

The view beyond venture capital

Dennis Ford & Barbara Nelsen

Fundraising is an integral part of almost every young biotech's business strategy, yet many entrepreneurs do not have a systematic approach for identifying and prioritizing potential investors—many of whom work outside of traditional venture capital.

Are you a researcher looking to start a new venture around a discovery made in your laboratory? Perhaps you have already raised some seed money from your friends and family and are now seeking funds to sustain and expand your startup. In the past, the next step on your road to commercialization would doubtless have been to seek funding from angels and venture capital funds; today, however, the environment for financing an early-stage life science venture looks strikingly different from that familiar landscape of past decades.

Following the economic downturns of 2008 and 2011, the profiles of those investing directly in biotech startups have changed; many traditional investors have curtailed their mandates and reduced their allocations to early-stage life science companies, and new types of investment entities have emerged in their stead. Entrepreneurs also have to come to grips with the shifting regulatory environment that defines how private capital is raised, who can serve as liaisons between entrepreneurs and investors and the type of individuals who can participate in financing a startup (**Box 1**).

If you are seeking funds for a startup, you need to be aware of the range of investors and investment vehicles available, as well as the pros and cons of each route. In this article, we provide a brief primer to help you navigate your path through the new investor landscape and find the right investment partners for your company.

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Why and how did the funding landscape change?

The big changes in the life science investor landscape start with the venture capitalist (VC). In the past, venture capital funds were typically capitalized by large institutional investors that consisted of pensions, endowments, foundations and large family offices with \$100 million to \$1 billion in capital under management. Traditionally, the majority of these institutions maintained a low-risk, low-return portfolio of stocks and bonds that offered predictable and stable returns. A few decades ago, fund managers adopted a strategy of putting a small portion of the assets under management into higher-risk, higher-return vehicles, such as hedge funds, private equity funds and venture capital funds. This generally worked well until the 2008 and 2011 economic downturns.

During the downturns, it quickly became apparent that entrusting capital to third-party alternative fund managers was no longer an effective strategy, and investors began to withdraw capital. The main reason for the withdrawal (especially from VCs in the early-stage life science space) was generally meager returns across the asset class; despite the high risk and long lockup periods that investors accepted in return for a promise of premium performance, VCs were often not returning any more capital than investors would have earned by making more liquid investments in the public small caps market. Returns from venture capital funds have not outperformed the public markets since the late 1990s (ref. 1). A second reason was that returns earned by investing in VCs were offset by substantial costs; fund managers typically charged a 2% management fee on the money they received. This of course is palatable

Box 1 State and federal fundraising regulations in flux

The US National Institutes of Health has redefined who can qualify for Small Business Innovation Research (SBIR) loans, opening the program up to companies who have venture capital investors, which was formerly a barrier to qualification. In addition, the passing of the Jumpstart Our Business Startups (JOBS) Act has added complexity to the regulatory environment surrounding financings, with Title II of the Act allowing companies to raise capital through general solicitation of accredited investors and Title III allowing companies to crowdfund equity investments from unaccredited investors. Federal and state laws have heavily enforced regulation on exactly who can invest—only those above a certain income and net worth can be deemed an accredited investor. Currently, these two new exceptions created by the JOBS Act cannot be used together as part of the same fundraising round, which leaves startup companies in a contradictory legal landscape.

In addition, the Financial Regulatory Authority and the Securities and Exchange Commission have clearly stipulated that any person or entity representing buyers and sellers of securities must be licensed to do so. As an aspiring entrepreneur in the life science arena, you will encounter a myriad of finders of capital, professional deal sourcers, third-party marketers, broker dealers and investment banks all aiming to connect you with capital. The important take-home message is *caveat emptor*, or buyer beware. The gray space surrounding the legal environment is in flux, and thus the viability of the entities involved in the raising of capital must be vetted and understood when entering into agreements.

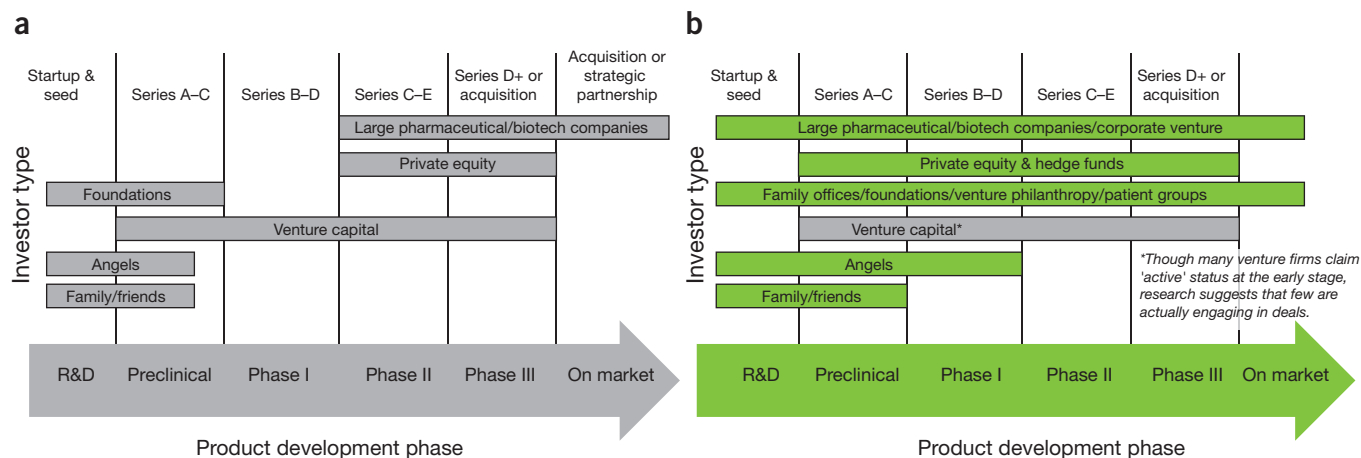


Figure 1 The life science investor landscape. (a) The traditional landscape. (b) What the new landscape looks like.

when a manager is returning great profits but is not such a strong proposition during a period of consistent losses. Yet another reason for the withdrawal, and the most troubling, was that a general lack of transparency and long lockup periods turned many funds into 'capital traps' from which investors could not withdraw and were unable to influence the decisions of the managers.

