COVID-19 Research and Education at Leiden Academic Centre for Drug Research (May 15, 2020).

Since the start of the Corona crisis, several COVID-19 related research and teaching projects were started at LACDR. The computational and teaching activities started right away, as well as a large-scale metabolomics screening program by Thomas Hankemeier's group. Other experimental activities are still in the start-up phase due to the access restrictions to our labs; fortunately, these restrictions were partly removed, so we hope to proceed with full speed. The following article gives an overview on all COVID-19 related activities at LACDR

Predicting and preventing serious COVID-19 symptoms. Every process in the body - including disease processes - leaves traces in the form of small molecules. These molecules in our blood provide a lot of information. For example, it is often possible to trace which foods or medicines have been swallowed or administered, or they can be used to determine whether someone has been exposed to air pollution. Some of these molecules in the blood are themselves the trigger for crucial processes in the body. These can be 'healthy' processes, but also unwanted ones, such as blood vessel leakage and blood clotting.

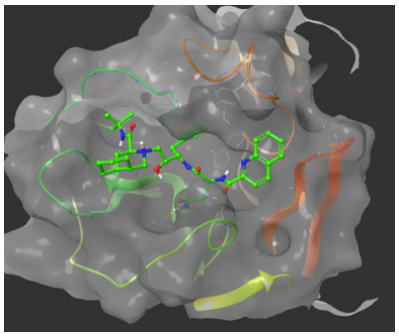
Thomas Hankemeier and colleagues have started systematically mapping all kinds of small molecules in the blood of COVID-19 patients: amino acids, fatty acids, bioactive lipids, small chemicals from the environment and many more. They will compare the resulting profiles to clinical data of the patients. In this way, they hope to find molecules that are predictors for certain COVID-19 complaints.

Dosing schedules of drugs. The group of Coen van Hasselt is focusing on drugs being repurposed for treatment against COVID-19. The group developed a web-based tool (www.covid19pkpd.eu) to investigate dosing schedules of drugs being investigated for treatments against COVID-19. Collaborations with clinical researchers elsewhere performing clinical studies in patients of potential COVID19 treatments are ongoing. Finally, the group is investigating adverse drug reactions associated with drugs being investigated for treatments against COVID19.

Piet van der Graaf published an editorial on the critical role of Clinical Pharmacology in repurposing existing drugs for COVID-19 "to get the right drug at the right dose in every patient as soon as possible" (https://ascpt.onlinelibrary.wiley.com/doi/abs/10.1002/cpt.1876), exemplified by a publication from the group of Catherijne Knibbe on chloroquine (https://www.ncbi.nlm.nih.gov/pubmed/32306288).

Repurposing of approved drugs and identification of new inhibitors to fight SARS-CoV-2. The computational drug discovery (CDD) group of Gerard van Westen has launched a virtual screening campaign, identifying small molecules active against SARS-CoV-2 infection

This includes the screening of all approved drugs (and promising analogues) for affinity towards known viral targets such as the viral protease. They have found some potentially active molecules that warrant follow up screening and biological validation.



Saquinavir docked to SARS-CoV-2 main protease.

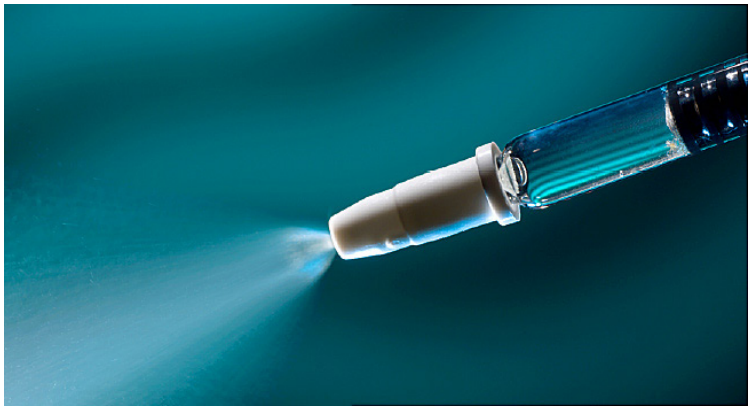
Currently, the CDD group is exploring options to collaborate within Leiden with LIC (Overkleeft, Van der Stelt, and Van Kasteren), IBL (Martin and Van Wezel), and

LUMC (Van Hemert) to expand this project and experimentally validate the computational predictions.

Innovative SARS-CoV-2 vaccine concepts. The current COVID-19 pandemic has spurred dozens of vaccine initiatives. The majority of these vaccines are injectables that are primarily aimed to induce systemic neutralizing antibodies. However, experiences with other respiratory viruses, such as influenza virus, have shown that next to systemic antibodies, both cytotoxic T-cells and local immunity in the respiratory tracts are important players in prevention of reinfection. The group of Bram Slütter aims to develop vaccines that exploit these additional layers of protection, which requires a re-tooling of the vaccine formulation and the route of administration.

His group collaborates with the group of Thomas Wirth (Medizinische Hochschule Hannover, Germany) and is developing a two-step (prime-boost) subunit vaccine that aims to induce a robust cytotoxic T-cell response to SARS-CoV-2 (next to neutralizing antibodies), based on a patented technique both groups have successfully deployed to induce tumor specific cytotoxic T-cells.

