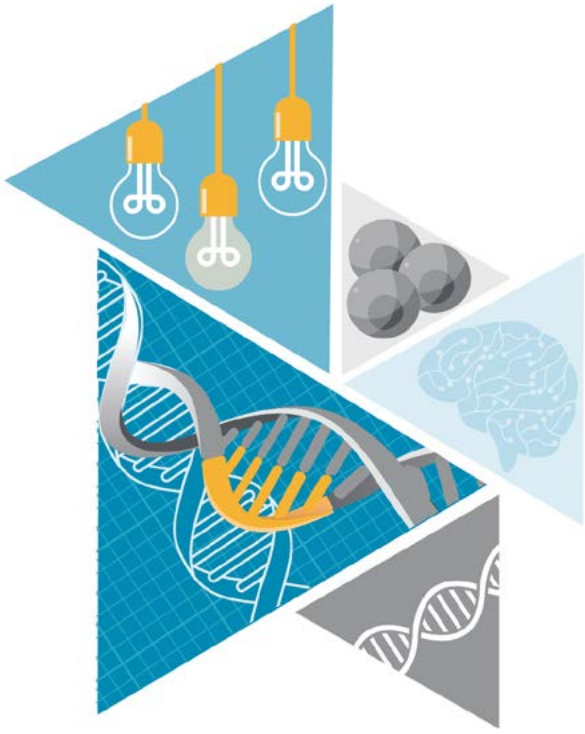
CELL & GENE THERAPY INSIGHTS



Innovation Insights

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INTERVIEW

Current and future directions for dendritic cell vaccines

GERARD BOS was born in Wageningen, The Netherlands. After Medical School and a PhD program on immunology (both at the medical school in Maastricht) Gerard Bos started training in internal medicine in Maastricht and The Hague. After training for internal medicine he was trained as a Hematologist followed with a fellowship at the Daniel den Hoed Cancer Centre, Rotterdam, for 3 years (head Professor Dr B Lowenberg). Thereafter he obtained a fellowship (Clinical Research Award by the Dutch Cancer Foundation) to perform a 2-year research program on tumor-immunology (Leiden, Brussels and Utrecht). He started in Maastricht 2000, as internist-hematologist. His extra focus is on M. myeloma and chronic myeloid leukemia. Preclinical research has a focus on cell therapy: development of cancer vaccines, the role of natural killer cells in the fight against cancer and immune reconstitution after bone marrow transplantation. Under this topic special attention is present for a possible role for vitamin C in immune reconstitution. In 2013, he was appointed a professor of medical education and tumor-immunology. In 2016, he was appointed a professor of immunology of cancer. Since 2015 he has been CEO of CiMaas, a biotech company with a focus on immunotherapy.

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Q Tell us about CiMaas and your current projects

GB: CiMaas is a start-up company from the University of Maastricht in The Netherlands, where we worked for 15–20 years on immunotherapy in general. One of the things that came out of that academic work was research relating to the activation of dendritic cells (DC) in order to get good antigen presenting cells. We observed that we could improve the maturation cocktail.

You have to mature a dendritic cell to make it a correct antigen presenting cell, and you can do this in several ways. While investigating these methods, we found out that interleukin (IL)-12 is an extremely important molecule to active immune cells, and T cells especially. We then worked on improving the IL-12 produced by dendritic cells, and that led to a patent that we believe is superior for a number of reasons to all other dendritic cells that have been assessed in clinical trials to date.

So we are now looking to test this approach in a clinical trial. We're starting in lung cancer and are currently talking to the authorities about what is the best way to do the Phase 1 followed by a Phase 2 clinical trial. We expect that we will be able to dose our first patients at the end of this year, providing all the regulatory aspects go smoothly.

We've chosen not to go to a CMO – we've built our own GMP facility close to Maastricht with this study in mind – again, we are just waiting for regulatory approval in order to be able to use that cleanroom facility to make the product ourselves.

Another key decision was to study our dendritic cell vaccine in clinical application not as a monotherapy, but only in patients who are also being treated with a checkpoint inhibitor. Checkpoint inhibitors are more or less the standard of care in several cancer indications now, including some patients with lung cancer. However, there is unmet medical need, because the value of checkpoint inhibitors is still limited: only a relatively small subset of patients really respond to them, and additionally, checkpoint inhibitors as a first line treatment don't necessarily offer a very long progression-free survival benefit – less than a year in metastatic lung cancer, for example – meaning that treatment is far from optimal.

