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Jumping Hurdles and High Jumps in Translational Research

How to generate additional speed on your journey from bench to bedside

To uncover the most significant obstacles faced by researchers on their bed-to-bedside journey, The Translational Scientist and Cytiva reached out to the translational science community.

We learned of diverse challenges – from finding funding to finding lab space, and from making therapies at scale to making a case to regulators – and sought out experts to present insights, solutions, and advice.

Here, we deliver all that knowledge – and select educational resources – to help you navigate your own hurdles and high jumps in style and at speed.

The journey is long and hard – paved in GMP awareness rather than yellow bricks. But the finish line represents gold for patients.

Rich Whitworth, Content Director,
The Translational Scientist

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Chapter 1: There Is No Yellow Brick Road

Tim O'Meara – researcher, entrepreneur, strategist – considers the translational journey ahead

For chapter 1, we tackle the following open-ended question rather than a specific bottleneck:

"I'm at an early stage in a promising project; therefore, I'm probably not aware of all the pitfalls! Any hints of what to expect? Any broad advice you can offer?!" – Anonymous survey respondent, June 2022

What can we expect on the road to translational success?

I think the first thing to accept is that there is no such thing as the yellow brick road in translational research! There are very few easy routes, and the journey is different for everyone. The analogy of hurdles and high jumps – and water traps and pitfalls – is realistic, and those obstacles will shape your path.

Speaking generally, I guess the first hurdle is deciding to go for it! And that's really about recognizing the potential translational value of your research. Once you believe you can make a difference, you won't need much motivation.

The next high jump can be invisible – and clearing it demands a full understanding of your end goal. When I talk with translational researchers, I ask them why they're doing what they're doing. Easy answer: To make a difference! Next, I ask them what difference it will make. And then I ask who it will make a difference for. You need to try to connect all the dots – and that probably means starting with a clear end goal in sight; the destination should also shape the journey.

When you know exactly where you want to go, you should pause to make a detailed map to guide development rather than racing ahead. Though time is important, mistakes made in haste early on can lead to seriously significant delays – and loss of intellectual property position – down the road. It's never too early to at least start thinking about your clinical studies and how you will make your product to the required good manufacturing practices (GMP) standard.

You may need help with all these early steps, so get out there and talk to clinicians, talk with people already marketing in your space, talk to those with experience in development and manufacture. Their input could be crucial to the success of your life-changing therapy. They say it takes a village to raise a child. Well, it takes many experienced and well-educated villagers to raise a therapy! You need a network of people around you.

At some point, you'll need to think about money – and that's surely a whole chapter on its own! I will say that, if you've adequately jumped the previous hurdles and high jumps, finding funding may be easier. (Sidenote: if you license your intellectual property [IP] to a company, you've sold it. If you sell your car, you wouldn't expect to drive it or tinker with it – even though you may still love it. It's the same with IP.)

A very lucky, tiny minority may not see any hurdles and high jumps, but those people are flying – and not everybody is designed to fly.

What comes next?

Let's assume you've sorted out your manufacturing process (you're making something that can go into humans) and you've done your first-in-human trial. And you've got sufficient cash to do phase II. You are now at the extreme pointy end of making a difference and understanding your indication. You're about to spend some serious money, so it's time to reflect on where you are – asking yourself the same questions as at the beginning. What difference are you going to make and to whom? It's incredibly important to fully understand the potential therapeutic benefits and to fully explore the competitive landscape. Has anything changed?

Get this part right, and you're probably looking to sell your company or license your technology – and that is definitely cause for celebration.

How does your own translational/startup experience help you guide others?

First, my experience has given me an incredible amount of enthusiasm for the startup culture and mindset; it's wonderful to see brilliant people starting up a business in any form.

Second, I've gained a lot of empathy. I know that it is not an easy road!

Third, I truly understand the importance of time. Time is your most valuable resource. And it plays a role at every stage; for example, if you push your product through to a phase I clinical trial when you say you will (or even earlier), you'll develop credibility – and you'll find it easier to gain funding for a phase II clinical trial. If investors see that you're hitting milestones, they develop confidence in you.

Fourth, I know that good partnerships help save time – the aforementioned most precious resource. The right clinical partner will make all the difference. The right development partner will make all the difference. The right manufacturing partner will make all the difference.

And partnership is more than just an agreement on paper – it's about trust, respect, and credibility. Never forget the human element. You need your partners to adopt the challenges that you're facing and, ultimately – hopefully, celebrate your success.

Can you offer a final parting shot – a single memorable take-home message?

Partner or perish!

The world's response to the pandemic is a prime example of time becoming the most critical factor. And to save time, partnerships sprang up everywhere – even between traditionally (often fiercely) competitive academic centers and companies. Once you truly recognize the value of time, partnerships cannot be ignored.

