TOREN FINKEL: It's a pleasure to be here. So I have nothing practical to tell you. So if you wanted to stretch your legs and go off, that'd be fine with me. I understand you've had a hard day. What I would like to talk to you about is something that may be practical maybe in 10 years or so, and that's the idea of sort of drugging aging-- that is, developing medicines that directly slow the rate that we age. And so the question is, why should we even study aging? And so I spend most of my time as a basic scientist, and for me it's the most interesting question in biology that we really have no idea why and how we age. And to me it's a great unknown, and therefore something worth studying.

But I think most people are interested in the biology of aging because of this sort of intimate relationship between getting older and the propensity for disease. And so as mentioned, I was trained as a cardiologist. I just want to go through really the magnitude of the effect of aging on disease propensity. So again, Framingham data and other epidemiological data has really made its clearly defined risk factors, as we all know. And so if your cholesterol is elevated, your risk for a cardiovascular event goes up about two-fold. Similarly if your blood pressure is above 180 over 100, your risk goes up roughly threefold over the next 10 years. Diabetes doubles it, smoking doubles it. But if you're 70 to 75 years old, your risk for a cardiovascular event goes up roughly seven-fold.

So that's the relative magnitude of age versus these other risk factors, and we've made really incredible strides in reducing the mortality from cardiovascular disease by treating what I would say would be relatively minor risk factors like cholesterol and blood pressure. And we've left really unaddressed or unattacked the single largest risk factor, which is age. And so most people say, well, that's not modifiable. But what I would like to convince you over the next 20 minutes is that that may not be true-- that aging, like any other biological process, can be modified. And I think this slide demonstrates what the potential implications of that. A slight modification of the rate that we ate would have a tremendous impact on cardiovascular disease.

But it's just not cardiovascular disease. So every disease that we worry about for ourselves, or our patients, for our family, almost every disease-- neurodegenerative disease such as Alzheimer's exponentially rises. Cardiovascular disease, as I say, exponentially rises as we age. And so does cancer. In fact, the risk for cancer above the age of 65 is tenfold higher than below the age of 65. Again, dwarfing any other risk factor for the condition.

And so what I'd like to talk about really is this idea that although we think about disease and we think about treatment for diseases, if you look at this graph-- I don't think I have a pointer, so I can't. But if you look at the graph, most of the therapies and most of the way we think about diseases are really focused upon the y-axis. That is, we try to get medicines that affect Alzheimer's, medicines that affect cardiovascular disease, medicines that can treat cancer.

And so what I'd like to talk about is trying to think about can we get medicines that affect the x-axis? And the idea would be that if you slow your progression along the x-axis, if you slow the rate of aging, you shift all of these disease curves to the right. And thereby, a single drug that affects aging really affects your propensity for all of these conditions. At least, that's the promise.

So the question is, how far can we shift these curves really reasonably to the right? How long can we live? And so the answer probably is shown here. This is Madame Jeanne Calment. This was on her 121st birthday. She lived another almost two years, almost to 123. And if you exclude Noah and Moses and other biblical characters, she's probably the oldest recorded individual in the history of the world.

I can tell you a little story. She had a lovely life. She lived in southern France in Arles. Her uncle owned an art supply store, and she as a child got to meet all the great French impressionist painters, had very nice things to say about Cezanne, was not very-- was very critical of van Gogh. Thought it was very rude and hard. But the story that I like to tell about her is that in France-- and they don't have it here, but in France if you have a nice house, a condominium, that somebody can pay you a small amount monthly retainer with the idea that when you die, they'll get to buy your house.

And so when she was in her late '80s, this very nice gentleman in his '50s began paying her this monthly retainer covering her apartment. And as you can imagine, as you got 30 years later when he passed away, she was still living in there. So no one else, even though she was about 110 at that time, no one else took her up on that deal.

So did she do anything that really-- that made her live this long? And the answer is no. This is her. She smoked. She smoked to 119, it turns out. So you could argue maybe it precipitated her death, but she drank every day. So she didn't do any of the things we tell our patients to do in terms of living up, and yet she had this extraordinary life.

And the reality is that her children did not have that long life. And so the question I would like to endoscopists audience of intelligent people is how much of your lifespan do people-- well, I should say it this way. Is your lifespan predominantly regulated by your genetic makeup? That is, is your lifespan mostly genetically or environmentally controlled? Who here thinks it's their genes? How about who says the environment? Pretty split, but I'm not going to let you off that easy.

