Binding Kinetics: Enhancing the Efficiency and Effectiveness of Drug Discovery and Development
Outline

• Binding Kinetics Basics and the Current Drug Discovery/Development Paradigm
• Show me the Money: Examining successful medicines on the market
• A Different Approach: Mechanism Matters/Molecular Mechanism of Action
Binding Kinetics Basics and the Current Drug Discovery/Development Paradigm
Traditional Target-based drug discovery
one size fits all/optimization by affinity

1. Target Identification
2. Screen for binders
3. Optimized for affinity
4. Check for pharmacological activity
5. Optimize drug-like properties and safety
6. Clinical testing

Target defines the mechanism
Affinity defined by binding kinetics: 
*Affinity is ratio of the association and dissociation rate constants*

- Binding kinetics are the rate of association, $k_{on}$ and dissociation, $k_{off}$

- At equilibrium, binding kinetics are captured by equilibrium dissociation constant ($K_I = k_{off}/k_{on}$)

- $K_I$ represents the intrinsic affinity for a molecular interaction
At equilibrium, competition reduces response due to affinity

*Competition increases the amount of drug required for activity*

- $IC_{50}$ relationship to affinity ($K_I$) depends on the binding mechanism
  - $IC_{50}$ is an operational term
  - Competitive inhibition $IC_{50}/K_I = 1 + [S]/K_m$

Substrate competition shifts dose response curve to higher dose

$IC_{50}$=concentration for 50% inhibiton

$S$=substrate

$K_m$=substrate affinity

+competing substrate
Fast and Slow Kinetics
At non-equilibrium, outcomes from binding kinetics depend on competing rates

• Definition of ‘fast’ and ‘slow’ with regard to binding kinetics is only relative to a competing rate
  – A turtle could be fast in comparison to a snail
• For example: a 10-min dissociation half-life is…
  – …very fast when the competing rate is elimination of medicine from the body with a half-life measured in hours
  – …very slow when the competing rate is opening and closing of a channel with a half-life measured in milliseconds
Binding kinetics at non-equilibrium

Slow kinetics can change the apparent mechanism of action

No competition
Drug effective at lower dose

+ competing substrate

Similar to irreversible inhibition, also known as insurmountable
Advantages of slow kinetics

- Change the mechanism
- Increase affinity
- Increase selectivity
- Increase therapeutic index
- Lower drug levels provide increased safety
- Increase duration of action
  - Pharmacodynamics outlast pharmacokinetics
Slow kinetics can improve selectivity
Slow-kinetics generally involve multi-step processes that increase selectivity.

- This is the mechanism of selectivity of the COX2 selective inhibitors

**On-target**

\[ E + I \xleftrightarrow{} EI \xleftrightarrow{} E*I \]

**Off-target**

\[ E + I \xleftrightarrow{} EI \]
Show me the Money: 
Examining successful medicines on the market
What are the features of successful medicines. 
*Observations from three studies*

Study 1. Successful medicines have mechanisms to achieve good biochemical efficiency

*Study 2. Successful medicines have multiple diverse Molecular Mechanisms of Action*  

Study 3. First in class medicines discovered in phenotypic assays; molecular mechanism of action is a key variable

*Swinney & Anthony, submitted (2010)*
Biochemical efficiency
Successful medicines efficiently couple binding to function

Biochemical Efficiency (BE)
Describes how efficient molecular interactions translate to a specific functional response
= binding affinity/functional response
= $K_I/EC_{50}$
-good BE enables efficacy at lower drug concentrations
-good BE increases therapeutic index
-good BE a property of many approved medicines

Biochemical efficiency a metrics for success
– A study of 50 medicines showed the percentage of marketed drugs with biochemical efficiency >0.4 maybe as high as 76%.

Biochemical efficiency is increasingly used as a metrics for decision making.
– To move compounds forward
  • Urotensin-II receptor antagonists/GSK Br J Pharmacol 161, 207 (2010)

– To terminate a program
  • MK2 inhibitors/Pfizer JPET 333, 797 (2010)
Mechanisms of successful medicines

Majority of approved medicines have competitive mechanisms of action

- All medicines approved by US FDA 4 year period 2001-2004
  - 70% competitive

We asked ourselves

How do these medicines avoid the potential pitfalls associated with competition?

Swinney Cur Topics Med Chem 6, 461 (2006)
Molecular Mechanisms of Action

*Market drugs use different molecular mechanisms*

- Equilibrium-response from concentration dependent binding
- Non-equilibrium-response driven by competing rates
- Conformation-response driven by shape/conformation of interactions

*Mechanism of approved drugs*

*Pitfalls of competition avoided by molecular mechanisms of Action that efficiently couple binding to desired response*
## Molecular Mechanisms of Action.

