SITC Initiatives: Cancer Immunotherapy Biomarkers and Beyond

Lisa H. Butterfield, Ph.D.
Professor of Medicine, Surgery and Immunology
University of Pittsburgh Cancer Institute
Director, UPCI Immunologic Monitoring and Cellular Products Laboratory
President, Society for Immunotherapy of Cancer

SOCIETY FOR IMMUNOTHERAPY OF CANCER — 31 years of advancing cancer immunotherapy worldwide

AT A GLANCE

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sitcancer.org

A MEMBER-DRIVEN SOCIETY WITH EXPANSIVE REACH

1,700+ MEMBERS

from **40 U.S. States** and **38 countries**

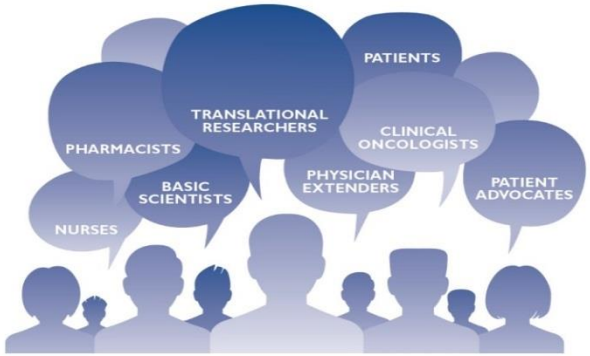
Nearly **500 member volunteers** on more than **30 committees** and **task forces**

61 Champions at cancer care institutes around the world

AT SITC THERE'S A PLACE FOR YOU!

Members specialize in the full spectrum of both solid tumors and hematologic malignancies.

SITC has expanded membership to include all members of the cancer care team including:



We welcome you to contribute your perspectives to the society and join the record number of members we have today.

COLLABORATION IS KEY

SITC has cultivated dozens of relationships to foster innovation within the field including these partners:

- American Association for Cancer Research
- American Cancer Society
- American Society of Clinical Oncology
- Association of Community Cancer Centers
- Association of Oncology Social Workers
- Bonnie J. Addario Lung Cancer Foundation
- Cancer Immunotherapy Trials Network
- Cancer Research Institute
- Cancer Support Community
- Commission on Cancer
- Food and Drug Administration
- Foundation for the Accreditation of Cellular Therapy
- Friends of Cancer Research
- International Society for Cellular Therapy
- Lung Cancer Alliance
- LUNGevity Foundation
- Melanoma Research Alliance
- Melanoma Research Foundation
- National Cancer Institute/ National Institutes of Health
- National Coalition for Cancer Research
- Stand Up to Cancer

Toxicity Management Workshop

- Friday, March 31, 2017 | 8 a.m. – 6 p.m. in Washington, D.C.

- 100 registered attendees
- Participating organizations include:
  - American Society of Clinical Oncology
  - Association of Community Cancer Centers
  - Friends of Cancer Research
  - National Cancer Institute
  - National Comprehensive Cancer Network
  - Oncology Nursing Society
  - Parker Institute for Cancer Immunotherapy
- Outcomes will be a publication

Toxicity Management Workshop

EDUCATION &
SCIENTIFIC EXCHANGE

- **Kidney:** **Published** November 15, 2016 in JITC
- **Prostate:** **Published** December 20, 2016 in JITC
- **Heme:** **Published** December 20, 2016 in JITC
- **Bladder:** *In Open Comment period for SITC members (3/2C*
  Will publish Q2 2017
- **Melanoma update:** *In development*
- **Lung:** *In development*

Cancer Immunotherapy GUIDELINES

Cancer Immunotherapy Guidelines (CIG)

SCIENCE & RESEARCH

SITC's Advances In Cancer Immunotherapy™

Educational Partners

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ACCC

American Academy of Emergency Medicine

Target Audiences

- Clinical Oncologists
- Nurses
- Pharmacists
- Emergency Physicians

Online Pre-Program Activity

- CME/CE, 45-minutes
- Immunology and Immunotherapy 101
- Helps attendees prepare before live event

