**Alex Zhavoronkov:** 0:00

It's very clear that the population is going to grow, regardless of whether we are going to identify anti-aging interventions or not. Because it just did right. So if you are concerned about overpopulation, you should stop reproducing right now. Right, are you willing to do that? Probably not. We realize that druggability is a big feature, right. So if you go after the top scoring target but it's not druggable, you might never be able to deliver a drug right On the market. You run out of money before you demonstrate that you can drug it. It's better to go off the targets that have a good balance of confidence and commercial tractability and novelty and also drugability. So if you know that it's going to be extremely difficult to drug, you are increasing the risk of the program.

**Craig Smith:** 0:48

Hi, I'm Craig Smith and this is Eye on AI. This week, I spoke to Alex Javronkov, founder and CEO of Encelico Medicine, about the application of artificial intelligence in drug development to advance the field of longevity research. He's committed all of his resources, as well as all of his remaining time, to extending healthy, productive longevity for everyone. In pursuit of this goal, Alex has developed an AI-driven platform to discover targets and an automated robotic lab to prepare molecules for clinical trials. I hope you find the conversation as inspiring as I did. Hi, good tech solves problems you know about. Great tech solves problems you haven't even thought about. What can the commerce platform trusted by millions of merchants do for you? It's time for Shopify, the commerce platform, revolutionizing millions of businesses worldwide. Whether you're a garage entrepreneur or IPO ready, shopify is the only tool you need to start, run and grow your business without the struggle. Shopify puts you in control of every sales channel. So whether you're selling satin sheets from Shopify's in-person point of sale system or offering organic olive oil on Shopify's all-in-one e-commerce platform, you're covered. Shopify powers 10% of all e-commerce in the United States and Shopify's truly a global force powering all birds, rothes and Brooklyn and millions of other entrepreneurs of every size across over 170 countries. Plus, shopify's award-winning help is there to support your success every step of the way. Sign up for a $1 per month trial period at Shopify Com slash IonAI. That's Shopify S-H-O-P-I-F-Y dot com. Slash IonAI. That's E-Y-E-O-N-A-I all run together. So sign up for a $1 a month trial period at Shopify Com slash IonAI. That's Shopify S-H-O-P-I-F-Y dot com. Slash IonAI. That's E-Y-E-O-N-A-I all lowercase, all run together. Sign up for a $1 a month trial period at Shopify Com slash IonAI. That's Shopify S-H-O-P-I-F-Y dot com. Slash IonAI. That's E-Y-E-O-N-A-I all lowercase, all run together. Go to Shopify Com slash IonAI to take your business to the next level today. Excuse me, sir, I couldn't help, but over here Did you say Shopify? Oh, shopify.com slash IonAI.

**Alex Zhavoronkov:** 4:14

Oh, carry on. So my name is Alex Chavronkoff. I am the founder and CEO of a generative artificial intelligence company that is utilizing generative AI for drug discovery, called InSilica Medicine, and founded the company in 2014. Never looked back. Now we're in a clinical stage. We have AI generated molecules in human clinical trials, so we've passed multiple preclinical experiments and managed to demonstrate that we can deliver both novel biology and novel chemistry utilizing AI that can be experimentally elevated. So very happy to be in humans, also do a lot of work in AI powered robotics and also now venturing into quantum computing Wow.

**Craig Smith:** 5:11

That's quite a list, and you're very active in the longevity space and that's something I wanted to talk to you about. First, on the process that you've developed, I mean we've spoken before, but there is pharma, ai, and then there's pandomics, and then there's chemistry 42. So can you sort of walk me through those three? And now there's the AI robotics lab. I'm not sure where that is, but I see that you guys are expecting to get that up and running this year. So can you kind of put together those pieces and explain how novel drug discovery works within Silico? So sure?

