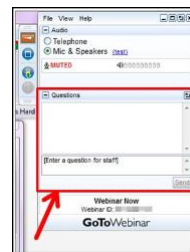




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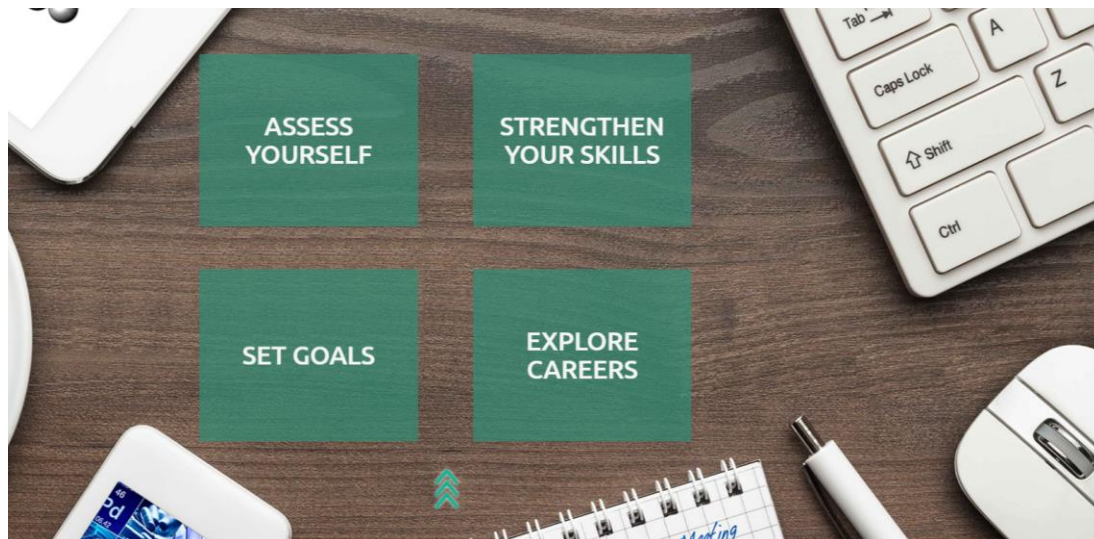
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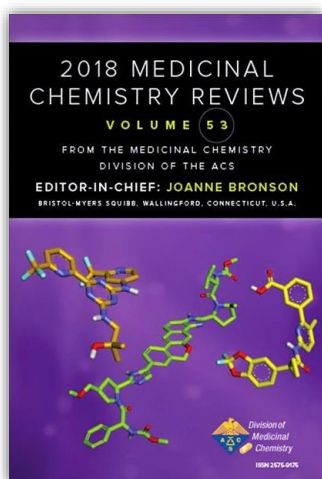


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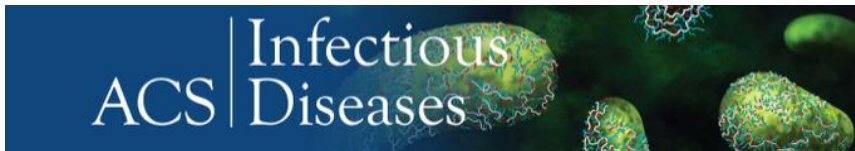
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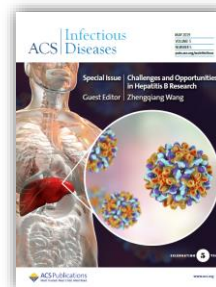
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Widening *the* Therapeutic Window

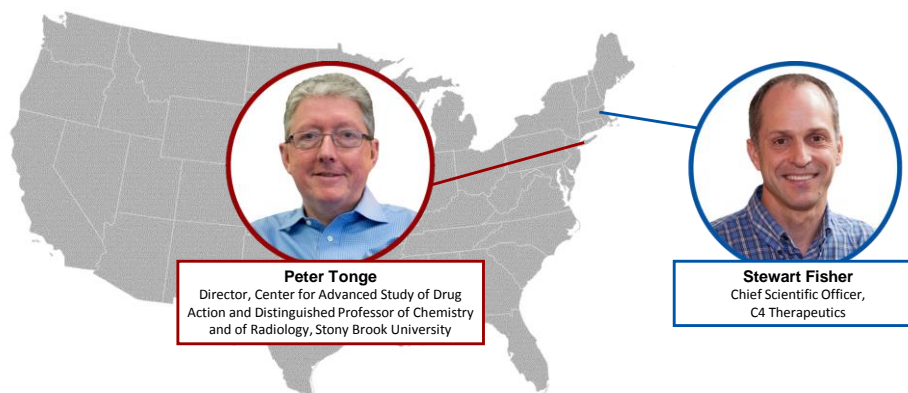
Kinetic Selectivity *and* Target Vulnerability

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Widening the Therapeutic Window: Kinetic Selectivity and Target Vulnerability



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The Challenge

- **Many (up to 90%?) of drug candidates fail in clinical trials**
 - Contributes to the high cost of drug discovery
- **Reasons include lack of efficacy and safety (can't dose high enough to get efficacy)**
 - Insufficient therapeutic window
- **Therapeutic window**
 - The ability of a drug to treat a disease effectively without causing unacceptable toxicity
- **How can kinetic selectivity improve the therapeutic window?**



The Premise

- **Drugs work when they are bound to their targets** and cause unwanted side-effects when they are bound to off-target proteins
- Thus, **one objective in the selection and optimization of drug leads is to maximize binding to the target and minimize binding to off-target proteins (if known)**
- **Where do kinetics fit into this?**



Outline

➤ Why are drug-target kinetics important?

- The human body is not at equilibrium
- Kinetic selectivity

➤ Using drug-target kinetics prospectively

- Reversible inhibitors of paLpxC* and saFabI**
- Target vulnerability
- A mechanistic pharmacokinetic/pharmacodynamics (PK/PD) model
- Covalent inhibitor of Bruton's tyrosine kinase (Btk)



* *Pseudomonas aeruginosa*

** *Staphylococcus aureus*



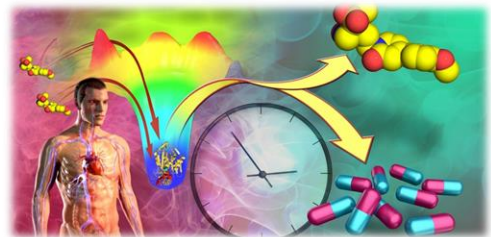
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➤ Why are drug-target kinetics important?

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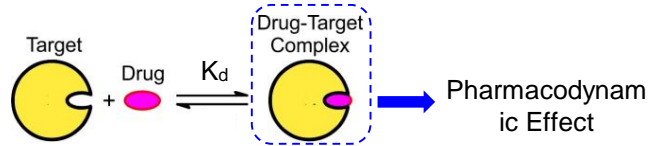
➤ Using drug-target kinetics prospectively

- Reversible inhibitors of paLpxC and saFabI
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- A mechanistic PK/PD model
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Thermodynamic Selectivity

- **“Corpora non agunt nisi fixata”** – substances do not act unless bound (P. Ehrlich, 1913).



- **Maximize target occupancy, minimize off-target binding**
 - Optimize potency, selectivity, safety
- **Use K_d , K_i , IC_{50} values to select and optimize compounds**
 - These are equilibrium constants measured at constant drug concentration
 - Many cell-based experiments are also performed at constant drug concentration
- **But...** drug concentration fluctuates in the non-equilibrium environment of the human body



