CREATING GROWTH, ENHANCING LIVES

Computational Chemical Biology and Fragment-based Design

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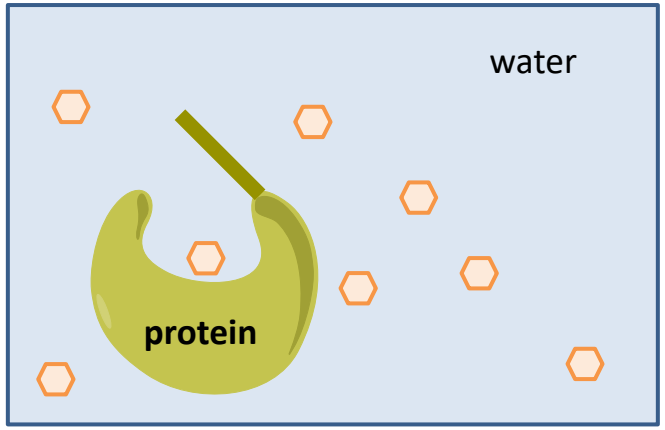
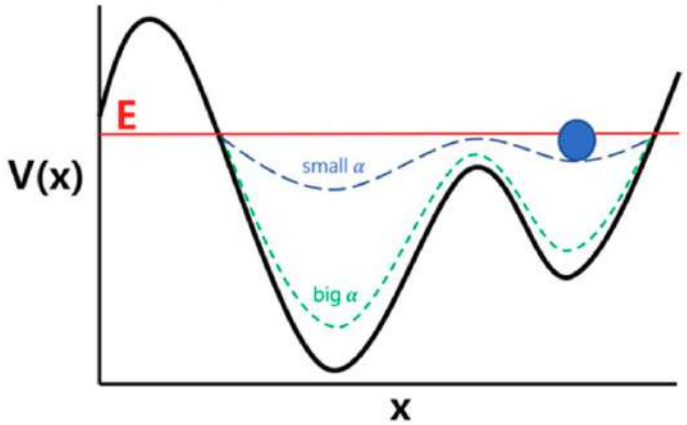
From 2022…
accelerated ligand-mapping molecular dynamics (aLMMD) detects cryptic binding sites

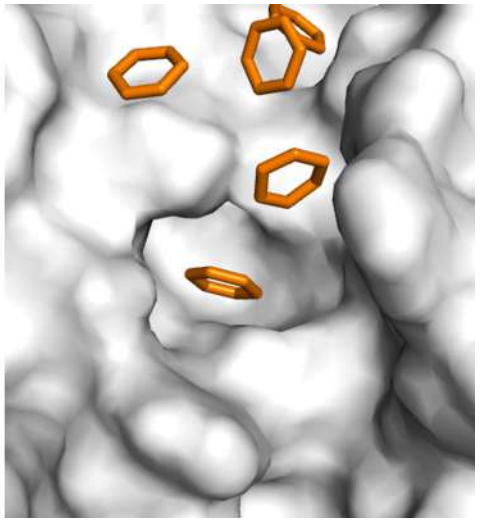


ligand-mapping molecular dynamics
(LMMD)

+



accelerated molecular dynamics
(aMD)

