Mining for Therapeutic Gold:
A More Strategic and Collaborative Approach to Drug Rescue and Repurposing

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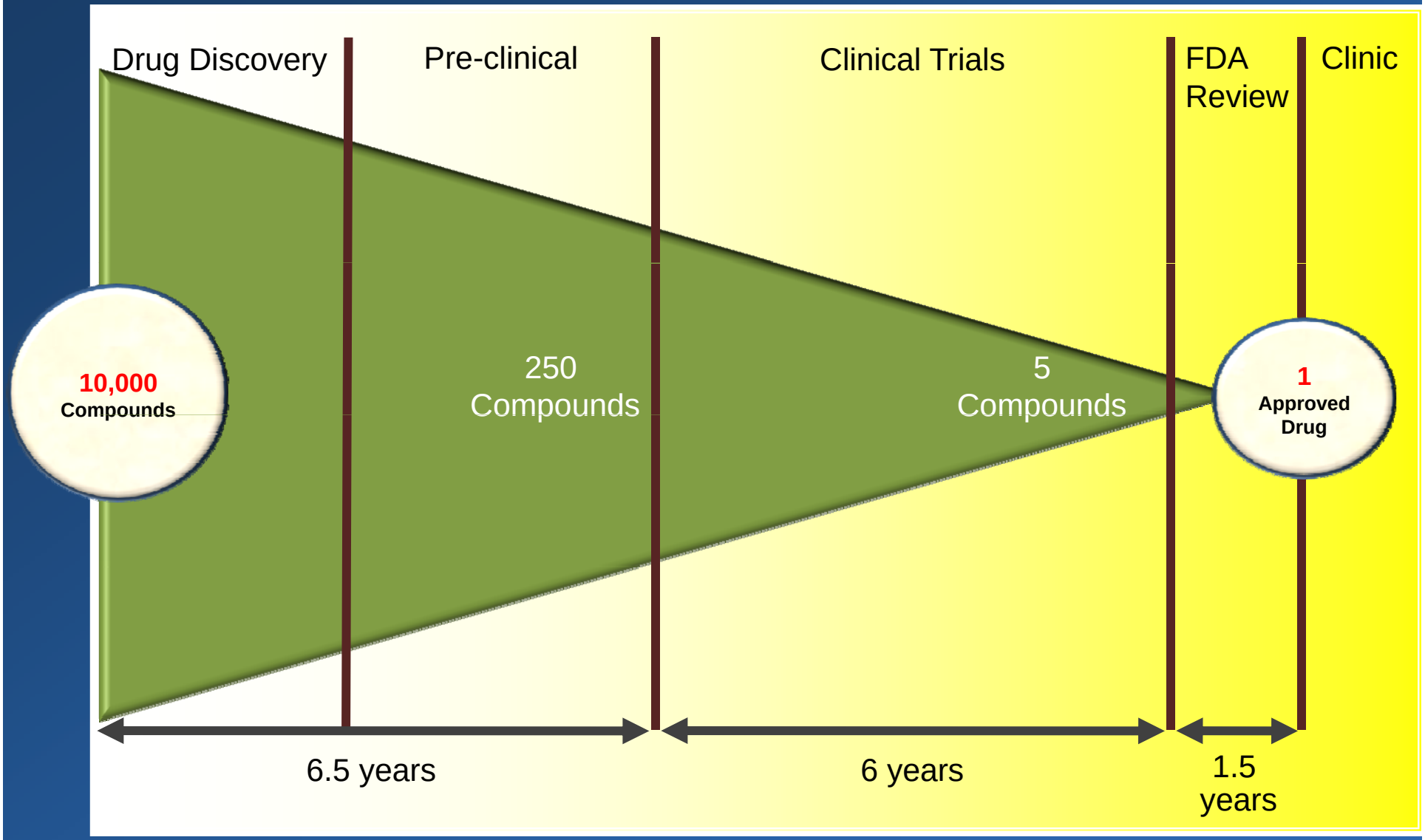
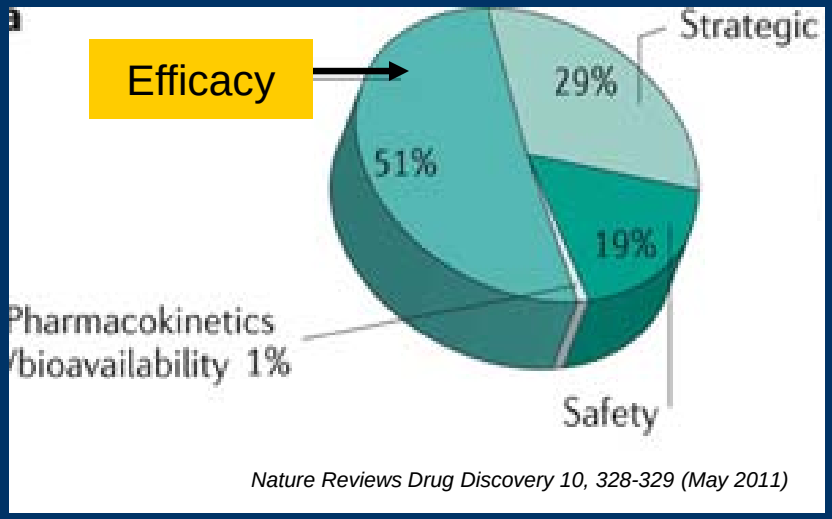
June 9-10, 2011

