

Speaker Biographical Sketches

Frederick W. Alt, Ph.D.

Dr. Alt received his Ph.D. in 1971 from Stanford University, where he worked with Robert Schimke to discover gene amplification in mammalian cells, a key mechanism of anticancer drug resistance and tumor progression. He completed his postdoctoral work with David Baltimore at MIT, where he helped elucidate many of the basic principles of the recombination events involved in generating the adaptive immune system. In 1982, Dr. Alt moved to Columbia University as an Assistant Professor; he became Professor of Biochemistry and Molecular Biophysics in 1985 and a Howard Hughes Medical Institute (HHMI) Investigator in 1987. At Columbia, he continued his studies of the immune system and discovered the *N-myc* oncogene based on its amplification in human neuroblastomas.

In 1991, Dr. Alt moved to Harvard Medical School, where he became an HHMI Investigator at Children's Hospital Boston and a Senior Investigator at the CBR Institute for Biomedical Research (CBRI) as well as a Professor of Genetics and Pediatrics. He was appointed the Charles A. Janeway Professor of Pediatrics in 1993 and Scientific Director of CBRI in 2005. Dr. Alt's work at CBRI and Children's Hospital continues to focus on lymphocyte development, genomic instability, and cancer. Of particular note, his group played a key role in elucidating the nonhomologous DNA end-joining pathway of DNA double-strand break repair in mammalian cells. More recently, his group has uncovered the role of other factors, including chromosomal proteins, in maintaining genomic stability and suppression of cancer in mice. Last year, Dr. Alt was named an Ellison Medical Foundation Senior Scholar in Aging, allowing him to initiate new work in that area.

Dr. Alt has authored more than 400 papers during his career. In 1994, he was elected to the National Academy of Sciences, the American Academy of Arts and Sciences, and the American Academy of Microbiology. He was elected as a Foreign Member of the European Molecular Biology Organization in 1999. Most recently, Dr. Alt received the Clowes Memorial Award from the American Association of Cancer Research, the Rabbi Shai Shacknai Prize from The Hebrew University, the Pasarow Foundation prize for Cancer Research, the Leukemia & Lymphoma Society de Villiers International Achievement Award, and the Irvington Institute Immunology Award.

Dr. Alt serves on numerous editorial boards and is Editor in Chief of *Advances in Immunology*. He also serves on many national and international advisory boards and has chaired the Scientific Advisory Board of the Irvington Institute for Biomedical Research and the Board of Scientific Counselors (basic) of the National Cancer Institute. Dr. Alt has mentored nearly 100 students and research fellows, many of whom have become leaders in the fields of immunology, genetics, and cancer biology. In 2003, Dr. Alt received the American Association of Immunologists Excellence in Mentoring Award in recognition of his training achievements.

Kenneth C. Anderson, M.D.

Dr. Anderson received his medical degree from The Johns Hopkins School of Medicine, trained in Internal Medicine at The Johns Hopkins Hospital, and completed Hematology, Medical Oncology, and Tumor Immunology training at the Dana-Farber Cancer Institute (DFCI). He is the Kraft Family Professor of Medicine at Harvard Medical School.

Dr. Anderson serves as Chief of the Division of Hematologic Neoplasia, Director of the Jerome Lipper Multiple Myeloma Center, and Vice Chair of the Joint Program in Transfusion Medicine at DFCl. He also serves as Chair of the National Comprehensive Cancer Network (NCCN) Multiple Myeloma Clinical Practice Guidelines Committee, is a Cancer and Leukemia Group B Principal Investigator, serves on the Board of Scientific Advisors of the International Myeloma Foundation, and sits on the Board of Directors and serves as Chair of the Scientific Advisory Board of the Multiple Myeloma Research Foundation and of the Leadership Committee of the Multiple Myeloma Research Consortium. Dr. Anderson is a Doris Duke Distinguished Clinical Research Scientist and has received long-term funding from the National Institutes of Health, including R01, P01, and Specialized Programs of Research Excellence (SPOREs) grants. His numerous awards include the 2001 Charles C. Lund Award of the American Red Cross Blood Services, the 2003 Waldenstrom's Award for research in plasma cell dyscrasias, and the 2004 Johnson & Johnson Focused Giving Award for Setting New Directions in Science and Technology.

