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Characterizing the public sector contribution to drug discovery and development: the role of government as a first investor

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This research is focused on examining the role of the public sector as an early investor in biopharmaceutical discovery and development. In the United States, the National Institutes of Health (NIH) is the primary source of funding for basic biomedical research designed to elucidate fundamental mechanisms of biology, health, and disease. This research is expected to establish the scientific foundation for the discovery and development of new biopharmaceutical products. This interim report reviews the linear model of innovation underlying these expectations, and evidence for the effectiveness of this pathway. We also describe new data demonstrating that every new drug approved by the Food and Drug Administration (FDA) for the decade from 2010-2019 was associated with basic science funded by the NIH.

This work identifies NIH funding for published research related to 356 drugs approved for the decade from 2010-2019 and the 220 associated biological targets.

- Drug searches identified >130,000 publications with NIH funding, approximately 30% of all publications. Research related to the drugs is classified as applied or translational research.
- Target searches identified >1.6 million publications with NIH funding, approximately 50% of all publications. Research on drug targets, but not the drugs, is classified as "basic" research.
- NIH funding contributed to drug-related research on 84% of the drugs and target-related research on 100% of the targets.
- NIH funding comprised >56,000 fiscal years of research related to the drugs and >500,000 fiscal years of research related to the drug targets.

These results are consistent with our previous report that the NIH contributed to research underlying every approved NME in the study period, and that approximately 90% of this funding was focused on the drug targets, rather than the drugs themselves.

1. The linear model of biopharmaceutical innovation

The process of discovering and developing new medicines is classically described in terms of a linear model of innovation. In its simplest form, the model posits that there is a linear flow of information and intermediate products from basic science, defined as research undertaken "without specific applications towards use in view," (NSF 2018), through applied and translational science (development), and finally introduced to the marketplace (Edgerton , Godin 2006, Balconi, Brusoni et al. 2010). This concept has been expanded by the growing appreciation of the importance of "use-inspired" basic research, which is "basic research" in its character, but undertaken with the purpose of advancing economic gains or the public good (Stokes 2011).

The concept of a linear progression from basic science to applications forms the basis of modern science policy, as envisioned by Vannevar Bush in The Endless Frontier (Bush 1945, Godin 2006, Narayanamurti 2016). Bush wrote: "*Basic research leads to new knowledge. It provides scientific capital. It creates the fund from which the practical applications of knowledge must be drawn*" (Bush 1945). This principle was

evident, for example, in the design of the "war on cancer" in the 1970s, which explicitly focused on a "massive investment in basic science" and "the assumption that unbiased fundamental research would hold the key to unlocking the secrets of cancer" (Haber, Gray et al. 2011).

In the United States, basic biomedical research is funded primarily by the National Institutes of Health (NIH) (Moses, Matheson et al. 2015), which allocates half of its research budget to "basic" science (Lauer 2016). The passage of the Bayh–Dole Act in 1980 established a legal structure by which federally funded basic research, performed primarily in academic or government laboratories, could be patented by the research institution and then licensed to industry for subsequent development (Mowery 2004).

The Bayh–Dole Act spawned a robust process of "technology transfer" from research universities to thousands of start-up companies dedicated to developing and commercializing these technologies as well as established companies seeking to add new intellectual property to their portfolios (Loise and Stevens 2010). While quantitative studies have questioned the efficacy of the Bayh–Dole Act, it remains the structural centerpiece of the process for developing new medicines from federally funded biomedical research.

There has been extensive scholarly debate about the veracity of the linear model of innovation and its utility in informing, or constraining, the progress of innovation (Balconi, Brusoni et al. 2010, Stokes 2011, Narayanamurti 2016). This simplified model does not account for the complexity of the dynamic interactions that occur at the boundary between the academic and commercial sectors (Cockburn and Henderson 1996), the contributions made to use-inspired basic research by scientists in the biotechnology and pharmaceutical industries (Reichert and Milne 2002, Zycher, DiMasi et al. 2010, Chakravarthy, Cotter et al. 2016), or recent efforts to promote translational science in the public domain (Varmus 2006, Collins 2011, Woodcock, Brumfield et al. 2014).

