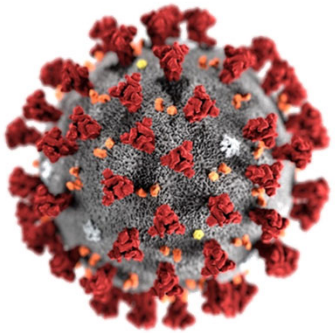


COVID-19 Pandemic:
Development of Recombinant Human ACE2 Fusion Protein Drug (SI-F019) for the Treatment of Patients with Novel Coronavirus Pneumonia

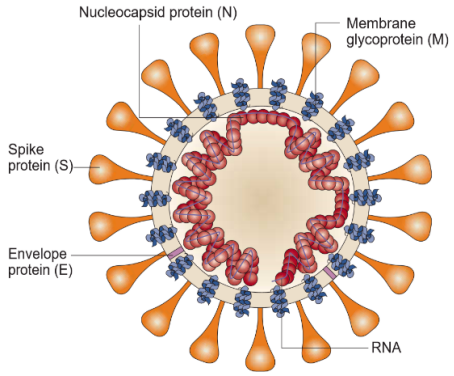
SYSTIMMUNE

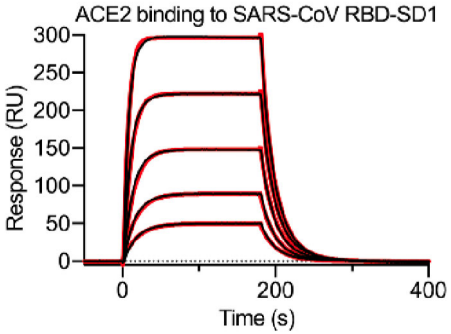
百利药业 BAILI PHARMACEUTICAL

健康与活力 生存的机会与希望!

SARS-CoV-2 Infection Mechanism

ACE2 is a receptor for SARS-CoV-2

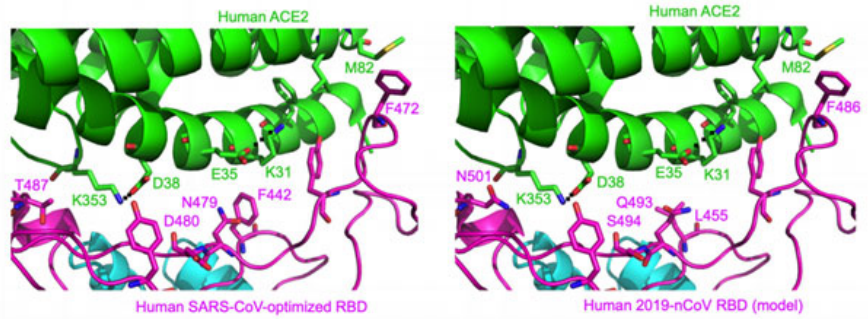




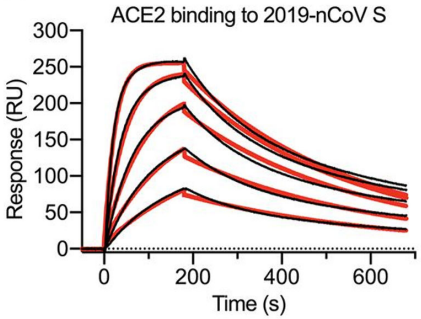
K_D = 325.8 nM
k_a = 3.62 x10^5 $M^{-1}s^{-1}$
k_d = 0.112 s^{-1}

