Summary of the US-Japan Workshop on Immunotherapy Markers in Oncology

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US-Japan Workshop on Immunological Biomarkers in Oncology

- **Support:**

  Office of International Affairs, NCI

  Japan Science and Technology Agency

- **Date: 23rd and 24th of March 2009**

- **Relationship to iSBT:**

  Related to a task force launched by iSBTc and US FDA to identify strategies for biomarker discovery and validation in the field of biotherapy.

US-Japan Workshop

23rd and 24th of March 2009@Hawaii Island

Background

Biomarkers

Currently, biomarkers are either not available or have limited diagnostic, predictive or prognostic value.

A)Lack of predictive biomarkers for the effective conduct of biotherapy trials (permitting optimization of patient selection/stratification)

B)Lack of surrogate biomarkers for early assessment of product effectiveness.

The iSBTc-FDA task force

• To address the need to expeditiously identify and validate biomarkers relevant to the biotherapy of cancer.

•Two principal components:

A)Validation and application of currently used biomarkers

B)Identification of new biomarkers and improvement of strategies for their discovery.

The purposes of the US-Japan workshop

a) **To discuss novel approaches to enhance the discovery of predictive and/or prognostic markers in cancer immunotherapy**

b) **To define the state of the science in biomarker discovery and validation.**

The participation of Japanese and US scientists provided the opportunity to identify shared or discordant themes across the distinct immune genetic background and the diverse prevalence of disease between the two nations.

Sessions

- **Immune response as prognostic signatures in cancer (part A)**
- **Immune response as prognostic signatures in cancer (part B)**

- **Markers predicting response to immunotherapy**

- **Genetic Background in Immune-relevant genes – relation to outcome –**

- **Immunotherapy Treatments and Markers in Clinical Trials Phase II and III**

- **Assay Validation and Clinical Evaluation – Are We Ready?**
- **Assay Validation and Clinical Evaluation – Are We Ready**

Predictive biomarkers

Biomarker	Therapy	Disease
Telomere length	*Adoptive therapy*	*Melanoma*
VEGF	*IL-2 therapy*	*Melanoma*
CCR5 polymorphism I	*L-2 therapy*	*Melanoma*
Carbonic Anhydrase IX	*IL-2 therapy*	*RCC*
IFN- γ polymorphism	*Immuno (IL-2)-chemo*	*Melanoma*
STAT-1, CXCL-9, -10, -11, ISGs	*IFN- α therapy*	*Several Ca's*
IL-1 α,-1 β,IL-6,TNF-a,CCL3,CCL4 I	*FN- α therapy*	*Melanoma*
CCL5, CCL11, IFN- γ, ICOS, CD20	*GSK/MAGE3 vaccine*	*Melanoma*
IL-6 polymorphism	*BCG vaccine*	*Bladder Cancer*
MFG-E8	*GM-CSF/GVAX (pre-clin)*	*Prostate*
T regulatory cells	*hTERT pulsed DCs*	*Solid Cancer*
K-ras mutation	*Cetuximab*	*Colorectal Ca.*
CCL2, -3, -4, -5 CXCL-9, -10	*Preclinical*	*Melanoma*
T cell mulifunctionality	*Preclinical*	
SNAIL	*Preclinical*	

Prognostic Biomarkers

(useful for patient stratification/data interpretation)

Biomarker	***Therapy***	***Disease***
Oncotype DX, Mamma Print	-	*Breast Cancer*
TGF-β	-	*Breast Cancer*
Korn Score	-	*Prostate Cancer*
IFN-γ, IRF-1, STAT-1, ISGs, IL-15, CXCL-9, -10, -11 and CCL5	-	Prostate Cancer
IFN-γ, IRF-1, STAT-1	-	*Colorectal Cancer*
VEGF	-	*Colorectal Cancer,* Nasopharyngeal Ca
ARPC2, FN1, RGS1, WNT2	-	*Melanoma*

Mechanistic/End Point Biomarkers

Biomarker	***Therapy***	***Disease***
IFN- γ*, IRF-1, STAT-1, ISGs, IL-15, CXCL-9, -10, -11 and CCL5*	IL-2 therapy /TLR-7 therapy	Melanoma/ Basal Cell Cancer
IRF-1, STAT-1, ISGs, IL-15, CXCL-9, -10, -11 and CCL5	Vaccinia virus (Xenografts)	Solid tumors
CXCL-9, -10	*Herpes simplex virus*	Ovarian CA (syngeneic model)
^{18}F-FDG localization	*Anti-CTLA-4 therapy*	*Melanoma*
Epitope Spreading	*DC-based therapy*	*Melanoma*
Kinetic regression/growth model	-	-

Identified converging concepts

Enhanced knowledge of interferon-related pathways was found to be central to the understanding of immune-mediated tissue specific destruction (TSD) of which tumor rejection is a representative facet.

Interferon-stimulated genes

- Although the expression of interferon-stimulated genes (ISGs) likely mediates the inflammatory process leading to tumor rejection, it is insufficient by itself and the associated mechanisms need to be identified.

- It is likely that adaptive immune responses play a broader role in tumor rejection than those strictly related to their antigen-specificity.

- Their primary role is to trigger an acute and tissue-specific inflammatory response at the tumor site that leads to rejection upon recruitment of additional innate and adaptive immune mechanisms.

Other candidate systemic and/or tissue-specific biomarkers

- Other candidate systemic and/or tissue-specific biomarkers were recognized that might be added to the list of known entities applicable in immunotherapy trials.

- The need for a systematic approach to biomarker discovery that takes advantage of powerful high throughput technologies was recognized.

- Immunotherapy is still in a discovery phase and only a few of the current biomarkers warrant extensive validation.

Need for validation

- While current technologies have almost limitless potential, inadequate study design, limited standardization and cross-validation among laboratories and suboptimal comparability of data remain major road blocks.

- The institution of an interactive consortium for high throughput molecular monitoring of clinical trials with voluntary participation might provide cost-effective solutions.

Conclusion

- Recurrent themes related to the diagnosis, prognosis and responsiveness to therapy are emerging in the context of cancer immunotherapy.

- Although relatively unrefined, these concepts appear to be valid.
- They have been reported in concordance by various groups
- Several of the observed biomarkers represent conceptually similar pathways involved in tissue rejection or tolerance.

- It is encouraging to see that among the thousands of biological permutations that could be considered at the theoretical level, direct human observation is providing a tool to restrict the inquisitive mind of scientists to a much more defined circle of possibilities to be explored in the future.

Commentary

Emerging concepts in biomarker discovery; The US-Japan workshop on immunological molecular markers in oncology

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