Innovation and Entrepreneurship

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Securing Early-Stage Funding for Retinal Innovations

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In the first 2 articles of the *Retina Times* Innovation and Entrepreneurship section, we discussed how to secure your intellectual property (IP), define your business model, assemble your team, and develop a quality management system (QMS). Here, we discuss fund raising for your idea.

We asked retina specialist and entrepreneur Firas Rahhal, MD, to assemble a group of experts and lead a roundtable discussion on early funding for retinal innovations. Our panel includes 2 seasoned inventor/entrepreneurs with a unique university perspective, a successful pharmaceutical start-up company chief executive officer (CEO), and a co-founder and partner of a venture capital (VC) firm specializing in biotechnology.

Many of the great innovations in ophthalmology originated in the university setting. What are your thoughts on potential sources of early-stage funding for university-based inventions?

Mark Humayun: Federal, state, and philanthropic funding sources are all typical, but they take a long time and often involve multiple application cycles, especially if the idea and program are revolutionary.

Mark Blumenkranz: For university-based innovators, grants and gifts are an excellent source of funding to enable filing of patents and initial work on proof of concept (POC).

> 'For university-based innovators, grants and gifts are an excellent source of funding to enable filing of patents and initial work on proof of concept.'
> —Mark S. Blumenkranz, MD, MMS

For independent innovators, typically friends and family are the best sources of capital, although Small Business Innovation Research (SBIR) grants are available to all comers and are awarded competitively based on the strength of the application including preliminary work, resources, and likelihood of success.

In certain areas of the country, there are increasing numbers of individual or group angel investors and investor clubs that look for interesting ideas to back—but they typically provide small funding and come with a fair amount of baggage. It would be unusual for venture funds, private equity funds, or strategic players to fund initial de-risking studies until there had been some reduction to practice or other POC, patent application, or actual invention, even if not animal or human studies.

How aggressively should early-stage innovators pursue non-dilutive funding sources?

Mark Blumenkranz: Non-dilutive funding sources are always worth trying—particularly grants and gifts where available—but usually because those prospects take time and are uncertain, many innovators either fund the initial costs or work through family and friends to get seed funding if they are not based in a university with access to grants and gifts.

Mark Humayun: Non-dilutive funding has its obvious advantages, but not at the expense of prolonging the development timeline.

Panelists

Mark S. Blumenkranz, MD, MMS
H.J. Smead Professor and Chairman Emeritus
Byers Eye Institute at Stanford
Founder and Managing Director
Lagunita Biosciences
Chairman and CEO
Kedalion Therapeutics
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Mark S. Humayun, MD, PhD, FASRS
Cornelius J. Pings Chair in Biomedical Sciences
Professor of Ophthalmology, Biomedical Engineering, and Integrative Anatomical Sciences
Director, USC Ginsburg Institute for Biomedical Therapeutics
Co-director, USC Roski Eye Institute
Keck School of Medicine University of Southern California
Los Angeles, California

Michael O'Rourke, BSc (Hons)
Chief Executive Officer
Re-Vana Therapeutics, Inc
Tampa, Florida and Belfast, Northern Ireland

Is intellectual property (IP) one use of these earliest funds?

Mark Humayun: Actually, these early funds are used primarily for research and development because most universities have a budget, albeit limited, to file provisional patent applications and in some instances even utility patents. However, most universities will not file the IP in many countries outside United States, if any, unless there is interest from a for-profit entity.

Mark Blumenkranz: Yes, IP is one of the absolute necessities, unless it is a method patent, in which case it may not be worth it because they are hard to get and even harder to enforce.

Stella Robertson, PhD
Co-founder and Partner
Bios Equity Partners, LP
Fort Worth, Texas

When is the right time to attempt to obtain outside/private funding?

Mark Blumenkranz: The right time to seek outside funding is when you have convinced yourself that the idea has real merit, it passes the other tests I outlined earlier, and you need to reduce the idea to practice and/or demonstrate POC but lack the funds to do it yourself.

Mark Humayun: The best time to pursue outside funding is when the product is ready to enter clinical trials and requires Food and Drug Administration (FDA) approval in the form of an investigational device exemption (IDE) or investigational new drug (IND) application. Universities, for the most part, like to have companies hold the IND and IDE and sponsor the clinical research.

