Challenges and Hurdles to Business as Usual in Drug Development for Treatment of Rare Diseases

ASCPT

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www.irnd3.org

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How can we do things differently to increase the number of medicines approved and patients cured of rare diseases?

1. How is drug discovery currently practiced for all diseases?
2. How successful is the approach?
3. What are some of the challenges to this practice?
4. What are the successes and strategies for rare diseases?
5. What new strategies are realistic to increase the numbers of patients cured?

Take Home messages

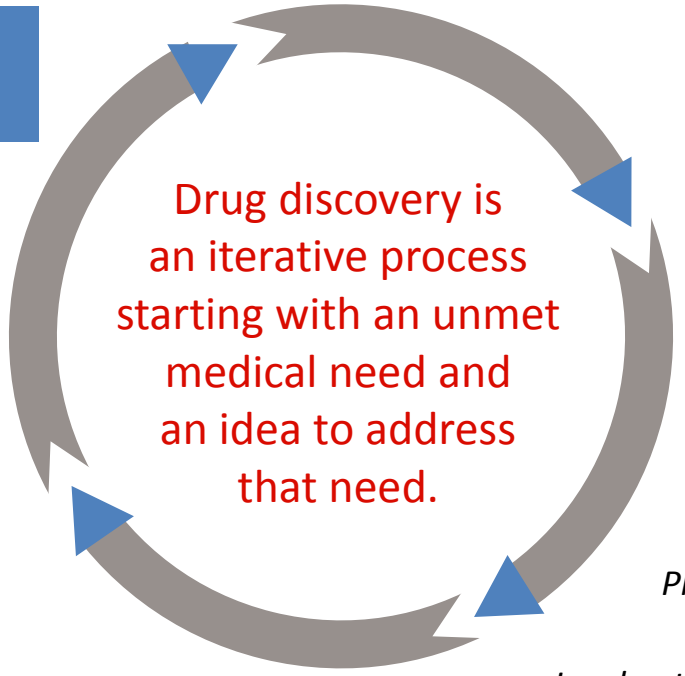
1. The knowledge that provides a blueprint for R&D is difficult to acquire, and rarely available for rare diseases.

2. Identification of a genetic cause, by itself, does not provide a blueprint.

3. Look for opportunities to leverage knowledge from other areas….repurpose.

4. Improve access to key available knowledge

How is drug discovery for all diseases currently practiced?



Medical Need

Basic research

Translation biomarker

Drug Approval

Starting pt (assay/target)
Discovery strategy

Lead identification

Phase 3 Efficacy

Development

Discovery

Proof of concept

Pharmacological mechanism

Lead optimization

Clinical safety

Drug Candidates

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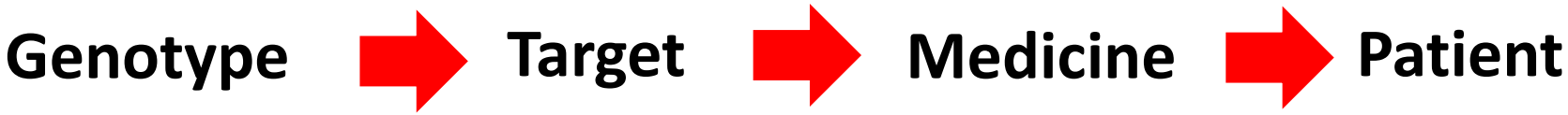
We look for knowledge to provide a blueprint for discovery and initial use of the medicines.



Determine activity by IC_{50}s (EC_{50}s) for active compounds against a target

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

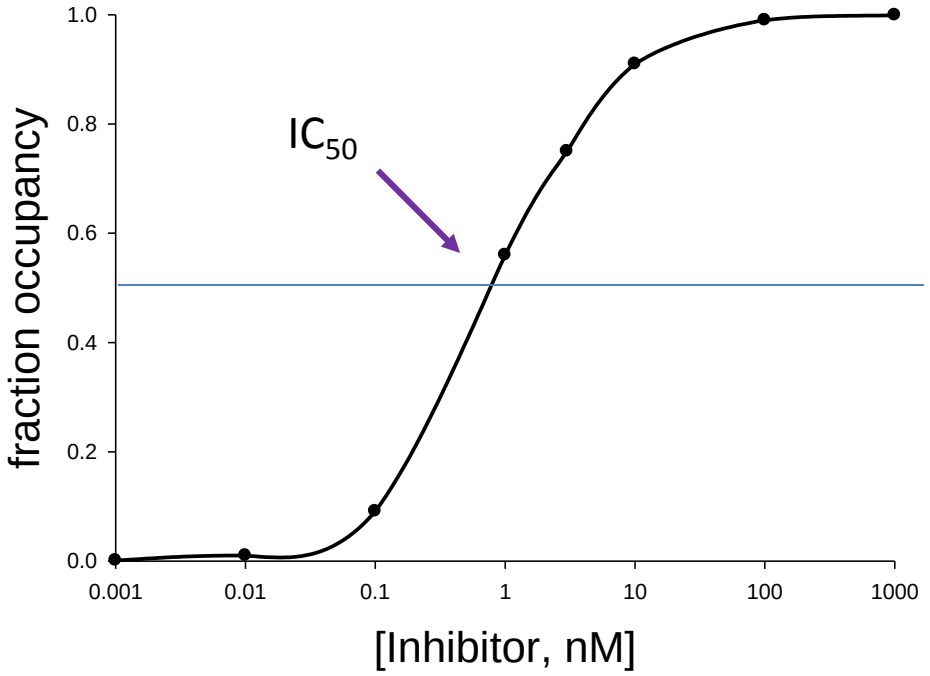
Fractional occupancy = $[I]/([I] + K_I)$

