

## The role of TMPRSS2 and TMPRSS2- Inhibitors in cell entry mechanism of COVID-19

Stefan Bittmann, Anne Weissenstein, Elena Moschüring-Alieva, Lara Bittmann, Elisabeth Luchter, Gloria Villalon

Department of Pediatrics, Ped Mind Institute (PMI), Gronau, Germany

\***Corresponding Author:** Stefan Bittmann, Head of the Department of Pediatrics and Ped Mind Institute (PMI)

Pediatrician, Hindenburgring 4, D-48599 Gronau, Germany.

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### **Abstract**

*The enzymes trypsin, furine and other proprotein convertases, cathepsin, transmembrane proteases (TMPRSS) and elastases play a role in the cell entry of coronaviruses (Coronaviridae). The proteases TMPRSS2 and TMPRSS11a, which are abundant in the respiratory tract and expressed on cell surfaces, promote the entry of SARS-CoV-1 viruses. For the TMPRSS protease TMPRSS11d - also known as human airway trypsin-like protease (HAT) - a proteolytic activation of the S- protein of SARS-CoV-1 was demonstrated. TMPRSS2, in turn, complexes with the ACE2 receptor, which allows efficient penetration of the virus directly at the cell surface. TMPRSS2 and TMPRSS11D activate the S protein by cleaving it into the S1 and S2 subunits, thus allowing endosome-independent cell entry at the cell membrane. Virus-based therapies include monoclonal antibodies, antiviral peptides that dock to the S protein of viruses, viral nucleic acid synthesis inhibitors and inhibitors for docking to other viral structures and accessory proteins*

### **Keywords**

Pneumonia; China; Camostat; COVID-19; Coronavirus Disease; Infection; Bromhexin; Ovomuroid.

### **Camostat**

Camostat is a synthetic low-molecular serine protease inhibitor used for the treatment of chronic pancreatitis and reflux esophagitis with minimal side effects [1]. Camostat is an antifibrinolytic agent with a molar mass of 398,41 g/mol. Camostat is a therapeutic agent against cancer, pancreatitis and liver fibrosis. In the treatment of human tracheal epithelial

(HTE) cells with a camostat concentration of 10 mg/mL, the influenza A virus H1N1 titer in the supernatant of the virus culture of strain A/PR/8/34 is significantly reduced [2,3]. Another study showed that camostat leads to a tenfold reduction of the SARS-CoV titer in Calu3 cells (human lung cancer cell line) [2]. At a camostat concentration of 10  $\mu$ M, the cell entry of MERS-CoV in Vero cells is inhibited by a factor of 14. Three days after MERS-CoV infection, the amount of viral RNA in the supernatant of the Calu3 cell culture is reduced 270-fold at a camostat concentration of 100  $\mu$ M [2].

### **Nafamostat, Bromhexin, Leupeptin and Ovomuroid**

The serine protease inhibitor nafamostat blocks MERS-CoV infection in vitro by suppressing TMPRSS2 activity and leads to a 100-fold reduction of virus entry at a concentration of 1 nM, which is more efficient than camostat [1]. Bromhexine hydrochloride (a component of antitussives that also suppresses prostate cancer metastasis in mice) could also be used as an inhibitor of TMPRSS2 for the treatment of influenza and coronavirus infections. Other FDA-approved serine protease inhibitor is leupeptin and has different antiviral activities. Ovomuroid, a trypsin inhibitor, inhibits the spread of influenza A virus H1N1 (strain A/Memphis/14/96) more efficiently than aprotinin at a concentration of 50  $\mu$ M [1]. 3-Amidinophenylalanyl Derivates, Benzamidine Derivates and Polycytidyl Acid. 3-amidinophenylalanyl derivatives could inhibit TMPRSS2 at a concentration in the nanomol range [1]. Furthermore, it has been shown that three benzamidine derivatives as peptide mimetics inhibit influenza A virus H1N1 infection of strains A/Memphis/14/96 and A/Hamburg/ 5/2009 differently in TMPRSS2- and HAT-expressed cells. In knockout mice in which the TMPRSS2 gene is inactivated, intranasal stimulation with polyinosinic: polycytidyl acid (an immune stimulant, poly I: C for short) resulted in an attenuated chemokine and/or cytokine response, which play a role in the immune system [1]. They also lost weight and the viral dynamics in the lungs decreased.

### **Conclusion**

In conclusion, TMPRSS2 plays an important role in the viral spread of MERS-CoV-2 and SARS-CoV within the respiratory tract of mouse models and in murine immunopathology [4,5]. A study conducted by Markus Hoffmann and Hannah Kleine-Weber of the German Primate Center together with other researchers, confirms that the SARS-CoV-2 virus also requires the presence of the ACE2 receptor and the TMPRSS2 enzyme in the cell membrane of lung cells, which cleaves the S protein on the virus envelope in order to be able to enter the lung cell [4,5]. According to this study, the known inhibitor of TMPRSS2, camostat, significantly reduces the probability of penetration of SARS- CoV-2 in cell experiments in vitro and could be suitable for treatment [2]. According to studies, SARS-CoV-2, the virus responsible for COVID-19, needs the TMPRSS2 present in the human body to enter the host cell, which could be a starting point for treatment. The efficacy of the drug in cell cultures has already been demonstrated [2-4]. Therapeutic efficacy in COVID-19 patients still has to

be tested in clinical trials. Likewise, the Primate Centre Göttingen will investigate whether the active substance can be injected directly into the lung. There are doubts whether camostat per se is sufficiently available in the lung. Foipan (camostat) is one of the drugs for which the German Federal Ministry of Health initiated centralized procurement in April 2020 for the treatment of infected and seriously ill COVID-19 patients in Germany. Since a COVID-19 therapy is an individual healing trial without clinical proof of efficacy, its use should be considered primarily for severe forms of COVID-19 on an individual patient basis [6].

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