Nicolaus Kröger – President, European Society for Blood and Marrow Transplantation (EBMT) (December 2020)



It was critical to build a coalition that is win-win for everyone

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Professor Nicolaus Kröger, president of the European Society for Blood and Marrow Transplantation (EBMT) introduces the multi-stakeholder GoCART Coalition and the impact that it stands to have on the cell and gene therapy field in Europe.

Nicolaus, could you introduce your background briefly?

I am the professor of medicine and I am leading the Department for Stem Cell Transplantation at the University Hospital in Hamburg, Germany. I am also the President of the European Society for Blood and Marrow Transplantation (EBMT) in addition to my position as the President of the German Society for Stem Cell Transplantation. My main scientific focus is on allogenic stem cell transplantation and cellular therapy, including CAR-T therapy but also genome editing, across different diseases and applications.

In the area of cell and gene therapy, how do you assess the European landscape, particularly against the global landscape?

Europe is currently regarding clinical studies behind the US and China, not in terms of basic research, where we do have a lot of deep expertise across European countries but in terms of

translational research especially regarding clinical studies. It takes still too long to advance ideas and programs from the lab into the clinic, and one of a major hurdle here is regulatory issues. We are lacking uniformity across the regions and nations in Europe. The European Medicines Agency (EMA) approves the therapy but then regulations for its adoption, reimbursement or the conduction of clinical trials differ within European countries. Strong regulations are important for the safety of patients, which we need to ensure, but the entire process from preclinical to clinical to commercialization simply takes too long. There has been some improvement over the past decade but more needs to be done.

Another issue is data protection. Europe implemented the General Data Protection Regulation (GDPR) in 2018, which is certainly important, but it has become another major hurdle and sometimes unnecessary delay for launching clinical studies. In my impression data protection has become the highest priority. Yet when it comes to scientific and clinical research, we are hindering the sharing and use of data that could support the development of life-saving therapies. But there is currently a strong feeling across Europe that we need to improve in this respect, which is very positive and encouraging.

Overall, I believe it is a question of harmonization and consensus in Europe. We all believe in the future of Europe and it is known that we need more harmonization, but we are made up of different countries and cultures, and achieving consensus is a challenge. It would be easier to move things forward if we build more political consensus across the regions and nations The EMA approves medicines but cannot determine or influence policy at the national level.

Today access to cell therapy is different in European nations. Access and affordibility are crucial

How do you see the role and positioning of the scientific and academic communities in Europe when it comes to supporting and advancing more translational research?

In my perception this is something that has changed a lot in the past five to ten years. Before, there was a reluctance to involve ourselves too much with business because the industry was for profit, and as academics and scientists, we are not driven by profit. Thus, enterprises, start-ups and hospitals cluster around universities and research institutions to build ecosystems were not common in Europe in the past. This is something that is fortunately now changing, first because politics now support scientific development and collaboration from academia with Industry which foster business growth and generate employment. Science helps to build new technologies and industries. Secondly, scientists and academics as well as industry have realized that they can

advance science and translation faster if they work more closely with each other rather than independently.

That is actually the core idea behind EBMT and our recent establishment of the GoCART Coalition in collaboration with the European Hematology Association (EHA)

Can you share more about the mission of EBMT and the motivation for establishing this Coalition?

EBMT was formed in 1974, when stem cell transplantation was still a very new technology. It had been developed by academics, and it was a very complex and potentially dangerous treatment. A number of small centres in Europe were administering this treatment but because they only saw around ten to 15 patients, they decided it was better to work together. As a society, we then also created a registry to collect all the data. This allowed us to perform more clinical studies and deliver more results to the community about the results of this therapy for different indications.

EBMT has grown over the years to include over 500 centres around the world, with over 600,000 stem cell transplants within our registry.

In terms of cell and gene therapy, we had also done a lot of research on this, and we had received permission from health authorities to advance our research but nothing was actually approved by regulators. The tipping point came when Dr Joseph Murray and Dr Donnall Thomas jointly won the Nobel Prize for Medicine in 1990 for discoveries relating to organ and cell transplantation. However, it was recognized that such cells could have therapeutic effects but also recognized that they might have side effects, so researchers started to work on developing or modulating cells, and this sparked the beginning of genome editing and the manipulation of T-cells. For the first time, the industry took an interest, and Novartis was the first company to really commercialize a product in this therapeutic modality. That acted as some sort of starting signal for the industry, and now many companies are working on CAR-T therapies, and cell and gene therapies in general. For the first time ever, cell therapies have become commercial.

Cell therapies are also very interesting because they are a type of living drugs, since the cells are alive within the patient, unlike conventional medicines, which are metabolized by the body. As a result, they are also potentially curative in nature, so they are a great treatment option.

But we also recognize there is a big hype surrounding them, so we thought it would be great to advance the field by establishing a CAR-T registry across Europe. This was also important because

there are so many stakeholders involved in cell and gene therapy. We have disease-specific groups, medical groups, industry groups, regulatory authorities, payers, hospitals and so on. A CAR-T registry could be of interest to all of them, so we decided to establish the GoCART Coalition.

How challenging is it to bring all these different stakeholders together within the Coalition?

