

THE COMPANY HISTORY OF CUREVAC

Bernd Eberhart

PREAMBLE

Dear readers,

We've all experienced it – the sudden flashes of inspiration that turn into obsessions we can't get rid of. That idea that consumes you, follows you wherever you go, grows and takes on a life of its own and that you no longer have any control over. More often than not, those kind of ideas take a hold of us much like a high, short-lived fever: They are like a raging fire burning us up on the inside for a couple of days, but quickly burn themselves out, leaving us with a vague feeling of surprise about the whole thing. However, in our case, we were gripped by just such an idea in our time as researchers at the University of Tübingen. And instead of burning itself out, it kept us in its grip, and continues to do so to this day.

Now, you may wonder what it was about that idea that stopped us from delegating it to some dark corner of our minds. What, initially, turned it into an intention, then a plan, a project, a start-up and, finally, a company with over 300 staff? We think it was a unique blend of favorable factors: Such as youthful enthusiasm, for example. And naivety. Colleagues that weren't just brilliant, but also good friends. A couple of really stubborn and obstinate people. Passion, a pioneering spirit and the courage to start something new. And a pinch of good luck. And, of course, the idea itself: an idea as simple as it was compelling in that it had the potential to help millions of people to live healthier lives. People have a tendency to forget what it was that inspired them in the first place and to dismiss how and why it came about.

Recognizing this tendency, it is important to us to preserve the inspiration and idea that gave rise to CureVac. To keep it alive, make it inspire our actions and be our motivation. For this reason, we would now like to treat you to the story of how our company came about and how it came to be what it is now. The majority of that story is made up of the early years, the ones filled with restlessness and uncertainty, because they are also the ones that are most at risk of being forgotten, and because they are a reminder of the core of CureVac as a company, its spirit and roots. Although you will be treated to the shortened version of the earlier part of CureVac's history, we by no means intend to belittle the significant successes jointly achieved by all of our **RNA people** during that period.

It makes us proud that our idea is thought through and further developed by so many bright people. And we love this history, which we share with so many friends, fellow believers and colleagues, and it is only thanks to having worked as a team, that we have been able to achieve all of the things we have. Looking ahead rather than back, we are also intrigued by what the future will bring as we are on the brink of a new chapter in medical history – which all of the **RNA people** will be making together. And we are very much looking forward to it!

The image shows two handwritten signatures in black ink. The signature on the left is 'Ingmar Hoerr' and the signature on the right is 'Florian von der Mülbe'. Both are written in a cursive, flowing style.

Your Ingmar Hoerr and your Florian von der Mülbe

PROLOG

All of life is based on just four miniscule building blocks, four elemental bases – adenine, guanine, cytosine and uracil – which, by remaining stable and continued replication have given rise to the stupendous diversity of life we see on earth. When bound to the sugar molecule ribose and, in turn, linked by a phosphate backbone, these nucleobases form a long-chained, single stranded macromolecule – ribonucleic acid, RNA for short.

Its ability to store information in the shape of specific sequences of these nucleobases and its replicability explain why RNA plays a key role in biology – a role that has evolved over millions of years. RNA fulfills a number of tasks. As a messenger molecule, it quickly mediates between the information permanently stored in a living being's genetic code and the production of the individual building blocks of which it is composed. Every protein, every enzyme inside our bodies was once created on the basis of a genetic blueprint mediated by RNA. Consequently, our bodies' cells are also capable of producing every conceivable protein and every imaginable enzyme from an RNA molecule with the corresponding base sequence.

This means that everything that the body needs in order to produce a vast number of different proteins – and hence a vast number of potentially therapeutic proteins – is the corresponding blueprint. This is why RNA has tremendous potential for a truly new and revolutionary approach to medicine: the medicine in the information age. However, is it possible to administer a specific RNA molecule to a person in such a way that it will actually be taken up

by his body and translated into proteins? What are the characteristics, combinations of other substances and dosages best suited for achieving this? The person or persons who are able to provide the answers to these questions will hold the key to the medicine of the future.

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On the morning before the most important talk in his career, Ingmar Hoerr found himself without a razor. On this day in the fall of 2005, his head was already spinning when he was getting out of bed and walking into the bathroom of his hotel room in Heidelberg. This was because it was just about five years since Hoerr and his friend and fellow student Florian von der Mülbe, and their colleague Steve Pascolo had founded the company CureVac. The following years had been a constant roller coaster ride. During that period, grand visions, euphoria and sudden flashes of inspiration alternated with sleepless nights, setbacks and very difficult times, while the young company met with much support and positive response, but also resentment and sudden pull-outs. Throughout this period, money continued to be a difficult issue – from finding investors to securing the necessary funding and narrowly escaping insolvency over and again. Despite all of these difficulties, the vision, pioneering spirit and team spirit at the heart of the company the firm belief that it was working on a revolutionary technology and our awareness of the incredible therapeutic and medical potential inherent in the RNA molecule, remained unchanged. This, then, was the company's greatest opportunity yet: a meeting with Dietmar Hopp – the founder of SAP, an investor and multi-billionaire. Ingmar Hoerr and CureVac's former finance director, Wolfgang Klein, are being expected in Hopp's private office at the St. Leon-Rot Golf Club, south of Heidelberg. They have been granted about 60 minutes to impress Hopp with their concept and company – ultimately, with a view to securing potential financing from his *dievini Hopp BioTech holding GmbH & Co. KG*. The shirt is ironed, the suit ready to go. Looking at himself in the bathroom mirror, the company founder, Ingmar Hoerr, notices slight butterflies in his

stomach and a sense of positive tension. As he is looking for his razor. And can't find it. Damn! Because in 2005, designer stubble hadn't made its comeback yet.



Clubhouse of Golf Club St. Leon-Rot – a historic place for CureVac
(picture source: golftime.de)

Despite the butterflies, the pitch delivered – freshly shaven, thanks to Wolfgang Klein's spare razor – in Dietmar Hopp's private clubhouse office went without a hitch. While the potential investor comes across as factual and a little detached, there is one thing that is subtle but clear from the start: the chemistry is right. Hopp is nearly motionless as he listens to Klein and Hoerr speak, has a serious look on his face, nods every so often and asks the occasional brief question. Most important of all however, is that he is giving the pair his full attention. Until at some point, it became clear that something had clicked – that CureVac's vision might indeed be falling on fertile ground. Dietmar Hopp finished the meeting by pronouncing the pitch »interesting« and expressing his intention to look deeper into this.

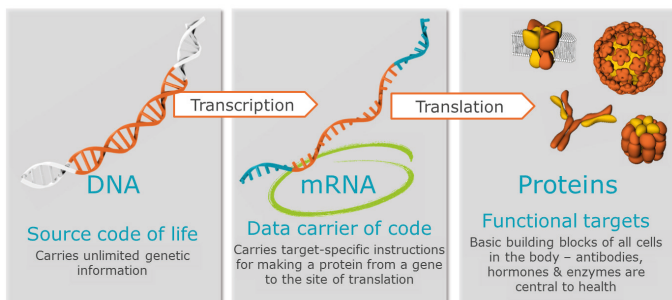
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Seven years earlier, nothing could have been further from Florian von der Mülbe and Ingmar Hoerr's thoughts than investors and golf clubs, because they were both busy doing doctoral research at the University of Tübingen. Von der Mülbe was awarded a PhD in biochemistry/organic chemistry under Günther Jung, while Hoerr was working towards a PhD in biology and divided his research between the institutes directed by Prof. Dr. Günther Jung and the immunologist Prof. Dr. Hans-Georg Rammensee.

The beginning of the 1990s marked the dawn of the age of gene therapy. At the time, the two young scientists were particularly impressed by research conducted by the biochemist and geneticist Jon A. Wolff from the University of Wisconsin published in the highly renowned magazine *Science*: Wolff and his team had been able to demonstrate that it was actually possible to perform experiments directly inside muscle cells, i.e. for mRNA to be converted into proteins, by injecting DNA and RNA segments directly into the muscles of mice. A revolutionary insight – because if you could make an ill person's body produce the very proteins it needed to heal itself, this would open the doors to as yet completely unimaginable treatment options.

Ingmar Hoerr also caught the gene therapy bug by the middle of the 1990s. As part of his doctoral research, he initially investigated the administration of DNA segments whose gene sequences contain the code or blueprint for specific proteins – that is, the very kinds that could potentially act as prophylactic or therapeutic vaccines against infections or cancer. However, he soon started to have doubts about DNA as a suitable molecule, because DNA segments injected into a cell nucleus' can potentially become permanently integrated in the genome, that is, become part of the patient's

genetic material. Further, on the one hand, they can potentially destroy important genes if they are integrated in an unwanted place and damage an existing gene sequence, and on the other, in such a case, it would not be possible to control the gene, such as in order to stop the production of a substance once a patient's health improves. Following these considerations, Hoerr soon made a pivotal decision, which was, instead of DNA, the stable, long-chained carrier of our genetic material, to use the more unstable RNA as the carrier molecule.



mRNA is able to deliver the formula for endogenous drugs

Ribonucleic acid, RNA for short, is structurally closely related to deoxyribonucleic acid, DNA. RNA has a number of different roles inside the body, one of which is to act as a messenger molecule. That is, if a particular protein needs to be produced in a cell, the cell needs the gene in our genetic material coded with the relevant information as a blueprint for producing this protein. This gene, alongside thousands of other genes, comprises a short section of

chromosome, that is, an incredibly long DNA molecule. To start with, this short DNA segment is copied – and that is, in the form of a RNA molecule. This messenger – which is why they are called messenger RNA or mRNA for short – transports the protein blueprint out of the cell nucleus. In the next step, based on this blueprint, the corresponding protein molecule is then built from a wide range of individual building blocks.

Hoerr was convinced that RNA would be much safer for therapeutic use than DNA. Because it has a different molecular structure than DNA, it cannot integrate itself in the genome. Furthermore, every cell also contains so-called RNAses, enzymes that, by way of a safety mechanism, catalyze the degradation of RNA into smaller components and deactivate them. This means that administering a drug in the form of RNA would make it possible to calculate the exact point at which the cells have digested the injected molecule – i.e. it has a clearly defined half life. This major advantage of RNA, its short life, also has its disadvantages. That is, at the end of the 1990s, many scientists believed that the watchful RNAses would have degraded the injected molecules long before they could have been translated into proteins in the cell. Like many other researchers, Ingmar Hoerr therefore came up with a trick: in order to extend the life span of RNA, Hoerr encapsulated them in liposomes, small spherical membranes that act as protective capsules. In 1998, with half of his doctoral research completed, Hoerr – by sheer coincidence – made a momentous discovery. This discovery would not only give his doctoral research a new twist, but also significantly impact on his life and future.

