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Recipient of the 2018 Brain Prize for research for groundbreaking research on the generic and molecular basis of Alzheimer's Disease, the UCL's Professor John Hardy discusses recent progress in dementia research, the strengths and weaknesses of the UK's medical research environment, and the potential effects of Brexit.

You were recently awarded the 2018 Brain Prize, along with Professor Bart De Strooper (UK Dementia Research Institute at UCL), for your groundbreaking research on Alzheimer's disease. Congratulations! Can you tell us about some of the key areas where you and your team have made the most progress in the field of dementia?

What was specifically mentioned in the prize was the amyloid hypothesis about Alzheimer's disease, which was based on our genetic findings, first in amyloid – finding mutations in the amyloid gene in Alzheimer's disease – and later, to a lesser extent, finding tail mutations for intertemporal dementia. And then most recently understanding the role of brain inflammation in Alzheimer's disease.

Genetics across the board in neurodegeneration has led us to understand the underlying biology of not just Alzheimer's disease, but the related neurodegenerative diseases – Parkinson's, frontotemporal dementia or motor neuron disease. For all of these diseases, we now understand

the genetic risk, which is of course that proteins are involved. As we put those proteins together in metabolic pathways, it gives us some of the underlying biology of the diseases. The prize is really the genetic component of that.

The other three people who shared the prize with me really detailed the important biology in the context of Alzheimer's disease. Bart De Strooper dissected the role of the amyloid metabolizing enzymes. He discovered that presenilin is a protein that 'cuts' other proteins into smaller pieces which is an important and complex process in normal cell signaling. Mutations in the presenilin genes cause Alzheimer's disease and Professor De Strooper found that these mutations lead to the production of abnormal amyloid which forms plaques in the brains of patients with Alzheimer's disease. Understanding how these mutations drive the dementia is important for identify new therapies. Professor Christian Haass showed the presence of amyloid in normal fluid and how that was affected by mutations. He has done excellent work in other neurodegenerative diseases. And Professor Michel Goedert has really been the key figure in understanding Tau biology in Alzheimer's disease.

How would you describe your current focus now, and what will be your top priorities going forward?

First, in all the neurodegenerative diseases, we have to get better in identifying people earlier. Detection is crucial before they are sick. Genetics is a big part of that. With Professor Valentina Escott-Price, from Cardiff University, we are using genetics towards prediction. We are now pretty good at predicting who in the general population has a high risk of getting Alzheimer's disease. Just as cholesterol tests are important for preventing heart disease, those genetic tests will be important.

Secondly, we have now got a lot of genes for all of these diseases. For Alzheimer's, we are up to about 40. It requires putting these genes into pathways, which is not just genetics, but bioinformatics. Bioinformatically, it is a matter of tying these genes into pathways. Those are the two areas of research that I am most interested in now.

You have played a very important role in positioning UCL as a world-leading institution in dementia research. How would you say the UK compares internationally in this research side of dementia and neurosciences at-large?

This institution is second in the world only to Harvard in terms of neuroscience. To give one example, John O'Keefe received the Nobel Prize for his discovery of Place Cells in the hippocampus. How nerves work all came from UCL. We are incredibly strong; I would say the strongest in the world, but Harvard might disagree.

In terms of neurodegenerative disease, the Institute of Neurology has been a world center for a reason having to do with the clinical structure of the country. If you had a rare disease in the southern half of the UK, you came to our partner institution right next door, and because there is a National Healthcare System, all people with rare forms of these diseases came to this particular hospital. That is unique in the world. Our nearest direct equivalent is The Institut du Cerveau et de la Moelle épinière – ICM (Brain & Spine Institute) in Paris. That has meant that this has been the best place in the world to do genetics.

In terms of cell biology in Alzheimer's disease, we have historically not been as good as we should have been. I think it is because of the way we funded research. Cell biology takes five to seven years of continuous funding. But we have been operating on three-year funding rounds. As a result, it has been very difficult to build up cell biology work. We, as a country, recognize that this was a weakness in the UK and we needed to sort it out. The Cameron government decided to invest in this and that's why we now have the Dementia Research Institute (DRI), for which we hired Professor Bart De Strooper who is one of the leading cell biologists in the world. We have hired him and given him a mandate and a budget to build this up with longer-term funding. It's like a soccer team – we were lacking a striker and we just hired a great one from abroad.

The UK has historically been one of the best places in the world to discover new medicines. You have traveled a lot and have vast experience here in the UK and internationally. Do you think the UK has lost some of its edge or will lose some of it because of Brexit?

