U.S. FOOD & DRUG ADMINISTRATION

Drug Repurposing and Development of New Indications

Clinical Investigator Training Course

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CURE ID Challenging cases... New approaches

Outline

- Drug Repurposing and Development of New Indications
- Advantages and Challenges of Drug Repurposing
- Repurposing of Drugs by Clinicians
- Case Studies: Castleman's Disease and Leg Cramps
- CURE ID Platform
- Regulatory Considerations for Repurposing
- Conclusions

What do these infectious diseases have in common?

Parasites/protozoa

Sarcocystis
Anasikiasis
Dracunculiasis
Dirofilariasis
Fascioliasis
Paragonimiasis
Clonorchis
Babesiosis
Anaplasmosis
Balantidium
Sparganosis
Microsporidiosis
Loa loa
Plasmodium knowlesi
Enterophthoromycosis
Toxoplasmosis in pregnancy
Trichinellosis
Myiasis
Balamuthia mandrillaris
Acanthamoeba
Naegleria

Bacteria

Melioidosis
Nocardia
Whipples disease
Oroya fever
Atypical mycobacteria
Buruli ulcer

Fungi

Penicillium marneffii
Mycetoma
Exerohilum rostratus

Viruses

Dengue
Japanese encephalitis
Rabies
CCHF
Marburg/Lassa/Ebola
Zika/Chikungunya
West Nile
Western/Eastern encephalitis
Powassan
California encephalitis
Rift valley fever
Yellow fever
Creutzfeldt-Jacobs
MERS
SARS

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SARS

COVID-19

They all lack sufficient approved treatments.

Current State….

Millions suffer from diseases like these with no approved therapies

Many more suffer from diseases for which limited approved therapies exist, but from which they are unable to benefit.

- drug intolerance,
- contraindication to existing treatment,
- unavailability of drug

Definition

Drug repurposing is the identification of potential novel uses of existing drugs.

Why drug repurposing?

Drugs may be useful for more than one disease:

- The same physiological drug targets are often shared by different diseases
  - Sildenafil for erectile dysfunction and pulmonary hypertension
  - carbamazepine for seizures and peripheral neuropathy

- Many drugs have off-target effects that may be useful in different diseases
  - minoxidil for hypertension and hair loss

- Multiple uses of drugs can be identified using
  - in silico modeling
  - high throughput screening
  - animal models
  - clinical experience in patients

Advantages of drug repurposing?

- Time and cost to develop an existing drug for a new indication may be significantly less compared to developing a new drug from scratch because:
  - Chemistry and manufacturing controls have been addressed
  - Toxicology has been studied in animals and other models
  - Clinical pharmacology is understood
  - Clinical safety has been characterized in humans

Unmet medical needs where drug repurposing may be particularly useful

- Rare diseases with poor investment returns
  - e.g., amebic encephalitis, buruli ulcer, rare cancers, rasopathies, Castleman's disease
- Sporadic diseases which are difficult to study
  - e.g., plague, lassa fever, ehrlichiosis
- Emerging diseases with no time for de novo drug
  - e.g., drug resistant gram-negative infections, exposure to environmental or bioterrorism agents
- Populations lacking approved therapies
  - e.g., neonates, pregnant women
- Combination treatments
  - e.g., for atypical mycobacterial infections
- Different diseases with shared drug targets
  - e.g., PD 1, immune modulators

