Forbes

Milepost ALZ-801. Martin Tolar leads one of the greatest Czech successes

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He came to America with a suitcase full of dictionaries because he didn't speak English well. After less than thirty years, he faces a breakthrough that can change the world and make him quite possibly the richest Czech ever. The story of Martin Tolar, holding in his hands a potential cure for Alzheimer's disease, fits all the features of a Hollywood blockbuster. And apparently a happy ending is approaching.

It's not just his story. It's about you and your loved ones, friends, or acquaintances. If you were to wish success to only one Czech, Martin Tolar would be a clear choice. Along with his Boston-based company Alzheon, the Czech neurologist is reaching for the medical Holy Grail: a cure for a disease that devastates the world's population in a frightening and unstoppable way, Alzheimer's disease.

With a unique pill that has been developed with investments of more than a half a billion dollars, Tolar wants to bring his treatment to the market relatively soon. It is with this pill that he intends to stop (and perhaps even prevent) a disease that ultimately deprives the victim of his life; but first of his reasoning and ability to perceive the world, so that he becomes a soulless being – a being who still resembles man in his body, but who is no longer human in the truest sense of the word. For according to Descartes' famous definition of man, "I think, therefore I am," a patient in the final stages of this disease is no longer human.

Does that sound cruel? This disease is cruel. Someone you know is suddenly completely lost, his personality, identity, past and present, fade away. "Sometimes I hear that the patient is like a child again. In reality, his condition is much worse – he is not here, he is not able to understand, to communicate, to react. Moreover, by the time the onset of clinical symptoms is recognized, the brain damage is already so severe that a person rapidly progresses from a relatively mild clinical impairment to a stage where he is unable to take care of himself. On average, it takes just a year or two from the point where you are a little forgetful to the moment when you fail to recognize your own children, your wife. Many patients need to be hospitalized at this stage because their families cannot take care of them. When grandma gets lost and sets fire to her own kitchen, it is too late for an effective

treatment," says Martin Tolar in the beautiful and bright courtyard of the Augustine Hotel in Prague's Malá Strana. Even in such a vibrant restaurant, his description of the disease gives you a feeling as if the room has suddenly darkened. The luxurious complex, which provided Tolar respite during his recent visit to his native country, is located at the site of a former monastery – but after hearing his description of the disease, God seems to have vanished, leaving only suffocating despair.

After all, the man who has seen many times with his own eyes the absolute and irreversible destruction caused by Alzheimer's is ordering a local dark beer – and at that moment the color of grief seems to fill every corner. But only momentarily, and that's a great relief. The scientist who transformed his knowledge into business is not discouraged, but rather filled with a contagious optimism. His optimism is based on the belief that he will help to eradicate Alzheimer's for good.

It is not only what Tolar says, but also the style in which he says it that is captivating. The important thing is that when Martin Tolar talks about ALZ-801, which is the prosaic name for – as it seems to a layman – a miracle pill, he does not say "we could have a cure," but "we have a cure." And lo and behold, the magic of the pill transforms the garden restaurant in the former monastery: the clouds recede, and the dark beer shines encouragingly in the divine light. It no longer has the veil of sorrow, but the shimmer of a diamond.

Can we really talk about your medicine as a done deal?
This is exactly what politicians, patients and investors are asking.

I can imagine. How do you answer them?
That we know how the drug works, at what dose and in which patients, that it works well and safely and that I see no scientific risk. We now understand the nature of the disease, what causes it, how to prevent it, and most importantly, we have data from more than two thousand patients that gives us confidence in our success. However, we now need to complete the third phase of the clinical trials and confirm our previous data. And we must do it well, that's the risk.

I'm sorry, but I don't understand. If the medicine works, what is the risk that the final phase of the tests will not turn out well?
You must find suitable patients and do this last study very well, which is not a trivial task. Phase 3 is a very complex program that is already underway in more than eighty institutions across America and Europe. You need to find patients with the correct genetic risk factor and properly assess their clinical condition and disease course, as well as imaging and fluid biomarkers. You need to do this efficiently and within budget. Our APOLLOE4 Phase 3 trial is crucial – this is the last step that can bring us to market.

When?
Our current plan projects commercialization in 2025. We will have the final data from the study in 2023, so if everything moves quicky and efficiently, we can get on the market even sooner.