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

For K_I = 1 nM

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

Assume one site binding



The Medicinal Chemist's Juggling Act

Selectivity/
Safety

Bioavailability

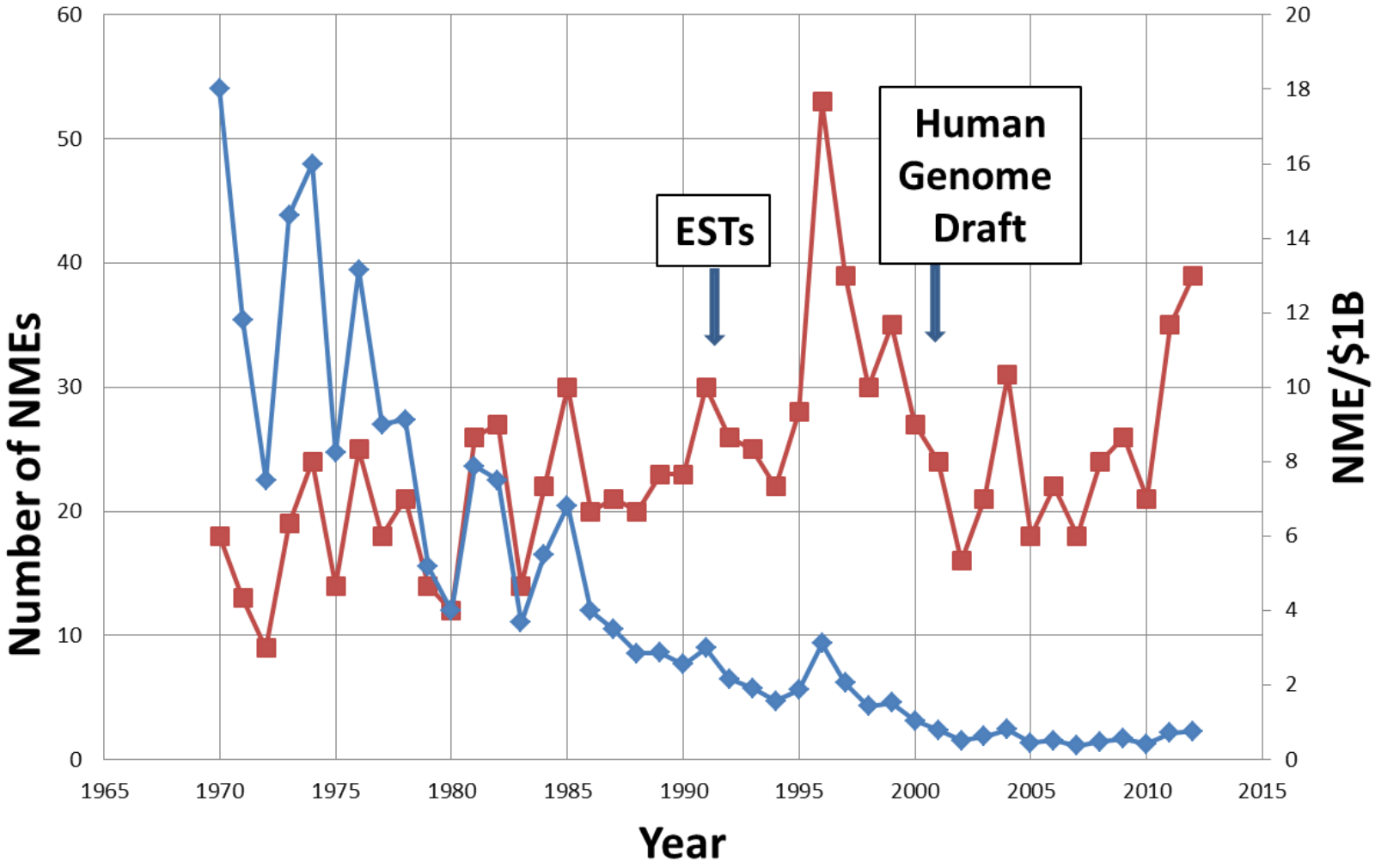
Pharmaceutics/
Scale -up

Biological
Activity

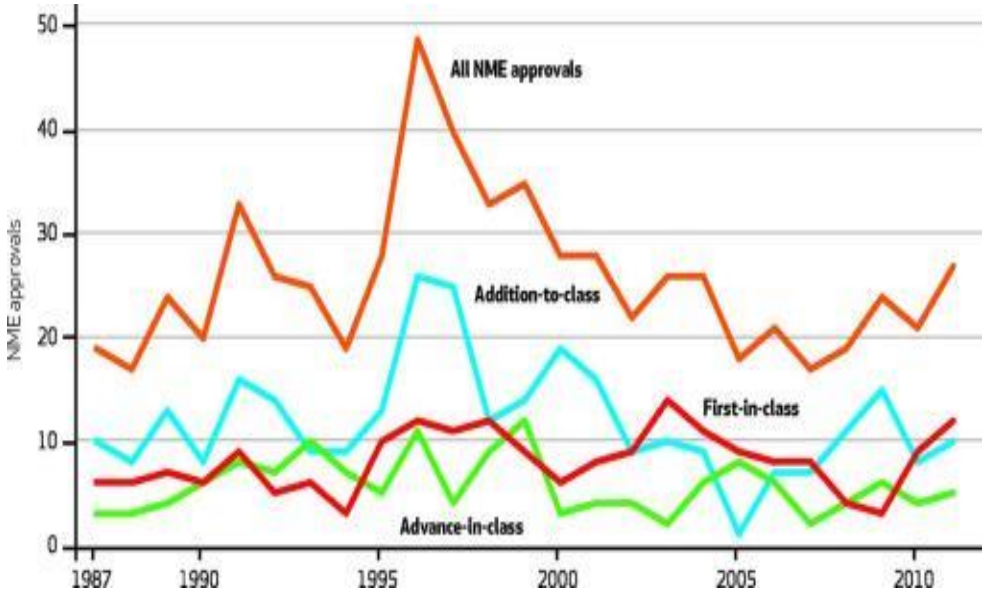
Intellectual
Property

How successful is drug discovery for all diseases?

