendments to set up the 7-Tesla MRI substudy within this project, with scanning commencing on a subset of 40 participants in January 2025.

INTREPID 7T MRI study

This study has recruited patients with MS who need to temporarily pause disease-modifying therapies for the purposes of treatment switching, which potentially raises the risk of recurrent disease activity during the transition period. Identifying ones at risk is challenging and there may be radiological disease activity without overt clinical relapses. In this pilot study we compared 7-Tesla MRI and research 3-Tesla MRI sequences performed before switching treatment, after switching treatment and 3 months later to assess evolution of lesions when switching medication. We have recruited 10 patients switching treatment and 10 age and sex-matched control patients continuing treatment.

In preliminary analyses, we observed altered diffusion, susceptibility and T1 values three months after stopping treatment, suggesting inflammation and demyelination. These metrics returned to baseline values three months after starting the new medication. More in-depth analyses are ongoing to compare 3T and 7T sequences and across the time points.

Presentations

My presentation 'Identifying and characterising antigenic epitopes for developing tolerogenic dendritic cell-based therapy for multiple sclerosis' was selected for a platform presentation session at the ANZAN Annual Scientific Meeting 2024.

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Publications and asbstracts

Li V, McKay FC, Tscharke DC, et al. Repurposing Licensed Drugs with Activity Against Epstein—Barr Virus for Treatment of Multiple Sclerosis: A Systematic Approach. CNS Drugs Jan 2025.

Li V, Binder MD, Purcell AW, et al. Antigen-specific immunotherapy via delivery of tolerogenic dendritic cells for multiple sclerosis. Journal of Neuroimmunology May 2024, volume 390, 578347.

Chataway J, Williams T, Li V, et al. Clinical trials for progressive multiple sclerosis: progress, new lessons learned, and remaining challenges. Lancet Neurology March 2024 23(3), p277-301.

Binder MD, Nwoke EC, Morwitch E, Dwyer C, Li V, et al. HLA-DRB1*15:01 and the MERTK gene interact to selectively influence the profile of MERTK-expressing monocytes in both health and MS. Neurology Neuroimmunology & Neuroinflammation. March 2024 11(2).

Another manuscript is in preparation for submission in early 2025, preliminarily titled "Identification of a novel antigenic epitope from RASGRP2 with specificity for HLA-DR15 in multiple sclerosis". I am the first author on this manuscript.

Clinical activities

RMH Neuroimmunology Centre

Weekly MS/neuroimmunology outpatient clinics
Involvement in weekly research meetings and clinical multidisciplinary meetings
Overseeing trainees and students in clinics
Participating in the biannual RMH Neuroimmunology Centre preceptorships
Attendance of weekly RMH Department of Neurology Grand Rounds
Neurology inpatient ward service

Awards and grants

Formally awarded PhD in August 2024
Jack Brockhoff Foundation Early Career Medical Research Grant (2 years)
Bethlehem Griffiths Research Foundation research project grant (1 year)
Another 3 year grant (currently undergo embargo)