Biotechnology Entrepreneurship

Leading, Managing and Commercializing Innovative Technologies

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Chapter 15

Licensing the Technology: Biotechnology Commercialization Strategies Using University and Federal Labs

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Chapter Outline

The Federal Government's Investment in Basic Biomedical Research

For many years the United States has led the world in government funding of nonmilitary research and development (R&D), notably support for basic and clinical research that directly relates to health and human development. While new biotechnology entrepreneurs often rely upon the "Three Fs" of founders, friends, and family for advice, assistance, and financing during the early years of their company, they often overlook a "Fourth F" that can be of major assistance during many phases of their growth—that being federal, especially federal labs and federally funded research in universities and academic medical centers (AMCs), also referred to as academic medical organizations (AMOs) across the United States. A longtime focal point for such federal investment by the US government in biomedical research has been the National Institutes of Health (NIH) through its intramural laboratories and the funding provided to most academic and university- or hospital-based research programs. Funding provided by the NIH alone reached $37.3 billion in the fiscal year 2018; approximately 10% of this funding was spent on internal NIH R&D projects

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(intramural research) carried out by the approximately 6000 scientists employed by the NIH. The balance was distributed in the form of grants, contracts, and fellowships for the research endeavors of more than 300,000 nongovernment scientists (extramural research) at 2500 colleges, universities, and research organizations throughout the world [1]. Each year, this biomedical research leads to a large variety of novel basic and clinical research discoveries, all of which generally require commercial partners to develop them into products for consumer, scientist, physician, or patient use. Thus federal laboratories and universities need and actively seek corporate partners or licensees to commercialize their federally funded research into products to help fulfill their fundamental missions in public health.

AMCs, with their dual components of research and clinical care, are in a unique position of being at the very beginning and very end of the science-to-business and product-to-patient chain. For example, the University of Massachusetts Medical School (UMMS) in Worcester receives $250 million in federal funding for its nearly 1100 investigators and Partners Health Care at Massachusetts General Hospital (MGH) and Brigham and Women's Hospital receives about $1.4 billion in federal funding for its approximately 1300 investigators. These AMCs use the very therapies and diagnostics that its researchers invent, for clinical care.

Translation of Academic Research to Products for the Public Good

Most biotechnology products have some history of their R&D that can be traced back to a basic research institution, most often funded by federal grants. Licensing and technology transfer programs at nonprofit basic research organizations provide a means for getting new inventions to the market for public use and benefit. From a research institution's perspective, this is quite desirable since the public and commercial use of inventions typically come with new recognition of the value of basic research programs at the university or organization that originated it. These inventions also serve as helpful means to attract new R&D resources and partnerships 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. A recent study by the Brookings Institute [2] offers useful insights about the academic innovation enterprise.

Universities and AMCs are known as centers of education, patient care, and basic research. This basic research, fueled largely by the curious mind and funding from the government, has transformed our understanding of important fundamental phenomena. This research activity results in publications that dictate the careers of those in academia and defines the institution's academic culture and spirit. Important discoveries are made at each of these institutions, but they are largely confined to the research realm. Starting from the early 1960s, the need to maximize the benefits from such intense and groundbreaking research was felt thanks to Jerome Wiesner, the scientific advisor to President John F. Kennedy. He recognized that most of the innovations which impacted everyday people were left primarily to the large companies of the day—Lucent Bell Labs, Kodak, Johnson & Johnson, to name a few—which held the most patents, and their products were known all over the world.

Bayh–Dole and the Birth of Technology Transfer (1980)

Picking up from the momentum of the policies of Presidents John F. Kennedy and Richard Nixon in 1980, Senators Birch Bayh and Bob 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 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 nonprofits for the good of the public who funded the research through their tax dollars.

The ownership right that universities have to these inventions comes with obligations. Primarily, it is the obligation to actively market and attempt to commercialize the invention, preferably through US-based business enterprises including start-ups to benefit the public. Thus was born the field of "technology transfer" and the mushrooming of technology-transfer offices (TTOs). Prior to Bayh–Dole, 28,000 patents were owned by the US government, less than 5% of which were commercialized. It has been reported that since the enactment of Bayh–Dole, 5000 new companies have been created, resulting in billions of dollars of direct economic impact within the United States and close to 600 products put in the market during these 40 years—all based upon university research.

Because a substantial portion of the inventions that arise from basic research programs are supported by research that is federally funded, there are also substantial legal obligations incurred by universities and AMOs to promote commercial development of such new inventions. Similarly, in the 1980s, federal intramural laboratories 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 to ensure that new technologies developed in federal laboratories were similarly transferred to the private sector and commercialized.

Commercialization of inventions from nonprofit basic research institutions typically follows a multistep process as academic and federal laboratories typically do not provide technology commercialization themselves. The inventions made by these researchers are converted into products and processes by for-profit companies. In the case of AMCs the clinical products often return to these AMCs for clinical collaborations including clinical trials. Thus these AMCs contribute twice at the very beginning, at the birth of the invention and at the end toward approval by regulatory authorities. For example, U Mass Medical School and several other academic medical centers conduct compassionate use clinical trials for the discoveries arising from their own biomedical research. The TTOs act as key liaisons to link these important connections between the academic/government, clinical, and the commercial world. In some cases, these inventions, protected through intellectual property (IP), are "transferred" to the company for product development via license agreements that give the company the rights to make the products or use these processes. In other cases, as a prelude to the license agreement or concomitant with it, a collaboration agreement or a sponsored research agreement (SRA) is negotiated by the TTO that allows a period wherein the research institution and company researchers jointly work on the invention prior to its complete transfer to the company. In exchange, financial consideration or other benefits are received by the research institution through what is often an agreement with a small company, which may bring in a large corporate partner during a later stage of development. This process has been likened to a relay race where there may be several baton transfers.

Since the 1980s, federal labs and universities have developed a strategic focus for their technology-transfer activities and they are particularly interested in working with bioentrepreneurs. This is because revenue enhancement from licensing is no longer the sole institutional goal. Instead, institutions find themselves also looking to increase company formation and new jobs based upon academic inventiveness, support faculty recruitment and retention, enhance research funding, create an entrepreneurial culture, attract venture investment to their regions, and the like. The economic development aspects of research are being recognized as a "fourth mission" for such institutions—going along with education, research, and public service. Bioentrepreneurs play a key role in this "fourth mission" by establishing companies driven by new research discoveries.

Accessing Academic Technologies and Collaborations

Generally, bioentrepreneurs can directly access research and inventions for product development from three main sources as shown in Table 15.1. For research funded by grants and contracts from NIH or other federal agencies (extramural research), the individual university or small business would control commercial rights, with only standard reporting and utilization obligations to the federal funding agency. Biomedical research conducted by the federal laboratory (intramural research program) is licensed directly through the TTO at the federal lab.

According to a 2016 annual survey from the Association of University Technology Managers (AUTM) [3], this incentivized approach, which dates from the Bayh–Dole Act, has contributed to the annual formation of more than two new products, and nearly three new companies each day through university technology transfer. Table 15.2 provides trends from the 2016 annual survey and underscores the volume of licensing activity that goes on in the United States from reporting universities and AMCs.

Each of these institutions has a robust research program "pipeline" that provides novel, fundamental research

TABLE 15.1 Federally funded technologies can be licensed from several sources.

- Federal lab research (from lab technology transfer office)
- University grantee research (from specific university technology transfer offices)
- SBIR and STTR small business programs (from small business awardees)

SBIR, Small Business Innovation Research; *STTR,* Small Business Technology Transfer Research.

TABLE 15.2 Volume of license activity at universities and academic medical organizations.

2017 AUTM survey figures	
Exclusive license agreements	2037
License option agreements	1566
Nonexclusive license agreements	4195
Active license agreements	45,657
New products launched	755
Licensing income	$3.14B

AUTM, Association of University Technology Managers.

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. In addition, overall product sales of all types by NIH licensees now exceed $6 billion annually. As mentioned previously, most technology transfer activities at NIH and other federal laboratories date from the Federal Technology Transfer Act of 1986 which authorized formal research partnerships with industry and provided incentives to these programs to license technology by allowing the federal laboratory to, for the first time, keep its license royalties and share them between the individual inventors and their laboratories or institutes.

Research collaborations or research assistance with research institutions can take several forms as these researchers and clinicians can work with industry under different collaborative modalities. For example, research institutions may need to access technologies developed by industry—an imaging tool, a sequencing platform, or a drug discovered and in development by a company. The TTO then works with companies and clinical partners to memorialize the understanding between the scientists and/or clinicians to allow the collaborations to happen. Of course, as with all arrangements, each party desires to obtain terms that they feel are the most equitable for the party they represent. The key components of a collaboration agreement that are often the subject of most negotiations are terms related to inventions, rights to inventions, confidentiality versus publication, managing conflicts of interest, and, finally, indemnification. Indemnification (having one party to bear the monetary costs, either directly or by reimbursement, for losses incurred by a second party) is very important to research institutions when working with new biotech technologies that will be used in patient care.

Academic–Industry Collaborative Research Agreements

There are several types of research or collaboration-related agreements that biotech companies will commonly encounter in working with universities and federal laboratories:

Confidential Disclosure/Nondisclosure Agreements

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 will negotiate a confidential disclosure agreement (CDA)/nondisclosure agreement that ensures the information disclosed is held confidential, is 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 the terms of the agreement.

Material Transfer Agreement, Sponsored Research Agreement, and Cooperative Research and Development Agreement

Companies, both small and large, have invested a lot of R&D dollars toward developing drugs or other biotech products. Research institutions have several programs that are geared toward understanding the fundamental biology underlying a wide variety of commercial products. When these two entities want to collaborate, they have very different things at stake. For the company, they are hoping to learn more about their product concept, get mechanistic insights they can exploit to position their product better in the marketplace, and have discoveries come out of this collaboration related to their product, which may extend the patent life of their eventual product. In the case of collaborations with AMCs, companies would like access to patient samples in addition to the valuable clinical insights they hope would guide them through the process of clinical validation of their product whether it be a drug, medical device, or diagnostic. For the academic and clinical investigator, they would like to test various drugs from various companies to build a scientific story or medical knowledge that they can publish. Even more importantly, with the dwindling of federal funds for academic research, their activities can be supported through cash from the company.

