

INTERVIEW

An Interview with Michel Sadelain, MD, PhD

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JA: *We are honored to have Dr. Michel Sadelain, Director of the Center for Cell Engineering at Memorial Sloan-Kettering Cancer Center, and one of the leaders in the field of chimeric antigen receptor (CAR)-engineered T cells. Dr. Sadelain, thank you for your time.*

MS: Thank you. It is a pleasure to be talking to you today.

JA: *With the first Food and Drug Administration (FDA) approval of CAR T-cell therapy for the treatment of hematologic malignancy last summer, the field has come a long way since the first pivotal reports in the late 1970s and early 1980s demonstrating that the immune system matters in cancer. Can you tell us about when and where your interest in CAR T-cell therapies originated?*

MS: 2017 is indeed a banner year for cell and gene therapies with the first approvals of CAR therapies, and likely many more to follow. This is the fruit of

decades of preclinical research on T-cell engineering. For me, this endeavor started about 30 years ago, when I was a PhD student in immunology after having previously obtained a medical degree. It was at the time becoming clear that the immune system could, on occasion, eliminate tumors. Oncologists had already observed rare, seemingly spontaneous tumor regressions occurring in association with autoimmunity; bone-marrow transplanters were coming to realize that much of the benefit of their transplants was due not to chemotherapy but to T cell-mediated graft-versus-tumor responses.

The latter was an accidental discovery of the potency of adoptive cell therapy insofar that the motivation for the transplant had been the need for hematopoietic rescue following intensive chemotherapy. The increased relapses that occurred when T cells were removed from the graft (to prevent graft-versus-host disease) made it clear that it was the T cells that eliminated residual tumor and prevented relapse.

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To me—I was a graduate student around that time—this realization meant that one could not rely on the unpredictable T-cell specificities of a graft to consistently achieve tumor rejection without inflicting collateral, occasionally lethal, T-cell damage. I concluded that engineering T cells to be tumor specific and safe could resolve this conundrum and that genetic approaches would be the best way to achieve this goal.

At the time (around 1986), nobody had ever engineered a T cell. In fact, there were only a handful of institutions in the world that were beginning to explore the construction of retroviral vectors for the transduction of primary cells. So, I went to the Whitehead Institute at the Massachusetts Institute of Technology (MIT) to study gene transfer biology. When I applied there for a post-doctoral position and told people, “I would like to engineer T cells,” the most common reaction was incredulous, like, “Why would you do that? What an esoteric purpose...”

The nascent field of cell engineering was at the time focused on monogenic blood disorders that could potentially be cured by introducing wild-type genes in hematopoietic stem cells or other cell types. Some thought that one could treat tumors with tumor suppressor genes or suicide genes. But engineering T cells just seemed to be the wrong trail to blaze.

And so while my official project was about something else (globin gene transfer for hemoglobinopathies), I of course started working on T-cell engineering. The first abstract that I published—which I think is the first report in the literature on the genetic engineering of primary T cells—was presented at the World Congress of Immunology in Budapest in 1992. For me, that marks the beginning of T-cell engineering—and that was exactly 25 years before the first approval of CAR therapies.

JA: *I think that is a great testament to the progress of the field.*

MS: Absolutely. It took years to introduce just one gene into T cells (which, by the way, was the *Escherichia coli* LacZ gene; this was before green fluorescent protein). It had taken me 3 years to succeed in reproducibly transducing a small fraction of murine primary T cells. Today, you can teach a high-school student in an afternoon how to introduce genes in 100% of freshly collected T cells, and we have a number of different techniques that are very efficient and nontoxic, spanning RNA vectors, DNA transposons, and a range of gene-editing tools. That is, as you say, testimony to the enormous progress in the field of gene transfer and cell engineering.

This also makes the point why T-cell engineering, building on the success of CD19 CAR therapy, is positioned to remain at the forefront of the clinical translation of a number of genetic engineering modalities. For example, the introduction of gene editing and CRISPR-based approaches in the clinic will likely begin with T-cell therapies because of the relative ease of T-cell manipulation and transduction, combined with the relevance of T-cell therapies to a large number of disorders, including cancer and others.

JA: *Following that train of thought, what do you think the defining feature of the next-generation CAR will be?*

MS: Today’s paradigm is CD19 CAR therapy. That is the setting where there is the largest collective experience and the deepest knowledge. We identified CD19 as an attractive CAR target in the late 1990s, which we reported in 2003 in *Nature Medicine*, based on a series of criteria (high and relatively homogenous expression in virtually all cancer cells and absence from vital tissues among others).¹ Future applications will build on this foundation. Different challenges will have to be addressed to apply the CAR concept to other cancers.

JA: *What do you think are the largest challenges?*

MS: There are a few. One is to decrease the toxicities that occur in a subset of patients undergoing CAR therapy. As you see from the recent FDA approvals, there are substantial restrictions on how and where this new medicine can be administered because of early toxicities such as cytokine release syndrome (CRS). The good news is that we have ways to manage CRS, but the broad use of present CAR therapy is limited by the need for specialized management. So, we have to understand the pathophysiology of the CRS in order to design better CAR T cells that are less prone to causing this syndrome and come up with better means not just to treat CRS but to prevent it. I am optimistic that will happen quite soon.

