



HOUSE OF LORDS

Science and Technology Select Committee

Corrected oral evidence: Ageing: Science, Technology and Healthy Living

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Members present: Lord Patel (The Chair); Lord Borwick; Lord Hollick; Baroness Manningham-Buller; Viscount Ridley; Baroness Sheehan; Baroness Walmsley; Baroness Young of Old Scone.

Evidence Session No. 6

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Questions 43 - 50

Witnesses

Professor Lynne Cox, Department of Biochemistry, University of Oxford;
Professor Jesus Gil, Professor of Cell Proliferation, Imperial College London and group leader at the MRC London Institute of Medical Sciences; Professor Arne Akbar, UCL, and President, British Society for Immunology.

USE OF THE TRANSCRIPT

This is a corrected transcript of evidence taken in public and webcast on www.parliamentlive.tv.

Examination of witnesses

Professor Lynne Cox, Professor Jesus Gil and Professor Arne Akbar.

Q43 **The Chair:** Good morning, professors. Thank you very much for coming today to help us with our inquiry. I note that you were listening to some of the last session; maybe you want to comment on that. Before we start, please introduce yourselves so that we get you on the record. If you wish to say anything as an introductory remark, please feel free to do so. Then we will go on to questions.

Professor Jesus Gil: Thank you. I work in the London Institute of Medical Sciences from the Medical Research Council, associated with Imperial College. I am a cell biologist and research cellular senescence and its regulation. I have also been interested lately in how to target senescence during cancer and ageing. I declare that I am a consultant for two companies, Unity Biotechnology and Geras Bio, which are trying to develop therapeutics on senescence.

Professor Lynne Cox: Good morning. I am an associate professor of biochemistry at the University of Oxford. For the past 23 years I have been running a research group in Oxford looking at the molecular and cell biology of ageing. My initial training was in cancer research. I am currently a trustee of the British Society for Research on Ageing, and I serve on the science, genomics and technology board of the All-Party Parliamentary Group for Longevity.

Professor Arne Akbar: I am a professor of immunology at University College London and the president of the British Society for Immunology, representing 4,000 members in academia, history and clinical practice. The society's aim is to promote excellence in research for the benefit of human and animal health. Wearing my other hat as a scientist, I am looking at the ageing of the immune system, especially in humans. My group has been trying to boost immunity, but by working with humans in real life rather than with mice or with humans cells in a test tube.

Q44 **The Chair:** Thank you very much. I will kick off with the first question, which relates to senescence and so-called senolytic drugs. Where in the development of the science and the drugs are we? Might drugs that either stop or reverse the ageing process be available? What possible timeframe might we be speaking about? How safe are they likely to be?

Professor Jesus Gil: This is a quickly developing area. The first scientific evidence that eliminating senescent cells can be beneficial for living longer and healthier came just eight years ago, in 2011. In 2016 the first drugs that are able to specifically kill senescent cells were described; they show some benefits on age-associated diseases and living longer and healthier in mice. The first clinical trials started last year, in 2018, specifically targeting osteoarthritis. As we heard from Professor Partridge, others have targeted idiopathic pulmonary fibrosis and so on. Five to 10 trials have either started now or are starting.

Discussing the timing of when we can have some of these drugs on the market is really just speculating. Some drugs are in clinical trials at phase 1 and some are starting phase 2. In the best-case scenario, if things go very well, it could be that in five to 10 years some of these senolytics are being used to treat specific ageing diseases—maybe osteoarthritis, glaucoma or others. The worst-case scenario is that all the excitement we have now eventually does not translate, for different reasons. Sometimes that can snowball, and it could be that people become not so excited any more and research into senolytics stops.

Professor Lynne Cox: I think the field has become incredibly mature incredibly quickly. We have gone from having just correlative data to causative data. One of the most compelling things for me was that the transplantation of senescent cells into young mice brought on a number of age-related diseases very quickly across a whole number of tissues and systems, and also functional decline in the mice. These things fulfil Koch's postulates; they are causative in disease, and removing them is beneficial for health.

Senolytics kill senescent cells. We may not want to kill senescent cells in every older person, particularly if they have a lot of senescent neurons, which we do not know at the moment. We might want to think in parallel about senomodifiers, things that can suppress the deleterious phenotypes of senescent cells without necessarily killing them. Senolytics are extremely exciting. There are lots of parallel streams of research, and we should not forget about things such as stem cell research and gene therapy, which is looking promising on other ageing fronts as well.

I am slightly more optimistic that some of the senomodifiers could be available within a very short period. ResTORbio, which was mentioned earlier, has a drug called RTB101 in phase 3 clinical trials¹ and is hoping to get FDA approval in the next two to three years based on those trials. From phases 2a and 2b it has already reported some very promising outcomes in both asthmatic and frail elderly patients, preventing respiratory tract infections on senomodification rather than senolytics.

