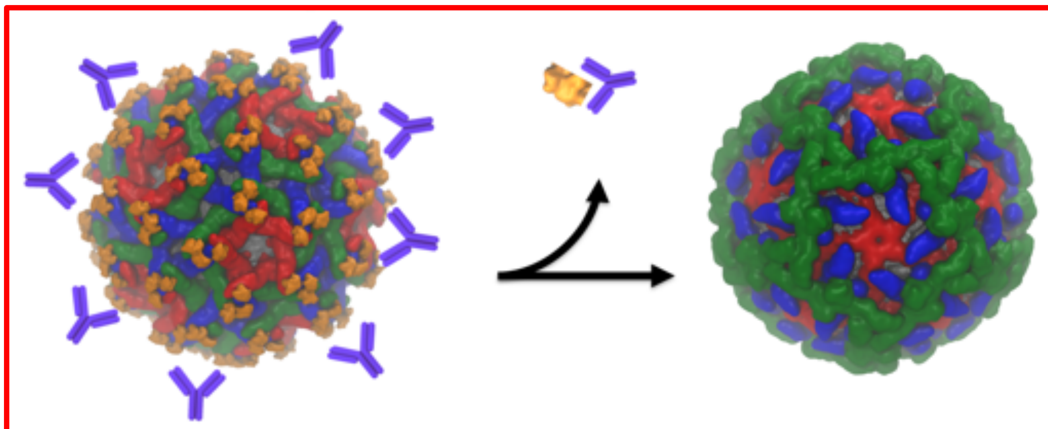
Multiscale Simulation, Modelling & Design: Infectious Diseases and the Host Response

Peter J. Bond



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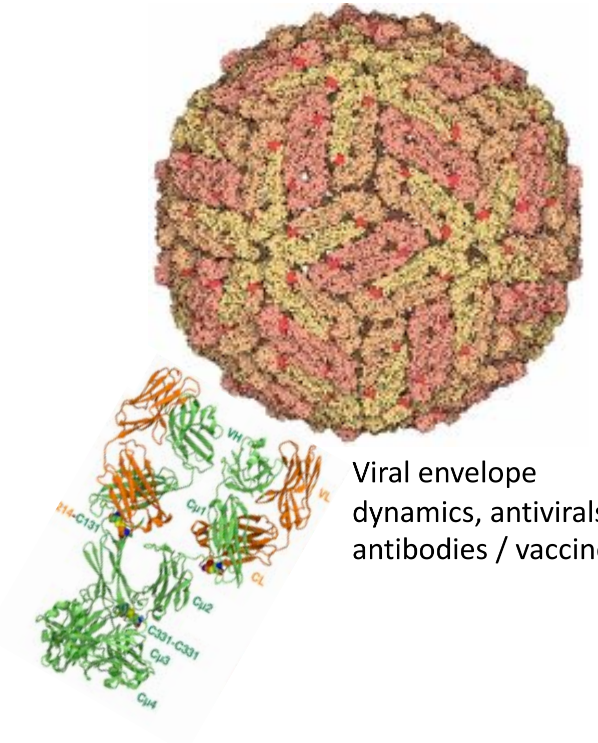
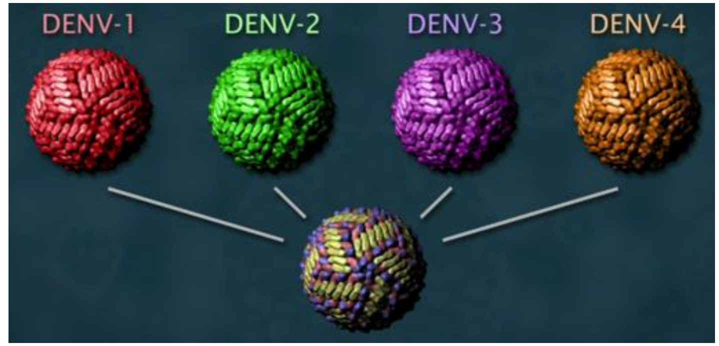
Research Focus: Host-Pathogen Interactions

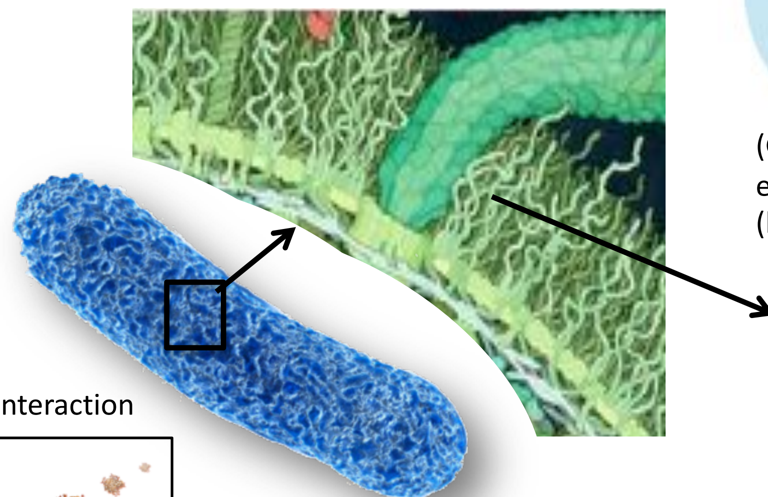


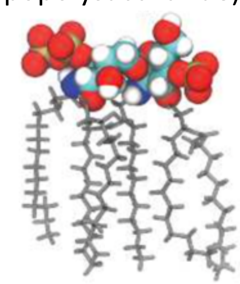
Viral envelope dynamics, antivirals & antibodies / vaccines



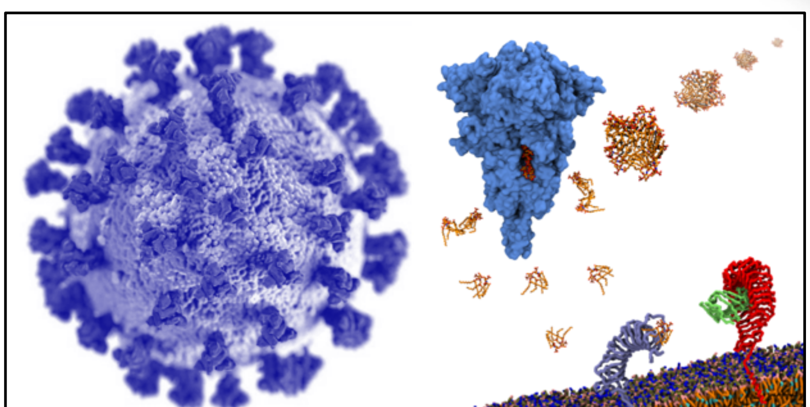
Dengue: flavivirus with lipid bilayer & envelope proteins

