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Introduction

R. Lee Clark, M.D., D.Sc. (Hon.),* Robert C. Hickey, M.D.,† and Evan M. Hersh, M.D.‡

**President, The University of Texas System Cancer Center, and Professor of Surgery, M. D. Anderson Hospital and Tumor Institute; †Executive Vice President, The University of Texas System Cancer Center, and Director and Professor of Surgery, M. D. Anderson Hospital and Tumor Institute; ‡Professor of Medicine, Chief, Section of Immunology, and Deputy Head, Department of Developmental Therapeutics, M. D. Anderson Hospital and Tumor Institute, Houston, Texas*

The concepts that human tumors are antigenically distinct from the host and might be subject to attack by host defense mechanisms, and that therapeutic manipulations might alter or augment these host defense mechanisms go back to the turn of the century and to the writings of Paul Ehrlich. These concepts remained highly controversial until the 1950s, when Ludwik Gross unequivocally demonstrated the presence of tumor antigens and tumor immunity in mouse tumor systems. During the last two decades, many studies have demonstrated that tumor-associated antigens and tumor-associated immune responses are present in many, if not all, experimental animal and human tumors. These responses include classic cell-mediated and humoral immunity as well as nonspecific host defense mechanisms involving the reticuloendothelial system and macrophages.

Slightly less than 20 years ago, it was demonstrated in mice that immunologic manipulation of the host, namely, administration of bacillus Calmette-Guérin (BCG), protects animals from the subsequent development of tumors induced by chemical carcinogens or oncogenic viruses. During the last decade, expansion of this experimental basis has laid the foundation for the gradually emerging clinical discipline of immunotherapy. Also during the last decade, development of techniques through which the human immune response can be critically evaluated, demonstration of the immunosuppressive effects of the tumor-bearing state, characterization of the immunosuppressive effects of conventional cancer treatment, and documentation of the relationship between immunocompetence and prognosis in cancer have added a strong, rational, scientific basis to this field.

During the first half of the 20th century, a number of empirical clinical trials of immunotherapy appeared positive. However, several subsequent clinical experiments, which now can be considered classic, have established the clinical foundations of immunotherapy. These include the demonstration by Professor Georges Mathé that remission duration in childhood acute leukemia can be

prolonged by the administration of BCG, irradiated allogeneic tumor cells, or both. Also important were the demonstration by Dr. Donald Morton that cutaneous, metastatic melanoma nodules can be induced to regress in immunocompetent patients through the intralesional injection of BCG, and the demonstration by Edmund Klein that a variety of primary cutaneous tumors can be caused to regress by the topical application of DNCB after sensitization of the subject to that hapten. In the latter study, it was most important that in patients with multiple, recurrent, primary skin tumors, the rate of new tumor formation was retarded after intralesional or topical therapy for a few primary tumors.

Tumor immunobiology and experimental and clinical immunotherapy have been prominent in the program at M. D. Anderson Hospital and Tumor Institute of The University of Texas System Cancer Center for some time. This is evidenced by the prominence of these topics in several of our annual basic science symposia and the presentation of the annual Ernst W. Bertner Memorial Award to Dr. Ludwik Gross in 1963 and to Dr. George Klein in 1973 for their preeminent work in tumor immunobiology and virology. Furthermore, our staff has developed a major program for both animal model work and clinical immunotherapy trials during the last seven years. Currently, there are more than 20 active clinical immunotherapy protocols at M. D. Anderson Hospital, and several thousand patients are receiving immunotherapy as an adjunct to conventional therapy.

As the science of modern immunobiology has developed, the various approaches to immunotherapy have become well defined; these include active-nonspecific immunotherapy with adjuvants such as BCG, active-specific immunotherapy by immunization with tumor cells or tumor antigen, adoptive immunotherapy with host defense cells or subcellular components such as transfer factor, immunorestorative immunotherapy with such agents as thymic hormones and levamisole, and possibly, passive immunotherapy with specific antitumor antibody.

