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

ASCPT
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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
Drug discovery is an iterative process starting with an unmet medical need and an idea to address that need.
We look for knowledge to provide a blueprint for discovery and initial use of the medicines.

Genotype ➔ Target ➔ Medicine ➔ Patient
Determine activity by IC$_{50}$s (EC$_{50}$s) for active compounds against a target

\[
\begin{align*}
E + I & \underset{K_i}{\rightleftharpoons} EI \\
\text{Fractional occupancy} & = \frac{[I]}{[I] + K_i} \\
\Delta G & = -RT \ln (K_i)
\end{align*}
\]

For $K_i = 1$ nM

<table>
<thead>
<tr>
<th>[I, nM]</th>
<th>% occupancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>9%</td>
</tr>
<tr>
<td>1</td>
<td>50%</td>
</tr>
<tr>
<td>3</td>
<td>75%</td>
</tr>
<tr>
<td>10</td>
<td>91%</td>
</tr>
<tr>
<td>100</td>
<td>99%</td>
</tr>
</tbody>
</table>

Assume one site binding

![Graph showing IC$_{50}$](image)
The Medicinal Chemist’s Juggling Act

- Bioavailability
- Biological Activity
- Selectivity/Safety
- Pharmaceutics/Scale-up
- Intellectual Property
How successful is drug discovery for all diseases?
Pharma Productivity has decreased 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
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)
Why is the productivity and success low?

Genotype ➔ Target ➔ Medicine ➔ Patient
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

Molecular Mechanism of Action (MMOA)

- MMOA: mechanism through which specific molecular interactions between the drug and its target result in an 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

• **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

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).

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**NMEs approved FDA 1999-2008**
- 259 total
- 183 small molecules
- 20 imaging agents
- 56 therapeutic biologics
- 75 first in class
- 164 followers
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?

Target
Asses.

HTS &
Lead ID

Lead
Opt.

EIH
Enabl.

Ph I
ECS

Ph II
ECE

Ph III
CE

Launch

Ph IV

Target

Genotype

IND Filed

Patient selection

IND Filed

Target

Go/No Go safety

POM

Clinical Efficacy

NDA Approved

NDA Filed

Ph IV
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

Genetic informed orphan NMEs discovered between 1999 and 2012

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

*first in class

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

Access of available knowledge
- Genomics, translational biomarkers
- Known Pharmacology
- Predictive experimental models

Modeling and simulation of systems pharmacology

Quantitative Systems Pharmacology

When quality beats Quantity
Scannell & Bosley, PLOSone 2016
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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.