Many VCs failed to prove to institutional capital managers that they were capable of identifying and vetting winners in the life science sector despite being paid handsomely to do just that. That said, of course there remains a subset of early-stage VCs who consistently pick winners and have outperformed through these tough times, but these well-known firms are in a distinct minority. Lack of returns and steep management fees became a bone of contention that prompted a lot of institutional investors to withdraw their capital from the fund managers and instead do their own alternative investing. Thus, VCs lost a valuable funding source (a Kaufmann Foundation report details one institution's reflections on backing away from VC investments)² and, as a result, institutional investors and large single- and multi-family offices often do direct alternative investment—essentially, taking a similar percentage of their funds and investing in early-stage opportunities with the same potential for high returns but in which the institution maintains control rather than ceding oversight to a VC. These investments can occupy anywhere from 2–10% of their assets under management.

This change in tactical investment technique coincides with a growing trend for passion, philanthropic and social investment as part of an investor's criteria. This is especially so in the life science sector, in which the social impact of investment dollars can be huge. New, more engaged and informed investment vehicles such

as patient groups and philanthropic venture funds have entered the space formerly occupied by underperforming VCs.

Corporate pharmaceutical companies are also undergoing drastic strategic changes. Facing aging portfolios of on-the-market drugs and an impending patent cliff, big pharma must restock the pipeline with innovative assets, and many companies are turning to academic research collaborations, licensing, investment—through corporate venture capital—and mergers and acquisitions as an alternative to in-house R&D at the early stage. This cherry-picking strategy of plucking innovation emerging from academia has become a ubiquitous strategy among the top pharmaceutical firms globally. Big pharma not only offers a huge source of capital for early-stage companies but also provides access to distribution channels for the market, discovery and development expertise and many other resources.

In addition, across the space, many of the remaining active VCs, new virtual pharmaceutical firms (for example, Eli Lilly's Chorus Group, based in Indianapolis; Karolinska Development, based in Stockholm; Accelerator Corp., based in Seattle; Apple Tree Partners, based in Princeton, New Jersey; and Velocity Pharmaceutical Development, based in San Francisco) and mid-level private equity entities (for example, Hercules Technology Growth Capital, based in Palo Alto, California; Burrill & Co., based in San Francisco; Omnes Capital, based in Paris; and Auxo Management, based in Mississauga, Ontario, Canada) are executing a business model of buying assets low, developing them through early-stage clinical trials and then selling them high. These entities essentially institute a strategy of aggregating low-cost, early-stage assets around particular indications, outsourcing the clinical process and then developing or redefining channel

relationships that can create outsized returns. They aim to maximize capital efficiency and create a lean portfolio of high-quality assets primed for market entry.

Focused investor mandates versus opportunistic investors

Two investment strategies dominate in today's investor environment. One is based on using traditional market analysis and creating a structured mandate to invest in a particular sector's products and/or services. Typical considerations include determining which key indication areas or phases of development will bring the greatest return on investment. This type of 'deep dive' market analysis will consider major epidemiological, macroeconomic, demographic, regulatory and reimbursement shifts. The result is a so-called investment mandate. The investor has predetermined what sector, indication and stage of development they wish to pursue and formalized the resulting research data into a specific set of criteria for investment. Remember, investing in an early-stage venture means getting in for less capital and more risk, and these two factors are all part of the bet. The goal of any life science entrepreneur is to find an investor that is a fit. Matching an investment mandate with your company's offering is one tried-and-true way to be considered for funding.

On the other end of the spectrum are opportunistic investors—ones that do not limit their investment mandates to a particular sector or indication (for example, small molecule or gene therapy, or diabetes or oncology). Rather than betting on a specific technology, disease, development phase or service, an opportunistic investor wants to play in the entire life science arena, and they believe that creating a specific mandate would limit the rest of the market outside that mandate; they prefer to pick and choose anything interesting and exciting that surfaces.

This could be the latest groundbreaking medical device, a new dynamic therapeutic or a next-generation diagnostic capability; all are fair game to an opportunistic investor. Oftentimes, these are 'gut' investors who are driven by a belief in the technology and/or management team, and they make judgments on a one-off basis regarding whether or not to allocate.

This dual dynamic of specific mandate versus opportunistic investment strategy permeates all the categories of life science investors, and indeed each has its upsides and downsides. Because there are experts in both strategies with capital to invest, a fundraising entrepreneur must be aware of this dynamic.

You will hear opinions from all over the life science universe about how to find investors and create a dialog with them. Life Science Nation (LSN), based in Boston and for which Dennis Ford is CEO, distributes a weekly newsletter that covers and frames current perspectives on life science investment (<http://blog.lifesciencenation.com/>).

