Conference Scene

Immunotherapy reaches new milestones in cancer eradication

Highlights of the 2nd International Cancer Immunotherapy and Immunomonitoring (CITIM) Conference

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Biotherapy is widely considered as the fourth treatment modality for patients with cancer, and uses the constantly increasing knowledge in molecular biology, cell biology and immunology. Biotherapy uses naturally occurring biological molecules (e.g., cytokines and antibodies) or works by the manipulation of normal biological mechanisms (controlling or inhibiting tumor growth). Important achievements in anticancer drug development are immunotherapeutic strategies recently approved by the US FDA as well as clinical data of the cancer patients treated in clinical trials. There is a need to expand these novel cancer immunotherapeutic modalities for cancer patients all over the world. To meet that goal, it is essential to spread the information, to summarize the new clinical data and to draw the conclusions from the clinical and preclinical investigations. These frontline tasks can be well advanced by organizing international conferences in this domain in less scientifically developed countries, with a significant tumor burden statistics. Therefore, special efforts were done to organize the 2nd International Cancer Immunotherapy and Immunomonitoring Conference (CITIM-2011) in Hungary.

Immunotherapy holds promise

The last decade's progress in tumor immunology has improved the understanding of the role of host immune system in cancer development, but the whole field is far from being completely understood. With the new technologies and improved molecular methods, potentially immunogenic tumor antigens could be identified, which can serve as suitable targets for immune effector cells in innovative immunotherapeutic strategies, as well as novel biomarkers for early cancer diagnosis. High-throughput gene-expression analysis has opened new opportunities for revealing key mechanisms of immune-mediated tumor rejection [1–3]. The variety of immunotherapeutic approaches to cancer treatment grows steadily, from non-specific immunotherapy to antigen-specific modalities, such as adoptive T-cell transfer and dendritic cell (DC)-based vaccines. The steadfast development of molecular immunological and biotechnological techniques, as well as genetic engineering and transfection approaches, resulted in new strategies such as chimeric antigen receptor (CAR)-modified T-cell technology that has already been successfully introduced into the clinic [4]. Here, we highlight some new and unique data that were presented at Cancer Immunotherapy and Immunomonitoring Conference (CITIM) conference. It became evident that all presentations at CITIM-2011 conference

provided additional answers for cancer immunological questions and might be developed into effective anticancer therapeutic approach in the future.

■ Main conference goals reached

Hot-topic keynote and plenary lectures, as well as selected talks and numerous poster presentations provided a considerable amount of new ideas in tumor immunology, cancer diagnostics and therapies, which can advance medical and biomedical immunological sciences and clinical practice. We focus here on selected topics since there are also other conference papers to be published [5,6]. Exploitation of immune mechanisms and evasion of immune surveillance are properties that cancer cells acquire during tumor development. Comprehensive cellular, molecular and genetic investigations have led to the evidence of immune hallmarks of cancer: chronically inflamed microenvironment, evaded immune recognition and suppression of immune reactivity, among others [7]. Taking into consideration the immune hallmarks of cancer and the possible countermeasures, doors open to widespread cancer immunoprevention and to innovative and more efficacious cancer immunotherapies. Novel concepts and strategies have been outlined to identify, monitor and predict efficacy of cancer immunotherapy protocols. CITIM

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conference attendees received a nice interpretation of current hot topic: ‘Immunity and the malignant process’. From other presentations we have learnt about various novelties in cancer immunotherapeutic approaches following the previous international meetings in the field [8–10].

Cancer has its questions & answers: an asset for therapeutic approaches

As an example, we heard comprehensive details about myeloid-derived suppressor cells (MDSCs) representing a key factor in the tumor escape processes. These immature cells of myeloid origin accumulate in tumor-bearing hosts, suppress immune responses, T-cell proliferation and cytokine production. Dmitry Gabrilovich (H Lee Moffitt Cancer Center, Tampa, FL, USA) has explained how the therapeutic targeting of MDSC can be reached in different ways, for example, using the differentiation agents, chemotherapy, tyrosine kinase inhibitor sunitinib, COX-2 inhibitors, among others. Susanne Ostrand-Rosenberg (Baltimore, MD, USA) gave further overview of the intensive investigations of the tumor microenvironment in terms of immune suppression mechanisms and the definition of multiple factors important in tumor progression. These studies help to overcome protumorigenic immune suppression that is a major obstacle to effective immunotherapy. Immunosuppressive pathways interfering with the antitumor immunity in cancer patients represent an area where molecular mechanisms, clinical relevance and suitability are still needed to be revealed. These and further ideas were discussed by Licia Rivoltini (Istituto Nazionale Tumori, Milan, Italy). We have learnt from Isaac P Witz (Tel Aviv University, Israel) how the nontumor cells in the tumor microenvironment, including lymphocytes, macrophages, fibroblasts and endothelial cells, shape the malignant phenotype of the tumor and its dissemination. The interactions of the tumor cells with the microenvironment of the specific organ sites regulate the site-specific metastases to these organs. Human-to-mouse xenograft models for melanoma and neuroblastoma help to establish a molecular signature of site-specific metastasis,

