Cancer Immunol Immunother (2010) 59:1895–1901
DOI 10.1007/s00262-010-0832-2

MEETING REPORT

Seventh annual meeting of the Italian Network for Tumor Biotherapy (NIBIT), Siena, 1–3 October 2009

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Received: 14 January 2010 / Accepted: 6 February 2010 / Published online: 5 March 2010

Abbreviations

ACT	Adoptive cell therapy
APC	Antigen-presenting cells
AS	Adjuvant system
CIK	Cytokine-induced killer
COA	Colon antigen
CRC	Colorectal cancer
CSC	Cancer stem cells
CTC	Circulating tumor cells
CTL	Cytotoxic T lymphocytes
CTLA-4	Cytotoxic T lymphocyte-associated antigen-4
CTX	Cyclophosphamide
DC	Dendritic cells
DXR	Doxorubicin
HDI	High-dose interferon-alpha-2b
IDO	Indoleamine 2,3-dioxygenase
IFN	Interferon
IL	Interleukin
mAb	Monoclonal antibody
MM	Metastatic melanoma
NB	Neuroblastoma
NGR	Asn-Gly-Arg
NHL	Non-Hodgkin lymphoma
NK	Natural killer
PC	Pancreatic cancer

The collaborators of NIBIT are given in the appendix.

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PTPRK	Protein tyrosine phosphatase receptor kappa
TAA	Tumor-associated antigen
TERT	Telomerase reverse transcriptase
TRAMP	Transgenic adenocarcinoma mouse prostate
Tregs	Regulatory T cells

Introduction

As for a consolidated tradition, the VII annual meeting of the NIBIT (acronym for the Network Italiano per la Bioterapia dei Tumori, Italian Network for Tumor Biotherapy) took place in the Certosa of Pontignano, a Tuscan Carthusian monastery near Siena, on 1–3 October 2009.

The congress gathered more than 40 Italian and international leading groups representing academia, biotechnology and pharmaceutical industry to cover and discuss several major topics related to immunology and immunotherapy of cancer as summarized in this meeting report.

Immunomodulation during target therapy

In the opening session, novel immunomodulatory strategies and their clinical potentials, as well as the characterization of suitable target tumor antigens for cancer immunotherapy have been discussed.

In his keynote lecture, *Ignacio Melero* (Pamplona, Spain) focused on CD137 (4-1BB), a surface costimulatory glycoprotein originally identified on activated T lymphocytes. Experimental evidence was shown supporting hematological malignancies, including multiple myeloma, as suitable targets for the treatment with agonist anti-CD137 monoclonal antibodies (mAb). Furthermore, a synergistic therapeutic effect of intratumor injection of type I interferon (IFN) and systemic administration of anti-CD137 mAb was described in mice. As repeatedly highlighted during the meeting regarding other therapeutic agents, Melero stressed that combination strategies will mark the future for the most effective therapeutic use of also CD137. Along this line, *Federica Moschella* (Rome, Italy) showed that chemotherapeutic agents such as cyclophosphamide (CTX) can modulate the immune response and potentiate the anti-tumor effectiveness of immunotherapy. In particular, she reported that CTX up-regulates the expression of genes involved in cell differentiation, migration and immune response, while it decreases the expression of genes controlling the cell cycle and metabolic processes in bone marrow, spleen and peripheral blood cells of tumor-bearing mice. *Anna Maria Di Giacomo* (Siena, Italy) gave compelling evidences on the feasibility, safety and clinical effectiveness of the anti-cytotoxic T lymphocyte-associated antigen (CTLA)-4 immunomodulator mAb ipilimumab in the common daily practice. She provided initial data on a "compassionate use" of ipilimumab in heavily pretreated, progressing metastatic melanoma (MM) patients: durable clinical benefit and long-term survivals were reported for a sizeable proportion of the 72 patients treated at 7 Italian Institutions.

