FINAL PROGRAM

SOCIETY FOR IMMUNOTHERAPY OF CANCER

26TH ANNUAL MEETING

NOVEMBER 4-6, 2011 • NORTH BETHESDA, MD

sitc

Society for Immunotherapy of Cancer

www.sitcancer.org

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Society for Immunotherapy of Cancer

Message from the President

Dear Colleagues,

Welcome to the SITC 26th Annual Meeting & Associated Programs in North Bethesda, Maryland! This has been an exciting year for the field of cancer immunology and immunotherapy. New fundamental mechanisms regarding the host immune response to tumors have been uncovered. In addition, new clinical successes with adoptive T cell therapy, immune-potentiating monoclonal antibodies, and vaccines have broken new ground. As the spotlight shines on cancer immunotherapy, I look forward to this week and the opportunity to share new ideas, discuss recent advancements, and guide progress within our field.

Since its inception in 1986, the SITC Annual Meeting has been the premier destination for scientific exchange, education and networking among basic researchers, clinicians, students, post-doctoral fellows, and allied health professionals who are dedicated to increasing our knowledge of cancer immunology and improving patient outcomes through immunotherapy. This year I am excited about our program that highlights these areas, through the following formats:

- **Timely Educational Sessions** – Sessions such as Uncoupling Negative Regulation in the Tumor Microenvironment and Prostate Cancer as a Learning Model will provide timely information on what's new and relevant to cancer immunology and immunotherapy. The prostate cancer session is the first of what we hope will be a regular feature focusing on immunotherapy of a specific tumor type each year.
- **Primer on Tumor Immunology** – Our renowned Primer on Tumor Immunology and Cancer Immunotherapy will provide a foundation of information for individuals new to the field or for those requiring a refresher, whether from academic, industry, or government organizations.
- **Innovative Workshops** – The one day Workshop on Immunotherapy Combinations will feature presentations by leaders in the field along with interactive panel discussions on how to approach combination treatment strategies with immunotherapeutics, with the ultimate hope of "raising the tail" on cancer patient survival curves.
- **New Initiatives** – Incorporated into multiple programs will be scientific perspectives from the Cancer Immunotherapy Trials Network (CITN), a new initiative that unites top academic immunologists to conduct prioritized multicenter clinical trials to provide a cohesive forward advancement of the field.
- **Hot Topic Symposium** – Leaders in the field will deliver dynamic presentations and engage in interactive Q&A on the topic "Targeting the Next Generation of Inhibitory Pathways."

As President of SITC, I encourage everyone to take full advantage of the outstanding educational and networking opportunities this year's Annual Meeting has to offer. I would like to thank in advance the faculty who share their knowledge, expertise, and time as well as the program organizers for their hard work and diligence in putting together an exceptional group of sessions. This will be an exciting week filled with innovative science, education, and collaboration in our field and I'm so pleased to be a part of it. Welcome to the SITC 26th Annual Meeting & Associated Programs!

Sincerely,

Thomas F. Gajewski, MD, PhD
SITC President

Meeting at a Glance

TUESDAY, NOVEMBER 1, 2011		
8:20 am – 5:00 pm	Summit on Cell Therapy for Cancer	NIH Campus, Masur Auditorium
WEDNESDAY, NOVEMBER 2, 2011		
8:30 am – 1:00 pm	Summit on Cell Therapy for Cancer	NIH Campus, Masur Auditorium
5:00 pm – 8:00 pm	Registration Open: Primer, Workshop, and Annual Meeting	North Bethesda Marriott Hotel
THURSDAY, NOVEMBER 3, 2011		
6:30 am – 6:00 pm	Registration Open	Main Level, Grand Ballroom Lobby
7:00 am – 8:00 am	Continental Breakfast	Grand Ballroom Foyer
8:00 am – 5:00 pm	Primer on Tumor Immunology and Cancer Immunotherapy	Grand Ballroom G-H
8:00 am – 5:00 pm	Workshop on Immunotherapy Combinations	Grand Ballroom E
FRIDAY, NOVEMBER 4, 2011		
6:30 am – 6:00 pm	Registration Open	Main Level, Grand Ballroom Lobby
7:00 am – 7:45 am	New Member Breakfast Gathering (All new members of SITC welcome to attend)	Lower Level, Brookside Room
7:00 am – 7:50 am	Continental Breakfast	Grand Ballroom A-D
7:50 am – 8:00 am	SITC 26th Annual Meeting Begins/President's Welcome	Grand Ballroom E
8:00 am – 8:45 am	Richard V. Smalley, MD Memorial Lectureship: Ralph M. Steinman, MD	Grand Ballroom E
8:45 am – 11:30 am	Plenary Session: Biology and Application of Dendritic Cells	Grand Ballroom E
10:15 am – 10:45 am	Break	Grand Ballroom A-D
11:30 am – 12:00 pm	Plenary Session: Late Breaking Oral Abstracts	Grand Ballroom E
12:00 pm – 1:30 pm	Lunch/Poster Viewing/Exhibits	Grand Ballroom A-D
1:30 pm – 3:00 pm	Concurrent Session I: Immunology of Cancer Stem Cells and Epithelial-to-Mesenchymal Transition (EMT)	Grand Ballroom E
1:30 pm – 3:00 pm	Concurrent Session II: Uncoupling Negative Regulation in the Tumor Microenvironment	Grand Ballroom G-H
3:00 pm – 3:15 pm	Break	Grand Ballroom A-D
3:15 pm – 5:15 pm	Plenary Session: Genetically Engineered Receptors and Adoptive Cell Therapies	Grand Ballroom E
5:15 pm – 5:45 pm	Cancer Immunotherapy Trials Network (CITN Update)	Grand Ballroom E
5:45 pm – 6:15 pm	SITC Membership Business Meeting	Grand Ballroom E
Immediately following Business Meeting – 8:00 pm	Poster Reception and Exhibits	Grand Ballroom A-D
8:00 pm	Early Career Scientists Networking Event	Lower Level, Brookside Room
SATURDAY, NOVEMBER 5, 2011		
7:00 am – 6:00 pm	Annual Meeting Registration Open	Main Level, Grand Ballroom Lobby
7:00 am – 7:45 am	Early Career Scientists "Meet-the-Expert" Breakfasts	Lower Level, Brookside Room
7:00 am – 8:00 am	Continental Breakfast	Grand Ballroom A-D
8:00 am – 8:45 am	Keynote Address: Katherine Fitzgerald, PhD	Grand Ballroom E
8:45 am – 11:30 am	Plenary Session: Characterization of Inflammatory Infiltrates in Human Cancers	Grand Ballroom E
10:15 am – 10:45 am	Break	Grand Ballroom A-D
11:30 am – 12:00 pm	Plenary Session: Late Breaking Abstracts	Grand Ballroom E
12:00 pm – 1:30 pm	Lunch/ Poster Viewing/Exhibits	Grand Ballroom A-D
1:30 pm – 3:00 pm	Concurrent Session I: State of the Art Animal Models & Veterinary Applications for Cancer and Immunology	Grand Ballroom E
1:30 pm – 3:00 pm	Concurrent Session II: High Throughput Technologies Immune for Monitoring	Grand Ballroom G-H
3:00 pm – 3:30 pm	Break	Grand Ballroom A-D
3:30 pm – 4:50 pm	Plenary Session: SITC Presidential Abstract Session	Grand Ballroom E
4:50 pm – 5:20 pm	Plenary Session: Cancer Immunotherapy Guidelines Update	Grand Ballroom E
5:20 pm – 5:35 pm	Plenary Session: National Cancer Institute, NIH Update	Grand Ballroom E
5:35 pm – 5:50 pm	Plenary Session: FDA Update on Regulatory Issues Related to Cancer Immunotherapy	Grand Ballroom E
5:50 pm – 6:15 pm	Award Presentations	Grand Ballroom E
Immediately following Awards Presentations – 8:00 pm	Presidential Reception with Poster Viewing and Exhibits	Grand Ballroom A-D
8:00 pm	Performance by the band The Checkpoints	Grand Ballroom E
SUNDAY, NOVEMBER 6, 2011		
7:00 am – 8:00 am	Continental Breakfast	Grand Ballroom Foyer
7:30 am – 12:00 pm	Annual Meeting Registration Open	Main Level, Grand Ballroom Lobby
8:00 am – 10:15 am	Plenary Session: Prostate Cancer as a Learning Model	Grand Ballroom E
10:15 am	Annual Meeting Adjourns	
10:25 am – 12:00 pm	Hot Topic Symposium: Targeting the Next Generation of Inhibitory Pathways	Grand Ballroom E

General Meeting Information

PURPOSE

The SITC 26th Annual Meeting provides a multidisciplinary educational environment composed of cutting edge research, oral presentations, scientific poster presentations, and networking opportunities, as well as updates on major national and international initiatives and important Society projects.

TARGET AUDIENCE

The target audience for this program is basic and clinical investigators from academic institutions, industry and regulatory agencies, including clinicians, basic and translational researchers, graduate students, post-doctoral fellows, and allied health professionals involved in cancer research.

POSTER AND SESSION TOPICS

Scientific posters with cutting edge research will be presented in all topic categories below, with ample time for poster viewing and one-on-one discussion with investigators. Some of these topics will be further explored by invited speakers, oral abstract presentations and interactive audience discussion in plenary and concurrent sessions.

- Biology and Application of Dendritic Cells
- Characterization of Inflammatory Infiltrates in Human Cancers
- Genetically Engineered Receptors and Adoptive Cell Therapies
- High Throughput Technologies for Immune Monitoring
- Immunology of Cancer Stem Cells and Epithelial-to-Mesenchymal Transition (EMT)
- Immunotherapy Combinations
- Innate Immunity in Cancer
- Prostate Cancer as a Learning Model
- State of the Art Animal Models and Veterinary Applications for Cancer Immunology
- Targeted Therapies and Anti-Tumor Immunity
- Therapeutic Monoclonal Antibodies in Cancer
- Tumor Vasculature, Chemokines and Lymphocyte Trafficking to the Tumor
- Uncoupling Negative Regulation in the Tumor Microenvironment

SPECIAL UPDATE SESSIONS

The SITC 26th Annual Meeting offers a unique forum for special updates on major national and international initiatives and important Society projects, including:

- National Cancer Institute, NIH Update
- U.S. Food and Drug Administration (FDA) Update
- Cancer Immunotherapy Trials Network (CITN) Update
- SITC Clinical Immunotherapy Guidelines Update

PROGRAM GOALS

The SITC 26th Annual Meeting provides a forum to:

- Exchange information on the most recent advances in tumor immunology and cancer immunotherapy
- Understand recent advances in biology and immunotherapy as they relate to specific cancers and various immunotherapy modalities, cell subsets, animal models, and aspects of negative regulation in the tumor microenvironment
- Identify promising research opportunities, new techniques and clinical applications incorporating these advances
- Establish dialogue between academia, industry and government on these advances

EXPECTED LEARNER OUTCOMES

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

- Summarize the most recent advances in tumor immunology and cancer immunotherapy
- Integrate recent advances in cancer immunology and immunotherapy into basic, clinical and translational research
- Incorporate new research and techniques into clinical applications for cancer immunotherapy
- Establish and solidify collaborations among the various members of academia, industry, government and clinical practices to promote clinical evaluation of these advances in more efficient trials

The SITC 26th Annual Meeting is a non-accredited continuing medical education event. No credits are offered for physician participation in this educational program.

SITC 26TH ANNUAL MEETING PROGRAM ORGANIZERS

Charles G. Drake, MD, PhD
Johns Hopkins University

Dolores J. Schendel, PhD
Helmholtz Zentrum Muenchen – German Research Center for Environmental Health Institute of Molecular Immunology

Jeffrey Schlom, PhD
National Cancer Institute, National Institutes of Health

Jedd D. Wolchok, MD, PhD
Memorial Sloan-Kettering Cancer Center

General Meeting Information

ABSTRACTS

Abstracts submitted in conjunction with the SITC 26th Annual Meeting are published in the November 2011 issue of the *Journal of Immunotherapy*, one of the Society's journals. Members of SITC receive this issue as well as online access to the Journal with their yearly subscription as a benefit of membership. For those not subscribing, abstracts are available on the SITC website, in the Poster Abstract Book and beginning on page 35 of this program.

ORAL ABSTRACTS

SITC has selected the highest scoring abstract entries for oral presentations within the various meeting sessions. Each oral abstract presentation is followed by a five minute question and answer period. For a complete listing of the selected oral abstract presenters, please see page 24.

POSTER ABSTRACTS

Accepted posters for the SITC 26th Annual Meeting are on display in the Exhibit Hall, Grand Ballroom A-D on the Main Level of the hotel. Posters are available for viewing Friday and Saturday of the Annual Meeting. Please see page 57 or the Poster Abstract Book for a listing of the posters on display. During the presentation times listed below, designated posters are staffed by their respective authors, allowing for information exchange and interaction between researchers and attendees.

POSTER HALL HOURS

Main Level, Grand Salons Ballroom A-D

Poster Set-Up by Author:

Friday, November 4:	6:30 am – 10:00 am
Friday, November 4:	10:00 am – 8:00 pm
Saturday, November 5:	10:00 am – 8:00 pm

POSTER NUMBERS

POSTER PRESENTATIONS / STAFFING HOURS

Odd Number Posters (authors are present)

Friday, November 4:	12:30 pm – 1:30 pm
	6:15 pm – 7:00 pm

Even Number Posters (authors are present)

Friday, November 4:	7:15 pm – 8:00 pm
Saturday, November 5:	12:30 pm – 1:30 pm

LATE-BREAKING ABSTRACTS

To fulfill SITC's commitment to the most cutting edge science, late-breaking abstract submission was offered from August 15 – August 31, 2011. Late-breaking abstracts will be published in the January 2012 issue of the *Journal of Immunotherapy*. The highest scoring submissions were selected for oral presentation.

EXHIBITS

The SITC 26th Annual Meeting showcases a number of exhibitors whose products and services are on display for all meeting attendees to view. Exhibit booths are located on the Main Level, Grand Ballroom Salons A-D of the North Bethesda Marriott. The hall is open Friday and Saturday with booths staffed throughout the day, during all lunches, and evening receptions. For a complete exhibit hall floor plan and exhibit company listings, refer to pages 29-31.

EXHIBIT HALL LOCATION & HOURS

Main Level, Grand Ballroom Salons A-D

Friday, November 4:	10:00 am – 8:00 pm
Saturday, November 5:	10:00 am – 8:00 pm

SITC "FRIEND OF THE SOCIETY" RIBBONS

SITC is committed to furthering the field of cancer immunotherapy/biologic therapy through the establishment of a Trust to support research, training and education. SITC members can show their support for this Trust and their commitment to their field, by purchasing a "Friend of the Society" ribbon at the SITC Registration Desk. The "Friend of the Society" ribbons are designed to be worn on the name badges of delegates attending the Annual Meeting. Ribbons may be acquired for a minimum donation of $50* and can be purchased personally or for distribution to other recipients. In addition to wearing ribbons, all supporters will be recognized on signs at the 2011 SITC programs.
**As a 501(c)(3) organization, donations made to SITC are tax-deductible as charitable contributions to the extent allowed by law.*

EVALUATIONS

Please take time to complete the evaluation form provided for each session you attend. Your input and comments are essential in planning future educational events. Completed evaluations may be returned to the SITC Registration Desk.

General Meeting Information

MEMBERSHIP

Meeting attendees who are members of SITC are designated by a red "Member" ribbon on their name badge. Information on membership classifications, benefits, and dues can be found on page 32. All non-members are invited to complete the membership application form on page 33 and return it to the SITC Registration Desk.

PHOTO/VIDEO POLICY

Photography and videography are prohibited in all SITC general session, poster and exhibit locations unless prior written approval is received from the SITC office. SITC often employs the services of a professional photographer/videographer at SITC events to capture images and audiovisual (AV) recordings for use in society archival and promotional material. Your attendance at SITC events implies your permission for images and AV recordings captured during these events to be used for purposes of SITC archival and promotional materials and publications and waives your rights for compensation or ownership of these images.

REGISTRATION

Registration packets are ready for pick up at the SITC Registration Desk located in the Ballroom Foyer on the Main Level for those pre-registered for the Annual Meeting. On-site registration for the SITC Annual Meeting & Associated Programs is accepted, space permitting. Separate registrations and fees are required for the Primer and Workshop on Thursday, November 3. The Hot Topic Symposium on Sunday, November 6 is complimentary for meeting delegates, but does require advance registration. Hot Topic Symposium only registration is $100.

GUEST REGISTRATION

Guest registration is available to people accompanying registered delegates, and grants admission to evening receptions, but does not permit attendance to scientific sessions. Guests may be registered at the SITC Registration Desk for a fee of $100. Badges for pre-registered guests are provided with the delegate's registration packet. Society members or authors/co-authors of abstracts may not utilize the guest rate.

REGISTRATION DESK LOCATION & HOURS

Main Level, Ballroom Foyer

Wednesday, November 2	5:00 pm – 8:00 pm
Thursday, November 3	6:30 am – 6:00 pm
Friday, November 4	6:30 am – 6:00 pm
Saturday, November 5	7:00 am – 6:00 pm
Sunday, November 6	7:00 am – 12:00 pm

SPEAKER PRESENTATION SLIDES

Following the Annual Meeting, all registered attendees will receive FREE access to faculty presentations as permitted. Presentations will be posted on the SITC website (www.sitcancer.org) by the end of November. Watch for an e-mail with viewing instructions.

YOUNG INVESTIGATOR MEETING FEATURES

SITC supports growth and achievement among young investigators and early career scientists in the field of cancer immunotherapy. To fulfill this mission, SITC offers three specialized opportunities for early career scientists in association with the 26th Annual Meeting: the Early Career Scientist Networking Event, "Meet-the-Expert" Breakfasts, and the Presidential and Travel Awards. See page 11 for more information on the Early Career Scientist Committee and the 2011 planned activities.

PURCHASE YOUR "FRIEND OF THE SOCIETY" RIBBON

Show your support for the field!
Purchase your "Friend of the Society" Ribbon at the SITC Registration Desk for a minimum donation of $50. All proceeds go to the SITC Trust to support research, training and education.

Hotel Information

The Bethesda North Marriott Hotel & Conference Center serves as the headquarters for the SITC 26th Annual Meeting.

Bethesda North Marriott Hotel & Conference Center
5701 Marinelli Road
Bethesda, MD 20852
Phone: 1-800-859-8003
1-301-822-9200
Fax: 1-301-822-3201

TRANSPORTATION OPTIONS

It's easy to get around Bethesda, with its easy-to-use public transportation system. The Bethesda North Marriott Hotel is located within 20 miles of Washington, D.C. and access to the city is easy with taxis or the Metro. Taxis are readily available within the city and the Metro train operates Monday through Sunday at varying hours.

The Bethesda North Marriott Hotel is located across the street from the White Flint Metro Station (Red Line). Base fares start at $1.65 per trip (including trips between all downtown points). One day tickets can be purchased for $7.80, which allows unlimited travel after 9:30 am on weekdays and all day on weekends. For complete information on the Meto, visit www.metroopensdoors.com.

BUSINESS SERVICES

A full-service business center is located within the hotel to assist guests with their fax, copy, internet and parcel/post needs.

RECREATION AND ENTERTAINMENT

A health club and pool are available 24 hours with your guest room key. The Bethesda North Marriott Hotel is just blocks away from area attractions. For complete information on local activities visit the Montgomery County Maryland Convention & Visitors Bureau at www.visitmontgomery.com.

Bethesda, Maryland is located within 20 miles of Washington, D.C. For more information on things to do within Washington, D.C., contact the Washington, D.C. Convention & Visitors Bureau at (202) 789-7000 or visit their web site at www.washington.org.

HOTEL DINING

Meritage
Meritage offers a casual, yet upscale environment where classic regional American cuisine is served with a Mediterranean flair and an extensive wine list. Open for breakfast, lunch and dinner.

On The Rocks
On The Rocks, opening daily at 2:00 pm, is the perfect spot to enjoy conversation and a cocktail. Casual dining, six LCD TVs, comfortable seating and a seasonal outdoor veranda is open for both lunch and dinner.

Hotel Map

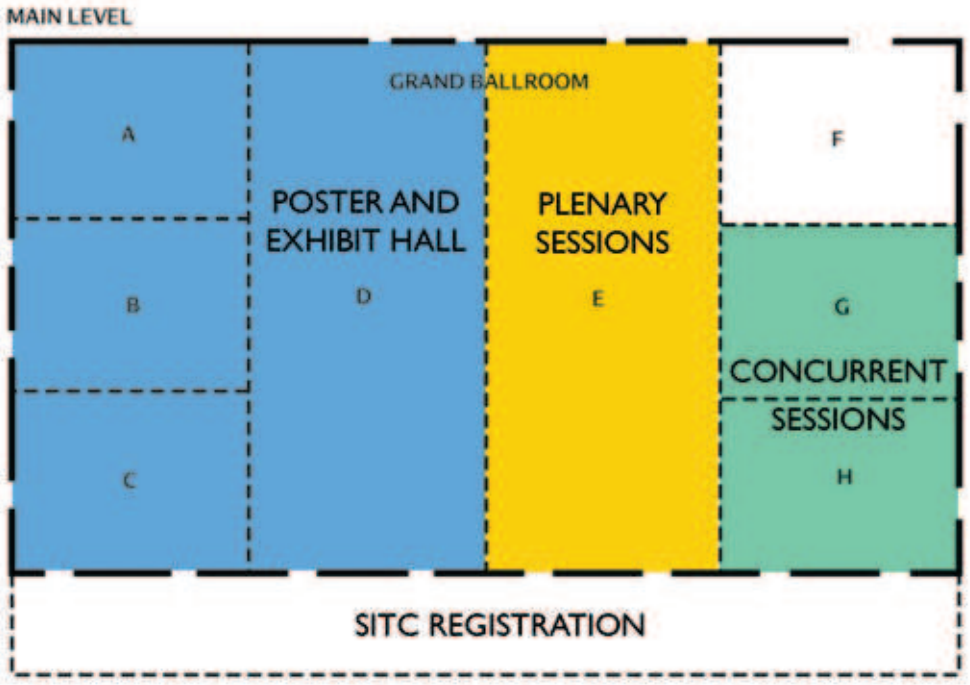
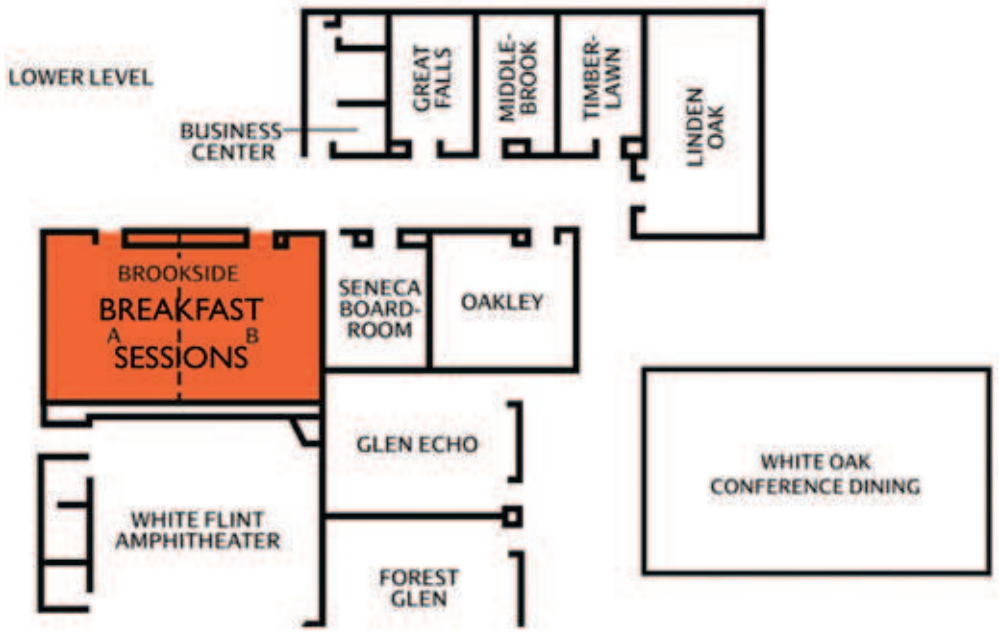


Exhibit and Poster Hall	Grand Ballroom A-D
Primer	Grand Ballroom G-H
Workshop	Grand Ballroom E
Plenary Sessions	Grand Ballroom E
Concurrent Session	Grand Ballroom G-H
"Meet-the-Expert" Breakfast	Brookside A-B
New Member Breakfast	Brookside A-B



Associated Programs

In conjunction with the Annual Meeting, SITC also offers four Associated Programs: the Summit on Cell Therapy for Cancer, the Primer on Tumor Immunology, the Workshop on Immunotherapy Combinations and the Hot Topic Symposium. These programs require separate registrations. For more information about these Associated Programs, please visit the SITC Registration Desk located in the ballroom foyer, on the main level of the Bethesda North Marriott Hotel & Conference Center.