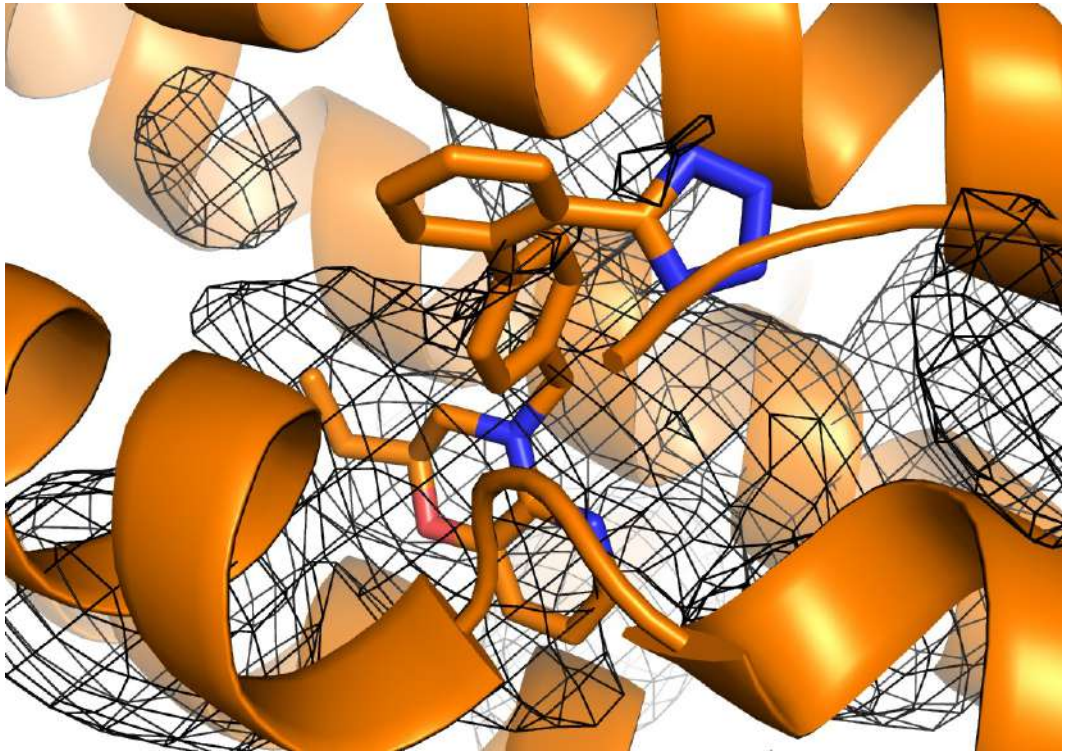


aLMMD
- 20 × 200 ns
- 0.2 M benzenes

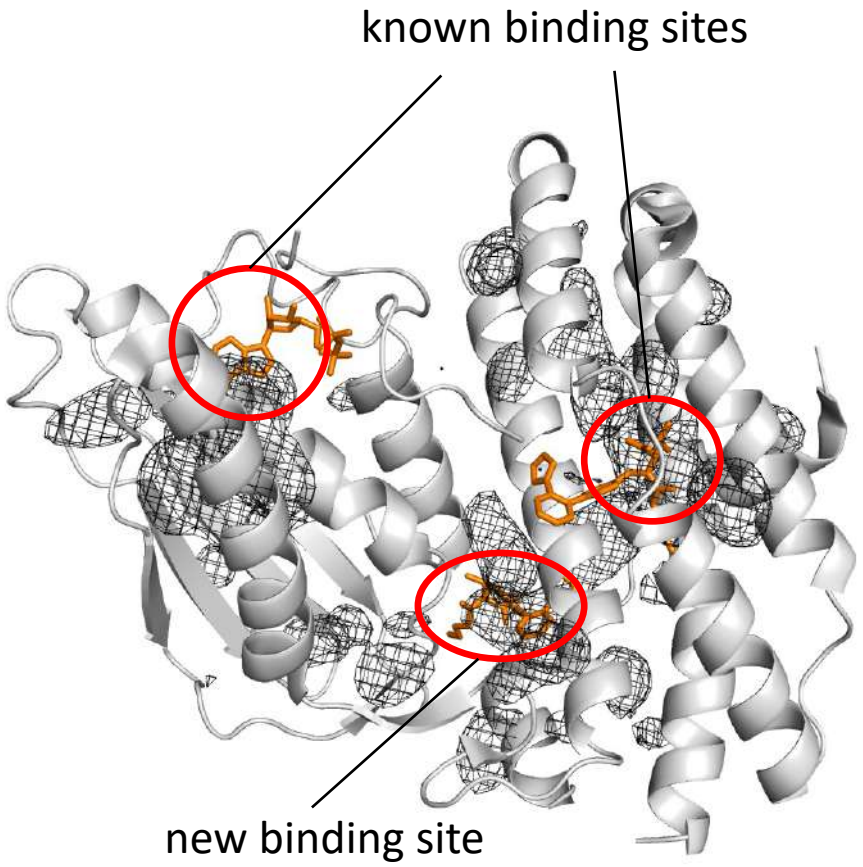
Justin

Ng JT & Tan YS. *J Chem Theory Comput*. 2022, 8, 1969-1981

Applying aLMMD to a drug target



Expanded cryptic pocket predicted by aLMMD and validated by new X-ray crystal structures



aLMMD predicted the two known binding sites and a new binding site

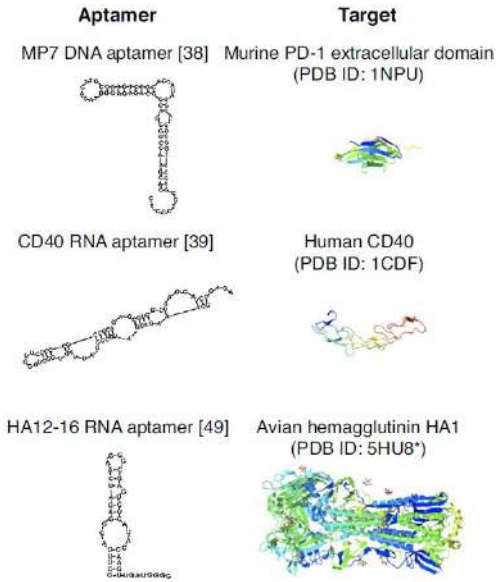
Weiping (IMCB)

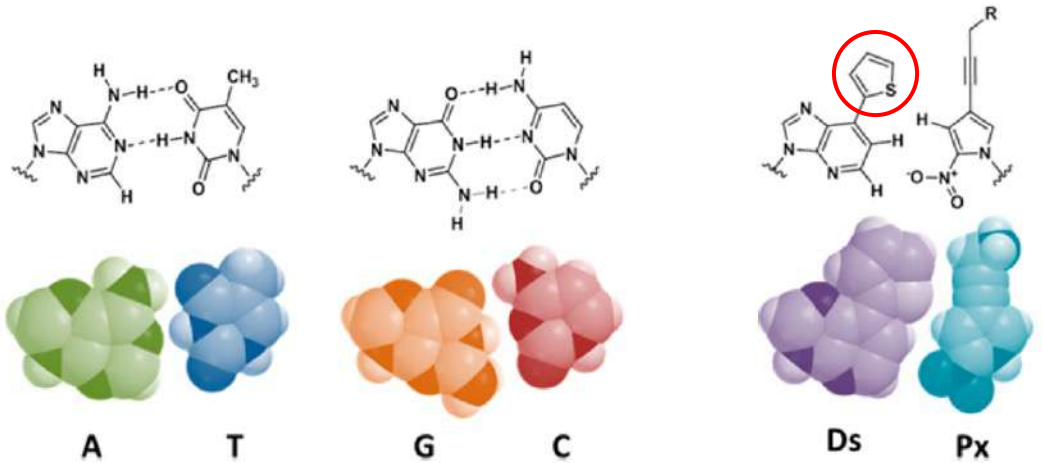
Qunxiang (IMCB)

Funded by STDR Pre-Pilot

Structure-based design of DNA aptamers

- Aptamers are single-stranded DNA or RNA molecules with unique tertiary structures
- They have limited chemical diversity because there are only 4 natural nucleotides available for selection
- Unnatural nucleotides could increase the functionality of aptamers by providing additional chemical and structural diversity beyond that provided by natural nucleotides
- Genetic alphabet expanded with development of Ds–Px paired bases
- Ds is highly hydrophobic and can strengthen interactions with hydrophobic pockets



