Vaccine adjuvants: in search of new paradigms

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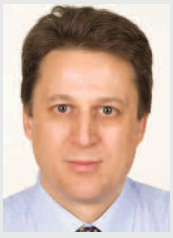

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Interview with Jenaid Rees, Commissioning Editor

Nikolai Petrovsky is the Chairman and Research Director of Vaxine Pty Ltd, an Australian biotech company that specializes in novel vaccine adjuvants. He also holds the position of Director of Endocrinology at Flinders Medical Centre (Adelaide, Australia), Professor of Medicine at Flinders University, Vice President and Secretary General of the International Immunomics Society and serves on the Editorial Board of our sister journal, *Expert Review of Clinical Immunology*. He completed his PhD at the University of Melbourne (Victoria, Australia) then moved to Canberra (Australia) where he held conjoint positions at the Canberra Hospital, University of Sydney, Canberra University, Australian National University and the National Health Sciences Centre. In 2004, he moved to his current position at Flinders Medical Centre. His research interests include vaccine adjuvants, autoimmunity and immuno informatics. In 2009, his company Vaxine won the AMP Innovation Award at the Telstra business awards and Australia's coolest company award from Australian Anthill magazine. He has been an investigator for major international diabetes studies including ADVANCE, FIELD and DREAM and is a principal investigator on several large grants from the NIH. He has authored over 140 scientific papers, and his team has developed novel vaccines against influenza, hepatitis B, sting allergy, malaria, Japanese encephalitis, rabies and HIV, in addition to developing the world's first effective H1N1/2009pdm (swine flu) pandemic influenza vaccine.

What inspired you to specialize in the field of vaccine development?

After completing my medical specialist training, I undertook a PhD in the immunology of Type 1 diabetes at the Walter and Eliza Hall Institute in Melbourne (Victoria, Australia). While the project focused on basic immunology mechanisms underlying this disease, our ultimate aim was to develop a vaccine against Type 1 diabetes. I was involved in human testing of various diabetes vaccines; but unfortunately, none of these were successful. This led to my view that such attempts were premature and more is needed to be known about both diabetes itself and what causes it in order to have a chance of designing an effective vaccine. I then had a chance meeting with Peter Cooper, a scientist from the Australian National University in Canberra, who had been working on a sugar compound called inulin, which he thought would make vaccines more effective. I tested this idea in mice in my laboratory at the Canberra Hospital in combination with a diabetes antigen to find whether like oil emulsion adjuvants it would help induce autoimmune diabetes; at the same time, I also tested it in combination with a more traditional hepatitis B vaccine. Thankfully it did not work for the diabetes antigen, but worked extremely well for the hepatitis B vaccine; so we then formed a company, Vaxine Pty Ltd (South Australia, Australia), to further advance this work, naming the sugar adjuvant we had discovered Advax™. From there, we were successful in 2005 in getting major funding from the NIH to apply this idea to the development of more effective biodefense vaccines, such as for anthrax, pandemic influenza, ebola and smallpox. This is an exciting and fast-moving area. For example, we hope in the immediate future to test Advax for its ability to enhance the immunogenicity of a vaccine against the new H7N9 high

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pathogenicity avian influenza virus that has recently caused multiple deaths in China and could potentially turn into the next big pandemic virus.

■ As the Chairman of Vaxine Pty Ltd what do you feel has been the biggest achievement of Vaxine to date and what are the future directions of the company?

Perhaps the biggest achievement of Vaxine in a broader context has been to reinvigorate the area of vaccine adjuvant research and in the process redefine what is an ideal adjuvant. We have shown that effectiveness of an adjuvant is meaningless if the adjuvant is not well tolerated and safe for human use, something that others in the field seem to have neglected. However, in terms of a single event, it was our achievement with our US partner, Protein Sciences (CT, USA) in developing the world's first effective vaccine against the pandemic influenza H1N1/2009pdm strain (swine flu) that swept around the world in 2009. Using Advax, our adjuvant and Protein Science's recombinant insect cell-derived protein antigen we were able to create an effective vaccine, manufacture it and get approval to commence human clinical trials in approximately 12 weeks from first identification of the new virus, a feat that to the best of our knowledge has never before been achieved in such a short time frame. It was very satisfying to see that our vaccine was highly protective and none of the 271 immunized trial subjects ever developed symptoms of swine flu, whereas many people who had not been vaccinated got sick with the virus. This highlighted the importance of our Advax inulin adjuvant in boosting the immunogenicity of the recombinant influenza antigen.

■ Your recent work has focused on developing carbohydrate-based adjuvants rather than the traditional aluminum adjuvants. What benefit do your Delta inulin adjuvants hold over alum and how do you see these being incorporated into vaccine regimens in the future?

