SAGE CROSSROADS - #25

SILLMAN: Welcome to SAGE Crossroads. I am Marcy Sillman, and we're coming to you today from the University of Washington Medical Center in Seattle.

On this webcast we are going to be covering the link between genetics and longevity. Our guests are Dr. Bryan Kennedy, assistant professor of biochemistry here at the University of Washington, and Dr. Matt Kaeberlein, who's a senior fellow in the Department of Genome Sciences.

Thank you both for being with us today.

I'd like to have us start with each of you talking a little bit about the work you do, the current research and what led you to it. Dr. Kaeberlein, we'll start with you.

KAEBERLEIN: OK. Sure. I'm happy to. I got interested in aging research as a graduate student at MIT, where I heard Dr. Lenny Guarente give a talk on the research in his lab, and became very excited by the idea that we could actually study the science—study aging as a science and use molecular biology and genetics to really try to understand the genes that cause aging. So I was a graduate student in Dr. Guarente's lab.

Then, after I finished my PhD, I actually took the—I guess a less traditional route, and started—or co-founded a biotech company to try to develop technologies to understand human aging.

About two years ago, I came to the conclusion that academic science was really where I wanted to be, and Seattle was really where I wanted to be for family reasons—and so started looking at the people who were here at the University of Washington, which has a fantastic biology of aging program. I got in touch with Bryan and with Stan Fields, who was my mentor at this time, and developed a project to try to take a step back and look on a genome-wide scale and try to understand out of all of the genes in the genome in a simple organism, in the budding yeast, what are the genes that affect aging?

Bryan and I have started a very fruitful collaboration to try to do exactly that—to look at aging on a genome-wide scale, and I guess you can sort of talk about that.

KENNEDY: Yeah. I also got interested in aging as a graduate student when I was at MIT. It was a time when Lenny Guarente was looking to expand his lab in new directions. So discussions between him and I and another graduate student, Nick Austriaco, led to starting the yeast aging project in his lab.

It was a very fun thing to work on for a number of years. I went off and did a post doc on—more on tumor suppressors and cancer research. But I never really got away from the idea of aging. So when I got a position, I wanted to redirect my lab, to some extent, back in that direction. So a large proportion of my lab now works on aging and yeast.

SILLMAN: Why yeast?

KENNEDY: I think the reason I like yeast is because you can really take a step back and ask unbiased questions to get answers. So in the (   ) cells—you know, a lot of aging research by necessity has been trying to make predictions about what's causing aging, and then go back and try to test those hypotheses. With yeast we have the opportunity to look at the whole genome in an unbiased way and not make presumptions about what's happening.

SILLMAN: How did you start with yeast? What made you think that this was the good organism to work with?

KENNEDY: Well, I wasn't sure when we started whether what we learned about yeast would tell us anything about mammals and aging. But essentially I think we started it because we thought it was a cool thing to study!

[Laughter]

KENNEDY: That's what really what drives us. But at the same time, we—it really wasn't a good model for eukaryotic aging at all at the time we started. Yeast is the simplest eukaryote you can work on. And by that I mean, it's a cell that's related to the type of cells we have in our body.

I felt like at the time that even if we didn't learn anything that directly applied to human aging, we would at least set a paradigm for how aging might occur. I think that it's still not entirely clear how related the two species are in terms of aging by any means. But there is accumulating evidence that there are going to be some things that are in common.

SILLMAN: So where did you start with the yeast? What do you look at first?

KENNEDY: There are really two assays to do yeast aging. The one that I've largely worked on is called replicative aging, which relies on the fact that you can tell the difference between two cells after they—one cell divides and becomes two cells. You can tell the difference. There is a mother cell and a smaller bud that's produced from the mother cell. You can take a needle and remove that small bud and just count how many times that mother cell can divide. It turns out that it's not an infinite division potential. Rather, after 20 or 25 generations, depending on the strain, the—or cell divisions, the mother cell stops.

Then you can ask, "Well, if I change the genetic makeup of those yeast cells, does it increase the number of times that cell can divide, or decrease the number?" So that's replicative aging. And not as (   ) chronological aging.

SILLMAN: What's the difference?

KAEBERLEIN: The difference there is it's a non-dividing assay, so you can keep the cells in a non-dividing state and ask how long do they maintain the potential to start dividing again.

I think this is an important point when talking about yeast as a model, because clearly all of us are a combination of dividing and non-dividing cells. You can at least have the potential to study aging in both of those cell types at a single cell level.

SILLMAN: So when you talk about replicative, how many times a cell can reproduce—you said the cell has a finite number of times.

KENNEDY: That's right.

SILLMAN: What determines how many times a cell can divide?

KENNEDY: That's what we've—I've spent the last twelve years trying to find out.

SILLMAN: Well, did you discover it?

KENNEDY: Well, we had essentially the same idea that we are pursuing now back when we started in Lenny's lab, and that was, "Let's try to do a genetic screen to find mutants that are longer lived."

It turns out that you can find a lot of mutations that make the cells divide fewer times. But it's really hard to say that that's advancing an aging program, or just making yourself sick. If you cause a defect in DNA repair, for instance, the DNA damage accumulates in the nucleus and the cell dies after three divisions, but that's not necessarily intrinsic to the normal aging program.

SILLMAN: OK.

KENNEDY: What we wanted were mutants that would extend the number of divisions that the yeast mother cell could undergo. So we set up a screen that was complicated, but it lead to the identification of the SIR proteins as regulating yeast aging.

SILLMAN: What does SIR stand for?

KENNEDY: SIR stands for silent information regulator. These proteins have been studied for a long time because they turn off genes at various places in the—turn off transcription of genes at various places in the genome. When we had found these SIR genes—this led to a lot of work in Lenny's lab by David Sinclair, and Matt, and a number of other people when they were there. It seems clear now that increased activity of these proteins allows the yeast cells to divide more times. There's evidence in flies and worms, also, that increased activity of the (orthologics) protein does the same thing.

KAEBERLEIN: Right.

