



SOCIETY FOR IMMUNOTHERAPY OF CANCER

Workshop – Focus on the Target: The Tumor Microenvironment

October 24–25, 2012 • North Bethesda, MD



Society for Immunotherapy of Cancer

www.sitcancer.org

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Message from the Organizers

Dear Attendees,

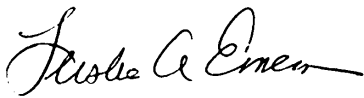
Welcome to SITC 2012 and the SITC Workshop – Focus on the Target: The Tumor Microenvironment. We are excited to present a two-day event featuring more than 20 of the field's leading experts who will present and facilitate discussion on the latest developments in cancer immunotherapy as they relate to the tumor microenvironment.

Historically, cancer therapies have largely focused on destroying the transformed cancer cell itself. However, recent findings surrounding the presence and role of CD8+ T cells in the tumor microenvironment have re-invigorated interest in exploiting the role of the immune system in cancer for both diagnosis and therapy. Currently, two major initiatives in the field of tumor immunology and immunotherapy are building as a result of these advances. First, incorporating the “immune score” as part of the routine diagnostic and prognostic assessment of tumors is a major effort. Second, the development of multi-faceted immune-based therapies that can reduce tumor-associated immune suppression to unleash either pre-existing or therapeutically-induced tumor immunity has become a significant goal driving the development of cancer immunotherapies.

This workshop aims to provide a solid foundation for these efforts by focusing on distinct aspects of the host-tumor interaction, and their implications for tumor immunotherapy. Using this science, treatment approaches that can reshape the host-tumor interaction and facilitate the development of personalized cancer immunotherapies will be discussed. The ultimate goal for the field is to develop integrative diagnostic and therapeutic strategies that are capable of promoting immune-based tumor rejection and increasing cure rates for cancer patients. This workshop has been designed with that end in mind.

We hope you will take this opportunity to learn the latest advances and development in the tumor immunology research and the application of cancer immunotherapy from the leaders who conduct the science. We'd like to thank the faculty who make this program possible for sharing their expertise and knowledge with the larger cancer immunotherapy community. Welcome to the SITC Workshop!

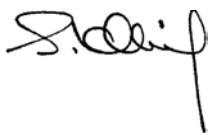
Sincerely,



Leisha A. Emens, MD, PhD
Workshop Organizer



Jerome Galon, PhD
Workshop Organizer



Samir N. Khleif, MD
Workshop Organizer



Samuel C. Silverstein, MD
Workshop Organizer



The Society for Immunotherapy of Cancer (SITC) was established in 1984 to facilitate the exchange and promotion of scientific information about the use of biological cancer therapies. SITC is a 501(c)(3) not-for-profit organization of medical professionals with a constituency of academic, government, industry, clinical and basic scientists from around the world. The Society was founded on the belief that new systemic therapeutic treatments would continue to complement chemotherapies and move into the mainstream in the fight against cancer. To aid in this effort, SITC provides intimate channels for the discussion of current clinical trial results and methodologies, as well as means to collaborate on new initiatives in tumor immunology and biological therapy. It is these key interactions and innovations that help advance the progress of cancer research and therapies and lead to better patient outcomes.

MISSION STATEMENT

It is the mission of the Society for Immunotherapy of Cancer to improve cancer patient outcomes by advancing the science, development and application of cancer immunology and immunotherapy through our core values of interaction/integration, innovation, translation and leadership in the field.

CORE VALUES

- Interaction/Integration: Facilitate the exchange of information and education among basic and translational researchers, clinicians, young investigators, societies and groups sharing the mission of SITC
- Innovation: Challenge the thinking and seek the best research in the development of cancer immunotherapy
- Translation: Facilitate the transfer of cancer immunology and immunotherapy research from the bench to the clinic and back
- Leadership: Define what is new and important and effectively communicate it to all relevant stakeholders

MEMBERS AND MEETING ATTENDEES

Society membership continues to grow and now includes more than 550 influential leaders and scientists engaged in immunotherapy/biological therapy of cancer, including academicians, senior researchers, clinicians, students, government representatives and industry leaders from around the world. SITC's members represent 17 medical specialties and are engaged in research and treatment of at least a dozen types of cancer. With major developments and recent FDA approvals in the field of cancer immunotherapy, the SITC Annual Meeting & Associated Programs attendance is growing as well, attracting over 800 of the brightest minds in the field. Both scientists and clinicians alike from around the globe convene at the SITC Annual Meeting & Associated Programs to share data, hear the most recent advances in the field and find collaboration opportunities.

Disease States Represented by SITC Constituents

SITC covers the full spectrum of both solid tumors and hematologic malignancies including:

- Breast
- Colorectal
- Head & Neck
- Hepatocellular
- Kidney
- Leukemia
- Lung
- Lymphoma
- Melanoma
- Neuroblastoma
- Ovarian
- Prostate
- Renal Cell

Medical Specialties Represented by SITC Constituents

- Cell Biology
- Dermatology
- Genetics
- Gynecologic Oncology
- Hematology
- Immunotherapy
- Internal Medicine
- Medical Oncology
- Microbiology
- Molecular Biology
- Pediatric Oncology
- Pharmacology/Toxicology
- Radiation Oncology
- Radiology
- Stem Cell Biology
- Surgical Oncology
- Transplantation

NEW SOCIETY JOURNAL — JOURNAL FOR IMMUNOTHERAPY OF CANCER

The *Journal for Immunotherapy of Cancer* (JITC) is the official journal of the Society for Immunotherapy of Cancer (SITC). JITC is comprised of four sections: Reviews/Editorials, Basic Tumor Immunology, Clinical/Translational Cancer Immunotherapy and Immunotherapy Biomarkers. JITC is a peer-reviewed, online, open access journal that aims to advance effective cancer immunotherapy by acting as a platform for the most important findings in the field. It encompasses all aspects of cancer immunology and immunotherapy, from basic research to clinical applications, and offers authors thorough peer review with immediate publication of accepted manuscripts. For more information, please see the back cover of this program or visit the SITC website.

SITC Membership Information

The Society for Immunotherapy of Cancer invites your support for our organization, its activities and events by becoming a member. SITC fills its membership with those from industry, academia and government, serving as clinical and basic scientists and industry representatives. Your contributions as a member can help shape SITC policy as we continue in our efforts to advance the development and application of cancer immunotherapy.

Through membership in SITC, you will be a member of an organization that is actively engaged in facilitating the implementation of timely, cutting-edge translational clinical research in cancer biotherapy.

SITC MEMBERSHIP BENEFITS

- FREE submission to the *Journal for ImmunoTherapy of Cancer* (JITC), SITC's NEW official open access and peer review journal comprised of four sections:
 - Reviews/Editorials
 - Basic Tumor Immunology
 - Clinical/Translational Cancer Immunotherapy
 - Immunotherapy Biomarkers.JITC encompasses all aspects of cancer immunology and immunotherapy, from basic research to clinical applications and it offers authors fast, fair and thorough peer review with immediate publication of accepted manuscripts.
- Reduction in registration fees for SITC Annual Meeting and Associated Programs
- Free access to speaker presentations and slide sets from past SITC live events
- Online directory of SITC members
- Access to "Members Only" section of SITC website: www.sitcancer.org
- Eligibility to serve on SITC committees
- Eligibility to serve on SITC Board of Directors (Regular members only)
- Discount on SITC enduring materials
- Access to the best science in the field
- Early access to timely information on what is new and relevant to biological approaches for the treatment of cancer
- Opportunities to participate in and shape discussions that guide progress in the field
- Opportunities to network with colleagues to develop new ideas, establish new collaborations to advance your work, and participate in active scientific exchange
- Access to luminaries in the field, including leading scientists and clinical researchers
- Guidance on relevant and timely issues
- The opportunity to advance your career

MEMBERSHIP TYPES

REGULAR MEMBERSHIP (\$220 ANNUAL DUES)

Available to individuals with an MD or PhD in a biological science or the equivalent who are active, bona fide representatives of the international scientific community with a specialty or interest in a field related to the biological therapy of cancer. Regular membership includes the right to vote. Business/educational resumé or Curriculum Vitae required for application.

AFFILIATE MEMBERSHIP (\$220 ANNUAL DUES)

Available to individuals active or otherwise interested in the biological therapy of cancer. Affiliate membership does not include the right to vote. Business/educational resumé or Curriculum Vitae required for application.

SCIENTIST-IN-TRAINING (STUDENT) MEMBERSHIP (\$50 ANNUAL DUES)

Available to individuals enrolled in MD or PhD academic programs or those participating in postdoctoral fellowships and residency programs who show a demonstrated interest in biological therapy of cancer. Student membership does not include the right to vote. Proof of enrollment and letter of recommendation or Curriculum Vitae required for application.

SITC Membership Application

Please check the membership category you are applying for:

Regular Affiliate Scientist-in-Training (Student)

Name: _____

Academic Degree: (please circle) MD PhD RN MS NP PharmD Other: _____

Institution/Company: _____

Title: _____ Dept: _____

Mailing Address: _____

City: _____ State: _____ Postal Code: _____

Country: _____ Email: _____

Phone: _____ Fax: _____

Work Sector (check one):

Academia Government Industry/Corporate Not-for-Profit Organization

Practice or Work Setting (check one):

Clinic Government Hospital Lab Lab & Clinic (translational) Medical School/University
 Pharmaceutical/Biotech None

Field(s) of specialty (check all that apply):

<input type="checkbox"/> Cell Biology	<input type="checkbox"/> Immunotherapy	<input type="checkbox"/> Pediatric Oncology	<input type="checkbox"/> Stem Cell Biology
<input type="checkbox"/> Dermatology	<input type="checkbox"/> Internal Medicine	<input type="checkbox"/> Pharmacology/ Toxicology	<input type="checkbox"/> Surgical Oncology
<input type="checkbox"/> Genetics	<input type="checkbox"/> Medical Oncology	<input type="checkbox"/> Radiation Oncology	<input type="checkbox"/> Transplantation
<input type="checkbox"/> Gynecologic Oncology	<input type="checkbox"/> Microbiology	<input type="checkbox"/> Radiology	<input type="checkbox"/> Others _____
<input type="checkbox"/> Hematology	<input type="checkbox"/> Molecular Biology		

Disease state(s) (check those most affiliated with your research or practice):

<input type="checkbox"/> Breast	<input type="checkbox"/> Hepatocellular	<input type="checkbox"/> Lung	<input type="checkbox"/> Neuroblastoma	<input type="checkbox"/> Renal Cell
<input type="checkbox"/> Colorectal	<input type="checkbox"/> Kidney	<input type="checkbox"/> Lymphoma	<input type="checkbox"/> Ovarian	<input type="checkbox"/> Others _____

Application Requirements

Regular applicants:

I will email my CV or educational resumé to info@sitcancer.org.
 My CV or educational resumé is enclosed.

Affiliate applicants:

I will email my business or educational resumé to info@sitcancer.org.
 My business or educational resumé is enclosed.

Scientist-in-Training (Student) applicants:

I will email my letter of recommendation or CV and proof of enrollment to info@sitcancer.org.
 My letter of recommendation or CV and proof of enrollment are enclosed.

Membership applications are reviewed throughout the year. Applicants will be contacted upon acceptance. Membership is valid from the date dues are paid in full until the end of that calendar year.

Membership Fee:

Regular/Affiliate (\$220) Scientist-in-Training (Student) (\$50)
 Check (enclosed) Make checks payable to SITC in U.S. dollars drawn from a U.S. bank.
 VISA MasterCard American Express Discover

Card Holder: _____

Card Number: _____ Exp: _____

Signature: _____ Date: _____

Return this form to: SITC • 555 E. Wells St., Suite 1100 • Milwaukee, WI 53202-3823
Tel: 414-271-2456 • Fax: 414-276-3349 • Email: info@sitcancer.org • Web: www.sitcancer.org

SITC Leadership and Executive Staff

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Did you miss SITC 2012?
Or do you want to share
the experience with your
colleagues?



Slides from SITC 2012
will soon be available
online. Check the
SITC website at
www.sitcancer.org
in early December.

Workshop Educational Overview

The development of cancer has historically been attributed to genomic alterations of normal host cells, with cancer treatments historically targeting the malignant cell itself. It is now clear that tumor growth and development is a complex process that involves both malignant transformation and the influence of normal host cells, including fibroblasts, endothelial cells, lymphocytes, monocytes and macrophages. The tumor microenvironment has emerged as a critical target for cancer diagnosis, prognosis and therapy.

