

How to Start a Biotech Company in the Longevity Industry

by Reason; <https://www.fightaging.org>

v2 - 06/01/2020

Contents

Executive Summary

Introduction

- Steps to Starting a Biotech Company in the Longevity Industry

- Aging is Damage, Rejuvenation is Damage Repair

- The State of the Longevity Industry in 2020

Meeting the Longevity Community

- Conferences

- Companies and Entrepreneurs

Selecting a Project for Your Biotech Startup

- Understand the Root Causes of Aging

- Read About the Science of Longevity

- Talk to the People Who Know of the Best Projects

- A Few Example Projects

Notes on Starting a Biotech Company

- Find a Mentor or Incubator

- Obtain a CMO Consultant to Teach You the FDA Process

- How Much Does Development Cost?

- Expectations on Raising Venture Funding

- Hire Scientists Early and Establish a Lab Early

- The Level of Specific Scientific Expertise Required is Greater than You Think

- Put the Therapy Into Mice Before You are Ready

- Delay the Scientific Advisory Board, as Indication Choice is Difficult

- Biotechnology is Slow and Prone to Delay

- The Literature is Frequently Wrong - Always Replicate First

- It is Protocols All the Way Down: Setup is the Cost

In Conclusion

Executive Summary

You are an entrepreneur who wishes to start a longevity industry biotech startup, but your experience to date is in a different industry. This document is an initial primer and guide to help you get started.

New classes of therapy, targeting the mechanisms of aging, have the potential to prevent and

reverse all age-related disease, and greatly extend healthy human lifespan.

The first rejuvenation therapies are already under clinical development in numerous startup companies.

This new longevity industry is growing exceptionally rapidly. Venture funding for longevity startups is increasing enormously year over year.

Yet there are far too few entrepreneurs and new startups in comparison to the available funding. Your arrival will be welcomed: this is a friendly, and close-knit community.

Introduction

You are entrepreneurial. You have heard the buzz about the new longevity industry: the rapid growth in funding, the numerous billionaires becoming involved, the new approaches to medicine that are targeting the mechanisms of aging to prevent and reverse the diseases and frailty of old age. You want to get involved, to start a company, to do something about aging ... to change the world for the better.

But how? Whatever your past industry, here you must be the business cofounder. Life science and its application to biotechnology is a vast, complex, intimidating field. Aging is its own highly specialized portion of that field. You need an understanding sufficient to identify a project to work on; you need a scientific cofounder; you need to know the investors and the movers and shakers. Where to even start?

This document is a starting point. We hope that it helps.

Steps to Starting a Biotech Company in the Longevity Industry

- 1) Understand at a high level the present view of what aging is and why it happens.
- 2) Meet the longevity community: entrepreneurs, investors, advocates, and scientists.
- 3) Learn more of the details of present classes of intervention in aging, improve your understanding of the science and the state of the industry.
- 4) Consult with experts in the field in order to determine which of the many possible projects to carry forward to clinical development.
- 5) Make the necessary partnerships, launch your company, raise seed funding, and get to work!

Aging is Damage, Rejuvenation is Damage Repair

Aging is nothing more than the accumulation of a few classes of molecular damage to cells and

tissues: some broken genes, some waste products of metabolism, some errant cells and their harmful behavior. Biology is ferociously complex, however, and that simple damage spirals out into chains of interacting causes and consequences, leading to exceptionally complicated modes of failure. We call those modes of failure “age-related disease”. Heart failure, Alzheimer’s disease, chronic kidney disease - while radically different, these ultimately fatal age-related conditions all emerge from the same few forms of underlying damage.

It doesn’t matter how complicated aging becomes. What matters is the simplicity of the root causes. Treating aging effectively means reversing or bypassing those root causes, the comparatively simple molecular damage, not the end results of that damage. It means repairing the damage. Sufficiently effective repair will produce rejuvenation as a consequence.

The root causes of aging are outlined in more detail later in this document. Understanding them is an important part of assessing potential projects for a biotech startup in the longevity industry, as not all potential interventions in aging are created equal. Not all produce repair of the damage that causes aging, and those that do not will be less effective, less likely to succeed in clinical trials.

The State of the Longevity Industry in 2020

The biotech industry is less affected than most by the market and logistical consequences of the COVID-19 pandemic. Preclinical startups in particular just keep working through market downturns and disruptive events, and are largely only impacted to the degree that they need to raise funding. Progress continues apace.

Senolytic therapies that remove senescent cells are leading the field, with perhaps a dozen biotech startups working on some form of senescent cell clearance. Senolytics have produced robust results, meaning actual rejuvenation, in mice. The first human trials have been completed with promising results, and more are in progress.

While senolytics are legitimately a form of rejuvenation, capable of reversing one of the causes of aging even at a very late stage, other technologies under active development, such as mitochondrial antioxidants, mTOR inhibitors, NAD+ enhancers, and so forth, are essentially compensatory, attempts to make the aged metabolism more resilient to underlying damage, or override some of its reaction to damage, without actually repairing that damage.

