# Atomistic Simulations & Design

BII PI seminars
April 2021

Understanding mechanism, designing molecules as probes/inhibitors/therapeutics
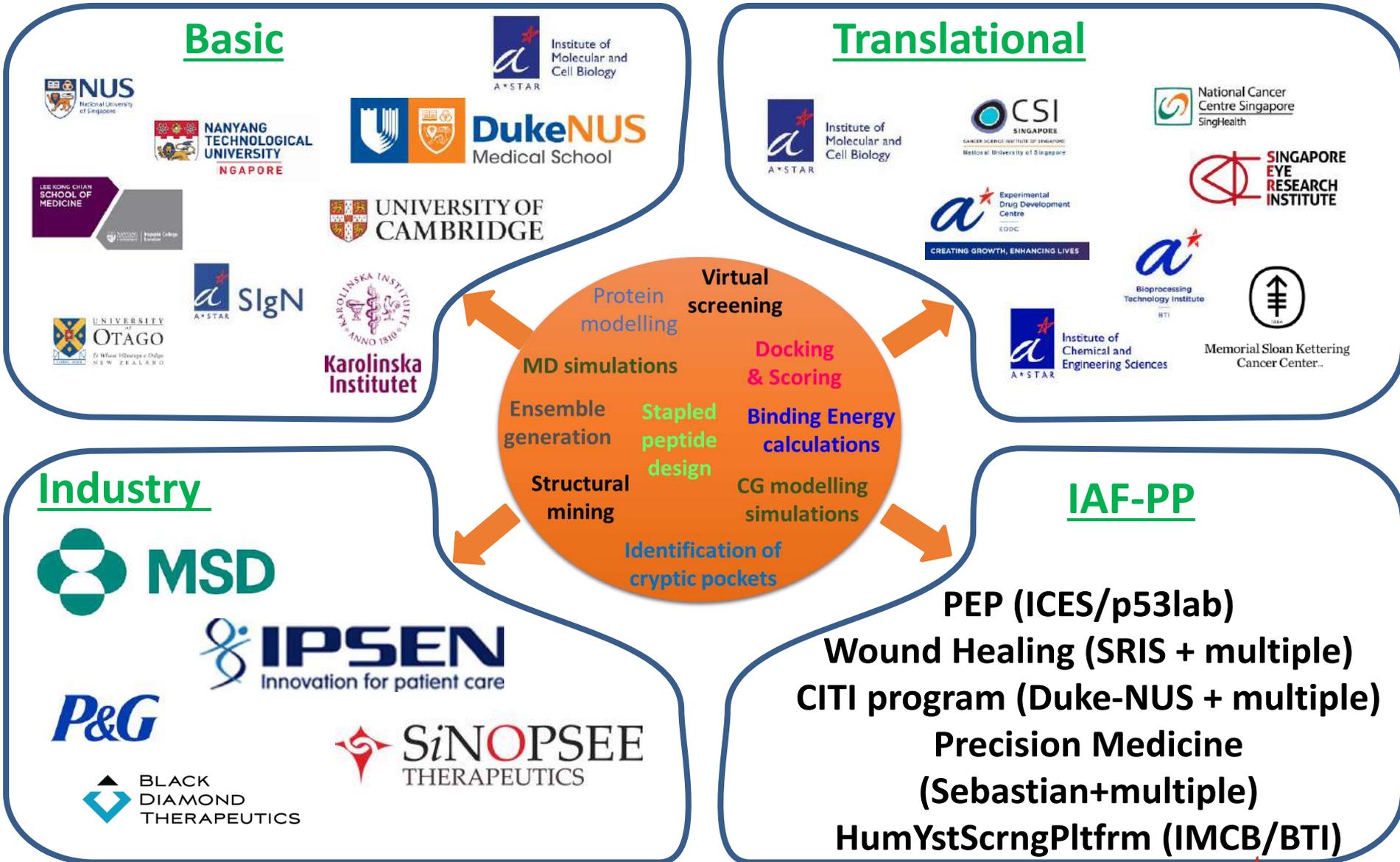
National Precision Medicine: SNPDrug3D
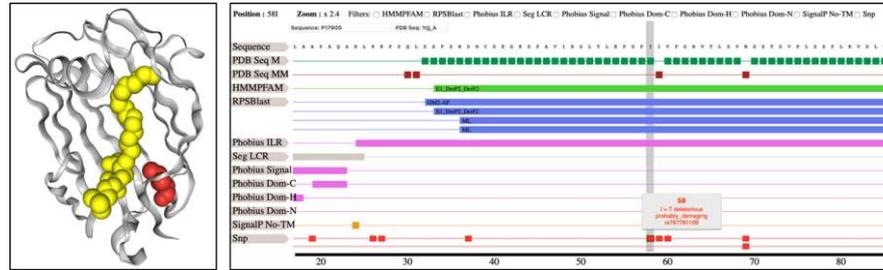
Phase I