SUMMIT ON CELL THERAPY FOR CANCER

Tuesday, November 1, 2011
8:30 am – 5:00 pm
Wednesday, November 2, 2011
8:20 am – 1:00 pm
Masur Auditorium, NIH Campus, Building 10, Clinical Center, Bethesda, MD
Presenter slides will be available on the SITC website following the program.

The Summit includes an exciting mix of perspectives, concepts and techniques related to cellular therapy that are not normally presented together at any single meeting, from research on induced pluripotent stem cells, to specific modalities and assessment of cell therapies for cancer. This novel assembly will generate new ideas and collaborations to accelerate research and clinical translation of cellular therapies as a cancer immunotherapy.

The program includes Keynote Addresses by the newly appointed Director of the NIH Center for Regenerative Medicine, Mahendra Rao, MD, PhD., and Steven A Rosenberg, MD, PhD, Chief of Surgery at the National Cancer Institute.

Organizers
David F. Stroncek, MD – *National Institutes of Health (NIH)*
John O'Shea, MD – *National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH*
Cornelis J.M. Melief, MD, PhD – *Leiden University Medical Center*

Participating Organizations

AABB (formerly the American Association of Blood Banks)

American Society for Blood and Marrow Transplantation (ASBMT)

American Society of Gene & Cell Therapy (ASGCT)

Cancer Immunotherapy Trials Network (CITN)

National Institutes of Health
Clinical Center
Department of Transfusion Medicine (NIH,CC,DTM)

Associated Programs

PRIMER ON TUMOR IMMUNOLOGY AND CANCER IMMUNOTHERAPY

Thursday, November 3, 2011
8:00 am – 5:00 pm
Grand Ballroom G-H, Bethesda North Marriott Hotel & Conference Center, Bethesda, MD
Presenter slides will be available on the SITC website following the program.

The Primer provides a foundation for understanding the principles of tumor immunology and immune-based cancer treatments, promoting appropriate clinical application of cancer immunotherapies to improve patient outcomes. This one day course for clinicians, fellows, students, researchers and industry professionals provides a series of dynamic lectures covering the biology of immune cells, cellular processes and the tumor microenvironment, as well as the clinical application and immune monitoring of various cancer immunotherapy modalities.

Organizers
Walter J. Urba, MD, PhD – *Earle A. Chiles Research Institute*
Mario Sznol, MD – *Yale University School of Medicine*

WORKSHOP ON IMMUNOTHERAPY COMBINATIONS

Thursday, November 3, 2011
8:00 am – 5:00 pm
Grand Ballroom E, Bethesda North Marriott Hotel & Conference Center, Bethesda, MD
Presenter slides will be available on the SITC website following the program.

The Workshop includes presentations by leaders in the field and panel discussions on strategies that combine various cancer immunotherapies and conventional cancer treatments. Logistical issues in immunotherapy combination trials will be presented from the regulatory, legal, and industry perspectives, and from the perspective of independent academic investigators. Current clinical trial efforts on immunotherapy combinations will also be discussed, emphasizing considerations and applications for future trials.

The program will feature a Keynote Address on "The CITN Perspective on Immunotherapy Combinations" by Martin A. "Mac" Cheever, MD, Principal Investigator of the Cancer Immunotherapy Trials Network (CITN), Fred Hutchinson Cancer Research Center.

Organizers
Alan J. Korman, PhD – *Bristol-Myers Squibb*
Ignacio Melero, MD, PhD – *University of Navarra*
Hideho Okada, MD, PhD – *University of Pittsburgh Cancer Institute*
Suzanne L. Topalian, MD – *Johns Hopkins University School of Medicine*

"HOT TOPIC" SYMPOSIUM: TARGETING THE NEXT GENERATION OF INHIBITORY PATHWAYS

Sunday, November 6, 2011
10:25 am – 12:00 pm
Grand Ballroom G-H, Bethesda North Marriott Hotel & Conference Center, North Bethesda, MD
Presenter slides will be available on the SITC website following the program.

This 1½ hour symposium will explore the latest data on blockade of inhibitory pathways in cancer immunotherapy, including CTLA-4 and the next generation of inhibitory pathways, B7x, Tim-3, VISTA, and IDO.

Chair
Antoni Ribas, MD – *UCLA Medical Center*

Speakers
James P. Allison, PhD – *Memorial Sloan-Kettering Cancer Center*
Ana C. Anderson, PhD – *Harvard Medical School*
Holly K. Koblish, PhD – *Incyte Corporation*
Li Wang, PhD – *Dartmouth Medical School*

The SITC 26th Annual Meeting and Associated Programs are non-accredited continuing medical education events. No credits are offered for physician participation in these educational programs.

Early Career Scientists Committee Information

The Early Career Scientist (ECS) Committee was established to partner with SITC leadership to address the needs of early career scientists in the fields of immunology and biological therapy.

Members of the ECS Committee include students, post doctoral fellows-in-training and early career professionals in academia, industry and regulatory agencies. ECS Committee members participate in many activities and continually seek opportunities for early career scientists to advance SITC's mission and programming. The main goal of the ECS Committee is to leverage Society relationships and resources to enhance the career development of outstanding young investigators in the field.

EARLY CAREER SCIENTIST ACTIVITIES

The ECS Committee has planned an evening networking event and the "Meet-the-Expert" Breakfast for students, post doctoral fellows-in-training and early career professionals in academia, industry and regulatory agencies.

Space for these events is limited and priority will be given to early career scientists. Please check the SITC Registration Desk for availability.

EVENING NETWORKING EVENT

Friday, November 4, 2011
8:00 pm

All students and early career scientists are invited to attend an informal networking event at 8:00 pm on Friday, November 4. Pre-registration is required for this event. For more information or to register, visit the SITC Registration Desk.

"MEET-THE-EXPERT" BREAKFAST

Saturday, November 5, 2011
7:00 am - 7:45 am

The SITC "Meet-the-Expert" Breakfast will focus on unique issues related to the career development of early career scientists. Key leaders in the field will facilitate round table discussions on particular areas of interest. Registered attendees of the "Meet-the-Expert" Breakfast may submit questions for discussion in advance or pose questions to the experts at the table. Experts will answer questions and lead informal dialogues to help provide guidance and direction. Separate registration is required for this event. Tickets for the "Meet-the-Expert" Breakfast have been included in the registration materials for those attendees who have pre-registered. Tickets may still be available; inquire at the SITC Registration Desk.

"Meet-the-Expert" Breakfast Topics *(ticketed event)*

- **Developing Successful Collaborations**
  Leader: Dolores Schendel, PhD – *Helmholtz Zentrum Muenchen – German Research Center for Environmental Health*
- **Finding Your Niche**
  Leader: Bernard A. Fox, PhD – *Earle A. Chiles Research Institute*
- **Publishing Papers**
  Leader: Francesco Marincola, MD – *National Institutes of Health*
- **Grant Writing**
  Leader: Lisa H. Butterfield, PhD – *University of Pittsburgh*
- **Translational Research**
  Leader: Paul M. Sondel, MD, PhD – *University of Wisconsin*
- **Managing a Research Lab**
  Leader: William J. Murphy, PhD – *University of California-Davis*
- **Work-Life Balance**
  Leader: Charles G. Drake, MD, PhD – *Johns Hopkins University*

Program Goals:

1. Assemble key constituents, produce scientifically significant discussions and provide information regarding issues relevant to the career development of students and early career scientists.
2. Provide students and early career scientists with an opportunity to meet key experts in the field and facilitate interactions in a small-group setting and through a Q & A forum.
3. Foster the mentoring of students and early career scientists on the state of research in today's environment through expert guidance on timely and relevant topics.
4. Educate students and early career scientists and provide them with the valuable perspective of senior investigators.

Intended Outcomes:

Upon completion of these breakfast roundtables, participants will be able to:

1. Locate resources available that will facilitate career development related to grant writing, finding a niche, publishing papers, collaborations, managing a research lab, translational research, and/or testing a hypothesis.
2. Develop a framework for action, with an understanding of the complexities and potential pitfalls related to the key issue under discussion.
3. Summarize answers provided by experts in the field to specific questions related to the career development topic.
4. Implement improved processes of communication between students and early career scientists and established researchers and experts.

Presidential and Travel Awards

SITC PRESIDENTIAL AWARDS

The SITC Presidential Award is presented annually to a young investigator demonstrating early career achievement through scientific excellence in abstract and oral presentation in the field of cancer immunotherapy and biological therapy. Qualified investigators are designated through the SITC abstract submission process and they are judged by a committee of SITC leasdership. Four abstracts submitted in any category and authored by young investigators have been selected for 20 minute oral presentations during the Presidential Session from 3:30 pm – 4:50 pm on Saturday, November 5 in Grand Ballroom E. Of those abstract presenters, all four will receive Presidential Travel Awards and one will be selected as the 2011 Presidential Award winner. Judging of the presentations will be done by a committee of SITC leadership.

(1) Presidential Award winner receives:
- $1,000 Honorarium
- Up to $1,000 in Travel Reimbursement
- 1 Year Membership in SITC
- Commemorative Presidential Award Plaque

(3) Presidential Travel Award winners receive:
- Up to $750 in Travel Reimbursement
- 1 Year Membership in SITC
- Presidential Travel Award Certificate

SITC TRAVEL AWARDS

SITC has offered six travel awards to selected young investigators presenting posters at the SITC 26th Annual Meeting. Judging was done by a committee of SITC leadership.

(6) SITC Travel Award Winners receive:
- Up to $750 in Travel Reimbursement
- SITC Travel Award Winner Certificate
- SITC Travel Award Winner Ribbon

2011 SITC TRAVEL AWARD WINNERS

PRESIDENTIAL AWARD

Join us on Saturday, November 5 at the Presidential Reception for the announcement of the 2011 Presidential Award Winner.

PRESIDENTIAL TRAVEL AWARDS

Joshua Brody, MD
Stanford University Medical Center
Stanford, CA

Lenka V. Hurton
MD Anderson Cancer Center
Houston, TX

Lorenzo Uccellini, PhD
National Institutes of Health
Bethdesda, MD

Yan Zheng, PhD
University of Chicago
Chicago, IL

SITC TRAVEL AWARDS

Jessica A. Chacon
University of Texas, MD Anderson Cancer Center
Houston, TX

Drew Deniger
University of Texas, MD Anderson Cancer Center
Houston, TX

Evripidis Lanitis
University of Pennsylvania, School of Medicine
Philadelphia, PA

Petra Prinz, PhD
Institute of Molecular Immunology
Munich, Germany

Emanuela Romano, MD
University of Lausanne
Switzerland

Seng-Ryong Woo, PhD
University of Chicago
Chicago, IL

Presidential and Travel Awards

2010 – WASHINGTON, D.C.

Presidential Award

Michael A. Curran, PhD
Memorial Sloan-Kettering Cancer Center
New York, NY

Presidential Travel Awards

Evripidis Lanitis
University of Pennsylvania, School of Medicine
Philadelphia, PA

Chao Ma, MS
California Institute of Technology
Pasadena, CA
Robbert Spaapen, PhD
University of Chicago
Chicago, IL

SITC Abstract Travel Awards

Maria Libera Ascierto
National Institutes of Health, CC, DTM
Bethesda, MD

David Bedognetti, MD
National Institutes of Health, CC, DTM
Bethesda, MD

Arianna Calcinotto
San Raffaele Scientific Institute
Milan, Italy

Mitsugu Fujita, MD, PhD
University of Pittsburgh
Pittsburgh, PA

Pawel Muranski, MD
National Cancer Institute – CCR
Bethesda, MD

Julie Urban
University of Pittsburgh
Pittsburgh, PA

2009 – WASHINGTON, D.C.

Presidential Award

Weiyi Peng, MD, PhD
UT MD Anderson Cancer Center
Houston, TX

Presidential Travel Awards

David M. Barrett, MD, PhD
Children's Hospital of Philadelphia
Philadelphia, PA

Sid Kerkar, MD
National Cancer Institute – NIH
Bethesda, MD

Justin P. Kline, MD
University of Chicago
Chicago, IL

iSBTc Abstract Travel Awards

Andrea Facciabene, PhD
University of Pennsylvania
Philadelphia, PA

Weiqing Jing
Medical College of Wisconsin
Milwaukee, WI

Christy Ralph
Paterson Institute for Cancer Research
Manchester, United Kingdom

Maria Grazia Ruocco, PhD
New York University, School of Medicine, Skirball Institute
New York, NY

Jochen Schaefer, MD
University of Virginia
Charlottesville, VA

Ryan Sullivan, MD
Beth Israel Deaconess Medical Center
Boston, MA

2008 – SAN DIEGO, CA

Presidential Award

Andrea Facciabene, PhD
University of Pennsylvania
Philadelphia, PA

Presidential Travel Awards

Erik Johnson, MD
University of Wisconsin-Madison
Madison, WI

Stephanie K. Watkins, PhD
National Cancer Institute – Frederick
Frederick, MD

Jianda Yuan, MD, PhD
Memorial Sloan-Kettering Cancer Center
New York, NY

iSBTc Abstract Travel Awards

Yong-Oon Ahn
Seoul National University College of Medicine
Seoul, Korea

Jack D. Bui, MD, PhD
University of California, San Diego
San Diego, CA

Shujuan Liu, PhD
MD Anderson Cancer Center
Houston, TX

Markus Schmid
Helmholtz Zentrum München, Institute of Molecular Immunology
Munich, Germany

Jason C. Steel, PhD
National Cancer Institute, Metabolism Branch
Bethesda, MD

Andrea Worschech, M.Sc.
National Institutes of Health, CC-DTM
Bethesda, MD

2007 - BOSTON, MA

Presidential Awards

Amy Wesa, PhD
University of Pittsburgh School of Medicine
Pittsburgh, PA

Susanne Wilde
GSF National Center for Environment and Health
Munich, Germany

Presidential Travel Awards

Talya Schwarzberg, MD
Beth Israel Deaconess Medical Center
Boston, MA

Laura Strauss, PhD
San Raffaele Telethon Institute for Gene Therapy
Milan, Italy

iSBTc Abstract Travel Awards

Arvind Chhabra, PhD
University of Connecticut Health Center
Farmington, CT

Hideo Komita, MD
University of Pittsburgh
Pittsburgh, PA

Kerrington Molhoek, PhD
University of Virginia
Charlottesville, VA

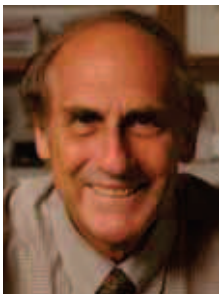
Marta Santisteban, MD, PhD
Mayo Clinic
Rochester, MN

James Thompson, PhD
Earle A. Chiles Research Institute
Portland, OR

Meghaan Walsh
National Cancer Institute
Bethesda, MD

Richard V. Smalley, MD Memorial Award and Lectureship

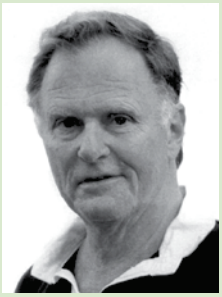
In memory of his many achievements, both professionally and personally, the Society for Immunotherapy of Cancer (SITC) established the annual ***Richard V. Smalley, MD Memorial Award*** in 2005. The Smalley Award serves as recognition of excellence in the field of therapeutic research with biological agents and is accompanied by an honorarium of $5,000. The Smalley Award recipient also provides an informative scientific lecture at the Annual Meeting as part of his/her acceptance.



2011 RICHARD V. SMALLEY, MD MEMORIAL AWARD RECIPIENT

In recognition of his outstanding research, work, and achievements in cancer therapy, the Society for Immunotherapy of Cancer (SITC) proudly presents the 2011 ***Richard V. Smalley, MD Memorial Award*** to Ralph Steinman, MD, of The Rockefeller University. Dr. Steinman will give the keynote address on Friday, November 4 at 8:00 am and be presented the award during the Presidential Reception on Saturday, November 5.

Ralph M. Steinman, MD co-discovered dendritic cells (DCs). His research characterized DCs as important and unique accessory cells in the onset of several immune responses, including graft rejection, resistance to tumors, autoimmune disease and infections. Dr. Steinman's work has led to a new understanding of the control of tolerance and immunity and it was the genesis for a new field of study within immunology: the role of DCs in immune regulation, their potential for discovering new vaccines and treatments of autoimmune disorders. Dr. Steinman's group is currently investigating active antigen-specific, suppressor or regulatory T cell mechanisms that allow DCs to induce tolerance. Dr. Steinman is currently Senior Physician, Henry G. Kunkel Professor, and head of the Laboratory of Cellular Physiology and Immunology at The Rockefeller University. He is a member of the National Academy of Sciences and the Institute of Medicine.



RICHARD V. SMALLEY, MD (1932 – 2004)

As one of the Society's charter members, Dr. Richard Smalley was an integral part of the Society's fabric from its inception. Dr. Smalley served on the original Board of Directors from 1984 – 1990, where he also served as the Society's third President from 1988 – 1990, leading the Society through some of its most formative years. In 1994 – 1998, while serving as SITC Treasurer, the environment for biological therapy began to change and the Society faced many challenges. During this time, Dr. Smalley showed inspirational devotion by meeting these challenges and administering the Society from his own home and nurturing its continued growth. SITC's success is due, in large part, to the consummate dedication and leadership of Dr. Richard Smalley.

Richard Vincent Smalley was born in New York City on June 21, 1932 and grew up in Larchmont, NY. He graduated from Hamilton College in 1953 and from the Temple University School of Medicine in 1957. After serving as a lieutenant in the United States Navy, he completed his residency at Temple University Hospital and his fellowship at Ohio State University.

Dr. Smalley was Professor of Medicine and Head of the Section of Medical Oncology at Temple University until 1981. He served as Branch Chief of the Biological Response Modifiers Program at the National Cancer Institute from 1982 – 1984. He worked in the Department of Human Oncology at the University of Wisconsin Cancer Center from 1984 – 1991, prior to starting his own cancer clinical trials management company, Synertron, Inc. A seven-year survivor of chronic lymphocytic leukemia, Dr. Smalley died of an unrelated brain tumor at his home in Edgewater, MD on January 17, 2004 at the age of 71.

PREVIOUS RICHARD V. SMALLEY, MD MEMORIAL AWARD RECIPIENTS

2010
James P. Allison, PhD
Memorial Sloan-Kettering Cancer Center

2009
Isaiah J. Fidler, DVM, PhD
MD Anderson Cancer Center

2008
Giorgio Parmiani, MD
San Raffaele Foundation

2007
Ernest Borden, MD
Cleveland Clinic Foundation

2006
Ronald Levy, MD
Stanford University School of Medicine

2005
Steven A. Rosenberg, MD, PhD
National Cancer Institute

Plenary and Concurrent Sessions

The following provides the context for the plenary and concurrent sessions.

BIOLOGY AND APPLICATION OF DENDRITIC CELLS

Plenary Session
Friday, November 4
8:45 am – 11:30 am
Grand Ballroom Salon E

Dendritic cells (DCs) play a central role in the immune response to tumors and for many immunotherapeutic strategies, understanding their complex biology continues to be of critical importance. Recent advances in knowledge about DC subsets and functions, as well as clinical trials of DC based vaccines will be discussed.

IMMUNOLOGY OF CANCER STEM CELLS AND EPITHELIAL-TO-MESENCHYMAL TRANSITION (EMT)

Concurrent Session
Friday, November 4
1:30 pm – 3:00 pm
Grand Ballroom Salon E

Recent data suggests that a minor subpopulation of tumor stem cells are involved in tumor initiation, and that the process of EMT drives a more metastatic and drug resistant population. Current treatment modalities target non-stem cells, thus tumor-initiating stem cells and/or cells that have undergone EMT may persist and repopulate/recreate the tumor. Clinicians and investigators need to be educated on the most recent understanding of the role of EMT and/or cancer stem cell subpopulations, and their differences in signaling, immune interaction and susceptibility to targeted killing by various immunotherapeutic strategies.

UNCOUPLING NEGATIVE REGULATION IN THE TUMOR MICROENVIRONMENT

Concurrent Session
Friday, November 4
1:30 pm – 3:00 pm
Grand Ballroom Salon G-H

Recent studies have shown that a major barrier to effective T cell-mediated tumor destruction involves negative regulatory pathways in the tumor microenvironment. The identification of these pathways has pointed towards new targets for immune potentiation. Blocking specific negative regulatory pathways has been effective in numerous preclinical studies, and is already leading to promising results in early phase clinical trials. Our current understanding of these inhibitory pathways, such as Tregs, MDSCs, CTLA-4, PD-1, and IDO will be discussed.

GENETICALLY ENGINEERED RECEPTORS AND ADOPTIVE CELL THERAPIES

Plenary Session
Friday, November 4
3:15 pm – 5:15 pm
Grand Ballroom Salon E

Adoptive T cell therapy is an evolving immunotherapeutic approach with promising clinical activity. Engineering T cells to express specific T cell receptors or chimeric receptors is allowing retargeting of specificity of adoptively transferred cells. By advancing techniques and understanding of the most recent clinical applications of autologous lymphocytes with engineered receptors, these promising cancer treatment approaches may be made applicable to a greater number of cancer patients with improved specificity and efficacy. Sharing information from the most recent scientific approaches and clinical trials will help researchers refine these novel cellular therapies.