This two-day workshop on the tumor microenvironment includes presentations from thought leaders in the field and cover topics from basic tumor immunobiology to clinical immunotherapy trials that incorporate agents that modulate the tumor microenvironment. It ends with a presentation of progress on the development of the immunoscore - an ongoing initiative to promote the incorporation of an analysis of immune infiltrates within primary tumors as part of their standard pathologic evaluation for cancer diagnosis, prognosis and therapy.

The audience for this program is basic scientists and clinical investigators from academic institutions, industry and regulatory agencies. The audience includes clinicians, translational and basic researchers, graduate students and postdoctoral fellows involved in cancer research.

TOPICS

- Cells of the Immune System in the Tumor Microenvironment
- Stromal Elements of the Tumor Microenvironment
- Inflammation and Immune Trafficking
- Remodeling the Tumor Microenvironment to Promote Tumor Regression
- Monitoring Immune Responses with the Tumor Microenvironment
- Clinical Trials: Provoking Immunity in the Tumor Microenvironment
- Immunoscore

PROGRAM GOALS

- Critically review the role of the immune system in cancer growth and progression and in cancer control and therapy
- Identify the distinct cellular and molecular components of the tumor microenvironment and how they interact in positive and negative ways with the host immune system
- Explore current data on the intersection of inflammation and immune infiltrates within the tumor site, defining mechanisms of immune cell trafficking, and identifying opportunities for therapeutic manipulation to improve immune-based therapies
- Discuss strategies for manipulating cells within the tumor microenvironment, including T cells, myeloid-derived suppressor cells and other inflammatory cells, to promote tumor regression
- Review approaches for characterizing and monitoring immune responses within the tumor microenvironment, including novel imaging techniques and innovative epigenetic and genomic technologies for profiling therapeutic responses
- Present what has been learned from successful clinical interventions that target the tumor microenvironment to enhance tumor immunity and highlight how to build on these observations to further improve cancer outcomes
- Discuss the progress, opportunities and challenges involved in developing the immune score as one standard component of the pathologic evaluation of newly diagnosed cancers

EXPECTED LEARNER OUTCOMES

Upon completion of this program, participants will be able to:

- Summarize how the immune system can promote evolving malignancies and, conversely, how it can control cancers and be harnessed for therapeutic benefit
- Explain the details of how a variety of cellular constituents and signaling pathways within the tumor microenvironment collaborate to promote tumor growth or regression
- Describe how immune cells gain access to tumors and how they can be characterized with new imaging techniques and measured with new technologies for both predicting and profiling responses
- Interpret the current rationale and clinical strategies for both profiling and therapeutically targeting the tumor microenvironment within cancer patients
- Describe the features and clinical relevance of the immune score and the challenges involved in harmonizing the methods and evaluation of immune infiltrates to facilitate the incorporation of the immune score into the standard pathologic evaluation of newly diagnosed tumors

Workshop Schedule

WEDNESDAY, OCTOBER 24

Day 1: An Integrative View of the Tumor Microenvironment		
7:00 am - 8:00 am	Registration	Grand Ballroom Foyer
7:00 am - 8:00 am	Continental Breakfast	Grand Ballroom Foyer
Session 100: Keynote Address		Grand Ballroom Salon E
8:00 am - 9:00 am	Immunity in Cancer Growth and Progression	
	Nicholas P. Restifo, MD - <i>National Cancer Institute</i>	
Session 101: Cells of the Immune System in the Tumor Microenvironment		
9:00 am - 9:30 am	Integrative Cancer Immunology: Importance of T Cells	
	Jerome Galon, PhD - <i>INSERM-Cordeliers Research Center</i>	
9:30 am - 10:00 am	T Lymphocytes in Human Melanoma Metastases	
	Pierre G. Coulie, MD, PhD - <i>De Duve Institute and University of Louvain</i>	
10:00 am - 10:30 am	<i>Refreshments and Networking</i>	Grand Ballroom Foyer
Session 102: Stromal Elements of the Tumor Microenvironment		Grand Ballroom Salon E
10:30 am - 11:00 am	Endothelial Regulation of T cell Trafficking in Tumors	
	George Coukos, MD, PhD - <i>University of Pennsylvania Medical Center</i>	
11:00 am - 11:30 am	Immune Suppression by Stromal Cross	
	David H. Munn, MD - <i>Georgia Health Sciences University</i>	
11:30 am - 12:00 pm	Relapse of Cancer: Stromal Cross-Presentation is Required for the Elimination of Escape Variants	
	Hans Schreiber, MD, PhD - <i>University of Chicago</i>	
12:00 pm - 1:30 pm	<i>Lunch Break and Networking (Lunch provided to registered attendees)</i>	Grand Ballroom Foyer
Session 103: Inflammation and Immune Trafficking		Grand Ballroom Salon E
1:30 pm - 2:00 pm	Innate and Adaptive Immunity Regulated Within the Tumor Microenvironment	
	Thomas F. Gajewski, MD, PhD - <i>University of Chicago</i>	
2:00 pm - 2:30 pm	Chemotherapy Alters a Tolerogenic Environment in the Spleen of Tumor-Bearing Hosts	
	Vincenzo Bronte, MD - <i>University of Verona</i>	
2:30 pm - 3:00 pm	An Experimentally Verified Quantitative Model and In Vitro Methods that Enable Cellular Immunotherapists to Calculate the Concentration of Cytolytically Active Immune Effector Cells Required to Produce Sterilizing Immunity in Neoplastic and Infectious Diseases	
	Samuel C. Silverstein, MD - <i>Columbia University</i>	
3:00 pm - 3:30 pm	Manipulating MDSC to Promote Regression	
	Dmitry I. Gabrilovich, MD, PhD - <i>H. Lee Moffitt Cancer Center and Research Institute</i>	
Session 104: Keynote Address		Grand Ballroom Salon E
3:30 pm - 4:30 pm	Mechanisms of Protective Tumor Immunity	
	Glenn Dranoff, MD - <i>Dana-Farber Cancer Institute</i>	

Workshop Schedule

THURSDAY, OCTOBER 25

Day 2: Manipulating the Tumor Microenvironment for Therapeutic Benefit		
7:00 am - 8:00 am	Registration	Grand Ballroom Foyer
7:00 am - 8:00 am	Continental Breakfast	Grand Ballroom Foyer
Session 200: Remodeling the Tumor Microenvironment to Promote Tumor Regression		Grand Ballroom Salon E
8:00 am - 8:30 am	Oncogene Inactivation and CD4+ T Cells	
	Dean W. Felsher, MD, PhD - <i>Stanford University School of Medicine</i>	
8:30 am - 9:00 am	Immune Checkpoint Modulation and the Tumor Microenvironment	
	Drew Pardoll, MD, PhD - <i>Johns Hopkins University School of Medicine</i>	
9:00 am - 9:30 am	Immune Impact on Cancer Stemness and Metastasis	
	Weiping Zou, MD, PhD - <i>University of Michigan</i>	
9:30 am - 10:00 am	Manipulating T Cells to Promote Regression	
	Laurence J.N. Cooper, MD, PhD - <i>MD Anderson Cancer Center</i>	
10:00 am - 10:30 am	<i>Refreshments and Networking</i>	Grand Ballroom Foyer
Session 201: Monitoring Immune Responses with the Tumor Microenvironment		
10:30 am - 11:00 am	Microenvironment Immunogenetics Biomarkers in Combination Immunotherapy	
	Samir N. Khleif, MD - <i>Georgia Health Sciences University</i>	
11:00 am - 11:30 am	Visualizing CTL and NK Cells Cytotoxic Activity in Solid Tumors	
	Philippe Bousso, PhD - <i>INSERM U668</i>	
11:30 am - 12:00 pm	Epigenetic Immune Cell Markers — Enabling Novel Clinical Trials with Robust Results from Frozen Whole Blood or Tissue	
	Thomas O. Kleen, PhD - <i>Epiontis GmbH</i>	
12:00 pm - 12:30 pm	Immune Response Signatures and Patient Survival	
	Mary L. Disis, MD - <i>University of Washington</i>	
12:30 pm - 2:00 pm	<i>Lunch Break and Networking (Lunch provided to registered attendees)</i>	Grand Ballroom Foyer
Session 202: Clinical Trials: Provoking Immunity in the Tumor Microenvironment		Grand Ballroom Salon E
2:00 pm - 2:30 pm	Combination Immunotherapies Designed to Target the Tumor Microenvironment	
	Leisha A. Emens, MD, PhD - <i>Johns Hopkins University</i>	
2:30 pm - 2:50 pm	MDSC Inhibition Augments Immune Function in Head and Neck Cancer Patients: Results of PDE5 Inhibition	
	Ivan Borrello, MD - <i>Johns Hopkins University School of Medicine</i>	
2:50 pm - 3:10 pm	Clinical Trials: Provoking Immunity in the Tumor Microenvironment	
	Antoni Ribas, MD - <i>University of California, Los Angeles Medical Center</i>	
3:10 pm - 3:30 pm	Sunitinib and Immunity	
	Brian I. Rini, MD - <i>Cleveland Clinic Taussig Cancer Center</i>	

Workshop Schedule

THURSDAY, OCTOBER 25, *continued*

Session 203: Immunoscore		Grand Ballroom Salon E
3:30 pm - 3:50 pm	The Immunoscore: A Proposal for a New Classification of Cancer in the Era of Immunotherapies	
	Jerome Galon, PhD - <i>INSERM-Cordeliers Research Center</i>	
3:50 pm - 4:10 pm	The Impact of Immune Cell Infiltration on Patient Prognosis	
	Alessandro Lugli, MD - <i>Institut of Pathology University of Bern</i>	
4:10 pm - 4:30 pm	A Strategic View of the Immunoscore	
	Bernard A. Fox, PhD - <i>Earle A. Chiles Research Institute</i>	
4:30 pm - 4:50 pm	Exploring Immune-Mediated Tumor Destruction in Humans	
	Francesco Marincola, MD - <i>National Institutes of Health</i>	
4:50 pm - 5:00 pm	Closing Comments	

Forward Fund

www.sitcancer.org/support/forwardfund

Show your support for the field and help move cancer immunotherapy *Forward!* Purchase your “Friend of the Society” Ribbon at the SITC Registration Desk for a minimum donation of \$50, or make a general *Forward Fund* contribution. All contributions to the SITC *Forward Fund* support research, training, education, faculty development grants and all SITC awards, including the Richard V. Smalley, MD Award and the Young Investigator Travel Awards.

Faculty Listing

Ivan Borrello, MD

John Hopkins University School of Medicine

Philippe Bousso, PhD

INSERM U668

Vincenzo Bronte, MD

University of Verona

Laurence J.N. Cooper, MD, PhD

MD Anderson Cancer Center

George Coukos, MD, PhD

University of Pennsylvania Medical Center

Pierre G. Coulie, MD, PhD

De Duve Institute and University of Louvain

Mary L. Disis, MD

University of Washington

Glenn Dranoff, MD

Dana-Farber Cancer Institute

Keynote

Leisha A. Emens, MD, PhD

Johns Hopkins University

Dean W. Felsher, MD, PhD

Stanford University School of Medicine

Bernard A. Fox, PhD

Earle A. Chiles Research Institute

Dmitry I. Gabrilovich, MD, PhD

H. Lee Moffitt Cancer Center and Research Institute

Thomas F. Gajewski, MD, PhD

University of Chicago

Jerome Galon, PhD

INSERM- Cordeliers Research Center

Samir N. Khleif, MD

Georgia Health Sciences University

Thomas O. Kleen, PhD

Epiontis GmbH

Alessandro Lugli, MD

Institut of Pathology University of Bern

Francesco Marincola, MD

National Institutes of Health

David H. Munn, MD

Georgia Health Sciences University

Drew M. Pardoll, MD, PhD

Johns Hopkins University School of Medicine

Nicholas P. Restifo, MD

National Cancer Institute

Keynote

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University of California, Los Angeles Medical Center

Brian I. Rini, MD

Cleveland Clinic Taussig Cancer Center

Hans Schreiber, MD, PhD

University of Chicago

Samuel C. Silverstein, MD

Columbia University

Weiping Zou, MD, PhD

University of Michigan

Biography not available at time of printing.

