

# Basic mechanisms of cancer immunotherapy







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XI Forum

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# Presentation

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The Special Forum “Basic mechanisms of cancer immunotherapy”, that took place in Lugano on June 16<sup>th</sup> 2017, was organized by IBSA Foundation during the 14-ICML (International Congress on Malignant Lymphoma), an important event for the international scientific community involved in the study and treatment of lymphoid neoplasms.

The meeting brought together prominent scientists from different countries who give a significant contribution to cancer immunotherapy, the revolutionary treatment that improve the innate power of the immune system to fight cancer cells. Thanks to the cancer immunotherapy, that represents the most promising new cancer treatment, now it is possible to manage difficult-to-treat tumors in a more successful manner.

The intent of the Forum was to focus on the novel findings on lymphoma treatment options, from expanded analyses of recently approved therapies to promising new drugs and experimental gene therapies.



# Immunotherapy comes of age

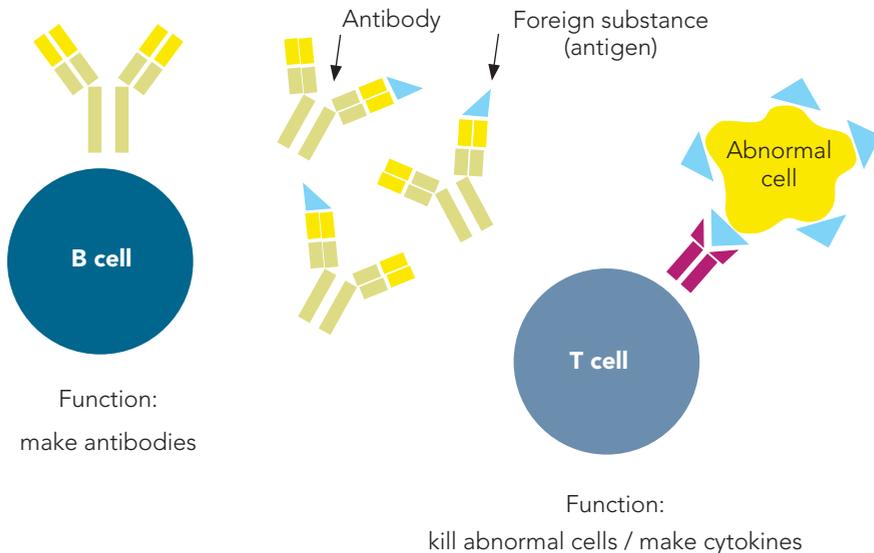
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Immunotherapy is a specific therapy with reduced toxicity. It can be divided into three categories: monoclonal antibodies, engineered T cells and cancer vaccination.

Immune system has two big arms: the B cell arms and the T cell arm. The first is deputed to recognition of foreign substances and the production of specific antibodies, which are released in the serum; the second one utilizes a different recognition system, at the cell surface, and produces cytokines to kill the abnormal cells (● **Figure 1**).

● **Figure 1.** The two arms of the immune system



To avoid the production of heterogeneous products in the antisera, monoclonal antibody have been produced by the hybridoma technology, where the fusion of antibody producing cells and cancerous cells leads to the inexhaustible production of antibodies. B cell are committed to make one specific antibody, so each lymphoma or leukemia B cell is able to make one specific antibody, expressing a tumor specific idiotype [1]. It is then fundamental to produce a specific tumor antibody by the hybridoma technique.

