What a Protein's "Dance" Says About Health and Disease

Dorothee Kern, Scripps Research Institute and Howard Hughes Medical Institute

What is a protein?

Food

Structure made up by 20 amino acids

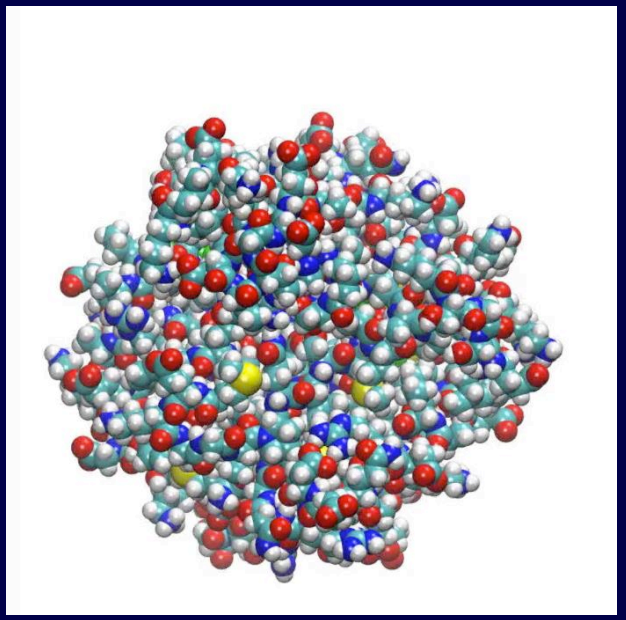
KLVYRGKPQKRWGGNLSNVLPACDNGS

Muscles

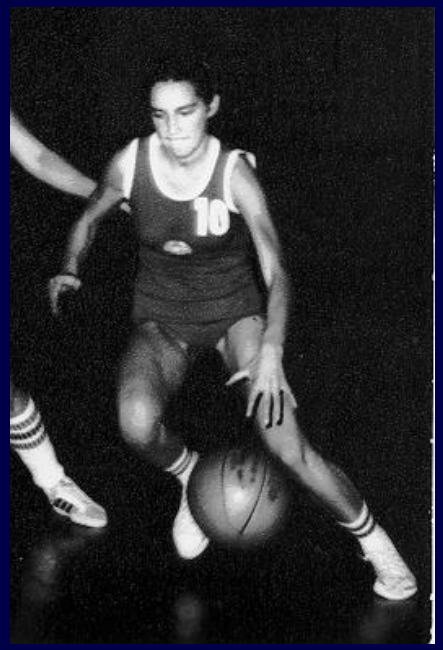
Nadja Kern - UCSD

Snapshot

The Dance

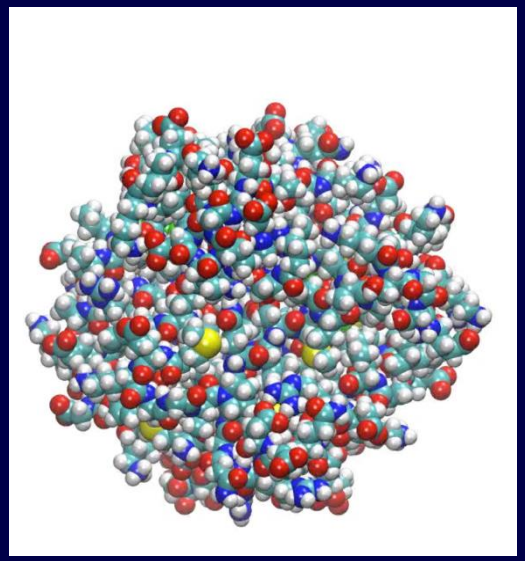


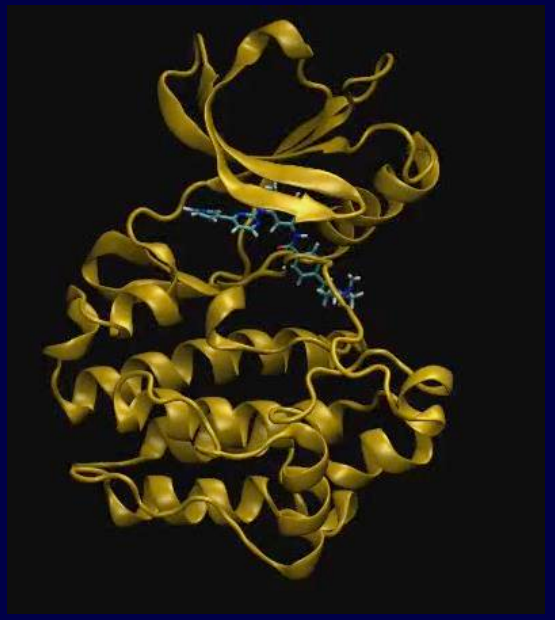
My Journey– from the Basketball Court Via Protein's Dance to Novel Cancer Drug Tactics



GDR- National Champion, National Team Captain

Protein's Dance





<u>Disclosure:</u> Founder of Relay Therapeutics and MOMA Therapeutics

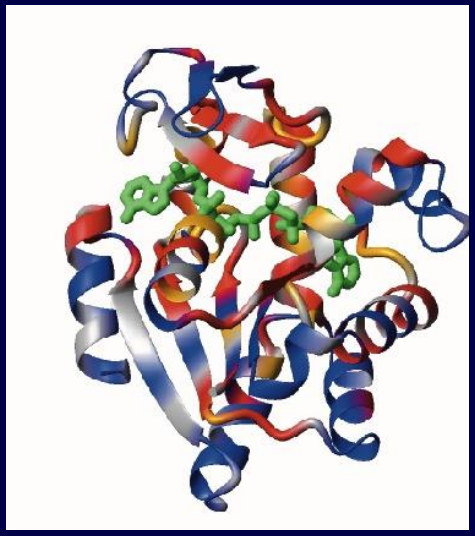
WHY The Proteins Dance? – Understanding Healthy Protein Function

Macroscopic

Julia Kern
Olympics 2026

Protein (Enzyme)
During Catalysis

Microscopic



Fun facts:

ATP is currency of cellular energy

Consumes ATP

t_{win} = 20 msec

Makes ATP

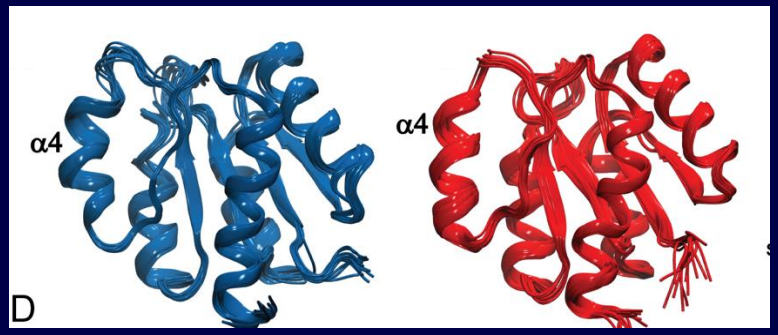
$t_{1/2\ uncat}$ = 7000 years

$t_{1/2\ cat}$ = 5 msec

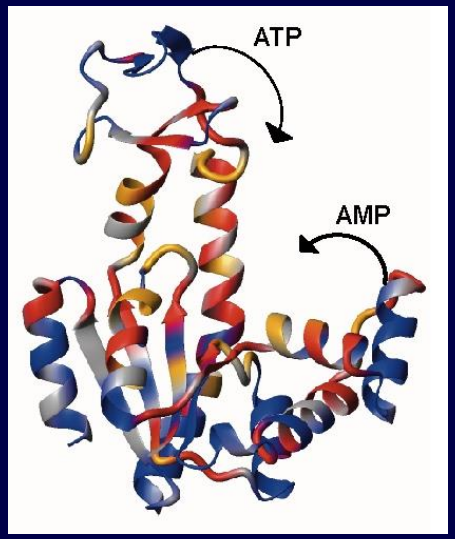
The Dream and The Journey

How Do Proteins Work

Signaling



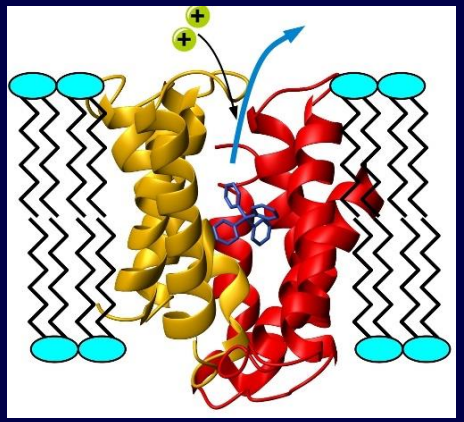
Catalysis
(Enzymes)



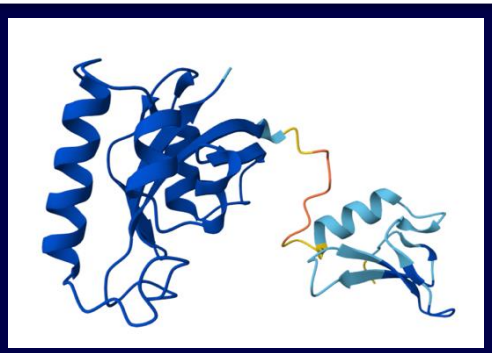
Drug Binding
(Gleevec)

Protein/Protein Interaction
(Vision)

Membrane Transport
(Multi drug transporter)



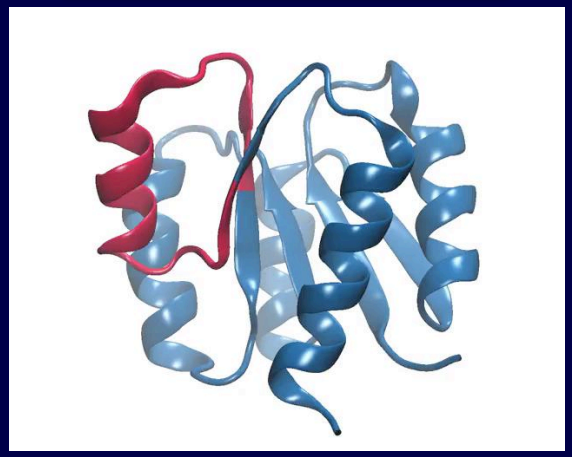
Long-Term Memory



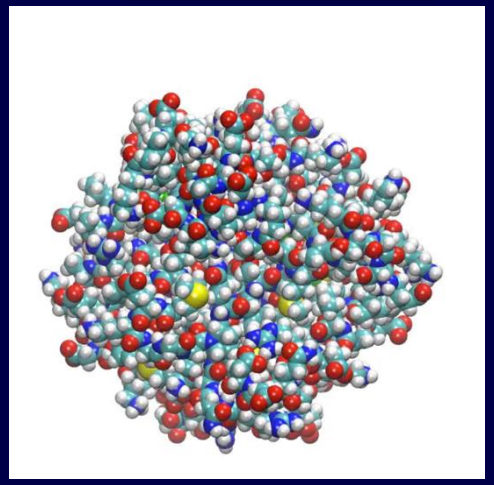
Static Structures → **We need to "watch" proteins in action, during function**

How Do Proteins Work - The Protein Dance

Signaling (active/inactive)

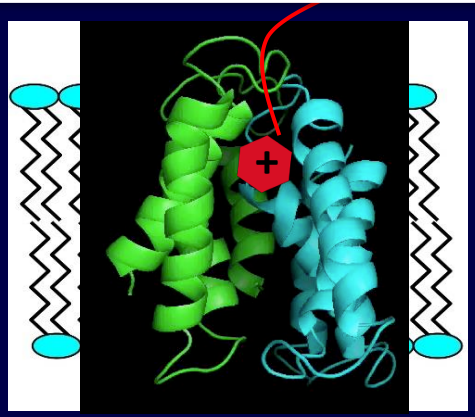


Catalysis (Enzymes)

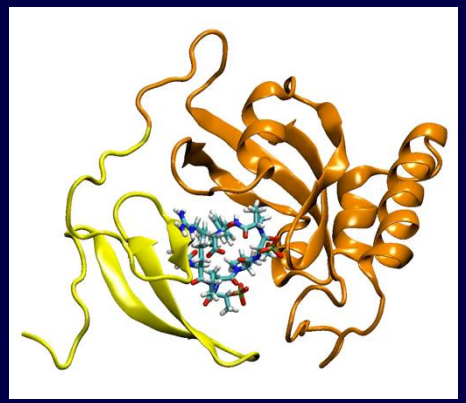


Drug Binding (Gleevec)

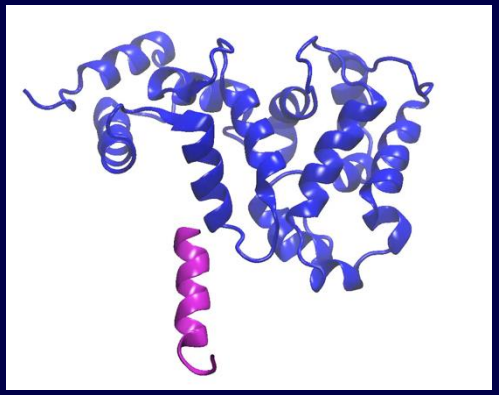
Membrane Transport (Multi drug transporter)



Long-Term Memory



Protein/Protein Interaction (Vision)

