A successful founder off the beaten path

Ingmar Hoerr

How to develop a new vaccine or therapeutic modality in a skeptical environment, with little biotech experience, limited resources and limited capital.

Transitioning a biological discovery from bench to business is difficult enough for a well-conceived and researched technology or product in a traditional biotech hub. But what about companies seeking to develop a novel product outside of the United States, where experienced tech transfer advice, seasoned management and knowledgeable investors all come at a premium? As a young and inexperienced CEO in Germany, I learnt many hard lessons as I built a startup, CureVac (Tübingen, Germany), from a doctoral thesis into what is now a company valued at more than a billion dollars.

In what follows, I provide an account of my experience building a company in Germany at the turn of the twenty-first century and the challenges I encountered. I conclude by providing some insights into how my experience can inform other entrepreneurs seeking to build a venture around an innovative new technology in a region not immediately recognized for its biotech prowess.

Early days

When I started my PhD in the mid-1990s, I was convinced that RNA could be a platform upon which a multitude of therapeutics could be developed, from prophylactic vaccines to immunotherapies. I was driven to make this vision a reality. However, as a scientist in academia with limited business experience, I knew there would be hurdles to overcome. What I did not realize at the time was how high or how many of these hurdles there would be.

CureVac was founded in a university based in Tübingen, Germany—where Friedrich Miescher discovered a substance he named "nuclein," later better known by the term deoxyribonucleic acid or DNA. Despite Tübingen's place in the history of science, it sits far outside the biotech hubs of Boston and San Francisco. Yet this is where my colleagues and I launched CureVac with the ambition of changing the fabric of medicine. Though naive about the challenges of launching biotech companies, we, like many other young entrepreneurs, were undeterred.

In retrospect, I am grateful for our naiveté, because had we known what challenges lay ahead, we might never have taken that first step. However, there I was in 2001 with an official certificate of incorporation in hand, sitting at a desk in my tiny apartment writing a business plan for CureVac's next five years with the goal of bringing the first therapeutic mRNA agents onto the market.

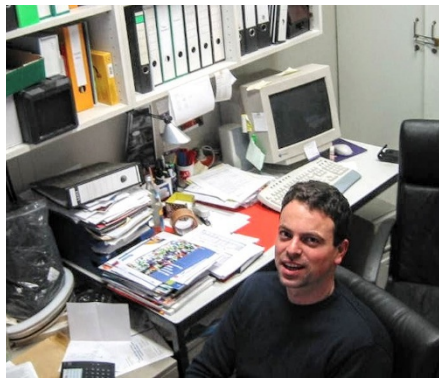
Like many scientists turned CEOs, I thought building a biotech required three simple steps.

1. Identify a groundbreaking scientific discovery.
2. Build a pipeline of products and execute a clinical trial program.
3. Raise financing for the company on the basis of its groundbreaking science.

To a scientist, steps 1 and 2 are familiar territory. Developing trial protocols and conducting experiments were second nature to me. Step 3 would follow easily enough, I thought. However, this seemingly straightforward process proved anything but.

Upon completing my doctoral studies, my colleagues and I approached the Federal Institute for Vaccines and Biomedicines in Germany and informed them we would like to begin clinical testing with our mRNA products. Not so fast, said the regulators.

We learned from our interactions with them that we needed to provide a data package and a clinical development strategy, and that good manufacturing practices (GMP) quality was required to even begin phase 1 testing. On top of that, we had yet to initiate (or complete) the preclinical animal models or provide clear statements about the pharmacodynamics, kinetics and toxicology of our mRNA technology.



CureVac

Ingmar Hoerr in an early, cramped CureVac office.

The obstacles seemed insurmountable to us. We were left wondering how we could make progress with the technology and secure adequate funding and resources to move this project forward.

Incubating the technology

My colleagues and I—all without formal business experience—convened and mapped out plans on overcoming the various barriers to clinical testing. Remaining at the university became our goal, and we were fortunate to participate in a 'young innovators' program that allowed us to use the university's laboratories and infrastructure. Looking back, I can say with absolute certainty that staying close to the university saved CureVac, even though at the time we felt like college graduates returning to our parents' basement.

Hunkered down in the university lab, we were able to modify the immune response of our mRNA construct and test various formulations that became the basis of a patent-protected technology. We also learned to

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prepare RNA with astonishing efficiency without RNase contamination and to develop a specific chromatographic purification process that would lead to one of our first production patents.