Professor Arne Akbar: One thing we have to bear in mind is that the immune system can also clear senescent cells; it can kill them. The question is: why does the immune system not do this when you get older? When considering the impact of senolytic drugs, we need to look at two things in parallel: the decline of the immune system—why it does not work as well to clear senescent cells—and the added benefit of having the drugs as well. We need to come to a point where both things are considered in parallel for maximum benefit.

Q45 Baroness Manningham-Buller: We heard some compelling evidence from the previous panel, which you listened to, about the use of old people with multimorbidity in clinical trials. Do you have anything to add to what Professor Witham said about that?

¹ It was reported on 15 October 2019 that these phase 3 trials did not meet primary endpoint; however, the science is still sound, and what I said at the time is still correct though time frame to approval may be longer.

Professor Lynne Cox: I have been looking at the maximum age in clinical trials. A study in Ireland assessed all clinical trials that have taken place. There is an arbitrary cut-off of 18 to 64 years in most clinical trials. Even if you include trials for geriatric patients, the average cut-off age is 69.2 years, which obviously is far too soon. The other issue is that a lot of trials will exclude patients on the basis of multimorbidity, which I am sure was covered earlier.

They are exactly the target population that will be taking anti-ageing medication, so it is absurd to have these arbitrary cut-offs. There are, of course, concerns about polypharmacy—patients coming in with multimorbidities and taking a large number of drugs. However, we need to get away from excluding older people from trials. There have been moves; we have just heard that the NIHR is making moves on this. The British Geriatric Society has been looking at this and has published a study on extending clinical trials to include far more older people. To tackle the hard-to-reach groups, you should recruit them when they come into GP's clinics or are acutely admitted to hospital, rather than designing the world's perfect trial then trying to recruit after the event.

Baroness Manningham-Buller: Just to pick up Professor Akbar's comment a minute ago about the decline in the immune system reaction, are trials on that happening?

Professor Arne Akbar: There are no trials specifically on the decline of the immune system. The problem with the immune system is that it is multifactorial. There are many different cell types, which all contribute to the immune system as a whole. A lot of studies have been going on with individual cells, but none looking at how the association between the cells changes with ageing. What is missing here is looking at the immune system of the whole organism during ageing. From that perspective—I know that most of you are not immunologists—the immune system is a unique organ, in that its cells invade and go into all the other tissues in times of health and in times of stress. It is an organ that interacts with every other organ, so any change in the immune system also effects changes in other organs. If the immune system goes downhill with ageing, organ function will generally be altered as well. So decline in immune function is likely also to affect many other organ systems.

Q46 **Baroness Sheehan:** Are treatments, both new and repurposed—that have already been tested in clinical trials—being targeted at individual conditions, multiple conditions or the ageing process as a whole? If they are being targeted at specific conditions, is there the potential for these drugs to have wider benefits?

Professor Jesus Gil: Yes. For example, the senolytic trials going on at the moment have been targeted to specific diseases, for instance osteoarthritis of the knee, glaucoma, idiopathic pulmonary fibrosis and chronic kidney disease. That is, in part, because it is easier to design a clinical trial against a specific disease or a specific end point. Because many of these trials have been targeting senescence as the root cause of many of those diseases, the assumption is that, even if it is effective just

in the disease involved in the trial, it might also have widespread benefits in some other multimorbidities. As was said in the previous session, we need to have more flexibility in designing these trials to enable us to have different end points and target multimorbidities.

Baroness Sheehan: What would fix that flexibility?

Professor Jesus Gil: One example is the TAME study on targeting ageing with metformin, a drug used for diabetes. There has been evidence for a number of years that people on this drug were doing better in other age-related diseases. Five years ago, retrospective studies were conducted in the States on almost 75,000 people who had been treated with the drug and it was realised that they had been doing better on some other outcome measures. They have been trying to get a trial with this safe drug to see its effect on multimorbidities and that is about to start. It has taken an immense amount of time to raise the money needed for this long and costly trial. If there were trials in which it was easier to dissect some of the multimorbidities and which were more flexible in their endpoint, the cost and duration of the trials might not be so much and it would be easier to get them in place.

Professor Lynne Cox: A lot of the trials have to be against a single indication because of current FDA and EMA regulations, and because of the precautionary principle. Unity Biotech, with which I am not associated, has decided to go for privileged compartments such as the knee and the eye, in case there are adverse consequences of a totally new type of therapeutic. If they can show safety and efficacy in an enclosed compartment, they may be happier to go to a more systemic application.

The TAME trial was remarkable in being approved by the FDA because it has a mixed endpoint; a first progression to any of a number of age-related diseases. That was the first time that the FDA changed from it having to be one specific disease to being any one of a number of different age-related diseases.