SNP database to help clinicians to make more informed decision.

Samples/Data contributors

Data integration, analytics and survey

Industry strategy

Translation into clinic

xDFG Mutations Trigger a Sensitivity Switch from Type I to II Kinase Inhibitors
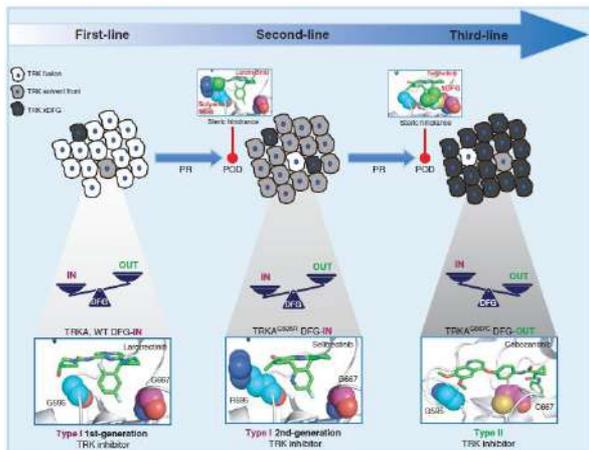
Cancer Discovery, 11, 126 (2021)

Acetylation reverses a locally observed mutant p53 and restores its activity

Nature Comm. 11, 2086 (2020)

FOXA1 Mutations Influence Therapeutic Response in Breast Cancer
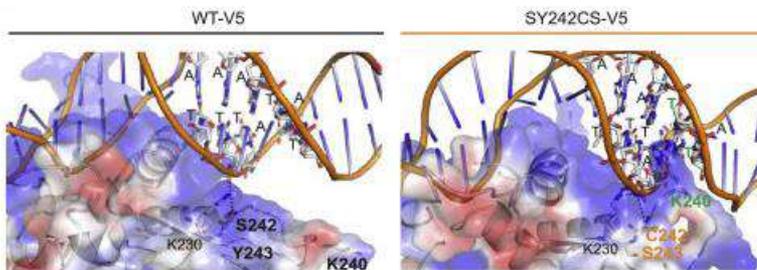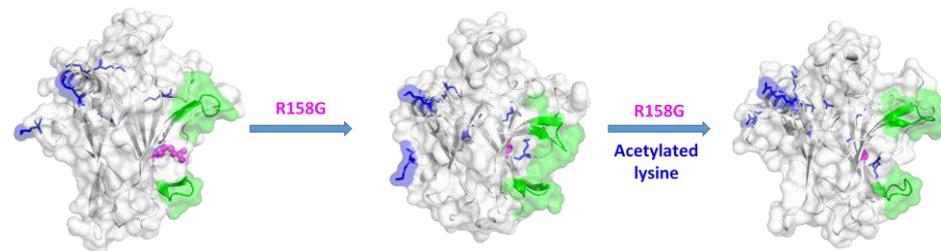
Cancer Cell. 38, 534 (2020)

A common local c-MET SNP drives SCLC cancer through Her2
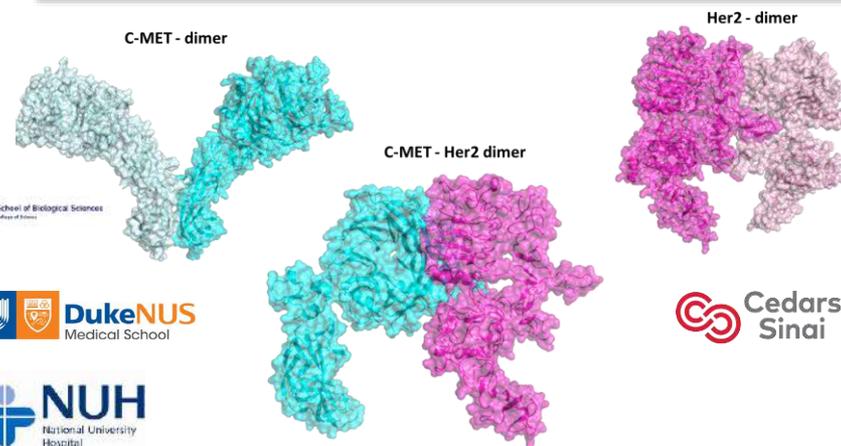
Nature Comm. 11, 1556 (2020)