Despite lacking cash, we were nimble in the lab, which allowed us to keep our focus on the science, where we were comfortable, and enabled us to build confidence in our business strategy. However, each success in the lab reminded us that step 3 in building a biotech company, securing a financing, was becoming more and more urgent.

Finding a true believer

Attracting investors is perhaps the most challenging aspect of being a biotech CEO. Many groundbreaking technologies fall by the wayside because of a CEO's inability to fund their development. When we approached the first of many venture capital companies, we realized we had a difficult undertaking ahead of us. In the middle of 2000, Germany experienced the same technology bubble implosion that crippled the United States. And while CureVac was not a technology company in the traditional sense, we were lumped into the category of 'high risk, unproven' businesses. For investors who had just lost tremendous amounts of money backing ideas that seemed sensible at the time, there was little appetite for risk, especially involving a scientific concept that, even with data showing its potential, read like pure science fiction.

Yet, there we were, emerging from academia as scientists in a geographic area where there were few biotech successes, with a team unfamiliar with ways to access capital, forging ahead with the aim of researching and developing therapeutic vaccines for cancer based on mRNA, a molecule that, at the time, was largely not considered a therapeutic platform.

Undeterred, we approached a multitude of investors. To our surprise at the time (but not as much in hindsight), we were repeatedly rejected, often before we had a chance to present our business plan. The specific reasons were many, but the consensus was the same. The risk of investing in an experimental technology being championed by a scientifically respected, but inexperienced management team, outweighed the high upside opportunity that mRNA represented.

As rational as this seems today, we were dumbfounded by the lack of interest. How could they not see the same potential in mRNA that we did? The disconnect was maddening, but also motivating; and eventually we found a private business angel who wanted to help us find other investors. Our prayers had been answered—or so we believed.

Unfortunately, our business angel suddenly got cold feet when he realized how long the road ahead was going to be and how little interest other investors had in us or our technology. He abruptly withdrew all his money just a few months later.

Complete turnarounds like this are, unfortunately, all too common when raising capital. However, when you're in a fight for your company's life, calm, rational thinking is often replaced by desperation. But we remained persistent and tried to find one last lifeline.

We found one—our first true savior. The fund was Leonardo Ventures (Mannheim, Germany), a small venture capital boutique that was prepared to invest a little money so we could at least move from the university into the nearby technology park.

Leonardo Venture was very interested in biotech but had no expertise of its own. This gave us the opportunity to convince them without losing too much time in a drawn-out, science-driven due diligence process. At the start of 2003, we secured €2.7 ($3.5) million, which enabled us to reach the next milestone: moving into the newly established technology park in the city of Tübingen.

Creating a flexible business model

While our operations were getting up to speed, our liquidity rapidly took a nose dive. We had difficulties convincing additional investors solely on the basis of our preclinical data. Simultaneously, the recession in German biotech was lingering and our existing investors did not have an adequate network to support us.

Although I would agree that biotech entrepreneurs require an unwavering belief in their vision and the potential of their technology, at times this zealousness must be tempered by practicality. For CureVac, this meant switching to 'emergency mode' and taking on service tasks for clients in our key area of expertise, RNA. This involved primarily manufacturing oligonucleotides (siRNA and antisense constructs) and making chemical modifications. We restructured our processes to meet these requirements.

Despite being disappointed in having to delay our own research and development, this period of time provided us with invaluable insights into our own technology and how we would want to eventually develop our own pipeline. When we were filling customer orders, we incorporated and tested a substantial number of different modifications using our technology. This experience reaffirmed our understanding that CureVac's products should continue to use natural RNA bases, without chemical modifications. In retrospect, working with clients allowed us to de-risk our approach by attempting different combinations, which proved a key advantage from both a development and cost perspective in drug development.

While we were inadvertently broadening our knowledge base by working on projects outside of the focus of our clinical development programs to earn enough money to keep the lights on, it was a difficult period from a psychological point of view because we had to temporarily shelve our core programs.

A turning point

Thankfully, good fortune shined on us again, and we met Friedrich von Bohlen, the former CEO of LION Bioscience (Heidelberg, Germany), the 'biotech star' of Germany. He was searching for a suitable investment and a company with an innovative technology platform enabling the widest possible range of therapeutically relevant information to be delivered into the human body, a vision he had long pursued for LION.