The other issue we have—touched on earlier—is that a lot of these trials take for ever, because we do not yet have readily analysable biomarkers where you can just take a quick blood sample and say, “Okay, this drug is efficacious; we have killed so many senescent cells using a senolytic”. Until we have really reliable biomarkers, the endpoints are going to be whether someone gets dementia or heart disease, rather than whether they show signs of improvement.

Professor Arne Akbar: This is possibly a little controversial. With all due respect to my colleagues here, and those who spoke earlier, the focus right now is on senescent cells; they are the cell of the moment. Everyone who works on ageing is interested in them. The way they are thought to be deleterious is by the inflammatory molecules that they secrete. We, and others, have shown that, when you get older, inflammation is bad for you, regardless of where it comes from. That can be targeted.

There are already drugs out there that different pharmaceutical companies have taken through phase 1 to phase 3 trials for their anti-inflammatory effects. In a recent, small, experimental medicine study, we have shown that we can boost immune responses in older humans by targeting inflammation with a GSK drug. It worked; we can actually boost the immune response in vivo, in the skin of older people. This may be working through senescent cells, not by killing them but by reducing the effect of the mediators that they produce. There are already therapies out there that could be repurposed.

The focus on senescent cells is good; senolytics are a good treatment, but they are not the whole story. There are other ways to target the problem.

Baroness Sheehan: So am I right in saying that there are drugs that will tackle inflammation and that they improve the health of the immune system at the same time?

Professor Arne Akbar: Many drugs were designed not for ageing but for inflammatory conditions such as arthritis, or for lung diseases such as COPD. With Medical Research Council support, we have been able to test how some of these drugs—one being from GSK—block inflammation temporarily, for four days. We then checked the immune response in the skin of older volunteers to see whether we could boost the response. The answer was, yes, we can block inflammation to enhance immunity in older humans. We do not know the long-term effects of this. Can we do this intermittently, because the drugs are toxic for long term treatment. In principle, you should be able to boost the immune system temporarily, for example before giving a vaccine to older people. We need more studies into this, looking at humans rather than experimental models that may or may not relate to the human.

Professor Lynne Cox: Inflammation is critical; it really does not matter where it comes from. Having a personal interest in this, I have been looking at long-term usage of anti-inflammatories. The literature suggests that taking anti-inflammatories for an extended period may be protective of a number of age-related diseases. They may have cardiovascular risk, so there is always a risk-benefit analysis, but when low-dose anti-inflammatories were tested for things such as dementia, the trial was pulled after two years. Yet follow-up showed that after four years there was benefit. A lot of trials are not taking long enough for age-related benefit to be seen. Anti-inflammatories are here now; they are in the clinic. I have been on them for 20 years, so I am a clinical sample for this.

Inflammation is incredibly important. The rapalogues that we have been talking about also support the immune system. Remarkably, rapamycin was used, in very high doses, as an immune suppressant to prevent kidney transplant rejection. However, the low doses—about a 120th of the maximum tolerated dose of - the drug RTB101 —that are being used as an anti-ageing therapy, suppress inflammation but support the immune system's ability to fight viruses, which is why they are so

effective in preventing elderly people getting respiratory tract infections. Those suppress inflammation but support the immune system's ability to fight viruses, which is why they are so effective in preventing elderly people getting respiratory tract infections.

Lord Borwick: When a new drug is an established out-of-patent drug and given a completely new use, it could, as you say, be tremendously helpful, but is there any argument for changing the international patent regulations to extend patents for new uses, or can that already be done?

Professor Jesus Gil: We talked earlier about the pros and cons of repurposing drugs, one of the cons being precisely that some pharma companies will not be interested because of intellectual property. As Professor Ferguson highlighted, there are often ways around it, such as doing a different formulation or creating a new chemical entity that modifies directly the repurposed drug. These are ways in which companies can already get around it. Very often, you need to modify the drug slightly because of the pharmacodynamic and pharmacokinetic properties. So, there might already be ways around intellectual property that do not stop the repurposing or modification of such drugs.

Professor Lynne Cox: I want to be controversial on that. If we want a drug that is going to treat a large swathe of the population, such as statins, we might not want a very expensive drug. If we are repurposing something that has come off patent, we might be able to get generics out to a wider population much more cheaply. The senolytics being used by the Mayo Clinic are dasatinib and quercetin. Dasatinib is an anti-cancer agent. At the moment, a single dose is about \$200 to \$2,000. An Indian company has suggested that it could make a generic for \$4. We might want a national drug development strategy that produces generics if we are to use such drugs at a population-wide level.

Professor Jesus Gil: I agree that having drugs that are off patent and cheap would be interesting for the NHS and the general public. Talking about senolytics, my group published earlier this week findings that cardiac glycosides such as digoxin, which are off patent and have been used for treating people with cardiac disease, are effective senolytics. They basically cost pennies at the moment. Of course, there are many more studies to do, but some repurposed drugs that are very cheap and off patent might have some of the activities that we are looking into—senolytics or the mTOR inhibitors that we talked about earlier, such as rapamycin or other modifications of it.