Venture funds are rapidly turning to support the longevity industry. Several \$100 million or larger funds and business development companies are dedicated to the longevity industry, such as Juvenescence, Life Biosciences, and the Longevity Vision Fund, all created in the past three years. More are being assembled, their progress in raising funds only somewhat slowed by the COVID-19 pandemic. Many existing biotech and technology funds are becoming involved. It is also the case that sizable numbers of angels and high net worth individuals have a personal interest in the treatment of aging and are investing in biotech startups focused on aging.

Perhaps 50 to 100 biotech companies and startups are carrying out work that may lead to a form of rejuvenation, or at least is arguably relevant to the treatment of aging, or is otherwise focused on interventions that target the mechanisms of aging. Near all of these companies are at most a few years old, in preclinical development or in early trials, and Big Pharma has yet to become earnestly involved in the longevity industry. The first approved therapies and the next step up in funding still lies ahead.

Politically, researchers and advocates continue to pressure the FDA to permit clinical trials for aging, and in particular the prevention of aging, rather than individual age-related diseases. The TAME metformin trial, for example, will be conducted purely as a demonstration that such trials can be organized. In that case, the FDA has agreed to conduct the trial with endpoints that represent aging. Others will follow in time.

Meeting the Longevity Community

The first step in understanding the longevity industry, and where you might fit in, is to meet the people: scientists, company founders, investors, and thought leaders. The best way to do that is to attend the conferences, particularly the newer conference series that are set up to have a healthy mix of science and business interests participating. Many of these conferences explicitly exist to help advance the field, particularly in the matter of connecting entrepreneurs and investors with scientific projects.

The second step is to talk to the highly networked nodes in the community, both on the research side and the business side of the house: the individuals who know everyone, have built large networks, and can help you to meet the people that will be most helpful to your projects. Finding these people is quite straightforward - all paths into the community lead to them.

Conferences

A great many scientific conferences are focused on aging, but the best conferences to attend when first entering the community are those in which there is a balance between business and science, and which are careful to open the doors only to legitimate science. It remains the case that the fraudulent anti-aging industry runs its own pseudo-scientific conferences - which can be confusing, since legitimate companies, advocates, and scientists often attend and present, in an effort to try to drive out the bad old fraudulent ventures, and replace it with the new, legitimate approaches to targeting the mechanisms of aging.

The following conferences are recommended as a starting point.

Ending Age-Related Disease

The Life Extension Advocacy Foundation puts on the excellent Ending Age-Related Disease series in New York each year. The attendance is biased towards preclinical startups, scientists with projects ready to make the leap to startups, and some of the core community investors and advocates.

<https://www.leafscience.org/ending-age-related-diseases-advances-in-aging-research-and-investment-prospects-2019/>

Longevity Therapeutics

The Longevity Therapeutics series consists of smaller business-focused conferences. The attendees are a good mix of people central to the early years of the longevity industry, and you are likely to make helpful connections here.

<https://longevity-therapeutics.com/>

Longevity Leaders Congress

The Longevity Leaders conference is distinguished by the presence of Big Pharma and large insurance concerns, alongside scientists and entrepreneurs in the longevity industry. It is a meeting of minds, a part of the efforts to sway the deepest pockets into both participating and an understanding of what lies ahead.

<https://www.lsxleaders.com/longevity-leaders-congress>

Undoing Aging

The Undoing Aging series is the latest evolution of a decade of conferences put on by the SENS Research Foundation, now in collaboration with the Forever Healthy Foundation, in recent years becoming much more focused in assisting the hand off of research programs from academia to industry. As such, the conferences see a lot of investor interest, and are a great place for new entrepreneurs to meet people.

<https://www.undoing-aging.org/>

Companies and Entrepreneurs

The Aging Biotech Info Resource

Karl Pflieger is an angel investor and philanthropic supporter of rejuvenation research who maintains a database of companies in the longevity industry. He adds notes on how far along they are, whether they are relevant to the SENS rejuvenation research goals, and some other useful facts. This is published as Aging Biotech Info:

<http://agingbiotech.info>

The Core of the Longevity Industry Entrepreneurial Community

The core of the longevity industry is that focused on rejuvenation after the SENS model, or at least companies that emerged from the advocacy and research communities closely associated

with the Methuselah Foundation and SENS Research Foundation. The companies noted here are a selection from a longer list, picked because the founders and executives are helpful, welcoming to newcomers, and well worth talking to.

Covalent Bioscience

Founded by Sudhir Paul and Richard Massey, Covalent works on catalytic antibodies capable of efficiently removing metabolic waste such as the amyloids that drive the onset of age-related disease.

Cleara Biotech

Founded by Peter de Keizer, Tobias Madl, and Marco Demaria, Cleara develops senolytics based on interference in the FOXO4-p53 pathway.

Ichor Therapeutics

Led by Kelsey Moody, Ichor heads a collection of spin-off companies working on senolytics, removal of metabolic waste via enzymes derived from bacteria, and a range of infrastructure projects.

Leucadia Therapeutics

Founded by Doug Ethell, Leucadia Therapeutics is focused on restored drainage of cerebrospinal fluid in old individuals as a way to clear out metabolic waste that contributes to neurodegenerative conditions.

Oisin Biotechnologies

Led by Matt Scholz, John Lewis, and Gary Hudson, Oisin Biotechnologies develops a senolytic suicide gene therapy. The spin-off OncoSenX applies this technology to cancer.

