Multiscale Simulation, Modelling & Design – Progress Report 2022

Peter J. Bond

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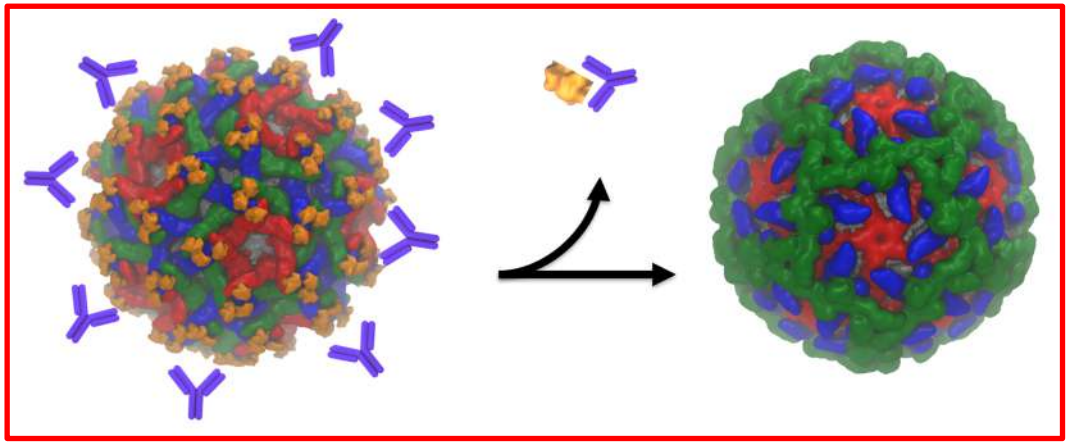

A*STAR BII

Multiscale Simulation, Modelling & Design Group

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Singapore (Duke-NUS, NUS, NTU, GIS, BTI, SIFBI)

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Rachel Ee Pui Lai
Koji Itahana

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Olivera Francetic
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Jim Warwicker
Tom Piggot
Syma Khalid
Luning Liu
Martin Ulmschneider
Ivo Martins
Slawomir Boncel
Duncan McMillan

"LPS network"

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Jitka Petrlova
Anna Petruk
Rathi Saravanan
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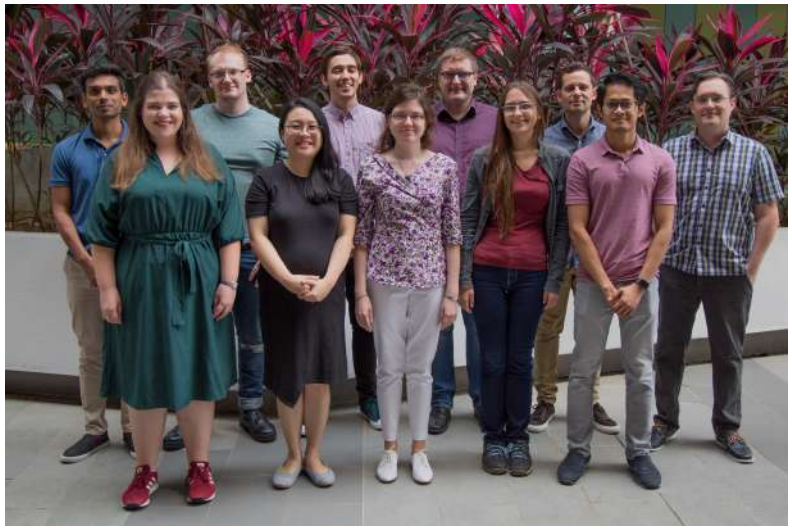
Graeme Lancaster
Mark Febbraio
(BakerIDI, Melbourne)
Clare Bryant
Nick Gay
(Cambrige)

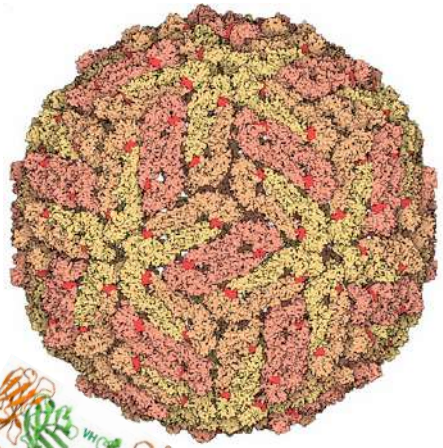


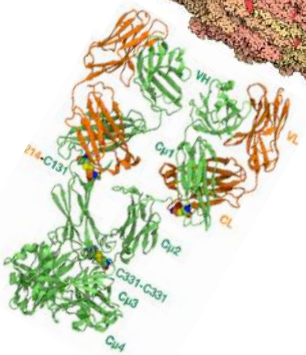
Jan Marzinek (YIRG)
Firdaus Samsudin (YIRG)
Alexander Krah
Palur Raghuvamsi

Callum Waller (ARAP)
Tom Davies (ARAP)
Dagnija Tupina (ARAP)

- ID HTPO Seed Fund – Glycan-Centric Surveillance of Viruses
- P&G Predictive Virus Inactivation Efficacy Model for Active/ Prototype Screening
- Singapore Food Story R&D Programme – Alternative Proteins Seed Challenge
- NMRC OF-IRG – drug transporter / resistance in cancers

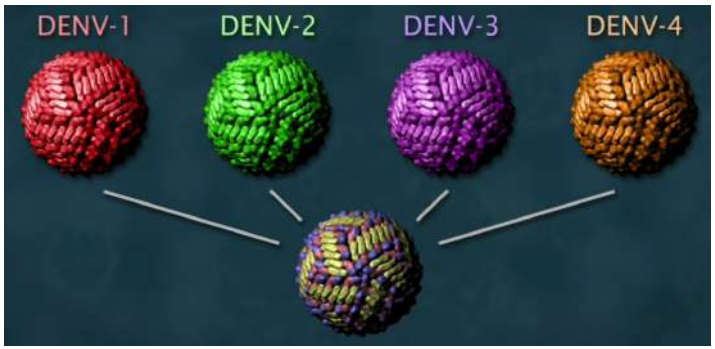
Research Focus: Host-Pathogen Interactions



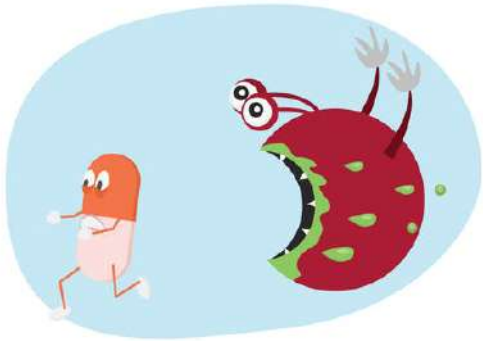


Viral envelope dynamics, antivirals & antibodies / vaccines

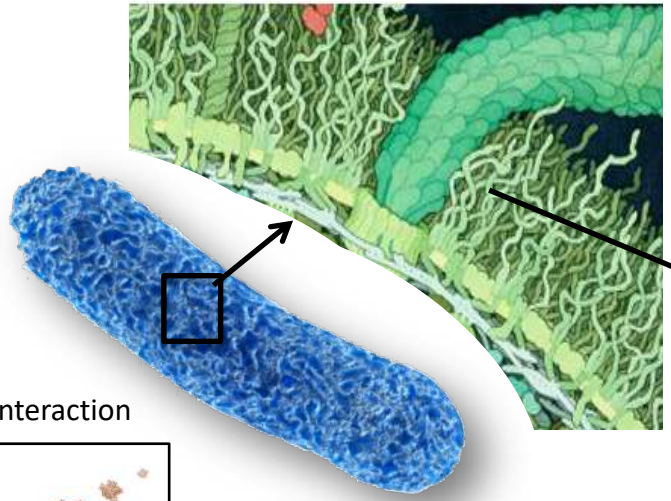
(also non-enveloped viruses…)

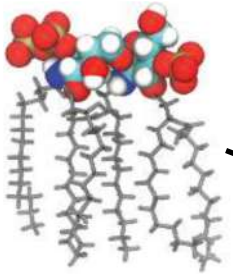


Dengue: flavivirus with lipid bilayer & envelope proteins

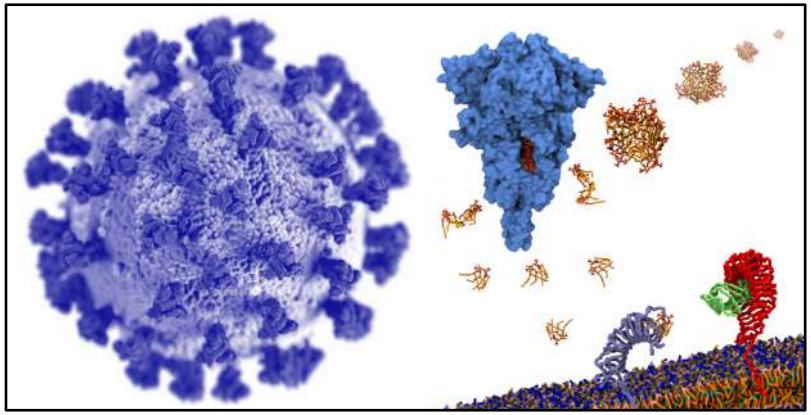


(Gram-negative) bacterial cell envelopes, membranes (lipopolysaccharide), & antibiotics

