Interview

An insight into cutting-edge tuberculosis vaccine research

Else Marie Agger speaks to Katie Lockwood, Assistant Commissioning Editor

Else Marie Agger was appointed Director of the Department of Infectious Disease Immunology, Statens Serum Institut in Denmark in 2011. Prior to this, she had been heading two different research groups focusing on tuberculosis (TB) vaccine research and adjuvant development, respectively. She holds a postdoctoral degree within immunology from the University of Copenhagen (Denmark). Agger has extensive experience within adjuvant research, TB vaccine research and preclinical development of vaccines. In addition, she has previously been involved in antigen discovery, primarily with a focus on developing novel diagnostic tests within TB. She has been involved in the coordination of vaccine delivery optimization within the EU-funded TBVAC and NEWTBVAC consortia and also has previous experience as a work-package leader within an EU-funded project, focusing on adjuvantation of influenza vaccines. Agger is the coinventor of several adjuvant patents and has published more than 60 papers within TB, vaccines and adjuvant research.

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■ **Why did you initially become interested in vaccine research?**

That's a really easy one. I studied biology at the University of Copenhagen (Denmark). There, I absolutely fell in love with immunology; reading through the material I thought, this is what I'm going to do in my future career. When I reached the end of my studies, I had to do a thesis and I decided to do my work related to the thesis outside the university environment because I wanted to do something that was more translational. I was very lucky that I could combine my interests in immunology with vaccine research, which has a very translational angle to it. The career path has been very satisfying as I am dealing with diseases posing serious problems to the human race and therefore my work can have a real impact – I am very proud of this.

■ **With such extensive experience in tuberculosis vaccine research & adjuvant development, could you indicate a personal highlight of your scientific career?**

One highlight, in particular, would be that we successfully moved a vaccine adjuvant all the way from research to clinical trial. We began with a crude formulation, which was sometimes a little bit foamy and very heterogeneous, but we solved these problems and were able to produce an adjuvant

that has been showing promising results in humans. So I think that has been the highlight – being able to start from scratch and take a brand new, novel adjuvant system to a first-in-man trial.

■ **Could you explain your involvement with EPI-Expose?**

EPI-Expose is a project which is funded by the Danish National Advanced Technology Foundation (Copenhagen, Denmark). The idea is that what is recognized by the immune system during disease is not necessarily what will protect you against the disease. Therefore, we want to induce the immune responses that are not there during infection. This work really derives from an old project, where we had observed that protection against tuberculosis (TB) arises not only from induction of the epitopes recognized during infection, but also new epitopes, which we can induce, such as cryptic/subdominant epitopes. We think that the infection pushes the immune system and it pushes the cytokine profile and the quality of the T-cell response against the very dominant epitopes. Therefore, responses against these very dominant epitopes will become exhausted over time. However, if you can induce responses that are not pushed by the infection, then we think you may see better protection against disease.

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This phenomenon is not only seen in TB patients, but also in HCV-infected individuals who are able to cure themselves. In these individuals, we see a very broad response against a range of epitopes. This is a very different pattern from what we see in chronically-infected HCV patients, who have a very restricted response towards very dominant epitopes. There are a range of other examples also from the HIV field where subdominant epitopes are believed to play a key role for maintaining control of infection. The aim of the EPI-Expose project was to really try to nail this down, using three different diseases: two of them being infectious diseases, TB and HCV, and the other being cancer. It is a very difficult project as although there are a lot of studies that support the idea of targeting subdominant epitopes, transferring this into a practical approach for vaccination is very challenging.

■ The EPI-Expose project has focused on vaccines for HCV, bone marrow & TB, are their plans for any other diseases?

No, not at the moment. We are doing a prostate cancer trial and will see how that works out. We are continuing studies on TB and will soon submit papers on this, as well as for HCV. As our work is dependent on external funding, the future direction of our research depends to some extent on the source of our funding.

■ With regard to your recent work with microsphere formulation & their method of antigen presentation, how do you think this will influence the field of TB vaccine research?