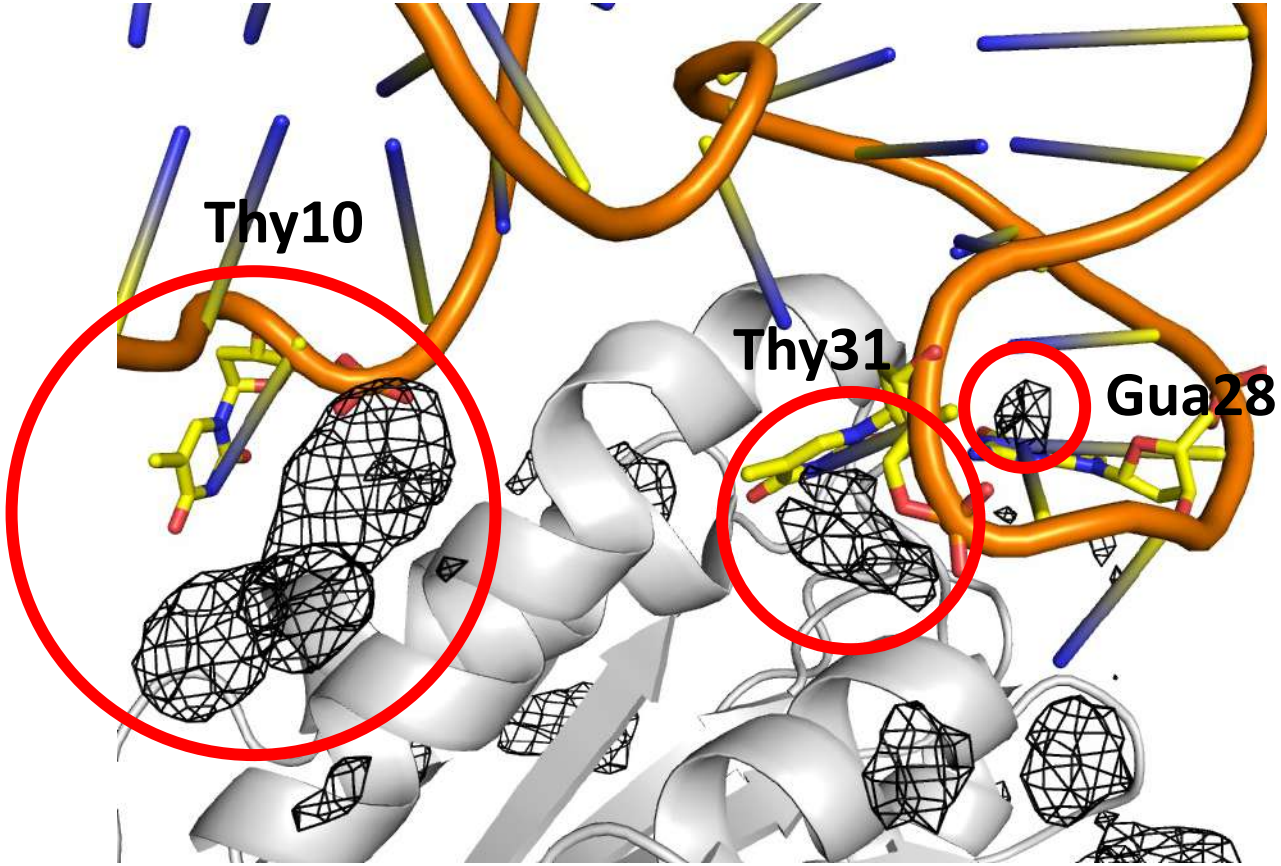


Ichiro Hirao
(formerly IBB)

Kimoto M et al. *Nat Biotechnol*, 2013, 31, 453-457

LMMD simulations identify three hydrophobic binding sites near aptamer binding interface with vWF