The identification of suitable tumor-associated antigens (TAA) is crucial to improve the effectiveness of cancer immunotherapy. To face up this issue, the round table entitled "Tumor antigens: which ones should be targeted in cancer immunotherapy?" was held. TAA currently utilized as therapeutic targets for vaccination in clinical trials are generally non-mutated proteins often shared by different cancer types. However, *Paolo Dellabona* (Milan, Italy) reported on the potential clinical efficacy of unique mutated antigens identified by massive sequencing approach in colorectal cancer (CRC) patients. With recent technologies it is now possible to use a high throughput approach to define the patient's unique tumor antigenome, namely: (1) the identification of a defined number of most frequently somatically mutated genes (*CAN*-genes) and; (2) the development of the massive parallel picotiter pyrosequencing technique permitting a rapid identification of all the somatic mutations in cancer cell genome. These methodologies provide an integrated strategy to identify patient-specific unique TAA in a relatively short time, which is compatible with their potential use in the clinical setting. On this same subject, *Chiara Castelli* (Milan, Italy) provided evidence suggesting the strong immunogenic potential of unique TAA for which a high frequency of specific circulating cytotoxic T lymphocytes (CTL) have been detected in patients with cutaneous melanoma and lung carcinoma. T cell responses to these unique TAA are often found in regressing lesions and in long-term surviving cancer patients. As an example of melanoma-unique antigen, the protein tyrosine phosphatase receptor kappa (PTPRK) was discussed. Data were reported on the crucial role of PTPRK in negatively regulating the transcriptional activity of β-catenin, providing the biochemical basis to the hypotheses that PTPRK functions as a tumor suppressor gene.

In his talk, *Andrea Anichini* (Milan, Italy) discussed on shared and unique T cell epitopes in B cell lymphomas, focusing on IgVH B cell receptor. The analysis of the tumor-derived IgVH region peptides in follicular B cell non-Hodgkin lymphoma (NHL) patients demonstrated the expression of multiple, unique T cell epitopes in each Ig protein, and showed that they were predominantly localized in the complementarity determining region domain. Furthermore, T cell-mediated responses against shared and unique IgVH-encoded peptides were shown in NHL

patients after vaccination with dendritic cells (DC) loaded with autologous tumor cells extracts.

As highlighted by *Cristina Maccalli* (Milan, Italy) T cell-mediated responses directed to over-expressed self-antigens, such as CEA, MUC1, Ep-CAM and survivin have been shown in CRC patients. However, vaccination with these TAA fails to translate into significant tumor regression. She reported data on a recently identified new CRC-associated antigen denominated colon antigen A (COA)-1 showing that both CD4+ and CD8+ T cells specific for different immunogenic epitopes of COA-1 can be isolated from metastatic CRC patients, suggesting this antigen as a suitable target to design innovative immunotherapeutic approaches in CRC.

Angiogenesis inhibition in cancer therapy: new approaches

Based on the notion that neoplastic cells are strictly dependent on blood supply for their growth and metastases spreading, targeting of tumor-associated vasculature is well-acknowledged as a highly promising approach for cancer treatment. Along this line, peptides containing the Asn-Gly-Arg (NGR) motif show neovasculature binding properties which can be exploited for targeted delivery of drugs and therapeutic particles to tumor vessels. *Angelo Corti* (Milan, Italy) demonstrated that in NGR-containing peptides and in fibronectin, which contains four NGR sites, the NGR sequence can rapidly convert to isoaspartate-glycine-arginine (*iso*DGR) by asparagine deamidation, generating $\alpha_v\beta_3$ ligands capable of affecting endothelial cell functions and tumor growth. The molecular mechanisms underlying the spontaneous transition of NGR to *iso*DGR, its potential role as a molecular timer for the activation of latent integrin-binding sites in proteins of the extracellular matrix, and its functional implications in cancer were discussed.

The use of vascular-disrupting agents, such as ligand-targeted and/or drug-conjugated liposomes, has recently shown a promising therapeutic potential in cancer. *Mirco Ponzoni* (Genoa, Italy) reported on the necessity to use innovative drug delivery systems like liposomes to improve the pharmacokinetics and bio-distribution of therapeutic drugs, and to increase their selective localization at tumor sites. Evidence was reported that liposomes-entrapped doxorubicin (DXR), targeting the tumor vasculature marker aminopeptidase N, displayed enhanced anti-tumor effects and prolonged survival in human neuroblastoma (NB)-bearing mice. Additionally, a peptide ligand of aminopeptidase A, discovered by phage display technology, was exploited for the delivery of DXR-liposomes to perivascular tumor cells. Consequently, novel aminopeptidase A-targeted, DXR-nanoparticles, were developed and are currently being tested, alone or in combination with aminopeptidase N-targeted DXR-loaded liposomes, in NB-bearing mice.

