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VOL. 2, NO. 2, 2017
ISSN 2452-302X
http://dx.doi.org/10.1016/j.jacbts.2017.03.004

TRANSLATIONAL TOOLBOX

Technology Transfer: From the Research Bench to Commercialization

Part 2: The Commercialization Process

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SUMMARY

Technology transfer (TT) encompasses a variety of activities that move academic discoveries into the public sector. Part 1 of this 2-part series explored steps in acquisition of intellectual property (IP) rights (e.g., patents and copyrights). Part 2 focuses on processes of commercialization, including the technology transfer office, project development toward commercialization, and licensing either through the establishment of startup companies (venture capital–backed or otherwise) or directly to industry. In private industry, TT often occurs through the sale of IP, products, or services, but in universities, the majority of TT occurs through the licensing of IP. (J Am Coll Cardiol Basic Trans Science 2017;2:197–208) Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Part 1 of this 2-part series explored steps in acquisition of intellectual property (IP) rights (e.g., patents and copyrights) (1). Part 2 focuses on technology transfer (TT), which encompasses a variety of activities that move academic discoveries into the public sector. Universities have a mission to ensure that their discoveries, inventions, and new science applications lead to useful products and services for the public. A university that is successful in TT has more opportunities for new research collaborations and funding and for the exchange of materials, information, and personnel with private industry, thus enhancing research opportunities for their faculty and students (2). In fact, faculty candidates are increasingly "interviewing" the technology transfer office (TTO) as part of their diligence process prior to choosing a home institution. Successful TT improves a university's competitiveness with other academic institutions and the private sector to attract and retain top faculty and researchers. TT may produce income from royalties and licenses that can be reinvested in new research and teaching programs, although a recent study by the Brookings Institution indicates that 84% to 87% of universities will not realize enough income to cover the costs of a TTO (3,4). In 2003, it was estimated that the average income per license was $66,645, and that 43% of licenses earned no royalties at all (5).

Acceptance of federal research funding obligates the recipient institution to: 1) obtain written agreements from employees to report inventions and discoveries and assign them to the institution; 2) disclose inventions to the federal agency supporting the grant; 3) elect title (if they are going to) to the invention within 2 years; and 4) file a patent application within 1 year of election of title. Institutional obligations are summarized in **Table 1** (6,7).

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All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Basic to Translational Science* author instructions page.

Manuscript received March 14, 2017; accepted March 14, 2017.

ABBREVIATIONS AND ACRONYMS

COI = conflict of interest

CRADA = cooperative research and development agreement

IP = intellectual property

MTA = materials transfer agreement

NIH = National Institutes of Health

SBIR = small business innovation research (grant)

SRA = sponsored research agreement

STTR = small business technology transfer research (grant)

TT = technology transfer

TTO = technology transfer office

VC = venture capital

The U.S. government retains some rights to all federally funded inventions from universities and other nonprofit organizations, as summarized in **Table 2** (6,8,9).

A successful TTO manages IP assets through knowledge of IP, licensing, and contract law; an understanding of business management and practicalities; and connections to outside industrial and investment communities (10). **Table 3** lists the top 10 U.S. universities according to number of patents (11). The TTO must furthermore carry out its tasks within the overall institutional context in which it operates—resolving conflicts between its internal activities and the academic and public missions of the university.

THE TT PROCESS

DISCLOSURE AND PATENTS. TT begins when the inventor discloses an invention to the university (although proactive TTO engagement may start even earlier). Initial steps in the TTO are to determine whether the invention is patentable; whether to take title to the invention and file a patent application; and the practical aspects of the patent application, such as whether funds are available for the application and how quickly the patent application must be filed. **Figure 1** shows a simplified overview of the commercialization process.

Considerations regarding whether to file a patent application include whether the discovery is patentable; what the likely uses of a discovery are; whether a discovery has "sufficient" commercial potential; whether significant additional investment (research, development, regulatory approval steps, marketing, and so on) is needed; and (in some institutions) whether the discovery is something without significant commercial value, but nevertheless has potential for social impact through noncommercial channels.

The decision that an invention has "sufficient" potential commercial value for a patent application varies from university to university and depends on many factors. One consideration is the anticipated future royalty revenue of the license. Stanford's Office of Technology Licensing, for example, reportedly often refuses to patent inventions that are not anticipated to eventually generate at least $100,000/year in royalties (7). Another factor is whether a commercial entity is already interested in the discovery and is capable of developing it. Inventions arising under sponsored research agreements (SRAs) (i.e., grants associated with commercial companies) are often subsequently developed by the sponsoring company. In other cases, the inventor may know of commercial entities that are engaged in similar research or that have related or complementary products. A third factor is how broad or enforceable the resulting patent is likely to be, and whether copyright is a more suitable IP tool. For instance, if the invention's patentability is doubtful but includes copyrightable subject matter and is otherwise very marketable, it may be best for the institution financially and for the scientific community in general to immediately license the invention without patent protection. The National Institutes of Health (NIH) developed streamlined processes by which TTOs may license nonpatented inventions created with NIH funds to ensure that the scientific community will have expedited access to needed research tools (**Table 4**) (7,12).