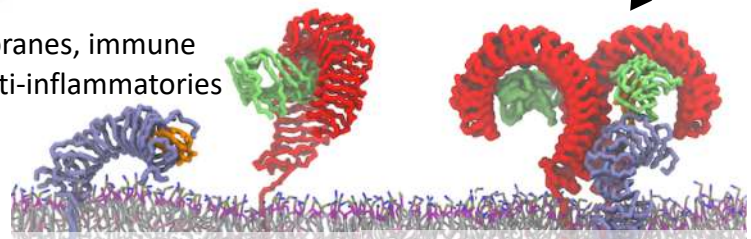




Coronaviruses: spike proteins & LPS – a novel interaction

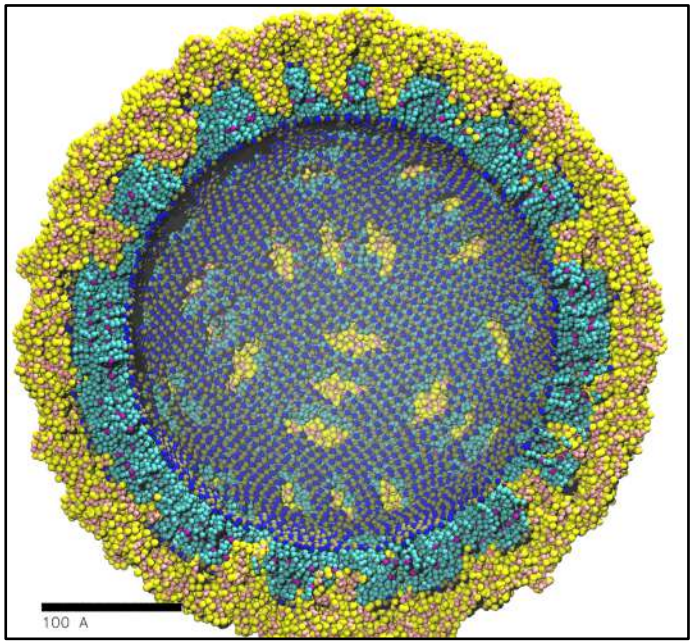


Host cell membranes, immune receptors, & anti-inflammatories

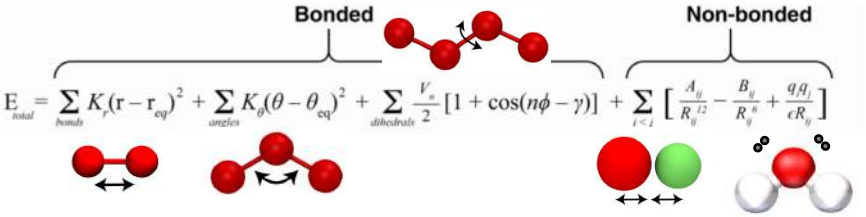


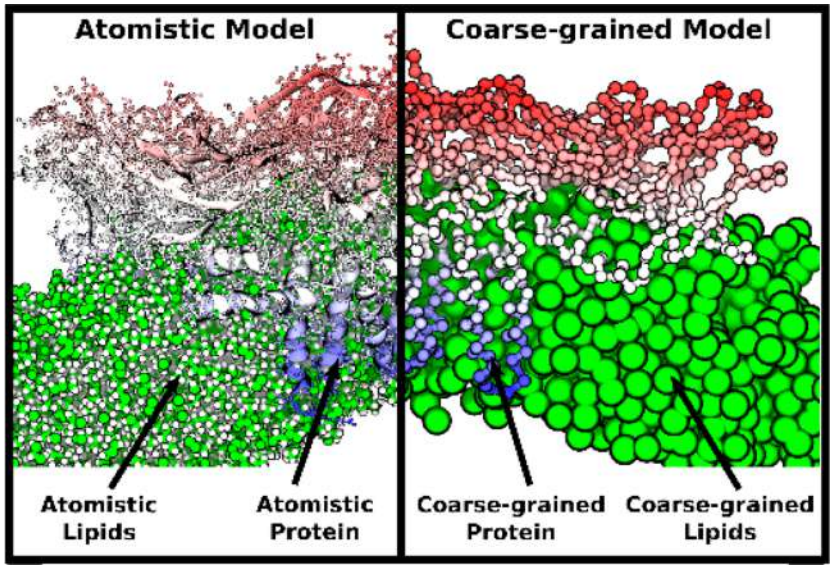
J Biol Chem (2020) 295:3417 *Structure* (2018) 26:1151
Nat Commun (2018) 9:2762 *PNAS* (2017) 114:E4213

Biomolecular Simulations & Multiscale Approaches



Methods of choice: (1) Molecular simulation.
(2) Integrative modelling.
(3) Multiscale approaches.

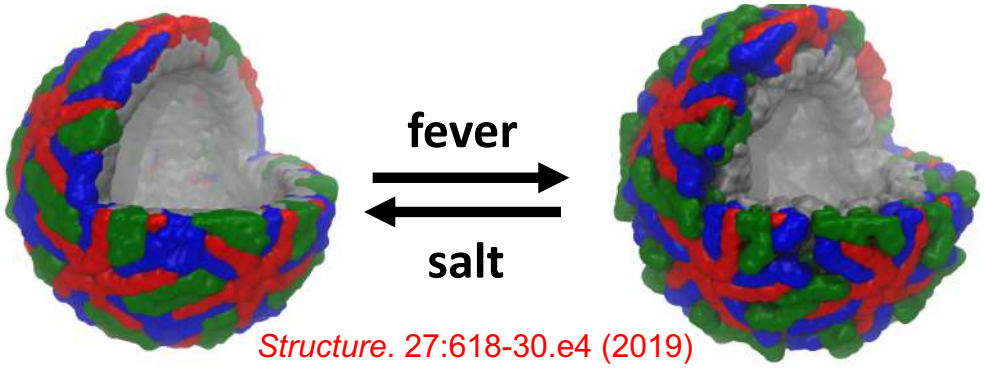




Structure (2016) 24:1410
Structure (2019) 27:253
Structure (2019) 27:618
Curr Opin Struct Biol (2020) 61:146
J Chem Inf Model (2020) 60:3864

Dengue – "Shape-Shifting" in the "Arms Race"

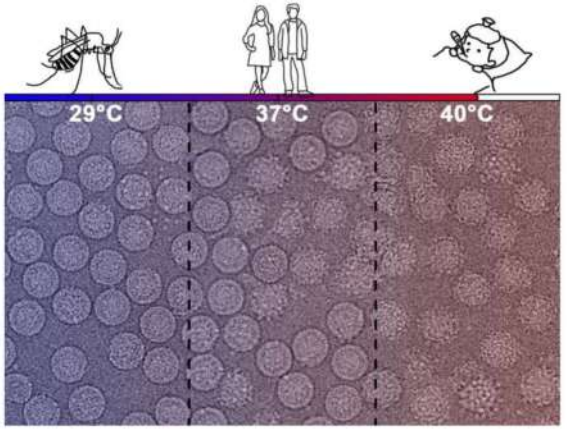
With SM Lok, Duke-NUS + NUS, SIgN, SGH (NRF CRP)



Structure. 27:618-30.e4 (2019)

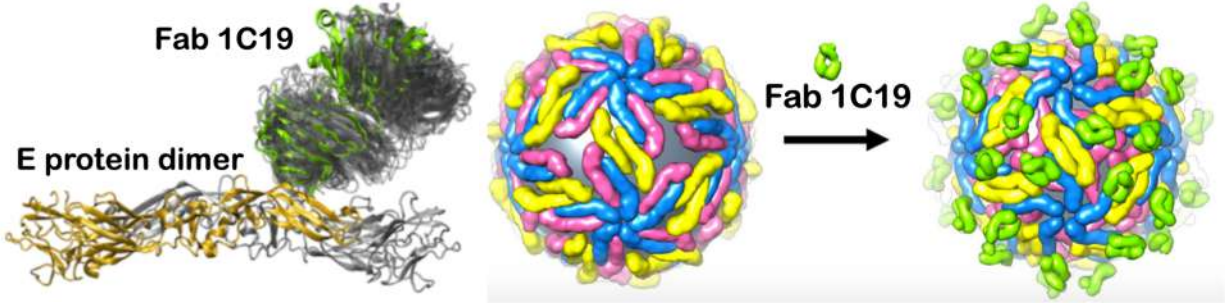
(1) Modelling & biophysics show that host environment leads to viral envelope "shape-shifting" between "smooth" and "bumpy" morphologies.

