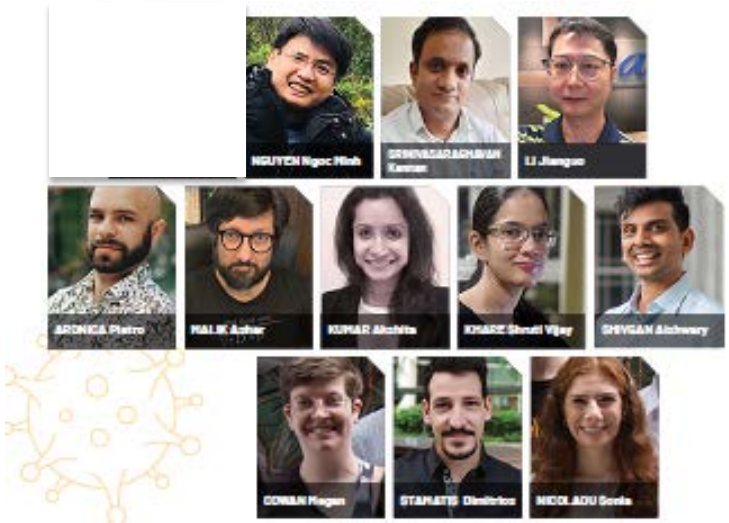
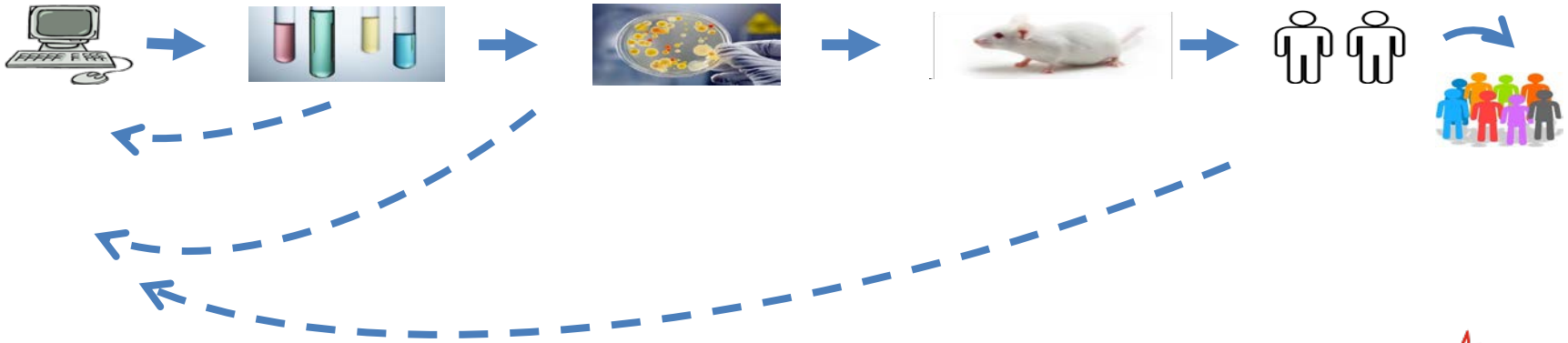
# Atomistic Simulations & Design

**Chandra Verma**
**chandra@bii.a-star.edu.sg**



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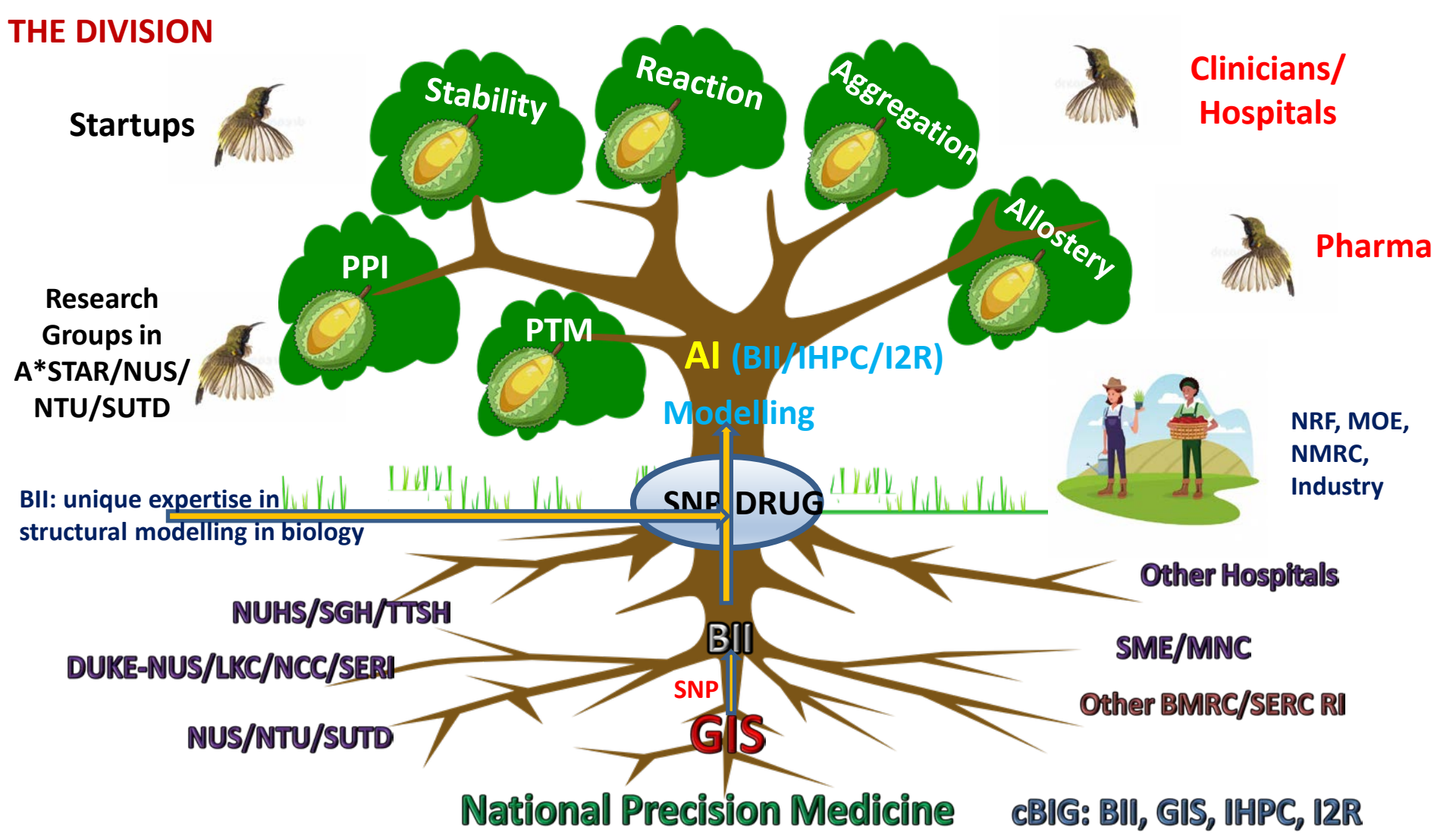
# THE DIVISION