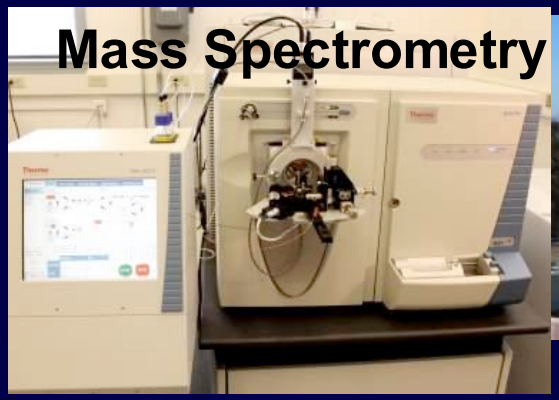


Static Structures → We need to "watch" proteins in action, during function

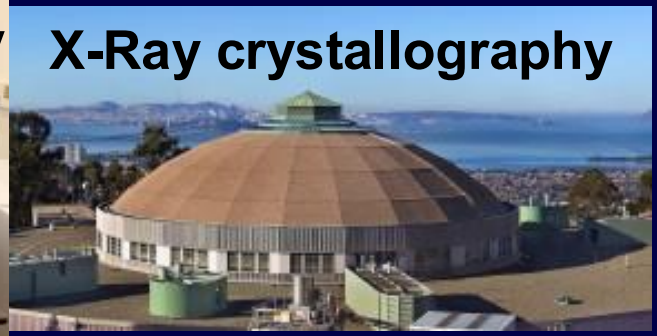
HOW?? Hybrid Biophysical Methods for "Seeing" the Invisible

NMR (Nuclear Magnetic Resonance)

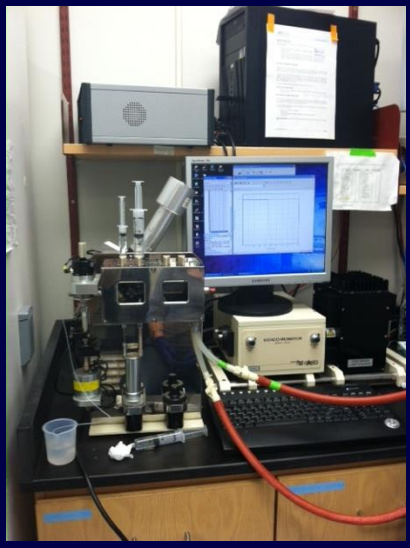
Mass Spectrometry



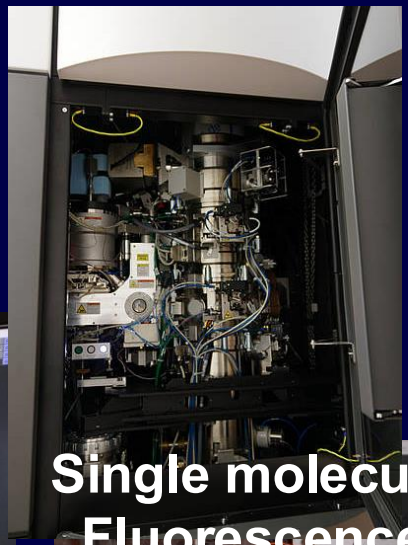
X-Ray crystallography

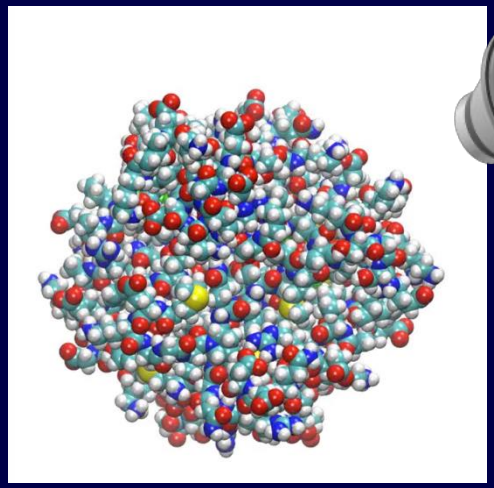


Stopped-flow

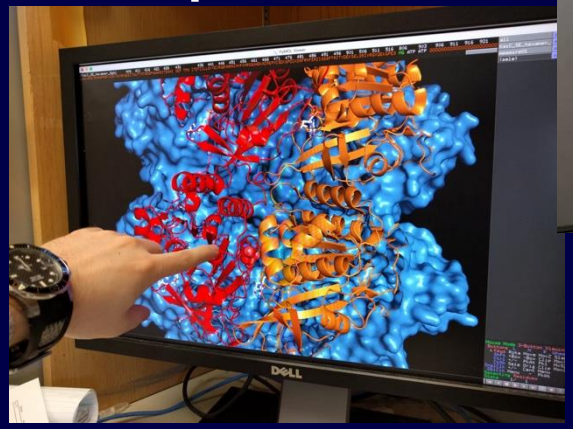


Cryo Electron Microscopy

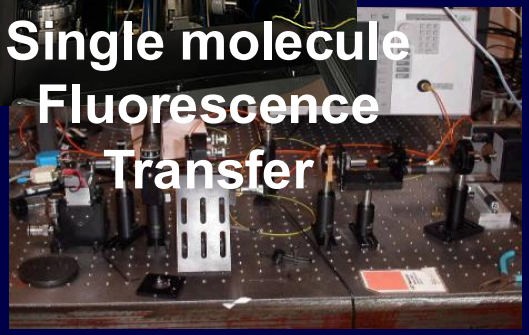




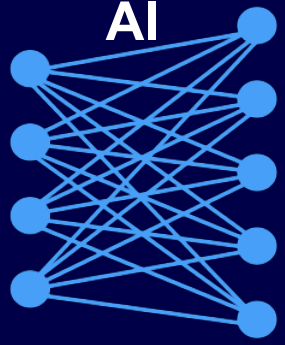
Computation



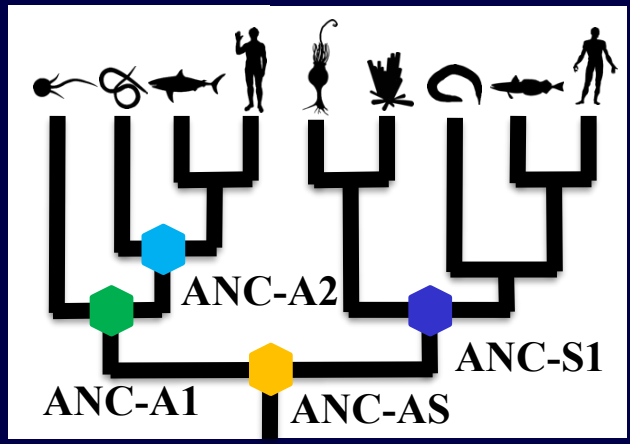
Single molecule Fluorescence Transfer



AI



Evolution

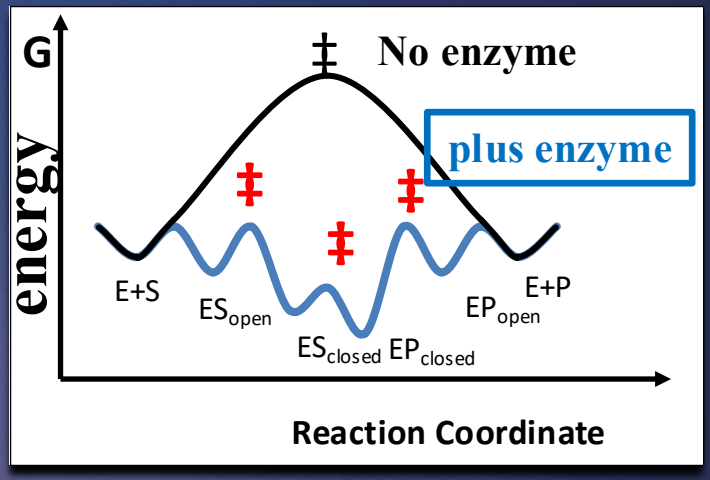


Concept: The Climb over the Mountain (Energy Landscape)

Transition States

High Energy States

Energy Landscape



Conventional structural biology
AI Methods: Alphafold2

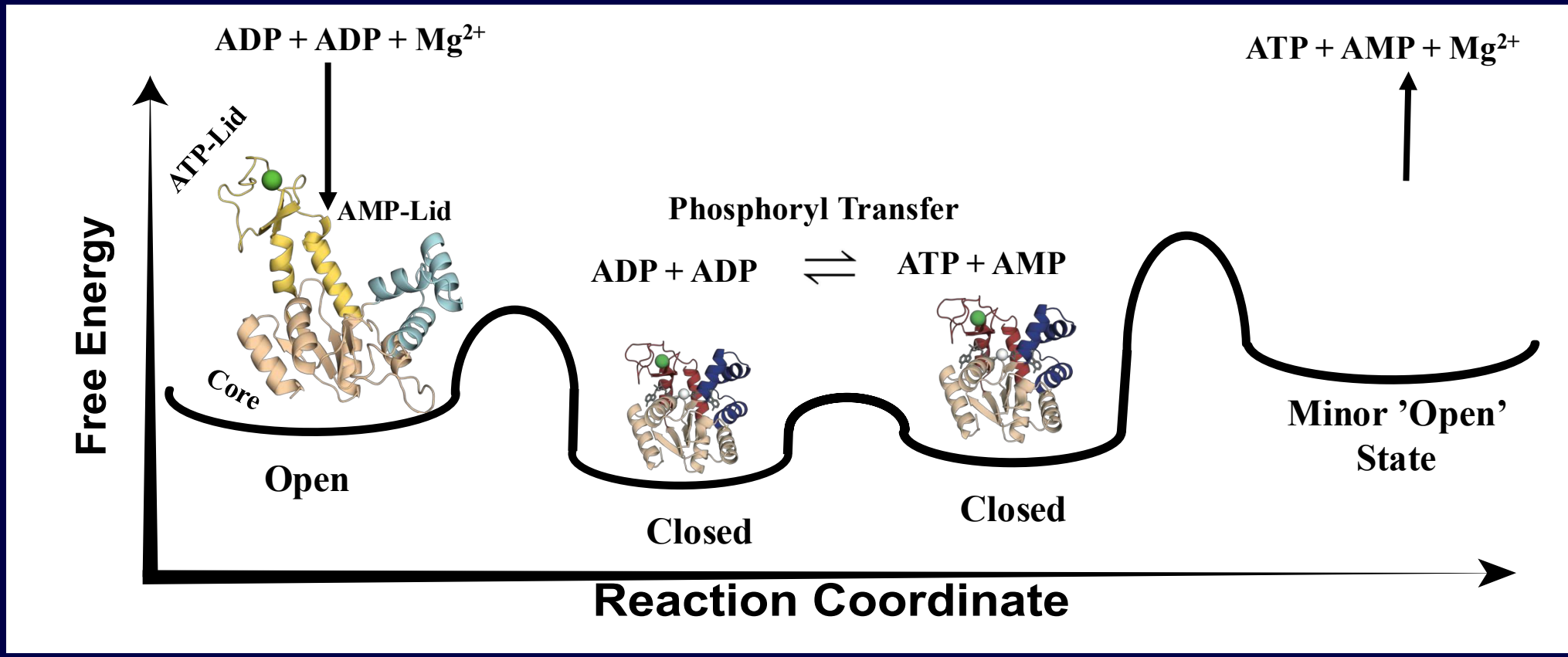
The Healthy Enzyme - Free Energy Landscape (Climbing the mountains) During Catalysis

Adenylate Kinase (Adk) – essential for every organism

MgATP + AMP ⟷ MgADP + ADP

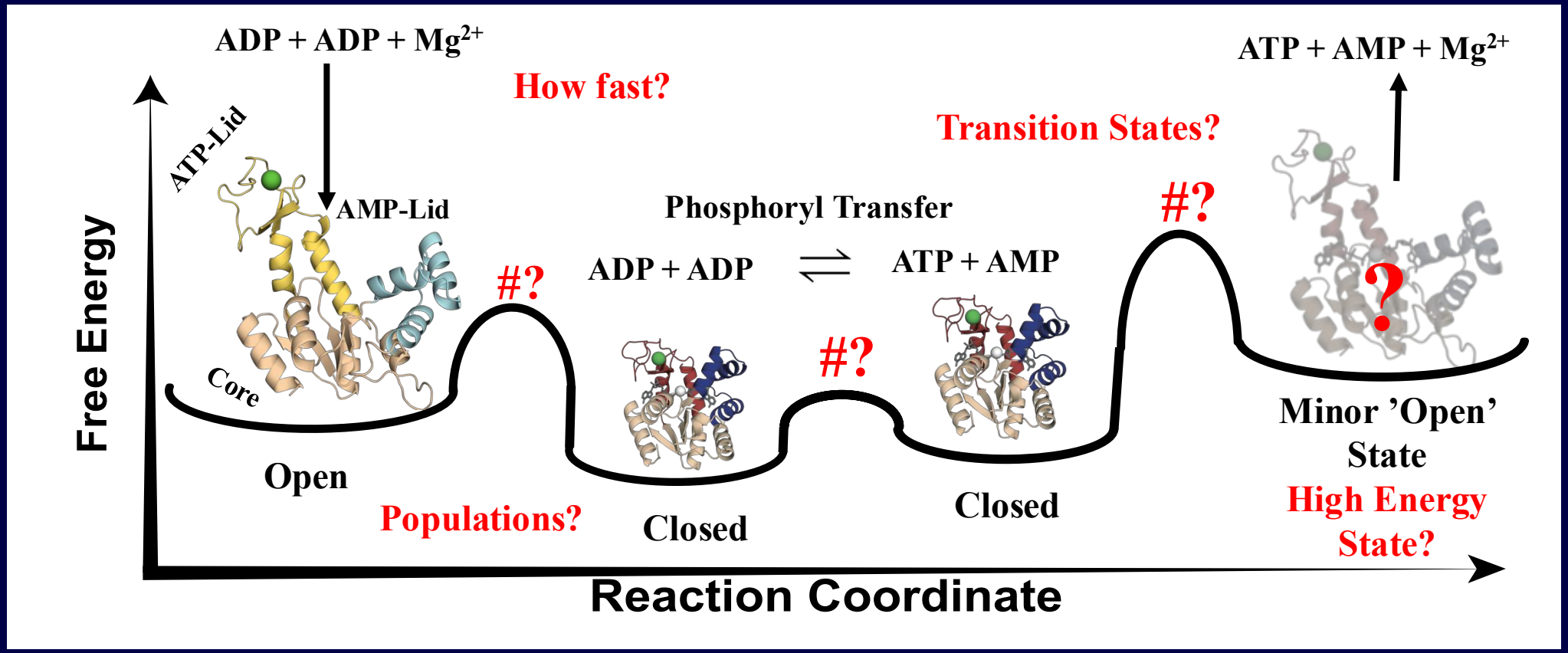
$t_{1/2\ uncat}$ = 7000 years

$t_{1/2\ cat}$ = 10 ms



Free Energy Landscape During Enzymatic Turnover

High Energy States and Dynamics



NMR as Tool to Study Protein Dynamics –The Physics

- Entire time range
- At atomic resolution
- Under physiologic conditions

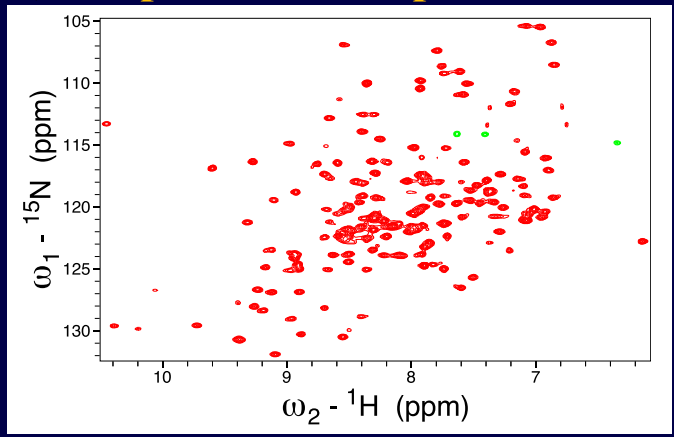
ps	ns	µs	ms	s	min	≥hr

MRI (Magnetic Resonance Imaging)

