Pre-clinical data of ensovibep, a multi-specific DARPin therapeutic with high potency against all frequent SARS-CoV-2 variants

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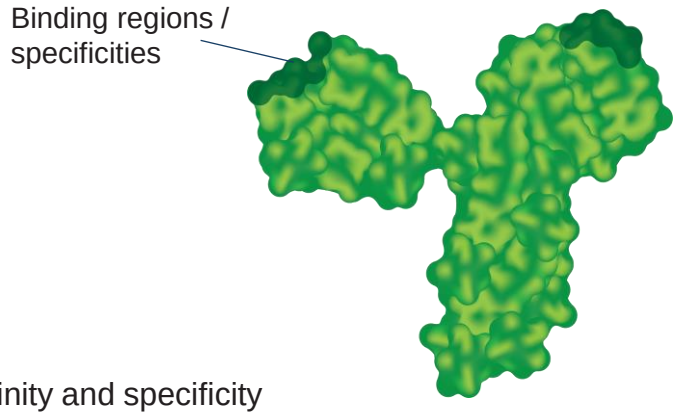
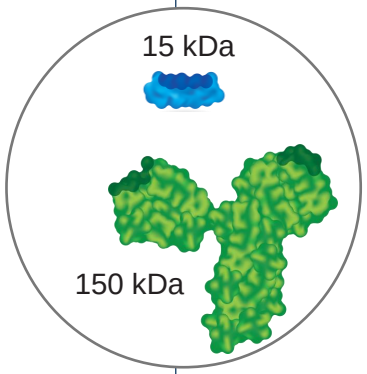
Molecular Partners AG: pioneering DARPin therapies to transform lives

- Molecular Partners AG is a biotech company with headquarters near Zurich city center, Switzerland.
- We are inventors and developers of a new class of therapeutics, DARPins, with unique features compared to antibodies

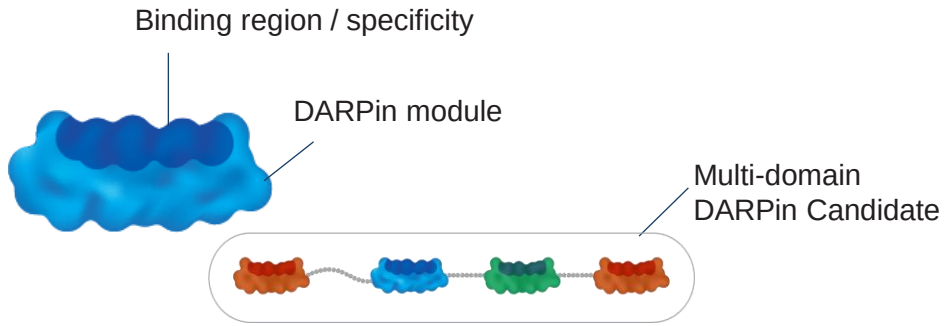
MONOCLONAL ANTIBODIES



- High affinity and specificity
- Large size: 150 kDa
- Complex architecture; 4 proteins with 12 domains
- Long half-life
- Mammalian expression
- Good safety & low immunogenic potential