CHARACTERIZATION OF INFLAMMATORY INFILTRATES IN HUMAN CANCERS

Plenary Session
Saturday, November 5
8:45 am – 11:30 am
Grand Ballroom Salon E

While melanoma has traditionally been focused upon for many studies of anti-tumor immunity and cancer immunotherapy, recent work has indicated that lymphocytic infiltrates with specific phenotypes can be observed in a wider range of cancers, and that this information can have prognostic importance. These observations suggest that therapies aimed at immune modulation could have broader application beyond melanoma, and also motivate the consideration of predictive biomarkers for clinical response to such interventions.

STATE OF THE ART ANIMAL MODELS AND VETERINARY APPLICATIONS FOR CANCER AND IMMUNOLOGY

Concurrent Session
Saturday, November 5
1:30 pm – 3:00 pm
Grand Ballroom Salon E

Many transplantable tumor models in animals are not accurately representative of the complexities of human cancer, therefore, more sophisticated animal models are being developed with the hope of having better predictive value for ultimate clinical benefit in humans. These include genetically engineered mouse models using defined permutations of oncogenes, as well as large mammal models in outbred veterinary populations.

HIGH THROUGHPUT TECHNOLOGIES FOR IMMUNE MONITORING

Concurrent Session
Saturday, November 5
1:30 pm – 3:00 pm
Grand Ballroom Salons G-H

Many translational clinical trials of immunotherapeutics have incorporated longitudinal monitoring of specific facets of the immune response. However, as scientific correlates to clinical response are still largely lacking, these techniques continue to evolve. New platforms for high throughput analysis for immune monitoring, including analysis of T cell receptors, antibodies, cytokines, gene expression and protein arrays, and germline DNA sequencing are continuing to advance the field.

PROSTATE CANCER AS A LEARNING MODEL

Plenary Session
Sunday, November 6
8:00 am – 10:15 am
Grand Ballroom Salon E

Rapid advances are being made in the understanding of the immunology and immunotherapy of prostate cancer. A growing body of knowledge regarding the interactions between prostate cancer cells and the host immune system is emerging, and the first approval of a therapeutic cancer vaccine has been in this disease. Prostate cancer therefore serves a valuable learning model for considering clinical trial endpoints, selection of patient populations, and clinical applications of cancer immunotherapies, as well as for understanding the tumor-host interaction.

Program Schedule

FRIDAY, NOVEMBER 4, 2011

6:30 am - 6:00 pm	**Registration Open**	**Grand Ballroom Foyer**
7:00 am - 7:50 am	**Continental Breakfast**	**Grand Ballroom Salons A-D**
7:00 am - 7:45 am	**New Member Breakfast Gathering**	**Brookside - Lower Level**
10:00 am - 8:00 pm	**Exhibit and Poster Hall Open**	**Grand Ballroom Salons A-D**
7:50 am - 8:00 am	**SITC 26th Annual Meeting Begins - President's Welcome** Thomas F. Gajewski, MD, PhD *University of Chicago, SITC President*	**Grand Ballroom Salon E**
8:00 am - 8:45 am	**Richard V. Smalley, MD Memorial Lectureship** Ralph M. Steinman, MD *The Rockefeller University*	**Grand Ballroom Salon E**
8:45 am - 11:30 am	**Biology and Application of Dendritic Cells** Chairs: Nina Bhardwaj, MD, PhD *NYU School of Medicine* Viggo Van Tendeloo, PhD *Antwerp University Hospital*	**Grand Ballroom Salon E**
8:45 am - 9:15 am	Optimizing T Cell Immunity with Prime-Boost Immunization Using Viral and Protein/Adjuvant Based Vaccines Robert A. Seder, MD *NIAID, NIH*	
9:15 am - 9:30 am	Human Langerhans Dendritic Cells Stimulate Robust Cytolytic T-Cells Against Tumor Antigens, Including WT1, by an IL15-Dependent Mechanism Emanuela Romano, MD *University Hospital of Lausanne*	
9:30 am - 10:00 am	Dendritic Cell Vaccines for Leukemia in an Adjuvant Post-remission Setting Viggo Van Tendeloo, PhD *Antwerp University Hospital*	
10:00 am - 10:15 am	The Host STING Pathway is Critical for Innate Immune Sensing at a Growing Tumor and Bridging to an Adaptive Immune Response via IFN-β Seng-Ryong Woo, PhD *University of Chicago*	
10:15 am - 10:45 am	**Break**	
10:45 am - 11:00 am	Adenovirus-Engineered Human Dendritic Cell Vaccine Induces Natural Killer Cell Chemotaxis via CXCL8/IL-8 and CXCL10/IP-10 Chemokines Lazar Vujanovic, PhD *University of Pittsburgh*	
11:00 am - 11:30 am	Modulation of Dendritic Cell Function by the Tumor Microenvironment Nina Bhardwaj, MD, PhD *NYU School of Medicine*	
11:30 am - 12:00 pm	**Late Breaking Oral Abstracts** Moderator: Francesco Marincola, MD *National Institutes of Health*	**Grand Ballroom Salon E**
11:30 am - 11:45 am	Phase I Study of Intravenous Recombinant Human Interleukin-15 (RH IL-15) in Adults with Metastatic Malignant Melanoma and Renal Cell Carcinoma Kevin C. Conlon, MD, MS *National Cancer Institute, NIH*	

FRIDAY, NOVEMBER 4, 2011

11:45 am - 12:00 pm	Reversal of Local Immune Evasion Mechanisms and Regression of Human Merkel Cell Carcinoma by Intralesional Injection of Interferon-Beta Kelly G. Paulson *University of Washington*	
12:00 pm - 1:30 pm	**Lunch with Exhibits / Poster Viewing and Presentations** (Box lunches provided to registered attendees.)	**Grand Ballroom Salons A-D**
12:30 pm - 1:30 pm	**Odd Numbered Poster Presentations by Authors**	
1:30 pm - 3:00 pm	**Concurrent Session I: Immunology of Cancer Stem Cells and Epithelial-to-Mesenchymal Transition (EMT)** Chairs: Malcolm A.S. Moore, DPhil *Memorial Sloan-Kettering Cancer Center* Jeffrey Schlom, PhD *National Cancer Institute, NIH*	**Grand Ballroom Salon E**
1:30 pm - 2:00 pm	Cancer Testis (CT) Antigens Expressed in Ovarian Tumor-Initiating Cells Malcolm A.S. Moore, DPhil *Memorial Sloan-Kettering Cancer Center*	
2:00 pm - 2:30 pm	Immunotherapeutic Approaches to EMT and Cancer Stem Cells Claudia M. Palena, PhD *National Cancer Institute, NIH*	
2:30 pm - 2:45 pm	Immunological Targeting of Epithelial to Mesenchymal Transition as a Strategy to Prevent Breast Cancer Metastases Sandra Demaria, MD *New York University School of Medicine*	
2:45 pm - 3:00 pm	Potential for Immunotherapeutic Control of CSC-like Cells Through their Expression of FAS and DR5 Death Receptors Trina Stewart, PhD *Peter MacCallum Cancer Centre*	
1:30 pm - 3:00 pm	**Concurrent Session II: Uncoupling Negative Regulation in the Tumor Microenvironment** Chairs: Lieping Chen, MD, PhD *Yale Cancer Center, Yale School of Medicine, Immunobiology* Hassane M. Zarour, MD *University of Pittsburgh*	**Grand Ballroom Salons G-H**
1:30 pm - 2:00 pm	Immune Checkpoints in the Cancer Microenvironment Lieping Chen, MD, PhD *Yale Cancer Center, Yale School of Medicine, Immunobiology*	
2:00 pm - 2:15 pm	IL-12 Triggers an Inflammatory Gene Signature that Reverses Dysfunctional Antigen-presentation by Myeloid-Derived Cells Residing within Tumors Sid Kerkar, MD *National Cancer Institute, Center for Cancer Research, NIH*	
2:15 pm - 2:30 pm	Acute Myeloid Leukemia Promotes Immune Evasion through Induction of Antigen-Specific T Cell Deletion Justin P. Kline, MD *University of Chicago*	
2:30 pm - 3:00 pm	Targeting Multiple Inhibitory Pathways to Reverse Melanoma-induced T Cell Dysfunction Hassane M. Zarour, MD *University of Pittsburgh*	
3:00 pm - 3:15 pm	**Break**	

FRIDAY, NOVEMBER 4, 2011

3:15 pm - 5:15 pm	**Genetically Engineered Receptors and Adoptive Cell Therapies** Chairs: Carl H. June, MD *University of Pennsylvania* Dolores J. Schendel, PhD *Helmholtz Zentrum Muenchen - German Research Center for Environmental Health Institute of Molecular Immunology*	**Grand Ballroom Salon E**
3:15 pm - 3:45 pm	Genetically Engineered Receptors in Adoptive Cell Therapies Laurence J.N. Cooper, MD, PhD *MD Anderson Cancer Center*	
3:45 pm - 4:15 pm	Selection of Allo-Restricted Peptide-Specific TCRs for Adoptive T Cell Therapy Dolores J. Schendel, PhD *Helmholtz Zentrum Muenchen - German Research Center for Environmental Health Institute of Molecular Immunology*	
4:15 pm - 4:30 pm	Differential Gene Expression Associated with Immune Down Regulation in TCR Gene-engineered T Cells Administered to Patients Daniel Abate-Daga, PhD *National Cancer Institute*	
4:30 pm - 4:45 pm	Active STAT5 Promotes Long-Lived Cytotoxic CD8 T Cells that Induce Regression of Autochthonous Mouse Melanoma Gregory Verdeil, PhD *Centre d'Immunologie de Marseille-Luminy, CIML*	
4:45 pm - 5:15 pm	Engineered T Cell Therapies for Hematologic Malignancies Carl H. June, MD *University of Pennsylvania*	
5:15 pm - 5:45 pm	**Cancer Immunotherapy Trials Network (CITN) Update** Mary L. (Nora) Disis, MD *Cancer Immunotherapy Trials Network (CITN); University of Washington*	**Grand Ballroom Salon E**
5:45 pm - 6:15 pm	**SITC Membership Business Meeting** *(All meeting attendees welcomed to attend)*	**Grand Ballroom Salon E**
6:15 pm - 8:00 pm	**Reception with Exhibits / Poster Viewing and Presentations**	**Grand Ballroom Salons A-D**
6:15 pm - 7:00 pm	**Odd Numbered Poster Presentations by Authors**	**Grand Ballroom Salons A-D**
7:15 pm - 8:00 pm	**Even Numbered Poster Presentations by Authors**	**Grand Ballroom Salons A-D**

Program Schedule

SATURDAY, NOVEMBER 5, 2011

7:00 am - 6:00 pm	**Registration Open**	**Ballroom Foyer**
7:00 am - 8:00 am	**Continental Breakfast**	**Grand Ballroom Salons A-D**
7:00 am - 7:45 am	**Early Career Scientists "Meet-the-Expert" Breakfasts** Separate registration required	**Brookside - Lower Level**
10:00 am - 8:00 pm	**Exhibit and Poster Halls Open**	**Grand Ballroom Salons A-D**
8:00 am - 8:45 am	**Keynote Address** Innate Immune Recognition of Nucleic Acids Katherine Fitzgerald, PhD *University of Massachusetts Medical School*	**Grand Ballroom Salon E**
8:45 am - 11:30 am	**Characterization of Inflammatory Infiltrates in Human Cancers** Chairs: George Coukos, MD, PhD *University of Pennsylvania Medical Center* Wolf Hervé Fridman, MD, PhD *INSERM*	**Grand Ballroom Salon E**
8:45 am - 9:15 am	Chemokine Regulation of T Cell Response in Ovarian Cancer George Coukos, MD, PhD *University of Pennsylvania Medical Center*	
9:15 am - 9:30 am	DC Vaccination Concurrently Reduces Treg and Enhances Activated CTL in Tumor Biopsies from Immunoresponsive Patients with Advanced Melanoma Massimo Guidoboni, MD *Immunology & Somatic Cell Therapy Lab*	
9:30 am - 10:00 am	Contrasted Prognostic Impact of Tumor Infiltration by Various Subsets of Immune Cells Wolf Hervé Fridman, MD, PhD *INSERM*	
10:00 am - 10:15 am	Topical TLR7 Agonist Imiquimod Can Induce Immune-Mediated Rejection of Breast Cancer Skin Metastases Sylvia Adams, MD *NYU Cancer Institute*	
10:15 am - 10:45 am	**Break**	
10:45 am - 11:00 am	Serial Imaging of Inflammation and Therapeutic Response with Clinically Translational 19F MRI Amy K. Wesa, PhD *Celsense, Inc.*	
11:00 am - 11:30 am	Post-translational Chemokine Modification Prevents Intratumoral Infiltration of Antigen-specific T Cells Vincenzo Bronte, MD *Verona University - Immunology Section*	
11:30 am - 12:00 am	**Late Breaking Oral Abstracts** Moderator: Francisco Marincola, MD *National Institutes of Health*	**Grand Ballroom Salon E**
11:30 am - 11:45 am	Frequency of Strong Antibody Responses Following Combination Immunotherapy Correlates with Increased PSA Doubling Time in Men with Androgen-Independent Prostate Cancer Sachin Puri, PhD *Earle A. Chiles Research Institute*	
11:45 am - 12:00 pm	IDO1 Activity Correlates with Hepatocyte Growth Factor Levels and Immune System Impairment in Multiple Myeloma Sergio Rutella, MD, PhD *IRCCS Bambino Gesù Children's Hospital*	
12:00 pm - 1:30 pm	**Lunch with Exhibits / Poster Viewing and Presentations** (Box lunches provided to registered attendees.)	**Grand Ballroom Salons A-D**

SATURDAY, NOVEMBER 5, 2011

12:30 pm - 1:30 pm	**Even Numbered Poster Presentations by Authors**	
1:30 pm - 3:00 pm	**Concurrent Session I: State of the Art Animal Models and Veterinary Applications for Cancer and Immunology** Chairs: Thomas Blankenstein, PhD *Max-Delbruck Center for Molecular Medicine* Jedd D. Wolchok, MD, PhD *Memorial Sloan-Kettering Cancer Center*	**Grand Ballroom Salon E**
1:30 pm - 2:00 pm	The Immune Response to Sporadic Antigenic Cancer Thomas Blankenstein, PhD *Max-Delbruck Center for Molecular Medicine*	
2:00 pm - 2:15 pm	NOD/scid IL2Rgnull Mice: A Model for Human Dendritic Cell-Based Immunotherapies Stefani Spranger *Helmholtz Zentrum München*	
2:15 pm - 2:30 pm	Intracranial Administration of Human Activated NK Cells in a Xenogeneic Model of Orthotopic Glioblastoma William J. Murphy, PhD *University of California-Davis*	
2:30 pm - 3:00 pm	Overcoming Vaccine Resistance in a Model of Spontaneous Melanoma Taha Merghoub, PhD *Memorial Sloan-Kettering Cancer Center*	
1:30 pm - 3:00 pm	**Concurrent Session II: High Throughput Technologies for Immune Monitoring** Chairs: Philipp Beckhove, MD *German Cancer Research Center* Sacha Gnjatic, PhD *Ludwig Institute for Cancer Research*	**Grand Ballroom Salons G-H**
1:30 pm - 2:00 pm	Tumour Reactive T Cell Responses as Biomarkers: Correlation to Tumour Cell Biology and Treatment Response Philipp Beckhove, MD *German Cancer Research Center*	
2:00 pm - 2:15 pm	Immunological Correlates of Long-Term Survival in Melanoma Patients Graham Pawelec, PhD *University of Tuebingen*	
2:15 pm - 2:30 pm	New Biomarkers for PROSTVAC-VF Discovered Using High-Throughput Glycan Microarrays Christopher Campbell, MD, PhD *National Cancer Institute*	
2:30 pm - 3:00 pm	Seromics: Measuring Antigen-Specific Serum Antibody Responses During Anticancer Immunotherapies for Correlation with Clinical Events Sacha Gnjatic, PhD *Ludwig Institute for Cancer Research*	
3:00 pm - 3:30 pm	**Break**	
3:30 pm - 4:50 pm	**Presidential Abstract Session** Chair: Thomas F. Gajewski, MD, PhD *University of Chicago, SITC President*	**Grand Ballroom Salon E**
3:30 pm - 3:50 pm	Immunotransplant for Mantle Cell Lymphoma: a Phase I/II Study Demonstrating Amplification of Tumor-Reactive T Cells Joshua Brody, MD *Stanford University Medical Center*	

SATURDAY, NOVEMBER 5, 2011

3:50 pm - 4:10 pm	IRF5 Gene Polymorphism in Melanoma Lorenzo Uccellini, PhD *National Institutes of Health, CC, DTM*	
4:10 pm - 4:30 pm	Improved in Vivo Persistence of CD19-Specific T Cells Expressing a Membrane-Bound Form of IL-15 Lenka Hurton *M.D. Anderson Cancer Center, The University of Texas-Houston*	
4:30 pm - 4:50 pm	Dysfunctional Tumor-Infiltrating T Cells Express the Anergy-Associated Molecules Lymphocyte-Activation Gene 3 (LAG3) and Class-I-MHC Restricted T Cell Associated Molecules (CRTAM) Yan Zheng, PhD *University of Chicago*	
4:50 pm - 5:20 pm	**Clinical Immunotherapy Guidelines Update** Howard L. Kaufman, MD, FACS *Rush University Medical Center*	Grand Ballroom Salon E
5:20 pm - 5:35 pm	**National Cancer Institute, NIH Update** William Merritt, PhD *National Cancer Institute*	Grand Ballroom Salon E
5:35 pm - 5:50 pm	**FDA Update on Regulatory Issues Related to Cancer Immunotherapy** Raj K. Puri, MD, PhD *Food and Drug Administration, CBER*	Grand Ballroom Salon E
5:50 pm - 6:15 pm	**Award Presentations**	Grand Ballroom Salon E
6:15 pm - 8:00 pm	Presidential Reception with Exhibits / Poster Viewing and Presentations	Grand Ballroom Salons A-D
8:00 pm	Performance by the band The Checkpoints	

SUNDAY, NOVEMBER 6, 2011

7:00 am - 8:00 am	**Continental Breakfast**	Ballroom Foyer
7:30 am - 12:00 pm	**Registration Open**	Ballroom Foyer
8:00 am - 10:15 am	**Prostate Cancer as a Learning Model** Chairs: Charles G. Drake, MD, PhD *Johns Hopkins University* James L. Gulley, MD, PhD, FACP *National Cancer Institute*	Grand Ballroom Salon E
8:00 am - 8:30 am	Immune Checkpoint Blockade in Prostate and Other Cancers Charles G. Drake, MD, PhD *Johns Hopkins University*	
8:30 am - 9:00 am	Repetitive DNA Vaccination Elicits PAP Antigen-Specific T Cell Immune Responses in Patients with Castrate-Resistant Prostate Cancer Douglas G. McNeel, MD, PhD *University of Wisconsin*	
9:00 am - 9:15 am	Intradermal Immunization with a Novel mRNA Based Vaccination Technology Induces Strong T and B Cell Responses in Phase I/ IIa Trials in Non-Small Cell Lung Cancer (NSCLC) and Prostate Carcinoma (PCA) Birgit Scheel, PhD *CureVac GmbH*	
9:15 am - 9:30 am	Lymphoid and Myeloid Biomarkers for Clinical Outcome of Ipilimumab and Prostate GVAX Treatment: Tumor-related CTLA-4 Expression by CD4+ T Cells as a Dominant Predictor of Survival Tanja D. De Gruijl, PhD *VU University Medical Center*	
9:30 am - 9:45 am	Comprehensive Characterization of Polyomavirus BK Large Tumor Antigen Epitopes to Promote the Expansion of Effector T Lymphocytes in Prostate Cancer Patients Maurizio Provenzano, MD, PhD *University Hospital of Zurich*	
9:45 am - 10:15 am	Combining Vaccines with Other Therapeutics: A Strategy to Accelerate Proof of Concept Studies James L. Gulley, MD, PhD, FACP *National Cancer Institute*	
10:15 am	**Annual Meeting Adjourns**	

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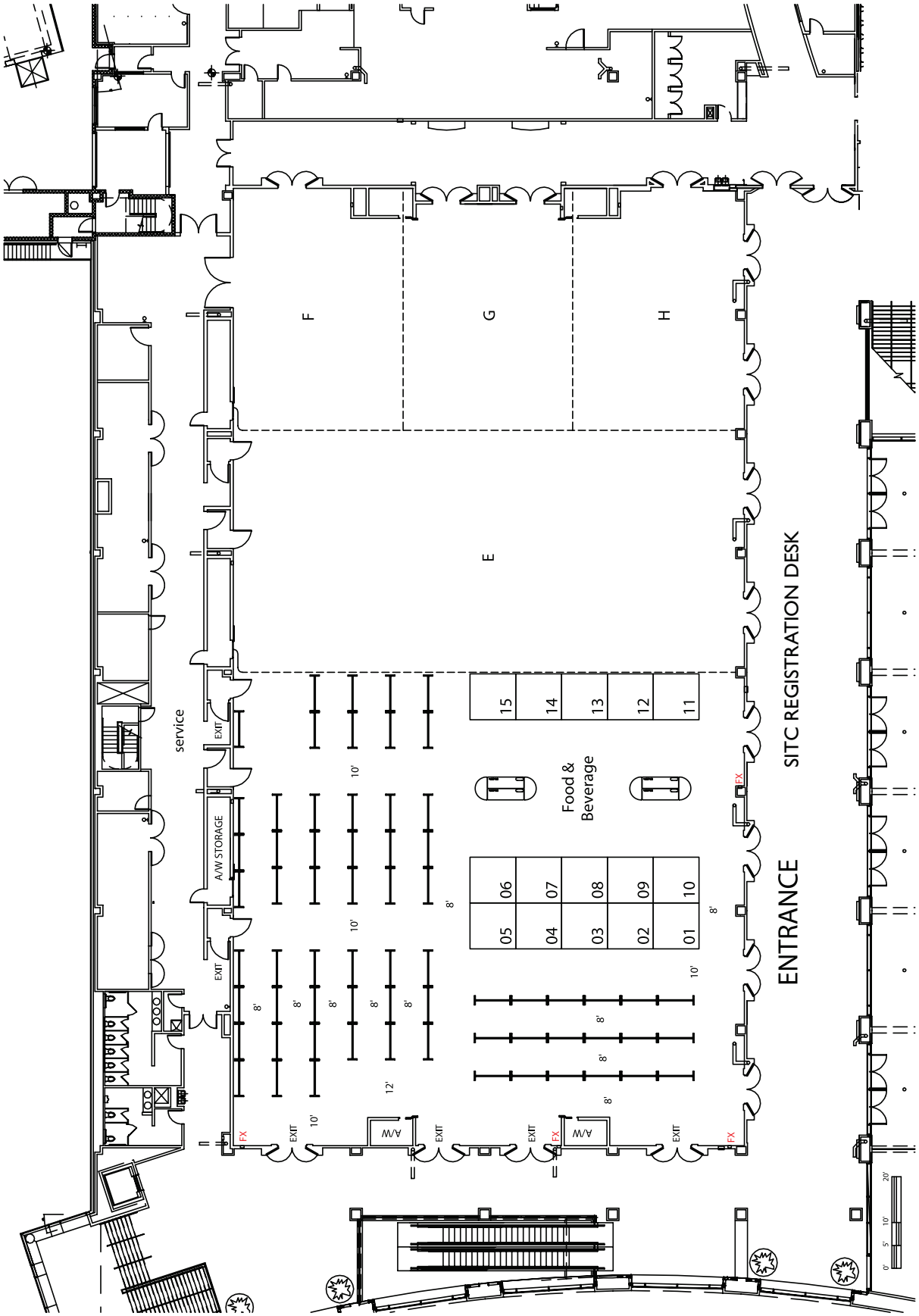

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CORE PURPOSE

To improve cancer patient outcomes by advancing the development and application of biological therapy/immunotherapy.