Examples of drugs repurposed for infectious diseases

Drug	FDA approved indications	Uses documented in Literature/Guidelines
Imipenem	Lower respiratory tract, Urinary tract, Intraabdominal, Gynecologic, Bacterial septicemia, Bone and Joint, Skin and skin structure, Endocarditis, Polymicrobic infections	Nocardia
Azithromycin	Bacterial exacerbation of chronic bronchitis, Bacterial sinusitis, Pharyngitis/tonsillitis, Skin infections, urethritis/cervicitis, Genital ulcers, Pneumonia (CAP),	Trachoma
Levofloxacin	Pneumonia (CAP), Skin infections, Prostatitis, Plague, Anthrax, Urinary tract infections, Bacterial exacerbation of chronic bronchitis, Bacterial sinusitis	Tuberculosis, Oroya fever
Pentamidine	Pneumocysits Jirovecii	Trypanosomiasis
Ambisome	Aspergillus, candida, Cryptococcus, febrile neutropenia, visceral leishmaniasis,	Acanthamoeba
Ivermectin	Strongyloides, Onchocerciasis	Lymphatic filariasis, Scabies, Lice
Atovaquone	Pneumocystis	Babesiosis
Ceftriaxone	Lower Respiratory Tract Infections, Skin Infections, Urinary Tract Infections Pelvic Inflammatory Disease Bacterial Septicemia, Bone and Joint Infections, Intra-abdominal Infections, Meningitis, Surgical Prophylaxis	Whipple's disease Lyme disease
Rifampicin	Tuberculosis, Meningococcal prophylaxis	Brucellosis

Examples of drugs repurposed for non-infectious diseases

Drug	FDA-approved indications	Uses documented in Literature/Guidelines
Sirolimus	Organ rejection post kidney transplant	**Castleman's Disease, Lymphangioliomyomatosis**
Cyclosporine	Organ rejection post liver, kidney, and allogeneic heart transplants. Graft vs. host disease. Amyotrophic lateral sclerosis. Bechet.	**Aplastic anemia, Duchenne muscular dystrophy, autoimmune hepatitis, Langerhans cell histiocytosis.**
Rituximab	Non-Hodgkin's Lymphoma, Chronic Lymphocytic Leukemia, Rheumatoid arthritis unresponsive to other therapies.	**Idiopathic Thrombocytopenic Purpura, multiple sclerosis, various debilitating and relapsing autoimmune conditions, systemic mastocytosis**
Pulse-steroid therapy using solumedrol	Allergic reactions, asthma, acute inflammation related to infectious disease or injury, arthritis.	**Hypomyelination with brainstem and spinal cord involvement and leg spasticity, Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation**
Amantadine	Influenza A, Parkinson's Disease	**Huntington's Disease**

Drug repurposing in clinical practice

Upon approval, drugs are labeled for those indications or diseases sought by the drug sponsor for which there is substantial evidence of effectiveness (other indications can be added through supplemental approvals).

Once a drug is approved, based on knowledge and professional judgement, physicians may take the responsibility for prescribing drugs for different populations, doses and diseases not listed in the approved label.

Repurposing of drugs by clinicians

- Drug repurposing is common in clinical practice based on academic publications, expert opinions, theoretical hypotheses, clinical hunches
- In many cases the risk-benefit of repurposed drugs is not well understood
- Some drugs that are repurposed in clinical practice may turn out to be ineffective or harmful
- Some repurposed drugs may become so commonly used that trials become difficult or unethical to do, and the true efficacy remains uncharacterized
- Dose and duration of therapy may be inappropriate for repurposed uses

Example of repurposing by clinicians: Castleman's disease

- David Fajgenbaum was a young medical student at Georgetown university, suddenly stricken with idiopathic multicentric Castleman's disease
- Despite desperate attempts by specialists to treat the disease with steroids and chemotherapy, he suffered several attacks with life-threatening multiorgan failure
- The attacks were characterized by extreme activation of his CD8 lymphocytes
- He studied his own lymph node biopsies in the lab, and he observed marked overactivity of the VEGF-A and PI3K/Akt/mTOR pathways during the periods prior to his relapses

Castleman's disease

- Sirolimus is a powerful immunosuppressant approved for the prevention of kidney transplant rejection
- David noticed that sirolimus inhibited lymphocyte activation via the VEGF-A and mTOR pathways; the precise pathways that were so active in his lymph node biopsies
- In desperation he began treating himself with sirolimus, with miraculous results
- He has now been healthy and relapse-free for more than seven years (previously he was relapsing on average every 8 months)

