Discovery and development of novel antivirals for control and cure of SARS-CoV-2 infection (COVID-19)

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The novel Coronavirus SARS-CoV-2 that emerged in China in December 2019 and is continuing to spread all over the world constitutes a major public health emergency. With currently almost 130.000 people infected and close to 5000 deceased from the Covid-19 disease the search for factors involved in virus spread and replication is paramount to develop tools to fight the ongoing pandemic.

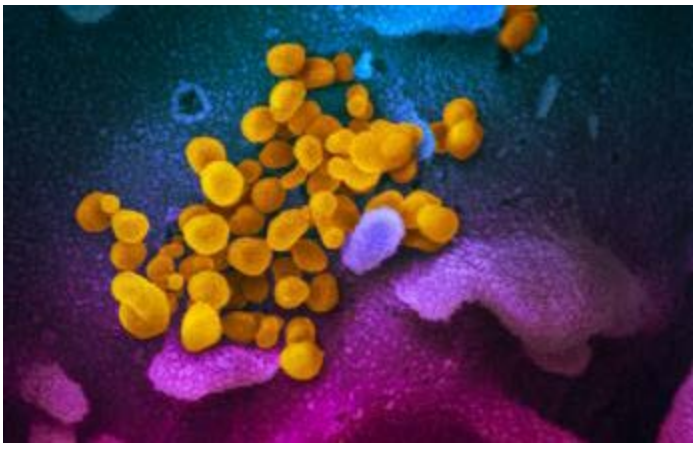

Figure 1:Scanning electron microscope image of SARS-CoV-2 (yellow), the virus that causes COVID-19—isolated from a patient in the U.S., emerging from the surface of cells (blue/pink) cultured in the lab. Credit: NIAID-RML

Many RNA viruses share common features of virus entry and replication. A promising candidate for treatment of Covid-19 appears to be the nucleoside-analogue remdesivir, that has been developed to treat ebola virus infection (Warren et al, Nature 2016, Mulangu et al, N Engl J Med 2019) and which has also been shown to efficiently block epidemic and zoonotic coronavirus infection (Sheahan et al, Sci Transl Med 2017), including SARS-CoV-2 (Wang et al, Cell Res 2020) and is now being used in compassionate use trials to treat patients affected by Covid-19.

This indicates, that antiviral research on other clinically relevant virus can generate synergies that can be directly applied in clinical use.

Along that line, a very recent publication showed that SARS-CoV-2 requires activation by the host cell protease TMPRSS2, which can be blocked by the clinically approved serine protease inhibitor camostat mesylate (Hoffmann et al, Cell 2020). The same protease, TMPRSS2 has also been shown to promote HCV entry (Esumi et al, Hepatology 2015), indicating common features of virus entry of SARS-CoV-2 and HCV. In a complementary project, our laboratory has shown that coronaviruses, including SARS-CoV require the HCV entry factor cyclophilin A (Carbajo-Lozoya et al, Virus Res 2014; Nakagawa et al, Gastroenterology 2005) for replication, and that infection of the world-wide circulating coronavirus NL63 than be inhibited by the cyclosporine-A derivate alisporivir (Figure 2) (Carbajo-Lozoya et al, Virus Res 2014), a compound that has initially been developed to treat HCV infection (Pawlotsky et al, Hepatology 2015), demonstrating that the two positive-strand RNA viruses HCV and coronaviruses share common host factors for viral cell entry and replication.

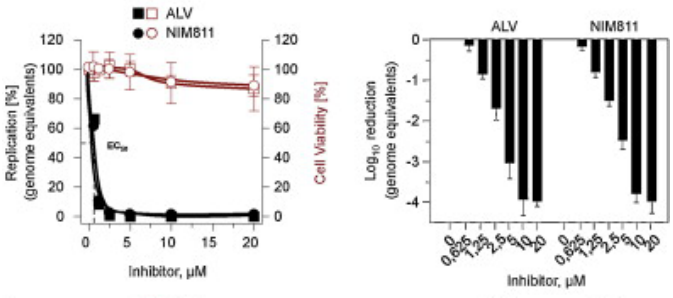

Figure 2: Antiviral effect of Alisporivir (ALV) and a FK506 derivative on HCoV-NL63 replication in Caco-2 cells. Genome equivalents were determined by qPCR and cell viabilities by Cell Titer Glow kit (Promega). Data shown are mean values of a representative experiment performed in at least triplicates. The graphs were plotted using Prism 5 (GraphPad Software, Inc.) and by a non-linear regression with a variable slope algorithm, the curve was fitted for each respective inhibitor and the EC50 calculated. Modified from Carbajo-Lozoya et al, Virus Res 2014.

Therefore, using our internationally recognized expertise to discover host factors as targets for antiviral therapy (Lupberger et al, Nat Med 2011; Zona et al, Cell Host Microbe 2013; Mailly, Nat Biotechnol 2015; Verrier et al, Hepatology 2016; Colpitts et al, Gut 2018, Verrier ER, Gut 2020; reviewed in Crouchet et al, Therap Adv Gastroenterol 2018) we have established the expertise and model systems to contribute to the global effort to find novel compounds to fight SARS-CoV-2 infection. Using established coronavirus model systems (Letko et al, Nat Microbiol 2020, Hoffmann et al, Cell 2020) we will discover host factors for the coronavirus life cycle focusing on virus cell entry and replication. Specifically, we will assess the antiviral activity of compounds targeting common host factors of HCV and coronaviruses. Collectively, we anticipate that our program will uncover novel strategies and compounds for antiviral therapy for urgently needed control and cure of coronavirus infection.

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