"TAKING OFF THE BRAKES AND FLOORING THE ACCELERATOR" OF THE ONCOLOGICAL IMMUNE RESPONSE

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Geert C. Mudde received a Ph.D. in immunology from the University of Utrecht in 1985 and started his international professional career at the Swiss Institute for Asthma and Allergy Research 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, at the Parke Davis Research Institute in Fresnes, France, at Ingenium Pharmaceuticals, Martinsried, Germany and at igeneon in Austria. In 2006, while joining Baxter BioScience in Vienna, he also co-founded the biotech company f-star, where he served as CSO. In 2010, together with Christof Langer, he founded the 1st S-TIR™ technology-based company S-TARget therapeutics GmbH, an allergy company. In 2013 they founded the spin-off companies OncoQR ML GmbH and TYG oncology Ltd, both focusing on active immunotherapy for oncology.

Would you say the hype surrounding cellular therapy in immuno-oncology is justified?

In general, I think especially the CAR-T cell is really hyped. This is a therapy that needs at least 10 more years of research before it becomes a drug for everybody. It's far too expensive and it is extremely dangerous. CAR-T cells are an artificial way of mimicking T cell responses and I don't think that's the way to go. One of the major concerns is that a CAR-T cell uses the specificity of a monoclonal antibody but with a much more vigorous killing mechanism. If for instance you take Herceptin, a monoclonal treatment for breast cancer. Herceptin kills HER2 expressing tumour cells per ADCC, however, the killing is not as efficient as when you would put that antibody on a T cell; it would kill with the same specificity but much stronger. This is dangerous, because where the monoclonal is still listening to the laws of immunology, meaning it doesn't kill unless the density of the target is high enough, the CAR-T cell doesn't care about density; it kills whenever it sees its target. This is extremely dangerous, because HER2 is also expressed at low density on normal cells. CAR T cells are good for leukemias. There we know that if you take all the B cells out, there's no problem, and they'll come back. However, for solid tumours, this is a no-go and it needs a lot of research to make it safe.

Looking beyond this kind of therapy, what strategy do you think could have a greater impact on cancer treatment?

I think it will go in the direction of combinations. The current immuno-oncology immunotherapies have become possible after the discovery of monoclonal antibodies, from the early 1990s until now. The funny thing is, they're always either mimicking a B cell response or they are mimicking a T cell response, never both. However, there is a reason why the immune system has developed B and T cells simultaneously. Today, there was somebody in the opening session who said "we have this checkpoint inhibitor and we're going to combine it with another passive immunotherapy". The problem is that these therapies are so expensive; you can't combine them, or nobody can afford them. When these artificial monoclonal immunotherapies, which are produced in large tanks of 20,000 litres (imagine what that does to the environment), were developed, there was no alternative specific therapy available. It was well known that the immune system could kill tumours, but it didn't do its job and it was unclear how to change that – well that's changed now. 10 years later, in the early 2000s, people started to understand what is necessary to turn an immune response on or off. We're putting that knowledge into our technology platform and as a result we have massive T cell and B cell responses in a polyclonal fashion, not a monoclonal response, where the tumour can modulate the epitope and escape. When it's polyclonal, the tumour cannot modulate that; it needs to take the whole protein away, in which case it can't use the function of the protein anymore. Simultaneously, to the induction of antibodies that recognise this cell surface target, we induce cytotoxic T cells that will also kill the tumour specifically. That's what nature has evolved towards over millions of years. Yet people are still looking only at T cells, never both parts of the immune system. I truly believe that both parts of the immune system are needed, current immunotherapies only use 1 side of the immune system at the time.

Could you tell me more about your company's platform itself and how you're approaching it?

The talk is about taking the brakes off and flooring the accelerator. Taking the brakes off means you take the negative checkpoints away and accelerating means you add activators, for example OX40 specific antibodies. Each individual may use a different set of positive and negative checkpoints, which are not induced by the tumour but by the immune system to prevent autoimmune disease. This is why it is so difficult to find biomarkers that predict the outcome of such treatments. With our technology, we're taking the brakes off completely and we are flooring the accelerator, without knowing which negative or positive checkpoint or which activating checkpoint are involved in the process. It is not necessary to know this because we do it through the antigen-presenting cell and in an antigen specific manner. By incorporating the tumour (auto)antigen into our technology platform, the autoantigen is presented by activated dendritic cells, never by an immature or resting dendritic cells. As a result, there's a fast and extremely strong immune response both at the B and T cell level. If you compare that to classical vaccines, like tetanus or rabies or Diphtheria Toxoid, the immunization schedule comprises of a priming injection, three months later a boost, and then six months later another boost. If you're lucky, you get 100 micrograms of specific antibody. In our case, within three weeks after only two injections, we already have 150 micrograms of IgG specific for the autoantigen. The difference is that the classic vaccines start from naive B cells, which need to multiply, mature and undergo an IgG class-switch. In our case we start from a pool of pre-existing circulating autoantigen-specific B cells, which have been shut down by the system to prevent autoimmune responses. We can activate these cells all at the same time, hence inducing a fast and strong response in a very short period of time. In fact, checkpoint inhibiting monoclonals try to do the same thing with the tumour specific T cells. However, these monoclonals are not specific for tumour specific T cells, so they activate every memory T cells with autoimmune disease as a result. In our case, we activate only those cells which are specific to the tumour antigen, which is part of the vaccine. We have seen no side effects.

