Optimizing ACE2 and antibodies against COVID-19

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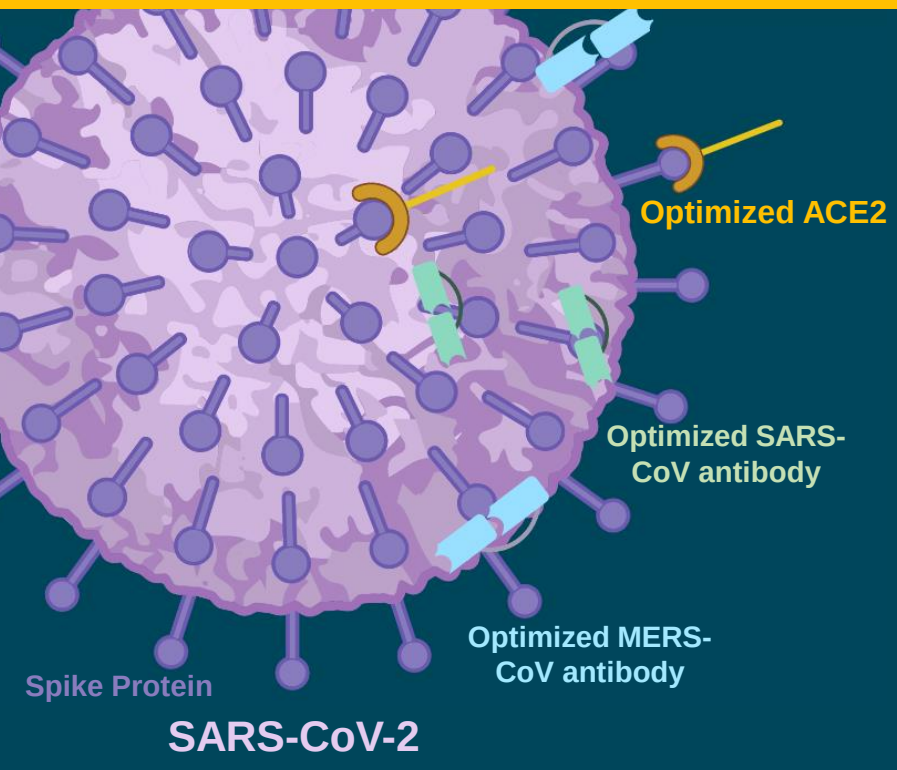
Therapeutic proteins to neutralize SARS-CoV-2



Why? Background

Emergent antiviral COVID-19 therapies target the receptor-binding domains (RBDs) of the SARS-CoV-2 trimeric spike glycoprotein, blocking viral attachment to host cells. We want to develop a robust platform from design to production and characterization of compounds that will inhibit the viral-host binding. Having SARS-CoV-2 as model, we will optimize its host receptor angiotensin converting enzyme 2 (ACE2) to use as a soluble decoy[1]. Optimized versions of the MERS-CoV and SARS-CoV antibodies will be used as neutralizing agents across the coronavirus family[2]. These two strategies combined - ACE2 and antibodies - will target different areas of spike protein tackling SARS-CoV-2 variants that can escape neutralization, preventing the evolution of COVID-19 to an uncontrolled pandemic[3]. Although vaccination plays a major role in controlling the pandemic, establishing an accessible platform for rapid biopharmaceutical production is key for tackling future viral outbreaks and/or the emergence of more virulent SARS-CoV-2 strains.

How? Research Design

Optimization

ACE2
SARS-CoV Antibodies
MERS-CoV Antibodies

Molecular Docking and Dynamics Simulations to improve sequence affinity to SARS-CoV-2

Production

Plant Transient Expression *Nicotiana benthamiana*

Plant Stable Expression *Nicotiana tabacum*

Bacterial Expression *Escherichia coli*

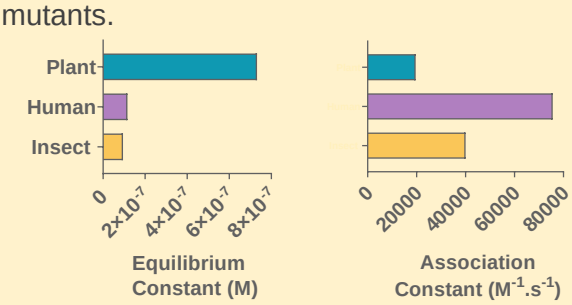
Iterations

Characterization

- ✓ Activity
- ✓ Structure
- ✓ Post translational modifications
- ✓ Binding to RBD of SARS-CoV-2
- ✓ *In vivo* neutralization (murine infection)

What? Initial Results

ACE2 wild type produced in *N. benthamiana* binds to SARS-CoV-2 RBD, validating expression in plants. However, this occurs with lower affinity compared to ACE2 expressed in human or insect cells. Further work will focus on improving binding and testing optimized mutants.



Acknowledgements: This work was funded through FCT– Fundação para a Ciência e a Tecnologia, I.P., Project MOSTMICRO-ITQB with refs UIDB/04612/2020 and UIDP/04612/2020, the R&D Unit, UID/Multi /04551/2013 (GREEN-IT - Bioresources for Sustainability) and FCT PhD fellowship 2020.10235.BD.

References:
1. Monteil, V. et al. Cell. 181, 1–9 (2020)
2. Wrapp, D. et al.Science. 1263, 1260–1263 (2020)
3. Greaney, A. et al. Cell Host Microbe. 29, 44–57 (2021)