We were once again able to talk about our actual approach. And von Bohlen quickly became enthusiastic when he heard what was actually possible with mRNA technology; within 30 minutes, he was convinced and decided to invest in our company. This was a turning point.

His interest in the company encouraged our existing investors to once again provide us with funds. By 2006, we were saved. Reinvigorated with fresh capital, we revised our business plan, and with the help of von Bohlen, we were connected with Dietmar Hopp, the founder of European software giant SAP (Walldorf, Germany). Known as the Bill Gates of Germany, Hopp was an investor we would have never considered given his primary interest in information technology. However, he turned out to be the perfect partner for CureVac because he could see what typical biotech investors could not. To Hopp, mRNA represented the computer code for the human body.

With Hopp's guidance, we chose our lead indication based on the size of the patient population and our knowledge about the relevant antigens. Hopp agreed to invest €35 ($38, at the time) million. With this fresh influx of capital, we no longer needed our emergency plan of customer service and dedicated ourselves once again to our true goal of bringing our mRNA technology into clinical use. In January 2009, we successfully inoculated our first patient with our proprietary formulation.

Growing pains

After many years of trial and error, repeatedly networking ourselves and drawing upon the criticisms and advice of multiple experts,

we were finally realizing our vision of transitioning from an academic concept to a viable biotech business. For the first time, we could define ourselves as a living and breathing company with substantial capital in hand, a network of investors and experts within arm's reach, and a business and clinical plan to bring our vision to fruition.

However, as clarifying as this moment was for the stability of CureVac, it presented new challenges for the growth of the company. Namely, we would now be expected to use this capital to build a real, functioning biotech business. For entrepreneurs, this realization can be even more daunting than the tooth-and-nail fight to raise capital because it requires the implementation of myriad operations and the management of numerous executives and employees.

Building the right team is ultimately the most important factor in a company's success, but it is particularly critical in the area of biotech. The complexity that defines the structure of a biotech company means that a single person can never cover all the expert skills needed. It is important that people with the appropriate strengths are taken on in all the essential areas—science, processes, business planning and control, finance, business development and human resources.

As CureVac grew, we realized that adding specialists (and supporting staff) in key areas helped to strengthen our overall business. However, conflicts repeatedly arose because of the different socialization of employees from the pharmaceutical industry, biotech and universities. Tough decisions had to be made, sometimes involving the removal of key personnel, when the collision of cultures and perspectives inhibited the growth of the company.

As a scientist, I am accustomed to binary outcomes and data-driven results. But as a manager of people, such black-and-white assessments are vastly more challenging. Initially, we grossly underestimated what was required to manage the constant change within the company as it grew. Seemingly, each solution led to a new set of complications.

However, we came to the realization that the same scientific discipline we adhere to in the laboratory needed to be applied to the management of our company. We determined that the individual interests of the various protagonists must be positioned within the context of the overall interest of the company. This also concerns the ongoing development of the founders who must continually adapt to the new circumstances. Just because we founded the company doesn't mean we're best equipped to handle every situation.

Five keys to flight

From this long process of building a company, I've come up with a handful of tips that can help innovative technologies get off the ground outside of a biotech stronghold. The five major ones are presented below.

First, for CureVac, incubating inside the university gave us a boost. Today, such tech transfer relationships are commonplace, as universities around the world recognize the value in aiding budding scientist–CEOs. Academic entrepreneurs should seek out these opportunities. Resist the desire to spread your business wings right away; stay close to the nest and investigate opportunities inside your university. It will allow you to grow in surroundings that are familiar, while giving you access to infrastructure that you'll only realize you need after you've begun your work. The university network can also be very advantageous.

However, be careful not to hand over too many rights to the university. This could be toxic for further financing rounds. What's more, conflicts can arise between professors and budding executives, owing to the natural friction between academia and business. If you find yourself challenged by your affiliated university, seek out others that might offer reasonable support for your startup, as this can not only help your bargaining power but also address conflicts with the institute to which you're currently affiliated.

Second, when we founded CureVac, we assumed that having a disruptive technology like mRNA would make finding investors easier. The opposite was true; disruption can be a distraction to more cautious investors. Therefore, you need to identify open-minded personalities who have a broad perspective on business and innovation. They often see the bigger picture, and can be a gateway to reaching other, like-minded influencers.