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

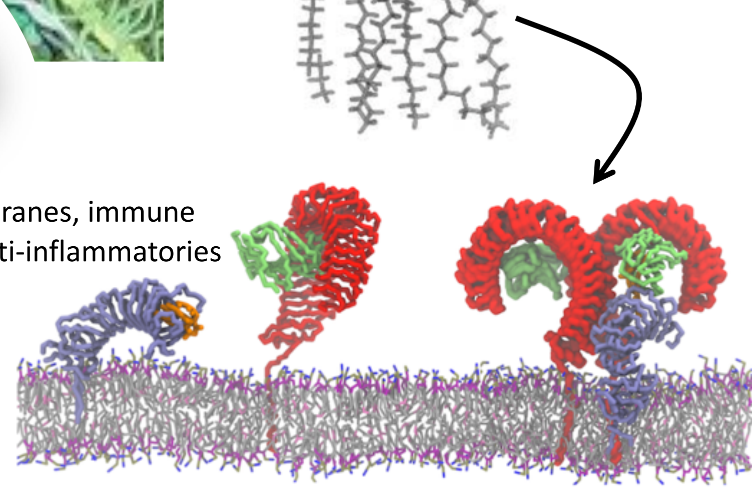




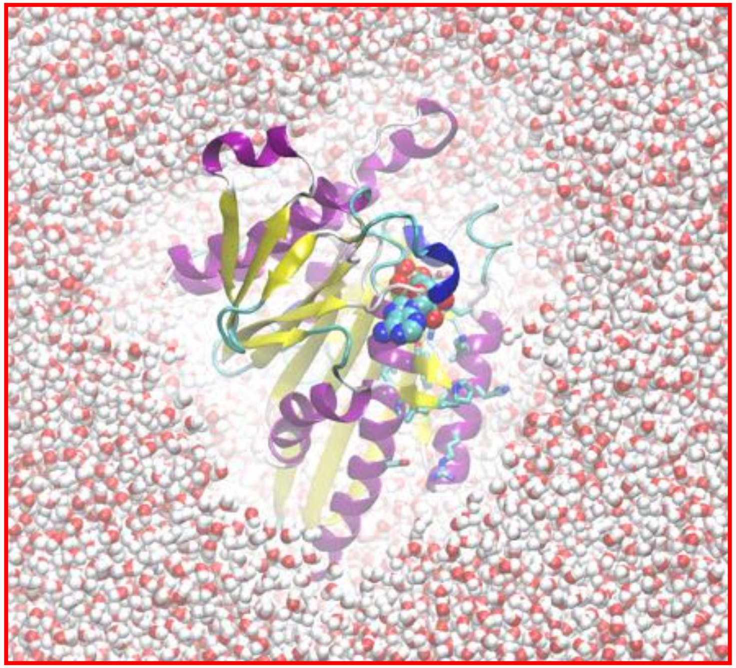
Coronaviruses: spike proteins & LPS – a novel interaction

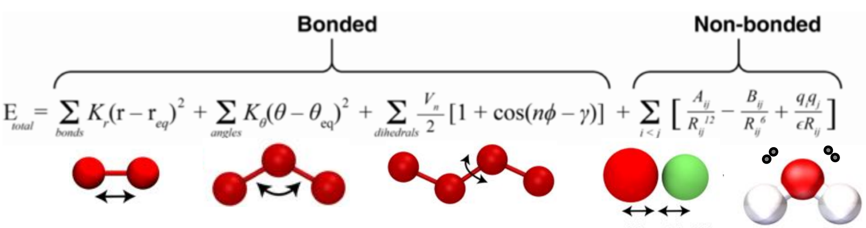


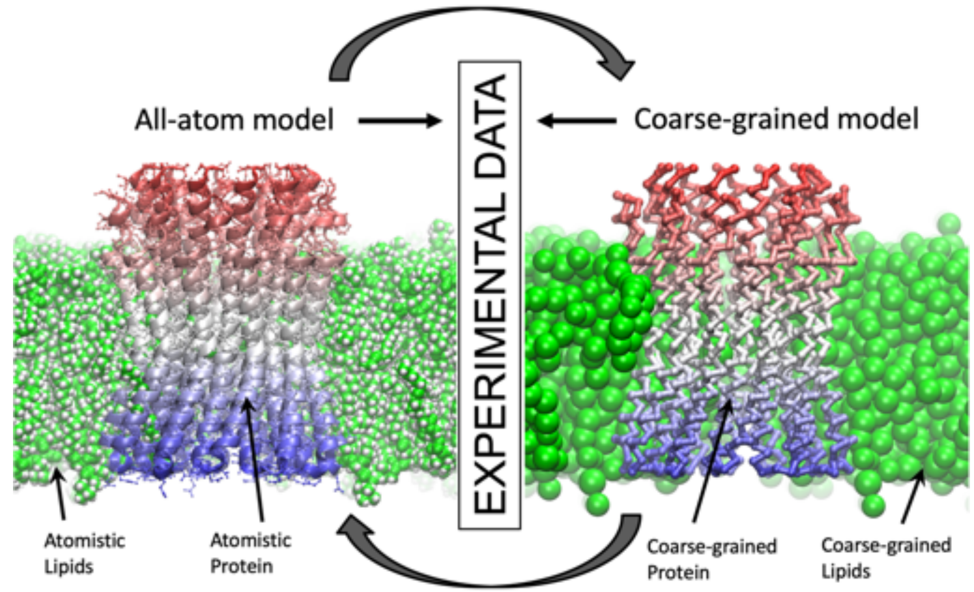
Host cell membranes, immune receptors, & anti-inflammatories



Biomolecular Simulations & Multiscale Approaches



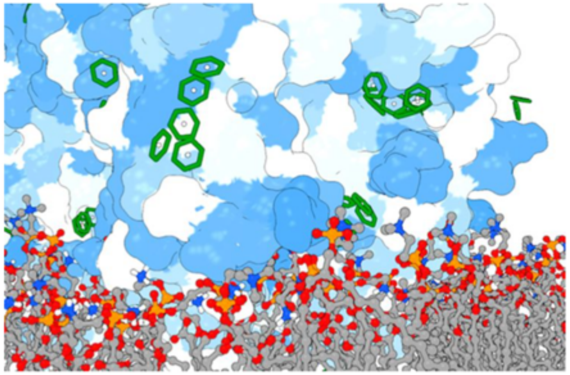




<u>Methods of choice:</u> (1) Molecular simulation.
(2) Multiscale approaches.
(3) Integrative modelling.