Another big challenge is to tackle other cancers, in particular solid tumors. There are two orders of challenges. One is finding suitable targets for these other cancers, and the other is adapting the CAR design to overcome the particular microenvironments associated with different tumors. The CARs that are currently approved have been optimized for use in hematological malignancies. They are effective against B-cell malignancies and will hopefully perform as well against myeloma and acute myeloid leukemias. I believe that for solid tumors, something

different and better adapted to the microenvironmental challenges will be necessary.

I think a third big challenge is to figure out ways to generate T cells at a lower cost. That too is a barrier to the broader use of this powerful technology, and to do that will require combining inventions of a biological or technological nature.

Can we identify the best T-cell subsets to engineer? Can we enhance the functional and metabolic properties of T cells through improved CAR designs? We need to generate (through selection and engineering) T cells that persist for as long as is needed without succumbing to T-cell exhaustion. Those are biological issues that bear on CAR engineering.

Then there are the device and technological issues. Can you robotize, miniaturize, and rapidly identify the best T cells for adoptive therapy? There are many new ideas today to advance T-cell manufacturing that are being developed at different academic centers or companies.

So, those are three issues: diminishing the toxicities, extending the approach to solid tumors and other cancers, and figuring out ways to make cells that are more efficacious, cheaper to make, and more easy to distribute. The so-called off-the-shelf approaches are a tantalizing albeit challenging vision to meet all of these goals.

JA: *Along those lines, what other disciplines would you specifically recommend be solicited to fill in those gaps?*

MS: That is a great question. Isabelle Rivière and I had a recent review in *Molecular Therapy* where we have a figure showing how CAR therapy was born at the intersection of different fields, spanning tumor immunology, genetic engineering, synthetic biology, and cell manufacturing sciences.²

CAR therapy feeds off a lot of tumor immunology, but it certainly is not conventional or orthodox immunology, as it is based on synthetic receptors and pharmacological circuit rewiring. A CAR is a synthetic molecule. Its individual components are natural, but they are assembled into a novel structure that only partially mimics natural functions and acquires new features. It is really a creation of humankind that is distinct from anything natural. It is fair to say that conventional immunologists did not accept the CAR concepts for a long time because of their synthetic nature.

CAR therapy requires the identification of different types of targets compared to those the immune system normally recognizes through the physiological receptor for antigen, which is called the T-cell receptor or TCR. The TCR normally recognizes

peptide–human leukocyte antigen complexes, unlike CARs, which recognize molecules on the cell surface. These do not have to be peptides or proteins. They can also be carbohydrates or glycolipids. So, what CAR T cells recognize and how they recognize it opens up a new way of looking for immune targets.

The field also draws on a number of technologies for cell manipulation. That too is a field that will likely develop a lot in the years to come. I am quite fascinated to see all the people who are now thinking of creating new devices, from closed bioreactors to microchips to isolate, separate, differentiate, and/or reprogram T cells better. There is a need for new devices and tools to expand cell therapies on a larger scale. I think that biophysics, microfluidics, and engineering will all contribute to advance the field.

The CAR paradigm is not only drawing on other fields but also giving back to some of them. Synthetic biology is a science that has long focused on creating genetic circuits in bacteria and simple systems. I am very excited when I go to places such as the MIT and see a new generation of young synthetic biologists who see T-cell engineering as a possible real-world outlet for their research. Synthetic biologists have explored and perfected the genetic rewiring of different cellular organisms, but rarely with a view to develop applicable medical solutions. CAR therapy provides an inspiration and a model for these researchers. Another field that may be spurred by CAR research is that of cell surface proteomics, which I hope will help identify new and better targets in different cancers. I really think that the success of CD19 CAR therapy is inspiring other fields of science and medicine, and it is wonderful to see that happen.

JA: *In closing, what is your prediction for the CAR T-cell therapy field in 10 years?*

MS: I believe that we will further advance the design of far-better T cells that are safer in their use and smarter in the way that they can discern tumor cells versus normal cells. I believe that by then we will have made considerable progress in other hematological malignancies, such as myeloma and acute myeloid leukemia. And I do think that there will be several successes in solid tumors.

There is no reason why engineered T cells could not have profound effects on solid tumors. We already know that T cells can be effective against melanoma, that tumor-infiltrating lymphocytes can be effective in various carcinomas, and that responses to checkpoint blockade are mediated by endogenous T cells. So, T cells definitely can do a great job against solid tumors. We need to find out what are the right tar-

gets and the right engineering strategies. This may not be easy, but it must be feasible.

I also believe that T-cell manufacturing will undergo a complete transformation. We are particularly interested right now in harnessing pluripotent stem cells to derive the entire T cell *in vitro*, rather than to having to start from blood collections in a personalized fashion. I am convinced that T-cell production will make enormous progress in the next 10 years.

Finally, I do hope that CARs will be explored beyond oncology. In principle, there is every reason to believe that engineered T cells could have a great impact in autoimmune diseases, organ transplantation, and the treatment of refractory infectious diseases. I hope that over the next decade, we will start seeing some examples of that.

JA: *Fantastic. Thank you so much for your time today.*

REFERENCES

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