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Granty

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- Grant Szybka ścieżka dostępu do Funduszy na badania nad COVID-19: „Ocena roli inflamasomu w patogenezie COVID-19 – opracowanie platformy badawczej *in vitro*”. NCN 2020/01/0/NZ6/00218. Kwota: 406 800zł

Project title: „Evaluation of the role of inflammasome in the pathogenesis of COVID-19- establishment of in vitro experimental platform.”.
Principal investigator: Tomasz Skirecki

The SARS-CoV-2 is a novel human coronavirus that cause severe pneumonia which in up to 20% cases leads to acute respiratory failure which often requires treatment in the intensive care unit. The illness has been termed the Coronavirus Disease 19 (COVID-19) and became the public health emergency concern all around the world. So far, no efficient treatment exists that would reduce the mortality or ease the symptoms of the disease. We hypothesize that the severe course of the disease is related to the excessive activation of one of the intracellular signaling pathway, namely the inflammasome complex. Forming of the inflammasome complex is early and potent mechanism of the cell's response to infection. Activation of inflammasome leads to the rapid release of strong acting inflammatory mediators like IL-1 and IL-18 and triggers cell death. Dysregulated activation of inflammasome has been shown to underlie severe course of other viral diseases such as influenza. SARS-CoV-2 can infect epithelial and endothelial cells in the lungs and presumably macrophages (which can also be activated by the mediators released by the infected epithelial and endothelial cells).

The primary aim of this project is to investigate whether the excessive activation of inflammasome in the lung cells plays critical role in the pathogenesis of COVID-19. Our hypothesis is that activation of the inflammasome triggers the lung cells death and drives the inflammatory response leading to acute respiratory failure. In order to verify this hypothesis, we designed a high-throughput platform enabling evaluation of the inflammasome activation by the selected viral proteins. Moreover, this model will be used to rapid assessment of the efficacy of clinically-available drugs with potent inflammasome inhibitory activity.

The SARS-CoV-2 proteins will be delivered to the human lung cells (epithelial and endothelial) by the molecular biology techniques. Analysis of the activation of inflammasome and cell death will be performed in real-time by the use of fluorescence- and luminescence-based imaging techniques. These experiments will be performed in both human cell lines and primary human cells. Because macrophages are major orchestrators of the lung immunity, it is also planned to investigate the effects of inflammasome-activated epithelial and endothelial released mediators on the human macrophage's activation. Importantly, we plan to test efficacy of two clinically-available drugs that are strong inhibitors of inflammasome pathway.

The proposed study will enable in-depth investigation of early phases of the lung cell's responses to the SARS-CoV-2 infection. The novel approach which combines molecular biology techniques to mimic aspects of the viral infection with the high-throughput methods of the analysis of inflammasome activation creates a unique opportunity to investigate interactions between the SARS-CoV-2 proteins and the host's cells and intercellular signaling. The findings of this project are expected to significantly increase the knowledge on the pathogenesis of SARS-CoV-2 infection.

Moreover, we plan to use our platform to test the efficacy of pharmacological compounds that in case of positive results could launch a fast- track pre-clinical and clinical testing.

- Grant Sonata: „Rola inflamasomu w immunopatogenezie oportunistycznych zapaleń płuc wywołanych przez pałeczki *Acinetobacter baumannii* w modelu septycznych myszy humanizowanych poddanych intensywnej terapii". NCN 2016/23/D/NZ6/02554. Kwota: 797.675,00zł

Project title: „Role of the Inflammasome in the Immunopathogenesis of Nosocomial Acinetobacter baumannii Pneumonia in the Model of Septic Humanized Mice Undergoing Intensive Therapy"

Principal Investigator: Tomasz Skirecki

The aim of the project is to investigate the role of the activation of protein complex of inflammasome in the response to Acinetobacter baumannii pneumonia secondary do septic peritonitis. Formation of inflammasome complex is one of major early mechanism of the host cells response to infection. It results in the release of active interleukin-1β and usually leads to the cell death. Our hypothesis claims that exaggerated activation of inflammasome in response to secondary A. baumannii infection impairs the protective immune response to this infection. Infections with multi-drug resistant A. baumannii strains became an emerging problem in the intensive care units (ICUs) worldwide. A. baumannii very rarely causes infections in healthy humans. In the ICUs the most common form of A. baumannii infection is pneumonia in septic patients with disturbed immunity who require mechanical ventilation. Infection with A. baumannii is a significant mortality risk factor in such patients. Due to the emergence of highly antibiotic resistant strains, immunomodulatory therapies may become one rescuing option. Development and clinical introduction of such therapies require, however profound understanding of the mechanisms of immunopathogenesis of a given infection. This knowledge should be gained in the context of specific clinical situation. For this reason in this proposed research we plan to develop a disease model on the mice with human immune cells. Such mice are known as the humanized mice. In our previous studies we have established a method of humanization of immunodeficient mice by the transplantation of human hematopoietic stem cells. Then, humanized mice were undergoing surgical cecum ligation and puncture (CLP) to induce septic peritonitis. This allowed us to evaluate the impact of sepsis on the human hematopoietic stem cells in bone marrow. In our current project, we intend to establish the humanized mice model using mice with the expression of human stem cell factor (SCF) which enhances development and maintenance of human immunocompetent cells. Humanized mice will then undergo the CLP surgery with following treatment with analgesics and antibiotics. Then, mice will be mechanically ventilated and receive intratracheally suspension of A. baumannii to induce pneumonia. By the measurement of early

mortality biomarkers the animals will be assign to groups of low and high probability of death. Mice will be sacrificed under general anesthesia and human myeloid cells from their lungs and bone marrow will be analyzed. The expression of inflammasome-related genes will be evaluated by Real-Time PCR technique. Inflammasome formation will also be investigated on the protein level using confocal microscopy on tissue sections. The comparison of the activity of inflammasome genes and proteins between groups of low and high risk of death will help to identify the protective and harmful effects of inflammasome activation. In order to confirm the outcome-related significance of the activity of inflammasome indicated in the abovementioned experiment, we plan to perform experiments with silencing of the expression of specified inflammasome gene. To accomplish this, we will use the siRNA knockdown technology dedicated to the in vivo application. The efficacy of gene silencing will be confirmed by the Real-Time PCR technique. The endpoints in this experiments will be the number of alive bacteria in the lungs and the degree of lung injury in mice infected 24 hours earlier.

By the use of a unique clinically-relevant model which is based on humanized mice we hope to indicate new targets for the immunomodulatory therapies in severe A. baumannii infections. Establishment of such complex model will also serve in the future as a translational research platform for the pre-clinical studies of immunomodulatory therapeutics.