Rare Bootcamp™

Small Molecules and Drug Repurposing

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Small Molecules

- Small molecules make up about 90% of pharmaceutical drugs (as of 2020) such as statins, aspirin, and antihistamines
- They also include biological therapeutics such as fatty acids, glucose, and amino acids, and secondary metabolites such as lipids, glycosides, alkaloids, and natural phenols
- They do not include larger molecules such as polysaccharides, proteins, **ASOs and gene therapies**

Small Molecules

Small molecule drugs have been the mainstay of the pharmaceutical industry for nearly a century

They are low molecular weight organic compounds (must have a carbon atom) with **distinct advantages** as therapeutics:

- most can be administered orally
- they can pass through cell membranes to reach intracellular targets
- they can also be designed to engage biological targets by various modes of action
- their distribution can further be tailored, for example to allow for systemic exposure with or without brain penetration, or perhaps to be maintained just within the GI system (Rifaximin)

Small Molecules

Small molecules also have some **disadvantages**

- Most are promiscuous-hit lots of targets and tissues
- Some do not cross the blood brain barrier (we wish they would!)
- Some suffer from “first-pass” degradation in the liver
  - Can be an **advantage** in liver diseases
- Some accumulate in certain tissues
  - This can also be an **advantage** in certain conditions
- Some have manufacturing or stability issues
  - Intermediates in the manufacturing process can be explosive!

Small Molecules

- **Drug-**Any substance (other than food) that is regulatory approved to prevent, diagnose, treat, or relieve symptoms of a disease or abnormal condition through a physiological effect
- **Nutraceutical**-a “biologically active substance” that has not been approved by a regulatory agency for a specific disease indication or condition but is available for human use
- **Shelved Compound**-a “drug-like molecule” that has been proven safe for human use in a clinical trial but has not been approved for a specific indication and IS NOT available for human use except in a clinical trial

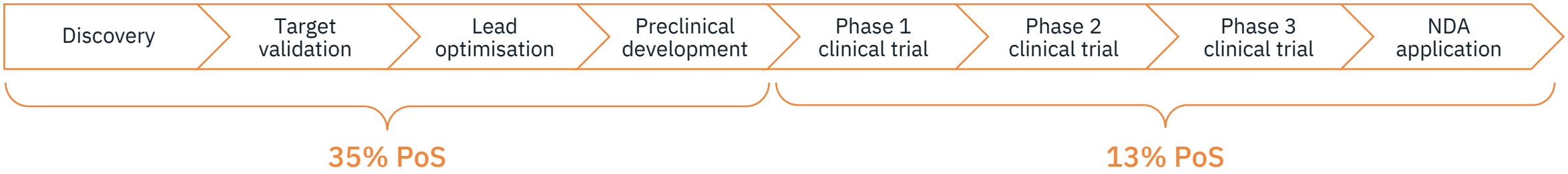
Small Molecules

- Ways to develop new small molecules
  - Developed through traditional rational drug design
  - Modified from existing drugs
  - Isolated from natural resources
  - Created by AI/ML techniques
- Traditional small molecule design includes
  - Biological target identification and validation
  - Making lots of molecules to hit the target
  - Determining which “hits” convert to “lead” molecules
  - Lead optimization

Redefining and de-risking new drug discovery

Traditional drug discovery process

12-14 years



Overall PoS = 5%

Mohs, R & Greig, N (2017) Alzheimer's & Dementia: Translational Research & Clinical Interventions, 3 (4) pp. 651-657

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Redefining and de-risking drug discovery

Traditional drug discovery process

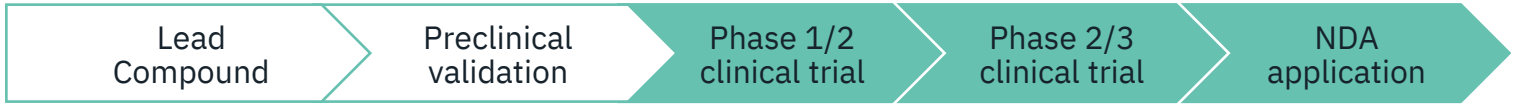
12-14 years

35% PoS

13% PoS

Drug Repurposing

6-8 years



60% PoS

30% PoS

Overall PoS = 18%

Mohs, R & Greig, N (2017) Alzheimer's & Dementia: Translational Research & Clinical Interventions, 3 (4) pp. 651-657
Schuhmacher A et al. (2016) Journal of Translational Medicine, 14 (105) p. 65