Immunotherapy, now in its earliest stages of development, should be considered the fourth major modality of cancer treatment. The immunotherapeutic agents and approaches currently available for clinical application are, in general, crude and poorly defined. The mechanism of action of many of the immunotherapeutic agents is poorly or incompletely understood. The optimal timing of immunotherapy in relationship to conventional therapy has not been worked out. Highly purified and specific immunotherapeutic agents are yet to be developed. Despite these obstacles, there is evidence that immunotherapy of various types has activity in terms of increasing the remission rate or prolonging remission duration and survival for patients with such diverse malignancies as acute leukemia, soft tissue and osteogenic sarcoma, and malignant melanoma, as well as the more common malignancies, such as gynecologic and genitourinary cancer, and carcinoma of the breast, colon, and lung. In addition, several newer and unique approaches, such as the use of thymic hormones or the immunorestorative agent levamisole, and specific immunologic maneuvers, such as plasmapheresis

to remove blocking factors, offer considerable promise for the future. It is our feeling that the proceedings of this conference adequately summarize the past development, current status, and future prospects for immunotherapy and will represent a landmark in its development.

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Contributors

William K. Amery, M.D.
Janssen Pharmaceutica
Beerse, Belgium

Jean-Louis Amiel, M.D.
Institut de Cancérologie et d'Immunogénétique
Hôpital Paul-Brousse
Dèpartement d'Hématologie
Institut Gustave-Roussy
94800 Villejuif, France

Ichiro Azuma, Ph.D.
The Third Department of Internal Medicine
Osaka University Hospital
Osaka, Japan

Shelley L. Bartold, Ph.D.
Department of Biomathematics
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

J. George Bekesi, Ph.D.
Department of Neoplastic Diseases
Mount Sinai School of Medicine
New York, New York 10029

Robert E. Bellet, M.D.
Melanoma Unit
Fox Chase Cancer Center
Philadelphia, Pennsylvania 19111

Dominique Belpomme, M.D.
Institut de Cancérologie et d'Immunogénétique
Hôpital Paul-Brousse
Dèpartement d'Hématologie
Institut Gustave-Roussy
94800 Villejuif, France

Robert S. Benjamin, M.D.
Department of Developmental Therapeutics
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

David Berd, M.D.
Melanoma Unit
Fox Chase Cancer Center
Philadelphia, Pennsylvania 19111

G. R. Blumenschein, M.D.
Department of Medicine
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

Joseph C. Bottino, M.D.
Department of Developmental Therapeutics
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

Werner Brehmer, M.D.
Robert Koch Institute
Berlin, West Germany

Michael A. Burgess, M.B.B.S.
Department of Developmental Therapeutics
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

A. U. Buzdar, M.D.
Department of Medicine
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

John L. Cantrell, Ph.D.
Rocky Mountain Laboratory
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Hamilton, Montana 59840

Albert Cattan, M.D.
Institut de Cancérologie et d'Immunogénétique
Hôpital Paul-Brousse
Dèpartement d'Hématologie
Institut Gustave-Roussy
94800 Villejuif, France

Michael A. Chirigos, Ph.D., D.Sc.
Virus and Disease Modification Section
Laboratory of RNA Tumor Viruses
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20014

R. Lee Clark, M.D., D.Sc. (Hon.)
President
The University of Texas System Cancer Center
Professor of Surgery
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

Janet Cuttner, M.D.
Department of Neoplastic Diseases
Mount Sinai School of Medicine
New York, New York 10029

Miguel Delgado, M.D.
Institut de Cancérologie et d'Immunogénétique
Hôpital Paul-Brousse
Dèpartement d'Hématologie
Institut Gustave-Roussy
94800 Villejuif, France

Francoise de Vassal, M.D.
Institut de Cancérologie et d'Immunogénétique
Hôpital Paul-Brousse
Dèpartement d'Hématologie
Institut Gustave-Roussy
94800 Villejuif, France

Richard Edelstein, M.D.
Chemotherapy and Immunotherapy Unit
University of Paris XIII
Centre Hospitalier Universitaire de Bobigny
93000 Bobigny, France

David Eidinger, M.D., Ph.D.
Department of Microbiology
Faculty of Medicine
University of Saskatchewan
Saskatoon, Saskatchewan S7N 0W0

Khoji Ezaki, M.D.
Department of Developmental Therapeutics
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