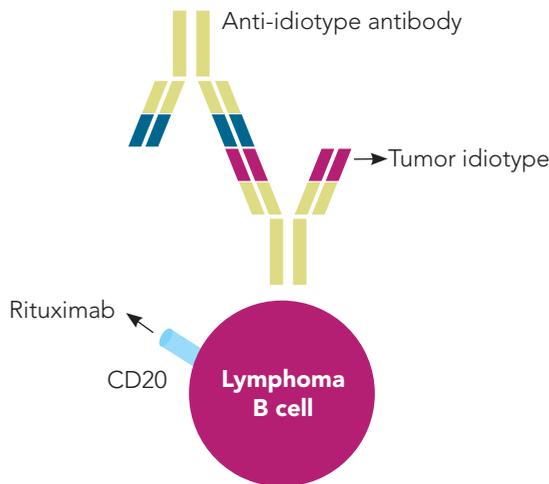
Unfortunately a customized strategy for each patient was not considered convenient by pharmaceutical companies, so it was attempted to design monoclonal antibody to target all lymphoma patients, and CD20 was recognized as a suitable target. Yet CD20 is expressed by all B cells, so a monoclonal antibody against CD20 could potentially destroy every B cells. Still, trial with rituximab identified a specific dose and a specific schedulation that reached the goal with minimum side effects (● **Figure 2**).

This finding led to the introduction of immunotherapy in the classical chemotherapy treatment plan of lymphoma, improving the efficacy of the therapy [2].

Nonetheless rituximab revealed to be useful in several others pathological conditions, such as Post Transplant Lymphoproliferative Disease, Hodgkin's Disease, Sjögren's Syndrome, ITP, TTP, Autoimmune Hemolytic Anemia, Autoimmune Neuropathy, Pemphigus Vulgaris, Myasthenia Gravis, Membranous Glomerulonephritis, Rheumatoid Arthritis, Multiple Sclerosis, SLE [3-6] (● **Table 1**).

What about the T cells? Their characteristic to express the T cell receptor can be utilized to produce a chimeric antigen. A special version of an engineered T cell that carries a receptor incorporating the recognition unit of an antibody against CD19 (CAR-T cells) is the latest and most exciting of the engineered therapies. This strategy

● **Figure 2.** Monoclonal antibody treatment



could be of substantial help when patients are refractory to other treatments, including the immunotherapies [7].

So far CAR-T cells could be efficient in Acute Lymphocytic Leukemia and in B cell Lymphoma, but their efficiency is still dependent on the specificity of the antibody. Nonetheless the therapy is toxic and side effects such as Cytokine Release Syndrome and Brain Syndrome could occur. Moreover, the CAR-T cells therapy is expensive, due to the customization of the procedure. However it should still can be a promising approach and considering that it is not durable, it could be a bridge to transplant or a replacement for autotransplant in not eligible patients (● Table 2).

The recent findings about the immune response in cancer has driven us to shift from the will to target tumor cells, to the will of targeting immune system.

To achieve optimal T-cell activation, both the recognition by TCR of T cells and the binding of costimulatory surface molecules on antigen-presenting cells and T

● **Table 1.** Use of rituximab in other diseases

Post Transplant Lymphoproliferative Disease	Pemphigus Vulgarus
Hodgkin's Disease	Myasthenia Gravis
Sjögren's Syndrome	Membranous Glomerulonephritis
ITP	Rheumatoid Arthritis
TTP	Multiple Sclerosis
Autoimmune Hemolytic Anemia	SLE
Autoimmune Neuropathy	

● **Table 2.** CAR-T cells: current scorecard

Acute Lymphocytic Leukemia - Dramatic
B cell Lymphoma - Worthwhile
Dependent on specificity of the antibody
- CD-19
- ? Others
Toxic
- Cytokine Release Syndrome
- Brain Syndrome
Expensive
- Custom Cellular Product
? Bridge to Transplant
? Replacement for Autotransplant

cells, are required. In addition to costimulatory molecules, there are also inhibitory molecules, such as CTLA-4 and PD-1, which induce signals to prevent T-cell activation. Once activated, cancer-specific T cells arrive at tumor sites and recognize tumor antigens expressed by cancer cells, thereby killing the cancer cells.

Recent clinical trials have demonstrated that blockade of PD-1 coinhibition with anti-PD-1 or anti-PD-L1 therapy enhances T-cell-mediated anticancer responses without severe adverse events. Antibodies against the host immune system (i.e. PD-1) are rapidly changing the field of cancer treatment and especially of Hodgkin's Disease, where durable response rates in excess of 80% have been observed, even in relapsed/refractory patients. Making the immune system able to target tumor cells and disturb the tumor microenvironment is a very promising strategy at the moment. However the immunotherapy can present various side effects, and an equip of different specialists should be involved in the care of the patient. Also, inhibition of CTLA-4 signaling has been shown to significantly improve the survival of patients with different cancers [8].

