Presidential Symposium: The Dark Side of Stem Cells

By Robert L. Redner, MD

Stem cells, near and dear to the hearts of hematologists, sources of life-savingtransplantations and Nobel Prizes — what evil could lurk therein? But, like Hyde to Jekyll, stem cells do indeed have a sinister side. Today's panel of preeminent scientists, assembled from across the globe by ASH President Andrew I. Schafer, MD, will share their insights into cancer stem cells.

The notion of cancer stem cells, or perhaps better termed cancer-initiating cells, has arisen over the past 30 years from observations that suggested that a biologically distinct and rare population of cells is responsible for sustaining tumor growth. An analogy can be made between tissue stem cells and cancer-initiating cells: Both enable tissue generation and regeneration, both maintain a de-differentiated state and self-renew, and both give rise to progenitors that proliferate and differentiate.

It is appropriate that John Dick, PhD, of the University Health Network, in Toronto, Ontario, Canada, was selected as today's first speaker, because his seminal work in the mid-1990s first identified cancer stem cells. Addressing the previously poorly understood observation that successful transplantation of leukemia required 10^5 or more cells, Dr. Dick identified a rare population of $CD34^+/CD38^-$ cells from patients with AML that could transfer leukemia to immunodeficient mice, whereas other populations of cells from the same leukemia did not. Indeed, very low numbers – nearing a single cell – of $CD34^+/CD38^-$ cells could give rise to leukemia.

The identification of these leukemia-initiating cells raised many questions, many of which remain incompletely answered a decade later. Where did they come from — mutation of normal stem cells or de-differentiation of more differentiated progeny? What are the biologic characteristics of these cancer stem cells? Does loss of the p53 pathway balance cell death with proliferation? Does over-expression of telomerase enhance their lifespan? CML cancer stem cells are dependent upon the WNT signaling pathway. Is this true for non-hematologic cancers? What is the role of the microenvironment? To date, cancer stem cells have been identified in leukemia as well as brain, breast, prostate, pancreatic, and colon cancers — will they be found in all malignancies? Today's second speaker, Hans Clevers, MD, PhD, of the Hubrecht Institute, Utrecht, Netherlands, will address many of these questions in his presentation on Gastrointestinal Cancer Stem Cells.

Many tumors respond well to initial treatment, only to recur. The stem-cell theory of cancer holds that cancer-initiating cells are resistant to chemotherapy, and though modern treatments might target the cells that comprise the bulk of a tumor, treatments that fail to target cancer stem cells are destined toward futility. Indeed, cancer stem cells have high levels of aldehyde dehydrogenase, which can confer resistance to cyclophosphamide, and have high expression of the ATP-binding cassette family of membrane transporters. The development of novel strategies to target cancer stem cells will be the topic of today's third speaker, Craig Jordan, PhD, of the University of Rochester Medical Center in Rochester, NY.