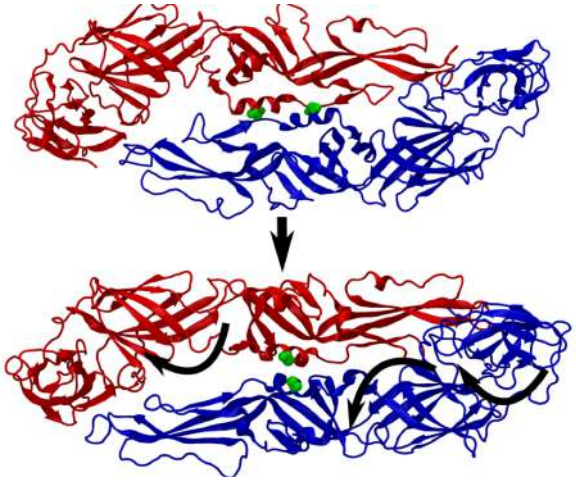
(2) Modelling of clinical vs. lab strains: envelope mutations alter virus morphology at different temperature (e.g. fever). Altered epitopes = resistance to antibodies/vaccines.



PLoS Pathog. 15:e1007996 (2019)

PLoS Pathog. 17:e1009331 (2021)

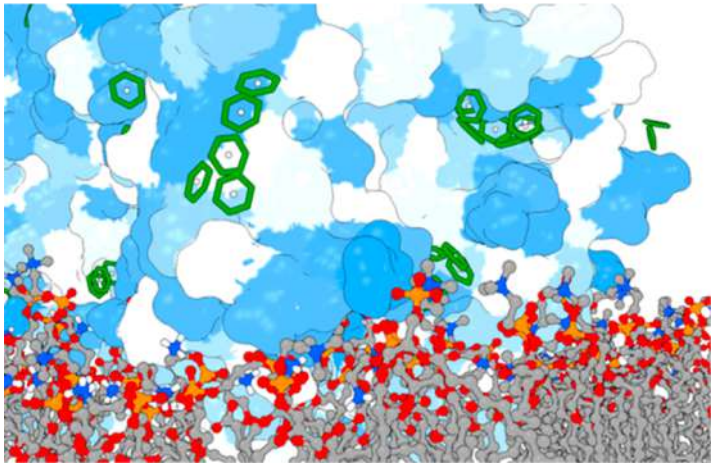




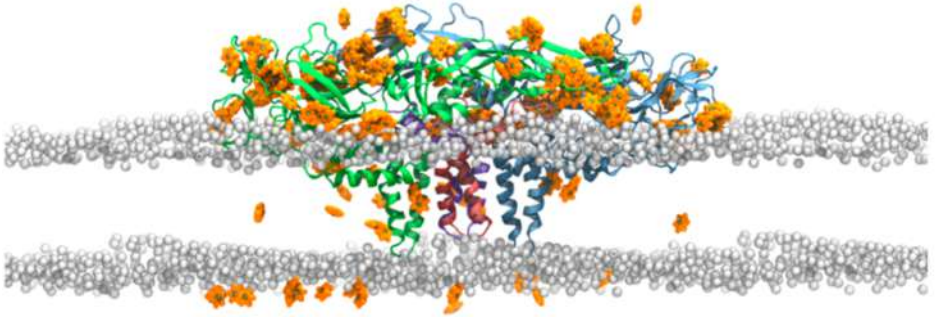
(3) Modelling & biophysics reveal antibody epitope hidden below viral surface – but a sufficiently strong antibody can force the virus to "shape-shift", exposing it for neutralization.

→ **Next-gen therapeutics: (a) high-affinity antibodies that (b) recognize diverse morphologies.**

Cryptic Pockets in the Envelope?

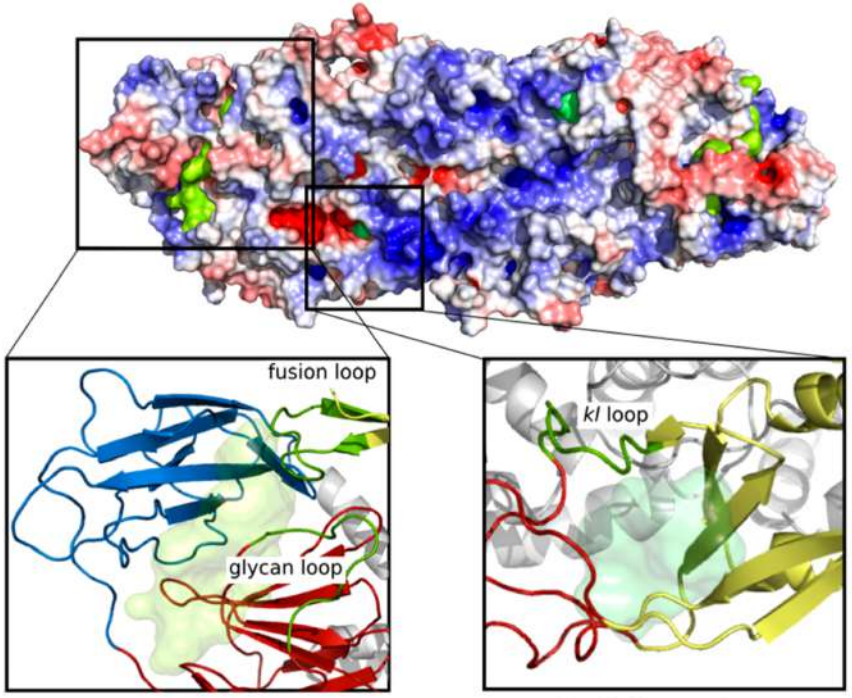


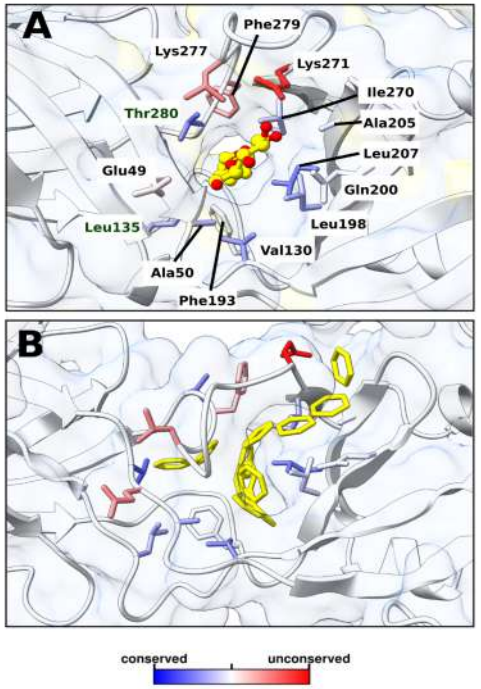
Benzene: a “virtual chemical probe” for uncovering cryptic sites… but what about membrane proteins?



J. Chem. Theory Comput. 16:5948-59 (2020)

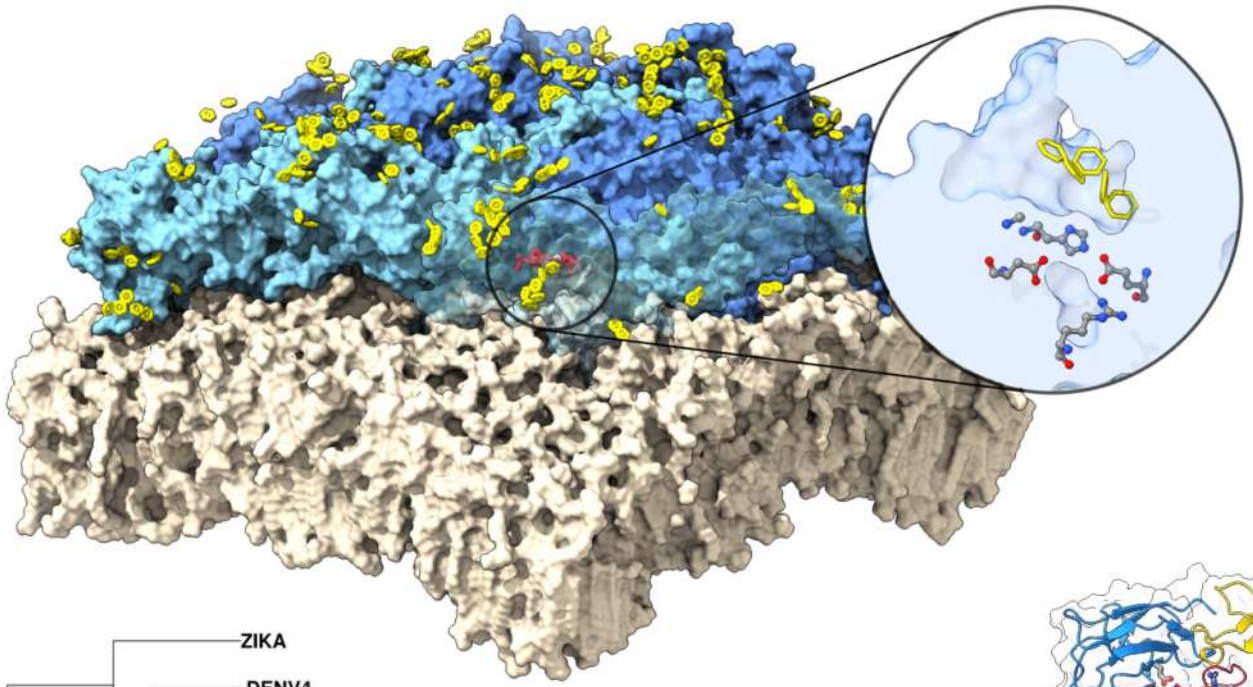
(hinge region between domains I & III, important in pH-switch)

