Guiding Cancer Immunotherapy / Biological Therapy from Bench to Bedside

International Society for Biological Therapy of Cancer
iSBTc

Final Program

25th Annual Scientific Meeting

October 2–4, 2010 WASHINGTON, D.C.
Hyatt Regency Washington on Capitol Hill

iSBTc 25th ANNIVERSARY 2010
www.isbtc.org

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Program at a Glance

* separate registration required

THURSDAY, SEPTEMBER 30, 2010		Location
8:00 am – 5:00 pm	Symposium on Immuno-Oncology Biomarkers, 2010 and Beyond: Perspectives from the iSBTc Biomarkers Task Force *	Masur Auditorium on the NIH Campus
5:00 pm – 8:00 pm	Registration Open at Hyatt Regency Washington on Capitol Hill	Regency Foyer
FRIDAY, OCTOBER 1, 2010		
6:30 am – 5:00 pm	Registration Open	Regency Foyer
7:00 am – 8:00 am	Continental Breakfast	Columbia
8:00 am – 5:00 pm	Primer on Tumor Immunology & Biological Therapy of Cancer *	Regency A
8:00 am – 5:00 pm	Workshop on Monoclonal Antibodies in Cancer *	Capitol Room, Lobby Level
SATURDAY, OCTOBER 2, 2010		
6:30 am – 6:00 pm	Registration Open	Regency Foyer
7:00 am – 7:45 am	Early Career Scientists "Meet-the-Expert Breakfasts" *	Capitol B, Lobby Level
7:00 am – 7:45 am	New Member Gathering	TBA
7:00 am – 8:00 am	Continental Breakfast	Columbia
7:50 am – 8:00 am	25th Annual Meeting Begins / President's Welcome	Regency A
8:00 am – 8:45 am	*Richard V. Smalley, MD Memorial Lectureship:* James P. Allison, PhD	Regency A
8:45 am – 11:30 am	Plenary Session: Dendritic Cells and Cancer	Regency A
11:30 am – 1:30 pm	Lunch / Poster Viewing / Exhibits *(box lunches available)*	Columbia & Ticonderoga
12:00 pm – 1:30 pm	Poster Presentations: Session I (Odd Numbers)	Ticonderoga
1:30 pm – 3:00 pm	Concurrent Session I: Targeted Therapeutics and Immunotherapy	Regency A
1:30 pm – 3:00 pm	Concurrent Session II: Innate/Adaptive Immune Interplay in Cancer	Capitol Room, Lobby Level
3:15 pm – 5:15 pm	Plenary Session: Clinical Trial Endpoints	Regency A
5:15 pm – 5:45 pm	Cancer Immunotherapy Guidelines: A New iSBTc Initiative	Regency A
5:45 pm – 6:15 pm	iSBTc Membership Business Meeting	Regency A
6:15 pm – 8:00 pm	Reception with Poster Viewing (Poster Presentations, see page 6 for more info)	Columbia & Ticonderoga
8:00 pm	Early Career Scientists Evening Networking Event (meet at 8:00 pm in the Hotel Lobby)	
SUNDAY, OCTOBER 3, 2010		
7:00 am – 5:00 pm	Registration Open	Regency Foyer
6:30 am – 7:30 am	Anniversary 5K Fun Run (meet at 6:15am in Hotel Lobby)	
7:00 am – 8:00 am	Continental Breakfast	Columbia
8:00 am – 8:45 am	Keynote Address: Cornelius J.M. Melief, MD, PhD	Regency A
8:45 am – 11:30 am	Plenary Session: Vaccine Combinations	Regency A
11:30 am – 1:30 pm	Lunch / Poster Viewing / Exhibits *(box lunches available)*	Columbia & Ticonderoga
12:00 pm – 1:30 pm	Poster Presentations: Session II (Even Numbers)	Ticonderoga
1:30 pm – 2:50 pm	iSBTc Presidential Abstract Session	Regency A
3:15 pm – 4:45 pm	Concurrent Session I: Countering Negative Regulation	Capitol Room, Lobby Level
3:15 pm – 4:45 pm	Concurrent Session II: Immune Cell Trafficking to Tumor Microenvironment	Regency A
5:00 pm – 5:30 pm	Update: 2009 iSBTc-FDA-NCI Workshop on Prognostic and Predictive Immunologic Biomarkers in Cancer	Regency A
5:30 pm – 6:00 pm	Cancer Immunotherapy Trials Network Update	Regency A
7:30 pm – 10:30 pm	Presidential / Anniversary Reception with Award Presentations (Shuttles run 7:00 pm - 11:00 pm; Badge & Ticket required)	Smithsonian National Museum of Natural History
MONDAY, OCTOBER 4, 2010		
7:00 am – 11:00 am	Registration Open	Regency Foyer
7:00 am – 8:00 am	Continental Breakfast	Columbia
8:00 am – 10:15 am	Plenary Session: Adoptive T Cell Transfer: The Next Wave	Regency A
10:15 am	Annual Meeting Adjourns	
10:30 am – 12:00 pm	Hot Topic Symposium: CTLA-4 Blockade as a Cancer Therapeutic: How Do We Build on a Successful Foundation?	Regency A

Message From the President


©Michael Hoetzel

Dear Colleagues-

A quarter century ago, a group of like-minded investigators recognized the potential promise the immune system held in the fight against cancer and formed this Society. While we continue to share those ideals and camaraderie, we have come a long way in those 25 years!

This year we witnessed the FDA's first approval of a therapeutic cancer vaccine, promising phase III data with anti-CTLA-4, and a host of exciting and promising reports on multiple fronts from adoptive immunotherapy and DC vaccines to new TLR agonists and signaling inhibitors. These findings continue to invigorate our field and provide hope for improved outcomes for patients with cancer. As it has for 25 years, the iSBTc Annual Meeting and Associated Programs will provide our field with a forum for colleagues from 25 countries to gather together, share data, critically review the latest findings, and provide opportunities to guide the development of these therapies to shape the future.

iSBTc 25th ANNIVERSARY 2010

As our field advances, our Society is also evolving to further support the needs of our members and the cancer immunotherapy community. This includes guidance on immunotherapy biomarker assessment, development of young investigators, an improved open access journal venue, and educational programs ranging from basic science to advice on patient treatment. Even the name of the Society is being considered to serve needs more fully and better reflect the make-up of our membership.

This revolutionary Society which has fostered so many people and advancements in this field is well prepared to lead the future with a renewed focus on collaboration and education for the cancer immunotherapy community. Through strategic partnerships and increased global outreach, we will advocate for and advance effective cancer immunotherapy for the betterment of cancer patients world wide.

At this milestone in the Society's history, we pause to reflect and recognize the contributions of the many teams of scientists and physicians who have worked together to translate immunotherapy from the bench to the bedside. This year, six teams will be recognized with the iSBTc Team Science Award for extensive and sustained contributions to our field. The Society will also recognize a number of individuals for their contributions to the Society.

As we reflect on an exciting past, we also look forward to a promising future. The creation of the Cancer Immunotherapy Trials Network (CITN) by the National Cancer Institute (NCI) will start to build on that promise. In support of the field and this progressive program, the Society has committed resources and future Annual Meeting sessions for progress updates from the CITN. Stay tuned!

It has been an exciting 25 years and the Society is off to a great start for the next 25 years, but we need you! These activities and programs, critical to advancing the field, need individuals to step forward, champion the cause, play active roles, and help the Society continue its legacy of excellence. If you are already a member, I thank you for your contributions and support and look forward to your renewed involvement. If you are not a member, I encourage you to join this progressive Society and help us continue to shape the development of cancer immunotherapy.

Support education, research, and honor President Bernie Fox with a "Friend of the President" ribbon (see page 6).

All funds are designated for the iSBTc Education and Research Trust.

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2010 Annual Meeting Program Organizers

Pierre Coulie, MD, PhD
de Duve Institute and University of Louvain
Brussels, Belgium

Elizabeth M. Jaffee, MD
Johns Hopkins University
Baltimore, MD

Pawel Kalinski, MD, PhD
University of Pittsburgh Cancer Institute
Pittsburgh, PA

Vernon K. Sondak, MD
H. Lee Moffitt Cancer Center
Tampa, FL

iSBTc Information and Leadership

iSBTc PROFILE

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

CORE PURPOSE

- To improve cancer patient outcomes by advancing the science, 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 iSBTc
- **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

iSBTc COMPOSITION

Disease States – iSBTc programming and membership covers the full spectrum of both solid tumors and hematologic malignancies including:

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

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

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

iSBTc LEADERSHIP

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Tara Withington, CAE
Executive Director

Jimmy Balwit
Director of Scientific Communications

Angela Kilbert
Director of Administration

Chloe Surinak
Project Manager

Roseann Marotz
Meetings Manager

Sonja Ortman
Membership Manager

General Meeting Information

WELCOME

The International Society for Biological Therapy of Cancer (iSBTc) welcomes you to a celebration of innovation, education, and interaction in the cancer immunotherapy field. For 25 years, iSBTc has been guiding cancer immunotherapy from bench to bedside with intimate meetings designed to gather luminaries, scientists, researchers, and students to network, exchange ideas, and move the science forward.

This year, we celebrate iSBTc's 25th Anniversary Annual Meeting October 2-4, 2010 at the Hyatt Regency Washington on Capitol Hill in Washington, D.C. with cutting-edge science, expert speakers and a special reception honoring leaders in the Society and the field. In addition to these special anniversary events, the Annual Meeting continues its tradition of offering delegates an international forum for education and networking where immunologic and biologic approaches to cancer treatment are showcased, discussed, and critically evaluated.

Within the Annual Meeting program, two exceptional keynote speakers are featured: James P. Allison, PhD from Memorial Sloan-Kettering Cancer Center and Cornelis J.M. Melief, MD, PhD from Leiden University Medical Center. In addition to these speakers, the Annual Meeting sessions include presentations from both invited speakers and abstract presenters selected for their outstanding science. For a complete schedule of these presentations, refer to page 20.

For additional interaction and networking, iSBTc hosts a poster presentation reception on Saturday evening as well as the 25th Anniversary Reception on Sunday evening. The poster reception provides all iSBTc Annual Meeting delegates opportunities to view and discuss posters, connect with authors and presenters, and network with colleagues. The 25th Anniversary Reception on Sunday takes delegates to the spectacular Smithsonian National Museum of Natural History to celebrate 25 years of innovation and a future of successes in the cancer immunotherapy field. This reception features an awards ceremony highlighting luminaries, Society leaders, young investigators and iSBTc's 2010 *Richard V. Smalley, MD Memorial Award* recipient. In addition, it offers delegates opportunities to interact, network, and collaborate in an extraordinary setting.

In celebration and recognition of his excellence in the field of therapeutic research with biological agents, iSBTc is proud to present the 6th Annual *Richard V. Smalley, MD Memorial Award* to Dr. James P. Allison during the Anniversary Reception on Sunday evening. In association with the award, Dr. Allison provides a keynote lecture on Saturday morning. More information about Dr. Allison and the *Richard V. Smalley, MD Memorial Award and Lectureship* can be found on page 11.

PURPOSE

The iSBTc 25th Annual Meeting provides a multidisciplinary educational environment composed of cutting-edge research, oral presentations, poster presentations, and networking opportunities.

TARGET AUDIENCE

The target audience for the Annual Meeting is basic and clinical investigators involved in cancer research comprising members of academic, pharmaceutical, and regulatory agencies including basic scientists, clinicians, graduate students, and post-doctoral fellows, as well as allied health professionals.

PROGRAM GOALS

To facilitate enhancing physician/researcher competence and performance in their daily activities, the iSBTc Annual Meeting provides a forum to:

- Promote scientific exchange of the most recent advances and data in the biological treatment of cancer, as well as advances in basic cancer biology with relevance for anti-tumor immunity.
- Promote the identification of new applications incorporating these advances and explore their potential for impact on treatment outcomes and personalized therapy.
- Discuss the latest clinical developments regarding the application of biologic approaches and establish dialogue between academia, government, and industry regarding implications as well as future directions.
- Educate and provide perspective to the audience on the broad range of scientific developments in cancer and biological approaches to therapy.
- Discuss therapeutic approaches to cancer immunotherapy including: vaccination strategies including combinations of vaccines and molecularly targeted therapies, adoptive T cell transfer, dendritic cells, innate/adaptive immune interplay, countering negative regulation, and immune cell trafficking to tumor microenvironment.
- Integrate novel clinical trial designs, new endpoints and new strategies for response assessment into clinical trials evaluating biologic therapy of cancer.
- Explore the role of biologic therapy in human cancers, in particular melanoma, colorectal, prostate and breast cancers, and hematologic malignancies.

EXPECTED LEARNER OUTCOMES

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

- Summarize the most recent advances in cancer biology, how they intersect with the immune system, and how these considerations are relevant for the biologic therapy of cancer.
- Establish collaborations among the various members of academia, industry, and clinical practices to initiate clinical evaluation of these advances in more efficient trials.

The iSBTc 25th Annual Meeting is a non-accredited continuing medical education event. No credits are offered for physician participation in this educational program.

General Meeting Information

ABSTRACTS

All abstracts submitted in conjunction with the iSBTc 25th Annual Meeting are published in the October 2010 issue of *Journal of Immunotherapy,* the official journal of iSBTc. Members of iSBTc 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 iSBTc website, in the Poster Abstract Book and beginning on page 55 of this program.

ORAL ABSTRACTS

The iSBTc 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 28.

POSTER ABSTRACTS

All accepted posters for the 25th Annual Meeting are on display in the Ticonderoga Room on the Ballroom level of the Hotel and are available for viewing throughout Saturday and Sunday of the Annual Meeting. Please see pages 55-78 or the Poster Abstract Book for a listing of the posters being displayed. During the presentation times below, designated posters are staffed by their respective authors, allowing for information exchange and interaction between researchers and attendees.

Poster Hall Hours

Ticonderoga, Ballroom Level

Saturday:	10:00 am – 8:00 pm
Sunday:	10:00 am – 5:00 pm

Poster Numbers

Adoptive T Cell Transfer: The Next Wave	1 - 20
Clinical Trial Endpoints	21 - 21
Countering Negative Regulation	22 - 37
Dendritic Cells and Cancer	38 - 54
Immune Cell Trafficking to Tumor Microenvironment	55 - 63
Innate/Adaptive Immune Interplay in Cancer	64 - 76
Targeted Therapeutics and Immunotherapy	77 - 149
Vaccine Combinations	150 - 159
Late-Breaking Abstracts	160 - 184

Poster Presentations / Staffing Hours

Odd Number Posters *(authors are present)*

Saturday: 12:00 pm – 1:30 pm & 6:15 pm – 7:00 pm

Even Number Posters *(authors are present)*

Saturday: 7:00 pm – 7:45 pm &
Sunday: 12:00 pm – 1:30 pm

LATE-BREAKING ABSTRACTS

To fullfil iSBTc's commitment to the most cutting-edge science, late-breaking abstract submission was offered from July – August. These abstracts are available for viewing as posters in the "Late-Breaking Abstract" category. Copies of the late-breaking abstracts are also available in the Poster Abstract Book distributed with the meeting materials. Late-breaking abstracts were not available for publication in the October 2010 issue of the *Journal of Immunotherapy*, but will be published in a subsequent 2011 issue.

EXHIBITS

The 25th 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 Ballroom Level of the Hyatt Regency Washington on Capitol Hill in the Columbia Room. The hall is open Saturday and Sunday and booths are staffed throughout the day and during all lunches and the Saturday evening reception. For a complete exhibitor map and listing, please refer to pages 17-19.

Exhibit Hours

Columbia, Ballroom Level

Saturday, October 2	10:00 AM – 8:00 PM
Sunday, October 3	10:00 AM – 5:00 PM

GUEST REGISTRATION

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

"FRIEND OF THE PRESIDENT" RIBBONS

iSBTc is committed to furthering the field of cancer immunotherapy/biologic therapy. In 2009, a Trust to support research, training and education was established. In support of this Trust, iSBTc offers a special opportunity to honor its President each year through the purchase of "Friend of the President" ribbons. Delegates with this special commitment to cancer immunotherapy and current President, Bernie Fox, are noted by the lavender ribbons on their name badges as well as on a sign at the conference. Show your support by purchasing a ribbon at the Registration Desk for a minimum donation of $50*.

*As a 501(c)(3) organization, donations made to iSBTc are tax-deductible as charitable contributions to the extent allowed by law.

General Meeting Information

MEMBERSHIP

Meeting attendees who are members of the iSBTc are designated by a red "Member" ribbon on their name badge. Information on membership classifications, benefits, and dues can be found on page 79. All non-members are invited to complete the membership application form on page 80 and return it to the iSBTc Registration Desk.

PHOTO/VIDEO POLICY

Photography and videography are prohibited in all iSBTc educational sessions, poster, and exhibit locations unless prior written approval is received from the iSBTc office.

iSBTc often employs the services of a professional photographer at iSBTc events to capture images for use in society archival and promotional material. Your attendance at iSBTc events implies your permission for images captured during these events to be used for the purposes of iSBTc archival and promotional material and publications and waives your rights for compensation or ownership of these images.

REGISTRATION

Registration packets are ready for pick up at the iSBTc Registration Desk located in the Regency Foyer on the Ballroom Level for those pre-registered for the Annual Meeting. On-site registration for the Annual Meeting and Associated Programs is accepted space permitting. Separate registration and fees are required for the Workshop and Primer on Friday, October 1. Both symposiums held on Thursday, September 30 and Monday, October 4 require separate registrations, but are complimentary for meeting delegates. Symposium only registration is $100.

Registration Desk Hours

Regency Foyer, Ballroom Level

Thursday, September 30	5:00 pm – 8:00 pm
Friday, October 1	6:30 am – 5:00 pm
Saturday, October 2	6:30 am – 6:00 pm
Sunday, October 3	7:00 am – 5:00 pm
Monday, October 4	7:00 am – 11:00 am

SESSION AND POSTER TOPICS

- Adoptive T Cell Transfer: The Next Wave
- Clinical Trial Endpoints
- Countering Negative Regulation
- Dendritic Cells and Cancer
- Immune Cell Trafficking to Tumor Microenvironment
- Innate/Adaptive Immune Interplay in Cancer
- Targeted Therapeutics and Immunotherapy
- Vaccine Combinations
- Late-Breaking Abstracts*

  **presentations for this category are posters only*

SPEAKER PRESENTATION SLIDES

All registered attendees of the Annual Meeting will receive FREE access to faculty slide presentations posted on the iSBTc website (www.isbtc.org) by the end of November. Access information will be sent to registered attendees upon availability.

YOUNG INVESTIGATOR MEETING FEATURES

iSBTc supports growth and achievement among young investigators and early career scientists in the field of cancer immunotherapy. In fulfillment of this mission, iSBTc offers three specialized opportunities for early career scientists in association with the 25th Annual Meeting: the Early Career Scientists Networking Event, "Meet-the-Expert" Breakfasts, and the Presidential and Travel Awards. See page 8 for more information on the iSBTc Early Career Scientist Committee and the 2010 activities.

Looking for the latest data in the field?

Visit the Late-Breaking Poster Section in the Ticonderoga Room.

Early Career Scientist Information

The Early Career Scientist Committee was established as a partner with iSBTc leadership to address the needs of early career scientists in the fields of immunology and biological therapy. Members of the committee participate in many activities and continually seek opportunities for early career scientists to advance iSBTc's mission and programming. The goal of both the committee and iSBTc leadership is to leverage society relationships and resources to enhance the career development of outstanding young investigators in the field.

WHO WE ARE

Members of the Committee include students, post doctoral fellows-in-training, and early career professionals in academia, industry, and regulatory agencies.

WHAT WE DO

The Committee's mission is to promote career development by utilizing the core knowledge and experience of established iSBTc members, ensure a voice within the iSBTc, and to provide access to the support and resources early career scientists require to succeed.

COMMITTEE HIGHLIGHTS

2009

- Young Investigator Task Force formed to give a voice to the specific needs of early career scientists
- Five Young Investigator "Meet-the-Expert" breakfast topics planned by the Task Force held during the iSBTc Annual Meeting with record participation
- Record number of abstract submissions received in the "Young Investigator" category
- 112% increase in student/young investigator registrants for Annual Meeting over previous year

2010

- Task Force granted committee status by the Board of Directors and renamed Early Career Scientist Committee
- Committee doubled in size to 12 members
- Seven "Meet-the-Expert" breakfast topics included in Annual Meeting schedule due to previous success and continued demand
- Social networking tools being developed to enhance networking among membership and greater cancer immunotherapy community
- A new evening networking event added for early career scientists at the Annual Meeting

EARLY CAREER SCIENTIST ACTIVITIES

The iSBTc Early Career Scientist Committee has planned the following events 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.

"Meet-the-Expert" Breakfasts *(ticketed event)*

Saturday, October 2, 2010
7:00 am - 7:45 am
Capitol B, Lobby Level

The iSBTc "Meet-the-Expert" Breakfasts focus on the unique issues related to the career development of early career scientists. Key leaders in the field facilitate small roundtable discussions on particular topics of interest. Registered attendees of the breakfasts submit discussion questions in advance or pose them at the table to which the experts provide responses and lead informal dialogues to help provide guidance and direction. Separate registration is required for this event.

Breakfast Topics

- **Developing Successful Collaborations**
  Leader: Michel T. Lotze, MD
  University of Pittsburgh Cancer Institute
- **Finding Your Niche**
  Leader: Francesco Marincola, MD
  National Institutes of Health
- **Grant Writing**
  Leader: Patrick Hwu, MD
  MD Anderson Cancer Center
- **Managing a Research Lab**
  Leader: William J. Murphy, PhD
  University of California-Davis
- **Publishing Papers**
  Leader: Robert O. Dillman, MD
  Hoag Cancer Center
- **Testing Your Hypothesis**
  Leader: Giorgio Parmiani, MD
  San Raffaele Foundation
- **Translational Research**
  Leader: Pierre Coulie, MD, PhD
  de Duve Institute and University of Louvain

Early Career Scientist Information

Breakfast Session 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.

EVENING NETWORKING EVENT

Saturday, October 2, 2010
8:00 pm – Meet in the Hotel Lobby

Traveling to:
The Dubliner Restaurant
Number 4 "F" Street
Washington, D.C.
Event Leader: Christian Capitini, MD

All students and early career scientists are welcome at an informal networking gathering on Saturday evening. The group plans to meet in the Hotel Lobby and walk to The Dubliner Restaurant for an opportunity to socialize with peers attending the iSBTc programs. Individuals will be responsible for their own costs. Questions about the event can be directed to Christian Capitini, MD or the iSBTc Registration Desk.

How to Participate

The above events are designed to enhance the experiences of early career scientists attending the iSBTc programs. Space is limited and priority will be given to early career scientists.

Tickets for the "Meet-the-Expert" Breakfasts have been included in the registration materials for attendees who have pre-registered for these events.

The Evening Networking Event is not a ticketed event. To participate, meet in the Hyatt Regency Lobby at 8:00 pm on Saturday, October 2.

Interested in joining the Early Career Scientist Committee?

Find one of the iSBTc members with the emerald green ribbon on their name badge or inquire at the Registration Desk.

Committee Members:

Co-Chairs:

Kerrington Molhoek, PhD
University of Virginia

Amy Wesa, PhD
Celsense, Inc.

iSBTc Leadership Mentor
Jon Wigginton, MD
Bristol-Myers Squibb Co.

Members:

Christian Capitini, MD
National Cancer Institute

Joshua Leonard, PhD
Northwestern University

Ulf Petrausch, MD
University Hospital of Zurich

Will Redmond, PhD
Providence Portland Medical Center

Jochen Schaefer, MD
University of Virginia

Anil Shanker, PhD
NCI - Frederick / SAIC – Frederick

Richard Wu, BS
University of Texas MD Anderson Cancer Center

Ben Zeskind, MD, PhD
Immuneering Corporation

25th Anniversary Activities

iSBTc commemorates its 25 years of guiding cancer immunotherapy from bench to bedside with several exciting activities. Come join the celebration!

ANNIVERSARY 5K FUN RUN

Sunday, October 3, 2010
6:30 am – 7:30 am *(Meet at 6:15 am in the Hotel Lobby)*
National Mall

This 5K run tours the length of the National Mall from Capitol Hill to the Washington Monument and back. Pre-registration is not required. Meet your colleagues for some early morning exercise while taking in the sites of the National Mall.

iSBTc MEMORABILIA

Reminisce about past meetings and marvel at how far the Society and field have come in 25 years! Special displays are available throughout the programs. Network with colleagues over shared memories.

ANNIVERSARY RECEPTION

Sunday, October 3, 2010
7:30 pm – 10:30 pm
(Buses available from the Hotel 7:00 pm – 11:00 pm)
Smithsonian National Museum of Natural History

Mingle with your iSBTc colleagues and gaze at many of the world's natural wonders as the Society celebrates 25 years. Activities take place inside the Baird Auditorium, Ocean Hall, and the Geology, Gem & Minerals Exhibit at the Smithsonian National Museum of Natural History.

Festivities begin promptly at 7:30 pm in the Baird Auditorium with awards for extensive and sustained contributions to the field and to the Society, and a gathering of the field's thought-leaders in an amazing venue.

Entrance tickets and your iSBTc name badge will be required for this event. Tickets for pre-registered delegates were provided in your registration packet.

Transportation to and from the Hotel and Museum is available. Marked shuttles begin at 7:00 pm outside the Hyatt's main entrance and run until 11:00 pm.

Reception support provided in part by a grant from the Chiles Foundation.

Smalley Memorial Award and Lectureship

In memory of his many wonderful achievements, both professionally and personally, the International Society for Biological Therapy of Cancer (iSBTc) 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.

2010 *RICHARD V. SMALLEY, MD MEMORIAL AWARD* RECIPIENT

James P. Allison, PhD

Memorial Sloan-Kettering Cancer Center

In recognition of his outstanding research, work, and achievements in cancer therapy, the International Society for Biological Therapy of Cancer (iSBTc) proudly presents the 2010 *Richard V. Smalley, MD Memorial Award* to James P. Allison, PhD. Dr. Allison presents the keynote address on Saturday, October 2 from 8:00 am – 8:45 am in Regency A.

Dr. James Allison has a longstanding interest the in the mechanisms of T cell activation and its regulation, as well as developing novel strategies for immunotherapy of cancer. He has made many significant contributions to our understanding of T cell costimulation and inhibition, and conceived the notion of immune checkpoint blockade for the therapy of cancer. He is currently the Chairman of the Immunology Program, Director of the Ludwig Center for Cancer Immunotherapy, David H. Koch Chair in Immunologic Studies, and Attending Immunologist at the Memorial Sloan-Kettering Cancer Center. He is also an Investigator of the Howard Hughes Medical Institute, a Member of the National Academy of Sciences, and of 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 iSBTc 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 iSBTc 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. iSBTc'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 iSBTc Smalley Award Recipients

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

Presidential and Travel Awards

iSBTc PRESIDENTIAL AWARDS

The iSBTc 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 iSBTc abstract submission process and are judged by a committee of iSBTc leadership. Four abstracts submitted in any category and authored by young investigators have been selected for 20-minute oral presentations during the Presidential Session from 1:30 pm – 2:50 pm on Sunday, October 3 in Regency A. Of those abstract presenters, all will receive Presidential Travel Awards and one will be selected as the 2010 Presidential Award winner. Judging of the oral presentations will be done by a committee of iSBTc leadership.

(1) Presidential Award winner receives:

- $1,000 Honorarium
- Up to $1,000 in Travel Reimbursement
- 1-Year Membership in iSBTc
- Commemorative Presidential Award Plaque
- "Presidential Award Winner" Ribbon

(3) Presidential Travel Award winners receive:

- Up to $750 in Travel Reimbursement
- 1-Year Membership in iSBTc
- Presidential Travel Award Certificate
- "Presidential Travel Award Winner" Ribbon

iSBTc TRAVEL AWARDS

iSBTc has offered six travel awards to young investigators demonstrating scientific excellence through abstract data who are presenting posters at the iSBTc 25th Annual Meeting. These posters are on display in the Poster Hall and are designated with award ribbons. Judging was done by a committee of iSBTc leadership.

(6) iSBTc Travel Award Winners receive:

- Up to $750 in Travel Reimbursement
- iSBTc Travel Award Winner Certificate
- "iSBTc Travel Award Winner" Ribbon

2010 TRAVEL AWARD WINNERS

Presidential Award

Join us for the announcement on Sunday, October 3 at the 25th Anniversary & Awards Reception.

Presidential Travel Awards

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

Evripidis Lanitis, BS
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

iSBTc Travel Awards

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

Davide 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

Presidential and Travel Awards

PREVIOUS iSBTc PRESIDENTIAL/TRAVEL AWARD WINNERS

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 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 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 Munchen, Institute of Molecular Immunology
Munich, Germany

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

Andrea Worschech, MSc
National Institutes of Health, CC-DTM
Bethesda, MD

2007 - Boston, MA

Presidential Award

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 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

Presidential Awards

2006 - Los Angeles, CA

Ulf Petrausch, MD
Earle A. Chiles Research Institute
Portland, OR

2005 - Alexandria, VA

Anne Letsch, MD
Charité - Campus Benjamin Franklin
Berlin, Germany

Ainhoa Pérez-Diez, PhD
National Institutes of Health
Bethesda, MD

2004 - San Francisco, CA

Luca Gattinoni, MD
National Cancer Institute - Surgery Branch
Bethesda, MD

Jiali Li, PhD
Stanford University
Stanford, CA

2003 - Bethesda, MD

Steven E. Finkelstein, MD
National Cancer Institute - Surgery Branch
Bethesda, MD

Christian Poehlein, MD
Earle A. Chiles Research Institute
Portland, OR

Associated Programs

In association with the Annual Meeting, iSBTc holds several highly regarded educational programs: the Symposium on Immuno-Oncology Biomarkers on Thursday, September 30 at the Masur Auditorium on the NIH Campus; the Workshop and Primer on Friday, October 1; and the Hot Topic Symposium on Monday, October 4 at the Hyatt Regency Washington on Capitol Hill. These programs require separate registration. For more information about these associated programs, please visit the iSBTc Registration Desk located in the Regency Foyer on the Ballroom Level of the Hyatt Regency Washington on Capitol Hill.

SYMPOSIUM ON IMMUNO-ONCOLOGY BIOMARKERS, 2010 AND BEYOND: PERSPECTIVES FROM THE iSBTc BIOMARKER TASK FORCE

Thursday, September 30, 2010
8:00 am – 5:00 pm
Masur Auditorium, NIH Campus; Bethesda, MD
www.isbtc.org/meetings/am10/biomarkers10/

The Symposium includes lectures and interactive panel discussions on immunologic monitoring and standardization of immunologic biomarkers for clinical trials, correlating immunity to clinical responses and potency assays, novel and high-throughput methodologies for immune assessment, and recommendations on the incorporation of biomarkers into the clinical arena.

Organizers:
Lisa H. Butterfield, PhD – *University of Pittsburgh*
Mary L. Disis, MD – *University of Washington*
Samir Khleif, MD – *National Cancer Institute (CCR)*
Francesco Marincola, MD - *National Institutes of Health (CC, DTM)*

WORKSHOP ON MONOCLONAL ANTIBODIES IN CANCER

Friday, October 1, 2010
8:00 am – 5:00 pm
Hyatt Regency Washington on Capitol Hill; Washington, D.C.
www.isbtc.org/meetings/am10/workshop10/

This interactive workshop is organized around lively discussion on mechanisms of action responsible for clinical efficacy of mAbs, mechanisms of resistance to mAbs, and how to best utilize current knowledge to develop more effective antibody-based cancer treatments.

Organizers:
Glenn Dranoff, MD – *Dana-Farber Cancer Institute*
Ira Mellman, PhD – *Genentech, Inc.*
George J. Weiner, MD – *University of Iowa*

PRIMER ON TUMOR IMMUNOLOGY AND BIOLOGICAL THERAPY OF CANCER

Friday, October 1, 2010
8:00 am – 5:00 pm
Hyatt Regency Washington on Capitol Hill; Washington, D.C.
www.isbtc.org/meetings/am10/primer10/

The Primer provides a one-day background on the foundations and basics of tumor immunology and immunological/biological therapies for cancer. A perfect program for students, clinical oncologists, and those needing a refresher!

Organizers:
Patrick Hwu, MD – *MD Anderson Cancer Center*
Walter J. Urba, MD, PhD – *Earle A. Chiles Research Institute*

Hotel Information

The Hyatt Regency Washington on Capitol Hill serves as the headquarters hotel for the iSBTc 25th Annual Meeting. It is located within walking distance to the Smithsonian, the National Mall, Union Station, and other area attractions.

TRANSPORTATION OPTIONS

It's easy to get around D.C., with its logically laid-out streets and easy-to-use public transportation system, plus, Washington, D.C. has one of the highest ratios of taxis per citizen in the country. Taxis are readily available within the city. The Hyatt Regency Washington on Capitol Hill is approximately three blocks from Union Station/Amtrak where you can take the Metro to area attractions or Regan National Airport (DCA).

BUSINESS SERVICES

A full-service business center with a FedEx Office is located within the Hotel to assist guests 24-hours a day. It is staffed Monday through Friday, 6:00 am to 6:00 pm. Should you require services after hours, use your guestroom key card and credit card for access.

RECREATION & ENTERTAINMENT

- The health club and pool are open daily 5:00 am to 11:00 pm with your guestroom key.
- Running maps by athletic-minded traveler® with a 5-mile jogging/walking route are available from the concierge.
- Area attractions such as Union Station, the US Capitol and the National Mall are only blocks away.

HOTEL DINING

Article One – American Grill

The restaurant offers a casual location for breakfast and lunch each day, while featuring upscale dining for dinner each evening. Choose from a selection of unique dishes blending local influences, organic products, and grilled favorites with a creative twist.

Open daily 6:30 am to 11:00 pm - Dinner service begins at 5:00 pm

Article One Lounge

Enjoy classy cocktails and delicious appetizers in this sophisticated D.C. Lounge.

Open daily 11:30 am to 2:00 am

Travel Traders Gift & Coffee Shop

Looking for a snack for on the go? Stop here to grab a cup of freshly brewed Starbucks Coffee, pastries, or snack item. The gift shop can also provide any last minute toiletry items, Washington, D.C. souvenirs, books, magazines, and much more.