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Finding a cure for a disease that is perhaps worse than death itself and comparable to burying a person alive, this would be tantamount to a victorious revolution – and it would not be Tolar's first. He was a key figure in the famous Velvet Revolution that led to the fall of the communist regime in former Czechoslovakia. And if this revolution in connection with the defeat of Alzheimer's is accompanied by the sound of a flood of dollars, during Tolar's first revolution it was the ringing of countless keys in Czech town squares in the 1980s, announcing to communist comrades that their time had expired.

This peculiar concert of the keys – a concert as a requiem of the abominable regime – was unleashed by the students. The revolution's leaders included Martin Mejstřík, Šimon Pánek, Jan Bubeník and Martin Tolar, a fifth-year medical student who still had hair at the time (he did not shave his head until he founded Alzheon, to have one less thing to worry about). "We were in our twenties and had no idea who was winning," says Martin Tolar as he smiles at the great adventure. He describes the November 1989 Velvet Revolution as the defining moment of his entire generation.

In leading the change, the medical student pushed himself in a direction he had not been able to dream of until then. Many other coincidences and circumstances also played a role in his search for a cure for Alzheimer's, but without the Velvet Revolution, no search would have taken place, no hope for the sick would shine in the present. If ALZ-801 develops as the coveted solution for an insidious disease, Tolar will ensure that the memories of the fall of communism will not be forgotten for the rest of his life – as these memories deserve.

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What first comes to mind from that time?
Imagine that you are in your early twenties and grandmothers are rushing towards you with kind words and gratitude, thanking you for your courage, telling you how much they trust you and thanking you for the chance that things will finally change after two generations of communist rule, bringing you cookies and cakes and donating their small savings to support the revolution. Cars stopping stop on the street, offering to take you anywhere for free. Incredible times! At first, we were very uncertain about the outcome and on edge, they told us that tanks were sent after us, and it was uncertain how everything would turn out. Fortunately, we did not think much about the fact that most revolutions in history did not end in a "velvety way". It was also the first realization of our responsibility for this country and its destiny.

After it all went well, we all felt a huge release of enthusiasm, energy, and most importantly the courage to dare and challenge even the seemingly impossible – suddenly it felt that everything was possible! I remember when the first Americans began to visit Prague, they were amazed: 'Wow, these 20-year-old kids are really running this country!' It is impossible to explain this whole experience to your children, it is non-transferable, completely incomprehensible to them... That you can't travel anywhere, you can't listen to forbidden music, you are not allowed to read certain books, you must pass state exams assigned by the communist party – my children couldn't imagine such a world, even if they wanted to. My eldest daughter was born by then, but in 1989 she was just a year old.

Did you have a daughter in medical school?
Yes – Veronika, that's how things were back then. But this experience of having a child at twenty gave me a direction and anchored me. Had it not happened, I would probably end up somewhere as a bohemian! My wife Danuška is an amazing woman, who later joined me in America with the baby, despite all the good-hearted advice and warnings from friends and family. She also studied medicine and appreciated the joke that a medical student who becomes pregnant during her studies lacks a basic understanding of human biology.

We met during our clinical internship in Ústí nad Labem. She was only nineteen and it was a dreamy, one and only, unforgettable summer of love. The Velvet Revolution was followed by our American adventure: universities, cities, New York, San Francisco, Boston, the oceans, the mountains, surfing in Hawaii, a whole new world full of incredibly interesting people, friends, experiences, and ideas. America opens your eyes, your mind, and your soul like no other place in the world. Danuška was and still is my best friend and partner through all the successes and struggles. Our daughter Veronika was later joined by my son, Lukáš and daughter Kristinka.

The momentous internship took place in Ústí, but you are from Prague, right?
From Zahradní Město, the Garden City part of Prague. Prague and the Czech Republic are among the most unique places in the world. This is the place where I played with marbles as a kid. I emphasize my Czech upbringing

everywhere when I am explaining where the determination and inspiration came from – and to let everyone know that a Czech boy dared to take on the cure for Alzheimer's! This is the place where I will always feel at home, where I got my first kiss somewhere on the playground, and here is my cultural background, my friends, and where I experienced everything that shapes a person in life. And most of all, I was very lucky to meet and be influenced along the way by some incredible people.

At my Omská primary school, my teacher Mrs. Homolková cultivated my interest in science and mathematics. At my university prep school Na Vítězné pláni, they let us live even under communism, and Professor Hoznauer even let us read the dissident literature from his personal library. I used to read constantly. I read thousands of books at that time, and I hoped to live through and experience the stories in those novels – so then I knew who I was and what I wanted from life. After graduation, our class principal Professor Peterková, a remarkable woman, returned to me a backpack full of books she confiscated from me for reading under the desk, saying that with my head in the clouds and an obvious lack of interest in formal studies, she did not believe that I would ever reach graduation.

