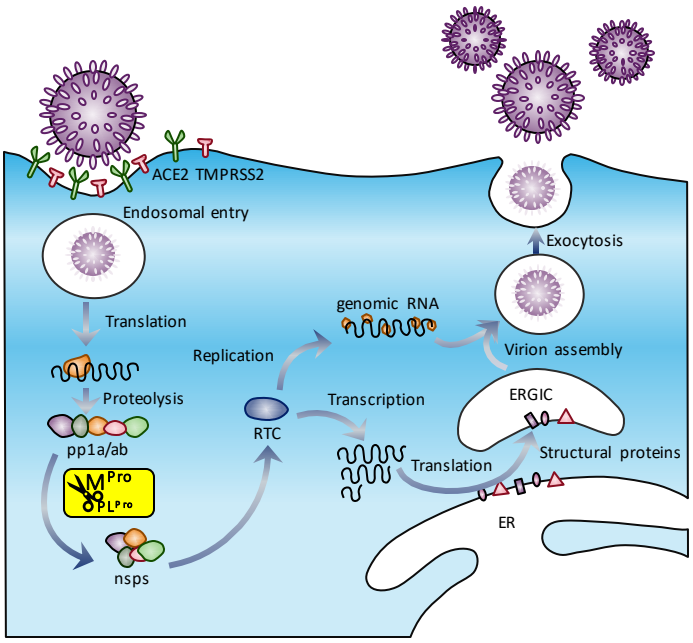
SARS-CoV-2 Main protease or M^{Pro} proteolytically cleaves the overlapping viral pp1a and pp1ab polyproteins into functional proteins. This is a critical step during viral replication. Replication-essential enzymes such as RdRp or nsp13 cannot fully function without prior proteolytic release, positioning **M^{Pro} as a key enzyme in the viral replication cycle**. Consequently, its inhibition can stall the production of infectious viral particles and thus alleviate disease symptoms.

Capitalizing on knowledge gained from structures and inhibitors of M^{Pro} from the closely related SARS-CoV and MERS-CoV, M^{Pro} is one of the most attractive viral targets for anti-viral drug discovery against SARS-CoV-2 and future variants of the virus. The high degree of **structural similarity of the active site between related viruses might prove valuable for the development of pan-coronaviral drugs**.



IN BRIEF | Excellent progress in design of inhibitors to fight SARS-CoV-2 and related human coronaviruses

TARGETING CORONAVIRUSES WITH SBDD

Primary objective: Design synthetic compounds that have the potential for optimization to an oral agent suitable for development as a treatment of COVID-19.

Secondary objective: Leverage highly conserved structure of M^{Pro} protease to design oral agents to treat disease caused by infection by a broader range of coronaviruses and other related viruses.

DRUG DISCOVERY

We sought to use our Structure Based Drug Design (SBDD) capabilities to design inhibitors of the M^{Pro} protease and focused on 3 chemical series. Here, we describe Series 3, which is currently most advanced.

This work has been done in close collaboration with Syngene International which has supported chemical synthesis, enzyme inhibition screening and characterization 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 characterization of compound binding. This and additional series are progressing through an international network of collaborators.

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 and related viral infections.

PROGRAM STAGE

Excellent progress has been made in three distinct chemical series of inhibitors, since project initiation in April 20.

Lead Compound identified suitable for further optimization to an oral drug.

NEXT STEPS

Identify a collaboration partner to accelerate progress into and through human clinical trials.

PROGRAM COLLABORATORS

Syngene · Domainex · Fidelta A Galápagos Company · o2h discovery · Piramal · 药明康德 WuXi AppTec · MRC Laboratory of Molecular Biology

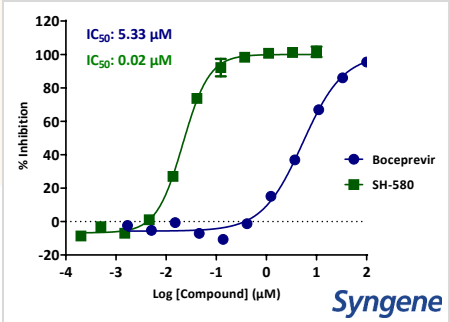
KEY RESULTS

Enzyme assays rapidly established for SARS-CoV2-M^{Pro} and related proteases through collaborators

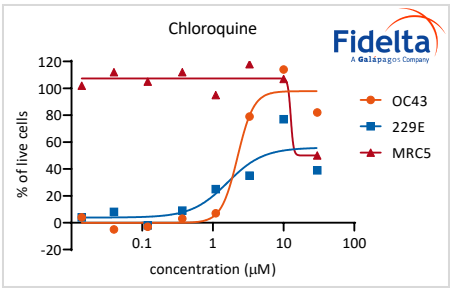
- Assays benchmarked with key literature / approved protease inhibitors
- Boceprevir (HCV protease inhibitor) is used as an assay standard; a proportion of SBDD efforts are derived from this scaffold with structural insights allowing M^{Pro} activity to be tuned