MDSC Inhibition Augments Immune Function in Head and Neck Cancer Patients: Results of PDE5 Inhibition

Myeloid derived suppressor cells (MDSCs) are increasingly recognized as major contributors to the cancer-associated immune suppression. This process is mediated through cell-cell contact with the production of nitric oxide (NO) and upregulation of arginase-1 (Arg1). We had previously shown that phosphodiesterase-5 inhibitors such as sildenafil and tadalafil could exert a measurable anti-tumor immunity in various murine models through downregulation of NO production and Arg1 synthesis and downregulation of IL4R α on MDSCs with resulting activation of T cells (primarily CD8) and an associated increase in activated tumor infiltrating lymphocytes.

We now report on the results of our first clinical trial examining the ability of the PDE5 inhibitor, tadalafil, to alter MDSC function in head and neck squamous cell carcinoma. This was a randomized, double-blinded, placebo controlled trial in which tadalafil was administered in newly-diagnosed patients prior to surgery. Patients were treated for two weeks with 20mg of tadalafil or placebo. To determine global systemic immunity, the Candida DTH response was determined prior to initiation of therapy and upon completion. Blood was analyzed to determine the impact of PDE5 inhibition on global immunity, MDSC number, phenotype and function, T cell phenotype and function and tumor specificity. The results of these findings will be presented and discussed. This approach demonstrates the ability to target MDSCs with an agent currently used in the treatment of erectile dysfunction and with no known direct anti-tumor cytotoxicity. As such, it represents a novel approach and underscores the biologic and clinical relevance of abrogating MDSC function in an effort to augment the efficacy of various anti-tumor approaches.

Philippe Bousso is an immunologist directing the Laboratory of Dynamics of Immune Responses at Institut Pasteur, Paris, France. His work has focused on studying the dynamics of T cell responses at the clonal and single cell level. During his PhD with Philippe Kourilsky, he showed that the naive TCR repertoire of syngeneic mice is mostly non-overlapping, reflecting individual variability of immune TCR repertoires. Subsequently, he analyzed how negative selection shapes the TCR repertoire specific for a self-antigen. During his postdoctoral work with Ellen Robey, Dr. Bousso developed an expertise in two-photon imaging for the study of immune cells in intact lymphoid tissues. His seminal work in this area resulted in the characterization of cell-cell contacts between thymocytes and stromal cells during the process of positive selection. He went on to measure the rate of DC-T cell contact in live lymph nodes and reported the cellular dynamics during CD8⁺ T cell priming. Since 2005, Philippe Bousso has been the head of the laboratory Dynamics of Immunes Responses at the Institut Pasteur. Research in his group aimed at elucidating how adaptive immune responses are regulated by cellular communications in vivo. In particular, his lab is dissecting how T cell collect activation signals in vivo and how they fulfill their effector functions in the tumor microenvironment or during chronic infections.

Visualizing CTL and NK Cells Cytotoxic Activity in Solid Tumors

Cytotoxic T cells and NK cells (CTLs) are key players of anti-tumor immune responses. CD8 T cells can recognize and lyse cells expressing tumor antigens while NK cells can kill tumor cells that have downregulated MHC class I molecule and/or upregulated ligands for NK cell activating receptor. To counteract the host immune response, tumors rely on a wide array of mechanisms to escape destruction by infiltrating cytotoxic effectors. Despite our fundamental knowledge on the interplay between the immune system and tumor microenvironments, we have a poor understanding on the efficiency with which intratumoral immune effectors find, interact and kill their targets. Clearly, a better understanding of how these events occur and change during the course of tumor development will help identify why immune responses often failed to clear tumors. We will discuss how intravital two-photon imaging combined with fluorescent probes to track tumor cell apoptosis in real time can provide quantitative information in tumor cell killing in situ. Moreover, we will present recent data showing that NK cells and CTL use strikingly different dynamics during tumor cell regression.

Dr. Vincenzo Bronte is currently Head of the Immunology Section in the Department of Pathology and Diagnostics of Verona University and Head of the U.O.C. of Immunology in the Policlinico G. B. Rossi Hospital. He is Full Professor of Immunology at the University of Verona. Dr. Bronte was awarded the PBI International Prize by SIICA in 1997, the International Prize “Francesco De Luca” for scientific oncology career by the Accademia Nazionale dei Lincei (Rome, Italy) in 2007, the “Timone d’argento” Prize by Lion’s Club in 2008, and the “Guido Venosta” Prize for oncology researchers by the Italian Foundation for Cancer Research (FIRC) in 2008. Dr. Bronte is member of the board of the Accademia Nazionale di Medicina and Italian Cancer Society (SIC), Italy.

Dr. Bronte is an expert in the field of cancer immunotherapy. One of Dr. Bronte’s major achievements has been the definition and characterization of immunoregulatory cells, now called myeloid-derived suppressor cells (MDSCs), whose negative influence on antitumor immunity represents an important obstacle to successful immunotherapy of cancer. Current projects in the laboratory are further exploring the cellular and molecular mechanisms underlying the biological properties of MDSCs, with particular attention to definition of novel drugs affecting their function to be used alone or in combination with active or passive immunotherapy approaches. He has published over 109 papers in international scientific journals and contributed 12 book chapters.

Chemotherapy Alters a Tolerogenic Environment in the Spleen of Tumor-bearing Hosts

Different chemotherapeutic drugs, endowed with dissimilar mechanisms of action but with the same ability to eliminate a specific pool of myeloid-derived suppressor cells (MDSCs) - phenotypically characterized as CD11b+/Gr-1int cells - were able to restore the immune responsiveness in tumor-bearing mice, even when administered at doses too low to exert a direct antitumor activity. CD11b+/Gr-1int cells possess peculiar characteristics since they are highly proliferating and likely the most immunosuppressive subset of MDSCs. The transfer of this population to drug-treated mice was sufficient to abrogate completely the immune adjuvant activity exerted by low dose chemotherapy on adoptive cell therapy (ACT), suggesting that this cell subset is indeed crucial to establish tolerance in tumor-bearing hosts. Interestingly, CD11b+/Gr-1int cells are recruited to the spleen by CCL2 and CCR2 expression by these myeloid cells is necessary for tolerance induction. CD11b+/Gr-1int cells are recruited to the marginal zone of the spleen where they encounter tumor-specific, memory CD8+ T cells, cross-present them tumor-derived antigens, and induce their inactivation. The splenic tolerogenic environment in the marginal zone is perturbed for a long time following chemotherapy. Moreover, we found that low serum CCL2 levels in cancer patients were associated with the translation of immune responses to prolonged overall survival. This observation was made in two independent immunotherapy trials in advanced renal cell cancer and colorectal cancer patients using two different cancer vaccines.

These data indicate that we need to consider an additional compartment for the tumor-induced tolerance and lay the basis for a rational use of low dose chemotherapy as immune adjuvant for the active immunotherapy of cancer.

Dr. Laurence Cooper is a tenured Professor at the University of Texas MD Anderson Cancer Center (MDACC), with joint appointments in the Division of Pediatrics and Department of Immunology. He is Section Chief of Cell Therapy at the Children's Cancer Hospital (CCH) at MDACC and additionally serves as director of the institution's Immunology Laboratory of Physician-Scientists. Dr. Cooper earned his medical and doctorate degrees from Case Western Reserve University in Cleveland, Ohio and completed his fellowship in Pediatric Hematology/Oncology at the Fred Hutchinson Cancer Research Center at the University of Washington in Seattle. In 2006, he was recruited to join the CCH at MDACC, where he cares for children undergoing bone marrow transplantation (now known as cell therapy) and leads scientific efforts to develop new treatment approaches which pair gene engineering with immunotherapy.

Dr. Cooper's research has resulted in founding a company and in multiple patents. A former National Institutes of Health Research Center Scholar, Scholar of the Sidney Kimmel Foundation for Cancer Research, and Leukemia Society of America Fellowship, Dr. Cooper is the principal investigator for numerous initiatives and trials. In 2007, he was elected to membership in the American Society for Clinical Investigation, which honors outstanding physician-scientists. Other tributes paid to Dr. Cooper include the 2010 "Best Boss" award MDACC, 2009 Faculty Scholar Awards MDACC, 2007 induction into the American Society for Clinical Investigation, 2004 American Society of Gene Therapy and 1999 American Society of Clinical Oncology Young Investigator Awards. Dr. Cooper has coauthored dozens of peer-reviewed journal articles, abstracts and book chapters. Since 2006, he has initiated five trials under IND using T cells and NK cells. He is undertaking the first trials using a new approach to gene therapy based upon the *Sleeping Beauty* transposon/transposon system and has helped develop clinical-grade artificial antigen presenting cells for numerically expanding lymphocytes. He combines his clinical duties with research and mentoring to help translate immunology into immunotherapy.

Manipulating T Cells to Promote Regression

T cells can be genetically modified to prevent and treat malignancies. However, immune tolerance prevents the identification and thus application of autologous T cells with desired specificity for tumor-associated antigens (TAAs). The enforced expression of TAA-specific immunoreceptors can redirect the specificity of clinical-grade T cells and early-phase human trials have demonstrated the safety, feasibility, and anti-tumor activity of such adoptively-transferred genetically modified cell products. Several clinically appealing approaches are now available to genetically modify T cells using viral- and nonviral-based technologies. Such gene transfer can occur in T-cell subsets that are predicted to have improved *in vivo* survival leading to augmented therapeutic effects. To further improve persistence, the recipient can be manipulated to generate an environment that promotes T cell engraftment. Such data have led to the clinical translation of genetically modified T cells, which stably express high affinity alpha/beta paired T cell receptors to recognize TAAs in the context human leukocyte antigen (HLA) and single-chain chimeric antigen receptor (CARs) to recognize cell-surface TAAs independent of HLA. When coupled with immunocorrelative studies, these trials confirm the premise and reveal the promise of clinical-grade T cells bearing defined transgenic immunoreceptors.

George Coukos, MD, PhD is the Celso Ramon Garcia Associate Professor of Reproductive Biology, Associate Chief of the Division of Gynecologic Oncology and Director of the Ovarian Cancer Research Center at the University of Pennsylvania Abramson Cancer Center. He is a member of the Society for Immunotherapy of Cancer, Society of Gynecologic Oncology, the American Society of Clinical Oncology, the American Association for Cancer Research and the Society of Gynecologic Investigation. George received the Penn Medicine Award of Excellence in 2006, and has been recognized by Philadelphia Magazine "Top Doctors" in 2007 and 2008 and by Best Doctors in America 2007-2008.

Dr. Coukos earned an MD degree, cum laude, from the University of Modena, Italy, and a PhD (Reproductive Biology) from the University of Patras School of Medicine, Greece. After his Obstetrics and Gynecology residency, he studied the cell biology of the human trophoblast with C. Coutifaris and JF Strauss at the University of Pennsylvania's Center for Research on Reproduction and Women's Health. He completed a clinical fellowship in gynecologic oncology with Steve Rubin at the University of Pennsylvania.

Endothelial Regulation of T cell Trafficking in Tumors

We have previously identified adhesive mechanisms of the blood-tumor barrier, a constellation of mechanisms by which the tumor endothelium resists T cell adhesion or homing. Tumor endothelial cells avoid circulating T cell adhesion by downregulating VCAM-1 and ICAM-1, or deregulating ICAM-1 expression, through the dispersion of ICAM-1 surface clusters, which are necessary for T cell adhesion and transmigration. We have shown that this effect is mediated by the endothelin B receptor (ETBR) through nitric oxide (NO) and can be abrogated by the ETBR inhibitor BQ-788 or by the NO antagonist L-NAME. We recently identified another mechanism through which tumor endothelium establishes immune privilege at the tumor site, through the upregulation of Fas ligand (FasL/CD95L), a potent inducer of apoptosis on Fas+ (activated) effector T cells. We found that the endothelium of most human solid tumor types expresses FasL, in contrast to normal tissue endothelium, where FasL is absent. Surface FasL expression was documented on endothelial cells isolated freshly from patient tumor samples. Importantly, tumors with little to no endothelial FasL expression showed markedly higher infiltration of CD8+ T cells. FasL surface expression was upregulated in microvascular endothelial cells (HMVECs) by the supernatants of ovarian cancer cells exposed to hypoxia. Moreover, treatment of HMVECs in vitro with prostaglandin E₂ (PGE₂), VEGF and interleukin 10 (IL-10) resulted in synergistic upregulation of FasL, and these cells were able to kill Jurkat target cells in a FasL-dependent manner. In mice bearing ID8-VEGF tumors (ID8-VEGF cells do not express FasL), COX inhibition with acetyl salicylic acid (ASA, aspirin) and VEGF blockade with neutralizing antibody B20-4.1 was sufficient to reduce endothelial FasL expression and resulted in marked increase in CD8+ T cell infiltration, which correlated with reduced tumor burden. We conclude that the endothelial barrier is mediated by more than one mechanism, which must be countered for successful immunotherapy.

