Ashlee: Give me the big picture of what Retro is trying to do.

Joe: We are working to add 10 years of healthy lifespan to humanity.

Ashlee: It's you guys picked that way to describe it I would imagine quite intentionally given that the longevity and aging field it can be. It can feel amorphous and ambiguous to people can feel sort of hypy over the years and when you launched I just felt like this must have been very specific that you want to put these boundaries around it and define the objective.

Joe: Absolutely there's is and has been a ton of hype in the longevity world where people are promising to help humans live for 5,000 years or whatever. People have been promising this century after century I think and then meanwhile there's like a conservative existing sort of biioarma world that's very incremental and one disease at a time. And any kind of thinking about extending the healthy lifespan of humans is not really they just don't look at it from that perspective. So I think 10 years is exciting enough to be motivating and is also now that the technology the biotechnology has moved along it's within reach. So it's like part of an art I guess of the startup is to pick something that's new enough to be ready for a startup but not too far beyond reach so that you can actually accomplish it within startup time frames venture time frames.

Ashlee: Yeah and that was my next question is kind of like why now. And even to me as somebody who's covered longevity for a long time in different shapes and forms it felt to me like something changed five years ago where you had this new breed of longevity companies appearing. And I guess I'm always trying to figure out why that this happened.

Joe: I think it's a number of factors coming together and now AI is like a later late comer to it that is sort of like throwing fuel on the fire. But wasn't necessarily there at the beginning but I think I've been paying attention to it since the early 2010s when I started a nonprofit in the space. But it didn't really seem like venturable then there's just some very very early academic stuff. But the academic field got started really kicked off in the early 90s with Cynthia Kenyon discovering that you can double the lifespan of an animal just by tweaking one

gene. I mean that's like what wait lifespans are you can mess with them. That brought a lot of people into the academic field but academics like it's the early part of thinking about it. So I think that a number of factors started coming together in sort of the end of the teens in the beginning of the 20s where we started to have amazing tools. That were hitching a ride on basically like the tech world like Mo's law is carrying a bunch of biology now because a lot of biology is becoming information science instead of just a pure wet lab kind of science. Like we have gene sequencers which generate terabytes of data from a single experiment and that tells you a huge amount about what's actually going on in the tissue. Before whereas before it was like you kind of poke it a little bit here and it does that and you try to draw some conclusions. But in terms of massively parallel tools that can really start telling us what is actually going on in a cell like we're we still have a long ways to go but it's starting to feel tractable now. People could track down the causal pathways in gene circuits using sequencing essentially but highly parallel microscopy has also gotten a lot better. And the academic field progressed and those aren't uncorrelated to the point where there are a bunch of things that are ready to try now. Also partial reprogramming is really exciting our adviser Alex Okampo discovered that you can decouple loss of identity from loss of age in cells during the reprogramming process. So that also seemed like something ready to jump on us like a new wave of medicine.

Ashlee: I saw Alex in the building today by no surprise special guest.

Joe: Yeah he's really excited about Retro and has been with us since almost the beginning and comes by often. To weigh in on scientific progress and helping us answer strategic questions and debug science experiments and kind of thing.

Ashlee: And explain the identity aging part of that to the audience.

Joe: When Yamanaka discovered these proteins that could take cells all the way back to the stem cell state it wasn't even really like an aging thing. It was we get access to stem cells that we can run experiments on instead of having to do more controversial methods to get them. And then Alex is the one who started to push this more in this aging longevity direction of can we reverse it a little bit and what does that do and what does that look like and can you restore a bit of

function as opposed to just a blank slate. So yeah Maka that was an incredible sort of industry transforming discovery. But as an overall phenomenon it wasn't anything new. It's been going on for millions of years like every time two 30-year-old people get together and produce a baby the baby starts off at age zero. So there somewhere inside there there is this piece of magic where like two 30-year-old cells created a zero-year-old cell and that's because reprogramming happened. And so he just figured out how to do the reprogramming without all the fun of the 30-year-olds getting together. But that miracle of the age reversal comes at a price of the cells also forgetting what they are.

Joe: We're at a lab people are labing. I don't know if that's

messing up your light but the noise is kind of bad probably.

Ashlee: Yeah light's okay it's just.

Joe: Okay I'll just start

over at that sentence.

Ashlee: Are they is it

going to come down.

Joe: Yeah it'll come

down later.

Ashlee: It's a delivery they're bringing into the warehouse.