Live ACI™ Programs

Making Connections
- Local IO Experts + Community Clinicians
- NCI Designated Cancer Centers + Regional Community Hospitals

Topic Areas
- Basic Principles
- Clinical Application
- Operational and Insurance Barriers
- Immune-Related Adverse Event Management

- CME/CE

Online Recordings

- Live ACI programs recorded and posted online for reference and reinforcement

Online Activities

- Best of live ACI talks turned into 12 online activities
- Earn CME/CE credit from modules independently or in addition to live ACI programs

Online IO Cup O' Joe

- 1 month and 3 months post live ACI
- Q&A
- Networking and referral

Online ACI Community

- Q&A
- Receive resources such as newest guidelines
- Network and referral

Continuous Learning and Collaboration

World Immunotherapy Council (WIC) Day

- Wednesday, November 8, 2017 | 2 p.m. – 8 p.m.

- Organizations have been invited and are confirming. Each participating organization will select one young investigator to present in the program
- 4 young investigators who spoke in 2015 will be selected to serve as junior co-chairs in the 2017 program. All 2015 young investigators will be featured in a “where they are now” section of the printed program.

- **Members**: Adoptive Engineered T Cell Targeting to Activate Cancer Killing (**ATTACK**), Association for Cancer Immunotherapy (**CIMT**), Australian Work Group, Canadian Cancer Immunotherapy Consortium (**CCIC**), Cancer Drug Development Forum (**CDDF**), Cancer Research Institute (**CIC-CRI**), Chinese American Hematology Oncology Network (**CAHON**), Chinese Society of Clinical Oncology (**CSCO**), Chinese Society of Immunology (**CSI**), Dutch Tumor Immunology Working Party (**DTIWP**), European Academy of Tumor Immunology (**EATI**), European Society of Cancer Immunology and Immunotherapy (**ESCII**), German Cancer Immunology Group in the German Immunology Society, Italian Network for Tumor Biotherapy (**NIBIT**), Japanese Association of Cancer Immunology (**JACI**), Middle Eastern and North African Interest Group, National Institute of Oncology Budapest, Progress in Vaccination Against Cancer (**PIVAC**), Scandinavian Network for Immunotherapy of Cancer (**SNIC**), Societa Compana di ImmunoTerapia Oncologica (**SCITO**), Society of Immunotherapy of Cancer (**SITC**), Tumor Immunology Meets Oncology (**TIMO**),Tumor Vaccine and Cell Therapy Working Group (**TVACT**)

Workshop on Single Cell Techniques in Immunology and Cancer Immunotherapy

- Thursday, November 9, 2017 | 8:00 a.m. – 5:00 p.m.

- Organizers
  - Gordon J. Freeman, PhD – *Dana-Farber Cancer Institute*
  - Nicholas McGranahan, PhD – *University College London*
  - Nir Hacohen, PhD – *Massachusetts General Hospital*

- Organizers and SITC scientific staff finalized Workshop purpose and objectives
- Faculty have been invited

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THE PLACE FOR CANCER IMMUNOTHERAPY EDUCATION

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RESOURCES FOR YOU

Cancer Immunotherapy
GUIDELINES

Available Now:
- Melanoma
- Kidney
- Prostate
- Hematologic Malignancies

Coming Soon:
- Lung

WORLD IMMUNOTHERAPY COUNCIL

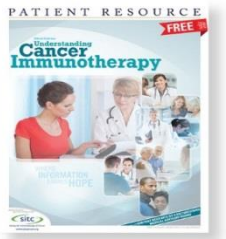
Group of 26 organizations that promote the research and translation of cancer immunotherapy to accelerate delivery of new immune-based treatments to patients with cancer throughout the world.

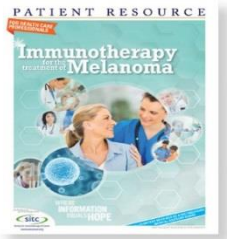
Journal for ImmunoTherapy of Cancer

Open access, peer-reviewed journal deemed the voice of the society. Free article processing charges for members!

