



Hyundai Hope on Wheels Hyundai Scholar Research

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“Characterization of Leukemia Stem Cells in Childhood Leukemia”

Acute leukemia is the most common malignancy in children. High risk leukemia patients have a poor outcome despite the most intensive treatment currently available. More intensive treatment is not an option, because it has a dose limitation due to major side effects to normal cells and leukemia cells acquire resistance to chemotherapy. Also, long term leukemia survivors show many side effects from chemotherapy and radiation therapy. Leukemia cells are believed to arise from leukemia stem cells (LSC). It is known that LSC are responsible for leukemia maintenance and relapse; therefore, it remains urgent to develop novel treatments to target LSC specifically. This treatment approach is also significant for children to spare normal cells from toxicities, since most leukemia survivors suffer from long term side effects from current treatments. Although extensive efforts have been made to develop LSC targeted treatments, there are very few LSC targeted treatments available to date since only a few LSC are identified.

Unique LSC markers have not been identified in childhood leukemia and different leukemia may have different LSC, since childhood leukemia is a heterogeneous disease. The goal of this project is to identify LSC in different types of childhood leukemia, which will lead to clinical development of new LSC targeted therapies. This project will be conducted by a multidisciplinary team. I am fortunate to have excellent mentors and collaborators, including Dr. Jan Nolte, Stem Cell Program, Dr. Kit Lam, Hematology/Oncology, James Chan, Center for Biophotonics Science and Technology, and Laurel Beckett, Biostatistics, CTSC.

Primary leukemia samples will be obtained from patients in Pediatric Hematology/Oncology at the UC Davis Medical Center. Sample collection will be coordinated by staff of Pediatric Hematology/Oncology. In order to identify LSC, we will use a combination of three methods; flow cytometry, one bead-one compound (OBOC) combinatorial library, and Raman

spectroscopy. Flow cytometry is a currently used technique which can identify and sort cells based on cell surface antigens. OBOC combinatorial library is a powerful new tool developed by Dr. Lam, to screen peptides on the cell surface. Raman spectroscopy is a laser-based technique for the analysis of intrinsic molecular vibrations reflecting cellular biochemical information. Recent application of this technique to analyze cells can provide a quantitative assessment of the levels of DNA, RNA, proteins, lipids, and carbohydrates in the cell, as well as molecular-level conformational changes. Flow cytometry and OBOC library will be used to find unique markers on the cell surface, whereas Raman spectroscopy will be used to find new optical markers inside the cells. Once several LSC candidates are identified and isolated based on the results of above methods, they will be transplanted into immunodeficient mice. Immunodeficient mice are known to accept and engraft human cells; therefore, they are used as a leukemia model. We expect the mice will develop leukemia if LSC are transplanted. Engraftment of leukemia cells will be analyzed by the same methods described above to confirm the characteristics of engrafted leukemia. Serial transplantation of LSC will be performed to confirm “stemness”.

Since preliminary data have shown that different types of human cells (blood cells, cord blood derived hematopoietic cells, and human embryonic stem cells) have unique Raman molecular signatures, we anticipate that unique Raman signatures of LSC will be identified in childhood leukemia. Dr. Lam has identified LLP2A, a marker for the malignant lymphoid cells, using OBOC libraries. We have recently tested 7 primary childhood leukemia cells for LLP2A binding and all samples showed binding at different strengths. Therefore, we anticipate that LSC will also bind to LLP2A. LSC from different leukemia may show different binding affinity. We also anticipate discovering novel markers using LSC as a cellular probe to screen OBOC libraries. Furthermore, using combinations of the three unique methods described above and the immunodeficient mice model, we anticipate identifying LSC in different types of childhood leukemia.

As you are aware, cancer research requires significant financial support. Funds from the Hyundai Scholar Program will be combined with a recently funded grant from the UC Davis Children’s Miracle Network. This additional support will allow us to expand and develop a treatment model using mice with leukemia and markers (antibodies or ligands) to deliver targeted therapy to LSC. Furthermore, we will include other childhood malignancies, such as solid tumors. These potential future directions, with the preliminary results obtained from this

project, will be submitted for further funding to the NIH, Leukemia and Lymphoma Society, and the California Institute for Regenerative Medicine.