Expanding the Drug Target Universe

Benjamin F. Cravatt, Ph.D.
Norton B. Gilula Chair of Chemical Biology
The Department of Chemistry
The Scripps Research Institute

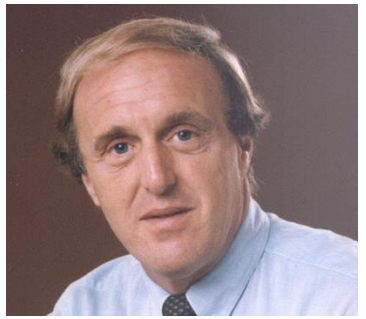
My Journey to Scripps

1998-92

Where I grew up

Scripps Research

1992-present



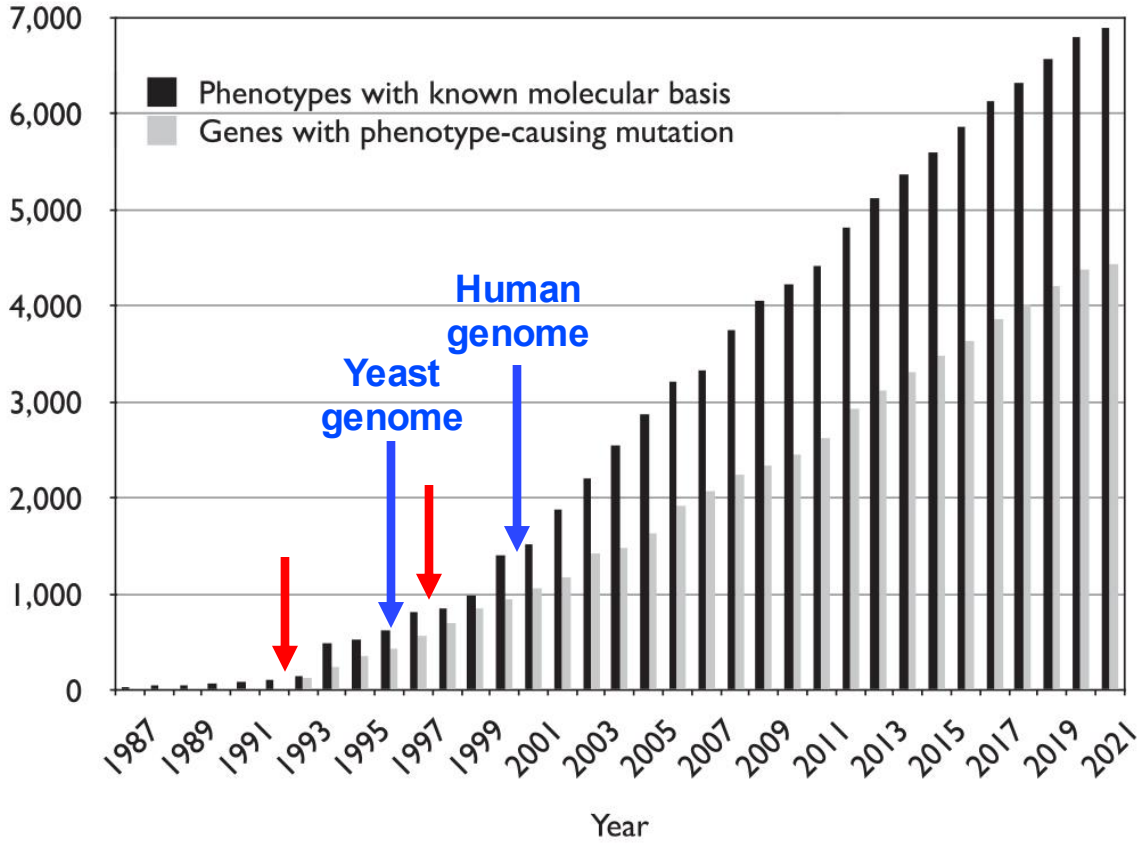
Richard Lerner

Dale Boger

Opportunities and Challenges in the Era of Human Biology Research

Opportunity – to understand human physiological and disease processes at a molecular level

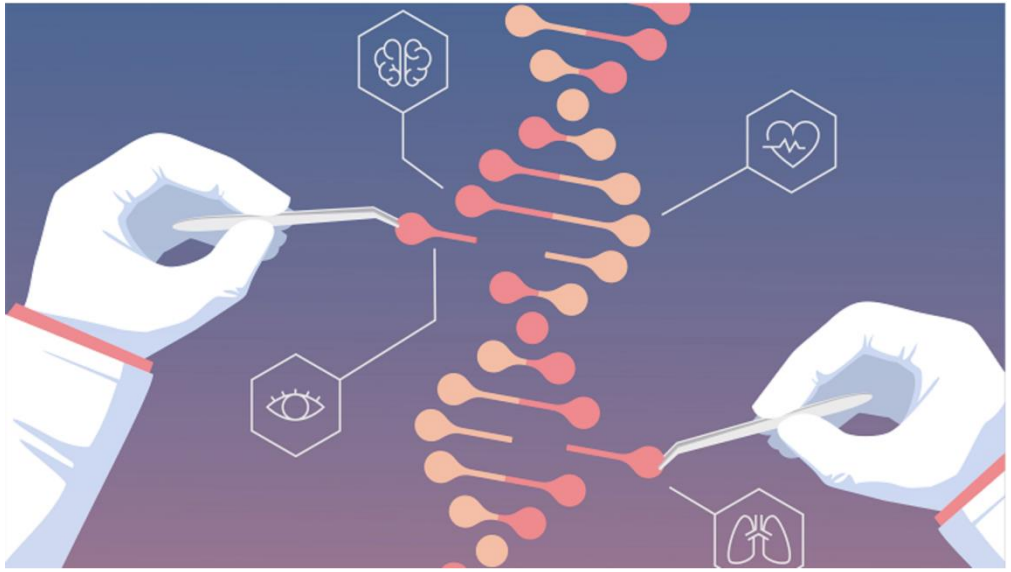
50 YEARS OMIM
Human Genetics Knowledge for the World



Opportunities and Challenges in the Era of Human Biology Research

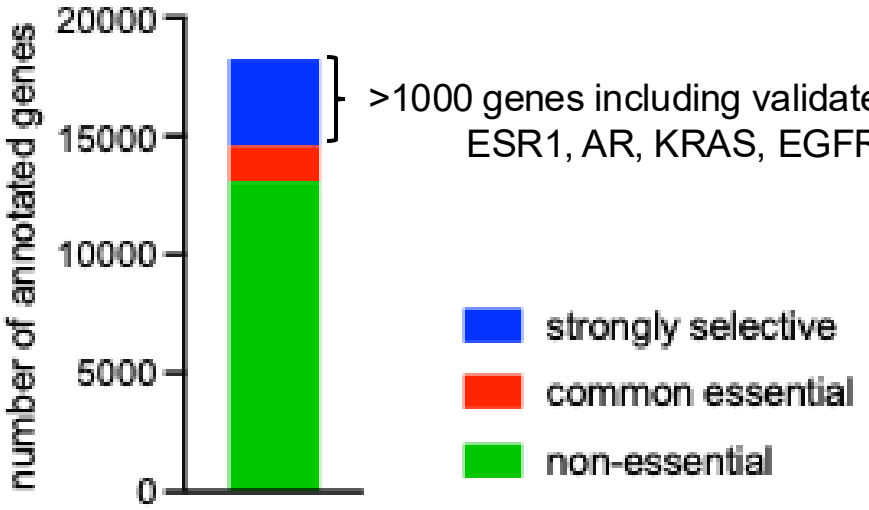
Opportunity – to understand human physiological and disease processes at a molecular level

CRISPR (gene editing)



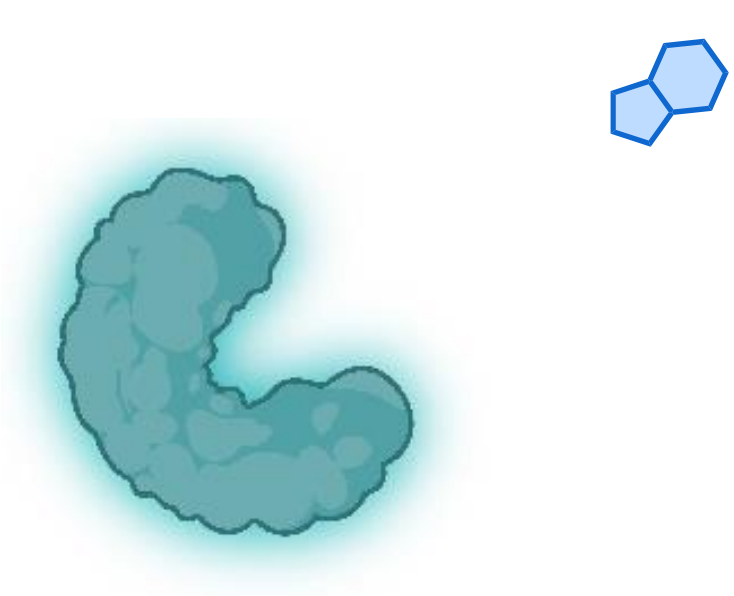
depmap portal

gene essentiality in cancer cell lines



Opportunities and Challenges in the Era of Human Biology Research

Challenge – human biology often directs researchers to currently "undruggable" targets



Classical druggable protein
(the past 50 years of pharma/biotech)

Undruggable protein
(today and the future)

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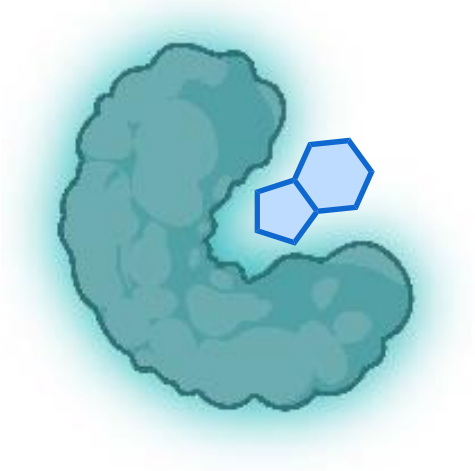

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Opportunities and Challenges in the Era of Human Biology Research

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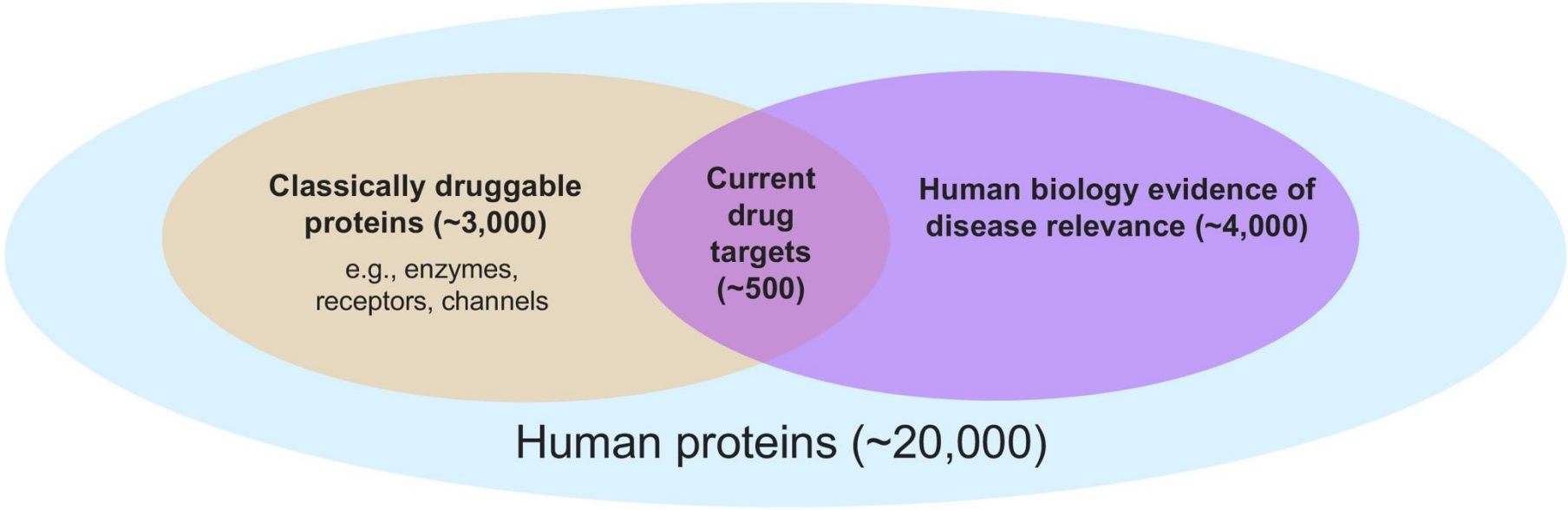

The Problem: Disease diagnosis is far outpacing disease treatment – how do we fix this?