BMRC; SERC; NUS; Duke-NUS; NTU; SUTD; Clinical-local; International

CRP; MoE Tier3, IAF-PP; CDAs, YIRGs, Covid grant, IAF-ICP

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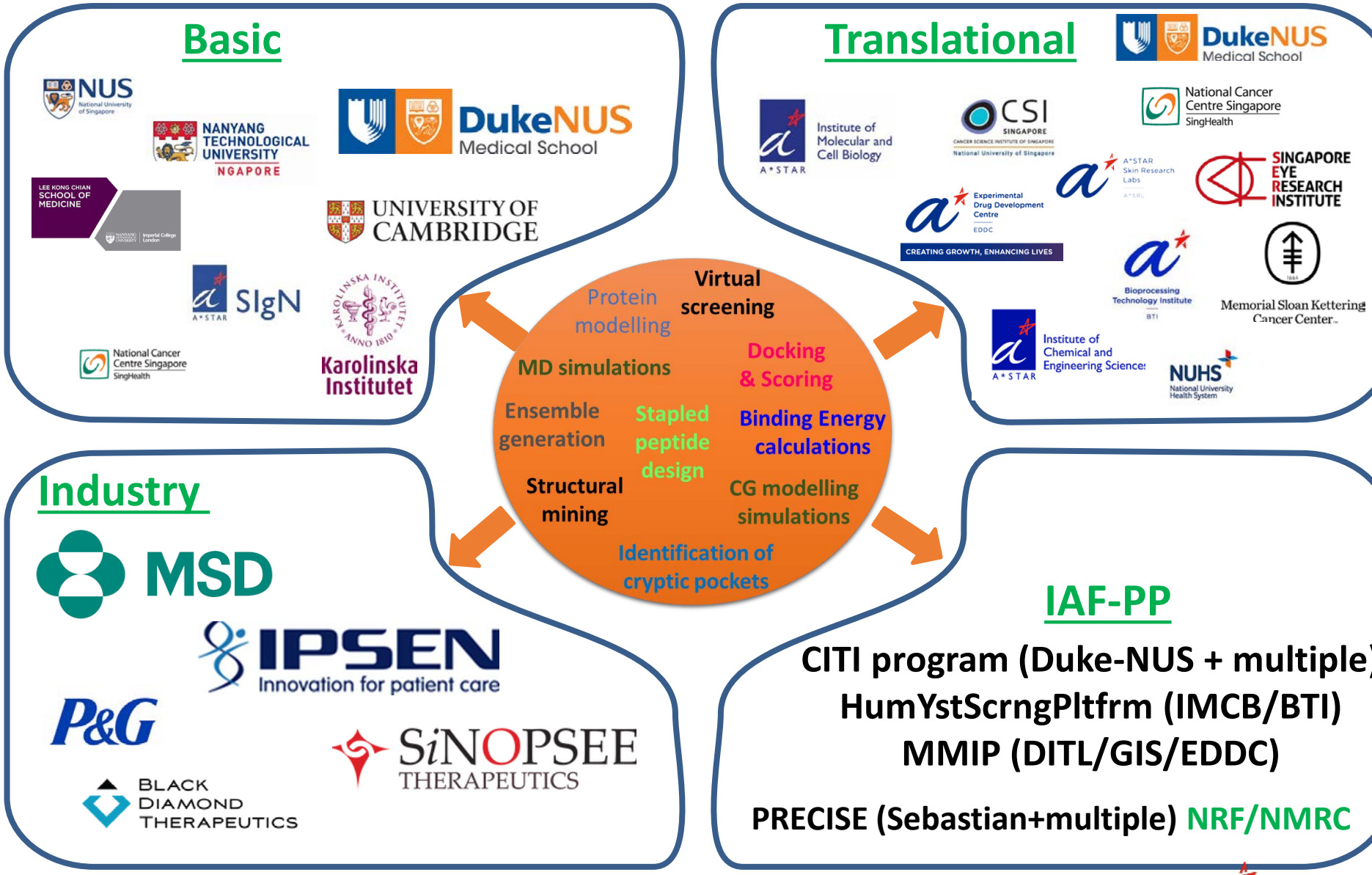
Basic
NUS National University of Singapore
NANYANG TECHNOLOGICAL UNIVERSITY NGAPORE
DukeNUS Medical School
LEE KONG CHIAN SCHOOL OF MEDICINE
UNIVERSITY OF CAMBRIDGE
A*STAR SIgN
Karolinska Institutet
National Cancer Centre Singapore SingHealth
Translational
DukeNUS Medical School
Institute of Molecular and Cell Biology A*STAR
CSI SINGAPORE
National Cancer Centre Singapore SingHealth
A*STAR Skin Research Labs
SINGAPORE EYE RESEARCH INSTITUTE
Experimental Drug Development Centre EDDC
CREATING GROWTH, ENHANCING LIVES
Bioprocessing Technology Institute BTI
Memorial Sloan Kettering Cancer Center
Institute of Chemical and Engineering Sciences A*STAR
NUHS National University Health System
Virtual screening
Protein modelling
Docking & Scoring
MD simulations
Ensemble generation
Stapled peptide design
Binding Energy calculations
Structural mining
CG modelling simulations
Identification of cryptic pockets
Industry
MSD
IPSEN Innovation for patient care
P&G
SiNOPSEE THERAPEUTICS
BLACK DIAMOND THERAPEUTICS
IAF-PP
CITI program (Duke-NUS + multiple)
HumYstScrngPltfrm (IMCB/BTI)
MMIP (DITL/GIS/EDDC)
PRECISE (Sebastian+multiple) NRF/NMRC
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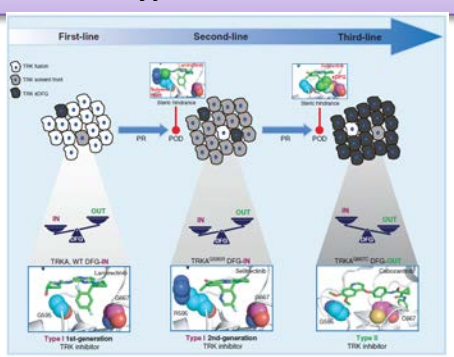
# Unravelling molecular mechanisms

*B Basic; C Clinical; T Translational; I Industry*

## MSKCC*

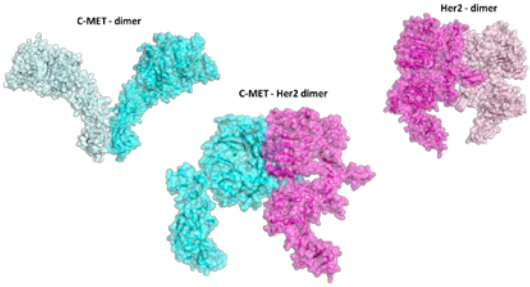
**xDFG Mutations Trigger a Sensitivity Switch from Type I to II Kinase Inhibitors**




*Cancer Discovery,11,126 (2021)* ***C***

## NUHS/NCCS**

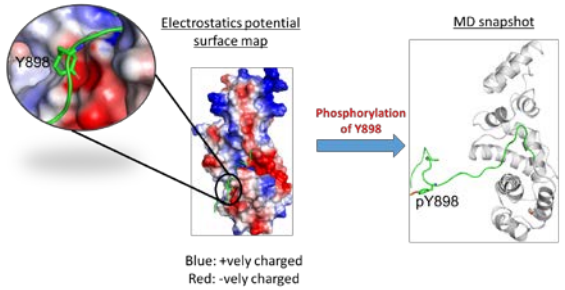
**A common MET SNP drives cancer through Her2**




