Department Chemie und Pharmazie

GRK 2504

FAU Friedrich-Alexander-Universität Erlangen-Nürnberg

# Novel peptide inhibitors of SARS-CoV-2 infection

Nina Raasch[1], Lucas Weißenborn[1], Elie Richel[2], Olena Denysenko[3], Simon Schäfer[3], Heinrich Sticht[3], Klaus Überla[2] and Jutta Eichler[1]

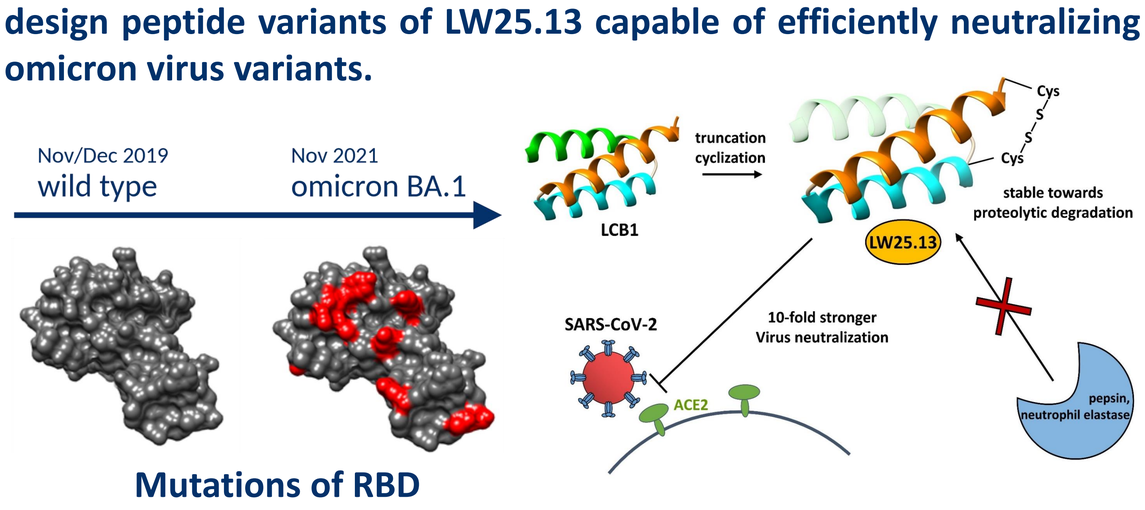
[1]Department of Chemistry and Pharmacy, Friedrich-Alexander-Universität Erlangen-Nürnberg, 91058 Erlangen, Germany
[2]Institute for Clinical and Molecular Virology, Universitätsklinikum Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, 91054 Erlangen, Germany
[3]Institute of Biochemistry, Friedrich-Alexander-Universität Erlangen-Nürnberg, 91054 Erlangen, Germany

