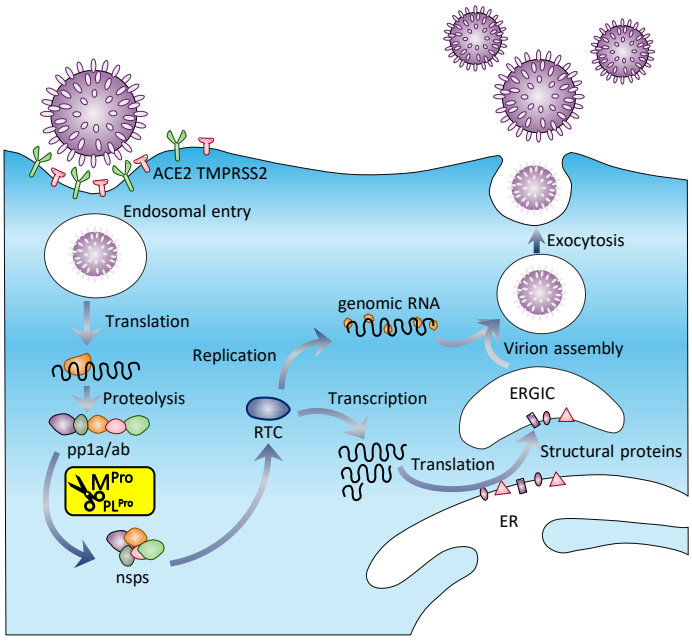
sosei HEPTARES



SARS-CoV-2 Main protease or M^{Pro} proteolytically cleaves the overlapping viral pp1a and pp1ab polyproteins into functional proteins which is a critical step during viral replication. **M^{Pro} is therefore a key enzyme in the viral replication cycle.** Consequently, its inhibition can stall the production of infectious viral particles and thus alleviate disease symptoms.

Despite ongoing vaccination campaigns, risk of disease still exists and vaccines might not remain effective against future variants. Therefore, there is a need for safe and convenient antiviral drugs. With knowledge gained from structures bound to inhibitors, M^{Pro} is one of the most attractive viral targets for antiviral drug discovery against SARS-CoV-2. The high degree of **structural similarity of the active site might prove valuable for the development of pan-coronaviral drugs**.

180+	75+	200+	500+	340+
EMPLOYEES WORLDWIDE	PHDS WITHIN THE COMPANY	SCIENTIFIC PUBLICATIONS	GLOBAL PATENTS	STRUCTURES SOLVED

IN BRIEF | Excellent progress in design of inhibitors to fight SARS-CoV-2

TARGET PRODUCT PROFILE

Once or twice daily oral agent for treatment of SARS-CoV-2 viral infection dosed immediately after a positive test result and for up to 2 weeks thereafter, with potential for broader application for intervention of associated human coronavirus infections

Program Stage

Excellent progress has been made in >1 chemical series of inhibitors, since project initiation April 20.
Potential clinical candidates have now been identified, suitable for further development

Next Steps

Identify a collaboration partner to accelerate progress to human clinical trials

TARGETING SARS-CoV-2 WITH SBDD

Objective: Identification of synthetic compounds which have the potential for optimisation to an oral agent suitable for human clinical use in the treatment of COVID-19. A secondary objective is to have specificity for a broader range of coronaviruses to allow use against other related viral infections. We selected the SARS-CoV-2 M^{Pro} protease as a suitable biological target to achieve these outcomes.

DRUG DISCOVERY

We sought to use our Structure Based Drug Design (SBDD) capabilities to design inhibitors of the M^{Pro} target, beginning in April 2020. we have now identified potential clinical candidates suitable for oral dosing, comparable head-to-head to clinical stage agents from Pfizer.
This work has been done in close collaboration with Syngene International (https://www.syngeneintl.com/) who have supported chemical synthesis, enzyme inhibition screening and characterisation of pharmacokinetic properties of key compounds. Sosei Heptares scientists have supported in silico drug design, protein production and X-ray structure solution to support SBDD and biophysical characterisation of compound binding.
This and additional series have progressed through a network of collaborators: Syngene, Fidelta, o2h, Piramal, WuXi and OncoDesign.