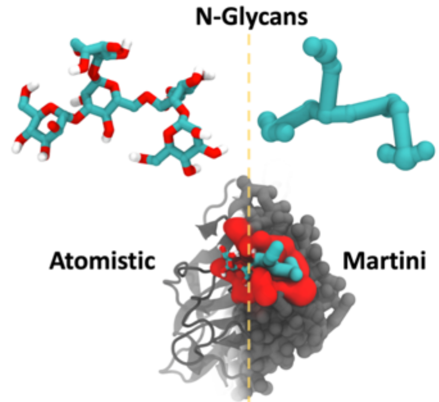
Method Development & Applications in Biology

Cryptic pockets in membrane targets



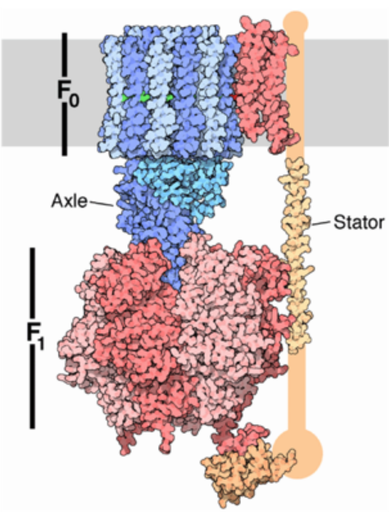
- Benzene mapping for lipid systems – novel druggable pockets discovered in dengue E protein.
  J. Chem. Theory Comput. 16:5948-59 (2020)

Multiscale library for N-glycans in glycoproteins

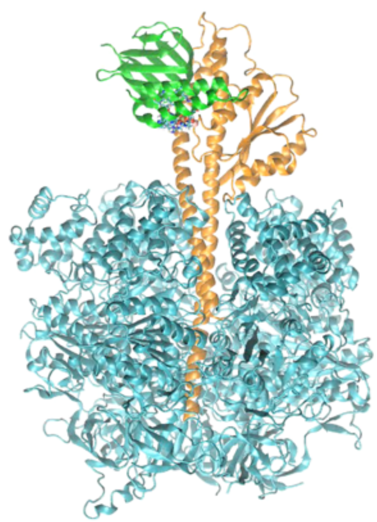


- Multiscale N-glycan library for glycoproteins (with Chandra - BII, NUS, Uni. Manchester)
  J. Chem. Inf. Model. 60:3864-83 (2020)

Membrane-embedded ATP-driven enzymes – sensors & targets



Actin-filament on stalk tagged with fluorescent dye (Noji et al)

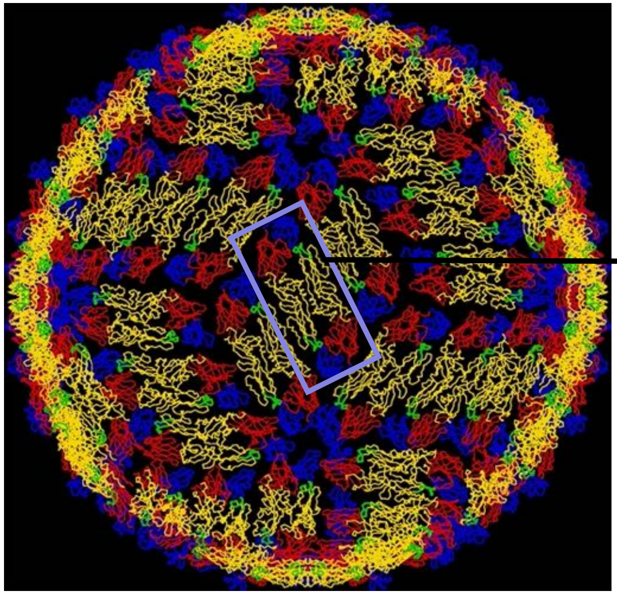


Diagnostic sensors (NUS, Delft Uni.) & antimicrobials (NTU, Dundee) / drugs targeting membrane transporters (Duke-NUS, Dundee), HIV enzymes (with Sam - BII), & flagellar motor machinery (Uni. Warwick).

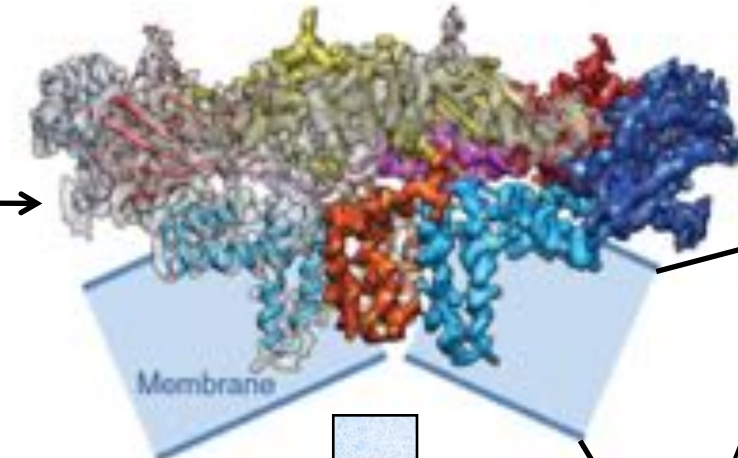
ChemPhysChem. 21(9):916-26 (2020); *ChemBioChem.* 21:3249 (2020); *J. Phys. Chem. B.* 124:7176-83 (2020); *Biochim. Biophys. Acta. Gen.* 1865:129766 (2020); *Biochim. Biophys. Acta. Biomembr.* 1862:183137 (2020); *Molecules* 25:5902 (2020)

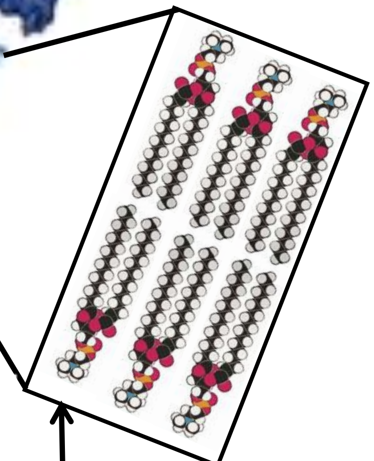
Integrative Modelling of Dengue Viral Envelope

