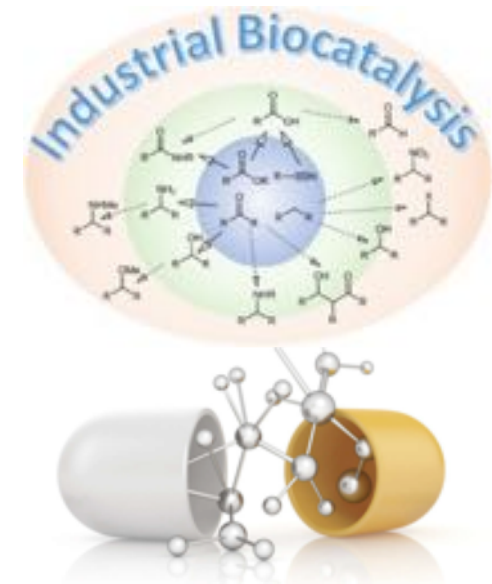
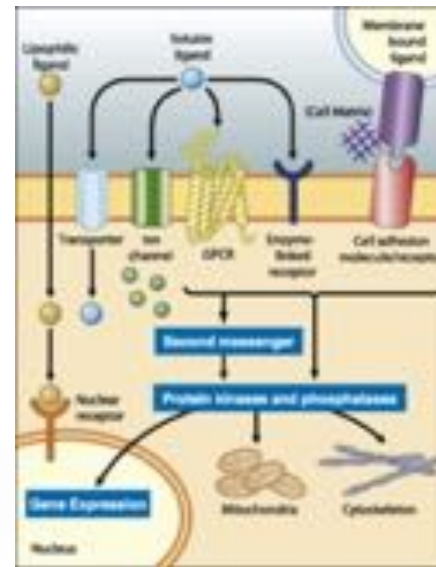
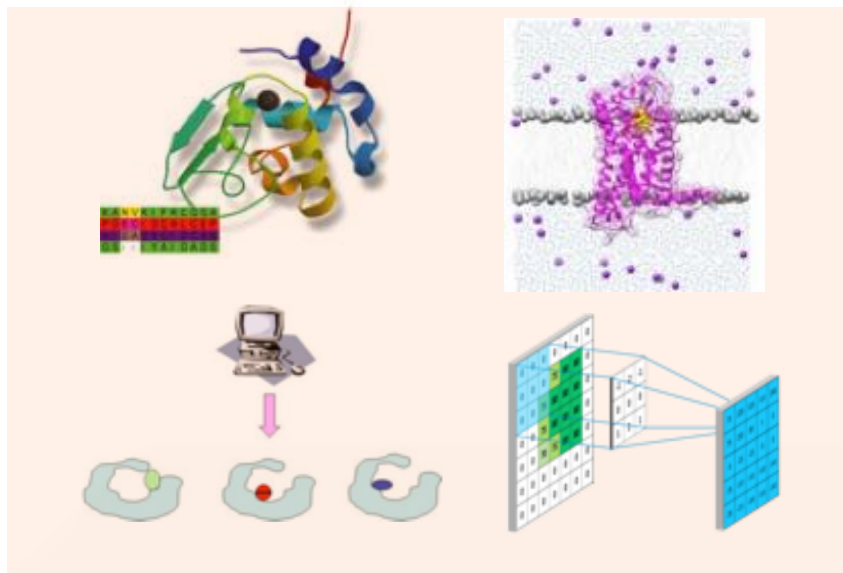
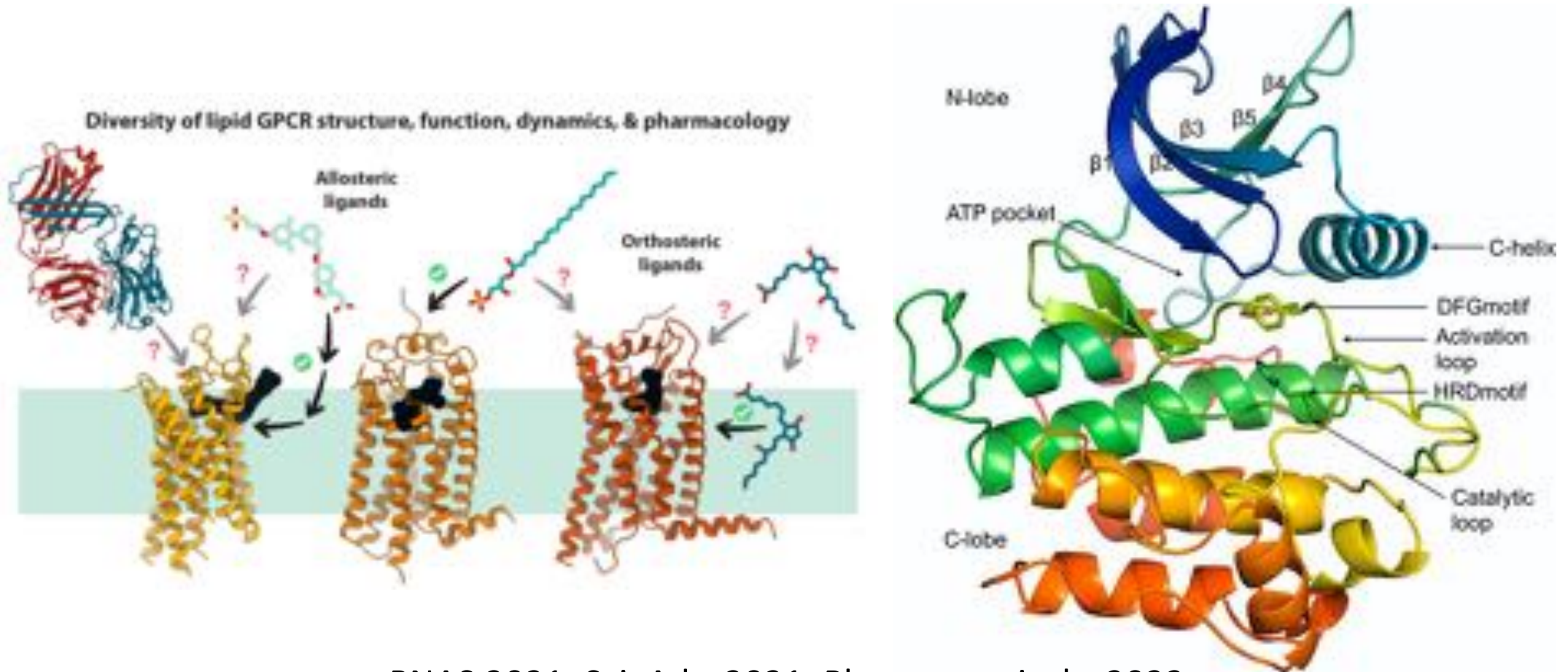


