



Futures in Biotech, 30: Aubrey de Grey on the Thousand Year Lifespan

Leo Laporte

Bandwidth for Futures in Biotech is provided by CacheFly at cachefly.com.

Marc Pelletier

This is Futures in Biotech episode 30, for Wednesday, March 26, 2008. Aubrey de Grey on the Thousand Year Lifespan. Futures in Biotech is brought to you by Audible.com, the Internet's leading provider of spoken word entertainment; to get a free audiobook download of your choice, you can sign up today. Log on to Audible.com/biotech today for details.

[Music]

Benjamin Franklin said: "In this world nothing is certain but death and taxes". But are we really sure about this, and if we are, for how long? Genes have been identified that upon activation can extend lifespan in most organisms tested. The great labs of Leonard Guarente at MIT featured by the way in episode 2, Cynthia Kenyon at UCSF, as well as Linda Buck, Nobel Laureate in 2004, are all working to elucidate the molecular details to slow down both the aging process and to extend lifespan.

Well, our guest today is a fairly controversial figure, because he said we should do away with death altogether – leaving only taxes, I suppose. He has recently laid out a roadmap to tackle aging in a book entitled *Ending Aging: The Rejuvenation Breakthroughs That Could Reverse Human Aging in Our Lifetime*. I'm not sure I agree with the scientific extrapolations but I'll let you decide. So here is our conversation.

Marc Pelletier

So how did you start? So you started your career as a – in computer science?

Aubrey de Grey

Yes, that's right.

Marc Pelletier

Could you tell us a little bit about how you did that transition?

Aubrey de Grey

Yes, sure. Yes, I started off in my undergraduate degree as a computer scientist and I worked in artificial intelligence research for six or so years, and during that period I met and married a biologist, a geneticist working with fruit flies and through her I learnt a great deal of biology I guess sort of initially by accident, over the dinner table. She is a lot older than me, she was already a full professor when we met.

Marc Pelletier

That's great.

Aubrey de Grey

And so she was, obviously a very natural teacher, having had a lot of teaching experience. Anyway, so during this period, first of all I, as you say I took a job in a bioinformatics role at the University of Cambridge. Now, that wasn't because I wanted to get into bioinformatics. That was actually because I wanted to get back into artificial intelligence research in my spare time, which is something that I had had to drop, maybe a year or two earlier because of running out of funds,

and this was a good way to do it because the job was really pretty undemanding and it gave me access to all the university facilities and everything.

So that was in '92, and after a couple of years when I had actually begun to get going on new artificial intelligence projects my interest began to shift to the biology of ageing, because I was increasingly becoming aware that biologists by and large didn't regard aging as a particularly interesting problem to work on, and certainly not an important problem to work on. And I was absolutely horrified by this because I had always known all my life ever since I was a kid certainly that aging was, first of all, a very bad thing, and secondly something that was basically an engineering problem, something that could in principle be addressed by technology.

And it was a complete shock to me that this was not widely appreciated. So eventually I began to realize that I was actually quite well placed to have a good chance of making a contribution in the field if I switched into it, because first of all people switching fields tend to do well in their new fields and they're sort of unencumbered by conventional wisdom and so on. And secondly if I did switch I wasn't going to become an experimental biologist, of which there are quite an abundant number already. I was going to come in very much as a generalist who did not have his own laboratory and would bring ideas together from disparate areas of the field and come up with new syntheses, very much in the way that theoreticians work in physics, for example.

Marc Pelletier

Do you find it more difficult to convince someone, using that approach to science than going in with 20 post docs' worth of data and laying a path of development?

Aubrey de Grey

Certainly, these days, now that I'm quite prominent, and of course quite controversial, occasionally some people use my lack of experimental training as an argument that they are entitled to ignore what I say.

But historically, that hasn't actually been the case. When I was a harmless hypothesis merchant back in the late '90s, I tended to find that it rather worked the other way, that certainly most experimentalists had a low opinion of most theoretical biology. But that opinion was perfectly justified because there was an awful lot of very, very bad theoretical biology out there. And that I, by contrast, when I came up with ideas that the experimentalists felt were actually quite good and thought, you know, why didn't I think of that – the fact that I didn't even know how to work a pipette actually sort of worked in my favor and began to – the deal was sort of, well, this guy's having a few good ideas even though he doesn't have experimental training, he must be really quite bright.

And so that actually helped me to become – to be able to treat the top people in the field as equals from a much earlier point in my biology career than otherwise would have been possible.

Marc Pelletier

[5:57] A lot of the science, though, is – so when you started to propose this in the '90s, the science was very early in the biology of aging and...?

Aubrey de Grey

Well, that's actually not the case, no. The biology of aging as gerontologists might typically define it, has certainly moved very fast in the past ten or so years. Really, it started to accelerate sharply in the early '90s with the discovery of the first genes, model organism genes that you could mutate and cause an increase in lifespan.

Marc Pelletier

We had Dr. Guarente on as our second guest because of his such fantastic work. But go ahead, yeah.

Aubrey de Grey

Yes. Now, of course it's great that some aspects of aging are genetically tractable and they're amenable to that sort of manipulation. But it's well understood – by most people anyway in the field – that most aspects of aging are not genetically tractable in this manner; that they are not the result of a genetic program. So we've definitely got much more to do in addition to the sort of things that people like Leonard Guarente and Cynthia Kenyon and David Sinclair and Tom Johnson have been at the forefront of the literature.

Marc Pelletier

And Linda Buck too, Nobel Prize winner, who's actually...

Aubrey de Grey

Sure, absolutely, absolutely. Yes, I mean the point here is really that most of the aspects of aging that I'm interested in are actually things that were understood in terms of what the problem is for a long, long time, since a long, long time ago. Certainly all of them had been characterized and discussed in the gerontology literature as potential contributors to aging in mammals by the early 1980s, if not a lot earlier. And so there was actually quite a lot to go on. Really now the seven point plan that I have, that I base my approach to combating aging on, is something that only has two components that are really due to me. The rest of them are ideas where not only the problem but also the solutions were already under active exploration, well before I came along.

Marc Pelletier

Do you want to describe those – how do you define it, the seven pillars of aging?