David's drug repurposing journey

directorsblog.nih.gov/tag/chasing-my-cure/

Chasing My Cure

Seven Questions for a Rare Disease Warrior

Posted on February 27th, 2020 by Dr. Francis Collins

Caption: David Fajgenbaum (right) and I pose for a photo a few years ago in Philadelphia.
Credit: National Disease Research Interchange, Philadelphia

Tomorrow is Rare Disease Day at NIH, marking the 12th year that this annual event has been held on the NIH campus. Similar gatherings have been organized independently around the world this week, all to raise awareness for the nearly 7,000 rare diseases, some affecting just a few dozen people. But, collectively, rare diseases are hardly rare. One in 10 Americans has a rare disease (defined as affecting 200,000 or fewer individuals in the US), and about half are children. Without needed treatments, about 30 percent of these children will die by age 5.

To join everyone in raising awareness, I wanted to feature on my blog a unique perspective about rare diseases, and David Fajgenbaum certainly has one. Fajgenbaum is an immunologist and NIH grantee at the Perelman School of Medicine, University of Pennsylvania, Philadelphia. When Fajgenbaum isn't running studies or clinical trials, he must remain vigilant of his own health. Fajgenbaum has a rare disease called idiopathic multicentric Castleman disease (iMCD), and this devastating condition, which emerged while he was in medical school, nearly claimed his life several times.

Now 34 years old and in a long remission, Fajgenbaum can discuss rare diseases as a doctor, as a patient, as a researcher, and as an advocate. His personal journey, published in his recent book *Chasing My Cure*, is a gripping read. Fajgenbaum was kind enough to answer a few of my questions on rare diseases and share some of his lessons learned.

Clinical studies of sirolimus in Castleman's disease

- Wanting to share this brilliant discovery with others suffering from this untreatable fatal disease, but recognizing the limitations of his own personal experience, however miraculous, David launched trials of sirolimus for iMCD

- In these trials, it became apparent that only ~1 in 3 patients seemed to respond, suggesting that sirolimus was only effective in a particular subpopulation with the disease

- Without formal study, many individuals might have been treated with a toxic medication with no benefit

Takeaways from the Sirolimus Example

Key Lesson: Formal study is essential, even when an approved drug looks promising

Identifying an effective repurposed drug is not just about finding a disease a drug is effective for, but also about what population of patients and what the dose, duration and route of administration should be for the new indication.

Example of repurposing by clinicians: leg cramps

- Quinine was used in millions of patients for putative benefit in leg cramps

- Efficacy for leg cramps has never been demonstrated in adequately controlled trials

Pharmacovigilance indicated serious adverse events

- In a survey of physician practices in the United States, ~92% of quinine prescriptions were associated with off-label use for leg cramps and muscle pain. Often the treatment was used for years
- Quinine carries a warning for hematologic events, primarily thrombocytopenia, but also ventricular arrhythmias, hypersensitivity reactions, and optic neuritis
- Of the 38 domestic cases of serious adverse reactions reported to FDA between 2005 and 2008, 17 required hospitalization and 11 were considered life-threatening and 5 were fatal.
- In only 1 of the 38 cases, quinine was used for the treatment of malaria (it's FDA-approved indication); in the remaining cases, it was used off-label for the treatment of leg cramps and other muscle cramps or the treatment of restless leg syndrome or neuropathy.

Source: https://www.medscape.com/viewarticle/771699#vp_1

Enforcement action taken by FDA to stop the use of quinine for leg cramps

- FDA issued warnings not to prescribe quinine for nocturnal leg cramps (an off-label use,) because there were risks of serious and life-threatening adverse effects, and the benefit was not shown.
- In 2010, the FDA issued a Risk Evaluation and Mitigation Strategy (REMS), which resulted in a decrease in off-label use.
- However, data as recent as 2011 indicate that the majority of quinine use in this country continues to be related to leg cramps and muscle pain, and serious adverse events continue to be reported."