Pharma Productivity has decrease while the number of NMEs are unchanged

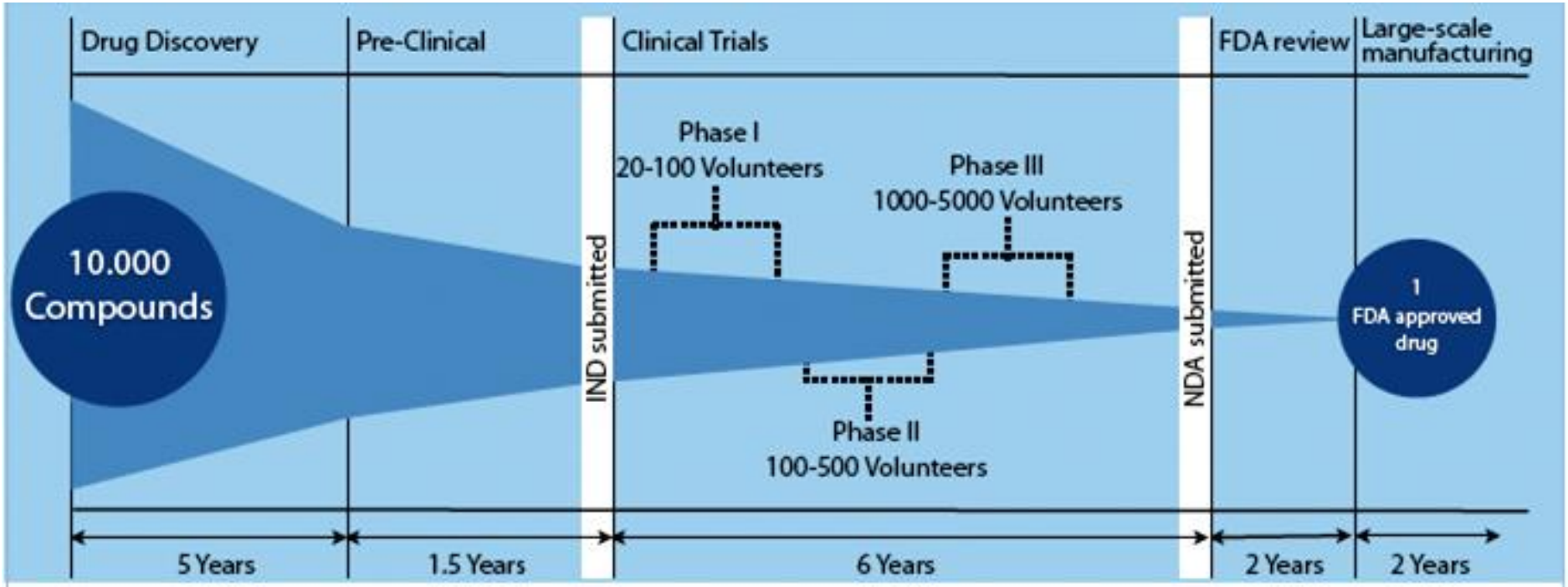


~Ten First-in-class medicines approved per year



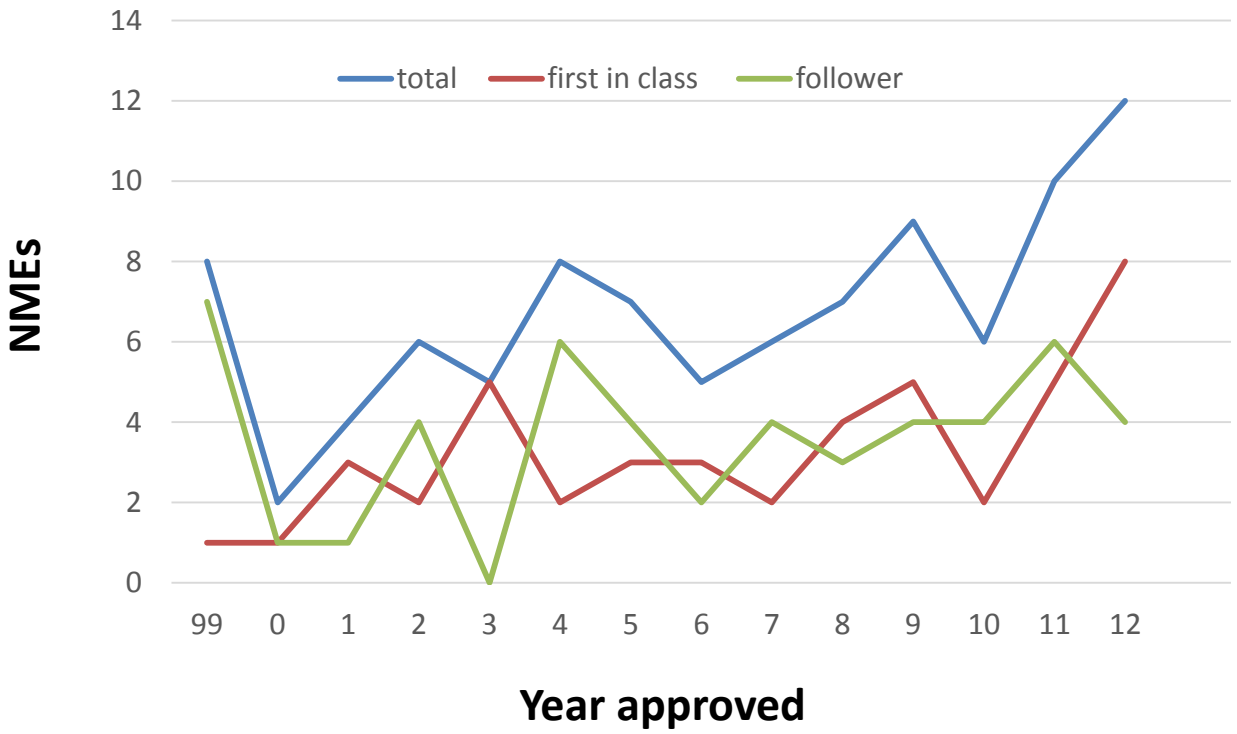
Improved Measures of Drug Innovation
(2013) Health Affairs 15, 1433

Successful programs take many years and resources



Source: PhRMA Profile.