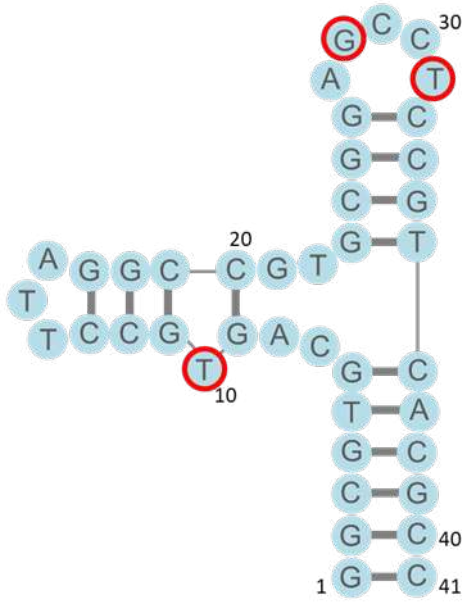
- von Willebrand factor (vWF) is a protein found in blood plasma that facilitates blood clotting
- As the Ds nucleotide is highly hydrophobic, benzenes were used in LMMD simulations to identify putative Ds interaction sites on A1 domain of vWF



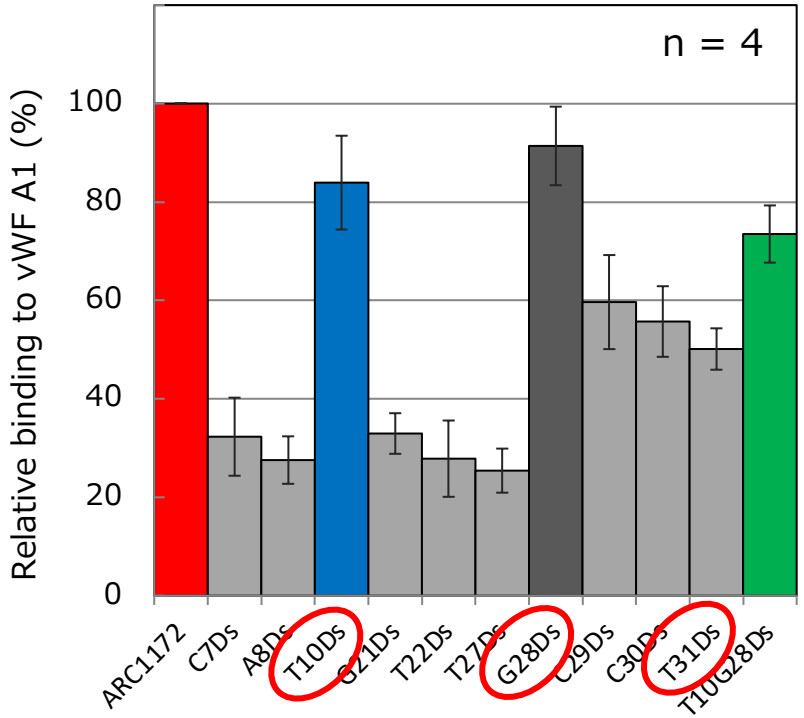
Benzene occupancy map of A1 domain of vWF

Ds substitutions at positions 10, 28 and 31 in aptamer ARC1172

- Ds substitutions previously introduced to ARC1172 at positions 10, 28 and 31
- Thy10Ds and Gua28Ds substitutions were tolerated (≈85% and 90% of original)
- Thy31Ds substitution led to significant loss of binding to vWF (≈50% of original)



