Defining the Critical Hurdles in Cancer Immunotherapy

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Abstract

Scientific discoveries that provide strong evidence of antitumor effects in preclinical models often encounter significant delays before being tested in patients with cancer. While some of these delays have a scientific basis, others do not. We need to do better. Innovative strategies need to move into early stage clinical trials as quickly as it is safe, and if successful, these therapies should efficiently obtain regulatory approval and widespread clinical application. In late 2009 and 2010 the Society for Immunotherapy of Cancer (SITC), convened an "Immunotherapy Summit" with representatives from immunotherapy organizations representing Europe, Japan, China and North America to discuss collaborations to improve development and delivery of cancer immunotherapy. One of the concepts raised by SITC and defined as critical by all parties was the need to identify hurdles that impede effective translation of cancer immunotherapy. With consensus on these hurdles, international working groups could be developed to make recommendations vetted by the participating organizations. These recommendations could then be considered by regulatory bodies, governmental and private funding agencies, pharmaceutical companies and academic institutions to facilitate changes necessary to accelerate clinical translation of novel immune-based cancer therapies. The critical hurdles identified by representatives of the collaborating organizations, now organized as the World Immunotherapy Council, are presented and discussed in this report. Some of the identified hurdles impede all investigators; others hinder investigators only in certain regions or institutions or are more relevant to specific types of immunotherapy or first-in-humans studies. Each of these hurdles can significantly delay clinical translation of promising advances in immunotherapy yet if overcome, have the potential to improve outcomes of patients with cancer.

Introduction

Globally, cancer claimed an estimated 7.6 million lives in 2008 and is on pace to double that number by 2030 [1]. The impact of this disease on humanity is difficult to measure. The Milken Institute estimates that in the United States (US) alone, a 1% reduction in cancer mortality has an economic value of $500 billion [2]. Currently the National Cancer Institute (NCI), National Institutes of Health (NIH), foundations, governments, biotechnology and pharmaceutical companies around the world are investing substantially in research to conquer this disease. Over the past decade, discoveries in basic cancer research related to this investment have provided an enormous number of insights, reagents, drugs and clinical protocols with potential to significantly improve cancer outcomes. Nowhere is this potential more striking and relevant to a wide spectrum of human cancers than in research on cancer immunotherapy, which has the capacity to provide durable clinical responses in even the most challenging cancers. Nonetheless, the translation of these discoveries from the "bench to the bedside" has been painfully slow.

In an effort to accelerate translation of new developments in basic immunology into patients with cancer, representatives from eight immunotherapy organizations representing Europe, Japan, China and North America (Figure 1) convened an "Immunotherapy Summit" at the 24th Annual Meeting of the International Society for Biological Therapy of Cancer (iSBTc; now the Society for Immunotherapy of Cancer, SITC). One of the concepts raised by SITC and defined as critical by all parties was the need to identify hurdles that impede effective translation of cancer immunotherapy. Subsequently, ten organizations (Figure 2) met again in late 2010 at the 25th Annual Meeting of SITC to discuss next steps and to commit to regular conference calls. While this is an important first step, identification of these hurdles is just the beginning. The development of collaborative, international working groups to identify solutions and help remove

these hurdles could increase the speed at which novel, effective immunotherapy strategies reach patients with cancer. That is the goal.

The hurdles identified by representatives of the (now fifteen) collaborating organizations (Figure 3) can be grouped into nine general themes (Table 1). In some instances an identified hurdle is substantially interconnected with another hurdle or set of hurdles. For example, the lack of validated biomarkers further complicates the design and evaluation of clinical trials that combine immunotherapeutic agents. Thus efforts to address the identified hurdles to the translation of cancer immunotherapy must be through a coordinated, integrated, multidisciplinary and international approach.