What did you read?
I was interested in philosophy, which led me to think about humanity, its foundation and essence, what makes us human and, as an extension, the inner workings of the brain. Those days were probably the oldest roots and inspirations for the founding of Alzheon, and I will get to that. I was also interested in computers, neural networks, and modeling, so I first studied at the School of Electrical Engineering at the Czech Technical University in Prague. Only later did the “medical genes” manifest. I am from a medical family – my grandfather Vojtěch Tolar taught internal medicine at Charles University until the famous Czech industrialist Tomáš Baťa asked him to move to Zlín. There he helped create the field of occupational medicine – building and providing free healthcare services for employees, which was rare at the time.

My parents are also doctors and scientists. They both worked at the Czech Academy of Sciences. My mother studied the genetics of cleft lip and palate at the Department of Plastic Surgery at Vinohrady University Hospital, and my father was a neurophysiologist at the Institute of Physiology of the Czech Academy of Sciences. So, I finally listened to my genes and in the middle of Czech Technical University, I entered medical school at Charles University in Prague and studied both fields simultaneously. A few years later, when I worked in Boston at Massachusetts General Hospital, my father told me that this was exactly where Tomáš Baťa had sent my grandfather half a century ago! The only difference was that I came on a plane arriving to America within a few hours, while it took my grandfather three long weeks by boat. I first arrived in New York in 1992 and…

I'm sorry, I have to jump in.
Jump in, this is what makes it lively, that's how I like it!

Did you really not know English?
I had learned a little English in school, but I couldn't ask for bread, and I didn't dare talk to people on the street, so that's why I filled half of my suitcase with English dictionaries. This is why America is so amazing: you can come there with one suitcase, take a chance to leave everything behind and yet have the entire world at your fingertips. It was all very exciting back then. I got off a plane in New York on a typical hot and muggy day in August. I lived in Brooklyn in the early 1990s, back when fires blazed from trash barrels and there was frequent gunfire on the streets at night. It was like living out one of Ed McBain's 87th Precinct stories. New York was a dangerous city at the time, but I got to know all sorts of interesting people and cultures and explore neighborhoods I used to read about only in novels. We listened to music and drank beer at bars in Greenwich Village, and we wandered around Chinatown and Broadway. There were a few other Czech students there and we had a lot of fun. Then they returned home to the Czech Republic.

Not you.
I always left one foot in the Czech Republic. As Velvet revolutionaries, we wanted to learn something and bring our experience back to the Czech Republic. A year later, when Danuška and Veronika came to America with me they kept asking, “When are we going home?” But there were other experiences, opportunities and new exciting challenges that were so enticing, we just had to stay.

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In America, Martin Tolar stood where Christopher Columbus had, exactly 500 years earlier, and he too set out to discover an unexplored new “continent”. The unexplored universe within the human body, in the human brain. "After receiving my degree in neuroscience, I found out how little we know about the brain and how it functions," he stated so passionately that the passing waiter stopped by to see if he wanted another dark beer. "The brain processes and evaluates trillions of pieces of information at any given time, so the complexity is incredible. And it is in the brain where humanity is formed and resides – and the consciousness that I had read about in the books of philosophers, during university prep school classes under my desk, is formed.”

The fact that we don't know much about the brain has an impact on our understanding of Alzheimer's disease. As a young man, Tolar graduated and defended his dissertation in neurosciences and the biology of Alzheimer's disease at the University of Cincinnati College of Medicine, completed a clinical specialization in neurology at the Boston Medical Center, and later worked and taught at the Yale University School of Medicine. He became fascinated and simultaneously worried that understanding of the cause of this disease is sorely lacking, which of course naturally leads to the absence of an effective therapy.

"Over the last ten years, $600 billion has been invested in the research and development of treatments for Alzheimer's, and there is virtually nothing to show for it," he lamented. "I was haunted by the idea of trying to develop a cure, which was the main motivation for working for the pharmaceutical giant Pfizer, a great company that was at the forefront of research at the turn of the century and also the most valuable company in the world. This was the best place I could be at that time and the experience introduced me to the new field of drug development."