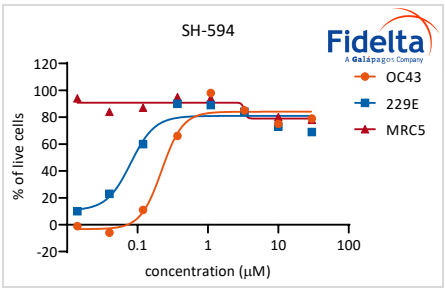
Cell-based anti-viral assay development completed

- Initial data in hand for HCoV-OC43, NL63 and 229E assays, demonstrating excellent potency
- Testing of key compounds in SARS-CoV2 replication inhibition assays planned

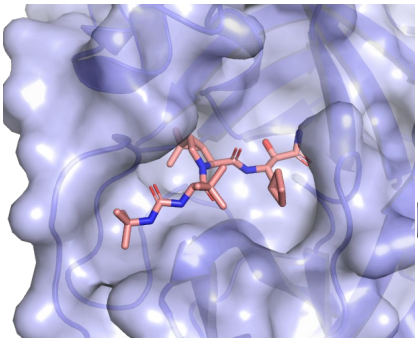


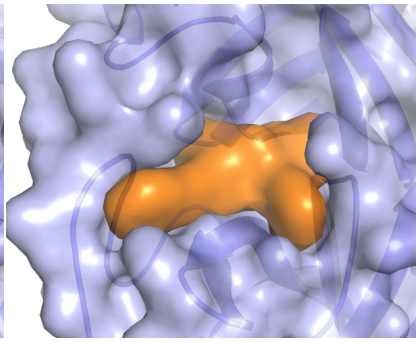
Series 3 compound SH-580 is more than **100-fold more potent *in vitro*** than Boceprevir as an inhibitor of the SARS-CoV-2 M^{Pro} viral protease, making it a much better start point for further optimization





Series 3 compound SH-594 shows **much greater anti-viral activity than Chloroquine** against a range of human coronaviruses





SBDD underpins the project, driven in-house at Sosei Heptares.

We exploited public domain structures for early design and **each chemical series is structurally enabled** with at least one high resolution in-house crystal structure.

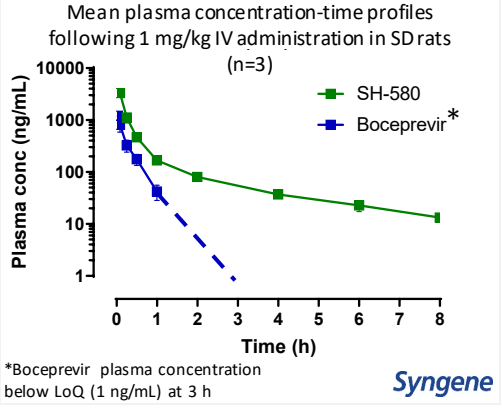
Crystal structure of SARS-CoV-2 M^{Pro} (blue) bound to Boceprevir (Left, Pink; PDB ID: 6WNP) and in-house crystal structure of SARS-CoV-2 M^{Pro} bound to an exemplar from the most advanced Series (Right, Orange) showcases the **power of SBDD to drive design and optimization of inhibitors towards better potency and drug-like properties**.

PROMISING PK RESULTS FROM OUR MOST ADVANCED SERIES

SH-580 and related examples in the series have lower *in vitro* clearance than Boceprevir, translating into **superior *in vivo* clearance and plasma exposure** critically important to inhibit the virus.

SH-580 has **comparable oral bioavailability to the marketed drug Boceprevir** with a clear and structurally enabled strategy in place to improve bioavailability within the series.

Cl 52 mL/min/kg $t_{1/2}$ 0.25 hr	**STRUCTURE-BASED DRUG DESIGN**	Cl 11 mL/min/kg $t_{1/2}$ 2.82 hr



SH-580 represents an excellent opportunity for further optimization to generate an oral drug for the treatment of COVID-19 and related viral infections

Sosei HEPTARES

ABOUT SOSEI HEPTARES

World leader in GPCR drug discovery and early development

Proprietary GPCR-targeted **StaR® technology** and SBDD platform capabilities

Japan-anchored biotech, with state-of-the-art R&D center in Cambridge, UK

Listed on Tokyo Stock Exchange (4565-JP)

160+	75+	200+	500+	300+
EMPLOYEES WORLDWIDE	PHDS WITHIN THE COMPANY	SCIENTIFIC PUBLICATIONS	GLOBAL PATENTS	STRUCTURES SOLVED

IN BRIEF | Unparalleled ability to deliver novel, high quality drug candidates into development pipelines

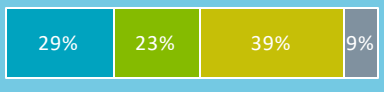
EVOLVING WITH A SPECIALIST THERAPEUTIC FOCUS

Sosei Heptares is advancing a broad and deep pipeline of partnered and in-house drug candidates in multiple therapeutic areas, including:

- Neurology
- Immunology
- Gastroenterology
- Other

Programs in Preclinical / Early Dev.

