Protein engineering for designing new antivirals

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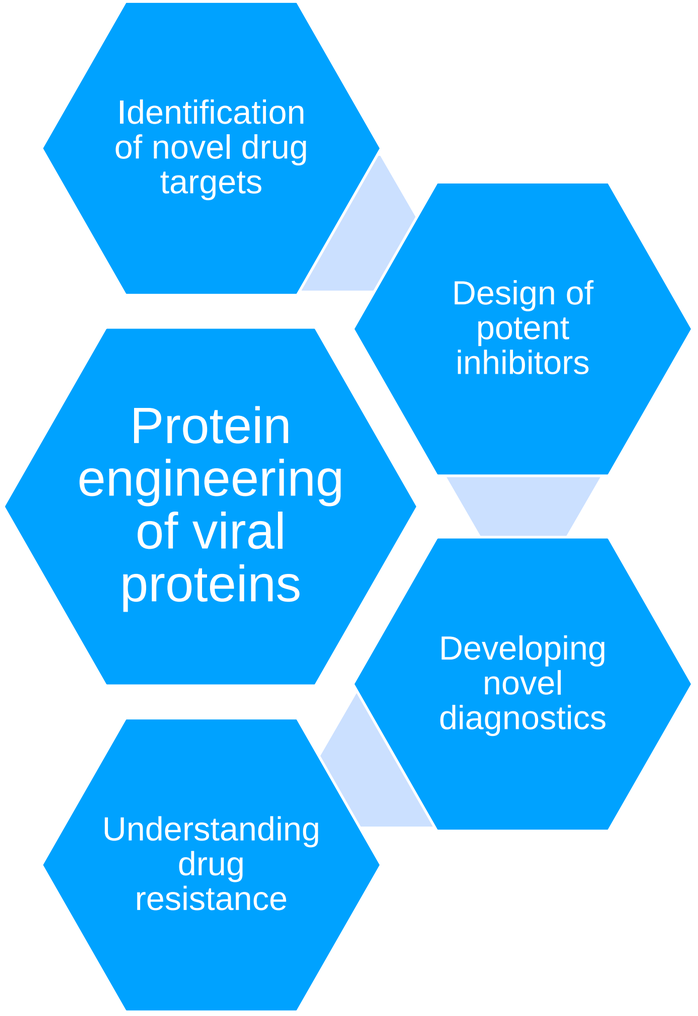
Protein engineering: antivirals and diagnostics

Challenge and Motivation

- Proteins in isolation (outside the cell) do not function well since they are missing co-factors and specific interactions
- This is especially true for viral proteins since the viruses have evolved to usurp the host cell proteins as co-factors.
- Protein engineering allows us to identify the mechanisms by which co-factors assist the viral proteins which can serve as potent targets for antivirals.
- We have recently developed a new framework for developing super-helicases from RNA viruses like dengue and zika.[1, 2]
- Super-helicases can enhance the diagnostics of viral RNA[3] and are good antiviral targets.
- Can we employ the super-helicases to identify antivirals against viruses?



[1]Patent application pending; [2]Banerjee et al. 2023
[3] Volloly and Roy Anal. Chem. 2022

Project plan

Goals of the project

Reverse engineer viral RNA helicases using functional protein design

A. Generate rationally designed viral RNA helicases

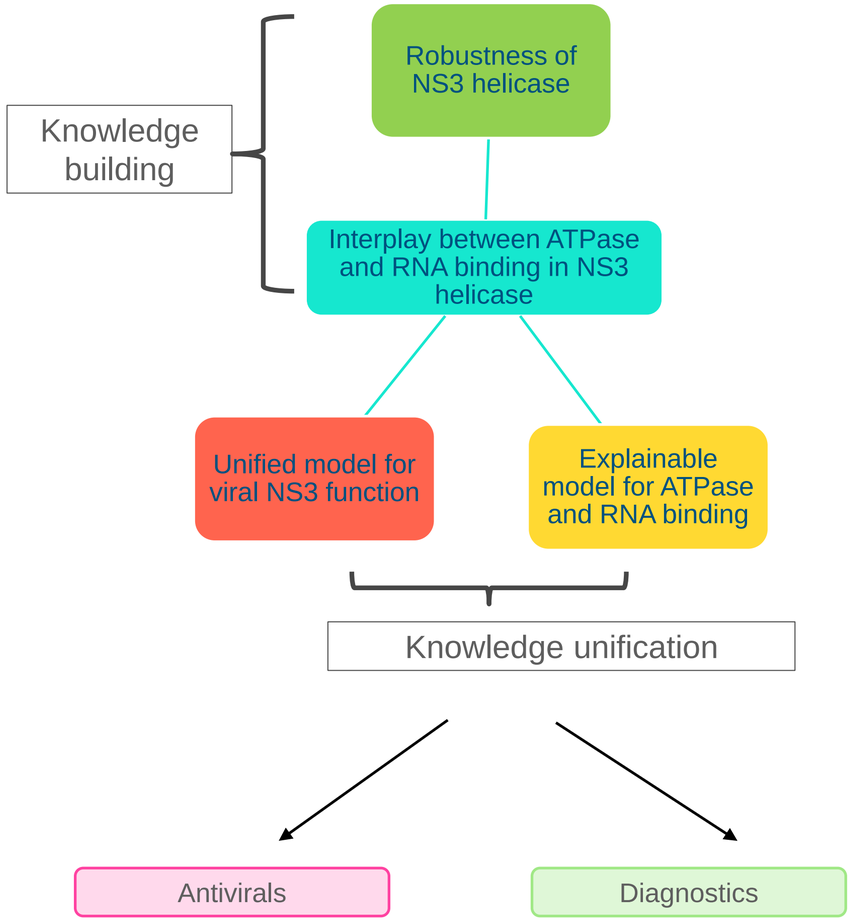
B. Evaluate their functional mechanism using single molecule force-fluorescence spectroscopy

