

# Targeting immuno-inflammation: where industry and academia interface

Although inflammation is a necessary biological process in response to injury and disease, at abnormal levels it is also responsible for a significant annual health burden. Immune-mediated inflammatory disease is present at a prevalence of about 7% in the Western world and with an ever aging population this is set to rise. While treatments for some of the more common inflammatory disorders such as rheumatoid arthritis (RA) do exist, there is still a large unmet patient need as many sufferers do not achieve remission of symptoms even when using currently available therapies. Immuno-inflammation is one of GlaxoSmithKline (GSK)'s key therapeutic areas of interest. Helen Albert speaks to Paul-Peter Tak, Senior Vice President and Chief Immunology Officer at GSK, about his career and the work he is doing at GSK to encourage scientific innovation and target unhealthy inflammation in all its forms.



**Paul-Peter Tak** began his career in academia with a PhD in Immunology at the University of Leiden in the Netherlands. He moved to the Academic Medical Center (AMC) of the University of Amsterdam in 1999, where he became Professor of Medicine. During that time, he worked very closely with the biotech and pharmaceutical industry as a consultant and started several companies including a biotech company developing a gene therapy for RA called Arthrogen. In 2011, he joined GSK as Senior Vice President and Global Head of Research and Development (R&D) in Immuno-inflammation, while still maintaining research links with the AMC. In Jan 2016, he started as Senior Vice President for a group of therapy areas covering immuno-inflammation, oncology, dermatology and infectious diseases. He also currently leads the Development Steering Team which oversees late-stage development in R&D at GSK.

## **What made you decide to move from academia to industry and how have you found the transition?**

I'm a physician, a physician scientist, and I studied medicine to influence the life of patients in a positive way. I've always focused on three things in academia - trying to be a really good physician for my patients and to listen to them and give them the best treatments of the day, that's one. Second, to start to discover and develop new medicines for the future, and the third is of course about training and education of physicians who became medical specialists. I was the head of department in Amsterdam for 12 years, but I thought perhaps I could have a bigger impact on patients' lives if I joined a company like GSK. If you develop medicines here that really make a difference, you have the potential to touch the lives of millions of patients. I decided that with the resources, the technology, the high level of the science and the academic collaborations that GSK has that I could make a big difference here. So that was the reason that I joined. Of course it was a big step, because I was in

a very senior role, also in an international organisation, and I didn't really know what I was signing up for. I had worked very closely with industry, but I'd never been an employee of industry. But I think from the day that I joined I really enjoyed it, it was like stepping into a warm bath in many ways. What I really liked was the rigour of the science here, the very high quality, the collaborative atmosphere and that people have a common goal to discover and develop medicines for patients who need them. At the same time, I have continued to be very strongly linked to the academic world, so I guess I have had the best of both worlds.

## **What is the GSK immunology network?**

We have a lot of collaborations with universities and academic institutions and also with biotech and other pharmaceutical companies. I think we have more than 500 research partnerships, some of them are very strong. The Immunology Network, as I've called it, is I think, a very innovative model of working with academia and has different components. The first pillar of the network is the External Immunology Board; we work with absolutely top immunologists from around the world who all have a slightly different profile. For example, some people are focused on neuroimmunology, others on immunometabolism and so on. Then the second pillar is the immunology catalyst and this is for senior academics who want to come into GSK for an extended sabbatical. If selected, they can come and work in our facilities in Stevenage in the UK, which is one of the two major Research and Development hubs in the world for GSK, where we give them support in terms of postdocs, personnel and the lab, but they continue to do their own independent research. They have a badge to get into our facilities, but they are not GSK employees. They continue to be employees from their university and we reimburse the university so they keep their academic independence, which is deliberately the model. The third



component is the Immunology Innovations Fund that I started. If there is a great idea in the Immunology Catalyst, which does not fit into one of the current funding schemes, then I can use money from the Immunology Innovation Fund to bring it to the next inflection point and then we may decide to start a biotech company around it if the academics are interested, and then they would become the founders, or we might internalise it and it could become a GSK program. The 4th and last pillar is the organization of the Immunology Network Summit Meetings where the external immunology board members come together with the immunology catalyst members and the immunologists in GSK. They are a bit like Keystone meetings, the level is similar, and it creates something completely new I think. So in part It is about internalising the external world and bringing in the independent academic voice into GSK.

