Transcript of **78th Paget lecture 2014: The Science of Healthy Ageing**, given by Professor Dame Linda Partridge, director of the UCL Institute of Healthy Ageing

00:13 Thank you very much Bernadette for a very kind introduction and thank you to Fran and the other organisers for the invitation to give this Paget Lecture. It really is a huge pleasure and honour to do it in the context of these inspiring awardees and also at the end of a list of really alarmingly robust predecessors, so thank you very much for the invitation.

00:36 So the theme of the lecture as you've heard is aging and I think ever since people have started writing down their ideas, there has been notions of immortality of being able to turn back the clock of time on aging, putting the old Rembrandt back to the young one and having perpetual youth. Just down the road at the Royal Society, I think one of the first of the first scientific statements of this came from Robert Boyle. He made a wish list of the things that he thought that science should solve, the most important scientific problems but the ones that were probably going to be the hardest to crack.

01:13 The two top items on his list were the prolongation of life through recovery of youth. He didn't live long enough to see it but the prolongation of life is something that has been happening very steadily in developed countries since the middle of the 19th century. It's illustrated here by the work of two demographers who have plotted against the year in which the births took place, life expectancy for the country that was the world leader at that time. So to start with this was the Scandinavian countries and went through various others, in the middle it's the Far East now, I think Hong Kong for women and Japan for men just at the moment.

01:52 And you can see this astonishing steady increase, it's gone up about 2.5 years per decade. The horizontal lines here simply represent various individuals and organisations, prediction of where the trend would top out, what the intrinsic limit on human life span would turn out to be. You can see its shot past all of them, this was the basic point of this article and it continues to be true. There is no clear signature in the demographic data of what the limit will be. Although in practice this trend at least in some countries may turn back with the tide of obesity and metabolic diseases amongst the young particularly.

02:30 But I think it's a trend to be celebrated because of improvements in civilisation, in health care, different things at different points in this trend, immunisation, antibiotics. Towards the end, the increases in life span are happening almost entirely in the elderly part of the population. As a result of these things people are staying healthier as they age and living longer.

02:56 The world record holder as some of you of may well be familiar with her, a French woman, Jean Carmel. She dies at the age of 122 and about a half and she actually met Van Gogh in her father's shop when she was young, he used to go there to buy paint. It's interesting I think to speculate about her, what her secret was. She came from a very long lived family and human life span is about 85% heritable although that heritability is concentrated in particular families. On the other hand she wasn't a terribly good advertisement for a healthy life style which we might expect to see. She actually gave up smoking when she was a 119!

03:39 So who knows what her secret was, but that's the positive side. Of course the aging, the increase in life span is coming with some downside, some of them temporary and some of them harder to crack. One is this one simply the change in age structure that's happening in most developed countries. So what we have got here is a stack of the different age classes the oldest at the top the youngest at the bottom. For 1901 on the left and 2010 on the right, this is just the British population. You see the Christmas tree shape gradually going apple shaped.

04:13 This is very typical for most developed countries including European countries. I noticed the Pope the other day described as elderly and haggard in Europe. This creates with economic problems particularly to do with pensions but also generational conflict over wealth and so on. For this evening's topic which is the science of aging, the problem is this one, which is that increase in age is the major factor for chronic and killer diseases so dementia, cardiovascular disease and cancer. These are just statistics from various UK and European sources that show the trend with age for the 2 sexes.

04:57 In cardiovascular disease there has been considerable progress and quite a bit with Cancer, the one that is proving really intractable at the moment is dementia and it's both very prevalent and very expensive. So these were just some figures forecast a few years ago now and the trend hasn't changed since then for what the prevalence of dementia in the UK will be by 2051, it's about 1.7 million people and that is not just for Britain but for developed countries generally, it's absolutely enormous and a significant proportion of the national budget potentially going on care.

05:34 There have been number of failed clinical trials for Alzheimer's very recently so it really is proving a hard one to solve. Interestingly and I know that there are some funders here who might be interested in this. Research into Dementia is really relatively under-funded, if you look at the cost per patient per year of treating, for Dementia it's much higher than for the other three, cancer, stroke or heart disease but if you look at the funding it is way down and so relatively I think we are not putting enough into this problem.

