Transcript

Kristen Fortney (KF):

Welcome to today's webinar on **AI: Drug Discovery and Longevity.**

The topic for today is **AI for longevity, drug discovery: breakthroughs and challenges.** We're really looking forward to the conversation.

I'm your moderator, **Kristen Fortney, PhD**, in biology and an AFAR grantee back in the day and currently the CEO and Co-founder of BioAge.

A bit more about our host, so AFAR if you work in aging biology, you're probably familiar with AFAR. They support a lot of talent and a lot of research in the field, deploying nearly $200 million to 4000 plus investigators, and are really important at fostering young talent as well.

I'm going to briefly introduce our panelists, and then we'll go into a longer self-introduction in just a couple of minutes.

We have **Ben Blue, PhD, CTO and Co-founder of Ora Biomedical**, joining us today.

Hanadie Yousef, CEO and Co-founder of Juvena Therapeutics.

Everyone is also a scientist and aging biology, so scientist and founder. We've got all that in common.

And of course, **Alex Zhavoronkov, PhD, CEO and Founder of Insilico Medicine**.

Really looking forward to it so let's get started. All right, so everyone sees your names, but let's talk a little bit more about what you do right. So, let's do some brief self-intros, one to two minutes tops, but maybe introduce what your company does and where are you in your drug development journey. You know we've got the whole spectrum here from like new company to you know deep clinical pipeline. Also relevant to today's topic; How are you using AI in your company? What are some of the key technologies that you rely on?

Hanadie Yousef (HY):

My pleasure. Kristen, really excited to be here today with everyone virtually. So, at Juvena Therapeutics, we are developing biologics for chronic and rare diseases including age-related diseases. We're doing it through a unique platform that's AI-enabled and enables us to mine protein secreted by stem cells to map their therapeutic potential to tissues and cells in which they can really have rejuvenating benefits. Once we do these mappings, we fully validate them and then translate them into engineered biologics for very specific disease indications with paths through regulatory to ultimately get them approved by the FDA and into the clinic and to the people who need them the most. In terms of the different technologies we're using, we are really using a variety of both computational bioinformatic and AI techniques, combined with different data modalities, including quantitative proteomics, single-cell transcriptomics, and other types of multi-omics high content imaging, and different really like AI and machine learning techniques such as neural networks, generative AI and others to really innovate at every step of the process of in silico, in vitro, in vivo screening and then lead optimization and protein engineering. And so that has today enabled Juvena actually over the last 6 1/2 years to really build a biologics pipeline with now two preclinical stage assets and actually one asset that we're in the midst of regulatory filing and we're going to be in phase one starting early this fall and it's for a Muscular Dystrophy known as Myotonic Distribute Type One. It is a biologic that can act across a variety of muscle wasting diseases and of course happy to share more a little later on about it.

KF: That's great. And Ben?

Ben Blue (BB):

I'm CTO of Ora Biomedical. Our platform is based on using robotics and neural networks to do high-throughput drug discovery with lifespan and aging biomarkers as the starting phenotype. So, we start with whole animals, the canonical and lovely invertebrates, the elegans to look first and foremost at what is modulating overall lifespan to identify Gero-Therapeutics. From there, our goal is to really expand outward and not just stay under the lamppost of, say, M Tor inhibitors and things that we know work and explore untouched regions of chemical space to find the next generation of longevity therapeutics. So, I'm really excited to be on the panel day. Honestly, I think that as the youngest of our four companies, and really, I just want to highlight the work that you three have done translating good geroscience into actual pharmaceutical pipelines. So, it is really inspiring to be a part of this today. So, thank you for the three of your companies and your work getting this going.

KF: And Alex?

Alex Zhavoronkov (AZ):

So a great pleasure to be with you today. These are the companies that are, I would say maybe, some of the most credible in the field. Insilico has been around for now more than 10 years. We were founded in 2014, and now it's our 10th year in existence. We started our own drug discovery journey where we decided to put our AI to work to discover our therapeutics and put them in clinical trials around 2019. And since then, we've managed to nominate 18 preclinical candidates. We now have seven drugs and human clinical trials. We have two in phase two. So, we're progressing. We use AI across every stage of drug discovery and development. So we have a tool called Biology 42, it's a platform that allows you to identify protein targets very efficiently and also kind of rank them by novelty, confidence, drug ability, and many other features, even commercial tractability, because as you know, if you are going after a novel target and if it's too novel pharmaceutical companies probably would see you in phase two complete, they don't like an ultra-high

novelty when you are a little bit later and you would also be able to evaluate the targets utilizing hallmarks of aging approaches, looking at in which hallmarks each target score is.

