DRUG REPURPOSING FOR PEDIATRICS:
A Clinician’s Perspective

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Disclosures

• Will be discussing products that are still investigational or not labeled for the uses under discussion
Overview

• Comparison of pediatrics and adult new drug development
• Why repurposing compelling in pediatrics
  – Cancer, non-Cancer
• What we are working on
New drug development is slower for children

- Begin pediatric phase I trials after completed in adults
  - Correlation is good between adult and pediatric MTDs
  - Greater IRB oversight?
- Limited patient numbers
  - Competing phase I trials
  - More potential targets, with genetic screening
- Lesser incentives to pharmaceutical industry
- Not all phase I drugs make it to phase II or III
# Drug Development

<table>
<thead>
<tr>
<th></th>
<th>Adult</th>
<th>Pediatric</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase I studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinicaltrials.gov*</td>
<td>9,585</td>
<td>1,370</td>
</tr>
<tr>
<td>cancer</td>
<td>5,702</td>
<td>678</td>
</tr>
<tr>
<td>PubMed Publications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cancer 2015-2019</td>
<td>~3,000</td>
<td>~220</td>
</tr>
<tr>
<td><strong>FDA approved</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015-6/2019</td>
<td>191**</td>
<td>213*</td>
</tr>
</tbody>
</table>

*8/10/2019
FDA labeling is only part of the problem

• Efforts since 1997 to:
  – *Incentivize* (FDAMA, [FDA Modernization Act])
  – *Mandate* (BPCA [Best Pharmaceuticals for Children’s Act]; PREA [Pediatric Research Equity Act])
  – *Promote* (Biologics Price Competition and Innovation Act)
  – *Pay for* (PDUFA [Prescription Drug User Fee Act])

  *Some, but not huge, impact on new drug development in children*

• Lots of information on drugs for which there are no pediatric labels: how to leverage this?
Advantages to Drug Repurposing in Pediatrics

• Using drugs with known safety profiles (whether or not FDA approved) streamlines the process by bypassing phase I

• Phase I market small in pediatrics
  – Most pediatric diseases are rare or orphan diseases
  – Especially true for childhood cancer, where cure rates already >80%

• Many parents don’t want to be part of phase I or II clinical trials
  – Using drugs with known safety profiles is likely to be more acceptable to parents and even to health care providers.
Repurposing already has a track record in pediatrics

- 404 drugs listed in Harriet Lane Handbook
- 40 repurposed for another pediatric application (10%)*

Repurposing underexplored in pediatrics

- **Hypothesis driven** (assumes knowledge of molecular targets; often based on adult studies)
- **Phenotypic** or Brute force (high throughput testing; often based on adult studies)
- **Serendipity**
Brute force method of drug repurposing*

- Phenotypic screening often uncovers unexpected new biology for an old target: e.g., sildenafil anti PDE-5 in lungs and also in corpus cavernosum, vascular malformations.
- Phenotypic screening sometimes uncovers a new target and new mechanism of action: e.g., propranolol beta blocker and anti-VEGF, anti SOX18.
- Phenotypic screening relies on libraries of drug repositories e.g., NCATS (NIH), Broad Institutes Drug Repurposing Hub.

*Ciallella JR, Reaume AG, Drug Disc Today Technol, 2017
These libraries fall short for pediatric drug development

• They contain a lot of drugs which haven’t been used in children.
  – HTS might identify pediatric targets but drugs would still need to go through phase I testing....
  – Would need to wade through data on lots of irrelevant drugs

• They don’t include all drugs which have been used in children.

• ~1000/4000 drugs in NIH repository used in kids;

Lack of a pediatric-centric drug library has been an obstacle to pediatric drug repurposing.
The Children’s Pharmacy Collaborative™*

- **Database of 1600+ drugs with a track record in kids**
  - Generic name, Brand name(s)
  - Chemical structure with links to SMILES
  - Category(ies) of drug
  - FDA approval: adult, pediatrics
  - Indications: original, and repurposed use; is repurposed use supported by clinical trials or other clinical data, or by in vitro data?
  - Mechanism of action
  - Supplier

*J Blatt, et al, Drug Disc Today 2014*
High Throughput Screening*

- 2 chemical libraries
  - MIPE: mechanistically annotated collection of investigational drugs with emphasis on oncology
  - NCATS Pharmaceutical Collection (NPC): collection of approved drugs
- Screened all against 20 pediatric solid tumor-derived cell lines (osteosarcoma, rhabdosarcoma, EWS, neuroblastoma, ATRT)
  - Of those also in CPC database, more than 30 not known to have anti-cancer activity had AC50’s of < 28uM (notably, antihelminthics, antimalarials, antiprotozoals...)