# Computational modeling of protein-ligand interactions



# Signaling proteins: structure and function mechanisms

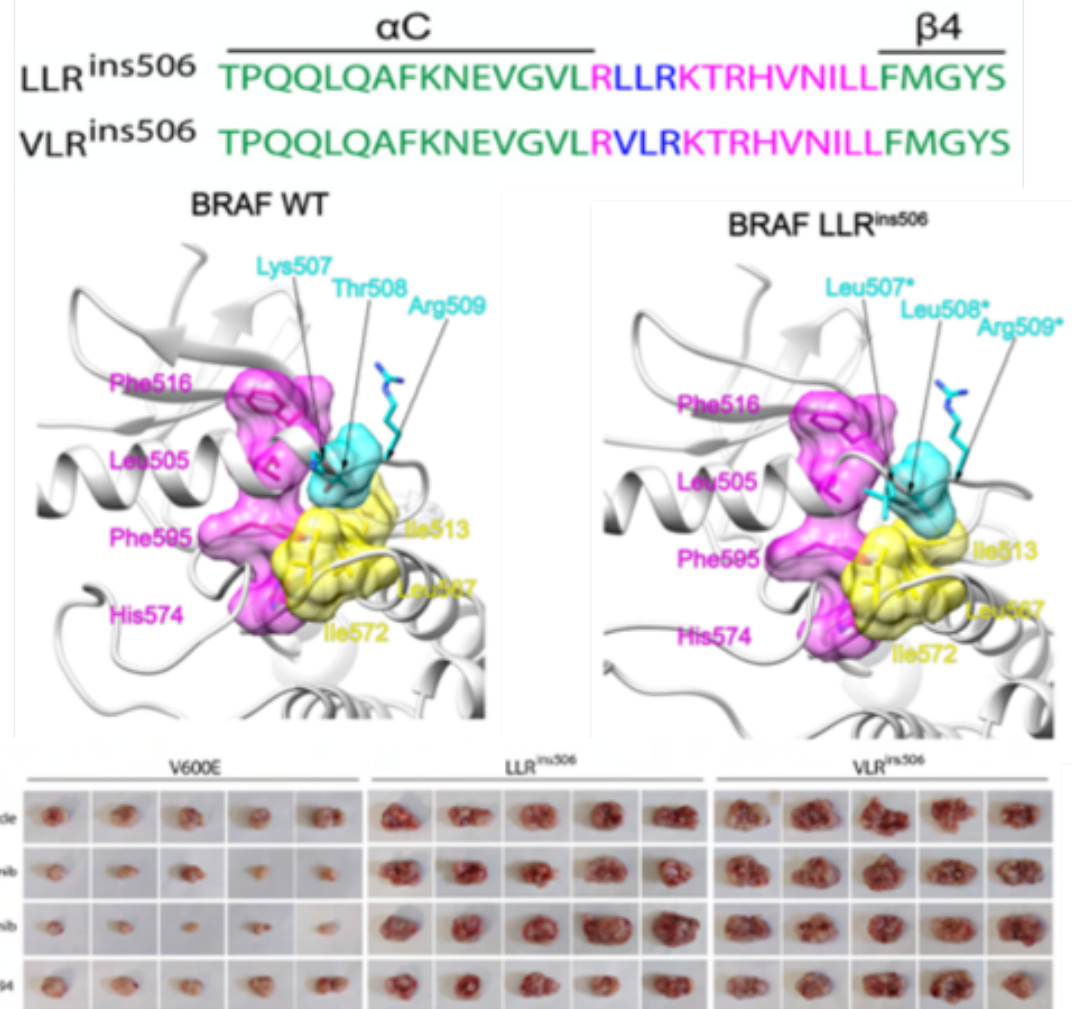


PNAS 2021; Sci. Adv. 2021; Pharmaceuticals, 2022

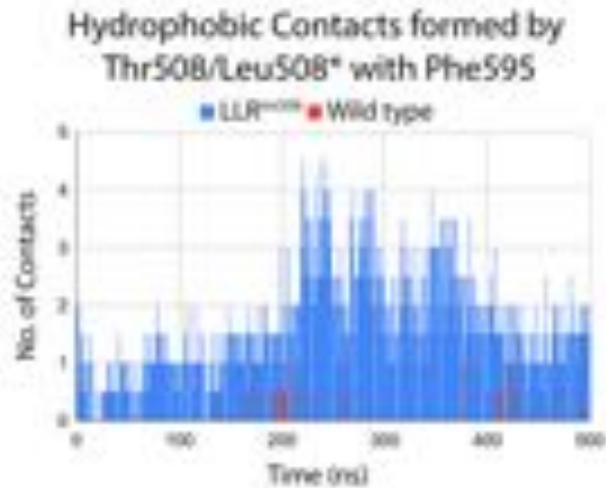
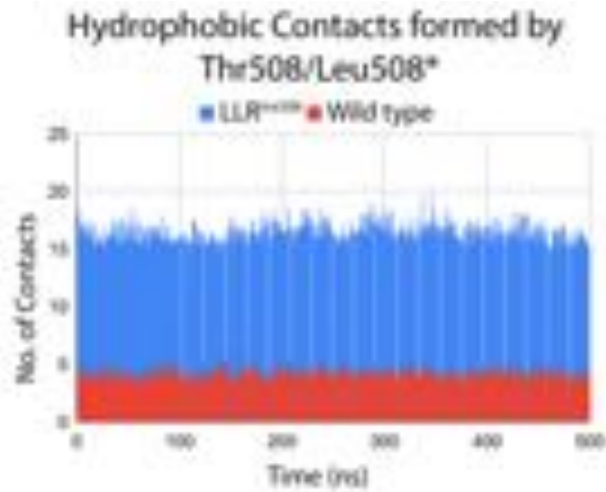
Krishna, Ravi, Yossa

# BRAF LLR<sup>ins506</sup> insertion mutations

- Mutation leads to constitutive activation of BRAF
- Mutant BRAF LLR<sup>ins506</sup> resistant to BRAF V600E drugs
  - dabrafenib & vemurafenib (approved)
  - PLX8394 (preclinical trails)
- Insertion occurs in  $\alpha$ C- $\beta$ 4 loop region
  - Part of dimer interface
  - Proximal to R-spine