https://doi.org/10.17952/37EPS.2024.P1087

nina.raasch@fau.de

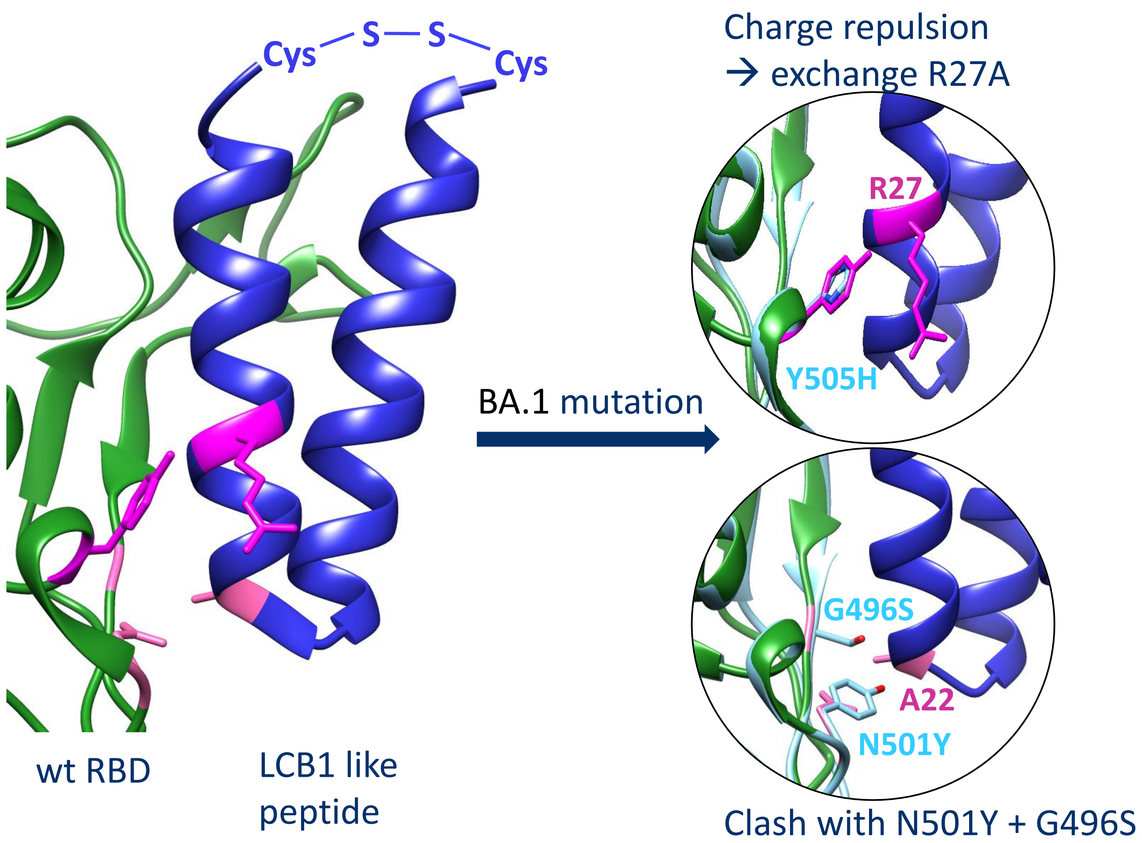
**Infection with SARS-CoV-2 is based on the interaction of the viral Spike (S) protein with the ACE2 receptor on the human host cell [1]. With the aim to increase virus neutralizing activity we have generated and characterized a truncated and cyclized peptide variant of the SARS-CoV-2 neutralizing miniprotein LCB1 [2]. The 10-fold stronger antiviral activity of this peptide (LW25.13), as compared to LCB1 to the wild-type Spike receptor-binding domain (RBD), as well as its substantially improved proteolytic stability, make it a better potential candidate for SARS-CoV-2 therapy [3].**

**Nevertheless, there is a need for optimization of the peptides in order to facilitate neutralization of newer virus variants, such as BA.1/ BA.2/ BA.5 (omicron variants). Therefore, we have combined reverse mutation strategies with structural and bioinformatic analysis to design peptide variants of LW25.13 capable of efficiently neutralizing omicron virus variants.**




## Results & Discussion

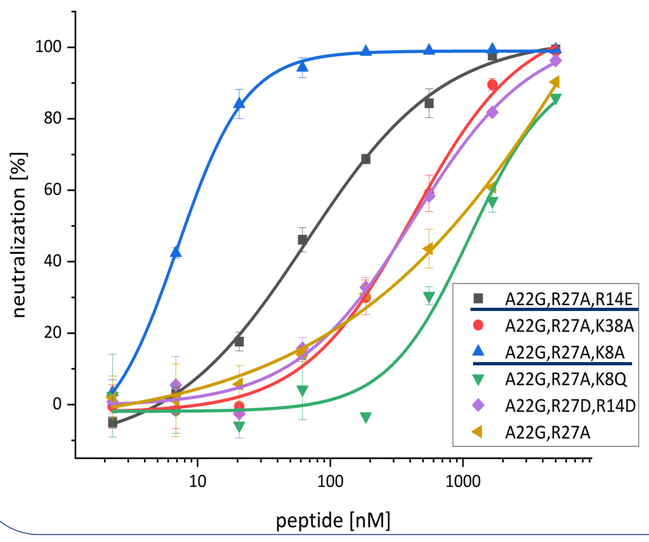
### 1) Peptide design and characterization




### 2) omicron BA.1 neutralization

- **Omicron RBD** has increased number of **positively** charged AA
- Reducing positive charge and insertion of negatively charged AA

