
Therapeutic agents targeting SARS-CoV-2 S protein biogenesis and function

Despite the 2003 SARS pandemic and the 2012 MERS outbreak, no approved specific antiviral drugs for the treatment of human coronavirus (CoV) infections exist. As a consequence, drug repositioning has received a significant amount of attention during the current SARS-CoV-2 pandemic. Our group has long-lasting experience in the area of antivirals, focusing especially in host-directed intervention as an antiviral strategy that may overcome problems associated with drug resistance. We are presently exploring the key components of CoV lifecycle from the perspective of the host cell, and how selected therapeutic agents are affecting these components by specifically targeting host cell enzymes/factors. In particular we have recently focused our attention on FDA-approved drugs able to interfere with SARS-CoV-2 spike biogenesis, folding and post-translational modifications, as well as on novel therapeutics targeting S protein binding and fusion activities. Using a variety of plasmids expressing different forms of the SARS-CoV-2 spike, we have established different models of SARS-CoV-2 S pseudotyped viral particles and developed different cell-based pseudovirus entry models to identify potential inhibitors of S protein infectious ability, as well as to investigate S protein/ACE2-driven cellular signaling pathways that may participate in coronavirus pathogenesis, with particular interest in stress-regulated HSF1/2, NF-kappaB and NRF2 survival pathways. We have also developed a pseudovirus-based neutralization assay for screening anti-SARS-CoV-2 S neutralizing antibodies, presently utilized in collaboration with pharmaceutical companies for the development of anti-SARS-CoV-2 spike monoclonal antibodies.

References:

Santopolo S, Riccio A, Santoro MG. The biogenesis of SARS-CoV-2 spike glycoprotein: multiple targets for host-directed antiviral therapy. *Biochem. Biophys. Res. Comm.* 2020, doi: [10.1016/j.bbrc.2020.10.080](https://doi.org/10.1016/j.bbrc.2020.10.080) [Epub ahead of print].

Piacentini S, La Frazia S, Riccio A, Pedersen JZ, Topai A, Nicolotti O, Rossignol JF, Santoro MG. Nitazoxanide inhibits paramyxovirus replication by targeting the Fusion protein folding: role of glycoprotein-specific thiol oxidoreductase ERp57. *Sci. Rep.*, 8: 1-14, 2018.

Coccia M, Rossi A, Riccio A, Trotta E, Santoro MG. Human NF- κ B repressing factor acts as a stress-regulated switch for ribosomal RNA processing and nucleolar homeostasis surveillance. *Proc. Natl. Acad. Sci. USA*, 114: 1045-1050, 2017.

Amici C, Di Caro A, Ciucci A, Chiappa L, Castilletti C, Martella V, Decaro N, Buonavoglia C, Capobianchi M and Santoro MG. Indomethacin has a potent antiviral activity against SARS coronavirus. *Antiviral Therapy*, 11: 1021-1030, 2006.

Santoro MG, Rossi A and Amici C. NF- κ B and virus infection: who controls whom.
<https://doi.org/10.1093/emboj/cdg267>

Keywords: Antivirals, coronavirus, drug repositioning, pseudovirus, stress response

Contacts: M. Gabriella Santoro santoro@uniroma2.it , Antonio Rossi antonio.rossi@ift.cnr.it