Material Transfer Agreements (MTAs) and Sponsored Research Agreements (SRAs) dictate the terms of transfer of material and money respectively, from company to the academic institution. Similarly, at federal labs, research projects for basic research or clinical studies are called cooperative research and development agreements (CRADAs). Due to their clinical hospitals and centers as well as other networks and facilities, the NIH and at least some universities can take some of their medical discoveries (or those of their partners) into clinical trials through clinical trial agreements (CTAs).

Key Elements of Collaborative Agreements

Provided in the following are key elements that are at the heart of the negotiation of these agreements:

1. ***Inventions***—The definition of "invention" is crucial. Academic centers will typically require that any inventions can be both conceived *and* reduced to

practice during the term of the collaborative research using the company material and/or money. Companies want it to be conceived "or" reduced to practice. The problem for the TTOs with agreeing to "or" is simply that academic researchers collaborate with lots of companies, often at the same time on similar broad programs but with different individualized projects. If institutions agree to the "or" language, it creates several issues: (1) it is nearly impossible for the TTOs to police when the conception of the invention happened and when it was reduced to practice and (2) the institution may end up with conflicting arrangements with companies. Federal laboratories (by statute) use the language "conceived or *actually* reduced to practiced" in their agreements. Practically speaking, TTOs may only hear of inventions when the researchers decide to disclose them as investigators at research institutions are not under as tight control as their counterparts in industry.

2. ***Ownership of inventions***—Companies may want academic researchers to assign their inventions to the companies. This is a hard one for academic TTOs to accept since in the instance of an MTA, there will likely be funding from the federal government, and under the terms of the grant, such assignments are prohibited without specific permission from the funding agency. Even under the terms of an SRA where the company is providing money in addition to providing the material, given the large amount of federal dollars that most academic institutions receive with the lab resources and several personnel being funded by the government, universities are unable to agree to the assignment of inventions to companies as it would again be in violation of the terms of the grant from the federal agency. Instead, typically the company will be granted the desired license options by the research institution to new discoveries during the collaborative or sponsored research program.
3. ***Rights to inventions***—Freedom to operate (FTO) rights are very important to a company. They have invested a lot of money into their drug discovery or device-development programs. Biotech companies do not want the academic research collaborator to make important inventions that are somehow related to their drug or device in development and then not have the needed rights to the inventions that they helped with their material and money to discover. There is often no right or wrong answer to this question and it can be subject to negotiation depending on what each party feels is equitable for the specific collaboration and can vary from a royalty-bearing to a nonexclusive royalty-free license or option to a license.
4. ***Confidentiality and publication***—An important aspect of the academic mission and spirit is to publish and disseminate the results of research widely to the public. This is typically at odds with the company's best interest which may need to keep things under cover until they are very sure and ready to disclose especially to their competitors. A typical compromise is for the publication/public disclosure to be provided to the company ahead of time and for the company to remove its confidential information while still providing for a meaningful publication in the journal of choice by the investigators. For example, if the journal required publication of the structure of the compound to make it meaningful, then if that were not already in the public domain through publication (journal or patent) of the company, then that constraint should be discussed at the time of the negotiation of the contract.

Technology Transfer Office Set-Up and Licensing from Universities and Federal Laboratories

Technology Transfer Office Operations

Fig. 15.1 provides an overview of the core operational elements and activities of TTOs at research institutions. There are several key areas of importance to the industry. In addition, several TTOs house an internal venture group or work with some outside venture funds for commercialization of their technologies in the form of a new company/start-up. The internal funds often serve several functions including educating the investigator/inventor as they work with outside venture capital (VC), bringing together several outside ventures, given their connections and expertise and work with the licensing staff within the TTO to help get the start-up off the ground.

Inventions and Intellectual Property Strategy

Inventions made by the research center's investigators are the currency that drives the licensing operations of a TTO. As summarized later in Fig. 15.2, the TTO personnel has the huge responsibility of reaching out to their research community to educate them about the process, evaluate and access patentability of inventions, devise simple to complex IP strategies for the inventions, and finally to work with attorneys to protect these inventions.

Disclosure of Inventions

When research findings are disclosed to the TTO, it typically goes through a triage process that involves accessing/scoring its scientific strength, its patentability in light of prior art, including the investigators' own prior public disclosures, its market potential, and commercial path. The TTO will also look for the investigators' availability

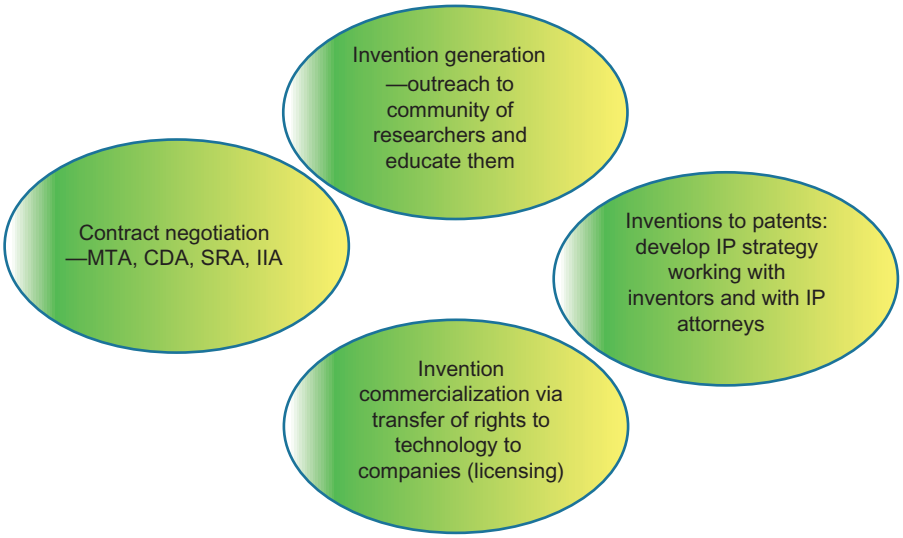

FIGURE 15.1 Core elements of a tech transfer office.

of resources including funding as well as their commitment to work with the TTO to move the invention through the next steps of validation that would add to its commercial value.

Some key challenges that TTOs face are (1) lack of control of the overall disclosure process since disclosure of inventions is purely voluntary—furthermore, investigators differ widely in what they would consider to be valuable inventions; (2) investigators do not sign documents assigning their inventions to their employer at the time of employment, rather they are obligated to do so under the institution's IP policies; and (3) investigators vary widely in their aptitude to work with the TTO to commercialize their inventions and get it into the marketplace. At UMMS, innovative initiatives are underway to address these challenges. The goal is to increase collaboration with investigators, throughput in processing disclosures, and the workflow overall.

Marketing of Inventions and Business Strategies

For companies looking to work with a TTO, there are both push (when the TTO reaches out to companies to license/partner the technologies) and pull (when companies contact the TTOs) marketing. Companies contact TTOs typically following a public presentation—a publication that's either in a journal or a patent. For companies seeking a license from a TTO the following outlines a good approach: (1) identify the university's technology that is of interest; (2) provide a path for diligent development of technology, if licensed, along with an estimated timeline; and (3) indicate if the technology will add to, replace an existing product, or be a new line of products for the company. Having this basic information available will accelerate the time to a term sheet and eventually a completed license.

Licensing Technologies—Working with the Technology Transfer Offices

From Universities and Academic Medical Centers

Once the academic and company feel there is a path forward to bring the technology into the company, then it proceeds to a license. Oftentimes, the company is not sure and needs to bring the technology in under an evaluation license to ensure that the technology works before they can commit to a license. This is accomplished via an option agreement that would (1) obligate the academic to hold the rights to the technology for a certain period of time within which it will execute a license to the company and (2) grant the company rights to test/evaluate the technology. These agreements are accompanied by nominal fee arrangements, oftentimes to cover patent costs previously incurred and/or that would be incurred during the option period. Once the parties are engaged in negotiations, it is typical to start with a term sheet. It is good to get all the deal breakers addressed in the term sheet and get a verbal understanding of the key terms before committing to paper. For universities and AMCs, a typical concern is companies not committing to diligent development of technologies they license. This would be an issue that is best addressed early on in the negotiation. A combination of an exchange of a written draft agreement and periodic verbal communication will ensure that things are proceeding on track.

Time periods to complete these transactions can vary widely. Option agreements typically take a few days to a month. Agreements for nonexclusive license to technologies take on average about 2–6 months to finalize.

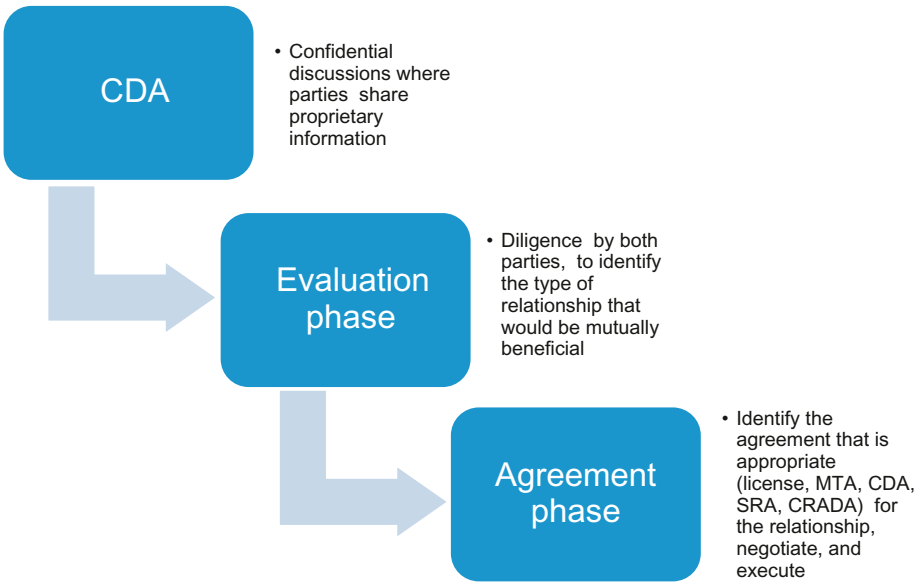

FIGURE 15.2 Fundamental steps leading to agreements with research institutions.

