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Thursday, May 7, 2015

"Science, Skepticism, and Knowledge: Three Tools for the Practicing Chemist"

David Ball, Professor of Chemistry, Cleveland State University
David Harwell, Assistant Director of Industry Member Programs, ACS

Thursday, May 14, 2015

"Evidence from the Smoking Gun: Organic Components of Gunshot Residue"

Suzanne Bell, Associate Professor, West Virginia University
Raychelle Burks, Postdoctoral Research Associate, Doane College

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AAPS/DDDI Regional Meeting

Drug Discovery Paradigm Shift?
Strategies to Improve Science, Timelines and Clinical Candidate Quality

Friday, May 29th, 2015 (8:00am-4:30pm)
Merck & Co., Upper Gwynedd, Pennsylvania

Expert speakers from the pharmaceutical field share views on drug design, discovery and early development in the areas of:
Medicinal Chemistry, Discovery Biology, Pharmacology, Pharmacokinetics, Pharmacodynamics, Drug Metabolism, Pharmaceutical Sciences and Toxicology

Speakers Include:
Nick Meanwell, Executive Director, Bristol-Myers Squibb
Caroline McGregor, Executive Director, Merck
Handan He, Director, Novartis

Website: http://www.aaps.org/DDDIRM15/
Registration: $100 for AAPS members, $150 for non-members

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2015 Drug Design & Delivery Symposium

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Module 1: Improving Drug Design Efficiency and Efficacy		
Jan 29	Designing Better Drug Candidates	*Dr. Paul Leeson*
Feb 26	Strategies to Improve Solubility of Drug Candidates	*Dr. Michael Walker*
Module 2: Activity/Potency Screening for Drug Lead & Candidate Optimization		
Mar 19	Fragment-Based Drug Design Strategies	*Dr. Dan Erlanson*
April 30	Screening Strategies	*Dr. David Swinney*
May 28	PAINS (Pan-Assay Interference Compounds)	*Dr. Jonathan Baell*
June 25	Positron Emission Tomography (PET) Labeling in Drug Discovery & Development	*Dr. Lei Zhang*
July 30	X-Ray Crystallography in Drug Discovery	*Dr. Jon Mason & Dr. Miles Congreve*
Module 3: Enabling Drug Discovery		
Aug 27	Choices and Trends in Solid Dosage Form Section	*Dr. Scott Trzaska & Dr. Ron Smith*
Sept 24	Delivery Options to Support Dose Escalation in Preclinical Toxicology and Pharmacodynamic Activity Studies	*Dr. Evan Thackaberry*
Module 4: Pharmacokinetics		
Oct 29	Pharmacokinetic Considerations in Drug Design and Development	*Dr. Punit Marathe*
Nov 19	Prodrugs in Drug Discovery	*Dr. John Higgins*

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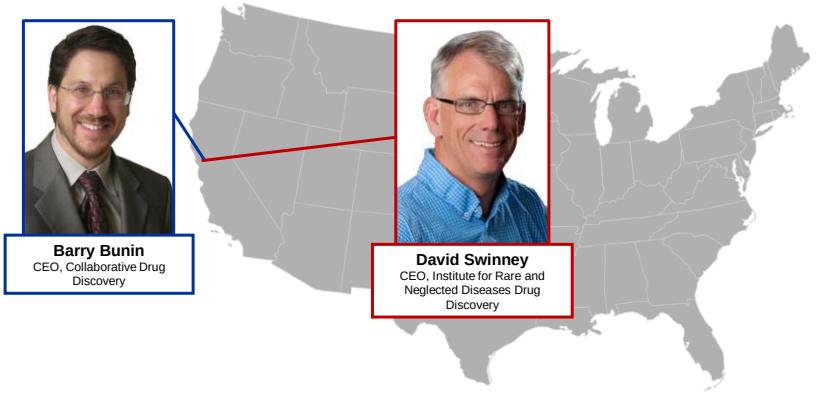
"2015 Drug Design and Delivery Symposium:
Picking the Right Screening Strategy"



