William Dameshek Prize to Reward Exceptional Research Into the Origins of Lymphoma

Today, Dr. Riccardo Dalla-Favera will receive the William Dameshek Prize, one of the American Society of Hematology's highest honors. The prize, awarded to an individual who has made a recent outstanding contribution in hematology, recognizes Dr. Dalla-Favera's relentless research into the origins of lymphomas.

"Dr. Dalla-Favera has made critical contributions to the understanding of lymphomagenesis and remains one of the absolute leaders in this field," praises Dr. Ari M. Melnick, Albert Einstein College of Medicine.

While Dr. Dalla-Favera's work on lymphomas has been extensive, perhaps one of his most critical discoveries has been the role that MYC and BCL-6 oncogenes play in B-cell lymphomas. Oncogenes spur cancer development by enabling regular cells to become cancerous tumor cells. The MYC proto-oncogene, for instance, is expressed in proliferating cells in the body, such as keratinocytes, hepatocytes, bone marrow cells, fibroblasts, and vascular smooth muscle cells. This gene normally promotes healthy cell proliferation and transformation by activating growth-promoting genes and repressing a growth-arresting gene. However, when dysregulated, the gene can put cells into cycle and keep them there, allowing for tumor growth. This dysregulation can be caused by a retrovirus or if the gene is displaced on the chromosome. The result is usually Burkitt's lymphoma, a rare and aggressive B-cell lymphoma that accounts for 30 to 50 percent of lymphomas in children but only 1 to 2 percent in adults. About 300 new cases are diagnosed in the U.S. each year. The condition proves rapidly fatal if untreated, but is curable with intensive chemotherapy.

The BCL-6 gene, meanwhile, normally codes for a transcriptional repressor, a special protein that serves as the master regulator for a specific stage of the B-cell life cycle. However, mutations can lead to the inappropriate expression of the gene, which allows BCL-6 to impede other genes throughout the genome that, under normal conditions, actively keep tumors in check. The resulting B-cell lymphoma can be very aggressive, with a short natural history but a long-term survival rate of about 30 percent with current therapies. Of the more than 50,000 Americans diagnosed with non-Hodgkin lymphoma every year, the majority of cases (about a third) are diffuse large B-cell lymphomas, or DLBCL. The BCL-6 oncogene is responsible for roughly 40 percent of cases of DLBCL.

Dr. Dalla-Favera has played a central role in identifying both MYC and BCL-6 as proto-oncogenes, leading to exciting new research into both the causes of, and potential cures for, B-cell lymphomas. "These oncogenes underlie the pathogenesis of almost all cases of high-grade lymphomas, and this discovery fundamentally advanced the lymphoma field," notes Dr. Melnick.

Additionally, Dr. Dalla-Favera identified a mechanism for B cell aquired BCL-6 dysregulation. He found that the enzymatic machinery that generates high affinity antibodies by mutating the immunoglobulin loci in B cells, called somatic hypermutation, often makes "mistakes." While somatic hypermutation mechanism normally targets the immunoglobulin genes in B-cells, it does not function properly in over 50 percent of cases of DLBCL. This mis-step results in the hypermutation of several genes, which leads to dysregulated expression as well as the production of mutant oncogenic proteins. Remarkably, the gene most commonly mis-targeted in this way is BCL-6, which as a consequence may become constitutively expressed. Dr. Dalla-Favera has gone on to show that this constitutive expression of BCL6 directly causes DLBCL.

Dr. Dalla-Favera has also conducted important research into AIDS-related lymphomas. Tumors of the lymphoid system are a major complication of AIDS, and their frequency is increased among HIV-infected individuals. AIDS-associated non-Hodgkin lymphoma, or AIDS-NHL, represents a group of diseases, including Burkitt's lymphoma, diffuse large cell lymphoma, and primary effusion lymphoma, all derived from germinal center B cells. Dr. Dalla-Favera's research has identified the altered genes in AIDS-NHL cells, as well as the oncogenes involved in NHL-specific chromosomal translocations.

His further research has focused on aberrant somatic hypermutation as it relates to AIDS-NHL, including identifying which genes are altered in these tumors, determining the functional consequences of these alterations, and testing their effects in transgenic mouse models, as well as analyzing the phenotype of AIDS-NHL subtypes, their possible further heterogeneity, and their relationship to normal B-cell subpopulations by gene expression profiling. Dr. Dalla-Favera has received an NIH MERIT Award for this research.

Although the Dameshek Prize represents an exceptional achievement, it does not signify a conclusion to that work. There are still many mysteries left for Dr. Dalla-Favera to unravel. To that end, he lists his current lines of

research as, "elucidating the role of chromosomal translocations involving the c-myc proto-oncogene locus and immunoglobulin loci in the development of Burkitt's lymphoma," and, "studying the normal and pathologic function of the BCL-6 gene," as well as "identifying novel oncogenes and tumor suppressors involved in the pathogenesis of lymphoma by virtue of their involvement in tumor-associated chromosomal translocations or by 'positional cloning' from chromosomal regions involved in tumor-associated deletions."

An ASH member since 1988, Dr. Dalla-Favera has contributed much of his time to the Society, currently lending his considerable expertise to the ASH Scientific Committee on Lymphocytic Biology. He has also completed two four-year terms on the editorial board of Blood, the most recent concluding in 2001. In addition to the Dameshek Prize, he has received numerous other honors, including several from the Leukemia Society of America, two NIH MERIT Awards, and his 1995 delivery of the Columbia Dean's Distinguished Lecture.

Born in 1951 in Legnano, a small city in northern Italy, Dr. Dalla-Favera studied at the University of Milan, where he received his MD, graduating *magna cum laude*. He then completed a residency in hematology, also at the University of Milan, before traveling halfway around the world to serve as a visiting fellow at the Laboratory of Tumor Cell Biology at the National Cancer Institute in the United States. From there, he moved on to various academic appointments, from New York University to Columbia, where he currently serves as a Professor in the Department of Genetics and Development, as well as Joanne and Percy Uris Chair, Director of the Institute for Cancer Genetics, and Director of the Herbert Irving Comprehensive Cancer Center.

Dr. Riccardo Dalla-Favera's accomplishments will be rewarded today at 10:30 a.m., when he receives the William Dameshek Prize during the Presidential Symposium. The Symposium will be held in Halls B3-B4.