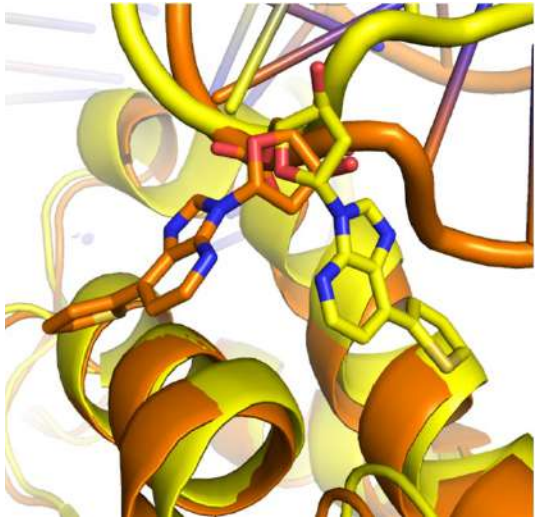
Ds substitutions in ARC1172



Kimoto M et al. *Phil Trans R Soc B.* 2023, 378, 20220031

Molecular modelling of Ds-substituted ARC1172 derivatives

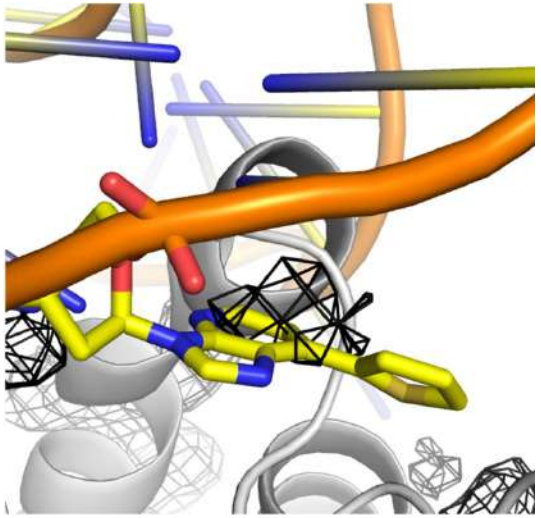
Ds10-ARC1172



MD snapshots showing alternative conformations of Ds10

(ΔG = -192.7 ± 4.3 kcal/mol)

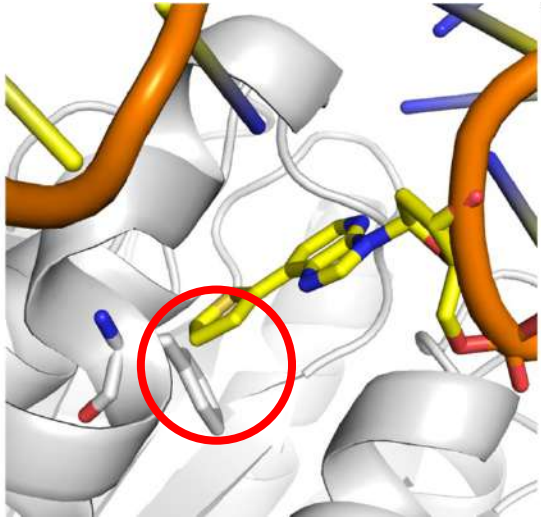
Ds28-ARC1172



Ds28 modelled onto crystal structure 3HXQ. Thiophene ring of Ds28 does not overlap with benzene map densities.

(ΔG = -193.9 ± 3.8 kcal/mol)

Ds31-ARC1172



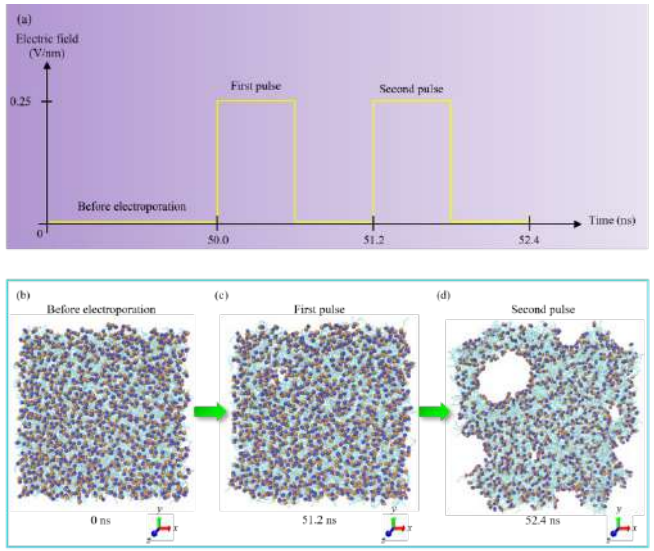
Ds31 modelled onto crystal structure 3HXQ. Thiophene ring of Ds31 clashes with Phe1397.