Barry Bunin
CEO, Collaborative Drug Discovery

David Swinney
CEO, Institute for Rare and Neglected Diseases Drug Discovery

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Picking the Right Screening Strategy

2015 Drug Design and Delivery Symposium
April 30, 2015

Dave Swinney
Institute for Rare and Neglected Diseases Drug Discovery
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What You Will Learn

- Screening links basic research to medicines
- Choice of screening strategy depends on the available mechanistic knowledge
- Strategies will change for first-in-class versus advances-in-class

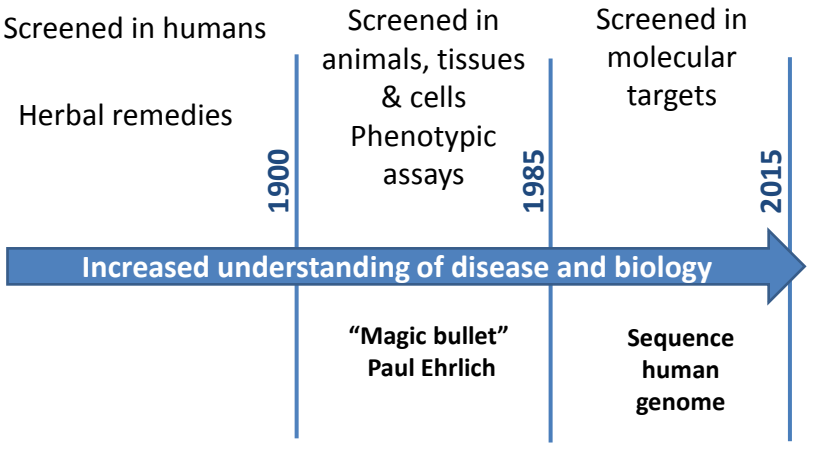
Outline

Part 1. Introduction/IC_{50}

Part 2. Molecular Mechanism of Action (MMOA)

Part 3. Phenotypic vs. Target Based Screening

Screening Identifies Active Compounds



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Considerations for Screening Strategies

- **Technical Considerations**
  - Assay formats
  - Source of reagents, cells, and tissues
  - Costs
- **Biologic/Medical Considerations**
  - Validation of biomarkers as predictors of clinical efficacy
  - Completeness of mechanistic understanding
  - Validation of targets
  - Source and properties of molecules to be screened
  - First in class vs advance in class.
  - Differentiation from other medicines
  - Site of action
  - Molecular descriptors
  - Polypharmacology

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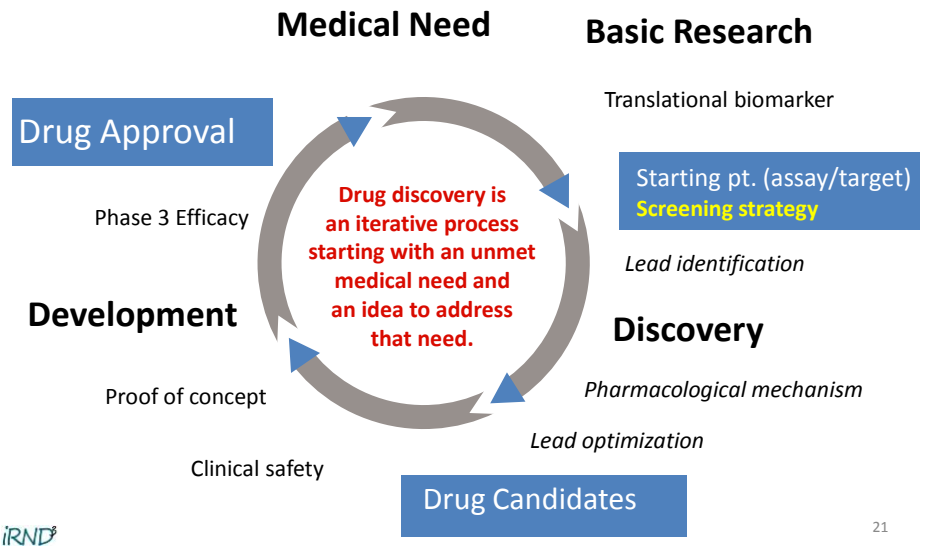
Screening is an Important Part of R&D Learn and Confirm Cycle