SILLMAN: So something turns on this protein and does what exactly?

KENNEDY: The more activity you have of this protein the more—the longer you live, at least in the simple model systems.

SILLMAN: The question now with SIR, with SIRtuins or SIRtu, what's happening? Does that work in mice? Does that work in mammals?

KAEBERLEIN: Right.

KENNEDY: Those experiments are under way by other groups.

KAEBERLEIN: But so—I mean, and this sort of gets back to what you asked—what limits the replicative life span of a yeast cell? We don't completely know the answer. We know that one thing that limits how many times a cell can divide is the accumulation of these extra chromosomal RDNA circles, which some people call ERCs, and SIRtu inhibits that process.

We now think that that's not the whole story, that there are other things going on. So the real question is—one thing that's interesting about these ERCs is that they seem to be specific to yeast. People have looked and there's no evidence that these circles accumulate or cause aging in other organisms. Yet it's very clear in yeast that that's how SIRtu is acting. So it's a burning question—SIRtu seems to regulate aging at least in yeast and worms and flies, apparently by different mechanisms. So that's one of the questions, how could such a system have evolved, and is there something else going on that we don't completely understand?

SILLMAN: So if it's regulating things in yeast and worms and mice—

KENNEDY: We don't know about mice—

SILLMAN: You don't yet know about mice.

KENNEDY: —for aging. We don't know the phenotype.

SILLMAN: You know about worms.

KENNEDY: Worms and flies.

SILLMAN: Worms—OK. So as you are moving towards Homo sapiens—

KENNEDY: Right.

KAEBERLEIN: Yeah. Yeah.

SILLMAN: I assume that's the direction that you are going.

KENNEDY: Again, this is work by other labs but yes, at this point, but yes.

SILLMAN: But each one builds on—say you're doing this specific work with yeast and someone else is looking at worms? Or…

KAEBERLEIN: The way it evolved was, as Bryan said, they had identified the SIRproteins as being involved in yeast aging. Then myself and Mitch McVeigh in the Guarente lab did some experiments focusing in on SIRtu, and then other people, based on that, started looking and asking, "OK, we know there are proteins that look like SIRtu and worms and flies," and asking whether they would also affect aging in those organisms.

SILLMAN: So SIRtu is a protein? Is it in every gene in our body?

KENNEDY: Every cell you mean.

SILLMAN: Every cell in our body?

KAEBERLEIN: Well, it's—the DNA is in every cell. Whether the protein is expressed in every cell, I think, is not clear. In humans, there's actually seven of what they call SIRtuins, so seven proteins in this family of SIRtu proteins.

Presumably in every cell type that one or more is expressed. But at this point we have no idea really. I mean we have some interesting clues as to what SIRtuins might be doing, but I would say the jury is still out, really, on what the function of these proteins is, and how they are acting in mammals is largely unknown.

SILLMAN: To go back to the yeast level where you are working, what would trigger it? I have read different articles about how much food, how much sustenance somebody takes in, and that might trigger it.

KENNEDY: Let me come to that answer and take a step back.

SILLMAN: Sure.

KENNEDY: When we started, we wanted—we realized that that initial screen that I told you about earlier that was done in Lenny's lab was very biased and that it only allowed us to identify a few of the genes affecting aging.

In the meantime, the yeast community has gone and made a deletion of every single gene, each in one strain. So there are 5,000 strains now that all have a deletion of each nonessential gene in yeast. What we're doing now is scanning through those, just randomly looking for ones that are long-lived. We're finding that there are a lot of other pathways in addition to SIRtu that are regulating aging.

The question about how it's activated, I think, gets to the point of calorie restriction or dietary restriction. One of the clues that aging is conserved in different organisms is that if you reduce caloric intake—and that's done in different ways in different organisms. But if you reduce caloric intake, do you extend life span? That works in yeast and flies and mice and monkeys, presumably. And maybe even us.

There is a big question: what is calorie restriction doing? One model that was put forth was that calorie restriction was leading to the activation of SIRtu. At least in the strains we work in, we think it is a lot more complicated than that, and that SIRtu may not be the link for calorie restriction. That doesn't mean it is not regulating aging, but we think that there are other pathways ( ) that calorie restriction are affecting that are causing aging.

SILLMAN: I want to ask you—you were talking about replicative studies and you were talking about chronological, so what specifically are you looking at?

KAEBERLEIN: Well, we're actually both involved in this large project to look at both types of aging across this 4,500 genes and the deletion set. For chronological aging the idea is the same. It's to ask what are genes that when deleted or when lost result in longer chronological life span. What we really think is going on, and actually there's been a lot of great work done by Walter Longo's lab on this, with respect to chronological aging is we really think it's a stress response primarily that affects chronological life span.

So—an increase in stress resistance seems to correlate very well with chronological life span.

So that was sort of out there in the background when we started this screen. What we found is very consistent with that. We found several genes that are known to be involved in nutrient response and activating a stress response when nutrient levels get low, which fits very nicely with calorie restriction.

SILLMAN: OK. So let me take a step back. When I hear something like "stress response," I think of lay articles that I've read, where it says "when I'm stressed, I'm actually inhibiting my life span. I'm taking years off."

KAEBERLEIN: Right. OK. Sure. Sure.

SILLMAN: What do you mean?

KAEBERLEIN: In yeast stress there's all sorts of stresses that you can apply to a cell or a person, obviously. But for a yeast cell, for example, we can grow them under high temperature, if that's a stress, or high salt.

These mutants that are long-lived chronologically are better able to grow under those conditions. This is true not just in yeast, but there is a lot of evidence in (sielegans), as well, that mutations in the Dower pathway or in the insulin-like pathway that cause increased life span in that organism, also cause resistance to stress—temperature or oxidative stress.

SILLMAN: Are these specific to—I don't know how—if you can differentiate an individual yeast like an individual person—but does an individual yeast respond differently so that I could then deduce that a human might have different combinations of genetic responses to these stresses?