Meet Your Mentor, Tim O'Meara

My background is in biomedical research. Like many others, I completed a PhD and followed the path of the scientist. But, to be a great scientist, I believe you've got to at least attempt to climb to the top of the pyramid – to become a world expert in something. Instead of finding total focus, I found myself asking many questions – not least of all: Why are we doing this? At some point, I realized that understanding the impact of the research became far more important to me than understanding the mechanisms behind the scientific results. I decided to trade in my lab coat for a suit and a tie (it was the early 2000s after all) to embrace the commercialization side of research.

It's important to note that I've been on my own translational journey; I had the absolute joy of being a cofounder of a startup company in the allergy space – a wonderful phase in my career. Next, I used the lessons learned in several business development and leadership roles at the Commonwealth Scientific and Industrial Research Organisation (CSIRO).

In short, I try to develop an environment that encourages researchers to extract more impact from their work. Clearly, these people are dedicated to their research and often doing a brilliant job, but they often benefit from an outside perspective on where their research could go. It's a strategic management role that sees me looking after not only research partnerships but also government partnerships; after all, translating research helps build the local biotech industry.

Tim O'Meara is Adjunct Professor, University of Technology Sydney, Australia

Chapter 2: Shoot for the Stars

The godfather of translational medicine – Eric Topol – grants us a few minutes of wisdom that could last a lifetime

For Chapter 2, we address a somewhat fundamental challenge:

"For me, the biggest hurdle of all is knowing which scientific ideas are suitable for translation!" – Anonymous survey respondent, June 2022.

What's the single most important piece of advice you can offer translational researchers?

Focus on something with transformative potential. Focusing on the small stuff or the arcane won't get you where you need to go – but it can often take just as much time as the big stuff. Put another way, you may as well shoot for the stars!

For example, the unequivocal need for individualized medicine lies at the heart of The Scripps Research Translational Institute – and to crack that massive challenge we're focusing on breakthroughs in two key areas: digital technologies and genomics.

Great – but how do we recognize something with transformative potential?

I think you can feel it in your bones. For example, with the birth of the smartphone, I recognized that the practice of medicine would change forever – we're not there yet and that's frustrating, but the huge potential of wireless digital technologies will feed the future of individualized medicine.

You should also ask yourselves some searching questions. Is this important? Is there an unmet need here? Do we really understand this? What is the promise or potential? In answering these questions, you should aim to gather a 360 degree view – bringing in the opinions of clinicians, nurses, pharmacists, other researchers in your field, and researchers outside of your field. And don't forget the patient.

I don't think we do this sort of soul searching enough – and that can lead a project off the tracks. It's easy to invest lots of resources into something that isn't centered on the root need – or something that isn't needed at all.

A related point – and one of my favorite topics of discussion – centers around another key piece of advice: don't accept any dogma. Maybe the sacred cow is not real. Question things that are widely accepted – you may just find something that upends an entire field.

Sadly, we can't all be Eric Topol – but how can we replicate or imitate some of your success?

I'm not sure you'd want to be me! But I would say that individualized medicine is dependent on many equally important layers – and you don't have to (and most likely cannot) focus on them all! If you're working on something that helps us understand why we're all unique, you increase your chances of making a difference or having a real impact. Notably, some of these layers get much more attention than others.

Alternatively, you could focus on enabling platforms; for example, there is real paucity of talent and expertise in the artificial intelligence space – and in data analysis more broadly. We have truly become overwhelmed with data and our ability to extract the meaningful essence of that data. With increasingly complex and multimodal data streams, it seems likely that translational success – or disruption – may come from non-traditional fields of research.

For me, a real advantage is that I see patients every week. And so I have a finger on the pulse of patient thoughts and concerns – and how that relates to the practice of medicine today. It's arguably the most effective way of finding the holes. My connection to patients has helped me tremendously over the decades.

Of course, we can't all be clinicians – but I think it emphasizes just how close the link between science and medicine should be if we want to find translational success.

Any final words of wisdom or encouragement?

Being part of the translational force that turns a big idea into reality is the most exciting thing you can do. And there's never been a better time to be doing it.

Meet Your Mentor, Eric Topol

Eric Topol is the Founder and Director of the Scripps Research Translational Institute (he's also Executive Vice President, Professor of Molecular Medicine, and Gary and Mary West Endowed Chair of Innovative Medicine at Scripps Research).

Clocking up more than 1,200 peer-reviewed articles and over 300,000 citations have made Eric one of the top ten most cited researchers in medicine. He's also found time to write three provocative bestsellers on the future of medicine:

- The Creative Destruction of Medicine
- The Patient Will See You Now
- Deep Medicine: How Artificial Intelligence Can Make Healthcare Human Again

Read more "Lessons Learned" with Eric Topol.

Chapter 3: Show Me the Money!

Research scientist-turned-investor Alex de Winter helps you run the funding gauntlet

For Chapter 3 (and – spoiler alert – Chapter 5), we tackle a hurdle raised by many survey respondents – and one that will inevitably attempt to trip up all translational scientists at some point or another.

