More on cancer vaccine

There was mainly good news at the 6th International Conference on Cancer Vaccine held from 5 to 9 October 1998 in Manhattan, NY, and organized by the Cancer Research Institute. First was the quality of the speakers. A panel of outstanding scientists offered significant research in cancer vaccines and basic immunology that have been carried out in the last few years. Second was the informal atmosphere of the conference. And last, but not least, were the topics of the meeting. All of these certainly contributed to clarify advances and progress in this field of promising therapeutic approaches.

Tumor-associated antigens

In the last three decades the research of immunogenic tumor-associated antigens, that can be recognized by autologous T cells, has been the object of intensive investigations (L. J. Old, T. Boon). In fact, the detection of these antigens and, moreover, the identification of the genes encoding for these proteins have provided potential targets for cancer immunotherapy. The applications of serological analysis of antigens by re-combinant expressing cloning (SEREX) approach, of the enzyme-linked immunospot (ELISPOT) assay and of the renewed techniques based on biochemical characterization of antigens have proven to be powerful methods for detection and monitoring tumor-associated antigens recognized by humoral immune system (M. Pfreundschuh; U. Sahin, Y.-T. Chen, H.-G. Rammen-see, P. van der Bruggen). Therefore, in the past five years, more than 600 new antigens have been defined and classified. Despite this huge number of detected tumor-associated antigens, however, the therapeutic impact of these findings on clinical trials is still modest. Consequently, attention has been focused on tumor immune responses.

Immune recognition and effector functions

The immune response, against tumors, is complex and only partially understood. Immunologic models and cancer vaccine trials have focused on the pivotal role of antigen-presenting cells (APC) and tumor killer cells. In vitro and in clinical trials, one of the crucial and therapeutically promising category of APC are the dendritic cells (DC). Their main activities are the recognition of the tumor-associated antigen and antigen uptake, the synthesis of major histocompatibility complex (MHC) and co-stimulatory molecules, the activation of helper T cells and the delivery of the processed antigen on killer T cells (A. Lanzavecchia, R. M. Stein- man, C. J. M. Melief, W. J. Storkus). DC can be harvested by leukophoresis, collected and purified from culture and tissues, stimulated (i.e., the administration of Flt3 Legand (FL)) and, furthermore, co-cultured 'pulsed' or loaded with exogenous tumor antigen or cellular RNA, transfected with virus carrying genes coding for tumor antigen and can present the antigen to elicit strong cytotoxic T-cell (CTL) responses. Moreover, pulsed DC, conditioned to prior signaling through the CD40 molecules (i.e., antibodies against CD40) under some conditions (i.e., in association of an adjuvant or particularly strong antigen) can generate CTL responses in the absence of CD4+ cells, confirming their active role in immune surveillance (J. Pardoll, A. Lanzavecchia).

Primarily, cytotoxic T cells and Natural Killer (NK) cells, and, in a subordinate way, macrophages (production of oxygen and nitrogen intermediates) and eosinophiles – both the latter two through the activation of Th2 helper cells – can kill or reject tumor cells. Adoptive T-cell therapy has documented therapeutic activity of cytotoxic T cells (i.e., T cells isolated from tumor infiltrates (TIL)). However, transferred T-cell clones require a concurrent CD4+ T-cell response to promote their survival and proliferation. Priming of naïve T-cells is mediated by the interaction of CD28 on T-cell surface with receptors of the B7 family on APC in the presence of interleukin-12. The legation of the CTLA-4 receptor (a homologue of CD28 that binds B7 receptor with highly affinity) can have an inhibitory function terminating T-cell response, but, confirming its alternative function, the infusion of anti-CTLA-4 antibodies or the combination of both CTLA-4 blockade and an administration of a specific vaccine can elicit an enhanced antitumor response (J. Allison, T. F. Gajewski). The development of MHC peptide tetramers used to directly identify antigen-specific CTL is an important advance in understanding the nature and the magnitude of the T-cell response (M. M. Davis). The application of these new technologies and the sequencing of extremely variable complementary-determining region (CDR) of T-cell receptor (TCR) have confirmed the polymorphism of the encoding genes and the specificity of CD8+ T-cell response (J.-C. Cerottini, P. Romero).

The exact capacity of NK to kill tumor cells in vivo is unknown (W. M. Yokoyama). The existence of both inhibitory (p58) and activatory (p50) receptors in human NK cells has been observed and, recently, two highly specific surface molecules (NKp46 and NKp44) involved in natural cytotoxicity have been detected (L. Moretta).