Yet some questions need to be solved about PD1/PD11 inhibitors, since only some patients or some tumors can respond, and toxicity is still to be reduced.

As said above, immune system is able to recognize specific peptides on cancer cells. Based on this, several new technologies have been developed. At the present moment we are on a trial in follicular lymphoma, on fine needle aspiration samples from treated and untreated sites. Through high dimensional flow cytometry analysis we found that immune cells from different sites show similar distribution. There is a fixed relationship between immune system cells and the tumors, which is specific for each patient.

Drop-seq is a technology that permits to analyze genome-wide gene expression in thousands of individual cells in a single experiment, for mapping cellular heterogeneity in diseased and healthy tissues. These analyses reveal that each tumor is different, showing a peculiar expression in tumor B-cells. Otherwise, normal B-cells tend to cluster together. This technique can lead to identify specifically the differences between the normal and the tumor cells for each patient.

When different patients have been analyzed it looks evident that both MHC class 1 and MHC class 2 were involved. It is then important to identify which immune response the tumor is trying to evade. Isolating both MHC class 1 and 2 from tumors and analyzing them by tandem mass spectrometry, led Khodadoust to discover neoantigens in human lymphomas. Those molecules were exclusively derived from the lymphoma immunoglobulin heavy- or light-chain variable regions.

Interestingly almost only MHC class 2 immunoglobulin variable regions show somatic mutations. Moreover, circulating CD4+ T cells specific for immunoglobulin-derived neoantigens were isolated and it was found that they could kill the autologous lymphoma cells. These findings indicate that patients themselves have neoantigen-specific CD4+ T cells able to kill their tumor, revealing that immunoglobulin neoantigens should be considered as target for lymphoma immunotherapy and that idiotype therapy may definitely deserve reconsideration.

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# Immunogenic cell death: explaining the success of cancer therapies

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Successful chemotherapies, radiotherapies or targeted therapies (that extend life by years) are *de facto* immunotherapies. In fact, successful chemotherapeutics induce a “desirable” combination of signals that facilitate immune recognition of stressed/dying cells [1, 2].

It has been widely demonstrated that chemotherapies are able to provoke immune-dependent effects; in particular, chemotherapies with anthracyclines or oxaliplatin can stimulate immunogenic cell death (ICD), thus transforming dying tumor cells into a therapeutic vaccine that triggers an immune response mediated by cytotoxic T lymphocytes against residual tumor cells. Thus, the condition of the immune system and its ability to respond to chemotherapy can dramatically influence the therapeutic efficacy [3, 4].

Underlying the immunogenic influence to chemotherapy success there are some cell stress and death processes. In particular, chemotherapeutic agents that stimulate ICD can stimulate macroautophagy (autophagy). In this process portions of cytoplasm are sequestered in autophagosomes, these are then fused with lysosomes and degraded by lysosomal hydrolases. Autophagy is essential for ICD, because it is required for the release of ATP into the extracellular space. There ATP can attract antigen-presenting cells near dying cells. Nonetheless autophagy dictates local immuno-surveillance and therapeutic outcome. The suppression of autophagy in tumor cells abolishes the capacity of chemotherapy to stimulate the invasion of tumors by antigen-presenting cells [5, 6].

The autophagic process induced in cancer cells can indeed influence the attraction of dendritic (DC), a type of immune cells that has the exclusive property of antigen cross-presentation, into the tumor bed. In addition, exposure of calreticulin (CALR) and other endoplasmic reticulum chaperones on the surface of malignant cells; the production of CXC-chemokine ligand 10 (CXCL10), and the release of high-mobility

group box 1 (HMGB1) and annexin A1 (ANXA1) can influence prognosis and response in cancer therapy, as exemplified for breast cancer [5].