It has not lost any edge yet. Not at all. In fact, I think that over the last couple of years it has gotten better. Are we worried about Brexit? Of course we are. I can illustrate it with the Brain Prize. I am English and my wife is Icelandic. Bart De Strooper is Belgian, and his wife is Belgian. Michel Goedert is from Luxembourg and his wife is a first-rate scientist from Italy. Would those people have here come before Brexit? I don't know. I guess it depends on what form Brexit takes. It's absolutely a concern. Over 50 of the people in my department are from Europe and they have uncertain status after this. What needs to be discussed is not just allowing scientists a free pass to

come in, but what about their spouses and children? This uncertainty is extremely damaging, and it is crucial that it is dealt with in the right manner.

What about the funding that the UK has been receiving from the EU all these years?

Exactly. The government says that they will replace it. Anyone who works in anything having to do with finance says to make sure you have diversification in where your money comes from. The good thing about EU funding is that it is a diversified source. If they take the whole EU budget that we have for science and put it into the Medical Research Council (MRC), that is dangerous because it only requires a change in policy to have a major effect. Currently it is only about 25 percent of our funding, but if it goes up to 50 percent, I believe it is a border-line situation. Diversification is very important for funding.

The other point is that science is now big science. My research depends on international collaborations. We have a great collaborative network on Parkinson's disease that involves Germans, Dutch, French, and Spaniards. That all requires travel and integration.

I am hence very worried about Brexit, and we will see where it goes. It has already caused some damage. The damage is not yet irreversible, but our number of post-doctorate and Ph.D. applications from Europe has already gone down. It is not good. It is survivable, but it is not good for the UK.

Taking a larger view of the UK, what are some of the strengths and weaknesses of the British medical research environment?

The NHS is both the biggest advantage and also the most frustrating advantage. It is so underfunded and it has gotten worse. My wife is a neurologist and she would say that the reason the system cannot cope with a huge number of people with Alzheimer's and Parkinson's is because the neurological services and psychiatric services cannot cope with the increased burden of the elderly. There are no efficiency savings, and that's very frustrating. But because it is one system it is a great benefit. The other strength we have is simply our history.

Why is it that the number of publications is so low in your area versus cancer and diabetes? In 2016 there were 7,000 dementia publications compared to 15,000 for

diabetes and 99,000 for cancer.

I am surprised to hear it is much lower than diabetes. But cancer has had higher levels of investment for a very long time and the field is much better developed. I think things are changing however.

One of the smartest things we have done in this department is hire a first-rate cancer cell biologist to work on Parkinson's disease. She came with a deeper understanding of cell biology than most people who work on neurodegeneration because she came from a really developed area.

Several Big Pharma have encountered successive failures in terms of drug trials in dementia, such as Pfizer who even recently announced they are pulling out of the field, or Lilly and Merck who also faced setbacks. Why is R&D so high-risk and costly with dementia?

We have been slow in recognizing the time frame of the disease. The data was there but it had not been appreciated that the disease starts 15 to 20 years before the patient goes to the doctor. In heart disease it's the same story. The cholesterol builds up 15 to 20 years ago, but people realize it and give statins long before. In Alzheimer's we have not appreciated that we needed to get into predictability long before clinical symptoms. So we have been testing statins against acute heart attacks. That realization has only come about in the last two to three years. We have not appreciated the long-term biology of the disease. Now we know what to do. Some of the things we need to do are being done.

Here I will mention the DIAN trial and the Alzheimer's disease prevention initiative (ADPI), which are the right sort of trials. Another trial we need to organize is a trial in Down Syndrome. All people with Down Syndrome develop Alzheimer's. If they live to 30 they will die of Alzheimer's. We should be testing people with Down Syndrome at the age of 30 to prevent Alzheimer's because they will get it unless we do something. Those trials are long and they are not cheap, that is a certainty.

The future is optimistic in your field.

Optimistic or pessimistic, we have to do this. Dementia is bankrupting Western Civilization, but it is also bankrupting developing nations. It is becoming a major issue in India and China for example. In China, it is a major issue because of the One Child Policy where you have one child and two

parents suffering from dementia. This is something that we can’t afford to lose. We won’t lose. It will work. We will beat it.

A few words to conclude that you would like to send to our international audience?

I was at a meeting with Takeda who wants to invest in academic investment partnerships. AstraZeneca wants to invest in academic partnerships. This, together with the open data philosophy, is really changing science. The fact that we can get companies to work together as partners as well as with academia will really make a difference. It is just too easy to portray the trials as failures, but what is important to bare in mind is that they have taught us so much. The trials are experiments and they have taught us a huge amount about the disease. As long as the data is made available afterwards, it has been transformative in what we learn about the disease.

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