NMEs approved with orphan drug status by US FDA between 1999 & 2012



13 year period
-102 total NMEs
-46 first in class
-51 followers
-5 imaging agents

>6800 rare diseases

Swinney & Xia, Future Med Chem 6, 987 (2014)

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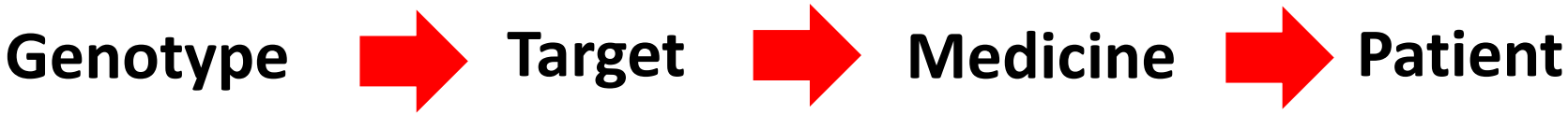
Why is the productivity and success low?



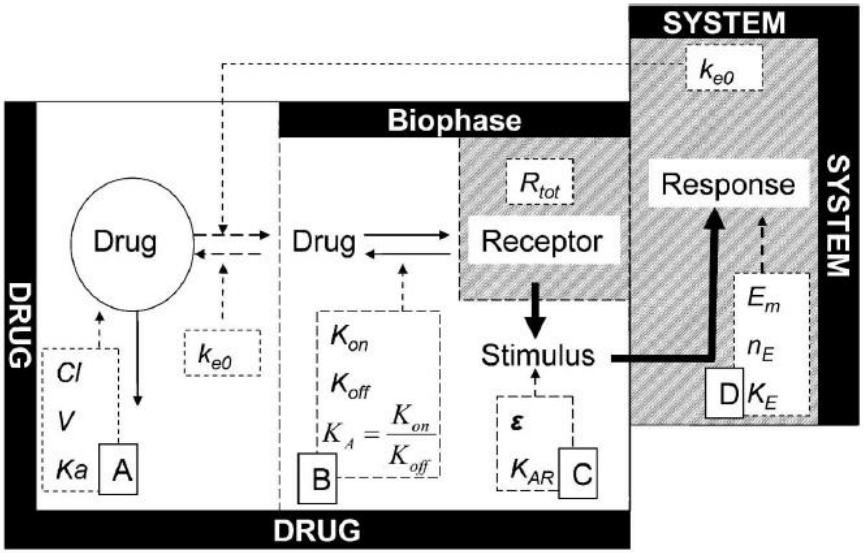
How do medicines work?