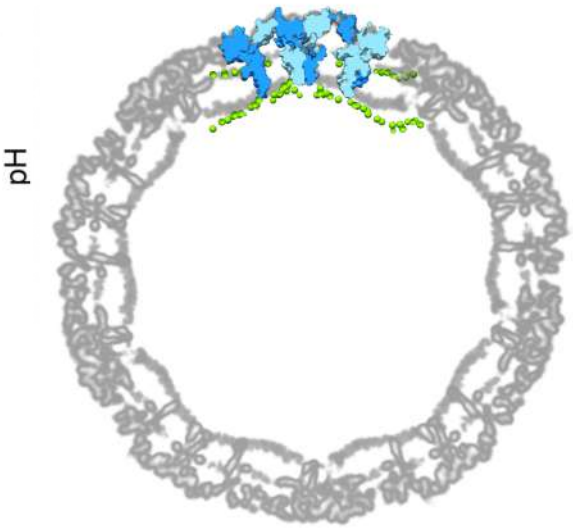


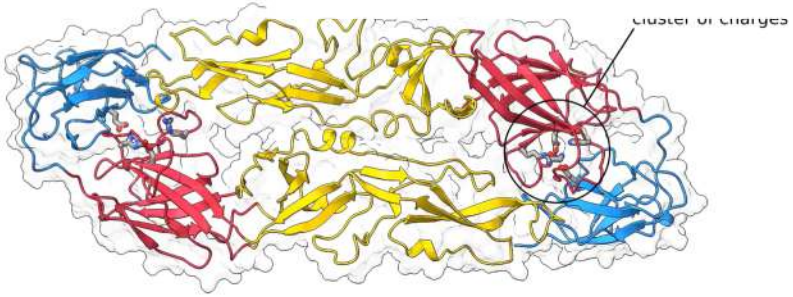


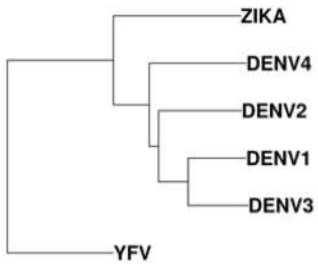
(underneath kl β-hairpin at domain I-II interface)

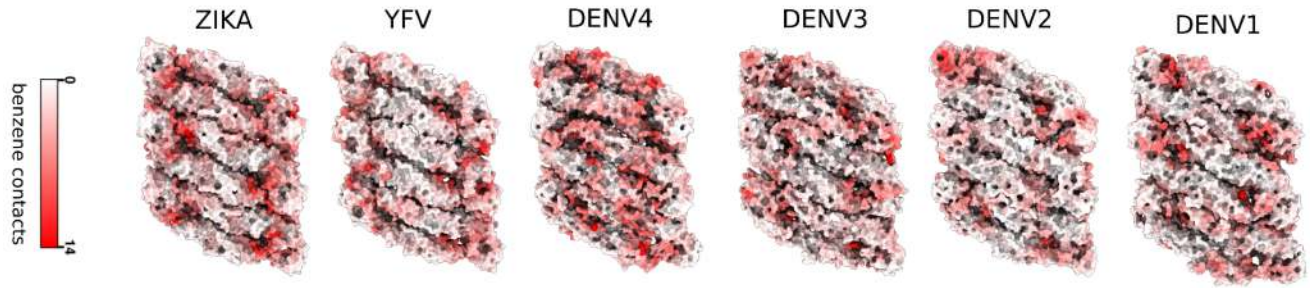
A Functional Role for the α-Pocket in Flaviviruses?









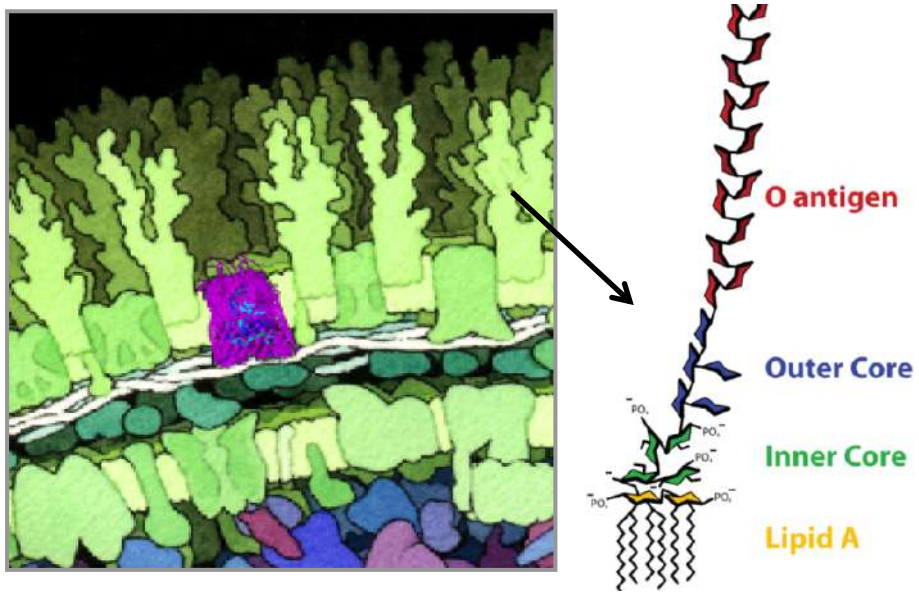


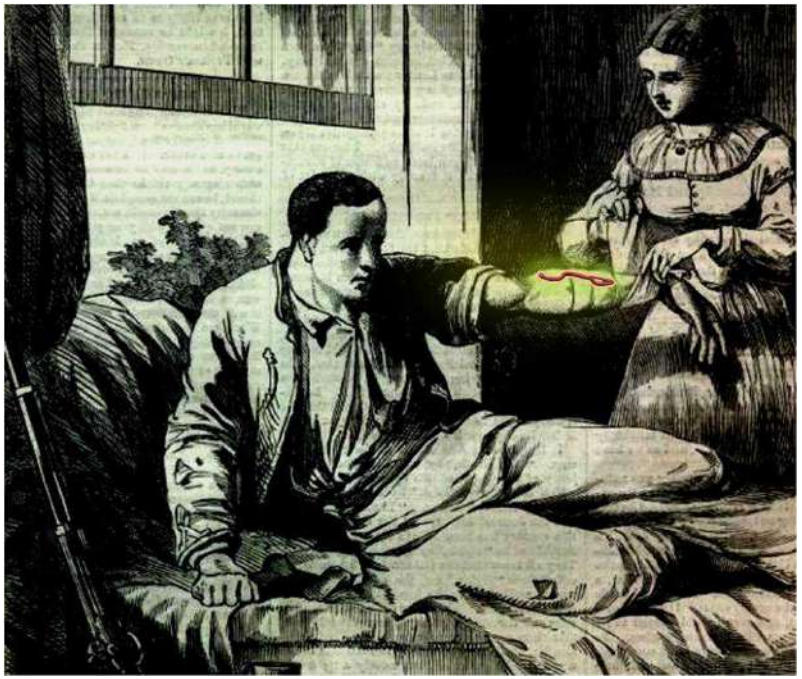
Constant-pH simulations:
low pH = cluster disruption
& release of domain III.

- Benzene binding pattern correlates with phylogenetic relationships.
- β-OG pocket: strain-specific; α-pocket conserved – and site of ionizable cluster.

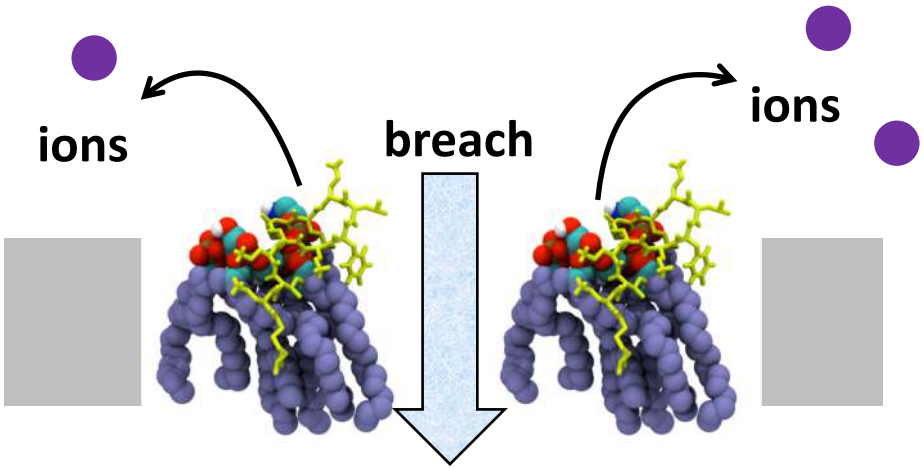
Zuzic et al. Submitted (2022)

