Phenotypic drug discovery

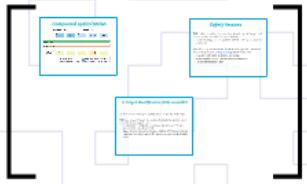
Opportunities and challenges in phenotypic drug discovery : an industry overview *John G. Moffat et al.*

Introduction

- Why is PDD interesting?
- Which areas could benefit from PDD?
- What are the current challenges and uncertainties associated with PDD?

Conclusion & Limitations

- Why is PDD interesting?
  Tool which addresses the complexity of diseases that are poorly understood.
- Which areas could benefit from PDD?
  Rare diseases, infectious diseases, cancer & neurological disorders)
- What are the current challenges and uncertainties associated with PDD?
  Requires knowledge at the molecular level of the causes and drivers of the disease



Definitions and core concepts

Table of contents

Hit triage

Building the Chain of Translatability

PDD Risks, Costs, and Potential Rewards

Library selection

- PDD object not only a selection of screening models but also of chemical models
- Looking at compound, which previously had biological effects
→ TC's a bit a contradiction of the main strategy

IMPORTANT:
- to assess the relevant compartment in the body
- PDD screening hit not only needs to selectively bind to the a macromolecular target but it also needs to modulate the function of it

Add vs Top

- PDD screenings collections compared with TDD screening collections are to place a premium on cellular permeability and to have sufficient structural complexity

Main Problem

- degree of compromise between throughput and assay complexity is a challenge

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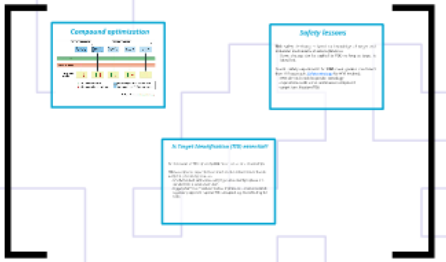

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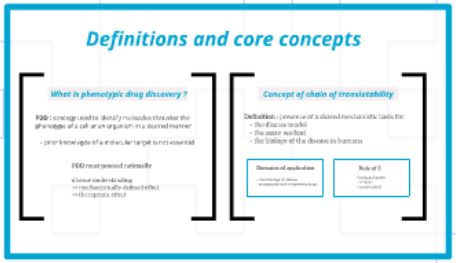

Table of contents

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What is phenotypic drug discovery ?

PDD : strategy used to identify molecules that alter the phenotype of a cell or an organism in a desired manner

- prior knowlegde of a molecular target is not essential

PDD must proceed rationally

disease understanding
=> mechanistically defined effect
=> therapeutic effect

Concept of chain of translatability

Definition : presence of a shared mechanistic basis for:

- the disease model
- the assay readout
- the biology of the disease in humans

Domains of application

- rare monogenic disease
- antibacterial and anti-parasite drugs

Rule of 3

- biological system
- stimulus
- assay readout

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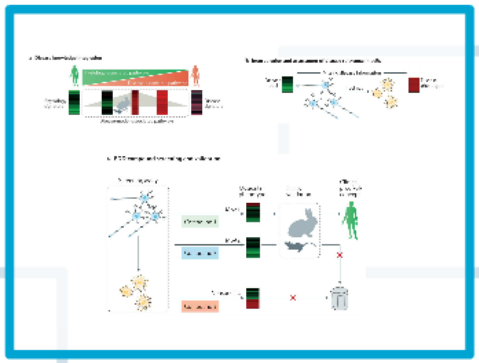
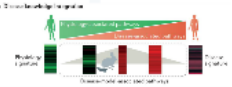


Disease Information

- Need molecular-level mechanistic understanding of a disease to validate best experimental cellular system and readout to use
- For some diseases, such information is available
  - e.g. kidney disease
- Incomplete disease understanding is a limitation for the validation of phenotypic models
  - e.g. Alzheimer disease
- ***The goal :*** Translation of disease information to a screen (ideally high-throughput and necessarily disease relevant)