Peptide (stapled) Design – Basic & Industry

A new kid in town
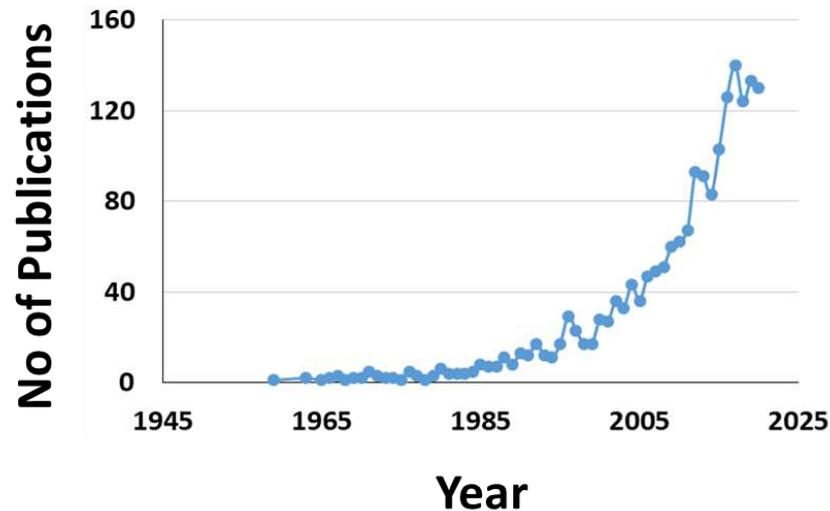
Raghav, Pietro, Shilpa, Jianguo, Minh +
Yaw sing, Sonia, Shruti, Minh, Aishwary,
Ashar

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Linear Peptide

Linkers

Constrained Peptide

Protein – Constrained Peptide complex
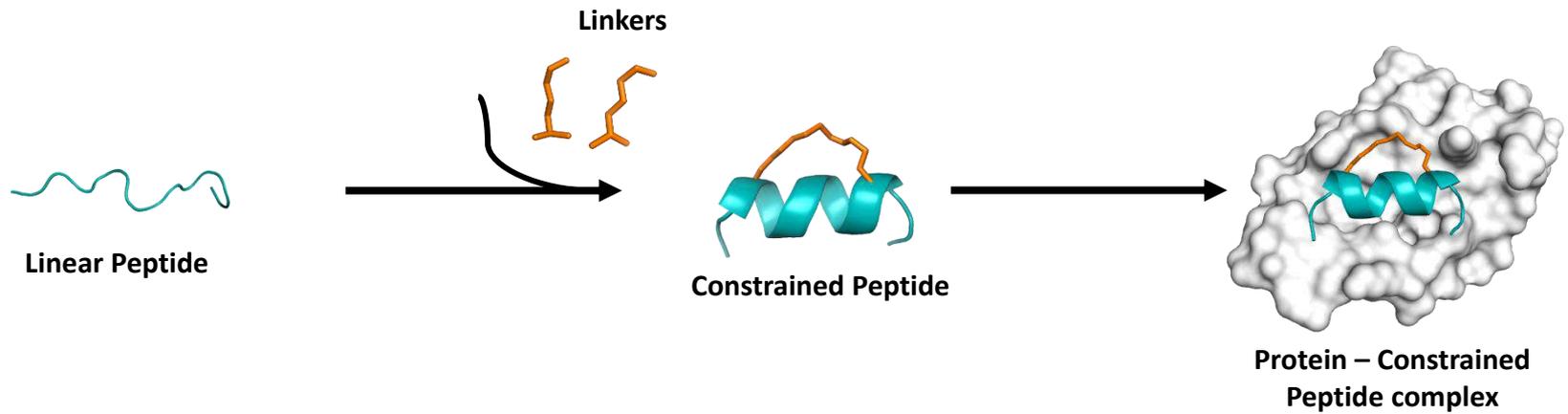
|	Small Molecules	Peptides			Biologics
		Linear	Cyclic	Stapled	
Potency/specificity/toxicity	- - - -	++	+++	++++	++++
Metabolic stability	- - - -	+- - -	++- -	++++	++++
Acquired Resistance	- - - -	++++	++++	++++	+++
Inhibition of PPI*	- - - -	+++	++++	++++	++++
Tissue penetration	++++	+- - -	+ - - -	++++	- - - -
Immunogenicity	++++	++--	++++	++++	- - - -
Patient compliance	++++	- - - -	- - - -	++++	- - - -
FDA approved drugs	2500	49	11	0	250