*Nature Comm. 11, 1556 (2020)* ***C***

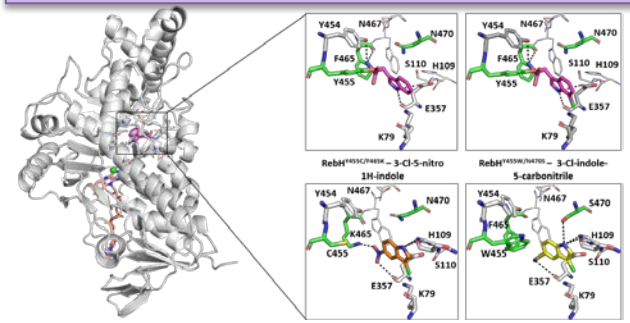
## IMCB

**Phosphorylation of GBF1 in membrane trafficking**




*eLife 2021;10:e68678* ***B***

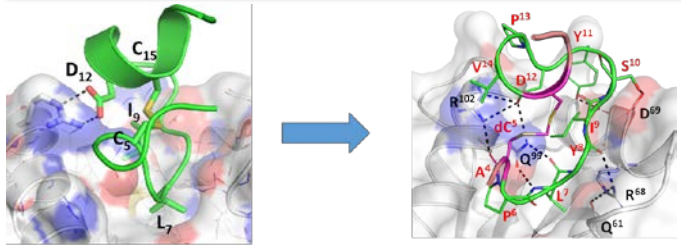
**Engineered selectivity in RebH Halogenase for regioselective synthesis of drug intermediates**



*ChemBioChem.22,2791 (2021)* ***T***

**IMCB-GSK-NRF**

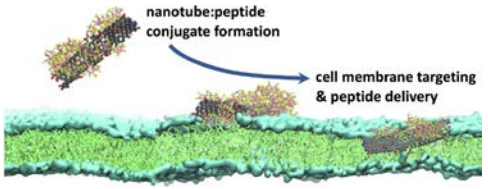
**Engineered permeability and stability of KRAS inhibitor with backbone and sidechain modification**



*Chem. Sci.*, 12, 15975 (2021) ***I***

**IMCB (Chris Brown)-ICES-MSD**

**Carbon nanotubes for cellular delivery of therapeutic peptides**




*JCIS*, 604, 670 (2021) ***B***

**Peter Bond**

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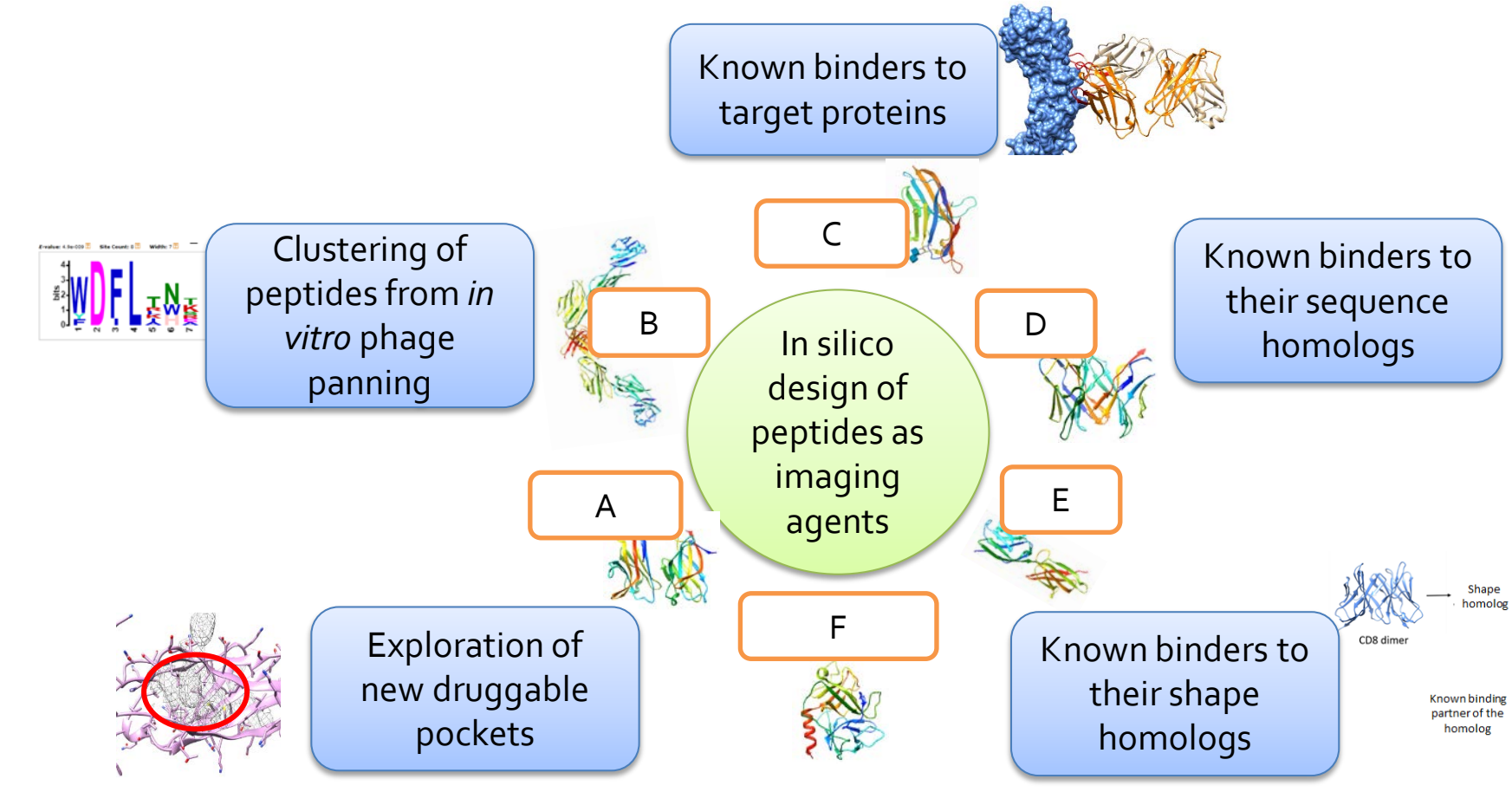
**** Guided patient treatment***

***** Lessons for alpha fold, regular MD; new clinical trial initiated***

# CITI Program - Cancer ImmunoTherapy Imaging
# IAF-PP Program in collaboration with Duke-NUS, NUS, NCCS and A*STAR (ICES, IMCB – Chris Brown, IBB, SiGN)




- 2 Lead peptides were identified based on *in silico* designing
- *In vitro* testing underway for other designs

Challenges:

- Unknown peptides
- Unknown binding sites

# Humanized yeast system as a novel screening platform

## For rapid identification of new therapeutic agents IAFPP

*Uttam Surana (IMCB) Hong Hwa Lim (IBB)*

***Have candidates for the following (nM IC50 in cells):***

- ***FTL3***
  ***Acute myeloid Leukemia***

- ***IDH1/IDH2***
  ***Mutations in two isoforms of isocitrate dehydrogenase IDH1 and IDH2 have also been found in a diverse array of cancers including acute myeloid leukemia and gliomas***

- ***Cdk4/Cyclin D***
  ***Drivers of cell division and promising targets for cancer therapy***

- ***Protein-Protein interaction disruptors***
  ***Apoptosis pathway: BCL2L10-BAX interaction***

- ***Allosteric inhibitors for Receptor Tyrosine kinase***
  ***PDGFR as an example***

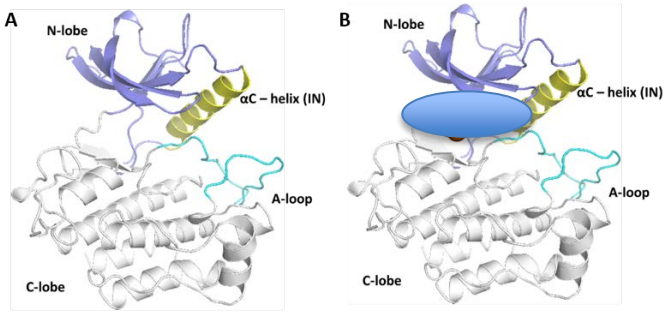



Fig 5: Overview of the structure of Flt3 kinase domain in its (A) Active conformation. (B) Predicted binding mode of the most promising hit molecule (F3) with the structure of Flt3 kinase in its active conformation. The N-lone (blue), C- lobe (grey), helix C ( yellow), activation loop (cyan) and the hit molecule (orange sphere) are highlighted.