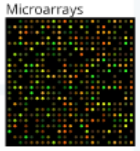


CoT - Molecular Phenotyping

- One Potential solution: **Molecular Phenotyping**
  - Ability to run high-throughput transcriptome analysis as 1st/2nd screen
- Delivers a pathway-centric view of a biological system
- Advantage in PDD: Decode effect of compounds on reg. pathways

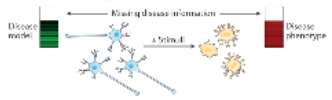
RNA seq

Microarrays



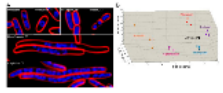
CoT - Advanced Cellular Models

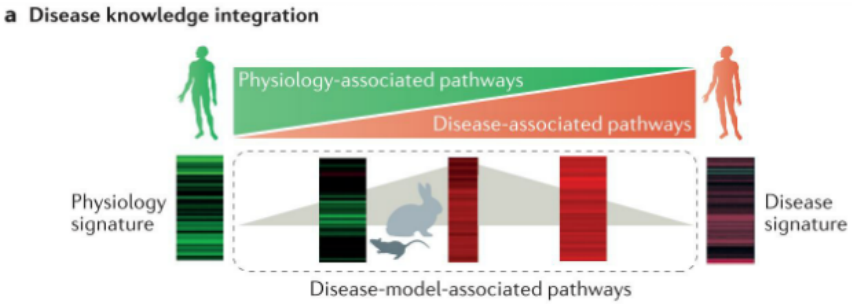
- *More closely model the disease-relevant tissue/cells*
- New technologies to complexity of *in vivo* tissue: 'tissue-on-a-chip', structured co-cultures, and multicellular organoids
- iPS cell-based models, e.g. coupled to molecular read-out such as endogenous gene expression → replicate "disease in a dish"