We have a system that allows you to generate small molecules with the desired properties, so it's called Chemistry 42. So, basically, once you zoom in on your target of interest, instead of looking for a needle in a haystack, you can generate a perfect needle. And then synthesize and test so that ensures that all your molecules are novel, patentable, and have the desired properties. We have a system called Inclinico which predicts the outcomes of clinical trials and usually, we also develop a biomarker for every drug that we take at the human clinical trials. Many of those software tools are available, so we actually sell them to and license them to a large community. And as the community uses those tools, those tools get better and get validated over time. We try to pick the targets that are implicated in aging and disease at the same time, and sometimes it's not trivial because we're going after cancer, but you know, 30% of the paper is about the target that might be in aging or associated areas.

Our core lead program is in Fibrosis, so we decided to go after Idiopathic Pulmonary Fibrosis first, even though that target scored a 6th hallmarks of aging. Surprisingly, I was just up to the Longevity Summit Dublin wonderful event which kind of elucidated some new functions of my target and one of the groups also showed that this target was picked up by Horvath's multispecies clock as regulated by one of the methylation sites, that scored it very, very highly. So, we're trying to go after targets that are implicated in aging disease, but we developed them for diseases in a very traditional approach in accordance with all the good drug development practices of a traditional biotech. Trying not to cut any corners nowadays, not to make any big statements anymore within real core credible, but the idea is to try to get the drugs approved for a disease and then use aging clocks to see if they work on aging currently again in phase two.

KF:

Thanks, Alex. No, I think that's a great point. That's something we all have to figure out, right? How to thread the needle of working on these aging targets with so much promise, but getting them approved for disease first, whether it's Dystrophy or IPF or Obesity in our case.

So, let's talk about some practical applications of AI. You know, in biotech, in aging drug discovery. And you know, with the view too of like, many people listening are probably not

in biotech or aging biology, they are even less familiar with AI too, right? So, I'd be curious to hear from each of you like, what sort of AI application you can't live without? Like, where do you think it's most essential in your pipeline? If you had to pick just one area, you know where the innovation for the last few years has been critical and are there any areas where you maybe thought it was going to be awesome and still have some work to do?

BB: Does drafting HR documents with chat GPD count?

KF: That sounds much less painful that way.

BB:

No, it's such a good question. I mean I see a lot of it is kind of two stages. So, one we use neural networks and AI to actually do data extraction. That's a lot of our pipeline, it allows us to move very quickly and very accurately. As we're growing, what we're finding is that now that we've kind of plumed some of the unseen depths in chemical space we're actually starting to able to do more predictive and starting to use generative AI on it to find our next set of candidates and go with a more structured hypothesis-driven approach versus the unbiased screening. So, we get the benefits of both worlds.

KF: Interesting, yeah.

HY:

I'd say at Juvena, it's really kind of integrating AI into sort of every step of the process from our ability in silico to rank, order and predict, you know, thousands of proteins that have the potential to have disease-modifying effects for a given tissue target based on targeting mechanisms involved in the loss of the health of tissues, known as tissue homeostasis

with aging, and so we're using also a variety of sort of neural networks to kind of do some of those predictions. But then as we kind of get a little further in the process, we're also integrating AI and some neural network-based techniques into our actual in vitro screening where we're doing things as simple as improving our quantitative abilities to predict fluorescent markers from bright-field images or to quantitate the behavior of our animal models after treatment with a specific protein therapeutic candidate.

As the field is evolving, we're really excited about some of the generative AI technologies and some of the new techniques that are really coming about specifically for predicting protein structure relationships as well as novel amino acid sequences that can bind particular receptor targets. So, we're basically learning and evolving as the field does and taking advantage of a lot of the new architectures to leverage, using them to actually train models based on our own internal data to customize them for our approaches. So I think it all is wonderful and it's really about kind of also making sure that there is in many ways a human in the loop so that we sort of understand noise from real data and signal and it's a combination of kind of pattern recognition but also a little bit of hypothesis-driven work integrated it into every step of the process for us.

KF:

And Alex, let's double-click on generative AI in particular because I know that you leverage that a lot in your work. And could you also just introduce it at a high level? So, we've talked about it a couple of times, but I'm not sure everyone's yeah aware of what it means.

