Alexander Fleming (00:00:24):

Alright. I believe we are just now opening our virtual auditorium, at 1:30 p.m. EDT, for our two o'clock session, two o'clock eastern time. This of course will be a global audience joining us. So let's just say welcome to everybody who's joining the anchor desk participants of our virtual conference. We like to do this to instill a sense of community.

Thomas Seoh (00:01:00):

We're having some technical issues with your audio breaking up a little bit. I don't know if you have earbuds or something you could put on. I see Saul

Alexander Fleming (00:01:11):

Gatherings so we have an opportunity. All right, well Thomas, keep going. I will see what I can do.

Thomas Seoh (00:01:21):

Well, I want to welcome Saul to our pre-game show here. Hi Saul. Hi, how are you? You see our anchor desk here. I don't know if it's top or bottom on your screen, but I see George Vradenburg, the founder and chair of the Us Against Alzheimer's not-for-profit, as well as the founder of the Davos Alzheimer's Collaborative. I see Joan Mannick, CEO of Tornado Therapeutics Science, a Long Bio company working on mTOR pathways compounds. I see Jamie Justice, she's the EVP of I hope I get this right: XPRIZE Health and the Executive Director of XPRIZE Healthspan. I think that prize is one of if not the largest prize to date in the XPRIZEs. I see Beth Stevens joining. So welcome.

Alexander Fleming (00:02:18):

Hi Beth. Hi. Thank you.

Thomas Seoh (00:02:21):

How's your audio? I've been tap dancing...

Alexander Fleming (00:02:24):

You tell me.

Thomas Seoh (00:02:25):

So far so good.

Alexander Fleming (00:02:27):

Well, sorry, I'm not sure what the issue is. I've actually been working on technical issues at my end, but do tell me if I stop being heard. Well, I think we can start our little chat among very esteemed anchor desk participants. We bring people with very different backgrounds, but they are all for ways of slowing the aging process in general and in various ways preventing age-related diseases. And we'd start with George Vradenburg, who is quite an amazing person, not only in his grasp of all the challenges scientifically and otherwise involved in finding approaches to treat and prevent Alzheimer's, but he really has been on the ground making things happen. And so George, we could go on and on about all the efforts you're leading, but why don't you give us an update on what you're doing right now and maybe we'll come back to you later for some follow up questions.

George Vradenburg (00:03:50):

Sure. I'll just take two or three things here that we're doing. First, we're just trying to get a second disease modifying drug that alters the course of Alzheimer's through the FDA. The FDA had an advisory committee meeting this week with a positive vote. So we anticipate what will be the second disease modifying drug. This drug has the effect of slowing down the progression of the disease by about five months over an 18 month trial. And modeling would suggest it could slow the progression of the disease from early to moderate disease by about a year and a half if you continue to take the drug [though it?] has side effects. So obviously we're looking for an innovation pipeline here that will get more powerful drugs and safer drugs. The next step obviously is to get these drugs actually embraced by a healthcare system that does not know how to deal with the brain at all in clinical practice.

(00:04:51):

And so we're working with a very, very large consortium, which we convene around blood-based markers around digital cognitive assessments. What are the qualifying criteria for good blood-based markers and not good blood-based markers and good digital cognitive assessments and not so good cognitive assessments and how do we get them actually built into the businesses of health systems where there isn't a clear reimbursement pathway nor a clinical pathway for doctors or for patients in terms of pathway for patients. Totally almost uncrowded field. Then obviously these two drugs that currently are on the market, these disease modifying drugs are now being tested in preclinical [pre-symptomatic] populations. The view that if you slow down this disease earlier in its course, you may be able ideally, eventually to be able to prevent symptomatic Alzheimer's much like we do with HIV AIDS. And then if you look further down the pike, probably about eight to 10 years out, we're now working with a consortium of companies, regulators and payers on Alzheimer's vaccines which are now in phase twos and which will take some time to go through those phase twos because they are being tested in preclinical [pre-symptomatic] populations and there has not been a history here yet of being able to approve vaccines based upon surrogate endpoints in Alzheimer's.

(00:06:25):

So we're working with regulators to anticipate those problems. Obviously if in fact some regulators actually approve the drug, what does the screening cost for people in preclinical populations who are a target for these vaccines? So we're trying to anticipate the preemption as catalyst has been talking about a preemption of this disease by going earlier in the disease course as we know that it begins 20 to 30 years before symptoms and either stop it or slow it early in its course. So we never get symptomatic disease. It's a goal that I think is within reach in the next 10, 15 years, but it is a 10 or 15 year process at least. And we as patients, as patient advocates, basically are trying to accelerate that process, anticipate problems, and solve them before we're confronted with actual drugs. So I'll stop there.

Alexander Fleming (00:07:25):

George, you are a key catalyst for those efforts and we need all the catalysts we can get. So keep at it and want to come back about vaccines in a moment. But good to see David Holtzman has joined us and so we're almost complete on our panel. Let's go now to Joan Mannick, who is sort of a legend in the field geroscience. She's taken a therapeutic agent further than anybody, an organization towards an age related indication that is targeted at a geroscience route. And in this case, Joan, you can maybe give a quick summary of what that was about, but give us an update on what you're doing right now.

Joan Mannick (00:08:24):

Thanks Zan. What I'm most passionate about is the mTOR pathway and a specific class of drugs of which rapamycin is the best known. They're called rapalogs. And the reason I love this pathway and this class of drugs is that rapamycin has extended lifespan in every species studied to date – yeast, worms, flies, in mice and data just is coming out in abstract form that it's extending lifespan in primates. So there's something fundamental about inhibiting mTOR, which is what rapamycin does and lifespan and exactly why inhibiting this one protein extends lifespan isn't clear, but in preclinical species it helps the function of certain aging organ systems, one of which is the brain. So this is an interesting sort of complimentary approach to the targeting of beta amyloid or tau in the Alzheimer's space. Could we also just try to target these fundamental pathways that underlie why aging organ systems decline as another approach? And it's much earlier than anything that George was talking about, but I think it's exciting. And so I love the mesh of this particular session where you have the experts in the neurodegeneration field and then you have sort of people in both fields like Saul and can we sort of span these two areas of aging biology and neurodegeneration?

Alexander Fleming (00:10:16):

Wonderful. Well so much more to talk about what you're actually doing right now, but we will come back to it. And by the way, we expect our anchor desk participants to engage with the panel later on towards the end of their discussion. But let's bring up Jamie Justice, who has made an amazing transformation just in the past year from a preeminent researcher investigator in the field of geoscience to now heading up a very exciting program at XPRIZE. So Jamie, without further ado, give us the summary of what you're doing at XPRIZE.

Jamie Justice (00:11:01):

Yeah, thank you Zan. It's an honor to be here. I'm an unrepentant academic still at heart. I still do hold a faculty appointment though adjunct only for the time being and last year after spending years working on frameworks for testing translation of therapeutics, whether against any variety of things that if you could actually target aging, how do you measure it, how do you test it, how does the regulation work? And so doing this work of going from cells, mice to human trials, whether these were early stage first in human trials, which we had done some work with Jim Kirkland and one of the first senolytic trials to where I got to know Zan and Kinexum better was actually spending years working with Nir Barzilai, Steve Kritchevsky and others on the TAME trial. So again, how do you go from a cell in a mouse up to something like a phase three regulatory facing trial for aging, in which we have to figure out how do you measure it, how do you think about it?

(00:12:09):

And as Joan said really eloquently, right, if we're looking at these upstream biologic factors, which I know Saul is going to talk about as well, and begin to look at some of these pathways for therapeutic opportunities that span any disease class, this is really where we begin to talk about aging, where certainly the brain is incredibly, incredibly important as both cause and consequence to many of the downstream factors. I mean it really is incredibly important, but how then do we also interface with aging, which is more than any one disease, more than any one phenotype. And so taking an approach that goes from function, phenotype and the biology and how we begin to test these frameworks. And so that's really what we have the chance to do with XPRIZE is having tried to do some of this network approach before as an academic, it's really hard to get alignment without either using a stick or a carrot.

(00:13:12):

And here was a chance that I got a call, cold call about a year ago that they had raised over a hundred million dollars and they needed somebody who was unbiased - my interest has always been in the testing and the frameworks and how we set this up and how we address the questions and actually do global community building. That's essentially what we've done is we have $101 million to dangle at the end of a very big stick and say, okay, if we're going to run these into early stage trials, let's at least have a level playing field so that we can begin to make comparisons across therapeutics and really push the field because things we don't know, right, first endpoints that we're looking at is that aging is more than one thing, but cognitive function is one of the key cornerstones as is physical function.

(00:14:05):

So like muscle, and Joan's work was really informative here - immune function - we just made it through a pandemic where we've learned that for older adults, the really important factors are to maintain productivity and engagement, have to have mental faculty in order to do so, cognitive ability, physical function to be able to participate in life physically and then have the resilience in order to leave your home comfortably and engage. And so these are really the cornerstones of what people often care about and it's not specifically disease-based, it's really function and engagement. And so how do we begin to build testing frameworks around that that still allow for the deep biology that still allow for testing of things that are very informative, important to specific disease processes like Alzheimer's disease, but still have a broad enough base that again we can move forward and questions we don't have answers to and allow the actual community to work together to begin to define them.

(00:15:06):

Who do you test these therapeutics in? George talked about this really well, about how early in the process do you go, where do you go with prevention versus treatment and leaving some of those questions up for competitors to innovate is that this is a great chance to actually let the global scientific community tell us how we should do this. All we're doing is laying a foundation, allowing people to come together and give us comment and help form the field together through a competition. Again, there's enough money out there that we're hoping to get people down that pathway to try to go forward and help actually form the field together as a collaborative rather than one-offs. So that's my whole spiel and I'm actually in a really fortunate position. That's a great spiel - rather than leading, I get a chance, I just get to be of service to the scientific community and I mean it really is, that's what this position feels like , very much like a nonprofit. So it's a whole lot of labor and a whole lot of love.

Alexander Fleming (00:16:05):

Well, so exciting. What specific carrots are you offering right now?