NMR (Nuclear Magnetic Resonance)

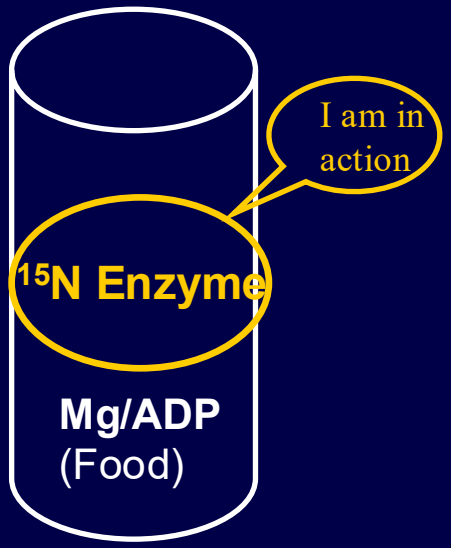
Radio frequencies as markers for nuclear spins
The song of a protein

Spectrum of a protein

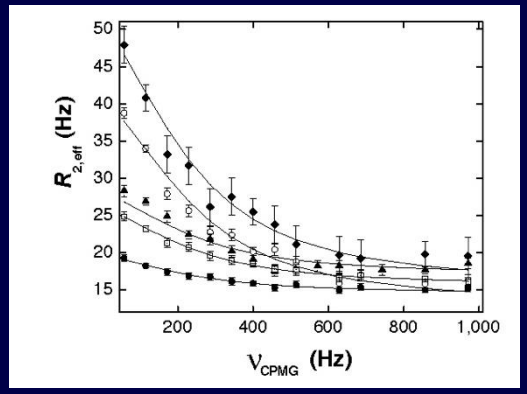


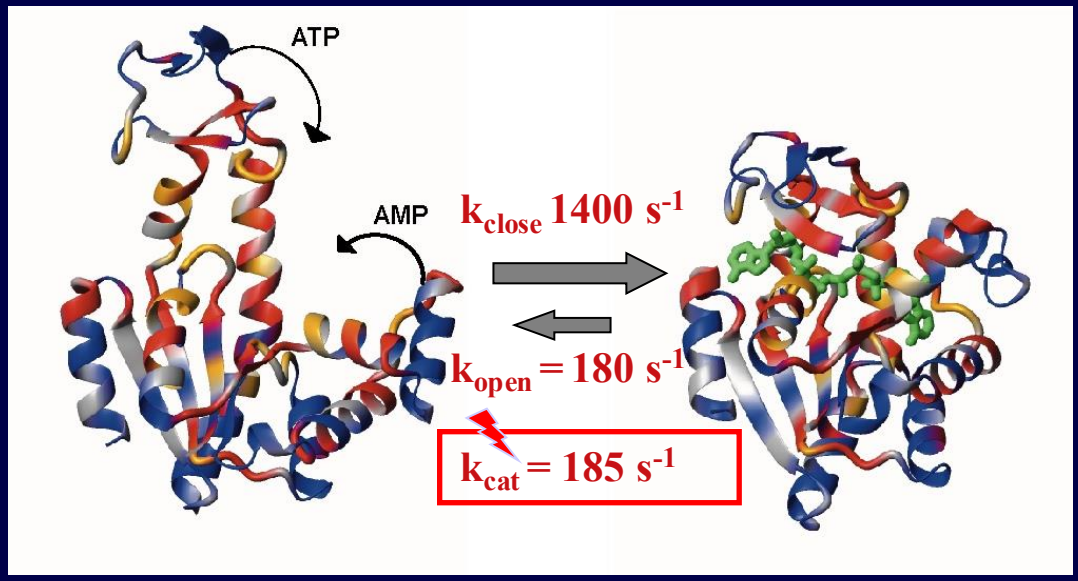
NMR Relaxation during catalysis - Rate limiting step is a conformational change

Solution NMR

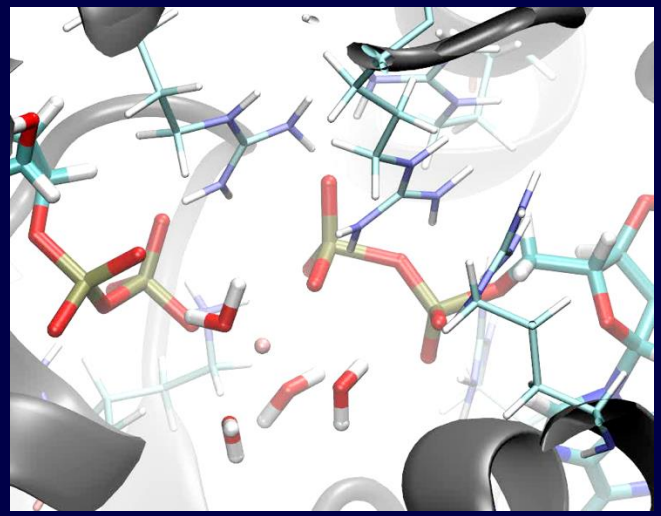


NMR Relaxation of every atom

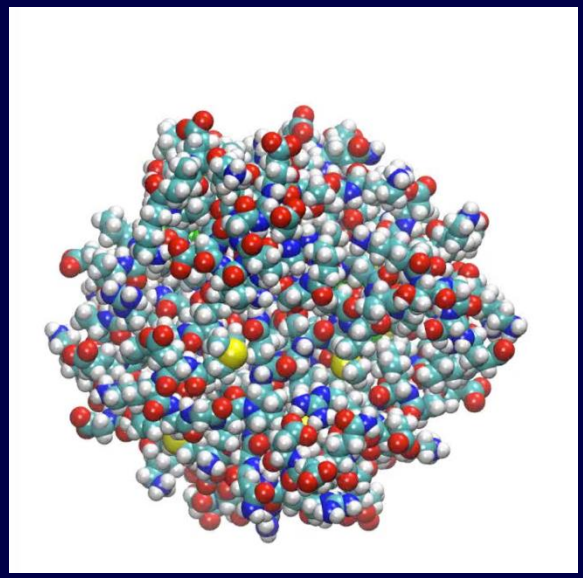




Chemistry being catalyzed



Opening/closing



J. B. Stiller et al, Nature Catalysis 2019

J. Stiller et al. Nature 2022, 603

G. Jara et al., eLife 2025

Applications of Basic Science Discovery:

Can we exploit the "dancing proteins" 

1. Medicine: New Vision for Drug Design Based on Protein Dynamics

Disclosure: Founder of Relay Therapeutics and MOMA Therapeutics

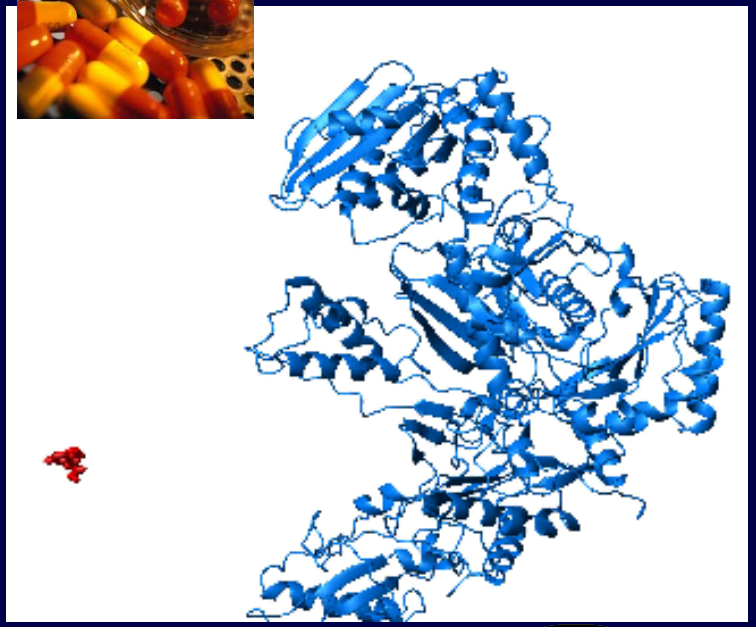
Patent: US 12,253,514 B2

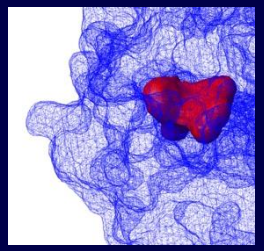
2. Better Green Biocatalysts (Enzymes)

Enzyme Glutenase as Therapy for Gluten Intolerance and Celiac Disease

Patent PCT/US2025/021803
WO2025207918A1

The Rigid-Body Docking Problem in Drug Design

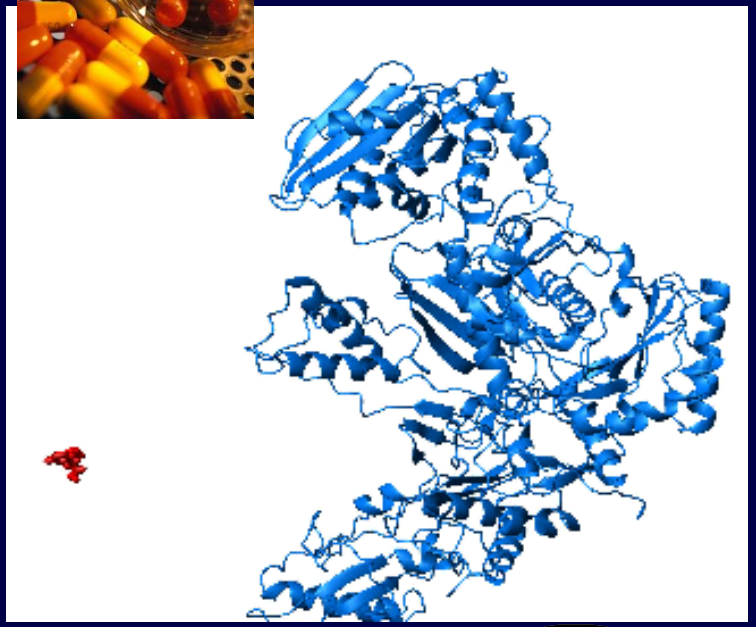


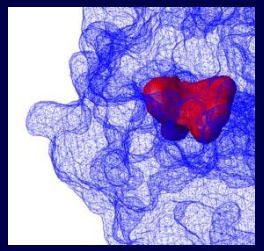


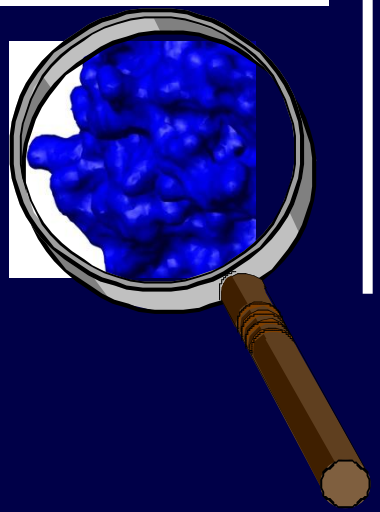
Overcoming the Rigid-Body Docking Problem in Drug Design

RELAY THERAPEUTICS

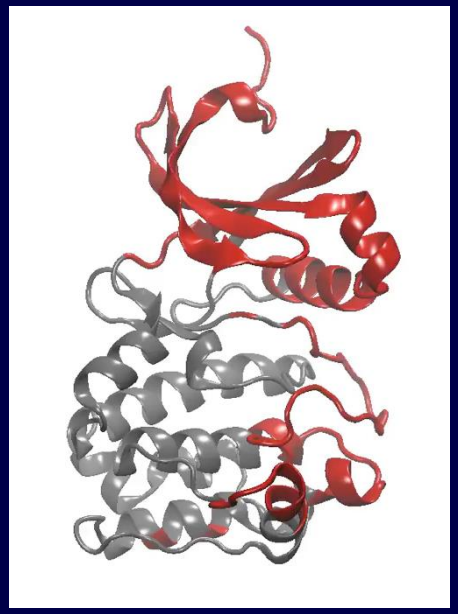
MOMA THERAPEUTICS

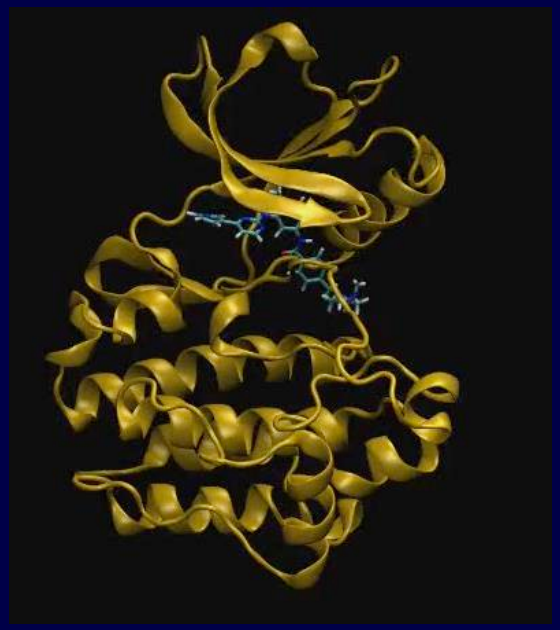


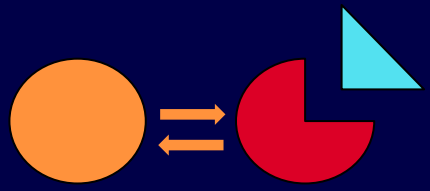


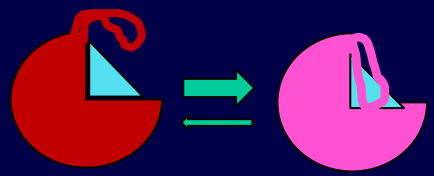


Protein Dynamics at the Heart of Drug Design









Empty protein

Protein/Drug complex

C. Wilson, et. al., 2015, Science

Protein Dynamics as Key for Drug Binding – General Principles

Design of Selective Kinase Drugs Big Challenge
Biggest drug targets of 21st century