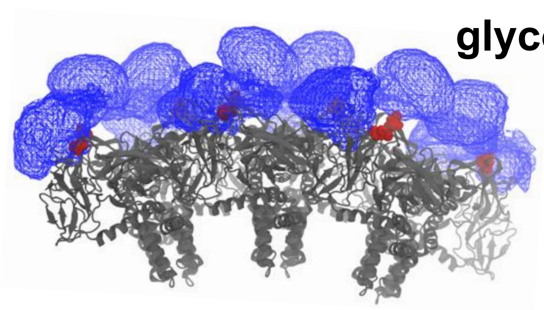
cryo-EM & other structural data



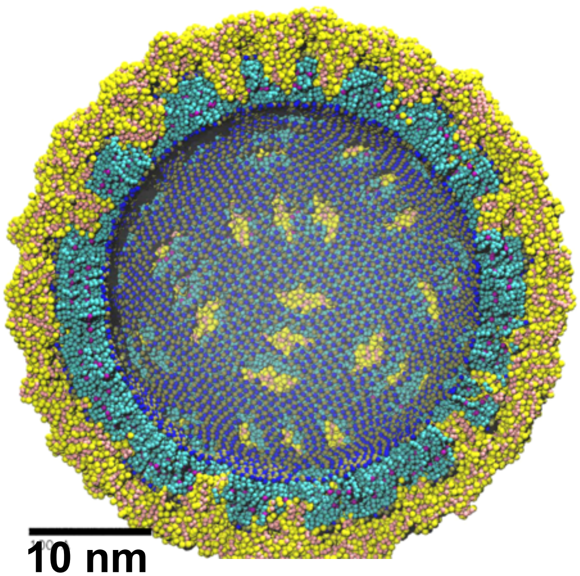
biophysics, e.g. HDX-MS



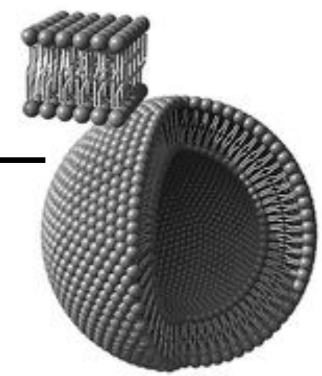




glycomics data



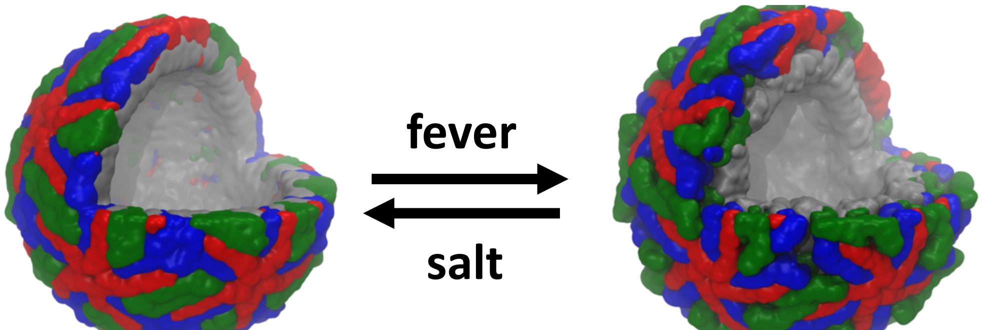
lipidomics data



Structure (2016) 24:1410;
Structure (2019) 27:253;
Structure (2019) 27:618;
Curr Opin Struct Biol (2020) 61:146

Dengue – “Shape-Shifting” in the “Arms Race”

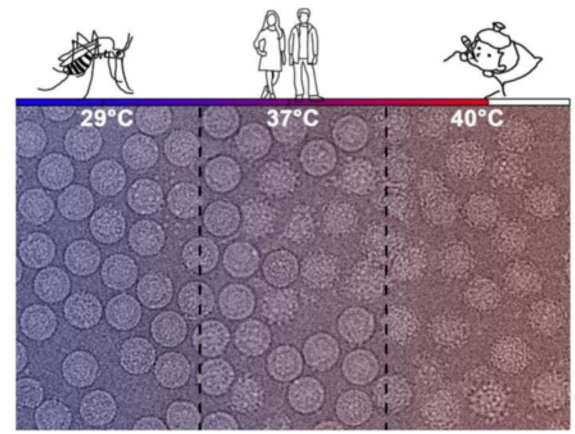
With Duke-NUS, NUS, SIgN, SGH (NRF CRP)



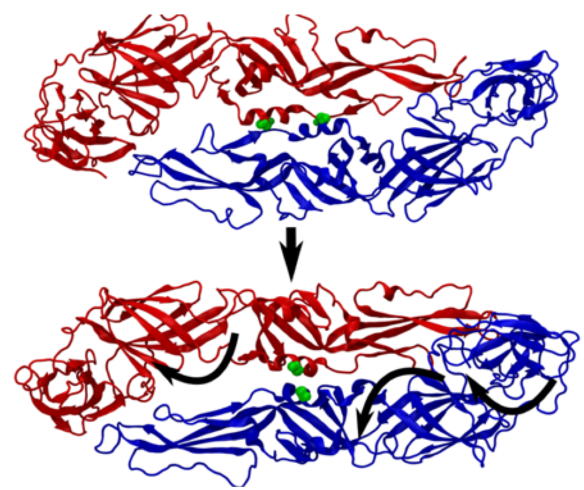
Structure. 27:618-30.e4 (2019)

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

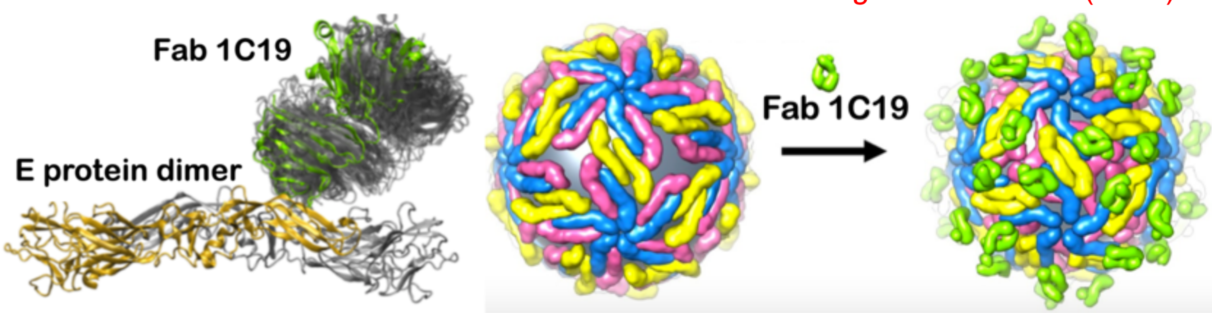
(2) Modelling of clinical vs. lab strains: envelope mutations alter virus morphology at different temperature (e.g. fever). Altered epitopes = resistance to antibodies/vaccines.



