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Center for Integration of Science and Industry - Response to OSTP Bioeconomy RFI

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RESPONSE TO:

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What specific actions could the U.S. Government take to reinforce a values-based ecosystem that will guide the transformation and expansion of the U.S. Bioeconomy, in both the short- and long-term?

This response addresses specific actions the U.S. Government could take to ensure sustainable funding for the basic research that provides the foundation for the U.S. Bioeconomy. Empirical evidence demonstrates that a mature body of basic research is essential for the efficient discovery and development of new medicines, and recent studies have demonstrated the scale of the public sector (NIH) contribution to this research. This funding is, however, under threat. U.S. Government action is required to ensure sustainable funding for basic research. Specific actions by the U.S. Government could include:

1. Make a long-term commitment to sustained public funding of basic science by the NIH at levels at least equal to 2003 in constant dollars;
2. Ensure equitable returns to the public sector from the licensing of federally funded research for development in the biopharmaceutical industry;
3. Require accounting recognition of basic and applied research spending as a capital investment that produces a tangible asset (intellectual property);

4. Facilitate innovative investment instruments that provide long-term support for basic and applied research through tax exempt bonds.

Threats to basic science funding from government and industry

Two threats to basic science funding threaten the future of the basic biomedical research that provides the foundation for the discovery and development of new medicines and the U.S. Bioeconomy.

Uncertain government funding. The first is uncertainty concerning the sustainability of government funding for basic science. In the U.S., the federal government is the primary source of funding for basic research with significantly smaller contributions from industry and philanthropy (Moses et al., 2015). From 2000-2016 the NIH received annual budget allocations totaling almost $550 billion, 90% of which funded biomedical research (https://www.nih.gov/about-nih/what-we-do/budget). Approximately half of the biomedical research budget was dedicated to basic research (Lauer, 2016). A 2017 study in the Proceedings of the National Academy of Sciences demonstrates that this basic science funding contributed to the scientific foundation of every new drug approved from 2010-2016 (Cleary et al., 2018).

An April 2019 report from the Congressional Research Service demonstrated that federal support for biomedical research peaked in FY2003, as estimated by the buying power of NIH funding adjusted for inflation using the Biomedical Research and Development Price Index (BRDPI). After FY2003, the purchasing power of NIH funding declined steadily from FY2004-2015 (excluding supplemental ARRA funding), before increasing from FY2016-FY2019. Despite these increases, the purchasing power of NIH funding remains below FY2003 levels today. On the horizon, continued growth of non-discretionary spending in coming decades will leave a smaller proportion of the federal budget available for discretionary spending, including biomedical research (Hourihan, 2018).

The decreasing purchasing power of NIH funding has a disproportionate impact on basic science. The NIH has traditionally prioritized funding for investigator-initiated, basic research (Bishop et al., 1993; Kornberg 1997; Tessier-Lavigne, 2013), and continues to direct more than half of its funding to basic, as opposed to applied, research. This funding is not readily replaced by industry or philanthropy.

Uncertain industry funding. The second is uncertainty regarding industry funding for basic biomedical research. Biopharmaceutical companies are primarily responsible for funding the applied, preclinical research and development required to bring new products to market, but spend little on basic research. In 2016, the top 369 pharmaceutical and biotechnology companies spent >$139 billion/year on R&D around the world (EU, 2017). The average out-of-pocket costs have been estimated to be $1.4 billion for each new product launch (DiMasi et al., 2016).

In contrast, the National Science Foundation estimates that pharmaceutical industry funding for basic science totaled $3 billion in 2008, rising to $8.1 billion in 2014 (Mervis, 2017). Industry funding for basic research, however, contributes to the science underlying less than half of the most transformative drugs or drug classes of recent years (Chakravarthy et al. 2016). While this increased funding during a time of unprecedented economic growth is laudable, continued growth may not be sustainable. Industry funding for research is threatened by mergers and acquisitions, which are commonly intended to reduce costs and bolster short-term earnings. Frequently, cost reductions are achieved by cutting research spending. The 2009 acquisition of Wyeth by Pfizer, for example, resulted in closure of six of the twenty research sites formerly maintained by these companies and a substantial reduction in total R&D spending (Rockoff, 2009). Similarly, the 2014 acquisition of Cubist by Merck resulted in the mass firing of Cubist's research staff and elimination of an important center of innovation focused on much-needed antibiotics for the treatment of resistant organisms (Lowe, 2015). Research funding is also threatened by activist shareholders, who realize little near-term economic benefit from long-term investments in basic science. Efforts by shareholders to maximize near-term value often result in dramatic reductions in R&D (LaMattina, 2011). Perhaps the most dramatic example of this was the investor-driven merger and subsequent break-up of Dow and Dupont, which explicitly curtailed research by two companies with a long tradition of leading chemical research (George, 2015). Increasing pressure on corporate profits in coming years is likely to increase pressure on companies to reduce R&D spending to boost earnings.