Unquestionably, the turning point in CureVac's growth was our relationship with Friedrich von Bohlen. Not only was he instrumental in facilitating a critical round of financing, but he also provided validation for us that paved the way to our meeting with Dietmar Hopp, our most significant benefactor. Attracting an advocate like Friedrich von Bohlen can be the essential ingredient that brings you to success, but identifying such personalities isn't easy, and even once they're identified, there is strong competition for their attention.

The best way to start this process is to build your own network from scratch. Get to know as many relevant people as possible, and talk to them plainly without overselling. Be patient and focus on developing a growth strategy that differentiates your company from others. Be authentic; never pretend to be something or someone you are not. For those companies not in biotech hubs, don't immediately think you must travel far and wide. Travel may become necessary later, but start networking closer to home first.

Third, investors are by definition risk takers, but they take calculated risks. This dichotomy can make it challenging to convince investors to gamble on emerging companies, especially ones that lack the geographic or industry pedigree. If you are a trailblazer in your field, as CureVac was in mRNA therapeutics, consider non-dilutive public funding programs. These programs usually are easier to access and will help you produce the meaningful data that can help secure investors. Valid preclinical data, and ideally broad patents, are essential. In addition, the personalities of the founding team play a crucial role. You need to be able to authentically demonstrate why your team will be successful. No investor will invest without strong confidence in the team.

Fourth, the adage in biotech, and all company formation, is to hire the best people you can. This can be hard outside of a biotech hub. To quote Jianming Li and William E. Halal, "Many biotechnology companies fail not because of bad science, but because their management personnel did not have the knowledge or skill to design and guide a complex research organization effectively" (*Nat. Biotechnol.* **20**, BE61–BE63, 2002).

I frequently reminded myself of this as CureVac grew. I knew the key to success was going to be cooperation. When building a company, you will never have enough resources. Consequently, you will be able to make progress only when cooperating intensively with other company members and external partners. This is why you need to hire people that share this cooperative spirit.

In the beginning, a startup company is not much different from an academic work group. You need to work with the team and elevate each member according to their respective strengths. In CureVac's early days, we had just a junior staff, hungry to build something 'big'. It was only after we had significant financing that we could acquire the knowledge of expensive experts.

When it is time to hire from outside, the solution *per se* is not to just bring aboard people with big pharma experience. They are accustomed to a work environment governed by process and protocol. That sort of steady hand needs to be balanced with the faster, more adventurous mindset of staff in biotech startups.

Be prepared to reinvent yourself several times as you grow; changes to the management team should be encouraged, not avoided. This can be difficult for entrepreneur CEOs to

accept because of loyalties to original team members. I have felt this myself. Instead, you must be objective in your assessment of your company, putting aside personal feelings. If personnel issues arise, act according for the needs of the company, not your wishes. You need to engage change and add new people to the management team. In these situations, it is important to communicate authentically and openly with all investors.

Once you reach a critical mass and validated technology, it is easier to find experts. One way to do this is by opening sites in hub cities. In our case, we opened a site in Frankfurt to gain clinical experts and a site in Boston to find business development specialists. It is easy to keep communication open these days, with video conferencing.

Finally, if you intend to remain CEO after launch, you will need to change as your company grows. At the onset, you first need to decide which role you would like to assume within the company. For me, being chief scientific officer was never an option; my strength lay in being a CEO rather than leading research. When you decide to be a CEO, delegate research-related topics to a dedicated colleague—heading research and being a CEO at the same time will not work out.

You might need training in management or leadership topics. Being a CEO primarily means delegating operative topics; founders that are not able to do this will fail. Moreover, you need to be honest with yourself about your skill set and the areas in which there are better qualified people than you. You then need the courage to hire those people.

I always keep in mind that a certain type of CEO is needed for every development phase of a company, and it is important to verify from time to time whether you still fit the requirements of the current (and future) development phase. For me, an important indicator is whether you still enjoy being a CEO—if you don't enjoy it anymore for a longer time period and you face some sleepless nights, it is time to consider other options. Remember, as much blood and sweat as you put into your company, the company is more than you.

COMPETING FINANCIAL INTERESTS
The author declares competing financial interests: details are available in the online version of the paper.