Viscount Ridley: This is a good moment to raise this point. Last week, we heard that the UK is in danger of missing the boat on a golden opportunity. In your written evidence, Professor Cox, I detected a note of real irritation. You said: "We don't need more gadgets to monitor people's health deteriorating, we need drugs to stop that deterioration ... the recently announced 'Healthy ageing grand challenge' has fallen directly into this trap, possibly driven by a tech-engaged DoH, and excluding biomedical research". Strong stuff. Is the biomedical side of this being neglected? Is that your case?

Professor Lynne Cox: My case is that it is falling between two stools. We have research councils, BBSRC, that fund healthy ageing; we have the Medical Research Council that funds disease. Ageing is a process that ends up with disease, and it is hard to fit the remit of either research council. We are missing out on that. A lot of the smaller charities are focused on their particular disease, whereas we think that we have a course of multiple diseases, so it is hard to rebadge for specific disease indications.

The funding situation is missing out on the biomedical sciences and what we can do. The UK has been fantastic at developing drugs. We have made a quarter of all the drugs in use globally. We have a wonderful pharmaceutical industry; we have fantastic universities. We do not seem to be joining them together in the way required. I do not know whether it is too premature to come on to this, but you were talking about a National Institute on Aging in the previous session. That is the only way that you can get an umbrella organisation that brings all these disparate parts together, but it would need a ring-fenced budget and longevity. It could not be yet another initiative for five years and then it dies a death. It would have to last and make a big difference.

Baroness Sheehan: To go back to the cost of anti-inflammatories, we often hear that things like chilli and aspirin are good anti-inflammatories. Is there much research into things like that? Is there simple dietary advice that we can give to the population to boost the anti-inflammatory response?

Professor Jesus Gil: I can mention a couple of things there. I am not sure that there is simple advice that we can give on how to direct the diet for inflammation. We were talking earlier about some of the senolytics and anti-inflammatories. Things like quercetin and fisetin are being used as senolytics. These are like polyphenolic compounds that are present in some vegetables. We also know about different foods that have anti-inflammatory properties. I am sure that something can be done, probably with epidemiologists, to look into that into more detail. I am probably not the one to give advice in that area.

Professor Arne Akbar: The problem with all these other possible anti-inflammatories is that we do not know what dose to take. How many chillies do we take for a certain level of blockade of inflammation, for example? With a drug, we know exactly how much is in there, so we can treat with the amount needed and there is advice on what you should take and not take because it has all been tested by the companies that made the drugs in the first place.

We have been talking about perhaps repurposing some drugs for things that they were not considered for initially. If we could use an anti-inflammatory to boost immunity, that would be great. People are now using drugs such as metformin for diabetes and for its anti-ageing properties as well. If you could have drugs that are already there but find a new purpose for them, all the R&D and the big, expensive stuff has been done already. We just need to be able to use those drugs in a

slightly different way that helps with the ageing process, but we need to understand the biology of that, too. It is easier to do it with a drug that has already been properly verified for dosage, tolerability and safety.

Q47 Baroness Walmsley: I would like to follow up on that and come to the next question. To do what you have just suggested, we need to understand the fundamental way in which such drugs work. To what extent do we understand the impact of ageing on the immune system? How does an ageing immune system interact with all the other systems in the body? It is clear from what you have said that the immune system is fundamental, but do we understand the mechanisms?

Professor Arne Akbar: We understand the mechanisms of how the cells work in the immune system. The harder thing to know is how they all co-ordinate their activity. When we get older, many different cell types that are inherent in the immune system all go wrong one by one, with a knock-on effect from one cell to another.

Even more complicated than that, because the immune system migrates around the body, if you have a defect in one cell type which then interacts with organ cells—your liver, your kidney or your muscle—that also changes. Given the additional, very interesting possibility that the immune system can recognise and clear away senescent cells from our bodies, that potentially also changes.

We can say as immunologists that we understand some of the changes that occur on a per cell basis. Missing are the in vivo experiments, especially in humans, to work out what changes in the whole immune system. Some experiments in my group are going on now where we can challenge people with antigens in the skin; other people are doing similar experiments.

Most of this work has been done in animals. If we try to equate the lifespan of a mouse, which is the common species that we all use, with that of a human, it is very different. Two years is an old mouse; 80 years is a relatively—but not terribly—old human. The constraints on how long cells work and how many senescent cells we generate all change. If the immune system goes downhill generally, its ability to target not just micro-organisms that attack us but senescent cells also goes down. To understand that process will be important. Can the immune system work together with the senolytic drugs to clear senescent cells?