MONO-DARPin PROTEINS



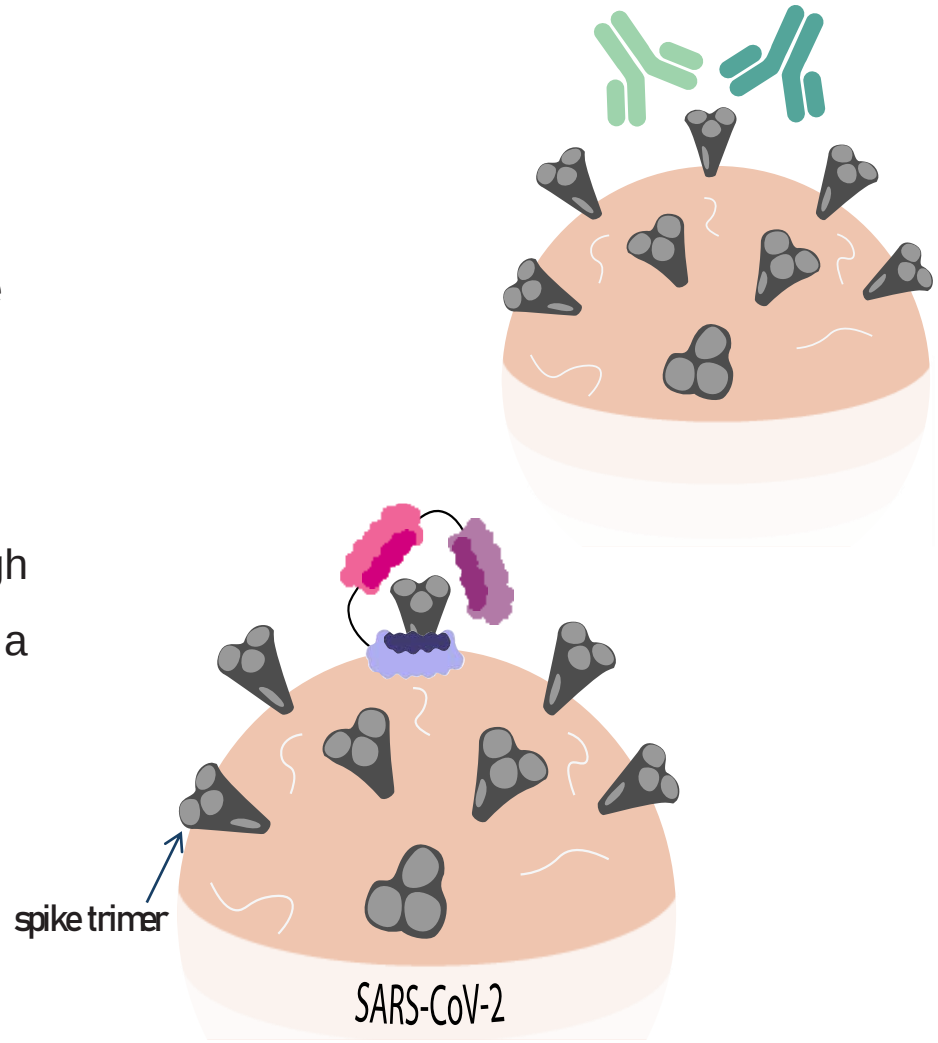
- High affinity and specificity
- Small size: 15 kDa (1/10 of a monoclonal antibody)
- Simple architecture; 1 protein with 1-6 domains
- Tunable half-life
- High-yield microbial expression; High thermo-stability
- Good safety & low immunogenic potential

The DARPin platform is ideal for COVID-19 therapeutics

COVID-19 therapeutics need to be:

- Able to neutralize upcoming SARS-CoV-2 variants
- Protective against viral escape upon therapeutic pressure
- Rapidly produced in large quantities

The DARPin platform can rapidly generate large quantities of high affinity multi-domain molecules, combining different binders in a single therapeutic agent without the need of cocktails.