*Marketed drugs use many different binding mechanisms.*

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>NMEs</th>
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<tbody>
<tr>
<td><strong>conformational change</strong></td>
<td><strong>Agonist</strong>- almotriptan, apomorphine, eletriptan, formoterol, frovatriptan, travoprost&lt;br&gt;<strong>Partial agonists</strong>- tegaserod, aripiprazole&lt;br&gt;<strong>Active antagonist</strong>- eplerenone, fulvestrant, pegvisomant&lt;br&gt;<strong>Conformational inhibition</strong>- fondaparinux, gemifloxacin, imatinib, pimecrolimus, epinastine, enfuvirtide&lt;br&gt;<strong>Allosteric/noncompetitive</strong>- rifaximin, cinacalcet, <strong>Uncompetitive-like</strong>- tadalafil, vardenafil, memantine</td>
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<td><strong>non-equilibrium</strong></td>
<td><strong>Chain termination</strong>- adefovir, emtricitabine, telithromycin, tenofovir&lt;br&gt;<strong>Irreversible</strong>- azacitidine, cefditoren, dutasteride, ertapenem, nitisinone&lt;br&gt;<strong>Slow dissociation</strong>- bortezomib, rosuvastatin, valdecoxib, aprepitant, desloratadine, olmesartan, tiotropium, duloxetine, palonosetron, oxaliplatin</td>
</tr>
<tr>
<td><strong>equilibrium</strong></td>
<td><strong>Competitive</strong> atazanavir, erlotinib, ibandronate, gefitinib, miglustat, seraconazole, voriconazole, abarelix, alfuzosin, bozantan, solifenacin, atomoxetine</td>
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</tbody>
</table>
How were new medicines discovered?

*First in class discovered using phenotypic assays*

- Total NMEs: **239**
- Novel NMEs (1\textsuperscript{st} in class, novel MoA, new targets): **55**
- Discovery strategies
  - Target-based- **15**
  - Phenotypic- **25**
  - Modified natural substances- **15**

**Followers discovered primarily via target-based strategies**
Target-based discovery

Target alone rarely sufficient...effective MMoA must be identified

• Kinase inhibitors imatinib and sunitinib binds to inactivated conformation of the enzyme form

• Maraviroc/CCR5 allosteric modulator induces receptor conformation that reduces interaction with HIV-1 GP-120

• Raltegravir/integrase interacts with a conformational intermediate (interfacial inhibition)
A Different Approach: Mechanism matters
New Algorithm
Account for MMoA in optimization

1st in class

1. Identify starting point/phenotypic assays
2. Optimize for efficacy according to MMoA
   - Equilibrium affinity
   - Kinetics \textit{iRND3}
   - Conformation
3. Evaluate biochemical efficiency
4. Optimized for drug-like properties and safety
5. Clinical testing

Followers

1. Optimize for efficacy according to MMoA
   - Equilibrium affinity
   - Kinetics \textit{iRND3}
   - Conformation
2. Evaluate biochemical efficiency
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Molecular Mechanism Matters for discovery

Mechanism matters

Drug development is a risky business. According to the US Food and Drug Administration (FDA), only eight percent of drugs that enter clinical trials are eventually approved. For a drug to gain FDA approval, it must be safe and show some efficacy. Because the FDA does not require any understanding of the mechanism by which a drug acts, it could be tempting to move into clinical trials without this knowledge. However, this may set the stage for failure. An investigational Alzheimer’s disease drug called Dimebon is a case in point.

It is true that we use many highly prescribed drugs without a clear idea of how they work—which targets they hit, what processes they alter and which of these actions are required for therapeutic efficacy. For instance, lithium, used to treat bipolar disorder, modulates many molecular targets, but which—or how many—of these are required for its beneficial effects is uncertain. Nevertheless, understanding a drug’s mechanism could guide drug development and help to prevent late-stage failures such as Dimebon’s.

Knowledge of a drug’s mechanism of action enables better dosing.

Volume 16 April 2010 pg 347
Translation of structure to functional response. 
*Contribution of both target and MMoA.*

Drug + target ⇌ Drug:target → response

- **Association rate**
- **Dissociation rate**
- **Fraction bound**
- **Residence time**

**DMPK**
- absorption
- clearance
- protein binding

**Coupling factors**
- Conformation
- Equilibrium
- Non-equilibrium

**MMoA includes both the target and the mechanism of communication with physiology**
Example of the contribution of target and MMoA to response.

