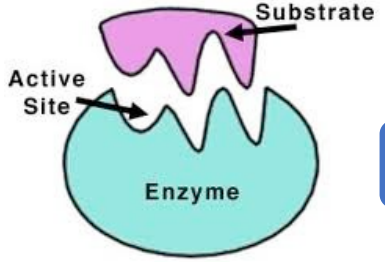
Multiscale

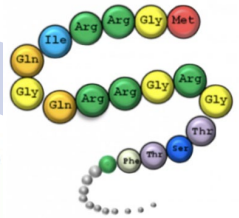
Allostery



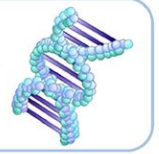
Function

Design (rna, proteins, enzymes, peptides)

Sequence

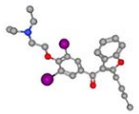


Disease-related genomics



Target identification & validation

Lead discovery & optimization



Drug candidates

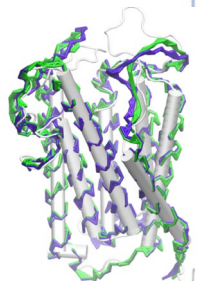
Preclinical studies:

- In silico ADMET
- Physiologically based pharmacokinetics (PBPK)

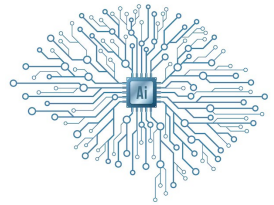
Feedback & optimization

Clinical trial

Dynamics

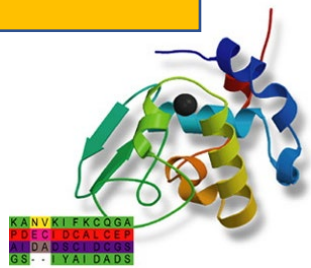


Structure



Fragments

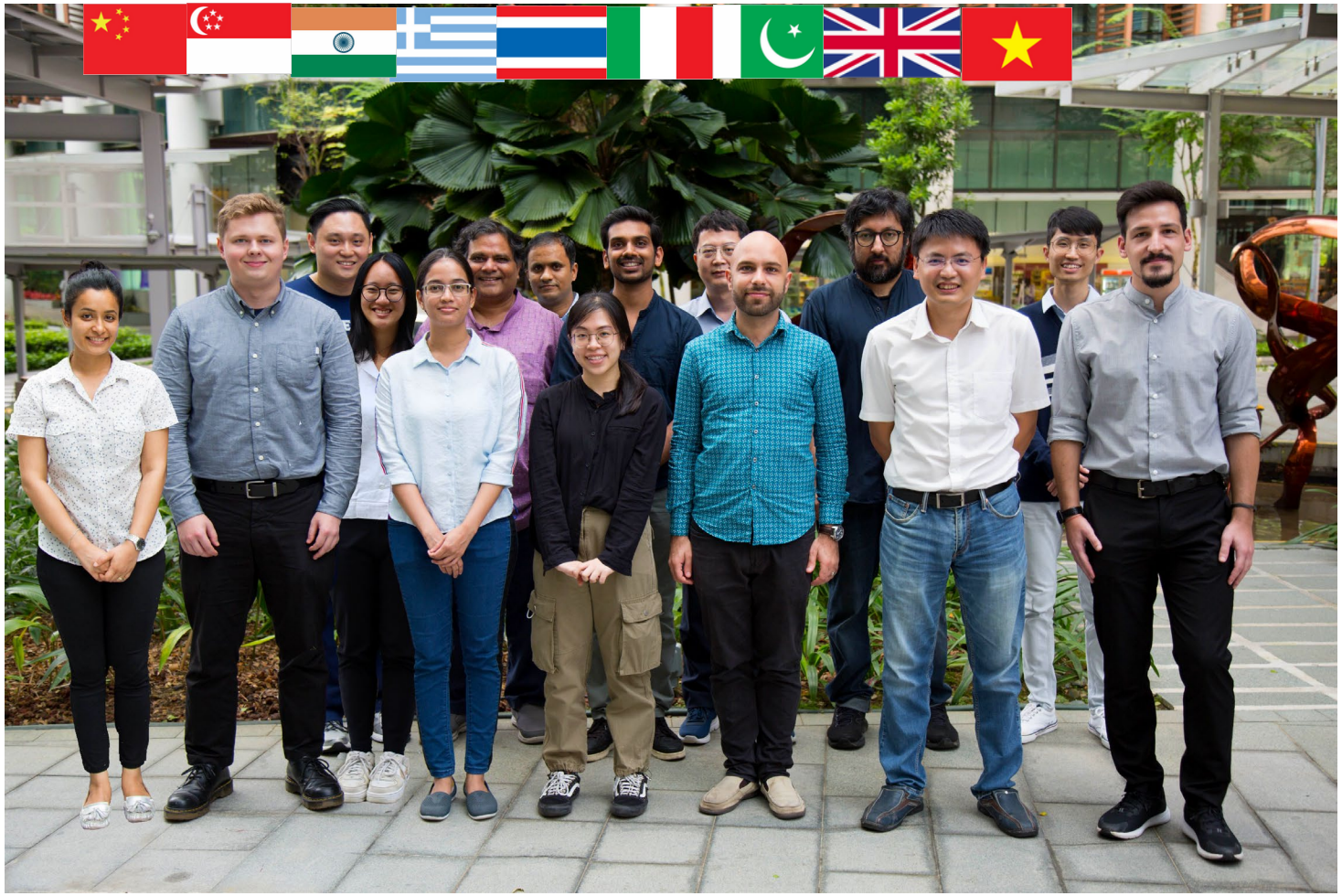
Small molecules



Cryptic pockets

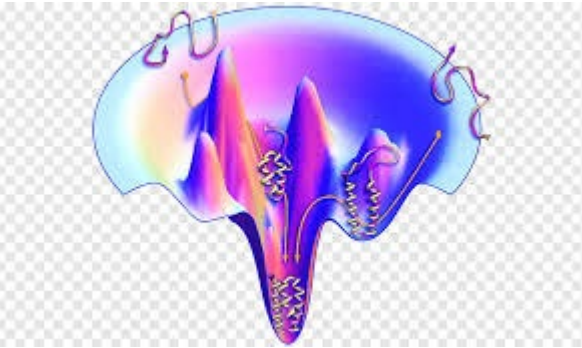
Atomistic Structure & Design Group

Biomolecular Structure to Function Division



“Sampling” problem

Conformational flooding



Article https://doi.org/10.1038/s41467-023-37223-3