OneSkin Technologies

Led by Carolina Oliviera, OneSkin is taking the cosmetics regulatory path to commercialization of senolytic small molecules.

Repair Biotechnologies

Founded by Bill Cherman and Reason, Repair Biotechnologies works on reversal of thymic involution in order to restore immune function in old individuals, and an approach to prevention and reversal of atherosclerosis.

Underdog Pharmaceuticals

Led by Matthew O'Conner and Mike Kope, Underdog is a spin-out of the SENS Research Foundation, focused on prevention and reversal of atherosclerosis via targeting 7-ketocholesterol.

Selecting a Project for Your Biotech Startup

The field of gerontology, the study of aging, is unusual in the life sciences in that translational research, meaning work aimed at the production of therapies, was actively suppressed for much of the last 50 years by leaders in the scientific community. Researchers studied aging, but did not attempt to intervene. This was a response to the existence of the anti-aging marketplace of fraud, supplements, and false promises, and greatly delayed progress towards the treatment of aging. Yet this has left the research community littered with promising projects, dormant or little worked upon, with great potential. All they wait for is a champion.

Understand the Root Causes of Aging

Not all projects are created equal, of course. Thus it is important to have a framework that allows evaluation of the potential for any given project to actually have a sizable effect on aging.

The causes of aging are outlined in the SENS rejuvenation research proposals, first established in 2002 and presently shepherded by the scientists of the SENS Research Foundation. We should pay attention to this definition of aging: the initial authors of SENS were, for example, the first to propose that senescent cells are a significant cause of aging, ten years prior to general acceptance of this point by the broader research community, and fifteen years prior to the launch of the senolytics industry focused on selective removal of senescent cells.

In the SENS view of aging, the following forms of damage are important and lie at the root of aging. When looking at potential therapies for aging, always ask whether or not they are moving the needle for any of these fundamental causes of aging. Is a given project actually repairing or meaningfully bypassing a specific root cause of aging? If it is not, then the odds of producing results for patients are much reduced.

Cell Loss and Tissue Atrophy

Some tissues steadily lose cells that are not replenished and thus progressively fail in their functions with advancing age, such as the heart and areas of the brain.

Cancerous Cells

Mutations and other haphazard alterations to our nuclear DNA occur throughout life, raising the risk of suffering just the right combination of mutations somewhere in the body that creates a cancerous cell, one that replicates uncontrollably to form tumors.

Mitochondrial Mutations

Our mitochondrial DNA lies outside the cell nucleus and thus accumulates damage more readily than nuclear DNA. This impairs its critical functions and leads to the creation of a small but significant population of dysfunctional cells scattered throughout the body, which cause harmful disruption to tissues and processes.

Extracellular Matrix Stiffening

Some of the proteins outside our cells, such as those vital to artery walls and skin elasticity, are created early in our life and never recycled or recycled very slowly. These long-lived proteins are susceptible to chemical reactions called cross-links that glue them together or otherwise degrade their effectiveness.

Death Resistant Cells

Senescent cells are those that have suffered damage or reached the evolved limits on cell division and shut down. They should be destroyed by the immune system or by their own self-destruction programs, but over the years they nonetheless accumulate where they are not wanted, such as in the joints. Senescent cells degrade the surrounding tissue integrity and also release harmful signals that raise the odds of nearby cells becoming senescent.

Extracellular Aggregates

As we age, a small handful of different proteins misfold and accumulate outside cells in clumps and fibrils known as amyloid. These are associated with many age-related conditions, such as Alzheimer's disease, but it is not yet fully understood how they cause harm.

Intracellular Aggregates

A few forms of hardy waste product build up within long-lived cells, such as those of the nervous system, impairing cellular housekeeping functions and ultimately preventing a cell from doing its job or causing it to malfunction.

Read About the Science of Longevity

As you become familiar with the longevity industry, take up the habit of reading popular science digests of work on aging and longevity. Work up to reading the actual papers. Then start searching for papers yourself. This takes practice, but you will have to learn enough to hold your own when talking to scientists. A few sources are suggested here.

Fight Aging!

Fight Aging! presents a daily selection of commentary on relevant new research in the field of aging and longevity.

<https://www.fightaging.org>

Life Extension Advocacy Foundation

The Life Extension Advocacy Foundation blog publishes interviews, conference proceedings, and commentary on recent new scientific publications in the field of aging and longevity.

<https://www.leafscience.org/blog/>

PubMed

The PubMed database offers a searchable interface to all published medical research papers. Search for “aging OR longevity” and sort by recent publications to view the feed on a regular basis.

<https://www.ncbi.nlm.nih.gov/pubmed/?term=aging+OR+longevity>

Talk to the People Who Know of the Best Projects

The only reason that matters have changed in the field of aging research is the work of advocates, philanthropists, and non-profits since the turn of the century. A great many of the people involved are very familiar with the field and the projects that they would like to see advanced, and have spent considerable effort in pulling in funding over the years.

