Meeting Report

The XVIII Symposium of the International Association for Comparative Research on Leukemia & Related Diseases (IACRLRD): Leukemia and Lymphoma/Pathogenesis and Treatment/Molecular Aspects

The XVIII Symposium of the International Association for Comparative Research on Leukemia & Related Diseases (IACRLRD), an international meeting hosted by Dr. Yoji Ikawa of the Tokyo Medical and Dental University, was held in Kyoto, Japan, October 29 through November 3, 1995. The meeting spanned 6 days and included 4 plenary sessions, 17 symposia, and 8 sessions of short presentations. In addition, there were three associated satellite symposia. The general meeting, attended by more than 400 participants, integrated thematically the contributions of genetic, cellular, and viral factors toward the development of leukemia/lymphoma and sought unifying concepts in leukemogenesis. More than 300 papers were presented.

The following brief overview illustrates, in a noncomprehensive manner, some of the presented works. (The 19th symposium will be held July 13–18, 1997, in Mannheim/Heidelberg, Germany. Organizer: Dr. R. H. Hehlmann, Klinikum Mannheim, Universität Heidelberg, Fax: 49-621-383-4201.)

Viruses and Cancer

Consistent with the meeting site being located in Japan, the molecular pathogenesis of HTLV-I2 was a highly discussed topic. HTLV-I is the etiological agent for adult T-cell leukemia and has been implicated also in the development of HAMs and TSP. Dr. M. Yoshida (Tokyo University, Tokyo, Japan) presented new evidence explaining how the HTLV-I viral transactivator Tax might dysregulate cellular metabolism. Yoshida showed that Tax bound p16ink4a, a cellular inhibitor of cdk4 kinase, directly. He reasoned that protein–protein complex formation between Tax and p16 perturbs cell cycle transition from G1 to S phase and contributes to overall dysregulation of cell growth. The role of Tax on cellular transformation was additionally discussed by two other groups. K.-T. Jeang (NIH, Bethesda, MD) presented findings suggesting that in some cells that are genetically deficient for p16ink4a, Tax expression can directly enhance cdk4 kinase activity. He reported on the isolation using the yeast two-hybrid system of novel cellular proteins that bind Tax. One of these Tax-binding proteins was identified as a human protein that functionally suppresses a constitutively activated Gβ subunit in the heterotrimeric G-protein signaling pathway, suggesting that a cellular mitogen-activated protein kinase pathway might be one contributory route to activating the HTLV-I long terminal repeat. Work from (O. P. Rosin and colleagues; Institute für Klinische und Molekulare Virologie, Erlangen, Germany) expanded on the role of the cyclic AMP kinase pathway in HTLV-I transformation of cells. These investigators engineered inducible expression of Tax using a Tet represor-controlled Herpesvirus saimiri vector. Using specific Tax point mutants, they separated the ability of Tax to activate gene expression through nuclear factor-κB from its ability to activate gene expression through cyclic AMP-responsive element binding protein/activating transcription factor. These investigators reported that Tax function for cellular transformation segregated with the latter. Recent epidemiology of HTLV-I and HTLV-II was reported by Guy de Thé (Pasteur Institute, Paris, France). M. Osame (Kagoshima University, Kagoshima, Japan) reported on HAM/TSP. Osame proposed that infiltrating mononuclear cells in the spinal cord are the major reservoir for HTLV-I and that the pathogenesis of HAM/TSP might be a consequence of a bystander reaction to these cells.

Pathogenesis of HTLV-I-associated neurological diseases was further presented in a symposium chaired by S. Jacobson (NIH) and T. Watanabe (Tokyo University). Here, S. Izumo (Kagoshima University) and Jacobson presented findings supporting the hypothesis that inflammatory T cells present in the CNS of patients with HAM/TSP contribute to the disease immunopathology that is seen in autopsy materials. Using in situ hybridization and in situ PCR, both investigators identified HTLV-I-infected target cells in CNS material from patients. Izumo found virus-infected CD4+ cells in spinal cord samples, and Jacobson localized the presence of Tax sequences in cells that appeared to be astrocytes. Taken together, the corroborating findings of HTLV-I in the CNS of HAM/TSP patients define a high probability of immunological mechanisms in the development of virus-associated neuropathies. Amplifying upon this theme, T. Watanabe presented compatible findings that demonstrated the important contribution of inflammatory T cells in HTLV-I-associated uveitis.

