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MEETING REPORT

# Eighth annual meeting of the Italian network for tumor biotherapy (NIBIT), Siena, October 7–9, 2010

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## Introduction

NIBIT (acronym for the Network Italiano per la Bioterapia dei Tumori—Italian Network for Tumor Biotherapy) is a non-profit association created in 2004 to promote and foster scientific and operative interactions among Italian professionals involved in the field of cancer bioimmunotherapy. To date, more than 100 members representing over 40 national academic, regulatory, and industrial groups are part of the NIBIT.

Aim of the annual meeting of the NIBIT is the discussion of recent preclinical and clinical results obtained by various Italian groups of the Network in the field of cancer immunology and biotherapy. Traditionally, the NIBIT meeting also hosts foreign speakers for keynote lectures on hot topics in the NIBIT field of interest.

Like every year, the eighth annual meeting of the NIBIT took place in the Certosa of Pontignano, a Tuscan Carthusian monastery close to Siena. The 2010 main topics were as follows: (1) immunology of cancer stem cells; (2) prostate cancer immunotherapy; (3) immunomodulation therapy; (4) new aspects in cancer vaccines; (5) NIBIT and other Italian clinical trials.

## Immunobiology of cancer stem cells

In his Keynote Lecture, **Piero Dalerba** (Stanford, USA) provided an excellent up-to-date overview on the growing

The co-authors of NIBIT are given in Appendix.

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body of experimental evidences pointing to cancer tissues as hierarchical systems, where cellular heterogeneity is largely the result of multilineage differentiation processes, and tumor growth is sustained by a subset of cells with stem cell properties. In particular, Dalerba stressed the concept that the analysis of the cancer stem cells (CSC) subset can provide important insights in the molecular mechanisms that control self-renewal and shed new light on the processes of tumor growth, relapse, and metastasis. On this line, he reported data on two important observations derived from the investigation of the differential gene expression profile of human "*breast cancer stem cells*" (Br-CSC) leading to: (a) the identification of a 186-gene Br-CSC gene expression signature that can be used to stratify breast cancer patients in different prognostic subgroups; (b) the identification of a novel microRNA (miR-200c) up-regulated during mammary epithelial differentiation and involved in the suppression of the self-renewal gene *BMI1*.

The potential key role of CSC in the long-term maintenance of tumor growth bears important implications for the design of novel immunotherapeutic approaches in human cancer. **Cristina Maccalli** (Milan, Italy) reported on a low immunogenicity and a high immunosuppressive activity by CSC isolated from glioblastoma multiforme (GBM), highlighting the need to identify immunomodulatory agents able to restore the expression of immunogenic molecules on CSC. Interestingly, the results of this study indicate indoleamine 2, 3-dioxygenase (IDO) as a candidate molecule that mediates immunosuppressive functions of CSC isolated from GBM patients.

As far as melanoma, **Michela Perego** (Milan, Italy) showed that metastatic cells contain a high frequency of cells able to grow as floating melanospheres when cultured in stem cell medium. These melanospheres were endowed with strong tumor initiating capacity in immune-compromised SCID mice and displayed a heterogonous phenotype for stem cells–associated markers, with no unidirectional association between tumorigenic potential and a given phenotype. Thus, melanospheres were utilized to investigate the role of immune-related factors in the modulation of melanoma heterogeneity and stemness properties. The results demonstrated that melanospheres secrete many factors involved in melanoma development and progression (i.e., interleukin (IL)-8, transforming growth factor-beta (TGF-beta), chemokine ligand-2 (CCL-2), epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), and vascular endothelial growth factor (VEGF)). Moreover, initial experiments suggest a differential role of some cytokines in modulating melanospheres behavior. **Barbara Stecca** (Florence, Italy) reported that Hedgehog (HH)-GLI signaling regulates the proliferation and survival of human melanoma cells and that local or systemic interference of HH-GLI function prevents growth, recurrence, and metastasis of melanoma xenografts in immune-compromised mice. Furthermore, she showed preliminary results suggesting that the inhibition of HH-GLI signaling pathway by short interference RNA directed against the cell membrane receptor Smoothened, or by cyclopamine, can reduce the proliferation and the self-renewal of CSC from melanoma, providing the rationale for the use of HH-GLI inhibitors for new targeted therapies in cancer.