CORE VALUES

- **Interaction/Integration** – exchange of information and education among basic and translational researchers, clinicians, and young investigators; societies and groups sharing the vision and core values of SITC
- **Innovation** – challenge the thinking and seek the best research in the development of biological therapy/immunotherapy
- **Translation** – promote the application and understanding of biological therapy/immunotherapy
- **Leadership** – define what is new and important and effectively communicate it to all relevant stakeholders

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

Medical Specialties – SITC members and delegates represent many areas of biological science including:

- Cell Biology
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- Gynecologic Oncology
- Hematology
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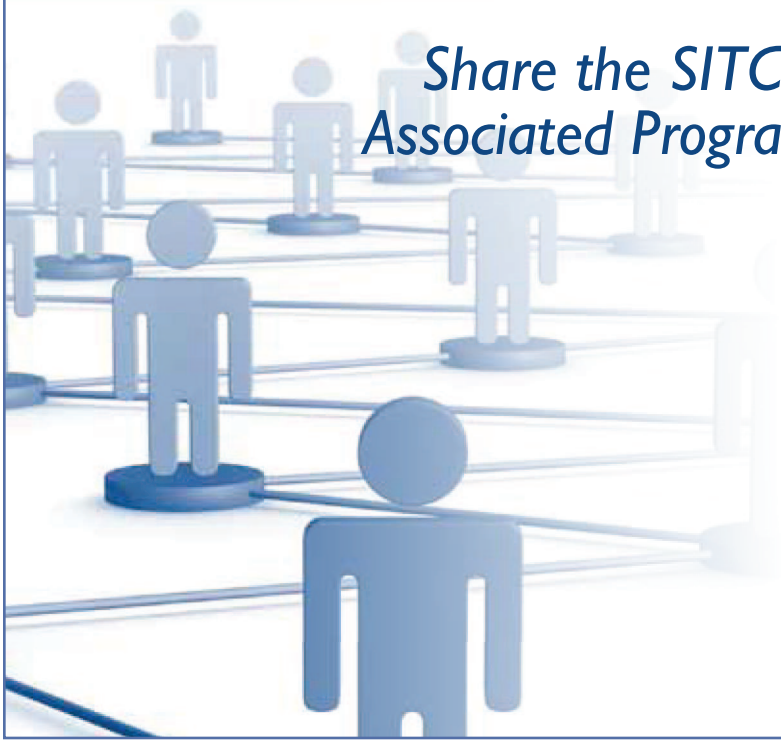

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FRIDAY, NOVEMBER 4, 2011

Presenting author underlined, *Primary author in italics*

BIOLOGY & APPLICATION OF DENDRITIC CELLS

HUMAN LANGERHANS DENDRITIC CELLS STIMULATE ROBUST CYTOLYTIC T-CELLS AGAINST TUMOR ANTIGENS, INCLUDING WT1, BY AN IL15-DEPENDENT MECHANISM

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Human Langerhans dendritic cells (LCs) are the most potent conventional DC subtype for stimulating CTLs against viruses and tumors in vitro. Compared with other conventional human DC subtypes, LCs produce the most IL-15. LCs also synthesize 3-5 fold higher amounts of IL15Rα than do moDCs ($P<0.001$ to 0.05), based on measurement of mRNA by RT-PCR or detection of receptor protein by digitalized immunofluorescent imaging. Freshly isolated LC crawlouts from human epidermal sheets also express IL15Rα. LC-stimulated T cells strongly upregulate pSTAT5, an early T cell activation event, with no enhancement by exogenous IL15 (10 ng/ml) (P=NS). In contrast, moDCs need exogenous IL15 to induce a comparable pSTAT5 response by T cells ($P= 0.008$). IL15Rα blockade of either moDCs or LCs completely inhibits pSTAT5. LCs thus have abundant IL15Rα to shepherd IL15 to the cell surface for presentation in trans to responder lymphocytes expressing IL15R-βγ. To capitalize on a broadly expressed, self-differentiation tumor antigen, LCs generated from CD34+ progenitors from healthy individuals underwent electroporation with WT1-mRNA. These LCs stimulate robust WT1-specific autologous CTLs, after a single 7d round of stimulation at a T cell:LC ratio of only 10 or 30:1, in the absence of exogenous IL-15. These CTLs lyse 85-95% of targets from a WT1+ tumor cell line and 63% (+/- 11% SEM) of primary WT1+ blasts from patients with AML in an HLA-restricted manner. MoDCs are completely incapable of generating WT1-specific CTLs under comparable conditions and require exogenous IL-15 to generate 70-80% specific lysis of WT1+ targets. Anti-IL15Rα opsonization of LCs during their 7d priming of T cells abrogates their ability to stimulate CTLs ($P = 0.001$). Activation of T cells by LCs therefore results in stimulation of both antigen recognition and IL-15 receptor pathways, leading to a fundamentally different set of intracellular signals from those arising during antigen presentation by moDCs. These data connect the abundant expression of the IL15/IL15Rα complex by human LCs to their superior stimulation of potent anti-tumor CTLs, which moDCs cannot achieve without exogenous IL15. These results support the use of mRNA-electroporated LCs as vaccines for cancer immunotherapy, thus overcoming tolerance against self-differentiation antigens shared by tumors.

Key Words: Active immunotherapy, Cancer vaccine.

DENDRITIC CELL VACCINES FOR LEUKEMIA IN AN ADJUVANT POST-REMISSION SETTING

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Messenger RNA (mRNA)-based gene transfer has gained an enormous interest over the last decade, especially in the field of dendritic cell (DC)-based cancer vaccines. In this area, most researchers have exploited low voltage electrical pulses (electroporation) as a means to introduce coding RNA into DC. Hence, mRNA electroporation has become the method of choice for transfecting DC given its superior cytoplasmic expression efficiency, its simplicity over viral transduction protocols and its clinically safe applicability because of a strictly transient expression profile and the inability to integrate into the host genome. Furthermore, it allows the simultaneous introduction of antigens and immunostimulatory proteins into dendritic cells through co-electroporation of multiple mRNA sequences. Recently, optimized strategies to produce highly translatable mRNA further advocates the use of RNA for vaccination purposes. Here, I will discuss the Antwerp experience with RNA-modified DC in cancer, more particularly our latest data on our phase I/II clinical trial using Wilms tumor 1 (WT1) RNA-electroporated DC in acute myeloid leukemia (AML) patients where we investigated feasibility, safety, immunogenicity and clinical effects. We show successful GMP-grade DC generation and vaccine production in all AML patients in remission and absence of severe toxicity (CTC<2) upon vaccination. Following intradermal administration of WT1 mRNA-electroporated dendritic cells, there was a clearly demonstrable anti-leukemic effect in half of the patients that were evaluable (9 out of 17 patients), as evidenced by induction of molecular remission and/or by conversion of partial to complete remission. WT1 antigen-specific T cell responses as well as innate immune activation features were detected post-vaccination, of which some were correlated with clinical responses. These data support the further development of vaccination with WT1 RNA-loaded dendritic cells as a post-remission treatment to prevent full relapse in leukemia patients. In conclusion, RNA-modified DC vaccination emerge as a feasible and effective strategy to control residual disease and prevent full relapse in AML.

Key Words: Cancer vaccine, Dendritic cell, Leukemia.

THE HOST STING PATHWAY IS CRITICAL FOR INNATE IMMUNE SENSING OF A GROWING TUMOR AND BRIDGING TO AN ADAPTIVE IMMUNE RESPONSE VIA IFN-β

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Adaptive T cell responses are required for effective anti-tumor activity, and spontaneous T cell responses against tumors occur frequently. However, the mechanisms by which innate immune responses become induced in response to cancer, and how they can bridge to T cell priming against tumor antigens, are poorly defined. We recently showed that CD11c+ cells produce IFN-β after tumor implantation and this IFN-β plays a critical role on intratumoral accumulation of CD8α+ dendritic cells. As such, spontaneous tumor antigen-specific T cell priming was defective in IFNα/βR or Stat1 knockout mice, and also in Batf3-deficient mice which lack the CD8α+ DC subset. Based on these results, it has become critical to identify the sensing mechanism that mediates production of IFN-β by host DCs in response to tumor-derived products. Using specific gene targeted mice, we observed that expression of MyD88, TRIF, or P2X7R was not required in host APCs for spontaneous T cell priming. In addition, no evidence was obtained to support a role for the inflammasome pathway in type I IFN production. In contrast, mice deficient in the molecule

STING (stimulator of IFN gene) were severely deficient in IFN-β production and T cell priming against tumors. In models of spontaneous tumor rejection, tumors grew progressively in STING-/- mice. Bone marrow derived dendritic cells from STING-/- mice showed markedly defective IFN-β production in vitro. Gene expression profiling of stimulated STING-/- DCs revealed defective upregulation of numerous additional factors, including CD40, CD86, CXCL9, IL-6, and TNF, suggesting a critical role for this pathway in a broad array of DC activation parameters. Our data suggest that the STING pathway in innate immune cells is one of the central mechanisms for IFN-β production and DC activation in response to tumor recognition and is required for effective spontaneous priming of anti-tumor T cells in vivo. Manipulation of this pathway could have important therapeutic implications.

Key Words: Cytokine, Dendritic cell, Innate immunity.

ADENOVIRUS-ENGINEERED HUMAN DENDRITIC CELL VACCINE INDUCES NATURAL KILLER CELL CHEMOTAXIS VIA CXCL8/IL-8 AND CXCL10/IP-10 CHEMOKINES

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Recombinant adenovirus-engineered dendritic cells (Ad.DC) are potent vaccine adjuvants for induction of anti-viral and anti-cancer T cell immunity. The effectiveness of Ad.DC vaccines may depend on the newly described ability of Ad.DC to crosstalk with natural killer (NK) cells via cell-to-cell contact mediated by transmembrane molecules, and to mediate activation, polarization and bridging of innate and adaptive immunity. In order for this interaction to occur in vivo, Ad.DC vaccine must be able to induce migration and attract NK cells from surrounding tissues and/or peripheral blood to the immunization site. In the present study, we developed a novel live animal imaging system-based NK cell migration test, and demonstrated for the first time that human Ad.DC induced mobilization and directional migration of NK cells across subcutaneous tissues, indicating that Ad.DC-NK cell contacts could occur in vivo. We also examined in vitro the mechanism of Ad.DC-induced migration of NK cells and determined that Ad.DC secreted a number of chemokines and induced chemotaxis of all major NK cell subsets. We determined that CD56loCD16+ and CD56hiCD16- NK cells migrated in response to proinflammatory CXCL8/IL-8 and immunoregulatory CXCL10/IP-10 chemokines, respectively. Our study shows that Ad-DC are able to induce recruitment of spatially distant NK cells to a potential vaccine site, and indicates that Ad.DC might do that via specific chemokines. Therefore, Ad.DC vaccine can induce cell-to-cell contact and interaction mediated by transmembrane mediators with endogenous NK cells, and consequently mediate Th1 polarization and amplification of immune functions in vivo.

Key Words: Chemokines, Dendritic cell, NK cells.

MODULATION OF DENDRITIC CELL FUNCTION BY THE TUMOR MICROENVIRONMENT

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Tumors are highly adept at evading the immune system through a multitude of mechanisms, including the secretion of factors that modulate both innate and adaptive immunity. Matrix metalloproteinase-2 (MMP-2) is a proteolytic enzyme that degrades the extracellular matrix and is over expressed by many tumors, including melanoma. We recently documented the presence of MMP-2-specific CD4(+) T cells in tumor-infiltrating lymphocytes (TILs) in several melanoma patients (Cancer Cell 19:333, 2011). Strikingly, MMP-2-specific CD4(+) T cells displayed an inflammatory T(H)2 profile, mainly TNF-α, IL-4, and IL-13 and expressing GATA-3. When exposed to MMP-2, immature human dendritic cells (DCs) primed naïve CD4(+) T cells to differentiate into an inflammatory T(H)2 phenotype through OX40L expression and inhibition of IL-12p70 production. MMP-2 was subsequently found to degrade the type I IFN receptor,

thereby preventing STAT1 phosphorylation, which is necessary for IL-12p35 production. Thus active MMP-2 acts as an endogenous type 2 "conditioner" providing an explanation for the observed prevalence of detrimental type 2 responses in melanoma. Novel properties of MMP-2 on other components of the immune system, and on tumor progression, will be discussed along with DC-based strategies using Toll-like receptor agonists to alleviate immune suppression (Cancer Research doi:10.1158/0008-5472)

Key Words: Cancer vaccine, Dendritic cell, Tumor microenvironment.

LATE BREAKING ABSTRACTS SESSION I

PHASE I STUDY OF INTRAVENOUS RECOMBINANT HUMAN INTERLEUKIN-15 (RH IL-15) IN ADULTS WITH METASTATIC MALIGNANT MELANOMA AND RENAL CELL CARCINOMA

Kevin Conlon[1], John Morris[3], John Janik[4], Donn Stewart[1], Steven A. Rosenberg[1], Tatyana Worthy[1], Tito Fojo[1], Thomas Fleisher[1], Enrico Lugli[2], Liyanage Perera[1], Elaine Jaffe[1], H.Cliff Lane[2], Michael Sneller[2], Stephen Creekmore[1], Carolyn Goldman[1], Bonita Bryant[1], Jean Decker[1], Thomas A. Waldmann[1]

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Interleukin-15 (IL-15) is a cytokine with unique biological features and may have increased potential as an immunotherapeutic compared to IL-2 due to its capacity to maintain the activation of central and effector memory CD8 T-cells without augmentation of T regulatory cell (TReg) function. Our group has demonstrated the activity of IL-15 in syngeneic murine tumor models (CT26 and MC38) and conducted a pharmacology toxicology assessment in rhesus macaques to support this first in human trial. A phase I, single institution, dose escalation trial with a standard 3+ 3 design to determine the safety, toxicity and maximum tolerated dose (MTD) in subjects with metastatic melanoma or renal cell carcinoma was initiated. Eight subjects have been treated to date and enrollment continues. Subjects were to receive a 30 minute intravenous (IV) infusion of rh IL-15 at doses of 3, 7, 10, 15, 20 or 25 mcg/kg daily for 12 doses. After dose limiting toxicities (DLTs) occurred in 2 of the first 5 subjects, the protocol was amended to add a 1 and 0.3 mcg/kg dose level. Most subjects treated at the 3 mcg/kg exhibited a common spectrum of treatment related side effects of fevers, rigors, decreased blood pressure (BP) with the nadir characteristically 4 1/2 to 5 hours after treatment. Nausea/vomiting and brief asymptomatic periods of decreased oxygenation were seen in 3 subjects. The 3 subjects treated to date at the 1 mcg/kg dose level have not shown any significant changes in their BP or oxygenation during treatment. No responses by RECIST criteria have observed, but disease stabilization and regression of some marker lesions has occurred most notably in the first subject treated at the 1 mcg/kg dose level who had near complete disappearance of one of his marker pulmonary lesions. Analysis of the inflammatory cytokines IL-6, interferon gamma (IFN γ), IL-1β, tumor necrosis factor alpha (TNFα) showed maximal levels for all these cytokines at the 4 hour post treatment time point. The pharmacokinetic (PK) analysis of serum IL-15 concentration showed maximum levels (Cmax of 20,000 to 90,000 picograms/ml) at the 10 minute time point with a rapid decline in IL-15 and short half life (t ½ alpha) of approximately 30 minutes and a terminal t ½ (β phase) of 2 to 3 hours. No subject developed anti-IL-15 antibodies. Substantial increases in the absolute lymphocyte count (1.5-4X), CD8 (1.5-3X) and NK cells (4-10X) numbers were seen in all multidose subjects.

Key Word: Interleukin-15.

REVERSAL OF LOCAL IMMUNE EVASION MECHANISMS AND REGRESSION OF HUMAN MERKEL CELL CARCINOMA BY INTRALESIONAL INJECTION OF INTERFERON-BETA

Kelly Paulson[1], Andrew Tegeder[1], Cristoph Willmes[2], Jayasri Iyer[1], David Schrama[2], Shinichi Koba[1], Renee Thibodeau[1], Olga Afanasiev[1], Kotaro Nagase[1], Janell Schelter[3], James Hardwick[3], David Koelle[1], Margaret Madeleine[4], Mary L. Disis[1], Michele Cleary[3], Shailender Bhatia[1,4], Hideki Nakajima[5], Shigetoshi Sano[5], Juergen Becker[2], *Paul Nghiem*[1,4]

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Merkel cell carcinoma (MCC) is an often-lethal neuroendocrine skin cancer associated with a recently discovered, common polyomavirus. Virus-encoded oncoproteins are persistently expressed in ~75% of MCCs, and these viral proteins have been shown to generate cellular immune responses in MCC patients. Although several forms of T-cell immunosuppression are associated with increased risk of MCC, over 90% of MCC patients have no known systemic immune suppression, and in these cases, T-cell evasion may be driven locally by the tumor. Here we report that 51% of MCCs (n=114) demonstrate tumor-specific down-regulation of class I MHC, an effective mechanism for evasion of cytotoxic T cells, which have been strongly associated with improved survival in this cancer. In MCC cell lines, MHC-I down-regulation was multifactorial and reversible by treatment with any of several interferons. Re-expression of MHC-I was persistent and stable in MCC cells after transient exposure to interferon followed by washout. Systemic interferon has been previously explored in the management of MCC but has been ineffective. Systemic administration may fail because of insufficient drug delivery to the tumor microenvironment, compensatory systemic immunoregulatory processes, or lack of a gradient in concentration focused at the tumor. Intralesional injection of interferon beta into MCC tumors was explored to potentially overcome these problems. This treatment led to restoration of MHC-I expression and recruitment of CD8+ lymphocytes to the tumor. Neo-

adjuvant intralesional treatment of eight MCC cases with IFN resulted in two complete responses, five partial responses and one non-response. Interestingly, in two cases, tumor-free enlargement of the draining lymph node developed and in a third case regression of non-injected MCC lesions was observed, further supporting an immunologic mechanism of regression. MCC tumors thus exhibit evidence of local immune evasion and intralesional cytokine therapy may be useful in promoting T cell recognition of this virus-associated malignancy.

Key Word: Merkel cell carcinoma.

IMMUNOLOGY OF CANCER STEM CELLS AND EPITHELIAL-TO-MESENCHYMAL TRANSITION (EMT)

CANCER TESTIS (CT) ANTIGENS EXPRESSED IN OVARIAN TUMOR-INITIATING CELLS

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Ovarian cancer (OC) is the 5th leading cause of cancer death in women. In order to identify patients with early stage disease, we are investigating the expression of CT antigens with high expression in normal testis and tumors but low or no expression in normal tissues. In serous OC a minority (<0.02%) of cells are capable of tumor initiation. We have developed a method for selective culture of tumor-initiating cancer stem cells (CSC) from a number of serous OC cell lines. These CSC divide rapidly but retain tight junctional connections resulting in formation of free-floating chains ("catena") of 4-72 cells with each cell capable of initiating a tumor when transplanted into NSG mice. Catena have an extensive pericellular glycocalyx that provides a barrier to chemotherapy, antibodies, and both innate and adaptive immunity. Enzymatic treatment with collagenase or hyaluronidase in vitro or in vivo can partially or completely remove the glycocayx and render the catena susceptible to antibody or cell-mediated immune killing. We have evaluated the expression of CT antigens by RT-PCR, Affymetrix U133 2 plus, and by SOLid and 454 mRNA deep sequencing of catena, more differentiated tumor of early and late stage, normal ovarian surface epithelium (NOSE), and fallopian tube epithelium. Currently 9 CTs are considered the most suitable for the development of an OC vaccine and immunotherapy (SPAG9/CT89, ACRBP/CT23, PIWIL2/CT80, CTAG2/CT2, CTAG1B/NY-ESO-1, SPA17/CT22, SSX2/CT5.2a, AKAP3/CD82, SYCP1/CT8). Of these, 5 were not detected in catena (including NY-ESO-1, currently in Phase I studies in OC), one was detected by both 454 and SOLid DS (SPAG9), three were detected by SOLid DS (SYCP1, SPA17, AKAP3). We identified 37 CT antigens expressed in CSC from one cell line by SOLid and 28 of these were also identified by 454 DS and RT-PCR. The most highly expressed were SPAG9, IMP-3, TEX15, JARID1B, PRAME, KIAA0100, PBK, RQCD1 and ATAD2. We screened for CT antigen expression in NOSE and found, surprisingly, a number of CT antigens expressed (GPATCH2, SPAG9, CEP290, CCDC36, AKAP3). This is significant since the absence of CT Ag expression reported in normal ovary is data based on whole ovary tissue rather than surface epithelium. In normal fallopian epithelium only one CT Ag was detected (OIP5). Our data indicates that the choice of CT antigen for both biomarker and vaccine therapy needs to take into account the selective CT Ag expression on CSC, the presence of some CT Ags in non-malignant ovarian and follicular tissue, and the immune barrier provided by the glycocalyx.

Key Words: Cancer vaccine, Ovarian cancer, Tumor associated antigen.

IMMUNOTHERAPEUTIC APPROACHES TO EMT AND CANCER STEM CELLS

Claudia M. Palena[1], Bruce Huang[1], Duane Hamilton[1], Ingrid Fernando[1], Fiorella Guadagni[2], Mario Roselli[3], Alessandra Jales[1], David Apelian[4], Jeffrey Schlom[1]

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The epithelial-mesenchymal transition (EMT) has recently been recognized as a process crucial to the progression of carcinomas, mediating the conversion of stationary epithelial tumor cells into mesenchymal-like, invasive tumor cells. We recently identified the T-box transcription factor Brachyury, a molecule predominantly expressed in human tumors but only rarely expressed in normal adult tissues, as a novel driver of the EMT process in human carcinoma cells. Brachyury was demonstrated to induce the expression of molecules associated with the mesenchymal phenotype, human tumor cell motility and invasiveness in vitro, as well as metastatic propensity in xenograft models. Analysis of expression in multiple human tumor tissues demonstrated a preferential expression of Brachyury in higher stage lung tumors, suggestive of a role of Brachyury in human lung cancer progression. Analysis of breast cancer tissues also revealed expression of Brachyury in primary breast tumor samples as well as in 100% of breast cancer metastatic lesions analyzed by immunohistochemistry. We have now shown a positive correlation between Brachyury expression in epithelial tumor cells and tumor resistance in response to treatment with various chemotherapeutic agents, including Taxotere, Cisplatin and Vinorelbine, as well as radiation. Additionally, the expression of Brachyury in epithelial tumor cells has been shown to directly correlate with the expression of markers of tumor stemness, including the ABCB1/MDR1 transporter protein and the self-renewal transcription factors Oct-4 and Nanog. We have previously characterized the immunogenicity of the Brachyury protein and identified a 9-mer epitope of Brachyury that was used in vitro to generate Brachyury-specific human T-cell lines from the blood of cancer patients. Brachyury-specific T cells have shown to be able to efficiently lyse Brachyury-positive tumor cells in an MHC-restricted,

antigen-specific manner. Currently, vaccine platforms that express the full-length human Brachyury protein are under development and a Phase I clinical trial of a heat-killed yeast-Brachyury vector is in preparation. We hypothesize that the eradication of Brachyury-expressing tumor cells via Brachyury-based immunotherapeutic approaches could be efficient at eliminating tumor cells with invasive/metastatic potential as well as tumor resistance to conventional therapies.