Domain-specific p53 mutants activate EGFR by distinct mechanisms exposing tissue-independent therapeutic vulnerabilities

p53 DNA-binding domain (DBD) and transactivation domain (TAD) mis-sense mutants unexpectedly activate pro-carcinogenic epidermal growth factor receptor (EGFR) signaling via distinct, previously unrecognized molecular mechanisms.

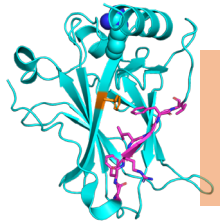
In multiple tissues, EGFR is stabilized by TAD and DBD mutants in the cytosolic and nuclear compartments respectively.

TAD mutants promote EGFR-mediated signaling by enhancing EGFR interaction with AKT via DDX31 in the cytosol.

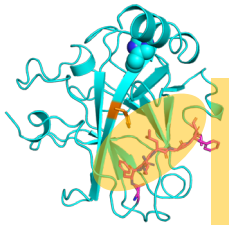
DBD mutants maintain EGFR activity in the nucleus, by blocking EGFR interaction with the phosphatase SHP1, triggering c-Myc and Cyclin D1 upregulation.

p53 mutants carrying gain-of-function, mis-sense mutations form new protein complexes that promote carcinogenesis by enhancing EGFR signaling via distinctive mechanisms

New clinically relevant therapeutic vulnerabilities.