Other presentations highlighted additional links between viruses and cancer development. H. Fan (University of California at Irvine, Irvine, CA) reported on preleukemic events associated with infection by a MuLV enhancer variants. Fan’s findings indicated that early infection of bone marrow is necessary for efficient leukemogenesis. He suggested that, mechanistically, decreased marrow hemopoiesis is compensated for by extramedullary hemopoiesis, which might be an early contributory event for leukemogenesis. M. Martin (NIH) presented unexpected observations of an array of MuLV-related elements in T-cell lymphomas found in rhesus macaques that were recipients of a retrovirus-mediated gene transfer experiment. Martin argued for the possibility of producing and transmitting replication-competent viruses with altered tropism and/or growth properties from packaging cells used to generate retroviral vectors. J. Dudley (University of Texas, Austin, TX) discussed the induction by MMTV of T-cell lymphomas, in addition to mammary carcinoma, in mice. She described MMTV proviruses from clonal T-cell tumors that invariably had large 350–500-bp deletions in the long terminal repeat that removed several negative regulatory elements of transcription. Dudley hypothesized that a key step in MMTV-induced leukemogenesis is the deletion of negative regulatory elements, which results in enhanced transcription in T cells. H.-J. Kung (Case Western Reserve University, Cleveland, OH) observed interesting interactions between retroviruses and MDV in avian lymphomas. Kung found that co-infections of MDV and avian retroviruses frequently exist in the same host, and in some cases, the retrovirus was found to be integrated into the MDV
has DNA-binding properties similar to Jun/Fos and activation properties of MDV. He described a putative MDV oncogene, meq, which has DNA-binding properties similar to Jun/Fos and activation properties similar to WT-1. Lastly, two investigators (M. Kent, Pacific Biological Station, British Columbia, Canada; D. Holzschu, Cornell University, Ithaca, NY) reported on new retroviruses that are associated with the development of plasmacytoid leukemia and dermal sarcoma in fish.

Events in Leukemogenesis

Myriad molecular events are associated with leukemogenesis. Some of these were highlighted in presentations. M. Cleary (Stanford University, Stanford, CT) and T. Yamamoto (Tokyo University) described chromosomal translocation events in leukemias/lymphomas. Cleary reported on a translocation in acute pre-B cell leukemias that fused the DNA-binding domain of PBX1, a divergent member of the homeodomain family, to the activation domain of the E2a protein. Pbx1-E2a fusions present altered activation potentials and interfere with normal Pbx-Hox heterodimer formation. Hypothetically, this would result in disruption of differentiation and induction of oncogenesis. Yamamoto described a chimeric p80 tyrosine kinase isolated from Ki-1 lymphoma cells that occurred as a consequence of a fusion of leukocyte tyrosine kinase and nucleolar protein B23/nucleophosmin, arising from a translocation. Overexpression of p80 in NIH3T3 cells was found to induce neoplastic transformation. Two other speakers (S. Waga, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY; H. Hirai, Tokyo University), as well as many others, presented examples of the critical role of cell cycle control on dysregulated growth. Waga detailed some molecular properties of p21, a CDK regulator. He and his colleagues found that p21 inhibited the in vitro replication of SV40 DNA by forming a direct complex with PCNA, a factor required for DNA replication and nucleotide excision repair. Waga postulated that p21, CDK, cyclin, and PCNA exist as a quaternary complex that regulates cell cycle transition, replication, and DNA repair in vivo. Disturbance of this normal interaction in tumor cells results in genomic instability and DNA damage. Hirai described a large multicenter study examining the intactness of the p16 gene in patient tumors. p16 is an inhibitor of the cyclin D/CDK4 complex and is a negative regulator of G1-S transition in cell cycle control. Results from 410 patients, examining p16 and two other adjacent markers (p15 and IFN-α), revealed that p16 was uniquely deleted in 59 patients and that from the total pool, only 74 patients had no evidence of change at this locus. These findings confirm the role of p16 as not only a cell cycle regulator but also as a tumor suppressor.