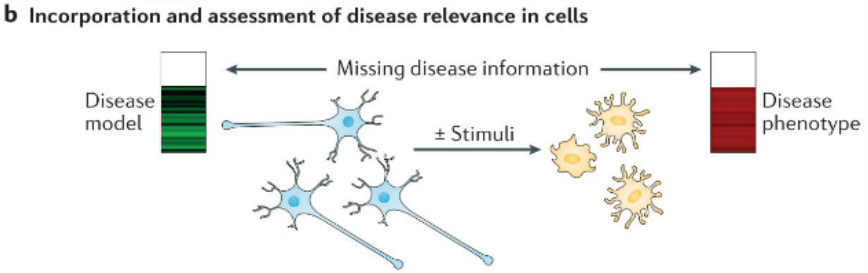


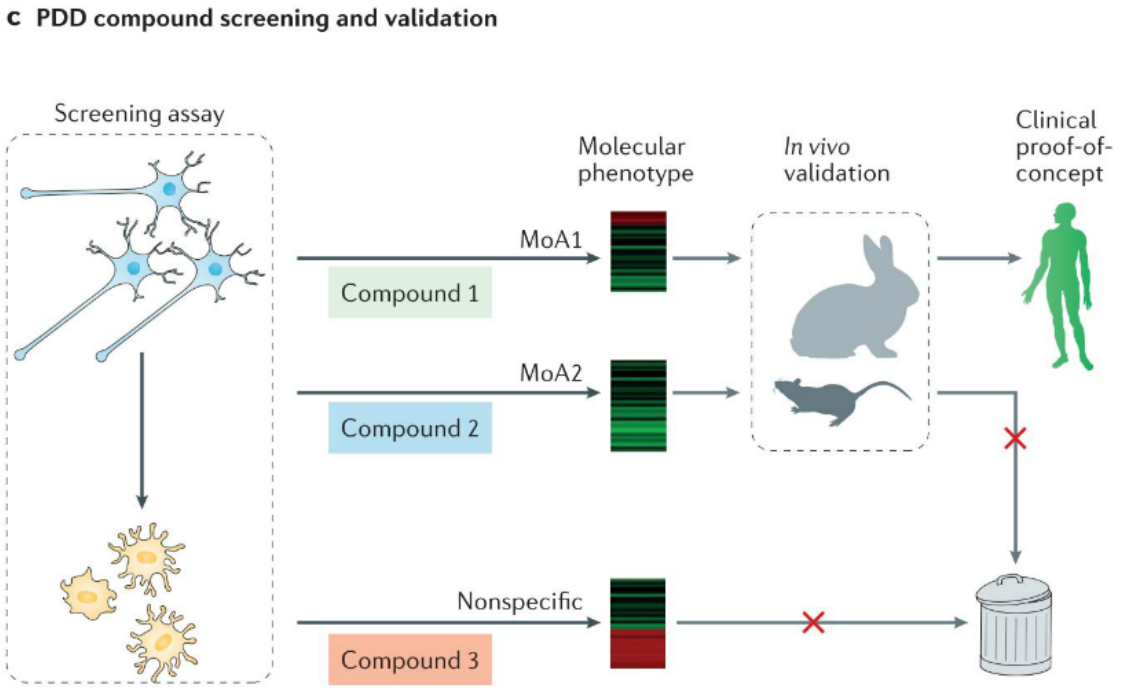
CoT – Advanced Cellular Models

- Do we always need complicated cellular models for PDD?
- As long as we can reproduce the disease MoA in the discovery, we are allowed to break the "rule of 3"
  - e.g. Novartis/Roche → spinal muscular atrophy
  - e.g. antibiotics
    - *in vitro* and *in vivo* efficacy are likely very similar.




a Disease knowledge integration
Physiology-associated pathways
Disease-associated pathways
Physiology signature
Disease signature
Disease-model-associated pathways


b Incorporation and assessment of disease relevance in cells
Missing disease information
Disease model
± Stimuli
Disease phenotype


c PDD compound screening and validation
Screening assay
Molecular phenotype
In vivo validation
Clinical proof-of-concept
MoA1
Compound 1
MoA2
Compound 2
Nonspecific
Compound 3

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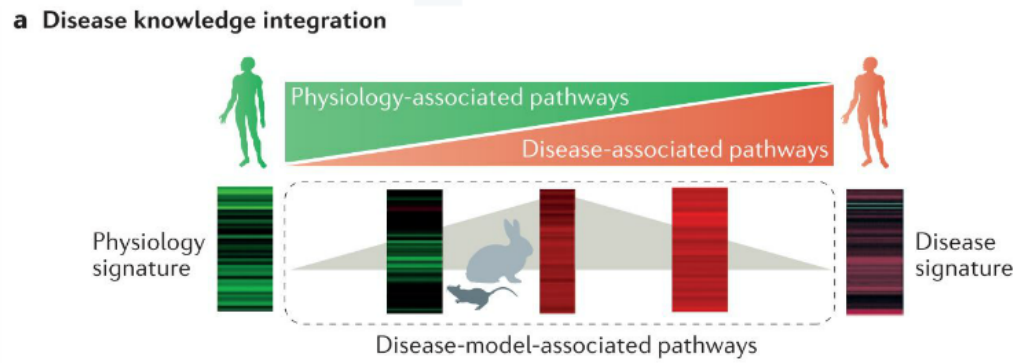

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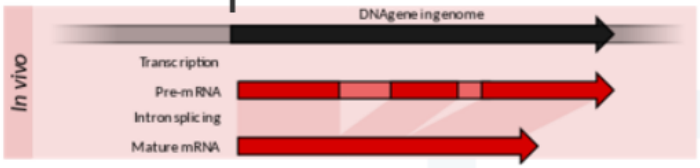

