Interview with Nikolai Petrovsky, Professor of Medicine at Flinders University

Alzheimer's Vaccine Breakthrough

By *Japan SPOTLIGHT*

With more than 7.5 million new cases of Alzheimer's disease a year, medical researchers are engaged in trying to discover not only an effective medicine for treatment of the disease but also a vaccine to make people immune to it. Professor Nikolai Petrovsky, director of endocrinology at Flinders Medical Centre in Adelaide with a concurrent position as professor of medicine at Flinders University and research director of a company called Vaxine Pty Ltd, has been working on developing many vaccines against influenza, malaria, and sting allergies, and his team in the United States and Australia have made a breakthrough discovery of a new potentially effective vaccine against Alzheimer's disease. In an interview on Feb. 9, 2017, he talked about both the academic and business aspects of his journey in moving a step closer to developing the world's first dementia vaccine.

History of Research on Vaccines

JS: You are an expert on vaccines. Could you explain your background?

Petrovsky: I originally trained in medicine back in the 1980s. When I completed my medical qualification, I became an endocrinologist and then, in order to get trained in research, I did a Ph.D. My Ph.D. project focused on how to prevent auto-immune diabetes (what we now call Type 1 diabetes). My research was attempting to create a vaccine against Type 1 diabetes, which was a very challenging topic and we still haven't solved that problem. When I finished my Ph.D. I went back to working as a hospital doctor, but also I had a small research laboratory and we started to use the knowledge that we had developed when we were trying to make a diabetes vaccine and not having a lot of success. So I started to wonder whether we could solve other vaccine problems using the same type of thinking. We started to work on more typical vaccines, particularly influenza vaccines and also hepatitis vaccines, to see whether we could improve the current vaccines and make them more effective using the lessons we'd learned when we were doing diabetes vaccine research. And we were successful. So we had found particular ways of taking existing vaccines and making them much more effective. About that time was the 9/11 anthrax letters attacks in the United States where a number of government workers had been killed. George W. Bush, who was the president at the time, announced that he was going to allocate several billion dollars to vaccine research to stop future bio-terrorist attacks, as vaccines were the best way to protect people against things like anthrax or other diseases that may be spread by terrorists. We were very fortunate. We had this research, which showed we could actually improve vaccines and so the US government gave us a grant to apply our technology to a large range of different vaccines, which were related to bio defense including anthrax, Ebola, Japanese encephalitis, and influenza, all organisms which terrorists might potentially use. That meant we started work on many different vaccines all at the same time with this US government money. This work has been very successful; we've developed many vaccine candidates and we started to publish the results of our studies, having developed improved vaccines against these infectious diseases.

Nikolai Petrovsky, Professor of Medicine at Flinders University

Then we started to be approached by different research groups around the world who were trying to develop different vaccines, but having trouble making the vaccines effective enough. One of those groups was based at UCI-Mind in California and they had been trying

to develop an Alzheimer's vaccine for quite some time. They read our scientific papers and they approached us saying can you help us to make our vaccine effective? So we started to collaborate with them — this was six or seven years ago — and we applied our technology to their ideas and we together successfully developed what is currently the most powerful Alzheimer's vaccine that's yet been developed.

A number of Alzheimer's vaccines have been tried in the past and seemed to work in animals but when they were tried on human subjects they failed because they weren't strong enough. Our vaccine is about 1,000 times more powerful than the previous vaccines that were tested over the last 10 years. As a consequence of that, the US government through its funding agency, the National Institutes of Health, has given a number of grants to our collaborators in California to move our vaccine to human subjects. So hopefully within the next two years we'll be able to do clinical trials in human subjects for the first time. Obviously so far we've tested it in different animal models with Alzheimer's disease and it's working extremely well, but of course until we do the human studies we still won't know whether it's truly powerful enough to prevent Alzheimer's if we give it to healthy people before they develop the disease, or whether it can reverse Alzheimer's in someone who has already got it. The current scientific evidence seems to suggest that the most effective strategy would be to prevent Alzheimer's or at least to start vaccinating people very early before there's a lot of damage to the brain. The more severe the Alzheimer's the less chance any of these therapies will work. Our aim now is to target people with very early Alzheimer's.

Ultimately we believe preventing Alzheimer's is a bit like the flu vaccine; it's no good having it after you're exposed to the virus; you have to have the vaccine when you're completely healthy. Hence Alzheimer's vaccines are likely to work best if given to completely healthy people. Alzheimer's develops very slowly and to make sure your vaccine is working you may have to do trials for five or 10 years. It takes a long time to get a result and it is also very expensive. So that's one of the challenges that we face as we go forward into the human studies: where do you find the large amounts of money you might need to do what we call a Phase Three clinical trial, a trial which actually proves without question that the vaccine is working and is safe? You might need to vaccinate hundreds of thousands of people, and of course it would cost hundreds of millions of dollars to do that sort of study. So that will be our biggest challenge. But first if we can prove that it is safe in small human studies and maybe collect some indirect data that suggests it's inducing the right type of antibodies and everything looks promising, then I imagine the money will be made available because the problem is just so big.