Aubrey de Grey

Yeah, that's right. Okay. So the seven problems are basically molecular and cellular changes that happen throughout life, as intrinsic and inevitable side effects of metabolism. In other words, side effects of the normal operation of the human body. And each of those types of change is what I call damage. It's a type of damage that is initially harmless; it doesn't cause any problem for the overall functioning of the body. But eventually, when there gets to be enough of it, it stops your body from working as well as it used to, and that's when we see age-related decline and age-related diseases, and eventually death.

So the seven things are as follows: First one is simple cell loss where cells die and they are not naturally replaced by the division of other cells. And of course another section of that that you will know about, it's basically stem cell therapy. Now naturally, there is a long way to go and I'm not saying there isn't, to develop stem cell therapies to be really safe and effective and comprehensive. But the progress is pretty rapid and some stem cell therapies are already in clinical trials.

Marc Pelletier

Absolutely. A lot of work is being done, for example, to develop myocytes, heart cells that can go and rebuild a heart after it's been damaged from a heart attack. There's some brilliant...

Aubrey de Grey

That's absolutely right. And it's going to be a bit harder to rejuvenate a heart that has had general, like, global damage going on rather than having acute injury to one part of the heart. But it's definitely something that's in sight.

Marc Pelletier

I think it's doable.

Aubrey de Grey

Okay. So then, that's number one. Number two is the opposite of number one; it's the accumulation of cells. Now I'm not talking about cancer here; I'll come on to cancer in a moment. I'm talking about the case where certain types of cells are supposed to die, and they don't die,

they accumulate and get in the way because they've forgotten to – they've forgotten how to understand the signals that are supposed to be telling them to commit suicide. And this is important in the immune system and probably also in diabetes because of the accumulation of fat in the abdominal cavity. So essentially we have to use methods to eliminate these cells, to basically get them to die even though they have forgotten how to. And there are various approaches to that that again are being explored in various labs around the world, and so again, this was very much not my idea.

Number three is mutations in our chromosomes. And that of course does mean cancer. There's good reason to believe that cancer is the only aspect of the accumulation of mutations in our chromosomes that we need to worry about in a currently normal lifespan. And cancer is a really, really hard one to deal with, as we all know. People have been trying to deal with cancer for a long time and haven't really got very far.

And this is one of the two components of the 7-point plan that is dear to me. I suggested back in 2002 that it might be possible to develop a method of eliminating the genes in our cells that encode the enzyme telomerase. Telomerase is an absolutely essential component of a cell that wants to divide indefinitely, which is what cancer does of course. Because it gives a way of compensating for the intrinsic loss of a few base pairs at the end of the chromosome each time a cell divides.

There is actually one other method, not quite so well characterized, but does the same sort of thing. If a cancer cell doesn't have a mechanism to compensate for that loss of DNA at the end of the chromosome, then it will never get big enough to kill us, it will just wither away before it gets anywhere near that size.

So I propose that we just eliminate the genes that give the opportunity to this, which are normally turned off, but the cancer mutates them and turns them on again. And we can stop that from happening by diluting the genes. This is going to have big side effects in terms of the ability of our stem cells and some continuously renewing tissues like the blood, the skin and the gut to actually keep going though a normal lifetime. But if that was all we did, we wouldn't die of cancer but we would die of other stuff instead.

Marc Pelletier

[12:10] If you are looking for a general vector that can genetically modify every single cell in the human body, you could add a dicistronic cassette – I hate to get technical here, but you could add a gene that has two switches, one on and one off depending in whether or it's a cancer cell or not.

Aubrey de Grey

Yeah, you've got to be very careful with anything that tries to identify a cancer cell and distinguish it from a non-cancer cell. That's basically the big mistake that cancer research has made throughout the whole of its history – and when I say a mistake, I'm being a little bit prejudicial, because they really didn't have much choice back then.

Because the problem is you see, that cancer cells are very good at masquerading as non-cancer cells, and that's why for example, chemotherapy has a therapeutic index. There's only so much of a chemical that you can put in, and it's not – it's generally not enough. Because some cells in the cancer will mutate to exclude or break down or in some other way resist the chemical. Since it's become apparent over the past several years that cancers have their own stem cells, cells that are resembling normal stem cells and are dividing rather slowly and so on, the problem of the therapeutic index, of cancer cells masquerading as non-cancer cells has become a bit more well appreciated, because those cancer stem cells are the ones that are really very effective at masquerading as normal stem cells.

So anything that tries to make that distinction is going to fail. You might get a little bit of increase of postponement of cancer, but you won't get the real deal, and that's why we have to do something much more aggressive which is the sort of thing I am talking about.

All right, that's number three.

Marc Pelletier

Before we go to number four, isn't cancer like – we use cancer cells or what we'll call transformed cells, which are basically cancer cells that we grow in vitro as cell models to study biology. And you know, there's a few cell lines that have been around for study for 25 years. And if you think about it, they've generated tons, literally tons and maybe hundreds of tons material, and they started from one human being. And they truly express the proof of concept to as cellular infinite life, basically. We can grow these ad nauseam. We can just keep on growing them and they undergo epigenetic variation. They don't age.

Aubrey de Grey

Sure. The thing is, it's not under control. And of course a very fashionable idea, back maybe 20 or so years ago, was that we might be able to achieve postponement or elimination of aging or at least a large part of that simply by stimulating this enzyme telomerase in all of our cells so that none of them got into a state where they couldn't divide anymore, the way that normal cells do if you grow them in cell culture for too long. But it's now pretty well appreciated that that's not going to help very much. It might not help at all. Essentially because cells that we have that actually need to divide a lot during a normal lifetime on the whole they express telomerase naturally. And the only cells that actually show robust Hayflick limit phenomenon, as it's called, in cell culture are ones which in the body don't divide very much.

A lot of people got confused about this way back, especially the non-biologists, because the typical cells that they used in cell culture work to demonstrate the Hayflick limit are ones that are from the skin, but the thing is they are not from the epidermis, the upper layer of the skin that's continuously renewing. So, they're the wrong sort of cells to look at this way. They're actually from the lower layer, the dermis, where cells are very, very good at dividing like crazy when they are required to do so like when there's a wound. But normally they just hang out. So over a normal lifetime, those cells called dermal fibroblasts just don't divide very much. And therefore it makes sense to those cells to turn their telomerase genes off really, really hard, which of course means that when they are tricked into thinking that they're in an infinite sized wound, which is essentially what cell culture is, then lo and behold, they can't cope.