RESOURCES FOR YOUR PATIENTS

PATIENT RESOURCE GUIDES





WHITE BOARD VIDEO

SAVE THE DATE

SITC'S 32ND ANNUAL MEETING & PRE-CONFERENCE PROGRAMS

November 8 – 12, 2017 • National Harbor, Maryland

This meeting features both **cutting-edge research** and timely education sessions that serve as catalysts for advancing the field, and **bridges the gap between translational research, development and clinical practice.**

SITC 2017
November 8-12
NATIONAL HARBOR MARYLAND
Gaylord National Hotel & Convention Center

Learn more at sitcancer.org

Cancer Immunotherapy CONNECT
Powered by sitc

What are the biomarker questions:

1. *Prediction*:
Who should be enrolled in this trial/receive this therapy?

2. *Prognostication*:
Who is benefitting from this therapy (in time to change course if needed)?

3. *Mechanism*:
What worked well/not well about this intervention?
Why or why not?
What should be combined with it?

Where do we still need biomarkers?

IL-2. Used since 1984, the Surgery Branch reported on …patients treated with high-dose bolus IL-2 with metastatic melanoma or renal cancer, ….409 consecutive patients: 15% incidence of objective regressions …with metastatic melanoma (7% were complete) and a 19% overall response rate …with metastatic renal cancer (9% were complete) . Twenty-seven of the 33 completely responding patients (82%) remained in CR ….and *appeared to be cured.* Rosenberg, 2014

The toxicities associated with high-dose IL-2 are severe but reversible; such toxicities sometimes included hemodynamic complications that required hospitalization in specialized or intensive care units.

IFNα. Three large meta-analyses have evaluated the survival benefits of adjuvant IFN-α, at various dose levels, durations, and routes of administration. … highly significant RFS benefits (HR, 0.83; p = 0.000003) and OS benefits that were less significant (HR, 0.93; p = 0.1) (*one year regimen*).

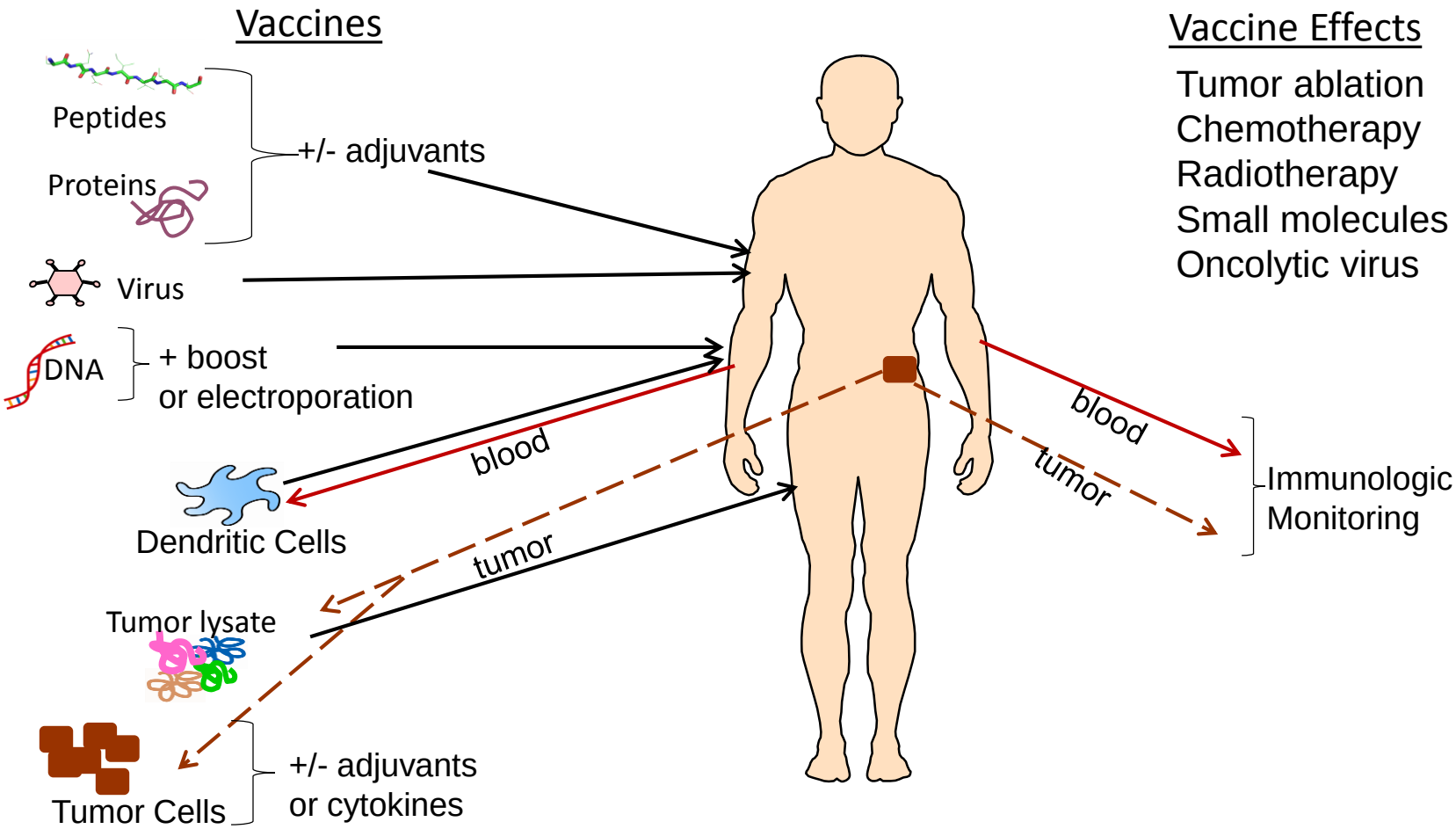
Attempts to identify a subset of patients likely to benefit from adjuvant treatment with IFN-α have failed to discover clinical or demographic features of true therapeutic predictive value. Tarhini, Gogas, Kirkwood, 2012