2. Defining the role of the public sector in biopharmaceutical innovation

Despite the centrality of this model in biopharmaceutical development, many quantitative studies have shown a limited role for government-funded, academic research in products coming to market. Stevens et al. estimated that from 1990 to 2007, 9.3% of new drug approvals were first patented in public sector institutions and transferred to industry (Stevens, Jensen et al. 2011). This fraction is similar to estimates by Kaitin et al., where 7.6% of drugs approved from 1981-1990 (Kaitin, Bryant et al. 1993) and 6.7% of new drugs approved from 1990-1999 (DiMasi, Hansen et al. 2003) had academic patents cited in the FDA's Orange Book (www.accessdata.fda.gov), as well as estimates by Sampat that 7.7% of all FDA approvals, and 10.6% of new molecular entities, are based on academic patents (Sampat 2009).

Studies of patents, however, may systematically underestimate the contribution of basic science. Issuance of a patent requires that the inventor establish that the invention is both "new and useful" (35 USC 101, www.uspto.gov/web/offices/pac/mpep/s2107.html) and that the patent is enabled by the work that has been done (35 USC 112, https://www.uspto.gov/web/offices/pac/mpep/s2164.html). This explicitly excludes basic research undertaken without specific ends in mind. Studies have shown that patent analysis is a poor measure of knowledge flow from public institutions or funding (Pavitt 1998, Roach and Cohen 2013). Case study methods are more likely to recognize the contributions of basic science or "fundamental scientific knowledge" (Cockburn and Henderson 2000), but may be similarly biased in favor of research that can be explicitly linked to a specific process or product. Thus, the methods used in previous studies may systematically underestimate the contribution of basic research, and thus public sector funded research, to new drug approvals.

Various approaches have been taken to more accurately assessing the public sector contribution to new drugs coming to market. Kneller examined not only patents related directly to the approved drugs, but also patents describing prototype compounds and the biological targets for these drugs. Findings

estimated that “non-profit research organizations” made the major contribution to the patent estate for 14% of drugs approved from 1998-2007, and made some contribution to patents related to 35% of these drugs (Kneller 2010). Sampat and Lichtenberg examined the prior art referenced in patents for new drug approvals, finding that from 1988-2007, 48% of approvals were associated with a patent that cited patents or publications from the public sector, despite only 9% being directly associated with a public sector patent (Sampat and Lichtenberg 2011). These results are similar to those described by Patridge et al. (Patridge, Gareiss et al. 2015), who found that 38% of the 1,453 FDA approved new drugs were first synthesized or purified in academic organizations.

Case studies provide similar results. Cockburn and Henderson examined the development of 21 drugs considered to have the most impact on practice from 1965-1992, finding that 76% were developed with some input from the public sector (Cockburn and Henderson 2000). Chakravarthy et al. examined the development of 19 of the “most transformative” drugs of the past 25 years, finding that, while only 15% of these drugs were discovered in the public sector, there was evidence of a public sector contribution for 54% of these products (Chakravarthy, Cotter et al. 2016). Using a cohort approach, Nayat et al. described that 19% of 248 new drugs approved from 2008-2018 had their origin in publicly supported research and development (Nayak, Avorn et al. 2019).

A 2018 study by Cleary et al. looked explicitly at the contribution of NIH-funded basic science to new drugs approved from 2010-2016 (Cleary, Beierlein et al. 2018). That study identified >2 million research publications in the biomedical literature (PubMed) in this interval, related to the 210 drugs approved or their 151 biological targets. Of these publications, >600,000 (29%) cited federal research support comprising >200,000 fiscal years of project funding (1985-2016) and >$100 billion in project costs since 2000 (Cleary, Beierlein et al. 2018). Significantly, NIH-funded research was identified in association with every new drug approved from 2010-2016.

Cleary et al. also demonstrated that more than 90% of the NIH-funded research was associated with basic science publications on the biological targets rather than the drugs. In contrast, less than 10% of the NIH funding was associated with applied (or translational) science for these specific drugs (Cleary, Beierlein et al. 2018). All of these products were subsequently developed and commercialized by for-profit, biopharmaceutical companies. Studies also suggest that a mature body of basic research is a necessary condition for successful drug development using contemporary targeted approaches. Using an analytical model to quantify the advance of basic biomedical science, McNamee et al. examined the relationship between the progression of this research on novel biological targets for drug action, and the first FDA approval of a new drug based on that research (McNamee, Walsh et al. 2017). These studies show that few biological products or NMEs discovered through targeted screening are approved when the underlying science is in an exponential growth phase, and that the first products arising from this science are approved an average of 14 years after the science reaches a numerically-defined "established" point. These studies also show that the average length of clinical trials was significantly shorter when clinical trials were initiated after this "established" point (McNamee, Walsh et al. 2017). This is consistent with the expectation that targeted drug discovery and biological development are enabled by a body of basic research, which identifies and validates drug targets associated with diseases, as well as potential mechanisms for therapeutic action (Swinney and Anthony 2011, Swinney 2013). A series of follow-on studies have extended this concept, showing that the first approval of targeted cardiovascular drugs, targeted cancer drugs, gene therapies, and nucleotide therapies all followed the maturation of the underlying basic biomedical research (Ledley, McNamee et al. 2014, Beierlein, McNamee et al. 2017, Beierlein, McNamee et al. 2017, McNamee and Ledley 2017, McNamee, Walsh et al. 2017).

