Chapter 54
Technology Transfer and Its Role in the Practice of Reproductive Endocrinology and Infertility

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Abstract This chapter is very different from the other chapters in this book. Rather than addressing specific reproductive endocrinology and infertility diagnostic and therapeutic needs and situations, it is intended to help clinicians who come up with ideas that have the potential to improve the practice of reproductive endocrinology and infertility ~~and~~ translate those ideas from bench to bedside.

Keywords Technology transfer • Intellectual property • Patents • Copyrights • Trademarks • Trade secrets and mask works

54.1 Technology Transfer

Technology transfer means the transfer of a technology from one party to another. So, when for example Hewlett Packard or IBM establishes a factory in Singapore or Bangalore to manufacture a product developed in the US, it involves a transfer of technology, from one country to another, but generally the technology stays within the same company.

In the US, however, the term "technology transfer" has come to mean the transfer of a technology developed at an academic institution, often with federal or philanthropic funding, to a company which can secure the necessary private funds to develop the technology, secure any necessary regulatory or standards approvals to market the product and then ~~to~~ manufacture and bring the product to market.

Academic institutions have developed offices and resources of varying degrees of sophistication to facilitate this process, which we will discuss later.

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54.2 A Brief History of Technology Transfer in the United States

Until 1980, if an academic researcher made an invention with federal funding, the government owned the resultant patent rights. The government had a firm policy that it would not grant exclusive licenses to inventions it owned, but would only license them nonexclusively. This meant that there was little incentive for companies to make the investment necessary to develop academic technologies because once they had made the investment and proved the viability of the technology, their competitors could then obtain a license on the same terms without having to make the same high risk investment.

As a result, in 1978 the government owned 28,000 academic patents and had licensed fewer than 4% of them. Inventions reported to NSF and NIH ~~are~~ declining even though federal funding of research was booming. And perhaps worst of all, companies would talk of research being "tainted" if it had received federal funding because of their fear of the government being able to grant nonexclusive licenses if it owned the patent rights (or even jointly owned them by virtue of having provided part of the funding to develop the technology).

Also at this time, the US economy was perceived as being in trouble under the double burden of high interest rates and high oil prices, coupled with a loss of leadership of manufacturing efficiency to Europe and Japan.

Senators Robert Dole (R., KS) and Birch Bayh (D., IN) led a bipartisan effort to help restore the vitality all of the US economy by removing the barriers to widespread integration of academic innovation into the mainstream economy.

In 1980, Congress enacted the Bayh–Dole Act [1] which allowed US universities, teaching hospitals, research institutes and small businesses to have the automatic right to take title to inventions made with federal funding.

The Act imposed a few requirements on institutions:

- Institutions ~~are~~ required to share any income they receive with inventors
- Institutions may only use the remainder on research and education

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- Institutions ~~are~~ expected to file patents on inventions they elect to own
- Institutions ~~are~~ encouraged to collaborate with commercial concerns to promote the utilization of inventions arising from federal funding
- Institutions ~~are~~ expected to give licensing preference to small businesses
- Products ~~patented~~ in the US ~~are to~~ be manufactured in the US
- The government retains a nonexclusive license to practice the patent throughout the world
- The government retains march-in rights to grant licenses in the public interest ~~to check~~ if the invention is not being exploited

Little was visible for quite some time. Institutions established offices of technology transfer to seek patent protection on these inventions and license them to existing and new businesses for development and commercialization, but there did not seem to be much impact on the economy at large. The 1980s were still a difficult time for the US economy, with oil prices reaching record levels in 1982 that were only exceeded in inflation-adjusted terms in the summer of 2008, and with the US semiconductor industry sustaining heavy losses and loss of market share in DRAM memory chips.

As recently as April 1992, the cover story of Business Week trumpeted gloom and doom and called on the government to establish an industrial policy. It said: "The very phrase rattles the teeth. It implies bureaucracy. It suggests that government will pick winners and losers. Done badly, it would certainly hurt America. But with the Cold War over and the global economy taking shape, American needs to shore up its competitiveness. How? Certainly by investing in education and infrastructure. But that's not enough. We must recharge the knowledge base – the basic science and technology that are the foundation of an advanced industrial society. Perhaps we should call it a "growth policy."

Just six months later, Business Week was trumpeting an entirely different message. "Hot Spots" was the theme off the issue with the subtitle "America's New Growth Regions." Inside it was clear that the recharging of the knowledge base had already taken place. A map showed a series of clusters from Ceramic Corridor in Upstate New York to Laser Lane in Orlando, Florida to optics Valley in Tucson, Arizona and up to Boomtown Boise in Boise, Idaho. The map stated that 600,000 people held high-tech jobs in these places.

As notable as anything was the omission of the traditional high-tech clusters of Route 128 in Boston, Research Triangle in North Carolina, and Silicon Valley in California from the map.

The article correctly identified the ingredients for a high tech cluster that hold true today, starting with a major research university:

- A major research university
- Quality of life
- Build on local industry
- Cooperation between local university, business and government
- Technology transfer from the university
- Funding sources – state, venture capital, angels
- Incubators.

54.3 The Impact of Technology Transfer

Since 1991, the Association of University Technology Managers has published an annual survey which has quantified the magnitude of the US's technology transfer enterprise [2]: For instance, in 2006, institutions

- Managed 18,874 new invention disclosures
- Filed 15,908 total U.S. patent applications
- Had 3,255 U.S. patents issued
- Signed 4,963 new licenses
- Managed 12,672 licenses and options that are yielding active income.
- Had 697 new products introduced to the market in 2006 from active licensees;
- Introduced more than 4,350 new products into the market in the nine years from FY1998 to FY2006.
- Launched 553 new startup companies in 2006 and 5,724 since 1980.

Academic technology transfer generates new products in a broad range of sectors of society and industry, but has had a particular impact on two sectors:

- Healthcare, reflecting the large amount of federal funding for healthcare research
- The Internet, reflecting its academic origins.

A recent study [3] quantified the considerable contribution to improve public health through the discovery, patenting, licensing and successful development of over 130 small molecule and biological drugs, vaccines and in vivo diagnostics,

Some of the contributions of academic institutions to the development of the Internet are shown in Table 54.1.

Table 54.1 Components of the internet that originated in academic institutions

Component	Originating institution
World Wide Web	European Organization for Nuclear Research (CERN)
Mosaic (Internet Explorer)	University of Illinois Urbana Champaign
Eudora	University of Illinois Urbana Champaign
Yahoo	Stanford
Lycos	Carnegie Mellon
Akamai	MIT
Google	Stanford

It is not surprising therefore that some institutions have garnered enormous returns from technology transfer. The 2006 AUTM Licensing Activity Survey showed that overall, US academic institutions received almost $2 billion in licensing income. However, this income is highly concentrated in a small number of institutions who have had one big success, frequently a drug – the so-called "big hit".

54.4 Intellectual Property

Technology transfer starts with intellectual property. Intellectual property is a blanket term for a number of different mechanisms for protecting the results of intellectual activity. The most common of these, and the most important in life sciences research, is the patent system. Other important mechanisms are copyrights, trademarks, trade secrets and mask works.

It may seem antithetical to the spirit of science to try and sequester knowledge, and certainly a number of the critics of technology transfer make that argument. However, this view reflects a fundamental misunderstanding of the intention and purpose of the patent system, which has always been to provide incentives to inventors to fully disclose their inventions to the world so that others may build on them, in return for the inventor being given a period of exclusive use of their innovation, rather than holding the knowledge close to their chest and practicing it in secret. By properly utilizing the patent system, a scientist can publish his or her findings and advance the body of scientific knowledge, while reserving for him or herself the exclusive commercial use of those findings. Indeed, a recent study of publications in Nature Biotechnology found that almost 50% of articles in that journal between 1997 and 1999 had a counterpart issued US patent by 2006, a phenomenon the author termed the Paper-Patent-Pair [4].