Jamie Justice (00:16:11):

That's great. So we're currently in a pre-registration phase for the rest of this month. We're still inviting public comment. We've had so much public comment and we're revising some of our testing frameworks. We re-envision what success would look like. How do you de-risk a larger phase three trial? These are phase two trials that we're going to be promoting and we're looking at those frameworks. We're in pre-registration now. We open for primary registration at the end of July. We were hoping that would be the beginning, but it'll be the end of July. Qualifying submissions for our interested teams will come in at the end of the year by December 20th. That's a pen and paper submission showing your research and discovery to date. And then going from there is by next year these teams need to be in early stage proof of concept studies. And again, the purpose there isn't really to get major measurement characteristics, it's to show us do you have a therapeutic that actually affects aging?

(00:17:08):

Do you have a clinical center you can test these in? Can you actually bring people into the center? Do you have data that can be submitted? I mean it's almost a run in for the finals. And given the [RD?] to date, the ability to recruit the strengths of the investigative team, the promise of the therapeutic, we will advance those on our finalist in 2026. Each of those teams will receive $1 million. I know it's not enough to run a one year trial. And we'll also be trying to set up with as many investment strategies and platforms as we can and funding opportunities for those teams. Finalists will go out, run a one year study and they have to show that their therapeutic within the course of that year can improve muscle brain and immune function. Not one or two but all three. And so it is a very rigorous design that will progress the field and they have the opportunity collectively, the total prize purse is $101 million, but for the finalist, the awarding of that will be dependent on the magnitude of the effect that's shown. So the best team to improve all three [dimensions] will win.

Alexander Fleming (00:18:16):

Wow. Well very exciting. We look forward to watching the progress of that competition

Jamie Justice (00:18:22):

And I look forward to hopefully having some of the people on this call [apply]. Again, we have an opportunity, what do we measure? What therapeutics work, what strategies can be used either alone or in combination? How do we actually get these out of the lab and to real people who need answers now?

Alexander Fleming (00:18:40):

Terrific. So much more to be said. And we are today focusing on neurodegeneration as a general target, but of course we're all interested in some of the other aspects of the aging process, all of them and Thomas, we do plan to come back to some other therapeutic areas that are, let's call them age-related conditions that are important to target. You might just sort of give us a glimpse of what we might be doing in the next six months.

Thomas Seoh (00:19:25):

You caught me a little bit with wide eyes because we are looking at, developing potential programs, e.g. in sarcopenia, medical devices, etc…. but what I can announce, and I was saving it with my closing little housekeeping spiel, is that we are organizing sessions on draft legislation actually for regulatory pathways for health span products. So I think you'll find it a little bit interesting, it's like watching the chef's kitchen table. You can watch the sausage being made of trying to figure out exactly how we can make tangible tractable progress in that area. Everybody wants to do it but it requires folks who are familiar with the process. Another one Zan's been working on is biomarkers, actually with one of Jamie's colleagues, Steve Kritchevsky, and endpoints as well, because that's really, really important. I mean everybody in the field is looking at biomarkers to start as surrogate markers, but Joan will know, I think she'll have opinions on registrable endpoints given her experience with the agency. We can certainly look for tangible clinical signs and they could be sufficient for normal approval. And George, obviously if we're able to get reversal of symptoms, that should be very a nice conversation with the FDA because they can clearly see what the clinical benefits are. So it'd be interesting to see what we can do in those areas. I see Larry has joined us, so we have both of our moderators here. So we're ready. We've got 10 minutes to the start of the seminar.

Alexander Fleming (00:21:08):

Well just to say that we will be coming back with what I believe would be a very rich offering of sessions if not in person or at least longer conference than the two hour session we're doing today. We're particularly interested in engaging FDA on regulatory pathways that will be suitable for the various candidates for geoscience related indications and there is complexity and challenges, it's time and resources and making things happen sooner than they otherwise will if we leave our current conditions as they are for evaluating and approving regulated products. So that is a major area of interest for us, and we're hoping to come back at the end of the year with a very robust effort that will engage FDA and other important stakeholders in this process.

(00:22:20):

So here we are with all of our panelists assembled and I'll start off acknowledging Lee Rubin at Harvard and thanking him heartily for agreeing to co-moderate this session and he has been working hard with Larry Steinman. Larry is another force of nature and a dear colleague of mine. We go back a number of years over a quest in another therapeutic area, but we also together co-founded the predecessor conference that started in 2017 in London and Larry, we often recall that he just stepped off the plane because of a family obligation and walked right into the conference right on time and it was great after…

Thomas Seoh (00:23:16):

Off a red eye from California to London.

Alexander Fleming (00:23:18):

Yeah, right, exactly the

Thomas Seoh (00:23:20):

That context is important, right?

Alexander Fleming (00:23:23):

Larry brings the long history, as a co-founder of this conference, as a mover and shaker in many other ways. So delighted to have Larry and Lee to moderate the session. Before we do get started with the panel, we have a few more minutes. There's no reason that David Holzman, you can't just chime right in. Saul, you've heard some things that might've piqued your, made you think, maybe you'd like to comment?

Thomas Seoh (00:23:58):

And Beth, and Tony.

Alexander Fleming (00:23:59):

And Beth and Tony, we're so honored to have all of you and we like to make this informal so we're not standing on ceremony. We're not going to formally start the session until the top of the hour, but we have a few more minutes before we do that and as our audience begins to or continues to grow.

Thomas Seoh (00:24:23):

And just a reminder that our conference brand is not to have a bunch of talking heads at a lectern. It's much more like a dinner salon. So just as if we're having a nice dinner and having a conversation about

topics of interest to us, please let's at it. The hypothesis is, and it's certainly [the case] for me, that the audience will find that actually very interesting and worthwhile.

Alexander Fleming (00:24:46):

And by the way though, I am so sorry that we can't just have people popping out of the audience going up to the microphone for questions. At least you can put your questions in the Q&A function of the Zoom feature and do use the chat function. We'd love to see your greetings from Madrid or wherever you may be right now. And we also like to see the substantial comments that are often made. We capture these and often we'll follow up with you and try to address.

Thomas Seoh (00:25:22):

There are actually some questions in the Q&A function already and there's a comment by Peter Kador of his therapeutic approach that could be relevant to Alzheimer's.

Alexander Fleming (00:25:32):

Yeah, and we did receive a number of impressive, very substantial questions from those who registered. So we've got more questions than we could possibly cover, but we'll do our best and we often will come back with some answers in our transcript that will follow and become available within a few days of this conference being completed.

Thomas Seoh (00:26:05):

I guess I'd also comment that most seminars, webinars, conference sessions are 'one and done'. Our vision, and we're not quite there yet, is that we'd like to build a community [for follow up discussions] - if there are follow on topics we could develop further, we're very friendly, we're open, please email us and we'll see whether we can't get a continuing conversation going with panelists and others. So don't think of it as you've attended something and you've gone home and that's it. Hopefully we can keep an exchange of ideas going.

Jamie Justice (00:26:40):

So Thomas and Zan, do you guys mind if I address [one of the questions that were posed?] Michael Goldstream is interested in behavioral health and lifestyle change versus predominantly pharmaceutical and I can't speak to what the panelists I believe today will speak about, but I can tell you from a position I now get to sit in is actually listening to what the research community globally is interested in working on. And I would say that at least when we're thinking about aging and also neurodegeneration from some of the groups that are coming in, certainly pharmaceuticals are a strong interest, but I would have to say almost about 50% of those who are pre-registering for this global prize that we're running are actually looking at things in combination with some lifestyle or behavioral intervention. So whether that is like a caloric restriction or other food or dietary restriction, or [timing of feeding], there is certainly a really rich history and conserved effects across species. Again, really going into some of those nutrient sensing pathways [mentioned by] Joan such as mTOR inhibition, there's a rich history of looking for things within lifestyle and behaviors, whether alone or in combination. And I would say certainly we're seeing it,

George Vradenburg (00:28:04):

I'll make a comment on this too because we get the national government to commit to a national plan to prevent Alzheimer's through reduction of risk factors. And so the most promising effort here, well there are a number of avenues that are being explored both in research and from an implementation point of view. The one that I am keen on is how to basically use the GLP-1s for cardiometabolic interventions in midlife and then demonstrate the cost effectiveness of doing that at a national level in order to reduce future Alzheimer's. That is a bit way out there in terms of a national plan, but if I can get a country to commit to using major screening and implementation of GLP-1s, I'm hopeful to get the GLP-1 providers to get their price down so that it becomes cost effective to actually not only reduce obesity and hypertension and diabetes, but demonstrate that in fact you're reducing Alzheimer's significantly over the next five to 10 years with respect to those populations.

Alexander Fleming (00:29:19):

Well George, indeed, the session you co-chaired [last September in Targeting Healthy Longevity on interventions in the pre-disease state] included the CEO of Lily famously making the provocative statement, speaking to the head of the UK FDA equivalent, the MHRA, to let's make the UK obesity-free.

George Vradenburg (00:29:46):

Demonstrating the cost effectiveness of that I think is a great challenge given the price of these drugs, but nevertheless, I think it is a viable strategy to reduce future dementia as well as reducing obviously obesity, diabetes, and hypertension.

Alexander Fleming (00:30:04):

Well, wonderful point and what a rich discussion. I wish we had about two hours more, but we are coming to the top of the hour and I want to welcome all of our participants and the audience, which is global and joining us for what will be such an important discussion about targeting neurodegeneration as a condition that should be approachable as a target for avoiding versus just treating. So enough for me, I would like to just turn the floor over to our co-chairs to whom I

Thomas Seoh (00:30:49):

Zan, do you want some housekeeping comments first, or…?

Alexander Fleming (00:30:52):

Oh yeah. Well we should very quickly thanks. Give us the housekeeping announcements.