> 'The best time to pursue outside funding is when the product is ready to enter clinical trials and requires FDA approval …'
> —Mark S. Humayun, MD, PhD, FASRS

Also, this phase requires considerably more funding and a development team—eg, contract research organization (CRO), regulatory experts, manufacturing and quality systems—that universities don't have.

When is the right time to incorporate and "spin out" a company? Initially, should it be virtual, ie, a legal entity, but not yet having a physical plant or (likely) full-time employees?

Mark Humayun: This can vary but usually if the idea is novel, it is hard to license it outright to an existing strategic partner/company; it requires development and de-risking in early clinical trials—hence the need for a "spin-out" or start-up company. Ideally, the company can start out virtually, but many funding sources such as VC like to see management in place above and beyond the technical team. The facilities and engineering for the most part can be outsourced during this initial phase.

Mark Blumenkranz: Almost all companies, especially those led by first-time or less-experienced entrepreneurs, start out virtually. Innovators might move straight to a traditional C or S corporation if a body of existing, substantial IP is involved, and they believe they have access to capital based on their track record, preclinical trials, or the strength of the IP.

Generally, the more work you can outsource to CROs at the beginning, even if you have a university lab, the better, since it will be trusted more by potential investors and you will encounter fewer conflict-of-interest issues.

Should tech transfer be on board right from the beginning?

Mark Blumenkranz: The most important challenge is managing conflicts of interest. Most university tech transfer offices prefer to license IP to smaller organizations formed for the express purpose of commercializing the technology and IP rather than larger organizations that have less commitment and motivation. The tech transfer office should be approached initially because sometimes or even often, they feel the proposed IP will not be as valuable as the inventor feels it will be.

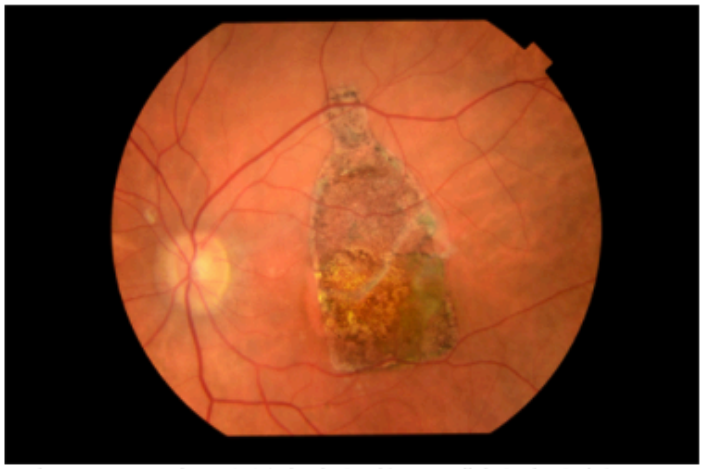
It is always important, though, for the inventor to share the proposed IP with the university because in most instances, if the work was done utilizing any other-than-incidental university resources, the idea (and resulting IP) is by default the property of the university, not the inventor. However, the inventor has some economic rights determined by the policies of the university, guided by the provisions of the Bayh-Dole Act (the Patent and Trademark Law Amendments Act).

If an idea generated and at least partially de-risked at the university, were subsequently commercialized outside the university without their knowledge or economic participation proactively, there could be serious negative consequences for the inventor.

Mark Humayun: Tech transfer from the university varies to some extent by the university; some university tech transfer agreements can be problematic—eg, in the restrictions on sublicensing. The university's tech transfer office needs to be engaged when you want a license, and that is the best time to engage them.

Michael, when is the right time for a new company, let's say a university spin-out, to start building a management team?

Michael O'Rourke: One mistake many university entrepreneurs make is starting the company too soon, leading to early failure due to a lack of planning and resources. Working early with the university is critical. Explore all ways the university can support the start-up, eg, IP support and cost deferment, lab space and equipment at favorable rates, post-doc PhD support, and networking with local investors.



Mark Humayun, MD, PhD, FASRS, is developing this stem cell-derived retinal pigment epithelial sheet implant with Regenerative Patch Technologies—one example of an advanced retinal implant developed in academia and transferred to industry. The implant now is in early clinical trials. From Kashani AH, Lebkowski JS, Rahhal FM, et al. A bioengineered retinal pigment epithelial monolayer for advanced, dry age-related macular degeneration. Sci Transl Med. 2018;10(435):eaao4097. doi:10.1126/scitranslmed.aao4097 Reprinted with permission from the American Association of the Advancement of Science.

