Phenotypic Screening: A new discovery paradigm or a return to the past?

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Background to presentation

- Current view of the Phenotypic screening renaissance
- A brief snapshot of Phenotypic Screening at GSK
- Perspectives on the future of Phenotypic Screening
Acknowledgements

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1) Current view of the Phenotypic screening renaissance
Phenotypic vs Target based drug discovery

- Up to the late 1980s most drug discovery used animal models and *ex vivo* samples for pharmacology profiling (classical pharmacology era)

- In the 1980s and 1990s recombinant DNA technology prompted the gradual realignment towards reductionist, target based approaches in the new HTS based era

- Advances in cell culturing has allowed cell/phenotypic based drug discovery but continuing debate between the target and systems (phenotypic) based camps on which is the “best” approach

The Screening Paradox: Inverse correlation with R&D productivity within the Recombinant Era

- Steady increase in screening capabilities but steady decline in productivity throughout this period
- Attrition primarily in the clinic - the most expensive stage for a drug to fail
- Increasingly failure at Phase II/III due to lack of predictivity of in vivo efficacy/toxicity from in vitro recombinant systems currently used in early stage studies
- Decreasing productivity has prompted a resurgence in systems/phenotypic screening approaches
Phenotypic Drug Discovery is significantly more successful in Identifying First-in-class Medicines (2011)

How were new medicines discovered?

David C. Swinney** and Jason Anthony *

Abstract | Preclinical strategies that are used to identify potential drug candidates include target-based screening, phenotypic screening, modification of natural substances and biologic-based approaches. To investigate whether some strategies have been more successful than others in the discovery of new drugs, we analysed the discovery strategies and the molecular mechanism of action (MIMO) for new molecular entities and new biologics that were approved by the US Food and Drug Administration between 1999 and 2008. Out of the 259 agents that were approved, 75 were first-in-class drugs with new MIMOAs, and out of these, 50 (67%) were small molecules and 25 (33%) were biologics. The results also show that the contribution of phenotypic screening to the discovery of first-in-class small-molecule drugs exceeded that of target-based approaches — with 28 and 17 of these drugs coming from the two approaches, respectively — in an era in which the major focus was on target-based approaches. We postulate that a target-centric approach for first-in-class drugs, without consideration of an optimal MIMO, may contribute to the current high attrition rates and low productivity in pharmaceutical
Phenotypic Drug Discovery is significantly more successful in Identifying First-in-class Medicines

- 62% Phenotypic
- 38% Target-Based

• Not weighted for the fact that major focus in this period was on target-based approaches!

Nature Reviews Drug Discovery 10, 2011, 507
Target-based drug discovery is perfectly acceptable for identifying Follow-on medicines

- Although still not normalised for type of drug discovery approach

Nature Reviews Drug Discovery 10, 2011, 507
Latest reviews less enthusiastic about phenotypic drug discovery (2014)

The discovery of first-in-class drugs: origins and evolution

Jörg Eder, Richard Sedrani and Christian Wiesmann

Abstract | Analysis of the origins of new drugs approved by the US Food and Drug Administration (FDA) from 1999 to 2008 suggested that phenotypic screening strategies had been more productive than target-based approaches in the discovery of first-in-class small-molecule drugs. However, given the relatively recent introduction of target-based approaches in the context of the long time frames of drug development, their full impact might not yet have become apparent. Here, we present an analysis of the origins of all 113 first-in-class drugs approved by the FDA from 1999 to 2013, which shows that the majority (78) were discovered through target-based approaches (45 small-molecule drugs and 33 biologics). In addition, of 33 drugs identified in the absence of a target hypothesis, 25 were found through a chemocentric approach in which compounds with known pharmacology served as the starting point, with only eight coming from what we define here as phenotypic screening: testing a large number of compounds in a target-agnostic assay that monitors phenotypic changes. We also discuss the implications for drug discovery strategies, including viewing phenotypic screening as a novel discipline rather than as a neoclassical approach.

Phenotypic screening in cancer drug discovery — past, present and future

John G. Moffat1, Joachim Rudolph2 and David Bailey5

Abstract | There has been a resurgence of interest in the use of phenotypic screens in drug discovery as an alternative to target-focused approaches. Given that oncology is currently the most active therapeutic area, and also one in which target-focused approaches have been particularly prominent in the past two decades, we investigated the contribution of phenotypic assays to oncology drug discovery by analysing the origins of all new small-molecule cancer drugs approved by the US Food and Drug Administration (FDA) over the past 15 years and those currently in clinical development. Although the majority of these drugs originated from target-based discovery, we identified a significant number whose discovery depended on phenotypic screening approaches. We postulate that the contribution of phenotypic screening to cancer drug discovery has been hampered by a reliance on ‘classical’ nonspecific drug effects such as cytotoxicity and mitotic arrest, exacerbated by a paucity of mechanistically defined cellular models for therapeutically translatable cancer phenotypes. However, technical and biological advances that enable such mechanistically informed phenotypic models have the potential to empower phenotypic drug discovery in oncology.
Latest reviews less enthusiastic about phenotypic drug discovery (2014)

The discovery of first-in-class drugs: origins and evolution

- Subdivide Swinney phenotypic to two systems-based approaches = phenotypic superiority
- Biopharm = target-based
- Not statistically different, and little knowledge on frequency of approach vs success rate
- Phenotypic screening is probably still more successful as a tactic
- Definitions important!!!
2) A brief snapshot of Phenotypic screening at GSK
Scaling Disease Relevance is challenging

- Recombinant Cells
- Primary Cells
- Tissues
- Disease Models
- Patients

Disease Relevance

Throughput

Cost
What does Phenotypic even mean?