Thomas Seoh (00:31:00):

So a housekeeping reminder to enter any questions for the speakers in the Q&A function or the chat function and the moderators will try to get to them as time allows. Similarly for the questions posed by registrants at the time of registration. As usual, a link to the recording [of this session] will be available , and slides (well, I don't think we'll have slides today). Transcript and chat log will be circulated to all registrants and will be made publicly available within the next day or two. A distinctive feature of our virtual conference session is that we've enabled the chat function for audience interaction. So just for warmup, those of you who are willing, please say hi in the chat, your affiliation if desired and from where you're logged in. So I'll turn the mic now over to Kitalys founder and President, Dr. Alexander Fleming, to introduce our speakers.

Alexander Fleming (00:31:45):

And I'll quickly pass the torch to co-founder Larry Stein Steinman and his colleague over in Boston, Lee Rubin.

Larry Steinman (00:31:56):

Hello, I'm Larry Steinman speaking from the Stanford campus. I co-founded the original series. We have a different name now back in 2017. I'm a neurologist at Stanford, very interested in longevity as I get older. And let me turn it over to Lee Rubin for his brief introduction. Then we'll go around to our panelists and have them describe their activities. Lee.

Lee Rubin (00:32:25):

Thanks Larry. I'm Lee Rubin. I'm a neurobiologist and stem cell biologist at Harvard University. I've actually known Larry on and off for many, many, many years now and I'm really happy that Zan, Larry and Thomas invited me to get involved with this organization and I'm particularly excited about the quality of the speakers that we have today and the breadth of approaches, many of which were raised already in the pre-session that they're going to cover.

Larry Steinman (00:32:54):

Thank you. Let's go around our panel and some brief introductions and I just want to remind people that this is going to be a conversation as if we were at a restaurant or sitting around in somebody's living room. We're going to answer questions from the audience. Some of them have come in already, some are around the chat, but let's just go around, we'll do Saul, Beth, Tony and David, and let's start out with Saul.

Saul Villeda (00:33:29):

All right, sounds good. Hi Larry, hi Lee. Thanks again for the invitation. So yeah, my name is Saul. I'm an associate professor at the University of California San Francisco and also the associate director of the Baker Aging Research Institute. A little bit about my background. I actually know a lot of the panelists. I actually did my training with Tony, so it's like second generation and first generation. On the panel I study systemic and lifestyle intervention. So everything from exercise, we've heard of caloric restriction, things like parabiosis - young blood administration. And I guess the idea behind the research we're doing is that there are signals - that you don't actually have to necessarily do the physical intervention, but that we can actually find mimetics, blood-based mimetics across different interventions as an alternative. And really the reason that we're thinking about that a lot is that oftentimes we know these things are great, but a lot of times people are frail, especially with neurodegeneration. So giving that benefit over without actually physically having to do a lot of these interventions is one approach that we're taking. So kind of big picture.

Larry Steinman (00:34:35):

Thank you. Beth?

Beth Stevens (00:34:40):

Hi everyone. My name is Beth Stevens. I'm a faculty at the Broad Institute and also Harvard Boston Children's Hospital and my lab is focused on understanding the glial cells in particular and immune cells like microglia and macrophages and their role both on normal aging and also in both risk and resilience.

In terms of mechanisms of neurodegeneration, I focused a lot on Alzheimer's disease I think for the last many years in part because emerging genetics more and more are sort of directly implicating myeloid cells in microglia. So that was a really nice convergence of where cell specific information and genetics landed in a cell type, which meant we were in a position then to dig deeper into the mechanisms in the biology using a combination of human cell models, IPS models, human samples, which now we have a rich source of tissue and CSF and blood from different cohorts and patients where we can look profile through unbiased approaches.

(00:35:40):

But in the end of the day, we really are all trying to get towards mechanism, both in terms of mechanistic biomarkers, which we'll hopefully talk more about here. I'm really interested in identifying immune biomarkers that change across disease progression that we could use in combination with other biomarkers [for] neurodegeneration, but also most importantly, how do we sort of narrow down on some potential therapeutic targets and pathways that we could translate to the clinic. So we could hopefully talk more about that, but it's, I really think the understanding of the baseline changes in normal aging more and more is a huge gap in the field. So I like to think more about how we could be bringing the expertise of this group in terms of normal aging together with some of the neurodegeneration mechanisms we've been thinking about. I think the two together are going to be really, really critical. So thanks so much for having me today.

Larry Steinman (00:36:34):

Thank you Beth, David.

Dave Holtzman (00:36:37):

Hi Larry, thanks so much for the invitation to be here. My name's Dave Holtzman. I'm from Washington University in St. Louis where I'm a neurologist and neuroscientist and I've been working on issues related to Alzheimer's disease for about 30 years or so. And a lot of our work is focused on trying to understand how Apo E, the largest genetic risk factor for Alzheimer's disease actually works. What's the mechanism by which it affects disease? By understanding more about it, can we actually develop better diagnostics and particularly better therapies? I think the other things that I've been very interested in in human studies is development of biomarkers for the disease. So my colleague Randy Bateman and I started a company 17 years ago called C2N Diagnostics that now has some of the amazing plasma biomarkers that can identify amyloidosis as early as 20 years before symptoms begin, and there'll be a new marker soon that we have in plasma that also identifies tau tangles accurately. So I think it's a really amazing time to be working on Alzheimer's disease for finally we have some therapies that do something and I think we hopefully will really advance the field even more over the next several years as we target some of the other important mechanisms such as inflammation and tau and other factors.

Larry Steinman (00:38:09):

Thank you very much. And last but not least, Tony.

Tony Wyss-Coray (00:38:14):

Thank you, Larry. Thanks for having me. We have the same similar background it seems. I'm a professor here at Stanford as well focusing on brain aging and neurodegeneration. I'm also directing the Knight Initiative for Brain Resilience and try to focus increasingly on finding factors of resilience, why some people don't get neurodegeneration or Alzheimer's disease. I have a longstanding interest in

understanding the relationship between the body and the brain, and we've shown, actually that was Saul's work a few years ago, that blood from young mice can rejuvenate brains of old mice and vice versa, old plasma or old blood can actually accelerate brain aging and impair cognitive function. We translated or are in the process of translating some of these findings to humans over the past few years. We have also tried to harness the composition of the blood more extensively to understand based on blood-based proteins, how the body ages and how specifically the human body ages. And what we found is that proteins that are derived from the brain but that you can detect in the blood can predict onset of dementia, can even tell you how long you're going to live. And it seems that some of these proteins are important determinants of brain function and longevity.

Lee Rubin (00:39:55):

Thanks Tony. So Larry, can I just jump in for a second and say please just to set the stage for questions. The way we set up this panel, again, it encompasses a variety of ways of thinking about the interaction between aging and diseases exacerbated by aging. And if you'll think about it from a little bit of an overly simplified point of view, we have David Holtzman talking specifically I think at least today, about newest approaches to treat or slow down the progression or intervene in even the onset of Alzheimer's disease. So that's what I'll call a disease specific approach. We have Beth talking about a cell which is involved in Alzheimer's disease genetics, as she said, says that very clearly, but also seems to be a mediator of many, many other neurodegenerative and maybe neuropsychiatric diseases. Then we have Saul and Tony talking about, as Tony mentioned, and Saul also mentioned the different, and my lab also works on the different ways in which the body and brain interact and that can be observed in many ways following exercise as Saul has recently studied quite a bit following.

(00:41:06):

As again Tony mentioned, the infusion of young blood into old mice following intermittent fasting and following even some of the work that my lab has done following the microbiome, all of these seem to result in what we normally call rejuvenation of the aging brain. So the amazing aspect of all of this is not only is there not only one thing that you can do at least in a mouse, to actually not just slow the progression of aging but reverse some of the things that have occurred during aging. But there's so many different ways of accomplishing this. So it's kind of a plethora of riches in terms of how we think about developing therapeutics that work the best or work at least a little bit to add to address the aging component that is common to many neurodegenerative diseases. So this includes lifestyle and the way lifestyle affects the brain. Again, exercise the way exercise affects the brain and many, many other aspects of the way in which the body can influence in a very important way brain function.

Larry Steinman (00:42:15):

Thanks Lee. One of the issues that we need to keep in mind is that will interventions targeting diseases of aging Alzheimer's to begin with necessarily help for healthy longevity and those of us who are fortunately not destined to get Alzheimer's and raises a lot of questions because maybe we should go around the panel. Lee mentioned lifestyle. Here's a softball question. Is lifestyle in talking about exercise and weight more important than anything else as far as we know now and being healthy as you get older? Feel free to speak up. None of us are reticent. Yeah,

Lee Rubin (00:43:20):

Tony or Saul maybe are the best to speak on this, I think they've done the kind of most work related to this.

Saul Villeda (00:43:29):

All right, Larry, I can give you the way I've been thinking about things a little bit now, which is starting point. I think starting point is really important now, and again, this is going to be from preclinical studies, we focus on animal models, but it's very different if you start out with an animal that's already kind of big and obese versus an animal that's lean. And we've been doing different interventions and they don't all work on every single animal, but different ones will eventually work on every single animal. So if one is refractory to exercise, then you try something else and it actually does move the needle. So I think I've been thinking a lot more about the starting point. Not everyone's going to get too late in life exactly at the same point, and I think that's going to be really important for therapeutics and really important as we start thinking about almost personalized medicine.

(00:44:18):

I think it's really important. We've talked a little bit about biomarkers. We need the biomarkers to understand what trajectory are we under. Maybe for Lee it's about inflammation. Maybe for Tony it's regeneration. Maybe for Beth it's the vasculature and maybe for me it's white matter, so we're going to be at slightly different places at the same age along aging. So I think understanding that having the biomarkers and then understanding which potential intervention works best at that point will be really key. So I think there's a lot still there, but it's changed the way I think. I really do think about sort of the starting point. Having said that, do I exercise now? Yes, I do. I'm in my forties now. I exercise a lot more. Do I prevent myself from having the fourth piece of bacon? I'm also looking at that now. So obviously I'm trying to calorically restrict myself a little bit. So obviously the further along we get in our path, the more we start looking at I think lifestyle in general.