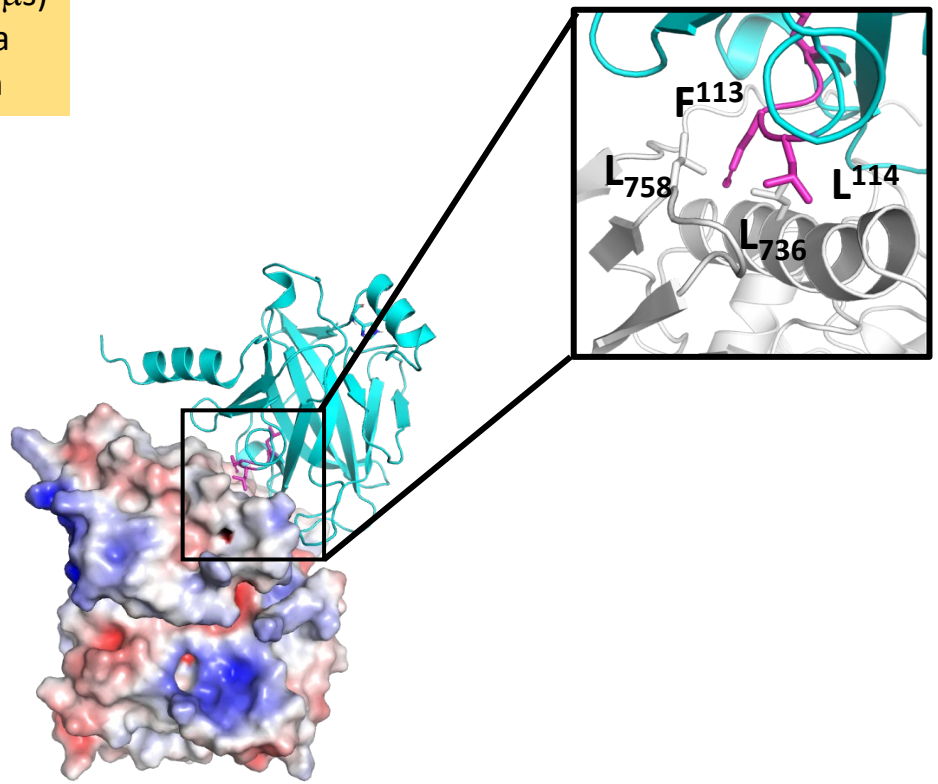


Conventional MD(5μs) simulations didn't reveal any structural changes



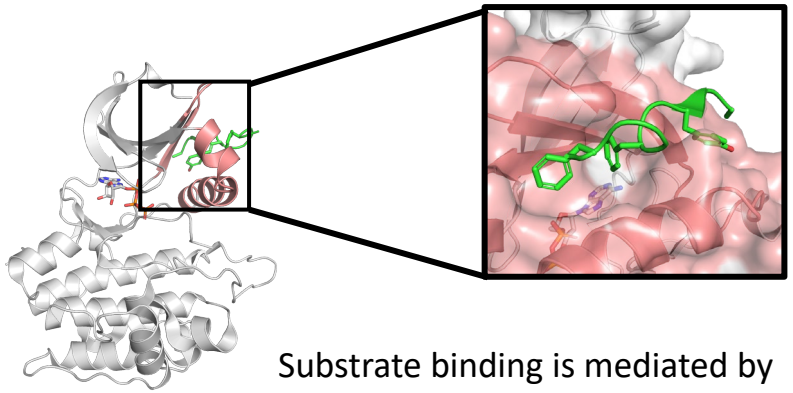
New advanced MD (3μs) methods exposed a hydrophobic patch

Modelling p53DBD^{MUT} – EGFR complex



- p53 DBD^{MUT} binds at the PIF pocket on the surface of EGFR
- Binding is mediated by the exposed hydrophobic patch in p53 DBD^{MUT}

