Next generation vaccine design against dengue virus

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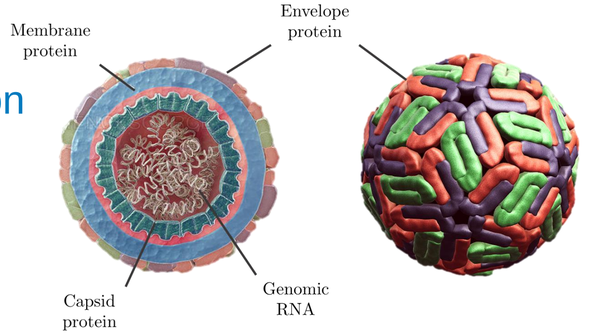
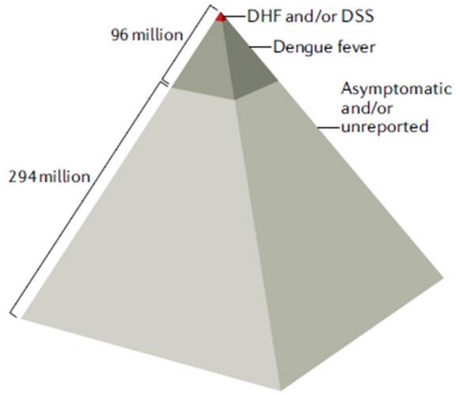
Why designing a dengue virus vaccine is hard?

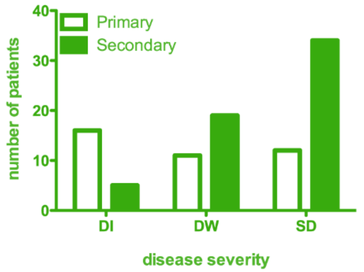
Challenge and Motivation

- Dengue is a group of four major RNA viruses that infects 400 million people annually and about half of the world population is at risk.
- There are no approved dengue vaccines and antivirals.
- Unlike other infections, the chance of severe disease increases severalfold if you have a prior dengue infection due to a phenomena called antibody-dependent enhancement (ADE).*
- We have shown that Dengue virus is evolving in India as a culmination of ADE and immune escape and giving rise to new and more infectious virus variants.#
- Can we learn and predict dengue virus evolution using high throughput experiments and mathematical modelling? Knowledge of such evolutionary mechanisms will allow us to build the next generation of dengue vaccines.

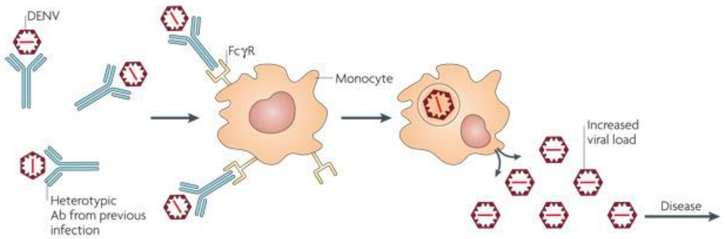




John A. & Rathore A., *Nature reviews* (2019)



Singla M. et al., *PLoS NTD* (2016)



Whitehead S. *et al., Nature Reviews Microbiology* (2007)

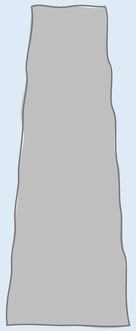
*More than half of the Indian population has had a prior dengue infection

Jagtap *et. al.* PLoS Pathogens 2023 (in press)

Tug of war: Viral infections and immune response

Factors

Transmission bottlenecks
Population immunity
Seasonality
Host movement
Interaction with other viruses