500 human kinases

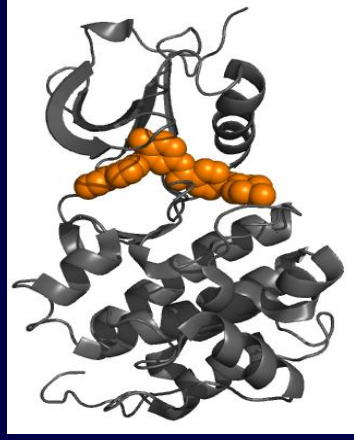
Problem:

All kinases have very similar active sites **(all bind ATP !!!)**

Most kinase drugs also inhibit other healthy kinases besides the disease kinase – side effects

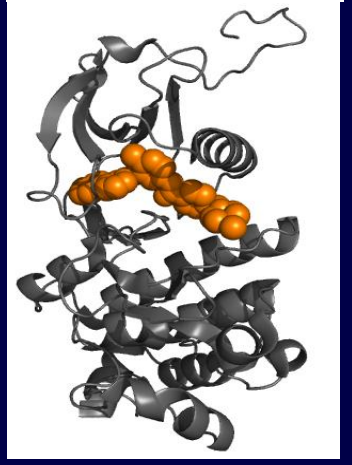
Leukemia

Abl kinase



Health

Src kinase

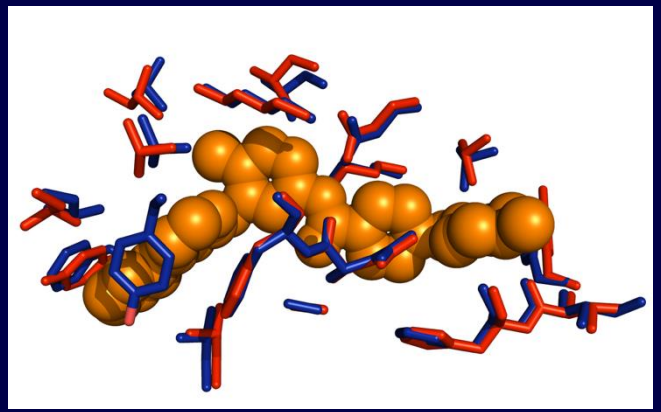


But: Gleevec (Wonder drug against Leukemia)

K_i (Abl)=10 nM;

K_i (Src)=30 μM **(3000-fold weaker binding)**

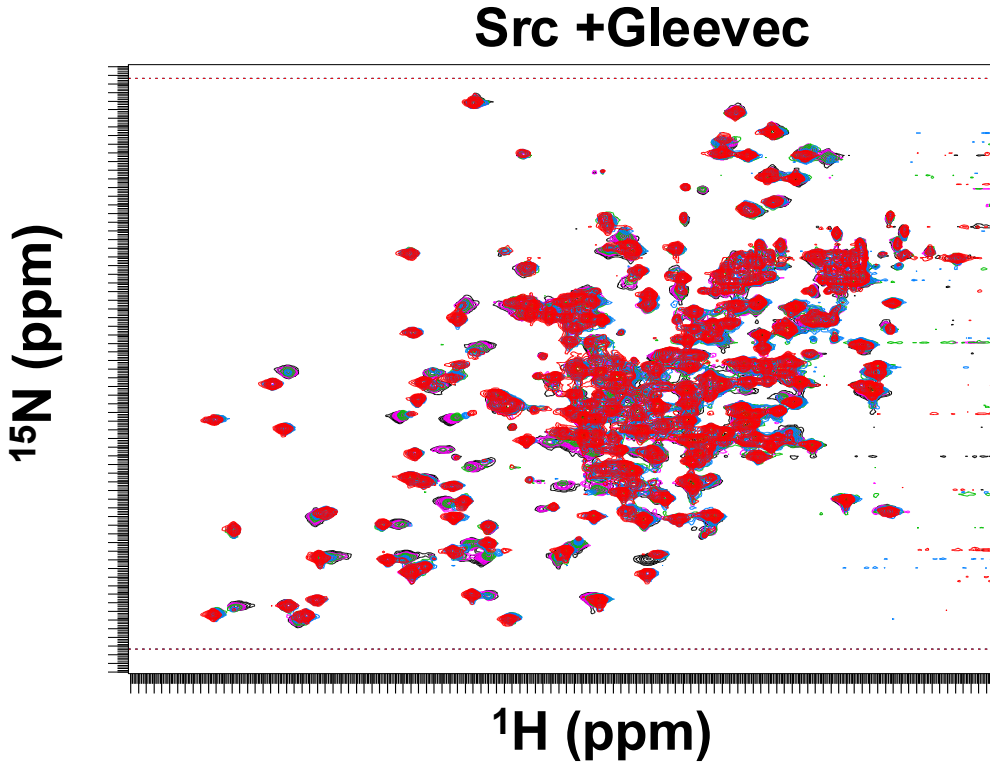
Identical Binding sites for Gleevec

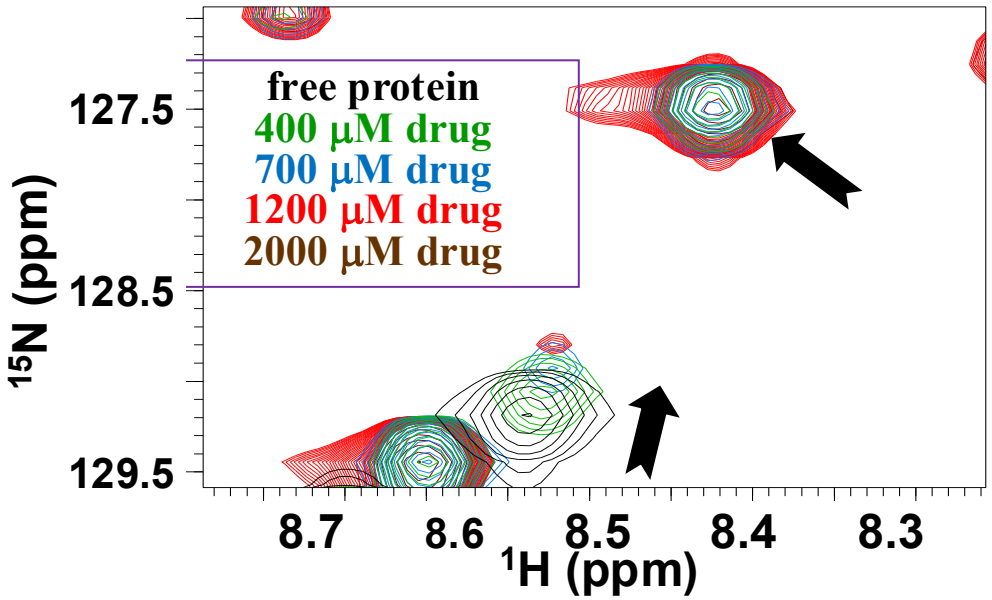


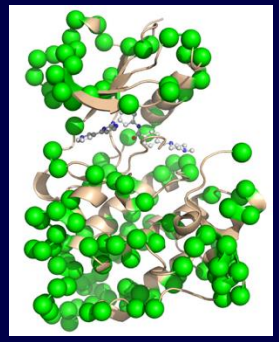
C. Wilson, R. Agafonov, et. al., **2015, Science**

Structures from **Kuriyan lab**

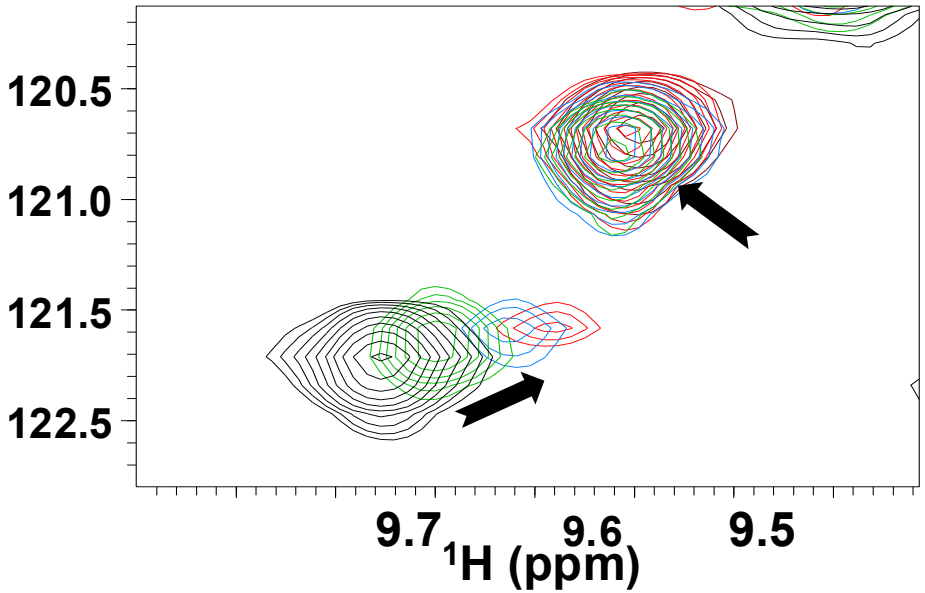
Answer must be in the dynamics! How NMR revealed why the cancer drug Gleevec is specific



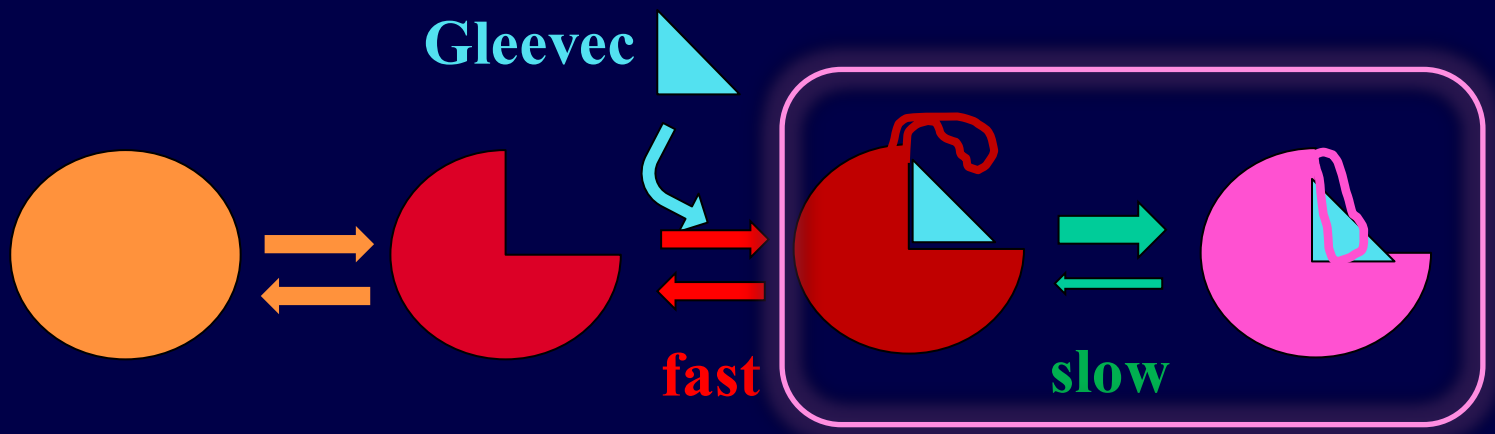




2-step drug binding
Fast and slow step



Slow Dynamics after Drug Binding Dictates Specificity



Probability (Abl)= 90%
Probability (Src)= 30%

K_1 =17 uM
K_1 =17 uM

K_2(Abl) = 4000
K_2(Src) = 6

Billions of $ wasted in industry

Docking
Identical!!