Over the last two decades, Dr. Anderson has focused his translational research studies on B-cell malignancies, especially multiple myeloma. Highlights of his contributions to science and medicine include: discovery of the first plasma-cell-reactive monoclonal antibodies; development of an immunophenotyping model for diagnosis and treatment of B-cell malignancies; pioneering novel methods to improve safety and efficacy of autografting and allografting in myeloma; characterizing the signaling cascades whereby cytokines mediate myeloma cell growth, survival, and drug resistance in the bone marrow microenvironment; developing *in vitro* and *in vivo* models to identify and validate novel therapeutic targets in the myeloma cell and its bone marrow milieu; translating these preclinical studies to the bedside in derived clinical trials; and establishing a new treatment paradigm using novel therapies targeting the myeloma cell tumor-host bone marrow interaction, and bone marrow microenvironment to overcome drug resistance and improve patient outcomes in myeloma. Dr. Anderson led both preclinical and clinical trials of the novel proteasome inhibitor bortezomib, which led to its rapid FDA approval, and has similarly identified and validated other novel targeted therapeutics, including immunomodulatory drugs, histone deacetylase inhibitors, and insulin-like growth factor inhibitors. His paradigm for identifying and validating targets in the tumor cell and its milieu has already provided novel therapies and offers great promise for improving patient outcomes in both hematologic malignancies and solid tumors.

P. Leif Bergsagel, M.D., F.R.C.P.C.

Dr. Bergsagel is Associate Professor of Medicine at the Mayo Clinic College of Medicine and an Associate Consultant at the Mayo Clinic Arizona. He received his M.D. from the University of Toronto and completed his residency training in Toronto and at Stanford University. He completed a fellowship in Medical Oncology at the National Cancer Institute and the National Naval Medical Center in Bethesda, Maryland. Prior to joining the Mayo Clinic, Dr. Bergsagel was Associate Professor of Medicine at Weill Medical College of Cornell University in New York City.

Dr. Bergsagel is the PI on several peer-reviewed grants from the National Cancer Institute, the National Institute on Aging, the Leukemia & Lymphoma Society, and the Multiple Myeloma Research Foundation. He has spent 15 years combining responsibilities in research and clinical care.

Dr. Bergsagel has earned a worldwide reputation for his work in myeloma research and has received a number of awards and honors, including the Henry Christian Award from

the American Federation for Clinical Research. He has authored more than 50 publications and a number of book chapters. Dr. Bergsagel also serves on the editorial boards of several journals.

Suzanne Cory, A.C., Ph.D., F.A.A., F.R.S.

Dr. Cory, Director of The Walter and Eliza Hall Institute of Medical Research since 1996, is one of Australia's most distinguished molecular biologists. She was born in Melbourne and graduated with a degree in Biochemistry from The University of Melbourne. Her research career began with a pioneering sequence analysis of methionine transfer RNAs conducted during her doctoral studies at Cambridge. Postdoctoral work in Geneva, Switzerland, which initiated her longstanding scientific collaboration with Dr. Jerry Adams, revealed unexpected secondary structure in messenger RNA and regions devoid of protein-coding potential. With Dr. Adams, Dr. Cory returned to Melbourne in 1971 to establish a molecular genetics laboratory at The Walter and Eliza Hall Institute of Medical Research. Their early work resulted in the discovery that mammalian messenger RNAs initiate with novel "cap" structures and contributed major insights about the organization of immunoglobulin (Ig) genes and the recombination events that occur in lymphocytes to create a functional Ig gene and switch expression from one class to another.

Drs. Cory and Adams then shifted their focus to the molecular genetics of cancer. They discovered that the chromosome translocations hallmarking Burkitt's lymphoma and mouse plasmacytoma fuse immunoglobulin gene loci with the *myc* oncogene, thereby establishing the link between chromosome translocations and oncogene activation. Following this paradigm, putative oncogenes have been identified from numerous translocations. The discovery in their laboratory that *bcl-2*, the oncogene activated by chromosome translocation in human follicular lymphoma, promotes cell survival rather than proliferation and accelerates *myc*-induced lymphomagenesis revealed for the first time that impaired apoptosis is central to tumorigenesis. Regulation of cell death by the *bcl-2* family is now the central focus of their research program, which hopes to develop more effective cancer therapeutics.

Dr. Cory's scientific achievements have resulted in numerous honors and awards. In 1998, she was a joint recipient of the Australia Prize and the prestigious Charles S. Mott Prize awarded by the General Motors Cancer Research Foundation. In 1999, Dr. Cory was appointed a Companion in the General Division of the Order of Australia. In 2001, she received a L'Oréal-UNESCO Women in Science Award, and in 2002, she was presented with the Royal Medal of The Royal Society in London. She was elected a Fellow of the Australian Academy of Science in 1986, a Fellow of the Royal Society in 1992, a Foreign Member of the U.S. National Academy of Sciences in 1997, a Foreign Member of the American Academy of Arts and Sciences in 2001, an Associate Foreign Member of the French Academy of Sciences in 2002, and an Academician of the Pontifical Academy of Sciences in 2004.

