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The U.S. National Institutes of Health: Inspiring Innovation in Biomedicine and Health

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Contents

Abstract

With its unique system of intramural and extramural research programs, funding for academic and corporate product development, the U.S. National Institutes of

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Health (NIH) has grown from very simple roots changing not only the face of healthcare, but also leading to the creation of the biotech industry in the USA. Whether your interest in biomedicine and health innovation from a scientific, medical, educational, or commercial perspective, the NIH should be a part of your future.

Keywords

Innovation · Biomedicine · NIH

5.1 Introduction

The start of National Institutes of Health (NIH), and thus the origins of its "innovation ecosystem" begins in 1887, when a one-room laboratory was created within the Marine Hospital Service (MHS), predecessor agency to the U.S. Public Health Service (PHS). The MHS itself had been charged by Congress in the 1880s to examine passengers on arriving ships for clinical signs of infectious diseases—especially for dreaded diseases of cholera and yellow fever—and prevent epidemics. Joseph J. Kinyoun, a young MHS physician trained in the new bacteriological methods being reported in Europe, was chosen to set up a one-room laboratory in the Marine Hospital at Stapleton, Staten Island, New York (Photo 5.1). Dr. Kinyoun (essentially the first NIH Director), called this facility a "laboratory of hygiene" to indicate the laboratory's purpose was serving the public's health. Within only a few months, Kinyoun identified the cholera bacillus in suspicious medical cases and used his Zeiss microscope to confirm his colleagues' clinical diagnoses. In stimulating and assisting other parties to improve healthcare, we see the very beginnings of this unique innovation ecosystem built around NIH.

Besides being the founding NIH Director, Dr. Kinyoun also focused on what we could call today bioentrepreneurship and technology transfer. Working first as a federal employee and later in the private sector, Kinyoun invented and patented multiple industrial disinfecting machines used in quarantine operations—such as the "Kinyoun Portable Bed Disinfectors." He developed the first smallpox immune serum; his "Kinyoun Method" of smallpox vaccination used until the 1960s. His "Kinyoun Stain," discovered for tuberculosis, is still in use today. Late in his career, he even worked in pharma for a firm that became a predecessor to Merck [1]. Clearly, Kinyoun led by example in founding NIH both an institution and innovation ecosystem.

Photo 5.1 Dr. Joseph J. Kinyoun, NIH Founder

5.2 NIH Today

Despite his own remarkable vision and activities, Dr. Kinyoun could hardly have imagined the size and scope of the NIH's present programs and the supportive environment for biomedical research and product development fostered today. From its humble beginnings as a single laboratory, the NIH has evolved into a comprehensive program of 27 institutes and centers (ICs) both national and international in scope.

As a result of the numerous scientific opportunities and funding programs that make up today's NIH, the environment it that NIH nurtures continues to accelerate even more significant contributions to human health, innovative medical products and economic development. Using innovations from federal labs to spur both technological and economic development arose from the 1986 Federal Technology Transfer Act. This act codified and promoted partnerships between NIH intramural research and the private sector to develop new medical products.

Around 90% of NIH's $48 billion FY 2024 budget went to more than 300,000 researchers at over 2500 universities, medical schools, companies and other research institutions in every state in the USA and throughout the world. The 1980 Bayh-Dole Technology Act codified and fostered partnerships between NIH-funded

extramural research and private-sector development of new medical products [2]. The remaining funding (~10%) was spent on internal NIH R&D projects (Intramural Research Program; IRP) carried out by the approximately 6000 scientists employed by the NIH. Dozens of NIH-supported scientists from its own faculty and around the world have received Nobel Prizes for their groundbreaking achievements in Physiology or Medicine, Chemistry, Physics, and Economic Sciences. To date, 174 NIH supported researchers have been sole or shared recipients of 104 Nobel Prizes. This number includes Noble Prize winners serving as NIH scientists in the IRP.

