

## Innovation in HEMATOPOIETIC CELL TRANSPLANTATION AND GENE AND CELLULAR THERAPIES Drive Results in Pediatric Oncology

**T**his is an exciting time in medicine, providing more novel treatments for patients with cancer blood disorders. Scientists are learning more about the human genome and its role in disease. This knowledge allows investigators to develop new diagnostic tools and therapeutic interventions to more specifically treat individual diseases. We are now identifying ways to correct disorders characterized by single gene mutations.

### Innovations in Clinical Development Yield Promising Results

New technologies, such as clustered regularly interspaced short palindromic repeats (CRISPR), allow scientists to excise a mutated gene and replace it with a non-mutated gene. Equally important, we are learning to harness the power of the immune system to treat cancer. We have learned that the human immune system can, in some cases, be tolerized to a patient's malignant cells, so that it does not mount an immune response

against the cancer, allowing the cancer cells to escape detection (and subsequent destruction) by the body's immune system.

New agents such as checkpoint inhibitors are showing promise in activating the patient's immune response against the cancer. In addition, we are now developing new therapies that enhance the immune system response against cancer. Investigators are studying ways to alter hematopoietic cell grafts to alter the immunologic power of the grafts, leading to reduction of graft-versus-host disease or enhancement of anti-leukemia effects. In addition, cytotoxic T-cell therapies are increasingly utilized to treat post-transplant viral infections such as EBV and adenovirus. Natural killer (NK) cell infusions are being explored for their leukemia cell-killing abilities, especially in AML when the donor and recipient are killer immunoglobulin-like receptor (KIR)-ligand mismatched.

### CAR-T cell Therapy for Patients with ALL and NHL

Finally, CAR-T cells, T-lymphocytes from a patient are genetically modified to express a leukemia-specific antigen, are showing great promise in patients with ALL and NHL. The first CAR-T cell products are projected to be approved by the FDA later this year. As we learn more about each of these technologies, they can be expanded to other cancers. With all of these new therapies, physicians will need to learn how to best identify which patients will benefit, how to identify and treat the new toxicities, and how to incorporate those active agents into current treatment guidelines. Taken together, these novel immunotherapy interventions expand our armamentarium of weapons against cancer, complementing or replacing existing therapies, with the ultimate goal of reducing acute and long-term toxicities and increasing survival. ●

Multikine is a mixture of cytokines that essentially activates T-cells to break tumor tolerance, says Geert Kersten, CEO of Cel-Sci. Multikine creates a change in the CD4/CD8 ratio in favor of the CD4 cells in the tumor microenvironment.

"Essentially, a major defense mechanism of a tumor is to make itself invisible to the immune system," he says. "Our drug changes the type of cells that infiltrate a tumor. In the process of doing so, the tumor becomes visible to the immune system so that it can 'see' and attack the tumor."

Multikine is currently being studied and is administered for three weeks as the first treatment a cancer patient gets before surgery.

"Immuno-therapies are still being developed the old-fashioned way: patients receive chemotherapy after they've failed surgery, radiation, and/or chemotherapy," Mr. Kersten says. "Think about what a patient's immune system looks like at that point. Patients would have a better chance if we gave a cancer immunotherapy while the patient still has an intact immune system."

Mr. Kersten says for its Phase III study, the last patient was enrolled last year, and the company is waiting for 298 events before the final data are available.

Industry leaders say there is a growing need to innovate, especially to address aggressive and treatment-resistant cancers. The previous big shift was from non-targeted chemotherapy and radiation, to targeted treatments. The first generation of these therapies were the anti-VEGFs (vascular endothelial growth factor receptors) and TKIs (tyrosine kinase inhibitors). Unfortunately, even with these advances tumors find other ways to grow.

"We are finding that selective targeting of just one element or one pathway supporting tumor growth is often not enough," says Dror Harats, M.D., CEO at VBL Therapeutics. "We have to come at the cancer from a few different directions to really make a big difference."

VBL's therapy, VB-111, in Phase III development for glioblastoma multiforme, was designed using advances in targeted gene therapy technology to deliver a genetic mechanism that stops tumor-supportive blood vessels from growing, while activating the immune system. VB-111 works through a dual mechanism to combine a viral immune oncology action, which brings the immune system — the CD8+ T cell response — to the tumor, with a targeted gene therapy technology, that eliminates the cells responsible for the tumor blood supply.

"We are stopping tumor growth by cutting off the blood supply, and recruiting the immune system to fight the tumor, in a single therapeutic," Dr. Harats says. "So far in the clinic this has translated to meaningful overall and long-term survival benefits in patients with advanced solid tumors, including recurrent glioblastoma multiforme, for which the current standard of care, the anti-VEGF drug Avastin, does not provide a benefit of overall survival."

Also part of this next wave of breakthrough therapies in immuno-oncology will be therapies targeting myeloid-derived suppressor cells (MDSC) in the tumor microenvironment, which help the tumor evade the body's natural immune response, and are associated with a poor prognosis. Blocking the suppressive functions of myeloid cells could restore the anti-tumor response of T-lymphocytes, which is a novel immune target for cancer.

OSE Immunotherapeutics' preclinical asset, OSE-172, is being developed to do just this, and the company is expected to complete preclinical studies at the end of 2018.

"Our program studying OSE-172 is guided by the paradigm that therapies regulating the immunosuppressive effects of MDSCs will allow effective engagement of the body's natural immune responses against tumors," Ms. Costantini says. ●