V-BIND: Leveraging AI to Design COVID-19 Therapies

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Research Proposal

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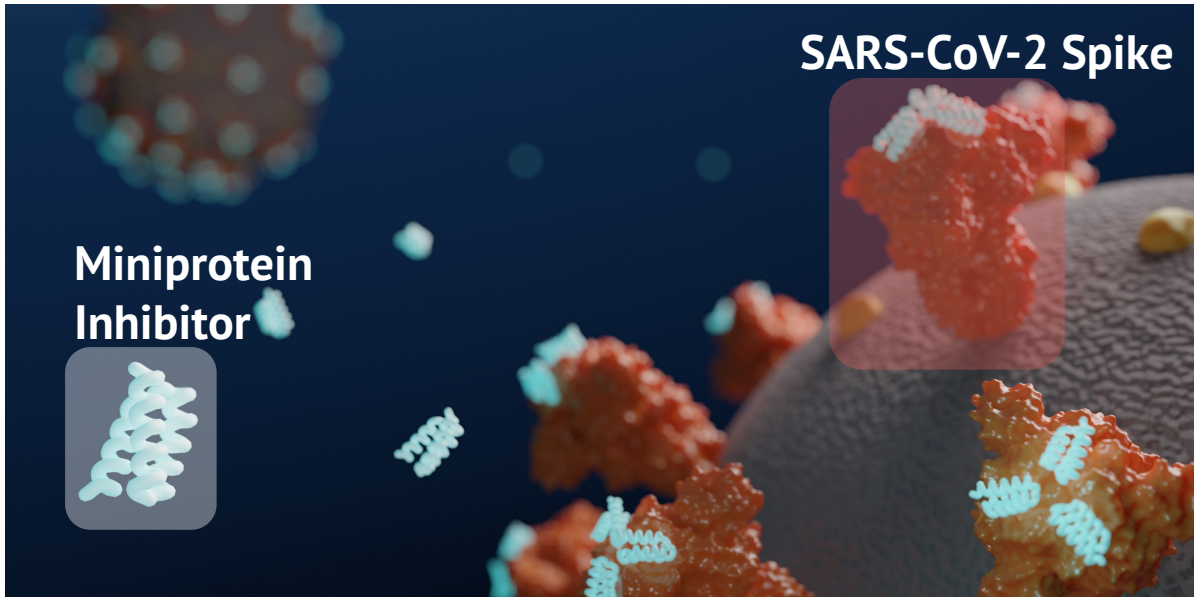
COVID-19 Drug Development

One potential therapy to mitigate the initial membrane fusion of the SARS-CoV-2 spike RBD and hACE2 is **miniprotein inhibition**.

Miniproteins have fast FDA approval times, interfere minimally with biological processes, and exhibit high specificity.[1]



This research applies AI-based design to miniprotein inhibitors.

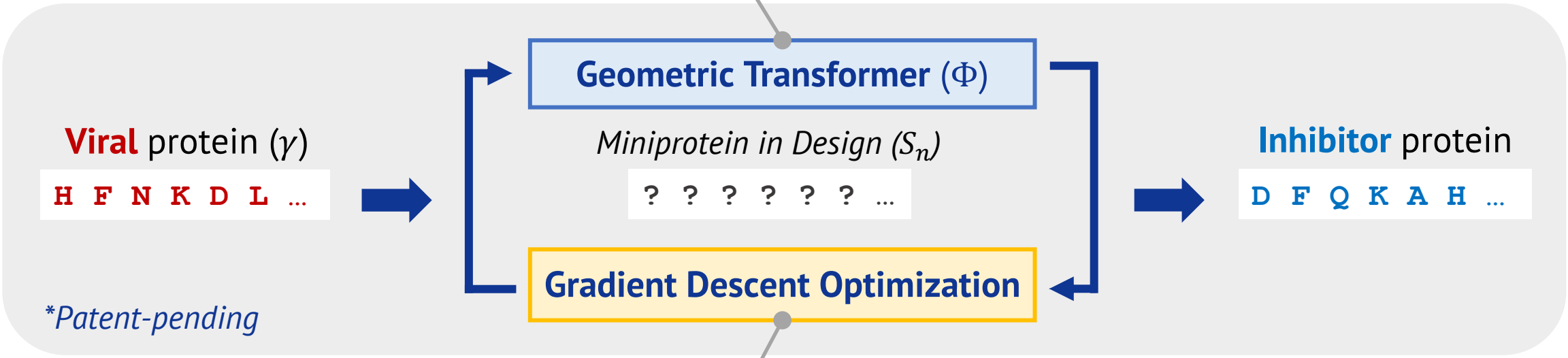
[1] Han, Y., & Král, P. (2020). Computational Design of ACE2-Based Peptide Inhibitors of SARS-CoV-2. ACS Nano, 14(4), 5143–5147. https://doi.org/10.1021/acsnano.0c02857