"Looking ahead, I want to know when and how to obtain different kinds of funding – and why!" – Anonymous survey respondent, July 2022.

At what stage(s) should translational scientists start thinking about funding? What specific points should translational scientists keep in mind?

Translational scientists, at least those who are at startups, should always be thinking about funding. Specifically, how much funding will it take to get to the next proof point, whether that's an in vitro proof of concept, a demonstration in a model system, or a clinical trial. Keeping in mind that it's impossible to schedule innovation, it's a good idea to forecast capital requirements needed to reach each of those milestones and then plan for how to fund those milestones.

What are the pros and cons of different sources of funding?

Angel investors

- **Pro:** Relatively quick and easy source of capital.
- **Con:** Can strain personal relationships, if the angels are family and friends.
- **Con:** Angels may have shorter investment horizons, so may want their money back before the startup is ready to exit, leading to strains between the founder and investor

Grants/Small Business Innovation Research (SBIR) funding

- **Pro:** Non-dilutive funding
- **Pro:** Limited oversight (no one looking over your shoulder)
- **Con:** Takes time and effort to apply for the grant
- **Con:** May not be that much funding relative to the effort and time required to secure funding

Venture capital (VC) investors

- **Pro:** Can provide large amounts of capital
- **Pro:** Usually provide good advice on building companies, managing through business hurdles, and hiring
- **Con:** Takes a lot of effort to raise funding from VCs (have to pitch many firms, be on the receiving end of endless diligence calls)
- **Con:** Some VCs are better than others (do your research)

Corporate venture capital (CVC) investors

- **Pro:** Can provide connections to parent corporation for expert advice and partnership opportunities
- **Con:** Usually don't write large checks
- **Con:** May add strings to their investment (find out why they are investing)

Public markets

- **Pro:** Finally, an exit for the founders, employees, and investors
- **Pro:** Can provide significant capital at the time of the initial public offering (IPO) and through later sales
- **Con:** Public investors have shorter investment horizons and will punish company (lower share price) if it underperforms quarter to quarter

What's the main pitfall for scientists attempting to secure funding?

Going for venture investment too early – either before the technology is mature enough or because the actual investment pitch isn't as polished as it could be.

To help make the technology more mature, it's generally a good idea to apply for grant/SBIR funding. Such funding can get the research to a more advanced state (de-risking the technology), is non-dilutive, and provides another point of validation (to investors) that the research

is worth further investment.

It's true that you don't get a second chance to make a first impression, so scientists should make sure their pitch is really ready before going out for venture funding. There are many resources out there on how to make a great investment pitch (for example, Pillar VC has an excellent series of videos).

What advice can you offer to someone seeking funding at different stages along their translational journey?

Network to find a friendly founder who can act as a mentor, ideally someone in a similar but not necessarily competitive field who has successfully started a company and/or received investment. You may be able to find a mentor through the alumni network at your university or through LinkedIn. The mentor can help you with the initial process of starting a company, reviewing your grant or investment pitch, and can help you navigate some of the pitfalls associated with running a startup. Also, if the mentor is high profile enough (and once you've formally incorporated a startup), you may want to add the person to your advisory board or board of directors, to formalize the relationship and give the person a stake in your startup's success.

Just how competitive is the funding landscape for translational research?

It has always been competitive, thanks to a well-documented "Valley of Death" for startups transitioning from preclinical proof of concept to clinical trials – caused by management issues, technical/scientific challenges, business model failures, or a combination of the three. Though there are grants (and some seed investors) available to fund early R&D, it is much more difficult for researchers to find the money to advance these experiments into the clinic. Many of these discoveries fail to obtain the funding needed to progress beyond the lab bench, which further contributes to the Valley of Death. Unfortunately, the recent downturn in the public markets and resultant pullback in venture investing will make the funding of translational research much more challenging, as VCs may become more risk averse.

How has the pandemic affected that landscape?

The pandemic temporarily increased funding for technologies related to COVID-19, so new tests and vaccines made it to market under the FDA's Emergency Use Authorization. The funding that brought those technologies to market wasn't technically translational funding, but the surge of funding (and interest) in diagnostics and therapeutics had a knock-on effect, increasing translational funding for earlier stage technologies that could also address the pandemic.Much of translational research is funded by healthcare VCs (at least, by the early-stage VCs). According to Silicon Valley Bank's Healthcare Investments and Exits 2022 Annual Report, the amount of capital that Healthcare VC firms raised to invest (at least partly in translational research) increased by 14 percent annually from 2011 to 2019 (from $3.7B in 2011 to $10.7B in 2019). Then, from 2019 to 2021, that amount jumped by 63 percent annually (to $28.3B in 2021). That's a huge increase in money available for translational research. And it's not all due to the pandemic, the last two years also saw an unusually active IPO market, which allowed private companies to go public, increasing the returns of VC firms and allowing them to raise more money.

