

The Innate and Adaptive T cell response to SARS-CoV-2

Introduction:

Over 84,000 research papers have been published on SARS-CoV-2 since its emergence in late 2019, with over 300 vaccines and prospective treatments currently in various stages of development. While it has quickly become one of the most researched viruses in history, several important questions remain to be answered.

One of the immunological discoveries I found fascinating about SARS-CoV-2, was the pre-existing T cell response in some unexposed individuals and the variation in T cell responses in patients, vaccinees and convalescents. This has been documented in several significant studies published in *Nature*, *Science*, and other high-ranking medical and scientific journals. Much of this research highlights the importance of T cell immunity as a determinant of recovery and long-term protection.

Background and statement of the problem in light of a literature review:

The diversity of T cell responses to SARS-CoV-2 includes pre-existing T cells cross-reactive with other coronaviruses, T cell responses associated with milder disease, T cell responses contributing to “Long Covid” symptoms, and detrimental SARS-CoV-2 specific T cells associated with severe COVID-19. There are many more aspects of the T cell response to SARS-CoV-2 available in the published literature, and I believe that my examination and comparison of this research in different patient cohorts will contribute greatly to our understanding of the roles of different T cell populations in immunity against and pathogenesis of COVID-19.

Research question, aims and objectives:

The goal of my proposed project is to analyse, collate and review the available data in terms of the variation in T cell response to SARS-CoV-2 and its relevance to SARS-CoV-2 Immunity, vaccine protection and COVID-19 pathogenesis. These data will include the results of ongoing research by my proposed supervisor and colleagues as part of the Trinity COVID-19 Immunology Project, a collaborative research project led by the Trinity Biomedical Sciences Institute and the Trinity Translational Medicine Institute and supported by the Clinical Research Facility in St. James’s Hospital.

As part of the Trinity COVID-19 Immunology Project, individual T cell subsets are being enumerated in blood samples longitudinally obtained from healthy donors, patients with mild, severe and long COVID-19, convalescents and vaccinees using multicolour flow cytometry. The responses of these T cell subsets to sets of overlapping peptides corresponding to SARS-CoV-2 proteins are also being investigated in assays of cytokine production. Particular emphasis is being paid to the roles of “innate T cells” (natural killer T cells gamma/delta T cells, and mucosa-associated invariant T cells), which are “master regulators” of innate and adaptive immune responses and which are most significantly depleted in patients who develop severe COVID-19.

Methodology:

I will perform a meta-analysis of datasets from available studies on T cell phenotypes in the various cohorts of subjects, their responses to SARS-CoV-2 peptides and recombinant proteins, and their effector activities, including cytotoxicity and cytokine production.

Participation in The Trinity COVID-19 Immunology Project will also allow me to analyse their T cell data as well as to keep abreast with developments in other areas of COVID-19 research via weekly online meetings.

I will also perform a number of lab experiments investigating the ability of SARS-CoV-2 peptides and proteins to stimulate innate T cells from healthy donors. Innate T cells recognise conserved non-peptide structures produced in response to infection, therefore, it will not be necessary to study COVID-19 patients, since similar responses are expected to occur in healthy donors. In these experiments, dendritic cells will be used as antigen-presenting cells. Dendritic cells will be pulsed with the viral peptides and proteins before adding purified innate T cells. The choice of innate T cells to be tested will depend on progress made prior to the summer of 2021 by other workers on the project. These experiments may help identify new players in the immune response against SARS-CoV-2.

Timeline:

In the first two weeks I will analyse, collate, and review the available data. This will allow me to produce a meta-analysis of quantitative datasets from available studies on T cell phenotypes in the various cohorts of subjects. In weeks 4 to 6, I will perform a number of experiments in the lab of my proposed supervisor (subject to COVID-19 restrictions), investigating the ability of SARS-CoV-2 peptides and proteins to stimulate innate T cells from healthy donors.

Week 1

- Aggregation of the available data on the general T cell response to SARS-CoV-2.
- Particular emphasis will be paid to the roles of “innate T cells”

Week 2

- Identification of T cell responses associated with milder disease, T cell responses contributing to “Long Covid” symptoms, and detrimental SARS-CoV-2 specific T cells associated with severe COVID-19.
- Variation in T cell responses in patients, vaccinees and convalescents.
- An identification of pre-existing memory T cells to seasonal coronavirus epitopes.

Week 3, 4 & 5

- Lab experimentation investigating the ability of SARS-CoV-2 peptides and proteins to stimulate innate T cells from healthy donors.

Week 6

- Integration of experimental data and studied material
- Preparation of reference lists
- Preliminary layout of research in terms of presentation and format
- Photoshop and formatting of presentation

Expected results and contribution to body of knowledge:

Ultimately, I would hope that the outcome of my research would contribute to our collective understanding of how various T cells affect immunity to and pathogenesis of COVID-19. This research would determine which T cells contribute to severity of disease and which T cells show cross-reactivity with prior coronaviruses, and if they contribute to immunity against SARS-CoV-2.

I would also hope to disseminate my research findings as a published paper in an international peer-reviewed scientific or medical journal.

Sinead Cummins

Requirements for equipment, materials, field trips, and funding (if applicable)

Given the uncertainty of COVID-19 restrictions and travel and the requirement for specialised training and laboratories for COVID-19 research, I would ensure that most of my research can be undertaken remotely. In terms of resources, much of the published data is freely available through Google Scholar, PubMed, or Medscape. For the lab work, all equipment and reagents are available in the lab of my proposed supervisor.