Quantifying the Impact of NIH Funding on Pharmaceutical Innovation

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Prior Evidence

• Several studies provide descriptive evidence of contributions of public research funding to drug development

• Theoretically, information (and trained PhDs!) produced by NIH-funded research may serve as a cost-reducing subsidy
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• Big Problem: What’s the counterfactual?
  – Case studies and firm surveys don’t tell us whether increases in NIH funding will yield more (better) drug treatments
  – Consider reductio ad absurdum...
Does Targeted, Disease-Specific Public Research Funding Influence Pharmaceutical Innovation?

Margaret E. Blume-Kohout
Research Questions

Do changes in the amount of NIH extramural research funding targeted toward a specific disease affect:

1. The number of new drug treatments that firms pursue in (human) clinical testing (Phase I)?
2. The number of drugs that make it to Phase III, the largest-scale RCTs?
Outcome Variable: Clinical Trials

- Source: Pharmaprojects
- Unit of observation: drug-class-year
- Variables extracted:
  - Drugs in Phase I and Phase III trials, by therapeutic class and year
  - Data also include specific indications explored
Known Unknowns:
NIH Funding by Disease-Year

ERA Commons
Computer Retrieval of Information on Scientific Projects

CRISP (Computer Retrieval of Information on Scientific Projects) is a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other research institutions. The database, maintained by the Office of Extramural Research at the National Institutes of Health, includes projects funded by the National Institutes of Health (NIH), Substance Abuse and Mental Health Services (SAMHSA), Health Resources and Services Administration (HRSA), Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDCP), Agency for Health Care Policy Research (AHCPR), and Office of Assistant Secretary of Health (OASH). Users, including the public, can use the CRISP interface to search for scientific concepts, emerging trends and techniques, or identify specific projects and/or investigators. Below you will be able to access additional general information about the CRISP database, as well as obtain answers to questions frequently asked about CRISP. In addition, this home page serves as the gateway to interactive searching of Current or Historical Award Information. From here, you may select from the following list to acquire further information about CRISP:

- General CRISP Description and Information
- Frequently-Asked-Questions (FAQ)
NIH RePORTER
Malaria

A protozoan disease caused in humans by four species of the PLASMODIUM genus: PLASMODIUM FALCIPARUM; PLASMODIUM VIVAX; PLASMODIUM OVALE; and PLASMODIUM MALARIAE; and transmitted by the bite of an infected female mosquito of the genus ANOPHELES. Malaria is endemic in parts of Asia, Africa, Central and South America, Oceania, and certain Caribbean islands. It is characterized by extreme exhaustion associated with paroxysms of high FEVER; SWEATING; shaking CHILLS; and ANEMIA. Malaria in ANIMALS is caused by other species of plasmodia.

Year introduced: MALARIA CONTROL was heading 1963-1966
MeSH: Synonyms & Hyponymys

Tree Number(s): C03.752.530
MeSH Unique ID: D008288
Entry Terms:

- Remittent Fever
- Fever, Remittent
- Paludism
- Plasmodium Infections
- Infections, Plasmodium
- Infection, Plasmodium
- Plasmodium Infection
- Marsh Fever
- Fever, Marsh

See Also:

- Antimalarials
MeSH: Synonyms & Hyponyms

All MeSH Categories
Diseases Category
Parasitic Diseases
Protozoan Infections
Malaria
- Malaria, Avian
- Malaria, Cerebral
- Malaria, Falciparum
- Blackwater Fever
- Malaria, Vivax
Method: Classifying Grants by Disease

1. Identify disease indications for each potential drug treatment reported in Pharmaproxects, by R&D stage
2. Match disease indications to MeSH descriptors
3. Map MeSH descriptor terms, synonyms, and hyponyms (keyword list) to each disease indication
4. Disambiguate duplicate MeSH entries (make it a tree)
5. Parse grant abstract html files and scan for all keywords
6. Code abstracts containing specific disease keywords to the corresponding disease indication
7. Write out grant number, funding amount, other metadata, and all disease categories found
Econometric Estimation