For an experiment with mice, Hoerr chose a RNA molecule coded for β -galactosidase, an enzyme often used as a marker in

molecular biology. He then injected these RNA samples, encapsulated in liposomes, into the auricles of mice. In this experimental design, there are two things that are subsequently relatively easy to keep track of: the first is whether the mice's cells actually produce the gene product, that is, whether the injected RNA is actually translated into β -galactosidase. And the second, whether the exogenous protein triggers an immune response – that is, whether the immune system creates antibodies and specific T-cells to fight the intruder.

The experiment's results were basically disappointing. The β -galactosidase formed by the cells in the ears of the treated mice was barely detectable and there was virtually no immune response. However, the control experiment run in parallel delivered an unexpected surprise: as a negative control, Hoerr had injected other mice with the same molecules, but as naked RNA, i.e. without the protective liposome membrane. Doing so was not anticipated to produce any effects, as the prevailing school of thought held that the unprotected molecule would be immediately digested by the omnipresent RNAses. You can therefore imagine Hoerr's surprise when this negative control produced a resoundingly positive response as early as the first injection: Hoerr verified the expression of β -galactosidase in the cells from the mice ears and identified corresponding antibodies in the blood. And, removing sample tissue from the mice's spleen just a couple of days later, he was able to identify specific T-cells. Contrary to all expectations, the naked RNA seemed to have triggered a strong immune response.

Initially, Hoerr thought that there had to be a mistake. That perhaps he hadn't paid attention or mixed up samples, as occasionally happens with lab work. While some researchers would have just

dismissed those results as meaningless – especially considering that the prevailing school of thought clearly didn't consider such a thing possible – Hoerr, was intrigued by these idiosyncratic results and, in true researcher fashion, spurred to investigate. As a result, he repeated the experiment, this time with extra care. And produced the same result. It was then that Hoerr suddenly realized that the generally held belief that naked RNA is immediately degraded had just been refuted – and that it opened up a completely new area of therapeutic possibilities that had the potential to radically change the field of medicine.

That same evening, very excited and being very secretive, Hoerr asked Florian von der Mülbe and Steve Pascolo to join him in this laboratory, where he shared his results with them for the first time. The next day, a Saturday in 1998, he picked up the phone and dialed the numbers of his doctoral supervisors Günther Jung and Hans-Georg Rammensee, to let them know that he urgently wanted to register a patent.



Fast forward to summer 1999, a sailing boat in the middle of the Baltic Sea, somewhere between Stralsund and Bornholm, where Ingmar Hoerr, Florian von der Mülbe and a colleague from the laboratory next door had come together to, rather grandly, hold a »Baltic Sea Symposium«. There was a lovely breeze, the sun was shining, and the sailors were in a happy mood. However, the relaxed atmosphere was misleading, as all of the ten attendees, each of whom was just about to complete their doctoral degrees, did feel rather lost. Unsure of what the future outside of the safety of their

university settings would hold and where to go from here. Unsure of whether they would actually be able to meaningfully apply all of the knowledge they had gained through countless seminars, lectures and experiments. These uncertainties arose from the fact that, while they had been perfectly trained to address extremely complex questions during their years of study, they had, like so many academics, received little training in how to deal with the realities of the world of business. Hoerr had just obtained his sailing license and was ferrying the group across the sea in the day time, while mornings and evenings were reserved for talks: every attendee gave a talk about their specialist area, about potential scientific and economic areas of application, opportunities and new approaches.



The »Ostseesymposium« during the summer of 1999 lays the foundation for establishing CureVac

On the return journey from Bornholm, the weather suddenly turned rough as the breeze turned into gales, and the young sailors had to deal with gale-force winds, tremendous waves, frothing foam and spray penetrating their every pore. However, they immediately stood together, got to work, shortened the sails and

resolutely faced the storm, which is when they realized that they can depend on each other. Despite that knowledge, there was a growing sense of unease, starting right in the gut and slowly spreading to the rest of their bodies. Even the skipper's hand started to shake slightly on the control. And yet, whether they liked it or not, there was only one way, and that was going forward and straight through the wind, waves and spray. By the time they were delivered into the safety of the harbor entrance by the last wave, although freezing and dripping wet, the entire gang – happy and relieved – stood together as one, welded into a team.



Ingmar Hoerr (in front, kneeling) and Florian von der Mülbe (far left) decide to establish their own company during the sailing trip in 1999

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One day next fall, Ingmar Hoerr, Steve Pascolo and Florian von der Mülbe were sitting together in Hoerr's small apartment in the western district of Tübingen, all cheerful but ready to attend to serious matters. They spent hours trying to think of a name – the name under which they were going to register their very own company. At the time, Pascolo was a postdoc working at the university. Von der Mülbe and Hoerr had successfully completed their doctoral degrees and were definitively about to enter professional life. Von der Mülbe had received an attractive offer to work for a pharmaceutical company, and Hoerr was temporarily working for a Tübingen start-up as an advisor to the company director. However, none of them were entirely happy with their traditional roles as small cogs in a machine, but they were also very aware that academic careers in science were hard to come by and that working for a commercial company would leave little room for personal initiative and creativity. At the same time, Baltic Sea winds were still inspiring in them a sound zest for entrepreneurial action and none of them had forgotten Hoerr's remarkable experimental findings. Furthermore, the things the three of them definitively agreed on were the immense potential inherent in technology, the possibility that this technology might one day help people, and that it might help them to heal or stay healthy. The University of Tübingen itself, by the way, had virtually no interest in continuing research into RNA-based therapy and even returned the rights to the patent to Hoerr in order to avoid having to pay for registering the invention. As things stood, the three of them were actually receiving a fair bit of ridicule from the scientific community for their idea and were even being laughed at – RNA? An unstable molecule? Used as a drug? Which just went to show how deep the dogma had infiltrated the thinking

of those scientists. At the same time, Hoerr was very aware that working in academic science would simply boil down to spending years conducting animal experiments without ever achieving any significant breakthroughs, as well as that developing a real proof of concept, data with relevance and the major steps required to develop a treatment, a real drug – would only ever be achievable within the context of complex clinical trials involving human participants. And yet the niggling question remained: was it right for the idea of RNA based vaccines to be put to rest in dark laboratory cabinets and the written pages of a thesis? Was the patent, which had been registered by now, destined to collect dust in an old folder or languish there until picked up by a smart American with the courage to invest in a risky business idea?

At the end of the 1990s, future technologies were booming in Germany and the market was in the grip of a gold rush-like atmosphere. As of 1997, the new market was in a complete frenzy and IT, multimedia and biotech start-ups were virtually inundated with willing investors. Which was when the three friends realized that they had no choice but to do their own thing. That they had to found their own company. Or, at the very least, give it a go.

When it came to deciding who would take what role, things couldn't have been any easier. Steve Pascolo, the trio's most experienced scientist, would take care of the scientific aspect. Florian von der Mülbe was the ideal candidate for taking care of everything that required planning, precision and issues of technical implementation. While Ingmar Hoerr would be in charge of vision, decisiveness and motivation. So there they were – three young men ready to take the bull by the horns and make history. Notwithstanding all of this, they had to come up with a fitting name for their enterprise

first. Which means they were still sitting in that apartment that night, deeply in thought. This name was to have a positive ring, be dynamic and forward looking. It definitely needed to be in English, as is the custom in the biotech sector, and virtually spell out the company's entire mission in a single smooth flowing word. It also had to include »RNA« somewhere in there? Or not? The trio went through countless plays on words and abbreviations, the whole range of conceivable letter combinations containing »RNA«, and finally settled on »RNAengine« as the preferred candidate for their company name. That is, until they remembered their vision: finding a new method for administering vaccines. And, in doing so, relieve people from their suffering and cure them – which all of a sudden made the words cure and vaccination stand out for them, and gave birth to »CureVac«. They liked it. When it came to a subtitle, the trio settled on »*the RNA people*«, because that's what they are.

Hoerr initially registered the company in his own name and, in the fall of 1999, he finally held their trade license in his hand and, by attaching a handwritten sign under the bell of his tiny apartment, turned his glorious abode into the company's official headquarters. At the time, the world was still in the middle of the transition from the analog to the digital age. The young entrepreneurs were connecting to the internet through a smooth purring modem; while the new company fax machine mostly spewed out junk faxes throughout the night, depriving Ingmar Hoerr of his sleep. In 2000, CureVac became a GmbH. Apart from Ingmar Hoerr, the shareholders included Florian von der Mülbe, Steve Pascolo and the doctoral advisors Günther Jung and Hans-Georg Rammensee. Both of the latter firmly believed in and fully supported the concept, but were unable to provide further financial backing. Initially, their

mission was to research therapeutic vaccines for treating cancer, to develop and then market them.

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In the meantime, Ingmar Hoerr had published the surprising discoveries made in his experiments with naked RNA together with his laboratory colleague Reinhard Obst, who introduced him to immunological methods, in a scientific paper. The paper had been reviewed by the reviewers of the highly regarded specialist journal Nature. One of these reviewers had been relatively open-minded, the second had been neutral to sceptic, and the third reviewer plainly derided it as complete and utter rubbish. In retrospect, this was incredibly lucky, because the attention the research would have received had it been positively regarded would, at the time, not only have resulted in a marginal advantage concerning expertise and patents, but would potentially also have brought powerful competitors to the fore. In January 2000, Hoerr et al.'s article *»In vivo application of RNA leads to induction of specific cytotoxic T lymphocytes and antibodies«* was finally published in the European Journal of Immunology – as the first article the journal published in the new century! The dawn of a new age and a new form of medicine is born ... what a potent omen for their enterprise!