Overview

- Activity-based proteomics
  - Discovering drug candidates in living systems
- Advancing covalent (permanent) chemistry with activity-based proteomics
  - Radically expanding the drug target universe

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- **Activity-based proteomics**
  - **Discovering drug candidates in living systems**
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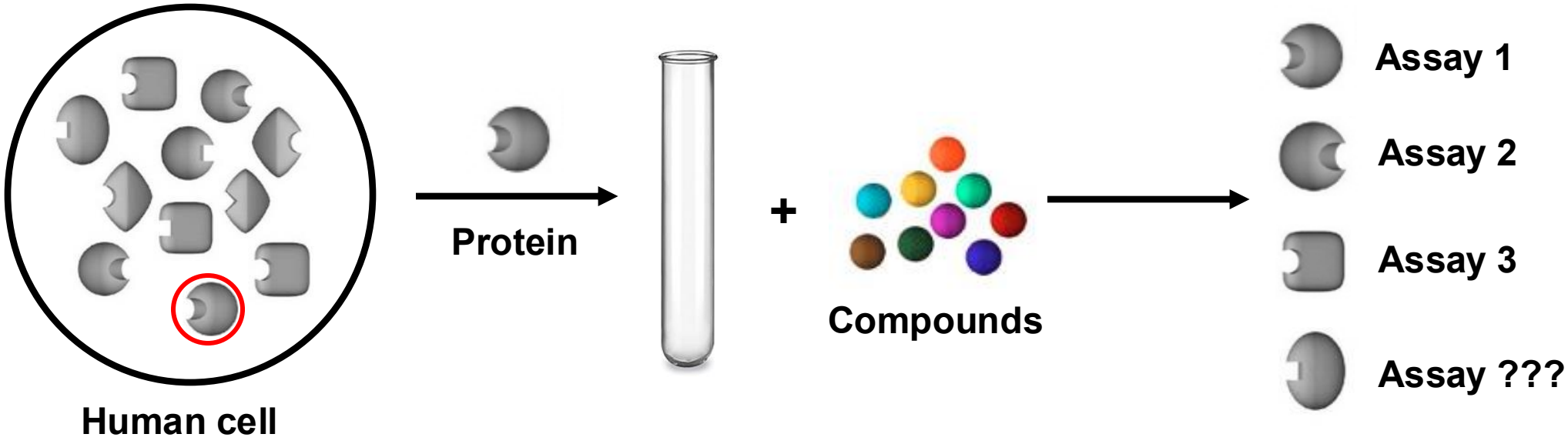
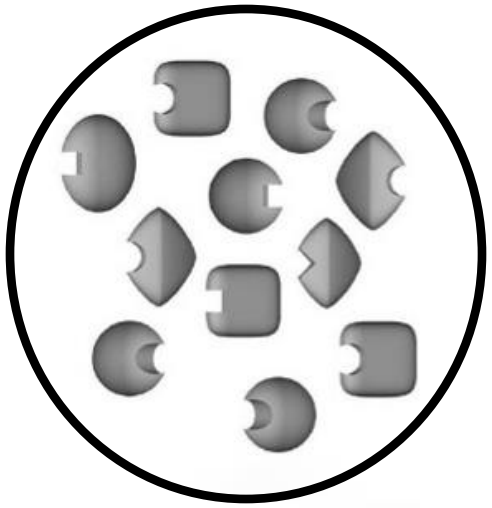
How Have Drugs Typically Been Discovered for Disease Proteins?



- One protein at a time
- Wrong protein forms (“proteoforms”)?
- Wrong neighborhoods?

Activity-Based Proteomics Provides a Near-Universal Assay for Drug Targets in Cells



Human cell

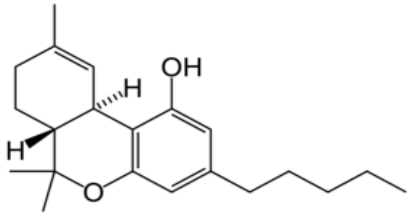
- Thousands of proteins at a time (“proteomics”)
- Right protein forms (“proteoforms”)
- Right neighborhoods

Overview

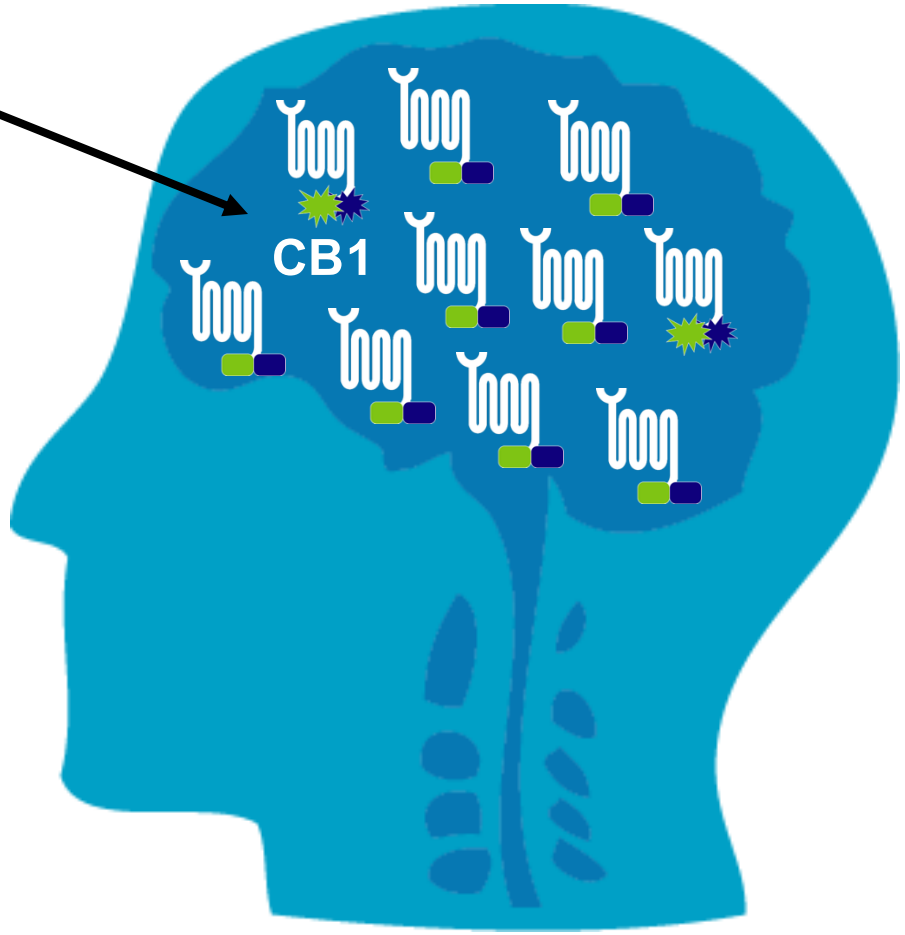
- Activity-based proteomics
  - Discovering drug candidates in living systems
- **Advancing covalent (permanent) chemistry with activity-based proteomics**
  - **Radically expanding the drug target universe**

The Endocannabinoid Pathway – A Key Regulator Of Nervous System Physiology

Exocannabinoids



Δ9-Tetrahydrocannabinol
(THC)



Behavioral effects

- analgesia
- anxiolytic
- motor deficits
- cognitive impairment

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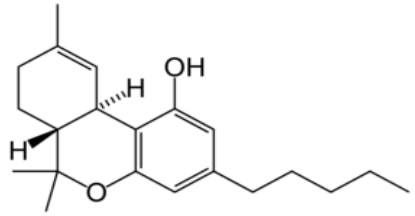

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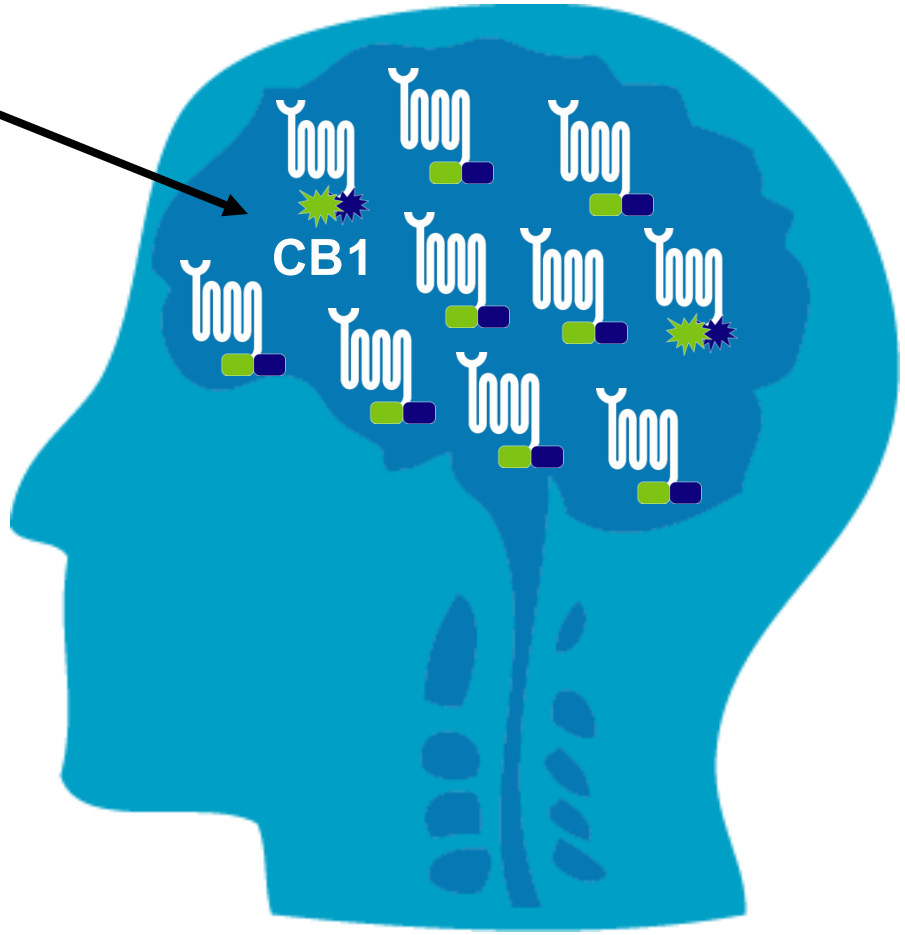

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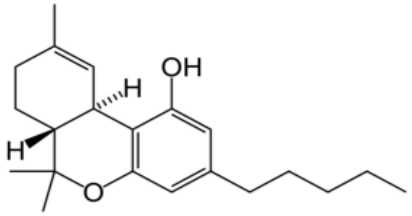