© Hyatt Regency Washington on Capitol Hill

Hotel Map

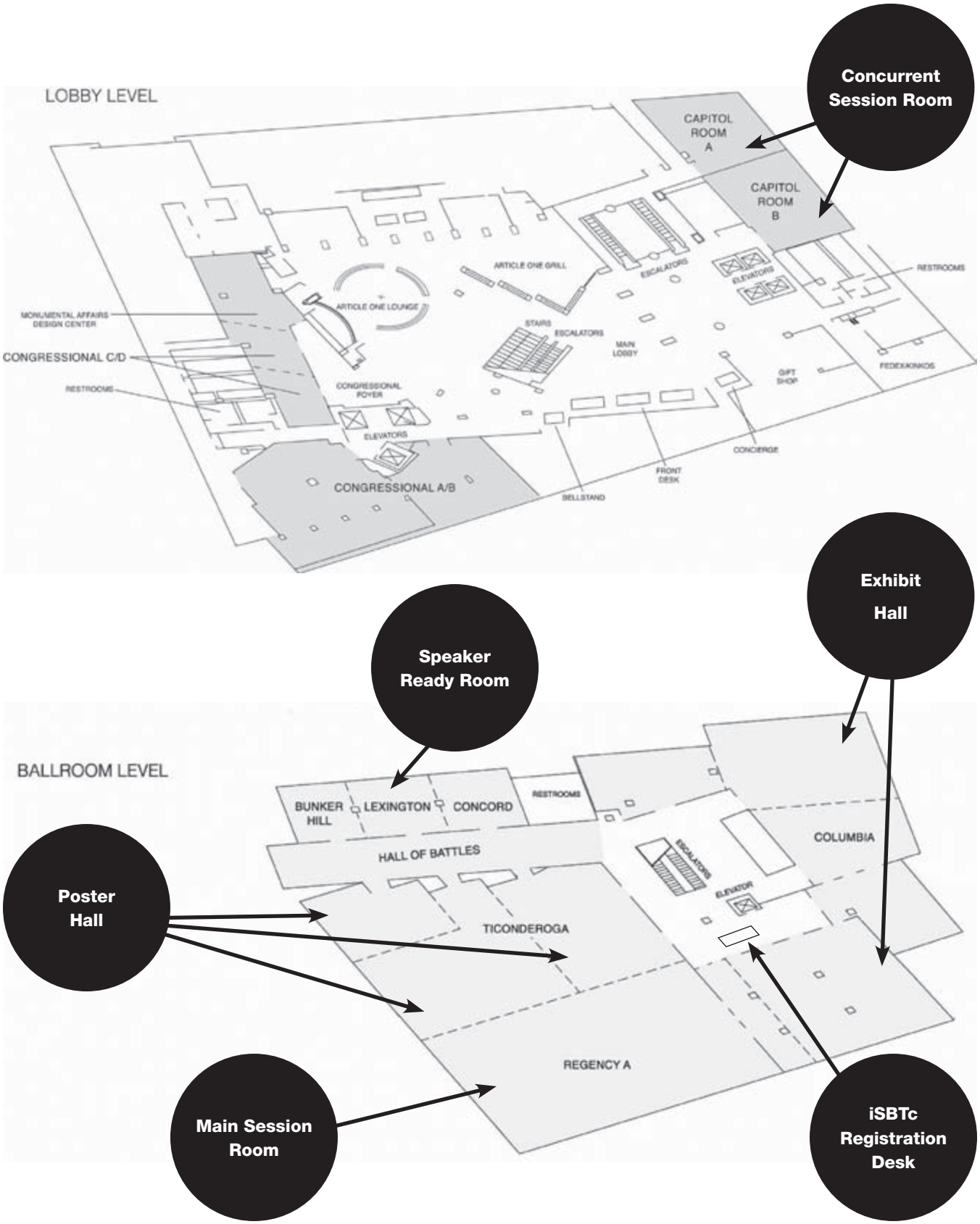
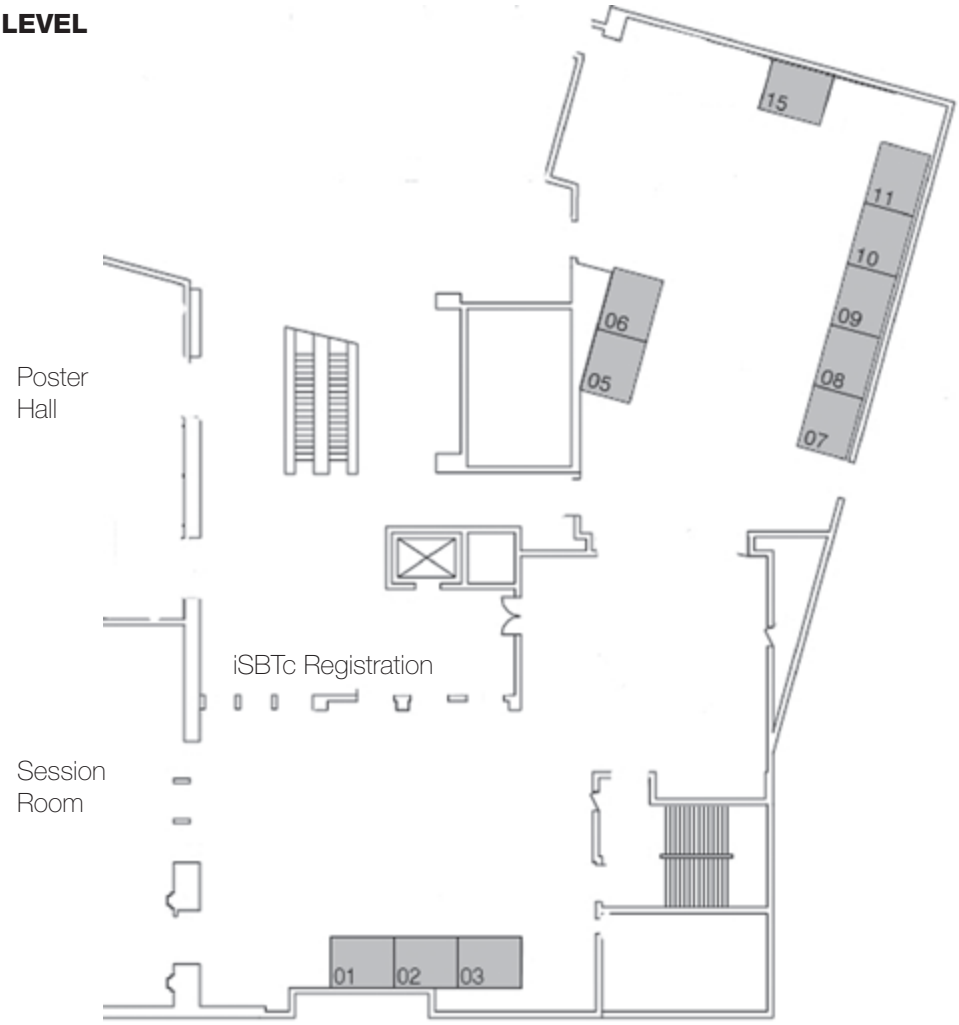

Concurrent Session Room
LOBBY LEVEL
CAPITOL ROOM A
CAPITOL ROOM B
ARTICLE ONE GRILL
ESCALATORS
ELEVATORS
RESTROOMS
ARTICLE ONE LOUNGE
MONUMENTAL AFFAIRS DESIGN CENTER
CONGRESSIONAL C/D
RESTROOMS
STAIRS
ESCALATORS
MAIN LOBBY
GIFT SHOP
FEDEX/KINKOS
CONGRESSIONAL FOYER
ELEVATORS
CONCIERGE
FRONT DESK
CONGRESSIONAL A/B
BELLSTAND
Exhibit Hall
Speaker Ready Room
BALLROOM LEVEL
BUNKER HILL
LEXINGTON
CONCORD
RESTROOMS
HALL OF BATTLES
COLUMBIA
ESCALATORS
ELEVATOR
Poster Hall
TICONDEROGA
REGENCY A
Main Session Room
iSBTc Registration Desk

Exhibit Map

COLUMBIA
BALLROOM LEVEL



BOOTH #	EXHIBITOR
01	EMD Serono
02	Cellular Technology Limited
03	FlexCare Clinical Research
05	Prometheus Laboratories Inc.
06	Immudex
07	Miltenyi Biotec GmbH
08	Seppic, Inc.
09	JPT Peptide Technologies GmbH
10	Mabtech, Inc.
11	Nexcelom Bioscience
15	CellGenix/American Fluoroseal

Exhibitor Listing

DELUXE EXHIBITORS

Immudex — Booth # 06

Immudex USA, LLC
4031 University Drive, Suite 200
Fairfax, VA 22030
Tel: 703-766-4688 or 301-606-9145
Email: sh@immudex.com

Immudex
Fruebjergvej 3
DK-2100 Copenhagen, Denmark
Tel: 45-60136-400 or 45-3917-777
Email: hp@immudex.com

Immudex develops and commercializes products for the quantitation, characterization, and generation of antigen specific T cell responses for life science research, in vitro diagnostics and vaccine development. Based on our proprietary MHC Dextramer technology, Immudex has a number of Research Use Only products on the market for the detection of antigen-specific T cells, two products under development for *in vitro* diagnostic use, as well as a vaccine candidate in development for one of the most deadly of human diseases.

Prometheus Laboratories Inc. — Booth # 05

9410 Carroll Park Drive
San Diego, CA 92121
Tel: 888-423-5227
Web: www.prometheuslabs.com

Prometheus is a specialty pharmaceutical and diagnostic company committed to developing and commercializing novel products to help physicians individualize patient care. We are a leader in applying the principles of personalized medicine to the diagnosis and treatment of gastrointestinal diseases and intend to apply these principles to oncology as well.

BASIC EXHIBITORS

CellGenix / American Fluoroseal — Booth # 15

CellGenix Technologie Transfer, GmbH
16 Am Flughafen
79108 Freiburg, Germany
Tel: 49-761-88889-100

US Operations:
303 Main Street, Suite 100-C
Antioch, IL 60002
Tel: 847-395-7277
Email: neubiser@cellgenix.com
Web: www.cellgenix.com

American Fluoroseal Corporation
431 E. Diamond Avenue
Gaithersburg, MD 20877
Tel: 301-990-1407
Email: info@toafc.com
Web: www.toafc.com

CellGenix manufactures both high quality GMP and research grade cytokines and GMP cell culture medium for use in ex-vivo dendritic, stem, NK, MSC, and T cell culture protocols. These products are marketed in combination with AFC's GMP closed system cell culture and unique cryopreservation containers made from clear, inert, non-leachable, gas permeable FEP film. Both CellGenix and AFC's focus is on high quality, individualized, ex-vivo, cell and gene therapeutics.

Cellular Technology Limited (CTL) — Booth #02

20521 Chagrin Boulevard
Shaker Heights, OH 44122
Tel: 888-791-4005
Web: www.immunospot.com

The success of cancer immunotherapy and biological therapy depends on a diversified approach. For nearly a decade Cellular Technology Limited (CTL) has provided the necessary tools and resources to industry, government and academic institutions. CTL offers contract research services for ELISPOT, ELISA and FACS, as well as a large library of cryopreserved human PBMC, and CEF-peptide pools. In addition, CTL markets the ImmunoSpot®/ BioSpot® plate reader systems for ELISPOT, viral plaque, clonogenic, genotoxic and stem cell assays.

Exhibitor Listing

EMD Serono **Booth # 01**
One Technology Place
Rockland, MA 02370
Tel: 800-283-8088
Web: www.emdserono.com

EMD Serono, Inc., an affiliate of Merck KGaA, Darmstadt, Germany, is a leader in developing innovative products in neurodegenerative diseases, fertility, endocrinology, and oncology. EMD Serono is focused on developing novel cancer therapies that combine approaches targeting the tumor cell, tumor environment and immune system to optimize treatment outcomes.

FlexCare Clinical Research **Booth #03**
8340 Northfield Boulevard, Suite 2660
Denver, CO 80238
Tel: 303-223-2322
Email: info@flexcarecr.com
Web: www.flexcarecr.com

FlexCare Clinical Research specializes in providing study visits in the home or alternate site settings via a network of highly skilled clinicians. FlexCare was created to meet growing demand from the biopharmaceutical industry to accelerate clinical trials and streamline study processes. FlexCare's service model is designed to take the study to the patient, fostering an increase in patient recruitment, enrollment, compliance and retention.

JPT Peptide Technologies GmbH **Booth #09**
Volmerstrasse 5 (UTZ)
12489 Berlin, Germany
Tel: 49-30-6392-7878
US Tel: 888-578-2666
Web: www.jpt.com

JPT Peptide Technologies is the leading provider of peptide microarrays worldwide for profiling humoral immune responses and identifying novel seromarkers on proteome wide levels. In addition, JPT provides innovative peptide based products and services such as antigen spanning PepMix™ - peptide pools and PepTrack™ - peptide libraries for T cell assays in clinical setups. SpikeTides™ - is a unique approach to provide small scale isotopically labeled peptides for protein quantification in proteomics.

Mabtech, Inc. **Booth #10**
3814 West Street, Suite 220
Cincinnati, OH 45227
Tel: 866-ELI-Spot or 513-871-4500
Web: www.mabtech.com

Mabtech AB, Stockholm, Sweden with subsidiaries/offices in Australia, France, Germany and the USA, is a leader in the development of ELISpot products, technology and methods for T cell detection and measurement. Products include B-cell ELISpot kits, Fluorospot kits for detection of dual cytokine secretion; newer systems include IL-17 and IL-23. Innovative development and high quality standards result in products meeting the needs of both frontline and clinical researchers. Mabtech products are for Research Use Only.

Miltenyi Biotec GmbH **Booth #07**
Friedrich-Ebert-Strasse 68
51429 Bergisch Gladbach, Germany
Tel: 49-2204-83060
Email: macs@miltenyibiotec.de
Web: www.miltenyibiotec.com

Miltenyi Biotec's company mission is to improve scientific understanding and medical progress by providing products and services for cellular therapies. With approx. 1100 employees in 18 countries, Miltenyi Biotec develops, manufactures, and commercializes innovations for both research and clinical applications. The portfolio provides integrated solutions for all areas covering sample preparation, cell separation, cell culture, flow cytometry, and molecular analysis.

Nexcelom Bioscience **Booth #11**
360 Merrimack Street
Building 9
Lawrence, MA 01843
Tel: 978-327-5340

Web: www.nexcelom.com

Nexcelom's Cellometer line of simple-to-use cell counters automate manual cell counting by obtaining accurate counts, viability, and cell sizes in less than 30 seconds with 20uL of sample. Dual-fluorescence detection capabilities enable immediate determination of GFP transfection efficiency, PI-viability and accurate cellcounts and viability in complex primary cell samples.

Seppic, Inc. **Booth #08**
30 Two Bridges Road, Suite 210
Fairfield, NJ 07004
Tel: 973-882-5597
Web: www.seppic.com

For more than 25 years, Seppic has developed vaccine adjuvants for human use. These adjuvants known under the trade name Montanide ISA 51 VG and Montanide ISA 720 VG, have been used widely in immunotherapy against cancer with Phase III clinical trials in progress. Please stop by our exhibit to get more information.

Program Schedule

SATURDAY, OCTOBER 2, 2010		Location
6:30 AM - 6:00 PM	**Registration Open**	**Regency Foyer**
7:00 AM - 7:45 AM	**Continental Breakfast**	**Columbia**
7:00 AM - 7:45 AM	**Early Career Scientists "Meet-the-Expert" Breakfasts** *Separate registration required.*	**Capitol B**
7:00 AM - 7:45 AM	**New Member Gathering**	**To Be Announced**
10:00 AM - 8:00 PM	**Exhibit Hall Open**	**Columbia**
10:00 AM - 8:00 PM	**Poster Hall Open**	**Ticonderoga**
7:50 AM - 8:00 AM	**President's Welcome** Bernard A. Fox, PhD *Earle A. Chiles Research Institute*	**Regency A**
8:00 AM - 8:45 AM	***Richard V. Smalley, MD Memorial Lectureship:*** **Checkpoint Blockade in Tumor Immunotherapy: New Insights and Opportunities** James P. Allison, PhD *Memorial Sloan-Kettering Cancer Center*	**Regency A**
8:45 AM - 11:30 AM	**Plenary Session: Dendritic Cells and Cancer** *Co-Chairs:* Carl G. Figdor, PhD *Nijmegen Centre for Molecular Life Sciences* Pawel Kalinski, MD, PhD *University of Pittsburgh Cancer Institute*	**Regency A**
8:45 AM - 9:15 AM	**Dendritic Cell Vaccination in Cancer: Achievements, Obstacles and Future Perspectives** Carl G. Figdor, PhD *Nijmegen Centre for Molecular Life Sciences*	
9:15 AM - 9:45 AM	**Progress in the Active Immunotherapy of Prostate Cancer: Sipuleucel-T, an Autologous Cellular Immunotherapy** David L. Urdal, PhD *Dendreon Corporation*	
9:45 AM - 10:00 AM	**Therapeutic Vaccination with Autologous mRNA Electroporated Dendritic Cells in Patients with Advanced Melanoma** Sofie Wilgenhof, MD *Universitair Ziekenhuis Brussel*	
10:00 AM – 10:30 AM	**Refreshment Break**	**Columbia**
10:30 AM - 10:45 AM	**Resistance to the Proapoptotic Effects of IFN-γ on Melanoma Cells Used in Patient-Specific Dendritic Cell Immunotherapy is Associated with Improved Overall Survival** Andrew N. Cornforth, PhD *Hoag Memorial Hospital Cancer Center*	
10:45 AM - 11:00 AM	**IFN-gamma is Central to Both Immunogenic and Tolerogenic Properties of Dendritic Cells After IL-12 and GM-CSF Microsphere Treatment** Jamie L. Harden *State University of New York, University at Buffalo*	
11:00 AM - 11:30 AM	**Polarized Dendritic Cells in the Immunotherapy of Established Cancer: Roles of Signal 3 and Signal 4** Pawel Kalinski, MD, PhD *University of Pittsburgh Cancer Institute*	
11:30 AM - 1:30 PM	**Lunch and Exhibits** *(Box lunches provided to registered attendees.)*	**Columbia**

Program Schedule

SATURDAY, OCTOBER 2, 2010		Location
12:00 PM - 1:30 PM	**Odd Numbered Poster Presentations** *(Authors present.)*	**Ticonderoga**
1:30 PM - 3:00 PM	**Concurrent Session I: Targeted Therapeutics and Immunotherapy** *Co-Chairs:* Mary L. Disis, MD *University of Washington* Keiran S. Smalley, PhD *H. Lee Moffitt Cancer Center & Research Institute*	**Regency A**
1:30 PM - 2:00 PM	**Immune Modulation of Breast Cancer** Mary L. Disis, MD *University of Washington*	
2:00 PM - 2:30 PM	**Overcoming BRAF Inhibitor Resistance in Melanoma** Keiran S. Smalley, PhD *H. Lee Moffitt Cancer Center & Research Institute*	
2:30 PM - 2:45 PM	**The High-Dose Aldesleukin "Select"; Trial in Patients with Metastatic Renal Cell Carcinoma** Kim A. Margolin, MD *Seattle Cancer Care Alliance*	
2:45 PM - 3:00 PM	**In Vivo Modeling and Detection of Ovarian Cancer Vascular Marker TEM1** Chunsheng Li, PhD *Ovarian Cancer Research Center, University of Pennsylvania*	
1:30 PM - 3:00 PM	**Concurrent Session II: Innate/Adaptive Immune Interplay in Cancer** *Co-Chairs:* Vincenzo Cerundolo, MD, PhD *University of Oxford - Institute of Molecular Medicine* Laurence Zitvogel, MD, PhD *Institute Gustave Roussy*	**Capitol Room**
1:30 PM - 2:00 PM	**The Role of Invariant NKT Cells at the Interface of Innate and Adaptive Immunity** Vincenzo Cerundolo, MD, PhD *University of Oxford - Institute of Molecular Medicine*	
2:00 PM - 2:15 PM	**Pathogenic Mast Cell / T Regulatory Cell Cross Talk in Colorectal Cancer** Khashayarsha Khazaie, PhD, DSc *Northwestern University, Robert Lurie Comprehensive Cancer Center*	
2:15 PM - 2:30 PM	**Myeloid-Derived Suppressor Cells and Decreased Interferon Responsiveness in Tumor-Bearing Mice** Bethany Mundy *The Ohio State University*	
2:30 PM - 3:00 PM	**The Desirable Cell Death for Chemotherapy of Cancer** Laurence Zitvogel, MD, PhD *Institute Gustave Roussy*	
3:00 PM - 3:15 PM	**Refreshment Break**	**Columbia**
3:15 PM - 5:15 PM	**Plenary Session: Clinical Trial Endpoints** *Co-Chairs:* F. Stephen Hodi, MD *Dana-Farber Cancer Institute* Vernon K. Sondak, MD *H. Lee Moffitt Cancer Center*	**Regency A**

Program Schedule

SATURDAY, OCTOBER 2, 2010		Location
3:15 PM - 3:35 PM	**Decoding the Tower of Babel** Vernon K. Sondak, MD *H. Lee Moffitt Cancer Center*	
3:35 PM - 3:55 PM	**Immune-Related Response Criteria - Finding Missed Signals of Activity for Immunotherapy** F. Stephen Hodi, MD *Dana-Farber Cancer Institute*	
3:55 PM - 4:15 PM	**Defining Response in Prostate Cancer Immunotherapy** Lawrence Fong, MD *University of California- San Francisco*	
4:15 PM - 4:35 PM	**Moving Beyond Tumor Size: A New Paradigm in Cancer Imaging** Annick D. Van den Abbeele, MD *Dana-Farber Cancer Institute*	
4:35 PM - 5:15 PM	**Panel Discussion**	
5:15 PM - 5:45 PM	**Clinical Immunotherapy Guidelines: A New iSBTc Initiative** Howard L. Kaufman, MD *Rush University Medical Center*	**Regency A**
5:45 PM - 6:15 PM	**iSBTc Membership Business Meeting**	**Regency A**
6:15 PM - 8:00 PM	**Reception with Exhibits and Poster Viewing**	**Columbia and Ticonderoga**
6:15 PM - 7:00 PM	**Odd Numbered Poster Presentations** *(Authors present.)*	**Ticonderoga**
7:00 PM - 7:45 PM	**Even Numbered Poster Presentations** *(Authors present.)*	**Ticonderoga**
8:00 PM	**Early Career Scientists Evening Network Event** *(Meet in Hotel Lobby. Prior registration not required.)*	

SUNDAY, OCTOBER 3, 2010		
6:15 AM - 7:30 AM	**Anniversary 5K Fun Run** *(Meet in Hotel Lobby. Prior registration not required.)*	**National Mall**
7:00 AM - 5:00 PM	**Registration Open**	**Regency Foyer**
7:00 AM - 8:00 AM	**Continental Breakfast**	**Columbia**
10:00 AM - 5:00 PM	**Exhibit Hall Open**	**Regency Foyer**
10:00 AM - 5:00 PM	**Poster Hall Open**	**Ticonderoga**
8:00 AM - 8:45 AM	**Keynote Address:** **Immunotherapy of High Risk HPV Infections** Cornelis J.M. Melief, MD, PhD *Leiden University Medical Center*	**Regency A**
8:45 AM - 11:30 AM	**Plenary Session: Vaccine Combinations** *Co-Chairs:* Pierre Coulie, MD, PhD *de Duve Institute and University of Louvain* Victor H. Engelhard, PhD *University of Virginia School of Medicine*	**Regency A**
8:45 AM - 9:15 AM	**Numbers and Functions of T Lymphocytes in Human Melanoma Metastases** Pierre Coulie, MD, PhD *de Duve Institute and University of Louvain*	

Program Schedule

SUNDAY, OCTOBER 3, 2010		Location
9:15 AM - 9:45 AM	**Phosphopeptides Presented by MHC Class I and Class II Molecules: a New Category of Tumor Associated Antigens with Immunotherapeutic Potential** Victor H. Engelhard, PhD *University of Virginia School of Medicine*	
9:45 AM - 10:00 AM	**Induction of CD8+ T Cell Responses Against Novel Glioma-Associated Antigen Peptides and Clinical Activity by Vaccinations with α-Type-1-Polarized Dendritic Cells and Poly-ICLC in Patients with Recurrent Malignant Glioma** Hideho Okada, MD, PhD *University of Pittsburgh Cancer Institute*	
10:00 AM – 10:30 AM	**Refreshment Break**	**Columbia**
10:30 AM - 11:00 AM	**Vaccine Combinations: Endogenous vs Exogenous Vaccination with CTLA-4 Blockade** Jedd D. Wolchok, MD, PhD *Memorial Sloan-Kettering Cancer Center*	
11:00 AM - 11:15 AM	**T Cell Activation, PSMA Seroconversion and Increased Th17 Rare are Associated with Favorable Clinical Outcome in Prostate Cancer Patients Treated with Prostate GVAX and Anti-CTLA-4 Immunotherapy** Saskia J. Santegoets, PhD *VU University Medical Center*	
11:15 AM - 11:30 AM	**Peptide/IFA emulsion Vaccines can Form a Sink and Graveyard for Tumor-specific CD8+ T Cells** Willem W. Overwijk, PhD *University of Texas, MD Anderson Cancer Center*	
11:30 AM - 1:30 PM	**Lunch and Exhibits** *(Box lunches provided to registered attendees.)*	**Columbia**
12:00 PM - 1:30 PM	**Even Numbered Poster Presentations** *(Authors present.)*	**Ticonderoga**
1:30 PM - 2:50 PM	**Presidential Abstract Session** *Chair:* Bernard A. Fox, PhD *Earle A. Chiles Research Institute*	**Regency A**
1:30 PM - 1:50 PM	**Interferon-ß Secretion in the Tumor Microenvironment can Cause Potent Tumor Control Through Host Cells Independently from Adaptive Immunity** Robbert Spaapen, PhD *University of Chicago*	
1:50 PM - 2:10 PM	**4-1BB Activation Induces the Master-Regulator EOMES and a Broad-Spectrum TH1 Phenotype which Synergizes with CTLA-4 Blockade to Reject B16 Melanoma** Michael A. Curran, PhD *Memorial Sloan-Kettering Cancer Center*	
2:10 PM - 2:30 PM	**Ovarian Cancer Cells Ubiquitously Express HER-2 and can be Distinguished from Normal Ovary by Genetically Redirected T Cells** Evripidis Lanitis, BS *University of Pennsylvania*	
2:30 PM - 2:50 PM	**Large-Scale Profiling of Circulating Serum Markers, Single Cell Polyfunctionality and Antigen Diversity of T Cell Response Against Melanoma** Chao Ma, MS *California Institute of Technology*	
2:50 PM - 3:15 PM	**Refreshment Break**	**Columbia**

Program Schedule

SUNDAY, OCTOBER 3, 2010		Location
3:15 PM - 4:45 PM	**Concurrent Session I: Countering Negative Regulation** *Co-Chairs:* Pierre van der Bruggen, PhD *Ludwig Institute for Cancer Research* Weiping Zou, MD, PhD *University of Michigan*	**Capitol Room**
3:15 PM - 3:45 PM	**Is it Possible to Correct the Impaired Function of Human Tumor-Infiltrating T Lymphocytes?** Pierre van der Bruggen, PhD *Ludwig Institute for Cancer Research*	
3:45 PM - 4:00 PM	**The Multikinase Inhibitor Sorafenib Reverses the Suppression of IL-12 and Enhancement of IL-10 by PGE2 in Murine Macrophages** Justin P. Edwards, PhD *Johns Hopkins University School of Medicine*	
4:00 PM - 4:15 PM	**Loss of HLA-DR Expression on CD14+ Cells; A Common Marker of Immunosuppression in Cancer Patients** Michael P. Gustafson, PhD *Mayo Clinic*	
4:15 PM - 4:45 PM	**Inflammatory Tregs in the Human Tumor and Chronic Inflammatory Microenvironments** Weiping Zou, MD, PhD *University of Michigan*	
3:15 PM - 4:45 PM	**Concurrent Session II: Immune Cell Trafficking to Tumor Microenvironment** *Co-Chairs:* Thomas F. Gajewski, MD, PhD *University of Chicago* Elizabeth M. Jaffee, MD *Johns Hopkins University*	**Regency A**
3:15 PM - 3:45 PM	**Trafficking of Positive and Negative Regulatory Immune Cells Into the Tumor Microenvironment** Thomas F. Gajewski, MD, PhD *University of Chicago*	
3:45 PM - 4:00 PM	**Spatial and Temporal Regulation of CXCR3 Chemokine Production and CD8 T Cell Infiltration in the Metastatic Melanoma Microenvironment** David W. Mullins, PhD *University of Virginia*	
4:00 PM - 4:30 PM	**Effector/Memory Regulatory T Cells and Their Role in the Tumor Microenvironment** Elizabeth M. Jaffee, MD *Johns Hopkins University*	
4:30 PM - 4:45 PM	**NGR-TNF, A Selective Vessel-Targeting Agent, Increases the Therapeutic Potential of Chemo-Immunotherapy** Arianna Calcinotto *San Raffaele Scientific Institute*	
4:45 PM - 5:00 PM	**Break**	
5:00 PM - 5:30 PM	**Update: 2009 iSBTc-FDA-NCI Workshop on Prognostic and Predictive Immunologic Biomarkers in Cancer** Lisa H. Butterfield, PhD *University of Pittsburgh*	**Regency A**

Program Schedule

SUNDAY, OCTOBER 3, 2010		Location
5:30 PM - 6:00 PM	**Cancer Immunotherapy Trials Network Update** William Merritt, PhD *National Cancer Institute* Speaker to be Announced *Principal Investigator of Awarded Center*	**Regency A**
7:30 PM - 10:30 PM	**25th Anniversary & Awards Reception** Awards Ceremony begins at 7:30 pm in the Baird Auditorium. *(Name badge and ticket required for admittance.)* Buses depart from Hotel Main Entrance 7:00 pm - 11:00 pm.	**Smithsonian National Museum of Natural History**

MONDAY, OCTOBER 4, 2010		
7:00 AM - 11:00 AM	**Registration Open**	**Regency Foyer**
7:00 AM - 8:00 AM	**Continental Breakfast**	**Columbia**
8:00 AM - 10:15 AM	**Plenary Session: Adoptive T Cell Transfer: The Next Wave** *Co-Chairs:* Patrick Hwu, MD *University of Texas, MD Anderson Cancer Center* Ton N. Schumacher, PhD *Netherlands Cancer Institute*	**Regency A**
8:00 AM - 8:30 AM	**Adoptive Immunotherapy for Subjects with Solid Tumors Using Genetically Modified Virus-Specific T Cells** Malcolm K. Brenner, MD, PhD *Baylor College of Medicine*	
8:30 AM - 8:45 AM	**Functional Reprogramming of the Tumor Stroma by IL-12 Engineered T Cells is Required for Anti-Tumor Immunity** Sid Kerkar, MD *National Cancer Institute, Center for Cancer Research, NIH*	
8:45 AM - 9:00 AM	**Noninvasive Positron Emission Tomography Imaging of Sleeping Beauty Modified CD19-Specific T Cells Expressing Herpes Simplex Virus1-Thymidine Kinase** Pallavi Raja Manuri, PhD *University of Texas, MD Anderson Cancer Center*	
9:00 AM - 9:30 AM	**Dissection of Therapy-Induced Melanoma-Reactive Cytotoxic T Cell Responses** Ton N. Schumacher, PhD *Netherlands Cancer Institute*	
9:30 AM - 9:45 AM	**Therapeutic Cell Engineering Using Surface-Conjugated Synthetic Nanoparticles** Matthias Stephan, MD, PhD *Massachusetts Institute of Technology*	
9:45 AM - 10:15 AM	**Adoptive T Cell Therapy for Metastatic Melanoma: The MD Anderson Experience** Laszlo G. Radvanyi, PhD & Patrick Hwu, MD *University of Texas, MD Anderson Cancer Center*	
10:15 AM	**Annual Meeting Adjourns**	
10:30 AM – 12:00 PM	**Hot Topic Symposium: CTLA-4 Blockade as a Cancer Therapeutic: How Do We Build on a Successful Foundation?** *(see following page for detailed program schedule)*	**Regency A**

Hot Topic Symposium

CTLA-4 BLOCKADE AS A CANCER THERAPEUTIC: HOW DO WE BUILD ON A SUCCESSFUL FOUNDATION?

Monday, October 4, 2010
10:30 am – 12:00 pm
Hyatt Regency Washington on Capitol Hill
Regency A

This cutting-edge session will present exciting new data on CTLA-4 blockade, including existing therapeutic combinations with anti-CTLA-4 that are poised for clinical use, potential future combinations, and insights into future directions in CTLA-4 blockade research and clinical translation.

Program Goals:

1. Present the latest pre-clinical and clinical data on CTLA-4 blockade in combination with other therapeutic agents.
2. Explore future therapeutic combinations and clinical applications of CTLA-4 blockade for cancer treatment.
3. Review clinical trial designs and biomarker endpoints to advance clinical translation of CTLA-4 blockade for cancer treatment.
4. Explore directions for future research and application of CTLA-4 blockade in clinical oncology.

Intended Learner Outcomes:

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

1. Discuss the latest clinical data on CTLA-4 blockade for cancer treatment.
2. Identify promising therapeutic combinations with CTLA-4 blockade.
3. Apply new considerations for clinical trial design and biomarkers in studies of CTLA-4 blockade.
4. Identify productive new research directions to advance CTLA-4 blockade and improve cancer outcomes.

