Interview

Experiences targeting B cells for the treatment of multiple sclerosis

Andrew Chan and Albert Jan Schutte speak to Jonathan Wilkinson, Commissioning Editor:

Andrew Chan obtained his bachelor's and master's degrees in chemistry from Northwestern University in Evanston (IL, USA) and his medical degree and doctorate in cellular and developmental biology from Washington University School of Medicine (USA). He completed an internship and residency in internal medicine at Barnes Hospital at Washington University School of Medicine in St Louis (MO, USA) before becoming a postdoctoral clinical and research fellow at the University of California, San Francisco. Dr Chan is Senior Vice President of Research Biology of Genentech Inc., a member of the Roche Group, San Francisco (CA, USA). Dr Chan's current focus is to define the heterogeneous causes of human disease and developing new therapies to attack the dominant pathogenic pathways that drive disease in each of these patient subsets. Dr Chan's laboratory is currently working on defining the role of immune cells in autoimmune disease, as well as understanding the mechanisms of action of anti-CD20 and other B-cell modulatory therapies. His research interests include basic discovery in understanding the underlying pathogenesis of human autoimmune and inflammatory disorders. He is also a frequent lecturer and has authored or coauthored more than 100 scientific articles. Prior to joining Genentech in 2001, Dr Chan was an associate professor in the Division of Rheumatology and the Departments of Medicine, Pathology and Immunology at Washington University School of Medicine in St Louis, where he was also a Howard Hughes Medical Institute associate investigator. Dr Chan is also a member of the American Association of Immunologists, the American Society for Clinical Investigation and the American Association of Physicians.

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In 2008, Albert Jan Schutte joined F Hoffmann-La Roche Ltd. in Basel (Switzerland) from Schering-Plough/Organon International (NJ, USA) to take over the leadership of the Ocrelizumab Multiple Sclerosis Life Cycle team. Since February 2013, he has been the Global Medical Director for Neuroscience and Cardiometabolism. Albert qualified as an MD at the Free University of Amsterdam (The Netherlands) and worked several years in Internal Medicine in Amsterdam. He started his career in Pharma as a Medical Advisor CNS with Solvay Pharma in Weesp, The Netherlands. He then joined Solvay Pharma International, where he, as Medical Manager, was responsible for the Middle East and Asian Pacific region. In 1998, he joined Organon International, where he worked almost exclusively in neuroscience (depression, bipolar disorder and schizophrenia). In 2002, he joined the US headquarters, where he was Executive Director for Neuroscience, acting both as Global Marketing Director and Global Medical Science Lead.

■ Could you briefly describe your roles at Roche?

A Chan:

I am the Senior Vice President of the research biology organization of Genentech in San Francisco (CA, USA). These include the areas of oncology, immunology, infectious diseases, neuroscience and ocular diseases.

AJ Schutte:

I am global medical director of Medical Affairs in neuroscience and cardiometabolism in Roche and based in Basel (Switzerland). I lead a team of medical managers or international medical leaders. Among others, we have teams working on late-stage development programs in schizophrenia, multiple sclerosis (MS) and

Alzheimer's disease, who are supported by these medical managers.

■ Can you describe the rationale behind targeting B cells for the treatment of MS?

A Chan:

From our experience, particularly over the past decade or so, B cells have been appreciated as having significantly important roles in a number of different human autoimmune disorders. B cells give rise to plasma cells that make antibodies, and there are many diseases in which antibodies mediate disease pathogenesis. However, it has also been appreciated that B cells are central in guiding the activation of a number of other immune cells in the body, including T cells, dendritic cells and others. In rheumatoid arthritis, vasculitis and, more recently, in MS, our experiences with targeting B cells have actually provided the first major piece of information telling us that B cells play a central role in a number of different human autoimmune diseases, MS being one of them. There are many additional preclinical data trying to understand precisely how B cells guide the immune system in MS. For example, in a number of mouse models of disease, when one gets rid of the B cells, the T cells become quiet, no longer activated, and do not go and destroy other cells types and tissues. In fact, in MS, B cells had been suggested to guide a particular subset of T cells called Th17 cells, which have been demonstrated to have a role in promoting MS disease.

