USC Dornsife
Department of Quantitative and Computational Biology

CNT3D
Center for New Technologies in Drug Discovery and Development

USC Michelson Center for Convergent Bioscience
Bridge Institute

Lead Discovery in Terra-Scale Chemical Spaces with Modular Screening and Deep Learning Approaches

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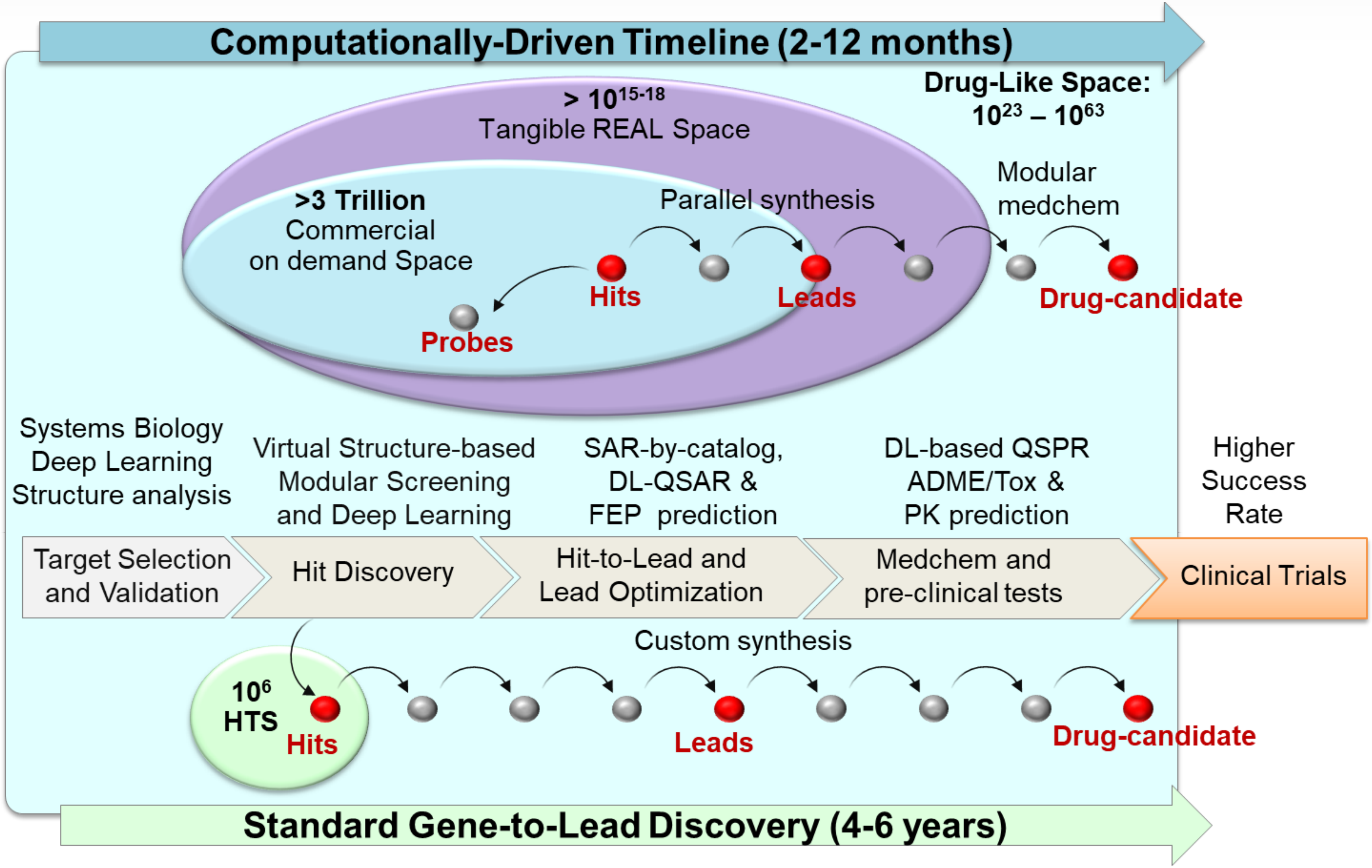
USC

NAS Webinar Series: Advancing Drug Discovery, May 15th, 2025

Computational/AI approaches streamlining early drug discovery



Sadybekov & Katritch (2023) ***Nature, 616: 7958***

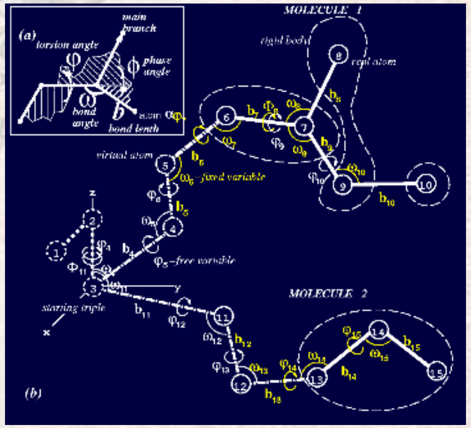
Core Computational Technologies in Drug Discovery

Physics-Based

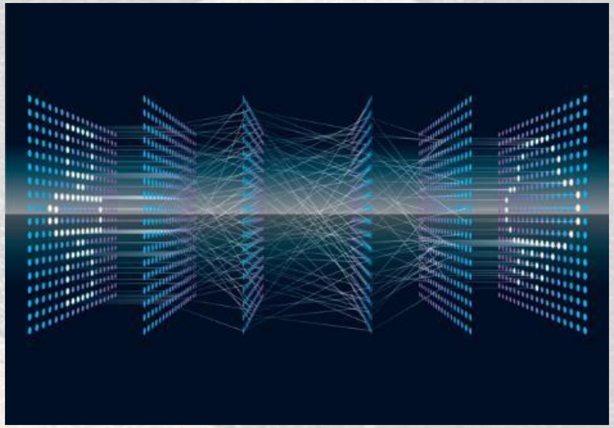
AI/Data-Based

Molecular Mechanics

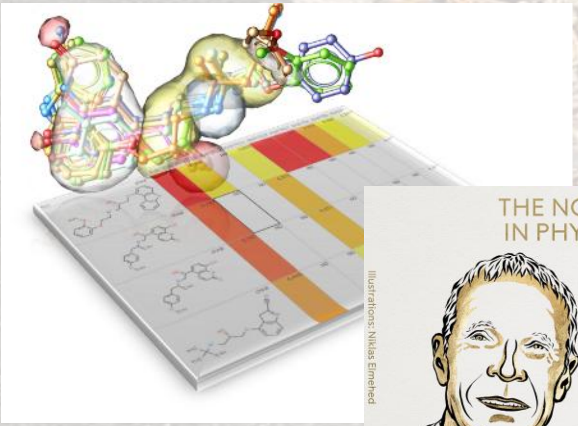
$E(\alpha) = \Delta E_{FF}+\Delta E_{EN}+\alpha_1 N_{at}+\alpha_2 \Delta E_{HB}+\alpha_3 \Delta E_{SE}+\alpha_4 \Delta E_{EL}+\alpha_5 \Delta E_{SO}$

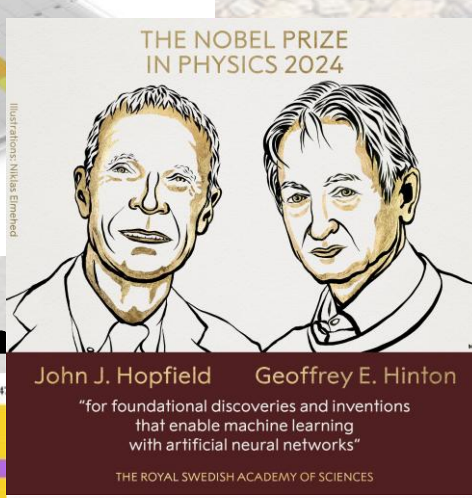


Machine Learning & AI

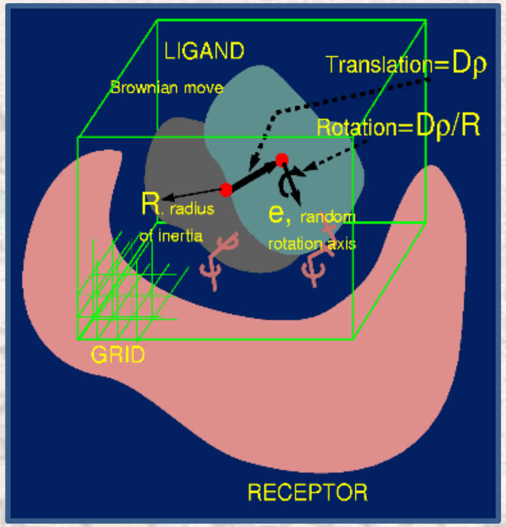


Cheminformatics

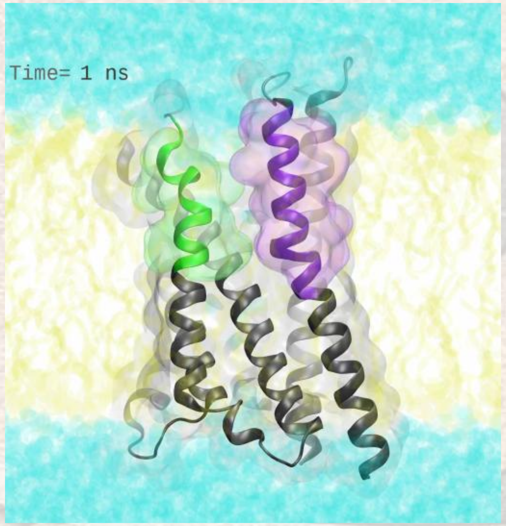




Molecular Docking

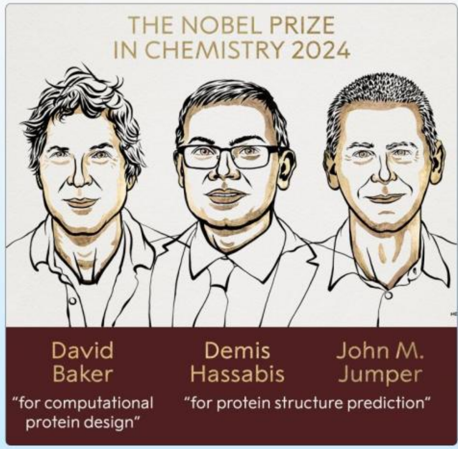


Molecular Dynamics

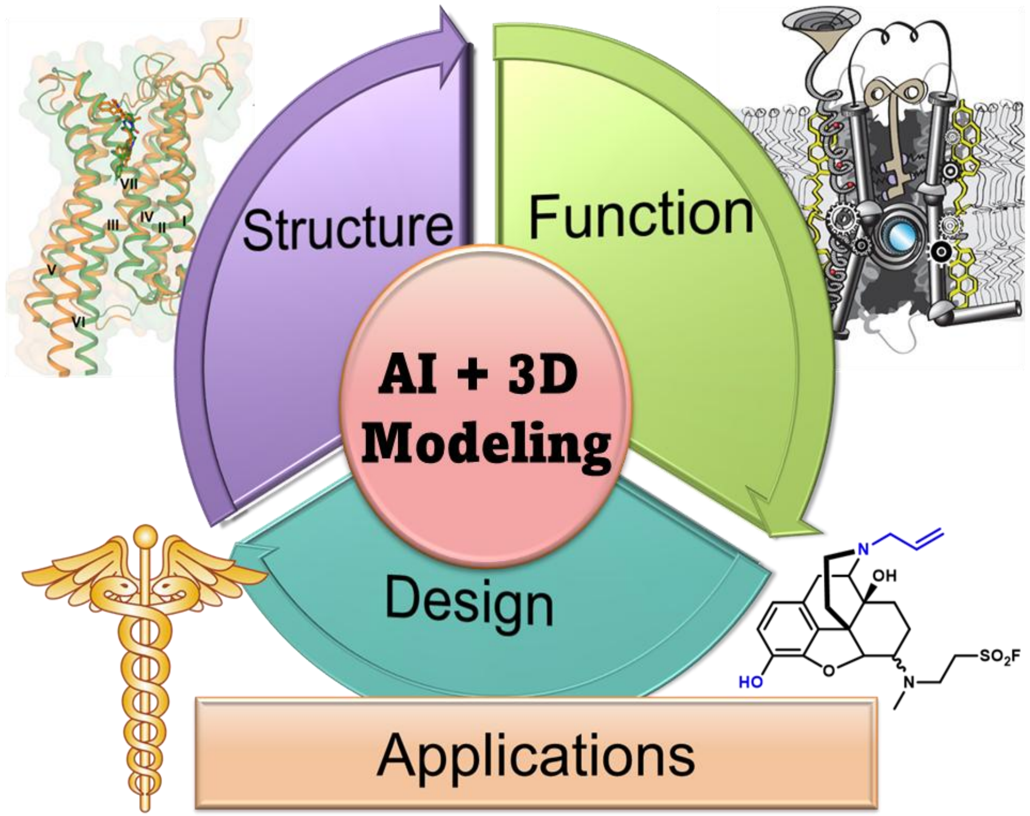


Structural data/Bioinform

Uniprot ID	...	7.36x35	7.37x36	7.38x37	7.39x38	7.40x39	7.41x40	7.42x41	7.43x42	7.44x43	7.45x45	7.46x46	7.47x4
5ht2a_bovin	...	N	V	F	V	W	I	G	Y	L	S	S	A
5ht2a_canlf	...	N	V	F	V	W	I	G	Y	L	S	S	A
5ht2a_crigr	...	N	V	F	V	W	I	G	Y	L	S	S	A
5ht2a_drome	...	S	L	F	L	W	L	G	Y	F	N	S	T
5ht2a_human	...	N	V	F	V	W	I	G	Y	L	S	S	A
5ht2a_macmu	...	N	V	F	V	W	I	G	Y	L	S	S	A
5ht2a_mouse	...	N	V	F	V	W	I	G	Y	L	S	S	A
5ht2a_pig	...	N	V	F	V	W	I	G	Y	L	S	S	A
5ht2a_ponpy	...	N	V	F	V	W	I	G	Y	L	S	S	A
5ht2a_rat	...	N	V	F	V	W	I	G	Y	L	S	S	A
5ht2b_drome	...	S	L	F	L	W	L	G	Y	F	N	S	T
5ht2b_human	...	E	I	F	V	W	I	G	Y	V	S	S	G
5ht2b_mouse	...	E	I	F	V	W	I	G	Y	V	S	S	G
5ht2b_rat	...	Q	I	F	V	W	V	G	Y	V	S	S	G
5ht2b_tetfl	...	E	I	F	S	W	V	G	Y	V	S	S	G
5ht2c_canlf	...	N	V	F	V	W	I	G	Y	V	C	S	G
5ht2c_human	...	N	V	F	V	W	I	G	Y	V	C	S	G



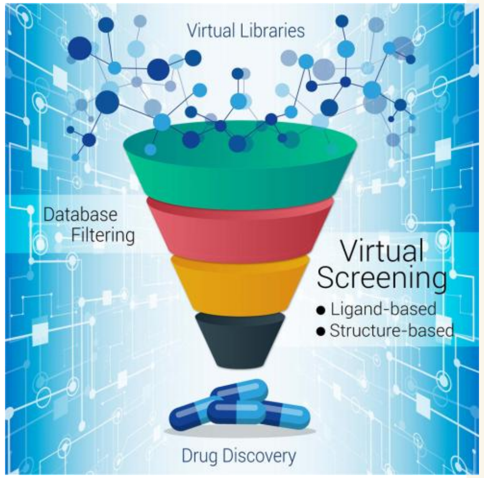
From Structure-Function to Discovery of Novel Ligands and Drugs



3D structure → Molecular Modeling → Virtual Screening → Drug Discovery

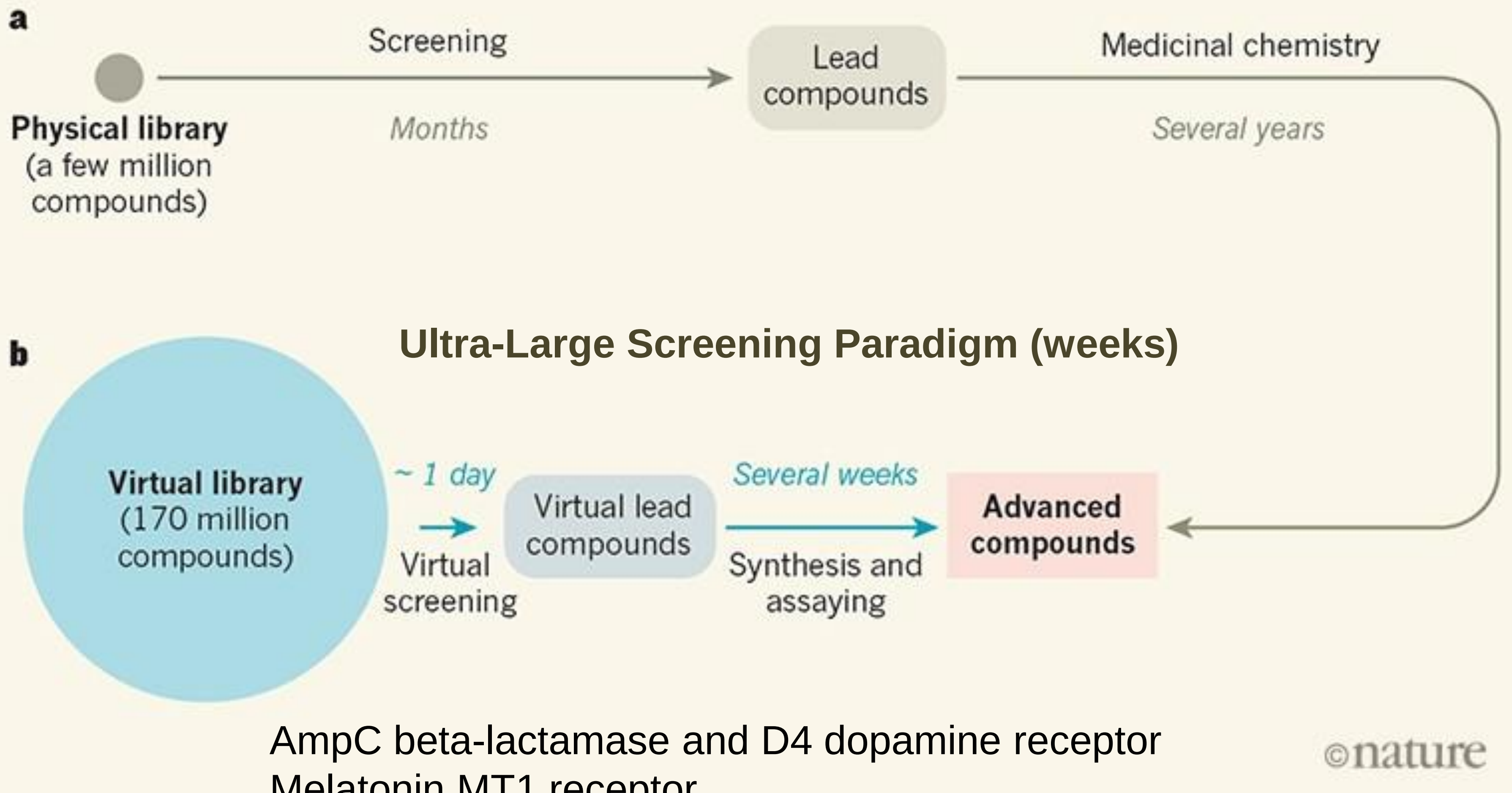
Molecular Modeling → Rational Design → Drug Discovery