That said, a minority of academic scientists make the effort to commercialize their scientific findings. A study of 3,342 science faculty at six universities over 17 years [5] found that almost 65% of faculty never disclose an invention, another 22% disclose an invention once or twice in their careers and fewer than 15% are prolific users of the commercialization process. The data are shown in Table 54.2.

Table 54.2 Faculty invention disclosure rates

Number of disclosures	%
Never disclose	64.2
Disclosed once	14.8
Disclosed twice	7.6
Disclosed three to five times	11.4
Disclosed eight or more times	2.0

Table 54.3 Relationship of faculty performance to industrial research support

Variable	No. of publications	Teaching time	No. of service activities	Publication-trends score
No industrial support	10.1	16.6	1.8	2.1
Industrial support	14.6	16.0	2.3	4.2
1–33%	16.8	17.7	2.8	5.0
34–66%	16.4	19.3	2.2	5.3
67–100%	12.1	15.8	2.1	2.5

Research has also shown that faculty who are involved with commercialization are better faculty, as measured by publication rate and participation on faculty committees than faculty who are not involved with industry [6]. The data are shown in Table 54.3. This relationship holds true until industrial support accounts for more than 2/3rd of total support for the lab.

54.5 Who Owns Your Invention?

Who owns your invention will have a lot to do with how it gets handled and how much you will benefit from it.

If you work for a company, you will have undoubtedly been required to sign an invention agreement when you join the company, in which you agreed to assign any inventions you made to the company.

If you work for a university or an academic medical center (AMC) which is affiliated with a university, then you will have signed also an invention agreement, commonly known as a patent policy or patent policy agreement, in which you also agreed to assign ownership of your inventions to the University or AMC. Unlike a company agreement, where you will most likely have been given "$1 and other good and valuable consideration (such as keeping your job)" ~~In contrast to the company agreement where you have not been promised any~~ share in the profits made from your inventions, the University patent policy agreement will probably include a detailed description of just how much of the university's income you will receive. As we noted earlier under the discussion of the Bayh–Dole Act, it is a legal requirement that the inventor share in the income. Theoretically, the university could have a separate policy for income from inventions that were not federally funded, but the majority of institutions have a single policy. Typical rates are from 25–35% though some institutions have tiered distributions which give a higher percentage of the early income to the inventors and lower percentages as income increases. There may be an additional percentage allocated to your own laboratory. If there is no lab share, there will undoubtedly be a share allocated to your department or college, and you should negotiate with the chair/chief/dean for somewhere

between one third to one half of this department/college share to be allocated to your lab account.

There will be an office of technology transfer/licensing/industrial relations to whom you should submit the invention disclosure and which will manage the process for you, with your enthusiastic support.

If you work for a community hospital, a for-profit hospital, a nonprofit HMO, a group practice or in private practice, then it is likely that the total basis for your employment is clinical practice with no research component to it. In those circumstances, there will likely be no policies on inventorship and ownership, in which case you will be free to pursue (and pay for!) your inventions entirely by and for yourself.

54.6 The Invention

In the course of your clinical practice, you will frequently identify an unmet medical need, something that you would buy and use if it were available, but which you find is not available commercially. It may be a new diagnostic test, a new instrument, an improvement on an existing instrument, a new drug, a new use for an existing drug, a combination of two existing drugs, a new way of delivering or dosing an existing drug, and so forth.

One thing that is no longer worth patenting is a surgical procedure. In the early 1990s, Dr. Samuel Pallin filed a patent infringement suit against Dr. Jack Singer alleging infringement of U.S. Patent No. 5,080,111 on a patented surgical technique for use during cataract surgery [7]. The case caused widespread outrage both within the medical profession, among the public and in Congress. The 1996 Omnibus Appropriations bill, Public Law 104-208, contained a section, which limited the legal remedies available for infringement of patents on medical procedures. That said, if you identify a new surgical procedure that you think has merit, the way to extract value from it would be to develop and patent a new instrument or machine to carry out the procedure.

54.7 Obtaining a Patent

The basic criteria for obtaining a patent are that the invention must be:

- Novel
- Useful
- Nonobvious; and
- Adequately described.

54.7.1 Novelty

Novelty means that the invention has not been identically described in the literature anywhere in the world, or put on sale in the country in which patent protection is being sought. In the US or Canada, an inventor can publish his or her invention and still apply for a patent within a year, and in Japan within six months. In the rest of the world, a patent examiner somewhere must be the first person to learn about an invention for it to be patentable, so a US inventor who takes advantage of this one-year "grace period" will lose the opportunity for worldwide protection. Fortunately, the advent of provisional patent applications in the US has greatly facilitated the patent application process for academic inventors, by reducing substantially the time and effort needed to file an initial patent application.

54.7.2 Utility

Utility means that the inventor must disclose a use of his invention. He or she doesn't have to disclose all the uses and doesn't even have to disclose the most important use he or she knows of. These can be added at a later stage.

54.7.3 Nonobviousness

Nonobviousness means that the invention could not have been anticipated by putting together two existing inventions. In many academic inventions, these are some of the most difficult arguments made by the patent examiner to overcome. A patent examiner frequently combines references from widely different areas of science and claims that these make the invention obvious.

This has always been one of the most difficult patent examiner objections to overcome, and the examiners' hands were strengthened by a 2007 Supreme Court decision, *KSR v. Teleflex*, which eliminated a relatively inventor-friendly test for determining obviousness.

54.7.4 Adequately Described

You must disclose your invention in sufficient detail that one ordinarily skilled in the art can understand it. For a medical invention this would mean say, another OB/GYN, not just your 10 closest academic competitors in the world.

You must also disclose the best way you know of to carry out the invention at the time you file the patent application – the

"best mode". You don't have to file updates if you subsequently learn even better ways of carrying out the invention.

You do not even have to actually carry out the invention have proven that it works. You can file a predictive patent application, politely called a "constructive reduction to practice". For example, the University of Rochester obtained a patent (US Patent 6,048,850 "Method of inhibiting prostaglandin synthesis in a human host") claiming all uses of drugs which selectively inhibited cyclooxygenase 2, but not cylcooxygenase 1. At the time the patent was filed, the university only had possession of two cell lines, one of which stably expressed Cox 1 and the other of which stably expressed Cox 2. The rest of the patent is devoted to predicting how one would use these two cell lines to identify compounds which inhibit Cox 2, but not Cox 1. Rochester subsequently sued Pfizer claiming infringement of the patent by Celebrex [8] and after an enormous (and enormously expensive) legal fight, the patent was later found invalid for lack of enablement.

54.7.5 Patent Systems

There are two patent systems in the world:

- First-to-invent
- First-to-file

The US is now alone in operating on a "First-to-invent" system. In this system, if two inventors can show that they are entitled to be awarded the same patent, then the patent will be awarded to the inventor who can show they were the first to make the invention. The process by which this determination is made, if there are two competing inventors, is called an "interference". It is an adversarial process conducted not in court, but before a special board of the Patent Office – the Board of Patent Appeals and Interferences. Their decision is appealable to the US Federal District Court and from there to the US Court of Appeals of the Federal Circuit, the national court of appeals for patent cases. An interference is an expensive process and can take a long time to complete – the battle between Shmuel Cabilly of City of Hope Hospital in Los Angeles and Michael Boss of Celltech in the UK over coexpression of both chains of a monoclonal antibody in a single cell – an enormously valuable patent, that is required in the production of any recombinant antibody – took 18 years from application to a final (negotiated) settlement after appeal to Federal District Court. (The patent has since been invalidated on re-examination by the US PTO, a decision itself being appealed to the Board of Patent Appeals and Interferences! [9], so the fight still isn't over!).

The rest of the world operates on a first to file system. In this system, if two inventors can show that they are entitled to be awarded the same patent, then the patent will be awarded to the inventor who first filed their application somewhere in the world.