This huge amount of VC funding seems at odds with my earlier statement that it'll be more difficult for startups to raise translational funding, but VCs will likely use their giant funds to support existing portfolio companies (which will be less able to raise funds in the public markets) and generally will be unwilling to fund riskier research because the good times are on pause (or maybe the good times are over).

Can you share an example of (stellar!) success when it comes to getting a venture off the ground?

I would say that Pacific Biosciences, where I worked as a research scientist, is a case study in funding success! The company spun out of Cornell University after receiving seed funding from Cornell's student-run Big Red Ventures (BRV) fund. Pacific Biosciences then raised Series A from Mohr Davidow Ventures, received grant funding from the National Human Genome Research Institute's $1,000 Genome Program to help extend the runway, then added funding rounds and investors ($350M in private investment) until it went public in 2010. It's now a one billion dollar company that makes an instrument for long-read DNA sequencing…

Any final advice on the topic of funding for translational research?

Apply for a grant with the National Cancer Institute SBIR program! I'm somewhat obliged to say that, as I review grants for the NCI – but, if your translational research is geared towards helping cancer patients, there are few better sources of early stage funding.

Meet Your Mentor, Alex de Winter

After a stint at Pacific Bioscience as a senior scientist, I've worked at three different VC/CVCs – Mohr Davidow, GE Ventures, and now Danaher Equity Ventures. At each place, we've selectively funded seed stage startups, where there is just a proof of concept and the scientists need funding to start a company, hire a management team, license the technology, and repeat the experiments outside of the academic lab.

When it comes to seed investing, the Valley of Death feels very real – there is inevitable risk. But the rewards are also very real. And there's a reason I've been in this game since 2009.

Alex de Winter is Vice President of New Ventures at Danaher Corporation, Cambridge, Massachusetts, US.

Chapter 4: Welcome to Your Shiny New Lab

Sabrina Carmichael – an experienced R&D scientist who's "been there, done that" – helps you settle into your new home in GMP city

For Chapter 4, we consider laboratory space as you transition from research to manufacturing.

"Our biggest concern is ensuring that our 'new' lab is fit for purpose – now and in the future." – Anonymous survey respondent, July 2022.

Could you share your personal experience of setting up a lab space from scratch?

When I joined GE Healthcare – now Cytiva – in 2017, my colleague and I were thrown in at the deep end – tasked with quickly setting up a cell therapy lab to start work on a couple of projects with very tight deadlines. In a story that may be familiar, we inherited a space that contained very little of what we actually needed. We faced a steep learning curve but came away with an excellent grounding for many other projects – internal and external – down the road. Here are three broad lessons:

1) Know what's in the realms of possibility! There will be certain things you feel you need or want to keep in house – but don't overstretch in terms of your skillset or space. Try to make wise decisions about what and when to outsource.

2) Go back to basics. If you're retrofitting a space, you'll need to consider some pretty fundamental requirements. First off, does the space satisfy your gas and power needs? In our new space, there were no gas lines, so we had to bring in cylinders. If you're running a process that lasts 14 days, you'll be sure to need an uninterrupted power supply (UPS) setup; we had regular outlets – and the need for UPS required some clever workarounds. If you're lucky enough to be starting with a blank slate and a wishlist, don't forget the basics.

3) Work within your planned timeline. As with skills and space, don't be tempted to stretch the time available to you and your team. In Chapter 1 of the series, Tim O'Meara put it like this: "Time is your most valuable resource. And it plays a role at every stage." If you have a small team, would you consider running a three-day assay time well spent? The answer is probably "no," as you have another 57 things to do. Again, outsourcing can be an attractive route forward – especially for analytical capabilities that demand highly complex and expensive instrumentation.

If someone is in the enviable position of starting with the blank slate and wishlist you mentioned, what advice can you offer?

I'm pleased to say I have experienced this as well. In the same building as my initial lab build, we also had some shell space – a truly blank slate, and we received a request for a new cell therapy FastTrak™ lab. I have to say, the lessons we learned the first time round paid dividends.

1) As I mentioned, start with the basics – the infrastructure – it's much easier to build it in at this stage. Don't forget power (UPS!), gas lines, and water requirements. And don't forget internet needs (something that may slip your mind in our increasingly connected world) – this is especially important if you plan on running automation software.

2) Focus on optimizing your floor plan to achieve your desired output. Put another way, how much equipment can you safely squeeze into the space to meet output needs for today and the future?

What other pointers can you offer to translational researchers looking to make the leap from research to manufacturing – and further scale up down the road?