For us, it was critical to build a coalition that is win-win for everyone. It is challenging because there is so much competition in the field, within the industry but also within the academic community, since we compete on publications, impact factors and so on. Therefore, we wanted to be careful about how we approached this. The first thing we did was to reach out to the European Hematology Association (EHA), which had always been a competitor of sorts. The idea was to show that, if two major scientific societies for hematology and stem cell transplantation in Europe could work together, other competing groups across academia, industry and elsewhere would also work together.

We understand that different stakeholders have different interests. The idea is to generate some consensus that can benefit everybody – and especially patients, who are the most important stakeholders at the end of the day. We are still at the beginning and there is still some uncertainty and reluctance, but we can only succeed if we work together. Nobody will win by doing it alone.

In terms of the structure, we have ownership of the registry but we allow each center to take their own data from the registry and analyze it. Through the registry, we can also offer services like benchmarking, quality systems, certification and so on. For instance, if a center comes to us with their own data, we can also provide them with the other data we have so they can compare their own performance and outcomes, and identify potential areas for improvement.

Speaking of data, we have heard so much about the power of Big Data and Real World Evidence (RWE) and so on. Is this again just something hyped up or have you seen real impact on clinical studies and results?

Certainly, we are already there, we are seeing results. For stem cell transplantation, for instance, we have data spanning 50 years. RWE is also very important for cell therapies, since most of the cell therapies are indicated for rare diseases, so they are usually approved based on Phase 2 studies data, and there is no randomization. But this means we do not have longer-term data on

these patients, and we do not know what would happen with the patients not selected to be part of the studies, since normally these studies are highly selective. RWE is essential for regulators and other stakeholders to see how these therapies really work in the real-world setting, outside of the artificial setting of clinical trials. The regulators cannot commission or create these datasets themselves so a registry would be incredibly helpful.

What do you envision as the initial impact of this coalition over the next few years?

I expect Europe to become the third player in cell and gene therapy in the world, after the US and China. I hope this will happen but I think we need something like the GoCART Coalition to bring everyone together. In the US, yes, there are different universities and states but at the end of the day, it is still a country with a federal system. China has a more unified system as well, whereas in Europe we have different nations, cultures and different regulations as already mentioned above, it is a question of finding consensus.

Our idea is therefore to bring all the stakeholders together – payers, regulators, industry, academics, patient groups, healthcare practitioners and so on – where they have access to data, and then hopefully based on that we can harmonize our approach to cell and gene therapy, and then in the longer run, we hope to be able to harmonize this with other regions, especially the US and Asia.

This is also important because medical centers and hospitals have to be trained to administer cell and gene therapies. Currently, each company has their own process. Imagine if you have ten approved products from ten manufacturers, the hospitals have to undergo ten different training programs, which is a little impractical. We need to have a qualification or accreditation system to certify hospitals in a standard way of administering such therapies.

We have created different working groups within the Coalition and one of the aims is to develop a common educational program. Once we do this, we can reach out to regulators to see if it can be approved. This would make things much easier for hospitals and healthcare practitioners.

We are still at the beginning of our journey and we expect to grow further.

How will this Coalition be funded?

For the time being, we have received some funds from EBMT and EHA to finance a core team to get the ball rolling, and we expect our stakeholders to finance some of the other costs for their projects, for instance, in the case of business travel, of course, post-pandemic.

We know that we do not want to be wholly dependent on industry funding so we will also likely be seeking funds from sources like the European Commission Horizon 2020 and other programs like that.

There is a big debate surrounding the longer-term sustainability of CAR-T therapies and other cell and gene therapies. Currently they are being used for rare diseases and usually in patients with end-stage disease where all other options have been exhausted. Do you see these therapies achieving wider adoption – in terms of patient numbers and also the types of disease indications – in the future?

I would say cell and gene therapies will not become mainstream like, say, medication for hypertension or antibiotics, for instance. I suspect it will be for specific groups of patients, perhaps mainly for hematological malignancies. But I do think they will be used for earlier disease stages, where they might not only be more effective but would also reach larger patient populations.

For the moment, the focus has really been on autologous CAR-T therapies, where the patient's own T-cells are extracted and manipulated, which is complicated. The manufacturing time was also an issue because sometimes patients at the end stage of cancer cannot wait that long. Allogeneic CAR-T therapies are more what we call 'off-the-shelf' therapies, they can be manufactured ahead of time but it is more complex to engineer because genome editing needs to be done to avoid host rejection. In addition, it is theorized that because the T-cells come from healthy donors, they might be less depleted than the T-cells extracted from cancer patients. Currently, only autologous CAR-T therapies have been approved by regulators.

What is exciting for autologous CAR-T therapies is the development of on-site or Point-Of-Care (POC) manufacturing. Companies are developing very small manufacturing plants that could engineer the patient's T-cells directly at the hospital or even by the patient's bedside, which would be a gamechanger. Some centers in Germany have already received approval from the regulators to trial this, and the government in Spain is also supporting such efforts, I believe.

A final message?

It is important to build this GoCART Coalition in Europe. We want to encourage everyone to join, and we want to ensure that everyone wins. We have seen during this pandemic that we need to work together urgently. You know, prior to COVID-19, the European health ministers have never sat together at the same table. Now they are finally coming together, and we should use this to push for more consensus and collaboration.

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