FACULTY

Chair

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

Invited Speakers

Rachel W. Humphrey, MD
Bristol-Myers Squibb Company

Ignacio Melero, MD, PhD
University of Navarra

Padmanee Sharma, MD, PhD
University of Texas, MD Anderson Cancer Center

SCHEDULE

Monday, October 4, 2010

10:30 am – 10:35 am	**Welcome & Introductions** James P. Allison, PhD *Memorial Sloan-Kettering Cancer Center*
10:35 am – 10:55 am	**Anti CTLA-4 Antibodies: Lessons Learned & Future Direction** Rachel W. Humphrey, MD *Bristol-Myers Squibb Company*
10:55 am – 11:15 am	**Up & Coming Combinations in CTLA-4 Blockade** Ignacio Melero, MD, PhD *University of Navarra*
11:15 am – 11:35 am	**Exploring Therapeutic Combinations with Anti-CTLA-4 Antibody** Padmanee Sharma, MD, PhD *University of Texas, MD Anderson Cancer Center*
11:35 am – 12:00 pm	**Panel & Audience Discussion** Moderator: James P. Allison, PhD *Memorial Sloan-Kettering Cancer Center*

Faculty Listing

ANNUAL MEETING ORGANIZERS

Pierre Coulie, MD, PhD
de Duve Institute and University of Louvain

Elizabeth M. Jaffee, MD
Johns Hopkins University

Pawel Kalinski, MD, PhD
University of Pittsburgh Cancer Institute

Vernon K. Sondak, MD
H. Lee Moffitt Cancer Center

RICHARD V. SMALLEY, MD MEMORIAL AWARD RECIPIENT

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

KEYNOTE SPEAKER

Cornelis J.M. Melief, MD, PhD
Leiden University Medical Center

SESSION CO-CHAIRS / MODERATORS

Vincenzo Cerundolo, MD, PhD
University of Oxford - Institute of Molecular Medicine

Pierre Coulie, MD, PhD
de Duve Institute and University of Louvain

Mary L. Disis, MD
University of Washington

Victor H. Engelhard, PhD
University of Virginia School of Medicine

Carl G. Figdor, PhD
Nijmegen Centre for Molecular Life Sciences

Bernard A. Fox, PhD
Earle A. Chiles Research Institute

Thomas F. Gajewski, MD, PhD
University of Chicago

F. Stephen Hodi, MD
Dana-Farber Cancer Institute

Patrick Hwu, MD
University of Texas, MD Anderson Cancer Center

Elizabeth M. Jaffee, MD
Johns Hopkins University

Pawel Kalinski, MD, PhD
University of Pittsburgh Cancer Institute

Ton Schumacher, PhD
Netherlands Cancer Institute

Keiran S. Smalley, PhD
H. Lee Moffitt Cancer Center & Research Institute

Vernon K. Sondak, MD
H. Lee Moffitt Cancer Center

Pierre van der Bruggen, PhD
Ludwig Institute for Cancer Research

Laurence Zitvogel, MD, PhD
Institute Gustave Roussy

Weiping Zou, MD, PhD
University of Michigan

INVITED SPEAKERS

Malcolm K. Brenner, MD, PhD
Baylor College of Medicine

Lisa H. Butterfield, PhD
University of Pittsburgh

Vincenzo Cerundolo, MD, PhD
University of Oxford - Institute of Molecular Medicine

Pierre Coulie, MD, PhD
de Duve Institute and University of Louvain

Mary L. Disis, MD
University of Washington

Victor H. Engelhard, PhD
University of Virginia School of Medicine

Carl G. Figdor, PhD
Nijmegen Centre for Molecular Life Sciences

Lawrence Fong, MD
University of California - San Francisco

Thomas F. Gajewski, MD, PhD
University of Chicago

F. Stephen Hodi, MD
Dana-Farber Cancer Institute

Patrick Hwu, MD
University of Texas, MD Anderson Cancer Center

Elizabeth M. Jaffee, MD
Johns Hopkins University

Pawel Kalinski, MD, PhD
University of Pittsburgh Cancer Institute

Ton Schumacher, PhD
Netherlands Cancer Institute

Keiran S. Smalley, PhD
H. Lee Moffitt Cancer Center & Research Institute

Vernon K. Sondak, MD
H. Lee Moffitt Cancer Center

David L. Urdal, PhD
Dendreon Corporation

Annick Van den Abbeele, MD
Dana-Farber Cancer Institute

Pierre van der Bruggen, PhD
Ludwig Institute for Cancer Research

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

Laurence Zitvogel, MD, PhD
Institute Gustave Roussy

Weiping Zou, MD, PhD
University of Michigan

Oral Abstract Presenter Listing

Arianna Calcinotto
San Raffaele Scientific Institute

Andrew N. Cornforth, PhD
Hoag Memorial Hospital Cancer Center

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

Justin P. Edwards, PhD
Johns Hopkins University School of Medicine

Michael P. Gustafson, PhD
Mayo Clinic

Jamie L. Harden
State University of New York, University at Buffalo

Sid Kerkar, MD
National Cancer Institute, Center for Cancer Research, NIH

Khashayarsha Khazaie, PhD, DSc
Northwestern University, Robert Lurie Comprehensive Cancer Center

Evripidis Lanitis, BS
University of Pennsylvania School of Medicine

Chunsheng Li, PhD
Ovarian Cancer Research Center, University of Pennsylvania

Chao Ma, MS
California Institute of Technology

Kim A. Margolin, MD
Seattle Cancer Care Alliance

David W. Mullins, PhD
University of Virginia

Bethany Mundy
The Ohio State University

Hideho Okada, MD, PhD
University of Pittsburgh Cancer Institute

Willem W. Overwijk, PhD
University of Texas, MD Anderson Cancer Center

Laszlo Radvanyi, PhD
University of Texas, MD Anderson Cancer Center

Pallavi Raja Manuri, PhD
University of Texas, MD Anderson Cancer Center

Saskia J. Santegoets, PhD
VU University Medical Center

Robbert Spaapen, PhD
University of Chicago

Matthias Stephan, MD, PhD
Massachusetts Institute of Technology

Sofie Wilgenhof, MD
Universitair Ziekenhuis Brussel

Disclosures

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DISCLOSURE LISTING

James P. Allison, PhD
Bristol-Myers Squibb, Consultant receiving Consulting fee; Bristol-Myers Squibb, Inventor of Intellectual Property receiving Royalties (future)

Jimmy Balwit
Ahrens Balwit & Associates, Inc., Employment/Management Consulting receiving Consulting Fee and Dividends

Malcolm K. Brenner, MD, PhD
No relevant financial relationships to disclose

Lisa H. Butterfield, PhD
No relevant financial relationships to disclose

Arianna Calcinotto
No relevant financial relationships to disclose

William E. Carson, III, MD
No relevant financial relationships to disclose

Vincenzo Cerundolo, MD, PhD
No relevant financial relationships to disclose

Andrew N. Cornforth, PhD
No relevant financial relationships to disclose

George Coukos, MD, PhD
No relevant financial relationships to disclose

Pierre Coulie, MD, PhD
Transgene, Advisory Committee receiving Honorarium

Michael A. Curran, PhD
No relevant financial relationships to disclose

Robert O. Dillman, MD, FACP
Stock and Equity Holdings in the following Companies: Abbott Labs, Aetna, Astrazeneca Plc, Bristol-Myers Squibb, Genentech, Gilead Scientific, GlaxoSmithKline, Johnson & Johnson, Novartis, Pfizer, Sanofi Aventis, and United Health

Mary L. Disis, MD
Hemispherex, Principal Investigator receiving Grant Funding; Olaxo, Principal Investigator receiving Grant Funding; VentiRx, Consultant receiving Consulting Fee

John P. Edwards, PhD
No relevant financial relationships to disclose

Victor H. Engelhard, PhD
No relevant financial relationships to disclose

Carl G. Figdor, PhD
No relevant financial relationships to disclose

Lawrence Fong, MD
No relevant financial relationships to disclose

Bernard A. Fox, PhD
Micromet, Scientific Advisory Board receiving Consulting Fee; Neopharm, Board of Directors/Scientific Advisory Board receiving Ownership Interest; Novartis, Advisory Committee receiving Consulting Fee; UbiVac, Co-Founder receiving Ownership Interest

Thomas F. Gajewski, MD, PhD
GSK-Bio, Consultant and Protocol PI, receiving Honoraria and Clinical Trial Support; Eisai, Consultant and Protocol PI, receiving Honoraria and Clinical Trial Support; BMS, Consultant and Protocol PI, receiving Honoraria and Clinical Trial Support; Novartis, Protocol PI, receiving Clinical Trial Support; Roche, Protocol PI, receiving Clinical Trial Support

Jared A. Gollob, MD
Alynlam Pharmaceuticals, Full-time Employee receiving Salary/Stock

Michael P. Gustafson, PhD
No relevant financial relationships to disclose

Jamie L. Harden
No relevant financial relationships to disclose

F. Stephen Hodi, MD
Bristol-Myers Squibb, Review Committee receiving Consulting Fee; Genentech, Consultant receiving Consulting Fee; Genzyme (Novartis), Consultant receiving Consulting Fee

Rachel W. Humphrey, MD
Bristol-Myers Squibb Company, Employee (self and spouse) receiving salary

Patrick Hwu, MD
No relevant financial relationships to disclose

Elizabeth M. Jaffee, MD
BioSante, Johns Hopkins has the Potential to Receive Royalties on Intellectual Property; Pfizer, PI on Research Project receiving Research Funds and Grants

Carl H. June, MD
Cerulean, Member Advisory Board receiving Consulting Fee; Celldex, Inc., Member Advisory Board receiving Consulting Fee/Stock Options; Globeimmune, Member Advisory Board receiving Consulting Fee/Stock Options

Disclosures

Pawel Kalinski, MD, PhD
Alpha-type-1 Dendritic Cells (αDC1s), which will be discussed in my presentation, are subject of a pending patent application. There are no active commercialization efforts and I do not receive any royalties or other forms of remuneration related to this IP. This situation is considered a minimal conflict of interest by the University of Pittsburgh.

Howard L. Kaufman, MD
Neogenix, Advisory Board receiving Honoraria; Novartis Oncology, Speakers Bureau receiving Honoraria

Sid Kerkar, MD
No relevant financial relationships to disclose

Khashayarsha Khazaie, PhD, DSc
No relevant financial relationships to disclose

Angela Kilbert
No relevant financial relationships to disclose

Evripidis Lanitis, BS
No relevant financial relationships to disclose

Chunsheng Li, PhD
No relevant financial relationships to disclose

Chao Ma, MS
No relevant financial relationships to disclose

Kim A. Margolin, MD
No relevant financial relationships to disclose

Roseann Marotz
No relevant financial relationships to disclose

Ignacio Melero, MD, PhD
Bristol-Myers Squibb, Consulting and Contributor to Invention receiving Honoraria/Ownership Interest; Pfizer, Inc., Advisory Committee receiving Honoraria/ Consulting Fee

Cornelis J.M. Melief, MD, PhD
ISA Pharmaceuticals, Chief Scientific Officer receiving 75% of salary (Other 25% Leiden University Medical Center); ISA Pharmaceuticals, Stock appreciation right receiving 2% of stock value

David W. Mullins, PhD
No relevant financial relationships to disclose

Bethany Mundy
No relevant financial relationships to disclose

William J. Murphy, PhD
No relevant financial relationships to disclose

Hideho Okada, MD, PhD
No relevant financial relationships to disclose

Sonja Ortman
No relevant financial relationships to disclose

Willem W. Overwijk, PhD
No relevant financial relationships to disclose

Laszlo Radvanyi, PhD
No relevant financial relationships to disclose

Pallavi Raja Manuri, PhD
No relevant financial relationships to disclose

Antoni Ribas, MD
Bristol-Myers Squibb, Advisory Board receiving Honoraria; DebioPharm, Advisory Board receiving Honoraria; MannKind Corp, Advisory Board receiving Honoraria

Saskia J. Santegoets, PhD
No relevant financial relationships to disclose

Dolores J. Schendel, PhD
No relevant financial relationships to disclose

Ton Schumacher, PhD
AIMM Therapeutics (biotech start-up), Scientific Advisory Board receiving Consulting Fee

Padmanee Sharma, MD, PhD
Bristol-Myers Squibb, Advisory Committee receiving Honorarium; Dendreon Corporation, Advisory Committee receiving Honorarium

Keiran S. Smalley, PhD
No relevant financial relationships to disclose

Vernon K. Sondak, MD
Abbott, Consultant / Advisory Board receiving Consulting Fees/Honoraria; Bayer/Onyx, Consultant / Advisory Board receiving Consulting Fees/Honoraria; BMS/ Medarex, Consultant / Advisory Board receiving Consulting Fees/Honoraria; Eli Lilly, Consultant / Advisory Board receiving Consulting Fees/Honoraria; Glaxo Smith-Kline/Synta, Consultant / Advisory Board receiving Consulting Fees/Honoraria; Merck (Schering), Speaker's Bureau receiving Honoraria; Merck (Schering), Consultant / Advisory Board receiving Consulting Fees/ Honoraria; Pfizer, Consultant / Advisory Board receiving Consulting Fees/Honoraria

Robbert Spaapen, PhD
No relevant financial relationships to disclose

Matthias Stephan, MD, PhD
No relevant financial relationships to disclose

Chloe Surinak
No relevant financial relationships to disclose

David L. Urdal, PhD
Dendreon Corporation, Employee receiving Salary/Stock

Annick Van den Abbeele, MD
No relevant financial relationships to disclose

Pierre van der Bruggen, PhD
No relevant financial relationships to disclose

Robert H. Vonderheide, MD, D.Phil
Dana-Farber/Whitehead, Inventor receiving patent on hTERT Therapy; Merck, Investigator receiving Research Funds; Pfizer, Investigator receiving Research Funds

Jon M. Wigginton, MD
Bristol-Myers Squibb, Employee/ Management Position receiving Salary/ Stock/Stock Options

Sofie Wilgenhof, MD
No relevant financial relationships to disclose

Tara Withington, CAE
Executive Director Inc., Employee/Partner receiving Salary/Ownership

Jedd D. Wolchok, MD, PhD
Bristol-Myers Squibb, Advisory Committee receiving Consulting Fee

Laurence Zitvogel, MD, PhD
Amplimmune, Consulting Fees and Research Contract; Innate Pharma, Research Contract

Weiping Zou, MD, PhD
No relevant financial relationships to disclose

Presentation Abstracts – Saturday *(primary authors listed in italics)*

RICHARD V. SMALLEY, MD MEMORIAL LECTURESHIP

CHECKPOINT BLOCKADE IN TUMOR IMMUNOTHERAPY: NEW INSIGHTS AND OPPORTUNITIES

James P. Allison
[1]Ludwig Center for Cancer Immunotherapy, Memorial Sloan-Kettering Cancer Center, New York, NY
[2]Howard Hughes Medical Institute, New York, NY

Over the past several years it has become apparent that the effectiveness of active immunologic strategies for cancer therapy have been limited by cell intrinsic and extrinsic regulatory pathways that act in concert to minimize harm to normal tissues. The prototype of cell intrinsic "checkpoints" whose blockade enhances anti-tumor responses is CTLA-4, which has been extensively studied in a large number of animal models and shown to be quite effective in achieving, either as a single agent or in combination with other agents, complete tumor eradication and long lasting tumor immunity.

Over 4,000 patients have been treated with an antibody to human CTLA-4 (Ipilimumab, Medarex and Bristol-Myers Squibb). Significant responses, including complete remissions, have been observed in about 15% of metastatic melanoma patients, with about 40% of patients showing survival benefit. In a recent Phase III trial, Ipilimumab was shown to prolong survival of stage IV metastatic melanoma patients, with 25% alive and ongoing at 4 years. This is the first drug ever to show a survival benefit in metastatic melanoma in a randomized trial.

This has led to considerable effort to identify biomarkers that would be useful in determining the impact of CTLA-4 on human immune responses in order to identify changes that might correlate with clinical responses, as well as to address combinatorial strategies that might enhance the effectiveness/frequency of clinical responses.

In both mouse and man, clinical benefit seems to correlate with an increase in the ratio of Teff/Treg cells and with an increase in the proportion of IFNγ producing Teff cells that express high levels of the CD28/CTLA-4 homolog ICOS. In human prostate and melanoma patients clinical responses appear to correlate with pre-existing or induced high titer antibody and polyfunctional CD4 T cells to the cancer testes antigen NY-ESO-1. In a presurgical bladder cancer trial it has been shown that anti-CTLA-4 treatment results in an increase in the ratio of IFNγ producing effector cells that express high levels of the CD28/CTLA-4 homolog ICOS. We have confirmed this in $ICOS^{high}$ CD4 T cells in metastatic melanoma and hormone refractory metastatic prostate cancer. In melanoma, our data suggest that the duration of elevation of $ICOS^{high}$ T cell numbers correlates with favorable clinical outcome.

We have begun to explore combinations of anti-CTLA-4 with other agents. We have found that with proper consideration of dosing and timing, anti-CLTA-4 can synergize with standard chemotherapy, cryoablation, and targeted therapies.

DENDRITIC CELLS AND CANCER

DENDRITIC CELL VACCINATION IN CANCER: ACHIEVEMENTS, OBSTACLES AND FUTURE PERSPECTIVES

Carl G. Figdor, Jolanda de Vries, Karlijn Bol, Erik Aarntzen, Joost Lesterhuis, Gosse Adema, Kees Punt
Tumor Immunology, Radboud university medical centre, Nijmegen, Netherlands

We exploit dendritic cells (DCs) to vaccinate melanoma patients. We recently demonstrated a statistical significant correlation between favorable clinical outcome and the presence of vaccine-related tumor antigen specific T cells in delayed type hypersensitivity (DTH) skin biopsies. While we find immunological responses in 30-50% of the patients, favorable clinical outcome is only observed in a minority of the treated patients. Therefore, it is obvious that current DC-based protocols need to be improved to increase clinical efficacy. For this reason, we study in small proof of principle trials the fate, interactions and effectiveness of the injected DCs.

We compared DC loaded with tumor antigen specific MHC class I binding peptides alone, in combination with MHC class II binding peptides or with defined tumor antigen mRNA (gp100 and tyrosinase). The results show that the presence of supplementary tumor antigen-specific MHC class II epitopes result in an T helper response that might be beneficial for the clinical outcome in these patients. Furthermore, comparing different routes of administration we observed that intranodal injection is not always successful (MRI) and that only a small proportion of the intradermally administered DCs reach the lymph nodes (scintigraphy). Our data clearly indicate that the cells that reach the lymph nodes are fully mature DCs that are able to induce an immune response in vivo.

We have begun to explore the potency of DC subsets in the peripheral blood. recently we have completed a phase I trail with plasmacytoid DCs. results will be discussed as well as the potency of other DC subsets.

This work was supported by grants 1999-1950, 2000-2301, 2003-2893, 2003-2917 and 2004-3127 from the Dutch Cancer Society, and EU projects DC-THERA, and CANCER IMMUNOTHERAPY, NWO- Spinoza, the TIL-foundation and the NOTK.

Presentation Abstracts – Saturday *(primary authors listed in italics)*

PROGRESS IN THE ACTIVE IMMUNOTHERAPY OF PROSTATE CANCER: SIPULEUCEL-T, AN AUTOLOGOUS CELLULAR IMMUNOTHERAPY

David L. Urdal
Dendreon Corporation, Seattle, WA

Sipuleucel-T is an FDA approved autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer. It consists of autologous peripheral blood mononuclear cells, including antigen presenting cells (APCs), which have been activated during a defined culture period with a recombinant human protein, PAP-GM-CSF, consisting of prostatic acid phosphatase (PAP), an antigen expressed in prostate cancer tissue, linked to granulocyte-macrophage colony stimulating factor (GM-CSF), an immune cell activator.

The development history will be summarized; the regulatory milestones will be described; and the lessons learned during the development of this novel approach to the treatment of prostate cancer will be discussed.

THERAPEUTIC VACCINATION WITH AUTOLOGOUS mRNA ELECTROPORATED DENDRITIC CELLS (DC) IN PATIENTS WITH ADVANCED MELANOMA

Sofie Wilgenhof[1,2], An MT Van Nuffel[2], Daphné Benteyn[2], Jurgen Corthals[2], Carlo Heirman[2], Lauranne Pierret[3], Arlette De Coninck[3], Aude Bonehill[2], Kris Thielemans[2], Bart Neyns[1]
[1]*Medical Oncology, UZ Brussel, Brussels, Belgium*
[2]*Laboratory of Molecular and Cellular Therapy & DC-bank, Vrije Universiteit Brussel, Brussels, Belgium*
[3]*Dermatology, UZ Brussel, Brussels, Belgium*

Background: mRNA electroporated autologous DC are under evaluation as therapeutic cancer vaccines. Potential advantages are the presentation of all tumor antigen confined epitopes by the patient's own HLA-molecules and the improved immunostimulatory capacity of the DC-formula. Combination of a therapeutic vaccine with cytokine therapy (IFN-a2b or IL-2) results in a synergistic anti-tumor effect.

Methods: Immature DC (derived from peripheral blood monocytes obtained by leucapheresis and cultured for 6 days in IL-4/GM-CSF supplemented medium) were electroporated with synthetic mRNA encoding a fusion protein between MAGE-A1, -A3, -C2, Tyrosinase, MelanA/MART-1 or gp100, and DC-LAMP, and poly-I:poly-C12U or mRNA encoding TLR-4, CD70 and CD40L (TriMix). DC (12.5 10E6 DC/antigen) were administered by 4 to 6 ID-injections q2w, and q8w thereafter. IFN-a2b (5 MIU TIW) was initiated at progression, concomitant or following the 4th vaccine, respectively in cohort 1, 2, 3, and 4. Immune monitoring was performed by skin biopsy of delayed type IV hypersensitivity (DTH) reactions.

Results: 70 melanoma pts were recruited between 06/'05 and 06/'09: 44M/26F; med age: 46y (27-75); AJCC stage III: 30, IV-M1a: 8, -M1b: 6, -M1c: 26; WHO-PS 0: 46, 1: 19, 2: 5. A total of 466 DC-vaccines were administered (median/pt: 6, range 2-18). Vaccine related AE's included: gr2 injection site reactions: all pts; gr2 fever/lethargy: 3 pts. Vaccinal-antigen specific DTH infiltrating lymphocytes: 0/6 pts tested at vaccine initiation and in 12/21 (57.1%) pts after the 4th vaccine. After a mFU of 30 mths, the mRFS for pts without evaluable disease (n= 30) is 23 mths (95% CI 11-34); 3 pts have died, mOS has not been reached. The tumor response among 40 pts with ED at baseline: 1 PR + 14 SD (disease control rate [DCR]: 38%) according to RECIST; 2 CR + 2 PR, and 14 SD (DCR: 46%) according to immune-related response criteria (irRC). The 6-mth PFS (32%) and 1-year OS rate (57%) in patients with ED at baseline compares favorably with historical controls. Baseline WHO-PS was identified as an independent covariable for PFS and OS, -CRP for PFS, and -LDH for OS. In a landmark survival-analysis from week 8, DCR by irRC was the strongest independent covariable for superior PFS and OS ($p<0.001$).

Conclusions: Therapeutic vaccination with autologous mRNA electroporated DC combined with IFN-a2b is feasible, safe, immunogenic and has anti-tumor activity in patients with advanced melanoma. Encouraging survival was observed in this single-arm study and DCR by irRC was strongly correlated with superior survival.

RESISTANCE TO THE PROAPOPTOTIC EFFECTS OF IFN-γ ON MELANOMA CELLS USED IN PATIENT-SPECIFIC DENDRITIC CELL IMMUNOTHERAPY IS ASSOCIATED WITH IMPROVED OVERALL SURVIVAL

Andrew Cornforth, Abner Fowler, Denysha Carbonell, Robert Dillman
Cell Biology Lab, Hoag Cancer Center, Newport Beach, CA

The use of whole cell tumor vaccines and various means of loading antigen onto dendritic cells have been under investigation for over a decade. Induction of apoptosis and the exposure of immune stimulating proteins are thought to be beneficial for use in immuno-

therapy protocols but conclusive evidence in the clinical setting has been lacking. Incubation of commercially available melanoma cell lines (A375, SK-MEL-5, SK-MEL-28) with interferon-gamma (IFN-γ) increased phosphatidylserine (a measure of early apoptosis) and calreticulin exposure but not in the interferon-gamma resistant cell line (Lu-1205). Short term autologous melanoma cell lines used for loading dendritic cells for immunotherapy showed differential response to the pro-apoptotic effects of IFN-g.

These IFN-γ treated tumor cells were irradiated and used for loading antigen for dendritic cell therapy. A log-rank comparison of survival for patients whose tumor cells were found to be either sensitive (up-regulated phosphatidylserine and calreticulin) or insensitive to IFN-γ, revealed a strongly significant correlation to progression-free ($p = 0.003$) and overall survival ($p = 0.002$) favorably in those patients whose cell lines were resistant to the proapoptotic effect of IFN-γ. A remarkable 10/23 patients in the insensitive cohort were still live after 60 months of follow up with 6 of those still remaining disease free. These results suggest that the use of IFN-γ in anti-melanoma dendritic cell-based immunotherapy may only be beneficial if the cells do not undergo apoptosis in response to IFN-γ and support the contention that the use of some apoptotic cells in vaccines may be detrimental.

IFN-γ IS CENTRAL TO BOTH IMMUNOGENIC AND TOLEROGENIC PROPERTIES OF DENDRITIC CELLS AFTER IL-12 AND GM-CSF MICROSPHERE TREATMENT

Jamie L. Harden, Tao Gu, Mehmet O. Kilinc, Lauren P. Virtuoso, Nejat K. Egilmez
Microbiology and Immunology, University at Buffalo, Buffalo, NY

A single intra-tumoral injection of IL-12 and GM-CSF microspheres results in tumor regression and initiation of an anti-tumor immune response. Activation of NK cells and CD8+ T-cells along with a decrease in T-regulatory cells, after treatment have been observed. The anti-tumor effects of GM-CSF and IL-12 microsphere treatment have been shown to be dependent on IFN-γ. However, further studies demonstrated that the immune response was transient and that the T-regulatory cells rebounded rapidly. Recent data from our laboratory suggested that indoleamine 2, 3 -dioxygenase (IDO), an IFN-γ-inducible immune-suppressive enzyme, may play a role in the post-therapy T-regulatory cell resurgence. Since dendritic cells (DCs) are central to both induction of an immune response, and have been shown to be significant producers of IDO, the effect of IL-12 and GM-CSF microsphere treatment on this potent antigen presenting cell was explored. We found that intra-tumoral injection of IL-12 and GM-CSF microsphere resulted in rapid recruitment of DC to tumors with subsequent migration to tumor-draining lymph nodes (TDLN). Post-treatment DCs displayed increased CD86 expression, a pro-inflammatory cytokine profile and effective CD8+ and CD4+ T-cell priming in vitro (immunogenic). By Day 7 post-treatment however, the priming ability of these DCs was completely lost (tolerogenic). Further analysis revealed that day 7 DCs expressed high levels of IDO, inhibition of which resulted in the rescue of the ability to prime T-cells. GM-CSF and IL-12 mediated induction of immunogenic DCs was completely abrogated in IFN-γ knockout mice, establishing the critical role of this cytokine in post-therapy immune activation. Importantly, TDLN DCs failed to upregulate IDO and IDO-inhibition did not restore priming function to day 7 DCs in IFN-γ knockout mice, revealing that IFN-γ was also responsible for the induction of tolerogenic function in DCs. These results establish the dichotomous role of IFN-γ in the regulation of IL-12-mediated antitumor immunity and identify DC as the primary conduit that mediate these effects. Furthermore, these data support the hypothesis that blocking IDO in therapeutic regimen designed to induce TH1 responses may prove useful by extending the window of T-cell priming and activation.

POLARIZED DENDRITIC CELLS IN THE IMMUNOTHERAPY OF ESTABLISHED CANCER: ROLES OF SIGNAL 3 AND SIGNAL 4

Pawel Kalinski
Surgery, University of Pittsburgh, Pittsburgh, PA

Cancer vaccines have been shown capable of prolonging survival of cancer patients, but their ability to induce regression of established tumors remains low. The use of ex-vivo-generated dendritic cells (DCs) helps to sidestep the dysfunction of endogenous DCs in patients with advanced cancer and to deliver the key signals needed for effective anti-tumor responses. Recently, we and others have shown that different DC populations can deliver specialized "signal 3" regulating the acquisition of desirable effector functions by T cells, and an additional "signal 4" that regulates T cell homing properties. Moreover, ex-vivo instruction of DCs can be used to preferentially activate CTLs, Th1- and NK cells, while limiting the undesirable activation of Treg cells. Type-1-polarized DCs (DC1) are characterized by strongly-enhanced, rather than "exhausted", ability to produce IL-12p70 and other CTL-, Th1-, and NK cell-activating factors. A single round of in vitro sensitization with DC1s loaded with tumor-related antigens induces 40-70-fold higher numbers of functional CTLs against multiple tumor-related antigens and multiple types of cancer cells (melanoma, glioma, CLL, CTCL, prostate, colorectal, endometrial and ovarian cancers), when compared with immature DCs and nonpolarized mature DCs. DC1s are particularly effective in inducing effector functions

in CD8+ T cells, NK cells, and Th1-type CD4+ Th cells (delivery of "signal 3"). They also induce a switch in the expression of chemokine receptors on naïve T cells (delivery of "signal 4"), promoting T cell responsiveness to tumor-produced chemokines. DC1-based vaccines are being currently evaluated in phase I/II clinical trials for patients with different forms of advanced cancer.

TARGETED THERAPEUTICS AND IMMUNOTHERAPY

IMMUNE MODULATION OF BREAST CANCER

Mary L. Disis, Hailing Lu, Yushe Dang, Jennifer Childs, Doreen Higgins, Meredith Slota, Denise Cecil, Ekram Gad, Mei Wu, Daniel Herendeen, Megan O'Meara, Lupe G. Salazar
Center For Translational Medicine in Women's Health, University of Washington, Seattle, WA

Breast cancer relapse after optimal therapy is a clinical issue that must be overcome to improve survival in breast cancer patients. Vaccines have been successful in infectious disease prevention but have shown little clinical effect in cancer therapy where immunization has been used as a treatment for malignancy. Vaccines targeting HER2 may prevent relapse in patients with HER2 overexpressing tumors, an especially high risk population. As most cancer antigens, including HER2, are not mutated, novel methods of immunization must be developed to overcome self tolerance.

Vaccine approaches focused on eliciting an antigen specific CD4+ T helper (Th)1 immunity may uniquely overcome mechanisms of cancer induced immune suppression. Th cells are central to the development of immune responses for protection against infections and possibly malignancy by activating antigen-specific effector cells and recruiting cells of the innate immune system such as macrophages, eosinophils, and mast cells. Moreover, antigen primed Th cells can directly activate tumor antigen-specific cytotoxic T cells (CTL). In addition to direct contact, Th can activate CTL through cytokines which stimulate the growth and expansion of effector T cells. Th1 can also induce the production of opsonizing antibodies that enhance the uptake of tumor cells into APC. These activated APC can then directly present tumor antigens and promote expansion of tumor-specific CTL. As a direct result of activating APC, antigen specific Th1 have been implicated as the initiators of epitope or determinant spreading. Epitope spreading is linked with the progression of several autoimmune disorders such as systemic lupus erythematosis, insulin dependent diabetes mellitus, and multiple sclerosis. Epitope spreading may not only be associated with the progression of these diseases but also with the tissue destruction observed with pathologic progression. Th1 cells influencing the tumor microenvironment may allow such tissue destruction in the tumor bed. The ability to elicit epitope spreading broadens the immune response to many potential antigens in the tumor and presumably would result in more efficient tumor cell kill due to heterogeneic tumor targeting by T cells.

We have developed antigen specific vaccines designed to stimulate Th1 tumor specific immunity. Evaluated in clinical trials, the vaccines are immunogenic, generate immunity that persists years after the end of active immunization, and epitope spreading is elicited. Early results from Phase II studies suggest that there may be a clinical benefit to vaccination. Pre-clinical studies in transgenic models of spontaneous breast cancer demonstrate that multi-antigen cancer vaccines may have potential in the prevention of disease.

OVERCOMING BRAF INHIBITOR RESISTANCE IN MELANOMA

Keiran Smalley[1,2,3], Inna Fedorenko[3], Kim H. Paraiso[3], Edward Flach[2], Alexander R. Anderson[2]
[1]*Cutaneous Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*
[2]*Integrated Mathematical Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*
[3]*Department of Molecular Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

The discovery that ~50% of human melanomas harbor activating V600E mutations in the serine/threonine kinase BRAF has raised the possibility that these tumors may be amenable to targeted therapy. The importance of mutated BRAF for the growth and survival of melanoma cells has since been validated in a large number of pre-clinical studies and clinical trials of the novel BRAF kinase inhibitor PLX4032 are now underway. Initial results from the phase II extension trial of PLX4032 in melanoma patients selected for the BRAF V600E mutation are highly encouraging, with responses reported in an unprecedented 81% of those treated. Although the clinical development of BRAF inhibitors is at an early stage, it is already clear that the impressive levels of response seen initially do not necessarily persist for extended periods of time. Recent data from our group and others suggests that melanoma cells re-wire their intracellular signaling when BRAF is inhibited and use parallel signal transduction pathways for their growth and progression. This presentation will discuss some of the putative mechanisms by which BRAF-mutated melanoma cells escape from BRAF inhibitor therapy and will outline how these contribute to both intrinsic and acquired resistance. It is expected that an enhanced understanding of the signaling cross-talk mechanisms present in melanoma cells will allow combination therapy strategies to be designed which will either delay or abrogate the onset of resistance when BRAF is inhibited.

Presentation Abstracts – Saturday *(primary authors listed in italics)*

THE HIGH-DOSE ALDESLEUKIN (HD IL-2) "SELECT" TRIAL IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA (mRCC)

D. McDermott[1], M. Ghebremichael[2], S. Signoretti[3], K. Margolin[2], J. Clark[4], J. Sosman[5], J. Dutcher[6], T. Logan[7], L. Appleman[8], M. Atkins[1]
[1]*Beth Israel Deaconess Medical Center, Boston, MA*
[2]*Dana Farber Cancer Institute, Boston, MA*
[3]*University of Washington, Seattle, WA*
[4]*Loyola University Medical Center, Chicago, IL*
[5]*Vanderbilt University Medical Center, Nashville, TN*
[6]*Montefiore Medical Center, New York, NY*
[7]*Indiana University, Indianapolis, IN*
[8]*University of Pittsburgh Medical Center, Pittsburgh, PA*

Background:
HD IL-2 received FDA approval for mRCC in 1992, producing a 14% major response (CR + PR) rate and durable remissions in Phase II trials. Retrospective studies suggested that tumor features could predict for benefit (Atkins et al, Clin Cancer Res 2003). The Cytokine Working Group conducted this prospective trial to identify patients (pts) likely to respond to HD IL-2.

Methods:
In this multicenter, prospective study pts with histologically confirmed mRCC, ECOG PS 0-1 and adequate organ function received HD IL-2. The primary endpoint of the study was to determine if the major response rate (RR) of pts with "good" predictive features was significantly higher than a historical, unselected population. All pts were consented to provide archived tumor tissue that would be used for pathology risk classification.

Results:
One hundred twenty eligible pts enrolled between November 2007 and July 2009. Seventy-two percent had ECOG PS 0, 71% were MSKCC intermediate risk, 96% had clear cell (cc) RCC and 99% had prior nephrectomy. There were 2 treatment-related deaths. At the time of this analysis the investigator assessed RR was 28% (34/120) (7 CR, 27 PR) and was significantly greater than the historical RR (95% CI = 21%-37%, p=0.0016). The median PFS was 4.2 months (mo) and 17 responses are ongoing (range 6-41+ mo). The RR for pts with ccRCC was 30% (35/115) (95% CI = 21%-39%, p=0.0004). Response to IL-2 was seen in pts in all MSKCC risk classifications, but was not seen in pts with non-cc histology (5 pts) or high UCLA SANI (survival after nephrectomy and immunotherapy) score (8 pts). Clear cell histologic classification and high CA-9 staining failed to further enrich for response to IL-2 (Table).

Conclusions:
The RR to HD IL-2 in this trial was significantly better than the historical experience. Analysis of tumor based predictive markers through central pathology review was unable to improve the selection criteria for HD IL-2. Efforts to validate other proposed biomarkers (e.g. CA-9 SNPs, B7H1 expression and serum VEGF) predictive of response to IL-2 are ongoing and will be presented at the meeting.

Response by Pathology Characteristics

Histology Risk Group	RR (95% CI)	P-value
Good (n=11)	36% (14%-34%)	0.61
Intermediate ((n=84)	26% (17%-37%)	
Poor (n=24)	33% (16%-55%)	
CA-9 Score		
High (>85% n=77)	23% (14%-34%)	0.13
Low (<85% n=39)	38% (23%-55%)	
Combined Score		
Good (n=74)	24% (15%-36%)	0.67
Poor (n=42)	36% (22%-52%)	

Presentation Abstracts – Saturday *(primary authors listed in italics)*

IN VIVO MODELING AND DETECTION OF OVARIAN CANCER VASCULAR MARKER TEM1

Chunsheng Li[1], Kosei Hasegawa[1], Ann-Marie Chacko[2], Vladimir Muzykantov[2], Chaitanya Divgi[3], Phyllis A. Gimotty[4], Luigi Grasso[5], George Coukos[1]

[1]Ovarian Cancer Research Center, Univ of Pennsylvania, Philadelphia, PA
[2]Translational Medicine and Therapeutics, and Environmental Medicine, Univ of Pennsylvania, Philadelphia, PA
[3]Dept of Radiology, Univ of Pennsylvania, Philadelphia, PA
[4]Dept of Biostatistics and Epidemiology, Univ of Pennsylvania, Philadelphia, PA
[5]Morphotek, Inc, Exton, PA

Rationale
Epithelial ovarian cancer (EOC) remains the most deadly cancer without efficient detection and eradication methods. TEM1 is over-expressed specifically in the vasculature of various tumors and has been implicated in promoting adhesion, invasion and metastasis. Since EOC responds well to vascular-targeted therapy, we hypothesize that TEM1 is a tumor vascular marker with diagnostic and therapeutic potential.

Specific aims
1)To characterize TEM1 expression in normal tissues and EOC samples; 2)to establish huTEM1 murine tumor vasculature model; 3)to develop a TEM1-specific PET imaging strategy.