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In vivo application of RNA leads to induction of specific cytotoxic T lymphocytes and antibodies

Ingmar Hoerr¹, Reinhard Obst², Hans-Georg Rammensee² and Günther Jung¹

¹ Department of Organic Chemistry, University of Tübingen, Tübingen, Germany

² Department of Immunology, Institute for Cell Biology, University of Tübingen, Tübingen, Germany

To study the efficiency of RNA-based vaccines, RNA coding for the model antigen β -galactosidase (β -gal) was transcribed *in vitro* from a lacZ gene flanked by stabilizing *Xenopus laevis* β -globin 5' and 3' sequences and was protected from RNase degradation by condensation with the polycationic peptide protamine. The liposome-encapsulated condensed RNA-peptide complex, the condensed RNA-peptide complex without liposome or naked, unprotected RNA, was injected into BALB/c (H-2^b) mice. All preparations led to protein expression in the local tissue, activation of L^d-restricted specific cytotoxic T lymphocytes (CTL) and production of IgG antibodies reactive against β -gal. RNA-triggered CTL were as efficient in the lysis of lacZ-transfected target cells as CTL triggered by a lacZ-DNA eukaryotic expression vector. Immunization with RNA transcribed from a cDNA library from the β -gal-expressing cell line P13.1 again led to β -gal-specific CTL and IgG induction. Thus, both naked and protected RNA can be used to elicit a specific immune response *in vivo*, whereby the protected RNA is stable *in vitro* for a longer period of time. RNA vaccines can be produced in high amounts and have the same major advantages as DNA vaccines but lack the potentially harmful effect of DNA integration into the genome.

Key words: RNA vaccine / CTL induction / RNA protection / RNA library / β -Galactosidase

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1 Introduction

A large number of human tumor-specific antigens have been identified which can be utilized for tumor gene therapy [1]. In addition there are some approaches for inducing tumor immunity without the need to identify the tumor-specific antigens, such as immunization with heat-shock proteins [2] or multiepitopic RNA derived from tumor cells [3]. Nucleic acids are important tools for somatic gene therapy and prophylactic and therapeutic vaccination against infectious and malignant diseases. Typically, DNA vaccines are bacterial plasmids carrying genes for pathogen or tumor antigens that are transcribed in the injected host using a strong viral promoter

[4]. They offer concrete alternatives to conservative methods for generating CTL by priming *in vivo* with traditional live attenuated virus [5] with its associated risks or by immunization with peptides [6] which may be limited in their suitability for genetically variant populations.

Since RNA is very prone to hydrolysis by ubiquitous ribonucleases, gene therapy approaches involving nucleic acids have focused on DNA. A potentially unique advantage of using RNA rather than DNA is that no virus-derived promoter element has to be administered *in vivo* and no integration into the genome may occur randomly or as a result of homologous recombination leading to mutational inactivation of cellular genes, and, more importantly, the possibility of oncogenesis [7]. It has been shown that naked RNA injected into mouse skeletal muscle does indeed lead to gene expression *in vivo* [8] and that cytotoxic T cells can be primed *in vivo* with liposome-encapsulated mRNA, which so far could only be prepared by a complicated procedure [9]. It also has been shown that a carcinoembryonic antigen (CEA)-specific antibody response could be induced by CEA

[1 20021]

CureVac company history

Not long after, a graphic designer friend set to designing the first CureVac logo, in which the lettering is framed by concentric ovals. It is reminiscent of the kind of ripples that a drop creates on the surface of water in the same way that a brilliant idea simply pops up, develops, grows and creates ripples that move in all directions.



Stand 2000



Stand 2001



Stand 2003



Stand 2007



Stand 2013

The CureVac logo through the ages

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In order to be able to draw on a solid understanding of the world of business alongside his biological and biotechnological expertise, Ingmar Hoerr enrolled on a *Master of Business Administration (MBA)* program at the Danube University Krems. The first – and pretty naive – business plan developed by the trio foresaw that CureVac would be bringing to market a therapeutic mRNA agent within the next five years. The intention was there. As was the energy – and that goes without saying. The only thing CureVac was missing that day in 2000 was money. This was very much a problem. Setting up the company had involved hefty costs, as had registering the patent, the costs for which Ingmar Hoerr and his two doctoral supervisors bore themselves after the university expressed its disinterest. At the same time, the economic climate had unfortunately changed completely within a matter of months, with prices at the new market experiencing a downward trend and the emergence of the first rumors of various bankruptcies. While the recent past had seen investors back and finance even the craziest of ideas, they started to be less and less forthcoming as time went on, to the point that it became nearly impossible for an unknown start-up to raise money through venture capital. One of the primary business activities undertaken by CureVac at the turn of the century was therefore taking part in business plan competitions. Those competitions allow young entrepreneurs to walk away with new-found confidence, as well as 1000 German Marks (DM) of capital funds, sometimes even 2000 DM. Far more important, however, were the contacts – with consultants, industry insiders and potential investors – that Hoerr, von der Mülbe and Pascolo were able to establish through those competitions. As a result, the founders were eventually approached by a venture capital firm from

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Jena in the wake of just such a contest. However, the Jena firm demanded a full 20 percent stake in the company in return for their financing – which the trio consider too high a price. Over the coming months, the founders are gradually coming to realize that getting their company going would not be quite as easy as they thought.



The founding team flanked by their scientific advisers (left to right): Prof. Hans-Georg Rammensee, Dr. Ingmar Hoerr, Dr. Steve Pascolo, Dr. Florian von der Mülbe and Prof. Günther Jung

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The essential question of how to enable CureVac to overcome the significant obstacles on the path to clinically trialing a drug were

consequently intensely and extensively debated by Hoerr, von der Mülbe and Pascolo. One day, a spur-of-the-moment decision saw them get into their car and drive to the Paul-Ehrlich-Institut, the German Federal Institute for Vaccines and Biomedicines, in the Hessian town of Langen, where they hoped they might receive help, advice and tips on how to proceed. However, the institute experts they met with were rather astonished, because business owners would normally come to them with ready established data and clinical development strategy plans. They were nonetheless forthcoming with information and advice – although the experience as a whole was rather sobering. One of things they learned was that in order to conduct phase 1 clinical trials, researchers had to have accumulated extensive preclinical data from animal models and definitive information on a substance's pharmacodynamics and toxicology. Above all, the laboratories used to produce an agent had to employ GMP-compliant equipment – a very strict standard used in pharmaceutical production. Where on earth were they now going to find a GMP laboratory, not only at short notice, but also at a price their limited budget would allow? As they were driving home, the trio's heads were spinning since, rather than becoming smaller, as they had hoped, their obstacles had just become greater and bigger, and seemed near insurmountable. It didn't take long, however, before there was a new glimmer of hope in terms of GMP when the Tübingen Regional Board provided the young company founders with solution-oriented and practical advice, which in turn reignited their ambition.

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Right from the beginning, one of the factors that has remained a constant throughout CureVac's history has been that famed light at the end of the tunnel that tends to appear out of the blue. As luck would have it, CureVac was treated to as much as two such lights in the middle of 2000, both of which originated from the Baden-Wuerttemberg Ministry for Science, Research and Art. Ingmar Hoerr and Florian von der Mülbe had both independently submitted applications for a promotional program for »Young Innovators' run by the ministry. This program is designed to help young scientists to further their ideas, and produce and sell their innovative products or methods independently. Both Hoerr and von der Mülbe had been invited to the Haus der Wirtschaft in Stuttgart for a short interview and to pitch their projects. Both times, the interviews were held in a tiny, stuffy room crammed with experts and assessors; and both times the CureVac founders were standing in front of an ancient projector, explaining the idea and concept behind their company, detailing its vision and targets. They did a great job with the first ever major pitches in the company's history. Both times, they received a letter in their company headquarters' letterbox in Tübingen shortly afterwards. Both of the letters were delivered in the dreary brown-grey kind of envelopes typical of official institutions. The letters' exterior was in stark contrast to their contents, which couldn't have been better: a positive decision concerning their applications for funding for a two year period – for each of them! It also meant that Ingmar Hoerr and Florian von der Mülbe could now officially call themselves »young innovators«.

Apart from the funding, it is the infrastructure that the young innovators were now being provided with that instantly gave rise to new opportunities. Sometimes, as events now demonstrated,

taking a step forward also entails taking one back – which in CureVac case entailed a return to university. That was because the ministry's innovator support package, known as an incubator system, included the possibility of enlisting the services of degree and doctoral candidates employed by the university, and – importantly – free use of a laboratory on the Tübingen Morgenstelle campus.



The »Morgenstelle« in Tübingen is CureVac's first official location

Not that the particular seminar room they were allocated on the campus was a particularly attractive option, but at least it was a beginning, and with the university behind them, the company was finally able to apply for further funding to buy basic laboratory equipment. To start with, they had two doctoral candidates,

Birgit Scheel and Jean-Philippe Carralot, come to work for them part time, as well as a number of interns that help on a weekly basis. The Ministry's funding and a loan subsequently obtained from a bank even allowed the company to hire two specialist staff, which made Lilia Gontcharova and Ladislaus Reidel CureVac GmbH's first ever real employees. Reidel even went as far as to move his entire family right across Germany to the neighboring town of Rottenburg especially for this job. He was so taken by the idea, by the vision of RNA-based therapeutic technology, that he was willing to build a completely new life for himself as part of the Tübingen company despite all of the uncertainties that plagued the small start-up.

On campus, the young company was being viewed with suspicion by some of the university staff, particularly those who were long established there and didn't welcome the alien intruders from the private sector. One morning, the CureVac crew even found that their company nameplate had been torn down. As a consequence, the company soon cut short its residence in this lab and instead moved to the neighboring Department of Chemistry, and onto the seventh floor. The move involved shifting an awful lot of old »tat« – from broken fridges and old chemistry lab equipment to bent old tables. Clearly, it was going to be a long haul before they would be able to turn their operations into a state-of-art biotechnology laboratory. As a former chemistry lab, the new room still offered a decisive advantage: in contrast to biotechnology labs, it was completely free from contamination with voracious RNases common in biotechnology labs, as they had been etched away by countless aggressive chemical experiments – making it perfect for producing RNA products.

LADISLAUS REIDEL

>> I have a degree in biology and also trained in IT. Back in 2002, I was looking for a job that would enable me to apply my training in biology practically while at the same time allowing me to draw on my IT skills.



As a recent graduate, it was really exciting to be able to work in so many different areas at once. We started with trying to find a scalable RNA isolation method, trying out different kinds of chromatography systems and methods, chemically synthesizing and extracting RNA, and cultivating bacteria. Being a start-up with a small budget, we often had to improvise. One of things I still remember really well is how we were buying computer parts – described as ‘fantastic deals’ by the seller – on eBay and fixing old computers thrown out by the university for our own use. I also still vividly remember the move from the university lab to the technology park, which we organized entirely by ourselves. <<

CureVac company history



Managing the company on 6 sqm – the first headquarters provided the founders – pictured: Ingmar Hoerr – with little space

The lab's distinct lack of equipment was addressed by an increase in its occupants' creativity. This included repairing a laboratory shaker thrown out by the laboratory next door, fixing old chromatographs discarded by other working groups, and making good use of even the smallest of spaces. Last but not least, in a communal effort where everybody lent a helping hand – from laying a new floor, cladding the walls with washable panels and connecting a sterile workbench – the team also converted a small storage room inside the laboratory into a fully-fledged lab. On completion of this, the company's first building project, CureVac was the proud owner of a biosafety level 1 lab. Far from spacious, but perfectly suited to producing the very agent that had come to represent the pinnacle

of achievement and is the object of the small team's dedication: ultrapure RNA.