Tony Wyss-Coray (00:45:13):

Thanks. Yeah, I agree with what all said. I think it'll come down to personalized interventions. I think that's going to be key. We see this even with animal models that while some strains of mice benefit, for example, from exercise for other strains is actually not good. The same with diet. I think the key for the audience to realize is that this is still mostly experimental research that we're discussing. There are almost no proven FDA approved interventions that target the aging process or anything like it. From the literature, it's clear that there's hundreds of studies that show the benefit of exercise, but to my knowledge, there are no real strong studies that show the benefit of certain types of diets or interventions, even caloric restrictions. I think this is still controversial, and if you look where people live to a hundred years on the globe, we call these the blue zones.

(00:46:20):

What you see is that they live in very different environments, very different genetic predispositions. They have very different diets, and I bet you none of them had restricted themselves voluntarily. They are now a hundred years old or over a hundred years old, and when they were younger, they certainly didn't care or what they're eating. So I think we have to figure out what is it about diets, what is it about restricted calories that exerts benefits in animal models, and then try to apply that to humans. But I bet it'll be in a personalized way, as Saul said.

Lee Rubin (00:47:07):

But to Saul and Tony's point, all the people in the blue zone diets do exercise until all day. So that still seems like a major intervention possibility

Tony Wyss-Coray (00:47:18):

If taking a walk is exercise.

Saul Villeda (00:47:22):

So I was going to mention that, which is activity, right? Leah, we think about exercise here because we're so sedentary. We're like, do I have my personal gym or am I going on the Peloton? But it's activity. I mean, these people are just more active than the general person sitting in an office. So I think I've also thought about the word exercise versus activity and what it does mean for the people in those blue zones.

Larry Steinman (00:47:45):

A couple of questions about activity. One is we talk about exercise as probably the most beneficial activity and exercise can mean a lot of things, but it's paradoxical in my opinion, that exercising your brain, I think of playing chess, playing music, speaking several languages, learning a new language at an old age. Why isn't that better than jogging six miles?

Lee Rubin (00:48:18):

Well, my understanding of some of that, and again, people who do more of this can correct it, but I think when people were doing mouse experiments on an enriched environments where it was thought that maybe it was more like reading was actually the part of the enrichment that was associated with improved neural function at old age, I think it actually turned out to be the exercise in those enriched cages. But again, other people know more about it than I do.

Beth Stevens (00:48:50):

I have a question for those that might know more about this from their models, but I mean I think the question of genetic background is obviously, is there any evidence either in animal models or in other models where there are those who benefit more from exercise versus others? Has there been any sort of studies of the genetics intersection with those findings to get a sense of the genetic vulnerability versus risk resilience in the context of exercise? I'm less familiar with that, but it would be one, it'd be great if someone had any data to support

Dave Holtzman (00:49:23):

Beth. There are some studies that have been published and people who are a Apo E4 positive or negative that are at different risks to convert from normal to cognitively impaired, suggesting that exercise is actually even more beneficial at that stage of conversion for people that are Apo E4 positive than negative. It's interesting, I might've thought. Yeah,

Beth Stevens (00:49:47):

Yeah,

Larry Steinman (00:49:48):

That was going to be one of my questions for you, David. Let's say you're a Apo E4 homozygous. Should you start exercising even more ferociously than somebody who happens to be not Apo E4 at all?

Dave Holtzman (00:50:10):

It's a good question, but I think there's no information about any of that. I do think that, I'm sure that certain lifestyle and dietary factors are super important for how you age and whether your risk for getting Alzheimer's disease, but I must say if you look at populations that have been really carefully studied that reach a hundred years old, the biggest determinants really are, well, a big part of getting that age is their own genetics. I think it's really going to be a mixture of these things together. I don't know if, I think as Tony was alluding to install, I mean we don't really know what is the optimal amount of exercise that people should have, and it may vary. So certainly if I was Apo E4, I certainly would be conscious to follow best recommendations for all those things, but I don't really know what is optimal.

Larry Steinman (00:51:12):

You spoke about organs, different organs have different ages. So if one had a young brain, but a very old heart, sounds like you'd be in serious trouble because without the heart ticking, it doesn't matter how young your brain is. Any comments?

Tony Wyss-Coray (00:51:32):

Yeah, I'll get to that in a minute. But just to follow up on Dave and Beth's comments. So there is a study that looks across multiple published studies. We call this a meta-analysis, of people who exercise. And that study reported in about 3000 people that up to 70% is genetic of whether you benefit from the effect of exercise. Now, that is just one way to look at this, but I think what I always find interesting is that some people hate exercising and some people love it, and whether there's even some genetic stare, and if you just have an affinity for exercising, you benefit much more from it than if you hate it. This is just an interesting observation. I don't know if there's any basis to that, but to your question, Larry, what research initially in flies has shown is that organs and even cells in an organism seem to have slightly different speed of aging, which means that one organ might age a little bit faster, and this was in flies again than let's say the heart ages a little bit faster than the brain, as you said.

(00:53:00):

And what that means is that a person, for example, who has a heart that ages faster may develop heart disease. And of course then as you said, it wouldn't help you to keep a young brain if you die from a heart attack. But I think having this knowledge will hopefully help individuals personalize interventions and target the weakest link, if you will. So if you knew a dozen or so of your organs, how they age as you get 50 or 60 years of age is one of these organs show a much faster pace of aging than the other organs. Maybe you would be able to do an intervention on that organ so that it doesn't fail and gives you kidney failure or heart disease or liver failure, and you can start to do a personalized regimen to try to prevent these organs from failing.

Lee Rubin (00:54:10):

That kind of raises another issue, which is from what I can see from the questions that were asked in advance and also from the list of participants, I would say the majority of people not on the panel are, let's say, more interested in aging per se than in individual diseases associated with aging. And I was just wondering how people on the panel, I think all of us probably focus more or think more, except maybe Tony about diseases than about prolonging self prolonging health span as opposed to prolonging lifespan or even just finding better treatments for diseases or alternative or additional treatments for ALS, other diseases like that. But how do people on the panel think about this? For example, can you imagine a time related to what Tony was saying where you might take an individual pathology based or disease-based treatment like an Apo E4 inhibitor or an Amyloid beta, a plaque burden, a lowering agent together with something that acts on the aging process and maybe the two together will not only slow

the progression but reverse some of the changes associated with the disease. Is that a common middle ground for people?

(00:55:29):

What are people's thoughts about that?

Dave Holtzman (00:55:34):

I think that's a really good idea to think about because there's certainly going to be specific things that are occurring in any disease, whether it's accumulation of a misfolded protein, an inflammatory response, but there's probably common mechanisms leading to injury, for example, in the brain in a lot of these conditions. And so if something that was used for aging organs also impacted on some of the common mechanisms, combining that with some of the targeted therapies is probably going to be a useful way to design trials in the future.

Lee Rubin (00:56:14):

And Beth, when you think about microglial cells in the context of disease and aging, do you have any particular comments that you'd like to make? I think you're more of a disease focused kind of person, but yeah,

Beth Stevens (00:56:26):

I used to be, but I've become more and more interested in aging. So I have some more pure aging related questions about microglia because I realize we actually look across multiple diseases and we're more and more leveraging human data, human samples, and using the mouse models that exist as sort of how much is this conserved across various models. But the human data, if you really take a completely unbiased approach and you say, all right, let's look at brain CSF, blood from individuals with Alzheimer's across disease progression, Parkinson's across disease progression, maybe another disease across disease progression. You put all that data together from multiple different compartments, brain blood, CSF, what's emerging from the unbiased data? And at the same time, if we also had normal aging data, the idea through integrative analysis on unbiased approaches, what's coming out of that that might be common to each disease and what is more convergent across all?

(00:57:24):

And if there are specific age related signatures that are essentially common across all of those neurodegenerative diseases, that would be really helpful to know. So we've been trying to take that approach, with colleagues and collaborators here at the Broad and through various consortia? And I think that's sort of changing the way I'm looking at aging because it turns out that a lot of the data is pointing to some really fundamental biology in different cell types, including microglia, which these changes are sort of common across all of these conditions, including aging meaning, if I could summarize, again, this is not conclusive, but just sort of what it's telling us, hints of biology, that these microglia and macrophages may be less apt to respond to sort of a challenge in the brain or in the periphery, whether that be a pathogenic protein or debris or degeneration could be an infection.

(00:58:17):

So they're less able to kind of fight off and respond and do their normal jobs. So if you can imagine if we could figure out how, for example, their ability to sense lipids and to sense particular signals in the brain, turns out the unbiased genetics are also pointing to lipid processing, lipid pathways, lipid degradation pathways. To me, that's pointing towards a common pathway across all. And then if you could come up with models, whether it's cell-based models or other ways to study the biology, then you're sort of

tackling a common denominator across all. So I think I've sort of changed my, in other words, I still am very interested in disease specific mechanism, especially in Alzheimer's disease where I told you already that the microglia and the macrophages are certainly, at least heritability is sort of enriched in those cells. But I also think there's something going on that probably by understanding normal aging is sort of fundamental to risk of all of those things, at least the timing maybe of the onset of disease. I'd love to hear other people's thoughts on this, but it kind of has changed my approach on, if you had asked me the same question two years ago, I probably would've answered very differently.

Tony Wyss-Coray (00:59:25):

Yeah, I might just take this a little bit further. You could postulate that the question of disease and aging is really semantic and that with age, all our tissues start to show increasing dysfunction, and once they reach a degree to which it impacts your daily activities and your function, you go to the physician and they check whether that organ is dysfunctional and if it's dysfunctional, we call it a disease. But it's really part of just the aging process. And whether you show kidney disease or lung disease or liver or heart disease or Alzheimer's disease is a question of lifestyle and genetics, which organ age is faster than the other ones, and that's the disease you get first. But I would say that eventually almost every organ will fail if you lived long enough. And that's what we see in really old people, that most of their functions, their organ functions are severely impaired, but they just hang in long enough to live to a hundred years. And in fact, most people who live to a hundred years are also demented, but there are some that are not. And what's really exciting is to understand why are these people maintaining their brain function? But again, I think the term disease is something that we invented and is a reflection of aging mostly apart from clear infectious diseases where you have a causative factor.

