49 GREEK STREET
LONDON
W1D 4EG

020 3389 7221
INFO@SARCOIDOSISUK.ORG
WWW.SARCOIDOSISUK.ORG

REGISTERED CHARITY 1063986

SILA* – BLF Sarcoidosis Research Grant 2015

Interim Report (Year 1)

Lay research title: Investigation of molecules leading to blood monocyte hyper-activation in sarcoidosis.

Scientific research title: Characterisation of monocyte CD200R in pulmonary sarcoidosis.

Grant holders and positions held: Simon P. Hart, Senior Lecturer in Respiratory Medicine**;** Michael G. Crooks, Senior Lecturer in Respiratory Medicine**;** Paul M. Kaye, Professor of Immunology

Research worker: Simon D. Fraser, research fellow

Research location: Castle Hill Hospital, Cottingham, HU16 5JQ

Grant start date: 1.3.2016 **Grant completion date:** 28.2.2018

What problem/need does this research aim to address? In sarcoidosis, granulomatous inflammation affects the lungs and often other organs. In the granulomas, cells of the immune system produce chemicals (cytokines) that drive the inflammation. Studying the immune response in sarcoidosis should identify targets for specific new therapies, which is important because current treatment options (steroids) do not affect the natural history of sarcoidosis and can cause distressing and sometimes serious side effects.

Our own recent research has demonstrated that the inhibitory molecule CD200R is reduced on circulating blood monocytes (white blood cells that mature into macrophages in sarcoidosis granulomas) in people with sarcoidosis compared with healthy subjects (Fraser SD et al, *Sci Rep.* 2016 Dec 8;6:38689). Lack of CD200R leads to hyper-activation of monocytes, which produce more inflammatory cytokines (proteins that drive inflammation in granulomas) when stimulated in the laboratory. CD200R normally serves to dampen down the immune response, so deficiency may explain the inflammation seen in sarcoidosis.

Using blood samples from people with sarcoidosis, we aim to investigate whether lack of CD200R on blood monocytes predicts who will have progressive disease needing steroid therapy, compared with those who improve without treatment.

Can you summarise the need for your research in one sentence? To better understand what drives the hyper-active immune response in pulmonary sarcoidosis, which could provide justification for clinical trials of novel therapies that stimulate the CD200R pathway.

How is the research being carried out? What have you achieved so far? Please also summarise the work that is to be completed during the remainder of the grant. We aimed to recruit 20 patients with sarcoidosis into a 1 year cohort study to monitor blood monocyte CD200R (and other markers) every 2 months. The aim

*SILA changed its name to SarcidosisUK in June 2017.

SarcoidosisUK

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of this substudy is two-fold: 1) to see whether CD200R is stable over time or fluctuates; 2) to determine whether CD200R can be used as a biomarker to predict disease progression or remission.

We began recruiting in August 2016, and we recruited our 20th patient last month, meeting the target. There have been no drop outs. We predicted that about one third would develop progressive disease needing steroid therapy. So far, this has not happened, but we are only half way through the study. We aim to recruit some additional patients over the next month as mitigation (we have REC approval to recruit additional patients).

The other aim of our study involves several laboratory studies of blood-derived monocytes from patients with sarcoidosis and healthy controls to explore mechanisms of CD200R regulation of immune function. These studies, which require single blood sample donations, will be performed in the second year (we focussed on recruiting to the cohort study in year 1). All regulatory approvals are in place.

Why is your work important to patients? What impact will this research have on patients in the short and long term?

- Short term: to better understand what drives the hyper-active immune response in the blood and in the lungs of patients with pulmonary sarcoidosis.
- Medium term: to provide information to support clinical trials of novel therapies that stimulate the CD200R pathway in patients with sarcoidosis.
- Long term: to provide information to support and direct future research into the cause(s) of sarcoidosis.

Have you encountered any problems or difficulties during the year? Please describe them. We are pleased with recruitment to the 1 year cohort study. Whilst we anticipated one third of subjects would develop progressive disease requiring steroid therapy, no patient has progressed yet. This may occur over the next year as the patients continue to be monitored. This is important because we would like to know of monocyte CD200R relates to progressive disease, and the effects of steroid treatment. If by month 18 there is still a low rate of steroid treatment, we have a mitigation plan to sample patients who are already taking steroid therapy as a comparison group.

Glossary of terms used:

CD200R – a protein found on the surface of blood monocytes that turns off immune responses

Granuloma – the characteristic organised pattern of inflammatory cells seen under the microscope in sarcoidosis

Monocyte – a white blood cell produced in the bone marrow that matures into a macrophage in inflamed lungs

Signed	Dr Simon Hart	Date	19/3/2017