AZ:

So sure, our first paper on generative AI for chemistry specifically generated with neural networks was published in 2016. And then we published many, many papers in 2017, 18, 19 utilizing different generative AI techniques to either generate synthetic biological data or generate small molecules with the desired properties. So, think of generative AI as AI imagination so many other forms of deep neural networks and other machine learning techniques are very good at prediction, generalization, and pattern recognition but if you want to generate novel objects, novel data with the desired properties, you have to go generative and one of the most popular generative AI techniques are transformer based

large language models that allow you to generate text. So, in this case, you are trying to predict the next token in a sequence, and those large language models are trained on massive numbers of tokens and parameters. So, you try to compress your understanding of the text universe into one small box and then try to query this box for the answer to your questions, trying to generate the pattern that learned and generating the next token. There are many, many different generative AI techniques. One of the most popular ones that we utilize for small molecule generation are generative tensorial reinforcement learning systems, where we have a combination of multiple generative techniques that generate molecules with the desired objective function, but at the same time you combine them with a reinforcement learning module where you've got multiple predictive models constantly evaluating the output of generative systems and either rewarding them or punishing them for generating good or bad molecules, or some other forms of data.

For example, biological data. Sometimes when you don't need to snap your response like in the case of ChatGPT, you can train those generative AI models and run them for hours or days and they become very good so you achieve molecular-level precision as we've demonstrated with our systems that allow generation with the desired properties over very complex molecular structures are very novel and actually to answer your question, your previous question like where AI can be applied and if I were to pick just one area, which one would I choose? That question was asked to me in 2016 by a very prominent French capitalist and I said, look, we are trying to combine all of these steps into one, right so in one workflow if we disconnect and just focus on just one thing, it's not going to be as beneficial as trying to look across the board, right? That's what pharma does very often they disconnect biology, chemistry, clinical trials, biomarker discovery, you know the payout structures, and even like PR, everything is completely disconnected. Generative AI allows you to connect the previously disconnected areas, especially the large language models that now can reason, and what we are very excited about now is the ability to use transformer-based large language models and other generative techniques to reason on the top-level and now run many other domain oriented AIs in very specific sequences with the desired outcomes, trying to steer them towards the desired objective function and the desired objective function is always in our case is pick the right target that is moderately druggable, moderately novel, or very novel, for which we can generate the small molecule very quickly with the desired properties that will provide the maximum benefit to the patient, right? So how do we go from zero to the patient in as short of time as possible with the highest efficacy? And those problems now can be pieced together by generative systems, and that's the most exciting part for me.

KF: That's really exciting. That's true.

Let's switch topics to another exciting area. You guys all work to some extent on automation, right? And there's this really nice, interesting interface with AI where you can have AI in the loop and have more hypothesis-free discovery. So I'd love to talk about your work there and how it connects to AI. What you're doing now that you couldn't do a few years ago?

And Ben, I know this is sort of the basis for your whole platform if you want to kick us off there.

BB:

Yeah. No, that's such a good question. I think that for us I see it as an accelerator that gets us moving as fast as possible, that lets us actually kind of disrupt some of the traditional paradigms of having to go with the target-based approach.

You know, one example that I was just thinking of as Hanadie and Alex were talking that kind of I think proves the point. As much as we can incorporate it effectively and accurately, it improves all of our research. You know, we're looking at libraries of drugs that have never been used at scale before. This is a very specific example and I hope some of the scientists in the room appreciate this. It's incredibly hard sometimes to work with novel compounds because you don't know how well they're going to dissolve in solution, and if you're working with a couple of 1,000 compounds that could actually be days, weeks, months of technician time wasted trying to get things to work. So, even our technicians in labs now use a neural network that predicts solubility in a solution so that we can quickly triage with those you know 10,000 compounds in the library, which are the 9000 that we should prioritize going as fast as possible with to start exploring this space. So, I. Think the more accessible and hands-on, we can make the AI tools we generate the faster we're all going to go as a field. Does that kind of get what you're asking, Kristen?

KF:

Yeah, definitely. I think that's interesting, right? I mean you're just sort of boiling the ocean to find novel pathways, which I think is important in our field.

BB: We're trying.

HY:

Yeah and maybe just to kind of add in terms of sort of like the automation, when it comes to proteins, it's actually quite hard to do very rapid high throughput screening where you know just the ability to sort of manufacture and have those, the physical amount of proteins you need to test is kind of the right limiting factor and so one of the ways that Juvena has obviated that or kind of reduced that necessity has been in some of the innovations we've done on the in silico predictions of proteins where we've developed a model that we've dubbed PQ net, which uses a boosted gradient decision tree architecture to essentially rank order proteins that are enriched in an in silico library of about 2000 proteins enriched in stem cell secretome using a variety of their features from biochemical, evolutionary conservation, biophysical and transcriptional profiles. Understanding how those proteins may act in healthy and diseased tissues to rank order and predict which ones are actually worth making and testing, and then when we get to the in vitro screening, we're also doing robotics enabled as what we consider high throughput and for example 384 well format and then doing high content imaging in single-cell RNA seek to then continue to generate a lot of that multi-omics data that we can leverage to better understand the function of proteins and also incorporating things like genetic perturbations and CRISPR screening to test more targets more rapidly.