One of the qualities that makes a dozen stories into Hollywood blockbusters is when a hero sets out and accomplishes the impossible, succeeding despite the odds stacked against him. Much like Frodo from The Lord of the Rings – although Frodo’s chances of bringing the ring to Mordor were perhaps a little greater than the chance of stopping this disease, the cure for which has been sought in vain since the disease was first described in 1906. The Czech scientist's journey to destroy the evil in the brain, like the hobbit’s journey to destroy evil in the world, is complicated and full of roadblocks.

At Pfizer, Tolar was initially in charge of clinical drug development, including Alzheimer's. He was then offered a promotion to business development, specifically leading a group analyzing other companies' research programs and buying those that appeared promising. Tolar then returned to graduate school for the fourth time, to complete the Executive Management Program at the Stephen M. Ross School of Business at the University of Michigan. After six years, he left Pfizer to pursue his growing interest in the field of biotech companies. He led three of them as CEO, and in 2013 he founded Alzheon in Boston, Massachusetts.

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How did this happen?
I don't know of any other company that was created without the initiative, influence, and support of venture capital, and moreover is still run by its original team after nearly a decade. A few people actually followed me from Pfizer to the three biotech companies and then finally to Alzheon. In the summer of 2013, I took a few hundred dollars to incorporate the company and we started looking for the right medicine. When Alzheon was first founded, we would all meet in my kitchen at home, where I cooked Indian and Thai dishes or spaghetti for everyone. We drank delicious wines for inspiration, and that's how it went for half a year. We traveled all over the world, including as far as India, to evaluate interesting programs. Our idea was to find a cure for Alzheimer's, but, unlike many of the failures before us, to focus initially on patients with an impactful genetic risk factor and...

I'm sorry, but I need to jump in again. You were the CEO, making a decent amount of money, but suddenly you decided to throw it all away. Wasn't this crazy?
In many ways this was the pivotal, existential moment in my life and an immense personal risk, far greater than launching the Velvet Revolution or packing a suitcase and going to America. It felt similar to how Jean-Paul Sartre described his feelings in his short stories from the Second World War. I also shaved my head at that time, on my way to India, in preparation for this fight. It seemed impossible to fund our idea, so we felt we had two options. Either we give up the dream and go back to working for someone else, or we continue to pursue what others considered crazy. We, of course, chose the latter. My advantage was that thanks to my role in Pfizer's business development group, I had developed strong working relationships and gained the trust of many companies in the industry, and they allowed us to investigate their drug development programs in Alzheimer’s. We analyzed thousands and thousands of pages of clinical data and finally found a program in which half a billion dollars had already been invested.

What was it about?
Montreal-based Neurochem had conducted two large Phase 3 clinical trials in 2,000 patients, which showed a significant clinical effect in patients with a high genetic risk for Alzheimer's disease. Thanks to our understanding of biology and genetics, which was part of my graduate school dissertation, we believed that this therapeutic approach could work for Alzheimer's. At the time, the people behind the program felt this signal was not strong enough, so everything was stopped. They gave up and put the whole thing on ice.

Did you pick up the project after that pause?
Yes, and so began Alzheon’s journey. This was my best deal ever! We got the data worth half-a-billion dollars for a kiss, because we were the only buyers – no one else wanted it. Fortunately, no one understood the use of precision medicine and how it could be applied to Alzheimer’s and the neurodegenerative diseases we studied and pioneered in our work. Nevertheless, I had to keep Alzheon afloat financially for two years on my own. My wife Danuška told me then: You're crazy! I always thought you were a rational person, and now we’ll all end up living under a bridge!

How much did it cost you?
The first investments were on the order of millions of dollars, which I was able to secure on my own. The problem was that at that time we could not know how long the development would take, how negative and hopeless the whole area of Alzheimer's drug research would be for almost ten years, and how many other obstacles awaited us.

We also had no idea that we would remain unique with our medicine and approach to treatment, as something like this is impossible to foresee. At that time, dozens of competing treatment programs were in progress at large Pharma companies, and no one gave us a second glance. And this is fascinating in America – one man's trash is another man's treasure! Literally. You can learn the most from failures and setbacks in science.

Did something you worked on implode?
Sure, at one of my previous companies our technology did not translate from animal models to patients, so we had to shut off the lights and start over. However, Alzheon was the first company we had built on our own and the risk was tremendous. I kept reassuring Danuška: Everything looks great, it's a clear win, everything will be fine! But I knew that the chances of things working out were one in a million, one in a hundred million, basically minuscule. I had no idea that we would find ourselves in the current situation where we are the only alternative to the antibody infusion programs developed by large Pharma companies. We have a far better and safer product, because we are the only company developing a drug that can be taken orally and without the side effects such as brain swelling and brain bleeding.