Carlo M. Croce, M.D.

Dr. Croce is world renowned for his contributions involving the genes and genetic mechanisms implicated in the pathogenesis of human cancer. During the course of his career, Dr. Croce discovered the juxtaposition of the human immunoglobulin genes to the *myc* oncogene, the deregulation of *myc* in Burkitt's lymphoma, the *ALL1* gene involved in acute leukemias, and the *TLC1* gene associated with T-cell leukemias; he also cloned and characterized the *bcl-2* gene involved in follicular lymphoma. Dr. Croce

has also uncovered the early events involved in the pathogenesis of lung, nasopharyngeal, head and neck, esophageal, gastrointestinal, and breast cancers. Recently, he discovered the involvement of *miR* genes in human cancer.

Dr. Croce's discoveries have led to revolutionary innovations in the development of novel and successful approaches to cancer prevention, diagnosis, monitoring, and treatment based on gene target discovery and verification and rational drug development.

Chi V. Dang, M.D., Ph.D.

Dr. Dang is The Johns Hopkins Family Professor and Vice Dean for Research at The Johns Hopkins University (JHU) School of Medicine. He oversees the Hopkins Institute for Cell Engineering and is a Professor of Medicine, Pathology, Oncology, and Cell Biology, with a joint appointment in Molecular Biology and Genetics. He received his B.S. (Chemistry, highest honors) from the University of Michigan, his M.D. from The Johns Hopkins University School of Medicine (with induction into Alpha Omega Alpha and Phi Beta Kappa), and his Ph.D. in Chemistry/Biochemistry (with distinction) from Georgetown University. He is board-certified in Internal Medicine and Medical Oncology. Dr. Dang was Director of the Hematology Division in the Department of Medicine at JHU from 1993 to 2003.

Dr. Dang is Senior Editor of *Cancer Research* and serves on the editorial boards of *Current Cancer Therapy Reviews*, *Drug Discovery Today*, the *Journal of Clinical Investigation*, and *Neoplasia*. He has authored more than 150 scientific articles and book chapters. He was a member of the National Cancer Institute (NCI) Board of Scientific Counselors and was elected to the Association of American Physicians. Dr. Dang was elected president of the American Society for Clinical Investigation in 2003. He holds an NIH/NCI MERIT award and has sponsored 8 NIH K08 physician-scientist awardees and mentored 12 Ph.D. doctoral candidates and 26 postdoctoral fellows.

The Dang laboratory has contributed to the understanding of the function of the *myc* cancer gene, which has emerged as a central switch in many different cancers. Dr. Dang defined the functional domains of the *myc* transcription factor. His current work focuses on the genetic program regulated by *myc*, allowing this oncogenic transcription factor to elicit diverse cellular phenotypes. On discovering that *myc* is able to activate the expression of genes involved in glycolysis, Dr. Dang's lab connected the *myc* cancer gene to an age-old observation that sugar metabolism is altered in cancers. He has launched a National Library of Medicine-funded public database on *myc* (www.myc-cancer-gene.org). This Web site provides a model of the much-needed integration of vast amounts of molecular, biological, and genetic information on key molecules and pathways relevant to human diseases.

Elaine S. Jaffe, M.D.

Dr. Jaffe completed her medical education at Cornell University and the University of Pennsylvania, receiving an M.D. from the latter in 1969. After an internship at Georgetown University, she joined the National Cancer Institute as a resident in anatomic pathology, subsequently completing a fellowship in hematopathology. She has been a Senior Investigator since 1974 and in 1980, became Chief of the Hematopathology Section. She continues to hold that position and is also Acting Chief of the Laboratory of Pathology.

As the Chief of the Hematopathology Section, Dr. Jaffe's clinical and investigational studies are intertwined to enhance the understanding of malignant lymphomas. One of her earliest papers on nodular lymphomas (1974), a Citation Classic, presented evidence for the origin of these tumors from follicular B cells. Since then, Dr. Jaffe's keen diagnostic eye and meticulous studies have helped recognize and define not only the more common malignant lymphomas, but also rare conditions that illuminate knowledge of the underlying biology, such as composite lymphomas and T-cell malignancies. Her work stresses the clinical implications of diagnoses, emphasizing the role of pathologists as clinical consultants.