identify cancer genes controlled by site-specific microenvironment and identify candidates for site-specific therapeutic targets. Numerous molecules involved in the tumor–stroma interactions might also serve as specific biomarkers or therapy targets. Defining inflammation and the presence of inflammatory cells in the tumor is another critical aspect of cancer pathobiology. Ron Apte (Ben-Gurion University, Beer-Sheva, Israel) pointed out that IL-1 is a major molecule that tilts the balance between destructive inflammation and activation of antitumor immunity, and that IL-1 α and IL-1 β differ dramatically in their effect on the malignant process. A talk of Zoltan Szekanecz (University of Debrecen, Hungary) was focused on the common targets of anticancer and anti-inflammatory therapy such as anti-cytokine agents, inhibitors of chemokines, adhesion molecules, T-cell costimulation and small molecules. There are interesting pathogenetic crossroads that link rheumatic diseases with cancer (e.g., angiogenesis inhibitors used in oncology have been introduced to arthritis trials). An intrinsic pathway of inflammation driven in tumor cells and an extrinsic pathway driven by chronic inflammatory conditions could be identified [11,12]. Novel results of Galina Shurin (University of Pittsburgh, PA, USA) demonstrated that accumulation of immune regulatory cells, such as MDSCs, regulatory DCs and regulatory T cells, is cancer and tissue specific and that different myeloid regulators might play different roles in tumor progression and inhibition of the antitumor immunity. Recent findings of Michael Shurin (University of Pittsburgh, PA, USA) proved for the first time that certain antineoplastic chemotherapeutic agents directly upregulate development, maturation and functional activation of conventional DCs (cDCs) *in vitro* and *in vivo* if used in ultralow noncytotoxic concentrations. This unexpected phenomenon was termed chemomodulation. Ultralow-dose nontoxic chemomodulation not only directly activated DCs, but also decreased tumor-induced suppression of cDC in the tumor microenvironment and could convert tumor-induced regulatory DCs into immunostimulatory cDC subsets. Thus, chemomodulation

of tumor environment may improve the efficacy of modern immunotherapeutic approaches for cancer. Viktor Umansky (German Cancer Research Center, Heidelberg, Germany) presented data on chronic inflammation and MDSC expansion and activation inducing immunosuppression in RET-transgenic spontaneous tumor model and suggested that the neutralization of MDSC immunosuppressive functions could be a key component of effective human melanoma immunotherapies. For instance, treatment of tumor-bearing mice with phosphodiesterase inhibitor or chemomodulation with ultralow-dose paclitaxel resulted in a marked delay of tumor progression and in a significant increase in animal survival. These effects were directly associated with a reduction in MDSC accumulation and function and increase in CD8⁺ T cells infiltrating skin melanoma and metastatic lymph nodes.

Human tumors produce different immunosuppressive factors, which by inhibiting the antitumor immune responses promote tumor progression. Theresa Whiteside (University of Pittsburgh Cancer Institute) focused on new pharmacologic blockade mechanisms related to the adenosinergic pathway that relieve suppression and restore immune responses. Anatoli Malyguine (NCI-Frederick, MD, USA) successfully developed and selected innovative *ex vivo* immunomonitoring methods and techniques that provide the most appropriate immune reactivity measures in determining the correlations between clinical and immunologic responses to specific immunotherapy in cancer patients. Paul Lehmann (Cellular Technology Ltd,

Shaker Heights, OH, USA) as the main conference sponsor being the founder of Cellular Technology Ltd in the USA and Europe, explained how to monitor both cytotoxic T-lymphocyte (CTL) frequency and functions with ELISPOT assays that gained increasing popularity for monitoring clinical trials worldwide.