This goes to my earlier point that most adjuvant developers seemed to have ignored the critical importance of a candidate adjuvant being safe and well tolerated for broad human use, including in young children and pregnant women. This is not easy to do and even alum, which has been in widespread use for over 90 years, periodically has questions raised about its safety. Concerns about adjuvant safety are more than theoretical. Going back to my autoimmunity research days, we used to use oil emulsion adjuvants such as Freund's adjuvant alone or in combination with self-proteins such as mylelin basic protein to induce adjuvant athritis or a severe autoimmune brain disease called experimental allergic encephalomyelitis in mice. If you do not add these oil emulsion adjuvants, then you could not induce the autoimmune disease, showing that the adjuvant was playing a critical role in breaking immune tolerance. Fastforward to the present, we have recent reports indicating that a swine flu vaccine containing a new oil emulsion adjuvant called AS03 caused at least a tenfold increase in narcolepsy, an autoimmune disease involving destruction of cells in the brain that keep us awake, in children in Europe who received this vaccine. While we cannot say for sure it was the oil adjuvant that caused the narcolespy, we do know that very similar swine flu vaccines used at the same time that did not contain the oil adjuvant were not associated with narcolepsy, implicating the oil adjuvant as the cause of narcolespy. For anyone who has worked in autoimmune disease models, this would come as no surprise. So when it comes to developing vaccine adjuvants, you simply cannot put enough emphasis on safety first. As a clinician myself, it is an inherent part of our training to put safety of our patients above everything else; and hence from the outset, we set out to make sure we were developing the world's safest adjuvant, not just the most effective. By working with a natural sugar-based structure rather than a highly inflammatory and unstable oil emulsion, we ensured that our delta inulin adjuvant meets every safety challenge thrown at it. For example, it does not cause autoimmune disease such as experimental allergic encephalomyelitis even when injected with self-protein. This initially disappointed us as we thought it meant it was not a potent adjuvant, but in retrospect, this was an amazingly positive finding for Advax, as it highlighted just how safe our delta inulin adjuvant technology is, in that it could not cause autoimmune disease even in a highly genetically susceptible animal model. Moreover, we have since gone on to show that this extraordinary safety profile does not stop Advax adjuvant being a highly potent adjuvant. This was clearly demonstrated when the US government contracted Lovelace Respiratory Research Institute in Albuquerque (NM, USA) to undertake independent studies in their ferret challenge model of our Advax adjuvant with the US's only approved avian (H5N1) influenza vaccine, which unfortunately is not very effective on its own. Advax enhanced the protection provided by the vaccine, so that 100% of the animals survived a lethal challenge, but Advax was able to do this with just a single dose of vaccine, something the contractors had not seen with any other adjuvants they had tested. So we have not only designed Advax to be safe and well-tolerated in humans but it also turns out to be a highly effective adjuvant. Over 20 published, peer-reviewed scientific papers attest to the effectiveness and safety of our delta inulin adjuvant. Many of these studies, including the ferret avian influenza study mentioned earlier, have been conducted by independent research groups. When it comes to properly addressing adjuvant safety issues, a head-in-the-sand mentality must be avoided, as ultimately an adjuvant technology, no matter how potent, will have no value unless it can be shown to be extremely safe in humans.

■ From your experience in leading & collaborating on clinical trials, what would you say are the major obstacles to advancing vaccine adjuvant development?

The single biggest obstacle to adjuvant development is funding. Everyone can see the value of investing in new vaccine antigens, but adjuvants are seen as being more generic, making it harder for people outside the field, such as venture capitalists, to see the value of adjuvants. Another challenge is finding good vaccine antigens with which to partner a new adjuvant. Everyone wants to give you their failed vaccine antigens in the hope that your new adjuvant might somehow turn them into successes, but the problem is that when such a vaccine fails you never know whether the problem was the adjuvant or the antigen. And of course, if

you go down this path and the vaccine fails, everyone is going to blame the adjuvant rather than the antigen! So I spend a lot of time trying to deal with unrealistic expectations by vaccine manufactures of what an adjuvant can and can not do. For example, an adjuvant can not fix the problem of the wrong antigen being selected as a vaccine candidate. Nor is an adjuvant on its own likely to fix the problem of HIV vaccine failure, which has many causes of which insufficient immunogenicity is just one. However, where an adjuvant can do a wonderful job is situations like influenza vaccines where we have vaccines that are only 50% effective by themselves, and we can show that we can use our adjuvants to take this closer to 100% effectiveness. Similarly, we have shown we can do this with a wide variety of other viral diseases such as hepatitis B, Japanese encephalitis, West Nile virus, rabies and so on. However, first you must always start with the 'right' vaccine antigen.

