DRUG REPURPOSING FOR PEDIATRICS:

A Clinician's Perspective

Julie Blatt, M.D.

Pediatric Hematology-Oncology

University of North Carolina at Chapel Hill

11/2019

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

	Adult 18-64 yr	Pediatric 0-17 yr
Phase I studies		
Clinicaltrials.gov*	9,585	1,370
cancer	5,702	678
PubMed Publications		
cancer 2015-2019	~3,000	~220
FDA approved		
2015-6/2019	191**	213*

*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*…)

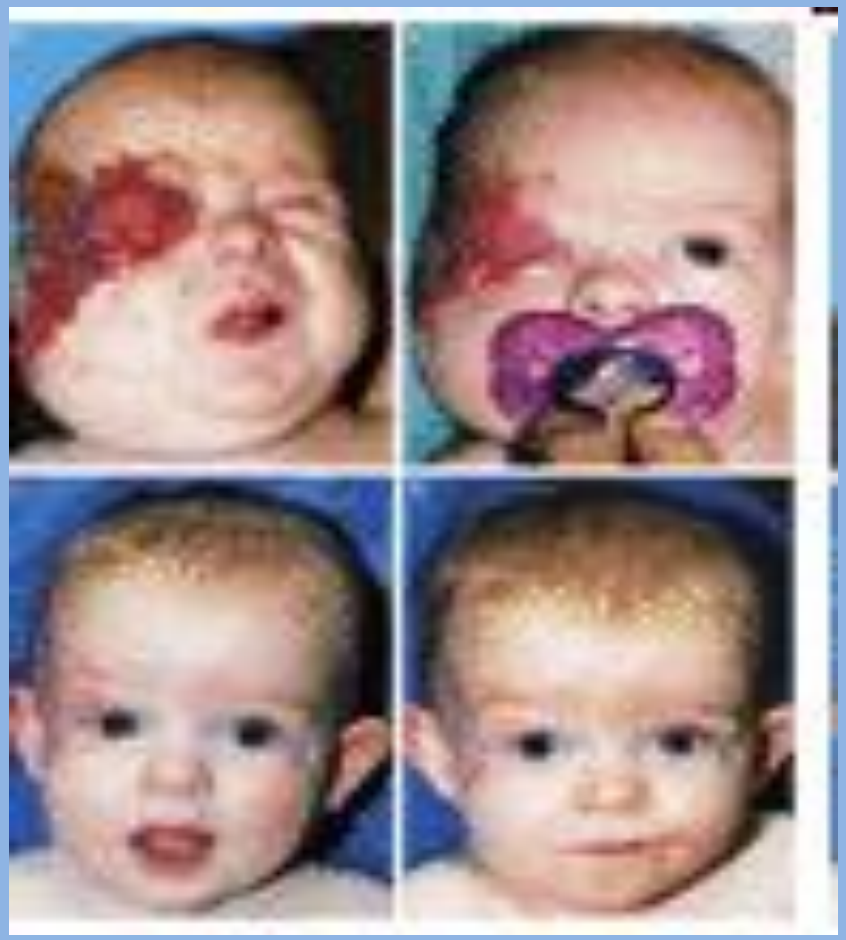
* M Shen, et al. Oncotarget 2017.

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



C Leaute-Labreze , et al. NEJM 2008.