Among different vasculature-targeting agents under development at Philogen, *Leonardo Giovannoni* (Siena, Italy) reviewed preclinical and clinical data obtained with human antibodies fused with cytokines and directed against two markers of angiogenesis: the F16 mAb directed to tenascin and the L19 mAb directed to fibronectin. The human antibody fragment single-chain (sc) Fv F16 fused to human interleukin (IL)-2 (F16-IL-2) showed therapeutic benefit both in a preclinical setting and in phase I/II clinical trial. Interestingly, this antibody increased the therapeutic efficacy of anthracycline- and taxane-based chemotherapy without apparent additional toxicity. Objective responses from ongoing DTIC combination studies in metastatic melanoma patients with the human scFv antibody L19 fused with IL-2 (L19-IL-2) were shown. The results indicated a very encouraging response rate in patients without other therapeutic options.

The revival of dendritic cells-based vaccines

Dendritic cells (DC) are clearly the most potent antigen-presenting cells (APC) and play a crucial role in the induction of antigen-specific T cell immune responses; thus, the use of DC for active immunotherapy has been extensively investigated in cancer in the past decade. In his keynote lecture, *Gerold Schuler* (Erlangen, Germany) underlined the reviving interest of this immunotherapeutic approach to develop cancer vaccines based on mature monocyte-derived DC. The data so far emerged from clinical trials in cutaneous melanoma indicated that DC-based vaccines induce a strong immunity in the initial course of vaccination that correlates with a favorable clinical course of disease in stage III but not in stage IV patients. Gene expression analysis of pre-vaccination metastases revealed that stage IV patients with prolonged survival displayed a favorable microenvironment, which may be critical for vaccine-induced T cells to exert their anti-tumor effects. Currently, induction of broad immune responses and complete clinical responses are being observed in stage IV chemotherapy-resistant cutaneous melanoma patients vaccinated with a new generation of mature DC, which are loaded by electroporation with mRNA coding for Melan-A, MAGE-A3, and Survivin. *Guido Ferlazzo* (Messina, Italy) reported on the interactions occurring between DC and natural killer (NK) cells to establish a protective immune response. The data presented demonstrate that: (1) DC are early activators of human NK cell functions; (2) NK cells can induce immunogenic DC

either by releasing DC-activating factors or by killing poorly immunogenic DC (editing); (3) activation of NK cells can elicit DC editing in vivo. Focusing on DC interactions with tumor cells, *Vincenzo Russo* (Milan, Italy) discussed the impairment of DC migration to draining lymph nodes. He presented data on a mechanism mediated by tumor-released soluble factors that block DC migration through the inhibition of the expression of CCR7 receptor on maturing DC. The inactivation of this mechanism was found to restore DC migration to draining lymph nodes as well as tumor growth control.

The ups and downs in clinical vaccination

Immunotherapy plays an important role in the treatment of cutaneous melanoma and durable tumor responses have been demonstrated with high-dose IL-2 and with anti-CTLA-4 mAb. In his keynote lecture Patrick Hwu (Houston, USA) highlighted that although clinical responses can be dramatic and durable in selected MM patients, the majority of them still does not respond to these immunotherapeutic approaches. He envisaged that due to the complexity of the cellular immune responses, it is doubtful that single agents will ever be effective in the majority of patients. For these reasons, rational combinations of immunomodulatory agents will likely be necessary for optimal clinical results. Currently, numerous clinical grade vaccine formulations, cytokines, Toll-like receptors agonists, and immunomodulatory antibodies are available and undergoing clinical trials. An immediate challenge and opportunity for the research community will be to rationally combine these agents to maximize the clinical benefit to patients. Along this line *Massimo Di Nicola* (Milan, Italy) discussed on how to improve the efficacy of active immunotherapy in follicular lymphoma. To this end, a novel vaccine formulation using heat-shocked, γ-irradiated and UV-C exposed whole tumor cells as source of antigens to engulf DC was generated. This vaccine presents the advantage of widening the spectrum of target TAA and promotes the efficient transfer of tumor antigens to the MHC class I processing pathway of APC, favoring the development of a therapeutic anti-tumor immune response.