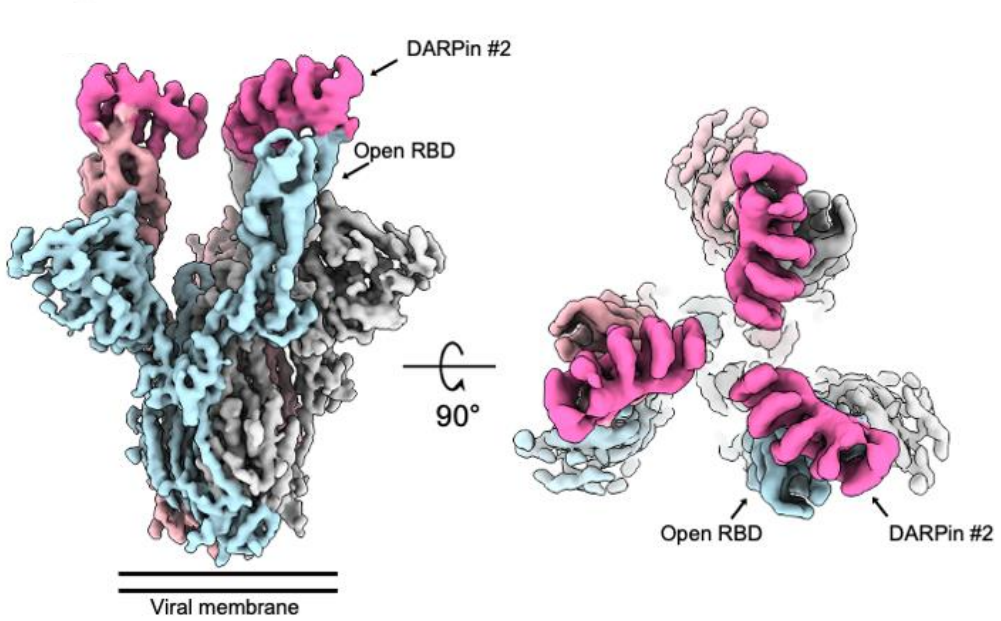
COVID-19 mAb therapeutics

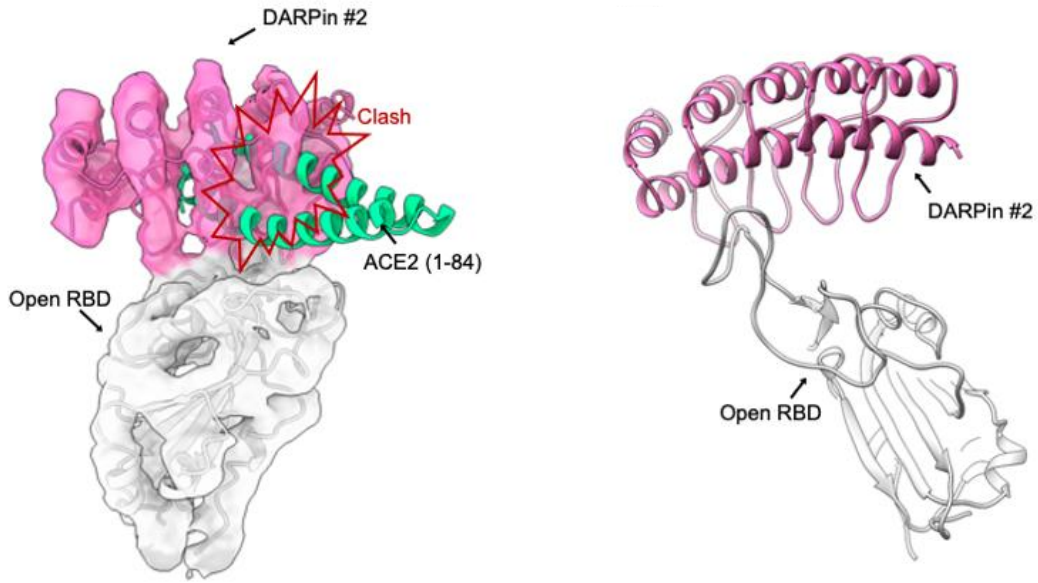
COVID-19 DARPins therapeutics

Ensovibep is the first tri-specific molecule against SARS-CoV-2 RBD

- Ensovibep is composed of 2 HSA-binding DARPins followed by 3 RBD-binding DARPins that are different, but with very similar binding regions

- Cryo-EM analysis of the Wuhan SARS-CoV-2 spike-DARPin #2 complex reveals interaction with the up-conformation of the RBD in a ACE2-competitive manner, thus impairing cell entry of the virus. The epitope of ensovibep comprises aa 450-493





Cryo-EM performed in collaboration with Bosch lab, Utrecht University.