Marc Pelletier

So number four, it's an amazing list.

Aubrey de Grey

Okay. Number four is again mutations. But this time it's not mutations in chromosomes, it's mutations in the mitochondria. And mitochondria are the only part of the cell apart from our nucleus that has its own DNA. The DNA in the mitochondrial genome, in the mitochondrion, is actually completely essential. But the interesting thing about it, it's very, very small, there are only 13 proteins encoded in the mitochondrial DNA.

But those 13 proteins as I say, they are essential, so if mitochondrial DNA accumulates mutations, then the cell doesn't do very well, just in the same way as nuclear mutations. And this time, those mutations don't cause cancer, but they may have a lot of indirect downstream effects, especially because the cells that they – the plethora of cascade – and accumulation of those mutations, don't actually die immediately, they tend to hang out and they are probably toxic in their environment.

Okay, so here's a suggestion – which again is not my suggestion, it was first put forward in the mid '80s – is to actually make the mitochondrial DNA unnecessary. And the way we would do that

would be to put copies of the mitochondrial DNA into the nucleus. Now you might think, well that's not going to work, is it? The DNA would be in the wrong place. And you're right up to a point. But it's not nearly so ambitious as it might sound, because the mitochondria is actually a really complicated machine that has over a thousand proteins in it. And only these 13 proteins are actually encoded in the mitochondrial DNA. All the others are already encoded in our nuclear genome, in the chromosome.

Marc Pelletier

[18:10] Why are they still there? Why is the DNA still there?

Aubrey de Grey

Well, that's a fine question. Okay, so first of all, these genes that are encoded in the nucleus, these proteins that are encoded in the nuclear genome, how do they get into the mitochondria? Well the answer is, there's machinery in the surface of the mitochondria, in the mitochondrial membranes that inputs, grabs the protein and feeds it into the cell – I'm sorry, into the inside of the mitochondrion.

So then you might ask, well okay, what's this – why does the mitochondrial genome still exist? And that's a very good question, because when – a billion years ago, or actually more like two billion years ago when mitochondria came into existence, they came into existence by something called the endosymbiotic event, which was the essential swallowing of a bacterium, a free-living bacterium by a non-bacterium, by a cell that became a normal eukaryotic cell. And at that point, the free-living bacterium had a great deal more than 13 protein coding genes, it had well over a thousand. And a lot of those, most of those genes got transferred to the nuclear genome really fast. Exactly why they get transferred is still debated, but there are plenty of plausible explanations for that.

The question is what – as you said, why didn't it run to completion? And the answer actually turns out to be fairly simple. It turns out that the machinery that I mentioned a moment ago – the machinery that pulls the mitochondrial proteins in if they are encoded in the nucleus and therefore synthesized in the cytoplasm, outside the mitochondrion. That machinery can't cope very well with proteins that have a very high what's called hydrophobicity. Proteins are very hydrophobic, that means they like to curl up into a ball and they don't like to be unwound, unraveled. It turns out that the machinery that does the protein input needs to unravel its cargo. So the most absolutely ultra-hydrophobic proteins are simply too hydrophobic for this machinery to cope with.

Okay, so then the question is what can we do? Well, there's a couple of other very simple things we have to do that I'll not bother going into. But the main thing we have to do is, we have to find some way to change these genes so that the hydrophobicity of the proteins is reduced, but without affecting the function of the protein so it'll work. And essentially what we're doing, and in fact this is work we are funding, that the Methuselah Foundation is funding in Paris at the moment, is to identify, base pair substitutions, amino acid changes that we will have exactly that effect.

Also in parallel with that, we're attempting another trick which actually was pioneered in the lab in Paris that we're funding. And that trick involves changing the non-coding part of the gene, part of the gene that encodes some RNA but does not encode enzyme, not encode amino acids, and it turns out that there's RNA you can stick on there that actually causes the messenger RNA itself to be located to the surface of the mitochondrion, so the protein import happens at the same time as protein synthesis, and that basically sidesteps the hydrophobicity problem completely, or it seems to sidestep it.

So that's number four.

Marc Pelletier

Yeah, I'm just trying to visualize this – this is outside my area of expertise though, although I have a general idea, I suppose of biology but not – you know all these topics. How bad is it to have the mitochondrial DNA – is a mitochondrial DNA more mutagenic than being in the nucleus?

Aubrey de Grey

Thank you very much. I should have mentioned that at the beginning really, shouldn't I? Yes, it certainly is. It's vastly more susceptible to accumulating mutations.

Marc Pelletier

Is that because it doesn't have the DNA repair mechanism?

Aubrey de Grey

It has some, in fact it has most of the DNA repair mechanisms that exist in the nucleus, but not all. However, there's another thing that makes this problematic which is it doesn't have histone. It's not wrapped around the special proteins called histones that are very protective to the nuclear DNA.

And the third thing, probably the biggest reason why the mitochondrial DNA is more susceptible to mutations, is that it's in the wrong place. It's right next to the main generator of things that cause mutations to occur, namely...

Marc Pelletier

There you go!

Aubrey de Grey

Yes, it's a bad place for DNA to be. However actually it's even worse than that. There's a fourth reason why it is a bad place for the DNA to be, which is that we have a lot of mitochondrial genomes in each cell. Now you might think, well that's actually a good thing, that would be a defense. It would mean that we can afford to have a bunch of them mutate and the cell would still be fine. And it's certainly true that the cell can afford to have, in fact most of its mitochondrial genomes being mutant.

But that's not the same. Because it turns out that at least some types of mutation in the mitochondrial DNA exhibit what's called a clonal amplification phenomenon. In other words, there's turnover of mitochondria all the time, with some mitochondria being destroyed, that is broken down, other ones being replicated. And that process allows essentially a process of natural selection, once there is any mutation, mutant mitochondrial DNA in the cell, then there's competition between that one and the other one.

And it turns out, as was discovered back in the early '90s, that some mutations just clonally expand. They actually take over the cell, copies of the same mutation without any additional mutational event. So the cell becomes completely lacking in normal working mitochondrial DNA.