Advisory Committee to the Director

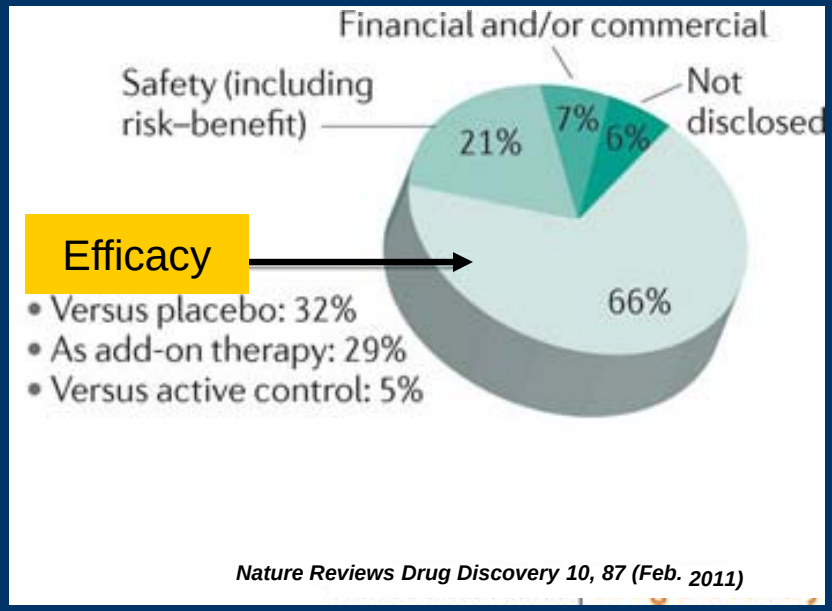
Development of New Therapeutics



High Attrition Rate of Late-stage Drug Development: Pool of Potential Candidate Compounds for Rescue



Nature Reviews Drug Discovery 10, 328-329 (May 2011)



Nature Reviews Drug Discovery 10, 87 (Feb. 2011)

- **Phase II failures (2008-2010):**
  - **51% due to lack of efficacy**
- **Phase III and submission failures (2007-2010):**
  - **66% due to lack of efficacy**

Drug Rescue and Repurposing

- A strategy to help reduce development timeframe, costs, and failure rates
- Leverages previous research and development efforts
- Can lead to remarkable outcomes

Thalidomide

Serendipity at work

- **Initially marketed as a sedative/analgesic/antiemetic**
- **Later shown to cause severe birth defects**
- **Observed to relieve pain and skin inflammation in leprosy**
  - **Approved as treatment for leprosy in 1998**
- **Later found to inhibit tumor necrosis factor alpha**
  - **Approved to treat multiple myeloma in 2006**