Key Words: Cancer vaccine, Tumor associated antigen.

IMMUNOLOGICAL TARGETING OF EPITHELIAL TO MESENCHYMAL TRANSITION AS A STRATEGY TO PREVENT BREAST CANCER METASTASES

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The identification of a subset of breast cancer (BC) cells with properties of cancer stem cells (CSCs), that are responsible for tumorigenesis, metastasis and recurrence, and are intrinsically more resistant to chemotherapy and radiation, provides an unprecedented opportunity to develop new treatment strategies. The transcription factor Twist plays a key role in induction of epithelial to mesenchymal transition (EMT) and acquisition of CSCs properties by BC cells. Twist is also a key regulator of metastasis in the 4T1 mouse model of breast cancer, and has been implicated in resistance to chemotherapy and radiation, and in early disease relapse after adjuvant treatment in patients. Therefore, strategies to target Twist could be effective for the prevention of metastatic BC.

Using the SYFPEITHI Epitope Prediction computer-based algorithm we have identified a Twist-derived peptide (pTw9) that forms stable complexes with H2-Kd with DC50 of >6 hr, and was able to sensitize P815 cells to lysis by 4T1 tumor-specific CTL isolated from mice that rejected 4T1 tumor. A pTw9-specific CTL line established by repeated in vitro re-stimulation specifically killed 4T1 cells, confirming that pTw9 is an endogenously produced CTL epitope. Immunization experiments with pTw9 confirmed that this peptide is immunogenic in naïve mice. To determine whether CTL targeting pTw9 can prevent the generation of CSCs in vivo and inhibit metastases, we have prepared 4T1 cells expressing ZsGreen-cODC fusion protein, which contains the degron of ornithine decarboxylase leading to rapid proteasome-mediated degradation of the reporter protein. Tumor cells that accumulate ZsGreen-cODC to detectable levels have the characteristics of CSCs and can be imaged in vivo (Vlashi et al., J Natl Cancer Inst. 2009, 101:350-9). 4T1-ZsGreen-cODC cells injected s.c. into RAG2-deficient mice were allowed to spontaneously metastasize to the lungs. Lungs were harvested 30 days later, digested, and analyzed by flow cytometry for the presence of EpCAM+ZsGreen+ tumor cells. ZsGreen+ cells represented on average 4.4 ± 4.9% of EpCAM+ tumor cells in the lung (range 0.6 to 15.0%). Since the injected population did not contain detectable ZsGreen+ cells, results suggest that 4T1 cells with CSC characteristics are generated in vivo and enriched in the spontaneous lung metastases.

Use of 4T1-ZsGreen-cODC cells will allow the tracking of tumor cells with CSCs properties in vivo. This system provides a unique tool to test the hypothesis that immunological targeting of Twist can inhibit EMT and the generation of tumor cells with breast CSCs properties.

Key Words: Breast cancer, CD8+ T cells, Tumor associated antigen.

POTENTIAL FOR IMMUNOTHERAPEUTIC CONTROL OF CSC-LIKE CELLS THROUGH THEIR EXPRESSION OF FAS AND DR5 DEATH RECEPTORS

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There is accumulating evidence for a role for cancer stem cells (CSC) in the recurrence of cancer and in the development of metastatic disease. Therefore, although CSC comprise only a small proportion of cells within a tumor, they should be considered an important population for therapeutic targeting. Since CSC are resistant to standard radiotherapy and chemotherapeutic treatments, identification of alternative treatment strategies, such as immunotherapeutic modalities, is required. Given the growing number of immunotherapies being used to treat cancer and the fact that some chemotherapies may actually prime immune responses, it is important that a better understanding of the susceptibility of CSC to various immunotherapeutic modalities is investigated. Therefore, the immunological characterization of CSC becomes essential for the identification of immune-associated molecules expressed by CSC, which can be potentially exploited as an immunotherapy. The majority of studies on CSC have utilized cells from patient samples or human cell lines. However, these xenograft models are conducted in immunocompromised mice, which limits our ability to investigate immune interactions and immunotherapeutic responses. Therefore, a CD44+CD24-/low subpopulation of cells within the murine AT-3 mammary carcinoma cell line was identified that had CSC-like characteristics, including an ability to differentiate and repopulate the line, and a resistance to chemo- and radiotherapy. These cells can then be used as a model system to study interactions between breast CSC and a competent immune system and to investigate their susceptibility to immunotherapeutic strategies. This AT-3 CSC-like subpopulation was immunologically characterized through their surface molecule expression profile and their susceptibility to a range of cell death pathways. Similar levels of the surface molecules Rae-1, CD155, CD54 (NK cell-killing); and higher levels of Fas (Fas-killing) and DR5 (TRAIL-killing) were expressed on AT-3.CSC compared to other non-CSC tumor cells. This expression profile correlated with an in vitro sensitivity to cell death by NK cells; and through the recognition of the death receptors, Fas or DR5, by either FasL- or TRAIL-expressing cells; or anti-Fas and anti-DR5 mAbs. Indeed, the AT-3.CSC were actually shown to be more sensitive to both

Fas- and TRAIL-mediated cell death pathways. Therefore, despite the refractory nature of CSC to other forms of therapy, the AT-3. CSC were not inherently resistant to specified forms of immune-mediated cell death. This sensitivity is support for continued investigations in the use of immunotherapeutic strategies to target the CSC component of breast cancer.

Key Words: Apoptosis, Breast cancer, Tumor microenvironment.

UNCOUPLING NEGATIVE REGULATION IN THE TUMOR MICROENVIRONMENT

IL-12 TRIGGERS AN INFLAMMATORY GENE SIGNATURE THAT REVERSES DYSFUNCTIONAL ANTIGEN-PRESENTATION BY MYELOID-DERIVED CELLS RESIDING WITHIN TUMORS

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Myeloid-derived cells comprising the tumor stroma represent a heterogeneous population of cells critical to the structure, function and growth of established cancers. We have recently found that engineering tumor-specific CD8+ T cells to secrete IL-12 (IL-12 cells) can lead to striking improvements in T-cell activity against established melanomas in murine models. Surprisingly, IL-12-dependent enhancement of CD8+ T-cell anti-tumor function did not occur through direct ligation of receptors on lymphocytes or NK cells. Instead, IL-12 created an inflammatory gene signature within tumors that sensitized tumor-infiltrating CD11b+ F4/80Hi macrophages, CD11b+/ClassIIHi/CD11cHi dendritic cells and CD11b+/Gr1Hi myeloid-derived suppressor cells to efficiently cross-present antigen naturally present within tumors. Interestingly, direct presentation of antigen by tumor was not necessary, but MHC class I expression on host cells was essential for IL-12 mediated anti-tumor enhancements. Upon successful treatment with IL-12 cells, we observed the selective elimination of tumor-infiltrating CD11b+ F4/80Hi macrophages, CD11b+/ClassIIHi/CD11cHi dendritic cells and CD11b+/Ly6CHi/Ly6GLow but not CD11b+/Ly6CHi/Ly6GHi myeloid-derived suppressor cells within regressing lesions. These results are consistent with a model whereby IL-12 triggers an inflammatory environment resulting in a programmatic change in the antigen-presenting cell population within tumors. This remodeling of the tumor microenvironment dramatically improves the ability of adoptively transferred T cells to collapse large vascularized tumors.

Key Words: Cytokine, Tumor microenvironment, Tumor stromal cells.

ACUTE MYELOID LEUKEMIA PROMOTES IMMUNE EVASION THROUGH INDUCTION OF ANTIGEN-SPECIFIC T CELL DELETION

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Spontaneous antigen-specific T cell responses can be generated in hosts with solid malignancies, but become subverted by immune evasion mechanisms active within the tumor microenvironment. In contrast to our knowledge about solid tumors, the mechanisms which regulate T cell activation versus tolerance to antigens expressed on hematopoietic malignancies have been under-explored. We therefore investigated antigen-specific T cell responses in a murine AML model using cells inoculated intravenously (IV) or subcutaneously (SC). Functional antigen-specific T cell responses were generated against AML cells following SC inoculation. In contrast, an IV AML cell inoculation led to minimally-detectable T cell responses, and also blocked the generation of functional T cell responses against a subsequent SC AML challenge, suggesting that disseminated leukemia actively promoted T cell dysfunction. This phenomenon was antigen-specific in nature, and did not result from suppression by regulatory T cells or myeloid-derived suppressor cells. T cell receptor transgenic $CD8^+$ T cells specific for a model antigen on AML cells proliferated but failed to accumulate and expressed low levels of effector cytokines in hosts with following IV AML induction, consistent with the induction of T cell anergy or deletion. Transgenic expression of Bcl-X_L in antigen-specific T cells nearly completely restored their ability to accumulate and produce effector cytokines following the IV induction of AML, arguing that T cell deletion was occurring. Hypothesizing that this process might be regulated by tolerogenic host dendritic cells, strikingly enhanced antigen-specific endogenous T cell responses were generated in mice with IV AML following in vivo dendritic cell activation with an agonist anti-CD40 antibody. In conclusion, antigen-specific T cell deletion is a potent immune evasion mechanism which occurs early following IV AML dissemination and is preventable following in vivo DC activation via CD40 ligation. Ongoing experiments will delineate the precise cellular mediators of T cell deletion and identify additional strategies to prevent this process with therapeutic intent.

Key Words: Animal model, Leukemia.

TARGETING MULTIPLE INHIBITORY PATHWAYS TO REVERSE MELANOMA-INDUCED T CELL DYSFUNCTION

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There is ample evidence that patients with melanoma can spontaneously develop immune responses directed against antigens expressed by their own tumors. Understanding the failure of spontaneous TA-specific T cell responses to promote regression of tumors is therefore critical for the design of novel therapeutic

interventions aimed at overcoming tumor-induced immune escape. The progressive loss of T cell function occurring upon chronic exposure to high antigen load, also called T cell exhaustion, has first been reported in mice chronically infected with LCMV. The exhausted antigen-specific CD8+ T cells upregulate multiple inhibitory receptors, including PD-1, 2B4, CTLA-4, CD160 and LAG-3. The expression of multiple inhibitory receptors by T cells is associated with greater exhaustion and more severe infections. Several lines of evidence support the role of inhibitory pathways in impeding effective anti-tumor T cell immune responses in cancer patients. First, we and others have shown that TA-specific CTLs present in PBLs or at tumor sites upregulate PD-1 expression and that PD-1 regulates the expansion of TA-specific CD8+ T cells. Second, we have shown that a highly dysfunctional subset of TA-specific T cells present at the periphery or at tumor sites, co-upregulates PD-1 and T cell immunoglobulin and mucin-domain-containing molecule 3 (Tim-3) expression. PD-1 and Tim-3 blockades act in synergy to enhance TA-specific CD8+ T cell numbers and functions in patients with advanced melanoma and induce tumor regression in animals. Here, we further show that a number of TA-specific CD8+ and CD4+ T cell subsets present at the periphery and at tumor sites, express different sets of inhibitory molecules including PD-1 and Tim-3 and exhibit variable levels of dysfunction. Notably, dysfunctional antigen-specific CD8+ T cells in cancer and chronic viral infections appear to upregulate overlapping but distinct sets of inhibitory molecules. Inhibitory pathway blockades can synergize to enhance TA-specific CD8+ and CD4+T cell expansion and to restore their ability to produce cytokines. Collectively, our findings support the targeting of a number of inhibitory pathways including PD-1 and Tim-3 to reverse tumor-induced T cell dysfunction in patients with advanced melanoma and increase the likelihood of tumor regression.

Key Words: CD8+ T cells, Melanoma, PD-1.

GENETICALLY ENGINEERED RECEPTORS AND ADOPTIVE CELL THERAPIES

GENETICALLY ENGINEERED RECEPTORS IN ADOPTIVE CELL THERAPIES

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The adoptive transfer of T cells can be used to prevent and treat pathogens and malignancies. However, immune tolerance to tumor associated antigens (TAAs) often precludes the emergence of a functional endogenous immune response that has a desired therapeutic anti-tumor effect. Therefore, investigators have genetically engineered T cells to recognize TAA. This is based on the observation that tolerance can be overcome in a subset of patients or in mice and these high infinity immunoreceptors can be harnessed to redirect specificity. Two types of immunoreceptors have been stably expressed in clinical grade T cells for the purposes of targeting (i) intracellular and (ii) extracellular TAA. In the first, the alpha/beta T-cell receptor (TCR) paired chains have been expressed to engineer specificity for TAA-derived peptides presented in the context of restricting HLA. In the second, single chain chimeric antigen receptors (CARs) have been developed to directly recognize cell surface TAA independent of HLA. Both of these immunoreceptors have shown efficacy in human trials and provide proof-of-principal that genetically engineered T cells can exert an anti-tumor effect in patients with advanced malignancies. In this presentation I will highlight the accomplishments that have combined T cell therapy with gene therapy to produce clinical grade reagents with therapeutic potential. I will focus on T cells as the cellular platform for introducing immunoreceptors, but recognize that specificity other cells (such as natural killer cells) can also be engineered. The modes of gene transfer will also be discussed focusing on the pros and cons of using viral as well as nonviral-based strategies.

Key Word: Adoptive therapy.

SELECTION OF ALLO-RESTRICTED PEPTIDE-SPECIFIC TCRs FOR ADOPTIVE T CELL THERAPY

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Adoptive transfer of "designer" T cells expressing transgenic T cell receptors (tg-TCRs) with anti-tumor specificity provides a new therapeutic strategy for patients with advanced tumors. There is a critical bottleneck to obtain high-avidity T cells with TCRs that efficiently recognize tumor cells. We developed a dendritic cell priming approach using allogeneic MHC molecules to present peptides of self-proteins to prime allo-restricted T cells that efficiently kill tumor cells as sources of tg-TCRs (Wilde et al. Blood 114, 2009; Leisegang et al., J. Clin. Invest. 120, 2010). Thereby we readily isolate many T cell clones restricted by different HLA allotypes and specific for different antigens.

Having large numbers of high-avidity T cells raises the problem of rapid selection of clones whose TCRs are suitable for further study. TCRs should display high peptide sensitivity and good tumor recognition after expression as tg-TCRs. Since these assessments require many cells, we sought surrogate parameters to identify relevant clones using many fewer cells. A retrospective analysis of T cell clones with identical MHC-peptide specificity but different peptide sensitivities was used to compare functional and MHC-TCR structural parameters. Greater capacity to bind MHC multimers and slower loss of bound multimers reflect stronger TCR-pMHC interactions, thus these parameters seemed suitable to quickly identify high-avidity CD8+ CTL. Large disparities were

found however between multimer binding, peptide sensitivity and tumor recognition. In contrast, CTL with greater antigen sensitivity and tumor recognition secreted the CD4-associated T helper 1 (Th1) cytokines IFN-gamma, IL-2 and TNF-alpha. Designer lymphocytes showed high antigen sensitivity, excellent tumor recognition and Th1-polycytokine secretion following tg-TCR expression of a Th1-like CTL. Use of a tg-TCR from a clone without a polycytokine profile was inferior in all these properties. Thus, Th1-polycytokine secretion seems suitable to identify clones whose TCR merit further evaluation, while requiring less than fifty thousand cells for an initial screen and capture of the TCR sequence.

Next we developed efficient methods to rapidly express tg-TCRs in recipient tumor cell lines lacking endogenous TCRs to assess peptide- and tumor-specificity. TCRs with required specificities are then expressed as tg-TCRs in human lymphocytes and studied in vitro and following adoptive transfer into NOD/SCID/IL-2Rg-/- mice that bear human tumor cells, in order to determine impact on tumor growth in vivo.

With this technology platform, we can now rationally build libraries of tg-TCRs with different MHC restrictions and antigen specificities for future use in adoptive therapy with designer lymphocytes.

Key Words: Adoptive therapy, Animal model, CD8+ T cells.

DIFFERENTIAL GENE EXPRESSION ASSOCIATED WITH IMMUNE DOWN REGULATION IN TCR GENE-ENGINEERED T CELLS ADMINISTERED TO PATIENTS

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Therapies based on the transfer of peripheral blood T cells genetically engineered to express tumor-targeting T-cell receptors (TCRs) have been shown to mediate objective tumor regressions. Nevertheless, a detailed analysis of transferred cells post-infusion revealed that these transferred cells gradually down regulated the expression of TCR, which was associated with a parallel decrease in the expression of endogenous T cell genes.

In order to better understand the molecular basis of this 'immune cool down' we performed a comparative transcriptomic analysis between TCR-transduced cells prior to and one month after infusion. FACS-sorting was used to isolate TCR+ cells from the peripheral blood of 8 patients that received gp100- or MAGE A3-specific TCR-transduced cells, and these were compared to matched infusion preparations. Within a panel of 84 genes involved in T-cell biology, we found 38 differentially expressed genes, by Q-RT-PCR analysis (fold change >2, $p<0.05$). Preliminary analysis revealed the following observations.

1. Within the group of differentially expressed genes, PDCD1, which encodes the inhibitory receptor PD-1, was over expressed in post-infusion samples as compared to infusion. PD-1 surface expression in circulating CD8+ T cells post-infusion was confirmed by flow cytometry in 5 of 6 samples analyzed. Furthermore, coculture of 1 month post-infusion T cells with tumor cell lines expressing its ligand, PD-L1, resulted in impaired secretion of IFN-gamma by TCR-expressing T cells, compared to those cocultured with targets that do not express PD-L1.

2. A group of functionally related genes (TNFSF14, TNFRSF14, BTLA and LTA), that can modulate T cell signaling, were found to be tightly regulated at the RNA level in the samples analyzed. Co-stimulatory genes LTA and TNFSF14 were up-regulated in infusion samples but down-regulated in post-infusion cells, whereas the co-inhibitory gene BTLA was down-regulated in infusion samples. The ligand for BTLA, TNFSF14 and LTA (encoded by the TNFRSF14 gene) was down-regulated in infusion cells but up-regulated post-infusion.

3. FoxP1, a transcription factor involved in the maintenance of T cell quiescence, was dramatically down regulated in infusion samples, but up-regulated in post-infusion cells.

These results may provide a rationale for a treatment based on the modulation of genes involved in T cell function, as a potential method to improve adoptive cell therapy for cancer.

Key Words: Adoptive therapy, CD8+ T cells, PD-1.

ACTIVE STAT5 PROMOTES LONG-LIVED CYTOTOXIC CD8 T CELLS THAT INDUCE REGRESSION OF AUTOCHTHONOUS MOUSE MELANOMA

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Immunotherapy based on adoptive transfer of tumor antigen-specific CD8 T lymphocytes (TL) is compromised by the poor expansion and tumor infiltration of the infused TL. To increase the efficiency of this adoptive transfer, large number of ex-vivo expanded cells need to be infused in irradiated patient with interleukin-2. We have previously shown that both the avidity of TCR stimulation and signals from the IL-2R affect the differentiation of fully competent CD8 effector TL. These results further support the use of IL-2 as adjuvant to increase reactivity of CD8 effector TL, as tumor antigens are generally of low antigenicity. However, IL-2 has been implicated in the expansion/function of CD4+CD25+ T regulatory cells with immunosuppressive properties, so the use of alternative approaches to improve the function and the in vivo expansion of CD8 eTL may be preferable.

We here report that when CD8 effector TL (eTL) expressing a constitutively active STAT5 transcription factor (STAT5CA) are infused in tumor bearing hosts, they show greatly enhanced tumor infiltration, tumor Ag -induced reactivation and granzyme B expression within the tumor. In the inducible TiRP mouse strain which recapitulates key aspects of human melanoma, developing melanomas are infiltrated by CD8 TL but these cells exhibit an « exhausted » phenotype associated with systemic chronic inflammation. When adoptively transferred in mice bearing

autochthonous or transplanted melanomas, the anti-tumor effects of STAT5CA-transduced CD8 TL were superior to those of control CD8 TL, even when the latter were combined with IL-2/IL-2mAb complex infusions. Additionally, endogenous CD8 TL present in the tumor demonstrated enhanced Granzyme B expression upon infusion of STAT5CA-transduced CD8 TL. Altogether, STAT5CA-expressing CD8 TL appeared to resist the immunosuppressive environment of melanoma tumors and to be beneficial for surrounding endogenous CD8 TL.

Key Words: Adoptive therapy, Animal model, CD8+ T cells.

ENGINEERED T CELL THERAPIES FOR HEMATOLOGIC MALIGNANCIES

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The majority of non-Hodgkin's lymphomas, acute lymphoblastic leukemias and chronic lymphocytic leukemias (CLL) express CD19, which is also expressed by normal B cells but not by hematopoietic stem cells or other tissues. Thus CD19 represents an attractive target for immunotherapy. Our preclinical studies show that combining robust T cell culture systems with lentiviral vector modified human T cells expressing CD19-specific Chimeric Antigen Receptor (CART-19) has potent anti-leukemic efficacy in mice bearing established leukemic xenografts. 4-1BB-containing signaling endodomains enhance this activity. In an ongoing feasibility and safety clinical trial, three patients with advanced treatment refractory CLL have been treated. CD3+CD45+ cells in leukapheresis products (range 2.3%-4.5%) were positively selected with anti-CD3/anti-CD28 magnetic beads prior to CART-19 lentiviral vector transduction and expansion. Patients were infused with a total of 0.3-5 x 109 total T cells, with 5%-27% of cells expressing CART-19. Two of three patients remain in complete remission beyond 8 months post infusion. The third patient had a very significant but partial response; he required corticosteroids 18 days after infusion, during an ongoing response, for symptoms presumably related to cytokine release. We observed significant in vivo expansion in two of three patients accompanied by long-term persistence in blood and migration to bone marrow, and delayed onset tumor lysis syndrome accompanied by elevated levels for a broad range of cytokines. Clinical responses were documented by normalization of blood counts, resolution of adenopathy, and clearance of MRD when assessed by flow cytometry and deep sequencing for IgH rearrangements, cytogenetics, and FISH studies in the bone marrow. On target toxicities have been observed in all patients, including cytokine release but not cytokine storm, B cell depletion, plasma cell depletion and hypogammaglobulinemia requiring replacement serotherapy. Confirmation of these observations that T cells expand and traffic to tumor sites, stimulate synergistic antitumor immune activity, and persist long term in vivo potentially offers significant therapeutic and economic advantages over existing therapies and should be confirmed in larger numbers of patients, however, the therapeutic index with potent cell based CAR therapies will depend to a large extent on the specificity of the target.

Key Words: Adoptive therapy, Leukemia.

