Laudatio
Robert D. Schreiber, Ph.D.

Dr. Robert D. Schreiber is the Alumni Endowed Professor of Pathology & Immunology at Washington University School of Medicine and Leader of the Tumor Immunology Program of the Washington University Siteman Cancer Center. He received his undergraduate and graduate training in Biochemistry and Immunology from the State University of New York at Buffalo, and his postdoctoral training in molecular immunology at the Research Institute of Scripps Clinic in La Jolla, California.

Dr. Schreiber has devoted the last 26 years of his research career to exploring the molecular basis of cytokine action particularly in the area of host responses to cancer. These efforts not only led to an enhanced understanding of how cytokines exert their pleiotropic effects on cells but also to the seminal finding that the cytokine interferon-gamma (IFNγ) and lymphocytes function together to prevent tumor outgrowth. The latter work stimulated a renewed appreciation of the protective role of the immune response in preventing tumor development thereby rekindling interest in the controversial but persistent concept of cancer immunosurveillance. At the same time, Schreiber and his colleagues showed that the immune system could also promote cancer growth by sculpting the immunogenicity of developing tumor cells. The dual host-protective and tumor-promoting functions of immunity were embodied into a process that Schreiber and his associates called Cancer Immunoediting. This hypothesis has now become a generally accepted paradigm of host-tumor interaction and has thereby contributed critical conceptual and practical support to the fields of tumor immunology and cancer immunotherapy.

The author of over 200 articles, Dr. Schreiber's contributions to the fields of cytokine biology, cytokine receptor signaling and tumor immunology are recognized internationally. Schreiber has received numerous awards and honors including the Coley Award for Distinguished Research in Basic and Tumor Immunology from the Cancer Research Institute, the Marie T. Bonazinga Award for Excellence in Leukocyte Biology Research, the Milstein Award of the International Society of Interferon and Cytokine Research. He is a member of the Board of Scientific Advisors for the National Cancer Institute (NIH), a Fellow of the American Association for the Advancement of Science, an Affiliate of the Ludwig Institute for Cancer Research, and an Associate Director of the Scientific Advisory Council of the Cancer Research Institute. Dr. Schreiber is a past editor of Immunity, a past president of the Society for Leukocyte Biology and has served on numerous committees for the American Association of Immunologists, the American Society for Investigative Pathology and the International Society of Interferon and Cytokine Research.

Charles Rodolphe Brupbacher Foundation

The
Charles Rodolphe Brupbacher Prize
for Cancer Research 2007
is awarded to

Dr. Robert D. Schreiber

for his contribution
to discovering and understanding the concepts of
Cancer Immunosurveillance and Cancer Immunoediting

The President
of the Foundation

Mrs. Frédérique Brupbacher

The President
of the Scientific Board

Dr. med. Erhart H. Brunner

Curriculum vitae
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Education and Training:

1968	B. A. Chemistry, State University of New York at Buffalo, Buffalo, NY
1973	Ph. D. Biochemistry, State University of New York at Buffalo, Buffalo, NY

Fellowships:

1973	Postdoctoral Fellow, Departments of Medicine and Biochemistry, State University of New York at Buffalo
1973-1976	Postdoctoral Fellow, Department of Molecular Immunology, Research Institute of Scripps Clinic, La Jolla, California

Positions:

1976-1978	Assistant Member I, Department of Molecular Immunology, Research Institute of Scripps Clinic, La Jolla, California
1978-1982	Assistant Member II, Department of Molecular Immunology, Research Institute of Scripps Clinic, La Jolla, California

1979-1980	Visiting Assistant Professor of Pathology, Department of Pathology, Harvard Medical School, Boston, Massachusetts
1982-1984	Associate Member without tenure, Department of Immunology, Research Institute of Scripps Clinic, La Jolla, California
1984-1985	Associate Member with tenure, Department of Immunology, Research Institute of Scripps Clinic, La Jolla, California
1985-1990	Professor, Department of Pathology, Washington University School of Medicine, St. Louis, Missouri
1985-	Professor, Molecular Microbiology, Washington University School of Medicine, St. Louis, Missouri
1990-	Alumni Endowed Professor, Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, Missouri

Other Appointments:

