CHIEF SCIENTIST OFFICE

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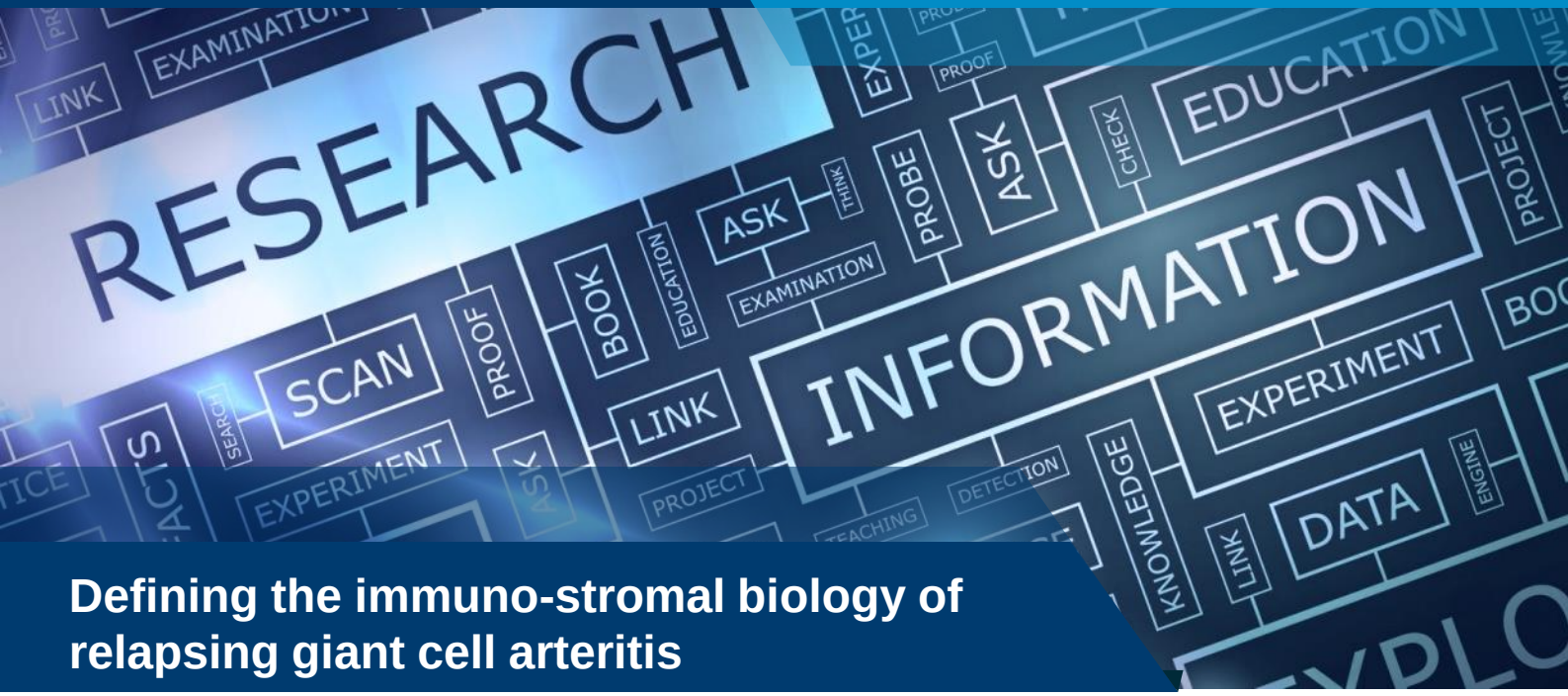
RESEARCH PROJECT BRIEFING




# Defining the immuno-stromal biology of relapsing giant cell arteritis

## AIMS

Giant cell arteritis (GCA) is a medical emergency which afflicts the elderly. Although there are drugs which can initially manage the disease successfully, it is very common for the disease to return (relapse). The biological characteristics of this relapse state is unknown and cannot assumed to be the same as disease onset. In order to inform future therapies for relapse, this fellowship aimed to address this knowledge gap by aiming to:

1. Characterise the most active genes in relapsing GCA tissue, with a focus on immune cells and fibroblasts (stromal cells)

2. Identify and define the distribution and clinical relationships of fibroblasts in relapsing GCA tissue

3. Examine the interactions of fibroblast and immune cells (immuno-stromal interactions) to determine the mechanisms by which they drive disease relapse.

## KEY FINDINGS

- Overall, fibroblasts are enriched in GCA tissues compared to controls.

- GCA relapse tissue demonstrated distinct T-cell and fibroblast signatures compared to GCA onset tissue

- Pathways significantly enriched in disease relapse include those of T cell differentiation (mainly Th1) as well as activation of the JAK-STAT pathway. These ex-vivo data were validated by in-vitro experiments with matched T-cells and fibroblasts from relapse patients.

## WHAT DID THE STUDY INVOLVE?

Patient partners were involved from the inception of this study and informed the study design. GCA patients who were experiencing a clinical relapse were recruited to the study as well as patients at disease onset who served as comparators.