So here are traits. Here are traits of individuals and their genetic components. So 1 would be completely genetically encoded, 0 would be no genetic component. So some of these are controversial like intelligence. People give an estimate anywhere from 50% to 80% is genetically encoded. But it's actually interesting is that verbal aptitude, as you can see, is much more strongly inherited than math aptitude. So when your children do well on essays, you can take credit for that. And when they do poorly on their math tests, it's not your fault.

[LAUGHTER]

So on this scale, with 1 being 100% and 0 being-- what would you say lifespan is? Anybody want give me a decimal that they think-- want to throw out what percent of your lifespan is genetic? So it's much lower. It turns out it's about 0.25 based on twin studies. So basically, for most of us-- which is great if your parents died young. Most of us only about 25% of how long we live it's really determined by our genes. The rest is sort of environmental influences. And we don't really understand what those influences are.

But there are some things that are known to make organisms live longer. Not necessarily people yet, because those studies are just not really haven't been done. But the string that's most clearly associated with an increase in lifespan and health span is this idea of caloric restriction. That is, if you reduce the amount of food an animal can eat, they live proportionally longer. In fact, the more you reduce it up to the point that they're at the boundary of starvation, all across that from eating all you can eat to that sort of boundary of starvation, you get an increase in lifespan.

So for animals that I tend to work with like mice, it's pretty profound. So if you give an animal all they can-- just as much food as they want, they live a certain-- usually about 2 and 1/2 years. And you get about a 30% or 40% increase in lifespan if you bring them down to so they can just eat what they need for their sort of daily requirement. So that's quite a large increase in lifespan, if you think about that translation to humans.

And the thing about this phenomena is that it's very well conserved. So you can see this type of thing, simple organisms like yeast, and flies, and worms, and as I said, mice. And there is actually a study going on. It's a long study of about 30 or 40 years involving chimps-- which is, you know, a non-human primate-- where, again, they've randomize chimpanzees to sort of an all you can eat diet or a caloric restricted diet. And they've asked how they do and how long they live.

Now, obviously they haven't finished that experiment. And unfortunately, there's been two groups doing this, and they disagree on the all you can eat diet. And so they've gotten somewhat conflicting results in large part because of that. But at least both of them agree that at least in terms of cardiovascular disease and metabolic diseases, there's a clear trend so far that the chimps that eat less are much healthier. So this probably extends to us as well in terms of lifespan and health span.

So that's something that none of us can-- most of us cannot do, that is, eat less as you had your lunch today. It's very hard to do, as you can see by the growing trends in weight in the US and other Western countries. So as scientists we say, OK, we know what works. Let's try to figure out how it works, and thereby maybe develop medicines that sort of mimic how it works.

And so over the last 10 or so years, a variety of laboratories have really described two pathways that appear to mediate-- molecular pathways in our body that appear to mediate these effects. That is, they somehow sense how much food is available and they use that information to somehow change the body. And then how they change it somehow produces an increase in lifespan for the organisms.

And I wanted to go through one example where we've manipulated one of these pathways just to show you the sort of ways that you can approach aging itself and the molecular basis of aging. And so these two pathways, one involved these proteins called the sirtuins, which my lab has been interested in, as well. And these are the proteins that some of you may know are the target of this hyped molecule called resveratrol, which is in red wine. And resveratrol is thought to directly activate these sirtuins, and that's how it was touted as sort of an anti-aging molecule.

But sirtuins are a very interesting pathway that link how much you eat to how long you live, and it may be things like resveratrol might activate that, maybe short circuit so that you can eat what you want but still live long. The other pathway, as shown on the left, is this protein called mTOR, which again senses the nutrients in your body. Here's an example of what mTOR-- mTOR is a protein in every one of your cells.

Again, it's conserved from yeast to us and it acts basically as a way that your body and the cells in your body know how much energy is there. It sort of sits inside and senses mostly the amino acid concentrations in your cells. And based upon that, it decides whether the cells should get bigger and grow or to begin to break down things and provide more nutrients. And again, in lower organs it's been shown that if you reduce the activity of mTOR, you produce this really long increase in lifespan in animals.

And so I just want-- again, no molecular biology will be on the board so you have to worry about that. But just to show you the way that we can go about these types of questions. So again, my lab mostly works on mouse models. In this case, we made a genetic variation in the mouse that reduced the amount of mTOR in the mouse ir every tissue in the mouse. And you can see that below there's a Western blot there looking at mTORic levels, and we reduced it to about 25% of the normal level in these mice.

And this is what happened. So these are the mice-- the lifespan of these mice. This is a long experiment, so obviously it takes about three years. But they lived much longer. Both the males and females lived about 20% longer. So that would be the equivalent in us of going from an average lifespan of about 75 years to now 90 years.