The new CureVac headquarters indeed offered very limited space and certainly not enough for any proper meetings, which is why CureVac subsequently held its meeting in a sitting area outside in the corridor. Not an ideal setting, as the meetings were being interrupted every couple of minutes by elevators announcing their arrival with a »bing« – opening of doors – irritated chemistry students, cigarette in hand, exiting through the elevator doors and disappearing down the hallway – closing of doors – back to the meeting ...



CureVac's first meeting room – silence and discretion are scarce

CureVac company history

In August 2002, CureVac hired yet another one of its earliest employees, the budding chemical engineer Thorsten Mutzke. For the interview, Mutzke duly arrived in a suit and tie, only to find himself seated amongst bins and laboratory bottles, next to an elevator and in the midst of a colorful bunch of CureVac people and doctoral candidates in the famed sitting area in the corridor. But that didn't deter him, because Mutzke is still part of the company now, in 2017.

* * *

THORSTEN MUTZKE

>> When I first came across CureVac, in 2002 at the IHK fair in Reutlingen, I thought it was a proper company because their stand was really well designed. I was studying chemical engineering in Reutlingen and was looking for a placement where I could complete my doctoral thesis. CureVac seemed interesting and I asked the two ladies at the stand a lot of questions, but they kept saying ›we have no idea, we really don't know‹ – I think they thought I was a spy sent over by the competition or something like that. In a roundabout way, I did manage to get invited to an interview after all, and made sure to look the part by turning up in a suit. However, what followed – being interviewed in this anteroom next to the elevator and a bunch of smoking students – was really bizarre.



I subsequently wrote a thesis about siRNAs, which was a really hot topic at the time. By the time the six months I spent at CureVac to complete my thesis had come to an end, we had only just managed to get a handle on our siRNA work, which was why I was able to immediately join CureVac for good in April 2003. I subsequently spent a long time taking care of siRNA production for customers during the period we were acting as a service provider – until Dietmar Hopp joined the company in 2006. That year also marked the point at which we were finally able to concentrate on our core business: mRNA. <<

By 2002, the young company was finally able to achieve some normality. Its research projects were gaining speed and its RNA production was gaining momentum. After work, Hoerr and von der Mülbe could often be found sitting at their desks till the early hours, writing patents for newly developed methods. This was a laborious process they worked through using a textbook from the university's library as a reference, because they were unable to afford a patent lawyer. All of the staff had settled into their roles, the team was constantly being expanded and the company was employing a total of six people by now. Thanks to having received a little more money from awards and grants, CureVac now also enjoyed a little more freedom, although its original dream was still in the distant future: a clinical trial, trialing its first mRNA agent, a real drug for curing real people. However, the company still lacked one of the essential requirements for achieving this vision: a GMP-compliant production facility – and of course, the significant funds required to set one up. Hoerr and von der Mülbe consequently set to work again to find more investors. And were lucky: a Scottish investor from the pharmaceutical sector who, as far as Hoerr and von der Mülbe are concerned, is the angel that had appeared to rescued them and was willing to invest in the company. The Scotsman travelled to Tübingen a couple of times to see the city and the company's business plans. Their relationship was amicable and uncomplicated, and after a couple of meetings 200,000 DM suddenly made their way into the company's account. There was no contract. However, amidst the general euphoria, nobody gave the lack of contract a second thought and, instead, *the RNA people* went straight to work spending the unexpected investment on materials and equipment. That is, until they found an ominous letter

from a lawyer in their mailbox, which talked about the absence of a contract, and money that has disappeared, although nobody at CureVac was really able to make sense of it. Since the Scotsman wasn't answering his phone, Ingmar Hoerr emailed their »rescuing angel' to ask what exactly the lawyer's letter was about. The answer he then received was pretty clear: »I want my money back.«

So, here they were again – inexperienced and full of enthusiasm as they were, they had gratefully accepted the funds and straight gone to work, without ever giving a thought to the possibility that things may not be what they seem. The money was consequently paid back, and CureVac's finances were severely damaged. A costly mistake, but one that was not going to happen again.



In the autumn of 2002, Ingmar Hoerr went on a trip to Hamburg to follow up on a potential investor: a consortium of three venture capital firms had expressed an interest in investing in CureVac. At this point, in November, their funds badly depleted from their encounter with their »rescuing angel«, this seemed to be the Tübingen company's last chance. The alternative was insolvency. They had already agreed most of the framework conditions, and were now about to finalize the contracts with the investor's representatives in an elegant Hanseatic business complex at a meeting with the Chamber of Industry and Commerce. On his arrival in Hamburg, Ingmar Hoerr was greeted by a dark sky and drizzle. The atmosphere at the meeting was similarly subdued from the word go and gradually worsened. As time goes on, Hoerr realized that two out of the three potential investors had started to waver, unsettled

by the company's experience with its »rescuing angel«. In the end, their resolve completely crumbled and they pulled out. And the third investor?

By this stage, Ingmar Hoerr was at his wits end. Sitting down on the steps of the building in the Hamburg drizzle and watching the red-carpeted entrance getting wetter and wetter, he was convinced that this spelled the end of CureVac. Feeling that all that was left was their vision – and the shattered remains of what they had built so far.

* * *

And then, just 24 hours later – their vision was back on track and shining with new brilliance. The dark clouds had parted and all thoughts of shattered remains were gone. Because the third investor couldn't have cared less about the consortium's break up and *Leonardo Venture GmbH & Co. KGaA* from Mannheim was more than happy to do the deal alone. At the time, all of the established biotechnology sector investors were still avoiding RNA at all cost; Hoerr and his colleagues still had to contend with the old dogmas and were still being given a hard time by the scientific community. However, thanks to Leonardo, CureVac GmbH was finally able to move into 2003 with a respectable amount of equity capital, which, further bolstered by other funds, meant that the company suddenly had EUR 2.7 million in its pockets. This sum would finally allow them to get serious.

* * *

THOMAS KETTERER

>> I am a chemist and have a PhD in organic chemistry. The doctoral research I did at the University of Tübingen was about the chemical synthesis of short DNA molecules. One day, Ingmar Hoerr approached me, probably while fetching coffee, which was where we would often bump into the CureVac people, and asked me 'Can you also do RNA?'. At the time, that was completely new to me and hardly anyone had ever done it. But it sounded exciting. A couple of days later I was approached by Steve Pascolo, who asked me exactly the same thing. And that's when I realized that they were serious. I consequently joined CureVac in 2003, just before it moved and while the labs were still at the uni. At the time, they were only a small bunch of people with very limited resources, but each one of them was completely convinced of this technology's incredible potential.



Next, we got to work attempting RNA oligonucleotide synthesis, so we synthesized short fragments of RNA molecules that contained between 10 and a maximum of 100 individual building blocks. The basic principle involved here is the same as for synthesizing DNA, but the particulars are very different. It took us over six months before we were able to reliably synthesize RNA. Based on this work, I later helped to set up the company's division offering services around specific RNA sequences. However, we stopped chemically synthesizing RNA in 2007 and have been producing all of our RNA molecules using biotechnology, because it is more efficient and makes it possible to work with significantly longer fragments. <<

At this time, CureVac was still an odd mixture of things – half business and half academic working group. The public was not yet aware of the existence of start-ups, spin-offs, incubators and young innovators. CureVac was also still viewed with significant distrust by some of the professors and university staff, and there was a general sense of suspicion about whether CureVac was actually legal and above board. And about how it was possible for a commercial company to be housed inside the university and at the same time pocket all its profits?

The gatekeeper in particular had serious misgivings about the entrepreneurs and eyed with suspicion all of the equipment they carried in and out; while plainly refusing to open the barrier to the university's access road for the CureVac bunch as a matter of principle. At one point, Ingmar Hoerr, having had enough, turned to the university's highest authority, after which the university's president personally issued the company with an official residence permit. A piece of paper that *the RNA people* then kept in their pockets at all times, all of which rather upset the gatekeeper.



It didn't take long, however, before the constant feeling of being merely tolerated became irritating and before the growing company was increasingly suffering from the lack of space. RNA production was going well and would have worked better still with larger cleanrooms. However, all of these issues continued to be overshadowed by the lack of a GMP lab and the resulting inability to produce agents for clinical trials. The reason this continued to be the company's biggest issue yet was because CureVac's actual ob-

jective and actual vision now as then was still to be able to produce medicines for ill people. However, it is extremely rare for an agent to even get anywhere near a real trial participant – let alone a real patient – without Good Manufacturing Practice. Which was why the email from Mr. Wilke from the Tübingen Business Development Agency that arrived in their mailbox around that time was perfect in terms of timing! The agency was still looking for tenants for a new technology park that was going to be built in the north of Tübingen, and asked for anybody with a need for modern laboratories to please get in touch. A little overenthusiastic, Ingmar Hoerr immediately got in touch. However, CureVac was still a nobody in the business world and there were far bigger and more successful biotechnology companies in Tübingen than the small start-up. The agency's response was consequently reserved, but the news soon arrived that the other companies had taken on too much and were having to curtail their expansion plans. All of a sudden, the City of Tübingen, which owns the technology park, was extremely interested in CureVac. The technology park was a prestigious project for the city – and having an innovative company like CureVac on board made it even more so.

The whole nature of the project meant that CureVac became involved as early as the park's architectural design phase, which in turned allowed it to raise the big issue of designing their laboratory's interior such as to be compliant with GMP requirements. The city was happy to do so, not least because it would also make the park more attractive to other future tenants. However, the GMP facility that was being built in the technology park was not an ordinary one because, even though there is no legal requirement to do so in Germany, the Regional Board in charge insisted that it also

CureVac company history

had to comply with the US FDA guidelines, the strictest standards there are. As a result, the Tübingen technology park became the site of the first GMP facility for producing mRNA for medical use worldwide.



