



## Futures in Biotech, 36: Avoiding Death, Not Taxes with Dr. Cynthia Kenyon

### Leo Laporte

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[Music]

### Marc Pelletier

Welcome back to Futures in Biotech. I am Marc Pelletier. This week, we are extremely fortunate because we have Dr. Cynthia Kenyon here to talk about her work on the genetics of aging. We've had a couple of shows on the topic, one with Dr. Leonard Guarente, who is a Novartis Professor of Biology at MIT and also Aubrey de Grey, who is a theoretical biologist. But I wanted to get us back into the lab, because it's the lab work that truly defines the state of the science. Now if you look back at history, life expectancy has gone from about 30 years in classical Greece to somewhere between 78 to 82 in some countries today. But if you look at the results coming out of the labs, we know that we are not living up to our true genetic potential. And if, I mean when, Dr. Kenyon's research gets translated to clinic, it will be a true game-changer for humanity. There is no doubt about it. So, without further ado, on to our interview.

So, I would like to know a little bit about how you got started in studying the biology of aging and also maybe how you got into the worm. I don't know which came first, but you're working on an interesting model.

### Dr. Cynthia Kenyon

Well, we have been studying the little worm, *C. elegans*, for a long time. But I became more and more interested as time went on in studying the process of aging, because aging is something that people have just generally thought happened in a kind of random and haphazard way. You just get old like an old car, and they didn't think there was really anything to study. But I had been studying other processes in biology, not aging, but other things, like how a fertilized egg develops into an animal, for example. And the kinds of things we were finding was that processes that you might think would happen in a kind of random, haphazard way tended actually not to. They tended to be subject to some kind of control by the genes.

And the other thing that people – our lab and many other labs were finding, was that things happened in a certain way in one animal, one species, tended to happen in the same way in another species even though it looks very different. So, for example, the way a cell is told to divide into two cells in a little worm is really the same way that our cells are told to divide into two cells. It is no different even though the worms look very different. And if you look around in the nature, all animals pretty much seem to age but they do so at different rates. That's what really interesting.

So, for example, our little worms, *C. elegans*, are microscopic. They are about the size of a comma in a sentence. They age really quickly. They're dead – they get old and they die in about a month or less, actually. Maybe two to three weeks on average. But a mouse lives for two years. A canary lives for 15 to 20 years and a bat can live to be 50. So, you see a huge difference in the rate of aging in different animals and so you have to ask, "Why is that?" It's not environment, because a bat, a canary and a

mouse will all have their different lifespans if they are living in the same place. So, it is the genes. The genes are making them age at different rates.

So, that's says right off the bat that there have to be genes that really have a really big effect on aging. And it also says that you have to be able to change lifespan by changing these genes, because remember, all these animals evolved from a common precursor during evolution. So, you probably had some primitive – simple animal with a short lifespan presumably eons ago and the way we all got our longer lifespans was from changing genes by mutations.

So, that suggested a whole different way of looking at aging. That aging could be – or the rate of aging would be controlled to a large extent by the genes and it would also be plastic. In other words, it would be not so difficult to change the rate of aging. So, for example, there are short-lived and long-lived mammals, there are short-lived and long-lived birds and there are short-lived and long-lived insects. So, that means the ability to live long had to have evolved more than once, right? In the first bird, in the first insect, in the first vertebrate, the first mammal – you see what I'm saying? So, it really suggests that there is a lot of plasticity there.

### **Marc Pelletier**

[6:02] Are there two related organisms that are very closely related genetically that have drastic aging differences?

### **Dr. Cynthia Kenyon**

Well, there is. Here is a good example. The honeybee. Bees can – with the same genes you can have the queen, which lives many, many years or a worker which has a much, much shorter lifespan; less than a year. So, these animals actually have the same DNA. So, that is sort of going against what I said because they have the same genes but they presumably are using the genes differently to have these different lifespans.

People don't really know what it is about the expression of these different genes that is affecting the rate of aging in the honeybee, but that would be an interesting thing to find in the future.

So, the idea then – so, I had this idea that aging was going to be something that was going to be subject to some kind of control. Some real control by the genes, and there were evolutionary arguments to suggest that could never happen because you don't start to age until after you've reproduced, so there wouldn't be a lot of selection on the aging process. But I thought that, nevertheless, something as fundamental and universal as aging might really be controlled in this more active way by the genes. There might be some beautiful regulatory circuitry that controlled aging.

So, we decided, if that's the case, we can take our little worms which have a short lifespan and we could look for mutants that would cause the worms to live longer or shorter. But the shorter ones, they just could be sick, but if you get a mutant that lives long – in other words, a mutant is an animal where – it's just like a normal animal except you have changed one gene, and that's the mutant. So, we wanted to find mutants that live long. And we were optimistic because there have already been the discovery in several other labs of a mutation in the worm, a change in a gene that increased lifespan at least to some extent. About 50%. But not much was known about the mutant. But at the least it was there. So that was pretty interesting.

So we set out to look for long-lived mutants and we found that – we found mutations that affected one particular gene, that had the name *daf-2*, that actually doubled the lifespan of the animal, which was really amazing. It was much – no one thought that was possible. It was – the whole fact that it was possible to take a multi-cellular animal, with a nervous system and muscles and intestine – everything that we have, well not – I mean – can't do arithmetic, but I mean they are real little animals. And you can change one gene and dramatically slow down the rate of aging. Keep the animals dancing around while the normal worms are in the nursing home, really.

### **Marc Pelletier**

Well, I can do arithmetic, and so if we have a conserved daf-2, couldn't you – or another gene very closely related. Could we, perhaps extend through one single gene the human lifespan to two hundred years?

**Dr. Cynthia Kenyon**

[9:03] Well that is a really good question. That's a really good – another way to put that question is the following. If we could do it, then why aren't those people out there? I mean, why aren't there sort of mutant people that live to be two hundred? So that's a really good question. It's not clear. It's not clear why – maybe it's not so easy in humans. Or maybe it could happen, but it hasn't happened, or it happened but the person was run over by a car. I don't know, but you don't see a lot of those people in nature.