D. Wrapp et al., Science 2020.

ACE2 is a common receptor for SARS-CoV-2 and SARS-CoV



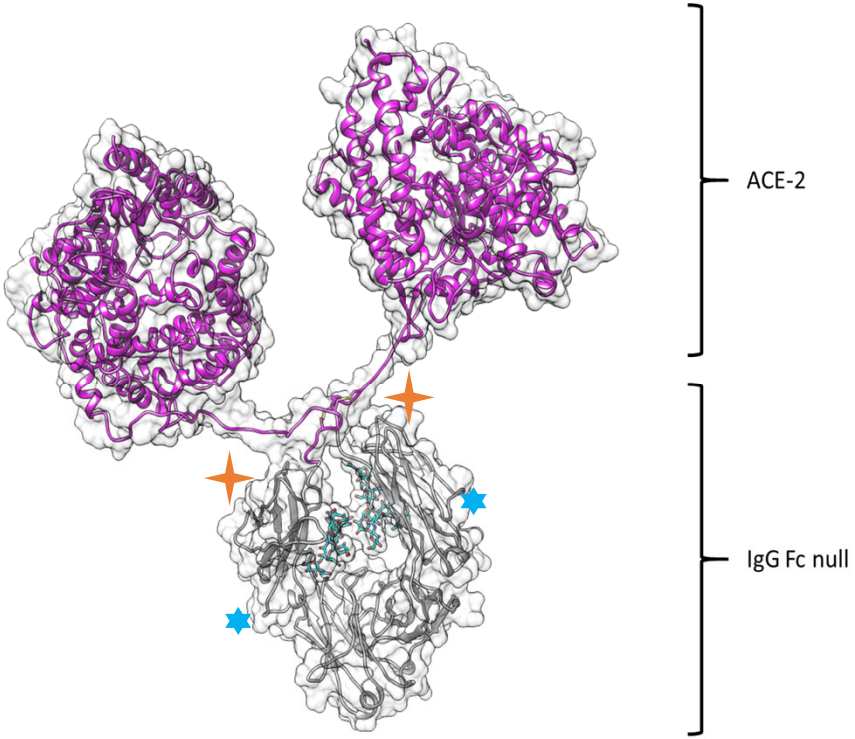
Yushun Wan et al., Journal of virology. 2020



K_D = 14.7 nM
k_a = 1.88 x10^5 $M^{-1}s^{-1}$
k_d = 2.76 x 10^{-3} s^{-1}

ACE2 has 20-fold higher affinity for SARS-CoV-2 than SARS-CoV
Higher affinity molecules are needed to neutralize SARS-CoV-2

SI-F019 Structure: Features and Advantages



SI-F019 Schematic Structure: Bivalent ACE2-Fc

1. Bivalent ACE-2 enhances binding to spike protein.
2. Fc null retains binding to neonatal Fc receptor which enhances mucosal targeting and increases half-life of SI-F019.
3. Fc null abolishes activation of macrophage proinflammatory functions of Fc gamma receptor binding and reduces clinical side effects caused by immune-mediated cell damage, cytokine storm, etc. (one of the main lethal causes of SARS).[1]
4. Eliminates the possible antibody dependent enhancement of viral entry (ADE).
5. Animal experiments and clinical studies have shown that the use of anti-SARS antibodies that retained Fc gamma receptor binding functions were likely to promote exacerbation of acute pneumonia and respiratory failure.