Together these studies paint a coherent picture of an ecosystem for biopharmaceutical discovery and development that is fueled by substantial investments in basic biomedical science from the public

sector. This investment focuses primarily on basic, or use-inspired, basic research. The impact of this research, however, is also evident in the fact that up to a third of patents governing newly approved drugs cite NIH-funded research as prior art and that, in less than 10%, the patent itself is an outgrowth of this funding.

The explicit mission of the NIH is to invest in the scientific and technical foundations advancing the public good. As such, it represents a model for understanding how government investments contribute to creating value in the form of products to prevent and treat disease, improve health outcomes and quality of life, create new jobs, and stimulate economic growth. Understanding how the NIH contributes as an "investor of first resort" in biopharmaceutical development can also inform an understanding of the role of government in creating value more generally (Mazzucato 2011, Lazonick and Mazzucato 2013, Hopkins and Lazonick 2014, Block and Keller 2015, Lazonick 2017, Mazzucato and Semieniuk 2017). Moreover, the ongoing policy debates about the price of drugs and corporate profits arising from government-funded innovation offers an opportunity to shape the future of the innovation ecosystem to better serve multiple public needs.

3. Interim results

3.1 Drugs and drug targets

A total of 332 new therapeutics (excluding vaccines, diagnostic agents, and blood products) were approved from 2010-2019, including 230 small molecule drugs (New Chemical Entities (NCEs)) and 102 biological products. Table 1 shows the breakdown of these products by product class and the number receiving expedited designations from the FDA.

Table 1. Number of New Molecular Entities approved 2010-2019

Year	NME 2010-16	NME 2017-19	Total 2010-2019
Total	218	138	356
Product class			
CDER Small molecule	139	91	230
CDER Biologic	62	40	102
CBER (Biologic)	17	7	24
Expedited designation			
Priority	90	84	174
Fast Track	77	47	124
Accelerated Approval	28	18	46
Breakthrough Therapy	29	44	73
Orphan Drug	81	66	147
First In Class	75	52	127

FDA product approvals from 2011-2014 were identified in annual reports on the FDA: CDER archive (http://wayback.archive-it.org/7993/20170111002417/http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/default.htm). Drugs approved from 2015-2019 were identified in annual reports at FDA.gov (https://www.fda.gov/drugs/development-approval-process-drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products). For drugs approved in 2010, Priority and Orphan Drug status were sourced from Nature Reviews annual report on FDA drug approvals(Mullard 2011). Accelerated and Fast Track status were identified from the 2020 FDA drug approvals database (https://www.fda.gov/drugs/drug-approvals-and-databases/compilation-cder-new-molecular-entity-nme-drug-and-new-biologic-approvals). Note that the Breakthrough classification was not established until after 2010.

3.2 Publications and Project Years

Searches in PubMed were performed for 356 drugs approved form 2010-2019 (DRUG search) and 220 biological targets for the products (TARGET search). NIH funding contributed to 30% of all publications identified in DRUG searches and 53% of publications identified in TARGET searches. NIH funding was associated with 84% of all DRUG searches, which is considered to be applied or translational research, and 100% of TARGET searches, which is considered to be basic research on the biological pathways and mechanisms. The NIH-funding for publications identified in this work comprised >560,000 fiscal years of Project Funding.

Overall, NIH-funded research was identified in association with every one of the 356 drugs or their biological targets. Of this, 92% of the NIH funded publications and 90% of the Project Funding years were focused on the biological targets for the drugs, rather than the drugs themselves.

Table 2. Research publications and NIH Funding Years associated with 356 New Molecular Entities (NMEs) approved by the FDA from 2010-2016 or their molecular targets.