PLoS Pathog. 15:e1007996 (2019)



PLoS Pathog. 17:e1009331 (2021)



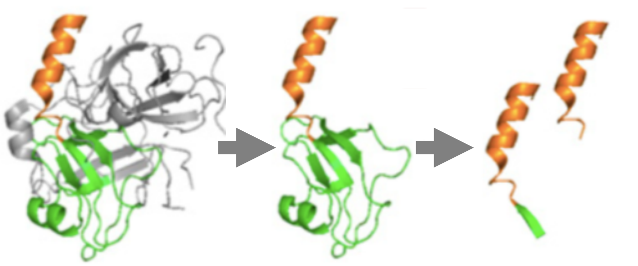
(3) Modelling & biophysics reveal antibody epitope hidden below viral surface – but a sufficiently strong antibody can force the virus to “shape-shift”, exposing it for neutralization.

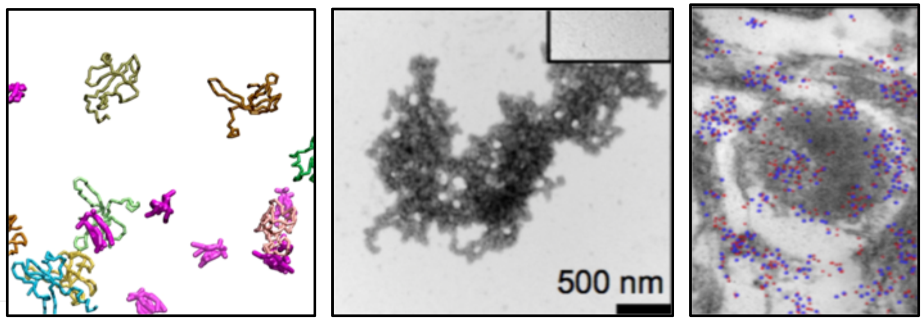
→ Next-gen therapeutics: (a) high-affinity antibodies that (b) recognize diverse morphologies.

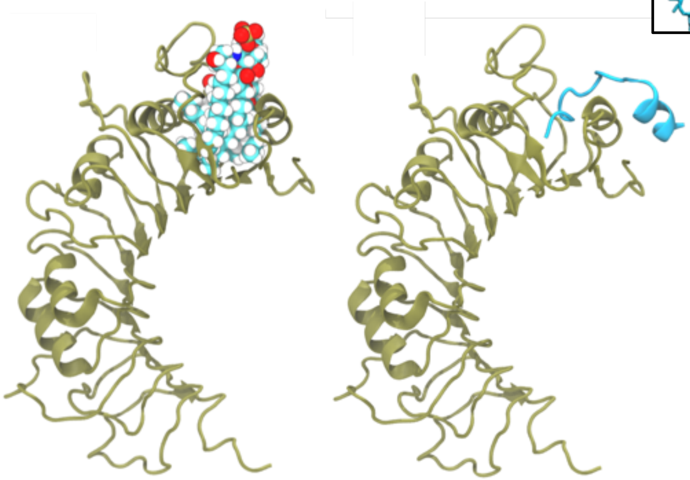
Anti-inflammatory & Antibacterial Peptides (1)

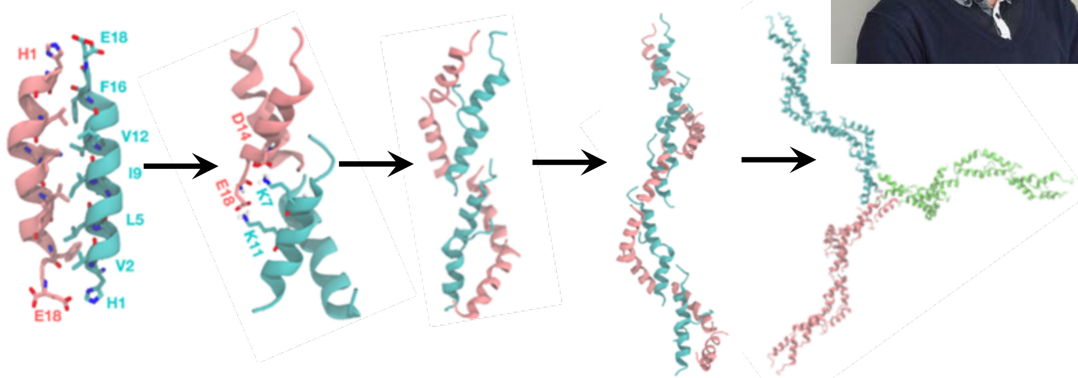
- Growing evidence that “membrane-busting” AMPs / HDPs may in fact be multi-faceted, and/or may target cell-surface receptors & enzymes.

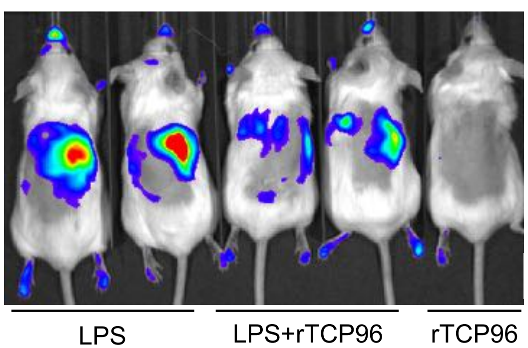
→ Thrombin-derived C-terminal peptides – anti-inflammatory potential.











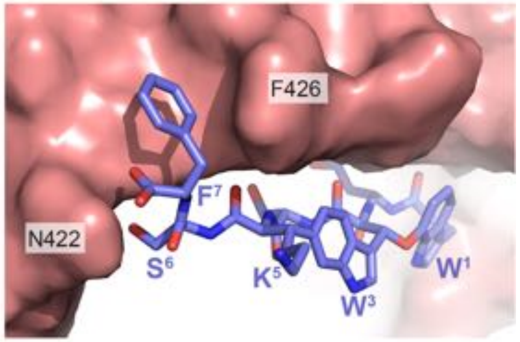
- Receptor binding mode, oligomerization, pH dependence, etc...
- Preclinical development for wound healing with Artur Schmidtchen, Jitka Petrlova, Anna Petruk (Lund University / In2cure), Rathi Saravanan (NTU / LKCMed)

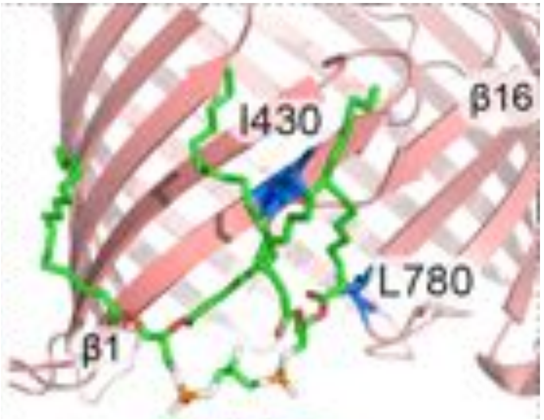
J Biol Chem (2020) 295:3417; *Biomolecules* (2020) 10:1572; *Pharmacol Res* (2019) 147:104372; *Nat Commun* (2018) 9:2762; *Structure* (2018) 26:1151; *BBA Biomembr* (2018) 1860:2374; *PNAS* (2017) 114:E4213

