



Hyundai Hope on Wheels Hyundai Scholar Research

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Acute Lymphoblastic Leukemia (ALL) is the most common cancer of childhood; about 2500 children are diagnosed with ALL each year in the United States. Outstanding clinical and basic research over the last two decades have led to a markedly improved survival; however almost 20% of children still succumb to this disease, mostly due to recurrence of the disease.

The most common questions coming from children with ALL and from their parents are: " why did I get leukemia", " will it ever come back" and "will I live a normal life after I complete the therapy". We are still very far from being able to answer these questions with certainty and to be able to guarantee cure after therapy. I am convinced that the answer to these questions will derive from the study and understanding of the molecular mechanisms that make a blood cell proliferate uncontrollably and sometimes become resistant to the chemotherapy. Revealing these mechanisms will set the ground for the discovery of new targeted drugs, likely to be less toxic and to have less long term side effects for the survivors so that they can enjoy a long life just like anybody else.

The laboratory I work in at the Columbia Medical Center is specifically interested in studying an aggressive subtype of ALL, called T cell ALL (T-ALL).

T-ALL has a worse outcome compared to a more common subtype of ALL and requires radiotherapy in addition to chemotherapy.

We are particularly interested in studying the role of NOTCH1 in T-ALL. NOTCH1 is a very important transcription factor that controls several steps of normal T-cell development and is mutated in more than half of patients with T-ALL. Abnormal activity of NOTCH1, due to the acquisition of mutations, leads to uncontrolled proliferation of a T-cell and development of leukemia.

We believe that abnormal NOTCH1 function may be even more common than what can be extrapolated from the frequency of the mutations known so far. We have recently described a new type of mutation of NOTCH1 as well as a new mechanism of aberrant activation of the pathway downstream of NOTCH1, proving that the role of NOTCH1 in the development of T-ALL is indeed far greater. In particular the new type of mutation confers a gain in activation of NOTCH1 that is superior to the previously reported mutations. We are currently studying more in depth how the new mutation works with the hope to identify new targets for therapy.

In addition, we have identified a T-ALL cell lines and several mouse T-ALLs that clearly carry aberrant activity of NOTCH1 despite the absence of any of the known mutations in NOTCH1. In the future, we plan to further characterize the T-ALL cell line and the mouse tumors to identify alternative ways of activating NOTCH1 that lead to the development of T-ALL. We are optimistic that the uncovering of the molecular basis for the development of T-ALL will lead to the development of new drugs and ultimately to a better outcome for patients.