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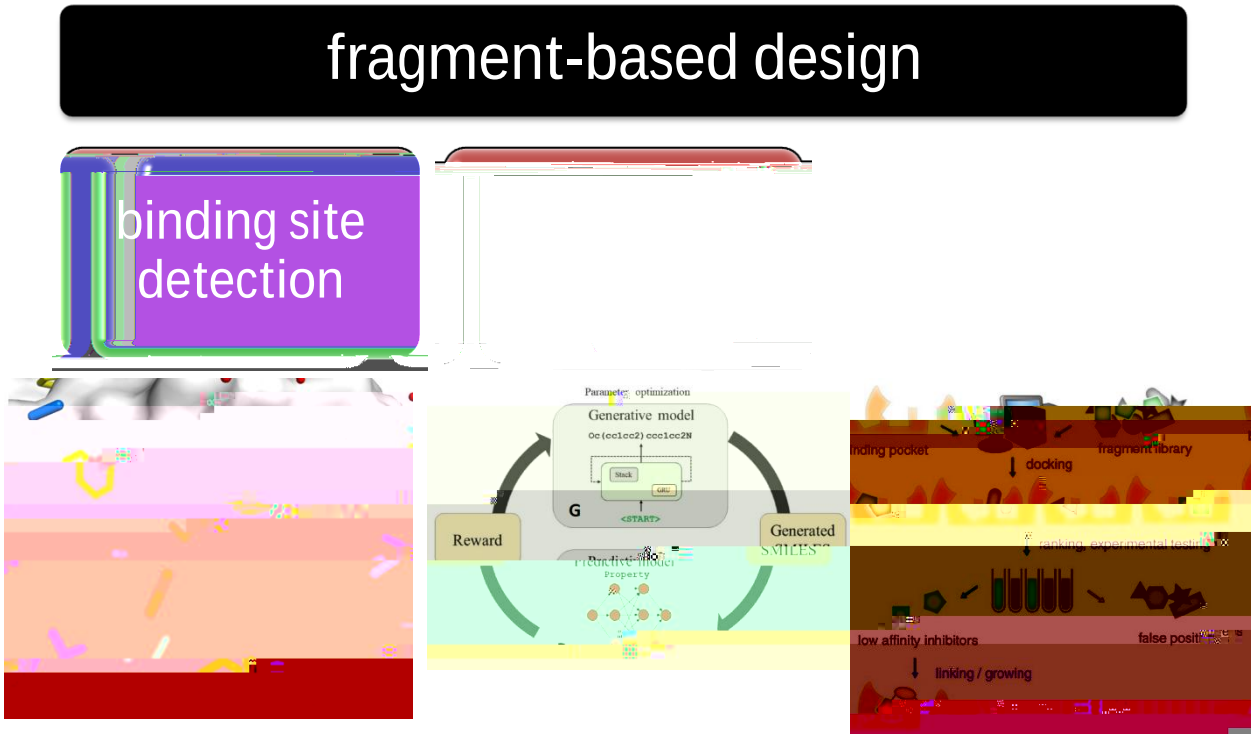
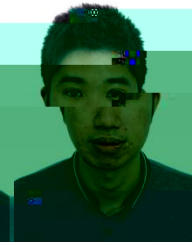
The year in summary (Apr 21 – Mar 22)