Size Matters: Ultra-Large Screening for Lead Discovery



Classical HTS approach and optimization (3-5 years)

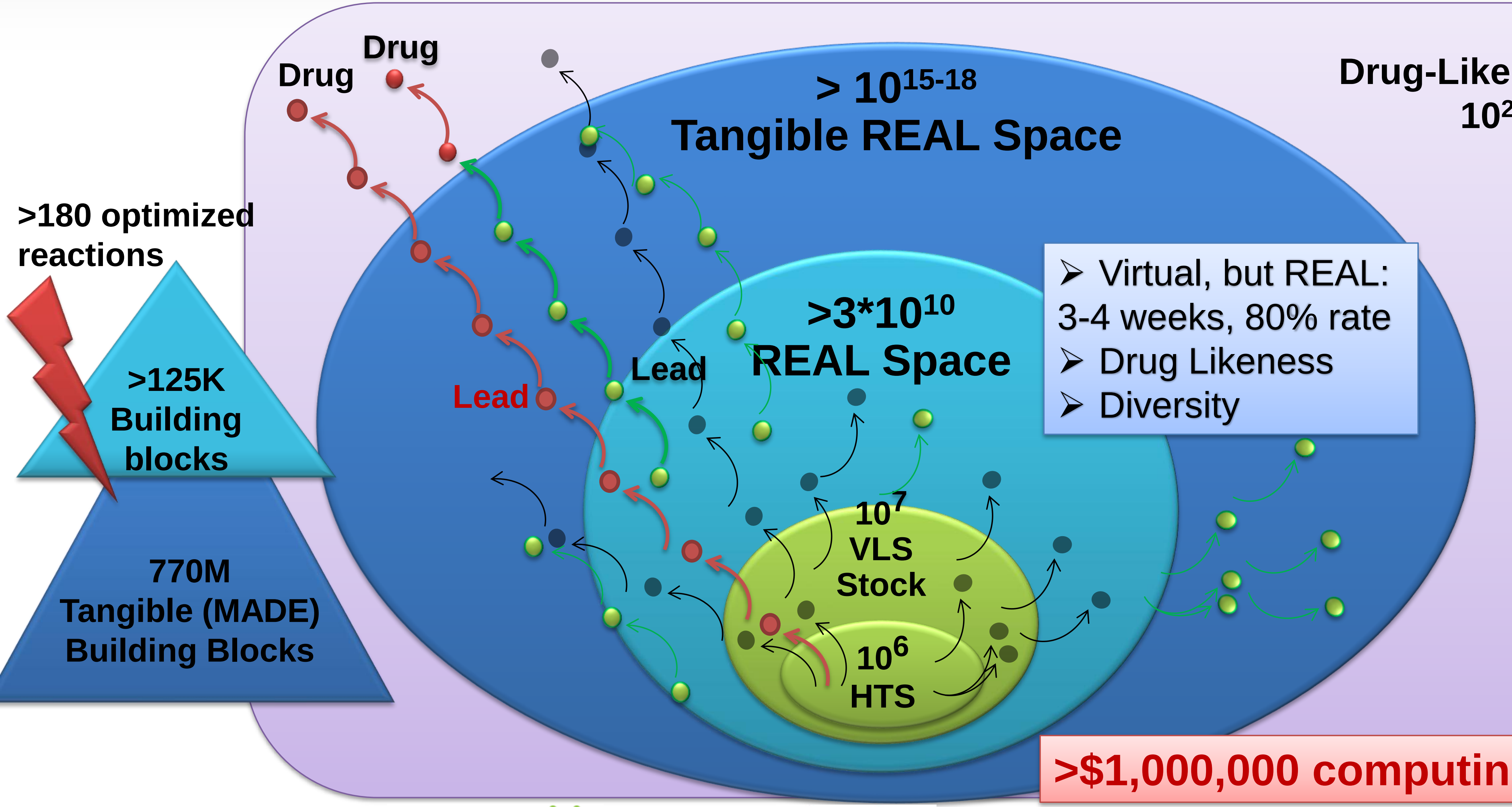
Ultra-Large Screening Paradigm (weeks)

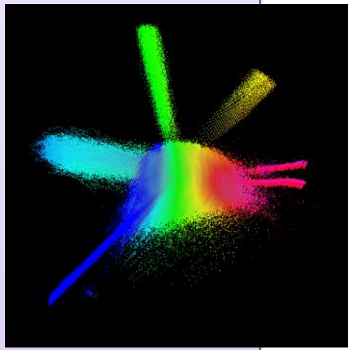


AmpC beta-lactamase and D4 dopamine receptor
Melatonin MT1 receptor

Lyu et al (2019) *Nature 566:224-229*; Stein et al (2020) *Nature* 579:609-614; Gloriam DE (2019) *Nature* 566:193-194

REAL Space: On Demand Virtual Libraries for Screening





- Virtual, but REAL: 3-4 weeks, 80% rate
- Drug Likeness
- Diversity

>$1,000,000 computing cost!

CHEM SPACE   Enamine

WuXi, Otava, Merck, GSK, AstraZeneca

Concept: Use chemical modularity of REAL libraries

Standard Ultra-Large Virtual Screening:

1. Fully enumerate and prepare the ligand library:
   - >10B cmpds – hard to work with
2. Screen by docking each molecule to the pocket
   - Years on a cluster or ~$1M on a cloud

$N_{dock} \sim N(R_1) \times N(R_2)$

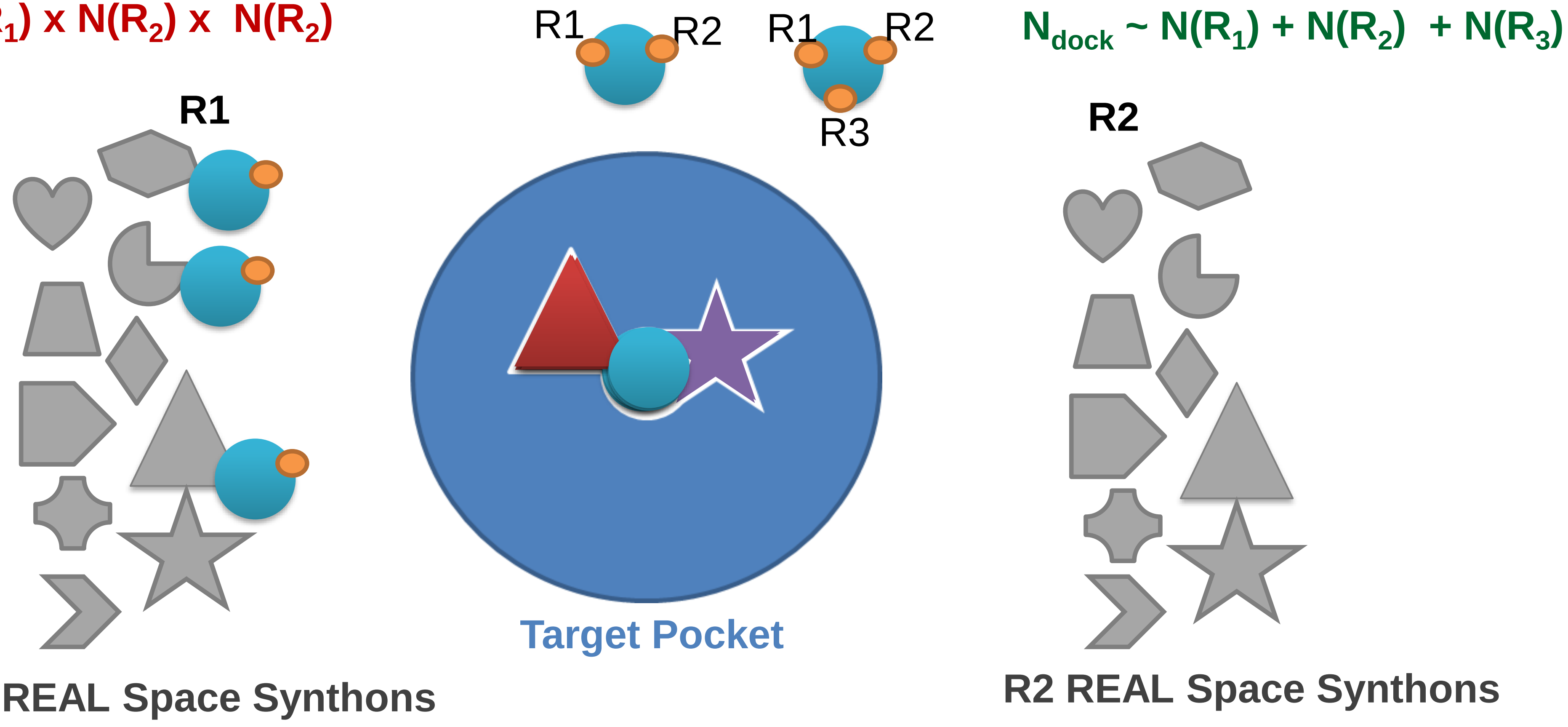
$N_{dock} \sim N(R_1) \times N(R_2) \times N(R_2)$

Modular chemical library Virtual Screening:

1. Screen for best scaffold-synthon combinations:
   - Medium size library suitable for docking
2. Enumerate only best scaffolds
   - Medium size library suitable for docking

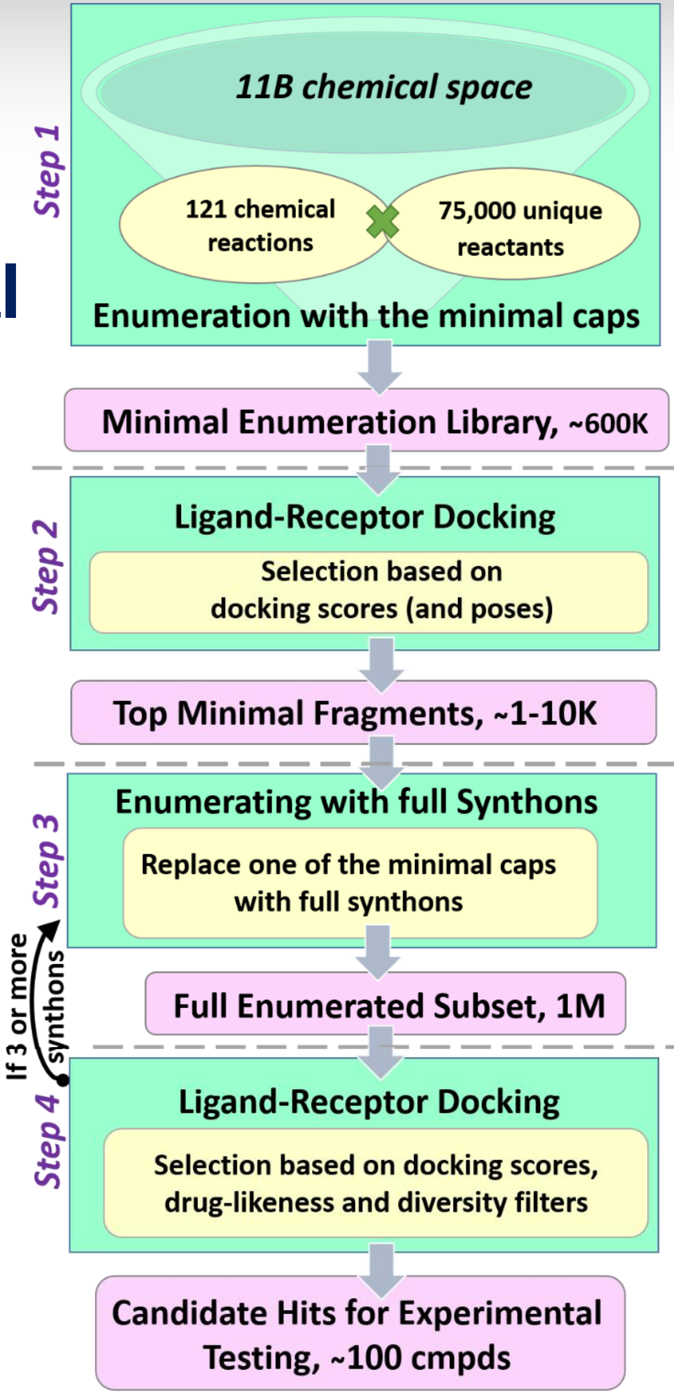
$N_{dock} \sim N(R_1) + N(R_2)$

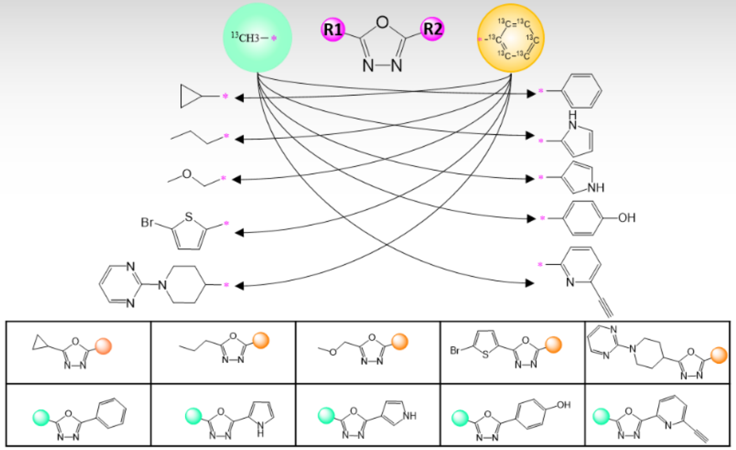
$N_{dock} \sim N(R_1) + N(R_2) + N(R_3)$

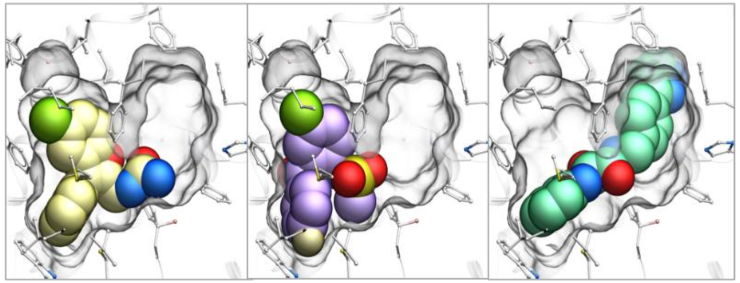


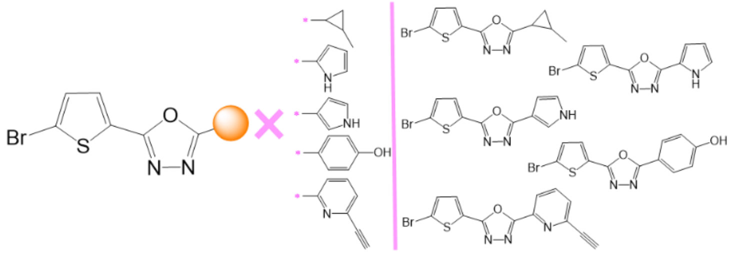
V-SYNTHES:

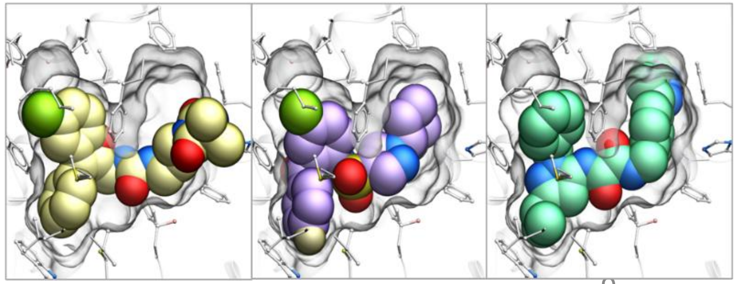
Virtual SYNThon Hierarchical Enumeration Screening







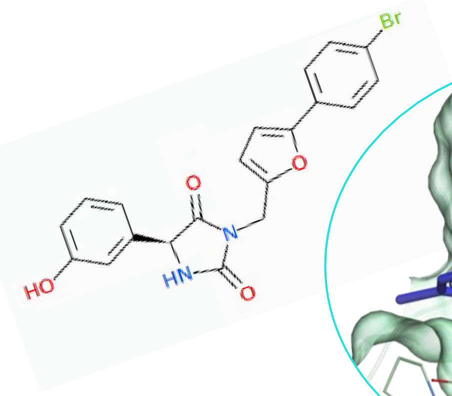


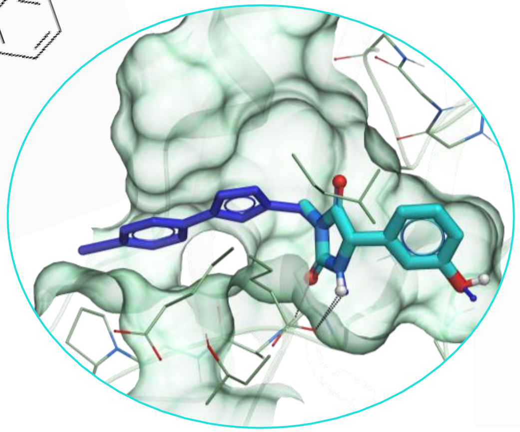


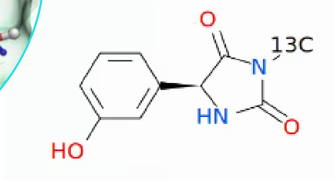
Sadybekov et al. *(2022) Nature 601:452-459*

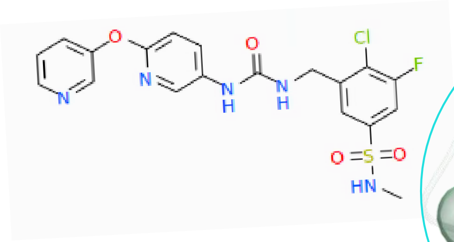
V-SYNTHES: How relevant are binding poses of MEL fragments?

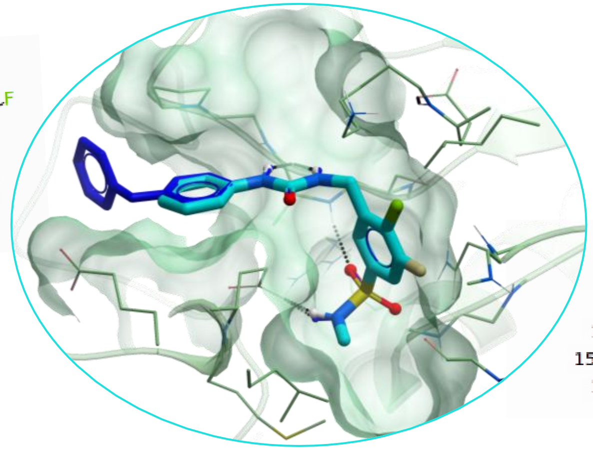
Pose reproduced in >90% of 100K top-ranking enumerated molecules!