Pierre G. Coulie, MD, PhD, born in Brussels in 1957, is Full Professor at the Université catholique de Louvain, Brussels, where he teaches immunology. Trained in immunology as a student by Prof. Jacques Van Snick, he worked on murine rheumatoid factor and on cytokines. In 1988, he joined the group of Professor Thierry Boon and switched to human tumor immunology. Investigator at the Brussels branch of the Ludwig Institute for Cancer Research from 1989 to 1995, he made important contributions to the identification of human tumor-specific antigens recognized by T lymphocytes. Pursuing his collaboration with the teams of the Ludwig Institute, he is primarily interested in human anti-tumor immunology in the context of therapeutic vaccination with tumor-specific antigens. His current work is focused on the mechanisms of the tumor regressions that are observed in some vaccinated cancer patients, in order to ultimately improve the clinical efficacy of these new and remarkably non-toxic cancer treatments.

T Lymphocytes in Human Melanoma Metastases

We combined immunohistochemical and genetic analyses to examine the functional status of T lymphocytes and qualify the immunosuppression thought to be present in subcutaneous metastases of human melanoma. We observed a specific inflammatory signature, quite variable between samples, and independent of the clinical evolution of the patients. It comprises T cell and macrophage markers, IFN γ target genes and the IFN γ gene itself. Immunohistology and microdissection on adjacent tumor sections indicated that this inflammatory signature correlates with immune cell infiltration. The source of IFN γ is almost certainly T cells, as NK cells are scarce in these tumors. The levels of expression of IFN γ -induced genes in these melanoma metastases can be as high as those measured with identical methods in rejected kidney allografts. Thus melanoma metastases host active Th1 inflammation, and we conclude that the immunosuppressive environment in these tumors does not result in a complete inhibition of T cell activation.

In 25% of the samples we observed ectopic lymphoid structures: lymphoid follicles comprising clusters of B lymphocytes and FDC, associated with high endothelial venules and clusters of T cells and mature DC. Some follicles contained germinal centers. Primary melanomas did not host follicles, but many contained high endothelial venules, suggesting incomplete lymphoid neogenesis. Analysis of the repertoire of rearranged immunoglobulin genes in the B cells of microdissected follicles revealed clonal amplification, somatic mutation and isotype switching, indicating a local antigen-driven B cell response. These results demonstrate the existence of lymphoid neogenesis in melanoma and suggest that the presence of functional ectopic lymphoid structures in direct contact with the tumor makes the local development of anti-melanoma B and T cell responses possible.

Mary L. (Nora) Disis, MD, is the Associate Dean for Translational Health Sciences at the University of Washington (UW) School of Medicine, Professor of Medicine and Adjunct Professor of Pathology and Obstetrics and Gynecology at UW and a Member of the Fred Hutchinson Cancer Research Center (FHCRC). She is the Director of both the Institute of Translational Health Science and the Center for Translational Medicine in Women's Health at UW. Dr. Disis received her MD from the University of Nebraska and completed a residency and Chief Residency in Internal Medicine at the University of Illinois College of Medicine in Chicago. She completed a fellowship in Oncology at the University of Washington/Fred Hutchinson Cancer Research Center where she has remained as faculty.

Dr. Disis is an expert in breast and ovarian cancer immunology and translational research. Her research interest is in the discovery of new molecular immunologic targets in breast and ovarian cancer for the development of vaccine and cellular therapy for the treatment and prevention of those malignancies. In addition, her group evaluates the use of the immune system to aid in the diagnosis of cancer and develops novel assays and approaches to quantitate and characterize human immunity. She holds several patents in the field of targeted cancer therapy and cancer diagnostics. Dr. Disis is a member of Alpha Omega Alpha Medical Honor Society, the American Society of Clinical Investigation, the Association of American Physicians and the Society for Immunotherapy of Cancer. She is the Deputy Editor for the *Journal of Clinical Oncology*.

Immune Response Signatures and Patient Survival

Recent investigations, evaluating several different tumor types, have demonstrated the importance of tumor infiltrating immune cells in predicting patient survival. The presence of tumor infiltrating activated T-cells and T-memory cells and the lack of infiltrating immunosuppressive regulatory cells has been shown to impact prognosis in both early and late stages of a variety of common solid tumors. Similarly, genes that are associated with a Type I tumor infiltrating T-cell response have also been associated with improved disease outcomes. These data suggest that some patients demonstrate a pre-existent immune response that has served to modulate the growth and progression cancer.

How can these observations benefit the clinical application of cancer immune therapy? Biomarkers that may predict response to immunotherapy can be categorized into two groups; (1) those markers that are present prior to treatment that may indicate the ability of an individual to respond to immunomodulation and (2) those markers that are specifically induced by an immune based treatment and may be predictive of a favorable clinical response.

There are several candidate markers that are present prior to the initiation of treatment that may predict the potential of a clinically effective immune response. As stated above, evidence of an evolving Type I T-cell environment in the tumor either via the "immune score" (Bindea et al, 2010) or an interferon predominant tumor specific gene signature may predict the ability to respond. In some tumor types, such as triple negative breast cancer, along with a strong Type I T-cell signal, genes related to B-cells also predominate (Rody et al, 2011). A combined T-B cell signature may indicate the development of intratumoral tertiary lymphoid organogenesis (TLO) indicating a vigorous ongoing immune response involving multiple immune effectors. Tumor TLO have been found to express genes associated with activated T-cells, lymphoid migration and cytotoxicity (Martinet et al *Ca Res*, 2011). As a peripheral blood correlate of productive intratumoral immune cell infiltration, investigators have studied the presence of pre-existent immune responses to common tumor antigens either by assessing specific T-cell responses or by the evaluation of a diverse tumor associated antibody repertoire. Studies are ongoing to determine whether these blood based markers are related to improved clinical outcome. Conversely, blood based biomarkers may also indicate an inability to mount a successful immune response. Elevated levels of peripheral blood T-regulatory cells or myeloid derived suppressor cells may inhibit the development of immunity unless depleted. Likewise, individuals may carry genes or polymorphisms in specific genes that prevent significant levels of immunity being induced.

Studies of blood based biomarkers induced by cancer immune therapies often center on the quantitative assessment of a specific effector response. There have been Phase II and III trials that have shown some significant associations of either a tumor specific antibody or T-cell response with clinical outcome. However, most immune therapy trials do not enroll sufficient numbers of patients and/or collect a sufficient number of patient samples to definitively validate any current quantitative immune biomarker. In addition, there is a question whether a single measurement of an individual effector cell population will be able to predict a beneficial clinical outcome. Indeed, some promising approaches evaluate both the elicited immune response as well as the ability of that immune response to modulate the tumor microenvironment. Approaches aimed at assessing the development of successful "cross-priming" in the tumor have been shown to be associated with favorable clinical outcomes after immune based cancer therapies. Such composite approaches may further refine immune response signatures that predict patient survival.

Glenn Dranoff, MD, is a Professor of Medicine at Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Harvard Medical School. He has developed a basic and translational research program to elucidate the cellular and molecular mechanisms underlying the generation of anti-tumor immunity. Work in his laboratory has given rise to multiple clinical protocols at the Dana-Farber Cancer Institute that have defined the biologic activity of several cancer immunotherapies in patients with solid or hematologic malignancies; these investigations have helped provide the foundation for the recent FDA approvals of the first therapeutic cancer vaccine and the first monoclonal antibody that blocks negative immune regulation.

Dr. Dranoff is the Leader of the Dana-Farber/Harvard Cancer Center Program in Cancer Immunology, a Co-Leader of the Dana-Farber Cancer Vaccine Center, the Director of the Dana-Farber Human Gene Transfer Laboratory, and the Principal Investigator of the Harvard Immunology Training Grant for Pre-doctoral Students in Cancer Immunology. He is the recipient of the Eli Lilly Biochemistry Award in Gene Therapy and the Stohler Scholarship of the Leukemia & Lymphoma Society, and was elected to the Academy of Cancer Immunology, the American Society of Clinical Investigation, the European Academy of Tumor Immunology, and the Osler Interurban Clinical Club.

Mechanisms of Protective Tumor Immunity

Efficacious cancer immunotherapies will likely require combinations of strategies that enhance tumor antigen presentation and antagonize negative immune regulatory circuits. We demonstrated that vaccination with irradiated, autologous melanoma cells engineered to secrete GM-CSF followed by antibody blockade of CTLA-4 accomplishes clinically significant tumor destruction with minimal toxicity in a majority of stage IV metastatic melanoma and some advanced ovarian carcinoma patients. The extent of tumor necrosis in post-treatment biopsies was linearly related to the natural logarithm of the ratio of infiltrating CD8⁺ effector T cells to FoxP3⁺ Tregs, suggesting that further Treg inhibition might increase the frequency of clinical responses. Through an analysis of cytokine deficient mice, we delineated a critical role for GM-CSF in Treg homeostasis. GM-CSF is required for the expression of the phosphatidylserine binding protein MFG-E8 in antigen presenting cells, whereas the uptake of apoptotic cells by phagocyte-derived MFG-E8 maintains peripheral Treg activity. The pharmacologic inhibition of MFG-E8 function through genetic or engineering-based approaches blocks Treg induction, which intensifies vaccine-induced responses, leading to the regression of established tumors in mice. The clinical translation of these therapeutic strategies to Phase I testing in humans is underway.

The detailed analysis of patients achieving sustained clinical benefits from irradiated, autologous GM-CSF secreting tumor cell vaccines and CTLA-4 antibody blockade also affords a rich opportunity to identify antigens associated with immune-mediated tumor destruction and to delineate mechanisms of therapeutic immunity. We elucidated several of the molecular pathways that underlie these anti-tumor effects, including the NKG2D system and multiple secreted/or cell surface proteins that contribute to tumor promoting inflammation. The therapy-induced antibodies manifest functional activity in vitro, antagonizing tumor cell survival, invasive potential, and angiogenesis. These findings support a key role for humoral immunity in tumor destruction and highlight interest in more detailed characterization of the anti-tumor B cell repertoire in vaccinated patients.

Leisha A. Emens, MD, PhD is an Associate Professor at the Sidney Kimmel Comprehensive Cancer Center at the Johns Hopkins University School of Medicine. She is a medical oncologist who specializes in breast cancer care and is developing innovative immune-based therapies that incorporate cancer vaccines, standard cancer drugs, and immune checkpoint inhibitors for the treatment of breast cancer and ovarian cancer. Dr. Emens received her BA in Biochemistry and Cell Biology from the University of California at San Diego in 1984. In the Medical Scientist Training Program at Baylor College of Medicine, she received her PhD in Cell Biology in 1993, and her MD in 1995. She completed her internship and residency in Internal Medicine at the University of Texas at Southwestern Medical School in 1998, and completed fellowship training in Medical Oncology and Hematology at Johns Hopkins University School of Medicine in 2001 when she joined the faculty. Dr. Emens is board-certified in internal medicine, medical oncology, and hematology by the American Board of Internal Medicine. She has received the Johns Hopkins University Clinician Scientist Award, the American Cancer Society Research Scholar Award, the YWCA President's Award, and the Maryland Governor's Citation for her work. She is a member of the American Society of Oncology, the American Association for Cancer Research, the American Society of Gene Therapy and the Society for the Immunotherapy of Cancer. She is also a member of the editorial board of the *Journal of Clinical Oncology*, and the FDA Advisory Committee on Cellular, Tissue and Gene Therapies.

Combination Immunotherapies Designed to Target the Tumor Microenvironment

Cancer vaccines are a unique, highly attractive therapeutic modality that may circumvent the drug resistance that underlies treatment failure in advanced cancers. However, their activity may be limited by intricate networks of immune tolerance and suppression, and by established burdens of disease. We have taken an integrative approach to immunotherapy by strategically partnering cancer therapeutics with vaccination to simultaneously harness the cytoreductive potential of cancer drugs, and their ability to impinge on immunoregulatory networks to favor tumor immunity. We have used the paired FVB/N—neu N mouse model of HER-2+ breast tumors (no immune tolerance/immune tolerance) to investigate mechanisms of potential synergy and antagonism between distinct drugs and tumor vaccines. HER-2-targeted, granulocyte-macrophage colony-stimulating factor (GM-CSF)-secreting vaccination alone induces strong HER-2-specific antibody and T cell immune responses that are curative in tumor-bearing FVB/N mice, but induces very weak antibody and T cell responses in tumor-bearing neu-N mice that fail to impact tumor outgrowth. Sequencing the vaccine with low dose Cyclophosphamide (CY) and Doxorubicin (DOX) cures about 30% of neu-N mice, in part by abrogating the influence of CD4+CD25+ regulatory T cells (Treg). Furthermore, giving the vaccine with both low dose CY and HER-2-specific monoclonal antibody (to passively restore the HER-2-specific humoral immune response) cures about 55% of neu-N mice. Adding HER-2-specific monoclonal antibody to vaccination increases tumor cell apoptosis and antigen processing and presentation by tumor cells, and augments the HER-2-specific CD8+ T cell response. Finally, HER-2-specific monoclonal antibody can augment vaccination by augmenting locoregional immune priming and establishing a durable population of central memory T cells.