Source: https://www.medscape.com/viewarticle/771699#vp_1

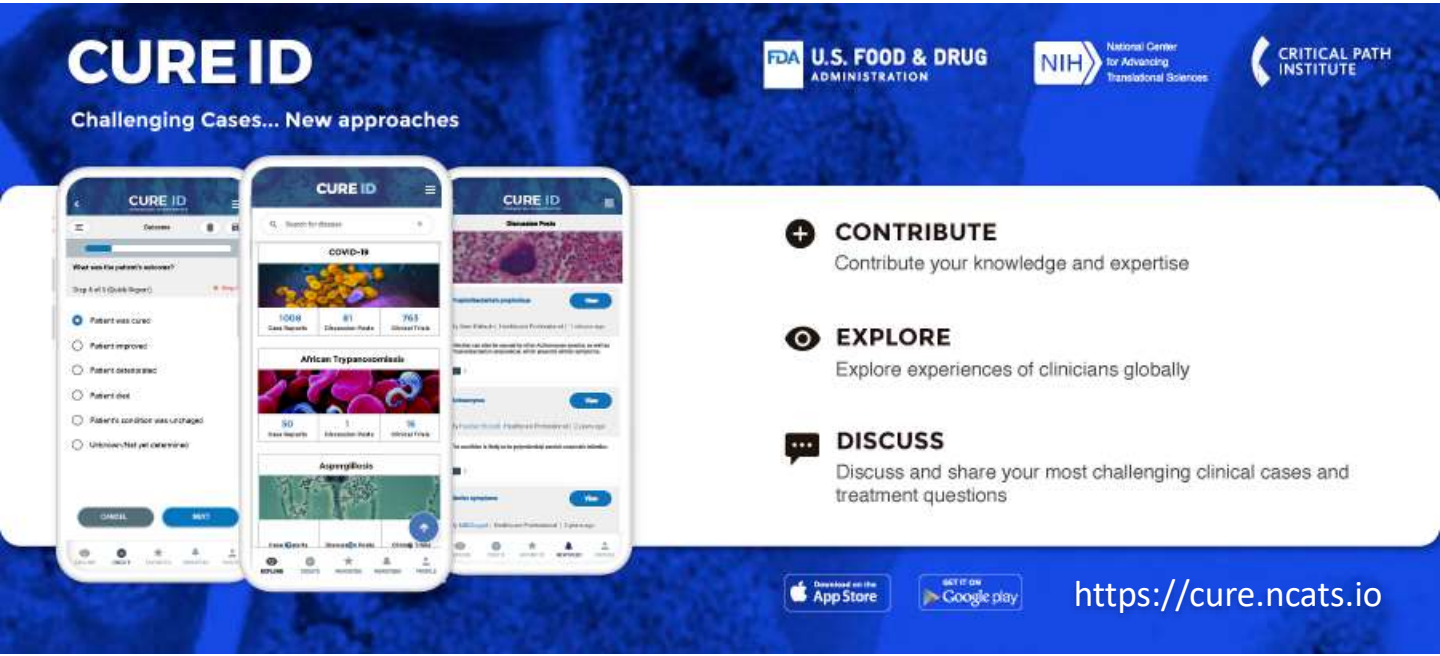
Take-Aways from the Quinine Example

- **Key Lesson:** Formal studies are needed to confirm efficacy. The risk-benefit ratio for unapproved indications may not be appreciated and may differ from that of the approved indication.

Understanding repurposing by clinicians is important

- Collecting clinical experience on how existing drugs are being repurposed may allow identification of:
  - Promising drugs, drug combinations, and treatment regimens for unmet medical needs
  - Treatments that are not effective
  - Treatments that are harmful

CURE ID: A Platform to Capture Novel Uses of Existing Drugs



Potential uses of CURE ID

- Serve as a rapid communication platform for healthcare providers during an outbreak, providing for systematic case-sharing, discussions, and the latest literature.
- Facilitate the sharing of information on potential therapies for diseases which lack available, approved treatments and inform current and future clinical trials, serving as an important step between unstructured anecdotal reports and the robust randomized trials ultimately required for drug approval.
- Enable the exchange of opinions from global communities of experts.
- Help to identify potential new uses for existing drugs and limit unhelpful or harmful uses.