Joe: Yeah so people copulating. That age reversal comes at a price the cells when they're being reprogrammed also completely forget what kind of cell they are. So if they were a liver cell before they go back to a pluropotent stem cell. So it doesn't really work as a rejuvenation method for an existing person say because if all your cells forget what they're doing you just turn into like a blob of jell-o.

But what Alex figured out is that you can start them on that journey back to pluropotent stem cell but before they completely forget what they are you stop and let them bounce back. And some of the age gets wiped away so it was the first inkling that those two processes could be somewhat decoupled. Super cool amazing right.

Ashlee: Yeah I mean this is like what got me interested in this new stage you guys and couple other companies hitting on this new ground to explore.

Joe: So most biotech companies that I've run across historically it's like some scientist in a lab has found this interesting molecule. We're going to raise some money to see how far we can push this thing either it works or it doesn't so we either go bankrupt or we IPO. You guys came out taking like a few shots on goal wanting to explore a few areas some of which had overlaps but a couple of which were quite sort of different from each other. And I mean that was very much on purpose right to it's not just that we're defocused. But you can found a company on different premises and usually in the standard bioarma playbook is it's a particular molecule or mechanism or discovery of some kind from academia that gets licensed out. And in our case the founding principle is this extending the healthy portion of human life and the mechanism is any means necessary. So we take it as our job to pick what we think are the highest leverage means necessary. So that but in the shortest amount of time or for the fewest number of millions of dollars we can make the biggest increment of improvement generally in people's healthy lives. And so we mix it up as necessary we've explored probably pretty deeply six different directions to potentially go to achieve that. And we've found three of them that we're excited enough about that we're taking them all the way to the clinic.

Ashlee: Now what are those three.

Joe: So yeah the first is a small molecule which is more like classic pharma so like a drug a drug. An oral orally available drug you don't even have to inject it once a week. That restores the autophagy process in cells it's just specifically we're focused on its utility for neurons. It crosses the blood brain barrier and that process which is one of sort of cellular recycling of old and broken proteins.

Ashlee: Like just kind of cleaning out.

Joe: Yeah and it's a lot of people have heard of it because it tends to be upregulated to some degree when during fasting because it's a time when the body is like I need more raw materials where's the food. And if you have a bunch of broken things lying around it can be a good time to recycle them. But in the case of age-related neurodegenerative diseases such as a particular Alzheimer's flavor they're going after initially that process is diminished is sort of interfered with. And so this molecule restores that process.

Ashlee: Okay so in your brain you're building up some kind of detritis that you don't want and the brain can't clear it and this pill has the potential to help clear that away.

Joe: Exactly.

Ashlee: Okay yeah so that's that'll be in clinical trials this year.

Joe: And then the other two programs are based on reprogramming. So the first program that mechanism was discovered as part of exploring how reprogramming works. And then we just came across this incredible molecule in the process with low toxicity and high efficacy it was just like we have to take this to the clinic. But the other two are more strictly based on reprogramming.

Ashlee: Okay and reprogramming of what type of cells.

Joe: So we've talked about partial reprogramming so far which is something that you do generally that you would do in the body that's how we think about it. But the easiest way for us to get started and in a way that's safe is to do the reprogramming outside the body. And so that brings us to the rejuvenation modality of replacement cellular replacement. So we can generate young cells outside the body and then replace older cells inside the body by putting them where they need to go. So we call that micro replacement because the brother version of it is macro replacement which is where you graft in whole tissues which requires surgery and is like very difficult to scale. It's kind of a little sketchy where you can get the tissue from in the first place. But micro replacement is doable today and we have like beautiful proofs of concept that we've already generated in our labs for doing it. So the two cell types I'll just start with the two cell types. I'm sure it's like of course it's right when we do our interview delivery time.

Ashlee: Voila thank you.

Joe: Two seconds we're still rolling.

Ashlee: Yeah you got to be in the same position same facial blood flow posture same heart rate same vocal.

Joe: You listen to audiobooks and the reader obviously took a break and came back and their voice is at a totally different pitch from what it was.

Ashlee: Yeah sometimes you can tell that like months have passed or like years or so some it sounds like a much older person I've had a couple of those.

Joe: It just does I guess there's like a pitch that someone's talking at and it's like sort of a flat or whatever and they come back on the and then they're talking at a different pitch and it's like so I always get high marks from our editors because apparently my voice over.

Ashlee: It's very consistent amazing amazing.