First of all, I'd recommend speaking with some reputable equipment manufacturers in your space. Undoubtedly, they will have worked on similar projects in the past and will have the experience to guide you down a sensible and well-trodden path. Likewise – but I guess outside the true scope of this article – you may wish to consider partnering with a reputable contract development and manufacturing organization (CDMO); again, these companies have

Meet Your Mentor, Sabrina Carmichael

After graduating from the Worcester Polytechnic Institute in Massachusetts with a degree in biology and biotechnology, I had a brief spell at Genzyme, working on prenatal diagnostics, before moving on to the Massachusetts Department of Public Health, where my interest in diagnostics continued but with a focus on HIV and hepatitis. I was then sucked into the world of platelet research for six years at Boston Children's Hospital.

I joined GE Healthcare (now Cytiva) in 2017 as a R&D associate – and that's where my very real-world experience of setting up a lab space began.

A couple of years later, I moved into a technical scientist role before assuming my current position in the CGT FastTrak Global Training team. There, I focus on the content and delivery of courses that cover cell therapy manufacturing processes and related technologies. And, given my experience within the company, I also work with process development scientists to initiate and lead new projects.

Sabrina Carmichael is CGT FastTrak Global Training Leader at Cytiva

vast experience and a proven track record of solution finding (or troubleshooting, if you're a pessimist).

Either way, if translational researchers are at that key point of thinking about manufacturing and scale up, discussions will always begin with the process (and if you haven't figured out your process, your first step should be to talk with a process development scientist!). The process and the required output will dictate the space, skills, and equipment required. And when you enter this world of good manufacturing practice (GMP), the keyword is safety, so the conversation will quickly turn to closing your process. Undoubtedly, your equipment needs (and the utilization of floor/bench space) will change dramatically; you may find it strange that something you were entirely reliant on in a research setting may suddenly face obsolescence in manufacturing.

Specifically from a cell therapy point of view, your needs will also be different depending on whether you've chosen to go down an autologous or allogeneic route. For autologous cell therapies, you'll be scaling out rather than scaling up – in other words, you may move from one bioreactor to ten – each one representing one patient. For allogeneic cell therapies, scale up follows a more conventional biopharmaceutical pathway, with increasingly large bioreactors – from one to 10 to 50 liters, for example.

You've worked in both (translational) research and manufacturing lab spaces – besides the equipment are there any other major differences?

When I worked at Boston Children's Hospital, I was in an academic lab that covered basic, translational, and clinical research. The layout and regulations at play in that lab were incredibly different to what I do at Cytiva – like night and day. And perhaps the most shocking revelations relate to i) documentation, ii) the need to follow processes to the letter, and iii) more documentation. Regulators really like documentation, so you may need a change in mindset. GMP manufacturing is a whole different ball game to academic research – and I think it's never too early to start educating yourself to prevent serious shell shock.

In your current role, you often interact with customers in their transition to a dedicated manufacturing lab set up...

That's right. People typically come to me with a specific process they want to run – and we'll build the appropriate process for them. We begin by discussing how many cell expansion and harvesting systems they'll need to treat a given number of patients per year, but also explore the optimum setup, the analytical capabilities required, and so on.

Every request is unique – and it's fair to say we sometimes have to get creative to work around space constraints. That said, small does not always mean impossible. To prove the point, our enterprise lab in Marlborough fits the entire cell therapy workflow – including double stacked incubators, a biosafety cabinet, and a cell counter – in a space the size of a walk-in closet. During facility tours, I love showing off this particular lab as an example of the smallest workable space – a concept that takes us right back to the "realms of possibility!" After all, there is a limit to creativity – I cannot magically break the laws of physics no matter how enthusiastic a potential customer may be.

When it comes to would-be drug manufacturers, the spectrum seems to run from virtual biotech (total outsourcing) to independent teams who want to control every single aspect of the development of their beloved "baby." What's your seasoned view?

Tough question. I would say that CDMOs exist for a reason. They do great work and they have amazing capabilities – and they instantly remove a lot of head scratching and headaches. I've worked with several such organizations to expand or enhance their cell and gene therapy capabilities, and so I know they can offer scale, expertise, and equipment that is hard to match when working alone. The caveat is that you become a customer in a line of customers, which can result in (or at least feel like) a loss of control.

On the other hand, if you're willing to invest the time and energy into developing your own manufacturing capability, I say, "Good for you, and good for science!"

Importantly, your question includes the word spectrum; I think it's important to note that every product and process is different, and every team has a different skill set, so every company – whatever the size – will have different requirements. Feel free to have conversations with multiple potential partners, network with companies in similar situations, and use whatever support, wisdom, and resources you need to help you succeed. And, whichever route you take, know that you don't have to do it alone.

Chapter 5: Investors Invest in People

Chris Lord has taken two companies from startup to exit. Here, he offers a personal glimpse into the realities of funding – and shares several key lessons learned for those wanting to follow in his entrepreneurial footsteps.

In Chapter 3, research scientist-turned-investor Alex de Winter offers his top funding tips in "Show Me the Money!" But, as we reviewed survey responses, it's fair to say that funding was a popular (or should I say, unpopular) high jump that requires additional help to clear.

