



## #393: Antagonize your ageing: The science behind living healthier for longer

VOICEOVER

This is Up Close, the research talk show from the University of Melbourne, Australia.

ANDI HORVATH

I'm Dr Andi Horvath. Thanks for joining us. Today we're bringing you Up Close to our ageing bodies and the connection with molecular activity in our cells. Life expectancy is now longer for both women and men. Plus more of us are living longer well into the retirement years. But the extra years mean many of us are living with age-related disease and disability. Managing this growing demographic poses real challenges for a nation's healthcare system. Whilst prevention is essential and preferred, there is also a need for future interventions for improving age-related health issues, that is, improving the human health span. A detailed understanding of the hallmarks of ageing at the levels of the genetic and molecular activity in our cells that affect the tissues of organs that make up the various functional systems in our body has to be the key. Here to take us on a journey into the cells of our bodies and talk about the possibilities for a future of ageing well is Andrea Maier, Professor of Gerontology at the University of Melbourne and Divisional Director of Medicine and Community Care at the Royal Melbourne Hospital. She is an internationally recognised expert and has worked with European Union initiatives in addressing ageing and the future wellbeing of the aged. Welcome to Up Close, Andrea.

ANDREA MAIER

Thank you very much.

ANDI HORVATH

All of us are ageing, but some people seem to be better at it than others. There's a broad difference in capability for people at the same age. What is the medical definition of ageing and how do we currently measure it in humans?

ANDREA MAIER

I don't have an answer for that, because we don't have a definition for ageing. So

we don't have a definition for old age. If you look at the literature, most of the times at the age of 65 we as researchers call somebody aged. We also have a definition for the oldest old, so these are the ones being 85 years and older. Then of course we have the nonagenarians, the centenarians, which are the ones being 90 and 100, but we really don't know when you are aged. So normally in literature we will find the cut-off as 65. However, personally I would say this is the second youth, because, hey, then retirement really starts and then you can go to the next career step, for example, because you won't die for the next 20 years.

ANDI HORVATH

But this second youth, as you called it, surely there are cognitive and physiological tests. Because there is a broad spectrum of people over the age of 65 and their capabilities.

ANDREA MAIER

That's true. So there is a difference between the chronological age ? the chronological age is the age in your passport ? and the biological age is the rate of ageing during your life history trajectory. As you can imagine, if you see somebody at the age of 80, somebody can be very, very vital, looking for the grandchildren, etcetera, being very, very enthusiastic at taking part of society, and another one being 80 can be wheelchair-bound, living in a nursing home, for example. So here you see that the chronological age of 80 can be very, very different in terms of the biological age. Somebody can be 70 or 90 or even younger or older. And actually this is very, very interesting that there is a huge difference between chronological and biological age and that starts very, very early. Already in the 20s, 30s, we can really see who is ageing faster, or the ones who are lucky, ageing in a slower pace.

ANDI HORVATH

Are there standardised tests for physical capability and cognitive capability?

ANDREA MAIER

Yes, there are. In clinical practice we use them. So I'm also a physician, I'm a geriatrician and specialist in internal medicine. So what we do in clinical practice is really looking at the capability of the human body, not only of the physical side, but also on the mental side and the cognitive side. So we have a standardised assessment called the Comprehensive Geriatric Assessment, so we really try to see how the human body is functioning. The interesting part is that we can do that at old age, but we already can do that at younger ages.

ANDI HORVATH

What about the cells? Are there urine tests and blood tests that can tell where we are in the biological ageing process?

ANDREA MAIER

We can, and this is really the topic we are working on here in Melbourne, my group in the lab. So in the last 50 years we really discovered why we age, so the ageing mechanisms. I talked about the hallmarks of ageing, so we've now discovered nine

hallmarks of ageing, really the processes why our human body is deteriorating, why our shape of our human body and our phenotype is changing, like grey hair and the wrinkles, more fat and the muscle mass we have. So everybody really knows how the phenotype of ageing looks like. So we right now understand the molecular and cellular mechanisms behind it. So if you measure these kind of molecular and cellular mechanisms in the human body, you can determine the biological age of somebody.