1990-1993	Co-Director, Graduate Program in Immunology, Washington University School of Medicine
1993-2003	Director, Graduate Program in Immunology
1998-	Program Leader, Tumor Immunology, Siteman Cancer Center, Washington University
2001-	Affiliate, Ludwig Institute for Cancer Research, New York, New York

Professional Recognition:

Appointments:

1986-1990	Treasurer, Society for Leukocyte Biology
1987-1989	Member, Graduate School Admission Committee
1988-1991	Program Committee, American Association of Pathologists
1990-1991	Secretary, Society for Leukocyte Biology
1990-1992	Block Chairman, Cytokines. American Association of Immunologists

1990-present	Consultant, American Institute of Biological Sciences
1992-1993	President-elect, Society for Leukocyte Biology
1992- present	Long Range Planning Committee of the Executive Faculty
1992- present	CSRB Construction Project Committee
1992- present	Per Diem Committee
1993-1994	President, Society for Leukocyte Biology
1994-2003	Program and Student Affairs Committee
1994- present	Transgenic Barrier Committee
1995-1996	International Board Member, ISICR
1997- present	Technology Transfer Committee

Honors and Awards:

1970-1972	Recipient, National Institutes of Health Predoctoral Fellowship.
1977-1982	Recipient, American Heart Association Established Investigatorship 77-202
1995-	Merit Award Grant #CA 43059, National Cancer Institute
1996	Distinguished Lecturer, National Jewish
1996	Milstein Award for Outstanding Achievements in Interferons and Cytokines, International Society of Interferon and Cytokine Research
1996	Fellow of the American Association for the Advancement of Science
1998	Marie T. Bonazinga Award for Excellence in Leukocyte Biology Research
2001	Coley Award for Distinguished Research in Basic and Tumor Immunology, Cancer Research Institute Institute
2003	41st Annual J.S. and H. R. Blumenthal Memorial Lecturer, University of Minnesota
2004	Organizer, Keystone Symposium, "Jaks and Stats: Development to Disease"

Representative Keynote and Special Plenary Lectures:

- First Hans J. Muller-Eberhard MD Memorial Lecturer, The University of Texas-Houston Health Science Center, Houston, TX, September 1999
- Annual Research Day Keynote, Cleveland Clinic, Cleveland, OH, October 1999
- First Finbloom Memorial Lecturer, National Institutes of Health, Bethesda, MD, March 2000
- AACR Special Conference in Cancer Research, Vail, CO, September 2000
- Keynote Speaker, 15th Annual Scientific Meeting of the Society for Biological Therapy, Seattle, WA, October 2000
- First Invited Lecturer, Cancer Biology/Immunology Program minicourse, Moscow University, Moscow, Russia, May 2001
- 5th Annual Meeting of the Society of Fundamental Cancer Immunology, Mie, Japan, July 2001
- ISICR Annual Meeting, Cleveland, OH, October 2001
- AAI Presidential Symposium, "Immunosurveillance and Immunotherapy of Cancer: New Views on Old Topics," New Orleans, LA, April 2002
- Symposium Launching the CRI/LICR Cancer Vaccine Collaborative, New York, NY, September 2002
- 41st Annual J.S. and H.R. Blumenthal Memorial Lecture, University of Minnesota, Minneapolis, MN, April 2003
- Robert A. Good Memorial Lecture, 7th International Symposium on Predictive Oncology & Intervention Strategies, Nice, France, February 2004
- Co-Organizer and Plenary Lecturer, Keystone Symposium, "Jaks and Stats: Development to Disease," Jak-Stat Pathway in Cancer session, British Columbia, Canada, April 2004
- 12th International Congress of Immunology and 4th Annual Conference on the Federation of Clinical Immunology Societies, Montreal, Canada, July 2004
- Opening Address, Cancer Research Institute Symposium, Cancer Vaccines 2004: the Next Decade, New York, NY, October 2004
- Apoptosis and Immunity 2005, Cairns, Australia, June 2005
- Keynote Speaker Robert Baldwin Symposium, Nottingham, United Kingdom, June 2005