The continuous process of biomedical research and product development requires a supportive environment and an innovative ecosystem. For new research to truly yield new drugs, devices and reagents, both public and private sector institutions need to use innovation to refine and build upon basic knowledge to enable the development of even better products. Uniquely for NIH, it does not matter whether an idea originates in a supported university laboratory, its own intramural research program or even the private sector. Nor does it matter the geographical origin of the innovation. Each new medical idea can be evaluated and supported based upon its own scientific and product merits—regardless of its origin. Collaborations, publications, and research tool sharing help ensure that important findings percolate through and invigorate the entire scientific community. For NIH's innovation ecosystem, new findings serve as a building block for establishing a deeper understanding of human health and disease and are supported through a wide variety funding, educational, training and developmental programs.

5.3 Structure of the NIH Innovation Ecosystem

To truly function as the foundation of an ecosystem, an institution or organization must realistically be able to help stimulate and sustain two primary functions—for biomedicine these two would be both new research as well as product development. Most biomedical products have of their research and development history that can be traced back to basic research institutions with the original research often funded by NIH or other governmental programs. Licensing and technology transfer programs at these federal labs or other non-profit research organizations then provide a means for getting new inventions to the market for public use and benefit. From a research institution's perspective, this portion of the innovation ecosystem is quite desirable. Public and commercial use of inventions typically comes with new recognition of the value of basic research programs at the university or organization in which it originated. These inventions also serve as helpful means to attract new R&D resources and partnerships within the ecosystem to these laboratories. Through licensing or other technology-transfer mechanisms, these institutions also receive a "return on investment"—whether that is measured in terms of financial, educational or societal parameters—or some combination thereof. An example of this would be the recently concluded *Public Health and Economic Impact Study of NIH Intramural Technology Transfer Licensing,* which measured and assessed

the significant impact the technology licensing program of the NIH IRP had in innovation, healthcare, and economic development [3].

5.4 NIH Innovation Keystone: Bayh-Dole and the Birth of Technology Transfer

In 1980, continuing the momentum of the policies of Presidents John F. Kennedy and Richard Nixon, Senators Birch Bayh and Robert Dole enacted legislation that gave universities, nonprofits, and small-businesses the right to own inventions made by their employees for federal government-funded research. The Bayh-Dole Act of 1980 (P.L. 96-517) reversed the presumption of title ownership by NIH in NIH grants and permitted a university, small business or nonprofit institution to elect and pursue ownership of an invention in preference to the government. The underlying spirit of this important piece of legislation was to maximally utilize the outstanding research at these universities and other recipients for the good of the public who funded the research through their tax dollars. This set the stage for explosive growth of a new system of innovation built around government biomedical funding agencies, such as NIH.

Though the ownership right that universities and other funding recipients have to these inventions comes with obligations, these also have stimulated activity in the ecosystem. The primary obligation for these institutions is to actively market and attempt to commercialize the invention, preferably through U.S.-based business enterprises (including start-ups) to benefit the public. Thus, was born the field of "technology transfer" and the establishment and growth of technology-transfer offices (TTOs) now part of every research campus. Prior to Bayh-Dole, 28,000 patents were owned by the U.S. government—less than 5% of which were commercialized. Since the enactment of Bayh-Dole, more than 7000 newly created companies are still operational. The combination of innovation and entrepreneurship resulted in billions of dollars of direct economic impact within the USA and more than 700 new products put in the market during those years—all largely based upon NIH or other agency funded research [4].

Similarly in the 1980s, federal intramural laboratories—including NIH—were also given a statutory mandate under the Stevenson-Wydler Technology Innovation Act (P.L. 96-480), the Federal Technology Transfer Act (P.L. 99-502), and Executive Order 12591. These actions ensured that new technologies developed in federal laboratories were similarly transferred to the private sector and commercialized. One metric of the success of NIH IRP innovations licensed by the private sector is the resulting 47 new FDA-approved drugs and vaccines [5].

Within the system of innovation, NIH and NIH-funded universities developed a more strategic focus for their technology-transfer activities that more fully supports working with entrepreneurs. Although licensing revenue is collected, maximization of such funds is not the goal. Instead, research organizations find themselves primarily looking for increased product launches, company formation and new job creation based upon NIH-funded inventiveness. This process also supports

faculty recruitment and retention, enhanced access to follow-on research funding and, in general, creating an entrepreneurial culture to attract venture investment. The economic development aspects of research are now recognized as a "fourth mission" for such institutions—along with education, research, and public service. Entrepreneurs play a key role in this fourth mission by establishing companies driven by new research discoveries—thus building out the innovation ecosystem.