Endogenous Peptides vs. Gram–Negative Bacteria

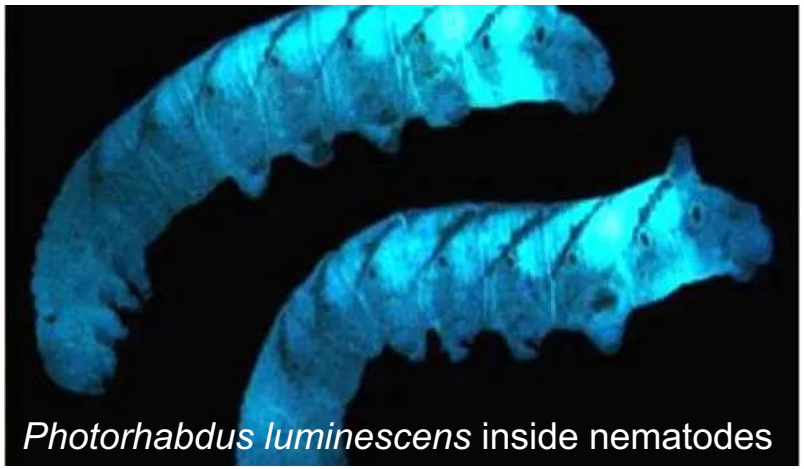




e.g. polymixins (but resistance & toxicity…)

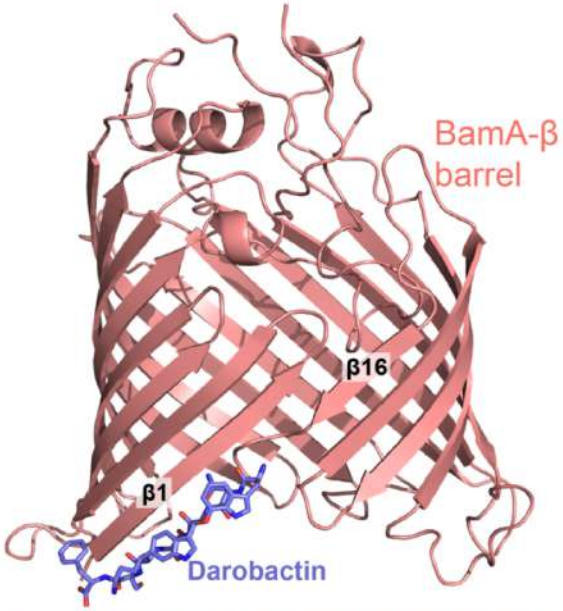


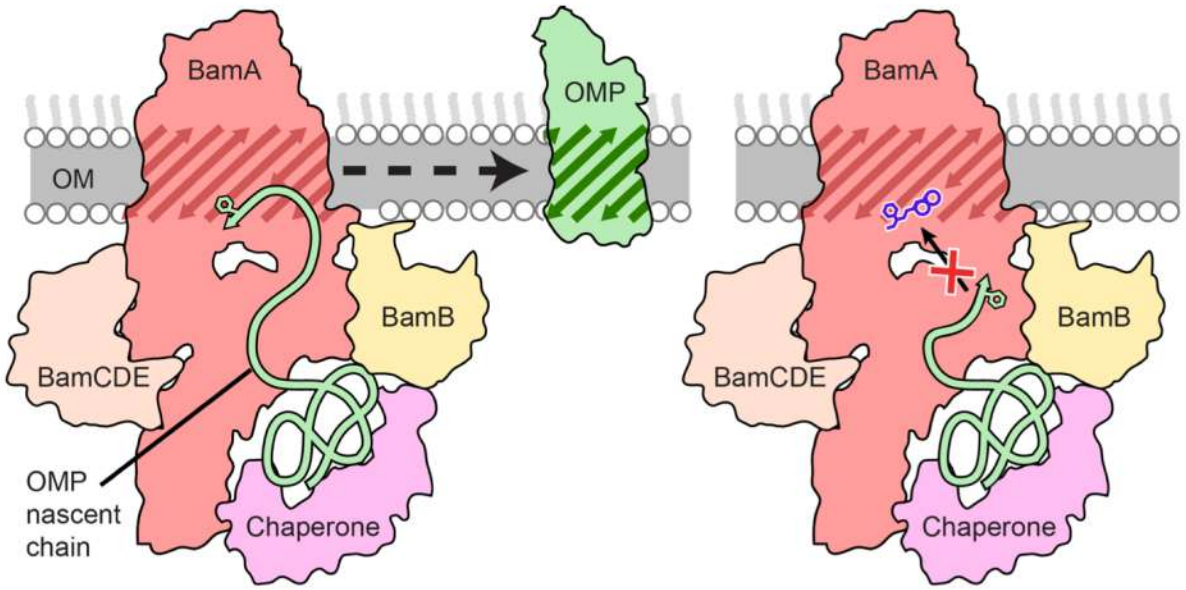
Exploiting an "Angel's Glow"…

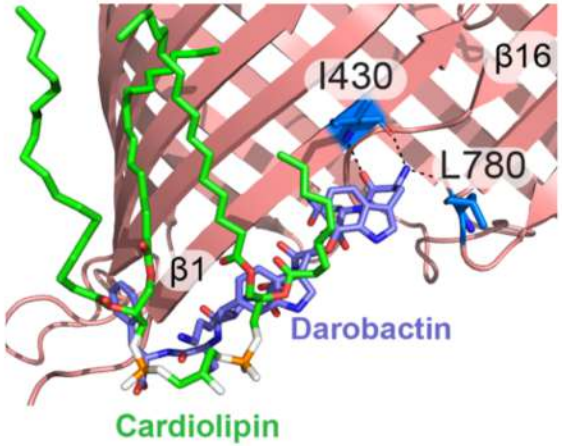


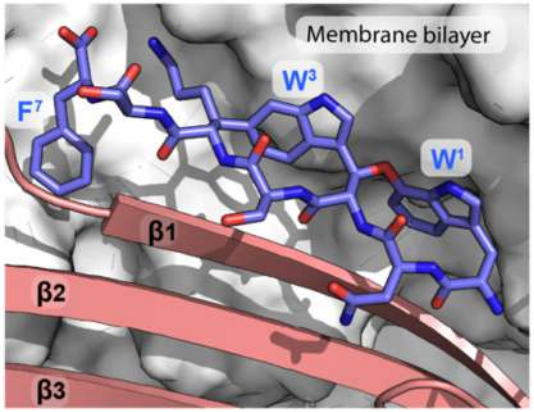
PLoS Comput Biol. **2015** 17;11(4):e1004180

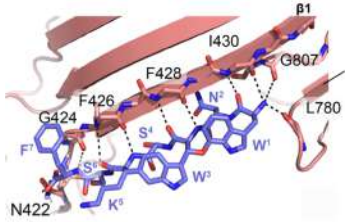
Selectively Inhibiting the Outer Membrane Insertase