Peptide (stapled) Design

First ever cell permeable stitched peptide
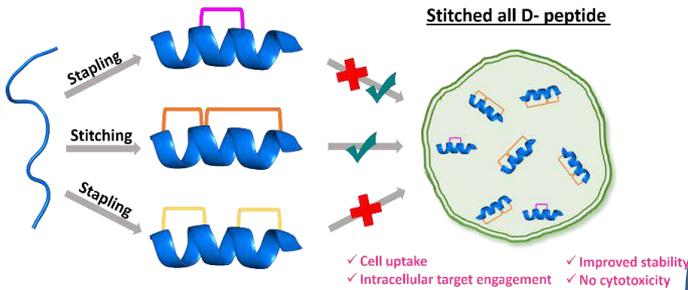
Chem. Sci., 11, 5577-5591(2020)

2 joint patents

Tailored Stapled-Peptides Targeting eIF4E

joint patent
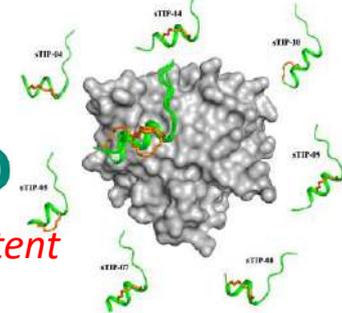
Chem. Sci., 10, 2489 (2019)

Covalent stapled peptide
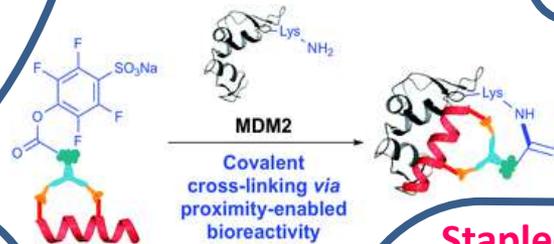
Chem. Sci., 10, 5056 (2019)

1ˢᵗ gen potent binders
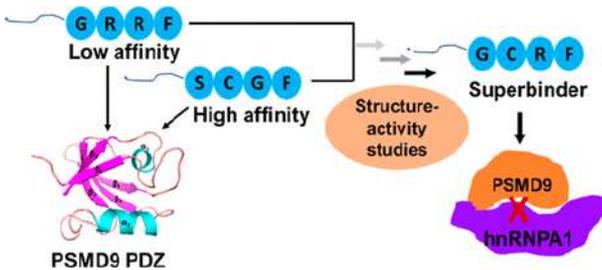
Biochemistry, 58, 3422 (2019)

Stapled non-helical peptide
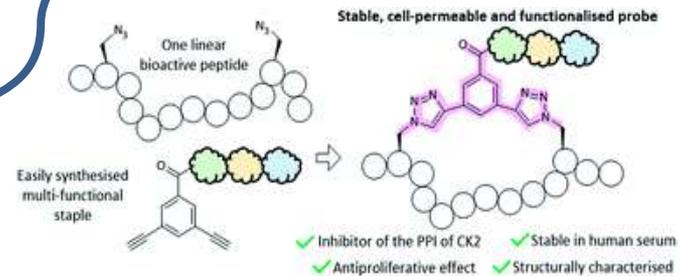
Chem. Commun., 55, 7914 (2019)

DStabilize

A server to generate enantiomers of peptides and proteins

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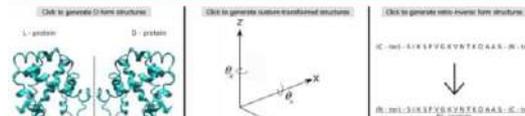
Some examples…..