5.5 Accessing Technologies and Collaborations in the NIH Innovative Ecosystem

Generally, bioentrepreneurs can directly access NIH-supported research and inventions for product development from three main sources, as given in Table 5.1. For research funded by grants and contracts from NIH (extramural research), the individual university or small business controls commercial rights. Biomedical research conducted by NIH itself (intramural research program) is licensed directly through the individual IC technology transfer offices or their service centers at NIH [6]. The full spectrum of NIH intramural technology transfer activities is given in Table 5.2.

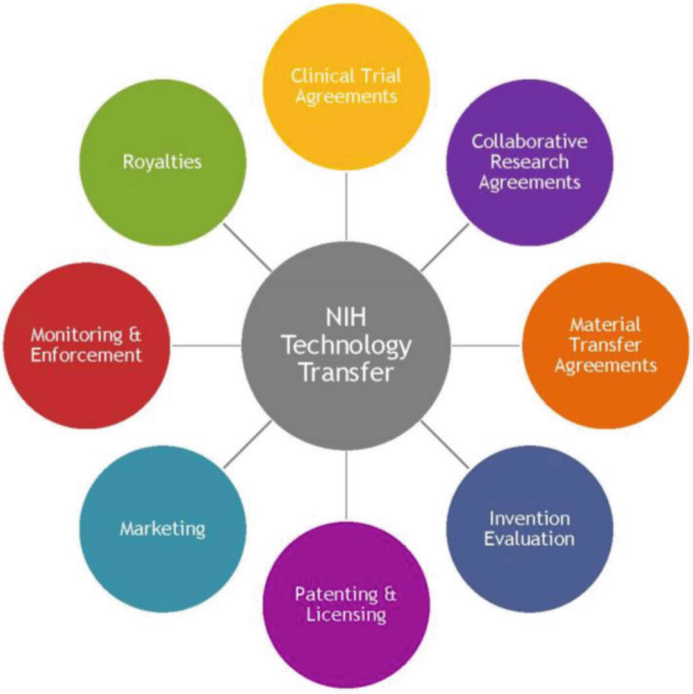
Both NIH and NIH-supported research institutions have a robust research program "pipeline" providing novel, fundamental research discoveries available for commercial applications. NIH, for instance, as both a large-scale provider and consumer, represents a sort of "supermarket" of research products or tools for its commercial partners and suppliers. Additionally, overall product sales of all types by NIH licensees generally are around $7 billion annually. As previously mentioned, most NIH intramural technology transfer activities date from the Federal Technology Transfer Act of 1986 which first allowed federal laboratories to keep their license royalties and share them between the individual inventors and further, internal reinvestment.

Research collaborations and assistance from NIH or NIH-funded institutions can take several forms as these researchers and clinicians can work with industry under different collaborative agreements. For example, research institutions may seek to access technologies developed by industry for research studies—an imaging tool, a sequencing platform, or a drug discovered and in development by a company. The technology transfer office then works with companies and clinical partners to memorialize the understanding between the scientists and/or clinicians to allow the collaborations to happen. The key components of these collaboration agreement are terms related to inventions, rights to inventions, confidentiality versus publication,

Table 5.1 Sources for accessing NIH-funded research in the innovation ecosystem

• Intramural Research (from institute technology transfer offices)
• University Grantee Research (from individual university technology transfer offices)
• SBIR and STTR Programs (from individual small business awardees)

Table 5.2 Intramural NIH technology transfer innovation ecosystem activities



managing conflicts of interest and indemnification—especially for work involving patient care.