20 s^{-1} 1.7s^{-1}
0.005 s^{-1} 0.3s^{-1}

Drug Affinity

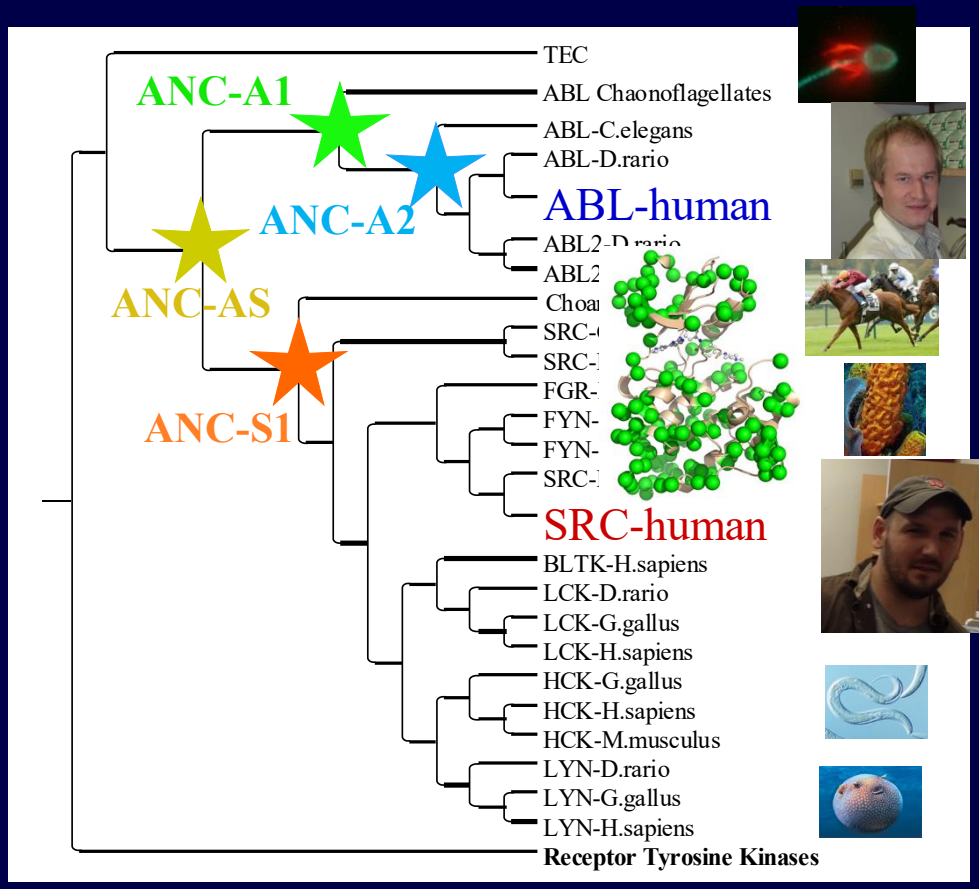
Abl = 8 nM
Src = $3x10^4$ nM

What are the atoms responsible for different dynamics?

The Evolution of Kinase Dynamics Over a Billion Years Reveals a Modern Cancer Drug's Mechanism

Ancestor Sequence Reconstruction

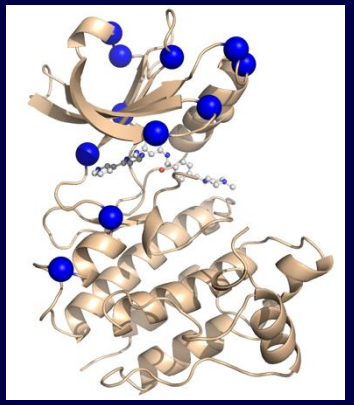
146 amino acid differences



1 Billion years → today

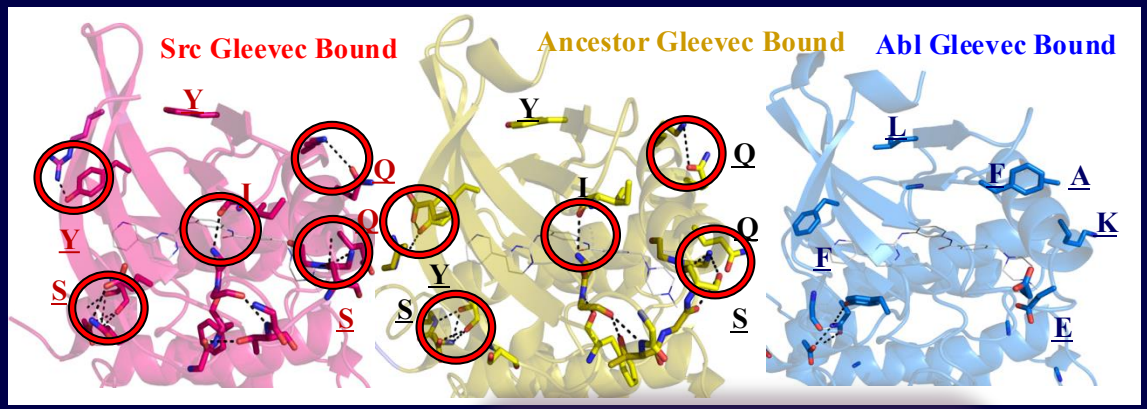
C. Wilson, R. Agafonov, et. al., **2015, Science 347**

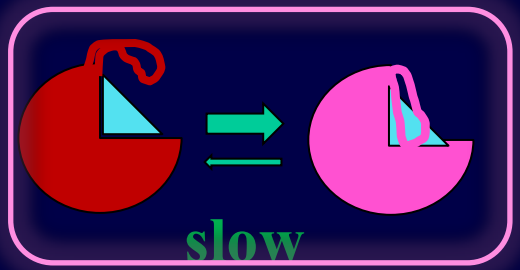
Finding the 15 residue differences responsible for Gleevec selectivity (differential dynamics)



Straitjacket in healthy Src — **Flexible in cancer Abl**

Hydrogen bonds





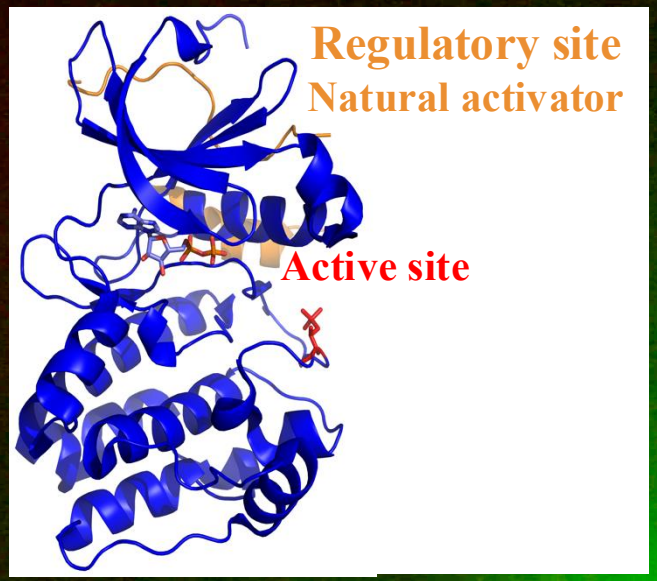
New Concept: Drug Binding to Regulatory Sites for Improved Selectivity!

Advantages:

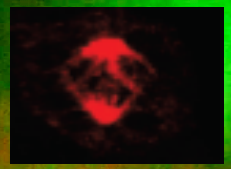
Regulatory sites Have Evolved for Differential Regulation in 500 kinases

1. There are more different than the active sites -> higher selectivity

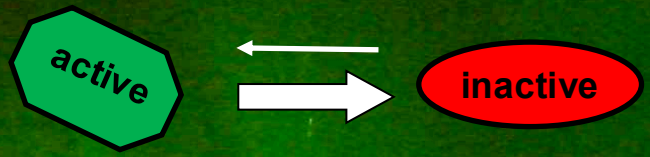
2. Development of Activators and Inhibitors



Aurora A- Kinase essential for cell division



aurora borealis
Photo by Julia Kern



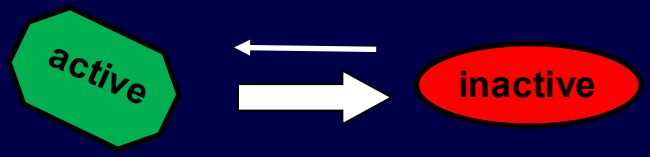
Screen for Activator and Inactivator (monobodies)

Collaborator: S. Koide

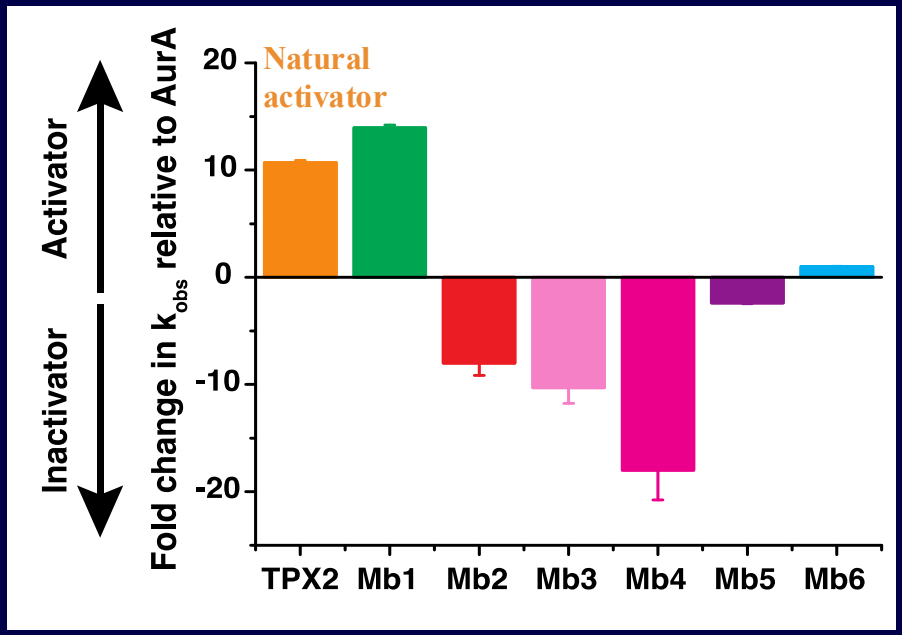
A. Zorba, et al. PNAS 2019

Inhibitors and Activators by Binding to Regulatory Sites!

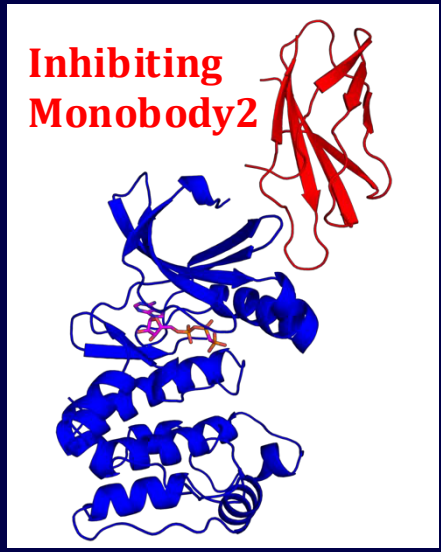
Dialing in Activity -100% selective

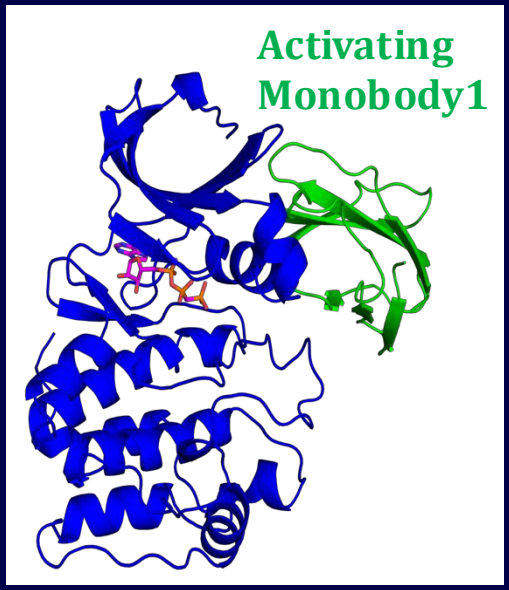


Activity



Structures





A. Zorba, V. Nguyen, M. Hoemberger, A. Koide, Y. Zheng, S. Kutter, S. Koide and D. Kern, PNAS 2019

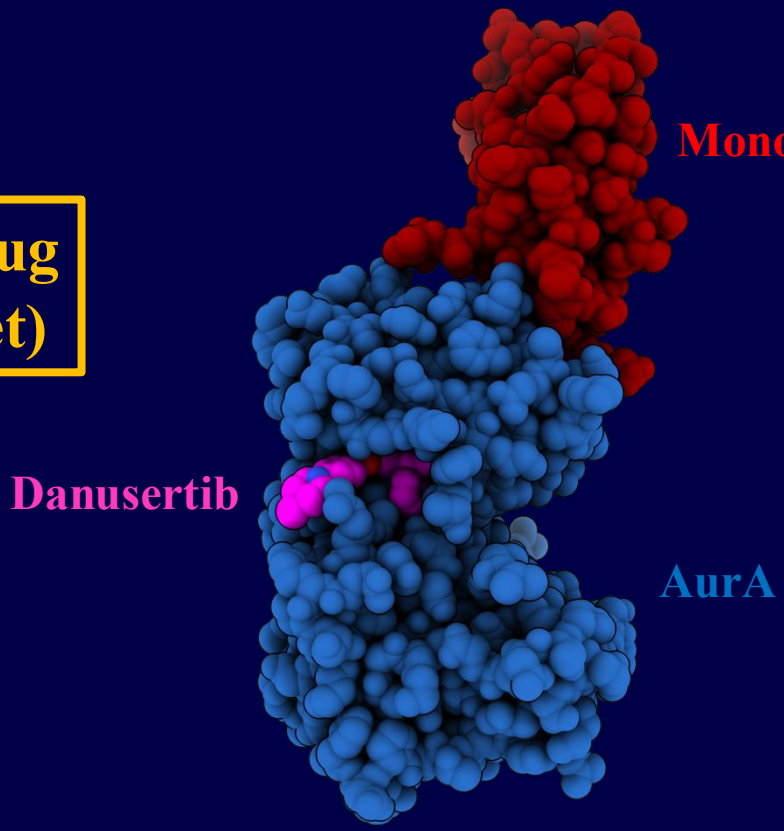
Overcoming Biggest Problem in Cancer Treatment – Drug Resistance

Multiplying Success- Combining Regulatory Site Drugs with Active Site Drugs

Double Drugging

Regulatory Site Drug

Active Site Drug (on the market)