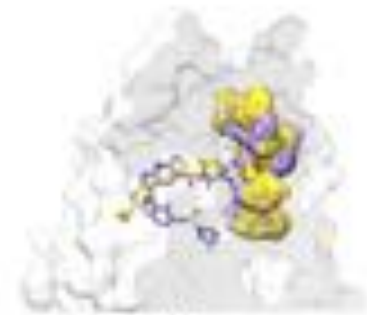
# Insights from computational modeling and simulations



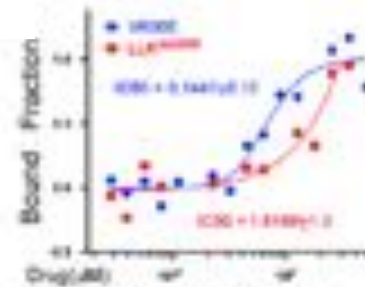
ChemPLP fitness scores  
 Vermurafenib v. R-spline<sup>T508</sup> = 114.02  
 Vermurafenib v. R-spline<sup>WT</sup> = 99.89



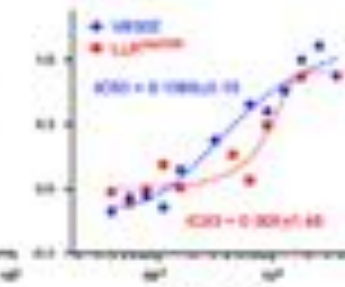
ChemPLP fitness scores  
 Dabrafenib v. R-spline<sup>T508</sup> = 115.62  
 Dabrafenib v. R-spline<sup>WT</sup> = 76.42



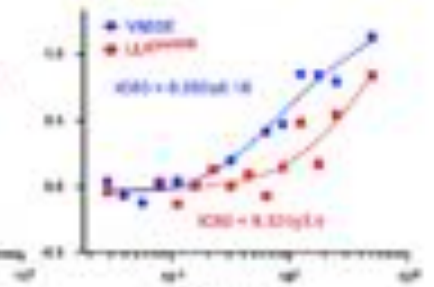
ChemPLP fitness scores  
 PLX8394 v. R-spline<sup>T508</sup> = 120.27  
 PLX8394 v. R-spline<sup>WT</sup> = 108.90



Affinity (uM)  
 Vermurafenib  
 V800E 0.144 ± 0.12  
 LLR<sup>T508</sup> 1.619 ± 1.3



Affinity (uM)  
 Dabrafenib  
 V800E 0.107 ± 0.15  
 LLR<sup>T508</sup> 0.908 ± 0.48

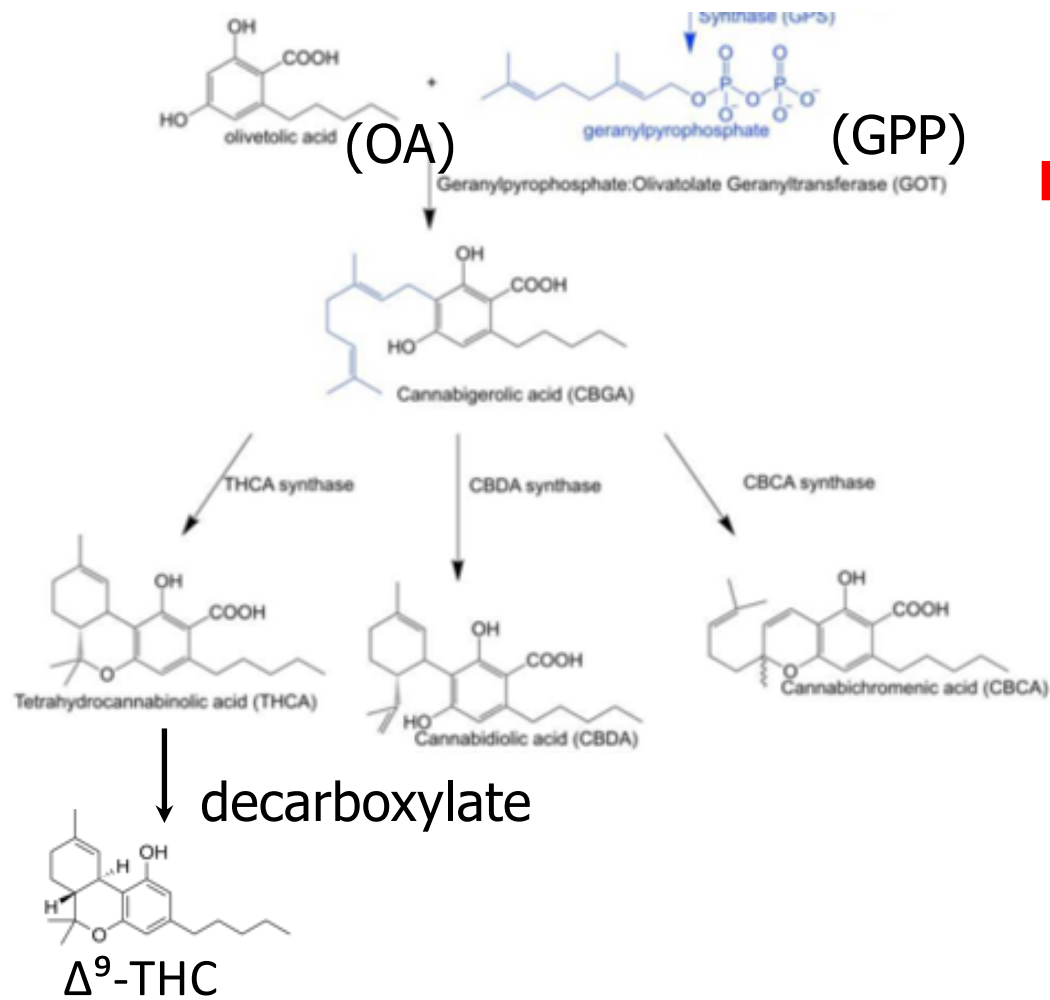


Affinity (uM)  
 PLX8394  
 V800E 0.293 ± 0.18  
 LLR<sup>T508</sup> 5.321 ± 3.4

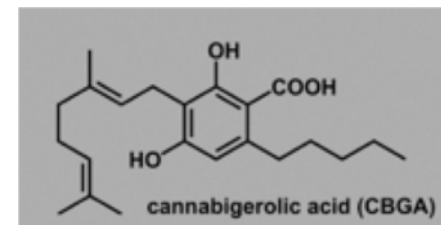
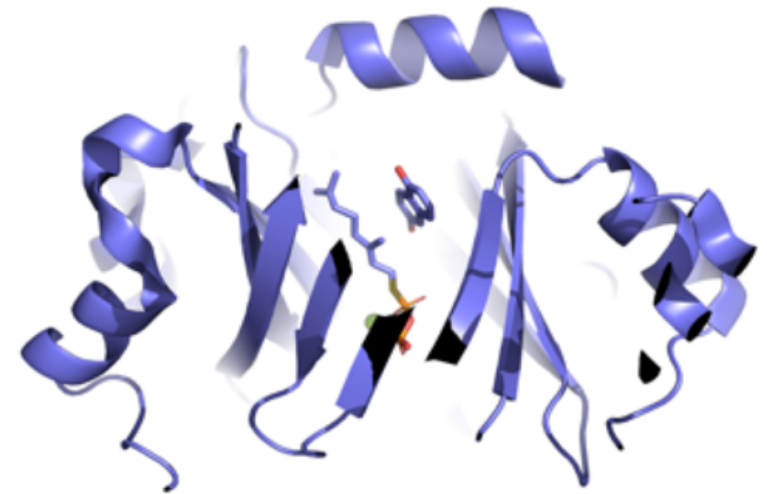
Krishna