Why don’t we have more useful Biomarkers?

Now that we have populations of clinical trial *clinical* responders:

1. We need the right specimens saved under standardized conditions. Variably banked specimens give noisy data. Many trials bank only non-viable tumor and serum samples.

2. Immune assays can be costly; testing small numbers don’t give robust, reproducible signals; guessing at 1-2 assays may miss the true biomarker.


Vaccines
Peptides
Proteins
+/- adjuvants
Virus
DNA
+ boost
or electroporation
Dendritic Cells
blood
tumor
Tumor lysate
Tumor Cells
+/- adjuvants
or cytokines
Vaccine Effects
Tumor ablation
Chemotherapy
Radiotherapy
Small molecules
Oncolytic virus
blood
tumor
Immunologic
Monitoring

Single or Combinations

Vaccines

Peptides

Proteins

Viruses

DNA

Prime-Boost

Dendritic Cells

Tumor lysates

Tumor cells

+

Standard of care

Ablation, Chemotherapy
Radiation, Small Molecules

Checkpoint Blockade

CTLA-4, PD-1, PD-L1, TIM-3…

Immunotherapy

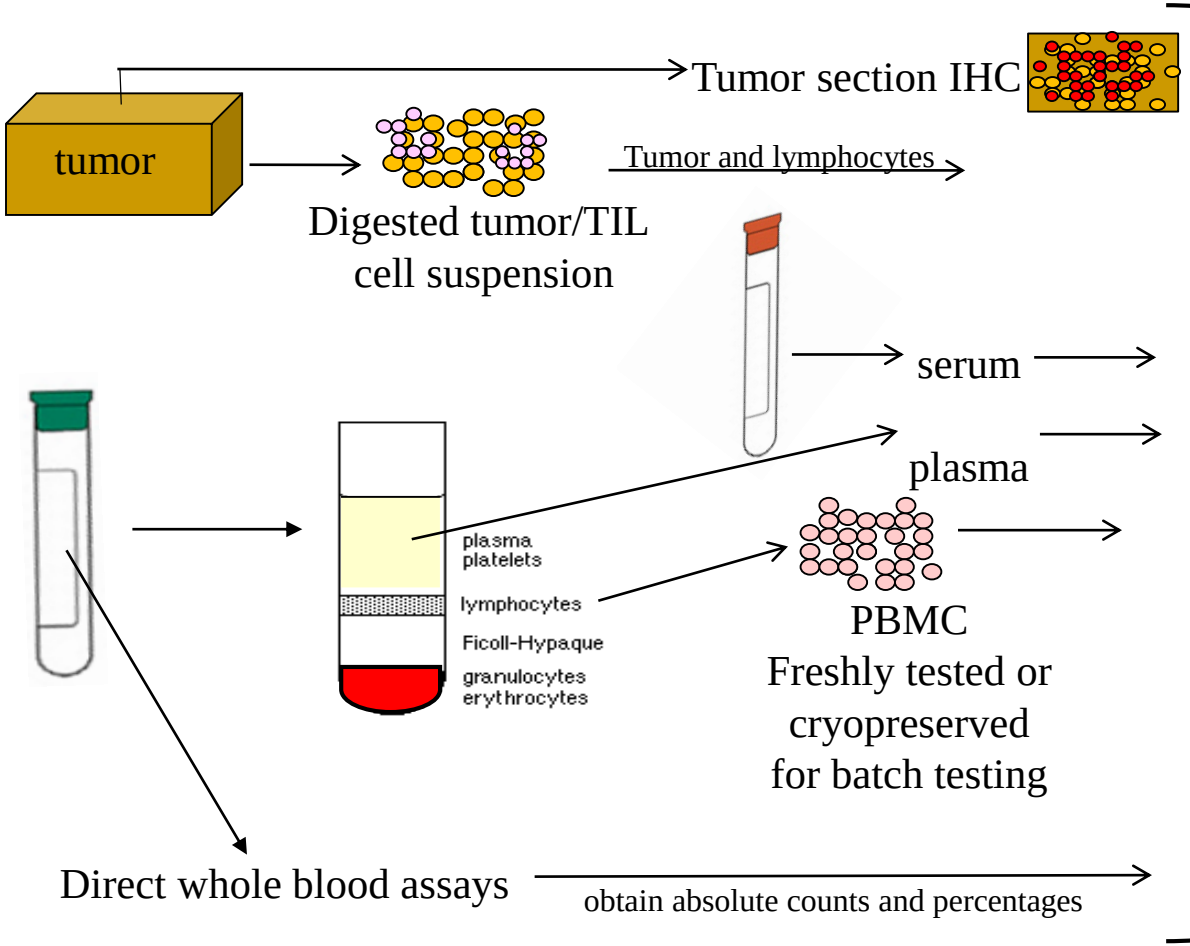
Cytokines (IL-2, IFNα, GM-CSF)

Co-stimulation (4-1BB, OX40, CD40)

Adoptive Transfer of Effectors (T, NK)

Suppression Reduction

Lymphodepletion
Treg, MDSC reduction/inhibition
Myeloid cell modulation



TESTING:

Total lymphocyte subsets

Antigen-specific T cells (CD4+, CD8+)

Antigen-specific antibodies

NK cells

Myeloid DC
Plasmacytoid DC

Cytokine/chemokines/ growth factors

Treg

MDSC

Frequency, phenotype, function, activation, suppression, expression of key molecules genetic polymorphisms RNA expression

Patient-derived specimens used in immunologic monitoring

Recommendations from the iSBTc-SITC/FDA/NCI Workshop on Immunotherapy Biomarkers

Source of Variability	Recommendation
Patient	Save DNA/RNA/cells/tumor to understand host variation include healthy donor control
Blood draw	Standardized tubes and procedures
Processing/cryopreservation/ thaw	Standardized procedures and reagents
Cellular product	Phenotypic and functional assays to characterize the individual product, development of potency assays
Assay choice	Standardized functional tests
Assay conduct	Standardized operating procedures (SOPs)
Assay analysis	Appropriate biostatistical methods
Data reporting	Full details, controls, quality control/assurance (QA/QC) MIATA guidelines
Newest, non-standardized technology	Sufficient blood/tissue to interrogate the samples *now*, as well as *later*, to generate new hypotheses