## Prostate cancer immunotherapy

In his keynote lecture, **Matteo Bellone** (Milan, Italy) underlined that prostate and many other types of epithelial carcinoma develop and progress in a dynamic cross-talk with the immune system, which is believed to restrain tumor progression to some extent, but eventually favors a more aggressive behavior of cancer cells. On this issue, animal models are essential tools to gain more information on such ambivalent interactions and to develop strategies to fruitfully harness the immune system against cancer. Mice in particular are being fundamental to the discovery of the biology of prostate cancer (PC) and its interactions with the immune system. Interesting results in preclinical animal models need to be weighted on the basis of the different physiology of men and mice and on the pathologic characteristics of spontaneous and experimental tumors.

PC is one of the leading causes of cancer death in man. Treatment of choice for advanced or inoperable disease is represented by androgen ablation. Unfortunately, despite initial high tumor response rates, eventually all patients progress to an androgen-independent status. In this context, **Sergio Bracarda** (Arezzo, Italy) showed that a possible further disease control advantage could be achieved by adding a non-steroidal anti-androgen drug from the beginning of the standard treatment or also as second-line hormone therapy. Nevertheless, the response is usually short lived and it does not result in an improved survival. The recent randomized studies TAX-327 and SWOG 99-16, using docetaxel and prednisone *vs* mitoxantrone and prednisone, demonstrated for the first time an increased overall survival in the docetaxel arm, suggesting that castration-resistant prostate cancer (CRPC) must be subsequently evaluated for this kind of therapy. Unfortunately, such improvement in survival does not yet indicate an increased possibility of cure for advanced disease, and prognosis of patients with CRPC remains extremely poor, even if significantly improved.

The modest immunogenic potential of tumor-associated antigens (TAA) expressed in PC indicates an immune-tolerant status. Moreover, there is convincing evidence for a suppressive activity of PC on dendritic cells (DC) or their

circulating precursors, as well as on cytotoxic T lymphocytes (CTL). **Lina Matera** (Turin, Italy) demonstrated that induction of post-apoptotic necrosis in vitro by ultraviolet C (UVC) and heat treatments overcomes tumor escape mechanisms of altered phagocytosis and maturation induced by PC cells on DC. Although both treatments induce strong release of high-mobility group protein B1 (HMGB1) and 70-kilodalton heat shock proteins (HSP) 70, 2 damage-associated molecular pattern molecules whose physiological role is to alert the immune system about major environmental changes, only UVC is able to reverse the tumor-induced inhibition of the CTL response. Given for granted that the whole tumor represents the best source of TAA, these findings suggest that death-inducing treatments such as UVC and heat, that revert PC immunosuppressive phenotype, should be introduced in the preparation of DC-based TAA vaccines.

**Licia Rivoltini** (Milan, Italy) reported on specific T-cell immune responses induced in PC patients by a cocktail of HLA-A2-restricted tumor peptides (i.e., proteasome subunit alpha type-1 (PSMA) 1, PSMA2, and survivin-1 (SVV)-1). Immunological data globally suggested that (1) the vast majority of patients with biochemical recurrence of PC mounts an immune response to peptide vaccination in a prompt and persistent fashion; (2) the vaccine mediates a clinically relevant increase in prostate-specific antigen (PSA) doubling time (PSADT) due to a consistent but transient decrease in PSA that requires intensive injection schedules to be maintained. In contrast, T cells primed with the native peptide from PSMA display significant tumor cross-recognition, correlating with clinical benefit, and immunization with HLA class I peptides promotes the in vivo priming of T cells with low proliferative capacity.