Considering the supporting data about the relevance of autophagy in the chemotherapeutic response, attention has been focused on the possibility to improve chemotherapy efficacy by stimulating autophagy during treatment. To this aim different strategies have been tested.

One particularly efficient strategy for increasing the efficacy of therapy in mouse models of cancer consists in combining chemotherapy with starvation. Nutrient starvation is also one of the most efficient ways to elicit autophagy. Based on these considerations, the hypothesis that starvation and pharmacological autophagy induction might stimulate anticancer immunosurveillance has been tested in mice.

We found that metabolome was strongly regulated by 48 h starvation in mice, as well as in humans. In particular, PBMC presented relevant changes in acetylation on both species [6].

Chemotherapy efficacy resulted to be improved by 48 h starvation in a model of breast cancer (MPA/DMBA induced), and this effect involved autophagy. We therefore investigated the capacity of several non-immunosuppressive autophagy inducers that mimic the metabolic effects of starvation, so-called caloric restriction mimetics (CRMs), to improve the therapeutic outcome of immunogenic chemotherapies and enhance immunosurveillance [6].

Interestingly, the treatment with hydroxycitrate in mice provoked an increase in ATP release upon chemotherapy, and together with autophagy induction, this was associated with an improvement of the efficacy of chemotherapy against several mouse cancers. Moreover, the use of SB-204990, spermidine, C646 and resveratrol, which triggers different pathways to autophagy, resulted in chemotherapy improvement [6].

In conclusion, caloric restriction mimetics (CRMs) enhance anticancer immunosurveillance, resulting in: improved chemotherapeutic outcome.

Those effects are exerted by the induction of autophagy in cancer cell, extracellular ATP in the TEM and might possibly involve additional effects on immune effectors (such as enhanced common lymphoid precursors and M1 differentiation).

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# Basic mechanisms of cancer immunotherapy. Why the immune response in lymphoma is inadequate

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Lymphomas are tumors that develop from the cells devoted to the body defense; they occur in classical sites and extranodal sites where they thrive within permissive tissue microenvironments. These tissue microenvironments are made of different types of cells, which contribute to the secreted microenvironments and the structural microenvironments.

All the microenvironments are involved in the process of tumor development, and in the inability of the immune system to act properly.

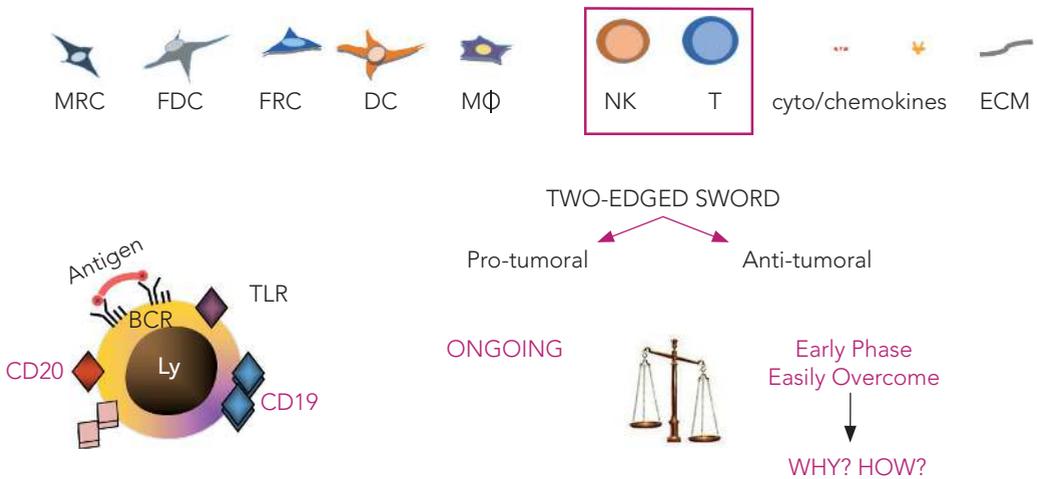
The main actors in the immune response in lymphomas are T cells, whose recognition, migration and activation are crucial.

