Oral presentation

Acriflavine as an inhibitor of PlPro SARS-CoV-2: repurposing an old drug for a novel challenge

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The recent SARS-CoV-2 pandemic caught us unprepared for a global health emergency. Structure-based drug discovery, while often effective for identifying new drugs, wouldn't have been suitable in such a situation due to the lengthy timeline from hit identification to a drug reaching the market. A valid alternative is repurposing drug discovery. Using a high-throughput screening (HTS), among a library of FDA already approved drugs, we identified *acriflavine as a SARS-CoV2 papain-like protease (PlPro) inhibitor*. NMR and X-ray crystallography confirmed that acriflavine acts by blocking the access to the catalytic pocket. We demonstrated that the drug inhibits viral replication at nanomolar concentration in cellular models, *in vivo* in mice and *ex vivo* in human airway epithelia, with broad range activity against SARS-CoV-2 and other beta-coronaviruses. Our findings offer potential for the development of enhanced drugs with broad-spectrum activity against coronaviruses, contributing to preparedness for future coronavirus outbreaks.