Pathogenesis

Many papers covered different aspects of retroviral pathogenesis in cells and in animal models. N. Copeland (National Cancer Institute, Frederick, MD) described a mouse model for juvenile CML. He reported that Ras signaling is commonly deregulated in these tumors. Copeland and colleagues constructed knockout mice for the Nfl locus, a tumor suppressor gene with GTPase-activating protein capacity for Ras, and found that reconstitution of mice with cells from these knockout animals resulted in the development of leukemia similar to juvenile CML. He also identified novel loci targeted by provirus insertion in myeloid tumors. These loci included the Hoxa7 and Hoxa9 genes. K. Radke (University of California at Davis, Davis, CA) and T. Yoshiki (Hokkaido University School of Medicine, Sapporo, Japan) described sheep and rat models for bovine leukemia virus and HTLV-I, respectively. R. Friedrich (Justus Liebig University, Giessen, Germany) described a new locus, Fre-1, which is frequently mutated by provirus insertion in Friend MuLV-induced tumors. L. Wolfe (National Cancer Institute, Bethesda, MD) similarly reported on retroviral insertions into the c-myb and Mmll loci in murine promyelocytic leukemia. Three other presentations updated studies of MAIDS. A. Ishimoto (Kyoto University, Kyoto, Japan) characterized an endogenous defective virus of B6 mice that is similar to the defective virus BM5d required for induction of MAIDS. An exchange and frameshift of p12 from endogenous defective virus with that of BM5d yielded an active virus. H. Morse (NIH) reported that MAIDS did not develop in mice deficient in MHC class II expression, suggesting that the disease is antigen driven. Analyses of mice lacking endogenous Mtv showed them to be disease susceptible, indicating that Mtv-encoded superantigens are not required for induction of MAIDS. P. Jolicoeur (Institute for Clinical Research, Montreal, Quebec, Canada) presented data suggesting that the Pr60ag protein encoded by the defective MAIDS virus functions as a signaling molecule. His group also isolated a number of cDNAs for candidate proteins that interact with Pr60ag using the yeast two-hybrid approach. S. Gisselbrecht (INSERM, Paris, France) presented evidence for constitutive activation of STAT5 in myeloproliferative leukemia virus-induced myeloproliferative disease in mice. The aberrant activation of various cellular signal transduction pathways was a common theme that was repeatedly observed in different systems and was discussed in many presentations. For example, Y. Ikawa (Tokyo Medical and Dental University, Tokyo, Japan) and S. Ruscetti (National Cancer Institute, Frederick, MD) both described the involvement of Jak/Stat pathway in FLV/F-SSFV-associated erythroleukemia. Ikawa commented on the involvement of Jak1 kinase and Stat5 in fresh F-SSFV-infected splenic erythroid cells. Finally, a new twist on transformation through dysregulation of the cellular translational machinery was reported by L. Levy (Tulane University, New Orleans, LA). In feline leukemia virus-induced thymic lymphoma, Levy found that five components of the translational apparatus were expressed at 5-fold higher levels than they are in normal thymus.