Professor Lynne Cox: As Professor Akbar has said, there is a huge interplay between the different systems—I do not know people's level of immunology knowledge—but B cells make antibodies, T cells tell B cells what to do and run around and kill things. Neutrophils will invade tissues. Professor Lord has incredibly interesting data which show that as the immune system ages, the neutrophils, which will normally run to the site of inflammation, can still 'smell'—or sense—that signal, particularly a signal that senescent cells are kicking out inflammatory cytokines. So they will try to move towards that signal, but their sense of direction and motility are affected, so instead of homing straight in on the damage—the

senescent cell—they create an enormous amount of tissue damage as they migrate to that scene.

There are a few other things about the immune system getting older. We know that cells such as macrophages will engulf and digest cellular debris and other cells like senescent cells, but as they age their lysosomes—the dustbins of the cell—become dysfunctional and so can no longer carry out that function.

Finally, senescent cells do something even worse: they kick out a pile of proteases that digest off their cell surface markers so that they almost become invisible to the immune system.

Baroness Walmsley: We know that there are drugs that will boost the production of neutrophils. Are there any that help with their sense of direction, as you put it?

Professor Lynne Cox: You are asking the wrong person; you should be asking your adviser. Yes, in fact, Professor Lord has a mechanism for all this. Statins are looking quite interesting in that context. You need to rearrange the cytoskeleton—the actin reorganisation of the cells that allows a cell to move through a tissue. In senescent skin cells we have some drugs that can influence that, and Professor Lord has very easy, cheap ways of improving neutrophil migration.

Baroness Walmsley: I am sure we can ask her about that later.

Q48 **Viscount Ridley:** I think my question has largely been answered, but I shall ask it in case anyone wants to add anything. It is, I suspect, mainly for Professor Akbar. Why does the immune system not kill senescent cells in older people? It is as simple as that.

Professor Arne Akbar: That is a very good question. This is what my group has been working on and has published on this year. Senescent cells put up inhibitory receptors on the cell surface, so the white cells, which normally recognise the senescent cells and kill them, are prevented from doing so. You can block those receptors by targeting at a genetic level to downregulate those receptors, or you can use antibodies to block the receptors so that they cannot be recognised by the white cells any more. If you do that, you clear the senescent cells.

I hate to add another way in which you could intervene in ageing, but you could look at immune targeting to improve senescent cell clearance. In the same way that you have all these checkpoint inhibitors to enable you to clear cancers more effectively, or to boost the immune response against cancers, you could easily boost the immune response against senescent cells as well by targeting receptors on the cell surface.

Viscount Ridley: It almost sounds as though the senescent cells are being cunning or malevolent if they are putting inhibitory proteins on the cell surfaces, or indeed clearing off the recognition, as Professor Cox said. What is going on here? Is it a sort of evolution, so that the ones that do this survive and the ones that do not do not, or something like that?

Professor Arne Akbar: Yes, I think it is exactly that.

Viscount Ridley: Right. By the way, we are talking about the adaptive immune system here. Is there anything in terms of senescence of the innate immune system that is relevant to this issue?

Professor Arne Akbar: The white cells that can clear the senescent cells are both the adaptive and the innate cells. Those are the natural killer cells—the innate ones—but T cells, interestingly, when they get older, acquire the ability to do so as well. T cells, when they get old, become a little more non-specific and a bit more like the innate cells. Both natural killer and old T cells can kill senescent cells T by the same mechanism.

Professor Lynne Cox: Senescent cells are nasty. They trigger their own innate immune response. The innate immune system evolved as a very primitive way of dealing with pathogens and it recognises patterns of things rather than specific antigens. One of the patterns is DNA in the cytoplasm. It is supposed to be tucked away safely in the nucleus and senescent cells leak their own DNA out into the cytoplasm; they trigger their own innate immune signalling pathways. That switches on a protein called NF-kappa B, which turns on production of inflammatory cytokines. So they are pushing out a whole inflammatory signalling cascade through innate immune signalling, but they are misrecognising their own DNA as a pathogen.

Professor Jesus Gil: I guess the flipside of the coin is that, although it is true that senescent cells have all these mechanisms in place to be non-detectable by the immune system but, as was mentioned, we can try to exploit those. There are checkpoint inhibitors but also CAR T cells or recombinant cells that are being used against cancer and can be directed against antigens of senescent cells. This is something that some groups are starting to explore, and they are also neutralising antibodies. So we can also try to exploit that to eliminate the senescent cells.

Viscount Ridley: How specific within individuals will these mechanisms be? In other words, is it likely that you will end up having to design a drug that works in you but not in me?

Professor Jesus Gil: I am not an expert, but with CAR T cells, it is one of the potential issues. I know there are now attempts to get off-the-shelf CAR T cells that will be able to be used in different people rather than having to be specifically developed—

Viscount Ridley: For cancer, specifically.

Professor Jesus Gil: For cancer, and I think this could be extended to senescence.

Q49 **Baroness Young of Old Scone:** Is there a risk that we could grasp the idea of a national institute for ageing to co-ordinate research and innovation across all these disciplines—social, medical, technological and so on? If you were queen for a day—or king, or any other gender of ruler; other genders of ruler are available—what would you prescribe as the

solution for this co-ordinating task?

