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LEGACY01: INTRODUCTION

In 1 collection

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ABSTRACT

This protocol provides introduction to an experimental medicine study of seasonal influenza vaccination responses in Lymph nodE single-cell Genomics in AnCestrY (LEGACY01).

ATTACHMENTS

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GUIDELINES

BACKGROUND

The efficient development of vaccines effective against global and emerging pathogens is complicated by geographic differences in vaccine responsiveness. The relative contribution of genetic and environmental factors to differential immune responses after vaccination remains poorly defined and is complicated by the spectrum of immune cell types involved. The Lymph nodE single-cell Genomics AnCestrY LEGACY01 study will create an ethnically diverse dataset with a single-cell atlas of lymph node (LN) and blood vaccine responses. Healthy volunteers of African and Asian ancestry who have immigrated to or were born in the UK will be invited to participate. They will be asked to donate blood and lymph node samples at specific timepoints pre- and post-immunisation. LN fine-needle aspirates (FNAs) will focus on the dynamics of germinal centre formation, capturing the interplay between lymphocytes, antigen-presenting cells and the stromal microenvironment. This will generate a curated data-structure of FNA single-cell (sc)RNA-seq, blood transcriptomic, cytometric, and serological analyses, with ethnicity, genetic, demographic and clinical metadata. To facilitate atlas utilisation and enable future international adoption of this approach, data, protocols and training materials will be

made open access.

RATIONALE FOR CURRENT STUDY

Recent infectious disease outbreaks, including the COVID-19 pandemic, have emphasized the critical need for rapid development of effective vaccines.[1-5] However, recognised variation in immune responses after vaccination across populations in different countries poses a barrier to progress, and it has yet to be determined whether this variation is due to differences in genetic background, in environmental influences including past or persistent antigenic exposure, and/or other poorly defined mechanisms.[6-9]Despite this known variation, the majority of mechanistic studies investigating immune responsiveness to vaccines have focused on populations of white European ancestry.[10,11] In the UK, this underrepresentation of ethnic minorities in vaccine experimental medicine research is at least partly due to vaccine hesitancy amongst these groups.[12]

A further challenge in addressing differences in vaccine response across populations is that studies have traditionally focused on the use of peripheral blood samples, even though inflammatory and germinal centre (GC) responses mounted in the draining LNs likely dictate vaccine priming efficiency and underpin protective efficacy.[13] Ultrasound (US) guided FNA is a tractable and safe approach for LN sampling, and its use has recently demonstrated a good representation of cell subtypes found in excisional biopsies, including GC cells, thereby opening invaluable new routes for assessing vaccine efficacy in humans in vivo.[14-17]

The LEGACY01 clinical study will address this by creating a dataset of unstimulated and stimulated in vivo immune responses to a model, seasonal influenza vaccine, from participants with African and Asian ancestry.

ROLE OF THE PARTNER INSTITUTIONS

Imperial College London is the Sponsor for the study. Recruitment and study visits will be at the NIHR Imperial Clinical Research Facility, Hammersmith Hospital, Du Cane Road, London W12 0HS. Imperial College London and Imperial CRF will manage the study. The University of Oxford will receive and process samples and run laboratory analysis of blood and lymph node tissues led by Dr Calli Dendrou at the Wellcome Centre for Human Genetics. The Uganda Virus Research Institute will support establishment of a framework for delivering single-cell vaccine studies at international sites such as Uganda. Specifically, they will appoint and support the training of a visiting Clinical Research Fellow to the UK at Imperial College London and the University of Oxford. All centres will support the patient and public involvement and engagement activities of the study.

HUMAN CELL ATLAS

LEGACY01 is one of the Ancestry Networks for the Human Cell Atlas funded by the Chan Zuckerberg Initiative. The goal of these networks is to generate single-cell data

from ancestrally diverse tissue samples, which will be uploaded and made available as open access research data for the Human Cell Atlas[18].

STUDY AIM, OBJECTIVES AND OUTCOME MEASURES

The aim of the study is to investigate human immune responses in lymph node cells before and after immunisation with a seasonal influenza vaccine

Primary objective: To generate a single cell atlas of lymph node cells before and after immunisation with seasonal influenza vaccine.

Secondary objective: To compare serum antibody responses before and after immunisation.
Exploratory: To compare immune responses in various immune compartments (e.g., blood and lymph nodes) against antigens including influenza before and after immunisation to help inform vaccine development and testing across different ethnicities.

Capacity building and training: To build capacity with respect to staff expertise and resource between the three partner institutions to support this project and future similar research.

Outcome measures may include but are not limited to the following assays:

1. Single cell RNA sequencing analysis of LNC and matched paired PBMC
2. Binding ELISA specific for influenza/A antigens e.g., haemagglutinin
3. Intracellular cytokine secretion or activation induced marker assay of PBMC and LNC
4. Genotypic assays such as HLA-testing.

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