Mayfield

Healthcare Pioneers Share Secrets to Building Iconic Engineering Biology Companies

2021

Here's to fighting for a better future, together.

Contents

Since March 2020, a pandemic and unprecedented environmental degradation have brought the twin crises of human and planetary health to the forefront. While it is easy to feel a sense of hopelessness in the face of seemingly intractable challenges, at Mayfield, we're eternal believers in the power of the entrepreneur. And over the past two years, we've seen incredible contributions from pioneers, led by Ugur Sahin of BioNTech and Stephane Bancel of Moderna, who brought their life-saving vaccines to market in less than a year, along with many other mission-based entrepreneurs.

We believe that climate change and preserving humanity is the greatest task of our generation, and also presents the greatest entrepreneurial opportunity of all time. By using biology as a technology to reinvent production of the food we eat, the clothes we wear and the places we live and work in, we have a path to zero carbon footprint societies. At the same time, marrying the engineering approaches of information technology with advances in biology will transform human life and save countless lives.

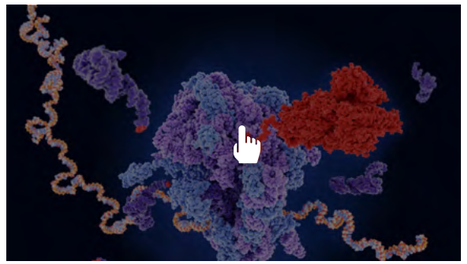
We have hosted and curated conversations with leaders to share non-obvious insights and collaborate on solutions. Our first gathering was the Health Innovator Summit in January 2020, which brought together innovators and leaders for an in person gathering in San Francisco. In 2021, we partnered with TechCrunch to host a series of online conversations at their annual Disrupt and Early Stage conferences, to engage with their network of global entrepreneurs. We are honored to do our part in inspiring the next generation whose mission is to create a better world for our generation and the next ones.

Here's to fighting for a better future, together.

Regards,

Ursheet Parikh & Arvind Gupta

Saving the World



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Darrell Etherington:
Great to have you both here, very excited of course. Ugur, I mean you're the best person to talk about mRNA that we could have hoped for so it's great to have you here and to talk a bit about your work on obviously the COVID-19 vaccine as well. Ursheet, lovely to have you here as well. Few people out there that I could imagine would have more perspective on what it takes to back life sciences companies and biotech companies out there emerging today. So very excited to have this conversation. Thanks for being here.

Ursheet Parikh:
Thanks for having us.

Ugur Sahin:
Thank you Darrell.

Darrell Etherington:
Great. All right. So let's... Uncreative starting, but let's start at the beginning. I do want to hear, Ugur, kind of how BioNTech got started. I mean I think that it will be illuminating to a lot of the entrepreneurs in our audience to hear a bit about your own journey as a founder, especially coming from the scientific technical background that you had.

Ugur Sahin:
Yeah. So let's start really with the mission. The story is a story, of also my wife, Ozlem Tureci, who is co-founder of BioNTech, and colleague Christoph Huber, who is also a physician.

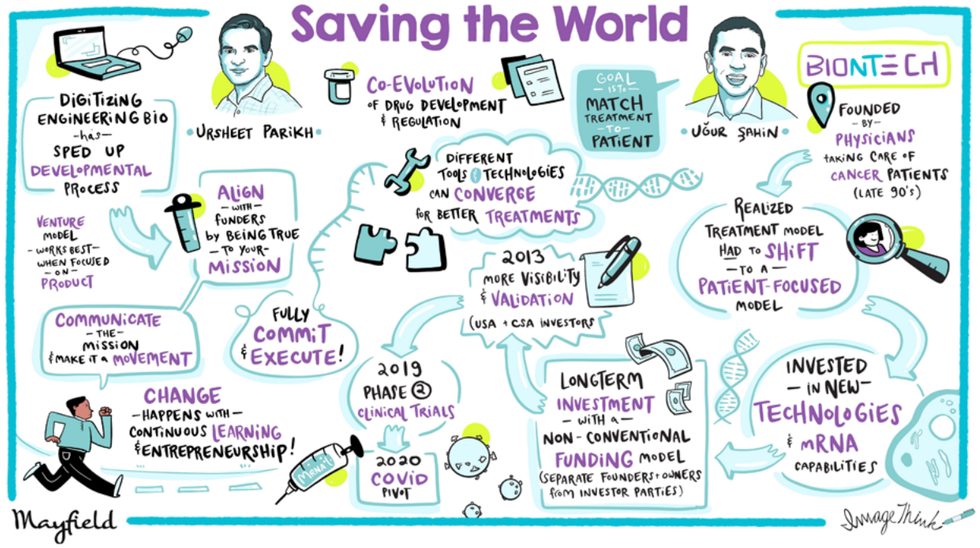
And as physicians, we were taking care of cancer patients in the university hospital. And we saw that we could not offer real effective treatment at that time for our cancer patients. And on the same day in the afternoon, we went to the labs and were doing experiments and reading all the progress in the field and saw that there is a big discrepancy between what is offered to cancer patients and what could be offered if innovation and ideas could be brought out there. And the way we think as physicians is really focusing 100% on the patient that you are treating. And when we consider to develop our treatments, we were not only interested to develop novel therapies, but to make the best possible treatment for the individual patient. And we realized the way cancer is treated is that you first develop a drug, and then ask the question, which patient fits to the drug.

Darrell Etherington:
Ah, right. So they reversed, then.

Ugur Sahin:
It's the reverse way. And we experienced with this with our first company where we had developed a great antibody product, which was successful, but it was only available for 40–50% of patients. And we had to tell the patients, or the physicians had to tell the patients, they are not eligible for this treatment. And so how can you change that? And for changing that we had the idea to develop individualized cancer therapies where we first analyze the tumor of the patient, and then if needed make a treatment for the patient. And of course, this was at the time when we started our research, it was the end of the 90s. This was incredible, and we didn't talk about that.

We had the vision, and started to develop technologies in the academic setting, because we knew with the existing technologies. So if you, for example, want to develop an antibody, you need at least two years to make the antibody. And then of course you can't, the patient can't wait two years with the existing tumor until the antibody is made. So that means we needed new technology. So we had research in the university, which we called NT, for New Technologies. And mRNA was one of those. Because we knew if you wanted to make an mRNA vaccine for mice, we could do that in just two weeks. And we thought this is a great potential. So it is a platform which can be applied where you can do engineering. But at that time, mRNA was not potent enough. It was just a weak molecule. But the idea was great.

So we invested many years in the academic setting to improve that. And in 2006 we realized, wow, this is now working. It's time to initiate a company. And at that time we got also funding to start a company. It was very clear that this will not be a home run. It will take further eight, nine years until this is a mature product. And we wanted to start a company just with us as founders and get funding without getting investors into that.



Darrell Etherington:
Oh, a tricky needle to thread.

Ugur Sahin:
Yeah. Because we said, this is not the classical investor case. For the classical investor case, you have to present every, at least every second year something which is a progress. But we were in touch with investors who had already been invested in our first company. This was a family fund. And they asked us, so do you have anything else? And we said, yes, we are working on new technologies, but this is not suitable for classical investments. And they said, let's share this.

Darrell Etherington:
Let's hear it anyway.

Ugur Sahin:
And we shared that and they were fascinated. And we said, but this is not going to work, because this will not be ready in two years. And they said, we will be patient. And the only way to prove that was to do an investment, which not only lasts two years, but which lasts for at least five to six years.

Darrell Etherington:
Wow. Okay.

Ugur Sahin:
So we agreed to start a company, BioNTech. So the name NT was not possible because of Windows. So therefore we went to the name BioNTech, but NT is in big letters for Biopharmaceutical New Technologies, and started the company. And we had a website, the website was stating 'under construction' and it remained under construction for five years. So no one knew that we were working and developing this new platform. And the time was really needed to make it in a, to bring it into an extremely potent form that it can be applied to patients. It can induce strong immune responses. And in 2013, we started to become visible and started to make our first years. The team was joined by our colleagues who can really address that and support the goals of the company. We made a number of deals, including one collaboration with Genentech, which was validating our technology. This is the classical validation that you need as a...

Darrell Etherington:
Right, you get the big name, the recognizable name, and everyone's like, okay. They got something.

Ugur Sahin:
Yeah. So we started to play like classical biotech, and got fantastic US investors into the company, did a Series A financing. And after the Series A financing, we went public in 2019. And at that time, end of 2019, we had multiple cancer treatments in early clinical trials, had started our first phase two clinical trial. And the plan was to, in 2020 just to proceed with that to generate data.

Darrell Etherington:
But plans change, obviously.

Ugur Sahin:
Yeah. The best laid plans.

Darrell Etherington:
Yeah. Yeah. No kidding. Ursheet, I want to ask you about listening to that, and your perspective as an investor who is more traditionally, like VC, Silicon Valley-based investor, right? What do you think about that? And the patience required, and then having to go to the family fund and basically getting a deal that does not adhere to traditional kind of timelines and returns, what does that look like now for you? That was a long time ago. Have things changed a lot now? Is it more possible to build the kind of thing we were just talking about now? Or is it still something that would take that kind of timeline and that kind of special arrangement?

Ursheet Parikh:
Yeah. Several vectors along which I can take this, but I think Ugur and a few amazing entrepreneurs like him from that era really had the vision to build these platform companies before the investor ecosystem was truly ready.

Darrell Etherington:
Right.

Ursheet Parikh:
And so, over the years we've spoken to several of them, and it's just truly humbling, and sort of deeply grateful for sort of the persistence, the grit that you had. Now, two things have changed today. First, the ability to digitize and engineer biology has made the innovation pace happen faster. And so new products can happen sooner. It's like moving from in the tech line, a mainframe model of developing new applications to leveraging building blocks from the ecosystem. There's also a lot more entrepreneurial advice available for people, right?

So science will start companies, but business models, deals, products sort of make companies. And there's a lot more expertise available around that. And so in a classic venture, a long-term traditional venture timeline of seven to 10 years, you can actually sort of go ahead and invest in platform companies that can be truly transformative.

And that has actually been something that's consistent for Mayfield as well, because Amgen, Genentech, Intuitive Surgical, these were also companies that were funded back by a previous generation of Mayfield investors, right around their inception as we are doing with the companies of the next gen as well. And what it does require, I think the venture model works best when we can focus on companies who will actually end up building products and getting them to patients and scaling up revenues.

And that's the mission, which works a lot better in a traditional venture model. Versus for a while, a lot of biotech investing had become about let's create some interesting data and then sell this asset to another larger company.

Darrell Etherington:
Oh, gotcha. Yeah. Right.

Ursheet Parikh:
And so the platform model then is much more about how do you sort of go ahead and maximize the odds of success of the platform, rather than a single asset sort of which in a venture fund model starts feeling, even though it's a risk model, starts feeling more like roulette. But also I deeply believe that if you're true to the mission, and Ugur mentioned about mission and that's the first thing that is required to recruit a team of align founders. You don't really realize your mission if these companies get sold very early into other large companies, right? Nine out of ten products never see the light of day. So if you are really true to the mission, you want to maximize the odds of actually realizing that mission, and the entrepreneurial path with an ecosystem where you can then sort of focus on development and de-risking. Or having deep trust relationships to take extra risks, whatever is needed. But I think it significantly allows for you to control the destiny of your mission.

Darrell Etherington:
Ugur, talk about that mission a bit. Were you approached at times by larger companies that were like, why don't you just come and do this? We'll give you the resources, we'll acquire you, we'll set you up.

How did you, did you have to be diligent to stay on the path towards achieving the mission that you recognized so early on? Or was it tempting to you to go do something else instead?

Ugur Sahin:
No, not really. So actually it was tempting to stay at the university, and do it in collaboration with big pharma. In the first years we tried that, so we had collaboration.

So we were the scientists in the university, and licensed our technology to big pharma. And then we realized after two years they stopped the project, not based on the results of the project, but because of the arrangement of company staff.

Darrell Etherington:
Right. That's basically what Ursheet was talking about. Right? Things just get kind of shelved because of internal politics or something.

> It was an understanding that you have to leave your comfort zone and start a company.
>
> – UGUR SAHIN

Ugur Sahin:
Yeah. And then it was an understanding that you have to leave your comfort zone and start a company. So in Germany, it is not the same culture as in the US. In the US you have enthusiastic founders. So we were not the enthusiastic founders.

Darrell Etherington:
You were reluctant founders.

Ugur Sahin:
We were the reluctant founders. Yeah. And now looking back, of course, we understand that this was the perfectly right move at that time.

Darrell Etherington:
Right. Yeah. Yeah. But it was looking back, I mean in the moment did you realize... Was there a lot of trepidation, were you kind of like, okay, I mean we want to back out, we just don't want to do this? Or how hard was the decision for you to make to actually do it? You said you were reluctant, but was it genuinely like, listen, we have to put everything at risk here to do this because the mission is so important?

Ugur Sahin:
Yes. It was. So we had really the experience that on the first 10 months of preparing this kind of business plan, explaining that to experts and coming up with competitor analysis, it was just taking time from our research.

Darrell Etherington:
Right. Yeah.

Ugur Sahin:
And the question was, are we losing scientific quality because we are dealing with all that? And then before making the decision, we really closed our eyes and said, we have now two options. We can just go as we did, or we can try it and go through all those challenges. What do we want? And then we extrapolated 10 years later and then we realized that we would never forgive us if we would not go through this, because we will never know.

Darrell Etherington:
Right. Yeah. None of those things could be possible if you didn't attempt it, at least.

Ugur Sahin:
Yeah. And this was the decision and once the decision was made, then you have to be fully committed and execute, and that's how we do things.

Darrell Etherington:
It's very interesting that you bring up the opportunity cost of the science. And I'm curious too, maybe you've seen this, Ursheet, talking to different companies, but you talked to a lot of founders about how difficult it is to raise and how difficult it is to just build a business. Building a business, regardless of what else is going on. Right? But their opportunity cost is like, well, maybe my consumer chat app doesn't get built quite as fast or something, or maybe somebody comes and builds it instead.

But yours is maybe advances that could save lives don't go to market as quickly, or don't go to market with the right attention. Which seems huge, right? I mean, is that an additional challenge for a scientific founder or a founder with a scientific background that you don't see in kind of traditional tech?

Ursheet Parikh:
So I do think it is. The business of moving electrons is much easier than the business of moving atoms. Right? So any time you have to kind of do something real, right? Because you can write, move electrons on your computer and the internet will carry it to everywhere in the world. While when you have to do this, and now in addition to that, when you add sort of healthcare where there's a lot of ethics and lives and a lot of these things involved. But it's so heartwarming to hear Google's story, right?

Because there are times when you have to kind of go do this and one of the core things about the founders is it does start with the mission that brings everything together.

Because the audacity of it, you can't sort of not talk, you have to be able to talk about it. And you have to then be able to build a platform that brings other amazing, great, amazing people because it's very hard to do solo founder companies in deep science. You sort of need that. Then somebody has to take on the task to become the best CEO that the company can have. And then either an early founder or a key early sort of executive has to then go and do the thing. So the founders then end up having to be reasonably clear about it because a lot of the scientists founders have not been CEOs before. Or even if they have been, they have gotten a product to market, but not scale revenues and business. So you have to be this amazing continuous learner who also has this very high IQ, can form deep trust relationships and is sort of very self aware. Right? And so these are all attributes that becoming a CEO is a full-time job in itself.

Darrell Etherington:
Yeah, yeah.

Ursheet Parikh:
The first task of a scientific founder CEO is to find a scientific co-founder who's better, ideally not equally good, but better at the science so that the science can progress, right? Otherwise, that trade-off just feels so hard and so difficult to make. And then there is this whole company building aspect of things, right? Which is that science will start companies, but the products the deals, make companies. And so getting into the frame of reference of all the stakeholders is how you sort of take this mission and make it a movement.

And we are so glad Ugur did what he did.We would not be here on the other side, or getting closer to the other side of the pandemic. But they all feel like these movements where it's often you look at all the people involved and it almost feels like it's crazy that all these people are kind of committing to it. That's how entrepreneurship is the primary source of truly realizing missions and impact. And I do a lot of sort of my foundation stuff on the education side, I was on nonprofit boards, but I've kind of come back to realize that if you want to make change happen you really have to be the continuous learner and the entrepreneur.

So that's something that's deeply felt and so great to see so many of those things that was there in Ugur's story.

Darrell Etherington:
Yeah, for sure. And I mean, it's hard to get a better example, case of sort of proof is in the pudding than your story Ugur, and BioNTech's story. I mean, obviously the COVID-19 vaccine is the thing that's top of the mind, but you also have a very rich pipeline. I know you have so many projects, you've announced quite a few even recently over this past summer. So do you want to talk a bit about what the potential is now? Because you said you couldn't see this happening, or it wouldn't happen unless you took the risk. But now you're here and it's 10 years later and it's happening. The things are blooming. So what is next in the pipeline? What has this enabled technologically for you?

> The first task of a scientific founder CEO is to find a scientific co-founder who's better, ideally not equally good, but better at the science so that the science can progress.
>
> – URSHEET PARIKH

Ugur Sahin:
Yeah, so we have a bold pipeline, and we are not only a messenger RNA company. So we believe that different tools and technologies converge and will be used in a combined fashion. For example, we have CAR T-cell therapies, we have T-cell receptor therapies. And we believe that the mRNA toolbox is ideally suited to further augment and explore the power of this technology. So for example, we have developed an approach where we use CAR T-cells against a new target and combine it with a messenger on a vaccine, which can further increase the CAR T-cell expansion. And you can just continue to ask the question, what are the weaknesses of certain technologies?