Lee Rubin (01:01:10):

Yeah, that's a really interesting perspective. I mean, I think if you think about what's happening biologically versus what's happening clinically, physicians obviously worry about the clinical aspects, but there's all this underlying biology which they tend to ignore if it's not clinically meaningful at that time. So in the extreme, Tony, if you imagine going back to your personalized medicine, if you imagine people age differently and the body connects with the brain and the parts of the body are aging differently and parts of the body are sources of factors that signal to the brain in the extreme, could you imagine targeting a susceptible tissue that is an important supplier of brain active factors, so that by treating the first to go in the body, you might slow the rate of progression of disease in the brain. Do you know what I mean? Really digging into that idea that the two systems are completely connected and some of the stuff in the periphery might happen before you detect stuff in the brain.

Tony Wyss-Coray (01:02:10):

Yeah, I think that's a great point. In fact, Saul has shown that some of the benefits of exercise are proteins that come from the liver. And so if your liver ages faster, it may not produce this beneficial factor and the brain may not benefit from it. In fact, a lot of proteins from the liver make it into the brain and may regulate function. It's just something that we have not, especially as neuroscientists, we have not considered brain was typically studied in isolation. And I think it starts to open up to really start looking at these interactions between organs that I think people are starting to consider.

Saul Villeda (01:02:58):

Hey, Lee, if I can jump in, I can tell you a little bit about even how we are designing our studies in the lab because we were looking for these mimetics, these blood factors, and then we want to eventually apply

it to disease. And we've done a really good job in science of teasing it apart. And I think that's because we love hypothesis. We love testing things, we love control, and we have these amazing models that say Alzheimer's models, they're super aggressive, they give us the pathology in a really young context, and then we have physiological aging that's progressive and we won't really see the functional outcomes until much later. And what we are doing is really asking, okay, what of these factors works in normal aging? And let's say we identify 10 of those 10, are there any that also work under the pathology condition independent of aging?

(01:03:46):

Because you could see a context where you find something in aging, you apply it when you have the disease on top of it, it doesn't work, but you can also see a context where you found something that's amazing for the disease pathology in a young context, but you add the aging component to it. So I think it's really important to find either factors or combinations that are targeting either common mechanisms or that can at least engage the mechanisms in both context. I think that's going to give us the biggest bang for our buck because if not, we're going to be identifying these targets and they're going to be great, but only within that one condition. So we really think about the first screen being physiological aging, the second screen being disease pathology, and I think that's really important. The nice thing is that I don't think you have to go into the brain for a lot of these things, and we've been talking about good factors, but there's also factors we can target to decrease.

(01:04:37):

Do we not want them to go in the immune system? We haven't talked about that, but that's a huge component that's secreting things that absolutely we want to decrease in levels. So I think there's different ways in which we can think about it, but trying to separate the two, the way that we do in basic science within the human context is trouble. I think it's what Tony's saying, they're definitions, and we're so used to it, so nice to be able to test it and tease it out, but we're not going to get away with that in a human.

Larry Steinman (01:05:09):

So you raised an interesting question. You commented about the immune system that maybe we don't want any of those bad mediators in the brain, but if you look at a lot of other organ systems and thinking particularly of muscle, which seems to be the consensus favorite for keeping the brain healthy, muscle will not atrophy unless there's a tad of inflammation. So after you have a good workout, you have this feeling of wellbeing, which includes some minor muscle soreness, not the kind of soreness that says, I don't want to move that extremity for a week because the pain signal is intense, so why not a little inflammation in the brain. It's almost as the words come out of my mouth, it's almost like, why are you saying that, Larry? But why the brain be so privileged that it can't take a little bit of inflammation to hypertrophy and do things that may be beneficial? Yeah. Beth.

Beth Stevens (01:06:19):

Beth. Yeah, so I think that Larry, I really like the way you frame that because I think first of all, sort of the term inflammation just sounds bad. You don't want to have inflammation in your brain, but I think what we're realizing is there are a lot of these cytokines, inflammatory mediators, certain things where at the right concentration are under the right conditions could become very detrimental to a tissue including the brain. But there's a lot of normal signaling that are going on through the same proteins, through the same mediators that can have beneficial effects in brain plasticity and cell plasticity and cell homeostasis. And I think what's been tricky about that is it all comes down to sort of context and how

do you sort of study that. So I agree that in some way having some kind of a small challenge to make sure cells are working and communicating and things are doing what they're supposed to do is actually probably there can be some beneficial aspect, but if suddenly the checkpoints, the brakes go off and now you don't have a way of bringing things back to homeostasis, that's where we start to have problems.

(01:07:26):

And either from genetics or through a more intense pathological situation, it might get really hard to keep that in check as you age or in a course of disease. But I think this sort of word inflammation or inflammatory signaling, we often put that into a bucket of bad, but I don't know, I think there could be some beneficial effects in the brain as well.

Larry Steinman (01:07:51):

Here's another one along the same line. The consensus for making a brain healthier is exercise. And the opposite of exercise in my opinion would be sleep sleep's probably as important or maybe more important than exercise. And probably looking at most of the people on this call, we probably didn't sleep as much as we want because we're so excited about getting up and conquering the next cool question. But what about sleep?

Dave Holtzman (01:08:27):

Well, it's a huge factor for many, many parts of the body getting appropriate levels of sleep. Certainly it's clear from a lot of animal and now human studies that the right amount of sleep is probably beneficial for delaying, for example, even Alzheimer's disease and allowing metabolism of different cells in the brain to really be optimal. So I think it's been not a lot more people are studying it in the context of aging and disease and I think there's probably going to be, there already are some trials that are starting to optimize sleep to actually try to even slow down the process of Alzheimer's disease in humans that have already started.

Larry Steinman (01:09:13):

I think at your institution, some of the work of your colleague Yoni Kinu directly gets to the milieu of the brain and getting rid of evil molecules that might accumulate occurs during sleep.

Dave Holtzman (01:09:31):

Right. Well, one of the things that our lab has recently found is that when you abnormal sleep deprivation actually causes, as Beth was alluding to a microglial response, that's probably not a good response always. So in addition to affecting production of proteins, clearance of proteins, sleep, optimal sleep probably also keeps the brain cells in a more optimal state, including the immune cells.

Larry Steinman (01:10:04):

We've heard a lot about neurons, which of course we think are the most important cells in the brain. They're all important. There's a great emphasis these days on microglia also to a certain extent, but a study that was published in Nature about a week ago says that myelination and even trenchant increases in myelin thickness by a few nanometers. It could be important they were looking at it in the context of opioids do that. But Dave, you made a comment that some people, or maybe it was Tony, I just don't like to exercise, so we could use some, maybe we could make processes that are not enjoyed more enjoyable if we could do something about myelination, it brings up another point. There was a

study of a few geniuses, gifted musicians, Michael Jordan as a basketball player and what they like do a gifted musician can play his instrument all day long and get tremendous joy if you're not so good after about half an hour you say, this isn't working out too well, you put down your clarinet or you stop playing the piano. But getting people to do something that they actually get positive reinforcement because they're good at it, might make a very big difference.

Beth Stevens (01:11:42):

Yeah, I think on the myelination front, Larry, I think there's a couple of aspects to that that I think are relevant for discussion. One is that myelin has a lot of other functions in the brain besides just sort of insulating our axons. It's really important for metabolic support of our axons and ourselves and our neurons in particular, but work by your colleague and my colleague Michelle Maje, who's there at Stanford, who's shown, and others have shown that it's really a very plastic process throughout life that these myelinating glia are really responding to local environmental cues and that their ability to myelinate and to sort of insulate and signal with neurons and other cells are really dynamic throughout the lifespan. And you can imagine when that process is stopping this plasticity, this can impair circuits and they're ultimately synopses and cognition. So there's that one aspect that suggests the myelin is much more than insulation.

(01:12:34):

That's one part. But the other that's really relevant to our discussion today is that again, through a lot of unbiased data from actually many here, including Tony's lab and others, where one of the brain regions that seems quite vulnerable in terms of cells that are changing and transcriptional signatures that are aging is the white matter. And the third component of that is also in Alzheimer's disease and other neurodegenerative diseases where we've all looked at the neurons and amyloid and now microglia. Again, the unbiased data is starting to point to oligodendrocytes. They also become very disease associated and dysfunctional. So I think that just like before when we were only focused on the neurons and then we started opening our eyes to other cell types, I think understanding the white matter and the myelination component of aging brain health and plasticity fundamentally is really going to be important. And then at the same time, thinking about therapeutics, that might be another aspect where we can focus in on that area the white matter, which is a very different environment than the gray matter of the brain. And I'm sure Tony and maybe Saul and others may have some points on this, but I think it's fairly understudied mechanistically and I think it's really important.

Lee Rubin (01:13:46):

Yeah, if I could just jump in for one second. I totally agree with that. And it does turn out to be true that myelin changes with aging for sure declines with aging. And that's at two different levels. One is the function of the mature oligodendrocytes, the amount of myelin proteins that they produce. And the other is the ability of oligodendrocyte for gender cells to differentiate into mature oligodendrocytes. Both are affected by aging, but as you point out, and Larry also said it's remarkable how plastic that system is as well. And it's remarkable how quickly you can see changes if you carry out certain manipulations. And as several people, including panel participants have pointed out that the cells that are affected most by aging are non neuronal cells in the brain and they are again among the most plastic. And the other thing that's become clear is as you pointed out, Beth, not only do oligodendrocytes play roles with respect to neurons that are other than providing an insulating wrap, but they signal to other cells in the brain including, for instance, endothelial cells. And so there's a lot more communication in the brain going on, again suggesting that the plasticity is, on the one hand it's

normally a one way street, but on the other hand it's so plastic in both directions that these can all be, I think ultimately modulated with therapeutics.

Larry Steinman (01:15:12):

Here's an idea that may be worth kicking around. Can old dogs learn new tricks and is it good for aging in the old dogs? So when I was a medical student, David Huble had stopped working on the visual system and on his trolley card ride to the Longwood Avenue stop from Newton or one of those lovely suburbs, he was studying Japanese for the first time. He said it was good for his brain. So if David Hubel would say that we ought to take it pretty seriously. So are learning new tricks as you're older a good idea for you?