What is Cancer Immunotherapy? Cancer immunotherapy is the original targeted therapy and includes any strategy that utilizes the anticancer immune response or components of the immune system, as cancer treatment. Seventeen immunotherapy products have received FDA approval in the past quarter century [3]. These include non-specific stimulators, cytokines, monoclonal antibodies, radiolabelled antibodies, immunotoxins, and cell-based therapy (reviewed in [3]). Further, the recent observations that immune response, characterized by immunohistochemistry, has better prognostic power than standard staging systems underscores the importance the endogenous immune response plays in patient outcomes and the potential impact boosting this immune response has for increasing survival [4] [5]. These findings may help to recast the current classification, and to identify the high-risk patients who would benefit the most from adjuvant therapy.

1. Limitations of Preclinical Animal Models

While preclinical animal models have provided the basis for our understanding of immune function and significant insights into the mechanisms that regulate therapeutic efficacy of immunotherapy, the current models have not been consistent predictors for the efficacy of cancer immunotherapy strategies that enter the clinic. One reason for this disconnect may be that small, transplantable tumors, established for 3-5 days in an animal model, fail to recapitulate the complex, integrated pathophysiological setting, in which patients can have a large tumor burden that they have lived with for months to years. Models that utilize advanced or spontaneous tumors may begin to address this shortcoming. Another limitation is the inherent "immunogenicity" of the tumor model used. Experiments with tumors expressing xenogeneic proteins are frequently coupled with transgenic T cells to address basic questions about T cell trafficking, cytokine profiles and clonal expansion, in addition to many other scientific questions relevant to understanding the immunological response to tumors. However, given the foreign nature of the xenogeneic protein and the ease with which an immune response can be generated against these targets in wild type (WT) mice, these tumors are considered inadequate for modeling the human immune response to immunotherapy strategies. In other cases, the use of transplantable tumors without xenogeneic protein constructs may be useful. Further, many of the frequently used tumor cell lines were generated 20 – 40 years ago; given the genetic drift possible in 100 generations, the inbred mice may exhibit substantial histocompatibility differences that can result in these tumors being more immunogenic today than when they were originally developed, potentially limiting their usefulness as models of human disease. Another limitation is that the vast majority of studies are done in genetically identical inbred animals that do not represent the genetic diversity found in humans or in young mice, lacking the impact of aging on the immune system [6]. Some therapeutic interventions are tested in human xenograft models in immune-deficient mice, in which effects on and by the immune system are not addressed [7]. Human xenograft models in which human immune cells are also transferred are a potential improvement [8], although the reality of a fully functional

human immune system in a mouse is still far away. Recently, severely immunodeficient mouse strains have been developed such as NOD.Cg-*Prkdc*^{scid} *IL2rg*^{tmWjl}/Sz (NOD/SCID/IL-2Rγ^{null} or NSG), which can be reconstituted with a human hematopoietic system through engraftment of human cord blood CD34^{+} cells [9]. These offer unique opportunities to study human grade immunomodulatory reagents. The development of spontaneous tumor models in transgenic mice (in which animals are tolerant to genes used to induce the malignant event) offer multiple advantages over transplantable tumors for many applications. The tumors in models using genetically engineered mice (GEM) often develop similar defects in the tumor microenvironment, limiting host immune responses. Moreover, tumor growth is quite heterogenic mimicking human tumors. The heterogenic phenotype of most GEM models requires larger numbers of animals to be studied to assess significance of the intervention. Unfortunately, the cost of generating and maintaining transgenic colonies of GEM can be prohibitive for many investigators. In addition, these models are usually based on the tissue-specific expression of a strong driver oncogene, which may overwhelm the immune-surveillance and immune-editing steps of cancer development. One example of an alternative approach to integrate an oncogenic signal in tissue has been recently reported [10]. Hydrodynamic co-delivery of genes encoding β-catenin (CAT) and MET or AKT induced steatotic hepatocellular adenomas that transitioned to hepatocellular carcinomas (HCC) or led to rapid induction of HCC, respectively. This innovative approach overcomes many of the afore mentioned limitations by providing a rapid and relatively inexpensive method for generating spontaneous tumors in mice of a specific MHC background, in specific gene knock-out, transgenic, or aged mice. Together the preclinical models remain an important "proving ground" for some classes of immunotherapies and for the evaluation of possible synergies with combination immunotherapies. While imperfect, advanced and spontaneous tumor models are still

considered to be more useful than in vitro studies at informing clinical trial designs of novel agents and combination immunotherapy.