Thus there is the hard way to develop an idea for a biotech startup in the longevity field: spend years reading the research and attending the conferences, becoming familiar enough with the science, and the scientists, in order to identify and understand the potential of specific projects, and pick one. Then there is the easy way: just ask one of the existing advocates who has already done all of this and has thus gained a good familiarity with the projects that should be carried forward, but are not. Many of these advocates are very interested in connecting entrepreneurs with scientists in order to ensure that those projects are in fact developed. A few suggestions are offered below.

Aubrey de Grey (SENS Research Foundation)

In the years since he first published the outline of the SENS proposals for the development of rejuvenation therapies, de Grey and his collaborators have built an impressive network of scientists and scientific projects. The SENS Research Foundation leadership have a very good idea as to the most relevant work presently taking place, or blocked, or awaiting an entrepreneur to carry it forward.

<https://www.sens.org>

Reason (Fight Aging!)

After fifteen years of patient advocacy for longevity, and publishing daily reports on new scientific papers in the field, Reason has seen a long, long list of intriguing research projects that have yet to be carried forward into clinical development.

<https://www.fightaging.org>

Kelsey Moody (Ichor Therapeutics)

Kelsey Moody is an enthusiastic advocate for the participation of more entrepreneurs in the longevity industry. His company, Ichor Therapeutics, spins off a large number of projects, but there are many more waiting than either he or indeed anyone else in the present industry can

undertake.

<https://ichortherapeutics.com/>

A Few Example Projects

The projects and categories noted represent just a few starting points to explore, out of the many possible, as a way to become familiar with thinking about the field and its potential. Many of the people noted in this document can elaborate or offer further pointers on these approaches.

Mining Bacteria for Enzymes to Break Down Age-Related Molecular Waste

A number of companies are developing drugs based on bacterial enzymes with the aim of breaking down harmful age-related metabolic waste such as glucosepane cross-links or components of lipofuscin. For cross-links, Revel Pharmaceuticals is a spinout from the Spiegel Lab at Yale, for example, while LysoClear is developing Methuselah Foundation and SENS Research Foundation funded work on clearing lipofuscin. There are many targets in the category of “harmful age-related metabolic waste”, however, far more than are presently being addressed by development programs. Mining soil and ocean bacteria for enzymes capable of digesting specific target molecules is arguably a more efficient approach to drug discovery than the standard screening of libraries; it is still quite new, but there are researchers with the necessary skills out there.

Champion the DRACO Project

DRACO (double-stranded RNA activated caspase oligomerizer) is a potentially revolutionary approach to dealing with untreatable viral infections. It works by killing cells before the virus can use them to replicate. A range of persistent viral infections are of interest in the progression of aging, in the context of Alzheimer’s or simply in immunosenescence. Unfortunately, as is the case for so very many promising projects, DRACO has not yet found a champion to carry it into clinical translation.

Delivery of Whole Mitochondria or Mitochondrial DNA to Aged Tissues

Mitochondrial decline is important in aging. A range of approaches are under development to improve mitochondrial function in old individuals, of widely varying quality and size of effect. These include selective destruction of damaged mitochondrial DNA, allotopic expression of mitochondrial genes to provide a backup of the proteins necessary for function, partial reprogramming of cells in situ to cause aggressive clearance of worn mitochondria, and delivery of NAD⁺ precursors. One class of approach yet to make it into clinical translation is the delivery of whole mitochondria or mitochondrial DNA in large volumes to a tissue. There are many examples of this in the literature, so plenty of researchers to talk to on the topic.

Deliver Senolytics to the Masses

Senolytic therapies such as the dasatinib and quercetin combination are proven to work in humans, capable of removing senescent cells and turning back measures of aging, with more data arriving each year from ongoing trials. These initial and readily available drugs and supplements should have sizeable beneficial effects. Yet they are not easily enough available to the tens of millions of ordinary individuals who might benefit. There is a gap in the market for a physician network and logistics company to provide senolytics in the same way as many other drugs are provided off-label, but at much greater scale, to every older individual.

Champion an ALT Inhibitor Project

The ultimate cure for cancer involves suppression of telomere lengthening; without this any and all cancers wither and die. They depend on it, they cannot work around it. Telomeres are lengthened by telomerase and alternative lengthening of telomeres (ALT) mechanisms. A number of research groups are working on sabotage of telomerase, but no-one is championing work on ALT inhibition at the present time, despite the fact that it is relevant in 10% of cancers, and is arguably an easier mechanism to target since it doesn't operate in normal cells.

Upregulation of LAMP2A in the Liver

The liver is a comparatively easy target for gene therapies that aim to upregulate expression of specific genes. Some years ago, LAMP2A upregulation was shown to produce quite profound reversal of decline in liver function in aged mice, via restoration of autophagy. Like so many promising projects, it has not been developed further than the initial demonstration, and awaits funding and interest.

Notes on Starting a Biotech Company

Medical biotechnology is a heavily regulated field, and as such the development path of a biotech company is quite unlike that observed in most other industries. It is important to get a handle on these differences as early as possible.

Find a Mentor or Incubator

The practicalities of running a medical biotechnology company are sufficiently different from other types of business that it is essential to find a good mentor or biotech incubator willing to teach the ropes. Incubation can take the form of joint venture deals or investment by existing companies in the space, and doesn't have to be limited to formal incubators, which are largely not specialized or particularly knowledgeable about the longevity industry.