(1) Liu L et al., JCI Insight 2019

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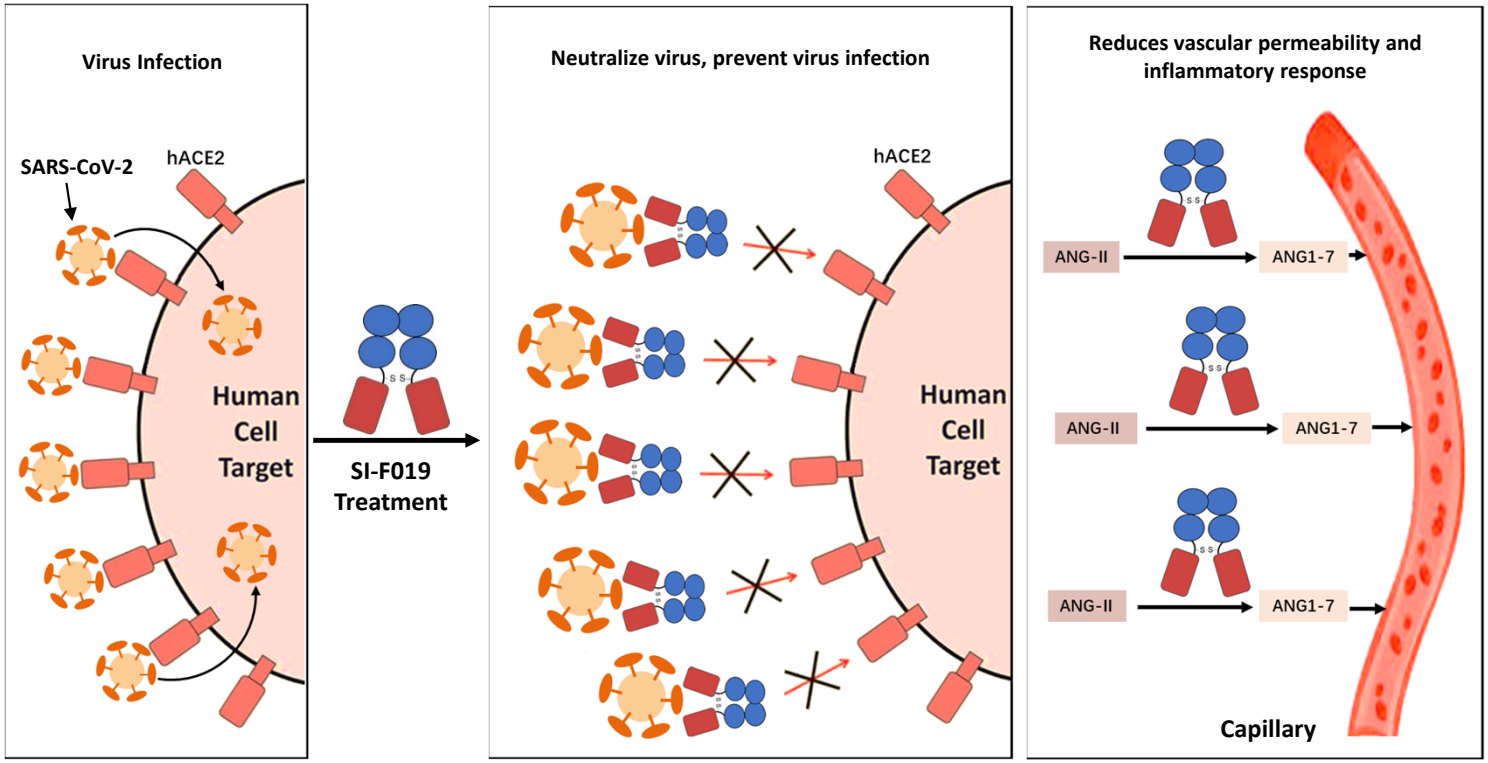
SI-F019 Mechanism of Action

- Neutralizes SARS-CoV-2 virus and prevents virus from infecting cells
- Angiotensin II (ANG-II) is hydrolyzed to ANG1-7, which reduces vascular permeability and inflammatory response



F1000Research 2020, 9:72

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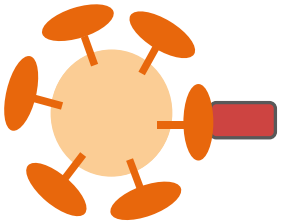
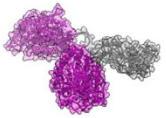
SI-F019's Unique Features

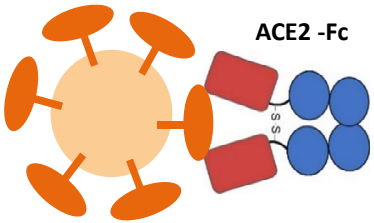
- Compared with monovalent ACE2, bivalent ACE2-Fc can improve binding with virus by several fold, thereby greatly enhancing the ability to neutralize virus