There are other differences between the two patent systems. Most notably, as noted earlier, outside the US "absolute novelty" applies – a patent application must be filed before the invention is published anywhere in the world. In the US and Canada, the inventor has 12 months from when they publish enabling details of the invention to file a patent application. In Japan, under some circumstances, the inventor has 6 months from publication to file a patent application.

What this means is that even the US applications should be filed before details of the invention are published, or else worldwide rights will be lost. In the past, this presented academics with a dilemma – should they risk losing scientific credit for being first to publish while they took one to two months to file a patent application, or should they publish first, take advantage of the one year "grace period" and file after publication and be content with the US rights only? Happily, since 1995, as discussed in the next section, a new form of patent application has been available that can be filed much more quickly and now it is possible to "have your academic cake and eat it too."

Another important difference between the US and European systems is that patents cannot be obtained for methods of treating people (e.g., a new use for an existing drug). Patent attorneys can formulate alternative ways to claim the invention to overcome this limitation.

54.8 Types of Patent Application

You will encounter a number of different types of patent applications.

54.8.1 Provisional Patent Application

Provisional patent applications have only been available in the US since 1995 when the GATT treaty came into effect [10]. A provisional patent application may be filed by an inventor by him or herself or their technology transfer office for a filing fee of $100 plus an Express Mail fee. A provisional application doesn't have to include any claims or even name any inventors. It must merely enable at least as broad a scope as the inventors ultimately wish to claim. A provisional patent application merely plants a stake in the ground and gives the inventor a year to convert the provisional application to a full utility application or PCT application and gain the benefit of the earlier filing date. If the inventor does nothing, then the provisional application dies and is never seen.

A significant benefit of a provisional application is that the one-year duration does not count toward the maximum 20 year lifetime of a utility application from initial filing. While nothing happens during that year toward examination and issuance of a patent, this de facto extension of the term of the patent is very valuable with life sciences invention, which will have to go through a protracted period of development before they can be commercialized. Pharmaceutical companies frequently prepare full utility applications on their inventions, but file them as provisional applications and then merely refile them as utility applications at their one-year anniversary.

54.8.2 Utility Application

A utility patent application is the main sort of US patent application and is intended to lead to issuance of the most important category of US patent, the utility patent (the others, which are encountered much less frequently are design patents and plant patents – only asexually reproduced plants such as potatoes).

Under the American Inventors Protection Act of 1999, US applications have been published since March 15, 2001. Previously, ~~the~~ US patent applications were confidential until the patent was issued.

54.8.3 PCT Application

The Paris Convention of 1883 allowed inventors a year to file corresponding foreign applications after the initial filing in one of the signatory countries. Today 169 countries are signatures to the Paris Convention.

PCT is an abbreviation for the Patent Cooperation Treaty and is the primary form of international patent application. The Patent Cooperative Treaty came into effect in 1978 and allows for a single worldwide filing to fulfill the Paris Convention requirements. There are currently around 133 signatories and they include all major economies except Taiwan, Malaysia, Thailand, Uruguay, and Venezuela. PCT applications are typically filed a year after the initial ("priority") application.

A PCT application can be filed in any language though effectively the choice is limited to Arabic, Chinese, English, French, German, Japanese, Russian or Spanish, and Dutch, Korean and certain Nordic languages. The overwhelming majority are filed in English.

A PCT application can undergo a preliminary examination at the international level, which can be helpful. A PCT application is published 18 months after its priority date, or six months after the PCT filing date.

After a further 12 months (i.e., 30 months from the priority date), the PCT application expires and applications must be filed in individual countries.

54.8.4 National Phase Patent Applications

These are applications in individual country patent offices or regional patent offices such as the European Patent Office. Academic institutions will generally not file outside the US unless they have a licensee to reimburse the costs.

Most licensees other than the very largest pharmaceutical companies will only file patent applications in developed countries. A typical group of foreign counterparts might include:

- European Patent Office ("EPO")
- Japan
- Australia
- New Zealand
- Canada

The next tier of countries might include China, India and South Africa.

54.8.5 European Patent Office

The European Patent Office is based in Munich, Germany and examines patents on behalf of 34 (as of January 1, 2008) European countries. All western European countries currently belong, and the countries formed by the breakup of the former Yugoslavia recognize EPO patents.

All examination and approval of patents, including the opportunity for companies to object to the issuance of a patent that has been approved for granting, occurs at the EPO level. The EPO doesn't issue patents – this is still done at the individual country level, and translation costs were substantial. In October 2000, the London Agreement substantially reduced the number of translations required. The London Agreement came into effect on May 1, 2008.

54.9 Prosecuting a Patent Application

When the patent attorney has finished working with you to prepare the patent, he or she mails it to the patent office using Express Mail. At the patent office, it is assigned to a patent examiner, who probably has a backlog of 120 or so cases. Examiners have to work through their backlog and dispose of eight cases per two week period.

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Eventually, ~~the~~ invention reach~~es~~ the top of the examiner's pile and the examiner reads it for the first time. The examiner's normal first reaction to a patent application is to decide that there are actually two or more separate inventions contained in the application and to split it up into two or more separate applications. Since the patent lies in the claims, the examiner may say something like: "The first invention is claims 1–4 and 6–10; the second invention is claims 5, and 11–15, and the third invention is claims 16–26." This is called a restriction requirement. The inventor now has to pick the application he/she wants to prosecute first. The inventor will normally pick either:

(a) The invention they think they have the best chance of getting issued; or
(b) The invention that they want the patent issued first for commercial reasons.

The inventions that the inventor doesn't pick sit at the patent office, and the inventor can come back and start prosecuting them when the one they prosecute first is allowed. The so sidelined inventions are called "Divisional applications."

After the inventor, through their attorney, picks which set of claims to prosecute, the substantive prosecution will commence in earnest. The next communication from the Examiner is likely to be a rejection of all claims, for a combination of prior art, obviousness lack of enablement or lack of specificity, and citing references. The attorney will have views on some of the Examiner's arguments and will write to the inventor laying out the Examiner's concerns, his proposed responses and asking for the inventors' views. It is critical that the inventor be engaged in the process, read these somewhat dry pieces of correspondence (the communications from the Examiner tend to be particularly dry), read the references and help the attorney mount the strongest possible response.

The prosecution will go back and forth in this way, with the attorney and the inventor hopefully whittling away at the Examiners' objections. An inventor has a right to talk to the Examiner, either by phone or in person at the Patent Office in Washington. This is often an effective way to overcome objections and get an allowance – it makes a very strong statement to the Examiner that the inventor truly believes they're entitled to something – and the inventor should be prepared to put in the effort to take advantage of such an opportunity if it is offered.

Hopefully, the Examiner will eventually be convinced and will mail a "Notice of Allowance" to the attorney. At that point, the attorney will pay the Issue Fee and about three months later, on a Tuesday [11], the patent will issue.

In the interim between when the fee is paid and the patent issues, it is time to go back and revisit the Divisional applications that were left on the table at the outset of the process. If the inventor wants to pursue them, the additional applications must be filed before the patent issues.

54.10 How Much Does it Cost to Get a Patent?

How long is a piece of string? As any attorney or economist likes to say: "It depends". However, in overview, healthcare inventions tend to be relatively expensive. The examples are highly technical, and the inventor will generally want to claim much more broadly than the specific examples they've carried out.

There are three elements to the cost of obtaining a patent:

- Attorney's fees
- Official fees
- Translation costs

Attorneys charge by the hour, in increments generally of 6 min (0.1 h). As of this writing in early 2008, partners at major law firms are charging $500–$750 per h; associates $250–$475 per hour, technical specialists with PhD's $125–$400 per hour, depending on experience. In New York City, rates may be even higher. Smaller firms are variable. Some may have very similar rates overall. Typically, the partners' rates will be lower, but the associate and technical specialist's rate may be essentially the same.

