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Euro Bioparma 2018: Next generation immunotherapy: tumour specific control of immune checkpoints- Geert C Mudde- OncoQR ML GmbH

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Using the S-TIR??? technology platform for human specific therapeutic vaccines OncoQR ML has developed two prototype vaccines for treatment of pancreatic cancer (TYG100) and breast cancer (OQR200). Vaccines derived from this platform consist of two modules, the disease specific module, ???immunogen??? and the generic module, ???warhead???, which directs the vaccines to CD32 on antigen presenting cells, especially pDCs and B cells. The immunogen in oncology is a tumour associated auto-antigen, against which under normal conditions no clinically relevant immune responses can be induced. We will present conclusive proof that it is finally possible to overcome all the tricks of cancer cells to prevent therapeutic immune responses. No more need for bulk infusion of very expensive and artificial monoclonal antibodies, which either try to mimic tumour specific B cell responses (e.g. Herceptin and Perjeta) or try to activate cytotoxic T cells that by chance may also kill tumours (e.g. Opdivo, Yervoy, Keytruda). S-TIR??? vaccines fully activate both arms of the patient???s own immune system resulting in tumour specific polyclonal IgG responses simultaneously with the generation and activation of tumour specific cytotoxic T cells. The responses are reversible and boostable, thus allowing fine-tuning of the clinical responses on a patient to patient basis. S-TIR??? vaccines in contrast to the current checkpoint inhibitors do not induce autoimmune disease and are tumour specific.

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.

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.

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 so by combining it in a vaccine we mimic that response and we take away any relevant checkpoint inhibitor and I don't know which and I cannot test it either because I have outbred monkeys, I do not have inbred monkeys

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