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Repurposing Pathways

- Patient/Caregiver Discovery-work with MD for “N of 1 study” (“Easiest”)
  - Use of AI tools/publication research, social media and other grassroots information
  - Some MDs may not be willing; + PoC could lead to larger trials
- PAG/Parent led investigator-Initiated Trial (IIT) to off-label use (“Possible”)
  - Small, open label, low cost/short time frame, publication critical
  - Depends on the disease endpoints, biomarkers, timeframe, pre-clinical data
- Patient Group led regulatory approval of generic drug (“Currently Hardest”)
  - Intermediate costs/time frame; can be challenging labeling requirements
  - Usually requires RCT pivotal study
- Full commercialization (Often no viability for Pharma, especially in rare)
  - Longer and more expensive; only if strong commercial potential
  - Modify an existing drug or repurposing a shelved compound

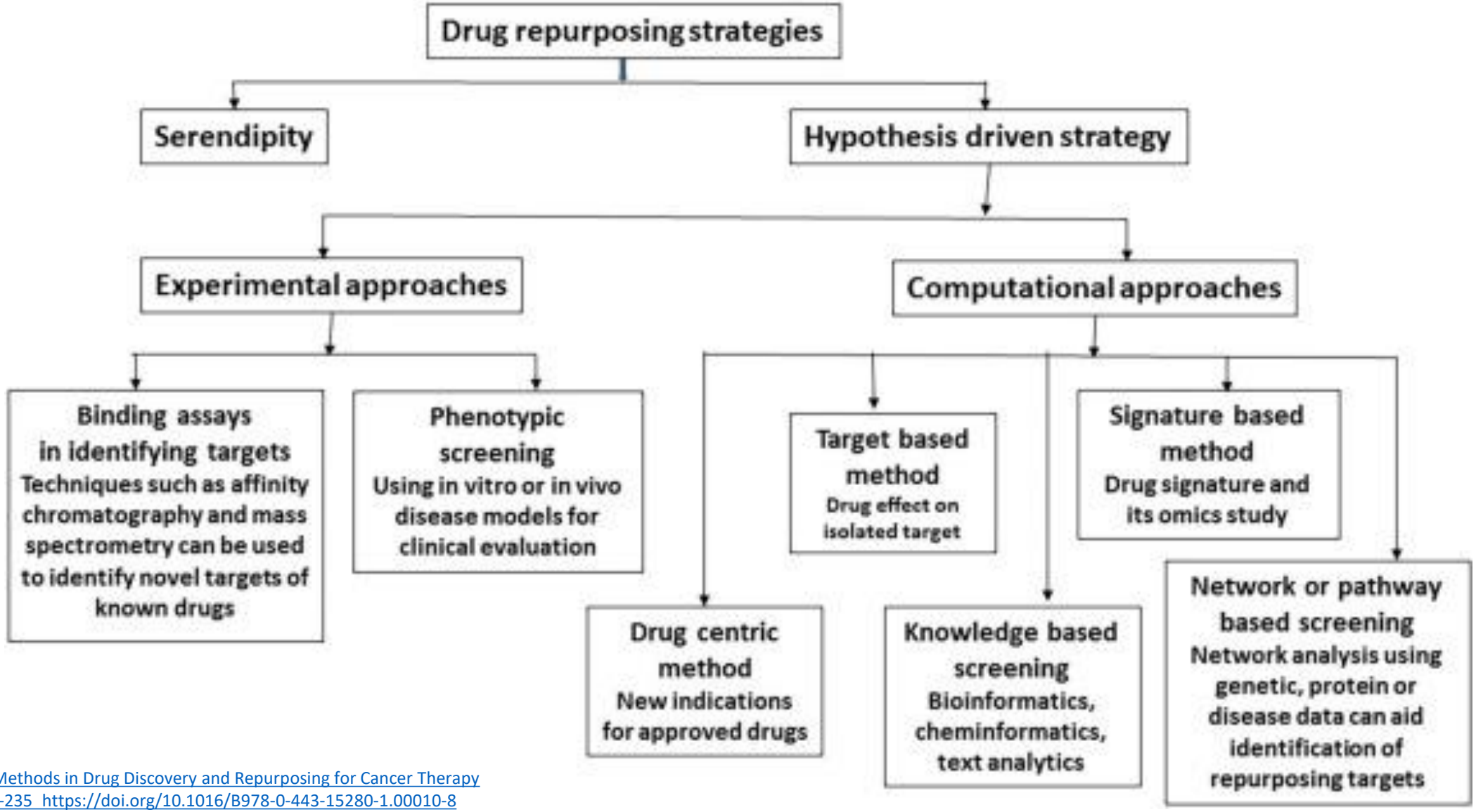
Drug Repurposing Identification

- **Serendipity**
  - Viagra, Minoxidil: side effect to therapy /pivot / almost direct to clinical trials
  - Neonatal Hemangioma: biology points to drug propranolol / direct to off label SOC
  - Cyclodextrin for Niemann-Pick Type C disease given to control animals improved condition and led to human use
- **Traditional Biology**
  - ALPS: gene discovery / elucidate target / obvious drug candidate / test in *in vivo* model / PoC clinical trial / change SoC / use off label / test on similar diseases
  - FD: gene discovery / elucidate protein function / assays built-biology confirmed / test nutraceuticals / **NO CLINICAL TRIAL** / patient+physician RWE testing / currently 8+ nutraceuticals combined restore 100% circulating protein
  - T1D-BCG vaccine repurposed to slowly change autoimmunity / traditional PH 1,2,3 clinical testing / $25M and 6+ years

Drug Repurposing Identification

- **Drug screening**
  - Assay development
  - Libraries
  - High throughput discovery to low throughput confirmation
- **Clinical observation**
  - Patients with co-morbidities
  - Physicians struggling for a solution
  - Patients self-treating
  - Social media/patient organizations
- **In silico screening**
  - Massive data