One popular theory behind the limitations of checkpoint inhibitors is that a lot of patients' tumors do not provide adequate antigens, meaning the immune cells do not know what to respond to. That's a problem we try to solve by giving a vaccine to a protein, WT1. In effect, we want to see whether the combination of a vaccine and a checkpoint is better than checkpoint alone.

Q What are the key challenges you're facing in the clinical translation of this technology?

GB: There are several, but number one is always money. Clinical trials are pretty expensive, at least for people like us

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who are used to working with scientific grant money. Validation of scientific work is a big step. Both the need to produce the cells in a GMP environment and organizing the trials are costly – we need a couple of million Euros to do a Phase 1/2 study. So finding investors is a big focus for us at the moment, because while we do have the money available for this initial study, the aim will of course be to continue with a larger Phase 2 study as quickly as we can.

Unfortunately, there is also a lingering negative perception of dendritic cell vaccines due to the fact they haven't been really successful in the clinic thus far. Provenge remains available on the market, but it has enjoyed limited success due to its relatively low efficacy. Again, though, we really feel that the combination of a dendritic cell vaccine with a checkpoint inhibitor can help overcome that particular issue and open the field up again.

Q How do you reflect upon the ups and downs for DC vaccines since Provenge started its pivotal clinical trial journey, and can you go into more depth on what gives you cause for new optimism today?

GB: I think the answer to that is simply 'more knowledge'. More knowledge on what a dendritic cell actually is, and on what the best dendritic cell might be. If you look at what those earlier programmes defined as a dendritic cell, it was different to what would be considered as an optimal dendritic cell today. And as I mentioned earlier, our scientific papers demonstrate that the amount of IL-12 produced by the dendritic cells is crucial – the more IL-12, the better the T cell response. That's relatively new knowledge. In the past, people were happy that their cells were producing any IL-12 at all, but our cells produce it on a totally different scale to those earlier approaches. That might also be true for other cytokines, such as IL-15.

So I really think it's our basic knowledge, that everyone is doing, not only we of course, a lot of people in the world study dendritic cells. And that will lead to a better chance to get a result.

It's the same as anything else – as CART, for example: it's the science that moves the field forward and spawns new generations, and we are fortunate to work in an area that has always attracted a healthy amount of academic investigation. That basic and translational science has

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really developed over the past decade – you could certainly argue that the early approaches that reached late-stage clinical trials and in the case of Provenge, the market itself, were just too early.

Of course, there are others who aren't keen on patient-specific therapeutics, period. That's another reason why the autologous DC vaccine field has moved forward in the clinic relatively slowly, and why other companies, such as DCprime in The Netherlands, are trying to work with dendritic cell banks to see if they can solve these patient-centric cell therapy concerns. But this concept is for leukemia only, as far as I know, and not for other diseases and indications. It is not a platform like our DC.

Q What are your thoughts on the allogeneic DC vaccine field and its prospects?

GB: It's a completely different concept, I think. Because the cell is allogeneic, it's liable to be destroyed by the patient's immune system so if you bring in antigens via a donor DC cell, you might profit from cross-priming. It has little to do with presenting peptides in an autologous class 1 or class 2 system, as our platform seeks to do. But let's certainly hope they are successful in leukemia.

Q What challenges do you foresee for your approach moving forward, and how will CiMaas seek to address them?

GB: One of the key issues in dendritic cell vaccination is still the route of administration. Where should you inject these dendritic cells – intravenously? Subcutaneously? Can you inject them intranodally? There still isn't any sort of agreement on the best option. Linked to this question of where the cell should be injected to get the best immune response is the question of how many cells you need.

With this uncertainty comes risk. You might have great cells but the wrong system to get them into the patient and to the right location for presenting antigens to the immune cells (which we consider to be the lymph node).

Some people are pursuing intranodal delivery, but that's not easy and also leads to the destruction of the lymph node. Will that lead to optimal presentation, though? We still don't know. And so we're still working, and will continue to work, on whether you can make comparisons of the routes of administration. People have already demonstrated good success via different routes, so we do know where to start in this regard.

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Q CiMaas also has an NK cell therapy candidate in development – what can you tell us about that?

GB: Our scientific and clinical interest in NK cells comes from the fact that as hematologists and transplant doctors, we worked in mice models on haploidentical transplantation – like many others, we were motivated to solve this problem of having to find HLA-matched donors for bone marrow transplantation by finding a universal donor for everybody. So we investigated whether it might be feasible because at that time, there was very little evidence that haploidentical transplant would be feasible in patients, due to the mismatch and graft-versus-host disease.