06:08 But coming on to the science, given that increase in age is the major risk factor for these conditions, one obvious way to set about potentially trying to tackle them might be to intervene in the underlying aging process itself because it's the common risk factor for all of them if we could intervene in that process then perhaps we could get rid of the major risk factor for all of them simultaneously and push back their instance or ameliorate it.

06.38 Until recently the prospect for doing that have not looked particularly rosy. One reason is that aging is a very complex process. So this is simply a picture of what was actually originally a table produce by a pathologist called George Martin and he listed the different human tissues and the things that can go wrong in them during the aging process. What you see is a picture of many different things happening within a single tissue and quite different **thi**ngs in other tissues. It looks as though what you have here is each tissue in parallel encountering different kinds of insults of daily living and developing damage in pathology accordingly.

07:19 There is no single aging process here, it looks unlikely that a simple intervention like a single gene mutation or a drug would be capable of capturing all of these or even a lot of them simultaneously and slowing them down. It looks like the case for at best piece-meal intervention into different problems. By the same token I think people have often though that a similar argument to these creatures, the laboratory model organisms because they are of course the real work-horses of modern bio medicine. Often if we want to understand a process we start simple either with a bacterium or a single celled. You carry it like the list at the top left, once we work there we go and look at the multi cellular invertebrates the worm, the fly and only then the more complex mammalian system.

08:14 And that whole process works because of the astonishing evolutionary conservation of many biological processes. For genetic transmission, expression of genes, metabolism, many things are so conserved that we can take a gene from one of these organisms or even from a human and put it into another and it works just fine in the new context, the function is that conserve.

08:38 It seems perhaps a little intuitively unlikely that's going to be true for aging. For a start these organisms have very different life span, the worm is about 3 weeks and the fly is about 3 months, the mouse is about 3 years. They have very different diets, they undergo different stresses, the conditions in which they live, their life histories are very different, three of them are cold blooded, why should they encounter the same kinds of insults of daily living, why should their problems as they age be the same?

09:09 Reasons ageing research has become really exciting in recent years is because of the realisation that at least to some extent those pessimistic ways of looking at the ageing process are wrong. The aging process does turn out to be malleable. It was first discovered through the work of the person who is my personal hero in this whole subject area who was called Michael Class and he did a very simple experiment with the worm.

09:37 What he did was to ask whether if he mutated, just randomly mutated the genome of the worms, whether he could recover long lived strains. So can a mutation in a single gene make the whole worm live longer? And he found that he could. This is an example of one of these mutations, actually this is more modern data collected by one of my colleagues at UCL, David Champs. What we have here is a single gene mutation, I'll explain what it is in a minute, with the control survival curve in blue and the mutant in red.

10:09 And you can see that there is an absolutely enormous increase in both the medium and the maximum life span of the mutant animal. Very interestingly this effect turned out to be evolutionary conserved because what we have here is a mutation in a single worm insulin-like growth factor receptor, a single pathway whose existence in the worm was not suspected actually until this gene was cloned and sequenced. What we are looking at here is a set of signalling pathways much more familiar in the context of control, of growth during development and in controlled metabolism but now turning out at least in the worm to be important in determining his life span

10:52 And this effect of insulin -------signally turned out to be conserve first to *drosophila* and then to the mouth. These are just some of the mutants, here you see the fly, in the middle this is

a mutation in the gene called Checo which encodes a protein which just sits just inside the receptor in the cell. You can see the nice extension of life span in the flies that have one either one carpean or injured both copies of the checo gene in red, quite a big extension of life span. On the right we have a checo mouse, so this is from the lab of my colleague Dominic Withers involved on a Wellcome consortium working on these mutations.

11.31 You could see that in this female mouse who has lost both copies of this Checo equivalent, again you see this nice increase in life span. One of the odd things about the pathway is that when we mutate it generally it extends life span more in females than in males, we don't know why that is at the moment but it is quite a consistent feature. Very importantly although life spans are a nice read out, it is the sort of gold standard for whether you have actually managed to slow down the aging process, it's also quite a blunt instrument because really the aim of this research is to try and improve function and health during aging.