Professor Arne Akbar: If I might start on that and then pass the question on, ageing is multifactorial. As we heard earlier today, there are the social aspects and the physical aspects, including being able to design appropriate living space for older people. There are the biological aspects and trying to work out ageing in different organs and cell types. An institute would have to be very broad in its remit to cover all these things and to have it co-ordinated.

How do you co-ordinate all these different areas? I think it would be much better to have focused areas of excellence, where people target one or other of these things that go wrong in ageing. Ultimately, if you can co-ordinate the whole range of different activities, that is great, but people work best in what they are good at. You need to get the best people we have to work in certain areas together.

What is missing from the biological aspect—what we do here—is proper interaction with industry. We know that it has the drugs but once a drug goes off target, industry is not interested any more. We need better experimental models to investigate changes in the immune system, in animals and humans, and we need people to be better co-ordinated.

I can give you one example of how this really worked for us about 20 years ago. Professor Dame Linda Partridge, Lynne Cox, Janet Lord and I were all associated with an initiative put forward by the BBSRC to bring all the researchers in ageing together for a couple of grant rounds. We were all funded and we got to know each other from that. Our interactions have been maintained since, but there has been nothing like that, where we have brought people together to try to consolidate the activities in certain areas since then.

Apart from us, there are other people we know now—Richard Faragher was here recently, and he was also involved with this. We have a cluster of ageing researchers—in many ways and one—who now all know each other. We may have slightly different ways of working, but we know what is going on and can go to any of these colleagues to ask for help in a particular area. That is what we need: consolidated areas in ageing—in our case, biological ageing. The same will apply for social ageing and mechanical ageing et cetera.

Baroness Young of Old Scone: Your colleague on the left is probably not ageing; he is a younger professor. Do you have the same solution, Professor Gil?

Professor Jesus Gil: Thanks very much. If I was going to be king for a day, I would probably have to abdicate. I will probably just talk about biomedical sciences.

I recognise that there are also technical aspects regarding ageing, and others that might be funded. But I agree with the previous witnesses that a bricks-and-mortar institute is not necessarily needed, but a virtual institute—funded in specific clusters—is. Another thing to highlight is that some of these experiments are time-consuming and costly. For example,

I am thinking about some of the lifespan experiments that might be done in mice. For that, having co-ordination, not duplicated effort, and the expertise of different groups working on different aspects of ageing would be beneficial. So, in principle, I am in favour of something like a virtual institute of ageing.

Professor Lynne Cox: I would like a virtual institute that brings together all the centres of excellence and individual expertise as well. You can get very good people in institutes that themselves might not be considered centres of excellence, but the people are excellent. Multidisciplinarity is where things really kick off. If you bring people together from different disciplines, you can have a really interesting explosion of ideas coming together, so I want that multidisciplinarity.

We are trying something in Oxford. We are trying to bring together the social sciences, humanities, arts, physical sciences and biological sciences, with the clinicians, into an umbrella virtual organisation, the Oxford Collaboration on Ageing Research². In a way, this is a mini model of how it might work to bring together lots of different, disparate disciplines. One of the difficult things at the outset is vocabulary. We all speak a slightly different language in ageing but, once you can overcome those sorts of hurdles, it is incredibly positive and you can start to get things moving.

You have the social context in which people are ageing. Again, Professor Lord has done some of this stuff, looking at the impact of mental health and bereavement on the ageing immune system. Bringing those two fields together is synergistic, so an umbrella organisation that can link people in the way that the SAGE and ERA grant rounds did, and the New Dynamics of Ageing that brought social, engineering and medical sciences together, would be incredibly beneficial.

Lord Hollick: We have seen some evidence from Professor Nazroo that showed the dramatic difference in ageing between different ethnic groups. When you do your trials, do you segregate the ethnic groups? Are there any clues coming from those trials about the biochemical reasons for increased morbidity at younger ages in certain ethnic groups that provide a bit of insight into how certain ethnic groups are possibly more able to deal with senescence?

Professor Arne Akbar: That is a very good question as well. We here are all basic scientists rather than clinicians, so we do not actually carry out trials, but in my research group we work on humans in small experimental medicine studies. We recruit people and check their immune responses. At the moment, we tend to focus on white Caucasians for our trials, because of the confounding issues relating to different ethnic profiles in responsiveness. I also collaborate with one of the big institutes in Singapore to ask whether what we have seen here in the UK populations also applies to populations over there. This is looking at the T lymphocyte function in relation to a viral infection called

² This was subsequently named the Ageing Research Collaboration Hub (ARCH).

cytomegalovirus. The details are not important, but at least in that case we were looking at two different populations, and they did show the same effects. I totally take the point and, yes, it will be very important to look at demographic differences in responsiveness.