A Novel Approach to Miniprotein Design

V-BIND* is a **fully deep-learning-based** pipeline for miniprotein design.

Geometric Transformer is a scoring function that evaluates the designed drug.

$$\Phi(\alpha, \beta) = \mathbf{ManfAttn}\big(\mathrm{Bert}(\alpha), \mathrm{Bert}(\beta)\big)$$

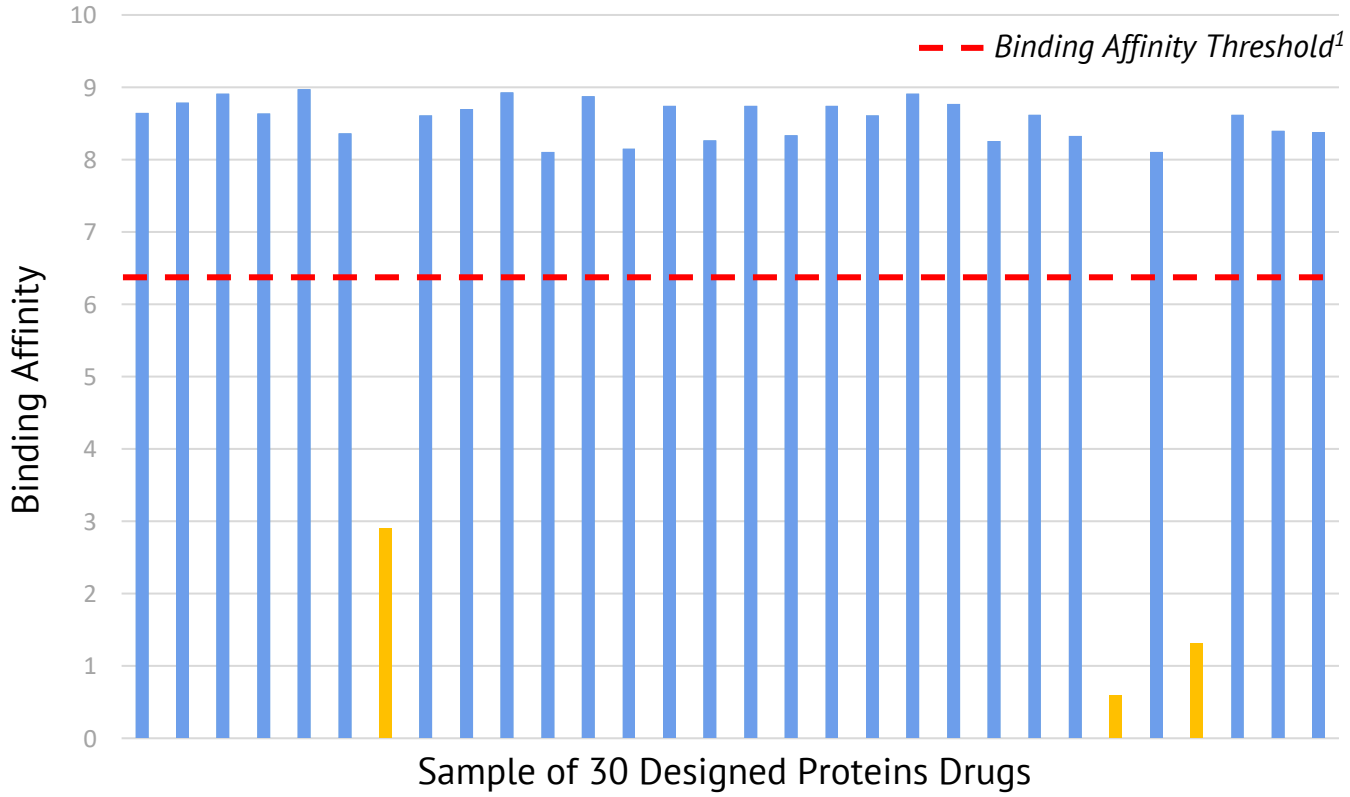


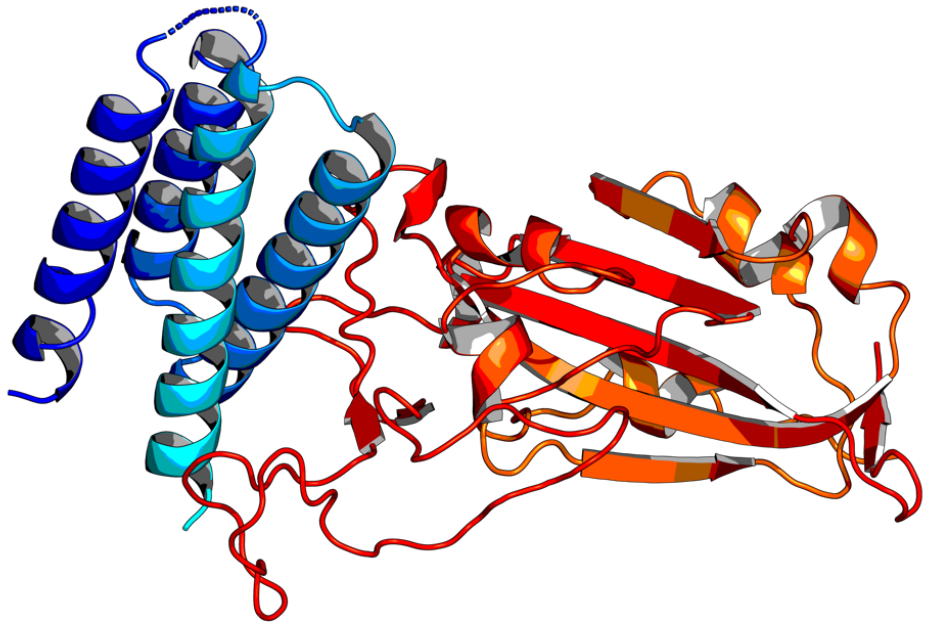
Gradient descent adjusts the miniprotein (S_n) according to Geometric Transformer's evaluation.

$$S_{n+1} = S_n - \lambda_n \nabla \mathcal{L}(\Phi[S_n, \gamma])$$

Efficacy of V-BIND

