

## “Effects of Caspase-1 activation by the NLRP-3 Inflammasome, a key effector of Dengue infection”

Dengue is a mosquito-borne viral disease that infects millions worldwide and is caused by the Dengue virus. Symptoms include flu-like illnesses such as high fever, severe headache, nausea and vomiting. Although dengue is a self-limiting infection, it can occasionally progress into a serious illness, dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS), which may lead to death. In Indonesia, dengue is considered one of the most prevalent diseases, with cases increasing every year since its discovery in 1968. Between 2018 and 2019, there was an increase of nearly two folds of dengue cases, with a majority of the cases located in Java and Bali.

During infection, dengue virus induces the assembly of the NLRP3 inflammasome, a cell signaling platform that activates an inflammatory protease called caspase-1. This enzyme cleaves specific proteins in the cells that are responsible for the generation of fever and the control of the infection. For example, it cleaves and enables cytokine secretion (IL1B and IL-18), leading to increased vascular permeability and resulting in the symptoms of DHF and DSS. It also causes the death of the infected cells.

This project aims to understand how caspase-1 enzyme activation affects the functions of the cell downstream of the NLRP3 inflammasome. The outcome expected from this project is to better understand the NLRP3 signaling pathway and caspase-1 activation, and possibly identify novel caspase substrates that may be important during dengue infection.

During the 5-6 week period, the first 4-5 weeks will be focused in the lab to observe the target signaling pathway. This will include several experimental approaches like immunoblotting, cell culture, ELISA, and cell viability assays. Activation of the NLRP3 inflammasome in human cell lines will use bacterial toxin. Afterwards, cellular responses resulting from the activation will be observed. The last week of the project period will be used to analyze and interpret the data collected, as well as formulating a conclusion.

One of the seven University research themes is health and wellbeing. This project will bring development to this sector of research as it aims to better understand the molecular and cellular mechanisms behind a key effector of neglected tropical infectious diseases like dengue. In addition to that, this project will also contribute to the university's area of focus on improving global health because it could be beneficial for countries where these diseases are prevalent.

With this project, the second summer could include a leadership placement within an organisation that focuses on Dengue virus. An example would be the World Mosquito Program, an organisation that aims to protect communities from mosquito-borne diseases, including dengue fever in Indonesia. The placement would give an insight into how the disease is being handled and treated in Indonesia. Besides that, it would give a deeper understanding on what regulations and treatments have been put into place, and how the research conducted could benefit these. Finally, leadership skills gained from the program could be applied to communicating the challenges faced during the project and raise awareness regarding these issues.