The SARS-coronavirus-2 (SARS-CoV-2) causes severe respiratory illness and pneumonia, called COVID-19. The disease has emerged as severe pandemic, claiming >69 million cases and >1.5 million deaths (till middle December, 2020). The COVID-19 symptom spectrum varies from asymptomatic or mild clinical to acute respiratory distress syndrome (ARDS) and death. For the time being, the only way to slow down the SARS-CoV-2 spreading are public health measures, because there is no efficient treatment, the clinical symptoms are often unspecific, the interval between the infection, the onset of symptoms is long, and asymptomatic carriers can transfer the virus to healthy individuals. To fight the virus infection, an efficient natural (innate) and adaptive response (production of specific antibodies) is crucial for the COVID-19 outcome. When activation of the innate immune system fails to eliminate pathogen directly or to induce development of an adequate adaptive response, persistent inflammation may contribute to high mortality. The inflammation manifests by cytokine storm leading to ARDS and organ failure.

The complement system is in the frontline of the interaction of the immune system with pathogens. Certain its factors may recognize major viral surface antigens of the SARS-CoV-2, including so called Spike glycoprotein (S-gp, surface protein decorated by sugar chains, named also glycans). It is highly similar to corresponding structure of SARS-CoV-1 and contains mannose. The high-mannose glycans may play a particularly important role in interactions with collectins like MBL, CL-K1, CL-L1 or SP-D. Recently, it was speculated that S-gp may also be a target for ficolins. Collectins and ficolins are factors of the innate immunity. They show quite similar activity to antibodies, but in contrast to them, their specificity (the ability to recognize microorganisms as the "foreign" or "non-self") is relatively broad. Collectins and ficolins recognize variety of glycans exposed on the surface of pathogens. Such sugar-specific factors are called lectins. With an exception for SP-D, they are able to activate complement *via* the lectin pathway, thanks to co-operating with complexed MASP enzymes. Some of these factors (MBL, CL-K1, SP-D) are known to recognize mannose. Based on data concerning SARS-CoV-1 and some recent reports related to SARS-CoV-2, we hypothesize that complement system recognizing major surface antigens of SARS-CoV-2 virus may be crucial for the disease outcome contributing to the virus elimination or, when over-activated, to development of severe adverse events, including shock, accompanied with organ dysfunction. The latter seems to be supported by promising attempts of COVID-19 treatment with inhibitors of complement (including specific inhibitor of the lectin pathway – narsoplimab). Moreover, the mentioned collectins and ficolins may modify the binding of specific antibodies to Spike glycoprotein – and depending on disease stage – may enhance or inhibit their anti-viral activity.

To determine the role of SARS-CoV-2 glycosylation pattern in the interaction with collectins and ficolins, we propose to test the binding of recombinant and natural (complexed with MASP serine proteases, able to activate complement) lectins to SARS-CoV-2 S-gp and its engineered glycosylation variants, as well as investigate whether lectin-glycoprotein interaction leads to complement activation. We plan to produce (in SARS-CoV-2-free system) S-gp, the same protein containing only high-mannose glycans, and its 3 glycosylation variants, to analyze glycopeptides and glycans derived from the Spike glycoprotein/its glycosylation variants and to evaluate the role of certain high-mannose glycans (called N-glycans) in SARS-CoV-2 recognition by selected lectins. The SARS-CoV-1 S-gp, expressed in the same cells, will serve as a positive control. We are going to determine binding of lectins to the mentioned antigens, and its certain biological consequences (complement activation as well as ability to modulate Spike-specific antibody binding) The following lectins will be tested: MBL, collectin liver-1 (CL-L1), collectin kidney-1 (CL-K1) and ficolins: ficolin-1, -2, -3. Furthermore, pulmonary surfactant protein D (SP-D) will be included. Although, as mentioned, it does not activate complement, it was selected for the reason of participation in both systemic and local (lung) immune defence and known interactions with viral antigens. Moreover, the influence of investigated lectins on interaction of antibodies induced in response to SARS-CoV-2 infection with Spike glycoprotein and the consequences of such interaction will be tested. For this study, the sera from patients suffering from paediatric inflammatory multisystem syndrome - temporally associated with SARS-CoV-2 (PIMS-TS) will be used. Although children generally appear to have less severe COVID-19 pulmonary manifestations compared with adults, they may develop PIMS-TS which is speculated to be a consequence of delayed immunological phenomenon associated with inflammation (hyperinflammation phase) following either symptomatic or asymptomatic COVID-19 infection. PIMS-TS shares features with other severe paediatric inflammatory conditions including Kawasaki disease, toxic shock syndrome, bacterial sepsis and macrophage activation syndrome. Initial reports demonstrated that many patients have myocardial dysfunction and coronary artery involvement in addition to gastrointestinal and systemic symptoms.

The outcome of the project may significantly influence the development of diagnostic procedures (i.e. personalized medicine based on patients' genotype related to the complement), treatment procedures (supplementation/inhibition therapy regarding the complement system) and prevention (active and passive vaccination strategies based on the identified glycans). It furthermore may contribute to better understanding of PIMS-TS, a new, still poorly understood, severe disease affecting children and adolescents.