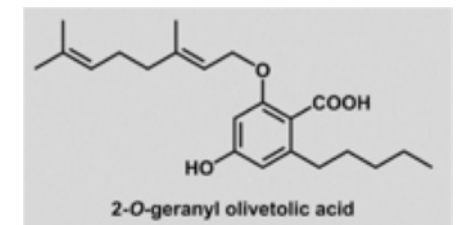
# Cannabinoid biosynthesis



**NphB is a promiscuous bacteria prenyltransferase**



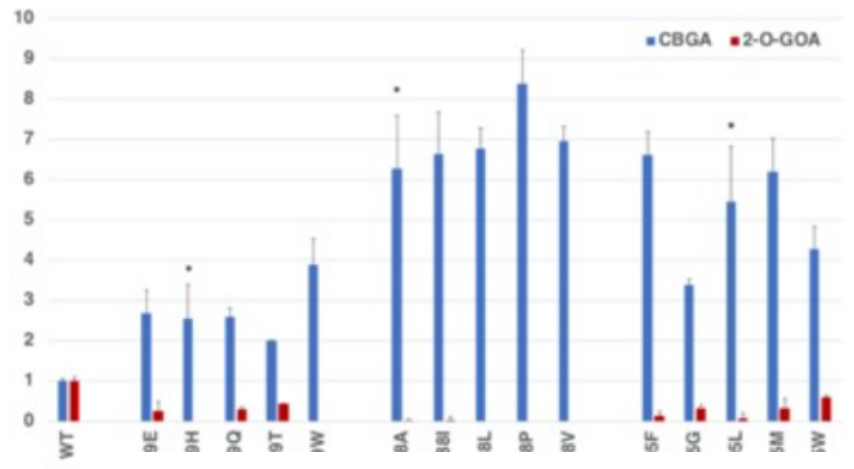
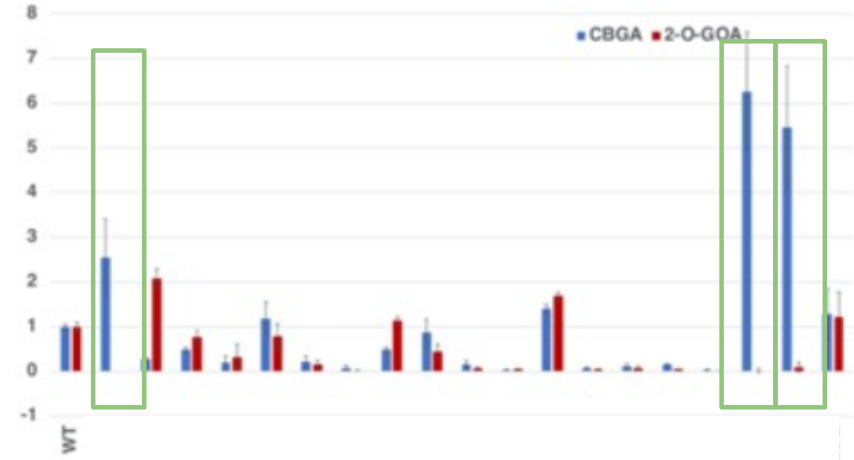
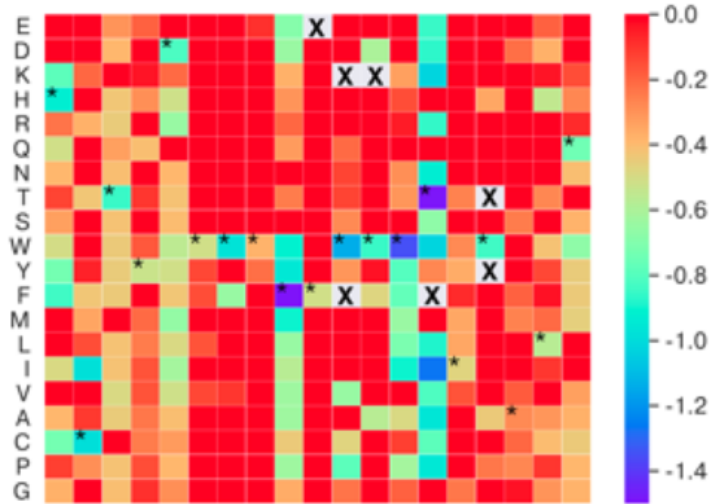
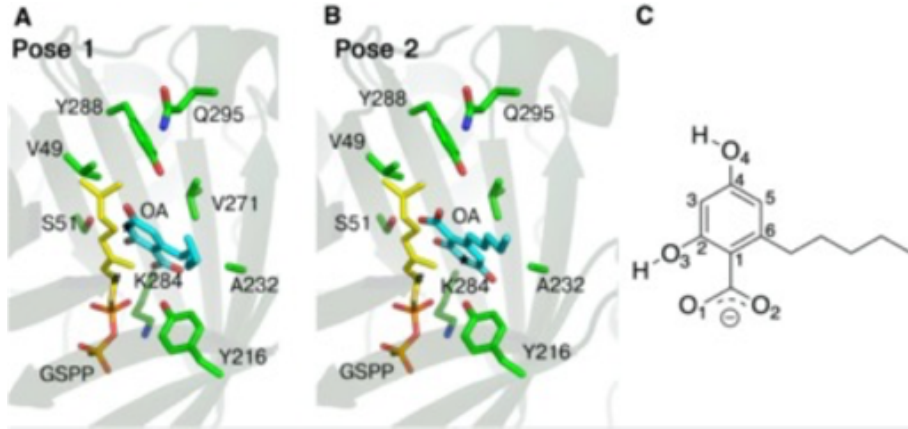
Desired product