From Kashani AH, Lebkowski JS, Rahhal FM, et al. A bioengineered retinal pigment epithelial monolayer for advanced, dry age-related macular degeneration. *Sci Transl Med.* 2018;10(435):eaao4097. doi:10.1126/scitranslmed.aao4097
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Ideally, a licensing agreement between the start-up company and the university will be an important step in this process. It is critical to negotiate an agreement that will be foundational to the start-up's long-term success. If improperly negotiated, the terms can adversely impact financing, third-party agreements, strategic collaborations, profitability, and acquisitions.

There may be legal requirements to incorporate the company, establish founders' equity and confidentiality agreements, and complete other foundational operating steps. Significant planning and market due diligence will be required before any management team outside the core founders can be employed. In addition, some level of capital will have to be raised or at least committed; this might be a convertible loan note before hiring a CEO to lead the company, generally regarded as the first critical management hire.

Beyond friends-and-family financing, most investors would expect a CEO and initial business plan in place covering all of the above before committing capital. In general, a follow-up round of seed capital may be required before the team can be expanded.

Start-ups and spin-outs are, of course, low on funds initially, "boot-strapping," so what are the minimal managerial needs to get the project moving forward in these early phases? How much of this can be done by part-time consultants?

Michael O'Rourke: The project will gain momentum when the product proposition is defined with early POC demonstrated, perhaps with in vitro data and key opinion leader support if applicable. Competitive advantages need to be confirmed, IP filed, and in the case of a university spin-out, a licensing agreement sealed. Some initial friends-and-family or university investment may be required to achieve these steps.

With most start-ups, cash flow can be challenging. Grant money, payments from third-party agreements, or other forms of financing often set up inconsistent cash flow. It is best to minimize the company's risk by keeping the team virtual for as long as possible. Thus, hiring consultants is a key strategy to turn work and expenses on and off as needed during times of unpredictable cash flow.

Part-time or full-time consultants can play a significant part in the early (and late) stages of the company. Often equity, if established, could be offered to offset capital expenditure in whole or in part. Consultants could have a role in providing expertise on business plan preparation, strategic planning, accounting, market dynamics, and regulatory issues— as well as Chemistry, Manufacturing and Control (CMC) planning, networking within the industry for an early review of collaborations, or introductions to VCs or other seed investors.

Stella, what earlier-stage funding would you like to see for a project before you become involved?

Stella Robertson: For VC firms, the type and amount of earlier-stage funding is not as important as the quality of the science and the management team. We have seeded a few companies from inception, and have invested in others funded by friends, family, and angel or prior VC investment ranging from about $1 million to $10 million.

Our firm considers the prior funding sources indicative of past and future investor interest. We primarily participate in seed and series A funding with our initial investments, and mainly invest in companies located in the central United States.

How important is early non-dilutive funding, or is that no longer relevant by the time VC would be interested or involved?

Stella Robertson: Non-dilutive funding, such as grants and awards, is highly relevant to VC investors when they are looking at an opportunity or throughout the lifetime of the investment. Non-dilutive funding provides validating evidence for the science and medical need of the opportunity, supports the financial health of the company, and is attractive to investors because it makes their overall investment stretch further to achieve the development goals.

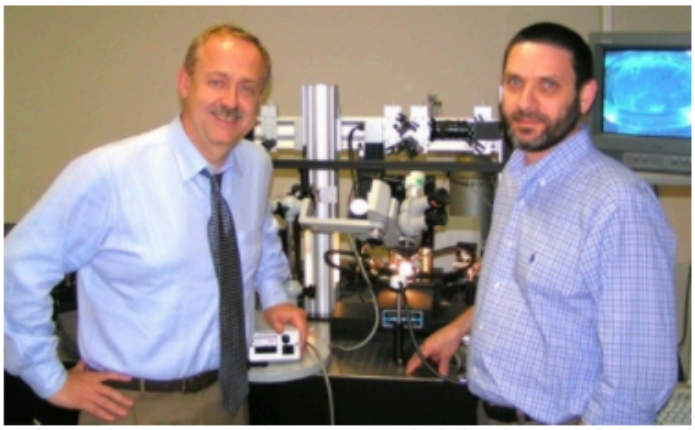
Where in the corporate maturation process should the company be, at a minimum? Is there a specific management structure you prefer to see in place prior to an investment?