Many of the existing startups in the longevity industry have gone through some kind of incubation process, and so talking to other entrepreneurs is probably the best way to understand the available options here.

Obtain a CMO Consultant to Teach You the FDA Process

The FDA process is very well documented at the high level. However the reality of the process is hard to discern from that documentation. The undocumented details and interpretation of rules matter greatly and thus the map is not the territory. Early in the process of preclinical development, engage a Chief Medical Office (CMO) consultant and have that individual explain exactly how engagement with the FDA works in practice, what the company must do in order to prepare, and the emphasis to place on particular projects and programs.

One item, for example, is that manufacture of the therapy is perhaps the most important, all-consuming, expensive aspect of early clinical development and trials. It is the part of the development process that receives the greatest amount of attention from regulators. It is of vital importance to be able to manufacture a therapy to a very high standard of consistency and safety, to prove that this is being done, and to satisfy regulators that there will never be shortages after approval - that all prescriptions will be filled. That very high standard and large burden of compliance requires a great deal of time and funding to ensure.

How Much Does Development Cost?

a) Preclinical development, and getting ready for the pre-trial engagement with regulators: design the overall development plan, rigorously develop the manufacturing process and implement the animal studies for initial safety assessment and other scientific building blocks such as mechanism of action and drug exposure. The doses in the animal models are much higher and exposure much larger than will be given to people and thus provide a safety margin. Costs depend on many factors, including whether the drug in development is a chemical or biological drug, the duration of intended treatment and number of patients dosed for instance. This initial work can easily cost \$4-10 million, of which about half goes to the manufacturing.

b) Phase I trials: the purpose is to establish safety in a limited number of people (first in man and thus limited exposure of number of individuals) and obtain a baseline set of mainly safety data across escalating doses. Expect at least \$2.5-6 million for the trial alone, and then an additional \$2.5-7 million for ongoing support and all of the other work necessary to run the development team and activities in a company.

c) Phase II trials: the purpose of phase II is to 1) expand the safety database on recipients of the study drug and to start understanding how the trial endpoints are changed due to exposure to the study drug, meaning the specific measurements of the disease needed to prove safety and effectiveness, and 2) obtain information on the optimal dosage. It takes often at least 300 patients to obtain a rigorous set of data for these items. Much depends on the magnitude of the difference in an endpoint between treated and control participants. This builds the necessary data to design a Phase III. Often multiple Phase II studies are needed. This will cost \$10-20 million for a single Phase II trial, and expect the average pharmaceutical company to spend another \$15 million or more on ongoing operations and related costs. The leap in cost between Phase I and Phase II is why many companies are acquired, go public, or enter into joint ventures with Big Pharma entities following Phase I.

d) Phase III trials: the purpose of Phase III is to determine the treatment benefit to a specific population. It also provides most of the safety data. Two such trials are typically needed, and these are the big, expensive, high-publicity projects. The cost will often run \$25-50 million for the trial alone.

Expectations on Raising Venture Funding

The dominant venture funding model in the broader biotech industry is one in which a single, usually institutional, investor makes a sizable early investment, (hopefully) sufficient to fund development from licensed drug candidate to IND application with the FDA, and owns a large fraction of the company. In some cases the investing entity actively selects the research and creates the company. The longevity industry at its outset from 2015 onwards was barely institutional, however: angels and high net worth individuals, more interested in funding therapies to treat aging than in making returns, outweighed the few funds. Further, much of the initial wave of the longevity industry was centered on the West Coast (home of tech investing) rather than East Coast (home of biotech investing).

This has meant that, unlike much of the rest of the biotech industry, there are many more companies in the longevity industry funded in a tech industry fashion during the first few years of work: a trajectory of pre-seed and seed rounds dominated by angels, followed by an institutional A round once there is sufficient success in development to carry out the work to prepare an IND application. As of 2019 this may be changing, as newly formed venture funds and business development companies dedicated to the longevity industry are tending to adopt the biotech investment strategy of a sizable early investment and owning most of the company as a result. Nonetheless, these two approaches to venture funding exist, and are in tension with one another.

Starting down one road largely precludes switching to the other, though a number of companies in the space have adopted some variant of the following strategy: start with the tech funding approach for a parent startup, run two or more development programs, and spin off those programs as they mature into wholly owned subsidiaries that are funded via the biotech model. This is very similar to the process of setting up and funding joint ventures between companies.

Whether it is easier at the outset to raise funds for a company in the tech model or the biotech model is very much a function of connections. If connected to angels and high net worth individuals in the longevity community, then the tech model is easier. Given good connections to those funds dedicated to the community, it may be easier to use the biotech model. There are advantages and disadvantages to both. The biotech model provides far greater support to the company from an established fund or other institutional entity, but will also leave entrepreneurs with lesser ownership stakes at the end of the day. If coming into this industry from the outside, then work to build connections with both the funds and the angel communities; leave the options open while settling on a project to carry forward.

Hire Scientists Early and Establish a Lab Early

A biotech company usually starts with the idea phase. Most of the work there is a matter of validation, involving a great deal of reading, searching the literature for related projects, reaching out to scientists in the field, engaging lawyers to investigate the patent landscape, and other items unrelated to laboratory work. Once that is done, it is definitely a good idea to hire a scientist or two prior to engaging one or more contract research organizations (CROs) to carry out early stage laboratory work. Effectively managing the relationship with a CRO, particularly when projects have a high chance of failure due to unknown factors, really does require a scientist with a deep knowledge of the details.