Science Watch named Dr. Jaffe one of the 10 most highly cited researchers in clinical oncology in both 1981 and 1998, and she is the only woman to appear on this prestigious list. She has been president of both the Society for Hematopathology and the United States and Canadian Academy of Pathology and was elected to the advisory board of the American Society of Hematology. In 1993, she was elected a Fellow of the American Association for the Advancement of Science (AAAS) and currently is Chair of the Medical Sciences Section of AAAS. Among her awards are the Fred W. Stewart Award from Memorial Sloan-Kettering Cancer Center and the Mostofi Award from the United States and Canadian Academy of Pathology. She has served on 12 journal editorial boards, including *The American Journal of Pathology*, *The American Journal of Surgical Pathology*, *Blood*, *Cancer Research*, and *Modern Pathology*.

Dr. Jaffe has been involved in numerous national and international advisory committees. She was a member of the Steering Committee and Senior Editor for the recently published (2001) WHO *Classifications of Tumors: Pathology and Genetics of the Hematopoietic and Lymphoid Tissues*. More than 100 internationally recognized hematopathologists, oncologists, and hematologists participated in this landmark effort that, for the first time, produced a classification that has received worldwide acceptance. The success of this project is a tribute to Dr. Jaffe's abilities to work with a large, international group of colleagues and bring clarity to the complexities of hematologic malignancies.

Thomas J. Kipps, M.D., Ph.D.

Dr. Kipps is a University of California, San Diego (UCSD), Professor of Medicine and Deputy Director of Research at the Moores UCSD Cancer Center. He is the holder of the Evelyn and Edwin Tasch Chair in Cancer Research. Dr. Kipps received his Ph.D. and M.D. from Harvard University and completed his residency and fellowship training in Internal Medicine, Hematology, and Genetics at Stanford University. Prior to joining UCSD, Dr. Kipps was an Associate Member and Co-Director of the Flow Cytometry Center at the Scripps Research Institute.

Dr. Kipps is the PI on several peer-reviewed grants, including a National Institutes of Health Merit Award and an award from the National Cancer Institute to fund the Chronic Lymphocytic Leukemia Research Consortium (CRC). The CRC is a multisite basic and clinical research consortium developed to accelerate discovery of curative treatment strategies for patients with this leukemia. Dr. Kipps has 20 years of experience combining research and clinical care responsibilities.

Dr. Kipps has earned a national and international reputation for his work in cancer research, immunology, and gene therapy and has received a number of awards and honors, including the Henry Ashbury Christian Award from Harvard University and the Stohman Memorial Scholar Award from the Leukemia Society of America. He has

authored more than 200 publications and a number of book chapters. Dr. Kipps is also on the editorial board of several journals.

Michael Kuehl, M.D.

Dr. Kuehl has achieved an international reputation for his groundbreaking studies of the molecular pathogenesis of multiple myeloma (MM). Together with P. Leif Bergsagel, M.D., initially a fellow in his lab but subsequently a continuing collaborator, Dr. Kuehl was the first to identify and clone five recurrent IgH translocations that are mediated mostly by errors in IgH-switch recombination in germinal center B cells. These recurrent translocations, which are present in nearly half of premalignant monoclonal gammopathies of undetermined significance (MGUS) and malignant MM tumors, appear to be primary events in pathogenesis. Drs. Kuehl and Bergsagel have also shown that dysregulation of a *myc* gene is a late progression event that is caused by complex secondary translocations and insertions that often do not involve juxtaposition of *myc* and an immunoglobulin locus. In addition, they have shown that secondary translocations involving an Ig locus and a promiscuous array of partner chromosomal loci seem to occur as progression events at all stages of pathogenesis. Most recently, Drs. Kuehl and Bergsagel have proposed that the dysregulation of a *CYCLIN D* gene—either with or without an Ig translocation—occurs as an early, unifying event in virtually all MGUS and MM tumors.

Dr. Kuehl received his M.D. from Harvard Medical School. After 2 years of residency in Internal Medicine at Case Western Reserve University, he completed postdoctoral fellowships at the National Institutes of Health and The Albert Einstein College of Medicine. Dr. Kuehl was hired as an immunologist in the Department of Microbiology at the University of Virginia Medical School, where he studied the regulation of immunoglobulin gene expression, including translational and posttranslational mechanisms in normal and malignant B cells. Dr. Kuehl attained the rank of Professor before joining the National Cancer Institute (NCI) as a Senior Investigator. At NCI, Dr. Kuehl's research focus gradually shifted from the genetics and development of normal hematopoietic cells to a focus on malignant hematopoietic cells. For the past 10 years, his research has focused almost exclusively on the molecular pathogenesis of MGUS and MM.

