Interview: Jos Raats â?? CEO, ModiQuest, The Netherlands

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The CEO and founder of ModiQuest discusses how, with its unique, fully-integrated antibody generation and development platform, the company is developing antibodies for potentially groundbreaking therapies for the prevention and treatment of rheumatoid arthritis and growing its already well-established CRO arm serving clients from around the world.

Could you introduce ModiQuest to our readers?

The company was founded in 2004 as a spin-off from the department of Biochemistry of the Radboud University of Nijmegen. Within academia, we discovered a novel, highly specific diagnostic for rheumatoid arthritis (RA) that was based on a protein modification called citrulline and we managed to patent this invention and start to commercialize it as the cyclic citrullinated peptide (CCP) test for RA. The inventors of this test, Prof. Ger Pruijn, Prof Walther van Venrooij, and myself, thought that we could use this invention to start a company in which we would embark on a quest for other protein modifications that might be of use for developing novel diagnostics, especially for

autoimmune diseases. Hence the name of our company: ModiQuest. Our scientific strategy was to focus on the discovery of novel biomarkers based on protein modifications to develop diagnostics for autoimmune diseases. However, this broad scope appeared a little over-enthusiastic, so quite quickly after the start of the company we decided to focus on the citrullinome and to dive further into the biology of citrullination to explore whether we can identify ways to improve the citrulline based diagnostics for RA and whether citrulline or the citrullination pathway can be used as a therapeutic target.

In order to carry out that R&D program, we set up a number of different technologies, the majority of which were focused on antibody generation from autoimmune patients. We initially focused on improving existing technology platforms rather than developing new ones. In the early days, when we started to do R&D in the area of autoimmune diseases and to be able to tap into the repertoire of autoimmune patients, we used different recombinant antibody generation technologies for the discovery and development of antibody tools and reagents for our diagnostics R&D. We used, for example, ModiPhage, and ModiSelect, an optimized B-cell selection approach, to clone antibodies derived from individual B-cells from patients and animals. Additionally, we vastly improved standard hybridoma generation methods by developing a very efficient electrofusion technology called ModiFuse to discover novel antibodies. Thus, from the start of the company, we had three different pillars, covering all possible antibody generation/discovery methods available, supporting our antibody discovery platform. Having all these different antibody generation technologies in-house, allowed us to use and make antibodies from human sources as well as from a range of other species, enabling us to take on difficult projects. Furthermore, we used phage display to assemble our in-house libraries based on patient repertoires, as well as fully naÃ¯ve human repertoires, which proved vital for the further development of the company.

As a result of having developed and/or improved these technologies, shortly after setting up the therapeutic arm, we received requests from companies asking us to generate antibodies for them. This is when we decided to start our services arm, ModiQuest Research. All technology developments were initially done jointly between the CRO and the therapeutic arm, allowing us to continuously improve our common technology platform, that we use to generate reagents, therapeutic lead molecules or diagnostic molecules either for internal projects or for our pharma and biotech client base, for therapeutics and diagnostics, human and animal applications.

Can you tell us a bit more about the current stage of development for your treatments for Rheumatoid Arthritis?

Everything that we have developed in the arthritis field is built on our core expertise, the citrullination pathway. Citrullination is the result of the activity of a family of enzymes, the Peptidyl Arginine Deiminases (PADs) that actually generate the citrullinated modifications on proteins not normally present in healthy individuals; they occur, for example, in areas of inflammation damage. Citrullinated proteins play a role in activating the inflammatory cascade, are damaging to tissues and might be causal to (e.g. RA), or at least are involved in the development of certain autoimmune diseases. The two approaches we have initially been following in order to interfere with the citrullination pathway, were 1) the use of PAD enzyme inhibitors; and 2) anti-citrullinated protein antibodies (ACPA). The latter , binding to specific epitopes generated by these PAD enzymes cause the inhibition of disease causing biology, resulting in a therapeutic effect.

Our therapeutic tACPAs were discovered when we were developing a more human disease like animal model for RA. We wanted to introduce the anti-citrulline antibodies from RA patients into these animal models, since these are also present in human patients. We obtained our first anti-citrulline antibodies from RA patients via recombinant antibody technology. After introducing a set of different ACPA into the mouse disease model, we were surprised to find that, rather than

aggravating the disease, one or two of these ACPA were actually preventing the inflammation. This observation was the start of our therapeutic anti-citrullinated peptide antibody (tACPA) programme that is now in an advanced pre-clinical phase. From this early finding, we have developed a family of tACPA antibodies. The current tACPA lead antibodies are capable of preventing the onset of inflammation in two RA animal models. We have shown that tACPAs interfere with a part of the innate immune system, the formation of Neutrophil Extracellular Traps (NETs) by neutrophils, which is one of the very first events to take place upon infection or at sites of cell/tissue damage. This Mechanism of Action opens up potential utility beyond RA including diseases like pulmonary fibrosis and colitis. In April 2015 we spun out a single asset company called Citryll (www.citryll.com) to further develop and commercialize the tACPA programme. This new company is headed by Helmuth van Es, an experienced bio-entrepreneur, who was also a co-founder of Galapagos, Audion Therapeutics, Antabio, and Effecta Pharma. He has been involved in numerous (pre)-clinical development programs. Currently we are in discussions with pharma and biotech companies as potential partners for a co-development alliance. We are also talking to selected venture and corporate capital funds and high net worth individuals. Attracting funds in The Netherlands for innovative, relatively high risk programs is challenging and we engage with selected internationally active funds as well as are exploring moving the company to the more innovation, friendly countries like Belgium, the UK and the US.