SATURDAY, NOVEMBER 5, 2011

Presenting author underlined, *Primary author in italics*

KEYNOTE ADDRESS:

INNATE IMMUNE RECOGNITION OF NUCLEIC ACIDS

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The considerable potency of nucleic acids as triggers of the innate immune response has gained considerable appreciation over the last few years. RNA recognition systems play important roles in immunity to viruses, bacteria as well as in the pathogenesis of autoimmune diseases such as Systemic Lupus Erythematosis where TLR7 on PDCs and B-cells is activated by RNA-containing immune complexes. It has also been known for over a decade that DNA, the most recognizable unit of life elicits an inflammatory response in cells. The discovery of Toll-Like Receptor-9, a type I transmembrane receptor which drives inflammation in response to hypomethylated CpG-rich DNA partially explained these findings. A number of new DNA sensing molecules have since been uncovered which contribute to various aspects of DNA-driven immunity. Many of these molecules are present in the cytosolic compartment. Through recognition of microbial genomes or nucleic acids generated during replication, DNA sensing from the cytosol has emerged as a central component of anti-viral and anti-bacterial defenses. In certain situations, nuclear DNA also alerts the innate immune system to the presence of nuclear replicating Herpesviruses. Aberrant sensing of host nucleic acids is also now directly linked to immune pathology and autoimmunity. The discovery of the TLRs, as well as cytosolic and nuclear DNA detection systems has therefore provided fresh insights into a growing number of infectious diseases and contributed greatly to our understanding of the pathogenesis of autoimmune and chronic inflammatory diseases. This lecture will provide an overview of these recognition mechanisms and their role in health and disease.

Key Words: Cytokine, Dendritic cell, Macrophages.

CHARACTERIZATION OF INFLAMMATORY INFILTRATES IN HUMAN CANCERS

DC VACCINATION CONCURRENTLY REDUCES TREG AND ENHANCES ACTIVATED CTL IN TUMOR BIOPSIES FROM IMMUNORESPONSIVE PATIENTS WITH ADVANCED MELANOMA

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Despite human melanoma cell is traditionally regarded as highly immunogenic, immunotherapeutic approaches so far developed had still not proved significant clinical efficacy. Among mechanisms known to hamper development of antitumor immunity, local immunosuppression by regulatory T cells (Treg) play a central role. Strategies aimed to remove inhibitory effects of these cells have been developed; in particular, inhibition of Treg by CTLA-4 blockade was recently shown to significantly improve outcome of patients with metastatic melanoma.

However, this approach may lead to severe autoimmune side effects.

Conversely, dendritic cell vaccines can efficiently induce antitumor immunity without significant side effects, although durable responses are obtained only in a limited fraction of patients. We have shown that patients developing tumor-specific delayed type IV hypersensitivity response (DTH) after DC vaccination have a better clinical outcome. However, also in the presence of efficient induction of antitumor immune responses by the vaccine, patients can still fail and we do not know whether this is due to progressive accumulation of inhibitory immune cell populations along multiple immunizations or to different mechanisms. Growing evidence points to the possibility that the relatively low clinical activity of dendritic cell vaccination in melanoma patients may be related to enhanced activity of Treg along treatment. In particular, repeated immunizations with dendritic cell vaccines might lead to expansion of circulating Treg which might home to tumor tissues and inhibit antitumor immune response.

To address this latter issue and to indagate whether immunologically efficient DC-based vaccine is able per se to modify the amount of tumor-infiltrating Treg alone, we evaluated quantitative changes induced by autologous tumor lysate-loaded DC vaccine in tumor-infiltrating Treg and activated cytotoxic CTLs in 8 immunological responder patients with metastatic melanoma for which both prevaccine and at least one postvaccine biopsy were available.

Our results showed that repeated vaccinations with autologous tumor lysate-loaded mature DC lead to considerable and statistically significant decrease of regulatory T cell infiltrating tumor tissue in the majority of patients indagated; moreover, concurrent enhancement of intratumor CD8+/Granzyme-B+ activated CTLs in postvaccine biopsies was found, indicating that vaccine-induced Treg decrease is functionally relevant.

Key Words: Dendritic cell, Treg cells, Tumor infiltration lymphocytes.

CONTRASTED PROGNOSTIC IMPACT OF TUMOR INFILTRATION BY VARIOUS SUBSETS OF IMMUNE CELLS

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The question of the role of the "in situ" type, location and functional orientation, i.e. the "immune contexture" was addressed inhuman cancers). Using high throughput analysis of the components of the immune system, we first established that the presence of a high adaptive immune infiltration in the center and in the invasive margin of colorectal tumors was the strongest prognosticator of disease free survival, recurrence and overall survival above the classical tumor associated factors, such as age, differentiation and lymph node involvment. Similar results were obtained in non small cell lung cancers, both adenocarcinomas and squamous cell, with the additional characterization of tumor-associated lymphoid islets as being the putative location of an anti-tumor immune reaction. A Th1/CD8 cytotoxic infiltration is associated with a favourable progosis whereas Th17 and NK cells infiltrations rather correlate with poor prognosis. We believe that the fact that adaptive immune reactions present in different human cancers are major prognosticators of clinical outcome supports the hypothesis of efficient immune responses which control in the long term the metastatic potential of circulating tumor cells are represent targets and for tools for immunointervention. To develop novel immunotherapies aimed to re-inforce or re-create a beneficial immune environment, it is essential to decipher the mechanisms underlying the shaping of an efficient immune response at the tumor sites. Chemoattraction and adhesion molecules were found associated with the densities of specific immune cells at the tumor site and with disease-free survival while another set of chemokines and cytokines, including IL-16, are involved in the formation of the tertiary lymphoid structures, adjacent to the tumoral nests, where an efficient disease controlling immune reaction may occur. Moreover, the expression of certain chemokines associated with the recruitment of selective T cell populations predicted patients survival. Modyfying the concentration and/or the activity of these chemokines may dramatically change the immune contexture of a tumor and subsequently the patients clinical outcome. Moreover, the better knowledge of the "important" immune cells which control tumors should guide selected cell therapies.

Key Words: CD8+ T cells, Chemokines, Tumor infiltration lymphocytes.

TOPICAL TLR7 AGONIST IMIQUIMOD CAN INDUCE IMMUNE-MEDIATED REJECTION OF BREAST CANCER SKIN METASTASES

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Purpose: Skin metastases of solid tumors remain a therapeutic challenge. Breast cancer is the most common tumor, excluding melanoma, to metastasize to the skin in women and often manifests as chest wall recurrence after mastectomy. Toll-like receptor (TLR)-7 agonist imiquimod (IMQ) has profound immunomodulatory effects on the tumor environment, and can induce immune-mediated rejection of primary skin malignancies when topically applied. We have previously demonstrated the ability of IMQ to augment immunity to tumor-associated antigens administered simultaneously into healthy skin of cancer patients. Here we tested the hypothesis that topical IMQ can stimulate local anti-tumor immunity and induce the regression of breast cancer skin metastases.

Methods: This trial was designed to evaluate the local tumor response rate (complete clinical response, CCR and partial response, PR) of skin metastases treated with topical IMQ. Safety and immunological correlates were secondary objectives. Women >/= 18 years of age with biopsy-proven breast cancer and measurable skin metastases not suitable for definitive surgical resection and radiation, adequate performance status, bone marrow and organ function were eligible. Concurrent systemic cancer therapy (hormones, biologics or chemotherapy) was only allowed if patients had been on stable regimen for >12 weeks and skin metastases were non-responsive. Informed consent was obtained from all patients; the study was approved by the institutional review board. Patients were treated with topical imiquimod 5% to chest wall and/or skin metastases of breast cancer, 5 days/week for an 8 week cycle.

Results: 10 patients were enrolled and completed the study, two patients received a second treatment cycle. IMQ was well tolerated, with transient local and systemic side effects consistent with the immunomodulatory effects of the TLR7 agonist. Clinical response to topical IMQ therapy was achieved in 2/10 patients, both of whom achieved a clinical PR. One of the two responders showed a marked increase in CD8 and CD4 T cells infiltrating the tumor cell nests post-treatment and histological evidence of tumor regression. Treatment-induced changes in the intratumoral cytokine milieu were consistent with tumor rejection and inflammation.

Conclusion: Topical IMQ can be a useful treatment modality for breast cancer metastatic to skin or chestwall and is well tolerated.

Importantly, data indicate that IMQ is able to promote a pro-immunogenic tumor microenvironment in breast cancer and support testing the combination of IMQ with cytotoxic treatments that have been shown to synergize with this immune response modifier in pre-clinical breast cancer models.

Key Words: Breast cancer, Dendritic cell, Tumor infiltration lymphocytes.

SERIAL IMAGING OF INFLAMMATION AND THERAPEUTIC RESPONSE WITH CLINICALLY TRANSLATIONAL 19F MRI

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Inflammation plays an important role in the development and progression of cancer. Non-invasive imaging of inflammation to monitor responses to immunotherapy targeting tumor associated macrophages and other phagocytic cells would permit early assessment of disease responsiveness or response to vaccine adjuvants. V-Sense, a perfluorocarbon contrast agent, labels phagocytic inflammatory cells, which are then recruited out of systemic circulation to sites of inflammation, enabling detection by 19F magnetic resonance imaging (MRI). With no 19F background in the host, detection is highly-specific, yielding a quantitative marker of the degree of inflammation present. To establish the use of V-Sense for serial imaging in therapeutic studies, a rat model of rheumatoid arthritis was used for proof of concept studies. Following induction of disease, progression in the rat hind limbs was monitored by caliper measurements and 19F MRI on days 15, 22 and 29, including the height of clinically symptomatic disease. The capacity of V-Sense to assess the effectiveness of therapy was studied in a cohort of rats administered oral prednisolone (an effective therapy) on days 14 to 28. The presence of disease on day 15 was detectable both by swelling and 19F MRI, and a linear correlation was observed between severity and the degree of V-Sense accumulation, while naïve rats had no detectable V-Sense accumulation in the hind limbs. Over serial imaging sessions, the degree of amount of V-Sense at the inflammatory site correlated with the extent of disease progression or regression. This study may support the use of V-Sense as a biomarker to clinically quantify and monitor the severity of inflammation, and to assess the effectiveness of immunomodulatory treatments or vaccines in arthritis or cancer.

Key Words: Cell trafficking, Macrophages, Tumor infiltration lymphocytes.

POST-TRANSLATIONAL CHEMOKINE MODIFICATION PREVENTS INTRATUMORAL INFILTRATION OF ANTIGEN-SPECIFIC T CELLS

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The goal of all immunotherapeutic approaches against solid tumors is the induction and expansion of tumor infiltrating T lymphocytes (TILs) capable of invading tumor mass and kill transformed cells. Unfortunately, in many tumors TILs are unable to reach the core of the tumor and concentrate at the border of the neoplastic lesion. Several barriers can limit complete trafficking and migration of lymphocytes within cancerous tissues. We evaluated the possibility that reactive nitrogen species (RNS) could affect chemokine biology and contribute to keep TILs distant from the tumor core. Chemokines are small cytokines with selective chemoattractant properties. Deregulated expression of chemokines and their receptors is a signature of many diseases, including autoimmunity and chronic inflammation, as well as immunodeficiency and cancer. We found that the chemoattractants CXCL12, CCL21, and CCL2 lost their ability to recruit T lymphocytes when exposed to peroxynitrite, a RNS produced within tumor microenviroment. However, the modified CCL2 chemokine retained its capacity of recruiting myeloid cells. These data indicate that RNS-altered chemokines modify the tumor microenvironment and favor immune escape by attracting tumor-promoting myeloid cells while restraining access to antitumor T lymphocytes. Based on our findings, drugs controlling the in situ production of RNS might be useful to aid immunotherapeutic approaches for the treatment of cancer, by creating a favorable tumor environment for lymphocyte recruitment and activation. Following an extensive in vitro and in vivo screenings, we developed novel small molecules aimed at interfering with multiple, interconnected metabolic pathways leading to RNS generation in the tumor microenvironment. Pre-conditioning of tumor microenvironment with novel drugs that inhibited RNS production facilitated CTL invasion of the tumor and promoted an effective cancer immunotherapy. These results unveil an unexpected mechanism of tumor evasion and introduce new avenues for immunotherapy of tumors.

Key Words: Adoptive therapy, Chemokines, Tumor microenvironment.

LATE BREAKING ABSTRACTS SESSION II

FREQUENCY OF STRONG ANTIBODY RESPONSES FOLLOWING COMBINATION IMMUNOTHERAPY CORRELATES WITH INCREASED PSA DOUBLING TIME IN MEN WITH ANDROGEN-INDEPENDENT PROSTATE CANCER

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Development of a strong immune response results in B cells and T cells being primed against the same antigens. For a B cell to switch from producing IgM to IgG requires CD4 T cell help. Therefore, we postulate that identification of IgG antibodies against possible tumor/tumor-associated proteins, identified by ProtoArray, will be a surrogate for a T cell response against that

same antigen. This strategy is strongly supported by reports in both human and murine settings (Valmori 2007 and Willimsky 2008). We used 8,217 protein spotted arrays (ProtoArrays, Invitrogen) to analyze antibody responses in sera from 10 evaluable patients on an investigator-initiated combination immunotherapy trial for men with advanced prostate cancer. While a small group, 3 men exhibited a 3 fold or greater increase in PSA-DT. The PSA-DT in the remaining patients was stable or decreased. Based on our analysis of these 10 evaluable patients, we found that men with an increase in PSA-DT (n=3) had a significantly ($p<0.05$) higher number of strong Ab responses (>15 fold increase) than men whose PSA-DT remained stable or decreased. This finding, in the cohorts of men receiving combination immunotherapy and who were hypothesized to respond better to vaccination, has encouraged us that our immunological monitoring strategy is reasonable. Characterization of the T cell responses to the identified antigens as well as the development of a high-throughput screening system using custom protein bead arrays are ongoing.

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Willimsky G. et.al., J Exp Med. 2008 Jul 7;205(7):1687-700.

Key Words: Antibody response, Biomarker.

IDO1 ACTIVITY CORRELATES WITH HEPATOCYTE GROWTH FACTOR LEVELS AND IMMUNE SYSTEM IMPAIRMENT IN MULTIPLE MYELOMA

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Purpose: Indoleamine 2,3-dioxygenase 1 (IDO1) degrades tryptophan into immune-suppressive kynurenines (KYN), thus inducing immune dysfunction through T-cell proliferative arrest, T-cell apoptosis and regulatory T-cell (Treg) differentiation. It is presently unknown whether plasma cells in multiple myeloma (MM) foster the differentiation of Treg cells through an IDO1-dependent mechanism and whether IDO1 activity correlates with over-production of hepatocyte growth factor (HGF), an immune-modulating cytokine implicated in MM pathogenesis.

Patients and methods: Thirty-four patients with plasma cell dyscrasia (27 newly diagnosed or relapsed MM, 4 smoldering MM and 3 MGUS) were enrolled in this study. Tryptophan and KYN were measured both in patients' serum and in bone marrow fluid with RP-HPLC. FoxP3-expressing Treg cells and NY-ESO-1+CD8+ T cells were quantitated with multiparameter flow cytometry. Conventional ELISA allowed the measurement of HGF levels both systemically and in the bone marrow microenvironment.

Results: The KYN-to-tryptophan ratio was significantly higher in patients compared with healthy controls, and correlated with serum β2-microglobulin, frequency of FoxP3+ Treg cells and HGF release. Interestingly, the frequency of NY-ESO-1-specific CD8+ T cells was significantly lower in IDO+ MM patients compared with the IDO- ones, and inversely correlated with the frequency of Treg cells. Myeloma cells, but not in vitro-expanded bone marrow stromal cells (BMSC), constitutively expressed IDO1, promoted the conversion of naïve allogeneic CD4+ T cells into Treg cells and inhibited the development of Th1, Th2 and Th17 cells. These effects were significantly albeit incompletely reverted by 1-methyl-tryptophan, suggesting that they were mediated by IDO1. In vitro mechanistic assays with IDO- MM cell lines showed the up-regulation of IDO1 expression by exogenous HGF. At variance with IDO- MM cells, IDO+ MM cells released high quantities of KYN in the culture supernatant and constitutively expressed phosphorylated Akt, an intermediate of HGF intracellular signaling.

Conclusions: We propose that IDO1 expression induced by HGF contributes to immune suppression in patients with MM and possibly other HGF-producing cancers. The HGF-IDO1 interaction represents a therapeutically exploitable molecular circuit to restore anti-tumor immunity.

Key Words: Multiple myeloma, Regulatory T cell, Indoleamine 2,3-dioxygenase 1.

STATE OF THE ART ANIMAL MODELS AND VETERINARY APPLICATIONS FOR CANCER AND IMMUNOLOGY

THE IMMUNE RESPONSE TO SPORADIC ANTIGENIC CANCER

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It has rarely been questioned that spontaneously occurring cancer cells have to escape T cell attack, even though it has not been directly demonstrated. Recently, it was shown that sporadic antigenic cancer at the time of initial recognition induces an aberrant rather than a protective T cell response, resulting in tolerance at the premalignant stage. Tumors that grew in the primary host despite initially functional tumor-reactive CTLs had a regressor phenotype upon transplantation. Thus, in a clinically relevant model cancer cells do not need to escape. General CTL hyporesponsiveness is a late event, probably involves immature myeloid cells, requires antigenic tumors and appears to be a

symptom, not the cause of tumor growth. Tumor infiltrating lymphocytes reflect cancer-induced inflammation, rather than immunosurveillance. In contrast, tumors induced by virus infection escape immunosurveillance by local tolerance.

Key Word: Adoptive therapy.

NOD/SCID IL2RGNULL MICE: A MODEL FOR HUMAN DENDRITIC CELL-BASED IMMUNOTHERAPIES

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Ex vivo-generated dendritic cell (DC)-based vaccines are a powerful tool to induce tumor-specific immune responses. Although several clinical trials have demonstrated the in vivo capacity of DC to induce antigen-specific T cell responses in cancer patients, an in vivo model has been missing to compare different protocols of human DC generation and application as a prelude to clinical studies. We compared different human-derived DC for vaccination in a newly developed xenograft mouse model. In this model, NOD/scid/IL2Rgnull (NSG) mice were reconstituted with human peripheral blood mononuclear cells (PBMC) and vaccinated with autologous human-derived mature DC expressing the MART-1 antigen and prepared using different protocols. As a first step, two regimens for reconstitution were evaluated for engraftment rates and activation status of human T cells, leading to the selection of a 4-week engraftment protocol for vaccine evaluation. Xenografted NSG mice were vaccinated twice with human-derived mature DC, comparing a newly developed 3-day protocol versus a more conventional 7-day protocol. The 3-day mature DC which were clearly superior at inducing antigen-specific immune responses in vitro (Burdek et al., 2010) also resulted in increased immune responses in vivo. In previous studies we investigated the use of Toll-like receptor (TLR) agonists to generate DC capable of polarizing Th1/CTL responses in vitro. Use of a maturation cocktail containing TLR agonists yielded DC secreting high levels of bioactive IL-12(p70), accompanied by tumor-reactive Th1 and CTL responses in vitro (Spranger et al., 2010). Consistent with these observations, vaccination using DC matured with a cocktail containing a TLR7/8 agonist (R848) resulted in enhanced immune responses in the NSG mouse model. Based on these results comparing different DC vaccine variations, we conclude that this new humanized mouse model enables investigation of human therapeutic cell reagents in an in vivo setting. In particular, this model allows in vivo comparisons of different vaccine strategies, different DC variants, as well as immunogenicity of different immunizing antigens prior to use in clinical studies.

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Key Words: DC-based vaccine, humanized mouse model.

INTRACRANIAL ADMINISTRATION OF HUMAN ACTIVATED NK CELLS IN A XENOGENEIC MODEL OF ORTHOTOPIC GLIOBLASTOMA

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Glioblastoma multiforme (GBM) is a highly invasive end-stage glioma which conveys an extremely poor prognosis. Based on our in vitro data showing very powerful anti-tumor activity of cytokine activated human natural killer cells against the GBM cell line U87MG, we sought to develop a xenograft model of GBM engraftment into immunocompromised mice which would be treated with intracranial human NK cells. Establishing human NK cell xenografts have proven to be notoriously difficult due to the short lifespan of NK cells, the requirement for exogenous homeostatic cytokines and the rejection of these cells by the murine host. We addressed these issues by using NOD-scid-IL2R KO (NSG) mice which lack functional T, B or NK cells. We also administered a human IL-15 gene therapy through a hydrodynamic technique which produces high amounts of IL-15 which can be detectable in the serum for up to 2 weeks. Human NK cells from healthy donors were expanded up to 1000-fold using a feeder cell line. These cells were highly cytotoxic and expressed high levels of activation markers including NKG2D and TRAIL. We administered these cells intracranially or intraperitoneal to monitor engraftment. While rhIL-2 administered every other day significantly increased NK cell engraftment compared to saline treated controls, hydrodynamic injection of human IL15-encoding plasmid resulted in increased engraftment in the brain, spleen, liver, bone marrow and peritoneal fluid 4 days after injection. Importantly, no overt toxicities were observed in mice receiving intracranial human NK cells. This therapy was then applied to a tumor model in which we injected 5×10^4 U87MG luciferin-labeled human glioblastoma cells stereotactically into the parenchyma of immobilized

and anesthetized mice. Four days after tumor infusion, mice received rhIL-15 hydrodynamic therapy followed by intracranial injection of 10^6 NK cells the next day. Tumor size was tracked by bioluminescent imaging every 3-5 days. While NK cell therapy provided a significant tumor volume reduction in the first several weeks after administration, this therapy was unable to protect mice in the long-term from tumor growth and death. These combined data demonstrate the feasibility of NK cell-based therapies for gliomas as well as their potential role as a secondary treatment to target chemotherapy- and irradiation-resistant tumor cells.

Key Words: Animal model, Adoptive immunotherapy.

OVERCOMING VACCINE RESISTANCE IN A MODEL OF SPONTANEOUS MELANOMA

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Melanoma provides an excellent model to study immune recognition of tumor antigens on cancer. We have explored: DNA vaccines using altered antigens to enhance immunogenicity of otherwise poorly immunogenic differentiation antigens, immune modulators such as anti-glucocorticoid induced TNF receptor like protein (GITR) and CTLA-4 blockade for their ability to overcome immune regulation, and optimized the use of adoptively transferred antigen-specific T cells. These treatments elicit immune responses that correlate with promising anti-tumor effects. However, these studies have been conducted with transplantable tumor models that do not accurately recapitulate the growth and progression of human melanoma. We have tested these immunotherapies in spontaneous mouse models (TG-3 and Grm1 transgenic mouse strains) of melanoma at different stages of tumor progression. Grm1 mice have a transgene expressing the metabotropic glutamate receptor 1, a G-coupled protein receptor that signals through the Ras-Raf-MAPK-Erk pathway, under the control of the melanocyte-specific DCT promoter. Grm1 is overexpressed in human melanomas, but not in benign nevi or normal melanocytes. Grm1 mice develop spontaneous melanocytic hyperplasia shortly after birth, with lesions apparent at 1-2 months of age, which progress to gross palpable tumors with death usually around 10-12 months of age. The TG-3 mice have ectopic expression of the Grm1 gene in melanocytes due to the random deletion in the second intron of this gene. TG-3 mice develop much more aggressive melanomas within 8-12 weeks. We have shown that immunization with optimized TYRP1 DNA prevents melanoma progression in Grm1 mice when immunization is started at 2-3 months of age; however, the same treatment is ineffective for the more aggressive TG-3 model. Both Grm1 and TG-3 mice respond to DNA immunization similarly. However TG-3 tumor bearing mice have higher levels of foxp3+ T cells in the spleen and DLN. These data suggests that the resistance to treatment is due to higher levels of regulatory T-cells in the more aggressive TG-3 mouse strain and emphasize the importance of elevating immune suppression during immunotherapy.