What are the main challenges you're facing then in the development process?

The main problem is that the checkpoint inhibition hype is taking away so many patients and is costing so much money, that there's no money available for new innovative approaches. Another real problem of the checkpoint inhibiting is the lack of biomarkers that predict which patient is going to respond apart from the 20% and 40% that respond by chance.

There's obviously so much hype around checkpoint inhibitors, but certainly some of the statistics regarding patient response are concerning. While it can be successful, do you think the cost and time it takes is justified?

That's why these treatments cost > €300,000 – it is because they're spending so much money on clinical trials, still failing to find biomarkers which increase the success rate. This has a direct effect on companies like us, there is not much money left and they are so focused on what they're doing right now that they're afraid of doing something new, as long as the competition is doing the same thing. I've worked for Big Pharma; I know how it works. They talk about being unique, but in reality, they usually do what the others are doing. Unless we are able to support the last step, and show human clinical (phase I) data, we will have to wait for a company that is brave enough to finally give it a try. Our unique selling point is at the same time a problem: our therapy is human-specific. It only works in humans and in non-human primates; we don't have mouse data. By the lack of tumour bearing mouse data we make use of reversed development; This means we look at the clinic and figure out which type of antibody/immune response works for which type of cancer. If we can show that those antibodies/immune responses are induced in our vaccinated animals, you have the best indication that the therapy works, especially because of >97% genetical homology between human and monkeys. This is what we've done for our prototype vaccines; we have demonstrated that our vaccines induce the therapeutic antibodies/immune responses, which have also been shown to be essential in the clinic and on the market. In addition to that, the response we induce are polyclonal (as nature wants it) so we induce multiple other antibodies, which have additional anti-tumour functions. Herceptin and Perjeta, for instance, kill HER2 expressing tumours by ADCC, but not by CDC. The animals that we vaccinated with our HER2 containing vaccine (OQR200/TYG200) produced antibodies which killed HER2 expressing tumours cells by ADCC but also by CDC. Apart from antibodies recognising the exact epitopes of Herceptin and Perjeta, as well as antibodies that recognize epitopes that allow CDC, we also induce cytotoxic T cells that recognize and kill cells expressing the same antigen., thus simultaneously attacking the tumour with all possible tools available to the immune system. I am very confident that this is going to work.

What are your main priorities across the next year?

We just need one company that is brave enough to take the money in hand and do the trial with us. The risk is not that big! We have very convincing monkey data. All companies are using mouse models. The mouse has only 70% homology with human immunology, the monkeys have 97%. So far, we have tested three different vaccines, on more than 60 non-human primates, and we have 100% of responders. Moreover, these are outbred animals, which means that individual monkeys will use different checkpoint combinations for to prevent auto immune disease against the same autoantigen. Let's assume that there are 2 patients who need to get treatment for HER2 over-expressing breast cancer. Both are tolerant to HER2. When treated with a checkpoint inhibitor, it could mean that one patient would be able to kill HER2 positive cells while the other patient would not. This is because they are using different checkpoints for the same autoantigen. These checkpoints were not induced by the tumour but by the immune system itself, to prevent autoimmune disease. However, in case those patients were to be treated with our vaccine, the checkpoints from patient 1, as well as those of patient 2 would be removed. It is not important which ones they are, as long as for the period of the treatment, all the relevant checkpoints are completely gone. Fortunately, when the treatment is stopped and the antigen is again presented under normal conditions, everything will return to normal and natural tolerance is restored. The only definite changes are that the pool of reactive cells is expanded, and we also have good indications for affinity maturation of the induced antibody response. Importantly, we are not causing any autoimmune diseases. As indicated above, when the antigens are presented in the absence of the vaccine tolerance will re-appear. So, both the tumour and the normal tissue will actively turn off the memory to prevent autoimmune disease. However, we can reactivate the response again anytime we want. As long and often as it takes to cure the tumour. In case of our pancreas cancer vaccine TYG100, we can give two immunisations in the first 2 weeks and then we can wait 6-7 months before we need to reimmunize, because the neutralizing IgG titers are slowly going down. In the case of a vaccine where T cells are also important (OQR200/TYG200), we'll probably have to re-immunise every 2-3 months.