V-BIND designed **30 COVID-19 miniprotein drugs**, of which **27** bind potently[1] to the virus.





V-BIND miniprotein (blue) binding to SARS-CoV-2 protein spike RBD (red)

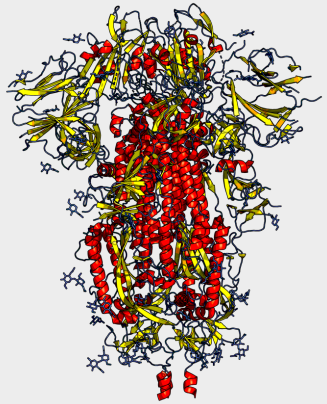
[1] Carlson, H. A., Smith, R. D., Khazanov, N. A., Kirchhoff, P. D., Dunbar, J. B., & Benson, M. L. (2008). Differences between High- and Low-Affinity Complexes of Enzymes and Nonenzymes. Journal of Medicinal Chemistry, 51(20), 6432-6441. https://doi.org/10.1021/jm8006504

Features of V-BIND

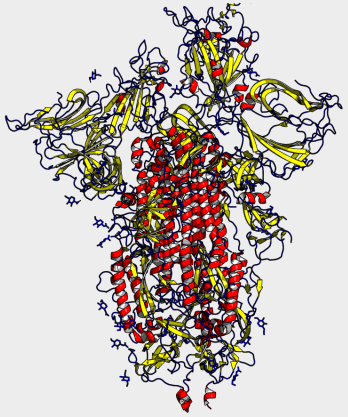
1. **Efficient:** design convergence after ~30 seconds
   → Potentially thousands of *de novo* drug candidates