Globally it's costing some $1 trillion a year to manage people with Alzheimer's disease and of course that cost is going to go up over the next 10-20 years because the number of older people who are alive is increasing all the time. So I think the projection is that in the next 10 years the cost of dealing with Alzheimer's is going to reach $2 trillion a year. So even if a clinical trial cost $1 billion, it's a very cheap investment for governments to make because they'll be saving trillions if they can actually develop a successful vaccine.

International Academic Collaboration

JS: Your university and the University of California at Irvine seem to be very successful in cooperating to develop an Alzheimer's vaccine. Do you think this kind of cooperation is very effective?

Petrovsky: Collaboration is essential for good research. For many years I was part of a Japanese international consortium managed by RIKEN Institute which was called the FANTOM Consortium and did early work on sequencing the mouse genome. Twenty years ago was the start of all the global genome projects. The Japanese were very good at sequencing and so they generated a lot of data and then they realized they didn't have enough experts to analyze the data. There weren't many people in the world who could do that. So they invited a few select people from around the world, including from Harvard University and Cambridge University, and I was invited to join as well as the only clinician on a team that was otherwise all genomics and bioinformatics scientists. So I would go to Japan twice a year and have a workshop, working together on this data. FANTOM has been one of the most successful international collaborations in the genome area and is still going. It's an extraordinary example of the importance of international collaboration because you often don't have enough experts in one country to solve really big challenges. Climate change is another example of an area where you need all the world's experts to work together to solve such a big challenge.

We see the same in nuclear physics where you have a linear accelerator and a whole lot of countries come together to use that facility. You need the best people in the world to solve big problems and Alzheimer's is a very big problem. It's not productive for individual countries or even individual universities to think they can solve this problem by themselves. It's not realistic. So all the vaccine science that we have done is through international collaboration. We have about 100 collaborations at any one time. We use these collective resources whenever we look at a problem, whether it's Alzheimer's or diabetes or pandemic influenza, and we ask who are the best people in the world that we know who we can bring together in a team to solve this particular problem. With the Alzheimer's project we're now working with a variety of experts to help solve the problem. So I think the future of science has to be in more international collaboration.

Testing for Alzheimer's

JS: You said it would be very important to have clinical tests for people in the early stages of Alzheimer's disease. How can you do that?

Petrovsky: There are different ways we can test for Alzheimer's. There are neuro-psychological tests; there are tools with which you can measure very minor changes in memory in people by getting them to do various exercises like play games. But even with small memory changes we now know there's already quite significant brain damage occurring. So that may already be too late. In order to go earlier than that, before people have any measurable symptoms, you need a bio-marker. People have been looking for bio-markers to detect someone who's going to get Alzheimer's. We know there are some genetic bio-markers. Some people because of their genetics are more at risk, so that's the first thing we can do: we can screen people's genomes for these genes and if they have the particular variants or what we call SNPs (Single Nucleotide Polymorphisms), which are slightly different from person to person, we can work out those who are at higher risk. We can then do blood tests to measure particular abnormal proteins in the blood and they again can indicate people who have risk of developing that disease.

We can also use brain scans, including CT, MRI and PET scans, to look for early brain abnormalities. These are now able to identify abnormal proteins building up in the brain of people who otherwise appear normal. More and more, brain scans are becoming major tools in clinical trials to identify people at risk but to follow them over time as if you can improve the scan; then maybe you are reversing the disease.

Now we have most of the tools we need to not just deliver a vaccine but to work out who should get the vaccine and then to measure whether it's being beneficial or not. It's only in recent years that all the different components have come together where I think we now have a chance to seriously tackle the problem. Now we have the science and the tools to do precise measurements and studies and we now have a better vaccine, so we hope by putting these components together we have a good chance of success.

JS: It might be difficult to say how long it would take to put this vaccine into practice. Some have said three to five years. Would you say longer?

Petrovsky: Yes. It's always hard when you have people who already have symptoms and problems who would like a cure straightaway. But the nature of clinical development is that it is extremely slow. That's the reality. The clinical trials, even once you have the funding, take a long time to organize and complete. Until that's done you can't say for sure that the vaccine is working. So I think three to five years is very optimistic for us to get to human trials. In truth, if it was 10 years that would still be an exceptionally good result because typically a new vaccine or drug can take 15 to 20 years to develop. So if we can do it all in say 10 years, that's still extremely fast.

JS: Money is clearly important in developing a new vaccine. Would you say that public-private partnerships are necessary in order to achieve a good outcome?