Why basic research matters

In engineering, it is well recognized that the most important determinant of successful product development is having technology, "advanced enough to meet requirements but also mature enough to be predictably managed" (GAO, 1999). This principle underlies the use of Technology Readiness Assessments by the Department of Defense, NASA, Department of Energy, and other government agencies in procurement and product design. (GAO, 2016)

Research demonstrates that the same principle may be true in biopharmaceutical development. Using an analytical model for the advance of basic biomedical science, studies have shown that few targeted or biological products are approved until the corpus of research on the drug target or class of chemical entities reaches an established threshold of technological maturation (McNamee and Ledley, 2017; McNamee et al., 2017; Beierlein, et al., 2017a; Beierlein et al. 2017b). These observations have significant implications for the relationship between basic science, the innovation ecosystem, and the Bioeconomy.

McNamee and Ledley (2017) modeled the maturation of basic cancer research from the outset of the War on Cancer in the 1970s to the present day. This work demonstrated that increased funding for cancer research in the 1970s stimulated the initiation of new areas of research in areas such as cancer genetics, cancer immunology, and cell death. This research, however, only reached the established stage of technological maturity after 2000. These data suggest that the often-discussed lag in emergence of new cancer therapies during the early decades of the War

on Cancer in the 1980s and 1990s reflected the immaturity of the science during this period, and that the dramatic increase in the number of new cancer therapies in this decade reflects the normative timeline for maturation of science initiated in the 1970s and the power of this now-mature body of scientific knowledge (McNamee and Ledley, 2017).

In a related study, McNamee et al (2017) showed that from 2010-2014, no targeted or biological products were approved before the body of research on the drug target passed an analytically defined established point. This work also demonstrated that the efficiency of clinical development was related to the maturation of the underlying science, with the timeline of clinical development being significantly longer for products that entered clinical trials before the established point compared to those that entered clinical trials only after the underlying technology was established. Similar associations between the maturation of basic science and efficiency of targeted drug development have been described for cardiovascular therapeutics (Beierlein et al., 2017a), nucleotide therapeutics (Beierlein et al., 2017b), and gene therapies (Ledley et al. 2014).

These analyses are consistent with expert reports suggesting that the rate limiting steps in translational science are related to the paucity of validated targets and novel compounds entering clinical trials, rather than roadblocks in clinical development or regulatory review (Woodcock, 2013). The dependence of modern drug discovery on mature basic science underlies the characteristic 20-30 year lag between new biomedical discoveries and the emergence of novel therapeutic products based on these advances (Hanney et al. 2015; McNamee et al., 2017) as well as econometric data suggesting that increases in basic research lead to disproportionately larger increases in the numbers of new drugs (Toole, 2012). In sum, these data demonstrate how a mature corpus of basic science research is essential for successful product development and the associated Bioeconomy.

Contribution of the NIH to new drug approvals

A 2017 study published in the Proceedings of the National Academy of Sciences USA examined the contribution of NIH funded research to each of the 210 new drugs approved by the FDA from 2010-2016 (Cleary et al., 2018). This work explicitly examined both the NIH contribution to applied research, defined in this study as research that explicitly mentioned the new drug (New Chemical Entity, NCE), and the NIH contribution basic research, defined as research focused on the drug's biological target that did not explicitly mention the drug. This study identified >2 million research publications related to the 210 NCEs approved form 2010-2016 or their 150 different biological targets. Of these, >600,000 publications cited NIH funding, which collectively comprised >200,000 fiscal years of funding (from 1980-2016) and a total of >$100 billion in Project Costs (2000-2016). Of this total, more than 90% of NIH funding was associated with basic science on the biological targets for new drugs, and less than 10% focused on the drugs themselves. Significantly, NIH funded research was associated with every one of the 210 approved drugs or their biological target.