Kinetic Selectivity

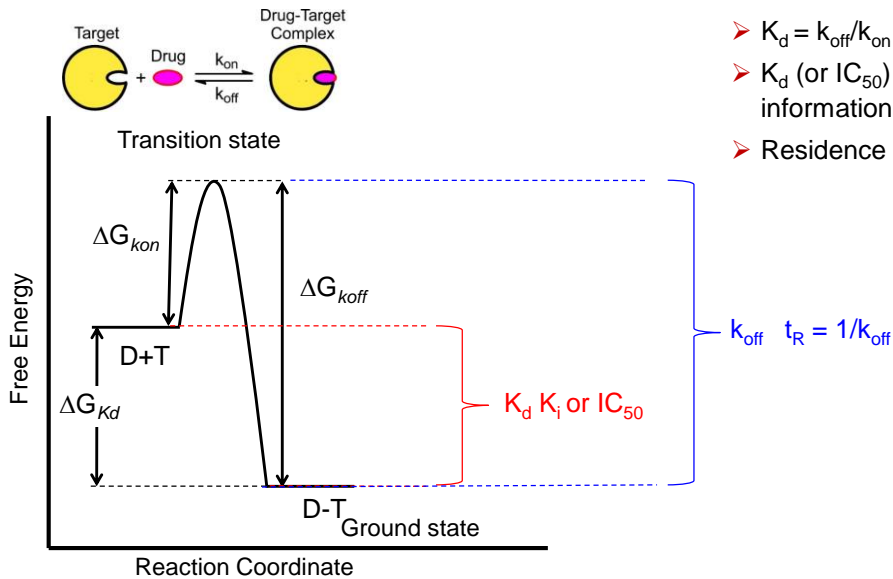
- If drug and target are not at equilibrium, how valuable are equilibrium constants for selecting and optimizing drug leads?
- Does the use of equilibrium constants contribute to our failure to accurately predict drug activity in humans?
- We need to predict time-dependent changes in target engagement as a function of drug concentration



- Residence time can be minutes, hours or days...
- A drug can bind to two targets with the same K_d but different k_{on} and k_{off} – **Kinetic selectivity**



Kinetics vs. Thermodynamics



- $K_d = k_{\text{off}}/k_{\text{on}}$
- K_d (or IC_{50}) does not provide information about rates
- Residence time (t_R) = $1/k_{\text{off}}$



Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT



- Compound **1** has a K_d for target A of 10 nM.
- Compound **2** has a K_d for target A of 1 nM.

Which statement is true?

- The residence time of **2** on target A must be 10-fold LONGER than that of **1**
- The residence time of **2** on target A must be 10-fold SHORTER than that of **1**
- The residence time of **2** on target A could be the same, shorter or longer than that of **1**
- All of the above
- None of the above

* If your answer differs greatly from the choices above tell us in the chat!

Many Drugs Exhibit Kinetic Selectivity

Infectious Diseases

 Tivicay [®] (dolutegravir) tablets	102 hr
 SELZENTRY [™] (maraviroc) tablets	14 hr
 INCIVEK [™] (telaprevir) tablets	3 hr
 Zithromax [™] (azithromycin)	1.1 hr
 ALTABAX [™] retapamulin ointment, 1%	1.4 hr

Oncology

 Tykerb [®] (lapatinib) 250 mg tablets	7 hr
 EMEND [™] (aprepitant)	> 1 hr
 VELCADE [®] (bortezomib) injection	> 24 hr

Respiratory & Inflammation

 SPIRIVA [®] HandiHaler [®] (tiotropium bromide inhalation powder)	39 hr
 VIOXX [™] (rofecoxib)	13 hr
sponsored by  CLARINET [™] (desloratadine) tablets www.clarinet.com	1.1 hr

Cardiovascular

 Atacand [™] (candesartan cilexetil)	3 hr
 CRESTOR [™] (rosuvastatin calcium)	

Central Nervous System

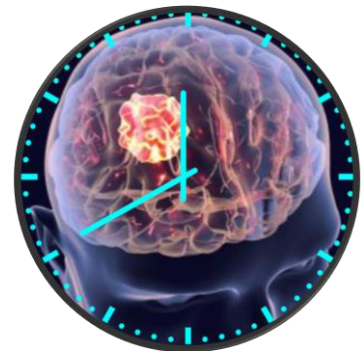
 Cymbalta [®] (duloxetine HCl)	
 Namenda [™] (memantine HCl) tablets 5mg and 10mg	2 sec



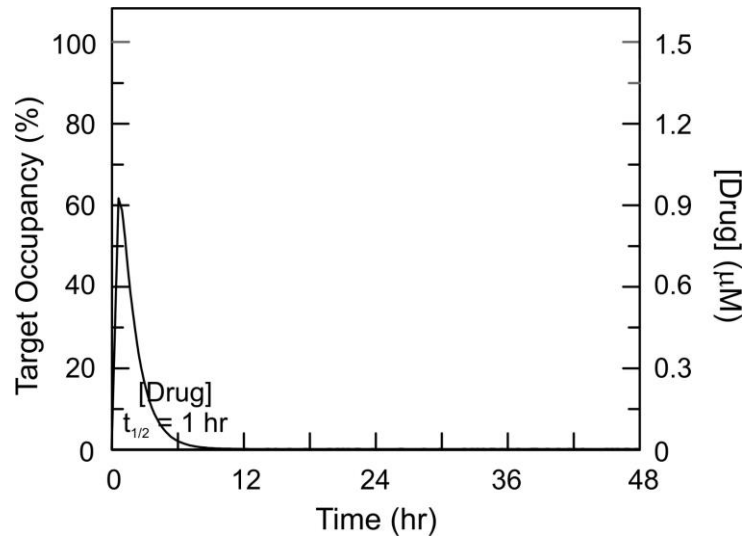
Kinetic Selectivity

➤ Thought experiment:

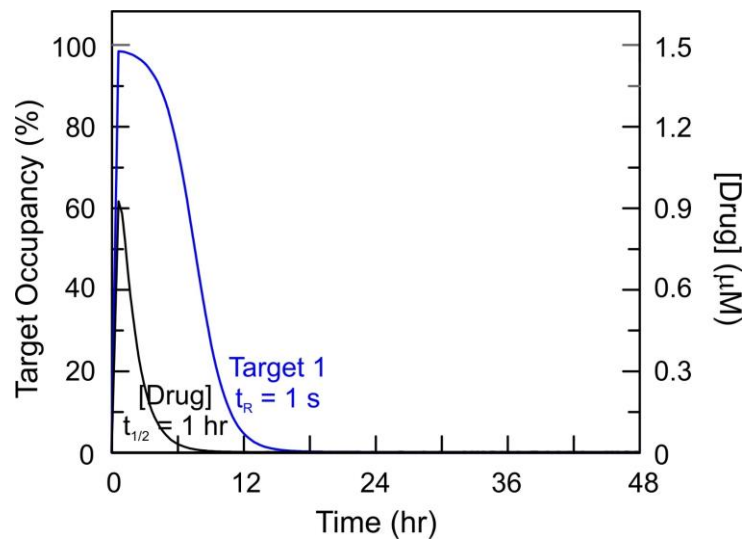
- Drug binds to three proteins with $K_d = 10$ nM:
One is the target, two are off-target proteins
- So no selectivity based on thermodynamic affinity
- But, residence times (t_R) of 1 sec, 10 hr and 50 hr



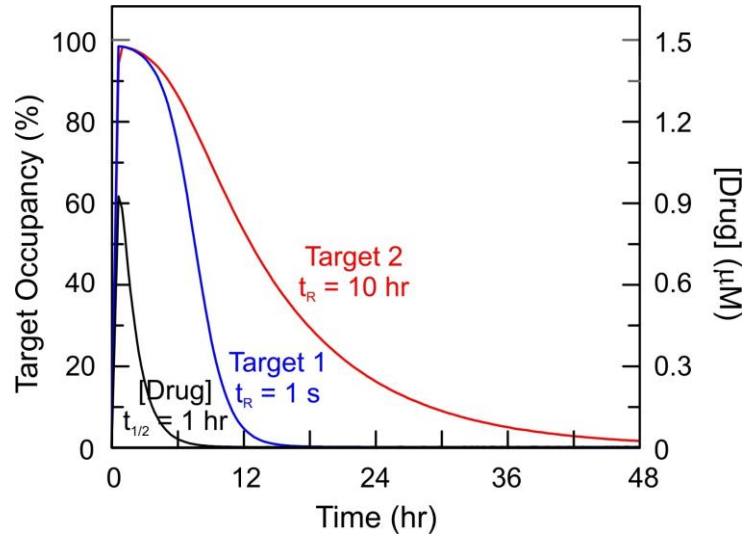
Drug PK: Dose $1.5 \mu\text{M}$, k_a 3 hr^{-1} , k_e 0.69 hr^{-1} ($t_{1/2}$ 1 hr)