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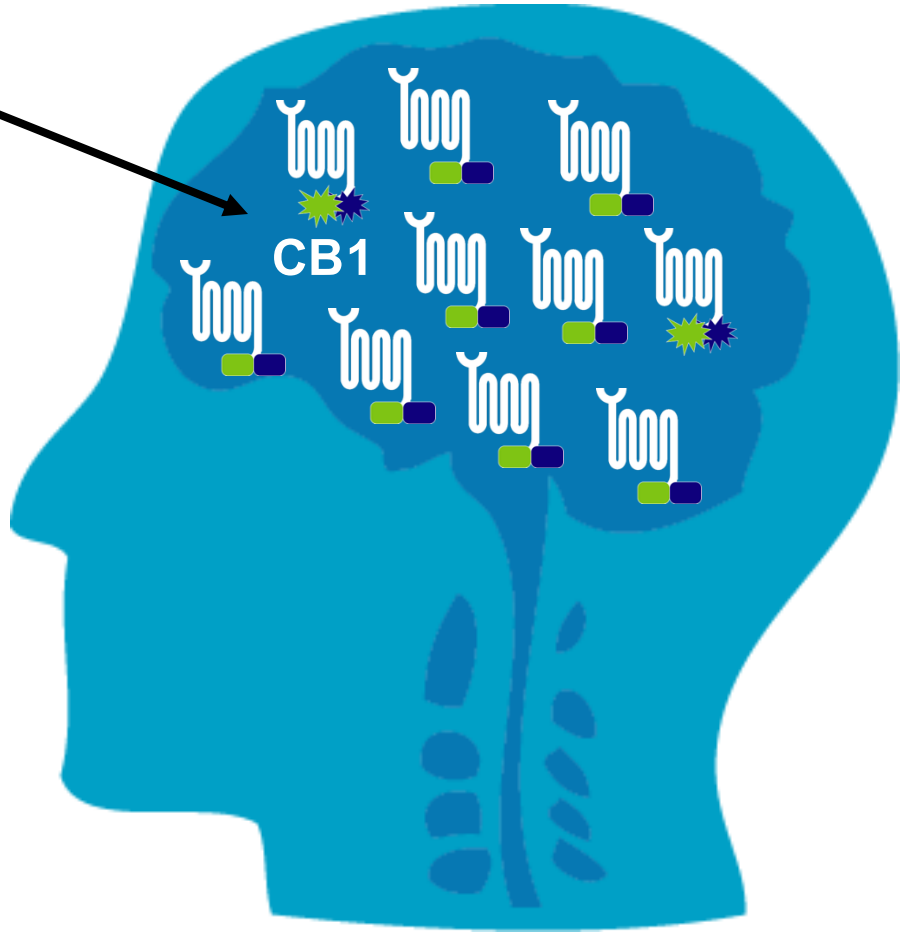

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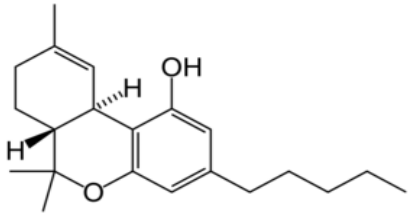

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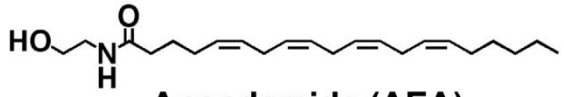
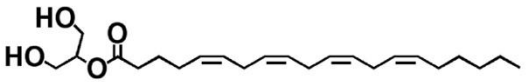
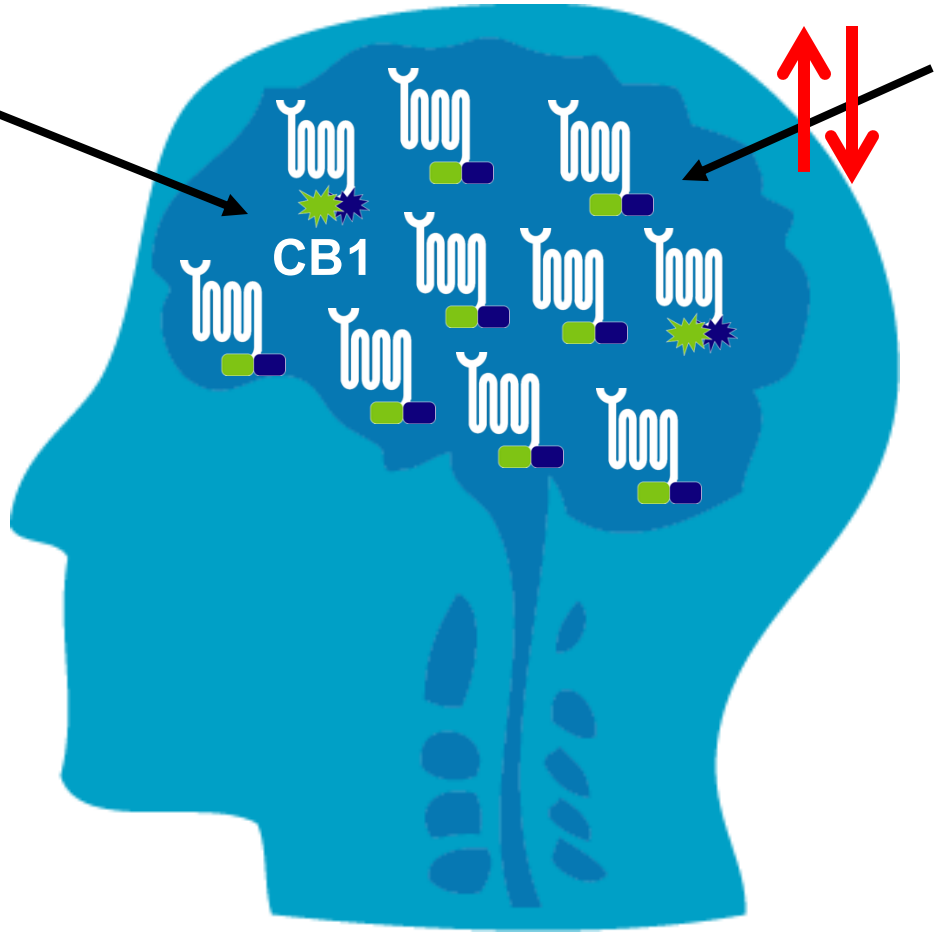


Anandamide (AEA)



2-Arachidonoyl glycerol (2-AG)



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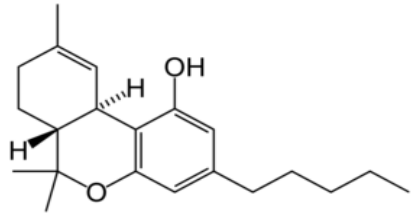

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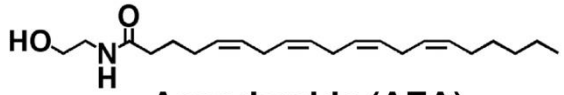

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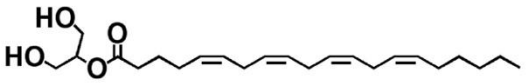

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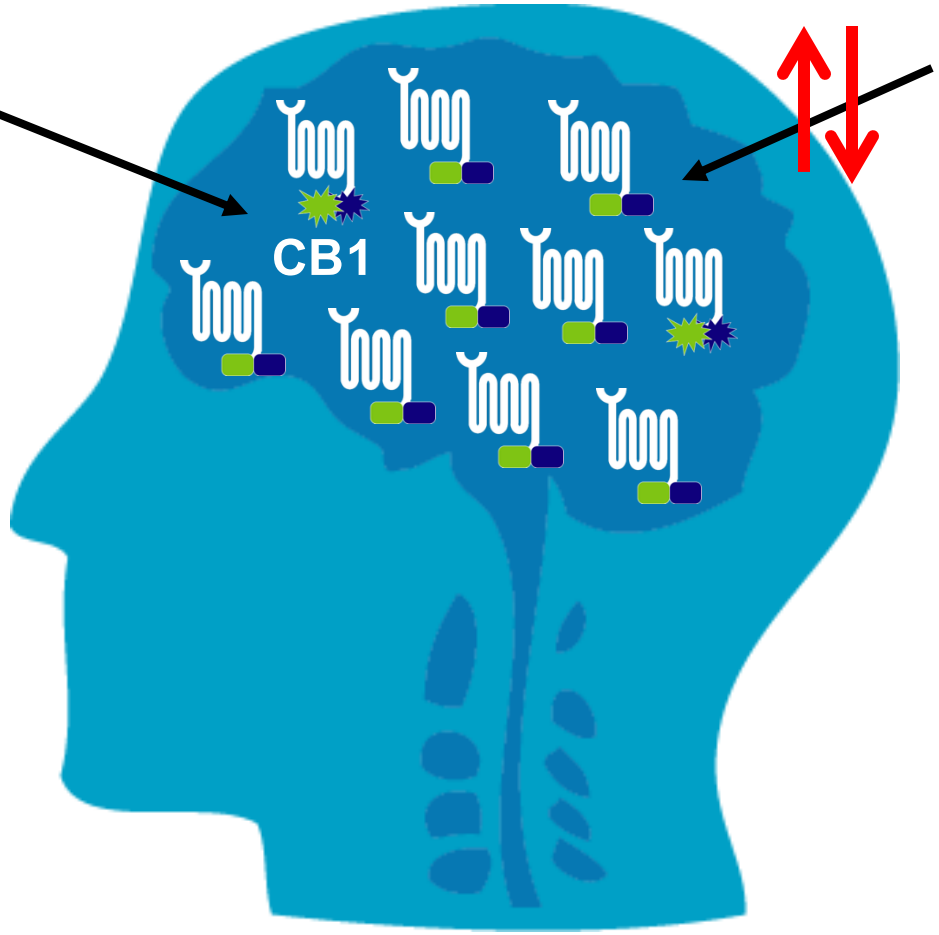

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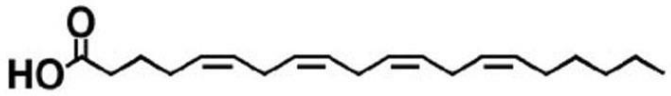
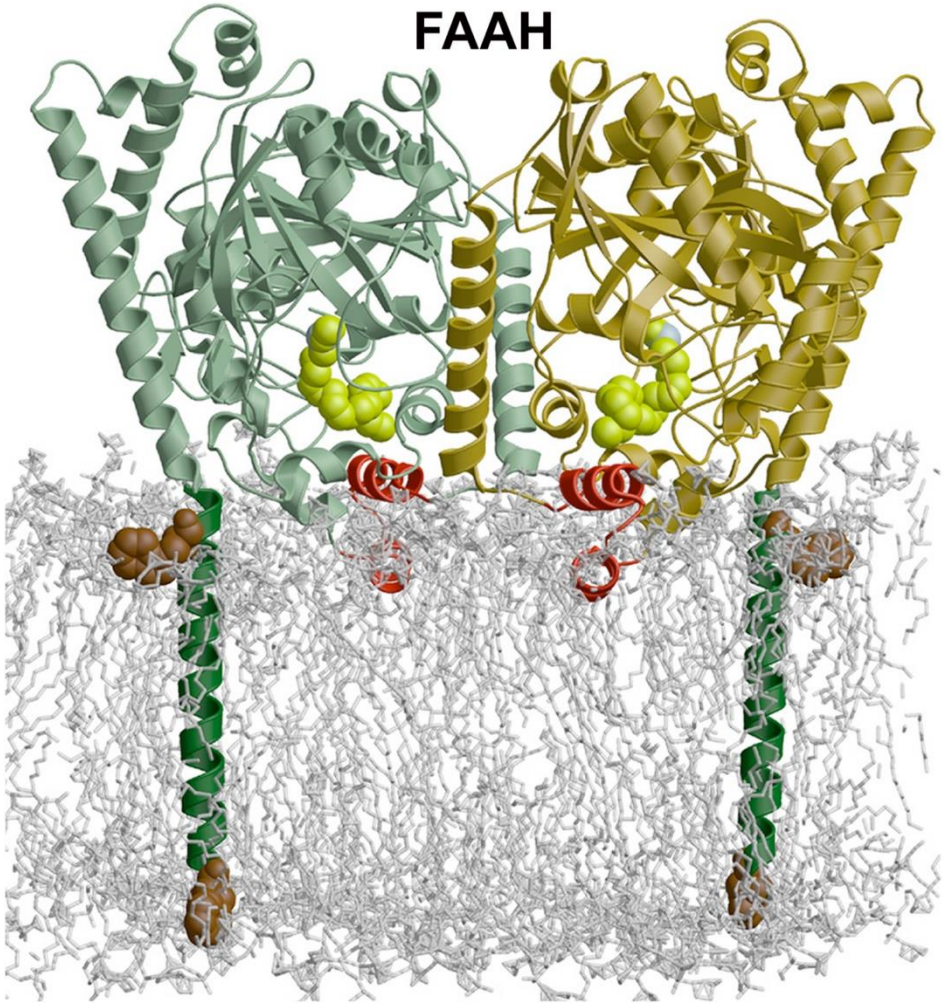
Anandamide Inactivation is Regulated by Fatty Acid Amide Hydrolase (FAAH)