Telomerase is essential for cell immortalization, and it is expressed by about 90% of tumors. Also, telomerase-specific CTL have been identified in 90% of cancer patients; thus, telomerase may be considered a potential "universal" TAA. **Gilberto Filaci** (Genoa, Italy) presented a clinical trial (protocol GX-301) aimed at testing the safety and the immunogenicity of a combination of four telomerase-derived peptides, chosen on the basis of their capacity to bind both HLA class I and II molecules, together with the administration of two adjuvants (Montanide ISA-51 and Imiquimod). Preliminary results from an ongoing phase I study in patients with advanced (stage IV) prostate or renal cancer, with 8 patients enrolled, indicate a good safety profile of treatment. In fact, only minor side effects were registered after a total of 59 immunizations. Interestingly, signs of immunological response were detected in 6 out of 7 evaluated patients, and clinical responses were also observed.

Great interest is currently focused on therapeutic targeting of prostatic acid phosphatase (PAP) that is expressed in 95% of prostate cancers. In this regard, **Riccardo Danielli** (Siena, Italy) focused his presentation on sipuleucel-T (Provenge; Dendreon), an autologous cellular vaccine consisting of autologous peripheral blood mononuclear cells (PBMC), activated for a defined time period in cell culture with recombinant PAP and granulocyte-macrophage colony-stimulating factor (GM-CSF). The safety and efficacy of sipuleucel-T, as well as the improvement in survival of CRPC treated in two randomized studies, made sipuleucel-T approved by the US FDA for the treatment of asymptomatic or minimally symptomatic metastatic CRPC in April 2010. In addition, Danielli reported preliminary evidences of anti-tumor activity of the anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) monoclonal antibody (mAb) ipilimumab, in a randomized, double-blind phase III trial (CA 184043) in patients with metastatic CRPC in progression after first-line docetaxel-based treatment.

## Immunomodulation therapy

The results of different clinical trials demonstrate the therapeutic potential of combining different immuno- and bio-therapeutic approaches with chemotherapy in cancer. In this session, data on the possible mechanism(s) of this synergistic effect and/or on new and potentially more effective therapeutic combinations were discussed. In this regard, **Arianna Calcinotto** (Milan, Italy) demonstrated that Asn-Gly-Arg-tumor necrosis factor (NGR-TNF), a peptide (CNGRCG) fused with TNF, and currently tested in phase II and III clinical studies, increases vessel permeability and favors the penetration of chemotherapeutic drugs and of antigen-specific CTL into tumor mass by modulating leukocyte adhesion molecules on the tumor-associated endothelium. Interestingly, pretreatment of B16 melanoma-bearing mice with NGR-TNF showed a synergistic anti-tumor effect with the combination of doxorubicin and adoptive or active immunotherapy.

**Enrico Proietti** (Rome, Italy) focused his presentation on the complex mechanisms accounting for cyclophosphamide (CTX) activity in enhancing immune responses in cancer, and on the optimal timing of its combination with immunotherapy. In particular, data were presented demonstrating that CTX induces homeostatic rearrangements of the DC compartment in the secondary lymphoid organs, improves infiltration of DC in tumor lesions and massive tumor cell death, and activates inflammatory mediators. This CTX-mediated immunomodulation was found to be early and transient, pointing out that, in order to be effective, chemotherapy and immunotherapy should be combined within a short time window.

**Andrea Balsari** (Milan, Italy) reported that repeated intraperitoneal injections of oligodeoxynucleotides (ODN)

containing CpG motifs (CpG-ODN) in combination with the mAb cetuximab and cis-platinum significantly increased survival and completely controlled ascites formation, without apparent toxicity, in mice bearing advanced ovarian xenografts. *In silico* analysis of DNA repair genes, performed to investigate mechanisms responsible for the improved anti-tumor effect of cis-platinum, revealed that CpG-ODN treatment reduced the expression of DNA repair genes in tumor cells, while in immune cells their expression was increased. These results expand the benefits of CpG-ODN therapy beyond the induction of a strong innate immune response and encourage clinical trials that combine peri-tumoral, not systemic, CpG-ODN treatment with DNA-damaging therapies and mAb.