2. **Tailorable:** drugs can be designed with specific parameters
   → Incorporate prior knowledge about virus

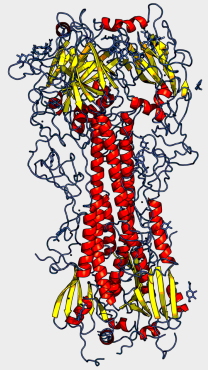
3. **Universal:** applies to any glycoprotein-mediated virus



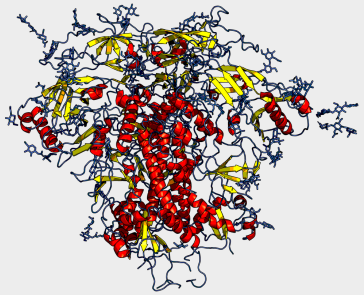
SARS-CoV-2



SARS-CoV-2 D614G



Influenza A



HIV-1

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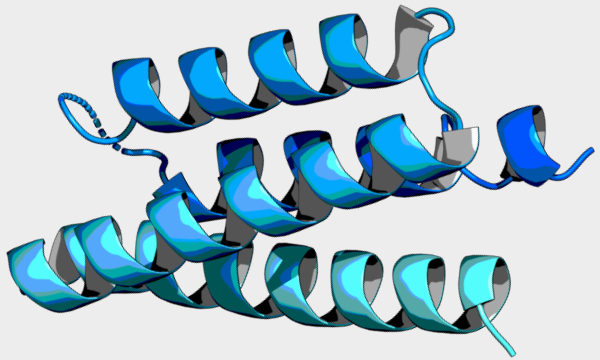
Next Steps for V-BIND

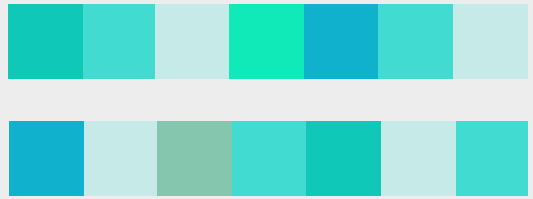
→ **Laboratory-driven research:** *in-vitro* confirmation of V-BIND's results

V-BIND Design Process



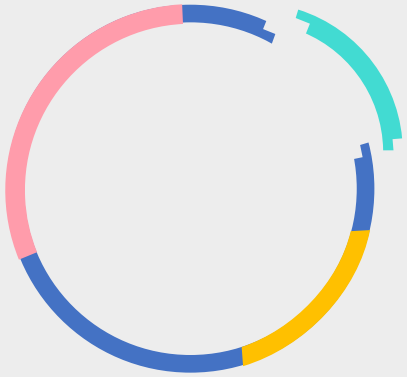
DNAWorks2.0

DNA Library Preparation



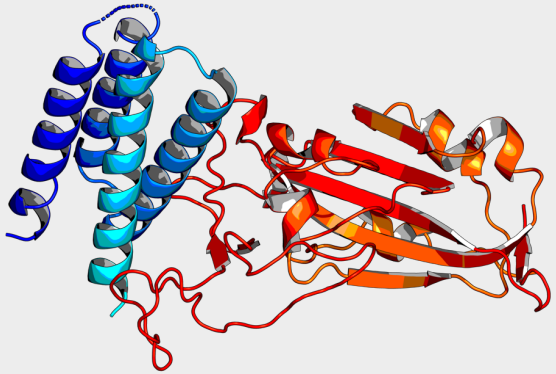
Plasmid DNA Recombination

Protein Expression



Binding assays

Biolayer Interferometry



Broader Applications of V-BIND

→ **Exploring new frontiers:** from ACE2 to Alzheimer's

- Small molecules can inhibit the formation of toxic Aβ aggregates linked to the onset of Alzheimer's Disease[1]
- V-BIND can design anti-aggregation miniproteins, just like it can design anti-COVID-19 miniproteins
- Larger scope: V-BIND aids in protein-mediated inhibition of toxic or viral compounds

[1] Nie, Q., Du, X. G., & Geng, M. Y. (2011). Small molecule inhibitors of amyloid β peptide aggregation as a potential therapeutic strategy for Alzheimer's disease. *Acta Pharmacologica Sinica*, 32(5), 545-551.