The PIF-binding pocket in PDK1 is essential for activation

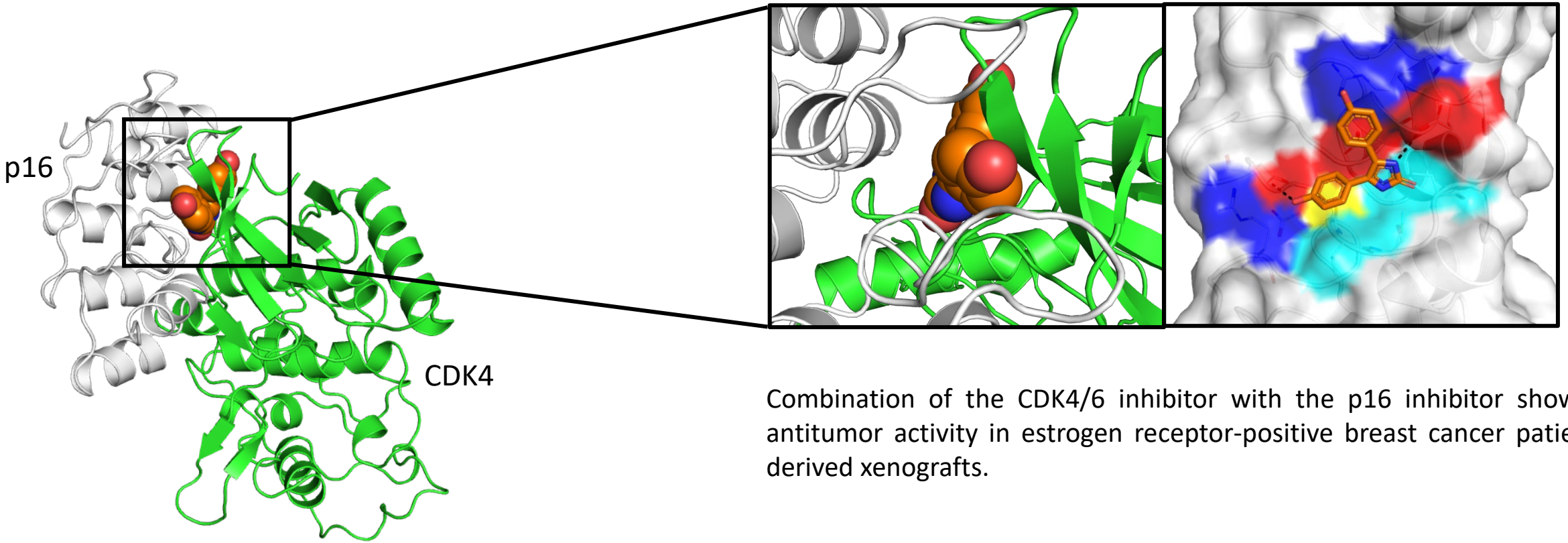


Substrate binding is mediated by hydrophobic amino acids

Inhibition of CDK4/6 by disrupting p16 – CDK4/6

Marta et al. Nature Communications 13: 5258 (2022)

- High p16 levels associated with lack of response to CDK4/6i in ER$^+$ BC patients
- p16 allosterically regulates CDK4/6
- Disruption of p16-CDK4/6 interaction sensitizes p16-high cells to CDK4/6i



Combination of the CDK4/6 inhibitor with the p16 inhibitor showed antitumor activity in estrogen receptor-positive breast cancer patient-derived xenografts.

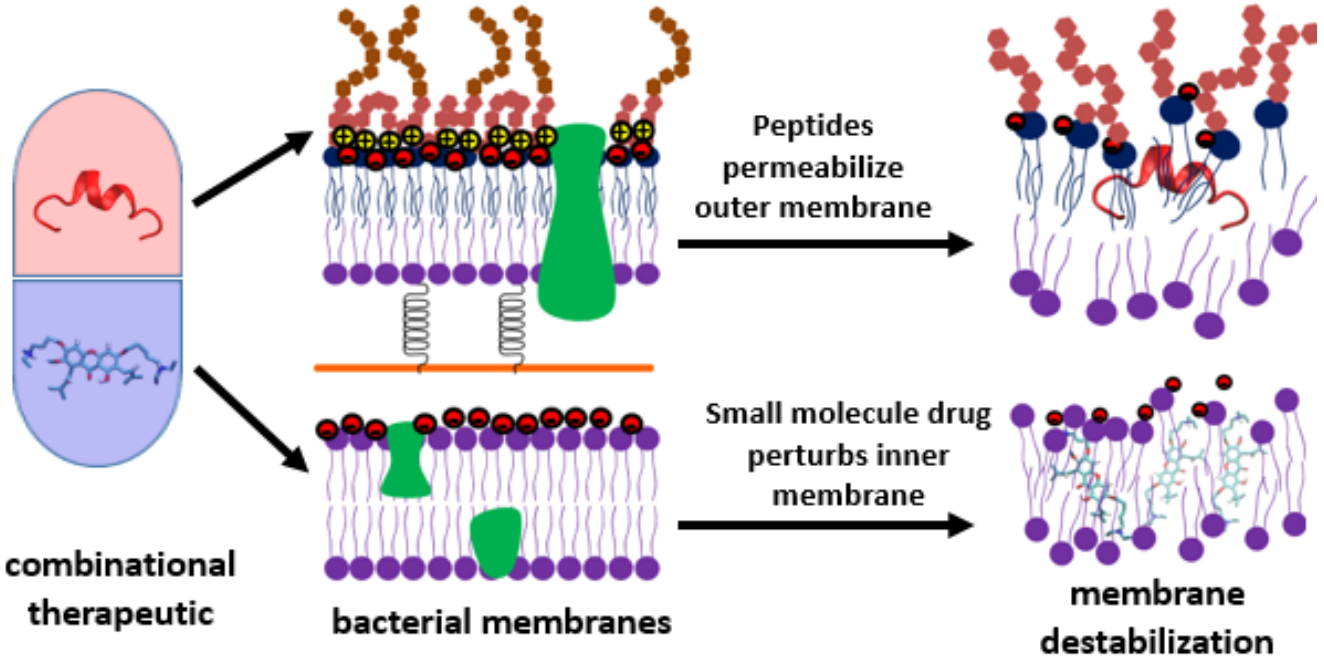
Bioinformatics Institute BII · VHIO Vall d'Hebron Institute of Oncology · Memorial Sloan Kettering Cancer Center · ICR The Institute of Cancer Research · Genentech A Member of the Roche Group