Methods
qPCR and IHC are used to characterize huTEM1 expression in normal and EOC samples. Luciferase positive huTEM1 expressing murine endothelial cell (huTEM1+ EC) lines were established and injected alone or with tumor cells onto nude mice and monitored by bioluminescent imaging.

An antiTEM1 Ab, MORAb004, was radiolabeled with 124I and injected venously. PET images were acquired at various time points to visualize hTEM1+ECs in vivo and corresponding biodistribution studies were performed.

Results
1)High TEM1 mRNA level correlates with poor outcome in 2 cohorts of EOC patients.
2)Positive TEM1 staining was observed in most EOC tissues studied, while no positive staining was seen in controls.
3)TEM1 expression in huTEM1+ ECs was confirmed by qPCR, western and FACS analysis.
4)huTEM1+ and control ECs can be detected in nude mice 5 wks p.i.
5)[124I]MORAb004 has been successfully labeled in high yield and without loss of immunoreactivity.
6)PET images revealed specific retention of [124I]MORAb004 in huTEM1+ xenografts and no discernible uptake in control of the same animal. The radioactivity in TEM1+ tumor lasted >6 days p.i.
7. Ex vivo biodistribution study at 48h p.i. revealed hTEM1+ xenograft to nontarget ratios (T/NT) upwards of 16, 84, and 9 for blood, muscle, and control xenograft, respectively.

Conclusions
1)Our data suggest that TEM1 is a rational diagnostic and therapeutic target for EOC.
2)We developed PET imaging strategy to visualize huTEM1+ cells in mouse model.
3)Our murine vascular model allows quantitative and specific monitoring of ECs by optical and PET imaging, therefore serves as an unprecedented platform for studying the function of tumor vascular markers, as well as testing new diagnostics and therapeutic agents against tumor vasculature in vivo.
4)Further studies will evaluate TEM1 as early detection marker and prognostic factor for EOC.

Presentation Abstracts – Saturday *(primary authors listed in italics)*

INNATE / ADAPTIVE IMMUNE INTERPLAY IN CANCER

THE ROLE OF INVARIANT NKT CELLS AT THE INTERFACE OF INNATE AND ADAPTIVE IMMUNITY

Vincenzo Cerundolo
MRC Human Immunology Unit, Nuffield Dept. of Medicine, University of Oxford - Inst. of Molec. Medicine, Headington Oxford, United Kingdom

Since the initial description of the presence of T cells with an invariant T cell receptor (TCR) in mice and humans and demonstration of their restriction by monomorphic CD1d molecules, tremendous progress has been made towards the understanding of the role in vivo of invariant NKT cells (iNKT cells), and on the identification of strategies to harness their ability to assist antigen specific T and B immune responses. It has become clear that iNKT cells are equipped to play a pivotal role at the interface between the innate and adaptive arms of the immune system as, while they are capable of recognizing a range of bacterial derived lipids, they also recognize endogenous lipids, a property that endows them with the ability to rapidly mature DC and B cells in a CD40 dependent manner. Self-reactivity of iNKT cells, which is amplified by TLR dependent signalling events, underscores iNKT cells' memory phenotype and their rapid response mode. In addition, since iNKT cells express a semi-invariant TCR, their frequency is orders of magnitude higher than the frequency of classical naive MHC class I and class II restricted T cells and they can therefore be mobilized in large numbers during inflammatory conditions, such as during infections and advanced cancer. Strategies to activate iNKT cells in vivo will be discussed

PATHOGENIC MAST CELL / T REGULATORY CELL CROSS TALK IN COLORECTAL CANCER

Khashayarsha Khazaie
Medicine & Microbiology-Immunology, Northwestern University, Robert H. Lurie Comprehensive Cancer Center, Chicago, IL

Colorectal cancer (CRC) is one of the most common fatal malignancies worldwide. Almost 5% of the adult population in the United States will suffer from CRC, and half of the affected individuals will die from this disease. CRC is driven by inflammation and understanding immune mechanisms that regulate inflammation could produce breakthroughs in the treatment of this disease. We have evidence suggesting that inflammation in CRC is regulated through the cross talk between tumor infiltrating mast cells (MC) and T regulatory cells (Treg). This is based on three sets of observations, first showing a causative role for MC in the progression of pre-neoplastic lesions to carcinoma, second demonstrating the inherent potential of Treg to suppress MC, inflammation, and polyp growth, and third our discovery that Treg in mice or patients with progressive cancer are reprogrammed to become pro-inflammatory and stimulate MC. Pro-inflammatory Treg express Foxp3 and are potently T cell suppressive, but have characteristics of TH17 cells, including expression of RORγT and IL17, and are poor IL10 producers. Genetic ablation of RORγT or IL17 or IL23 in bone marrow attenuates polyposis and blocks the pro-inflammatory differentiation of the Treg.

Our observations are consistent with the notion that Treg have an anti-inflammatory and protective role in CRC, however this role is compromised by their interaction with MC in the course of progressive disease. Thus, the cross talk between MC and Treg determines the level of inflammation in CRC. The shift of Treg to a pro-inflammatory phenotype is a turning point in the escalation of cancer-associated inflammation (Blatner et al., 2010; Gounaris et al., 2009)(see commentary (Colombo and Piconese, 2009)). Based on these observations we propose that MC and their interaction with Treg are suitable targets for effective therapeutic intervention in CRC.

Blatner, N.R., Bonertz, A., Beckhove, P., Cheon, E.C., Krantz, S.B., Strouch, M., Weitz, J., Koch, M., Halverson, A.L., Bentrem, D.J., and Khazaie, K. (2010). In colorectal cancer mast cells contribute to systemic regulatory T-cell dysfunction. Proc Natl Acad Sci U S A.

Gounaris, E., Blatner, N.R., Dennis, K., Magnusson, F., Gurish, M.F., Strom, T.B., Beckhove, P., Gounari, F., and Khazaie, K. (2009). T-regulatory cells shift from a protective anti-inflammatory to a cancer-promoting proinflammatory phenotype in polyposis. Cancer Res 69, 5490-5497.

Colombo, M.P., and Piconese, S. (2009). Polyps Wrap Mast Cells and Treg within Tumorigenic Tentacles. Cancer Res.

Presentation Abstracts – Saturday *(primary authors listed in italics)*

MYELOID-DERIVED SUPPRESSOR CELLS AND DECREASED INTERFERON RESPONSIVENESS IN TUMOR-BEARING MICE

Bethany L. Mundy[1], Gregory Lesinski[2], Kristen Benninger[3], Mahmood Khan[3], Periannan Kuppusamy[3], Kristan Guenterberg[4], Sri Vidya Kondadasula[3], Abhik Ray Chaudhury[3], Melanie Kreiner[3], Gregory Young[3], Denis Guttridge[3], William E. Carson[4]

[1]*Integrated Biomedical Sciences, The Ohio State University, Columbus, OH*

[2]*Internal Medicine, The Ohio State University, Columbus, OH*

[3]*The Ohio State University, Columbus, OH*

[4]*Surgery, The Ohio State University, Columbus, OH*

Our group and others have determined that immune effector cells from patients with advanced cancers exhibit reduced activation of IFN induced signaling pathways although the mechanisms underlying this observation have not been delineated. We hypothesized that increases in myeloid-derived suppressor cells (MDSC), which are known to be elevated in the setting of advanced cancers, could interfere with the host immune response to tumors by inhibiting immune cell responsiveness to interferons. The C26 murine adenocarcinoma model was employed to study immune function in advanced malignancy. This model can mimic advanced disease in humans by the development of cancer cachexia which is associated with weight loss, aggressive tumor growth, and elevated levels of IL-6. Splenocytes from tumor-bearing mice exhibited reduced phosphorylation of STAT1 (P-STAT1) on Tyr 701 ($p<0.0001$) in response to IFNα or IFNγ. This inhibition was seen in CD4+ and CD8+ T cells, as well was CD49b+ NK cells in mice. C26 bearing mice had significantly elevated levels of GR1+CD11b+ MDSC as compared to control mice ($p<0.0001$). In vitro co culture experiments revealed that MDSC inhibited IFN responsiveness of splenocytes from normal mice. Treatment of C26-bearing mice with gemcitabine or an anti-GR1 antibody led to depletion of MDSC and restored splenocyte IFN responsiveness. Spleens from C26 bearing animals displayed elevated levels of iNOS protein and nitric oxide (NO). In vitro treatment of splenocytes with a nitric oxide donor led to a decreased STAT1 IFN response. The elevation in NO in C26-bearing mice was associated with increased levels of nitration on STAT1. Finally, splenocytes from iNOS knockout mice bearing C26 tumors exhibited a significantly elevated IFN-response as compared to control C26 tumor bearing mice. These data suggest that NO produced by MDSC can lead to reduced interferon responsiveness in immune cells.

THE DESIRABLE CELL DEATH FOR CHEMOTHERAPY OF CANCER

Laurence Zitvogel, *Guido Kroemer*

Department De Biologie Clinique, Institute Gustave Roussy, Villejuif, France

Therapy-induced immunogenic cancer cell death can stimulate a therapeutic anti-cancer immune response that then contributes to the control (or even to the elimination) of residual tumor cells. Indeed, some chemotherapeutic agents (e.g. X Rays, oxaliplatin and anthracyclines) can induce immunogenic apoptosis, while others cannot (e.g. cisplatin, mitomycin C and etoposide) {Casares, 2005 ;Obeid, 2007 ;Apetoh, 2007 ;Obeid, 2007, Ghiringhelli, 2009}. Thus far, we know that the immunogenicity of tumor cell death is closely linked to the surface exposure of calreticuline (CRT), the secretion of ATP and the release of HMGB1 that bind to CRT receptor, P2RX7 and TLR4 on host dendritic cells respectively. Chemotherapeutic agents that fail to induce CRT exposure or HMGB1 release are unable to induce immunogenic cell death. Our published data indicate that two loss-of-function alleles (that affect toll-like receptor-4 [TLR4] and purinergic P2 receptor X7 [P2RX7] of 12 and 30% of Caucasians, respectively) reduce the efficacy of conventional anticancer therapies, for instance in anthracyline-treated breast carcinomas and in oxaliplatin-treated colon cancers. We have determined novel defects in the emission or perception of immunogenic cell death signals negatively affecting the therapeutic response of human cancers that will be presented. Mouse preclinical models allowed us to unravel novel cellular and molecular pathways involved in the immunogenicity of cell death. Notably, we now show an important role of gdT cells producing IL-17 correlating with IFNγ producing CTL in tumor infiltrating lymphocytes post-chemotherapy, both subsets being mandatory for the success of therapy in three distinct tumor models. The regulation of gdT cell activation will be presented.

Presentation Abstracts – Saturday *(primary authors listed in italics)*

CLINICAL TRIAL ENDPOINTS

DECODING THE TOWER OF BABEL

Vernon K. Sondak
H. Lee Moffitt Cancer Center, Tampa, FL

The past two decades have seen a dramatic increase in the number of phase II and III trials evaluating biologic therapy for the treatment of solid tumors, especially melanoma, yet very few new biologic agents have been approved for widespread use. In fact, in melanoma, no new biologic agents have been approved by the US FDA since high-dose interferon alfa in 1995 and high-dose interleukin-2 in 1998. Even those approvals have not resulted in the uniform adoption of the approved drugs - only a minority of melanoma patients meeting the label indications for these two drugs ever receive them. Worldwide, these two drugs are used even more infrequently than in the US.

Although the reasons behind the limited penetration of biologic therapy into the routine management of melanoma and other solid tumors are manifold, a recurring theme has been the inability to agree on fundamental principles relating to clinical trial design and interpretation, which in turn complicates acceptance of clinical trial results and makes it more difficult to identify the best agents and regimens for testing in large-scale studies. Examples of the contentious issues that have faced melanoma clinical trialists include choosing the optimal choice of "control" regimens against which investigational drugs should be compared, whether placebos should be utilized, and identifying the ideal patient population to study (examples include allowing previously treated vs. treatment naïve patients; restricting eligible populations based on stage, serologic markers of disease burden, HLA haplotype, or the presence of a mutation or expression of defined antigens on a tumor biopsy specimen; and allowing or excluding patients with central nervous system metastasis). But perhaps no area has been more controversial than the optimum choice of endpoints for melanoma clinical trials.

Improvement in overall survival is widely accepted as the ultimate proof that a therapy has provided clinical benefit, but is it always required for a biologic therapy to be adopted? A number of factors can limit the ability of a clinical trial to detect an overall survival benefit with the use of an efficacious therapy, such as crossover (either explicitly as part of the study design or more insidiously in cases of patients crossing over to the same or a closely related drug once off-study), salvage therapy with a different class of effective agent, and early termination of a trial due to an evident progression-free survival or objective response advantage at an interim analysis. In the past, the likelihood of salvage therapy resulting in improved survival for patients failing protocol therapy was considered remote, but that can no longer be assumed to be the case. Objective response rates, widely used in other solid tumors particularly to identify which investigational therapies merit testing in phase III trials, have proven to be poor predictors of success for phase III trials of biologic therapy in melanoma. Whether modified criteria tailored to detect "atypical" response patterns associated with some modern forms of biologic therapy remains to be seen, and another relatively unrecognized problem with modified criteria is that we do not have any validated database for how often non-biologic agents, like single or multi-agent chemotherapy, show atypical response patterns in melanoma. It is not safe to assume that atypical response patterns never or rarely occur with melanoma chemotherapy. Regardless, objective response as an endpoint is not useful for agents that act by delaying tumor progression without leading to substantive shrinkage of individual tumors. It is not at all unreasonable to expect many biologic agents to exert a major antiproliferative effect even if they do not cause tumor regression, and for these agents objective response would be a poor endpoint for clinical trials.

Progression-free survival is an endpoint that encompasses both tumor regression and stabilization without regression, and so is an attractive alternative to objective response rate. However, assessments of progression can be subjective - and hence subject to observer bias in unblinded studies. Moreover, some patients with slowly progressing tumors meet criteria for "stable disease," overstating the effect of treatment. But the biggest criticism of progression-free survival as an endpoint is that minor delays in time to progression do not constitute clear evidence of "clinical benefit" of therapy. For all these reasons, progression-free survival benchmarks - most commonly the percentage of patients who are alive and progression-free at 6 months after protocol entry - have become increasingly popular as a relatively objective endpoint with readily apparent clinical benefit. The six-month progression-free survival percentage is often paired with the twelve-month overall survival percentage.

A recent meta-analysis tabulated the six-month progression-free and twelve-month overall survival percentages for 70 phase II trials involving 2100 stage IV melanoma patients and calculated 95% confidence intervals around the median. These confidence intervals, which take into account the size of the trial, serve as another barometer of whether the results seen with a new agent in early phase trials are sufficiently interesting to merit testing in a randomized phase III trial. Like all trial endpoints, they have their limitations, and ongoing clinical trial experience is beginning to bring some of these limitations to light. It remains unknown which of these two benchmarks is most predictive of efficacy, and it is also unclear how these benchmarks will translate to study populations other than the relatively unfavorable cooperative

group melanoma patients that comprised the meta-analysis. Nonetheless, using these benchmarks and understanding the meta-analysis results can clearly help us decode the Tower of Babel, and help us recognize and develop active biologic agents in melanoma more quickly and effectively than in the past.

IMMUNE-RELATED RESPONSE CRITERIA — FINDING MISSED SIGNALS OF ACTIVITY FOR IMMUNOTHERAPY

F. Stephen Hodi
Dana-Farber Cancer Institute, Boston, MA

Effective anti-tumor immune therapies result from enhancement of pre-existing immune responses or by the induction of new cancer specific ones. Clinical response patterns are therefore likely to differ from those of cytotoxic agents. Ipilimumab represents a new class of treatment that has recently been demonstrated to offer a survival advantage for patients with metastatic melanoma. Anti-tumor activity can be revealed by immediate responses, delayed responses after initial progression, or responses in the presence of new lesions. Currently accepted response criteria such as RECIST or WHO were developed to assess the immediate effects of treatment, and therefore fail to appreciate potential patterns of response following immune therapies. Novel immune relates response criteria (irRC) were proposed utilizing the experiences from the ipilimumab Phase II program treating metastatic melanoma patients. Four response patterns were defined: 1) immediate response; 2) durable stable disease; 3) response after initial tumor volume increase; and 4) response following presence of new lesions. These criteria have been developed in order to capture all patterns of response that have been associated with favorable outcomes. Possible mechanisms for these include: required additional time needed by the immune system, availability of antigens for immune recognition, and the radiographic appearance of tumor sites involving immune cell infiltration. Pathologic evidence from biopsies of pre-existing tumors following therapy supports such mechanisms. Prospective evaluation of irRC is being performed in ongoing clinical trials.

DEFINING RESPONSE IN PROSTATE CANCER IMMUNOTHERAPY

Serena Kwek[1], Vinh Dao[1], Ritu Roy[2], Yafei Hou[1], Jeff Simko[3], Eric Small[1], Lawrence Fong[1]
[1]Dept. of Medicine- Hem/Oncol, University of California- San Francisco, San Francisco, CA
[2]Biostatistics, UCSF, San Francisco, CA
[3]Pathology, UCSF, San Francisco, CA

CTL-associated antigen 4 (CTLA4) is a costimulatory molecule expressed on activated T cells that delivers an inhibitory signal to these T cells thereby serving as an immune checkpoint. Blocking CTLA4 with antibody treatment can induce tumor regression in cancer patients. While CTLA4 blockade can induce significant clinical responses in advanced prostate cancer patients, the antigen specific recognition that mediate these responses are unknown. Identification of these antigens may provide new insights into the immune recognition of prostate cancer including the development of future vaccines. We conducted a phase I clinical trial of anti-CTLA4 antibody (ipilimumab, BMS) combined with GM-CSF (sargramostim, Genzyme) in patients with castration resistant prostate cancer. To define the endogenous antigens against which immune responses are induced, we screened sera from clinical responders and non-responders for treatment-induced IgG antibodies with arrays spotted with over 8000 human proteins. We confirmed immune responses to these antigens by western blotting as well as detection of T cell immune responses to these antigens in the study subjects. We also assessed prostate cancer tissue for expression of these antigens. We found that antibodies to over 100 different antigens were increased in the clinical responders' sera after treatment compared to non-responders. Some of the antigens were shared between some of the clinical responders. These results demonstrate that CTLA4 blockade can induce immune responses to shared endogenous tumor antigens.

MOVING BEYOND TUMOR SIZE: A NEW PARADIGM IN CANCER IMAGING

Annick D. Van Den Abbeele
Dana-Farber Cancer Institute, Boston, MA

Over the last decade, there has been a significant shift in the paradigm of cancer diagnosis and drug discovery. Increasingly, cancers are being classified on the basis of genetic and molecular abnormalities and drug design and therapies are being directed at these cancer-specific molecular targets. These so-called targeted therapies hold the promise of greater specificity and efficacy. Cancer imaging is likewise no longer confined to the mere assessment of tumor size. Rather, over the past 10 years, imaging has been increasingly focused on approaches that interrogate tumors at the cellular and molecular level (i.e., functional and molecular imaging). With functional and molecular imaging, response to drug treatments can be assessed much earlier, in some cases on the order of hours to a few days. In addition, much more specific mechanisms of tumor biology can be measured rather than the traditional approach of waiting for the tumor to either shrink or grow. Functional, molecular, and anatomic imaging will indeed play an increasingly important complementary role not only in preclinical, translational, and clinical cancer research, but in drug and probe design, and in our ability to deliver personalized medicine.

Presentation Abstracts – Sunday *(primary authors listed in italics)*

SUNDAY KEYNOTE ADDRESS

IMMUNOTHERAPY OF HIGH RISK HPV INFECTIONS

Cornelis J. Melief
Leiden University Medical Center, Leiden, Netherlands

Therapeutic vaccination of persistent virus infections and associated diseases including (pre-)cancer so far has largely evaded success, mainly due to the fact that insufficiently consistent and robust effector T cell responses were induced by the commonly used vaccine constructs and formulations such as recombinant viruses and bacteria, recombinant proteins, DNA constructs, Dendritic Cell (DC) vaccines and exact HLA class I binding peptides (short peptides). Problems have been severe antigenic competion from vector sequences by recombinant viruses and bacteria, insufficiently powerful T cell generation by DNA constructs, insufficient homing to lymph nodes injected DC and antigen presentation of short peptides by non-professional antigen presenting cells in vivo, causing tolerance instead of immunity. Much more robust and consistent T cell responses can be obtained by vaccination with long (28-35 amino acid long) synthetic peptides. Such immunogens are more efficiently processed and presented than intact proteins by DC and only DC can efficiently perform this task. Moreover only concentrated antigen of choice is offered and antigenic competition therefore plays no role.

In earlier work we showed that therapeutic vaccination with a synthetic long peptide (SLP®) vaccine mediated the eradication of established human papilloma virus type 16 (HPV16)-positive tumors in mice and controlled wart growth and latent virus infection in rabbits persistently infected with cottontail rabbit papilloma virus. Subsequent phase I/II studies with an HPV16 SLP® vaccine, consisting of 13 long peptides covering the HPV16 E6 and E7 antigens, in patients with advanced HPV16-positive cervical cancer, revealed that this vaccine was safe and highly immunogenic. We then tested the clinical efficacy of this HPV16 SLP® vaccine in HPV16-induced high grade vulvar intraepithelial neoplasia (VIN3), a premalignant epithelial disorder, spontaneous regression of which occurs in less than 2% of patients and in which recurrence after standard treatment is high.

In a phase 2 trial, 20 women with VIN3 were vaccinated three times sc in the limbs with a mix of the HPV16 E6 and E7 synthetic long peptides formulated in Montanide ISA-51. The endpoints were objective clinical responses, defined as reduction of at least 50% in lesion size (partial response) or complete regressions, and HPV16-specific T cell responses.

The vaccine was safe. At 3 and 12 months after the last vaccination an objective response was observed in 12/20 (60%) and 15/19 (79%) patients respectively. Nine of them showed a complete and durable regression of the lesions at 12 months and at 24 months. The strength of the vaccine-induced HPV16-specific T cell response was significantly higher in the group of patients with a complete regression of their lesions compared to non-responders. Patients with large lesions were less likely to experience a complete clinical response than patients with small lesions and we ascribe this to a larger proportion of vaccine induced HPV-specific regulatory cells in the patients with large lesions.

In conclusion, treatment with the HPV16 SLP vaccine is clearly effective in patients with established VIN disease. The SLP platform lends itself for development of therapeutic vaccines against many other chronic infections and non-viral cancers. In patients with cancer, it is attractive to combine this type of vaccination with immunogenic forms of cancer chemotherapy and with immuno-modulatory drugs.

VACCINE COMBINATIONS

NUMBERS AND FUNCTIONS OF T LYMPHOCYTES IN HUMAN MELANOMA METASTASES

Nicolas van Baren[1,2], Arcadi Cipponi[2], Teofila Seremet[2], Pierre Coulie[2]
[1]*Ludwig Institute for Cancer Research, Brussels, Belgium*
[2]*de Duve Institute, University of Louvain, Brussels, Belgium*

Phase I/II vaccination trials in advanced metastatic melanoma patients have used tumor-specific antigens administered as peptides, proteins, dendritic cells pulsed with peptides, or recombinant poxviruses. Objective tumor regressions were observed in 10-20% of the vaccinated patients, with a real clinical benefit in 6%. Analysis of the anti-vaccine T cell responses indicated that the anti-vaccine CTL were surprisingly few, even in patients displaying tumor regression. Detailed analysis of a patient indicated that (i) tumor regression was associated with activation of CTL recognizing tumor-specific antigens absent from the vaccine, (ii) some of these CTL were already present in blood and metastases before vaccination, (iii) new CTL appeared after vaccination: new clones against antigens that were already targeted prior to vaccination (clonal spreading), and new clones against antigens that were previously ignored (antigen spreading). The most likely explanation is that melanoma patients spontaneously mount anti-tumor CTL responses, which eventually become

inefficient at rejecting the tumor ought to local immunosuppression or decreased antigen expression. Vaccination activates a few anti-vaccine CTL that upon arrival in the tumor relieve the suppression, sparking the activation of many more anti-tumor CTL, responsible for tumor regression.

We compared the gene expression profiles of pre-vaccine cutaneous metastases from melanoma patients who showed either complete tumor regression or no regression following vaccination with MAGE tumor antigens (MAGE-A3 peptides administered alone, or recombinant canarypoxviruses encoding MAGE-A1 and MAGE-A3 antigenic peptides). We observed no relevant difference between the two groups. But we noticed the presence of a specific inflammatory signature, quite variable between samples, and independent of the clinical evolution of the patients. It comprises T cell and macrophage markers. The T cell signature includes activation markers, IFNγ target genes, and the IFNγ transcript itself. Using immunohistology on adjacent tumor sections, we established that this inflammatory signature correlates with the degree of immune cell infiltration in these tumors. Thus melanoma metastases host various degrees of active Th1 inflammation, and we conclude that the immunosuppressive environment in these tumors does not result in complete inhibition of T cell activation.

PHOSPHOPEPTIDES PRESENTED BY MHC CLASS I AND CLASS II MOLECULES: A NEW CATEGORY OF TUMOR ASSOCIATED ANTIGENS WITH IMMUNOTHERAPEUTIC POTENTIAL

Victor H. Engelhard[1], Angela L. Zarling[1], Mark Cobbold[1,5], Jenny Cottine[2], Kara Cummings[1], Florence R. Depontieu[3], Michelle English[2], Yili Li[4], Fiyaz Mohammed[5], Andrew Norris[2], Rebecca C. Obeng[1], Jle Quan[2], Jeffry Shabanowitz[2], Roy A. Mariuzza[4], Suzanne L. Topalian[3], Benjamin Willcox[5], Donald F. Hunt[2]

[1]*Microbiology, University of Virginia School of Medicine, Charlottesville, VA*

[2]*Chemistry, University of Virginia, Charlottesville, VA*

[3]*Surgery, Johns Hopkins University School of Medicine, Baltimore, MD*

[4]*Cell Biology and Molecular Genetics, University of Maryland, Rockville, MD*

[5]*University of Birmingham, Birmingham, United Kingdom*

Melanoma is among the most immunogenic of all human cancers, and has been the prototype for defining tumor antigens (Ags) recognized by T lymphocytes and for developing cancer immunotherapies. Although a large number of melanoma Ags complexed to MHC molecules and recognized by tumor-reactive T cells have been identified, almost none of these are derived from proteins associated with cellular transformation and/or metastasis. Ags derived from proteins linked to cellular growth control, survival, or metastasis are particularly appealing as immunotherapeutic targets, since their alteration as a means of immune escape may compromise functional aspects of malignancy.

Phosphorylation is the most common form of enzyme-mediated post-translational protein modification, and transient phosphorylation of intracellular signaling molecules regulates activation and proliferation of many cancers. We have developed an approach to identifying phosphorylated tumor Ags, detecting MHC I- and II-associated phosphopeptides by “sifting” complex peptide mixtures with mass spectrometry to isolate a small number of peptides highly relevant to malignant cellular characteristics. Phosphopeptides are presented by a variety of prevalent human MHC class I and II isoforms and are displayed on melanoma, lymphoma, breast, ovarian, and colon carcinoma. Importantly, their source proteins are linked to cell cycle or transcriptional regulation, cytoplasmic signaling, protein metabolism, or cellular structure, and many are known to be upregulated in one or more types of solid tumors, and to play central roles in processes associated with cellular transformation or metastasis. These results establish that analysis of class I and II MHC associated phosphopeptides can lead to the identification of potentially important peptide Ags derived from proteins associated with cellular transformation or metastasis.

Melanoma-associated phosphopeptides are immunogenic, inducing both human and murine CD8 T cells that specifically recognize these phosphopeptides and discriminate them from their non-phosphorylated counterparts. These T cells also recognized melanoma cells. More recently, we have solved the 3 dimensional structures of several phosphopeptides complexed to MHC I and II molecules. These structures demonstrate that the phosphate is readily accessible for direct recognition by the T cell receptor. However, it also makes contacts with parts of the MHC molecule itself. These interactions can enhance the binding of phosphorylated peptides relative to their unphosphorylated counterparts affinity, and can also modify the conformation of the peptide. Thus, phosphorylation can create new Ags by several distinct processes. These results establish the potential of MHC-restricted phosphopeptides as targets for melanoma immunotherapy.

Presentation Abstracts – Sunday *(primary authors listed in italics)*

INDUCTION OF CD8+ T CELL RESPONSES AGAINST NOVEL GLIOMA-ASSOCIATED ANTIGEN PEPTIDES AND CLINICAL ACTIVITY BY VACCINATIONS WITH α-TYPE-1-POLARIZED DENDRITIC CELLS AND Poly-ICLC IN PATIENTS WITH RECURRENT MALIGNANT GLIOMA

Hideho Okada[1,2], Pawel Kalinski[1,2], Gary Kohanbash[2,3], Todd A. Reinhart[2,3], Theresa L. Whiteside[1,2], Lisa H. Butterfield[1,2], Ronald L. Hamilton[1,2], Douglas M. Potter[2,3], Ian F. Pollack[1,2], Andres M. Salazar[4], Frank S. Lieberman[1,2]

[1]*University of Pittsburgh School of Medicine, Pittsburgh, PA*

[2]*University of Pittsburgh Cancer Institute, Pittsburgh, PA*

[3]*Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA*

[4]*Oncovir, Inc., Washington, DC*

Purpose: α-type-1-polarized dendritic cells (αDC1) are able to produce high levels of interleukin (IL)-12 and induce long-lived type-1 adaptive immune responses against tumor-associated antigens more efficiently than standard mature DC. A phase I/II trial was performed to evaluate the safety and immunogenicity of a novel vaccination with αDC1 loaded with synthetic peptides for glioma associated antigen (GAA) epitopes and administration of poly-ICLC in human leukocyte antigen (HLA)-A2+ patients with recurrent malignant gliomas. GAAs for these peptides are EphA2, IL-13 receptor (IL-13R)α2, YKL-40 and gp100.

Patients and Methods: Twenty-two patients (13 with glioblastoma multiforme [GBM], 5 anaplastic astrocytoma [AA], 3 anaplastic oligodendroglioma [AO] and 1 anaplastic oligoastrocytoma [AOA]) received at least one vaccination, and 19 patients received at least four vaccinations at two αDC1 dose levels (1x or 3x 10^7/dose) at two-week intervals intranodally. Patients also received twice weekly intramuscular injections of 20 μg/kg poly-ICLC. Patients who demonstrated positive radiological response or stable disease without major adverse events were allowed to receive booster vaccines. T lymphocyte responses against GAA epitopes were assessed by enzyme-linked immunosorbent spot and HLA-tetramer assays.

Results: The regimen was well tolerated. The first 4 vaccines induced positive immune responses against at least one of the vaccination-targeted GAAs in peripheral blood mononuclear cells in 11 of 19 (58%) patients. Booster vaccines induced positive responses in 4 additional patients. Analyses of peripheral blood demonstrated significant up-regulation of type-1 cytokines and chemokines, including IFN-γ and CXCL10. Eight (4 GBM, 1 AA, 2 AO and 1 AOA) achieved progression free status lasting at least 12 months. One patient with recurrent GBM demonstrated sustained complete response. IL-12 production levels by αDC1 positively correlated with progression-free survival.

Conclusion: These data support safety, immunogenicity and preliminary clinical activity of poly-ICLC-boosted αDC1-based vaccines.

VACCINE COMBINATIONS: ENDOGENOUS VS EXOGENOUS VACCINATION WITH CTLA-4 BLOCKADE

Jedd D. Wolchok

Memorial Sloan-Kettering Cancer Center, New York, NY

Blockade of immunologic checkpoints results in durable regressions in a variety of malignancies. Specifically, the use of the CTLA-4 blocking antibody, ipilimumab (ipi) results in improved overall survival in patients with refractory melanoma. Other agents, such as MDX-1106 an antibody blocking PD-1 also mediate durable responses in melanoma, renal cell carcinoma and non-small cell lung cancer. Important questions include identification of targets for antigen-specific immunity which are mechanistically linked to clinical benefit and the role for vaccination in enriching the population of patients who have clinical benefit. The results of a recently completed phase III randomized trial comparing ipi with or without HLA-A*0201 restricted gp100 peptides or gp100 alone in patients with refractory melanoma show that the ipi containing groups have improved overall survival compared with peptides alone. The use of peptides with ipi did not improve the overall survival and, interestingly, resulted in slightly inferior radiographic response rates and progression-free survival. One hypothetical explanation for these results is that the introduction of a small number of antigens from one protein (gp100) during the time of immune potentiation biases the dis-inhibited immune response to a repertoire skewed to those specific peptides, which may or may not be relevsnt to all tumors in all patients. Eventually, the broad immune potentiation mediated by ipi allows for the amplification of responses to other antigens as overall survival is not affected by the use of peptides. The data from this study are even more intriguing when put in the context of results from a trial using high-dose bolus IL-2 with or without gp100 peptide, which showed an improvement in progression free survival and response rate with the combination, compared with IL-2 alone, but no change in overall survival.

In considering how to best build on these results when designing clinical trials using immune modulators and vaccines, it is best to consider the differences between exogenous and endogenous vaccination. We, and others, have investigated antigens recognized by patients treated with ipi and have found that those who have pre-existing or induced immunity to NY-ESO-1 are more likely to achieve

durable disease control. The mechanistic versus surrogate role of immunity to this particular antigen is remains a question; nonetheless, it is instructive to learn that patients have spontaneous immune responses to this protein which may be broadened (more epitopes) or improved (addition of CD8+ polyfunctional T cells to an existing antibody or CD4+ response) after CTLA-4 blockade. Additional ways to improve clinical response need careful consideration. Single epitope antigens present the risk for the emergence of escape variants, so the use of proteins, whole cells or even cellular libraries of antigens (such as heat shock protein-96 conjugated peptides) are important considerations for future combination trials. Timing of administration of vaccine may also be critical as expansion of cells already primed in the repertoire by vaccination in the past may be advantangeous compared with concurrent vaccination. Finally, the use of endogenous means of vaccination should be considered. Necrotic or apoptotic tumor is a source of antigen for patients responding to immunotherapy. Therefore, local tumor destruction and rational inclusion of systemic therapies with immune modulation are obvious next-steps. Systemic therapies could include either chemotherapies which now have well-described immunologic effects as well as signal transduction pathway inhibitors which also possess the ability to arrest tumor growth in appropriately genotyped patients.