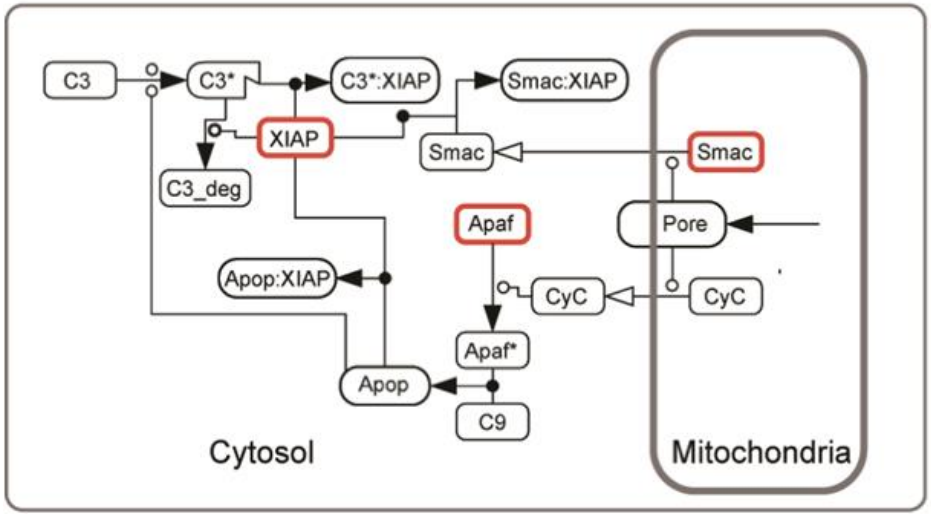
Drug action begins with binding

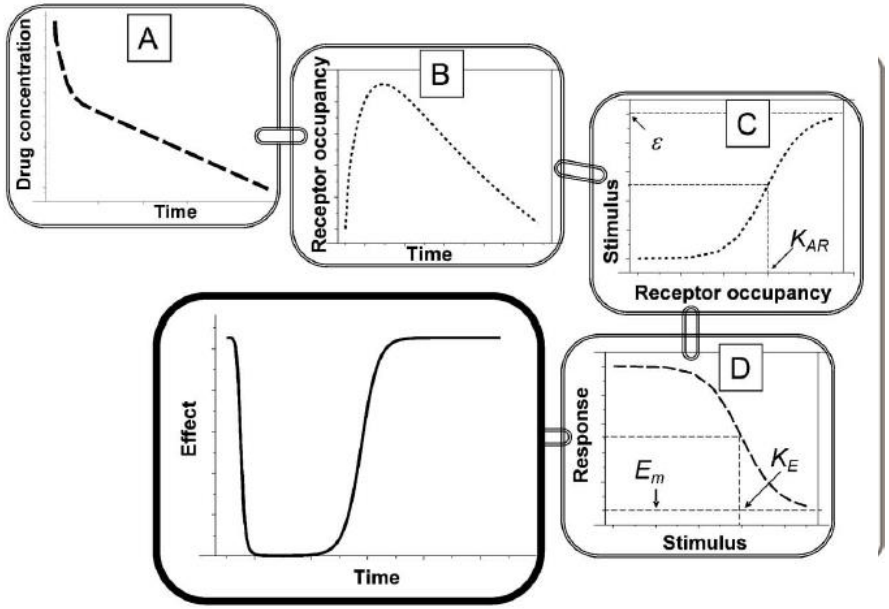
‘Corpora non agunte nisi fixata’

A substance will not work unless it is bound

-Paul Ehrlich, 1913







Ploeger BA, van der Graaf PH, Danhof M. Drug Metab Pharmacokinet. 2009;24:3-15.

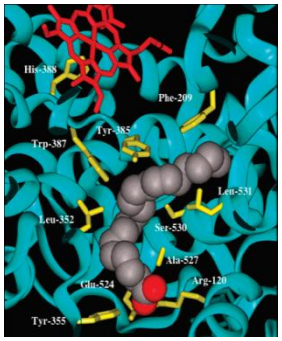
Molecular Mechanism of Action (MMOA)

- MMOA: mechanism through which specific molecular interactions between the drug and its target result in a effective and **safe** pharmacological response.
  - Includes **binding kinetic** and **conformational** changes that specifically provide a therapeutically useful response.

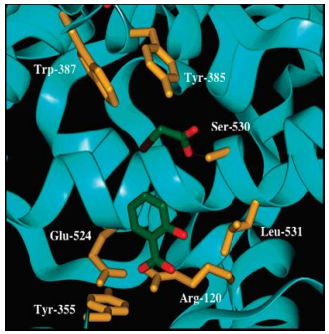
MMOA-pharmacological hot spot

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

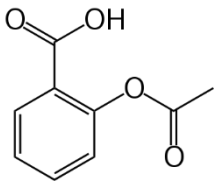
- **Aspirin has anti-platelet activity whereas NSAIDs do not**
  - Effective for prevention of atherothrombotic disease
- **Both bind to the active site of cyclooxygenase 1 and 2**
  - Aspirin irreversible inactivation via acetylation of Ser530
  - Ibuprofen and other NSAIDS are reversible
- **Irreversible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