Intent and Limitations of Data

- It is important to note that CURE ID is not intended to be used by pharmaceutical companies or manufacturers to advertise or promote unapproved uses of drugs.

- Case reports from clinical experience can provide signals and help to generate hypotheses for future clinical study, but such anecdotal evidence is insufficient to establish the safety or effectiveness of a new use of an existing product.

- Inclusion of data in the CURE ID repository also does not indicate that FDA, NIH, or other CURE ID partners endorse its validity, reliability, or usefulness in making individual patient treatment decisions.

Regulatory considerations

- Repurposing should be based on substantial evidence
- New Drug Applications for repurposed drugs may rely on
  - Clinical trials performed by a sponsor
    - NDA 505(b)(1) (original data)
      - Relies on studies performed by the Sponsor
      - Typically includes 2 or more Phase III randomized studies
  - Reference to published literature
    - A 505(b)(2) application is one for which one or more of the investigations relied upon by the applicant for approval "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted" (21 U.S.C. 355(b)(2)).
    - Guidance for Industry: Applications covered by 505(b)(2): https://www.fda.gov/media/72419/download

Conclusions

- Drug Repurposing offers significant promise as a tool for identifying treatments for unmet need
- Repurposing experience of clinicians may be important to identify promising new uses of existing drugs, as well as ineffective or harmful uses
- Adequate and well-controlled studies are still needed to ultimately determine whether a drug is safe and effective for a new use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Case example: Sirolimus for Castleman's Disease

https://pubmed.ncbi.nlm.nih.gov/31408438/

Fajgenbaum DC, Langan RA, Japp AS, Partridge HL, Pierson SK, Singh A, Arenas DJ, Ruth JR, Nabel CS, Stone K, Okumura M, Schwarer A, Jose FF, Hamerschlak N, Wertheim GB, Jordan MB, Cohen AD, Krymskaya V, Rubenstein A, Betts MR, Kambayashi T, van Rhee F, Uldrick TS. Identifying and targeting pathogenic PI3K/AKT/mTOR signaling in IL-6-blockade-refractory idiopathic multicentric Castleman disease. J Clin Invest. 2019 Aug 13;129(10):4451-4463. doi: 10.1172/JCI126091. PMID: 31408438; PMCID: PMC6763254.

Identifying a biological target and finding an existing drug that acts on that target

- "Studies of 3 IL-6 blockade–refractory iMCD cases revealed increased $CD8^+$ T cell activation, VEGF-A, and PI3K/Akt/mTOR pathway activity.
- Administration of sirolimus substantially attenuated $CD8^+$ T cell activation and decreased VEGF-A levels.
- Sirolimus induced clinical benefit responses in all 3 patients with durable and ongoing remissions of 66, 19, and 19 months."

Source: https://www.jci.org/articles/view/126091

Even a “successful” repurposed drug may help some patients, but not all

- NCT03933904 – “Sirolimus in Previously Treated Idiopathic Multicentric Castleman Disease”
- Preliminary data suggests only 1/3 of patients seem to respond to treatment with Sirolimus in a single arm*, open-label, multicenter study (amongst those with an already very specific subtype of Castleman’s disease)

(Source: Personal Communication with Study PI)
*Previous randomized, placebo-controlled trial had shown 0% response in placebo group, so single arm design was chosen for larger study

Differing benefit/risk assessments for different indications

- "When we assess risk/benefit, we have to consider the seriousness of the disease or condition being treated, the duration of drug exposure, and the seriousness of the adverse events.
- Untreated *P falciparum* malaria is potentially fatal, and the duration of treatment with quinine is generally limited to 7 days. The risk/benefit assessment of quinine for the treatment of *P falciparum* malaria is favorable.
- In contrast, given the lack of substantial evidence of efficacy and the considerably longer duration of treatment for leg cramps, the risk/benefit assessment for this off-label use of quinine is not favorable. This is reflected in the product labeling for quinine."

- Dr. Hala Shamshuddin, FDA in Medscape article

Source: https://www.medscape.com/viewarticle/771699#vp_1