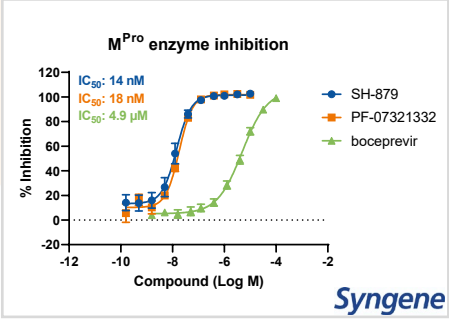
KEY RESULTS

Enzyme assays (SARS-CoV-2 M^{Pro} and related proteases) rapidly established with collaborators

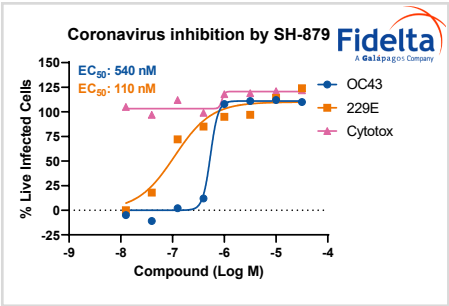
- Good *in vitro* enzyme inhibition observed
- Boceprevir (HCV protease inhibitor) is used as an assay standard; a proportion of SBDD efforts are derived from this scaffold with structural insights allowing M^{pro} activity to be tuned

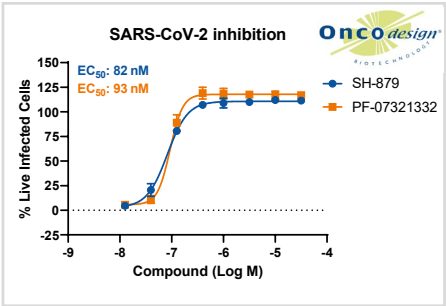
Cell-based antiviral assay data obtained for key exemplars

- HCoV-OC43, NL63 and 229E assays, demonstrating broad anti-viral potency
- Gold standard VeroE6-TMPRSS2 SARS-CoV-2 assay reveals excellent potency in head-to-head with Pfizer compounds

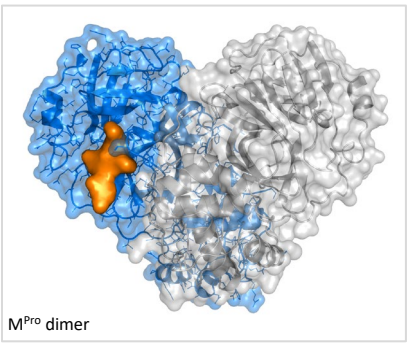


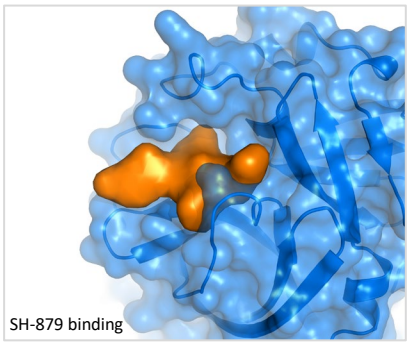
M^{Pro} enzyme inhibitor **SH-879** is more than **100-fold more potent *in vitro*** than **boceprevir** and **comparable** to oral candidate **PF-07321332** as an inhibitor of the SARS-CoV-2 M^{Pro} viral protease, supporting further development.





M^{Pro} inhibitor **SH-879** shows **comparable antiviral activity** to oral candidate **PF-07321332** against SARS-CoV-2 in cell based assays


M^{Pro} dimer


SH-879 binding

Structure-Based Drug Design (SBDD) underpins the project, driven in house at Sosei Heptares

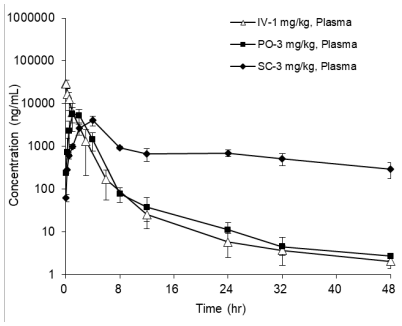
We exploited public domain structures in early design and **each chemical series is structurally enabled** with several high resolution in-house crystal structures

The structure of SARS-CoV-2 M^{Pro} (blue) bound to SH-879 (orange) determined by X-ray crystallography showcases the power of SBDD to drive design and optimisation of inhibitors towards better potency and properties

PROMISING PK RESULTS FROM OUR MOST ADVANCED ASSET

- **SH-879 has low *in vitro* clearance**, lower than boceprevir, and **superior in vivo clearance,** plasma exposure critically important to inhibit the virus.
- PK in rat is dose proportional. **Bioavailability** in rat and dog is in the range of **20-25%** across several studies.
- **SH-879** gives very high exposure from a low dose and **has a half-life of over 10 hours in dog**.
- **SH-879 does not likely require co-dosing with ritonavir for PK boosting in human clinical trials**.
- From subcutaneous dosing, exposure is high and sustained, opening up an alterative route of administration for clinical study, e.g. in a hospital setting.

Mean plasma concentration-time profiles of SH-879 after an IV dose of 1 mg/kg, a PO dose of 3 mg/kg and a SC dose of 3 mg/kg in Beagle dogs (N=3/time point)



SH-879 represents an excellent opportunity for further development as an oral drug for the treatment of COVID-19, differentiating from PF-07321332

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