With regard to predicting safety of novel antigen-based cancer immunotherapies by using animal models, numerous limitations exist. Vaccination with antigens relies on the species- (and allele-) specific binding of antigen to human leukocyte antigen (HLA) receptors (in the case of short peptide antigens) and species-specific processing of antigens by a complicated interplay involving different proteasome species, other proteases, heat shock proteins, TAP transporter and finally, again, binding to HLA receptor (in the case of protein, long peptide, RNA or DNA vaccines). Even if mice were generated that expressed the appropriate HLA type and the human antigen sequences, such models might not adequately predict safety or autoimmune effects based on the diversity of the other components of antigen processing machinery involved.

Preclinical animal studies have also been used to assess potential toxicity of immunologically active agents. In the absence of in vivo preclinical data, in-vitro assays have been used to identify the 'minimum anticipated biological effect level' (MABEL). A recent report offers a protocol that provides increased sensitivity to detect soluble T cell stimulants [11]. Alternatively, micro dosing or flat dose escalation studies have been proposed. The lethal toxicity associated with chimeric antigen receptor (CAR) gene-modified T cells is an example where a preclinical model did not exist to appropriately test the potential toxicity [12,13]. The two reported cases led to both National Institutes of Health (NIH) and the US Food and Drug Administration (FDA) review and resulted in modifications to clinical trial design where the dose of adoptively transferred gene-modified T cells is escalated from a much lower dose than where toxicity was observed. As new agents and combinations of immunotherapies are evaluated,

flexibility of the regulatory agency providing oversight will be critical for the efficient translation of these strategies to patients.

Opportunities:

Could standards be suggested for investigators using preclinical models to improve the utility or interpretation of animal studies? Are there other instances when proof-of-concept studies in animals can be waived? Additionally, the limitation of assessing toxicity of immunological agents, specifically monoclonal antibodies, in non-human primates has been raised at several SITC conferences. These studies, due to their high cost, limit the number of agents that are moved to the clinic. How often are such studies instructive of clinical toxicities and when is it appropriate to discuss with regulatory agencies the elimination of these studies?

2. Delayed Institutional, Administrative and Regulatory Approval

The time to obtain approval to initiate a clinical trial has been identified as a critical hurdle for some investigators. In the global science community there are academic institutions where administrative review can add as much as seven months to the approval process. At other centers, thanks in part to standardized procedures and protocols, and institutional familiarity with the proposed investigational strategies, administrative and institutional review board (IRB) approval can be obtained relatively quickly. Consistent with the difficulties perceived in the U.S. to open trials, there has been a large movement of cancer trials to Europe and Asia due to the slow activation of trials in the U.S.

With regards to regulatory approval within the US, FDA reviewers must respond to the application for an investigational new drug (IND) within 30 days of submission. While this efficient review process provides no guarantee for rapid approval, the feedback that the agency provides, sometimes prior to the 30 day window, allows for modifications that can sometimes

resolve issues and avert a clinical hold on the application. Health Canada employs the same 30 day rule for review of clinical trials. Similarly, the European Medicines Agency (EMA) has the option of an accelerated review procedure for products of major therapeutic interest. In contrast, regulatory agencies in some countries may take a year or more to approve a comparable application.

Another major difference between nations is the disparity in production requirements for the biologics or drugs used in the clinical trials. In the US, FDA exempts most Phase 1 drugs, including biologics, to adhere to Current Good Manufacturing Practice (cGMP) regulations [14]. In contrast, the European Union has implemented a rule that all early phase studies must be performed under GMP. While the use of GMP in the European Union is thought to have increased the quality of clinical trials, especially of investigator-initiated trials, it has clearly added significant cost and limited the capacity of many academic institutions to perform translational cancer immunotherapy trials.

Opportunities:

A cost-benefit analysis of restrictions that limit translation of novel therapies to patients with advanced cancer may be appropriate. Are there other processes, short of GMP, that might be employed to increase quality but not the cost of some early phase clinical trials? This is a particularly important issue since there is great variability in access to facilities that function using cGMP and GMP guidelines that also have the technologies available to produce novel biologics developed by academia. Even when a facility can be identified, traditional funding mechanisms rarely pay for the production of the new biologic.