Actually my first paper in the field back in 1997 was to propose a detailed mechanistic explanation for this.

Marc Pelletier

The – mitochondria as well, we had Dr. Evangelos Michelakis on a previous episode. He was studying some molecules that modified the metabolism of cancer cells through their modulating – the way the mitochondria works.

Aubrey de Grey

Right.

Marc Pelletier

[23:59] And what he found really interesting as well was that by modulating the metabolism of the cancer cell, which had a defective mitochondria in sorts, it actually triggered cell death as well.

Aubrey de Grey

Yes.

Marc Pelletier

So the mitochondria have a pretty important part into the age of cells.

Aubrey de Grey

You're absolutely right. You're absolutely right. Cancers seem to be very reliant on having dysfunctional mitochondria one way or another, having mitochondria not work very well. They need mitochondria to work a little bit. We never see complete knockout mutations accumulating in cancers. But we very often, in fact usually see mild mutations, mutations that will somewhat diminish the functioning of the mitochondrion.

The effect that Michelakis found – and the general decline of the metabolism – the mitochondrial metabolism in the cancer cell – is actually a bit different, because he was – as you mentioned, he was able to reverse that phenomenon using a drug. Now of course if the phenomenon was resulting from mutations, then a drug wouldn't work, because the mutations are just there, they can't make the right protein anymore. So this is a sign that it's not just mutation accumulation that's causing cancer cells to have dysfunctional mitochondria, it's also an adaptation of gene expression that essentially is being selected for within the cancer cell.

Marc Pelletier

This is fun stuff. And so what's number five?

Aubrey de Grey

All right, so number five is the other one that I came up with. And the problem here – again the problem is something I didn't come up with, it's a solution I came up with. The problem has been known since at least the 1950s. And it is the accumulation of indigestible molecules of one sort or another. So, obviously cells are making molecules all the time that they didn't mean to make or they only need for sometime or another. And when those molecules pass their sell-by date, they need to be destroyed or excreted.

And for all molecules that are created and become unwanted at a respectable rate, evolution has had the job of making sure that we can get rid of it, because otherwise we'll die, from you know, too much garbage. But there are some molecules that are only created at a very, very slow rate, so that even in a normal lifetime, they only accumulate to a tolerable level.

Now, when I say a normal lifetime, of course, I mean a normal lifetime in the wild. And so now, when we are living to ages where evolution hasn't been paying any attention, we have a problem. And indeed, it turns out that most of the major age-related diseases come down to this one problem, or at least they are predominantly caused by this.

Cardiovascular disease in particular is caused by the accumulation of modifications of cholesterol in the artery wall, and basically modifications that engulfed by cells, the cells called macrophages that enter the artery wall, but that the macrophage then can't cope with. And the macrophage then basically becomes dysfunctional, it can't even do the things it used to be able to do, and it fills up with all manner of stuff, and lo and behold, we end up eventually with an atherosclerotic plaque. And similarly in neurodegeneration, in all the various neurodegenerative diseases, we see an accumulation of protein aggregates of one sort or another in the cell. In Alzheimer's disease it's neurofibrillary tangles made of tau; in Parkinson's Disease it's Lewy bodies made of alpha-synuclein and so on.

So the question is, what do we do about this? And I could go on of course. Blindness is another one, by the way.

Marc Pelletier

No, it's a good example, yes.

Aubrey de Grey

Yes, blindness is the third best example, which is macular degeneration. That's the result of the accumulation of nasty molecules that are formed by the reaction of photoreceptive material with membranes.

Okay, so then what do we do? Well, a good idea I had back in '99 was that we might be able to use technology from way outside the gerontological realm and actually from outside of the whole of biomedical research. This is a really great demonstration of the value of having people like me pacing up and down and talking to themselves, and not actually spending all their time in the laboratory, because we've got time to read widely and study widely enough to bring these ideas together from far apart. So the idea that I brought to bear on this was actually a subset of the field of environmental decontamination, specifically a field called bioremediation.

Now bioremediation is a very successful – both commercially and academically – field that began back in the 1950s when a guy called Ed Gayle wrote a paper entitled “The Microbial Infallibility Hypothesis.” And his idea was like this. He said, well, look, some bacteria grow faster than others. Now, in the wild, in any environment, you're going to have competition between different bacteria. And if you can grow faster than any of your competitors, then you're going to win. And so there shouldn't be much diversity of microbial ecology in any one particular environment. In fact, if you go and look, we see an immense diversity in pretty much every environment, what's going on?

And you realize that the solution to this paradox is that there is a second way in which a bacterium, a bacterial species can survive, and carve out an ecological niche. It doesn't have to grow as fast as everybody else, so long as there's something in the environment that it can eat and live off – make energy from, extract energy from – that its faster growing competitors, for whatever reason, can't metabolize. And in particular, that means that if there's something in the environment that is intrinsically quite difficult to metabolize, but if you could metabolize it, then it's energy rich, you can extract energy from it.

Marc Pelletier

Microbes have the fantastic ability to metabolize anything, as long as it's got carbon, they'll take the paint off a wall.

Aubrey de Grey

Different microbes can metabolize different things, this is the key point. And so basically, he wrote – what Gayle realized was that if you have an environment with something [indiscernible], then it will impose selective pressure on the microbial ecology in that environment to develop, even if it doesn't – hasn't already the ability to break the thing down. And that is indeed exactly what we see. As you say we can use this, for example, to decontaminate disused airfields that have got TNT in the soil in order to build a housing estate on them. You go to the side of the highway and find bacteria that can break down rubber, because there's pulverized rubber coming off tires all the time. And so on.

Anyway, so my realization was that actually, you know, the human body is accumulating these various indigestible molecules that have exactly the right character. First of all, they are organic and energy rich. And secondly, by definition, they are hard to break down.

So, maybe if we're looking in environments that are enriched in human remains, like for example, graveyards, we will find bacteria that are able to break down these substances. And then, of

course, my suggestion is not that we should isolate these bacteria and then inject them into our bodies, but rather that we should isolate the bacteria and then identify the genetic basis for this ability, the genes that they're encouraging and the enzymes that are doing the work, and we should get those genes or those enzymes into our bodies. And that will have the same effect, it will allow us to break down these various things that we can't naturally break down.