Petrovsky: I don't think a vaccine is possible without private industry commitment. But it's also not possible without public commitment. The US government under President Barack Obama dramatically increased the government budget for Alzheimer's research to over $1 billion a year. This money is going to be essential for trials like the ones we'll be proposing to get vaccine candidates to the level where private industry feels that some of the risk has been removed. If private industry looks at early stage research, they usually say it's just too risky and will lose them money. So public funds are needed to support the research to the point where the private companies can see it's almost there, they can then come in and commit hundreds of millions or even billions of dollars to the project because they know it has a good chance of success. Hence you won't have an Alzheimer's vaccine unless there's both strong public and strong private commitment.

Research & Business

JS: You're the founder of the company that's working to create novel vaccine technologies. How did that come about?

Petrovsky: I founded the company Vaxine in 2002 because I could see that if you just do academic research it may result in scientific publications and grants but it doesn't often translate into improvements in human health such as new drugs or vaccines. Someone else has to do that translational work and typically that is for-profit companies. So I thought that if my research was ever going to generate products that would help people, then the best way would be to still run a university laboratory but also have a partner company that could look after the commercialization aspects. The idea was if we had the two together, then it should be an integrated whole. It's really a public-private partnership within an academic research group. That was the motivation and it's worked extremely well. It's been a great model for success because we were able to attract funding for our vaccine projects from the Industry Department. We would apply through the company and the government was happy because we were trying to develop products and that would be good for industry, whereas on the academic side we were able to get grants for research.

So this provided us with funding from both private and public

sources. But in return we've successfully delivered on what we promised. We continue to publish very good scientific papers and do very good basic research. At the same time the company has been able to commercialize products and do human trials to prove that the technologies we've developed are working. It really has been an extraordinarily successful private-public partnering model even though it was initially an unusual model.

JS: Innovative technology is not restricted to vaccines but also applied to such things as Artificial Intelligence. These key technologies appear to need venture activity.

Petrovsky: We've won many innovation prizes, maybe because we always try and be innovative in what we do. This applies whether it's the model of having private companies embedded in hospitals and universities, rather than having them separate, or our approaches to development of new technology where, for example, we are a leader in the use of Artificial Intelligence in vaccine design, having published and given many talks on the topic of "Intelligent Vaccine Design". We also do a lot of work at the cutting edge of nanotechnology. We find by doing futuristic basic research, we can make better products.

JS: You work in Australia and California, which is well known for entrepreneurship. Do you think the venture in California is working well in stimulating innovation in medical science?

Petrovsky: Absolutely. The reason I go to the US so often is their model of bio-technology, which involves a lot of public infrastructure as well as private and public universities, spinoff companies and venture capitalists with a lot of money. The US has a great culture of entrepreneurship. This creates an amazing environment. Nowhere else in the world has even come close to being able to match this; it's the global gold standard. I would encourage our government to embrace this culture but it has been hard to replicate it in Australia as our capital markets are just too weak. The capital in the US is completely unregulated but it works. To be successful in bio-technology you need complete freedom as you can't determine in advance who is going to be successful. The best approach is to give lots of money to very bright people and some will succeed while others fail. This formula generates some amazing successes, whereas I think most other countries don't succeed in biotech because they are too afraid of failure.

Promise of the Vaccine

JS: Whether you're afraid of failure or not, prolonging the human lifespan could provide a huge incentive. How much longer are people able to live with these vaccines?

Petrovsky: One of the problems with Alzheimer's disease is it doesn't kill you any faster. Cancer and heart disease are not such an overwhelming problem for the health system because ultimately they kill you, at which point the healthcare costs stop. A problem with Alzheimer's costs is patients live the same time as people without the condition. The cost and difficulty of managing these people with Alzheimer's is enormous. Our vaccine isn't designed to make people live longer, it's to make them live at a much higher quality of life. This way they'll stay functional and the overall cost to the health system will be dramatically lower.

JS: The Japanese are talking about working into their 90s thanks to these vaccines. Do you think that's possible?

Petrovsky: I know it's possible. The original inventor of our technology, Dr. Peter Cooper, from whom I inherited this research, still works with us. He's 89 and he's still helping me write scientific papers. He has a very active mind. There's a classic example of someone who next year will be 90 who is still able to keep up with the latest in science and make a very valuable contribution.

JS: In order to achieve this it will be necessary to provide these vaccines at a less expensive price.

Petrovsky: If we look at it purely economically, you could argue that we don't have to reduce the cost. Even if the vaccine cost the Japanese government $2 billion or $3 billion a year that would be very affordable because you're actually going to be saving 10 or 100 times that in costs of Alzheimer's to the health system. So for wealthy countries I don't think it's necessary to drive the vaccine cost down to some low level. Even if the vaccine cost several thousand dollars per person, that's still a very cheap investment and a lot of people would pay it. We currently have cancer vaccines that cost several hundred thousand dollars per patient and still governments are paying that money although a lot of us think that's too expensive, particularly if you're only getting a few extra months of life from the treatment. Here you may get an extra 20 or 30 years of high-quality life from our Alzheimer's vaccine. What is that worth to the individual, let alone to the government? JS

Written with the cooperation of Ian de Stains OBE who is a writer and consultant.