For example, antibodies are great molecules, but making biospecific antibodies is difficult. So we developed the technology to make mRNA included by specific antibodies, which reduces dramatically time to clinic and circumvents a number of problems associated with biospecific antibodies.

Darrell Etherington:
But I mean, it sounds like the whole, the ultimate goal... And this is what struck me during this conversation that I didn't really realize before, but you set out to, your main goal is to match the treatment to the patient and their specific needs. Right?
So mRNA happens to be the technology you've used to do that, but it sounds like what you're saying is that still remains the goal. Right? And then you'll use any combination of technologies required to activate that.

Ugur Sahin:
Yes, absolutely. And we can develop classical pharmaceuticals, like a vaccine. But on the other side we really continue to follow our vision from day one. So our vision is very complete.

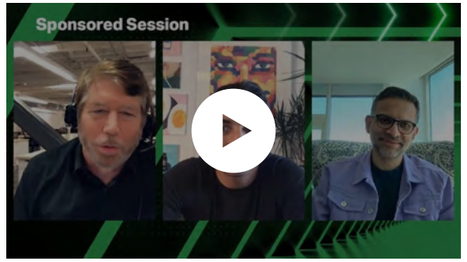
What we want to accomplish is at a certain time to provide the patient the best possible treatment based on the extra knowledge of the planet at that time. And this is in the time where information is so fast changing. So we are talking for example, about adapting our vaccine to COVID-19 variants. But the same can be considered for adapting a vaccine of a cancer patient to its changing tumor. So it's technically the same step. And so that means that is what we do. We can apply principles to, for treating patients. And this is the exciting prospect, regardless of all the products that we are developing.

Darrell Etherington:
Yeah. No, that sounds amazing. Because as you're saying, it's like, I think people discount the environmental impact on disease or on disorder. Right? And so even that as the environment is rapidly changing because of global warming, et cetera, things will change and therapies will become more or less effective and need to be adapted to handle that even as well. Right? As changing the patient, changing exterior circumstances, changing everything.

Ugur Sahin:
Yeah. And treatments, many, many treatments will become processes. So we see a treatment as a virus today, but we strongly believe that treatments will become processes. And so that means if taking the sample of a patient, analyzing the tumor and applying a vial which is adapted to the patient tumor. And so this is of course, a code evolution of drug development as well as regulation. We have been able to convince regulators that this type of drugs are useful, and there is now regulation in place. And then, so the environment is prepared for this kind of innovations.

Darrell Etherington:
Excellent. Well, I'm very excited to see what the future brings and I'm glad that you were able not only to help change the science, but also change the attitudes towards these things. So thanks very much. But I think that about does it for time, unfortunately for us gentlemen, but thanks for joining us Ugur and Ursheet. Really loved the conversation today.

Scientist Entrepreneurs – Scaling Breakout Engineering Biology Companies



WATCH RECORDING

Po Bronson:
Hi, welcome. I'm Po Bronson. I'm the managing director of IndieBio, and a general partner at SOSV. And in this hour, I've got two wonderful VCs from Mayfield, Ursheet Parikh and Arvind Gupta, who lead their engineering biology practice. Today we're going to talk about something dear to everyone's heart, building companies to make an impact on human and planetary health, which this year has really reached a crisis stage. Hi, Arvind. Hi, Ursheet.

First question to you Ursheet, and then to Arvind, just introduce yourself to our audience, but I want you to finish with a quick lightning round. Drop in no more than five companies you've done that exhibit your work in this space.

Ursheet Parikh:
Sure. I am a former entrepreneur. Actually, a Mayfield entrepreneur who then joined Mayfield in 2013. I invest in enterprise technology, and then with Arvind, co-lead our engineering biology practice. It's great to be in this particular practice because whether we are investors in a company or not, we really want everybody we meet, every company in the domain to be successful because it makes all of our lives better.

And to your lightning round question, Mammoth Biosciences, Endpoint Health, Nēsos, Mission Bio, and Qventus are some of the publicly known companies where I've had the opportunity to champion founders and leaders.

Po Bronson:
Thanks, Ursheet. Arvind, follow up as well to you.

Arvind Gupta:
Gosh. So my background is genetic engineering. I'm also a designer. And blending those two backgrounds together, I had the idea to start IndieBio, which I founded in 2015. And the whole premise is that scientists can become entrepreneurs and build product-driven companies that can change the world. And that could extend beyond just therapeutics, into worlds that people hadn't previously imagined from food to fashion and beyond.

Recently, as Ursheet and you've mentioned, I joined Mayfield. I'm very proud of that. I'm very proud to work alongside Ursheet and Navin and others to extend that mission and to drive more capital and more resources into that purpose.

Po Bronson:
Okay. Lightning round, remember five companies.

Arvind Gupta:
Five companies. There are so many. I've invested in over 150 companies. Five off the top of my head. Let's see. Memphis Meats is really well known. MycoWorks, Geltor, Prellis, and NotCo.

Po Bronson:
Awesome. So it's fascinating, because to both of you, when you describe these companies, we all know you are both taking a lot of risk. You're going into areas the world thinks are risky. Ursheet – sepsis, the brain, CRISPR. Arvind – barely know where to start with you, but human immune system outside the body, leather without the cow, first VC into cultured meat. Tell me a little bit about your feelings about risk, how much you like it, how you manage it.

Ursheet Parikh:
Go ahead, Arvind.

Arvind Gupta:
So my whole life has been about managing risks. And not many people know this, but I was a base jumper and I don't base jump anymore, but now I'm a rock climber. I've climbed El Cap. And it's really not about getting away with it, it's about figuring out how to do it safely. And that's carried over into my venture career and in doing improbable things. I often see founders that say or show what they're doing and you'll be like, "Well, why tackle that problem when the much bigger problem is right next to it, and you can easily do it with your technology and your mind?"

And they say, "Well, most VCs tell us that's more risky." Well, what's riskier, going after the smaller idea that isn't going to go very far, even if you're successful, or changing the world with what you can make and what you could produce with your own mind and creativity? I fully go for the latter. I think that is where the right risk is. And it allows everyone to align. It's not about trying to make some money. It's actually providing value to people that could change our lives.

And in doing so, you're using capitalism to fight the old capitalism that has led us down to the path we're on, which is ruinous destruction and climate change.

Po Bronson:
Ursheet, what do you think of that, and how do you think about risk? Same way?

Ursheet Parikh:
Actually, I think it's a little bit of a mirror image, but very consistent. When I look at the problems we have with regards to global health or the health of our planet, they are the biggest entrepreneurial opportunities of all time. There's no fixed formula around it, but two things really stand out for us in the way we look at it. The first is it starts with people, and it doesn't matter how awesome the starting technology is – people are the ones who build the companies. So you've got to really understand them, their mission, how they operate, how they learn.

Two of the most important attributes in entrepreneurs that probably are not spoken about enough are intellectual honesty along with continuous learning and the ability to learn. Because entrepreneurs just do amazing things. To do that, they end up having to learn a lot in a very, very fast time period. The second thing is it often requires some really good first-principles thinking. It does require understanding why the world is broken the way it is. You cannot necessarily ignore it – you want to make new mistakes, not the same ones that people have made before, but it does require first-principles thinking.

A good example of this is Jason, Diego, and Leo Teixeira at Endpoint Health, who had been on a mission to save lives for the top killer in hospitals, which is sepsis. And it really started with understanding why that was happening. And besides the core understanding of the disease, the business model of that category of therapeutics was broken, and so it required a new way to look at it.

When we saw CRISPR, it felt like a core bioengineering technology. And rather than our company Mammoth Biosciences trying to keep a monopoly on that technology, it became much more about enabling an ecosystem to build many new applications with such a platform. You get a similar bioengineering platform.

When we were looking at Nēsos, it was the realization that therapies for brain diseases are so far behind other areas. And it's maybe because we have been looking at the brain all wrong. Think about it. The brain is reshaped every time you sleep, train, hear, talk. And at the same time, it's designed to be different from animals, so the classic drug development model may not work. And it's also designed to not take a lot of new drugs.
And so maybe there is a new version of therapy that is actually understanding the communication language of the nervous system, which is electrical signals, and using that to unleash the power of the brain to control the immune system.

And so as crazy as it sounds, these were some of these first-principles starting points with amazing people and partners. And then as Arvind said, fundamentally, it's about managing risk. So where do you take something from science, which is not what the entrepreneurial ecosystem is set up well to find. It's not science, but it's like taking that science into a product that actually can then become the basis for a business, and then building a platform company. Those are the things that we love to partner with people on.

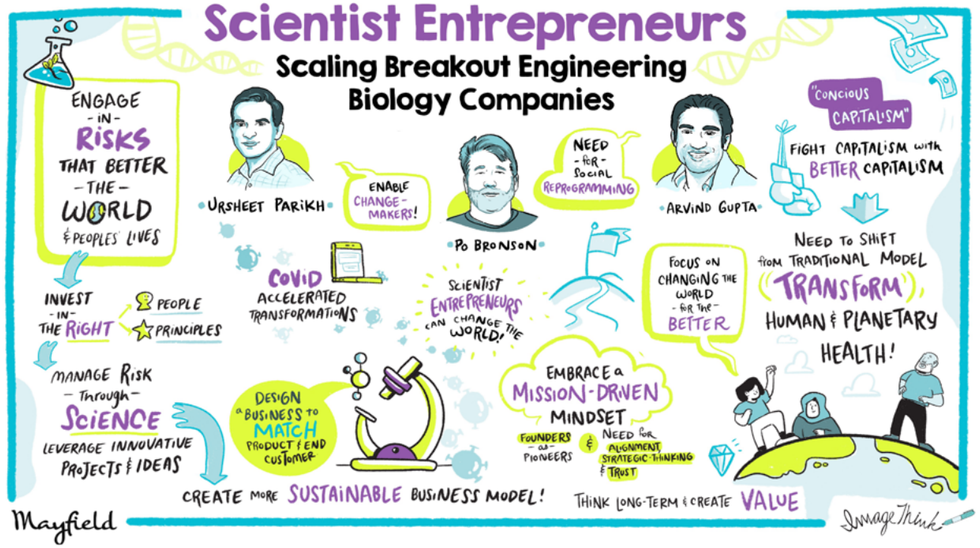
Po Bronson:
So I want both of you to apply to this, but stick with science just for a sec, because we are going to get to scaling business. But Ursheet, you said something fascinating to me last week. A lot of VCs, we talk about programmable biology, but you took it to another level. You were like, it's programmable, but it's programmable and far more than genetic code. It's programmable with any form of energy. And I think you were just speaking to that. I thought it was brilliant. What are some other examples of how we can program biology, not just with the genetic code itself?

Ursheet Parikh:
So I think if we look at biology, biology as it exists on the planet is responding to many, many different forms of energy. I was just talking about electrical signals, and you can have the same thing happening with light. You can have the same thing with materials. And then if we go back and look at traditional cultures, they've had different attributes of how wellness and other things play out.

I think the key is you have to take ideas or concepts which are not accepted in the mainstream and make them real. The onus does end up on the company to actually create the evidence and business models that can sustain the companies through leading that change and really creating a movement, and then getting everybody to board and join that movement, but ... Sorry. Go ahead.

Po Bronson:
Well, no, that's good. But Arvind, I'm going to push you now. Let's talk about scaling a bit. It starts with the fact that a platform isn't a product. Everyone wants a platform, but it's not a product. And you said to me the other day, there are no biotech companies.

There are only consumer companies and enterprise companies, which was a hot take, and I want you to unpack it for people.



Arvind Gupta:
It's less of a hot take and more obvious. Biotech is simply a foundational technology. It doesn't imply any value creation. Consumer companies focus on products that end people use and buy, whether it's in stores or wherever. That requires a full value stack. That requires communication of what the product is. It requires all of the things that are necessary for a solution to a problem that a person has, getting into their lives.

And likewise, it's the same thing for an enterprise company. That type of company just has a different sales channel. It has a different end customer. That end customer is a business with different margin structures. So how you design the business from the very beginning is completely different.

And if you don't design the business from the very beginning to match the product and the end customer, you're hosed, because you're going to run out of runway, you're going to have to pivot around. It's going to cause all sorts of heartache and real issues. I learned this from Ursheet, and I learned this from Mayfield really. As I was going through all the IndieBio companies, as they were scaling, it was a real eye-opening experience for me. As they started to hit the market realizing, oh, actually, distribution channels, putting chemicals on trains and the volume it takes directly affects your margins. Because how many train cars do you need to lease?

It's mind blowing. And so if you don't think about all of these specific things in a margin structure that makes sense for your business, you don't have a business anymore, and therefore you don't have the change you can create. We're using capitalism. One of the reasons I joined Mayfield is Navin coined this phrase, conscious capitalism. And you and I, Po, wrote about it in our book as fighting capitalism with capitalism.

Po Bronson:
With better capitalism.

Arvind Gupta:
With better capitalism. And that's it. It's about building these businesses in the right way. And going back to programming biology with anything, Ursheet talked about making movements right at the end. And I want to make sure we put a pin in that, because if you abstract it all the way out, to create movements, you're actually reprogramming biology with culture. So you could extend all the way, and-

Po Bronson:
I like that. You're reprogramming biology with culture by collective mass movements that's inspired by the companies and the founders voting with their dollars-

Arvind Gupta:
That's exactly-

Po Bronson:
...and their culture is literally reprogramming the sustainability of the planet. That's fascinating.

Arvind Gupta:
That's what we're doing. And whether we recognize it or not, for everyone in our industry, that's what we're doing. And when you see news articles and industry reports about making leather without the cow or whatever product you're reading about, that's what's happening. It's a reprogramming of society. And-

Po Bronson:
I'm going to interrupt you. Because I'm the host, so I get to do that to keep us on track. Because I want to establish how much contrast is there or not. Obviously, where engineering biology has taken biology is into lots and lots of markets, but you're still firmly rooted in human health. And so let me ask you how different the engineering biology practice at Mayfield is vs traditional biotech. One might say you're reinventing the economics, reinventing the nature of the risk, or one might say, "Hey, it's biology. There's always huge upside and fundamental risk there."

So in your minds, do you feel like you're doing biotech, or life sciences, or do you feel like you're doing something different? How unique is it?

Ursheet Parikh:
So I think we have the benefit of being at a firm which has been in business for over 50 years, has had a chance to create profound companies in biotech itself, the Amgen and the Genentechs, and the Intuitive Surgicals of the world. But in the current incarnation, the genesis of what we are really started with the mission of transforming human and planetary health. And that has been a big thing.

But if we are thinking about it, we think that you can program biology with many things, ranging from drugs, to electricity, to light, or any of that. To transform human and planetary health, there have been other technologies that have existed. There's been Silicon, there's been software, there's consumer companies that we have like Grove Collaborative. There's companies like Poshmark, which are recycling clothes. There's companies like Tonal, which are really about transforming consumer health.

And so one thing I ended up learning from Arvind five years ago is to really start thinking about biology as a technology that can be used to solve this full set of problems. And then as we start looking at this as an additional technology to solve these problems, fundamentally how we think about company building differs from traditional biotech.

Traditionally, biotech was also like tech, designed to go build companies. Then in the '90s, as the tech and the bio innovation space changed, a lot of bio-investing and the entrepreneurial and venture ecosystem really became about taking a project out of academia, funding some additional clinical research on it, taking the data and then selling the asset. Now, one thing that we're really passionate about at Mayfield is if we are going to have the solutions for human and planetary health, they're not going to come from a lot of the large companies who've watched these problems as they emerged in the first place.

So we're going to have to have a set of entrepreneurs that build the next generation of lasting companies. So now, if we have to do that with engineering biology, it can't happen in a traditional biotech model, because as soon as you flip your asset, your mission's lost. It's become a cog in the wheel of a different entity. And they just are not going to be able to really make the automation their own.

All of this starts with the very foundation of a company. How do you get the stakeholders aligned for the long haul? How do you design your business? How do you set up that culture? How do you think of your technology as not a project, but a product? How do you get it to market? How do you then show commercial scalability? How do you raise the capital, run the industry conversation out on that? And how do you build a commercial org to get success with your first product? Then you take that footprint and get a lot more products in the pipeline and partnerships with the ecosystem to really create a platform and a company.

And none of the success is accidental. So it's great to be in this time where despite COVID in the last 24 months, we've seen several of these platform companies make it in both planetary health and human health.

Po Bronson:
We'll come back to COVID in just a second, but let me stick with what you're describing about alignment. And let me ask this question in the form of just two words. Lightning round question. I'm going to say two words, and then Arvind, you can start. I just want you to react. Alrighty? Two words. Mission driven.

Arvind Gupta:
Founders

Po Bronson:
No. You don't get one word. You got to react. This isn't therapy, man. Expound. Mission driven. How do you think about mission driven?

Arvind Gupta:
So mission driven. First of all, the first thing that comes to me is founders, because it's the founders' mission in the end. It can't be mine. And so I think often times, venture capitalists will project what they want onto others. So first of all, I'm excited to meet founders that are mission driven, that have the ability to start movements, to program culture, and reprogram society through their actions.

