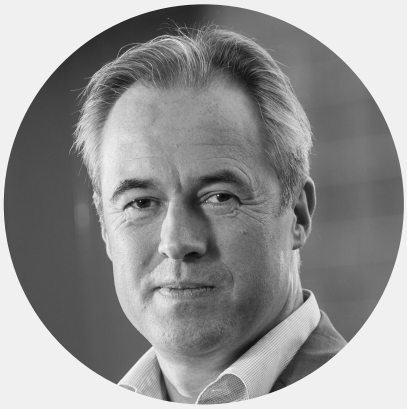
Interview: Bart Roep – Director, Diabetes Expert Center, Leiden University Medical Center (LUMC), the Netherlands



16.10.2015

Tags: Pharma, pharmaceuticals, the Netherlands, research, r&d, life sciences, type 1 diabetes, diabetes research, embryonic stem-cell therapy

Winner of the Dutch Prix Corona Gallina in 2011, Prof. Dr. Bart Roep discusses his groundbreaking research into type 1 diabetes; his wishes to deal with the cause rather than the symptoms of this disease and the current research climate in the Netherlands.

Introduction to Bart Roep and his current research and academic responsabilities.

I studied life sciences and medicine and I found it much more rewarding to treat the cause rather than deal with the symptoms. As such, over the last 25 years, I have been working on understanding the cause of type 1 diabetes; the treatment of which has been limited to dealing with the symptoms for the last two thousand years. It has really become my life's mission to understand the cause of this inflammatory and auto-immune disease and develop intervention therapies to deal with it because there is a real unmet medical need. It is a very interesting arena because, as there is no established medication, we have no competition and we have a blank slate. We have already gained spectacular new insights into diabetes and I am delighted to have been able to contribute to that. We are currently in the process of translating these findings into effective immune intervention therapies and although inflammatory diseases are usually dealt with systemically, we are assessing a novel, tissue-specific therapy. In that sense, diabetes is ahead of

the troops in terms of MS and other diseases where we know less about the particular components which contribute to the disease.

I also discovered which immune cells are important for destruction and what they recognize and I pioneered gene therapy and, for my current arena, tissue specific vaccination with a group at Stanford. I am a member of big consortia such as TrialNet of the National Institutes of Health (NIH), the Juvenile Diabetes Research Foundation (JDRF) and Innodia which is an IMI2 (Innovative Medicines Initiative) partnership between the industry, academia and clinics. I think that the experts who I am working with there have received around thirty-four million euros in funding so this is a very interesting, new time. When I started, pharmaceutical companies were not interested in our type of therapies but that has changed completely and now big companies such as GSK, Sanofi, J&J and Novo Nordisk are partnering so that we can move forward more quickly and be more focused.

You have been active internationally as a lecturer and with organizations such as the JDRF; how would you assess the Dutch research environment compared to other countries?

Dutch medical research has always been very strong and, in fact, we rank third or fourth in the world in this arena. All the Dutch universities rank in the top 100 in international ranking and the combination MD/PHD is a real hidden gem in Dutch medical science academia. In immunology we have had major contributors and discoveries in the past and more recent times. However, in terms of type 1 diabetes, there are relatively few players so we work globally with a European Consortium, North American-European Consortium and we receive international funding which is quite unusual. Normally, the NIH may be less keen to sponsor overseas but they do in the diabetes arena and so does the JDRF which looks at who is doing the research rather than where it is being done. As a consequence, I have not had funding problems. Traditionally the Netherlands has a fantastic history in charity. We are, therefore, used to depending on door-to-door fundraising and having attractive, huggable studies that people can relate to.

In terms of funding, I know many of my friends here in the Netherlands have, unfortunately, had huge problems funding their research, particularly if it is not obviously translational. Funding problems started creeping in around 2008 and the fact that I chose a field which appeals is not a merit, its luck and it doesn’t make my work better than that of my colleagues who are not receiving funding.

Are there areas in which the university's life sciences research activities could be improved?

The Netherlands has an excellent reputation for new technologies and Philips has integrated this into their core business. However, we still need a lot of emphasis on new technologies such as imaging, closed loops, better sensors and better prediction algorithms because bioinformatics is an incredibly important area. In addition, we need to conduct investigations based on individuals rather than big groups: in the past we looked for magic bullets which simply did not exist and when you revisit the patients you treated there are sub-groups with particular benefits and groups suffering adverse reactions or even acceleration. There is an urgent need for sophisticated precision medicine and I think this will be the future of medicine in the Netherlands and beyond.