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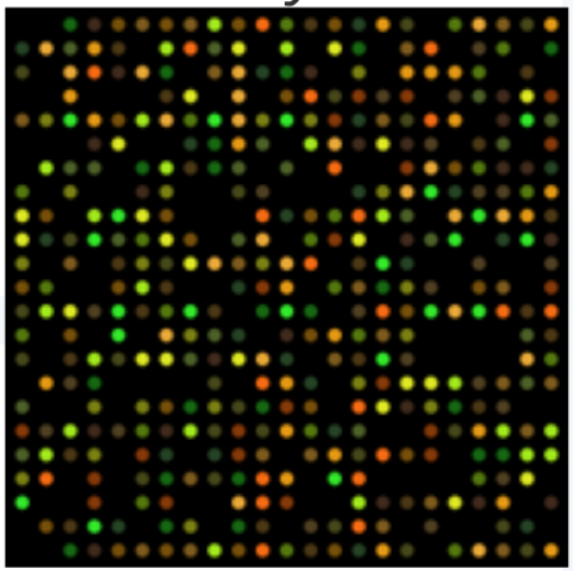

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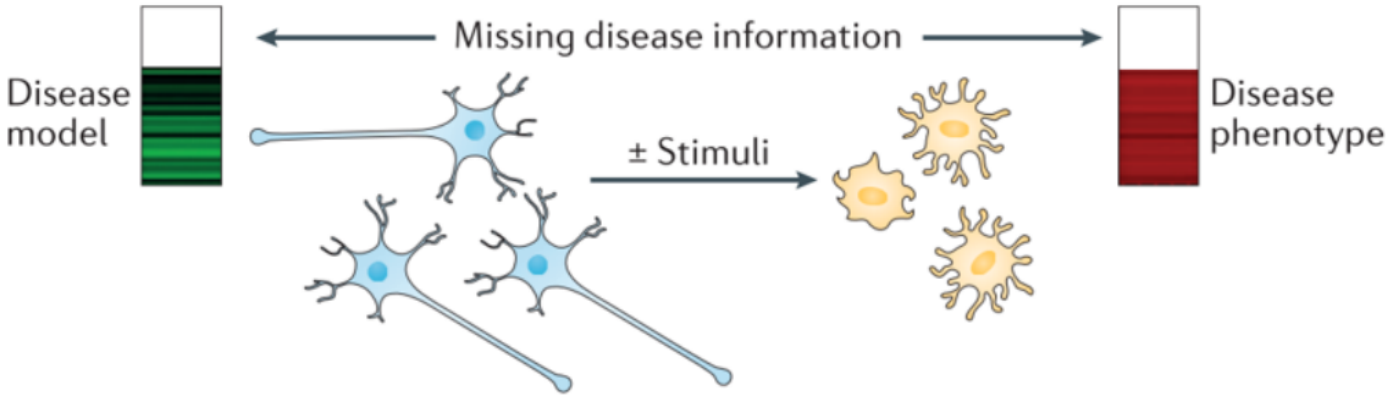

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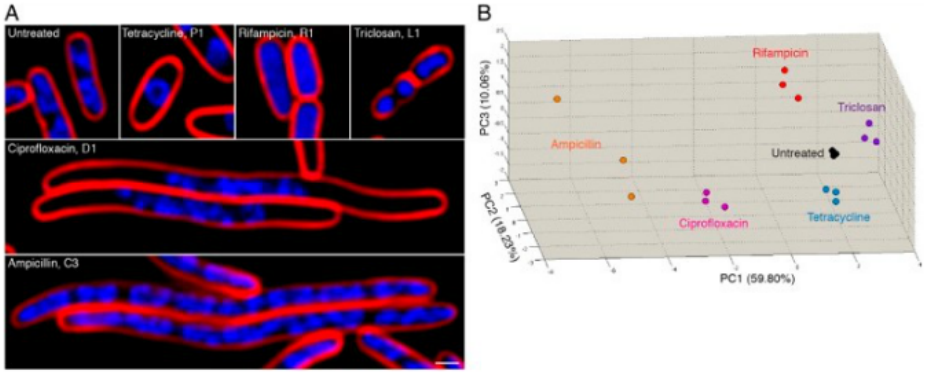