AZ:

So, I'll also add, I guess if you haven't seen my lab just you know, go to YouTube and search for 6th generation laboratory robotics by Insilico. So, I have a facility with six interconnected rooms fully robotized, so I've got multiple islands in every room. The original idea for this facility was to generate a lot of machine-learnable biological data, providing very high-quality data for machine learning predominantly for target discovery so

we can process cells organoids, and primary tissue in humans and animals to identify a variety of targets using different target discovery techniques in a fully automated manner where we don't even have human in loop, sometimes you need to exclude human analog from the loop to de-bias the system and just get the kind of novelty and the risk profile that the researcher is willing to take for a specific target selection philosophy and the system automatically identifies the targets from the samples that you give it, and also tests very large compound library on the samples that you provide. However, I actually realized that there are certain limitations to robotics. And I think, Kristen, I'm not sure how much you use robotics for BioAge, but you probably realize that in many cases, it's not necessary, right? So, once you've got $2 trillion of publicly available data from the NIH and other sources, from the entire web and you've got powerful generative AI technologies, plus massive buyer banks that are available out there, you realize that there is no shortage of targets. So, I've got probably several thousand disease target associations, high value with a lot of experimental evidence on the high throughput. But once you are going to bet on every single target, you should be prepared to, you know, go all the way and put you know 30 million bucks behind the program and that is very quickly going to get into the area where you are very resource-constrained.

So, what we realized is that the main idea behind the target Discovery Lab that we've built is now kind of shifting into indication expansion. So since now, we have this Inflation Reduction Act, which kind of requires you to go off patent at some point in time, right? So, that prevents many of the pharmaceutical companies from going into small molecule space and most likely it will also touch biologics very soon and pretty much every drug to make it cheaper. And that act regulates how long your patent is going to last, right? And if it takes you to, you know, 15 years to develop a drug and the patent lasts for 20 years, it means that you only have five years to kind of milk it, right? To return the funds to the investors and ensure that it is profitable for people to invest in biotech and one of the ways to fight it is to instead of you know, trying to lobby the regulators to give you more patent protection to see where else your drug works and the fact that if the drug works in aging, it's likely to work in many diseases.

The question is which ones, right and which ones would you want to test it in and which drugs do you want to combine it with? And that's where the laboratory automation facility comes into play in a very powerful way. So, you can very rapidly test your already existing drugs with a variety of target hypotheses and combos in a variety of experimental models and see and evaluate the probability that this drug is going to work in alternative diseases. And if you see the drug is likely to work on many diseases, you should prioritize that one, right? It is most likely you're going to get much more substantial returns on that drug, but also, you're going to help many more patients.

KF:

Definitely. Let's take one step back to aging biology, right, which is sort of where we all came from as scientists and where we're trying to work on targets and advance them. So, what can we do as a field, what are we learning from major biology that that is useful? How is what we're doing feeding back into aging biology research? There are certainly areas like biomarkers, but if anything else comes to mind I would love your thoughts on fruitful collaborations etcetera.

HY:

Everything we do at Juvena is really based on this underlying desire to really understand and target the biology of aging and mechanisms associated with tissue degeneration to restore what we call homeostatic signaling. So we're, we're specifically really looking at it from the angle of proteins and secreted proteins in the way that they really are acting as biochemical signals to induce complex signal transduction cascades that will instruct cells and tissues in our body to do things like activate progenitor cells to promote tissue differentiation, to activate the immune system to really react to various types of diseases or infections. So what's really exciting also about our approach of then marrying that to really understanding how proteins secreted by stem cells, which are such a high sore rich source of regenerative factors, what we're seeing is that by doing this phenotype first unbiased screening we're starting to really unravel a lot of novel disease biology and even new kind of underlying pathways and mechanisms associated with the loss of our tissues' health and function with aging. So, there's so much that we're doing I think as an industry, us and others, that it's really kind of opening doors to ways in which not only are we understanding the way we age better, but we're actually leveraging that to target those mechanisms and really restore tissue health and promote Healthspan.