Key Words: Active immunotherapy, Animal model, Combination immunotherapy.

HIGH THROUGHPUT TECHNOLOGIES FOR IMMUNE MONITORING

TUMOUR REACTIVE T CELL RESPONSES AS BIOMARKERS: CORRELATION TO TUMOUR CELL BIOLOGY AND TREATMENT RESPONSE

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Spontaneous T cell responses against tumour associated antigens occur frequently in cancer patients. We use functional T cell assays, such as ex vivo IFN-gamma Elispot analysis and Treg specificity analyses to study such responses in large numbers of patients with a broad range of different tumour entities in order to assess their clinical relevance and conditions of their generation. In a study of 207 untreated primary breast cancer patients and 12 Her-2/neu-specific CD8 T-cell lines derived thereof we used tetramer analysis, ex vivo IFN-gamma ELISPOT, cytotoxicity assays, and ELISA to evaluate tumor-specific T cells (TC) in the bone marrow or MUC1-specific antibodies in the blood. In addition, we quantified in these patients 27 intratumoral cytokines, chemokines, and growth factors and compared the results with clinical parameters of the patients and tumors. Interestingly, presence of tumor-specific type 1 TC responses correlated on the one hand with specific features of tumour cell biology which was characterized by high differentiation, strong estrogen receptor expression, low proliferative activity, and with a reduced cancer mortality risk and on the other hand with increased intratumoral, but not plasma, concentrations of IFN-alpha and reduced transforming growth factor (TGF)beta1. In an in vitro priming experiment these two cytokines increased or inhibited, respectively, the capacity of dendritic cells to induce tumor-reactive TC. In contrast, tumor-specific B-cell responses correlated with advanced tumor stage, increased TGFbeta1, reduced IFN-alpha, and absence of TC responses. Thus, different types of immune responses are linked to distinct cytokine microenvironments and correlate with prognosis-relevant differences in tumor cell biology. These findings shed light on the relation between immune response and cancer prognosis. We further investigated in a study of metastasized breast cancer patients whether palliative cytostatic treatment with low dose cyclophosphamide supports the induction of tumour reactive T cell responses and whether these predict response to treatment and subsequent survival. Cyclophosphamide treatment reduced only transiently the frequencies of regulatory T cells which did not correlate to treatment response of overall survival, while tumour-reactive T cells were induced in over 80% of treated patients

within two weeks and persisted throughout the whole observation period of 3 months. Interestingly, increased frequencies of tumour reactive T cells but not frequencies of regulatory T cells correlated with prolonged overall survival in a dose dependend manner. We conclude that tumour reactive T cell responses can serve as valuable biomarkers for early response prediction and prognosis.

Key Words: Tumor associated antigen.

IMMUNOLOGICAL CORRELATES OF LONG-TERM SURVIVAL IN MELANOMA PATIENTS

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It is proposed that all anti-cancer treatments depend for their long-term success at least partly on the generation of tumour antigen-specific T-cells capable of maintaining anti-tumour immune responses. We aimed to determine whether the presence of certain specific functional T-cells in peripheral blood of individual cancer patients was associated with a more favourable prognosis, regardless of treatment received (including chemotherapy, DC+peptide vaccination, RNA vaccination, ipilimumab treatment, etc). We have analysed CD4+ and CD8+ T-cell responses against 4 prominent melanoma-associated antigens, NY-ESO-1, MAGE-A3, Survivin and Melan-A assessed by intracellular staining for 6 different cytokines (IFN-γ, TNF, IL-2, IL-4, IL-10 and IL-17) on PBMC stimulated with nested peptides. Use of 14 colour flow cytometry allowed analysis of the T cell phenotype and effector functions (pro- versus anti-inflammatory response). PBMCs from 84 stage IV melanoma patients before treatment were tested, and then followed prospectively. Patients were stratified as long-term survivors (LTS, >18 months), medium (6 - 18 months) or usual poor survivors (<6 months). Over half the LTS patients had either CD4+ and/or CD8+ NY-ESO-1-specific T-cells with a pro-inflammatory profile in the peripheral blood. Shorter survivors had significantly less or no such cells, or included anti-inflammatory responses. Melan-A responses were also significantly associated with LTS, but only when mediated by CD8+ T cells (CD4-reactivity was associated with poorer survival). Responses against MAGE-A3 were detected more frequently, but did not correlate well with survival time. Survivin responses were rare. These results document the potential power of establishing functional immune signatures in predicting melanoma patients survival, most likely via mediation of autologous anti-tumour reactivity. Thus, assessing CD4- and CD8-mediated pro-inflammatory responses against NY-ESO-1 and CD8-mediated responses against Melan-A could be good markers to predict the clinical outcome of an individual patient. Moreover, these data suggest that MAGE-A3 vaccines could be less effective, and that Melan-A vaccines, unlike NY-ESO-1 vaccines, should not incorporate CD4-stimulating epitopes.

Key Words: CD4+ T cells, CD8+ T cells, Melanoma.

NEW BIOMARKERS FOR PROSTVAC-VF DISCOVERED USING HIGH-THROUGHPUT GLYCAN MICROARRAYS

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New tools are needed to investigate why seemingly similar patients can receive different survival benefits from the same cancer vaccine. Better understanding of in vivo function should improve vaccine design, clinical trials, and ultimately routine use. Largely overlooked so far in immune testing have been glycans (carbohydrates linked to proteins and lipids) on tumors and vaccine components. In particular, serum anti-glycan antibodies are a potentially untapped reservoir of easily accessible biomarkers. Even for vaccines that do not specifically target glycans, immune responses to glycans warrant investigation. Many targets of cancer vaccines are glycoproteins, and antigen spreading could occur to tumor-associated glycans. Anti-glycan antibodies also possibly influence how viral vectors are taken up and processed. We analyzed serum anti-glycan antibodies of 141 subjects from two phase II studies of PROSTVAC-VF, a promising vaccine for advanced prostate cancer. These multiplex arrays provided a comprehensive profile of serum antibodies using only 6 µL of serum from each subject. Interestingly, post-vaccination survival correlated with pre-vaccination levels of several anti-glycan antibodies. Additionally, subjects who responded to the terminal disaccharide of Forssman xenoantigen (GalNAcα1-3GalNAcβ) had longer post-vaccination survival than those with little or no response. A four-fold increase in total serum anti-Forssman antibodies (IgM + IgG + IgA) was associated with an eight month improvement in median survival. Odds of long-term survival steadily improved with the magnitude of response to Forssman disaccharide. Median survival was 3.5 years (almost two years longer than placebo) for subjects with a ten-fold or larger increase. These correlations were consistent in two independent, blinded sample sets, and they were statistically significant even after adjusting for multiple comparisons. Since similar responses were seen in the placebo group, the antibody increases appeared to be a response to PROSTVAC's viral vectors. Forssman antigen was found on the vectors (vaccinia and fowlpox), which likely carried over glycans from the chicken embryo dermal cells used for vaccine production. Our findings are translatable into new biomarkers for predicting and monitoring an individual patient's response to PROSTVAC-VF and possibly other cancer vaccines

that use pox viral vectors.

Key Word: Prostate cancer.

SEROMICS: MEASURING ANTIGEN-SPECIFIC SERUM ANTIBODY RESPONSES DURING ANTICANCER IMMUNOTHERAPIES FOR CORRELATION WITH CLINICAL EVENTS

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The immune system recognizes antigens expressed in cancer cells, thereby generating antibody and T cell responses that can be measured from peripheral blood and tumor sites. By knowing the nature and quality of immune responses generated in an antigen-specific manner to cancer as well as immunoregulatory processes involved, one can design immunotherapeutic strategies to affect the clinical course of cancer using vaccines and immunomodulators. To this end, antibody responses occurring either spontaneously or as a result of immunotherapy were analyzed by ELISA for model cancer/testis antigen NY-ESO-1, and linked to CD8 and CD4 T cell responses as well as to antigen expression. Serological analyses were then extended to 35+ known tumor antigens, to establish a general immunogenicity profile. Finally, humoral immune responses were characterized in a comprehensive manner using protein microarrays for antibody profiling of >8000 antigens. This strategy was used for monitoring immunological events during CTLA-4 blockade.

Blockade of CTLA-4, a molecule that acts as a natural break to prevent immune responses from going into overdrive following T-cell activation, with monoclonal antibodies such as ipilimumab has shown durable clinical activity and improved overall survival in advanced melanoma patients (N Engl J Med 2010;363:711-23). This activity is likely linked to the prolongation of immune responses directed against tumor cells; however, the exact immune responses targeted by anti-CTLA-4 therapy remain unclear, as does the reason why only some patients benefit from the drug.

Autoantibody responses were measured before and after treatment with ipilimumab to provide further insight into the mechanism of action of such immunotherapy and identify factors that help to predict patients who are most likely to derive clinical benefit from treatment. Changes were detected in autoantibody levels in treated patients relative to samples prior to treatment and to controls, suggesting that some targets may have been "hit" by the immune system as potential interesting rejection antigens that help explain the mechanism of action of the drug. Extended serological analyses are also useful to identify preexisting antibody signatures associated with clinical response to anti-CTLA-4 and other therapies, to define the subset of patients most likely to experience clinical benefit

These approaches provide a broader scope of immune responses occurring in cancer, and may be useful for finding new targets of cancer vaccines and selecting biomarkers with predictive value for therapeutic treatments, as well as for establishing correlations with tumor characteristics and with clinical events.

Key Words: B cell, Ipilimumab, Melanoma.

PRESIDENTIAL ABSTRACT SESSION

IMMUNOTRANSPLANT FOR MANTLE CELL LYMPHOMA: A PHASE I/II STUDY DEMONSTRATING AMPLIFICATION OF TUMOR-REACTIVE T CELLS

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Mantle cell lymphoma (MCL) has a poor prognosis. Though autologous transplant prolongs survival, novel therapies are needed to target residual, myeloablation-resistant tumor cells that result in relapse.

Trials of CpG-based vaccines for low-grade lymphoma have shown induction of anti-tumor T cells and clinical responses [Brody et al, JCO 2010]. In a pre-clinical model, we developed 'immunotransplant', combining: 1) CpG-based vaccination, 2) vaccine-primed T cell harvest, 3) myeloablation with stem cell rescue, and 4) T cell re-infusion. Immunotransplant amplifies the proportion of anti-tumor T cells by an order of magnitude and cures even bulky, systemic lymphoma [Brody et al, Blood 2009].

Methods: We initiated a phase I/II study of immunotransplant for newly diagnosed MCL patients to test the hypothesis that immunotransplant amplifies anti-tumor T cells as seen pre-clinically. Tumor-reactive T cells are assessed by co-culturing autologous tumor with peripheral blood T cells and measuring their production of: IFNγ, TNF, IL2, CD137, perforin and granzyme by multiplex surface and intracellular flow cytometry. Using high-throughput sequencing, we have initiated assessment of the peripheral blood TCRβ repertoire, obtaining at least 1e6 sequence reads per time point.

Results: Accrual has been rapid with 24 patients enrolled in 22 months and 13 patients completing the complete protocol so far. Flow-cytometric immune response testing has demonstrated that immunotransplant amplifies the proportion of tumor-reactive T cells in 83% of patients thus far. Notably, we have observed some patients with primarily CD8 T cell responses, some with CD4 T cell responses, and some with a combination. In some cases, tumor-reactive T cells have been tested for reactivity to autologous, non-malignant B cells and have demonstrated that a significant proportion are tumor-specific. High throughput sequencing of TCRβ repertoires have also demonstrated instances of significant clonal amplification after immunotransplantation, up to two orders of magnitude. In extreme cases, these have yielded dominant clones comprising as much as 50% of a patient's entire peripheral blood T cell repertoire post-transplant.

Conclusions: Pre-clinically, amplification of anti-tumor T cells correlates with cure of myeloablation-resistant disease. The

reiteration of anti-tumor T cell amplification in our preliminary clinical data raises the possibility that immunotransplant may improve clinical outcomes. Our ongoing molecular residual disease testing should suggest whether certain patterns of T cell response correlate with clinical benefit and whether the cohort has a better-than-expected molecular remission rate.

Key Words: Adoptive therapy, Cancer vaccine, Lymphoma.

IRF5 GENE POLYMORPHISM IN MELANOMA

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Background: Prediction of patient with melanoma responsiveness to immunotherapy is uncertain. A connection between autoimmunity and benefit of interferon alpha-2b therapy was recently suggested. IRF5 is a transcription factor involved in the type I interferon and the toll-like receptor signaling. Previously, IRF5 has been found associated with several autoimmune diseases and, therefore, is a good candidate for autoimmunity. Thus, we examined whether polymorphisms of IRF5 associated with autoimmunity might also be associated with immune responsiveness of melanoma.

Method: Four single nucleotide polymorphisms (SNPs) and one insertion-deletion in the IRF5 gene were genotyped by sequencing in 142 Tumor Infiltrating Lymphocytes (TILs) from melanoma patients. Haploview v3.2 was used to generate haplotype frequencies and calculate the significance of association. Gene-expression profiling was assessed by Affymetrix Human Gene ST 1.0 array.

Results.: The genotype and allelic frequency distribution showed significant differences between responders vs. non-responders. Presence of GG genotype in rs10954213 and rs11770589 was higher in non-responders (28%-10%, P=0.0076; 42%-18%, P=0.0051). Presence of exon 6 deletion was higher in responders (27%) than in non-responders patients (17%, P=0.0076). The allele rs10954213 A and rs11770589 A frequencies are higher in responders (.069 vs 0.37, P=0.000007, OR=3.08, 95%CIs =1.86-5.103 and 0.54 to 0.37, P=0.003, OR=1.99, 95%CIs=1.24-3.19). Exon 6 insertion was higher in non-responders patients (63% vs. 46%, P=0.003). The presence of rs10954213 and rs11770589 G allele and exon 6 insertion was associated to non-response (p=0.0046, p=0.0016 and p=0.0016 respectively). Exon 6 indel is in linkage disequilibrium with all the other IRF5 SNPs beside rs2004640 in both responders and non-responders groups. Haplotype analysis defined as negative prognostic factor rs10954213 G, rs11770589 G, rs6953165 G, rs2004640 T, exon6 insertion (p=0.009) in agreement with resistance to development of autoimmunity. mRNA variation by gene expression analysis on the same TILs did not correlate with IRF5 polymorphisms and was not associated with response to therapy.

Conclusions: This study is the first to analyze associations between melanoma immune responsiveness and IRF5 polymorphisms. The results support a correlation between IFN-mediated autoimmunity and melanoma immune responsiveness.

Key Words: Adoptive therapy, Melanoma, Tumor infiltration lymphocytes.

IMPROVED IN VIVO PERSISTENCE OF CD19-SPECIFIC T CELLS EXPRESSING A MEMBRANE-BOUND FORM OF IL-15

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Clinical responses in adoptive immunotherapy are associated with in vivo expansion and persistence of the transferred antigen-specific T cells. Therapeutic efficacy is hampered by a lack of persistence of infused T cells. Interleukin (IL)-2 is used in adoptive therapies to stimulate T cell expansion and promote their survival. Systemic administration of IL-2 is limited as its use is associated with toxicity and expansion of regulatory T cells. IL-15 may be a more suitable cytokine as it promotes memory CD8+ T cell survival and can re-establish the functionality of T cells. To deliver localized IL-15 signaling to T cells, we generated a version of IL-15 as a membrane-bound molecule (mbIL15). The mbIL15 construct was electro-transferred with a CD19-specific CAR (on day 0) into primary human T cells as Sleeping Beauty DNA transposon plasmids. Numeric ex vivo expansion of these genetically modified T cells was achieved by co-culture on CD19+ artificial antigen presenting cells derived from K562, but without additional soluble cytokine supplementation. Preferential outgrowth of T cells expressing both mbIL15 and CAR was attained, while CAR+ T cells receiving no soluble cytokine supplementation did not undergo expansion. In our culture system, mbIL15-modified T cells acted in synergy with exogenous IL-21 to achieve superior expansion and maintained a mixture of effector and central memory phenotypes. Signaling through the IL-15 receptor complex in mbIL15+CAR+ T cells was validated by phosphorylation of STAT5. The mbIL15+CAR+ T cells demonstrated redirected specific lysis of CD19+ tumor targets equivalent to the standardly cultured CAR+ T cells. Adoptive transfer of modified T cells into immunodeficient mice demonstrated stable persistence of mbIL15+CAR+ T cells greater than 35 days, whereas CAR+ T cells were not detected past 4 days. In mice bearing CD19+ malignancy, mbIL15+CAR+ T cells demonstrated both homing and anti-tumor effects. These data demonstrate that mbIL15 can be expressed by CAR+ T cells to enhance their proliferation and in vivo persistence without the need for exogenous cytokine support. The use of this fusion molecule: (i) provides stimulatory signals via STAT5 leading to augmented in vivo T cell persistence while maintaining tumor-specific functionality, (ii) eliminates the need for IL-2 for T-cell expansion and persistence, and (iii) mitigates the need for clinical-grade IL-15. These results have implications for the design

of adoptive immunotherapy clinical trials to evaluate whether mbIL15+CAR+ T cells can improve therapeutic potential.

Key Words: Adoptive therapy, Chimeric receptors, Cytokine.

DYSFUNCTIONAL TUMOR-INFILTRATEING T CELLS EXPRESS THE ANERGY-ASSOCIATED MOLECULES LYMPHOCYTE-ACTIVATION GENE 3 (LAG3) AND CLASS-I-MHC RESTRICTED T CELL ASSOCIATED MOLECULES (CRTAM)

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Anergy is one of the mechanisms contributing to T cell dysfunction in the tumor microenvironment. However, the lack of a specific marker to define anergic T cells, along with the fact that anergy has generally been defined by a process (TCR ligation in the absence of costimulation) in concert with a subsequent dysfunctional state (the associated defective TCR/CD28-mediated activation), has limited the ability to clearly identify anergic cells. We have recently reported that the transcription factor early growth response factor 2 (Egr2) is a central regulator of T cell anergy, and deletion of Egr2 prevents anergy induction in vitro and in vivo. In an effort to map the complete Egr2 transcriptome of anergic T cells, we combined Egr2-driven gene expression profiling and ChIP-seq, and identified a set of cell surface molecules including Lag3 and Crtam, which were highly upregulated in anergic cells. Lag3 and Crtam have been implicated in regulating T cell activation, and we proposed that they might be useful markers to identify the anergic phenotype. To analyze the expression of Lag3 and Crtam in the context of tumor-induced T cell dysfunction, C57BL/6 mice were subcutaneously injected with SIY-expressing B16 melanoma, and tumor-infiltrating lymphocytes (TILs) were analyzed by flow cytometry. Crtam and Lag3 were upregulated in 40-60% TILs, on both CD4+ and CD8+ subsets, and their expression was largely overlapping. Interestingly, these cells represented a subpopulation of PD-1+ cells. Functionally, upon restimulation with anti-CD3/CD28 mAbs in vitro, Lag3+Crtam+ T cells were defective in IL-2 production, whereas the remainder of the PD-1+ T cells were functionally intact. In contrast, IFN-γ production was mostly preserved, similar to the phenotype of T cells anergized in vitro. Additional analysis revealed, among the CD4+ T cells, a large fraction of the Lag3+Crtam+ TILs were Foxp3+, representing T regulatory cells (Tregs). Thus, upregulated expression of Lag3 and Crtam could indicate antigen-activated Tregs. The CD8+Lag3+Crtam+ cells were Foxp3-. Analysis of human CD8+ TILs also revealed constitutive expression of the anergy-associated transcription factor Egr2. Further characterization of the Lag3+Crtam+ TILs is ongoing to interrogate for other definitions of the anergic state, including expression of defined anergy-associated genes, defective TCR-induced ERK phosphorylation, and reversibility of dysfunction upon proliferation to homeostatic cytokines. In addition to Lag3 and Crtam serving as cell surface markers to identify anergic T cell, they might be useful therapeutic targets for immunotherapy aimed to reverse TIL dysfunction.

Key Words: Treg cells, Tumor infiltration lymphocytes, Tumor microenvironment.

SUNDAY, NOVEMBER 6, 2011

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PROSTATE CANCER AS A LEARNING MODEL

REPETITIVE DNA VACCINATION ELICITS PAP ANTIGEN-SPECIFIC T-CELL IMMUNE RESPONSES IN PATIENTS WITH CASTRATE-RESISTANT PROSTATE CANCER

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Background: Randomized clinical trials conducted in patients with advanced, metastatic prostate cancer targeting prostatic acid phosphatase (PAP) by means of antigen presenting-cell vaccines have demonstrated clinical benefit in terms of improved overall survival. These results suggest both that prostate cancer is an appropriate disease in which to further evaluate anti-tumor vaccines, and that PAP is a rational vaccine target antigen. Ultimately, however, tumor vaccines may be most effective in the setting of minimal residual disease. Given the long natural history of prostate cancer, and the ability to detect prostate cancer recurrence prior to radiographic evidence of metastases, we have investigated plasmid DNA vaccines encoding PAP in patients with early recurrent prostate cancer, with rising serum PSA but no radiographically-apparent metastases. We report here preliminary clinical and immunological results for the first 11 patients from a pilot trial in which patients with castrate-resistant, non-metastatic prostate cancer were vaccinated multiple times up to two years on either a defined schedule of immunization, or one defined by immune monitoring conducted in real time, using a plasmid DNA vaccine encoding PAP (pTVG-HP).

Methods: Patients with clinical stage D0.5 prostate cancer (castrate-resistant, rising serum PSA level, and no radiographic evidence of metastases) were immunized six times at 2-week intervals, and then either every 3-months or continuing at 2-week intervals until evidence of an immune response by antigen-specific T-cell proliferation, IFNγ ELISPOT, and/or granzyme B ELISPOT. Vaccinations were administered intradermally with 100 mcg plasmid DNA and 200 mcg GM-CSF co-administered as an adjuvant. Other measures of immune response were assessed.

Results: 9/11 patients remained on study for over 12 months, with 2 discontinuing for evidence of disease progression. No significant adverse events were observed except an immediate allergic reaction occurring after the 11th immunization in one patient. The median number of immunizations received per individual to date was 13 (range 7-24). PAP-specific T-cell responses were detectable even prior to immunization in 7/11 individuals by one or more methods of evaluation, primarily by IFNγ ELISPOT, but were significantly augmented in 2 of 7 of these individuals. PAP-specific CD4+ proliferative T-cell responses were elicited in 6/11 patients, and PAP-specific granzyme B responses were elicited in 6/11 patients, 5 of whom also had augmented PAP-specific proliferative CD4+ T-cell responses. IgG responses to PAP have not been detected in any individuals, even after 24 immunizations. Favorable changes in serum PSA kinetics (increased PSA doubling time) were detected in 7/11 patients, and this was associated with the detection of PAP-specific granzyme B responses after immunization ($p=0.02$). Studies of antigen-specific regulatory T-cell responses that might have been elicited with multiple repetitive immunizations are currently underway.

