ACE2-DERIVED PEPTIDES WITH ENHANCED EFFICACY FOR INHIBITION OF SARS-CoV-2

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INTRODUCTION

The coronavirus disease (COVID-19) has originated the current world-wide pandemic situation. This disease is caused by the severe acute respiratory syndrome-coronavirus 2 (**SARS-CoV-2**). Structural and biochemical characterization has showed that the receptor binding domain (**RBD**) of the virus surface spike protein interacts with the peptidase domain (PD) of angiotensin-converting enzyme 2 (**ACE2**) [1-3], being this interaction the main entrance mechanism of the virus.

Most of the interactions between RBD and ACE2 reside on the helix 1 of ACE2. [4] Design of **ACE2 based peptides** that bind the RBD of SARS-CoV-2 could **prevent the virus entry** to the host cell and consequently, reduce the infectivity potential of the virus.

OBJECTIVES

- Design and development of ACE2-based peptides inhibitors of SARS-CoV-2.
- Different strategies are explored:
  - Long-range macrocycle ACE2 derived peptides with enhanced α-helix structure
  - Irreversible peptides inhibitors
  - Multivalent inhibitors

REFERENCES

[1] P. Karoyan, V. Vieillard, E. Odile, et al. Eur. bioRxiv. 2020, 1-17.
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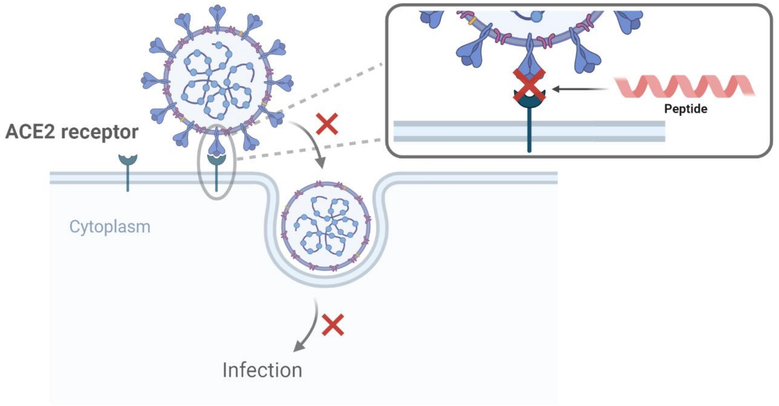
[3] R. Yan, Y. Zhang, Y. Li, et al. Science. 2020, 367, 1444-1448.
[4] F. Curreli, S. Victor, X. Tong, et al. MBio. 2020, 11, 1-13.

STRATEGY

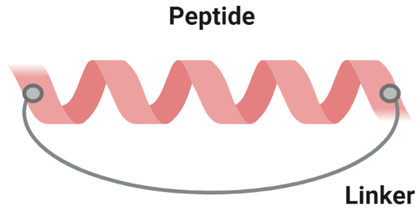
1 Cell-infection inhibition of SARS-CoV-2



2 α-helix stabilization

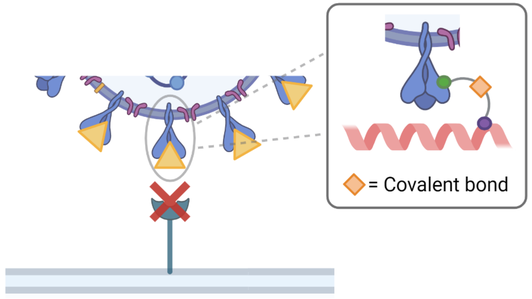
It has been reported that the α-helix secondary structure is essential to obtain antiviral activity against SARS-CoV-2. [4]

Covalent constraints of the peptide candidates will be synthesized to stabilize the desired structure.



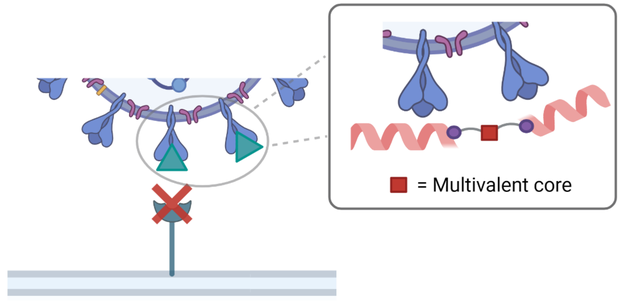
- α-helix is induced and constrained via chemical modifications of the linker.
- Essential amino acids are not hindered.
- Linker length was calculated by tight-binding DFT theory

3 Irreversible inhibitors



Chemical modifications of the peptides will be conducted to obtain irreversible versions of the peptides. These should be chemically stable and maintain the binding properties.

4 Multivalent platforms



Multivalent platforms derivatized with ACE2 based peptide inhibitors may bind synergically to different spike proteins from one virus entity and improve the inhibition efficacy.