BB:

Yeah, I think one of the things that got me excited about being a researcher in this field is aging is both universal and heterogeneous. So, you know I was lucky enough. This is a little

bit of a personal anecdote. My great-grandmother lived to 111, she helped raise me alongside my grandmother. She was the oldest woman in Alaska and looking at even between those three or four generations of our family, all of us are aging very differently. I used to say I am an aging biologist now I say I'm an aging biologist, and so what I love about what we do is that it is somewhat universally applicable, but our challenge, and I think as entrepreneurs and researchers, is to figure out creative avenues that let our foundational insights into aging biology and health get to patients and to market. And so, I think all of us have probably felt constrained by the market and to pushing down the traditional pharma pipeline and I think that there are some aspects of that, those are the needs of the environment that we are in and we have to work around those. But I think we also have to push ourselves to be as creative as possible.

You know, one example that Ora Biomedical, we just started a partnership with the US Air Force and Space Force because astronauts exhibit progeria-like symptoms, so why not try and take Gero-Preventative interventions and use them prophylactically? It's very early stages, and there's a lot of work to be done but I think the kind of work that we need to do as a field to really progress human health in the way that I think aging interventions can. And I think one of the things I'm so excited about being on this panel with the three of you and your companies is that we're all doing drug development. Which, if we think about the access and equitability of our insights. So many more people can be affected by a drug as opposed to parabiosis treatment or one of the more out-there therapies that other people are advocating for. So, it's just a really exciting space to be in.

KF: Yeah, definitely.

AZ:

So yeah, and one area that I'm very excited about in aging biology is our fundamental understanding of biology being improved by the science of aging clocks. So since the publication of the first methylation agent clock in 2013/2012, when Stephen Horvath and Hannum published their first predictors, this field has advanced dramatically and we

started gaining this ability to track aging and time, and to also try to correlate specific types of biological processes with those aging clocks, and also try to link it to phenotype.

Generative AI transformed this field beyond recognition. So now we can feed and separately tokenize multiple different omics data types into transformer-based models that learn to generalize between methylation, transcriptomic, and phenotypic data types, learn the interdependencies between the different features in those data types, and enable you to either identify promising protein targets, get new biological insights. So now we can basically chat to those biological data types. We are planning to open-source our PreciousGPT 3 soon. Have a look at our precious one and precious two are being published right now. So those tools allow you to generalize among the different data types, and get new insights. And I actually think that nowadays generative AI systems, once you want to teach it the concept of time, you have to teach it aging and the only way is to teach it and train it on longitudinal data from cradle to the grave and everything in between, preferably with all the epigenetic and metadata are associated with it so we can see what kind of factors and stress factors affect our aging processes and what happens in between and correlate that with the disease. And now transformer-based models allow you to do that, and I think that this is the area where we should focus more nowadays than anything else. Transformer-based models for multimodal multi-omics multi-species data analysis.

BB: Alex, can I ask you a quick question, if that's alright?

AZ: Sure.

BB:

Alex, I love the fact that you're making some of your tools open-source. Do you worry about calling it precious GPT given the use case for the original ring of power was to undermine and influence the people that it was gifted to, to bring power back to the dark lord? I just-had a technical question and I'm sorry but I had to ask.

AZ:

Very good question. But I think that they forgot to open source the ring. So instead of that they decided to melt it, right?

KF: Had enough of them.

AZ:

If they were to, you know turn it into dust and give it to everybody. I'm pretty sure it would have been better, and they could have maybe put it to good use, right? One problem that I have.

BB: I guess the Lord of the Rings was a longevity intervention?

AZ:

Yeah, well, it was actually an anti-longevity intervention if you look at Gollum, look at what happened to him, right?

KF: We all hope we can do better than that.

BB:

Yeah, I think it's a good principle of extended life, that poor quality of life, his health biomarkers. I'm sorry, I have fully derailed this. I really apologize, Kristen.

KF:

No, no excellent awesome question, Ben. On that note, it's about time for us to shift gears and move to the audience questions before that one super quick round. I'd love for each of you to share one technology in the space of AI and drug discovery that you're excited about and what you think it will be for the field in five to 10 years. Who wants to go first?

HY:

I mean, I can kind of start it, I think I'm going to sort of chime in and really support a lot of what Alex is saying. With a lot of the generative AI techniques, I think what we've become so excited about recently at Juvena is really leveraging some of these transformer models, these protein language models, and open access resources such as Alpha Fold in order to really identify and predict new kind of amino acid sequences based on natural protein sequences, where it's improved versions of these proteins with greater stability, stronger binding, greater efficacy. So, I really see so much potential for just how this is going to revolutionize the way that we're making new molecules. Not just small molecules, but proteins and probably, you know, larger macromolecules going into the future.