This is actually what I did in the Netherlands a few years ago, where we asked 60 year-olds to donate some blood and some skin, and also looking at the outer side, so looking at their face and their wrinkles and how they look like. So what we did, for example, we determined the biological age in the skin by measuring senescent cells. Senescent cells are the cells who are very old and do not replicate anymore, very old, ugly-looking cells in the human body. And if you accumulated more of these senescent cells, your phenotype on the outer sides, if I look at you, you look older, you have more wrinkles, and you are very likely to have diseases.

ANDI HORVATH

Now, I'll come back to these senescent cells, the cells that stop dividing, later on, but I do want to ask about age-related diseases. It seems as though when you hit a certain decade you are prone to certain cancers. Tell us a little bit about how these diseases are connected to the age groups. Is there a correlation, or is there a causation?

ANDREA MAIER

That's a good question. So we know that chronological age is the most important risk factor for age-related diseases. Now, when we talk about age-related diseases we're talking about hypertension, diabetes, osteoporosis, sarcopenia, dementia, etcetera, etcetera. We know all these age-related diseases being associated with a lot of costs, of course, for the healthcare system. So with the chronological age we accumulate these age-related diseases. So 60 percent of our society at the age of 60 have age-related diseases, two or more, and the data show that at the age of around about 45 as a female and 49 as a male we have the first chronic disease, so this is very early. So the first 45 years of our life we are in a healthy shape and then we have the age-related diseases from the age of 40 to 50 onwards and then we accumulate these.

So then of course is the question, is it just organ failure by itself ending up with a disease, or is there a common pathway? And the common pathway is ageing itself. So we know why we age. It's an accumulation of damage in all our organ systems and we will have an age-related disease in the end if the damage accumulates in one or the other organ systems. It seems to be a causal relationship, because in animal systems, if animals have age-related diseases and we remove the ageing factor and we intervene in the ageing system, then the age-related diseases are cured and these animals look younger again and they are younger and their functionality is better.

ANDI HORVATH

So how much of ageing well or longevity is really due to luck in the genetic lottery

and therefore some people seem to be more resilient to bad lifestyles? Tell us about that.

ANDREA MAIER

There are huge projects around the world, especially in the US and Europe, right now looking at the genotype of human beings, to really see and disentangle what is the genetic make-up being associated with longevity and what are the other factors in the contribution, for example, of the maintenance of our human body and the use of our human body, which means what is the lifestyle contribution. So actually we now think that round about 20 to 30 percent of the longevity is due to our genes, which means that 70 to 80 percent is not genetically related. Which if I speak to either colleagues not in the field or to the general population as, hey, what's the genetic contribution of your genes to your longevity, most of them will say, it's 80 - 90 percent. I can't do anything about it. This is not true. So we spend a lot of money in [the]CGA study really looking at all the DNA sequences and we just thought that 20 to 30 percent related genetic make-up the reason why you are ? in the end why you are older or growing old.

ANDI HORVATH

I'm curious from the evolutionary perspective, comparing perhaps even humans to animals, the reasons - I've heard the reasons humans live beyond their reproductive years is that it was selected for as grandparents can help the survival of the tribe or the clan. Does that hold water, those theories about why humans can live way beyond their reproductive years?

ANDREA MAIER

There's a theory called the grandmother hypothesis and for years we really thought, okay, the only need that mothers should be on earth after reproductive phase is caring for their children. Actually there was a very nice study in Ghana in Africa showing that this is not true. So independently of having a mother there was no relationship with childhood longevity, so if they really survived the first years. So having a grandmother, of course, gives fun in your life, but doesn't mean that you will live longer or your life expectancy will be higher. But I think the books are not closed, as very often it occurs in research.

ANDI HORVATH

Good news for nan and pop.

ANDREA MAIER

There is still hope. Maybe related to that, if you care as a grandmother or grandfather for your grandchildren, your life expectancy will be higher, because you care for somebody and you are able to do that. So this is very positive. So grandmothers, grandfathers listening, that's a good sign. You will be very likely to live longer.