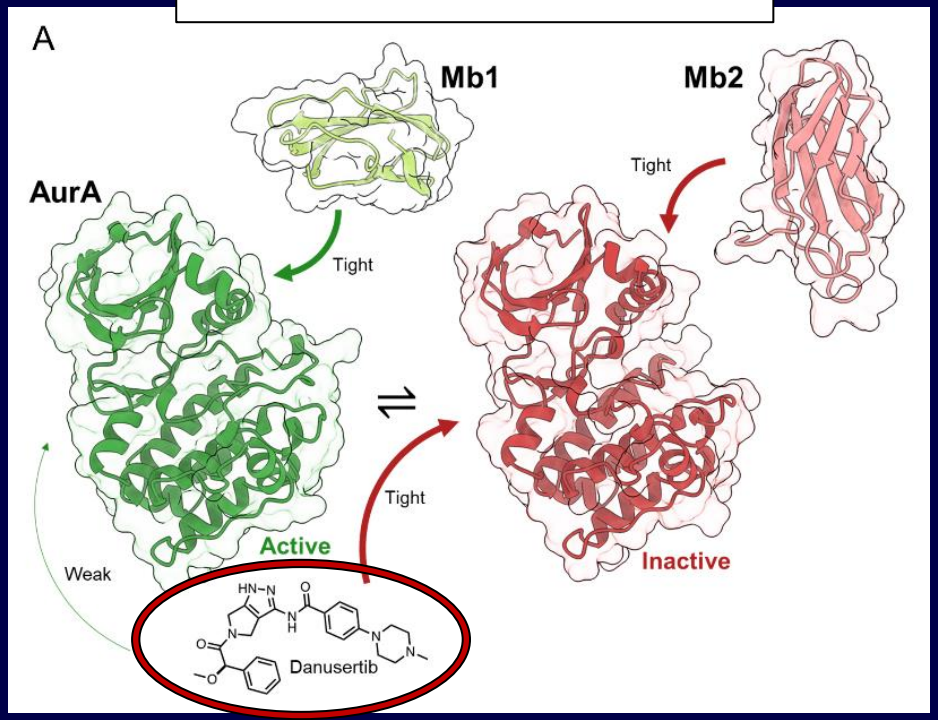
3 Major Advantages:

1. **Preventing Development of Drug Resistance: Multiplying Mutational Probabilities**
2. **Vastly Improved Inhibition – Additive Effect**
3. **Increased Drug Selectivity (removal of side effects) – Positive Cooperativity**

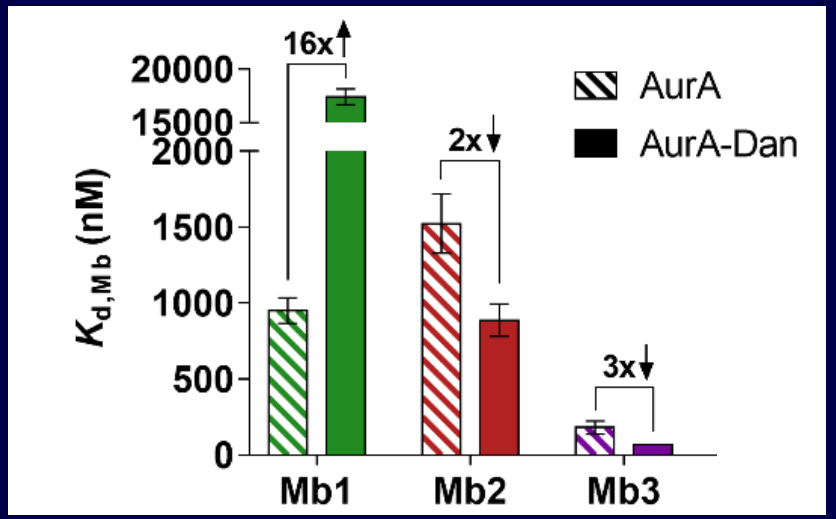
C. Kim, H. Ludewig, A. Hadzipasic, S. Kutter, V. Nguyen, D. Kern , 2023. PNAS 120

Finding 2 drugs working together and (not against each other) in double drugging

Active ⇌ Inactive



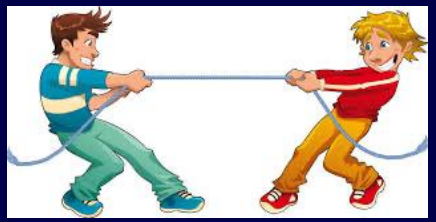
Affinity



Activity

Both drugs are inhibiting

20-fold less of chemical drug Danusertib needed!!! for same inhibition



Negative Cooperativity

Positive Cooperativity

Active site drug becomes much more selective!
Minimizing toxic side effects

My Journey: Proof of Concept Results From Academic Research Transferred to Developing Medicines

hhmi

Brandeis UNIVERSITY

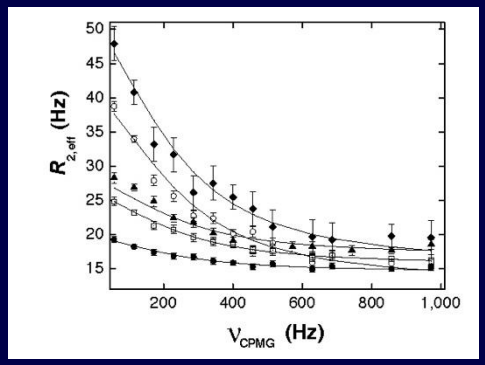
Scripps Research

RELAY THERAPEUTICS

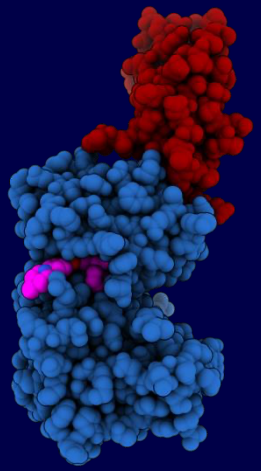
MOMA THERAPEUTICS

Molecular Dynamics simulations

NMR Relaxation



X-ray Crystallography



Clinical trials:

Relay-drug in Cholangiocarcinoma and Pancreatic cancer:
First FGFR2-selective inhibitor
Lirafugratinib

- **88% Overall Response Rate (compared to 23-36% of approved drugs)**
- **Removal of side effects**

Disclosure: Founder of Relay Therapeutics and MOMA Therapeutics

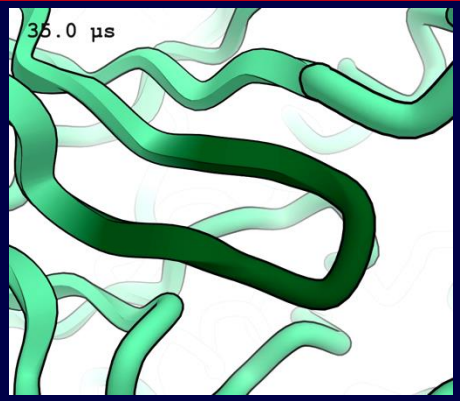
Development of first fully FGFR2 selective drug by exploiting differential protein dynamics in FGFR2, FGFR1 and FGFR4

RELAY THERAPEUTICS

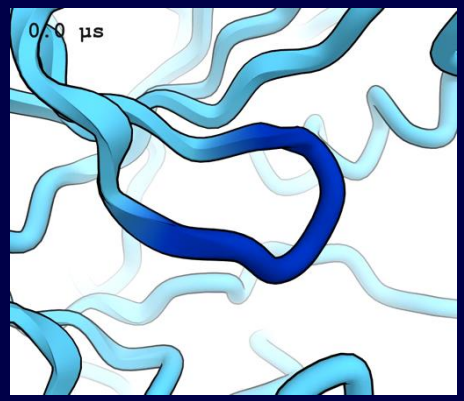
Current FGFR inhibitors (Futibatinib) in the clinic for cancer cause FGFR1 and FGFR4-mediated toxicity (hyperphosphatemia and diarrhea)

Identical drug binding site for FGFR2, 1,4, but we discovered differential dynamics in adjacent P-loop

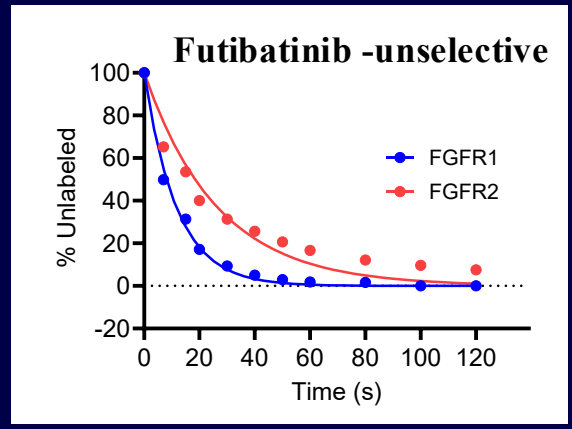
FGFR2 – the cancer target



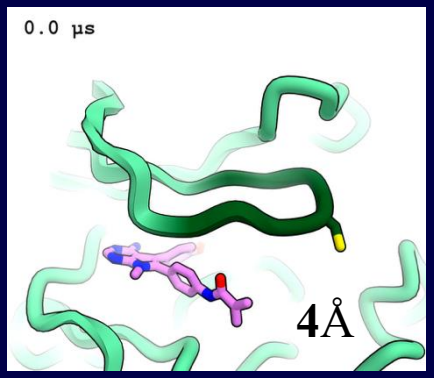
FGFR1 inhibition – causing side effects



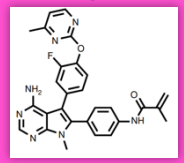
P-loop covalent binding

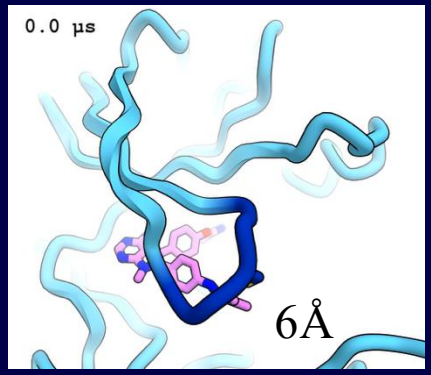


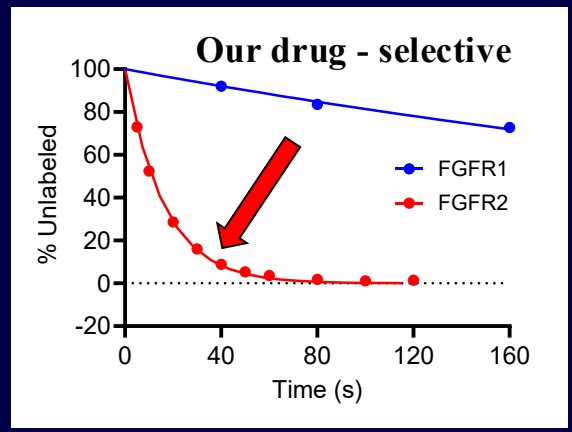
Designed selective drug for FGFR2 by exploiting differential dynamics!!!



Lirafugratinib







Figures courtesy of Jim Waters, CSO Relay Therapeutics

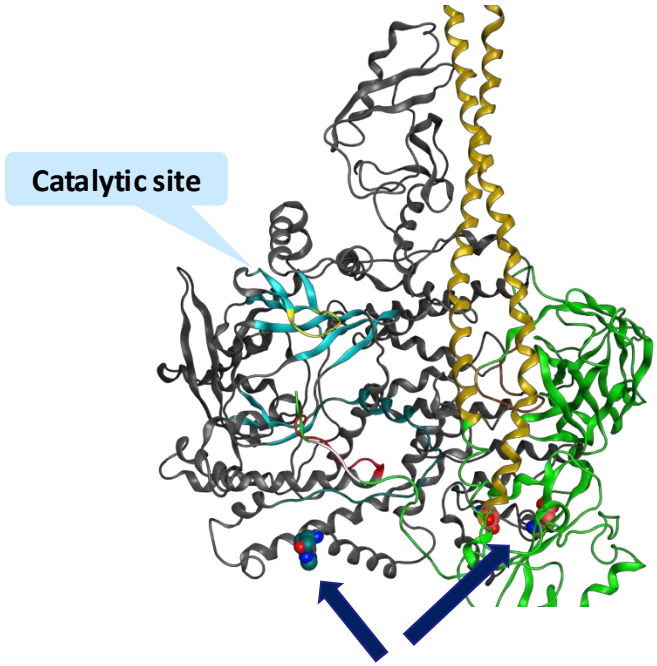
Removal of toxicity

PI3Kα Kinase is the Most Frequently Mutated Kinase in Solid Tumors
Stage 2 Clinic Trials in Breast Cancer

RELAY THERAPEUTICS

Toxicity due to wildtype (healthy protein) inhibition limits existing therapies against PI3Kα

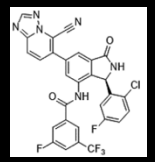
Relay developed a selective drug that only inhibits the mutated protein in cancer! HOW?