Joe: So unfortunately there aren't very many tissues that can be replaced like that because most tissues are pretty complex and the cells are all kind of intertwined together in very perfectly balanced ways. But there are a few the two that are the most amendable for our purposes including having an effect on preventing age- related disease or restoring function in people with degeneration are microglia which are one of the four fundamental brain cell types. And HSC's which are hematopoietic stem cells which is a ridiculously long way of saying blood stem cells. They live in your bone marrow and they make all your blood. So it's those two cell types so we make young versions of those outside the body and then inject them into the body.

Ashlee: So you guys are going big brain and immune system like off the bat for sure.

Joe: And the you mentioned one for the autophagy

would be a pill the others would those would be an

injection or. Joe: Yeah those would be injections.

Ashlee: And the cells these refreshed versions of the cells just replace whatever the less functional kind of crappy ones that were there before or do you have to excise out things to make room for the new cells or how does that.

Joe: It's slightly different in each of the cases for the blood stem cells for instance initially the patients like we in general have to start with more specific indications.

For brand new experimental things where there's an acute need and the patients are dying quick soon if nothing is done to save their lives. And that helps create the incentive for health authorities to try experimental therapies for them. And then as they're proven safer and safer and safer they can eventually work their way toward being used ultimately preventatively because that's our vision for medicine. Right now we have sick care and we want to create health care where like you apply medicine and stay healthy sort of like ancient traditional Chinese medicine a doctor's job is to keep you healthy. So in the case of the HSC's initially the patients will be in situations where their bone marrow is just devoid of blood stem cells or they've been in situations where they've had to have the existing ones abladed or blown away by chemotherapies. And then that makes room for these new blood stem cells. Later once the safety is shown we can use more gentle methods of making just a bit of room in the bone marrow without blowing away your whole existing immune system. So let's say you'd just like open up a quarter of the spaces and keep three quarters of your old immune system and put one quarter of new immune system. And then come back a couple weeks later and do it again. And you can do a few waves of this and essentially have a completely fresh zero age set of blood for the next however many years until you do it again.

Ashlee: Okay and how would it work in the brain I feel like it'd be bit of a trickier I guess it's all tricky but that seems like a trickier operation to me intuitively.

Joe: I mean it's it sounds scary but it's actually becoming a fairly well-developed intervention to make injections into brains. There are some big targets in the brain that are essentially hollow and filled with fluid so it's pretty easy to hit it accurately with a needle. And then you can inject they're called ventricles and then you can inject intraventricularly. I've been having trouble with hemopatic. So you can inject intraventricularly cells which then distribute through channels that are part of the normal fluid flows inside the brain.

Ashlee: So when Yamanaka factors came out then we pushed more toward this cellular reprogramming this partial cell reprogramming the field was so excited billions of dollars rushed in. People are still exploring this you guys are

exploring it in different ways. How like now that you've been at this for a few years do you still feel like this is going to be this is just the start of what will be a broadly applicable technology. Has it been more frustrating than you found it I'm trying to gauge where we're at.

Joe: We're very pragmatic both Sam our investor and I are from Y Combinator and we're like very product oriented. We're going to build things that people need and can use right away. And so these cell replacement modalities are super practical for right now because you can establish safety you can do quality control outside the body. But the invivo partial reprogramming like you're talking about is one of the main modalities for basically all of the rest of the body. There's only half a dozen cell types that you can replace as individual cells from outside the body. And so that's a long game but we have to proceed more carefully because you're like reprogramming in place in the body. And if you screw something up it's bad.

Ashlee: So this is the idea that you have liver damage or something like that and you're rewiring rejuvenating your liver inside of you as you're going about your life.

Joe: Yeah and so that was actually our first target in the partial reprogramming space. And we have just incredible results for liver partial reprogramming in mice. We can rejuvenate the livers of mice by a huge like a quarter of their lifespan worth of age and it seems to persist long after the intervention. Then their livers are better at they reduce their fatty liver. They regenerate better they're more able to withstand chemical insults because some of those people get liver injury from overdoses on drugs and that kind of thing. Amazing results but the most obviously patient need-oriented one of those would be reducing steatosis which is fatty liver. And then right about the time that we were getting these incredible results like much faster than I expected to get positive results from our lab. And like multiply confirmed and like yeah we are actually really nailing this this is beautiful. It was about the same time that Ozempic and the other GLP-1 agonists were out there hitting the market. And the primary cause of fatty liver starting to shrink down as it were with people losing tons of weight. And so that's my sense of that market is I can't predict because it takes a long time to develop these

drugs. It probably be like 5 years before it hits the clinic and maybe 8 years before we see a drug approval or more. I want to produce things that will be practical and be used and actually help people's lives. And I can't like with a clear vision or a good conscience like say "Yeah the fatty liver market is going to be important to people in eight or 10 years." I think it might not so that's interesting. So I think it's still beautiful as a mechanistic proof of concept

for us and it emboldens us that like we can do this really well. But so we're in the process of exploring several other tissues to be our first inhuman for partial reprogramming.