**Alex Zhavoronkov:** 6:11

We have three pieces of the puzzle that span the entire pharmaceutical research and development cycle. So we have a tool that allows you to identify the novel protein targets that are driving a variety of diseases so we can work with many different disease types and subtypes, including aging, and to identify protein targets and also formulate disease hypotheses. We have a tool called pandomics. This tool integrates more than 20 deep learning and machine learning models trained on both biological data types and text, and many other data types to produce valuable hypotheses and try to identify previously unnoticed links between protein targets and diseases. And also, this tool allows us to go very deep into the mechanism of disease and, unlike many other tools, this tool is very interpretable, so a biologist would be able to make use of it, even though it has very powerful AI machinery underneath it. It's very interpretable and you can go down to the level of individual genes, proteins, mechanisms of action, signaling pathways and interpret the mechanism of disease in a very standard way that is very familiar to bioinformaticians and biologists. So to build this tool, we collaborated with many pharmaceutical companies, with many key opinion leaders globally, and spent many years trying to understand how targets are discovered, how people think about polypharmacology, how people try to prioritize the different genes when it comes to diseases, especially broad spectrum diseases that are not driven just by one protein, but it's usually a huge network and many interconnected processes. However, when you're discovering and developing a drug, usually you start with a protein target. So this tool is utilized by hundreds of key opinion leaders globally university professors, pharma, drug hunters. Even high school students can use it, and recently we introduced additional tools that allow you to talk to this tool in natural language. So we call it chat panda, gpt, where you create a knowledge graph of the promising protein targets that you've identified utilizing biological or text research, and then you can chat to this graph, basically trying to ask questions in natural language. Prioritize targets Once you've identified your protein targets of interest, you need to prosecute it with real chemistry or antibodies. My philosophy is that if you are really good at chemistry, you should not do biologics because you need to inject them. They are unstable. Usually you have to store them in a very specific way. So, yes, it's usually faster and a little bit easier to develop biologics. That's why a lot of pharmaceutical companies are going that route. But we've developed a tool that's called chemistry 42,. It has multiple generative chemistry models. Generative chemistry means that instead of searching for a needle in a haystack trying to identify a perfect needle for your target or perfect molecule for your target, you generate needles with the desired properties from scratch. So you basically use this form of quote, unquote AI imagination and in this case, kind of guided AI imagination to create novel molecular structures that already look like great drugs from every perspective. So AI can optimize chemistry with many, many different parameters, and the desired parameters are usually you need to bind your protein target of interest with specific potency. So it needs to be very, very active against the protein of interest. Preferably it needs to be very, very potent and selective. So hit your target and no other targets. So it has to basically minimize off target liabilities. And you also need to be novel. So if somebody already developed a molecule that hits that target really well and has patented, or it's already off patent, then this molecule is not going to be commercially tractable and you are not going to impress the community by demonstrating you know old chemistry. So at least those three parameters need to be in all the time. However, there are many, many other parameters like, for example, the molecule has to be stable, metabolically stable so, and preferably not produce any metabolites that might be toxic or not produce any metabolites at all. You know, our body is truly amazing in its capacity to degrade small molecule chemistry or to degrade anything, right. So we, technically, are great processors of food, right? So if we were to let all the chemistry pass through our GI tract and get into our bloodstream and stay in the bloodstream for a long time, we would not survive for a very long time. So, evolutionarily, we evolved to process pretty much anything. So it's very, very difficult to make great, metabolically stable molecules, and AI is very good at doing that. Then, if you want to reach the brain, for example, you need to penetrate the blood-brain barrier, and there are many, many other, you know, tissue specific chemistry types that go into specific tissues and not the others, so you need to be able to do that. And you also need to account for the possible interactions of this molecule with other molecules, so you need to ensure that it's also very, very safe, right, and does not interact with other stuff. So those are just a few parameters that I'm talking about. There are a huge number of other parameters that you want to have in a perfect molecule, and chemistry 42 has over 40 generative models that compete for generation of those great molecules with desired properties when you give this system a crystal of the protein or alpha fold or some other predicted protein structure, or you give it a template molecule that you want to start with and optimize. So there are over 40 generative models. Some of them are GPTs, some of them are generative adversarial networks, different architectures, variational autoencoders, genetic algorithms and, most importantly, we have in that system a reinforcement learning component. So all those molecules that are generated using those AI imagination techniques, they are reviewed by a huge panel of judges. Those are predictive models. Also, most of them are deep learning that evaluate the output of each generator and judge whether the molecules are good or bad and then reward or punish each individual model. And so usually you give 70-12 hours for the system to warm up, even though the generative models are already pre-trained, and the system starts generating really perfect molecules for your desired protein of interest. You synthesize tests, see which ones worked extremely well, and then you feed those molecules back into chemistry for you too, together with the protein structure, and it generally optimizes them for additional properties, so that iterative generative design allows you to get really nice molecules. Finally, we have a system called Inclinico which utilizes GPT-like systems, but also biological and text-based systems that evaluate how implicated the target is in a disease and also evaluate the clinical study. Design and utilizing those many, many different scores, evaluation score, evaluation criteria, the system predicts whether the phase 2 clinical trial, where you test efficacy, is going to succeed or fail, and then it interprets those results and tell you which feature, which factor is likely to contribute to the success or failure of a clinical trial so you can optimize it. Or this system is actually quite actively piloted by hedge funds and banks so you can trade on small and medium type biotechs based on your prediction of whether the clinical study is going to succeed or fail. We like to work with those analysts because usually those are actually some of the smartest humans. Sometimes they are more careful and more deeply thoughtful than pharmaceutical industry leaders, because pharmaceutical company executives can go to another company. Usually it's not exactly noticeable how well they did in the company, but for a hedge fund manager it's very, very apparent, because if they lost money they lost money and usually there is a huge paper trail behind every one of those managers. So they are extremely careful when making those decisions and they utilize many, many different sources of information now, including in clinical. And finally, we combine many of those tools that I've just described. Plus, we have a system on top of those tools that allow you to run those tools in a fully automated manner and on top of a robotics facility. So the robotics facility that we've briefly mentioned is actually in operation already. So it's not like we are building, so we thought it was already operational in January this year. Now we are, of course, optimizing, debugging, putting new equipment in, putting new software on top of the platform, ensuring that the pipelines work smoothly, trying to experiment with different diseases, trying to do different types of experiments pertaining to aging research, to disease research, trying to develop the system so that you can miniaturize it and possibly put it in the hospitals one day and significantly accelerate it using supercomputers. So it's already in action. So you can visit it in Suzhou and, if you're a big pharma executive, see how it works.

**Craig Smith:** 18:35

Yeah, wow, that's quite a bit. That's a wet lab, the automated lab.

**Alex Zhavoronkov:** 18:43

Yeah, so it is a wet lab. There is, of course, a dry lab component to it, but it's embedded in several machines that are installed in the lab.

**Craig Smith:** 18:56

Yeah, and why in Suzhou?

**Alex Zhavoronkov:** 19:00

So, as you remember, 2020 to 2022 or 2023, we had the COVID pandemic. Nowadays, you know, it's like childbirth. People tend to forget what it entails, right, and all the pain and suffering. Suddenly we forget and try not to remember. But during that time the world was very unstable. It was very difficult to work anywhere, equipment suppliers were also unstable, people were quarantined from time to time and China, despite the popular belief, internally remained open. So once you get in, you actually can operate, and in most cases, even without the mask. So whatever story you hear about, you know China. Most of them are not true and, by the way, Chinese love you and everybody else on the planet, so they do not really have those hateful feelings that you see in the West toward China.