One promising approach to cancer therapy is the induction of tumor-specific responses that selectively target the cancer. Straightforward steps could be made by tumor vaccines as well as adoptive transfer of tumor-specific T cells [13–15]. There has been a pressing need to identify immunological biomarkers predictive of therapy outcome that can be used to select patients and improve the response rates. From the presentation of Laszlo Radványi (MD Anderson Cancer Center, Houston, TX, USA), it was interesting to hear about functional aspects of Treg cells during high-dose IL-2 therapy of patients with melanoma and about changes in Treg cells associated with the treatment outcome. He found that 50% of human metastatic melanomas expressed inducible costimulator (ICOS)-ligand and provided ICOS costimulation through ICOS-ligand facilitating rapid expansion of an ICOS⁺ Treg cell subset capable of IL-10 production and enhanced suppressive function. The ICOS⁺ and – Treg cell subsets showed characteristic changes in the course of the therapy. Eva Rajnavolgyi (University of Debrecen) spoke about DC subsets as the adjuvants for immunomodulatory vaccines. The inflammatory nature of CD1a⁺ DC was attributed to the expression and function of special intracellular sensors responsible for IFN- β

Figure 1. Main conference organizer and invited speakers. Anatoli M Malyguine, Viktor Umansky, Eva Klein and Michael R Shurin (conference chair; from left to right).

production through the IRF3–TRIF pathway that ensures to create an inflammatory tissue environment.

Studies are further focused on the understanding of the relationship between immune and cancer cells and the context of the tumor microenvironment. Learning the basic mechanisms that can switch a chronic inflammatory process into an acute reaction with the power of destroying completely the triggering cause will be of help to guide the development of novel therapeutic strategies. Francesco Marincola (NIH, Bethesda, MD, USA) highlighted two molecular phenotypes being observed when cancers become established: one is characterized by the tumor microenvironment infiltrated by immune cells bearing transcriptional signatures consistent with a status of partial activation. Immune infiltration is considered to have a favorable prognostic or predictive association with the history of the disease or response to therapy. This overview on the common signatures of rejection with overlapping mechanisms leading to tumor rejection and other immune-mediated tissue-specific destructions (allograft rejection, graft-versus-host disease, acute clearance of pathogens and autoimmunity) gave a strong impression on the achievements in the field [12].

Identification of interferon (IFN) resistance gene signatures of human melanoma to improve patient selection for conventional therapy could be an example to emphasize the importance of these investigations. Jozsef Timar (Institute of Pathology, Semmelweis University, Budapest, Hungary) gave an essential information about the *in vivo* establishment of human melanoma IFN resistance gene signature consisting of 32 genes. The overwhelming majority of these genes (78%) was found to be upregulated. Since cytokine resistance is connected to metastatic phenotype, a human melanoma spontaneous metastasis model was tested, where metastatic potential-related metastasis-initiating gene signature could be identified in metastatic versus non-metastatic primary tumors and metastasis-maintenance gene signature could be obtained by comparing metastasis with the primary tumors.

There were only few people who presented studies on B cells at CITIM conference. Nevertheless the field is slowly accumulating relevant tumor immunological information. Everybody gladly greeted Eva Klein (Karolinska Institute, Stockholm, Sweden) in Hungary and learnt a lot from her previous pioneering and present novel studies on lymphokine modification of the expression of epstein-barr virus-encoded proteins in B lymphocytes. Galina Kaseko (Stephen Sanig Research Institute, Sydney, Australia) reported an efficient method of immortalizing rare B lymphocytes by using one-on-one electrical cell hybridization with their established human hematopoietic hybrid cell line as partner cells. The approach allows a fast establishment of unique B-cell-derived hybridoma bank for structural and functional analysis of natural tumor antibody repertoire. Small quantities of B cells can be found in tumors (tumor-infiltrating lymphocytes [TILs] such as TIL-B) and this and other methods, the efficient TIL-B antibody phage display, may help to understand the mechanisms underlying the natural antibodies responses to tumor antigens and to identify novel tumor associated antigens. This was already proved in a previous paper of Beatrix Kotlan (National Institute of Oncology, Budapest, Hungary) in relation to unique sialylated glycosphingolipids, GD3 gangliosides [16]. The presented results evidenced that the TIL-B approach is promising for the development of anti-tumor antibodies. The developed single-chain Fv immunoglobulin variable-region gene fragments of human origin were proved to be directed against specific disialolactosyl ceramides (GD3) and might be a tool for the early detection of unique glycosylated residues. The importance of natural antibodies was further emphasized in the lecture of Miri Blank from Yehuda Shoenfeld's group (Sheba Medical Center, Tel Aviv University, Israel) discussing their studies on intravenous immunoglobulin preparations in malignant conditions. intravenous immunoglobulin serves as an example of harnessing the innate immunity for treating incapacitating medical conditions, such as autoimmunity and cancer [17]. Paolo Ascierto's (Istituto Nazionale per lo Studio e la Cura dei Tumori 'Fondazione Pascale', Naples, Italy)

Figure 2. Welcome of Cancer Immunotherapy and Immunomonitoring Conference (CITIM) 2011: organizers and participants. SM Mansour Haeryfar, Paolo Ascierto, Beatrix Kotlan, Michael Shurin, Sylvia Kotlan and Anatoli M Malyguine (from left to right).