When asked about the biggest challenge ahead in their translational research project, one survey respondent wrote: "*To obtain any kind of funds/scholarships.*"

Another simply replied: *"Funding, funding, and funding."*

Here, we return to the topic of funding with entrepreneur Chris Lord, who not only knows how to talk the talk, but has demonstrably walked the walk.

What's your personal experience of securing funding in the translational science space?

I fell into life sciences by accident. Around 10 years ago, my business partner and I were exploring disruptive ways to get the world's one billion smokers into something safer. We were among the first to bring a vaping product to market – and the only ones ever granted a UK medical license for a vaping device and pharma grade e-liquid. That was our first business – CN Creative – which we sold for £40m. And then we built another, Nerudia, creating over 1,000 patented innovations, and selling for around £106m. This was all in the span of eight years. The journey required us to go through a range of fund-raising activities – all culminating in our businesses being acquired.

You make securing funding sound relatively easy...

Well, a basic rule of thumb is that it's not easy! But know that, to obtain funding, you'll mainly be selling yourself, your idea, and often – to limit risk – your intellectual property.

In fact, it's all about risk. Investors need to believe in you as a founder. They need to believe you can deliver the vision and hit the milestones. Even with the best idea and the most brilliant scientific minds, if you're unproven as an entrepreneur you represent a high risk. And if you're competing for funding with someone who has already built and sold a business, it can be tough. Trust me on that.

When it comes to funding for medicine and life sciences specifically, the routes are even more narrow as you're restricted to certain investors that favor that sector.

Ultimately, the parties providing funding are looking to make a return on their investment. Typically, they make this return through an acquisition (although it might be an IPO), so they look for IP that fits with an acquirer's business plan – or, more specifically, the business plan that they may have in a few years. And that's hopefully what you are also anticipating. This reality can create some tension; you might have a world-changing discovery, but if it doesn't help an acquirer deliver financial returns, you'll struggle to get funding early on. Sadly – to borrow from another sector – no one wants to make lightbulbs that last for a hundred years…

When should translational scientists start thinking about funding?

Well, that's the $64,000 question, as the saying goes. In a nutshell, my advice is to think about your exit strategy first and the funding you need to get there second. And you probably need to think about both of these aspects before even starting the business in the first place, as both will almost certainly be required to commercialize your idea.

Money speeds things up enormously, so to get to your goal faster, you'll need more money. And the goal we're talking about is an exit. Everyone exits their business at some point, so most entrepreneurs are looking to control how they depart via a planned sale. For translational scientists who want to help patients, you need to realize that acquisition might be necessary for your company to achieve its mission.

If you want (or are content) to grow slowly – perhaps organically by reinvesting profit – you may need less or no external funding. On the other hand, if you want – or need – to move fast (for example, to beat a competitor to the punch), you will need funding. (For reference, we sold our first life sciences company within four years – and within 24 months of our first venture capital raise).

When you raise capital, you have milestones designed to prove the concept you have pitched. Often, tranches of money are released once each milestone is reached, and the risk accordingly reduced with each

success. For CN Creative, some key success milestones were: a successful clinical trial for the vaping product; successful stability trials of the e-liquid; and ultimately granting of the medical license. Each of these steps vastly increased the chances of the product succeeding in the marketplace – and therefore reducing the investment risk.

Investing money is seriously risky. VCs will take half of your company – enough to make a tidy return, but not so much as to demotivate you. Even so, you and your startup represent a gamble. Sure, you can invest £1m of your own (company's) money, but then you have no one to share the risk with. And if you fail your clinical trial, you have to wait 12 months to get a new one and you will need enough financial runway to absorb that cost. So, you might give away a chunk of your company, but you also get to share the risk – and likely reach your goal faster.

Can you share more details about your experiences?

Together with my business partner, David Newns, I've raised many rounds of funding now – and it gets (a little) easier with experience, but I can remember my first venture capital raise vividly! After numerous trips from our lab in Manchester to offices in London and countless pitches to mainly venture capitalists but also other investors (all of which had politely declined), we had a date with one of the largest VCs in Europe: Advent Life Sciences. In truth, this was our last pitch (and therefore slightly desperate as we had almost run out of money).

Our advisor had said he kept this pitch until last because it was the most important – all the others had allowed us to refine our pitch and learn from them. We didn't discuss the topic much on the train down; I think we both knew this was our last hope, and we didn't want to get nervous and therefore fail.

On arrival, they thanked us for coming and invited us to pitch. David is a natural orator: so he typically started our pitches – and often finished them too. He explained our personal history and the background of CN and then followed with a flawless (as usual) overview of what we had done, what we were going to do, and how we were going to get there. He eloquently explained that the reason for the funding was purely to maintain our time advantage over competitors and that, without it, we would and could continue but at a reduced pace. (This was true, though we hadn't fully figured out how to continue without a cash injection!) He added that we required £2m over the coming 24 months, which didn't raise an eyebrow.