BB:

Yeah, I'll jump in and say I'm really excited about the advent of more in-depth AI-driven tools to measure human health biomarkers. You know there's such incredible work out there with all the different clocks that are available, but I think we need more as we think about trying to get our treatments into actual clinical practice. I'd highlight the work of my former PI Matt Kaeberlein and the Optispan group that he started. I'm lucky enough to be a trailblazer and be a beta tester for all of the different diagnostics that they've run, and it's incredible seeing how your aging Biomarkers can, even with just lifestyle intervention much less a drug intervention, shift in just a matter of time.

AZ:

Uh, well, I am excited about three things, so one, of course, generative AI transformer-based models for multi-omics and multi-species understanding, and at the same time you can query them for targets, discover drugs, and use the same transformer to then evaluate the efficacy of the intervention. So, I'm very excited about that.

I'm actually very excited about your company, Kristen. So, I like this concept where you can search through massive amounts of longitudinal data nowadays that is becoming more available also with generative AI and then in license and put the drug into human clinical trial faster. I think that this kind of approach is pretty pioneering, and you should talk a little bit more about your company as well here even if you're moderating because I think that if I were to do it all over again, I'd probably not do my chemistry, because the probability of success, I mean where we are, I could have failed like many times and you've seen other companies failing in the same area on chemistry very, very easy. But I think that we need to find new uses for drugs that are currently in development and do indication expansion into age-related diseases.

KF:

Yeah. Thanks guys. And yeah, totally aligned, Alex, right? It's very much like your strategy of looking at different indications. There are so many other molecules out there that have these broader potentials. All right. We have a whole bunch, a lot of audience questions. So, we're just going to get started and see what we can get through by the top of the hour.

So first, what do you think the field of aging biology needs to focus on to help biotech companies like yours? I guess from a science and maybe also a talent pipeline kind of question.

HY:

I mean for me; I think it's the issue for a lot of us is kind of that bottleneck of as you kind of go through development. You know I think on the kind of research side, the innovative side, the platform side, we're all doing fantastically well, but it really comes to that point where now we have to kind of grow up and mature into these drug development companies where

more traditional investors that traditionally write much larger checks are needed for us to get our products to market and to help people. And there are just such huge bottlenecks in sort of regulatory and acceptance I think broadly and globally for this approach of healthcare versus sick care.

AZ:

I'd like to resonate with that, and I think that what the industry needs is one drug approval for a dual-purpose therapeutic that targets aging and disease at the same time. So, with GLP ones, we saw some kind of early birds of that kind of process happening where they targeted a core biological process, got lucky, and now people who are wealthy and obese at the same time can now be wealthy and not obese and maybe live a little bit longer. But at the same time, very few people in our industry had hands-on experience with drug development, you go to any drug discovery conference for aging research, for example, and there will be very, very few people in the room who ever nominated the preclinical candidate. There will be even fewer who did the phase one study right? Even fewer did the phase two. So sometimes there were no, no, no hands in the room. And I think that one of the reasons for that is those processes take a very long time. You need to stick with the program with one company for about a decade or more and spend your life doing that and not something else. And that requires dedication, and we need to get some approvals and show the investors that it's commercially viable. If we don't show investors that this is a gold mine, we can, you know appeal to altruistic reasons and altruistic emotions all we want but unless we put some real capitalist drive behind aging research, we are not going to see an avalanche of companies popping up and going to the clinic.

KF:

Yeah, I'm going to add to that actually because I think there is so much good science and aging biology, there are a lot of ideas that can be translated. And I think we are held back a little bit by that, relative to other areas, there's sort of less of an interface with industry, right, like to your point Alex, like a lot of conferences on oncology, there's a huge biotech presence, there's a huge pharma presence. That's not true in aging, with the one exception of Alex's conferences right there (AARD). But like you have a few pharma coming, right,

Alex, like they're willing to talk to us now, they're interested like Novartis, Samedan like they're interested in aging biology. They want their ideas.

AZ: Eli Lilly.

KF:

Yes, Eli Lilly, of course, can't forget lilies. Yeah, but, you know, I think there's a lot of willingness on their part to sort of engage, right? And there's a lot to be learned on both sides in terms of science but also in terms of the challenges of translation, yeah.

BB:

Yeah, echoing that, you know, I think it's so great, the ARRD, I look forward to it every year and looking at the talks that come out of it. I think that you know, one of the things to flip it around a little bit is showing the researchers and academic aging research what it looks like on the other side, and so just like I think you were getting at, you know, I've been spending ten years going to aging conferences and maybe there are one or two companies that show up and I think that we lose a lot of potential talent because they don't, you know, academia is not for everyone clearly, and academia still has its strengths, but we have to show these developing and younger scientists that are in training, you know, what are the potential outcomes? Because then they'll invest in their training and then funnel into our actual talent pipelines. I'm excited about that, I love the idea of education and more, and it also improves the likelihood that they, as educators, and ourselves, as community members, are telling traditional VC, that aging is, as Alex said, a gold mine. And, you know, we're no longer digging with shovels, we've got backhoes. All four of our companies have these great platforms and you know it takes actualization of that.

