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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 insulin, 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 (small) organic compounds 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

Small Molecules

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Small molecules also have some disadvantages

- Most are promiscuous-hit lots of targets and tissues
- Some do not cross the blood brain barrier
- 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

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- Ways to develop new small molecules
  - Developed through traditional rational drug design
  - Isolated from natural resources
  - Created by AI/ML techniques
- Traditional small molecule design includes
  - target identification
  - target validation
  - hit identification
  - hit to lead
  - lead optimization

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

Redefining and de-risking new drug discovery

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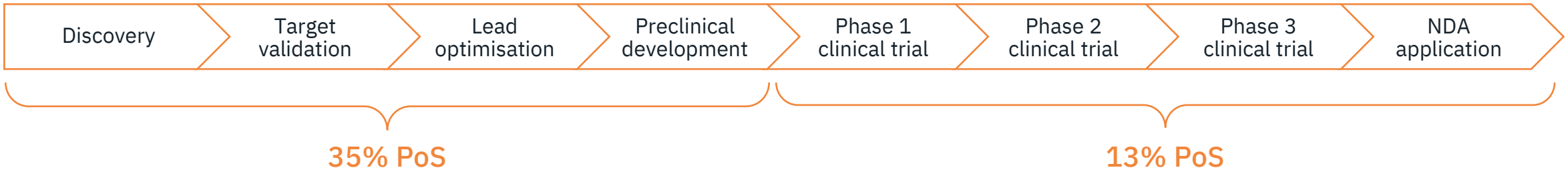
Traditional drug discovery process

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

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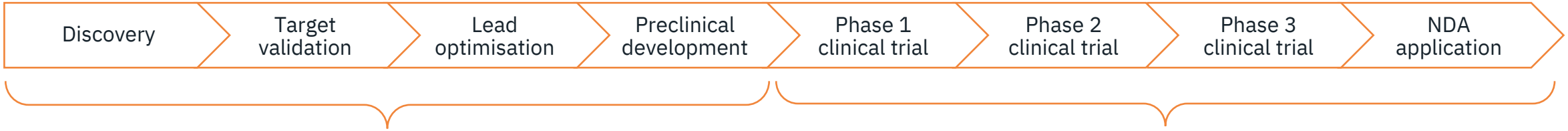
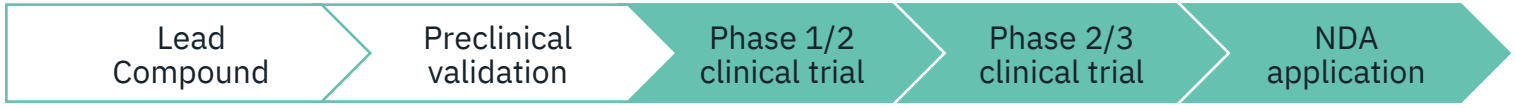


35% PoS

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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Drug Repurposing Identification

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- **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 discovered / target elucidated / obvious drug candidate / build and t4st in *in vivo* model / clinical trial-off label use / test on similar diseases
  - FD. gene discovered / protein function elucidated / assays built-biology confirmed / selective testing of 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

Drug Repurposing Identification

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- **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

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AI and Repurposing

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- **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

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- **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 and Commercialization

- Composition of Matter IP versus Method of Use IP
- ODD (Orphan Drug Designation)
- Pediatric or other Priority Review Voucher
- Cost differentials
  - Patient Group led investigator-initiated trial to off-label use
    - Could be very low cost and very short time frame
    - Depends on the disease endpoints, biomarkers, timeframe
  - Patient Group led regulatory approval of generic drug
    - Intermediate costs and time frame
    - Label change issues
  - Full commercialization
    - Longer and more expensive
    - Modify an existing drug or repurposing a shelved compound

Types of FDA Drug Reviews

- 505(b)(1) - applicant own or have a right of reference to all of the investigations relied upon by the application to support approval of the NDA
- 505(j) - generic application
- 505(b)(2) – a New Drug Application (NDA) that relies for approval on investigations not conducted by or for the applicant and for which the application does not have a right of reference
- Label changes

Thank You!

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