ACE2

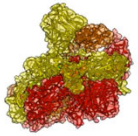
Binding = Affinity





ACE2 -Fc

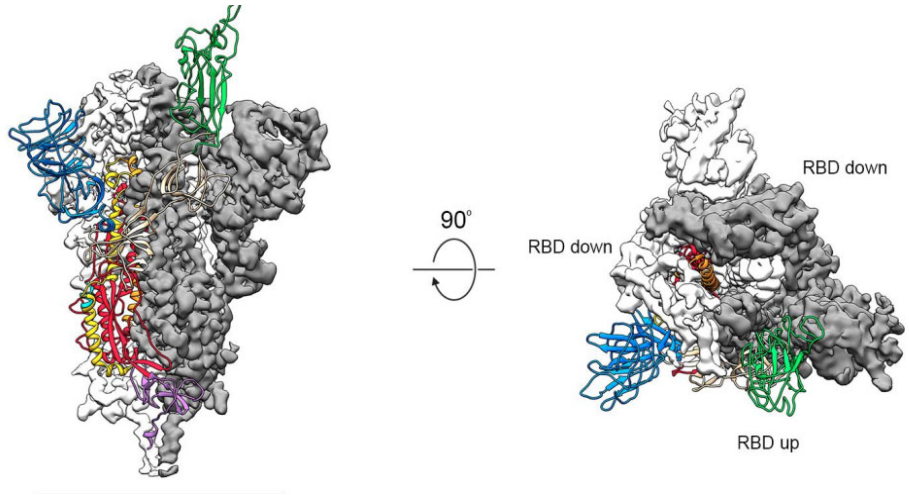
Binding = Avidity >> Affinity



Structural Model of bivalent ACE2-Fc interaction
with SARS-CoV-2 virus spike protein

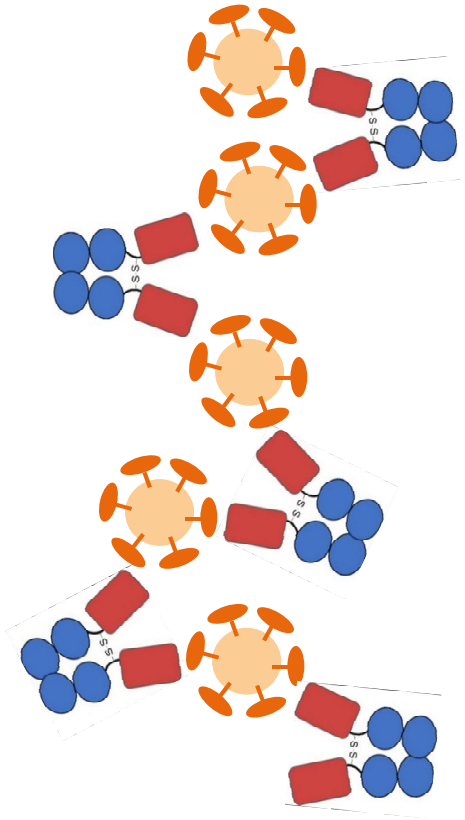
SI-F019's Unique Features

- The bivalent + Fc structure of SI-F019 can bind virus antigens and form cross-links, which can neutralize viruses more effectively