## New aspects in cancer vaccines

In his keynote lecture, **Sjoerd H. van der Burg** (Leiden, The Netherlands) focused on the success and failure in virus-induced malignancies treated with synthetic long overlapping peptide-based vaccines. More particularly, he reported that synthetic long overlapping peptide-based vaccines against HPV16-induced (pre-) malignancies are as follows: (1) highly immunogenic; (2) predominantly presented by DC; (3) cross-presented for a long time by DC. Additionally, he showed evidence that their success was dependent on local presentation and that the locality of presentation depended on the length of the chosen peptide. Moreover, evidence was presented that long overlapping peptides have a better capacity to activate CD8 T cells than whole proteins and that a pool of such peptides induced broad CD4 and CD8 T-cell responses in humans.

Spontaneous anti-tumor T-cell response in cancer patients is strongly controlled by regulatory T cells (Tregs), and increased numbers of tumor-infiltrating Tregs correlate with reduced survival. Along this line, **Philipp Beckhove** (Heidelberg, Germany) used a broad panel of long synthetic peptides of defined TAA, and normal tissue antigens, to identify and compare ex vivo the antigen specificities of Tregs with those of effector/memory T cells in peripheral blood of colon rectal cancer (CRC) patients and healthy subjects. The results indicated that tumor-specific effector T cells were detectable in the majority of CRC patients but not in healthy individuals. In addition, Tregs were highly specific for a distinct set of only a few tumor antigens in CRC patients. Furthermore, differences in the repertoires of antigens recognized by Tregs and effector/memory T cells were detected in the majority of CRC patients, and only effector/memory T-cell responses against antigens recognized by Tregs strongly increased after Tregs depletion.

Recent evidences, presented by **Angela Santoni** (Rome, Italy), showed that myeloma cells treated with low doses of therapeutic agents such as doxorubicin, melphalan, and bortezomib, capable to trigger the DNA damage response (DDR), up-regulate both DNAX accessory molecule-1 (DNAM-1) and NKG2D ligands. By contrast, activation of heat shock response by treatment with HSP90 inhibitors resulted in the up-regulation of NKG2D ligand only. Drug-induced up-regulation of ligand expression was associated to an increase in NK cell-mediated killing of multiple myeloma cells. Similar data were also obtained using ex vivo primary plasma cells derived from multiple myeloma patients. In this matter, genotoxic agent-induced DNAM-1 and NKG2D ligand expression was abolished following treatment with pharmacological inhibitors of DDR and reactive oxygen species (ROS) generation and was preferentially associated with senescent cells arrested in the G2 phase of the cell cycle and expressing p14 senescence marker. Altogether, those findings demonstrate a major role of NK cell-mediated stress surveillance in tumor cell recognition and suggest its possible exploitation for optimizing cancer therapy. Furthermore, **Gabriella Pietra** (Genova, Italy) demonstrated that melanoma cells interfere with the activity of NK cells by modulating their phenotype and cytotoxic function. In particular, Pietra showed that in co-culture experiments, melanoma cells act by interfering with the IL-2-driven up-regulation of major surface triggering NK receptors (including NKp30, NKp44 and NKG2D), thus markedly affecting the NK cell-mediated cytolytic activity against various melanoma cell lines. Finally, she presented data showing that the inhibition of NK cell function is mainly mediated by melanoma-derived immunosuppressive soluble factors, including IDO and prostaglandin E2.

The ErbB-2 (neu in rat and HER-2 in humans) tyrosine kinase receptor is a self-tolerated tumor-associated molecule directly involved in cancer progression, representing an ideal therapeutic target. In this context, **Federica Cavallo** (Turin, Italy) showed that DNA electroporation with a plasmid encoding the extracellular (EC) and transmembrane (TM) region of the rat ErbB2 oncogene prevents both the growth of ErbB2-positive transplantable tumors and spontaneous mammary carcinogenesis in BALB/c mice transgenic for this oncogene. Despite its effective prevention, however, this vaccination was unable to cure clinically detectable tumors. To trigger a response circumventing tolerance, two chimeric plasmids encoding the EC-TM region of ErbB2, namely rat–human RHuT and human–rat HuRT, were generated. Utilized in CB6F1 mice, both plasmids induced a stronger protective response compared to plasmids encoding the same portions of the entire human or rat ErbB2. These findings suggest that the presence of a heterologous part of a vaccine may overcome immune tolerance for the target protein and thus constitute a promising clinical strategy. Along this line,