I've seen it many, many times in companies I've founded. And so there's an obsession with those types of founders about the end consumer or customer that they're reaching. They have to feel like that is their goal. Not the gizmo necessarily that's going to get them there. The gizmo could change, but the end customer or consumer, and giving them a better life that results in a better society or better future, those two things, that Venn diagram that's in between, that is the sweet spot when I think of mission driven.

Po Bronson:
Ursheet, how do you think about mission driven?

Ursheet Parikh:
I think it's mission ahead of everything else. It also means that it literally translates to entrepreneurship because there are a few things out there, few constructs that can allow for the change that is needed to realize the mission the way entrepreneurship can. No amount of publishing papers, no amount of nonprofit boards and conversations will go out and do that. And then that moves to this built to last concept. Because realizing that mission cannot happen in a short time, and so it requires great tactical execution as well as amazing strategic thinking.

Po Bronson:
Let's use an example. So I want to give you one. It's quite an interesting story with Mammoth Biosciences. You all became the first CRISPR product to market, which is amazing. And with COVID testing, an incredible pipeline of partners there for Mammoth. But not that long ago, when you started with Trevor it was going to do STD testing and it was going to be 2024 before it reached the market. So how did you get from that plan to what you incredibly have done today? That's scaling in a way that we often don't hear in this industry.

Ursheet Parikh:
So when we met with Trevor for the first time, his mission was where he saw that CRISPR was a technology to program life – to read, write and edit the code of life. And his mission was that the long-term company would be something that powers the whole ecosystem, like Intel Inside. In fact, they literally had a version of that Intel Inside logo. And then as they were given feedback by the entrepreneurial ecosystem, it was something that had to be put away, maybe in the appendix and not early on. And so they took that feedback and figured what would be the first insertion product and came up with what would be an STD test that would be in the consumer self pay model that could come to market faster.

So that is how they were...The opportunity we had was to really understand what they wanted. We participated in their seed round and then spent a good amount of time trying to peel the onion on the core vision. And then it became pretty clear that what we needed was a CRISPR platform company. And to that effect, while the company had licensed something out of UC Berkeley, they needed a core innovation engine, and they needed a lot of the heft on the IP side.

And so we got into a conversation with Jennifer Doudna and shared our vision. She had a certain direction and vision back then. And there was another company that was coming out of her lab. Two of the best graduate students she had out in her career. And you could see that these founders were quite aligned in their mission and direction. They wanted to get it to market.

I think we have the benefit of being at a firm which has been in business for over 50 years, has had a chance to create profound companies in biotech itself, the Amgen and the Genentechs, and the Intuitive Surgicals of the world.

– URSHEET PARIKH

While CRISPR was coming with therapeutics everywhere, they wanted to see the impact in patients. They felt diagnostics was going to be a fast way of doing it.

The conventional wisdom was to do a diagnostics company or a therapeutics company.

It wasn't recognizing that this technology was starting with a CRISPR innovation engine that would find new CRISPR systems, develop new CRISPR systems for different applications. And then diagnostics and therapeutics were just two applications.

There are other applications in ag and then bio-defense and a range of other places. And so we were able to go ahead and align on that mission, and then design the company and the business and all the stakeholders on that journey to form very deep trust relationships.

When you have very deep trust between the early stakeholders, founders, investors and other advisors and mentors, it really allows for an exponential speed up. It's one of those slow down to speed up things. And so the whole process to figure this thing out, this business design, took us three to six months to figure it all out. But when that happened, you can see three years since, the company has accelerated so much. And about a year ago when COVID was first happening, they were so well poised to actually go ahead and bring the first CRISPR-based products to market with the COVID test.

And their recently launched COVID CRISPR test increased the capacity of our country to do COVID testing by an order of magnitude with the existing labs. So I think it's a privilege to have been in those conversations. And there's a lot that goes into this – it takes a village.

I think one of the biggest things is really understanding how to topple incumbents. Truly thinking all the way through. Not just getting these companies started, but all the way when it gets into the nitty gritty.

– ARVIND GUPTA

Po Bronson:
Well, let me give Arvind a chance here to add some of this. Because Ursheet, you talk about essentially being on a team with the founder. Arvind and Ursheet, you guys are on a team. And Navin and Tim are on your team in this space.
Arvind, you've known the guys at Mayfield for at least six years, but nine months of working together. Ursheet earlier mentioned stuff he learned from you and what you're doing at IndieBio. Tell us a little bit about what you've been learning from them at Mayfield since you've been there.

Arvind Gupta:
Man, it's been a massive learning curve, as you could imagine. That was the goal of working with Mayfield, and that goal is being accomplished. I think one of the biggest things is really understanding how to topple incumbents. Truly thinking all the way through. Not just getting these companies started, but all the way when it gets into the nitty gritty...How do you keep going and not become part of the problem and get shuttered? How do you go around that and make it all the way to IPO and then continue in the public markets and continue to create value dependably?

That's the timeframes we're talking about. That's the timeframes that Ursheet, Tim, and Navin have built value in companies, literally. That's something that's rare and something that I'm excited about continuing to learn. And it's different for different companies, it's different for different founders, different industries.

And so it really requires this long-term thinking and this ability to build, not just, "Okay, we got to get a series A company funded," or, "It's series B, we got to get it funded." A, funding is not success. It just allows you to play a little bit longer and achieve your goals. And so if you don't have clear goals and ways to achieve that long-term thinking, you're getting sloshed around by turbulent seas and you end up drowning usually. But with that long range North Star, you could chart your own course and make it all the way through. That to me is really exciting. And that's what I've been learning in spades and I could write a book about it.

Po Bronson:
So you're describing the challenge of knocking off incumbents. Do you have a framework? You guys just get to know you're coming one at a time? Do you have a playbook here? Boy, who wouldn't love to know how to knock off incumbents?

Arvind Gupta:
It is a playbook. I'm not sure. Some of it can't be shared here obviously, because these are the learnings of the past 20 years. Navin was one of the very, very few venture capitalists that made money in the clean tech 1.0 wipe out. And there's some very distilled learnings and a playbook that's come out of that. And that's directly being used right now in some of the companies we're using. And so it's good.

Po Bronson:
I don't want to push too much. Let's go with as you mentioned, because you just mentioned clean tech and making money in clean tech. One of the only people. A few. You've been doing human and planetary health for quite a long time. A lot of people are just jumping on to it today. Recently. We say, how many carbon funds have we seen in the last year? You guys have been doing this a long time. So I'm curious what's your newest evolution of your thinking here around doing companies to make an impact on planetary health?

Arvind Gupta:
Specifically on the planetary health side? I think really understanding that there are more markets than just food. I think that people are just starting to wake up to that. MycoWorks is a great example of the first breakout. There are going to be many, many more. Think of it this way. If a lot of this behavioral change, social reprogramming that we're talking about is occurring because of climate change, what you eat immediately goes in your stomach. What you wear doesn't. That is a billboard for what you stand for all day long. So I'm going to leave it at that, and you can imagine where these things go.

Ursheet Parikh:
We're beginning to see more and more examples of that. I have a teenage daughter and it's amazing how much she really worries about what's happening out with the world. And really what is more worrying is that the majority of the world doesn't care. But guess what, there is a subset that does. And so if you can enable them to vote with their dollars on your innovation, then they become the people who program the culture and make that change happen.

And so the business design, often a lot of companies are made by scientists and entrepreneurs, and the right engineers. And so there's a strong desire to just go and build a set of things. But I think if you could get the business design right, so those constraints bring focus, that helps actually make the problem narrower. Those constraints bring so much focus that it actually creates for a lot less trashing data and a more successful company.

So I think in the newer incarnation, we definitely encourage entrepreneurs to think about how, just because we are doing the right thing, people will buy it or will follow versus who really cares about this and how do we enable them to vote with their dollars.

Arvind Gupta:
That's right. That's a real focus for us. I could say for all the founders out there who are building product-driven companies that have an angle into impacting climate change or planetary health, that's what we do.

Po Bronson:
Ursheet, you mentioned this earlier, that the pandemic altered things, is often called the great accelerator. Certainly pushing people online and watching more Netflix and the like. How has it impacted the human and planetary health sectors?

Ursheet Parikh:
I like to call them the silver linings from the COVID era. I think the first is we've had the e-commerce moment in healthcare. It had been building up for a while, and the technology was all largely available, but it just required COVID to get people to break out of the habit of always asking to see patients in person. It never made sense from a first-principles perspective to take an infectious disease patient and get them into the clinic rather than seeing them on the telephone.

But not only that, it makes a case for making health equity happen much more easily. It's a luxury to be able to take two or three hours off from your weekday to go see your doctor for a preventative care thing. And there's a lot of people who are working hard to make ends meet, who just don't have that time. There's the convenience that comes along with the ability to get your medication quickly. So I think it's going to be a big factor in changing practices to make our care system better and lower cost.

But the other thing that it did is it changed processes everywhere, even at the FDA, for example. We had two fundamental platform technologies get their first products to market during COVID. mRNA vaccines, they've been trying to get the cancer vaccines to market for seven, eight, ten years, and we were able to get a vaccine to market in a year or less, to hundreds of millions of people within a year. And then CRISPR's first clinical products as we've seen come in with diagnostics.

So I think these things happened not because the scientists were working as hard, but a lot of the large company ecosystems that you depend on to build the products or the government processes and practices evolved as well. The other thing it did is it also accelerated transformation in other industries.

For example, wellness in the home, with companies like Tonal and Peloton. You saw that break out.
But as people spent more time in the home, they started caring about what products they're using.

And there's a company called Grove which gives you cleaning products that are better for you and better for the planet. And that's an example of a company that really broke out.

Initially it was because people couldn't go out shopping as much or they were afraid, but then the other part is even as COVID is coming more and more in control, the business continues to grow.

Because people can see, why do you need to take so many petrochemicals and have them in such proximity when there are better other alternatives that could work as well? Why do you need packaging versus you could have something this small and just add water to it and things like that.

Po Bronson:
It's interesting. I love how you're elucidating all this. And I like the framing of silver linings very much. But I want to acknowledge that we probably have a lot of founders in the audience. These are spirited people who the world probably hasn't heard of, at least not yet. So for both of you, let's imagine ... Arvind, you'll start with this one. Let's imagine they get in a room with you. All right. So give me some red flags, some no-nos. And what gets them a second meeting with you?

Arvind Gupta:
Oh, gosh. Well, one, you have to be mission-driven. And that's hard to fake. I think really, really focused on the customer, really care about your innovation making into the world rather than proving your innovation can work. Those are two very different things. And I'm looking for founders that are talking more about how they see it getting to people and changing their lives and what that world will look like.

> The entrepreneurs really are the ones who change the world, make our lives better.
>
> – URSHEET PARIKH

Po Bronson:
Little less prove me it works, and a little more prove me people care.

Arvind Gupta:
There's plenty of time to prove that it works. You asked for the first meeting, the first thing that matters is if it did work, whose life changes, and does that sum up to a world changing? Does history change?

Po Bronson:
Ursheet, for you, red flags, turn-offs, or other things that you particularly love to hear?

Ursheet Parikh:
So I don't have a set formula. I can share a wishlist. But I've had the great fortune of working with founders who've come right out of college to founders that have taken products to market, to commercial scale, and companies that are billions of dollars. Konstantinos at Nēsos, or several other folks like that. I think on my wishlist is in that first meeting, rather than tell me what you think VCs want to hear, telling us what's really in your mind, what you want to do, why you want to do it. Recognizing that of anything that anybody can choose to do, entrepreneurship is probably the hardest thing to do.

There are just easier ways of making money than entrepreneurship. So it does start with a certain degree of authenticity and then a certain willingness to engage in conversation and learn. And not everybody is going to be great at everything, but we clearly want to walk out of that thing feeling really healthy respect for something that you are doing, or something that's new or novel or something that I learned in conversation that I wasn't aware of.

And given that one of the best privileges of our jobs is we get to learn from the smartest people every day, which are the entrepreneurs changing the world, if we try and say something, it's really coming with the intent of enabling their success. I think that Arvind, you know there is a promise that you don't have to worry about what we say versus what we mean. As what I said at the beginning of this session, anything that is said is coming really with the intent of whether we are investors in the company or not. We want the company to succeed. The entrepreneurs really are the ones who change the world, make our lives better.

Po Bronson:
So I think you identified something. Is the founder really ready for the life of an entrepreneur? Now, that's an internal state. How does an entrepreneur themselves know whether they're really built for this or not? Is there any way that you've found to work with them to help them understand whether they're right for this, Arvind? You've got less than 30 seconds.

Arvind Gupta:
I think don't think, do. You'll find out along the way. It's like saying, "Am I ready to take a grappling match?"

Po Bronson:
I love that answer. So thank you Ursheet and Arvind and the engineering biology team of Mayfield. Thank you for spending time with me today. Really appreciate your insights in this event for TechCrunch. Thank you very much.

The New Human and Planetary Health Pioneers

WATCH RECORDING

Arvind Gupta:
Today, it's my true pleasure to introduce two of the fastest rising stars in human and planetary health, Matias Muchnick, CEO of NotCo, and Trevor Martin, CEO of Mammoth Biosciences. Mammoth Biosciences, co-founded by Nobel Laureate Jennifer Doudna, is the industry's first CRISPR platform company. It has already delivered a breakthrough COVID test and is in partnerships for novel CRISPR products with leading healthcare companies. NotCo is combining artificial intelligence and deep science to reinvent the food industry starting with a milk alternative product with many more to come. Both have recently achieved unicorn status by reinventing their respective industries.

I also have the pleasure of personally knowing both gentlemen for years – Matias through IndieBio and Trevor through Mayfield. I'm excited to hear their thoughts in scaling the next generation bioplatforms for human and planetary health and sharing that with you. So, let's go ahead and get started with Matias. How is NotCo reinventing our food system?

Matias Muchnick:
Well, Arvind, I think from the get-go, we had this vision of taking the animal out of the equation with food. And consuming food really as it is, right? It's not only something that keeps us alive, but really something that we enjoy the most. And we've sacrificed already too much in this world to actually sacrifice the taste of food. Now, the way we're creating the food that we love to eat is inefficient, unsustainable, the overuse of resources; water, land, energy, CO2 emissions, you name it. The animal industry has become one of the major environmental detriments known to humankind. Deforestation, water scarcity, ocean depletion, loss of species, and I can go on. So one of the biggest problematic things that we saw is that we don't understand food. And the food system has been operating under an obsolete technology for the last 80 years.

So using AI, using science, using technology, how can we create the products that we love, but coming from sustainable sources, such as plant-based ingredients? Now, plant-based ingredients were absolutely unknown. So, there are more than 300,000 species of plants in the world that we have no idea what they can do. And we're human, so we're biased, right? We have no idea if the combination of pineapple and cabbage can create the taste of milk. And it does, right? So that's how we're utilizing AI to debunk, to hack the system of plants, to really bring all of those tastes and textures that we like in food, and that nutrition, but in very, very sustainable ways. That's how we're doing that. In Latin America, we started, and then deploying in the US and Asia and probably more and more regions in the world.

Arvind Gupta:
Amazing. Thanks for that. And Trevor, how is Mammoth reinventing our healthcare system today?

Trevor Martin:
Yeah, at Mammoth, what we're really excited about is, in short, delivering on the promise of CRISPR. And in particular, what we've done at Mammoth is that we've built up the world's largest toolbox of novel CRISPR systems. And if you've heard about CRISPR, then you might've heard about Cas9 or Cas12a. And these kinds of legacy systems are really doing amazing things. And there's really exciting work that's being done. And I think there's really great therapies that will be created with them, but there are limitations to what they can do. At Mammoth we're all about pushing CRISPR beyond its boundaries and really enabling new types of products with these new proteins. And that's the foundation of Mammoth, is that kind of CRISPR toolbox of proteins like Cas14 and CasPhi, and others. And then on top of that, we build products and diagnostics and therapeutics. Both internally at Mammoth and with partners. And in diagnostics, what we're really focused on is really democratizing access to high quality molecular information.

I think unfortunately, during the pandemic, we've seen that it's actually pretty difficult to get high quality molecular information anytime and anywhere. And you almost face this choice of, do you want a result that's extremely accurate and molecular, like say a PCR? Or do you want a result that's very accessible and maybe easier to use like a lateral flow or an antigen or antibody test? But you can't have your cake and eat it too.

And I think what we're excited about at Mammoth is that you really can design something that has that high molecular accuracy with that more accessible profile, being more similar to a pregnancy test.

And I think we've seen our diagnostics work accelerated during the pandemic. We've gotten lots of great partnerships with organizations like GSK and the NIH who we're really honored to work with to advance these technologies.

So, that's one of the things that excites us on the diagnostic side. And on the therapeutic side, what we think is really enabled there, is in particular, permanent genetic cures and in vivo editing. So, in vivo editing means rather than taking cells out of the body and then changing them, and then putting them back in, which is how many of the therapies are done today, what if you actually could edit the cells in the body without having to remove them? And that really opens up a lot of doors about different diseases that could be treated and tackled. And there, we've really innovated around what we call these ultra small CRISPR systems. So you can think of it as a little, tiny, compact car versus a huge freight truck in terms of what you're trying to deliver on a ship or something.