KAEBERLEIN: So, if I understand what you are asking correctly, the answer is yes. There are many different strain backgrounds, and Bryan alluded to this a little bit. That's where some of this controversy over what SIRtu is or isn't doing derives from.

SILLMAN: Right.

KAEBERLEIN: And yes. So it's very clear that different strains and the way that they are different is because of different genetic make-up, just as you and I—

SILLMAN: Sure.

KAEBERLEIN: —have different genetic makeup. They respond to some of these longevity-promoting mutations differently. Certainly there are differences in that context of individual yeast.

Now, one of the reasons that we like to work with yeast is because we can make large numbers of yeast cells that are all the same. We can do very controlled experiments on large numbers of genetically identical cells.

SILLMAN: So when you talk about bias inherent in experiments, if everything is the same, then you are starting from a level playing field. And when you tweak things, then you know that what you've tweaked is actually making the change happen.

KENNEDY: Yeah. Yeah.

KAEBERLEIN: That's the whole—

KENNEDY: That's the real advantage of yeast. And some of this other, simply cariotic systems as well.

SILLMAN: So when we talk about response to stress, for example, if you restrict caloric intake, that was one of the stressors, and something switches on and it lives longer, is the idea sort of in your mind down the road that when you look at a human being there are certain things that you could do or that you could create that would help us turn those cells on in our own bodies?

KENNEDY: Well, I think that the—if we can discuss this in the context of calorie restriction, it might be. Because that is one of those—you know, reducing nut—same thing as reducing nutrient intake in yeast.

The way I see it is that it's not a highly—it's not something that a lot of people want to do. I mean, we are talking about serious calorie restriction to have a benefit.

KAEBERLEIN: Right.

KENNEDY: I think there's a lot of interest in looking for things that might uncouple having to actually restrict your calories from getting the benefits of that.

If you knew what calorie restriction was doing, you could look for pharmacological agents that might mimic those effects without having to actually—and still, you know, get your McDonald's…

[Laughter]

SILLMAN: Well, that's in a whole other topic—what we should eat.

[Laughter]

But the—the number, when they talk about calorie restriction, the number that I've read in some of the literatures, 70 percent, we're eating 70 percent of what a normal person might eat?

KAEBERLEIN: At least a 30 percent reduction, yeah.

KENNEDY: That's about the—yeah, that's about the rate in mice, certainly.

SILLMAN: Well, when you do your studies, is that when you find these things out about yeast? Do you try these things on yourselves at home?

[Laughter]

KAEBERLEIN: No! No.

SILLMAN: You guys restricted your…?

KENNEDY: Although there was a recent report that red wine was good and so we've been trying—

KAEBERLEIN: I'm happy to try that! Yeah.

[Laughter]

SILLMAN: I read about peanuts, as well.

KAEBERLEIN: Right. So I think, I mean, this is sort of a little bit of a different topic, but I think, you know, in terms of taking what we are finding in basic research and applying that to human—particularly aging research, where clearly there's a huge incentive financially as well as there's a lot of people that just want to live a long time.

I think we have to be a little bit careful not to get ahead of ourselves.

I don't think that there's anything that I'm doing particularly based on my own aging research to try to live longer. Clearly there are things like exercise and trying to eat right that are going to be beneficial, but, you know—

SILLMAN: Sure.

KAEBERLEIN: I certainly enjoy red wine, but I'm not—I'm not drinking red wine every day, you know, just to try to get enough resveratrol, or whatever.

SILLMAN: Talk about what there is in red wine that you think might increase longevity.

KAEBERLEIN: If I had to make a guess, I think that the ethanol, itself, is part of the beneficial effect in people on cardiovascular disease, primarily, or particularly. That's true because you can get benefits from beer as well as wine, and other types of alcohol.

Then there are all sorts of things like resveratrol and other compounds that are in red wine at a low level that may have something to do with the longevity aspect, but really nobody knows at this point.

SILLMAN: Just don't know.

KENNEDY: Well, it might actually switch on some of these proteins.

KAEBERLEIN: That sort of gets to an area where Bryan and I have gotten interested, and I would say caused a little bit of controversy with resveratrol. The story there is that it was published that resveratrol activates these SIRtuins and increases life span in yeast, and then more recently, in worms and flies. What we found is that we were unable to reproduce the results in yeast, and then we did some biochemical studies to—that indicate, at least, that resveratrol may not actually activate SIRtuins towards real biological proteins.

Now, having said that, we don't know that there aren't some proteins out there that do—that resveratrol does activate SIRtuins toward. But I'm highly skeptical about taking resveratrol in—with the goal of activating SIRtuins in my body, I would say.

SILLMAN: What exactly is resveratrol?

KENNEDY: It's a small polyphenolic compound that is present in a lot of plants and in grapes.

SILLMAN: In grapes.

KENNEDY: That's why it's in red wine. Actually it's quite an interesting molecule if you—there are over a thousand papers that discuss activities of resveratrol on a number of different potential proteins in the cell. It may, indeed, have biological activities. I'm not—by no means convinced. But it's certainly possible that it does.

Whether it activates SIRtuins or whether it's doing any of ten or fifteen other things that have been suggested for it, I think is an open question at this point.

KAEBERLEIN: Yes. I'd just like to clarify because I don't think you said exactly what you mean. Resveratrol clearly has biological activity, so it does affect cells. Whether it's—whether it's slowing aging, I think—

KENNEDY: Yeah.

KAEBERLEIN: —is still unknown.

SILLMAN: You said that you caused a bit of controversy among your fellow researchers? Who, exactly? And what was controversial?

KAEBERLEIN: We've caused a fair bit of controversy on several fronts, actually, over the last year.

Our findings on resveratrol were clearly counter to what the Sinclair lab had found. We don't completely understand what the differences are at this point.

SILLMAN: Which was that was turning on the SIRtu.

KENNEDY: Yes.

KAEBERLEIN: Right. So there are two aspects of that. One is the life span effect in yeast, where we attempted to do the same experiments and could not get the same results.