The investor landscape has changed, and the old and new categories of investors are morphing as the life science market changes and moves forward (Fig. 1). Let us take a fresh look at the current lineup of life science investors.

Getting started

Raising funds for a venture is a process not wholly unlike that of obtaining grants for

research. Not only do you need to identify and approach the right funding bodies (and ascertain that you are eligible and understand how much money is available) but also you need to appreciate what specific areas of research are 'hot', what the application guidelines are and how to tailor your application to best appeal to evaluators and showcase your research so you have the best chance of getting an award.

Beyond turning to the people who know you best and already have cause to believe in you (friends and family), the key to fundraising success is identifying the right pool of potential investors for you (Box 2). Some of these are traditional funders of early-stage ventures who will doubtless be familiar to you but whose attitudes toward investing are changing; others are new players in the space or new entities entirely.

Venture capital. Historically, venture capital has been a primary source of funding for startup and growth companies, but in recent years the life science space has witnessed a contraction of venture capital funds, with many active funds moving investments to later-stage companies. First-round funding has especially fallen off.

Data from the National Venture Capital Association in Arlington, Virginia, and media and information firm Thomson Reuters in New York show that in 2006, 294 first-round allocations were placed into life science companies, representing 23% of the total; by 2012,

the corresponding figures had decreased to 149 rounds and 12.8%. In fact, 2012 saw the lowest level of first-round venture capital financings of life science companies since 1995 (ref. 3). A recent evaluation of deals by the online newsletter *Xconomy* cites only 32 venture capital firms investing in early-stage life science companies in the past few years⁴. Financial database provider PitchBook, based in Seattle, recently published a report that documents the decline in volume of VC deals while showing that the median valuation of companies receiving venture capital funding has been rising⁵—a sure indication that VCs are backing away from risky early-stage projects and are instead putting their shrunken supply of dry powder into less risky, more developed companies.

One additional wrinkle on the early-stage investment landscape is that many venture capital firms, such as Atlas, Third Rock and Flagship, all based in Cambridge, Massachusetts, now create companies in-house and are not typically conduits for funding external startups. They rely heavily on their own internal networks of key opinion leaders and entrepreneur insiders for these ventures. Kevin Starr, a partner at Third Rock, said recently, "Last year, we saw 982 outside plans. We invested in zero"⁶.

The good news is that Third Rock and others are looking for transformative platforms and technologies to build new companies. If you are thinking of starting a company, you should

Box 2 A glossary of investors

Angels. High-net worth individuals usually with an interest in a particular type of product, service or industry. Many are successful entrepreneurs themselves.

Corporate venture capital. Large pharmaceutical and biotech companies' investment arms. For these strategic funds, investments are driven not only by financial returns but also by the development of relationships that could lead to future strategic collaborations and product opportunities.

Family and friends. These personal contacts typically provide capital for products that are in the earliest phase and are drawn to invest on account of a close connection to the founders of the company. As they are not professional investors and may lack familiarity with the life science industry, they may not have realistic expectations for the development of the venture. Using these personal bonds as a source of capital runs the risk of straining them.

Family offices and/or private wealth. Family offices and/or private wealth firms represent the collective estate and assets of ultra-high-net worth individuals. They have large amounts of capital, a sophisticated institutional approach toward investments and a long-term outlook, and many also have an interest in philanthropy.

Foundations, nonprofits and patient advocacy groups. Often grouped under the heading of venture philanthropy, these groups not only provide grants for basic academic research but also use

venture investing principles to speed the development of drugs in their areas of interest and return capital for the fund's future work. (For an inventory of these groups, see <http://train.fastercures.org/TRAINInventory/>).

Federal government. In the United States, federal funds are available from the Small Business Innovation Research Program (SBIR), the Small Business Technology Transfer Program (STTR) and the US National Institutes of Health, in addition to other government departments that have an interest in some specific life science projects, such as the Department of Defense or Department of Agriculture.

Regional economic development agencies. Economic development groups provide resources to start companies locally. These can take many forms such as job growth incentive tax credits, the Strategic Cash Fund Incentive, enterprise zone tax credits, local government initiatives, state college spin-out funds and venture capital funds seeded by regional governments. Visit your local and state economic development agencies to learn the variety of resources available to you.

Super angels. Large groups of angels that increase the effectiveness of angel dollars. These investors have organized themselves into regional or national networks to increase the size of their investment pool and develop new strategies.

Table 1 Venture and hybrid funds for institutional inventions and startups

Fund name	Website
5AM Venture Management	http://5amventures.com/
Allied Minds	http://www.alliedminds.com/
Atlas Venture	http://www.atlasventure.com/
BioMotiv	http://www.biomotiv.com/
Canaan Partners	http://www.canaan.com/
Connecticut Innovations	http://www.ctinnovations.com/
Domain Associates	http://domainvc.com/
Flagship Ventures	http://www.flagshipventures.com/
Illinois Ventures	http://www.illinoisventures.com/
Kleiner Perkins Caufield & Byers	http://www.kpcb.com/
Lilly Ventures	http://www.lillyventures.com/
Novartis Option Fund	http://www.venturefund.novartis.com/
Polaris Partners	http://www.polarispartners.com/
PureTech Ventures	http://www.puretechventures.com/
T1D Innovations	http://jdrf.org/
Third Rock Ventures	http://www.thirdrockventures.com/
Sofinnova Ventures	http://www.sofinnova.com/
State venture capital funds	http://www.treasury.gov/resource-center/sb-programs/Documents/VC%20Report.pdf
SV Life Sciences	http://www.svlisa.com/
Venrock	http://www.venrock.com/

consider developing relationships with these funds and their partners now. All have scientific advisory boards, and all use scientific domain experts to evaluate opportunities. Let them know who you are, your area of expertise and why you are interested in working with them.

