PROJECT TITLE

Generating an anti-BCMA trispecific natural killer engager for use in multiple myeloma

PRINCIPAL INVESTIGATOR

Dr. Alissa Visram, The Ottawa Hospital

Dr. Scott McComb, National Research Council of Canada

PROJECT SUMMARY

Multiple myeloma (MM) is a cancer where specialized antibody-producing immune cells, called plasma cells, start to grow uncontrolled within the bone marrow. In recent years, MM patient survival has improved greatly with development of targeted frontline therapies (called proteasome inhibitors, immunomodulatory drugs, and anti-CD38 monoclonal antibodies) which are widely used in newly diagnosed and relapsed settings. Despite progress, MM remains an incurable cancer and patients who do not respond to these three frontline therapies (known as triple-refractory patients) having a typical survival time of less than nine months. New advanced immunotherapies (called CAR-T and T-cell engager therapies) can allow a patient's T-cells, a kind of immune cell, to recognize specific markers expressed on the surface of MM cells, leading to strong killing of the MM cells. The most well-tested MM marker for CAR-T or T-cell antibody engager therapy is called the B-cell maturation antigen (BCMA). While BCMA-targeting therapies offer hope to patients, they are unfortunately not currently accessible to patients in Canada. We wish to address this by developing a new and potentially safer form of BCMA therapy, where we can manufacture many doses of the therapy at a centralized location and have them ready to give to patients immediately when they are needed. This could allow us to more rapidly open clinical trials for MM patients across Canada, rather than being restricted to the few sites where it is possible to manufacture CAR-T therapies.

Specifically, we will design and test a new antibody-type treatment that can make a patient's own natural killer cells find and kill MM cells. By engaging natural killer cells rather than T-cells, we hope that this therapy will effectively kill MM cells while causing much less of the dangerous inflammatory side effects associated with CAR-T or T-cell engager therapies. We will also enhance this therapy by integrating technology developed at the National Research Council of Canada (NRC) to extend the time that this therapy can circulate in patient blood and continue killing MM cells. As this therapy will integrate BCMA-targeting, natural killer cell targeting, and circulation time extending elements, it is called a tri-specific killer engager (a TriKE). In this proposal, we will combine the valuable tools which we have already created at the NRC, to create new TriKE candidates. We will then screen against MM cells we grow in the lab and MM and immune cells from patient donors, to find the most active molecules. Finally, we will develop a method which can produce a version of our best BCMA-TriKE molecule at a quality and purity that would be needed for human clinical trials. This project could create an important pipeline for advanced off-the-shelf cancer-targeting immunotherapies for clinical trials in Canada aimed at improving outcomes in MM and other cancer diseases.