KF:

So, we have a number of different questions all around the FDA and FDA's engagement with the concept of aging and what that means. So, I'm just going to read a couple of them and then we can engage with them.

So one, does the FDA recognize aging as something that can be targeted or treated for clinical trial purposes? If it did, would that impact the pace or impact of your interventions, and if it didn't, would that be a bottleneck to your work?

AZ:

I can very quickly answer this question. I think Kristen you should be answering this question because you know this kind of you have a black belt on this and I just wanted to say that I love the FDA. There were three-letter words I previously kind of disliked before I got into clinical trials. Now I think it's a well-oiled machine that wants to talk to you and they have been polished by many patient advocacy groups over the past couple of decades to be super responsive, to be pro-patient, to be pro-company. They want to ensure safety and effectiveness, they won't let you know bad things pass, but they have very specific response times that they have to adhere to. So that's kind of the intro.

You don't need to recognize aging as a disease to get an aging drug approved because investors want you to approve the drug for a specific disease, and it might be an easier way to do that because, you know, imagine a phase three study for aging, you would probably need to have a massive number of patients pretty much like for obesity. That's probably not something that you would want to do commercially. You would want to try to get a drug approved for an indication that is age-related, you know onset 60, 65 years old. So that's why we decided to go for IPR. Then, with minimum resources required try to prove that it works somewhere else. If it does, you would be able to do indication expansion if you're fast enough within your patent life. So, you don't need to get aging recognized as a disease. It could be an impediment, in my opinion.

HY:

Maybe just to kind of you know, Echo Alex there you know while the FDA doesn't recognize aging as a disease, there are many diseases of aging as well as chronic conditions such as obesity that are associated with and due to unhealthy aging. So, there are a lot of ways that

we can get our therapeutics to market by targeting a specific you know disease, but then expanding. And so for example with Juvena, our first therapeutic that will enter phase one this fall activates AKT signaling specifically and acts to enhance muscle regeneration and muscle metabolism, and we're seeing that it's showing efficacy across not just aged animals, cyclopedic animals, but also a variety of diseases that have this kind of progeroid accelerated aging like associations such as many dystrophies. So, if you're kind of savvy and understand the regulatory process there are ways in which you know, we hope, to get our products to market first for one disease, but then because it's affecting multiple organ systems or can target multiple other diseases within that that tissue realm, we can expand.

BB:

Yeah, I think that echoing both their points, I think it is, right now we are constrained at going basically after age-associated biomarkers. I do think you know to echo again the sentiment of education for people that are not in aging biotech, in research.

I mean again I came out of Matt Kaeberlein's group, so we're all intimately familiar with rapamycin. You know rapamycin is essentially where medical marijuana was 20 years ago, where if you have enough money and you can find the doctor, you can get it prescribed. No, it's true. And I think that despite the FDA not approving aging, there are people out there taking stuff for aging right now and these are FDA-approved molecules. I know it's going to be a long barrier to get that to the point of actually really getting something out there for aging specifically, despite the wonderful market cap, if that were to be the case for any of our compounds, right?

But I think that in this context, we as longevity biotech do kind of have this obligation to be somewhat creative with how we go after these. And I think everyone here has kind of acknowledged that you're going after aging biomarkers, but you know, if we think about what's going to move the needle forward any success on goal, as Alex said earlier, is going to push the needle. And so that may be an off-label interaction from one of the things that we've got for a disease, it could be even getting it through companion animals. You know The Dog Aging Project is ongoing with trying to get things moving in that front, but even that alone would be a huge indication and may have a lower barrier than the traditional clinical trial that we think about for aging, that we probably can't do right now.

KF:

Yeah, The Dog Project is super creative. I think for those of us working in humans right now, there are really two main points, right, one is that as we've touched on these aging-type diseases. So often, these aging targets most of the time, are also disease-relevant, right, which is the scientific/philosophical point. But the other one, which is important, is that it's just really a practical point, right? Like if we are going to do an aging trial in phase three, it's going to be huge, it's going to be long. If you have, you know, call it $50, 100 million to deploy on trials, what would you rather do? Make one big bet on one mechanism or make more smaller bets, some sort of more focused on these specific things? So it's challenging.

Even if there were a regulatory path, that many ways would still not be sort of the right strategy for most of us, especially for new medicines. I think it might be different arguably for things like Rapamycin or Metformin where there's human data already, but for new medicine, you don't quite know what they're doing yet or even if they're safe. A different strategy will probably also still be the right one.

