SITC Immunotherapy Biomarkers Task Force 2015-2016

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Presenter Disclosure Information

Lisa H. Butterfield, Ph.D.

The following relationships exist, possibly related to this presentation:

Kite Pharma, stock options
Caladrius (formerly NeoStem), Scientific Advisory Board member,
Oxford Immunotec, Affymetrix/eBioscience, Merck, Biodesix, Verastem, Astra Zeneca: consultant/advisory board

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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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: 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
3. Biomarker Technology short reports (1/month in JITC)
4. Clinical trial analysis project: standard cellular/cytokine assays and high throughput molecular analyses--ongoing
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*]

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

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

Leader: Sacha Gnjatic, PhD

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)

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

Biomarker Technology short reports (1/month in JITC)

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* September 2016

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Taskforce Contributions to the field:

1. Preamble/overview commentary (JITC March 2015)

2. Recommendations/white paper 1/WG (JITC: 3 published 2 submitted)

3. Biomarker Technology short reports (1/month in JITC x 12 months)

4. Clinical trial analysis project: standard cellular/cytokine assays and high throughput molecular analyses—ongoing agreements….
   ECOG1608/Hodi Melanoma, ipilimumab +/- GM-CSF 245 pt.

5. Summary meeting: April 1st 2016, NIH (450 attendees, Meeting Report drafted)

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