

# Immune therapies in children's cancer

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Great advances have been made in applying chemotherapy and targeted drugs to improve the survival rate of children and adolescents with cancer, from a survival rate of less than 20% in the 1960s to an expected overall survival rate of 85% in 2017.<sup>1</sup> The improvements in survival rate occurred primarily due to the fact that pediatric cancer research has been highly collaborative since the 1960s, using scientifically-based studies with a high number of children treated on treatment protocols set within National Cancer Institute (NCI)-funded US cooperative groups. The current NCI pediatric cancer cooperative group is the Children's Oncology Group (COG), which includes over 230 centers in Canada, the US, Australia, and New Zealand. With a long life expectancy, children cured of cancer have a big positive impact in our society. While immune therapies are currently at the forefront of research, only recently has the COG been able to offer therapies directing the immune system against children's cancer.

The concept of using the immune system to treat cancer has been considered for many decades. Immune therapy is based on the concept that cancer is not 'self' and cancer cells should be recognized by the host's immune system as foreign cells to be removed, destroyed, or suppressed. Immune therapies attempt to utilize all aspects of the immune response, including the innate (initial response) and adaptive (memory) immune responses. Treatments exploiting the innate immune response have included developing natural killer cells and adjuvants that induce inflammatory responses; these potentially are the first step in a specific response to the malignant cells. Other approaches have included using cancer-specific responses by cytotoxic T cells, which are very specific and restricted to small peptides on the cell surface in the context of the major histocompatibility complex or human leukocyte antigens (HLA) in humans. Such a response is very specific, but the development of treatments using these approaches has been limited over the last 30 years by the low concentration of cancer-specific antigens processed by the malignant cells and antigen presenting cells.

Moreover, there are very few of the specific cancer-reactive T cells, resulting in difficulty finding those rare cells to be increased for therapy. Another approach using the adaptive immune system has been to utilize monoclonal antibodies against cancer antigens. Unlike the antigens for T cells, responses are not specific to just the malignant cells. The big advantage is that antibodies are not restricted to antigens displayed by the HLA molecules, allowing for a much broader response. To date, immune therapies using monoclonal antibodies have been incorporated with conventional chemotherapy, resulting in significantly increased survival in both high-grade neuroblastoma and lymphomas.<sup>2,3</sup>

The only truly immune cell-based therapy is hematopoietic stem cell transplantation (HSCT) or blood and marrow transplantation (BMT). HSCT has been used to significantly improve the cure rate for children and teenagers with high-risk leukemia that does not respond to standard chemotherapy approaches. Since the 1980s, allogeneic BMT has become the established immunotherapy for a number of cancers, including leukemia and lymphoma, but has not done well outside of the blood cancers. Allogeneic BMT relies on donor immune system recognition of cancer cells and constitutes all of the aspects required for induction of a long-lasting immune response against malignancy, including an initial innate response with inflammation and an adaptive immune response including T cell-mediated cancer killing

and induction of B cell derived antibodies against foreign malignant cells.<sup>4</sup> Most important is the induction of immune memory that helps to maintain a long-term immune response, for a permanent curative outcome. One of the big drawbacks is an off-target response called "graft-versus-host disease," the induction of an autoimmune disease that may attack any organ in the body.<sup>5</sup>

BC Children's Hospital (BCCH) has been a world leader in HSCT, providing leadership of the largest HSCT network for children, the Pediatric Blood and Marrow Transplant (BMT) Consortium. BCCH also currently provides scientific leadership for both the Canadian BMT Group and Canadian National Transplant Program. BCCH has developed adjuvant immune therapies that have resulted in early phase clinical trials in leukemia; as well, it has the largest biomarker research group worldwide, targeting rejection after HSCT in children and adolescents. HSCT, with significant contributions by BCCH researchers, has informed the fundamental design of all the new and novel cellular immune therapies currently being designed. Through donations by Mining for Miracles, BCCH is now developing the beginning of cell manipulation of hematopoietic cells. Because almost every child has a living parent, over 95% of children have an available donor. Using this novel transplantation approach we can expand it to serve as a template for the addition of other cellular therapies in the future.

An exciting recent advance has been to re-target cytotoxic T cells by genetically engineering the cells to express a new chimeric antigen receptor (CAR). This allows all T cells—irrespective of what antigen is recognized by their T cell receptor—to be engineered to express the CAR receptor, resulting in all T cells attacking malignant cells.<sup>6</sup> This has been so successful that the FDA approved the first CAR T cell for leukemia in August 2017.<sup>7</sup>

The current status of immune therapies for children in BC is very exciting. There have been phase III trials using monoclonal antibodies in neuroblastoma in the multicenter COG trials, and the first phase III trials using a bi-specific antibody to activate T cells against leukemia show a significant decrease in the therapeutic toxicity compared to conventional chemotherapy. In addition, the COG is planning the first phase III clinical trials to evaluate CAR T cells against leukemia next year. Children and adolescents in BC will also have increased access to early-phase immune therapy studies as one of the two selected Canadian sites for the NCI-funded Pediatric Cancer Immune Therapy Network, which is focused on applying novel non-cellular immune therapies to pediatric cancer. The BCCH, in collaboration with the BC Cancer Agency, is also one of the primary target identification sites for the Saint Baldrick's-funded immune therapy network for childhood cancer. Lastly, with support by the Michael Cuccione Foundation, BCCH is now the only Canadian CureWorks center and will be offering early-phase trials for cutting-edge interventions using CAR T cells for leukemia, neuroblastoma, and brain tumors starting in 2018.

Overall, a time with new hope has begun in British Columbia for children with cancer. We are one major step closer to achieving a cure for every child or teenager with cancer.

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