- Joint Meeting, "CIMT Meets Strategies for Immune Therapy," Mainz, Germany, May 2006
- First Joint Meeting of European National Societies of Immunology, Paris, France, September 2006
- Second Bernard Halpern Symposium of Immunology, Paris, France, October 2006

Editorial Boards:

- Journal of Biological Chemistry, 1992-1996
- Immunity, 1994-1996
- Immunity, Editor, 1997-2000
- Immunity, Associate Editor, 2000-present
- International Immunology, Transmitting Editor, 2000-present
- Cancer Immunology Immunotherapy, 2005-present

Advisory Boards:

- Experimental Immunology Study Section, NIH, 1984-1988
- Cancer Research Institute Review Committee, 1997-present
- Cancer Research Institute Scientific Advisory Council, 1997-present
- Associate Director of the Scientific Advisory Council, Cancer Research Institute, 2002-present
- Member, Kennedy Institute of Rheumatology, Scientific Advisory Board, 2002-present
- Finance Committee, The American Association of Immunologists, 2003-2005
- Chairman, TTT Study Section, NIH, 2004-2006
- Member, Board of Scientific Advisors, National Cancer Institute, 2006-present
- Nominations Committee, The American Association of Immunologists, 2006-2007
- Publications Committee, The American Association of Immunologists, 2006-present

Professional Society Memberships:

- American Association of Immunologists
- American Society for Investigative Pathology
- American Association for the Advancement of Science
- Society for Leukocyte Biology
- International Society for Interferon and Cytokine Research
- International Cytokine Society
- American Society for Biochemistry and Molecular Biology
- American Association for Cancer Research

Publications:

Over 250 original publications in international scientific journals, invited reviews and book chapters.

Cancer Immunoediting: Deciphering the Complex Interaction Between Immunity and Developing Tumors

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Introduction:
The birth and premature death of the cancer immunosurveillance hypothesis

Paul Ehrlich was one of the first to predict that the immune system might repress a potentially "overwhelming frequency" of carcinomas (1). However, this prediction was not vigorously pursued until nearly fifty years later when the existence of "tumor specific antigens" was unequivocally established and the basic immunologic processes responsible for eliminating tumors in inbred strains of mice were elucidated (2, 3). These seminal findings provided a theoretical cornerstone for the development of the cancer immunosurveillance hypothesis proposed in the late 1950s by Sir Macfarlane Burnet and Lewis Thomas (4, 5). Cancer immunosurveillance was envisaged as a process in which the unmanipulated immune system recognized and eliminated nascent transformed cells with lymphocytes, and particularly T lymphocytes, playing a key sentinel role. Although the cancer immunosurveillance hypothesis grew largely out of the musings of two brilliant minds, it was not heavily grounded in solid experimental fact. Nevertheless it received rapid and enthusiastic acceptance within the immunological and medical communities. However, this enthusiasm was short lived for when the logical predictions of the hypothesis were tested experimentally, no evidence for its existence could be found. Perhaps the strongest challenge to the cancer immunosurveillance hypothesis came from Osias Stutman who noted that, compared to genetically matched wild type mice, nude mice (mice with a significant but incomplete immunodeficiency) did not form more carcinogen (methylcholanthrene, MCA)-induced tumors, did not show a shortened tumor latency period following MCA injection, and did not display statistically significant differences in the incidence of spontaneous tumors of non-viral origin (6). Despite limited knowledge about either the incomplete immunologic defects in the nude mouse or strain dependent differences in the enzymes required for bioconversion of MCA for in vivo carcinogenesis (which, retrospectively, bring into question the conclusions of the Stutman experiments) the Stutman results were considered to be so convincing at the time that they caused the rapid abandonment of the immunosurveillance hypothesis. As quickly as the field had jumped onto the cancer immunosurveillance "band-wagon", it now jumped off and during the ensuing fifteen years, little interest was paid to the possibility that the immune system could prevent the development of non-virally induced tumors.