Frederic Lehmann (Rixensart, Belgium) presented data from the randomized open-label phase II study (EORTC 16032-18031; NCI NCT00086866) designed to evaluate the immunization with the MAGE-A3 recombinant protein combined with two different adjuvant systems (AS) (AS02B and AS15) as first-line treatment of MAGE-A3+ cutaneous MM patients. The results of the immune response analysis and the comparable toxicity observed with the immunological AS utilized, suggested a better efficacy for the AS15 formulation. Interestingly, using gene expression profiling of tumor biopsies taken prior to treatment, a gene signature predictive of clinical response was identified in treated patients. Confirming the predictive value of this gene signature will provide a patient-tailored treatment.

Giorgio Parmiani (Milan, Italy) reported on the vaccine clinical trials performed at the Istituto Nazionale Tumori of Milan, Italy, in collaboration with *Licia Rivoltini*. Immunological data on specific T cell immune responses induced in early stage melanoma and prostate carcinoma patients by cocktails of HLA-A2-restricted tumor peptides, globally showed that: (1) melanoma and prostate carcinoma patients with early or limited disease mount specific immune responses to vaccinating peptides in a prompt and persistent fashion, achieving, however, relatively low frequencies of antigen-specific T cells; (2) in prostate carcinoma patients the vaccination mediated a consistent but transient decrease of prostate-specific antigen (PSA), requiring intensive injection schedules to be maintained; (3) in melanoma, no improvement in disease-free survival was observed; (4) the limited clinical efficacy in melanoma patients could be attributed to the reduced ability of T cells activated by peptides to cross-recognize tumor cells.

Adoptive immunotherapy of cancer

A reviving interest is being focused on adoptive T cell transfer for cancer immunotherapy. Along this line, *Matteo Bellone* (Milan, Italy) showed that transplantation of non-myeloablative minor histocompatibility mismatched hematopoietic stem cells and donor lymphocyte infusion, in combination with cancer vaccination, can induce prostate cancer remission and the establishment of protective immunosurveillance in TRAMP mice. Tumor rejection was achieved through the generation of both tumor- and minor histocompatibility antigen-specific effector T lymphocytes. In fact, while donor-derived tumor-specific T cells readily differentiated into effector cells and infiltrated the tumor soon after infusion, they were alone insufficient for tumor eradication, which instead required the concomitance of minor antigen-specific CTL responses.

In her presentation, *Daniela Montagna* (Pavia, Italy) reported on the "compassionate use" of autologous CD8+ CTL, generated and expanded in vitro using whole autologous tumor cells, for the treatment of patients affected by solid tumors of different histotype. Before CTL-based immunotherapy, patients were not eligible to further treatments and showed large tumor masses progressing after having failed conventional therapies. Following lymphoablation with fludarabine/CTX, patients received a variable number of CTL infusions depending on the clinical response. The results initially obtained demonstrate

that CTL can be transferred safely in advanced tumor patients and may provide clinical benefit.

Cytokine-induced killer (CIK) cells also appear promising tools for adoptive cancer immunotherapy both in the autologous setting and after allogeneic hematopoietic stem-cell transplantation. On this issue, *Dario Sangiolo* (Turin, Italy) showed that CIK cells can efficiently kill colorectal, breast and osteosarcoma cancer cells in vitro. This anti-tumor activity of CIK cells was found to be perforin-mediated and triggered by the interaction of NKG2D molecules with specific targets (MIC-A/B; ULBPs) on the cell membrane. The expression of MIC-A/B can be increased by stress conditions or pharmacological treatments, with a consequent improvement of the ability of CIK cells to kill neoplastic cells. Additionally, Sangiolo demonstrated that alloreactivity and anti-tumor activity of CIK cells segregate within two different cell subsets and could consequently be separated. CIK cell alloreactivity is limited to CD3+CD56− cells and their depletion allows to purify a CIK subpopulation devoid of any alloreactivity but retaining the full tumoricidal activity. The potential of CIK cells as adoptive immunotherapy in cancer is currently being exploited in clinical trials.