What you do see, though – you see people who live to be a hundred, and the ability to live to be a hundred runs in families. So that does tell you that there are forms of genes – of human genes, you know we have 20,000 genes in our bodies 20 to 30 whatever 20,000. I'm sorry we don't have 20,000, we've about 35,000 genes. Sorry about that.

Worms have 20,000 we've about 35,000 genes. But you can – the genes, you know, that I have and my next neighbor have, even though they're the same gene they might not be identical to one another. They could differ slightly from one another. And so the idea then would be that some slight difference in one particular gene might be responsible for a person's ability or a family's ability to produce or contain many people who live to be a hundred. And it turns out, actually, that the same genes that we've first discovered in the worm that I'm going to tell you about, there are forms of these genes that do seem to allow people to live to be very old.

**Marc Pelletier**

Well...

**Dr. Cynthia Kenyon**

So they do seem to be having an effect – not two hundred, but at least one hundred.

**Marc Pelletier**

So this worm is relevant – a relevant model with respect to human aging.

**Dr. Cynthia Kenyon**

Yeah, that's what has been so absolutely fantastic about what we've discovered. So basically, what – so you wanted – so the first question is, what does the gene that we change do? How did we affect the lifespan of the animal?

**Marc Pelletier**

Let me ask one question before that because this is for general audience. What exactly is the roundworm? So that people know what...

**Dr. Cynthia Kenyon**

Oh, okay

**Marc Pelletier**

You did say it was a small worm about the size of a comma. But where is this found in nature? How do you – maybe how do you work with it? And then how do change a gene? And then maybe...

**Dr. Cynthia Kenyon**

Okay

**Marc Pelletier**

If you could explain how daf-2 works?

**Dr. Cynthia Kenyon**

Okay. So basically, they are very small, like I said, about the size of a comma. You need a microscope to see them. They live in the soil. They are harmless. They are called, also called nematodes. Their scientific name is *Caenorhabditis elegans* or *C. elegans* for short. And *elegans* sounds like the word elegant and I think it's because they are so beautiful. They look like horse's tails. They are very – they're very pretty. They move in a sort of sinusoidal way across the plates. We grow them on little plates with agar, which is like jello, and then with a little lawn of bacteria on top and the worms eat the bacteria. Bacteria ...

**Marc Pelletier**

Are they easy to catch?

**Dr. Cynthia Kenyon**

What?

**Marc Pelletier**

Are they easy to catch? Or did you spend the a few days chasing them or..?

**Dr. Cynthia Kenyon**

Yeah you can. You can just – if you go outside and you dig up a teaspoon of soil, especially from a compost heap or something. You bring it in and put it under the microscope; you'll probably find some *C. elegans*. So they are very common.

**Marc Pelletier**

Wow. I also meant – in the lab when you are working with them, sometimes fruit flies can tend to escape or get away you know...

**Dr. Cynthia Kenyon**

Oh.

**Marc Pelletier**

Everybody knows when there is a fruit fly lab around because they see...

**Dr. Cynthia Kenyon**

No, they are pretty easy to keep. They are not difficult. They're very – they are cheap to work on. They are easy to keep and they grow rapidly. They have a three-day generation time. They only have about a thousand cells in their whole body. But we know what all the cells are and they all develop exactly the same way in every animal.

So, it is a fantastic little animal to work on. And actually other people, before we came along, had investigated other biological processes in *C. elegans*. And they had discovered genes that do things like control cell division or the ability of cells to live or die at certain times. This is different from the animal's death. This is the death of individual cells in the animal. It's a process called apoptosis. Anyway, so basically these genes were first discovered in worms and then shown to be present in all animals doing the same things, including humans. So we were quite optimistic and hopeful too that the genes we found that controlled aging would also control aging in animals besides worms. And they do – that's what's so cool.

So basically, if you make the same gene change that we made in our worms in a fruit fly or a mouse or potentially a human, like I said there are forms of this gene in humans that are associated with the ability to live to be a hundred. It's not so clear in humans because it is more difficult to study, but anyway, at least going from worms to flies to mice you get a lifespan extension.

And here's the other thing that's really cool; if we know that in order – so, this is interesting. So we change this gene in the worms and the worms live longer. So, that tells you – so, the question is what is the normal function of the gene? It turns out the normal function of the gene is actually to speed up aging

and slow and – and shorten lifespan. It's like the animal is working against itself. It's like the grim reaper inside of it, because when we change the gene we're making it not work so well.

**Marc Pelletier**

[14:18] How do you select for that, again? If it's – a gene that causes death?

**Dr. Cynthia Kenyon**

You don't actually, what you do is you just – you just change one – genes at random. Just change them randomly. And then ...

**Marc Pelletier**

But how did the – how did this gene evolve? How did the organism adapt or come to have this gene?

**Dr. Cynthia Kenyon**

It has other important functions in the animal. So I'll tell you about that.

But, shall I first – let me finish my thought here that I was just telling you about the evolutionary conservation and then we can talk about what the gene's actually doing. So that gene is called daf-2, and when you remove the gene then – or you damage it, worms live long, mice live long, fruit flies live long and possibly people.

When you – there is another gene though that's needed for that lifespan extension and that's a gene called daf-16. Think of it as sweet 16, because it keeps the animal young. When you change the daf-2 gene in order – in a way that makes the little worms live longer, what you do is you make the gene daf-16 more active. And that turns out also to be conserved, and in this case it's even a stronger case. The conservation's even stronger in humans.

The mice – again, fruit flies live long. The long-lived mice that you produce by changing the first gene I told you about, in that daf-16 for mice is more active. And now there are – changes in that gene have been associated with the ability to live to exceptional – to reach exceptional ages in humans, too.

So that's – it's very, very exciting. It really looks like these – that these discoveries in *C. elegans* really apply to humans.

**Marc Pelletier**

It's pretty remarkable I mean, we're talking not only a paradigm shifting understanding of biology, but sort of the age old quest of the fountain of youth....

**Dr. Cynthia Kenyon**

Absolutely, it's a mind-boggling. Yes, it's really amazing.

**Marc Pelletier**

Modulating the function of one gene leads to the activation of a second gene, so daf-2 leads to an up-regulation of daf-16?

**Dr. Cynthia Kenyon**

That's right, exactly. And I'll start to tell you what they do and you will see how it really works.

**Marc Pelletier**

Sure.