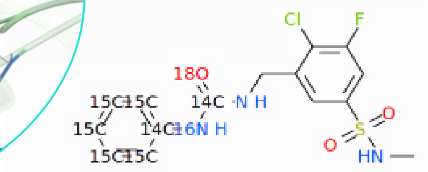


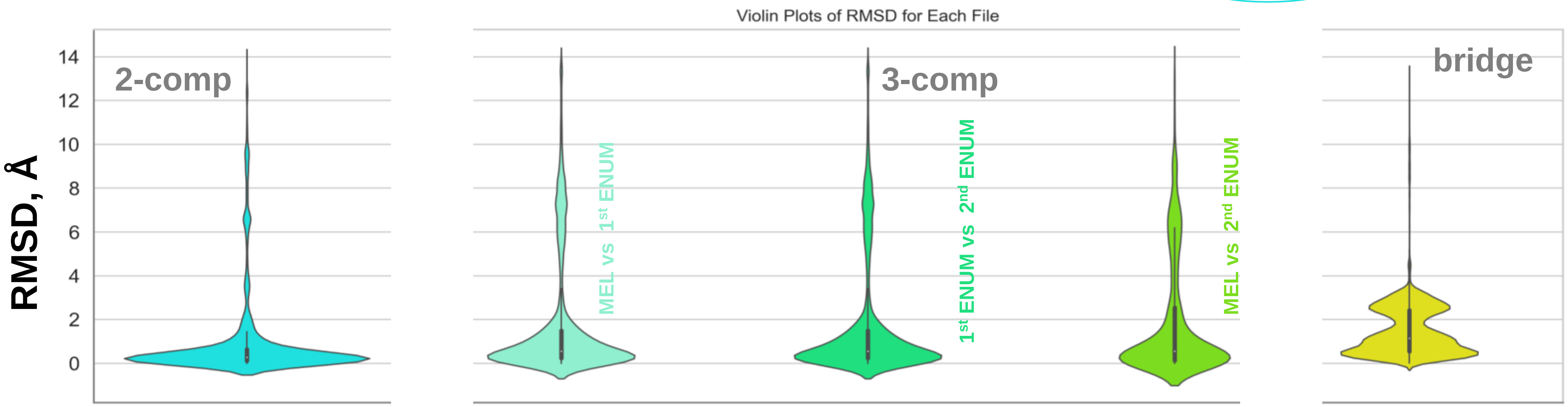








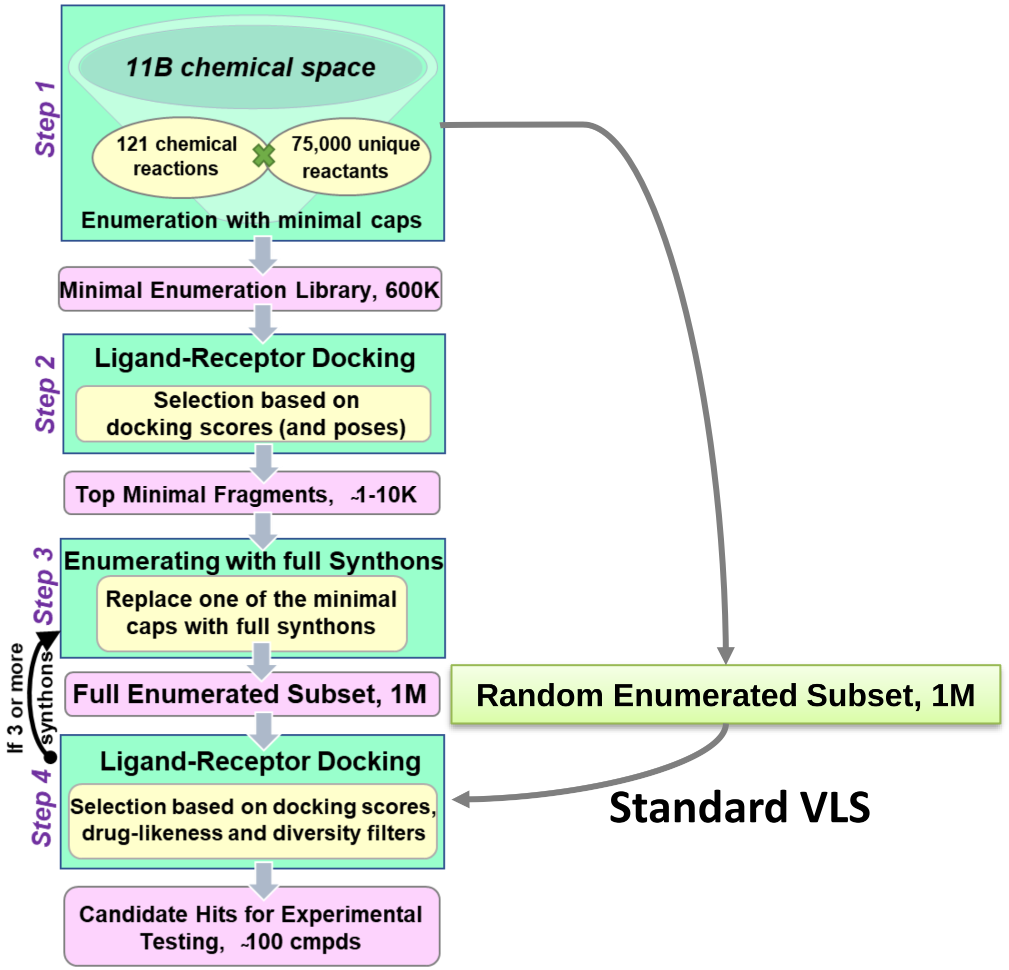


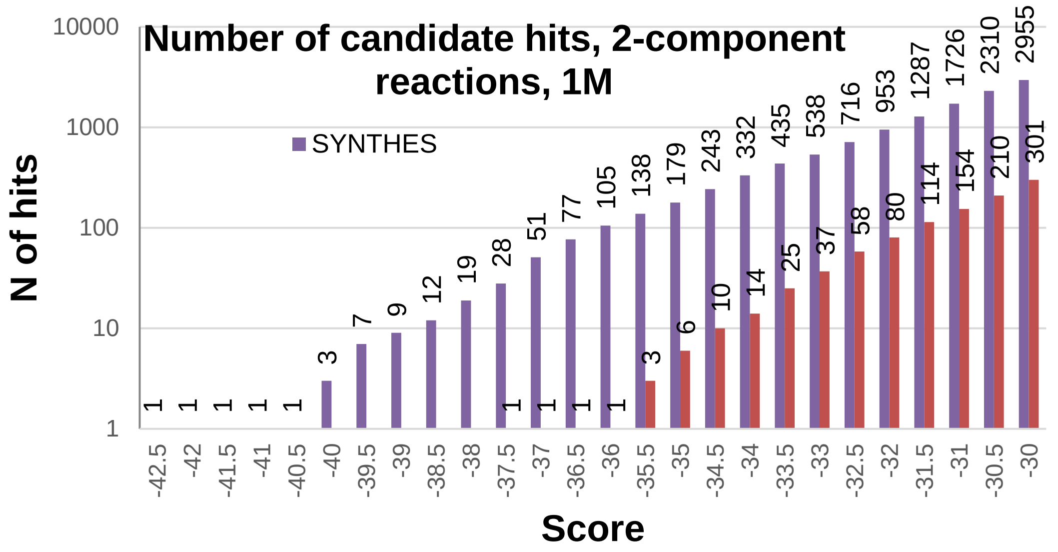


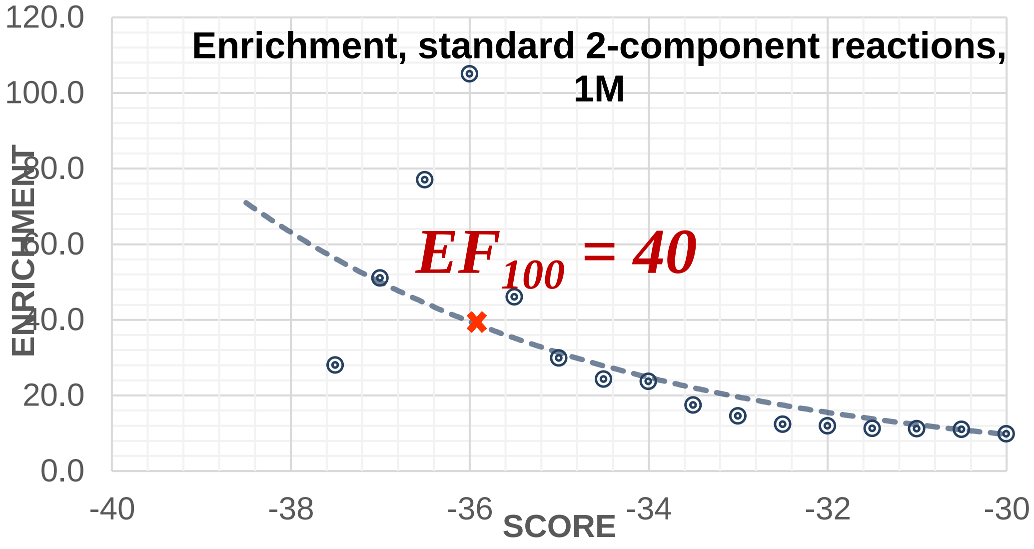
cPLA2_ICM: top scored 30K compounds

Manuscript in preparation

V-SYNTHES: How relevant is MEL fragments selection in Steps 1-2?



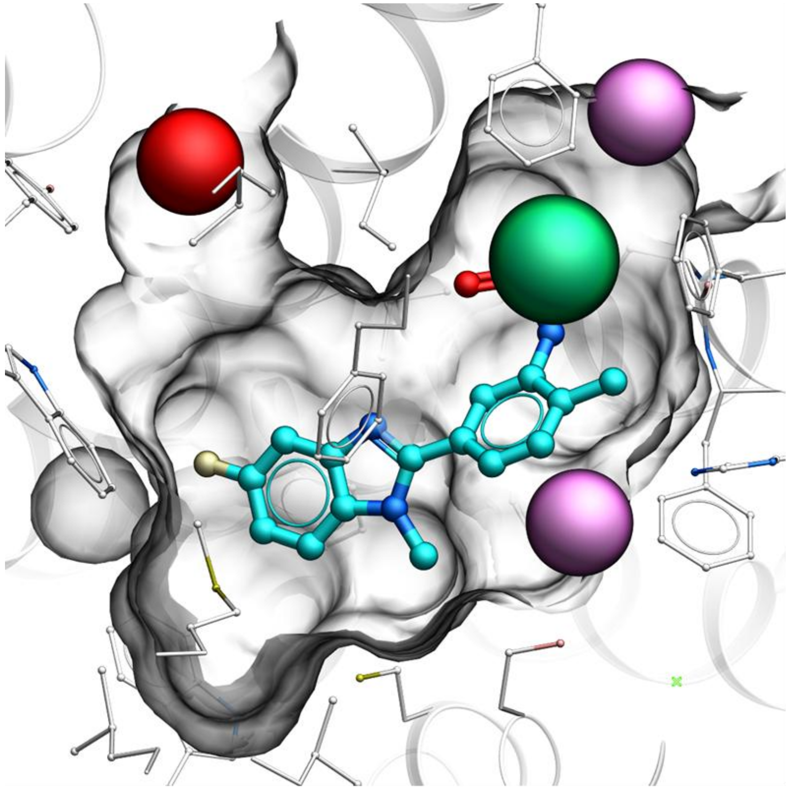




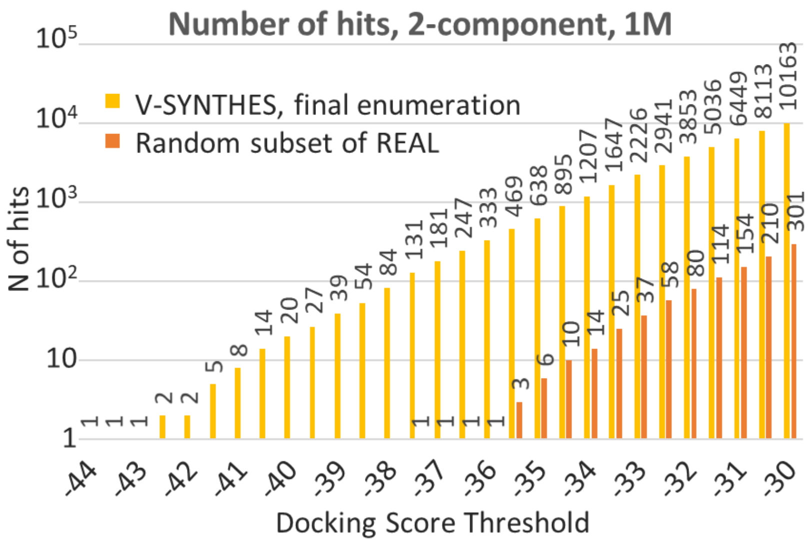
$$EF\ (X) = \frac{N\ of\ hits\ with\ scores < X\ in\ SYNTHES}{N\ of\ hits\ with\ scores < X\ in\ standard\ VLS}$$

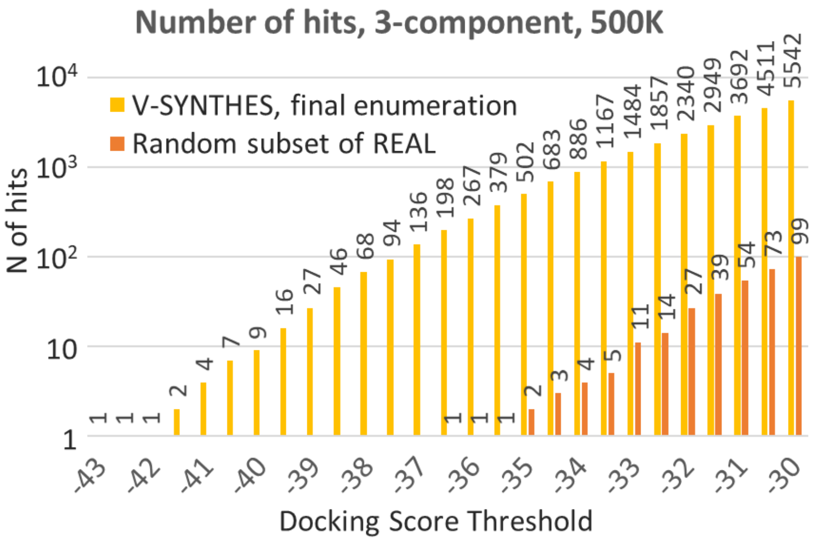
Sadybekov et al. *(2022) Nature 601:452-459*

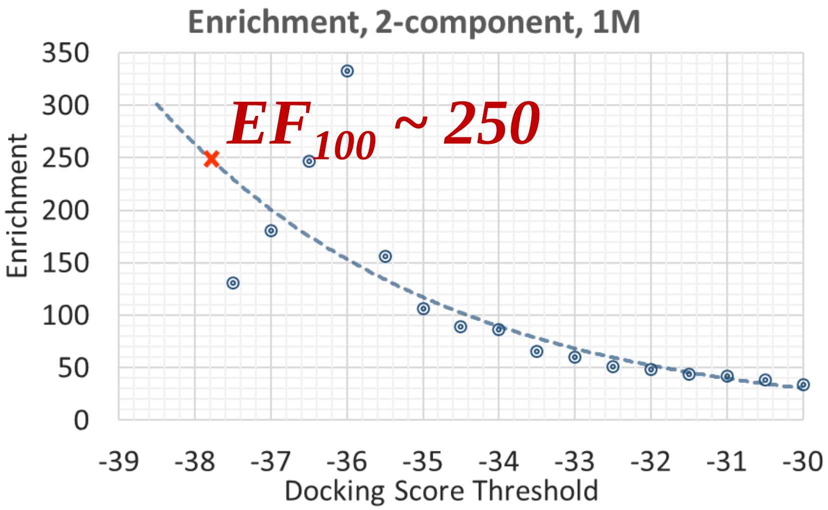
V-SYNTHES: How relevant is MEL fragments selection in Steps 1-2?

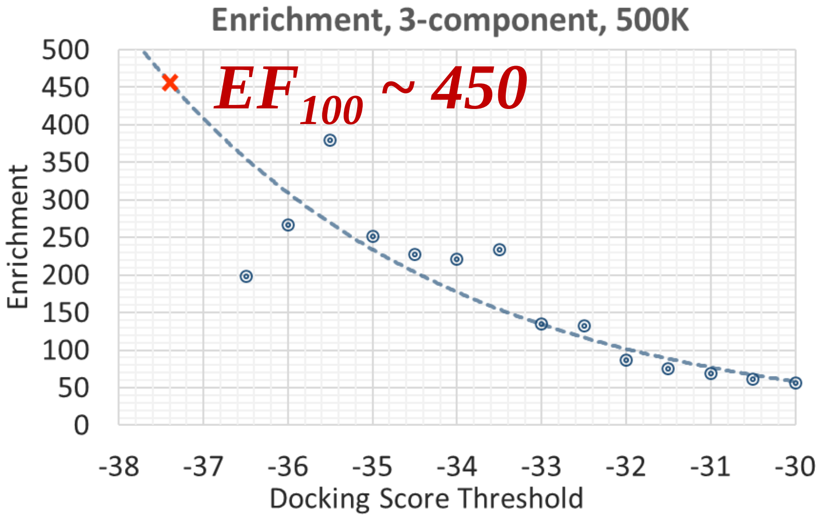


dummy atom water minimal cap









Sadybekov et al. *(2022) Nature 601:452-459*

V-SYNTHES: Does it work in prospective screening? (Discovery of selective CB2 Antagonists)

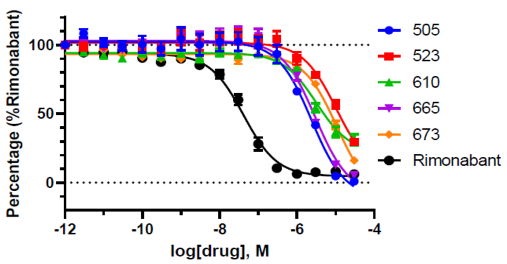
Bryan Roth

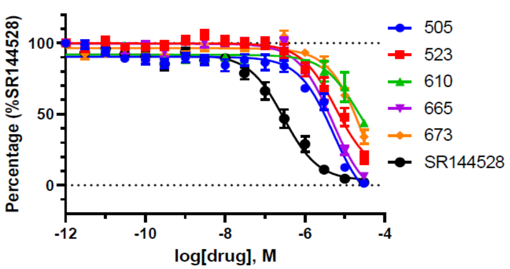
Alex Makriyannis

V-SYNTHES for 11B Enamine REAL Space

- Synthesized and tested 60 cmpds
- 19 hits Ki<10μM   14 hits Ki<1μM

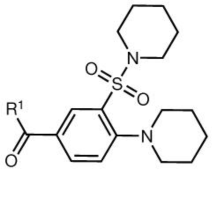
#	PDSP ID	CB_1 Antagonist potency		CB_2 Antagonist potency		CB_1 affinity		CB_2 affinity		Tanimoto distance
		K_i, uM	95% CI	K_i, uM	95% CI	K_i, uM	95% CI	K_i, uM	95% CI	
505	56707	**0.28**	**0.22 - 0.36**	**0.54**	**0.43 - 0.67**	16.4	8.6 - 31.3	1*	N/D	0.38
515	56731	**0.94**	**0.76 - 1.16**	3.81	2.89 - 5.09	6.1	2.9 - 13.0	2.85	1.9 - 4.1	0.39
520	56717	1.07	0.84 - 1.37	5.20	3.82 - 7.22	11.6	3.7 - 35.7	12.8	4.8 - 34.2	0.40
523	56737	1.82	1.46 - 2.28	1.59	1.27 - 1.98	12.0	5.4 - 26.7	**0.85**	**0.69 - 1.05**	0.39
544	*56724*	***0.69***	***0.57 - 0.84***	*7.78*	*4.66 - 16.8*	*5.0-7.2**	N/D	*2.5**	N/D	*0.34*
559	56715	**0.98**	**0.80 - 1.20**	4.25	3.15 - 5.90	N/D*	N/D	12.2	2.1-69.6	0.43
565	*56684*	***0.46***	***0.40 - 0.54***	*3.77*	*2.71 - 5.53*	*4.5**	N/D	*13.6*	*8.4-22.0*	*0.37*
566	56708	2.05	1.63 - 2.60	4.04	3.02 - 5.48	6.9*	N/D	1.2	0.84 – 1.57	0.43
580	56727	5.80	4.55 - 7.55	6.92	5.51 - 8.80	1.0-9.0*	N/D	1.5*	N/D	0.36
599	56723	2.33	1.82 - 3.01	2.44	2.06 - 2.89	26.5*	N/D	10.4	7.1 - 15.1	0.34
610	56696	**0.76**	**0.62 - 0.93**	4.17	3.14 - 5.62	**0.62**	**0.34 - 1.13**	**0.28**	**0.12 - 0.69**	0.31
619	56695	**0.05**	**0.04 - 0.06**	**0.11**	**0.09 - 0.13**	45*	N/D	0.9-2.5*	N/D	0.42
633	56726	**0.23**	**0.19 - 0.28**	1.53	1.18 - 1.98	10*	N/D	0.7-0.9*	N/D	0.50
650	56725	3.22	2.61 - 4.01	12.2	7.85 - 20.7	45*	N/D	0.9-2.5*	N/D	0.48
661	56685	**0.55**	**0.43 - 0.70**	4.37	3.37 - 5.74	19*	N/D	4.0	2.4- 6.7	0.39
663	*56687*	***0.59***	***0.46 - 0.75***	*14.5*	*9.89 - 23.0*	*12.5**	N/D	*14.3*	*6.6 - 30.9*	*0.36*
665	56732	**0.39**	**0.32 - 0.47**	**0.82**	**0.71 - 0.95**	>7*	N/D	6.7	4.2 - 10.6	0.47
668	*56691*	***0.43***	***0.33 - 0.56***	*4.78*	*3.60 - 6.42*	*5.5-6.9**	N/D	*5.2*	*2.5 – 11.0*	*0.40*
673	56683	**0.97**	**0.84 - 1.14**	3.66	2.98 - 4.51	4.2	2.9 - 6.0	2.2	1.4 - 3.4	0.46
681	56701	**0.42**	**0.32 - 0.55**	1.86	1.52 - 2.30	8.2	5.2 - 12.7	4.2	2.5 - 7.2	0.42
684	56689	1.16	0.93 - 1.43	7.28	4.50 – 14.4	25.5	16.6 - 39.0	5.3	3.5 - 8.1	0.48
SR144528		N/D	N/D	0.052	0.041 -0.066					
Rimonabant		0.006	0.005 -.008	N/D	N/D					
CP55940&		0.017		0.028						