Most meetings covering oncogenic retroviruses seem to provide a session on HIV. A symposium devoted to HIV pathogenesis was chaired by M. Essex (Harvard University, Boston, MA) and S. Harada (Kumamoto, Japan). Presentations included discussions by S. Mori (Tokyo University) on EBV lymphomas in AIDS, M. Hayami (Kyoto University) on SIV/HIV-1 chimeric viruses as candidate vectors for live-attenuated vaccines, and J. Yamamoto (University of Florida, Gainesville, FL) on empirical experiences with FIV vaccines. Other talks included an elegant presentation by Essex on the heightened mucosal transmissibility of the clade E HIVs from Thailand and a thoughtful discussion by M. Wainberg (McGill University, Montreal, Quebec, Canada) on resistant HIV-1 that appeared after 3TC treatment. Wainberg found a M184V substitution in RT after monotherapy with 3TC. However, despite drug resistance, he found that treatment with 3TC for more than 48 weeks is associated with a lower plasma viral burden than at baseline. A remarkable finding was that there was increased reverse transcriptase fidelity engendered by the M184V mutant reverse transcriptase when compared to wild-type enzyme. A related symposium on suppression of HIV replication was chaired by A. Rein (NIH) and K. Shimotoho (National Cancer Center Research Institute, Tokyo, Japan). In this session, J. Coffin (Tufts, Boston, MA) discussed the population dynamics of HIV in infected individuals. Rein described a new class of anti-retroviral drug that kills the virus by attacking the zinc fingers in the nucleocapsid protein of the virus. Shimotoho analyzed HIV mutants, the RNA of which would not be expected to form dimers, according to current models. Surprisingly, he reported that these mutants are still capable of replication in
permissive cells. Y. Koyanagi (Tokyo Medical and Dental University) described a HU-PBL-NOD-SCID system that can be infected by HIV-1 with high efficiency such that HIV-1 viremia in mice was easily detected.

**Cellular Factors in Differentiation and Transformation**

In addition to the viral and viral-host interaction systems examined during the presentations, cellular determinants of development, differentiation, and malignant transformation-progression were a prime focus. Efforts to identify novel cellular proto-oncogenes and tumor suppressor genes, their genetic modes of alteration, and associated biochemical functions were most apparent. Almost every molecule in the cellular signal transduction pathway mediating growth control was represented, including analyses of growth factors/interleukins, growth factor receptors, intracellular signaling molecules (such as small GTP/GDP-binding protein), and serine/threonine/tyrosine kinases. However, most apparent was the emphasis on gene regulatory molecules, specifically, sequence-specific DNA-binding proteins as targets for both dominant and recessive modes of oncogenic compression. The study of molecular genetic defects in human leukemias has provided an incredible wealth of information regarding transcription factor dysfunction and cancer.

Dr. T. Rabbitts (Medical Research Council, Cambridge, United Kingdom) and Y. Kaneko (Saitama Cancer Center, Saitama, Japan) chaired a session on leukemogenesis and gene rearrangements. Rabbitts presented a comprehensive analysis of the LMO2 gene from chromosome 11p13, which is frequently rearranged in adult T-cell leukemia. LMO2 encodes the novel zinc-binding LIM domain of unknown function and very likely participates in transcriptional regulation via protein-protein interactions. Remarkably, LMO2 interacts directly with the basic helix-loop-helix transcription factor TAL1/SCL1 and acts in concert with this protein to mediate normal erythropoiesis and, when altered, abnormal T-cell development and tumors. Rabbitts showed that transgenic mice expressing LMO2 from the CD2 promoter develop T-cell tumors after long latency; however, coexpression of the TAL1 transgene shortened these latencies dramatically. Thus, this system will be invaluable for elucidating the secondary events that must occur for LMO2/TAL1-mediated leukemogenesis. The role of the AML1 gene in leukemogenesis was a very common theme among presentations at the meeting. The remarkable interest and progress was evidenced by the fact that a full-day satellite symposium titled “Roles of Transcriptional Regulator RUNT/AML1/PEBP2/CBF in Development, Differentiation, and Carcinogenesis,” chaired by Dr. Y. Ito (Kyoto University), was dedicated to this oncogene. The overall theme that emerged from the AML1 presentations was that of a highly pleiotropic regulator of gene expression wherein strict genotype-phenotype correlations are difficult to draw. However, clearly aberrant transcriptional regulation via AML1 binding sites in specific target genes is critical to the transformation process.