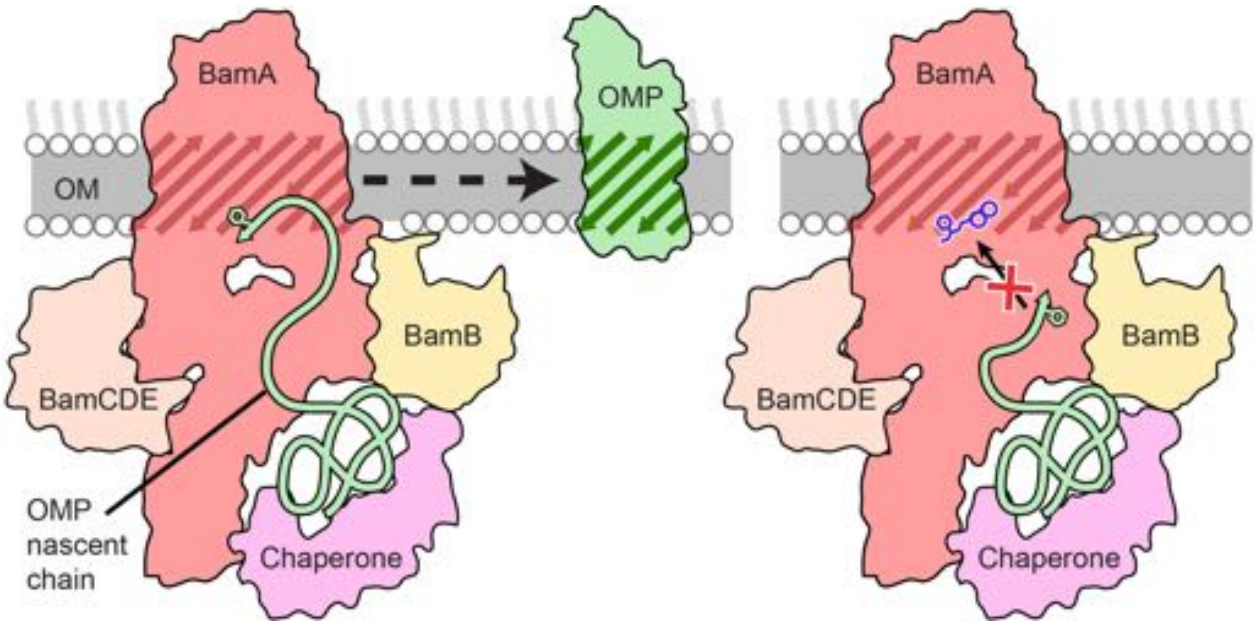
Anti-inflammatory & Antibacterial Peptides (2)

- Growing evidence that "membrane-busting" AMPs / HDPs may in fact be multi-faceted, and/or may target cell-surface receptors & enzymes.

→ Antibiotics targeting Gram-negative bacteria: (last new class, quinolones >50 years ago).





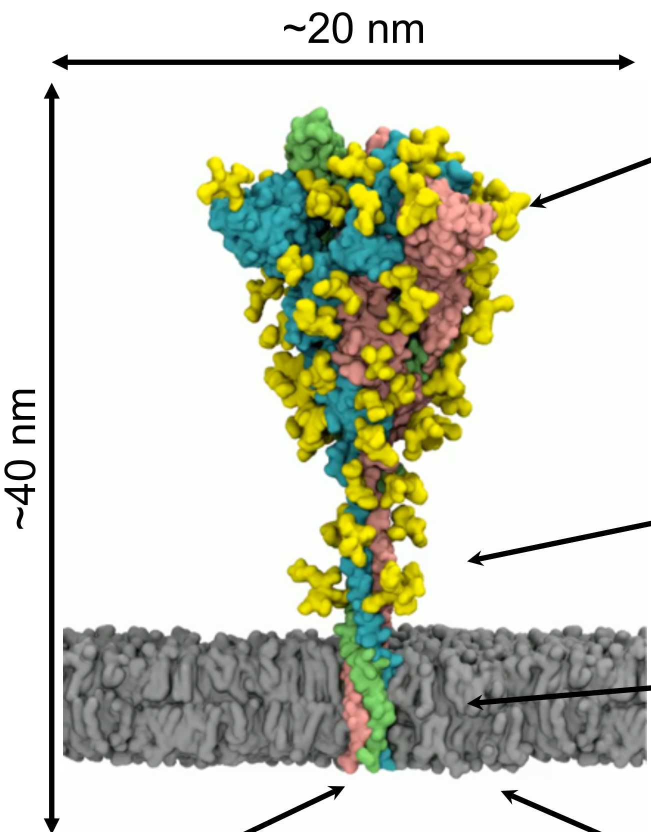


The antibiotic darobactin mimics a β-strand to inhibit outer membrane insertase. *Nature.* Epub, April 2021

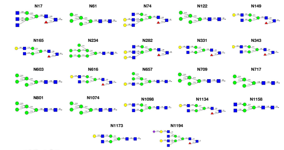
- Darobactin β-hairpin peptide binds to OMP insertase (BAM complex), blocking native substrates.
- Replaces cardiolipin molecule: membrane environment is an unusual "extended binding pocket".
- Interaction mediated via backbone: uniquely robust against potential resistance mutations.
- Jan, with Sebastian Hiller (Uni. Basel) & Polyphor; other scaffolds under investigation…

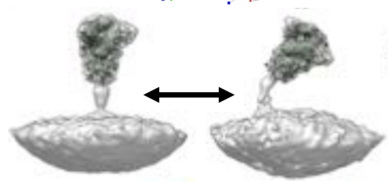
Understanding Structure-Function of SARS-CoV-2 Spike

- **Firdaus, Lorena, Raghu, Aishwary, Jan, Alex**
- **Ganesh Anand (NUS, Penn State), Artur Schmidtchen (Lund), Max Crispin (Soton)**
- **BII collab's - Igor, Sebastian**



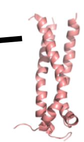
66 N-linked glycans





Cryo-ET (Ke et al, 2020)