I think maybe the most important thing deriving from this work, is that we now know a lot more about how adjuvants actually work. Adjuvants are known as immunologist's 'dirty little secrets,' meaning we know it works, but we don't know how it works, we just add it. Therefore, adjuvant research has been very empirical, basically just a trial-and-error approach. I think it is really important that we know a lot more on how the adjuvants work and that is the key thing, not only for TB vaccine research, but for all diseases where you need a cellular immune response. We don't

have an adjuvant at the moment, which is approved and which gives rise to a T-cell response, but we need that. Knowing more about how the adjuvants work and what we should do to optimize them will be crucial if we are ever going to get an adjuvant on the market that can give rise to a cell-mediated immune response.

■ Do you think that the new insights you revealed in the trehalose dibehenate adjuvant mechanism will open up opportunities in terms of vaccine development?

Indeed, we are getting more and more knowledge, not only on how the various adjuvant formulations work, but also on the different immunomodulators that we are adding into our adjuvants. However, in order to make real 'smart vaccines,' for example, adjuvants customized to different disease targets, we really need to improve on our knowledge further. Toll-like receptors (TLRs) have really been the topic over the last decade but now we have started to see other types of ligands being tested. In this regard, trehalose dibehenate (TDB) is not a TLR ligand, TDB is targeting the C-type lectin receptor, and I think there will be a lot more of these non-TLR immunomodulators that we can use as immunomodulators, and combine into adjuvant formulation. Therefore, I think in that sense it has been quite important to see that TDB can also generate a very vigorous immune response and be used in a practical setting in an adjuvant formulation.

■ You showed that Th17 memory can be induced by immunization. Do you think the Th17 response is something that should be further investigated due to its protective potential against mycobacterial infections?

Yes, definitely. We can induce different types of immune responses, at least in the laboratory, and being able to transfer that into a practical situation and into an adjuvant that can give rise to the Th17 memory will be very important. We now know that there are a lot more T-cell subsets than we originally thought and we need to investigate the details behind this if we want to

make really smart vaccines, where we can design or customize our adjuvants for the various diseases that we want to vaccinate against.

■ **Peptide vaccination strategies have shown some success in recent years, what do you predict to be the greatest challenges of this field in the coming years?**

The strategy that has been used is to select the most immunodominant epitopes, or the ones which are expected to be recognized based on *in silico* predictions. Based on these predictions 10–15 peptides of interest are then identified, combined into one formulation and used for vaccination. We know from *in silico* prediction what is recognized; we may also have tested this in human individuals using blood samples from patients, but what's really lacking is the knowledge of what happens if you take these 15 different peptides and add them together in the same formulation. Will some maybe inhibit the response to others? If some are much more dominant than others, will you only see a response towards the most dominant peptides? What adjuvant is really optimal for this? Is it different if you vaccinate with peptides in oil and water emulsion compared with, for example, liposomes? Can we integrate the peptides inside the liposomes and, if so, would that be preferable? Could it then protect them against degradation? So we lack a lot of information on the formulation and what happens when we combine these 15 peptides together and inject them. This will be a personal focus for me in the coming years.

■ **What do you envisage the future of TB vaccine to look like?**

Just recently there was quite a big event in the TB vaccine research field. The results of the first proof-of-concept efficacy trial were revealed by an Oxford group [1]. The group has been testing a MVA85A vaccine

in South Africa in almost 3000 babies. The babies were monitored for up to 3 years following vaccination to look at protection in vaccinated versus placebo groups. Surprisingly, there was absolutely no effect of the modified Vaccinia Ankara vaccine. This result has been quite a shock for the entire field and we are still trying to find our footing and determine how we should proceed. There is a lot of animal data from the MVA85A studies, which needs to be revisited in order to assess whether or not they really predict that we were not going to see any protection or whether we need to improve our animal models. Therefore, it is a critical time point in TB vaccine research as the first, clinical proof-of-concept study has failed. It is difficult to predict what will happen after this, but we may see many of the approaches being reassessed to determine if what we are doing is good enough.

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Reference

- 1 Tameris MD, Hatherill M, Landry BS *et al.* Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled Phase 2b trial. *Lancet* 381(9871), 1021–1028 (2013).