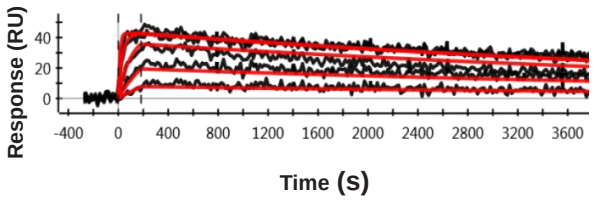
HSA, human serum albumin
ACE2, angiotensin converting enzyme 2;
Cryo-EM, Single-particle cryo-electron microscopy;

Walser M., *et al., Biorxiv*. 2021. https://doi.org/10.1101/2020.08.25.256339

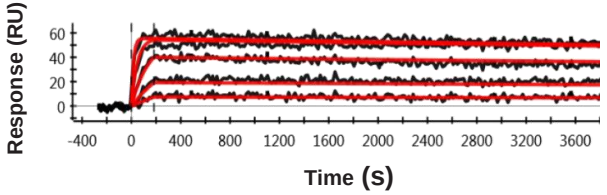
Ensovibep can engage all 3 RBD domains at once

Ensovibep can bind to all RBDs of the SARS-CoV-2 spike trimer. This leads to very high avidity effect and affinity.

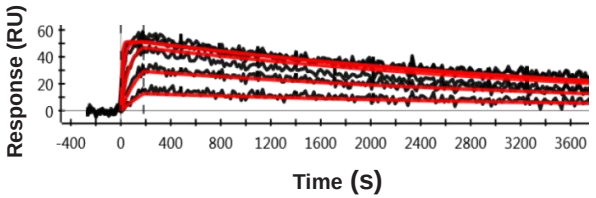
DARPin #1; Kd: 80 pM

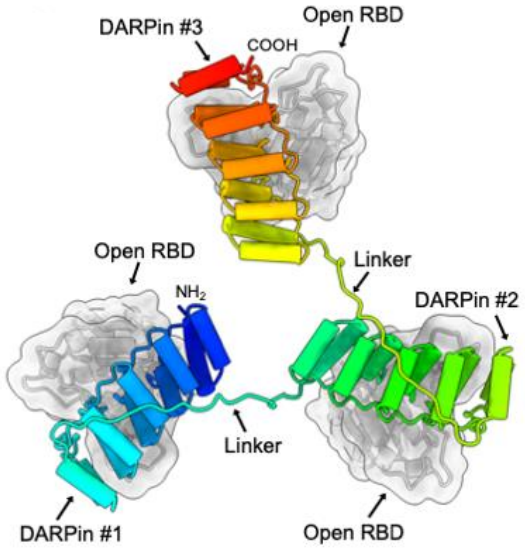


DARPin #2; Kd: 30 pM



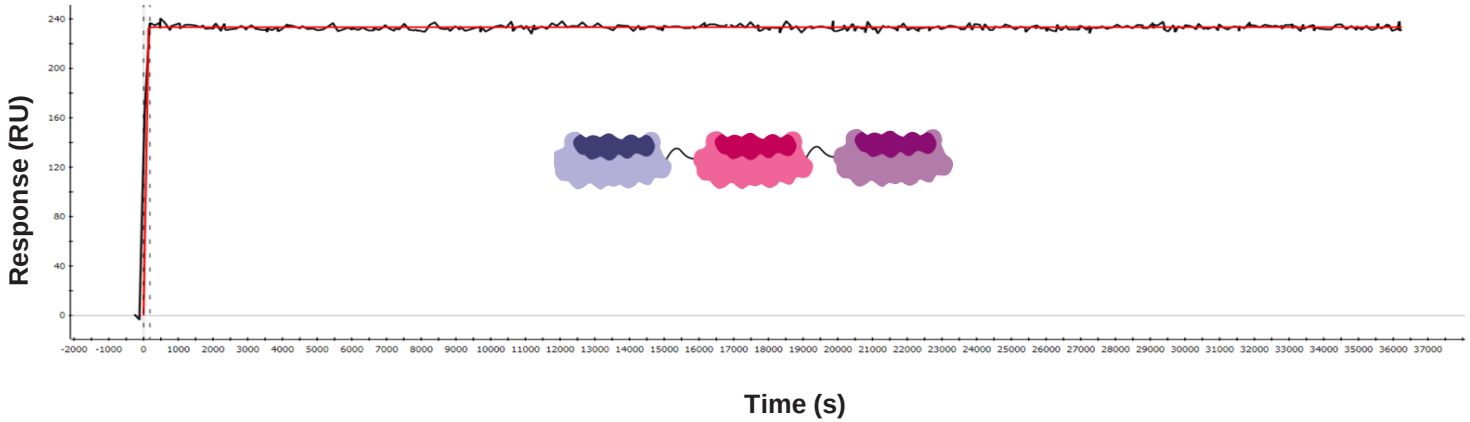
DARPin #3; Kd: 90 pM





Tri-domain DARPin #1 - #2 - #3; Kd: sub pM

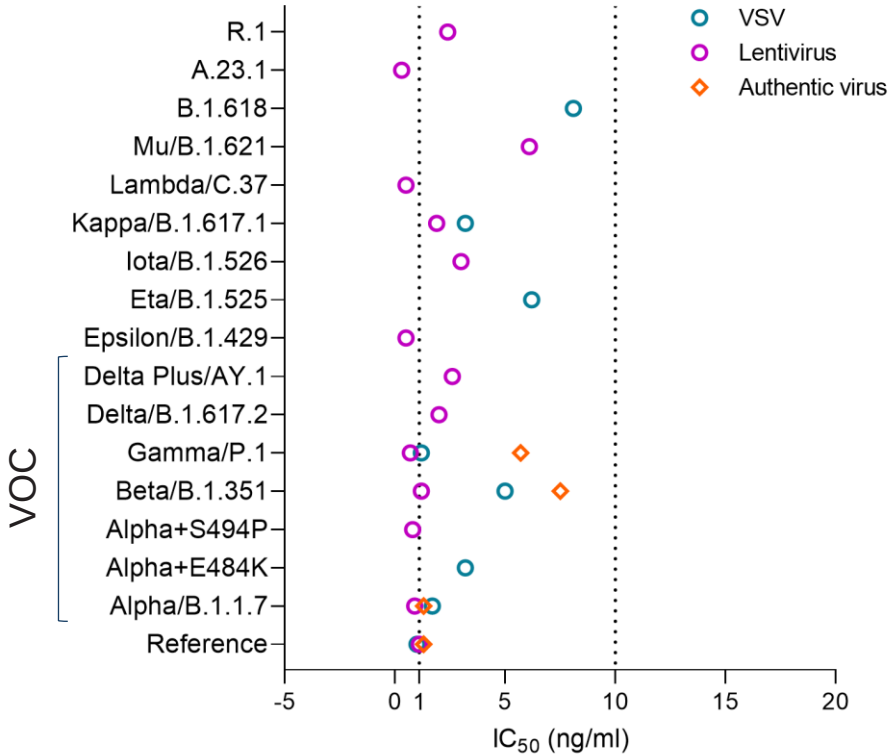
>10 hours off rate