Ananadamide (AEA)

FAAH

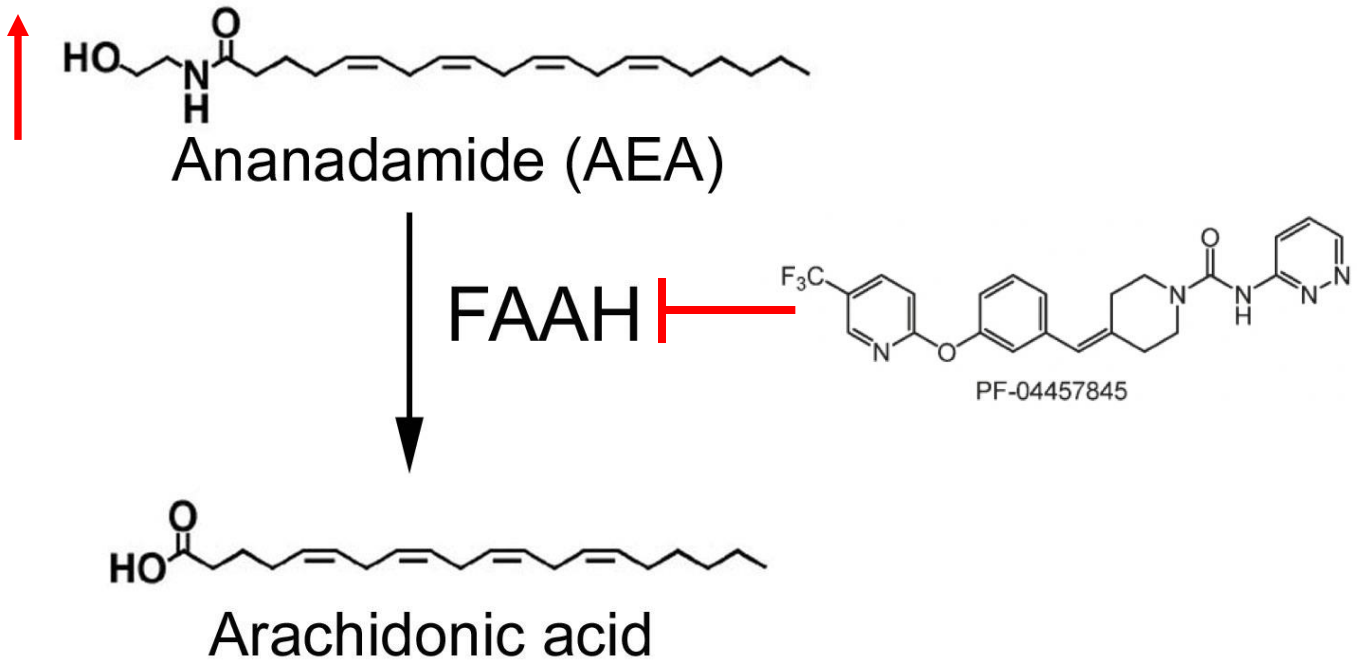


Arachidonic acid



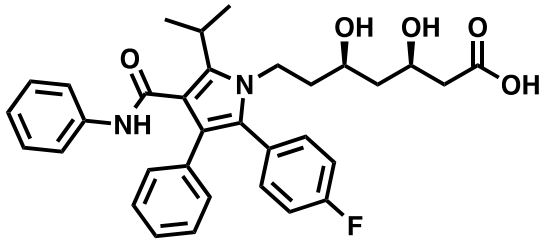
Cell membrane

Serendipitous Discovery of Inhibitors that Permanently Bind to FAAH *(with Pfizer; 2005-2007)*

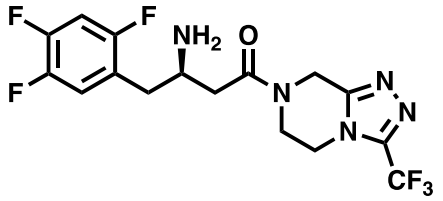


Covalent bond

Most Drugs Bind *Reversibly* to Proteins

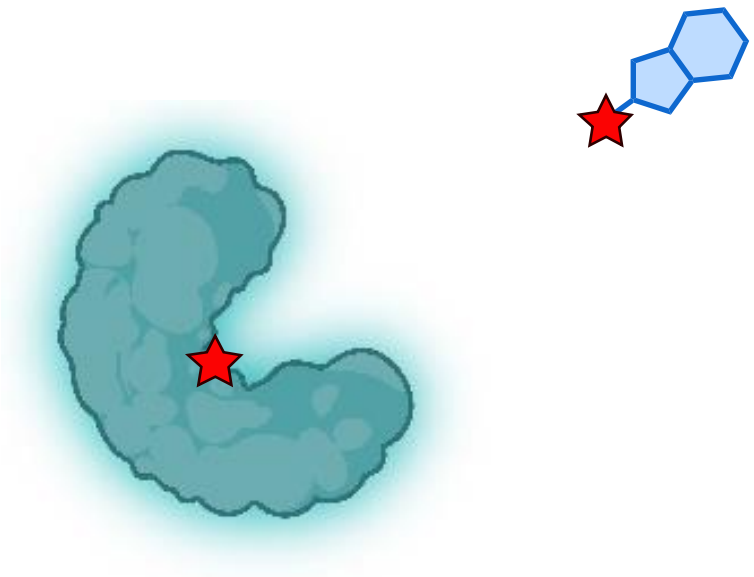


atorvastatin/Lipitor™
(cardiovascular disease)

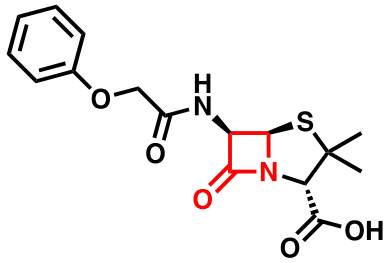


sitagliptin/Januvia™
(diabetes)

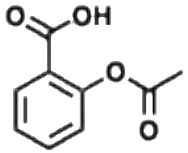
Some Important Drugs Bind Permanently to Proteins



- ***Serendipitous discoveries***
- ***Begrudgingly tolerated***

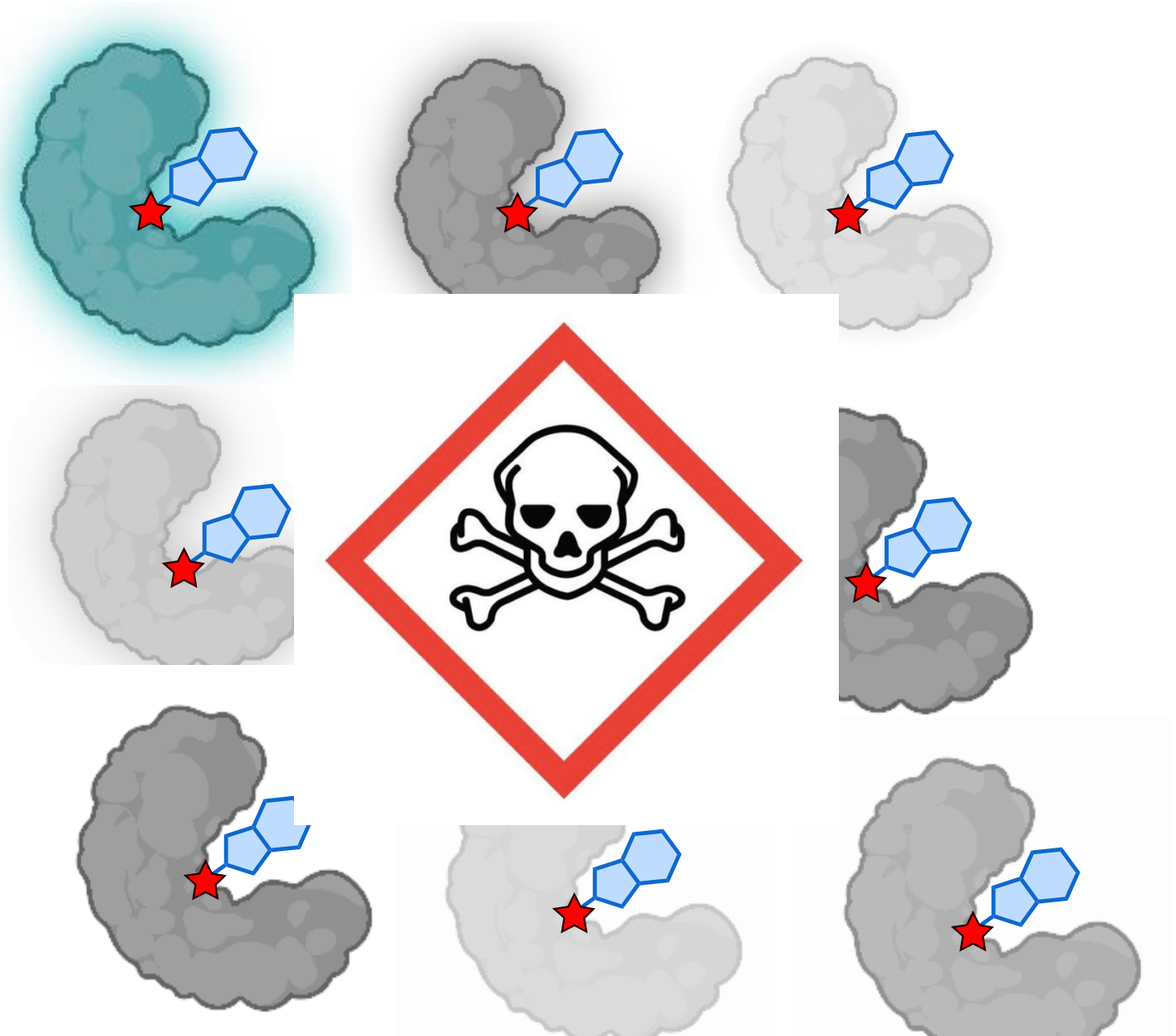


penicillin V
(bacterial infection)



aspirin
(pain, inflammation)

What is the Concern with Permanent Drugs?



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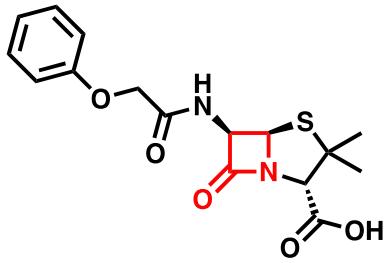

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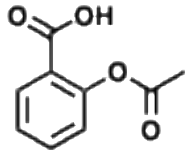