Side product

# Rational mutagenesis

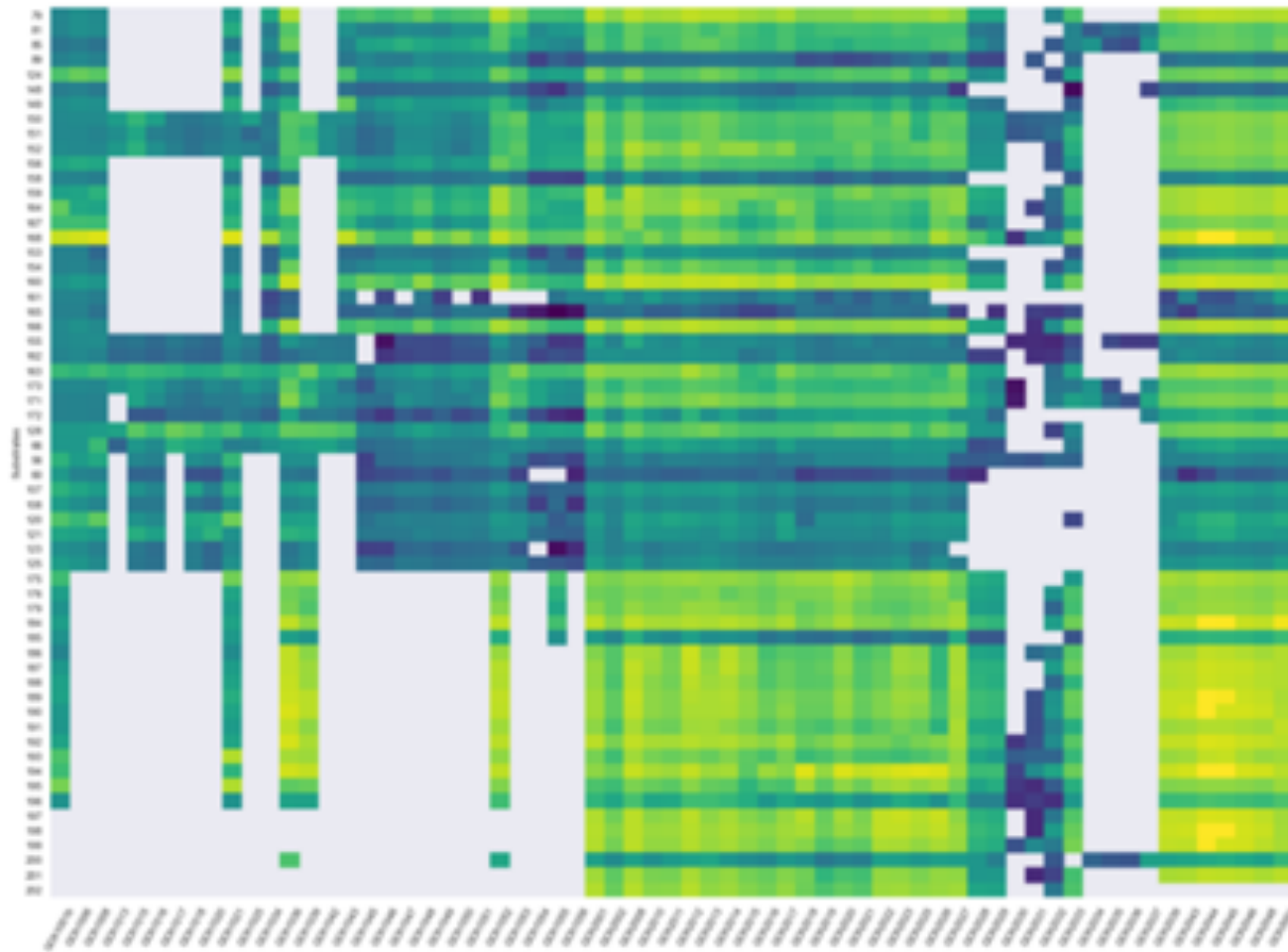
Glide XP docking score wrt WT



ACS Catal. Accepted.