NIH Activity in Drug Rescue and Repurposing: Selected Examples

Drug	Brand Name	Initial Indication	Subsequent Indication(s)
AZT	Retrovir	Antineoplastic	HIV/AIDS
Ceftriaxone	Rocephin	Bacterial Infection	Amyotrophic lateral sclerosis
Hydroxyurea	Hydrea	Cancers	Sickle-cell Anemia
Metformin	Glucophage	Type 2 diabetes	Breast cancer
Pioglitazone	Actos	Type 2 diabetes	Hepatic steatosis
Raloxifine	Evista	Osteoporosis	Breast Cancer
Tamoxifen	Novaldex	Breast cancer	Bipolar disorder

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Zidovudine/Azidothymidine (AZT)

Intentional approach to R & R

- **1984: NCI program to develop anti-HIV drugs**
  - **Collaborated with Burroughs-Wellcome scientists studying murine retroviruses as a model for AIDS**
  - **A BW compound—AZT—found to be effective against HIV**
- **NIH and BW collaborated with Duke University to conduct clinical trials**
  - **Demonstrated antiviral activity of AZT in humans**

Metformin

Epi and meta-analysis at work

- Approved for use in diabetes
- Epidemiological studies and meta-analysis revealed that metformin use is correlated with decreased risk of breast cancer
- Metformin observed to inhibit growth of several types of cancer cells *in vivo*
- Ongoing NCI-sponsored phase III trial for treatment of early-stage breast cancer

Moving Forward

- Range of successful approaches:
  - Serendipity and luck (e.g., thalidomide, sildenafil)
  - Observations, epidemiology, and meta-analysis (e.g., metformin)
  - Intentional pursuits (e.g., fexinidazole, AZT) and screening (e.g., ceftriaxone)
- Need to poise ourselves to pursue future efforts more strategically and comprehensively
- Need to use rescue and repurposing efforts as case studies in drug development process
  - Opportunity to study and re-engineer the process (e.g., optimized target validation)
- ***Why now?***

Scientific and Technologic Advances: Creating Opportunities in Therapeutics Development

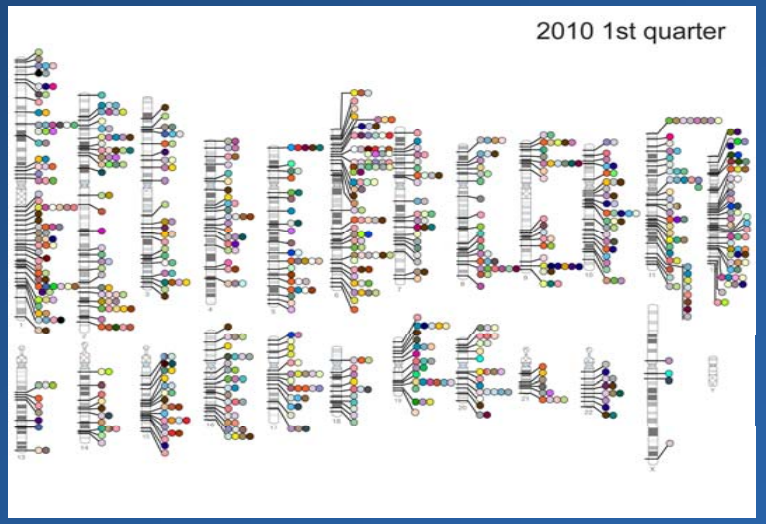
Scientific advances have

- Generated a large inventory of potential targets for new diagnostics and therapeutics

  Refined processes for identifying candidates for clinically useful compounds

- Enabled stratification of patient populations

- Growing interest and expertise in therapeutics development in academia



Key Challenges

- **Availability of and access to key resources:**
  - **Compounds and associated data are not readily available**