• Poisson finite distributed lag

\[ E \left[ Drugs_{d,t} \right] = \exp \left( \sum_{i=i^*}^{L} \beta_i \ln \left( NIHfund_{d,t-i} \right) + \mu \ln \left( MktSize_{d,t+f} \right) + \tau_t \right) \]

• Maximum L allowed = 22 years

• Model & estimation also control for:
  – Unobserved differences across diseases in their average # of trials, by year
  – Possible ‘shock’ affecting both funding & trials
  – Possible feedback effects
Results

• **Sustained** 10% increase in disease-specific R&D funding => 4.5% increase in drugs entering Phase I trials, after lags up to 12 yrs

• **No evidence** of any effect for Phase III
  – No apparent effect on likelihood of success
  – No apparent effect on supplemental indications
Interpretation?

- Phase I effect consistent with previous studies of R&D funding effects on patents and industry R&D expenditures

- Phase III?
  
  “The results reported here should not be interpreted as asserting that all disease-specific public research funding is impotent with respect to pharmaceutical innovation.” (p. 656)
Interpretation?

• Analysis examines traditional, investigator-initiated extramural RPGs
  – Not clinical research centers, translational research, traineeships or fellowships, or intramural funding

• Evaluates effects of changes in funding levels, not aggregate (total) impact

• Focus on ‘policy lever’ of disease-specific funding ignores potential spillover effects and serendipity
Example: Romidepsin (Istodax)

- 1985/86: NIH-funded researchers publish three key papers cited below
- 1989: Initial patent filed by Fujisawa (Japan), Ueda et al. listed as inventors
- 1994: Ueda et al. publish on discovery, found cytotoxicity in lung, stomach, breast, and colon cancer lines; cite research noted above
- 1995: NIH-funded Postdoc & team achieve total synthesis
- 1996: CRADA between Fujisawa & NCI, NCI files IND
- 2002: Fujisawa begins conducting its own clinical trials
- 2004: Fujisawa/Astellas licenses to Gloucester Pharma, Gloucester seeks Fast Track status, begins its Phase II trials
- 2008: Astellas files two covering patents
- 2009: Gloucester Pharma receives fast-track/ODA approval for cutaneous T-cell lymphoma; drug acquired and marketed by Celgene in 2010
- Today: NCI M01-funded Cancer Centers still conducting new research on combination therapy
NIH’s Roles?

• Fundamental science: characterization & methods
  – Ensuring global public access, communication of results

• Training biomedical sciences workforce (including chemists, pharmaceutical scientists...)

• High risk, small market, long window, translational
  – Strong response in Phase I & II for T-cell lymphomas, BUT
  – Little impact on leukemias, lung cancer, renal cell cancer, prostate cancer, and no effect on colorectal cancer (all Phase II)

• Intramural & extramural support for research on new uses of existing drugs

• Spurring ‘triple-helix’ collaboration
Directions for Future Research (1 of 2)

• Machine learning & statistical text analysis to better capture NIH role in genesis & evolution of ideas
  – How should pubs & patents be weighted for quality or relative importance, when generated or cited?

• Restricted/administrative data to follow NIH-funded students’ careers
  – NIH R&D funding to universities has huge impact on students entering PhD programs and new PhDs’ choosing R&D jobs
    Blume-Kohout & Clack 2013, Blume-Kohout & Adhikari 2016
  – If a graduate student is supported directly or indirectly by NIH, how often do they choose a career/research in pharma or drug development?

• Effects on biologics (not in FDA Orange Book)
Directions for Future Research (2 of 2)

• Effects of different funding mechanisms
  – Prior research on SBIR/STTR programs finds mixed results; NAS (2015) report indicates data limitations
  – Which funding mechanisms are most effective overall in generating **useful** innovation? Does the answer differ by disease or therapeutic area?
  – Consider specific influence of NIH translational science, collaborative research (CRADA, U01, etc.)