

Defining the Critical Hurdles in Cancer Immunotherapy*

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***Identified by the iSBTc and Collaborating
Associations**



Collaborations Group:

Last year, at the 24th Annual Meeting of the International Society for Biological Therapy of Cancer (iSBTc), representatives from eight immunotherapy organizations representing Europe, Japan, China and North America convened to discuss areas for collaboration to improve development and delivery of cancer immunotherapy.



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The Problem:

Scientific discoveries that provide strong evidence of antitumor effects in preclinical models often encounter significant delays before being tested in patients.

While some of these delays have a scientific basis, others do not.

We need to do better.

The Solution

Identify the hurdles to the effective translation of cancer immunotherapy (N. Disis).

Develop International working groups to make recommendations.

Have these vetted by participating organizations.

Use to facilitate changes that accelerate translation of novel immune based therapies.

Critical Hurdles in Cancer Immunotherapy Identified by the iSBTc and Collaborating Associations

1. Animal models inadequate predictors of efficacy
2. Prolonged time to obtain approval for clinical trial
3. Complexity of cancer biology/immunology
4. Inability to obtain approval to combine most promising new agents for in immunotherapy trials
5. Lack of definitive biomarker(s) for assessment of clinical efficacy of cancer immunotherapies
6. Paucity of translational research teams
7. Insufficient exchange of information critical to advancing the field

1. Animal models inadequate predictors for cancer immunotherapy strategies

- small tumors, established for 3-5 days
- inherent “immunogenicity” of the tumor model or xenogeneic proteins.
- Age of tumor cell lines - genetic drift possible in 100 mouse generations.
- Tg models (some) great tools
 - Other issues: Tolerance, precursor frequency, influence of tumor burden.
 - Model dependent (TCR Gene transfer)

SOLUTIONS?

- While no model is perfect.. alternatives that can be tested to see if they are better predictors..
- Human xenograft models? Effects of immune system addressed?
 - Human xenograft models with human immune cells.
- Development of spontaneous tumor models in transgenic mice
 - Tolerant
 - Similar defects in the tumor microenvironment
 - tumor growth is quite heterogeneous
 - * mimics human tumors.

Problems?

- Heterogenic phenotype of most GEM models requires larger numbers of animals to be studied to assess significance of the intervention.
- Cost of maintaining transgenic colonies of GEM can be prohibitory.

2. Prolonged time to obtain approval to initiate clinical trials.

- Critical (Institutional) hurdle for some investigators.
 - can add seven months to approval process
- National regulatory approval
 - FDA and EMEA short turn around
 - Other countries may take a year

3. Complexity of cancer biology/immunology

- Cancer heterogeneity
 - propensity to develop resistance
 - cancer histology: not a single disease
 - variables that influence a patient's ability to generate and maintain an effective anti-tumor immune response.
 - overall immune status*: age, previous therapeutic interventions, elements directly and/or indirectly related to the tumor.
- * *no consensus on biomarker(s) for assessing immune status.*

4. Inability to combine promising new agents for immunotherapy trials

- Preclinical studies document significant synergies and improved outcomes
- Promising: wide range of active agents being combined with immunotherapy
- Trials with combined agents may present additional complexities and risks to the drug developer and patient.

Problems*:

- Approved agents: the hurdles may be restricted to cost.
 - Agents in development: corporations may not want to risk that the combination trial may interfere with their drug development plan.
 - Investigators may invent something that could limit the utility of that drug or negative results may devalue intellectual property (IP).
 - Alternatively, mechanism of action studies may lead to broad claims by the investigators further limiting a company's IP.
- * will take much longer to put together the “dream teams” of immunological agents

5. Lack of definitive biomarker(s) for assessment of clinical efficacy of cancer immunotherapies

The iSBTc Taskforce for immunotherapy biomarkers, composed of nine societies and participating organizations, has addressed this in detail

(Butterfield L., et al., submitted*).

builds on NCI's REMARK criteria, MIFlowCyt, MIACA and MIATA

Eight of the nine challenges identified by this Taskforce were related to immunological monitoring and included:

challenges identified by Taskforce related to immunological monitoring:

1. Processing and storage of blood samples to bank PBMC and serum for immunologic studies.
2. Assay standardization and harmonization before testing patient samples
3. Centralization of immunological monitoring
4. Standardized assays that should be used for clinical trial antitumor immune response determination
5. How assay data should be analyzed for “responder” and “non-responder” identification
6. Reporting immunological monitoring data in publications
7. Validation of specific assays and/or analytes as biomarkers of clinical response
8. Novel assays in development for immunological testing of patients

At the heart of the immunological monitoring hurdle is.....

The limitation that despite substantial efforts from many groups, we do not know which parameters of immune responses are important, and which assays used to assess these parameters are optimal for correlation with efficacy analysis.

Indeed, the tumor-specific cellular immune response promoted by immunization often has not correlated with clinical cancer regression

6. Paucity of teams dedicated to translational research in cancer immunotherapy ?

- Far too few for diseases that need help.
- Given cost, industry cannot do it all.
- Academic translational investigator teams, close to both basic and clinical science, are likely in the best position to move “their” agent to clinic.
- Requires an investment in infrastructure:
 - Simple clean rooms or GMP
 - Human capital
 - Leadership: ability to organize, lead, motivate, meld and sustain diverse groups of investigator in translational teams (Transl. Science. Disis and Slattery, 2010).

7. Insufficient exchange of information critical to advancing the field ?

Given the increasing complexity it is becoming less feasible for a single group to have the detailed knowledge and resources to investigate, analyze, select and implement the best strategies to move forward in clinical trials for any given indication.

Possible Solution

- link clusters of investigators with common interest (D. Schendel).
- The histocompatibility/HLA field might serve as an example
 - participants from around the world supplied reagents, ideas, shared projects to move the whole field of transplantation forward.
 - Enabled continual progress over several decades.
 - Laid the foundation for all transplantation
 - not have been feasible through the efforts of one single individual or organization

Associations Collaborating with iSBTc on this Project

Association for Immunotherapy of Cancer (CIMT)

Biotherapy Development Association (BDA)

European Society for Cancer Immunology and Immunotherapy (ESCI)

Italian Network for Tumor Biotherapy (NIBIT)

Japanese Society of Cancer Immunology (JSCI)

Nordic Center for Development of Antitumour Vaccines (NCV-network)

Chinese Society of Clinical Oncology (CSCO)