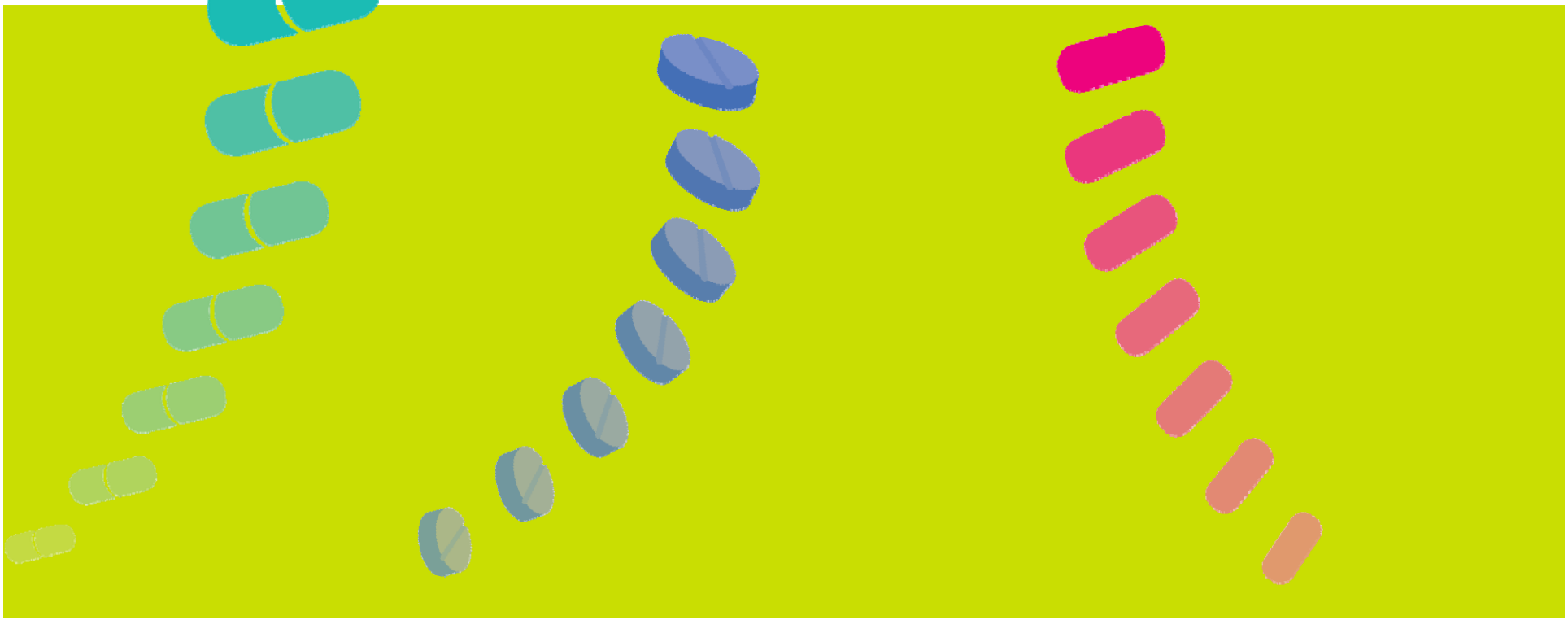
    Original investigator experience and expertise may be needed
- **Safety and liability concerns:**
  - **Safety concerns may emerge during the course of research and may have implications for approved products and liability**
  - **Concerns about making toxic compounds available**

Key Challenges

- Need for umbrella framework and master agreement that can be tailored for specific projects
- Need incentives for industry and academic sector participation:
    - May be especially challenging when there is a small market or short patent life on the compound
    - Potential solutions to explore: changes to IP or data exclusivity, financial incentives, innovative approaches (e.g., patent pools, dual markets)

NIH – INDUSTRY ROUNDTABLE
APRIL 21-22, 2011

Exploring New Uses for Abandoned and Approved Therapeutics



Roundtable Participants

- Leaders and experts from:
  - Industry
  - Academia
  - Non-profit
  - Government

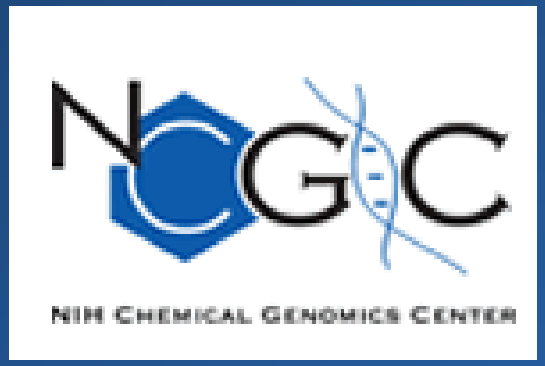
Roundtable Goals and Accomplishments

- Developed a collective understanding of the landscape of drug rescue and repurposing—scientific, commercial, and regulatory
- Reviewed illuminating case studies and lessons learned
- Explored cross-sector partnerships
  - Identified attributes for success
- Articulated the core elements of a framework agreement for access to materials and data