For exclusive license agreements the period varies quite widely. If there are two committed parties that want to get a deal done, it can be as quick as 3–4 months. An average deal would probably take 6–9 months to complete. In all instances of licenses, TTOs always prefer to start from their template. Given that companies' license agreements are designed for company-to-company transactions, it is very cumbersome and time-consuming for the academic licensing professional to adapt the company template to fit the academic's needs. If the institution has previously licensed the technology either nonexclusively or exclusively in another field, there would be a constraint to using terms they have agreed to with the other parties on the same technology. Moreover, if that company and the academic have a prior license agreement, the quickest way to a deal would be to start with that as a template for at least the nontechnology-specific terms.

From the National Institutes of Health

As is the case with universities, the NIH is not able to commercialize its discoveries even with its considerable size and resources—it relies instead upon partners. Commercializing technologies, such as vaccines or drugs and then marketing them successfully in a worldwide market, thus cannot be the responsibility or mission of research institutions or government agencies. Companies with access to the needed expertise and money are needed to undertake continued development of these inventions from the NIH or other research institutions into final products. Typically, a royalty-bearing exclusive 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 or vaccine product concept to the market. Exclusivity is almost always the norm for the US Food and Drug Administration (FDA)-regulated products due to the risk involved in time, money, and regulatory pathways to companies and their investors. Financial terms of the license agreement are negotiable but do reflect the nascent, high-risk nature of the discovery. Because the technologies coming from NIH or NIH-funded research are most typically preclinical inventions, most licensees are early-stage companies or start-ups rather than larger firms that typically want more proven ideas for new products. 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 on the product technology. When the licensee can sufficiently "de-risk" the technology through its various efforts, these companies then sublicense, partner, or get acquired by larger biotech or pharmaceutical firms for the final, most expensive stages of development with the large company expected to sell the product once it reaches the market.

Since the 1980s, federally funded health research institutions, such as the NIH and AMCs, have 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 in the health-care area which are 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, attracting venture investment and development to their specific region (universities) or to the health sector in general (NIH).

Start-Ups and Other Licensing Vehicles for Technology Transfer

The licensing practices for most nonprofit research institutions including federal institutions and universities have changed significantly over recent years with respect to biomedical inventions [4]. With its ever-increasing consolidation, large pharmaceutical firms are typically no longer looking to directly license early-stage technologies for commercialization, whereas the number of licenses signed with start-ups as well as small-to-medium-sized biotechnology companies is on the rise. Indeed, typically around 70% of the total license executed by universities and AMCs are to start-ups and small biotech firms. Unlike 15−20 years ago, when all or most of the high-revenue medical products based on licenses from university or federal laboratory research came from direct agreements with large pharmaceutical firms, most of the latest 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), and Taxus Express (a paclitaxel drug-eluting coronary stent used to prevent restenosis from Angiotech). Although these firms or their successors are all substantive, well-known companies now, at the time the underlying technology was licensed to them, they were not large corporations. The UMMS is unique in its structure in that it includes not only the medical school and the powerful biomedical research powerhouse but also Mass Biologics, the world's only Good Manufacturing Practices (GMP) biologics manufacturing facility operated by a nonprofit, and Commonwealth of Medicine, a unique health-care consulting operation. Further, UMMS has 40 + cores and a voucher program that allows start-ups to use these facilities at a steep discount. Companies with 1−10 employees get a 75% discount and companies with 10−50 employees get a 50% discount.

Many products developed at UMMS are already creating impact. Rabishield (Rabies vaccine, approved for sale in India) and Zinplava (*Clostridium difficile* infections, Ph 2) are monoclonal antibodies developed at Massbiologics and licensed to Serum Institute of India and Merck, respectively. Spinraza that treats spinal muscular atrophy was discovered at UMMS. It was partnered with Biogen that launched the product in 2017. Other recent products impacting patients include gene therapy technology to treat Canavan's disease—one patient was successfully treated. Technology was basis of the UMMS start-up Aspa Therapeutics (2018). Also, Onpattro—the first siRNA therapeutic launched by Alnylam in 2018—includes vital technology from UMMS.

Many models of licensing are used with a goal to get technology in the hands of commercial entities so there can be an impact on patients. In certain instances, licensing offices prefer licenses to a start-up company because unlike big companies, start-ups are motivated to rigorously work on their founding technology to raise funds from VC and are unlikely to "shelve" technology. Most of the time, this option is viewed more favorably to licensing the technology to a very large company where several similar technologies would typically be developed concomitantly. The risk is that the university or federal research institution's technology may get scuttled due to business factors or viewed as being of a high-risk nature. The biggest challenge of licensing the technology to a start-up company, however, is "cash uncertainty," that is, whether the start-up company will be able to secure future capital to develop the technology in a timely fashion. It is, therefore, important that bioentrepreneurs do the right thing in the right way at the right time to keep a strong relationship with the federal lab or university/AMC and its venture fund group as described in later sections of this chapter. One vehicle for bioentrepreneurs to engage with universities/AMCs is to work with them as an entrepreneur-in-residence that allows them to do prediligence on the technology working closing with the academic innovators and bringing in a business perspective that kick-starts the eventual start-up.

Basic Licensing Principles of University and Federal Laboratories

Compared to biomedical licensing from corporations, the federal laboratories and universities bring a different focus and perspective to the table when negotiating its technology transfer agreements. Because these agreements are used to further overall institutional missions, representatives from such nonprofit institutions consider the public consequences of such licenses as their first priority, not the financial terms that may be involved.

For example, federally funded nonprofit institutions, compared with their peers in the industry, 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, where 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 federal laboratories). In their agreements, federal 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 intramural program, universities, or companies. Because the commercial rights granted represent institutional (and often 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.

Fig. 15.2 illustrates the fundamental steps that lead up to a license or other types of agreements with research institutions. In a license agreement the academic 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 academic center owns and/or controls. In some instances the academic center also grants the company rights to use technological information/know-how or materials that go 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 university TTO and is the core of its set-up, post-Bayh–Dole. However, both academic centers and federal labs function as nonprofits and do not and cannot have a product commercialization arm and so cannot themselves convert inventions into commercial products and processes. They must partner with industry to do that. Hence these out-licensing activities are the key to fulfilling the core of Bayh–Dole and other federal mandates of commercializing inventions that arise from federal funding.

Characteristics of Typical Biotech License Agreements

Generally, it is considered good business practice in licensing from a research institution that the organization would standardize license terms to the extent possible. Standardizing nonfinancial license terms levels, the playing field for licensees (an important concept for public institutions), and creates a common understanding of the balance of risks acceptable to a research institution (which may differ markedly from the for-profit sector).

Royalty rate negotiations with these institutions are influenced by factors (Table 15.3) commonly encountered in other negotiations of early-stage biomedical technologies. Unique to federal laboratory and university negotiations are factors relating to the public health interest in the technology being licensed and the products to be developed from it (so-called white knight clauses). Examples of this may include supply back of materials for clinical use, indigent patient access programs in the United States, commercial benefit sharing for natural product source countries, or incentives for developing world access to the licensed products.

The royalty payments (Table 15.4) consist of license payments received for execution royalties, minimum annual royalties (MARs) (received regardless of the amount of product sales), earned royalties (a percentage of product sales), benchmark royalties, and payments for patent costs. To date the NIH has not sought equity payments in licenses or directly participated in company start-ups due to conflict of interest concerns. Instead, in lieu of equity, the NIH can consider equity-like benchmark royalties that track successful commercial events at the company. However, many universities do take equity payments in their license agreements to assist a

TABLE 15.3 Factors influencing royalty rate negotiations with research institutions.

- Stage of development
- Type of product
- Market readiness and value of product
- Uniqueness of biological materials
- Scope of patent coverage
- Research institution "Content"
- Public health significance

TABLE 15.4 Typical types of fees and royalties in licenses agreements with research institutions.

- Execution fees
- Minimum annual royalty (regardless of the amount of net sales)
- Earned royalties (fixed percentage of net sales)
- Benchmark royalties
- Patent costs
- Sublicense fees (percentage of income)
- Equity (varies by institution)

new start-up company even though there is considerable risk in accepting equity in lieu of cash payments since such equity is illiquid and has no present value at the time license is executed.

Licensing institutions will often opt to take an equity or equity-like position when available from their licensees for several reasons. For example, equity would provide for additional revenue in addition to the licensing royalties, especially if the licensed product failed in development but the company itself later became successful. Equity also can be seen as a risk premium for the research institution that provides additional inducement to grant the license to a new start-up company verses a more-established firm. Importantly, and perhaps most important for bioentrepreneurs, equity allows a licensee who is cash poor but equity rich to substitute an ownership position for a cash payment (in full or in part) for an up-front licensing fee and/or a reduced royalty rate. Finally, research institutions accept this risk to support its mission to assist in commercialization of early-stage technologies, which may not be turned into marketable products otherwise and to encourage small business development. However, universities and AMCs recognize that holding ownership rights in a start-up company creates a potential conflict of interest and adopts various internal policies that mitigate and/or manage such conflicts.

Unlike their corporate counterparts, inventors at nonprofit research institutions do receive a share of the royalties generated from the licensing of their inventions. However, each institution might have a slightly different revenue-sharing policy with respect to the percent of licensing revenues that are shared with inventors. Next, we discuss what might be some of the typical license agreements that a bioentrepreneur would come across in dealing with a nonprofit research institution.

Types of License Agreements

Universities and federal research institutions negotiate a variety of different types of license agreements for use and development of biomedical technologies. Besides offering exclusive and nonexclusive commercialization agreements for patented technologies, commercialization agreements are negotiated for unpatented biological materials. Being increasingly more selective as to what type of technologies they seek to patent, both types of institutions are unlikely to patent research materials or research methodologies that can be easily transferred for commercial use by biological material license agreements or publication. For patent rights or materials that are not to be sold as commercial products but are useful in internal R&D programs, both federal research institutions and universities would typically negotiate nonexclusive internal use license agreements. In addition, companies may obtain evaluation agreements to new technologies as well as specialized agreements relating to interference or other patent dispute settlements. Finally, for bioentrepreneurs interested in a technology that was jointly invented by two or more institutions, an interinstitutional patent/licensing management agreement would be negotiated so that the bioentrepreneur would be able to obtain an exclusive license by only dealing with one party.

TABLE 15.5 Major types of licenses agreements involving research institutions.