Combination therapy against Gram negative superbugs

❖ **Antimicrobial resistance**
- Kills more than HIV and malaria
- >10 million in 2050

❖ **Antibiotic shortage for Gram negatives**

❖ **Membrane targeting antimicrobials**
- Low probability of resistance development
- Rapid killing kinetics



- Peptide Colistin: permeabilizes outer membrane
- Designed Small molecule: disrupts inner membrane

Biomaterials. 122004 (2023)
JCIM, 60, 4975-4984 (2020)
BBA-Biomem. 1862, 183297 (2020)

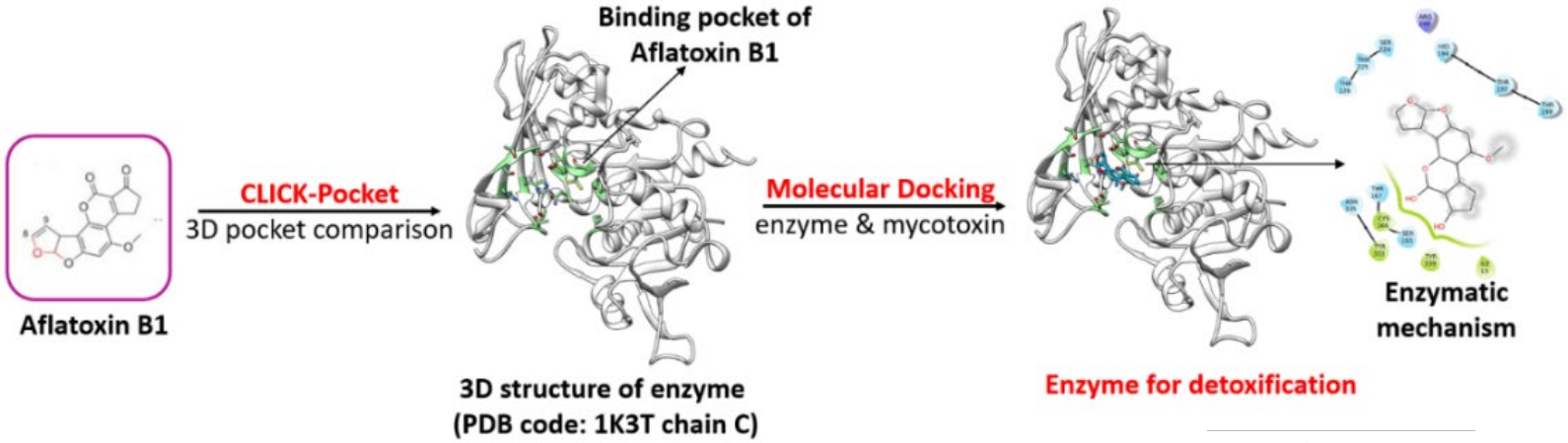
A*STAR CDA, 2021-2024; Wuxi AppTec (2023)

PCT/SG2020/050292

Tan Tock Seng Hospital
Singapore Eye Research Institute
A*STAR Bioinformatics Institute