Building on these preclinical studies, we have completed two clinical studies that demonstrate the safety and bioactivity of these combination vaccine approaches for breast cancer. The first clinical study investigated a human HER-2+ GM-CSF-secreting vaccine with a range of low dose CY (200, 250, and 350 mg/m²) and DOX (15, 25, and 35 mg/m²) in 28 patients with metastatic HER-2-negative breast cancer. The vaccine delivers multiple antigens, including HER-2, and we evaluated immune responses specific for HER-2 as a surrogate marker of vaccine activity. This study demonstrated that the vaccine alone or sequenced with chemotherapy is well tolerated, and that doses of 200 mg/m² CY and 35 mg/m² DOX optimize HER-2-specific CD4+ T cell-dependent immunity. Relative to vaccine alone or CY at 350 mg/m², CY at 200 and 250 mg/m² selectively depleted peripheral memory Treg relative to peripheral naïve Treg. The second clinical study investigated the same vaccine with low dose CY and standard weekly Trastuzumab (a therapeutic monoclonal antibody specific for HER-2) in 20 patients with metastatic HER-2-positive breast cancer. This study demonstrated that the vaccine given with both CY and Trastuzumab is well tolerated, with clinical benefit rates at 6 months and 1 year of 10/20 (50%) and 7/20 (35%) respectively. HER-2-specific DTH developed in 7/20 subjects (35%); four (57%) of these had a clinical benefit. We are now testing CY-modulated vaccination with a single immune-modulating dose of Trastuzumab given at the time of immune priming in patients with metastatic HER-2-negative breast cancer. In order to more directly explore the impact of the tumor microenvironment on these combination vaccine regimens, we are exploring integrating anti-angiogenic therapy and immune checkpoint blockade with CY-modulation. These studies should lend insight into mechanisms of local and systemic tumor immunity operative in breast cancer patients, and how best to strategically toggle them to maximize immune responses for breast tumor rejection.

Dr. Dean W. Felsher is an Associate Professor of Medicine and Pathology and currently is the Director of the Translational and Applied Medicine Program at Stanford University. During his career, spanning more than 20 years, his experience working with experimental transgenic mouse models has pioneered the utilization of the Tet System to generate conditional transgenic mouse models to study the general concepts of the reversibility of cancer, oncogene addiction and tumor maintenance. His work has most recently suggested an essential role for immune effectors in the mechanism of oncogene addiction.

Oncogene Inactivation and CD4+ T-cells

Cancers are largely caused by the activation of oncogenes. We have developed a unique experimental system to model and predict the therapeutic efficacy of targeted therapy of oncogenes. Using the Tet system, we can conditionally regulate oncogene expression *in vivo* in a temporally controlled and tissue specific manner. We have shown that many oncogenes (MYC, RAS, BCR-ABL) induce tumorigenesis that is completely reversible upon their inactivation. We have described this phenomenon as oncogene addiction. Oncogene addiction is associated with proliferative arrest, apoptosis, differentiation, cellular senescence and the shut down of angiogenesis.

The specific consequences of oncogene inactivation depend both on the genetic and cellular context. In some cases, even brief inactivation of an oncogene can result in sustained tumor regression. In other cases, oncogene inactivation is associated with tumor dormancy. Tumor cell intrinsic and host-dependent cell autonomous mechanisms are involved. Tumor cell intrinsic mechanisms appear to involve mechanisms that are dependent upon DNA repair processes, the regulation of protein synthesis and of cellular metabolism. Host-dependent mechanisms include the regulation of angiogenesis and immune cell elimination. In addition, tumor cells secrete autocrine factors critical to oncogene addiction.

We have uncovered that oncogene addiction is not cell autonomous and requires an intact host immune system. CD4+ T cells are required for MYC or BCR-ABL inactivation to induce sustained tumor regression. In the absence of an immune system, oncogene inactivation failed to both induce cellular senescence in tumor cells as well as to shut down angiogenesis. We have identified several secreted cytokines that appear to be associated with the ability of oncogene inactivation to elicit oncogene addiction. We have shown that TSP-1 expression in lymphocytes is required for oncogene inactivation to elicit oncogene addiction. Our results illustrate that for targeted oncogene inactivation to be therapeutically effective it is essential to have an intact immune system and we have identified CD4+ T-cells as a critical component.

Dr. Bernard A. Fox earned his PhD from Wayne State University, Detroit, Michigan in 1985. His postgraduate training was with Dr. Steven A. Rosenberg, NCI, NIH. Prior to coming to Portland, he was on the faculty at the University of Michigan Medical School. Since 1994, he has been the Chief of the Laboratory of Molecular and Tumor Immunology at the Robert W. Franz Cancer Research Center, Earle A. Chiles Research Institute, Providence Cancer Center, Providence Portland Medical Center, Portland, Oregon. He is an Associate Professor, Molecular Microbiology and Immunology, Oregon Health and Science University and co-leader of the Tumor Immunology Focus Panel for the Knight Cancer Institute. Dr. Fox's research efforts are divided between preclinical animal models, the development, performance and monitoring of immunotherapy trials for patients with cancer and the training of the next generation of translational investigators. He is currently involved with translational immunotherapy trials for patients with melanoma, prostate, breast and non-small cell lung cancer. He has served as a member of review committees and/or advisory boards for the NCI, NIH, FDA, universities, philanthropic and governmental organizations in North America, Europe and Asia, is on the editorial boards of seven scientific journals, lectures widely, and consults for the biotechnology/pharma sector. Dr. Fox is the Immediate Past President of the Society for Immunotherapy of Cancer (SITC) and is a co-founder of UbiVac, a biotech with novel vaccine technologies.

A Strategic View of the Immunoscore

Validation of immunoscore as a prognostic biomarker in colon cancer will provide both opportunities and challenges. At the same time, it will help refine a central question in tumor immunology: How do you induce a therapeutic anti-cancer immune response in a patient who has cancer? One interpretation of existing data is that current approaches have been ineffective at accomplishing this task in patients that lack a pre-existent anti-cancer immune response. What does this tell us about our current approaches? Are immunoscore negative patients examples of immunoediting where the immune cells have disappeared or has the immune system effectively ignored the cancer? Are any therapies effective in immunoscore negative patients? If so, why? Is there an immune component in immunoscore negative patients who respond to treatment? How does immune suppression impact immunoscore and patient response?

Over the next year or two, we should begin to appreciate whether any of the next generation cancer immunotherapies have efficacy in immunoscore negative patients. While a possibility exists that they will do so, the significant but still relatively low objective response rates (<50%) of these therapies suggest that they, at least as single agents, may not effectively reverse the impact of a negative immunoscore. These points outline a major challenge for the next decade. From my perspective, inhibiting checkpoints and providing costimulation, while providing critical elements to the anti-cancer immune response, will not be sufficient to provide therapeutic effects to a majority of patients. Success will require a better understanding of T cell priming, regulation and suppression as well as the appreciation that a limited T cell receptor repertoire may contribute to the challenge.

Dmitry I. Gabrilovich is Robert Rothman Endowed Chair and Head of the Section of Dendritic Cell Biology, H. Lee Moffitt Cancer Center and a Professor of Oncologic Sciences and Molecular Medicine, University of South Florida. His lab is studying molecular mechanisms regulating myeloid cell differentiation, function of immune system in cancer and cancer immune therapeutics. Dr. Gabrilovich investigates the role of myeloid derived suppressor cells in immune suppression and molecular mechanisms of DC differentiation and function in cancer.

Manipulating MDSC to Promote Regression

Myeloid-derived suppressor cells (MDSC) are a major factor responsible for tumor escape. These cells accumulate in large numbers in tumor-bearing hosts, where there is a constant influx of myeloid cells from the bone marrow to other peripheral organs. Soluble growth factors and certain cytokines produced by tumor cells modulate, expand and differentiate these immature myeloid cells by interacting with the receptors on their surface and converting them to a suppressive phenotype. Recently, "two-signal" model of MDSC accumulation was proposed, suggesting accumulation of MDSC can be separated into two processes governed by different signal transduction pathways. The first process is predominantly responsible for MDSC expansion, and it is induced by various cytokines and growth factors produced by tumors or bone marrow stroma in response to chronic stimulation. It involves such factors as GM-CSF, M-CSF, G-CSF, IL-6, VEGF, etc and signals primarily via STAT3 and STAT5. This signaling prevents differentiation of MDSC and promotes proliferation of immature myeloid cells. However, MDSC require a second activating signal, responsible for driving MDSC activation, which manifests in up-regulation of arginase, NO, production of immune suppressive cytokines, etc. This type of signaling is provided by pro-inflammatory molecules such as IFN γ , IL-1 β , IL-13, TLR ligands, etc. It utilizes the STAT1 and NF- κ B transcription factors, and Cox2 upregulation. The validity and practical utility of this concept is currently being tested.

Therapeutic targeting of MDSC is based on current knowledge of the mechanisms responsible for their accumulation and function and include differentiation agents all-trans retinoic acid (ATRA) and vitamin D₃; elimination of MDSC using chemotherapy; inhibition of MDSC expansion using tyrosine kinase inhibitor sunitinib; elimination of MDSC using COX-2 inhibitors; inhibition of MDSC function by phosphodiesterase-5 inhibitor sildanefil; inhibition of MDSC function by triterpenoids - methyl ester of 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO-Me).

In a clinical trial of patients with extensive stage small cell lung cancer (SCLC), we tested the possibility that targeting MDSC can improve the effect of cancer vaccine. Forty-one patients with extensive stage SCLC were randomized into three arms: arm A - control, arm B - vaccination with dendritic cells transduced with wild-type p53, and arm C - vaccination in combination with MDSC targeted therapy with all-trans retinoic acid (ATRA). Pre-treatment levels of MDSC populations in patients from all three arms were similar. Vaccine alone did not affect the proportion of MDSC, whereas in patients treated with ATRA the MDSC decreased more than two-fold ($p=0.02$). Before start of the treatment, no patients had detectable p53 specific response in IFN- γ ELISPOT. Sequential measurements did not show positive p53 responses in any of the 14 patients from arm A. After immunization, only 3 out of 15 patients (20%) from arm B developed p53-specific response ($p=0.22$ from control). In contrast, in arm C, 5 out of 12 patients (41.7%) had detectable p53 response ($p=0.012$). The proportion of granzyme B positive CD8⁺ T cells was increased only in patients from arm C but not from arm B. Thus, depletion of MDSC substantially improved the immune response to vaccination suggesting that this approach can be used to enhance the effect of immune interventions in cancer.

Dr. Gajewski directs an immunology research laboratory, oversees the melanoma oncology clinic and is the Leader of the Immunology and Cancer Program at the University of Chicago Comprehensive Cancer Center. Dr. Gajewski received his MD and his PhD in Immunology from the University of Chicago. He undertook postdoctoral studies on T cell activation and anti-tumor immunity at the University of Chicago and at the Ludwig Institute for Cancer Research in Belgium. He also did a clinical fellowship in Hematology/Oncology at the University of Chicago Department of Medicine before joining the faculty in 1997. His research interests include the molecular and cellular regulation of T lymphocyte activation and differentiation, and the application of this information to preclinical and clinical efforts to promote anti-tumor immunity in vivo.

Dr. Gajewski has published more than 120 papers in peer-reviewed journals on aspects of T cell biology, anti-tumor immunity, and melanoma therapy. He is on the editorial board of *Cancer Research* and other journals, has served on numerous NIH grant review committees, is an elected member of ASCI and the Henry Kunkel Society, has served on programming committees for ASCO and AACR and is the current President of the Society for Immunotherapy of Cancer.