We developed a model in breast cancer and it turned out that about 50% of the mice were cured by this haploidentical transplant. Around that time, a very famous paper came from Italy (Ruggeri *et al.*) where they found that in haploidentical transplantations where you have a mismatch, you can have activity of donor NK cells that is different from that with HLA-identical transplantations, where the donor NK cells will be non-respondent to HLA identical cells. In other words, the mismatch will lead to better NK cell activity. We then went back to our mouse model for breast cancer and observed to our surprise that the cure of these mice was completely dependent on NK cells, not on T cells as we and most others in the field of bone marrow transplantation (where T cells do induce the graft versus leukemia activity) had expected.

We looked to see if the same might be true for myeloma *in vitro* and *in vivo* models – whether the NK cells could kill myeloma cells. We found that they could *in vitro*, and we even observed a small clinical benefit in a mouse model for myeloma.

That secured our interest, but you need a lot of NK cells to treat patients. However, we then met some people in the United States who were to later form the company, CytoSen. They had a patent on NK cell proliferation by using tumor cells that are transduced with IL-21, and they made particles out of that so that you don't have to use the tumor cells, because K562 as you probably know is a tumor cell line. We were lucky to collaborate firstly with the academic group and later with CytoSen. We discussed and agreed upon a license agreement allowing us to use the particle from them in myeloma and breast cancer in Europe, but while we were waiting for the final signature on the agreement, Kiadis took over CytoSen, and they did not want us to have a sub-license agreement anymore. Suddenly, we had no commercial approach to use the particles, which was of course a big disappointment for us.

CiMaas is now working on its own methodology to make sufficient NK cells in order to be able to develop and commercialize an NK cell approach. But still, as a clinician, I think the patient is more important than money in a company, so in the meantime, we continue working on NK cells (and myeloma especially) in the clinic. We did a haplo bone marrow transplantation trial to see whether NK mismatched donor transplant can cure

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patients. We found it could not, but we did make some interesting observations, which lead us to believe that NK cells do really work in patients with multiple myeloma. For example, one patient got progressive disease after the transplant, but 3–6 months after the transplant, the NK cells from the donor came up from the bone marrow and at that time point, the disease disappeared. There was a clear coincidence between getting the donor NK cells into the blood and into the bone marrow, and a response to the disease. So we do feel there is some argument apart from preclinical work that donor NK cells can be active in myeloma. We're currently applying for an academic-level grant to conduct a trial with haplo transplantations and NK cells.

So that was a challenging pathway, and it's still challenging. We unfortunately learned the hard way that life is not all about science and patients, but even more so about patents and freedom to operate.

In general, I think the NK cell approach is a good one, although that is based on relatively little data. There has been little evidence to date in solid tumors, but some good evidence in leukemia – for instance, a group from Houston demonstrated that there is probably better survival with transplant-plus-NK cells. There is also data for response in leukemia with donor NK cells without a transplant, but then you still have to continue the treatment with something else, because NK cells will probably not cure the patient by themselves. (There needs to be more follow-up done around these studies to know for sure). Perhaps NK cells' greatest utility will be as a bridge to another treatment?

Many people work with iPS-derived NK cells and to create NK cell banks, but our approach is to try to do it in combination with the donor transplantation, as explained above. The reason why we are not in favor of cell lines is because you then risk introducing the host vs donor NK cell issue. We think it is optimal to firstly try this approach in combination with the transplant, as was proven successful by Dr Ciurea in Houston in leukemia. If it doesn't work in that context, I don't think it will work via donor NK cells on their own, based upon the current data – again, unless you intend to use the donor NK cells as a bridge to another treatment.

Q Can you summarize your key priorities and goals for your work at CiMaas over the foreseeable future?

GB: Firstly, to get our dendritic cell vaccine clinical trial up and running, and to proceed past the Phase 1, ensuring that the combination of our cells and a checkpoint inhibitor is safe.

Secondly, because our dendritic cells more or less represent a platform, we can now start with WT1 as tumor antigen. We start with lung cancer, but WT1 is actually on a lot of

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tumor cells, including leukemia and colon carcinoma. If we pass the safety hurdle, I think the challenge will be to do as many Phase 2 trials as possible. Of course, we need co-partners to develop because for a small company like CiMaas, that would mean a very big investment. We will hopefully be able to share the results of that Phase 1 study very soon.

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AUTHORSHIP & CONFLICT OF INTEREST

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