> You can have the best product in the world, but if you don't have great execution, then the company is not going to fly at all.
>
> – MATIAS MUCHNICK

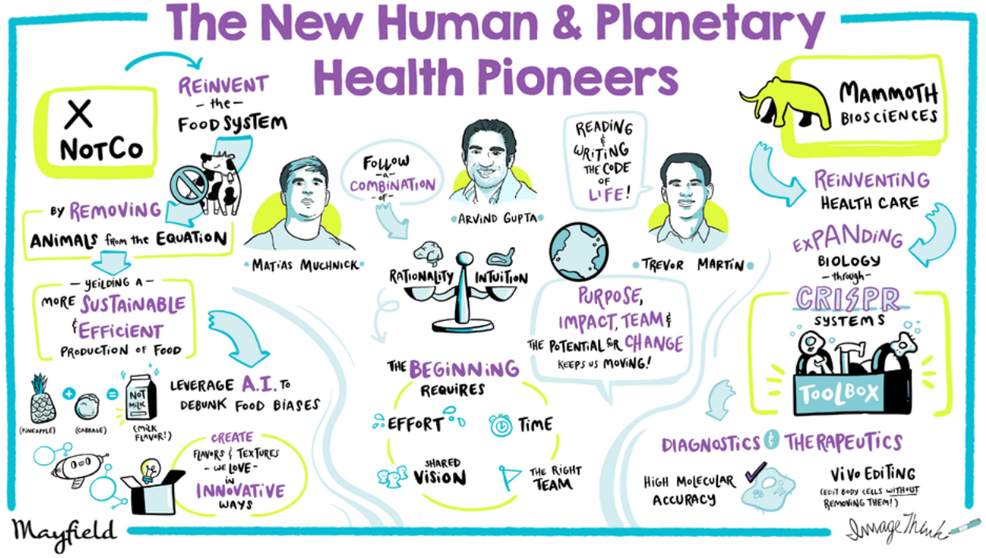
And on the diagnostic side, it's just a totally new way of thinking about CRISPR, where you're actually using on this property called collateral cleavage to actually amplify and read out a signal. These are both just things people didn't think were possible or things that CRISPR could do, could be that compact, could do that kind of collateral cleavage. And I think that's only the beginning of what's possible is what's really exciting. And Mammoth is going to continue to innovate in diagnostics and therapeutics, and really is at the forefront of building out this toolbox of what's possible with the next generation of CRISPR.

Arvind Gupta:
Yeah. Thanks. And it's amazing what both of you guys have created at this point, right? Both of you have companies that have massive technological platforms that are driving innovation very deeply in your respective industries. But it wasn't always that way, right?

I mean, I'm an inception stage investor and it's remarkable how different the beginnings are from where things end up going. So, for the audience, I think it's always nice to hear about these beginnings. So, Matias, we can start with you. Tell me, was there a founding moment? What was it like in the very beginnings of NotCo? Did you think this would happen? I mean, how did you think this would happen?

Matias Muchnick:
I probably would be lying if I said yes. I didn't think this was going to happen. Now, the vision was less. Now, probably someone told me what getting here was going to take, I would've not done it, right? Because it takes so much time, it takes so much effort, so many sacrifices and the chances of failing in the middle are so, so high. And so, how was NotCo? Literally, and I'm not going to see at the beginning, it's only two years ago. We were valued at $1.5 billion, but let's not forget what it was two years ago. I was calling the guy who was delivering cases in the supermarket, if the cases were right or wrong. And so, that only happened two years ago. So, the unicorn status, or wherever we are right now, Trevor and I, doesn't imply that we're not operating this company, we're analyzing the strategy where we need to go, right?

But at the beginning it's a vision. It's a team aiming to execute what the vision is. And building, in the building blocks of what do you really need to do in order to become a billion dollar company? And sometimes you fail miserably on those building blocks, because they weren't the building blocks that you needed to do and construct in order to get where we are, right? So, at the beginning, it's very purpose driven. It's very visionary, but if I need to give any advice, it is that vision and that romantic speech has to be mandatory, converted into execution by an A-team. And the team makes, and people make companies. Not anything else. You can have the best product in the world, if you don't have great execution, then the company is not going to fly at all. So, I think those three things, what NotCo has done to become the company that produces products faster, better, more accurately, and less costly than anyone in this space. Nothing more than that.



Arvind Gupta:
Wow. That's, that's amazing. And I was very privileged to see some of those beginnings. And Trevor, tell me about how Mammoth came together and how, how it happened for you.

Trevor Martin:
Yeah. Mammoth is a rare Stanford-Berkeley team-up.

Arvind Gupta:
Yeah, Rare.

Trevor Martin:
Being graduate students, maybe, by a little bit, lessened the rivalry. But yeah, no, I think to one of the points Matias mentioned, it really all comes down to sharing that same vision of what's possible. Whether you think you can achieve it, or how crazy it is, maybe the crazier the better, but I think that's really what draws you together, and then what binds you for the journey. Because yeah, there's going to be ups, of course, but then there's going to be big downs. And, I also agree with Matias as well that, markers on valuation, like unicorn stuff are exciting and should be celebrated, but they're really just markers of other more important value that's being created. And it's also just the beginning, right? I think when you have these kind of, really crazy visions about the impact you can have, that's still early days, frankly, for what these companies can accomplish.

And I think that what's really cool is that you don't want to lose sight of what you've accomplished, but also that's just building a stronger and stronger foundation for really tackling these really audacious goals that maybe you didn't even think you could get to at the beginning of it. And for us, what really bound us together was this idea of delivering on the promise of CRISPR and really saying, "Can we leverage something that's really fundamental science? And as quickly as possible, bring that through to diagnostics and therapeutics that can benefit patients?" And that's a very audacious goal in itself and a huge journey. And I think you have to be a little bit crazy to think you can do that, especially with brand new technologies that are coming right out of the lab. But I think that's what's exciting about startups and what makes Silicon Valley, Silicon Valley.

And now I think that mentality is becoming more global, which is awesome, is that idea of just why not you and why not now, right? And yeah, it's going to be really hard and there are going to be many, many failures, right? It doesn't guarantee success, but really having that opportunity, I think is one of the most exciting things.

Arvind Gupta:
Right. Yeah, well I'm glad that the people can hear that you guys even, both of you building these large companies that are just getting larger and tackling bigger problems, started somewhere. It's hard to remember that sometimes.

And so, I always say that that platforms aren't products, and people buy products, right?

But founders go and talk to investors about, "We have a platform. It can do all of these things." It's always interesting, this tension between this whole platform idea versus, "Hey, we're going to have this product and a singular focus." We'll start again with you Matias, how did you create focus for NotCo and choosing NotMilk, or some of the products that you have? What I first tasted, the NotMayo? How'd you choose those products versus the literally infinite other products you could have made?

Matias Muchnick:
Yeah. It's always a matrix of decisions. There are different dimensions of complexities in the decision-making of what's the next product to actually launch. Now the important thing is to really say no to 75% of what you're thinking you're going to launch. And really achieving the 25%, because that's literally the 80/20 rule of startups, right? We had the idea, and you tasted it.
There are probably products in the market that we've prototyped in the past that never reached the market. And they didn't reach the market because we said, "Okay guys, what's the mission of NotCo really in this world, right?" It's to move the needle of sustainability. It's to move the needle of the CO2 emissions. How are we going to do that? Is this going to be through a cheese? A yogurt? A Nutella? It's going to be with milk, Right?

Where's the biggest opportunity, as well, in the market, right? Who are the first movers? So there's many dimensions, but what is the complexity of scaling this product, right? Who are the players? Why are we better? What's the value proposition? Is it clear or no? What's the market feed of products? So there's many, many layers of complexity as you might guess, but there's an underlying gut feeling that drives a lot of what the entrepreneurship spirit is. If you're analyzing absolutely all the data, let me tell you, you're not the first one to do that. You know? People have been drawn by the data and understood that data before you did. But, that's what entrepreneurship really is, that gut feeling of there's something there that no one else, even the data, is not telling you, right? So you need that spirit as well. So it's a very good combination between rationality and the gut feeling, or the intuition of an entrepreneur.

Arvind Gupta:
That's amazing, that you don't hear that very often, this idea of, "oh, there's all this data out there," but really, if you don't trust your gut, that data can lead you astray. And Trevor, with Mammoth, it's an incredible platform of technology. How are you navigating the future and choosing what to do, and what not to do?

Trevor Martin:
Yeah, I think saying no is the hardest thing. And that's also the most important thing when you have a platform, because, there's the common adage that startups are more likely to die of indigestion than starvation. And I think, there's definitely some qualifiers on that, around, I think it is good at the right stage of the company to really open up and explore. But I think you need to know when is the time to then constrain the exploration and really focus down on a product, because the product does make the platform, at the end of the day.
And I think that intuition going to that gut idea. I don't know if data will ever necessarily get you there. You definitely want to have as much data as possible. And you don't want to just blindly make these decisions, but, yeah, you can definitely fall into analysis paralysis.

And at the end of the day, is that intuition around when is the time to go from exploration to focus? And maybe back to exploration in other areas, and just a constant cycle of trying to determine that. And I think that's one of the most important skills that any platform company, really, is being able to strike that balance.

Arvind Gupta:
Yeah. Got it. And so, both of you guys have recently achieved unicorn status, which is something that all founders are looking forward to. And, as a milestone, as a marker, right? It's not the end, it's not the goal, but it's a marker in the journey of entrepreneurship, and in the maturation of a company.

So I'll ask the same question to both of you guys, right? What keeps you going when you hit this milestone? And is there a vision that you're trying to get to, or is that vision always changing and moving? Kind of like the horizon, right? As you chase, it just keeps staying in the distance. How do you manage this? And what keeps you going through all this? Matias, you go first.

Matias Muchnick:
Yeah. I mean, it's a great question to which, unfortunately, I don't have a great answer to. I think there's a combination of things that keeps me going. I founded this company to move the needle. If we're not in a report of sustainability saying, "Hey guys, you know what, in the world, the CO2 emissions have been reduced because you have NotCo," we're not ready. We haven't complied with the mission.

So what keeps us going is the purpose of why we created this company. It's the mission why we created this company. More importantly than professional or economic development of myself or the management team or the founders, that's not the case. It's very mission-driven. It's very purposed. And, every time we're going and climbing this mountain, we see another mountain and another mountain and another mountain. And you need to enjoy the ride, and being on the top of the mountain, it's pretty unbelievable to look around and say, "Holy hell, what did we do to get here?" It's amazing. So, yeah.

Arvind Gupta:
Oh, that's great. Trevor, what about you?

Trevor Martin:
Yeah, no, I think if you enjoy what you do, it is like the horizon. You'll always fall into that, it's not a trap, but it's like, you'll always have, as soon as you achieve something, that's old news. And now, there's something else like, "Ah, if I just get that done, then I'll feel like we've had more of an impact." But yeah, I think for us, it really is down to the potential of CRISPR. And there's so many thousands and thousands of diseases that could be diagnosed and cured, and we could spend the rest of ten lives working on that. And I think that's why we also do things not just internally, but work with partners to try and scale our ability to have that type of impact. And in general, if we can just keep having cures and keep having diagnostics, I don't think anyone on the team will ever get tired of that, basically.

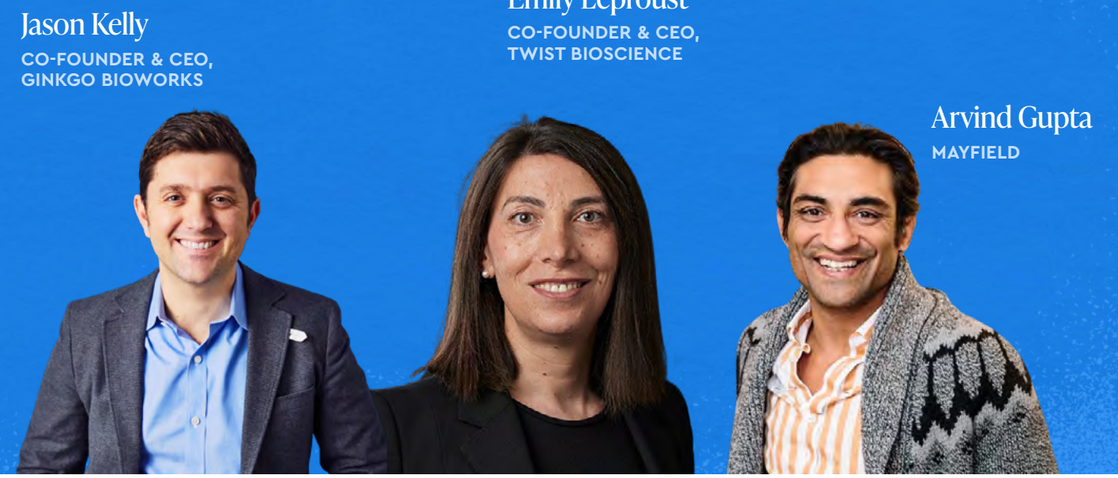
Especially if we can always be innovating on the backend and just constantly pushing the envelope of what's possible. And I think in terms of what keeps us going, I know for me personally, it's the team that you work with, right. I mean, that's probably true for anything, whether it's personal life or professional life, as long as you work with people that you respect and you think are really awesome and invigorate you, you could probably do literally anything for decades. So I think that's a really key part of any startup growth, as well as building that team that you just want to go in the trenches with no matter what.

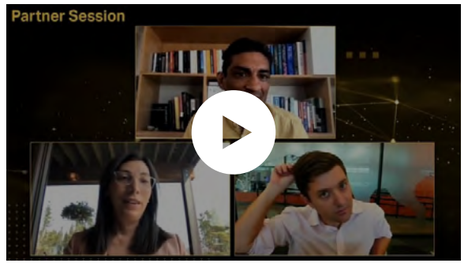
Arvind Gupta:
Yeah. It's kind of interesting, you guys both said it at different times, but I think the secret to the success that both of you have in completely different industries are common, right? Incredible team, and an incredible vision of the change you want to create in the world. That's been clear from this conversation, from my perspective. There's no wavering on what it is that both of you are setting out to do and being surrounded by people that you love and are capable of making it happen.
Well, I think we're out of time here, unfortunately. I can keep going with you guys forever, but thank you so much for making the time to join me and talk to the audience at TechCrunch. And I hope everyone learned as much from it as I did and had as good a time as me. Thank you guys again.

As long as you work with people that you respect and you think are really awesome and invigorate you, you could probably do literally anything for decades.

– TREVOR MARTIN

Bioplatforms for Saving the Planet





WATCH RECORDING

Arvind Gupta:
It is my pleasure to introduce two powerhouses of the current synthetic biology revolution, Emily Leproust, CEO of Twist Bioscience, and Jason Kelly, CEO of Ginkgo Bioworks. Twist's synthetic DNA is reinventing the fields of medicine, agriculture, industrial chemicals, and data storage. Ginkgo has developed custom strains of organisms to make fragrances, fertilizers, alternative proteins, hunt for natural antibiotics and engineer probiotics. Both companies are leaders in the current biology revolution. I'm super excited to hear their unique perspectives from the cutting edge of our future. Emily, this is the transistor moment for biology as a technology. If we're to continue that computer metaphor for biology, how do you see writing DNA as being able to write the software for life?

Emily Leproust:
Thanks Arvind, thanks for having me and you're right, that it is the transistor moment – what happened with Fairchild and with the companies in Silicon Valley when they decided to manufacture transistors and miniaturized them. That really unleashed all the amazing things we've seen with computers and at Twist that's what we're doing. We're taking the known chemistry for writing DNA, miniaturizing it and we can write DNA better than before. And basically every piece of DNA we make is kind of like a line of code. And so our customers buy a bunch of lines of code and then they have to...

Jason Kelly:
Have to pay by the bin.

Emily Leproust:
Yeah, yeah. To compile them. And so, we send them to Ginkgo and many others and unfortunately for the field, bio is still difficult. And so that means that our customers need a lot of lines of code to combine them and find the one that works for them. And so what will happen is as there are more lines of code compiled, there'll be a bigger knowledge base. And people will be able to advance biology much faster at the same time as we keep shrinking the DNA and keep blowing the curve, increasing the throughput.

Arvind Gupta:
Fascinating. And so really you're seeing DNA writing as being, not just putting together base pairs, but actually the compilation layer for the entire language of life.

Emily Leproust:
Yeah, exactly. And I am a very bad coder. I was a bad coder, now I'm a terrible coder. But when I used to code every time I would write a line I would have to compile right away to make sure that the code worked. I'm a chemist by training. So I have some excuses, but yeah, exactly. That computation takes time. Our customers use the design, build, test, learn engineering principle. And so our customers design the line of code. We build it and then they go test it and, and they learn from it.

Arvind Gupta:
Got it. And so you mentioned that you and Ginkgo are working together. So Jason, how is Ginkgo using the software of life to make organisms do useful things for humanity and further to that are organisms actually the programming language of life?

Jason Kelly:
Yeah. So, well, I think I'll start just to mention, Emily kind of mentions off the cuff that they print DNA, but let's just pause for a minute of how insane that is. Right. So just for, for folks who might not know this field, right? This literally means going in a computer you're typing, ATC, GGG up into the kind of thousands of letters of code, you're hitting print. And then off goes in order to Twist and they literally build the piece of DNA that you want. And then our version of sort of installing code in a cell means that you're going to open the genome of a cell. So think of like a bacterial cell would have a three million letter piece of DNA that tells that thing how to swim and grow and eat. And you're going to install maybe 10,000 new letters of code in there.