PDD Risks, Costs, and Potential Rewards

Payoffs

- PDD-discovered molecules translate to *in vivo* and clinical efficacy studies moreso than TDD
- Sampling of greater target space → more likely to discover novel MoA or targets than in TDD
  - e.g. PCSK9 phenotypic screen
  - e.g. fingolimod used to treat MS
- Treat a disease without a known target
- Explore 'undrugged' targets belonging to well-known target classes

Downsides

- Without high-confidence chain of translatability, risk of failure is about on par with TDD, assuming poorly-validated target
- Front-loading of costs (i.e. up to clinical stage):
  - *Higher complexity screening assays*
  - *Challenging hit validation and target identification*
  - *Emphasis on biological function will spend effort on in vivo toxicology*
- Risk associated with moving forward with compound without MoA or target
  - *Look at activity in vitro and in animal disease model to decide if worth it*
  - *Consider strength of chain of translatability, existence of predictive biomarkers, medical need, competitive landscape*
  - *Risk mitigation: Accumulation of mechanistic information may alleviate safety concern.*
  - *May not be an issue: About 7% to 18% of of FDA-approved drugs have no known target*

Summary

- Risk of failure early on:
  - *Challenging assay development*
  - *High false-positive hit rate*
  - *Inability to establish SAR from phenotypic assay*
  - *Inability to identify target*
  - *Inability to generate molecule on which* in vivo
- Main take-away:
  - ***Cost-benefit ratio for PDD comparable to several hypothesis-driven TDDs***

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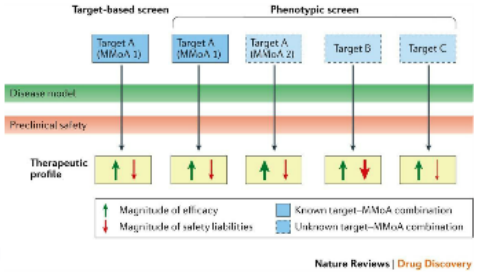
Hit triage

Table 1 | **Comparison of priorities for phenotypic and target-based drug discovery**

	Phenotypic drug discovery	Target-based drug discovery
Hit triage goals and priorities	Counter-screen to remove technical false positives	Counter-screen to remove technical false positives
	Extensive counter-screening to address undesirable biological mechanisms is essential	Filters for binding, potency, selectivity and novelty are negotiable depending on strategy
	Cluster hits based on chemical structure, mechanisms of action and molecular signatures	Cluster hits based on chemical structure
	–	Confirm cellular target engagement and modulation of desired phenotypic biology
	Recommendation: exclude hits not displaying the full phenotypic profile	Sub-optimal profiles can be rescued and low-affinity hits can be pursued
Lead optimization goals and priorities	Potential for different targets and mechanisms of action between series	Possible to combine different pharmacophores based on structural understanding of binding and to evaluate SAR for different properties independently
	SAR for cellular activity can be confounded by compound properties and off-target pharmacology	–
	Recommendation: molecular profiling to ensure mechanism of action stays the same, and to start to define biological mechanisms	–
	Recommendation: prioritize early optimization for *in vivo* proof-of-concept	*In vivo* proof-of-concept timing depends on target or mechanistic hypothesis novelty

SAR, structure–activity relationship.

Compound optimization



Safety lessons

TDD safety de-risking is based on knowledge of target and molecular mechanisms of actions (MMoAs).

Same strategy can be applied to PDD as long as target is identified.

Overall, safety experiments for **PDD** need greater investment than TDD approach. **Safety strategy** for PDD involved:

- iPSC-derived model to predict toxicology
- experiments with active and inactive compound
- target identification (TID)

Is Target Identification (TID) essential?

An alternative to TID is given by **SAR** (Structure-activity relationship).

TID has a greater impact in the context of *clinical development* than in early drug discovery processes.