**Pier-Luigi Lollini** (Bologna, Italy) discussed oncolytic viruses that selectively lyse tumor cells and spare normal cells, a property obtained through genetic manipulation of wild-type viruses by Gabriella Campadelli-Fiume (Bologna). He demonstrated that the herpes simplex virus (HSV) can be fully detargeted from its natural receptors and retargeted to tumor antigens via specific scFv, and that HER-2 retargeted oncolytic herpes-virus R-LM249 selectively kills HER-2 + tumors cells in vitro and is an effective therapeutic agent in vivo.

The application of therapeutic vaccines to cancer is nowadays an attractive possibility, thanks to advances in molecular engineering and the use of novel technologies. In this setting, **Luigi Aurisicchio** (Rome, Italy) illustrated a genetic vaccination platform based on the use of muscle DNA electroporation and adenovirus. The application of this technology to TAA in immunologically tolerant preclinical rodent models resulted in the induction of measurable antigen-specific responses. Importantly, these results were confirmed and implemented in large animal models, such as dogs and non-human primates. A relevant efficacy proof-of-concept of this technology was recently achieved in a veterinary field study conducted in client-owned pet dogs affected by B-cell lymphoma; results showed a significant immune response against a TAA and an increased overall survival of vaccinated animals in combination with chemotherapy.

In his guest lecture, **Lucio Luzzatto** (Florence, Italy), Scientific Director of the Istituto Toscano Tumori, reviewed some of the past and present achievements in the area of immunotherapy. He pointed out that, like other approaches to the treatment of cancer, immunotherapy can be more or less targeted. For instance, the use of thymosin $\alpha 1$ and ipilimumab is promising, relatively non-targeted attempts to control cancer by modulating the immune system. On the other hand, considering that the immune system has evolved to achieve the most sophisticated degree of specificity, ultimately one would want to exploit this fully for the most pointed targeting of cancer cells. To this end, there are probably only two alternatives: (1) we can focus on where molecules within cancer cells differ from the self-molecules from which they originate, by targeting somatic mutations characteristic of tumor cells; (2) we can try to break through tolerance, i.e., to deliberately exploit auto-immunity as a tool against cancer cells (e.g., by optimizing antigen presentation or by manipulating Treg cells).

## NIBIT and other Italian clinical trials

In the last few months, different immunotherapeutic agents have demonstrated to induce survival benefit in cancer patients. In particular, exciting results of a phase III study demonstrated that the administration of the anti-CTLA-4 mAb ipilimumab, alone or in combination with a gp-100 vaccine, improved the median and long-term survival in patients with unresectable stage III/IV melanoma who had failed a first-line treatment. In his keynote lecture, **Ramy Ibrahim** (USA) highlighted the progress of knowledge in cancer immunology and that immuno-oncology now represents a new evolving scientific discipline. In particular, the identification of new patterns of clinical response that are not considered by standard response criteria led to the development of novel criteria for the evaluation of immunotherapy in solid tumors. Overall, lessons from the development of ipilimumab contributed to a new clinical paradigm for cancer immunotherapy. To this end, the Cancer Immunotherapy Consortium, founded to improve patient care by making cancer immunotherapy part of the standard-of-care in oncology, has evolved novel endpoint recommendations to give a more realistic and useful model for immune-based clinical investigation in cancer (http://www.cancerresearch.org/consortium).