12:08 So there has been a lot of work on these mutants, looking at whether what we are seeing here is simply an extension of the moribund period the end of life or an improvement in health. For the two invertebrates there are a number of read outs one can use, usually based on mobility but also learning ability in tactness and function of individual tissues and so on, and these mutations do improve the health and function.

12:33 Very importantly in the mouse this particular movement was quite thoroughly phenotype and what they found was the sort of broad spectrum improvement in health that we hadn't been expecting to see. So these mice as they age, they actually start out life slightly insulin resistant when they are young, they look as though they might get diabetes when they get older. In fact as they go through middle and old age they cross over with the controls and later on their glucose handling and insulin sensitivities are very much greater. They have got a better immune profile, more naive T cells, they maintain their motor performance better, they can hang on to a rotating rod better as they age and they also show a delayed onset of some specific aging related pathologies that these mice get. So they get less osteoporosis, less cataract, you can see on the control mouse the right eye as we look at it has got a cataract and also you can see ultradermatities on the head and the nape. About 40 % of the control strain get that at some point during aging. The mutant mice are completely free of it, we have never seen a case.

13.43 So these systems obviously don't have a connection with each other, all improved by this none lesion and a single gene. I think it is this sort of finding that's making people stop and pay attention. Of course what is important here is this going to be the case in humans. There are a number of studies of aging human populations looking both at their physiological and other characteristics but also at their genetics. The way that is usually approached because of limitations on sample size, is to look in humans at the genes that are the equivalents of the one that have turned out to be important in the animal studies.

14:25 To look at whether particular variants of those genes are associated with survival to a late age. These are just some of the results from those kinds of studies. You will see on the left here this foxo comes up a lot, foxo is a particular type of transcription factor that turns expressions of genes on and off. They are key players in this insulin growth factor signally pathway. It turns out that in humans key genetic variant in two of them are associated with

survival to 90, 100 or even beyond 100. So also are variants in the insulin like variant receptor, that's also turned out to be an important player. Its early days but the genetics is quite encouraging and particularly the physiological characteristics of these survivors. It really does look as though the insulin, IGF and also associated target of Rapamycin pathway are very important in determining the health of people as they get older.

15:30 So what we have got here as I've said is a signalling network that normally senses the nutrients status of the animal, the presence of growth factors, certain stresses that it might be subject to and then decides how much of metabolically expensive processes can be afforded. So how much growth, how much reproduction, what type of metabolism are now turning to be important in life span. Almost certainly what we have tapped into here is the physiological mechanisms that bring about the response to an environmental interventions that has been known about for a lot longer which is dietary restriction.

16:11 It was first discovered in rats way back in the 1930's that if you put the animal on a diet, so you force it to eat say 60% percent of what the rat would like to eat if say left to choose for itself, you see a big increase in life span and very broad spectrum improvement in health during aging. That's also turned out to be true in mice and then subsequently in all of these, both model and highly non model organisms seems to be a very evolutionary wide-spread response and recently there has been a couple of studies in the United states on rhesus monkeys, very long term studies because they live for up to 40 years, so pretty heroic work to do it.

16:54 From the first one to be published it's on the left here and in this study there was constant study they found both an increase in life span of restricted monkeys , they took them down to about 70 % of the intake of the controls and a huge protection against various cancers, diabetes, there was virtually no diabetes in the dietary restricted monkeys, improved cardiovascular health and also improved cognitive performance. So again this broad spectrum effect. The second study actually didn't find any increase in life span but it did find health and disease improvement, very similar to the first study and the difference between the two I think would be explained quite easily by details of the way they were done if anyone wants to discuss it later.

17:45 In humans there isn't a huge amount of data, the main reason being that most humans don't have the self-discipline to subject themselves to dietary restrictions, it's an extremely difficult thing to do, to actually eat little enough to get health benefits. There are a few individuals who are prepared to do it, mostly men interestingly, there is quite a sex bias there. This was just an example of one study where they looked at voluntary restrictors and looked at them once they have been doing it for about 7 years versus controlled who were matched for various characteristics.

18:24 In this particular study there was a big improvement in eight different markers that are risk factors for arteriosclerosis. We don't know with humans really yet how effective this intervention is going to be, there is a very big long term study just set up in the United States called Calori, they have a web page and they have just recruited their cohorts. I think it's going to be very interesting to see the outcome of that one.

