Department of Chemistry
The University of Hong Kong

29th Symposium on Chemistry Postgraduate Research in Hong Kong

Chemical synthesis of glycosylated spike RBD peptides

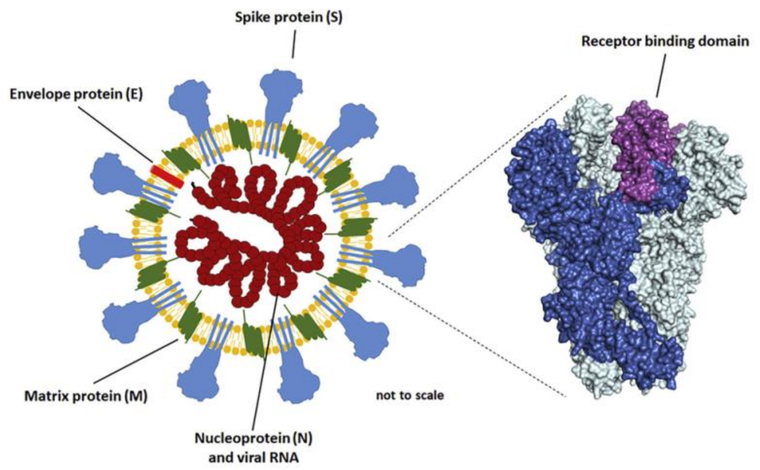
Dongfang LI and Xuechen LI*
Department of Chemistry, The University of Hong Kong

Introduction

SARS-CoV-2 has a linear single-stranded positive-sense RNA genome, encoding 4 structural proteins [spike (S), envelope (E), membrane (M), and nucleocapsid (N)]. Among these proteins, the S protein (**Figure 1**) is the major focus of current research, as it facilities viral attachment, entry and membrane fusion. The infection of host cells is initiated by the interaction of the viral S protein with receptors on the cell surface, hence it has a crucial role in the spread of the virus. There is surely an urgent need to develop a vaccine to halt the viral infection and curb the pandemic.

Li, F. *Annu Rev Virol,* **2016,** *3 (1),* 237-261; Amanat, F.; Krammer, F. *Immunity* **2020,** *52 (4),* 583-589.

Figure 1

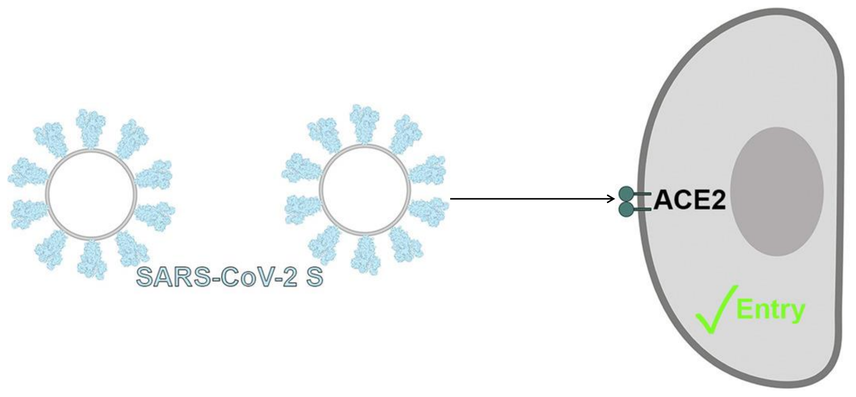


Introduction

The human angiotensin-converting enzyme 2 (hACE2) is the entry receptor for SARS-CoV-2 (**Figure 2**). As vaccine developments aim to elicit adaptive immunity via an antibody response at the sites of viral entry, one main strategy for vaccine development is to use peptides derived from S protein as the antigen to generate the antibody. The S-peptide induced antibody can potentially block the entry of SARS-CoV-2 to the host cell.

Watanabe, Y.; Allen, J. D.; Wrapp, D.; McLellan, J. S.; Crispin, M. *Science,* **2020,** *369 (6501),* 330-333; Zhang, H.; Penninger, J. M.; Li, Y.; Zhong, N.; Slutsky, A. S. *Intensive Care Med,* **2020,** *46 (4),* 586-590.