**Craig Smith:** 20:19

Yeah, I actually. I spent most of my adult life in China, so I'm very familiar with it.

**Alex Zhavoronkov:** 20:25

Yeah, yeah, so super friendly. So if you don't do anything, you know crazy or stupid, you're good for business. You're always welcome.

**Craig Smith:** 20:36

Right. So if you have an equity partner in China, or I know that you were using a lab in Wuhan I think a wet lab, at least the first time we spoke- so equity partner.

**Alex Zhavoronkov:** 20:53

We have a bunch of investors from all over the world, including Asian countries. They're not majority shareholders in any way, so we don't have any substantial investors from that region. But we do work with a lot of partners in China. So, as a matter of fact, biotech kind of turned out to be very similar to IT, so the industry that I kind of came out of, where you can pursue the Apple model, where you design anywhere in the world but you can make stuff in China quickly. And in biotech, instead of contract manufacturers you've got contract research organizations where you can hire a massive number of scientists, qualified scientists, to perform your chemistry, biology experiments on contracts. So they will not be part of your company but they will do the work that you order them to do and in massive infrastructural settings, right, so without robots or partly by robots, and you can basically synthesize and synthesize your chemistry, all those you know toxic chemicals that you don't want to deal with in your own lab. You can ask them to make them very quickly. That was the lab in Wuhan that was doing that, and also in Shanghai and in Suzhou and in Guangzhou. So we use more than 40 of those partners for chemical synthesis and tests, and we still do so. The lab that we built is built for a slightly different purpose, right? So it's not for chemical synthesis, it's predominantly for target discovery and target validation. So that's a state of the art biological research, something that very often human CROs do not know how to do contract research organizations, and we are very good at that. Right, because we demonstrated our ability to utilize artificial intelligence to identify targets a long time ago and now you know many dozens of research papers later, we are turning that into a robotics lab. We turned it into a robotics lab. We already have this capability and we own this lab 100% in Suzhou. We didn't get government funding to do that. We put our own money and we worked with multiple robotics vendors. The main one was X Imaging. It's a company which makes those super smart robotics arms and autonomous guided vehicles and the systems that allow you to connect many of those lab equipment pieces together. So that company helped us build the infrastructure, deliver the infrastructure. We have our own kind of R2D2, like robots everywhere that transport the microplates and the samples and reagents from island to island, and we have multiple fully robotic islands that do sample processing. So sample intake, sample processing, quality control, compound management, high throughput screening. We have a massive imaging station with many, many different imaging machines in there, fully automated. We've got the NGS Next Generation Sequencing Prep Room where we can do many, many different Next Generation Sequencing Laboratory Preps in fully automated mode. For those of the listeners who have ever been in a lab and did their own alley quads or let's say, pcr preps, sequencing preps, and when you need to pipet in 96 well plates, I always made errors Pretty much when I was in grad school. I sometimes don't even remember if I pipet it into one well or not and how many microliters of what. So here it's fully automated, 100% quality control. You can do it in a specific atmosphere In very, very clean room. Humans do not need to come in there and we've got Next Generation Sequencing Facilities. We've got CRISPR facilities and we are adding additional capabilities to this lab all the time. So if we see that some experiment can be automated and it's valuable and there is a need for a specific equipment type, we install that equipment in a lab.

**Craig Smith:** 26:18

Yeah, and so, for example, I was reading you have a molecule in clinical trials now to treat idiopathic pulmonary fibrosis, and can we just use that as an example? I mean, I guess first, when you're looking at targets, do you choose a disease to tackle or do you do a search of similar molecules to molecules that are being used in various drugs today and then, depending on their characteristics, decide whether they would be good? I mean, which is it, that you choose the disease first or you choose a molecule to work with first?

**Alex Zhavoronkov:** 27:20

So for us, we always choose the disease first, and then we choose the target and then we design the molecule. So those targets that we choose within the disease usually possess several properties. So the most important properties that you need to optimize for are confidence. So you need to ensure that this target works in a disease of interest. So if it doesn't work, was the point right, yeah, then you need to optimize for novelty. So, again, if it's not novel, somebody has already prosecuted the target. They have chemistry for it or biology, and it's not going to. You would not be able to patent the chemical matter and you are not going to be the first in the market, or you won't be able to be within the first kind of set of companies that are competing for that specific biology. And the most important property nowadays is commercial tractability. So you need to understand the competitive landscape, to understand what other targets are out there, because maybe the current standard of care or something that is in phase one, phase two, clinical trials, is going to outperform the target you choose. And once you spend four, five, six, even ten years developing the chemistry and investing hundreds of millions of dollars into the program, once you reach the market. Yes, the molecule may work. Yes, that's going to be the second or the third or the fourth molecule to treat that disease, but it's not going to be commercially viable, right, investors are not going to make money on that, they're going to lose money, and that's something that you don't want to happen, right? Of course you need to think about the patient as the most important stakeholder at all times, right, and try to deliver the drugs to the patients as fast as possible. But if you are not commercially tractable, you can maybe do it once or never, because investors are not stupid, right, by technology investors usually those are people with PhDs betting huge amounts of money on a specific single program or several, and usually they won't give you the money to move forward if they do not believe that the molecule is going to be commercially tractable. So the more novel, high confidence and commercially tractable target is, higher the probability of success. And later we design the molecule. So for us, molecular design is more of an automated process, right? So of course, for some protein targets it's extremely difficult, or sometimes close to impossible, to design a small molecule therapeutic that is perfect, and there are many, many targets that are still considered to be undruggable and we do go after a few of these, but we always start with a target. We can do repurposing as well, but we can do it for a partner. We can also, once we develop a molecule and we see that it works against a specific target, we can later see where else it can work. But the most important part is to do novel biology.