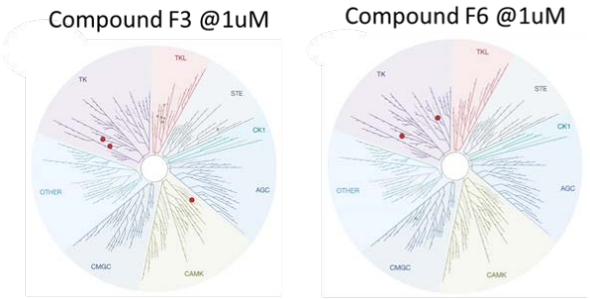
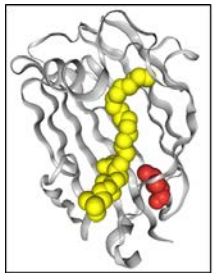
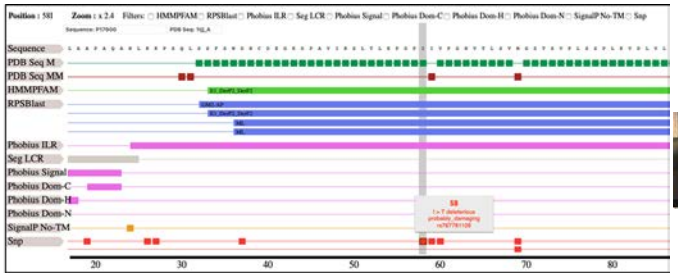



Fig 4. in-vitro enzyme inhibition assay. Hit compounds F3 (left) and F6 (right) were tested against a panel of 320 kinase protein from human kinome at 1uM and % inhibition was measured (>50% inhibition scored as positive).

# National Precision Medicine: SNPDrug3D

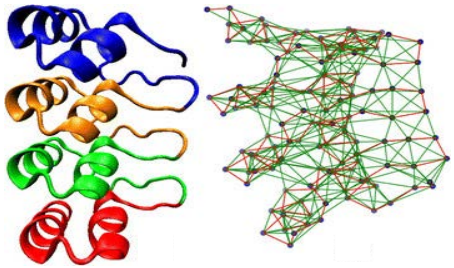




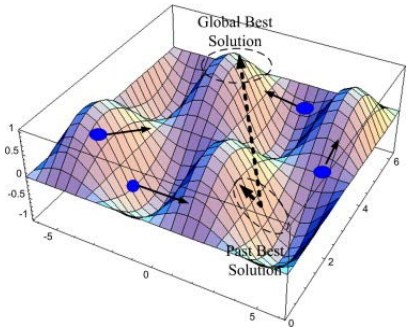

SNP database to help clinicians to make more informed decision. **Collabs: Sebastian/Ken/Dimitar/NTU/GIS/NUHS**

*submitted*

# Quantum Computing for Biomolecules



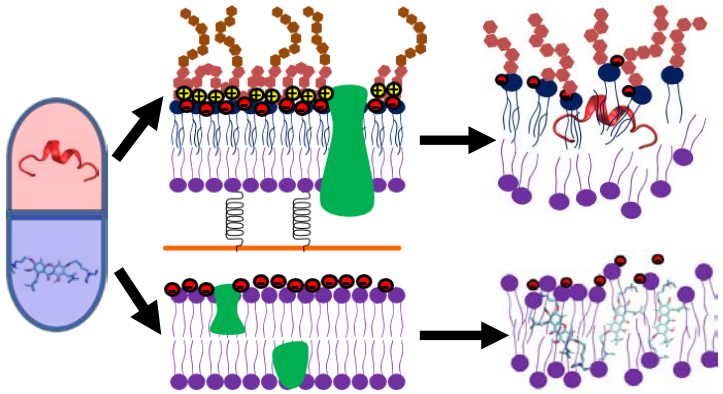
Protein Structure depicted as a network, comprising nodes and edges.




Protein-ligand interaction visualized as a optimization problem

**Collabs: SERI/TTSH**

# Combination therapy - superbugs



**Collabs: SERI/TTSH**

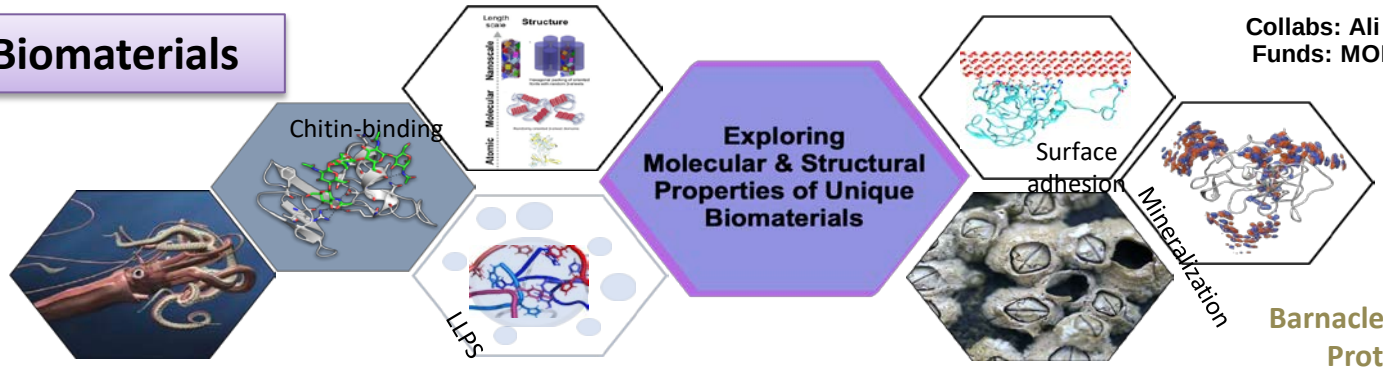
**Antimicrobial peptides permeabilize bacterial outer membrane**

**Semi-synthetic natural products perturbs bacterial inner membrane**

*J. Chem Info Model., 60, 4975 (2020)*
*PCT/SG2020/050292, filed*

**CDA**

# Biomaterials




**Collabs: Ali Miserez (NTU)**
**Funds: MOE AcRF Tier 3**

**Barnacle Cement Proteins**

*J. Struct. Biol. (2021)*

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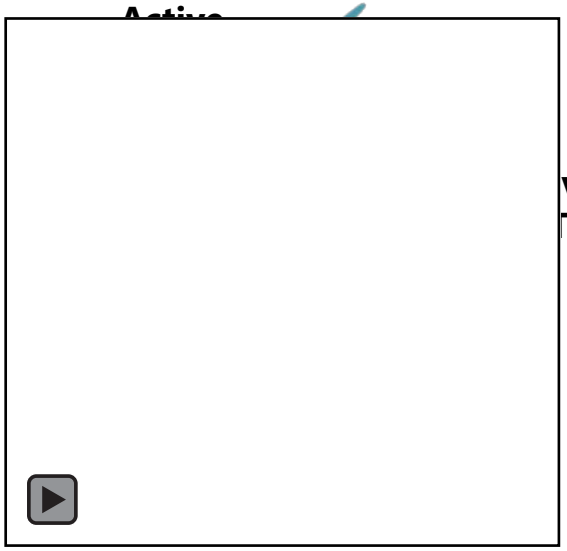
# Activating mechanisms of oncogenic mutations in EGFR
# The Ins and the OUTs : all atom/coarse grained simulations





