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

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Associate Director for Science Policy
National Institutes of Health

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Advisory Committee to the Director
Development of New Therapeutics

- Drug Discovery: 10,000 Compounds, 6.5 years
- Pre-clinical: 250 Compounds
- Clinical Trials: 5 Compounds, 6 years
- FDA Review: 1.5 years
- Clinic: 1 Approved Drug
High Attrition Rate of Late-stage Drug Development: Pool of Potential Candidate Compounds for Rescue

- 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

<table>
<thead>
<tr>
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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
- 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
### 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**

<table>
<thead>
<tr>
<th>Term</th>
<th>Number FDA-Approved</th>
<th>World-wide (UK, Canada, EMEA, Japan)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tylenol, Aspirin Free Anacin, DayQuil, Ny-Quil, Xcel, Lekadol, Uthermol, Apcel, Par alien, Phenaphen......</td>
<td>&gt;100,000</td>
<td>NA</td>
<td>A commercial product approved for marketing in the US with a defined package size, route of administration, dose, and formulation of an API or set of APIs.</td>
</tr>
<tr>
<td>Acetaminophen/Paracetamol</td>
<td>&gt;10,000</td>
<td>&gt;25,000</td>
<td>The brand or generic name of a product approved for marketing that defines the API or set of APIs used.</td>
</tr>
<tr>
<td>103-90-2</td>
<td>5,445 (5,206)</td>
<td>9,700 (9,524)</td>
<td>Physical substance or mixture of substances intended to be used in the manufacture of a drug product (including salt form, purity, physical behavior, COMP, etc.). <a href="http://www.fda.gov/cder/dmpdf/7550-0202-CDER.pdf">http://www.fda.gov/cder/dmpdf/7550-0202-CDER.pdf</a></td>
</tr>
<tr>
<td>Molecular Entity (ME) / Chemical Entity (CE)</td>
<td>2,508 (2,356)</td>
<td>4,034 (3,936)</td>
<td>Chemical entity of defined structure amenable to high-throughput screening including solubility in aqueous media, stability at ambient temperature in DMSO, and competent to generate a pharmacological action in an appropriate in vivo model setting.</td>
</tr>
<tr>
<td>HTS Suitable</td>
<td>1,817 (1,685)</td>
<td>2,750 (2,668)</td>
<td></td>
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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
**Mining for therapeutic gold**

Franca S. Cellano

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

Innovations about the traditional bioidentical pathways of drug development are being fueled by advances in clinical and preclinical research, which is resulting in a pipeline of new compounds that have the potential to treat a wide range of diseases. However, the traditional drug development pathway is not without challenges. The cost of drug development is estimated to be around $2.6 billion, and the success rate of bringing a new drug to market is around 5-10%. On average, a drug that enters clinical trials to enter phase III and when all factors are accounted for ends up with a cost of $1.2 billion, according to a report released by the Pharmaceutical Research and Manufacturers of America (PhRMA). This strategic read in the journal **Nature Reviews Drug Discovery** discusses how a collaborative approach, in which the pharmaceutical industry, academia, and non-profit organizations pool their resources to identify and develop novel uses of approved and abandoned drug compounds, could advance translational research.

The strategy of mining for therapeutic gold involves identifying approved drug compounds that have the potential to treat a wide range of diseases. This strategy has the potential to reduce the cost and time required to bring a new drug to market, as the compounds have already been tested for safety and efficacy. However, the strategy also faces challenges, including the need for new regulatory frameworks and the potential for intellectual property issues.

**Could pharma open its drug freezers?**

The NIH is set to create a database of approved drugs to enable the investigation of new uses of approved and abandoned drug compounds. This approach could accelerate the development of new treatments for a wide range of diseases and reduce the cost and time required to bring a new drug to market. The NIH is currently in the process of creating a database of approved drugs, which will be made available to researchers through a collaborative approach. This initiative is expected to have a significant impact on the development of new treatments for a wide range of diseases, including cancer, infectious diseases, and neurological disorders.
More than 80% of the gold in the Mother Lode is still in the ground.