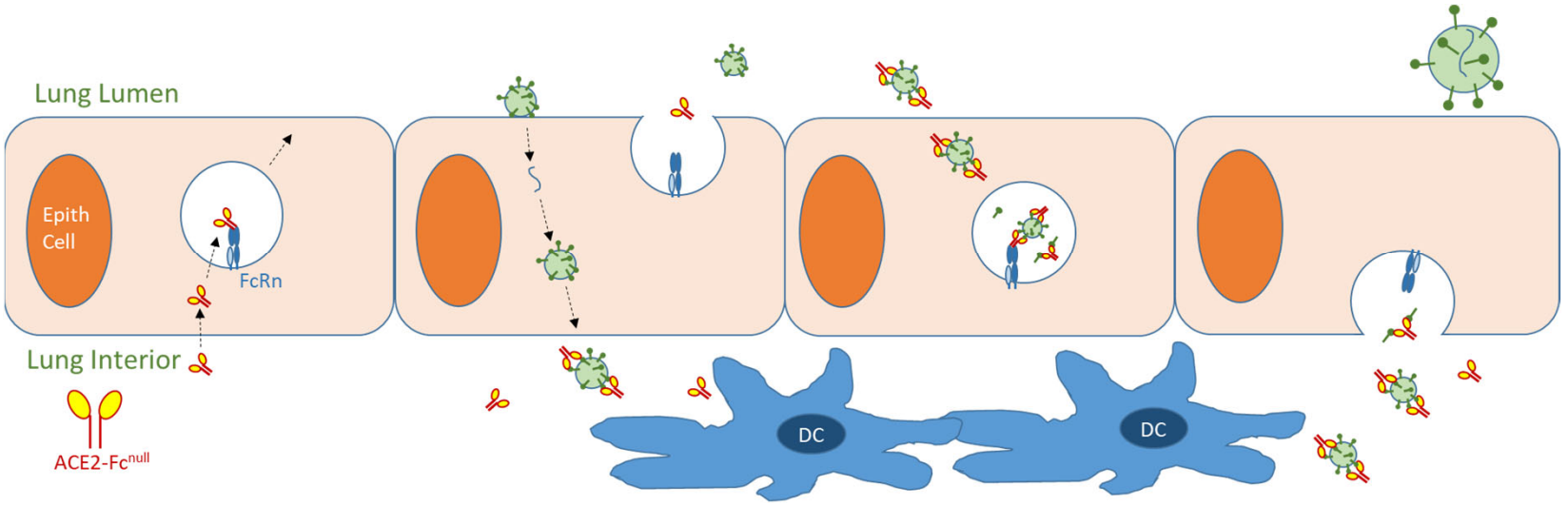
D. Wrapp et al., Science 2020.

The S protein of SARS-CoV-2 is a trimer with three receptor binding domains (RBDs) and can simultaneously bind three ACE2 monomer molecules.



SI-F019's Unique Features

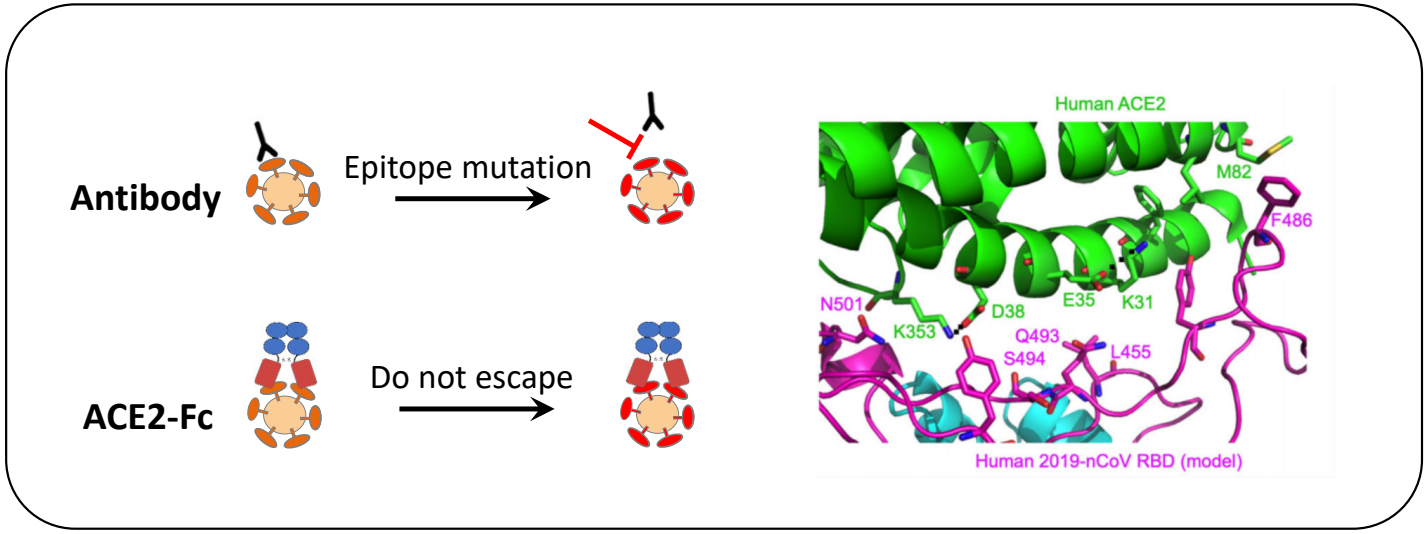
- Neonatal Fc receptor (FcRn) binding capability in SI-F019:
  1. Facilitates passage through alveolar epithelial cells, entry to alveolar mucosa, allowing for neutralization of SARS-CoV-2 virus and prevention of virus from infecting lung cells.
  2. Effectively extends half-life of the drug in patient and improves the efficacy.
  3. Lowers need for repeated dosing at short intervals.