To examine the scale of NIH investment necessary to achieve a level of technological maturity sufficient to launch novel, first-in-class products, we examined funding associated with the targets for the 87 NCEs directed against novel biological targets. An average of >$800 million in NIH funding was related to the research performed on these novel biological targets before a first-in-class drug was successfully launched (Cleary et al., 2018). While this research is likely to have spillover effects beyond the first-in-class product (e.g. follow-on products, diagnostics, improvements in practice), this analysis demonstrates the scale of federal funding necessary to create an established body of biological research sufficient to launch novel therapeutic products.

Recommended actions by the U.S. Government

These recommendations focus on ensuring sustainable funding for the basic science that underlies the innovation ecosystem and the Bioeconomy.

1. **Make a long-term commitment to sustained public funding of basic science by the NIH at levels at least equal to 2003 in constant dollars.**

First, we add our voice to that of others who argue for a long-term commitment by the government to fund basic biomedical science at levels sufficient to maintain, or expand, the scientific enterprise (Bluestone et al., 2018). Our work quantifying the NIH contribution to new drug discovery highlights the scope and significance of public investment in the development of new therapeutics and the risk that reduced research funding would slow the pipeline of new cures for morbid disease.

Our work also suggests that federal funding for basic research is a remarkably efficient instrument for stimulating the Bioeconomy. The $100 billion in NIH funding that can be directly linked to new drug approvals over a six year period (2010-2016) represents ~20% of the total NIH budget allocation from 2000-2016 and ~40% of the total allocated by the NIH leadership to basic research. This funding has already contributed directly to private sector investments in the applied and translational science required to bring new products to market, new jobs in the discovery, development, manufacture, and marketing of new drugs, and improved health outcomes for patients. *Accordingly, we call for the U.S. government to make a long-term commitment to sustained public funding of basic science by the NIH at levels at least equal to 2003 in constant dollars.*

2. **Ensure equitable returns to the public sector from the licensing of federally funded research for development in the biopharmaceutical industry.**

For almost 40 years, the Bayh-Dole has played a central role in facilitating the transfer of government funded scientific advances from universities or government laboratories to industry for development. (Congressional Research Service, 2012). The Bayh Dole act stimulates the U.S. Bioeconomy in two ways. The first is by enabling the protection of intellectual property and licensing of this property to industry. This act played a critical role in the emergence of a

vibrant biotechnology sector in the United States. The second is by empowering non-profit institutions to receive payments for the licensing of intellectual property in the form of research funding, royalties, milestone payments, or equity that can be reinvested in the public interest. Recent studies, however, suggest that there is a need for greater equity in the returns to the public sector from these licenses.

Edwards (2017) has compared the terms of licensing agreements between universities and corporations with those between corporations. Top line analysis of these agreements demonstrates that the average maximum royalty rate for licenses from universities was ~4%, while the average maximum royalty rate for licenses from corporations was >14%. This discrepancy is not fully accounted for by the larger number of late stage products involved in corporate license agreements or other license terms such as exclusivity or the licensed rights. This research is ongoing.

The returns to public institutions from the license of scientific advances and inventions represent an important source of revenue for ongoing academic research and education (Pressman, 2017). Maximizing the returns from such licenses could provide a sustainable source of funding for basic research. *Accordingly, we call for the U.S. government to implement policies that ensure equitable returns to the public sector from the licensing of federally funded research for development in the biopharmaceutical industry.*

3. Require accounting recognition of basic and applied research spending as a capital investment that produces a tangible asset (intellectual property).