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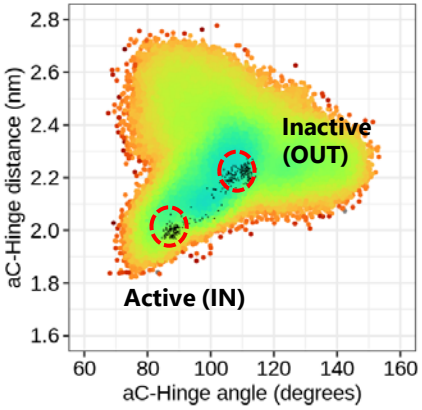
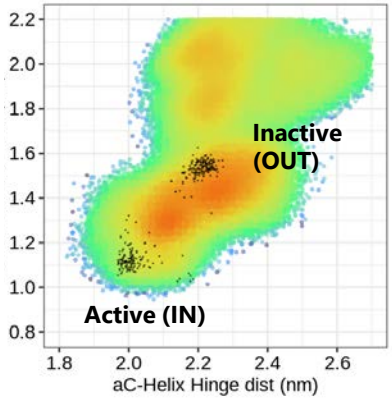
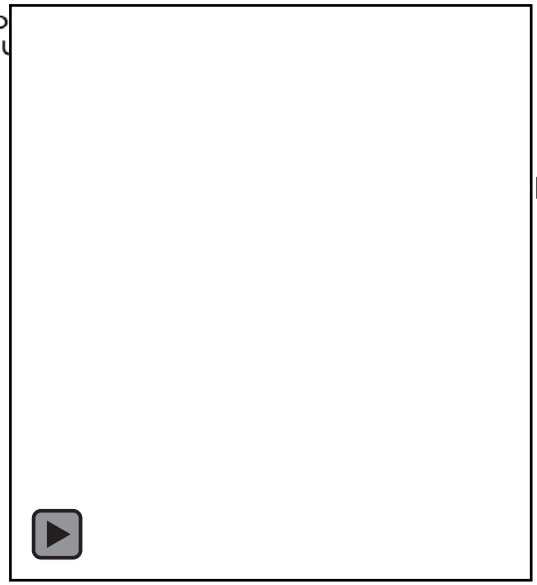
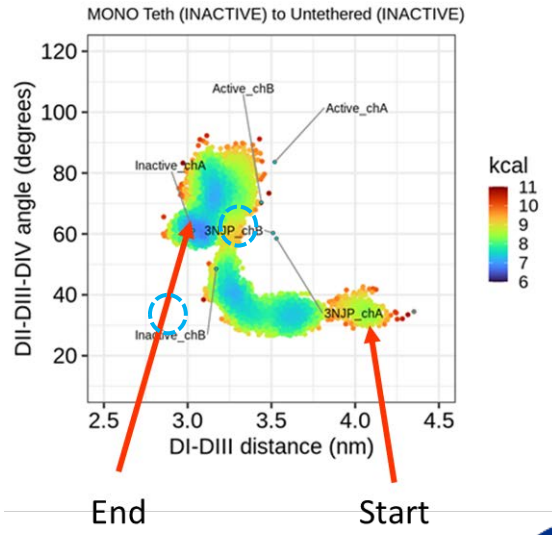



BLACK DIAMOND THERAPEU



DI-DIII distance

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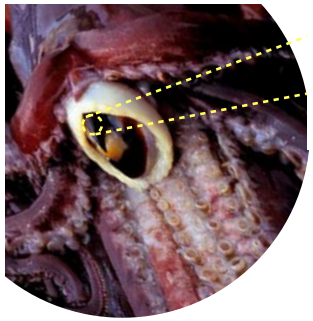
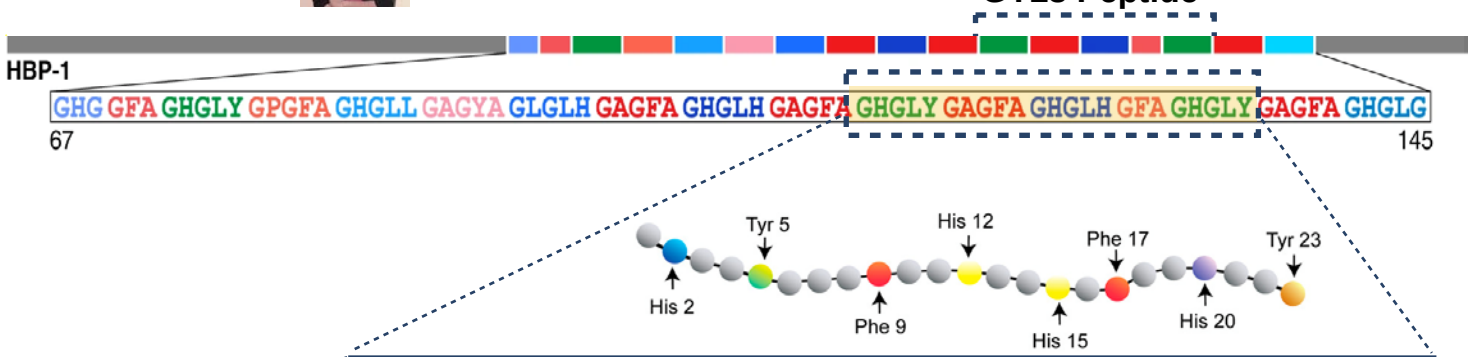
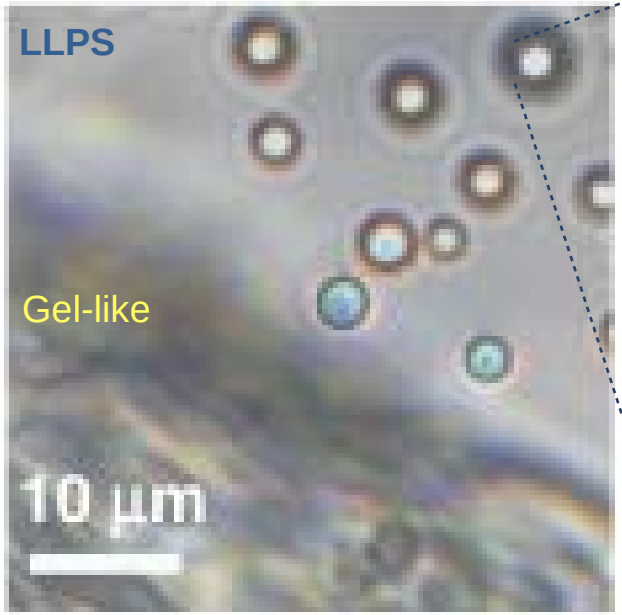
# Exploring Inter-atomic Interactions in a Squid-beak Derived Peptide that Regulate LLPS