Screening Provides IC_{50}s (EC_{50}s) for Active Compounds

$E + I \underset{}{\overset{K_I}{\rightleftharpoons}} EI$

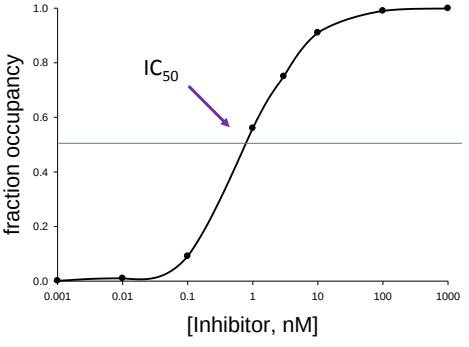
Fractional occupancy = $[I]/([I] + K_I)$

$\Delta G = -RT \ln (K_I)$

Assume one site binding

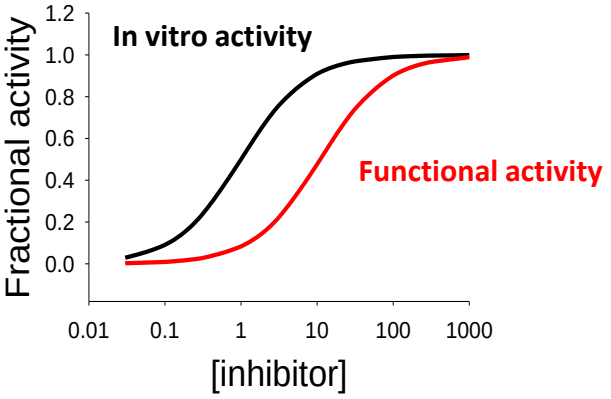
For K_I = 1 nM

[I, nM]	% Occupancy
0.1	9%
1	50%
3	75%
10	91%
100	99%



Dose Response Curves (IC_{50}) can Shift Between Assay Formats

Fractional Occupancy = Drug/(Drug + K_I)



In vitro- purified protein- **target**
Functional- cells, tissues, animals- **phenotypic**

Audience Survey Question

ANSWER THE QUESTION ON SCREEN

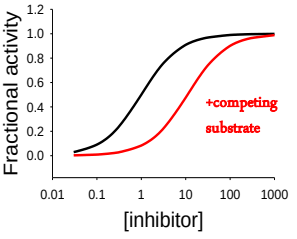
What are potential explanations for the shift in IC50 between target and phenotypic screening assays?

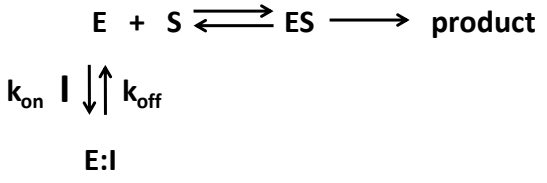
- ADME problems. Drug does not get into cells or tissues due to poor permeability, poor solubility or metabolism
- High serum protein binding
- The target is not correct for the phenotype
- The mechanism of action is not efficient
- All of the above

ADME- Absorption, Distribution, Metabolism, Excretion

Competition May Cause a Shift in Dose Response Curves Under Equilibrium Conditions

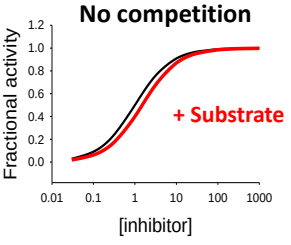
- IC_{50} relationship to affinity (K_I) depends on the binding mechanism
  - IC_{50} is an operational term
  - Competition shifts dose response curve
  - $IC_{50} = K_I (1 + S/Km)$