ANDI HORVATH

I'm Andi Horvath and you're listening to Up Close. In this episode we're talking about ageing of our cells and a future of ageing well with gerontologist, Andrea

Maier. Now, Andrea, take us to the level of the cell. Tell us more about the ageing process there. Can we tell, say, with a skin cell where it's in the life span, because cells have a limited life span, don't they? What are the clues for ageing and the status of health, because there are two issues there, isn't there?

ANDREA MAIER

So since 1960 we really know that cells cannot replicate enormously, so there is a limit of their replicative capacity. That was Leonard Hayflick discovering it and actually I spent my PhD on that, really seeing if the replicative life span of cells is associated with either the chronological age of persons or the biological age of persons, so the rate of the ageing trajectory. And actually I showed that neither the chronological age nor the biological age is associated with the replicative life span of in this example, fibroblasts. So that was very disappointing. But if we look in situ, so if we take biopsies from either the skin or the muscle or the heart or the brain of human beings we can look into the hallmarks and see how old cells really are.

So we have molecular markers to distinguish between the ones - the cells - who are very young and who are older. For example, we can measure the telomere length. So the telomeres are at the end of the chromosomes and with each replication the telomere lengths will shrink. And if a cell has a short telomere length, then it's very likely that that is a really old cell. We also can look at the quality of the telomeres, for example. The quality of the telomeres, independently of the length of the telomeres, is a very good indication of the health of a cell. But telomeres are not the only ones. We can also look at mitochondrial function. Are the engines of our cells working well? We can also look at, for example, epigenetic changes. Epigenetic changes are changes on the DNA. It's like a layer of sugar on the DNA. And dependently of our lifestyle, of our environment, this epigenetic layer can change during lifetime, which is very, very interesting.

It seems that we can also influence these epigenetic changes. A very interesting topic in the ageing research is the accumulation of senescent cells. The senescent cells are the ones who cannot replicate anymore, but they are still in our human body and they accumulate with a lifetime. And these senescent cells, they influence the microenvironment negatively. What they do, they just lie in our organ system and they secrete some signals and most of the times these are pro-inflammatory signals, which means inflammation is no good, and say, hey, I'm a senescent cell. I need help. There is something wrong with me. Sending these signals and therewith negatively influencing the environment by inducing inflammation. This inflammation is very, very likely to induce, for example, other diseases, like atherosclerosis, like cancer, etcetera. So now we know that the ageing mechanisms and ageing itself and the accumulation of damage will induce age-related diseases. If we look in organ systems with diseases, we see more of these senescent cells, cells with short telomere lengths, with telomere damage, so all of these old, accumulating cells in our human body.

[Over speaking]

ANDI HORVATH

? it's interesting.

ANDREA MAIER

Yeah.

ANDI HORVATH

So what exacerbates these various assaults on the cells. Like, we hear a lot about ? as you mentioned ? the inflammation compromising our health status and/or ageing. But what in particular triggers that inflammation or the accumulation of senescent cells?

ANDREA MAIER

Basically it?s living. Like, we are breathing right now, our heart is beating, so there are ways we use our organ systems and by using our cells there will be damage on molecular level because of the use of our human body.

ANDI HORVATH

Right, simple wear and tear and damage and repair.

ANDREA MAIER

That?s true. So, independently of your genetic makeup and how you treat your body, so how you use it and how you maintain it, you will accumulate more of the damage compared to others. So it?s not only accumulation of the damage, but also repair of the damage.

ANDI HORVATH

Now, can molecular markers be used to assist us in a clinical settings to measure where the ageing or health status is and therefore can we actually counteract it - can we antagonise and prevent ageing at that cellular level?