**Dr. Cynthia Kenyon**

I will tell you how it really works. But – now that doesn't mean – so these genes, daf-2 and daf-16, they – no gene works in isolation. They all work in a – they encode proteins that have jobs to do in the cell and proteins interact with other proteins and talk to other proteins. So that's what daf-16 and daf-2 are doing

as well in humans and in worms. So the interactions that these gene products have with others is really important. So, shall I tell how it actually works at the molecular level?

**Marc Pelletier**

Sure, go ahead.

**Dr. Cynthia Kenyon**

Would you like me to do that?

**Marc Pelletier**

We'll see if I get it.

**Dr. Cynthia Kenyon**

Okay. So what is daf-2? Well, the daf-2 gene encodes a protein that functions as a receptor for hormones. So you know what hormones are. They are small substances that circulate in the body and they cause the tissues to behave in some different way. So, for example, the hormone testosterone causes the fertilized egg with an XY chromosome complement to become a boy, and then it causes that boy to grow beard and so forth. So in other words, when it becomes a man.

So basically, hormones cause the tissues to behave in ways that they otherwise would not behave in. So the daf-2 gene and the way the tissues respond to the hormones is through hormone receptors, which are just what it sounds like they are. They're proteins that sit on the surface of the tissues that grab the hormone and send signals inside the tissues, initiating a cascade of events that leads to, for example the growth of a beard. In the case of testosterone.

In our case, obviously, the hormone is signaling the receptor to tell the cell to get old faster. Okay, it's kind of counterintuitive. Now what – so we have these hormone receptors, so what are they? Well my answer may surprise you, because you may not think – it may not seem to make any sense at the beginning. But the receptors that look most like the daf-2 receptor are the receptors for the hormones insulin and another one called insulin-like growth factor, or IGF-1. And – insulin is very famous because people that lack it, or lack the ability to respond to it correctly, get diabetes. So that tells you right off the bat that you can't just change this hormone receptor any old way and live to be a hundred. You might die. Okay? You might just get diabetes and die.

[19:04] And so it looks – so that's kind of a paradox, but it looks like what gives you a long lifespan is – are changes in the genes that – in the receptor – that lower the activity of the receptor or the hormone, you can do it that way, too, a little bit but not a huge amount. And what happens when you do that – so first, let me back up just a second to explain this. When you eat a meal, the level of sugar in your blood rises and it's the sugar, or glucose, that causes the pancreas to release insulin. And that triggers a whole series of events that allows your tissues to take up the nutrients into them and it allows them to grow and to store food and sort of lets them live a kind of a well-fed life.

But when you've lower food levels, you've lowered insulin levels. And so you've lowered the level of signaling through this insulin pathway, so less signal gets into the tissues. And what that seems to do is to shift the animal, shift the whole physiology of the animal to a state that's more concerned with just maintenance rather than growth. So you switch on a lot of genes in the genome that protect the cells. That protect their antioxidant genes, they strengthen the immune system, they change the way metabolism takes place. They do a number of different things. They help proteins fold correctly and keep them folded. So basically what that – so first I have to back up. So, when you lower the level of insulin or IGF-1 or the receptors for these genes – I am sorry for these – I am sorry, let me say it again.

When you lower the level of – yes I said the right, insulin or IGF-1 or their receptors, the first thing that happens is that the daf-16 protein, also called FOXO, it has two names, it's called FOXO in higher organisms and daf-16 in *C. elegans*, so it's a FOXO protein. And that protein becomes more active. Now that protein goes into the nucleus where the DNA is and it binds to individual genes and switches them on or off. So when you lower the level of insulin or IGF-1, or the response to it, you activate daf-16/FOXO, it

goes into the nucleus, sits down on the DNA in front of particular genes that can protect the cells, and switches them on.

So there's maybe a – there's between 100 and 500 or so genes that get switched on or off in the DNA, in response to changes in the activity of the insulin hormone or its receptor, or the IGF-1 hormone and its receptor. And it's the activation of all these different genes that leads to lifespan extension. You can think of it like an orchestra, where you have the flutes and the violins, and the violas and the cellos, which will be like the antioxidant genes, the protein folding genes, the immunity genes, the metabolic genes, all doing something different but doing them at the same time, so that you can really protect the cells, kind of, from the ravages of time, if you will, so that the animal can stay young for a longer time.

**Marc Pelletier**

Wow.

**Dr. Cynthia Kenyon**

Okay? So that's how it works, it makes sense. And so these changes in the daf-16/FOXO, in humans, seem to be associated with the ability to live longer and to stay disease free for a longer time. So it's really amazing.

**Commercial**

I'd like to take a minute to thank audible.com for sponsoring Futures in Biotech. Considering his recent passing, I think it'd be great to recommend a book by Michael Crichton, and that book is entitled "Prey". What I am going to do is going to play an audio sample. Here it is.

"As a concept, nanotechnology dates back to a 1959 speech by Richard Feynman, called "There's Plenty of Room at the Bottom." Forty years later, the field is still very much in its infancy despite relentless media hype. Yet practical advances are now being made, and funding has increased dramatically. Major corporations, such as IBM, Fujitsu and Intel, are pouring money into research. The U.S. government has spent \$1 billion on Nanotechnology in the last two years. Meanwhile, nanotechniques are already being used to make sunscreens, stain-resistant fabrics and composite materials in cars. Soon they will be used to make computers and storage devices of extremely small size, and some of the long-anticipated miracle products have started to appear as well. In 2002, one company was manufacturing self-cleaning window glass; another made a nanocrystal wound dressing with antibiotic and anti-inflammatory properties.

At the moment, nanotechnology is primarily a materials technology, but its potential goes far beyond that. For decades, there has been speculation about self reproducing machines, in 1980, a NASA paper discussed several methods by which such machines could be made. Ten years ago, two knowledgeable scientists took the matter seriously, and I quote them, "Within fifty to a hundred years, a new class of organisms is likely to emerge. These organisms will be artificial in the sense that they will originally be designed by humans. However, they will reproduce and will "evolve" into something other than their original form; they will be "alive" under any reasonable definition of the word. The pace of evolutionary change will be extremely rapid. The impact on humanity and the biosphere could be enormous, larger than the industrial revolution, nuclear weapons, or environmental pollution. We must take steps now to shape the emergence of artificial organisms." end of quote."