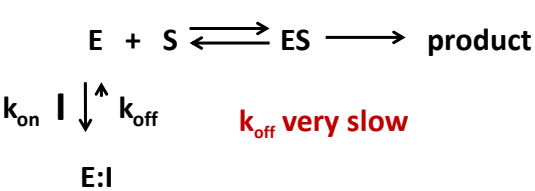




Slow Binding Kinetics can Limit Competition in Non-equilibrium Systems

- Irreversible
- Slow dissociation kinetics in non-equilibrium system
- Functionally irreversible (insurmountable)





k_{off} very slow

Mutations to EGFR Kinase Increase Affinity for ATP
- Decrease effectiveness of inhibitors because of equilibrium competition
- Next generation inhibitors limit competition with irreversible or slowly reversible binding kinetics

Part 2: Molecular Mechanism of Action (MMOA)

- **MMOA:** Biochemical mechanism through which the structural interactions between the drug and its target result in a functional response.
  - Includes **binding kinetic** and **conformational** changes that specifically provide a therapeutically useful response.

- **Differentiated from Mechanism of Action:** Systems definition of how a drug works
  - Anti-inflammatory
  - Anti-histamine
  - Anti-viral

MMOA-pharmacological hot spot

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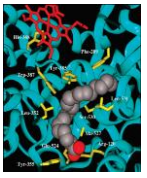
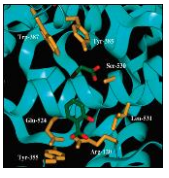
Aspirin and Ibuprofen: Two Medicines, One Target, Different Molecular Mechanisms, Different Uses

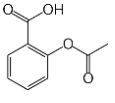
- **Aspirin has anti-platelet activity whereas NSAIDs do not**
  - Effective for prevention of atherothrombotic disease
- **Both bind to the active site of cyclooxygenase 1 and 2**
  - Aspirin irreversible inactivation via acetylation of Ser530
  - Ibuprofen and other NSAIDS are reversible
- **Irreversible action of aspirin in platelets leads to long lasting anti-thrombotic effects**
  - Platelets do not have the capacity to resynthesize new protein

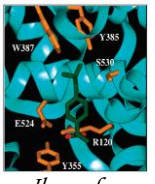


Substrate - arachidonic acid

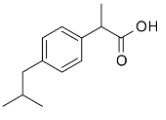


Aspirin





Ibuprofen



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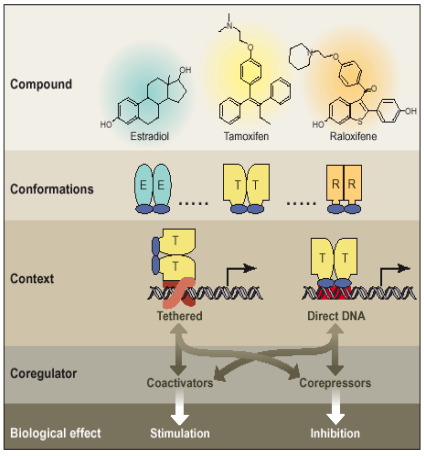
Estrogen Receptor Modulators
One Target, Different Molecular Mechanisms, Different Uses

Ligand induced conformational changes recruit coactivators and corepressors in a context specific manner.

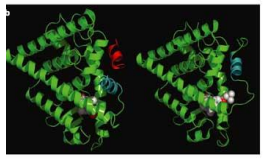


Brzozowski, AM et al Nature 389, 753 (1997).

Differentiated therapeutic use depends on unique ligand induced conformations.