Butterfield, CCR 2011

What is new:

New areas of biology impacting immune response

Metabolism, microbiome, signaling pathway modulation

New technologies and high throughput approaches

Mass cytometry, exome sequencing, TCR diversity, epigenetics

New and old drugs impacting immunity:

Chemotherapy, Radiation, Ablation, signal transduction pathway inhibition

Bioinformatics, complex data analysis, and new biological samples

Immunotherapy Biomarkers Task Force History

Previously

Society Workshops: Immunologic Monitoring

2002 Keilholz Workshop summary paper

2005 Lotze Workshop summary, state-of-the-art and recommendations

2008: assembled current Steering Committee:

Preamble ms JTM 2008;

SITC Workshop 2009 and meeting report JTM 2009

Taskforce meeting at the NIH 2010 and *"Recommendations" paper (CCR '11) and Resources document (JTM '11)*

Biomarkers Task Force: Steering Committee:

Lisa Butterfield, PhD, Nora Disis, MD

Bernie Fox, PhD, Samir Khleif, MD

Francesco Marincola, MD

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Society for Immunotherapy of Cancer

Immunotherapy Biomarkers Task Force: 2015-2016

GROUP 1: "Immune monitoring assay standardization and validation—update" *Leaders: Magdalena Thurin, PhD and Giuseppe Massucci, MD*

GROUP 2: "New developments in biomarker assays and technologies" *Leader: Jianda Yuan, MD*

GROUP 3: "Assessing Immune Regulation and Modulation Systematically (high throughput approaches)" *Leader: David Stroncek, MD*

Group 4: "Baseline Immunity, tumor immune environment and outcome prediction" *Leader: Sacha Gnjatic, PhD*

Taskforce Contributions to the field:

1. Preamble/overview commentary (JITC March 2015)
2. Recommendations/white paper 1/WG (WG2 JITC Mar. 2016)
3. Biomarker Technology short reports (1/month in JITC)
4. Clinical trial analysis project: standard cellular/cytokine assays and high throughput molecular analyses--going
5. Summary meeting: April 1st 2016, NIH (450 attendees)

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Immunotherapy Biomarkers Task Force: 2016

GROUP 1: "Immune monitoring assay standardization and validation—update" *Leaders: Magdalena Thurin, PhD and Giuseppe Massucci, MD JITC, Nov. 2016*

Volume 1:
INTRODUCTION
Assays Examples
1. Flow Cytometry
2. Enzyme-Linked ImmunoSpot (ELISpot)
3. Single Cell Network Profiling (SCNP)
4. Immunohistochemistry
5. Genomic landscape
6. Immunosequencing
7. Multiplexed-gene expression profiling

PRE-ANALYTICAL AND ANALYTICAL VALIDATION
Pre-Analytical Validation
1. Whole blood and specific immune cell subsets assays
2. Tissue-based assays

Analytical Validation
Precision
Multiparametric assays
Reference materials for immune assays
Post-Analytical Criteria
CONCLUSIONS AND RECOMMENDATIONS
RECOMMENDED GUIDELINES

Validation of Biomarkers to Predict Response to Immunotherapy in Cancer
Volume I: Pre-Analytical and Analytical Validation

Giuseppe V. Masucci, MD, PhD[1]; Alessandra Cesano, MD, PhD[2]; Rachael Hawtin, PhD[3]; Sylvia Janetzki, MD[4]; Jenny Zhang, PhD[5]; Ilan Kirsch, MD[6]; Kevin K. Dobbin, PhD[7]; John Alvarez, MD, PhD[8]; Paul B. Robbins, PhD[9]; Senthamil R. Selvan, PhD[10]; Howard Z. Streicher, MD[11]; Lisa H. Butterfield, PhD[12]; Magdalena Thurin, PhD[13*]