  - AI/ML
  - Discover new biology / existing drugs can lead to improved new chemical entities

Drug Repurposing Strategies



Computational Methods in Drug Discovery and Repurposing for Cancer Therapy
2023, Pages 223-235 https://doi.org/10.1016/B978-0-443-15280-1.00010-8

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AI and Repurposing

- **Positives**
  - **Faster** to patients
    - Lead compounds can get to clinical trials in under 2 years
    - Might be able to skip Phase I
    - Physician use without clinical trial validation
    - Off-label use after clinical trial validation
    - 505(b)2 FDA approval pathway
  - **Safer**
    - Known dosing, side effects, drug-drug interactions
    - Some repurposing is not in new indication (adult to child)
    - May need new tox studies for repurposing in a new rare indication

AI and Repurposing

- **Positives**
  - **Cost**
    - Can be cheaper to manufacture, buy, test, market
    - Downside is that repurposing generics have poor commercial viability
  - **Availability**
    - Often available to test (FDA Import Program)
    - If successful often generic and globally available to buy/use clinically
    - If not available in most countries, may be a way to create exclusivity
  - **Knowledge**
    - Data available for research (standard research and *in silico)*

Exclusivity, Development Benefit, Commercialization

- ODD (Orphan Drug Designation)-treats a disease affecting <200K people in the US, or >200K but no chance of commercial success
  - Tax credits for qualified clinical trials; Exemption from user fees
  - Potential seven years of market exclusivity after approval
- Fast Track-expedite the review of drugs to treat serious conditions and fill an unmet medical need
- Accelerated Approval-allows drugs for serious conditions that fill an unmet medical need to be approve based on a surrogate endpoint.
- Breakthrough Designation-expedite the development and review of drugs which may demonstrate substantial improvement over available therapy
- Pediatric or other Priority Review Vouchers-Fungible voucher that can be redeemed to receive priority review for a different product

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