Yossa

# Enzyme engineering for industry biocatalysis

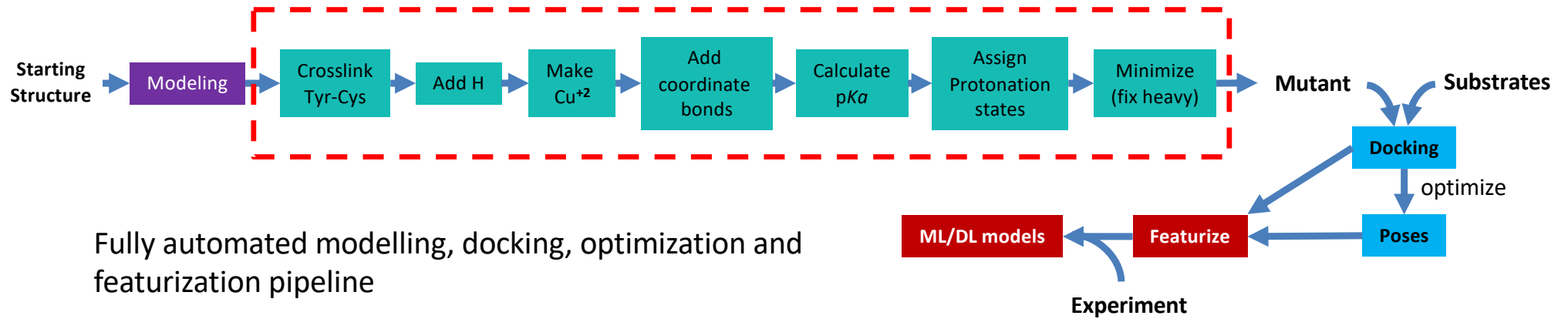


## colorimetric data

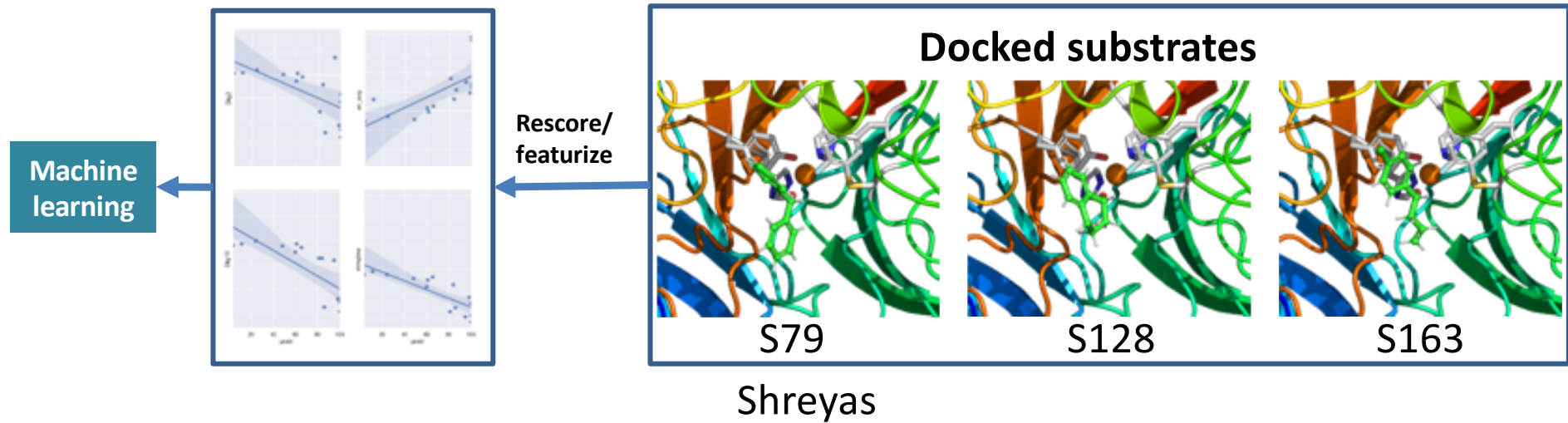
- 55 variants/mutants
- 60 substrates
- Total ~ 3000 datapoints

BII, ICES, SIFBI, IHPC  
Pfizer, gsk, MSD,  
syngenta

# Modeling → Docking → AI pipeline



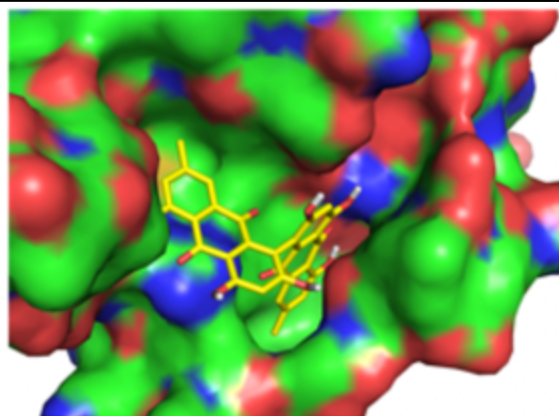
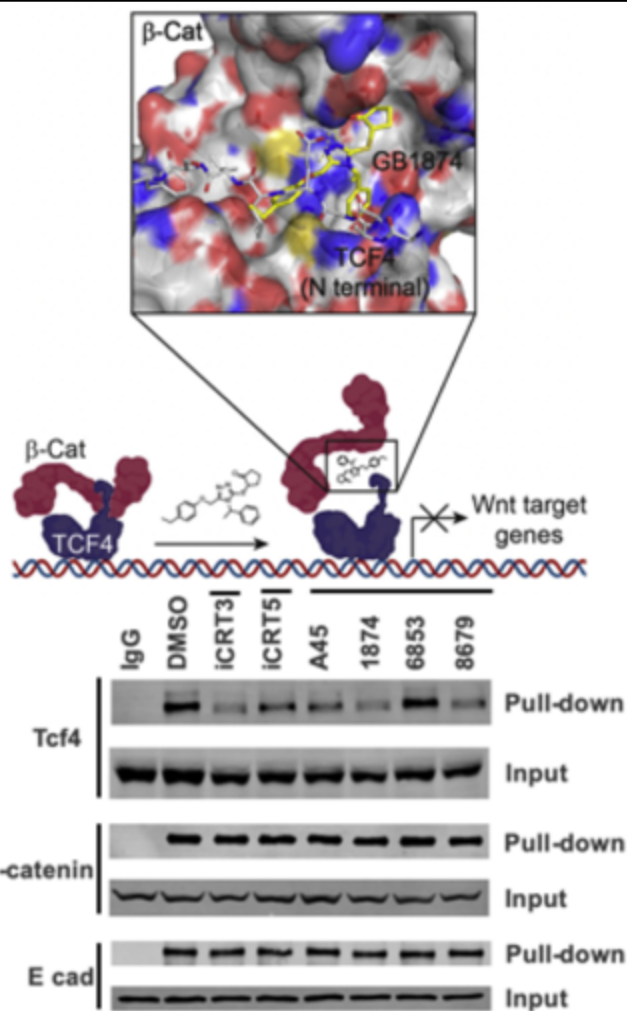
Fully automated modelling, docking, optimization and featurization pipeline



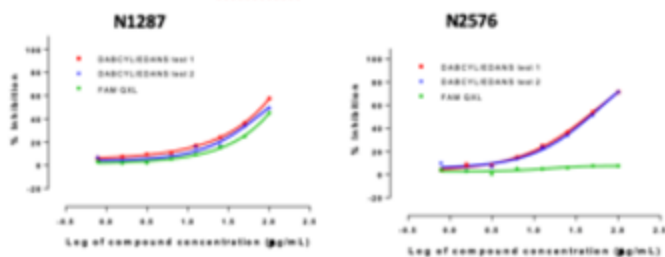


# Ligand discovery

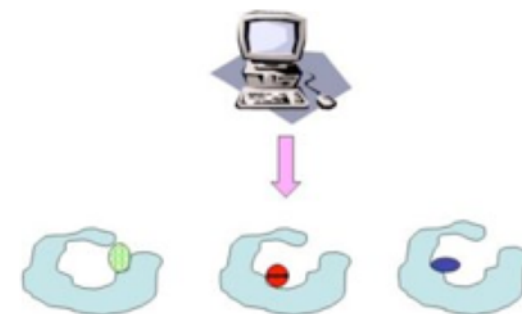
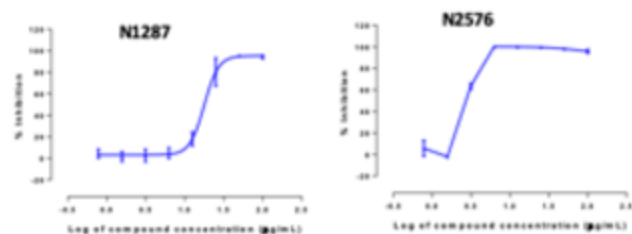
(GIS, SIFBI, NCCS)



Sortase A enzyme assay:



*S. mutans* whole-cell assay:



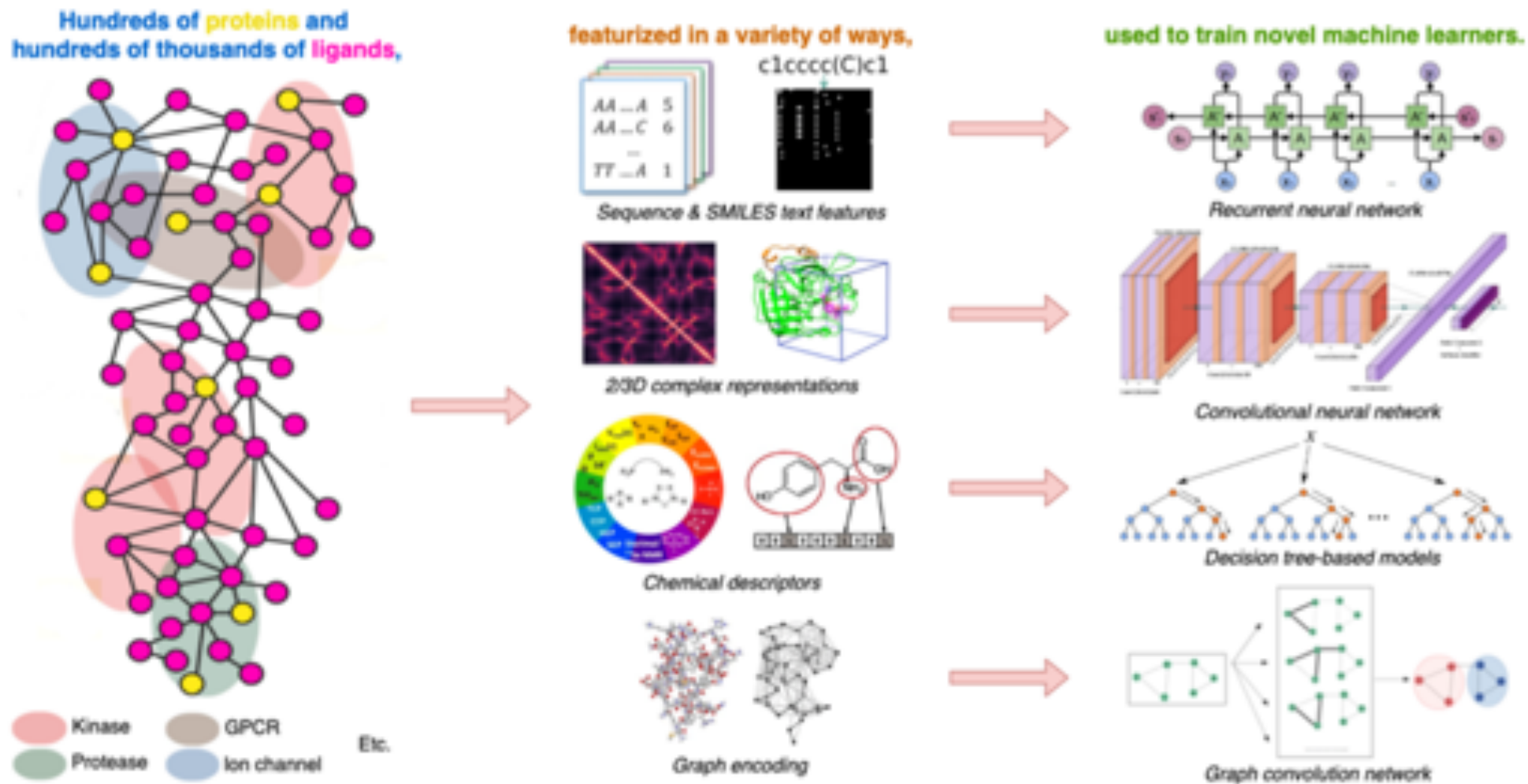
Novel RAF inhibitors confirmed by experiments

iScience 2021; IJMS 2020, Joint TD 2021

Weina, Lina

# AI-enhanced ligand discovery

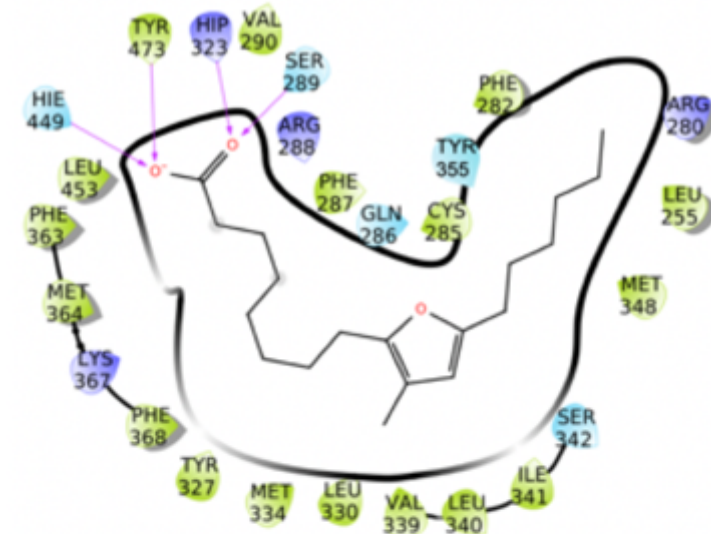
(BII)



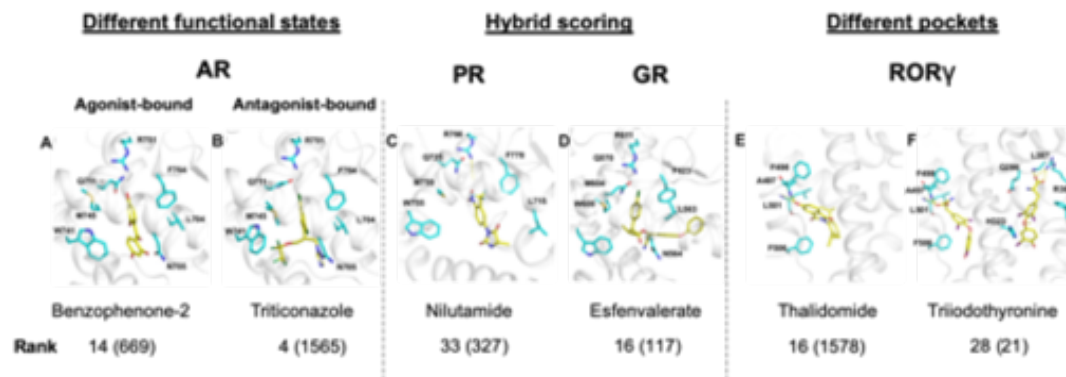
Catharine, Achal, Chaitanya

# Food and chemical safety: nuclear receptors

(BII, IMCB)