By retaining an attorney and asking them to do something for you, you are essentially giving them a blank check – you are saying "Take as long as you need to get this job done, multiply by your hourly rate and send me the bill and I'll pay it." To avoid unpleasant surprises, it's advisable to ask the firm to cap the fees, by asking them to commit to a "Not to exceed" figure. For repetitive matters such as writing a patent, firms have a lot of experience and will generally be ready to do this.

Official fees are reasonable in the US. The US PTO charges modest fees and gives a 50% discount to small companies (less than 500 employees), not-for-profits and individuals. Once a US patent is issued, maintenance fees are due at 3½, 7, and 11½ years. ~~The fees increase at each milestone.~~

Foreign patent office fees tend to be higher. PCT filing costs are $3,000–$4,000. EPO fees are substantial and there are significant maintenance ~~costs~~ each year.

Technical translation costs are expensive. The major cost of filing a Japanese patent application is the cost of translating the application into Japanese.

In ball park terms, it should be possible to file a provisional patent application for a healthcare invention for $2,000–$7,000, depending how much additional work is put into converting a publication into a patent application. Converting this to a utility application will cost up to $20,000. Prosecuting a typical application to issuance will typically cost a further $20,000 over its life in the U.S. Filing a US

utility application as a PCT application will cost $3,000–$5,000 in filing fees. A modest suite of national phase filings – Japan, EPO, Canada and Australia – will cost $25,000–$30,000. The costs to obtain and issue a patent are relatively modest in Canada and Australia. They are substantially higher in the EPO and Japan, typically about the same as in the U.S. In addition, the official fees for maintaining both the pending patent applications and the issued patents in effect in these countries is quite expensive – typically from $500–$1,500 per year per country. Thus, a lot of thought needs to be given to foreign filings.

54.11 Licensing The Patent

Getting a patent is relatively straightforward – have an original, creative idea, pay your attorney, and you will get a patent. However, the only reason for an academic scientist or physician to get a patent is to use it to induce a company to make the necessary commitment of human and financial resources to develop the invention and bring it to the market, and this is a lot more difficult. Anecdotally, one hears it said that fewer than 5% of patents are actually practiced though the data to support this is hard to come by.

Just as with prosecuting the patent, it is critical – in fact even more critical – that the inventor be very involved in the process. In a long term study [12] of 1,140 licenses completed by six institutions – the University of Florida; Massachusetts Institute of Technology; Oak Ridge National Laboratory; Oregon Health Sciences University; Tulane University; and the University of Utah – the authors confirmed the results of a preliminary study that had been carried out at MIT that the bulk of the leads that lead to completed licenses come from faculty (Table 54.4).

This may lead the inventor to ask: "If I made the invention and I find the licensee, what do I need these guys for, and in particular, why on earth are they going to get 70% of the money the technology brings in?"

The reason why the inventor is the source for over half the leads is quite simply that the inventor lives, eats, and breaths the science underlying the technology, while the technology transfer office has to work with the technologies of every professor and physician at the university. The inventor will know which companies are publishing in that space, attending the conferences and professional association meetings in that field, hiring his graduate students and post docs and so forth.

What the technology transfer office brings to the table is a business perspective on how to translate the invention into products, sources of information and experience in valuing the technology and in negotiating with companies. And of course the funds to pay for the patent application process.

Table 54.4 Sources of leads that lead to signed license agreements at six institutions

Source	%
Inventor	56%
Marketing efforts of OTT	19%
Company called university	10%
Research sponsor requested license	7%
Unknown	7%

54.11.1 Types of Licensee

Universities classify the companies that license their inventions into three categories:

- Large companies
- Small companies
- Start-up companies

In this scheme, a start-up company is one that is formed specifically to develop the technology. Small companies are those with fewer than 500 companies, which makes them eligible for various forms of government support, such as reduced fees at the patent office, access to the facilities of the Small Business Administration and eligibility for Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) grants.

In general, academic technologies tend to be so early stage, uncertain and with such a low probability of leading to a successful product that large companies find it hard to make the sorts of commitments that universities require from licensees, so the majority of academic licenses are with small companies, and only a third or so are with large companies. Table 54.5 shows the data for 2006 [13]:

This distribution between the types of licensee companies has held fairly constant for approaching 20 years.

Clearly, starting a new company is an important pathway for commercializing academic technology and we will consider this in some detail later in the chapter.

54.11.2 Finding a Licensee

Universities usually use a combination of passive and active marketing to find potential licensees.

Table 54.5 Licensees of US academic inventions in 2006

Type of company	Number	%
Large companies	1,648	34.1%
Small companies	2,416	50.0%
Start-up companies	764	15.8%
Total	4,828	

54.11.2.1 Passive Marketing

Passive marketing is usually achieved through having a searchable website where a non-confidential description of the technology is posted. This website is usually reached through the technology transfer office's section of the university's website. It is still laborious for prospective licensees to search each universities website in turn, so there are a number of websites that accumulate technologies from a number of sources. Some of these are commercial – e.g., Yet2.com [14] and UTEK [15] – though this has turned out to be a difficult business model to generate a return on capital (at the height of the dot.com boom there were over 40 technology matchmaking sites). Others are not-for-profit. The pioneer was created by the Massachusetts Association of Technology Transfer Offices and the Massachusetts Technology Transfer Center and provides access to technologies from all the universities, teaching hospitals and research institutes in Massachusetts [16]. The states of Florida and Texas have implemented similar systems. The Kauffman Foundation has supported another not-for-profit, iBridge, to create another website that appears set to become the dominant standard [17].

An important component of passive marketing is a one or two page (no more) non-confidential description ("NCD") of the technology that can be freely distributed to "sell" the technology. This document should focus on the advantages of the technology and the benefits it can bring to the users of it, not on the technical features, and should summarize all the work that has been done to demonstrate that the invention works – animal data, prototypes, etc.

Another powerful passive marketing tool is the press. Issuing a press release to coincide with the publication of a key paper in a respected journal, or receipt of an important grant can generate coverage in the business press that can reach the attention of prospective licensees.

Active marketing involves directly approaching companies with interests in the area. The normal course of events would be to identify a contact, either technical or in business development and establish contact by phone or email and send them the NCD. Another highly effective active marketing approach is for the inventor to give talks at professional association meetings. There are also companies which organize small, expensive conferences on areas of science that are "hot" areas of innovation. Attendance is free for speakers.

54.11.2.2 Reeling the Prospect In

Once a company has been identified which is interested in the technology, the next step may be to send them the patent application. The next step will usually be a technical meeting conducted under a confidentiality agreement. This may lead to the company doing some work to replicate the scientific conclusions, perhaps using samples provided by the inventor under a Material Transfer Agreement. The step after that will be to send the company a term sheet, a high level, 4 or 5 page documents that summarizes the key aspects of the agreement. If the parties can reach an agreement on a term sheet, the next step will be negotiation of a license agreement and perhaps sponsored research agreement.

The entire process can take from 3 to 12 months from initial contact to signed agreement.

54.11.2.3 Deal Structure

There are three important aspects of license agreements:

- the due diligence commitments of resources and/or progress milestones that the licensee will agree to in order to successfully bring the technology to the market;
- the business arrangements by which the university will share in the financial success of the product; and
- the contractual terms that will govern the relationship, assign risk and management responsibilities.

The term sheet will handle the first two of these in some detail, but will only summarize the contractual aspects.

Due Dilligence

Due diligence commitments are both general and specific. General legal standards include:

"Best Efforts", which means that the company will work harder on this project than any other. Companies will rarely agree to this standard.

"Commercially Reasonable Efforts", which means that the company will work as hard on this project as it will on its internal projects of comparable market potential. This is the normal standard agreed to.

Specific commitments tend to fall into two categories – resource commitments or effort and achievements or outputs.