Then what?

• Even with a pediatric-centric drug repository
• Even when drugs are identified as interesting to test in patients based on *in vitro* study
• **How does one prioritize what drugs to study for repurposing in phase II trials?**
Serendipitous discovery of Propranolol for treatment of hemangiomas

- **Proband:** 9 wk, “capillary hemangioma” rx steroids; obstructive cardiomyopathy treated with propranolol; within 24 hrs, lightened in color and softer; flat by 14 months
- 11 patients: ibid
- Mechanism: nonselective β blocker:
  - Vasoconstriction
  - Decreased VEGF, bFGF expression?
  - Apoptosis of capillary endothelial cells?
  - SOX18 inhibition

Serendipity: a few other examples

<table>
<thead>
<tr>
<th>DRUG</th>
<th>INDICATION 1</th>
<th>INDICATION 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>Arthritis</td>
<td>Desmoids</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Malaria*</td>
<td>Sideroblastic anemia</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Reflux</td>
<td>Warts</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Seizures</td>
<td>Neuropathy</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Fungal infections</td>
<td>Cheloids</td>
</tr>
<tr>
<td>Lithium</td>
<td>Bipolar</td>
<td>Neutropenia</td>
</tr>
<tr>
<td>Nifurtimox</td>
<td>Chaga’s disease*</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Pulmonary hypertension</td>
<td>ED, Hemangioma</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Bacterial infections</td>
<td>lymphoma, myeloma</td>
</tr>
</tbody>
</table>

Many examples buried in the literature. How many of these did you know about?
Serendipitous drug repurposing can be fast

- Not only does serendipity bypass Phase I, it may bypass need for *in vitro* models, provides additional in human preliminary data
- Compelling justification for Phase II trials
- Can serendipity be done more efficiently?
  - Do kids have enough pathology to make serendipity feasible?
  - Can we bypass insurance companies?
  - Do we have to rely on the observant clinician?
    - *Global Cures*
Prevalence of Any Chronic Condition in Children*

There is an audience for pediatric drug development, and an opportunity for drug repurposing.

*J. Van Cleave et al. JAMA 2010.
Social Media to Systematize Serendipitous Drug Repurposing?

- Adverse events/safety
- Therapy adherence
- Patient medication and monitoring preferences
- Interventions (drug, tobacco abuse)
- Specific disorders and categories of disease
  - Ophthalmology, Cardiology, Psychiatry and neurocognitive issues, Cancer, Obesity, Orphan Diseases

- Almost nothing on use of SM for drug repurposing
  - Heavy emphasis on mining existing SM databases
Consumer-based Drug Repurposing: a Survey

• Have you ever taken a medication meant for any disease or symptom and thought that it helped treat another disease or symptom?

• If your answer was “yes”, please list the drug, the problem you were taking the drug for, and the other problem it seemed to treat. **We are interested in any and all medicines** (including prescription drugs, over-the-counter drugs, herbals, etc...), and **any and all problems**, both medical and psychological, even if they seem small

• **Adults and parents of minors**
Social Media to Systematize Serendipity*

• Survey to 40,000 UNC Facebook friends demonstrated feasibility and ease:
  – 49 responses within a week

• Scientific curating of results
  – 2 responses actually interesting

• Ramp up numbers, maybe to millions!

• **Focused queries** targeting **specific disorders** across the **globe**

Repurposing through consumers, not just the observant clinician

Vascular Anomalies
Repositioning, if not Repurposing: Vascular Malformations

- Sirolimus (rapamycin): mTOR inhibitor
- ARQ 092 (Miransertib): potent selective, allosteric AKT inhibitor
- BYL719 (Alpelisib): PIK3CA inhibitor
- Trametinib (Mekinist): MEK1, MEK2 inhibitor
- Notch inhibitors=Gamma secretase inhibitors
Conclusions

• Drug repurposing/repositioning is ideally suited to children

• Drug repurposing can be specifically addressed for a range of childhood disorders (some of which also occur in adults) including vascular malformations and cancer

• Need better models and more $

• Partner with industry, insurance companies, and the public
  – Social media, crowdsourcing