Target Engagement for $t_R = 1 \text{ sec}$

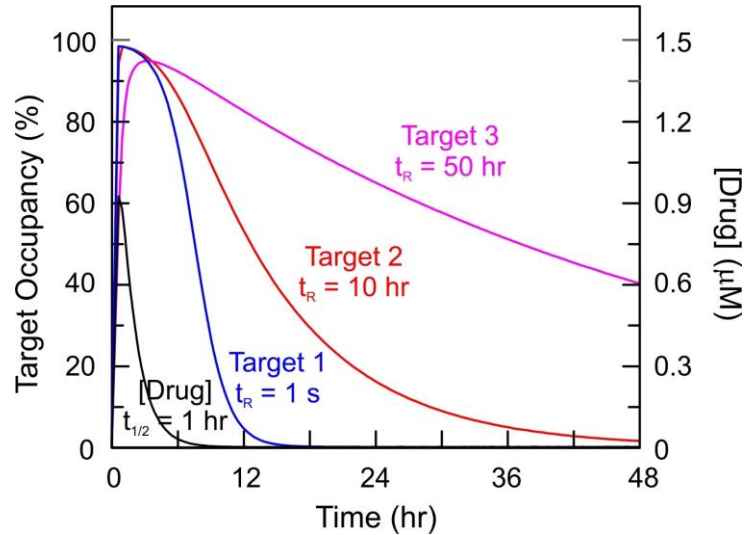


Target Engagement of $t_R = 10$ hr



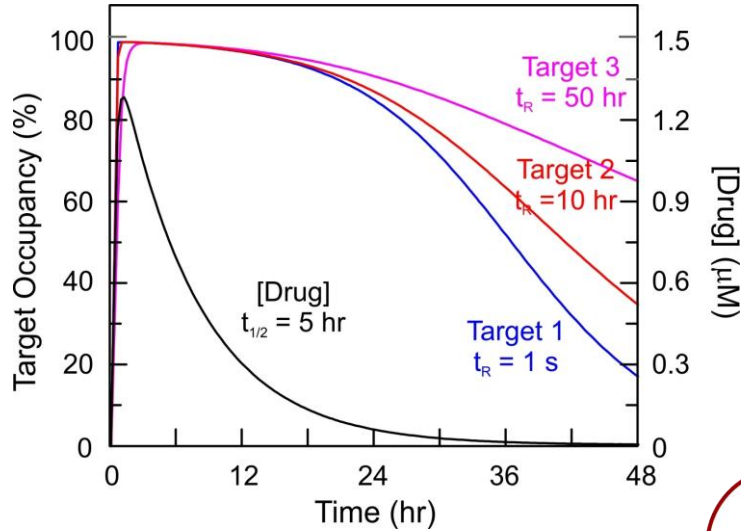
Target Engagement for $t_R = 50$ hr

Kinetic but not thermodynamic selectivity!



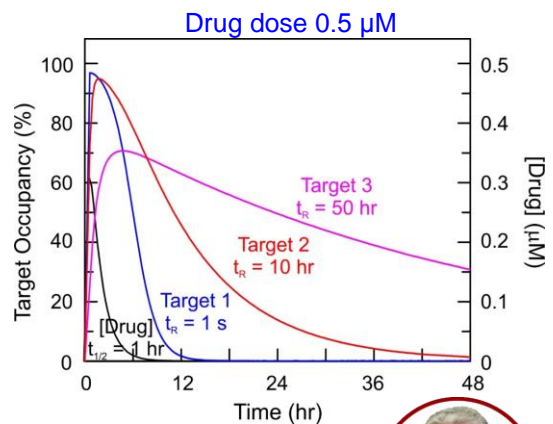
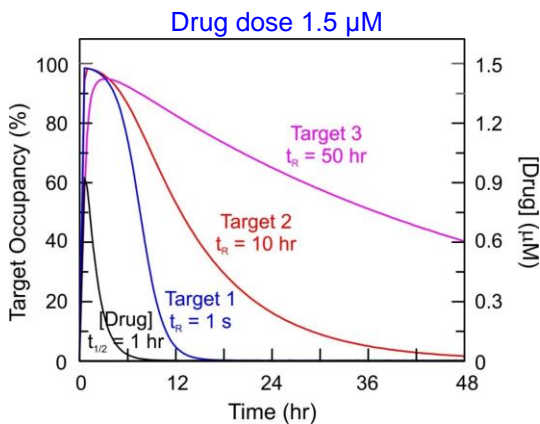
Kinetic Selectivity is Intimately Related to PK

- Slower elimination:
Less discrimination
between targets
- Drug dose $1.5 \mu\text{M}$, k_a
 3 hr^{-1} , k_e 0.139 hr^{-1}
($t_{1/2}$ 5 hr)



Changes in k_{on} May Impact the Maximum Level of Target Occupancy

- If K_d is constant then decrease in k_{off} will be accompanied by decrease in k_{on} .
- Assume k_e 0.69 hr^{-1} ($t_{1/2}$ 1 hr). Reduce dose from $1.5 \mu\text{M}$ to $0.5 \mu\text{M}$.



- Lower k_{on} may lead to $<100\%$ occupancy, again showing the importance of PK



Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT



Which of the following statements are true?

(Multiple correct answers may apply)

- Long residence time is important when compared to rate of drug elimination
- Selectivity has both thermodynamic and kinetic components
- There can not be kinetic selectivity without thermodynamic selectivity
- Slow elimination will increase the benefit of kinetic selectivity
- Slow elimination will reduce the benefit of kinetic selectivity

** If your answer differs greatly from the choices above tell us in the chat!*

Summary 1

- **Long residence time is important...but what is long?**
 - Long compared to rate of drug elimination
- **Selectivity has both thermodynamic and kinetic components**
 - There can be kinetic selectivity without thermodynamic selectivity
 - Maybe there was kinetic selectivity in programs canceled due to insufficient (thermodynamic) selectivity?
- **Pharmacokinetics are critical**
 - Slow elimination will reduce the benefit of kinetic selectivity
- **Benefits of kinetic selectivity**
 - Drug remains bound to target even after free drug has been eliminated
 - Prolonged cellular and *in vivo* efficacy at low [drug]
 - Dose at lower levels and/or less frequently: **Improved therapeutic window**



Evaluating the Translation of Binding Kinetics

- Does slow dissociation of drug from target translate to extended activity at low [drug] ?
- Develop compounds with **altered kinetic profiles**.
- Evaluate time-dependent drug activity at the **cellular level** and in ***in vivo* disease models**.
- Develop PK/PD models to **link target occupancy, drug concentration (PK) and efficacy (PD)**.
- **How to alter binding kinetics?**
 - **Empirical:** develop structure-kinetic relationships (SKR).
 - **Rational:** structure of both ground and transition states on the binding reaction coordinate.
 - Protein dynamics are important: MD simulations and NMR spectroscopy.

Li et al. (2014) ACS Chem Biol 9, 986-993.
 Spagnuolo et al. (2017) J Am Chem Soc 139, 3417-3429.
 Lu et al. (2018) Curr Opin Chem Biol 44, 101-109.



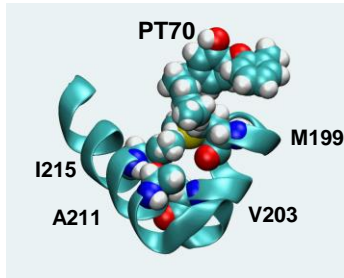
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 - The human body is not at equilibrium
 - Kinetic selectivity
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 - Target vulnerability
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 - Covalent inhibitor of Btk



Translate Binding Kinetics from In Vitro to In Vivo

Expts on Purified Target

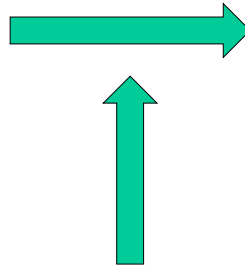


Kinetics, Med chem,
Fragment based inhibitors,
NMR, MD simulations,
Structural biology

In Vivo Studies



PK, drug distribution, PET
PD, efficacy, Tox
Extend to humans.



Time dependent expts on whole cells to
bridge the gap



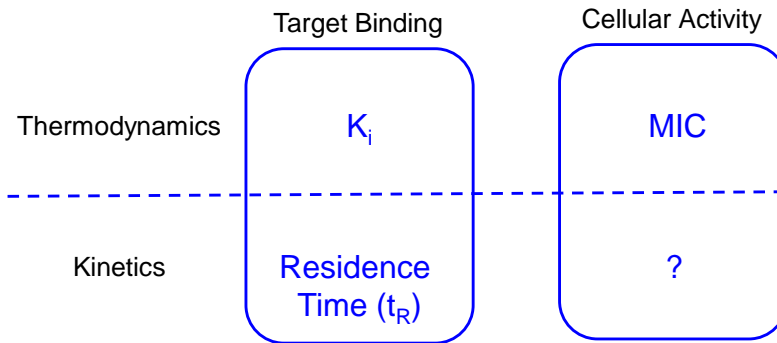
Time-Dependent Cellular Experiments: Does Residence Time Translate?