Discoveries relating to materials that do not have significant commercial value but may be useful in noncommercial research are sometimes nonexclusively transferred to other parties via materials transfer agreements (MTAs) (13–15); NIH guidelines for MTAs are listed in **Table 5** (12). Examples of discoveries that generally fall under MTAs include cell lines, monoclonal antibodies, reagents, animal models, growth factors, deoxyribonucleic acid (DNA) libraries, clones, laboratory methods, and some computer software. A historical example of such nonexclusive licensing is the recombinant DNA—or gene splicing—technology of Cohen and Boyer, for which Stanford University and University of California applied for joint patent in 1974. They then licensed this technology nonexclusively for a $10,000 1-time payment per license. This technology is so widely used that the 2 universities became the leading earners of licensing income in the United States, with the license generating $250 million in revenue between 1981 and 1997 (7,14).

FINDING A LICENSEE. Assuming a patent will be sought, the TTO will then partner with the inventor to market the patent to find a licensee (or even establish a new commercial entity to be the licensee) and, as is necessary in most cases, provide resources for technology derisking to increase its marketability. This process often begins as soon as a patent application is submitted, because patent application can take 2 to 5 years. It is generally in the university's interest to involve commercial entities as early as possible in the development process to be able to recoup the costs of obtaining a patent as well as to support any additional research that is required before product development can proceed. For example, the research necessary to obtain market approval for new drugs typically takes about 12 years (16); thus, the right investor must have

TABLE 1 Obligations of Institutions Accepting Federal Funding for Research

Obtain written agreements with employees to disclose discoveries and assign them to the institution.
Disclose invention to the federal agency providing support within 2 months of employee disclosure.
Elect title (if they are going to) within 2 years after federal disclosure.
File a patent application within 1 year after election of title.
Include a statement with patent application that the U.S. government has rights to the invention and identifying the federal agency providing support.
Submit a confirmatory license to the federal agency providing support.
Notify the federal agency within 10 months of filing of the application and countries in which the patent will be pursued.
Submit periodic reports annually to the funding agency regarding use of the invention.
Give preference to issuing licenses to small businesses if they have the resources and capability to commercialize the invention.
NOT assign the rights to inventions to third parties, including the inventor, without prior approval of the funding agency.
Require any exclusive licensee to substantially manufacture within the United States any product that will be sold in the United States, unless this requirement is waived by the funding agency.
Share with the inventor a portion of any income the institution receives from licensing of the invention.
Use the balance of income from licensing of the invention (after costs of patent and license processes are reimbursed) to support education and research.

a long product-planning horizon to even consider investing in a university-based drug patent. Investing companies with appropriate planning horizons benefit from investing early (by purchasing a product license), because it protects them from competition during product development and launch (6).

To match appropriate investors with products, a successful TTO understands the fields in which the university is productively inventing, and develops knowledge about and relationships with commercial entities whose unmet needs tend to lie in those fields. If the invention fits into a well-known category of development at the university, chances are that at the time of disclosure of an invention the TTO will already know of potential fruitful partnerships and can facilitate introductions between the relevant entrepreneurs and mentors, or industry business development professionals and researchers. TTOs may publish lists of their available technologies or mail information about new technologies to specific companies who fit the profile of potential licensees. The inventor may have an existing research partnership with a commercial entity, or know of commercial entities whose interests and existing technologies suggest that they would be appropriate potential licensees. Emerging technologies may be advertised at trade shows or professional association meetings. In many cases, the best "advertisement" for a technology is publication in a high-impact journal, or via a university's public relations department. It is also not unusual for investors or industrial entities to contact TTOs to obtain updates about emerging technologies.

Most importantly, studies suggest that longstanding *personal* contacts within the TTO or with the inventor are the most effective means by which commercial entities are introduced to emerging technologies (17). Face-to-face meetings, teleconferencing, and invitations to visit university laboratories are examples of common introductory methods. In 2008, the Director of Technology at Florida University, 1 of the top university patent holders in the United States, indicated that, for most inventions, the TTO typically contacts approximately 100 potential licensees (18). Because the TTO is so critical in disseminating and commercializing discoveries,

TABLE 2 U.S. Government Rights Regarding Inventions That Result From Federally Funded Work and Research

Rights to a nonexclusive, nontransferable, irrevocable, paid-up license to the invention, to practice it or have it practiced on its behalf throughout the world.
Can require the university to assign title to the government if the university fails to report the invention, does not elect title, or does not file for patent within the required period of time.
Can require the university to license the invention to third parties (including the right to require the university to cancel existing exclusive licenses), or the right of the government itself to grant those license (so-called "march-in rights"), *provided 1 of the following circumstances occurs:* 1) the invention has not been brought into public use within a reasonable time; 2) where health or safety needs are not being met; or 3) where the U.S. manufacturing requirement has not been met and was not waived by the funding agency.
Can make a Determination of Exceptional Circumstances that there are compelling reasons why the right of the university to retain title should be restricted or eliminated.