- Smaller biotech companies, carrying studies mainly in phase I/II, conduct TID in parallel with SAR.
- Bigger pharma companies, involved in phase II/III studies towards regulatory approval, requires TID. (exception e.g. Novartis drug for SMA)

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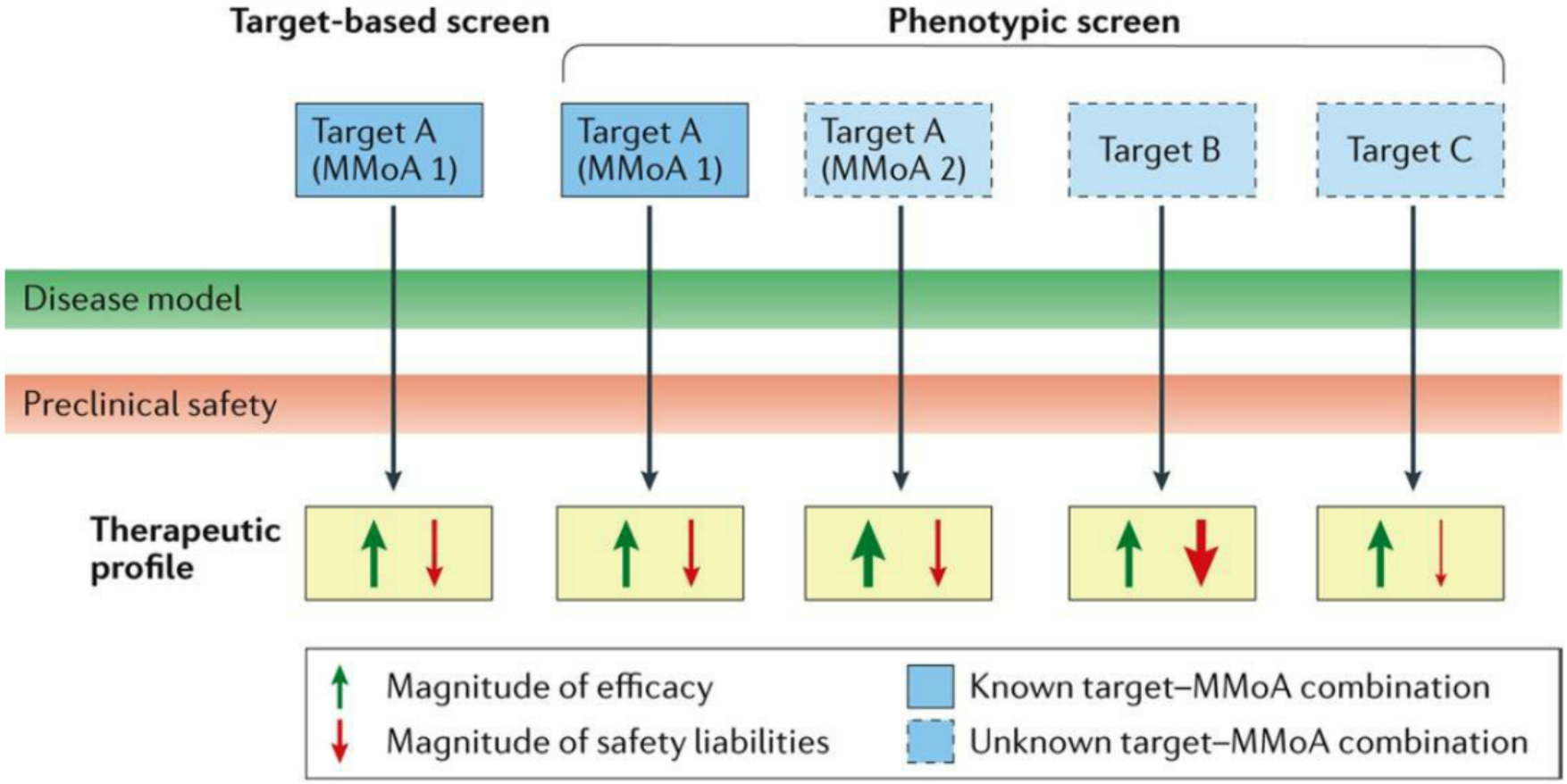

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