As said above, the microenvironment itself represents an important immune protector and a tumorigenic habitat constituted by different types of cells. Among them the T and the NK cells play a crucial role in defining a protumoral or an antitumoral response, where the protumoral effect is extended throughout the disease, whereas the antitumoral one happens in an early phase, to be then easily overcome by the protumoral effect (• **Figure 1**).

Understanding the mechanisms that allow immune escape is vital to intervene in lymphomas.

One mechanism is the failure to express cell-surface molecules necessary for the recognition of tumor cells by immune-effector cells because of mutations or deletions, such as  $\beta$ 2-Microglobulin gene in DLBCL [1]; dysfunction of T cell immunological synapse in CLL, FL and DLBCL, which leads CLL tumor cells to actively suppress CD8+ T cell lytic signal transduction [2]; cytokines that, when T cells are exposed to prolonged stimulation with antigen, lead to a profound inability of T cells to respond to activation signals [3]; enrichment of immune cell subsets that suppress an efficient immunological response against the tumor such as FoxP3 regulatory T cells (Tregs); accumulation of M2-polarized tumor associated macrophages (TAMs) that induce an immunosuppressive Th2 response [4].

● **Figure 1.** The microenvironment along the trail of lymphoma development and progression: immune-protected, tumorigenic habitat

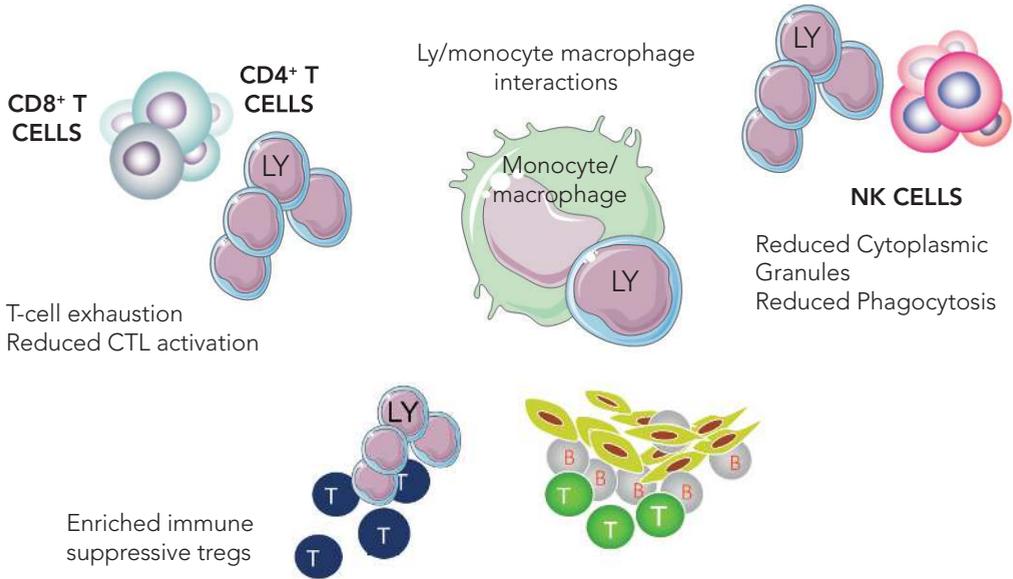


Lymphoma cells can communicate with the microenvironment by different mechanisms: one is the intercellular communications that allowed the reprogramming microenvironment to switch from an antitumoral to a protumoral response. For example CLL-derived exosomes have a paracrine effect on stromal cells residing in the TME. The transfer of exosomal cargoes (miRNA and proteins) to target cells (bone marrow, BM-MSCs, and endothelial cells) induces an inflammatory CAF phenotype in these cells that assume an aberrant stimulatory, protumoral role (increased angiogenesis, release of pro-survival chemokines/cytokines) [5].