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**Marc Pelletier**

[25:34] Do the – do the worms – when you so – you have knock outs that actually increase the lifespan twofold? Do you have mutants that are partial mutants that lead to even further increase in lifespan? And what do the worms look like? Are they – there's living a short happy life and then there's living a long, lousy life with that.

**Dr. Cynthia Kenyon**

A long, miserable life, yes. Well, okay, so first of all I have to tell you, if you knock out this receptor, the *daf-2* gene, which encodes the receptor for insulin and IGF-1, so in worms, there's only one receptor, for both the hormones. IGF-1 is a hormone that's a little like, it's a bit like insulin, but it mainly promotes growth. Small dogs, actually, this is interesting, small dogs live a lot longer than large dogs as it turns out, and that's because they have less IGF-1, it's been shown. They are small because they have less IGF-1, and they live longer because they have less IGF-1. So, isn't that neat?

**Marc Pelletier**

Yes.

**Dr. Cynthia Kenyon**

Now, as it turns out, if you start with a normal worm that has its normal size, or not a worm, let's start with a mouse, because we know more about mice, and you start lowering IGF-1 levels, or the level of signaling through this pathway, the first thing that happens is that the mouse lives long, but it has a normal size. And then it looks like if you keep lowering the level, then it lives long and has a small size. So, the size and the lifespan don't have to go together. You see what I am saying?

**Marc Pelletier**

Um hum.

**Dr. Cynthia Kenyon**

You don't – in other words, these animals, these long-lived animals, they are not always small.

**Marc Pelletier**

Are there other, other genes as well that – you're mentioning that in other labs they identified other pathways. Do these pathways, can they work in an additive fashion or...

**Dr. Cynthia Kenyon**

Yes, that's a great question, that's a great question. Okay, first off, I have forgot to tell you, you mentioned about – do we have partial gene mutants, that live – anyway, if you knock out completely – if you completely remove this receptor in any animal, the animal dies. Okay?

**Marc Pelletier**

That's right, you did mention that.

**Dr. Cynthia Kenyon**

Or, it doesn't develop, so it's completely essential. So all the mutations that increase lifespan are partial loss of function mutations, or mutations that just affect a certain tissue. You know? That's – those are the kind that can increase lifespan. Yes, can you make an animal that lives even longer? Yes, you can. We did it several years ago. We discovered in our lab that the reproductive – signals from the reproductive system affect lifespan. And if you change the reproductive system in certain ways, then the animals live long, and if you do – if you have the *daf-2* mutant, and you also fool around with the reproductive system, now the worms can live six times as long as normal. And again, and in both the *daf-2* mutants and these sixfold mutants, the thing that makes them so amazing is that they stay young longer, that's the thing that boggles the mind, because you're sort of brought up thinking that there's death and taxes, and there's just nothing you can do about it. You know?

**Marc Pelletier**

That's right.

**Dr. Cynthia Kenyon**

That's, and so that's so amazing. You change one gene and the animal, it's not that they live long so much as that they stay young long. It's looking at these animals, looking at a plate of animals, it's like you have two plates, on one plate, these are little agar dishes where we keep our worms – on one agar dish,

we have lots of normal worms, and if you wait a couple of weeks and look at them, they are almost all dead or they are just barely hanging on. And you look at the mutants, and they are moving around, they look young, so, it's like magic. It really is. It's like you had a magic wand, and you – and they live, they are not old. And then you, I mean, so then of course the first thing you think, is well, hey wait a minute, maybe I don't really have to be old either even though I am, I didn't maybe, didn't have to be. And I think that's probably true, that we probably didn't have to be old, it's we're – our genes are set in a way that we are, but it didn't have to be that way. Just as it doesn't have to be that way for the worm.

**Marc Pelletier**

So...

**Dr. Cynthia Kenyon**

But it's this youthfulness that is so striking and so counterintuitive.

**Marc Pelletier**

[29:25] This would be interesting of course to the pharmaceutical industry, to push back age-related diseases, right? The three largest killers are cardiovascular disease, cancer and stroke.

**Dr. Cynthia Kenyon**

Yup.

**Marc Pelletier**

And if you could delay the onset of those, you are going to save millions of lives, billion, zillions of lives.

**Dr. Cynthia Kenyon**

And actually, we already know that if you make changes that would be predicted to extend lifespan, you do – in mice for example, you do delay cancer and you do delay atherosclerosis, you delay heart disease in fruit flies, protein aggregation diseases in lots of different kinds of animals are delayed. So it really looks like you're – it makes sense in a way, the animals aren't old. So they are not susceptible to the age-related diseases until later when they are old.

Here's a way I like to put it. Suppose you are a guy, maybe thirty years old, or maybe let's say forty-five years old. And you are single and you'd like to get married so you, or whatever, meet someone. So, you start dating and you date someone. You find a lovely woman that you like a lot, you go out, having dinner and you think she's just great. And you ask her at one point, "How old are you?" and she says, "I am ninety."

That's what we're talking about. That's the thing that's so hard to – I mean, really honestly that's what one worm would say to another. It would say, "How old are you?"; "I'm ninety". You know what I'm saying?

**Marc Pelletier**

Yes. This is absolutely amazing

**Dr. Cynthia Kenyon**

So, people don't get – they always think, they always think that the person looks ninety but they're healthy. But it's not that way. They look like this lovely – not that ninety year old people aren't lovely, they are. But they look different than people who are forty.

So, it's – it's, anyway. There you go.

**Marc Pelletier**

Our guest, two shows ago, was ninety. Her name – Brenda Milner, she was ninety.

**Dr. Cynthia Kenyon**

Wow!

**Marc Pelletier**

And she was great. She was absolutely fantastic, sharp.

**Dr. Cynthia Kenyon**

That's great.

**Marc Pelletier**

It was fun. So, this is very dramatic science, right? This is not traditional biology you're trying to study a biochemical pathway or signaling pathway to making membranes, or how does the cell control its biological clock.