- Many cell-based experiments are performed at constant [drug] to give a cellular IC_{50}
- Use cell washout experiments to assess the sustained physiological effect after [Drug] ≈ 0
- Assess the translational potential of sustained target engagement

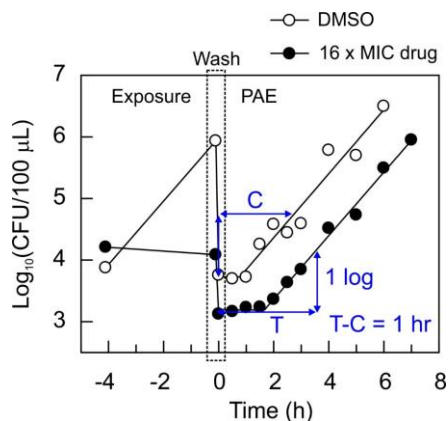


Time-Dependent Cellular Experiments: Does Residence Time Translate?

- In antibacterial space, cellular activity is assessed by the minimum inhibitor concentration (MIC)



In Antibacterial Space: Time-Dependent Cellular Activity is Post-Antibiotic Effect (PAE)



Bacteria regrowth following compound washout

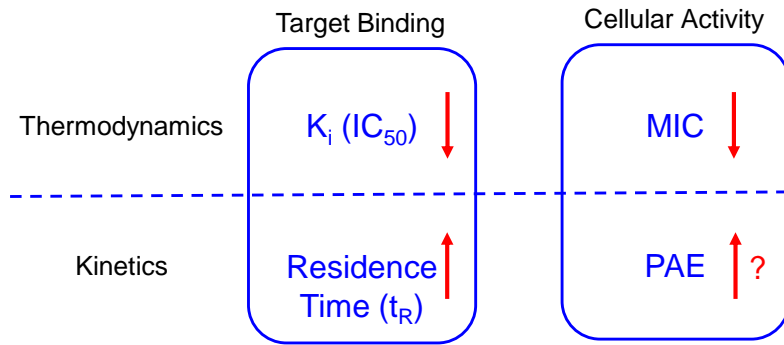
- Add drug at $t = -4$ h
- Dilute cells at $t = 0$
- Measure regrowth time for 1 log

$$\text{PAE} = \text{Drug treated recovery time}_{(1 \log \text{ CFU})} - \text{Control Recovery Time}_{(1 \log \text{ CFU})}$$



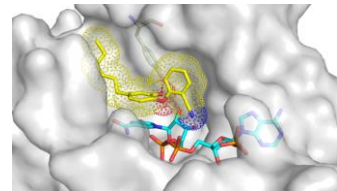
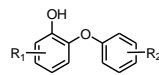
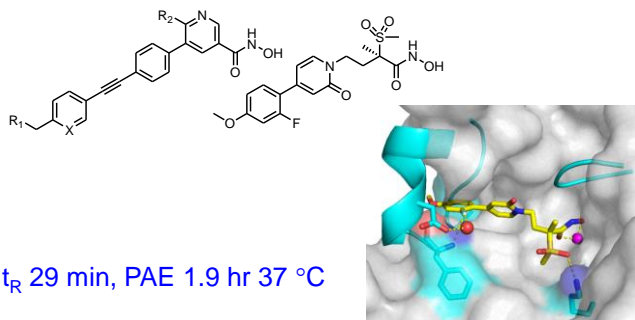
In Antibacterial Space: Time-Dependent Cellular Activity is Post-Antibiotic Effect (PAE)

- Examine the relationship between t_R and PAE



Residence Time and PAE for Two Antibacterial Targets

- The zinc metalloamidase LpxC
 - LPS biosynthesis
 - A target in Gram-negative bacteria
 - *Pseudomonas aeruginosa*
 - Hydroxamate inhibitors
- The enoyl-ACP reductase FabI
 - Fatty acid biosynthesis.
 - A target in Gram-positive and Gram-negative bacteria
 - *Staphylococcus aureus*
 - Diphenyl ether inhibitors

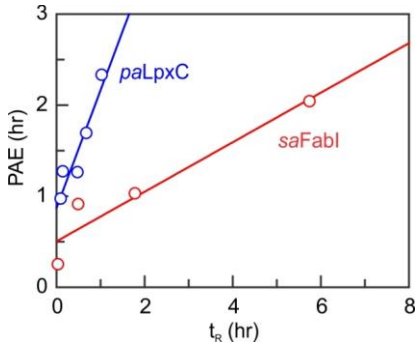


t_R 1.8 hr, PAE 1.0 hr 37 °C



Increase in Residence Time = Increase in PAE?

- For **paLpxC** and **saFabI** we have compound series with different residence times



➤ The t_R v PAE correlations have different slopes – why?

➤ What controls the coupling between residence time and PAE?

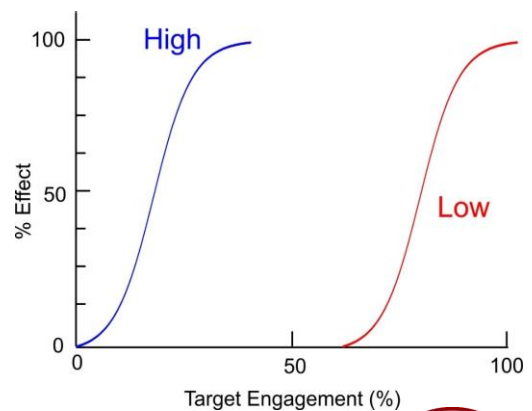
- Target vulnerability
- The amount of target that must be engaged to achieve the desired pharmacological effect



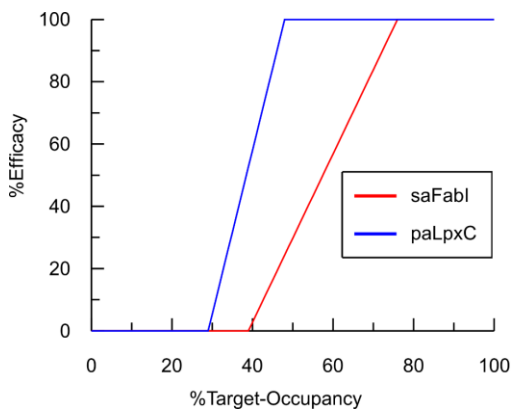
Target Vulnerability

- What is the relationship between engagement and effect?

- High vulnerability:** low levels of engagement lead to the desired effect
- Low vulnerability:** high levels of engagement needed for the desired effect



paLpxC is More Vulnerable than saFabI



➤ **paLpxC:** max effect at TO=40%

➤ **saFabI:** max effect at TO = 75%

Daryae et al. Chem Sci 2016



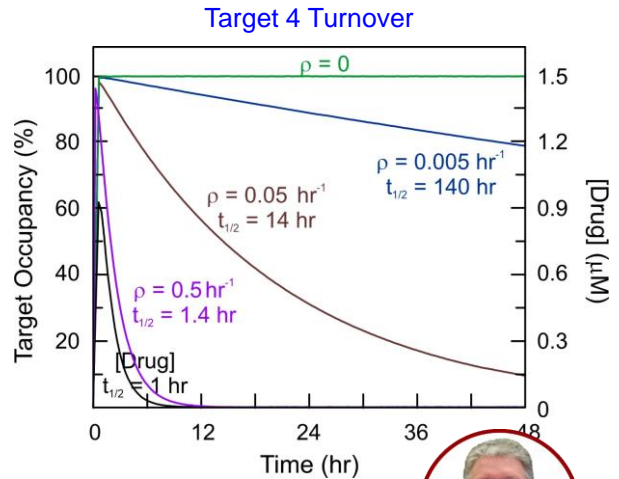
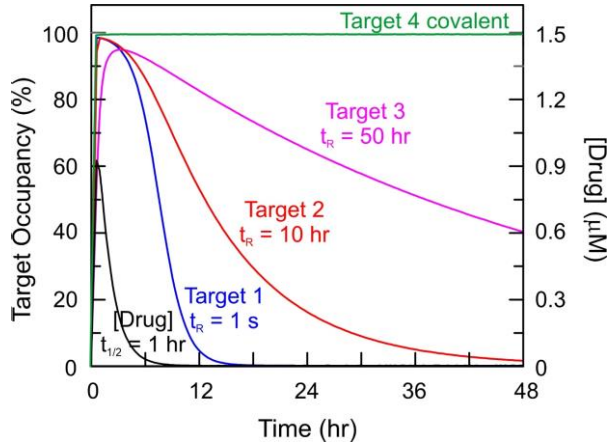
What Factors into Target Vulnerability?