Non-scientific biotech startup founders usually have enough life science knowledge to be a danger to themselves. By this is meant that they can read scientific papers and set strategic direction, but these skills are far removed from the hands-on experience needed to lead teams of scientists and lab technicians. The fine details at the interface of theory and praxis are important. But that point is all too easy to forget in the enthusiasm of the moment. There is the temptation to set forth and rapidly engage a CRO with the idea that the CRO staff can provide the scientific knowledge needed for the early proof of concept stages ... and this is where founders get themselves into trouble. This just doesn't work, while all along the way to the inevitable failure it seems plausible to a non-scientist that it can work. It is very likely that all of the funds assigned to a CRO in this scenario will be wasted.

Projects undertaken with a CRO can be high friction when, as is often the case in startups, the goal is a moving target or there is little in the literature that can be used as guidance when any particular protocol or study or experiment fails. There are any number of smaller projects, such as quick cell studies, or the optimization of a finicky assay, that are an exercise in frustration to run via a CRO, even a small and responsive one. Turnaround will be slow, and it may be quite hard to gain enough access to staff and inner workings at the CRO in order to fully understand why a specific small task is not proceeding as expected.

Thus all CRO relationships must involve a scientist on your side: an individual with specific domain knowledge who can vet the CRO and their activities, manage the design of studies, and stay on top of the unexpected technical issues that always arise. Always hire the first scientist or two before engaging a CRO. Doing otherwise is just throwing away money and time.

Since having scientists on hand is already a good idea, why not put together a small lab to carry out the smaller projects that will be painful to run via a CRO? Yes, using a CRO is a good choice over the cost and time required to assemble the necessary facility and staff to carry out in vivo and other expensive studies in the first year or two of startup development. But it really doesn't cost that much in the grand scale of things to build a lab for one to three scientists that is equipped for small cell studies, protein studies. Having such a lab space for the small and fiddly tasks with high failure rates, such as assay optimization, will pay for itself when compared to trying to run that work via a CRO.

CROs are, in general, perfectly happy to accept funds, carry out a task, and then shrug

apologetically when it fails. If you want to try again, that will be another invoice. Some CROs are better than others in terms of providing scientific review of proposed studies, but in all cases the onus is on the customer to provide study designs that will function as intended. A non-scientist cannot review lab notes sufficiently well to understand why a protocol fails. A non-scientist cannot identify subtle flaws in a study in advance. A non-scientist cannot troubleshoot a low-level assay with CRO staff in order to determine whether or not they carried it out correctly. Few projects in the life sciences are so simple and straightforward as to avoid these sorts of issues.

The key to a cost-effective first laboratory for a biotech company lies in finding a shared lab space that already has the basic infrastructure in place: water; gas; cabinets and freezers; electrical for the heavier equipment; regulatory compliance; access to shared equipment for the larger, more expensive items; and so forth. Just setting up basic infrastructure and furniture in a building not already converted into a lab space is an expensive, time-consuming proposition. Fortunately most larger cities, and even smaller cities with significant universities, have some sort of incubator or lab space rental concerns that can offer suitable accommodations for a few years at reasonable rates.

Given that space, one can purchase the few pieces of equipment needed, perhaps second-hand given the thriving marketplace for used lab machinery, and that will prove to be the largest cost of setup. Then forge ahead! It will become obvious when a larger and more capable laboratory is required, in order to take on more of the work that previously ran through CROs.

The Level of Specific Scientific Expertise Required is Greater than You Think

Biotechnology, and research and development in the life sciences in general, is an industry characterized by enormous degrees of specialization. At the lower levels of expertise, lab staff can always be trained to any new program. At the higher levels, knowledge of work in one area provides next to no guarantee of competency in even what might appear to be closely related areas. Someone who works on gene therapies for the brain will have no deep knowledge of the unwritten ins and outs of gene therapies for the liver. Working with neuron cell lines provides little insight into working with hepatocyte cell lines. Working with AAV vectors gives little insight into working with lipid nanoparticle vectors. And so forth.

When hiring the scientists who will design and run your development program, one must get as close as possible to someone who has done exactly what you want to do already. Obviously there can never be a perfect fit to that goal, as you are working on a novel project, but if you are producing a gene therapy for the brain, for a specific condition, then your cofounder or CSO must be someone who has run a clinical program to produce a gene therapy for the brain, and preferably for that condition.

There is just too much specialist, unwritten knowledge connected to the target tissue, the type of therapy, and the surrounding state of the art in development. Which cell lines to use, and how exactly to work with them. Who is worth talking to in the research community. Which vendors

are best to use. Which strategies work well with this tissue, which assays, how exactly to conduct them. It is all very different from tissue to tissue and therapy to therapy. A highly talented individual who has not led exactly the type of program that you are conducting will struggle to deliver the results you need in the time you have.