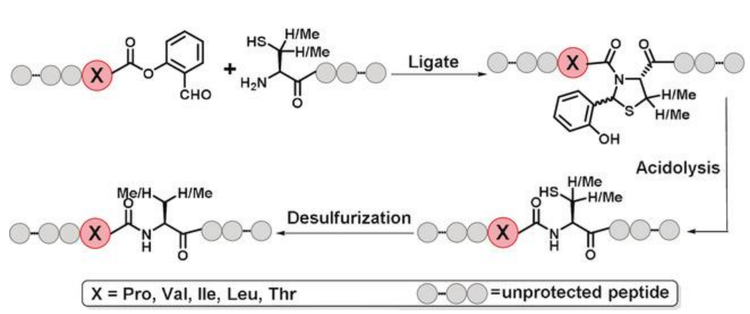
Figure 2



Ser/Thrligation (STL) and Cys/Pen ligation (CPL)

In general, the chemical synthesis of a complex glycopeptide/protein involves two key phases: (1) generation of moderately sized peptides or glycopeptides (~ 20-30 amino acids)by solid-phase peptide synthesis (SPPS) and (2) joining these (glyco)peptide segments together. Towards the goal of chemical protein synthesis, our laboratory has developed in-house chemoselective peptide ligation methods over the past decade, including **Ser/Thrligation (STL)** in 2013 and **Cys/Pen ligation (CPL)** in 2020. STL and CPL could provide many choices for disconnection. The biantennary N-glycan (**Figure 3**) will be obtained by isolation of a sialoglycopeptide (SGP) from egg yolk. After we get glycopeptides by our 'N+1' strategy, we use STL and CPL to ligate then followed by refolding to get the target glycoprotein (**Figure 3**).

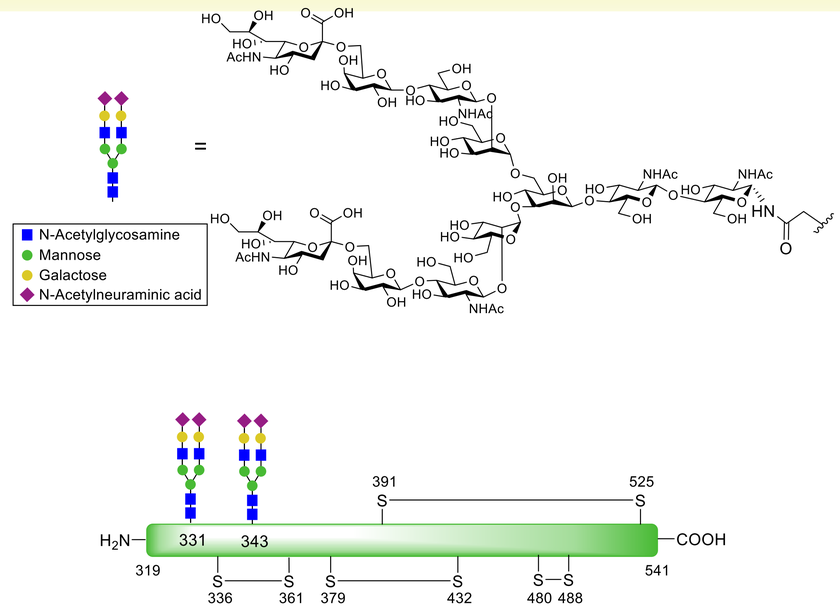
STL



CPL

Zhang, Y.; Xu, C.; Lam, H. Y.; Lee, C. L.; Li, X. *Proc Natl Acad Sci U S A,* **2013,** *110 (17),* 6657-62.
Tan, Y.; Li, J.; Jin, K.; Liu, J.; Chen, Z.; Yang, J.; Li, X. *Angew Chem Int Ed Engl,* **2020,** *59 (31),* 12741-12745.

Figure 3



Acknowledgements

Thanks to Prof. Xuechen LI's guidance and all our group member's help. Thank the organizer for giving me the opportunity to present.

Contact information

Dongfang LI (lidf2019@connect.hku.hk) and Xuechen LI* (xuechenl@hku.hk)