Getting to "Yes" -- A Draft Framework for Negotiating Agreements

- Prepared as background for meeting participants:
  - Principles and basic concepts inherent to NIH's collaborations
  - Draft NIH policy for collaborative rescue and repurposing research
  - General terms for collaborative agreements
    - Rights to publication
    - General intellectual property framework
    - Statutory requirements—for collaborations and license agreements
    - Best practices
    - Regulatory considerations
    - Data sharing considerations
  - Scenarios applying the draft policy

Next Steps:
Centralize Access to Resources & Expertise



- **Augment the NIH National Chemical Genomics Center Pharmaceutical Collection**
  - **Purpose: facilitate understanding of drug mechanisms**
    - **Ongoing effort to construct a definitive informatics and screening resource for drug repurposing**
  - **Current Scope:**
    - **Lists all small-molecule drugs approved for human or veterinary use (U.S. and worldwide)**
    - **Offers a physical collection of small molecules amenable to HTS**
    - **Contains ~9,000 unique MEs**
  - **All data publicly available**

Augmenting the NIH National Pharmaceuticals Collection:

Enabling Cross-walk Between Drugs and Diseases

- **Data on investigational (clinical trial stage) drugs from biopharmaceutical partners, with affected targets/pathways, and possible indications**
  - **Currently NPC contains any registered investigational drug, but without data on their activities or stage of development**
- **Listing of all human diseases, affected genes/pathways/organ systems, and drugs with efficacy data (but not approved)**
  - **Currently NPC only has diseases that are indications for one or more approved drugs**