A. Thomas Look, M.D.

Dr. Look received his M.D. and postgraduate training in Pediatrics from the University of Michigan in Ann Arbor and his fellowship training in Pediatric Oncology at St. Jude Children's Research Hospital in Memphis, Tennessee. Dr. Look then accepted a faculty position at St. Jude and remained on the faculty for 20 years, ultimately becoming the Chair of the Experimental Oncology Department. In June 1999, he joined the Dana-Farber Cancer Institute in Boston, Massachusetts, as Vice-Chair for Research in Pediatric Oncology and Professor of Pediatrics at Harvard Medical School.

Tak W. Mak, Ph.D.

Dr. Mak has achieved an international reputation for the high caliber of his work in immunology and molecular biology. He is best known for his groundbreaking discovery of the T-cell receptor, a key component of the immune system, which advanced the understanding of how the immune system works.

Dr. Mak has been a Professor in the Departments of Medical Biophysics and Immunology at the University of Toronto since 1983. Presently, he is the Director of the

Advanced Medical Discovery Institute and Campbell Family Institute for Breast Cancer Research.

Since 1991, Dr. Mak and his research team have developed more than 100 strains of mice to help scientists around the world as they work to understand and cure such diseases as cancer, AIDS, diabetes, and multiple sclerosis. Each strain has separate genes in the immune system, a tumor-suppressor gene deleted, or another alteration that allows scientists to study immunology and cancer pathways in isolation from one another.

Dr. Mak has coauthored more than 550 scientific papers and was one of the scientists ranked, as of late 2000, for publishing the greatest number of highly cited papers. He has been recognized by the scientific community through a number of awards and honors, including Germany's most prestigious research award, the Emil Von Behring Prize (1988), the Gairdner Foundation International Award for outstanding contributions in the field of medical science (1989), the King Faisal International Prize for Medicine (1995), and the Alfred E. Sloan Prize from the General Motors Cancer Foundation (1996). Dr. Mak was also a recipient of the 1996 National Cancer Institute of Canada R.L. Nobel Prize. In 1998, he received the Novartis Immunology Prize from Novartis, Inc. in Basel, Switzerland. Dr. Mak was awarded the Order of Canada in 2000 and elected a Foreign Associate of the National Academy of Sciences (U.S.A.) in 2002. He is also a member on numerous advisory boards of scientific journals and medical centers.

Ari Melnick, M.D.

Dr. Melnick is a graduate of the University of Buenos Aires School of Medicine. He completed clinical training in Internal Medicine and, then, Hematology and Oncology at the Mount Sinai School of Medicine in New York City, followed by a postdoctoral fellowship with Dr. Jonathan Licht—also at Mount Sinai. Dr. Melnick's scientific training is in the molecular basis of transcriptional deregulation in hematologic malignancies.

Dr. Melnick is currently the Diane and Arthur B. Belfer Faculty Scholar in Cancer Research and an Assistant Professor at the Albert Einstein College of Medicine in New York City. His work is focused on the transcriptional and biological mechanisms and action of the BCL6 protein in normal and malignant B cells, mechanisms of epigenetic silencing during malignant transformation of cells, and epigenomic integrative analysis of leukemias.

Work from Dr. Melnick and his collaborators on the transcriptional mechanism of action of BCL6 and its cofactors led to the design of a specific BCL6-inhibitor drug that can phenocopy the BCL6 phenotype when injected into animals and that kills B-cell lymphomas both *in vitro* and *in vivo*. This work was recently published in *Molecular Cell* and *Nature Medicine* and was featured in the plenary session of the 2004 Annual Meeting of the American Society of Hematology.

Laura Pasqualucci, M.D.

Dr. Pasqualucci received her medical degree and completed her training in Hematology at the Institute of Hematology and Clinical Immunology in the University of Perugia Medical School in Italy. After a year of training in Hematopathology at the Free University of Berlin (Germany) and a postdoctoral fellowship in the laboratory of Riccardo Dalla-Favera (Columbia University), Dr. Pasqualucci joined the Columbia University College of Physicians and Surgeons as Assistant Professor of Clinical

Pathology in the Institute for Cancer Genetics in the Department of Pathology, where she is a senior member of the research team led by Dr. Dalla-Favera.

