Drug Repositioning: Existing approaches and applicability for Duchenne Muscular Dystrophy

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Introduction
Drug Repositioning (DR)

What is it?

- The process of finding new indications for existing drugs
  - Also known as redirecting, repurposing and reprofiling
  - Approved or discontinued drugs
- Based on...
  - Serendipity
  - Informed insights
  - Systematic analytical platforms
Introduction

Why DR?

▶ + Faster development
▶ + Reduced uncertainty (safety & pharmakokinetic)
▶ - Intellectual property & commercial viability

Drug Repositioning

1-4 years
- Compound identification
- Compound acquisition
1-6 years
- Development (clinical trials)
1-2 years
- Registration
Market (3-12 years)

De novo discovery and development

4-9 years
- Target discovery
- Discovery and screening
- Lead optimization
- ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity)
5-6 years
- Development (clinical trials)
1-2 years
- Registration
Market (10-17 years)

Based on Ashburn and Thor, 2004
Introduction
Central idea in DR

One drug for many diseases

- "on-target": A target may be relevant to multiple diseases
  - Establish relevance to a new disease
- "off-target": A drug often interacts with multiple targets
  - Identification of secondary drug actions
Approaches for DR
General Approaches

Drug repositioning

Drug oriented
- FDA off-label use
- Clinical adverse effects
- Phenotypic screening
- Chemical information
- Target

Disease oriented
- Genetics
- Genomics
- Proteomics
- Metabolics
- Disease omics data
- Pathway

Treatment oriented
- Genetics
- Genomics
- Proteomics
- Metabolics
- Targeted pathway

Blinded
- Target based
- Knowledge based
- Signature based
- Pathway or network based
- Targeted mechanism based

Serendipitously tested and screened
- Cheminformatics and bioinformatics
- Network biology and systems biology

Mechanism or knowledge

Jin and Wong, 2014
Drug Discovery Today
Approaches for DR

Drug oriented

- Phenotypic data from off-label use or side effects
- Phenotypic screening
  - High-Throughput (HTS) and High-Content Screening (HCS)
- Virtual screening - *in silico*
  - Ligand-based
  - Structure based (Docking)

Blinded or target based
Approaches for DR
Disease and drug oriented

Knowledge based

- Aiming to predict new targets (for a disease or a drug)
  - Computational estimation of similarities
  - Integration of available information
  - Literature mining
Approaches for DR
Disease and treatment oriented

Signature based methods

- Gene expression data (microarrays)
- Connectivity Map, CMap (Lamb et al. 2006)
- Oposing signatures
Approaches for DR
Signature based methods

Sirota et al. 2011

Katie Ris, nature.com Lamb et al. 2006
Approaches for DR
Treatment and disease oriented

- Pathway/network based (molecular pathology)
  - Reconstruct new disease-specific pathways
- Targeted mechanism based (molecular activity)
  - Delineate unknown mechanisms of action of drugs
  - Drug combination effects
Computational methods
Computational strategies for Drug - Disease association
Computational methods
Similarity based

Network representations

- Drug chemical similarity
  - Similarity Ensemble Approach, SEA (Keiser et al. 2007, 2009)
- Molecular activity similarity
  - Mode of Action by Network Analysis, MANTRA (Iorio et al. 2010)
- Shared molecular pathology
  - Conserved Anti-coexpressed Gene Clusters (Molineris et al. 2013)

Combination of data sources

- Chemical structure, protein sequence & side-effects similarity.
  - Similarity-based LArge-margin learning of Multiple Sources, SLAMS (Zhang et al. 2013)
Computational methods

Interactions based

Interactions only

- Network-Based Inference, NBI (Chen et al. 2012)
  - Bipartite network of drug-target interactions
  - Comparison to drug/target-based similarity inference

Combination with similarities

- Drug pairwise similarity method (Li & Lu, 2012)
  - Drug structural similarity
  - Drug target-profiles similarity
    - Drug-Protein Interactions (DPI) and Protein-Protein Interactions (PPI)
Literature-Based Discovery (LBD)

- "ABC model" (Swanson, 1986)
- Inferring implicit relations between concepts
  - Different islands of knowledge
- Closed / open discovery process
Computational methods
Literature mining

LBD related fields

- Text retrieval (mainly titles and abstracts of scientific papers)
- Named entity recognition
- Co-occurrence analysis and lexical statistics
- Natural language processing and syntactic analysis
  - Type of the relationship / interaction
- Logic and rule based algorithms
- Semantic web technologies and biomedical ontologies
  - Semantic MEDLINE (Kilicoglu et al. 2008)
## Computational methods

### Literature mining

#### Combination with other resources

- **PROMISCUOUS** (von Eichborn *et al.* 2011)
  - Uniform data set for further analysis
  - Drugs, proteins and side-effects
  - Drug-target/side-effect/drug relations and PPI (literature mined)

- **Disease specific CMap** (Li *et al.* 2009)
  - Seed disease-related proteins expanded using known PPI
  - Lexical statistics to produce Drug-Protein CMap.

- **Clinical Outcome Search Space, COSS** (Lekka *et al.* 2011)
  - Systems Literature Analysis, SLA (Persidis *et al.* 2004)
  - Context-crossing relations among biomedical entities
  - Biomedical data from a comprehensive set of resources
  - Used for DR and adverse events prediction
Applicability for DMD
Duchenne Muscular Dystrophy (DMD)

What is DMD?

- Progressive muscle-wasting genetic disease
- Dystrophin-deficiency
DMD - associated abnormalities in muscle

- Membrane structure and function
  - Increased fragility and leakiness of the cell membrane
- Calcium homeostasis
  - Increased intracellular calcium levels
- Proteolysis
- Oxidative damage
  - Increased creatine kinase (CK) activity
- Apoptosis and necrotic myofibers
- Inflammation and fibrosis
- Regeneration impairment and tissue replacement
- Vascular problems and functional ischemia
Applicability for DMD

Therapies for DMD

Therapeutic approaches

- Corticosteroids
- Anti-inflammatory
- Anti-oxidants
- Proteolysis inhibition
- Improve vasorelaxation capacity
- Increase density of vascular network
- Gene therapy
  - Dystrophin cDNA transfer
  - Dystrophin producing cells introduction
  - Utrophin upregulation
  - Splicing modification of pre-mRNA
  - DNA repair in situ
Applicability for DMD
Prioritizing and integrating existing methods

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Applicability for DMD

Which alternative?

- Blinded and targeted
  - Important experimental part
  - Low advantage from available knowledge
- Knowledge based
  - Method specific data availability and existing systems results
  - Biological knowledge and therapeutic approaches
- Literature based discovery
  - No need for specific data
  - Combination with other data sources / methods
  - Could detect non obvious ideas for DR
- Treatment oriented
  - Data / knowledge availability
  - Towards specified treatment approach
  - Could lead to ”new knowledge” about a treatment approach
Thank you!

Any questions, ideas or comments?
References

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