Project title: Elucidation and treatment of a cytokine storm syndrome as an approach to combat fatal complications of COVID-19

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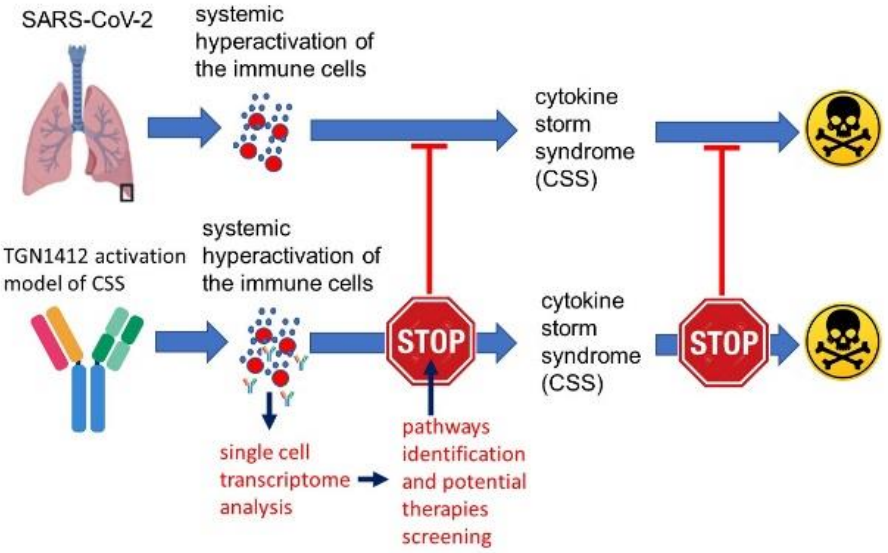
The main objective of this project is to unravel the mechanisms of the cytokine storm syndrome (CSS) and to develop and test methods of therapeutic prevention or treatment of this condition. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clinical spectrum of COVID-19 ranges from mild to moderate symptoms seen in majority of the patients to approximately 20% cases that develop severe pneumonia. Approximately 3% of patients progress into a most dangerous form of the COVID-19 that results from development of the acute respiratory distress syndrome (ARDS), septic shock and/or multiple organ failure. These symptoms are associated with a cytokine storm syndrome (CSS). The CSS during COVID-19 has a very bad prognosis and is a major cause of the fatality associated with the SARS-CoV-2 infection. Therefore elucidation of the mechanisms leading to the CSS during COVID-19 and identification of methods of elimination of hyperinflammation is urgently needed to reduce the rising mortality of SARS-CoV-2. To this end we will use a model of CSS based on the *in vitro* stimulation of the human heathy volunteers peripheral blood mononuclear cells (PBMCs) with a superagonist anti-CD28 monoclonal antibody, TGN1412. This model is a result of the failed clinical trial when phase I participants have been injected with TGN1412 that led to CSS in all of them. Thus the use of the TGN1412 resembles the pathology driven CSS. In order to facilitate the understanding of the mechanisms of CSS and to quickly and efficiently screen potential methods of the therapeutic intervention in this condition we set to use an *in vitro* model of the condition using PBMCs and stimulation with TGN1412. In order to study in detail the mechanisms of CSS we will apply methods of the high throughput single-cell transcriptome analysis in this model. Furthermore our group has an extensive experience with research on the proautoimmune populations of the immune cells. We have been studying these cells as an orchestrators of the immune pathology during autoimmune destruction in multiple sclerosis patients. We will apply our expertise to unravel mechanisms controlling CSS development as well as identify the major pathways that can be targeted for a therapeutic intervention in this condition. Finally we would like to use a TGN1412 *in vitro* model as a testing ground for several already available methods of the immunomodulation and for screening of effective ways to downregulate CSS. We believe that our platform for CSS treatment screening will facilitate a translation of our findings into the successful clinical trials in COVID-19 patients.



A scheme of the study: TGN1412 stimulation as a model for the studying mechanisms of the cytokine storm syndrome in COVID-19 as well as a platform to develop and test mechanisms of this fatal immune hyperactivity.