■ Roche is currently developing the antibody ocrelizumab for the treatment of MS. Could you describe its history and mechanisms of action?

A Chan:

Genentech/Roche, in collaboration with Biogen/IDEC, developed the first anti-CD20 antibody, rituximab, which was launched and approved for the treatment of non-Hodgkin's lymphoma in 1997. In 2006, rituximab was approved for the treatment of patients with rheumatoid arthritis who failed anti-TNF therapy. Again, we have had over a decade's worth of experience and understanding of how B-cell depletion therapy may be helpful in

autoimmune diseases. In 2006, we made the discovery that B cells play an important role in MS. This was reported in the HERMES study, a Phase II study of rituximab, for relapsing remitting MS [1]. At that time, however, based on our knowledge of monoclonal antibodies in autoimmune diseases, we knew that the use of chimeric antibodies (such as rituximab) in the long term was not ideal as a treatment option for chronic conditions. We generated a humanized monoclonal antibody called ocrelizumab for the treatment of MS of the chronic nature of this disease. This antibody is a humanized antibody, so it has human components in well over 95–96% of the amino acids and has a far better immunogenicity profile. When we use chimeric antibodies, such as rituximab, in the chronic setting, patients can develop their own immune response to the drug: antidrug antibodies. In the long term, the development of these antidrug antibodies is not good for patients because they clear and get rid of the drug they are receiving. So it was with this intention that we began these studies with ocrelizumab in MS.

■ Could you describe the background of the Phase II trials for ocrelizumab?

AJ Schutte:

The HERMES study was a proof-of-concept study of rituximab in patients with relapsing-remitting MS, providing the first clinical data that supported the theory behind B cells in MS [1]. In HERMES, we saw surprisingly high efficacy, as measured by a reduction in gadolinium-enhancing lesions, a marker of inflammatory activity in the brain that can be quantified on MRI scans. In addition, there was also a reduction in annualized relapse rate, a clinical measure of disease activity [1]. Nobody expected the effect to be so profound because, until then, the disease was considered to be primarily a T-cell-mediated disease.

The ocrelizumab Phase II study consisted of a 24-week primary comparison of ocrelizumab (a treatment course of two infusions) versus placebo and an exploratory comparison with IFN- β -1a in patients with relapsing-remitting MS [2]. Thereafter, all patients received open-label ocrelizumab for three courses of up to 2 years and were

then followed for safety for an additional year. The results from the study supported what we saw with rituximab in the proof-of-concept study [3]. There was a significant decrease in gadolinium-enhancing lesions – lesions were reduced by 89% versus placebo [2]. For the annualized relapse rate, there was a reduction of 80% versus placebo and 66% versus interferon. So, the results of the ocrelizumab confirmed our assumption that B-cell therapy could potentially be a new treatment strategy in MS.

■ **Could you tell us what work has been started with the Phase III trials?**

AJ Schutte:

The ocrelizumab Phase III clinical program (ORCHESTRA) consists of two studies in patients with relapsing MS (OPERA I and II) and one study in patients with primary progressive MS (PPMS; ORATORIO) [101–103]. They are fully enrolled. In the relapsing MS trials, we're comparing ocrelizumab with IFN- β , and we expect results in 2015.

The ORATORIO study in PPMS is based on the OLYMPUS PPMS trial with rituximab [3]. Although the primary end point was not met in OLYMPUS, a prespecified subgroup analysis showed that rituximab had a treatment effect in younger patients who had more active disease by the presence of gadolinium-positive lesions [3]. Based on those data, we took ocrelizumab forward in Phase III in PPMS, a patient population for which it is an unmet medical need because there is currently no approved products for the treatment of PPMS [3].