And you're going to do that by opening the genome, kind of cut and pasting it in. If you've heard of things like CRISPR, that's the kind of technology that allows that cutting and pasting, you put that new DNA in and then the cell reads it and executes it. And so really that sort of programming metaphor, it's pretty strong here, right? DNA is literally digital code and Emily has the world's biggest compiler and you pay by the bit. That's what's going on.

And what Ginkgo does is we operate as essentially cell programmers, right? So we're making use of Emily's compiler, we're Twist's biggest customer ordering that DNA. And then when we get it shipped to us, we install it in the genome, grow the cell up, and then basically run a debugger.

I'm sitting in front of a 200,000 square foot debugger, which is basically a bunch of robotics and all automation that opens the cell up, looks at what happened based on the changes you just made to the DNA. Is it making the right proteins, the right small molecules, what's going on? Because as you know, as a software developer, you're not going to get it right the first time, you're going to want to see the output of that debugger. You're going to want to make some changes to the code, hit compile again, get another order from Emily, put it in and see if it worked and go through that. Ultimately, hundreds of thousands of versions of that code until you get the one that does what a customer wants. And so that's Ginkgo's business. We essentially operate as an outsource programming shop. We have our own debugger. We order from Emily's compiler, we build you a cell, and then you, our customer go off and bring that, that cell app to market. And we take a royalty kind of like an app store economy, basically.

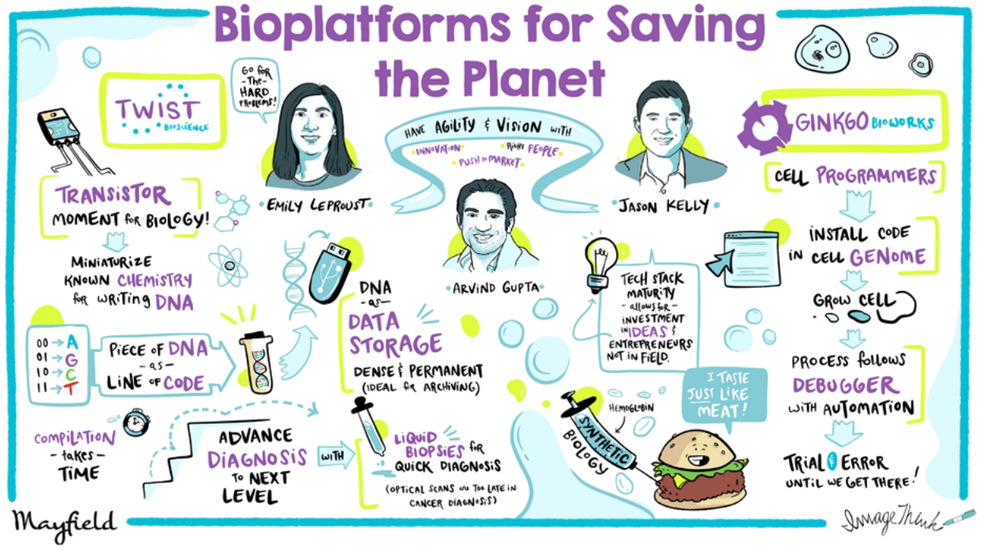
Arvind Gupta:
Wow. And so really, this metaphor's working out quite well, all the way to the consumer end that you're talking about Jason.

Jason Kelly:
Yeah. I mean, to give you some examples, we have customers in the animal-free meat space, who are engineering and you know this well Arvind.

Arvind Gupta:
Yes, I'm familiar.

Jason Kelly:
IndieBio really launched this whole area. But, what people are looking for is an animal-free product that still tastes good. And the way you do it is you basically engineer cells to produce animal proteins by taking the code, like a company, like Impossible Foods would take the code for hemoglobin, which is the protein that makes blood red. They put that ATCGG in a computer, hit print, get the DNA from Emily, install it into a brewer's yeast, brew it up and instead of beer coming out, Hemoglobin comes out, you add that to a burger and suddenly it smells right and tastes right and cooks right. It's an Impossible Whopper. That's a consumer product with synthetic biology on the backside. There're many things like that that we're working with. We work in the agricultural space on microbes that produce fertilizers. The applications for this are quite broad.

Arvind Gupta:
Yeah. And I think you're getting to the actual underlying power of biology as a technology. Right. I mean, how many industries did you name just rattling off your customers?



Jason Kelly:
Well here's, what's interesting. Again, people that understand computers get this, right? If you were like, what industries will computers impact? And, the answer is, well, every industry that uses information, right? Because fundamentally a computer is a programmable device that moves bits around, it moves information around. So what did it disrupt? Media, telecom, finance, advertising, anything that involved pushing bits, right. What didn't computers disrupt, hamburgers. Because hamburgers aren't made out of bits, right. Hamburgers are made out of atoms. And biology, programmable, I swear to God, it runs on digital code. It's crazy. Okay. You put new code in, it does new things, but it doesn't move bits. It moves atoms. And so if you think about the industries that bio and engineered cells are going to disrupt, it's all the physical goods industries, and yes, that's going to range from pharmaceuticals to building materials, to agriculture, to medicines, right down the list. Anything with an atom.

Arvind Gupta:
Fantastic way of putting it. Jason, thank you. And for me personally, I'm so excited because I think we could be using this technology to fight climate change and improve human health and all of the above, and really advance that quite quickly. And so Emily, you're talking about DNA printing, right. And actually making these, but I know that Twist is doing so much more than just that or what else can we do with printing DNA, other than putting base pairs together?

Emily Leproust:
Yeah. So in addition to enabling customers like Ginkgo to do the great thing that Jason just outlined, there's a few other areas where you can leverage DNA. One of them is in advancing diagnostics to the next level. So if you take the example of cancer, for instance, most cancers are found at phase three or phase four because you feel you have a mass and then they can always be seen in an optical scan, a C scan or an x-ray. And it's often too late because despite hundreds of thousands dollars maybe even millions of dollars to treat, survival rates are actually pretty low. But you can use the power of DNA to take a blood sample and then use our DNA to extract the cancer genes, and just read that. And so what that means is, and it's called liquid biopsy and it is delivering the fact that cancer cells are always shedding DNA.

So even though you have just a few cells, here's a phase one phase two, there is part of that DNA in the blood cell. It's almost like a shadow of the cancer cell. And then if you can, using Twist we can extract that those cancer mutations and sequence them.

And you can get a diagnosis at phase one of phase or phase two, it's a lot cheaper to treat and the survival rates are much higher. So that new field of liquid biopsy is absolutely enabled by the DNA that we make. Another exciting field, which is very different, is around data storage. So we are frankly, on a path where we are actually running out of sand, running out of silicon. If you plug the amount of data being created and you do the math just in the not so distant future, actually there won't be enough silicon to store all the data that's being produced.

> If you think about the industries that bio and engineered cells are going to disrupt, it's all the physical goods industries, and yes, that's going to range from pharmaceuticals to building materials, to agriculture, to medicines, right down the list. Anything with an atom.
>
> – JASON KELLY

There's a better way to store data than on silicon, that's using DNA. Our DNA is our hard drive, but you can find men with DNA that's a million years old and you can see with it. And so DNA has the potential to be basically a per manage storage media. It's also super dense. So you could put hundreds of Google data centers in a sugar cube, which obviously takes a lot less energy than those millions of square feet data centers. And so the density and the permanence means that we are pushing the technology to enable DNA to be the media of choice for archiving. So it's not going to be hot data storage where the data is in and out all the time. But if you're going to read the data once a year or less, DNA is going to be perfect.

That data layer is actually 60% of the market. So those are kind of two exciting new applications of DNA. There are more. We're mostly working with pharma partners to discover drugs against how to drug target. So we are becoming the drug discoverer of last resort. If you've tried to find a drug against a target, you can't, you come to us and we'll do it for you.

It won't be cheap. It'll be a premium offering. You'll have to pay royalties. But so far, we're batting a thousand for heart targets.

Arvind Gupta:
That's so cool, what you guys are doing and storing DNA, storing information in DNA. I think, all of the things you talked about is that you have a bigger complier. So finding drug targets for therapeutics speaks to that database. So the more information you have, the more power you have in biology – is that fair to say?

Emily Leproust:
Yeah. And especially in drug discovery, it's really a numbers game. People talk of one in a billion, right. You have to try a billion antibodies to find the one. And so if you have the machine that rises to the billion, well, you have a better shot at finding that one antibody. So there's still a need for traditional ways. The traditional ways where you take a target, like COVID, for instance, and you immunize a rat or a mouse or a rabbit or shark or llama, and then you extract the antibodies produced by the animal.

But it doesn't work for many targets where there is ology between human and the animals. So that's where we come in and we can really move the needles for those diseases.

Arvind Gupta:
Thank you for that service as well. So, Jason, if we're going to extend this idea that we're starting to see emerge here, that there's a tech stack, for biology. That's very similar to the tech stack for IT. How do you see the industry expanding? You're touching all of these different industries through your offering, where do you see this tech stack going and how does it push the boundaries of what's possible?

Jason Kelly:
I'll make one quick comment on the data storage thing. I think it's so cool. DNA is basically the product of who knows how many millions of years of evolution, upstream of DNA to choose that as a medium, to transmit information across generations. You're going to pass on your genetics to your offspring. DNA is basically what God invented to do that. Right? It makes sense that it's so information dense. It makes sense that it uses basically no power to store that information.

It's like the evolutionary end to data storage and it's really cool. So it's really exciting to connect the dots between that and sort of our electronic data needs. So I think it's a super cool area. It's orthogonal to, well, everything we're talking about on the cell programming side, right?

Like the cell programming side is boy, we need everything for programming cells. We're so bad at it right now. We're basically writing assembly code, jamming in bits. We have no higher order to answer your question on the tech stack. There's no basic. We're writing assembly. But there's no reason that stuff can't get built. There was a day in computing where we wrote assembly. And so that's kind of what I feel like we're in today, we're sort of in the mainframe era of computing, right? Like it's, you're still at the metal, you got to be an electrical engineer to be a computer programmer.

That's sort of the era. And what we're trying to do with Ginkgo is increasingly extract more and more of that away from the end customer of the platform. In other words, take for example, a company that got built on our platforms, a company called Motif. So it's in that same animal-free meat space. They want to do egg proteins, milk proteins. They just raised a 226 million dollar round a few months ago. This is a company that didn't exist three years ago. What they did on day one was they said, all right, we're not going to build a lab. We're not going to get a bunch of laboratory equipment, hire a bunch of scientists. We're going to outsource the cell engineering to Ginkgo's platform. And they got to make use of all my infrastructure on the first day and really catch up in that area. They didn't have to be bio technologists.

You know, the folks who run Motif, they're experts from the food industry. And so I think that's one of the changes we're hopeful to make happen as the tech stack matures, is if you're an entrepreneur and you know some particular area, it could be fashion. It could be building materials, whatever, and biotech could be disruptive in that area. You could use Ginkgo, get the biotech disruption without having to be a PhD scientist. And that allows for a new kind of breed of entrepreneur in the synthetic biology space. I'm really excited to try to make that happen. Cause I think there's a lot more ideas for what to do with biotechnology and people that can bring those to market than there are PhDs like me in bioengineering. Right. So that's one of the goals.

Arvind Gupta:
Yeah. No, that's absolutely right. And it's really amazing. I know that you guys just signed a partnership with Huue as well, doing sustainable and nontoxic indigo dies. And so yeah.

Jason Kelly:
Genes for jeans.

Arvind Gupta:
That's right. Watching Ginkgo enable all of these companies I think is just utterly massive.

Jason Kelly:
Again, Huue is going to get access to a few hundred million dollars of infrastructure here and it's a 15, 20 person company, right? Like that's the idea, again, this will make total sense to people, in sort of the TechCrunch crowd. Like it's the same story as AWS, right? Amazon invests billions of dollars in data centers, so you don't have to. That's the general model here. It's not that complicated for the tech crowd – actually, for biotech people, it's a bit more of a new model. But for the tech and software people, it's pretty obvious.

Arvind Gupta:
And so Emily, I think Twist is known for its incredible ability to expand and grow. And I think you're behind so much of that. What's the driving principle behind your agility and vision? What makes this happen?

Emily Leproust:
Like you said, we are addicted to revenue growth. That's what we want to deliver. That's what our investors expect. It's three things. One thing is innovation. For instance, for data storage, we are increasing the number of features on the silicon chip by a million times, right. We go from a million pieces of DNA to a trillion. We're skipping the billion. So massive innovation and go for the really hard problems and just crush it.

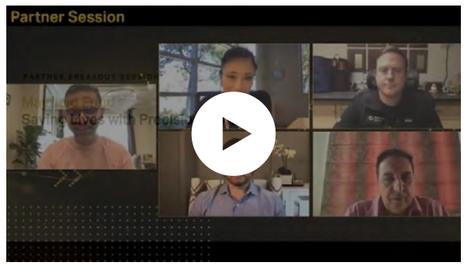
The second is, frankly, very violent commercial execution, right? You just, we have to go take market share. And so we just are very aggressive commercially. And then the third thing is the people. If you start a company, you have A level people, if you're not careful and you let the A people hire B people, the B people hire C people, and then they C people hire losers and then you're a big company. So where we're super careful to only hire A people and enable our employees to do the great things we need.

Arvind Gupta:
Amazing and yeah, clearly, right? You could see immediately why you two are not only super successful leading the way, but also two of my favorite people in the world. So I really appreciate you guys just taking 20 minutes out of your extremely busy days to speak with us and educate us on where the future is going. So thank you guys so much.

We are increasing the number of features on the silicon chip by a million times, right. We go from a million pieces of DNA to a trillion. We're skipping the billion.

– EMILY LEPROUST

Saving Lives with Precision Biology



WATCH RECORDING

Ursheet Parikh:
The session that we had with Ugur Sahin was about BioNTech's journey and how they became the platform company that has saved millions of lives for us this year. As you can see, BioNTech represents a new way of innovation, where advances in engineering, biology, and information technology come together to help us transform healthcare. We are now seeing the emergence of a whole new class of companies. Several of them will be created by our panelists in the room today.

It is my honor to introduce our panelists. First off, we have Chad Robins. Chad is co-founder and CEO of Adaptive Bio. They are powering the age of immune medicine. Chad has led Adaptive from concept to category leadership and a $5 billion market cap to build this enduring company.

With him, we also have Mostafa Ronaghi. Mostafa is the co-founder of GRAIL. GRAIL is one of the leading companies for early cancer detection. It was recently acquired by Illumina for $8 billion, and Mostafa has also been the CTO of Illumina, which is a leader in genomic sequencing. He's also the CEO of SPAC.

We also have two rising stars: First, Yan Zhang, the CEO of Mission Bio. Mission Bio unlocks single cell biology to help discover, develop, and deliver new treatments for cancer cell and gene therapies.

Finally, we also have Diego Rey. Diego is a serial entrepreneur. He was also the first bio investing partner for Y Combinator, and he's now the co-founder of Endpoint Health.

Endpoint is a precision therapeutics company that is focused on immune-driven illnesses, where one of their top indications is actually critical inflammatory disorders like sepsis. That is the number one killer of people in hospitals. A lot of COVID-19 deaths have been because of sepsis, and they are soon to be starting several phase three trials.

All of our panelists have been using the engineering marriage of biology and technology, and are going to be saving so many lives. It's truly an honor and pleasure to have all of you with me here today. Let me start with Chad. Chad, can you share with us what Adaptive does, and how that is saving lives?

Chad Robins:
Sure. Thanks Ursheet for having me on the panel today. Adaptive is an immune medicine platform. What our real goal is, is to learn how the adaptive immune system naturally sees disease so that we can diagnose disease by reading or decoding how the immune system naturally would diagnose disease, and at the same time, we can harness the power of the immune system for drug discovery.

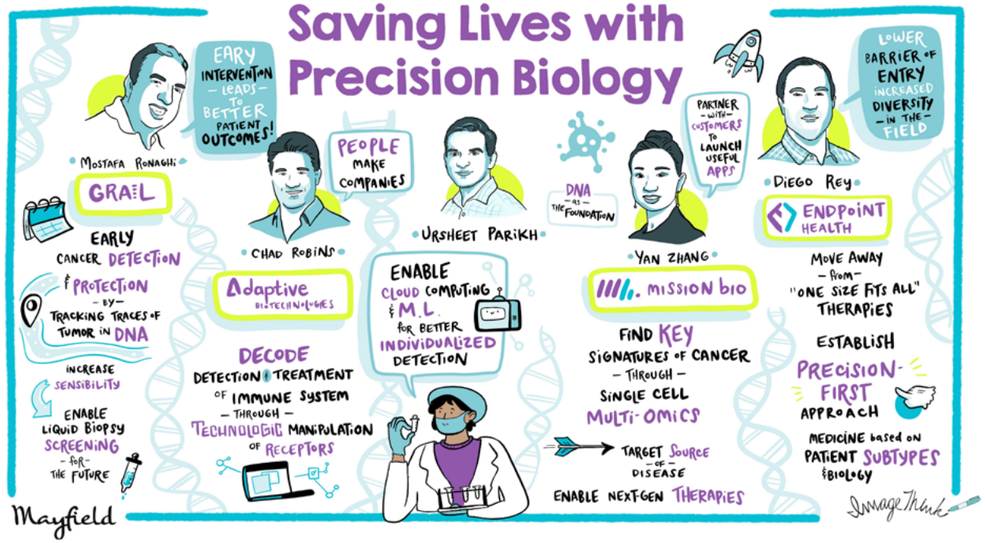
Your immune system does two things: it detects, and it treats. So essentially, what we've done at Adaptive is we've created a series of technologies to be able to decode, down to the DNA level, your immune receptors. We can not only decode them and sequence them, we can then match them to the diseases that they see and bind to, and ultimately go in and target and kill.