The tumor immune responses assume pathways of activation and tolerance (D. M. Pardoll). Chemokine receptor expression, timing of chemokine production
and generation of activated (mature or professional) cells play a central role in the mechanisms that orchestrate cellular interactions and modulate tumor surveillance (A. Lanzavecchia). Pro-inflammatory cytokines (i.e., interleukin-12 and -18) and specific subtypes of chemokines (i.e., interferon-γ) can enhance effector mechanisms (G. Trinchieri). Conversely, MHC down regulation (i.e., class I HLA in humans) allele loss (i.e., LOH in colorectal cancer), expression of inhibitory molecules (i.e., tumor necrosis factors (TNF)β and Fas ligand) by tumor cells can reflect tumor escape (F. Garrido). Moreover, the modulation of chemokine receptor expression and chemokine production provide active cell migration (E. Maraskovsky). This concept is well demonstrated in DC where the specific expression of the chemokine DC-CK1 induces the preferentially attraction of naïve T cells (CD45 RA) (G. J. Adema).

Development and clinical testing of cancer vaccines

In the past, in solid human cancers, only sporadic and partial results, in terms of disease control, have been obtained with immunotherapy. The growth of immunologic knowledge and the demonstration of the effectiveness of anti-idiotypic antibodies to target and kill B-cell lymphomas and the application of DC in pilot clinical trials have indicated the future potential of tumor vaccination.

In 39 melanoma patients (14 of them went in accelerated progression) three monthly subcutaneous injections of MAGE-3A1 peptide alone elicited seven tumor regressions (of these three were complete responses; T. Boon). In a pilot trial of 31 patients, immunization with gp100 209-2M peptide alone or together with IL-2, IL-12 or GM-CSF obtained cancer responses in 40% of cases (S. A. Rosenberg). Moreover, the observation of vitiligo in individual responder patients provides additional evidence that this immunizing antigen, that can produce immune reaction to normal tissue (that may express tissue-specific differentiation antigen), is indeed the antigen responsible of tumor regression. In a phase I clinical study conducted to investigate the biologic activity of vaccination with irradiated autologous melanoma cells engineered to secrete human GM-CSF, an anti-tumor immune response (pathologically destruction of at least 80% tumor cells) has been observed in 11 of 16 tested patients (G. Dranoff).

One point was admitted by all participants: future prospects of cancer vaccines are growing. However, methodological studies to ascertain the role of vaccine treatment schedules are needed and randomized controlled clinical trials are essential to validate and confirm preliminary study reports.

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Large increase in support for US cooperative groups

The NCI-supported clinical trials cooperative groups can expect their funding to increase by 20% to 35% in 1999. This was announced by NCI Director Richard Klausner in a speech at the plenary session of the SWOG yearly meeting on 23 October.

Klausner said that the new funding, about $30 million, will bring the overall NCI allocation to cooperative groups for 1999 to about $125 million, adding that the promise of a more effective system for cancer clinical trials was a persuasive argument in the appeal to Congress for an NCI funding increase (Cancer Lett 1998; 24: 42).

In his speech Klausner insisted that cooperative groups should become more competitive and more open in order to permit 'idea generators' to introduce new approaches into disease-specific concepts. He also contended that the clinical trial system should move toward an integrated, paperless informatics system, so that cooperative groups can talk to everyone else.

The NCI Director was able to announce another important step at that meeting. After more than two years of negotiation, the Office for Protection from Research Risks will allow one cooperative group (CALGB) to test the value and utility of a central IRB for multicenter trials. "If this works, it will take away an extremely important impediment to rapidly initiating trials, especially across multiple centers," Klausner said (Cancer Lett 1998; 24: 42).

Sunshine over ESMO in Athens

The temperature in Athens was very mild, when on 6–10 November 1998, almost 6000 participants gathered there for the 23rd ESMO Congress. The quality of the Congress, however, was so high that only a few attendees took the occasion for a last swim in the sea. For the first time the congress began with a 'Super Friday', during which all 13 Satellite Symposia were held in order to allow the scientific program to proceed without commercial interruption.

The education program on Saturday was of outstanding quality, which was reflected also in a highly praised education book: many participants commented that the level was at least comparable to that of the ASCO education program.

The rule that each ESMO member could sponsor only one abstract, in effect for the first time for this congress, restricted the amount of submitted material. However, thanks to the very stringent selection by the scientific committee, chaired by D. Kerr of Birmingham, UK, most proffered sessions were of high quality. Particularly well attended were the traditional contro-