5.6 Industry Collaborations in the NIH Innovation Ecosystem

There are several types of research or collaboration-related agreements that companies commonly encounter in working with NIH and NIH-funded institutions:

Confidential Disclosure/Nondisclosure Agreements (CDA/NDA) Prior to engaging in any collaboration, each party may need to disclose to the other party some proprietary information that—if passed on to third parties—might be detrimental to the interest of the disclosing party. Such a discussion is a necessary first step to determine the interest in, and the breadth and scope of any potential collaboration. The parties negotiate a CDA/NDA ensuring the information disclosed is held confidential, only used for establishing the collaboration, stipulates a term of how long the information needs to be held confidential and describes the consequences of nonadherence to agreement terms.

Material Transfer Agreement (MTA), Sponsored Research Agreement (SRA), Research Collaboration Agreement (RCA), Clinical Trial Agreement (CTA), and Cooperative Research and Development Agreement (CRADA) Companies, both small and large, typically need to invest a significant research and development funds toward developing drugs or other biomedical products. NIH and NIH-funded research institutions have several programs key towards understanding the fundamental biology underlying a wide variety of commercial products. When companies and research institutions seek to collaborate, they often have very different focuses. A company seeks to get through regulatory requirements and onto the market as expeditiously as possible. Their aim is better understanding the mechanism-of-action to penetrate as many verticals as possible and have discoveries arising from collaborations improve the addressable market for their eventual product. In the case of collaborations with NIH-supported clinical programs, access to patient samples may be an option. Samples provide valuable insights the company hopes will guide them through clinical validation of their product—be it a potential drug, medical device, or diagnostic. In contrast, NIH or university investigators are often interested in testing experimental solutions from companies to build a scientific insight or medical knowledge that is publishable. The good news is that agreements are crafted to satisfy the needs of both parties. And it is possible under CRADAs (for NIH) or SRAs (for NIH-funded entities) for the investigator to receive additional funding support from the company for basic or clinical research programs, in turn, enhancing commercial development.

MTAs and SRAs are agreements dictating the terms of the transfer of material and/or money from the company to the academic institution. Similarly, at NIH, joint projects with companies for basic research or clinical studies can be formalized as CRADAs. RCAs are more appropriate when no IP options or provided funding are anticipated. Because of their clinical hospitals and centers as well as other networks and facilities, the NIH and at least some of its supported universities can also take some medical discoveries (or those of their partners) into early clinical trials through CTAs.

5.7 Licensing Technologies from the NIH Innovation Ecosystem

Basic Licensing Principles of University and Federal Laboratories Compared to technology licensing with corporations, NIH and NIH-supported institutions bring a different focus and perspective to the table when negotiating technology transfer agreements. These agreements are used to further overall institutional missions. Therefore, representatives from such nonprofit institutions consider the public consequences of such licenses as their priority—not the financial terms involved. For example, when compared with their peers in industry, NIH-funded institutions have the mandate to make new technology as broadly available as possible. This means that there is a strong preference to limit the scope of a

license to only what is needed to develop specific products. Exclusive licenses are quite typical for biomedical products such as vaccines, therapeutics, and others. The underlying technologies require substantial private risk and investment (and a prior public notice and comment period in the Federal Register in the case of NIH). In their agreements, NIH laboratories and universities would also typically expect to retain the right to permit further research use of the technology whether to be conducted either in the NIH intramural program, universities or companies. Because the commercial rights granted represent institutional (and public) assets, these agreements have enforceable performance benchmarks to ensure that the public will eventually receive the benefit (through commercialized products) of the research it funded. Regulations governing the license negotiation of federally owned technologies and their mandated requirements are described in more detail at 37 Code of Federal Regulations (CFR), Part 404, while those for federally funded technologies can be found at 37 CFR Part 401.

In a license agreement, the research entity essentially grants rights to a company to make, use and sell products that were it not for the license, would infringe on the patent rights that the research center owns and/or controls. In some instances, the research center also grants the company rights to use technological information/know-how or materials that goes together with the information in the patent application and that is valuable to the company as it hopes to commercialize the technology into products. Licensing is at the heart of operations of a technology transfer office since NIH or NIH-funded universities function as nonprofits. They do not and cannot have a product commercialization arm. NIH or NIH-funded universities cannot convert inventions into commercial products and processes. They must partner with industry to do that—as is often the case with NIH-funded U.S. small businesses under the Small Business Innovation Research (SBIR) programs. Thus, these out-licensing activities are the key for research programs to fulfil the core of the Bayh-Dole Act and other federal mandates to commercialize arising from NIH funding.

