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Sent: Wednesday, April 8, 2020 2:49 AM
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Subject: WG: Inhibit cytokine storm in COVID-19 patients by Velcade Bortezomib
Importance: High

Inhibition of cytokine storm in COVID-19 patients with acute respiratory distress syndrom by PROTEASOME INHIBITORS e.g. Velcade (Bortezomib)

Dear Dr. Fauci,
dear Madams/Sirs,
I want to bring to your attension some potentially important experimental data and a new proposal for treatment of COVID-19 patients with acute respiratory distress syndrome and organ failure. Sorry for the broad distribution but I wanted to make sure that my message reaches you.

Similarly as has been described earlier for SARS-CoV, MERS-CoV (Channappanavar & Perlman, 2017), H5N1 and some heavy H1N1 Influenza A infections, also COVID-19 patients have been reported to show significantly increased systemic cytokine release (i.e. cytokine storm), particularly those patients with lung failure or systemic organ failure (***Chaolin Huang et al. Lancet vol 395, 2020, ref 1***).

Previous studies at **Virologik GmbH, Erlangen, Germany,** in colaboration with the **Friedrich-Loeffler-Institut, Tuebingen, Germany** have shown, that H5N1 (or alternatively LPS) -induced **Cytokine storm *in vivo* can be inhibited by application of Proteasome Inhibitors** (***E. Haasbach et al, Antiviral Res. 91, 2011, ref. 2***), via **the inhibition of translocation of the NF-κB transcription factor** to the nucleus (see ***Fig. below***). The mechanism of NF-κB inhibition by proteasome inhibitors is well described, and works via the inhibition of the proteasomal degradation of the cytosolic inhibitor IκB, this way keeping NF-κB bound in the cytosol and thereby inhibiting the otherwise induced (by cytokine or LPS- or RNA virus) translocation of NF-κB to the nucleus where it would initiate the transcription of many cytokines. This effect of proteasome inhibitors seems to work in most cell types, we could demonstrate this effect in several different cell types (including macrophages) after stimulation with TNFa in vitro and in H5N1 (or LPS) treated mice in vivo (see manuscript and Figs. attached).

Inhibition of NF-κB by proteasome inhibitors provides the unique potential to inhibit the release of many cytokines simultaneously, in particular strongly proinflammatory cytokines **IL-1α, IL-6, TNFα, MIP-1β...)** (whereas some other cytokines involved in antiviral immune response, such as IFNγ probably seem to be not/less affected (because of different transcription pathway).