Marc Pelletier

And so we interviewed – I'm pulling out all these interviews. And the reason why I make reference to the past interviews is that the projects that you're proposing go and tackle every aspect of human biology, basically at the end state of human biology. So there's always these fantastic references, your science sort of raises a lot of interesting biotechnological challenges, and I guess that's what I'm sort of programmed to do. We do have tenfold more bacteria on us than we do human cells.

Aubrey de Grey

That's right.

Marc Pelletier:

Right. So – and those genomes are currently being sequenced as we speak.

Aubrey de Grey

That's right.

Marc Pelletier:

[32:06] In the metagenomic area, what's it called – I'll refer people back to Jeff Gordon's interview. But it's scary that we are carrying about three pounds of – is it? No, three kilos of bacteria.

Aubrey de Grey:

Yes, that's right.

Marc Pelletier:

But we could look in there if they're there too.

Aubrey de Grey:

So, this seems to be something that a lot of biologists have taken a liking to pretty quickly. I've had no real trouble persuading people that this actually is a plausible idea. And we are again, funding a couple of labs already – three labs already, and we're going to be funding more – to work on early stages of these projects. And it's going very nicely, bacteria are being found that can break down the important things that we want to break down, and we've already made the first steps toward identifying the genes that are responsible for that, so the project is going according to plan. So that's number five.

Marc Pelletier

I'd like to take a minute to thank audible.com for sponsoring Futures in Biotech. If you're in the U.S., you can download a free audiobook from over 45,000 titles by going to audible.com/biotech. This week, my pick is *The Age of Turbulence: Adventures in a New World* by Alan Greenspan, read by Robertson Dean. It's a really powerful book, written by someone who could, in just a few words, influence the entire world economy. It's pretty amazing. Here's a clip:

Alan Greenspan (read by Robertson Dean)

"I was confident that he and our colleagues would be taking the necessary steps to keep the world dollar system flowing. Yet, even as I thought about it, I doubted that physically disrupting the financial system was what the hijackers had in mind. Much more likely, this was meant to be a symbolic act of violence against capitalist America, like the bomb in the parking garage of the World Trade Center eight years earlier. What worried me was the fear such an attack would

create, especially if there were additional attacks to come. In an economy as sophisticated as ours, people have to interact and exchange goods and services constantly, and the division of labor is so finely articulated, that every household depends on commerce simply to survive. If people withdraw from everyday economic life, if investors dump their stocks or businesspeople back away from trades or citizens stay home for fear of going to malls and being exposed to suicide bombers, there's a snowball effect. It's the psychology that leads to panics and recessions. A shock like the one we've just sustained could cause a massive withdrawal from, and major contraction in economic activity. The misery could multiply."

Marc Pelletier

So if you'd like to download Age of Turbulence or any other audiobook, go to audible.com/biotech. You sign up for a subscription, you get a free download, and you also get discounts on future audiobooks. Though if you want, you can simply cancel within 14 days and there will be no charge and you get to keep the book.

That said, let's get back to our conversation with Dr. Aubrey de Grey.

Aubrey de Grey

All right, number six is another one that was very much thought up by somebody else and it's going very well. And this is the accumulation of indigestible molecules not inside the cell but outside, and especially between our cells. Now this turns out to be a problem in a number of interesting aspects of aging. And it's almost the work of the same type of molecule that accumulate namely a type of protein and accumulating in the same sort of structure. The general name for all of these is called amyloid. The most famous amyloid is beta-amyloid, which accumulates in the brain of patients that have Alzheimer's disease and there are other types that accumulate in the heart, a different protein called transthyretin and in the pancreas a different protein called amylin. Now, in the case of Alzheimer's disease about 10 years ago, a group in Northern California identified that it was possible to immunize against this stuff, you could actually....

Marc Pelletier

I would like to point out for the audience, not to scare off the audience with the word amyloid, it's simply a nanoscale fiber that is pretty indestructible that as you mentioned accumulates in...

Aubrey de Grey

That's right...

Marc Pelletier

We don't know if it's the intermediate or the final product that's toxic really...

Aubrey de Grey

Yeah, there's quite a bit of evidence that actually some intermediates in the formation of amyloid fibrils are the most toxic components, in Alzheimer's disease. But that's not to say that it wouldn't help to get rid of the amyloid itself, because that might make it more easy for the precursors to be aggregated into these perhaps less harmful large aggregates, so they're actually good reasons to want to go for the aggregates anyway.

All right. So what's happening with this, is that people have figured out in my specialty, about 10 years ago that you could vaccinate against this stuff. You could stimulate the immune system to identify amyloid as foreign and the results in the case of mice that were engineered to get Alzheimer's, you could actually get the immune system in the brain, cells called microglia to swallow this stuff, to engulf bits of amyloid. And it turns out that amyloid seems pretty indestructible but it's actually not quite so indestructible as all that. The only reason it hangs out is because the degradation machine that we have in the extra-cellular space is a lot more feeble than the degradation machine we have inside our cells.

What happens when the macrophage do this is they get it inside the cell and then it's exposed to the much more powerful machinery that we have there to break things down and it doesn't immediately disappear but at a respectable rate it just goes away. So in another words, just getting it into the right place it seems to be a pretty comprehensive solution and this went well enough that very impressively enough that they – that the group in San Francisco actually were able to set up a clinical trial pretty quickly about six years ago – seven years ago. In fact it was a bit too quickly. They did it wrongly and the result was that there were – the trial had to be ended prematurely because the side effects were quite severe on the part of a small minority of the patients.

[38:20] But, first of all they understood what the problem was very quickly. And secondly, everyone knows, of course, Alzheimer's is really quite a serious problem, so the result was they were able to embark on a second improved clinical trial almost at once. And that has now moved to Phase III as of a few months ago. So the news is very, very good, especially – particularly the indication is that the Phase III trial was initiated before the Phase II trial had even reported. That really shows that they knew that the Phase II results even at an interim level were going incredibly well. And I want this same approach to be followed in respect of other amyloids, ones in the pancreas and the heart and so on that I mentioned earlier.

Marc Pelletier

The one in the heart, transthyretin...

Aubrey de Grey

Yeah.