Programs in Pre-Discovery / Discovery



TECHNOLOGY & PLATFORM

Sosei Heptares has developed a unique and powerful platform technology capability called StaR® (Stabilized Receptor) that, for the first time, enables powerful structure-based drug design (SBDD) approaches to be applied to functional, stabilized GPCRs.

DRUG DISCOVERY

Sosei Heptares' StaR®/SBDD platform capabilities allow us to develop better, differentiated drug candidates against established and emerging novel GPCR target mechanisms. Our highly productive discovery engine has generated 24 high quality novel preclinical candidates and produced seven IND clinical candidates in the last 10 years. This rate is well above industry averages.

EARLY DRUG DEVELOPMENT

Sosei Heptares has fully established early development teams in the UK and Japan. Multiple clinical and non-clinical programs are underway both in-house and through our partnerships with leading global pharma companies.

PRODUCT PIPELINE

Product/Program	Modality[1]	Indication	Partner	Collaboration Type
Marketed Products				
Seebri® Breezhaler®	SME	COPD	NOVARTIS	Royalty
Ultibro® Breezhaler®	SME	COPD	NOVARTIS	Royalty
Enerzair® Breezhaler®	SME	Asthma	NOVARTIS	Royalty
ORAVI®	SME	Oropharyngeal candidiasis	FUJIFILM	Product Sales
Phase 2				
A_{2A} antagonist combo	SME	mCRPC	AstraZeneca	Out-licensed
M_1 agonist[1]	*SME*	*DLB (Japan)*	SOSEI HEPTARES	In-House
Phase 1				
A_{2A} antagonist	SME	Solid tumors	AstraZeneca	Out-licensed
M_1 agonist	SME	Alzheimer's disease	abbvie	Out-licensed
M_4 agonist	SME	Alzheimer's disease	abbvie	Out-licensed
GLP-1 agonist	SME	T2DM/Obesity	Pfizer	Out-licensed
CCR6 antagonist	SME	Inflammatory bowel disease	Pfizer	Out-licensed
$mGlu_5$ NAM	SME	Substance Use Disorders	Tempero	Asset centric company
$SSTR_5$ agonist	Peptide	Endocrine disorders	SOSEI HEPTARES	In-House (Pre-partnered)
Preclinical				
Single target	SME	Metabolic and other	Pfizer	Out-licensed
CXCR4 mAb	mAb	Immuno-oncology	kymab	Co-development
CGRP antagonist	SME	Migraine	SOSEI HEPTARES	In-House (Pre-partnered)
H4 antagonist	SME	Atopic Dermatitis	SOSEI HEPTARES	In-House (Pre-partnered)
EP4 antagonist	SME	Immuno-oncology	SOSEI HEPTARES	In-House (Pre-partnered)
GPR35 agonist	SME	IBD	SOSEI HEPTARES	In-House (Pre-partnered)
GLP-2 agonist	SME	Intestinal failure	SOSEI HEPTARES	In-House (Pre-partnered)
GPR52 agonist	SME	Neurology diseases	SOSEI HEPTARES	In-House (Pre-partnered)
PAR2	mAb	Atopic dermatitis	SOSEI HEPTARES	In-House (Pre-partnered)
Discovery				
Multi-target	SME/LME	Multiple indications	Genentech	Out-licensed
Multi-target	SME/LME	Multiple indications	Takeda	Out-licensed
Multi-target	SME	Multiple indications	Pfizer	Out-licensed
Single target	SME	Inflammatory diseases	abbvie	Out-licensed
Single target	Peptide	Inflammation	Ono	Co-development
Orexin agonists	SME	Narcolepsy	Orexia	Asset centric company
Orexin agonists	SME	Narcolepsy	INEXIA	Asset centric company

BUSINESS DEVELOPMENT

Sosei Heptares is recognized globally for challenging the frontiers of science, having solved more than 300 structures from more than 30 different GPCR targets. Large and untapped regions of the GPCR target universe, previously regarded as undruggable, are now tractable for rational drug discovery using our StaR® technology and SBDD platform. Our strategic focus is to leverage our world-leading technology platform and generate valuable, high quality novel clinical drug candidates which are attractive to innovative pharmaceutical and biotechnology companies.

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[1] Note: SME = small molecule; LME = large molecule; mAb = monoclonal antibody. [2] Phase 2 trial of HTL0018318 for DLB in Japan has been withdrawn. The Group plans to resubmit a new clinical trial notification for HTL0018318 (or another novel M_1 agonist) to the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) in the future