Fragment-based design



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

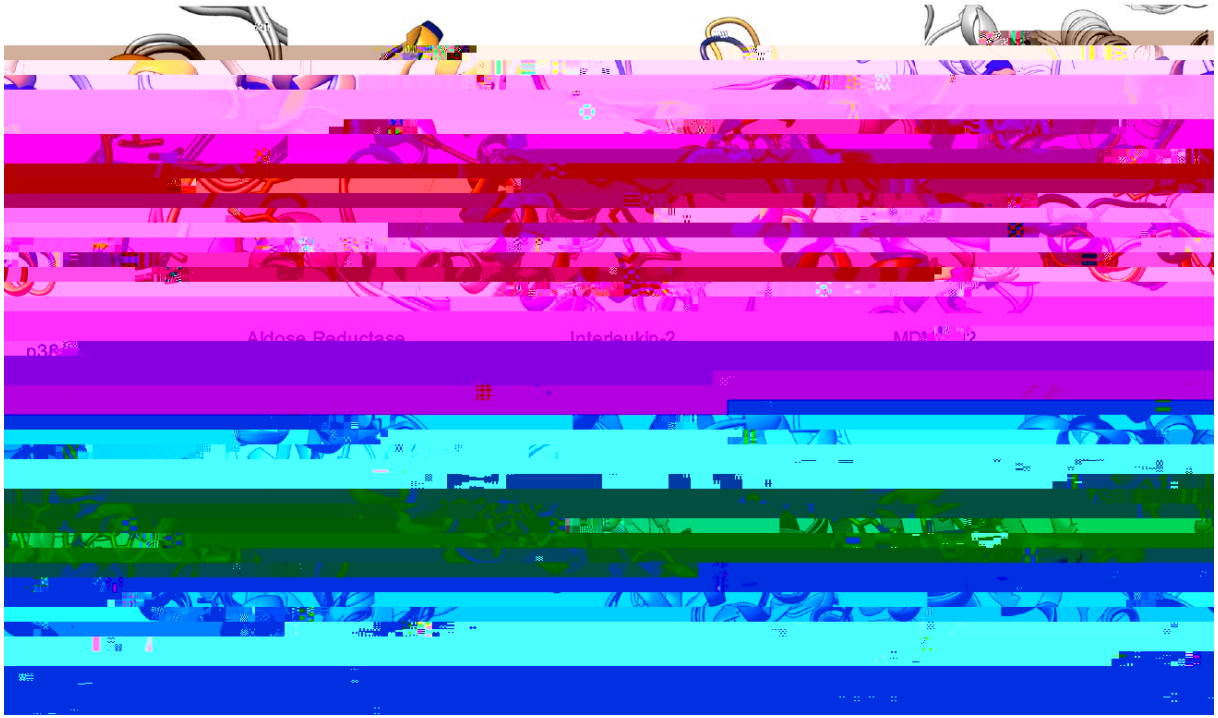


Justin

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= , orange=

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

“Challenging” binding pockets

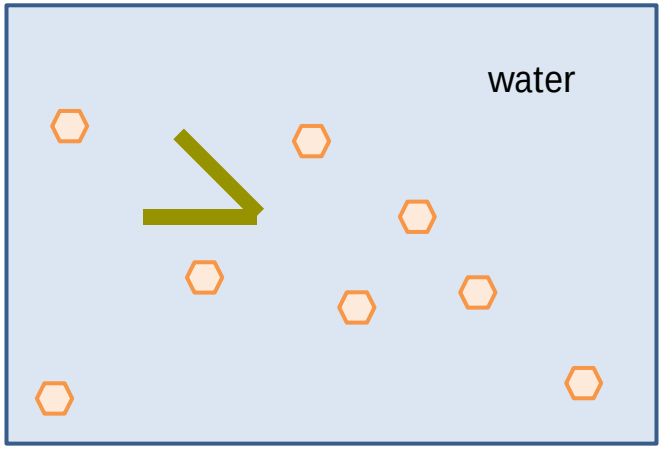