Ingmar Hoerr, Florian von der Mülbe and Günther Jung (from left) inspecting the construction site of the first worldwide GMP facility to produce medically usable mRNA

As might have been expected, the construction company's cost estimate turned into a shock as building the facility was going to be significantly more expensive than anticipated. When it came to the GMP standards, CureVac's commitment and creativity was – because of its notoriously limited resources – called into question yet again. When it came down to it, nobody within the company actually had any idea about cleanrooms or GMP processes, nor did

the company have the funds to hire an expensive advisor. Von der Mülbe therefore set out to educate himself and read his way through specialist literature and the official rules and standards, while both von der Mülbe and Hoerr repeatedly went to see the Regional Board in the south of the city to quiz the officials in charge. Those officials, in turn, were rather vexed by those visits, because they didn't normally provide advice on these matters, they were in charge of monitoring compliance with them. Occasionally, they would just send the clueless developers back home and tell them to come back only once they are able to submit the required information. However, as time went by, their relations improved and the officials became more supportive and accommodating – quite possibly because they were impressed by the pair's tenaciousness, their plain enthusiasm and the big vision they were perusing.

But when it came to the new facility's construction, it wasn't just design but also practical matters that required the entrepreneurs to step in. Florian von der Mülbe could be seen running around the building shell for hours – measuring tape in hand – and painstakingly measuring corners and angles, crawling over the floor, marking points for power sockets on the walls.



In April 2003, the building was ready to move in. The company picked up a small van from a local car dealership, which they were officially going to »test drive«. This van was subsequently crammed with all of the eclectic equipment the company had collected so far. The team of six had especially chosen a Friday afternoon for the move, because that's when they would draw the least attention

CureVac company history

carrying all of their equipment, plus their own two clean benches, out of the university. The company's new home in the Tübingen technology park at the Oberen Viehweide was all brand new and shiny. But it was also a little lonely here, as the huge building was only occupied by one other tenant so far.



CureVac is among the first tenants of the technology park Tübingen opened in 2003; the building is still the company's headquarters to this day

The new headquarters represented a tremendous step forward for CureVac, even though the move still felt just like moving home rather than moving a business. It was only when all six of them were standing on the top floor looking out of the window that the significance of this new chapter in the company's history was really sinking in for both Ingmar Hoerr and Florian von der Mülbe. An important moment, as they were standing there, taking in their new

home. But one that only lasted briefly as, in true German fashion, the day's true highlight approached in the form of their first cups of celebratory coffee from their new machine.



For the time being, lack of space was now truly a thing of the past. But their tight budget problems persisted, even in their new home where, in fact, they were being exacerbated by the rent for their new premises, which made a big dent in the limited funds they had. At the time, some of the more suspicious observers even went as far as accusing CureVac of having delusions of grandeur and were convinced of its imminent demise. They were obviously not aware of the team's iron will, their persistent belief in their vision and the potential of RNA to revolutionize the medical world, or the solidity of the scientific data they have collected over the years.

However, in the fall 2004, their bank balance was still rapidly hurtling towards zero again. The company had long since switched to emergency mode; had largely put on hold its big vision and, with a heavy heart, switched to providing services as a contract producer of RNA in order to generate the money necessary to keep the company going and survive the current dry spell. These services primarily involved the production of so-called siRNAs (*small interfering RNA*), for customers from the research and industrial sector. siRNAs are synthetically synthesized, short RNA sequences that interfere with the translation of RNA and stop specific proteins from being produced in a cell. In research, they are, among other things, used for researching protein functions. This phase in the company's history also had its positive sides: the experience gained

with customers from the industrial sector taught the company the importance of establishing appropriate processes, of paying careful attention to customers' needs and of continuing to try to find good solutions within the scope of their limited means.

Despite these developments, the company's management was in a very subdued mood around Christmas 2004 in particular, because they were only going to find out whether or not their investors would provide an additional year's funding at the end of December. It was also around that time that a new potential investor appeared on the scene. Friedrich von Bohlen, a biochemist with a PhD in neurobiology and co-founder of the Heidelberg company *Lion Bioscience AG*. Hoerr, von der Mülbe and Pascolo had been able to completely convince him of CureVac's vision during their first meeting, to the point that Von Bohlen was completely on board and willing to go so far as to promise a significant investment that he would finance out of his own pocket.

That was, on one condition: that *Leonardo Venture GmbH & Co. KGaA* would provide further financing. If not, he wasn't prepared to act on his offer. But the Mannheim firm hesitated. Which meant that the company's future was going to be decided at the turn of the year. Straight after the Christmas holiday, CureVac's managing directors, Hoerr, von der Mülbe and Klein, subsequently travelled from different corners of Germany to Mannheim to *Leonardo's* headquarters – a small office in the loft a terraced house – where they then engaged in a war of nerves. The discussion was heated, involved ranting and raving, stepping out of the room in anger – before returning with newfound composure, and re-entering negotiations. Following many hours of tough negotiations, *Leonardo Venture GmbH & Co. KGaA* finally agreed to provide another

round of capital. Von Bohlen subsequently also provided financing and promised to search his extensive network of contacts for more investors – a promise that would propel CureVac into a new era.

The process of signing the contract at the notary in Ludwigs-hafen also took an inordinately long time as the solicitor took the contract apart point by point for the benefit of the Tübingen company. By the time all of the stakeholders finally signed the paper, it had turned night. CureVac had been granted another lease of life. It had the means to survive yet another year. A few days later, and the company would have had to declare bankruptcy.



*Appointment with the notary to found the company
– the start of the RNA people's story*

* * *

CureVac company history

Little by little, CureVac started to have success with another therapeutic RNA-based approach, details about which were, among other information, made public in 2004 in a scientific paper published in the *European Journal of Immunology*. This technology uses long-chain, non-coding RNA molecules that, in contrast to mRNA sequences, do not contain a blueprint for proteins. With the right formula, these molecules can enhance the effects of conventional vaccines when administered at the same time as the other active substance. These so-called adjuvants also increase the effectiveness of cancer immunotherapy. The choice of name for this new technology was consequently obvious – RNAdjuvant®.



The staff in the year 2004 – the team works at full speed to extent the proprietary technology platform

FLORIAN VON DER MÜLBE

» There are many special moments that are iconic to me in terms of certain aspects of CureVac's history. I remember our ›Baltic Sea Symposium‹ sailing trip, for example, really well, which was before the company was even founded. None of us had any sailing experience to speak of and it was just ironic that, of all things, we should end up sailing into a storm. It was a really dangerous situation. But the fact and the way we ended up working as team to get us out of that situation made it a truly defining experience. That experience is also a fitting analogy for the years we subsequently worked together: constantly on the move, on a great journey into the unknown, solidarity, risks, storms, surges, waves and then again a tailwind ...



Looking back, the funding we received through the ›Young Innovators‹ program was another definitive event. I still have vivid memories of the presentation in Stuttgart, the tiny room crammed with assessors, the heat and airlessness. It was simply great when we received the confirmation letters and learned that we had made it.

Another vivid memory for me is our 2002 Christmas party, when we were housed in an empty lecture room on the top floor of the university's chemistry building and had raclette. There were around ten or twelve people which were either working for or had dealings with us. Seeing that high-spirited group of people there, all of whom were working on the same mission – our mission – was a really special moment for me at the time. Although, I remember that, as the party went on that day, we suddenly found ourselves in the dark! We had plugged so many raclette grills into the multiple plugs that all of the fuses had blown. <<

CureVac company history

One day, in the summer of 2005, the majority of CureVac's workforce – the team having grown to twelve employees by now – was busy in the office kitchen making sandwiches. Although their budget was limited, they had no intention of letting their guests go hungry – particularly such important guests. The occasion for the festivities was the official opening of the company's GMP laboratory, as part of which the Mayor of the City of Tübingen, Brigitte Russ-Scherer, and former Baden-Württemberg Secretary of Commerce, Walter Döring, were dressed in blue lab coats and given a tour of the brand-new rooms. Although officially opened, the official GMP-certification for producing drugs and hence the next major step towards the longed for clinical trials were still some time away.



The newly equipped GMP laboratories are shown to Walter Döring (right), former Secretary of Commerce in Baden-Württemberg



In the fall of 2005, Ingmar Hoerr and the company's finance director Wolfgang Klein commenced their memorable trip to the Golf Club St. Leon-Rot, uncertain of whether they would actually be able to get Dietmar Hopp on board. Uncertain of whether *dievini Hopp BioTech holding GmbH & Co. KG* would really invest in CureVac and make *the RNA people's* financial worries a thing of the past.

Following their meeting, the SAP founder took his time to come to a final decision. Despite the fact that Hoerr and Klein were under the distinct impression that Hopp was fundamentally interested in their technology, he was not forthcoming with any definitive information.

Several weeks after the initial meeting, the entrepreneurs met for another meeting at the golf course in St. Leon-Rot. This time, all of the *dievini* – and CureVac – had been invited to attend. A promising sign?

And indeed it was! At the beginning of 2006, CureVac received a definitive »yes« from Hopp's club house. *dievini Hopp BioTech holding GmbH & Co. KG* initially invested EUR 22 million in one fell swoop in CureVac GmbH. Friedrich von Bohlen had kept his promise and used his network or, to put it another way, he had extended his previous investment to include investment from *dievini* Holding, which he had co-founded in 2005.

CureVac's entire workforce breathed a sigh of relief as the deal marked the end of their emergency mode! The company celebrated the happy ending in the canteen of the Tübingen Max Planck Institute, right around the corner from the technology park. The new funds finally allowed them to put in place long-term plans and

to look to the future with new confidence. It also meant that they could now get to work pursuing their original mission – seriously this time.

* * *

However, over time, it became clear that CureVac's three founders' interests did diverge on some points. Florian von der Mülbe and Ingmar Hoerr, for example, were convinced that the only way to help as many people as possible with RNA drugs one day was through refining production, a free economy and pharmaceutical industry. Steve Pascolo, the other hand, was seeing himself as solidly anchored in the academic world and basic research. Regardless of all the years he had spent at CureVac, he had remained a scientist at heart. A purist who, above all, considered creativity and independent research conducted without any ties to third parties the most worthy of scientific achievements. Following this latest round of financing, he consequently realized that this was where their paths split and that he now had to go his own way. After all of their years together, their adventures, after having successfully weathered so many storms and gone through thick and thin together, this move turned out to be a very difficult and emotional step for everyone involved. Steve Pascolo eventually left the company in the summer of 2006.

* * *

REBECCA ERNST

» My specialization is actually in plant biology, but I also developed an interest in information technology from an early stage. In the middle of the noughties, bioinformatics was really up and coming, but there were few specialists with any explicit training, which allowed me to laterally move into this field. I subsequently joined CureVac in 2006



and, together with two other employees, was part of the first »wave of new employees' after the first Hopp investment. At the time, CureVac was employing about 25 people, and everybody still knew everybody within the company, and it was still possible to have direct conversations with everybody there. And there was a tremendous spirit of optimism – because from here on, there was only going to be one way, and that was forward.

