CREATING GROWTH, ENHANCING LIVES

Bioinformatics Institute
BII

Computational Chemical Biology and Fragment-based Design

Dr. Tan Yaw Sing

Assistant Principal Investigator

Biomolecular Structure to Mechanism Division

tanys@bii.a-star.edu.sg

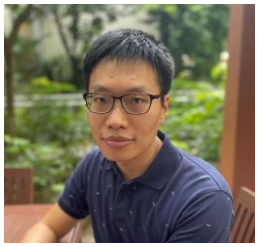
BII Conference 2022

29th March 2022

The year in summary (Apr 21 – Mar 22)

2 staff

Dr Justin Ng



Dr Meng Zhenyu

4 interns

Charlene Kok (University of Glasgow)
Development of small-molecule inhibitors of the YAP-TEAD protein-protein interaction by in silico fragment screening
Ishaan Bharadwaj (Mallya Aditi International School)
Assessing the druggability of proteins in SARS-CoV-2
William Guo Shi Yu (University of Cambridge, A*STAR scholar)
Characterising the interaction between PD-1 and PD-L1
M K Rahim (Nanyang Technological University)
Mechanisms of type2 diabetes-associated coding variants

6 publications

Ng JT & Tan YS. *J Chem Theory Comput*. doi: 10.1021/acs.jctc.1c01177 (2022)

Chan SS, Lee D, Meivita MP, Li L, Tan YS, Bajalovic N, Loke DK. *Nanoscale Adv*. 3, 6974-6983 (2021)

Amirruddin NS, Tan WX, Tan YS, Gardner DS, Bee YM, Verma CS, Hoon S, Lee KO, Teo AKK. *Diabetologia.* 64, 2534-2549 (2021)

Holdbrook DA, Marzinek JK, Boncel S, Boags A, Tan YS, Huber RG, Verma CS, Bond PJ. *J.Colloid Interface Sci*. 604, 670-679 (2021)

Vu QN, Young R, Sudhakar HK, Gao T, Huang T, Tan YS, Lau YH. *RSC Med Chem*. 12, 887-901 (2021)

Low BSJ, Lim CS, Ding SSL, Tan YS, Ng NHJ, Krishnan VG, Ang SF, Neo CWY, Verma CS, Hoon S, Lim SC, Tai ES, Teo AKK. *Nat. Commun.* 12, 3133 (2021)