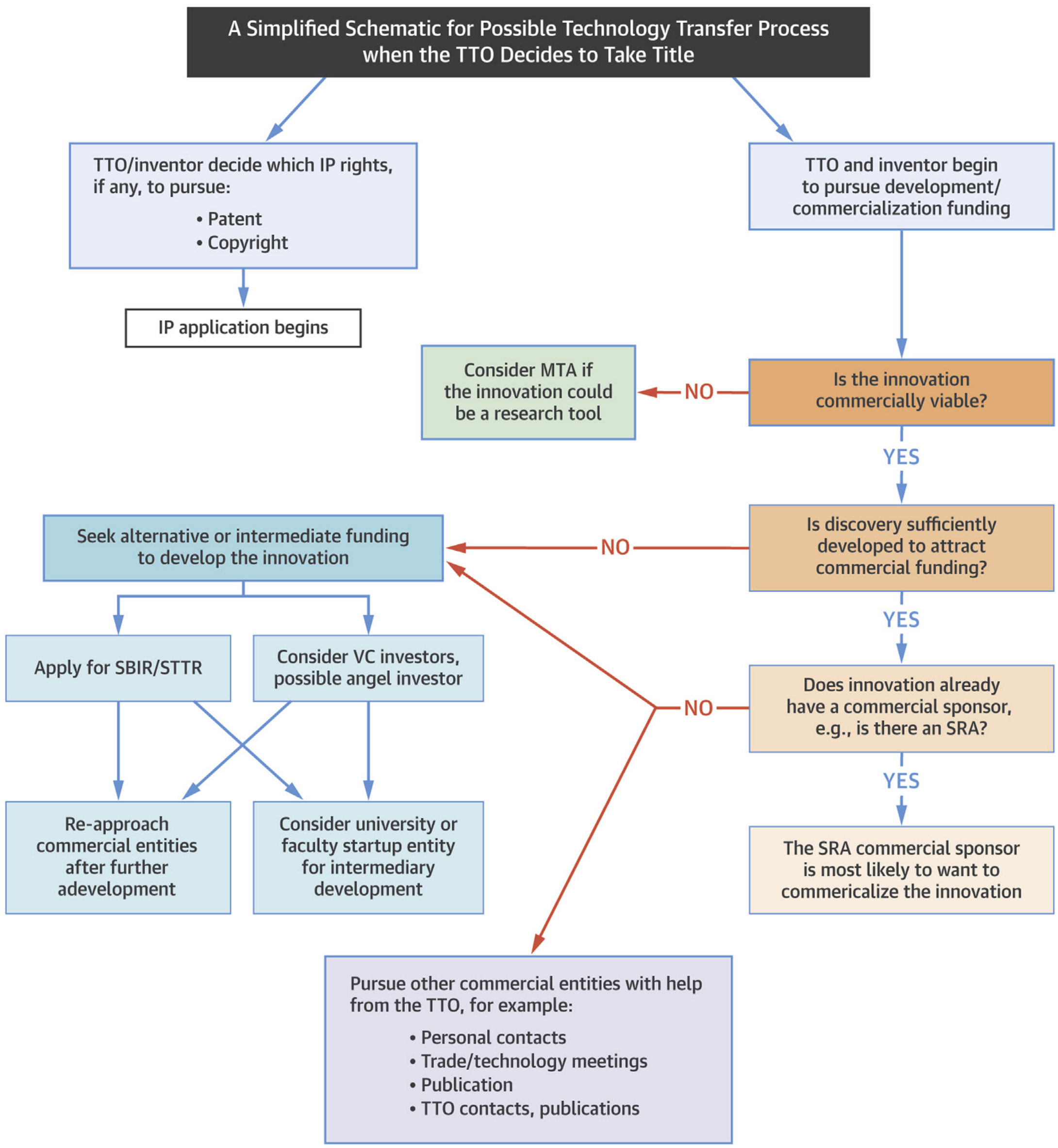
TABLE 3 Top 10 U.S. Universities by Cumulative Patents Issued From 1969 to 2012

University	Number of Patents in 2012	Cumulative Patents 1992–2012
University of California entities	361	7,586
Massachusetts Institute of Technology	216	4,017
Stanford University	182	2,405
California Institute of Technology	136	2,382
University of Texas	141	2,337
University of Wisconsin	167	2,194
Johns Hopkins University	79	1,557
Cornell University	55	1,366
University of Michigan	97	1,267
University of Florida	70	1,238

From U.S. Patent and Trademark Office. U.S. Colleges and Universities Utility Patent Grants, Calendar Years 1969–2012. Available at: https://www.uspto.gov/web/offices/ac/ido/oeip/taf/univ/org_gr/t250_univ_ag.htm. Accessed February 11, 2017.

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 2, NO. 2, 2017
APRIL 2017:197-208

FIGURE 1 Simplified Schematic for Commercialization of University Innovations



Note that the pathway for every innovation may be significantly different, depending on the presumed commercial versus research value of an innovation; whether the innovation was made in the course of a sponsored research agreement; whether the inventor and innovation are likely to be successful small business innovation research (SBIR)/small business technology transfer research (STTR) grant candidates; whether the innovation falls into the "niche" of a venture capital (VC) investment firm or commercial entity; and what resources of the individual technology transfer office (TTO), university, and inventor have, among many other factors.

researchers contemplating employment by a particular university should familiarize themselves with the breadth and type of personal contacts within the TTO. A list of some basic questions for researchers to ask their TTO is included in Table 5.

Once possible licensees are identified, the TTO helps to select the licensee (if there is more than 1 possible qualified investor) and negotiates the license.