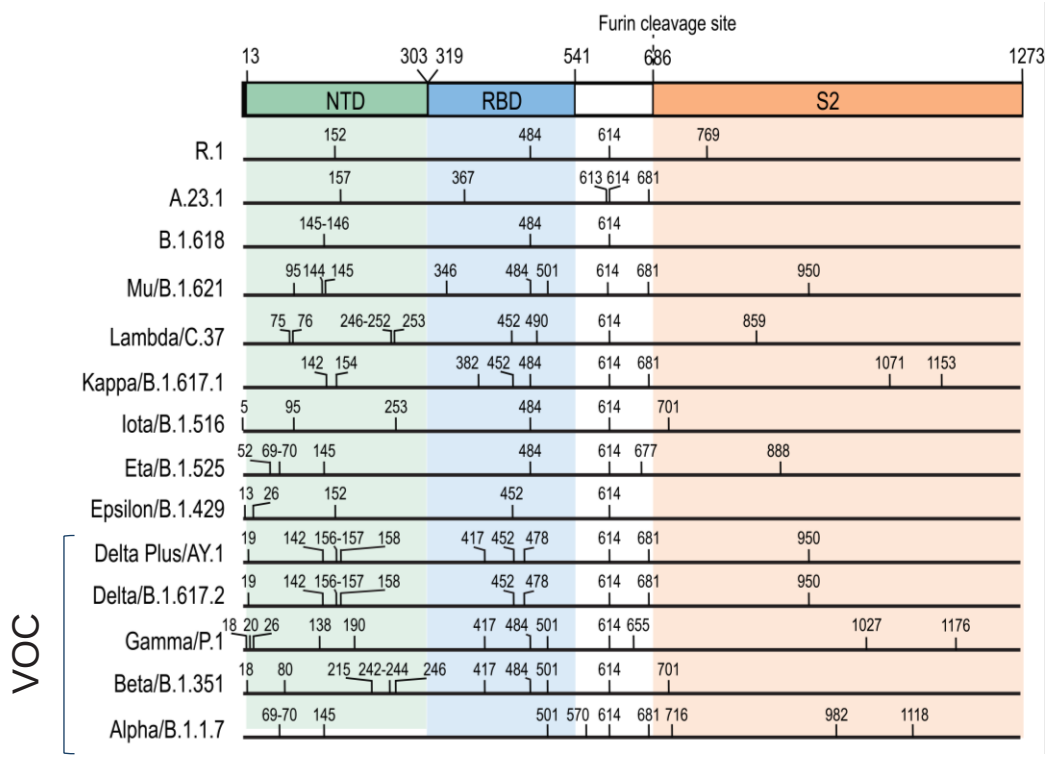


Walser M., *et al., Biorxiv*. 2021. https://doi.org/10.1101/2020.08.25.256339

Ensovibep shows high potency on all frequent variants to date

- Neutralization assays on Lentivirus or VSV-based pseudoviruses, as well as on authentic SARS-CoV-2 virus, demonstrate high potency (IC_{50}: ~1-8 ng/ml) against all frequent variants to date (October 2021)