Tony Wyss-Coray (01:16:02):

I'm sure it doesn't harm.

(01:16:07):

No, I think we don't have placebo cultural clinical trials. It's of course not possible to do that. But the question is what you brought up earlier, Larry, is your predisposition and your reward system, do they play into that Learning a new language when you're 70 or 80 is not something that every one of us can do and that we have to predisposition or the will. If you want to do something like that on a regular basis, finding that out, what facilitates that or enables that I think would be extremely interesting. But it's more related to, again, the reward system and maybe more psychiatric or psychological article questions rather than what we're discussing here. But I think from a perspective of can you regenerate the white matter clearly, what the animal studies show is that it's possible with the different interventions that were mentioned earlier. One of my fellows, Tal Iram has shown that even infusing cerebrospinal fluid from young animals or young people into old mice can regenerate the myelination and the precursor cells in particular that give rise to the myelinating cells. So I think on a biological level, there is potential for increase in plasticity on myelination.

Larry Steinman (01:18:01):

I always think of the Goldilocks phenomenon that there's a rare but disabling neurologic disease caused by too much myelin, a duplication of one of the myelin proteins, PMP 22 and sharpen Marie tooth one A. And if we're going to work on any of these pathways, it has to be just right. It can't be too little, it can't be too much. And it is a challenge. But another thing that you were saying, maybe learning a new language at an old age, unless we're Dutch or Swiss or come from one of those countries where three or four languages immediately during childhood might be tough on us people who've lived in the United States all our lives, and you may as well do something that's not only beneficial but fun. If it's not fun, it's probably not beneficial. That's just a hypothesis.

George Vradenburg (01:19:02):

May I ask a question? This is George Vradenburg. I am curious in any of your work in this aging process, whether disease specific or more general, whether you are seeing sex differences or race differences in these aging processes?

Saul Villeda (01:19:24):

Disease. So for us, from the preclinical models, so the animal models, absolutely there's sex differences, not necessarily on whether it works or it doesn't, but the magnitude of the benefit can be really different and whether it works or not can be really different. So I think that's a huge consideration. And

then there's the genetic component to it, right? The level of resilience that we have just from whether it's male or female. So I think that that's a huge consideration and when we're doing this research to make sure that we are looking at them across sex is to understand, okay, this is more of a male, female or both.

George Vradenburg (01:20:04):

How about race differences? You work in humans and if you're working in humans, are you working in diversified representation populations? We have a problem in Alzheimer's. Where are we finding, since we've done most of our research in white European populations, that as we begin to test new biomarkers or even the drugs, there are either mixed dimensions or there are different performance or cutoffs in some of the biomarkers that have racial differences. Not seeing it so much in sex yet, but I don't think we focused on that so well in Alzheimer's. But certainly in race, we're seeing differential performance of diagnostics and potentially meds.

Thomas Seoh (01:20:56):

George, we can follow up later, but Zan and I were recently speaking with Tom Perls at BU. He's got a publication coming out that's looking at racial differences, among others, in lifespan, but you have to sort of prune out the different protective factors that are different among races and other characteristics for diseases that'll knock you off, that'll cull you if you will. And then when you finally get to the centenarians, the supercentenarians, he's hoping that they're looking at it, but I don't think it's been published yet.

Lee Rubin (01:21:33):

And David, I was going to just say David, if I'm not mistaken, you've had some interesting sex related differences in one of your microbiome mouse studies recently.

Dave Holtzman (01:21:45):

Well, I think in a lot of the preclinical studies in animals, whether it's on aging, but certainly on diseases, we often, we've seen, for example, when we saw effects of the microbiome manipulation on tau mediated neurodegeneration, a common mechanism both in Alzheimer's and primary. There's differences based on Apo E variant that you have as to the magnitude of the effect you would see. And some of the effects were only seen in males and not females. So yeah, I think a lot of these, the model systems can tell us what's happening in that model. Whether that translates into humans, we don't know, but certainly there can be big effects of sex and other factors.

Tony Wyss-Coray (01:22:38):

And I think also in just pure rejuvenation interventions, whether it's diet or exercise or young blood, there are genetic difference in genetics that modify the effect size. This has not been studied broadly. Usually we focus on one strain of mice most of the time, but when people look at different genetic strains, then the effects are different.

Alexander Fleming (01:23:11):

Well, this is a rich discussion and it's focusing a lot on tissues and organ systems, but what about drilling down to fundamental housekeeping, metabolism, energy balance, mitochondrial function, what connections can we make to these sort of elemental ways of maintaining life? And maybe this relates

even to this big boom in GLP-1 agonists for treating obesity and the perception that this is going to be a solution for some forms of neurodegenerative disease and it wouldn't be surprising. Understanding that obesity, of course is a big driver of neurodegeneration. So are there some thoughts about more fundamental circuits for intervening doing so in a way that is not just going to be for people who are obese, but people who are fit and relatively healthy?

Larry Steinman (01:24:34):

Along those lines, Novo Nordis is doing two simultaneous phase three trials in Alzheimer's. The question would be, certainly obesity is a risk factor for Alzheimer's, but what about people of normal weight? Would they benefit Or if your normal weight, does it just make you nauseated and take away one of the joys of life called eating? Also?

Dave Holtzman (01:25:06):

I think that's going to be a key question in those trials because I think most of the people within those trials that have just been ongoing are not in people that are overweight, right? They're people with mild dementia due to Alzheimer's and most of the people are not overweight. So

Lee Rubin (01:25:25):

Yeah, I think it's the same in Parkinson's. There have been some encouraging results in a phase two study with GLP-1 agonists and I think, and so on the plus side, it seems to have all these unexpected positive effects. On the minus side, there are several unexpected or maybe expected side effects including muscle wasting. And when people contemplate how the GLP-1 agonists act on all of these different tissues, I think that they normally invoke metabolism slash systemic inflammation as being involved in some of the effects. So it'll be interesting to see how that plays out. Again, in the extreme as a joke, maybe you'll only need one drug to take for your entire life and it'll treat everything the Ozempic-like molecules, especially the muscle sparing ones. But it is interesting to see how they're progressing in the clinic.

Larry Steinman (01:26:15):

One

Tony Wyss-Coray (01:26:16):

Related to that, I think the same or very similar results from the metformin studies, whether metformin will be useful in people who are not diabetic, who don't take the drug for clinical reasons and even exercise to some extent. It's interesting, you see the biggest benefit in people have never exercised before. If they exercise, they get a big boost, but people who are regularly exercising and then you do some more, it may not be as prominent. So it's interesting, again, to come back to the earlier discussion points, the context and the individual person will be important to study and see which drug actually helps them. And we may not be able to easily push back age, biological age in humans broadly.

Larry Steinman (01:27:15):

One of our early conferences, we were speaking a lot about metformin, and there's always been the standard comment that if we added to the drinking water, metformin, an ACE inhibitor, a statin, and now maybe A GLP, we'd all be living way too long for the good of the economy. But it raises a question, and I think Tony and Saul studied it very comprehensively that there are many protective molecules that

could protect the brain and other organs from aging. Some of those protective molecules actually form amyloids. I'm talking about making beta sheets that aggregate. Any comments on that? One is heat shock protein, small heat shock protein five, it's the major protein in the lens of the eye called alpha B crystalline. It's hugely protective in heart attack, ischemic FTIC neuropathy, all sorts of animal models, and it forms amyloids.

Saul Villeda (01:28:38):

Larry, I can tell you how I think about any of these factors, which is we try and identify them in interventions. Let's say if it's caloric restriction, exercise, it doesn't matter. We just try and get to the levels that normally physiologically would be induced by that intervention. Or if you're looking at young and old, we're not boosting it, let's say in a young animal, but we're trying to get back to the levels of a young animal because your body was naturally able to handle it at that particular level. I think it's once you start boosting something above, right above physiological levels where absolutely you can engage in things that predominantly it wouldn't be doing when it was at the levels that your body was used to. So we look at that as a criteria for even the factors that we do pursue functionally and with the manipulations that we do. We try as best we can to try and mimic it up to that level with its own limitations, but that's at least how we're thinking about it.

Larry Steinman (01:29:32):

If one had to pick one nerve, this is a leading question, that you might want to stimulate because it seems to have a lot of benefits in animal models. I won't ask it as a question. What do you think of vagal nerve stimulation? Healthier people have slower pulse rates and you can cure a lot of experimental diseases with a vagal nerve stimulator?

Dave Holtzman (01:30:09):

Well, there's certainly a lot of communication going on between different places. The vagal nerve goes to such as the gut and the brain, and I think obviously it's being used as a neurologist? for certain types of epilepsy, but I think for more general aging effects, it'd be interesting to continue to pursue understanding whether that might be something viable

Larry Steinman (01:30:36):

Interesting. And thank you. I agree. The brilliant work of a guy named Kevin Tracy, he publishes in Nature and Science quite regularly on the immune reflux. And for those of us who straddle a lot of fields, even though it's in these prominent journals, it doesn't seem to get too much traction, but something to think about and people who are really in good condition do have slower pulse rates and we attribute that to vagal nerve vitality.

Lee Rubin (01:31:15):

Well, when all of this work emerged about the connection between the body and the brain, basically it focused on blood at the beginning. But the vagus is a clear pathway, as David said, from at least the gut and other organs directly to the brain. And I think one should not underestimate? that. And as you probably know, Parkinson's disease, for example, in particular, people have talked a lot about retrograde transport of alpha synuclein from the gut to the brain. So some people think it starts in the gut and then spreads to the brain. I don't think that can explain all of the work that Saul and Tony have done. I think pretty much the blood is a conduit, but it doesn't mean that it's always the conduit

depending on which tissue, tissue brain interactions you're looking at. But I think a lot of people have started focusing much more on the gut than they used to, and particularly on the vagus nerve,

Larry Steinman (01:32:08):

A general question, it seemed that a lot of the people who live to a hundred or so have all sorts of diets and all sorts of different levels of things including alcohol consumption and levels of exercise. But on the other hand, we hear, at least in the news media that I look at the Mediterranean diet, you hear about that nonstop. Are there diets that are actually better for longevity and healthy longevity? We also noticed that with the 4th of July coming up, that the man who keeps winning the Nathan's hot dog contest switched over to having vegetable hot dog. So he was fired by Nathan's. We're working for a competitive company, but it does raise an important question, what should we be eating? It is clearly not too much of anything, but should we give up Omaha steaks which are being advertised widely for Father's Day, somehow thinking that men like their steaks? But I could go on before I bury myself. Any comments?