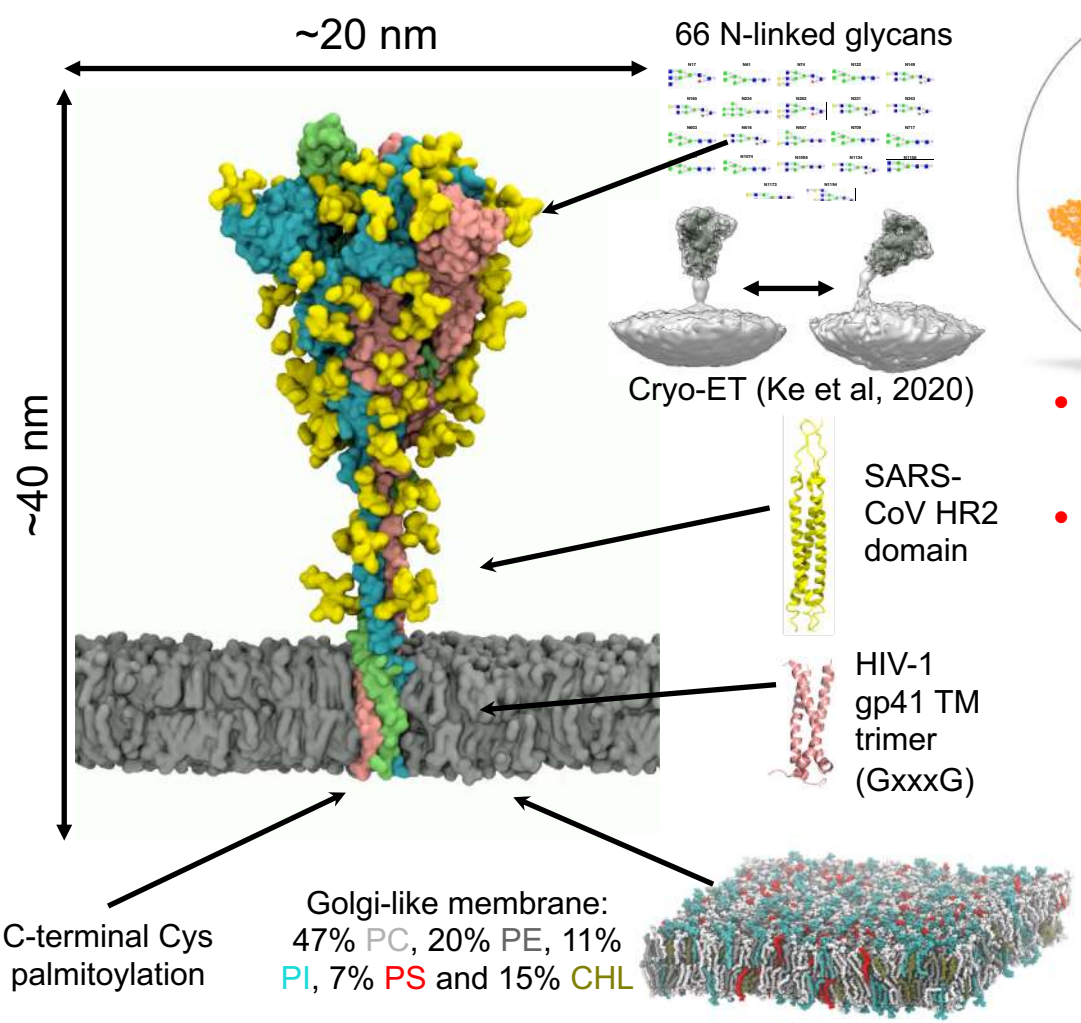


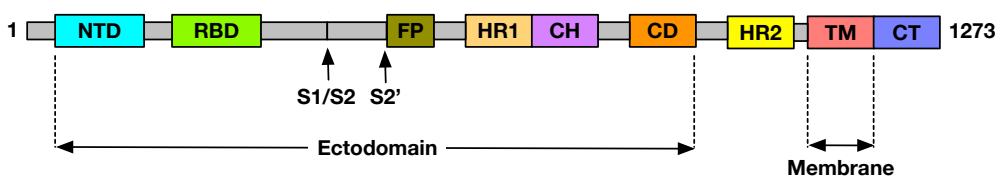


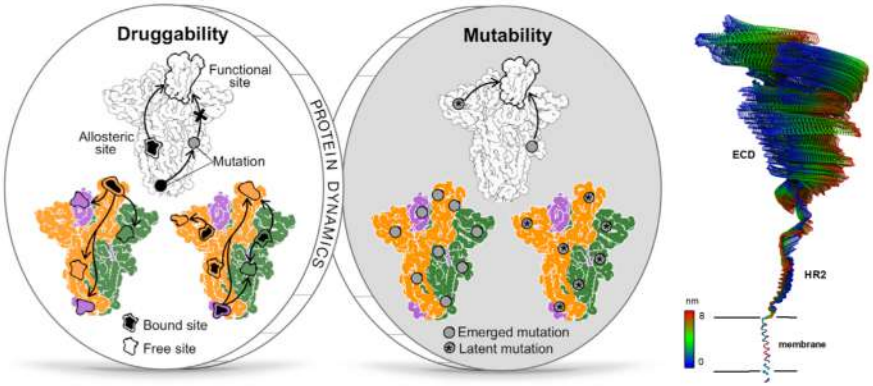
The antibiotic darobactin mimics a β-strand to inhibit outer membrane insertase. *Nature*. 593:125 (2021)

- Darobactin β-hairpin peptide binds to OMP insertase (BAM complex), blocking native substrates.
- Cardiolipin "plug" is replaced by darobactin - an unusual "extended binding pocket".
- Interaction mediated via backbone: uniquely robust against potential resistance mutations.
- Antibiotics targeting Gram-negative bacteria: last new class, quinolones >50 years ago.
- With Sebastian Hiller (Uni. Basel) & Polyphor; other scaffolds under investigation…

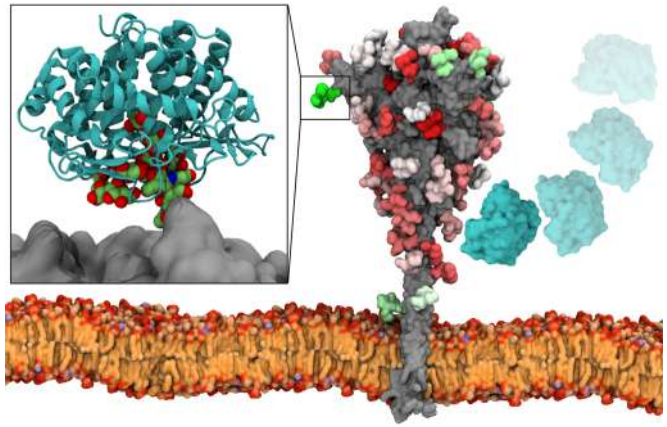
SARS-CoV-2 Spike: Dynamics & Some Surprising Interactions







- SARS-CoV-2 S protein:ACE2 interaction reveals novel allosteric targets. *Elife.* 17:e1009331 (2021) – with Ganesh Anand & Paul MacAry
- Allosteric perspective on mutability & druggability of SARS-CoV-2 Spike protein. *Structure* (2022) – with Igor, BII

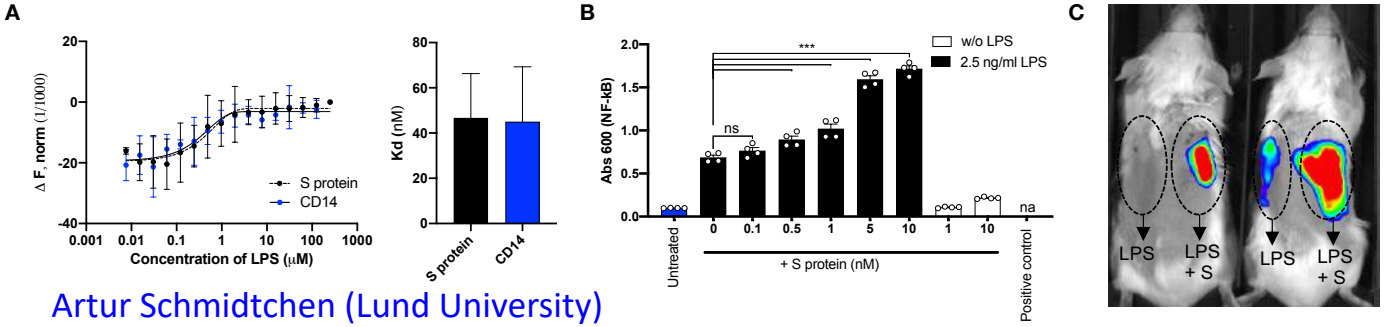


- Site-specific steric control of SARS-CoV-2 spike glycosylation. *Biochemistry*. 60:2153 (2021)
- Glycosylation and serological reactivity of an expression-enhanced SARS-CoV-2 viral spike mimetic. *J Mol Biol.* 434:167332 (2022)

– with Max Crispin

Defining a Novel Interaction: SARS-CoV-2 Spike / LPS

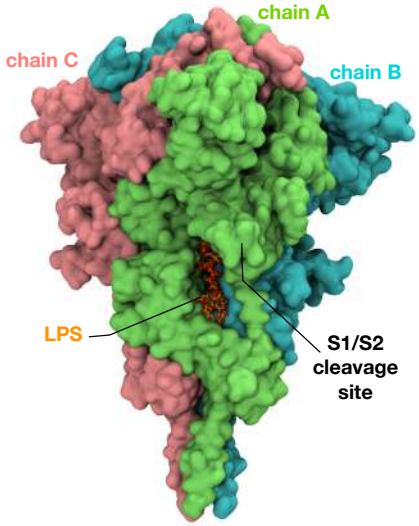
(A) Spike protein:LPS affinity ≡ CD14 (microscale thermophoresis).
(B) Spike protein boosts NF-κB response to LPS.
(C) Inflammation in NF-κB reporter mice.

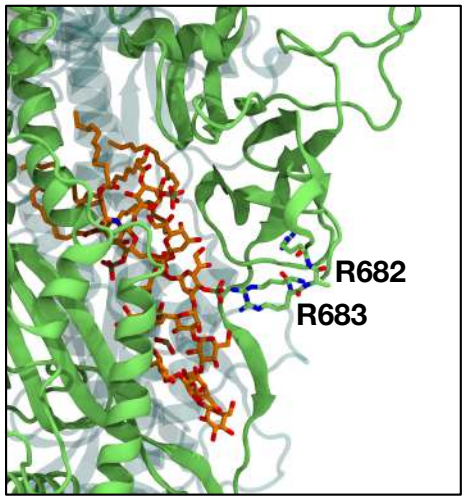


Artur Schmidtchen (Lund University)

Metabolic syndrome
↓
High blood level of LPS
↓
SARS-CoV-2 infection
↓
Hyper-inflammation

SARS-CoV-2 spike protein binds to bacterial lipopolysaccharide and boosts proinflammatory activity. *J Mol Cell Biol* (2021) 12:916