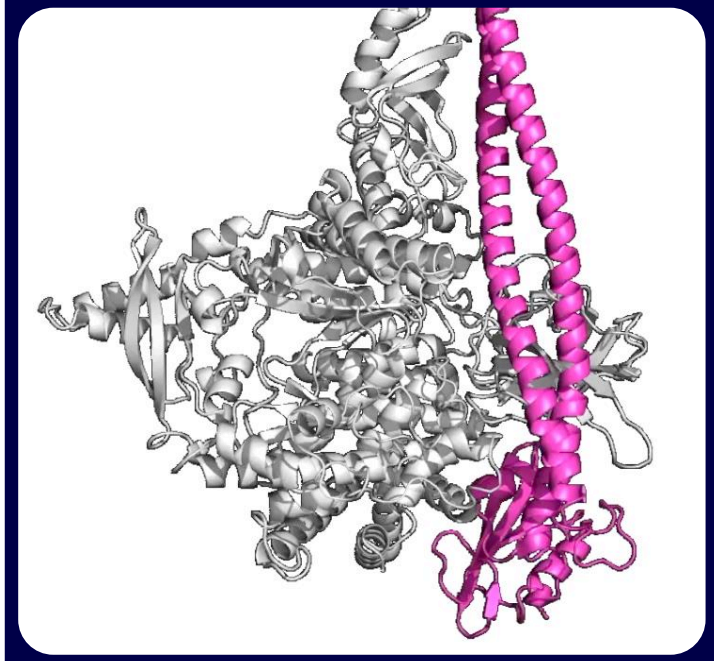


Cancer causing mutations located away from the active site

Discovery of novel drug binding pocket for mutant kinase

RLY-2608





→ **Reduction of Side Effects**

→ **Breast Cancer: Zovegalisib (RLY-2608) + Fulvestrant Tumor Reduction: 80.6%**

Figures courtesy of Jim Waters, CSO Relay Therapeutics

2. Development of Biocatalysts (Enzymes):

"Ancestral Enzymes to the Rescue for Modern Gluten Intolerance"

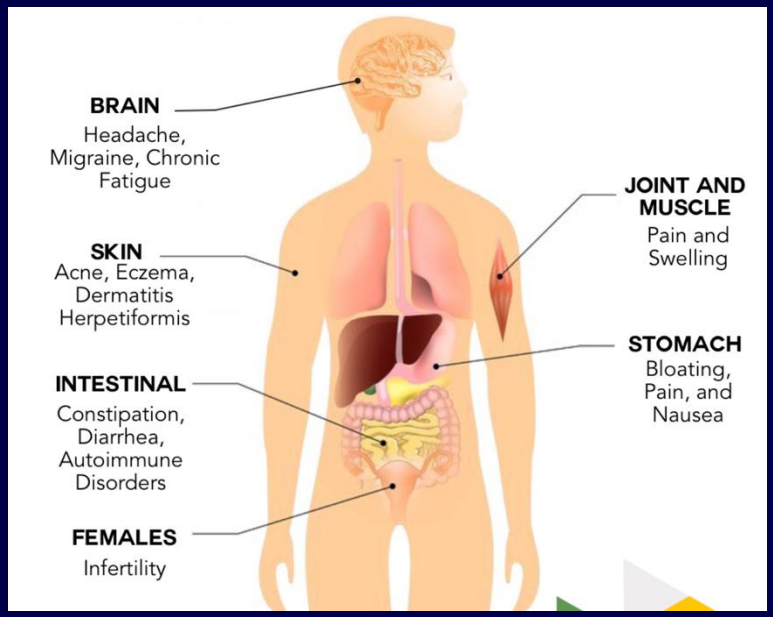
Celiac Disease

1% of population

But over 80% of those with celiac in the U.S. are undiagnosed,

-> actual patient base is much larger than current diagnoses suggest.

Symptoms



https://paleofoundation.com/gluten-intolerance/

Gluten Intolerance

6-10% of population

Market:

1. *Treatment*
2. *Diagnostics*

Currently NO TREATMENT!!

What if we can develop a simple oral enzyme therapy?

Goal: Develop Protease that Cleaves Gluten Into Small Nonimmunogenic Peptides in the Stomach Given as Oral Pill

Gluten: "33-mer" immunogenic protein (33 amino acids) that resists digestion in the stomach:

Protease

LQLQPF-PQPQLPY-PQPQLPY-PQPQLPY-PQPQPF

needs to be digested into peptides smaller than 9 amino acids

Therefore, enzyme (Glutenase) needs to act in stomach (pH 2-5), Needs to be very fast!

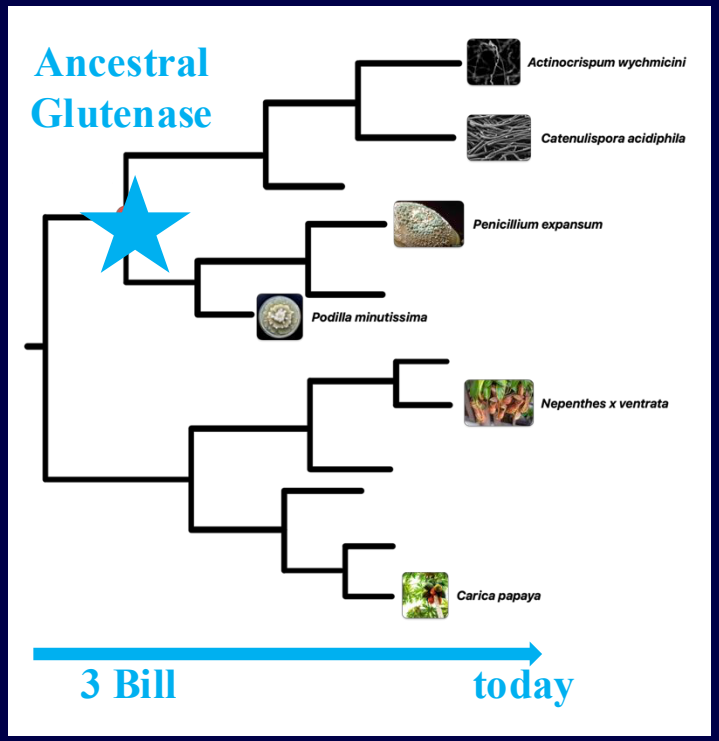
Stable against Pepsin (natural enzyme that degrades proteins such as chicken, cheese, fish)

pepsin

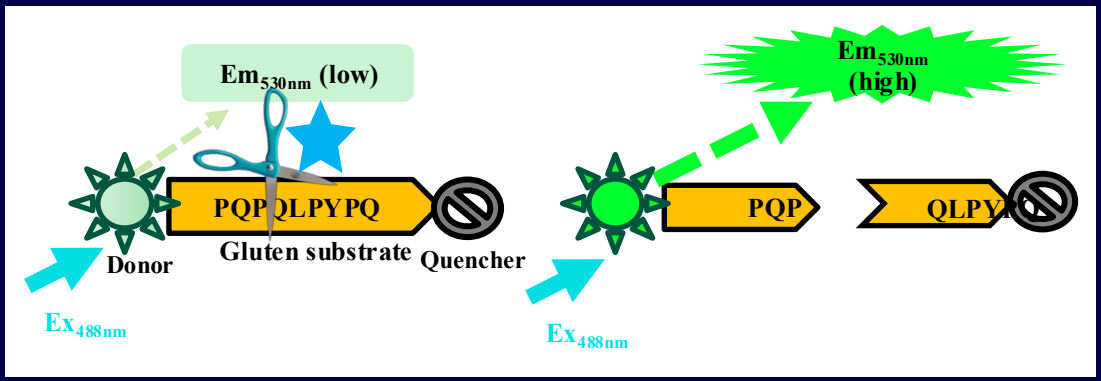
We Evolved a Novel Glutenase with Novel Approach that is Very Active, Stable and Selective for Gluten

Ancestor Sequence reconstruction of
3 Bill year old enzyme – WHY?

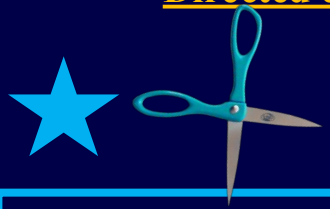
1. **Ancestors are more evolvable!!**
   = we find more winners



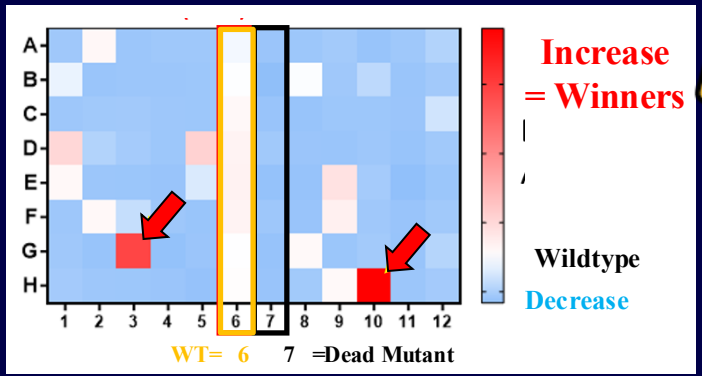
2. Developed a fast high-throughput assay done with cell lysates



3. Found winners in directed evolution experiments (96 well-plate)
<u>Directed evolution: Make 10,000 variants, then screen for winners</u>



- High Yield in E.coli produced
- Thermostable, acid stable, protease stable
- Highly active at pH 2-5!

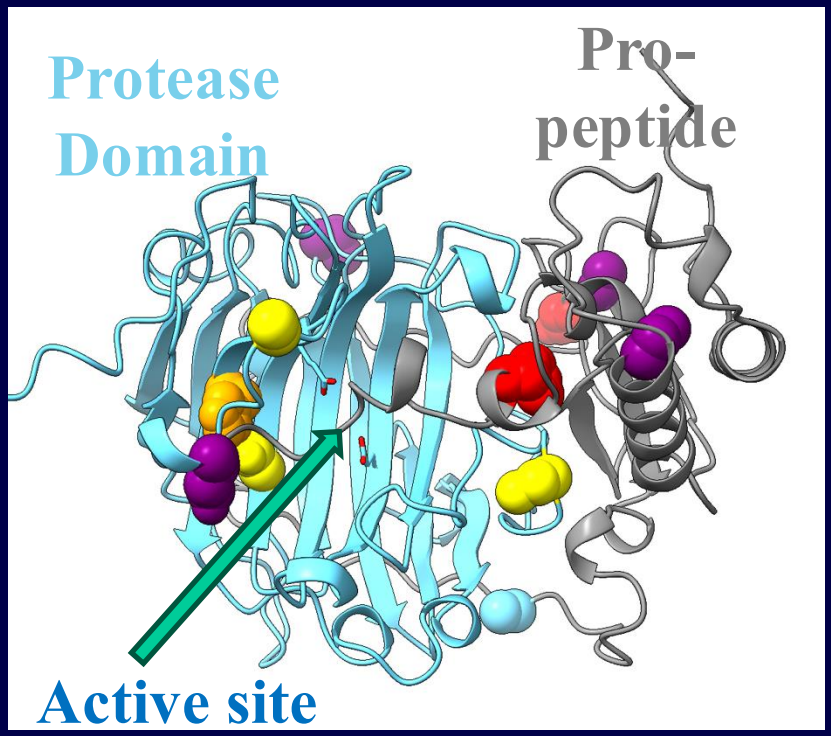


Time Travel into the Past (Resurrection of Ancestral Enzyme) and into the Future (Directed Evolution and AI)

GlutenBolt

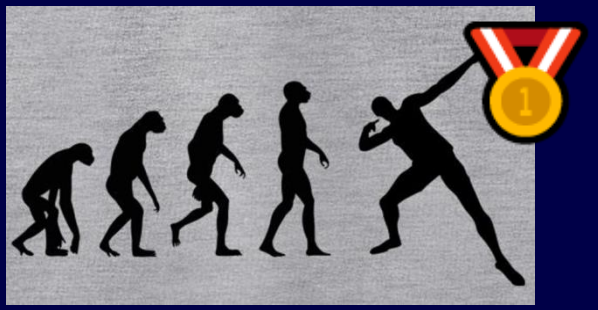
Ancestral Glutenase to Evolved GlutenBolt

3 bill. years old

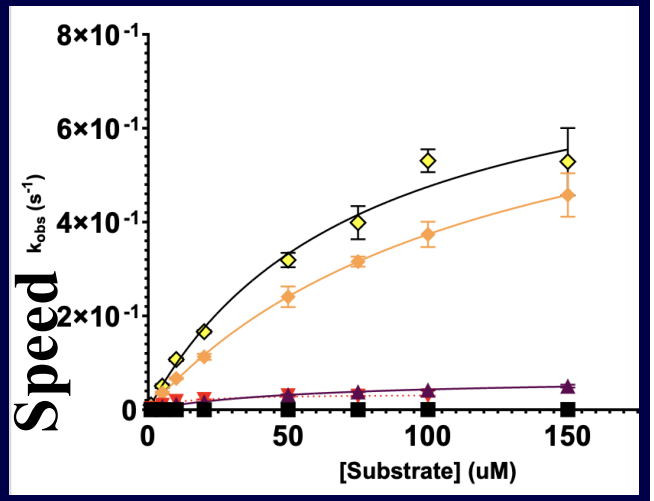


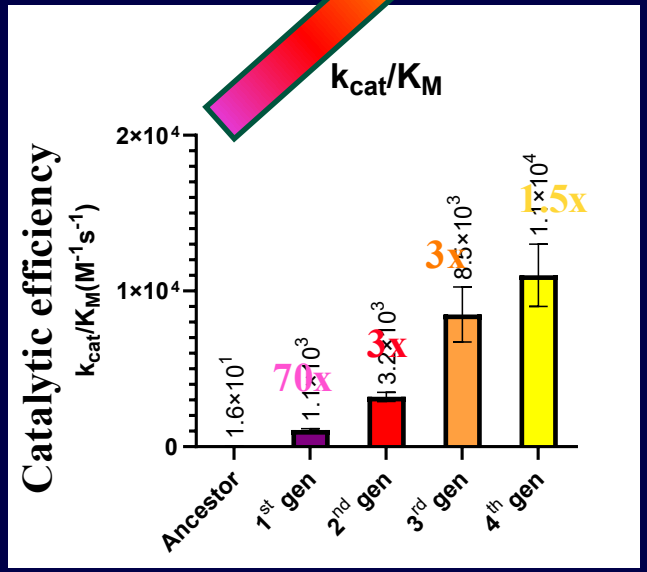
Directed Evolution

Ancestor
1st generation
2nd generation
3rd generation
4th generation

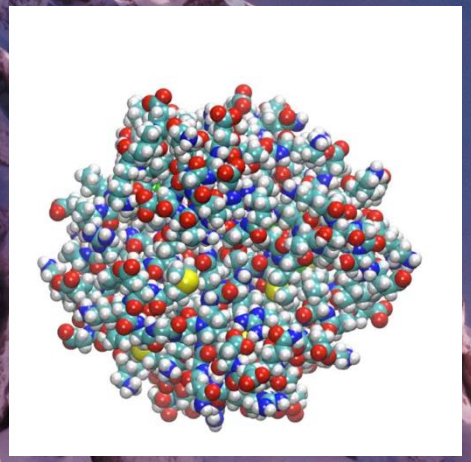


Speed 700-fold





What if we could predict the protein's dance – development of novel AI approaches



Problem: not enough data

(Compare to ChatGPT: lots of language and pictures available!)