We've developed a series of products from research, that no matter what you're doing in the immune system, now you have a much more powerful set of tools to be able to do the research, to clinical diagnostics, to be able to diagnose disease, to drug discovery, to harness the power of the new medicine to treat disease.

We've got a couple of marquee partnerships that are helping us along the way. One is with Microsoft to be able to essentially create this extremely large map of how our bodies see disease. This is your T-cell to antigen map or T-cell receptor to antigen map, and that's for early detection of disease. We also partner with Genentech in drug discovery. We're attacking cancer in an entirely new way in cell therapy by essentially creating a personalized therapy for each patient based on what your immune system sees in your individualized cancer.

Ursheet Parikh:
Chad, that's pretty awesome, and it's great to see Microsoft and Genentech as strategic partners talking about the marriage of tech and bio.

Mostafa, congratulations again on the acquisition of GRAIL. It was a long journey. Well, can you tell our audience, what are the fundamental innovations in liquid biopsy that GRAIL pioneered, and how that is going to transform healthcare?



Mostafa Ronaghi:
Thank you Ursheet for having me at this panel among other friends. It is a pleasure to be here. The way we looked at blood was basically a switch in the body, and whatever happens in the body, it would end up in the blood, and you would see the traces of DNA. In the late 2000s, we started seeing a few publications showing that fetal DNA can be detected in the blood, and that grabbed our attention to look for basically traces of tumors in the blood system.

So, we started the research activities that ended up being four companies, actually, from Illumina. The first one was Guardant. The second one was AccuraGen, and then AccuraGenDX, and the last one was GRAIL.

In GRAIL, we took a fundamentally different approach. We had to increase the sensitivity by at least another hundred-fold to have the ability to detect cancer in earlier stages. We believe that cancer is a curable disease, and the best cure for cancer is actually surgery, but you have to detect it early.

So we started actually a multi-pronged approach, a technical approach, to tackle the sensitivity issue. Of course, cheaper sequencing helped a lot in that regard, and we expanded the panel, and we started looking at RNA, DNA, and mutilation, and then we decided mutilation is going to give us the sensitivity and specificity related to the tissue.

So, we basically created a good tool set of technologies and technical tricks around mutilation to offer the GRAIL test, and I'm happy to see that the test was launched a couple of months ago, and we're already actually saving lives.

Ursheet Parikh:
That's great. So, can we expect to just go see our doctors once a year and along with our cholesterol and diabetes screening, also start getting cancer screening?

Mostafa Ronaghi:
Yes, I do believe that, actually. This kind of liquid biopsy test is going to be the standard annual checkup kind of test. In the long run, I do believe that liquid biopsy is going to be used for other diseases, and this is going to be the first line of screening tests that you would do, replacing medical imaging in the next couple of decades. It's not going to happen in this decade, probably, as we are going to need medical imaging to compliment this data, but eventually we are going to actually replace medical imaging as a first line of screening for all kinds of diseases.

Ursheet Parikh:
Yeah, that we truly believe, and we have a company at Mayfield called Mirvie that is actually doing liquid biopsy to predict and prevent pregnancy complications, so really buy that.

Moving over to you, Yan, there's been a war on cancer for 50 years, right? How come we've not cured it? How is Mission Bio helping find cures for cancer and other genetic diseases?

Yan Zhang:
Thank you so much, Ursheet, first of all, for having me at the panel amongst some of these most prestigious and brilliant colleagues here. We have been at war against cancer for 50 years. We have not been standing still. So frankly, a huge amount of technical advancement, including for example, next generation sequencing pioneered by Illumina in the past decade has built a strong foundation for us to actually much, much better understand the genomics and the underlying mechanisms and diseases, as well as the therapeutic advancement, such as what Chad had already elucidated.

I think we're at the junction, because all of the new technologies are coming together in addition to genomics, in addition to cell biology, in addition to all of the IT and big data. We are at the cross section where we actually now have the ability and have the knowledge to go one step further, so that's where Mission Bio comes in.

Our technology is microfluidics, where we can enable a deeper understanding of biology and of diseases and therapeutics at a single cell level. We can't be here without all of the other advancements that have already happened in the past 50 years. We're really lucky to be at the intersection.

So how we think about cancer is we really need to get to the root of the disease. The root of the disease is genetics. It is the protein that it produces and the pathways. It is at a single cell level. We actually, frankly, have not won the war against cancer. A big part of that is because of drug resistance.

There was a small body of the cells, which we actually today, the therapeutics don't treat, but those are the ones that continue to evolve and respond, as well as there are many other factors that really come back stronger, possibly because of a co-occurrence of many mutations and really adaptive to the therapies.

To really understand at the single cell level and understand the fundamental genetics against them, we'll be able to help society and the community to design better drugs, design better therapies, as well as be more effective in clinical trials. So we're really glad to play a very big role, and we believe that will potentially move treating from just prolonging life for months or years to actually curing cancer.

So that's a big ambition, but we're not stopping there. Using the tapestry platform at the single cell multiomics, we actually also play a very big role to be the analytical platform for cell gene therapy. As Chad mentioned, cell gene therapy is really the new frontier of treatment of not just cancer, but many genetic diseases.

These rare diseases cumulatively account for hundreds of millions of people who suffer, and many of them don't have cures, and in the past we tried to cure symptoms, but with the new gene and cell therapy, we can actually cure the disease itself by making changes to our human genome.

But it is the frontier. The frontier is going to require the whole ecosystem to help support those new therapeutic ideas to be a reality to be successful. So by deploying single cell multiomics, we can help the industry to better understand the therapeutics, to characterize and quantify the therapeutics in terms of the safety, efficacy, to actually accelerate the development and quantification, and help deliver them back to the patients. So we are extremely excited to participate and to lend our hand to this entire ecosystem so we can, as a society, win the war.

Ursheet Parikh:
Yan, that's well summarized. I think someone I respect just mentioned that they look at you as an ETF for the whole sector, because you are powering and enabling so many... An exchange-traded fund for the whole sector, because you're empowering and enabling so many of these next gen therapies. Diego, I got to put you on the spot. I get to work with you. Mayfield's been partnering with amazing entrepreneurs from inception, be it founders of Genentech, Amgen, Millennium Pharmaceuticals. But when I met you for the first time, I really paused, and just to be sure I'd heard right, because you said you wanted to reinvent pharma. Endpoint is well on its way to building a new class of pharma company, so tell us how.

Diego Rey:
Sure. Thanks, Ursheet. Great to be here. Yeah, didn't mean to really pick on any particular company, but in the past, pharma companies were built on what I would call a molecule-first approach, and it's because this is what really worked. Taking a molecule and then turning it into a drug is a huge feat, so it made sense to start with a drug, and then to see what illnesses can the drug actually go and help.

One of the issues, though, is that this approach can lead to a one size fits all therapy that doesn't always work for everybody.

Today, the world is very different. Now we have new enabling technologies and infrastructure that we've been discussing here, thanks to companies like Illumina, and these things really enable us to harness a huge amount of biological data that we couldn't before.

So, instead of starting with a molecule, we can now start with a, very much like Chad said, start with individual patients and data from these individual patients, even within the same illness, and then figure out how to help each of these patients based on their unique needs.

Endpoint is a therapeutics company with what we call a precision-first approach that is really only made possible today. So, instead of starting with a molecule, what we do is we start with patient biology to develop and later commercialize new medicines based on patient subtypes that we can go in and identify. At the end of the day, we believe that this will enable enormous improvement in patient outcomes.

> In the past, pharma companies were built on what I would call a molecule-first approach...one of the issues, though, is this approach can lead to a one size fits all therapy that doesn't always work for everybody.
>
> – DIEGO REY

As an example that you highlighted earlier, in critical care, where we're starting, this is an area where there's more deaths than there are in all cancers combined, and at the same time, it's an area where there are very few, if any, effective therapies. So this is an area with this approach that we think will bring to market some of the first life-saving therapies for these patients.

So, to answer your question, I think what we realized is that a fully integrated therapeutics company with a precision-first approach is not only now possible, but it's really, really badly needed, and so we're building it, and that's Endpoint Health.

Ursheet Parikh:
So in many ways, what you're saying is you're really focusing on truly understanding the disease and subtyping the disease, and then finding what would be the best treatments for it. Well, we really wish you a lot of success because we do want to see these treatments come to market. Earlier this year I spent about 10 days in an ICU for a close family member, and that was very sobering.

Chad, moving on to more fun stuff, how are you looking at the convergence of biology and technology, and how do you see that transforming healthcare, and what is the next frontier for it?

Chad Robins:
Yeah, sure. I thought, because this is traditionally a tech conference, I would give an analogy that I think is applicable to the audience, although I do have to say that probably one of the largest opportunities in tech is this convergence and this application of technology and machine learning to biology.

But if you think about it, and because we have Mostafa here, we'll take a little bit, think about this as 1.0, 2.0, 3.0. If you think about the hardware, 1.0 being the IBM, if you will, over time got faster, cheaper, smaller, easier to use. The same thing happened with sequencing, right? You had these large sequencers that took up pretty big areas that got smaller, faster, cheaper, easier to use, and now if you think about that, that is really 1.0. 2.0 is, what are the applications of these machines in the parlance of tech. Microsoft came along and made it so that the everyday person could use these machines. So 2.0 to me is how do you use this instrumentation for diagnosis and/or drug discovery? I think my 3.0 is really now layering on machine learning on top of that, which is not just machinery. It's the power of cloud computing and machine learning that now can take the information that's generated from these machines and the applications on top of these machines to then make a patient decision.

Another thing that Mostafa said is the concept of early intervention leading to better patient outcomes. So now, and I will also say that what Diego and Jason are doing at Endpoint Health is really sifting through this information combined with biological information to determine how these drugs are going to work on patients on an individualized basis based on their biology.

Specific to Adaptive, and you asked what's next in the new frontier, I'm going to highlight our work with Microsoft, explain how that works, which is essentially... Let me first give you some biological stats. The human genome is fixed, right? You've got about 30,000, other than some pointless mutations, you have 30,000 genes in the human body. Your immunome, or your adaptive immune system genes, each person has about a trillion of them in the body, about a hundred million unique. In the population, there's about 10 to the 16th or 10 to the 18th, like trillions of choices.

Why I'm saying this is because our body's job is to be able to recognize anything, any potential invader, anything foreign that it could potentially see, find it, and then go kill it.

So what we're doing with Microsoft essentially is building this massive map between your T-cell receptors or your immune receptors that recognize disease and antigens. Antigens are signals of a disease. So, what happens is every disease has editors that are specific for that disease, and it's a little flare, think of it. It goes up on the outside of the cell, your T-cell recognizes it, it springs into action and kills it.

So the idea in, let's use Microsoft Excel since we were on the tech analogy, we're essentially building this massive VLOOKUP table, disease by disease, between your T-cells and your antigens.

We're able to feed that through chemistry, some proprietary assets or technologies that we have, where we can physically start creating these connections. But that only starts it going. What happens is then Microsoft on top of that, we have all this machine learning to impute and come up with more connections that essentially build out that map.

Now the idea, and you asked about, hey, when can you go into a doctor's office and get a screen for cancer? The idea here is that we'll start with one disease at a time. We did this for COVID, and T-Detect. There's a franchise called T-Detect. We did T-Detect COVID, we're now doing it for Lyme disease. We're also in process for irritable bowel, basically a differential diagnosis between Crohn's, IBS, celiac. So if you walk in with the same set of symptoms, we can rule in, as opposed to a rule out test, where you go from specialist to specialist, doctor to doctor over a two-year patient odyssey, now we can definitively diagnose based on your immune receptors, based on your body, what it's seeing, referencing this map. We were never going to get every receptor, so again, that's where this machine learning power comes in and says, we can be 99.99% confidence that if you have a receptor, that it binds to a certain antigen, and that's specific for the disease, so you can reverse diagnose disease from the receptor itself.

So that's what we're doing, and eventually going from one disease to differentiated panels or differential diagnosis to essentially an immune checkup, where you go into your doctor's office, and we've mapped hundreds, if not thousands of diseases, including our approach to cancer, which is instead of looking at the cancer itself, we're looking at the immune response to the cancer that clonally expands, and it might be complementary to some of the liquid biopsy approaches that GRAIL and others are doing.
So, that's really the next frontier for us is diagnosing disease essentially from reaping your immune system.

Ursheet Parikh:
That's amazing. We are going to get truly a fundamental understanding of the human state and the state when things go off track, so that's great. Mostafa, what are the big entrepreneurial and investment opportunities you see?

> I'm very hopeful that cell therapy is going to be the next generation therapeutics.
>
> – MOSTAFA RONAGHI

Mostafa Ronaghi:
I'm actually very excited about the rise of cell therapy. That's an area that has shown a lot of recent progress, and we see that there's actually is working on a lot of different approaches that have been implemented, so I'm very hopeful that cell therapy is going to be the next generation therapeutics, at least against immunological disorders like cancer and other diseases and so on. Chronic diseases.

The single cell technologies and the spatial biology approaches are a trend that's going to continue. We really need to have the same cost trajectory as we had for sequencing to reduce the costs, to tackle this issue, to provide much more comprehensive information to understand the cells much better. The tool sets like synthetic biology tools are very exciting now actually being implemented in cell therapy, and it's giving you actually the specificity and the sensitivity for the therapy.

Ursheet Parikh:
Yeah. Yeah, I think that the ability to truly engineer the cells and the genome and how that creates therapeutic effect along with an ecosystem that allows for mass production on these things. I think these are so fundamental, so seminal, and clearly a big area of investment for us at Mayfield.

Diego, I wanted to get to you next. You've been an entrepreneur and an investor at YC. How do you see company building in engineering biology different from just a tech or a software company?

Diego Rey:
Sure, yeah. Actually, maybe to start with a similarity, based on something that Chad mentioned, he put it I think really well that I think that because of all these advancements in technology and infrastructure that we're seeing, we've been discussing here on the panel, I think the barrier to entry to building companies in engineering biology has really lowered. So now, we can really build applications, just like Chad said, in an analogous way maybe that the tech industry went from, for example, building chip foundries to building apps.

> In our small company, we have statisticians, bioinformaticians, engineers, and biologists - all of us, and then we come together to solve one single problem. I think that's amazing.
>
> – YAN ZHANG

So I think this has really opened the door to a lot of first-time founders, and this is now increasing diversity in our field, which is really a great thing. At the same time, I think unlike tech, engineering biology still takes a lot more time. Sometimes it could cost more, and it also takes more diligence from an investor as well, so those would be some key differences.

Another observation though is actually one from a former colleague of mine, Jared Friedman, a partner at YC, and what he pointed out was that life sciences founders, from his point of view, of all the companies YC is seeing, they now have over 400 life sciences companies. He's noticed that life sciences founders are more hesitant to start a company, even though in many cases what they've developed is more mature than what most tech founders have when they're starting their company. So, I'd say that we really need more life sciences founders to go and start their companies.

Ursheet Parikh:
Yeah. I mean, I recognize that while there's a lot of similarities, one thing is that the business of moving atoms has always been harder than the business of electrons, right? Software has been amazing because you can sit on your laptop and just move electrons and magic happens, and so it becomes easier to iterate, pivot, all of those things like that, and it does require a different mindset and view.

But you're right that what has been amazing is that 20 years or 10 years ago, starting one of the life sciences companies required $10 to $20 million, and now we have a very, very large number of amazing companies that we started out with the first couple of $200,000 to $300,000 with a whole ecosystem here in the Bay Area. So, that's great.

Yan, we are clearly very impressed with you and your leadership at Mission Bio. Given all the opportunities you had, what made you pick Mission Bio as the company to lead?

Yan Zhang:
Yeah, great question. I'm still learning to be an entrepreneur, I feel like. I spent about 20 years with the larger companies, but it's such an exciting space to be. But I think how we can be successful, is the intersection we talked about the building applications. That's Mission Bio's philosophy. We're not launching just a platform, we're really launching the applications. But in order to be successful in identifying those applications, killer apps, and actually be useful, and translate that to market acceptance, we have to collaborate and partner very closely with our customers. In this case, academic cancer center KOLs, or the pharma companies, other entrepreneurs, to make sure our tools and our applications can meet their needs.

So that's what's really attractive to me is that to be able to come with a commercial mindset and really collaborate with a lot of creative minds who are driven by technology, but bring those creative minds together, while really solving a practical problem with the partnership. I think that's an amazing thing. In our small company, we have statisticians, bioinformaticians, engineers, and biologists, right? All of us, and then we come together to solve one single problem. I think that's amazing. That's what I think we can do together to achieve the unthinkable from the past.

Ursheet Parikh:
Got it. So it's like you pretty much found Mission Bio to have this platform that then allowed you to build applications around different disease areas.

Yan Zhang:
That's right.

Ursheet Parikh:
And really make it easier for various drug developers to develop that.

Yan Zhang:
Yeah.

Ursheet Parikh:
That's great. Chad, you did a bio platform company in a decade when most bio platform companies failed, right? Is there one or two things that you can talk of as how you succeeded while most of your peers didn't make it?