This is probably the right time to introduce the pill.
Sure, so… Wait, please wait a minute, let me quickly say hello to my friend.

The acquaintance was Mario Egger, the Austrian manager of the Augustine Hotel, where Tolar stayed when visiting the Czech Republic. With his busy schedule, he has turned this garden restaurant into a kind of auditorium, where he invites friends and business partners to meet. The hotel manager quickly turned into a potential business partner: he came not only to shake hands, but also to figure out how he might invest in Alzheon. It was a perfect

demonstration of how the former poor Cinderella became a much sought-after hot commodity. The interest testifies to the credibility of the path that Tolar's company has taken and the diamond that shines at the end of the journey. And since the finish line is already in sight, the glare is dazzling.

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The ALZ-801 introduction will take place soon, but before this, let's first talk about investments. I am trying to imagine how you approach a potential investor at the beginning of your journey, and you can't promise him anything, you can't guarantee the success, rather the exact opposite...
It was an extremely difficult period for Alzheon. Every time we advanced in our development another Alzheimer's program exploded somewhere else. We felt like we were on a battlefield, where grenades and landmines are exploding all around you. However, anyone working in pharmaceutical development realizes that in this business, multibillion-dollar investments are necessary to develop life-changing products. It is an enormous market, and something investors really want to tap into – but in our case, no one believed that our novel approach could work, or that we could compete with the massive Pharma conglomerates with access to almost unlimited capital and many other advantages.

Well, right! Of course, now it's quite easy to imagine a fairytale ending, but for me it's all about how you convinced investors at the beginning, when the end seemed so far away and riddled with obstacles, a project of crazy dreamers.
The people who invested in us wanted to help patients and society, they shared the same mission that we have at Alzheon. In short, they placed their bets on us. Of course, everything was very risky – even though we had cutting-edge science, experience, and previous successes in the field. For instance, at our first biotech company, we closed a billion-dollar deal with the second largest Japanese Pharma company. At Alzheon, we did not have a leading institutional investor and that was a major difference from other companies I had worked for in the past. However, such an investor always wants a quick return on his investment and immediate results, so he is always pushing you into things that will help him raise additional funds. We had no such supervision and control, so we were for the first time in our careers completely free to do what was right for our program and the company. It was priceless. And do you know what our biggest advantage was?

Tell me.
Time. Thanks to our independence, we had time to thoroughly study and understand the scientific problem of Alzheimer's disease, to complete our discoveries and publish them, and to build a robust foundation for our treatment program. It's a very small world in biotechnology in Boston, and fifteen years ago Stéphane Bancel – this is the guy who founded Moderna – asked me to join him. I also had many offers from other companies, but I knew that we had something unique and just needed time to prove that the idea could work.

We've had eight years to build our understanding of Alzheimer’s and develop our therapeutic program, but the fact of the matter is – without the clinical data we initially bought from Neurochem, I would have never touched the product. Without clinical data? Never!

You may find intriguing scientific experiments or studies in animal models of the disease, but without clinical data you never know how the drug will work in humans – so it's still a huge risk. I bought the data from two thousand patients for a penny because I saw that the patients responded well and how safe the medicine was. Before launching their Phase 3 studies in which they invested $3 billion dollars, Biogen had data from just 160 patients, but we had 2,000 – that’s the difference, you know?

I get it, but that's why I don't quite understand why Biogen is currently ahead of your program, at least in commercialization. Their antibody infusion Aduhelm was approved in June by the U.S. Food and Drug Administration (FDA).

This approval is a landmark success for Alzheimer's and has validated our science as well as our approach to treatment. Their approach targets the toxic amyloid with an infusion of monoclonal antibodies. However, Biogen's data package was far from the standard metric required by FDA regulators for drug approval. They jumped straight from their first clinical phase to the third and, therefore, didn't fully evaluate the dosage or understand the side effects of the treatment. The main problem with Biogen's dataset is that they actually stopped their Phase 3 trial in the middle because, after analyzing the data, they were certain that their treatment would not work. For this reason, a large part of the expert public was against the approval of the drug.

Then why was it allowed?