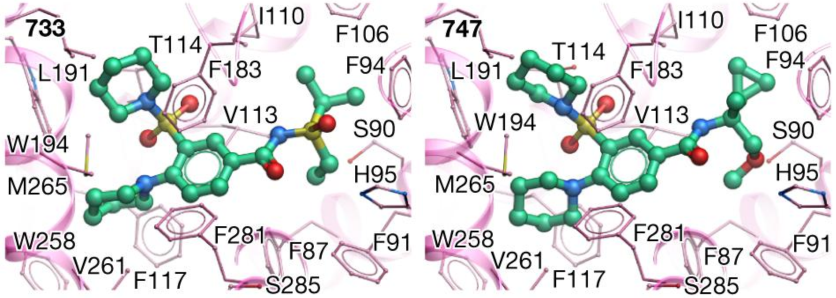


SAR-by-catalog for 3 best hits

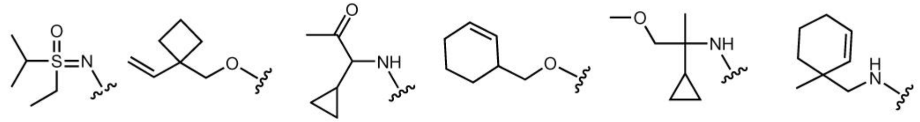
- Made and tested 109 cmpds (#523- best series)
- 5 hits Ki<10nM, best Ki =0.9nM, CB2/CB1>200x

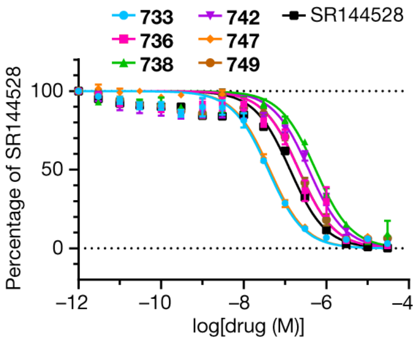


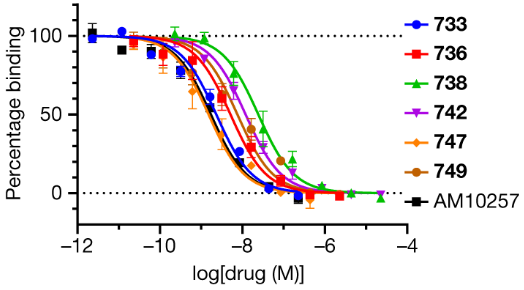
523 scaffold



R1







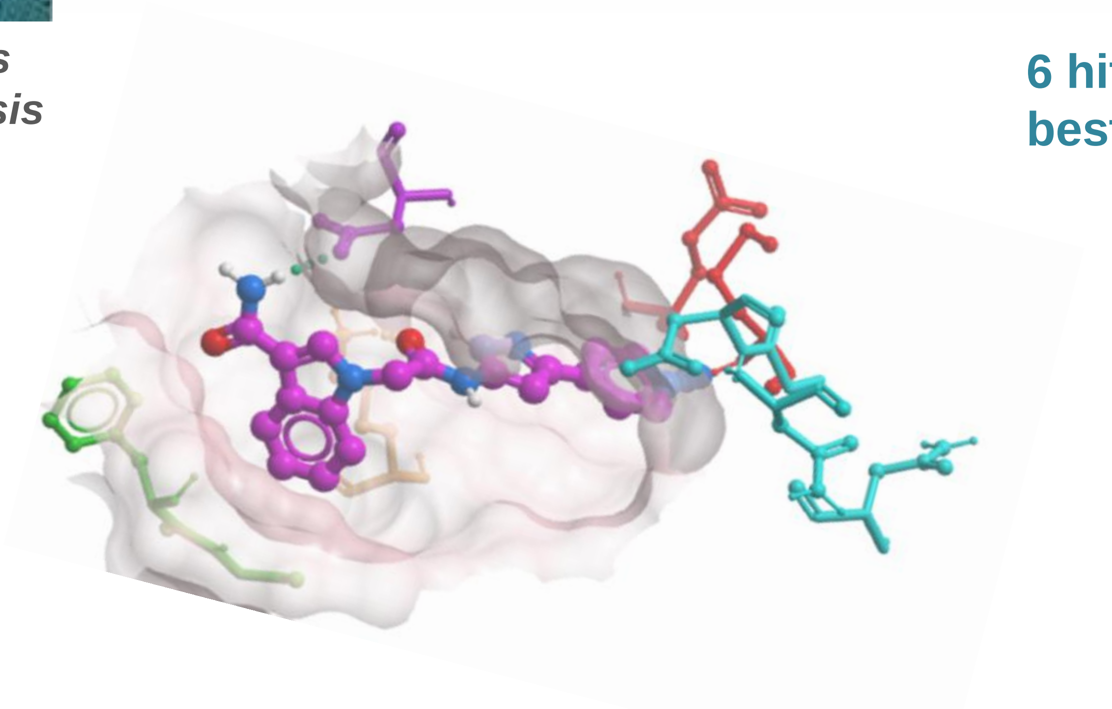
Sadybekov et al. *(2022) Nature 601:452-459*

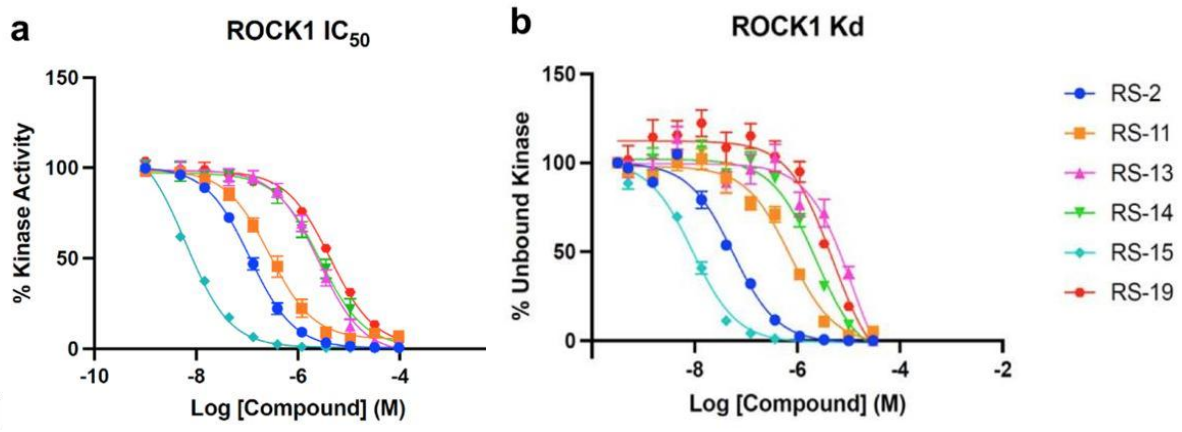
Nikos Petasis

V-SYNTHES application to ROCK1 kinase

Blake Houser

6 hits (28.5% hit rate) better than Ki<10μM, best IC50 and Ki < 10nM

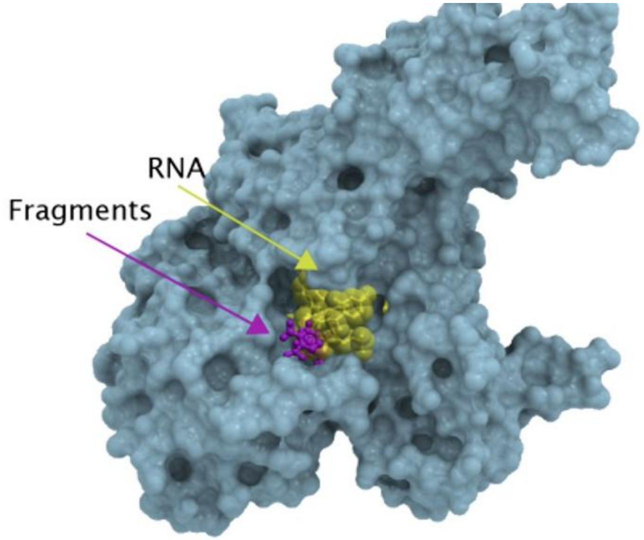




Compound ID	ROCK1 IC_{50} (μM)	95% CI, (μM)	ROCK1 K_d (μM)	95% CI, (μM)
RS-1	>100	N/D	N/D	N/D
RS-2	**0.11**	**0.10 - 0.13**	**0.055**	**0.046 – 0.067**
RS-3	>100	N/D	N/D	N/D
RS-4	>100	N/D	N/D	N/D
RS-5	~14*	N/D	N/D	N/D
RS-6	>100	N/D	N/D	N/D
RS-7	>100	N/D	N/D	N/D
RS-8	~17*	N/D	N/D	N/D
RS-9	>100	N/D	N/D	N/D
RS-10	~26*	N/D	N/D	N/D
RS-11	**0.28**	**0.22 - 0.35**	**1.83**	**0.66 – 4.73**
RS-12	~16*	N/D	N/D	N/D
RS-13	**2.59**	**2.01 - 3.32**	**11.7**	**6.06 – 25.2**
RS-14	**2.74**	**2.07 - 3.62**	**2.31**	**1.80 – 2.98**
RS-15	**0.0063**	**0.0055 - 0.0072**	**0.0079**	**0.0077 - 0.011**
RS-16	~16*	N/D	N/D	N/D
RS-17	>100	N/D	N/D	N/D
RS-18	>100	N/D	N/D	N/D
RS-19	**4.35**	**3.47 - 5.44**	**4.88**	**3.04 – 7.99**
RS-20	>100	N/D	N/D	N/D
RS-21	>100	N/D	N/D	N/D

Sadybekov et al. *(2022) Nature 601:452-459*

Critical assessment of computational hit-finding experiments (CACHE Challenge 2)



Crystal structures of SARS-CoV-2 NSP13/helicase bound to fragments (5RLH, 5RLZ, 5RML, 5RMM) and RNA (7CXM).

- 23 computational teams
- 1957 compounds tested experimentally

A dozen double-digit μM hits

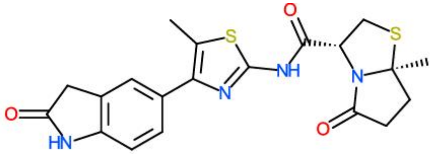
Examples

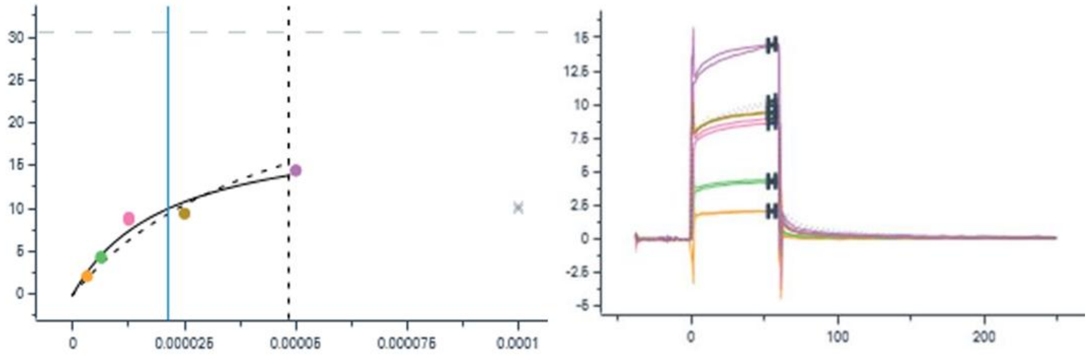
https://cache-challenge.org/results-cache-challenge-2

- Extremely challenging target: best hits are 15-150 μM potency
- Methods: combination of physics-based docking, machine learning, and “crowdsourcing” – contributing to the best results

ChemSpace was one of the top 5 teams, used V-SYNTHES/ICM-Pro (best cmpd 21 μM, selective):

CACHE2-HO_1418_1
K_D (3% DMSO) = 21 μM (solubility issues) – 65% binding
Selectivity (unrelated WDR5 protein) – Yes
%inhibition@50 μM_ATPase = 13





Manuscript in preparation (including CACHE #4 results)

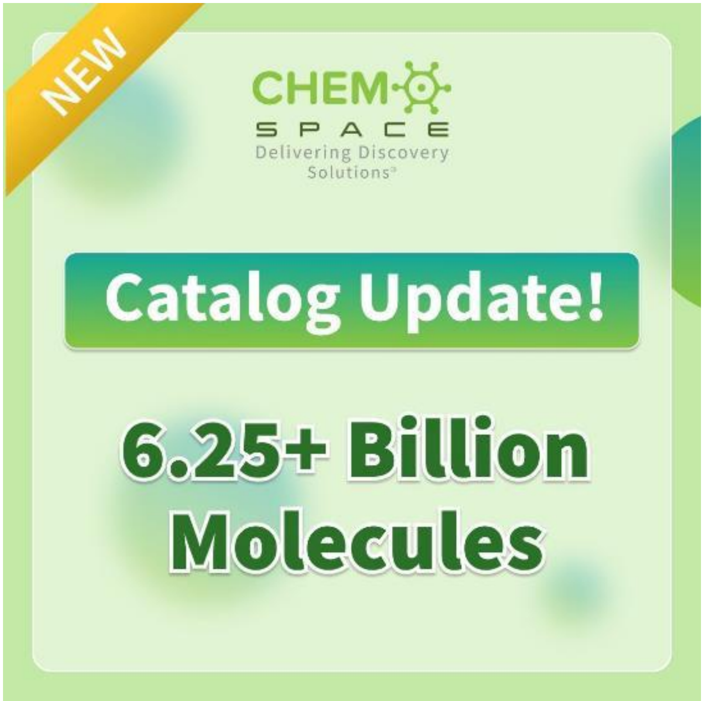
Olga Tarkhanova

Mikola Protopopov

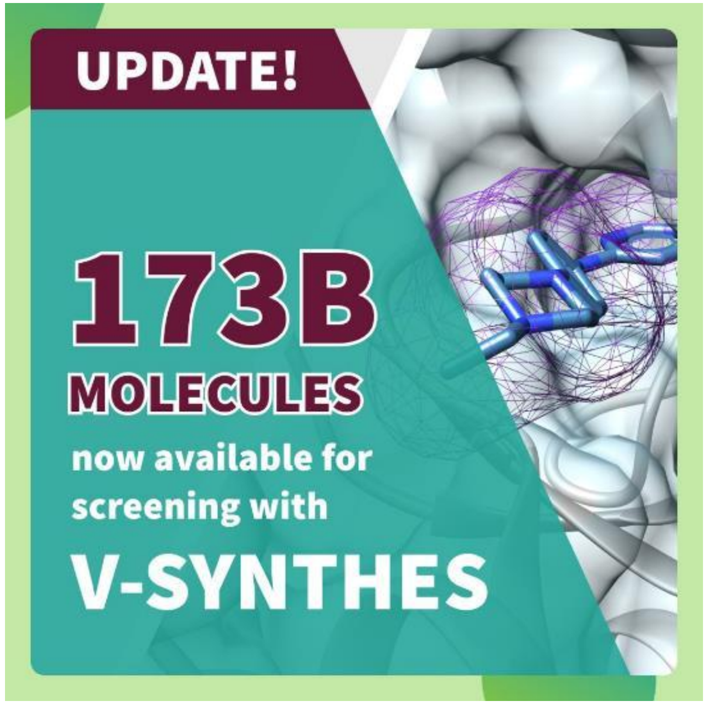
On-demand chemical spaces as "unlimited" source for drug discovery: the Bigger, the Better!!!