18:54 That's just a brief account of the developments in the research area over recent years, what I would like to do for the next bit of the talk is just talk a little bit about dementia and the nervous system and the way that some of these interventions into aging may give us some hope that there could be ways of preventing dementia and specifically Alzheimer's disease.

19:19 I do a lot of my work with fruit flies, *drosophila*, also with mice but the work I'm going to tell you about that we've been doing is mainly with the fly and then I'll include some mice work as well. So what we wanted to do is to develop a fly model of the normal form of Alzheimer's disease. So as I'm sure most of you are very well aware, it's the most common form of dementia and at the histological level if you look at the brain of patients then there are two very obvious markers of the disease. One is amyloid plaques which are made of a little peptide called *Abeta* and the other is neurofibrillary tangles which are inside the cells, plaques are outside and the tangles are made of a protein called TAM.

20:02 Unfamilial cases, there is early onset Alzheimer's disease which has a clear family pedigree associated with it but the vast majority of cases are actually sporadic and with no previous obvious risk factors apart from aging which is the major risk factor for the disease. So what we wanted to do in the fly and these are the people who did, 3 post docs and a grad student called Ian Rogers, was to deve*l*op a fly model of the sporadic late onset form of the disease.

20:35 So what we decided to do was to produce a fly that goes through its development completely normally, so it come through to adulthood fine but then we arranged to turn on in the nerve cells of the fly this peptide, this amyloid beta, a very short peptide that's associated with the disease in humans so we actually used a human peptide. The fly has an equivalent of protein that in human gives rise to the *Abeta* fragment by cleavage. But if you give the fly protein that bit is not conserved and it's not toxic. So what we are doing is introducing a new potentially toxic protein into the brain of the fly.

21:15 To get it expressed only in nerves and only in adults we used a system for gene-less expression in the fly which is derived from yeast, it called the GAL4-UAS system. What you have is a GAL4 driver which drives the expression of the gene that you are interested in and you can put a promoter in front of it, in this case *LOV*, which is expressed only in nerve cells. You then cross that fly with one which is carrying the upstream activating sequence which is driven by GAL4 and then expresses the AB to toxic peptic

21:48 It is only expressed in the presence of an inducer, if we put these two together in the progeny and just leave them nothing happens. So they can come through development normally but we then add to the food the inducer which is just a steroid hormone a drug called IU4A6. It's actually the active constituent of the morning after pill and if you add that now the GAL4 really binds to the UAS and drives expression. So what we can do is to confine expression to the adult neurons of the fly.

22:18 So we did that with a known toxic form of *Abeta* and had a look at what happened to the fly. First thing was there was quite clear evidence of neuro-degeneration. This is shown here what you are seeing here is the mosaic appearance of the eye of the fly, this is made up of lots of parallel photo receptor, what you can see at the bottom is one of the photo receptors

the one in the middle has actually been lost in that fly, whereas they are all present their should be seven in the top *fly*

22:48 As the flies get older, we have got two controls here , we have the driver to make sure that it's not doing anything naughty to the eye of the fly, we have got a non-toxic form Abeta and this toxic one that we are interested in. You can see that as the flies get older what we see is a progressive loss of the photo receptors when the toxic protein is present and in fact by day 25 they are all dead so we couldn't measure it. So there is clear neuro-degeneration in the flies. We can also show that there is a decline in the function of the nervous system using electro-physiology. So to do that we can use this particular part of the nervous system in the fly which mediates the escape of the response to a frightening visual stimulus.

23:34 So it is perceived at the front end and then goes back through those two giant interneurons in red and either synapses directly with the motor-neuron to *drive* ……muscle which depresses the leg so the fly jumps or indirectly through an interneuron with the motor neuron that **innervates** the dorsal longitudinal muscle which is the flight muscle of the fly so it then flies away

24:00 this is a simple and very well characterized system, we know what the synapses are made of and the exact anatomy and we can put electrodes into the eye of the fly and record from the muscles. So we can stimulate through the eye and then asking the muscle how well is the electrical impulse being transmitted through this system to affect the escape response. What we found was in these Alzheimer's flies it's impaired as the flies get old. You can look simply at how long it takes the impulse to get there, the latency and you can see that in the old files, here the red the Alzheimer's flies are taking longer. You can also give the fly repetitive train impulses and see how many of them are picked up by the muscles which is a measure of how quickly the system recovers from a previous impulse and can respond again.