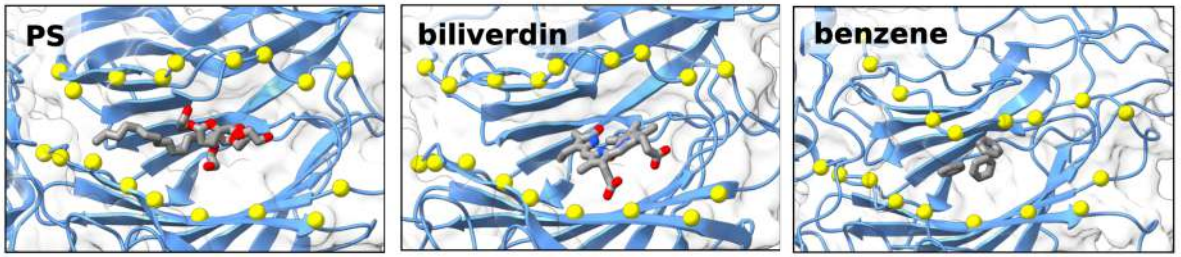




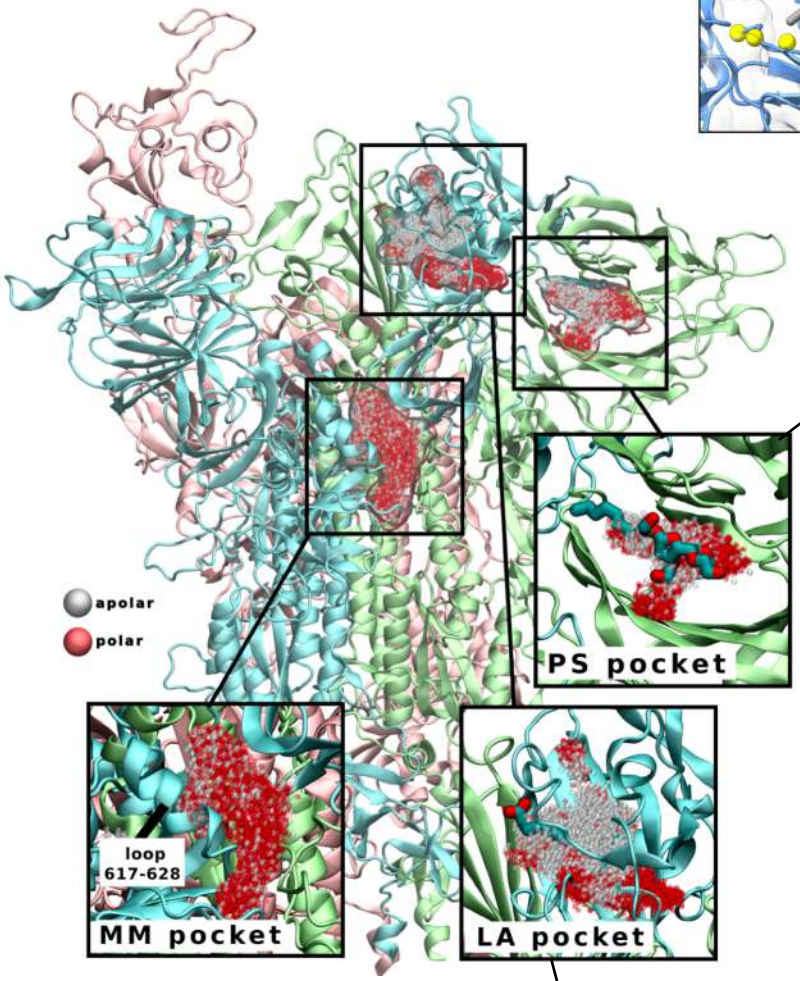
- Severe COVID19 common in those with metabolic syndrome (diabetes, obesity etc.) linked with raised LPS levels.
- Metabolic syndrome predisposes patients to severe COVID19: Hyper-inflammation in lungs → respiratory failure, sepsis & death.
- Surprising reports of "TLR4 interaction"…

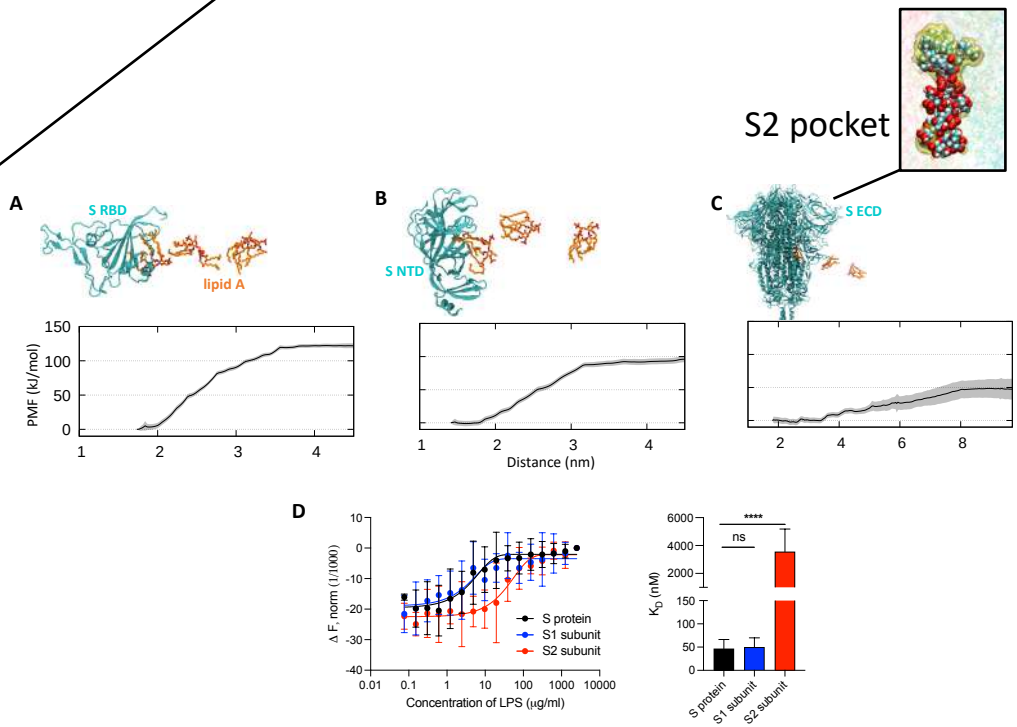
- LPS sites: docking (S1+S2) / simulations – S2 site.

Benzene Mapping of Spike & LPS Binding



NTD – polysorbate (PS) + haem metabolites



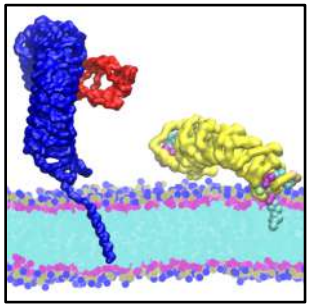


- PMFs for LPS to S1 & S2 – low & high affinity sites.
- Microscale thermophoresis: K_D's ~nM (S1) & μM (S2).
- Supported by HDX-MS, & in vivo S1/S2 "boosting".

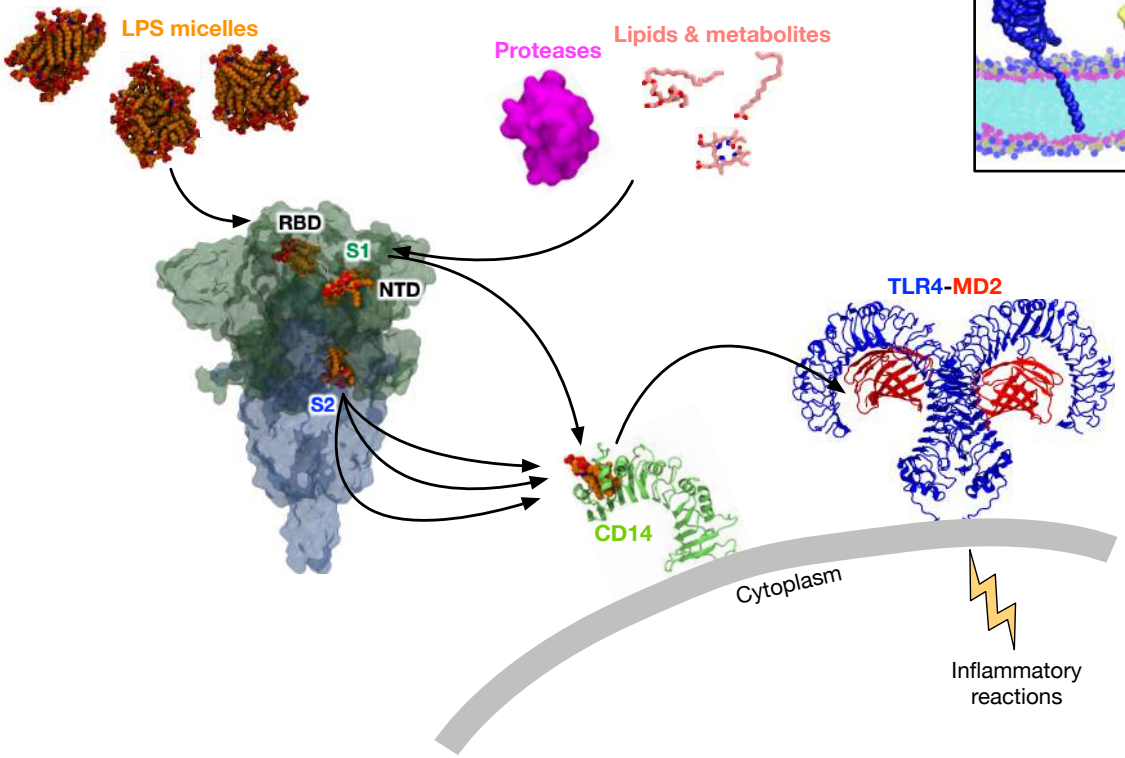
Zuzic et al. Submitted (2022)