J. L. Fahey, M.D.
Department of Microbiology and Immunology
UCLA School of Medicine
Los Angeles, California 90024

David Farquhar, Ph.D.
Department of Developmental Therapeutics
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

Isaiah J. Fidler, D.V.M., Ph.D.
Biology of Metastasis Section
Cancer Biology Program
Frederick Cancer Research Center
Frederick, Maryland 21701

Stanley A. Gall, M.D.
Department of Obstetrics and Gynecology
Duke University Medical Center
Durham, North Carolina 27710

Edmund A. Gehan, Ph.D.
Department of Biomathematics
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

Marianne Gil, M.D.
Institut de Cancérologie et d'Immunogénétique
Hôpital Paul-Brousse
Dèpartement d'Hématologie
Institut Gustave-Roussy
94800 Villejuif, France

Allan L. Goldstein, Ph.D.
Department of Biochemistry
The George Washington University Medical Center
Washington, D.C. 20037

Christine H. Granatek, Ph.D.
Department of Developmental Therapeutics
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

Jordan U. Gutterman, M.D.
Department of Developmental Therapeutics
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

M. G. Hanna, Jr., Ph.D.
Cancer Biology Program
Frederick Cancer Research Center
Frederick, Maryland 21701

Maurice Hayat, M.D.
Institut de Cancérologie et d'Immunogénétique
Hôpital Paul-Brousse
Dèpartement d'Hématologie
Institut Gustave-Roussy
94800 Villejuif, France

Evan M. Hersh, M.D.
Department of Developmental Therapeutics
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

Robert C. Hickey, M.D.
Executive Vice President
The University of Texas System Cancer Center
Director
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

James F. Holland, M.D.
Department of Neoplastic Diseases
Mount Sinai School of Medicine
New York, New York 10029

Ariel C. Hollinshead, Ph.D.
Department of Medicine
The George Washington University Medical Center
Washington, D.C. 20037

G. N. Hortobagyi, M.D.
Department of Medicine
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

Kou M. Hwang, Ph.D.
Department of Developmental Therapeutics
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

Lucien Israël, M.D.
Chemotherapy and Immunotherapy Unit
University of Paris XIII
Centre Hospitalier Universitaire de Bobigny
93000 Bobigny, France

Claude Jasmin, M.D.
Institut de Cancérologie et d'Immunogénétique
Hôpital Paul-Brousse
Dèpartement d'Hématologie
Institut Gustave-Roussy
94800 Villejuif, France

Anne Kennedy, B.A.
Department of Biomathematics
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

H. Sherwood Lawrence, M.D.
Infectious Disease and Immunology Division
Department of Medicine
New York University School of Medicine
New York, New York 10016

David Machover, M.D.
Institut de Cancérologie et d'Immunogénétique
Hôpital Paul-Brousse
Dèpartement d'Hématologie
Institut Gustave-Roussy
94800 Villejuif, France

Mary Anne Malahy, Ph.D.
National Large Bowel Cancer Project
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

Gailen D. Marshall, Jr., M.S.
Department of Biochemistry
The George Washington University Medical Center
Washington, D.C. 20037

Michael J. Mastrangelo, M.D.
Melanoma Unit
Fox Chase Cancer Center
Philadelphia, Pennsylvania 19111

Georges Mathé, M.D.
Institut de Cancérologie et d'Immunogénétique
Hôpital Paul-Brousse
Dèpartement d'Hématologie
Institut Gustave-Roussy
94800 Villejuif, France

Giora M. Mavligit, M.D.
Department of Developmental Therapeutics
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

Charles M. McBride, M.D.
Department of Surgery
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

Martin F. McKneally, M.D., Ph.D.
Department of Surgery
Albany Medical College
Albany, New York 12208

Charles A. McLaughlin, D.V.M., Ph.D.
Rocky Mountain Laboratory
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Hamilton, Montana 59840

Marion J. McMurtrey, M.D.
Department of Surgery
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

Jean-Louis Misset, M.D.
Institut de Cancérologie et d'Immunogénétique
Hôpital Paul-Brousse
Dèpartement d'Hématologie
Institut Gustave-Roussy
94800 Villejuif, France

Dexter Morris, B.A.
Department of Developmental Therapeutics
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

