A mark of success: Untangling the link between skin reactions to BCG vaccination and improved newborn health outcomes

Background: Bacille Calmette Guerin (BCG; a live vaccine containing attenuated *Mycobacterium bovis*), the vaccine against Tuberculosis (TB), is one of the oldest vaccines still given and one of the most administered in vaccine history. The benefits of BCG vaccination extend far beyond offering protection against TB and have been found to reduce risk for serious infections resulting in deaths or hospitalizations from unrelated infections; called *non-specific* or *pathogen-agnostic* effects of the BCG vaccine. These pathogen-agnostic effects are especially powerful when BCG is given to newborns, who are at exceptionally high risk to die of infectious diseases; BCG-vaccinated newborns in low resource settings have half the risk to die compared to unvaccinated newborns. These effects involve the way that the BCG vaccine alters innate immunity. BCG induces a process called "trained immunity", which epigenetically reprograms stem cells in the bone marrow to give rise to monocytes that are "trained" to mount a more robust inflammatory response to unrelated stimuli. In newborns, our team discovered that BCG also induces a process called "emergency granulopoiesis (EG)", or a rapid production of mature neutrophils, which are then able to rapidly clear invading microbes. EG explains the beneficial pathogen-agnostic effects of BCG vaccination in newborns. The cytokine Granulocyte-Colony Stimulating Factor (G-CSF) initiates EG. However, we have not identified how BCG initiates the production of G-CSF: which molecular sensors are used, and which cells mount this initial response. Also, why BCG induces G-CSF and EG in newborns, but not in adults is also a mystery. Given that BCG is given into the skin as an intradermal injection, the answer likely lies in this tissue.

Project details: You will be joining our team within the Canadian Centre for Vaccinology, and the I3V research cluster at Dalhousie University in Halifax, Canada. The goal of this project is to fill the knowledge gap linking BCG to G-CSF and EG by employing preclinical models to scrutinize the local skin responses to the BCG vaccine across the age spectrum, and identify correlates between the tissue and systemic responses to BCG vaccination. We have also designed a human study, whereby skin biopsy and blood samples were collected to determine the local skin responses via spatial genomics and multi-omic systemic responses to BCG vaccination between 1 and 14 days following vaccination. Analyses of these data will complement the design of preclinical investigations. The ultimate goals of this project are to identify the mechanism by which BCG initiates EG, and to design strategies to improve the recognition of the BCG vaccine in newborns and adults, thereby improving on pathogen-specific and agnostic benefits of this vaccine. This project blends experience working with preclinical mouse models, performing techniques such as histology, flow cytometry, and supernatant cytokine analysis while applying bioinformatics to gain insight from omics data. The project also offers opportunities for collaborative exchanges to work with large animal models with our collaborators at the University of Copenhagen, or to Guinea Bissau to supervise ongoing human field work related to the study.

Candidate characteristics: Prior experience in either wet bench/preclinical work, bioinformatics, or both. Individuals with a strong motivation to learn would also be considered. Candidates should be self-driven and take initiative to drive their work forward, while adhering to lab processes for data collection, data analysis using R programming, and record keeping. Given the collaborative nature of our work, the individual must be adaptable and motivated to work in diverse team settings. This includes responding well to feedback and being willing to follow or to lead, as the situation demands. Our team has a strong commitment to EDIA and expects all lab members to undertake EDIA training to create an inclusive and welcoming environment where students and staff from low- and high-resource settings can learn together and thrive.

Interested? Get in touch!
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