Ashlee: Okay and since I wasn't able to come here at the very earliest days because you guys were in stealth mode I didn't know about you. But I came here fairly early on I mean I love you've got like kind of this old office and this new office now. The old office I don't you guys just always have this cool vibe in the offices themselves just unusual decoration that you wouldn't usually find at a typical company. And then this laboratory I mean tell me the story about this and you sort of had to build this during COVID and do it do a lot of the stuff yourself and just get it up and running and.

Joe: Yeah well when we first started off there were probably a thousand COVID companies trying to make a go of it. And I'm very glad for all the progress we made during COVID and saved many lives to that we were able to ramp up the therapeutics. But the world probably doesn't need a thousand there's probably 10 COVID companies would be pretty good. But all the lab space is full like there was a 0.07% vacancy rate of lab space in the Bay Area. So it's pretty much impossible to build a lab but that was the time for me to build a lab. So what am I going to do I guess we have to build our own labs and I love building things anyway. So we rented this warehouse which wasn't labs was just like an old factory from the 1940s. And rented also another space over in Oakland American Steel which is place where people would often fabricate big beautiful sculptures from Burning Man. And just had them start building these labs out of shipping containers over there. And then we revamped this space and put it fixed up the floors and painted it. And then just started every couple weeks a new lab would be finished over there and wheel it in here and just park it screw it down and attach like a source of pure conditioned filtered air to it and power and away we went.

Ashlee: Which and the air and everything I

mean you guys built a lot of this yourselves.

Joe: We built all of it yeah.

Ashlee: How embarrassingly I designed it just because I've had a long sort of pent-up interest in energy conversion and HVAC kind of stuff over the decades.

Joe: And some of them are like you said it's laboratory it's places where people would do their day-to-day lab work. And then part of it is a vivarium it's where the mice are hanging out. We as a field in the 2020s don't understand biology well enough just to say it looks good on paper it looks good in the petri dish let's take it to people. We have to test it in some intermediate species and mice are pretty much the standard for that.

Ashlee: And you guys I mean I've been to a lot of labs with mice and they're often universities in these well manicured buildings I've been in these. I mean you guys actually even I know they're shipping containers and people might think of it as less refined than some university lab. But you guys are doing like temperature control light control on levels that I haven't seen in any other mice lab.

Joe: I'm pretty fidious about mouse research my last company was all about making the world's best mouse research gear. So there are some problems with the existing industry especially one of them that is a like a special peeve of mine is that these are incredibly light sensitive creatures. Like you have to really be careful caring for their lighting environment if like in a university if some grad student like blunders into the lab and flips on the lights accidentally in the middle of the night it's a calamity. It's like the ending days as far as the mother mice are concerned they'll eat their babies and run or try to it's literally horrific. So they're super light sensitive in a normal vivarium the cages don't have their own light sources and so they're in these tall racks that are taller than a person. And then the whole place is lit by a fluorescent light on the ceiling. So that the light intensity is the square of distance so if you have these ones at the top that are pretty close to the lights and the ones at the bottom that are literally getting 100 times less energy per fewer watts per square meter of light at the bottom. And yet they're considered to be sort of uniform experimental conditions. So there have been so many problems with mouse research over the decades and people like someone does the study someone else does the study get a different answer like that's tragic. Not only because the research is called a question but these are

little lives and it's I consider it part of our responsibility to make sure we do a really good job with the sacrifice they're making. And that if we're getting crappy data out of it then it's a terrible waste. So that's why I take it so seriously.

Ashlee: And the mice I mean the key part to a lot of this is testing these therapies bit by bit and then now okay so now you're entering clinical trials with that will that'll be with humans is the next stage.

Joe: Yeah that's where the but it gets expensive we've been doing this for four years we've had this vibrarium going for a long time. One of the reasons we have such a large vivarium has a 10,000 mouse capacity is that we are making therapeutics for the elderly. And but most of the mouse research gets done on very young mice that's the most convenient time as soon as they're born okay let's go. But we think it's silly to try out therapeutics for the elderly in super young animals. So one of the reasons for having a large vivarium is that you can keep a cohort of animals alive and we obviously treat them very very well. Certainly better than most people treat their pets they have like frequent access to veterinary care and like consistent food and water sterile environments well controlled temperature all that kind of thing. But they get to live out their days and then have a proper model for testing. So yeah once a therapeutic makes it through those hurdles it's time to try it in people.

