Former Clinical Investigator Discusses Next-Generation CAR T-Cell Therapies

"Ultimately, we want to cure the many forms of cancer, but one strategy is not going to work for all, thus the need for innovation," says Jakob Dupont, MD.

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Former Clinical Investigator Jakob Dupont, MD, was working on cellular immunotherapies as part of his Damon Runyon-funded research long before chimeric antigen receptor (CAR) T-cell therapies grabbed headlines for their ability to cure certain blood and bone marrow cancers when traditional options such as chemotherapy and radiation therapy had failed.

More than a decade later, Dupont has come full circle as the newly appointed Global Head of Research and Development at Atara Biotherapeutics in South San Francisco. Atara is developing next-generation "off-the-shelf" allogeneic T-cell and CAR T-cells that offer potential solutions to some of the problems facing current commercially available CAR T therapies. While promising, autologous CAR T-cells, derived from the patient's own cells, have encountered challenges in the inherently complex logistics and manufacturing process, side effects, and durability of this therapy.

Dupont discussed his career and the future of cellular immunotherapies with us:

Can you tell us about the Atara Biotherapeutics approach to "off-the-shelf" cellular therapies and its benefits?

My mentor Richard O'Reilly, MD, from Memorial Sloan Kettering Cancer Center is one of the scientific founders of Atara, and the therapeutic approach we are using is based in part on work that I conducted with him during my Damon Runyon award.

Current cellular therapy, including CAR T cell, involves removing immune T cells from a cancer patient, genetically tailoring them in the lab to recognize that patient's individual cancer, and then injecting the engineered cells back into the body to find and kill tumor cells. Unfortunately, the quality of the product is dependent on a patient's immune cells, which may be faulty or too few for collection.

To improve expansion and persistence of cells in the body, Atara's approach starts with healthy donor T-cells, which are stimulated using antigens from Epstein-Barr virus (EBV). These EBV-specific T-cells can be used to treat EBV-related cancers (a drug candidate called Tab-cel) or

multiple sclerosis (a drug candidate called ATA188), or they can be engineered into allogeneic CAR T cells (drug candidates like ATA3271, ATA3219) to recognize cancer cells. These cells can be mass produced with quality control and preserved to be used by any patient with matching HLA alleles. The advantages of off-the-shelf cell therapy include potentially better efficacy by utilizing cells from a healthy donor, and better logistics, so patients don't have to wait for their cells to be collected and engineered. We are seeing very little graft-versus-host-disease which happens when a patient's body rejects the donor cells, without suppressing a patient's immune system, and long-term persistence of the cells.

You were working on adoptive cell therapies in 2004, 13 years before the first CAR T therapies were FDA approved. Was there skepticism that this approach would work when you initiated your Damon Runyon project?

I have been interested in how to augment the immune system to target tumors for a long time. This was really out-of-the-box then, and many were skeptical about immunotherapy before checkpoint inhibitor or CAR T clinical trials. The fact that some researchers took a risk to make this a feasible option shows us that there is always a need to innovate. Initially, we had chemotherapy and radiation, then targeted therapies that are great for a subset of tumors. More recently, we added checkpoint inhibitors that boost the immune system to fight cancer. Next, we want to innovate "off-the-shelf" cellular therapy to help patients. Ultimately, we want to cure the many forms of cancer, but one strategy is not going to work for all, thus the need for innovation.

How did the Damon Runyon Clinical Investigator Award help launch your early career as a physician-scientist?

This was a risky project in that the concepts were unproven at the time, so it was empowering to have the Damon Runyon funding. It provided financial support including medical school repayment, intellectual validation, and protected time from the clinic to do research. This award also opened doors to new opportunities and a network of experts. It was a launching point for the career moves I have made since then.

Why did you decide to take your career on the biotechnology path instead of the academic?

Being on the industry side, I have the opportunity to conduct the research and design the clinical trials that can change the standard of care for patients with cancer. My favorite career moments have been the unblinding of a clinical trial, when we learn what our treatment has done to help patients. In my career, I have contributed to the regulatory approval of 10 different drugs, including a number of therapies from Genentech for patients with breast and gynecologic cancers. Ultimately, I want to contribute to improved outcomes for more patients with cancer.

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