M. Ohki (National Cancer Center Research Institute) demonstrated that overexpression of the AML1 MTG8 fusion gene rendered hematopoietic cells resistant to G-CSF-induced maturation. This was well correlated with dramatically up-regulated G-CSF receptor synthesis and may be mediated by direct binding of the aberrant transcription factor to the G-CSF promoter region. This set the stage for a number of presentations describing the target genes for AML1, which include the TCRα and TCRβ promoters, the CSF1 receptor promoter, and the myeloperoxidase promoter. G. Nuciffora from the Rowley Laboratory (University of Chicago, Chicago, IL) described a number of therapy-related AML1 chromosomal translocations, some of which fuse AML1 to a repression domain, and suggested that direct competition between activators and repressors at AML1 binding sites may be responsible for transformation. Y. Ito provided a thorough picture of AML1 and runt domain proteins in development disease. Highlights included demonstration of cooperativity of AML1 with ETS domain proteins on the TCRβ enhancer, regulation of α and β subunits by regulated nuclear cytoplasmic localization, and finally, successful targeting of the AML1 breakpoint in RNA using antisense oligonucleotides. Highlights from the Satellite Symposium on AML1 included: (a) a demonstration that AML1 was embryonic lethal when homozygously deleted, probably due to blockage of hematopoiesis and hemorrhaging (N. Speck, Dartmouth College, Hanover, NH); (b) identification of AML1 transcript isoforms in developing testis (M. Satake, Sendai, Japan); and (c) identification of Drosophila and Xenopus homologues of AML1, which seem to play a role in multiple developmental pathways in metazoan development (J. P. Gergen, State University of New York, Stony Brook, NY). Indications were that study of AML1 should continue to provide exciting insights into transformation, organogenesis, and transcriptional control.

In contrast to genetically and biochemically dominant alterations in transcription factor-mediated leukemogenesis, an emerging theme involved recessive defects. The session on tumor suppressor genes in leukemogenesis, cochaired by S. Yang (National Cancer Institute-Division of Cancer Treatment, Bethesda, MD) and M. Sasaki (Kyoto University), examined this topic, which prominently featured p53 pathways. S. Benchimol (University of Toronto, Toronto, Ontario, Canada) convincingly demonstrated that two functions of p53, G1 arrest and promotion of apoptosis, could be uncoupled by using growth factors as survival agents in murine erythroleukemia cells. V. Rotter (Weizmann Institute of Science, Rehovot, Israel) presented similar results in HL60 cells using a novel p53 vaccinia virus system. The results clearly showed that levels of p53 may determine the choice of differentiation or apoptosis, suggesting important implications for use of p53 vectors in human gene therapy. Work from R. Takahashi (Kyoto University) demonstrated cross-talk between the Fas/Apo-1 and p53 apoptotic pathways in B cells. K. Ishizaki (Aichi Cancer Center Research Institute, Nagoya, Japan) reported that fibroblasts from p53-deficient mouse embryos showed increased sister chromatid exchange and delay in entitling S-phase due to UV irradiation, confirming the aberrant checkpoint in these cells. Finally, other important work on p53 to emerge from the meeting was presented by S. Waga (laboratory of B. Stillman, New York, NY). They showed that the p53 target gene, p21, forms a quaternary complex with CDK, one of the cyclins, and PCNA, thereby integrating p53-mediated control of the cell cycle DNA replication and DNA repair.

This theme was continued and expanded in sequential sympsoias on “Cell Cycle Regulation and Cyclin Inhibitors,” which brought us up to date on mechanisms of checkpoint control and genome stability. J. Kato (Nara Institute of Science and Technology, Nara, Japan), who cochaired the session with M. Yanagida (Kyoto University), summarized the role of D1 cyclins in G1 progression and their regulation by growth factor stimulation. Induced D-type cyclins are recruited into holoenzyme complexes in a highly ordered manner. Antiproliferation signals induce the CDK inhibitors, which serve to buffer the whole system. Key elements of this process are tightly controlled posttranslational modifications of pRb and other substrates, the identification of which is an important future goal. H. Toyoshima (The Salk Institute, La Jolla, CA) reported the distribution of p27/Kip1 in cyclin/CDK complexes at various points in the cell cycle. Interestingly, p27/Kip1 is dramatically redistributed between CDK4 and CDK2 in normal cell cycle progression, implying a broader role in controlling CDKs at different points in the cell cycle. The dramatic influence and awesome power of yeast genetics on our understanding of cell cycle was evident from the talks of A. M. Carr (University of Sussex,
Brighton, United Kingdom) and M. Yanagida. Carr spoke about a gene from fission yeast, rad3, which encodes a "lipid" kinase with extensive homology to the ATM ataxia telangiectasia gene. A second human gene in the Rad3 family further suggests close symmetry among cell cycle checkpoints in yeast and metazoans. The talk of M. Yanagida highlighted work on the cut5 locus, which is allelic to rad4 mutants and renders cells resistant to a replication checkpoint induced by hydroxyurea. Cut5 is a nuclear protein associated with chromatin, which encodes NH₂-terminal repeats found in a mammalian proto-oncogene, Ect2.

