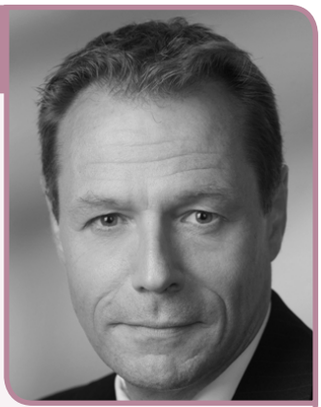
IN CONVERSATION WITH **GEERT MUDDE**

Chief Scientific Officer, OncoQR ML GmbH



Geert Mudde, Chief Scientific Officer, OncoQR ML GmbH

Dr. Geert C. Mudde received a Ph.D. in immunology from the University of Utrecht in 1985 and started his international professional career at the SIAF in Davos in 1989. In 1992, he joined the pharmaceutical/ biotech industry, where he held several senior management positions at the Novartis Research Institute in Vienna, Austria, the Parke Davis Research Institute in Fresnes, France, Ingenium Pharmaceuticals, Martinsried, Germany, and at igeneon AG, Vienna, Austria. Finally, in 2006, while joining Baxter BioScience in Vienna as interim manager, Dr. Mudde co-founded the biotech company f-star Biotechnology, where he served as "Chief Scientific Officer" from 2007 to 2009. In 2009, together with Christof Langer, he started to develop the S-TIR™ technology platform for human specific therapeutic vaccines which led to the foundation of S-TARget therapeutics GmbH in 2010. Since then he serves as CSO and managing director for S-TARget therapeutics as well as for the S-TIR™ technology spin-off companies OncoQR ML GmbH and TYG oncology Ltd., which were both founded in 2013.

On the auto-antigen specific B-Cells, the vaccine co-crosslinks with CD32B with a B cell receptor. This is a negative feedback signal that normally prevents further antibody formation. How is it possible that antibodies are generated?

This is a very important question and yes, when I designed the vaccines I was afraid that this would be a negative factor in our technology. The fact that we co-crosslinked CD32B and the B cell receptor is a negative signal, but we already have a signal or a cell that is shut down anyway. Apparently, activation of TLR9 completely overrules all the negative feedbacks that you could think of. Especially in the B cells the feedback that we co-crosslinked the CD32B and the B cell receptor, this still leads to internalisation of the CbG parts of agonist of the TLR9 ends up in the endosomes and that overrules the negative feedback loop that normally happens.

You generate very strong auto-antibody titrates, why are there no side-effects?

Side-effects of a cancer immuno-therapy are very much dependant on the target that you chose. If we look at the gastrin target of tick 100 then it is proven that you can live without it. So if you completely neutralise G17 which is a factor that under normal conditions regulates the PH of stomach in adults, it is also a tigrine growth factor for pancreatic cancer cells. If you remove gastrin, as we do with the enormous number of antibodies that we use, there is no issue, so the knockout mouse is happy if you knock it out as an adult. For her too it is slightly different, you know that her septine may have an occasional side effect profile, usually related to pre-treatment with chemotherapy, but there can be some side-effects. There are some animals not treated with chemo-therapy, so we do not have that kind of potent shade of side-effects. I think that the most important thing here is that if you use an antibody as a monoclonal and you infuse a bulk at the same time, then all of the receptors will be occupied by the huge number of antibodies that you have used and they get killed at the same time. This leads to cytokine storms and all kinds of other effects.

In our case we induce an immune response which acts quickly, but not too fast. It acts in days rather than in minutes and that means that you can slowly start to generate antibodies which then slowly start to bind the receptors. Then you get the killing much more gradually. In addition, the first four antibodies that are induced are of less affinity than the ones that we have after three of four immunisations, so this is the most likely reason we do not see side effects. We have looked at everything that we can without killing the animals and haven't seen any side-effects and the histology is completely gone so it is functional.

You claim that you control the negative checkpoints that prevent the immune system from responding to the tumours. Which checkpoints are these and do they include PD1, PDL1 etc.?

This is a question that I get regularly when I present this data. I think we don't yet know all the checkpoints that are available. Currently PD1, PDL1, LEC3 etc. are in the middle of the intention because we have monoclonal antibodies against them, but I think that there are a lot more and if we go on researching them there will be many, many more. That is probably the reason why just inhibiting one with a PD1 inhibitor or a PDL1 is not successful in all cases, you most probably must control or inhibit multiple checkpoints with the risk of course of inducing even more auto-immune disease. Apparently by activating the PDCs, the significant role in the immune system through TLR9 you take away any relevant checkpoint. I don't know which one they are for this antigen, but I can see from our data that all of them are gone because we get huge responses, more than you would expect and more than I expected at the beginning. It is also known that if you inject that into a solid tumour the tumour goes away. All the tumour infiltrating T-cells which are shut down by the tumour and the dendritic cells which are in the tumour will become activated and kill the tumour directly. Of course, you can only do this with a solid tumour which is big enough to inject into. By combining it in a vaccine, we mimic that response and we take away any relevant checkpoint inhibitor. I don't know which and I cannot test it either because I have outbred monkeys, I do not have inbred monkeys.