- Commercial evaluation/Option license agreement
- Internal commercial use license agreement
- Research products commercialization license agreement
- Vaccine, diagnostic, therapeutic, or medical device product commercialization license agreement. Increasingly, there are evolving models of agreements for access to data and health apps developed by universities and academic medical centers.
- Interinstitutional agreements (for joint inventions)

Typically, federal research institutions and many universities have the types of license agreements shown in Table 15.5 and described in the following [5]:

1. ***Commercial evaluation/option license agreements*** are short-term nonexclusive license agreements to allow a licensee to conduct feasibility testing but not the sale of products developed from a technology. These typically run no longer than a few months, have a modest cost associated with them, and include relevant materials that are supplied by inventor(s). Screening use is not permitted but the agreement has proven to be ideal for feasibility testing of new technologies that have a wide variety of possible useful (but unproven) applications. "Screening use" implies use of the licensed material in the discovery or development of a different final end product. For example, a reporter cell that expresses an oncogene can be tested to screen drug candidates that could potentially be effective in certain cancer therapeutics. Some universities may also use this type of agreement in the form of a short-term exclusive option agreement for a nascent technology with the hope that a long-term diagnostic, vaccine, or therapeutic product commercialization license agreement will later be completed.
2. ***Internal commercial-use license agreements*** are another nonexclusive license arrangement that allows a licensee to use (but not sell) technology in its internal programs. Here materials (either patented or unpatented) are provided, and screening uses are permitted. The financial structure of this agreement can be either

a "paid-up" term license or annual royalty payments each, however, without any "reach-through" royalty obligations to other products being used or discovered by the licensee. A "paid-up term" license would be a license in which the company makes a one-time lump sum payment to obtain the rights to use the licensed technology for the duration of the license. On the other hand, "reach through" royalty provisions in a license agreement create royalties to the licensor on the future sales of downstream products that are discovered or developed using the licensed technology, even though the final end product may not contain the licensed technology. In other words, reach-through royalties are royalties that are due to a licensor even though manufacture, use, or the sale of the final product does not infringe any patents claiming the licensed technology. Internal commercial-use agreements themselves historically have been very popular with medium-to-larger biomedical firms who are eager to acquire reagents to speed their internal development programs. Popular technologies licensed in this manner include animal models and receptors.

3. ***Research products commercialization license agreements*** are another nonexclusive license agreement but allow a licensee to sell products to the research products market. Here materials (either patented or unpatented) are also generally provided with smaller firms predominating as licensees. For federal laboratories, US manufacturing is required even for nonexclusive product sales in the United States unless a waiver is granted. Waivers are granted based on a lack of manufacturing capacity in the United States or economic hardship for the licensee. The financial structure of these licenses generally involves low up-front royalties but relatively high earned-royalty payments since the materials provided are frequently close or very close to the finished product that is to be sold. Popular research products licensed in this manner include a wide variety of monoclonal or polyclonal antibodies or other research materials used in basic research.
4. ***Vaccine, diagnostic, therapeutic, or medical device product commercialization license agreements*** are agreements that can be exclusive if such is necessary for product development due to the capital and risk involved for the licensee. Important for bioentrepreneurs is the fact that by law, small, capable biomedical firms receive preference from federal laboratories and federally funded universities as exclusive licensees. At NIH and other federal laboratories, all prospective grants of exclusive licenses (identifying the licensee and technology by name) are published in the *Federal Register* for public comment or objections for a minimum period of 15 days. A detailed development plan with product benchmarks or milestones is expected for licenses in this area. Collaborative research with federal laboratories regarding further preclinical or clinical development of the technology is encouraged but not required to obtain a license and is negotiated separately by the individual laboratory program. These agreements also have a requirement for US manufacturing for US product sales unless a waiver is granted. The federal laboratory can typically grant waivers only when US manufacturing sites are unavailable or manufacturing in the United States is economically infeasible. The financial structure of these licenses can involve substantial up-front royalties, but much more moderate-earned royalties (since the technology is typically not close to a finished product) and appropriate benchmark payments. Other provisions to be negotiated include a share amount of sublicensing proceeds, any of the public health "white knight" provisions described earlier, as well as licensee performance monitoring and audit requirements.
5. ***Interinstitutional agreements (IIAs) or joint invention agreements (JIAs)***. Many commercializable technologies will often have inventors from more than one university or federal laboratory due to the collaborative nature of science. The institutes will often execute an IIA or JIA so one entity takes the lead in working with the external partner. This mitigates risk for investors, since, especially for US patent rights, all owners have the ability to license separately. In addition to mitigating risk, IIAs or JIAs help bioentrepreneurs since they would have to negotiate with only one research institution to secure an exclusive license to the technology.
6. ***License agreements with non-US firms*** are an increasingly common occurrence from NIH and universities due to the global nature of healthcare markets and the growing biotechnology sector in a number of areas of the world. While for US federally funded inventions there is a preference for US firms, this would typically be applied only in instances of exclusive license agreements—meaning that nonexclusive agreements such as those for research materials and tools would be available to all firms. In addition, some medical technologies only have patient populations and markets outside the United States, so license agreements for these types of inventions are often most appropriate for non-US firms. This is because the US manufacturing requirement required (unless a waiver is granted) in federally funded technologies applies to only products to be sold in the United States. Products to be sold outside the United States can be thus manufactured anywhere. Special circumstances can allow for a waiver of the US

manufacturing requirement, such as documented lack of manufacturing capacity for the product within the United States or the risk of an economic hardship for a licensee of replicating an existing FDA-approved manufacturing facility outside the United States within the United States solely to make the new product in question.

Universities and AMCs have had to adapt to increasingly global nature of the biotech world. Many international companies and investors, particularly from China, are interested in working with US universities and AMCs.

Components of a Biotechnology License Agreement

1. ***Breadth of rights***—This depends on the technology that is being licensed and the size and need of the company. If the patent rights/technology is specific to a certain company's drug, for example, something that arose from a SRA (described earlier in this chapter), then it would be typical to give the company exclusive license rights to all fields available within the patent rights. For platform technologies that have broad uses in very different medical applications—for example, micro-fluidic IP—field specific but still exclusive licenses would be appropriate.
   a. For diagnostic technologies, the trend is to grant nonexclusive rights to the technology, but with an eye toward incentivizing the companies to invest into developing the technology. For research-tool technologies, it is typical to grant nonexclusive access to use the technologies in their internal research, for example, in their drug discovery, programs.
   b. There is another dimension to consider in addition in the case of start-ups—for the fledgling company to attract investment, a broader field of use is appropriate. But if it is a small company, a recent start-up from another university perhaps and a second university's technology is offering a solution to a specific problem, then only narrow rights to the company from the second university would be appropriate.
2. ***Signing fees and patent costs***—Having invested in the technology through IP protection, the academic institution would typically reimburse themselves for the patent costs incurred to date. A license is their exit, and the minimum terms of this exit is to recoup patent costs, and further, a modest signing fee is appropriate at the time of signing of a license.
3. ***Sublicense fees***—The statistics are that most technologies are not developed by the first licensee of the technology but by the company's further licensee (the "sublicensee"). Typically, this sublicense happens when the original company licensee has developed and validated the technology further. Depending on the situation, a fixed percentage or a sliding scale of percentage sublicense income back to the original licensor is considered equitable.
4. ***MARs/Milestone fees***—A certain percentage of royalty on net sales of the product comes back to the licensor (academic institution). To ensure diligent development, having a set annual payment is customary. Sometimes this is termed "annual maintenance fee" that is credited against royalty upon product launch. The diligent development of the product, covered next, is a key element to the contract. Payments to the academic institution upon reaching key milestones in the path to the product are customary.
5. ***Diligent development of the licensed technology***—For technologies that are funded in whole or in part with federal funding, this is an absolute requirement. Companies are required to give the TTOs their product development plan along with the expected timelines. The consequence of not meeting these diligence goals is termination. A key item to remember is that research institutions have the flexibility to work with licensees and can accommodate changing needs. The key is to have a mechanism of communication and cooperation between both parties. If the company is really "shelving" the technology, the university or federal lab needs to be able to get it back to seek and find another licensing partner to commercialize these technologies.
6. ***Reserved rights***—As per Bayh−Dole for government-funded technologies, academic centers are required to reserve rights for their continued use of the technology for further academic research. Typically, the academic center reserves rights not only for its own use but also for the research use of other academic centers. For hospitals, this would include clinical research use as well, since patient care is part of the institutional mission. The reason for this clause is for licensees not to block anyone from continuing research on the technology that could benefit the public given that it was funded by the tax dollars from the public in the first place. For government labs, the reserved right is for any governmental purpose and is required by statue.
7. ***Enforcement***—Patent rights are enforced by the owner or in cooperation from the owner. An "infringer" of the technology is hurting the market share of our licensee. As the patent owner, universities and federal labs are affected since the patent licensees are affected. Typically, exclusive licensees seek to get first rights to go after infringers but the actions by licensees might drag the TTOs into lawsuits and potential invalidation of the patent claims. Academic

centers do not have the appetite (or the money) for lawsuits. A common approach is, therefore, to have the first right to pursue infringers when informed by our companies to encourage them to take a license from our licensees. Failing this, it is typical to have licensees pursue infringers.

8. ***Indemnification and insurance***—AMCs have to protect themselves from lawsuits that may arise from patients who may be injured by the products that companies make, market, and sell. When sponsored research is performed and broad access is given to all results that arise from the collaborations, judicious use of the results in the drug-development process is the company's responsibility and the terms of the agreement in this section are designed to protect the TTOs. Thus, in their agreements, companies are required to provide evidence that they have the necessary backing via insurance protection. This is a requirement from institutional insurance carriers and therefore this term is typically nonnegotiable from the TTO's side.
9. ***Conflicts of interest***—This is a very significant and real issue particularly for teaching hospitals, AMCs, and federal laboratories that are doing both clinical and basic research. Conflicts are managed by ensuring that at the time of the licensing of inventions to a company related to a certain drug, the medical center does not have any sponsored research collaboration on the same drug with the same investigator whose invention(s)/technology was licensed. Moreover, the investigator cannot consult for the company whose drugs are in clinical trials under his or her guidance. Additional conflict of interest rules apply to federal scientists. The conflict of interest policies of research institutions are typically available on their public websites.