NEGOTIATING THE LICENSE. Factors that the TTO will consider in negotiating the license include the type of technology, the perceived risk of the technology, the current stage of development of the discovery, the projected cost of bringing a product to

TABLE 4 Materials Transfer Agreements: National Institutes of Health Recommended Elements

Ownership remains with the Provider (of the material).
Provider is not liable for any damages arising from the Recipient's use of the material.
No reimbursement is required of the Recipient, except the Provider's preparation and distribution costs of the material.
No use in humans.
No commercial research use.
No distribution to third parties.
The Recipient must acknowledge the Provider as the source.

TABLE 5 Basic Questions for Researchers to Consider When Contemplating University Employment or Transfer

Does the university have a TTO and how is it staffed? For example, is there adequate breadth of legal guidance for IP law, contract law and federal regulations? Would the researcher receive individual attention from a TT manager?
How does the TTO manage disclosures of inventions? What percentage of disclosures result in patents?
How successful has the university been in the past in translating discoveries/innovations into commercial licenses?
In what fields has the TTO been most active in commercializing discoveries? What are examples of patents or licenses that have been issued in the researcher's field of exploration or related fields?
How does the TTO advertise/promote innovation in the commercial community? Do they have "incubators" for inventions? Do they actively participate in trade/technology meetings?
What personal contacts does the TTO have with commercial companies in the researcher's field?
What are some examples of SRAs that have been developed with assistance of the TTO?
Is the TTO's turnaround time on SRAs reasonable?
How responsive are the TT managers, and how long does a typical license negotiation take?
Does the university support faculty startups? What are examples of startups that have arisen out of faculty discoveries?
How does the TTO approach VCs? Does the university have VC funds from which to sponsor eligible startups? What does the TTO see as the inventor's responsibility in finding commercialization funds, including VC funding or other investment? What personal contacts does the TTO have with VC firms and regional investment community?
How does the university typically allot royalties to inventors?
What policies does the university have in place regarding conflicts of interest in commercialization of inventions?
How has the university generally handled IP rights and licenses when faculty: 1) enter employment with IP and licenses that have been generated at another university; or 2) leave the university for either other academic environments or commercial employment?
Who are the faculty members who have commercialized their discoveries with the TTO, or who have had commercial failures, and how can the inventor contact them?
What has the TTO experience been with software patents, copyrights, trademarks, and licenses?
What is the level and quality of resources that the TTO offers to support commercialization? (e.g., medical regulation consulting; clinical trials consulting; experienced entrepreneurs in residence and mentors representing diverse industries; internal gap funding programs; commercialization education programs to faculty; commercial advisory boards; efficient public relations machine; seasoned TT managers)

IP = intellectual property; SRA = sponsored research agreement; TT = technology transfer; TTO = technology transfer office; VC = venture capital.

market, the size of the potential market, the anticipated profit margin, the strength of the patent claims, whether a patent has actually been issued, the prospects for pending patent applications, estimated cost of research that lead to the invention, the scope of the license being issued (e.g., exclusive vs. nonexclusive, geographic scope, and field of use), and known royalty rates for comparable inventions.

Initial licensing fees tend to be lower (<$100,000)—and may even be zero in case of startups—when the technology is in early development, because commercial potential is uncertain and significant investment may be required before the invention is commercially viable. Federal law imposes certain requirements on the granting of licenses for inventions made with government funding (8). The inventor(s) must receive a share of the royalty, and the remainder must go to research, education, and to recoup expenses associated with technology management. The university must make reasonable efforts to give licensing preferences to small businesses if it is equally likely as a large business to bring the invention to practical application (7), and they must substantially manufacture the product resulting from the license within the United States. This last requirement can be waived under special circumstances (e.g., if the invention does not cover the U.S. market, the rapid availability of the invention benefits the public health and requires non-U.S. manufacture, the licensee makes investments within the United States in research and facilities, or the invention will create greater U.S. jobs or more skilled U.S. workers). The university must report annually to the funding agencies about the utilization and development status, date of first sale, and royalties received, preferably via the NIH iEdison reporting system (19). The government must be granted a nonexclusive, nontransferable, irrevocable royalty-free license to practice the invention (this provision generally excludes government commercialization of the invention or government assistance to competitors of the licensees). The government can require third-party licensing if the university licensee is not taking effective steps to develop the invention (i.e., the government can exercise its "march in rights") (5,6,16). Finally, the university must acknowledge government support and the government's rights in the patent application, and inform any licensees of these rights and other requirements as set forth by the Bayh-Dole Act (8).

A partial list of common license conditions is included in **Table 6**. A TTO may recommend an exclusive licensing agreement with 1 entity, or may

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 2, NO. 2, 2017
APRIL 2017:197–208

TABLE 6 A Partial List of Common Elements in a License Contract

Exclusive or nonexclusive license
Field of use
Geographic restrictions
Term of license
Diligence requirements - performance milestones
Annual reviews
Licensing renewal intervals and fees
Royalties and sublicensing provisions
Reimbursement of University costs (e.g. costs of obtaining a patent)
Indemnifications and insurance
Research and development funding
Equipment and facilities
Consulting agreements
Access to proprietary and technical information about the invention
Whether equity shares (in the case of startups) may serve as payment

Adapted from Razgaitis (20).

suggest that separate uses of a particular discovery or invention be each licensed exclusively to different entities (6). For example, if a new discovery allowed the rapid identification of a particular pattern of DNA associated with abnormalities in both glucose and lipid metabolism, the TTO may suggest licensing a “field of use” exclusively to a company involved in diabetes therapeutics, and another field of use exclusively to a company with extensive involvement in laboratory identification of inherited disorders of lipid metabolism.