Marc Pelletier

I mean, the way that protein sort of – it forms an amyloid, it – so it's a normal protein, then it decides okay, I don't want to be normal protein, I want to unfold and pick up the structure of a fiber that forms like a polymer, right, it's a long chain of this protein that reaches on forever, but it's only a few nanometers in diameter.

Aubrey de Grey

Right.

Marc Pelletier

If you're looking at a long-term strategy for life extension, are you also looking at the possibility of finding the people, of course genomics has to play part of this because our molecular anatomy is based on our genome, right? To get an understanding of who we are down to atomic level, you have to have the genome.

Aubrey de Grey

Yeah.

Marc Pelletier

So, for those people that are predetermined to have early onset amyloidosis as a result of these mutations, could you think of just giving them a cocktail of pharmacological drugs that would prevent the transition into the accumulation of those products that you want to get rid of too, I mean there is two sides of every coin...

Aubrey de Grey

Maybe you could do that, however, it may turn out that the most straightforward way to treat early onset amyloidosis, whether from transthyretin or from anything else is actually simply to use the same treatment that we developed for age-related amyloidosis, but to use it more aggressively. For example, if we take the analogy of intracellular aggregates that I was mentioning a moment ago, actually we already do that. So there are plenty of early onset diseases of accumulation of stuff in the cell which are caused by simply the absence of a protein that's supposed to break

them down, of an enzyme of that's supposed to break whatever it is down that we – that most of us have. And the approach to treating that, which has been successfully used in the clinic for over 40 years now is simply to inject the right quantity of that enzyme into the bloodstream and it gets...

Marc Pelletier

Are we talking emphysema, alpha-1 antitrypsin?

Aubrey de Grey

I'm actually talking about lysosomal storage diseases like Gaucher's disease and Tay-Sachs and so on. In the case of Tay-Sachs the therapy is still a little bit more experimental but in the case of Gaucher's and one or two other diseases which are very much of the same character, these things have been in use for a long time. And I think works really well. So that may be simply the way that these early onset diseases both for intracellular and extracellular accumulation of stuff can be addressed.

Marc Pelletier

Enzyme replacement?

Aubrey de Grey

Yeah.

Marc Pelletier

Cool. What's number six?

Aubrey de Grey

I'm sorry?

Marc Pelletier

That was number five.

Aubrey de Grey

Extracellular aggregate was number six. Intra – yeah, okay, so number seven and the last one is crosslinks. So there are in the extracellular space not just molecules that are garbage, accumulating just lying around, there is also molecules that are there on purpose to hold our body together, to give them the structure that they have. And the ones that matter most here are ones that are laid down early in life and are not replaced thereafter. So in this case, I'm not talking about bones for example, bones are remodeled all the time. I'm mainly talking about things like the walls of our arteries or the lens of the eye.

Now, the important things about these structure is that they are made of proteins and yet they are bathed in the extracellular fluid all the time. Now, the extracellular fluid has chemicals in it that are somewhat reactive and – albeit not very reactive, but reactive enough that if something is bathed in them for decades then stuff is going to happen. And the big thing that happens is that the proteins that these structures are made of react with sugar and the reactions with sugar are very complicated, there are a lot of people studying the detailed chemistry of this area. But essentially, there's one big thing that occasionally happens which is that a sequence of reactions occurs that ends up with a new chemical bond, a chemical structure formed between one protein and another protein that was lying beside it but was not previously attached to it. And that turns out to be really important, because if you get a gradual accumulation of these random crosslinks between proteins in a structure like the artery wall that's supposed to be elastic, then the structure becomes less elastic, it becomes progressively stiffer. And of course that means it isn't able to do its job so well. And the same applies in the lens of the eye. The lens of the eye needs to be elastic in order to focus on things that are nearby.

[43:45] So that's part of aging. And we need to fix it, especially in the artery wall because that is life threatening, it causes high blood pressure and so on. So the question is how do we fix it? Well the good news is that this – these very elaborate sets of reactions between proteins and sugars are also very, very weird and in particular the chemical structures that happen at the end of the process are completely unlike the structures that we see that are laid down on purpose by our enzymes which means that there is a respectable chance of developing drugs that even if they're not particularly specific from the point of view of their objective chemistry nevertheless they will be specific in terms of their biology. In other words there won't be any other molecules – if they target the molecule we want them to target then it wouldn't be too hard to get them to target only that molecule. Because other molecules that are similar to them are simply not around, we don't need to worry about whether they react with those or not.

Anyway, so progress on this area has also been reasonably good. The whole concept of molecules – of drugs that might break these crosslinks was put forward first in the mid '90s, so again not my idea. And was taken forward again through a number of clinical trials. At this point the whole process has started to hit a few barriers, certainly we're finding that the development of these drugs is not as easy as it began to seem in the mid '90s. But the general approach is definitely still valid and there's good reason for optimism. Okay, so that's it, those were the seven things.

Marc Pelletier

It's a phenomenal roadmap, one that – I don't know, I suppose I am an optimist in that I believe that we're going to be able to tackle human biology really as a substrate for engineering and I am not quoting myself here, I am quoting Drew Endy who is at MIT, in biomedical engineering. And you know we are going to reach a point where we have handle of all the molecular events and be able to regulate them. I don't see it happening within my lifetime, maybe my kids', I know that in our lifetime, we will reach the simpler forms of single gene expression changes that might lead to a better metabolism to delay death, but what you're proposing is a complete biological control of...

Aubrey de Grey

Well actually, no. Let me make you perhaps a little bit more optimistic on this. The things I'm proposing are certainly more complicated than single gene modifications. But they are not – they are not massively more complicated. If you look at – if you add together all of the things that I am talking about, that I've described in simple terms over the past half hour or so, then it comes down to inserting perhaps 20 or 30 genes into – new genes. It comes down to knocking out, maybe three or four genes. It comes down to, you know, a few vaccines, a few drugs, perhaps half a dozen different types of stem cell therapy. You know, so doing all of those things simultaneously to one person every 10 years or so is certainly a big step forward, but it's not an unimaginable step forward.