Resource commitments could include an agreement to spend specific amounts per year for a specified number of years, or to commit to devote so many FTE's to the project or to carry out specific experiments.

Achievement commitments are usually tied to preclinical and clinical development stages – prototyping of diagnostics and devices and selection and preclinical testing (tox, ADME) of lead compounds, followed by entering successive stages of clinical testing and submission for regulatory approval.

To prepare for either resource or achievement due diligence negotiations, the inventor should prepare what (s)he believes is a reasonable development plan, estimate the resources

needed and the likely timeline, and be prepared to discuss these with the company. It is critically important that there be well defined milestones every six to twelve months, particularly in the first two or three years, so that if the company reduces the priority of the project in this time frame, the university will be able to detect this, terminate the license and find a new licensee.

Business Arrangements

The business arrangements will be divided into a number of places in the license agreement. Some will pertain to reimbursing expenses – patent expenses both past and future and the costs of any technical assistance the licensee will want the university to provide – some to payments to be made while the product is in development and some to payments to be made after the product has reached the market.

As a general proposition, academic inventions are generally licensed at a very early stage, when the probability of successful product introduction is relatively low. The value of the technology at that stage is therefore relatively low, but will rise as the product moves through the development process. A lot of the negotiations will be devoted to agreeing how much the value has increased by what stage and how much of that increase in value should be shared with the university.

Another critical part of the negotiations will focus on the expected commercial pathway the licensee will follow – specifically, whether the initial licensee will be the one that takes the product to market or whether they will develop the product a certain distance down the developmental pathway and then sublicense the product to a larger company which will actually take it to market. This decision has enormous commercial implications.

Specific Business Terms

Patent Expenses

The university normally will expect to see all its patent costs reimbursed at the closing of the deal and for future expenses to be reimbursed within 30 days.

Upfront Fee

The university will expect to receive an upfront fee to reflect the initial value of the technology. This will likely be between $10,000 and $1 million.

Annual Minimum Royalties

Annual Minimum Royalties ("AMR") are royalty payments that are made whether the product is on sale and paying earned royalties or not. They generally start at a relatively modest level of $10,000 or 20,000 per year (and may not even start for 2 or 3 years after the license is signed) and then escalate over a 5 year period to around $100,000. AMR's are generally payable on January 1 of each year and are creditable against earned royalties, milestone payments etc. due in the remainder of the year.

As well as guaranteeing a minimum level of income, AMR's serve as a due diligence mechanism – if the company has stopped developing a technology, then the company will generally terminate the license rather than making the AMR payment.

Milestone Payments

These are payments made to reflect the achievement of points where the technology has increased in value. These are frequently the same as some or all of the due diligence milestones, but there may be additional ones such as patent issuance, achieving certain levels of sales volume etc.

Milestone payments for starting clinical testing are generally fairly modest, but product approval milestone payments should be around $1 million for a device and upward of $5 million for a drug.

Sublicense Income Sharing

If the initial licensee is a small company, then they may well not have the resources, both financial and sales and marketing, to take the product all the way to regulatory approval and into the market. The license agreement should anticipate that the company will be sublicensing rights to a larger company, and should provide for the university to receive a percentage of all payments the licensee receives from the sublicensee. This percentage should be in the range of 15–25%, with higher rates due for payments received if the sublicense is issued closer to the date of the original license, and lower rates if the licensee spends a longer period of development and more of its own funds to get the technology to the point, where a large company is ready to take it over.

One of the difficult issues is the way the university will share in the sublicensee's sales of products. Say the license provides for the licensee to pay a 5% royalty on its own sales of the product. Will the licensee agree that the university will receive 5% of the sublicensee's sales? The answer is probably "No" because at the time the license is signed, the licensee will have no idea of what royalty rate they will receive from their sublicensees. If the licensee can only negotiate an 8% royalty on the sublicensee's sales and has agreed to pay the university 5% of the sublicensee's sales, then they will only be left with 3% to compensate them for all the time and money they put into the development of the technology. Therefore, the licensee will normally agree to pay the university a percentage of the royalties they receive from the sublicensee,

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perhaps the same percentage as they agree to pay of lump sums they receive from the sublicensee.

We have recently observed that if the agreed royalty rate is 3% or less, then it is generally possible to get the licensee to agree to pay that royalty rate on sublicensee sales too.

On the other hand, if the licensee is a large company, the agreement will probably provide for the university to receive the same set of payments and royalties whether the licensee sublicenses the technology to another company or takes it to market itself, and for the university not to share in any payments the company receives from sublicensing.

Royalties

Royalties are the payments the university will receive on the basis of the sales of the product. In general, royalty payments will provide the greatest economic return to the university if its technology does reach the market.

Royalties should be expressed as a percentage of sales, rather than say profits since sales is a very easy number for an auditor to verify when the university subsequently audits the licensee to ensure that the university is being paid all that it is entitled to receive.

One of the fundamental concepts of licensing is that the licensor should receive 25% and the licensee 75% of the pre-tax profits generated by a licensed product. This principle is known as the Goldscheider Principle or the 25% Rule, after Robert Goldscheider who first enunciated it. Goldscheider recently wrote an excellent review of the history, evolution and application of the rule [18]. The rule is a guide and provides onlya starting point only and many other considerations must be taken into account in applying it, but the clear implication is that the more profitable the product, the higher the royalty rate. So, for instance, if the licensee suggests that as sales increase the royalty rate should go down (the implication being that you've made so much money already, the rate should go down), the counter would be that since products, particularly pharmaceuticals, get more profitable as sales increase, the royalty should actually be higher at higher annual sales levels, not lower.

Another issue that comes up with royalties is royalties that have to be paid to others. The licensee will generally ask to be allowed to offset some or all of royalties that have to be paid to third parties. If you are negotiating a relatively high royalty rate – say 6 to 10% – this will probably be a legitimate request. However, the licensee should only be allowed to deduct 50% of the third party royalties so that they have a strong incentive to negotiate low third party royalties. If you are negotiating a relatively low royalty rate – say below 5% and certainly below 3% – you should reject the request. The risk of a licensee having to license a third party patent that they didn't know about at the time of the negotiation has been substantially reduced since 2001 when US patent applications started being published (as noted above, previously they were confidential till issued). It is legitimate therefore to ask a licensee to show you the third party IP they think they will need to license in order to practice the IP they're licensing form you.

Auditing: The Ronald Reagan Principle

Ronald Reagan once famously said "Trust – but verify". This is very true of license agreements. The only knowledge that the licensor has of what the licensee is doing is what the licensee chooses to tell the licensor. After product sales start, the licensee sends the licensor a quarterly statement that sys "Here's what I've sold and here's what I owe you." It is essential that the licensor have the ability to verify what the licensee is telling them. This is achieved through an audit provision.

The licensor will generally have negotiated the right to send an independent CPA into the licensor's business offices once a year, with suitable notice, with the right to examine the licensee's business records for the prior three years (which is the length of time the IRS requires companies to keep records). Audit clauses in licenses generally require the licensor to pay the costs of the audit, which will generally be around $30,000–$40,000, unless the auditor discovers a shortfall in any payment of 5% or more, in which case the licensee has to pay the cost of the audit. Most red blooded auditors will be confident of their ability to find such a discrepancy, and studies have shown that audits generally do find shortfalls.

It is therefore generally a prudent policy to audit licensees every three years when annual royalties reach $1 million and annually when they reach $5 million.

54.12 Forming a Start-Up Company

Forming a start-up company is a particularly hallowed vehicle for technology transfer. As noted earlier, a dedicated start-up is the chosen commercialization pathway for about 15% of academic technology transfer transactions. It has considerable potential for creating substantial wealth for the inventor and the university. That said however, forming a start-up is not a pathway that should be pursued lightly or without a deep appreciation of the effort and commitment that will be required of the inventor.