Corporate venture capital. The corporate VC is distinct from a traditional VC on many levels. Corporate VCs are largely the product of profound shifts among large pharmaceutical and biotech companies. As mentioned previously, an aging marketable drug portfolio among the top pharmaceutical companies has led to a scramble for assets to feed dry pipelines. In the past, such pipeline gaps would be filled by the work of in-house pharmaceutical R&D, but in recent years this internal research has been cut from big pharma's budgets. Instead, companies have been finding it more cost effective to outsource the risks of early-stage research by acquiring emerging assets from third parties and by making use of virtual development services.

Entrepreneurs and scientific founders need to appreciate the distinction between corporate development and corporate venture. Corporate venture capital invests in companies developing breakthrough technologies that the firm believes have long-term disruptive potential; corporate development seeks to make tactical partnerships to fill near-term pipeline requirements by purchasing or licensing an asset. Because of this distinction, pharmaceutical companies often

provide several different funding sources for emerging companies. This fundamental business change is creating more opportunities for startups to engage with the pharmaceutical giants, which offers great possibilities for a new entrepreneur.

Recently, several pharmaceutical firms have launched innovative fund concepts targeting life science entrepreneurs. For example, both the Novartis Option Fund and the Boehringer Ingelheim Venture Fund, which recently opened in Cambridge, Massachusetts, provide seed capital to highly innovative ventures, and Lilly Ventures funds external molecule development⁷. More information about pharmaceutical venture funds specifically focused on university inventions and spin-outs is provided in **Table 1**, and information on databases can be found in **Box 3**.

Angels. In addition to family and friends, angels and 'super angels' typically provide capital for companies that are in the earliest phase. In 2012, angels invested a total of \$1.1 billion in 783 deals (primarily in first funding), with 27% of that invested in the healthcare and life science sector⁸. National chapters, syndications with other angel funds and single-source online application platforms (for example, <http://gust.com/>) have made it easier for a bioentrepreneur to gain access and visibility with angel investors. Angels are now part of larger investment pools and have the ability to execute sophisticated investment strategies and provide funding at higher levels than in the past, perhaps

participating in multiple rounds of financing. This makes these groups a viable form of financing your startup through an exit, depending on the capital needs and time horizon of your venture. The top ten groups in terms of activity are shown in **Table 2**. To find comprehensive information about angel investment funds, who and where they are, what they invest in and the best way to set up a meeting with them, visit the Angel Resource Institute website and the Angel Capital Association website.

Remember that you may be getting more than money when an angel fund invests in your company. An angel group can be a source of deep expertise and connections that provides more value in growing the company than the capital itself. Many life science angels are themselves successful entrepreneurs in the field and may offer you access to the resources and partnerships that supported their own success. You should put just as much effort into your business plan and investor pitch as you would when approaching a typical venture capital firm.

Government agencies. This is a very broad category ranging from funds within research institutions to local economic development initiatives to national and international entities. The level of Small Business Innovation Research (SBIR) funding is set to *grow* in the next year. If you have not already considered applying for SBIR or Small Business Technology Transfer (STTR) grants, you should do so immediately. A concise overview on how to apply for these funds was published in *Nature Biotechnology*⁹.

The US National Institutes of Health has many funding options available for entrepreneurs and young companies, particularly for those conducting clinical or translational research. The total dollar value awarded for clinical research at the NIH reached more than \$10 billion in 2012, and in 2013 it was larger than the total awarded to any other specific field or stage of research¹⁰. Eighty percent of National Institutes of Health funding opportunities are not part of the request-for-proposal process, so you will need to work directly with program directors to apply. This may seem daunting, but direct outreach to the agencies or to those who assist in developing nondilutive funding (for example, the FreeMind Group) is the best route¹¹.

Many local and regional government agency funds also exist for innovation and startups in the life science area. The most visible of these are in states, such as Massachusetts and California, that have mounted large initiatives to grow sectors of the life science industry. In Massachusetts, the \$1 billion Life Sciences Initiative provides funding in multiple

Box 3 Databases and other resources to start your search for investors

You will need to find the database providers producing the most relevant and up-to-date information to help you in your search for investors. In choosing a source, you will want to understand how the database aggregates information. Some of these vendors collect data by amassing publicly available content such as press releases. Others follow websites that cover licensing deals or financings that have been made public, or they consolidate articles from certain publications. The databases with the most up-to-date information leverage a team of researchers to collect data through one-on-one interviews with investors. The fresher the data, the more effective and efficient you can be in fundraising. To help start your search, we provide a list of starting points for a search in **Table 5** below.

Table 5 Advisors and/or database providers that can help your search for early-stage life science investors

Database	Website
Angel Capital Association	http://www.angelcapitalassociation.org/
Angel Resource Institute	http://www.angelresourceinstitute.org/
BioCentury	http://www.biocentury.com/
Biotechgate	http://www.biotechgate.com/
FasterCures	http://www.fastercures.org/
FreeMind	http://freemindconsultants.com/
Life Science Nation	http://lifesciencenation.com/
Massinvestor	http://www.massinvestor.com/
National Venture Capital Association	http://www.nvca.org/
Thomson Reuters	http://www.recap.com/

ways, including up to \$750,000 for new life science companies to help leverage additional sources of capital. The California Institute for Regenerative Medicine (CIRM), based in San Francisco, still has \$1.8 billion in unearmarked funds to invest in stem cell and regenerative medicine, and it funds companies at every stage provided they have a substantial presence in California. As with all funding sources discussed in this article, substantial research may be required to find these funds, identify their criteria for investment and determine how to apply for them. But it is well worth the time and energy; these groups are committed to the success of life science startups in their region and, in addition to funding, will offer you access to a wealth of local resources and industry expertise.