**Craig Smith:** 31:03

Yeah, and and then, once you've designed a molecule, you send it to a partner lab for synthesis. You're not synthesizing in your lab.

**Alex Zhavoronkov:** 31:16

No, and then we can, but it's usually something that you don't want to do yourself. Just like you know, Apple doesn't make its own iPhone.

**Craig Smith:** 31:25

Yeah, and then, once you've taken it through preclinical trials, do you then license it to a pharmaceutical company to take it into Clinical trials, or do you see it through like phase one or phase two before and then do you license it or sell it?

**Alex Zhavoronkov:** 31:51

So we try to take it as far forward as possible Yourself. So for as long as we can do this financially, because Partnering it out if you didn't, if you have not partnered at the preclinical candidate level so basically one step away from human clinical trials you better do it yourself, right, because is Offloading the program midway, phase one or phase two? It's not exactly something that is easy and also the pharmaceutical companies are Usually very good at clinical styles, the trial design right, so usually they're better than us. They sometimes make stupid decisions, right, and we see that very clearly through in clinical, because, you know, some of the programs are there for strategic reasons. Some of the programs are terminated for strategic reasons that's even more painful, right, and because it's likely to work. But they terminate anyway because they decided to, you know, exit the specific therapeutic area. That's very painful and you want to complete the clinical trial yourself. If you have started it and then demonstrate that the molecule is safe and you have another window for partnering I. You start phase two and there you can maybe get an option where an option agreement, where, if it works, the company will pay you a lot of money and Do the rest of the development right. But there again, I want to ensure that my Product, which is the patients and helps the patients, right. I want to see it within my lifetime, within my time at and silica, and the probability of that is increased if we do it in house. Yeah so for as long as possible right, and how many do you have?

**Craig Smith:** 33:57

How many molecules do you have in phase one clinical trials right now?

**Alex Zhavoronkov:** 34:03

So currently we have two in phase one and one just has completed phase one, so it is going phase two and which disease is that targeting? So the one that just has completed phase one, that is Anti-fibrotic, currently proposed towards IPF, but it also we nominated a preclinical candidate for the same target for kidney fibrosis. We can also inhale. It worked reasonably well in skin fibrosis and showed very promising results and it does seem to be very active. So it's a very promising target also for several types of cancer, because you know fibrosis is one of the Biological processes heavily implicated on certain cancers. In some cases it's actually one of the mechanisms cancer is using to defend against you knowing the body is recognizing it as cancer and killing it. And that one is just completed phase one does look like it may work in aging as well. That's at least how we Prioritized it. So you know that everything I do used to have some kind of aging research components and the rest of the two programs. So one is pure play. Cancer synthetic lethality that's a target called usp1. There is one other company that is ahead of us with this target. There are nine months to a year, maybe even more, on Ahead, but there we still decided to prosecute the target, but with truly amazing chemistry, right. So our molecule is extremely selective, very potent and has many other properties that are Desirable in a molecule that you want to take forward and, uh, usually in the target space that you go after, you actually want to have a few players right, because, from a cynical companies, when somebody succeeds they want to partner with somebody else. They're like me to players. Yeah, it's fashionable, it's kind of like target fashion.

**Craig Smith:** 36:35

Yeah, and You're choosing diseases that have some Relation to aging. Is that right?

**Alex Zhavoronkov:** 36:45

That's correct. So everything that we do, it has to be in one way or another age related.

**Craig Smith:** 36:51

Yeah, can. Can you talk a little bit about your interest in longevity? I mean, we're all interested in longevity here, most of us but where did that? When did that begin? What was the initial impulse? And then I wanted to ask you about some of the other Early research that's going on in that field.