3. Complexity of Cancer, Tumor Heterogeneity and Immune Escape

Clearly cancer is a complex problem and this complexity has been identified as a critical hurdle to the application of cancer immunotherapy. The heterogeneity of the cells making up the cancer and their propensity to develop resistance to any form of therapy is well established [15, 16]. Further, histology results suggest that a specific cancer, for example melanoma, is not a single disease, but likely 13 or more different diseases [17], all of which may ultimately be found to respond uniquely to therapeutic interventions [18]. Also, local stromal non-cancer cells have a direct influence on tumor progression and outcome [19], illustrating the complexity of tumor microenvironment. In addition to the potential heterogeneity within each tumor is the likelihood that tumor at each metastatic site is heterogeneous in expression of antigens, or lack thereof, and/or escape mechanisms; substantially increasing the complexity of the disease in each patient far beyond the simple categorization of that disease.

On top of the complexities directly related to the tumor are variables that can influence a patient's ability to generate and maintain an effective antitumor immune response. A major factor in this setting is the overall immune status of the patient. This is influenced by age, previous therapeutic interventions as well as by elements directly and/or indirectly related to the tumor. The status of the patient's immune system and its impact on clinical outcome has important implications for the identification of host-related prognostic markers, of host-related predictive markers to classical chemotherapies and radiotherapies as well as that of novel innovative immunotherapies. Unfortunately, there is no consensus on a biomarker(s) for assessing immune status of individuals enrolling in immunotherapy trials [20], however this should not prevent investigators from incorporating novel strategies to assess immune competence of patients enrolling in trials. Recent reports suggest that the immune signature at the tumor site, characterized by genetic or histological assessment, may predict responsiveness to therapy [21,4]. Additional studies have also shown that pre-surgical clinical trials can be used as a mode of investigating the impact of immunotherapeutic agents on human immune

responses in both the systemic circulation and tumor microenvironment, thus providing a feasible platform on which to obtain crucial data that can then be applied to larger clinical trials [22,23]. Support for these types of Phase Ia or Phase IIa trials [24], which are designed to investigate mechanisms and biologic endpoints, is necessary in order to identify potential biomarkers that correlate with benefit or resistance to therapy.

While additional validation is required, these observations are encouraging investigators to redouble their efforts to assess immune competence of patients entering immunotherapy trials. Also important to these efforts, is the need to encourage testing of new agents in the neo-adjuvant setting to allow improved assessment of potential biomarkers of early response.

Another level of complexity is the ability of cancer cells, under the selective pressure of an antitumor immune response, to shed targets or accessory molecules in ways that allow them to evade detection and killing by immune cells [25,26,27]. Alternatively, tumors may express inhibitory molecules that impair the antitumor immune response and limit the impact of the therapeutic intervention. While the complexity of this problem is considered a critical hurdle, appreciating this complexity and designing therapeutic combinations to augment immune responses and neutralize escape mechanisms holds substantial promise for improving the effectiveness of cancer immunotherapy.

Opportunities:

Since the characterization of tumors prior to and following immunotherapy has not been well studied, the consortium might encourage a multicenter evaluation of such specimens. This could include the development of a taskforce to provide input on a global standardization of the tumor microenvironment. In support of this concept on October 24-25, 2012, SITC will provide opportunities for the consortium to gather in North Bethesda for a two-day workshop on evaluation of the tumor microenvironment. Performing systematic biopsies of tumor lesions

considered as representative targets should also be considered and ethically admitted in most protocols to allow a dynamic characterization of immunomodulation. Further, modifications to some informed consent documents should be considered to ensure that patient specimens could be used to aid biomarker development. Additionally, better identification of major immune defects in patient groups may lead to more appropriate therapies.