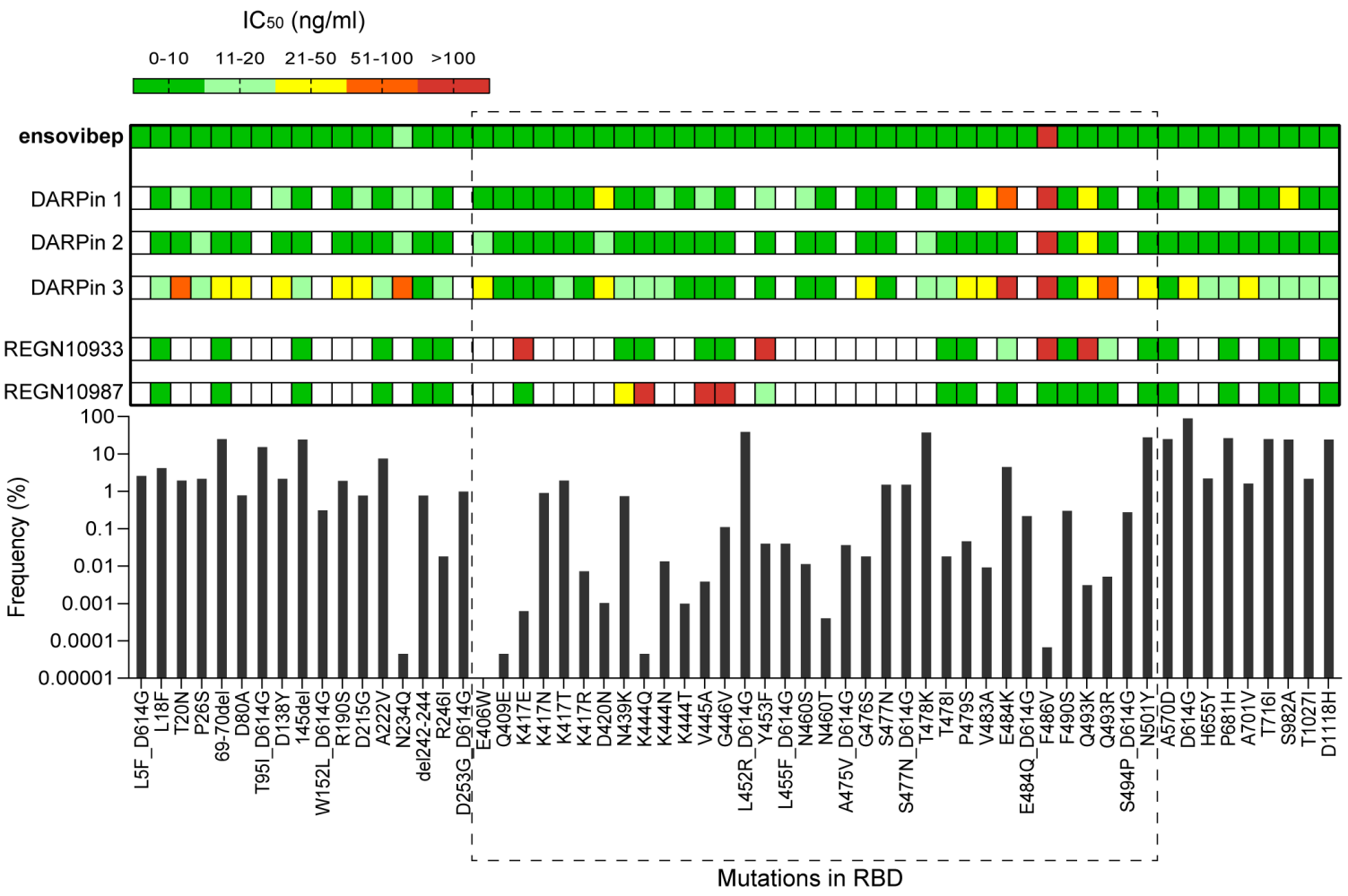




Neutralization assays performed in collaboration with CHUV, Lausanne, CH; Spiez Laboratory, CH; ACTIV consortium/FDA

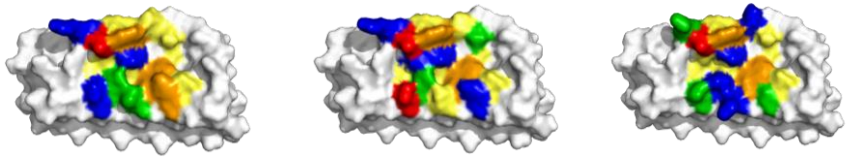
Rothenberger S., Walser M., *et al., Biorxiv*. 2021. https://doi.org/10.1101/2021.02.03.429164
Molecular Partners data on file

Cooperative binding- therapeutic design matters



Amino acid characteristics of DARPin paratope:

- Aromatic
- Hydrophobic
- Polar
- Positively charged
- Negatively charged



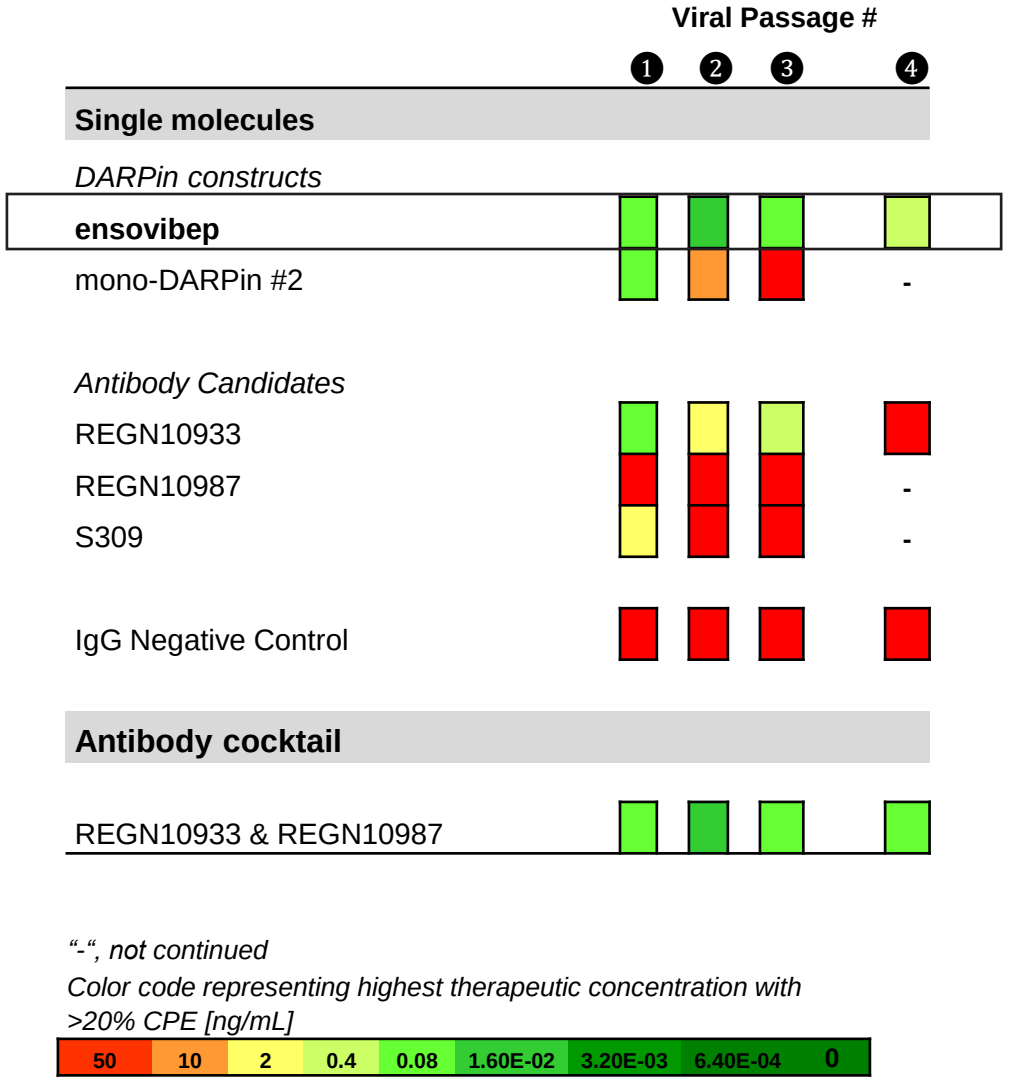
DARPin #1 **DARPin #2** **DARPin #3**

- Ensovibep is potent even on mutations where the single mono-DARPins show reduced activity (ex. E484K and Q493K), thanks to the cooperative binding and complementarity of the mono-DARPins
- Exception is F486V, a mutation present in very low frequency (from GISAID database, October 2021) due to impaired ACE2 interaction

PsV neutralization assays performed in collaboration with CHUV, Lausanne, CH; ACTIV consortium/FDA

Rothenberger S., Walser M., *et al., Biorxiv*. 2021. https://doi.org/10.1101/2021.02.03.429164
Molecular Partners data on file

Ensovibep is protective against viral escape mutations



- Ensovibep protects across 4 passages against the development of escape mutations in a viral passage experiment using SARS-CoV-2 virus (Wuhan strain)
- The performance of ensovibep is superior to the other single agents tested (RBD-2 and mAbs) and is comparable to the REGN antibody cocktail

Assay performed in collaboration with Spiez Laboratory, CH

Rothenberger S., Walser M., *et al., Biorxiv*. 2021. https://doi.org/10.1101/2021.02.03.429164
Molecular Partners data on file

Conclusions

- Our DARPin generation platform provided a lead candidate in less than 9 weeks
- The multi-specific design of ensovibep enables high SARS-CoV-2 neutralization potencies on all most frequent variants (October 2021) and on point mutations that were shown to impact other therapeutics
- Ensovibep provides protection comparable to a mAb cocktail with respect to the development of escape mutations in viral passage experiments
- Thanks to its unique features and rapid large-scale production capabilities, ensovibep may be an attractive COVID-19 therapeutic
- Two phase II/III clinical trials are ongoing (EMPATHY and ACTIV-3)→ for details on the EMPATHY study design, see poster #**114,** Marianne Soergel

Acknowledgments

Molecular Partners AG – entire COVID team

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Group of Olivier Engler, including Sylvia Rothenberger's group at CHUV Lausanne, for performing PsV and authentic virus assays.

University Utrecht
Group of Berend-Jan Bosch for cryo-EM analysis.

National Institute of Health (NIH)
ACTIV team for conducting PsV neutralization assays in collaboration with the Carol Weiss group.

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Backup slides