- Ds10 and Ds28 derivatives remained bound to vWF through MD simulations
- Binding free energies are not significantly different from ARC1172 (-188.3 ± 3.1 kcal/mol)

Kimoto M et al. *Phil Trans R Soc B.* 2023, 378, 20220031

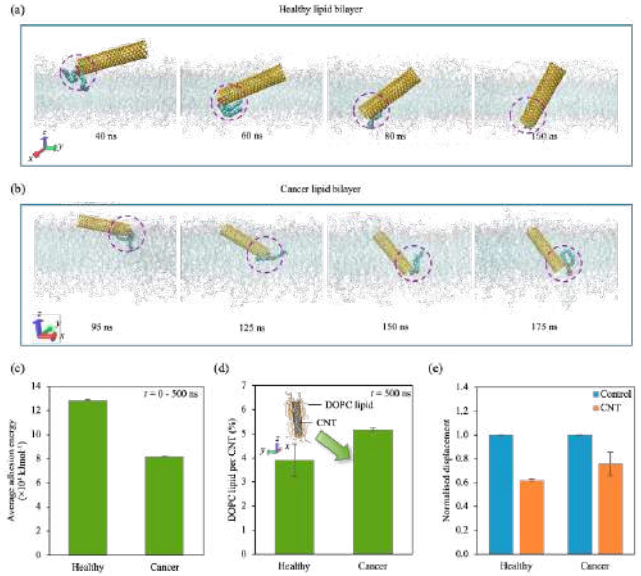
Bioelectronics

Effect of electric pulses on membrane permeabilisation



Second electric pulse induces higher degree of membrane permeabilisation

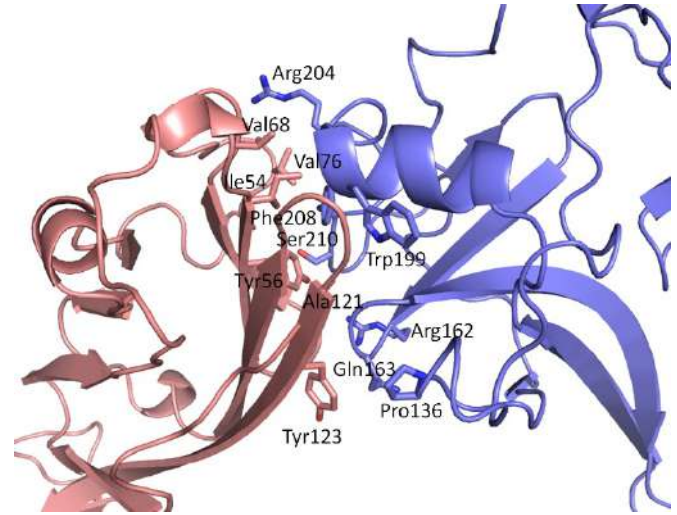
Effect of carbon nanotubes (CNTs) on electrical conductivity of cancer cells



- Larger increase in current observed for cancer cells than healthy cells when they are perturbed by CNTs
- MD simulations suggest CNTs rigidify cancer cell membranes less than healthy cell membranes -> more CNTs can insert into cancer cell membranes

Lee D et al. *Nanoscale*, 2022, 14, 7934-7942
Chan SSY et al. ACS Omega, 2022, 7, 18459-18470
Meivita MP et al. *Pharmaceutics*, 2023, 15, 106