Now, all we've done is change one out of 30,000 genes in the body. And we've not even done that much, we've just tuned it down to about 25% of its normal activity and produces profound change in the lifespan of the organism. In this case, a mammal. And again, this pathway is completely conserved in us, as well.

Not only did they live longer, but they're healthier for the most part. And so here's an example. I won't go through the details, but this is a test of memory and learning in the mouse. And the higher the [INAUDIBLE], the worse the animal is in terms of learning. And as the mice get older, the control mice ability to remember and learn got degraded, as is common in us, as well. And the mice that had this reduced level of mTOR that lived longer at the same age were not perfect, they weren't youthful, but they were much better. It's saying that their brains had aged slower, as well. Not only were they living longer, but as best we can tell in mice-- which is hard, we can't ask them questions, but we can test them for things. And as far as we can tell, the quality of their life was improved by doing this, suggesting that these types of interventions might have real effects in people's quality of life, as well as the duration.

So how does it do this? How do any of these things work? And we don't really know. mTOR is this very important protein that, again, senses energy and then makes a lot of decisions for yourself. I just want to talk about one thing that we're focusing on which, again, I think is really important for the aging process, and this is this process known as autophagy, depending upon-- I should just skip over this. But this is a pill that inhibits mTOR protein-- I'm sure I have to mention this-- called rapamycin that some of you know is clinically used in some cases for immunosuppression. But it does it by inhibiting mTOR. And it made mice live longer as well, suggesting that again these pathways are very druggable.

OK, so going back how the mTOR works, we're talking about this process of autophagy. This process was described again in yeast and actually won the Nobel Prize two years ago for the Japanese investigator who described it. And again, it was a process that really wasn't described when I went to medical school or known when I went to medical school, but it's basically the way that your body, your cells in your body get rid of debris.

So how do you get rid of large protein aggregates that accumulate as we get older? How do you get rid of mitochondria that get damaged? What is the cellular machinery for this? And what this Japanese investigator was able to show is that it occurs to this process of autophagy. And again, what this process does is it recognizes the trash in your cells and it does that through a very complicated molecular tagging system. But it recognizes and then it formed basically a trash bag around the other thing which is called the autophagosome, which is a new membrane that's grown in the cell that sort of wraps up that trash and then it delivers it to another part in your cell called the lysosome, which is where it gets degraded. And this whole process is called autophagy, and it's the process by which all the time your cells and tissues are getting rid of damage in your body.

Now, that's the good news. The bad news is that this process gets worse as we get older. And this whole process of removing trash and garbage gets impaired. And so the natural consequence of that, we think, is that when you look at all tissues pathologically, you see a lot of debris and damage. And what we think is happening is that it's not that they're producing more damage necessarily, but they're not getting rid of it as effectively as we get older.

And so we first wanted to prove that this process really was slowing down. And again, I won't go through all the details here, but we developed this assay that allows us to look in animals and look at this process of turnover. And it's a complicated assay, I won't go through all the details. But it basically involves this fluorescent protein which we call keima. Just let me show you what your brain looks like-- or if you're a mouse, maybe a human too-- as you get older.

So the green here represent normal mitochondria, and the red here represents mitochondria that have been removed because they're damaged. And on the left, I don't know if you can see it, I see it here well. But what we're looking at here is the area in your brain that encodes new learning and memory, it's called the hippocampus. And in the young mouse, that's very, very orange and red, which means that there's a lot of turnover and a lot of damaged mitochondria are being removed. And then the old brain that's not happening, suggesting that this whole process of autophagy has slowed down in animals. And we think that's partially why these animals cannot learn and remember. And so we're actively trying to find drugs that stimulate this process as a way of reversing this.

Let me just end with, again, some clinical interventions that we're undertaking here that sort of exploit this knowledge and I think are the harbinger of how this sort of very complicated biology is going to intersect with clinical practice. So first, one of the problems in aging is that although it's very interesting, no one agrees really why it happens. There is no universal theory of aging at this point. So in that vacuum, let me show you the theory that I've proposed.

And it basically is this idea that we eat food and we make energy, and then we have to decide how to use that energy in our body. And so some of that goes around for walking, and eating, and breathing. It all takes energy in our body. Some of it, our energy-- for those sort of daily activities. If we're in a reproductive age, we need energy to reproduce. All the time we're making new components in our cells and tissues, so we need to use energy for new biosynthesis, and then we need to protect what we have. We have a variety of systems of quality control to repair and maintain our body at all times. And for some reason, we set how much energy we're using in all of these various functions.