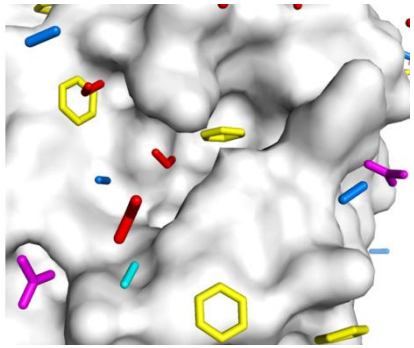
Fragment-based design

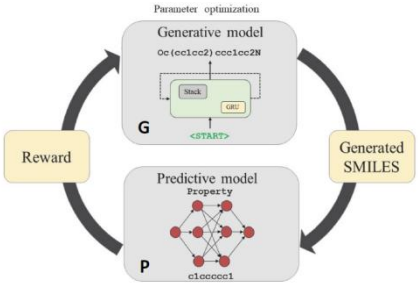
fragment-based design

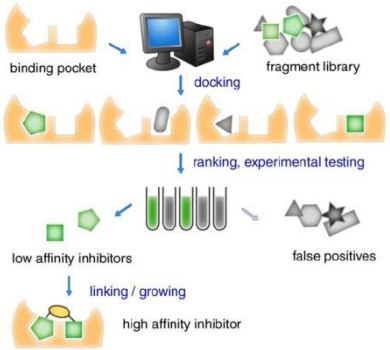
binding site detection

AI-guided drug design

fragment docking







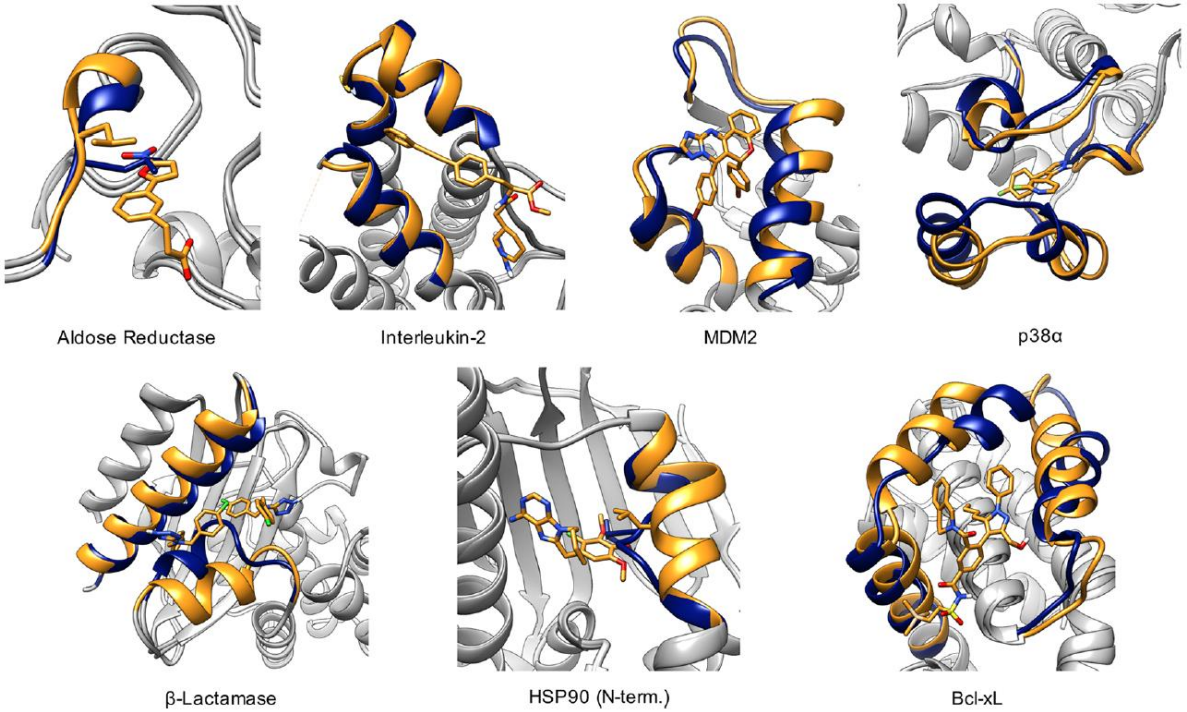
Bioinformatics Institute
BII

Accelerated LMMD for the detection of recalcitrant cryptic pockets and occluded binding sites

Justin

Cryptic binding pockets

- Cryptic binding pockets do not appear unless they are bound to a ligand
- Require movement of protein side chain/s or backbone to expose



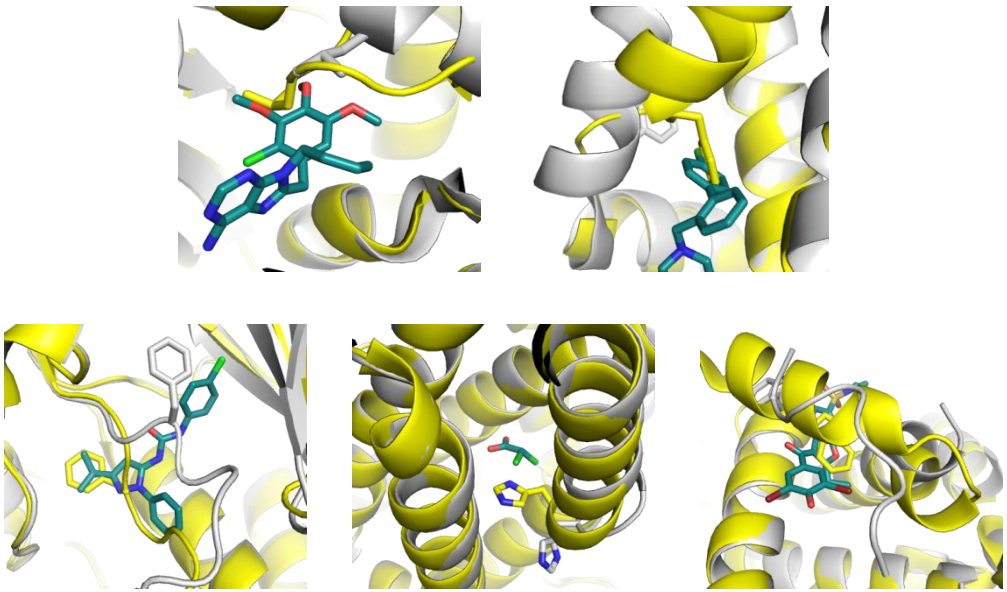
cryptic pockets in proteins
blue=**unbound**, orange=**bound**