It sounds like a really unique therapy as it can prevent the onset of RA. Is there anything else which sets it apart?

Unique about our approach is the pathway, as citrullination was relatively obscure until a few years ago, and more importantly, the mode of action (MoA) of our tACPA therapy. It is truly a multipronged approach that extinguishes the source of auto-antigens and NETs derived toxic molecules instead of broadly targeting inflammation or acquired immunity. The latter are the MoAs of the current medicines like anti-TNF antibodies, small molecule Jak inhibitors and antagonists of B cell biology like anti-CD20 antibodies. We believe that drugs that block NET based auto-antigen production have the potential to create fundamentally, potentially game changing, new treatments to prevent or treat autoimmune diseases including RA. There is at least one other company looking to inhibit the PAD enzymes but this approach has quite a high risk of side-effects since the PAD enzymes also have an epigenetic function and so if you fiddle around with them it is a slippery slope in regard to safety. Our antibody approach only targets the epitopes once NETs have formed, it can not interfere with gene regulation, and being an antibody not a small molecule, with other intra-cellular processes in healthy cells. The primary niche we are looking at is in early RA as our therapeutic approach prevents inflammation and exacerbation of the disease, and prevents joint damage. We observed in animals that if you treat them early on they suffer no tissue damage to the joints. Because we target NETs we target the source of autoantigens, preventing the onset and/or exacerbation of RA.

In the last ten years, ModiQuest Research has successfully completed over 250 antibody generation and development projects for clients in Europe, the US, Asia and Russia. So what is it about the services of ModiQuest that is so unique as to attract clients from all over the world?

When we began, as far as I know, we were the only company which used a very broad spectrum of different technologies for antibody generation and that was one aspect that our clients liked. In addition, the fact that we usually succeed with difficult targets (companies who tried something somewhere else and when it didnâ??t work they came to us, and got their antibodies), means we have a good track record, and a stable pool of recurrent work form clients. We also have a good mixture of clients from different background (biotech and pharma) which is ideal as it allows us to work on a large number of different projects and, in this way, we constantly are able to improve our technologies. We continuously invest in R&D and everything we work on for our internal research

programs will benefit our clients in terms of the services we can offer them. It is essential to continue improving our company and ensure we can meet our clientsâ?? needs, otherwise one would lose out. For example, we are currently offering our new technology ModiVacc which is a new vaccination approach allowing us to generate antibodies against cell-surface proteins that are very hard to generate in a classical way. This novel approach has attracted a lot of interest from big biotech and pharma, and allows us to generate business around lead generation for intractable targets that is at the high end of the CRO market.

What attracts companies to seek the services of a company like ModiQuest in the Netherlands as opposed to in other countries where prices may be lower?

Well companies do, of course, also go elsewhere. They will go to, for example, China and India for standard research projects but often, for more difficult projects which werenâ??t successful in these locations, they come to us. Another important factor for our clients who are outsourcing more and more, is proximity, ease of communication, short communication and decision lines, as well as price. These matters are very important if you engage in complex collaborative R&D projects where exchange of material, and quick decision-making is essential to success. Ultimately, companies come to us because we offer something unique, provide quality and reliability and have a good track record.

As a service provider, what are the main challenges which you face with regard to meeting the needs of your clients?

You have to keep track of the needs of your clients as these change over time, which means you have to bring in new technology to the table regularly to tap into a new target space and individual, validated targets. Targets are becoming more and more difficult, the therapeutic focus changes and you have to make sure that you have the right offerings to be able to accommodate your clients. Although, not everything that we do is unique, we are very skilled at what we do, the combination of novel proprietary and more established approaches and technologies that we provide, allows us to mix and mingle all kinds of different technologies and platforms to fit seamlessly into our clients needs, which in fact makes us quite unique.

Is there a moment that you are most proud of?

I am most proud of where we are now because, without external investment, we have built an innovative pipeline of molecules ready for clinical testing. We have also succeeded in establishing a CRO service that is well recognized within Europe and the US and which is growing rapidly. In 2004 we started with half an FTE and there are now around twenty people in the company, and this year we had a revenue growth rate of at least 30% that we project to be even higher by the end of the year, so I am very proud of that achievement. On the therapeutic side, I am very proud of the fact that we discovered the CCP RA diagnostic, and from that we were able to build our own therapeutic pipeline of tACPA molecules, and we now reached a point that we are ready to go to the clinic with our lead molecule.

What is your personal vision for both the therapeutic and CRO arms of ModiQuest over the next five years?

My personal vision for the CRO side is that we keep on growing and that we develop a well-established business relationship with most of the big and medium pharma and biotech in Europe and the US. For the therapeutic arm, I really want to get our tACPA lead molecules into the clinic as quickly as possible. It is innovative, fits in the sweet spot of current healthcare thinking of personalized and preventive medicine, and is not limited to RA but with potential for various other diseases where NET dysregulation is contributing or causing the pathology. Moreover, we strive

towards repeating the tACPA example and generating value for our other therapeutic programs and bringing them towards clinical testing.

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