Licenses can be exclusive (granted to only 1 entity) or nonexclusive (licenses for the same use are granted to multiple entities). Exclusive licenses are generally desirable when the licensee is making a high-risk investment, whereas nonexclusive licenses are more desirable when the invention is a broadly useful process that may appeal to multiple licensees, and exclusivity is not needed to generate interest in the license.

The TTO commonly inserts residual “ownership rights” in the license, including the right to revoke the license if certain development benchmarks are not met. For example, in licensing a patented drug, the university may require that the licensee complete basic pharmacological and toxicology testing within 2 years as well as meet standard key milestones in the drug regulatory approval process, or risk revocation of the license. Commercial entities seeking a license present business plans in support of their license application, and license requirements are often developed directly from those plans.

Financial aspects of licenses include licensing fees, royalties, reimbursement of the university patent costs, annual license renewal and maintenance fees, and potential equity shares in the company developing the innovation. Royalties are usually specified as a percentage of the sales of the product or service covered by the patent, rather than net profit. Royalty rates for university inventions commonly run between 1% and 10% (20,21), but in some circumstances can be considerably higher (6,10,22). Licensing fees can also be quite significant: Rockefeller University received $20 million in upfront royalties from Amgen in 1995 for an exclusive license of the mouse leptin gene (22), and Northwestern University sold its royalty rights for Lyrica (Pfizer, New York, New York) for $700 million (10).

WHAT IF AN INVENTOR MOVES TO ANOTHER UNIVERSITY OR COMPANY? When IP rights are created at a university, IP ownership remains with the originating institution. Thus, if research is continued at another institution (whether university or commercial entity) on the same project or on projects requiring the use of the patented materials, then the TTO may negotiate how such materials might be managed within the transfer. There are a number of possibilities. If the inventor moves to a commercial entity and such entity is interested in commercially pursuing such inventions, it will request to license the innovation from the originating institution. The inventor may request transfer of the IP rights to the inventor. When the inventor moves to another university and is likely to develop licensable improvements or follow-on IP, it is common for the institutions to negotiate an interinstitutional agreement regarding how IP rights will be bundled for marketing and licensing, who will manage these rights, and whether they will be jointly managed (23).

COMMERCIAL-RESEARCHER PARTNERSHIPS: SRAs AND COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENTS. SRAs are contracts between a commercial entity and a university researcher to develop and commercialize a discovery. Identifying SRAs for the inventor is another function of the TTO. SRAs benefit the university by creating interesting research opportunities for faculty and students, employment opportunities for graduates, interplay with commercial scientists, and (through the agreement itself and from the income generated) additional research funding (13). SRAs and are important source of university income; income from SRAs exceeds that from licensing by almost 3 to 1 (7).

The Federal version of an SRA (i.e., an agreement between a federal NIH laboratory and a commercial company or other nongovernment entity to develop a discovery) is called a cooperative research and development agreement (CRADA), the conditions of which are also set forth in the Bayh Dole Act (7,8). CRADAs are similar to licensing agreements between universities and commercial companies, but have special restrictions. CRADA opportunities must be advertised in the Federal Register prior to execution (unless only 1 company would be a qualified partner). The government must retain a nonexclusive, irrevocable, paid-up license to any CRADA inventions, even if they are manufactured solely by the commercial entity. CRADA partners have only 30 days to contest publication of CRADA data or to prepare a patent application. CRADA partners also have exclusive rights to use CRADA data for drug approval or other regulatory applications (7,24).

SRAs AND ACADEMIC FREEDOM. SRAs are an important source of university income, but they pose serious dilemmas. SRAs raise serious concerns about academic freedom, can shift focus inappropriately away from fundamental research, can present institutional and personal conflicts of interest (COIs), and can misdirect or misappropriate publicly funded research for commercial and for-profit pursuits. One study found that faculty receiving industry funding had more peer-reviewed publications than peers without such funding, but those who received more than two-thirds of their support from industry were *less* academically active than those with less support (24). Faculty with industrial support were >3× more likely to report that their work resulted in trade secrets (24). Researchers with commercial support were almost twice as likely to refuse to share information or biomaterials with colleagues than those who did not (11.1% vs. 5.8%) (24). Although researchers with industrial support were more likely than those without to have applied for a patent (61% vs. 37%), received a patent (35% vs. 22%), or started a new company (22% vs. 12%), they were *less* likely to report that their research had resulted in a product under regulatory review (14% vs. 30%) or on the market (20% vs. 29%) (25). More than one-third of industry-sponsored researchers reported delaying publication of their results “to protect their scientific lead” (25). Such delays run counter to the academic missions of most universities.