Protein binding pocket similarity virtual screening

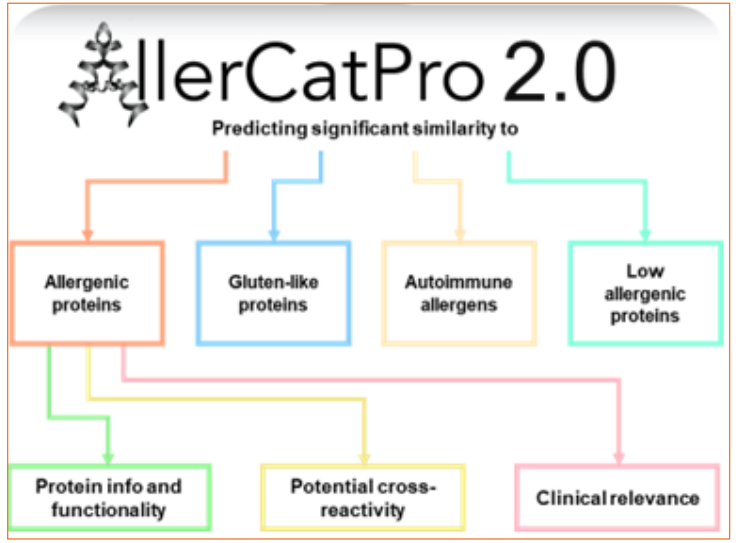
https://mspc.bii.a-star.edu.sg/minhn/3dclick.html



Singapore Institute of Food and Biotechnology Innovation
SIFBI

Career Development Fund
Singapore Food Story Grant

Protein allergenicity potential prediction



https://allercatpro.bii.a-star.edu.sg/

Nucleic Acids Research (2022)
Bioinformatics (2019)
Singapore Food Story Grant 2022

Bioinformatics Institute
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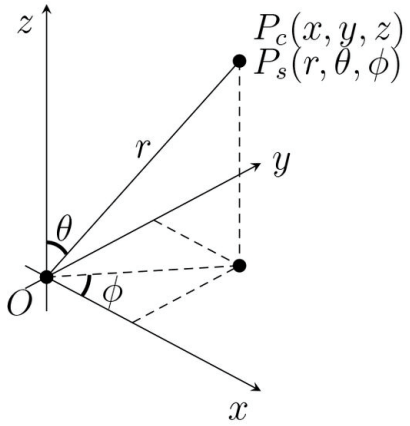
Quantum computing and geometry optimization

Encoding



(a) Coordinate system

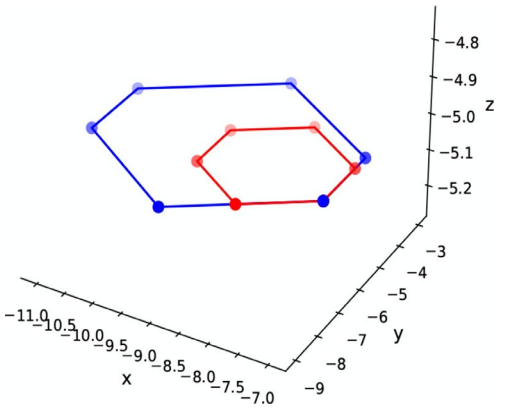
Quantum circuit

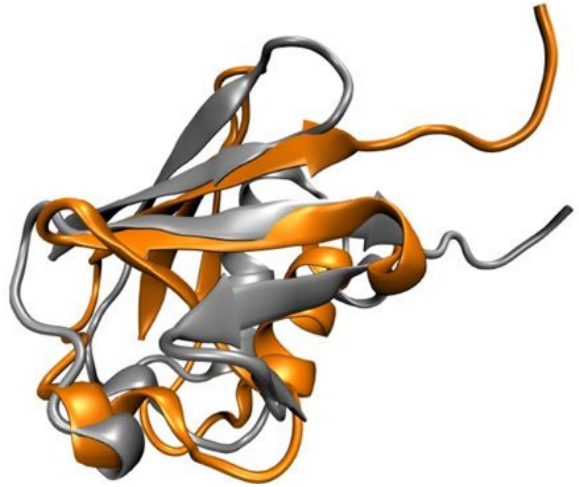
Spherical coordinates to encode classical problems.

(1) A non-optimum state (blue) of a benzene ring can be optimized.
(2) Structural alignment of transformed proteins.
(3) Generation of random numbers which can find utility in Monte Carlo simulation of protein side chain state-sampling.