Our brilliant and helpful would-be investors, Raj and Kaasim, both interrupted politely a couple of times and asked questions, but the pitch went very smoothly. After David, it was my turn. I gave a more detailed explanation of the Nicadex device (which David could also do, but I needed to prove my worth); I have a natural tendency to go into detail and try to pick the right aspect to focus on according to the audience. I felt it was important for me to show a thorough and unparalleled technical understanding so that they knew I was genuinely leading this development from the top (rather than being led by the team I had working for me).

After the pitch we concluded and welcomed any questions. The questions were minimal. But I most distinctly remember Raj turning to Kaasim and saying, "Kaasim, I've often told you about spotting guys with a passion and with a clear and precise goal and method of reaching their goal. Watch these two guys, because these two gentlemen are the perfect example of what I've been telling you and that's the reason we are going to invest in them."

We were unknown and unproven entrepreneurs, but we had managed to convince them.

We nailed it! Raj continued, "Gentlemen, your pitch was excellent and like I've just told Kaasim, we are going to invest in you – in you two personally! If you do what you say you are going to do, we will exit in 24 – 36 months for £40 million." I've just got goosebumps saying that because I remember it so vividly and how I felt at the time.

Great story – and some lessons there. What other advice can you offer scientists who may feel less... entrepreneurial?

Not understanding the commercial landscape can make life difficult for scientists. And it's true that few scientists are also entrepreneurs, but that shouldn't demotivate them when moving forward. Often, it's a case of finding the right business partner – someone who has the right knowledge and skills (and experience, if possible). You should be looking for an entrepreneurial character who has a broad range of expertise – indeed, they need to be savvy with all the aspects of the "business," as well as the science and/or engineering.

Thinking back about our pitch to Advent Life Sciences, it's clear that investors invest in people. So, make sure you have the right people – they may be critical to your success!

Meet Your Mentor, Chris Lord

Chris Lord is an entrepreneur with a proven track record. He built two consecutive tech/medicinal companies from start up to successful exit in four years – with a combined exit value of around US$150m.

Chapter 6: Protect IP – ASAP!

Life science patent specialists Alice Jefferies and Simon Kiddle present their quick start guide to looking after your most precious asset: intellectual property

So far, we've outlined the potential hurdles and high jumps ahead, tackled the need for a transformative idea, considered funding and investment, thought about a shift in gear to GMP, and told you how to sell yourself.

In short, we've cracked some tough nuts with the help of our esteemed mentors. Now, we turn our attention to a topic that's easy… to get wrong.

Chapter 6 explores the why, when, and how of protecting your baby (research) – now and in the future. And who better to walk us through the main intellectual property (IP) points than Alice Jefferies and Simon Kiddle from "forward-looking IP firm" Mewburn Ellis.

What's the best piece of IP advice for translational scientists?

The most important thing for translational scientists to think about when considering any potential IP is to really understand what the most important, innovative aspect of the work is – and that raises a whole host of basic but hugely important questions: What has been done before? What have you improved with your invention? Why hasn't anyone tried it before? What problem does it solve? How could it be used/applied?

Scientists are inevitably experts as far as their own innovation is concerned, but considering these questions before embarking on any IP project can help secure and strengthen their position from the get-go.

What are some of the main pitfalls that scientists fall into?

Much of IP and patent law relies on dates of disclosure. Why? Because, when filing a patent application, you state that the contents have not yet been divulged to the public and that you are the first to attempt such work – this even applies to your own work. It's really important to discuss any intention for publication – for example, journal articles, conference abstracts, informal lectures, internet disclosures – with a patent attorney.

When should translational scientists start thinking about IP?

ASAP! In fact, many of the spin-out companies we work with are born from patented technology we have procured for universities and research institutions!

What steps should people take to smooth the process?

Sharing the "story" of how an invention came to be can be really useful when drafting a patent for scientists. Thinking about the story can help identify and define the true inventiveness of the technology in question. Often what a scientist may think is the "main invention" or even primary application of the invention may not be the case at all. Likewise, one invention may actually be made up of multiple patentable inventions, thus diversifying the IP portfolio and broadening the potential scope for protection.

Given that translational science moves forward by definition, how can scientists ensure continued protection for improvements to therapies or devices?

It is common for work to continue on an invention and for improvements to be made. It is possible to file new patent applications that originate from or disclose material present in previous applications by adding additional features or methods, if a technical advantage can be demonstrated. In this way, it is possible to add improvements made to a therapy, device or process into new applications, usually as long as this is done within 12 months of the first application. Multiple applications also help broaden and diversify protection.

Who should translational scientists turn to for advice?