Schmidt D et al. *J Chem Theory Comput*, 2019, 15, 3331-3343

“Challenging” binding pockets

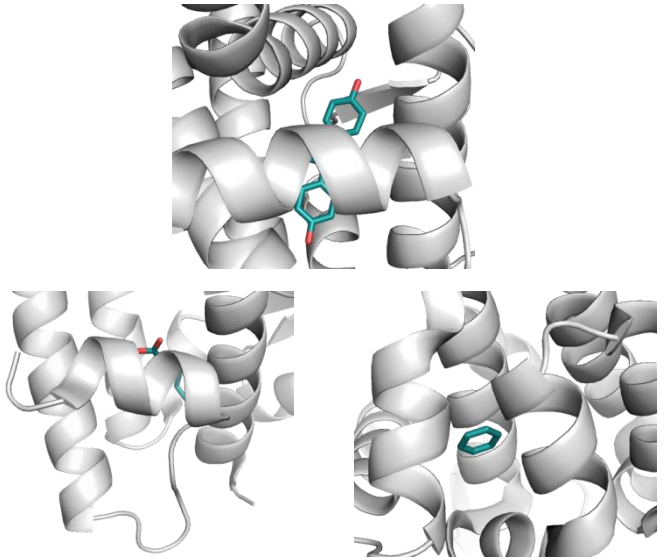
Recalcitrant cryptic pockets

- absent in unbound protein structures
- deeply buried
- require large movements of protein backbone to open

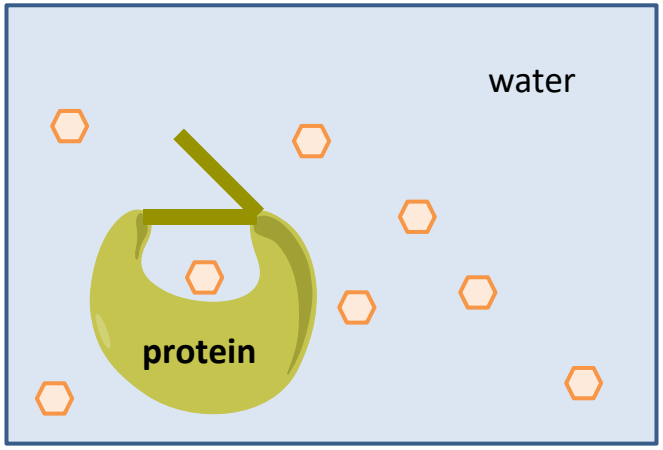


Occluded binding sites

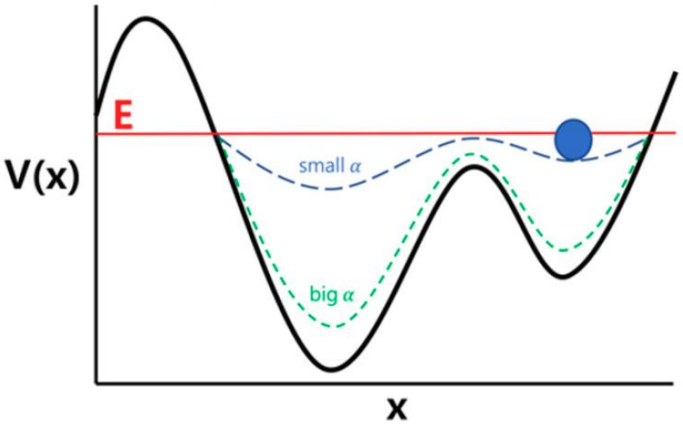
- pre-exist in unbound protein
- not accessible to the solvent



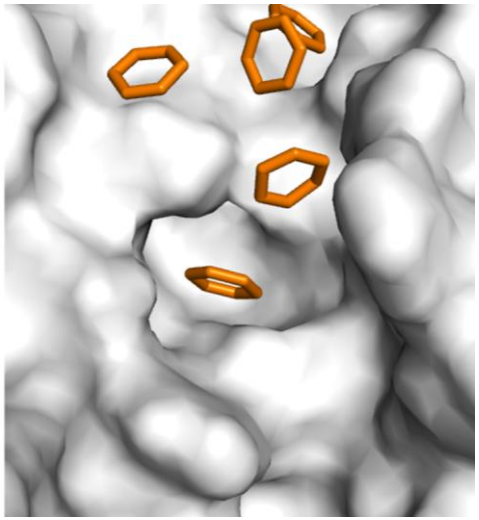
Accelerated ligand-mapping molecular dynamics (aLMMD)



ligand-mapping molecular dynamics
(LMMD)