After that, CureVac grew very quickly and all of a sudden we had to restructure many divisions or make them more professional. I was originally responsible for establishing and expanding project management within the company and for obtaining third-party funding, but as the number of employees and the company's structures grew, we also had to introduce document management and review a lot of processes. The point at which it became necessary for CureVac to rent an additional building – by which time we had increased to over 150 employees – subsequently marked the start of a completely new chapter for the company. We called the new building Ponderosa Ranch, but it wasn't really much more than a wooden shed – badly soundproofed, but also very cozy. Another very special thing at the time was when we started to have our first CureVac babies, where both of the parents were working for the company. And, the first time I met a member of staff in the corridor that I had never seen before, I finally new that CureVac had grown up. «

CureVac company history

The latest round of financing had blown fresh wind into CureVac's sails and the company consequently took off at high speed. The technology park also saw a huge surge in new employees as CureVac's workforce was more than doubled and increased from 12 to 26, during 2006.



Despite all of that, CureVac still had to reach an important milestone on its way to producing a marketable product: its laboratories still had to pass an inspection by the experts from the Tübingen Regional Board (RB) in order to officially become a GMP-compliant production facility in 2006. It was only once the company had officially become GMP certified that it would be able to produce active substances that could actually be administered to humans. The RB scheduled a full three days for their GMP audit. During it, the inspector asked to see all of the company's plans and documents again, inspected every single room, climbed onto ladders and even inspected the tops of the cupboards. Ingmar Hoerr, Florian von der Mülbe and Tom Ketterer, who had just become the company's production manager, followed the inspector everywhere he went, eagerly answered questions and provided details. Soon after, the company received the RB's official decision: they had passed the inspection and the laboratories officially complied with GMP. This meant CureVac now had official approval to produce RNA-based drugs!

As of 2006, *the RNA people* would become the only company worldwide in a position to produce long chain RNA for use in clinical trials. CureVac was finally able to conduct clinical trials.

The team subsequently worked extremely hard to further develop CureVac's RNaive® technology for treating cancer and prophylactic vaccines. In both areas of application, the specific RNA molecules, which can be administered by injection under the skin, can both give rise to a cellular as well as a humoral immune response, meaning a response mediated through antibodies.

However, the RB's positive decision meant more than just a »go ahead« for production, because it constituted objective feedback and CureVac first external validation – and hence a clearly measurable success.

Florian von der Mülbe received the good news by text from his colleague Susanne Bauer while at a business lunch near the Tübingen observatory. It's a text message destined to stay on his cellphone forever.

* * *

Hoerr had already written about the fact that the human body can be made to produce any kind of proteins – and hence a sheer infinite repertoire of potential therapeutics – itself for a short period of time through the administration of natural RNA in this doctoral thesis in 1999. Since this effect only lasts a couple of days, the process is not associated with any longer term, uncontrollable consequences. The effects of this process can be used in a number of ways. One of these is for vaccinations that activate the immune system. Called »protein replacement therapy«, this method can, for example, help people with metabolic disorders and whose body is unable or not properly able to produce a particular enzyme. As of 2006, CureVac was now – thanks to Dietmar Hopp's investment

– also in a position to pursue this highly promising approach. CureVac subsequently established this new approach to using RNA in molecular therapy as another pillar within its technology platform – and called it RNArt®. It quickly emerged that this approach can also be used for passive immunization, in which case the administered mRNA molecules contain code for specific antibodies that bind to pathogens. In recognition of the exceptional nature of this particular RNArt® technology, the company made a point to come up with special brand name for this process, and called it RNAntibody®.



Fast-forward to January 2009 and a treatment room in the urology unit at the University Hospital of Tübingen, where a doctor was having to deliver the unfortunate news of a diagnosis of end-stage prostate cancer to one of his patients. A patient who had already undergone countless treatments, radiation therapy, surgery and hormone therapy. Despite all of their efforts, the doctors had been unable to stop the mutated cells, which had now metastasized throughout the patient's whole body. The patient only had months left to live. Highly experienced, the doctor next got ready a syringe and injected a fluid straight under the patient's skin – the first mRNA-based vaccine against prostate cancer.

There were a total of 48 other people taking part in the trial – the first clinical trial that CureVac was conducting with an RNA drug. These participants were being treated at the Charité in Berlin and the university hospitals in Aachen, Dresden and Freiburg, as well as in another six German cities, and in Milan. The prostate cancer patients were being treated with the mRNA

BIRGIT SCHEEL

» I joined CureVac to complete my doctoral research. I initially approached them because of a small note they put up in the biology department. The three founders immediately accepted me after I gave my presentation on my thesis. To start with, we were still working in the first lab we had been given, and then in the lab in the chemistry department. Our bosses were away a lot trying to raise funding, so that just left us, the doctoral researchers, and we'd turn up the music and do endless experiments trying to find out all of the things you could do with RNA. In 2003, we moved to the technology park – we were a handful of people then, took down all of our equipment ourselves, drove it over and then set it all up again. We then did the same again with the desks, chairs and wall cabinets. When we had finished, we found ourselves in these huge rooms, all alone, in this massive building.



Most of the people who were there when we moved are also still with us now. However, we are now spread over six buildings on our ›campus‹ and have another two facilities – one in Frankfurt and one in Boston, USA. We have conducted clinical trials, developed strategic partnerships and entered into a number of meaningful deals. I don't think any of us could ever have imagined what our future would hold at the time. «

immunotherapeutic vaccine CV9103, an RNAActive® formula, whose safety and effectiveness were being investigated in the trial.

For Ingmar Hoerr and Florian von der Mülbe, this trial marked the beginning of a new phase in the company's history, a new stage in their fight against cancer and other diseases. They had spent years fighting for their technology, collecting methods and data, making discoveries and writing patents, building a company and creating an almost infinitely expandable platform for mRNA drugs. They had constantly run into obstacles and time and again managed to overcome them one by one. They had had to face seemingly unshakable truths and deeply entrenched convictions, contend with the ridicule of their peers and rigid officials, as well as overcome their own fears and ongoing threat of insolvency. And they had fought hard for their vision, for the medicine and for the sake of peoples' health.

As a result, seeing one of their RNA agents being used for the first time in a trial with real patients was a very moving moment for the two founders. All of the fruits of their ideas and work, all of the things that they were producing in their own GMP labs, which they themselves had helped to build, was now actually being set to unfold its effects under the skin of a human being. This moment was also making them aware of their significant responsibility towards their current – and future – patients. More than anything however, this moment was just making them proud.

And, they were also both proud of the fact that CureVac had acquired so many fantastic new employees and loyal companions along the way, without whose tireless efforts, including over the difficult periods the company had faced, this success would never have materialized.



The rollercoaster ride, the rough ride over many highs and lows, had finally come to an end and the initial difficulties and obstacles had been successfully overcome. The company would, of course, continue to face challenges, as setbacks are a perfectly natural part of scientific progress. However, the bottom line was that the research and development work undertaken by CureVac in subsequent years has been moving in a single direction, and that is: forward and upward.

By 2009, the company's workforce had increased to 65 and it set up a new facility at Frankfurt am Main. The people working there under the direction of Ulrike Gnad-Vogt are specialized in the design and performance clinical trials.

In 2009, the company also commenced a clinical trial for an mRNA agent to treat lung cancer. The company presented the first positive data from the trials in 2011: both vaccines, CV9103 against prostate cancer and CV9201 against lung cancer, had proven safe and triggered significant immune responses. The following year, CureVac's scientists published an article on an mRNA-based prophylactic vaccine against the flu virus in the renowned journal *Nature Biotechnology* in collaboration with the Federal Research Institute for Animal Health, the Friedrich-Loeffler-Institut in Greifswald. The data showed that the method has great potential for effectively protecting people from infectious diseases. As of October 2013, the company was also able to test this approach on humans as it commenced phase I of a clinical trial of a prophylactic rabies vaccine in Munich with over 100 healthy participants.

Protective efficacy of *in vitro* synthesized, specific mRNA vaccines against influenza A virus infection

Benjamin Petsch^{1,5,6}, Margit Schnee^{2,6}, Annette B Vogel^{1,5}, Elke Lange², Bernd Hoffmann⁴, Daniel Voss², Thomas Schlake², Andreas Thess², Karl-Josef Kallen², Lothar Stitz^{1,2} & Thomas Kramps²

Despite substantial improvements, influenza vaccine production—and availability—remain suboptimal. Influenza vaccines based on mRNA may offer a solution as sequence-matched, clinical-grade material could be produced reliably and rapidly in a scalable process, allowing quick response to the emergence of pandemic strains. Here we show that mRNA vaccines induce balanced, long-lived and protective immunity to influenza A virus infections in even very young and very old mice and that the vaccine remains protective upon thermal stress. This vaccine format elicits B and T cell-dependent protection and targets multiple antigens, including the highly conserved viral nucleoprotein, indicating its usefulness as a cross-protective vaccine. In ferrets and pigs, mRNA vaccines induce immunological correlates of protection and protective effects similar to those of a licensed influenza vaccine in pigs. Thus, mRNA vaccines could address substantial medical need in the area of influenza prophylaxis and the broader realm of anti-infective vaccinology.

Few diseases have had a greater impact than influenza on human public health and global economic output¹. Although seasonally evolving influenza infections are generally self-limited, dangerous secondary complications that require hospitalization and result in high mortality, especially in the elderly, infants and immunocompromised patients, can arise². Influenza pandemics characterized by aggravated disease, increased mortality and rapid worldwide spread of infection can occur when a genetically reassorted influenza A virus that transferred from an animal host into the human population acquires the ability to undergo human-to-human transmission^{3,4}.

Influenza viruses are single-stranded RNA viruses of types A, B and C, with type A causing epidemic or pandemic outbreaks in animals and man, even with potential animal-to-human and human-to-animal transmission⁵. Serologically, influenza A viruses are classified based on expression of one of the 17 different subtypes of hemagglutinin (H1 to H17) and 9 different subtypes of neuraminidase (N1 to N9)⁶. Effective vaccination is complicated by the tendency of influenza A viruses to undergo gradual or rapid changes in the sequence of their hemagglutinin (HA) and neuraminidase (NA) antigens (denoted as 'drift' and 'shift', respectively). This antigenic variability ensures the availability of susceptible hosts and facilitates the repeated occurrence of epidemics and pandemics. It also currently necessitates the annual revision and redesign of seasonal influenza vaccines, which involves predicting which strains will come into circulation. If a strain not included in the seasonal vaccine unexpectedly comes into circulation, it is difficult to rapidly synthesize a vaccine to it because of the variable yield of antigenic material from eggs or tissue culture and long production times. Thus, there is an unmet need for new technology that would allow

rapid adaptation of vaccines to match currently circulating influenza strains^{7,8}; ultimately, a broadly protective vaccine is needed^{9,10}.