PERSPECTIVE

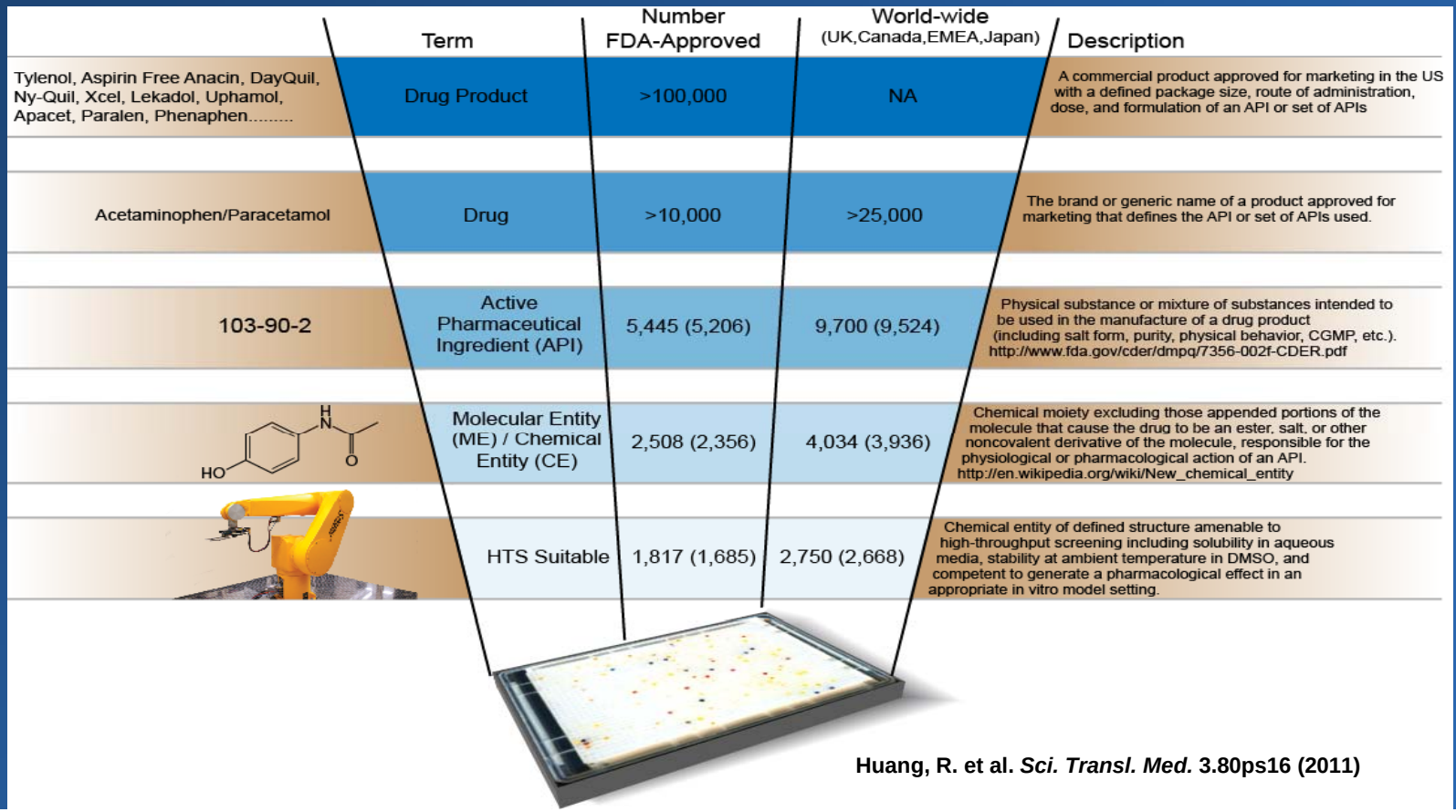
Science Translational Medicine

27 April 2011 Vol 3 Issue 80

PHARMACOLOGY

The NCGC Pharmaceutical Collection: A Comprehensive Resource of Clinically Approved Drugs Enabling Repurposing and Chemical Genomics

Ruili Huang,* Noel Southall,* Yuhong Wang, Adam Yasgar, Paul Shinn, Ajit Jadhav, Dac-Trung Nguyen, Christopher P. Austin†



Huang, R. et al. *Sci. Transl. Med.* 3.80ps16 (2011)

Next Steps: Resources & Expertise

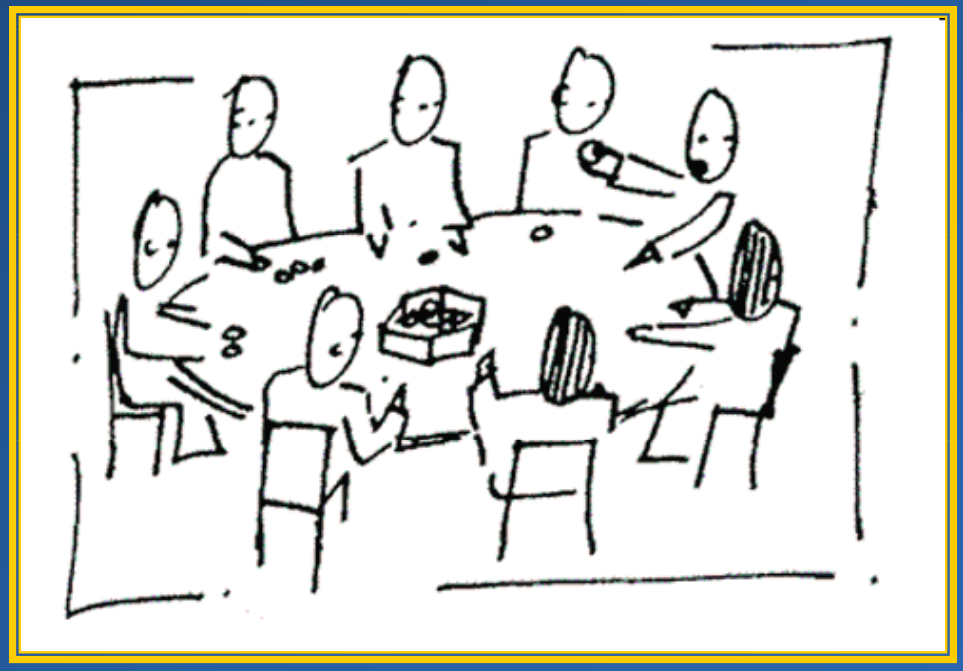
- Work with industry to identify collections of abandoned compounds and their associated data that could be made broadly available
- Explore with FDA:
  - Periodically querying industry about potentially abandoned compounds ("dormant" files)
  - Making a broader set of data available at the time of drug approval