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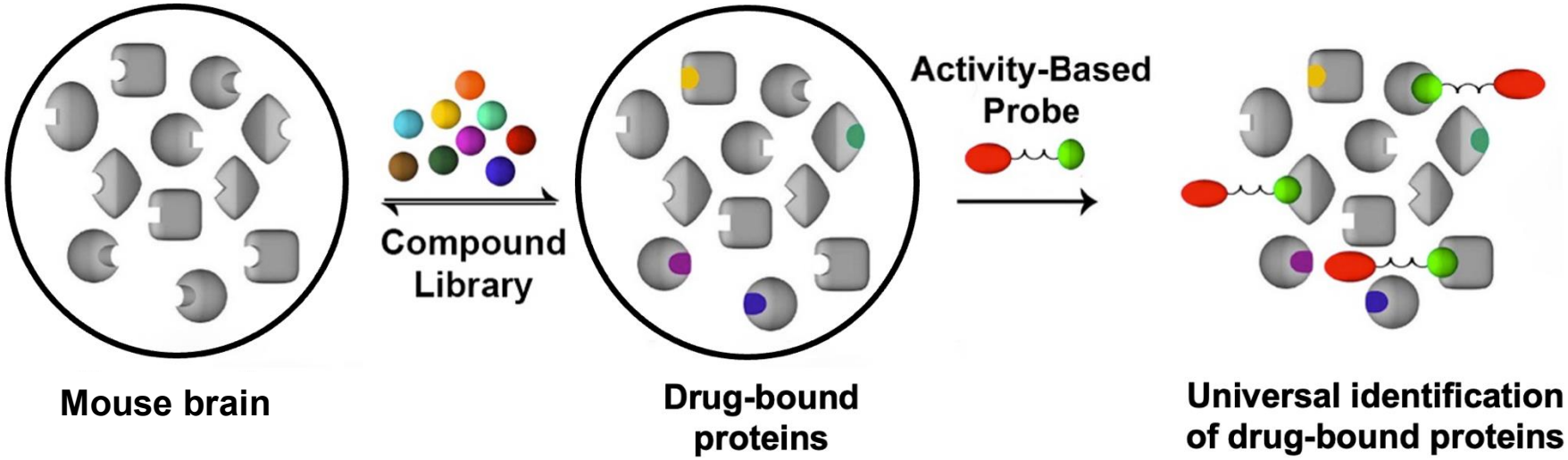
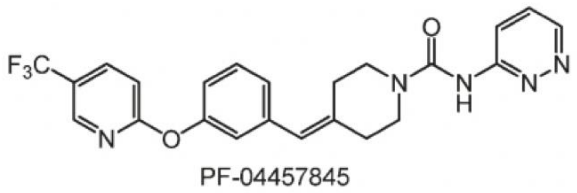
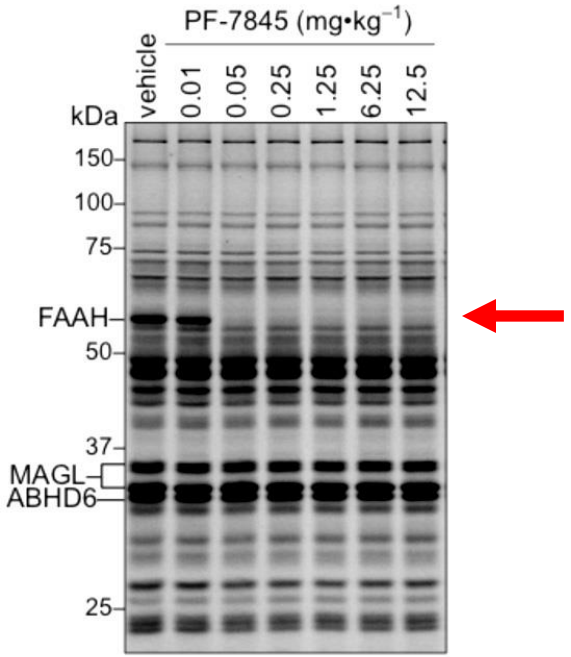
Evaluating Permanent FAAH Inhibitors by Activity-Based Proteomics







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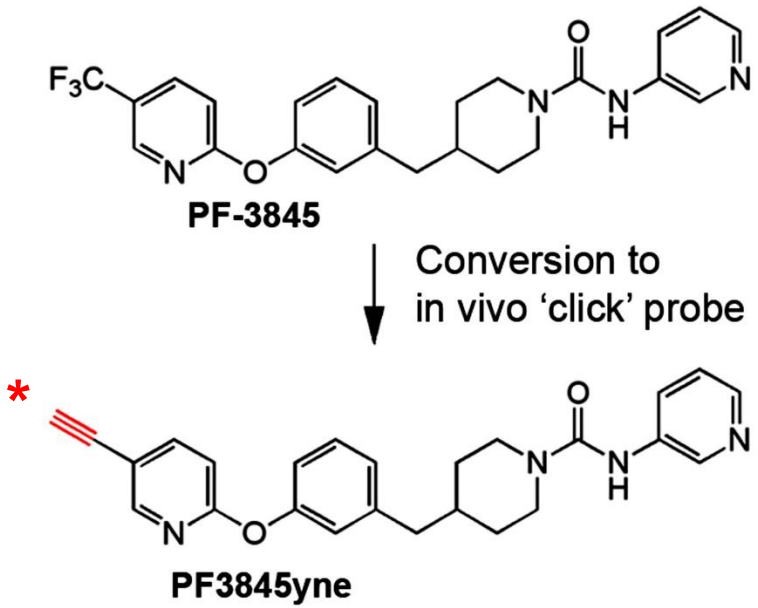


*Click chemistry (KB Sharpless, Nobel 2022)

FAAH Inhibitors in the Clinic – A Long and Winding Road

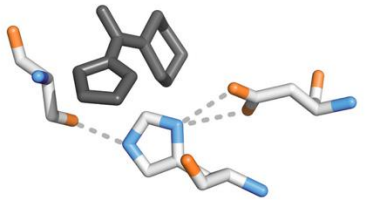
PNAS

Dual blockade of FAAH and MAGL identifies behavioral processes regulated by endocannabinoid crosstalk in vivo

Jonathan Z. Long[a], Daniel K. Nomura[a], Robert E. Vann[b], D. Matthew Walentiny[b], Lamont Booker[b], Xin Jin[a], James J. Burston[b], Laura J. Sim-Selley[b], Aron H. Lichtman[b], Jenny L. Wiley[b], and Benjamin F. Cravatt[a,1]

20270–20275 | PNAS | December 1, 2009 | vol. 106 | no. 48 www.pnas.org/cgi/doi/10.1073/pnas.0909411106

2007-2009



ABIDE THERAPEUTICS

2012-2019

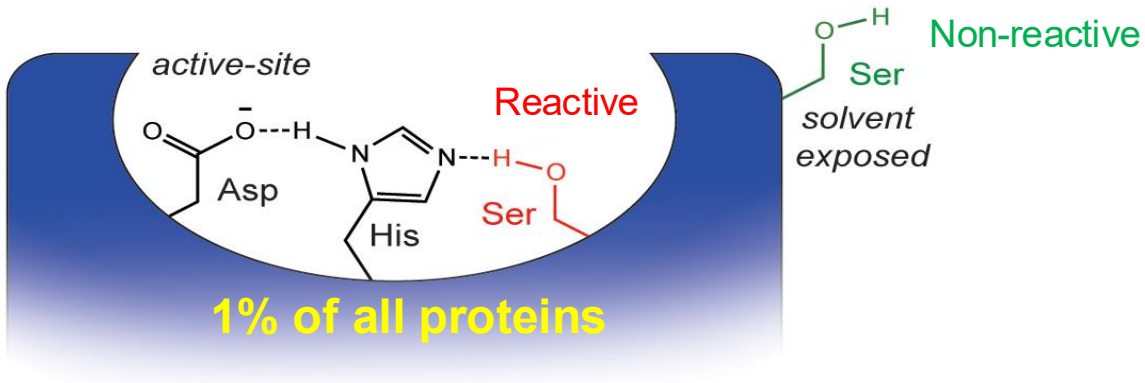
Bristol Myers Squibb™

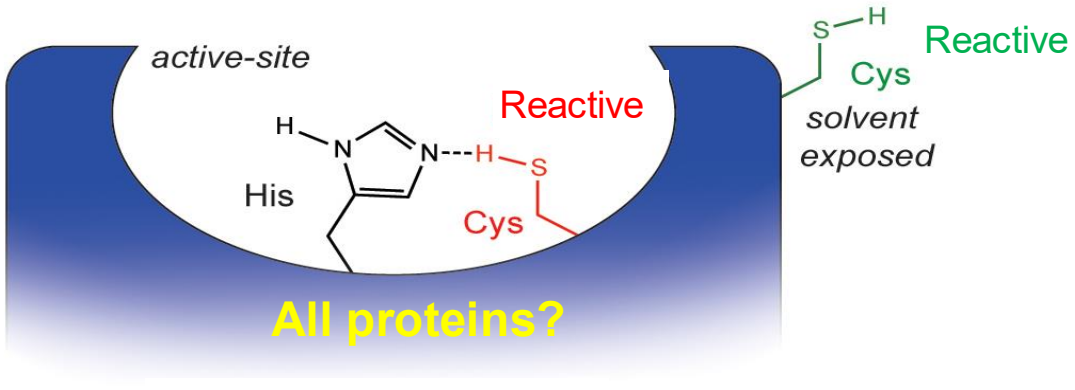
2019-present

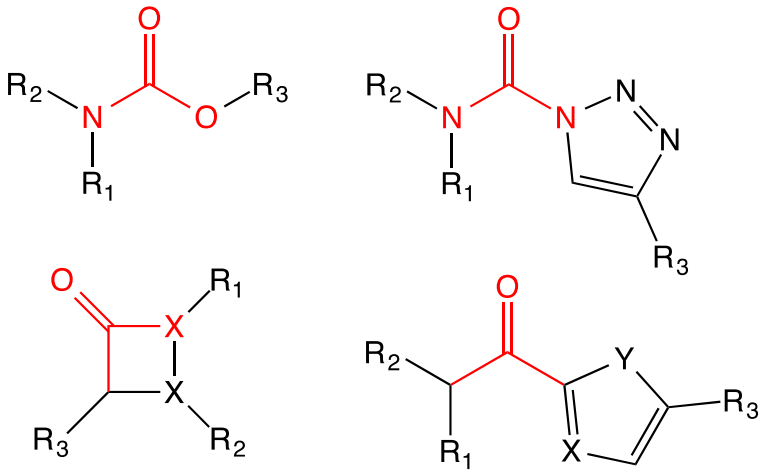
BMS-986368 (FAAH/MAGL inhibitor)

Indication	Multiple Sclerosis Spasticity (MSS)	Alzheimer's Disease Agitation (AAD)
Phase/Study	Phase II - BALANCE-MSS-1	Phase II - BALANCE-AAD-1
# of Patients	N = 200	N = 120
Design	• BMS-986368 Dose 1 • BMS-986368 Dose 2 • BMS-986368 Dose 3 • Placebo	• BMS-986368 Dose 1 • BMS-986368 Dose 2 • Placebo
Endpoints	• Primary: Change from Baseline in Numeric-transformed Modified Ashworth Scale-Most Affected Lower Limb (TNmAS-MALL) at week 6 Key secondary: • Change from baseline on the numeric rating scale spasticity (NRS-S) score at week 6 • Change from baseline on the MS spasticity scale (MSSS-88) total scores at week 6	• Primary: Change from Baseline in Cohen-Mansfield Agitation Inventory (CMAI) score up to Week 8 Key secondary: • Neuropsychiatric Inventory Nursing Home Version (NPI-NH) total score up to week 8 • NPI-NH agitation/aggression domain score up to week 8
Status	• Recruiting • Projected data readout 2026	• Recruiting • Projected data readout 2027
CT Identifier	NCT06782490	NCT06808984