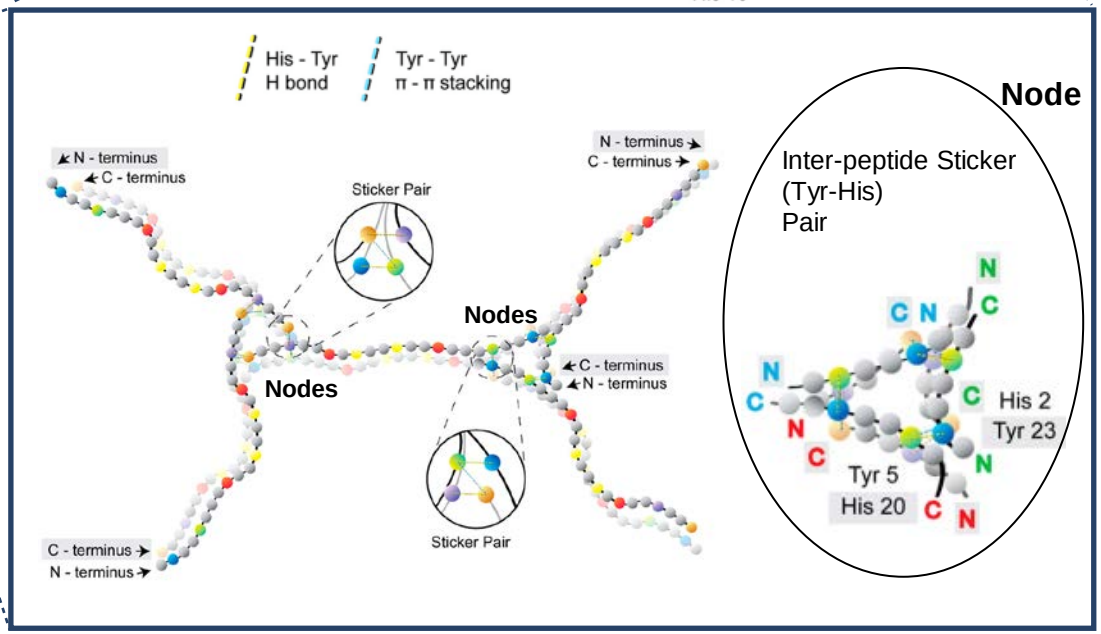











Modelling Atomic level interactions in GY23 that govern LLPS

**Collab: Biological and Biomimetic Material Laboratory (NTU) Ali Miserez**
*J. Phys. Chem. B* 2021, 125, 25, 6776-6790 | Funds: MOE AcRF Tier 3

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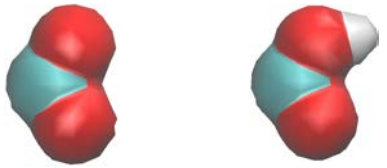
# New molecular descriptors for the prediction of the membrane permeability of cyclic peptides

Two new parameters shows enhanced correlation to the experimental membrane permeability of cyclic peptides

1. cPSA (charge reweighted polar surface area) take into account the atom polarity

Current definition: $PSA = \sum PSA_i$

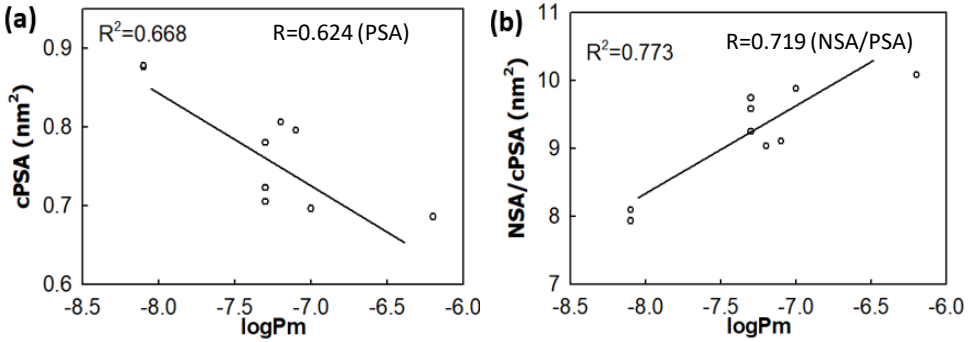


PSA_COO- < PSA_COOH and Pm_COO- < Pm_COOH → conflict

Solution: charge reweighted PSA: $cPSA = \sum q_i * PSA_i$

| peptide | sequence | log $P_m$ |
|---|---|---|
| 1 | cyclo[d-Leu-d-Leu-Leu-d-Leu-Pro-Tyr] | −6.2 |
| 2 | cyclo[d-Leu-d-Leu-d-Leu-d-Leu-Pro-Tyr] | −7.0 |
| 3 | cyclo[Leu-Leu-Leu-d-Leu-Pro-Tyr] | −7.1 |
| 4 | cyclo[Leu-d-Leu-d-Leu-d-Leu-Pro-Tyr] | −7.2 |
| 5 | cyclo[Leu-Leu-Leu-Leu-d-Pro-Tyr] | −7.3 |
| 6 | cyclo[d-Leu-d-Leu-d-Leu-d-Leu-d-Pro-Tyr] | −7.3 |
| 7 | cyclo[Leu-Leu-d-Leu-d-Leu-Pro-Tyr] | −7.3 |
| 8 | cyclo[Leu-d-Leu-Leu-d-Leu-d-Pro-Tyr] | <−8.1[a] |
| 9 | cyclo[Leu-d-Leu-Leu-Leu-d-Pro-Tyr] | <−8.1[a] |

2. NSA/cPSA (the ratio of non-polar surface area to polar surface area) take into account the contribution of both polar and non-polar atoms




*J. Chem Phys 2022 156 065101*

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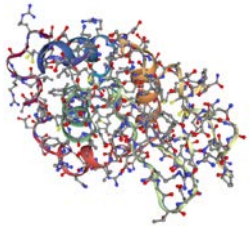
# Collaborations with the AI team

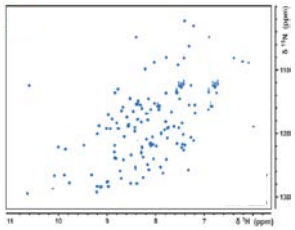
## NMR Chemical Shifts Prediction Based On Protein Structure

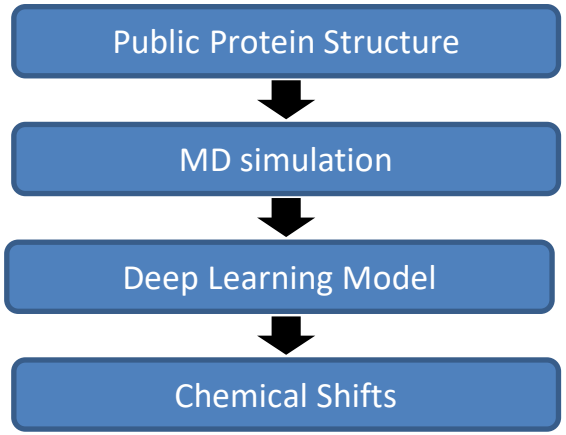
**Objective:** based on atom coordinates only, to predict protein chemical shifts with high accuracy.