HTS

Standard VLS

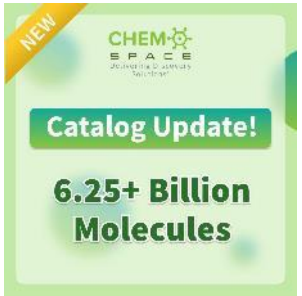


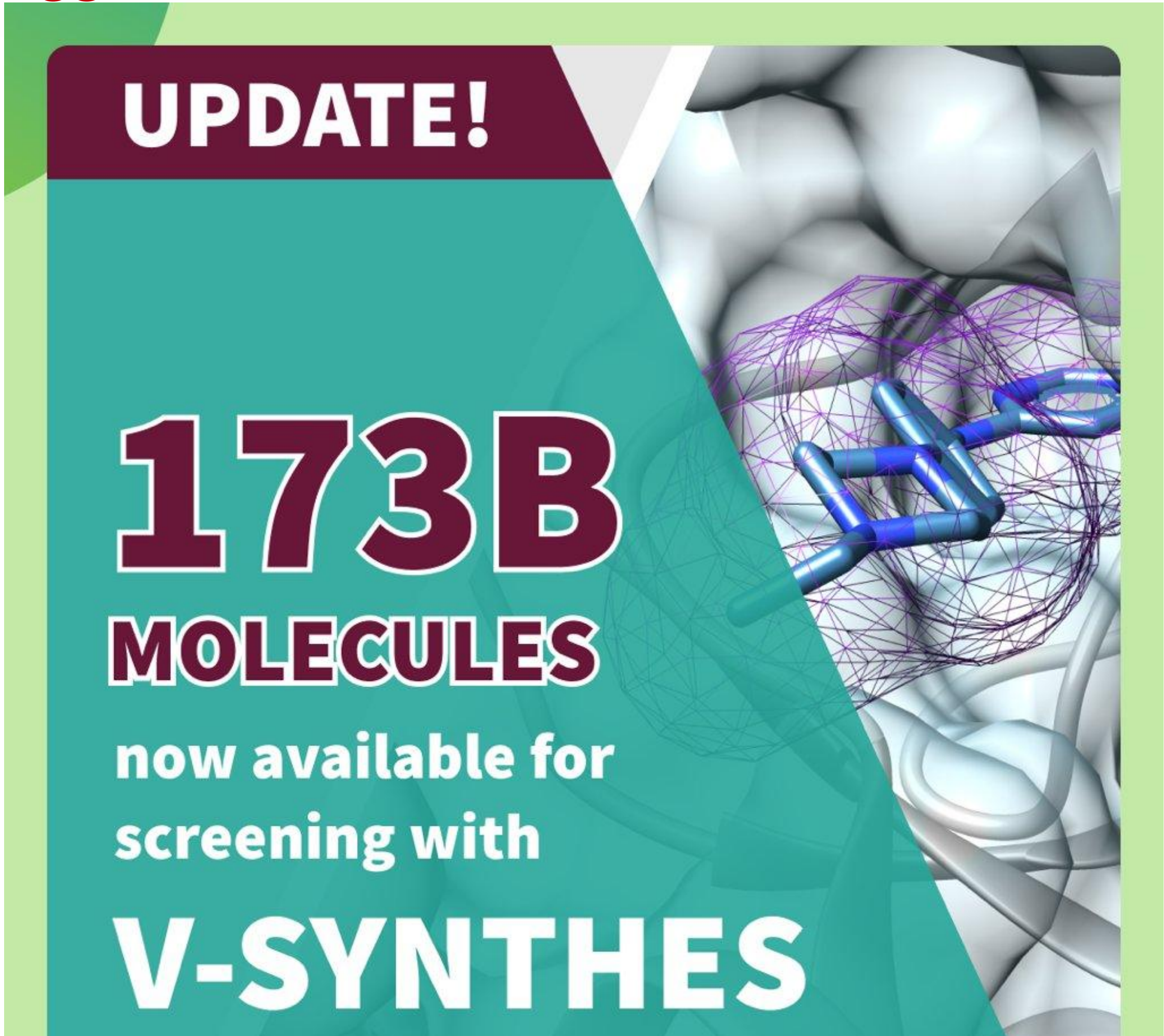
V-SYNTHES



CHEM SPACE Enamine

On-demand chemical spaces as "unlimited" source for drug discovery: the Bigger, the Better!!!

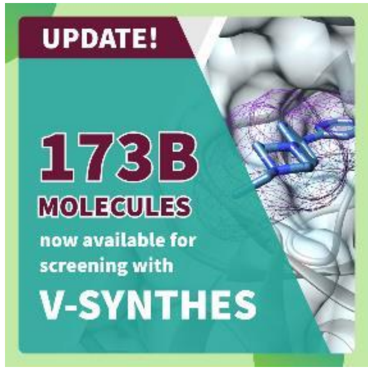




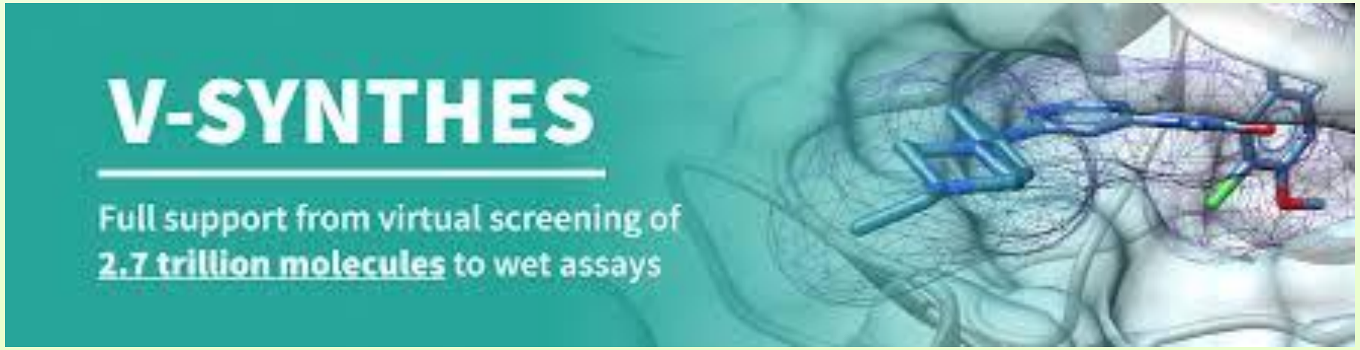
CHEMSPACE Enamine

On-demand chemical spaces as "unlimited" source for drug discovery: the Bigger, the Better!!!

>$100K,
No IP



~$20K
Unrestricted IP



xREAL
~3 Trillion Compounds

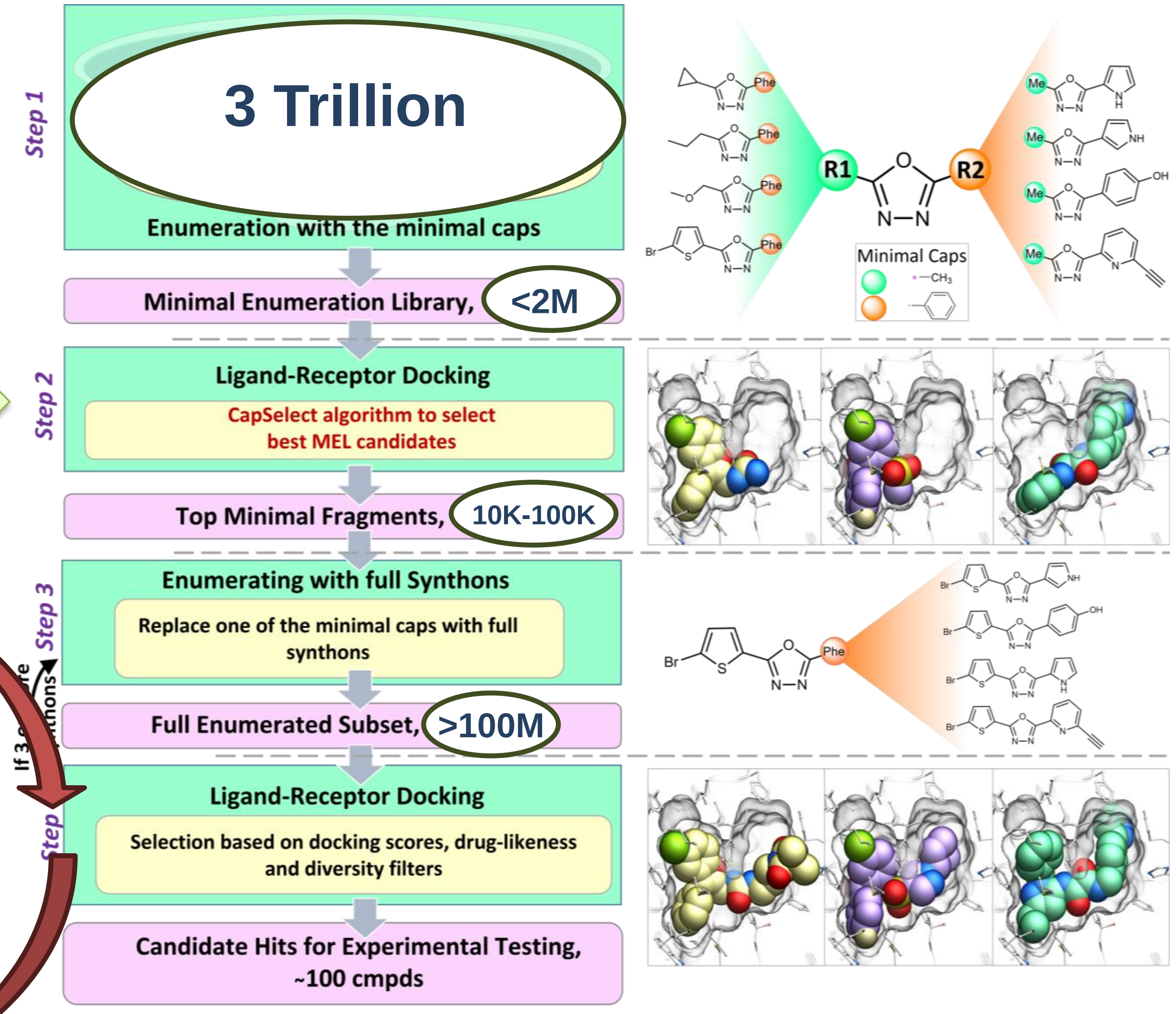
- ✓ More diverse
- ✓ More non-planar
- ✓ Suitable for larger pockets

How to scale from Billions to Trillions & more?

**V-SYNTHES-DL:
AI to the rescue!**

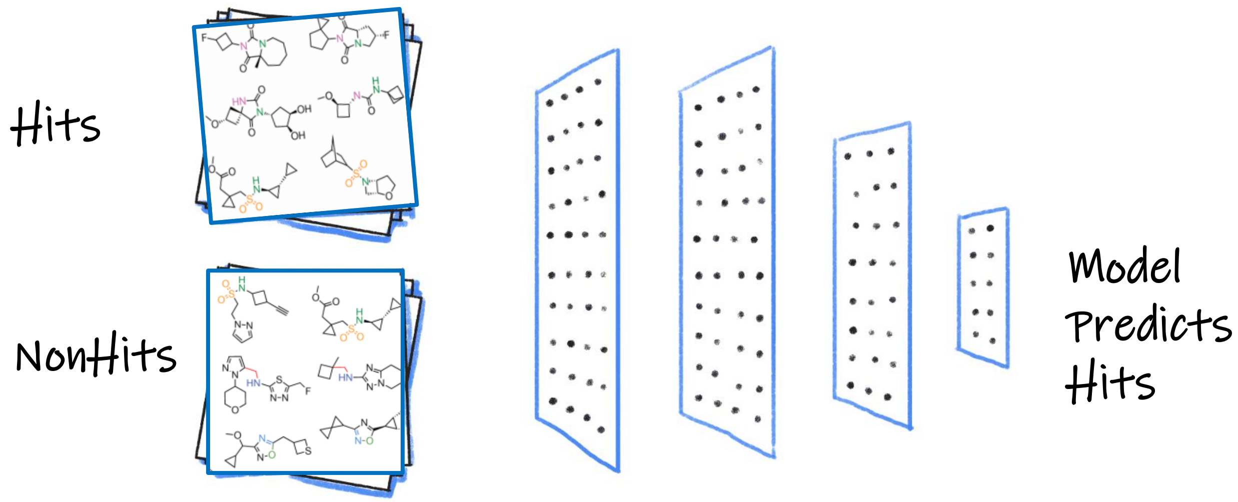
RTCNN Docking Score

Deep Learning - accelerated screening



V-SYNTHES-DL accelerator:
Deep Learning filter yields additional >200-fold speedup

Anastasiia Sadybekov



Graph-CNN model

Train on 0.5M compounds

Apply to 100M compounds

>90% recovery

>200-fold speedup

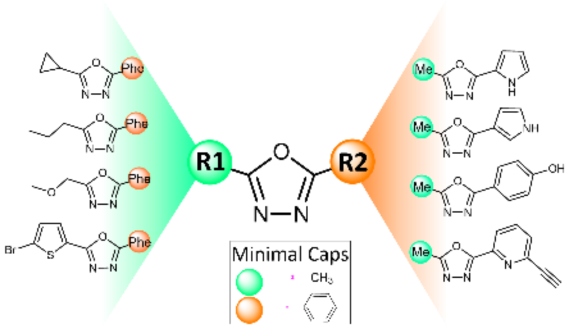
>1,000,000 total speedup!!

Step 1

3 Trillion

Enumeration with the minimal caps

Minimal Enumeration Library, <2M

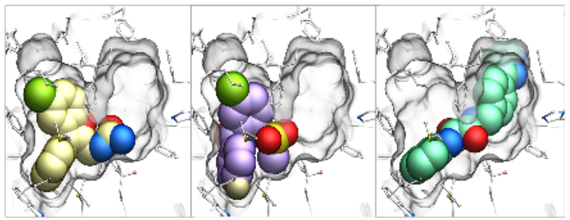


Step 2

Ligand-Receptor Docking

CapSelect algorithm to select best MEL candidates

Top Minimal Fragments, 10K-100K

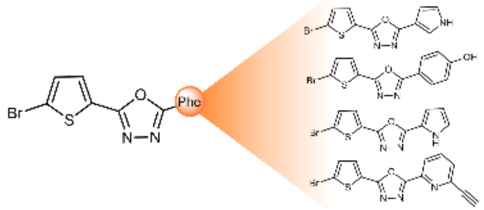


Step 3

Enumerating with full Synthons

Replace one of the minimal caps with full synthons

Full Enumerated Subset, <100M

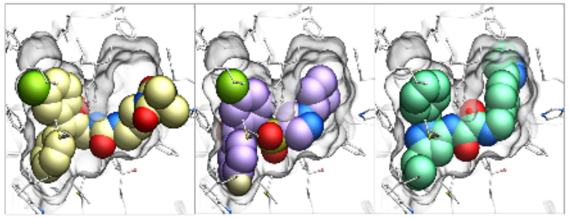


Step 4

Ligand-Receptor Docking

Selection based on docking scores, drug-likeness and diversity filters

Candidate Hits for Experimental Testing, ~100 cmpds



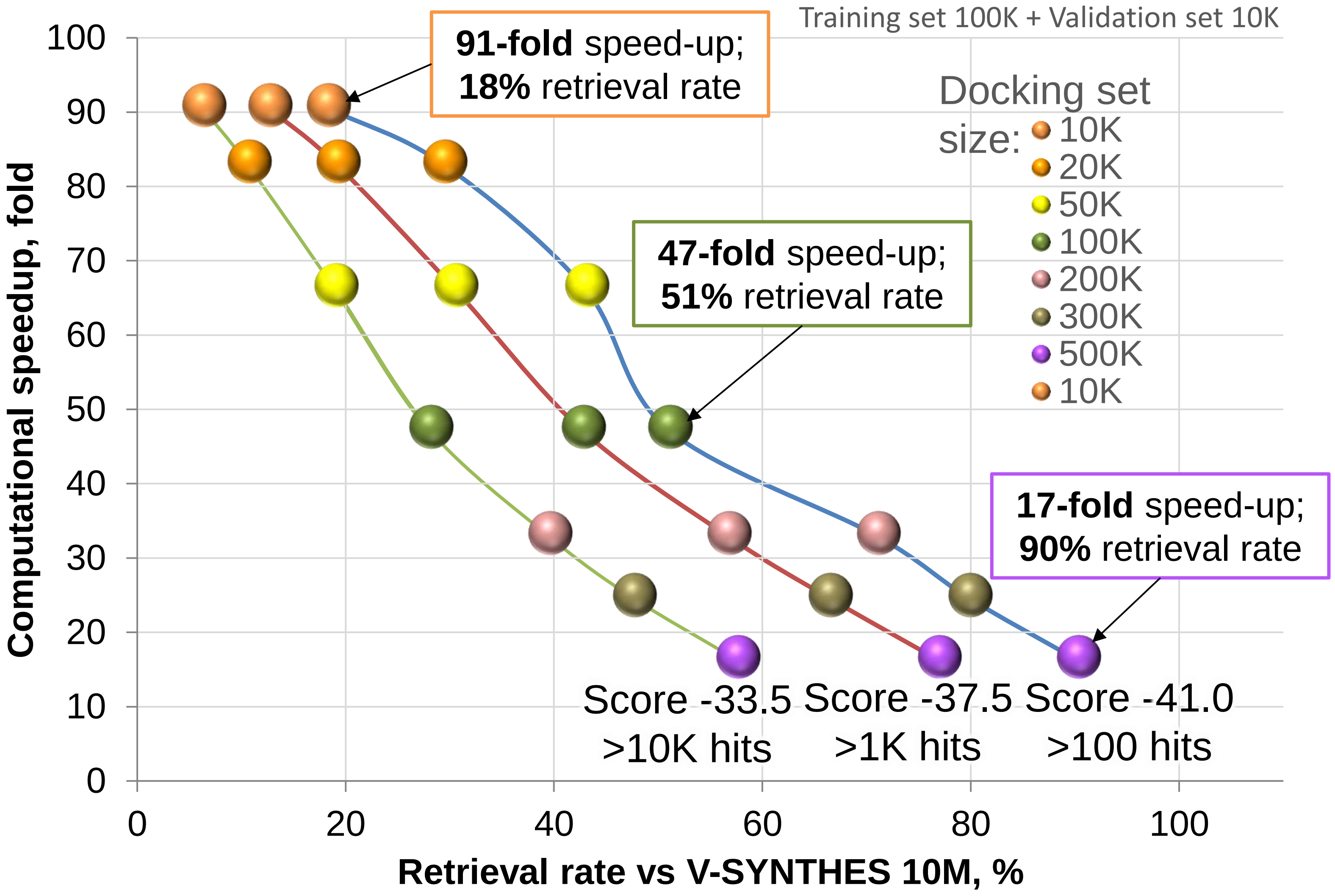
Manuscript in preparation

Computational efficiency of V-SYNTHES-DL vs V-SYNTHES 10M

$$Speedup = \frac{N\ of\ docking\ VSYNTHES\ DL}{N\ of\ docking\ VSYNTHES\ (10M)} =$$

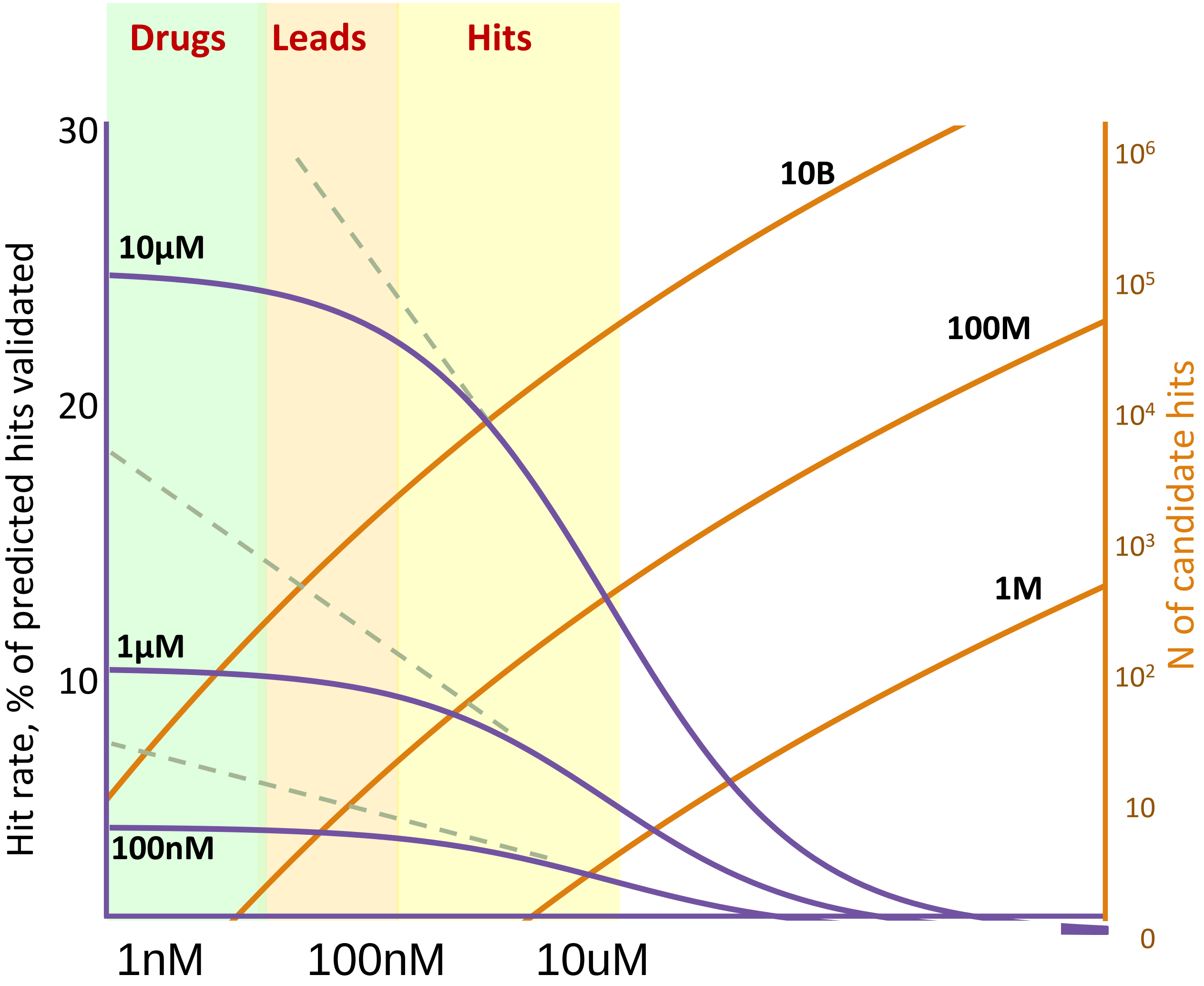
$$= \frac{N\ of (Training\ set + Validation\ set + Docking\ set)}{10M}$$

- Choosing docking set size, one can chose the best compromise between speed and retrieval
- The speed advantage will further grow with the space size



Sadybekov et al. *(unpublished)*

Do we need such huge screening spaces?