Financial terms for nonexclusive license grants including license grants to research-tool technologies can vary widely. These licenses would not have all the elaborate terms described earlier but rather would have a fixed annual fee-type structure or even have a one-time "fully paid-up" financial structure. Table 15.6 gives some ranges of financial terms for exclusive licenses. Note that while these terms are typical ranges, when an AMC has a clinical candidate that is being licensed, as in the case of gene therapy with Adeno-associated virus (AAV) vectors being the clinical candidates, the up-fronts can be in the millions.

Advantages for a Biotech Start-Up to Work with the National Institutes of Health and Universities

Why Start-Ups Should Work with National Institutes of Health and Universities

National Institutes of Health's New Low-Cost Start-Up License Agreements

To better facilitate this "fourth mission" of economic development in conjunction with increased development of new therapeutic products, the NIH has developed a new short-term Start-Up Exclusive Evaluation License Agreement (Start-up EELA) and a Start-Up Exclusive Commercial License Agreement (Start-up ECLA) to facilitate licensing of intramural NIH and FDA inventions to early-stage companies. Similar "express" or "start-up" agreements are available at many universities as well. The NIH start-up licenses are generally provided to assist those companies that are less than 5 years old, have less than $5 million in capital raised, and have fewer than 50 employees, which can obtain an exclusive license from the NIH for a biomedical invention of interest arising from the NIH. NIH start-up licenses are offered to those companies developing drugs, vaccines, therapeutics, and certain devices from NIH patented or patent-pending technologies that NIH determines will require significant investment to develop, such as those undergoing clinical

TABLE 15.6 Common ranges of financial terms for exclusive license agreements.

Term	Diagnostic	Therapeutic
License signing fee[a]	$25–$50k	$50–$200k
Sublicense fees[b]	10%–40%	10%–40%
Annual fees or annual minimum royalties	$10–$50k	$10–$100k
Earned royalties[c] (percentage of net sales)	2–15	2–6
Total milestone payments	$1–$3m	$1–$7m

[a] *Start-up or express agreements may have substantial milestone, liquidity, or equity payments in lieu of early fees.*
[b] *Higher percentage in payments maybe appropriate if the company intends to monetize the technology through further licensing rather than through product development.*
[c] *Stacking of royalties to allow company to further in-license other technologies for the development of product is typical. With stacking/offsets the lower end of the range may be applicable.*

trials to achieve FDA approval or Class III diagnostics. The new company must license at least one NIH-owned US patent and commit to developing a product or service for the US market. The licensee may also obtain in the license related NIH-owned patents filed in other countries if the company agrees to commercialize products in those countries as well.

Financial terms for the start-up licenses are designed with the fiscal realities of small firms in mind and feature either a 1-year exclusive evaluation license with a flat $2000 execution fee (this license can be later transitioned to become an exclusive commercialization license) or an immediate exclusive commercialization license. The Start-Up Exclusive Commercial License includes the following:

- A delayed tiered up-front execution royalty, which would be due to the NIH upon a liquidity event such as an initial public offering (IPO), a merger, a sublicense, an assignment, acquisition by another firm, or a first commercial sale.
- A delayed MAR or a MAR that is waived if there is a CRADA with the NIH (or FDA) concerning the development of the licensed technology and providing value comparable to the MAR. In addition, the MAR will be waived for up to 5 years during the term of a Small Business Innovation Research (SBIR) or Small Business Technology Transfer Research (STTR) grant for the development of the licensed technology.
- An initial lower reimbursement rate of patent expenses that increases over time to full reimbursement of expenses tied to the earliest of a liquidity event, an IPO, the grant of a sublicense, a first commercial sale, or upon the third anniversary of the effective date of the agreement.
- Consideration by the NIH of all requests from a start-up company to file new or continuing patent applications if the company is actively and timely reimbursing patent-prosecution expenses.
- A set earned royalty rate of 1.5% on the sale of licensed products.
- A set sublicensing royalty rate of 15% of the other consideration received from the grant of a sublicense.
- An antistacking royalty payment license provision can be negotiated by a company if it encounters a stacking royalty problem. A stacking royalty problem could potentially occur when a licensee's third-party royalty obligations add up to such a high total royalty percentage such that the project becomes unattractive for investment, sublicensing, or self-development due to low profit margins. Royalty stacking can especially be a problem in the development of biologics due to the breadth of a possible third-party IP that may be needed compared with traditional small molecule drugs.
- Mutually agreed-upon specific benchmarks and performance milestones that do not require a royalty payment but rather ensure that the start-up licensee is taking concrete steps toward a practical application of the licensed product or process.
- NIH start-up commercial licenses represent a significant front-end savings in negotiation time and money for new companies. An exclusive license, for a new technology (even early-stage), might have expectations prior to negotiations (for a large-market indication) of an immediate execution fee of up to $250,000 or more, a MAR due in the first year and beyond of up to $25,000 or more, immediate payment of all past patent expenses and ongoing payments of future patent expenses, benchmark royalties in the range of up to $1 million or more, significant sublicensing consideration, and earned royalties in the range up to 5% or more depending on the technology.

Because many, if not most of the technologies developed at the NIH, are early-stage biomedical technologies, the time and development risks to develop a commercial product are high. Depending on the technology and the stage of formation of the potential licensee, the company may prefer to enter into the Start-up EELA to evaluate their interest before committing to a longer-term Start-up ECLA. Bioentrepreneurs can identify technologies of interest by searching licensing opportunities on the NIH Office of Technology Transfer (OTT) website [5], by email notification via Real Simple Syndication (RSS) feed and by getting in touch with the listed licensing contact. Usage of the start-up agreements varies by institute TTOs at NIH, including a new "Start-Up 2.0" Agreement version at the National Cancer Institute (NCI). Details for the start-up licenses and other information on the licensing process are published on the OTT "Start-up Webpage" and the NCI "Start-up 2.0 Webpage" [6].

Unique Features of Biotech Start-Up Licenses

While start-ups can be seen to have the potential to produce significant opportunities for the inventors, investors, the research institution, and regional economies, such projects involve more work and are riskier than a traditional license to an existing, capitalized company. Although research conducted at federal laboratories and universities is not specifically designed to lead to a new company formation, such activities are a way for such institutions to support the economic development aspects of their licensing- and technology-transfer programs as previously described. Successful start-up companies and bioentrepreneurs are highly prized because of the direct benefits to the community, region, state, and country in terms of new employment and tax revenue. Because of this, some

research institutions have in-house business development professional dedicated to working with inventors as they consider start-up opportunities for their technology. However, many institutions handle this as part of the activities of the regular TTO staff. Several institutions have in-house incubators and bridge funds due to the "valley of death" in funding for academic technologies.

A typical practice for a research institution that is licensing to a start-up company is to first confirm that there is no other prior claim of rights from a commercial sponsor and to then execute a confidentiality agreement, a letter of intent or other indication of interest, which should be followed quickly thereafter with an option agreement to a future exclusive license. If the bioentrepreneur has substantial resources already in place it may be possible to grant the license directly in place of an option when it is merited. Whatever the nature of the agreement, it is generally expected that the negotiation be with an officer of the new venture (or their attorney) and not a university faculty member who may hope to be involved in the company. Agreements should also contain clear timelines to enforce the diligent development of the technology toward commercialization. Particularly critical are deadlines for raising predetermined levels of initial funding to establish and operate the venture. To avoid conflict of interest problems at the research institution, the new company should operate separately from the inventor's lab, with a local incubator or business park space being ideal. Most research institutions have policies around faculty inventors not holding fiduciary responsibility at the companies they help start. Generally, a federal laboratory inventor is not able to have an active role in the company without leaving federal employment. The share of equity held by a university in these circumstances can vary by the type of technology.

The actual share amount held by the research institution, or the equivalent value to be paid to it, is often not that critical as the overall goal for the university or federal laboratory to develop a robust local, regional, or national corporate research community that closely complements and interacts with ongoing research at the institution. It is also a way to support university or former federal faculty members who are themselves entrepreneurial and willing to commit their time and often their own money to bringing their inventions to the marketplace.

Advantages to Working with Universities and Federal Laboratories

Within these basic licensing structures, however, there are several advantages that bioentrepreneurs can utilize in their product development efforts since federal laboratories and universities offer favorable treatment to small businesses to create an attractive playing field for them to get into new areas of product development. For example, start-ups can utilize the expertise of the patent law firm hired by the institution to manage the patent prosecution of the licensed technology. This is particularly useful for small firms that may not yet have internal patent counsel or the resources to retain a top IP law firm.

Another useful example is that license agreements with federal laboratories and universities (in contrast with corporate license agreements) do not require bioentrepreneurs to cross-license existing rights they may own, give up any product marketing rights, nor forsake any downstream developmental rights. Also, research-tool licenses negotiated through the NIH and many universities carry no grant-backs or reach-through rights. For instance, when a research-tool technology is licensed to a company by the NIH, the licensee is not required to grant back any usage rights to the improvements that it may develop after the license agreement. Also, the licensee is not required to share with the NIH any future profits that may be made because of improvements to the original discovery. In other words, IP derived from new discoveries made with NIH-licensed tools will remain clear and unencumbered.

Another advantage for a bioentrepreneur to license a technology from a nonprofit institution is the flexibility in the financial terms. While the NIH and many research institutions have "Start-up" or "Express" template agreements with favorable terms already in place, these can typically be negotiated separately. For example, reimbursement of back patent expenses, which the licensee typically pays upon the signing of the license agreement, could be deferred for a certain period. Similarly, the license deal could be structured to be heavily back-end loaded and/or equity-based to allow the bioentrepreneur to apply its cash toward R&D. Unlike many research institutions that take equity in lieu of cash, federal institutions and some universities do not consider equity-based license deals but do take roughly equivalent equity-like benchmark payments. The resulting lack of equity dilution may become an important feature as the bioentrepreneur looks to raise capital through additional rounds of financing.

A bioentrepreneur could also take advantage of the capabilities and technical expertise residing in the licensor's laboratories by collaboration and/or sponsorship of the research needed to expedite the development of the technology. While sponsoring research at the inventor's laboratory may in some circumstances raise conflict of interest issues, many institutions are willing to put together a conflict management plan with the engaged parties in order to help the start-up to exploit all the resources offered by the licensor. Many research institutions would, however, execute an agreement separate from a license agreement to formalize, such an arrangement.