Marina Musset, M.D.
Institut de Cancérologie et d'Immunogénétique
Hôpital Paul-Brousse
Dèpartement d'Hématologie
Institut Gustave-Roussy
94800 Villejuif, France

Nicholas Papadopoulos, M.D.
Department of Medicine
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

Yehuda Z. Patt, M.D.
Department of Developmental Therapeutics
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

Juan Pena-Angulo, M.D.
Institut de Cancérologie et d'Immunogénétique
Hôpital Paul-Brousse
Dèpartement d'Hématologie
Institut Gustave-Roussy
94800 Villejuif, France

Leona C. Peters, B.S.
Cancer Biology Program
Frederick Cancer Research Center
Frederick, Maryland 21701

Lester J. Peters, M.D.
Department of Radiotherapy
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

José-Luis Pico, M.D.
Institut de Cancérologie et d'Immunogénétique
Hôpital Paul-Brousse
Dèpartement d'Hématologie
Institut Gustave-Roussy
94800 Villejuif, France

Carl Plager, M.D.
Department of Medicine
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

Pierre Pouillart, M.D.
Institut de Cancérologie et d'Immunogénétique
Hôpital Paul-Brousse
Dèpartement d'Hématologie
Institut Gustave-Roussy
94800 Villejuif, France

Patricia Ribaud, M.D.
Institut de Cancérologie et d'Immunogénétique
Hôpital Paul-Brousse
Dèpartement d'Hématologie
Institut Gustave-Roussy
94800 Villejuif, France

Edgar Ribi, Ph.D.
Rocky Mountain Laboratory
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Hamilton, Montana 59840

Stephen P. Richman, M.D.
Department of Developmental Therapeutics
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

Adan Rios, M.D.
Department of Developmental Therapeutics
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

Ernesto Rivera, M.D.
Department of Developmental Therapeutics
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

Jimmy J. Romero, B.S.
Department of Medicine
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

Marvin M. Romsdahl, M.D., Ph.D.
Department of Surgery
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

Claude Rosenfeld, M.D.
Institut de Cancérologie et d'Immunogénétique
Hôpital Paul-Brousse
Dèpartement d'Hématologie
Institut Gustave-Roussy
94800 Villejuif, France

Roger D. Rossen, M.D.
Department of Microbiology and Immunology
Baylor College of Medicine
Houston, Texas 77030

Jeffrey L. Rossio, Ph.D.
Department of Microbiology and Immunology
Wright State University School of Medicine
Dayton, Ohio 45431

Raymond Samak, M.D.
Chemotherapy and Immunotherapy Unit
University of Paris XIII
Centre Hospitalier Universitaire de Bobigny
93000 Bobigny, France

Maurice Schneider, M.D.
Institut de Cancérologie et d'Immunogénétique
Hôpital Paul-Brousse
Dèpartement d'Hématologie
Institut Gustave-Roussy
94800 Villejuif, France

Léon Schwarzenberg, M.D.
Institut de Cancérologie et d'Immunogénétique
Hôpital Paul-Brousse
Dèpartement d'Hématologie
Institut Gustave-Roussy
94800 Villejuif, France

Joseph G. Sinkovics, M.D.
Department of Medicine
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

S. Michael Strain, B.S.
Hamilton Biochemical Research Laboratory
Hamilton, Montana 59840

Raoul Toubiana, Ph.D.
CNRS Institute de Chimie des Substances Naturelles
Gif sur Yvette, France

Ruth Waldinger, R.N.
Department of Nursing
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

Roy Weiner, M.D.
Institut de Cancérologie et d'Immunogénétique
Hôpital Paul-Brousse
Dèpartement d'Hématologie
Institut Gustave-Roussy
94800 Villejuif, France
Present address: Division of Medical Oncology
University of Florida
Gainesville, Florida 32611

David W. Weiss, Ph.D., D.Phil.Med.
Lautenberg Center for General and Tumor Immunology
Hebrew University—Hadassah Medical School
Jerusalem, Israel

C. Wiseman, M.D.
Department of Medicine
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

Yuichi Yamamura, M.D.
The Third Department of Internal Medicine
Osaka University Hospital
Osaka, Japan

Nancy Zatopek, B.A.
Department of Developmental Therapeutics
The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas 77030

Contents