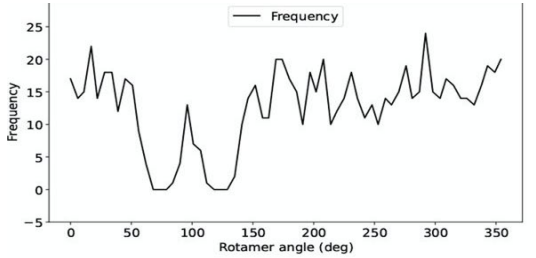
No quantum advantage, but demonstrates possibilities ways in which biological data can be used with quantum computers to eventually achieve it.

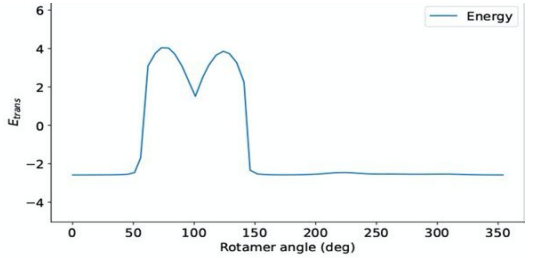
Geometry optimization





Monte Carlo sampling





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Precision Medicine

...AGCAAAAGCAGGGGAAAACAAAAGCAA
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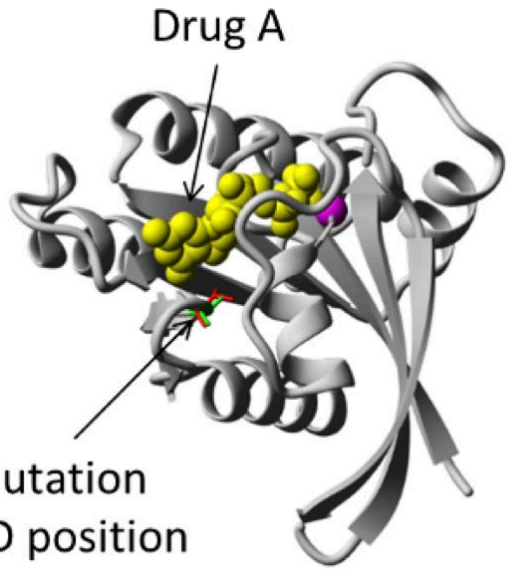
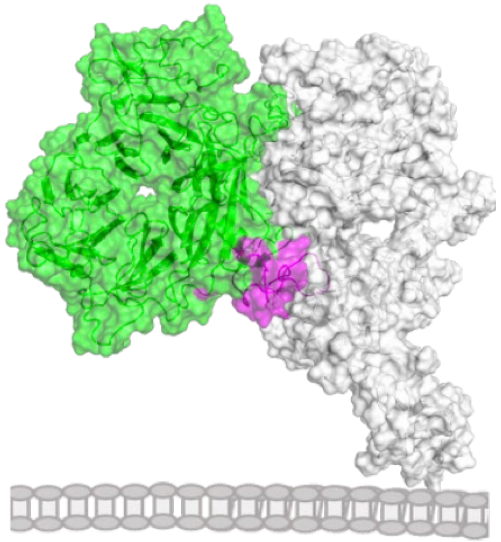
Sequence SNP/variant X



https://commons.wikimedia.org/wiki/File:Doctor_with_Patient_Cartoon.svg



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Patents

1. Patent filed: Priority application filed - Cell permeable Macrocyclic Peptides useful for Eif4E Cap-Binding site inhibition.
2. Patent filed: Priority application filed - P53 Peptidomimetic Macrocycles (Serial number: 63/288204)
3. Patent Filed: National Phase application filed for “p53 activator peptidomimetics macrocycles” (WO2020257153A1)
4. Patent filed: National phase application filed “ Compounds for treating eye diseases and methods thereof” (US20210061800A1) **IAF-PP**
5. Patent filed: National phase application filed for “macrocyclic peptide as potent inhibitors of K-ras G12D mutant” (WO2021126799A1).

TDs Filed

1. C-terminal extended p53 activator crosslinked peptidomimetic macrocycles against MDM2/MDMX - Priority application filed
2. p53 peptidomimetic macrocycles - Priority application filed
3. Cell permeable macrocyclic peptides useful for eIF4E cap-binding site inhibition - Priority application filed
4. Highly potent PET imaging agents targeting Granzyme B as biomarkers for cancer immunotherapy stratification – **CITI IAF-PP**

Thank You