Applications in:

➢ **Oncology**

➢ **Infectious Diseases**

➢ **Inflammation**

➢ **Opthalmology**

Circles around "In-silico Modelling":
- CK2α/CK2β
- TNKS-PARP
- NLRP3 - ASC
- Mdm2-p53
- Ace2 – RBD
- eiF4E – eiF4G
- ATRX - DAXX
- S100B – p53
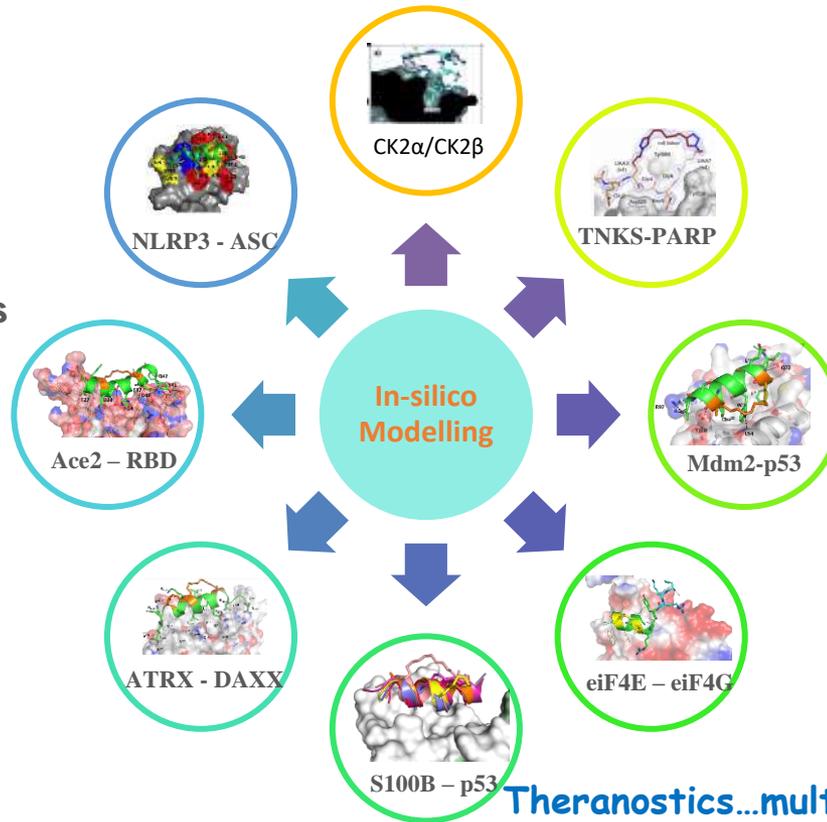
➢ **>60 publications** (JACS,PNAS, ACS Chem Biol, Chem. Sci, Angew. Chem Int Ed., NRDD, DDT)

➢ **10 patents filed/granted/process**

➢ **Pharma collaborations (Ipsen, MSD)**

➢ **Developed several first in class molecules**

Theranostics…multiple myeloma novel approach..NUH

Stratification of immunotherapy patients: CITI program pan Singapore

Shruti, Raghav

Bioinformatics Institute
BII

Jianguo

Combating antimicrobial resistance: Superbugs succumb to combination therapy
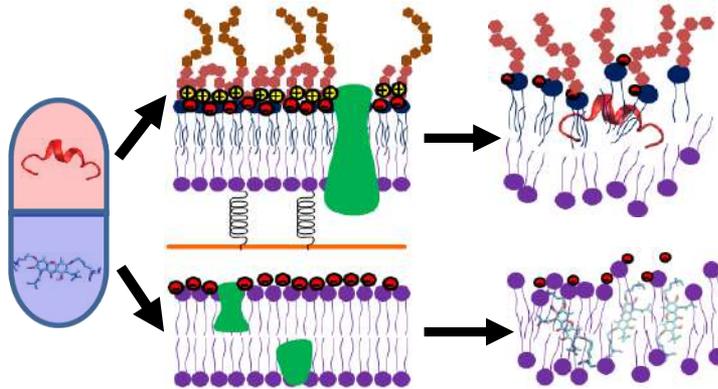
Antimicrobial peptides permeabilize bacterial outer membrane