24:48 Again very obviously as the flies get older you start to see an impairment in flies expressing the toxic protein so definitely an impairment of function and we know actually that this is to do with impairment of synaptic function in the system. We can also do a behavioural output with the fly, one of the things about flies is that they like moving upwards, generally you usually find them at the top of the ……., so you can measure the extent to which they are capable of exerting that preference by banging onto the bottom of the …….. and looking how long they take to get to the top.

25:25 This is shown here from the controls on the left in the ….. flies at the right and you can see that the wild types are coming up nicely, whereas although they are moving the Alzheimer's flies are stuck at the bottom, so there is a behavioural impairment. This is just a quantification of that, so it is a response that also go down with ageing. Older flies don't respond so readily and you can see that the age related decline is much sharper in the Alzheimer's flies and also they show a decline in life span.

25:58 I think here we have a quite reasonable fly model of many of the things that are known to go on in the nervous system in mammals during ageing. We used it to ask two very simple questions, one of which is, why is ageing a risk factor for Alzheimer's disease, what is it that is actually going wrong in the neurons of the fly when this protein is present and why is it

worse when they are older. The second was, can we rescue any of these phenotypes that I've told you about with auto …….GNF signalling, the kinds of mutants that also extend the life span of the fly. So as far as why is aging a risk factor goes we can look at this at the molecular level, by asking first of all how does the fly handle the toxic protein. Is there a problem with getting rid of it from the cells?

26:48 We can also ask, supposed there is a fixed amount of the protein present, do the ageing neurons respond worse to the presence of that peptide? So those are the two experiments that we did with this set up. So again as I'm sure almost everybody knows there are two stages in gene expression, when a gene is expressed to produce a protein there is an immediate marker called RNA and then eventually that goes on to translation to produce the protein and in this system what we can do is to arrange to give the flies a pulse of the RU486 inducer that produces exactly the same level of the RNA in flies that are induced when they are young, in 5 days old or at 20 days old. The minute that we remove the inducer, almost within hours all of the RNA disappears, so intermediate molecule is a very acute response to the presence of the inducer.

27:47 We can look at what then happens to the Abeta peptide in these neurons and I think what's interesting here – so this is the flies after the inducer has been removed, so there is no further RNA present. You can see that in the young flies there is a much lower level of the protein. Neither of them manages to clear this protein it's insoluble after the inducer has been removed, it stays the same for the rest of their lives but its level is much higher in the flies that were induced when they are old. For some reason they can't clear this protein when it's produced even though presumably it was being produced at the same level. We think that is to do with a decline in the activity of the proteasome in the nerve cells, it very clearly does go down with the age of the fly.

28:29 The result is that this brief pulse of induction at different ages actually result in a major reduction in life span in the flies that were induced later so it catches up with them later on. So that's one reason the nerve cells have a problem, they can't clear the protein if it's present. It also turns out they have a problem with the protein itself even if it's present at the same level as in the young fly – and this is shown here. Again what we did was to titrate this system with the dose of 486 that we gave them, to produce flies that had got the same level of that insoluble protein left after the RNA had disappeared with induction at 520 or 30 days of age. So we are asking is it worse for you to have this stuff present entirely in the old part of your life span, we looked at what happened to them subsequently.

29:24 You can see that on the right the later it is induced, the worse off they are with respect to controls of the same age. So it's having a much more toxic effect on the neurons of the older flies. So there seems to be two different things that go on, we don't yet know the reason for the second effect. We are doing a lot of work on this at the moment but one of the nice things about the flies of course is that you can through these experiments relatively quickly.

29:52 There seem to be clear molecular reasons for why things go wrong with age. The second thing we have been looking at is the potential rescue of the Alzheimer's disease pathology with instant pathway mutants. We have taken a number of different approaches to this

with different mutants, I'll just tell you about one of them because I think that it is particularly relevant actually to the human condition and therefore of the greatest interest. This involves a protein called Glycogen synthase kinase 3, GSK3 – much studied. This is very heavily implicated in the etiology of Alzheimer's disease in humans. Although in quite a complicated way that doesn't always go in the same direction. So it's a key player in the insulin pathway itself, it's involved in the storage of glycogen hence its name. It's increased in the blood cells of Alzheimer's disease patients, it's present at higher concentrations. In mammals it's required for the generation of this Abeta peptide from the precursor protein that gives rise to it.