Innate and Adaptive Immunity Regulated Within the Tumor Microenvironment

Even the most potent immunotherapy approaches for melanoma induce clinical activity as measured by tumor shrinkage in only a subset of patients. This observation has prompted careful analysis of the tumor microenvironment to probe for biologic correlates to clinical response and also to identify mechanisms of tumor resistance. Two major categories of melanoma metastases have been observed. One subgroup of patients has an inflamed phenotype that includes expression of chemokines, T cell markers, and other immunoregulatory factors. Clinical responders to melanoma immunotherapies appear to fall within this subset. This group also contains the highest expression of negative regulatory factors, including PD-L1, IDO, and FoxP3, and has T cells showing an anergic phenotype, suggesting that these immune suppressive mechanisms may dominantly inhibit anti-tumor T cell function in those patients. Preclinical experiments have confirmed a critical role for all 4 of these mechanisms in limiting anti-tumor T cell efficacy in vivo, giving candidate treatment strategies for translation back into the clinic. These include IDO inhibitors, anti-PD-1 mAbs, and approaches to deplete CD25+ Tregs or promote anergy reversal through homeostatic proliferation. A second major subset of patients is represented by tumors which are non-inflamed and lack chemokines for T cell recruitment. Therefore, a major barrier in these cases appears to be failed T cell migration into tumor sites. Experimental strategies to augment promote local tumor inflammation and trigger T cell migration can have important anti-tumor effects in preclinical models. The presence of the “inflamed” gene signature was associated with a type I IFN transcriptional profile, and murine experimental models have confirmed a critical role for type I IFN signaling in mediating innate immune “sensing” of a growing tumor in vivo and promotion of adaptive immunity. Intratumoral type I IFNs also can have a powerful therapeutic effect. Our results confirm that molecular profiling of melanoma metastases may be useful as a predictive biomarker for response to melanoma vaccines. Specific features identified in defined subsets of patients offer new therapeutic strategies based on overcoming resistance mechanisms. Understanding the molecular mechanisms that underlie these two distinct phenotypes should receive a high level of attention.

Dr. Jérôme Galon is Research Director at INSERM (National Institute of Health and Medical Research) and leads an INSERM laboratory (Integrative Cancer Immunology) at the Cordeliers Research Center in Paris, France. He was trained as an immunologist at the Pasteur Institute and at the Curie Institute (Paris, France). Between 1997 and 2001, he worked at the NIH (National Institute of Health, Bethesda, MD) on functional genomics, bioinformatics and immunology on fundamental and clinical research. In 1999, he received the fellow Award for Research Excellence at NIH (USA).

Recruited at INSERM, Dr. Galon directed an interdisciplinary research team between 2001 and 2006. Work from his laboratory on comprehensive analysis of the tumor-microenvironment and bioinformatics demonstrated that the adaptive immune reaction within the tumor was a better predictor of survival than traditional staging, based on the cancer's size and spread. In 2007, he became Research Director at INSERM, and the head of the INSERM Integrative Cancer Immunology laboratory (Paris, France).

Dr. Galon was awarded for his work on cancer research by the French foundation (Schaeverbeke Award, 2008) and by the Medical Research Foundation (Rose Lamarca Award, 2008). He received the prestigious William B. Coley Award for Distinguished Research in Basic and Tumor Immunology (Cancer Research Institute, New York, NY, 2010), an award from the National Academy of Science (Simone et Cino del Duca Cancer Research Award, 2011) and an award from the National Academy of Medicine (Gallet et Breton Award, 2011).

Integrative Cancer Immunology: Importance of T Cells

To date, the anatomic extent of tumor (TNM classifications) has been by far the most important factors to predict the prognosis of cancer patients. However, this classification provides limited prognostic information in estimating the outcome in cancer and does not predict response to therapy. Using large-scale approaches and quantitative measurements, we evaluated the importance of the host-immune response. We showed that tumors from human colorectal cancer with a high density of infiltrating memory and effector memory T-cells (TEM) are less likely to disseminate to lymphovascular and perineural structures and to regional lymph nodes. We showed that the combination of immune parameters associating the nature, density, functional orientation and location of immune cells within the tumor was essential to accurately define the impact of the local host immune reaction on patients' prognosis. We proposed to define these immune criteria as "immune contexture." A routine evaluation of the immune-cell density and location within the tumor was performed.

Such quantification of the intratumor immune reaction was defined as the "Immunoscore." Analysis of whole cancer slide section in a routine manner demonstrated the feasibility of the Immunoscore to evaluate the prognosis of cancer patients. The Immunoscore had a prognostic value that was superior of those of the TNM classifications. Tumor invasion parameters were statistically dependent on the host-immune reaction.

The Immunoscore: A Proposal for a New Classification of Cancer in the Era of Immunotherapies

An ongoing worldwide Immunoscore validation task force, created in order to propose an international standardized assay to routinely measure the immune status of a cancer patient, will be discussed.

Dr. Khleif earned his MD from the University of Jordan in Amman, Jordan. He completed his residency in Internal Medicine at the Medical College of Ohio and his fellowship in Medical Oncology at the National Cancer Institute in Bethesda, Maryland. Until recently, Dr. Khleif served as the Chief of Cancer Vaccine Section at the National Cancer Institute, National Institutes of Health and a Professor of Medicine at the Uniformed Services University for Health Sciences (USUHS), in Bethesda, Maryland. In February 2012, Dr. Khleif was appointed the Director of the Georgia Health Sciences University Cancer Centre and a Professor of Medicine.

Dr. Khleif's research program focuses on the development of novel immune therapeutics and vaccines against cancer. Dr. Khleif's team pioneered some of the early cancer vaccine clinical trials directed against specific genetic changes in cancer cells and currently works on understanding the mechanisms of the inhibitory arm of the immune system and developing strategies to suppress such mechanisms to enhance therapy against cancer. Dr. Khleif's lab is working on identifying novel regulation pathways of the T regulatory cells and co-inhibitory molecules such as PD1 and developed novel strategies to manipulate such pathways and selectively inhibit these cells and suppressive mechanisms. Furthermore, his group works on developing novel targets for immune therapy including tumor anti-angiogenesis vaccines and vaccines against novel human papilloma virus (HPV); and developing of strategies to enhance the role of the immune system as a forth modality to treat cancer.

During his tenure at the NCI, Dr. Khleif served as a Special Assistant to the FDA Commissioner from 2006-2009, led the FDA Critical Path for Oncology, was appointed by the US Secretary of the Department of the Health and Human Services as the Director General and Chief Executive Officer of the King Hussein Institute for Biotechnology and Cancer 2006-2009 and served as the Chief Executive Officer and the Director General of the King Hussein Cancer Centre in Amman from 2002-2006. Under his tenure, the centre was transformed into an internationally recognized, comprehensive cancer center of excellence.

Dr. Khleif also serves as a medical oncology and opinion leader on many international committees, working groups and expert panels in the U.S. He is the author of many book chapters and scientific articles and is the editor of a textbook on tumor immunology and cancer vaccines. He has organized and chaired many national and international scientific conferences and has been a visiting professor and an invited speaker in many prestigious scientific conferences and academic institutions. He has received numerous awards including: induction into the American Society for Clinical Investigation, the National Cancer Institute's Director Golden Star Award, the National Institutes of Health Award for Merit, Lifetime Achievement Award by General Union of Physician in the Arab World for seminal contribution to medicine in the Arab World, the Jordan Minister of Health Honorary Plaque, the Commendation Medal of the U.S. Public Health Service and the Career Development Award presented by the American Society for Clinical Oncology.

Microenvironment Immunogenetics Biomarkers in Combination Immunotherapy

Immune correction of the suppressive tumor microenvironment is thought to be a feasible strategy that could result in better anti-tumor effects of immunotherapy. To date, we and many other groups are investigating the strategies to target Tumor-Immune Modulating Network (TIMN) in both preclinical and clinical settings. We have demonstrated that combination of simultaneous targeting of effector and suppressor arms of immunity is a very promising approach. We believe that investigation of underlying mechanism and cross-talk between different compounds within combinational treatment is crucial in order to improve the overall efficacy of treatment. Another important approach for successful immunotherapy is the identification of appropriate prognostic and predictive biomarkers that will allow delivering the most suitable drugs to patients and avoiding ineffective treatments.

Using mouse tumor models and multi-compound combinational treatment, we developed a strategy that allows us to evaluate genetic changes within tumor microenvironment at different time-points. We found over 200 genes that were specific to combinational treatment with at least 3 fold expression changes compared to all control groups. Analysis of the correlations between tumor microenvironment gene profiles, tumor-infiltrated immune cell profiles and therapeutic efficacy of treatment revealed a strong correlation between numbers of specific subsets of infiltrated cells and changes in cell-specific gene expressions. In addition, we detected several genes with significantly increased or decreased expression when responders versus non-responders were compared within the same group, as well as when different time-point biopsies within a group were analyzed.

Using this approach we were able to: i) compare the expression of thousands of genes in tumors from mice after different treatments to understand the interactions and synergy between different compounds of combinational treatment; ii) follow-up on gene expressions within the same treatment groups at different time-points, to understand changes in gene expressions at different stages of tumor development and growth; and iii) compare the tumor microenvironment genetic profiles after similar treatment between responder versus non-responder groups to identify the biomarkers responsible for the efficacy. We believe this approach is a feasible tool for identification of novel immunogenetic biomarkers within the tumor microenvironment and for better understanding of mechanisms of interactions between compounds within combinational treatment in order to develop novel targets for improvement of the efficacy of immunotherapy.

Dr. Kleen is currently the Executive Vice President of Immune Monitoring at Epiontis GmbH, Germany. Prior, he held the position of Director of Business and Technology Development and the function of Director, Assay Development and R&D at CTL, USA. Dr. Kleen is member of the iSBTC/SITC Biomarker Task Force since 2009 and served on the iSBTC/SITC Development Committee (2008 – 2011). He earned his Doctorate 2004 in Biology with specialization in Immunology and Virology from the Bayerische Julius-Maximilians-University, Würzburg, Bavaria, Germany. During his PhD studies at Case Western Reserve University in Cleveland, Ohio, he investigated conditions of the human immune system in patients with HIV and conducted research on umbilical cord blood stem cell transplantation for adult patients with life-threatening hematological disorders and malignancies.

Epigenetic Immune Cell Markers – Enabling Novel Clinical Trials with Robust Results from Frozen Whole Blood or Tissue

Immune monitoring during clinical trials for Immunotherapeutics and vaccines is becoming essential. The changes in the immune system are routinely described by cell counts and ratios of different leukocyte subpopulations. Flow cytometry in peripheral blood and immunohistochemistry (IHC) in solid tissues are current gold standard methods, but have a limited ability for exact cell quantification either due to arbitrary/subjective gating protocols for FACS or a lack of precision for IHC. In addition, based on complicated assay steps and many non-standardized reagents, it often has not been feasible to carry such technologies through larger pre-clinical or clinical trials. The assay specific stability of blood samples is a big hurdle in particular when involving sample collection from multiple clinical sites. For regulatory T cells (Tregs), additional problems are manifested due to lack of specificity of Treg identifying proteins (CD25, FoxP3). Both proteins are synthesized also in activated effector T-cells, leading to detection of mixed cell populations.

The discovery of cell type specific epigenetic markers allows precise and robust quantitation of immune cells in all human samples. The tests are based on quantitative PCR targeting genomic DNA. Therefore, readout is stable and samples can be frozen and easily shipped. This allows monitoring of patients in multicenter studies, retrospective studies, comparison of results between different studies and routine monitoring.

Application of epigenetic assays for Tregs, overall T-cell population, NK cells and further subpopulations will be presented in cancer and immune disease patients. The results reveal the same trends as measurements with alternative methods, while showing higher precision. Furthermore, the tests can be applied on both blood and tissue allowing measurements of circulating and tissue-infiltrating immune cells.

Alessandro Lugli is a graduate from the University of Zürich, Switzerland where he received his medical degree in 1996. After two years of residency in Internal Medicine at the Cantonal Hospital of Baden, Switzerland, he began his Pathology residency in 1999 at the Institute of Pathology, Triemli City Hospital in Zürich and after one year joined the Institute of Pathology at the University Hospital of Basel. In 2004, he was promoted to the position of Attending Pathologist and in 2005, he worked as a research fellow in Professor Jeremy Jass' lab where he focused on the pathogenesis of colorectal cancer, molecular aspects and biomarkers. In 2006, he returned to the University of Basel where in 2008 he was promoted to the position of Associate Professor. Since 2011, he heads the Clinical Pathology Division at the Institute of Pathology, University of Bern, Switzerland and is responsible for the Gastrointestinal Pathology Unit. His main research focus includes Epithelial Mesenchymal Transition (EMT) and the tumor microenvironment, molecular and pathogenetic aspects of colorectal cancer as well as prognostic and predictive biomarkers.