Semi-synthetic natural products perturbs bacterial inner membrane

Singapore National Eye Centre
SingHealth

DukeNUS
Medical School

Tan Tock Seng
HOSPITAL
National Healthcare Group

SinSa
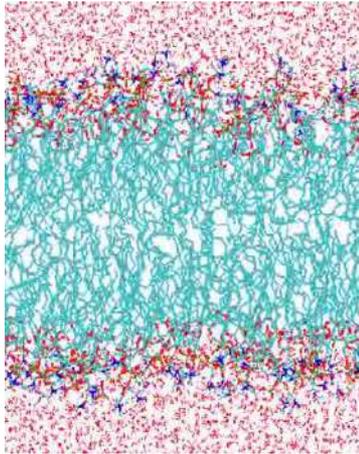
Fragment based drug design
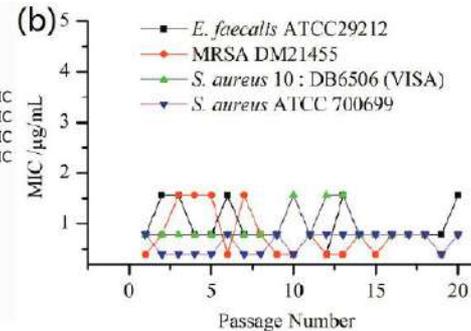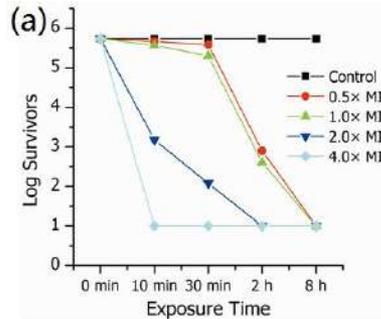
AM016 displays rapid bactericidal effect and low tendency to induce resistance

Multiple publications inlcuding J Med Chem, BBA-Biomem, JCIM 4 patents

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Computational Biomaterial Science

Underwater Adhesion

Barnacle Cement Proteins

Disorder-order Interplay

Surface adhesion

Mineralization

Protein-based Materials

Squid Sucker Ring Teeth

Squid Skin
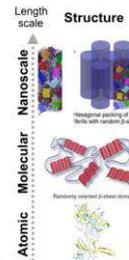
Reflectin proteins

Exploring Molecular & Structural Properties of Unique Biomaterials

Chitin-binding

Squid Beak

LLPS

Ministry of Education
SINGAPORE
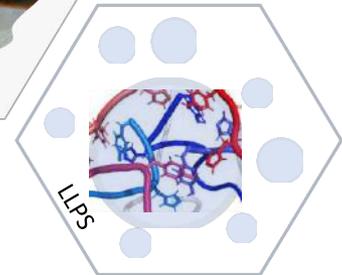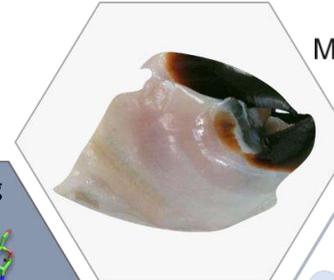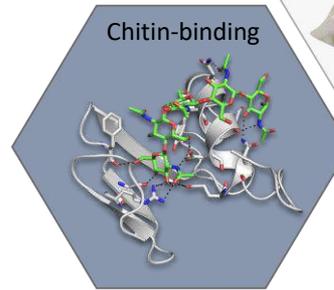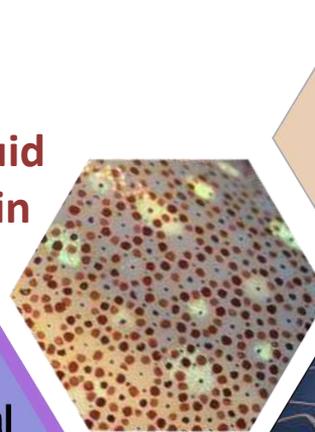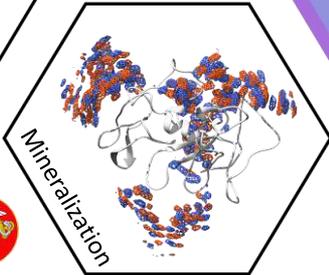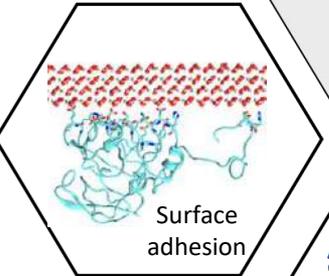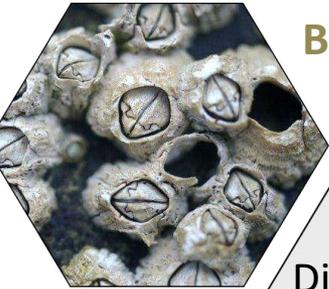
J. Struct. Biol. (2021)
Chem. Mater. (2020)
Phil. Trans. R. Soc. B (2019)