Dr. Pasqualucci's research is focused on lymphoid neoplasia—particularly the molecular mechanisms of genetic lesions that are involved in the pathogenesis of human B-cell lymphomas. In Dr. Dalla-Favera's lab, Dr. Pasqualucci demonstrated for the first time that the somatic hypermutation mechanism normally acting on the antibody genes can physiologically target other genomic regions in normal germinal center (GC) B cells—namely, the 5' noncoding region of the BCL-6 proto-oncogene. More recently, she identified a novel mechanism of genetic damage associated with diffuse large B-cell lymphoma (DLBCL), the most common form of non-Hodgkin's lymphoma.

Dr. Pasqualucci found that in approximately half of these tumors, the somatic hypermutation mechanism misfires and targets aberrantly multiple genes, including known proto-oncogenes—often, concomitantly in the same tumor cell. This finding identifies a powerful mechanism of genetic instability that may play a major role in DLBCL development and may help identify novel targets for diagnosis and therapy.

Dr. Pasqualucci is a Special Fellow of the Leukemia & Lymphoma Society and has authored various publications in internationally recognized journals.

Maurizio Pellecchia, Ph.D.

Dr. Pellecchia is a medicinal chemist with a strong background in biophysics and NMR-based drug design. He received his Ph.D. in Pharmaceutical Sciences from the University of Naples in Italy. Dr. Pellecchia trained at the ETH–Zurich with Dr. Kurt Wuthrich, the 2002 Nobel Laureate, and at the University of Michigan. Prior to his recruitment by The Burnham Institute as an Associate Professor, Dr. Pellecchia worked in the pharmaceutical industry.

Dr. Pellecchia's research is centered on the determination of protein structures, the characterization of intermolecular interactions, and the development of small-molecule inhibitors capable of antagonizing interactions in systems involved in cell signaling and apoptosis for the treatment of several human diseases. The goal of Dr. Pellecchia's laboratory is to successfully bring together basic sciences involving modern nuclear magnetic resonance spectroscopy (NMR) techniques and computer modeling and traditional medicinal chemistry to elucidate the molecular basis of disease and develop novel therapeutics. An area in which his laboratory remains particularly active is the development of novel NMR-based techniques to aid in the characterization of protein-protein and protein-ligand interactions. Dr. Pellecchia has authored several publications in these areas of research.

Klaus Rajewsky, M.D.

Dr. Rajewsky received his medical degree from the University of Frankfurt/Main in 1962. He continued his scientific training as a Postdoctoral Research Fellow at the Institut Pasteur under Dr. Grabar before returning to Germany to work as a Research Assistant in Dr. Henning's laboratory at the Institute of Genetics at the University of Cologne. In 1966, Dr. Rajewsky was selected to head the newly established Immunology Unit at the Institute of Genetics, and by 1970, he had undertaken the additional responsibilities of a Member of the Board of Directors and Professor of Molecular Genetics at the University of Cologne.

In 1996, Dr. Rajewsky began a part-time appointment as Program Coordinator for the Mouse Biology Program of the European Molecular Biology Laboratory (EMBL) at

Monterotondo near Rome, Italy. In 2001, he retired from his positions at the Institute of Genetics and EMBL and immigrated to the United States, becoming a Professor of Pathology at Harvard Medical School and Senior Investigator at The CBR Institute for Biomedical Research.

Dr. Rajewsky's research involves the study of mechanisms of lymphocyte development and antigen-receptor diversification. His laboratory has developed and is still in the process of optimizing and speeding up methods of conditional gene targeting in the mouse; this allows the introduction of targeted mutations in a cell-type-specific and/or inducible way. The process includes the construction of genetic switches through which genes can be turned off or on or replaced by others. Using this general approach, Dr. Rajewsky's team is able to understand how B-cell (and T-cell) lymphocytes develop from their progenitors; how they are selected and maintained in the immune system, on the basis of antigen-receptor expression and specificity; and how the latter can be modified by secondary immunoglobulin gene rearrangements and somatic hypermutation when the cells enter into the immune system and when they differentiate, in so-called germinal centers, into memory cells whose receptors bind antigen with high affinity. A recent focus of Dr. Rajewsky's work is on the role of the NfkB-signaling pathway in lymphocyte physiology.

In addition, Dr. Rajewsky's research uses conditional gene targeting to generate mouse models of human diseases, with an emphasis on B-cell-based autoimmune diseases and lymphomas originating from mature B cells. By analyzing human B-cell lymphomas it has been learned that these tumors are derived mostly from germinal center and post-germinal center B cells; it has been hypothesized that this is due to an increased risk of malignant transformation of the cells in the germinal center microenvironment, which is characterized by intense cellular proliferation and programmed DNA double-strand breaks in the immunoglobulin gene loci.