Yes!!! – The more the better!

- The bigger the library, the more potential hits with good scores (Millions!!!)
- **"hit rates improved with library size, as did the potency of the inhibitors"** (Liu et al, Nature Chem. Bio. 2025.)

How to exploit this embarrassment of riches to get better leads and drug candidates?

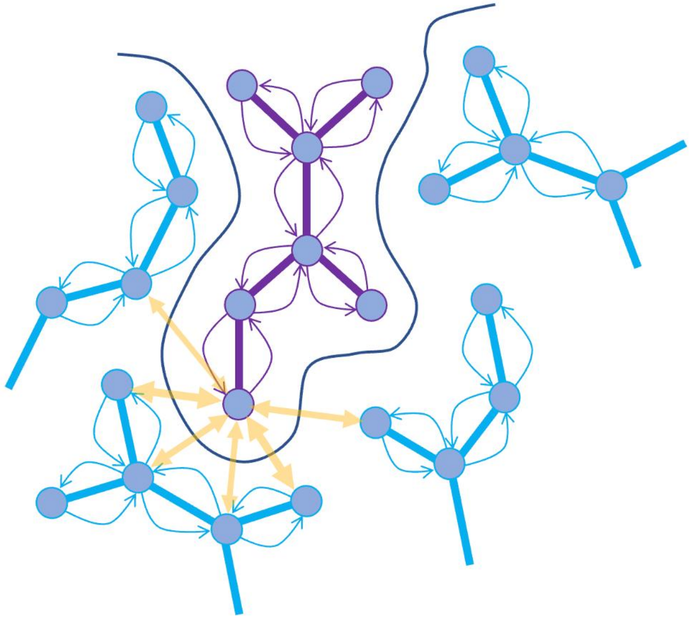
- Consensus of several orthogonal scoring functions, especially DL-based (e.g. RT-CNN)
- More rigorous (but slow) affinity predictors like abFEP
- Apply additional predictive DL filters (bioavalability, BBB, selectivity etc.)

Sadybekov & Katritch (2023) ***Nature, 616: 7958***

RTCNN – a Neural Network Score

molsoft
molecules *in silico*

- **R**adial **C**onvolutional **N**eural **N**et with 2 types of layers:
  - **T**opological (chemical graph) convolutions
  - 3D **R**adial convolutions
- Trained on clean PDB and generated **decoy** ligand/receptor poses



CASF 2016 screening benchmark EF1%

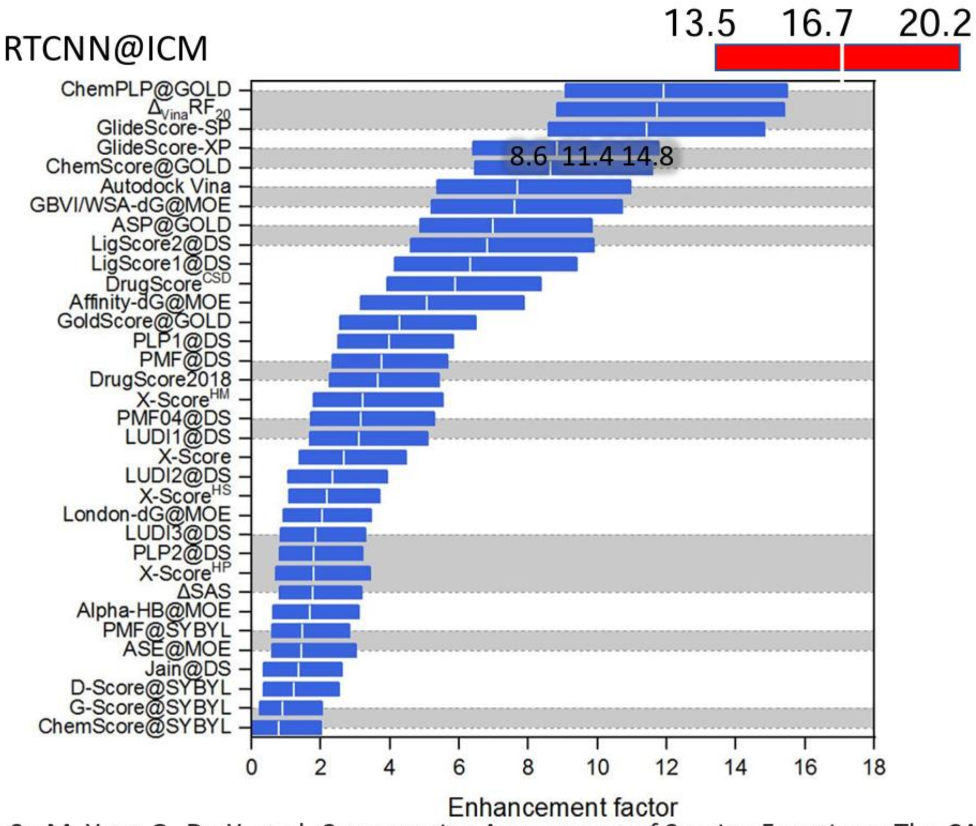


Figure: Su M, Yang Q, Du Y, et al. Comparative Assessment of Scoring Functions: The CASF-2016 Update. *J Chem Inf Model*. 2019;59(2):895-913.

Can be used as an "orthogonal" filter with physics-based docking score.

https://molsoft.com/RTCNN.html

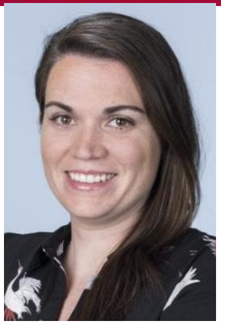
V-SYNTHES collaborative applications to diverse targets

Michelson Center The Bridge @ USC


Charles McKenna


Xiaojiang Chen


Cornelius Gati


Kate White

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

CHEM SPACE

Enamine

molsoft molecules in silico

Google Cloud

aws

V-SYNTHES-DL

Added key AI components

Scales 11B to 10^{15} cmpds

Easy Lead Optimization

Tested on many targets

CNT3D Center for New Technologies in Drug Discovery and Development

Keck Medicine of USC


Hussein Yassine


Yali Dou


Steven Grossman


Steve Kay

Northeastern University 1898 LVX VERITAS VIRTVS

Penn University of Pennsylvania

VE RI TAS HARVARD

Washington University in St. Louis

THE UNIVERSITY OF TEXAS MD Anderson ~~Cancer~~ Center

UT Southwestern Medical Center

CNT3D drug discovery pipeline (since 2023)

CNT3D
Center for New Technologies in Drug Discovery and Development

Target ID → Quality hits → Hit-to-Lead → Lead Optimization → Preclinical Studies → Clinical Trials

AT_2R antagonist for neuropathic pain (UH3 grant)	Collab w/ Drs. Cherezov (USC) Shepherd (MDACC) & Majumdar (WashU)
$cPLA_2$ antagonist for Alzheimer's	Collab with Dr. Yassine (USC Keck)
Covalent MOR blocker as fentanyl antidote (licensed)	Collab with Drs. Fokin (USC Dornsife) & McLaughlin (UF)
Optically controlled analgesic (IP)	Collab with Drs. Levitz (Cornell) & Trauner (UPenn)
D_2R PAMs for Parkinson's	Collab with Dr. Rosenbaum (UTSW)
DOR bitopic agonist for chronic pain	Collab with Drs. Majumdar & Tao (WashU)
Addiction disorders	Collab with Dr. Majumdar (WashU)
Glioblastoma	Collab with Dr. Kay (USC)
Fungal infection	Collab with Dr. McKenna (USC)
>10 targets	

- **partnered**
- **seeking a partner**
- In development

V-SYNTHES-DL

AI components

> 3 Trillion compounds

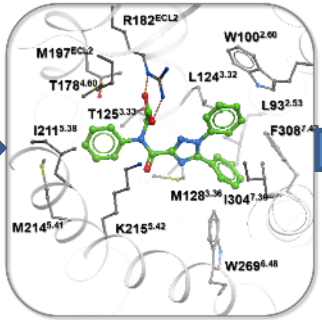
Easy lead optimization

AT_2R antagonist for neuropathic pain

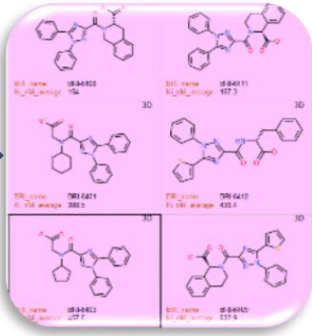
from first hits to a pre-clinical candidate BPN-36970

Vadim Cherezov *Sush Majumdar* *Andrew Shepherd*

Giga-VLS → *Initial Hit (K_i=903 nM)*



SAR-by-Catalog → *Analogs (Ki =154-600 nM)*



Potency Optimization → *Leads (Ki =1-10 nM)*

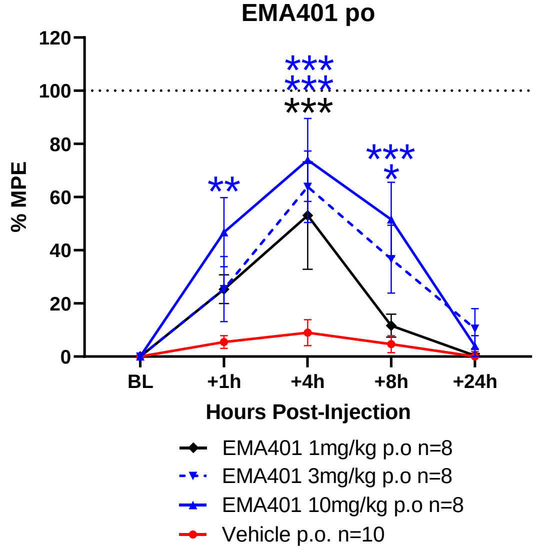
- 2 key groups
~200 cmpds synthesized
- *In vitro* potency
- *In vivo* efficacy

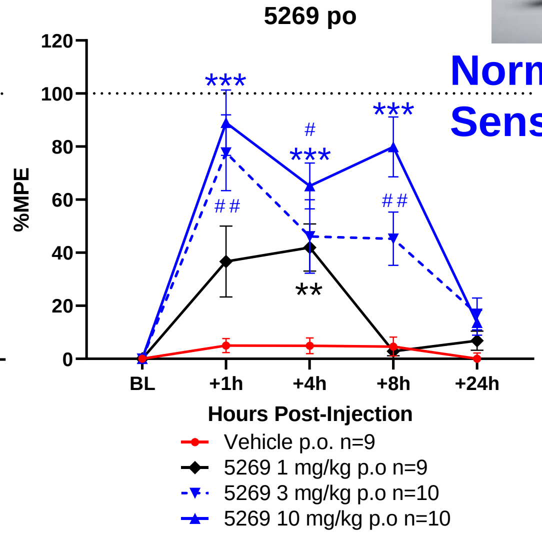
Medchem → *Optimized properties*

- 953 cmpds synthesized
- In vitro ADME
- In vivo PK

→ Preclinical Candidate

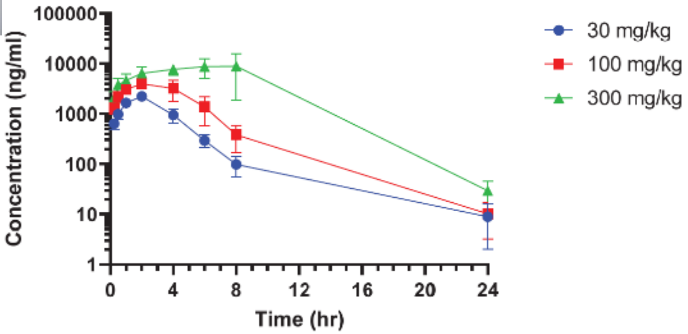
Improved Neuropathic pain relief (SNI model)





Normal Sensitivity

High bioavailability and PK in oral delivery (rats)



Rat	Test Article	Route	(mg/kg)	$t_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/ml)	AUC_{last} (hr•ng/ml)	AUC_{inf} (hr•ng/ml)
1	BPN-35269	po	30	3.04	2.00	1,920	7,210	7,240
2	BPN-35269	po	30	3.62	2.00	2,350	7,000	7,090
3	BPN-35269	po	30	2.60	2.00	2,420	9,440	9,450
		Mean		*3.09*	*2.00*	*2,230*	*7,880*	*7,930*
		SD		*0.51*	*0.00*	*271*	*1,350*	*1,320*

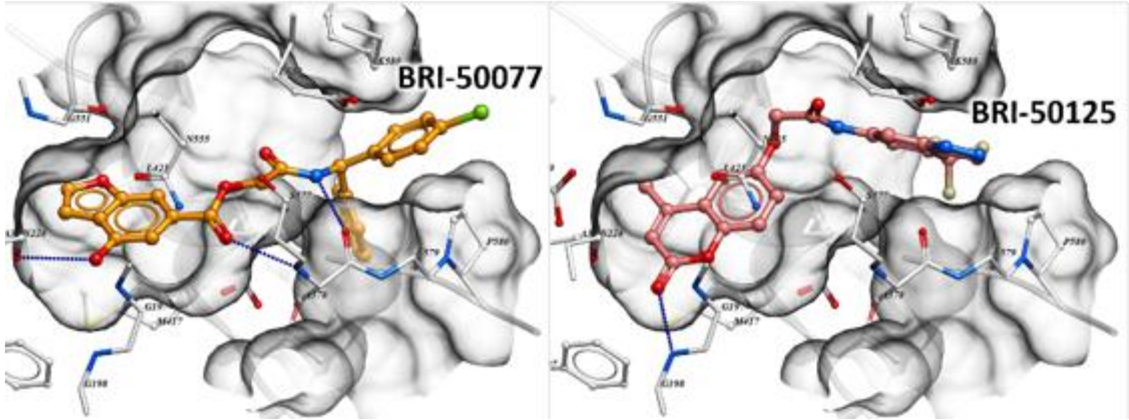
UG3NS116929 and BPN CRO services

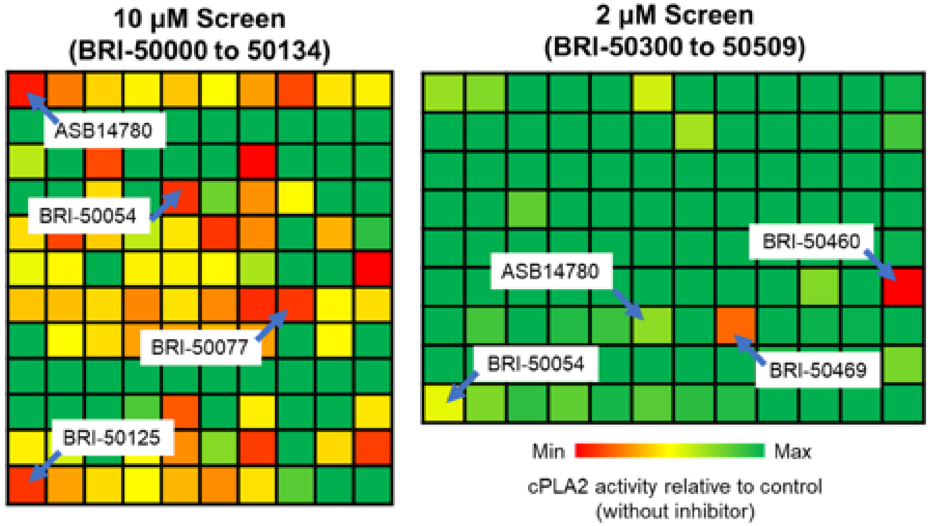
Stan Louie

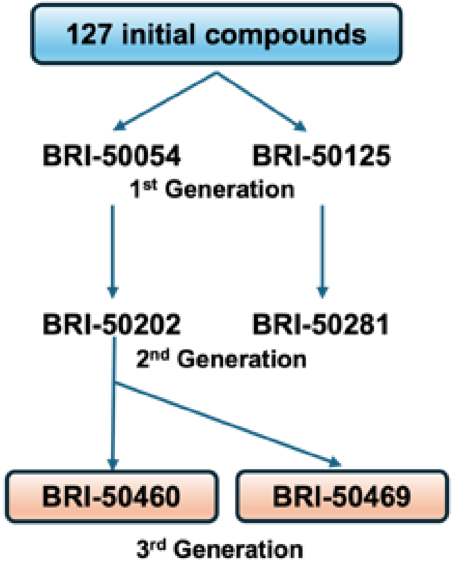
cPLA2 antagonist BRI-50460 as anti-inflammatory treatment of Alzheimer's disease

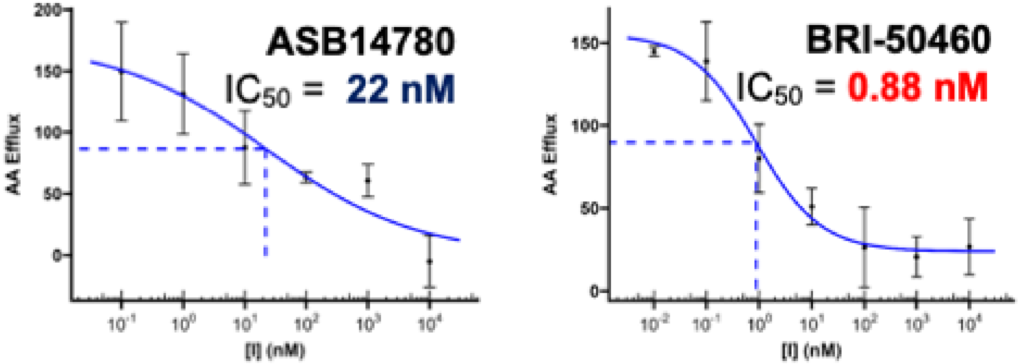
Hussein Yassine

- **Target**: cPLA2 in APOE4 pathway, strongly associated with early Alzheimer's
- **V-SYNTHES screen of >18B compounds in Enamine "REAL" space**