30:59 It's level is regulated by Abeta peptide so there is a mutual interaction between them and the molecular mechanism by which that happens is very well understood. It phosphorylates that tower protein which is the one that makes the neurofibrillary tangles inside the cells of Alzheimer's patients. There is a precise fly orthologue of the human protein, it's very conserved. It's actually called shaggy for reasons of the phenotype that it produces when it's mutated. Mutations of fly genes often have very capricious kinds of name.

31:33 We were interested in the potential interaction between GSK3 and our Alzheimer's disease fly model. What we found was that actually if we produce mutations in GSK3 and particularly if we over expressed it, that we could indeed rescue some of the phenotypes. So this is shown here for the climbing phenotype, I showed you that decline in the ability of the flies to climb with age and the fact that it was further impaired and you can see that again here in red with the presence of the Abeta peptide. What is shown in green, is what happens actually if we over-express GSK3. You can see that there is a complete rescue of the climbing phenotype.

32:16 So this, the life of the fly, that intervention is very highly beneficial. It also somewhat rescues the reduced life span, not completely it is not as complete as this rescue. There is clear age specificity of the affects and also there is a ying and yang with mis-expressing GSK3 because it effects tend to go in opposite ways in the nervous system and in the rest of the fly. It is not a simple situation but it's very clear that it's over expression here in the nervous system can rescue the presence of that peptide. Again the down-stream mechanisms involved in doing that are something that we are pursuing heavily at the moment. Interestingly and I think somewhat in the other direction we also managed to get a pharmacological rescue of this one, actually with treatment with lithium which of course actually supresses the activity of GSK3 beta.

33:08 We think this is going through a completely different route, it's actually at a dose of lithium that has very little effect on GSK3. What lithium seems to be doing is increasing some of the stress response pathways in the nerves, in the nerve cells of the flies, particularly the Cap'n'collar transcription factor. There are a number of different things going on here which are providing a way in to interfering with the toxic effect of this protein in the nerve cells of the fly and I think intervening in these aging pathways may well be a powerful way in here. Interestingly these kinds of affects are conserved in mice. I'm going to show you the work from a colleague …… Dylan was working at the Salk institute when he did this work, he has actually since moved to Berkeley. What he did was to ask whether one of the mutations that

somewhat controversially actually in the mouse extends lifespan could also rescue the pathology associated with the mouse model of Alzheimer's disease.

34:15 The basic approach he took shown here, he got a long lived IGF1 receptor mutant mouse. It's actually a *Hydrocynus* mouse which he crossed with a double mutant Alzheimer's disease mouse, so it's a mutation both in the Alzheimer's precursor protein and in one of the proteins one of the presenilins that cleaves it. These are two different mutations that in humans are associated with familial Alzheimer's disease and from that cross of course he can generate for different genotypes. The one he is particularly interested in is the one on the right which is the rescue of the pathology of the Alzheimer's disease on its own.

34:54 They took a number of approaches to looking at this but one was this classic test of cognitive ability in mice, the morris water maze. The way that this test works is that, what we have is a platform there just hidden under the surface of the cloudy water. The way that the mouse is trained initially is with the platform above the surface of the water. The mouse is then introduced to the murky water and swims. It can see the platform, so it swims straight toward it. It gets the idea that if it swims it is going to be able to get itself out of having to swim. Actually a minority of mice rollover on their backs and float don't play the game but most of them do.

35:43 What you do then is to take the platform below the surface of the water so the mouse can no longer see it. You can see these land marks on the wall at the back of the maze and the mouse can use those to learn the location of the platform which it's also had an opportunity to see previously. So what happens with an Alzheimer's - double mutant Alzheimer's mouse is that they swim well enough at this age, although that becomes impaired progressively later on. They don't have a clue where the platform is, they don't even search in the right quadrant they are just all over the place.