It's the sort of step forward that – a step forward that's comparable to what we achieve in most disciplines in let's say a few decades. You know, if you look at for example powered flight, going from the Wright Brothers just about getting off the ground to Lindberg getting across the Atlantic, you know, that's a pretty damn big change, and it happened in only 24 years. If we look at Lindberg getting across the Atlantic and then the first commercial jetliner, the Comet getting across the Atlantic you know, that's pretty unimaginable, that's pretty damn big as well, but that was only 22 years, you got the idea right, it's not an unprecedented rate of progress that I am predicting here.

Marc Pelletier

No, absolutely not. And I think there is some major changes in human biology that will take place as many of these discoveries, and you know the by-product of the research is therapies that you know save someone's life and maybe prevent them from getting Alzheimer's or diabetes or age-related diseases. So there is no question, it's a worthwhile endeavor and one that should be sought after. It's – sometimes the scientific community tends to think in very conservative ways in

that what is attainable and partly be – it's because, it's very difficult in the labs sometimes just to get, maybe one gene inserted, sometimes depending on what's happening but...

Aubrey de Grey

Certainly, one thing we need to do, there's no question about it, is to improve our ability to do safe and effective gene therapy. But if we think about that now, genes, we are already pretty good at gene therapy in mice, the only real reason why gene therapy is going so slowly in human is because we are so fixated about not killing anybody. You know, it's silly really if you think about it because when for example Jesse Gelsinger died of anaphylactic shock – you know, the gene therapy trial, back in 1990, he shouldn't even have been admitted into. You know, all gene therapy trials worldwide shut down for about a year, now that will not delay the advent of safe and effective gene therapy by a whole year, but it will probably delay it by about a month or more in the long run. And you know that's going to be one hell of a lot of more than one life, so you know I think if we start to take a better sense of proportion about this and not be so fixated in terms of first do no harm, then progress might be a lot faster. And I expect that that's going to happen when the proof-of-concept of all of this technology in the laboratory is achieved and becomes known about and we start what I think is legitimate to call a war on aging, where people are willing to embrace a certain amount of risk and a certain amount of diminution of standard of living in the short term just in order to end the slaughter as soon as possible.

Marc Pelletier

[50:04] That was an interesting point though that if we are so cautious about our methods of development in the human system, we are worried about one person dying where we could benefit greatly in terms of knowledge by, if people did die. You certainly don't want the disadvantage being taken advantage of, to do this. But imagine, if you're doing space exploration, if we actually sent a man to Mars now without having to have him return but we could sustain him for a certain amount of time, the amount of knowledge we would have on Mars will be dramatically improved over the robots that we're sending over there now – I suppose?

Aubrey de Grey

That's right. And we would've got to Mars some time ago, except that we couldn't be bothered. You know, if there had been the same degree of national pride attached to it as the world attached to getting in to the moon in the '60s, then we certainly would be there by now.

Marc Pelletier

But you know I am not one to, I believe in safety too and a cautious approach to doing this. But inevitably human biology as a technology will develop and I don't see it slowing down but accelerating and some of the enabling technologies are really accelerating things, so it's going to be a very, very exciting century. You've had an evolution of sort of people's acceptance of your proposals, I suppose?

Aubrey de Grey

Yeah, it's certainly my – the thing that drives me is the drive to save lives absolutely and to alleviate suffering. I know that the timeframes I'm putting forward are inevitably very speculative because we're talking about even the timeframe I put forward of something like 25 or 30 years from now, before we actually achieve these technologies. And any technology if you're talking about that sort of timeframe then you might well be very wrong. So, you know, if I were thinking purely personally in terms of whether I would save my own this way or my wife's life or whatever, then it would be hard to get worked up about it because even if I were to change to hasten the development of these technologies by as much as five or ten years which I think is the most I could possibly hope for by my own efforts, then you know that still wouldn't make very much difference to the probability of making the cut for any given particular person. Well, if you think clearly in terms of the number of lives saved, the number of people that die of aging and age-related things each day, then it's about 100,000, two-thirds of all deaths worldwide and 90% of all deaths in the industrialized world. And therefore, I only have to make a very small difference today in order to feel pretty good about the way I've run my life.

Marc Pelletier

Yeah, I'd like to talk a little about the prize that you've set up. I can't pronounce it too well, Methuselah Mouse Prize?

Aubrey de Grey

You can pronounce it fine, that is exactly right.

Marc Pelletier

So can you tell us a little bit about that?

Aubrey de Grey

We're actually taking pity on people like you at this point, we call it "The MPrize".

Marc Pelletier

Oh, thank you. Well, "The MPrize", very interesting idea. And how is that working out, in terms of being able to drive innovation?

Aubrey de Grey

It's working out really well. So as with any prize effort – prize initiative there are really two goals involved. One is to incentivize the people with ideas for how to make progress in a particular area to actually put more effort in and more money in than they otherwise would have.

And the other is just to raise the profile of the whole field, so that it's not necessarily the actual amount of money in the prize or the kudos of winning the prize is the driving force but just people who aren't necessarily interested in the prize, think about it more and are perhaps more enthusiastic about it and it changes the culture of thinking about the problem.

So, I don't think at this point that we have had much progress in terms of actually changing people's – what science they're doing. I don't think we've actually been able to get very many scientists to do experiments they were not otherwise doing already. Though that certainly may happen. I think at this point the prize has a pot of \$4.5 million which is pretty big and it is going up all the time. So, you know, that may happen.

But I think we've been very successful in the other factors, the raising the profile of life extension itself. So the rules, it's very straightforward, you just have to beat the world record mouse lifespan and the amount of money you get is a proportion of the prize fund that is determined by how much you beat the previous record by.

And there are actually two prizes: the first one that we've put into place is a very straightforward one, very simple, it's just you've got a world record mouse lifespan for an individual mouse, and you just have to beat that. And it doesn't matter what you do with the mice, they've got to be a *Mus musculus*, the species used mainly in the laboratory. But apart from that, you can do anything genetically with them, you can feed them strange things, you can do what you like.

That prize is simple to understand but scientifically and in terms of its relevance to future biomedical interventions, it probably isn't very important and sure enough it hasn't attracted very much of the funding that we have in the prize pot. The one that has most of the funding is called the rejuvenation prize, and it had a couple of differences.