Being over-expressed in human tumors and implicated in the maintenance of transformed phenotypes, telomerase reverse transcriptase (TERT) is a good candidate as universal TAA for cancer immunotherapy, as shown by *Vincenzo Bronte* (Padua, Italy). In transgenic adenocarcinoma mouse prostate (TRAMP) mice, which develop prostate cancer, adoptive cell therapy (ACT) with TERT-reactive T lymphocytes halted the progression to more aggressive, poorly differentiated tumors, and significantly prolonged mice survival. Furthermore, human cancer stem cells (CSC) were shown to be targeted in vivo by TERT-specific CTL. ACT with TERT-reactive T lymphocytes also caused a transient B cell depletion in primary and secondary lymphoid organs. Interestingly, the administration of some chemotherapeutic agents provided a significant adjuvant activity to ACT.

Understanding the immunobiology of pancreatic adenocarcinoma

Pancreatic cancer (PC) is a very aggressive disease with a dismal prognosis, showing a peculiar tumor microenvironment characterized by an extensive fibrotic stroma, which favors rapid tumor progression. In the study presented by *Maria Pia Protti* (Milan, Italy), anti-CEA and anti-viral CD4+ T cell immunity were evaluated in PC patients. The results suggest that the immune T cell suppression in PC is tumor-related since a Th2 skew in the anti-CEA, but not in the anti-viral CD4+ T cells, was found. Interestingly, CEA-specific CD4+ Th2 cells were endowed with functional plasticity, and their treatment with IL-2 and IL-27 partly reverted their functional phenotype by reducing the production of Th2 cytokines and inducing IFN-γ release.

The limited effectiveness of available treatments for PC patients is prompting the development of novel gene therapy approaches for the direct delivery of pro-apoptotic signals, for the modulation of the tumor microenvironment or for directly induced oncolysis. In this context, *Vladia Monsurrò* (Verona, Italy) provided evidence on the identification of two PC phenotypes that display different permissivity to viruses commonly utilized for gene therapy and oncolytic therapies. These two PC phenotypes may be differentially susceptible to virally mediated gene therapy, and may therefore affect the long-term outcome of the disease in response to tailored gene therapy.

Tumor perineural dissemination is a hallmark of PC and represents a major source of local tumor recurrence after surgery. *Paola Allavena* (Milan, Italy) showed that the chemokine receptor CX3CR1 expressed on PC cells is involved in their neurotropism to local peripheral nerves, and that it is a relevant and independent risk factor to predict an early local tumor relapse in surgically resected patients. In particular, its analysis in PC specimens revealed that 90% of investigated samples were CX3CR1-positives with a heterogeneous pattern of expression. Furthermore, regression analyses demonstrated that high CX3CR1 expression and perineural invasion were strongly associated with local and early tumor recurrence.

Update on immune escape mechanisms and tumor immunosuppression

The session closing the VII NIBIT meeting focused mainly on the analysis of regulatory T cells (Tregs) in the course of different cancer immunotherapies and on novel mechanisms of tumor escape.

An altered tryptophan catabolism was reported in several pathological conditions such as chronic inflammation, autoimmune diseases and tumors. Indoleamine 2,3-dioxygenase (IDO) is an intracellular enzyme which catalyzes tryptophan and is involved in suppressing T cell responses and in promoting immune tolerance. IDO is expressed in mature but not in immature DC and can be involved in the downmodulation of activated T cell by acting as a bridge between DC and Tregs. On this topic, *Paolo Puccetti* (Perugia, Italy) proposed a model of transplantation tolerance in which different cytokines, including type I and type II IFN as well as TGF-β, act on potentially tolerogenic DC to activate IDO, resulting in the onset of specific tolerance through the induction of tryptophan starvation and the

production of immunomodulatory tryptophan catabolites (i.e., kynurenines).