Licensing from NIH and NIH-Funded Laboratories Commercializing technologies (for example, vaccines or drugs) and then entering world-wide markets cannot be the responsibility or mission of research institutions or government agencies. As is the case with its funded universities, the NIH is not able to commercialize its discoveries even with its considerable size and resources. Instead, it relies instead upon industry partners. Companies with access to the needed expertise financial resources are needed to undertake continued development of these inventions from the NIH or other research institutions into final products. Typically, a royalty-bearing license agreement with the right to sublicense is given to a company from NIH (if NIH-owned) or the university (if university-owned) to use patents, materials or other assets to bring a therapeutic, vaccine, or other product concept to market. Exclusivity is almost always the norm for the U.S. Food and Drug Administration (FDA)-regulated products due to the risk involved in time, money and regulatory pathways involved for companies and their investors. Financial terms of the license agreement are negotiable but typically reflect the nascent, high-risk nature of

the discovery. Technologies coming from NIH or NIH-funded research are often early-stage; many years prior to generating revenue as a commercialized product. Consequently, most licensees are early-stage companies or start-ups. Larger firms typically want assets further along in the product development continuum. In addition to the license agreement, there will often be research collaborations between the licensee and the NIH or university to assist with additional work needed. When the NIH licensee can sufficiently "de-risk" the technology, these companies then sublicense, partner or get acquired by larger biotech or pharmaceutical firms. Extensive resources are needed for the final, most expensive stages of development with the large company expected to sell the product once it achieves regulatory marketing approval.

Start-Ups as Licensing Vehicles in the NIH Innovation Ecosystem Since the 1980s, federally funded health research institutions developed an active but increasingly strategic focus on improving public health through technology-transfer activities. As such, they are particularly interested in working with start-ups and other early-stage companies looking to develop and deliver innovative products. Rather than just seeking a financial return through revenue generation, these institutions are looking to utilize licensing of nascent inventions to increase new company formation, support faculty recruitment and retention, enhance research funding and create in general a more entrepreneurial culture within the organization. Successful start-ups attract venture investment and develop the product for as many indications as possible.

The licensing practices for most NIH-funded nonprofit research institutions changed significantly over time with respect to biomedical inventions [7]. Until the last 20 or so years ago, most of the important medical products based on licenses from university or federal laboratory research came from direct agreements with large pharmaceutical firms. With its ever-increasing consolidation, large pharmaceutical firms are typically no longer looking to directly license early-stage technologies for commercialization. In contrast, the number of licenses signed with start-ups as well as small- to medium-sized biotechnology companies is rising. Typically, around 70% of the total licenses are executed with start-ups and small biotech firms. Most success stories tend to be from those originally partnered with biotech or other smaller companies at the time of the original license agreement. Some examples from the NIH licensing program are:

- Kepivance® (a human growth factor used to treat oral sores arising from chemotherapy licensed to Amgen).
- Velcade® (a small molecule proteasome inhibitor used to treat multiple myeloma from Millennium).
- Synagis® (a recombinant monoclonal antibody for preventing serious lung disease caused by respiratory syncytial virus in premature infants from MedImmune).

- Prezista® (an HIV protease inhibitor used to treat drug-resistant AIDS patients from Tibotec).
- Taxus Express® (a paclitaxel drug-eluting coronary stent used to prevent restenosis from Angiotech).

Although these firms or their successors are all now late-stage, well-resourced companies, they were early, small companies when the underlying technology was licensed to them.

5.8 Funding in the NIH Innovation Ecosystem

NIH is well known as the largest public funder of biomedical research in the world and invests roughly $43 billion a year to support outside institutions to enhance life and reduce illness and disability. This level of funding supports a strong research ecosystem that has led to breakthroughs and new treatments, helping people live longer, healthier lives, and building the research foundation that drives discovery. NIH offers funding for many types of grants, contracts, and even programs that help repay loans for researchers.