4. Limited Availability of Reagents for Combination Immunotherapy Studies

While many preclinical studies have documented significant synergies and improved outcomes when immunotherapy is combined with a wide range of agents, trials with combined agents may present additional complexities and risks to the drug developer and patient. One problem is the classical method to find the maximum tolerated dose (MTD) in phase I studies. Biological products, in particular vaccines, have less toxicity and may have a bell-shaped dose immune response curve. This has promoted the idea of dosing based on biological activity assessed by a biomarker.

Opportunities:

Developing a strategy that takes into consideration both toxicity grade and the "immune response score" could provide an optimal biologically active dose. While some investigators are implementing such strategies into their studies, consensus on this matter would likely aid the implementation of combination immunotherapy trials.

It is becoming increasingly apparent that many standard cancer treatments may enhance the effectiveness of immunotherapy, possibly due to increased inflammation, release of antigen and danger signals, immunogenic cell death pathways and dampening the effects of regulatory cells. Indeed, many investigators are exploring immunotherapy combinations with other

immunotherapeutic agents, biologicals, targeted therapeutics, chemotherapy, radiation and/or surgery as promising strategies to improve cancer outcomes [28,29,30,31,32]. This enthusiasm has been driven by the appreciation that even agents long thought to work solely on tumor cells can have potent effects on the anti-cancer immune response.

For agents that are already approved, the hurdle may simply be limited resources or high costs necessary to acquire the specified treatment for a combination study unless the company marketing the product is willing to supply the agent for the study. However, for agents that are in early/late phase clinical trials and are not already approved, pharmaceutical sponsors may not want the added risk that the combination trial may interfere with their drug development and registration plan. One concern is that a novel strategy employing company A's agent X in combination with company B's agent Y, may result in a severe adverse event (SAE) that raises regulatory concerns about either drug, X or Y, as a single regimen. This may prompt additional patient safety monitoring requirements in all ongoing trials with drug X or Y, which pose particular challenges if either drug is in large, multi-national registration trials. Given the SAEs that have been observed with single agents (IL-2, anti-CTLA-4) and the limited experience with combining immune-potentiating biologicals, [33,34,35] there exists the possibility that combinations may increase toxicity. However, the potential to improve efficacy significantly, without concomitantly increasing toxicity, as has been observed in preclinical and a few clinical studies, provides a compelling rationale for combining immune-potentiating agents. It is important to continue the discussions in this area and try to agree upon a compromise that will allow earlier testing of combinations particularly in diseases that are in desperate need of new therapies. Most cancers are not cured by one agent. It is critical to take this into account and to work toward developing a mechanism for testing combinations where the scientific rationale supports the trial design.

Other concerns surround the possibility that investigators could discover something that might limit the utility of that drug or obtain negative results that devalue intellectual property (IP). Alternatively, mechanism of action studies may lead to broad claims by the investigators, further limiting a company's IP. Finally, integration of clinical and regulatory operational efforts between two companies poses challenges. These include selection of only one of the companies or academic institutions to hold the IND and assume full regulatory responsibility for a combination trial as well as dissemination of all single agent IND safety reports from each company to all investigators involved in the combination trial. If these hurdles cannot be addressed, it will take much longer to put together the "dream teams" of immunological agents that many in our field are eager to evaluate in the clinical setting based on synergisms observed in preclinical studies. At the 2010 Collaboration Summit on cancer immunotherapies hosted by SITC the ten participating organizations agreed that promoting innovative trials of combinations is a high priority. Late last year the NCI took constructive action by launching the Cancer Immunotherapy Network (CITN), providing a mandate to develop and conduct clinical trials with prioritized immunotherapy agents alone or in rational combinations [36,37,38]. While resources will be limited, the CITN establishes a cooperative, multicenter framework to advance a number of critical studies. But this is not enough. More needs to be done to enable exploratory trials of immunotherapy combinations.

Opportunities:

One strategy may be to increase the number of academic manufacturing facilities that could provide clinical grade materials for clinical trials. Particularly for clinical grade agents that large pharmaceutical companies are not interested in and that small biotech may not be able to distribute to all the potential partners involved. This may be particularly helpful for vaccine components such as recombinant proteins, synthetic peptides, TLR agonists, etc. One solution would be to have GMP facilities supported in academic institutions, for instance in the pharmacy