T CELL ACTIVATION, PSMA SEROCONVERSION AND INCREASED Th17 RATES ARE ASSOCIATED WITH FAVORABLE CLINICAL OUTCOME IN PROSTATE CANCER PATIENTS TREATED WITH PROSTATE GVAX AND ANTI-CTLA-4 IMMUNOTHERAPY

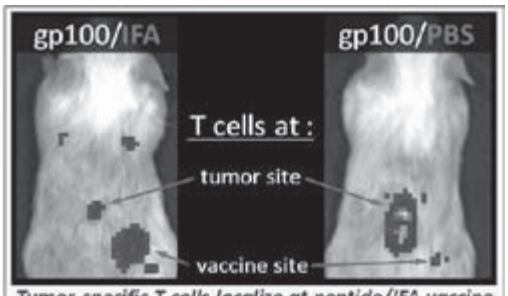
Saskia J. Santegoets[1], Alfons J. van den Eertwegh[1], Anita G. Stam[2], Rik J. Scheper[2], Sinead M. Lougheed[1], Petra E. Scholten[2], Mary von Blomberg[2], Helen Gall[1], Karin Jooss[3], Nathalie Sacks[3], Tom Harding[3], Kristen Hege[3], Israel Lowy[4], Winald R. Gerritsen[1], Tanja D. de Gruijl[1]
[1]*Medical Oncology, VU University Medical center, Amsterdam, Netherlands*
[2]*Pathology, VU University Medical center, Amsterdam, Netherlands*
[3]*Cell Genesys, South San Fransisco, CA*
[4]*Medarex, Bloomsbury, NJ*

The effects of Prostate GVAX and the anti-CTLA-4 antibody Ipilimumab were investigated in a Phase I dose escalation/expansion trial of patients with prostate cancer. Results showed that the GVAX/Ipilimumab combination was clinically active with PSA declines of more than 50% (Partial Response, PR) in 5 of 22 patients and PSA stabilizations (Stable Disease, SD) in 7 of 22 patients in the higher (3-5 mg/kg) Ipilimumab dose levels. Immune response monitoring was performed to identify changes that might predict or correlate with clinical efficacy. Most notably, pronounced and significant increases in frequencies of activated CD4+ and CD8+ T cells were observed by HLA-DR and ICOS expression upon administration of high (3 - 5 mg/kg) but not of low (0.3 - 1 mg/kg) Ipilimumab dosages. Of these, only early HLA-DR up-regulation might be useful as a marker for response prediction, since it was observed to significant levels in PR or SD, but not in PD patients. As an indication of tumor-specific responsiveness we tested NY-ESO-1 and PSMA specific seroreactivity and HLA-Tetramer (Tm) binding. For NY-ESO-1, GVAX/Ipilimumab-induced increased seroreactivity was observed in 6/28 patients. In 2 of 3 of these patients, increased NY-ESO157 T cell rates were also found, whereas no Tm reactivity was detected in 8 patients without NY-ESO-1 seroreactivity. Interestingly, PSMA seroconversions were observed in a total of 12/28 patients and were found to associate with improved overall survival. However, so far no PSMA Tm positivity was found. In addition, GVAX/Ipilimumab administration was found to induce Th2/Th17 profiles, as determined ex vivo by intracellular staining of peripheral T cells. Significantly increased levels of IL-4 in both CD4+ and CD8+ T cells were observed in patients with PR or SD, but not in patients with PD. Of note, Th17 spikes in 3/5 patients coincided with autoimmune breakthrough events and PSA responses. In summary, our data show that PSMA seroconversion, early HLA-DR up-regulation on T cells and increases in Th17 rates are associated with a favorable clinical outcome. Together these data point to a mechanism of action whereby combined Prostate GVAX and anti-CTLA-4 immunotherapy can induce both Th2/humoral and Th17/cell-mediated immune responses, resulting in tumor destruction and collateral autoimmunity.

Presentation Abstracts – Sunday *(primary authors listed in italics)*

PEPTIDE/IFA EMULSION VACCINES CAN FORM A SINK AND GRAVEYARD FOR TUMOR-SPECIFIC CD8+ T CELLS

Yared Hailemichael, Zhimin Dai, Nina Jaffarzad, Brian A. Rabinovich, Yang Ye, Patrick Hwu, Willem W. Overwijk
Melanoma Medical Oncology, University of Texas MD Anderson Cancer Center and the Center for Cancer Immunology Research (CCIR), Houston, TX



Tumor-specific T cells localize at peptide/IFA vaccine depots rather than tumors – reversal by using water-based vaccines. Albino C57BL/6 mice with 7-day s.c. B16 melanomas received luciferase-transduced pmel-1 T cells i.v. and peptide vaccination s.c. with gp100/IFA or gp100/PBS, combined with anti CD40, imiquimod and IL-2. T cell localization at tumor and vaccine sites was imaged 7 days later.

Many current clinical cancer vaccine trials are based on minimal determinant peptides administered in vaccine vehicles that form stable depots, such as water-in-oil emulsions with Incomplete Freund's Adjuvant (IFA). Here we show that bioluminescent tumor antigen-specific CD8+ T cells preferentially localized to antigen-containing peptide/IFA vaccine depots rather than to antigen-positive tumors. Furthermore, T cells initially responded to peptide/IFA vaccination by proliferating but then rapidly disappeared without apparent memory formation. Peptide/IFA vaccination strongly prevented virus-induced T cell memory formation and destroyed pre-established T cell memory. This apparent tolerizing capacity of the peptide/IFA vaccine persisted for more than 30 days in vivo and correlated with chronic peptide antigen presentation in the vaccine-draining lymph node. Addition of CD40, TLR agonists, IL-2 or IL-23, while all boosting initial T cell response to peptide/IFA vaccination, did not prevent subsequent T cell tolerance. Peptide vaccination in saline, without IFA, failed to induce any T cell priming or tolerization, but peptide in saline with aCD40, TLR triggering and IL-2 support induced strong primary and secondary responses. Importantly, while IFA-based vaccines induced tumor-specific T cell localization at the vaccine site, water-based vaccines did not and instead resulted in T cell localization to the tumor site and superior anti-tumor activity. We propose that long-lived IFA vaccine depots such as currently used to vaccinate cancer patients can function as a sink and possibly graveyard for tumor-specific T cells, thereby limiting their therapeutic efficacy. Reducing vaccine depot half-life in vivo may result in more effective cancer vaccines.

iSBTc PRESIDENTIAL SESSION

INTERFERON-β SECRETION IN THE TUMOR MICROENVIRONMENT CAN CAUSE POTENT TUMOR CONTROL THROUGH HOST CELLS INDEPENDENTLY FROM ADAPTIVE IMMUNITY

Robbert M. Spaapen, Mercedes B. Fuertes, Justin P. Kline, Yan Zheng, Thomas F. Gajewski
University of Chicago, Chicago, IL

Innate immune recognition of tumors is essential for generating a natural adaptive anti-tumor immune response. We have recently shown that host interferon-β (IFN-β) production is required to generate a primary adaptive immune response against B16-F10 melanoma and other murine transplantable tumors. This fundamental observation generated the hypothesis that provision of exogenous IFN-β in the tumor microenvironment might augment spontaneous adaptive immune responses even further, perhaps to the point of promoting complete tumor rejection. To test this notion, we retrovirally transduced the murine IFN-β cDNA into B16-F10 melanoma cells, which expressed the model SIYRYYGL (SIY) antigen to enable monitoring of T cell dynamics. In an autocrine manner, these cells subsequently secreted the chemokine CXCL10 and upregulated MHC class I surface expression, supporting a positive immunomodulatory effect. Upon implantation into C57BL/6 mice in vivo, IFN-β expressing B16-F10 tumors initially grew but then were potently controlled, even at doses up to 6 x 10^6 cells. A mixed population of wildtype and IFN-β-expressing B16-F10 melanoma cells was also completely controlled. Moreover, 10-day established B16-F10 tumors were completely rejected after intratumoral injection of IFN-β-expressing B16-F10 melanoma cells, arguing for a potent bystander effect. Expression of the type I interferon receptor (IFNAR1) on host cells was required to mediate this suppression of tumor growth. However, tumor control was not associated with significantly increased T cell responses as measured by IFN-γ ELISPOT or tetramer analysis specific for the SIY antigen, suggesting that improved adaptive immunity might not be the mechanism at work. Strikingly, identical tumor control was observed in $Rag2^{-/-}$ mice, arguing that T cells and B cells were dispensable. In addition, mice depleted of NK cells also demonstrated control of IFN-β-expressing tumors. Interestingly, IFN-β-expressing tumors showed a massive increase in macrophage infiltration in the tumor microenvironment, which may be immune effectors in this setting. Therefore, local IFN-β expression in the tumor microenvironment can mediate strong anti-tumor effects mediated by the host, independently of T, B, or NK cells.

Presentation Abstracts – Sunday *(primary authors listed in italics)*

4-1BB ACTIVATION INDUCES THE MASTER-REGULATOR EOMES AND A BROAD-SPECTRUM TH1 PHENOTYPE WHICH SYNERGIZES WITH CTLA-4 BLOCKADE TO REJECT B16 MELANOMA

Michael A. Curran[1], Myoung-joo Kim[1], Aymen Al-Shamkhani[2], James P. Allison[1]
[1]*Howard Hughes Medical Institute, Department of Immunology, Memorial Sloan-Kettering Cancer Center, New York, NY*
[2]*Tenovus Research Laboratory, Southampton General Hospital, Southampton, United Kingdom*

Antibodies which block the co-inhibitory receptor CTLA-4 or which activate the co-stimulatory receptor 4-1BB can promote the rejection of some murine tumors, but fail to cure poorly immunogenic tumors like B16 melanoma. We find that combining these two antibodies in the context of a Flt3-ligand, but not a GM-CSF, based B16 melanoma vaccine promoted synergistic levels of tumor rejection. 4-1BB activation elicited strong infiltration of CD8+ T cells into the tumor and drove the proliferation of these cells, while CTLA-4 blockade did the same for CD4+ effector T cells. Anti-4-1BB depressed regulatory T cell infiltration of tumors and this effect was dominant over the tendency of αCTLA-4 to expand them. 4-1BB activation strongly stimulated TH1-type inflammatory cytokine production in the vaccine and tumor draining lymph nodes as well as in the tumor itself. The addition of CTLA-4 blockade further increased IFN-γ production from CD4+ effector T cells in the vaccine draining node and the tumor.

A hallmark of 4-1BB agonist antibody treatment is the upregulation of the lectin KLRG1 on tumor infiltrating CD8+ and CD4+ T cells. We find that these KLRG1+ T cells in the tumor express high levels of multiple killing-associated genes and may be responsible for the increased anti-tumor cytotoxicity which has been attributed to α4-1BB treatment. Further investigation revealed that formation of these cells is driven by high-level expression of the master-regulatory transcription factor Eomesodermin (Eomes) in both the CD8+ and CD4+ T cell compartments.

To determine the pathway leading from 4-1BB agonist antibody to induction of Eomes expression, we have characterized the direct effects of α4-1BB on cytokine production from antigen presenting cells. Further, we have used a series of gene-specific knockout mice to validate candidate cytokines and transcription factors involved in this pathway. These findings reveal a previously unappreciated role for Eomes in generating extremely potent tumor-specific effector T cells which may be critically important for understanding and augmenting the effects of TNF-receptor family agonist antibodies as well as for T cell adoptive transfer therapies.

OVARIAN CANCER CELLS UBIQUITOUSLY EXPRESS HER-2 AND CAN BE DISTINGUISHED FROM NORMAL OVARY BY GENETICALLY REDIRECTED T CELLS

Evripidis Lanitis[1,2], Ian Hagemann[3], Degang Song[1], Lin Zhang[1], Richard Carroll[4], Raphael Sandaltzopoulos[2], George Coukos[1], Daniel J. Powell Jr[1]
[1]*OCRC, UPENN, Philadelphia, PA*
[2]*MBG, Democritus University of Thrace, Alexandroupolis, Greece*
[3]*Pathology & Lab Medicine, UPENN, Philadelphia, PA*
[4]*AFCRI, UPENN, Philadelphia, PA*

Background: HER-2-specific T cells can be induced by vaccination or generated de novo by genetic engineering, however it remains uncertain to what extent T cell-based HER-2-directed immunotherapy can be utilized for the treatment of advanced ovarian cancer. Objective: To validate HER-2 as a well-suited tumor antigen for widespread T cell-based adoptive immunotherapy of ovarian cancer. Methods: HER-2 expression was first evaluated using immunohistochemical analysis (IHC) in 50 high-grade ovarian serous carcinomas. To determine the relative expression of HER-2 in ovarian cancer cell lines, patient tumor samples and normal ovarian surface epithelial cells (OSE), Q-PCR, FACS and western blot was performed. Human T cells were genetically engineered to express the C6.5 HER-2-specific chimeric immune receptor (CIR). HER-2-redirected T cells were tested for their capacity to recognize and kill HER-2 expressing tumors and OSE cells. Results: IHC analysis showed HER-2 expression in 52% of primary OvCas ; 26 cases had HER-2 expressed at one or more tumor sites while HER-2 was undetectable in 24 samples. However, Q-PCR, FACS and western blot analysis demonstrated HER-2 expression in all established ovarian tumors (13/13) and short-term cultured tumors (7/7). Consistent with these results, all tumor cells derived from primary ascites (24/24) and solid tumor (12/12) expressed HER-2, albeit at variable levels. Compared to tumor, all (n=4) normal OSE expressed lower but detectable HER-2 levels. Genetically redirected T cells recognized and reacted against all ovarian cancer cell lines (14/14), primary ascites (5/5) and solid tumor (5/5) tested, however little or no reactivity was observed against normal OSE (1/4). Conclusions: Our results show that IHC under represents the frequency of OvCas that express/overexpress HER-2 which may exclude patients with low HER-2 expressing tumors from receiving HER-2 targeted therapy. Utilizing more sensitive detection methods, we found that OvCas ubiquitously express HER-2, and generally at higher levels than normal

ovary tissue. Importantly, all HER-2 expressing tumors are recognized by HER-2-redirected T cells and the latter are sensitive to even low levels of HER-2 expressed by OvCas. Importantly the CIR is able to distinguish recognition of ovarian cancer from normal targets, despite the fact that the normal cells do express HER-2 and therefore may minimize the potential for "off target" reactivity. These findings provide the rationale for the development of HER-2-redirected T cell-based immunotherapeutic approaches in women with ovarian carcinoma.

LARGE-SCALE PROFILING OF CIRCULATING SERUM MARKERS, SINGLE CELL POLYFUNCTIONALITY AND ANTIGEN DIVERSITY OF T CELL RESPONSE AGAINST MELANOMA

Chao Ma[1], Ann Chueng[1], Begonya Comin-Anduix[2], Thinle Condon[2], Antoni Ribas[2], James Heath[1]
[1]NanoSystems Biology Cancer Center; Physics; Chemistry, Caltech, Pasadena, CA
[2]Medicine, UCLA, Los Angeles, CA

Background: Highly multiplexed, sensitive and single cell profiling at multiple levels is likely to provide important information to advance immunotherapy for cancer, due to complexity of antigen specificity within cancer-targeting T cell populations and large varieties of effector molecules produced. Herein we report on immune monitoring studies using newly developed platforms analyzing samples from 8 patients enrolled in an ongoing clinical trial involving adoptive cell transfer (ACT) of lymphoyctes genetically modified to express a T cell receptor (TCR) specific for MART-1, which are administered to patients with metastatic melanoma together with dendritic cell vaccination after non-myeloablative lymphodepleting chemotherapy.

Methods: Miniaturized, highly multiplexed microchip based technology was adapted to follow the time course of immune responses focused on: (1) melanoma specific T cell repertoire enumeration that simultaneously detected 35 mutated, overexpressed or cancer-germline melanoma antigen specific T cell populations; (2) single cell secretome profiling of 20 cytolytic, inflammatory cytokines and chemokines from sorted phenotypically defined antigen-specific cytotoxic T lymphocytes and different helper T cell subclasses; (3) measurement of 35 blood melanoma tumor markers and immune proteins.

Results: MART-1-specific T cells peaked at 8-14 days after ACT with frequencies varying from 1 to 60% of CD3+ T cells in peripheral blood. Over 5 fold expansions in frequency was demonstrated by T cells specific for the melanoma antigens tyrosinase, NY-Eso, Mage 3, Mage 10 and GnT-V ($p<0.001$), indicating the broadening of immune response. Recovered MART-1-specific T cells had remarkable functional diversity (>50 different functional subtypes) and polyfunctionality, characterized by strong perforin, TNFα, IL1β and chemokine secretion. However, more than 90% of MART-1 T cells at day 30 lacked TNFα or IFNγ responses, suggesting a dysfunctional or partially exhausted phenotype. Tumor markers and T cell effector proteins in serum, including perforin, granzyme B and cytokines, were significantly released into peripheral blood soon after T cell reinfusion and melanoma associated markers and T cell growth factors followed similar dynamics, which indicated concurrence of tumor destruction and T cell expansion and attack.

Conclusions: Our results indicate importance of epitope spreading, T cell diversity and polyfunctionality for patient's response after the ACT of TCR transgenic lymphocytes; Tumor elimination is closely related to immune response quality. Ongoing experiments will explore quantitatively significance of each marker measured.

COUNTERING NEGATIVE REGULATION

IS IT POSSIBLE TO CORRECT THE IMPAIRED FUNCTION OF HUMAN TUMOR-INFILTRATING T LYMPHOCYTES?

Grégoire Wieërs[1,2], Nathalie Demotte[1,2], Pierre van der Bruggen[1,2]
[1]Ludwig Institute for Cancer Research, Brussels, Belgium
[2]de Duve Institute, Université catholique de Louvain, Brussels, Belgium

The identification of tumor-specific antigens recognized by T lymphocytes on human cancer cells has elicited numerous vaccination trials of cancer patients with defined tumor antigens. These treatments have induced T cells responses but have shown a low clinical efficacy in tumor-bearing melanoma patients. We believe that progress depends on unraveling the different blockages for efficient tumor destruction. One of the blockages could be the immunosuppressive environment of the tumor. We have observed that human CD8 tumor-infiltrating T lymphocytes (TIL), in contrast with CD8 blood cells, show impaired IFN-γ secretion upon ex vivo re-stimulation. We have attributed the decreased IFN-γ secretion to a reduced mobility of T cell receptors upon trapping in a lattice of glycoproteins clustered by extracellular galectin-3 (Demotte et al., 2008). Indeed, we have previously shown that treatment of TIL with N-acetyllactosamine (LacNAc), a galectin ligand, restored this secretion. Why do galectin-3 ligands improve human TIL function? Our working

hypothesis is that TIL have been stimulated by antigen recently, and that the resulting activation of T cells could modify the expression of enzymes of the N-glycosylation pathway and change the structure of N-glycans exposed at the cell surface, as shown for murine T cells. We surmise that the recently activated TIL, compared to resting T cells, harbor a set of glycans that are either more numerous or better ligands for galectin-3. Galectin-3 is abundant in many solid tumors and carcinomatous ascites, and can thus bind to surface glycoproteins of TIL and form lattices that would thereby reduce TCR mobility. This could explain the impaired function of TIL. The release of galectin-3 by soluble competitor ligands would restore TCR mobility and boost IFN-γ secretion by TIL. We recently strenghtened this hypothesis by showing that $CD8^+$ TIL treated with an anti-galectin-3 antibody had an increased IFN-γ secretion.

Galectin competitor ligands, e.g. disaccharides, lactose and LacNAc, are rapidly eliminated in urine, preventing their use in vivo. Other compounds that could block interactions between galectin-3 and glycoproteins are under development by several groups. We found that a plant-derived polysaccharide, which is in clinical development, detached galectin-3 from TIL and boosted their IFN-γ secretion. Importantly, we observed that not only $CD8^+$ TIL but also $CD4^+$ TIL that were treated with this polysaccharide secreted more IFN-γ upon ex vivo re-stimulation. In tumor-bearing mice vaccinated with a tumor antigen, injections of this polysaccharide led to tumor rejection in half of the mice, whereas all control mice died. In non-vaccinated mice, the polysaccharide had no effect by itself. These results suggest that a combination of galectin-3 ligands and therapeutic vaccination may induce more tumor regressions in cancer patients than vaccination alone. We therefore intend to pursue clinical trials involving the use of these agents in combination with anti-tumoral vaccination.

Further reading:

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THE MULTIKINASE INHIBITOR SORAFENIB REVERSES THE SUPPRESSION OF IL-12 AND ENHANCEMENT OF IL-10 BY PGE2 IN MURINE MACROPHAGES

Justin P. Edwards, Leisha Emens
Department of Oncology, Johns Hopkins School of Medicine, Baltimore, MD

Classical activating stimuli like LPS drive macrophages to secrete a battery of inflammatory cytokines, including interleukin (IL)-12/23, through toll-like receptor (TLR) signaling. TLR activation in the presence of some factors, including prostaglandin E2 (PGE2), promotes an anti-inflammatory cytokine profile, with production of IL-10 and suppression of IL-12/23 secretion. Extracellular signal regulated kinase (ERK) is a key regulator of macrophage IL-10 production. Since it inhibits ERK, we investigated the impact of Sorafenib on the cytokine profile of macrophages. In the presence of PGE2, Sorafenib restored the secretion of IL-12 and suppressed IL-10 production. Moreover, IL-12 secretion was enhanced by Sorafenib under conditions of TLR ligation alone. Furthermore, the impact of tumor culture supernatants, cholera toxin, and cAMP analogs (which suppress IL-12 secretion), was reversed by Sorafenib. Sorafenib inhibited the activation of the MAP-kinase p38 and its downstream target mitogen and stress activated protein kinase (MSK), and partially inhibited protein kinase B (AKT) and its subsequent inactivation of the downstream target glycogen synthase kinase 3-β (GSK-3β). Interference with these pathways, which are pivotal in determining the balance of inflammatory versus anti-inflammatory cytokines, provides a potential mechanism by which Sorafenib can modulate the macrophage cytokine phenotype. These data raise the possibility that the use of Sorafenib as cancer therapy could potentially reverse the immunosuppressive cytokine profile of tumor-associated macrophages, rendering the tumor microenvironment more conducive to an anti-tumor immune response.

LOSS OF HLA-DR EXPRESSION ON CD14+ CELLS; A COMMON MARKER OF IMMUNOSUPPRESSION IN CANCER PATIENTS

Michael P. Gustafson[1], Yi Lin[2], Stacy C. League[1], Peggy A. Bulur[2], Roshini S. Abraham[1], Stanimir Vuk-Pavlovic[2], Dennis A. Gastineau[1], Allan B. Dietz[1]
[1]*Laboratory Medicine and Patholgy, Mayo Clinic, Rochester, MN*
[2]*College of Medicine, Mayo Clinic, Rochester, MN*

Cancer-associated suppression of immunity must be countered if immunotherapy is to be effective. To study the nature of this immunosuppression, we have systematically assessed patient immunity by phenotyping leukocytes directly from peripheral blood. We have used this approach to qualitatively and quantitatively measure 40 phenotypes in more than 145 patients representing several diseases including glioblastoma, lymphoma, and prostate cancer. Cancer patients (prior to treatment, or more than 2 months after treatment) are

characteristically lymphopenic, with the deficit primarily due to loss of CD4 T cells, and heterogeneous levels of regulatory T cells. However, the most profound change is the loss of MHC class II expression (measured via HLA-DR) on CD14+ monocytes. In all malignancies measured to date, CD14+HLA-DRlo/neg monocytes are significantly elevated in peripheral blood of patients including glioblastoma patients (about 24 ±20.0% of CD14+ monocytes were HLA-DRlo/neg; n=24), lymphoma (27.8 ±3.1%; n=40), and prostate cancer (30.7 ±15%; n=22) compared to healthy donors (8.5% ±8.0; n=15). These percentages were converted into absolute cell counts and, in healthy donors, the absolute cell count of CD14+HLA-DRlo/neg monocytes ranged between 8-70 cells/ul with a median of 35 cells/ul compared to 134 cells/ul (range of 1-794 cells/ul) in GBM patients, 155 cells/ul (range of 25-591) and for lymphoma patients. These values have a large dynamic range in cancer patients, suggesting clinical and pathological heterogeneity within disease categories. CD14+HLA-DRlo/neg monocytes are functionally immunosuppressive as they inhibited T cell proliferation in an antigen independent manner. Most significantly, CD14+HLA-DRlo/neg monocytes were refractory in their ability to differentiate into mature dendritic cells that was independent of the maturation signal used. These findings have significant implications on the generation (both in vitro and in vivo) of DC for clinical use. Independently, others have shown CD14+HLA-DRlo/neg monocytes to be prognostic in the outcome of other immunosuppressive settings like sepsis. Our immunophenotyping analysis of a cohort of patients with/or at risk of acute lung injury with or without infection revealed that these patients had a median of 264 cells/ul (range of 31-1443; n=29). Our data suggests that CD14+HLA-DRlo/neg cells may be a useful marker of immunosuppression in cancer patients as well as for patients at risk of infection. As such, the immunosuppressive functions of CD14+HLA-DRlo/neg monocytes should be considered during the development of novel biological therapies of cancer.

INFLAMMATORY TREGS IN THE HUMAN TUMOR AND CHRONIC INFLAMMATORY MICROENVIRONMENTS

Weiping Zou
University of Michigan, Ann Arbor, MI

Foxp3+CD4+ regulatory T (Treg) cells inhibit immune responses and temper inflammation. IL-17+CD4+ T (Th17) cells mediate inflammation of autoimmune diseases. Treg and Th17 compartmentalization and trafficking may be tissue or/and organ-specific. Distinct chemokine receptor and integrin expression may contribute to selective retention and trafficking of Treg and Th17 cells at sites where regulation and function are required. Emerging evidence has demonstrated that once T cell subsets traffic to peripheral environment, the phenotype (or/and the lineage development) of T cell subsets including Treg, Th17 and Th1 cells may be highly modulated. Environmental stimuli may contribute to the plasticity of T cell development. For example, a minor IL-17+Foxp3+CD4+ T cell population has been observed in human peripheral blood. However, their biology is undefined. Here we studied this population in patients with chronic ulcerative colitis and colon cancer. This population was selectively accumulated in the colitic microenvironment and associated colon carcinoma. Their phenotype and cytokine profile was overlapping with Th17 and Treg cells. Myeloid antigen presenting cells, IL-2 and TGFβ are essential for their induction from memory CCR6+ T or Treg cells. Functionally, these cells suppressed T cell activation, and stimulated inflammatory cytokine production in the colitic tissues. Furthermore, these cells highly expressed IL-8, and promoted neutrophil trafficking. Altogether, the data indicate that IL-8+ and IL-17+Foxp3+ cells represent a unique "inflammatory" Treg population. This population may contribute to the pathogenesis of ulcerative colitis, and mechanistically link human chronic inflammation to tumor development.

IMMUNE CELL TRAFFICKING TO TUMOR MICROENVIRONMENT

TRAFFICKING OF POSITIVE AND NEGATIVE REGULATORY IMMUNE CELLS INTO THE TUMOR MICROENVIRONMENT

Thomas F. Gajewski, Robbert Spaapen, Mercedes Fuertes, Yuanyuan Zha
University of Chicago, Chicago, IL

Recent evidence from analysis of human melanoma metastases has suggested that at least two broad categories of tumor microenvironment can be identified with distinct mechanisms of immune escape. One subset of tumors has characteristics of inflammation which includes the presence of multiple immune cell types including dendritic cells and CD8+ effector T cells. These tumors also have signs of innate immune activation and a type I IFN signature. However, the presence of multiple defined negative regulatory mechanisms (Tregs, IDO, PD-L1, and T cell anergy) likely explains tumor resistance to immune destruction. The second subset of tumors is bland, lacks signs of inflammation, and does not contain intratumoral T cells. These tumors are also more vascular, and show evidence of activation of additional oncogenic pathways at the level of the tumor cells. Therefore, lack of effective immune cell recruitment in the tumor microenvironment likely explains tumor escape in these instances. Therefore, understanding the regulation of immune cell

trafficking into the metastatic melanoma tumor microenvironment is a critical question that could enable new therapeutic strategies to support the effector phase of the anti-tumor immune response. In murine models, we have found that host type I IFN signals are critical for recruitment of the CD8α+ DC subset into the tumor site, and that this is necessary for endogenous priming of CD8+ T cells against tumor antigens. A set of 6 chemokines has been identified that appear to contribute to recruitment of CD8+ effector T cells into the tumor microenvironment. On the other side of the equation, we have found that CCL22 produced by activated CD8+ T cells contributes strongly to intratumoral recruitment of CD4+CD25+FoxP3+ Tregs. Finally, preliminary data have suggested that disruption of specific angiogenic factors within the tumor site can markedly augment T cell accumulation there. Together, these studies have highlighted specific molecular pathways that are amenable to manipulation to improve upon trafficking of desired immune cell subsets in the target tissue of metastatic tumor deposits.

SPATIAL AND TEMPORAL REGULATION OF CXCR3 CHEMOKINE PRODUCTION AND CD8 T CELL INFILTRATION IN THE METASTATIC MELANOMA MICROENVIRONMENT

David W. Mullins, Sarah J. Conine, Eleanor Clancy-Thompson
Cancer Center, University of Virginia, Charlottesville, VA

Effective immune therapy of cancer requires infiltration of the tumor microenvironment (TME) by tumor antigen (TA)-specific $CD8^+$ T cells (T_{CD8}), a concept demonstrated in murine models and underscored by the prognostic significance of infiltrated T_{CD8} in human tumors. Infiltration of T_{CD8} into the TME is regulated, in part, by chemokines, yet the spatial and temporal regulation of chemokine production in the TME remains poorly characterized. We reported that the presence of circulating TA-specific T_{CD8} expressing the chemokine receptor CXCR3 correlated with a survival advantage in patients with resected stage III metastatic melanoma; further, we have observed that T_{CD8} cells infiltrating human metastatic melanoma are predominantly $CXCR3^+$. However, the induction of $CXCR3^+$ TA-specific T_{CD8} has no prognostic significance in patients with established disease. These data suggest that CXCR3 may facilitate T_{CD8}-mediated immune surveillance and eradication of early metastatic lesions, but that CXCR3 is insufficient to mediate infiltration of late-stage tumors. We hypothesized that the differential capacity of $CXCR3^+$ T_{CD8} to mediate anti-tumor efficacy may reflect the chemokine status of the TME. Therefore, we characterized the spatial and temporal regulation of CXCR3-cognate chemokines in the metastatic melanoma microenvironment. In a murine model of metastatic melanoma growing in the lungs, production of CXCR3-cognate chemokines (CXCL9, CXCL10, and CXCL11) was induced in vascular endothelium adjacent to tumor deposits from day 6 to day 13 of tumor growth. Chemokine production was interferon-gamma (IFN-γ)- and natural killer (NK) cell-dependent, and the presence of chemokine correlated with the capacity of TCR transgenic TA-specific T_{CD8} to infiltrate the tumor-bearing tissues in a CXCR3-dependent manner. In late tumors (> day 13), endogenous IFN-γ and CXCR3-cognate chemokines were not detected, and tumors were refractory to infiltration by TA-specific T_{CD8}, regardless of CXCR3 expression. Exogenous IFN-γ induced CXCL9, CXCL10, and CXCL11 production in the late stage TME and restored CXCR3-dependent T_{CD8} infiltration. Dysregulation of CXCR3-cognate chemokine production in the late-stage tumor was mediated by adenosine; specific blockade of adenosine signaling restored IFN-γ and chemokine production and infiltration of $CXCR3^+$ T_{CD8} in the TME. Thus, early-stage and late-stage tumors are differentially susceptible to immune-mediated infiltration and elimination by effector T_{CD8} as a consequence of the temporal dysregulation of IFN-γ and IFN-γ-induced chemokine production.

EFFECTOR/MEMORY REGULATORY T CELLS AND THEIR ROLE IN THE TUMOR MICRO/ENVIRONMENT

Elizabeth M. Jaffee
Dept. of Oncology, Johns Hopkins University, Baltimore, MD

T cell responses are observed in cancer patients who have been treated with antigen-specific vaccines. However, the majority of responses are often weak and ineffective at controlling tumor growth. This may be due to an ineffective vaccine approach. However, in many cases mechanisms of T cell tolerance to specific tumor antigens are at play. Understanding these mechanisms in the context of tumor antigens is critical for the development of interventions that can reverse the tolerant state and allow these T cells to more effectively respond to tumors. We have described the existence of immune tolerance in the HER-2/neu transgenic (neu-N) mouse model of breast cancer and used these mice to understand the mechanisms that suppress high avidity antigen-specific CD8+ T cells. We previously reported that CD8+ T cells specific for the immunodominant neu epitope, RNEU420-429, were identified only in Cy plus vaccine treated neu-N mice that rejected tumor challenge, but not in neu-N mice given vaccine only. Furthermore, high avidity RNEU420-429-specific CD8+ T cells were also identified in vaccine treated mice that were first depleted of CD25+ T regulatory cells (Tregs). More recently we have developed T cell receptor (TCR) transgenic high and low avidity mouse colonies that are specific for the same RNEU420-429 epitope. We have used these mice to evaluate differences in tumor-trafficking and function of high versus low

avidity cancer antigen-targeted T cells. Adoptive transfer of naïve T cells from these mice into tumor bearing neu-N mice have identified a sub-set of Tregs that block high avidity T cell trafficking and activation in neu-expressing tumors. The results of these studies will be discussed. In addition, data will be presented evaluating these findings in a neo-adjuvant and adjuvant vaccine study in patients with pancreatic cancer.

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NGR-TNF, A SELECTIVE VESSEL-TARGETING AGENT, INCREASES THE THERAPEUTIC POTENTIAL OF CHEMO-IMMUNOTHERAPY

Arianna Calcinotto, Matteo Grioni, Elena Jachetti, Flavio Curnis, Giorgio Parmiani, Angelo Corti, Matteo Bellone
San Raffaele Scientific Institute, Milan, Italy

Novel therapeutic strategies for cancer implement the combination of active and/or adoptive immunotherapies with chemotherapy (chemo-immunotherapy). Indeed, the immune system can target and eradicate small tumor masses, or even single neoplastic cells, but usually fails against bulky tumors. Chemotherapy can reduce the tumor mass, favor the induction of specific immune responses and increase the effector lymphocyte:tumor cell ratio. Unfortunately, the abnormal tumor vasculature and the altered composition of stromal components may significantly impair the penetration of drug and/or effector T lymphocytes into neoplastic tissues, therefore limiting the therapeutic potential of chemo-immunotherapy. One possible strategy to overcome this anatomical and functional obstacle would be to selectively deliver tumor necrosis factor alpha (TNF), a cytokine that can transiently alter the endothelial barrier function, to the tumor vessels.

NGR-TNF is a novel vascular targeting agent currently tested in phase II and III studies in patients with solid tumors. This drug consists of CNGRCG, a peptide capable to home to tumor blood vessels, fused to TNF. In the B16 mouse melanoma and other preclinical models the pre-treatment with picograms of NGR-TNF increases vessel permeability and favors the penetration of chemotherapeutic drugs.

We have found that, at variance with TNF, pre-treatment with NGR-TNF favored the induction of leukocyte adhesion molecules on the melanoma-associated endothelium and the penetration into the tumor mass also of antigen-specific cytotoxic T lymphocytes (CTL) induced either by vaccination or adoptively transferred. In both experimental settings, endogenous and adoptively transferred CTL maintained their effector functions for several days after NGR-TNF treatment, and this phenomenon correlated with a prolonged and statistically significant animal survival. The therapeutic effect of the combined treatment was amplified by the addition of chemotherapy.

Hence, NGR-TNF favors penetration of both drugs and effector T lymphocytes into the tumor mass, and acts in synergy with active and adoptive immunotherapy against melanoma.

Presentation Abstracts – Monday *(primary authors listed in italics)*

ADOPTIVE T CELL TRANSFER: THE NEXT WAVE

ADOPTIVE IMMUNOTHERAPY FOR SUBJECTS WITH SOLID TUMORS USING GENETICALLY MODIFIED VIRUS-SPECIFIC T CELLS

Malcolm K. Brenner, *Antonio Di Stasi*
Baylor College of Medicine, Houston, TX

The clinical and commercial successes of monoclonal antibodies and the effectiveness of donor lymphocyte infusion for treating relapse after stem cell transplantation has encouraged further investigation aimed at exploiting T cell immunity against cancer. A cellular immune response may have superior ability to kill malignant cells and improved bio-distribution (transit through multiple tissue planes), as well as increased long-term persistence. Moreover, improvements in cellular biology and our ability to manipulate gene expression in cells of the immune system have facilitated and enhanced efforts aimed at developing T cell therapies for malignancy.