While perhaps best known for grants to academic scientists throughout the world, NIH also provides private sector U.S. entities with nondilutive funding through the Small Business Innovation Research (SBIR) and Small Business Technology Transfer Research (STTR) programs which are now known collectively as the NIH Seed Fund [8]. The NIH Seed program is perhaps the most valuable and stable funding source for new companies. These grant funds do not need to be repaid—unlike small business loans or convertible notes.

Other noteworthy advantages of the NIH Seed Program for small companies (eligibility as defined by the U.S. Small Business Administration) include:

- retention by the company of any intellectual property rights from the research funding,
- receipt of early-stage funding that doesn't impact stock or shares in any way (e.g., non-dilutive capital),
- national recognition,
- verification and visibility for the underlying technology,
- generation of a leveraging tool that can attract other funding from private venture capital or angel investors.

The SBIR program itself was established in 1982 by the Small Business Innovation Development Act to increase the participation of small, high technology firms in federal R&D activities. Under this program, departments and agencies with R&D budgets of $100 million or more are required to set aside 3.2% of their R&D budgets to sponsor research at small companies. The STTR program was established by the Small Business Technology Transfer Act of 1992 and requires

federal agencies with extramural R&D budgets over $1 billion to administer STTR programs using an annual set-aside of 0.45%. In FY 2023, NIH's combined SBIR and STTR grants totaled over $1.3 billion [9].

The STTR and SBIR programs are similar in that both seek to increase small business participation and private-sector commercialization of technology developed through federal support of R&D. The SBIR program itself funds early-stage research and development at small businesses. The unique feature of the STTR program is the requirement for the small business applicant to formally collaborate with a research institution in Phase I and Phase II.

However, the SBIR and STTR programs at NIH differ in two major ways. First, under the SBIR program, the principal investigator must have their primary employment with the small business concern at the time of the award and for the duration of the project period. However, under the STTR program, primary employment is not so stipulated. Second, the STTR program requires research partners at universities and other nonprofit research institutions to have a formal collaborative relationship with the small business concern. At least 40% of the STTR research project is to be conducted by the small business concern and at least 30% of the effort is to be conducted by the single "partnering" research institution.

As a major mechanism at the NIH for achieving the goals of enhancing innovation and public health via commercialization of new technology, the NIH SEED Program presents an excellent funding source for start-up and other small biotechnology companies. They are structured in three primary phases: Phase I (feasibility), Phase II (development), and Phase III (commercialization).

In addition to receiving funding through the NIH SBIR and STTR programs, small companies may also be eligible for technical and management assistance programs designed to increase their chances for successful commercialization of the funded technology. Initially, the SBIR and STTR programs provided little or no assistance beyond the funds itself. More recently, many initiatives have been established to educate, mentor and connect awardees to valuable stakeholders. These are a key part of the NIH innovation ecosystem and include:

NIH Entrepreneurship Bootcamp—The NIH Entrepreneurship Bootcamp is designed to equip life science investigators and nascent companies with specialized innovation and entrepreneurship training. The course requires no prior experience. It uses a life science-focused customer discovery process to assess customer and stakeholder needs, and teaches participants to develop stronger business models, market strategies, and commercialization plans prior to their initial SBIR/STTR application.

Innovation Corps (I-Corps™) at NIH—The I-Corps program provides funding, mentoring and networking opportunities to help SBIR Phase I awardees commercialize promising biomedical technology. During this 8-week, hands-on program, companies learn how to focus their business plans and get the tools to bring their treatment to market. Program benefits include funding up to $55,000 to cover direct program costs; training from biotech sector experts; expanding

professional networks; creating a comprehensive business model; and gaining entrepreneurial skills.

Technical and Business Assistance Needs Assessment—The Needs Assessment Report provides a third-party, unbiased assessment of an NIH Phase I project's progress in technical and business areas that are critical to success in the competitive healthcare marketplace. This no-cost report helps companies strategize a project's next steps.