**Alex Zhavoronkov:** 37:17

So sure. My interest in aging began in very early childhood, so when I was a little boy who was, you know, thinking a lot about the meaning of life and also what like, what does the future look like? And when you look at the big picture right, you step outside your you know mundane current problems. I, you look at life and you see that we come into this world, we compete, we grow, we Reproduce, take care of our young, reach our peak and then decline and die. And Most of the diseases that are out there, they transpire after we reach our peak right, so after we start degrading and dying. And some of those diseases are driven by aging, some are, some are facilitated by aging because in the young organism many systems that are responsible for quality control and cancer detection and detection of many other Pathologies, so they work extremely well. And when we're older they don't. And Most of the drugs that we see today on the market they're treating symptoms or specific disease drivers and not the underlying Main cause, right? So I realized, okay, well, aging is the mother of most diseases and if we want to target most of the diseases, you actually need to target aging and Try to target it before it deconvolutes into diseases. Right, because once the disease starts, you actually do need to target the disease and Usually we're just trying to make people live to their average lifespan. We're not trying to save their lives, so to speak. Right, so saving a life in our current context, in the traditional medicine context, is basically not letting the person die at this moment. So you might add a few years to life, but you haven't really saved it. And that was the paradigm that I was not very comfortable with. I'm still not comfortable with that. So when somebody says, well, this doctor saved my life, well, kind of yes or no, because you're gonna die anyway, and not that You're not gonna have, you know, significantly more years just because you, you were treated and you are still in the same path, or maybe you lost a few years anyway to your Expected, to your life expectancy, and I was very concerned about this paradigm. So, unfortunately, when I was growing up, but we did not have the resources to go right away into aging, so I had to go and computer science, I Made some money and then decided to, you know, educate myself and biotech, so did an entire nine yards in grad school and Published a large number of papers. I also realized that aging is a much more complex biological process than most people think. So, just looking at animals that live longer or shorter lives, we can either, you know, learn from them or Extend their life and learn from them. That's not going to help much because we're just very different and we cannot become, you know, whales Quickly. And even if we do, we Largely increase lifespan and we still accumulate many, many, many types of damage that we are accumulating today. So we are already a very perfect organism, designed for long life, and I realized that there are many, many, many processes that you need to understand in order to understand aging. And I actually worked for a year for a company that was organizing many, many, many biotechnology Conferences, but it was called GTC bio. I don't think they're around anymore, but they were one of the really top top ones back in the you know five to 2010, and I Helped organize over 30 biotechnology conferences in different fields, no more than drug discovery and development. It's massive conference stem cells, regenerative medicine, vaccines, many, many, many, many others and got to speak with many key opinion leaders, because you know when you're organizing conference, even though you're still a young scientist, you can still I Get in touch with the top people and realize that you know aging is probably Better to tackle it using AI right, because you need to integrate massive Amounts of information. You need to, so one single silver bullet is not gonna work. So even if you are going after a drug that kills eight aged cells and essence cells, you would need to have the entire plethora of technologies to support that drug. You would need to first ensure that those precines and cells are safe, right and Preferably rescued. After you kill those innocent cells, you need to ensure that there is no fibrosis. I Need to ensure that those cells are being repopulated. Those niches that Feed up. They need to be revived, rejuvenated. I need to ensure that New cells come to you to ensure that the extra cell or matrix is ready for that right. Usually it's already a stiff and Calcified mineralized. There are also advanced locations and products in there and many, many other Forms of extracellular junk, so it's very difficult for Stem cells to go there to ensure that your immune system works well and Clear is this junk at the extracellular and cell level. I need to account for the system's level of damage and aging, because very often, once you start an anti-aging therapy like the one I'm describing and that's one out of the hundreds of alternatives, you already have a lot of fibrosis in the tissue. A lot of really useful tissue has been replaced by fibrotic buildup and you need to figure out how to clear that. Well, that's one of the reasons why my program is going after fibrosis, because we realize that if you have a lot of fibrosis, that's it right. We actually cannot do much. So we need to figure out how to Get rid of fibrosis and if you have an effective tool to do that, great.

**Craig Smith:** 45:03

Now you have a major you know element in your toolkit that you need to go after aging yeah, and and so you're attacking it sort of by identifying things like fibrosis that contribute to aging or or Contribute to disease as you age. There's other work and I'm wondering whether you're involved at all. I had a Vittorio Sebastiano on the podcast a year or so ago talking about his work with Yamanaka factors to reprogram cells and, in effect, roll back the age of cells. Have you done any work with that?

**Alex Zhavoronkov:** 45:58

So of course, chemical reprogramming is something that we can actually do in the lab. So study that at scale, because now we can test hundreds of thousands of compounds on many different cell types and tissue types and different kinds of organoids to see what kind of transcriptional methylation changes and phenotypic changes those compounds and use. And that's exactly what you want to study if you want to understand the potential of those drugs and drug combos for in vitro or in vivo reprogramming. So yes, we do that, but that's not our core line of work, it's a bonus.

**Craig Smith:** 46:51

Mm-hmm. There's a whole philosophical, ethical debate about tackling aging, because the population has doubled in my lifetime. I'm getting old and I'd like another 50 years if I could manage it, but the planet can only support so many people and the increased population leads to all sorts of other problems of mental illness and conflict and that sort of thing. Have you thought about that? Or do you feel that those problems can be tackled once aging is not solved but at least extended?

**Alex Zhavoronkov:** 47:49

Well, that problem is much, much easier to tackle. So that's why, very often, people who do not understand science very well they like to, or they're just not really good aging scientists. They try to go into those philosophical aspects. Right, because it's easy to debate. They can look smart and make all kinds of arguments, but it's very clear that the population is going to grow, regardless of whether we are going to identify anti-aging interventions or not. Because it just did right, so if you are concerned about overpopulation, you should stop reproducing right now. Right? Are you willing to do that? Probably not Many people are willing to do that. So, for example, I do not have children and I do not plan to in the near future, just because I think I can be very productive as an individual without the need to pass my genetic material onwards. And usually we see that a lot of smart people do not really have successful kids. So it's better to support somebody else rather than to follow the evolutionary call and foster your own. So I actually like to give grants to students that demonstrate superior abilities. I don't think that my genes will make a difference, and many smart people do not have many kids. Usually reproduction is very correlated with intelligence and education, and we see that in pretty much every country in every culture. So once people get to a certain level of income and education, they start having fewer kids, and currently the population is still growing. It's predominantly growing in the developing countries, where the level of education is lower and poverty is higher, and we cannot really do anything about it. The problem that we are facing are the people who have aged and are not doing productive work, but at the same time, they are drawing massive resources in terms of health care and social security, and they also vote. So in democratic countries now, the percentage of elderly is very, very high and usually they vote for something that they need, and we've seen what happened in France recently. The retirement age goes from 62 to 64. While the lifespan has increased to 85 plus. It just doesn't compute. It's not economically feasible, so the country will be deeply in debt and it's already not as productive as some developing countries, and people will still vote for politicians that allow them to enjoy early retirement and massive benefits, and we're going to see the second row. So we're likely to see the collapse of some of those civilizations that rely on the elderly to have the same vote as the young people, and we should probably worry about that right and not about overpopulation or how we're going to allocate the resources, because otherwise we should just limit lifespan. Right, why not say that look Well, the maximum lifespan that you are allowed to achieve is 75. Done right, so we are going to support you till that time, extremely well. And after that, well, let's not draw the Medicare, medicaid right. So I think people who are not ready to do that, they should not philosophize right.