**Deliverable in Biology:** a tool to facilitate protein structure analysis in NMR experiments.

**Deliverable in AI:** a customized AI framework can extract physicochemical features from 3D structure of molecules.








Team: Li Jianguo, Liu Wei, Lee Nicole

Liu Wei (Imaging Division) + Nicole Lee (Hwa Chong)

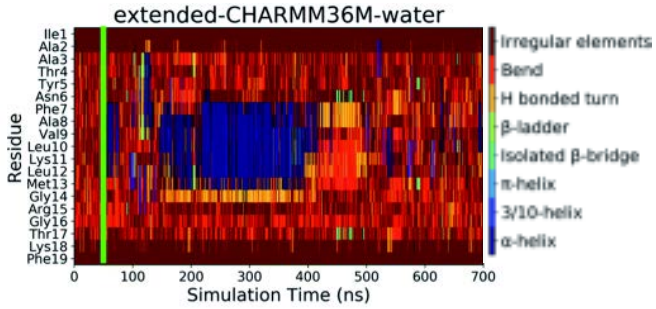
Machine learning guided discovery of highly selective antimicrobial peptides for treatment of drug resistant bacteria

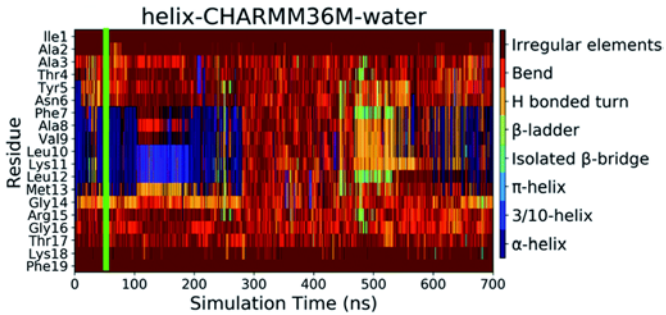
AI3 HTPO

Eddy Tan Wei Ping (Imaging Division)

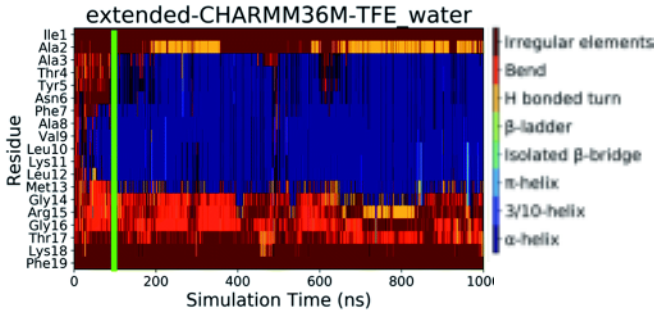
# Replica Exchange Simulations Reveal Conformational Transitions of IDPs in Membrane-Mimicking Solvents

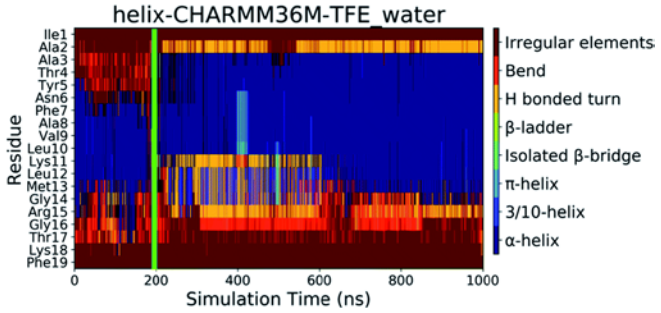
PLP peptide in water:

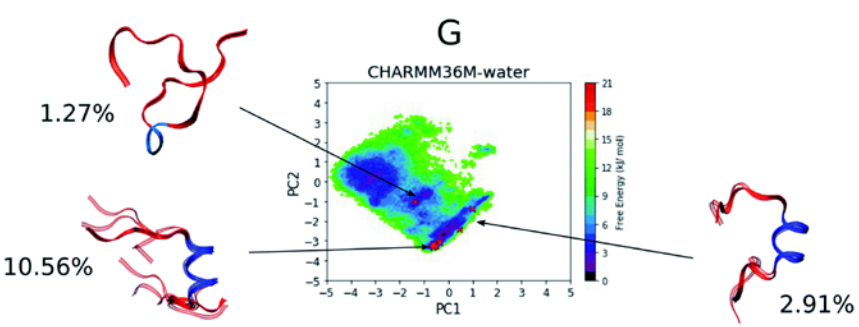


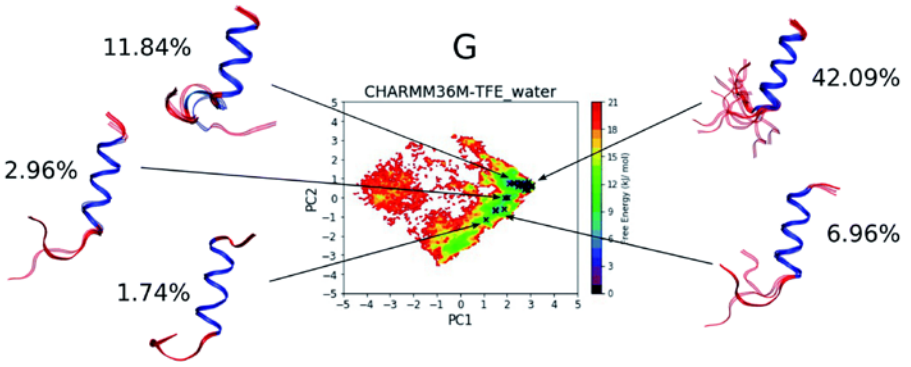




PLP peptide in membrane mimic solvent:



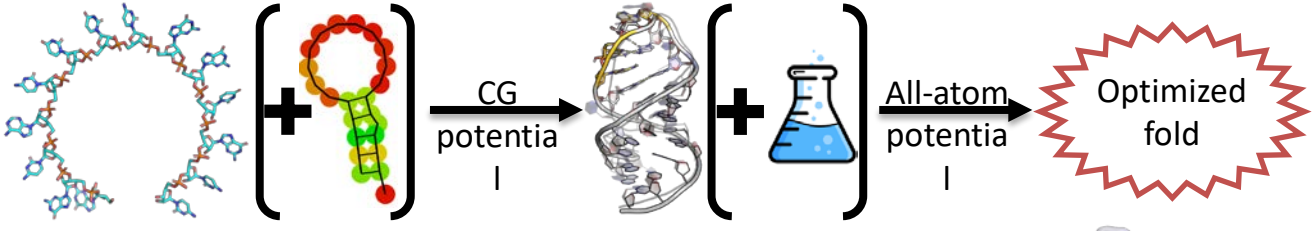




Agreement with NMR and CD data:

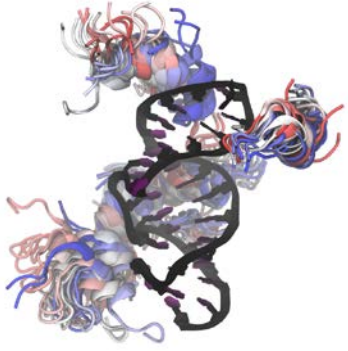
CHARMM36 = CHARMM36m > Amber14SB > Amber14SB-IDPs

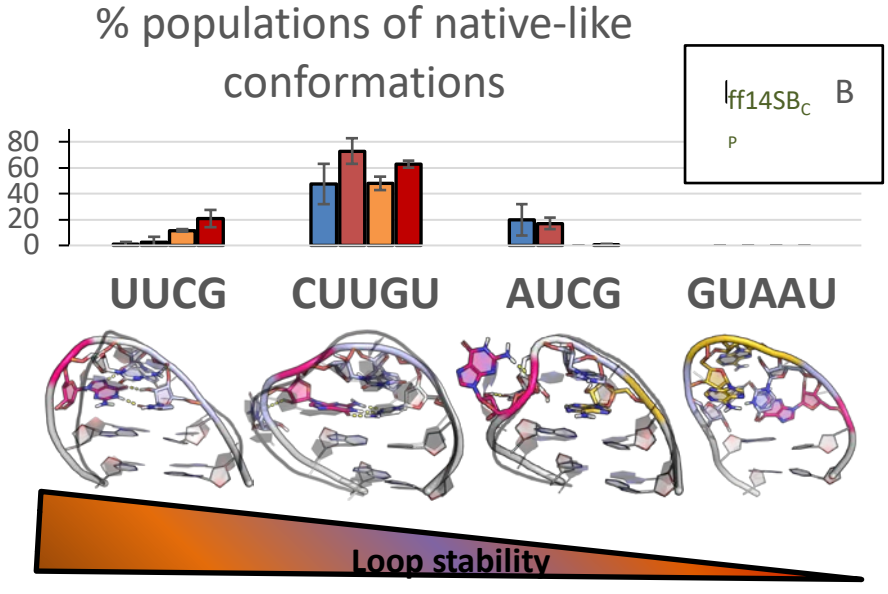
*Chem. Sci. 2022, 13, 1957-1971* **Collabs: Univ Southampton, Astra Zeneca Cambridge**