The Impact of Immune Cell Infiltration on Patient Prognosis

The TNM staging system proposed by the UICC/AJCC is still the gold standard for stratifying colorectal cancer (CRC) patients into prognostic subgroups. Nevertheless, there is evidence that a subgroup of stage II CRC patients has a similar outcome as stage III patients, although an adjuvant therapy is normally applied only in the latter. Consequently, many prognostic biomarkers have been proposed over the last years to improve the prognostic stratification of CRC patients, but none of these have successfully been integrated into daily diagnostic practice, mainly due to the lack of reproducibility, standardized scoring systems and acceptable intra- and inter-observer variability. This inundation of biomarker studies in the CRC medical literature has led to the publication of the REMARK Guidelines, which try to improve the design of proposed prognostic biomarkers studies.

In the last years, the epithelial-mesenchymal transition (EMT) and the tumor micro-environment seem to reflect an optimal "battlefield" in terms of prognosis, as they include tumor related and host-related prognostic factors as well. Indeed, very promising host-related factors include biomarkers CD45RO, CD3 and CD8 that define an immune-score proposed by Galon, Pagès et al. Our own research group has published single and multi-marker studies and made the observation that in all studies, the lack (or low number) of CD8 positive lymphocytes has an adverse effect, independently of the clinical endpoint (local recurrence, overall survival) and the tumor location (colon and rectal cancer). This observation was additionally confirmed by a recent study in which the combination of TIA-1 and CD8 seems to play a strong prognostic role. We also introduced a "defender-attacker model" with the aim of defining a simple and reproducible prognostic scoring system taking into consideration both tumor-related and host-related factors. Indeed, the use of CD8 and/or CD68 and FOXP3 positive cells in combination with tumor budding seems to improve the prognostic impact of CRC patients when compared to the single biomarkers used in other studies. It has to be stated that the standardization of scoring systems is a big challenge, which can only be resolved by an interdisciplinary task force performing multi-center studies with large sample size.

Dr. Marincola is the Chief of the Infectious Disease and Immunogenetics Section (IDIS), Department of Transfusion Medicine, Clinical Center and Associate Director, trans-NIH Center for Human Immunology (CHI), National Institutes of Health, Bethesda, Maryland. He is also the Director of the Federation of Clinician Immunology Societies (FOCIS) Center for Excellence (FCE) at the NIH and the Greater Washington Area. Dr. Marincola is a NIH tenured senior investigator. Dr. Marincola received his MD, summa cum laude, from the University of Milan and his surgery training at Stanford University, where he also completed a postdoctoral fellowship in Surgical Research. He joined the Surgical Oncology Branch of the National Cancer Institute, NIH, in 1990.

Dr. Marincola is an author of about 500 peer reviewed research articles and over 100 abstracts. He has been invited to speak at over 300 national and international meetings. Dr. Marincola is the second most cited scientist in melanoma during the last ten years, with 55 papers cited 3,704 times to date. Dr. Marincola is Adjunct Professor at Peking Union Medical College, Beijing, China, First Military Medical University, Tonghe, Guangzhou – China, Shenzhen Institute of Xiangxua Biomedicine, Shenzhen, China and Universidad del Rosario, Bogota, Colombia. He is the incoming President of the Society for the Immunotherapy of Cancer and President Elect of the International Society for Translational Medicine. Dr. Marincola serves at the Editor-in-Chief of *Journal of Translational Medicine*; Co-Editor-in-Chief of *Clinical and Translational Medicine*; US Senior Editor of *Immunotherapy*, Associate Editor for *The Journal of Immunotherapy*, *Tumori*, and *Clinical Cancer Research*; Section Editor for *Expert Opinion in Biological Therapy*; Editorial Board, *Cancer Immunology & Immunotherapy*, *Journal of Experimental and Clinical Cancer Research*.

Exploring Immune-mediated Tumor Destruction in Humans

A cancer immune signature implicating good prognosis and responsiveness to immunotherapy was described that is observed also in other aspects of immune-mediated, tissue-specific destruction (TSD). Its determinism remains, however, elusive. On one side it appears that the genetic background of the host bears significantly on immune responsiveness, on the other it appears that tumor can behave differently within the same genetic background. This apparent paradox can only be explained by a multi-factorial model of cancer immune responsiveness. It could be postulated that some patients carry a genetic background that makes them resistant to immunotherapy by effecting either the biology of the immune response, the biology of the cancer cells, or both. On the other hand, “an immune-responsive genotype” may still be limited by the genetics of the tumors: in other words, although the patient may be predisposed to cancer rejection, the tumor lacks additional properties necessary for its recognition by the immune response. In this model, a favorable genetic background of the host is necessary but not sufficient for tumor rejection.

David H. Munn, MD, is a Pediatric Hematologist-Oncologist at the Medical College of Georgia, Georgia Health Sciences University. His research focus is on tumor immunology and molecular mechanisms of immune suppression and tolerance. Dr. Munn's laboratory studies the regulation of T cell activation by tolerogenic dendritic cells and regulatory T cells (Tregs) in the setting of cancer. A major focus of the laboratory is the immunoregulatory role of tryptophan metabolism via the enzyme indoleamine 2,3-dioxygenase (IDO). Active projects include preclinical/basic-science studies of the role of IDO-expressing plasmacytoid dendritic cells in tumor immunology; regulation of Treg suppressor activity and functional Treg reprogramming by IDO-expressing APCs; and clinical/translational strategies to enhance anti-tumor immune responses using IDO-inhibitor drugs. Dr. Munn's research is supported by the National Cancer Institute and charitable foundations in pediatric oncology.

Immune Suppression by Stromal Cells

Suppressive stromal cells in tumors can include tolerogenic DCs, myeloid-derived suppressor cells, tumor-associated Mφs and dysfunctional endothelial cells. Relevant molecular mechanisms include expression of PD-ligands and other factors that are discussed elsewhere; the current presentation will focus on immunoregulatory metabolic pathways mediated by indoleamine 2,3-dioxygenase (IDO) and Arginase-I (Arg-I). These enzymes can be expressed by stromal cells (DCs and Mφs) in tumors, and IDO is also found in many tumor-draining LNs. IDO and Arg-I can create local depletion of amino acids (tryptophan and arginine) with consequent activate the GCN2 stress-kinase pathway. This can result in direct suppression/anergy of effector T cells, and (with more widespread systemic consequences) potent activation of Tregs in tumor and draining LNs. Amino acid deprivation can also affect the nutrient-sensitive mTOR pathway. IDO produces downstream kynurenine-pathway metabolites that bind to the aryl hydrocarbon receptor (AhR), which can act as both an immunosuppressant (by activating Tregs) and in some cases as a possible growth factor for tumors. In certain tumors, a third enzyme, tryptophan dioxygenase (TDO), may mediate analogous effects via kynurenine production. Thus, cells in tumor stroma can express multiple "metabolic" regulatory pathways that inhibit local immune activation and contribute to tumor-induced immunosuppression.

Dr. Pardoll is an Abeloff Professor of Oncology, Medicine, Pathology and Molecular Biology and Genetics at the Johns Hopkins University School of Medicine. He is Director of the Cancer Immunology Program in the Sidney Kimmel Comprehensive Cancer Center. Over the past two decades, Dr. Pardoll has studied molecular aspects of immune regulation, particularly related to mechanisms by which cancer cells evade elimination by the immune system.

Immune Checkpoint Modulation and the Tumor Microenvironment

Regulation of responses involves counterbalancing stimulatory and inhibitory signals. Many of these signals are only operative in lymphocytes when their antigen receptor is engaged – these are called co-stimulatory and co-inhibitory signals, respectively. While some inhibitory receptors, such as CTLA-4, regulate the initial stages of T cell activation, others, such as PD-1, play a major role in down-modulation of effector responses in tissues and also in tumors, where its ligands are up-regulated. Blockade of both of these receptors results in enhanced anti-tumor responses via very different mechanisms. It is now clear that multiple co-stimulatory and co-inhibitory receptors work are co-expressed and work in concert. We have demonstrated that LAG-3 is co-expressed together with PD-1 on a subset of intra-tumoral lymphocytes and works together with PD-1 in blocking anti-tumor responses and in maintaining self-tolerance. Double knockout or antibody blockade of PD-1 and LAG-3 enhance anti-tumor immunity significantly. This represents an example of combinatorial therapeutic approaches that block multiple inhibitory pathways in the immune microenvironment.

Dr. Restifo, a 1983 honors graduate from Johns Hopkins University, obtained his MD in 1987 from New York University. He did postdoctoral training at the Memorial Sloan-Kettering Cancer Center and the NCI before becoming a principal investigator in 1993. He has authored or co-authored more than 250 papers and book chapters on cancer immunotherapy, and his published work has received more than 20,000 citations.

The goal of his scientific work remains to design curative immunotherapies for patients with advanced cancer. His focus has been on the iterative development of novel cancer immunotherapies through a deeper understanding of inter-relationships that transformed cells have with host immune cells and with stromal cells. He has made contributions to our understanding of immune escape by tumor cells through modulation of host myeloid cells. He has also studied how tumors subvert the cellular machinery that enables antigen processing. He has spent many years studying recombinant and synthetic vaccines used alone or in combination with adoptively transferred T cells. His most recent work has focused on exploring the qualities of highly effective anti-tumor T cells in both mice and humans and on how tumor conditions can be manipulated to enable anti-tumor T cells to reach their full therapeutic potential.

He has actively participated in the Society for Immunotherapy of Cancer since attending his first meeting at Williamsburg, VA in 1993. He has since been involved in the training and mentoring of many current members, including Drs. Vincenzo Bronte and Willem Overwijk, both major participants in recent meetings, and Drs. Steven Finkelstein and Luca Gattinoni, both of whom won the Presidential Award for the best abstract at the Annual Meeting. He has been a contributing author to the *Journal of Translational Medicine* and has served as an Associate Editor at the *Journal of Immunotherapy* for more than a decade.

Immunity in Cancer Growth and Progression

Established tumors are complex masses that contain not only neoplastic cells but also nontransformed cellular elements such as neovasculature, stromal cells, and the full gamut of immune cells. However, unlike cells found in healthy lymphoid organs productively responding to acute infections, immune cells in tumors are dysregulated and functionally impaired.

The tumor immune microenvironment is demonstrably 'corrupted' and rife with regulatory lymphocytes, myeloid-derived suppressor cells and alternatively activated DCs and macrophages. T cells entering this environment are bathed in immunosuppressive cytokines and are exhausted by their encounter with chronic antigenic stimulation.

Ablation or reprogramming of this aberrant microenvironment can dramatically augment cancer therapies, and T cells can be rehabilitated by removing them transiently from this suppressive environment. A better understanding of the mechanisms involved in immune evasion has enabled the deployment of new cell-based immunotherapies that can be curative for patients with metastatic cancer.

Antoni Ribas, MD, PhD is a Professor of Medicine, Surgery and Molecular and Medical Pharmacology at the University of California, Los Angeles (UCLA). He trained at the University of Barcelona, Spain, with postdoctoral research and clinical fellowship at UCLA. He is the Director of the Tumor Immunology Program at the Jonsson Comprehensive Cancer Center (JCCC) and the Chair of the Melanoma Committee at SWOG. Dr. Ribas is also a permanent committee member of the National Cancer Institute (NCI) grant review panels and an elected member of the American Society of Clinical Investigation (ASCI). As a physician-scientist, Dr. Ribas conducts laboratory and clinical research in malignant melanoma, focusing on adoptive cell transfer with T cell receptor (TCR) engineered lymphocytes, anti-CTLA4 antibodies, BRAF-targeted therapies and nanoparticle-siRNA. Dr. Ribas also serves on the SITC Board of Directors.