**Anna Maria Di Giacomo** (Siena, Italy) reported on the first trial sponsored by the NIBIT, entitled: "A Phase II Study of the Combination of Ipilimumab and Fotemustine in Patients with Unresectable Locally Advanced or Metastatic Malignant Melanoma". The study was designed to investigate the safety and efficacy of the combination of ipilimumab and fotemustine, in patients with metastatic melanoma with or without brain metastasis. The different nature of the 2 compounds and their well-known safety profile allows testing the combination with no expected dose-limiting overlapping toxicities. Patients' enrollment started on July 2010, involved eight Italian institutions and will be likely completed in 18 months.

To understand the impact on the immune system of the treatment of melanoma patients with ipilimumab and fotemustine, different studies were designed to monitor melanoma-specific immune response in treated patients. As summarized by **Giorgio Parmiani** (Milan, Italy), the main objectives of these studies are to investigate: (1) the influence of the treatment on immune-related progression-free survival (irPFS), brain PFS, and overall survival (OS) in relation to changes in humoral immune responses; (2) the influence of the combination on irPFS, brain PFS, and OS in relation to changes in the phenotypic profile of PBMC, and in the frequency of selected PBMC subsets; (3) the influence of the combination on irPFS, brain PFS, and OS in relation to constitutive gene profiles of melanoma cells. Preliminary results are expected 1 year after the end of patients' enrollment.

The anti–CTLA-4 mAb ipilimumab and tremelimumab represent the prototypes of a new class of immunomodulating agents that have demonstrated encouraging clinical

activity in melanoma patients. Along this line, **Luana Calabrò** (Siena, Italy) focused her presentation on phase II clinical trials concluded or currently ongoing in patients with thoracic malignancies. Preliminary results in advanced non small cell lung cancer patients showed that treatment with ipilimumab combined with chemotherapy was generally well tolerated and induced an increased immune-related progression-free survival compared to patients treated with chemotherapy alone. Promising results were also reported for a second-line, single Institution, single arm, phase II clinical study with tremelimumab, as monotherapy in patients with unresectable malignant mesothelioma that are being treated within the study: "A second-line, single Institution, single arm, phase II clinical study with Tremelimumab, a fully human anti-CTLA-4 monoclonal antibody, as monotherapy in patients with unresectable malignant mesothelioma".

As also previously shown in the session "Immunomodulation Therapy", different preclinical studies support the idea that low doses of NGR-hTNF in combination with immunotherapeutic approaches might increase the clinical outcome. **Lorenzo Pilla** (Milan, Italy) reported on a planned pilot phase I and II study of NGR-hTNF in combination with NA17 HLA-A2 or MAGE-A3 HLA-A1 restricted peptides-based vaccine in Stage IV melanoma patients. The two peptides were selected due to their predominant expression on melanoma cells, for their good safety profile and their ability to elicit CTL response, as well as clinical response in previous clinical trials. Primary objectives of the study are feasibility, safety, and immunogenicity. The study plans to enroll 30 patients in 18 months.

The targeted delivery of therapeutic agents to newly formed blood vessels is particularly attractive for cancer therapy, because of the dependence of tumors on new blood vessels to sustain growth and invasion, and because of the inherent accessibility of neovascular structures to intravenously injected therapeutic agents. Tenascin-C is a glycoprotein of the extracellular matrix, up-regulated in chronic inflammation and in cancer, which was shown to promote cell migration and proliferation, and angiogenesis. **Leonardo Giovannoni** (Siena, Italy) reported interesting preliminary clinical results from three ongoing trials with F16 mAb recognizing the extradomain A1 of tenascin-C either fused to the human cytokine IL-2 or chemically conjugated to $^{131}$I, in melanoma, breast, and lung cancer patients.

Bevacizumab is a humanized mAb directed against VEGF approved in humans for the treatment of metastatic CRC in combination with chemotherapy. **Pier Francesco Ferrucci** (Milan, Italy) showed preliminary results of a phase II study using dacarbazine in association with bevacizumab for the treatment of chemotherapy-naïve advanced melanoma patients. This single institution study enrolled 36 patients after an interim analysis performed after 18 patients to verify efficacy and toxicity. Ferrucci reported that the combined treatment was well tolerated, being mild side effects easily treated by symptomatic therapy. Furthermore, exploratory data analysis show a 50% clinical benefit defined as Complete/Partial Responses + Stable Diseases lasting at least 24 weeks and a 16.5-month median survival. Translational studies targeting VEGF, VEGF receptor, and other cytokines are ongoing in order to identify possible biomarkers to be used in future phase III trials.