5.9 Using NIH Basic and Clinical Research Assistance to Enhance Innovation

Basic and clinical research assistance from the NIH institutes is also available to companies or other partners through specialized services such as drug candidate compound screening and preclinical and clinical drug development and testing services—offered by several programs. These initiatives are particularly targeted towards developing and enhancing new clinical candidates in the disease or disorders strategically aligned with NIH's mission. The largest and perhaps best-known of these programs are found in the National Cancer Institute (NCI) [10]. The NCI has played an active role in the development of drugs for cancer treatment for over 50 years. This is reflected in the amazing fact that approximately one half of the chemotherapeutic drugs currently used by oncologists for cancer treatments were in some form discovered and/or developed with NCI. Its Developmental Therapeutics Program (DTP) promotes all aspects of drug discovery and development before testing in humans (preclinical development) as part of the Division of Cancer Treatment and Diagnosis (DCTD). NCI also funds an extensive clinical (human) trials network to ensure that promising agents are tested in humans. NCI's Cancer Therapy Evaluation Program (CTEP), also part of the DCTD, administers clinical drug development. Compounds can enter at any stage of the development process—even those needing extensive testing before applying for human trials. Drugs developed through these programs include well-known products such as cisplatin, paclitaxel, and fludarabine. Clinical, translational and pre-clinical research collaborations are also available with intramural investigators in all 27 NIH institutes.

Established in, the National Center for Advancing Translational Sciences (NCATS) is designed to assist companies with the many costly, time-consuming bottlenecks that exist in translational product development [11]. In partnership with both the public and private organizations, NCATS develops innovative ways to reduce, remove or bypass such bottlenecks to speed the delivery of new drugs, diagnostics, and medical devices to patients. NCATS does not conduct its own drug development—as would a company. Instead, it focuses on using science to create powerful new tools and technologies for wide adoption by translational researchers in all sectors. NCATS-supported programs and projects also produced numerous tools to help basic and clinical researchers advance translational science.

Programs of note for the NIH innovation ecosystem from NCATS include:

- *Bridging Interventional Development Gaps (BrIDGs)* which enables research collaborations to advance candidate therapeutics for both common and rare diseases into clinical testing.
- *Clinical and Translational Science Awards (CTSA)* support a national network of medical research institutions that work together to improve the translational research process to get more treatments to more patients more quickly.
- *Therapeutics for Rare and Neglected Diseases (TRND)* offers collaborative opportunities to access rare and neglected disease drug-development capabilities, expertise, and clinical/regulatory resources.

There is additional assistance available from other institutes in a wide range of unmet medical needs—including infectious diseases, drug abuse, and others; too many to be highlighted here. All in all, such efforts can provide a wide variety of technical assistance (typically at modest or no cost) for preclinical and even clinical development of novel therapies or other biomedical products by a variety of partners within the NIH innovation ecosystem.

5.10 Contracting Opportunities with NIH and NIH-Funded Institutions

One of the most overlooked opportunities by biomedical-focused companies is the ability to sell products and services to the NIH and NIH-funded centers. This opportunity is relevant and highly valuable to companies with a business model viewing NIH as a customer rather than development partner. Indeed, the NIH may be the first customer for start-up companies looking to develop new products used in conducting basic, translational or clinical research. With an intramural staff of about 18,000 employees, laboratories in several regions of the country (most at the main campus in Bethesda, Maryland), and an annual intramural budget of over $4 billion, the NIH is perhaps the largest individual institutional consumer of bioscience research reagents and instruments in the world. A variety of mechanisms for selling products and services to the NIH are possible, including stocking in government storerooms and general contracting opportunities. Companies providing products and services to NIH laboratories and programs generate cash flow and revenues to fuel their own R&D. Moreover, they start to demonstrate commercial acumen to buy-side stakeholders. As the world's largest biomedical research organization, the NIH has hundreds of contracting opportunities. Specific information on such opportunities is found on the NIH Office of Acquisition Management and Policy website [12].

A series of annual research festivals are also an excellent starting point for companies hoping to sell products to the NIH [13]. These events are held at the Bethesda and Frederick, Maryland campuses. Part scientific, part social, part informational and part inspirational, such events draw a variety of small- to medium-sized bioscience firms to exhibit their product and services available to NIH. They are cost-effective since NIH does not profit from exhibitors. Lastly, they are quite

egalitarian since all allotted exhibition space is identical regardless of a company's size and resources.