This presentation will describe how adoptively transferred T cells can be used in the therapy of both hematological and epithelial malignancy. Although many challenges remain, significant response rates (including >50% sustained CR in relapsed and primary resistant EBV+ lymphoma and nasopharyngeal carcinoma) are now obtained, even in patients with relapsed or primary resistant disease. These CTL can be further modified with chimeric antigen receptors (CAR) to provide them with dual specificities, for EBV- infected and for tumor targets. In pre-clinical studies such CTL have superior persistence and effector function against malignant cells than CAR expressing primary T cells, apparently because of the co-stimulation they receive when their native receptor is engaged by EBV-expressing target cells. Our clinical study in patients with neuroblastoma, confirms the in vivo superiority of CAR-CTL over CAR-T cells and indicates a means by which T cell therapy for cancer can be improved. We are now testing our approach in patients with lung cancer and have opened studies in patients with Glioblastoma. In these studies we also engineer the CAR-CTL to be resistant to the major immune evasion strategies used by the tumors, and we are expressing the CARs in T cells that are specific for additional viruses to allow enhanced in vivo expansion following vaccination. Finally, the use of new suicide genes such as icaspase9 which are of all human origin, do not require a prodrug with therapeutic activity to be used for activation, and which kill even non-dividing human cells within minutes, may improve the safety of the approach. Our early clinical results using icaspase9 will be presented.

FUNCTIONAL REPROGRAMMING OF THE TUMOR STROMA BY IL-12 ENGINEERED T CELLS IS REQUIRED FOR ANTI-TUMOR IMMUNITY

Sid P. Kerkar[1], Robert Reger[1], Pawel Muranski[1], Zhiya Yu[1], Douglas Palmer[1], Dhanalakshmi Chinnasamy[1], Christopher A. Klebanoff[1], Yun Ji[1], Luca Gattinoni[1], Steven A. Rosenberg[1], Giorgio Trinchieri[2], Nicholas P. Restifo[1]
[1]*Center for Cancer Research, National Cancer Institute, Bethesda, MD*
[2]*Cancer and Inflammation Program, National Cancer Institute, Bethesda, MD*

Bone marrow derived stromal cells within the tumor microenvironment are capable of cross presenting antigens to cytotoxic T lymphocytes (CTL). We found that the adoptive transfer of tumor-specific CD8+ T cells gene-engineered to secrete IL-12 led to the increased local infiltration of adoptively transferred T cells and caused the regression of large established B16 melanomas. The autocrine effects of IL-12 resulted in the production of large amounts of IFN-γ by T cells. Surprisingly, we found that IL-12-engineered T cells that lacked the ability to receive signals from IL-12 (Il12rβ2-/-), and indeed T cells that lacked the ability to produce IFN-γ (Ifnγ-/-), retained all of their ability to trigger tumor destruction. However, tumor treatment efficacy was abrogated when the cells in host mice lacked IL-12 receptors (Il12rβ2-/-), IFN-γ receptors (IfnγR-/-) or the ability to produce IFN-γ. Thus, sensitization of host cells and not the transferred T cells within the tumor microenvironment was critical for successful anti-tumor immunity. We measured increased endogenous CD8+ and host NK cells within the tumor but treatment responses remained robust in mice completely devoid of T and B cells (Rag-/-) and depleted of NK cells. We found that the majority of cells expressing the IL-12Rβ2 receptor within the tumor were CD11b+ myeloid cells. Transfer of IL-12-producing anti-tumor T cells triggered significant in situ changes in CD11b+ cells including increased expression of H-2Db along with up-regulation of Fas (CD95), and FADD. In addition, both the numbers and percentages of CD11b+ cells dropped just prior to tumor regression. Tumor treatment was abrogated in mice deficient in MHC class I (β2M-/-) but not class II (I-Ab-/-), indicating the functional importance of antigen cross-presentation in vivo. These results are consistent with a model whereby IL-12 triggers the functional maturation of in situ APCs capable of cross-presenting tumor antigens. Licensed recognition of these antigens by tumor-specific T cells may in turn trigger the collapse of the tumor stroma and its vasculature.

Presentation Abstracts – Monday *(primary authors listed in italics)*

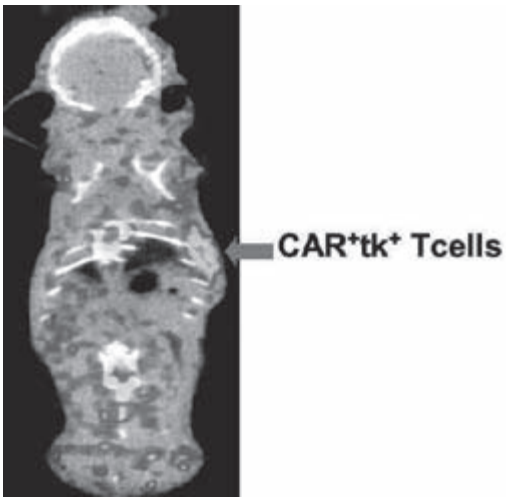
NONINVASIVE POSITRON EMISSION TOMOGRAPHY (PET) IMAGING OF SLEEPING BEAUTY (SB) MODIFIED CD19-SPECIFIC T CELLS EXPRESSING HERPES SIMPLEX VIRUS1-THYMIDINE KINASE (HSV1-TK)

Pallavi Raja Manuri[1], Simon Olivares[1], Amer M. Najjar[3], Tiejuan Mi[1], Helen Huls[1], Elizabeth J. Shpall[2], Richard E. Champlin[2], Juri Gelovani[3], Laurence J. Cooper[1]

[1]*Pediatrics Research, U.T. MD Anderson Cancer Center, Houston, TX*

[2]*Stem Cell Transplantation and Cellular Therapy, U.T. MD Anderson Cancer Center, Houston, TX*

[3]*Experimental Diagnostic Imaging, U.T. MD Anderson Cancer Center, Houston, TX*



PET imaging is an attractive approach to monitor infused genetically modified Tcells as it is non-invasive and generates quantitative, longitudinal, and spatial in vivo information about the dynamic status of infused T cells. In this study, we constructed SB DNA transposon vectors encoding a panel of transgenes expressing the wild type HSV1-tk fused to hygromycin phosphotransferase (in vitro selection) and FLAG tag (expression level). Primary T cells were co-electroporated with tkHy SB transposon and a CD19-specific chimeric antigen receptor (CAR) SB transposon and propagated on CD19-specific artificial antigen presenting cells in the presence of cytocidal concentrations of hygromycin B. After 4 weeks of numeric expansion (i) 90% of the T cells were CAR+tk+, (ii) accumulated high amounts of [3H] 2'-fluoro-2'deoxy-1-β-D-arabionofuranosyl-5-ethyl-uracil (iii) were ablated in the presence of ganciclovir and (iv) exhibited redirected killing of CD19+ tumor targets. The CAR+tk+ T cells could be visualized by µPET imaging in mice (Figure). This is the first report showing that SB transposition can generate CAR+tk+ T cells which can be imaged by µPET in vivo. We have adapted SB system for human application (IND # 14193), and thus this study has immediate translational application to infuse CD19-specific T cells co-expressing HSV1-tk for imaging.

Figure : Accumulation of 18[F]-FEAU in CAR+tk+ T cells. Mice were anesthesized and CAR+tk+ T cells were injected subcutaneously in the right flank. PET/CT images were acquired 2h after intravenous administration of 18[F]-FEAU using Inveon micro-PET/CT scanner. Images were reconstructed by two dimensional ordered subsets expectation maximization (OSEM) algorithm. PET and CT image fusion and analysis were performed using vendor software Inveon Research Workplace.

DISSECTION OF THERAPY-INDUCED MELANOMA-REACTIVE CYTOTOXIC T CELL RESPONSES

Ton Schumacher

Department of Immunology, Netherlands Cancer Institute, Amsterdam, Netherlands

There is strong evidence that melanoma-reactive T cell responses induced by immunotherapeutic interventions such as anti-CTLA4 treatment or TIL therapy can exert clinically meaningful effects. However, at present we do not know which cytotoxic T cell reactivities mediate cancer regression. Furthermore, as the number of melanoma-associated antigens to which these responses can be directed is very high, classical strategies to map cytotoxic T cell reactivity do not suffice. Knowledge of such reactivities would be useful to design more targeted strategies that selectively aim to induce immune reactivity against these antigens.

In the past years we have aimed to address this issue by designing MHC class I molecules occupied with UV-sensitive 'conditional' peptide ligands, thereby allowing the production of very large collections of pMHC complexes for T cell detection. Secondly, we have developed a 'combinatorial coding' strategy that allows the parallel detection of dozens of different T cell populations within a single sample. The combined use of MHC ligand exchange and combinatorial coding allows the high-throughput dissection of disease- and therapy-induced CTL immunity, and we have now used this platform to monitor immune reactivity against a panel of over 200 melanoma-associated epitopes. First data on the composition and engraftment of TIL products used for adoptive cellular therapy will be presented.

Presentation Abstracts – Monday

(primary authors listed in italics)

THERAPEUTIC CELL ENGINEERING USING SURFACE-CONJUGATED SYNTHETIC NANOPARTICLES

Matthias T. Stephan[1,2,3], James J. Moon[1,2,3], Soong Ho Um[1], Anna Bershteyn[1,2,3], Darrell J. Irvine[1,3,4]
[1]*Department of Material Science and Engineering, Massachusetts Institute of Technology, Cambridge, MA*
[2]*Department of Biological Engineering, Massachusetts Institute of Technology, Cambridge, MA*
[3]*Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, MA*
[4]*Howard Hughes Medical Institute, Massachusetts Institute of Technology, Cambridge, MA*

Adoptive cell therapy (ACT) with tumor-specific T cells is a promising approach for cancer therapy, but strategies to enhance the persistence and functionality of ACT T cells are still sought. Meanwhile, the use of synthetic nanoparticles as carriers to deliver drugs to tumor environments has become of increasing interest, with the goal of targeting drugs to tumor sites. We will describe a strategy combining these two approaches, based on the chemical conjugation of adjuvant drug loaded nanoparticles (NPs) to lymphocytes for ACT. Using a simple ex vivo conjugation process, drug-loaded particles are attached to T cells without interfering with intrinsic cell functions, including tumor/lymphoid tissue homing. We demonstrate how ACT T cells carrying cytokine-loaded NPs (to permit pseudo-autocrine self-stimulation following transfer into tumor-bearing hosts) are capable of massive in vivo expansion and robust anti-tumor responses, enabled by minimal doses of cytokines that by comparison have no therapeutic effect when given in a soluble form systemically. This approach is a facile and generalizable strategy to augment cytoreagents while minimizing systemic side effects of adjuvant drugs. Based on the wealth of available NP-formulations tailored to deliver small molecule drugs, proteins, or siRNA, the range of therapeutic or diagnostic cargos that can be attached to therapeutic cells extends far beyond the small molecules and recombinant proteins tested in our studies. In addition, our results suggest therapeutic cells are promising vectors for actively targeted drug delivery.

ADOPTIVE T CELL THERAPY FOR METASTATIC MELANOMA: THE MD ANDERSON EXPERIENCE

Laszlo G. Radvanyi, Chantale Bernatchez, Minying Zhang, Priscilla Miller, Michelle Glass, Nicholas Papadopoulos, Patrick Hwu
Melanoma Medical Oncology, M.D. Anderson Cancer Center, Houston, TX

Adoptive cell therapy (ACT) using tumor-infiltrating lymphocytes (TIL) is a promising treatment for metastatic melanoma. Here, we report on the results of an ongoing Phase II clinical trial testing ACT in metastatic melanoma patients regardless of HLA subtype. Autologous TIL were expanded in large-scale using anti-CD3 and IL-2 and then infused into patients following transient lymphodepletion. This was followed by high-dose IL-2 therapy. The best overall response was determined and correlated with T cell phenotype as well as telomere length. The persistence of specific TCR clonotypes after infusion was also tracked. Altogether, 30 patients have been treated with clinical response data available from 25 patients (as of June 20, 2010). Overall, 13/25 (52%) patients have had a clinical response (PR/CR), with one patient having an ongoing PR for >22 months and another patient having a CR. A higher percentage and number of CD8+ T cells ($P<0.05$) and a lower percentage of CD4+ T cells ($P<0.05$) in the infused TIL was associated with a higher probability of clinical response. The degree of tumor shrinkage of major recorded lesions also had a significant correlation with increased percentage and total number of CD8+ TIL infused ($P<0.05$). Phenotypic analysis using flow cytometry revealed that infused TIL of clinical responders had significantly more CD8+ T cells with a differentiated effector phenotype (CD45RA-CD27-). Unexpectedly, we found that responders had a higher percentage of CD8+ TIL expressing the negative costimulation molecule “B and T lymphocyte attenuator” (BTLA) and were infused with significantly higher numbers of CD8+BTLA+ T cells than non-responders ($P<0.002$). Tumor regression was also associated with the persistence of dominant TIL TCR V-beta clonotypes in vivo for at least 3 months, while expansion of subdominant TIL clonotypes after 6 months was associated with clinical response after a prolonged period of stable disease in some patients. Interestingly, so far no significant difference in relative telomere length of TIL between responders versus non-responders was evident. In conclusion, this ongoing ACT trial is achieving a high clinical response rate for metastatic melanoma. CD8+ T cells appear to be critical in driving tumor regression. Our results also suggest that the differentiation status of TIL and specific phenotypic subsets (activated/differentiated BTLA+ T cells) are more predictive of clinical response than relative telomere length. In addition, the finding that some patients have delayed clinical responses after a period of stable disease suggests that it is critical not to perform additional therapies on patients compromising T cell function or survival until clear evidence of disease progression is found.

Poster #: *(primary authors listed in italics)*

ADOPTIVE T CELL TRANSFER: THE NEXT WAVE

1 DEVELOPMENT OF A GAMMARETROVIRAL VECTOR FOR THE EXPRESSION OF ARTIFICIAL miRNAS IN HUMAN T LYMPHOCYTES
Daniel Abate-Daga, Tristen S. Park, Douglas C. Palmer, Nicholas P. Restifo, Steven A. Rosenberg, Richard A. Morgan
Surgery Branch, National Cancer Institute. NIH, Bethesda, MD

2 DEPLETION OF NK CELLS ENHANCES THE EFFECTIVENESS OF ADOPTIVE CELL THERAPY WITH NAIVE TUMOR-SPECIFIC CD4+ T CELLS THROUGH SURFACE BOUND IL-15
Kristina Harris[1], Lukas Pfannenstiel[2], Malcolm Lane[1], *Paul A. Antony*[1]
[1]Program in Molecular Microbiology and Immunology and the Department of Pathology, University of Maryland School of Medicine, Baltimore, MD
[2]Department of Head and Neck Surgery, University of Maryland School of Medicine, Baltimore, MD

3 EVALUATION OF CXCR3 AND CCR5 POLYMORPHISMS AND GENE-EXPRESSION AS PREDICTIVE BIOMARKERS OF CLINICAL RESPONSE TO ADOPTIVE THERAPY IN MELANOMA PATIENTS
Davide Bedognetti[1,2], Lorenzo Uccellini[1], Ena Wang[1], Mark E. Dudley[3], Zoltan Pos[1], Maria Libera Ascierto[1], Valeria De Giorgi[1], Hui Liu[1], Jingou Chen[1], Mario Roberto Sertoli[2], Francesco M. Marincola[1], Steven A. Rosenberg[3]
[1]Department of Transfusion Medicine, CC, National Institutes of Health, Bethesda, MD
[2]Department of Oncology, Biology and Genetics, University of Genoa, Genoa, Italy
[3]Surgery Branch, NCI, National Institutes of Health, Bethesda, MD

4 DEVELOPMENT OF HLA-A2 RESTRICTED TCR AGAINST CANCER TESTIS ANTIGEN SSX-2 FOR ADOPTIVE IMMUNOTHERAPY OF CANCER
Nachimuthu Chinnasamy[1], Jeremy L. Davis[1], Mahadev Rao[1], David S. Schrump[1], Daniel E. Speiser[2], Steven A. Rosenberg[1], Richard A. Morgan[1]
[1]Surgery Branch, National Cancer Institute, Bethesda, MD
[2]Ludwig Institute for Cancer Research Ltd., University Hospital Lausanne, Lausanne, Switzerland

5 IN VITRO GENERATION OF MULTIANTIGEN-SPECIFIC CD4+ AND CD8+ T CELLS FOR ADOPTIVE IMMUNOTHERAPY
Anna Foerster, Verena Lasmanowicz, Olaf Brauns, Sven Kramer, Jürgen Schmitz, Stefan Miltenyi, Georg Rauser, Mario Assenmacher, Anne Richter
Miltenyi Biotec GmbH, Bergisch Gladbach, Germany

6 HYPOTHESES FOR IMPROVING DESIGNER T CELLS; PHASE I TRIALS
Richard Junghans[1,2], Ritesh Rathore[1,2], Barti Rathore[1,2], Qiangzhong Ma[1,2], Anthony Bais[1], Erica Gomes[1], Ryan Harvey[1], Nithiandan Selliah[1,2], Shah Miah[1,2], Pam Davol[1], Steven Cohen[1], Samer Al Homsi[1,2]
[1]Surgery, Roger Williams Hospital, Providence, RI
[2]Boston University School of Medicine, Boston, MA

7 MONOMERIC DESIGNER T CELLS KILL IL13Ra2 EXPRESSING GBM MORE EFFICIENTLY
Seogkyoung Kong, Richard P. Junghans, Prakash Sampath
Neurosurgery, Boston University School of Medicine, Roger Williams Medical Center, Providence, RI

8 DEVELOPMENT OF A CHIMERIC ANTIGEN RECEPTOR FOR PROSTATE CANCER STEM CELL ANTIGEN FOR ADOPTIVE CELL THERAPY OF CANCER
Kiran H. Lagisetty[1], William Burns[2], Zhili Zheng[1], Steven A. Rosenberg[1], Richard A. Morgan[1]
[1]Surgery Branch, National Cancer Institute, Bethesda, MD
[2]Department of Surgery, Johns Hopkins Medicine, Baltimore, MD

9 LARGE-SCALE PROFILING OF CIRCULATING SERUM MARKERS, SINGLE CELL POLYFUNCTIONALITY AND ANTIGEN DIVERSITY OF T CELL RESPONSE AGAINST MELANOMA
Chao Ma[1], Ann Chueng[1], Begonya Comin-Anduix[2], Thinle Condon[2], Antoni Ribas[2], James Heath[1]
[1]NanoSystems Biology Cancer Center; Physics; Chemistry, Caltech, Pasadena, CA
[2]Medicine, UCLA, Los Angeles, CA

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ADOPTIVE T CELL TRANSFER: THE NEXT WAVE (CONTINUED)

10 ADOPTIVELY TRANSFERRED ANTI-TUMOR Th17 CELLS ARE LONG-LIVED AND EVOLVE INTO A HIGHLY ACTIVE MEMORY POPULATION WITH A UNIQUE MOLECULAR SIGNATURE

Pawel J. Muranski[1], Zachary Borman[1], Sid Kerkar[1], Yun Ji[1], Luca Gattinoni[1], Robert Reger[1], Christopher Klebanoff[1], Zhiya Yu[1], Gabriela Ferreyra[2], Steven Kern[2], Robert L. Danner[2], Nicholas P. Restifo[1]

[1]*National Cancer Institute, Bethesda, MD*

[2]*Critical Care Medicine Department, Clinical Center, NIH, Bethesda, MD*

11 ARTIFICAL MICRORNA TARGETING PROGRAMMED DEATH RECEPTOR-1 TO ENHANCE ADOPTIVE CELL TRANSFER THERAPY FOR CANCER

Tristen S. Park, Takashi Inozume, Mojgan Ahmadzadeh, Ken-ichi Hanada, James Yang, Steven A. Rosenberg, Richard A. Morgan

Surgery Branch, National Institutes of Health, Bethesda, MD

12 EXPANSION OF AUTOLOGOUS HUMAN Vγ9Vδ2 T CELLS EX VIVO: POTENTIAL FOR ADOPTIVE T CELL THERAPY OF PROSTATE CANCER

Andrew Roberts[1], Maria Serrano[1], Elisa Binda[1], Pierre Vantourout[1,2], Hardev Pandha[3], Adrian C. Hayday[1,2]

[1]*Peter Gorer Department of Immunobiology, King's College London, London, United Kingdom*

[2]*London Research Institute, Cancer Research UK, London, United Kingdom*

[3]*Postgraduate Medical School, University of Surrey, Guildford, United Kingdom*

13 A DATA MINING ARCHITECTURE FOR STUDYING CYTOKINE PRODUCTION AND T CELL REPERTOIRE OF TUMOR-SPECIFIC T CELLS GENERATED FROM TUMOR-INFILTRATING LYMPHOCYTES

Janet C. Siebert[1], Sachin Puri[2], Tarsem Moudgil[2], William Miller[2], Edwin B. Walker[2], Carlo Bifulco[2], Brendan D. Curti[2], Walter J. Urba[2], Bernard A. Fox[2]

[1]*CytoAnalytics, Denver, CO*

[2]*Robert W. Franz Cancer Research Center, Earle A. Chiles Research Institute, Providence Cancer Center, Portland, OR*

14 IMPROVED PERSISTENCE AND IN VIVO ANTITUMOR EFFICACY OF HUMAN T CELLS ENGINEERED TO EXPRESS A 4-1BB COSTIMULATED ALPHA-FOLATE RECEPTOR-SPECIFIC CHIMERIC IMMUNE RECEPTOR

Degang Song[1], Carmine Carpenito[2], Mathilde Poussin[1], Silvana Canevari[3], Carl H. June[2], George Coukos[1], Daniel J. Powell[1,2]

[1]*Department of Obstetrics and Gynecology, University of Pennsylvania, Philadelphia, PA*

[2]*Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA*

[3]*Department of Experimental Oncology and Molecular Medicine, Istituto Nazionale dei Tumori, Milan, Italy*

15 FRATRICIDE OF RECIPIENT LYMPHOCYTES EXPRESSING SURVIVIN-SPECIFIC TRANSGENIC T CELL RECEPTORS

Stefani Spranger[1], Matthias Leisegang[2], Susanne Wilde[1], Slavoljub Milosevic[1], Bernhard Frankenberger[1], Wolfgang Uckert[2,3], Dolores J. Schendel[1,4]

[1]*Institute of Molecular Immunology, Helmholtz Zentrum München, German Research Center for Environmental Health, Munich, Germany*

[2]*Max-Delbrück-Center for Molecular Medicine, Berlin, Germany*

[3]*Institute of Biology, Humboldt University Berlin, Berlin, Germany*

[4]*Clinical Cooperation Group Immune Monitoring, Helmholtz Zentrum München, German Research Center for Environmental Health, Munich, Germany*

16 ENRICHMENT OF AML-SPECIFIC T CELLS WITH SUPERIOR FUNCTIONAL CAPACITY AND TRANSGENIC RECEPTOR EXPRESSION FOR ADOPTIVE T CELL TRANSFER

Stefani Spranger, Susanne Wilde, Dolores J. Schendel, Bernhard Frankenberger

Institute of Molecular Immunology, Helmholtz Zentrum München, German Research Center for Environmental Health, Munich, Germany

17 DEVELOPMENT OF A NOVEL CHIMERIC ANTIGEN RECEPTOR TARGETING THE MELANOMA ANTIGEN gp75

Heather VanSeggelen[1], Galina Denisova[1], Carole Evelegh[1], Brian Rabinovich[2], Jonathan Bramson[1]

[1]*Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada*

[2]*MD Anderson Cancer Center, Houston, TX*

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18 GENERATING POTENT ANTI-TUMOR CD62LHIGH CD8+ T CELLS FOR ADOPTIVE IMMUNOTHERAPY
Shicheng Yang, Ling Zhang, Zhili Zheng, Tristen Park, Steven A. Rosenberg, Richard A. Morgan
Surgery Branch, National Cancer Institute, Bethesda, MD

19 IMPROVING ADOPTIVE CELL THERAPY BY BLOCKING THE TGFβ PATHWAY AT THE TUMOR ENVIRONMENT
Ling Zhang, Daniel Abate-Daga, Jeremy L. Davis, Nachimuthu Chinnasamy, Steven A. Rosenberg, Richard A. Morgan
Surgery Branch, Center for Cancer Research, NCI, NIH, Bethesda, MD

20 PROTEIN L: A NOVEL REAGENT FOR UNIVERSAL DETECTION OF CHIMERIC ANTIGEN RECEPTOR EXPRESSION BY FLOW CYTOMETRY
Zhili Zheng, Richard A. Morgan
Surgery Branch, National Institutes of Health, Bethesda, MD

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21 THE IMPACT OF STORAGE TEMPERATURE ON PBMC ISOLATION, VIABILITY AND IMMUNOLOGIC FUNCTION
Walter Olson[1,2], Mark E. Smolkin[3], Craig L. Slingluff[1,2]
[1]Surgery, University of Virginia, Charlottesville, VA
[2]Human Immune Therapy Center, University of Virginia, Charlottesville, VA
[3]Dept. of Public Health Sciences, University of Virginia, Charlottesville, VA

COUNTERING NEGATIVE REGULATION

22 IMMUNE PERFORMANCE PROFILE IN PANCREATIC ADENOCARCINOMA PATIENTS
Silvia Coin[1], Giuseppe Malleo[2], Martina Farronato[1], Nadia Brutti[1], Francesca Paolinelli[1], Claudio Bassi[2], Paolo Pederzoli[2], Vladia Monsurrò[1]
[1]Pathology and Diagnostic, University of Verona Medical School, Verona, Italy
[2]Surgery, University of Verona Medical School, Verona, Italy

23 REVERSAL OF IMMUNE SUPRESSION IN CANCER BY MANIPULATION OF TUMOR IRON METABOLISM
Robert L. Elliott, Xianpeng Jiang, Jonathan F. Head
Elliott, Elliott, Head Breast Cancer Research and Treatment Center, Baton Rouge, LA

24 INDUCTION OF DIFFERENT CD4+ T CELL SUBSETS BY HLA-DR- MYELOID DERIVED SUPPRESSOR CELLS AND CD14+ HLA-DR+ MONOCYTES
Tim F. Greten[1,2], Bastian Hoechst[1], Fei Zhao[1,2], Jaba Gamrekelashvili[1,2], Michael Manns[1], Firouzeh Korangy[1,2]
[1]Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany
[2]Medical Oncology Branch, NCI/NIH, Bethesda, MD

25 BLOCKADE OF THE PD-1 PATHWAY IMPROVES IMMUNOTHERAPY FOR MULTIPLE MYELOMA
William H. Hallett[1], William R. Drobyski[2], Bryon D. Johnson[1]
[1]Pediatrics, Medical Colllege of Wisconsin, Milwaukee, WI
[2]Medicine, Medical Colllege of Wisconsin, Milwaukee, WI

26 TLR LIGANDS INDUCE SOCS2 GENE EXPRESSION IN HUMAN MONOCYTE-DERIVED DENDRITIC CELL VIA NF-κB
Jin Hu[1], DaoHua Lou[1], Gunnar Norstedt[2], Ann-Charlotte Wikström[3], Ola Winqvist[1]
[1]Dept of Medicine, Karolinska Institute, Stockholm, Sweden
[2]Dept of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Sweden
[3]Department of Biosciences and Nutrition, Karolinska Institute, Stockholm, Sweden

27 RE-PROGRAMMING OF TUMOR DERIVED T REGULATORY CELLS
Mehmet O. Kilinc, Jamie L. Harden, Rachael B. Rowswell-Turner, Lauren P. Virtuoso
Microbiology and Immunology, State University of New York at Buffalo, Buffalo, NY

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COUNTERING NEGATIVE REGULATION (CONTINUED)

28 A STATE OF DOMINANT TOLERANCE IS RAPIDLY INDUCED WITH INTRAVENOUS DISSEMINATION BUT NOT WITH SUBCUTANEOUS IMPLANTATION IN A MURINE LEUKEMIA MODEL

Justin Kline[1], Long Zhang[1], Thomas F. Gajewski[1,2]

[1]*Medicine, University of Chicago, Chicago, IL*

[2]*Pathology, University of Chicago, Chicago, IL*

29 MHC CLASS II-DEPENDENT STRAIN-SPECIFIC DIFFERENCES IN PHENOTYPE AND FUNCTION OF TUMOR-INFILTRATING MYELOID CELLS ARE ASSOCIATED WITH DIFFERENTIAL OUTCOME OF TRAMP-PSA TUMOR GROWTH IN HLA-DR2b TRANSGENIC MOUSE MODEL

Elena N. Klyushnenkova[1,2], Surmeet Singh[2], Richard B. Alexander[1,2]

[1]*VA Maryland Health Care System, Baltimore, MD*

[2]*Surgery, University of Maryland, Baltimore, MD*

30 HUMAN MYELOID SUPPRESSOR CELL INDUCTION AND FUNCTIONAL ANALYSIS

Melissa G. Lechner, Alan L. Epstein

USC Keck School of Medicine, Los Angeles, CA

31 IL-6 AND IL-10 ARE CORRELATED WITH DISTINCT MDSC PROFILES IN PATIENTS WITH GASTROINTESTINAL MALIGNANCY

Gregory B. Lesinski, Bethany L. Mundy, Gregory S. Young, Todd Bauer, Elaine Binkley, Mark Bloomston, William E. Carson, Tanios Bekaii-Saab

Internal Medicine, The Ohio State University, Columbus, OH

32 EVALUATION OF MYELOID AND LYMPHOID REGULATORY CELL POPULATIONS IN THE PERIPHERAL BLOOD OF PATIENTS RECEIVING GM-CSF IN A VACCINE-BASED IMMUNOTHERAPY CLINICAL TRIAL

Walter C. Olson, Chantel McSkimming, Craig L. Slingluff

Surgery, University of Virginia, Charlottesville, VA

33 BLOCKADE OF TGF-β RECEPTOR TYPE I SIGNALING REDUCES THE ABILITY OF FOXP3+ CELLS TO INHIBIT PROLIFERATION AND IFN-γ PRODUCTION IN EFFECTORS CELLS

Magdalena J. Polanczyk, Daniel Haley, Edwin Walker, Emmanuel T. Akporiaye

Providence Medical Center, Earle A. Chiles Institute, Portland, OR

34 CHRONIC CHEMOIMMUNOTHERAPY MAINTAINS LONG-TERM ANTI-TUMOR CD8+ T EFFECTOR CELL ACTIVITY AND RESULTS IN THE CURE OF ADVANCED SPONTANEOUS TUMORS

Rachael B. Rowswell-Turner, Lauren P. Virtuoso, Tao Gu, Mehmet O. Kilinc, Nejat K. Egilmez

Microbiology and Immunology, University at Buffalo, School of Medicine and Biomedical Sciences, Buffalo, NY

35 CD4+FOXP3+ REGULATORY T CELLS ARE DEPENDENT ON PI3K PATHWAY ALLOWING FOR THEIR SELECTIVE INHIBITION

Raed N. Samara, Yujun Dong, Maher Abdalla, Mikayel Mkrtichyan, Laurent Ozbun, Yufei Jiang, Jiahua Qian, Samir Khleif

Vaccine Branch, NCI, Bethesda, MD

36 ASSESSING AND COUNTERING NEGATIVE IMMUNE REGULATION IN RENAL CELL CANCER PATIENTS - RESULTS OF A RANDOMIZED PHASE II TRIAL WITH IMA901

Steffen Walter[1], Norbert Hilf[1], Regina Mendrzyk[1], Dominik Maurer[1], Toni Weinschenk[1], Alexandra Kirner[1], Vincenzo Bronte[2], Susanna Mandruzzato[2], Graham Pawelec[3], Evelyna Derhovanessian[3], Arnulf Stenzl[3], Carsten Reinhardt[1], Harpreet Singh[1]

[1]*Immatics Biotechnologies, Tuebingen, Germany*

[2]*University of Padova, Padova, Italy*

[3]*University of Tuebingen, Tuebingen, Germany*

37 A SINGLE DOSE OF ONTAK ADMINISTRATION IS NOT SUFFICIENT TO DEPLETE TREGS IN STAGE IV MELANOMA PATIENTS

Yuanyuan Zha[1], Thomas F. Gajewski[1,2]

[1]*Human Immunologic Monitoring Facility, University of Chicago, Chicago, IL*

[2]*Department of Medicine, University of Chicago, Chicago, IL*

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DENDRITIC CELLS AND CANCER

38 DCS MATURED WITH LPS/PGE$_2$ INDUCE THE DIRECT DIFFERENTIATION OF NAÏVE CD8$^+$ T CELLS INTO CENTRAL-MEMORY CELLS

Erik Berk[1], Payal B. Watchmaker[1], Ravikumar Muthuswamy[1], Robbie B. Mailliard[1], Julie Urban[1], Pawel Kalinski[1,2,3]
[1]*Surgery, University of Pittsburgh Cancer Institute, Pittsburgh, PA*
[2]*Immunology, University of Pittsburgh, Pittsburgh, PA*
[3]*Infectious Diseases and Microbiology, University of Pittsburgh, Pittsburgh, PA*

39 DENTRITIC CELL-BASED CANCER THERAPEUTIC VACCINE TARGETING HAAH USING NANO-PARTICLES TO OVERCOME TOLERANCE AND AVOID AUTO-IMMUNE RESPONSE

Biswajit Biswas[1], Marjan Alaghmand[1], Hossein A. Ghanbari[2], Ilham Bensmail[1]
[1]*Cancer Vaccine, Panacea Pharmaceuticals, Gaithersburg, MD*
[2]*Cancer Diagnostic, Panacea Pharmaceuticals, Gaithersburg, MD*

40 GLOBAL GENE EXPRESSION ANALYSIS OF 15 kD GRANULYSIN STIMULATED MONOCYTES COMPARED TO GM-CSF

Luciano Castiello[1], Michael W. Finn[2], Francesco M. Marincola[1], Alan M. Krensky[2], Carol Clayberger[2], David F. Stroncek[1], Marianna Sabatino[1]
[1]*Department of Transfusion Medicine, NIH/CC, Washington, DC*
[2]*Laboratory of Cellular and Molecular Biology, NIH/NCI, Washington, DC*

41 FEATURES ASSOCIATED WITH SURVIVAL IN METASTATIC MELANOMA PATIENTS TREATED WITH PATIENT-SPECIFIC VACCINES CONSISTING OF PROLIFERATING AUTOLOGOUS TUMOR CELLS AND AUTOLOGOUS DENDRITIC CELLS

Robert O. Dillman[1], Gary B. Fogel[2], Andrew N. Cornforth[1], Carol DePriest[1]
[1]*Hoag Cancer Center, Newport Beach, CA*
[2]*Natural Selection, Inc, San Diego, CA*

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Lotte Engell-Noerregaard, Eva Ellebaek, Trine Zeeberg, Kirsten Nikolajsen, Per thor Straten, Mads H. Andersen, Inge Marie Svane
Department of Hematology and Department of Oncology, Centre for Cancer ImmuneTherapy (CCIT), University Hospital Herlev, Herlev, Denmark

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Lotte Engell-Noerregaard, Troels H. Hansen, Özcan Met, Mads H. Andersen, Inge Marie Svane
Department of Hematology and Department of Oncology, Centre for Cancer ImmuneTherapy (CCIT) University Hospital Herlev, Herlev, Denmark

