

Key note lectures

001 KAPLAN LECTURE: MOLECULAR PATHOGENESIS OF B CELL LYMPHOMAS: FROM CYTOGENETICS TO GENOME SEQUENCING

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B cell non-Hodgkin Lymphomas (B-NHL) represent a biologically and clinically heterogeneous set of malignancies, most of which deriving from germinal center (GC) B cells. Analogous to most types of cancer, the pathogenesis of B-NHL is associated with the alteration of various proto-oncogenes and tumor suppressor genes. These alterations occur by mechanisms common to other cancer types, such as gene amplification and deletion, as well as by mechanisms that involve errors in Immunoglobulin gene remodeling processes, i.e. V-D-J recombination, somatic hypermutation, and class-switch recombination. These processes, and the unique biological milieu of the GC, are intimately connected with the pathogenesis of B-NHL.

As for most cancer types, it is believed that alterations of multiple genes are needed for lymphomagenesis. Thus, the identification of such somatic alterations and the cellular pathways that they affect has been the central theme of research on the pathogenesis of B-NHL. With a focus on Diffuse Large B-cell Lymphoma (DLBCL), the lecture will review the progress in this area starting from the identification of proto-oncogenes involved in chromosomal translocations, through the improved understanding of the role of these genes in pathways critical for GC development, toward the very recent discoveries obtained via genome-wide analysis of DLBCL cases.

Indeed, the coupling of next-generation whole-exome sequencing with genome-wide copy-number variation analysis is identifying a novel set of recurrent genetic lesions, which, in turn, are identifying novel pathways relevant both for the pathogenesis and the specific therapeutic targeting of DLBCL.

002 RAPPAPORT LECTURE: MODELING HUMAN LYMPHOMAGENESIS IN MICE

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Tailored mouse models of human lymphomas have become widely available through methods of conditional gene targeting, which allow the introduction of targeted loss- and gain-of-function mutations into any given cell type in the living mouse and subsequently analyze their role in malignant transformation. Thus, choosing candidate oncogenic events presumed to be involved in the pathogenesis of a given human malignancy, and targeting them into the respective tumor progenitor cell, one can directly analyze whether these events are causally involved in cancerogenesis individually or in combination. One can also analyze arising tumors for additional oncogenic events and trace them back to their human counterparts. Finally, genetically modified mice of this kind can serve as preclinical models, in which new therapies can be developed.

I will exemplify these strategies by two specific experimental approaches, which we have developed in the laboratory. In the first, two distinct oncogenic mutations are targeted into a small fraction of prospective tumor progenitor cells such that these cells carry either one of the two mutations or both of them. As either mutation can be traced

by a reporter, one can study in this model side-by-side the fate of (rare) cells expressing either of the two mutations or both. A clear case of oncogene collaboration in a particular type of tumor emerges from these experiments.

The second example addresses the role of Epstein-Barr-Virus driven lymphomagenesis, a major clinical problem in e.g. post-transplant patients. Targeting expression of a major oncogenic EBV protein, latent membrane protein 1 (LMP1), into B cells in the mouse, we found that potent immune surveillance of the LMP1 expressing cells is induced, and that breaking immune surveillance results in rapid, fatal lymphomagenesis. This mouse model of Post-Transplant Lymphoproliferative Disorder (PTLD) thus assigns a crucial role in both the induction of EBV dependent immune surveillance and lymphomagenesis to a single EBV protein, and offers itself for preclinical studies.

003 ULTMANN LECTURE: TREATMENT OF MYELOMA: CURE VERSUS CONTROL

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“Cure versus control” is the dominant philosophical difference that splits the myeloma scientific community today, and underlies the marked heterogeneity in overall strategies, trials, and clinical practice recommendations for this disease. For example, should we treat myeloma with multi-drug, multi-transplant combinations with the goal of potentially curing a subset of patients? Or should we address myeloma as a chronic incurable condition with the goal of disease control using sequential use of the least toxic regimens? The first approach is based on a belief that it is possible to cure myeloma today, if only we can achieve and maintain complete response. The latter approach asserts that while progress has been made there are no known curative regimens and that “complete response” in myeloma is a misnomer, since almost all patients relapse. The “cure” approach recognizes that the risk of adverse events and impact on quality of life will be substantial with aggressive strategies. The “control” approach emphasizes a balance between efficacy and quality of life. Those who favor “cure” are willing to trust surrogate markers such as complete response and progression free survival. Those who favor “control” require a clear overall survival advantage to be proven first before adopting aggressive treatment strategies. What is common to both camps is that both groups believe that they are acting in the best interest of myeloma patients.

The “cure” versus “control” debate in the last few years is a result of many remarkable advances in myeloma therapy, with several new drugs including thalidomide, lenalidomide, bortezomib, liposomal doxorubicin, with many more active drugs that are expected to be approved shortly including pomalidomide and carfilzomib. In clinical practice, the debate affects choice of initial therapy (three and four drug combinations versus two drug combinations), role of autologous stem cell transplant (early versus delayed), recommended number of transplants (single versus double), role of allogeneic stem cell transplant, and the use of post transplant maintenance therapy. In clinical trials, the split affects clinical trial design, selection of endpoints, and most importantly interpretation of clinical trial results.

Although this topic is on myeloma, the cure-versus-control debate is relevant to other similar chronic malignant and non-malignant disorders as well, and therefore has broader implications. Cost of care and Patient-choice are important factors that will play a bigger role in the debate in the future.