First of all, it's not just for one mouse. What you have to do is actually an experiment that's thorough enough to be publishable in a proper peer-reviewed journal, and you have to use a lot of mice in order to do that, you'd have to let's say get twenty or thirty mice and treat them. And the record that you have you beat is the lifespan, not of the absolute single oldest mouse but the average lifespan of the top ten percent of the cohort that you're looking at.

But the second thing is probably the most important difference from the other simple prize, which is that you're not allowed to start until halfway through the mouse's natural lifespan. So in other words, you can't do anything genetic unless you do it by somatic gene therapy in middle age. You can't do anything pharmacological or dietary until middle age, either. And of course, the world record for that is a lot smaller than the world record for the other one, but it's a lot more relevant. So that's the prize that we really want to promote, and luckily that's the prize that has indeed attracted most attention.

Marc Pelletier

[56:19] I'm wondering, maybe that would be the first step, but is regeneration necessary once you've tackled the issues? So you do see regeneration as the way to maintain life?

Aubrey de Grey

I think it's absolutely clear that regeneration is the way to go, yes. I think that we can say clearly at this point that there is only one aspect of aging that can be addressed by, if you like, tuning our metabolism in ways that extend lifespan. That is the sort of thing that we were talking about towards the beginning of the interview, the sort of thing that people like Cynthia Kenyon and Leonard Guarente and David Sinclair and so on are working on.

And that's better than nothing, but as you may know, I think that those types of approach are unlikely to give humans very much of an extra life extension. Because essentially, the evolutionary pressure to respond to nutrient deprivation by aggressively slowing down one's aging, has just not been as strong as it has been for shorter lived organisms like mice.

So that means we really need to look at something else. And if we try to actually not just elicit the genetic pathways that already exist in the body, like essentially tricking the body into thinking it's being nutrient deprived, for example, if we try to actually improve on the genetic pathways that are present and clean up metabolism, so it doesn't lay down these seven types of damage that I've been talking about, then we're not going to be able to do that. We're not going to succeed anytime soon.

The reason we're not going to succeed is because we just don't understand metabolism anywhere near well enough. It's just too complicated and too poorly understood. We're going to end up having more side effects than we're going to do any good about. So that's why it's simpler to intervene later on in the chain of events.

Not so late as a geriatrician would intervene when the pathologies are already emerging, but to intervene at – to target these various types of molecular damage, molecular and cellular damage. Because you see, those targets are initially inert. They're laid down as side products, side effects of metabolism, but until they accumulate to sufficient abundance, they're harmless. So that's a great window of opportunity that we can dive into.

Marc Pelletier

There's a technical glitch here, but that's okay because it was me and I was asking a question and the question was, how does changing human lifespan affect the global population?

Aubrey de Grey

I personally have never wanted children, but I know that most people do. However, one thing that we need to bear in mind is that over the past half century or so, there's been a progressive and rather rapid decline in the number of children that women are having. And as a result, there is an actual shrinkage of the population in some countries, certainly in most of the developed world if we exclude immigration. And of course the most populous countries of the world, China and India, are becoming developed and industrialized pretty rapidly, and sure enough their birth rates are plummeting too.

Now, if we look more closely at this phenomenon, we can see that there's another very important feature of it, which is not just that women are having fewer children; it's about having them later. And by and large, women that have a career and in whatever way are making the most of their lives because of their education and emancipation and all that, seem to prefer to do a lot of that sort of stuff, and only have children at an age when it's then or never, because of menopause and you know the risk of chromosomal aberrations that cause Down's Syndrome and stuff like that.

So now what we must ask ourselves is, what would women tend to do on average if we actually eliminated all of those age-related problems, eliminated menopause, eliminated the decline of performance and so on, by rejuvenating the ovary. Now what it would mean, it seems to me, is that women would have the opportunity to delay their childbirth further and despite the fact that they want children eventually, the trend – the natural implication of what's happening already is that the average woman would have their children considerably later.

Now it turns out if you do the arithmetic that the age at which the average woman has her first child is – has an absolutely dominant effect on the trajectory of global population. How old you are when you have your second and third child matters less, because essentially the exponential rate of growth that you can see when your own child has their child and so on, is faster for the first child.

And so actually, this is a good reason to believe that any overpopulation problems that might result from a dramatic reduction of the death rate due to the cure of aging would be very attenuated, perhaps eliminated entirely by choice, by the actual choice that women would make when they were able to delay their childbirth indefinitely if they wanted to.

So that's pretty good news. However, it's reasonable to respond and say, well, yes, that might happen but it might not. Supposing it doesn't happen, we do actually have enough women wanting to have children young that we have a big problem anyway. And I say, yes, I know that that's a possibility. But then the question is what's the option?

The options are either to restrict birth rate below what we would like, by whatever means, I'm not saying how we would necessarily do it. Or the other alternative is to restrict use of therapies that defeat aging or in some other way to keep the death rate high. And again, I'm not saying how we would do that, I'm just saying that one way or another we would have to keep the death rate and the birth rate broadly in line with each other over a long time, over the long term.

Now my point here is, I don't know which of those solutions is better and I certainly don't know which of those solutions humanity of the future will decide is better. But I do know that we have an absolutely clear and present moral obligation to give the future of humanity that choice. And if we were to prevaricate now and say, well, oh dear, overpopulation, let's not go there, let's not develop these therapies, then what we would be doing would be imposing our values on the humanity of the future by not giving them that choice, by forcing them into a situation where – condemning them, essentially, to an unnecessarily early death as a result of our decision that they would want to have children. And that we clearly have a moral obligation not to do that because they have the right to make the choice themselves.

Marc Pelletier

I'm going to direct people to your book again. It's Ending Aging: The Rejuvenation Breakthroughs That Could Reverse Human Aging in Our Lifetime. It's definitely a thought-provoking book, and I think we're going to hear a lot more of this as it – of you and your work as it moves forward. Very, very exciting. I really appreciate your time.

Aubrey de Grey

Well, thank you very much.

Marc Pelletier:

I'd like to thank our guest, Dr. Aubrey de Grey, for being so generous with his time. Thanks to Will Hall for the opening and closing themes; to Leo Laporte for helping co-produce the show. Last but not least, I'd like to thank the listener. Many thanks for your donations. For Futures in Biotech, I'm Marc Pelletier.