One strategy for rapid adaptation involves genetic vaccines like those composed of plasmid DNA or replicating synthetic vectors; these are very adaptable owing to their simpler structure and means of production^{11,12}. Nevertheless, many genetic formats still have drawbacks, including insufficient clinical efficacy and safety, or residual vector immunogenicity. In this context, the use of mRNA—the minimal genetic vector—as a vaccine appears particularly attractive. mRNA vaccines contain an optimized mRNA containing an open reading frame that encodes only the antigen of interest, and 5' and 3' untranslated regions that affect the efficacy of translation and the intracellular stability of the molecule¹³. Addition of protamine to mRNA vaccines can influence the stability and activity of the vaccine^{14,15}, including TLR7-mediated effects¹⁵. In addition, the production of mRNA vaccines is flexible and highly scalable. Based on the scenario of the 2009 influenza pandemic, provision of ready-to-use, clinical-grade product from a pilot facility could be achieved within 6–8 weeks from publication of the influenza antigen sequence. This includes template generation, *in vitro* transcription, purification, formulation and quality control testing (including tests for sterility).

So far, successful mRNA immunization resulting in protection from infectious disease has never been reported. In mice, intradermally injected, protamine-complexed mRNA encoding a tumor antigen elicits a protective tumor-specific T-cell response¹⁵. mRNA vaccine production, according to current good manufacturing practice, is established and accepted by the US Food and Drug Administration and the European Medicines Agency

¹Institute of Immunology, Friedrich-Loeffler-Institut, Tübingen, Germany. ²CureVac GmbH, Tübingen, Germany. ³Department of Experimental Animal Facilities and Biologic Management, Friedrich-Loeffler-Institut, Greifswald-Isel Riems, Germany. ⁴Institute of Diagnostic Virology, Friedrich-Loeffler-Institut, Greifswald-Isel Riems, Germany.

⁵Current addresses: CureVac GmbH, Tübingen, Germany (B.P.); Institute of Immunology, Friedrich-Loeffler-Institut, Greifswald-Isel Riems, Germany (A.B.V. and L.S.).

⁶These authors contributed equally to this work. Correspondence should be addressed to L.S. (lothar.stitz@fli.bund.de) or K.-J.K. (karl-josef.kallen@curevac.com).

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An article about influenza vaccines based on mRNA is published 2012 in the renowned journal Nature Biotechnology by CureVac and the Friedrich-Loeffler-Institut

This event also marked an important milestone for the young company, as this was the first time in medical history that healthy participants were given a prophylactic mRNA vaccine. The authorities are extremely critical of studies that enlist healthy participants, which was why everybody helped to meticulously produce all of the data required for the trial's approval. The entire CureVac team made a tremendous effort – and they were successful, because three years down the line there was solid evidence that the prophylactic RNActive® vaccine truly causes the body to produce rabies-specific, protective antibodies. And far from stopping here, CureVac subsequently started developing prophylactic vaccines against a wide range of other infectious diseases.

In 2015, CureVac also started the development work for a vaccine against HIV. The company will be contributing to the development of a vaccine against AIDS that can be introduced into patients' bodies with the help of mRNA technology as part of the *International AIDS Vaccine Initiative (IAVI)*.



In 2015, CureVac also succeeded in jumping over the Atlantic, where it founds the US-American subsidiary CureVac Inc in the biotechnology hotspot of Boston. The company's presence in the USA gave the Tübingen people access to a wide range of networks, research and business opportunities and, by doing so, was intended to help the company expand its mRNA technology platform and clinical product development activities.



At this stage, the constantly increasing numbers of research groups and companies, and their publications on the therapeutic potential of this cellular messenger, clearly showed that the positive attributes of RNA were finally, after years of skepticism, after having doggedly defended it on countless occasions, not only being accepted but celebrated within the scientific community.

In order to bring together, create a dialog amongst the new enthusiastic mRNA community and collectively drive forward this medical revolution, CureVac subsequently founded the *International mRNA Health Conference*. This conference, which CureVac organized in collaboration with the University of Tübingen, was a two-day event to which mRNA experts from all over the world were invited. And they came: more than 180 participants reported, lectured, discussed, informed and networked in the grand old assembly hall, the oldest university building in Tübingen. In the evening, the conference attendees moved to nearby Castle Hohentübingen – a site of enormous significance – because this is where the medical scientist Friedrich Miescher made the discovery of the nucleic acids, DNA and RNA, in 1869. This makes Tübingen the very place where the molecule that is now well on its way to making medical history was originally discovered.

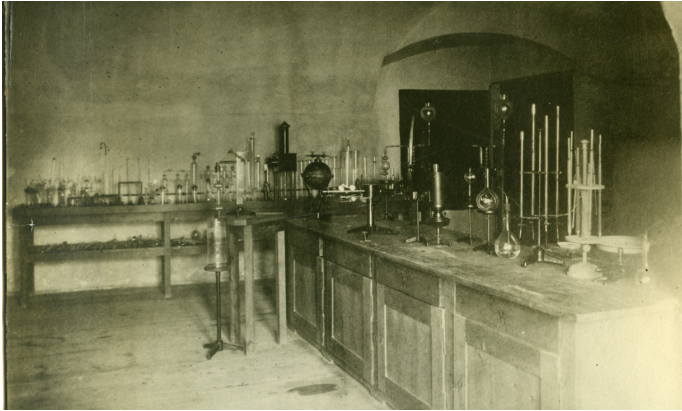


In 2013 the »1st International mRNA Health Conference« gathers mRNA experts from all over the world in Tübingen – in the following years, the number of participants increases continually

The conference also showed that CureVac was no longer the only company working with mRNA and that the field is now being shared by a number of powerful and accomplished competitors. But the plan worked, the protagonists within the sector got to know, respect and talk to each other; and the whole conference had an amicable atmosphere. Although it may be true that there is now competition – it was honest.

* * *

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The former castle kitchen of Hohentübingen castle served as chemical laboratory since 1817; here Friedrich Miescher discovered the nucleic acids DNA and RNA in 1869 (picture source: Museopedia)



The cradle of biochemistry becomes a museum – with support from Curevac, a museum is opened at the site of the first worldwide biochemical laboratory and the place of discovery of the nucleic acids DNA and RNA at Hohentübingen castle in 2014

CureVac has also finally overcome its financial difficulties since *dievini Hopp BioTech holding GmbH & Co. KG* came on board as an investor in 2006. The company from St. Leon-Rot will be investing over EUR 150 million over the next years over a total of four financing rounds.

CureVac's success has also drawn a number of other interested parties and partners towards the company. As a result, CureVac will be entering into industry partnerships with *Sanofi Pasteur SA* and *Boehringer Ingelheim Pharma GmbH & Co. KG*, two renown pharmaceutical companies. CureVac signed a number of contracts for developing RActive® vaccines against various infectious diseases with *Sanofi*, the French vaccine specialist, in 2011; these projects, which are worth USD 33 million, are also financially supported by the *Defense Advanced Research Projects Agency (DARPA)*, an agency of the US Defense Ministry.

The *Sanofi* deal is CureVac's first major collaboration with a pharmaceutical company. It opens up new, promising prospects and requires a completely new way of thinking and working, which involves joint discussions and agreeing how to proceed, as well as working hand in hand – which often takes its time.

In 2014, CureVac's circle of co-operation partners was joined by *Boehringer Ingelheim Pharma GmbH & Co. KG*, a German privately-owned company. The contract negotiations between the two companies were rather strange as they dragged on for months, including over the summer holiday period. CureVac's principal negotiator was Franz Haas, who joined the management in 2012 as Chief Corporate Officer. During the negotiations, he would often dial into the countless telephone conferences from his motorhome in the Australian outback in the middle of the night while on

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holiday with his family. Ingmar Hoerr, on the other hand, was holidaying in Latvia with his wife at the time, and was constantly being contacted on his cellphone while trying to enjoy his idyllic surroundings. Elmar Maier, the company's long-standing adviser in all matters of business development, was on holiday in Turkey with his family at the time. Then again, the Boehringer people were also scattered and holidaying all over the world as they continued their negotiations. And yet, the foundation was right, and the beginning of September saw the two companies finally agree on a deal. That is, they had agreed to collaborate on the further development and commercialization of the active agent called CV9202. This agent is a therapeutic vaccine for treating lung cancer. Once the contract was signed, Boehringer paid CureVac EUR 35 million; the agreement includes additional payouts of up to EUR 430 million for successively achieved milestones – and payment of the licensing fees when the product is ready to be marketed.

* * *

INGMAR HOERR

>> It all started with an experiment that went wrong – or rather, with unexpected data. Data that demanded a completely new approach to interpretation and suggested the possibility of developing a completely new medical treatment option. We soon found more concrete evidence in support of this approach and vision and, over the years, were able to collect a solid base of promising results, patents and methods on the subject of RNA vaccines.



What often surprises me when looking back is that we were the only people seriously researching the use of RNA as a basis for drugs for such a long period of time. That we should have been the only ones in such a highly diverse field to recognize this potential and to have this vision of a new form of medicine. Not that it wasn't hard, because we had to overcome countless obstacles – from financial bottlenecks, to criticism from scientists within the DNA community, and the uncertainties that are generally associated with research.

And yet here we are – no longer considered the crazy dreamers from Tübingen. We have been able to demonstrate the validity of our vision to scientists across the world and paved the way for inspiring competitors to join the field. We are right at the center of a growing field of research that is being contributed to by working groups and young companies from all of the world, in one of the most courageous and innovative sectors in medical science. At the moment, we are experiencing a revolution, a break with what went before, as medicine as a field transitions into the age of information technology. CureVac has been one of the companies that have initiated this shift. But there is plenty more to do, and even if that is going to be difficult at times, it will always be rewarding. We are committed to continue to fight – for science. For RNA and for the health of people <<

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CureVac subsequently even went on to making headlines at the highest EU level and won the European Commission's *Vaccine Prize* in March 2014. The prize was two million Euro and the competition launched with the aim of finding simple cooling solutions for transporting and storing vaccines. The winner was to receive two million Euro as »bounty« for the perfect cold chain; all of the other competitors' solutions revolved around solar-powered refrigerators. CureVac, on the other hand, set out to address the problem by working on the product itself – RNActive® vaccines do not require any refrigeration whatsoever and can be transported and stored without any precautions even in tropical temperatures.