Do not be discouraged if you are not in a funding hub such as Massachusetts or California. The large number of angel funds, innovation centers and venture capital firms in these locations come with an equally high level of competition for these resources. For entrepreneurs outside of these clusters, there are many other government and economic development initiatives that can be tapped. These most often take the form of seed-stage investment funds whose mandate is to facilitate startup activity from local institutions (particularly state universities) and to recruit companies to the region by offering relocation grants and access to biocluster

facilities. Representative examples include Connecticut Innovations in Rocky Hill, Connecticut; the Kentucky Seed Fund in Louisville, Kentucky; the Maine Technology Institute in Brunswick, Maine; and Illinois Ventures in Chicago. Many such funds exist; in the United States, there are currently 36 state-run venture funds in 30 states¹². Economic development groups also provide resources to start companies locally. These can many forms, including convertible debt, equity investment, infrastructure support, shared resources and tax credits, refunds and incentives. Many states also encourage innovation by providing tax credits for angel investors. To date, 27 states provide such credits

(see <http://www.angelcapitalassociation.org/public-policy/existing-state-policy/>). Get more information from your local or state economic development agency about options available in your area. Do not underestimate their desire to keep you local and grow the local economy. We have seen cases in which economic development groups put together new funding mechanisms to keep break-through technology in-state for company formation.

New sources of funding for startups

With reduced resources and less appetite for risk, VCs are moving away from high-risk, early-stage companies. Fortunately for entrepreneurs, other classes of investors are coming to the fore to take advantage of the VC retreat. These include patient advocacy groups and foundations, big biotech and pharmaceutical companies, and venture philanthropists.

Table 3 represents the results of a search we did in the Life Science Nation investor database. The goal was to ask a simple yet compelling question: How many investors and what investor category are presently interested in investing in early-stage therapeutics from preclinical discovery all the way to phase 1 trials?

There are thousands of VCs globally. Of those that Life Science Network has researched or interviewed, 572 claim that they are investing in early stage life sciences. However, stated activity does not necessarily reflect actual activity, as published deal flow metrics do not support these claims on a total basis. It is common for investors to claim that they are active to 'stay in the game', even when they are not investing.

Patient advocacy groups and foundations.

Foundations, nonprofits and venture philanthropists have traditionally been more focused on funding academic research. Indeed, collectively these entities provide more than half a billion dollars in biomedical research grants

Table 2 Angels at work

2012 rank by number of deals	Group	Location
1	New York Angels	New York
2	Tech Coast Angels	Southern California
3	Launchpad Venture Group	Boston
4	Central Texas Angel Network	Austin, Texas
5	Golden Seeds	New York, Boston and San Francisco
6	Sand Hill Angels	Sunnyvale, California
7	Investors' Circle	National
8	Alliance of Angels	Seattle
9	Common Angels	Boston
10	Maine Angels	Portland, Maine

2013 Halo Report, Angel Resource Institute.

annually. Most such groups are focused on curing one specific disease, so qualifying for funding from them requires a clear connection between your innovation and their mission. Beyond the well-known groups, such as the Michael J. Fox Foundation in New York, the Juvenile Diabetes Research Foundation in New York, Susan G. Komen for the Cure in Dallas and the Leukemia and Lymphoma Society (LLS) in White Plains, New York, there are many less prominent nonprofits that also fund research, such as the Bluefield Project in San Francisco, which funds research on treatments and cures for frontotemporal dementia. Although these groups are historically best known for supporting academic research, the vast majority—90%—will now consider part-

nering with commercial biotech companies¹³. Partnerships can span all stages of research and development, from discovery through clinical trials. More than one-third of these entities have supported at least one clinical trial. Indeed, Todd Sherer, CEO of the Michael J. Fox Foundation has said, “We are definitely seeing the need for foundations to support companies even through a phase 2 clinical trial.”

LLS provides a clear example of how the work of foundations is changing. This foundation has been in existence for 60 years, but up until 6 years ago, it funded only academic or institutional research. When funding began to migrate away from early-stage, LLS's leadership decided to change direction. According to John Walter, the foundation's CEO, “We saw that venture

dollars were drying up in the blood cancer area, and there was insufficient funding going into preclinical and clinical research. So strategically, LLS made a shift to fund this gap.”