36:19 Whereas if we look at one of the rescued mice here, he largely confines his search to the right bit of the maze and actually quite quickly finds the platform. [*There he goes, the other one as you can see still hopelessly swimming around*] If you quantify that, so this is the rate at which the mice learns, we have got the three controlled genotype, the two controlled genotypes and the rescue down below and the Alzheimer's mice at the top in red. You can see that there is a very significant impairment of their ability to learn the platform. The IGF1 mutant is affecting a rescue of this learning problem and also to some extent rescuing these other features of this mouse model.

37:06 They gradually do lose their motor-coordination and the mutant somewhat rescues that. You can see the neuro-inflammation, this is astrogliosis in histological sections of the brain of the mouse. You can see how marked that is and the Alzheimer's disease is second from the right, the rescue is to the right of it so it's not a full rescue, not as good as the two controls but a lot better than the mutant and it also rescues the actual loss of neurons in the model.

37:35 The mechanisms for that one are not understood at all, it's very slow work trying to go downstream in the mouse but it's clear that similar kinds of phenomena to the ones that we can analyse more quickly and that flies in the norm may well be going on. It's not a simple

one to one mutant sitic stanic life span rescue pathology in these kinds of models. Some of the mutants that affect a rescue, for instance the mutation in IRS2 – the second insulin receptor sub stroke in the mouse very clearly don't extend life span, those mice actually get diabetes and they die young. None the less those mutants in the nervous system can sometimes rescue. So we really do need to understand what the rules are to figure out what going on here but clearly it's something interesting.

38:23 What we would like to be able to do is to manipulate these kinds of systems pharmacologically, we are talking about drugs, what we would like to be able to do is to recapture in animals and humans the effects of dietary restriction but without the dietary restriction. There is a lot of interest in drugs that can extend life span, one of the ones that has come to light recently which is again part of this nutrient sensing network is *rapamycin*, which of course inhibits the target of *rapamycin* and hence its name TOR - which is a crucial inter-cellular nutrient sensing kinase which interacts – its pathway interacts at multiple points and feeds back on the insulin signalling pathway, though really just one great big signally network.

39:12 There was a lot of excitement a few years ago when it was found that feeding *rapamycin* to mice extends their life span. You can see from the dairy where the successful feeding started, they actually thought they were administering drug before that but it wasn't getting into the mouse. They eventually formulated it correctly, you can see the increase in life-span. Those are actually accumulative results three independent studies in three different centres in the US, it's part of the national institute of ageing intervention testing program. Each year they take on three or four drugs and tests them in these three centres and *rapamycin* came up in all of them. They also did male and they saw an extension ……. again less than in females but it was there.

39:57 *Rapamycin* is a licensed drug, which makes it of particular interest. It's on-licence applications are for preventing restenosis after cardiac surgery, as an immunosuppressant in tissue transplant and because of its growth inhibitory factor – an anti-cancer chemotherapeutic. As you would expect from a drug that may be interfering in the actual ageing process itself, it's turning out to have a much wider therapeutic range than anybody realised so these are just a couple of … The first one is actually a study of the consequences of inoculation against influenza in mice. If you infect young mice with influenza virus – you can see the dark line going down – that's what happens to the survived young mice without immunization, this is a very challenging virus. The horizontal line at the top is what happens in the young mice if you do immunize it, so the immunization is extremely effective.

41:03 However, the dotted line sadly is what happens if you immunize an old mouse and then challenge it with the virus. It almost as badly off as a young mouse that was never immunized. What they found in this study was that if they pre-fed or pre-treated the old mice with *rapamycin* and then immunize them, they are actually part of that horizontal line at the top. There are two lines there, they could completely restore their response to immunization. Eventually they figured out that it was an effect on the pneumatic pretic stem cells which of course are important in mediating the response. I think that nobody suspected this because *rapamycin* at much high doses is used an immunosuppressan.