ANDREA MAIER

So these are two questions. The first question, can we really measure it? Yes and no. So actually this is really the question we have and we try to answer in our lab. So on a physical level we can determine the biological age, for example, by measuring grip strengths, by measuring endurance, by measuring cognitive function of the human being. This is the comprehensive geriatric assessment. We really work on the biological geriatric assessment. We really look at the molecular level if we can determine the biological age, not only at the phenotypic level and the functional level, but on the molecular level. And this is not very easy right now, so right now we are looking at the molecules really being associated with the clinical phenotype to really help the clinicians in better understanding of the biological age of that human being. And this is very, very important, because in clinical practice we always have to make decisions, do we go for an intervention, or don?t we go for an intervention? Do we take the risk of a side effect? For example, giving chemotherapy if somebody has cancer. Is that person and that human body able to cope with these stressors? So we really try to get a model where we stress cells, see if it relates to the human body, to also help clinical decision-making. So that?s the first part. So we are not there yet to really introduce it into clinical practice, but we will be there in a few years hopefully. The second question was, can we intervene? Of course, there is also the

answer, yes and no. Yes, we can in animal models and we maybe can also already in human beings.

So if we look at pharmaceuticals being used in animal models, for example, by removing senescent cells, these are really success stories. Since already five years we are able to remove senescent cells, so the ones who cannot replicate anymore, from, for example, mice. If we do that, these mice are young again, their functionality is better, their cognition is better, their organ makeup is better. So we can already rejuvenate old mice into young mice. If we look at the human beings, this is a little bit more difficult, because right now we try to get the animal pharmaceuticals into the human beings. There will be a Phase I study next year, already trying also to remove the senescent cells in human beings and look at side effects. However, we already can do something.

There is a very, very nice paper showing that if 50 to 60 year olds increases the physical activity level and reduces weight then senescent cells will be removed. So they did a study. They took blood and skin biopsies beforehand and, of course, after the intervention and the result of the study was that the overall telomere lengths is longer after that physical exercise, the senescent cell load was lower, so there was a kind of rejuvenation also in human bodies already by introducing a very healthy lifestyle.

ANDI HORVATH

So we can't escape that old chestnut of diet and exercise, can we? Yet it's so hard to implement in some societies, or is it?

ANDREA MAIER

We are very, very lazy and we are a very lazy species and we just have to overcome that. And actually at the moment we do a study, that's in Europe, a multicentre study, funded by the EU really to make life difficult. So what do I mean with making a life difficult? It's making life physically difficult. So introducing a lot of physical activities, for example, while sitting or while doing nothing normally. So we are sitting right now and hopefully the listeners, they are running and listening to this broadcast. But already by sitting here we could be physically active. For example, we could strengthen our muscles already by sitting. We could try to stand up only using one leg compared to using two legs, what we normally do. If we are standing and brushing our teeth, for example, we could do that on one leg and strengthening our balance. So there are huge opportunities independently of going to gym classes, already introducing it into the normal life to strengthen not only your muscle strength and the balance, but also introducing more physical activity in daily life and therewith delaying the ageing trajectory and therewith preventing age-related diseases and, as a side effect, living longer.

ANDI HORVATH

So it sounds like we can't escape it. But I've heard of so-called senolytics, or therapies that are supposedly anti-ageing. Tell us more about those.

ANDREA MAIER

So the senolytics is seno, so it's old, and lytics is removing something, so removing

senescent cells. These are the cells already being tested in mice since a couple of years. So if you remove senescent cells from a body, and in this term animal bodies, these animals will be younger in the end. They regain their functionality, they regain their cognition and their physical capability to, for example, work. Nobody knows, of course, if quality of life in these animals will improve, but the physical and the cognitive function improves. So this is very, very likely that, like antibiotics, like chemotherapy, this will be a new drug introduced in clinical practice in humans to remove senescent cells or to stop the accumulation of senescent cells. So either removal or stop the accumulation of these senescent cells.

ANDI HORVATH

So how do humans compare to other mammals when it comes to ageing? I know we use mouse models in the lab, but give us some perspective of the mammalian system and where it could help humans.