In this next fiscal year, close to 30% of LLS's funding allocation will be invested in new therapies and companies that are making a difference to patients. And this strategic shift also brings success to the companies in which LLS invests. Currently, LLS is actively shepherding 15 assets through its Therapy Acceleration Pipeline program, which seeks to bring blood cancer therapies to market. These assets range from preclinical to phase 3, and LLS has successfully brought several of its Therapy Acceleration Pipeline companies toward the market with great speed. This is accomplished by

Table 3 Active investors in seed/venture stage seeking discovery through phase I therapeutics

Disease area	Number of investments by type of investor (number of investors)										Total (1,447)
	Angel (83)	Venture capitalist (572)	Corporate venture capitalist (50)	Endowments/foundations (108)	Family office/private wealth (59)	Government organization (77)	Hedge fund (12)	Institutional alternative investor (54)	Big pharma/biotech (46)	Private equity (386)	
Neoplasms/cancer/oncology	29	136	26	42	17	37	2	22	19	63	393
Infectious and parasitic	37	176	26	21	18	35	3	9	15	51	391
Nervous system	26	165	29	29	15	37	1	18	18	52	390
Cardiovascular	29	158	30	16	9	26	1	14	13	59	355
Endocrine and metabolic	27	141	29	22	11	33	3	14	16	46	342
Blood and immune	28	149	27	18	10	24	1	14	16	38	325
Digestive system	20	115	20	7	9	21	1	8	8	36	245
Eye	16	121	18	6	10	18	0	6	11	32	238
Genitourinary system	20	115	16	6	9	17	0	6	13	34	236
Mental and behavioral	18	105	20	13	6	18	2	7	10	29	228
Congenital deformity and chromosomal defects	11	92	12	9	5	14	0	5	5	21	174
External causes morbidity and mortality	15	92	13	5	5	16	0	4	4	16	170
Ear	13	91	12	5	5	13	0	2	4	15	160
Prenatal	11	86	12	3	5	13	0	3	3	15	151
Respiratory	9	56	13	10	5	13	0	12	8	25	151
Musculoskeletal and connective tissue	11	33	8	12	2	11	1	13	8	18	117
Skin and subcutaneous tissue	6	40	4	7	2	9	0	11	7	21	107
Pain and inflammation	4	7	8	1	1	3	0	0	2	8	34
Physical injury/poisoning	0	10	2	1	0	6	0	1	3	5	28
Pregnancy, childbirth and puerperium	1	8	2	2	0	0	0	1	2	0	16
Opportunistic ^a	17	219	5	9	14	6	5	14	13	218	520

^aInvestors willing to consider diseases across areas. Source: Life Science Network investor database.

collaborative resource sharing, investment and creation of the right industry connections. One notable example was when LLS provided capital to Avila Therapeutics, which was based in Cambridge, Massachusetts, to initiate clinical trials of one lead candidate; Avila was subsequently acquired by Celgene, based in Summit, New Jersey, in 2012. Another example came when LLS also committed to provide up to \$7.5 million in milestone-based funding to Epizyme, based in Cambridge, Massachusetts, in 2011, which went to support a phase 1 trial for a mixed-lineage leukemia therapy.

These partnerships often focus on funding a specific project, such as a clinical trial, and may include milestone payments for development success; in the case of Onconova Therapeutics in Pennington, New Jersey, for example, LLS provided \$8 million in funding to pay for a phase 3 trial. Foundations also are providing money for seed funding enterprises; for example, Beats of Laughter in Westport, Connecticut, a foundation specializing in oncology, provides tranches of \$200,000 for seed investments; the Beyond Batten Disease Foundation in Austin, Texas, provides funding for ventures as well as research in academic institutions focusing on the neurological disorder; and Cures Within Reach in Skokie, Illinois, also offers funding (~\$100,000) for ventures focusing on unmet needs.

Applying to a nonprofit or foundation for a basic research grant in your area of study can be an effective way to gain visibility and credibility with the organization; building these early connections can be of great use for developing and funding a startup in the future. Much like the other organizations that you are accustomed to applying to for grant funding, these organizations will put out requests for proposals for basic research and translational development projects, and they have links and program coordinators listed and accessible through their websites. Many of these groups can be accessed through FasterCures, who has The Research Acceleration and Innovation Network (TRAIN), which lists profiles for 55 organizations that provide \$600 million in medical research grants annually. About half of TRAIN groups have supported at least one clinical trial, more than half incorporate advocacy efforts into their work in fighting disease and nearly 9 out of 10 partner with biotech and pharmaceutical companies. Foundations that are not able to provide you with financing may still wish to partner with you to share other resources (for example, access to their scientific expertise) and vital research resources (for example, tissue samples or registries of patients who may be able to participate in human clinical trials).

Big biotech and pharma. In the past, large pharmaceutical and biotech companies stayed away from investments in very early-stage companies because of the amount of risk involved. Any involvement in startup companies was through their corporate venture funds. Now, however, that is changing. Several firms are looking for opportunities to fund assets in earlier stage development, and many of the larger firms have decided that early-stage direct investment may be a viable alternative to spending funds on traditional in-house R&D.

One new avenue for big biotech involvement is the creation of incubators, such as New Brunswick, New Jersey-based Johnson & Johnson's Innovation Centers in California, Boston, London and Shanghai; Boston-based Boston Scientific's center in Shanghai; and Leverkusen, Germany-based Bayer's CoLaborator in San Francisco. These centers provide early-stage researchers with space, equipment, operations, business support, industry networks and conduits to strategic partnering. By working at an innovation center, a startup can enjoy a 'big-company advantage' that is more robust than what is offered by traditional, stand-alone incubators.

Family offices. These entities are entrusted with the money of wealthy individuals and families. There are two types of family office: single-family offices (SFOs), in which a group of financial professionals manages capital for one family, and multi-family offices (MFOs), which invest on behalf of a number of client families. As maintaining a family office is expensive, SFOs tend to be the preserve of only the wealthiest; typically, SFOs are only formed by families with a net worth exceeding \$100 million. These families are therefore often well known; they either own companies, such as Andersen Windows in Bayport, Minnesota; Jennie-O Turkey in Austin, Minnesota; and Hormel in Austin, Minnesota, or founded enterprises, such as Fidelity in Boston; Cargill in Minneapolis; and Carlson in Minnetonka, Minnesota. In addition to managing the vast fortunes of these families, family offices also perform other functions, such as generational planning, legal and tax services and preserving the family's legacy through philanthropic work; it is these additional functions that distinguish MFOs from other multi-client financial advisors or wealth managers.

