Chronic Myeloid Leukemia (CML)

CML is a specific type of leukemia that is usually diagnosed in a chronic phase before evolution to an acute phase that used to be inevitable in patients not given a bone marrow transplant. With the introduction of tyrosine kinase inhibitors as therapeutics for CML, Imatinib Mesylate (IM, sold in Canada as Gleevec) is now the first-line treatment for patients with newly diagnosed CML in chronic phase. This drug gives high rates of response with minimal toxicity in 80% of patients, and emerging evidence suggests a proportion of those patients are cured within 5-10 years. In 20% of patients, however, the disease is either immediately unresponsive or later develops resistance to this drug. Scientists think that the reason for this resistance is due to the creation of mutant CML stem cells. CML stem cells are very rare cells in the patient from which all of the rest of the CML leukemic cells arise. These stem cells have many different properties by comparison to the majority of the leukemic cells in the same patient, and some of these differences affect their response to drug treatments. There currently are no established tests to identify AT DIAGNOSIS those patients who are destined to be IM failures. The CML group has recently compared the blood stem cells of newly diagnosed patients who did and did not respond to IM, and found that the stem cells of patients who failed to respond to IM treatment showed a reduced response to IM in the lab. If this finding can be confirmed in a larger cohort of patients, this predictive test could be used to better design treatment plans for patients, with the possible early addition of alternative therapies.

The group is also interested in the role that the Ahi-1 gene plays in CML. The amount this gene is expressed in cells normally decreases as both mouse and human blood cells develop; however, in human leukemic cells, particularly in CML, the gene escapes regulation and is expressed at higher levels than normal. Research is now further characterizing the function of Ahi-1 during normal mouse development and during early stages of normal blood cell development, and examining the biological changes of human Ahi-1 in human leukemic stem cells. If we are able to determine the biological role of Ahi-1 in CML, it could potentially help us develop new molecularly-targeted therapies for the disease.

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Acute Myeloid Leukemia (AML):

Most patients with AML eventually become resistant to standard chemotherapy drugs by mechanisms that are currently not well understood. One reason is that pathways that control cell growth are often abnormally activated in AML so that the leukemic cells can continue to grow rather than be killed by the chemotherapy drugs. We propose to study molecules that block these activated pathways to determine if such inhibition will kill chemotherapy-resistant AML cells. These studies may provide a rationale for testing new drug therapy in AML patients. We are also working to identify biologically different subpopulations of AML cells, and develop anunderstanding of how these cells change under the pressure of chemotherapy. This knowledge may be then translated into clinical practice by allowing us to detect resistant cell populations at diagnosis in patients with AML and therefore identify patients who may benefit from the early administration of additional or alternative treatments. For these studies, it is critical to have access to AML cells isolated directly from patients, as well as normal human cord blood, peripheral blood and bone marrow cells for comparison.

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Myelodysplastic Syndrome (MDS):

MDS and AML are overlapping diseases characterized by the production of dysfunctional blood cells which dominate the blood-forming system and result in failure of normal blood cell production; this is associated with infections, bleeding, organ damage and other medical problems. Certain genetic tests can be used to predict whether a patient will be a good candidate for a stem cell transplant, or whether conventional chemotherapy is a more appropriate treatment option. Unfortunately, many patients are under - or over - treated because these tests are limited in their ability to determine the outcome of such patients with current therapies. Our MDS working group is investigating new tests using microarrays and sequencing, and comparing these results to current clinical tests and known treatment outcomes, to determine the feasibility of using one or both of these new tests for predicting outcomes in patients with MDS or AML. These tests are being conducted on banked patient samples from the HCB.

MDS is frequently caused by structural anomalies in the genes of the cell, including deletions or duplications of large amounts of genetic material. Deletion of the long arm of chromosome 5 (5q) is the commonest structural anomaly seen in MDS. Our group has recently demonstrated that microRNAs (genetic regulatory molecules) that are encoded by DNA on the long arm ofchromosome 5 act to regulate signaling in immune cells. We are working to establish how alterations in expression of these microRNAs cause the manifestations of MDS. If we are able to determine the role of these microRNAs in MDS, they may become a target we can use to develop future therapies

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Normal Hematopoiesis / Cancer Stem Cells

The ability of the body to continuously replenish our blood cells throughout life depends on a very small subset of primitive cells in the bone marrow called stem cells. These blood stem cells have the unique potential to divide and make more of themselves (self-renew) or to divide and give rise to cells that can further divide and ultimately mature to the specialized cells that make

up our blood (e.g. red and white blood cells).

The study of normal hematopoesis has direct clinical applications as blood stem cell transplants are now widely used to reconstitute normal blood formation in patients whose ability to make blood is innately defective or has been damaged by the use of lethal doses of drugs used to combat a life-threatening cancer or leukemia. Nevertheless, many more patients who might in theory benefit from this type of life-saving therapy cannot because an appropriate source of cells is not available. Exciting new methods are now under development to enable this type of treatment to be extended to patients who do not have a suitable donor or that involve genetically correcting a defect in the patient's own cells in the laboratory prior to re-infusion.

Cancer Stem Cells (CSCs) are cancer cells that possess characteristics associated with normal stem cells, and have the ability to give rise to all cell types found in a particular cancer sample. In parallel to the investigation of the characteristics and molecular mechanisms governing normal stem cells, the group is also applying this knowledge to cancer stem cells. Recently, improved methods — for studying CSCs and for demonstrating the potential relevance of CSCs to tumour biology and clinical oncology — have profoundly expanded interest in targeting these cells.

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