Ashlee: Okay that makes tons of sense. Sam has Sam's made I think four big bets that I can think of one quite clearly is Open AI he's got a couple energy nuclear bets. There's Worldcoin or World now which is more on like the identity kind of finance front and then you guys are the big biotech bet. That was just something that you two saw eye to eye on that you brought to him or because you were into it how did this come about.

Joe: When we were at Y Combinator I think we both I mean it's obvious to me and that's sort of why they invited me in to be a part-time partner is that they want to do more biology. It's just obviously one of the main new sort of tech things like I was mentioning earlier but biotechnology is becoming more and more information technology which is what people call tech. And so I and Sam another guy created this experimental program called YC Bio to see if we could

get more biology startups to go through Y Combinator. So there's just an innate interest among us to get biology stuff going. And is and I think for people who kind of tend to try to like I think there's something about Silicon Valley that tends to attract first principal thinkers. And if you're kind of zooming out if you want to invest into the future then you have to kind of abstract a little bit from today and just think what are the big broad brushstrokes things that are important. What's going to be important 10 years from now 20 years from now obviously energy or like we're going to need a better way of doing identity if AI is going to be able to fake everybody that kind of thing like zooming out. When you zoom out around health it's just obvious it's one of the most fundamentally important things to in any single person's life like if you're not healthy you can't enjoy anything else. So it's a viewpoint that Sam and I both shared just from looking at the human condition from first principles.

Ashlee: And then critics of this space and Silicon Valley in general they always go to the oh well this is like a very male-dominated thing it's all these rich people want to live forever for some reason. I'm sure you've heard this before for many years what what is your reaction when people there in fairness it has geared a little bit more male as far as the people not like universally but it's skewed that way to me a little bit. And then I wanted to say so at Retro but generally as like Silicon Valley tech like I don't think it's at Retro and I don't think it's among like the researchers that I run across as scientists. I think the impression is oh well we hear like Peter Teal Sam Brian Johnson the people the big names that get attention who are funding this stuff.

Joe: Got it got it yeah and then and so then it looks like oh well this is the obsession of that group of people. Well it's one of our fundamental sort of marching orders or like aspects of our charter that we make therapies that can be scaled really broadly. Because our mission is extending healthy lifespan of humanity not of Sam Alman not that we would exclude Sam but we're just saying like we don't want something expensive where you have to have your own like blood boy slave in order to get the plasma from them just to live longer. We want to make things that can be for instance like pills that you can make billions of for everybody to benefit. So that's part of just how we think how we

strategize how we decide of which programs go forward and which ones don't like does this how to is this scalable on can we actually distribute this to people. And I think I mean I think there are structural things that are completely separate from thinking about biology or thinking about the human condition or whatever that's just sort of lead to the like the existing I think male bias in the wealth and Silicon Valley. The totally other topic that I'm not really qualified to talk about even I'm sure there's some sociologists understand it better than I do.

Ashlee: And then you mentioned it and I know this just because we've known each other for a while you've been interested in longevity and aging for quite a while. The company's mission is to add this 10 years of healthy lifespan which I think like just about anyone would be excited about is why not have like a better way about going about things in your later years. But where do you fall on like in your most idealistic version not just for Retro but for this field in general I mean where do you fall on the spectrum of your hopes and dreams are you a live forever type or what do you want to see humanity do in the years to come.

Joe: Well I think 10 years is a great mission for a venture for like a new pharma company which is what Retro is. And Retro is on its way to becoming one of the next household name sort of large pharma companies hopefully not as bureaucratic. Please interview me again when we get there and like criticize the hell out of my bureaucracy cuz I will take that very seriously. But I think that it is a compassionate mission I mean as is all of all of medicine basically your prospect is here's a

potential sickness direction and you can intervene and you can create health. That is the sort of honorable profession of doctor really at large like Retro succeeds at its mission say it's 15 years down the line. We have a combination of medicines all of which together create this arithmetic result of 10 healthier years do we stop right there. I would say not because then we're still at this sort of you're always at this juncture where like well okay we can work even harder and then there are the next things. As our mission right now you can basically boil it down to like trying to figure out how to make the 80s awesome because people transition from the 70s to 80s and they can go down the left hallway or the right hallway. And it we all got like a torn rotator cuff that won't go away I could use the 40s being we've all seen the 80s. It's like I don't need to describe-didn't describe that but there are people in their 80s who are like going hiking and picking up their grandkids and that's our project right now. But we get there and then people are like okay peace out we're just going to go live on a beach in Thailand no I already tried that 15 years ago I was like no sitting around just does not feel right to me. Someone says "Okay you have a bunch of cash in the bank you're a Retro one of the biggest pharma companies of the world now what?" Well there are all these people who are having a horrible time in their 90s of course we're going to work on that.