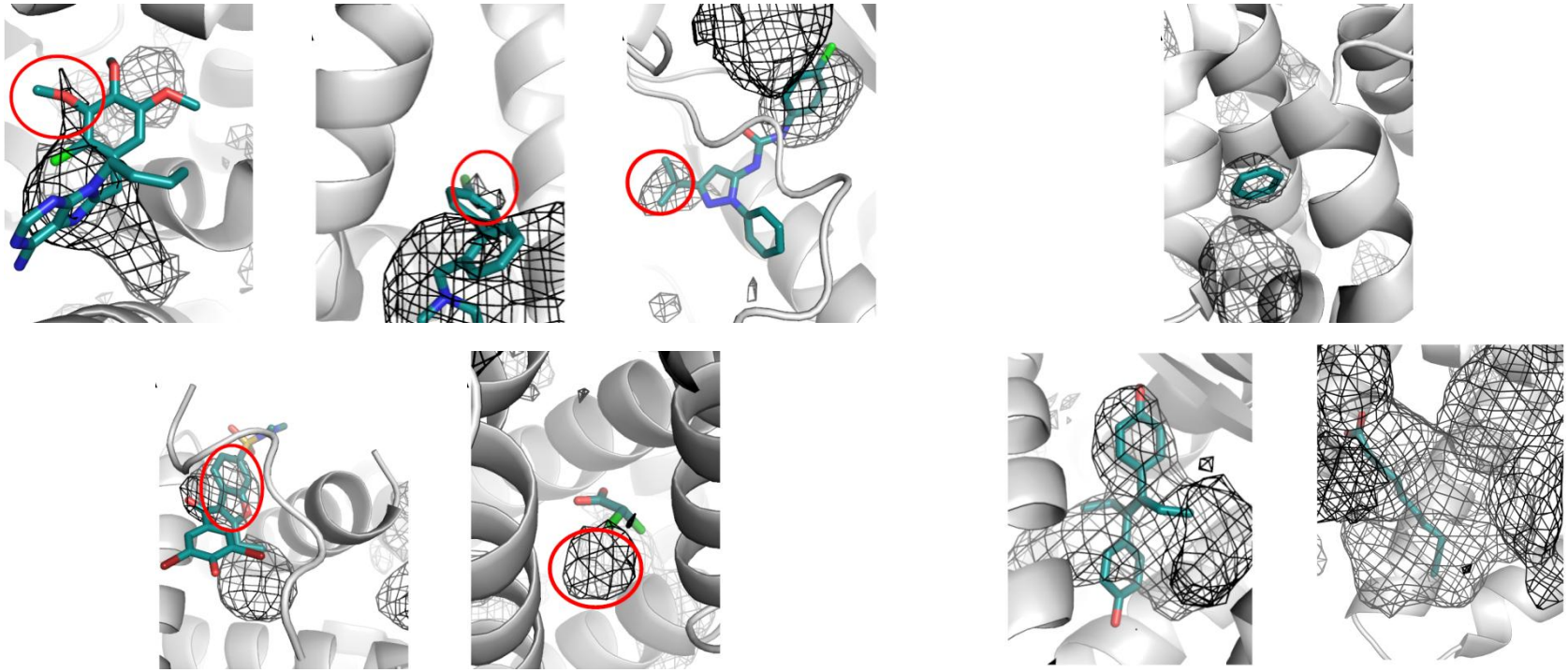


accelerated molecular dynamics
(aMD)



aLMMD
- 20 × 200 ns
- 0.2 M benzenes

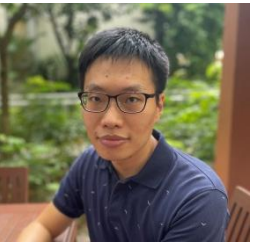
Accelerated ligand-mapping molecular dynamics (aLMMD)



- LMMD was able to map only one of the eight “challenging” pockets
- aLMMD was able to map all of the cryptic pockets and occluded binding sites in the test proteins
- aLMMD is a valuable tool for structure-based drug discovery