The other side of that is whether resveratrol activates SIRtuins at all toward real biological substrates. That's an open question. We found no evidence for that. Another group, led by John (Deneu), found no evidence for that. But, you know, it's always possible there's something real there.

KENNEDY: It's hard to prove something doesn't happen.

SILLMAN: So why was that controversial, that you couldn't replicate an experiment?

KENNEDY: Well, I think that that's—I actually think that trying to replicate other experiments is a good thing for the field, but it's certainly—if you have two groups that can't get the same results apparently doing the same experiment, it leads to—

SILLMAN: So does that mean, then, that you sort of set it all back in terms of what you know about genes and aging?

KAEBERLEIN: Actually, we think we brought it forward. There were a lot of people, when the initial reports on resveratrol came out, that were using resveratrol as a reagent, saying, "We wanted to know what happens if we activate SIRtu-1 which is the human SIRtu protein.

So we threw resveratrol on the cells and looked at what happens. What we are saying is, "Now, wait a minute. Resveratrol doesn't really activate SIRtu-1, or at least there is good evidence to suggest it doesn't. So you need to be a little bit careful here."

I think it's important and it's hard to do. In fact, it's more difficult than you might think to publish results that are counter to what is almost dogma in the field. But I think it's important, if you've got good reason to think that there's a problem, to stand up and say so.

SILLMAN: You said testing on human cells. You're working with yeast and I—

KAEBERLEIN: Although not completely.

KENNEDY: No. ( ) also works in human cells and in worms. So—

SILLMAN: Are you working with humans?

KENNEDY: Primarily—

SILLMAN: And so human cells—are there any limitations on the kind of research you can do with a human being in terms of aging and turning things on and off in cells?

KENNEDY: It's very limited in the sense that you're essentially restricted to working in cells that are—derived in cell culture. There are a lot of interesting things you can do. But it's harder to relate those directly back to aging, which is an organismal phenotype, you know, and not a cell phenotype.

KAEBERLEIN: I think there's a lot of skepticism, too, about the cell culture model, and how closely that really replicates the physiological conditions of our cells and our bodies.

KENNEDY: I think that, you know, this kind of gets to the issue which we think is important and that's the—everyone's making discoveries about genetic interventions that affect longevity in their organism, and it's time to really start to address this across organisms.

KAEBERLEIN: Right.

KENNEDY: We've gotten a lot of funding from the Ellison Medical Foundation. One of the things that that's allowing us to do is to take the things that we identify in yeast and immediately go into worms and ask—are those—is this analogous gene in worms also regulating aging? Then if it works in two very disparate organisms like yeast and worms, there's a good chance it's going to work everywhere. So then the things that work in both cases we're going to go into mice with and ask whether this regulates aging in mice.

SILLMAN: At what point do you get to find out about humans? Or can you just say when you test them in mice that it's going to be the same in a human?

KAEBERLEIN: You can't say that.

KENNEDY: You can't say that, but I think there's a strong likelihood.

KAEBERLEIN: I think—I mean, the model, at least for the pharmaceutical and biotech companies that are interested in anti-aging interventions, is that because aging is not defined as a disease. If we have a protein that we have good confidence affects aging in yeast and worms and mice, and we make a drug that affects the activity of that protein the way that we would expect to have an effect on longevity, then you look at age-associated diseases—you know, dementias, cardiovascular disease, any—

SILLMAN: Sure.

KAEBERLEIN: —age-associated disease, and you see if you can get it through clinical trials for treatment against that disease.

SILLMAN: Well, so what's the climate in this country like right now for clinical trials on humans?

KENNEDY: Um—

KAEBERLEIN: I would say I'm not the best person to answer.

KENNEDY: Certainly. I know there has been some controversy with regard to that, but I think that—it's one of those things that has to be done. There are always going to be issues that come up with regard to doing it.

But, you know, the question really is—with relation to aging, is that since aging is not defined as a disease, then how do you test a drug that supposedly slows the rate of aging?

I think the thinking is going to be that it's—if you slow down the rate of aging, you are going to slow down the rate of onset of a number of these age-related diseases, neurological disorders, some types of cancer.

So the idea is that a drug might be developed that delays the onset of that—and tested for that purpose.

KAEBERLEIN: Yeah. It's also possible—I mean, there's really so much that we don't know about aging, it's also possible that there are things out there that are natural products. And clear—I mean, I sort of hesitate to get into this, because there are people who are taking all sorts of wild stuff, which I don't condone, so stop if you're doing it!

But I mean, there may be something out there that doesn't have to go through FDA trials.

If resveratrol, hypothetically speaking, really did slow aging in people, then you wouldn't have to go through human trials to put that on the market.

KENNEDY: But essentially we want to take the step of looking across organisms and get the right targets.

KAEBERLEIN: Right.

KENNEDY: Things that work in different systems. And it's—being able—being here is—we're well placed to do that because we have people like Peter Rabinovich and Warren Ladiges to help us with our mouse studies, and Jim Thomas to help us with the worms. So—

SILLMAN: You mentioned that there is a center on the study of aging here. Do you all get together and talk about what you're doing?

KENNEDY: Yes. So this grant is actually—

KAEBERLEIN: We get together a lot.

KENNEDY: —funds more than our lab. It funds work done by—in Warren's lab on mice, too, and other labs.

We have routine meetings to discuss how to go forward and—we also—Peter Rabinovich runs—there's a Nathan Shock Center of Excellence for the Basic Biology of Aging here, as well, which funnels—takes a lot of money from the NIH and funnels it into aging research here.

Tthose things coupled are really allowing us to ask these sorts of questions on a large scale.

SILLMAN: So if this is all coordinated, started from yeast and the Center on Aging—

KENNEDY: Yeah, yeah.

SILLMAN: —a discovery that you might make in your lab could then be taken forward into the other organisms—

KENNEDY: That's the idea.

SILLMAN: —ultimately into—

KAEBERLEIN: In fact, that's what we're doing.

KENNEDY: That's exactly the plan.