Ashlee: What is like since you started this company I mean the Ozempic and all the GLP stuff has taken off. It's interesting that like Sam made a huge bet on this company Altos Labs was a massive bet New Limit and then the GLP stuff came in the middle of that like what has that done to the longevity market and invest I mean there must be so much everyone must be hunting for the next big peptide.

Joe: That generates this enormous business it's a has it's an interesting it's such a windfall like I'm really really happy about it every time I think about it just like how much health and joy that's going to create is already creating and will. But because we had a mission at the beginning of the company and not a particular molecule or mechanism we had to kind of lock ourselves in rooms and be like how are we going to go after this mission. What we want is like products we want like the shortest path to actually creating all this health for people how do we add 10 years. And one idea came up is like well you could just get people to

quit smoking and if you succeed at that that will definitely add 10 years to their lifespan. And then so we're like okay that's probably an app or something like that it's not really a biotech company probably per se. Bio bio farmer tried it and that was a pharma tried this they created Nicorette gum which gives you oral source of nicotine which didn't seem to stop the smoking epidemic. Plenty of propaganda nasty pictures and stuff it's a tough one but we're a biotech company not an app company. But that kind of
soul-searching got us to sort of refine how we state our mission which is that we are helping people who are already in the sort of upper half of healthiness to live even longer and stay healthier longer. So the people who are sort of actively involved in kind of killing themselves is that's not really our target market. I feel for them and I want them to do better and I want smoking to be eradicated from the planet and for obesity to go away. And I understand that even though they may be actively killing themselves they're not like intentionally choosing to kill themselves they're just hungry and they want to eat. But that's not our target market so it's just amazing it's amazing and beautiful that these technologies have come along to help this other part of the market. So basically in a way that sort of doubles our market.

Ashlee: And I'm still trying to wrap my head around this a little bit I mean there was the companies that I mentioned like you guys New Limit Altos Labs. Those are the ones that are jumping first to mind I mean it was piggybacking off this immense interest in partial cell offpo's discovery right and like so and it seems like well we don't know what Altos Labs is doing because they're quite secretive. New Limit has put out updates here and there you guys are walking through what you found like do you feel like the field is as excited as they were five years ago about because it's still such early days with technology but is there that same buzzer on this.

Joe: And I was just trying to calibrate where I'm mostly an internally focused leader so I hang with my peeps and we build work on the product. So I'm not that highly attuned to what everybody's saying in the outside world. I would say that from our perspective we've been continuously like climbing up that hill of how do you apply partial reprogramming to extending health and I'm excited by

our progress. But it's brand new technology it's like yeah CRISPR how long did it take from when the CRISPR is first discovered till like the first patient was it sequencing the genome for sure in general yeah. So I'm under no illusions that there are a lot of people running around saying oh my god Yamanaka factors they create rejuvenation we're just going to like put them into a vector and inject them systemically into people. And like both me and like was one of the reasons sort of like I think that I and Alex Okampo kind of bonded initially is we're just like this is horrible like they're going to kill people.

Ashlee: They should the first time you hear about it is really exciting I mean I was like I didn't even know this existed and I heard I'm like what somebody cracked the code on this. This must be there must be ways to make interesting stuff out of this.

Joe: For sure and I'm horribly impatient and I want things to go faster. But because it's pretty fundamental this rearrangement of like the fate of a cell by getting in there and monkeying with its core machinery we have to be really careful.

Ashlee: But this idea of now we have lab grown stem cells that we can manufacture these IPSC's I do see this in one startup after another. That is fascinating whether it's you guys whether it's like Colossal Biosciences is trying to bring back the dodo and the woolly mammoth companies doing interesting things with IVF and fertility. Like I'm kind of blown away I don't think if there's no way the average person on the street like I don't even think has ever heard of an IPSC. To me this seems like maybe it needs a better name.