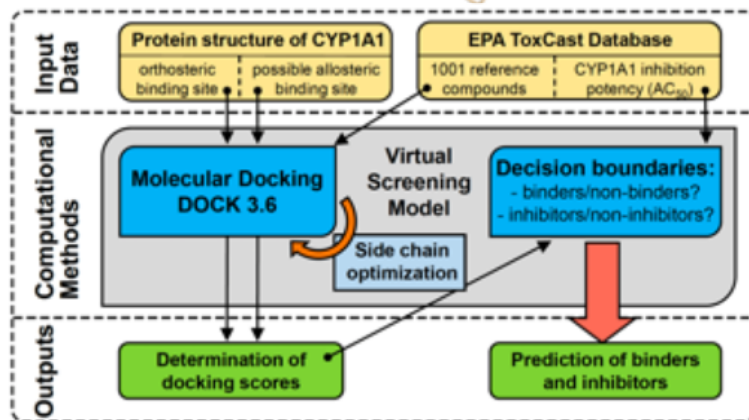
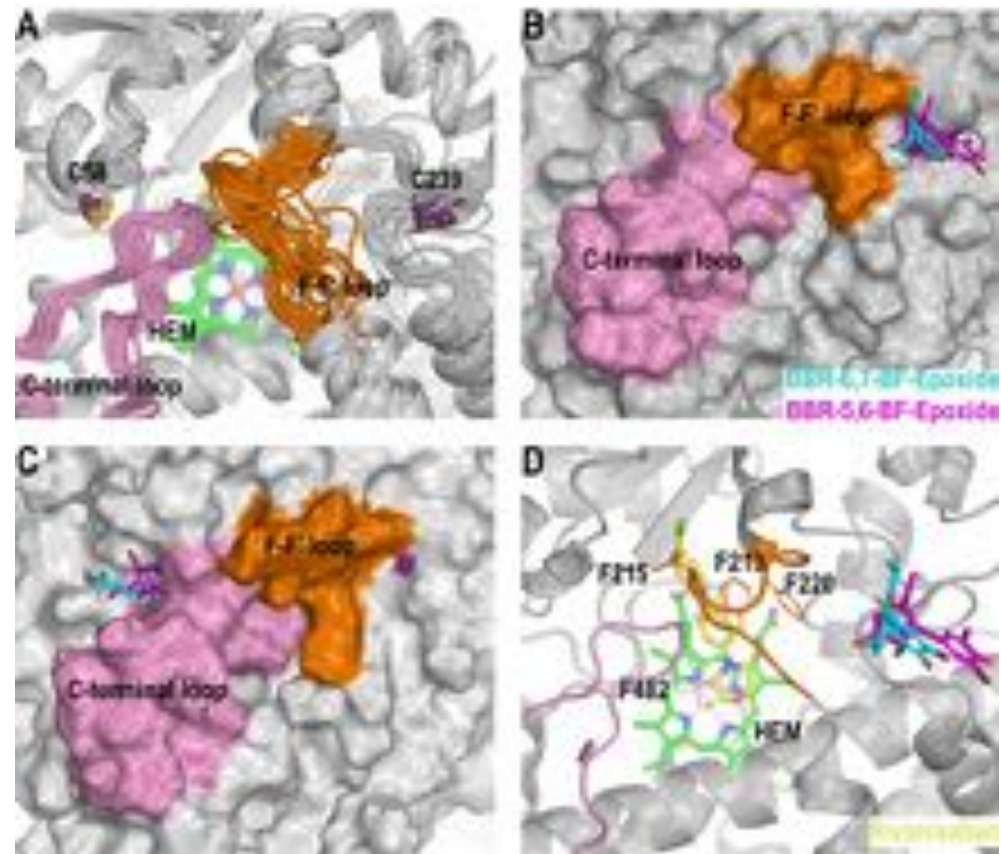
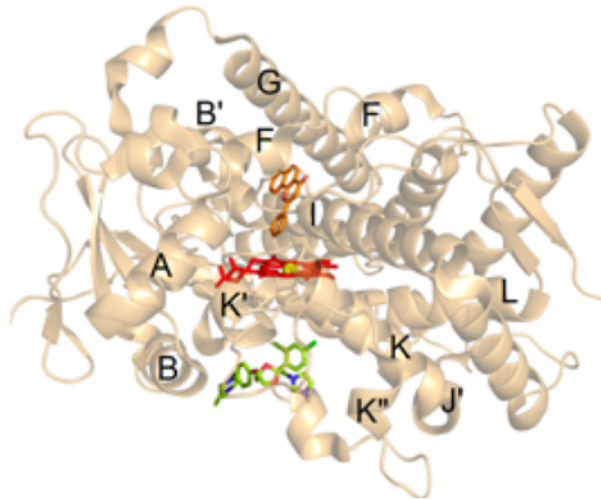
Fatty acids	Hybrid Score	Kd (μM)
<b>Furannonanoic acid (FNA)</b>	-11.19	135.7
<b>Furanundcanoic acid (FUA)*</b>	-11.16	248.7
Docosahexaenoic acid (DHA)	-11.14	593
Eicosapentaenoic acid (EPA)	-10.12	629.4
Doceapentaenoic acid (DPA)	-10.10	3960
Eicosatrienoic acid (ESA)	-10.01	>10000.00
<b>Phytomonic acid (PTA)</b>	-9.89	102.9
Ricinoic acid (ROA)	-9.70	>10000.00
Pinolenic acid (PLA)	-9.27	>10000.00



Arch. Tox. 2021 (1). Chaitanya

# Food and chemical safety: cytochrome P450 enzymes

(BII, NUS)



Arch. Tox 2021 (2), Mol. Pharm. 2021 (1,2), DMD 2021, DMD 2022

Julian, Ravi, Wan, Fu



# Acknowledgement

---

## My group

R.N.V. Krishna Deepak  
Yossa Dwi Hartono  
Shreyas Supekar  
Weina Du  
Lina Zhao  
Catharine Wing Kwan Lo  
Achal Ajeet Rayakar  
Chaitanya Kumar Jaladanki  
Julian Behn  
Ravi Kumar Verma  
Wan Wei  
Fu Lin

## Collaborator

Cheng Zhang  
Jiancheng Hu  
Wen Shan Yew  
Sebastian Maurer-Stroh  
Yee Hwee Lim  
Ee Lui Ang  
Ramanuj DasGupta  
Siew Bee Ng  
Yoganathan Kanagasundaram  
Hwee Kuan Lee  
Li Cheng  
Lit-Hsin Loo  
Eric Chun Yong Chan

## Funding



**A\*STAR IAF-PP:  
PIPS, ToxMAD,  
SURPASS**