Put the Therapy Into Mice Before You are Ready

As soon as you have a prototype therapeutic, even the rudiments of one, and a little data from cells in petri dishes to show that it does something, then you should contract with a CRO and put it into mice. Set up a simple study, using a couple of doses, that assesses the most plausible biomarkers in the most plausible tissues for the therapeutic to act on. Does the therapeutic localize to those tissues? Does it have anticipated effects on cellular biochemistry? Then run the study. It will certainly take a little time to set up the CRO relationship and manufacture of the therapeutic, but all of that is good practice for later.

The scientific team might think that you are not ready, and that there is much more to be done before running a rational series of animal experiments. Yes, that will always be true; programs proceed cautiously, step by step. But a single exploratory study is cheap in the grand scheme of things. There is a good chance that you will learn a great deal from this exercise, and some chance that you will gain data that will be very helpful in later seed stage fundraising. It is well worth the shot. So do it, and then go back to the slow and steady process of building the later development program.

Delay the Scientific Advisory Board, as Indication Choice is Difficult

By all means think about populating your scientific advisory board - it is important in the longer term. Look for potential members, make connections, talk to the scientific community. But delay, delay, delay, on actually making anything official.

Why say this? The primary reason is that a scientific advisory board must be aligned with the indication or indications that you intend to pursue with regulators. Many founders feel a certain sense of urgency to have the public blessing of noted authorities, in the belief that it will sway investor sentiment. Yet you will already be associated with the scientists needed for credibility with investors by virtue of the biotechnology under development. Either the inventors of that biotechnology will be your co-founders, or they will be your initial advisors, but in these or other ways they will be involved from the outset. Further, the investors worth having are not all that interested in appearances; they will want to know about you, your technology, and your approach, and little else.

Most past medical biotechnologies had the potential to treat at least a few different conditions, all closely related to the targeted mechanisms. That is changing, however, the options expanding. In the case of rejuvenation biotechnologies that target molecular damage at the root of aging, or biotechnologies that can suppress major downstream consequences of that

damage such as blood pressure or chronic inflammation, there may be scores of possible uses, each one of which splits into multiple indications. These clusters of indications tend to be associated with a range of different academic and research communities, the members of which are specialized and know little of one another's fields. Thus how will you choose the right scientists without knowing which condition it is that you will be trying to treat on your first run at the regulatory gauntlet?

Picking an indication isn't a simple choice. The broader the influence of a particular mechanism and biotechnology the harder it becomes to make that choice. A great deal of research and outreach is involved to weigh the pros and cons. Is the biotechnology very likely viable as treatment for this condition? Is there unmet need in the patient population? What is the competitive landscape of potential treatments? Is there a compelling case for the payers in the medical industry, the insurance providers and others, to approve payments for patient treatment? Is there an active patient advocacy community to fight with the payers on this topic? It isn't unreasonable for founders and early employees to take months to answer these questions, work carried out in parallel with early scientific and development programs.

What is the purpose of scientific advisors? It isn't in fact to look good for investors. It is to open doors and guide you in the challenging matter of translating a medical biotechnology into a therapy. This is difficult, very difficult, and not just technically, but also in the matter of relationships and logistics. You will need alliances with the patient communities, the centers that treat the specific condition that you are targeting, the leading researchers in that field. You will need to learn more than you ever wanted to know about manufacturing and preclinical testing, all the little details that will vary widely depending on exactly which type of medical condition is being targeted. Having the appropriate connections and the appropriate advisors is essential.

Solid advisory relationships require equity grants, and an advisory board cannot be so large as to be unwieldy. A dozen members is too many. There are only so many slots that can usefully be filled, only so much advice, and only so many connections that can be usefully assimilated by a startup company in a given period of time. Filling out an advisory board early will only mean that you likely choose poorly, spend time with people who cannot greatly help your final choice of strategy, and have to replace those advisors. Better not to get into that situation in the first place.

Biotechnology is Slow and Prone to Delay

Few things are as satisfying to behold as a neatly formatted Gantt chart for a life science study; all of the interlocking pieces of modern biotechnology as it is practiced; the ordering of reagents and mice, preparation of cells, management of equipment, scheduling of researchers, and so forth. It is usually the case that a considerable amount of reading, discussion, and negotiation goes into the preparation of a study and its accompanying schedule. There is the feeling of having accomplished something to get to the end of that planning and have the proposal represented in Gantt form. Which is fair enough - planning can be hard work. Just don't for a moment imagine that in reality things will happen as neatly as is described in the proposal on

the screen.

Firstly there is the ordering, whether reagents, cells, mice, or equipment. A surprisingly large fraction of orders cross international borders. Anything involving DNA, such as viral plasmids, has some chance of being held up at those borders, for no apparent reason, for days or a week or more. There is nothing much to be done but wait. This can happen to equipment as well, and that is even before the question of whether the vendor schedule slips on their side. It is a bad idea to place oneself in a situation in which materials absolutely must arrive by a given date, in order to prevent other work and materials from being discarded and redone. Set up the potential for that problem to occur, and it will happen.

For example, many mouse models require significant setup time, from HIV models to atherosclerosis models, and following that setup their useful study lifespan is limited, sometimes dramatically so. There is always the obvious incentive to run manufacture and ordering in parallel to the mouse setup - but then one risks the materials arriving late enough to compromise all of the expense invested in the mice.