Ng JT & Tan YS. *J Chem Theory Comput*. 2022, doi: 10.1021/acs.jctc.1c01177

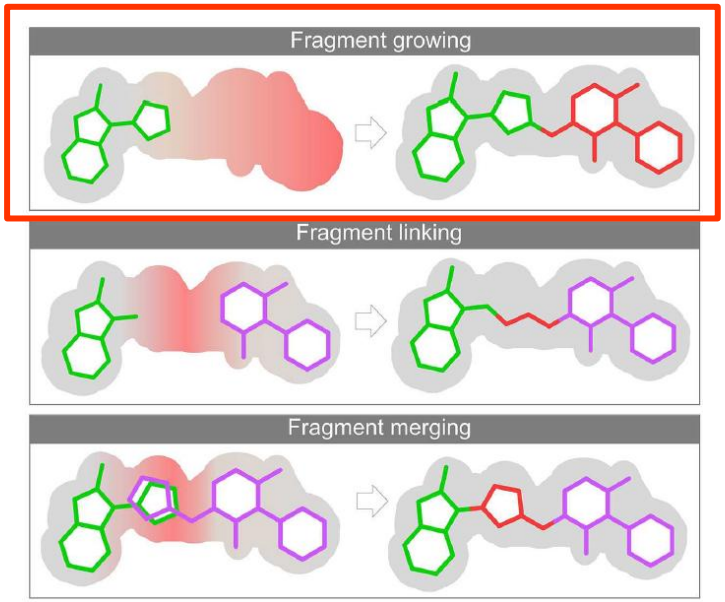
AI-guided fragment-based drug design

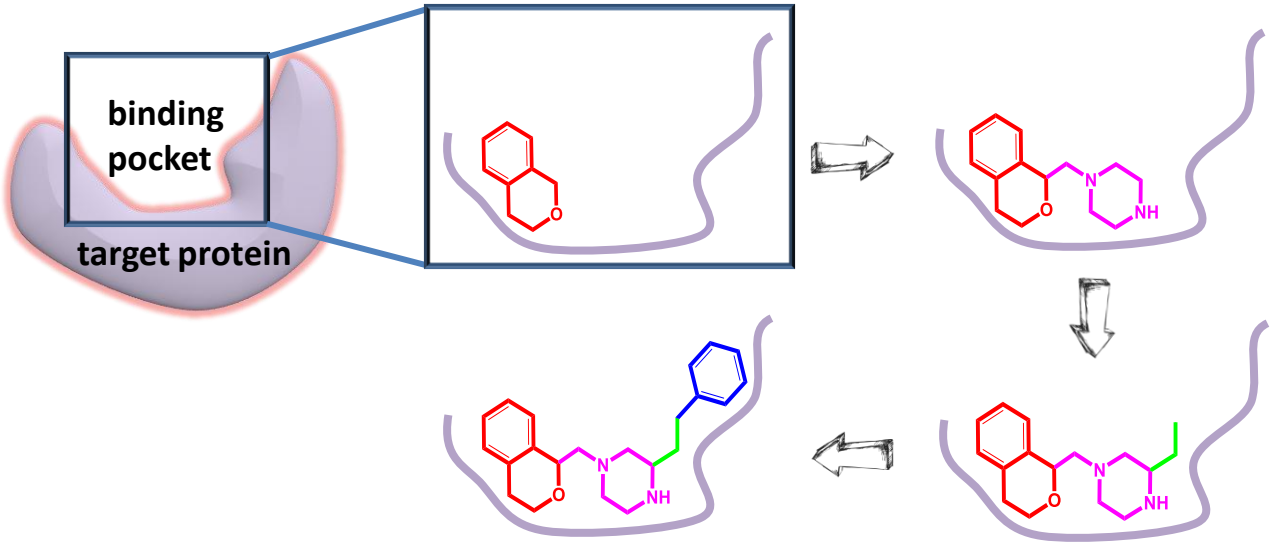


Zhenyu

In collaboration with Hwee Kuan and Chandra

Fragment-based drug discovery

