# TRAM MB-PhD Project Summary

(The completed form should not exceed 2 pages)

| **PhD project Title** |
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| **Mechanisms & modification of vascular injury & increased cardiovascular disease risk in large vessel vasculitis** |


| **Lead PhD supervisor (please provide name, affiliation and email)** |
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## Background

Large vessel vasculitis (LVV), which consists of giant cell arteritis (GCA) and Takayasu arteritis (TAK), is a common rheumatological condition and the most common primary vasculitis worldwide. It is characterised by chronic inflammation of medium and large arteries. Though immunosuppressive treatments are effective in the short term, more than half of patients will relapse, and many develop significant vascular complications. In the longer term, cardiovascular disease (CVD) risk is elevated.[1] This is particularly true for TAK, which typically affects those under 40 years,[2] and where CVD mortality is increased 2-3 fold.[2,3] Currently, the mechanisms contributing to vascular injury and to increased CVD risk in LVV are poorly understood.

*Endothelial dysfunction & the role of endothelin-1 in LVV*

Endothelial dysfunction is a common feature of many inflammatory conditions and may contribute significantly to the development of vascular injury and longer-term CVD risk in patients with LVV. Few data exist but endothelial dysfunction has been reported using doppler ultrasound in patients with TAK,[4] though this was not replicated in a group with GCA.[5] The GCA group was, however, composed primarily of those with cranial GCA, and results may not be reflective of the GCA population as a whole.

Endothelin-1 (ET-1) is the most potent endogenous vasoconstrictor. ET-1 also contributes to vascular inflammation and endothelial dysfunction. Pre-clinical studies have demonstrated upregulation of ET-1 in temporal artery tissue from patients with GCA.[6] ET-1 may promote migration of vascular smooth muscle cells towards the arterial intima, thus causing intimal hypertrophy, arterial narrowing, and ultimately tissue ischaemia. From a clinical perspective, ET receptor antagonists (ERAs) are currently available in the clinic, licensed for use in patients with pulmonary arterial hypertension and scleroderma digital ulceration. No study to date has evaluated their potential benefits in patients with LVV.

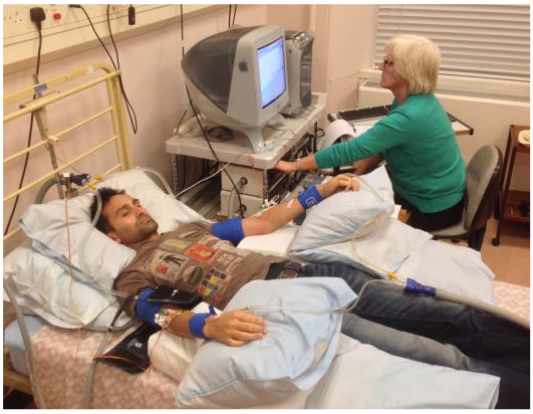
***We hypothesise that patients with LVV will have clinically important endothelial dysfunction and that ET-1 contributes to this. Using an ET-1 blocking approach, we hypothesise that we can improve endothelial function which, if maintained in the longer term, will reduce CVD risk.***

## Aims

***Cross-sectional Study 1:*** Using gold standard forearm plethysmography, we will assess endothelial function in 20 representative patients with LVV and in 20 age- and sex-matched patients with rheumatoid arthritis and 20 matched healthy volunteers. We anticipate patients with LVV will have worse endothelial function than healthy volunteers as well as those with rheumatoid arthritis.

***Interventional Study 2****:* the 20 patients with LVV from study 1 will then take part in an experimental medicine study, receiving treatment with either 6 weeks of the ERA, bosentan, or matched placebo. Endothelial function will be re-assessed using forearm plethysmography at the end of the study period. We anticipate that ET blockade will improve endothelial function.

## Training and experience provided



The successful candidate will be supported to lead all aspects of this project including trial design, ethical approval, subject recruitment, forearm plethysmography (left) and data synthesis and analysis. Laboratory experience will be provided where necessary. The candidate will form part of a friendly and ambitious research group. Collaboration within the group, and with local, national, and international partners, is part of our ethos. As a result, support is always close at hand, and opportunities to become involved in parallel projects are plentiful.

## Expected outcomes

In addition to the award of PhD, it is anticipated that this programme of work will generate several high-impact publications. The successful candidate will be encouraged to present at prestigious international conferences such as the International Vasculitis and ANCA Workshop and the American College of Rheumatology Convergence. Following completion of their medical degree, the successful candidate would be well placed to pursue a clinical academic career within the exciting landscape of LVV research. LVV is a condition gaining significant research focus currently with several areas of unmet need. As such, this project represents a unique opportunity to be part of a rapidly evolving research agenda, with several future possibilities following successful completion of this programme of work.

## References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2. Mirouse A, *J Autoimmun*. 2019;96:35-39. DOI: 10.1016/j.jaut.2018.08.001.
3. Park SJ, *Int J Cardiol.* 2017;235:100-104. DOI: 10.1016/j.ijcard.2017.02.086.
4. Alibaz-Oner F, *Acta Cardiol*. 2014;69:45-9. DOI: 10.1080/ac.69.1.3011344.
5. Hafner F, *Eur J Clin Invest*. 2014;44:249-56. DOI: 10.1111/eci.12227.
6. Planas-Rigol E, *Ann Rheum Dis.* 2017;76:1624-1634. DOI: 10.1136/annrheumdis-2016-210792.

**Pugh D, *Nature Rev Dis Primer.* 2022. Large Vessel Vasculitis**