54.12.1 Finding a Business Partner

The first requirement for a professor who wants to form a start-up (beyond an invention that is sufficiently disruptive to attract the investment needed to successfully commercialize the invention) is going to be a business partner.

How to find such a brave soul? There turn out to be a surprisingly large number of sources in the communities in which most academic medical centers are located. Some universities can supply this capability through a group whose job it is to help faculty start companies. If the university does not directly provide this assistance, the Office of Technology Transfer may know individuals who are suitably experienced and who are looking for their next "gig."

Professional advisors whom the Office of Technology Transfer uses, particularly lawyers, frequently have good contacts with the entrepreneurial community and will know suitable individuals. The alumni or development office may be able to introduce the inventor to an alumnus or alumna who is involved in the industry. The university's Business School may have professors or alumni who have suitable industrial contacts. Other sources may be people the inventor has met through prior consulting relationships – say a VP of Business Development of a biotechnology company which has licensed one of their earlier inventions and who wants to start their own company. Other sources may be people to whom the inventor is referred by colleagues who have been down this path before. Some states have biotechnology centers with an economic development mandate that can provide contacts or provide direct assistance (e.g. Ohio's Thomas Edison Program [19]; Pennsylvania's Ben Franklin Program [20]; New York's Center of Excellence Program [21].

Many states have biotechnology associations that are natural congregating points for biotechnology entrepreneurs.

It is critical that the business partner has credibility in the life sciences start-up community. Resist the temptation to team up with say a stock broker or real estate executive or business lawyer (all of whom the author has seen inventors team up with, generally with frustrating and unsatisfactory results) because they have more with familiarity business than the professor does. They will be a negative as you move down the road and will probably quickly lead you astray.

54.12.2 Working with Students

Before sitting down with a potential business partner, the inventor needs to have captured the vision he has for the company. This presents a chicken and egg situation – you need the commercial vision to engage a business partner, yet you need the business partner to develop the commercial vision. One way of cracking this egg is to see if your business school (or a nearby business school if you are at a hospital or practice that's not part of a university) has courses that require the students to write a business plan or develop a business strategy or do a market research study. The professors who run these courses always have a need for business and product ideas for the students to work on, so finding and making contact with such professors may be productive. You'll need to keep the academic calendar in mind – most likely there will only two starting opportunities available – September and January, and the professor will want to have everything lined up at least a month, probably two, before the start of the semester. That said, the quality of work you can get from a dedicated inter-disciplinary team of students working for 14 weeks is stunning.

54.12.3 Communicating the Idea

Ultimately, you will need four documents to "sell" a company concept to all the stakeholders you're going to need – employees, investors, landlord, customers, etc.

In order of difficulty, and effort to generate them, these four documents are:

An Elevator Pitch
A PowerPoint presentation
An Executive Summary
A full Business Plan.

54.12.3.1 Elevator Pitch

The elevator pitch is a two minute summary of the opportunity – what you are doing, the scale of the opportunity, what's unique about your approach to solving the problem, how you ~~will~~ are going to change the world and how the person will profit enormously by joining you on the adventure. The term comes from the idea that you get on an elevator and suddenly realize that your fellow passenger is an ideal potential investor/employee/customer/whatever and that you have them captive for the duration of a 60 floor elevator ride.

The inventor should have an elevator pitch integrated into their psyche and be ready to launch into it at a moment's notice, tailoring it to the specific audience – potential investor/employee/board member/customer, etc. A good elevator pitch takes a lot of practice. It's very easy to go into too much technical detail or to stay stuck on the product idea and the company concept and not get to asking your captive audience for what you think they can contribute and how they'll profit from working with you.

If you can't capture the idea in two minutes, you haven't thought about it sufficiently. To be able to bring together all the resources you need, you have to be able to boil the opportunity to a simple, attractive summary that can be communicated in two minutes.

Some people advocate practicing at the mirror or giving the pitch to your dog. As the last step before going "live," you should give it to your mother and see if she "gets it".

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The sole purpose of the elevator pitch is to ~~get~~ the person you're giving it to that they want to hear more and will agree to meet with you later to learn more.

54.12.3.2 The PowerPoint Presentation

If you get that next meeting, you'll need a PowerPoint presentation, which is the heart and soul of communicating a new company concept. Like an elevator pitch, it must flow seamlessly and communicate the opportunity, the company's approach to filling the need, the status of the technology, what's unique about the company's approach, including the management team and the intellectual property position that will keep the enemy at bay, the company's financial projections, the investment the company is looking for and how the investors will make money – the "exit".

The individual slides of the presentation should be attractively designed, not cluttered with too many words and should use visuals where ever possible – a picture is worth a thousand words, and a video's worth ten thousand. A good presenter will take one and a half or 2 ~~min~~ per slide, so a presentation for a 1 ~~h~~ meeting – 40 ~~min~~ plus 20 ~~min~~ Q&A – should be 20 to 25 slides~~, no more~~. Use a large "clean" sans serif font like Arial rather than say Times Roman. Always try giving the slide show using an LCD projector in a sunny room before the first meeting – slides that look great on a computer screen can have insufficient color contrast and be difficult to read under "real world" conditions. Take and use your own laptop rather than downloading via a flash drive to their computer – that way you know you'll have compatible software versions, have all the plug-ins you'll need – particularly important if you're using video. Take a laser pointer with you to emphasize the talk.

In short, look technically competent, professional, organized and in control when you give a presentation on your company.

54.12.3.3 The Executive Summary

The executive summary is a five to ten page summary of the company's business plan that summarizes the presentation. If the audience liked the PowerPoint presentation, they'll ask for an executive summary and a copy of the PowerPoint to share with people within their firm that they want to get excited about the opportunity. It is probably the longest written description of the company that people will ever read.

54.12.3.4 Business Plan

The company must always have a Business Plan, which is a complete description of where the company is, where it's going and what it needs to get there. It documents the scale of the market and the opportunity, and demonstrates the company's ability to meet the need. It analyses the planned pricing of the product. It describes and justifies the viability of the company's business model – how the company will generate revenues. It describes the management team and how that will evolve. It identifies the partnerships with other companies that the company will need to get to the market. It looks at potential competition and how the company's intellectual property position will keep competition at bay. It contains detailed financial projections – development costs, capital needs, operating costs, profitability and financial return.

A company's business plan is constantly evolving. At a minimum, it should be reviewed every three of four months in the light of changing market circumstances and the company's progress. The initiation of a round of fund raising will normally trigger a new edition of the business plan.

Few outside the company will ever read the business plan cover-to-cover. However, your ability to answer detailed questions that come up in your presentations will critically depend on the thoroughness of the thought and analysis that went into the preparation of the business plan. You write it for yourself not for others.

54.12.4 Forming the Company

You can (and should) test the waters for your company concept without actually incorporating. You can project a very professional image for the company with do-it-yourself computer graphics without actually incorporating. Nobody will check at this stage. The story of how Larry Page and Sergei Brin raised the seed round financing for Google is a Silicon Valley legend. They were introduced to Andy Bechtolstein, the Co-Founder and Chairman of SUN Microsystems and a fellow Stanford alumnus. He liked the story, went out to his Ferrari, got his checkbook and wrote a check for $100,000. Brin and Page had to quickly incorporate the company in order to be able to open a bank account to cash the check.

You should check out that the company's name has not been taken by another company in the same technical area as yourself, together with a suitable URL. It may be worth paying the modest fee to reserve the URL at this stage.

However, if you start to get the sense that the company is going to be investable and so may be viable, then you will want to move ahead and incorporate. Although there are an enormous number of web sites that will offer to incorporate a company for you for as little as $99, you should use the services of a major law firm. Particularly in the major innovation hubs, the large law firms understand that mighty oaks from tiny acorns do indeed grow and that their future major clients start out as impoverished start-ups. Many of these law

firms have fee deferral programs under which, for a small retainer, they will accumulate the fees incurred by the company until some significant funding threshold is reached, at which point the accumulated fees become due.

