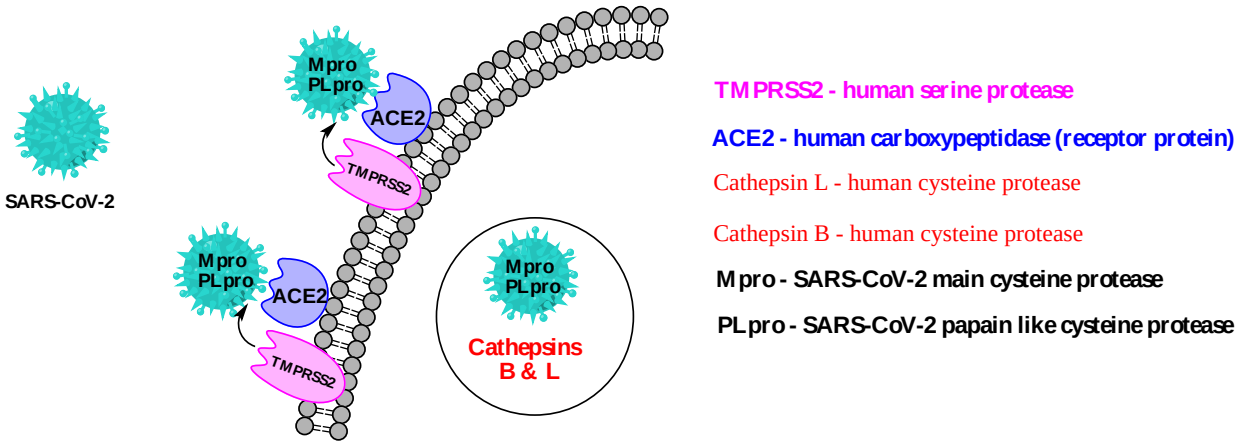
Principal investigator: prof. Marcin Drąg
Project title: **Retargeting of known drugs towards proteases involved in the development of COVID-19 disease**

In December 2019, a severe respiratory disease of unknown origin emerged in Wuhan, Hubei province, China. Symptoms of the first patients were flu-like and included fever, cough and myalgia, but with a tendency to develop a potentially fatal dyspnea and acute respiratory distress syndrome. Genetic analysis confirmed a betacoronavirus as the causing agent. The virus was initially named 2019 novel coronavirus (2019-nCoV), but shortly thereafter, it was renamed to SARS-CoV-2. Currently, there is no approved vaccine or treatment for COVID-19. While it may take several months (optimistic prognoses predict Spring/Summer 2021) for effective vaccine development, one of the most promising strategies is retargeting already known drugs towards COVID-19 treatment. One of the most interesting groups of molecular targets for drug retargeting constitute proteolytic enzymes involved in viral infection. Studies with previous SARS (2002/03) and studies with current virus demonstrate that there are four human (ACE2, TMPRSS2, cathepsins L and B) and two viral proteases (M^{pro} and PL^{pro}) implicated in SARS-CoV-2 infection and replication. Just published studies about retargeting of known drugs for M^{pro} confirms that this strategy may lead to identification of promising candidates, which prevent the virus from replication. Therefore we postulate that the same approach should be applied for other five proteases. Human angiotensin converting enzyme 2 (*ACE2*) is a carboxypeptidase and was identified as critical receptor for *SARS*-CoV-2 for cell entry. Human transmembrane protease, serine 2 (TMPRSS2, epitheliasin) is a serine protease responsible for spike (S) protein of SARS-CoV-2 activation and processing. Also human endosomal cysteine proteases cathepsins B and L are used by virus for S protein priming. Studies show that inhibition of both cathepsins is required for robust blockade of viral entry. Viral cysteine protease PLpro has deubiquitinating activity and broad specificity towards other substrates and is also considered as attractive target for drug development. **The aim of this project is to screen library of several thousand FDA and others accepted drugs towards five proteases (ACE2, TMPRSS2, Cathepsins B & L, SARS-CoV-2-PL^{pro}) in order to find molecules, which can inhibit any of these proteases involved in SARS-CoV-2 invasion and COVID-19 development. Identification of such molecules would immediately yield an information about candidates for drugs retargeting.**



Scheme. Proteases participating in COVID-19 development.

Obtained information could be used immediately by medical doctors for research focused on drugs retargeting, but also by virologists to work on virus models to better understand the mechanism of action. Moreover, leading structures identified for each enzyme may be very useful to medicinal chemists and for in silico calculations and docking for further structure optimization, what may result in development of new drugs structures. Additionally, molecular biologists and biologists may use it to investigate interactions between drug and target enzyme.