Publication delays have “real-world” consequences (26–30). In 1997, University of California San Francisco researchers studying the bioequivalence of a synthetic levothyroxine, Synthroid (then manufactured by Flint Laboratories, which was later purchased by Knoll Pharmaceuticals, and is now owned by Abbott Laboratories, Lake Bluff, Illinois) were prevented from publishing their findings (that several competing, much less expensive versions of synthetic levothyroxine were bioequivalent to Synthroid) for more than 7 years by their commercial research sponsor. Flint Laboratories first impugned the quality of the research (which they themselves had helped design) and then later reanalyzed the data in such a way as to reverse results of the study. They then published their analysis in a journal whose board included a senior researcher at their company (26). When University of California San Francisco researchers attempted to publish the unadulterated results anyway, they were stymied by the original research contract that allowed the company the right to prevent publication (27). Knoll Pharmaceuticals and its parent company were sued for $8.5 billion, ultimately settling for $135 million (29). In the meantime, patients paid inflated prices for a drug that was no better than equivalent, much less expensive drugs for 7 years before the study results became public.

The Knoll case is only 1 example of well-known cases in which a research sponsor attempted to prevent publication of results that might be detrimental to their commercial interests (31), but the Knoll case resulted in tightening of sponsored research agreements at U.S. universities. Withholding of data and material among academic researchers nevertheless remains common. Up to 47% of scientists report being denied information, data, or materials regarding published research, with 28% stating this prevented them from confirming published study results (32). A total of 27% of those who denied requests for data or materials did so to meet the requirements of a commercial research sponsor, and 21% did so to protect the commercial value of their results. A total of 24% of researchers who were denied materials indicated that it resulted in significant delay of publication, and 21% abandoned promising research because of it. Over one-half indicated that such denials adversely affected the research of others and the education of students and post-doctoral fellows. Another survey demonstrated that similar conduct among doctoral students and post-doctoral fellows was significantly associated with commercial research sponsorship. Over one-half of doctoral students and post-doctoral fellows indicated that withholding of data and materials had affected their research, 45% indicated it had adversely affected their relationships with academic scientists, and 33% felt that it had adversely affected their education (33). By 2013, exchange of information among researchers had fallen significantly; 24% of researchers reported intentionally excluding pertinent information from a manuscript submitted for publication “to protect their scientific

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 2, NO. 2, 2017
APRIL 2017:197–208

lead," and 39.5% admitted excluding pertinent information from a presentation of published work at a national conference or meeting (34).

VENTURE CAPITAL, FACULTY STARTUP COMPANIES, AND GOVERNMENT COMMERCIALIZATION GRANTS

VENTURE CAPITAL. The relationship between the academic environment and startup companies and/or venture capital (VC) investors is more common and much stronger in the United States than in many countries in Asia and Europe (7), although a surge in such relationships outside of the United States is occurring (35).

VC is defined as equity or equity-linked investments in nascent, privately held companies, in which the investor is a financial sponsor. The investor typically may then also act as a director, advisor, or manager of the company developing the product (35). The VC industry in the United States dates to 1946, when the first VC fund (the American Research and Development Fund) was formed. However, the flow of money into VC funds was relatively quiescent until the 1970s and 1980s, when government regulations allowed pension managers to invest in high-risk, VC assets. This resulted in a sharp increase in VC funding of innovations, which in turn promoted a marked increase in the number of patent applications and issuances (35). Analysis indicated that VC has a strongly positive effect on innovation; a 1998 study suggested that although VC represented <3% of corporate research and development in the United States, it commanded 15% of U.S. industrial innovations (35).

The main role of VC is to "take over" the role of promoting and developing promising university inventions that are in an intermediate stage of development and not yet ready to attract a larger commercial sponsor (36). The involvement of TTOs in startups and VC varies widely. Some universities are active in connecting researchers with entrepreneurs for the sake of formation of startup companies, and some have even established their own VC funds. Although all universities expect their faculty to participate in the search for investments through their own contacts, professional meetings, and technology gatherings, some provide more resources than others (37). In the past, the process to obtain VC funding began with a startup entrepreneur (usually endorsed by the inventor) seeking out and presenting a "pitch" to a VC firm to obtain capital investments. However, VC relationships are evolving; in the last 10 years, the process has become more collaborative between VC firms and entrepreneurs, with VC firms scanning academia through TTO contacts or professional meetings for new and innovative concepts and discoveries, and then moving proactively to approach inventors and form companies around those innovations (38).

FUNDING IS ABOUT RELATIONSHIPS. Understanding the motivations of investment firms or individual investors ("angels") is fundamental to the success of a researcher and his or her TTO in securing investment. In the words of Ellen Rudnick, executive director of the Michael P. Polsky Center for Entrepreneurship at the University of Chicago, "It's not just about money. It's about *chemistry*" (39). The relationship between the researcher and the investing firm is critical. Investors seek trustworthy partners who understand the business aspects of the investment and have good rapport with them. Furthermore, a great idea is not sufficient alone to secure funding: investors today seek great ideas that have a likelihood of financial success and that represent departures, and not merely stepwise changes, from previous technology. Bruce Booth of Atlas Ventures states, "We focus on finding innovative science and medicine around which to nucleate a future great company" (38). He points out that business plans and market models, expected by VC firms in the past, are no longer as strongly emphasized: "Market models have too little accuracy and too much false precision to be either relevant or valuable . . .[a drug discovery startup] needs to have a credible thesis for how they will address an important medical issue in a transformative way, differentiated from other approaches, and a path for progressively de-risking that opportunity" (38).