It will ultimately be to the company's considerable advantage to be seen to be using the services of a top tier law firm. They will have expertise, experience and contacts to contribute as well, and the quality of your advisors does speak legions for you.

They will also prevent you from making the Number One mistake of start-ups, which normally occurs at this point – giving out Founders' stock to the Founders without an earn in. Since start-ups are generally planned by people who are still working for someone else, or are looking at multiple opportunities, it is quite likely that one or more members of the Founding team at the "virtual" stage will decide not to join the company, or may quickly move on. It is critical that the same amount of the company's stock not be held by people who aren't fully committed to the company as by those who have staked their future financial well being on the company's success. Therefore, it is a standard practice to make people earn-in their stock over 4 or 5 years. If they leave sooner than this, whether of their own volition of at the company's request, they forfeit the balance. This keeps them motivated, preserves fairness and prevents unnecessary dilution of the company's stock.

A good law firm start-up package will include things like employment contracts, confidentiality agreements, consulting agreements, board meeting minutes and corporate resolutions, in addition to the standard Certificate of Incorporation, By-Laws and Shareholders agreements and share certificates.

54.12.5 The Initial Funding

The Founders will normally buy their stock in the company at "Par Value", a purely nominal value that is printed on the share certificates and is typically 1¢ or oven 0.1¢ per share. So, if they decide to issue themselves 5,000,000 shares, they will contribute $5,000 at 0.1¢/share or $50,000 at 1¢/share, enough to pay the legal costs of incorporation, but no more.

The first "real" money that goes into the company and that will be used to start its operations can come from any one of a number of sources:

- Second mortgage/credit cards
- Bootstrapping – selling products and services
- Friends and family
- Angels or Angel Groups
- SBIR/STTR grants
- Corporate partnerships
- Venture capital

Table 54.6 Initial sources of funding for university spin-outs, FY 2004

	Number	%
Individuals		49.34%
Friends and family	94	20.52%
No external funding	57	12.45%
Individual angel(s)	49	10.70%
Angel network	26	5.68%
Institutional sources		44.54%
Venture capital	85	18.56%
State funding	36	7.86%
SBIR/STTR	32	6.99%
Corporate partner	25	5.46%
Institutional funding	26	5.68%
Other	28	6.10%
Total	458	100.00%

In 2004, the AUTM Survey asked respondents what the initial sources of funding for their spin-out companies were. The results are shown in Table 54.6.

It is clear that university spin-outs more frequently attract their initial funding from individuals than from institutional sources.

A more detailed source of these funding sources follows.

54.12.5.1 Second Mortage/Credit Cards

This is a classical method of starting a company, but probably doesn't have much relevance to a life sciences startup because of the total financing needs the company will have.

54.12.5.2 Bootstrapping

This is when a company has early sales opportunities – say selling reagents to the research market – and can use the revenues to fund developing its main products. Bootstrapping can reduce capital needs, but will rarely totally eliminate the need for investment sources.

54.12.5.3 Friends and Family

Also known as "friends, family and fools", this approach involves passing the hat round the more affluent members of the inventor's family, social and even professional circles. This can raise a significant amount of money, but comes with strings. As several inventors have observed to the author: "It does make for some tense Thanksgiving dinners" when the company hits the inevitable patch of turbulence.

If the company plans on raising later rounds of financing from institutional sources, it may find that they won't want to have a large number of small shareholders, and it may be

appropriate to have them invest by buying a membership interest in an LLC company, so that there would be a single voting entity representing all the investors in that round.

54.12.5.4 Angels or Angel Groups

Angel investors are rich individuals to whom the inventor is not related and who invest some or all of their wealth in young start-ups. They are generally people who have made their money themselves entrepreneurially rather than having inherited (when it is normally tied up in trusts and protected by zealous and very conservative trust attorneys).

Some Angel groups have a pooled fund and invest out of that, while others operate as meeting conveners and bring a number of Angels to a monthly breakfast or lunch meeting at which companies make presentations, and each individual investor decides if he/she wants to invest in a particular opportunity and, if so, how much.

The more highly developed a region is as an innovation hub, the more likely it is that there will be organized Angel groups operating. For instance, there are close to 20 organized Angel groups operating in Massachusetts.

54.12.5.5 SBIR/STTR grants

The Small Business Innovative Research Program and the Small Business Technology Transfer Research Programs [22] have been mainstays of the US economy for 30 years since the SBIR program was "test marketed" by the NSF starting in 1978 and expanded to all federal agencies in 1982.

They are Federal grant programs and so are a particularly attractive way to fund a company's development since they are nondilutive – the Government asks for nothing in return other than a commitment by the company to commercialize the research.

Currently, all Federal agencies with an external research budget of $100 million or more have to dedicate 2.5% of their budget for SBIR grants and 0.3% to STTR grants, so over $2.3 billion is available for these grants, a substantial pool of nondilutive investment funds. There are three solicitations a year and proposals are solicited for specific fields that the agency has established as a priority. The grant proposals are of limited length.

The Phase I awards are for $100,000 for six months and are intended to demonstrate feasibility of proof of principle. Phase I recipients are eligible to submit Phase II proposals, which are worth $750,000 over two years and are intended to carry out the project.

The PI of an SBIR must be employed at least 51% by the company at the time of the award (not the time of the submission, and the company must be able to demonstrate that it has adequate facilities to carry out the research. A collaboration with a university is not required, but upto 30% of a Phase I award and 50% of a Phase II award can be subcontracted to a university.

A STTR is by contrast at an earlier stage. It *requires* a collaboration with a university. At least 30% and as much as 60% of the work can be done at a university. The PI can be either at the university or at the small company.

54.12.5.6 Corporate Partnerships

It may be possible to fund the company's start-up and early stage development through a partnership with a larger company though it is highly likely that at the time the technology is transferred from the university, it will be at too early a stage and too low a probability of success to be attractive to a larger company and for this to be a viable approach. Corporate partnerships tend to be important later in the company's development.

54.12.5.7 Venture Capital

Venture capital funds are pools of funds invested by university endowments, very rich individuals, insurance companies, pension funds and so forth. These investors, who are known as Limited Partners, can afford to tie up their money for a long time in order to secure a superior rate of return. This is critical for venture capital funds because the fund will make investments in early stage, privately held companies and will most likely not be able to sell the investment for many years. Therefore, the Limited Partners typically are asked to invest their funds for ten years with no right to ask to be repaid.

Some companies have their own venture capital funds, but these tend to be more fickle investors. They rely on the parent company to make new funds available each year, and corporate venture funds are frequently throttled back in times of economic downturn when the parent's cash flow suffers.

The actual investments are made by General Partners. These are the people that the founders of the company will deal with. General Partners are generally people who have had a successful operating track record in large technology-based companies, or more likely in small venture-backed companies that the venture investors have made a lot of money in. A few grow from freshly minted Associates recruited fresh from their MBA's into partners, and a very few service providers such as lawyers have become successful venture capitalists.

The General Partners will normally draw 2.5% of the funds under management each year to operate the partnership – pay the rent, salaries, travel, legal expenses etc. This means that over the ten year life of the fund, 25% of the invested funds will go to operate the fund, and only 75% will actually be

invested in companies. In addition, when the fund makes a profit on an investment, the limited partners will first have their investment returned to them, and the General Partners will receive 20% of the net profits from that investment.

If a venture capital fund makes ten investments, it will expect to write off four (i.e., lose its entire investment), make a two or three times return on four, and a ten times or higher return on the final two. If you run the numbers, allowing for 25% of the fund going for operating expenses, and the General Partners getting 20% of the net profits on the successes, this will result in a 25–30% annual return to the Limited Partners. This will then allow the General Partners to go back to the same Limited Partners when they are starting to raise their next fund. Venture Capital is a very Darwinian business – their first objective is to successfully reproduce themselves!