- **Estradiol** agonist
  - ➢ postmenopausal hormone deficiency
- **Tamoxifen** SERM (selective estrogen receptor modulator)
  - ➢ breast cancer
- **Raloxifen** SERM
  - ➢ osteoporosis

ER ligand binding domain

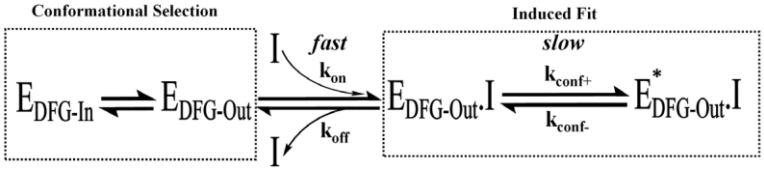


Nature Reviews | Drug Discovery

Molecular Mechanism of c-abl kinase Inhibitor, GleevecSelectivity Involves Induced Fit

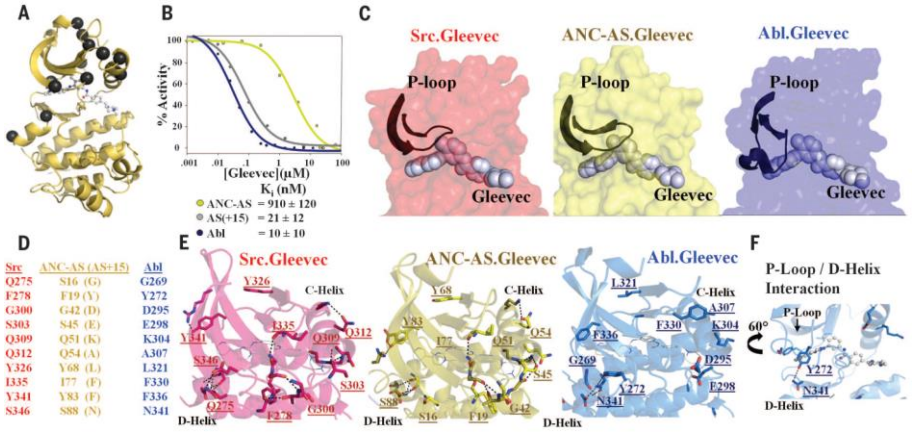
Using ancient protein kinases to unravel a modern cancer drug's mechanism

C. Wilson, R. V. Agafonov, M. Hoemberger, S. Kutter, A. Zorba, J. Halpin, V. Buosi, R. Otten, D. Waterman, D. L. Theobald, D. Kern. Science, 347, 882 (2015)



Gleevec affinity is gained by shifting an induced-fit equilibrium that is also disrupted in the clinical T315I resistance mutation.

Molecular Mechanism of c-abl kinase Inhibitor, GleevecSelectivity Involves Induced Fit



- The binding/unbinding step is similar between weak and strong binders
- Affinity and selectivity are provide by the induced fit step

Communication of Information as an Analogy of MMOA

- Proximity is rarely sufficient for effective sharing of specific information
- ***MMOA is a language to communicate specific information.***

Mechanistic Paradox

- **MMOA defines medicines utility by**
  - ➢ bridging between molecular interactions and physiology
  - ➢ Connecting genotype to phenotype
- **MMOA is difficult to *a priori* predict**

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Part 3. Target-based vs. Phenotypic

Definitions:

Phenotypic Screening - Any screening in which the molecular mechanism of action (MMOA) that provides a tolerable therapeutic index is not assumed.

- ➢ In this context the phenotypic screening is a synonym for **empirical** screening.
- ➢ Using this definition phenotypic screening includes all screening that is not target-based.

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Conclude the Value of Phenotypic Assays is to Discover New MMOAs which are Difficult to *a priori* Predict

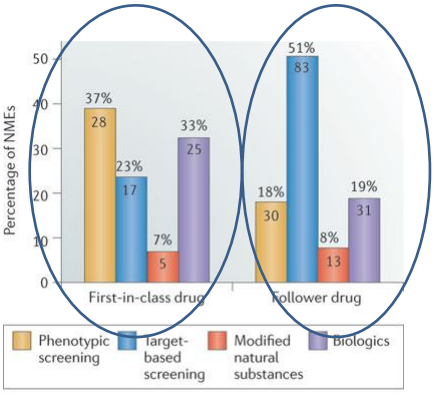
NMEs approved FDA 1999-2008
259 total
183 small molecules
20 imaging agents
56 therapeutic biologics

75 first in class
164 followers

The majority of small molecule

-**first in class** medicines were discovered with **phenotypic** strategies (28 to 17)

-followers were discovered with **target-based** strategies (83 to 30).