■ **Why is targeting B cells with anti-CD20 antibodies such an appealing treatment strategy?**

A Chan:

It's through the rituximab and ocrelizumab experiences that we have learned the most about B cells in human autoimmune diseases. There was a concern that B-cell treatment strategies would result in a loss of a significant part of immune protection. Children born without B cells have significant immunodeficiency; they cannot mount an antibody response and require lifelong immunoglobulin replacement to maintain health. What the

experiences with the anti-CD20 antibodies have taught us over the past 15 years is that it is a fairly safe approach. While the B cells are reduced, plasma cells, which are end products of B cells, do not express CD20. Pre-existing antibodies that protect against influenza, chicken pox, pneumococcus, tetanus and so on, are preserved following treatment with anti-CD20 antibodies. What we have learned is that anti-CD20 antibodies selectively remove a portion of the immune system critical in promoting inflammation. Based on the data that we have today, patients treated with rituximab or ocrelizumab preserve critical B-cell subsets lineage cells that are important in immunity. Over time, the B cells come back after therapy is stopped, but the B cells that come back are what are known as naive B cells that are less likely to cause disease. They can become the first line of defense again for the generation of antibodies. I think the surprise was that this is an efficacious drug, with respect to MRI lesions and annual relapse rates based on studies to date. In any therapeutic paradigm we always look at the therapeutic index; the amount of benefit that one gets over the risk of the therapy. So far, based on the preliminary data that we have, it appears that the benefit:risk ratio is actually quite favorable for patients with MS.

■ **How important do you think immunotherapeutic strategies could become in the treatment of neurological disorders such as MS?**

A Chan:

Up until now, the entire field has focused on therapies that predominantly target T cells. Clearly, T cells, the other arm of the adaptive immune system, are important. However, T cells are likewise important for protection against infections, particularly viruses. Similarly, the therapeutic index, or risk:benefit ratio, is quite distinct. What one has to look at when we're prescribing drugs for patients with MS is what the benefit relative to the risk is.

■ **Finally, do you have any thoughts as to where the field is heading?**

A Chan:

Currently, MS is now experiencing an extremely exciting time for drug discovery

and development. There have been a number of major scientific advances over the past 5 years that make us want to re-enter the field. These include all the human genomics that have been done; understanding the risk genes that increase risk for patients. There are a number of whole-genome sequencing efforts identifying molecular pathways that either makes one more or less susceptible; Alzheimer's disease is another example of this. I think the entire area of neurodegeneration, which has always been a black box, is slowly being opened. The application of novel technologies and great science in an area of unmet medical need is usually what the equation is for us at Roche and Genentech to succeed.

References

- 1 Hauser SL, Waubant E, Arnold DL *et al.* B-cell depletion with rituximab in relapsing–remitting multiple sclerosis. *N. Engl. J. Med.* 358(7), 676–688 (2008).
- 2 Kappos L, Li D, Calabresi PA *et al.* Ocrelizumab in relapsing–remitting multiple sclerosis: a Phase 2, randomised, placebo-controlled, multicentre trial. *Lancet* 378(9805), 1779–1787 (2011).

- 3 Hawker K, O'Connor P, Freedman MS *et al.*; OLYMPUS trial group. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. *Ann. Neurol.* 66(4), 460–471 (2009).

■ Websites

- 101 A study of ocrelizumab in patients with primary progressive multiple sclerosis. <http://clinicaltrials.gov/show/NCT01194570>

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The opinions expressed in this interview are those of the interviewees and do not necessarily reflect the views of Future Medicine Ltd.

Financial & competing interests disclosure

A Chan is an employee of Genentech Inc. and AJ Schutte is an employee of F Hoffmann-La Roche Ltd. A Chan and AJ Schutte 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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- 102 A study of ocrelizumab in comparison with interferon beta-1a (Rebif) in patients with relapsing multiple sclerosis. <http://clinicaltrials.gov/show/NCT01247324>
- 103 A study of ocrelizumab in comparison with interferon beta-1a (Rebif) in patients with relapsing multiple sclerosis. <http://clinicaltrials.gov/show/NCT01412333>