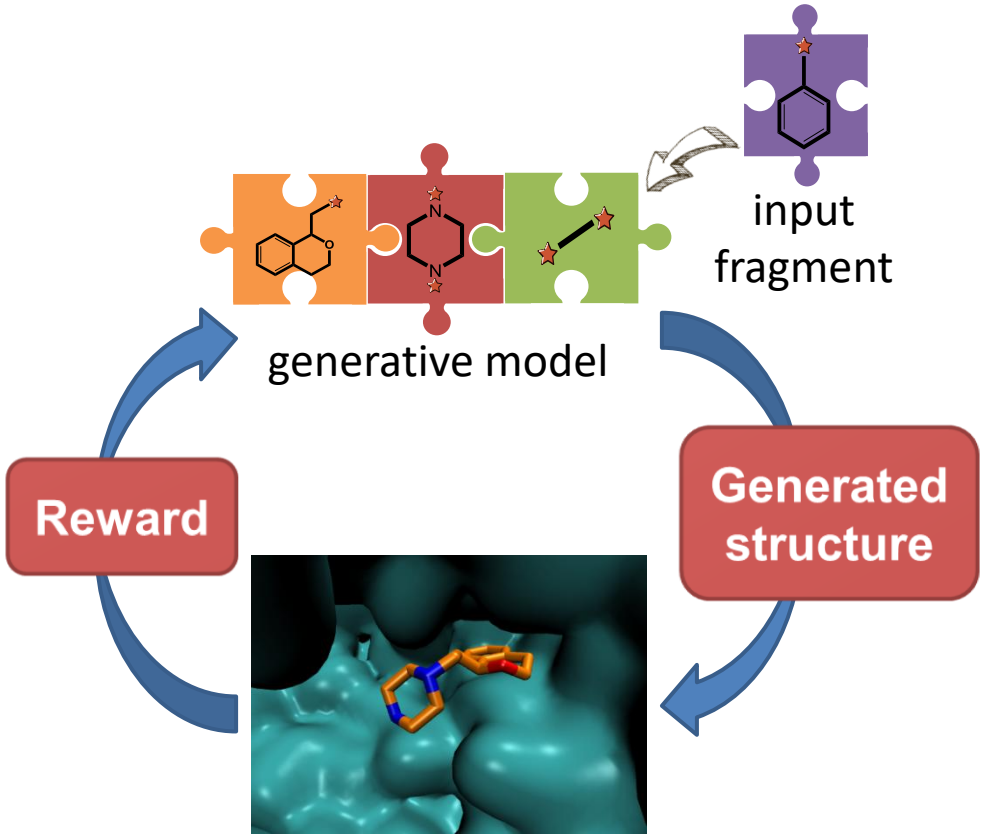


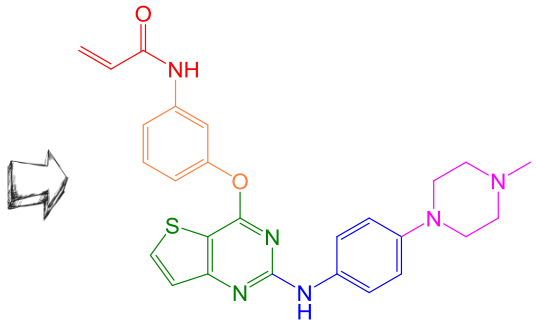


Fragment growing as an iterative process

AI-guided drug design

Aim: Use machine learning algorithms to guide the design of specific and potent ligands starting from an input fragment.