In the last session of the congress, **Silvano Ferrini** (Genoa, Italy) gave an update of IL-21 on preclinical and clinical cancer immunotherapy. IL-21 is the lastly discovered member of the IL-2 cytokine family, known to co-stimulate the proliferation and functional activities of T and NK cells and also to regulate B-cell survival, differentiation, and immunoglobulin production. IL-21 was utilized in melanoma and renal cancer in phase I and II clinical trials, demonstrating disease stabilization and milder toxicity. Overall data from early clinical trials are promising and indicate that IL-21 warrants further testing, particularly in combination with blockade of immune-response checkpoints or with tumor-targeted therapies.

## Special report: the AIRC funding programs

The Associazione Italiana per la Ricerca sul Cancro (AIRC) is a private non-profit organization established through the initiative of researchers at the Cancer Institute of Milan, with the support of Italian entrepreneurs. Since its creation in 1965, AIRC has been committed to promote cancer research and it is presently the largest Italian financing Agency of research projects in this area. To date, AIRC has 17 Regional Committees and nearly 1.8 million members. In this context, **Maria I. Colnaghi** (Milan, Italy), Scientific Director of AIRC, was invited to illustrate the funding programs of AIRC, in particular the newest special program "5 per mille". Within this program, research projects able to generate results that can reach the bedside of cancer patients at the end of the 5-year funding are granted. The money for this special program derives from the endowment of the 5‰ of the taxes that the Italian tax-payers can liberally devolve to support non-profit organizations. Among the 30 applications received, 5 projects were selected by 18 foreign referees, top leaders in the field of clinical and basic cancer research. These projects are currently supported with a total 5 years funding of about 60 million Euros.

## Conclusion

The presentations delivered during the VIII meeting of the NIBIT provided an in-depth overview on emerging topics

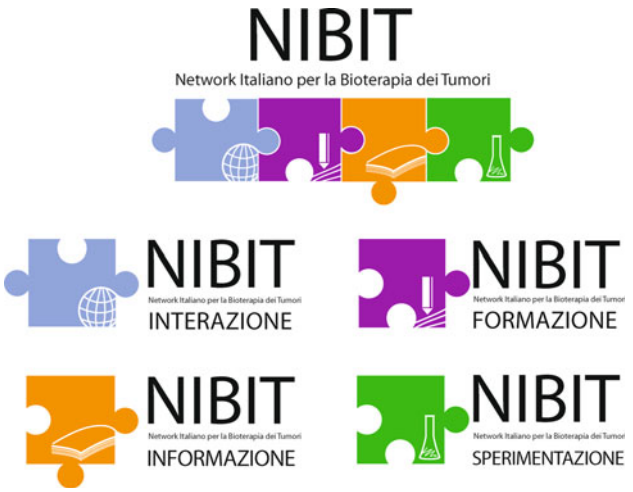


**Fig. 1** NIBIT logo

in cancer immunotherapy that represents the most promising research area for the treatment of human malignancies. The clinical translation of these therapeutic novelties is clearly improving the clinical outcome of cancer patients. Along this line, it is of note that the first clinical trial entirely designed within the NIBIT has started the enrollment of patients. 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 multicenter clinical studies at national level, to help to overcoming the regulatory, ethical, and legal challenges facing the clinical application of new modalities of cancer bioimmunotherapy. The new logo of the NIBIT (Fig. 1) has been approved by the board of Directors and the general NIBIT members Assembly, representing the core values of the association: scientific networking, education, dissemination, and experimentation. All in all, this meeting offered the opportunity to continue and strengthen the existing collaborations both nationally and internationally between basic scientists, clinical researchers, and industries to overstep obstacles in cancer care improvement.

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## Appendix

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