Rath T et al., Front Immunol 2015

SI-F019's Unique Features

- ACE2-Fc has a broad neutralizing effect: As the natural receptor for the virus it can effectively respond to the resistance of SARS-CoV-2 virus to antibody neutralization by only allowing viral mutations that block its binding to target cells.



Yushun Wan et al., Journal of virology. 2020

- It is effective not only for SARS-CoV-2, but also for viruses that use ACE2 as a receptor, such as SARS-CoV.
- Intact ACE2 enzymatic activity reduces undesired pathological effects of angiotensin on respiratory and cardiac function.

R&D Team and cGMP Manufacturing

Sponsor : Baili Pharmaceutical Co., Ltd.

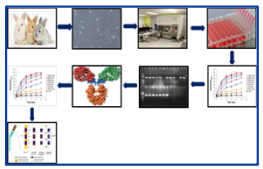
- This project is collaborated within Baili subsidiary Chengdu R&D Center, Chengdu Antibody/Protein Manufacturing and Seattle R&D Center (USA)

Chengdu R&D Center

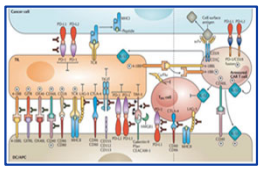
Chengdu Antibody/Protein Manufacturing

Seattle R&D Center (USA)

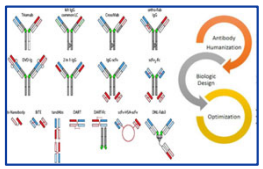
- Has jointly built a complete core technology platform for antibody / protein drug discovery, development and manufacturing
- Large scale cGMP production capabilities for biologics



Antibody / Protein Drug Discovery Platform



Efficacy Evaluation & Screening Platform



Antibody / Protein Engineering Platform

Antibody / Protein Process Development Platform

Antibody / Protein Large Scale cGMP Platform

- Early R & D and pilot production of multiple antibody drug have been completed.
- Two bispecific antibody drugs have been approved for clinical trial
- Two first-in-class multi-specific antibody drugs will be filing IND in 2020 Q2

Proposal and Timeline

1) To meet urgent unmet needs: Short-term goals and progress
   - 2020 Feb 5th : Begin candidate design and engineering (Completed)
   - 2020 Feb 10th : Complete candidate design (Completed)
   - 2020 Feb 24th : Complete plasmid construction (Completed)
   - 2020 Feb 24th : Begin transient expression and stable cell line development (Completed)
   - 2020 Mar 4th : Complete1st production lot (Completed)
   - 2020 Mar 31st : Complete stable cell line mini pool development (Completed)
   - 2020 Apr 24th : Complete 50L production run protein expression
   - 2020 Apr 30th : Complete 50L production run protein purification. Produce more than 10 patients drug product for clinical trials
   - 2020 May 10th : Complete drug product lot release for clinical trial

2) Routine development plan: Long-term goal and progress
   - 2020 Feb 5th : Begin candidate design and engineering (Completed)
   - 2020 Feb 10th : Complete candidate design (Completed)
   - 2020 Feb 24th : Complete plasmid construction (Completed)
   - 2020 Feb 24th : Begin transient expression and stable cell line development (Completed)
   - 2020 Mar 4th : Complete1st production lot (Completed)
   - 2020 Mar – Jun : Lead candidate stable cell line development
   - 2020 Mar – Jul : Product quality study and characterization. Finalize lot release specification
   - 2020 Jun – Aug : cGMP scale up production run
   - 2020 May – Nov: Animal efficacy, pharmacokinetics, pharmacology and toxicology
   - 2020 Nov : IND filing (China)
   - 2020 Dec : Initiate clinical trial (China)