Extending the Reach of Permanent Chemistry







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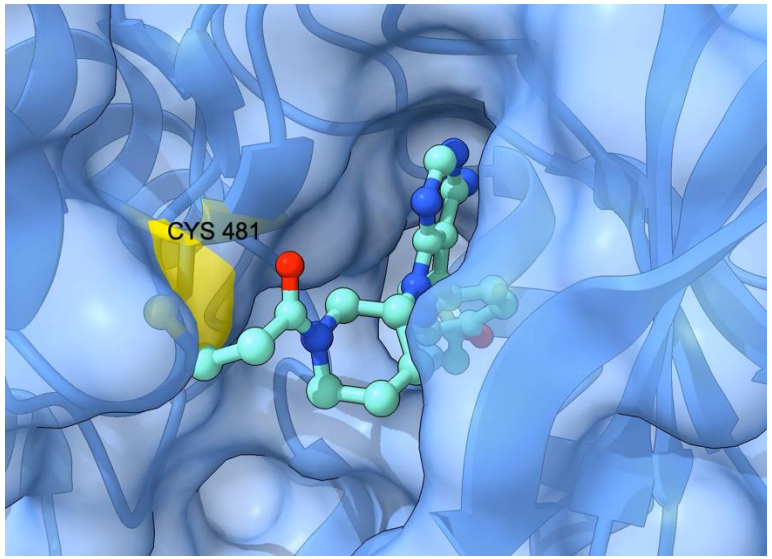
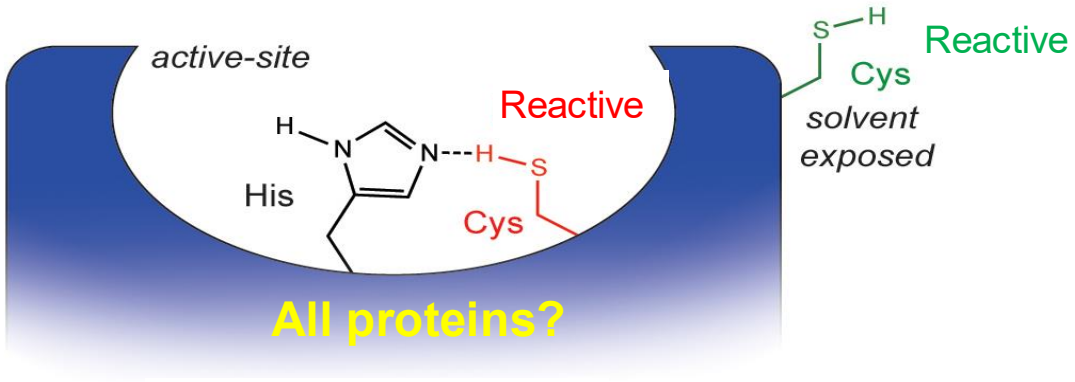
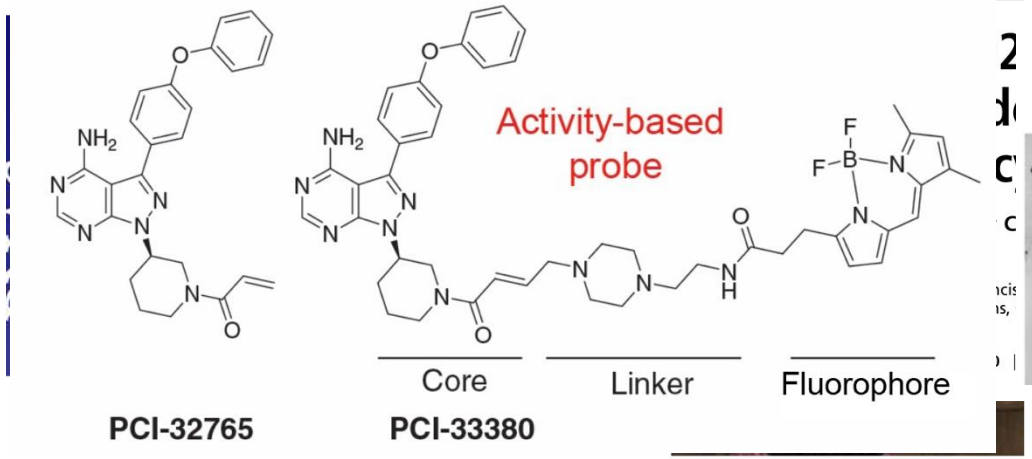
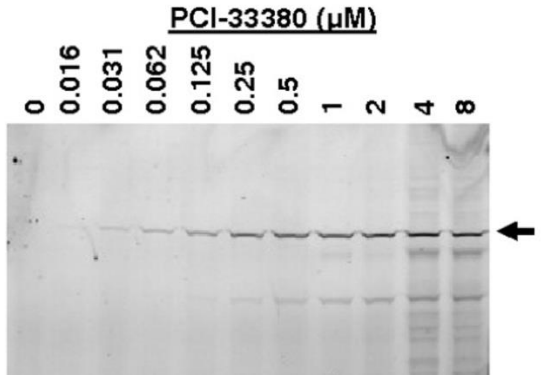


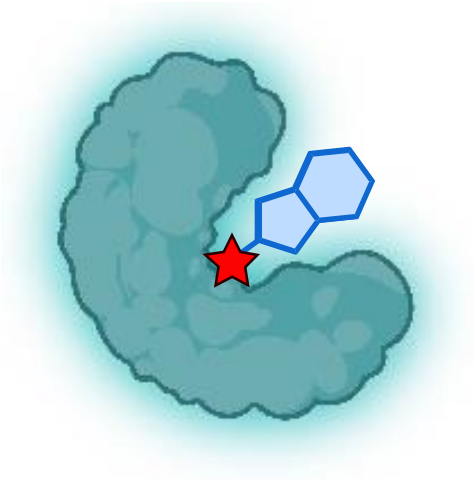






Ibrutinib (leukemia)
Acalabrutinib (leukemia)
Zanbrutinib (leukemia)
Afatinib (lung cancer)
Dacomitinib (lung cancer)
Osimertinib (lung cancer)
Neratinib (breast cancer)
Futibatinib (cholangiocarcinoma)
Ritlecitinib (alopecia)

Most Drugs Bind Proteins with Deep Pockets;
But Many Important Disease Proteins Lack Deep Pockets



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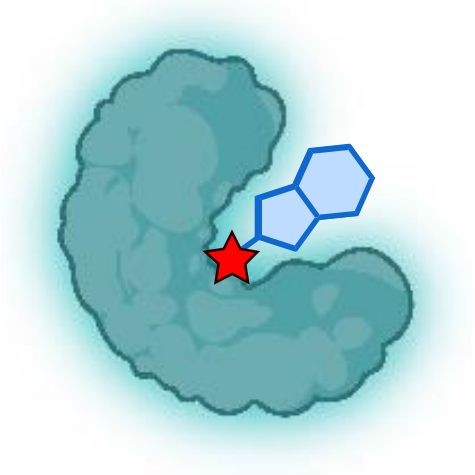
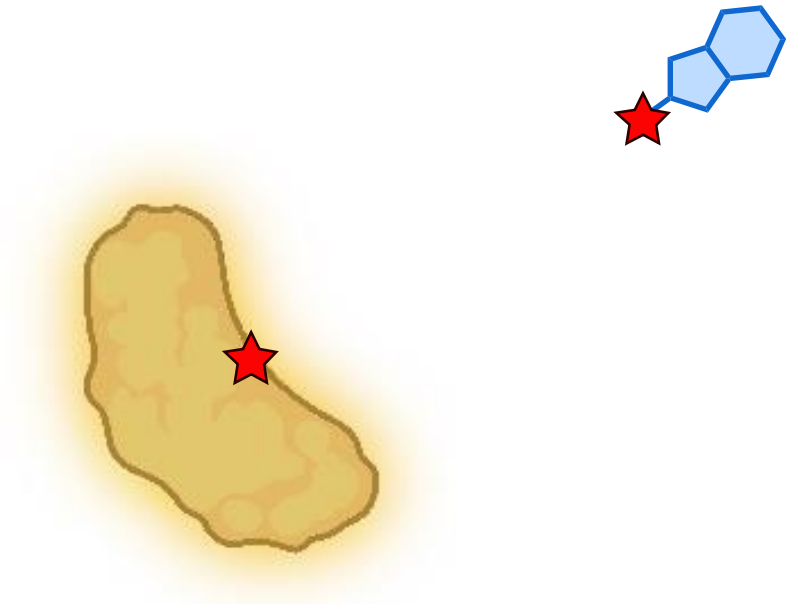
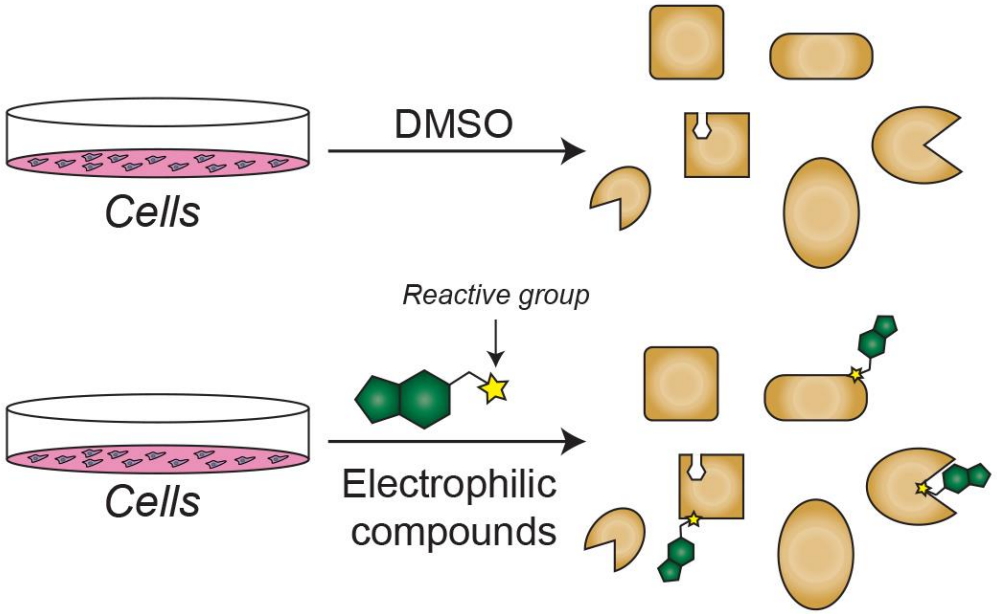


Addressing Challenging Proteins with *Permanent Chemistry*



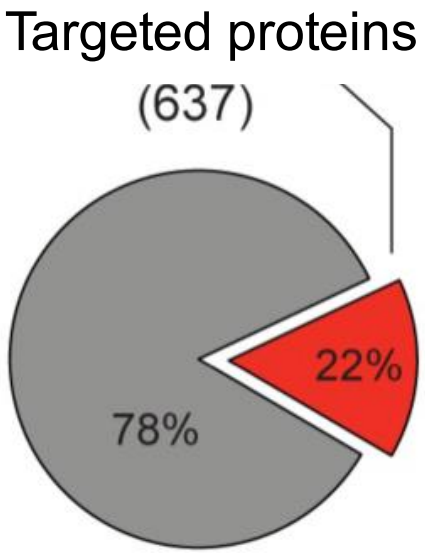
Extending the Reach of Permanent Chemistry

(No cheat codes)



Backus KM *et al. Nature* 2016

Global Discovery of Permanent Chemistry by Activity-Based Proteomics



Numerous proteins *can be* targeted at shallow/cryptic pockets with permanent chemistry

Backus KM *et al. Nature* 2016

vividion THERAPEUTICS

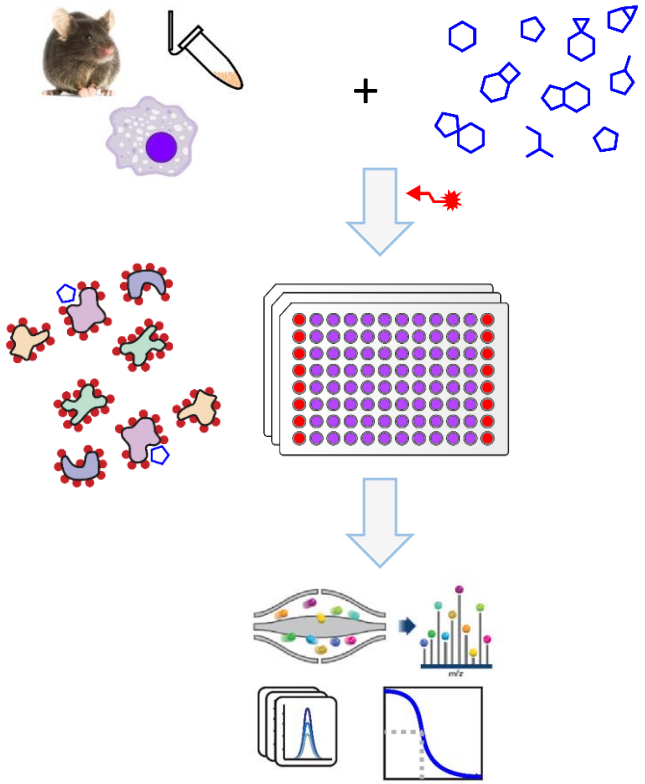

Phil Baran


Jin-Quan Yu


Tom Daniel

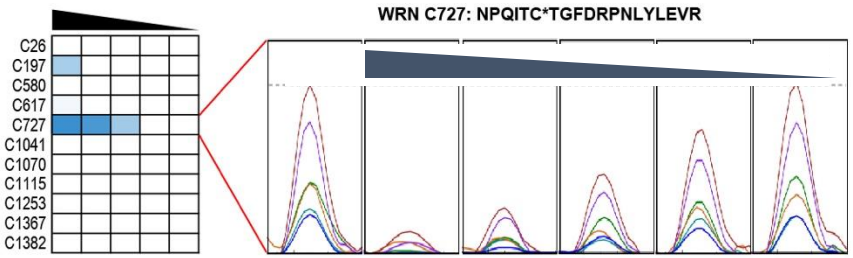

Rich Heyman

vividion THERAPEUTICS



Covalent chemistry library
(> 10,000 compounds)