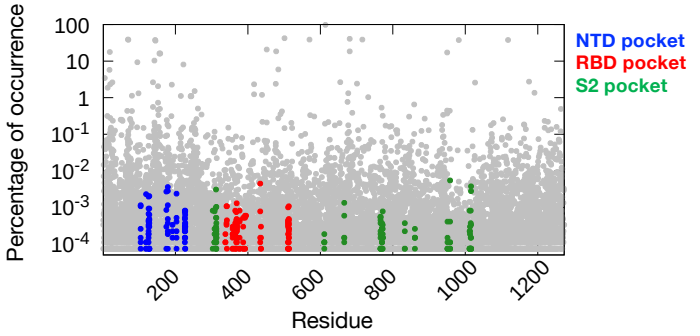
RBD – linoleic acid (LA)

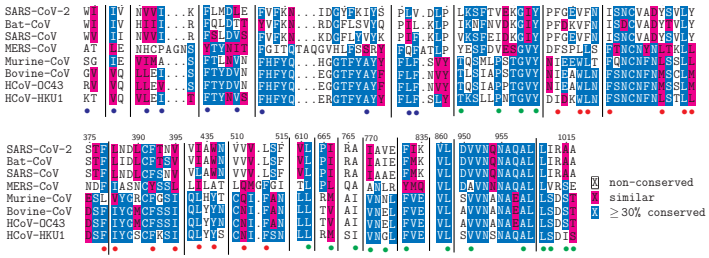
Defining a Novel Interaction: SARS-CoV-2 Spike / LPS



A Thermodynamic Funnel Drives Bacterial Lipopolysaccharide Transfer in the TLR4 Pathway.
(2018) *Structure* 26:1151



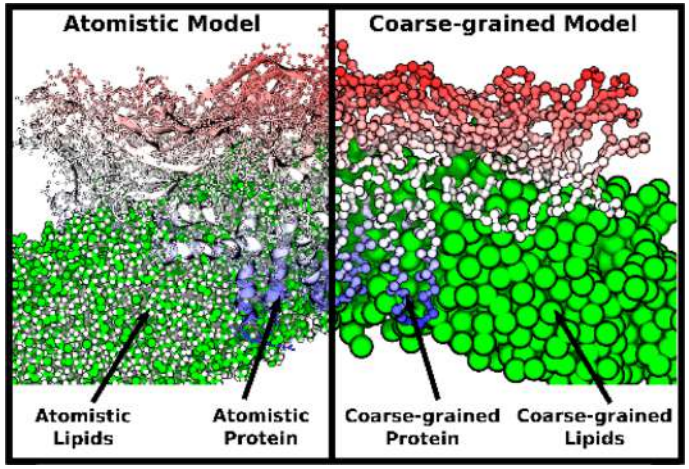


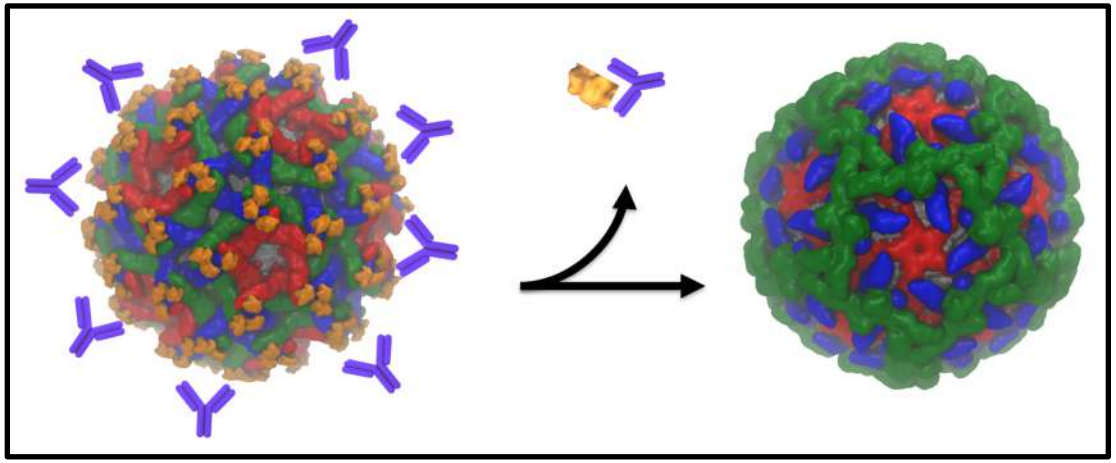


- Spike protein boosting effect on LPS-mediated proinflammatory response.
- Multiple recent papers: (i) “direct” activation of TLR4 – unlikely; (ii) raised LPS/intestinal permeability & sepsis in COVID19 patients…
- Key LPS-interacting residues conserved (<0.01% in all reported sequences in GISAID).

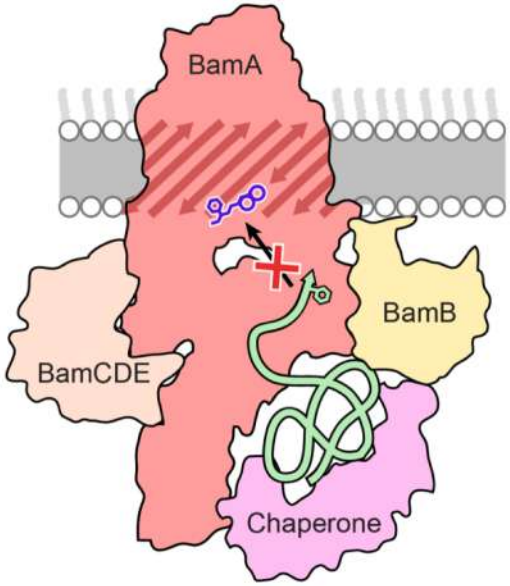
Samsudin et al. Submitted (2022)

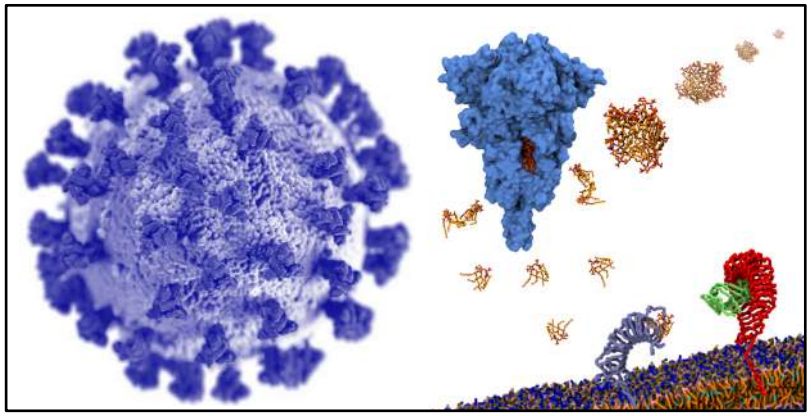
Summary: Multiscale Host-Pathogen Interactions





- Multiscale models of dengue envelope – insights into viral life cycle, antibodies, hidden pockets...





- Bacterial membranes & LPS: antimicrobial & antiseptic routes inspired by nature.
- Coronaviruses – bacterial LPS interaction & possible role in pro-inflammatory states.

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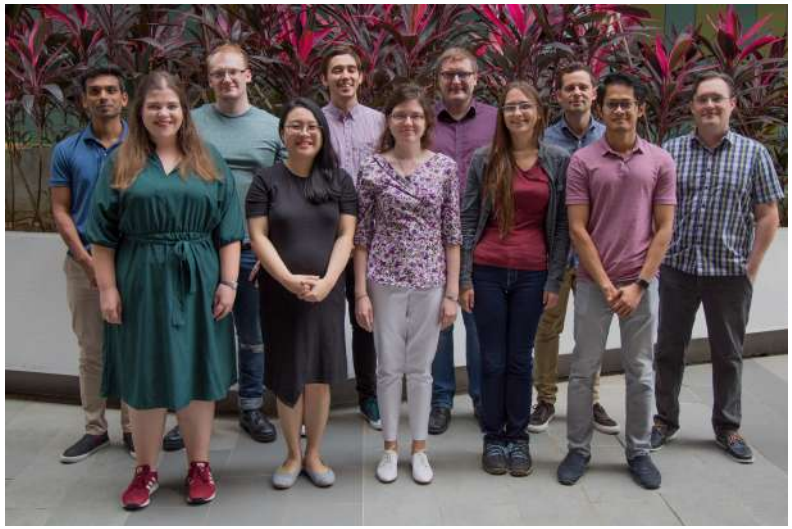

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- ID HTPO Seed Fund – Glycan-Centric Surveillance of Viruses
- P&G Predictive Virus Inactivation Efficacy Model for Active/ Prototype Screening
- Singapore Food Story R&D Programme – Alternative Proteins Seed Challenge
- NMRC OF-IRG – drug transporter / resistance in cancers