**Craig Smith:** 52:27

Can you take us through the process, for example, with this IPF drug that you say is finished phase one trials, so just a very relatively high level, but not that high level because the listeners are mostly AI practitioners of some level. So you pick a disease like IPF. There are many targets, presumably, and then sort of starting there, what's the process? How do you decide on which target you're going to design a molecule for?

**Alex Zhavoronkov:** 53:14

So sure? Well, first of all I recommend the listeners to look at our papers that describe pandemics and also dual purpose therapeutics. So if you just look for a dual purpose aging disease therapeutics, you'll find a bunch of papers that were published describing many methods that were used to identify promising targets implicated in fibrosis and other diseases. And also we just published a really fun transformer model called Precious One, gpt, which learns on the basic biology from methylation and transcriptomic data and then transfer is the weights onto the model, which is trained on different diseases to identify targets that can be prioritized for age-associated diseases. And then we give it to pandomics to assess commercial tractability, novelty and confidence using many, many different models. So this is pretty much the process that we went through with our program, one with the anti-fibrotic. So we looked at the targets that are likely to work in basic aging and also in a variety of fibrotic diseases, using different machine learning techniques. Then we prioritized 20 targets that are less heterogeneous in the patient population, because you want to see something that is occurring in many, many, many people and scoring at the very top. It might not be the number one or number two target, but it's going to be consistently high in many, many people. So that's what you want in order to achieve maximum benefit for everybody and for as many as possible. And then we prioritized 20. Like that, we could manage to test only five because for many of the top 20, the assays were not available. So that's actually one of the big problems that you face in biological AI. So very often you come up with a really great hypothesis that's validated by other kinds of pockets of evidence. But in order to perform the experiment, you really need to be able to have this biological target available as a protein structure, as a protein, as a ready-made protein, and you need to have a molecule to test it, or you need to be able to knock out that gene and very quickly see if it works in a specific disease model. And very often it's just not available. So we could test only five and one target showed. So all of them worked, but one target was scoring at the top. And also we realized that druggability is a big feature. So if you go after the top scoring target but it's not druggable, you might never be able to deliver a drug on the market. You run out of money before you demonstrate that you can drug it.

**Craig Smith:** 56:33

What does that mean? Drugability.

**Alex Zhavoronkov:** 56:36

So it means that some proteins are easier to develop small molecules or antibodies against than the other is. So there are grant prizes in chemistry right now, like, for example, cimic, a very famous oncogene. So if you can drug it with a small molecule that is safe and effective and you can disable CIMIC or some associated proteins in the complex, it's a grant prize. It's billions of dollars because many cancers are driven by CIMIC. However, it's very difficult to take drugs. So we have spent several years developing a degrader now for CIMIC and then you realize even the biology of this target is very difficult. It's just being produced very, very quickly and degraded quickly. So if you figure out how to degrade it, you also need to ensure that you degrade it extremely quickly, quicker than it gets produced. So there are many, many challenges with some of those difficult to drug targets because sometimes it's just a flat surface. Imagine a wall that you want to climb on and there is nothing to grab. So some of the proteins are like that and you want to ensure that the complexity of the protein and the. So you need to find the target that you can drug within a certain time before you run out of money without a huge amount of resources. So some targets have a lot of those, some of those mountains, they have a lot of those pockets where you can grab and nobody has grabbed those pockets before. But you see that they are there and it's better to go off the targets that have a good balance of confidence and commercial tractability and novelty and also drugability. So if you know that it's going to be extremely difficult to drug, you are increasing the risk of the program.

**Craig Smith:** 59:08

Yeah, and you're talking about proteins and the druggability depends on the shape of the protein. Is that right?

**Alex Zhavoronkov:** 59:24

That's one of the features. Yeah, so it's not only the shape. Sometimes it's part of a very large complex that is not exactly well understood. Sometimes it is the pocket that you need to drug. That is part of the protein-protein interaction and that's very difficult to drug and to fit the molecule in that specific pocket. So it's the structure, but also many other things.

**Craig Smith:** 59:53

Yeah, and also going back to targets for which you don't have assays. I didn't understand that. What does that mean? I mean there are. Is it proteins, for which they don't know the shape, or what is the issue?

**Alex Zhavoronkov:** 1:00:16

So now you can actually do something similar to AlphaFold to create the shape right. But it's just very often it's very difficult to drug even if you have the shape. So again, it's either flat surface or it is the structure for which you know that a lot of groups tried over the many years and failed to deliver. So usually you don't want to go that route unless you are very, very confident in your system. And at that time, when we started Program 1, we didn't know that we could drug many other protein classes. Now it's an industrial strength platform and we have much higher confidence in our AI that manages to achieve very high levels of druggability. But at that time we decided to go after a very balanced target right. So we knew that we could drug it. It belonged to the protein class that is druggable and it didn't have any molecules available for it. So we decided to go after Program 4 for that specific target.