G. Peters (Imperial Cancer Research Fund, London, United Kingdom) described the specificity of CDK inhibitors for recruitment into and inhibition of various cyclin-CDK complexes. Interestingly, in familial melanoma, some of the mutations of the CDK inhibitor p16 are temperature sensitive when assayed for CDK binding. In addition, a novel mechanism was proposed whereby gradual accumulation of p16 RNA and protein in a population eventually levels to pRb phosphorylation and senescence. N. Nakanishi (Jichi Medical School, Tochigi, Japan) presented a comprehensive structure function analysis of p21 protein for CDK binding, PCNA binding, and E2F inhibition. An interesting p21 mutant was described that lacked CDK and PCNA binding activity yet still inhibited DNA synthesis in a cell type-dependent manner. As yet unidentified functions/pathways for the multifunctional p21 molecule were hypothesized. H. Matsuishi (Institute of Medical Science, University of Tokyo, Tokyo, Japan) showed that the M015 holoenzyme phosphorylates CDK4 and that this activity was inhibited by p27/Kip1. It was suggested that density-arrested rat fibroblasts contain unphosphorylated CDK4 complexes and that although M015 is active in arrested cells, it is denied access to CDK4 by p27/Kip1. Finally, M. Pagano (Mitotix, Inc., Cambridge, MA) reported that the ubiquitine proteosome pathway plays a key role in mammalian cell cycle progression by ubiquinating/degrading p27 in a cell cycle dependent manner. This pathway may thus hold key targets for small molecule-targeted cancer therapeutic strategies.

Retinooids

The influence of the retinoid system in the development of disease and therapeutics was highlighted in a session chaired by A. Kakizuka (Kyoto University). The laboratory of R. Evans (The Salk Institute) updated the rapid evolution of our understanding of the PML-RAR oncogenic fusion protein in acute PML. The wild-type PML protein is normally localized to very discreet nuclear subdomain dot structures termed PODs, which form in early G1 and then are lost in late S phase of the cell cycle. When PML is fused to RAR in APL patients, discreet PODs are not observed. Remarkably, relocalization to PODs can be induced by exposure with retinoic acid, a treatment that is extremely effective for APL induction therapy. A novel PML-associated protein (PIF31A) was described (isolated via the yeast two-hybrid system), which is also present on the surface of the POD structure and may mediate its functions. Further study of this system will almost surely lead to a molecular mechanism for the therapeutic efficiency of retinoic acid in APL and serve as a unique tool for targeting disease-specific transcription factors with small molecules for therapeutic benefit. A. Kakizuka reported the successful design and use of dominant-negative RARs via a single amino acid substitution based upon the human genetics of thyroid hormone resistance. Expression of dominant-negative RAR targeted to the mouse epidermis demonstrated dramatic suppression of epidermal differentiation. These results suggest that a dominant-negative strategy may be viable in human gene therapy contexts. Finally, the role of the RAR system in Drosophila development was highlighted by G. Eichele (Baylor College of Medicine, Houston, TX), who showed that correct spatiotemporal expression of homeobox genes requires RAR and retinoid X receptor ligands during development and that cross-species (chicken-Drosophila) complementation of hox gene function was possible.