Recalcitrant cryptic pockets

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

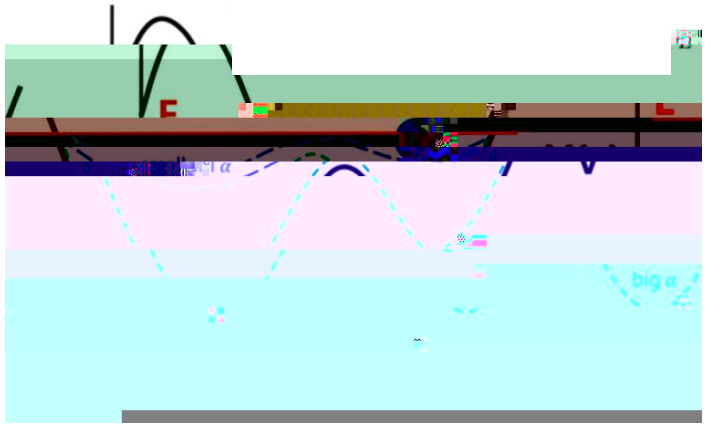
Occluded binding sites

- 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

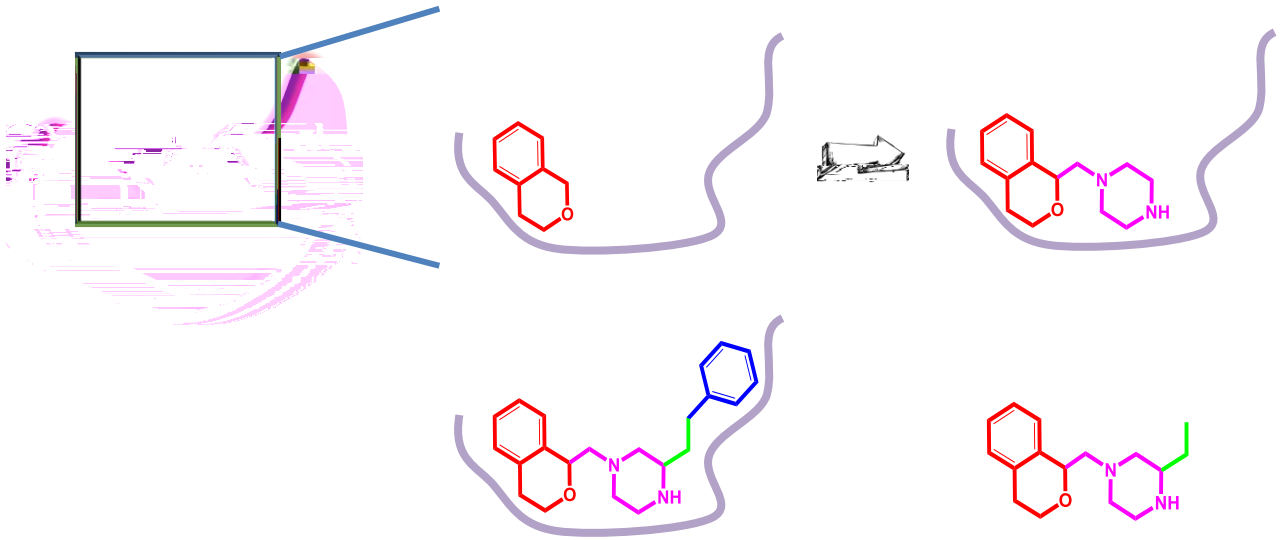
aLMMD is a valuable tool for structure-based drug discovery