Next, cells are unpredictable beasts. It can take weeks to vet a simple, "how could they get this wrong" cell line from a new vendor when it fails to show the expected surface markers during quality control. Is the literature misleading? Does the vendor have quality control tests that sound good at first glance, but are actually inadequate for this particular cell type? Is the problem in one's own assessment and equipment? Testing one's way around an issue with cells failing to behave as expected is a laborious affair, and can swallow weeks of time.

Lastly, the combination of machinery and consumables, while allegedly reliable, can turn out in practice to be just as ornery as cells. Does the preparation of plasmid DNA fail in strange ways, with some quality assurance passing and other tests failing? Is it the DNA, the test, the preparation process, the machinery to run the process, the consumable kits, or user error? It will usually take at least a few days to answer that question for the strange behavior of even simple, regularly performed processes. It might be easier just to switch vendor to use another kit, or try again rather than diagnose. All of which still consumes time. What happens when complicated processes that take a week fail in this sort of manner? One is lucky to lose only a week.

The bottom line to all of this is that delays of this nature will occur in every project. It is inherent to work in the life sciences. Absolute reliability is a mirage, studies are complex undertakings, and delays will take place far more often than anyone would want or expect. When time is critical, as is usually the case when wages and rent are being paid, it can make a lot of sense to structure a study to have fallback options and parallel paths - to be more robust to failures and delays. Culture one's own cell line from mice as well as ordering cells from a vendor; buy viral plasmids from two vendors; and so forth. It winds up being a good insurance policy, and almost always costs much less than the delay caused by the failure or unexpected postponement of a critical component.

The Literature is Frequently Wrong - Always Replicate First

The scientific literature is not a pristine repository of truth, and peer review is no guarantee that a finding or a paper is in fact correct. Or correct for anything other than the specific cells used by the researchers, or that requires some poorly understood and undocumented aspect of the experimental setup in order to work, and so forth.

Thus the first step in any development project is to replicate the literature. Rerun exactly the same study, to the best that it is possible to replicate the methods and conditions. Contact the researchers involved when there is any question or doubt as to how a specific aspect of the study was carried out. Many authors skip over a protocol that justifies a lengthy write up with a single sentence and no reference.

Without replication, be suspicious of any claim: certainly, do not base any significant expenditure upon it without ensuring first that it does in fact work as described, in your hands, in your lab, with protocols that can be managed by your team.

It is Protocols All the Way Down: Setup is the Cost

Exploratory development in any given field of interest tends to become cheaper and easier as it progresses in a biotechnology company. This is not really driven by the team gaining experience, even though that is important for any number of other reasons, but rather because in the later stages of a project, more of the essential components of development have already been set up, and it is the setup cost that is largest in time and funding.

In any given line of development, a team might need cell lines, reagents, specific experimental procedures in cells and mice, the use of novel equipment, and so forth. Anything a team has already carried out and reduced to practice can be accomplished again with modest incremental effort, but each of these items requires a significant amount of effort to set up the first time. This is the nature of biotechnology, and it is why most contract research organizations are very limited in the services they can offer. It is thus also why more exploratory work than would be optimal must be taken in house by most biotechnology startups.

To take just the first of the line items mentioned above, cell lines can certainly be ordered from vendors or quickly generated from mice, but don't think that this means it is easy to obtain useful cell lines. A cell line from any source requires careful assessment and quality assurance before the cells can be used, as the rate of failure and contamination is high even for commercial products. So we must ask questions such as whether or not the cells exhibit the right surface markers. Is there consensus on what those markers should be? That is not always the case. Do the cells behave as they should in some standard assay? Does that standard assay exist, or are there other ways to answer the question, and has the team already worked with those protocols? If not, then validating the cell line will require a new protocol to be set up, and the protocol itself must be validated. That may require a new vendor and that vendor's products to be evaluated and the processes set up for their use by lab technicians. The rabbit hole can be quite deep even for items that might at first appear to be simple.

This exercise of validation can well turn out to involve anything from a couple of weeks to a couple of months of work, depending on the depth of the rabbit hole and the setbacks encountered along the way. But once the cell line is in hand and properly managed, and all the protocols written, and the team experienced in their use, any future project that can use the cell line no longer needs the lengthy setup process. It will thus be that much faster to carry out.

In later stages of investigation and development, it will often be the case that only one or two items are novel for any given project. Everything else is already in hand, or in the freezers, waiting to be reused. This can result in a factor of two or three difference in cost and time. On the flip side of the coin, everything in the early stages of a biotechnology startup is frustratingly slow and expensive. Expect it to take at least six months to get up to a reasonable speed in any one area of development, and that assumes no major diversions or changes in direction.

In Conclusion

Treating aging as a medical condition will be the largest industry the world has ever seen, and produce beneficial change to the human condition throughout the world on a scale and magnitude to match. The medical biotech industry is very different from most other industries, but it isn't impenetrable to a determined entrepreneur willing to learn. There is tremendous opportunity at this time in the field of rejuvenation, aging, and longevity: scores of valuable projects are undeveloped and awaiting champions.

We hope that this document helps you to start on an exciting journey into the longevity industry, to bring great benefits to humanity in addition to returns to your investors.