At a basic level, the success of a new biotechnology venture depends on six key ingredients: (1) technical expertise, (2) IP assets, (3) business expertise, (4) physical space, (5) human capital, and (6) money [7]. Institutional scientists or faculty entrepreneurs themselves can provide the needed technical expertise (especially if students or postdocs can be hired by the new venture) and the research institutions of course can license key patent rights to the company. But business expertise, space, and money are often more difficult to come by. Research institutions often try to help new firms bridge this gap by providing more than just IP licensing and technical expertise. This is because commercial partners, especially small, innovative ones, are essential to the role of federally funded research institutions in delivering novel health-care products to the market. There is now an attractive array of available options or opportunities for new biotech firms beyond just traditional licenses or start-up license agreements, and several of these options will be examined in more detail.

Research Collaboration Programs for Start-Ups

For some entrepreneurs, there is a misperception that NIH scientists (unlike their university counterparts) are not allowed to interact with private-sector firms due to the implementation of strict government ethics and conflict of interest rules. While it is true that NIH investigators, in general, cannot engage in outside consulting with biotechnology and pharmaceutical companies in their personal capacity, the fact is that technology transfer–related activities are actually among the "official duties," in which NIH scientists are encouraged to participate. These activities may include the reporting of new inventions from the laboratory and assisting technology-transfer staff with patenting, marketing, and licensing interactions with companies. NIH scientists can also officially collaborate with industry scientists through the use of various mechanisms, including more complex CRADAs and CTAs as well as simpler CDAs and MTAs.

In a CRADA research project, which could run for several years, NIH and company scientists can engage in mutually beneficial joint research, where each party provides unique resources, skills, and funding, and where either partner may not otherwise be able to solely provide all the resources needed for the successful completion of the project. In such an arrangement, the details of the research activity to be carried out and the scope of the license options granted to discoveries emanating from the joint research are clearly spelled out in advance. A CTA would typically involve the clinical testing of a private-sector company's small molecule compound or biologic drug. The company gains access to the clinical trial infrastructure and clinical expertise available at NIH; however, unlike what occurs with a CRADA, the company partner does not have any licensing rights to IP that is generated during the clinical research project. The NIH usually enters into these agreements only in cases where such trials would be difficult or impossible to run in other places. The NIH is particularly interested in clinical trials involving rare or orphan diseases that affect 200,000 or fewer patients per year in the United States. An MTA is a popular mechanism for exchanging proprietary research reagents and is used by scientists worldwide. NIH investigators actively use this mechanism to share reagents with scientists in other nonprofit organizations. Proprietary and/or unpublished information can be exchanged between NIH researchers and company personnel in advance of making a decision to enter into a formal CRADA or CTA via the use of a CDA.

Of the collaborative mechanisms described earlier, a CRADA is perhaps the most comprehensive and far-reaching agreement for federal laboratories. Such agreements can provide additional funds for an NIH lab while providing the collaborating company with preferential access to the NIH scientist's future discoveries and access to scientific and medical expertise during the research or clinical collaboration. A CRADA is not, however, intended to be a means for the NIH to provide funding for a new company; in fact, the NIH cannot supply any funding to its CRADA partners. The easiest way for an entrepreneur to access this expertise is to simply approach the agency officially either by contacting a scientist directly or by contacting the institute TTO and/or technology development coordinator [8].

If an early-stage company needs access to NIH materials for commercial purposes outside a formal collaboration, this usually would be done utilizing an Internal Commercial Use License Agreement rather than MTA. As noted before, these are nonexclusive license agreements to allow a licensee to use (but not sell) technology in its internal programs. Here, materials (either patented or unpatented) are provided, and drug screening uses are permitted. The financial structure of this agreement can be either a single payment, a paid-up term license, or annual royalty payments, though the second structure is more popular with start-up companies.

Funding Opportunities for Start-Ups—Small Business Innovation Research Programs

In addition to contracting opportunities, the NIH and other federal labs can provide private sector entities with nondilutive funding through the SBIR and STTR programs [9]. The NIH SBIR program is perhaps the most lucrative and stable funding source for new companies and unlike a small business loan, SBIR grant funds do not need to be repaid.

Other noteworthy advantages of SBIR programs for small companies include retention by the company of any IP rights from the research funding, receipt of early-stage funding that doesn't impact stock or shares in any way (e.g., no dilution of capital), national recognition for the firm, verification and visibility for the underlying technology, and the generation of a leveraging tool that can attract other funding from 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% (for FY 2017) 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% (for FY 2017). In FY 2017 NIH's combined SBIR and STTR grants totaled over $971 million.

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 R&D. The SBIR program funds early-stage R&D 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 Phases I and II (see description later).

Thus the SBIR and STTR programs differ in two major ways. First, under the SBIR program, the principal investigator must have his or her 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 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 public health through the commercialization of new technology, the SBIR and STTR grants present an excellent funding source for start-up and other small biotechnology companies. The NIH SBIR and STTR programs themselves are structured in three primary phases:

Phase I—The objective of Phase I is to establish the technical merit and feasibility of the proposed R&D efforts and to determine the quality of performance of the small business prior to providing further federal funding in Phase II. Phase I awards are normally $150,000, provided over a period of 6 months for SBIR and $150,000 over a period of 1 year for STTR. However, with proper justification, applicants may propose longer periods of time and greater amounts of funds necessary to establish the technical merit and feasibility of the proposed project.

Phase II—The objective of Phase II is to continue the R&D efforts initiated in Phase I. Only Phase I awardees are eligible for a Phase II award. Phase II awards are normally $1 million over 2 years for SBIR and $1 million over 2 years for STTR. However, with proper justification, applicants may propose longer periods of time and greater amounts of funds necessary for the completion of the project.

SBIR-Technology Transfer (SBIR-TT)—Under this program (SBIR-TT) undertaken at the NCI at the NIH and other NIH institutes, SBIR Phases I and II awards are given in conjunction with exclusive licenses to selected underlying background discoveries made by an intramural research laboratory at the institute.

SBIR Phase IIB Bridge—The NCI SBIR program has created the Phase IIB Bridge Award for previously funded NCI SBIR Phase II awardees to continue the next stage of R&D for projects in the areas of cancer therapeutics, imaging technologies, interventional devices, diagnostics, and prognostics. The objective of the NCI Phase IIB Bridge Award is to help address the funding gap that a company may encounter between the end of the Phase II award and the commercialization stage. For any single year of the project period, budgets up to $2 million total costs may be requested. However, the combined budget requested for the entire project period must not exceed $4 million total costs. To incentivize partnerships between awardees and third-party investors and/or strategic partners, a competitive preference and funding priority will be given to applicants that demonstrate the ability to secure substantial independent third-party investor funds (i.e., third-party funds that equal or exceed the requested NCI funds). This funding opportunity is open to current and recently expired SBIR Phase II projects.

Fast track—Fast-track incorporates a submission and review process in which both Phases I and II grant applications are submitted and reviewed together as one application. Because both phases undergo review at the same time, the NIH Fast-Track mechanism can reduce or eliminate the funding gap between phases.

Direct to Phase II—This recently reestablished program provides authorized NIH that may issue a Phase II awards to a small business concern that did not

receive a Phase I award for that research/R&D. This type of award is appropriate for technologies where the phase flexibility studies have already been completed.

Phase III—The objective of Phase III, where appropriate, is for the small business concern to pursue with non-SBIR/STTR funds the commercialization objectives resulting from the Phase I/II R&D activities.

In addition to receiving funding through the 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. These would include the following:

Niche Assessment Program—*For SBIR/STTR Phase I Awardees*—The Niche Assessment Program is designed to help small businesses "jump start" their commercialization efforts by providing market insight and data that can be used to help such companies strategically position their technology in the marketplace. The results of this program can help small businesses develop their commercialization plans for their Phase II application and be exposed to potential commercial partners.

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.

Commercialization Accelerator Program (CAP)—NIH CAP is a 9-month program open to SBIR/STTR Phase II awardees that is well regarded for its combination of deep domain expertise and access to industry connections, which have resulted in measurable gains and accomplishments by participating companies. Offered since 2004 to address the commercialization objectives of companies across the spectrum of experience and stage, 1000 + companies have participated in the CAP. The program enables participants to establish market and customer relevance, build commercial relationships, and focus on revenue opportunities available to them.

SBIR/STTR key points—Those who hope to receive an SBIR or STTR grant from the NIH must convince the NIH that the proposed research is unique, creates value for the public at large through advancements in knowledge and treatment of disease, and is relevant to the overall goals of the NIH. It is important to contact the program officials ahead of time within the component of the NIH from where funding is sought to determine whether the proposed research plan fits these criteria. For start-ups, generally SBIR applications are most successful when they include an entrepreneur-founder with experience in the field, a highly innovative technical solution to significant clinical needs, an end product with significant commercial potential, a technology in need of more feasibility data that the proposed research project would generate, and finally a project that, if successful, would have reduced risk and become more attractive for downstream investment. At the NIH, grant applications are currently reviewed three times a year (April 5, August 5, and December 5) and contract proposals the first week in November. Note that both programs are subject to periodic reauthorizations and changes by the US Congress.

New and Innovative Programs as We Move Toward "V2.0" of Technology Transfer

Basic and Clinical Research Assistance from the National Institutes of Health

Basic and clinical research assistance from the NIH institutes may also be available to companies through specialized services such as drug candidate compound screening and preclinical and clinical drug development and testing services, which are offered by several programs. These initiatives are particularly targeted toward developing and enhancing new clinical candidates in the disease or health area of focus at various NIH institutes. The largest and perhaps best-known programs of these types at the NIH are those that currently run in the 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 fact that approximately one half of the chemotherapeutic drugs currently used by oncologists for cancer treatments were in some form discovered and/or developed at NCI. The Developmental Therapeutics Program promotes all aspects of drug discovery and development before testing in humans (preclinical development) and is a 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, also a part of the DCTD, administers clinical drug development. Compounds can enter at any stage of the development process with either very little or extensive prior testing. Drugs developed through these programs include well-known products such as cisplatin, paclitaxel, and fludarabine.

In the beginning of 2012, the NIH established a new center called the National Center for Advancing Translational Sciences (NCATS) that is designed to assist companies with the many costly, time-consuming bottlenecks that exist in translational product development [11]. Working in partnership with both the public and private organizations, NCATS seeks to develop innovative ways to reduce, remove, or bypass such bottlenecks to speed the delivery of new drugs, diagnostics, and medical devices to patients. The center is not a drug development company but focuses more on using science to create powerful new tools and technologies that can be adopted widely by translational researchers in all sectors.