In my interpretation of the literature, things that make us live longer shift this balance. We don't really understand, so this is sort of a global view, but they shift it such that we're using more of our energy for maintenance and repair. And there's something about doing that that it may make you grow a little slower, or not as big, or whatever, but it makes you stronger against a variety of stresses by doing that. And that seems to translate, at least in model organisms, to a longer life.

And so that's my general sort of theory on aging. And the reason that's important because it suggests that how we use energy and how metabolism happens in our body, if we can manipulate that, that might have advantages in terms of protecting us, making us live healthier and being protected against some stresses.

So are there drugs that we have already approved that might do this? And one of them that's received a lot of attention lately is this very commonly used drug for diabetes, metformin, which works-- it's complicated how it works and not completely agreed on how it works. But most people feel that it affects your mitochondria and activates an energy sensing pathway inside your cells.

And so it sort of redirects a lot of metabolism in your cells and tissue a little bit towards its maintenance and repair pathway. And consistent with that notion, if you look at animals given metformin in their diet-- these are non-diabetic animals-- they live longer. And this is very well conserved-- again, lots of animals from very simple animals, in this case in mice, as well.

And if you look epidemiologically in people getting metformin who are diabetics, obviously, compared to non-diabetics, for instance, or other diabetics getting other oral agents. And here's the example for cancer incidence. There's a clear reduction epidemiologically in cancer incidents in patients getting metformin compared to patients of that same age who are not on metformin.

Again, this is not what you would predict from glucose lowering agent, particularly from the glucose lowering effects of metformin. This is effects that has really nothing to do with diabetic control, this reduction in cancer. And again, it comes back to this idea that metformin, by activating this particular protein AMP kinase, which regulates energy metabolism, may be really resetting that pie chart that I showed you. And that's sort of consistent with this notion that it has this broad pleiotropic effects on humans as well as animals.

So there is actually going to be soon an NIA-- National Institutes of Aging-- funded study based on these types of data, a trial that University of Pittsburgh will be a part of. A large trial using metformin in patients over the age of 70 to see if it can reduce disease incidence in that population. So that's going to be a five or seven year study where people-- non-diabetics will be randomized to metformin to see if it has this anti aging or improves health span in the elderly. That's a large study.

We are actually going to do a study here at Pittsburgh only that's being funded by UPMC. So again, we're going to do a study-- again, this idea that stress resistance, and aging, and agents that intervene in that might be useful. Our paradigm is a little bit different, and we're going to be looking at-- and this is a study done by Mackey Neil in surgery. We're going to be taking patients who are elderly, who are coming in for major elective surgery, who are non diabetic, and asking whether or not metformin prior to surgery can essentially pre-habilitate people and that, it will protect them against the oncoming stress that we know they're going to have with this major surgical event. Again, translating this notion of aging biology directly into patients at the center.

And the reason we're doing that is because we've looked back-- Oscar Marroquin, who heads clinical analytics for UPMC, has looked back at the data of diabetic patients on oral agents coming in for major elective surgery over the last 10 or so years into the various UPMC affiliated hospitals. And there's been about 20,000 or so such patients in two equal groups of about 11,000 each on metformin versus on another oral agent, we asked how they did in this elective surgical stress. In general, they were-- as best we could relatively equal in terms of the risk for surgery.

And here's what the data looks like. Again, not prospective, not randomized. But as you can see, there was a reduction in hospital mortality 30 day, 90 day, 180 day, and 365 day mortality in this group in those diabetics getting metformin compared to those diabetics on other agents. Again, consistent with this idea that we could maybe alter the stress resistance of elderly people by targeting the basic biology of aging. And so we're very excited about this study which as I said will begin in the next three to four months. So here's just a design. Again, this will be run out of the Department of Surgery by Mackey Neil.

So does that mean we can cure aging? I don't know. I don't know if that means we can all start smoking, and drinking, and still hope to live to 119, but I do think that there's been incredible progress in understanding the basic biology, the basic biochemistry of aging. And I think there's been really a change in how we view this process from being random bad luck to under the regulatory control of key biochemical and genetic pathways.

And the good news, I think all of those pathways are very approachable by the same sort of techniques of any other problems like hypertension and high cholesterol, and they can be intervened on with drugs. And I think the promise of doing that is, again, as we attack this x-axis, that the medicines that we develop, we hope, will be really useful in many conditions. That the drugs that affect aging will not only reduce cardiovascular disease, not only lower your risk of cancer, but also lower the risk of Alzheimer's and all other age related maladies. And so that's really the promise and perhaps a little bit of the hype, but certainly the promise of what we'd like to do.