**Dr. Cynthia Kenyon**

Let me just tell you that so far you get these absolutely phenomenal changes in *C. elegans*. There's actually – somebody recently has extended the lifespan of worms by a factor of ten and again they seem to stay young longer which is just amazing. And nothing like that has happened in mice. For example, the changes that you get in mice now tend to be about 40% at the most from say 15 to 20 to 40%. There are some mice that live maybe 50% longer. But you're not getting three or fourfold changes. But at the same time it's – there really haven't been that many long-lived mutants in mice at all. And it makes sense that most of them wouldn't live that long and just some would live really long. So, maybe we haven't worked enough. Remember, evolution did it – evolution could go from a worm's lifespan of two weeks to a human lifespan of seventy, eighty years, which is thousands of folds longer. So, the potential – evolution did it already.

**Marc Pelletier**

That's right. That's right.

**Dr. Cynthia Kenyon**

It can happen; it has happened and, as I say, multiple times. But anyway, so far we do see this correlation between having certain versions of the *daf-16/FOXO* gene and an increased lifespan in people. But the increase isn't a doubling. It is more frequent in people who live – these forms of the gene are more frequent in people who live longer, suggesting that if a biotech company were to go in and make a drug that could – whatever is changing in protein to let these people live a little longer, maybe if you sort of go further along that route, maybe you could allow them to live a lot longer.

**Marc Pelletier**

At what stage is the current pharmacological development for these genes in terms of proving that they're an actual drug target that you can actually modulate their activity in vivo.

**Dr. Cynthia Kenyon**

Okay.

**Marc Pelletier**

All the animal models are knock-outs or mutants that are genetic-based, but can this be done with pharmacology?

**Dr. Cynthia Kenyon**

[33:45] Yes, I think – yes, it should be possible. Now, all right, so one, there's one protein which you know about called – a family of proteins called the sirtuins. And those proteins, when over-expressed at least in worms and in yeast, possibly flies as well, can extend lifespan. It's not – it hasn't been done in mice. We don't know yet for mice. But the proteins have also been implicated in many different age-related diseases.

And there are companies – there's a company, Sirtris, which has been looking for drugs that activate the sirtuins hoping to be used to combat age-related metabolic disease or whatever other potential kind of diseases. And Sirtris has drugs that are apparently behaving well in clinical trials. I don't know if the

clinical trial data are known, but at least in animal trials they were behaving nicely. And Sirtris was purchased recently by GlaxoSmithkline.

**Marc Pelletier**

700 million?

**Dr. Cynthia Kenyon**

Yes, that's right. So, that's – and Sirtris – by the way, at least in *C. elegans* the way that sirtuins extend lifespan is by activating daf-16/FOXO. This protein I've been talking about. So these are not different worlds here, this is a very interconnected kind of system.

**Marc Pelletier**

I'll refer the guests back to episode two, which was a couple of years ago with Leonard Guarente. They can also get a little bit of background on sirtuins.

**Dr. Cynthia Kenyon**

I mean, another way you can look at is that, at least in worms, you can get worms to live long by lowering the level of insulin/IGF-1 signaling, which activates daf-16. Or, you can get them to live long by activating the sirtuins, which also activates daf-16. So, there's different – and in fact there's four or five other things you can do in worms that also increase lifespan by activating daf-16. So, daf-16 seems to be a very central player, and I think that's probably why you're seeing this effect on human longevity, these polymorphisms that affect humans, because it seems to be such a central protein.

**Marc Pelletier**

And this is a...

**Dr. Cynthia Kenyon**

But yeah, so basically – so here's – it's really interesting. I'm sorry I cut you off...

**Marc Pelletier**

No, it's okay.

**Dr. Cynthia Kenyon**

You go ahead.

**Marc Pelletier**

You go.

**Dr. Cynthia Kenyon**

Okay. So I think what's – people – I mean, obviously you can't make a drug in a pharmaceutical company for aging, at least not right now. But you can certainly make drugs for diseases of aging. And since all these longevity pathways also affect diseases, what you can do is you can target a known longevity pathway and look for efficacy in combating a certain disease – cancer, diabetes, whatever.

I founded a company with Lenny Guarente called Elixir, and our company has been trying to – has been developing drugs for another target called the ghrelin receptor. So, ghrelin is a hormone that affects appetite and also metabolism. And it's a component of this large insulin/IGF-1 regulatory network, and we've developed compounds that allow mice that are fed a high-fat diet to be much healthier than they would normally be. And so again what we did is we thought, "Okay, look here's a pathway, a general pathway that we know affects aging, but we think it also has links to metabolic disease, and so let's go after that." And so that's what we've done at Elixir.

**Marc Pelletier**

You know, you said you can't develop a drug in a pharmaceutical setting to combat, to, for...

**Dr. Cynthia Kenyon**

You can do, it but you have to do it – but you can't – you have to get it approved for a disease. But that's okay.

**Marc Pelletier**

Why is that? Is that...

**Dr. Cynthia Kenyon**

Oh, it's just because – there's a couple of reasons. We don't have really good markers for aging. We don't have good biochemical markers that would say that you could, if you could do a clinical trial in a year, for example, and if you – there was something you could measure, like some level of some protein that would tell you, okay, this person's rate of aging has slowed down, that would be great. But there isn't anything like that. We call that a biomarker. There's nothing like that right now, whereas there are proteins that get glycosylated or damaged in diabetics, and you can look at those proteins and – biochemically – and you can say yes, in a year, or even less, you can say "Yes, if they take this drug, this protein is less damaged, so the drug is working". So just from a practical point of view, just the expense and the time constraints, it's much easier to assay something having to do with a disease than the process of aging. At least now, because we don't know how to measure aging over short time periods.

**Marc Pelletier**

[38:30] Right. You could do the forty-year clinical trial, but I suppose that doesn't make sense. I thought it was because, maybe, some ethical issue of trying to...

**Dr. Cynthia Kenyon**

No, I don't think so.

**Marc Pelletier**

Those who could afford to, maybe, could gain the benefit of living longer.

**Dr. Cynthia Kenyon**

Yeah, yeah, yeah. I mean you can... Anyway, that's the way it's working, right. And plus the other thing is, the approval process by the FDA is for diseases right now. There's no approval process for an anti-aging drug. It just doesn't exist. Which doesn't mean it couldn't exist in the future, but there's just not a regulatory framework there. But that's fine because, like I said, these aging pathways are inextricably linked to diseases. They're, all these age-related diseases seem to be delayed, a whole variety, in long-lived mutants. So why not just go after diseases, and maybe as a sort of nice side effect you'll live longer too. And not because – not only because you don't die from the disease, but because you're just generally younger.