	DRUG Search	TARGET Search	
PubMed search results			
Searches	356	220	
Publications in PubMed	464,725	3,091,761	
RePORTER Link table results			
Publications with NIH funding (1980-2016)	138,383	1,626,564	
Fraction of publications with NIH funding	30%	53%	
Searches with NIH funding	299	220	
Fraction of searches with NIH funding	84%	100%	
	DRUG	**TARGET only**	**Total**
Funding Years and Costs			
Unique Funding Years	56,802	503,346	560,148

This report used a modification of the method reported in Cleary et al. (Cleary, Beierlein et al. 2018). In brief, molecular targets for each drug were determined from FDA labels and other pharmacological databases. Optimized PubMed searches were run for each drug and biological target to identify publications in the PubMed database related to the search terms and recover the PubMed IDs (PMID) for each publication. PMIDs were identified for the years 1960 through the year of first FDA approval for each drug or first drug approval with each target. The NIH RePORTER/ExPORTER database (NIH 2017),(Health 2017), was used to link the PMIDs to NIH-funded projects. Data cleaning included eliminating duplicate entries, and excluding publications predating a grant or grants predating publications by more than 4 years.

3.3 Time course of NIH funding

Figure 1 shows the number of research publications identified by year in searches for the 356 drugs and their 220 biological targets. The blue bars represent the total research publications identified in each year. The orange bars represent the proportion identified in searches for the drug. These are considered to be applied or translational research, while those identified only in target searches are considered to be basic research.