- **The physiological response to target engagement**
- **Target replenishment:** rapid resynthesis will reduce the impact of kinetic selectivity



Target Turnover affects Occupancy even for a Covalent Inhibitor

- Dose 1.5 μM , k_e 0.69 hr^{-1} ($t_{1/2}$ 1 hr)
- Target occupancy by a covalent inhibitor



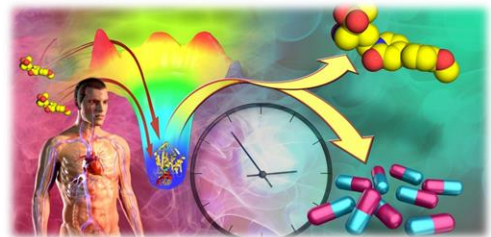
- Rapid target turnover will reduce the benefit of kinetic selectivity

Daryae & Tonge
COCB 2019



Outline

- Why are drug-target kinetics important?
 - The human body is not at equilibrium
 - Kinetic selectivity
- Using drug-target kinetics prospectively
 - Reversible inhibitors of paLpxC and saFabI
 - Target vulnerability
 - A mechanistic PK/PD model
 - Covalent inhibitor of Btk

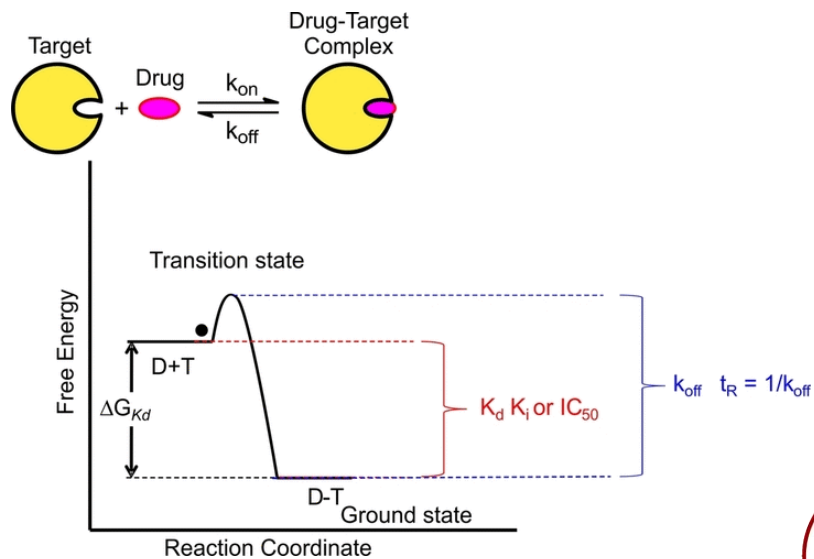


Use Drug-Target Kinetics to Predict In Vivo Drug Activity

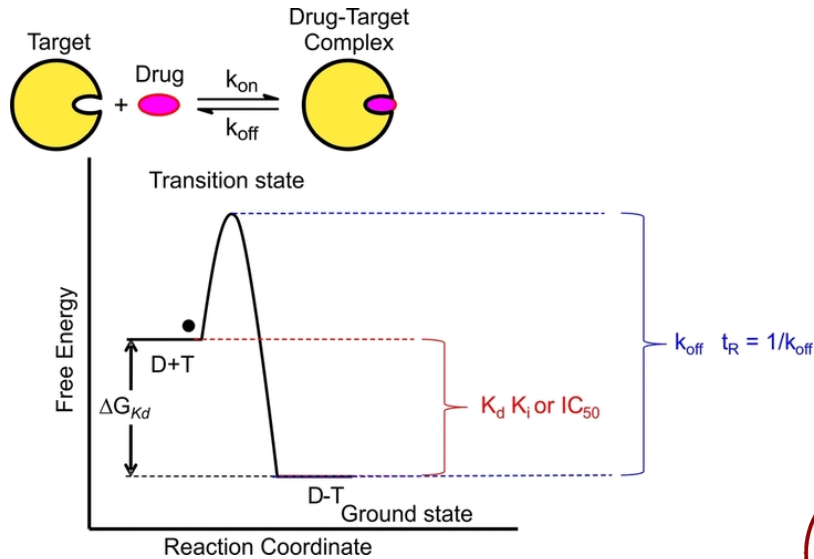
- Pharmacokinetic/Pharmacodynamic (PK/PD) models predict the effect time-courses resulting from administration of a drug dose



Models that Predict Drug Activity Assume Rapid Equilibrium

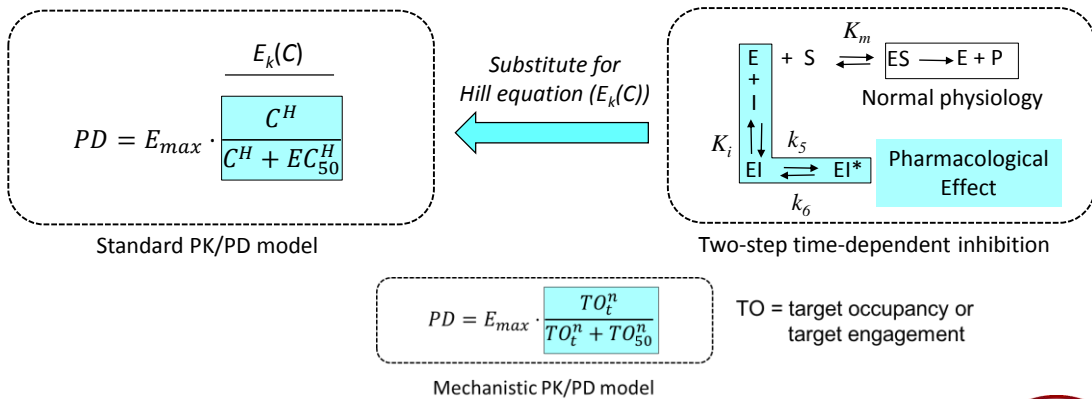


...but Binding and Dissociation may be Slow



Translate In Vivo: Mechanistic PK/PD Model

- Incorporate drug-target kinetics into predictions of drug activity
- $E_k(C)$: Replace Hill receptor binding (rapid equilibrium) with drug-target kinetics

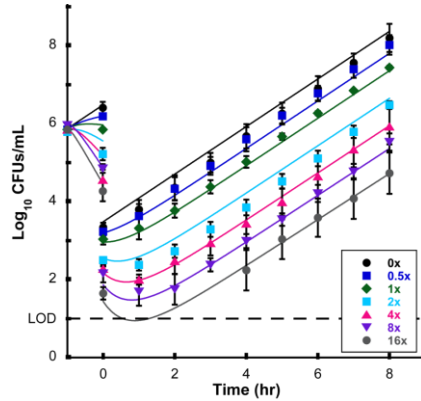
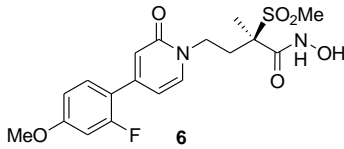


- Calculate target engagement as a function of [drug] (PK) and time
- Relate engagement to pharmacological effect to predict *in vivo* efficacy



paLpxC: Antibacterial Target in *P. Aeruginosa*

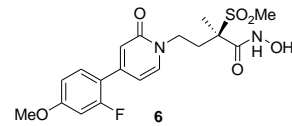
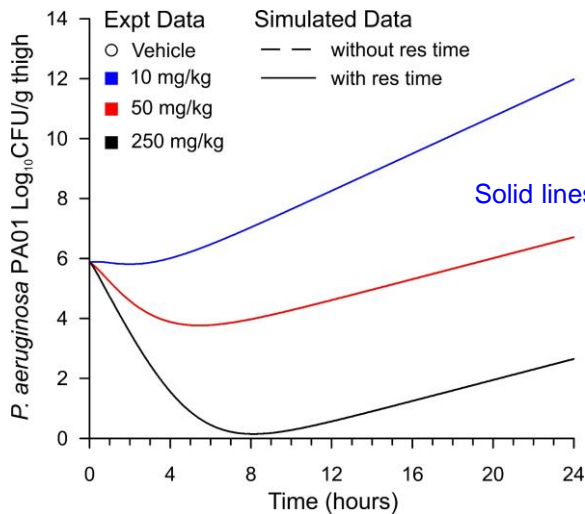
- *In vitro* experiments to obtain input parameters for PK/PD modeling
- Measure PAE at different initial [drug] and fit the *in vitro* PAE data to the PK/PD model