5.11 Training and Education in the NIH Innovation Ecosystem

In addition to traditional scientific training supported at all educational levels, NIH, and NIH-funded universities have set up or have access to educational programs that train scientists and engineers to greater appreciate the importance of commercialization. These programs are often funded and supported at NIH institute training offices. Furthermore, the NIH Office of Intramural Training and Education (OITE) provides resources and information to enhance the educational experience of NIH trainees. It assists with finding appropriate workshops, arranging individual career counseling and identifying other NIH resources to meet trainee needs. OITE resources are also available for trainees in the extramural NIH community. Other options for education and training include entrepreneurship centers and small business assistance programs at many NIH-funded universities as well as the Federal Laboratory Consortium for Technology Transfer that is also funded by NIH and other federal labs.

5.12 NIH Innovation Ecosystem Has Spurred Biotechnology Industry Growth

As previously noted, the economic development potential of biomedical research is being recognized as a "fourth mission" for research institutions such as the NIH—along with education, research, and public service. Thus, it is in this fourth mission that bioentrepreneurs and NIH find themselves again sharing the common goal of having new companies established based upon developing innovative research discoveries.

The economic importance of licensing and technology transfer has become better recognized in recent years and some of the figures can be quite striking. For example, the overall product sales of all types by licensees of NIH intramural research reported by the NIH Office of Technology Transfer are nearly $7 billion annually—equivalent to mid-tier Fortune 500 companies. Economic development also was the focus of a U.S. Presidential Memorandum entitled "Accelerating Technology Transfer and Commercialization of Federal Research in Support of High-Growth Businesses" [14]. This White House directive recognizes the economic aspects of innovation and technology transfer for federal research in the way it fuels economic growth as well as creating new industries, companies, jobs, products, and services, and improving the global competitiveness of U.S. industries. The directive requires federal laboratories such as the NIH to support high-growth entrepreneurship by increasing the rate of technology transfer and the economic and societal impact from federal R&D investments.

Looking at the university and academic medical center figures reported by the Association of University Technology Managers (AUTM), there are similar economic indications for the impact of technology transfer and the initial funding of research from NIH and other federal programs [15]. For 2023, AUTM reported 9299 new license agreements and new research expenditures of $104.9 billion by reporting universities. That same year, more than 7214 start-ups remained operational from prior years. By the end of 2023, 714 new products had been introduced into the marketplace.

5.13 NIH Innovation Ecosystem: Results to Date

With leading-edge research programs and focus on the healthcare market, NIH and NIH-funded research programs have an exemplary record in providing opportunities for bioentrepreneurs to develop both high-growth companies and high-impact medical products. Indeed, an early study from 2007 described over 100 drug and vaccine products approved by the U.S. FDA based at least in part on technologies directly licensed from university and federal laboratories. Federal labs (e.g., NIH) provided nearly 20% of the total [16]. A later study from 2009 showed that university-licensed products commercialized by industry created at least 279,000 jobs across the United States during a 12-year period. Further, an increasing share of the United States GDP each year was attributable to university-licensed products [17]. A 2011 study published in the *New England Journal of Medicine* [18], based upon their 2007 preliminary study, showed the intramural research laboratories at the NIH as by far the largest single nonprofit source of new drugs and vaccines approved by the FDA. Finally, a 2017 study from the NCI SBIR Development Center showed that out of 690 SBIR grant awards, 368 (53%) had already resulted in sales. Total cumulative sales were $9.1 billion, which equates to average sales of approximately $24.8 million for each of the 368 awards [19].

These strong sales underscore the significant impact of the NIH innovation ecosystem. It is strong and will be increasingly effective and important going into the future. Although new knowledge and product development has been a model in showing the value of the NIH innovation ecosystem from NIH and NIH-funded institutions, it is not the entire story. The final tally must include not only the full societal value and economic impact both of new companies, but more importantly the life-saving or impactful therapeutics, vaccines, diagnostics and other biomedical products on the market having origins in federally funded research. This is believed to be the truest measure of a system of innovation as well demonstrating the value and importance of having the growth of the intramural and extramural research programs of the NIH since its humble origins in 1887 [20].

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