BB:

Totally. And I really defer to your experience actually being further down the clinical pipeline than we are right now. Do you think that if there were better biomarkers of human health that you could look at over six months to a year in terms of looking if something is truly Gero-protective, do you think that might make it easier to get some of these to patients sooner?

KF:

I think that I mean, biomarkers are certainly useful in lots of clinical indications, right? So in many cases, even though they're not surrogate endpoints yet in the sense that the FDA will use them to approve a drug, we can still look at them, right? And they're still incredibly useful from a research perspective and giving us a lot of confidence about these mechanisms useful in a practical sense too of like ‘hey fund my giant trial off label and this giant population ‘look at my biomarker’, right? So, I don't know how much the regulatory aspect of it is that much of a barrier, but I think there are certainly intermediaries that frustrate me, right? Like I would love there to be a regulatory path for Sarcopenia and

frailty, which I think is important, and there's sort of milestones along the road that I think we still need to work on as a field.

Let's see, all right. We're almost done, so I'll maybe I'll just ask one question. Again, going back to talent and as a young scientist in the field, what skills would you recommend we start learning to stay current with the rapidly advancing AI landscape?

AZ:

Kristen, would like to start yourself first because you are hiring a lot of young scientists as well, right? And you were a young scientist yourself, I remember you when you were a master's student and now, you're the CEO of a giant company.

KF:

Yeah. No, it's a great question. The landscape has changed so quickly and there's so much online now too, right? I mean, I think you can immerse yourself in, in the field and computational biology in general. I mean, you can probably get a start with online courses, but then you can probably also work with a company or get involved and get exposed to what's being translated. The advice I often give personally to people in the field is just to go to conferences. You know, nothing beats walking around posters and talking to people about their science, learning about what's cutting edge and what's exciting to you, and then learning, you know, once you believe in a problem, kind of learning all the tools you need for that problem, whether it's AI or whether it's molecular biology.

AZ:

I agree 100%. I think that the best way to prepare yourself for the industry is to try to see yourself as a pharmaceutical industry executive 15 years down the road and plan your career backward. So go to a good school, don't skip anything, don't cut corners, try to talk to as many big Pharma people as possible.

You know, even Apple learned something from Xerox. You might want to look at the pharma companies as those Xeroxes where you can find this mouse that you can repurpose and that you don't take it to the next level. So I think that's very important to spend some time in Big Pharma before you go into biotech, it also will give you some understanding of the regulatory landscape, and the traditional processes, and then when you look at the industry from the outside, right, from the outside Pharma, it will be easier for you to partner because you will know how those large mechanisms work and they're not going to go away.

HY:

And I think you know, one additional thing to add is just this idea of interdisciplinary learning and training where you don't necessarily have to be the expert and you know coder that knows how to train these models or build the architecture but just know what's out there, what's available. So, if you are a biologist and an expert in one area, you can start to leverage the latest, you know, cross disciplines and across AI to potentially improve your ability to identify solutions and to problem-solve. So that also entails partnering with people from other disciplines and kind of just having that open mind.

BB:

Yeah, echoing that, I think that's such a great point focusing on problem-solving and being able to adapt to the new tools. I'll be fully honest I use ChatGPT to help me write software every single day, but it's about having a higher-level idea of how those pieces fit together so that you can adapt to all these tools as they come and figure out the best way to most efficiently use them. It’s a great question.

KF:

That's a good point. Like, this whole landscape evolves every year, right, and you have to stay on top of it, and that's also a lot of the fun, right?

Well, let's wrap it up. Thank you so much, I really enjoyed speaking with all of you.

So AFAR will be sharing a recording on their website, and over social media as well. You can follow AFAR on LinkedIn, Twitter, and Facebook. And finally, please support AFAR with a donation to help them continue to build free webinars like this one and circulate them to the community. And yeah, thanks again, all of you really enjoyed the conversation.

AZ: Thank you AFAR and please attend ARDD.

HY: Thank you all.

AZ: All of us are going to be there.

BB: Yeah, thank you all so much, Kristen. AFAR out job moderating.

KF: Awesome. It was easy.

HY:

Everyone do reach out on LinkedIn and social networks. If you have further questions that we weren't able to answer live, I'm always happy to try to chat with folks and hopefully, if you see me at conferences come say hi.

KF: Some very quotable moments. Thank you, guys.

AZ: Take care.

HY: Take care. Bye.

Watch a recording of the "AI for Longevity Drug Discovery: Breakthroughs and Challenges" Webinar here.