Professor Lynne Cox: Richard Aspinall in Coventry is trying to engage the hard-to-reach communities, particularly Asian women who do not speak English and are culturally excluded from the rest of society. They are extremely hard to reach but, because of diet, lack of exercise and some cultural norms, they may be ageing worse than we would anticipate for people living in this country. They are going through local community groups and local commerce, trying to recruit from the hard-to-reach groups. It is extremely difficult, but incredibly important, to get people like that into trials. There are studies about responses of the black African population to blood pressure medications. Many do not respond in the same way because of a few genetic variations. I was talking to Genomics England, which apparently is finding it very hard to recruit different ethnic groups into the genomes project. It is a case of doing a lot more outreach to get people into the trials and the cohorts.

Professor Arne Akbar: If you are doing work on humans and trying to work out immune responsiveness in humans, it is very hard to get funds to carry out these studies. No one is really interested in trying to work out what is actually happening in a human population. In some studies this is because people say it is too difficult to get a mechanism—but we have shown that you can get mechanisms out of this. It is very hard to do; you need ethical approval. If you are going to try to intervene with a drug, you also need to associate with drug companies. All that is difficult, but not impossible. The Medical Research Council funded this. If there could be more of this strategic funding, more people would engage in this kind of research. There is a dearth of research working with humans, and some of us here have had the problem of trying to get funding to be able to do this—but it is possible; it can be done.

Professor Jesus Gil: What they mentioned is completely right, but apart from ethnicity there is also gender. Again, we are basic scientists, but one thing we know from some of the experiments done on mice is that some interventions will extend the lifespan of male but not female mice, or the other way around. That is also something to consider. From the point of view of designing trials, even with mice, just to assess the effects this has on the lifespan of males and females, you have to duplicate the cohorts, which duplicates the cost of the experiments—but this is necessary.

Viscount Ridley: I return to the issue of the national institute. Am I right in detecting an ever so polite disagreement between Professors Cox and Akbar on this? Professor Akbar, you were talking about the importance of letting people stick to their specialities and be expert and very good at what they do, whereas Professor Cox, you were talking about the importance of multidisciplinary and, presumably, the social ageing people coming up against the biological ageing people and the mechanical ageing people in one seminar or whatever. Are you

disagreeing? May I probe that a bit further?

Professor Arne Akbar: I do not think we disagree, in the sense that we both recognise the importance of all these different areas. It is about how to do this effectively when you are bringing people together either artificially or with the same interest to try to move an area forward. If you were to put me together with a bioengineer and to say, "Work on ageing together", that would be very difficult for me. Bioengineering for ageing is very important, but it is something that I do not work on right now.

Viscount Ridley: Are you saying that it is a bad idea to have you and this bioengineer chap under the umbrella of a national institute?

Professor Arne Akbar: I think it is a bad idea. It would be interesting to hear what they are doing, but I would find it very hard to know how I could contribute to his or her research, or vice versa. If there was a common goal—if you were looking at biomechanics, artificial limbs and how the immune response would change in the limbs you are putting into a new person—then yes, there is a way forward there. There is always a way, but there has to be funding to take that kind of research forward as well, rather than saying virtually, over a cup of coffee, "It would be a good idea if we could do this".

Viscount Ridley: So interdisciplinarity for its own sake can be a mistake.

Professor Arne Akbar: Yes.

Professor Lynne Cox: I agree with that as well. You cannot force these things; they have to happen organically. I now have a collaborator in Israel because I spoke at a conference, she presented at the conference and we realised that there was commonality of purpose. It was not forced on us. It happened because we had research interests that came together and met in the middle. If you have an organisation in which you can bring interested people together and showcase all the work, you can find those common interests and create multidisciplinary research programmes without any artificial intervention.

Baroness Walmsley: If you are dealing with human beings, you are going to need their co-operation and, therefore, their understanding, so my question is about communication with patients. I wonder whether the clinicians from our earlier session would like to get involved with this question as well, because I remember Professor Witham saying that there were side effects from some drugs that made people more susceptible to falling over, delirium or that kind of thing. I came across a situation recently in which somebody was not told about a very common side effect of a drug they were taking, and it caused a great deal of problems. How important is communication with patients? What can we do to improve that? If we did improve it, would that help to reduce polypharmacy problems and drug interaction problems as people come forward earlier to say, "Hang on a minute, there's something going wrong

with me”?

Professor Arne Akbar: Working with humans—exclusively, in my group—we need to recruit older people from the population. We work only with healthy humans at this stage, because you need to understand what is happening with healthy ageing before you can superimpose a disease process on to that.

What is ageing and what is the disease? If you do not know how normal people respond, you do not know what is disease and how it shapes the immune response of the older person. To recruit these individuals, we have open days at UCL, to which we invite healthy people from clinics, from the University of the Third Age and from other age-associated focus groups. They all come along and listen to the research. We talk to them very informally and have question and answer sessions afterwards, normally over coffee and cake. We say, “Here is the research: if you would like to take part, please do”. We advise them of the side effects, if there are any—there have not been with our studies—and they keep coming back.