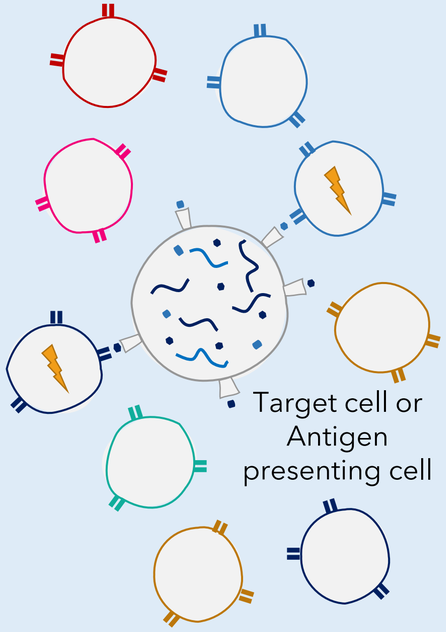


Virus particles

Selection

Virus grows in number and mutates

T cells



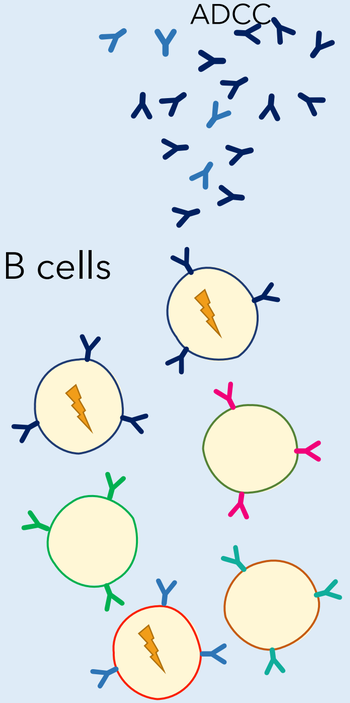
Activated T cells

Help B/ CD8+ cells
Antiviral/cytotoxic activities
Tissue homing
Memory T cells

Antibodies

Neutralize virus
Agglutination
Complement mediated killing
ADCC

B cells



Activated B cells

Plasma cells
Long-living plasmablasts
Memory B cells

Viral transmission

Heterogeneity in viruses

Adaptive immune response in host

Project plan

Goals of the project

Evaluate immune evasion and antibody-dependent enhancement mediated dengue virus evolution

a) Develop a high throughput pipeline to evaluate dengue virus evolution immune selection pressure

b) Use an evolutionary viral dynamics model to identify conditions/strategies that remove/reduce ADE

c) Bonus: Develop a nanoparticle Dengue RNA virus vaccine

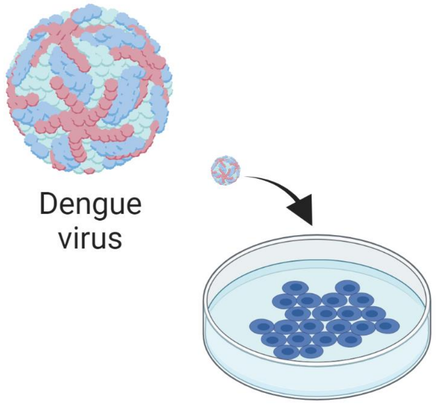
Methods and Outcomes

Methods

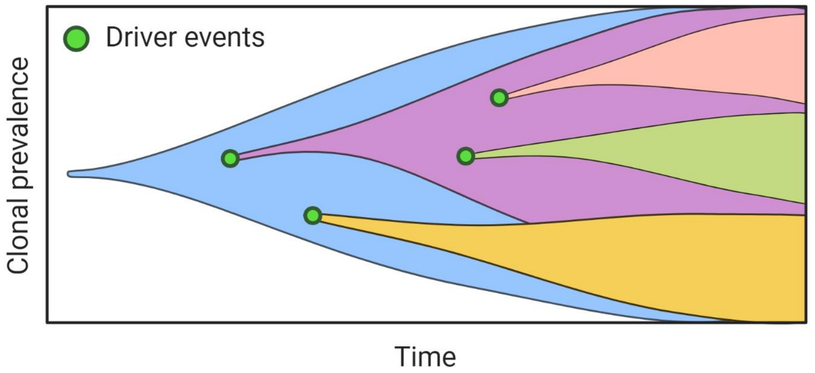
- Virus evolution experiments under immune selection pressure
- Single-cell virus sequencing
- High throughput and automated virus variant characterizations
- Modeling of virus evolution
- Design and development of RNA nanostructure virus mimics as vaccine candidates

Outcomes

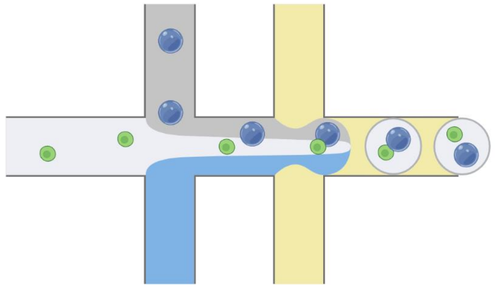
- Immune selection pressure predicted virus evolution strategies
- New methods for understanding virus evolution
- Designer RNA nanostructure virus mimics as vaccine candidates



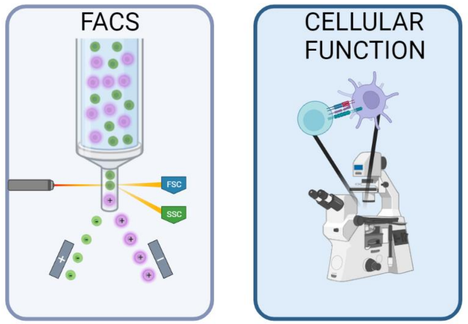
Virus evolution under immune selection pressure



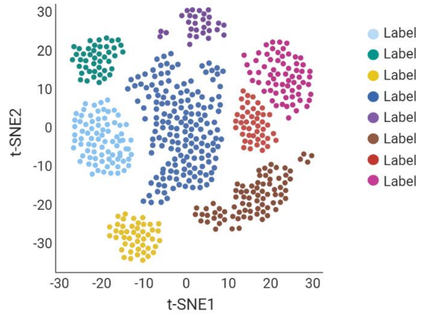
Single cell sequencing to identify virus variants



Virus Profiling



Statistical analysis and modeling



Synthetic designer RNA virus mimics