■ As the Chairman of Vaxine Pty Ltd, in your opinion, how has business and other such issues influenced the progression of the field of vaccine adjuvants over time?

By and large, in my opinion, large vaccine manufacturers have hindered rather than helped the adjuvant field, as they are likely to be looking for the quickest and cheapest solution, rather than necessarily the best conceivable candidate. This explains the high use of alum adjuvant, despite the fact that they could potentially make more effective and potentially better-tolerated vaccine by adopting newer adjuvants. Inclusion of a new adjuvant is an additional risk that risk-adverse manufacturers may not be prepared to accept, particularly where they do not own the adjuvant technology outright themselves. Alum is cheap and is already contained in approved vaccines; hence, a vaccine containing alum is not going to be knocked back by regulators on grounds of insufficient safety data on the alum adjuvant. Fortunately, some biotechnology companies that are developing new vaccines want to design the best vaccines possible and do not see it as a very big risk to include a newer adjuvant in their vaccine formulation. Our biggest successes have come from working with smaller and more nimble biotechnology companies rather than conservative big pharma companies.

■ You are well known for your breakthrough in developing the world's first effective swine flu vaccine. What achievement are you most proud of?

I am most proud that we completed the development of the world's first effective swine flu vaccine with absolutely no external funding. It was a big achievement to make the first effective vaccine and to do it without any external support. The typical development cost of a new vaccine quoted by industry is approximately US$1.4 billion; so, creating a new vaccine and confirming its effectiveness in the clinic in the space of a few months with no external funding was nothing short of miraculous. Of course, we are very grateful for all our partners who helped us in this endeavor including our clinical investigators at Flinders Medical Centre where the trial was conducted, the trial subjects and, of course, Protein Sciences Corp. who provided the vaccine antigen.

■ I understand you also have research interests in the field of mucosal-based adjuvants what are you currently/planning to work on in this area?

While injected vaccines that induce systemic immunity will remain important long into the future, we recognize there are situations where it is important to generate immunity at mucosal surfaces. Key examples of this are for protection against herpes virus infection or respiratory viruses. We have, in fact, shown that Advax has a mucosal adjuvant effect if administered intranasally, but the effects of the pilot studies were modest. Fortunately we have access to another adjuvant technology based on alpha galactosyl ceramide that activates natural killer T cells and is proving to be a very potent mucosal adjuvant. We would anticipate having these mucosal adjuvants in human testing within the next few years.

■ Whose work in the field of vaccine adjuvants do you admire?

I admire Alexander T Glenny who is the undisputed father of adjuvants. In 1926, inspired by the observation that horses injected with diphtheria toxin that developed an abscess made higher antitoxin antibodies, Glenny empirically tested a broad range of household chemicals for their ability to enhance antibody production, and thereby discovered the adjuvant properties of aluminium salts. Despite his research being completely empirical, the resounding success of alum as a vaccine adjuvant over the following 90+ years attests to Glenny's skill in deciding aluminium salts exhibited the best balance between potency and tolerability. However, adjuvant developers are now trapped into thinking that only compounds that induce inflammation make good adjuvants. Advax blows that paradigm wide apart as the first noninflammatory adjuvant. Advax is a potent adjuvant, thereby proving that adjuvant action does not have to be dependent on inflammation. In fact, inflammation such as that caused by oil emulsion adjuvants appears to be the cause of many problems, including injection site reactogenicity and the risk of autoimmune disease induction. Get rid of the inflammation as we have with Advax and potentially you remove the problems that have held back new adjuvant development for the 90 years since Glenny developed alum adjuvants.

■ Do you have any words of advice you would give a young researcher entering the field of vaccine development?

Young scientists should not believe everything they are told and in particular should never trust in dogma. The best discoveries always come from ignoring existing paradigms and finding out the answers for yourself by critically analyzing the data. We were told in the early days that Advax could not work well as an adjuvant because it did not induce an inflammatory response, but the data told us otherwise. Fortunately, we realized early on that it was the dogma that was wrong, not our adjuvant! The other thing a young researcher must do to be successful is to show tenacity – it can take a long time for the rest of the research community to accept you are right – in our case, it has taken over 20 years to get to the point where the broader vaccine

community is starting to understand that what we have in Advax is really novel and exciting. So young researchers need to remember that behind any successful vaccine is at least 20 years or more of hard work!

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Financial & competing interests disclosure

The author has financial involvement with Vaxine Pty Ltd, an Australian vaccine development company with proprietary interests in adjuvant technologies that may compete with adjuvants mentioned in this article. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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