KAEBERLEIN: So—we're in fact—already Erica Smith, who's a post doc in Bryan's lab and myself, are looking at the genes in worms that correspond to the genes we're finding in yeast, and asking if we knock down the function of those genes, does that increase life span in worms? Then Warren and Peter are going to make mouse models of those.

I mean, I think that that's—you know, that approach has a couple of big advantages, as Bryan and I have hit on a few times. It is unbiased. We didn't pick a model and start from that and say, you know, we are going to only look at things in this pathway. And, we get to the evolutionary conservation.

If it works in yeast and worms and mice, I think there's a very good chance—

KENNEDY: It's a good target.

KAEBERLEIN: —there's a very good chance it's going to have the same role in humans.

SILLMAN: How many other centers around the country are working on this similar kind of model as far as aging goes?

KAEBERLEIN: I don't know of anybody who's taking this multi-organism approach like we're taking—looking in three different organisms at least, and trying to find things that act the same way.

I think there are five Nathan Shock centers throughout the country. Then there are also—I know that David Sinclair just got a grant to start a center at Harvard from the Glenn Foundation, I think.

KENNEDY: I think that's correct.

KAEBERLEIN: So there are—there are other centers out there that are focused on aging research. But I think we're pretty unique and well positioned in the approach that we are taking.

SILLMAN: I want to go back, Bryan, to something that you were talking about, which was looking at, if not something that would help people prevent aging, but these ideas that you might have someone that you could give genetic therapy for Alzheimer's or some of the other diseases that emerge.

I don't know if they are caused by aging, or just because we're older, we're more prone to them. Do you think of it as kind of a building block approach? Ultimately there would be something that might be given to a person that would slow the effects of aging?

Or are you really looking at it as a disease-by-disease approach?

KENNEDY: Well, I think we're looking at it more in the terms of a general program of aging. I think your point was correct. Then when it comes to these age-associated diseases like Alzheimer's disease, it's still an open question as to whether aging is necessary for the onset of these diseases, or they just happen in old people.

But in either case, it may be that if you slow down the whole process, it delays the onset.

The question among aging researchers, I think, is whether—there are some scientists that believe that aging is really a multi-pathway thing, and each and every type of cell in the body is going through its own aging process—

KAEBERLEIN: That's right.

KENNEDY: —in which case there isn't some sort of master regulator of aging that's controlling how things age.

Then there are other scientists, and I think we would be more on this side, who believe that there are things that control the intrinsic rate of aging in an organism. In fact, single gene changes in mice can have 30 percent effects on longevity.

If there is this—these sort of intrinsic over-riding pathways, then by slowing them down, I would predict that at least some of these age related diseases would be delayed at onset.

SILLMAN: Then ultimately you're looking for sort of a master gene, a master aging gene?

KENNEDY: Well, I wouldn't go so far as to say one gene.

KAEBERLEIN: Right.

KENNEDY: I think we're looking for the few pathways that control the intrinsic rate of aging.

KAEBERLEIN: Although we may find a master gene. I mean—but—we would both be hesitant to say that we're looking for the master regulator of aging. I think that gets used a little too much.

SILLMAN: The master cylinder.

KENNEDY: It's overused. Yeah.

SILLMAN: One of the things I've read about is something that's kind of a cap on our—a telomere?

KENNEDY: Yes.

KAEBERLEIN: Yes.

SILLMAN: I am wondering if you can explain what that is and if that's something that's different in different individuals?

KENNEDY: Yeah. You have these repeats in small—sets of DNA at the end of each chromosome. And in these repeat in cell cultures. This involves taking cells, like fiberplasts, out of your body and growing them in culture.

Just to take a step back, if you keep doing that, these cells—the whole culture will just stop dividing after a couple of months in culture and—and senesce—go through a process called senescence—and that seems to be related to the shortening of these telomere ends. When one of them gets—or several of them—get too short, they signal the cell to undergo this senescing program.

KAEBERLEIN: So the question really is whether that relates to normal aging or not. So there—that's still a very open question. There are certainly—if you look for these types of senescent cells in individuals, you can find them, not at a really high rate. It's unclear whether that program is related to aging.

What it is doing, though, is probably a break on cancer progression. The thinking is that this is a mechanism to limit the proliferation potential of cells. If the cell's going to become a tumor cell, it has to find some way of getting around this break. So it's another stop to the progression of a tumor.

SILLMAN: I guess in the back of my mind, when I asked you that question, I wondered if there are families, certainly a center on aging would be looking at them—families that are more long-lived than others.

KENNEDY: Yes.

SILLMAN: Do they have longer telomeres on the ends of their chromosomes?

KENNEDY: I think that there are a number of groups that are doing those kinds of things. In other words—but they are not looking strictly at telomeres. They are looking across the whole genome; and they are trying to ask what kinds of mutations or polymorphisms or changes that naturally occur in individuals—which ones of those are associated with longer life span? Ultimately the idea would be to figure out what genes harbor those changes, and figure out if they are regulating aging.

SILLMAN: And so do telemeres exist in the yeasts that you are looking at?

KENNEDY: Yes, they do. But they don't—we were a little confused by this initially, because the SIR proteins that we studied regulate telomeres. However, telomere length is not related directly to the replicative life span of the yeast cell.

KAEBERLEIN: In fact, that seems to be true in worms and flies and mice, as well. So, I mean, the telomere hypothesis in people was—ten years ago was *the* aging hypothesis. We were all going to live forever by lengthening our telomeres. And, you know, there may certainly be a role for telomere shortening in human aging, but I think that has clearly fallen out of favor. The evidence from the model organisms is that telomeres may not be as important as people thought.

SILLMAN: —as we thought. You both are hard scientists. You are no bio-ethicists. But—

KAEBERLEIN: That's for sure!

SILLMAN: —do you ever sit back and wonder, do we want to find this set of genes that turns aging on and off? Is that a—do we want to stop aging? Do you think about that? Do you talk about it?