C. Develop new viral diagnostics assays with super-helicases

D. Identify ways to inactivate them with

   a) Allosteric inhibition

   b) Inhibition of interaction partners



Methods and Outcomes

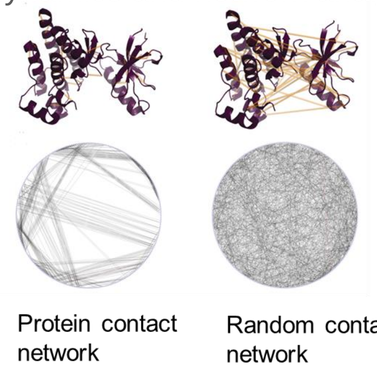
Methods

- Virus evolution experiments under immune selection pressure
- Single-cell virus sequencing
- High throughput and automated virus variant characterizations
- Modeling of virus evolution
- Design and development of RNA nanostructure virus mimics as vaccine candidates

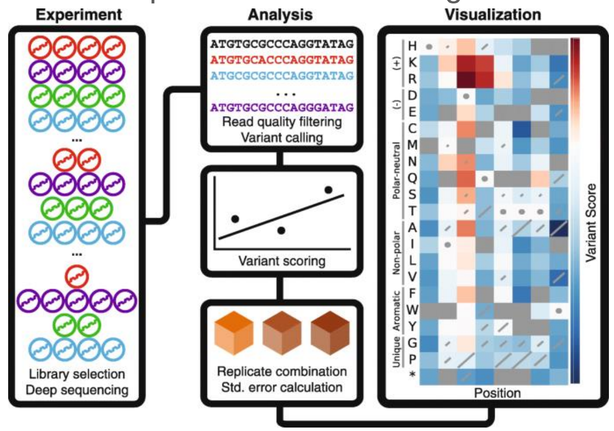
Outcomes

- Immune selection pressure predicted virus evolution strategies
- New methods for understanding virus evolution
- Designer RNA nanostructure virus mimics as vaccine candidates

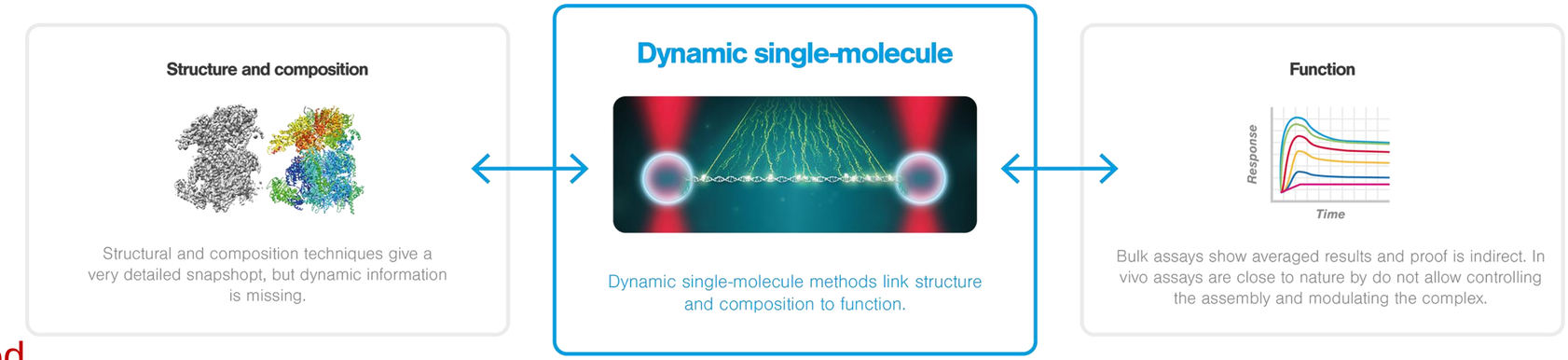
Structural dynamics and network analysis with ML



Deep mutational scanning



Single molecule experiments to characterize super-helicases



Anti-virals against RNA helicases