Nature Reviews | Drug Discovery

iRND3 *Swinney & Anthony NRDD, 10, 507, 2011*

NME- new molecular entity

Audience Survey Question

ANSWER THE QUESTION ON SCREEN

Which of the following statements is TRUE with respect to the MMOAs of new NMEs?

- The mechanisms for many medicines are unknown
- There are many diverse MMOAs discovered in a number of different screens
- Both are true
- Both are false

NME- new molecular entity

Successful Mechanism and Screening Strategies

Mechanisms of Approved NMEs

- Reversible, irreversible, competitive, noncompetitive, block activation, stabilize substrate, agonists, partial agonist, antagonist, induced degradation, allosteric modulator, slow k_{off} DNA alkylation, photosensitizer, allosteric modulator, unknown

Types of Screens

- Fragments
- Targets
- Pathways
- Cells
- Animals
- Human
- Biologics
- Nucleotides
- Small molecules
- Proteins

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One size does not fit all

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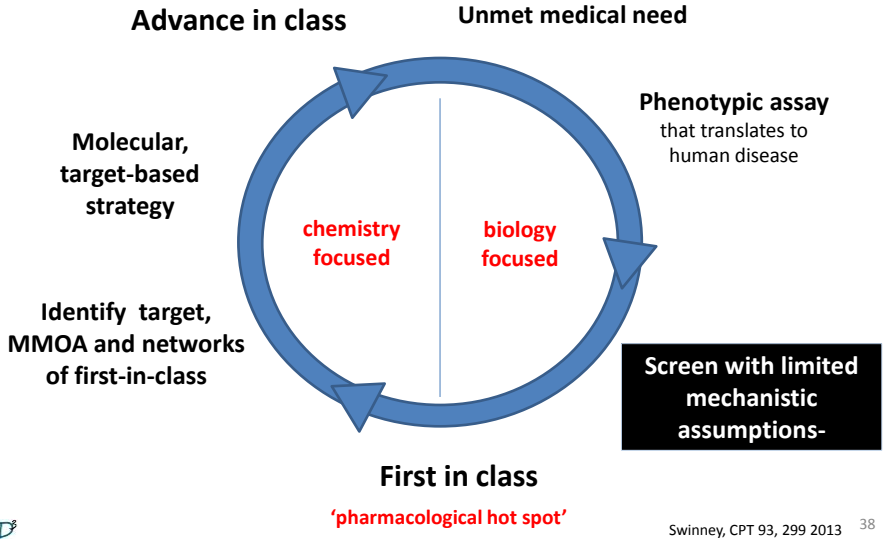
Identification MMOA (pharmacological hot spot) Informs Screening Strategy



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Swinney, CPT 93, 299 2013

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Strengths of Target-based Drug Discovery

- Provides a rational approach, analogous to **engineering**
- Aligns **genotype** with phenotype
- Informs **patient** selection for clinical trials
- Uses structure based design in **optimization**
- Establishes clinical **doses** related to target occupancy
- Provides a **metrics** of risk

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Weaknesses of Target-based Drug Discovery

- Target identification and validation
- Does not account for MMOA
- Actives against a target may not work in phenotypic assays.

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Strengths of Phenotypic Drug Discovery

- Physiological relevant assays
- Fewer mechanistic assumptions
- Early safety evaluation

PDD Challenges

- *Development of phenotypic assays that are predictive of human disease**
- *Identification of validated phenotypic biomarkers**
- Unknown mechanisms of action
- Not enabled by structure based chemical optimization
- Challenges to select correct patients for clinical trials
- Dose setting for clinical trials