Industrialized screening
(> 1000 samples/week)



WRN Helicase – The "Not So" Long Road from Discovery to Drug Candidate in the Genome Era

LETTER

https://doi.org/10.1038/s41586-019-1102-x

WRN helicase is a synthetic lethal target in microsatellite unstable cancers

Edmond M. Chan[1,2,12], Tsukasa Shibue[1,12], James M. McFarland[1], Benjamin Gaeta[1], Mahmoud Ghandi[1], Nancy Dumont[1], Alfredo Gonzalez[1], Justine S. McPartlan[1], Tianxia Li[2], Yanxi Zhang[2], Jie Bin Liu[2], Jean-Bernard Lazaro[3], Peili Gu[4], Cortt G. Piett[5], Annie Apffel[1], Syed O. Ali[1,2], Rebecca Deasy[1], Paula Keskula[1], Raymond W. S. Ng[1,2], Emma A. Roberts[3], Elizaveta Reznichenko[3], Lisa Leung[1], Maria Alimova[1], Monica Schenone[1], Mirazul Islam[1,2], Yosef E. Maruvka[1,6], Yang Liu[1,2], Jatin Roper[7], Srivatsan Raghavan[1,2], Marios Giannakis[1,2], Yuen-Yi Tseng[1], Zachary D. Nagel[1,5], Alan D'Andrea[3], David E. Root[1], Jesse S. Boehm[1], Gad Getz[1,6], Sandy Chang[4,8,9], Todd R. Golub[1,10,11], Aviad Tsherniak[1], Francisca Vazquez[1,2,13]* & Adam J. Bass[1,2,13]*

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Article

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Chemoproteomic discovery of a covalent allosteric inhibitor of WRN helicase

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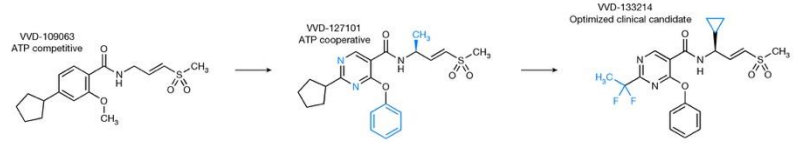
Kristen A. Baltgalvis[1], Kelsey N. Lamb[1], Kent T. Symons[1], Chu-Chiao Wu[1], Melissa A. Hoffman[1], Aaron N. Snead[1], Xiaodan Song[1], Thomas Glaza[1], Shota Kikuchi[1], Jason C. Green[1], Donald C. Rogness[1], Betty Lam[1], Maria E. Rodriguez-Aguirre[1], David R. Woody[1], Christie L. Eissler[1], Socorro Rodiles[1], Seth M. Negron[1], Steffen M. Bernard[1], Eileen Tran[1], Jonathan Pollock[1], Ali Tabatabaei[1], Victor Contreras[1], Heather N. Williams[1], Martha K. Pastuszka[1], John J. Sigler[1], Piergiorgio Pettazzoni[2], Markus G. Rudolph[2], Moritz Classen[2], Doris Brugger[2], Christopher Claiborne[2], Jean-Marc Plancher[2], Isabel Cuartas[3], Joan Seoane[3], Laurence E. Burgess[1], Robert T. Abraham[1,4], David S. Weinstein[1], Gabriel M. Simon[1], Matthew P. Patricelli[1]✉ & Todd M. Kinsella[1]✉



2024

Recruiting

A Study to Evaluate the Safety, Pharmacokinetics, and Anti-Tumor Activity of RO7589831 as Monotherapy and in Combination With Pembrolizumab in Participants With Advanced Solid Tumors

ClinicalTrials.gov ID NCT06004245

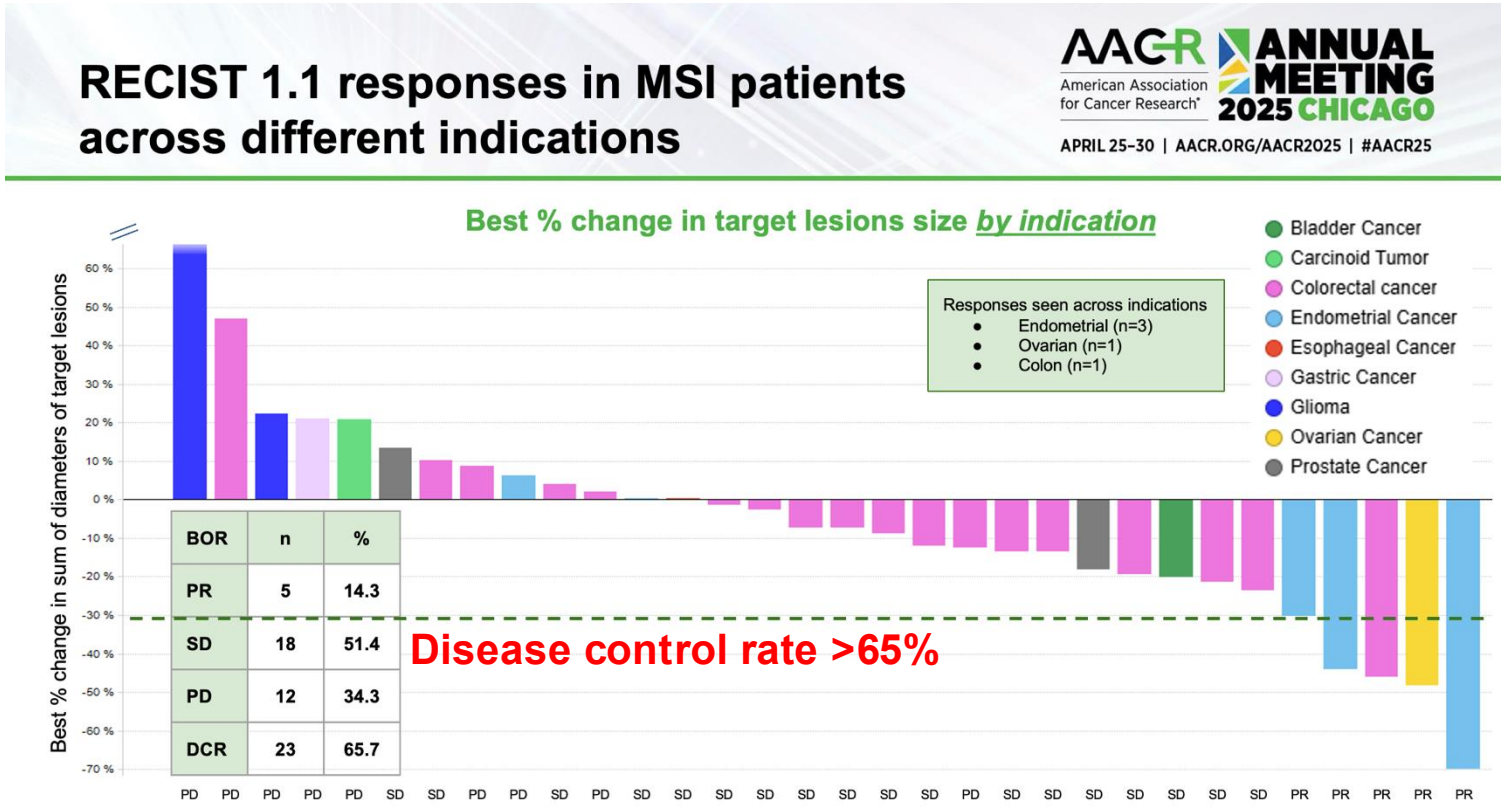
Information provided by Hoffmann-La Roche (Responsible Party)

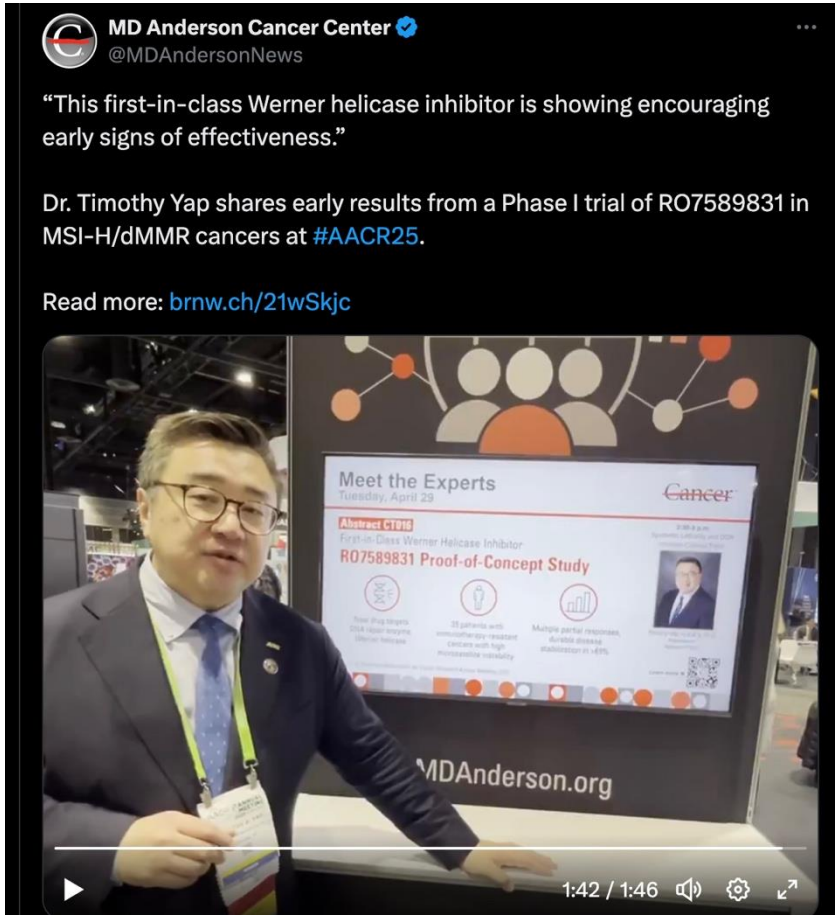
Sponsor Hoffmann-La Roche

Last Update Posted 2025-08-03

2024

Vividion WRN Inhibitor – Initial Clinical Activity in Microsatellite Instability (MSI) Cancers