**Craig Smith:** 1:01:35

Yeah, and how long? For example, with this IPF drug, from identifying that you want to tackle this to identifying the target, to identifying, to generating a molecule or multiple molecules and then evaluating, deciding which ones you want to put into preclinical trials and then clinical how long is that process now using your system, as opposed to what it has been historically?

**Alex Zhavoronkov:** 1:02:16

Yeah. So for our Program 1 to get to the preclinical candidate stage. Preclinical candidate stage meaning that we have validated the target, we have already selected the molecule. Out of the many options, out of those many perfect needles that we generated, we selected one and we've conducted substantial safety studies on that perfect needle and on the target. So that's a preclinical candidate. So from zero to preclinical candidate it took us 18 months originally. So which is actually for a new target, it's a very short period of time when you're talking about really good molecules that are also easy to synthesize. And then it took us 30 months to get into Phase 1 and Phase 1 took almost a year to complete. So it still sounds like a very long time because it's 40 months to Phase 1 complete, so just under four years. But using traditional approaches it takes significantly longer. So usually it would take you at least two, three years longer and the probability of success, probability of getting there, is much, much lower. So now we have done that many, many times over. So now we've nominated 13 preclinical candidates today, right, so nine preclinical candidates just last year. And to put it in perspective big pharmaceutical companies using internal R&D in small molecule space. They usually nominate four to five.

**Craig Smith:** 1:04:07

And I've spoken to Daphne Coller about her company. I've had around the podcast and she's. If I understand it, it was a number of years ago, but she's looking at the universe of molecules and trying to identify, based on the qualities of similar molecules, a space in which to search. Am I getting that right? For then choosing existing molecules to test? Is that right? That's the way that the research has progressed. I mean, she's using AI, obviously, to speed it up.

**Alex Zhavoronkov:** 1:05:00

So you know, everybody is using AI nowadays. High school students use AI and I don't know what Daphne Coller is doing, right? So, as a matter of fact, you know the level of transparency there is not exactly very high. They like to provide really great power points, but we really want to see the results. So I guess once we see our molecules in, you know, phase one, phase two clinical trials, then we probably also have some kind of record of how they were discovered and then we might be able to do some comparison. But currently I just have not seen any of that. Right, so the technology is being developed, I guess. Right so it's a pretty credible scientist, but I have yet to see the value of that research. So currently there are only several companies that managed to take AI designed or AI discovered molecules into human clinical trials, and there are less than a handful of them. So I don't think Daphne Coller's company is in that league yet.

**Craig Smith:** 1:06:21

Yeah, your process that you've created. Presumably you can begin scaling it up, doing it in parallel or, you know, licensing it to others to do it. Do you think that we're on the cusp of a huge number of new drugs and of solving or curing, or at least treating many, many diseases that have been untreatable?

**Alex Zhavoronkov:** 1:07:04

So yes and no. So yes, we can definitely generate a very large number of preclinical candidates and even clinical candidates very quickly. So we've demonstrated this ability and in order for us to significantly progress, the pharmaceutical companies need to change a little bit as well, because the level of productivity within the pharmaceutical companies has been historically low. One curse that we see within the pharmaceutical industry is that the management changes very quickly, so usually so. I've been in Silicon since 2014. Within pretty much every pharma company, with exception of maybe a couple, I've seen management changes three times. So they basically live on three to four year cycles and then they recycle everything and the level of productivity in internal R&D is very, very low. So, yes, there are sometimes very promising and really great results. So sometimes they do produce blood busters, but most of the time they don't, and the model has to change so that the pharmaceutical companies focus more on licensing and very rapid progression of the programs into the proof of concept. So phase two completes in the areas where you've got significant un-mathematical needs and the partnering needs to just speed up. So I actually think that nowadays they should be using AI to pick the partners, because many humans are just not effective. I mean chat, gpt can actually very rapidly show you which company has which target, which is better, which has demonstrated more results, which published more credible work. For big pharmaceutical companies, what we see is that a lot depends on relationships and trust. So they usually build up relationships with scientists and other biotechnology company executives that do the same thing all over again, and they just partner within a very small circle. So I think that there needs to be a very effective partnering strategy within at least some pharmaceutical companies, based on merit and based on equal opportunity and based on the good to the patient. So how do we benefit the patient the most? And, of course, assessing commercial tractability. So once this happens, we're going to see massive acceleration, but in order for us to get there, we will see a lot of failures in between. So we see that some pharma companies like to partner with university startups that don't have anything, no proven concept, nothing. So they support them with 20, 25, 30 million upfront and then they hope that something is going to happen and historically, it just never happens. Or you see the bets after phase two complete and those will be in billions of dollars so many billions of dollars spent and in the meantime they could have made 100 bets with lower money and much cheaper and tried many more approaches. So instead of trying to get one de-risked asset in phase two, they can make 50 bets on something that is a little bit more risky in terms of commercial tractability, viability, but once the process is streamlined it could dramatically impact R&D. But it also needs to start with investors, and I'm talking about large institutional funds that currently would not invest in pharma companies that don't spend, let's say, 15%, 20% of their revenue on internal R&D. That's just standard and they just have to put the money in. And the amount of money is massive. We're talking about Novartis ' $9 billion a year. So of course, a large part of that are clinical trials, but much of that is basic research. And well, it's great right, but where are the drugs? And one idea is those $9 billion could be spent on partnering with companies like ours at a little bit earlier level and just focusing on clinical study design, on ensuring that the drug which is the right patient, on ensuring that the drug is combined with the current drug within big pharma that has demonstrated efficacy and that is improving patients' lives, and working with the FDA to ensure that the outcome measures are consistent with what the FDA wants, because FDA is the ultimate authority and, by the way, a lot of people criticize the FDA I can tell you that in some areas, this machine is a Ferrari, so they have already sold it. Those many, many patients and patient advocacy groups ensure that they have standardized response times right 30 days, 60 days, 90 days so you have very, very quick interactions with them. They're very open. So I think that the integration on the clinical level and also regulatory level, that's something that big pharma companies should focus on more. And then they just need to streamline and automate the partnering apparatus and introduce AI there, so that, for all the AI folks that are listening, if you create a really nice partnering portal that matches the demands of big pharma with the supply of high quality assets, that's what's needed, right? You just need to be able to remove the huge overhead, inefficiency and waste in this partnering space, right? So then it's going to be dramatic, right? Of course, we're also working in this space, and you know me, right? So if I say something, I make every effort to deliver. So we are on the track to deliver those partnering deals and we've partnered with many, but we of course, want to just streamline that and ensure that it's as automated as possible.