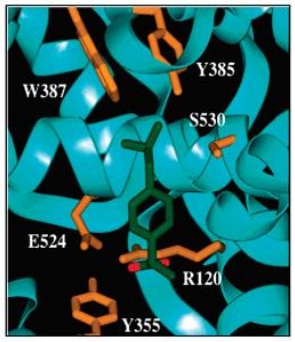


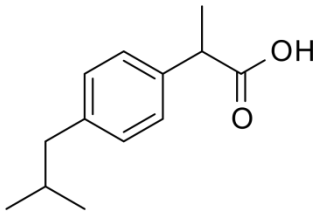
Substrate - arachidonic acid



Aspirin



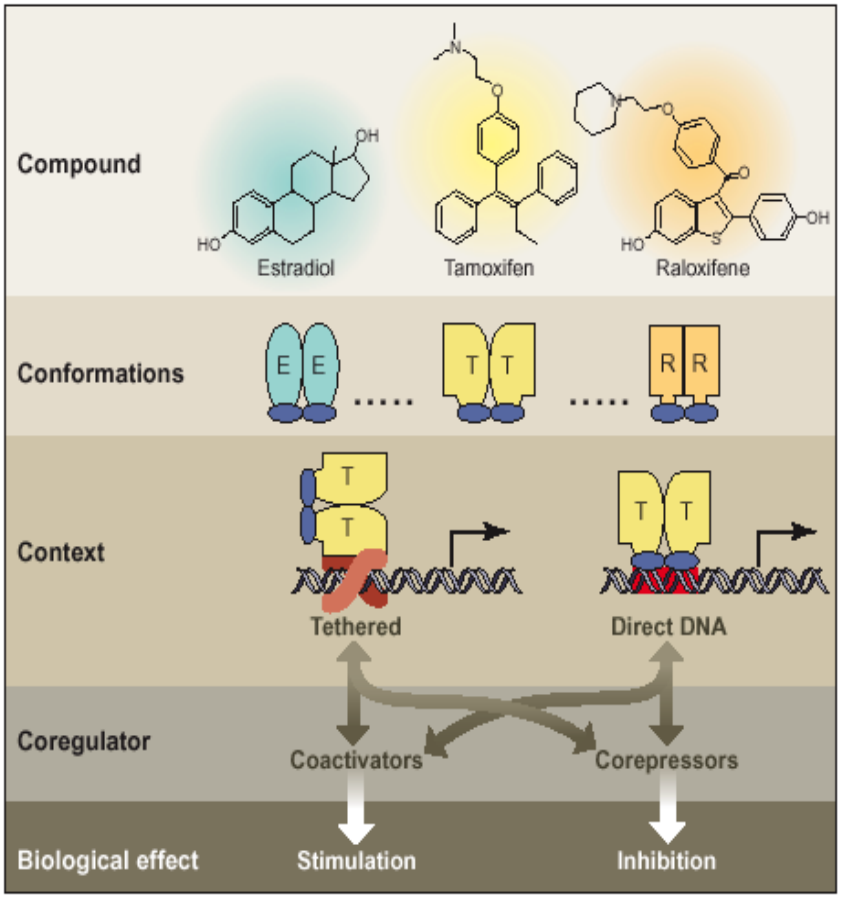




Ibuprofen

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

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



Differentiated therapeutic use

Estradiol agonist

- postmenopausal hormone deficiency

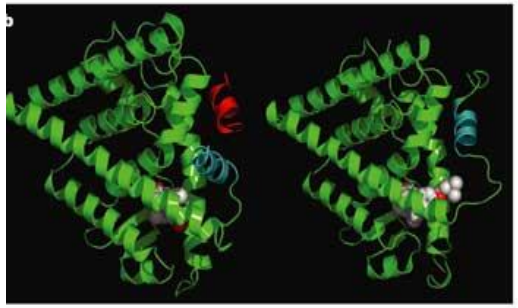
Tamoxifen SERM (selective estrogen receptor modulator)

- breast cancer

Raloxifen SERM

- osteoporosis

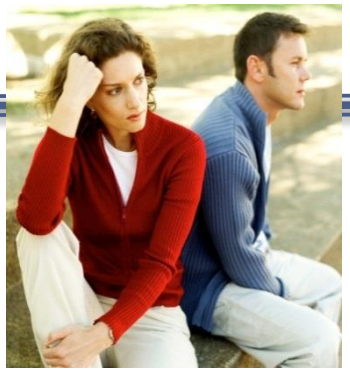
ER ligand binding domain



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





- **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.**

'Pharmacological hot spots'

Conclude the value of phenotypic assays is to discover new MMOAs which are difficult to *a priori* predict

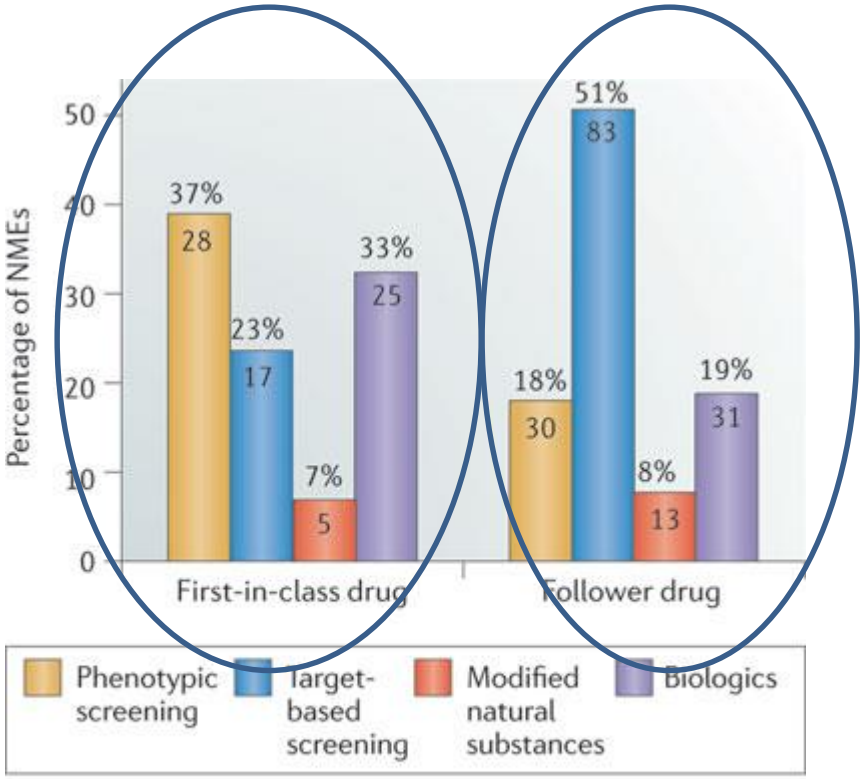
NMEs approved FDA 1999-2008
259 total
183 small molecules
20 imaging agents
56 therapeutic biologics