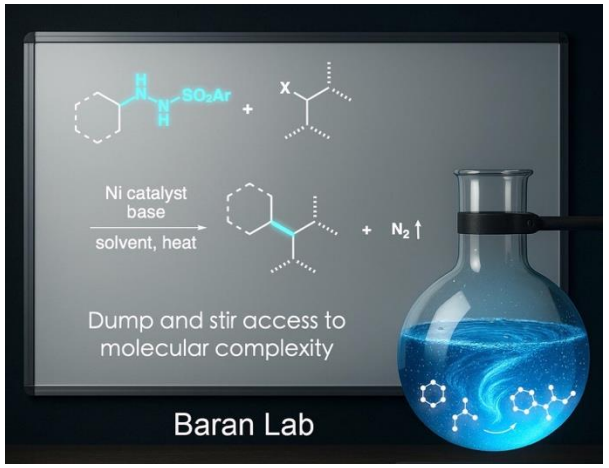


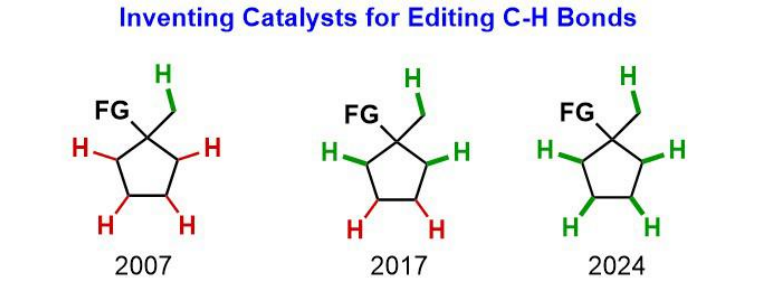


https://x.com/mdandersonnews/status/1917642912948425008?s=42

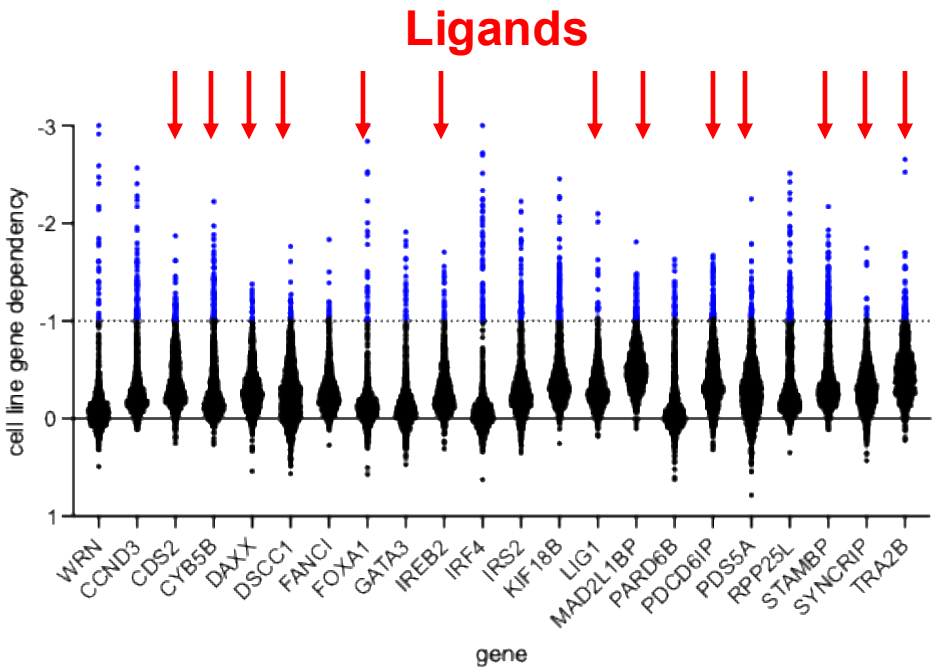
Going Forward – Opportunities and Challenges

- **Opportunity –** Treating the diseases that we understand with innovations in chemistry





- **Challenge –** Better understanding diseases to know how to treat them

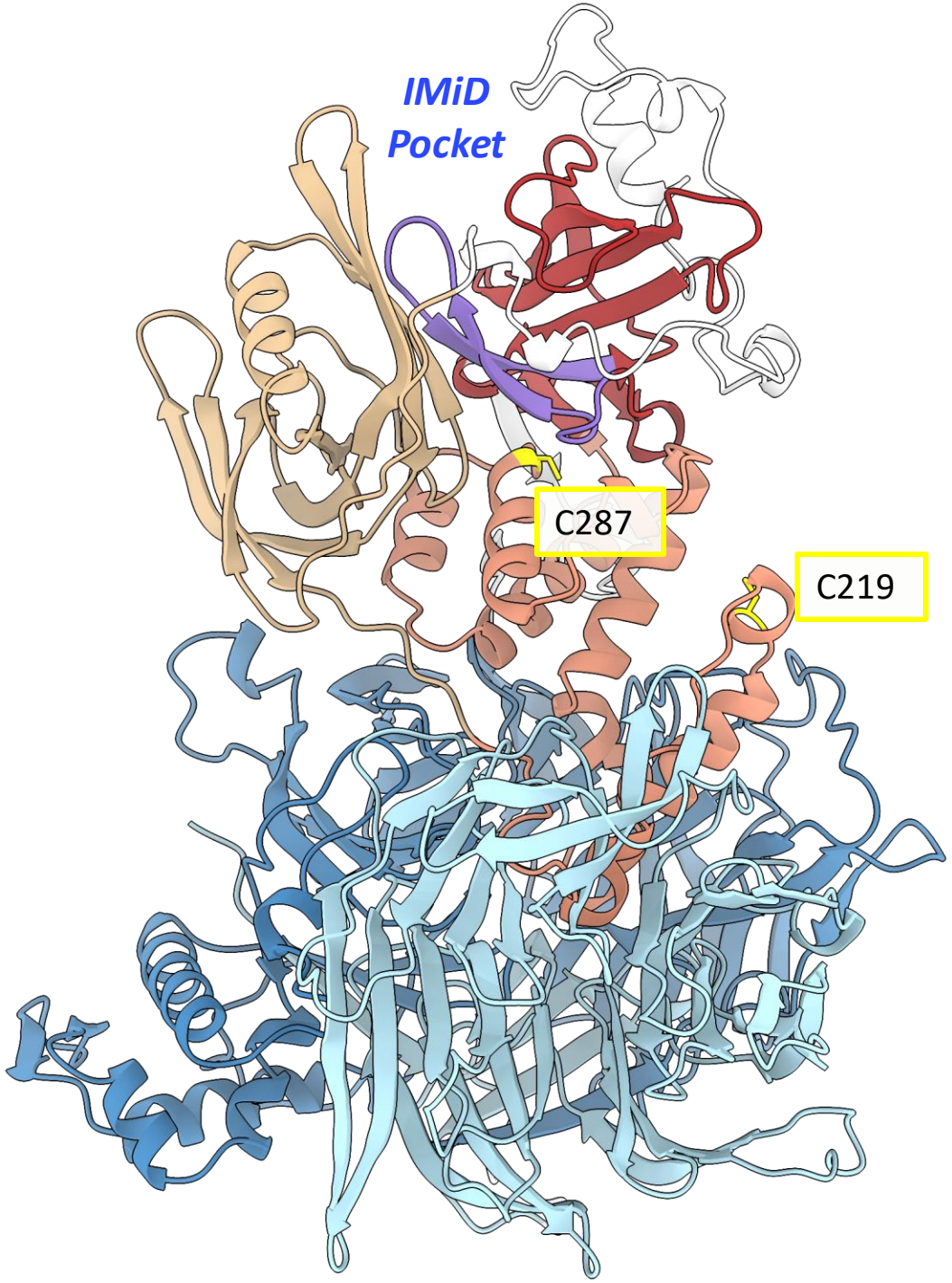


How to Predict Cryptic Druggable Pockets?

AI/ML Is Not (Yet) the Answer

CRBN (Cereblon):

- **One well understood (orthosteric) pocket (IMiD)**
- **Two cryptic (allosteric) pockets (C219 & C287)**



How to Predict Cryptic Druggable Pockets?

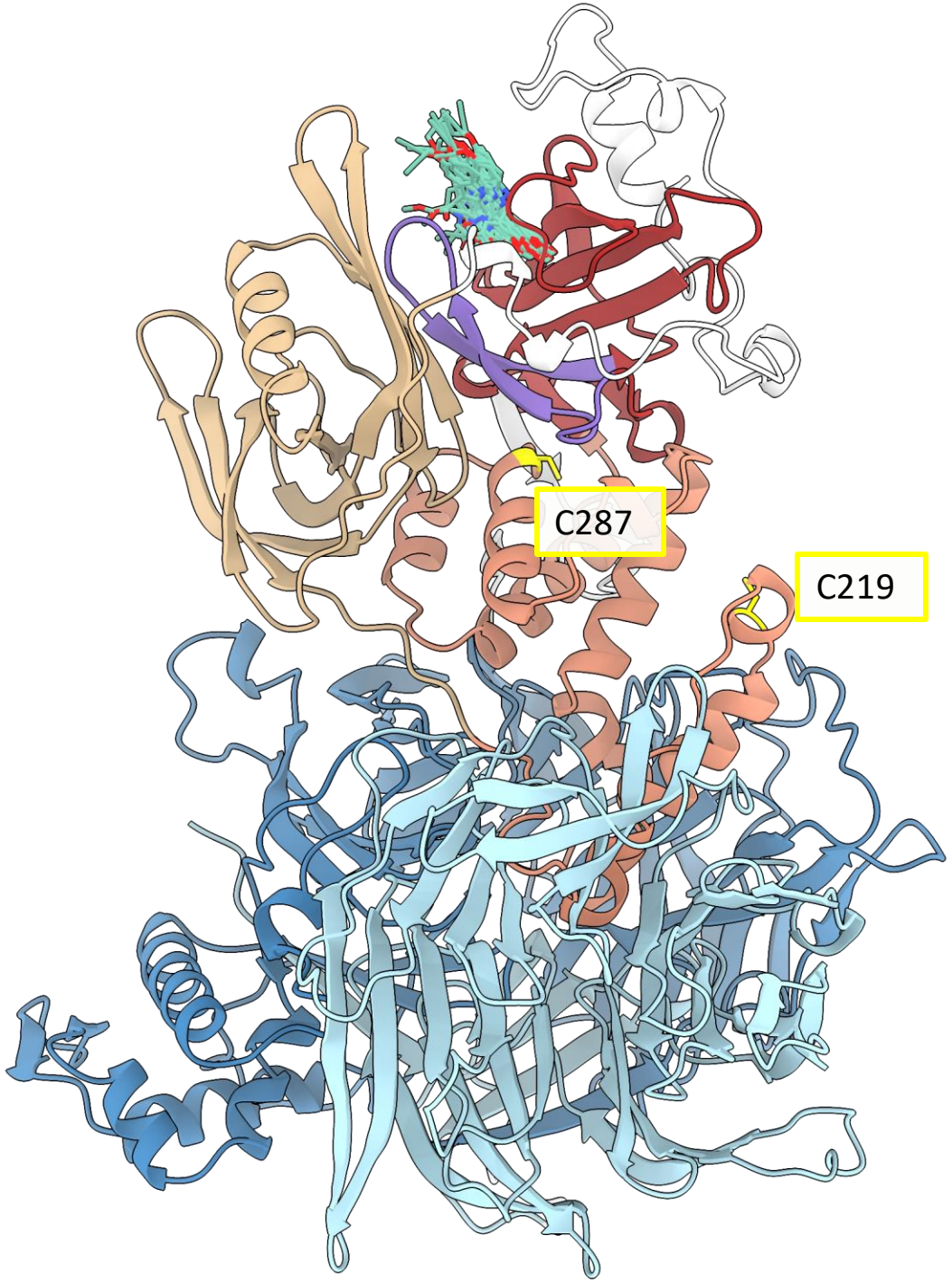
AI/ML Is Not (Yet) the Answer

CRBN (Cereblon):

- **One well understood (orthosteric) pocket (IMiD)**
- **Two cryptic (allosteric) pockets (C219 & C287)**

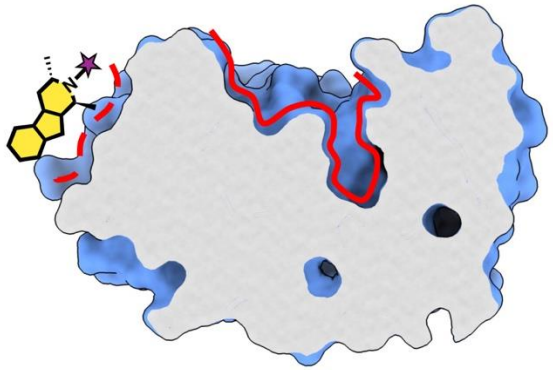
AI/ML predictions:

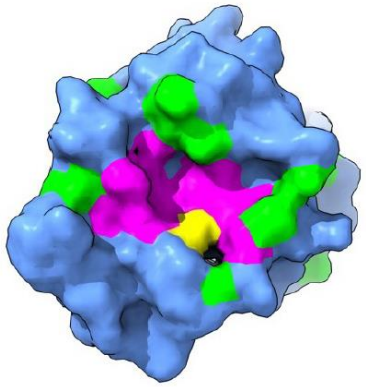
- **All allosteric ligands are placed in the orthosteric pocket: *orthostery burnout?***



Challenges Ahead

- **A complete map of cryptic pockets in disease-relevant proteins**





Ligand pocket
Genetic variants

Our Lab’s Achievements Are Entirely Due to Scripps

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Lab members

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Nori Kaneshige

Arthur Kim (w/ Teijaro)

Haoxin Li

Garrett Lindsey

Xuanmeng Luo

Ben Pang

Aidan Pezacki

Zack Potter

Lingqi Qui

Chris Reinhardt

Hermione Ren (w/ Shenvi)

Logan Sigua (w/ Li)

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Kay Ahn, Doug Johnson (Pfizer)

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Richard, Lerner, Dale Boger

Entrepreneur Mentors

Tom Daniel, Rich Heyman, Paul Schimmel

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