*required for both TDD and PDD

Strengths of PDD and TDD Compliment Their Respective Weaknesses

	TDD	PDD
STRENGTHS	**Knowledge Based** • Structure based design • PK/PD predictions • Patient selection	**Empirical** • System-based • Identification of MMOA • Early safety evaluation
WEAKNESSES	• Most available knowledge is incomplete • Not systems based • Target selection • Identification of MMOA	• Difficult to use empirical findings with • Structure based design • PK/PD predictions • -Patient selection

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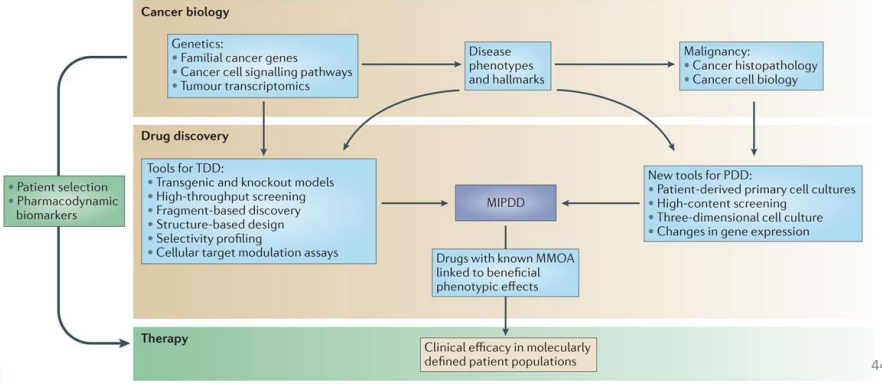
Phenotypic Screening in Cancer Drug Discovery: Past, Present and Future - Moffat, Rudolph & Bailey NRDD, 13, 2014

- In practice many projects are not target agnostic; and conversely many target-based discoveries rely heavily on phenotypic assays
- They proposed that mechanistically informed phenotypic drug discovery (MIPDD) provides a basis for opportunities to better identify the causal relationships between target inhibition and phenotypic effects

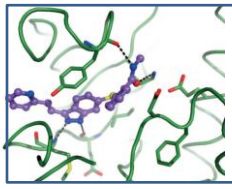


Nature Reviews, Drug Discovery

Example: Phenotypic Screening of Known Cancer Drugs

Axitinib effectively inhibits BCR-ABL1(T315I) with a distinct binding conformation. Pemovska et al. *Nature* 2015.

- **PDD**
  - Phenotypic screen
  - Primary cells CML & ALL patients
  - 252 oncology compounds
- **TDD**
  - Binding mechanism confirmed by x-ray
  - Biochemical mechanism confirmed in cells
  - Provide rational for testing clinical utility in specific patients



Axitinib-ABL1(T315I) A-loop in the DGF-in conformation

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Lessons Learned

- Screening links basic research to medicines
- Choice of screening strategy depends on the available mechanistic knowledge
- Strategies will change for first-in-class versus advances-in-class

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Additional Resources

Institute for Rare and Neglected Diseases Drug Discovery

www.irnd3.org

Mission: Discover medicines for rare and neglected diseases

Value Proposition: Use our collaborative preclinical discovery paradigm to identify quality drug candidates that have a greater chance for clinical success.

501c3 non-profit
lab located in Mountain View CA, USA
Screening platforms in kinases and mitochondria
Programs in trypanosomes and cancers
Funding from NIH

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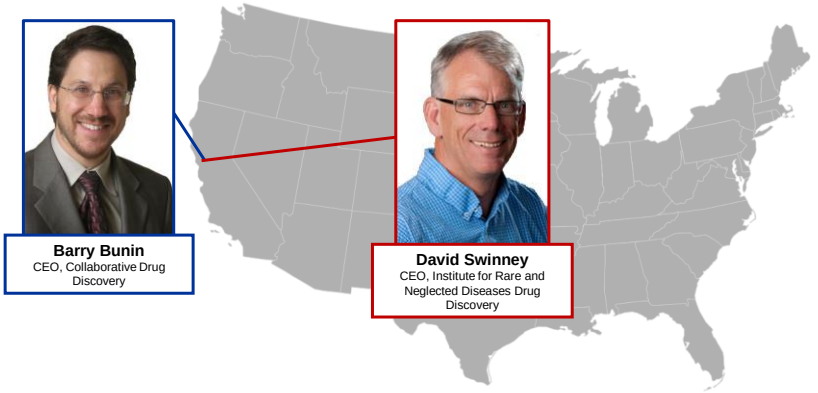