AI-guided fragment-based drug design

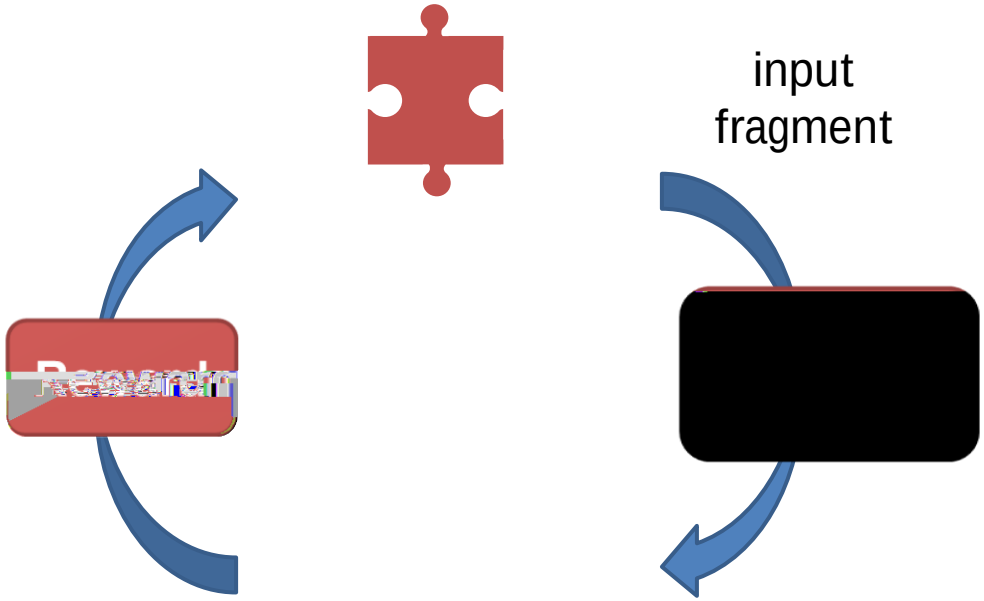
Zhenyu

In collaboration with Hwee Kuan and Chandra

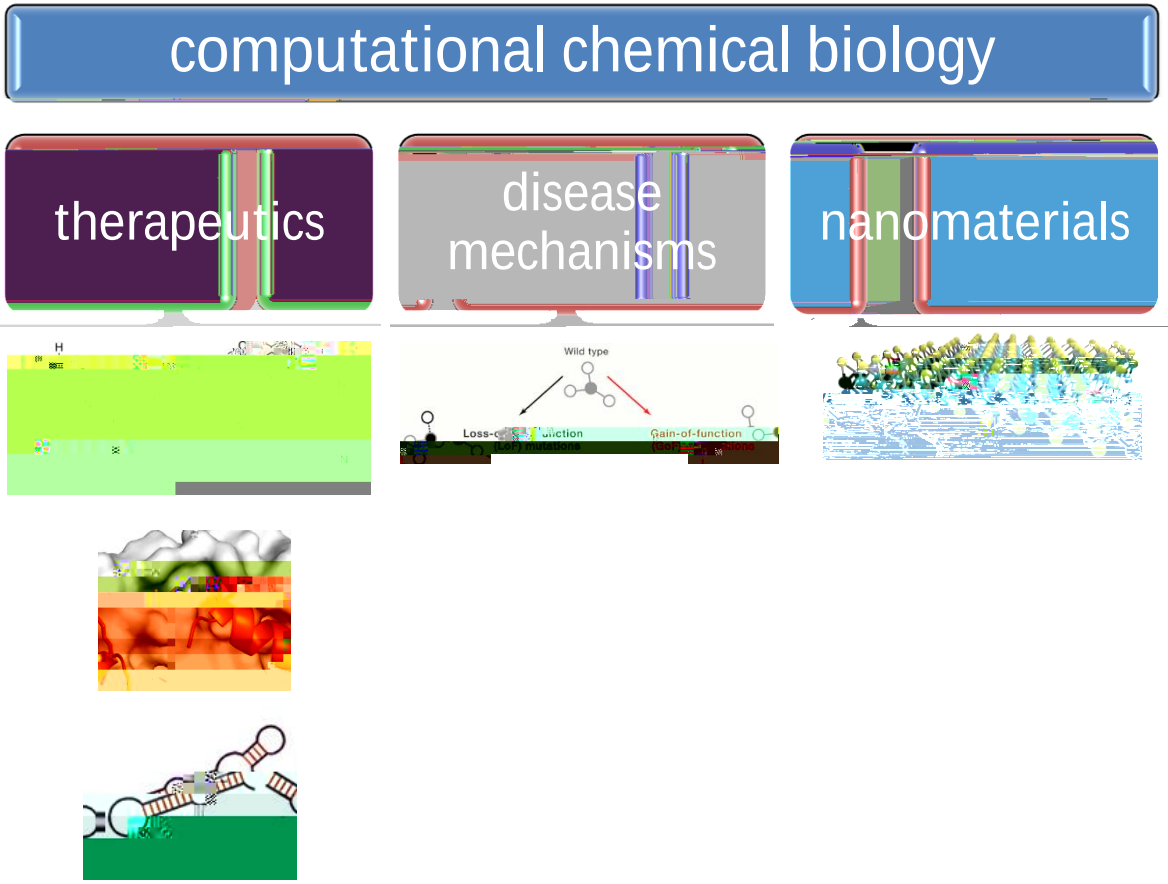
Fragment-based drug discovery



AI-guided drug design



Computational Chemical Biology



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

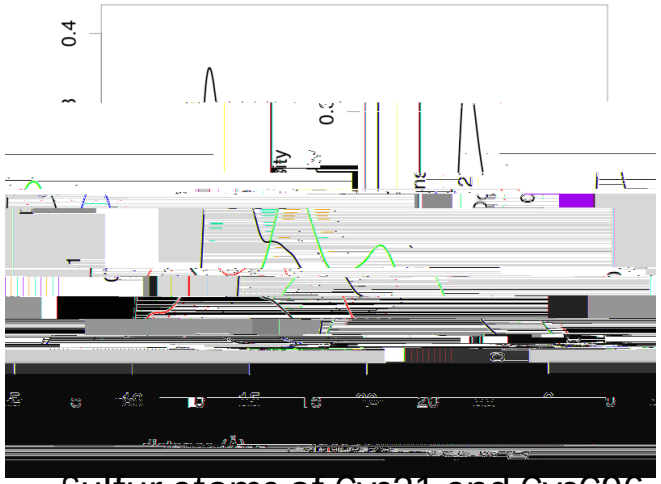
≈15.7 million drug-

Molecular mechanisms of diabetes-causing mutations

Occurs in the first 6 months of life

Caused by single mutations in the gene in ≈20% of cases

and insulin mutations studied



Sulfur atoms of Cys31 and CysC96

mutation

Cys109–Cys43 disulfide bond breaks

→ widening of insulin hydrophobic core

→ improper pairing of cysteines

Molecular mechanisms of diabetes-causing mutations

Early onset (before 25 years old)

Caused by mutation in a single gene e.g. α

mutation studied

Adrian Teo
(IMCB)

Dr. Lim Su Chi
(KTPH)

Interactions of nanomaterials with cell membranes

Cancer cells show increased electrical resistance after incubation with molybdenum disulfide (MoS_2

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