KENNEDY: Yeah. I think it's interesting how the culture thinks about aging, because people get cancer, people get other diseases, and everybody thinks this is a tragic event; we need to do something about it.

What really is different from that than people aging?

KAEBERLEIN: Right.

KENNEDY: I mean, I think the main difference is that everyone ages. People think of it as a natural process, as something we are programmed to do, and it's part of the human life cycle.

But the other way of thinking about it is it's really just a disease that hits everybody. I think that—I'm not trying to sway people's opinions about it; they are welcome to believe what they want. But I think that either of those arguments can be made. But I think that that sort of thinking has delayed, a little bit, research on aging, because it's, "Oh, well, that's just what happens."

But, you know, a lot of these diseases only happen in old people, too. And so—

SILLMAN: Do you make a distinction, then, between the diseases that, at this point, we think of as diseases of aging and the idea of extending our life spans?

KAEBERLEIN: Well, I think—I mean, I think that there's—yes, and no. I think that one approach to studying aging is to try to understand specific diseases of aging and develop treatments for those specific diseases of aging. That's not the approach that we take in the sense that we want to try to understand aging at a more fundamental level.

But I also want to point out, you know, one of the issues that gets brought up in the ethical debates about whether we should be studying aging or not is that calorie restriction and the other mutations that increase life span in model organisms—it's not simply a case of increasing life span where you are old for the second half of your life. It's increasing, you know, what people sometimes call health span where you are not just remaining—you are not just living longer, but you are remaining young longer. In very long-lived people, the centenarians and super-centenarians, it seems clear that they also maintain their youthfulness almost 'til the end of their lives, and then it's a very rapid decline. I think that that's something that, you know, that every person would have a hard time saying they wouldn't enjoy having that added to their life.

So I mean, I personally don't have any ethical problems with studying aging and the idea of maybe eventually being able to lengthen human life span. I think it's a good thing.

KENNEDY: It's an interesting thought. I just—I go into my son's class and give lectures every year. And he's—he's Cole—he's in the second grade now.

SILLMAN: You give lectures on this every year. OK.

KENNEDY: I said, "Why do you think we age?" They are all eight-year-old students. I got a whole range of answers from, you know, "We can't go to heaven if we don't get old and die." I got, "Well, if we didn't age, there'd be too many of us on earth."

KAEBERLEIN: Which is actually one of the arguments people make.

KENNEDY: Which is not too far from—it's interesting how even at young ages people are thinking about this. It's something that cultures are already having to come to grapple with. Two hundred years ago people were dying and the average life span was forty or fifty. The advent of antibiotics—we don't think of that as an anti-aging program, but effectively that's—what it's done is allow people to reach—more people to reach their maximum life span. It's had a profound effect on culture.

I think that there are ethical issues that are going to have to be dealt with, and I think they are going to have to be dealt with as potential therapies come up, because we just don't know what's available right now.

SILLMAN: But there's a distinction. Dr. Kaeberlein mentioned the distinction between—it's not that you're looking to live forever but the distinction is living to a certain age, with less health than somebody who might be one of these super-centarians who has a very, relatively good physical quality of life until the very end.

That might be preferable in your mind to sort of degenerating for years and years.

KAEBERLEIN: Yeah, yeah. Absolutely. I think it's—

KENNEDY: You know I think that—sorry.

KAEBERLEIN: No. Go ahead.

KENNEDY: I think that anything that is going to actually delay the progression of aging is going to—it's not going to be like—if you imagine the life span as a piece of string, it's not going to be like tying more string on to where you're sick.

There are programs that you can influence what they're going to do, and this is what happens in the model system, is that it will be like stretching the string out. So what's happening is the period of time when you are healthy is going to be expanded as well, you know, until the end, when you are still going to get sick.

If therapies become available, I imagine that's what they are going to do.

KAEBERLEIN: I'd just like to mention that I think these questions of overpopulation and other potential downsides to dramatically enhancing human longevity are things that people should pay attention to. They are important questions.

But I also think that saying—the position that we shouldn't be studying aging or trying to extend human life span because of these potential problems is—I mean, that's ridiculous. Nobody can predict where society is going to go if tomorrow, you know, we had an intervention that could dramatically increase life span.

So it's something we should think about and we should be prepared for because it might happen.

KENNEDY: It's worth pointing out that there are small populations of individuals who age prematurely. I don't think anyone would—that's now a disease because they age prematurely. They have a lot of phenotypes of premature aging.

By learning normal aging you might be able to delay that onset too.

SILLMAN: Well, it strikes me listening to you, you have used the word "if, if, if," but it sounds like "when." It's—I mean, is it feasible that we will find a—that you will be able to identify biomarkers for aging in the body?

KAEBERLEIN: I think that's our skeptical nature, that we keep using if, if, if.

KENNEDY: Yeah. I—actually hear a lot of "when, when, when" and that makes us skeptical. I think that it is "when," but what the "when" is is a lot more open than—

KAEBERLEIN: Right. Whether it is going to be in time for any of us, I don't know.

SILLMAN: I won't ask you then to predict a timeframe.

But it seems that genome sciences have their—at an exponential rate of discovery that it was slow and now we find out about—every day you can open the paper and hear about a new cancer treatment that's targeting a specific gene. So it seems that the field that you're working in is rapid.

KENNEDY: I think it's rapid. I think it will happen. I think that it's also fair to say that where we are on aging research is not where we are on cancer research.

KAEBERLEIN: And we still don't have a cure for cancer.

KENNEDY: For a lot of cancers, we don't. And so I think that—

SILLMAN: You mean you are further back in aging research?

KENNEDY: Yeah.

KAEBERLEIN: There is so much more money and emphasis put on cancer research over the last several decades that there's just been more progress made. I think that I'm happy to say that if more money could be devoted to aging research, which is affecting all of us, then that would speed up the rate of discovery.

But it's going to happen—I don't think it's—I have to be very cautious about saying on what time frame.