Beth Stevens (01:33:42):

I'll just comment on that. Of course, I think one aspect that's really interesting, which also can be modeled is the idea that mechanistically what's going on with a high fat diet versus let's say a Mediterranean diet. And one of, again, sort of the themes of high fat diet is it does influence the immune system, immune cells, macrophages, and I think if you put that together based on the cell types of interest, of course I'm biased, this is the cell I'm studying quite a bit, but we do see some really interesting cell states and cell functional changes when you challenge the brain or even specific cell types like myeloid cells with lipids and high fat diets. And I think the more we understand mechanistically what is going on there, that could give us a little bit of insight. And then again, some people are somehow resilient to this based on their genetics. So I think understanding that intersection and better models could be helpful including human cell models, but maybe others have more evidence to support the diet aspect.

Lee Rubin (01:34:47):

You know what Michael Pollan says, don't eat a lot, eat a lot of greens, eat local. That's his advice. Looking across the spectrum of what people around

Alexander Fleming (01:34:56):

The need, we've gotten a lot of questions and they're really great, worth looking at. Some relate to repurposing already approved drugs that might have a role in slowing age-related neuro degeneration, and maybe doing so in combination. But just as a general reaction, do you see some hypotheses to test with available agents that level role in early intervention against neurogeneration, dementia in particular?

Dave Holtzman (01:35:46):

I think as Beth's been pointing out, I think there's probably different drugs that are approved for a variety of conditions now that affect either the innate or adaptive immune response, which certainly could be assessed in some of the preventing or treating some of the neurodegenerative diseases. I think a lot of labs are trying to elucidate, which might be the right ones to test next, but some of the things that are used, for example, for MS that Larry is very familiar with, rheumatoid arthritis, psoriatic

arthritis, things like that. Some of those agents I think would be worth testing once there's a little more evidence from animal and cellular models as to what might be the most potentially effective.

Alexander Fleming (01:36:45):

Joan, you have an interest not in repurposing so much, but improving upon a particular drug class and applying that towards and immune function. But what do you think the prospects are for neurodegeneration?

Joan Mannick (01:37:08):

Well, I've found the discussion fascinating. So my company works on rapamycin derivatives, and of course there's lots of preclinical data that rapamycin has benefits in Alzheimer's, a variety of neurodegenerative diseases, but we've always thought you have to have a rapalog that crosses the blood-brain barrier to have benefit. And the data we've gotten is that at least rapamycin doesn't cross the blood-brain barrier well at all in humans. And so we thought maybe it's just not going to work. But if as you've pointed out, exercise has all these benefits and its muscle coming from the periphery signaling to the brain, could a drug that is just acting in the periphery and perhaps even just acting on immune function in the periphery, would you expect that will, for instance, Beth, impact microglia states in the brain like a peripherally acting drug on macrophages or innate immune cells in the periphery? What would you expect that would do?

Beth Stevens (01:38:24):

I think that's such an interesting question. I think this could be systematically addressed, right? To see how, first of all, which cells are most affected, the fact that the peripheral immune cells don't necessarily have to directly go into the brain to have their impact. They can be signaling at the brain borders, and a lot of the effort has been focused on cells that reside within the brain, but I think the field is starting to appreciate the sort of borders of the brain, whether that's the perivascular borders, the meninges, the cord plexus, these are all areas that are rich in immune cells that serve as a nexus of communication between the periphery and the brain. So I think it would be really interesting to ask systematically how clinically approved drugs like that impact cell states in the borders too. And that might be kind of getting at mechanistically what's going on even if they don't technically cross.

(01:39:16):

And that's true of the opposite, when you have an infection or even a peripheral when people use LPS to modulate an infection, those don't necessarily get into the brain, but they certainly have impact on the brain. How does that work? So it's sort of the reverse, I think understanding how those signals are communicated to the brain, not just via vagus and sort of these pathways, which I think are also super important, and also the work of Tony and Saul understanding how blood factors are getting in, but even at the very margins and borders of the brain, what's happening when you change that niche? How does that therefore change the signaling that's going on locally in the brain between the periphery and the brain? I think that's going to be really important to understand could open up new targets, more selective,

Joan Mannick (01:40:00):

And we've focused a lot in previous companies I've worked at on rejuvenating the immune system peripherally, but it would be interesting, does that rejuvenate the immune system or the function of aging organ systems in general? And I would love to hear the panel's thought, how much do you think

it's really the immune system, whether it's the microglia, are peripheral cells, is going to be key to neurodegeneration beyond just targeting amyloid?

Dave Holtzman (01:40:38):

Yeah, no. Well, it's clear that a lot of different manipulations of the innate and recently even the adaptive immune system in models that develop different aspects of Alzheimer pathology has profound impacts on the disease process that is probably downstream of let's say tau or amyloid. And so if those kind of findings can be translated into humans, I think it has huge implications. We haven't been able to do that yet in a degenerative disease as effectively as it has been done in MS, but I think there should be some great opportunities to try to do that.

Thomas Seoh (01:41:21):

This actually reminds me of an early question [from the Q&A] for the panel. Do you think that long Covid could adversely impact the prospects of Alzheimer's downstream? Now, long Covid has been around what, four years? So maybe it's very premature to draw conclusions, but I'm also curious about diagnostics - Beth - going into the cellular and molecular levels is great, but there are interesting digital tools for testing function, VR [mediated devices and diagnostics] that are testing 300 different things and AI can maybe look at patterns where you can go directly to a clinical function, not just physiology. Any comment from the panel?

Dave Holtzman (01:42:12):

Yes, not certainly.

Larry Steinman (01:42:15):

I had a similar question to you, Thomas, about any ideas from the panel on brain fog and what could be about that vexing problem and long Covid. And I should also add for there's many students we see in the college environment who have long mononucleosis, they miss a year of school, they miss a year and a half of school, and a common thread between long covid and long mono may be the same virus, even

Saul Villeda (01:42:52):

Larry, I am thinking a little bit about some work from Michelle Monje where she looked. She also modeled some sort of cognitive decline related and she had samples from humans and she identified a lot of the same factors that we're seeing as aging sort of immune factors. A lot of these chemokines, I think she looked at CCL 11 and she showed that those same mechanisms that are engaged in this cognitive decline that we see with aging are upregulated in the context of brain fog or some of this cognitive decline associated with covid. So I think there's definitely parallels that are emerging from work.

Larry Steinman (01:43:29):

Yeah, it seems like the dominant, there was an article about the NIH spending a lot of money on long covid and getting nowhere, and a lot of it has to do with retesting and retesting Paxlovid with all due respect, it doesn't seem to be working. And yet there are other, if a virus is at the root of it, there are other antivirals. But in the field where I spend most of my time in MSs, we had the big breakthrough that EBV is the cause, but we still don't have an ongoing trial with an antiviral in that disease. I guess people are waiting for the perfect, but they ought to do something.

Beth Stevens (01:44:20):

Just to follow up on that, I think one of the things that we're actually working a bit with Michelle and others on sort of mechanistically trying to understand what's happening in that neuroimmune axis in the context of long covid versus let's say other post-infection models. And I think one thing to say about that is what's interesting is the infection is long cleared and then some percentage of animals or people end up with these sort of cognitive brain fog and other inflammatory states in the brain. First of all, why some people and not others? That's one question. And then is it possible then back to the idea of you, I don't want to use the word activated, but you sort of primed the immune cells in the brain and then when later that kind of triggers or sort of prematurely start to process, at least in some individuals that might've taken a lot longer, where suddenly now you're sort of on a different state in the brain neuro immune state.

(01:45:17):

So I'm just trying to understand mechanistically how that's working. I think it's going to be really important. It's probably beyond covid, it's probably a lot of other examples like West Nile virus, there's a lot of cognitive sequelae and a lot of those individuals that have West Nile virus and other examples I could list as well. So maybe there's some common denominators across these post sort of post infection states in the brain that could be clues about how that might set the stage for if you then are predisposed to Alzheimer's or Parkinson's disease, then how do the two work together to increase risk?

Lee Rubin (01:45:54):

Do you think of that as part of a more general kind of two hit hypothesis situation where there are the genetics of disease and a lot of genes are not, even if they're sort of penetrant like LRRK2 for example, they're only about 50% penetrant and you need some other push if you have that mutation, maybe it's less of a push, but you need the two together to get you over the edge and develop Parkinson's. Do you think it's something like that?

Beth Stevens (01:46:20):

It could very well be. I mean, I think it could be this balancing act and for certain people there could be a bigger challenge. In this case, long covid would certainly be a big one. It kind of sets the stage. And we can even talk about things like traumatic brain injury and TBI, how individuals that have a concussion or TBI earlier in life, first of all, they develop a lot of the pathology, but then they're more prone to develop these neurodegenerative diseases. So could that be a similar idea that you sort of initially sort of started a cascade, but at that point if you're younger, you have a healthier brain, things are more sort of pliable and plastic, but the damage may still be there even if we never saw it right. Cognitively? I would love anyone's thoughts on that.

Dave Holtzman (01:47:13):

Totally right. I think you're right. I think the two hit issue is probably what could easily be going on. The problem with studying something like long covid on some of the diseases of aging is that the diseases start so long before the actual gets severe enough that symptoms emerge. It could be that there's an effect, but by the way that we're designing studies to follow it, we are probably not going to see what's going on because you'd have to follow people for 25 years to really figure out if it's affecting disease. So

Joan Mannick (01:47:52):

I was just going to say I'm actually an infectious disease physician. So I used to see a lot of chronic fatigue, chronic EBV patients, and they were almost always depressed. And you don't know, is it the depression that's making them susceptible to the impact of the virus or are they depressed because the virus is making them fatigued? But I think there's also an interesting interaction of any hit and just being depressed.

