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.
  - Most are natural substances, some are new chemical entities
- **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

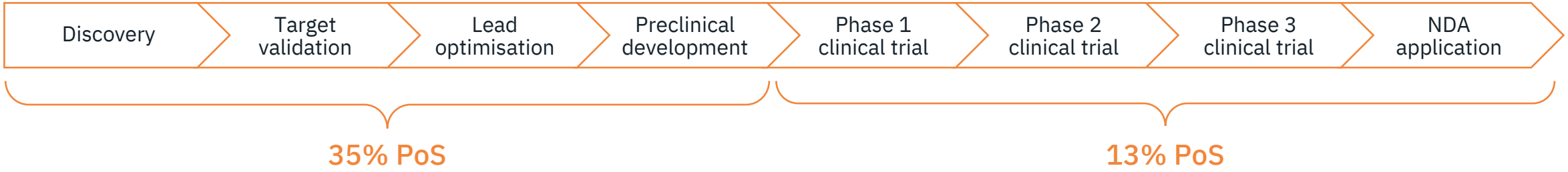
# Small Molecules

- 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

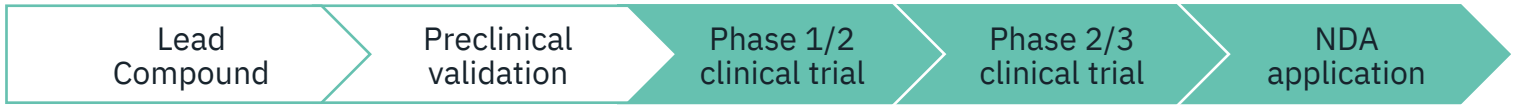
12-14 years


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/Parents work with MDs for “N of Some” observational repurposing study (“Moderate”)
  - Small, open label to gather information that could lead to a “real” study
  - Syngap Drug Repurposing of Tanganil; Fortuity Pharma / amlexanox

- 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

# Repurposing Pathways

- 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

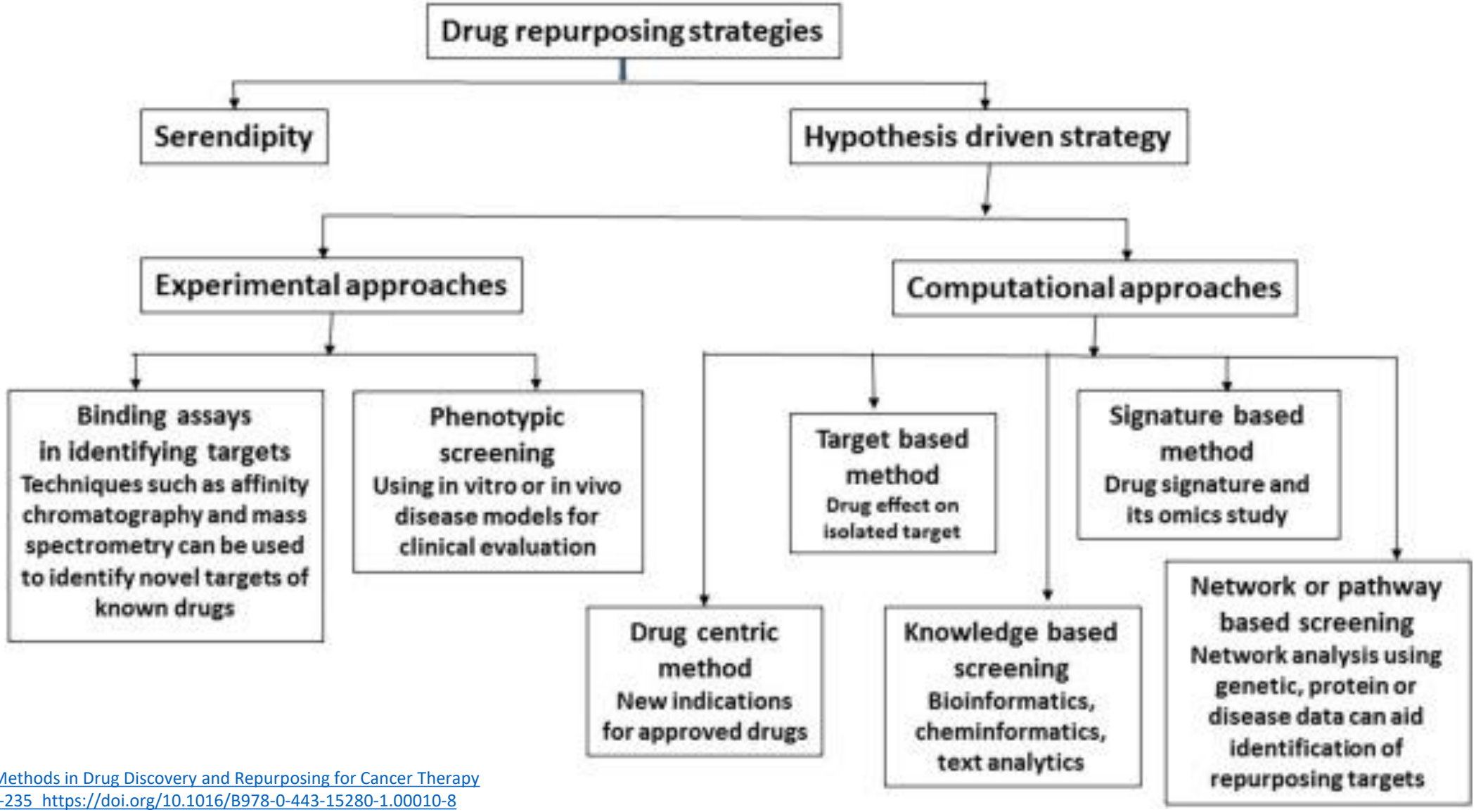
# Drug Repurposing Identification

- **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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# Drug 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

# DrugRepurposing

- **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

# Additional Resources

- NIH Translator AI/ML prediction generator for drug repurposing: https://ui.transltr.io/

- Companies that will do AI/ML predictions for PAGs:
  - BioVista https://www.biovista.com/solutions/drug-repositioning/
  - Purposeful https://purposeful.eu/diseases/

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# Thank You

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