**MMoA differentiation of aspirin and ibuprofen.**

- Aspirin and ibuprofen bind to the cyclooxygenase 1 and 2 active sites.
- Aspirin irreversible inhibitor.
  - Irreversible action of aspirin in platelets leads to long lasting anti-thrombotic effects
  - Platelets do not have the capacity to resynthesize new protein
  - Effective for prevention of atherothrombotic disease
- Ibuprofen and other NSAIDS are reversible
Why is MMoA important?
MMoA will affect the therapeutic index.

No Mechanism based toxicity

- hit target as hard as possible
- increased efficiency
- results in lower concentrations of drug
- increase therapeutic index
  - full agonist
  - irreversible inhibitors
  - insurmountable antagonists
  - noncompetitive inhibitors
  - slow dissociation

Mechanism-based toxicity

- MoA can provide opportunity to differentiate efficacy from mechanism-based toxicity.
  - rapidly reversible inhibitors
  - uncompetitive
  - partial agonists
  - functionally selective receptor modulators
  - use dependent channel blockers

At non-equilibrium, competing rates can change the MMoA provide irreversible behavior that increases efficacy

- Mechanisms of complete inhibition
  - Concentration dependent occupancy (functionally competitive)
  - Irreversible (functionally noncompetitive)
  - Insurmountable: Reversible slow-dissociation in non-equilibrium system (functionally noncompetitive)

- Many drug classes have evolved to provide irreversible or insurmountable inhibition when there is no mechanism-based toxicity
  - Angiotensin receptor antagonists, anti-histamines, anti-muscarinics
Medicines with slow or irreversible binding kinetics. 
*They are discovered in many therapeutic areas*

- **Slow dissociation reversible (t\(_{1/2}\))**
  - Amlodipine (77 min) hypertension
  - Aprepitant (154 min) emesis
  - Buprenorphine (166 min) pain
  - Candesartan (11.5 h) hypertension
  - Darunavir (>240h) antiviral
  - Desloratadine (>6 h) antihistamine
  - Efavirenz (4.1 h) antiviral
  - Lapatinib (300 min) anticancer
  - Maraviroc (10.5 h) antiviral
  - Olmesartan (72 min) hypertension
  - Oseltamivir (33-60 min) antiviral
  - Raltegravir (6.7 min) antiviral
  - Saxagliptin (5.1 h) diabetes
  - Telaprevir (2.9 h) HCV (phase III)
  - Tiotropium (34.7 h) COPD

- **Irreversible**
  - Aspirin; anti-platelet
  - Azacitidine; anticancer
  - Cefditoren; antibiotic
  - Celecoxib; RA
  - Clavulanic acid, Sulbactam, tazobactam; β-lactamase inhibitors
  - Finasteride; BPH
  - Formestan; anticancer
  - Omeprazole, Lansoprazole; GERD
  - Orlistat; obesity
  - Penicillin; antibiotic
  - Procarbazine; lymphoma
  - Selegiline, Tranylcypromine; depression
  - Ticlopidine, clopidogrel, prasugrel; ant-platelet
  - Vigabatrin; epilepsy
Example: Angiotensin II receptor blockers
slow binding kinetics provide pharmacodynamic advantage

- Comparative pharmacodynamics and pharmacokinetics of candesartan and losartan in man.  
  - Candesartan:
    - slow dissociation,
    - insurmountable,
    - dissociation t_{1/2} 112 min
  - Losartan:
    - fast dissociation,
    - surmountable,
    - dissociation t_{1/2} 2.5 min
  - Pharmacokinetic profile similar
  - Similar antagonist activity in plasma measured by radioreceptor assay

The pharmacodynamic effect of candesartan was more effective than losartan, despite equivalent angiotensin II antagonistic activity in plasma.
A helping hand: How can iRND3’s approaches be leveraged
Binding kinetics as a drug discovery tool

*Provide efficient MMOAs*

- Application of slow-kinetics (not applicable to all targets)
  - No mechanism-based toxicity
  - Communication affected primarily by residence time versus conformation
  - System not at equilibrium
    - Irreversible
    - Insurmountable (slow dissociation in non-equilibrium system)
  - MMOA identified
Drug discovery process:
*iRND3 can add value to target validation and lead optimization*

<table>
<thead>
<tr>
<th>Target</th>
<th>LI</th>
<th>LO</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
</table>

**Where iRND3 can add value.**

- Phenotypic screens, Target selection
- Hit/MoA validation
  - use irreversible
  - use biochemical efficiency
- Develop irreversible
- Morph to Slow off
- not validated

**lead** | **potency** | **ADME** | **safety** | **Clin cand**