**Marc Pelletier**

That makes a lot of sense, I mean, you – with this one framework you're going to be tackling the three major pathologies that affect humankind.

**Dr. Cynthia Kenyon**

That's right. I mean, think of a tree, with all those, you know, there's a trunk, and there are the limbs, and then there are the little twigs. And at the end of each twig you could have an age-related disease that you could make a drug that goes after a twig, this twig or that twig, or you could make a drug that goes for the trunk of the tree, and that would be aging. So if you delay – aging is the biggest risk factor for a whole variety of diseases, bigger than smoking for cancer. Age is a bigger risk factor for cancer than smoking is. So, it's huge, and it's not just cancer, it's many, many, many different diseases. So, yeah, if you could go after that risk factor, you could benefit lots of diseases. And that's why it is becoming of interest to pharmaceutical companies. When Lenny and I were starting our company, we went around and talked to pharmaceutical companies, thinking ahead that we might eventually want to partner our programs with them, and we talked to various ones. And they all said, "Well, we can't do that, we don't have an aging program, we have a program, you know, for this disease and that disease..."

**Marc Pelletier**

They should though, and they will.

**Dr. Cynthia Kenyon**

Well, they do. Novartis now has established a program in aging. So I see this as a watershed event. You know. Here's a big major pharmaceutical company, and they've looked at this kind of research, and they've said, "Yes, we need an institute for aging research". And they have it now within their company. Or not really research but development, yeah.

**Marc Pelletier**

Before we get to the last segment of this interview, I'd like to thank GoToMeeting for sponsoring Futures in Biotech. Currently, they're offering a 30-day free trial of GoToMeeting. That means you get a free month of online meetings. It works both on your PC and your Mac, so it's cross-platform, you don't have to worry about it. One of the reasons I like having GoToMeeting as a sponsor is that it's a product that I can really endorse. It is a tremendous tool for the scientific community. Rather than sending out PowerPoint files, which may be large, out to your colleagues, or trying to get a PDF document, you can actually work and crunch the numbers together, do your data analysis together. Everybody can make a contribution. They see your desktop, they can manipulate your desktop, and you can really get everybody's input on that data. So, certainly it saves you on traveling, it's easy, takes two minutes to set up, it's secure, there's a very low rate, even scientists can afford it. And, oh right now they're offering that one month of free service, unlimited meetings. Go visit [gotomeeting.com/biotech](http://gotomeeting.com/biotech). Now, back to the interview.

What are the ethical issues, I suppose, in terms of...?

**Dr. Cynthia Kenyon**

[42:22] They're huge. They are huge and they're complicated. So, basically – right now, what we're hoping, what I think we can hope for is a pill that would keep you young, maybe a few years longer, and would delay a lot of diseases, or if you get the diseases, maybe that you wouldn't have such a hard time with them, maybe you would be, somewhat a little more resistant to them. That's what we're thinking right now. So, people are already out there making drugs to cure diseases. They've been doing that for a long time, and there's no ethical issue. There's nobody saying, "Oh, it's unethical to cure cancer." No one says that, and it's not, it's good.

**Marc Pelletier**

Right.

**Dr. Cynthia Kenyon**

But the consequence is people don't die of cancer, so they stay alive and they're older. So, we change the demographic distribution toward the elderly. We have more elderly people alive now, needing care actually, than we used to when they died of even infections. So, we've changed the demographic distribution of ages in the world by doing, by making drugs for diseases, so that has a consequence. Now, if you – and I think it's a good consequence. I mean, we have to figure out how the society is going to care for these people that are old, the baby boomers for example. That's – it's an issue, that's a big important issue out there.

But, okay, so our drug, a drug that you would take that would delay aging, would – it would be different, at least theoretically, in a way, in the sense that people wouldn't – people would actually be getting old at a slower rate. So, they would be productive for a longer time, so they may not have to retire at age 65 or 70, they may be able to work, they may want to work, they may feel young and look young at older ages, you see. So, that's good, it keeps – they'll remain productive for a longer period of time. Eventually, they'll get old but they won't spend a larger proportion of their lives in the nursing home than anybody else does, probably about the same proportion, or maybe even less, a smaller fraction of their life. So, that's all good.

What's, what is – but there's all sorts of implications for that. If you – first of all, well, we'll have more people in the world, right, if they're not dying. So, the birthrate probably has to come down overall in the

whole world, or we'll just fill up the world with, I mean, we – the world can't support an infinite number of people. So, it has to come down, and it would have to come down more if there are more people living longer, okay? Do you see what I'm saying?

**Marc Pelletier**

Yeah, I suppose that would be, and not – as countries gain in economic status, I suppose, birthrates tend to drop anyway.

**Dr. Cynthia Kenyon**

Yeah. And there are a number of countries right now that have negative birthrates. You know where the replacement – people aren't even replacing themselves, already. So, for those countries, you can see, well gee, if everybody stayed young longer that would be actually good. So, it wouldn't be that aspect of the issue...

**Marc Pelletier**

Society is reactive to that, I suppose.

**Dr. Cynthia Kenyon**

That's the key!

**Marc Pelletier**

And we are living longer. So, the countries that live the longest have the lowest birthrates. So, I think it's not mandatory. There's no social policy that needs to be in place. It tends to just happen, I suppose.

**Dr. Cynthia Kenyon**

I think that's right. And you could imagine – so, here's the thing, now this is where fantasy starts, or speculation starts, but we tend to think of the world as always being the way it is now, but it doesn't have to be. For example, the Chinese have a – they right now have a policy of the one child policy, and that's one country and that's their policy. And we don't have that policy. We used to have a policy in this country of eugenics, in a sense, where we aborted babies, or not aborted them but, I guess, sterilized people who were mentally defective, which we all see as abhorrent, and I see that as abhorrent. And I'm not crazy about the one child policy. So don't – I'm not advocating those. But what I'm saying is that what a society thinks will always have to be the way it is, won't always necessarily have to be way it is. So for example, suppose everybody, let's just fantasize here for a second and suppose people live to be two hundred and at age one hundred they were sort of like 50 year olds are today, they're still very productive. Let's just suppose. Okay, so they're aging more slowly and living longer. Now, what would happen? Well, first thing that would happen, I think, is you wouldn't be given tenure at a university at age 35 anymore, right? If you're not going to retire until you're 107.