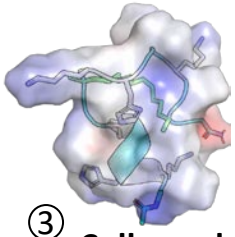
# Modeling RNA-peptide functional complexes



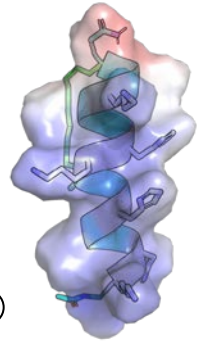

Complex assembly



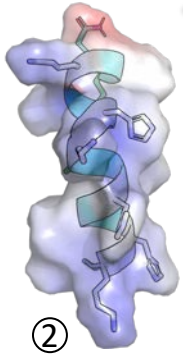


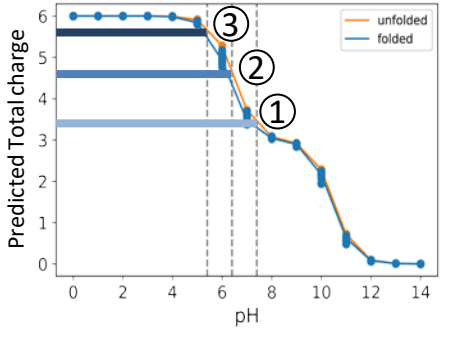
③ **Collapsed**



① **Straight α-helix**



② **Bent helix**




*Manuscript in preparation*

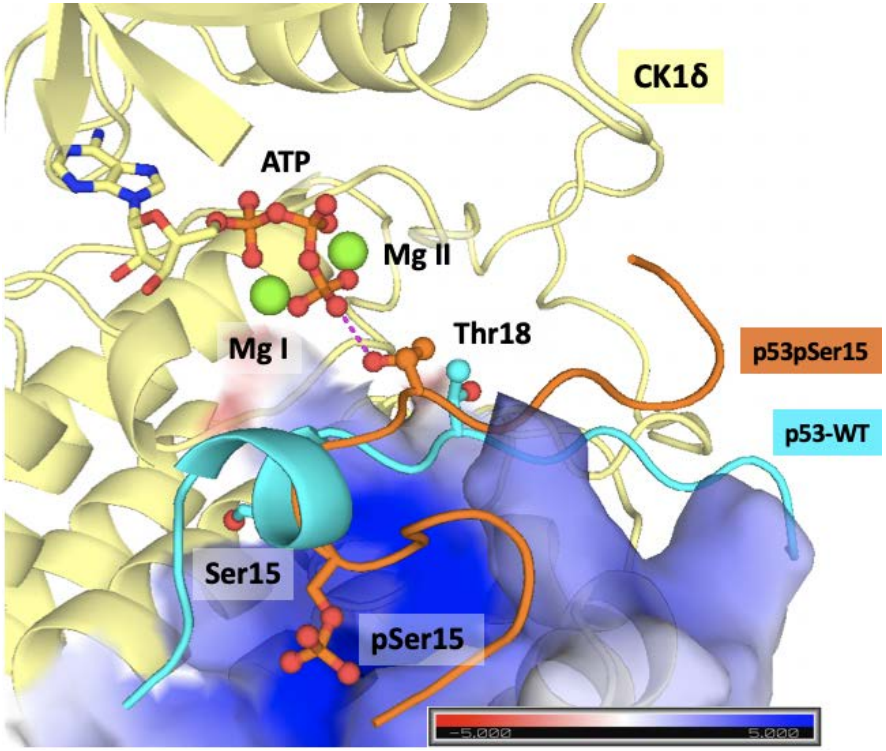
**Staple peptides to transport RNA modulators into cells**

# Mechanisms of multiple phosphorylations in signalling

**Sequential phosphorylation required for p53 activation**

Sonia Nicolaou

Jim Warwicker
University of Manchester




- Why is Ser15 phosphorylation a prerequisite for Thr18 phosphorylation by CK1δ?
  - Cationic pocket in CK1δ – sequestration of pSer15
  - Thr18 is placed in vicinity of ATP for phosphate transfer

***Manuscript under review***

Positively charged feature conserved across organisms – suggests mechanism evolved to ensure finely tuned control of p53 activation

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**Patents filed (p53lab/IMCB (Chris Brown) + ICES)**

1. Priority application - Cell permeable Macrocyclic Peptides useful for Eif4E Cap-Binding site inhibition

2. Priority application filed - P53 Peptidomimetic Macrocycles (Serial number: 63/288204)

3. National Phase application filed for “p53 activator peptidomimetics macrocycles” (WO2020257153A1)

4. National phase application filed for “macrocyclic peptide as potent inhibitors of K-ras G12D mutant” (WO2021126799A1)

Others:

1. Molecular Design Of New Antibiotics And Antibiotic Adjuvants Against MCR Strains – filing several countries

2. Non-Membrane Disruptive P53 Activating Stapled Peptides – filing in countries

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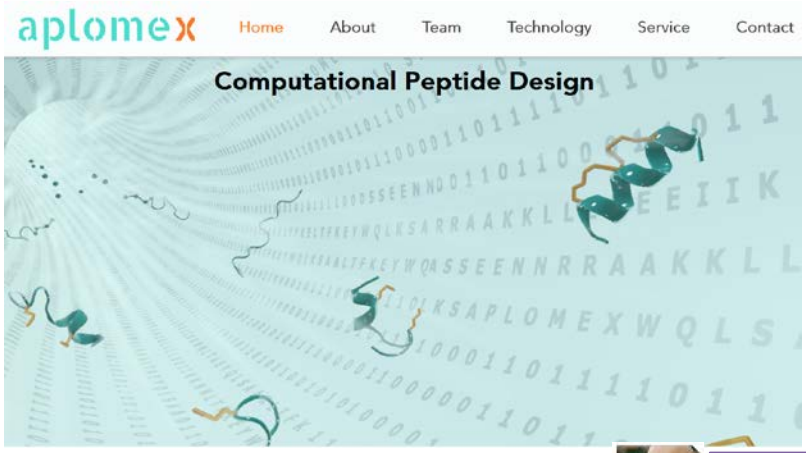
# Thank You


**T-up**

**Aishwary, Akshita, Ashar, Jianguo, Minh, Pietro*, Raghav, Shruti**
**Dimitrios, John, Megan, Sonia**
**Jessica**

**Other teams in BII**
**& ASTAR**

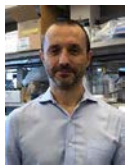
## Job seekers

**Shilpa: ProteinQure, Canada: Protein drugs**
**Mara: DioSynVax, Cambridge – ML in vaccine design**
**Lauren: Medchemica, UK – Medchem**
**Dale Sutchfield: Peak.ai, UK – Data & AI**
**Binh – Univ of Melbourne/Queensland**

**Special thanks to**
**Our Admin team**
**Our IT team**





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