presentation on immunomodulating antibodies gave a perfect view of the state of the art of targeted therapies [18] and of the different approaches to improve the efficacy of melanoma therapies. Monoclonal antibodies that block the CTL-associated antigen-4 (CTLA-4) potentiate the T-cell response against tumor; preliminary data showed their good tolerability and efficacy in the treatment of metastatic melanoma. Some other approaches (e.g., agonist antibodies directed to CD137 on antigen-primed T cells, interference with PD1 cell surface molecule or its ligand), are under investigation and used in clinical trials. As new class of drugs in cancer therapy, immunostimulatory monoclonal antibodies lead to the redefinition of tumor

response criteria and potential combination therapies (immunotherapy, biotherapy and chemotherapy).

The lecture of Malcolm Brenner (Baylor College of Medicine, Houston, TX, USA) provided a fascinating picture of how improvements in cellular biology and the ability to manipulate gene expression in cells of the immune system have influenced the development of T-cell therapies. The presentation described how adoptively transferred T cells can be used in the therapy of solid tumors and hematologic malignancy. Their clinical study of neuroblastomas confirmed the *in vivo* superiority of CAR-CTL over CAR-T cells and indicated a means by which T-cell therapy for cancer can be improved. Laurence JN Cooper (MD

Figure 3. Welcome of Cancer Immunotherapy and Immunomonitoring Conference (CITIM) 2011: organizers and participants. Mepur H Ravindranath, Samuel JK Abraham, Beatrix Kotlan and Francesco M Marincola (from left to right).

Anderson Cancer Center) presented a novel nonviral approach for the gene transfer of CARs into T cells, the electrotransfer of ‘Sleeping Beauty’ (SB) transposon and transposases system. They developed the human application for improvement of this strategy. The SB system was used to express a transposon coding for a single-chain CAR redirecting T-cell specificity for a tumor-associated antigen, such as CD19. As further innovation, the DNA plasmids coding for the CAR (transposon) and hyperactive transposase (SB11) could be produced as a clinical grade material at many facilities [19]. Clinical trials could be initiated under the auspices of the US FDA to patients with aggressive B lymphoid malignancies.

Mepur Ravindranath (Terasaki Foundation Laboratory, CA, USA) presented their interesting findings on HLA class Ia and HLA-E antibodies in melanoma patients in response to autologous vaccine. The expression of HLA-E is augmented when the expression of MHC-Ia alleles is downregulated in tumor cells. Concomitant with the increase in anti-HLA-E IgG, the patients also showed an increase in antibodies reacting to HLA-B and -Cw alleles. HLA-E and HLA-Ia reactivities of the sera could be inhibited by peptide sequences shared by HLA-E and the allo-HLA-B and -Cw alleles. Soluble HLA-E shed from the tumor cells *in situ*, may expose immunogenic cryptic domains that may elicit antibodies that react with HLA-E and HLA-Ia alleles that share the peptide sequences.

Joseph G Sinkovics (St Joseph Hospital’s Cancer Institute, Moffitt Comprehensive Cancer Center, Department of Molecular Medicine, University of South Florida College of Medicine, FL, USA) interestingly summarized the processes of inflammatory carcinogenesis, in terms of ‘The wild-type original and the tamed contemporary DNA’ and how the molecular mediators promote carcinogenesis. To get more detailed view on that, we recommend his relevant book [20].

Conclusion

This international conference on immunotherapy, the first in Hungary, gave a platform for the presentation and discussion of a great variety of scientific results, already clinically introduced novelties ‘on the

way to clinical trials’. The future is going towards a combination of immunotherapy, biological therapy and chemotherapy [21]. The aim of advancing the understanding and application of immunotherapy helps to reach next milestones for better cancer cure rates.

Take-home message

The CITIM-2011 conference presentations and discussions gave strong evidence that we might look to a brighter future of the immunotherapeutic protocols as the therapeutic tools to fight against cancer (FIGURES 1–3). The extension of the valuable information about these new modalities in a translational form is a considerable asset for Central and Eastern European countries, from where scientists and clinicians could come to this meeting. This way, the novel ‘scientific milestones’ could reach out to farther ‘geographic milestones’ and will help a more broad group of patients suffering from cancer. Anticancer drug development has been going through a transition and now this transition is passing into clinical practice. Through better understanding of cancer biology, the therapies should be targeted to act specifically on cancer cells. Either a smaller or a larger number of cancer patients in our countries or all over the world will benefit from the novel immunotherapeutic strategies, the input effort into this conference was certainly not in vain. Additional information about this and future CITIM conference can be found at [101].

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Website

- CITIM 2011 Budapest conference homepage www.CancerITIM.org