Society for Immunotherapy of Cancer

Immunotherapy Biomarkers Task Force: 2016

GROUP 1: "Immune monitoring assay standardization and validation—update" *Leaders: Magdalena Thurin, PhD and Giuseppe Massucci, MD JITC, Nov. 2016*

Volume II: INTRODUCTION
CLINICAL VALIDATION
Clinical Validity and Utility
Challenges in Clinical Validation
Recommendations for the clinical validation of a robust predictive marker
Validation of Clinical Utility
Clinical trial design for assay clinical validation and validation of clinical utility

Recommendations—criteria for evaluating the performance of a predictive biomarker

REGULATORY CONSIDERATIONS FOR ASSAYS SUBMISSION TO FDA
Regulation of diagnostic tests in the United States
Companion Diagnostics (CDx)
Regulatory considerations for development of predictive biomarkers
Regulation of biomarkers in the EU
CONCLUSIONS

Validation of Biomarkers to Predict Response to Immunotherapy in Cancer
Volume II: Clinical Validation and Regulatory Considerations

Kevin K. Dobbin, PhD[1*], Alessandra Cesano, MD, PhD[2*], John Alvarez, MD, PhD[3], Rachael Hawtin, PhD[4]; Sylvia Janetzki, MD[5]; Ilan Kirsch, MD[6]; Giuseppe V. Masucci, MD, PhD[7]; Paul B. Robbins, PhD[8]; Senthamil R. Selvan, PhD[9]; Howard Z. Streicher, MD[10]; Jenny Zhang, PhD[11]; Lisa H. Butterfield, PhD[12], Magdalena Thurin, PhD[13]

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Immunotherapy Biomarkers Task Force: 2016

GROUP 2: “New developments in biomarker assays and technologies”

Leader: Jianda Yuan, MD

Novel technologies and emerging biomarkers for personalized cancer immunotherapy

Jianda Yuan[1*], Priti S. Hegde[2], Raphael Clynes[3], Periklis G. Foukas[4,5], Alexandre Harari[4], Thomas O. Kleen[6], Pia Kvistborg[7], Cristina Maccalli[8], Holden T. Maecker[9], David B. Page[10], Harlan Robins[11], Wenru Song[12], Edward C. Stack[13], Ena Wang[14], Theresa L. Whiteside[15], Yingdong Zhao[16], Heinz Zwierzina[17], Lisa H. Butterfield[18] and Bernard A. Fox[10*] *JITC* Mar. 2016

Topics in the white paper:

Emerging checkpoint blockade biomarkers

neoantigen discovery

Epigenetics, seromics

flow and mass cytometry

TCR seq., multicolor IF

3D cultures, data analysis

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Immunotherapy Biomarkers Task Force: 2016

GROUP 3: "Assessing Immune Regulation and Modulation Systematically (high throughput approaches)" *Leader: David Stroncek, MD, JITC* Mar. 2017

INTRODUCTION
MONITORING A STUDY
MATERIALS TO BE EVALUATED:
- Serum and plasma
- Leukocytes
- T cells
- Myeloid cells
- NK cells and monocytes

Tissue Analysis
- Tissue collection and variability
- Multi-institutional studies
- Other sources for variability
- Early insights into the TME and immunotherapy

Bone marrow
- Collection and adequacy of the specimen
- Specimen transport and initial processing
- Further processing and downstream applications

Microbiome
- Modulation of cancer initiation, progression and response to therapy
- Development of microbiome studies
- Collection of specimens
- Sequencing and analysis

IMMUNE MONITORING ASSAYS
High-throughput proteome-based technologies
(i) SEREX
(ii) PROTEOMEX/SERPA
(iii) Protein arrays
(iv) SomaScan
(v) Luminex
Transcriptomics, Genome mutation analysis

ANALYSIS OF THE SYSTEMIC HOST RESPONSE
CLINICAL APPLICATION OF IMMUNE MONITORING
Approach to monitoring immunotherapy for *GI malignancies*
- Mismatch repair deficiency and anti-tumor immunity
- Anti-viral responses as surrogate markers for an active immunotherapy
- Liver toxicity, Endoscopy

Biomarkers and cell therapies
- Characteristics of transferred cells associated with better clinical outcomes
- Tumor-trafficking potential of adoptively infused T cells
- Monitoring the levels of adoptively transferred T cells
- Cytokine release following cell infusion

CONCLUSIONS AND RECOMMENDATIONS

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Immunotherapy Biomarkers Task Force: 2016

Group 4: "Baseline Immunity, tumor immune environment and outcome prediction"

Leader: Sacha Gnjatic, PhD (revised, JITC)

BACKGROUND

Multiplex blood profiles – can this be a window into the tissue microenvironment?