**Marc Pelletier**

No.

**Dr. Cynthia Kenyon**

So that you can see is going to change right away.

Second thing is, what happens when you check into the nursing home? If you're taking this pill, are you going to be able to take the pill if you're in the nursing home already? Or will there be laws passed saying that no, you can't take it anymore because when you're in the nursing home and someone else is supporting you, maybe you should just die at your normal rate, right? So you can imagine that kind of a law being passed.

Here's another law you can imagine. You can imagine that the insurance companies would make you take the pill, because if you took the pill you'd be more resistant to disease. So, you could imagine that you would have to, just to get insurance, or you would get a discount if you took the pill.

You could imagine – let's see. Here's another thing. If you – right now people can run countries or companies or stay in universities, and so forth, often until they pretty much die, stay on the Supreme Court, you know, as long as they want. If a person could really live to be 200, that would probably change. I sort of said that before with tenure, but that can be – that whole concept can be expanded to include lots of other things. So probably there would be more mandatory retirement from one job, accompanied by re-training programs, or at least incentives to change, or maybe people would just want to change. But I think that would be a fundamental change in our society that we don't see right now.

**Marc Pelletier**

These aren't small changes to society; these are massive, or very large changes to society.

**Dr. Cynthia Kenyon**

[48:12] They're humongous, but again remember, we don't have that pill right now. And let's suppose – but let's suppose I went into my lab tonight and I made the pill, and tomorrow I arrive with the pill, okay? And I give it out and people start taking it, all right? They start taking it tomorrow. What does the world look like in five years? Well, it doesn't look very different from what it looks like now. People who are 55 right now, instead of looking 60, well maybe they'd look, I don't know, 57.5, it's not that different. And five whole years have gone by. And that's a pill that doubles your lifespan, which we're not going to make right now. Do you see what I'm trying to say?

**Marc Pelletier**

Right.

**Dr. Cynthia Kenyon**

Probably what we're going to make in a lab is a pill that adds maybe two or three years to your healthy lifespan at the beginning. We might not. No one expected to find, change one gene and double the lifespan of a worm. So I cannot tell you that we can't do that with a person, maybe we could, we could find a pill that would just – it could happen, but we – I still don't see it. I don't know, it seems unlikely. But you could. More likely you will get these little incremental changes. So society is going to have a huge amount of time to react to this, enormous, lots of discussions, lots of time.

**Marc Pelletier**

I suppose until, for example, the risks of these new pharmacological products are assessed, the only people who are really going to want to take them are people that, where the benefit is absolutely clear, one, heart disease, diabetes.

**Dr. Cynthia Kenyon**

Absolutely. Absolutely.

**Marc Pelletier**

So, they're going to be our guinea pigs, I suppose. But I mean...

**Dr. Cynthia Kenyon**

You know, they're kind of imperfect guinea pigs, in a sense, for aging, because they already have a disease.

**Marc Pelletier**

And their lifespan is already shortened prematurely. So they're going to...

**Dr. Cynthia Kenyon**

Right.

**Marc Pelletier**

...be able to maybe live to a normal life.

**Dr. Cynthia Kenyon**

But maybe people – for example, maybe people who have a genetic predisposition towards cancer would take it, just naturally, maybe they would take it, and even when they're not sick. And maybe you would realize that these people – well, people were taking estrogen, right, that's a nice big experiment done on the whole population. People – women were taking estrogen, lots of them, thinking of course that any hormone that becomes – that goes down, probably – it's probably, you get old and the hormone goes down, so probably if it didn't go down, you'd be healthier. But actually maybe we're healthier probably because it goes down, because people who were taking estrogen became susceptible to lots of different age-related diseases, and so, these were healthy people, right? These were healthy people that were taking it, and you got to see all these – it wasn't an experiment but had it been designed that way, it would have been a very interesting one. And it, kind of, is equivalent of an experiment. Kind of scary in a way. But the other thing is, we were to able figure that out, probably before it did a huge amount of harm to this society.

So, I think, if there's an anti-cancer pill or anti-heart disease pill, people will probably take it, like they're already taking statins. And statins actually turn out to have benefits above and beyond the purpose for which they were first developed. So it'll be interesting, I don't know that statins are anti-aging drugs, I have no idea. But it'll be interesting to see if people are starting to take them, just as a preventative measure. So, if that ever happens to an anti-aging drug, then you'll start to see, wow you look at the incidence of various diseases and these people aren't getting them as much. So, you'll get – even before you know how old they are, you'll see that they're resistant to lots of diseases. And so, more people will start taking the drugs, I think. That's how it will probably distribute itself through the world, just because people will be healthier.

**Marc Pelletier**

I guess countries where the healthcare is universal, Canada, the European countries, I suppose that government would have a huge incentive to, of course, make it free for everybody, and then there wouldn't be a selective process within the communities to take it. So – or...

**Dr. Cynthia Kenyon**

Right, right.

**Marc Pelletier**

You might see some countries now experience far greater discrepancies in lifespans between, for example, Canada and the U.S., where the diet is the same, the lifestyle is the same, the number of miles people walk per day is pretty much the same.

**Dr. Cynthia Kenyon**

[52:28] But this is where social policy comes in. Okay, let's suppose only the rich could take the pill, okay? So you have all these rich people that aren't getting any diseases, whereas poor people are. I mean, I'm not saying they won't get any diseases, I'm exaggerating, just to make my point here. Okay, but suppose there's this wonderful pill and rich people are taking it. And they're doing so well. What's going to happen? The poor people, they're not going to want that. People like Obama, he's going to say, look if you elect me as President I'm going to make this pill available for everybody. People are going to want it and they're going to get it. I mean, unless it's intrinsically almost impossible to make, which is very hard to believe. Almost anything if you want it enough, you can figure out a way to make it pretty cheaply.

**Marc Pelletier**

Sure.