Joe: Well it definitely because the name stem cell has been sullied by like all of these like snake oil purveyors who like I'll give you a stem cell treatment for 30k in Mexico. You immediately think of like embryos and all these things.

Ashlee: But I also don't think most people know that we can grow these things in a lab now. And then when I even looked at the New York Times and I was looking how many articles they had written about IPSC's recently it was like basically one in the last few years I don't know. But then so I don't know if I'm just cuz I get into this stuff and I'm overly excited but to me this seems like a

whole new avenue of companies and science for sure.

Joe: Okay I mean I say it is it like opened up biology to creation right like before reproduction was the only window we had in like the creation of life. Now Yamanaka said "Hey you can create brand new cells that can become a whole person." Just these magic four factors so and he so we've been lucking with the magic four factors too in our scientist got it because he got a Nobel Prize like six years after he did this discovery which is pretty quick on reasonably quick. There have been a few faster ones but it was pretty quick but like it seems the science world clearly understood some of the ramifications even before Alex and all these startups came that were piggybacking off this.

Joe: So we did a collaboration with OpenAI which was secret for quite a while until because we both our sort of general culture and theirs is like you don't just like talk about what you're doing all the time. And like you do cool stuff and if it really works then you talk about it. But like finally a month and a half ago or so like stuff really worked in a way that kind of surprised both of us. And specifically we set about trying to build a large language model by bringing in native biodata and training a new model that we called GPT4B for bio. And the test we put it to is can it design new Yamanaka factors and to explain that to people I mean he identified these four specific factors that are natural human genes or mammalian genes. They're pretty universal across quite a wide range of different animals throughout evolution. But there's this thought that there's probably other combinations of proteins that will do interesting things right some people have been exploring well what if we try different combinations of other existing similar proteins that sort of guide sulfates. And just we can just try thousands and thousands of different combinations of those and maybe we get lucky. What we asked is what if we just redesigned them ourselves which you normally don't ask because that's super hard from normal the normal kinds of biology or bioinformatics that people have had up until a few months ago. You mean like a protein structure or yeah the whole like the like some sometimes people will try to optimize a protein by saying like well there's this region of like three or four amino acids where it contacts this other protein and if we could tweak those maybe we could get slightly better binding or something like that you. So they'll

you protein has about a thousand amino acids just say plus or minus but that's a common number we'll tweak these three to five it'll try all the combinations and there's 20 different amino acids that can go in each slot so you it becomes like tens of thousands of different ones to experiment with and you can hone it a little bit. But we just we built this model that is it's generative AI and we said here's this a sequence of these types of proteins that are like better and better or like different across different different ranges of variation. Try rewriting new versions of these so the model just spit out like these 30 different new ones and said "What about these?" And some of them and like most of them worked like the weird thing is like they folded and became proteins that in itself is really hard. And then they functioned in a cell and they weren't like toxic or killed the cell or whatever and most of them a huge number of them were like way better at reprogramming than the natural ones. On top of that many of them had up to 80% of all the amino acids changed from the original. It was like rewritten and we have like kind of no idea how or we don't really understand how the function works. So the model's spitting it out and then you're translating it to the wet lab we take we take it right out of the model. We send it off to have the the DNA for that sequence printed for 30 different versions. And then we clone those into cells and try it out in the lab and you guys we've already done that and like like some of the best ones were over two orders of magnitude more powerful at reprogramming this is I mean this is in terms of huge in terms of efficiency and time. Faster and a higher ratio of you have like the initial Yamanaka based reprogramming you start with say a million starting cells and you end up with a small handful okay of of IPS-C's at the end. It's extremely inefficient I see. But we're getting like multiple orders of magnitude higher efficiency okay so I take a thousand skin cells and instead of just getting four or five you guys are able to convert yeah multiple percentages of the original. Where where is this so it's early earlyish days with that but then so this this could lead to I mean we already have like a zillion. So the Open AI team and we both saw this and we're like what yeah that's amazing. We should we should tell the world about this so we you