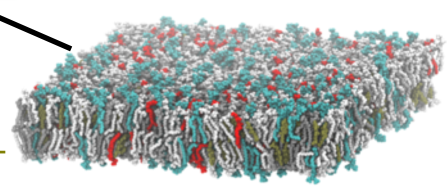
SARS-CoV HR2 domain

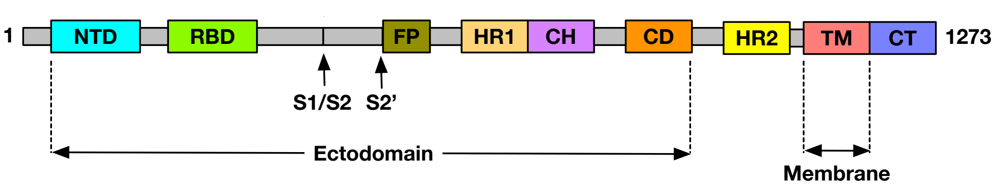


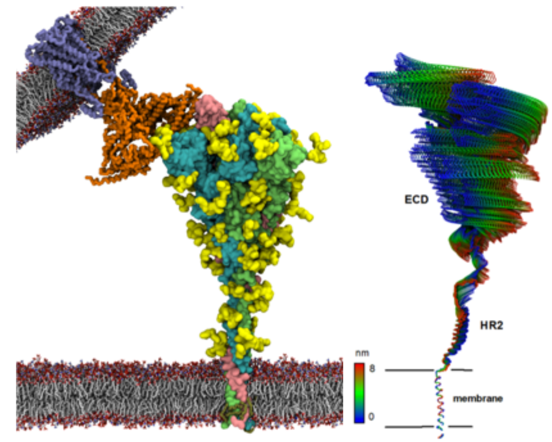
HIV-1 gp41 TM trimer (GxxxG)

C-terminal Cys palmitoylation

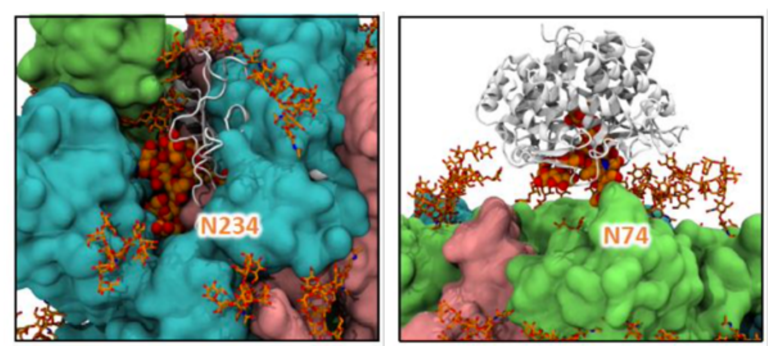
Golgi-like membrane: 47% PC, 20% PE, 11% PI, 7% PS and 15% CHL







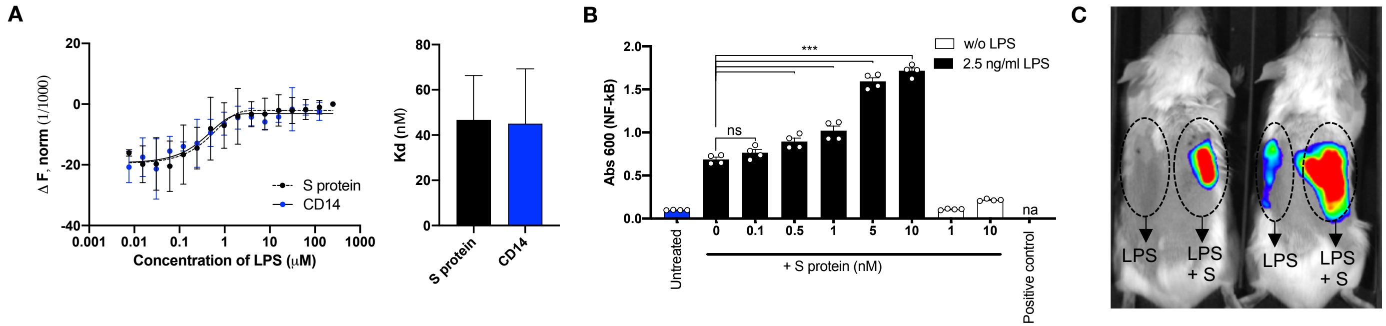
SARS-CoV-2 S protein:ACE2 interaction reveals novel allosteric targets. *Elife.* 17:e1009331 (2021)

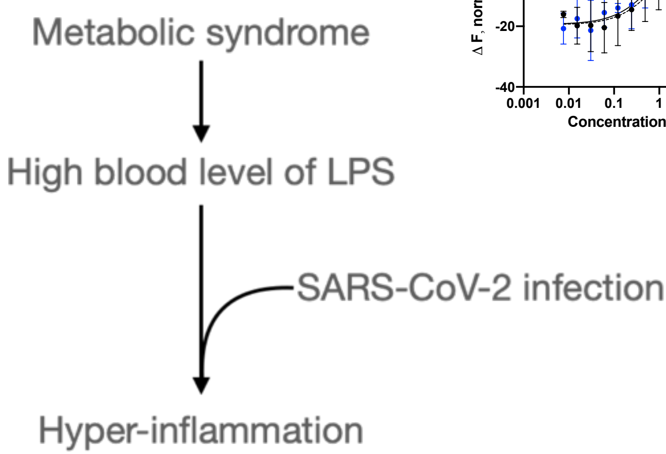


Site-specific steric control of SARS-CoV-2 spike glycosylation. *bioRxiv* (doi: 10.1101/2021.03.08.433764)

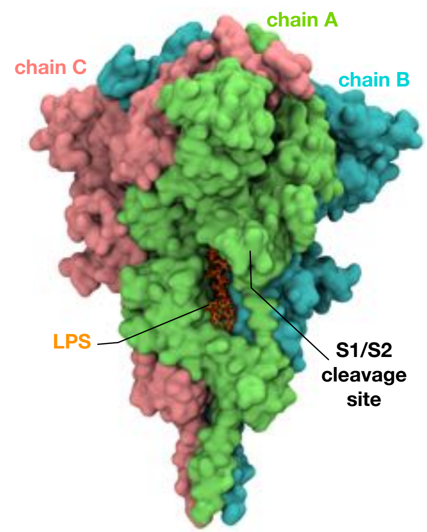
Defining a Novel Interaction: SARS-CoV-2 Spike / LPS

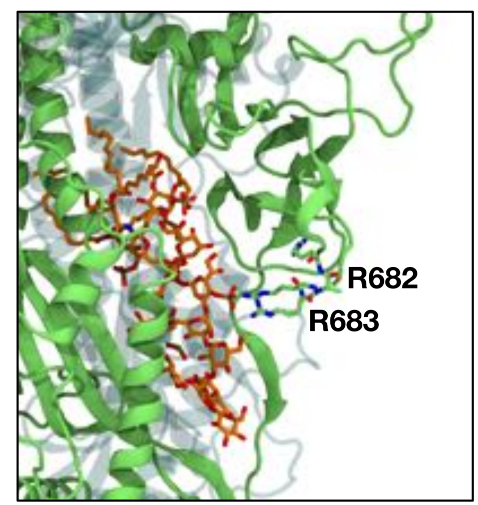
(A) Spike protein:LPS affinity ≡ CD14 (microscale thermophoresis).
(B) Spike protein boosts NF-κB response to LPS.
(C) Inflammation in NF-κB reporter mice.