Also, the lack of a national registry is a big problem because we do not know how frequently some diseases occur, for example, figures vary from 80,000 to 120,000 thousand cases of type 1 diabetes. If you cannot get the numbers right, it will make it very difficult for our stakeholders, including the insurance companies to make up their minds. However, this problem will not be easily solved.

What can other countries learn from the Dutch?

Being half Danish, I can look at the Dutch from a different perspective and I would say that the Dutch have a very direct approach to many issues; they don't beat around the bush and that saves a lot of time. Moreover, the Dutch system is horizontal so students will tell me when I am wrong whereas in neighbouring countries this would be completely unheard of. But I think it's great when a student disagrees with me because it means they are engaging with the work and it makes me think and I would rather that *they* told me than someone at a Keystone symposium! This is a quality which I really appreciate and value. Also, the Dutch are free thinkers used to thinking out of the box and, to mention just a few, they are the inventors of wi-fi, Bluetooth, compact disks and doughnuts. Another advantage here is that, as a small country, we have a very international mindset.

LUMC has been involved in many ground breaking developments recently including demonstrating the relationship between celiac disease and type 1 diabetes. What sort of impact are these studies having on diabetes research worldwide?

Well, it was a bit of an eye-opener if not a wake-up call. The fact that many inflammatory diseases result from modifications is a lesson learnt from celiac disease ten years ago or from cancer which we could have translated much sooner. It is changing the way of thinking completely because the

text book definition of auto-immune diseases is a mistake of the immune system but, in a way, it may be a response of the immune system with the best of intentions to deal with cancer or stressed tissue. That is a different concept because it brings the tissue into the picture which is something that we, immunologists, have been forgetting. We need to remember that it is a dialogue and if we bring in the tissue we may realize that some of the medication which is effective for type 2 diabetes may also benefit type 1 diabetic patients in a different way. I think this illustrates the importance of a multidisciplinary approach.

We are also involved in embryonic stem-cell therapy where the diabetes field is a pioneer and it is very exciting because of the potential impact it could have on patients who have been told that they have an incurable disease. There is, therefore, a lot of pressure from all the stakeholders which is the disadvantage of being a pioneer but the cherry on the cake is, of course, that if it works it could make a real difference. In the past, people said that a diabetes vaccine would be impossible but now I am wondering if that is really the case.

Could you elaborate on the project which you led to develop an “integrated approach from basic research to treatment”?

Sometimes you have to take a step back and one of the frustrations I have always had with genetics is that yes it is important to know which genes but it is more important to know how and benefit from that to translate it to therapies. With stem-cell therapy around the corner, I am trying to understand how genetic protection works because we are not too far from gene therapies or regenerative medicines. In this way, it is like taking a step back to see what more we can learn from the basics.

The other part of that program was the translational thrust for which we wanted to have short programs which could reach clinical assessment within five years. This was actually successful and I almost get goose bumps because it is so exciting to conceive an idea from the basics and then start to treat patients and see whether it works. In terms of speed, we are not hindered by the current medication which is suppressing the immune system; if you bombard the immune system into submission then it is very difficult to teach it how to do it right. Moreover, we convinced our regulatory agency that animal models were a distraction rather than a requirement and, although it does not always apply, that is a major mind changer. I am not against animal models but I am against wrong models and if I want to treat children with type 1 diabetes and I take human proteins then I don’t really care what happens in mice and that saves a lot of time.

What would you like to accomplish over the next five years at the LUMC?

Now that I have recognized that you can complete the translational path, I have become even more ambitious. In the past, I was not allowed to speak about curing diabetes and now I am invited to do so. In terms of strategy, I am aiming to step outside of the box over the next few years and use biologicals and cell therapy. For this, I am collaborating with an organization in California which knows how to use biologicals and is in the top ten for cancer therapies. There is a lot of collateral damage from cancer therapy and it is related to auto-immunity so I can learn a lot from this and perhaps tweak it to cure auto-immune disease. Industry collaboration and an integrative approach are also among my priorities because multidisciplinary research in a multidisciplinary setting is the key to success.

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