We compiled a benchmark of 134 proteins with NMR dynamics data

- Not enough! But used to evaluate our new AI model

Current AI Methods: Alphafold2, Language models can only predict static structures in the valley

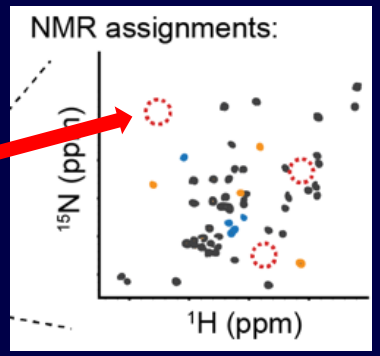
How Can We Get from 134 Proteins to Thousands?

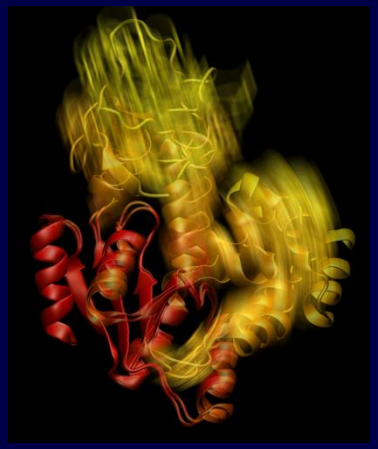
There are 10,00 proteins with NMR assignments online

Bold Call: Amino acids with missing assignment are due to dynamics!!!
Now we have 10.000 protein data set! = created a huge new language for a proteins dance

KLVYRGKPQKRWGGNLSNVLPACDNGSS…

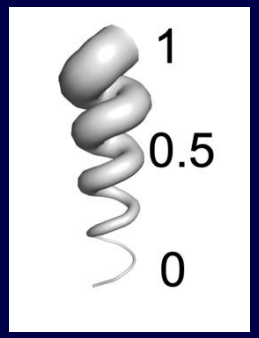
Present=static Missing=dynamic

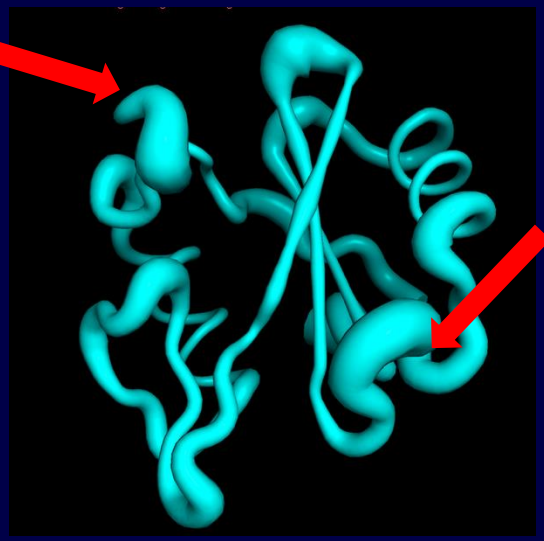




Trained novel AI model with these NMR data: Dyna-1

Input: Protein
Output: Probability for dynamics





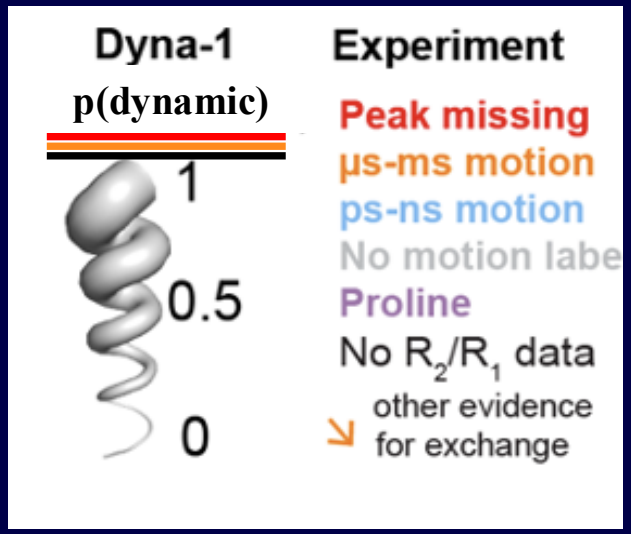
dynamic

Experiments take months, expensive
Dyna-1 prediction: 30 seconds, free

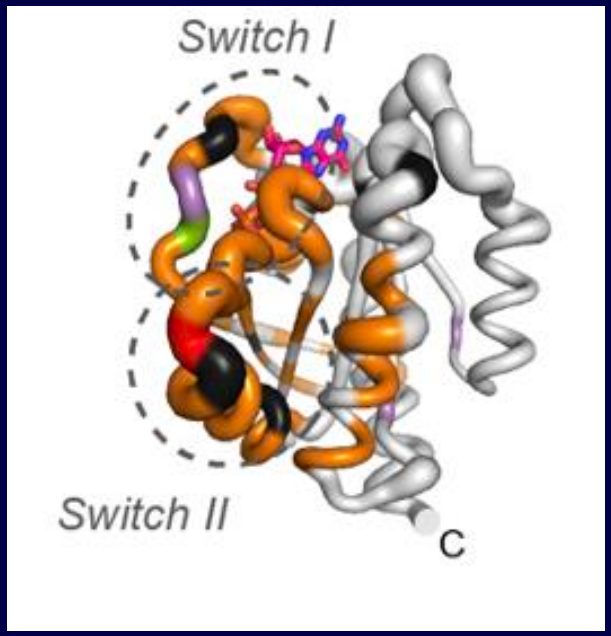
Dyna-1- "Learning Millisecond Protein Dynamics from what is missing in NMR Spectra"
bioRxiv preprint, in revision at Nature

Is Our Prediction Just Scientific Hollywood, or the Truth?

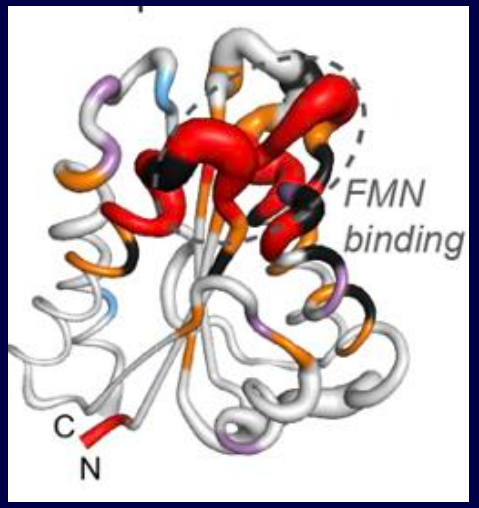
Evaluation against known NMR data!

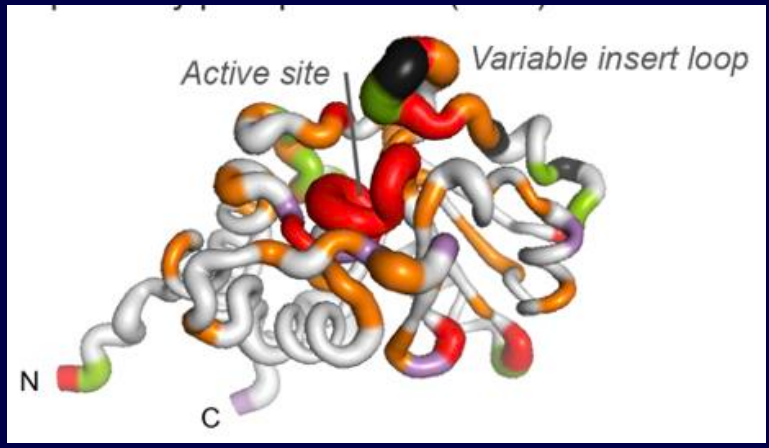


K-Ras: Big cancer target



Other enzymes





Dyna-1 predicts biologically-important micro-millisecond dynamics in NMR data!!

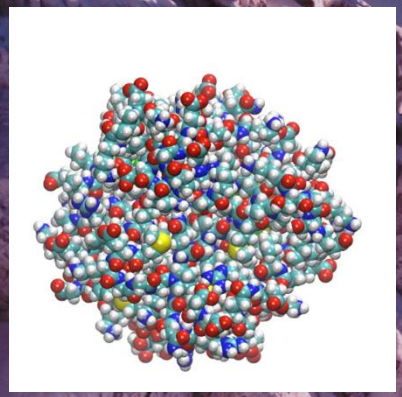
As easy to use as ChatGPT

What a Protein's "Dance" Says About Health and Disease

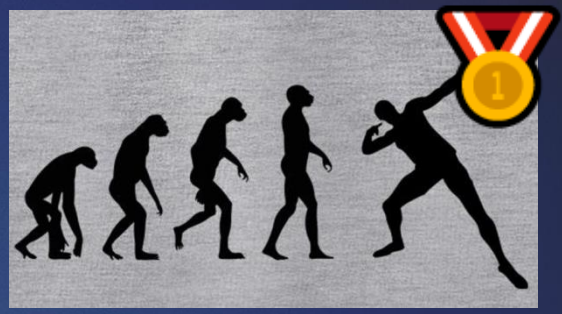
GlutenBolt

Methods

Experiments



Use Knowledge of Protein Dynamics for Enzyme Design



Exploit Dynamics for Drugs without side effects

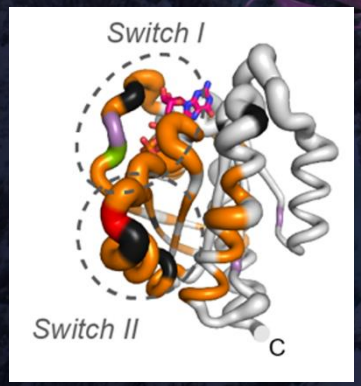
Protein Dynamics at the Heart of Drug Design

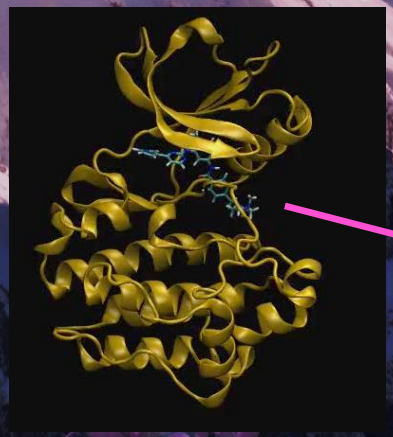
Double drugging

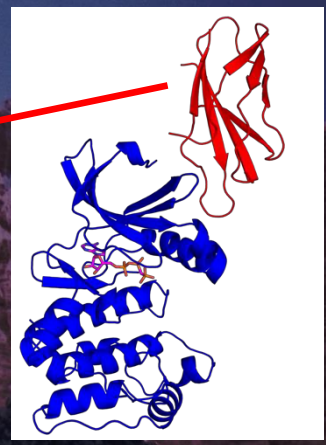
Active site Drugs

Regulatory site Drugs

Prediction of dynamics by AI

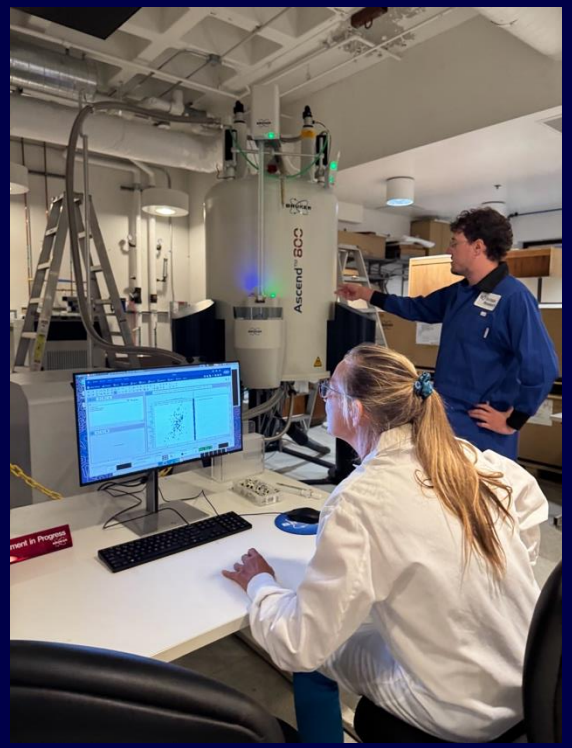






To understand healthy function of proteins and to cure diseases

THE DREAM TEAM

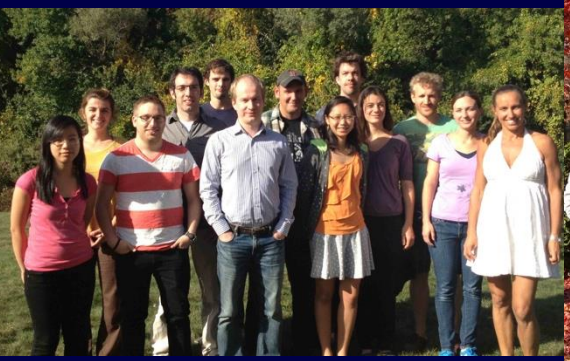


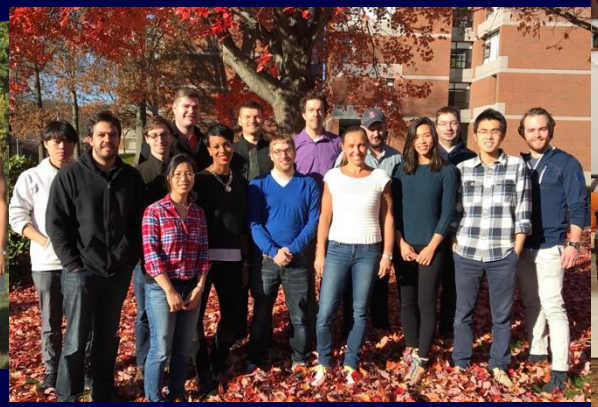
The Scripps Research Institute

Plus the Relay and MOMA teams!

The Kern gang: 1998- today

Biochemist
Biophysicist
Physicist
Biologist
Engineer
Chemist





Gerhard Hübner
Nadja Kern Dunstone
Gunther Kern