Dr. Rajewsky's team is now trying to model lymphomagenesis in germinal centers of the mouse via conditional targeted mutagenesis. This process includes an attempt to generate a mouse model of Hodgkin's lymphoma by expressing genes of the Epstein-Barr Virus specifically in germinal center cells in accordance with a scenario of the pathogenesis of this tumor that has been worked out in the laboratory.

John D. Shaughnessy, Ph.D.

Dr. Shaughnessy received his Ph.D. in Molecular Biology in 1993 through a joint program of the NCI Laboratory of Genetics and the University of Maryland. Following a postdoctoral fellowship in the NCI Mammalian Genetics Laboratory, Dr. Shaughnessy joined the Myeloma Institute for Research and Therapy (MIRT) at the University of Arkansas for Medical Sciences (UAMS), where he is a Professor in the Department of Medicine. Dr. Shaughnessy has been Director of the MIRT Lambert Laboratory of Myeloma Genetics since 2000; he is also Director of Basic Sciences at MIRT.

Dr. Shaughnessy built the world's most comprehensive molecular genetics database in human myeloma. His laboratory was the first to draw attention to the molecular basis of the high-risk myeloma associated with chromosome 13 deletion. He identified a novel recurrent immunoglobulin gene translocation activating cyclinD3 at chromosome 6p21. His landmark paper on global gene-expression profiling of purified plasma cells opened novel research avenues for the entire myeloma community. Dr. Shaughnessy demonstrated that myeloma could be divided into distinct molecular entities according to discrete stages of B-cell differentiation. He was one of the pioneers in the use of genomics as applied to translational cancer research and this achievement was

highlighted in *U.S. News and World Report* in June 2002. Dr. Shaughnessy's greatest discovery to date was the recognition that the Wnt antagonist gene, *dickkopf-1 (DKK-1)* contributed a novel mechanism of myeloma bone disease. Published in the *New England Journal of Medicine*, this report received international attention, including highlights on CNN and NPR on Christmas Day 2003. This finding may have applications in bone loss in other cancers, as well as postmenopausal osteoporosis.

Dr. Shaughnessy has set a premier example of translational investigation, enabling many joint publications with clinical faculty members on the topics of myeloma disease classification and prognosis.

Dr. Shaughnessy and his team recently identified what appears to be a critical mutation in human myeloma cells that promotes the development of a highly aggressive form of the disease. The mutation is near a mutation "hot spot" seen in many human cancers. If the mutation does indeed contribute to aggressive disease, the discovery could lead to a revolution in cancer diagnostics, prognostics, and therapy. Dr. Shaughnessy and his team are developing screening assays and, in collaboration with NCI, new drugs that target the molecular pathway in the mutating cells. A paper detailing this process has been submitted to and is under review by the *New England Journal of Medicine*.

Margaret A. Shipp, M.D.

Dr. Shipp is an Associate Professor of Medicine at Harvard Medical School and the Director of the Lymphoma Program at the newly expanded Dana-Farber/Harvard Comprehensive Cancer Center. Dr. Shipp received her medical degree from Washington University School of Medicine and completed her residency in Internal Medicine at Barnes Hospital in St. Louis, Missouri. She completed a fellowship in Medical Oncology at the Dana-Farber Cancer Institute and subsequently joined the faculty.

Dr. Shipp's clinical and laboratory research focuses on the clinical and molecular heterogeneity of the most common lymphoid malignancy, diffuse large B-cell lymphoma (DLBCL). Dr. Shipp coordinated the development of the International Prognostic Index that is used worldwide to individualize treatment approaches to DLBCL and many other lymphoid malignancies. Recently, she has led efforts to develop molecular signatures of DLBCL outcome, identify discrete subsets of DLBCL, and credential novel rational treatment targets in this disease. Dr. Shipp and her colleagues are utilizing powerful new gene-expression profiling platforms and recently developed analytical methods to determine why certain tumors are curable with available chemotherapy and others are resistant to treatment. These studies are already leading to more specific and, hopefully, more effective treatment approaches.

Dr. Shipp is the recipient of numerous awards, including an American Cancer Society Junior Faculty Award, a Leukemia Society of America Scholar Award, membership in the American Society of Clinical Investigation and Association of American Physicians, and designation as a Stohlman Scholar of the Leukemia & Lymphoma Society of America as well as a Doris Duke Distinguished Clinical Scientist. She is also the Principal Investigator of a program project grant entitled *Molecular Targets of Germinal Center B-Cell Lymphomas*.