Stella Robertson: Management needs, at a minimum, to demonstrate that they are passionate about the project, can think strategically, execute a plan, budget and track finances, and help raise funds. Some VC firms may be willing to work with first-time CEOs and founders to help them build out their corporate structure. An early-stage company should have at least a CEO, chief scientific officer (CSO) or chief operating officer (COO), and comptroller or certified public accountant services.

Michael, how much of this early management needs to be—or should be—done by the innovator/founder/scientist?

Michael O'Rourke: The very early work will inevitably lie on the innovator's doorstep on the assumption it's their own original idea. This role is not for the fainthearted due to the required time commitment. Support may be available; perhaps members of the innovator's scientific team could contribute, though confidentiality provisions would have to be in place.

Founders will, however, need to surround themselves with some trusted advisors with start-up experience to help wade through the myriad issues that have to be managed and planned in the early stages. Often, universities will provide assistance through interns and in-house CEO mentoring programs.



Mark Blumenkranz, MD, MMS, and co-inventor Daniel Palanker, PhD, MSc, with the earliest benchtop version of what eventually became CATALYS, the first femtosecond laser developed for cataract treatment, produced by Optimedica Corporation.

Image courtesy Mark Blumenkranz, MD, MMS.

How difficult—and how common—is it to have to reduce (diplomatically) a founder or innovator's managerial role and duties?

Michael O'Rourke: It is often challenging for founders to cede control of the company; the research has been an important part of their lives. Trusting an individual whom they do not know to ensure the success of their technology is not a simple process. Finding a successor can also be difficult. Being a CEO involves a significantly different set of responsibilities than leading a lab.

Once the founder has expressed the desire to transition the management role to a third party (CEO), networking with people the founder respects and trust is an excellent starting point. When the right person has been identified, the founder's mind-set needs to change from that of a creator to an enabler to assure and support the successor. This is a critical step; many start-ups have failed early due to animosity or lack of a productive working relationship between the founder and external CEO and/or other key external team members.

As the start-up develops and capital is raised, inevitably there comes a point when the new CEO takes overall leadership of the company or, for example, a new head of research and development joins and adopts many of the roles previously held by the founder.

Normally, the founder should welcome this step as a demonstration of company progress; however, challenges will arise, eg, when there's a disconnect on development strategy. It's critical to agree on a working relationship early with clearly defined roles, titles, and responsibilities. The new management team must work *with*, not *around* the founder.

The founder rightly will expect to remain involved, even at a distance, and to be part of the new board and/or scientific advisory team. He or she will expect equity and potentially monetary compensation, so a formal legal consulting agreement should be developed. There needs to be respect and flexibility on all fronts so when challenges arise, they are worked through succinctly and professionally.

In the event of a capital raise, the founder's equity ownership may decrease, and that often will require an explanation. New, less-experienced academic founders may struggle initially to grasp the nuances of VC, so the CEO should take the time to explain outcomes so there are minimal surprises. Any obvious signs of conflict with a founder are sure to deter investors.

Stella, how active a role do most VC firms take in the management process?

Stella Robertson: VC firms often become active investment partners with one or more board seats, depending on the type or size of the investment. They typically do not serve in the day-to-day company management.

Rather, VC firms work closely with certain portfolio companies to cultivate their success—help them solve problems, evaluate opportunities, find and screen personnel, vet their capitalization table, and meet their strategic and financing objectives. The goal is to help companies identify other capital partners and create meaningful exits, providing a return on investment to all stakeholders and allowing product development to continue toward commercialization.

What other management personnel would you like to have on board, if any?

Michael O'Rourke: Each company is unique, of course, but beyond the internal development team of scientists, it's valuable to appoint several key consultants with experience in raising capital, preclinical and CMC experience, an accountant for financial management, IP attorney with relevant industry knowledge (eg, ocular drug delivery), and a legal contact. It also can be of great value to appoint a world-class scientific advisory board with equity compensation.

Stella, where in the scientific development plan does a project need to be, ie, what milestones need to have been reached, for VC to have serious interest? Is this different for a therapeutic vs a device, and for a biologic vs a small-molecule therapeutic?