**Dr. Cynthia Kenyon**

So, it's going to be available. And I think it's going to be available very fast, actually. If it really has an effect against a lot of diseases, of course it will be, because the society will make it.

**Marc Pelletier**

Democracy, they'll say.

**Dr. Cynthia Kenyon**

They'll demand it. They'll – you'd have a revolution. I mean, think about it. So, I'm not worried about that aspect of it.

**Marc Pelletier**

I suppose that goes without saying that if it's really good for the community, all parties would embrace it on a political level, I mean, when there was a...

**Dr. Cynthia Kenyon**

Of course.

**Marc Pelletier**

...economic crisis, both McCain and Obama went to Washington and tried to...

**Dr. Cynthia Kenyon**

Absolutely.

**Marc Pelletier**

...have a positive effect. So, they didn't – no one neglected the issue per se.

**Dr. Cynthia Kenyon**

Now the other side, though, is, another one to think about is, what if the pill has a side effect, right. You don't know that it won't. Or what if it doesn't actually act the same way in everybody. These of course are concerns with all pills that anybody takes. But, if you take a pill every day of your life, starting to take it say at age 30 or something, you really have to start worrying about side effects. So, those are issues also that are going to be important. There may be people that won't take it just because they're – I don't take Resveratrol, for example, Resveratrol apparently has a lot of good health benefits and can extend the lifespan of a lot of animals. But I don't take it because I just don't, I don't know, I'm just scared really, I'd rather wait until there have been a lot of trials before I subject my body to that. I do take aspirin every day, a little aspirin. So, maybe I am – but, I don't know...

**Marc Pelletier**

But that's been vetted, that drug is as safe as a drug can get.

**Dr. Cynthia Kenyon**

Aspirin, I think it is. So, I take it, because it has benefits.

**Marc Pelletier**

When the populations that need to push back age-related diseases, if you have diabetes and you want to push it back 15 years or 20 years, and you know that can happen, and the risk of, perhaps, a non-desired side effect is – you evaluate that, I guess, you make that decision yourself and then you...

**Dr. Cynthia Kenyon**

Yeah you do, yeah, yeah. And probably, and you know actually, also the other thing is people will give it to their pets, of course, and they'll see their pets are in great shape, living longer and running around. So, I think there's that too, that kind of thing will happen. That could actually be a big factor in spreading the use of a drug like this. But you never know, I mean you have to, you have to worry, but even then – nowadays we've become so good, I think, at looking for little things that go wrong that are harbingers of a disease – a change in cholesterol levels or something – you can, you may even be able to pick up side effects. And that's the other thing, science is going to be marching on in parallel to the development of these anti-aging drugs. And scientists are going to find, hold on just a second, scientists are going to find ways of, for example, learning which people have different susceptibilities to different kinds of drugs, which people might be at risk for certain side effects, by examining the effects of changes, differences in the genomes between different people, that's happening. So, that's a kind of science that can be brought to bear on this as well.

**Marc Pelletier**

[56:31] Personalized medicine, yeah. Proteomics and – I think there's a grant application out there that's going around, they're asking for about a billion dollars to do the human proteome.

**Dr. Cynthia Kenyon**

Oh, great.

**Marc Pelletier**

I think that'll push human medicine, or personalized medicine...

**Dr. Cynthia Kenyon**

Oh, yeah it's wonderful.

**Marc Pelletier**

These are really exciting times.

**Dr. Cynthia Kenyon**

They are. Now don't your hold breath for this aging pill though.

**Marc Pelletier**

All right, my kids though, they might be able to benefit, though we don't have any major diseases in our family that, other than...

**Dr. Cynthia Kenyon**

Oh, that's good. Listen, I have to go now, because I have an appointment at 4. Is that okay, is that enough?

**Marc Pelletier**

Yes, I think we did, we've got everything. So, just as a closing, I'd like to thank you very much for coming on the show.

**Dr. Cynthia Kenyon**

Okay, you're welcome. And I enjoyed it too.

**Marc Pelletier**

I'd really like to thank Dr. Cynthia Kenyon for her time today and the great discussion, who is a professor in the Department of Biochemistry and Biophysics at the University of California, San Francisco. She's also the Director of the Larry Hillblom Center for the Biology of Aging.

I'd also like to thank Phil Pelletier and Will Hall for the opening and closing themes. And if you'd like the transcripts to today's episode, they've been kindly provided by the folks at Pods in Print, you can visit them at [podsinprint.com](http://podsinprint.com). If you'd like to get some transcripts done, as you can tell, they can cover very specialized topics and they do it really well. So, they'll find a specialist to tackle the subject that you're – that you need transcripts for.

Lastly, I'd like to thank Leo Laporte and Dane Golden for coproducing this podcast. For Futures in Biotech, I'm Marc Pelletier. Oh, by the way, before we go, I have permission from the folks at Small Pictures Productions to play the audio from a John Cleese podcast, and it's John Cleese's take on human genetics. Here's the audio.

[Music]

Hello, we scientists have now located a gene which we scientists believe gives people the need to believe in God. In other words, this God gene releases chemicals into our body which create the impression that there is meaning in the universe. And this God gene is just here between the gene which we scientists

now know makes us eat coconut ice cream after a fish dinner, and this gene here which causes people with weak egos to grasp around desperately for simple explanations.

Now, the discovery of this God gene is a big step forward in our quest to show that every bit of human behavior can be explained away mechanically, because we've now also located the gene which makes some people believe that every piece of human behavior can be explained away mechanically. And it's here, right next to the gene that makes you go to see Nicolas Cage movies – so, that's another puzzle solved – and right under this gene, which can cause you to forget that since the 1920s quantum physics has destroyed forever the idea that everything can be explained mechanically.

Now, the gene which causes us to forget this obvious fact is very dominant in some people, especially me. And we scientists now know that it's closely linked to this gene here, which gives you such a weak sense of self that you hang on to anything that makes you feel more secure emotionally, whether it's fundamentalist religion or a reductionist view of the universe, which is right over this gene here that makes you want to punch people in the head when they take the scientific process and subject it to their pathological literal mindedness. [Punch] Thank you, I needed that. And by the way, we now know that there is a gene that causes you to say thank you, I needed that, just there, when you are punched in the head... [punch]

[Music]