Clinical Trials: Provoking Immunity in the Tumor Microenvironment

The ultimate goal of tumor immunotherapy is achieving an intratumoral infiltration of effector immune cells that have ability to kill cancer cells. This final step in an effective antitumor immune response is limited by the hostile tumor microenvironment. Several approaches being tested in the clinic are being effective in inducing intratumoral infiltration by activated T cells, leading to improved success in patients. Immune modulating antibodies such as blocking antibodies to CTLA4 or PD-1, and activating antibodies to CD137, result in intratumoral infiltration by T lymphocytes in preclinical models. Similarly, releasing CTLA4 and PD-1 blockade with monoclonal antibodies increases intratumoral infiltration by activated T cells in humans. There is a lot of interest to combine these active immunotherapies with other therapies that could efficiently modify the tumor microenvironment and improve antitumor responses. Direct inhibition of immune suppressive cells or proteins, such as Treg, IDO and others are being tested in combination with ipilimumab. Also, inhibition of driver oncogene signaling in cancer cells can alter the tumor microenvironment and potentially make it more permissive to T cell infiltration. These combinatorial approaches may improve the antitumor activity of tumor immunotherapy strategies.

Brian I. Rini, MD, FACP is a Professor of Medicine at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University in Cleveland, Ohio. A staff member of the Department of Solid Tumor Oncology and Co-Leader of the Genitourinary Program of the CASE Comprehensive Cancer Center, Dr. Rini's work focuses on genitourinary malignancies. Dr. Rini earned his medical degree at the Ohio State University College of Medicine. Dr. Rini completed a residency program in Internal Medicine and a fellowship in Hematology / Oncology at University of Chicago Hospitals. Dr. Rini was an Assistant Professor at the University of California, San Francisco before moving to The Cleveland Clinic.

Dr. Rini's primary research has been in renal cell carcinoma (RCC) and prostate cancer, with special focus on antiangiogenic therapy and immunotherapy. Dr. Rini has been involved in the initial and ongoing development of targeted agents for metastatic RCC and was an integral investigator in the clinical development of several agents, which are now FDA approved. Dr. Rini was the Principal Investigator of an international phase III cooperative group trial of bevacizumab plus interferon and the PI of the phase III axitinib trial in metastatic RCC that lead to FDA approval and is currently the PI of several global phase III trials in RCC.

Dr. Rini's research has been published in peer-reviewed journals that include *Journal of the National Cancer Institute*, *Journal of Clinical Oncology*, *Cancer*, *Lancet* and *JAMA*. He is a member of the editorial boards of *Journal of Clinical Oncology* and Co-Chair of the NCI RCC Task Force.

Sunitinib and Immunity

Select tyrosine kinase inhibitors (TKIs) such as sunitinib that target VEGFR/PDGFR (and other receptors) have demonstrated clinical efficacy in the treatment of metastatic renal cell carcinoma (mRCC). We and others showed that sunitinib can also favorably immunomodulate in the host by reducing the number of myeloid derived suppressor cells (MDSC) and T-regulatory cells as well as partially restoring a T cell IFN γ response. These effects on immune cell populations may be associated with clinical outcome in RCC patients receiving sunitinib. Additional studies are testing the idea that persistence of T cell suppression and angiogenesis in some RCC patients post sunitinib treatment may be related to the persistence of immunosuppressive and angiogenic granulocytic MDSC and neutrophils. The persistence of these myeloid cells may be mediated by RCC tumor products that can activate and prolong their survival. Ongoing clinical trials are now investigating the combination of VEGF-targeted therapy such as sunitinib and immunotherapy to explore additive and/or synergistic clinical benefits.

Dr. Hans Schreiber is a Professor of Pathology in the Cancer Research Center at the University of Chicago, IL. He received his MD and DMSc. from the University of Freiburg and his PhD from the University of Chicago. The main focus of his laboratory is to study the fundamental mechanisms that govern the interaction of cancer cells with the immune system. In particular, they are trying to exploit the fact that cancer cells usually carry cancer-specific mutations and antigens, and that, under certain conditions, the immune system can destroy cancer cells even after they have disseminated in the body. His research has been published in *European Journal of Immunology*, *Journal of Immunology*, and numerous others.

Relapse of Cancer: Stromal Cross-Presentation is Required for the Elimination of Escape Variants

Relapse is the key problem of cancer therapy and our goal is prevent to cancer recurrence. Present failures of clinical immunotherapy may well be due to extrapolating results from irrelevant laboratory models to practice (1-3). Many preclinical studies ignore or neglect relapse by: (i) cutting off experimental tumor growth curves before relapse occurs, (ii) targeting far too few cancer cells (usually the minimum size of a human cancer that is diagnosable is ~1cm and contains about 10^9 cancer cells or 10^6 variants, a conservative estimate considering that cancer cells often have a much higher spontaneous mutation), and (iii) treating cancer cell inocula much too early before true establishment of the stromal tumor microenvironment (e.g., before proper deposition of extracellular matrix (ECM) components that give powerful prosurvival signals to cancer cells).

We find that the requirements for destruction differ from those required eradication, and the time points and sequence of events are also different. For destroying the bulk of even large tumors by adoptive T cell transfer, direct presentation of the target antigen on the cancer cell can be sufficient. However, if there are any T cell-resistant cancer variants in the tumor as is usually the case, cancer will recur unless there is cross-presentation by tumor stroma (4-7). Thus to prevent relapse, it is essential that antigens released from the cancer cells are cross-presented to the T cells by stromal cells. Loading of stromal cells by the cancer cells occurs via microvesicles, microblebs and/or exosomes. Using longitudinal intravital imaging of tumors established for weeks, we observe tumor destruction coincides with early vascular effects while eradication requires an intense and prolonged "sweeping action" occurring days after tumor destruction, i.e., T cells stably engaging with stromal cells to release cytokines. This is essential for the eradication of cancer variants as bystanders.

Dr. Silverstein earned his MD from Albert Einstein College of Medicine in 1963. He was a Medical Intern at the University of Colorado from 1963-1964, a Helen Hay Whitney Fellow in the Laboratory of Cell Biology at the Rockefeller University from 1964-1967, Assistant Resident in Medicine at the Massachusetts General Hospital from 1967-1968, a member of the Laboratory of Cellular, Physiology and Immunology at the Rockefeller University from 1968-1983, the John C. Dalton Professor and Chairman of the Department of Physiology and Cellular Biophysics and Professor of Medicine at the College of Physicians and Surgeons at Columbia University from 1983-2002. Since 2003, he holds the position of Professor of Physiology and of Medicine at Columbia University.

Dr. Silverstein's principal research contributions include the roles of lysosomes in destruction of antibody-neutralized virions, uncoating of viruses containing double-stranded RNA genomes, and asymmetric replication of the genomes of these viruses, the "Zipper" mechanism of phagocytosis, discovery that *Legionella pneumophila* is a facultative intra-cellular pathogen, and development of the critical leukocyte concentration concept. He is founder (1990), and Director of Columbia University's Summer Research Program for Science Teachers. His National Service includes: FASEB President (1994-95), ASCB Councilor (1988-1992), NIAID Councilor (1995-1998), Damon Runyon Cancer Research Fund Board (1990-present). Principal honors include election to membership in the Institute of Medicine (1996), American Academy of Arts and Sciences (2003), Fellowships AAAS (1991), NYAS (2000), and American Academy of Microbiology (1993), National Geographic Society's John Oliver La Gorce Medal for Antarctic Exploration, Albert Einstein College of Medicine's Distinguished Alumnus Award (1987), NY City Mayor's Award, Public Understanding of Science and Technology (2003), ASCB's Bruce Alberts Award, Excellence in Science Education (2005) and honorary member, Phi Beta Kappa, Dartmouth College (2008).

An Experimentally Verified Quantitative Model and In Vitro Methods that Enable Cellular Immunotherapists to Calculate the Concentration of Cytolytically Active Immune Effector Cells Required to Produce Sterilizing Immunity in Neoplastic and Infectious Diseases

A fundamental shortcoming of contemporary cellular immunotherapy of cancer and infectious disease is the lack of a generally applicable, experimentally verified quantitative model that defines the number and quality of immune cells that must be elicited in a patient's blood, or administered to a patient to produce sterilizing immunity. In this presentation, I will describe a mathematical model and methods of in vitro analysis that together enable investigators to measure these parameters. Further, I will show that investigators armed with this information will be able to predict whether the immune effector cells elicited by a given immunization strategy or obtained by ex-vivo growth of autologous leucocytes have the power to produce sterilizing immunity.

The model shows that a critical concentration of cytolytically active tumor- or infectious agent-antigen specific immune cells must be delivered to and maintained in a tumor bed or infected tissue until all tumor cells/infectious agents have been eradicated. The critical concentration can be determined precisely by in vitro measurements of killing of tumor cells and/or infected cells by co-incubation of these cells with host immune cells in three dimensional collagen-fibrin gels, using the equation (Eq.1) $b_t/b_o = e^{-kpt + gt}$ as described by Budhu et al. b_t is the experimentally determined concentration of tumor or infected cells/ml of gel, tumor, or infected tissue remaining after t minutes of co-incubation with immune cells, b_o is the initial concentration of tumor or infected cells, k is the experimentally determined killing constant, p is the concentration of cytolytically active immune effector cells in the population of cells to be used for adoptive transfer or the concentration of these cells in the blood of an immunized patient, and g is the experimentally determined rate of growth of tumor cells or increase in infected cells. The critical cytolytically active effector cell concentration = g/k (Eq. 2), as described by Li et al. The experimentally determined values of b_t , b_o , g and p can be used to calculate values of k , which vary inversely with p , and limiting dilution assays and the Poisson distribution can be used to determine the fraction of cytolytically active, tumor- or infectious agent-specific immune cells in populations of in vivo-elicited or in vitro-expanded immune cells.

Once the relationships between k and p are known, Eqs. 1 and 2 can be used to determine the concentration of cytolytically active immune effector cells that must be maintained in tumors or in infected tissues until all tumor or infected cells have been eliminated. Immunotherapists can use this model and these methods to establish standards by which to characterize and compare different populations of these cells and to predict the likelihood that a given population of immune effector cells will produce sterilizing immunity.

Weiping Zou is a Professor of Surgery, Immunology and Cancer Biology at the University of Michigan. His research interests are in tumor immunopathology and immunotherapy, with an emphasis on the cross-talk among immune cell subsets, stromal cells, tumor cells and tumor stem cells in the tumor microenvironment, and its impact on tumor immunity, tolerance and therapy.

Immune Impact on Cancer Stemness and Metastasis

We have studied the cross-talk between immune cell subsets and tumor/stem cells in the tumor microenvironment and its impact on tumor immunity and therapy. Our prior research efforts demonstrate that the tumor microenvironment is comprised of immune cells that have been reprogrammed by active tumor-mediated processes to defeat tumor-specific immunity and promote tumor growth in a highly effective manner. These studies have helped define the nature of immune responses in the tumor microenvironment, and provide new insights into designing novel immune therapies to target the immune suppressive mechanisms including Tregs and inhibitory B7 family members and treat patients with cancer.

We recently investigated Th17 cells in the tumor microenvironment. Th17 cells phenotypically resemble two terminally differentiated memory T cells, but express polyfunctional cytokine profile, have stem cell property (long-lived, self-renewal and persistence) and mediate anti-tumor immunity. The signaling pathways of hypoxia inducible factor (HIF)1 α , Notch and Bcl-2 control Th17 stemness.

In this talk, we focus on the interaction between tumor cells and host immune system in the cancer microenvironment patients with ovarian cancer. We demonstrate that immune cells can alter cancer stem cell gene expression, sphere formation and cancer metastasis. This is associated with patient outcome. We will further discuss the cellular and molecular mechanisms by which immune cell subsets control cancer stemness and tumorigenesis. We suggest that targeting the interactive network between tumor and immune cells might be a valuable strategy in anti-cancer therapy.



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Journal for ImmunoTherapy of Cancer

ABOUT THE JOURNAL

The Journal for Immunotherapy of Cancer (JITC) is the official journal of the Society for Immunotherapy of Cancer (SITC). It is an open access, online journal created by the Society for the many stakeholders in the tumor immunology and cancer immunotherapy community.

Through the development of our 2012-2015 Strategic Plan, it was clear that there was a need for an outlet and targeted publication platform dedicated to advancing the science of tumor immunology and cancer immunotherapy. The Society is thus responding to the tremendous excitement in the field and the increased momentum brought about by the latest approvals of immunotherapy-based treatments in various cancer types.

FREE SUBMISSION FOR SOCIETY MEMBERS

As a way to say thank you to the dedicated Society members who tirelessly work to advance the science and ultimately to improve the lives of patients with cancer, SITC is pleased to offer Society members waived article processing charges for manuscripts accepted before the end of 2013.

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The Editorial Board is comprised of internationally recognized thought leaders in the field and experts in their content areas. They are also members of SITC and deeply committed to advancing the knowledge about, and integration of, cancer immunotherapy research into the clinical setting.

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Society for Immunotherapy of Cancer

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