Chad Robins:
Well, truth be told, we had a vision that the immune system absolutely was a platform. Platform was a dirty word when we got started, but my brother and I had no experience in biotech, so we really had no other opportunities for funding. So we said, hey, we're going to go with our vision, and before we raised a hundred million dollars five years later, we bootstrapped it with friends and family money.

Essentially, we're trying to land a rocket booster on a platform in the middle of the ocean on a pretty frequent basis, and in order to do that, we have got to get people to believe that the impossible is possible. We're trying to cure cancer. One of the things that we're doing with Genentech is essentially, Mostafa talked a lot about cell therapy, but that is what we're trying to do. Vein to vein, we're trying to essentially see how your immune system sees your individualized cancer, take that out, reprogram it, put it back in 30 days, and have an individual therapy.

So to do that, people have to believe, and that means you have to create an environment, you've got to create a set of values and culture that really allows it. People make companies, right?

Ursheet Parikh:
Yep.

Chad Robins:
We've got great technology and IT, but it's the people who make companies. I call myself a CCO or the chief cultural officer, and probably the most important job that I do is to hire and retain the best talent and create a culture that makes people believe that we can do the impossible.

Ursheet Parikh:
That is so well said and it's something we believe in so deeply. I think we're almost out of time, and so I was going to leave with the last question for Mostafa, on what would you pick as one silver lining coming onto the other side of COVID?

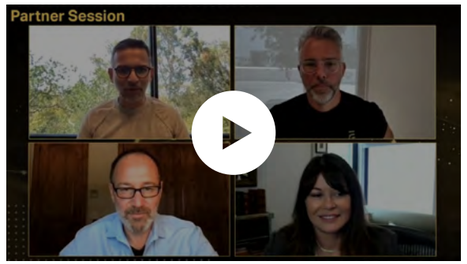
Mostafa Ronaghi:
I think the opportunity in biology has expanded vastly, and I'm happy to see a lot of entrepreneurs from other spaces actually coming into the biology space, like Chad. It's amazing to have those mindsets.

The funding environment is actually very healthy, and this is going to continue for the next few years. Love to see foundational technologies and also foundational therapies, therapy platforms that will emerge in the next decade.

> Essentially, we're trying to land a rocket booster on a platform in the middle of the ocean on a pretty frequent basis, and in order to do that, we have got to get people to believe that the impossible is possible.
>
> – CHAD ROBINS

Ursheet Parikh:
That is awesome. Thank you so much, Chad, Mostafa, Yan, Diego. Delight to have this conversation with you.

Rewiring the Brain to Improve the Quality of Life



WATCH RECORDING

Ursheet Parikh:
What we are going to talk about next is really more mind-bending than my favorite movie Inception. I've always been fascinated with the brain, but at the same time just frustrated by how slow new treatments for our physical and mental health that involve the brain have been in coming to market. It's not uncommon for new treatments to take 10 years only to find that they don't work and cost several hundred million dollars. We think that part of it is because the brain is just a very unique organ. It's different between animals and humans, so a lot of the traditional sort of drug development pathways don't work. It's also designed to keep drugs out of the brain, but at the same time, it's very, very pliable and constantly forms new connections based on what we see, what we think, what we hear consciously as well as subconsciously.

And so we thought that it's time there was a new way, so we started thinking about rewiring the brain. And at Mayfield, we believe in partnering with pioneers. None of them are bolder than the ones who are going to be on this panel, who are rewiring the brain to make our lives better. It sounds like science fiction, but this is all very real. And we'll look to our panelists to convince us what they're doing is real here and now. And so with that, it's with delight and pleasure that I get to introduce this amazing panel of serial entrepreneurs. One is a former gaming executive, one is a neuroscientist, one is a physician, and they're all building breakthrough businesses that involve working with the human brain.

First off, we have Nanea Reeves. She is the founder and CEO of TRIPP. She's also a former gaming exec and she's building a digital psychedelic platform that exposes us to alternate realities for improving mental and emotional wellbeing. We also have Konstantinos Alataris. Konstantinos is an entrepreneur that has actually built one of the biggest successes in the human computer interface world. He did a company called Nevro, which is a spinal cord stimulator to alleviate pain. It's a $5 billion company, and he's on doing his next company Nēsos. Nēsos is purpose-built earbuds that actually connect your brain to activate it and get it to control your immune system. It's a new class of therapeutics called e-muunotherapeutics and we are excited to hear about what he has to say and where they're going.

And then finally, we have Paul Dagum. Paul's the former CEO and founder of Mindstrong Health, which is transforming mental health with virtual care data measurement and data science. And he's onto his next company called Applied Cognition, and that's addressing disease conditions in neurodegeneration, like Alzheimer's. So Nanea, Paul, Konstantinos welcome. Glad to have you all with me today. Paul, let's start with you. What is your vision for Applied Cognition?

Paul Dagum:
Thank you for having me on your panel, Ursheet. Today we have 47 million Americans who have preclinical Alzheimer's disease.

Those numbers are growing, and many of them will progress to cognitive impairment or dementia. Our mission is to develop the first FDA approved digital therapeutic for Alzheimer's disease.

Ursheet Parikh:
And how is this going to get delivered?

Paul Dagum:
How far have we gone in our vision? We've assembled an amazing team of micro technology engineers, material scientists, product and industrial designers, mechanical engineers, software engineers, clinical scientists and Alzheimer's neurologists. They each come from iconic institutions, have achieved tremendous individual distinction in their respective fields, and they share our passion for our mission. Where we're at in terms of development, we are using and leveraging advances in microtechnology, in material science and AI to develop sensors that can measure the neuropathology of Alzheimer's disease in an unobtrusive and continuous way.

Ursheet Parikh:
That's pretty amazing. As you were talking about sort of the type of team members that you have, it's amazing that so many different disciplines are coming together to take on what has become the big... While we are in COVID and there's one pandemic, they're dealing with the long term epidemic around mental health.

So delighted to see you out on this journey. Nanea, what is your mission and inspiration for TRIPP?

Nanea Reeves:
Well, I think the thing we're most excited about at TRIPP is really believing in the future of computing moving from the hand to the head and being the next gen wellness application for that transition. We're very much committed as a team to create heart-centered experiences that help people transform the way that they feel, but we work very closely with academia and medical in the neuroscience community to make sure that we're measuring and validating all of our design choices. And it's a very cool experience, it sits somewhere in between mindfulness, producing the effects of mindfulness and psychedelics, and we deliver through VR and AR currently.

Ursheet Parikh:
Yeah. I've seen that it's featured as one of the top applications on Oculus.

Nanea Reeves:
Yeah.

Ursheet Parikh:
What are the other platforms besides Oculus?

Nanea Reeves:
We're also on PlayStation VR. So that gives us the largest audience in XR wellness to date. And we very recently launched on the Nreal glasses, our first wave of augmented reality experiences. So we think of it less vertically about VR versus AR, really there's a convergence into one device that we'll see over time. It's really, for us, about how do we innovate around reality layering and do that all within this wrapper of creating beneficial experiences. And it's kind of a narrative violation to use tech for making you feel better, but we really find that that mission is really exciting, not only to the end user but also to attract really great talent who want to use their skills to make a difference in the world.

Ursheet Parikh:
Yeah. I know, a lot of the smartest people of my generation have spent their life creating digital addicts, selling digital dope.

Nanea Reeves:
Yep. Yep.

Ursheet Parikh:
I'm sure lots of my friends are excited about the prospect.

Nanea Reeves:
Yeah. And you think about using AI in ways that we have in the past to manipulate you to feel so badly about yourself that you'll buy something to fix you. Can we kind of reframe that in ways that make you feel good?

Ursheet Parikh:
Great. Konstantinos, you've had an amazing history even before starting Nēsos, but what inspired you to start Nēsos and what does Nēsos do?

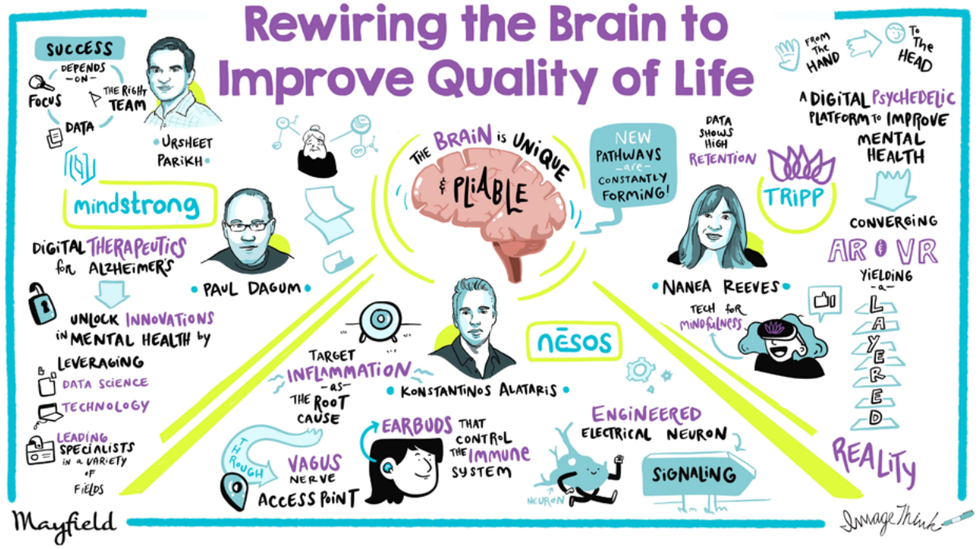
Konstantinos Alataris:
So for us, a starting point, frankly, was the role of inflammation – understanding more research around chronic underlying inflammation as one of the root causes in many diseases, from mental health, neuropsychiatric, neurological and autoimmune disorders. The other part of this equation was the fact that there is a lot more research and understanding. First of all, understanding that the brain and the immune system are in communication and interaction, constant interaction, with something that kind of recent in the last 20–30 years, we kind of understand more. And there is masonry through which the brain, not only senses, but can control inflammation levels mainly through the autonomic side of the brain.

So that, for us, those two elements and previous work that we've done that allows us to start interfacing with the autonomic part of the nervous system give us the idea that maybe now we can target this pathway that controls inflammation through engineered neural signaling. So that's kind of what we're trying to do and right now the best way to prove it is going to the clinic. So we have three programs in the clinic that span neuropsychiatric to autoimmune diseases.

Ursheet Parikh:
Konstantinos, that's great. I'd love to get into exploring - how do we know this stuff is real? But can you just elaborate a little bit more on how the product works? Do I kind of inject myself, do I get operated on to put something in my head? What made it possible for you to sort of go from that category of products that you did 10 years ago to this new category of products?

Konstantinos Alataris:
Yeah, a little bit, the anatomical solution was that there is a branch of the vagus nerve, which is a big part of the autonomic nervous system, that actually is external, outside of your ear. So we have an access point.

So for us, the access point is on the outer ear and the way we're accessing or delivering the therapy, which is engineered nerve signals, is through an earbud.



So that's what makes it a kind of a form that people are familiar with and easy to use. So these are earbuds that you need to place in your ear for a few minutes a day. And through that, we're trying to intervene into that masonry and retrain it to control it as it used to, because we know in the disease progression, it stops controlling it as well as it used to.

Ursheet Parikh:
Just mind blowing, right? No pun intended that you actually put a new kind of airpod and you don't listen to any music through it, but it kind of goes and tells your brain to activate the immune system to fight disease.

This does sound like science fiction. So how do we know this thing is working? Why should people believe this stuff is real?

Konstantinos Alataris:
Well the clinical data, which is from one study, we've published in the Lancet, the rheumatology edition, and there are more publications coming up. There is quite a lot of research from many academic institutions and researchers that have published the data that have shown the connection, the ability of that pathway to relate information to the brain about inflammatory levels.

But also the other way from the brain to send instructions to the spine in order to modulate pro inflammatory cytokines. So that pathway has been very well enumerated, right now we're trying to see how well we can restore that pathway.

And there are other approaches with more invasive tools. For us, given that we have this access point, we plan to fully explore that among different indications. So that's how we came here.

Ursheet Parikh:
That's great. Yeah. I've seen your paper that was published in Lancet, which is unlike a lot of the other journals like Nature and Science.

All the doctors I know do read Lancet and the fact that the success of your first trial was covered in that and now you're running randomized control trials.

So the net of what I'm taking is that you're going to say, "We're going to let the data do the talking." And it won't be on just surveys, it'll actually be on diseases, like rheumatoid arthritis, where you actually have objective endpoints that you can see in x-ray to show that it kind of works out on that end.

Konstantinos Alataris:
For us, just because of the diseases that we're trying to treat, there's very well defined endpoints. So the data has to talk and develop the credibility around this therapeutic approach. I think that's the best rather than pointing to preclinical work, which is relevant at the beginning. Now we're in the clinic, as you said, we are doing randomized placebo control studies.

Ursheet Parikh:
Yeah, so Nanea, Konstantinos is actually going with a pure therapeutic label and so he's going to go do the trials and then prove it and then kind of get the claims. You have dipped in the market available to consumers as we speak. How are you demonstrating the effects and the benefits of TRIPP?

Nanea Reeves:
Well, we don't currently make any claims on efficacy, especially with the consumer product. We think there's a lot that can be done to support people in the subclinical dimension with our wellness offering. But what we have found is that the body of data being produced by our service, we collect survey data in app with every session. And now because we have a significant audience producing over two and a half million sessions, that data actually has become very meaningful to researchers, et cetera. It's enough data to train AI as well. So in addition, though, we have throughout the years, and it does move at a much slower pace than my startup motor, we've stood up some clinical trials. We have received funding from the national institutes of health, specifically, NIDA, for use in addiction recovery. We are now approved to move into phase two on that research.

I think coming from a sense of purpose will help you stay narrowly focused on surviving as a startup, especially in the face of opposition. It keeps me going to know that I really do feel mission driven and I think anything is hard to do, especially from the ground up.

– NANEA REEVES

We have some exciting RCTs up and running with the New York Office of Mental Health and other entities analyzing our product and the effect on their population. So eventually we could start to target more focused interventions for different in indications, but right now we see that the data itself that our services producing has really helped just harden our engagement in a way that a lot of the other clinically focused XR companies aren't able to do at the scale that we have. We have excellent retention. And when you look at even the attrition rate in clinical trials and XR wellness, especially in mental health apps, we're blowing doors off that data currently with our largest monthly cohort using TRIPP four months or longer. And so for any kind of intervention, if you don't have adherence and especially in a digital therapeutic, I think it is going to be a commercial failure after years of development.

Ursheet Parikh:
Yeah. I think you touched upon two very key points. One is you want to have these products and that these products have to engage. But the second is that these are sort of connected products and you get a closed loop view and the data actually helps make the treatments better over time.

Nanea Reeves:
Correct.

Ursheet Parikh:
And so that kind of accelerates the pace at which new products can kind of be created. Paul, what would you like to tell the audience who say this is sounding like science fiction? How do you sort of convince them?

Paul Dagum:
Yeah, I think what I would say to the audience is, I think we all are aware of, there's a tremendous amount of research in Alzheimer's and we're really tapping into amazing work being done by scientists and clinicians around the planet. One of the things that we've learned recently in the last few years is the interplay between neurophysiology, cerebral vasculature and neurovascular that you're coupling and the importance of that house and the neuropathology of Alzheimer's. So what we're doing is we're tapping into that mechanism and we're instrumenting it and hoping to be able to measure target engagement of our therapeutic interventions. I think a lot, like what we heard from Konstantinos, our journey is a regulatory pathway so we have to be very scientific and evidence based. And the bar is the FDA at the end of the day for us. So that's what I would share with the audience.

Ursheet Parikh:
Yeah. It's great that while these things can kind of be made to work in a certain way that you guys are putting this level of sort of rigor in development, because for a whole new class of acclaim that is so groundbreaking, that level of rigor is going to be key to adoption. I think we're going to be out of time soon. And so I want to move to a lightning round. All of you are immensely successful, I believe no success is accidental. And so, what would be the one learning that you have from your journey so far that you'd like to tell our audience, right? Nanea, do you want to go first?

Nanea Reeves:
Sure. I think coming from a sense of purpose will help you stay narrowly focused on surviving as a startup, especially in the face of opposition. It keeps me going to know that I do feel mission driven and I think anything is hard to do, especially from the ground up. So if you don't have that connection, it's going to make it infinitely much more difficult to succeed.

Ursheet Parikh:
Yeah, no, that's that's well said. Paul.

Paul Dagum:
Yeah. I would share that from my experience going from science to product takes a lot longer than you think. And so I would encourage young entrepreneurs to find patient investors.

Ursheet Parikh:
Thanks. Konstantinos.

Nanea Reeves:
Like Ursheet.

Konstantinos Alataris:
Well, for me, it's always coming from a culture that talks about the journey, but the journey is about the people that you go with. I do believe that the people that come with you, the team, has importance even as far as making the right steps to discover what's in front of you. So although I went alone, you shouldn't go alone and the people that are with you determine your success. That's my lesson.

Ursheet Parikh:
Well, that's very well said. At Mayfield we've had this strong people-first philosophy and it goes back to our founder, Tommy Davis, who started Mayfield in 1969. He famously said, "People make products. Products don't make people." And so I think mission, purpose, patience, people, are all hard learned lessons, but as relevant as they've always been. I could go on for hours with you guys, right, I mean, there's just so much that I think you guys have to offer and so much fun we could have talking about more stuff. But I think we are out of time and thank you, Nanea, Paul, Konstantinos for making this happen and thank you TechCrunch for hosting us.