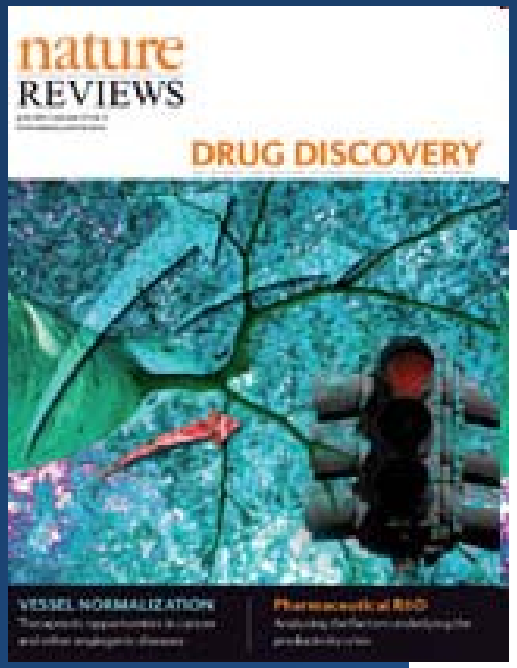
Next Steps:
Facilitate Collaborations and Partnerships

- **Match-making**
- **Master agreements**
- **Incentives**

Establish a Cross-Sector Roundtable on Translational Science as a Standing Forum

- **Future topics:**
  - **R & R**
    - **Master agreement**
      How to incentivize
    Opportunities in biologics & device development
    Need for intermediate endpoints
    Improving predictive tox
    Target validation
    Combination therapies
  - **Clearinghouses for precompetitive data**
  - **Innovative clinical trial design**





COMMENT

Mining for therapeutic gold

Francis S. Collins

A comprehensive and collaborative strategy to enable the investigation of new uses of approved and abandoned drug compounds could advance translational research.

Discoveries about the molecular basis of disease are providing unprecedented opportunities to translate research into clinically useful products. However, the translational process is fraught with frustration: failure rates can be as high as 95%, the average time from target selection to approval is ~13 years and, when failures are accounted for, the cost of bringing a new drug to market exceeds US$1 billion[1]. So, strategies to reduce the time frame, decrease costs and improve success rates are urgently needed.

Drug rescue and repurposing can be one of those strategies, and it offers the key advantage of harnessing previous research and development (R&D) efforts. Approved drugs and many abandoned compounds have already been tested in humans, and so detailed information is available on their pharmacology, formulation, dosing and potential toxicity. This can enable the rapid testing of new clinical hypotheses, leading to remarkable health outcomes. For example, in the early days of the HIV epidemic, investigators at the US National Institutes of Health (NIH) collaborated with academic and industry experts to rescue AZT — a compound that was originally investigated for use in cancer but abandoned owing to lack of efficacy — and it became the first drug to treat patients with HIV.

Looking to the future, much could be gained by wider application of comprehensive collaborative approaches to drug rescue and repurposing. However, there are scientific, economic and administrative challenges that need to be addressed, including the collection and organization of compounds and data, incentives for further development and commercialization, safety issues and intellectual property considerations. The private sector holds a substantial proportion of the assets, data and knowledge needed for drug rescue and repurposing, but the ideas and wherewithal to advance new applications, especially for rare diseases, may come from different companies, the non-profit sector or academia.

To explore ways to approach drug rescue and repurposing more strategically and comprehensively, the NIH held a round-table meeting with leading representatives of academia, government and private sector R&D on 21–22 April 2011. Acknowledging the value of drug rescue and repurposing, participants at the meeting discussed ways to make the process more practical and less burdensome (see page 399). Furthermore, it was agreed to establish a round table as a standing forum for fostering cross-sector efforts in translational science to tackle challenges for which such collaboration is critical for success.