Inventors must plan strategically; an inventor who believes he or she is likely to seek investor funding should be cautious about entering into early binding agreements with other investors or license holders, because such relationships will usually be seen as limitations to profitability by any investor. Robert Nelson, cofounder of ARCH Venture Partners, comments that "the biggest mistake faculty members make is to partner with entrepreneurs who are not of the quality or experience that venture investors will accept" (39). Furthermore, early in development, it is often best to secure funding only for the short term (12 to 18 months) rather than seeking long-term funding that is reassuring, but may require trading away more of the enterprise to achieve. Once the startup has contracted with its first client, long-term funding will often be achievable for terms that are more favorable to the inventor/university.

In selecting which investors to approach, the researcher should examine what type of companies the investors have supported in the past, and understand both the successes and failures that the firm has experienced. Colleagues and TTO officers may well have useful information about possible VC or other investors and their reputation, and be able to recommend or even arrange company contacts.

STARTUP COMPANIES. In some cases, inventors may decide to form a new company (a "startup") around the innovation that will then develop, market, and sell the discovery (13). Rarely, the inventor himself or herself may even decide to direct or manage the company (sometimes referred to then as a "faculty startup"). Before going the route of a startup, however, a researcher should seriously consider several issues.

How supportive is their institution to startup development? Despite potential benefits to the university, not all academic institutions offer resources to support startups. Apart from examining the institutional policies and discussing startup formation with the TTO, an inventor should try to discover the experiences of other faculty members in startup endeavors. Was the university supportive? Was there significant resistance, and of what nature?

How personally involved does the researcher really want to be in developing the technology? Startup businesses are complex and require heavy personal investments in time and effort. Is the researcher willing, for example, to potentially give up his or her academic position to be involved in the company? How much time does the university allow a researcher to devote to outside activities?

How skilled in business development is the researcher? Business success will depend on acquiring skills in accounting, marketing, financing, and regulatory issues, among other things, and the development of a viable business plan. Successful businesses require a quality innovation, the right personnel and partners, and adequate funding.

Can the inventor separate himself or herself emotionally from the invention? Even if the researcher desires personal involvement in the business, at some point he or she will almost certainly need to set company interests ahead of his or her own and rely upon business experts to help take the discovery to the market.

What are the funding possibilities for a faculty startup? In general, commercial loans (and debt accrual) are difficult to obtain and may not represent a wise fiscal choice in the early stages of a startup, when diversion of cash flow related to debt service may restrict research and development. Alternative investor possibilities include "angel investors" (i.e., wealthy individuals seeking investment opportunities), and federally funded small business grants known as Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) grants are other possibilities, and do not require transfer of startup equity to the funding institution (see the following text) (40).

Is the inventor prepared to manage conflicts of interest? Startup ventures present potential conflicts of interest for faculty inventors who intend to have a significant financial interest in them, particularly if the inventor is considering a business leadership position in the company, or is considering having his or her students work in the startup. The primary interest of a startup is profitability (including personal profitability for the inventor), and the primary interests of most academic environments are education, innovation and discovery, and benefitting the public. These interests are not always aligned.

SBIRs AND STTRs. As discussed previously in *JACC: Basic to Translational Science* (41), the federal government SBIR and STTR programs represent the largest seed-stage funding sources for companies in the world, totaling more than $2.2 billion each year (41). SBIRs and STTRs are government grants, based on 3 "phases" of innovation development. Phase I SBIR and STTR grants assess technical merit, feasibility, and commercial potential of the invention, and offer relatively lesser amounts ($150,000 and $100,000, respectively) over very brief periods of time (6 and 12 months, respectively). About 13% of applicants for Phase I grants received funding in 2013 (42). Phase II grants are only awarded to Phase I award recipients, to continue research and development efforts started in Phase I. They normally do not exceed $1 million or $750,000 respectively over 2 years. Fewer applications are presented for Phase 2 awards, but 2013 Phase II success rates are much higher than Phase I success (54%), presumably because Phase II grants rely on successful Phase I innovations (42). In Phase III of development, the inventor is expected to find funding in the form of VC or commercial partnerships, and does not receive support from SBIR or STTR grants. Non-SBIR, non-STTR contracts can sometimes be obtained with federal agencies for products or services intended for use by the U.S. Government (40). The successful SBIR/STTR grant applicant has well-developed preliminary studies, novel drug targets and cutting-edge technology (e.g., devices, diagnostics, and delivery systems), a well-qualified principal investigator, a reasonable budget, and access to necessary resources

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 2, NO. 2, 2017
APRIL 2017:197–208

(e.g., facilities, analytical instrumentation) (40). The overall combined success rate for Phase I and Phase II SBIR and STTR grants is 15% to 25% (42).

MANAGING CONFLICTS OF INTEREST IN COMMERCIALIZATION

A primary mission of universities and their faculty is to develop new knowledge, and to promote scholarship and education for public benefit and not private good. Although TT serves part of this mission by carrying university-based discoveries into the public sector through commercialization, commercial entities involved in such transfer have clear profit motives (13). The more academic faculty and universities themselves become directly involved in commercialization and reap financial profits from it, the more COIs can arise between the university and inventors' academic missions for public benefit and the commercial influences on academic centers (43–45). This in turn, if not properly controlled or managed, negatively affects public trust.