The biopharmaceutical industry has ample capital resources to make grater investments in biomedical research. Companies the pharmaceutical & biotechnology sector already invest a greater fraction of revenues on R&D than companies in other sectors (15.8% vs 3.3%) (EU 2017). The pharmaceutical industry has the capacity to invest more. We recently examined the finances of 35 large pharmaceutical companies from 2000–2018. These companies reported revenue of $11.5 trillion, gross profit of $8.6 trillion, earnings before interest, taxes, depreciation, and amortization (EBITDA) of $3.7 trillion, and net income (earnings) of $1.9 trillion. A large fraction of the earnings are not reinvested, but returned to shareholders in the form of dividends or stock buybacks (Oner and Lazonick, 2018)

One impediment to industry investing a greater fraction of revenues on biomedical research is the accounting standards that treat R&D as an expense, which reduces corporate earnings, rather than a capital investment, which produces a tangible asset (intellectual property) The U.S. Generally Accepted Accounting Practices (US GAAP) are based on guidelines promulgated by the Financial Accounting Standards Board (FASB). These guidelines require R&D spending to be treated as an expense (FASB ASC 730-10-25-2, FASB 2018), which directly reduces corporate earnings and adversely impacts a company's bottom line and, consequently, their stock price.

Studies show that R&D provides a positive return on investment (ROI), with each dollar spent on R&D producing more than one dollar in revenue (Grabowski et al., 2002; Grabowski and

Vernon 1994; Deloitte 2016; Meyer 2011). However, studies also show that there can be a lag of 5-10 years between R&D spending and revenue generation (DiMasi et al., 2016). Thus, expensing R&D spending at the time the research is performed makes companies less profitable in the short term, while offering the expectation of greater revenues and profits in the future. If R&D spending were capitalized when performed, with the intellectual property resulting from R&D treated as an asset that is depreciated over time, the short-term, negative impact of R&D spending on earnings could be eliminated, and the depreciation of these assets could be synchronized with the revenues expected to accrue from such investments.

The current FASB standards requiring the expensing of R&D (FASB ASC 730-10-25-2) date from 1975, and were adopted in the face of conflicting evidence that the policy would adversely impact R&D spending (Horwitz and Kolodny, 1981). Allowing the capitalization of all, or part of, R&D spending could provide a more accurate reflection of its economic value (Healy et al., 2002) and reduce its adverse impact on company earnings and shareholder value. This could lead to greater investment in basic and applied research by the pharmaceutical industry, which ultimately stands to profit from this research.

We would note that a similar change in the treatment of R&D was made in the National Accounting System used to calculate the Gross Domestic Product (Crawford et al. 2014). In the 2013 comprehensive revision to the GDP by the Bureau of Economic Analysis (2013), the BEA recognized expenditures by business, government, and nonprofit institutions on research and development (R&D) as fixed assets and recorded R&D spending as investment in gross domestic product (BEA 2013). These expenditures were, thus, added to the GDP calculations, and were depreciated over the useful life of the investments. A*ccordingly, we call on the U.S. Government to require accounting recognition of basic and applied research spending as a capital investment that produces a tangible asset (intellectual property).*

4. Facilitate innovative financial instruments that provide long-term support for basic and applied research through tax exempt bonds.

Finally we call on the U.S. Government to facilitate the emergence innovative financial instruments designed around the timelines for commercializing innovative products from basic research. Financial markets are unparalleled in their ability to generate capital for novel instruments and opportunities. Properly constructed investment instruments can align the opportunity for investors with the timelines and costs of both basic and translational science (Fernandez, Stein, and Lo 2012), while also providing investors with opportunity to trade on the fair-market value of the instruments.

We believe corporate bonds may be a particularly attractive instrument for supporting basic research. In 2018, corporations issued $1.2 trillion in investment grade bonds, many with timelines of 30 years or more. These timelines are commensurate with those required for the maturation of scientific discoveries and development of products based on this science. We would envision instruments could be issued by pharmaceutical companies, investment banks,

or industry consortia, which function like Special Purpose Entities (Schiff and Murray 2004) to invest in basic science in both the public and private sector and provide returns when this science bears fruit in the form of novel biopharmaceutical products. *We call on the government to facilitate the development of innovative financial instruments that provide long-term support for basic and applied research through tax exempt bonds.*

Conclusion

We are concerned that threats to sustained funding from basic research from both the public and private sectors could compromise the future of the U.S. Bioeconomy. We call on the U.S. government to take the lead in developing a new blueprint for funding biomedical science with a broader base of support that includes substantive contributions from the industry alongside those of government and philanthropy. The foundation of this blueprint will continue to be sustained government funding for basic research, but should also include equitable returns from the licensing of government-funded research to industry, and actions that enable industry to shoulder more of the burden for the basic research that makes their enterprise possible.

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