Tregs represent a distinct T cell lineage that plays a central role in the immune homeostasis and in the maintenance of peripheral tolerance. They are present in the tumor microenvironment and in tumor-draining lymph nodes, and Tregs depletion improves anti-tumor immune responses and enhances the efficacy of immunotherapy in animal models. Based on these notions, *Ruggero Ridolfi* (Meldola, Italy) reviewed emerging data showing that dioxin might induce Tregs proliferation through its binding to the aryl hydrocarbon receptor expressed on their cell membrane. This evidence was thought particularly intriguing in light of the carcinogenic activity of dioxin, which is largely present in the food chain, and of the increasing incidence of cancer worldwide.

Different strategies are currently being developed to modulate Tregs activity in cancer patients. Along this line, *Giusy Gentilcore* (Naples, Italy) presented a study aimed to investigate circulating Tregs in melanoma patients treated with intravenous high-dose interferon-alpha-2b (HDI), demonstrating a clear trend in reducing circulating Tregs by HDI. However, she pointed out that final conclusions about the role of such reduction in terms of response to treatment or as prognostic marker cannot be drawn at present and that further data are required to verify if Tregs reduction in the course of HDI treatment may contribute to anti-tumor responses.

A large amount of data indicates that elevated levels of circulating Tregs have a negative impact on the survival of cancer patients. Accordingly, blocking of CTLA-4 constitutively expressed on Tregs by anti-CTLA-4 mAb is currently utilized in the clinical setting of cutaneous melanoma and of other human tumors of different histotype. *Luana Calabrò* (Siena, Italy) investigated the effects of the anti-CTLA-4 mAb ipilimumab on the levels of peripheral blood Tregs in patients with heavily pretreated MM. Though preliminary, the data presented demonstrated that treatment with ipilimumab significantly affected baseline levels of circulating Tregs in MM patients: objective clinical responses were associated with decreased circulating Tregs. Furthermore, increased levels of circulating T cells with activation and memory or effector markers were also observed in MM patients following ipilimumab treatment.

Chiara Camisaschi (Milan, Italy) reported on the effect of low-dose CTX and low-dose IL-2 on circulating Tregs in a phase II randomized trial of multipeptides vaccination in stage IIB-C/III cutaneous melanoma patients. The immune monitoring of treated patients demonstrated that peptides combined with Montanide significantly boosted antigen-specific T cell-mediated immunity in the majority of vaccinated patients. Moreover, CTX did not mediate significant changes in the frequency of circulating Tregs characterized by the CD4+ CD25highFOXP3+ phenotype. Instead, the number of Tregs increased after IL-2 administration, but their enhanced frequency did not seem to significantly affect immunization of patients.

Marco Danova (Turin, Italy) focused on a new method for the isolation of circulating tumor cells (CTC) in cancer patients by microchips and nanotechnology, and discussed its perspective clinical application in oncology. Isolation of CTC in cancer patients could present several advantages: (1) CTC might give a "real-time" information of the biology of the tumor; (2) might represent a prognostic tool in patients with advanced disease; (3) could provide useful clinical information in the course of the disease, and lastly; (4) might represent secondary end-points for the evaluation of tumor response in clinical trials.

Conclusions

The presentations delivered during the VII meeting of the NIBIT provided an up-to-date overview on the most promising research areas of cancer immunobiology and immunobiotherapy on which the scientific community is focusing. The clinical translation of these novelties will undoubtedly improve the outcome of cancer patients hopefully in the near future. Along this line, the first clinical trial entirely designed within the NIBIT group and entitled: "A phase II study of the combination of ipilimumab and fotemustine in patients with unresectable locally advanced or metastatic malignant melanoma" was presented during this national annual meeting. This study will involve eight Italian Institutions with the primary objective of perspectively assessing the immune-response disease control rate (irDCR) using the immune-related (ir) tumor response criteria of the combination of the anti-CTLA-4 mAb ipilimumab and fotemustine in patients with unresectable locally advanced or MM. The activation of this study clearly represents a major success of the NIBIT group as one of its statutory goals and objectives is to design, develop and coordinate multi-center clinical studies at national level, to help to overcoming the procedural, ethical, and legal challenges facing the clinical application of new modalities of cancer bioimmunotherapy.

Acknowledgments This work was supported in part by grants from Associazione Italiana per la Ricerca sul Cancro and Alleanza Contro il Cancro.

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