The renaissance of cancer immunosurveillance

By the mid-1990s, the field of immunology had undergone explosive growth, fueled in part by the development of gene targeting and monoclonal antibody based methods allowing investigators to study physiologically relevant immunological processes in vivo. At that time, two key findings incited renewed interest in the process of cancer immunosurveillance. The first came as a result of a collaborative effort between my laboratory at Washington University in St. Louis and Dr. Lloyd Old in New York. We showed that endogenously produced interferon-γ IFN-γ (an important immunomodulatory cytokine produced by T cells and natural killer (NK) cells) protected mice against the outgrowth of transplantable tumors as well as primary carcinogen induced and spontaneous tumors and that both the tumor cells themselves as well as host cells were important targets of IFN-γ (7, 8). The second came from Mark Smyth and his group in Australia who showed independently that mice lacking perforin (a cytotoxic molecule produced by T cells and NK cells) were also more prone to MCA-induced tumor growth and formed more spontaneous tumors compared to their wild-type counterparts (9-11). The findings that definitively linked these observations to the cancer immunosurveillance hypothesis came when both groups showed that gene-targeted mice lacking recombinase-activating genes (RAG)-1 or -2 (and therefore lacking T, NKT and B lymphocytes) displayed the same enhanced susceptibility to carcinogen induced and spontaneous tumor development as either the IFN-γ unresponsive or perforin deficient mice (12, 13). These observations thus demonstrated that lymphocytes indeed played a physiologically important role in controlling primary tumor development in mice. Subsequent studies by several other laboratories have supported this conclusion (14, 15).

In addition to these mouse studies, compelling clinical data from other groups showed that cancer immunosurveillance also occurs in humans. Specifically, (1) immunosuppressed organ transplant patients display increased rates of non-viral cancers compared to nonimmunosuppressed individuals; (2) cancer patients frequently develop immune responses against the tumors that they bear; and (3) a very tight relationship exists between the quality and quantity of the anti-tumor response within tumors and patient survival (14-17). Together, this large body of data now overwhelmingly confirms and extends

the basic tenets of the cancer immunosurveillance concept as originally envisaged by Burnet and Thomas – namely, that the unmanipulated immune system is indeed capable of recognizing and eliminating primary tumors in mice and humans and that lymphocytes and the cytokines they produce play a major role in this process.

Cancer immunoediting versus cancer immunosurveillance

While this work was ongoing, additional experiments performed in my laboratory in collaboration with Lloyd Old showed that MCA sarcomas arising in immunocompetent versus immunodeficient mice were qualitatively distinct (12, 18). All sarcoma cells isolated from either immunocompetent wild type mice or immunodeficient RAG-$2^{-/-}$ mice formed progressively growing tumors when transplanted into RAG-$2^{-/-}$ recipients. Moreover, all sarcoma cells from wild-type mice grew progressively when injected into naïve syngeneic immunocompetent hosts. In contrast, forty percent of sarcoma cell lines from RAG-$2^{-/-}$ mice were rejected when transplanted into immunocompetent hosts. Thus, tumors formed in the presence of an intact immune system are less immunogenic than those that arise in immunodeficient hosts. This finding showed that immunity could "edit" a tumor's immunogenicity leading to the emergence of tumor cell variants with reduced immunogenicity that are better able to escape immune detection and elimination in vivo.

This concept was broadened by work from other labs showing that tumors from immunocompetent wild type mice can often attenuate protective immune responses by mechanisms involving regulatory T cells and myeloid suppressor cells (15, 19). Thus, a growing tumor can sometimes "edit" the development of tumor specific protective immunity. Taken together, these results showed that tumors are imprinted by the immunologic environment in which they form. This imprinting process can result in the generation of tumors that are better able to withstand the extrinsic tumor suppressor actions of the immune system either through mechanisms that lower tumor cell immunogenicity or inhibit the anti-tumor immune response. In either situation, the immunologic sculpting of tumor cells provides them with a survival advantage in the immunocompetent host.

Based on these findings, we argued that the term "cancer immunoediting" more accurately described the dual host-protective and tumor promoting actions of immunity on developing tumors than "cancer immunosurveillance" (12, 18). We envisaged the scope of this process to be very broad such that it could promote complete elimination of some tumors, generate a nonprotective immune state to others, or favor the development of immunologic anergy/ tolerance/ indifference. Moreover, we envisioned important roles for components of both the innate and adaptive immune systems in this process. Over the last six years our concept of cancer immunoediting has continued to sharpen and we now think of it as a process comprised of three phases: Elimination, Equilibrium, and Escape. We call these the three Es of cancer immunoediting (14). Immunosurveillance occurs in the elimination phase, while the Darwinian selection of tumor variants occurs during the equilibrium phase. This in turn can ultimately lead to escape and the appearance of clinically apparent tumors. The three E model of cancer immunoediting has become the master blueprint for the research program of my laboratory and we continue to pursue a better understanding of each phase of the process.