- **Output parameters:**
- k_5 , k_6 , K_i , $M (=K_m/[S])$, k_{growth} , k_{kill} and drug permeability
- Used for simulating *in vivo* activity



Predict *In Vivo* PAE: *P. aeruginosa*

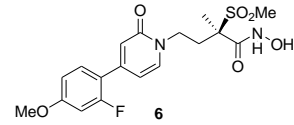
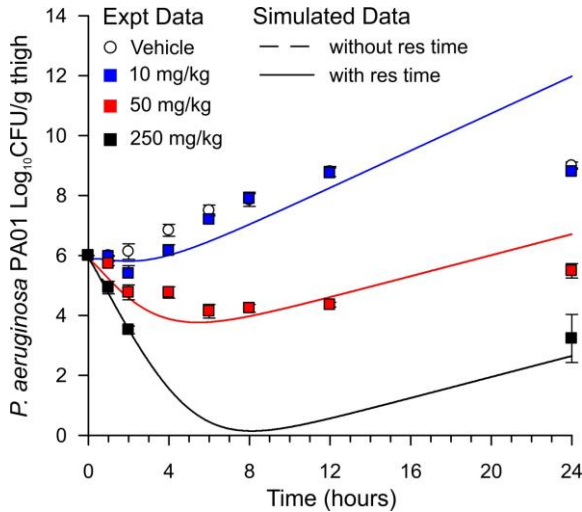


Solid lines are simulated activity from the PK/PD model

Walkup et al Nat Chem Biol 2015



Predict *In Vivo* PAE: *P. aeruginosa*



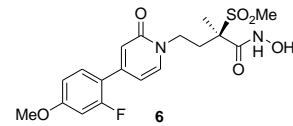
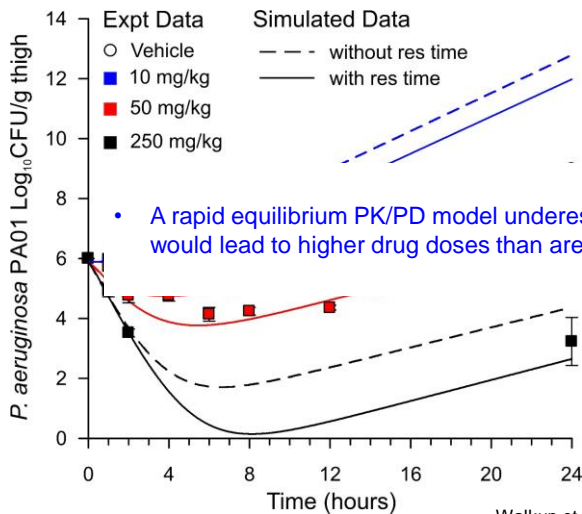
- What if we assume rapid equilibrium like the Hill receptor model
- No residence time effects included in the modeling?

Walkup et al Nat Chem Biol 2015

- Excellent prediction of *in vivo* bacterial growth observed with cpd 6



Predict *In Vivo* PAE: *P. aeruginosa*



- What if we assume rapid equilibrium like the Hill receptor model
- No residence time effects included in the modeling?

Walkup et al. (2015) Nat Chem Biol 11, 416-423.

- Excellent prediction of *in vivo* bacterial growth observed with cpd 6.



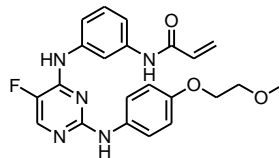
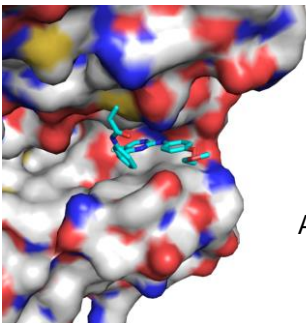
Direct Measurement of Target Occupancy

- The mechanistic PK/PD model calculates **target occupancy as a function of time and [drug]** and **predicts PD based on target occupancy**
- **In a system with irreversible inhibitor:**
 - Target occupancy (TO) can be directly quantified
 - The role of target turnover can be directly assessed



Bruton's Tyrosine Kinase (Btk)

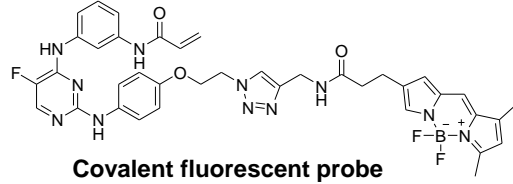
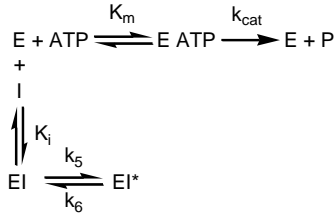
- Non-receptor tyrosine kinase in the B-cell antigen receptor (BCR) signaling pathway
- Target for treating B cell malignancies and autoimmune diseases
- Irreversible inhibitors such as ibrutinib and [CC-292](#)



Acrylamide warhead forms a covalent bond with Cys-481



Btk: TO and Predicting Efficacy of CC-292



- Need estimates of K_i , k_5 ($k_6 = 0$), ρ (turnover) and M ($= K_m/[\text{ATP}]$)
- We can measure TO directly in the cell using a covalent probe
- Quantify K_i for cellular BTK engagement using extracellular [drug]
- Permeability factor no longer needed
- Ratio of K_i for pure Btk and cellular $K_i = 80$
- Predict efficacy of CC-292 in rat collagen-induced arthritis model using CC-292 PK

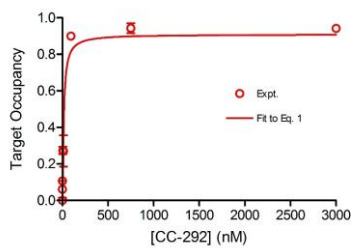
Daryae et al Chem Sci 2017



K_i , k_5 , ρ and M

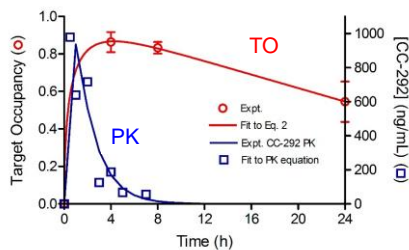
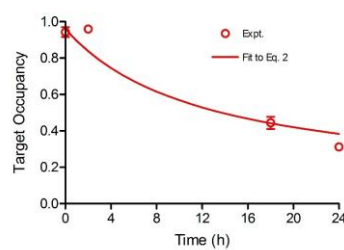
Measure TO in Ramos cells at equilibrium:

K_i and k_5



Measure time-dependent TO in Ramos cells:

ρ (turnover) and M



Measure time-dependent TO in B cells (rat):

obtain optimized kinetic values

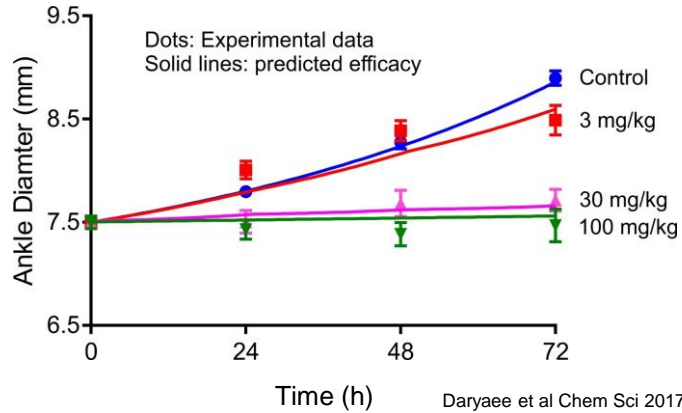
Compare **TO** with **PK**

Daryae et al Chem Sci 2017



CC-292 Rat Collagen Induced Arthritis Model

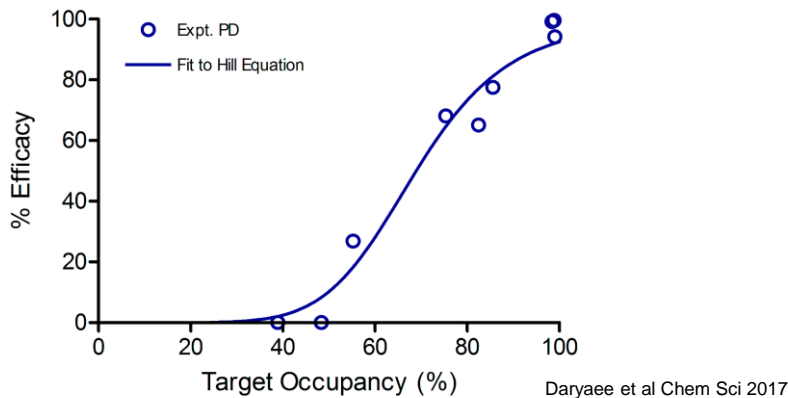
- The model accurately predicts CC-292 efficacy
- Determine the Btk vulnerability function