SILLMAN: Well, it also—not to harp back on a DNA strand, but it seems that the more that you know about genetics, the more that all of these things sound like they are linked together. That if you are talking about aging, and if things like neurologic Alzheimer's or cancer or heart disease—some of the diseases we think of as being associated with older people, that you—that they are all combined—that once you work on one you are going to necessarily go to the other.

KAEBERLEIN: It depends on how you work on one. I think with aging, at least my viewpoint is that there are certain underlying pathways or underlying molecular changes that cause many of the different age-associated diseases.

If you attack the age-associated disease itself, then you may not learn anything about aging. Whereas if you look at how does calorie restriction do all of these things, and at least in mice, it is very striking; calorie restriction really retards almost all of the aspects of aging that we can look at.

If the same thing is true in people, and I think that it will be, at least to some extent, then it's—then that does give us optimism that you can really affect all of these degenerative changes at the same time by some—by a single intervention or a single pathway.

SILLMAN: I just have to go back to calorie restriction, because the question comes to mind: quality of life—I mean, I'm not sure—you talked about a Big Mac. I don't eat Big Macs, but do I want to give up pasta and carbs, which are part of the quality of life, so that I can live longer?

KENNEDY: I think we should make a distinction before we go forward, and say that there are really two things going on. There's eating a healthy diet, and then there is the diet that a lot of Americans are eating now, which is unhealthy.

That's not a question of extending or not extending maximum life span. That's a question of not getting to your maximum life span. I think that—

KAEBERLEIN: Right.

KENNEDY: —eating healthy and having exercise is what—if people were really worried about aging, that's what they should be doing right now.

Now, in terms of going further down from what we would call healthy to what you need presumably to affect life span, that's a major step. There are people who are doing it, and it's very hard to get the right dietary intake at that low level of calories, and there are side effects of it.

SILLMAN: You have sort of talked about your reluctance to talk about a timeline. But you talked about if there was the same kind of funding going towards aging research as to cancer research, for example—you'd be further along. So what is the biggest challenge to what you're doing?

KAEBERLEIN: It's hard. Aging is very complicated.

[Laughter]

KENNEDY: People live a long time.

KAEBERLEIN: I think money is—you know, being able to get the funding to do what we think is the right approach or a good approach, you know, is hard to do. Although I must say, having something like the Ellison Foundation out there has allowed us to really—to be able to move forward.

KENNEDY: Pursue this.

KAEBERLEIN: I think certainly that as the NIH budget is shrinking funding for aging research and other aspects of science, it will become a limitation. That's probably—you know, in terms of what the government could do, and this again isn't just for aging research, I think that more money definitely needs to be put into the NIH budget.

KENNEDY: The other factor is aging research is just difficult. I mean, mice live two or three years. You can't do your experiment and then come back next week and get the result. If you are doing a true longevity experiment, you are waiting three to five years to see if your mutant lives longer.

That just slows down the rate of progress and there's not much that can be done about it, although the model systems, like yeast, you can go faster—and worms. That's one other thing that makes them of interest, to us at least.

SILLMAN: We've all heard about public discourse about stem cell research, for example. Is there a certain climate of opinion on the kind of work that you do? Or do people not know enough about it?

KENNEDY: We try to keep—

[Laughter]

KAEBERLIN: I would say within the field, I would say that the work that we're doing has gained a lot of credibility. People were skeptical that yeast could be used as a model to understand the aging in humans. I've been skeptical, as well.

But I think as we find genes that share the same roles in yeast and worms and flies, and we are starting to get the picture the same thing is true in mice, then you've—at some point you've got to say, "At least some of the aspects of aging are conserved."

I think that there has been growing recognition that these types of approaches are valid.

KENNEDY: Yeah. George Martin, who's really the senior aging researcher and really has brought aging research to the forefront here at the University of Washington, has this idea of—or has brought forth this idea of public and private models of aging.

KAEBERLEIN: Right.

KENNEDY: In other words, a private pathway of aging would be something that might only affect yeast, or might only affect worms. But there are also going to be these public pathways of aging that affect everything. Really what we want to do is try to take the things that we find and make that distinction. What are the public ones and what are the private ones? I think that for us is the most unbiased and direct way to go forward.

KAEBERLEIN: Now, you mentioned stem cells and I think that's another—that's an example again of something that—where the field is being held back. Because we don’t—there are certainly a lot of reasons to think that if we could learn exactly how some stem cells were working and learn to manipulate them and use them as therapies, that they would be useful treating diseases of aging. Clearly the political climate has held back research on stem cells.

I think that’s another example of how politics can impede the progress of research in this field, and in others.

SILLMAN: Has it had a direct effect on what you are doing?

KENNEDY: Well, we are—that’s another advantage of yeast.

KAEBERLEIN: Right!

[Laughter]

SILLMAN: Nobody cares about yeast?

KAEBERLEIN: Nobody complains—yeah.

SILLMAN: Nobody cares about it.

KENNEDY: Not at this stage.

SILLMAN: So you don’t want to look out long-term in terms of sort of the overall progress. But in terms of your research here at the university, what is an immediate goal, say in the next year or two.

KAEBERLEIN: I’m not unwilling to look long term. I’m just unwilling to make the argument that interventions that delay aging are going to be available in five years or ten years.

SILLMAN: OK. I see. OK.

KAEBERLEIN: I think what we’d like to do in a reasonable time frame is help—and others are interested in this, too, in different ways—figure out what the public pathways of aging are. That’s going to tell us if we really want to slow aging, what are the targets that we need to be thinking about hitting to actually influence aging in humans?

SILLMAN: So do you have some ideas of what they might be?

KAEBERLEIN: Well, yeah. It’s been known in yeast that a number of these cytokines pathways, these signaling pathways, that tell the yeast cell what level of nutrients are in the environment. Then they act to change the growth properties of the cell—that they are really going to be important for aging and the TOR pathway, in particular, is one that we are focused on now.

SILLMAN: The TOR pathway?