I would encourage young entrepreneurs to find patient investors.

– PAUL DAGUM

I do believe that the people that come with you, the team, has importance even as far as making the right steps to discover what's in front of you.

– KONSTANTINOS ALATARIS

Taking Care of the Next Generation

WATCH RECORDING

Kamini Ramani:
Welcome, everyone. I'm Kamini Ramani, CMO of Mayfield, and I'm thrilled to chat with three amazing entrepreneurs who are taking care of the next generation by making our world safer and healthier for families and kids. To start at the very beginning of life, we have Maneesh Jain, a serial entrepreneur of many breakout healthcare companies, including as founding CEO of Cirina, which was acquired by GRAIL, which is now part of Illumina. Maneesh leads Mirvie, which is redefining pregnancy health with an early detection RNA test. Welcome, Maneesh.

Maneesh Jain:
Thanks, Kamini. Pleasure to be here.

Kamini Ramani:
Next, we have Sandra Oh Lin, an engineer and the former head of eBay's fashion business, who leads KiwiCo, which has delivered over 25 million creativity kits to everyone starting from newborns to the kids at heart. Welcome, Sandra.

Sandra Oh Lin:
Thank you, Kamini. It's great to be here.

Kamini Ramani:
And finally, we have Stu Landesberg, a former TPG private equity executive turned founder of Grove Collaborative, a digital-first eco-friendly CPG brand and marketplace. Welcome, Stu.

Stu Landesberg:
Glad to be here.

Kamini Ramani:
So to start with, can each of you take us back to your founding moment, which propelled you to start your company? We'll start with Sandra, whose company KiwiCo is about a decade old, followed by Stu, and then finally with Maneesh. Sandra.

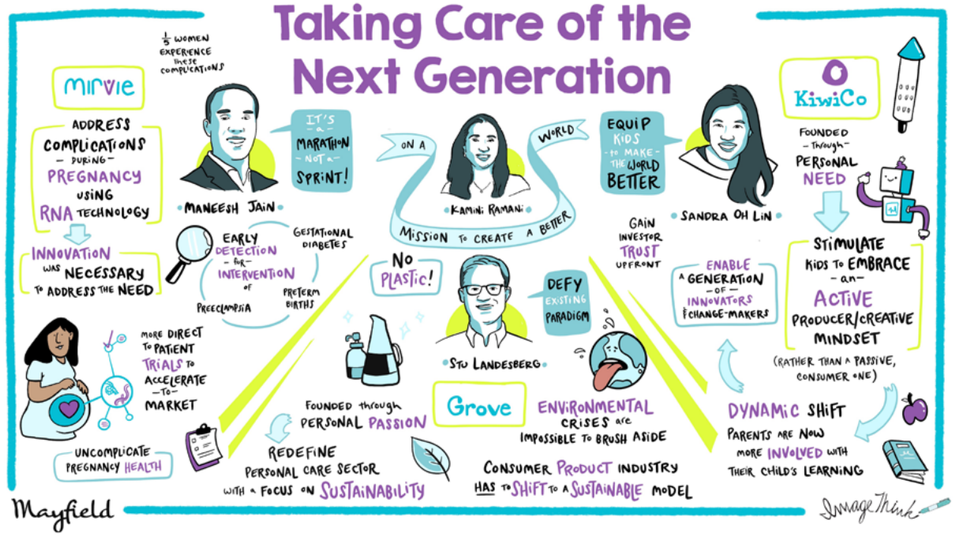
Sandra Oh Lin:
Absolutely. So KiwiCo was born partially out of personal need. My two youngest children were getting to that age where I wanted them to get hands-on. I thought it was a great outlet for them to exercise their creativity, see themselves as makers and creators. And so, I started to pull these projects together. And as an engineer by training and as kind of a maker and creator growing up, this was something that was really important to me so that hopefully they would see themselves as producers and not just as passive consumers. And as I started to pull these together, lo and behold, I was not the only busy well-intentioned parent that wanted these types of enriching activities for their kids. And so that's how KiwiCo was born. And we still continue to pursue that vision and mission, not just for my kids now, but for millions of kids around the world.

Kamini Ramani:
Thank you. Stu.

Stu Landesberg:
So love that story. Grove was also born from a personal passion for the category. Grove seeks to redefine the home and personal care categories – hand soap, dish soap, laundry detergent, paper towels, shampoo – categories that have for a long time been a harmful force in human and environmental health in many ways. The founding moment for Grove really came after a lifetime of being focused on sustainability. In my prior life I came head-on with the reality that although the majority of consumers prefer conscientious products, in broad distribution in most retail outlets, the vast majority of shelf space and the vast majority of purchase still goes to conventional brands. And so I started Grove really to change the category and change the products that people are buying to ones that we can all feel really good about in terms of the impact that the products have not only on us as people, but also on the planet around us.

Kamini Ramani:
Sounds great. Maneesh.

Maneesh Jain:
Thanks. That's much needed for sure. Our story goes to the beginning of life. And so, the problem we're trying to address is really the unexpected complications that develop in pregnancy. I think the statistics here are just staggering.



One in five women experiences complications like a preterm birth or preeclampsia, gestational diabetes in the course of pregnancy. And it's about five times the rate of cancer incidents.

So for my co-founder Steve Quake and I, it was not just a statistic. It was also personal. We experienced unexpected complications through our own journeys to becoming parents, respectively. And our founding moment came really in the summer of 2018. So Steve had spent about 10 years at Stanford with an international collaboration using RNA technology to predict complications like preterm birth months in advance. And I had just come off developing the first early detection test for cancer at Cirina and GRAIL. And so we knew this was possible and we really felt compelled by having a potential solution to address this big need, which can help families right at the beginning.

Kamini Ramani:
You know, all really important stuff. Thank you. Thank you for your vision and your dedication. And we are proud to be partners with you on this journey. Maneesh, the life-saving stuff you've built has got to be just so needed in the world and so easy to deliver, but it's incredibly hard to get it to market. Why? And what are you doing about making it easier?

Maneesh Jain:
Yeah, great questions. I think, particularly as we look at women's health and pregnancy health, we know that it really hasn't had a lot of innovation for decades. And I think there are a few reasons.

One is that historically it's been an area that's underinvested, and certainly, Mayfield and other firms are helping to change that. So we definitely appreciate that. The second piece is that technology was really not available to tackle the complexity of biology for some of these conditions. And that's changing as well with our RNA technology. And finally, frankly, a lot of the talent has chased cancer diagnostics and cancer therapeutics.

And so it's time to move some of that to women's health, and we are hoping to make that difference as well at Mirvie. I think finally, I'll just add that I think aside from those more systemic factors, just the process to get these products to market, to get innovation to market, is rate limited by clinical trials. And as we all know, it can take very long. It can be very expensive. And that really is a barrier sometimes to innovation getting to market, particularly in this age of the pandemic where that has been exacerbated.

So one of the areas that we really had to innovate around was to do more Direct-to-Patient trials. So we could really accelerate that path to market, and we are being fairly successful there. So potentially, that's a new paradigm to accelerate innovation to market.

Kamini Ramani:
Thank you, Maneesh. And I'm glad to see that you've been able to thrive even during the pandemic in terms of achieving your goals. And I know that interestingly enough the pandemic, Sandra, has been a force that's actually lifted your business in the era of Zoom school.

Kids like Stu's daughter interrupting his Zoom calls routinely and parents being more involved in their kids' lives. How have the needs of modern families changed, and how has that actually accelerated KiwiCo's adoption?

Sandra Oh Lin:
Yes, we've all been there, Stu. So I can definitely empathize with those moments. Yeah. I mean, I would point to a couple of things that we've seen in terms of the dynamic shifting and families really evolving. So one is for sure I think parents have become much closer to their children and not just in terms of perhaps being physically stuck with one another at some point at the beginning of the pandemic, but really beyond that. So if you think about having a real front-row seat into your child's education, that is something that definitely happened across the US and around the world. And so you see the combination of virtual schooling or schooling from home, learning from home, as well as schooling in school. Those two are coming together, and there's a real partnership between those activities. So the learning that's happening at home, as well as the learning that's happening at school.

And I think that what we're seeing is, as kids head back to in-person school, we are continuing to see that partnership remain relatively strong as parents lean into their kids' educations. The other thing that I would point to is I think generationally, you end up reflecting and saying, "Are we teeing up this world in a way that's better for the next generation?" And I think given where we are right now and in the situations that we're in, I think parents are really asking themselves this question. Is the world better for this next generation, with the divisions that we see, with a raging pandemic, with climate change, et cetera?

And so, what we are trying to do as parents then is think of ways in which we can actually equip our kids to become those creative problem solvers. To become those active citizens, to become those people, hopefully in the future, who can envision this better world and actually make that happen. So that's another thing that we're seeing these days too.

Kamini Ramani:
That's amazing. And you know what? You don't need to talk to Stu about climate change. He lives it. I'm so sorry about Hurricane Ida and the Tahoe wildfires. It's a scary place to be in the world.

And so, Stu, what I wanted to ask you was, you're upending an industry in CPG, which has classically been known as a bad player when it comes to plastics and other things.

So how are they reacting to this climate change acceleration and environmental disaster zone that we're going into?

> What we are trying to do as parents, then, is think of ways in which we can actually equip our kids to become those creative problem solvers. To become those active citizens, to become those people, hopefully in the future, who can envision this better world and actually make that happen.
>
> – SANDRA OH LIN

Stu Landesberg:
It's really interesting. I feel like we...many of us grew up in a time where the brewing environmental crises were optional to pay attention to, right. It feels only like in the last few years that it has become so in our faces that climate change is going to change all of our lives. And I think when we look out at our industry, consumer products have been a huge contributor to many of the environmental crises that exist today.

To take probably the single largest issue there just as an example. We, as a society, create one trillion pounds of plastic, with a T, every year, one trillion pounds, of which almost half is single used plastic packaging that's used for less than six months. And the industry that contributes sort of in the biggest weight of that, I bet you can guess, is the consumer products industry. So this is an industry that absolutely needs to change. But it's also an industry that's invested, truly, hundreds of billions of dollars in building brands and physical infrastructure around legacy products that have negative footprints. I mean, if you imagine, for example, your laundry room as a kid. Think of what color the laundry bottle is there. It's the same color you imagine in the laundry aisle, right? That is an iconic piece of plastic that generates billions of dollars of free cash flow every year and has billions of dollars of infrastructure behind it.

The challenge for these companies, and I think one of the reasons that our industry is so slow to act, is the entrenched sort of infrastructure dollars are so material that it requires a company like Grove who has no attachment to the legacy system to come in and say, "We're going to create an entirely different supply chain.

We're going to use plant-based ingredients. We're going to use infinitely recyclable packaging and try to move entirely away from plastic." And we can do that because we don't have the attachment to the sort of legacy base of embedded assets. And I think when you look out at the industry as a whole, you see this incredible contradiction where people genuinely, I think, recognize the crises to which their industries have contributed and genuinely want to create change.

I think Sandra said it well about leaving the world better for our children. People who work in the industry aren't evil. We all get it. But I think it's really hard for large organizations to move at the speed that the problems require. And so that, I think, is the opportunity for Grove and where we try to be able to differentiate is really by moving more quickly and more aggressively on urgent problems that defy the existing paradigm.

> People who work in the industry aren't evil. We all get it. But I think it's really hard for large organizations to move at the speed that the problems require.
>
> – STU LANDESBERG

Kamini Ramani:
Hey, we're at TechCrunch Disrupt. It's all about disrupting, right. So all for that. Now it's great to have a vision. You're amazing entrepreneurs. Zeitgeist is lifting your businesses, but you need money. And the three of you have followed very different strategies. It's almost like the Goldilocks story where Sandra only has raised 10 million in the lifetime of KiwiCo. Stu, you raised upwards of 450 million, and Maneesh has raised 30 million so far for Mirvie, but he's obviously a very experienced fundraiser from his prior companies. How did you get investors to believe in the promise of your company? And how did you build a zone of trust with them? I would say, at this point, any one of you who wants to jump in to answer can. There's no particular order. But maybe we start with Maneesh.

Maneesh Jain:
Sure. I think just to build on what Sandra and Stu said, the time for disruption is right. And I think one thing the pandemic has done is it has given us all time to really think through that and not just go on with life as it is. So I think it really comes down first and foremost to a shared vision in terms of attracting the right investors.

I think the phrase, "It's a marathon, not a sprint," is definitely front and center. If you want to make life better for the next generation, it's not going to happen in one year, right. We need to think a little bit longer term. And if it's a worthy goal, it's going to take time. So I think alignment around that is a pretty fundamental thing that is important at the beginning. For us, the other thing was coming from the cancer world, which is, there's lots of capital and lots of companies. Coming to women's health and pregnancy health, it's really been underinvested. So part of the journey is really explaining to investors that underinvested historically also means that there's a very large untapped opportunity here. So in our case, there's about $50 billion spent every year for unexpected complications in the medical system, and that could be reduced drastically.

So I think just making that connection between historically underinvested equals high untapped potential is a connection we try to make. I think the last thing I'll add is just in terms of keeping up with the trust because I think that trust is pretty important between investors and entrepreneurs. It's really, do what you say, right. We all have big visions and things we want to accomplish. But what is the first, second, third step? And it's really delivering on those smaller goals along the way, I think, that just helps foster trust and attracts more investors. We're excited for what's ahead.

Kamini Ramani:
Thank you, Maneesh. Sandra and then Stu, quickly on journey to investors and continuing to stay in the zone of trust. And then leave me a minute for my lightning round.

Sandra Oh Lin:
Yeah, absolutely. I mean, I agree with a lot that Maneesh actually said. And I think that foundation of trust is absolutely imperative. If I think about our investors and our board members, I think it's a matter of, as he mentioned, kind of alignment or around ambition and vision.

But it's also gaining their trust upfront around decision-making and doing what's right for all stakeholders. And so, in my opinion, I think that means being very upfront, being very forthcoming with opportunities, as well as with challenges so that they believe that you're going to be very considerate in terms of your decision-making and your planning. And they trust you to do your job basically is what it comes down to. And we've been really in a very fortunate position where we've been profitable and cash flow positive now for over five years and running. And so, it definitely has been a marathon and not a sprint. So, absolutely agree with that sentiment.

Kamini Ramani:
Stu.

Stu Landesberg:
Yeah, I would just... I mean, the thing I would add is I think financing is, you often, or at least I often see the headlines and it all feels inevitable. We've had a number of financings, as you mentioned. Our series A took us four years to raise, and I pitched 175 investors, 100% of whom said no. And eventually, I was able to get somebody to scrap and claw a little bit in. And 175 no's and half a yes, still is a successful financing. And so, ultimately, I think of fundraising a little bit as, it's a necessary thing to get the resources to go create the vision. And also something that's just a process just like anything else in the business and just like any other sort of business process and partnership to about preparation, perseverance and ultimately the people on the other side, right. Are you bringing in someone who's going to be a productive force for the company over the long term, because it's certainly been my experience that we are better because I have great investors as partners.

Kamini Ramani:
Absolutely. And thank you for sharing that vulnerability. It wasn't easy in the early days. And I think the entrepreneurs in this audience need to hear that because we at Mayfield say we partner with founders from inception to iconic, and Stu, you're definitely getting to iconic status, whether you like it or not, but the inception stage was tough. So we have two minutes to go, lightning round. It's the year 2030. You're still leading your companies. In a word or a phrase, how would you measure your impact? Sandra.

Sandra Oh Lin:
Generation of innovators and change-makers.

Maneesh Jain:
If I had to pick a phrase, I'd say pregnancy health uncomplicated.

Stu Landesberg:
No plastic.

Kamini Ramani:
Love it. And since we have a little bit of time, if any of you want to share taking care of the next generation, what's one cool thing that your kids are doing during the pandemic? Anybody.

Stu Landesberg:
Well, my kids like to join my Zoom calls, as you already sort of shared with the audience. Princess fairy Francis Margaret Landesberg appreciates the shout-out. No, but I think, at least for me, I think my children have taken a materially bigger interest in all of the things around the house because we're around somewhere often... so much more often. And so, I think that it's amazing to have them be a more active participant in all of the elements of life, including my Zoom calls.

> If you want to make life better for the next generation, it's not going to happen in one year, right. We need to think a little bit longer term.
>
> – MANEESH JAIN

Kamini Ramani:
And Sandra's kids are doing cubicle kits. We know that.

Sandra Oh Lin:
They're doing cubicle kits. I mean, they did... It was fun. They put together Zoom kind of recipe trading and cooking with their friends and that type of thing. I mean, one thing that I would say was really great about that time, and this is kind of seeing the silver lining in it is that I felt like I was able to see them in a different light. I got to see them with different angles that I wouldn't necessarily have had visibility into. And I think they saw the same for me as not only a mom but as an entrepreneur and as a leader because they would pop in like Stu during Zoom calls and that type of thing. And I think that was something that was actually quite special that they were able to see me as a multidimensional person. And I am able to see them as multidimensional people too.

Kamini Ramani:
That's great. Maneesh, Anything to add?

Maneesh Jain:
Well, I'll just say, closer connection to teenagers is a good thing, maybe too close from their perspective.

Kamini Ramani:
Thank you. Thank you so much. Taking care of the next generation, and we are honored to have you here. And hopefully, our audience has enjoyed this chat. So onward and upward.

Mayfield