Most universities and research institutions have in-house IP teams that can offer advice at all stages of the process. Indeed, in-house instruction can help tailor guidance towards the specific commercial interests of the company. Alternatively or additionally, a third party,

Meet Your Mentors, Alice Jefferies and Simon Kiddle

Alice Jefferies has industrial experience – gained at a drug delivery start-up – as well as experience working in collaborative academic research at the Francis Crick Institute. Alice's areas of expertise include immunotherapy, metabolism, stem cells, and antibodies. During her Masters at Imperial College London, Alice carried out a project investigating the impact of immunotherapy on the haematopoietic stem cell niche in acute myeloid leukemia. Today, Alice is a Patent Technical Assistant at Mewburn Ellis, working in the life sciences sector.

Simon Kiddle has more than 30 years' experience in original patent drafting, patent strategy, oppositions and appeals, and due diligence work across the life sciences field. Simon has worked on the portfolios that comprise many top selling biologics and has been at the forefront of patenting in the field of precision medicine and life cycle management for therapeutics. A Partner at Mewburn Ellis since 1997, Simon heads up the firm's Life Sciences practice group and is a member of the management board.

such as a patent attorney from private practice, can join the conversation at any stage of the IP life cycle. Patent attorneys are scientists too, and so can comprehensively discuss your technology, whilst providing strategic legal and commercial advice. Patent attorneys have detailed experience in writing applications, advising on strategy, and (importantly) getting applications granted to give the broadest possible protection. There is a great deal of law to consider in the application process, and there may be instances where misunderstanding that law can be fatal to the application. Patent attorneys can also advise on technology access through pipeline agreements, technology transfer arrangements, as well as dealing with IP license negotiations, and drafting license documents.

What would you say to a scientist who is keen to research patent law and go solo?

Though scientists may be worried about revealing their exciting research or "secret sauce" to external parties, patent attorneys are bound by rules of conduct that prevent us from telling anyone about your invention without your consent. So the first thing to say is that you won't have to worry about public disclosures in this situation.

Although anyone can file a patent application, hiring a patent attorney to handle the process can pay dividends. Yes, employing a patent attorney may increase costs in the short term, but it is likely to give you a more secure patent that is able to stand up against legal attack down the road. And a strong IP portfolio is extremely attractive to investors, who often drive scientific development (as per Chapters 3 and 5 in this series!). Bearing these two key points in mind can truly help the longevity of your work.

Chapter 7: Fast Track Training for Translational Scientists

In the first six chapters, Cytiva and The Translational Scientist have explored the tough challenges in moving from bench to bedside. To conclude, we dip into just some of the resources that can help you run faster and jump higher!

"Like night and day."

"A whole different ball game."

Those are the words used by Sabrina Carmichael, CGT FastTrak Global Training Leader at Cytiva, in Chapter 4 to describe the differences between an academic lab and a GMP manufacturing setting.

Carmichael continues, *"I think it's never too early to start educating yourself to prevent serious shell shock."*

Fortunately, having helped many partners in the transition from research and into cell therapy manufacturing over the years, Cytiva has excellent resources and training on hand to help you get up to speed (while avoiding shell shock).

Interactive eLearning

A gentle – and free – first step into cell therapy GMP manufacturing is provided by "**Introduction to cell therapy (eCELLT1).**"

Over the course of 285 interactive minutes, you'll receive comprehensive training on all aspects of cell therapy manufacturing across eight lessons, each of which take 30–50 minutes to complete:

- Overview of cell and gene therapy
- Thawing and isolation technologies
- Key cell types in immunology
- Affinity cell isolation and activation
- Cell culture explained
- Expansion technologies
- Harvesting, formulation and cryopreservation technologies
- Documentation, digitization and automation

Face-to-face: Taking training to the next level

Once you've completed eCELLT1, you will likely be hungry for more. Here, **Advanced cell therapy (CELLT2)** – a three-day, face-to-face, classroom- and laboratory-based training session – will dive deeper into cell therapy processes and cell manufacturing under good manufacturing practice (GMP) procedures.

More information on "Introduction to cell therapy (eCELLT1)" is available here.

What learnings can you expect to come away with?

A comprehensive understanding of upstream, cell expansion, and downstream applications within cell therapy GMP manufacturing.

- The ability to identify bottlenecks and fix issues within your own specific processes.
- Competence in industry standard techniques related to cell therapy manufacturing.
- A deeper knowledge of process optimization and evaluation.

Learn about course availability near you here.

Covering all bases

As Cytiva says, "Working scientists make the best trainers," and the company's rich offering of training across numerous manufacturing steps and techniques all connect you with top industry experts.

Those scientists have one objective in mind: to help you develop the skills, knowledge, and experience you need to survive and thrive in the brave new world of GMP manufacturing.

Good luck out there!

LINKS

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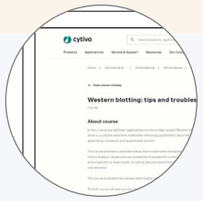

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