mentioned it to some press outlets and now we've been getting bombarded with people who are like we want to really try these new Yamanaka factors on like there's some animals that just won't reprogram nobody knows why. Which means there's all kinds of biology you can't do in that animal there's like different agent cells don't reprogram well. So there's experiments that we probably were going to do rather than collaborate just because we have everything that we need to do here like see if if we can get better reprogramming going in older older people. Oh aging yeah aging it just they don't reprogram as well. But now we have these reprogramming factors that are organism to more potent so that's another area to try I mean that's just on the first things that our models spit out. But some of them are also a lot shorter than the native Yamanaka factors which means that we can compact all the Yamanaka factors into one vector that's easier to make into a medicine. So we're going to try that in these same types of modes that we were doing the invivo partial reprogramming you in mouse litters before. And then others it's also faster so some of our you call our blood stem cell program we start with we start with the human human cell from the patient and we're making new blood cell bloods that that are your own DNA. So it's basically your blood so like most of the you stem cell like HSC transplants bone marrow transplants in the medical field are are someone else's someone else's bone marrow. So there's a really high rate of of complications adverse reactions and like immune rejection and that kind of thing. But so this this loop comes from your cells they reprogram rediffiate to HSC's and then go back into you. So that round trip takes a while so being able to shorten that is great for patients because if you when you need new blood you need new blood. That's another another direction why why that is is exciting I don't are we how are we on time.

Ashlee: No idea usually I talk to you and I know that's why I still stilt skin and it's like 20 years later this is why I checked just cuz I I just want to ask two more questions on that are you guys okay.

Joe: Yeah the you're running out of film or whatever.

Ashlee: I was just trying to think of the things we still have to do so the I mean

it's just it's not intuitive that a language model would be able to do should be good at that. It's not totally crazy because language models work on sequential data types where there's a bunch of symbols all in a row that because of their position sequentially have function basically and yeah and like DNA and we went first for the like the first practical results we decided to get in protein sequence but it's basically a direct map from from DNA sequence and sequence matters it's another sequential data type that I see okay and what didn't what was it fed with initially just like vast quantities of publicly available proteomics data okay that we curated and then brought to the OpenAI partnership good. So you're already testing out some of these directions of where it will take you is this yeah I mean do you have a feel for you seem super enthused like this could actually be the start of like another new therapy or it's too early to tell on something like that.

Joe: I mean we have this philosophy of vertical integration because we like speed we think generally bio farmer is just too slow. And one of the reasons is people operate across company barriers a lot and things get incredibly slow as soon as you cross the border from your company to some other company like lawyers and waiting for meetings and joint steering committees and like weeks slow down into months and years or whatever. So we generally like get a feel for which which like we have this sort of good vendor bad vendor heristic we use inside and if there's like a nice competitive sphere out there of of vendors who are all jockeying for space to be responsive and provide competitive quality and pricing and so on then great we'll do that out of house. But anytime something feels like like hitting molasses territory then yeah fine we'll just integrate it internally like a vivarium is one example of that the whole process of going outside for animal studies is incredibly slow and inefficient and very hard to translate the science across those barriers and you have long long meetings and you probably have like a 100 hours of meetings with people to do like 10 hours of work whatever. So I think that AI is just another one of the of the things we have a microscopy core all these tools to yeah we have a vibrarium we have a big computational biology career separate from our AI team there's a bunch of stuff that we have to do for ourselves. We have our labs and having the ability to

design our molecules that we're trying which is basically what AI can do for us was like well it's just an obvious function that we have to have so it's not you we don't aim to be a service provider or like a product product you design a design as a service building AI products for the world or whatever it's just like an obvious thing that will make everything we do faster excuse me okay.

Ashlee: Last question and then we'll field trip we have so many drugs these small molecule-based therapies they always seem to fix thing but come with consequences. And I know all these people they're on so many pills every day it seems like it's nice that it helps you not get a heart attack or something but it seems to affect other things as well these GLPs the the OEMex and things they seem to come along and fix like lots of stuff at once where things that are IPSC based that are partial cell reprogramming based these new therapies that could be coming is it thought that they would come with less consequences than a small molecule drug do we have a feel for how that shakes out is it you is it all pro or is there baggage that comes with it.

Joe: Oh no I think there is an overall perspective shift when you start thinking about age as the primary risk factor for 85% of all the diseases that we attend to in our developed world. The reason people take lots of pills today one of them is that our pharma industry is focused on coming up with cures for individual diseases and this is later down the line once they've all manifested. But since most of the diseases are age-related diseases at least in any given hospital you go into that'll be like 80 or 90% of of everything there addressing aging as the root cause prevents multiple downstream diseases. So taking one one therapeutic that could say you give you a brand new blood system can prevent a bunch of downstream different diseases that you get from having old blood. So it's our thought that you having taking one injection earlier can prevent you from lots of pills and other injections and surgeries and that kind of thing later okay.

Ashlee: Can we field

trip to see some mice.

Joe: Yeah okay.