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

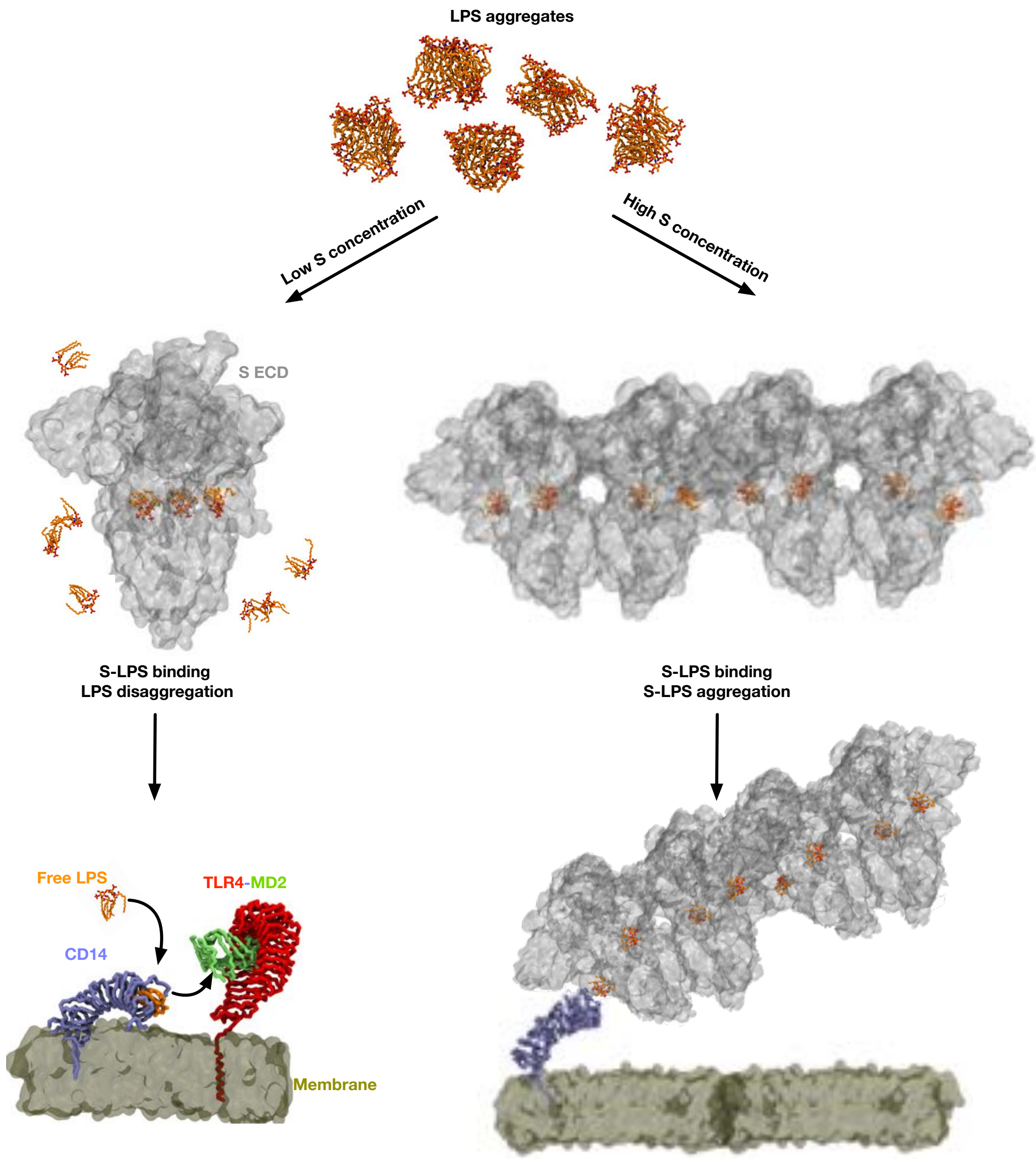




- Severe COVID19 common in those with metabolic syndrome (diabetes, obesity etc.) linked with raised LPS levels
- Metabolic syndrome predisposes patients to severe COVID19: Hyper-inflammation in lungs → respiratory failure, sepsis & death.
- **Multiple recent papers: (i) raised LPS/intestinal permeability & sepsis; (ii) "direct" activation of TLR4 by spike...**

- Conserved LPS site detected via docking, solvent mapping.
- **Validation and follow-up studies underway.**

Viruses vs. Bacteria vs. Host…



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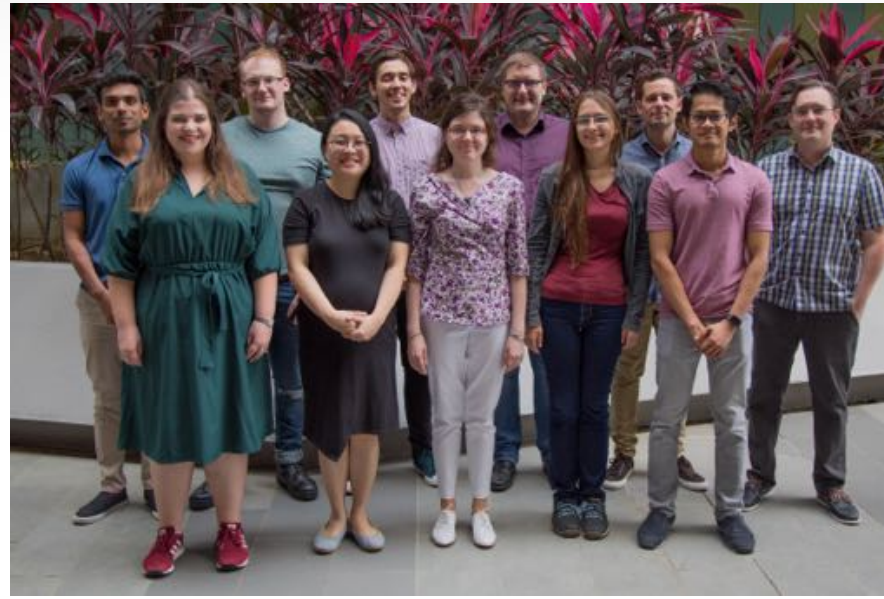

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NRF CRP19 (S$3.7M) – Flavivirus-Antibody Epitope Discovery

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