- A greater emphasis in GSK on phenotypic screening and translational assays led to lots of questions on the area
  - what is a Phenotypic Assay/Screen? (try Googling!)
  - are phenotypic screens always disease relevant?
  - when is a cellular assay phenotypic?

- Some definitions might help!

Melanoma cells in 3D culture from Meenhard Herlyn lab, Wistar Institute
Phenotypic Assay

“An assay which measures a desired, endogenous effect in a biological system, that effect being agnostic of a defined target”

Cellular Target assay

“A cellular assay where the measured effect is directly dependent on a known molecular target or pathway”

Human Disease Relevant Assay (HDRA)*

“An assay which recapitulates aspects of human pathobiology and which measures changes in a disease-relevant biomarker”

*A subset of phenotypic/cellular/biochemical assays with characterised disease relevance
Changing Phenotypic Screening Rationales

**Phenotypic/HDRA Assay**

- **Target-specific screen**
- **Diverse library**
- **Annotated library**
- **RNAi Screen**

**Drug discovery program w/o target ID**
- **Novel drug (MoA unknown)**
- **Re-positioned drug or asset**
- **Target & Disease Biology**

**Repurposing of known compounds**
- **Drug discovery program with target and MOA knowledge**
- **Novel drug (Known MoA)**

**Desired outcomes**
Phenotypic for Target ID

Phenotypic/HDRA Assay

Diverse library (typically larger)

Annotated library (typically smaller)

RNAi Screen

Target-specific screen

Diverse library

Drug discovery program w/o target ID

Drug discovery program with target and MOA knowledge

Drug discovery program w/o target ID

Repurposing of known compounds

target ID (eg chemoproteomics)

Target & Disease Biology

Novel drug (MoA unknown)

Re-positioned drug or asset

Novel drug (Known MoA)

Desired outcomes

Phenotypic deliverables 2014
Improving disease relevance in GSK phenotypic screens

- Better upstream characterisation of disease to identify target relevant phenotypes
- Increased use of complex 3D, co-culture and primary/disease human cells (humanised drug discovery)
- Increased emphasis on disease phenotype maintenance during scale up and screen – Imaging, HT Flow, qPCR
Scarring
Liver fibrosis
Idiopathic pulmonary fibrosis
Renal fibrosis
Cardiac fibrosis

Fibrosis: Improved cellular models for phenotypic screening

Integrating mechanisms of pulmonary fibrosis, JEM doi: 10.1084/jem.20110551
Physiologically relevant model

Primary Human Pulmonary Fibroblasts

Patient → Lung tissue dissected post mortem → Outgrowth phase → Expansion phase → Cryo-preservation

Collaboration between Fibrosis DPU, Reagent Scale-up and Screening groups
Collagen Synthesis \textit{in vitro}\textsuperscript{a}

\textbf{Key:}

- **Hoechst**: Collagen

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\textit{Scar in a Jar}  

Chen et al., 2009

TGF-\(\beta_1\) alone

Ficoll media

TGF-\(\beta_1\) + Ficoll media
3) Perspectives on the future of Phenotypic Screening
Phenotypic Screening: Some thoughts...

- Phenotypic/disease relevant approaches are *probably* better at identifying the best targets and/or chemical equity
  - Based on First-in-class statistics but need to normalise appropriately
  - Desire to screen in more translatable assay systems as in previous DD eras
  - We now have a better understanding of target/pathway disease mechanisms

- But some problems remain
  - Scalability of primary/disease cell models to HTS scale and maintenance of phenotype
  - Target ID creates downstream deconvolution/mechanism challenges
  - After MOA is determined, downstream target dependent disease predictive assays and models are still highly challenging
Phenotypic Screening is evolving rapidly

- More complex disease models to increase translatability of screening systems
- Rationale for Target/Mechanism ID in addition to lead discovery
- Greater use of annotated compound sets to probe disease biology
- RNAi screens more prevalent, viral shRNA for primary/complex cell systems
- Though challenging, increasingly powerful downstream deconvolution/Omics techniques to determine target/MOA
- Use of powerful analytics platforms eg Palantir to link complex data sets
Summary

• We are seeing a return to more holistic, systems base approaches, as seen in previous eras

• Phenotypic screening is increasing in frequency, which is expected to continue via compound and genetic approaches

• However screening rationales, biological systems, technologies and IT analytics are completely different from previous incarnations of systems based approaches

• Current and near-future phenotypic screening space therefore represents a new phase in Pharma R&D evolution
Thank you