In the past, family offices have invested in alternative assets, such as VCs and hedge funds as limited partners. But the poor returns from these funds have encouraged family offices to take more control of their own alternative investments. Some SFOs have formed family investment vehicles that invest as VC or private

equity funds but which do not accept outside capital; others see direct private placements as one of a diverse range of assets in which to place the family's wealth. Family offices have already played a role in early-stage life science investing, especially in Europe¹⁴.

Beyond the basic distinction between SFOs and MFOs, family offices can be highly varied. Some family offices combine investment and philanthropic goals, whereas others have formed family not-for-profit foundations that are administered separately from the family's wealth-preservation activities. A family office's philanthropic work will be directed by the personal goals of the family; within the life science sector, this may mean a focus on a disease that has affected the family or a high-impact area in which the family feels it can make a real difference in the world. Like other nonprofits in the life science space, family philanthropic foundations may have historically focused on basic research but are now supporting commercial research for much the same reasons; basic research takes a long time to deliver new treatments to patients, and wealthy families want to see the social impact of their investments in a shorter time frame. As with disease foundations, receiving an academic research grant from a family foundation may serve as a gateway to future startup funding.

Some family offices have created innovative business models to transition scientists' discoveries to commercial entities. One example is the Harrington Project in Cleveland, a \$250 million US initiative to support the discovery and development of therapeutic breakthroughs by physician scientists. Created by a family office, the Harrington Project starts with a grant-funding phase open to inventors nationwide for advancing discoveries through an innovation center that supplies hands-on resources and expertise. Then inventions and platforms are moved to an accelerator, BioMotiv, to create companies.

Family offices have a reputation for elusiveness and secrecy, but LSN has discovered that this is ultimately misleading. As with other types of investor, LSN researchers call family offices and conduct interviews regarding their investment criteria. These one-on-one interviews result in written mandates approved by the family office, and companies that use LSN as a fundraising partner can vet themselves against these mandates to assess whether they are a good fit for the family office's criteria.

Like many investors, family offices often have a 'keep below the radar' mentality, as financial confidentiality and protecting proprietary strategies are of great importance to investors (perhaps more so to SFOs than

to many firms because their investors are so easily identifiable and have a distinct need for privacy). However, all investment entities need some visibility to attain deal flow. A typical family office might receive a hundred blind e-mails or cold calls a week, and because many of these solicitations are poorly matched to the office, they create a lot of needless noise and wasted time. One way family offices filter their deals is to use trusted networks, such as LSN, which provide a flow of suitable opportunities that fit the firm's mandate. Being a perfect fit can be worth more than getting a direct referral, as a referral that is a poor fit is still a waste of a family office investor's time.

More about seed funds

BioMotiv, the aforementioned institutional startup seed fund, is one of the many new funds and funding models that have arisen to address the funding gap for early-stage technologies. Some funds, such as Allied Minds in Boston, appear on the surface to be fairly traditional venture capital firms. But they have an unusual mandate—in this fund's case, commercializing early-stage, government-owned technologies to create startup companies from innovations in US universities and federal research institutions.

Another example is T1D Innovations. Recently created through a partnership between the Juvenile Diabetes Research Foundation and PureTech Ventures in Cambridge, Massachusetts, T1D is focused on finding promising, transformational ideas in the area of type 1 diabetes from research institutes and developing them from concept to company. Beyond the specific therapeutic mission, T1D's 'syndicate now' strategy is unique; the fund has attracted \$30 million in funding from other nonprofits and strategic and financial investors and will use the cash to start eight to ten projects. For those projects that survive to become new spin-out companies, T1D hopes that these companies will go on to find a pharmaceutical partner to help further develop their programs, or land a series A round from traditional venture investors to get themselves off the ground.

Internal or external outbound direct canvassing

There is a risk that academics and early-stage entrepreneurs will be drawn into a Wild West of business coaches, mentors, accelerator programs and venture centers that broadcast a flood of 'expert fundraising advice' either from advisors who have not raised money themselves lately or from consultants and mentors who have not ever actually raised capital. The reality of outbound campaigns and 9–12-month fundraising roadshows is

Table 4 Budgeting for an outbound fundraising campaign

	Required commitment	
	Time required	Estimated cost
Developing marketing materials and content		
Executive summary, two pages (professionally advised)	30–40 h	\$1,000–\$5,000
Pitchbook Powerpoint presentation, 10–12 pages (professionally advised)	80–100 h	\$5,000–\$10,000
Website (professionally built)	200–250 h	\$6,000–\$15,000
Investor database		
Quality investor database ^a	–	\$7,000–\$10,000
List and task management application (for example, http://salesforce.com/)	–	\$50–\$250
E-mail delivery, tracking and reporting application (for example, iContact)	–	\$100–\$600
Content-developing application (for example, Wordpress)	–	Typically free
Ongoing e-mail canvassing	40 h	Salary dependent
Ongoing phone canvassing	150 h	Salary dependent
Roadshow (9–12 months)		
Travel, food and hotels (regional campaign)	–	\$40,000–\$50,000
Travel, food and hotels (global campaign)	–	\$60,000–\$80,000
TOTAL COST	–	\$60,000–\$120,000 (plus salary)

^aA quality investor database should provide about 5,000 global investors across 10 categories, allowing you to filter down to a target list of 300–500 investors that are a fit for your offering.

unknown to these advisors, and they may waste a new entrepreneur's time by perpetrating myths and promoting strategies from an outdated playbook. There are plenty of third-party fundraising entities that have updated, relevant experience and are indeed good. The good ones have strong connections and a current Rolodex, but their reach is often regional; the best have a global investor network.