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Steven E. Finkelstein, Dmitry Gabrilovich, Timothy Carey, Ingo Fricke, Daohai Yu, Mary Dunn, Adil Daud, Ronald DeConti, Scott Antonia, *Mayer Fishman*
Moffitt Cancer Center, Tampa, FL

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Brooke M. Helfer[1], Anthony Balducci[1], Robbie Mailliard[1,2], Eric Ahrens[3,4], Pawel Kalinski[5], Amy Wesa[1]
[1]*Research and Development, Celsense Inc, Pittsburgh, PA*
[2]*Infectious Deiseases and Microbiology, University of Pittsburgh, Pittsburgh, PA*
[3]*Biological Sciences, Carnegie Mellon University, Pittsburgh, PA*
[4]*Pittsburgh NMR Center for Biomedical Sciences, Carnegie Mellon University, Pittsburgh, PA*
[5]*Department of Surgery, Carnegie Mellon University, Pittsburgh, PA*

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[1]*Ovarian Cancer Research Center, School of Medicine, University of Pennsylvania, Philadelphia, PA*

[2]*Radiology, University of Pennsylvania, Philadelphia, PA*

[3]*Northwest Biotherapuetics, Bethesda, MD*

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H. K. Lyerly[1], JeanBernard LePecq[2], Zach Hartman[1], Tim Clay[1], Alain Delcayre[2], Yanal Murad[1]

[1]*Comprehensive Cancer Center, Duke University, Durham, NC*

[2]*Exothera, Menlo, CA*

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Moffitt Cancer Center, Tampa, FL

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Ke Pan, Hui Wang, Jing-jing Zhao, Jian-chuan Xia

State Key Laboratory of Oncology in Southern China, Sun Yat-sen University Cancer Center, Guangzhou, China

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Carlos A. Parra-López[1], Darnel A. Marchena[2], Mauricio Urquiza Martínez[3], Johanna Melo Cárdenas[3], Magnolia Vanegas[3], Manuel E. Patarroyo Murillo[3]

[1]*Microbiology and Immunology, Universidad Nacional de Colombia, Bogotá, Colombia*

[2]*Immunology and Oncology Research Group, Fundación Salud de los Andes, Bogotá, Colombia*

[3]*Virology Group, Fundación Instituto de Inmunología de Colombia (FIDIC), Bogotá, Colombia*

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Marimo Sato-Matsushita[1], Kimiyasu Yoneyama[1,2], Takafumi Nakamura[1], Yuko Kitagawa[2], Hideaki Tahara[1]

[1]*Institute of Medical Science, The University of Tokyo, Tokyo, Japan*

[2]*Department of Surgery, Keio University School of Medicine, Tokyo, Japan*

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Jaime M. Thomas[1], Zoltan Pos[1], Richard Y. Wang[1], Ena Wang[1], Paolo Lusso[2], Harvey J. Alter[1], Francesco M. Marincola[1]

[1]*Infectious Diseases and Immunogenetics Section, Department of Transfusion Medicine, Clinical Center - NIH, Bethesda, MD*

[2]*Laboratory of Immunoregulation, Immunopathogenesis Section, National Institute of Allergy and Infectious Diseases - NIH, Bethesda, MD*

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Julie Urban[1], Brooke Helfer[2], Steven Thorne[1], Eric Ahrens[3], Amy Wesa[2], Pawel Kalinski[1]

[1]*Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA*

[2]*Research and Development, Celsense, Inc., Pittsburgh, PA*

[3]*Biological Sciences, Carnegie Mellon University, Pittsburgh, PA*

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[1]Dept. of Medical Oncology, VU University Medical Center, Amsterdam, Netherlands
[2]Dept. of Pathology, VU University Medical Center, Amsterdam, Netherlands
[3]Dept. of Surgical Oncology, VU University Medical Center, Amsterdam, Netherlands

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[1]NIH, Bethesda, MD
[2]Virginia Commonwealth University, Massey Cancer Center, Richmond, VA

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San Raffaele Scientific Institute, Milan, Italy

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Gulsun Erdag[1], Jochen T. Schaefer[1], Mark E. Smolkin[2], James W. Patterson[1], Gina R. Petroni[2], Craig L. Slingluff[3]
[1]Pathology, University of Virginia, Charlottesville, VA
[2]Public Health Sciences, University of Virginia, Charlottesville, VA
[3]Surgery, University of Virginia, Charlottesville, VA

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Gulsun Erdag[1], Jochen T. Schaefer[1], Mark E. Smolkin[2], James W. Patterson[1], Gina R. Petroni[2], Craig L. Slingluff[3]
[1]Pathology, University of Virginia, Charlottesville, VA
[2]Public Health Sciences, University of Virginia, Charlottesville, VA
[3]Surgery, University of Virginia, Charlottesville, VA

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Mohan Karkada[1,2], Tara Quinton[1], Genevieve Weir[1], Drew Debay[3], Sarah LeBlanc[3], Chris Bowen[3], Marc Mansour[1]
[1]Cellular Immunology, Immunovaccine Inc., Halifax, NS, Canada
[2]Microbiology and Immunology, Dalhousie University, Halifax, NS, Canada
[3]Biodiagnostics, National Research Council, Halifax, NS, Canada

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Yong-Man Kim, Shin Wha Lee, Dae-Yeon Kim, Jong-Hyeok Kim, Joo-Hyun Nam, Young-Tak Kim
Department of Obstetrics and Gynecology, University of Ulsan, Asan Medical Center, Seoul, Republic of Korea

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Beatrix Kotlan[1], Mepur H. Ravindranath[2], Mark C. Glassy[3]
[1]Center of Surgical and Molecular Tumorpathology, National Institute of Oncology, Budapest, Hungary
[2]Terasaki Foundation Laboratory, Los Angeles, CA
[3]Nascent Biologics Inc., San Diego, CA

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[1]*Surgery, University of Pittsburgh, Pittsburgh, PA*

[2]*Infectious Diseases and Microbiology, University of Pittsburgh, Pittsburgh, PA*

[3]*Statistics, University of Pittsburgh, Pittsburgh, PA*

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Brooke Helfer[1], Anthony Balducci[1], Robbie Mailliard[1,2], *Amy Wesa*[1]

[1]*Research and Development, Celsense, Inc., Pittsburgh, PA*

[2]*Department of Infectious Diseases and Microbiology, University of Pittsburgh, Pittsburgh, PA*

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[1]*The Ohio State University, Columbus, OH*

[2]*Cleveland Clinic Children's Hospital, Cleveland, OH*

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William Buchser[1,2], Thomas Laskow[1,2], Tara Loux[1,2], Pawel Kalinski[1,2], Per Basse[1,2], Herbert Zeh[1,2], Michael Lotze[1,2]

[1]*Surgical Oncology, University of Pittsburgh, Pittsburgh, PA*

[2]*UPCI, University of Pittsburgh, Pittsburgh, PA*

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Valeria De Giorgi[1], Maria Libera Ascierto[1], Zoltan Pos[1], Luigi Buonaguro[2], Franco M. Buonaguro[2], Ena Wang[1], Francesco M. Marincola[1]

[1]*Department of Transfusion Medicine, National Institutes of Health, Bethesda, MD*

[2]*Laboratory of Molecular Biology and Viral Oncogenesis & AIDS Reference Center, Istituto Nazionale Tumori "Fondazione G. Pascale", Naples, Italy*

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Michael J. Gough[1], Benjamin L. Cottam[1], Cynthia Nguyen[1], Marka R. Crittenden[1,2]

[1]*Earle A. Chiles Research Institute, Providence Portland Medical Center, Portland, OR*

[2]*The Oregon Clinic, Portland, OR*

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[1]*Oncology, Centre Hospitalier de l'Université de Montréal Research Center (CRCHUM), Montréal, QC, Canada*

[2]*Urology, Centre Hospitalier de l'Université de Montréal (CHUM), Montréal, QC, Canada*

[3]*Thoracic Surgery, Centre Hospitalier de l'Université de Montréal (CHUM), Montréal, QC, Canada*

[4]*Pathology, Centre Hospitalier de l'Université de Montréal (CHUM), Montréal, QC, Canada*

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Gary Kohanbash[1], Arlan H. Mintz[1], Kayla McKaveney[1], Heather A. McDonald[1], John R. Ohlfest[2], Hideho Okada[1], Mitsugu Fujita[1]

[1]*University of Pittsburgh, Pittsburgh, PA*

[2]*University of Minnesota, Minneapolis, MN*

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Smita C. Pawar
Genetics, Osmania University, Hyderabad, India

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Karsten A. Pilones[1], Noriko Kawashima[1], James Babb[2], Sandra Demaria[1]
[1]Pathology, NYU School of Medicine, New York, NY
[2]Radiology, NYU School of Medicine, New York, NY

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Hong Qin[1], Soung-chul Cha[1], Xiao-Feng Qin[2], Yong-Jun Liu[2], Larry W. Kwak[1]
[1]Lymphoma and Myeloma, The University of Texas, MD Anderson Cancer Center, Houston, TX
[2]Immunology, The University of Texas, MD Anderson Cancer Center, Houston, TX

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University of Chicago, Chicago, IL

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Lazar Vujanovic[1,2], Wenners Ballard[3], Nikola L. Vujanovic[1,3,4], Lisa H. Butterfield[2,3,5]
[1]University of Pittsburgh Cancer Institute, Pittsburgh, PA
[2]Medicine, University of Pittsburgh, Pittsburgh, PA
[3]Immunology, University of Pittsburgh, Pittsburgh, PA
[4]Pathology, University of Pittsburgh, Pittsburgh, PA
[5]Surgery, University of Pittsburgh, Pittsburgh, PA

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Prakash Thapa[1], Pramod Nehete[2], Hong He[3], Bharti Nehete[2], Stephanie Buchl[2], Lara M. Bull[4], Jianfei Qian[5], Qing Yi[5], Hongzhou Lu[6], Haoxiang Zhu[7], Jiming Zhang[7], Peng G. Wang[8], Roberto C. Arduino[9], Jagan Sastry[2,3,10], *Dapeng Zhou*[1,10]
[1]Melanoma Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX
[2]Veterinary Sciences, University of Texas MD Anderson Cancer Center, Houston, TX
[3]Immunology, University of Texas MD Anderson Cancer Center, Houston, TX
[4]Clinical Epidemiology and Outcomes Division, Baylor College of Medicine, Houston, TX
[5]Lymphoma and Myeloma, University of Texas MD Anderson Cancer Center, Houston, TX
[6]Shanghai Public Health Clinical Center, Shanghai, China
[7]Laboratory of Viral Hepatitis, Huashan Hospital, Shanghai Medical Collge, Shanghai, China
[8]Chemistry and Biochemistry, Ohio State Univeristy, Columbus, OH
[9]Section of Infectious Diseases, University of Texas Health Science Center at Houston School of Medicine, Houston, TX
[10]Graduate School of Biological Sciences, University of Texas Health Science Center at Houston, Houston, TX

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Cindy L. Zuleger[1], Michael D. Macklin[1], Michael A. Newton[1,2], Mark R. Albertini[1,3,4]
[1]Univiersity of Wisconsin Carbone Comprehensive Cancer Center, University of Wisconsin School of Medicine and Public Health, Madison, WI
[2]Statistics, University of Wisconsin School of Medicine and Public Health, Madison, WI
[3]Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI
[4]William S. Middleton Memorial Veteran's Hopital, Madison, WI

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[1]*New York University Cancer Institute, NY, NY*

[2]*Graceway Pharmaceuticals, Exton, PA*

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[1]*Washington University School of Medicine, St. Louis, MO*

[2]*University of Arkansas for Medical Sciences, Little Rock, AR*

[3]*Brigham and Women's Hospital, Boston, MA*

[4]*SciClone Pharmaceuticals, Foster City, CA*

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Postgraduate Medical School, University of Surrey, Guildford, United Kingdom

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Postgraduate Medical School, University of Surrey, Guildford, United Kingdom

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[1]*Fundación Ciencia y Tecnología para el Desarrollo, Santiago, Chile*

[2]*Research and Development, Biosonda Corporation, Santiago, Chile*

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[1]*Department of Trasfusion Medicine, National Institute of Health, Bethesda, MD*

[2]*Genelux Corporation, San Diego, CA*

[3]*National Cancer Institute, Bethesda, MD*

[4]*Fox Chase Cancer Center, Philadelphia, PA*

[5]*Department of General Pathology, Naples, Italy*

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[1]*Clinical Tumor Immune-Biology Unit, Ludwig Institute for Cancer Research Ltd., Lausanne, Switzerland*

[2]*University Hospital Center, University of Lausanne (CHUV), Lausanne, Switzerland*

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Dannie Bernard[1], Julian J. Lum[2], Yonghong Wan[1], Jonathan L. Bramson[1]

[1]*Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada*

[2]*Deeley Research Center, BC Cancer Agency, Vancouver Island, BC, Canada*

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George G. Chen, Chris Z. Zhang, Paul B. Lai

The Chinese University of Hong Kong, Shatin, NT, Hong Kong

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[1]*Fujian Tumor Hospital, Fuzhou, China*

[2]*Biotech Pharmaceutical Co Ltd, Beijing, China*

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Arvind Chhabra

Department of *Medicine, University of Connecticut Health Center, Farmington, CT*

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Arvind Chhabra, Bijay Mukherji

Department of *Medicine, University of Connecticut Health Center, Farmington, CT*

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[1]*Cancer Bioimmunotherapy Unit, Centro di Riferimento Oncologico di Aviano, Aviano, Italy*

[2]*Division of Medical Oncology and Immunotherapy, University Hospital of Siena, Siena, Italy*

[3]*SuperGen, Dublin, CA*

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Michael A. Curran[1], Myoung-joo Kim[1], Aymen Al-Shamkhani[2], James P. Allison[1]

[1]*Howard Hughes Medical Institute, Department of Immunology, Memorial Sloan-Kettering Cancer Center, New York, NY*

[2]*Tenovus Research Laboratory, Southampton General Hospital, Southampton, United Kingdom*

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[1]*Medical Oncology and Immunotherapy, University Hospital-ITT, Siena, Italy*

[2]*Medical Oncology A, IST, Genoa, Italy*

[3]*Melanoma and Sarcoma, IEO, Milan, Italy*

[4]*Northern Institute for Cancer Research, Newcastle University, Newcastle upon Tyne, United Kingdom*

[5]*Medical Oncology, IOV, Padua, Italy*

[6]*Immunotherapy and Somatic Cell Therapy, IRST, Meldola, Italy*

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T. Daniels[1], G. Helguera[2], R. Quintero[1], E. Ortiz-Sánchez[1], J. Rodríguez[1], B. Schultes[3], M. Penichet[1], C. Nicodemus[3]

[1]*UCLA, Los Angeles, CA*

[2]*CONICET & FFyB, University of Buenos Aires, Buenos Aires, Argentina*

[3]*Advanced Immune Therapeutics, Charlestown, MA*

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Soheir R. Demian[1], Mona El-Sayed[1], Enas Ali[2], Bassma Mersal[1]

[1]*Immunology, Medical Research Institute,Alexandria University, Alexandria, Egypt*

[2]*Medical Research Institute,Alexandria University, Alexandria, Egypt*

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Evelyna Derhovanessian[1], Henning Zelba[1], Steffen Walter[2], Andrea Groeger[1], Benjamin Weide[3], Claus Garbe[3], Harpreet Singh[2], Graham Pawelec[1]

[1]*Center for Medical Research, University of Tuebingen Clinical School, Tuebingen, Germany*

[2]*Immatics Biotechnologies GmbH, Tuebingen, Germany*

[3]*Department of Dermatooncology, University of Tuebingen Clinical School, Tuebingen, Germany*

95 EARLY DEVELOPMENT OF CDX-1401, A NOVEL VACCINE TARGETING NY-ESO-1 TO THE DENDRITIC CELL RECEPTOR DEC-205, IN COMBINATION WITH TOLL-LIKE RECEPTOR AGONISTS

Madhav V. Dhodapkar[1], Mario Sznol[1], Ding Wang[2], Ellen Chuang[3], Richard Carvajal[4], Harriet Kluger[1], Venky Ramakrishna[5], Laura Vitale[5], Thomas Davis[5], Ralph M. Steinman[6], Tibor Keler[5]

[1]*Yale Cancer Center, New Haven, CT*

[2]*Henry Ford Health Systems, Detroit, MI*

[3]*Weill Cornell Medical College, New York, NY*

[4]*Memorial Sloan-Kettering Cancer Center, New York, NY*

[5]*Celldex Therapeutics, Needham, MA*

[6]*Rockefeller University, New York, NY*

96 UNRAVELING THE PARADOXES OF ATM RESENSITIZED DYNAMICS IN LNCaP CELL LINE VIA EPIGALLOCATECHIN-3-GALLATE

Ammad A. Farooqi, Shahzad Bhatti

Molecular Oncology, IMBB, Lahore, Pakistan

97 IMMUNE RESPONSE AGAINST DKK1 IN COMMON CANCERS

Marie-Andree Forget[1], Simon Turcotte[2], Rejean Lapointe[1]

[1]*Oncology, Centre Hospitalier de l'Université de Montréal (CRCHUM), AND Institut du Cancer de Montréal, Montreal, QC, Canada*

[2]*Surgery branch, National Cancer Institute/NIH, Bethesda, MD*

98 DEVELOPMENT OF A NEW FORMULATION TO ENABLE SUSTAINED IL-2 RELEASE IN VIVO

David M. Foureau[1,2], Chase P. Jones[1], Katherine Weaver[3], Regina M. Vrikkis[1,3], Douglas R. MacFarlane[4], Iain H. Mckillop[1,2], Jonathan C. Salo[2], Gloria D. Elliott[3]

[1]*General Surgery Research, Carolinas Medical Center, Charlotte, NC*

[2]*Blumenthal Cancer Center, Carolinas Medical Center, Charlotte, NC*

[3]*Department of Mechanical Engineering, UNC Charlotte, Charlotte, NC*

[4]*School of Chemistry, Monash University, Monash, VIC, Australia*

99 HISTONE MODIFICATION UPREGULATES EXPRESSION OF IL-13Rα2 IN HUMAN PANCREATIC CANCER CELLS AND ENHANCES THE EFFECTIVENESS OF IL-13 RECEPTOR TARGETED IMMUNOTOXIN IL-13-PE IN ANIMAL MODEL OF HUMAN PANCREATIC CANCER

Toshio Fujisawa, Bharat H. Joshi, Raj K. Puri

Division of Cellular Gene Therapy, Center for Biologics Evaluation & Research/FDA, Bethesda, MD

100 COX2 BLOCKADE SUPPRESSES GLIOMAGENESIS BY INHIBITING CCL2-MEDIATED ACCUMULATION OF MYELOID-DERIVED SUPPRESSOR CELLS IN GLIOMA SITES

Mitsugu Fujita[1], Gary Kohanbash[1], Heather A. McDonald[1], Louis Delamarre[1], Stacy A. Decker[2], John R. Ohlfest[2], Hideho Okada[1]

[1]*Neurological Surgery, University of Pittsburgh, Pittsburgh, PA*

[2]*Pediatrics, University of Minnesota, Minneapolis, MN*

101 ELEVATED MDSCS IN PANCREATIC AND ESOPHAGO-GASTRIC CANCER PATIENTS CORRELATES WITH POOR PROGNOSIS

Nicola E. Annels[1], *Rachel F. Gabitass*[1,2], Hardev Pandha[1], Gary W. Middleton[2]

[1]*Postgraduate Medical School, University of Surrey, Guildford, United Kingdom*

[2]*St Luke's Cancer Centre, Royal Surrey County Hospital, Guildford, United Kingdom*

Poster #: *(primary authors listed in italics)*

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102 SUMMARY ANALYSIS OF BRAIN CANCER PATIENTS TREATED WITH PRITUMUMAB

Mark C. Glassy
[1]*Integrated Medical Sciences Association Foundation, San Diego, CA*
[2]*Nascent Biologics, Inc, San Diego, CA*

103 GENE EXPRESSION SIGNATURE ALLOWS PREDICTION OF NK CELL CONTENT IN TISSUE AND SURVIVAL OF RENAL CELL CARCINOMA PATIENTS

Judith Hosse[1], Alexander Buchner[2,3], Rainer Riesenberg[2], Petra U. Prinz[1], Sabine I. Siegert[4], Robert Kammerer[5], Peter J. Nelson[6], Elfriede Noessner[1]
[1]*Helmholtz Zentrum München - German Research Center for Environmental Health, Institute of Molecular Immunology, Munich, Germany*
[2]*Ludwig Maximilians University, Tumor Immunology Laboratory, LIFE Center, Munich, Germany*
[3]*Ludwig Maximilians University, Department of Urology, University Clinic Grosshadern, Munich, Germany*
[4]*Ludwig Maximilians University, Institute of Pathology, Munich, Germany*
[5]*Friedrich-Loeffler-Institut, Institute of Immunology, Tübingen, Germany*
[6]*Ludwig Maximilians University, Clinical Biochemistry, Medical Policlinic, Munich, Germany*

104 ENHANCED ANTI-TUMOR EFFECT OF COMBINATION THERAPY WITH ANTI-CD40 ANTIBODY AND THE MTOR KINASE INHIBITOR AZD8055

Qun Jiang[1], Jonathan M. Weiss[1], John R. Ortaldo[1], Timothy Back[1], Sylvie Guichard[2], Anjan Thakurta[2], Robert H. Wiltrout[1]
[1]*NCI-Frederick, Frederick, MD*
[2]*AstraZeneca, Rockville, MD*

105 TARGETING OF MORTALIN-MUTANT p53 INTERACTIONS BY MORTALIN shRNA LEADS TO SELECTIVE APOPTOTIC DEATH OF HUMAN HEPATOCELLULAR CARCINOMA

Wen Jing Lu[1], Nikki P Lee[1], Ronnie T.P. Poon[1], Sunil C. Kaul[2], Renu Wadhwa[2], John M. Luk[3]
[1]*Surgery, The University of Hong Kong, Hong Kong, Hong Kong*
[2]*National Institute of Advanced Industrial Science & Technology (AIST), Tsukuba, Japan*
[3]*National University of Singapore, Singapore, Singapore*

106 DEVELOPING A NEOADJUVANT MURINE SURGICAL MODEL OF CANCER USING VESICULAR STOMATITIS VIRUS

Agnieszka Kus[1,2], Lisa Mackenzie[1], Chantal Lemay[1,2], Kelley Parato[1], Harold Atkins[1], John Bell[1,2], Rebecca Auer[1]
[1]*Ottawa Hospital Research Institute, Ottawa, ON, Canada*
[2]*University of Ottawa, Ottawa, ON, Canada*

107 THE IMMUNE ENHANCING EFFECTS OF IL-7 ON HUMAN T CELLS ARE DUE TO ACTIVATION OF STAT SIGNALING BUT NOT REPRESSION OF Cbl-b

Guenther Lametschwandtner[1], Thomas Gruber[2], Gottfried Baier[2], Dominik Wolf[3], Isabella Haslinger[1], Manfred Schuster[1], Hans Loibner[1]
[1]*Apeiron Biologics AG, Vienna, Austria*
[2]*Experimental Cell Genetics Unit, Innsbruck Medical University, Innsbruck, Austria*
[3]*Tyrolean Cancer Research Institute, Innsbruck Medical University, Innsbruck, Austria*

108 OVARIAN CANCER CELLS UBIQUITOUSLY EXPRESS HER-2 AND CAN BE DISTINGUISHED FROM NORMAL OVARY BY GENETICALLY REDIRECTED T CELLS

Evripidis Lanitis[1,2], Ian Hagemann[3], Degang Song[1], Lin Zhang[1], Richard Carroll[4], Raphael Sandaltzopoulos[2], George Coukos[1], Daniel J. Powell Jr[1]
[1]*OCRC, UPENN, Philadelphia, PA*
[2]*MBG, Democritus University of Thrace, Alexandroupolis, Greece*
[3]*Pathology & Lab Medicine, UPENN, Philadelphia, PA*
[4]*AFCRI, UPENN, Philadelphia, PA*

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109 CLINICAL AND IMMUNOLOGICAL ANALYSIS OF A PHASE I TRIAL EVALUATING MVA-BN®-PRO IN PATIENTS WITH NON-METASTATIC CASTRATION RESISTANT PROSTATE CANCER

Fatema A. Legrand[1], David McLeod[2], David Bilhartz[3], Marc Gittleman[4], George Adams[5], James Cochran[6], Richard Reiling[7], Henry Ruiz[8], Gary Karlin[9], Rachel Owen[1], Anh-Tuan Nguyen[1], Olivia Hwang[1], Gayatri Paranjpe[1], Leilani Fernandez[1], Leslie Brand[1], Reiner Laus[1], Alain Delcayre[1], Wayne Godfrey[1]

[1]BN ImmunoTherapeutics, Mountain View, CA
[2]Walter Reed Army Medical Center, Washington, DC
[3]Urology Associates P.C., Nashville, TN
[4]South Florida Medical Research, Aventura, FL
[5]Urology Centers of Alabama P.C., Birmingham, AL
[6]Urology Clinics of North Texas, Dallas, TX
[7]Presbyterian Hospital Center for Cancer Research, Charlotte, NC
[8]Urology Associates of South Texas, McAllen, TX
[9]Lawrenceville Urology, Lawrenceville, NJ

110 EXTENDED IMMUNOLOGICAL ANALYSIS OF TWO PHASE 1 CLINICAL TRIALS OF MVA-BN®-HER2 IN HER-2 OVEREXPRESSING METASTATIC BREAST CANCER PATIENTS

Fatema A. Legrand[1], Rachel Owen[1], Michael Delacher[1], Anh-Tuan Nguyen[1], Ulf Reimer[2], Holger Wensucht[2], Reiner Laus[1], Wayne Godfrey[1], Alain Delcayre[1]

[1]BN ImmunoTherapeutics, Mountain View, CA
[2]JPT Peptide Technologies GmbH, Berlin, Germany

111 ANALYSIS OF INTRA-TUMOR IMMUNOLOGICAL CHANGES INDUCED BY IMMUNIZATION WITH TWO-COMPONENT MESSENGER RNA-BASED ANTI-CANCER VACCINES

Christina Lorenz, Mariola Fotin-Mleczek, Katharina M. Duchardt, Karl-Josef Kallen
CureVac GmbH, Tübingen, Germany

112 IMMUNOMODULATION OF T CELL-MEDIATED ACTIVITY BY CANCER STEM CELLS ISOLATED FROM HUMAN GLIOBLASTOMA

Cristina Maccalli[1], Tiziano Di Tomaso[1], Ena Wang[2], Stefania Mazzoleni[3], Gloria Sovena[1], Rossella Galli[3], Francesco M. Marincola[2], Giorgio Parmiani[1]

[1]Unit of Immuno-biotherapy of Solid Tumors, San Raffaele Foundation Scientific Institute, Milan, Italy
[2]Department of Transfusion Medicine, National Institutes of Health, Bethesda, MD
[3]Neural Stem Cell Unit, San Raffaele Foundation Scientific Institute, Milan, Italy

113 ANTI-TUMOR EFFICACY OF MVA-BN®-HER2 IS MEDIATED BY HER-2-SPECIFIC TH1- IMMUNITY AND THE CONTROL OF TUMOR-INDUCED IMMUNOSUPPRESSION

Stefanie J. Mandl, Ryan Rountree, Katie Dalpozzo, Lisa Do, John Lombardo, Peter Schoonmaker, Thierry Giffon, Reiner Laus, Alain Delcayre
BN-ImmunoTherapeutics, Mountain View, CA

114 ALLOGENEIC TRANSPLANTATION AND TUMOR-SPECIFIC VACCINATION PROMOTE INFILTRATION AND ERADICATION OF ADVANCED PROSTATE CANCER

Teresa Manzo[1,2,3], Rodrigo Hess Michelini[1,2], Massimo Freschi[4], Maurilio Ponzoni[4], Elizabeth Simpson[5], Matteo Bellone[1,6], Anna Mondino[1,2]

[1]Program in Immunology and Bio-Immuno-gene therapy of Cancer, San Raffaele Scientific Institute, Milano, Italy
[2]Lymphocyte Activation Unit, San Raffaele Scientific Institute, Milano, Italy
[3]Vita-Salute San Raffaele University, San Raffaele Scientific Institute, Milano, Italy
[4]Department of Pathology, San Raffaele Scientific Institute, Milano, Italy
[5]Department of Immunology, Hammersmith Hospital, Imperial College, London, United Kingdom
[6]Cellular Immunology Unit, San Raffaele Scientific Institute, Milano, Italy

Poster #: *(primary authors listed in italics)*

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115 IPILIMUMAB MONOTHERAPY IN MELANOMA PATIENTS WITH BRAIN METASTASES-UPDATE OF A PHASE 2 STUDY

K. Margolin[1], O. Hamid[2], D. McDermott[3], I. Puzanov[4], M. Sznol[5], J. I. Clark[6], J. Wolchok[7], F. S. Hodi[8], K. Heller[9], D. Lawrence[10]
[1]*University of Washington, Seattle, WA*
[2]*The Angeles Clinic and Research Institute, Santa Monica, CA*
[3]*Beth Israel Deaconess Medical Center, Boston, MA*
[4]*Vanderbilt-Ingram Cancer Center, Nashville, TN*
[5]*Yale Cancer Center, New Haven, CT*
[6]*Loyola University Medical Center, Maywood, IL*
[7]*Memorial Sloan-Kettering Cancer Center, New York, NY*
[8]*Dana-Farber Cancer Institute, Boston, MA*
[9]*Bristol-Myers Squibb Company, Plainsboro, NJ*
[10]*Massachusetts General Hospital, Boston, MA*

116 CLINICAL AND IMMUNOLOGICAL RESPONSE IN CASTRATION-RESISTANT PROSTATE CANCER PATIENTS TREATED WITH AN EPIDERMAL GROWTH FACTOR-BASED VACCINE

Zaima Mazorra[1], Xitlally Popa[1], Beatriz García[1], Camilo Rodríguez[1], Jorge García[2], Antonio Bouzó[2], Joaquín González[3], Karla Fuentes[1], Zuyen González[1], Carmen Viada[1], Tania Crombet[1]
[1]*Clinical Research Direction, Center of Molecular Immunology, Havana, Cuba*
[2]*National Institute of Radiobiology and Oncology, Havana, Cuba*
[3]*Hermanos Ameijeiras Hospital, Havana, Cuba*

117 A PARADIGM SHIFT IN OVARIAN CANCER IMMUNOTHERAPY: BREAKING IMMUNE TOLERANCE REDIRECTING T HELPER DIFFERENTIATION WITH CANCER/TESTIS ANTIGEN VACCINATION

Leonardo Mirandola[1,2], Yuefei Yu[1], Marjorie R. Jenkins[3,2], Everardo Cobos[1,2], Martin J. Cannon[4], Caroline Chapman[5], W. Martin Kast[6], Maurizio Chiriva-Internati[1,2]
[1]*Division of Hematology & Oncology, Texas Tech University Health Sciences Center and Southwest Cancer Treatment and Research Center, Lubbock, TX*
[2]*The Laura W. Bush Institute for Women's Health and Center for Women's Health and Gender-Based Medicine, Amarillo, TX*
[3]*Departments of Internal Medicine and Obstetrics & Gynecology, Texas Tech University Health Sciences Center, Amarillo, TX*
[4]*Department of Microbiology and Immunology, University of Arkansas for Medical Sciences, Little Rock, AR*
[5]*Division of Breast Surgery, The University of Nottingham, Nottingham, United Kingdom*
[6]*Departments of Molecular Microbiology & Immunology and Obstetrics & Gynecology, Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA*

118 CHARACTERIZING HOST RESPONSIVENESS TO INTERFERON BY EX VIVO INDUCTION OF INTERFERON-RESPONSIVE mRNAS

Masato Mitsuhashi[1], Taolin Yi[2], Emese Hollovary[2], Barbara Jacobs[2], Ernest C. Borden[2]
[1]*Hitachi Chemical Research Center, Inc., Irvine, CA*
[2]*Cleveland Clinic Taussig Cancer Institute, The Cleveland Clinic, Cleveland, OH*

119 PEGYLATED ARGINASE I: A POTENTIAL THERAPEUTIC APPROACH IN T-ALL

Kevin Morrow[1], Claudia Hernandez[1], Jovanny Zabaleta[1], Rosa Sierra[1], John Cole[2], Paulo Rodriguez[1]
[1]*LSU Health Sciences Center, New Orleans, LA*
[2]*Ochsner Clinic Foundation, New Orleans, LA*

120 COMPARISON OF GMP AND NON-GMP ENZYMES FOR THE ISOLATION OF TUMOR CELLS AND TUMOR-INFILTRATING LYMPHOCYTES FOR THE IMMUNOTHERAPY OF MELANOMA

Tarsem L. Moudgil[1], Todd Coffey[1], Sachin Puri[1], Christopher Fountain[1], William Wood[1], John Vetto[2], Carlo Bifulco[1], Brendan Curti[1], Walter J. Urba[1], Bernard Fox[1,3]
[1]*Robert W. Franz Cancer Research Center, Earle A. Chiles Research Institute, Providence Cancer Center, Portland, OR*
[2]*Department of Surgery, OHSU, Portland, OR*
[3]*Department of Molecular Microbiology and Immunology, OHSU, Portland, OR*

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121 EFFECT OF IgE ON CANCER

M. Muthumariapan

BioSciences Research Institute, Chennai, India

122 IPILIMUMAB IMPROVES OVERALL SURVIVAL IN PREVIOUSLY TREATED, ADVANCED MELANOMA PATIENTS WITH GOOD AND POOR PROGNOSTIC FACTORS

Steven J. O'Day[1], David F. McDermott[2], Walter J. Urba[3], Jedd D. Wolchok[4], Caroline Robert[5], John B. Haanen[6], Reinhard Dummer[7], Marianne Messina[8], Axel Hoos[8], F. Stephen Hodi[9]

[1]*The Angeles Clinic and Research Institute, Los Angeles, CA*

[2]*Beth Israel Deaconess Medical Center, Boston, MA*

[3]*The Earle A. Chiles Research Institute, Portland, OR*

[4]*Memorial Sloan-Kettering Cancer Center, New York, NY*

[5]*Institut Gustave Roussy, Villejuif, France*

[6]*Netherlands Cancer Institute, Amsterdam, Netherlands*

[7]*University Hospital, Zürich, Switzerland*

[8]*Bristol-Myers Squibb, Wallingford, CT*

[9]*Dana-Farber Cancer Institute, Boston, MA*

123 DESIGNING A NEW CHIMERIC ANTIGEN RECEPTOR FOR THE TUMOR ANTIGEN ALK

Rimas J. Orentas[1], Anton Wellstein[2], Richard A. Morgan[3], Crystal L. Mackall[1]

[1]*Pediatric Oncology Branch, NCI, NIH, Bethesda, MD*

[2]*Pharmacology and Oncology, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC*

[3]*Surgery Branch, NCI, NIH, Bethesda, MD*

124 SUBCLONING AND ANTIVIRAL PHENOTYPE SEGREGATION IN PANCREATIC CANCER CELL LINE SUBPOPULATIONS

Francesca Paolinelli[1,2], Daniela Marzioni[2], Silvia Coin[1], Martina Farronato[1], Teresa Lorenzi[2], Nadia Brutti[1], Giulio Innamorati[1], Mario Castellucci[2], Vladia Monsurrò[1]

[1]*Pathology and Diagnostic, University of Verona, Verona, Italy*

[2]*Pathology and Innovative Therapy, Università Politecnica delle Marche, Ancona, Italy*

