2015 KIDS WALK IMPACT

USING BISPECIFIC ANTIBODY TO HARNESS T LYMPHOCYTES TO DESTROY LEUKEMIA AND HEPATOBLASTOMA

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Memorial Sloan Kettering Cancer Center (MSK) has always been on the frontier of advances in all areas of cancer treatment and research. One extremely promising area of research currently underway is focused on gaining a better understanding of the body's immune system response to cancer—and how we can leverage this knowledge into creating more effective treatments for pediatric patients.

Declared by *Science* magazine in 2013 as the most important advance for all fields of science, cancer immunotherapy holds enormous potential. In adult cancers, physician-scientists have shown that a patient's own immune system, if properly harnessed, can dramatically enhance the work of traditional cancer drugs. And now, at MSK, a team led by **Nai-Kong Cheung, MD, PhD**, is eager to exploit this to benefit pediatric patients.

In the past three years, a series of discoveries have shown that antibodies can harness T-lymphocytes (also called T-cells) and effectively control and cure cancer. As the front-line defense of our body's immune system, T-cells are professional killers of tumor cells. While these advances are rapidly made in adult cancers, treatment of pediatric cancers has lagged far behind. Over the last two decades, however, Dr. Cheung's laboratory has made significant progress in using antibody-based immunotherapy to treat neuroblastoma—efforts that have led to long-term survival, and likely cure, of this form of pediatric cancer. Now, MSK's researchers want to use these discoveries to make T cell-engaging antibodies to fight acute myeloid leukemia (AML) and a rare pediatric liver tumor known as hepatoblastoma.

An antibody is a type of protein used by the body's immune system to identify the right targets to attack. Antibodies typically do this by latching on or "binding" to a specific protein or sugar marker on the cancer cells. Bispecific antibody (BsAb) is a type of laboratory-engineered antibody that has the binding receptors for two different targets—one receptor is to bind and activate T-cells; the other is to handcuff T-cells to the tumors. This induces T-cells to do what they do best: be serial killing machines. With BsAbs, tumors can no longer escape the immune system because these "activated" T-cells are delivered directly to the tumor, and the expression of "stimulating" antigens on tumors is no longer necessary to generate a robust immune response. This means that nearly all of a patient's T-cells can be recruited, and they no longer need to be sensitized to the tumor.

Early studies using BsAbs to treat leukemia and lymphoma have produced promising results. However, these studies have focused on adult cancers, with one exception: a pediatric cancer known as CD19-positive leukemia. Unfortunately the CD19 protein is not expressed in other pediatric cancers, so Dr. Cheung's lab is starting to develop BsAb that enable T-cells to recognize tumor markers on AML, hepatoblastoma, and neuroblastoma. So far, Dr. Cheung's laboratory has developed the "humanized"

versions of anti-GD2 antibodies that carry fewer side effects and highly promising anti-cancer capabilities. neuroblastoma. Thus far, our laboratory has developed the 'humanized' versions of anti-GD2 antibodies with fewer side effects, as well as their BsAb forms with highly promising anti-tumor properties.

The funds raised by the 2015 Kids Walk will be used to study the efficacy of these new BsAb drugs in preclinical models of AML, hepatoblastoma, and neuroblastoma. Our hope is to develop antibodies for the treatment of patients whose cancers are resistant to treatment or have come back. If proven safe and effective, these BsAbs may have broad application not only for pediatric solid tumors—but for adults with AML and other solid tumors with similar markers, which include breast, colon, stomach, liver, lung, ovary, pancreas, and prostate cancers.