Larry Steinman (01:48:25):

There's an interesting intersection between drugs that are termed drugs for psychiatry. I'm thinking of even SSRIs and neuroinflammation because when you give SSRIs to that classic model of neuroinflammation that's been around 90 years, paralyzed animals start walking around. So just because a drug has an FDA label as a antidepressant, these are dirty drugs to begin with. I don't say dirty as not sterile, but they have a lot of receptors, same receptors in the immune system and the nervous system. And what I said about SSRIs also applies to clonazepam, and there's a whole list of drugs, again in the field of MS, the control groups keep having lower and lower annual relapse rates since the 1990s. And it may be because of addressing general health with maintaining high levels of vitamin D, but also treating depression. And the depression treatments may be as good or better as some of the high priced medicines we pay for to reduce inflammation. But it all has to be tested. But in animals, it was pretty clear.

Alexander Fleming (01:49:59):

Well, Larry related to that, but on the adversity side, there is evidence that just over the counter anticholinergic agents, antihistamines and so on have an adverse effect on at least cognitive function. And maybe I'm not sure on dementia itself. Is there a sense that there are drugs out there that are actually doing harm that we're using without awareness of their adverse effects on cognitive function at dementia risk?

Dave Holtzman (01:50:42):

This happens all the time. As a neurologist, you see patients and they're come in and they're older and they're on 20 drugs, several of which could easily be affecting, do affect their memory and thinking that are anticholinergics, antihistamines, et cetera. So even though people know that that's the case, that the advice about what to do with these things is not always followed.

Larry Steinman (01:51:04):

So true and Zan, you would know best from your regulatory perspectives. How do the regulatory agencies monitor for things like that? I mean, they just picked up on some drugs don't work at all and they should not be sold even over the counter. But what about impacting people negatively? It's a huge amount of work to sift those things out.

Alexander Fleming (01:51:33):

Indeed. I did want to come back to Joan's probing of the crosstalk between CNS and peripheral tissues and go maybe to Saul and Tony as a way of understanding what their parabiosis studies might be teaching us. And I understand that you can now directly at least exchange cerebral spinal fluid, but typically you're doing systemic parabiosis. And so it's that narrowing the field of factors that you are looking at or pointing down on that could explain the effects you you're observing.

Saul Villeda (01:52:23):

Yeah, and I don't know if Lee wants to comment as well with the parabiosis. I mean, the first thing I think that we observed is that it's bi-directional, right, that there are indeed circulating factors that promote, but they're circulating factors that also can cause the decline. We know that they can be circulating because you can just transfer the plasma alone and get both effects. So it's great from a therapeutic standpoint, I think it's always easier to target something or get rid of something or block something than it is to come up with a molecule recombinant protein to increase it. And I think there's a lot more labs around the world doing this work. So we've come up with different subset of factors that work. Each one seems to either impact inflammation or vasculature or neurogenesis. So I think it kind of gives us different mechanisms to pursue based on the factors. Some of them may have side effects, others may have different ones. So I think we're still at that stage in terms of understanding how they work, but at least we do. We've started making at least a list of some that potentially could work. And I know Lee's been doing a lot of work in that space as well.

Lee Rubin (01:53:30):

Yeah, so if you look at Saul's most recent review, at least that I saw, there are kind of more than 20 individual factors that affect the brain. And interestingly, as he already said, they fall into the good and bad categories the way I think of them. And then also they fall into categories that some get into the brain, some don't even get into the brain. And that indirectly, as he said, either through the vasculature or by regulating the production of something else from a systemic tissue, that itself gets into the brain. So on the one hand, it's very, very, very complex. On the other hand, there are a lot of choices, and it doesn't mean that they'll all be the same or all work to the same degree, but a lot of them may do something. And then it comes down to real drug development. Which ones can you manufacture effectively? Which ones have good side effect versus side effect ratio? But it's not like we've been struggling in the desert for a thousand years and can't come up with anything. It's in fact quite the opposite now. So I think we're all encouraged by these recent developments.

Thomas Seoh (01:54:33):

We're kind of coming down to the short strokes, so maybe I can be a little bit provocative and ask: neurodegeneration. One of the approaches would be for regenerative medicine. And Lee, I'm kind of looking at you on Zoom with your stem cell work and so forth, but what are the prospects eventually for stem cell cell therapy, gene therapy for not just preventing or slowing, but treating, curing, reversing neurodegenerative diseases?

Lee Rubin (01:55:05):

For sure, I would say. And if you just imagine all these blood factors and that affect the brain, well in other ways you are pointing out to as a thinking about it is what if you were to either use gene therapy to deliver the most effective factor into the brain at clinically effective levels, or if you were to not think of regenerative medicine - and I think the way most people think about it as cell replacement therapy, but as a drug delivery system where let's say Saul identifies five highly active factors, you can use a cell, an astrocyte or another cell that's long in the brain to actually as one therapeutic, but would have a big payload because it would contain multiple factors. So I think the way, this is not science fiction anymore, this is really now getting down to the level of real thoughts about how to develop therapeutics from what we even know now, let alone what we'll know in the next few years. I think this field is accelerating and there's no reason to be pessimistic, certainly in the long term, and I think maybe even in the near term. Saul, any comments on that?

Saul Villeda (01:56:19):

And Teresa, we've been thinking a lot about, I guess more gene therapy because factors that we're finding are from the liver, and the liver is so accessible from the blood. So we've been looking at even some mRNA based ways of even acutely or temporarily upregulating the factors that we're finding. We want to make sure as we're thinking about therapeutics, that there's also washout periods, ways in which we can stop it. So we don't want to just incorporate it into the genome and have it elevated forever. So yeah, we've been playing with how do we target the liver, how do we play with it? There's a lot more technology coming out on mRNA based delivery, on different things that we can use to target the liver. So we've been focusing more on peripheral tissues to manipulate it from that gene therapy perspective, knowing that it will have an effect on the brain. So that's kind of the approach that we've been taking it. But I love what Lee said. There's been so many advances right now with CRISPR CAR T cells. You can manipulate circulating immune cells. Yeah, you can absolutely piggyback off of that and have them to create the factors that we would like, right? So I think that's another avenue that's pretty exciting.

Lee Rubin (01:57:24):

So I know we're getting close to the end, David or Beth or Saul, of course. Any other final comments that you'd like to make or Zan, any burning questions from the audience?

Alexander Fleming (01:57:37):

Good burning questions, but let's hear from our panelists.

Dave Holtzman (01:57:41):

Just one comment about neurodegenerative diseases in general, which it wasn't that long ago where we had absolutely nothing that we could do that was at least pharmacologic or antibody based. Nothing did anything. And now it's obvious in several neurogenerative diseases, there are examples where the diseases are being slowed or at least in some cases maybe even partially reverted with different new therapies. So I think this is just an incredibly exciting time and I think it's a great time to build on everything that we've taken 30, 40 years to get to the point where now we have a few things. Let's really go for it and do even better.

Beth Stevens (01:58:32):

I'll just add, well said, Dave. I think it is a really exciting time. We have now some examples where we're moving the dial and there's a lot of new work coming that you can imagine bringing in other targets, having combination approaches that target other pathways, including some of these immune pathway we've been talking about. But I also think the idea that we could also develop more mechanistic and prognostic biomarkers that we could use to stratify these patients that often have multiple, they're not sort of just Alzheimer's or Parkinson's or somewhere in between to try to understand the staging. I think trying to get earlier and trying to really get back to that precision medicine with sort of a suite of immune related and other biomarkers that can be used in conjunction with amyloid, tau, synuclein, the idea that we could start to stratify better. I think that would really be a game changer because some of the therapeutics and things that weren't as successful as hoped, maybe with the right patient population and earlier they may have been,

Larry Steinman (01:59:38):

I think there would be a great opportunity for the future. Michael Brighton, the book's been written well already, but if we get too good with some of these interventions and they become economically feasible, what are we going to do as a society if there aren't people to take care of those of us who benefited from that therapy, who still have slower recoveries in other organs? In other words, we're going to need help. And if medicine gets way ahead of what we need to do as a society, if we have more healthy old people, could be a problem. I think the Creighton, the next Michael Creighton could do a good job on that one.

Alexander Fleming (02:00:36):

Well, this is where we roll that theme from 2001 Space Odyssey. That's a really visionary way to end this amazing session, but it took some magic to get everybody in this virtual room. We can't thank you enough for being willing to spend such a time out of your day. And I know the audience has been so glad that they attended. We of course, will make these recordings available, so a far greater number of people will actually see this session than watching it right now. But again, we thank you. We thank the audience for joining us. And Thomas, you can end with a few housekeeping announcements, and we're going to hang on those who would like to in the audience and any of the panelists who are able, I know that some will need to take off, but we'll have that kind of gathering around the podium for informal chatter.

Thomas Seoh (02:01:44):

Stepping off the dais. Yeah, so as Zan said, all registrants will receive the link to the recording within a day or so. We're hoping that our Zooma Sayief can make that happen today. We do have, as I mentioned at the top of the proceedings, future sessions for THL 24, include one on draft legislation for new regulatory pathways for health span products, as well as one on biomarkers and endpoints for health span products. We do have a session on August 8th, which will be a joint free virtual webinar with the Diabetes Technology Society on Advanced Glycation Endproducts, which have been investigated over some years in relation to diseases like diabetes, but which have generally would fit generally within senolytics and other dysfunctions at the molecular, not just cellular level. So all registrants to today's webinar will receive information on all these future sessions by email. So please be on the lookout. And I guess with that, let's thank the speakers and the audience for your attendance. Wish you all a good day and we'll keep the virtual room open for those who are able and can tarry. Thank you.

Alexander Fleming (02:02:55):

Thank you so much. Thank you. Thanks.

Post discussion

Peter Libby -