#### **What do you think are the hot topics in inflammation research right now?**

Well there is a lot going on in inflammation. We call it immuno-inflammation, because it's quite difficult to distinguish between the immunology and inflammation, as it's so strongly linked. It is a very important field in terms of the prevalence of disease. Immuno-inflammatory disorders are common and there is still a very big unmet need. There are many conditions where we don't have any treatments. For some of the conditions where we do have quite a lot of treatments, like RA, there is still a very big unmet need, because at least 50% of the patients do not achieve remission and that is the goal of treatment. In the last 5 or 6 years, immuno-inflammation at GSK has been quite successful. We've built a very strong and holistic portfolio. I will give you a few examples, as these are what we believe are hot topics. One example is the world of epigenetics, where of course we enter a completely new field where you ask the question, what are the factors that determine whether a gene is activated or switched off? How can we interfere with that? Another very hot area for us is the world of pattern recognition receptors. A very specific program, a key programme in our immune-inflammation therapy area unit, is around receptor-interacting protein 1

(RIP1) kinase, which plays a pivotal role in necrosis, apoptosis and necroptosis, all different forms of cell death, but also in cytokine signalling. So it plays a very important role in different diseases. Because this is such new biology, where we have developed a kinase inhibitor that only touches RIP1 kinase, you can see we have something that could be very interesting in terms of benefit-risk ratio. We have very strong preclinical package in a whole variety of disease models and we've published extensively on this. But then of course with such new biology the question is where is it going to work? Therefore, we're using a systematic experimental medicine approach, where in parallel we are testing the effects of a RIP1 kinase inhibitor in RA, psoriasis and ulcerative colitis, but there are also other programs outside the immune-inflammation area where we are exploring the role of RIP1 at this moment. So that is something that is very exciting for us. In addition, we have a focus on T-cell biology, especially Th17 biology, which is for us a very important field. We are also working on cytokines, chemokines and complement, and these are all key areas that I find very exciting at this moment in immuno-inflammation.

#### **What have you discovered in your studies of vagus nerve stimulation in rheumatoid arthritis and why does the bioelectronic treatment approach hold promise for individuals with immune-mediated inflammatory disease?**

This is work I completed outside of GSK. I am still affiliated at the University of Amsterdam and am still a non-salaried Professor there. I did this work during the last 10 years in Amsterdam and I've tried to





### **What research is GSK carrying out to help develop better treatments for RA?**

We have several programs in RA, which is the most common chronic autoimmune disease. However, we are definitely not limited to RA in immuno-inflammation. We have a focus on rheumatology, so also the other rheumatological syndromes like osteoarthritis, Sjögren's syndrome, systemic sclerosis etc., but also gastroenterology and dermatology, so that all sits in immuno-inflammation. The programs that we have that are developing treatments for RA at this moment at GSK include the interleukin (IL)6 monoclonal antibody sirukumab, which is currently under review by the regulators. The difference between sirukumab and let's say tocilizumab, the anti-IL6 receptor antibody from Roche which is on the market, or sarilumab, which was recently approved, is that these other two medicines target a receptor, whereas sirukumab targets the ligand. We partnered with Johnson & Johnson on that program. In addition, an anti-granulocyte macrophage colony-stimulating factor (GM-CSF) monoclonal antibody is being tested for treatment of RA and currently in phase IIb trials. This may have different advantages compared to other medicines. First it's a very different pathway targeting really the key effector cells in RA, namely the macrophages in the synovial tissue and the neutrophils in the synovial fluid. It works in a slightly different way to TNF blockers and it actually targets the monocytes and the macrophages that are the major sources of proinflammatory cytokines in the joint. But it has also been shown in preclinical models that GM-CSFs play a particularly important role in pain, so we are quite interested in the specific effect on pain in RA and osteoarthritis. And then I think there is still an outstanding requirement for a safe and effective small molecule and we hope that RIP1 kinase inhibitor might play that role. Then we have a few other programs that we have not disclosed as well.

### **What promising developments in the inflammation arena in general have made over the last couple of years, both by GSK and others?**

Well I would pick probably the IL17 inhibitors and the IL23 inhibitors, as I think they are very important. I think anti-GM-CSF also has enormous potential. We are very excited by this medicine for a variety of immune mediated inflammatory disorders, some of which I have spoken about. I think we have a systematic approach to extend this to different indications, where a specific mechanism may play an important role. Again with RIP1 there is huge interest from the

complete that. I discovered that the so-called alpha-7 nicotinic acetylcholine receptor (alpha-7) plays a key role in the joints in controlling inflammation. This is how we got interested in it. I used alpha 7 knockout mice and found that in models of chronic inflammation in RA these mice have increased arthritis and increased distortion of the joints. If you do the reverse and you give these mice nicotine, which triggers the alpha-7 receptor or specific alpha-7 agonists that activate this pathway, you can inhibit arthritis. In a collaboration with a company called SetPoint Medical, based in the US, we stimulated the vagus nerve, which also leads to activation of the same pathway, for 60 seconds per day and we found that you can reduce inflammation and protect joint destruction. We then did a clinical trial in humans and when we implanted the device in humans with RA, we could show there was a beneficial effect even in patients who are therapy resistant.

scientific community, so I think that's another very important development as well. And then of course there are the Janus kinase (JAK) inhibitors, the highly selective JAK1 inhibitors, which are of interest. Of course we need to see over time what the benefit-risk ratio is, if we get more experience, but definitely an interesting development.