Immunoprofiling of antigen-stimulated blood, supernatant multiplex analysis and complements in tissue biopsy

T cell receptor diversity in anti-tumor response

Adjuvant Therapy and Biomarkers

Prognostic/predictive value of serological markers and B cells in cancer

MDSC and suppressive cells in the microenvironment

- Introduction
- Technology/examples
- MDSCs and immunotherapy
- Future developments

Multiplex IHC in clinically annotated material – Where are we and where are we going?

How the tumor microenvironment at a cellular level determines therapeutic approaches

How the tumor microenvironment at a genetic level determines therapeutic approaches

Gene Expression

Single nucleotide polymorphisms

- Introduction
- Importance of SNP in assessing immune responses

Recommendations and potential future directions

CONCLUSIONS AND RECOMMENDATIONS

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Biomarker Technology short reports (1/month in JITC)

1. Immunosequencing Ilan Kirsch

Journal for ImmunoTherapy of Cancer 2015, 3:29 (25 June 2015)

2. Enzyme-linked immunospot (ELISPOT) and Fluorospot assay Sylvia Janetzki.

JITC 2015, 3:30 (21 July 2015)

3. Single Cell Network Profiling (SCNP)

Rachael E. Hawtin and Alessandra Cesano. J*ITC* 2015, 3:34 (18 August 2015)

4. Flow and mass cytometry

Holden T. Maecker and Alexandre Harari. *JITC* 2015, 3:44 (15 September 2015)

5. Clinical validation for predictive markers Kevin K. Dobbin. *JITC* 2015, 3:40 (20 October 2015)

6. Quantitative real-time PCR assisted cell counting (qPACC) for epigenetic-based immune cell quantification in blood and tissue Thomas Oliver Kleen and Jianda Yuan. *JITC* 2015, 3:46 (17 November 2015)

Biomarker Technology short reports (1/month in JITC)

7. nCounter® PanCancer Immune Profiling Panel (NanoString) Alessandra Cesano. *JITC* 2015, 3:42 (15 December 2015)

8. Protein microarray ('seromics') Jianda Yuan, Ena Wang and Bernard A. Fox. *JITC* 2016, 4:2 (19 January 2016)

9. Multiplexed Tissue Biomarker Imaging Edward C. Stack, Periklis G. Foukas and Peter P. Lee *JITC* 2016, 4:9 (16 February 2016)

10. Immunoprofiling of Antigen-stimulated blood Laura Rosa Brunet, Samuel LaBrie and Thorsten Hagermann *JITC* 2016, 4:18 (15 March 2016)

11. Whole exome sequencing for neoantigen discovery and precision oncology

Pia Kvistborg, Raphael Clynes, Wenru Song, and Jianda Yuan *JITC* 2016 (19 April 2016)

12. Immunoscore Colon Fabienne Hermitte *JITC (20* September 2016)

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Immunotherapy Biomarkers Task Force: 2015-2017

Taskforce Contributions to the field:

1. Preamble/overview commentary (JITC March 2015)
2. Recommendations/white paper 1/WG (JITC: 4 published ,1 submitted/revised)
3. Biomarker Technology short reports (1/month in JITC x 12 months)
4. Clinical trial analysis project: standard cellular/cytokine assays (Pittsburgh) and high throughput molecular analyses (Sidra, Qatar). Approved. ECOG1608/Hodi Melanoma, ipilimumab +/- GM-CSF 245 pt.
5. Summary meeting: April 1st 2016, NIH (Meeting Report JITC Mar. 2017)

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