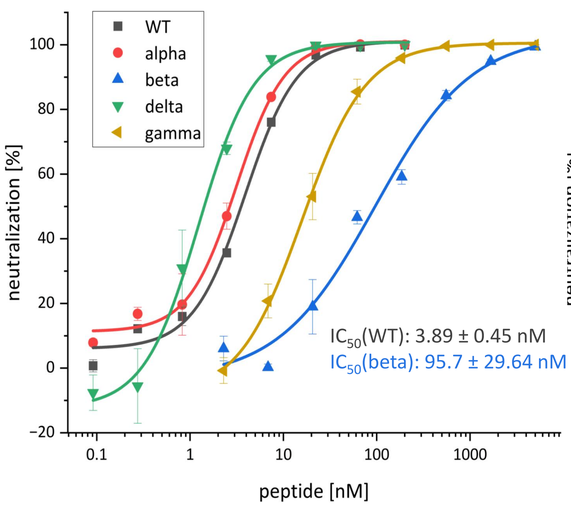

neutralization omicron BA.1



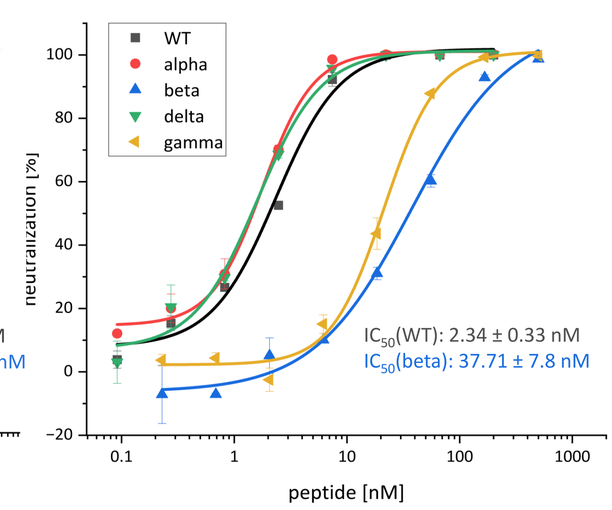

$IC_{50}$ (A22G,R27A,K8A): 7.06 ± 0.35 nM
$IC_{50}$ (A22G,R27A,R14E): 65.85 ± 0.45 nM
$IC_{50}$ (A22G,R27A): > 1000 nM

### 3) Virus variant selectivity

neutralization A22G,R27A + **R14E**



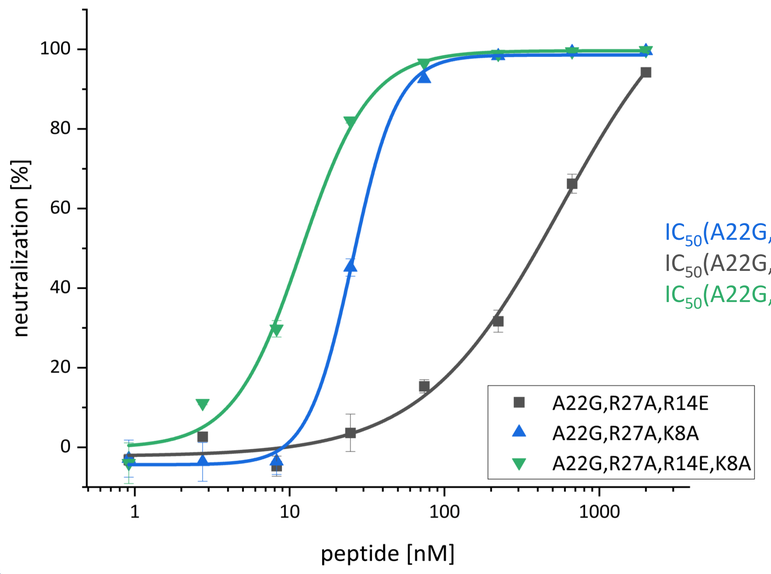

neutralization A22G,R27A + **K8A**




- Both charge exchange variants are **broadly neutralizing** peptides
- Peptide variants **gain neutralization activity**

### 4) Combined peptide variant

neutralization omicron BA.1




$IC_{50}$(A22G,R27A,K8A): 12.36 ± 0.06 nM
$IC_{50}$(A22G,R27A,R14E): > 500 nM
$IC_{50}$(A22G,R27A,R14E,K8A): 11.95 ± 1.16 nM

### 5) Discussion and Conclusion

- Targeting critical RBD mutations is the main goal in future peptide design → scaffold for "pandemic preparedness"
- Charge exchange variants of LW25.13 have a higher neutralization capacity against the BA.1 omicron variant
- **Broadly neutralizing peptides**

## Outlook

- Further optimization of combined peptide variant
- H21 charge exchange variants
- Generation of bispecific antiviral peptides

**References**

[1] Jackson, C. B. et al. Nature Rev. Mol. Cell Biol. **2022**, 23(1), 3 - 20.
[2] Cao, L. et al. Science **2020**,370(6515), 426 - 431.
[3] Weißenborn, L. et al. Int. J. Mol. Sci. **2022**, 23(11), 6309.

LinkedIn