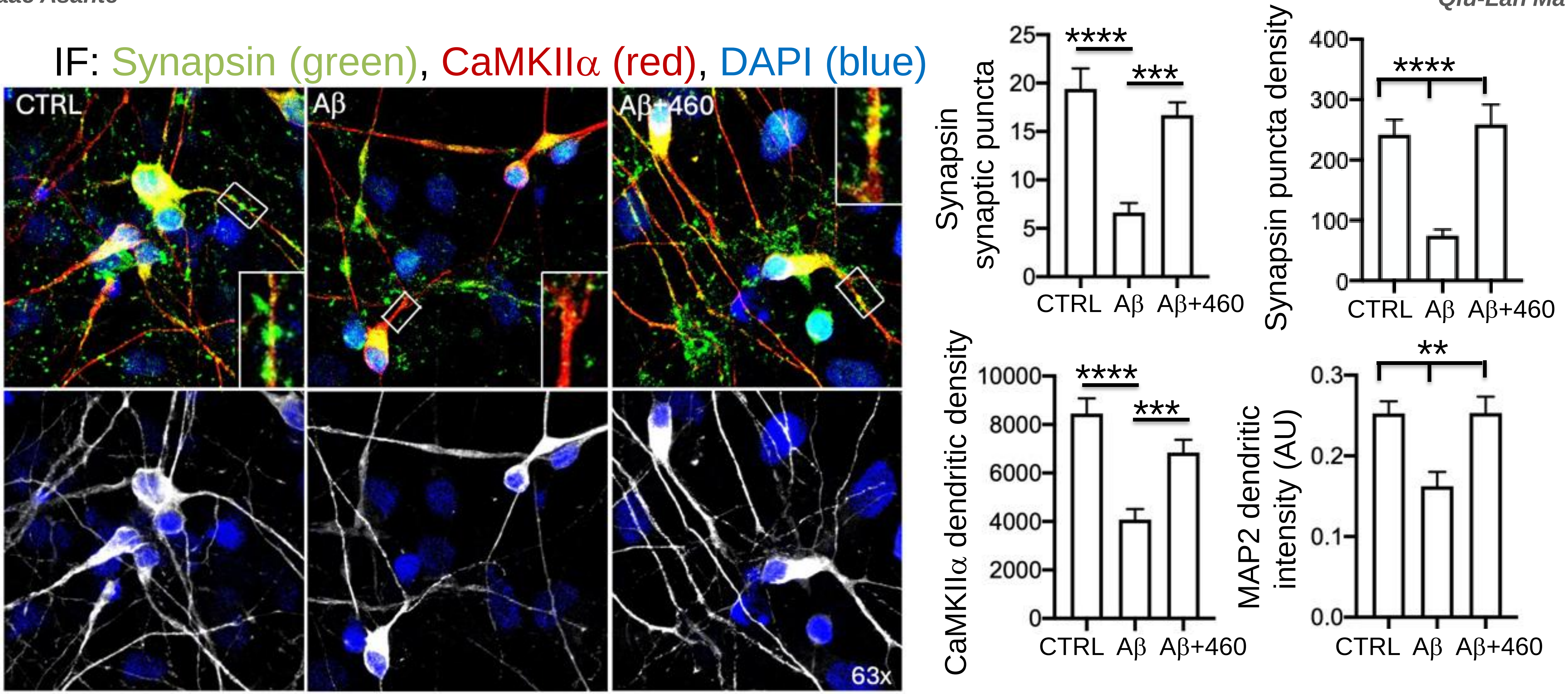
Sadybekov et al. 2025, BioRxiv https://doi.org/10.1101/2025.03.09.641748

BRI-50460 protects against Aβ42 oligomer-induced synaptic loss in human iPSC-derived neurons

Isaac Asante

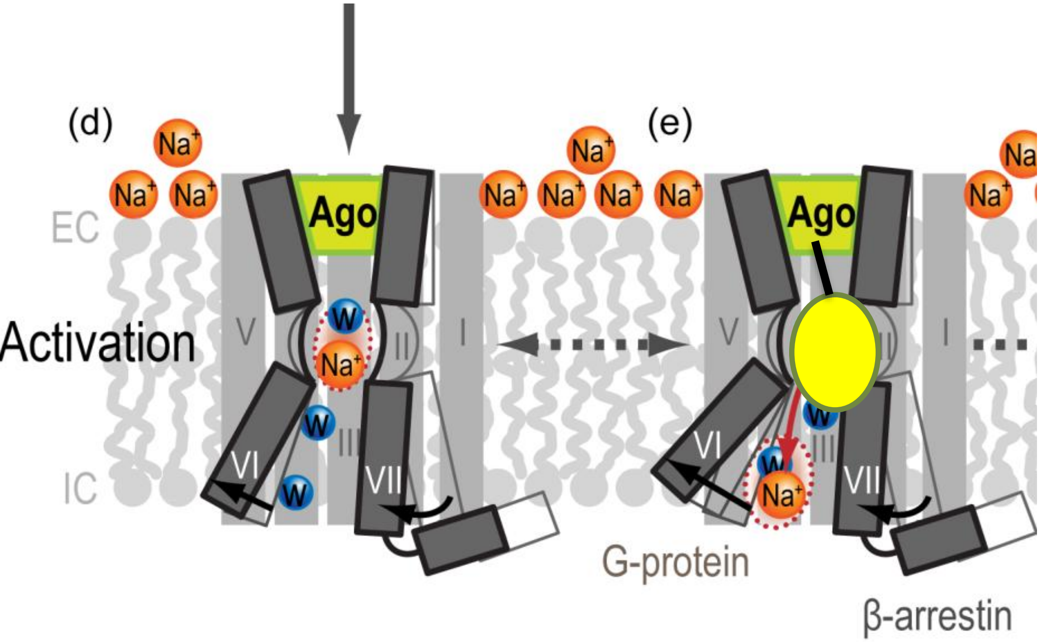
Qiu-Lan Ma

IF: Synapsin (green), CaMKIIα (red), DAPI (blue)

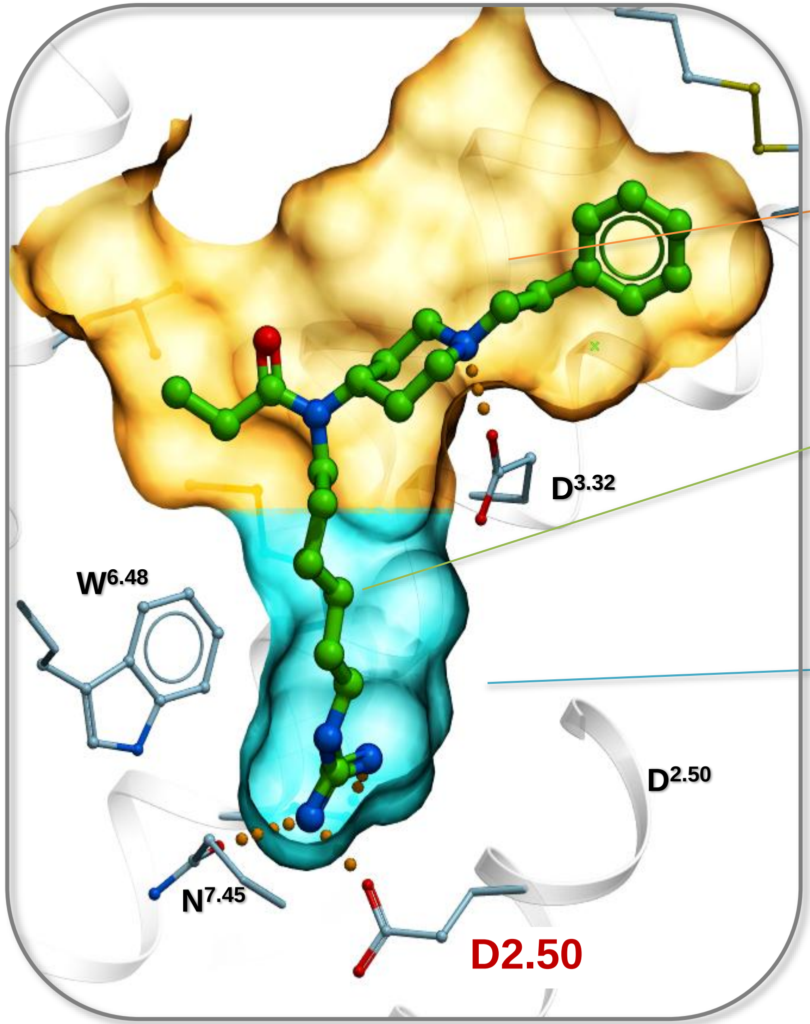


Sadybekov et al. 2025, BioRxiv https://doi.org/10.1101/2025.03.09.641748

Design of bitopic ligands for μ-Opioid Receptor



Modulate Function!



Orthosteric Pocket: Affinity, Selectivity

Flexible Linker

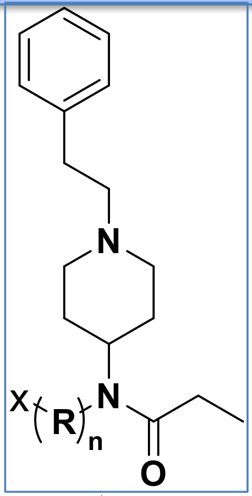
Allosteric Pocket: Modify Function

Liu et al. 2012 Science 337, 232-236; Fenalti et al. 2014, Nature 506, 191-196.;
Katritch et al. (2014) *TiBS* 39:233-44; Zarzycka et al (2019) Pharmacol. Reviews 71:571-595

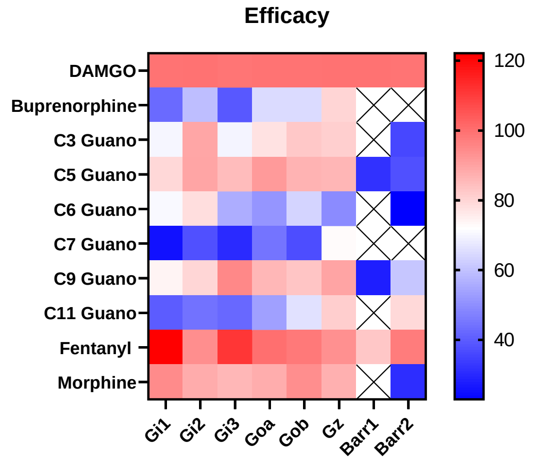

Converting Fentanyl into a safe non-addictive painkiller

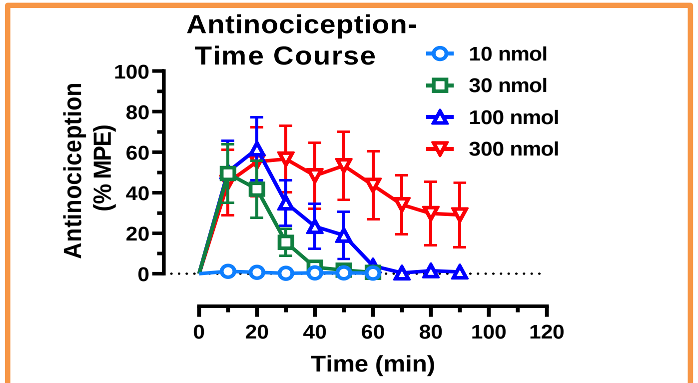
(no respiratory depression, no addiction)

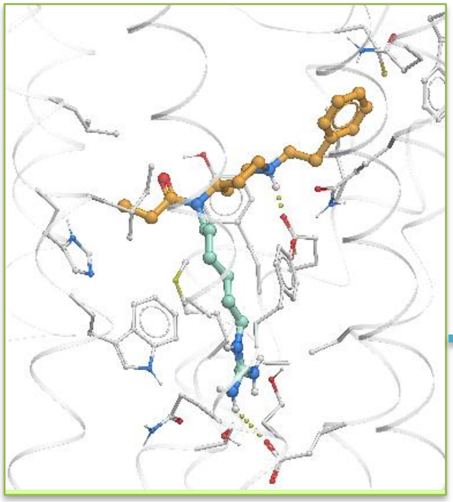

Synthesis
Majumdar, WashU



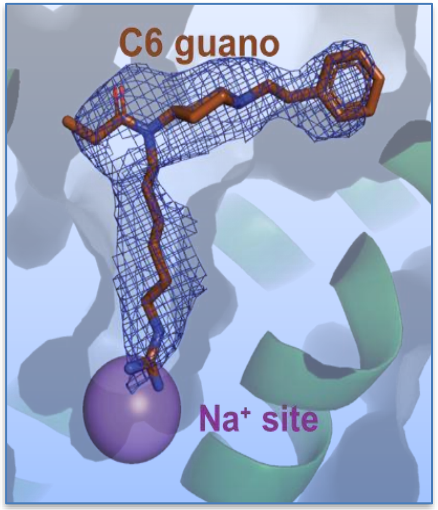
In vitro
Majumdar/Che, Roth (UNC)



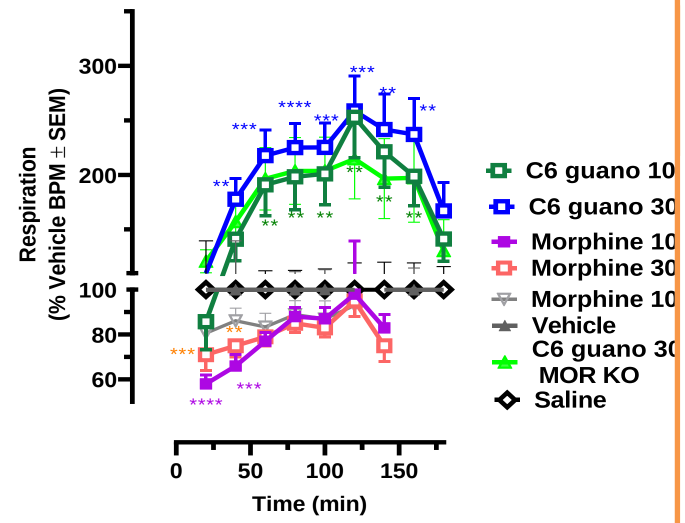




Design / Modeling
Katritch, USC



CryoEM of μ-OR
Skiniotis, Stanford



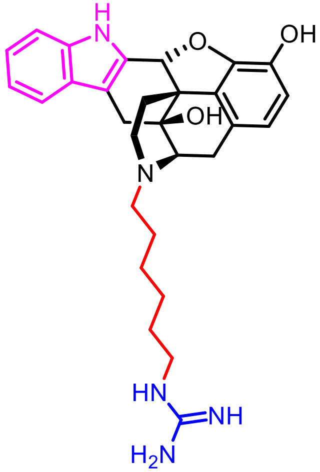
***In vivo* pharmacology**
McLaughlin, UF

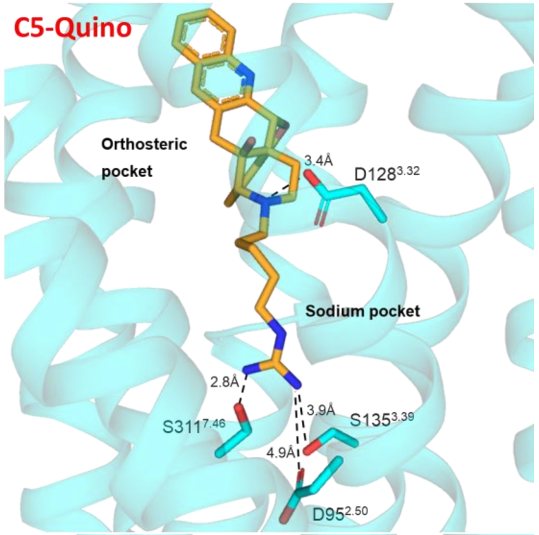
μ-Opioid: Faouzi et al (2022) ***Nature. 2023;613(7945):767-74***

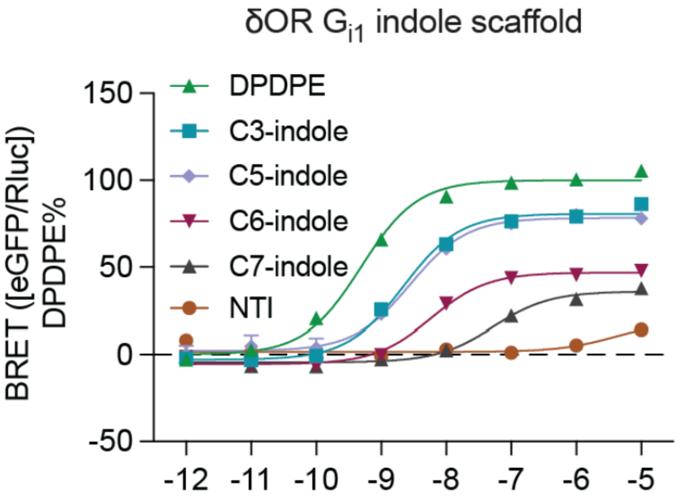
Naltrindole-based δ-OR bitopic agonists: Analgesia without Seizures

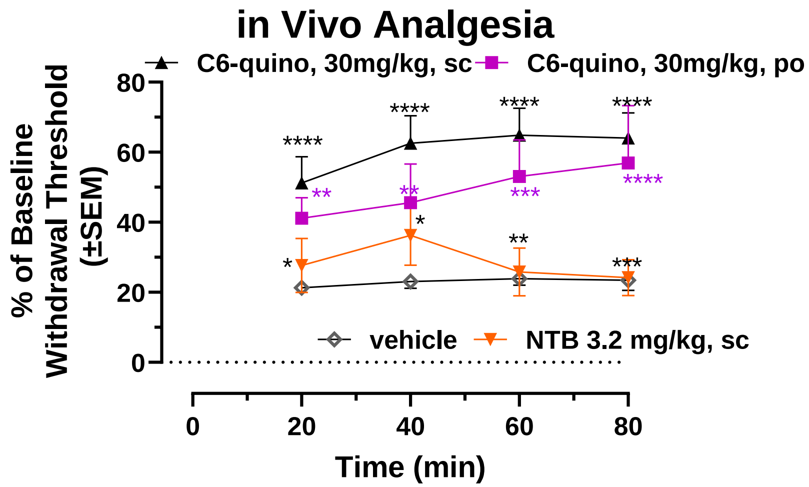
Sarah Bernhard *Balazs Varga* *Sush Majumdar* *Tao Che*