Stella Robertson: Each VC firm has different requirements for investment; many will seriously look at projects at the preclinical or early clinical stage. The project needs to have in vitro and in vivo preclinical evidence related to mechanism of action, POC efficacy and safety, and ideally, be within 12 to 18 months of the IND or IDE. Other VC firms invest only in phase 2 or later clinical-stage projects.

For a small-molecule drug or a biologic therapeutic, VC firms expect some pharmacokinetics and distribution data, and CMC data supporting how the therapeutic will be made, delivered, and stored. Well-organized laboratory reports are encouraged; Good Laboratory Practices (GLP) and Good Manufacturing Practices (GMP) data are not required, but obviously de-risk a project.

For a device, a working prototype, POC studies, early safety data, and initial manufacturing concepts are expected. Completion of phase 1 or initial clinical POC studies enhances VC interest in both therapeutics and devices.

How long does the due diligence process usually take for a final affirmative decision on an investment?

Stella Robertson: Diligence usually takes 4 to 6 months from initial conversations to investments. Some companies such as ours invest in less than 2% of the deals we receive. It is common to follow very early-stage projects for a year or more prior to initiating formal due diligence.

There is often an underlying fear—if not paranoia—among innovators, that VCs will "take over" the project and dismiss the important input of founders at some point. I have not found this to be the case.

What has been your experience in the collaborative process between VCs and founders? Are there any differences in how the collaborative process plays out in different stages of development?

Stella Robertson: We have heard this fear and paranoia among innovators and have not found it to be the case. Our experience is that the best outcomes result from a collaborative process between VCs and founders. We aim to cultivate collaboration based on mutual respect, trust, and transparency.

The hardest thing for founders, or anyone highly invested in an idea, is the realization that the skill sets needed for success change as the company grows. For instance, basic science is paramount early on, but as the company grows and must follow a regulated development plan, more emphasis must be found for operations—applied science and clinical, regulatory, investor relations, and fundraising skills. Because budgets get very large, much time is spent on operational financial management.

We see that the most successful founders know their own strengths and likes, and hire others with complementary or alternate skill sets. Sometimes that means at some point, the founder, if a scientist, decides to become the CSO and/or stay in academics or in the clinic, and hire a CEO, or COO and chief business officer (CBO), to manage the operations and fundraising.

The toughest period for funding is somewhere between seed/"friends and family" rounds and series A. What is your advice to founders/CEOs regarding raising capital in this stage?

Mark Humayun: Raise the right amount to get to the next value inflection point. Work with investors with whom you have good chemistry and who truly understand, want to advance the program, and can invest in follow-up fundraising rounds.

rounds.

Stella Robertson: We advise founders and CEOs to raise and take the money they need, from as many investors as reasonable. This shares the risk, and having more than one person or group as investors in a company makes for a stronger investor base. This is especially important for pharmaceuticals or biologics, which are expensive to develop ($30 million to $50 million or more, to clinical phase 2), and may require multiple rounds of financing.

Mark Blumenkranz: Yes, the period between seed funding and series A is the so-called valley of death for companies. A number of people have identified this as a serious unmet need in the venture and pre-venture ecosystem, but it is particularly risky since we know that the number of companies that progress from phase 1 studies to successful phase 3—let alone only preclinical studies—is unfortunately very low.

One might overgeneralize by saying that strategic players with strong balance sheets would prefer to overpay for a fully de-risked asset than to take a chance on an earlier-stage asset that doesn't pan out and becomes a total loss, as well as an embarrassment to the company.

The one caveat more recently, with the frothy public markets hungry for biotech, is that a number of companies not yet ready for acquisition were able to take advantage of investor appetites and go public prior to full POC and commercial viability.

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Dr. Blumenkranz – BEAVER-VISITEC INTERNATIONAL: Board of Directors, Stockholder, Salary; COMBANGIO CORPORATION: Founder, Board of Directors, Stockholder, Stock; IVERIC BIO: Board of Directors, Stockholder, Salary, Stock Options; JELLISEE OPHTHALMICS, INC: Consultant, Stock Options; KEDALION THERAPEUTICS: Founder, Board of Directors, Employee, Stockholder, Salary, Stock; LAGUNITA BIOSCIENCES: Founder, Board of Directors, Employee, Stockholder, Salary, Stock; ONE MEDICAL: Board of Directors, Stockholder, Salary, Stock Options; VERANA HEALTH: Founder, Board of Directors, Stockholder, Stock; XYENCE: Board of Directors, No Compensation Received.

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