41:44 It also turns out to be effective against these animal models of Alzheimer's disease, this is shown in this paper here that came about four years ago now. They simply treated one of the Alzheimer's mouse models with *rapamycin* and again affected quite a major rescue leading to this really quite thoughtful review about *rapamycin*. Again flies are proved very useful here because they also respond to *rapamycin* with an increase in life span. This is some work that was done by Ivana Bedof, who was a post doc in the lab at that time. She actually now has her own lab at the UCL Cancer Institute. She was able to go down stream fairly rapidly and work out which targets of TOR are important in the response. She found that the …… Kinase and the increase in autophagy that happens in response to treatment with *rapamycin* were both required for the increase in life span. I think much to most people surprise, probably would be P, which mediates the response in protein synthesis, was completely unimportant. Mutant flies that completely lack that protein respond normally to *rapamycin*.

42:49 Interestingly, it's since turned out that the …… kinase, again this is a result of our welcome consortium work in Dominic Withers lab. If you knock out the …… kinase 1 in mice he sees a very nice increase in life span. I think that as a result of that there are quite a few clinical trials starting up in various places with lower doses of *rapamycin* than are normally used. This is just one that was highlighted in Science News at the end of last year, they are looking at a group of older men, they are looking at progress from our cognitive impairment and also the effect on the mobility of the men in the trial.

43:31 This theme of broader therapeutic range of existing drugs is becoming an increasingly frequent one, so metformin, I think it's a very interesting case, it's now the first line of defence against type2 diabetes when its diagnosed but it wasn't always so and at the time when metformin was used but so were two other treatments including direct treatments with inuslin – because they kept such good clinical records in Tayside, they were able to compare other outcomes, other health outcomes in diabetes in individuals who were either allocated to metformin or to two other treatments. Very interestingly they found that the instance of various cancers were almost half in the people who were treated with metformin. It really is a very big effect and it's several different cancers.

44:28 Which I think is very interesting and even the humble aspirin, I'm sure you have seen this in the news, it's turning out that users of low long term low dose aspirin are also protected against various cancers. I think the way people in this field are starting to think is that if you want to protect against the diseases of ageing, then there is a prospect of protecting against the ageing process itself as the underlying risk factor. To produce something of a parody if we think about the major bad diseases that can happen with ageing at the moment – the research is not entirely separate but it is true that we all tend to work in different research institutes with the name of our disease as the headline for the work at the Institute. We go to different conferences and don't necessarily communicate very much with people working on other organs or problems and that maps pretty well onto the different clinical specialities.

45:31 I think what we have with the animal work is proof of principle that we could be trying something else in parallel and I think we should be, which is intervening in the underlying

ageing process itself to try and ameliorate these conditions simultaneously. This growing interest in the health economics of this, this was an article that was produced quite recently, just looking at how much money would be saved if this approach was used and is effective as it might be at fairly modest assumptions. I think increasingly people are thinking in these terms. I've mentioned that a lot of existing drugs could be repurposed and that's true. We would also very much like license drugs against some targets for which there aren't any particularly the canonical insulin signalling pathway itself. There in the development of new drugs I think there are going to be major challenges. These are some of them, so the goal is to keep people healthy as they age, aging isn't recognised as a diseased for a clinical trial so there is a problem there straight away that you would have to specify the sub aspect of disease as things stands.

46:41 We also don't know even from the animal models because this information is so relatively new, how long and when we would actually have to treat. People are looking at timing, does the animal have to take it from the beginning of adulthood? Is it good enough to start in middle age? and so on but we don't know that and obviously if it's lifelong it could be problematic. There is a huge amount of feedback in these pathways so we would almost certain be looking at a combination of drugs to try and prevent the pathway fighting back if you inhibit a particular pathway. So long term and perhaps more than one ingredient, major safety issues, clinical trials – the usual kinds of problems.

47:21 How much we are going to see the development of new drugs in this area, I'm not so sure but we will see. To summarise, I think what we have found over recent years is that the aging process really is malleable to genes and diet and drugs and the long lived animals are healthier and they are protected also against pathology associated with specific ageing related diseases. I think we hope we have the prospect for a broad spectrum of preventative medicine for the diseases of aging. Finally it's a great pleasure to show you the people I work with, so I'm very, very lucky actually to have two labs. I have a fly lab here at UCL where I'm involved in this wonderful Welcome collaboration and I also have a max plank lab where we work mainly on mice. This was the joint lab meeting of the two groups earlier this year and these are the four people who you see here, in particular involved on the work I've talked about today with the Alzheimer's model in the fly. Finally I would like to thank you very much for your attention.