Consented participants underwent a temporal artery biopsy (a common target of GCA) and donated blood. The tissue was split longitudinally, half entered the study, and half was processed by the local NHS Pathology laboratory for usual care clinical reporting.

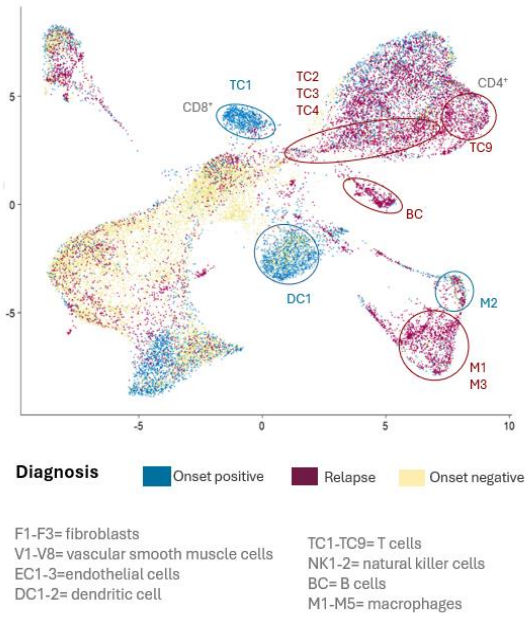
Tissue was subsequently enzymatically digested in order to help separate out our cells of interest. The resultant suspension was then processed using advanced gene processing platforms (single cell RNA sequencing by 10x Genomics and Illumina). Gene expression profiles were generated and were bioinformatically analysed using R studio and Python softwares. By utilising established bioinformatic packages supported by these platforms, differential gene expression was uncovered between different cell types and a comparison between disease onset and disease relapse was made.

Lastly fibroblasts expanded from the remaining temporal artery tissue were then explored in vitro with stimulated T-cells from matched donors to assess the interactions between fibroblasts and T-cells in a co-culture method. Proteins of interest were then validated using immunohistochemical methods.

## WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

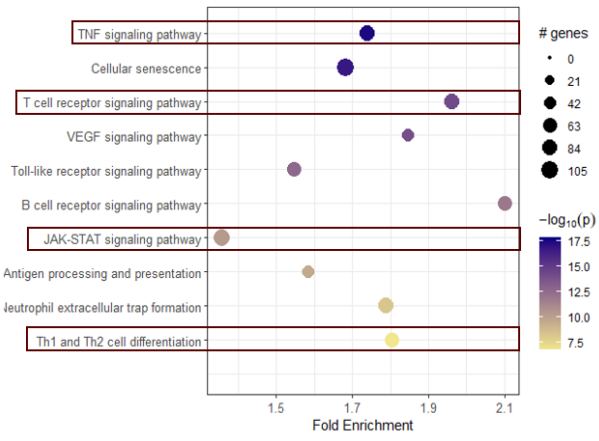
Differences between disease onset and disease relapse temporal artery tissue were identified both in terms of cellular abundance but also pathway enrichment. Pathways involved in T cell differentiation and signalling, as well as the JAK-STAT pathway were more enriched in relapse patients. Such findings provide novelty to the field as no studies to date have explored relapse tissue using unbiased methodologies, whilst biological differences at a tissue level have never been demonstrated.

**On the left, single cell RNA sequencing data showing different cell populations to be abundant in disease relapse (red) as compared to disease onset (blue).**
**On the right, TNF signalling, T cell receptor signalling, Th1/Th2 differentiation and JAK/STAT signalling are the signalling pathways most enriched in GCA lesions**




F1-F3= fibroblasts
V1-V8= vascular smooth muscle cells
EC1-3=endothelial cells
DC1-2= dendritic cell

TC1-TC9= T cells
NK1-2= natural killer cells
BC= B cells
M1-M5= macrophages



## WHAT IMPACT COULD THE FINDINGS HAVE?

- This study has, for the first time, characterised transcript differences between GCA onset and relapse. This can have a number of implications:

a) GCA patients at disease onset and disease relapse should not be grouped together in clinical trials when assessing for drug efficacy or deriving epidemiological and disease outcome data.

a) Targeted pathway modulation, such as JAK/STAT inhibition (which have already been successfully tested in other diseases) may be especially beneficial in relapsing GCA.

a) The ultimate targeting of fibroblasts in GCA may offer alternative/complementary therapies for this major clinical unmet need.

## HOW WILL THE OUTCOMES BE DISSEMINATED?

The dissemination plan involves high impact publications summarising the findings of this work as well as presenting this work in additional prestigious conferences such as the European Alliance of Associations for Rheumatology and the American College of Rheumatology.

This information will further be disseminated to participants and PPI groups.

## CONCLUSION

This study has revealed biological differences at tissue level between GCA disease onset and disease relapse. Fibroblasts are important in GCA pathogenesis and in particular in GCA relapse. In addition, JAK/STAT inhibition may play important roles in GCA-relapse therapeutics.

## RESEARCH TEAM & CONTACT

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