Conclusions: Repetitive DNA immunization of patients with minimal residual prostate cancer appears safe and is immunologically active, eliciting primarily T-cell-biased responses. However, some individuals did not develop detectable PAP-specific immune responses, even following multiple immunizations. The impact of DNA immunization on disease progression awaits results from randomized, placebo-controlled clinical trials.

Key Words: Cancer vaccine, Prostate cancer, Tumor associated antigen.

INTRADERMAL IMMUNIZATION WITH A NOVEL mRNA BASED VACCINATION TECHNOLOGY INDUCES STRONG T- AND B-CELL RESPONSES IN PHASE I/ IIA TRIALS IN NON-SMALL CELL LUNG CANCER (NSCLC) AND PROSTATE CARCINOMA (PCA)

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CV9201 and CV9103 are novel cancer vaccines against NSCLC and PCa composed of self-adjuvanted mRNA molecules that are administered intradermally, CV9201 is constituted of mRNAs coding for NY-ESO1, Mage-C1, Mage-C2, Survivin and 5T4, CV9103 of mRNAs coding for PSA, PSCA, PSMA and STEAP-1. The final analysis of a phase I/ IIa trial with CV9103 in castrate-resistant PCA, revealed good safety with possibly related serious adverse observed in only 3 out of 44 patients. Immunomonitoring demonstrated T- and B-cell responses (ELISPOT, ICS, tetramer, ELISA) against at least one antigen in 79% of the evaluable patients. Importantly 63%

of the immunological responders reacted against more than one antigen. A PSA decline > 80% was observed in 1 patient.

CV9201 was tested in a phase I/IIa trial in NSCLC patients (stage IIIb/ IV) with at least stable disease after 1st line chemo with standard chemotherapy or chemoradiotherapy. Treatment related side effects were mainly grade 1/2 injection site reactions or fever. Neither dose-limiting toxicities nor related serious adverse events were observed. 31 patients received up to 5 vaccinations and were immunologically evaluated two weeks after the 3rd and 5th vaccination. Antigen-specific B- and T-cell responses as assessed by ELISA (IgM, IgG), ELISPOT, ICS and tetramer analysis were detected in 65% of patients, 56% thereof multiple responders. Remarkably, a significant, 2.5 - 13 fold shift from naïve B-cells to pre-germinal center B-cells was detected in 61% of patients which suggests activation of T-cell help in draining lymph nodes. The presence of antigen-specific B cells was shown exemplarily with a B-cell proliferation assay.

These results strongly suggest that intradermal immunization with self-adjuvanted mRNA vaccines constitutes a safe, flexible and highly immunogenic vaccination approach able to induce antigen-specific humoral and cellular immune responses in the majority of PCa as well as NSCLC patients.

Key Words: Cancer vaccine, Lung cancer, Prostate cancer.

LYMPHOID AND MYELOID BIOMARKERS FOR CLINICAL OUTCOME OF IPILIMUMAB AND PROSTATE GVAX TREATMENT: TUMOR-RELATED CTLA-4 EXPRESSION BY CD4+ T CELLS AS A DOMINANT PREDICTOR OF SURVIVAL

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Immune checkpoint blockade can enhance anti-tumor responses and prolong survival, but it can also lead to the development of severe and potentially life-threatening immune-related adverse events (IRAE). To avoid unnecessary exposure to this risk, it is essential to identify biomarkers that correlate with clinical activity and can be used to recognize and select patients that will benefit from immune checkpoint blockade. We therefore performed extensive immune monitoring in a phase I/II dose escalation/expansion trial of combined Prostate GVAX and ipilimumab immunotherapy in patients with Castration Resistant Prostate Cancer (CRPC).

The GVAX/ipilimumab combination was clinically active with PSA declines of more than 50% in 5, and PSA stabilizations in 12 of 28 patients. Flowcytometric monitoring of lymphoid and myeloid subsets in peripheral blood before and after Prostate GVAX/ipilimumab treatment revealed striking differences between patients who benefited from therapy and patients who did not. Treatment-induced CD4+ T cell differentiation and CD4+ and CD8+ T cell activation was associated with clinical benefit. Moreover, significantly prolonged overall survival (OS) was observed for patients with high pre-treatment frequencies of CD4+CTLA-4+, CD4+PD-1+, or differentiated CD8+ T cells, or low pre-treatment frequencies of differentiated CD4+ T cells or CD4+CD25hiFoxP3+ regulatory T cells. Treatment-induced activation of CD1c+ conventional Dendritic Cells (cDC) and 6-sulfo LacNAc+ inflammatory DC were similarly associated with significantly prolonged OS. In contrast, increased frequencies of granulocytic Myeloid-Derived Suppressor Cells (MDSC) and high pre-treatment frequencies of monocytic CD14+HLA-DRlo/- MDSC were associated with reduced OS.

Together these data provide an immune profile to predict clinical outcome. Importantly, cluster analysis revealed pre-treatment, CRPC-associated expression of CTLA-4+ by circulating CD4+ T cells to be a dominant predictor for OS after Prostate GVAX/ipilimumab therapy. It may thus provide a potentially useful and easy-to-use biomarker for patient selection and should be validated as such in other patient groups treated by antiCTLA-4 blockade.

Key Words: Cancer vaccine, CTLA-4, Prostate cancer.

COMPREHENSIVE CHARACTERIZATION OF POLYOMAVIRUS BK LARGE TUMOR ANTIGEN EPITOPES TO PROMOTE THE EXPANSION OF EFFECTOR T LYMPHOCYTES IN PROSTATE CANCER PATIENTS

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Introduction: The involvement of Polyomavirus BK (BKV) in prostate cancer (PCa) is still controversial but it seems that its main regulatory protein large tumor antigen (L-Tag) acts as enhancer of regulatory profiling governing PCa. The question whether L-Tag could be a main target for a competent immune surveillance in PCa patients has never been addressed before. Thus, also the identification of immunogenic BKV L-Tag peptides in PCa has not been attempted so far.

Material and Methods: Eleven in silico-predicted peptides within BKV L-Tag were use to ex vivo stimulate PBMCs of 16 PCa patients, 10 age and gender-matched benign prostatic hyperplasia (BPH) patients and 10 gender but non age-matched healthy donors (HDs). The gene expression of pro-inflammatory (IFN-γ, TNF-α) and regulatory (IL-10, TGF-β1) cytokines was assessed in a first screening. A mini-pool consisting of gene expression-based selected peptides (pL-Tag) was employed to in vitro expand specific T cells. Clones of single IFN-γ secreting T-cells were generated and used to test peptide-specific cytotoxicity.

Results: Four peptides (L-Tag27-41; L-Tag172-185; L-Tag212-226; L-Tag531-545) induced a significant ex vivo pro-inflammatory cytokine gene expression in almost 50% of BKV seropositive PCa patients and in almost 70% of gender-matched HDs. No significant induction of regulatory cytokines was detected. Similar data, although to a lesser extent, were obtained in BPH patients. Mini pL-Tag-specific IFN-γ-producing effector/memory CD4+ and CD8+ T cells were seen in 8 and 4 out of 8 in vitro expanded PCa T cells, respectively. Same cells also showed a significantly increased mobilization of CD107a. A helper phenotype was also seen in pL-Tag- treated IL-2-producing CD4+ T cells. Four clones generated from single IFN-γ secreting T-cells (CD4/L-Tag27-41, CD8/L-Tag172-185, CD4/L-Tag212-226 and CD4/L-Tag531-545) showed target-specific cytotoxicity with a delta specific lysis (ΔSL) at a 10:1 ratio between 20 and 40% and significant expression of lytic machinery components. In addition, all batches of cells were PD-1 negative.

Conclusion: We identified four candidate immunogenic peptides selected within the main regulatory L-Tag with the strong ability to reactivate and maintain cytotoxic T cells in PCa patients with a tolerogenic signature.

Key Words: Cancer virus, Cellular immunity, Prostate cancer.

COMBINING VACCINES WITH OTHER THERAPEUTICS: A STRATEGY TO ACCELERATE PROOF OF CONCEPT STUDIES?

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One recurrent finding in recent large controlled cancer immunotherapies studies has been improved overall survival (OS) without improvement in median progression free survival (PFS). This provides a hurdle for timely completion of proof of concept efficacy studies. This lack of improvement in PFS with eventual demonstration of improved OS may be due to the time lag between administering immunotherapy and a clinically significant immune mediated slowing of the growth of the tumor.

Approval of the first therapeutic cancer vaccine has conferred higher priority on combining therapeutic vaccines with standard therapies. Careful preclinical studies have highlighted the ability of standard therapies to a) kill cells in an immunologically relevant manner and b) phenotypically modulate surviving cells making them more susceptible to immune mediated recognition and killing. This has led to rationally designed studies combining therapeutic cancer vaccines with standard therapies. These recent preclinical and clinical studies have demonstrated the ability to mount immune responses to vaccine despite standard therapies (e.g., chemotherapy).

These combination studies provide a platform for testing the ability of combination strategies to impact more traditional phase 2 endpoints such as PFS. If the above hypothesis on growth rate is correct, it suggests that if one could rationally combine therapeutic vaccines (associated with delayed effects) with standard therapies (associated with early but transient decrease in tumor volume) in a manner that doesn't decrease the immune responses, then one might be able to use PFS to discriminate between standard of care and combination regimens. Preliminary data from 2 ongoing prostate cancer trials and a breast cancer study support this hypothesis. The prostate cancer trials suggesting an improvement in time to progression (TTP) for the combination are Quadramet +/- vaccine (2.1 vs 3.9 months, n=32) and flutamide +/- vaccine (88 vs 185 days, n=34); and the breast cancer trial compares docetaxel +/- vaccine (2.9 vs 8.0 months, n=21).

Thus rationally designed combination studies have the potential to significantly speed up efficacy analysis in proof of concept efficacy studies (phase 2). This approach may be especially useful in tumors with an increasing number of therapies available that impact OS, and earlier in the disease course when follow-up for survival is more remote. Final analysis of ongoing studies may ultimately determine the utility of this approach.

Key Words: Combination immunotherapy, Phase II, Prostate cancer.

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BIOLOGY & APPLICATION OF DENDRITIC CELLS

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COMBINED USE OF POLARIZED AND NON-POLARIZED DCs FACILITATES ACCELERATED GENERATION OF HIGH NUMBERS OF Ag-SPECIFIC CTLs

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SOURCING HUMAN BLOOD-DERIVED RAW MATERIAL: OPTIMIZATION, QUALIFICATION AND CONTROL

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DENDRITIC CELL DIFFERENTIATED WITH 15 KD GRANULYSIN: A REPLACEMENT FOR GMCSF?

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AUTOPHAGY INDUCED BY INTERFERON-GAMMA IN MELANOMA CELLS IS ASSOCIATED WITH BETTER CLINICAL OUTCOMES IN PATIENTS RECEIVING CELL-BASED IMMUNOTHERAPY AGAINST MELANOMA

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MELANOMA PATIENTS TREATED WITH DENDRITIC CELL VACCINATION, INTERLEUKIN-2 AND METRONOMIC CYCLOPHOSPHAMIDE - RESULTS FROM A PHASE II TRIAL

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RNADJUVANT, A NOVEL HIGHLY POTENT RNA-BASED ADJUVANT SUPPORTS INDUCTION OF BALANCED IMMUNE RESPONSE (TH1 AND TH2) AND ANTI-TUMOR ACTIVITY

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TUMOR CELLS CONTAIN 'VETO' FACTORS LIMITING IMMUNOGENICITY OF STERILE NECROSIS AND CONTROLLING CD8$^+$ T CELL ACTIVATION

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IMMUNOGLOBULIN-LIKE TRANSCRIPT (ILT) RECEPTORS ON HUMAN DERMAL CD14+ DCS ACT AS A CD8-ANTAGONIST TO PREVENT EFFICIENT CTL PRIMING

Eynav Klechevsky[2,1,4], Sandra Zurawski[1], Jean-Philippe Blanck[1], Dorothee Duluc[1], Yanying Cao[1], Luann Thompson-Snipes[1], Karolina Palucka[1], Yoram Reiter[4], Gerard Zurawski[1], Marco Colonna[2], Jacques Banchereau[3,1]

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FACILE GENERATION OF APCS USING SOLUBLE MULTIMERIC CD40L AS A B CELL PROLIFERATION STIMULUS
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HUMAN DENDRITIC CELLS DIFFERENTIATED IN THE PRESENCE OF ADENOSINE RECEPTOR AGONISTS DISPLAY A TOLEROGENIC PHENOTYPE AND FAIL TO PRIME CD8 T CELLS
Bruno Laugel[1,2], Pierre Farmer[2], Marie-Laure Curchod[2], Mireille Guerrier[2], Catherine Salvat[2], Andrew K. Sewell[1]

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DENDRITIC CELLS AND TUMOR CELLS INTERNALIZE ALPHA-FETOPROTEIN, A HEPATOCELLULAR CARCINOMA TUMOR ANTIGEN, VIA DISTINCT ENDOCYTOSIS MECHANISMS
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EXAMINING FACTORS LEADING TO PRODUCTION OF HIGHLY IMMUNOGENIC MONOCYTE DERIVED DCS SUITABLE FOR CANCER IMMUNOTHERPY IN COLOMBIAN INDIVIDUALS
Diana R. Tovar[1], Carlos A. Parra-López[2,1], David A. Bernal[1,2]

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INNATE AND ADAPTIVE IMMUNE RESPONSE INDUCED EX VIVO BY AN IDIOTYPIC VACCINE FOR HCV-RELATED LYMPHOPROLIFERATIVE DISORDERS
Annacarmen Petrizzo[1], MariaLina Tornesello[1], Riccardo Dolcetti[2], Luca Romagnoli[3], Ena Wang[4], Franco M. Marincola[4], Franco M. Buonaguro[1], Luigi Buonaguro[1]

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DC-NILV: A DENDRITIC CELL-TARGETING NON-INTEGRATING LENTIVIRAL VECTOR PLATFORM FOR DIRECT ADMINISTRATION IN IMMUNOTHERAPEUTIC CLINICAL SETTINGS
Scott Robbins[1], Brenna Kelley-Clarke[1], Jared Odegard[1], Semih Tareen[1], Neal Van Hoeven[1], David Campbell[1], Chris Nicolai[1], Megan Slough[1], Chintan Vin[1], David Baltimore[2], Steve Reed[1], Tom Dubensky[1]

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TISSUE IMAGING VISUALIZES LYTIC DEFICITS IN TUMOR-INFILTRATING CD8 T LYMPHOCYTES IN SITU AND COMBINED WITH IN VITRO MODELS UNCOVERS A PIVOTAL ROLE OF THE TUMOR MICROENVIRONMENT IN CAUSING CELL DEVIATIONS RELATED TO TUMOR IMMUNE ESCAPE

Elfriede Noessner, Petra Skrablin, Ilias Masouris, Ainhoa-Marie Figel, Adriana Turqueti-Neves, Petra Prinz, Dorothee Brech, Anna Mendler, Ramona Schlenker

Helmholtz Zentrum München, Institute of Molecular Immunology, Munich, Germany

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POSITIVE FEEDBACK BETWEEN PGE2 AND COX2 DIVERTS DC DIFFERENTIATION INTO MDSCS AND SUSTAINS THEIR IMMUNOSUPPRESSIVE FUNCTIONS AND CXCL12/CXCR4-DEPENDENT TUMOR HOMING

Natasa Obermajer[1], Ravikumar Muthuswamy[1], Jamie Lesnock[1], Kunle Odunsi[2], Robert Edwards[1], Pawel Kalinski[1]

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CD4+CD39+FOXP3+ REGULATORY T CELLS HYDROLYZE ADENOSINE TRIPHOSPHATE AND MAINTAIN AN INTENSE CROSS-TALK WITH CD39+FOXP3NEG EX-TREG

Patrick Schuler[1,2], Edwin Jackson[3], Jonas Johnson[2], Stephan Lang[1], Theresa Whiteside[2]

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IMMUNOSUPPRESSION IN TRANSGENIC MOUSE MODEL OF SPONTANEOUS SKIN MELANOMA AND ITS NEUTRALIZATION

Alexandra Sevko[1], Marcel Ramacher[1], Michael Shurin[2], Michal Baniyash[3], Viktor Umansky[1]

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LISTERIA MONOCYTOGENES-BASED CANCER IMMUNOTHERAPIES REDUCE IMMUNOSUPPRESSION IN THE TUMOR MICROENVIRONMENT

Reshma Singh, *Anu Wallecha*

Advaxis Inc, Princeton, NJ

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THE IMMUNOSUPPRESSIVE ROLE OF WNT/BETA-CATENIN SIGNALS IN MELANOMA CANCER MICROENVIRONMENTS

Tomonori Yaguchi[1], Yasufumi Goto[2], Tomoki Kurihara[1], Asuka Kobayashi[1], Kenji Morii[1], Hidetoshi Sumimoto[1], Yutaka Kawakami[1]

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HUMAN CCR4+CCR6+ TH17 CELLS SUPPRESS AUTOLOGOUS CD8+ T CELL RESPONSES

Fei Zhao[1], Bastian Höchst[2], Jaba Gamrekelashvili[1], Michael P. Manns[2], Firouzeh Korangy[1], Tim F. Greten[1]

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DYSFUNCTIONAL TUMOR-INFILTRATEING T CELLS EXPRESS THE ANERGY-ASSOCIATED MOLECULES LYMPHOCYTE-ACTIVATION GENE 3 (LAG3) AND CLASS-I-MHC RESTRICTED T CELL ASSOCIATED MOLECULES (CRTAM)

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TUESDAY, NOVEMBER 1, 2011		
8:20 am – 5:00 pm	Summit on Cell Therapy for Cancer	NIH Campus, Masur Auditorium
WEDNESDAY, NOVEMBER 2, 2011		
8:30 am – 1:00 pm	Summit on Cell Therapy for Cancer	NIH Campus, Masur Auditorium
5:00 pm – 8:00 pm	Registration Open: Primer, Workshop, and Annual Meeting	North Bethesda Marriott Hotel
THURSDAY, NOVEMBER 3, 2011		
6:30 am – 6:00 pm	Registration Open	Main Level, Grand Ballroom Lobby
7:00 am – 8:00 am	Continental Breakfast	Grand Ballroom Foyer
8:00 am – 5:00 pm	Primer on Tumor Immunology and Cancer Immunotherapy	Grand Ballroom G-H
8:00 am – 5:00 pm	Workshop on Immunotherapy Combinations	Grand Ballroom E
FRIDAY, NOVEMBER 4, 2011		
6:30 am – 6:00 pm	Registration Open	Main Level, Grand Ballroom Lobby
7:00 am – 7:45 am	New Member Breakfast Gathering (All new members of SITC welcome to attend)	Lower Level, Brookside Room
7:00 am – 7:50 am	Continental Breakfast	Grand Ballroom A-D
7:50 am – 8:00 am	SITC 26th Annual Meeting Begins/President's Welcome	Grand Ballroom E
8:00 am – 8:45 am	Richard V. Smalley, MD Memorial Lectureship: Ralph M. Steinman, MD	Grand Ballroom E
8:45 am – 11:30 am	Plenary Session: Biology and Application of Dendritic Cells	Grand Ballroom E
10:15 am – 10:45 am	Break	Grand Ballroom A-D
11:30 am – 12:00 pm	Plenary Session: Late Breaking Oral Abstracts	Grand Ballroom E
12:00 pm – 1:30 pm	Lunch/Poster Viewing/Exhibits	Grand Ballroom A-D
1:30 pm – 3:00 pm	Concurrent Session I: Immunology of Cancer Stem Cells and Epithelial-to-Mesenchymal Transition (EMT)	Grand Ballroom E
1:30 pm – 3:00 pm	Concurrent Session II: Uncoupling Negative Regulation in the Tumor Microenvironment	Grand Ballroom G-H
3:00 pm – 3:15 pm	Break	Grand Ballroom A-D
3:15 pm – 5:15 pm	Plenary Session: Genetically Engineered Receptors and Adoptive Cell Therapies	Grand Ballroom E
5:15 pm – 5:45 pm	Cancer Immunotherapy Trials Network (CITN Update)	Grand Ballroom E
5:45 pm – 6:15 pm	SITC Membership Business Meeting	Grand Ballroom E
Immediately following Business Meeting – 8:00 pm	Poster Reception and Exhibits	Grand Ballroom A-D
8:00 pm	Early Career Scientists Networking Event	Lower Level, Brookside Room
SATURDAY, NOVEMBER 5, 2011		
7:00 am – 6:00 pm	Annual Meeting Registration Open	Main Level, Grand Ballroom Lobby
7:00 am – 7:45 am	Early Career Scientists "Meet-the-Expert" Breakfasts	Lower Level, Brookside Room
7:00 am – 8:00 am	Continental Breakfast	Grand Ballroom A-D
8:00 am – 8:45 am	Keynote Address: Katherine Fitzgerald, PhD	Grand Ballroom E
8:45 am – 11:30 am	Plenary Session: Characterization of Inflammatory Infiltrates in Human Cancers	Grand Ballroom E
10:15 am – 10:45 am	Break	Grand Ballroom A-D
11:30 am – 12:00 pm	Plenary Session: Late Breaking Abstracts	Grand Ballroom E
12:00 pm – 1:30 pm	Lunch/ Poster Viewing/Exhibits	Grand Ballroom A-D
1:30 pm – 3:00 pm	Concurrent Session I: State of the Art Animal Models & Veterinary Applications for Cancer and Immunology	Grand Ballroom E
1:30 pm – 3:00 pm	Concurrent Session II: High Throughput Technologies Immune for Monitoring	Grand Ballroom G-H
3:00 pm – 3:30 pm	Break	Grand Ballroom A-D
3:30 pm – 4:50 pm	Plenary Session: SITC Presidential Abstract Session	Grand Ballroom E
4:50 pm – 5:20 pm	Plenary Session: Cancer Immunotherapy Guidelines Update	Grand Ballroom E
5:20 pm – 5:35 pm	Plenary Session: National Cancer Institute, NIH Update	Grand Ballroom E
5:35 pm – 5:50 pm	Plenary Session: FDA Update on Regulatory Issues Related to Cancer Immunotherapy	Grand Ballroom E
5:50 pm – 6:15 pm	Award Presentations	Grand Ballroom E
Immediately following Awards Presentations – 8:00 pm	Presidential Reception with Poster Viewing and Exhibits	Grand Ballroom A-D
8:00 pm	Performance by the band The Checkpoints	Grand Ballroom E
SUNDAY, NOVEMBER 6, 2011		
7:00 am – 8:00 am	Continental Breakfast	Grand Ballroom Foyer
7:30 am – 12:00 pm	Annual Meeting Registration Open	Main Level, Grand Ballroom Lobby
8:00 am – 10:15 am	Plenary Session: Prostate Cancer as a Learning Model	Grand Ballroom E
10:15 am	Annual Meeting Adjourns	
10:25 am – 12:00 pm	Hot Topic Symposium: Targeting the Next Generation of Inhibitory Pathways	Grand Ballroom E


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Society for Immunotherapy of Cancer
SAVE THE DATE
SITC 27th Annual Meeting & Associated Programs
October 25-28, 2012
North Bethesda, MD