In Brussels, the CureVac team receives the Vaccine Prize of the European commission endowed with 2 Mio. Euro

CureVac's RNA platform impressed the EU jury, beat the refrigerators and added an extra two million Euro prize money to the company's funds over night – making this another special moment in the company's history. However, during the prize award ceremony in a basement room at a Brussels conference center, the small CureVac delegation nearly disappeared amidst the general chaos: a makeshift stage wedged between room dividers and standing tables, loudspeaker announcements that Ingmar Hoerr had to compete against during the short speech he delivered on accepting the prize, the audience's general indifference, the fact that the celebration dinner with Commission President José Manuel Barroso took place without José Manuel Barroso, and the use of a piece of cardboard to represent the award certificate. All of which meant that hardly anyone noticed the Tübingen team's early departure – to find a fitting venue in the old town in the center of Brussels for a private celebration. Chaos notwithstanding, the figure on the cardboard certificate – EUR 2,000,000 – was so impressive that Verena Lauterbach, who is in charge of press relations, proudly displayed it in the window facing the street, making passers-by stop and stare. It was only at this point that the CureVac team slowly realized the significance of the day's events and the recognition they had just received – as well as the implications of this recognition from so high up.

Back in Tübingen, the management decided to celebrate again, this time properly, to make up for all of the glamour that had been missing in Brussels. The festivity's dress code subsequently was strictly red carpet, and the entire workforce and board of directors – as well as Dietmar Hopp – were invited to attend.

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Dietmar Hopp and Ingmar Hoerr on the red carpet at the company's own Vaccine Prize party



The fact that CureVac won the *Vaccine Prize* was also picked up upon by a true heavyweight, one of the superstars of the business world, a legend. The richest man in the world. With a foundation capital of over USD 40 billion, this man's *Bill & Melinda Gates Foundation* is the largest private foundation in the world. One of its three primary aims is »Global Health«, which, amongst others, it aims to support through global vaccination programs and the development of new vaccines. The foundation's scientists had long been searching for a suitable, flexible platform that would make it possible to supply vaccines more quickly and cost effectively in developing countries. For this reason, *the RNA people* obviously had

Bill Gates, the founder of Microsoft, and his foundation already on their radar as a potential co-operation partner, and had already tried contacting the team in Seattle a couple of times. Following a number of unsuccessful attempts, the Tübingen and Seattle team finally managed to hold their first real telephone conferences – often interrupted by chaotic switching and poor reception, involving a dozen participants, all of whom tended to be on the road to somewhere most of the time. Eventually the Americans got fed up with the lousy quality of the telephone conversations and sent a delegation to Germany.

Once in Tübingen, they were given a tour of CureVac's headquarters, inspected the laboratories and production facilities, asked to have the RNA principle explained to them again in detail – and were thrilled. By the end of the day, the *Bill & Melinda Gates Foundation* representatives were convinced that CureVac's approaches – in particular RActive® technology for prophylactic vaccines – have the potential to revolutionize the world of vaccines. Inexpensive to produce, easy to store and transport, simple and safe to administer: a fully developed RNA vaccine would have everything that a drug needs in order to be of benefit in particular to the people who need it the most. At the end of their visit, one of the Seattle science managers announced: »CureVac, you have a real platform. It's the first time we have seen a real platform for vaccines against all kinds of infectious diseases«.

A short time later, the company received a call from Seattle to be informed that Bill Gates would be in Paris in June 2014, and that he would like to have a meeting with Ingmar Hoerr. Hoerr subsequently went to the hotel at the edge of France's capital where the meeting was to take place together with Florian von

der Mülbe and their Chief Scientific Officer, Mariola Fotin-Mleczek. On their arrival, rather than being ushered into the luxury suite that Gates had chosen for the meeting, or the private area in the hotel's bar, the team were escorted to a room in the basement and found themselves in a situation that could have been straight out of a movie. Bare concrete walls, drainage pipes descending from the ceiling and a table in the center of the room lit by a single lamp. The billionaire welcomed them with a short »Hello« and was wearing a T-shirt from an American university over a checked shirt. As soon as the CureVac team had taken a seat, Gates said »You can start« and subsequently leaved through the printed slides at an incredible speed – clearly demonstrating his wish for an analog presentation. He skimmed the introduction, company history, visions and the like. He was after the hard facts, and only stopped when he reached the scientific diagrams, after which he bombarded the Tübingen team with detailed technical questions about production data, vaccine doses, number of animals used in research, implementation plans. Fotin-Mleczek, von der Mülbe and Hoerr were impressed and found it difficult to keep up with the speed those questions were fired at them.

By slide 30, Bill Gates seemed to relax a little and the corners of his mouth took on an angle that might be interpreted as a slight smile. The 20-minute meeting they had been invited to turned into half an hour, then 45 minutes. At the end of which Gates said »Congratulations to Dietmar. Good investment.«

However, the negotiations that followed were difficult. Over the coming weeks, the parties negotiated the terms of their collaboration by phone and email, and the CureVac team was fully under the impression that most matters are settled by the time Franz Haas

and Ingmar Hoerr, together with a delegation from *dievini*, set off to Seattle to finalize the contract. And yet, on their arrival, they found a lot of work waiting for them. There were many points that haven't been agreed on yet and the negotiations were tough. The team soon realized that they had not completed their mission and returned to Tübingen with a lot of unanswered questions.

Not having seen anything of the city, Haas and Hoerr managed to fit in a quick trip to Seattle's most iconic landmark just before taking off home. On their arrival on the Space Needle, the two of them took in the sight of the city below, with Elliot Bay and Mount Rainier on the horizon, the Pacific Science Center and the headquarters of the *Bill & Melinda Gates Foundation*. It is then that they realized how tense they were and that they keep wishing that they had yielded on some of the more important points of the negotiation.

However, in September, they got another call from the *Gates Foundation* and were told that the *Bill & Melinda Gates Foundation* accepts the terms set out in several other talks. At the beginning of 2015, after Hoerr and Hass had signed the contract at a notary in Frankfurt, it slowly but surely started to sink in that Bill Gates, the richest man in the world, was now a co-owner of CureVac!

The media response was huge, not least because of the rumors and false reports that had been circulating days before the official press release. Somehow, some of the information had made it to the outside and had been grossly exaggerated and blown up, with the result that people were now talking of an alleged three billion deal. The *Bill & Melinda Gates Foundation* and CureVac subsequently saw themselves forced to act and jointly held an impromptu live press conference at one in the morning.



The cover of »BILANZ – Das deutsche Wirtschaftsmagazin« in March 2015
(picture source: BILANZ)

This made it official. The news was out in the world and the hype took its course: the *Bill & Melinda Gates Foundation* is investing EUR 46 million in CureVac to contribute to the funding for the new industrial GMP production facility. At the same time, the companies are also entering into agreements concerning the development of a large number of vaccines based on the company's RNA technology. Countless requests for interviews, newspaper articles, television teams followed – putting the company at the

center of the German and international media's attention. And so finally, finally – after countless dismissals, years of criticism, skepticism and a downright hostile reception by the scientific community – it has finally made it big on the title page; this thing that has been the driving force and core of the company, CureVac's secret star: RNA.

* * *

EPILOG

The fall of 2016 saw the end of yet another financing round, which left the company with an additional EUR 127 million in its company account. The private placement involved a number of new investors, most notable of which was the Scottish asset management firm Baillie Gifford. The total equity capital raised by CureVac consequently increased to over EUR 350 million.

The company had already changed its legal form to a corporation in 2015. CureVac AG has a clear mission: *to continue its international growth.*

On 11 January 2017, CureVac presented groundbreaking results from its clinical trials at the 35th Annual J.P. Morgan Healthcare Conference in San Francisco. However, the company also experienced a setback with the results from the phase IIb trial of the mRNA-based prostate cancer vaccine CV9104 commenced in 2013. The trial, conducted in eight European countries, had a total of 197 participants, about half of whom were given the newly developed drug and the other half of whom received a placebo. However, the results from these two groups were disappointingly similar and the trial's primary objective – to increase overall survival amongst the patient group treated with the mRNA agent – was not achieved. That notwithstanding, CureVac has already struck a new path and is testing mRNA-based cancer immunotherapies in combination with checkpoint antibodies – a highly promising method that *the RNA people* are working on at full speed.

In contrast to this vaccine, CureVac's prophylactic mRNA vaccines have been a great success: All of the participants of the phase I trial conducted in Germany had formed neutralizing antibodies against the rabies virus after having been given the mRNA-based RNaive® rabies vaccine developed by CureVac. This means that the proof of concept for this technology has been achieved and clearly demonstrates that mRNA-based prophylactic vaccination is a promising method for protecting people from dangerous infections. CureVac is currently working on an optimized formula with the aim of making the vaccines more effective still.

2017 is also a year of construction, as the company is building its third GMP facility in its existing building and is planning to make the shift to a new dimension of active agent production in its first own newly-built plant. This plant will become the first production facility worldwide where RNA will be produced at an industrial scale.

To date, the company employs 350 people – and this figure is continuing to grow.

Although the structures and procedures employed by CureVac today are a world apart from the small, intimate and improvised start-up that started its life in a basement lab at the University of Tübingen, its spirit is unchanged! CureVac and the people who work here continue to be driven by the same fierce, visionary and pioneering spirit and belief in a powerful agent that can be used

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to fight a large number of diseases as it did from the word go. Inventiveness, courage, innovation, ambition and solid research continue to combine in novel ways to give rise to new ideas and concepts for active agents that have the potential to help millions of people in the world. This means that that fresh breeze carried by the Baltic Sea winds has continued to blow through the Tübingen technology park now as it did then.



CureVac's Executive Board in the year 2017 (from left): Dr. Ingmar Hoerr, Dr. Ulrike Gnad-Vogt, Dan Menichella, Pierre Kemula, Dr. Florian von der Mülbe, Dr. Mariola Fotin-Mleczek and Dr. Franz-Werner Haas

WE ARE
»*THE RNA PEOPLE*«!

WE FIGHT FOR
HUMAN HEALTH.

BECAUSE WE CAN.
BECAUSE IT'S WORTH IT.



IMPRINT

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CureVac AG

Paul-Ehrlich-Str. 15

72076 Tübingen

www.curevac.com