Akshita

Exploring Applications of Quantum Computing to understand Biomolecular Mechanisms

By recasting certain biological problems existing hybrid Quantum-Classical computing methods can be used on near-term noisy quantum computers to enhance our understanding of
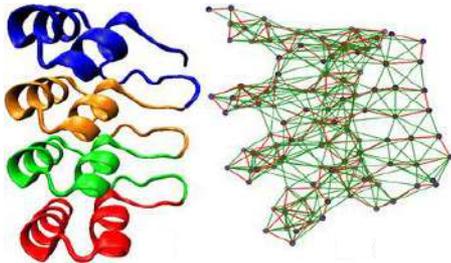

Protein Structure depicted as a network, comprising nodes and edges.
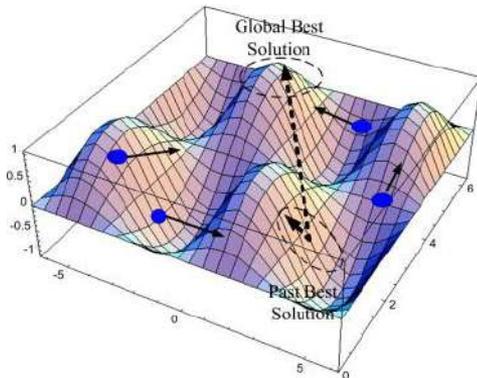
Protein-ligand interaction visualized as a optimization problem.
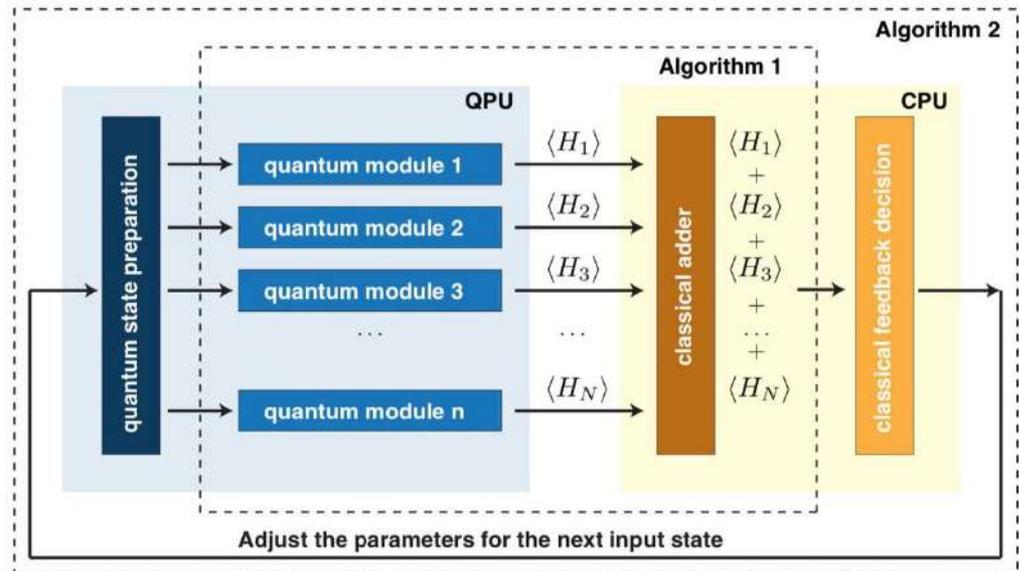
Use of hybrid Quantum and Classical computing, in VQE to address problems solvable by near-term noisy quantum computers.

Thank You