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David Ball, Professor of Chemistry, Cleveland State University
David Harwell, Assistant Director of Industry Member Programs, ACS

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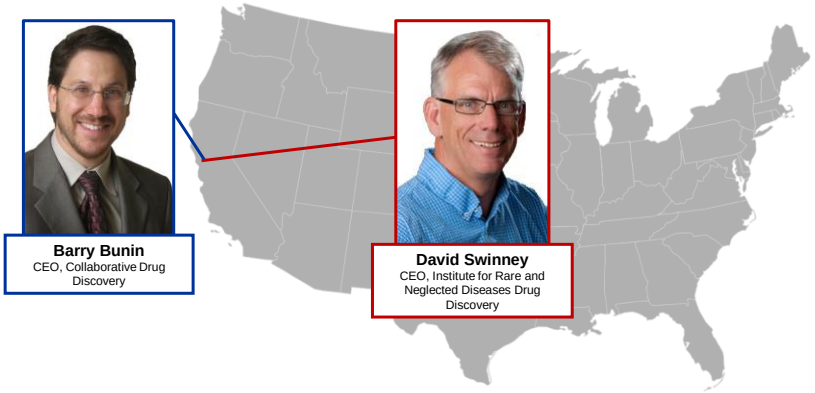

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AAPS/DDDI Regional Meeting

Drug Discovery Paradigm Shift?
Strategies to Improve Science, Timelines and Clinical Candidate Quality

Friday, May 29th, 2015 (8:00am-4:30pm)
Merck & Co., Upper Gwynedd, Pennsylvania

Expert speakers from the pharmaceutical field share views on drug design, discovery and early development in the areas of:
Medicinal Chemistry, Discovery Biology, Pharmacology, Pharmacokinetics, Pharmacodynamics, Drug Metabolism, Pharmaceutical Sciences and Toxicology

Speakers Include:
Nick Meanwell, Executive Director, Bristol-Myers Squibb
Caroline McGregor, Executive Director, Merck
Handan He, Director, Novartis

Website: http://www.aaps.org/DDDIRM15/
Registration: $100 for AAPS members, $150 for non-members

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2015 Drug Design & Delivery Symposium

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Module 1: Improving Drug Design Efficiency and Efficacy		
Jan 29	Designing Better Drug Candidates	*Dr. Paul Leeson*
Feb 26	Strategies to Improve Solubility of Drug Candidates	*Dr. Michael Walker*
Module 2: Activity/Potency Screening for Drug Lead & Candidate Optimization		
Mar 19	Fragment-Based Drug Design Strategies	*Dr. Dan Erlanson*
April 30	Screening Strategies	*Dr. David Swinney*
May 28	PAINS (Pan-Assay Interference Compounds)	*Dr. Jonathan Baell*
June 25	Positron Emission Tomography (PET) Labeling in Drug Discovery & Development	*Dr. Lei Zhang*
July 30	X-Ray Crystallography in Drug Discovery	*Dr. Jon Mason & Dr. Miles Congreve*
Module 3: Enabling Drug Discovery		
Aug 27	Choices and Trends in Solid Dosage Form Section	*Dr. Scott Trzaska & Dr. Ron Smith*
Sept 24	Delivery Options to Support Dose Escalation in Preclinical Toxicology and Pharmacodynamic Activity Studies	*Dr. Evan Thackaberry*
Module 4: Pharmacokinetics		
Oct 29	Pharmacokinetic Considerations in Drug Design and Development	*Dr. Punit Marathe*
Nov 19	Prodrugs in Drug Discovery	*Dr. John Higgins*

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