KENNEDY: Yeah. The TOR is named for Target of Rapamyacin. There was a drug that Rapamyacin used—just a little bit tangential to this point. But so this is this path—it recognizes the level of nutrients in the environment, and it tells the cell how much to grow.

That same pathway is regulating growth in worms and flies and mice. What we're finding is that if you reduce signaling through this pathway, you get a much longer-lived yeast.

KAEBERLEIN: It's worth mentioning that's true for both the replicative and the chronological life span. There are relatively few of these that we've found, thus far, that do both—that you can get increase in both types of aging in yeast, which we think is probably significant.

KENNEDY: It's already been reported that TOR affects aging in worms and flies. So this to us is a very exciting target to look at.

SILLMAN: So that would be one of the public pathways.

KENNEDY: I think so.

KAEBERLEIN: We think so. It's intriguing that it is responsive to nutrients. And, clearly that, you know, calorie restriction is a deprivation of nutrients. So things are going the right direction.

I think we're still not completely convinced. You know, we don't want to come out and say, you know, "Calorie restriction is acting by decreasing TOR," but it's intriguing and we are interested in it mechanistically.

I think that's also—

KENNEDY: And of course—

KAEBERLEIN: One of the things we really hope to find out is how is calorie restriction working, not just in yeast but in every organism where it increases life span.

I hope that will come out of the types of studies that we are doing.

KENNEDY: We spent a lot of time sort of fleshing out this TOR pathway. But then, the next question is, all right, you reduce nutrients. You decrease signaling. What does that do?

KAEBERLEIN: Right. Exactly.

KENNEDY: What we're trying to figure out now is what are the targets of this pathway that are important for aging? And as we go through the whole genome, we are getting more and more candidates for those targets.

SILLMAN: So how far ahead are you planning the research that you are doing?

KENNEDY: Well, you have to plan ahead in terms of getting into the mice, because you know—

SILLMAN: Sure.

KENNEDY: —it takes a year to generate the mice, and then three years to age them. Sso essentially what we are doing is we are pushing the yeast as fast as we can, taking the long-lived yeast strains and going immediately into worms, using RNAI technology to get the knock-down expression of the gene that we are interested in.

Then anything that works in both we're initiating the mouse study. Everything is sort of going simultaneously.

KAEBERLEIN: In some cases like TOR, it's already known that this gene has a role in worms and flies. Cynthia Kenyon and Gary Rivkin—they have both done large-scale RNAI studies in worms.

So in some cases we get a gene and we are like, "Oh, they've already found that this—this affects aging in this other organism. Let's look and see if anybody's doing it in mice."

SILLMAN: Hmmm. So a public—I think genes in yeast and worms and mice are all great. At some point how will you look at genes in humans to find out if the public pathway is followed to the end?

KENNEDY: Yeah. I think that you're going to have to go in terms of looking at targets, pharmacological targets, to go after human genes, human proteins on the presumption that that's going to do the same thing. Then test the target—test the pharmaceutical reagent when you develop it.

KAEBERLEIN: Another approach that people are taking is to look and ask in different people. "We've got a gene that we think is interesting. If we look at the sequence of this gene in different people, are there differences in sequence that may or may not correlate with their longevity?

I'm not convinced that that approach—I think that's a difficult approach because most of what you are going to see there, I think, are genes that affect heart disease or other common diseases.

But it's a reasonable approach to take and there are people doing that.

KENNEDY: Yeah. One thing I would like to point out is that we are trying to—we're really large-scale in terms of yeast aging now. We're trying to get that way in terms of mice, as well.

So one of the things we are trying to do with this money that we've been given is to be as collaborative as possible. There are labs out there that have work on yeast, or mice, and they are hesitant to get into longevity studies. And we're happy to help out in any way we can.

SILLMAN: So connecting with labs and other institutions.

KENNEDY: Yeah.

KAEBERLEIN: Yeah. Yeah.

SILLMAN: How would that further what you are doing here?

KENNEDY: Well, I think it—you know, it provides a bigger picture on what's going on in regulating aging. It's certainly—just because we are taking this very unbiased approach doesn't mean that people aren't onto things. They may have interesting genes that they think affect yeast aging. But they are studying that gene for some completely other reason and don't want to do these laborious assays.

I think by interfacing—bringing more connections between the aging community and even other types of biomedical research, we'll have to learn more in the long run.

SILLMAN: So when you each sit back at—I mean, I don't know how far back you can pull from the yeast and what you're doing, but when you sit back at the end of the day, say you were talking to your second grade or third grade son—of what you are doing, what do you consider to be the most important thing that's going to come out of your lab?

KENNEDY: I think we want to—I've said this previously—but I think we want to really start to think of aging as a big picture thing—you know, what—let's stop focusing on our favorite gene and look and try to get a—I mean, all of biomedical research right now is going to these genome mind views as to what's going on. I think we are trying to bring aging there. I think that's what we want to do.

KAEBERLEIN: Yeah. I think, also, you know, I think we're both convinced that we are going to learn things that are—about aging that are shared, at least up to mice and we keep going this divide between mice and humans.

But I would be personally very surprised if a gene that affected aging in yeast and worms and flies and mice didn't affect aging in humans. But we are also, I think, hoping to be able to answer the question by looking across the entire genome, how much of aging is conserved. At this point, nobody really knows.

People argue back and forth, “Oh, you can’t learn anything about human aging from a yeast or from a worm or from a fly.” But nobody knows. I think we’ll soon be able to answer that question—at least again up to mice.

It’s very hard to know how to go from a mouse to a human. That’s one of the real challenges for the field, I think.

SILLMAN: But you believe that there is a connection?

KAEBERLEIN: Absolutely.

KENNEDY: Yeah.

SILLMAN: I’d like to thank both of you so much, and I look forward to those papers when you are studying humans. I volunteer! You can look at my genes.

KAEBERLEIN: We’ll put you on the list!

SILLMAN: Dr. Bryan Kennedy and Dr. Matt Kaeberlein at the University of Washington. Thank you.

KAEBERLEIN: Thank you.

KENNEDY: Thank you!

[END]