**In addition to developing new treatments for inflammatory disease, have you had much success repurposing old drugs for new indications?**

I would not even call it repurposing of medicines, because ideally we need to do this at an early stage of development and go into different indications where we believe a specific mechanism plays a role. I think RIP1 is probably a very good example, but for all medicines developed, we take the approach to investigate multiple indications. Especially in medical specialities like rheumatology and gastroenterology, what we call a disease is not really a disease, it's a syndrome defined by clinical signs and symptoms. These conditions are heterogeneous, and may be driven by completely different mechanisms. Interestingly, you can see on average the same efficacy if you treat a patient with RA with different therapies that target different pathways. For example, TNF blockers compared to rituximab, which targets the B cells, compared to tocilizumab, which targets the IL6 receptor. The mechanisms are completely different, but also the patients who respond to these treatments not the same necessarily, highlighting the importance of individualized health care approaches to improve treatment effects. The other way around, all of these medicines may work in diseases other than RA. Another example would be belimumab, which has been approved for treatment of lupus now in four phase III clinical trials. They were all positive which is quite amazing, because it's such a difficult disease to treat and many competing molecules have failed. Then the question is could it work in other autoantibody dependent immune mediated inflammatory disorders? And we've tested it in different conditions. There is a clinical trial going on in Sjögren's syndrome, another autoimmune disease characterised by autoantibodies. We have also tested it in very rare diseases like idiopathic membranous glomerular nephritis, which is a truly autoantibody dependent disease. In a small experimental medicine study, we could show that there was a very significant decrease in the levels of autoantibodies, followed by a very significant decrease in proteinuria, which is a key hallmark of the disease. So that's an example of what I call expansion of indications, where you really get more confidence in the mechanism and where you can see based on the molecular events rather than just on signs and symptoms. Maybe a good example from respiratory would be mepolizumab, an anti-interleukin

5 antibody that we have developed for asthma that we are now testing in a variety of different diseases that are all characterised by increased eosinophils, because IL5 drives eosinophilia. We have just announced that we are going to start a phase III clinical trial in nasal polyps. We are testing it in COPD, there is a condition called hypereosinophilic syndrome (HES) where we are testing it. There is a condition called eosinophilic granulomatosis with polyangiitis (EGPA), where we have published positive results. We are also testing it in atopic dermatitis, so I think that creates a very mature example of how based on the mechanism in common diseases like eczema, it is also possible to treat rare diseases like EGPA.

**What do you think the future holds for inflammation research and the development of new therapies for inflammatory disease?**

The future is to induce remission in all patients. Something that we only achieve in a minority of patients at the moment and in many diseases we don't achieve it at all. To do this, we need to use different modalities where necessary. I spoke about small molecules and biopharmaceuticals, but we will also use other approaches. Ultimately the goal should be to cure the patients or to even prevent the disease. You may have heard me speak about type 1 diabetes in the past, which is also an autoimmune disease. Based on autoantibody profiles you can identify people who are at risk of developing the disease and during that stage you could perhaps interfere and stop the process from developing towards full-blown clinically established disease. I have done a similar study in RA, wearing my academic hat again. So I think that is the future - remission, cure, prevention - using different modalities and with a deep molecular understanding of the subsets of the disease. ■

**Further reading**

- Nature Jobs Blog - From academia to industry with Paul-Peter Tak <http://blogs.nature.com/naturejobs/2015/01/12/from-academia-to-industry-with-paul-peter-tak/>
- GSK website - Targeting the immune system through open innovation [www.gsk.com/en-gb/behind-the-science/innovation/targeting-the-immune-system-through-open-innovation/](http://www.gsk.com/en-gb/behind-the-science/innovation/targeting-the-immune-system-through-open-innovation/)
- F. A. Koopman, M. A. van Maanen, M. J. Vervoordeldonk, P. P. Tak. Balancing the autonomic nervous system to reduce inflammation in rheumatoid arthritis. *J Intern Med.* 2017; 282(1):64-75. <http://dx.doi.org/10.1111/joim.12626>