Serendipity: a few other examples

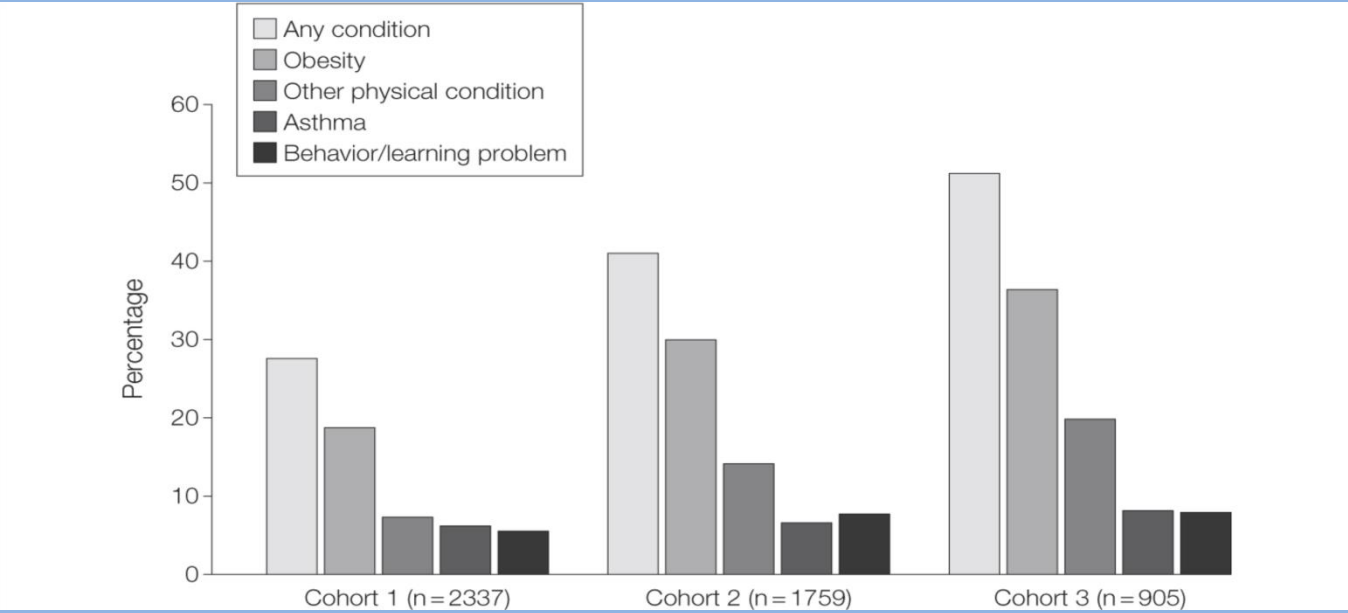
DRUG	INDICATION 1	INDICATION 2
• Celecoxib	Arthritis	Desmoids
• Chloroquine	Malaria*	Sideroblastic anemia
• Cimetidine	Reflux	Warts
• Gabapentin	Seizures	Neuropathy
• Itraconazole	Fungal infections	Cheloids
• Lithium	Bipolar	Neutropenia
• Nifurtimox	Chaga's disease*	Neuroblastoma
• Sildenafil	Pulmonary hypertension	ED, Hemangioma
• Clarithromycin	Bacterial infections	lymphoma, myeloma

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*

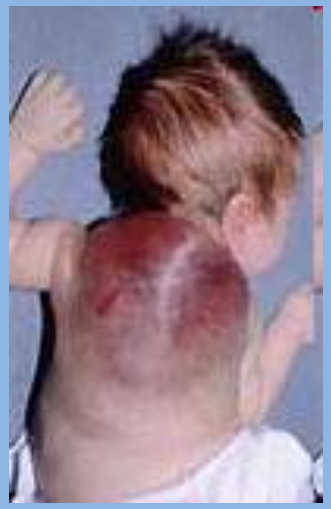
Social Media to Systematize Serendipity*

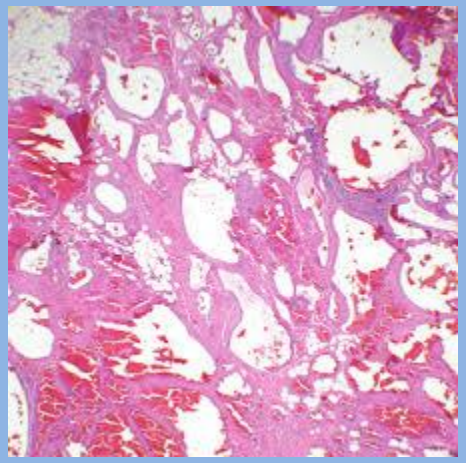
- Survey to 40,000 UNC Facebook friends demonstrated feasibility and ease:
  - 49 responses within a week
- Scientific curating of results
  - 2 responses actually interesting
- Ramp up numbers, maybe to millions!
- **Focused queries** targeting **specific disorders** across the **globe**

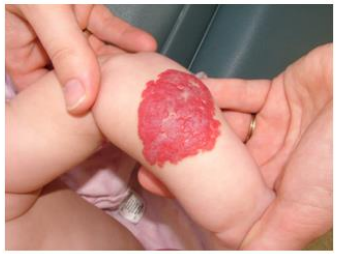
Repurposing through consumers, not just the observant clinician

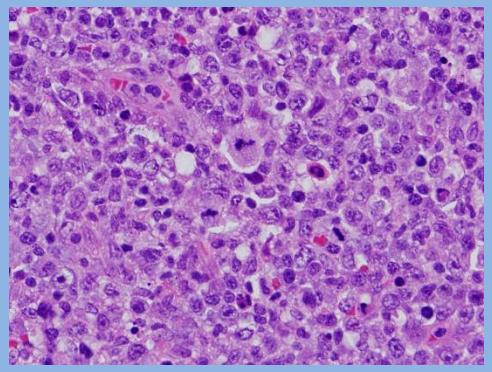
*DP Kelly, J Blatt. Drug Disc Today 2019.

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