NCATS was formed primarily by uniting and realigning a variety of existing NIH programs that play key roles in translational science along with adding key initiatives. Programs of note for bioentrepreneurs at NCATS include the following:

1. ***Bridging Interventional Development Gaps (BrIDGs)*** enables research collaborations to advance candidate therapeutics for both common and rare diseases into clinical testing. Investigators do not receive grant funds through this program. Instead, selected researchers partner with NCATS experts to generate preclinical data and clinical-grade material through government contracts for use in Investigational New Drug applications to a regulatory authority, such as the FDA. In general, BrIDGs provides synthesis, formulation, pharmacokinetic, and toxicology expertise and resources to its collaborators.
2. ***Clinical and Translational Science Awards (CTSA)*** support a national network of medical research institutions—called hubs—that work together to improve the translational research process to get more treatments to more patients more quickly. The hubs collaborate locally and regionally to catalyze innovation in training, research tools, and processes. CTSA program support enables research teams including scientists, patient advocacy organizations, and community members to tackle system-wide scientific and operational problems in clinical and translational research that no one team can overcome.
3. ***Chemical Genomics Center (National Chemical Genomics Center (NCGC))*** is one of the centers in the Molecular Libraries Probe Production Centers Network. Through this program, biomedical researchers gain access to the large-scale small molecule screening capacity, along with medicinal chemistry and informatics necessary to identify chemical probes to study the functions of genes, cells, and biochemical pathways. These chemical probes may also be used in developing of new drugs.
4. ***Therapeutics for Rare and Neglected Diseases (TRND)*** offers collaborative opportunities to access rare and neglected disease drug-development capabilities, expertise, and clinical/regulatory resources. Its goal is to move promising therapeutics into human clinical trials. Selected applicants can partner with TRND staff on a joint project plan and implement a drug-development program. Applicant investigators provide the drug project starting points and ongoing biological/disease expertise throughout the project. A collaboration agreement is established between TRND and successful applicants.

NCATS-supported programs and projects have also produced numerous tools to help basic and clinical researchers advance translational science. These resources include clinical research tools and resources to aid in such activities as patient recruitment, clinical study management, and public−private partnership development as well as preclinical research tools and resources to help researchers explore the functions of cells at the genome level, including more than 60 chemical probes.

There is additional assistance available from other NIH institutes to firms in a variety of disease areas including infectious diseases, drug abuse, and others—many more than can be highlighted here. All in all, such efforts can provide a wide variety of technical assistance (often at modest or no cost) for preclinical and even clinical development of novel therapies or other biomedical products by start-up firms.

Selling Products to Universities and Federal Labs

One of the most commonly overlooked opportunities by biomedical-focused companies is the ability to sell products and services to the NIH and similar research centers. Indeed, for start-up companies looking to develop new products used in conducting basic or clinical research, the NIH may be their first customer. With an intramural staff of about 18,000 employees, laboratories in several regions of the country (with the Bethesda campus in Maryland home to the majority), and an annual intramural budget of more than $3 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. Selling to the NIH can be seen as a daunting task for new companies because of the US government's complex acquisition process. However, there are a few simple steps that companies can take, such as establishing a Blanket Purchase Agreement (BPA) with the NIH and getting their goods and services into the NIH stockroom. Once these hurdles are cleared, it is much easier for NIH

scientists to buy from such companies, and if the quality of goods and services provided by a biotech company is superior, an NIH scientist can justify buying solely from that very source.

Companies that provide products and services to NIH laboratories can not only generate cash flow and revenues to fuel R&D but also begin to demonstrate their commercial acumen to would-be partners and investors. Being a large research organization, the NIH has numerous R&D contracting opportunities. For specific information on such opportunities, visit the NIH Office of Acquisition Management and Policy website [12].

The annual NIH Research Festival is also an excellent starting point for companies hoping to sell products to the NIH [13]. This event is held every fall at the Bethesda, Maryland campus and every spring on the Frederick, Maryland campus. Part scientific, part social, part informational, and part inspirational, this 3-day event draws a variety of small-to-medium-sized bioscience companies. These events attract almost 6000 NIH scientists, many of whom come to these gatherings to learn about and potentially purchase the latest research tools and services.

Translational Research Center—A Newer Model of Technology Transfer

AMCs such as the MGH are also evolving into this new model of technology commercialization that places a greater emphasis on the translational aspects of research. In the traditional technology transfer model, as you recall, the academic entity has used its intellectual capital to make breakthrough, cutting-edge discoveries, protecting them with patent picket-fences, and "transfers" it out to the company for them to develop these stellar scientific discoveries into products. These institutions recognize that to have the best patient outcomes for these new inventions, there is also a need to participate further in the translation of the early discovery to actual products.

The pictorial in Fig. 15.3 illustrates this model of a collaboration with a company that was used at the MGH and it is evident from this depiction that the huge advantages can be had from the utilization of the complementary strengths of the two parties in such a translation research effort. As illustrated, the research center brings to the table the technology, the IP, the know-how, and deep understanding of the inner workings of the technology, and in the case of MGH, significant biological and clinical insights. The company would provide the funding, the product development expertise, the regulatory expertise, and finally and importantly the marketing and product-positioning expertise. One such center was established at MGH with funding from a large company in the fall of 2010. The product is a next-generation diagnostic for cancer care—one that may fundamentally change therapeutic decisions for cancer patients. For this program, the TTO was instrumental right from the start in nurturing/protecting and maintaining the IP from its early days, working with the investigators to attract companies to the table, doing the deal with the company, and of course helping see this technology being translated into a product.

Impact of Technology Transfer

Licensing has Spurred Biotechnology Industry Growth

As mentioned before, the economic development potential of biomedical research is being recognized as a "fourth mission" for research institutions—going along with education, research, and public or community service. Thus it is in this "fourth mission" that bioentrepreneurs and research institutions find themselves again sharing the

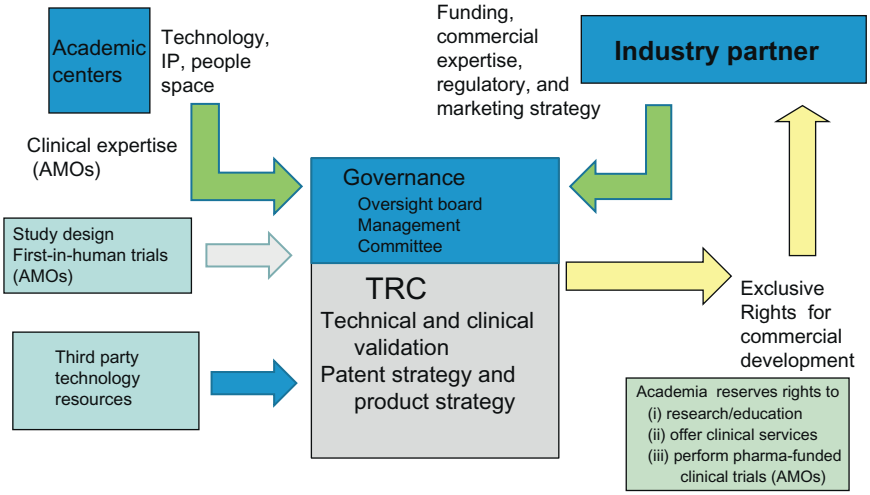

FIGURE 15.3 A business model for tech transfer: TRC. *TRC*, Translational Research Centers.

common goal of having new companies established based upon innovative research discoveries.

The economic importance of licensing and technology transfer has become better recognized during the recent recessionary period and some of the figures can be quite striking. For example, the overall product sales of all types by licensees of NIH intramural research is now reported by the NIH OTT as being over $6 billion annually, the equivalent of mid-tier Fortune 500 companies. Economic development also was the focus of the October 28, 2011 US Presidential Memorandum entitled "Accelerating Technology Transfer and Commercialization of Federal Research in Support of High-Growth Businesses" [13]. This directive from the White House recognized 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 US 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 over a 5-year period. During this period, federal laboratories, such as the NIH, will be (1) establishing goals and measuring progress toward commercialization, (2) streamlining the technology transfer and commercialization processes, especially for licensing, collaborations, and grants to small companies, and (3) facilitating the commercialization of new technology and the formation of new start-up firms through local and regional economic development partnerships.

Looking at the university and AMC figures reported by the AUTM, we find similarly strong figures for the economic impact of technology transfer. In 2016, AUTM reported that license income generated almost $3 billion and an additional $4 billion came in through industry-sponsored research. In 2016, more than 1000 start-ups were formed of which approximately 750 were doing business in the same state as the university/nonprofit from which the technology arose. By the end of 2016, 800 new products were introduced into the marketplace. In addition to the employment created by these start-ups, the tech-transfer industry itself has created significant employment both directly and indirectly through the related businesses it has helped to spawn.

In addition, many universities and the NIH have set up or have access to educational programs that train scientists and engineers to have a greater appreciation as to the importance of commercialization. These include entrepreneurship centers and small business assistance programs at many universities [14], and such things as the "Advanced Studies in Technology Transfer" program given at the Foundation for Advanced Education in the Sciences Graduate School at the NIH [15].

Maximal Leveraging of Technologies from Universities and Federal Labs

With their leading-edge research programs and focus in the health-care market, the federal laboratory and university-based research programs have an exemplary record in providing opportunities for bioentrepreneurs to develop both high-growth companies and high-growth medical products. Indeed, a preliminary study from 2007 has shown that more than 100 drug and vaccine products approved by the US FDA were based at least in part on technologies directly licensed from university and federal laboratories with federal labs (NIH) providing nearly 20% of the total [16]. Further, another study from 2009 has shown that university-licensed products commercialized by industry created at least 279,000 jobs across the United States during a 12-year period and that there was an increasing share of the United States GDP each year attributable to university-licensed products [17]. In addition, a study published in the *New England Journal of Medicine* [18] in 2011 based upon the earlier 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. This is an indication that the impact of licensing by universities and (by extension) federal laboratories will be increasingly effective and important in the future. Even with this success, there is movement toward a new, more collaborative horizon, especially with a "bench-to-beside" style collaboration as show in Fig. 15.4.