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

Swinney & Anthony NRDD, 10, 507, 2011

NME- new molecular entity

Conclusions

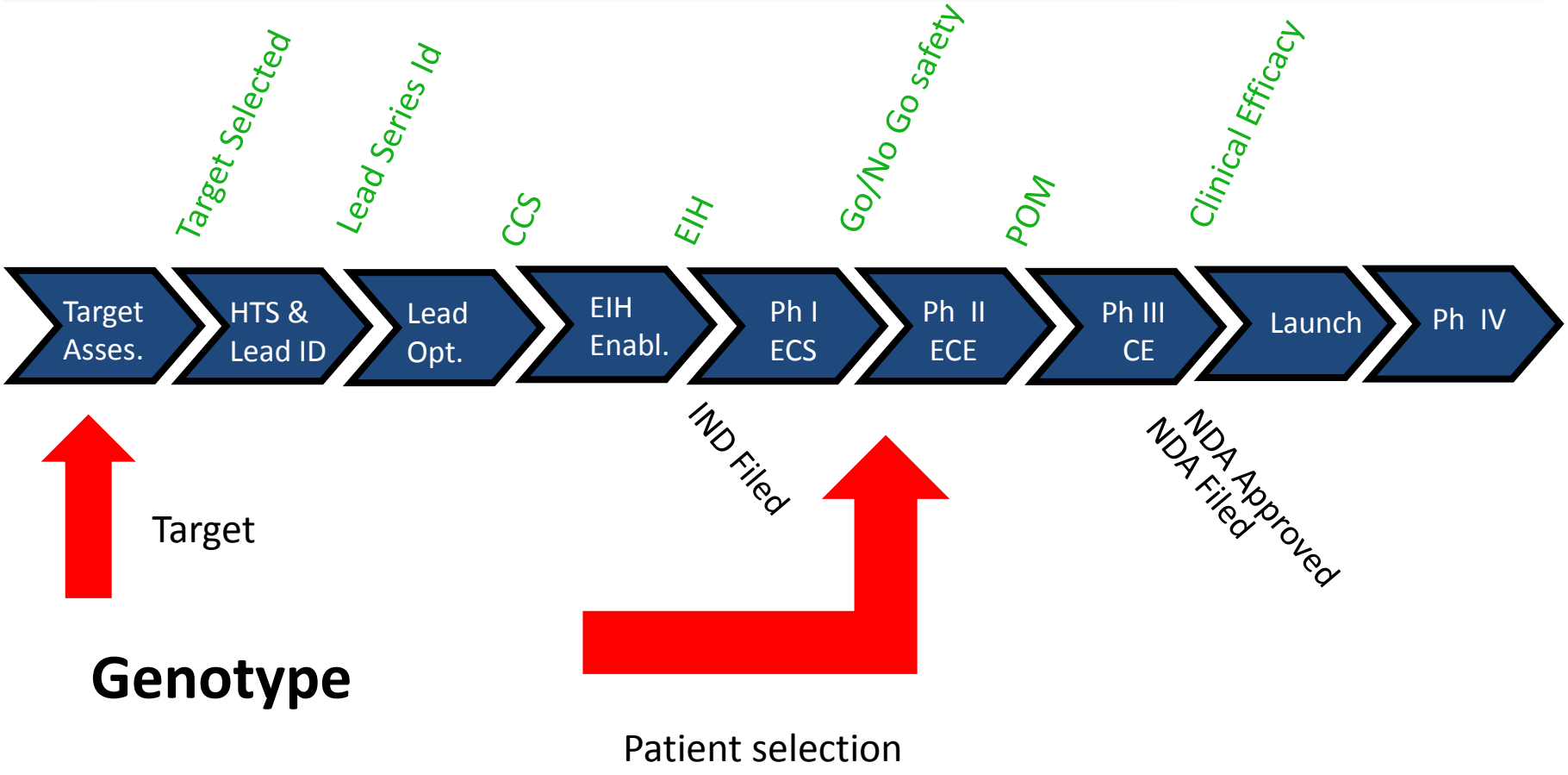
- First-in-class medicines discovered with empirical strategies
- Majority of resources on reductionist target-based strategies

mechanistic paradox

- the knowledge of mechanism (e.g. how a drug works) is very helpful to discover and precisely use medicines

- the knowledge available is rarely sufficiently complete to provide a blueprint for discovery and initial use of the medicines.

What are the successful strategies for rare diseases? Do genetics help inform strategies?