Informed by these discussions and in close collaboration with industry, academia and non-profit organizations, the NIH will be launching a comprehensive effort to identify appropriate abandoned compounds, establish master agreements, match partners, make data and resources available, and provide a central access point to relevant resources and expertise. This will facilitate a full range of scientific approaches to drug rescue and repurposing — from serendipitous discovery of new applications, to targeted matching based on known mechanisms of action, to systematic screening using relevant assays drawn from multiple sectors. This latter option will be particularly useful for phenotypic screens in which the actual target is not known. There is also a key role for the US Food and Drug Administration (FDA) in advancing drug rescue and repurposing efforts (for example, for rare diseases?), and the recently established NIH–FDA Leadership Council could be a forum for exploring strategies and driving progress.

As one immediate step, the NIH will be augmenting activities that are underway to organize available data on drugs and investigational compounds through the NIH Chemical Genomics Center Pharmaceutical Collection (NPC)[3]. As a publicly accessible database and a full physical collection of small molecules that are approved for human use, the NPC is intended to aid collaboration by enabling high-throughput screening and drug repurposing efforts across a range of diseases. Such research will also be an important focus of the NIH's proposed National Center for Advancing Translational Sciences (NCATS). Indeed, drug rescue and repurposing research overall offers a key opportunity to learn from our collective past as we shape our future — a future in which translational science is more efficient and effective at delivering therapies and diagnostics to patients.

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doi:10.1038/nrd3461

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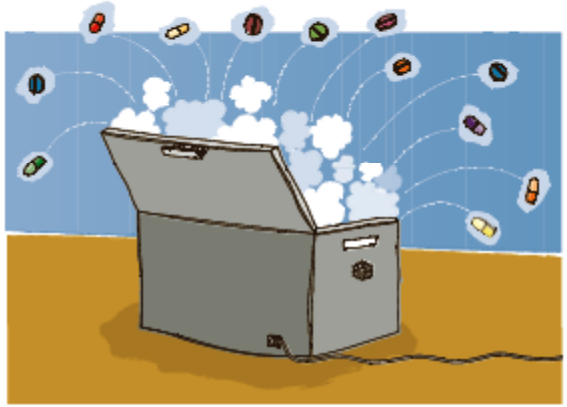
2. USFDA. http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanDesignation/default.htm (2010).
3. Huang, R. *et al. Sci. Transl. Med.* **3**, 80ps16 (2011).

Competing interests statement
The author declares no competing financial interests.

NEWS & ANALYSIS



Could pharma open its drug freezers?

The NIH wants industry to contribute old, new and experimental drugs to a systematic, collaborative approach to drug rescue and repurposing.

Asher Mullard

Around 80 representatives from the pharmaceutical industry, government and academic institutions met for 2 days in April 2011 to discuss repurposing and rescue efforts for old and new drugs. Although drug repositioning is not a new concept, US National Institutes of Health (NIH) officials asserted that the different sectors could better capitalize on advancing science and accumulating clinical data by working together on a systematic approach for screening clinical-stage, shunted and approved compounds for new uses.

Already, plans are underway to embed such a strategy into the new National Center for Advancing Translational Sciences (NCATS). "So far as repurposing gives us a running start on development activities, it will be an important activity of the NCATS," says Amy Patterson, Associate Director for Science Policy at the NIH. (See also accompanying Comment on page 397 and news in brief on page 403.)

Repositioning has already yielded several successes — including the rescue of thalidomide through the discovery of its efficacy in both leprosy and multiple myeloma. It is also already broadly pursued as a route to cost-effective drug development for compounds with known safety profiles. Pfizer's Indication Discovery Unit (IDU) is dedicated to repositioning, biotechnology companies have built business models around the strategy, and academic groups have applied this approach to neglected diseases. "Repositioning is very fertile ground," says Garret FitzGerald of the Institute for Translational Medicine and Therapeutics.

But whereas current attempts are limited by the scope of an organization's chemical library and assay know-how, the NIH hopes that a collaborative approach encompassing a broader science base would be more fruitful. "By pulling resources together and working in a synergistic fashion, we can distribute the risk and hopefully come up with something that's a win–win for everyone," says Patterson.

If all goes to plan, drug firms will open their freezers to the NIH, sharing compounds and the

Nature Reviews Drug Discovery **10**, 397 (June 2011)

Final note

More than 80% of the gold in the Mother Lode is still in the ground.