With the rising costs of traditional drug discovery and mounting pressures on health-care costs, companies are starting to adopt the model of a joint venture with academia. For example, Pfizer has embarked on a novel academic–industry partnership paradigm with the establishment of its Center for Therapeutic Innovation (CTI) program. By the end of 2011, CTI has established partnerships with 20 leading AMCs across the United States and supports collaborative projects from four dedicated labs in Boston, New York City, San Francisco, and San Diego. Another example is the establishment of Innovations Centers by Johnson & Johnson in Boston, San Francisco, Shanghai, and London. Scientists from academia are embracing this model as well given the pressures of funding their research as well as their drive to see their work not only published in leading journals but also seeing the products of their research turn into a product that can benefit the public at large.

Although this commercial success has been a model in showing the value of technology transfer from federal laboratories, universities, and similar nonprofit research 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 as

FIGURE 15.4 NIH and academic medical centers: Bench—bedside collaborations. *NIH*, National Institutes of Health.

well as the life-saving or enhancing therapeutics, vaccines, diagnostics, and other biomedical products on the market that have origins in this federally funded research. This is believed to be the truest measure of the value and importance of licensing and technology transfer from research institutions.

Case studies in biotech commercialization using university and federal labs

Case study 1: licensing of human papillomavirus vaccine technology

The human papillomavirus (HPV) vaccine is a vaccine that prevents infection against certain species of HPV associated with the development of cervical cancer, genital warts, and some less-common cancers. Although most women infected with genital HPV will not have complications from the virus, worldwide there are an estimated 470,000 new cases of cervical cancer that result in 233,000 deaths per year. About 80% of deaths from cervical cancer occur in poor countries.

The research that led to the development of the vaccine began in the 1980s by groups primarily at the University of Rochester, Georgetown University, the German Cancer Center (DKFZ), Queensland University in Australia, and the NIH. This work, and the work of others, eventually became the basis of Gardasil (sold by Merck) and Cervarix (sold by GSK)—blockbuster products in terms of public health and market impacts.

MedImmune, Inc., then a very small development-stage vaccine company based in Gaithersburg, Maryland, licensed the HPV vaccine technology available from all US institutions as well as the DKFZ in the early 1990s. GSK later received a license to all the rights held by MedImmune; Merck received a license from the NIH as

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well as to the Queensland rights. All of the license agreements were exclusive; those granted by NIH (who had been conducting separate clinical trials) were nonexclusive. The discoveries made at the research institutions were all very close in subject matter in what was then a relatively small research field and thus overlapping in terms of patent applications. Multiple patent interferences and patent oppositions resulted in patent offices around the world.

While patent interferences and oppositions can be expensive and difficult to resolve, the underlying technology proved to be extraordinarily successful in its clinical applications by both Merck and GSK—results that were confirmed in separate trials by the NIH. Given the strong clinical efficacy for these vaccines based upon the underlying technology discovered at the research institutions, a comprehensive settlement agreement was reached (regardless of the procedural outcomes at the patent offices around the world) whereby both Merck and GSK received coexclusive rights to the patent rights of all the research institutions, permitting the launch of similar (but slightly different) versions by both companies of these very important cervical cancer vaccines.

Discussion questions

After reading this chapter along with others in this book:

1. consider the role of MedImmune in the development of this vaccine. How risky was the strategy to acquire either control or access to nearly all the available license rights at a preclinical stage?
2. how did the strategy of the NIH work out, conducting some independent clinical trials and licensing both major developing parties originally on a nonexclusive basis?

(*Continued*)

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Case study II—sponsored clinical research agreement

The company in this case study was providing drugs as well as money (to the tune of millions of dollars over a few years) to the hospital. The drugs were in development at the company and were poised to enter the clinic (company's prized "Clinical Candidates"). The collaboration with the TTO was going to be in two phases—a preclinical research collaboration and a clinical collaboration in that order. The terms described later apply for the preclinical research collaboration.

Inventions were defined as those that were made during the term of the collaboration with funding from the company. Because inventorship follows US patent law, it was decided that ownership would follow inventorship making for three categories of inventions—company solely owned, hospital solely owned, and jointly owned. The parties would work together to protect inventions via patent applications. The company would pay for patent protection for all inventions in these three categories and in exchange would receive the rights later described. If the company did not see the value in any hospital solely owned inventions, then they would not pay for the protection of these inventions nor receive rights to these inventions.

The company retained full rights to use their own inventions. For jointly owned inventions, they had nonexclusive rights to access the inventions for internal research and all commercial purposes by virtue of their joint ownership. For hospital solely owned inventions, they received free rights for their internal research purposes. As compensation for paying for the patent costs to support the inventions, they also received an option to license the inventions at a later time. As the collaborative research informs them about the commercial prospects of this clinical candidate coupled with their separate ongoing internal efforts in this program, they would make a decision during a defined option period about exclusive or nonexclusive licensing. The option period had a time window of 2.5 years from the time of the initial filing of the patent application to protect the invention. This coincides with an important decision point in the life of a patent application, the decision to file for patent protection in specific individual countries—a very cost-intensive decision. Notably, through the option to license, the academic center is providing a route to obtain rights to the inventions developed in the collaboration or the FTO rights that is a must-have for the company as described earlier.

The terms of the license would be standard between academia and industry for such technologies (see Table 15.6). Such a license would involve the hospital's rights in both jointly owned inventions as well as in its solely owned inventions.

Publication versus confidentiality

Being clinical candidates, the company was very averse to any publications until the collaborative research was completed. This would mean publications could not happen for 2, maybe even 3 years from the start of the work. While this may be the actual timing of the publication, as an academic

(*Continued*)

(Continued)

institution the hospital could not agree to an apparent delay of the publication for a very long time. As per the guidelines under which academic research institutions operate, they cannot "withhold" publications for longer than 2–3 months. This issue was resolved by tasking the steering committee that was set-up with members from both institutions with finding a reasonable solution at the time when publication of the work is imminent. It was likely that the work will be published only when it is complete which may be 2 years from the start of the research anyway, so there will be no issue to resolve. But if there was a disagreement and a long 2–3-year delay to provide for patent protection, then the committee will come up with a reasonable compromise.

Discussion questions

1. What were the sensitive issues during the negotiation of the research collaboration agreement between the two parties and how did they resolve their differences?
2. Do you think either of the parties had to unnecessarily compromise on any basic principles in order to reach agreement? Discuss these points in more detail.

References

[1] National Institutes of Health. NIH overview, 2018. <http://www.nih.gov/about/budget.htm/> [accessed December 19, 2018].

[2] Brookings Institute. University start-ups: critical for improving technology transfer, 2013. <http://www.brookings.edu/research/papers/2013/11/university-start-ups-technology-transfer-valdivia> [accessed December 19, 2018].

[3] Association of University Technology Managers (AUTM). AUTM U.S. annual licensing survey highlights, 2017. <https://autm.net/surveys-and-tools/surveys/licensing-survey/2017-licensing-activity-survey> [accessed January 1, 2019].

[4] Ben-Menachem G, Ferguson S, Balakrishnan K. Doing business with NIH. Nat Biotechnol 2006;24(1):17–20.

[5] Ferguson S. Products, partners and public health: transfer of biomedical technologies from the U.S. government. J Biolaw Bus 2002;5(2):35–9.

[6] National Institutes of Health. Office of Technology Transfer. Startups, 2019. <http://www.ott.nih.gov/nih-start-exclusive-license-agreements> [accessed December 19, 2018].

[7] MacWright R. The University of Virginia Patent Foundation: a midsized technology transfer foundation focused on faculty service, operated using a deal-based business model. In: AUTM technology transfer practice manual. 3rd ed. 2(2.3a), pp. 1–21, 2019.

[8] National Institutes of Health. Office of Technology Transfer. Public health service technology development coordinators, 2019. <http://www.ott.nih.gov/technology-development-coordinators> [accessed December 19, 2018].

[9] National Institutes of Health. Office of Extramural Research. Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) Programs. <http://grants.nih.gov/grants/funding/sbir.htm> [accessed 12.19.18].

[10] National Institutes of Health. National Cancer Institute. Developmental Therapeutics Program and Cancer Therapy

Evaluation Program, 2018. <http://dtp.nci.nih.gov/> and <http://ctep.cancer.gov/> [accessed December 19, 2018].

[11] National Institutes of Health. National Center for Advancing Translational Science, 2018. <http://ncats.nih.gov/> [accessed December 19, 2018].

[12] National Institutes of Health. Office of Acquisition Management and Policy, 2018. <http://oamp.od.nih.gov/> [accessed December 19, 2018].

[13] National Institutes of Health. NIH Research Festival, 2018. <http://researchfestival.nih.gov/> [accessed December 19, 2018].

[14] Johns Hopkins University, Carey Business School. Discovery To Market (D2M) Program, 2019. <https://carey.jhu.edu/current-students/carey-life/experiential-learning/experiential-courses/discovery-to-market/> [accessed 01.01.19].

[15] Foundation for Advanced Education in the Sciences (FAES). FAES Graduate School at NIH Certificate Program, 2018. <http://www.faes.org/grad/advanced_studies/technology_transfer> [accessed December 19, 2018].

[16] Jensen J, Wyller K, London E, Chatterjee S, Murray F, Rohrbaugh M, et al. The contribution of public sector research to the discovery of new drugs. In: Personal communication of poster at 2007 AUTM annual meeting, 2007.

[17] Roessner D, Bond J, Okubo S, Planting M. The economic impact of licensed commercialized inventions originating in university research, 1996–2007. In: Final report to the Biotechnology Industry Organization, 2019. <http://www.bio.org/articles/economic-impact-licensed-commercialized-inventions-originating-university-research-1996-200> [accessed January 1, 2019].

[18] Stevens A, Jensen J, Wyller K, Kilgore P, Chatterjee S, Rohrbaugh M. The role of public-sector research in the discovery of drugs and vaccines. N Engl J Med 2011;364:535–41.

Further Reading

National Institutes of HealthNational Institutes of Health. Office of Technology Transfer. Licensing opportunities, 2018. <http://www.ott.nih.gov/opportunities> [accessed December 19, 2018].

The White HouseThe White House. Office of the Press Secretary. Presidential memorandum—accelerating technology transfer and commercialization of federal research in support of high-growth businesses, 2011. <http://www.whitehouse.gov/the-press-office/2011/10/28/presidential-memorandum-accelerating-technology-transfer-and-commerciali> [accessed December 19, 2018].