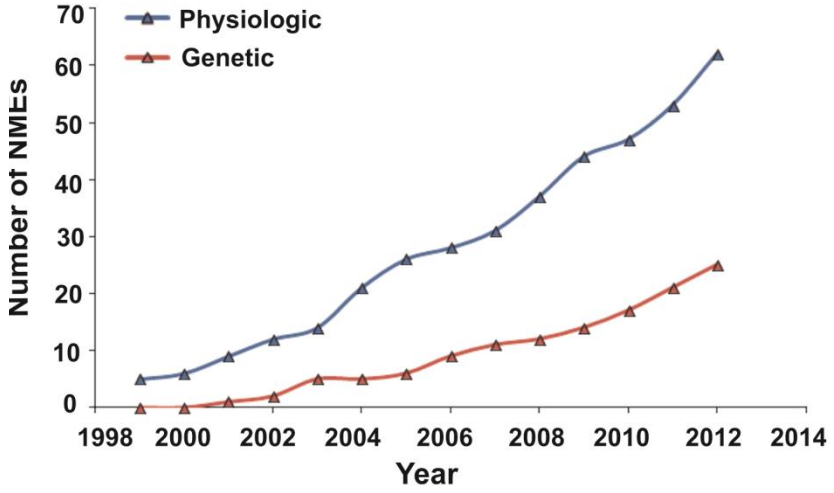


What was the contribution of genetics to new medicines approved for rare diseases?

>80 % of 6800 rare diseases have a genetic origin.

NMEs with orphan status US FDA 1999-2012
102 total

Genetic contributions (25%) were under represented with respect to the number of genetic diseases (>80%).



Strategies identified as genetics influenced when disease associated mutation directed drug discovery

Swinney & Xia, *Future Med. Chem.* (2014) 6(9), 987–1002

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Genetic informed orphan NMEs discovered between 1999 and 2012

Kinase/target	Enzyme replacement	Mechanism informed
ruxolitinib*	velaglucerase alfa	nitisinone*
crizotinib*	taliglucerase alfa	carglumic acid*
vemurafenib*	alaglucerase alfa2	ivacaftor*
imatinib mesylate*	alglucosidase alfa*	ecallantide*
bosutinib monohydrate	idursulfase*	icatibant
ponatinib	galsulfase*	canakinumab*
nilotinib	laronidase*	rilonacept
dasatinib	agalsidase beta*	eculizumab*
		miglustat*

*first in class

Swinney & Xia, *Future Med. Chem.* (2014) 6(9), 987–1002

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Genetics informed discovery

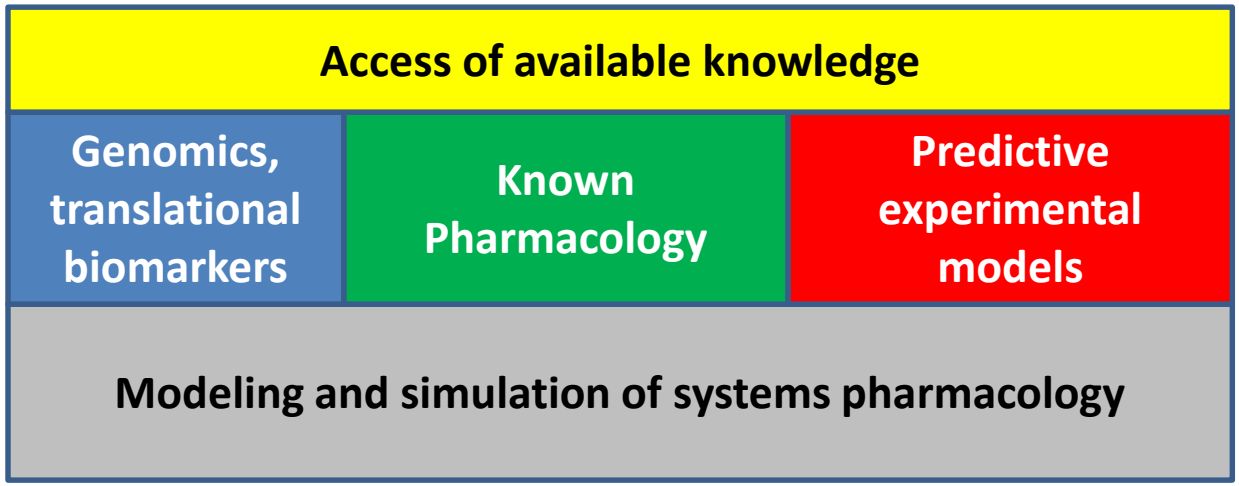
- Chance for success enhanced by understanding
  - -**genetic cause** of disease
  - -**physiological systems** to that relate genotype to phenotype
  - -**validated assays** to measure disease relevant phenotypes

How can we do things differently to increase the number of medicines approved and patients cured of rare diseases?

Precision medicine initiative

repurposing

When quality beats Quantity
Scannell & Bosley, PLOSone 2016



Quantitative Systems Pharmacology

Take Home messages

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2. Identification of a genetic cause, by itself, does not provide a blueprint.

3. Look for opportunities to leverage knowledge from other areas….repurpose.

4. Improve access to key available knowledge

Institute for Rare and Neglected Disease Drug Discovery
iRND3

Non-profit 501c3 drug discovery organization
Well equipped laboratory Mountain View, CA, USA
Experience drug discovery team with many years of Pharma experience
www.irnd3.org

Mission

iRND3's mission is to discover new medicines for rare and neglected diseases

Vision

-to utilize our understanding of how successful new medicines are discovered to implement and execute drug discovery strategies that supply our growing pipeline of new candidate medicines for rare and neglected diseases.

-to evolve an innovative, socially responsible operational model for successful collaborations between the non-profit, private and public to translate scientific discoveries to a continuous source of new medicines.