ANDREA MAIEROf course human beings are not mice and we are not flies and we are not *C. elegans*. However, we share - if you look at the genetic make-up, not 100 percent of the genes. So, in terms of the mice, it's like 30-40 percent. We are not mice. However, if we really look at a very important genetic make-up, the insulin signalling pathways, we share a lot of these pathways with other animals. And if you look at different pathways, one we share more with *C. elegans* or with *Drosophila*, for example. However, there are also a lot of studies with monkeys looking, for example, at caloric restriction and we have a lot of in common with monkeys, with primates. So we cannot translate one to one the results of mice studies to human beings, but we can learn a lot in terms of the pathways. If we then translate it either to dogs, to pigs, and to monkeys, we can translate it.

So also if you look at the evolution of other research, for example in oncology and cardiology, we learn so much from the animal systems and in the end, of course, we have to prove that it's also true for human beings. But it's very likely that we learned a lot and in the end we can translate it into human beings. Actually there are already some studies now ongoing, especially in the US, in trying to antagonise the ageing process with medication, with known medication already in human beings. For example, there is a trial with metformin in thousands of Americans, looking if metformin there was interfering with the glucose handling system, if we can delay the ageing process.

ANDI HORVATH

Metformin, is in fact a diabetic drug.

ANDREA MAIER

Yes, that's true. So we already give it in human beings, of course, for diabetes. Now it's given for the ones not having diabetes and the idea is, if you lower your glucose level, therewith your cells are not exposed to a higher glucose level and therewith do not age so rapidly. So in non-diabetic human beings we try this drug to delay the ageing process by lowering the glucose levels.

ANDI HORVATH



Just remind us, *C. elegans* is a?

ANDREA MAIER

It's a very tiny, little worm, living for three weeks, and if you extend the life expectancy of that worm, we can do that by 100 percent and the worm lives six weeks.

ANDI HORVATH

*Drosophila*, they're the flies.

ANDREA MAIER

Yeah, that's a very, very nice fly. A lot of ageing researchers make use of *Drosophila*.

ANDI HORVATH

I'm Andi Horvath and our guest today is gerontologist, Professor Andrea Maier. We're talking about understanding and enhancing wellbeing in ageing societies here on Up Close. Andrea, are there different social attitudes to ageing around the world? I know you were surprised when you first arrived in Australia that we were still debating if we should allow voluntary euthanasia and there are some nations who have moved on as to when, and not if, we allow euthanasia. Tell us about that.

ANDREA MAIER

That's a difficult topic, because we are talking about the end of life decision. So is somebody capable to just say, okay, my life is finished, and therewith I would like euthanasia? So, as you know, I'm coming from the Dutch system. Actually, I'm German. In Germany we really don't talk about euthanasia, but having lived for the last 13 years in the Netherlands I really learned a lot. So we have a huge debate about euthanasia and actively practising that also in the Netherlands. So if there are medical conditions which really interfere with your quality of life then you have the right, in the Netherlands, as a human being to ask for euthanasia, which is of course not the case right now in Australia. And the Netherlands is even more progressive. Right now we have the debate if even we can ask for euthanasia without chronic diseases. For example, if somebody is 95 or 100, having seen everything, without any chronic disease, we have the debate, is that person [is] allowed to ask for euthanasia?

ANDI HORVATH

Is it right to think of ageing as a disease?

ANDREA MAIER

I would say, yes, and it's a disease with a 100 percent prevalence, because everybody is suffering. Why do I call ageing a disease? Because we can antagonise ageing and we can therewith rejuvenate a human right. If we do that, then we should call it a disease because we are interfering. If we in the end would like to have an anti-ageing drug, then we should treat the disease.

ANDI HORVATH

Andrea, tell us about the initiatives that you've been involved with. I know you've been inputting into the European Union's initiative in addressing the ageing population issues. Tell us about those.