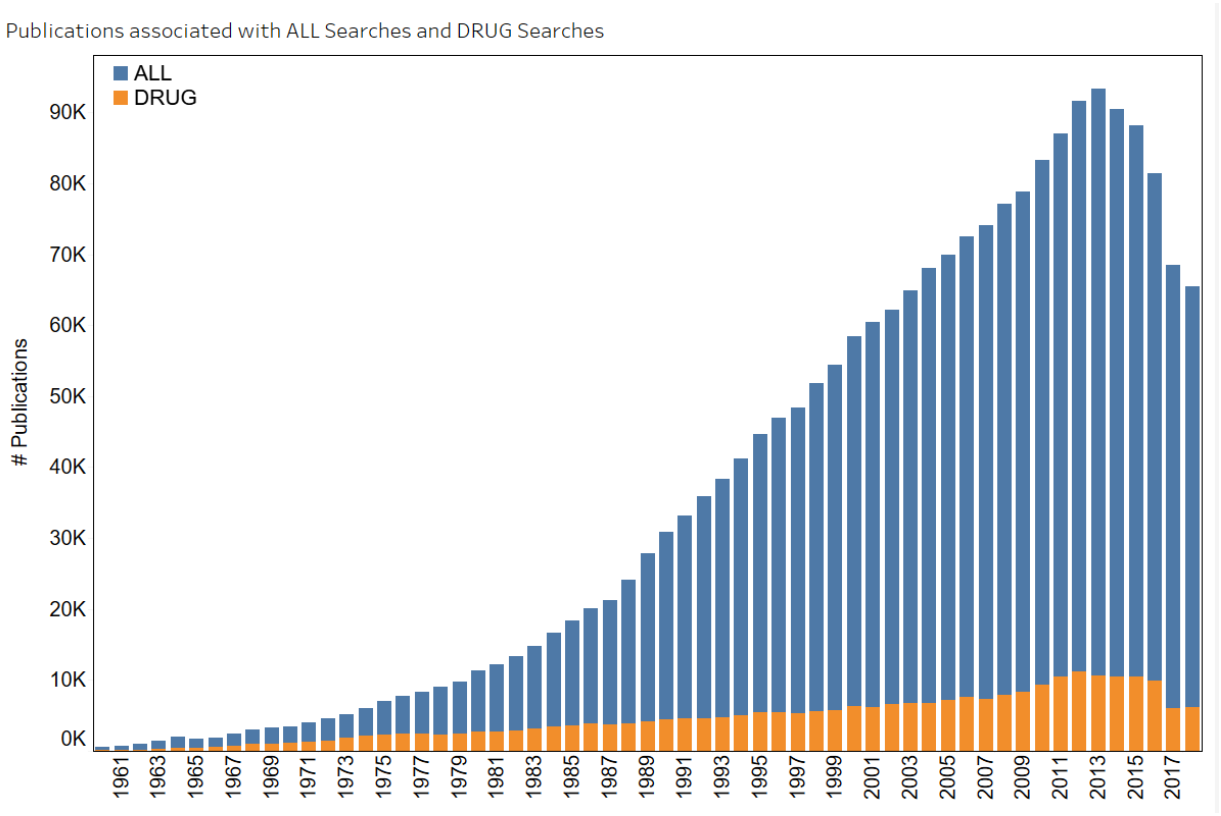
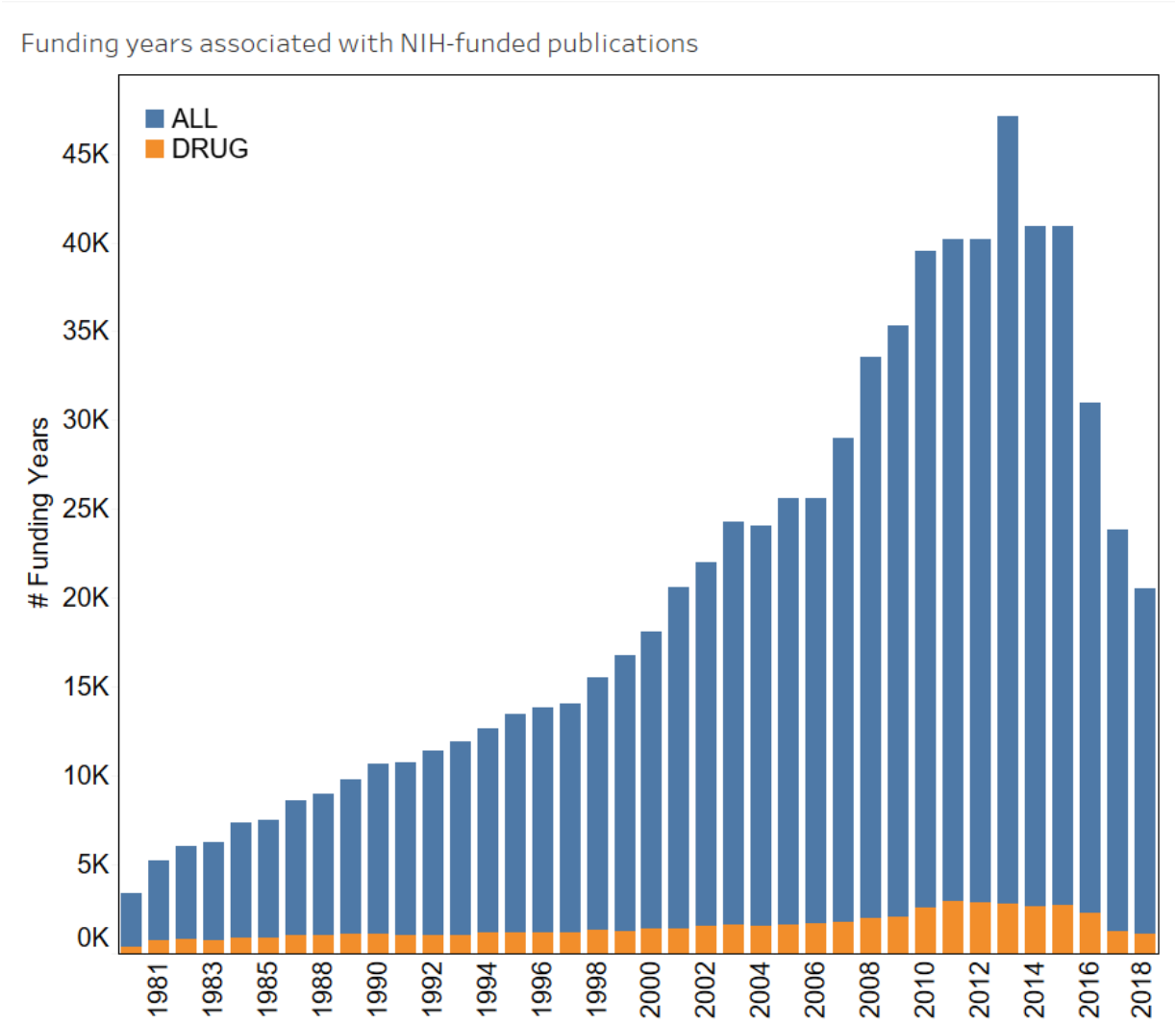


Figure 2 shows the number of funding years (grants) for each year that contributed to published research identified in searches for the 356 drugs and their 220 biological targets. The blue bars represent the total number of funding years. The orange bars represent the proportion of funding years with publications directly related to the drug. Funding years resulting in drug-related publications are considered to support applied or translational research. Those funding years resulting only in publications related to the drug targets are considered to support basic research.



4. Ongoing research

This project describes the data collection phase for a more detailed examination of how public sector (NIH) funding for basic and applied biomedical research contributes to value creation in the form of new products for the prevention and treatment of disease.

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