The key conclusion from this analysis is that if you want to attract venture capital investment, you must be able to show that venture capitalist that if the company is a success, they will make 10× their investment. If you think it will take an investment of $20 million to launch your products, then you must be able to show the VC's that your company will be worth $200 million.

As Table 54.6 shows, venture capital is the second largest source of funding for university spin-outs, but is the initial source of funding less than 20% of the time. Most technologies are simply too untested when they're transferred out of the university to be ready for venture capital. This is particularly true in the case of drugs. VC's are generally going to be ready to invest in a new drug company only when the company is a year away from starting human clinical trials, and very few academic drug discoveries are that far along when federal funding runs out. The entrepreneur's challenge is going to be how to fund the gap between the expiration of federal funding and when the company is ready for venture capital. VC's are more likely to fund a start-up diagnostic or medical device company.

54.12.5.8 Who Gets How Much: The Capitalization ("Cap") Table

There are normally two types of stock in a start-up company:

Common stock

Preferred Stock

Common Stock

Common stock is generally a reward for effort or the provision of services in kind – the original "sweat equity". The founders will receive common stock, as will the management team for their future services and the university (whose investment of intellectual property in the new venture represents past effort).

Preferred Stock

Preferred stock is normally reserved for investors who pay cash for it. It's full name is generally Preferred, Redeemable, Convertible Stock.

Preferred means that the stock enjoys various preferences over common stock. Redeemable means that the investors can force the company to repay their investment under certain circumstances.

Convertible means it's convertible into Common stock under certain circumstances. The first round of investment will normally be called the Series A preferred, the second round of investment will be called the Series B Preferred, etc. Each successive round normally takes priority over the previous round if times get tough. (When time is good, everybody does well!)

Dividing Up the Founders Stock

This will undoubtedly be the subject of intense debate between the founders. One common philosophy is that the two equal components of a start-up company are the technology and the management team that's going to stake its financial security on this new venture. The technology is equally divided between the intellectual property, which the university owns, and the know-how, which is in the inventor's head, and which he can monetize by agreeing to consult exclusively for the new venture. This philosophy would result in a Founders' stock distribution of:

25% to the inventor

25% to the university

50% to the management team

Another philosophy has the university being another founder alongside the founding management team.

In yet another philosophy, the university will ask for a relatively small stake – say 5% – but that they be protected from dilution till a specified amount of investment capital has been raised by the company – say $5 million.

It is critically important that the management team's stock be earned in over typically four years. The management team share should include adequate provision for the additional employees who will need to be hired until the next financing.

The Investor's Stake

The investors will normally expect to get control of the company for their initial investment. The implication of this is that the company should not sell itself too cheaply. If you're going to have to give up half your company, then give it up for $5 million, not $1 million. Go out with an ambitious technical plan that requires $5 million to achieve. The VC's may balk at investing $5 million in an initial investment in a

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totally untried management team, and one way to finesse this calculation is to stage the release of the funds – say $1 million initially, to get the company to a certain technical achievement, with another $2 million released when that milestone is reached, and the final $2 million released when the company successfully achieves a second technical (or business) milestone.

The Next Round

The number of shares in the company will normally be adjusted (by splitting or reverse splitting) so that the price of the Series A stock is $1/share. If the company makes good progress, the Series B will hopefully be sold at a higher per share price – say $2/share or $3/share, perhaps even $5/share. This means that the company will give up less of itself proportionately to raise the next round of financing, and the value of the existing shareholders stake will grow, even though they won't be able to sell their stake and it will be a paper profit only.

If the company doesn't do well, then the next round may have to be sold at a lower per share price than the previous round. That's when things start to get ugly, and is beyond the scope of this chapter. Hopefully, it'll never happen to you.

What About the Seed Investors?

If the company raises a relatively small amount of money, from friends and family or Angel investors, the investment will probably be made not by a purchase of stock, but in the form of a loan secured by a note which is convertible into stock in the future. This has a number of advantages:

- The legal costs are much lower
- The value of the company can be set when a more substantial amount of money is raised from sophisticated investors a little later

The seed round investors are generally rewarded for investing early by converting their loan into stock at a lower per share price than the Series A investors – say at a 20% discount. So, if the Series A per share price is $1/share, then the seed round loan will be converted into stock at a price of $0.80/share, so they will receive 25% more share per dollar invested ~~as~~ the Series A investors.

Subsequent Rounds

The prior arguments will apply to subsequent rounds of financing, which will be labeled Series B, C, D, E etc. High tech companies will generally be expected to raise only A, B and C rounds and then to have achieved self sufficiency. Life sciences companied may need additional rounds of financing. Acusphere, an MIT spin-out developing in vivo diagnostics for cardiovascular conditions, went as far as a Series J before pulling off an IPO. Each round's investors will have priority over those in the prior round.

The Exit

At this stage, the company is still privately held, and there is no market for the stock. While the value of the company may have increased substantially, this is still all on paper, and neither management nor investors can actually sell their stock and realize any part of that value.

At the end of the day, being able to realize the value that has been created is what people will care about, and that is achieved through an exit.

There are only two possible exits that will put cash in founders', managements' and investors' pockets:

- Acquisition, for cash or for stock in a publically traded company, or
- An Initial Public Offering ("IPO") through which the company's shares are listed on a stock market, generally the NASDAQ.

Another exit mechanism is acquisition by or merger with another privately held company. This may help build value, but it will still be "paper profits" until one of the prior two events happens.

The acquisition route may seem more attractive, but venture capital investment terms and conditions, specifically "liquidation preferences" may skew distribution of the proceeds toward the investors and away from founders and management.

IPO's have become considerably more expensive and difficult to pull off since the passage of the Sarbanes–Oxley Act in the wake of the Enron debacle. The benefit of an IPO is that it allows for the stock price to increase after the IPO (and equally to decrease!). The negative is that the shareholders from the company's private days will be required to sign a lock-up agreement, in which they agree not to sell their stock for six months (12 months for European stock exchange IPO's). Most new companies founded currently are founded in the expectation that the exit will be by acquisition.

54.13 Case Study

54.13.1 CALM

Institution: McGill Univ. *Location:* Québec, Canada *Field of:* Obstetrics

Emily Hamilton, M.D., a McGill University obstetrics and gynecology professor, was teaching at Montreal's Jewish General Hospital when it occurred to her that doctors and nurses could better evaluate the progress of delivery if they knew how their patients were compared with others.

"Students were asking simple questions like, 'How do you know when labor is slow?'" Hamilton says. Doctors were relying on a small study of women conducted in the 1950s for information about delivering babies, yet a number of medical developments, such as epidurals, greatly influence the average length of labor. When Hamilton looked at the big picture, she saw that the power of computing combined with large-scale studies could tell physicians and nurses what comprised a normal labor for different women.

Her revelation occurred in the early 1990s, and today the Computer-Assisted Labor Monitoring, or CALM™, system is installed in numerous North American hospitals. Hamilton's studies show that the technology can reduce Cesarean sections. Fewer Cesareans mean less pain and quicker recuperation for women and less time required by surgeons. The CALM system tells medical personnel when a labor that appears long may, in fact, be progressing normally. After inputting information about the patient, a simple-to-read graph appears on the screen. The graph shows three lines: the woman's progression of labor, and the high and low limits of statistically normal progression, based on data from other women with similar clinical characteristics. Doctors can quickly and easily update the touch-sensitive screen.

In addition to her position on the McGill faculty, Hamilton now serves as vice president for medical research and scientific advisory board chair for LMS Medical Systems Ltd., which distributes and monitors CALM in North American facilities. The company is based in Montreal, and Hamilton continues to hire engineering and computer science graduates from McGill and Université de Montréal as the company expands. Read more at http://www.lmsmedical.com

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