SPOTLESS - Screening of small molecules to fight SARS-CoV-2 by combining novel approaches and sustainability

The novel SARS-CoV-2 is a lethal human pathogen with no FDA approved vaccines or drugs. An important step of the virus life-cycle is the viral glycoprotein S activation by Proprotein Convertases (PCs) which are proteases with a broad spectrum of cellular substrates. Inhibition of the processing step locks the virus into a form which eventually is no more pathogenic. Therefore, PCs represent attractive drug targets to fight against SARS-CoV-2. To date, there are no PCs inhibitors available for the in vivo use. Here, I propose three approaches to look for small molecule inhibitors of PCs, exploiting the virus cleavage site. Beside the classical in vitro screening, I aim to exploit novel PCs sensor platforms based on innovative ideas to ameliorate and simplify the readout. One attempt will see the use of luciferase reporters on the blueprint of sensors that I have recently published; following a second method, I will take advantage of the cellular death machinery as an on/off cleavage signal. In turn, these virtuous assays will contribute to a sustainable research approach. Novel PCs inhibitors are of great value against Covid-19 infections. Importantly, the inhibitors can be re-purposed against novel emerging pathogens, if necessary. Indeed, PCs dependence is becoming a distinctive mark of severe pathogenicity.

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