**Craig Smith:** 1:14:47

Yeah, Okay, well, we're over an hour. But the last question on longevity or anti-aging. I mean, certainly lifespans have increased in our lifetimes, but do you think, do you expect results that will impact your life and how long do you think you'll live with those advances?

**Alex Zhavoronkov:** 1:15:22

So you know, to answer this question, we developed an annual conference. It's called ARDD, aging pharma org. It's the largest one in the world in the field of aging biotech. You know, hundreds of key opinion leaders travel there every year. So, at the end of August, beginning of September, there will be a five day event. So you know, you're going to see David Sinclair, Vadim Gladyshev, Eric Verden, and all the big names. They present their research and then we try to assess. You know, how far did we process progress? There is now also the longevity biotechnology association. So, with that kind of disclaimer, I think that we might be already there, right? So we might be already on the path of longevity escape velocity where, you know, the longer we live, the longer we should expect to live, because technology is becoming exponential. Unfortunately, there are many threats to that right, because, first of all, it's not for everybody. So if you're, you know, 70, right now, that exponential touch may not be, you know, soon enough for you, right? But it might be there for the current 20-year-olds and 30-year-olds, right? Because, again, the level of progress that we see in the world is huge, right? And now, when I entered the field, we couldn't even like there were no books. There were a couple books, three books maybe that you could read on the biology of aging and the current state of affairs. Now, I even wrote one and it's already old, and now we have courses that thousands of physicians take and thousands of scientists. We now even have, you know, investing in longevity course for free, multi-many hours, by pharma experts, by VCs, by medical doctors, and which is actually a cautionary tale, more or less, and currently it's very hard to say where we are, but we are definitely moving closer to the longevity escape velocity. So many factors, like geopolitics, for example, that might impede this progress dramatically. For example, you know there are dictators with a red button they can push right now and the entire world goes to hell, right, whatever progress we've achieved, and we're probably as close to midnight as we have ever been. So a lot of people are thinking, you know, longevity bunkers to ensure that we at least can preserve some knowledge and some people. But in general, I think that we are on the exponential track and I don't like to make predictions in terms of how long you can live. You should not have that limit. If you want to have a limit, you know, set something achievable. You know, maybe 120, 150, 120 has been achieved already. So how much worse are you than Jean Calment? I don't know. A lot of people don't want to go that route, but intuitively they do. They just don't want to make an effort, and I think that nobody should be pessimistic. So optimism is the number one component in longevity.

**Craig Smith:** 1:19:18

Yeah, Okay, that's terrific. I actually asked myself one more question. I may cut it, but what is this multimodal transformer based aging clock that I've read about?

**Alex Zhavoronkov:** 1:19:34

All right, so precious one GPT.

**Craig Smith:** 1:19:37

Oh, that's precious, one GPT.

**Alex Zhavoronkov:** 1:19:39

Yeah, that's the precious one GPT. So we've got methylation and transcriptomic data used for prediction of age. So you built a massive transformer which is trained on many, many, many data sets of biological data and metadata to predict age and actually that's not going to be as accurate as a purpose built fit forward, you know not, for example, but it can make a very useful inference into the various biological processes that are not apparent and I think you cannot get out of other deep learning techniques and then you transfer the weights onto the model which is trained on diseases.

**Craig Smith:** 1:20:22

I see and you're looking at, you're predicting. I don't know.

**Alex Zhavoronkov:** 1:20:32

Just to explain that you're predicting the age of a person or yeah, so originally yeah, originally you built a predictor so that that system can do many tasks. Right, it can perform many tasks. One of those tasks is prediction of chronological age. So basically, train the transformer to predict the chronological age of a person using two data inputs: methylation and transcriptomics, and, of course, a lot of metadata. So this transformer learns the fundamental basic biology of aging, right, and you can also query it for the different relationships between methylation sites and expression of individual genes. And it can do many other things, right, but it can predict age. Now we are working on another release which will help you generate biological data, such as synthetic methylation and transcriptomic data, with age as a generation condition and a few other things. So those transformers acquire the ability to again comprehend the basic biology and then you learn from basic biology into diseases. Aging research is the most impactful area you can go into. You can go into AISafety, you can go into whatever security, but everything is valuable. But aging research will produce the maximum number of quality adjusted life years for everybody on the planet. You develop a drug that increases everybody's life by one year. You just generated 8 billion life years in today's terms. Right, if you look at net present value people are producing. You generated many, many billions of life years, so that's a very worthy goal to go after.

**Craig Smith:** 1:22:42

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