In collaboration with Wim Jiskoot, Gideon Kersten and Peter Soema (Intravacc, Bilthoven NL), Bram's group aims to develop a SARS-CoV-2 subunit vaccine that is administered intranasally. This administration route exploits the natural route of viral infection and can induce local antibody and cytotoxic T-cell responses.



Flumist is an example of a successful nasal vaccine, which has been shown to provide more local immunity than injectable influenza vaccines. (source https://www.webmd.com/)

Repurposing of drugs. The two candidate Ebola drugs, FX06 and melatonin, that have been recently proposed and tested by the group of Alireza Mashaghi Tabari and their industrial partner using an organ-on-chips (Junaid et al. iScience 2020) are now going to be repurposed and tested in trials for SARS-CoV-2. FX06 targets cellular junctions and suppresses Ebola virus disease by stabilizing cell-cell junctions. Combination of mercaptopurine and melatonin may offer a potential combination therapy for SARS-CoV-2 by synergistically targeting papain-like protease, ACE2, c-Jun signaling, and anti-inflammatory pathways.

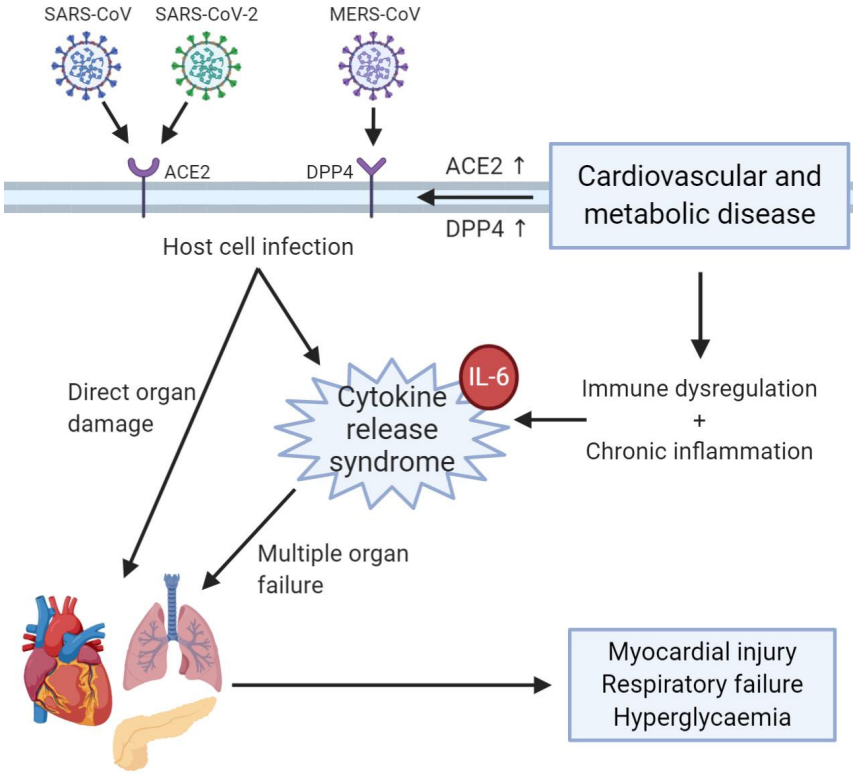
COVID-19 literature reviews and Bachelor internship assignments.

Vaccine development is also a focus of a group of Bachelor students studying Bio-Pharmaceutical Sciences that perform their final research projects under general supervision of Jeroen Bussmann. While they would normally be performing experiments in the lab, they are now each designing a novel vaccine – including a proposal for the experiments required to develop and test these novel vaccines for future translation. One example is the development of an alternative vaccine delivery route, such as a microneedle-based vaccine that would allow widespread needle-free vaccination campaigns, also in areas with restricted access to refrigeration. The students get expert advice on vaccine development

from LACDR researchers Bram Slütter, Wim Jiskoot and Gideon Kersten and meanwhile obtain general knowledge on vaccinology by following online courses and through group discussions on recent literature.

Besides the last-year Bachelor students, also the Bio-Pharmaceutical Sciences Master students were forced to stop their running experiments from one day to the next. As an alternative until the lab also reopens for them, Jeroen Bussmann supervised a group of 5 students in writing a literature review on one specific class of COVID-19 vaccines that are currently under development – theses based on synthetic mRNAs. Development of these mRNA vaccines is a recent and exciting area of research allowing very rapid development – key during a pandemic. The students investigated several topics, including formulation and adjuvant-effects of mRNAs, processing in antigen-presenting cells, the role of glycosylation and the challenges for large-scale manufacturing.

Miranda van Eck supervised two master students with a literature review on the link COVID-19 disease severity and the underlying mechanisms of the association with a background of cardiovascular and metabolic diseases. Due to the corona measures the students had to pause their research projects, but by writing these literature reviews they have been able to continue their studies and contribute to the science in this important field. The literature reviews will form a basis of review article that will be submitted for publication in an expert journal on cardiovascular disease.



From: Literature review of Mart de Boo, MSc student Bio-Pharmaceutical Sciences (Leiden University)