Because the other development programs, including ours, have shown that the overall approach is correct and that their drug probably works, and no one wants to lose another five years – which is what it would take to repeat the third phase of testing. Caring for Alzheimer's patients costs half a trillion dollars a year in the United States alone, and until recently there was no prospect of anything working. Infusions of Aduhelm antibodies can slow the progression of the disease in patients by about thirty percent. So, it's not that it stops Alzheimer's disease completely, but it does slow it down at a statistically significantly rate. The main handicap is that the drug does not get into the brain well, only about one percent of the active drug will make it past the blood-brain barrier, and it is not selective for the toxin. Another problem is that Aduhelm washes away plaques in the walls of blood vessels and this causes serious side effects – swelling of the brain in a third of patients along with bleeding in the brain.

In addition, antibodies must be infused for several hours, which is a hallmark of the leading Alzheimer's drugs being developed by our other rivals, the Pharma giants Eisai and Eli Lilly. Another big controversy is how much Aduhelm costs. Biogen originally asked for $56,000 a year for one patient, which is a lot for a drug that may be needed by millions of patients. The Medicare insurance program, which cares for the elderly in the United States, has an annual budget of $40 billion for *all* drugs, and Aduhelm alone would cost many times more. That being said, Biogen had the courage to take a big risk and should be applauded for this.

Because many other companies have given up on it?

Almost all other pharmaceutical companies, when they realized the astronomical risk and high development costs, immediately said: We will not even touch a drug for Alzheimer's! Forget it!

Isn't that unethical?

Well, drug development is a business, there is no doubt about it, but I am also a physician and I believe that rich companies have a responsibility to try to solve important medical problems and need to ensure that patients have access to the medicines they need. Still, everyone has been running away from developing the treatment for Alzheimer's for many years, which is why the U.S. Congress has had to take a unique step. Congress passed an unprecedented law to support the fight against the disease, and we were the only Alzheimer's company to receive full funding for our Phase 3 trial – a $47 million grant to support the final clinical phase of our patient trials.

When you mention the price for Aduhelm from Biogen – how much will a pill from Alzheon cost?

Our drug may have sales in the of tens of billions of dollars, but its price? We do have some initial projections, but this early, it's difficult to be specific. In any case, our pill will be very cost-effective, given its accessibility and ease of manufacturing. Because it's a pill, everything with respect to administration becomes much simpler. You can have it in the cupboard, while special stations must be built for infusions and millions of patients must come there every month, which is a major complication for many sites and clinics. The $56,000 dollars that Biogen is asking for includes just the direct cost of the drug, but someone must also pay for the infusion stations, imaging assessments to assure that patients don't have brain swelling or bleeding, and much more. The real cost can easily climb to over a hundred thousand dollars per patient per year. The cost of our pill will be substantially lower.

This finally brings you to try to introduce me to ALZ-801.
The human brain is the most metabolically active organ of the human body. Twenty percent of energy used by your body is burned in the brain, which leads to the formation of toxic byproducts that weigh as much as the brain itself, about three pounds, and these must be flushed from your brain every year. At first the brain can do it on its own, but around the age of forty, it loses this ability – just like when you have a car and your exhaust slowly become clogged. The toxins then begin to accumulate in the brain, creating a fire that destroys the brain cells, their connections, and the entire structure of the brain tissue. Our pill can put out the fire.

How?
Don't jump in now, please let me talk for a moment. The toxin is a cluster of a protein called beta amyloid, which is the key driver of brain damage in Alzheimer's disease. Beta amyloid protein, when in its original healthy, monomeric, single molecule form, acts as a defensive shield against brain injury, brain infection, and even stress. Lizards already had this defensive system in place 400 million years ago. In the event of an injury, your amyloid levels will skyrocket and protect your brain.

A useful shield?
Exactly, but as you age, you are no longer able to clear the amyloid from your brain effectively and the monomeric amyloid molecules clump together to form toxic clusters, called amyloid oligomers. Furthermore, the brain protects itself by forming insoluble aggregates of amyloid, called plaques, which are basically brain scars that sequester and neutralize toxic oligomer clusters. These amyloid plaques are what Professor Alzheimer found in the brains of patients when he first described the disease. In addition, two thirds of Alzheimer’s patients have a copy of the APOE4 gene, which impairs the clearance of amyloid and increases the risk of the disease several-fold.

In these patients the disease starts many years earlier and its course is more aggressive. These high-risk patients are the initial target population for our drug, in line with our philosophy of applying precision medicine in the development of the ALZ-801 tablet. However, we believe that with the same treatment, we can eventually help all Alzheimer's patients.