lead compound

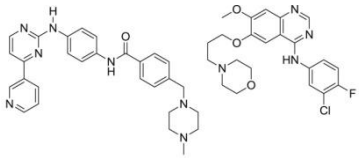
Computational Chemical Biology

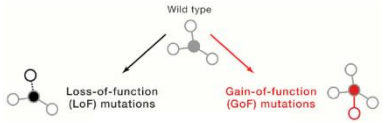
computational chemical biology

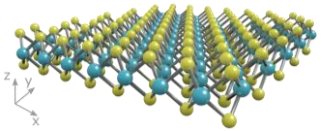
therapeutics

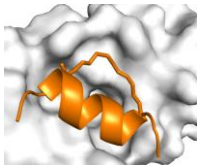
disease mechanisms

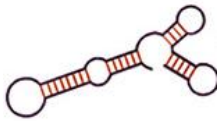
nanomaterials





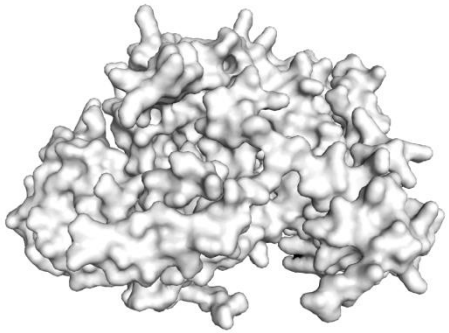




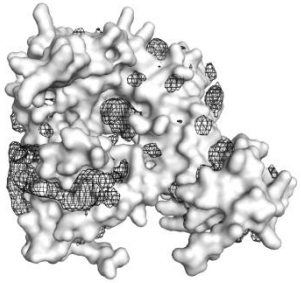


A novel drug target

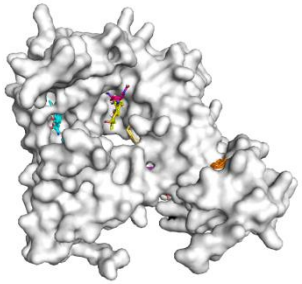
- In collaboration with IMCB and EDDC funded by TTC
- Protein X is implicated in breast and lung carcinogenesis → potential anticancer target
- ≈15.7 million drug-like compounds docked, 21 purchased, 6 show binding, 1 shows concentration-dependent inhibition of protein complex formation



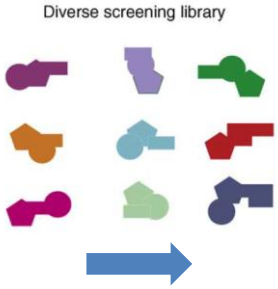
Protein X complex with extensive binding interface



LMMD



FTMAP



docking

fragment-based approaches to find suitable binding site to target

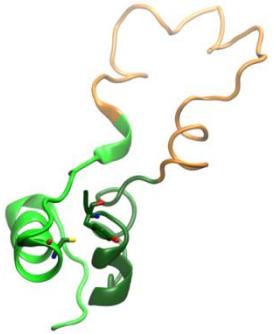
Carol Koh (EDDC)

Wee Wei Tee (IMCB)

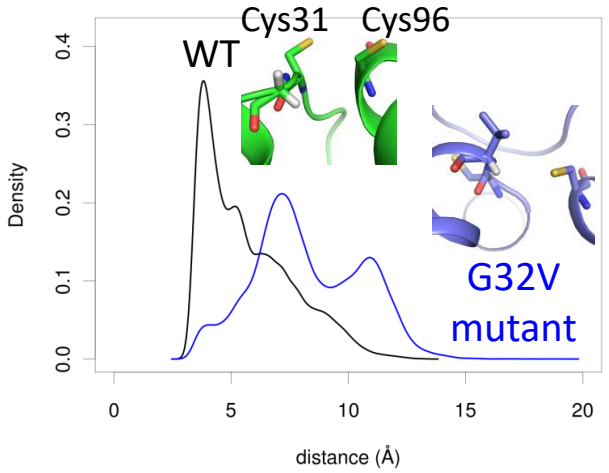
Molecular mechanisms of diabetes-causing mutations

Neonatal diabetes mellitus (NDM)

- Occurs in the first 6 months of life
- Caused by single mutations in the **insulin** gene in ≈20% of cases
- **C109Y** and **G32V** insulin mutations studied



C109Y mutation
Cys109–Cys43 disulfide bond breaks
→ widening of insulin hydrophobic core
→ improper pairing of cysteines



Sulfur atoms of Cys31 and CysC96 are further apart in **G32V** mutant
→ hinders disulfide bridge formation


Adrian Teo (IMCB)

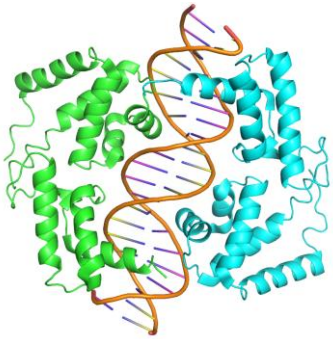

Dr. Lim Su Chi (KTPH)

Amirruddin NS et al. *Diabetologia*, 2021, 64, 2534-2549

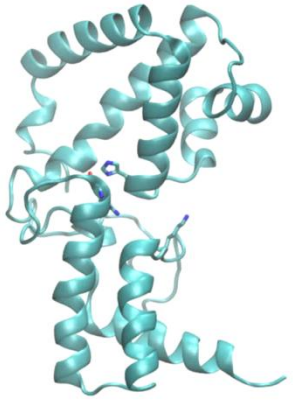
Molecular mechanisms of diabetes-causing mutations