C6-Indole

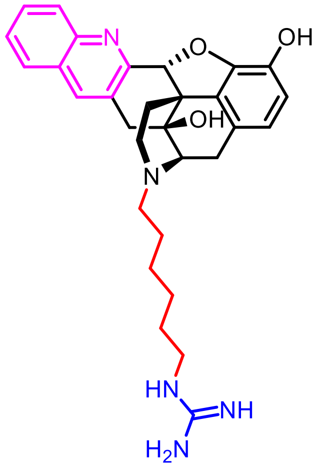


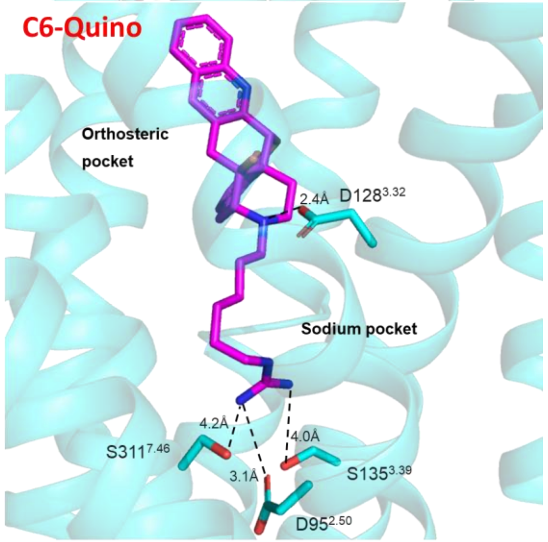


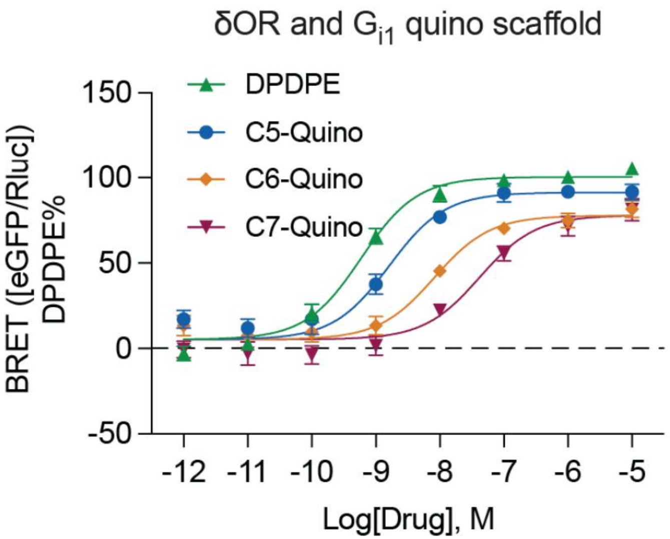


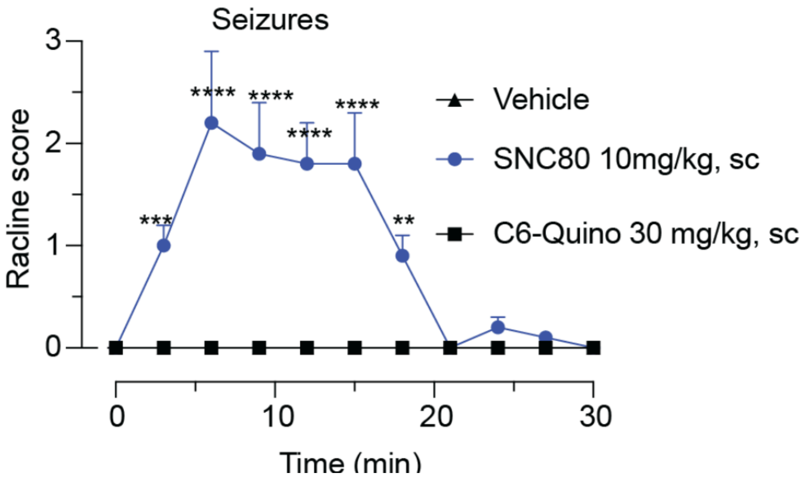


C6-Quino









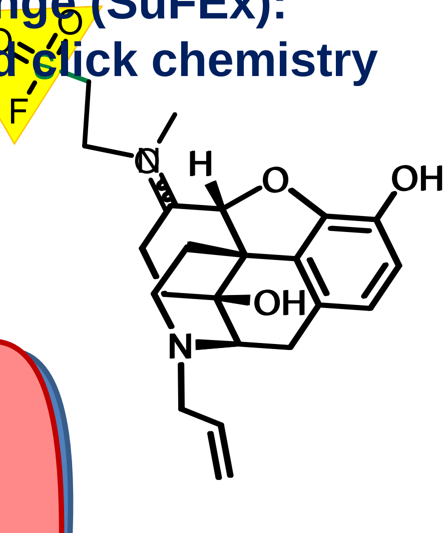
Varga et al (2025) ***Nature Com*** 16:2518

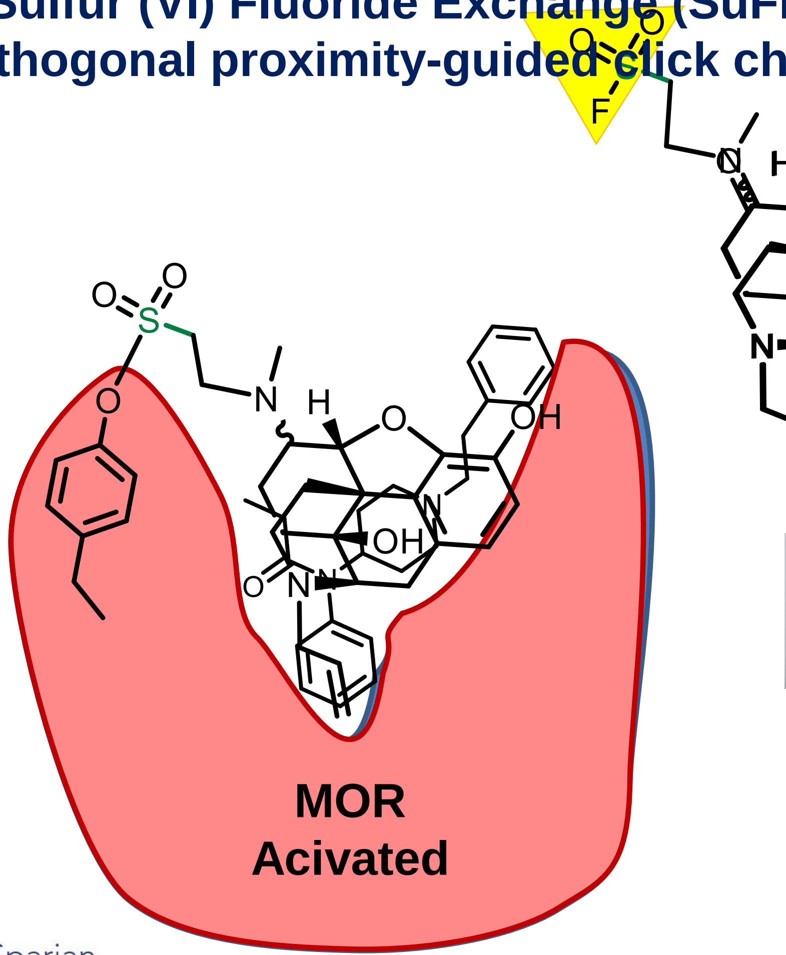
Valery Fokin

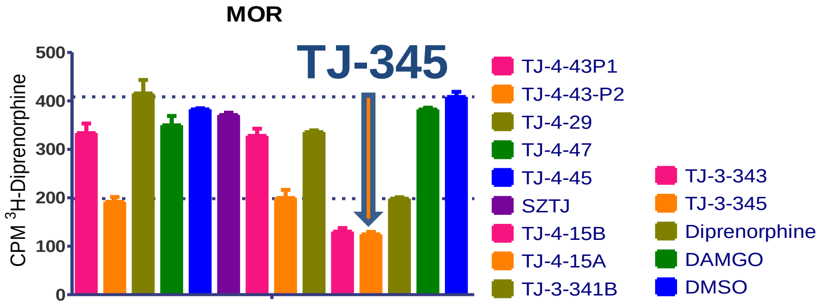
Functionalized naloxone for selective irreversible inhibition of fentanyl at MOR

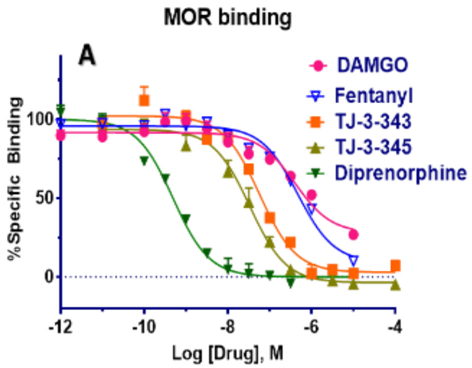
Jay McLaughlin

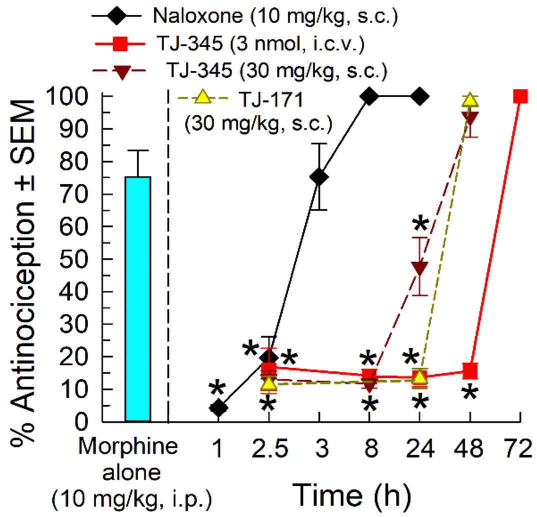
New Sulfur (VI) Fluoride Exchange (SuFEx): bioorthogonal proximity-guided click chemistry

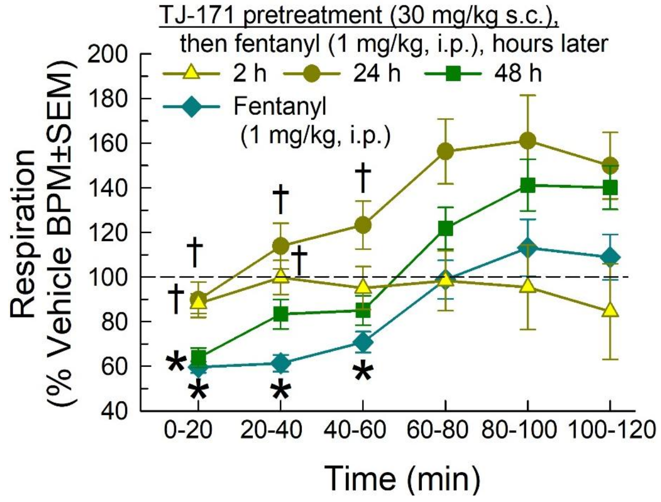










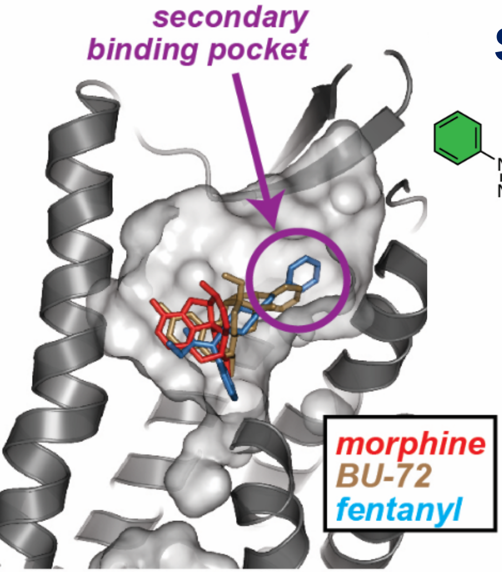


Spartian Biosciences

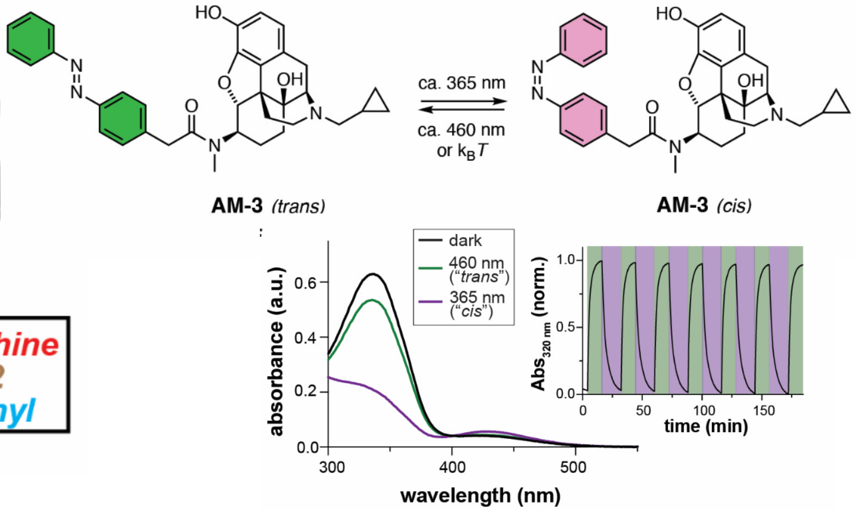
- Quickly reverses fentanyl respiratory depression
- Long – term action (>24 hours in mice)
- Compatible in vivo with s.c. or i.m. delivery

PCT Patent Application (USC)
Manuscript in preparation

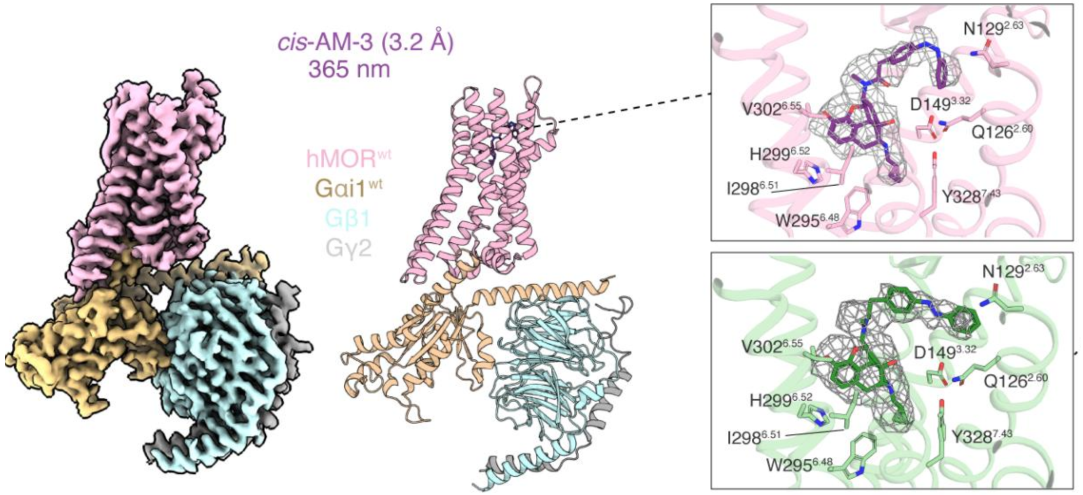
Optical control of peripheral analgesia by reversible MOR photoswitches



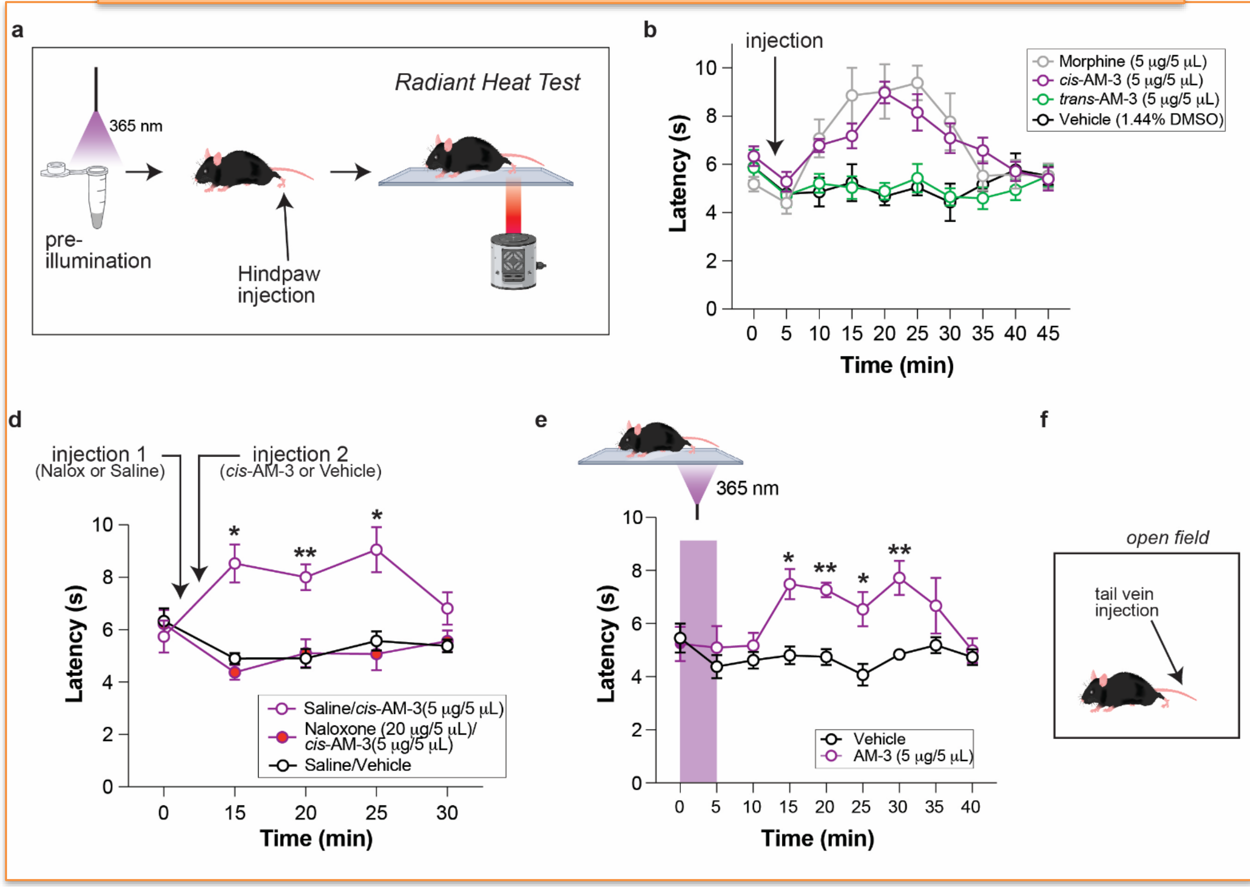
Structure-based design of AM-3



Cryo-EM validates design



AM-3 optically controls *analgesia in vivo*



Posa et al (2025) https://doi.org/10.1101/2024.12.16.628735

Small Molecule Computer-driven Drug Discovery: Applications

Physics-Based | **AI/Data-Based**

- Initial Hit Identification (Protein Structure-based)
- Scaffold hopping, optimization (Ligand-based)
- Rational design (bitopics, conjugates, covalent)
- Property predictions (solubility, PK, ADMETox)
- Fragment-based drug design
- Lead optimization for potency & selectivity

Take home message

- Modular V-SYNTHES approach makes possible fast structure-based screening of on-demand chemical spaces of billions of compounds
- Combination of Physics-Based Docking and Deep Learning approaches in V-SYNTHES-DL enables further growth into terra-scale space screening `
- V-SYNTHES and rational design provide cost effective entry points for drug discovery for challenging clinically relevant targets
- Accurate structural information is critical for both initial hit/lead finding and rational design of new functionalities

USC University of Southern California

Quantitative and Computational Biology

Michelson Center

The Bridge @ USC

National Institute of Neurological Disorders and Stroke

National Institute on Drug Abuse
The Science of Drug Abuse

National Institute of General Medical Sciences

Thanks!

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R61 NS136307

U01 NS120824; R61 DA051529 ;
R35 GM153437; R01 DA045020

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Questions?