Elimination phase

We currently know the most about the elimination phase since it encompasses the original concept of cancer immunosurveillance. Using tumor models similar to those described previously, we and others have shown that the elimination phase is the result of a collaboration between molecules and cells of the innate and adaptive immune systems (15, 19, 20). Components known to play critical roles in the elimination phase include: immunomodulatory cytokines such as IFN-γ (that exerts its effects on both host immune cells and tumor cells), IFN-α/β (whose action is restricted only to host hematopoietic cells), and IL-12; cell surface molecules involved in innate and antigen-specific recognition such as NKG2D, CD1d and MHC class I; and immune effector molecules such as perforin and TRAIL. We also know that several lymphocyte populations are involved in the elimination phase although their relative importance may differ according to tumor type, anatomical location and rate of growth. These include lymphocytes that promote innate immunity such as NK, NKT and $\gamma\delta$ T cells as well as those that mediate adaptive immunity such as $CD4^+$ and $CD8^+$ lymphocytes expressing $\alpha\beta$ T cell receptors.

Yet despite knowing a significant amount about this phase, there remains much to learn. Currently, we are focusing our efforts on identifying the cellular targets of the interferons within the host immune compartment, elucidating the molecular and cellular dynamics that underlie development of protective versus immunosuppressive anti-tumor responses, and defining the nature of the antigens that are expressed by unedited tumors.

Equilibrium phase

Until recently, the least was known about the equilibrium phase and the primary focus of our work in this area has been to critically evaluate whether it indeed exists. We envisaged equilibrium as a phase where tumor cell variants, not destroyed during the elimination phase, would persist in the host and undergo editing. Our concept of the equilibrium phase was shaped largely by two sets of clinical findings: (1) the well documented fact that immunosuppressed organ transplant recipients have significantly higher rates of non-viral cancers than normal non-suppressed individuals and (2) reports of transmission of cancer from organ donor to organ recipient (14, 15). However, these clinical observations did not provide us with an experimentally tractable system to study equilibrium. Therefore, we have spent the last four years establishing a model experimental system with which we have been able to validate the existence of the equilibrium phase and are now defining its molecular and cellular basis. Mark Smyth and Lloyd Old have joined us in these studies and thus this project represents a formal collaboration between our laboratories. We are also exploring whether the equilibrium phase represents a dynamic balance between immune tumor destruction and tumor growth or is a state of tumor cell dormancy in which cancer cells persist without dividing. We hope that this work will someday lead to the development of new immunotherapeutic protocols that facilitate cancer control in human cancer patients.

Escape phase

In the escape phase, tumor variants that acquire insensitivity to immunologic detection and/or elimination begin to expand in an uncontrolled manner resulting in clinically observable malignant disease. Entry into the escape phase can occur as a result of immunologic or non-immunologic mechanisms (14,

15). In addition, recent data by others has revealed that a dysregulation in either the levels or activation state of the latent cytosolic transcription factors STAT3 and STAT5 (which are anti-inflammatory, growth promoting and, in some cases, transforming) and/or STAT1 (which is pro-inflammatory, anti-proliferative and inhibits transformation) can lead to a variety of different escape mechanisms (21-23). We have made the observation that female mice lacking STAT1 develop high-grade, poorly differentiated mammary gland adenocarcinomas with high frequency. The cancer these mice develop shows remarkable similarity to certain types of human breast cancer as evidenced by developmental, histological and morphological criteria. Interestingly the mammary gland tumor cells from these mice display an unusual dysregulation of the JAK-STAT signaling pathway that is recapitulated in a subset of naturally occurring primary human breast cancers. As we continue to work on this novel mouse model of cancer we not only continue to learn more about the molecular basis of cancer development in general but are also obtaining unique insights into the origins and progression of human breast cancer in particular.

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