CONFLICTS OF ACADEMIC COMMITMENT. University faculty members are expected to have primary allegiance to the institution, and make commitments of time and energy devoted to their academic pursuits (education, research, and scholarship). In return, faculty members benefit from the reputation of the institution to which they are connected. Although most universities allow and encourage outside activities that enhance the faculty's academic pursuits, reputation, and contacts, conflicts can occur when such activities encroach on the time and efforts the faculty members devote to their primary relationship with the academic institution, which in turn may reflect on the public's perceptions of the institution's academic research integrity and objectivity. This conflict is particularly strong if the faculty member has a direct personal financial interest in some of the commercialization activities that arise out of his or her research.

FINANCIAL COIs AND RESEARCH BIAS. A key concern regarding the conduct of research is whether a physician-researcher's financial interests may introduce conscious or unconscious bias to the research. There is strong evidence that commercial research funding and SRAs bias research conclusions (46) as well as published results. In 1 analysis, 62% of the abstract of reviewed research publications with commercial funding was found to contain favorable conclusions *that did not agree with the results section of the paper*, a phenomenon the authors referred to as "spin." This was not the case in any reviewed noncommercially funded studies (47). Indeed, one need look no further than the infamous case of Andrew Wakefield, who lost his physician's license in the United Kingdom after being accused of falsifying tests and data to "prove" a link between autism and childhood vaccinations, while planning to launch a private commercial venture with his father on the back of a vaccine scare to profit from his own patented medical tests and expert testimony (48,49). A 2012 British court ruling reinstated his medical license, but nevertheless did not reverse the findings regarding his research: the court stated that "There is now no respectable body of opinion which supports (Dr. Wakefield's) hypothesis, that MMR vaccine and autism/enterocolitis are causally linked" (50). Such COIs have serious consequences; in the aftermath of Wakefield's now discredited publication, vaccination of children in the Western world against measles, mumps, and rubella fell, and prevalence of these diseases, with their morbidity and mortality, rose (51).

INSTITUTIONAL COIs. Just as individual researchers can have personal conflicts of interest between their academic mission and commercialization of their discoveries, so institutions and universities can also experience conflicts. Professional and government groups such as the NIH have examined COIs in commercial sponsorship and suggested policies and procedures to identify and minimize conflicts (16,43,52). Although the individual researcher is not the main target of these guidelines, anyone considering a research position should familiarize themselves with the university's policies and procedures regarding such conflicts.

HOW MUCH WILL AN ACADEMIC INVENTOR BENEFIT FINANCIALLY FROM ROYALTIES?

Under federal law, universities are obliged to share revenues received from royalties and licensing fees with the inventor, after recouping costs of patenting and development (6). But, obtaining a patent far from guarantees any such revenues. Patent filings occur at very early stages in innovation development, but fewer than one-third of university patents are ultimately licensed (53). Once licensed, relatively few innovations earn significant revenues. Of those revenues, the most commonly reported share paid to the inventor is 30% of revenues earned by the institution, after deducting patent and marketing expenses (53).

COMPUTER SOFTWARE, MULTIMEDIA, OR WEB-BASED INNOVATIONS

Unlike rights to inventions, there is no overall statutory authority over rights to technical data and computer software resulting from federal awards (54). Computer programs can involve a patented algorithm, a copyrighted code, and a trademarked identifying logo. The patentability of some elements of computer software has been well established, and for those elements, Bayh-Dole invention rights apply. But, some computer programs may fall under both patent rules and copyright rules, and the ownership of IP rights for computer software that is developed under federal grants is inconsistent and confusing. Under certain government awards (federal assistance awards), nonprofit recipients may own the IP rights to computer software outright. For software developed under federal contracts (as opposed to grants and awards), the rules depend on whether the contract is through the Department of Defense versus federal civilian agencies. The scope of the rules governing licensing of software developed under federal programs is thus beyond the scope of this review; however, the academic researcher should be aware that software poses special challenges with regard to ownership and licensing, and should consult early with the TTO to determine which laws and regulations apply. A detailed and helpful summary can be found at the website of the Council on Governmental Relations (54).

CONCLUSIONS

Universities and academic researchers share motivations to move basic research discoveries and inventions into the public sector. Commercialization of research is managed through the university TTO, largely by licensing patents and copyrights to commercial entities. Although the university usually retains ownership rights to IP and innovations that occur in the course of a faculty member's employment, the inventor nevertheless stands to benefit in a variety of ways, including royalty income, commercial funding for their research, and societal impact. Because the goals of commercialization (profit) are sometimes at odds with the goals of academic endeavor (exploration, education, and discovery for the public good), managing COIs is an important part of commercialization. When exploring potential employment with a university, researchers should become familiar with the university's IP policy and whether the TTO's experience and goals are well aligned with the researcher's field of endeavor.

ACKNOWLEDGMENTS The authors thank Bruce Booth and Steven Robinette of Atlas Ventures for their assistance in finding invaluable resources when preparing this paper.

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KEY WORDS commercialization, licensing, technology transfer, venture capital