ANDREA MAIER Actually in the last 10 - 15 years the European Union has spent a lot of money into the ageing research. So the European Union has a goal to extend in the whole population a life expectancy of two years, not only two years, but two years without disease, so a very, very healthy two additional years. So that's a goal. We had a lot of discussion in the EU so how to age, how to treat ageing societies. What is the contribution of an aged one in society? My group is still involved in EU projects. For example, really defining nutritional needs, physical needs of an ageing society in different set-ups. So most of our studies we do always within the EU, multi-centre, different countries, which really improves our research because we do it multicultural and we do it with different researchers, different opinions, different cultures, and different cultural backgrounds, which also means that our results will be translatable also to other countries.

ANDI HORVATH

How big are the economic benefits in the communities who age well?

ANDREA MAIER

I can't tell you actually the numbers, but we know that especially in the last year of life we spend a lot of money in improving our life at that stage. Actually, we also know that if we are ageing healthy then, of course, the productivity during our lifetime as an employee is much higher. So it already starts in very, very early ages that, if we prevent age-related diseases, we have more productivity for society, but also, of course, for the individual, having a happier life without diseases and all the medications.

ANDI HORVATH

Now, it might sound like I'm trying to get out of diet and exercise again, but I do have to ask?

ANDREA MAIER

You really have to do that.

ANDI HORVATH

?what about technological enhancements to my biology as a solution to ageing?

ANDREA MAIER

At the moment we have a change of lifestyle, which is very important to do, because we already know that if we change our lifestyle, so more physical activity, better diet, including fruit and vegetables, etcetera, we all know this, not smoking, not too much alcohol, that we will extend our healthy life expectancy already if we do that by around about 10 - 15 years. That's massive. None of other drugs, for example cholesterol inhibitors, do that. So it's so powerful already, lifestyle. So that's the first

thing. Then there are the other developments in really interfering with the ageing trajectory. For example, the discoveries of senolytics which will in the end reach the human body and the human being. That's my prognosis. However, I think it will always be a combination between a good lifestyle and then adding anti-ageing drugs. We have the same discussion, for example, in endocrinology where we give anti-diabetics in persons who do not lose weight. So I think if we talk about anti-ageing drugs we should combine the good lifestyle together with other medicine, new drugs to really prevent age-related diseases and enhance our lifespan.

ANDI HORVATH

Andrea, there are skills in getting your body healthy, but there's also a mindset that can get your body healthy and sometimes our mindsets undo us.

ANDREA MAIER

Yes, very true. So there is a very nice study looking how people rate their life, so how happy they are. So if you have a happiness scale from zero to 10, Dutch people, for example, give an eight for happiness, how they feel. We are very happy people. There is a study showing that if you are more happy, then also you have less age-related diseases. It doesn't mean that being happy prevents age-related disease. Of course, there can also be lifestyle factors, because we know that happy people also do the better things. They do not smoke, etcetera, we all know this, but it's related with less age-related diseases. I would like to tell you another story. A dear colleague of mine, she asks people if they are married, if they are not married, and if they are happily married, so three choices to answer. Then they look at the immune system and what she was able to show is, after giving a vaccination and then looking at the response of the vaccination, the ones who said, I'm happily married, had the best response to the vaccination. So there is a distinction in the ones saying, I'm married, or, I'm happily married. So here you really see a possible influence of happiness or how you feel and how you deal with life to the human body, to the cells. So cells may react really on your emotional characteristics and your feelings. I'm so glad that you are smiling. You are such a happy person.

ANDI HORVATH

Again, that's extraordinary. I just find that extraordinary. So really, it's not just connectedness and community usefulness, it's happy connectedness and usefulness.

ANDREA MAIER

That's true.

ANDI HORVATH

Andrea, thanks for being our guest on Up Close.

ANDREA MAIER

Thank you very much. Enjoy life.

ANDI HORVATH

We've been speaking about understanding ageing with a view to optimise ageing well with Professor Andrea Maier from the University of Melbourne. You'll find a full transcript and more info on this and all our episodes on the Up Close website. Up Close is a production of the University of Melbourne, Australia. This episode was recorded on 12 April 2017. The producer was Kelvin Param, audio engineering by Gavin Nebauer. I'm Dr Andi Horvath. Cheers.

#### VOICEOVER

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