Clinical Implications

The topics of "Clinical Studies in Leukemias" and "New Therapeutic Methods against Leukemias and Retroviral Models" occupied two consecutive symposia and offered the translational research area to the Congress proceedings. At the basic science level, talks address-
ing alteration of transcription factors as markers of disease progression or as potential gene therapy reagents were offered. K. Mitani (University of Tokyo) reported that AML-1-Evi-1 fusion resulting from the t(3;21) translocation in myelodysplastic syndrome-derived leukemia is oncogenic and dominantly suppressed transactivation by wild-type AML1. Targeting of this fusion may be possible because antisense oligonucleotides spanning the AML-1-Evi-1 fusion junction specifically inhibited cell growth in cells carrying the t(3;21) translocation. This theme was further addressed by T. Papas (Medical University of South Carolina, Charleston, SC), who showed that a wild-type ETS-1 gene reversed the transformation process and in vivo tumorigenesis in colon cancer cells. Reversion was dependent upon intact transcriptional activation properties of ETS-1. The diagnostic and prognostic potential of detecting minimal residual disease via PCR was highlighted by M. Tanimoto (Nagoya University). Using the BCR/ABL translocation, the investigator found that PCR in CML after transplantation reliably indicates the existence of graft versus leukemia, which may be clinically useful for monitoring CML patients. Using similar reverse transcription-PCR assays for BCR/ABL and long-term culture, this group (C. Eaves, Terry Fox Lab., University of British Columbia, British Columbia, Canada) has identified growth conditions that stimulate expansion of normal marrow stem cells and that may be “dominant” in their growth properties in the marrow.

Memorial Lectures

This meeting was also an occasion to honor some of the giants in the fields of leukemia and lymphoma. Five memorial lectures commemorated the outstanding accomplishments of past colleagues. The Howard Temin Memorial Lecture was introduced by John M. Coffin (Tufts) and was delivered by Mitsuaki Yoshida (Tokyo University). Yoshida discussed “Molecular Biology of HTLV-I: Deregulation of Host Cell Gene Expression.” Charlotte Friend was honored in a memorial lecture delivered by J. Hartley (NIH). Hartley was introduced by John B. Moloney and spoke on “Murine Leukemia Virus Tumorigenesis.” Dr. F. Barre-Sinoussi (Pasteur Institute) presented the Frank Rauscher Jr. Memorial Lectureship. Barre-Sinoussi was introduced by H. Sugano (Cancer Institute, Tokyo, Japan). She spoke on “AIDS: A Consequence of a Complex Interplay between a Retrovirus and Its Host.” The Kenneth McGredie Memorial Lecturer was K. Takatsuki (Kumamoto University School of Medicine, Kumamoto, Japan). Takatsuki’s lecture, introduced by D. S. Yohn (James Cancer Hospital, Columbus, OH), was “Adult T-Cell Leukemia/Lymphoma.” The final memorial lecture, honoring Yohei Ito, was presented by C. M. Croce (Jefferson University, Philadelphia, PA). Croce was introduced by R. Gallo (NIH) and spoke on oncogene activation in preleukemic T-cells.

Concluding Comments

In summary, the scientific sessions of this meeting offered a comprehensive multidisciplinary glimpse of our state of the art knowledge regarding viral and cellular patho-oncology. There are few forums in which investigators from even more specialized disciplines can write a “big picture” with which to focus and launch the next experimental and clinical studies. It is clear from the success of this meeting that the IACRLRD will continue to play a key role in shaping the focus of successive generations of research scientists as it has in the past. We thank Dr. Ikawa for organizing a stimulating meeting and look forward to the next meeting of the IACRLRD, to be held in Mannheim/Heidelberg, Germany.

Acknowledgments

We thank Paul Jolicoeur, Mark Wainberg, Herbert Morse, Alan Rein, and Steve Jacobson for comments and suggestions. We appreciate Yoji Ikawa’s persistence in encouraging us to complete this meeting review. Due to the large number of excellent presentations, we could not cover all topics. We apologize for this limitation.

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