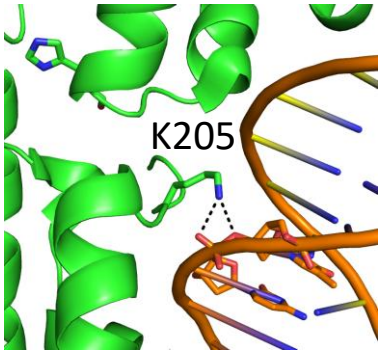
Maturity onset diabetes of the young (MODY)

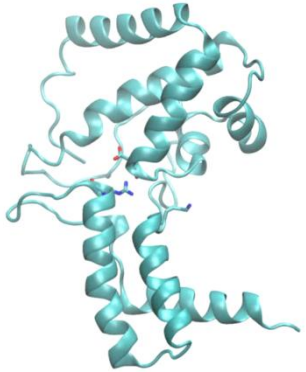
- Early onset (before 25 years old)
- Caused by mutation in a single gene e.g. **HNF1α**
- **H126D** mutation studied

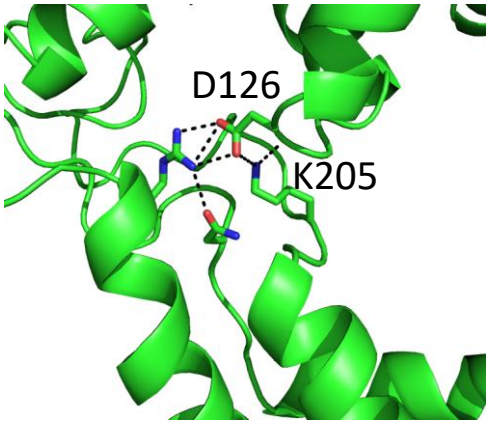


HNF1A bound to DNA









WT

- High flexible and can adopt open conformation
- allows K205 to be exposed for binding to DNA

H126D

- High rigid and adopts a closed conformation
- K205 sequestered by D126 and unavailable for binding to DNA

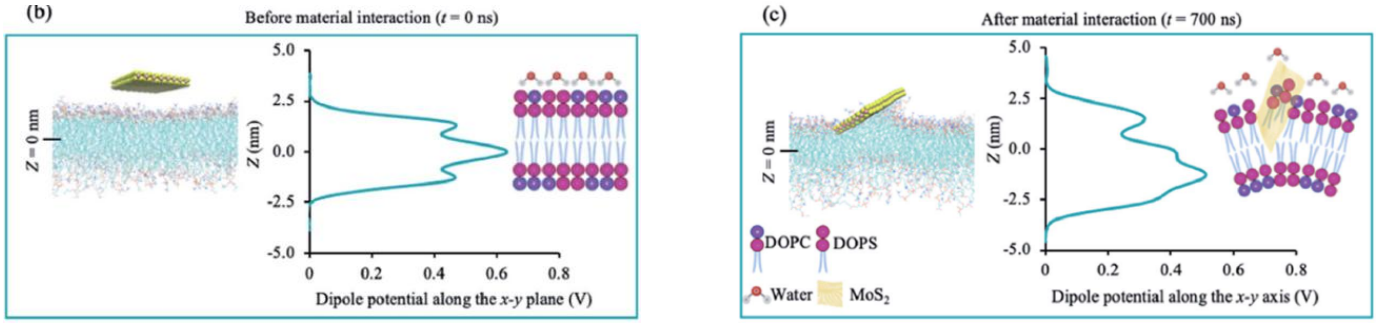
Adrian Teo (IMCB)

Dr. Lim Su Chi (KTPH)

Low BSJ et al. *Nat Commun*, 2021, 12, 3133

Interactions of nanomaterials with cell membranes

- Cancer cells show increased electrical resistance after incubation with molybdenum disulfide (MoS_2) nanosheets
- MD simulations were performed to understand how MoS_2 interacts with a model cancer cell membrane (outer and inner leaflets have almost equal distribution of phosphatidylserine)



Dipole potential before and after MoS_2 interaction

- Maximum dipole potential across membrane decreases on interaction with MoS_2
- Perturbation of cell membrane by MoS_2 likely creates resistance to current flow

Desmond Loke (SUTD)

Chan SS et al. *Nanoscale Adv*, 2021, 3, 6974-6983

Acknowledgements

Funding:
A*STAR CDA
BII core funds

Chandra Verma
Lee Hwee Kuan
Peter Bond

Adrian Teo
Tee Wee Wei

Carol Koh-Stenta

Ichiro Hirao
Michiko Kimoto

Lim Su Chi

Desmond Loke

David Spring
Laura Itzhaki

Yu Heng Lau