Louis M. Staudt, M.D., Ph.D.

Dr. Staudt received his B.A. from Harvard College in 1976, graduating *cum laude* in Biochemistry. He was awarded a Medical Scientist Training Program fellowship at the University of Pennsylvania School of Medicine, where he received his M.D. and Ph.D. degrees in 1982. Following Internal Medicine training, he joined Nobel Laureate David

Baltimore's laboratory at the Whitehead Institute as a Jane Coffin Childs Fellow. There, he cloned and characterized the first tissue-specific transcription factor, Oct-2. In 1988, Dr. Staudt established his laboratory in the Metabolism Branch at NCI, where he currently studies the molecular basis of human lymphoid malignancies.

Dr. Staudt's laboratory initiated the use of genomic-scale gene expression profiling to define the molecular basis of therapeutic response and survival in lymphoid malignancies. This effort revealed that the most common non-Hodgkin's lymphoma, diffuse large B-cell lymphoma, is actually three distinct diseases with different responses to chemotherapy. His laboratory discovered that the expression of a single gene, *ZAP-70*, can be used to diagnose two forms of chronic lymphocytic leukemia. Further, his group developed gene expression-based prognostic tests that can predict the length of survival of patients with diffuse large B-cell lymphoma, mantle cell lymphoma, and follicular lymphoma. Dr. Staudt's laboratory discovered that the NF- κ B pathway is a new therapeutic target for a subset of diffuse large B-cell lymphomas defined by gene-expression profiling.

Dr. Staudt directs the NCI Lymphoma/Leukemia Molecular Profiling Project (LLMPP), a multi-institutional consortium that aims to develop a new molecular framework for the diagnosis of all lymphoid malignancies and that can identify the optimal therapy for each patient. The consortium currently consists of the University of Nebraska Medical Center, British Columbia Cancer Agency, Southwest Oncology Group, University of Würzburg, University of Barcelona, St. Bartholomew's Hospital, and Norwegian Radium Hospital. The LLMPP is using various high-throughput molecular profiling methods to study thousands of lymphoma biopsy specimens, with the goal of creating molecular diagnoses that will improve the clinical management of patients.

Dr. Staudt serves as an editor of *Cancer Cell*, *Immunological Reviews*, and *Genome Biology*. He received the Stuart Mudd Award in Microbiology and the Baldwin Lucke Memorial Prize in Experimental Medicine and Biology from the University of Pennsylvania School of Medicine, awards from the Cancer Research Institute and the American Federation for Clinical Research, and the Arthur S. Fleming Award for Scientific Research in the Federal Government. He also received two NIH Director's Awards and an NIH MERIT Award. Dr. Staudt delivered the 2002 Kenneth B. McCredie Memorial Lecture of the Leukemia and Lymphoma Society and the Leukemia Research Fund 2003 Annual Guest Lecture. In 2004, Dr. Staudt was elected to the Association of American Physicians.

Julie Teruya-Feldstein, M.D.

Dr. Teruya-Feldstein is a board-certified surgical pathologist with expertise in diagnosing neoplastic hematologic malignancies. Her research focuses on the identification of key genes and proteins involved in lymphoma for clinical prognostic and potential therapeutic targets. She is an active investigator and collaborator in the areas of transplantation, myeloma, and exploration of novel molecules in preclinical murine models.

Dr. Teruya-Feldstein received her M.D. in 1992 from the University of Hawaii. She completed residency training, followed by a Hematopathology fellowship, both at the National Cancer Institute in Bethesda, Maryland. Dr. Teruya-Feldstein joined the Department of Pathology at Memorial Sloan-Kettering Cancer Center in 1999 and has recently been promoted to Associate Member and Attending. She serves on the Institutional Review Board and Therapeutic Response Review Committees.

Wyndham Wilson, M.D., Ph.D.

Dr. Wilson obtained his M.D. and Ph.D. in 1981 and served his medical residency in 1984, all at Stanford University. Following a fellowship in Medical Oncology at the NCI in 1988, Dr. Wilson joined the faculty of the NCI as the Special Assistant to the Director and Senior Investigator. Dr. Wilson is currently the Chief of the Lymphoma Section in the Center for Cancer Research at NCI, where he directs Phase I and II translational studies in lymphomas. Dr. Wilson is actively involved with the development of new agents and regimens for lymphomas, as well as studies on lymphoma biology and pharmacodynamics. He currently serves on the editorial boards of *Clinical Lymphoma* and *The Oncologist*, as well as on the *Physicians Data Query* (PDQ) External Advisory Board.