Again. How?
Our drug compresses the amyloid monomer into a shape that prevents its aggregation and subsequent formation of the toxic oligomer forms. The amyloid molecule is shaped as a “V” and this “V” tightens in response to our drug. This change in the shape of the amyloid molecule prevents its aggregation and allows the toxin to wash away from the brain. It is a simple, almost physical mechanism, and it is also measurable and controllable. Another advantage of our pill is that it safely boosts the innate system in the brain that has developed during millions of years of evolution to prevent the formation of the toxin. ALZ-801 supports this innate defense system, increasing its effectiveness about twelve times – and even in older people, for whom this system has already failed.

Your Phase 3 APOLLOE4 study, which is essential for market entry, confirms all of this?
I'll start with Phase 2. More than eighty patients are currently receiving our drug in this trial, and this study, which will run for two years, showed after just three months of dosing that the drug works exactly as we predicted – it washes away amyloid and prevents neurodegeneration of the brain. The APOLLOE4 Phase 3 trial, for which we have secured financing, looks very promising and many investors and Pharma companies are already interested. The study is underway in America, Canada, England, and France, and we are now initiating study sites in the Czech Republic, Germany, and the Netherlands. Most people can't imagine how organizationally demanding such a study is.

You need to have a drug substance manufacturer, a tablet manufacturer, you need to find and organize all the clinical institutions involved in the study, pay them, assign who gets the drug and who gets the placebo, you need to monitor clinical and other data as they roll in, report frequently to regulators, conduct the appropriate analysis of your data and so on. The main point is that we understand how the pill prevents the formation of the toxin that causes Alzheimer's. In addition, there is the potential for expansion – we will eventually start working on other therapeutic indications.

What are you referring to now?
The most common reason for blindness is degeneration of the seeing part of the eye that is called the retina; this disease is age-related macular degeneration – it affects 60 million people globally and there is no cure. The retina is in fact a part of the brain extending into the eye and the basis of retinal degeneration is very similar to that of Alzheimer's. ALZ-801 enters the eye tissues very effectively and world experts in this area are asking us to start a study to evaluate the impact of our drug as soon as possible. Therefore, we are planning a trial both in America and with Dr. Pavel Němec at the Department of Ophthalmology at the University Hospital in Prague Střešovice.

So, ALZ-801 could not only work in Alzheimer's, but also in curing blindness?
Exactly. Another potential indication is Down Syndrome, which affects 400,000 people in the United States alone. Or brain injuries… However, our priority and focus is, of course, Alzheimer's. But, we must also think about what to do and where to go next. We have strong interest from investors to move forward in these additional clinical indications, and these will require much lower investments compared to Alzheimer’s, at least in terms of the cost of the initial proof-of-concept studies. For example, for the first trial in age-related macular degeneration we will need approximately twenty million dollars.

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In addition to business meetings, Martin Tolar also had a bit of fun during this August visit to his home country. For example, he attended a reunion with his classmates from elementary school – that is, former kids with whom he played with marbles. The entire planet would profit from Alzheon's Alzheimer's drug, but the place in which he grew up could benefit especially.

In May, Alzheon's partnership with the Prague Institute of Organic Chemistry and Biochemistry of the Academy of Sciences (IOCB) was announced, to which Tolar commented: "We are Czech boys and we started it together."

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What is this partnership about?
First of all, we partner with many Czech clinics, institutes, companies, and startups. For example, in our clinical studies we work with Jakub Hort at Motol University Hospital in Prague and with Katka Sheardová in the St. Anne University Hospital in Brno. We are also working with Vláďa Mařík and the Czech Institute of Informatics, Robotics and Cybernetics of the Czech Technical University in Prague on application of artificial intelligence in drug development and with Loschmidt laboratories at Masaryk University in Brno on other molecules and indications for our therapeutic platform. However, even in the European setting IOCB is an exceptional and amazing institute. We were looking for someone to work with us on the development of a test for the detection of the toxic amyloid oligomers in the brain, to support the diagnosis of Alzheimer's, because...

The sooner you catch the disease, the better?
Exactly. When you start to show clinical signs of Alzheimer's, you are already at the terminal stage of the disease – at which point substantial brain injury has already occurred. For the first twenty to twenty-five years, the disease is almost invisible, but when you start to show clinical symptoms, there begins a rapid decline, which I have already described: from mild forgetfulness you will soon lose yourself and forget your loved ones – this is the tragedy of this disease. Therefore, an early diagnosis is key.