As an early-stage entrepreneur, you have to make a fundamental judgment call as to whether you should conduct business development and investor outreach activities in-house using your existing management team or hire one or more experienced fundraisers to do it for you (**Box 1**). If you decide it is not something your team can usefully put their time toward, the alternative is to outsource the process to a third-party fundraising partner. It is essentially a matter of matching commitment and ability and knowing what you can and cannot do. If you cannot make outbound calls and send engaging e-mails to strangers, then you need to partner with someone who can.

It costs money to raise money. Creating effective marketing materials, conducting a targeted campaign and following up on funding leads demands both a time and financial commitment, and fundraising therefore requires that you have the necessary dedication right from the start.

To raise money effectively you must think strategically. The place to start is to think

about the major expenses in a money-raising campaign (**Table 4**).

Devising a strategy

Given the challenges and opportunities that this article has outlined, how should bioentrepreneurs prioritize the options potentially available for funding their new enterprises? A closer look at just a few companies who raised money in the past year shows a mix of traditional and new investors participating in a single deal (**Fig. 2**). A review of deals this past year in California and Massachusetts, the two states with the greatest amount of investment in life science, demonstrates the broad variety of these funding alternatives in addition to traditional venture capital. You should thus consider them all.

Initially, the stage of development of your enterprise is a key filter in helping to identify the types of investors that would likely be a fit. Having identified investors compatible with your stage of company development, you should then target those whose market focus and key investment criteria fit with your firm's goals and profile. Are you addressing an unmet need for a particular patient population? Does your innovation solve a problem that is relevant to the military or veterans? The answers to questions like these will help you identify which of the various sources of capital described above—angel funds, foundations, nonprofits or corporate venture funds—are most likely to provide funding to you. Almost all investors have a particular focus, and identifying those

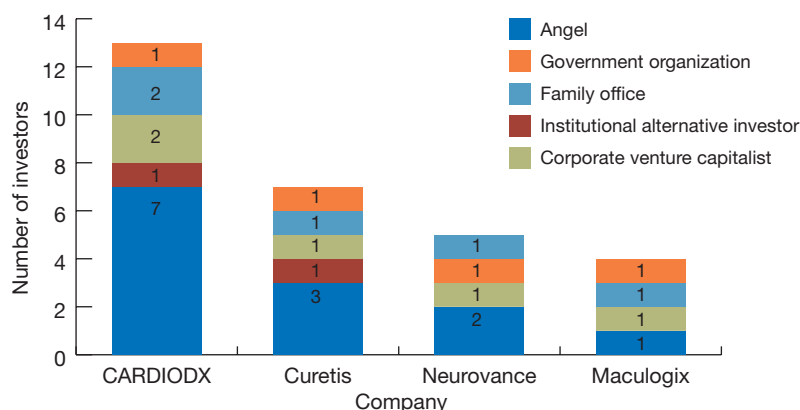


Figure 2 Examples of investor diversity in fundraising for early-stage life science companies. Data from deals closed in the last 12 months.

that match your company will improve your fundraising chances.

Lastly, do not forget geography. Are any investors a walk, car ride or short plane trip away? This may seem an obvious approach from a logistics perspective, but there are multiple reasons to look locally. Investors need to be courted over long periods of time. Proximity makes this easier, particularly when you are engaging with smaller investment groups that have more limited footprints; most angel networks invest only in a particular locality.

It is worth considering not only your present capital needs but also your company's projected future needs. If you are developing a drug or a medical device, your company will need as much as tens of millions of dollars of external funding from several capital raises spread across a span of years before attaining a revenue stream. It is never too soon to think about what your company will need further down the line. Establishing a dialog with later-stage investors early and visiting often streamlines the financing of the organization over time, reducing the amount of effort and resources required for further rounds over the organizational life cycle.

Attempting to identify the appropriate investors to contact now and in the future can be a challenging endeavor, but there are many database services that provide information on the variety of investors available (Box 3 and Table 5). These services can aid you in developing an outreach strategy tailored to your profile, position and objectives.

Conclusions

The fundraising landscape for early-stage life science companies has changed dramatically over the past several years. Venture capitalists may not always be the first, or even the most attractive, category of investor for your company. Entrepreneurs and young com-

panies need to look toward new, emerging categories of investors to provide the funding that was historically provided by venture capital. Corporate venture funds, angels and angel networks, government agencies, foundations, patient advocacy nonprofits, family offices and hybrid funds are all actively investing in this sector.

This pace of change in the investment landscape now requires, more than ever, that entrepreneurs be nimble, informed and flexible. Creating a target list of investors that includes the newly emerging sources of capital, and focusing on those with a clear fit and strong interest in the company's stage and business, will increase the probability of fundraising success.

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First Rounders Podcast:

Harvey Berger

Berger was the principal founder of Ariad and has served as its chairman and CEO for more than 20 years. Trained initially as a physician, he spent time at Centocor before starting up Ariad out of his home. *Nature Biotechnology* spoke to him about developing Iclusig, the difference between managing a patient's health and running a company, and how a public entity deals with bad news. <http://www.nature.com/nbt/podcast/index.html>