We have more and more people each time. We have to engage; if you do not, you have no volunteers to work on. It will not be the same for my clinical colleagues and how they interact with their patients, which might be very different.

Baroness Manningham-Buller: We have been talking about a virtual or other institute. Obviously, we are already beginning to think about what our recommendations will be at the end of this process. We have noticed that some which Dame Linda contributed to in 2005 have not yet been implemented, so we do not have an enormous amount of confidence in our ability to get our recommendations agreed. If you are not in favour of a virtual institute, or you are, what other things would any of you like to see in our recommendations at the end of this inquiry? You are allowed only one each.

Professor Arne Akbar: There was a recent survey of at least 50 big pharma companies by the Association of the British Pharmaceutical Industry. They all agreed that there is a very big shortfall in immunology research. The only way you can encourage people to do the research we talked about, such as looking at the effects of the immune system on senescent cells et cetera, is by funding them. If there is a shortfall, and everyone in the industry agrees that there is a shortfall in immunology research, and you do not fund people coming in to do the work in the appropriate, important areas—not just senolytics—the work will not progress. We will get one or two people with fixed ideas doing the research without any new input or cross-fertilisation from anywhere else. We need to do a bit less of that.

Professor Lynne Cox: Mine would be budget. The NIA takes up 10% of the NIH budget. That comes in at \$3.9 billion a year at the moment, slightly more than we can probably afford. It is hard to get a definite figure for UKRI funding but it is about £6 billion, 10% of which is £600 million. That sounds horrendous, but it is 0.4% of what we spend on

treating illness in the NHS, instead of keeping people well. It would be incredible value for money. With that budget, I would support long-term cohort studies, long-term lifespan studies, long-term drug development and core resources. We have lost a few core resources, including a stem cell bank because funding was not renewed after the statutory five years. The Shared Ageing Research Models resource, which keeps all animal work on ageing in a freezer for any researcher to call up their favourite tissue, has gone because of lack of funding. All these wonderful initiatives have died a death, which is why I am pushing for longevity in the funding process, so that all the resources are maintained.

Professor Jesus Gil: I agree with the last point on the long-term funding for these costly projects. It is not directly my area of research, but I would like to mention the need for structures that allow flexibility for clinical trials on multimorbidities. The flexibility to have a trial, not on one disease or outcome but involving different diseases and outcomes, would advance drugs that can target the root causes of ageing.

Q50 **Baroness Young of Old Scone:** I want to get your views about whether researchers into ageing without a specific disease focus find themselves at a disadvantage in competition for funding, in the way that funding calls are structured.

Professor Jesus Gil: There is specific funding for things such as the root causes and the molecular and cellular causes of ageing. The BBSRC and MRC fund medical research on healthy ageing. For example, I am researching cellular senescence. We are researching the process at the cellular and molecular level and are not necessarily focusing on a specific disease. There is funding for that. You might be at a disadvantage if you were integrating that research more translationally into specific diseases. Some more focused calls could be useful.

Baroness Sheehan: Is this impacting on the number of new researchers coming in to ageing research?

Professor Jesus Gil: Some of the ageing studies are very long, as Professor Partridge mentioned in the previous session. New researchers are not necessarily going to get involved in those, because they will have to produce some results in five years' time, to have their funding renewed. There might be a barrier there.

Baroness Young of Old Scone: Theoretically, we should be at that wonderful point where UKRI is capable of taking a much more co-ordinated view, and where the Government have set up an initiative on healthy ageing. Why are neither of those doing this?

Professor Lynne Cox: I have been talking to the healthy ageing initiative people about the challenge. It is very much driven by business, rather than science. It is all about making money and the post-Brexit economy. Tech looks like it is going to be a quick fix for the economy, whereas pharmaceutical industries take a while to build and to bring

funds in. I am controversial in my views, but tech has definitely been the focus rather than the biomedical sciences.

Professor Arne Akbar: I find it very difficult to get funding in the UK for ageing research, so much so that I have a joint grant applied for with the NIA in Bethesda. I have a grant application in with a colleague in California to work on an ageing process which we identified here in the UK. I cannot get funding for that, so I am going to the USA to try and get it.

Professor Jesus Gil: UKRI has been part of a big reorganisation. Some of the councils, such as the MRC, are targeting multimorbidities. The BBSRC is targeting healthy ageing. UKRI has scope to fund these grand challenges: healthy ageing is one of those. Maybe it is still a bit early to see how this will be implemented, but challenges going across the councils was one of the reasons for UKRI. If it is implemented well, it might be useful. The question is how it is implemented.

The Chair: I think we have exhausted our questions. I thank you all for coming today. It has been most helpful and interesting.