Electrothermal therapy for cancer mediated by M13 bacteriophage

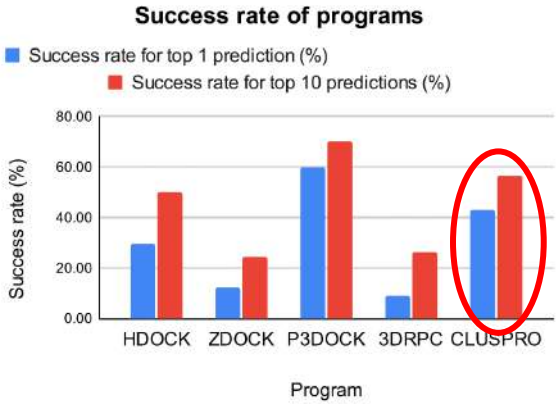


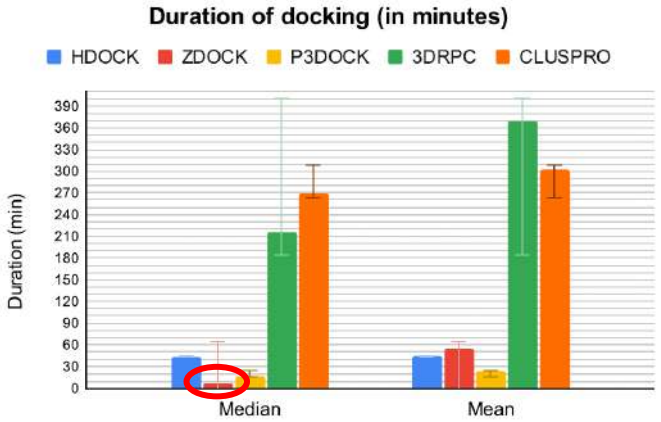
- MD simulations suggest **M13 coat protein** binds to **PD-L1**, a protein overexpressed on the surface of cancer cells
- MoS_2 conjugated to M13 phage can selectively increase conductivity of cancer cells, allowing them to be killed by electrothermal therapy

Desmond Loke (SUTD)

Interns' research

Evaluation of protein-RNA docking methods

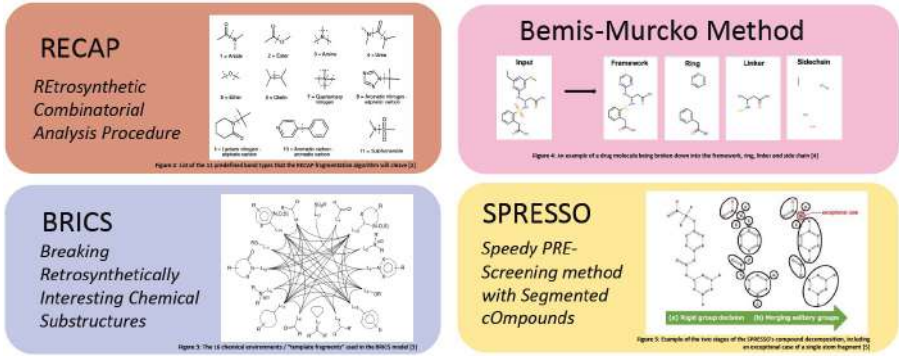




- P3DOCK stopped working halfway through the project and so number of test cases was small
- Accuracy: **ClusPro** > HDOCK > ZDOCK > 3dRPC
- Speed: **ZDOCK** > HDOCK > ClusPro ≈ 3dRPC

Clara Tan, Harishiga Ilangovan and Lim Yu Jing (SRP) obtained Silver award at the SSEF.

Evaluation of different fragmentation methods for fragment database preparation



SPRESSO was the best fragmentation method as it generates fragments that:

- are highly unique
- follow the "rule of three" to the greatest extent

Hayley Lim (H3) obtained Bronze award at the SSEF.

Acknowledgements

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Harishiga Ilangovan (SRP)
Lim Yu Jing (SRP)
Hayley Lim (H3)

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