Contribution ID: **95** Type: **Oral presentation**

RNA-viruses inhibitors: unintended consequences of the target driven approach

Wednesday, 14 September 2022 16:00 (15 minutes)

Targeting, in silico, the RNA dependent RNA polymerase (RdRp) of Dengue virus, we selected a class of pyridobenzothiazolones (PBTZs, from a proprietary library), which showed broad-spectrum antiflaviviral activity. In contrast to the enzyme kinetic measurements that showed a non-competitive inhibition, the X-Ray crystal structure of the targeted RdRp in complex with one PBTZ, suggested a competitive inhibition mechanism [1]. Furthermore, cell-based experiments with one of the most potent compounds of the class (HeE1-17Y) indicated that the antiviral activity was unrelated to the polymerase inhibition [2]. Indeed, we observed that viral infectivity was drastically reduced by incubating the compound with the virus before infection, suggesting its direct interaction with the viral particles.
The mode of action of HeE1-17Y has been studied for West Nile virus taking advantage of non-infective reporter replication particles (RRPs), that were analysed by a preliminary cryo-EM experiment, showing their identity to the native virions.
Electron microscopy analysis (negative staining) of RRPs incubated with the inhibitor revealed a reduced number of virions, that were severely compromised showing a “gruyere” aspect (Figure 1).
We demonstrated that HeE1-17Y is an antiviral compound whose mechanism of action is based on the destruction of viral particles (virucidal activity), selective against several enveloped viruses (ineffective against different non-enveloped viruses). Given the low toxicity for cells, the potential use of PBTZs also in disinfectants, repellents, skin creams, aerosol, sanitizing product and nasal spray could be of particular interest to prevent viral infections, including flavivirus and coronavirus [3].
This work shows how, starting from a classical target driven approach, by means of a combination of different experimental strategies, it is sometime possible to unravel an unpredictable path to disclose the true nature of a novel class of active compounds.

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Session Classification: MS

Track Classification: Current Approaches in Structural Biology