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Btk Vulnerability

- $TO_{50} = 69\%$ and Hill coefficient = 7
- Btk has to be >50% occupied for any PD and 90% for maximum PD
- The Hill coefficient of 7 indicates a steep response



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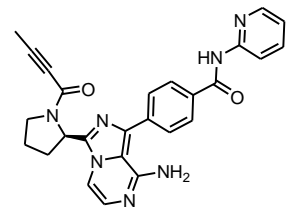
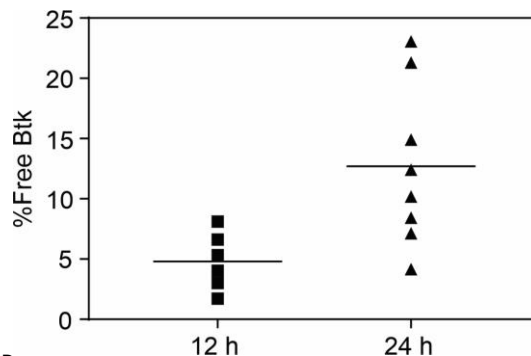
The Vulnerability Function Can Be Used for Other Inhibitors

- If the binding kinetics and PK are known, then the vulnerability function can be used to predict the activity of other Btk inhibitors, both covalent and reversible, in the same disease model
- Further translation requires a vulnerability function in the disease state and information such as the rate of target turnover
- We have modeled the occupancy of several Btk inhibitors in animal models and in humans including the covalent inhibitor acalabrutinib
- Recent data on acalabrutinib suggest the importance of target turnover..



In Vivo Btk Occupancy and Target Turnover

- Variability of Btk occupancy in patients with chronic lymphocytic leukemia (CLL) treated with acalabrutinib is proposed to result from differences in Btk synthesis rates across subjects.
- 12 h: 100 mg BID (twice per day) of acalabrutinib on day 3 of treatment, 12h after dose.
- 24 h: 200 mg QD (once per day) of acalabrutinib on day 3 of treatment, 24h after dose.



Summary 2

- **Cellular washout:** insight into time-dependent drug activity
- **Target vulnerability:** what fraction of target must be inhibited for desired PD
 - Use cell washout experiments to assess translational potential
 - Target (re)synthesis
 - The physiological response to target engagement
 - Vulnerability may be context dependent
 - For a low vulnerability target you need good PK/safety
- **To take advantage of kinetic selectivity** (e.g. for a covalent inhibitor) **you need:**
 - Relatively high vulnerability, slow resynthesis
 - 'Good' PK: Sufficient C_{max} to load the target but then rapid elimination
- **Include drug-target kinetics in a mechanistic PK/PD model to improve the prediction of PD**
 - Target vulnerability functions predict efficacy if binding kinetics and PK are known



Drug-Target Kinetics: An Additional Dimension of Information

- **Two types of selectivity:** kinetic and thermodynamic
 - But IC_{50} measurements dominate biological SAR (don't use for irreversible inhibitors!)
 - Most programs only use thermodynamic selectivity (e.g. kinase panels) to make decisions
- **Target occupancy is controlled by both drug and target concentration as well as by both thermodynamic and kinetic parameters**
 - Prolonged occupancy can result from rebinding rather than slow dissociation
 - Target mediated drug disposition
- **Methods to quantify target engagement in cells/*in vivo* will improve PK/PD models**
 - Cellular binding kinetics, nanoBRET; PET imaging
- **Rational approaches to altering drug-target kinetics need GS and TS structures**
- **Drugs with prolonged activity after drug has been eliminated:** lower/less frequent doses, improved compliance, increased therapeutic window



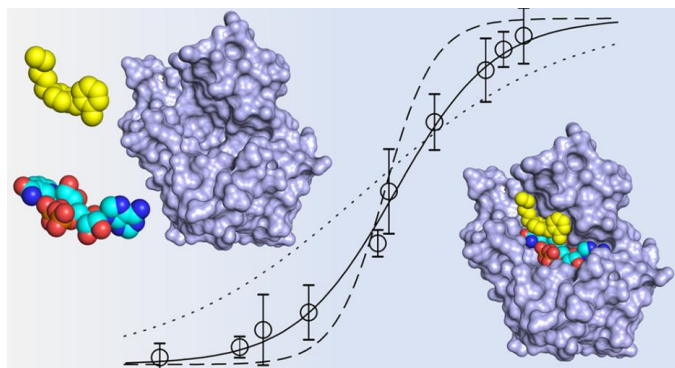
Stony Brook: Center for Advanced Study of Drug Action (CASDA)

- **Which targets are suitable for kinetic selectivity?**
 - Need data on additional systems: collaborations, academic/industrial partnerships
- **Use kinetics prospectively**
 - Develop methods to calculate on and off rates and rationally alter residence time
 - Develop target vulnerability functions
- **Rescue programs/drugs using kinetic selectivity**
- Develop methods to **non-invasively interrogate target engagement** and **extend into humans**
- **Positron emission tomography radiotracers**
- Preclinical and clinical **radiochemistry/imaging facilities** at Stony Brook



Perspective in *ACS Infectious Diseases*

- Tonge, (2019) **Quantifying the Interactions between Biomolecules: Guidelines for Assay Design and Data Analysis.** In press.



Abstract

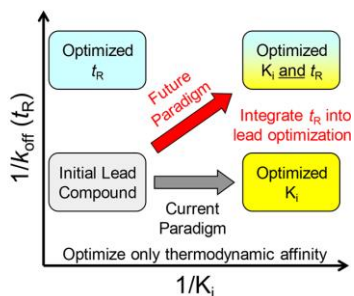
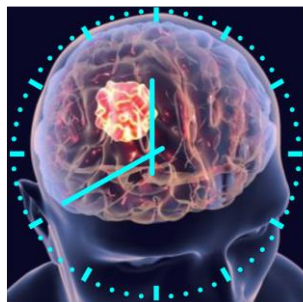
The accurate and precise determination of binding interactions plays a central role in fields such as drug discovery where structure–activity relationships guide the selection and optimization of drug leads. Binding is often assessed by monitoring the response caused by varying one of the binding partners in a functional assay or by using methods where the concentrations of free and/or bound ligand can be directly determined. In addition, there are also many approaches where binding leads to a change in the properties of the binding partner(s) that can be directly quantified such as an alteration in mass or in a spectroscopic signal. The analysis of data resulting from these techniques invariably relies on computer software that enable rapid fitting of the data to nonlinear multiparameter equations. The objective of this Perspective is to serve as a reminder of the basic assumptions that are used in deriving these equations and thus that should be considered during assay design and subsequent data analysis. The result is a set of guidelines for authors considering submitting their work to journals such as *ACS Infectious Diseases*.

<https://pubs.acs.org/doi/10.1021/acsinfecdis.9b00012>



Review in ACS Chemical Neuroscience

- Tonge, (2018) Drug-Target Kinetics in Drug Discovery. 9, 29-39.