125 EVALUATION OF HER2/NEU AND FOLATE BINDING PROTEIN PEPTIDES IN IMMUNOTHERAPY FOR ENDOMETRIAL CANCER

Ritesh Patil[1], Guy T. Clifton[2,3], Cathy Ciano[3], Athena Zacharia[3], Mohamed Mursal[3], Yusuf Jama[3], Thomas Krivak[4], G. Larry Maxwell[5], George Peoples[2,3], Sathibalan Ponniah[3]

[1]*Joyce Murtha Breast Care Center, Windber Medical Center, Windber, PA*

[2]*Department of Surgery, Brooke Army Medical Center, Fort Sam Houston, TX*

[3]*Cancer Vaccine Development Program, Department of Surgery, Uniformed Services University of the Health Sciences, United States Military Cancer Institute, Bethesda, MD*

[4]*University of Pittsburgh, Pittsburgh, PA*

[5]*Gynecologic Cancer Translation Research Center, Department of Obstetrics and Gynecology, Walter Reed Army Medical Center, Washington, DC*

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126 FREQUENCY OF CIRCULATING REGULATORY T CELLS AND TUMOR-SPECIFIC EFFECTOR T CELLS IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA UNDERGOING THERAPEUTIC TUMOR CELL VACCINATION

Heike Pohla[1,2], Alexander Buchner[1,3], Bernhard Frankenberger[2], Birgit Stadlbauer[1], Udo Baron[4], Sven Olek[4], Ronald Frank[5], Alfons Hofstetter[1], Ralph Oberneder[6], Antonio Pezzutto[7], Thomas Blankenstein[8], Dolores J. Schendel[2]

[1]*Laboratory of Tumor Immunology, LIFE Center, Ludwig-Maximilians University, Munich, Germany*

[2]*Institute of Molecular Immunology and Clinical Cooperation Group Immune Monitoring, Helmholtz Zentrum München, German Research Center for Environmental Health, Munich, Germany*

[3]*Department of Urology, Ludwig-Maximilians University, Munich, Germany*

[4]*Epiontis GmbH, Berlin, Germany*

[5]*Department of Chemical Biology, Helmholtz Center for Infection Research, Braunschweig, Germany*

[6]*Urological Clinic, Munich-Planegg, Germany*

[7]*Department of Hematology, Oncology, and Tumor Immunology, Charité-University Medicine, Campus Virchow, Berlin, Germany*

[8]*Institute of Immunology, Charité-University Medicine, Berlin, Germany*

127 ARTIFICIAL NEURAL NETWORK AND IMMUNE MONITORING ANALYSIS FOR PATIENTS WITH PROGRESSIVE CASTRATION-RESISTANT PROSTATE CANCER UNDERGOING THERAPEUTIC TUMOR CELL VACCINATION

Heike Pohla[1,2], Thomas H. Brill[3], Alexander Buchner[1], Hubert R. Kübler[4], Birgit Stadlbauer[1], Michael Osthoff[1], Udo Baron[5], Sven Olek[5], Tibor Schuster[6], Bernd Eisele[7], Falko Fend[8], Rudolf Hartung[4], Dolores J. Schendel[2], Bernd Gansbacher[3]

[1]*Laboratory of Tumor Immunology, LIFE Center, Ludwig-Maximilians University, Munich, Germany*

[2]*Institute of Molecular Immunology and Clinical Cooperation Group Immune Monitoring, Helmholtz Zentrum München, German Research Center for Environmental Health, Munich, Germany*

[3]*Institute for Experimental Oncology and Therapeutic Research, Technical University, Munich, Germany*

[4]*Department of Urology, Technical University, Munich, Germany*

[5]*Epiontis GmbH, Berlin, Germany*

[6]*Institute of Medical Statistics and Epidemiology, Technical University, Munich, Germany*

[7]*VPM GmbH, Hannover, Germany*

[8]*Department of Pathology, Technical University, Munich, Germany*

128 ANTIBODY RESPONSE FOLLOWING IMMUNOTHERAPY IDENTIFIES NOVEL ANTIGENS THAT ARE EXPRESSED BY CIRCULATING TUMOR CELLS IN MEN WITH HORMONE-REFRACTORY PROSTATE CANCER

Sachin Puri[1], James A. Thompson[1], Janet C. Siebert[2], Tarsem L. Moudgil[1], Daniel Haley[1], Christian H. Poehlein[1], Edwin Walker[1], Nathalie Sacks[3], Kristen Hege[3], Hong Ming Hu[1,4], Carlo Bifulco[1], Walter J. Urba[1], Brendan Curti[1], Bernard A. Fox[1,5]

[1]*Robert W. Franz Cancer Research Center, Earle A. Chiles Research Institute, Providence Cancer Center, Portland, OR*

[2]*CytoAnalytics, Denver, CO*

[3]*Cell Genesys Inc,, South San Fransisco, CA*

[4]*Department of Radiation Oncology, OHSU, Portland, OR*

[5]*Department of Molecular Microbiology and Immunology, OHSU, Portland, OR*

129 IMMUNOLOGICAL FINDINGS IN A PHASE II IMMUNOTHERAPY STUDY USING ALLOGENEIC LUNG CANCER CELLS MODIFIED TO EXPRESS ALPHA(1,3)GAL EPITOPES IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

Gabriela R. Rossi[1], Nicholas N. Vahanian[1], John C. Morris[2], Anatoli Malyguine[3], Susan Strobl[3], Lucinda Tennant[1], Jay Ramsey[1], Charles J. Link[1]

[1]*Tumor Immunology, NewLink Genetics, Ames, IA*

[2]*Metabolism Branch, NCI, Bethesda, MD*

[3]*CMI, SAIC, Frederick, MD*

130 EXOSOME-TARGETING OF TUMOR ANTIGENS EXPRESSED BY MVA-BN®-PRO IMPROVES ANTIGEN IMMUNOGENICITY AND ENHANCES ANTI-TUMOR EFFICACY

Ryan Rountree, Stefanie Mandl, Katie Dalpozzo, John Lombardo, Lisa Do, Peter Schoonmaker, Reiner Laus, Alain Delcayre

BN-ImmunoTherapeutics, Mountain View, CA

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Rikke B. Sørensen, Per thor Straten, Mads H. Andersen
Center for Cancer Immune Therapy (CCIT), University Hospital Herlev, Herlev, Denmark

132 IN SITU CTLA-4 BLOCKADE MEDIATES REGRESSION OF LOCAL AND DISTANT TUMORS WITH MINIMAL SIDE EFFECTS
Linda C. Sandin[1], Sara M. Mangsbo[1], Angelica S. Loskog[1], Peter Ellmark[2,3], Thomas H. Tötterman[1]
[1]Oncology, Radiology and Clinical Immunology, Clinical Immunology, Uppsala, Sweden
[2]Immunotechnology, Immunotechnology, Lund, Sweden
[3]Alligator Bioscience AB, Lund, Sweden

133 GENE EXPRESSION PROFILING USEFUL FOR PREDICTING CLINICAL RESPONSES TO PERSONALIZED PEPTIDE VACCINATION
Tetsuro Sasada[1], Nobukazu Komatsu[1], Satoko Matsueda[1,2], Tetsuya Ioji[1], Shigeki Shichijo[1], Masanori Noguchi[3], Satoru Kuhara[4], Kyogo Itoh[1,3]
[1]Department of Immunology and Immunotherapy, Kurume Univeristy School of Medicine, Kurume, Japan
[2]Kurume Research Park, Kurume, Japan
[3]Research Center for Innovative Cancer Therapy, Kurume University, Kurume, Japan
[4]Graduate School of Genetic Resources Technology, Kyushu University, Fukuoka, Japan

134 TARGETING HGF IMPACTS BOTH MELANOMA CELLS AND LYMPHOCYTES: IMPLICATIONS FOR CLINICAL USE OF HGF BLOCKADE
Amber L. Shada, Kerrington R. Molhoek, Craig L. Slingluff
Surgery, University of Virginia, Charlottesville, VA

135 MOLECULAR BASIS OF ABERRANT EXPRESSION OF ALKALINE PHOSPHATASE IN RENAL BRUSH BORDER MEMBRANE FROM RENAL CELL CARCINOMA PATIENTS
Ujjawal Sharma[1], Sarwan K. Singh[2], Rajendra Prasad[1]
[1]Biochemistry, PGIMER, Chandigarh, India
[2]Urology, PGIMER, Chandigarh, India

136 SUPERIOR KILLING CHARACTERISTICS OF A TUMOR-TARGETED, GENETICALLY ENCODED TRAIL TRIMER (TR3)
Dirk Spitzer[1], Jesse Gibbs[1], William G. Hawkins[1,2]
[1]Department of Surgery, Washington University School of Medicine, St. Louis, MO
[2]Siteman Cancer Center, Barnes Jewish Hospital and Washington University School of Medicine, St. Louis, MO

137 PENTOSTATIN PLUS CYCLOPHOSPHAMIDE TO ELIMINATE IMMUNOGENICITY OF ANTI-MESOTHELIN IMMUNOTOXIN (SS1P)
Justin Taylor, Miriam E. Mossoba, Paul R. Massey, Masanori Onda, Ira Pastan, Daniel H. Fowler
National Cancer Institute, Bethesda, MD

138 HUMANIZATION OF A HIGH AFFINITY, NEUTRALIZING ANTIBODY AGAINST HEPATITIS B SURFACE ANTIGEN
Ashutosh Tiwari[1], Navin Khanna[2], Subrata Sinha[1]
[1]Biochemistry, All India Institute of Medical Sciences, New Delhi, India
[2]Recombinant Gene Product Lab, International Center for Genetic Engineering and Biotechnology, New Delhi, India

139 DEVELOPMENT OF CANCER STEM CELL VACCINE
Toshihiko Torigoe, Yoshihiko Hirohashi, Akari Takahashi, Satoshi Nishizawa, Rena Morita, Satoko Inoda, Noriyuki Sato
Dept. of Pathology, Sapporo Medical University, Sapporo, Japan

140 EVALUATION OF FOXP3 MICROSATELLITE POLYMORPHISMS IN HIGH-RISK MELANOMA PATIENTS RECEIVING ADJUVANT INTERFERON
Ena Wang[1], Helen Gogas[2], Alessandro Monaco[1], Lorenzo Uccellini[1], Charalampos S. Floudas[2], Yanis Metaxas[2], Urania Dafni[2], George Fountzilas[2], Maria Spyropoulou-Vlachou[2], Francesco M. Marincola[1]
[1]Department of Transfusion Medicine, National Institutes of Health, Bethesda, MD
[2]Hellenic Cooperative Oncology Group, Athens, Greece

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141 RESHAPING CD4 AND CD8 MEMORY T CELL PROLIFERATION BY TREATING CANCER PATIENTS WITH AN OX40 AGONIST: IMMUNOLOGIC ASSESSMENT OF A PHASE I CLINICAL TRIAL

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Robert W. Franz Cancer Research Center, Earle A. Chiles Research Institute, Portland, OR

142 CHARACTERIZATION OF ANTIGEN SPECIFIC T CELL ACTIVATION AND CYTOKINE EXPRESSION INDUCED BY SIPULEUCEL-T

Johnna D. Wesley, Eric Chadwick, Ling-Yu Kuan, Corazon dela Rosa, Mark Frohlich, David Urdal, Nadeem Sheikh, Nicole M. Provost

Dendreon, Seattle, WA

143 THE EXPRESSION OF FOXP3 IN TUMOR TISSUES AND CANCER CELL LINES OF EPITHELIAL OVARIAN CANCER

Shin Wha Lee, Yong-Man Kim, Dae-Yeon Kim, Jong-Hyeok Kim, Joo-Hyun Nam, Young-Tak Kim

Departments of Obstetrics and Gynecology, University of Ulsan, Asan Medical center, Seoul, Republic of Korea

144 IMPACT OF HLA-A2 STATUS ON IPILIMUMAB EFFICACY AND SAFETY: POOLED DATA FROM FOUR PHASE II TRIALS IN ADVANCED MELANOMA

Jedd D. Wolchok[1], Jeffrey S. Weber[2], Omid Hamid[3], Celeste Lebbé[4], Michele Maio[5], Dirk Schadendorf[6], Veerle de Pril[7], Ramy Ibrahim[8], Axel Hoos[8], Steven J. O'Day[3]

[1]Memorial Sloan-Kettering Cancer Center, New York, NY

[2]H. Lee Moffitt Cancer Center, Tampa, FL

[3]The Angeles Clinic and Research Institute, Santa Monica, CA

[4]Institut Gustave Roussy, Villejuif, France

[5]University Hospital of Siena, Siena, Italy

[6]University Hospital Essen, Essen, Germany

[7]Bristol-Myers Squibb, Braine-l'Alleud, Belgium

[8]Bristol-Myers Squibb, Wallingford, CT

145 NY-ESO-1-SPECIFIC CD8 T CELL RESPONSE IN NY-ESO-1 SEROPOSITIVE METASTATIC MELANOMA PATIENTS TREATED WITH IPILIMUMAB CORRELATES WITH CLINICAL BENEFIT

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[1]Ludwig Center for Cancer Immunotherapy, MSKCC, New York, NY

[2]Ludwig Institute of Cancer Research, NY Branch, MSKCC, New York, NY

[3]Medicine, MSKCC, New York, NY

146 IMMUNOTHERAPY OF ADENOCARCINOMAS WITH GC PROTEIN-DERIVED MACROPHAGE ACTIVATING FACTOR, GcMAF

Nobuto Yamamoto, Masumi Ueda, Kazuya Hashinaka

Socrates Institute for Theapeutic Immunology, Philadelphia, PA

147 ANTI-TUMOR ACTION AND TOLERANCE OF ORAL SHP-1 INHIBITOR TPI-1a4 IN MOUSE MODELS

Taolin Yi, Mingli Cao, Keke Fan, Dan Lindner, Ralph Tuthill, Ernest Borden

Cleveland Clinic, Cleveland, OH

148 A FLOW CYTOMETRY METHOD TO QUANTITATE INTERNALIZED IMMUNOTOXINS IN VIVO EXPLAINS TAXOL AND IMMUNOTOXIN SYNERGY

Yujian Zhang, Johanna K. Hansen, Laiman Xiang, Seiji Kawa, Masanori Onda, Mitchell Ho, Raffit Hassan,, Ira Pastan

Laboratory of Molecular Biology, National Cancer Institute/NIH, Bethesda, MD

149 L-PG-CpG, A NANOPOYMER FORMULATED IMMUNOMODULATOR WITH ENHANCED ANTICANCER ACTIVITY

Dapeng Zhou[1], Xiaoxia Wen[2], Prakash Thapa[1], Chengwen Liu[1], Patrick Hwu[1], Chun Li[2]

[1]Melanoma Medical Oncology, University of Texas MD Anderson Cancer Center, Housotn, TX

[2]Diagnostic Imaging, University of Texas MD Anderson Cancer Center, Houston, TX

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VACCINE COMBINATIONS

150 AUTOLOGOUS VACCINE, ACTIVE IMMUNOTHERAPY OF CANCER PATIENTS ACCORDING TO TNF-α, IFN-γ, sIL-2R, sIL-6R MONITORING
Hannes Anthopoulos
K-BIO Institute for Cellbiotechnology and Immunology GmbH, Groebenzell, Germany

151 CHEMOKINE EXPRESSION FROM ONCOLYTIC VACCINIA VIRUS ENHANCES VACCINE THERAPIES OF CANCER
Jun Li[1], Mark E. O'Malley[1], Julie Urban[1], Z. Sheng Guo[1], Pawel Kalinski[1,2], Steve H. Thorne[1,2], *David L. Bartlett*[1]
[1]Surgery, University of Pittsburgh, Pittsburgh, PA
[2]Immunology, University of Pittsburgh, Pittsburgh, PA

152 IMMUNIZATION OF DISEASE-FREE MELANOMA PATIENTS WITH DIFFERENT HLA-A2 PEPTIDES: RESULTS OF A RANDOMIZED PHASE IB/II TRIAL COMPARING PEPTIDES ALONE, PEPTIDES IN MONTANIDE, PEPTIDES + IMP321 (LAG-3Ig, AN APC ACTIVATOR), PEPTIDES IN MONTANIDE + IMP321
Jean-Francois Baurain[1], Pierre Coulie[2], Frédéric Triebel[3]
[1]Saint Luc Hospital, Brussels, Belgium
[2]Catholic University Louvain, Brussels, Belgium
[3]Immutep S.A., Orsay, France

153 TWO-COMPONENT MESSENGER RNA-BASED VACCINES PROVIDE STRONG ANTI-TUMORAL EFFECT ESPECIALLY IN COMBINATION WITH RADIATION THERAPY
Mariola Fotin-Mleczek[1], Christina Lorenz[1], Katharina M. Duchardt[1], Stephan Huber[2], Karl-Josef Kallen[1]
[1]CureVac GmbH, Tübingen, Germany
[2]Radiooncology, Universitätsklinikum Tübingen, Tübingen, Germany

154 HOST IMMUNITY AND DISEASE FREE SURVIVAL ARE IMPROVED IN BREAST CANCER PATIENTS RECEIVING AN AUTOLOGOUS VACCINE
Jonathan F. Head, Robert L. Elliott
EEH Breast Cancer Research and Treatment Center, Baton Rouge, LA

155 AUTOLOGOUS HUMAN VACCINE, AHICE, FOR MULTI-PRIMARY CANCER THERAPY
Konstantinos I. Papapolychroniadis[1], Hannes Anthopoulos[2], Aristidis Ioannidis[1], Epaminontas Fahantidis[1], Julia Papapolychroniadou[1], Mairi D. Georgiou[1]
[1]1st Surgical Propedeutical, Aristotle University of Thessaloniki, Thessaloniki, Greece
[2]Cell Biotechnology and Immunology, Clinical Biochemical Institute, Munich, Germany

156 LONG TERM SURVIVAL OF A RARE PRIMARY RENAL CANCER CASE FOLLOWING BILLATERAL NEFRECTOMY, HAEMODIALYSIS AND EFFECTIVE FINAL IMPULSE OF AUTOLOGOUS HUMAN IMMUNE VACCINE THERAPY
Konstantinos I. Papapolychroniadis[1], Hannes Anthopoulos[2], Dimitris Panagiotou[1], Julia Papapolychroniadou[1], Epaminontas Fahantidis[1]
[1]1st Surgical Propedeutical, Aristotle University of Thessaloniki, Thessaloniki, Greece
[2]Cell Biotechnology and Immunology, Clinical Biochemical Institute, Munich, Germany

157 ADOPTIVE IMMUNOTHERAPY FOR RECURRENT OVARIAN CANCER USING AUTOLOGOUS WHOLE TUMOR ANTIGEN-PRIMED T LYMPHOCYTES
Daniel J. Powell[1,2], Lana Kandalaft[1], Lori Smith[1], John Liao[1], Andrea Hageman[1], Janos Tanyi[1], Qunrui Ye[1], Andrew Best[1], Drew A. Torigian[2], Christina S. Chu[1], Stephen C. Rubin[1], Edward Stadtmauer[2], Marnix Bosch[3], Bruce L. Levine[2], Carl H. June[2], George Coukos[1]
[1]Department of Obstetrics and Gynecology, University of Pennsylvania, Philadelphia, PA
[2]Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA
[3]NW Biotherapeutics, Inc., Bethesda, MD

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158 VACCINE INDUCED INCREASE OF CCR7+ CD8+ T CELLS IS ASSOCIATED WITH FAVORABLE CLINICAL OUTCOME IN A WILMS TUMOR GENE 1 PEPTIDE- VACCINATION TRIAL IN LEUKEMIA PATIENTS

David E. Stather[1], Carmen Scheibenbogen[2], Anne Marie Asemissen[1], Antonia Busse[1], Eckhard Thiel[1], Ulrich Keilholz[1], Anne Letsch[1]

[1]*Hematology, Oncology, Charité Berlin, Berlin, Germany*

[2]*Institute of Medical Immunology, Charité Berlin, Berlin, Germany*

159 THERAPEUTIC VACCINATION TARGETING INDOLEAMINE-2,3 DIOXYGENASE USING A IDO DERIVED CLASS I RESTRICTED PEPTIDE IN COMBINATION WITH ALDARA AND MONTANIDE FOR PATIENTS WITH LOCALLY ADVANCED OR METASTATIC NON SMALL-CELL LUNG CANCER. A FIRST-IN-MAN PHASE I TRIAL

Trine Zeeberg, Rikke B. Sørensen, Anders Mellemgaard, Per T. Straten, Mads H. Andersen, Inge Marie Svane

Dept. of Haematology and Dept. of Oncology, Copenhagen University Hospital, Herlev, Denmark

LATE-BREAKING ABSTRACTS

160 EXPRESSION OF CANCER TESTIS ANTIGENS IN HUMAN BRCA-ASSOCIATED BREAST CANCERS - POTENTIAL TARGETS FOR IMMUNOPREVENTION?

Sylvia Adams[1], Luba Greeder[1], Elsa Reich[1], Sandra Demaria[1], Achim Jungbluth[2]

[1]*NYU Cancer Institute, New York, NY*

[2]*Ludwig Institute for Cancer Research, New York at Memorial Sloan-Kettering Cancer Center, New York, NY*

161 ASSOCIATION OF CTLA-4 GENE POLYMORPHISMS WITH SURVIVAL IN MELANOMA PATIENTS TREATED WITH INTERFERON

Elizabeth I. Buchbinder[1,2], Wei Wang[2], David J. Panka[1,2], Michael B. Atkins[1,2], Henry B. Koon[3]

[1]*Hematology/Oncology, Beth Isreal Deaconess Medical Center, Boston, MA*

[2]*Harvard Medical School, Boston, MA*

[3]*Medical Oncology Cutaneous Malignancy Program, Case Western Reserve University, Cleveland, OH*

162 USING TIMING TO SYNCHRONISE IMMUNOTHERAPY THROUGH MICROMANIPULATION OF THE UNDERLYING TUMOR IMMUNE RESPONSE: FROM COLEY TO ROSENBERG, LOTZE, ALLISON, WOLCHOK AND BEYOND!

Brendon J. Coventry[1], Martin L. Ashdown[2], Svetomir N. Markovic[3]

[1]*Surgery and Immunology, University of Adelaide, Adelaide, SA, Australia*

[2]*Medicine, University of Melbourne, Melbourne, VIC, Australia*

[3]*Medical Oncology, Mayo Clinic, Rochester, MN*

163 TLR8 AGONIST AND DOXIL CHEMOTHERAPY POTENTLY ACTIVATE HUMAN ANTITUMOR IMMUNE RESPONSE IN A HUMAN IMMUNE SYSTEM MOUSE MODEL

Andrea Facciabene[1], Alexander Malykhin[1], Chungyun Fang[1], Gwen-äel Danet-Desnoyers[2], Maura-Ann Matthews[3], Gregory Dietsch[3], Robert Hershberg[3], George Coukos[1]

[1]*School of Medicine, Ovarian Cancer Research Center, PENN, Philadelphia, PA*

[2]*School of Medicine, PENN, Philadelphia, PA*

[3]*VentiRX, VentiRx Pharmaceuticals, Inc., San Diego, CA*

164 DYSFUNCTIONAL TUMOR ANTIGEN-SPECIFIC CD8+ T CELLS UPREGULATE Tim-3 AND PD-1 IN MELANOMA PATIENTS

Julien Fourcade[1], Zhaojun Sun[1], Mourad Benallaoua[1], Philippe Guillaume[2], Immanuel Luescher[2], Cindy Sander[1], John Kirkwood[1], Vijay Kuchroo[3], Hassane M. Zarour[1]

[1]*Medicine and Immunology, University of Pittsburgh, Pittsburgh, PA*

[2]*Ludwig Institute for Cancer Research, Epalinges, Switzerland*

[3]*Center for Neurologic Diseases, Harvard Medical School, Boston, MA*

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165 HELIOS POSITIVE THYMIC-DERIVED REGULATORY T CELLS CONTINUE TO DOMINATE IN PBMC OF PATIENTS FOLLOWING COMBINATION IMMUNOTHERAPY WITH NONMYELOABLATIVE CHEMOTHERAPY, ADOPTIVE TRANSFER AND VACCINATION

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[1]Earle A. Chiles Research Institute, Providence Cancer Center, Portland, OR

[2]Cell Genesys Inc, South San Francisco, CA

166 ARTIFICIAL ANTIGEN PRESENTING CELLS ENHANCE THE PRODUCTION OF TUMOR-INFILTRATING LYMPHOCYTES FOR ADOPTIVE CELL THERAPY

Kevin M. Friedman, Steven A. Feldman, Steven A. Rosenberg, Mark E. Dudley

Surgery Branch, National Cancer Institute, Bethesda, MD

167 A NOVEL STAT3 INHIBITOR REVERSES TUMOR-ASSOCIATED IMMUNOSUPPRESSION AND ENHANCES THE EFFICACY OF ADOPTIVE T CELL THERAPY OF CANCER

Hiroaki Ikeda[1], Daisuke Sugiyama[2], Daisuke Muraoka[2,3], Naoko Imai[1], Naozumi Harada[2,3], Yasuto Akiyama[4], Akira Asai[5], Hiroshi Shiku[1,2]

[1]Department of Immuno-Gene Therapy, Mie University Graduate School of Medicine, Tsu, Japan

[2]Department of Cancer Vaccine, Mie University Graduate School of Medicine, Tsu, Japan

[3]Basic and Preclinical Research Department, ImmunoFrontier, Inc., Tokyo, Japan

[4]Immunotherapy Division, Shizuoka Cancer Center Research Institute, Sunto, Japan

[5]Drug Discovery Center, University of Shizuoka Graduate School of Pharmacology, Shizuoka, Japan

168 SYNERGISTIC ANTITUMOR EFFICACY OF AN INHIBITOR OF IDO1 AND CYTOTOXIC AGENTS WHICH INDUCE IDO ACTIVITY

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Incyte Corporation, Wilmington, DE

169 SAFETY AND PHARMACODYNAMIC RESULTS OF A PHASE I/IIA TRIAL WITH A DIRECTLY INJECTABLE MESSENGER RNA-BASED VACCINE CV9103 ENCODING 4 DIFFERENT PROSTATE ANTIGENS IN PATIENTS WITH HORMONE-REFRACTORY PROSTATE CANCER

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CureVac GmbH, Tuebingen, Germany

170 TUMOR-DRIVEN DEVIATION OF MONOCYTE COMMITMENT TO DENDRITIC CELL PATHWAY CAN BE COUNTERACTED BY INDUCING IMMUNOGENIC TUMOR CELL DEATH

Lina Matera, Davide Brusa, Stefano Garetto

Internal Medicine, University of Turin, Turin, Italy

171 FIRST-IN-MAN PHASE I CLINICAL TRIAL OF VTX-2337—A SELECTIVE TOLL-LIKE RECEPTOR 8 AGONIST—IN ONCOLOGY PATIENTS

Donald Northfelt[1], Ramesh Ramanathan[2], Peter Cohen[1], Daniel Von Hoff[2], Kristi Manjarrez[3], Gregory Dietsch[3], Robert Hershberg[3]

[1]Mayo Clinic, Scottsdale, AZ

[2]TGen Clinical Research Services, Scottsdale, AZ

[3]VentiRx Pharmaceuticals, Seattle, WA

172 MECHANISMS OF IFN-α RESISTANCE IN RENAL CELL CARCINOMA

Eric Pathe[1,2], David J. Tate[1], Janie Trinh[1], Beatriz Finkel-Jimenez[1], Arnold H. Zea[1,3]

[1]Stanley S. Scott Cancer Center, LSUHSC, New Orleans, LA

[2]University of Maryland, College Park, MD

[3]Microbiology, Immunology and Parasitology, LSUHSC, New Orleans, LA

173 TARGETING THE MUC1-SEA MODULE WITH ANTIBODIES FOR ABLATING HUMAN MUC1 POSITIVE CANCER CELLS

Edward Pichinuk, Daniel Wreschner

Cell Research and Immunology, Tel-Aviv University, Tel-Aviv, Israel

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Antoni Ribas[1], Dmitri Pavlov[2], Margaret A. Marshall[2]
[1]*University of California Los Angeles, Los Angeles, CA*
[2]*Pfizer Oncology Global Research & Development, New London, CT*

175 SALMONELLA-INDUCED CONNEXIN 43 IS REQUIRED FOR AN EFFECTIVE IMMUNOTHERAPY AGAINST THE MURINE B16 MELANOMA

Fabiana Saccheri[1], Chiara Pozzi[1], Deepak Mittal[1], Francesca Avogadri[2], Sara Barozzi[1], Mario Faretta[1], Paola Fusi[3], Maria Rescigno[1]
[1]*Experimental Oncology, European Institute of Oncology, Milan, Italy*
[2]*Immunology, Memorial Sloan-Kettering Cancer Center, New York, NY*
[3]*Biotechnology and Biosciences, University of Milano-Bicocca, Milan, Italy*

176 CHRYSOTILE-INDUCED GENE EXPRESSION PROFILE IN HUMAN BRONCHIAL EPITHELIAL CELLS

Yoo-Na Seo[1], Young-Jin Lee[2], Mi-Young Lee[1]
[1]*Medical Biotechnology, SoonChunHyang University, Asan, Republic of Korea*
[2]*Medicine, SoonChunHyang University, Cheonan, Republic of Korea*

177 COMPARISON OF TUMORICIDIC PROPERTIES OF ANTI EGFR IgG AND IgE ANTIBODIES

Josef Singer[1], Melanie Plum[2], Ingke Braren[2], Panagiotis Karagiannis[3], Diana Mechtcheriakova[1], Regina Knittelfelder[1], Edzard Spillner[2], Erika Jensen-Jarolim[1]
[1]*Institute of Pathophysiology and Allergy Research, Medical University of Vienna, Vienna, Austria*
[2]*Institute of Biochemistry and Molecular Biology, University of Hamburg, Hamburg, Germany*
[3]*St. John's Institute of Dermatology, King's College London, London, United Kingdom*

178 A POTENTIAL INSIGHT AGAINST BREAST CANCER CELLS: SHORT PEPTIDES SELECTED TO HER2

Eloah R. Suarez[1], Edgar J. Paredes-Gamero[1], Auro Del Giglio[2], Helena B. Nader[1], Maria Aparecida S. Pinhal[1,3]
[1]*Biochemistry, Universidade Federal de São Paulo, São Paulo, Brazil*
[2]*Oncology, Faculdade de Medicina do ABC, Santo André, Brazil*
[3]*Biochemistry, Faculdade de Medicina do ABC, Santo André, Brazil*

179 HELPER ACTIVITY OF NATURAL KILLER CELLS DURING THE DENDRITIC CELL-MEDIATED INDUCTION OF MELANOMA-SPECIFIC CYTOTOXIC T CELLS

Jeffrey L. Wong[1], Robbie B. Mailliard[2], Stergios J. Moschos[3,4], Howard Edington[2,4], Michael T. Lotze[2,4], John M. Kirkwood[3,4], Pawel Kalinski[2,1,5]
[1]*Immunology, University of Pittsburgh, Pittsburgh, PA*
[2]*Surgery, University of Pittsburgh, Pittsburgh, PA*
[3]*Medicine, University of Pittsburgh, Pittsburgh, PA*
[4]*Melanoma Center, University of Pittsburgh Cancer Institute, Pittsburgh, PA*
[5]*Infectious Diseases and Microbiology, University of Pittsburgh, Pittsburgh, PA*

180 EPITOPE ARRAYS FOR MULTIPLEX MONITORING OF AUTOANTIBODIES IN CANCER PATIENTS

Gang Zeng[1], Chong Xie[1], Alan J. Pantuck[1], Alex de la Taille[2], Hideki Mukouyama[3]
[1]*Urology, University of California Los Angeles, Los Angeles, CA*
[2]*Urology, APHP, CHU Henri Mondor, Créteil, France*
[3]*Urology, Okinawa Nanbu Tokushukai Hospital, Yaese, Japan*

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Aizhi Zhao[1], Chunsheng Li[1], Daniel Ricklin[2], Tamara Seedial[1], George Coukos[1], Nathalie Scholler[1]
[1]*University of Pennsylvania, Philadelphia, PA*
[2]*Ovarian Cancer Research Center, University of Pennsylvania, Philadelphia, PA*

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Ning Ning[1,2], Seagal Teitz-Tennenbaum[1], Ji Yet[1], Jeffrey S. Moyer[1], Christophe Ginestier[1], Max S. Wicha[1], Yingxin Xu[2], Alfred E. Chang[1], Qiao Li[1]

[1]University of Michigan, Ann Arbor, MI

[2]PLA General Hospital, Beijing, China

183 ALTERED IMMUNE MODULATORY ACTIVITY AND DIFFERENTIAL PROTEIN EXPRESSION PATTERN OF TUMOR CELLS UPON TREATMENT WITH THE TYROSINE KINASE INHIBITOR AXITINIB

Barbara Seliger, Anja Mueller, Corinna Giersberg, Franziska Leich

Institute of Medical Immunology, Martin Luther University, Halle, Germany

184 ON THE LONG TERM USE OF A THERAPEUTIC CANCER VACCINE

Gisela Gonzalez, Tania Crombet, Agustin Lage

CIM, Havana, Cuba

iSBTc Membership Information

iSBTc PROFILE

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

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 iSBTc
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- **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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☐ Genetics	☐ Medical Oncology	☐ Radiation Oncology	☐ Transplantation
☐ Gynecologic Oncology	☐ Microbiology	☐ Radiology	☐ Others _____
☐ Hematology	☐ Molecular Biology		_____

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Affiliate applicants:

☐ I will email my business or educational resumé to info@isbtc.org.

☐ My business or educational resumé is enclosed.

Student applicants:

☐ I will email my letter of recommendation and proof of enrollment to info@isbtc.org.

☐ My letter of recommendation and proof of enrollment are enclosed.

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

MEMBERSHIP FEE:

☐ Regular/Affiliate ($220) ☐ Student ($50)

☐ Check (enclosed) ☐ VISA ☐ MasterCard ☐ American Express

Card Holder: _____

Card Number: _____ Exp.: _____

Signature: _____ Date: _____

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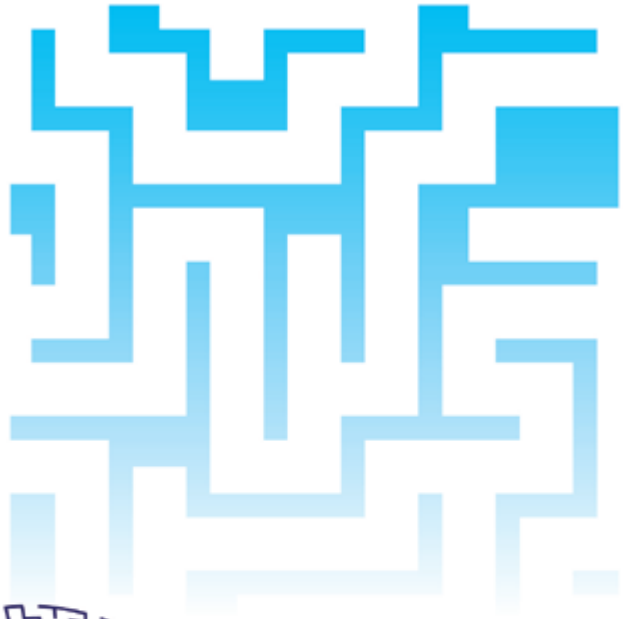
Tel: 414-271-2456 • Fax: 414-276-3349 • Email: info@isbtc.org • Web: www.isbtc.org



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