And will the IOCB provide a solution?
Ever since we discovered the mechanism of our drug and the technology to detect and quantify the toxin, we have been looking for a partner to develop the Alzheimer's diagnostic that can detect the disease in the human brain. This is a completely new technology and we have not been able to find the right partner for years, not even at American universities, companies, or institutions. Then, during one of my visits to Prague, I met with the Director of IOCB Zdeněk Hostomský and Professor Martin Fusek, who leads the technological transfer and business development at the institute. We found out that at IOCB Josef Cvačka's unique scientific group has experience with the development of diagnostics and also has the right equipment, each machine is worth millions of dollars. The result is a very productive collaboration, which has been running for almost two years now and was officially announced in May.

By the way, the fact that we arranged and formalized this partnership so quickly is also because my current transaction lawyer, Bob Jones from Cooley in San Francisco, once went to then communist Czechoslovakia to negotiate a licensing deal for the U.S. biotech firm Gilead with the legendary Professor Antonín Holý, who worked at the IOCB. Gilead applied the IOCB chemical platform to the successful development of drugs for HIV/AIDS and hepatitis B. Royalties from this collaboration are why the IOCB is a uniquely wealthy institution and can afford to pay the best people and purchase the highest quality devices. The group of experts at IOCB knows exactly how to approach this complicated problem and work towards a diagnostic. When all of this comes to fruition, an incredible opportunity can arise from early diagnosis and treatment.

Which will also benefit the Czech investors who initially gave money to Alzheon, right?
I can talk about two investors, because they already publicly announced their investments. These are Zbyněk Frolík, the owner of Linet, a company that builds hospital beds, and Prague lawyer Radek Pokorný, who runs the law firm Pokorný, Wagner & partners. But there are more Czech investors in Alzheon, and they account for about

five percent of the total amount of money invested. It is not only about investors, however – this drug can potentially generate tens of billions of dollars, which I would like to use for several projects in the Czech Republic, including a foundation that could help set certain things in motion.

What things?
I discussed the needs and possibilities with many businessmen, politicians and even artists. With former presidential candidate Honza Švejnar, with diplomats Vašek Bartuška and Petr Kolář, and with Monika Vondráková, who runs the Neuron Endowment Fund supporting science in the Czech Republic. I would like to help build an effective venture capital ecosystem here, because there are a lot of people and companies coming to me who have great ideas, but don't know how to build their own companies or how to develop their products. They also don't have the right investors behind them. Of course, we can continue to assemble cars, brew beer, and entertain tourists in the Czech Republic, but there is also enormous potential for passionate and educated individuals who have the ideas and courage to try new things and become the real future of this country. They just need a little help, a nudge forward.

Like those marbles.
Right, it's almost as simple as playing marbles – just a smart light tap can help you get to the right place! It is clear what is needed.

What is needed?
A functioning technological ecosystem for biotechnology and informational technology companies is based on three pillars. One is already well established in the Czech Republic: top universities that educate creative people with great ideas. Unfortunately, the other two essential components are missing here. You need people capable of building an effective executive team – management that knows how to make the right decisions, including financial ones, at the right time. Finally, the third thing you need is access to capital. You don't need that much: five or ten million dollars can push you to the desired global visibility and the level where more resources and opportunities will open. It would be very helpful to establish a venture fund in the Czech Republic, and that is exactly what I am trying to do. This country has the opportunity to become a technological powerhouse, so we should boldly bet on that.

Was that like the courage needed to initially bet on Alzheon?
Exactly. We were very honest with the investors who showed interest in supporting us and we shared all our calculations and analyses. However, at the time we spoke with them the failure rate of programs pursuing Alzheimer’s therapeutics was 99.6 percent! For typical venture or private equity funds it would have been an absurd investment and so, of course, they declined. However, a number of private investors did see the rationale. These investors shared our vision, they were able to understand our scientific discoveries and advances, and our pioneering precision medicine approach made sense to them despite the poor prospects. Success like ours can’t be planned because it depends on a rapidly evolving science and business environment. The cure for Alzheimer's has been sought in vain for over a hundred years, but now we are closer than ever before.

At Alzheon we had made major scientific discoveries – what causes the disease, how to prevent toxin formation, the important genetic risk factors, how to apply them in drug development, how to find the right patients who respond best, how to treat them, and so on. We also built a global team of several hundred people. Still, we had no idea how many battles were still ahead of us – so it was a big surprise to come out ahead of everyone.

And you know what, Filip? Now we finally got the marbles in the right spot, we really believe we have found the big breakthrough. The sensational part is how everything has come together perfectly for our drug to be successful and how our approach and science has been validated over the past six months. It seems like just yesterday when we were cooking and dreaming about Alzheon in my kitchen.

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