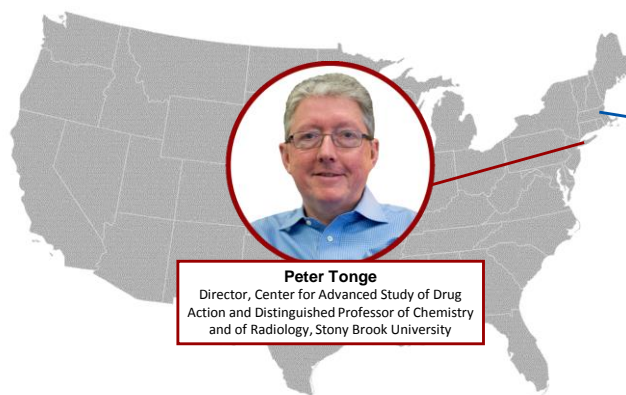
Abstract

The development of therapies for the treatment of neurological cancer faces a number of major challenges including the synthesis of small molecule agents that can penetrate the blood-brain barrier (BBB). Given the likelihood that in many cases drug exposure will be lower in the CNS than in systemic circulation, it follows that strategies should be employed that can sustain target engagement at low drug concentration. Time dependent target occupancy is a function of both the drug and target concentration as well as the thermodynamic and kinetic parameters that describe the binding reaction coordinate, and sustained target occupancy can be achieved through structural modifications that increase target (re)binding and/or that decrease the rate of drug dissociation. The discovery and deployment of compounds with optimized kinetic effects requires information on the structure-kinetic relationships that modulate the kinetics of binding, and the molecular factors that control the translation of drug-target kinetics to time-dependent drug activity in the disease state. This Review first introduces the potential benefits of drug-target kinetics, such as the ability to delineate both thermodynamic and kinetic selectivity, and then describes factors, such as target vulnerability, that impact the utility of kinetic selectivity. The Review concludes with a description of a mechanistic PK/PD model that integrates drug-target kinetics into predictions of drug activity.

<https://pubs.acs.org/doi/10.1021/acchemneuro.7b00185>



Widening the Therapeutic Window: Kinetic Selectivity and Target Vulnerability



Peter Tonge
Director, Center for Advanced Study of Drug Action and Distinguished Professor of Chemistry and of Radiology, Stony Brook University

Stewart Fisher
Chief Scientific Officer, C4 Therapeutics

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Nathan Tupper - Pfizer Ariel Sanner - Seattle Genetics</p> <p>Nucleic Acids Therapeutics: Making Sense of Antisense Oligonucleotides Ruth Sarn - Ionis Richard Ooper - BMS</p> <p>Cryoelectronography as a Drug Design and Delivery Tool (Special Topic) Robert Hancock - Crystal Pharmacia Vincent Spill - Abbvie Andrew Burdick - Merck</p> <p>III - Pharmacology Revisited</p> <p>Dealing with Reactive Drug Metabolites in Drug Discovery: Can We Predict Toxicities of Drug Candidates that form Reactive Metabolites? Debbie Davis - Pfizer Priscilla Patel - Guangzhou - Vanderbilt University</p> <p>Rational Design of Small Molecules Targeting RNA Mati Deryn - Scripps RI Florida Almaza Garner - University of Michigan</p> <p>Cell Penetrating Peptides to Improve Cellular Drug Uptake Dehua Pei - The Ohio State University Justin Mann - Bristol-Myers Squibb</p>	<p>I - Fighting Cancer</p> <p>Fighting Cancer: Targeting Cdk5 Malignancy with Kinase Inhibitors Timothy P. McElroy - Genentech Mark Williams - Bristol-Myers Squibb</p> <p>Fighting Cancer: Epigenetic targets for Oncology Suzett Conroy - Oxford Sharan Bagai - AstraZeneca</p> <p>Fighting Cancer: Allostery and Targeting Cancer Cell Metabolism Stefan Gross - Agos Scott Edmundson - AstraZeneca</p> <p>Special Broadcast:</p> <p>Cure Through Discovery of CPTM Modulators Peter Doppmann - Vertex Nick Meehan - Bristol-Myers Squibb</p> <p>II - Anti-infectives</p> <p>Anti-infectives: Rational Approaches to the Design and Optimization Jason Sells - Brown University Courtney Adkin - University of Minnesota</p> <p>Tuberculosis: An Introduction for Medical Chemists Carl Nathan - Hoffmann-La Roche Christopher Boyce - Merck</p> <p>Special Broadcast:</p> <p>Viral Inhibitors: The Search for a Cure Mike Scola - AstraZeneca Stephan Mason - Cardion Corporation</p> <p>Special Broadcast:</p> <p>Small Molecule Anticancer Kevin Hedges - Harvard Medical School Alyson Westermann - ACS Publications</p> <p>III - Immunology</p> <p>Peptidic Treatment and Novel Approaches Rami Nard - AstraZeneca John Morrison - Bristol-Myers Squibb</p> <p>Lipid Treatment and Novel Approaches Laurence Menard - Bristol-Myers Squibb Mary Bruchers - Bristol-Myers Squibb</p>	<p>A New Strategy in Drug Discovery: Protein-Induced Protein Degradation Jan Churher - Biogen/Illinois Aaron Baig - Bristol-Myers Squibb</p> <p>Women in Drug Discovery and Development: How to Succeed as a Female in Academia and Industry Annette Slav - AstraZeneca Danna Murray - University of Pittsburgh Eric Arango - Bristol-Myers Squibb NurJahan Zaman - AstraZeneca Therapeutics</p> <p>A Nanomedicine Overview for mRNA Delivery: Innovative Methods Using Lipid Nanoparticles Naravane Venk Anand - AstraZeneca Dennis Luong - Genentech</p> <p>Nanomaterials for Fighting Antibiotic Resistant Bacteria and Mitigating Resistance Christopher Christ - American Chemical Society</p> <p>Advanced Nano-Delivery Systems: Facilitating Tumor Delivery and Mitigating Resistance Manoor Anji - Northeastern University Venkat Krishnamurthy - AstraZeneca</p> <p>Methods and Promises of Central Nervous System Drug Discovery Yipeng Gong - Hoffmann-La Roche Nicholas Meemwell - Bristol-Myers Squibb</p> <p>How to Optimize Central Nervous System Therapeutics: Med Chem Strategies, Tactics, and Workflows Craig Lindley - Vanderbilt Center for Neuroscience Drug Discovery Amy Newman - Hoffmann-La Roche Research Program, Inc.</p> <p>A Novel Strategy for the Treatment of Chronic Pain: Antagonizing PAR2 with a Monoclonal Antibody Paul Thomson - AstraZeneca NurJahan Zaman - AstraZeneca Therapeutics</p> <p>How to Predict Human CNS PK/PD: Preclinical Experiments and Advanced Mathematical Modelling Elizabeth De Lange - Linden Academic Center for Drug Research Alexander Troshch - University of North Carolina</p> <p>Human Exosome: An Ideal Vehicle for Delivery of Therapeutic RNA to Cells and Organs Hadi Valad - University of Gothenburg Alexander Kapustin - AstraZeneca</p>

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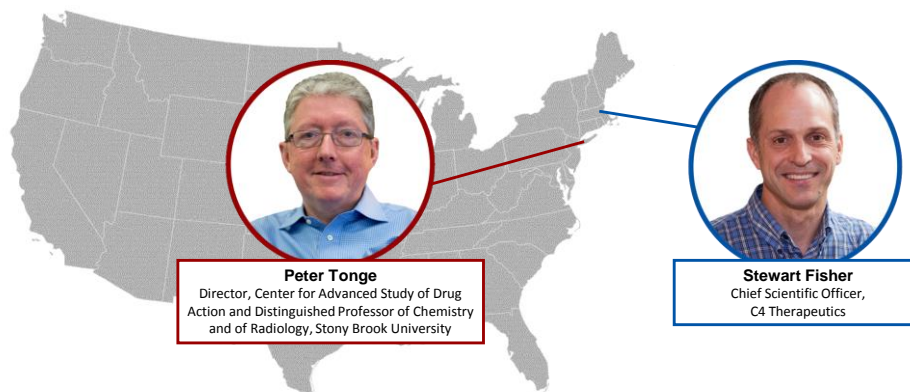
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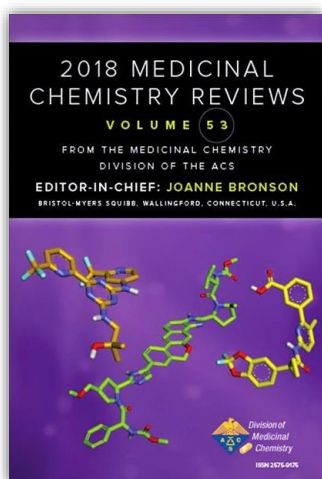



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