Hence Ly cells escape immune attack because of T cell exhaustion, reduced cTL activation, reduced cytoplasmic granules in NK cells and reduced phagocytosis by NK cells. Together with the immune suppressive accumulation of Tregs and the activity of monocytes and macrophages the final immune response is abolished (● **Figure 2**).

In addition, malignant cells subvert normal cells of the immune system to protect themselves from attack, so that tumors co-opt immune checkpoints pathways to evade immune attack. One of the mechanisms for this action is the binding between the programmed death receptor (PD-1) on the T cell, and the programmed death ligand (PDL-1) on the tumor cell, that causes T cell deactivation. To note cancer cells are able to upregulate PD-1 ligands and their binding to PD-1 on tumor specific CD8+T cells, which can be caused by interferon gamma production or genetic alteration in chromosome 9p24 in CHL [6].

• **Figure 2.** Summing up how lymphoma cells evade immune attack



Nonetheless malignant cells are able to protect themselves from the immune system attack by mutational escape.

Taking all these facts in consideration, what are the chances to circumvent these mechanisms for treatment?

One possibility could be to reactivate the T cell by specific monoclonal antibodies which interfere with the ligation of PD-1 to PDL-1, to let T cell free to activate.

So far many checkpoints inhibitors have been designed.

Another chance is to overcome the mutational landscape of cancers by means of genetically modified chimeric antigen receptor (CAR)-T cells, where T cells are engineered to recognize molecules typically expressed on the surfaces of malignant Ly cells, such as CD 19, and to express activation and costimulatory domains which can further activate T cells.

In conclusion, concerning the possible immunotherapy of lymphomas, two strategies appear to be the most conceivable:

- the blockade of receptors that inhibit the immune response, which shows the possibility to eradicate or hold on leash lymphoid malignancies;
- the genetically modified chimeric antigen receptor (CAR)-T cells, which overcome the mutational landscape of cancers [7].

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# Pre-clinical development of novel combinatorial therapies against MYC/Bcl2 double-hit lymphoma

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The Myc oncoprotein belongs to a proto-oncogenic transcription factor family playing a central role in growth control, cell transformation and tumorigenesis. In the adult Myc expression is generally low and confined to proliferating and regenerative cells. However Myc is regulated in tissues, being a target and an effector of various growth regulatory pathways, such as cell growth, cell cycle, apoptosis, energy production, DNA replication and RNA biology.

The identification of specifically Myc target genes in specific tumors, as well as their role in tumor progression and maintenance is a central question in cancer research. It could be interesting to exploit some of these Myc effectors therapeutically [1].

Toward this aim, we investigated Myc-regulated transcriptional programs during B cell lymphomagenesis in mice, through genome-wide chromatin immunoprecipitation and RNA expression profiles, and followed this up with an *in vivo* reverse-genetic screen aimed at the identification of Myc-activated genes involved in tumor maintenance [2, 3].

This uncovered a critical role for the mitochondrial ribosomal protein (MRP) Ptdcd3 in tumor maintenance. Together with Ptdcd3, many other MPR coding genes were coordinately upregulated by Myc in lymphomas, suggesting that the mitochondrial translation machinery could play an important role in this context. Consistent with this notion, the antibiotic tigecycline, known to inhibit the mitochondrial translation, was toxic to tumor cells *in vitro*, and significantly extended lifespan in lymphoma-bearing mice, opening new therapeutic perspectives in Myc-overexpressing tumors [3, 4].

We therefore asked whether tigecycline could be effective therapeutically in other tumors, or act in combination with other drugs. Considering the co-activation of Myc and Bcl2 in double-hit lymphoma, we tested tigecycline together with the Bcl2 inhibitor venetoclax.

Our results showed these drugs cooperate in inducing apoptosis of DHL cells either *in vitro* or *in vivo*, providing strong anti-tumoral activity in a pre-clinical setting.

Altogether, our data indicate that the mitochondrial translation machinery is a critical effector of Myc and defines a new therapeutic target in Myc-associated lymphomas.

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# Conclusions

The Forum was opened by Andrea Alimonti, Switzerland (ERC Investigator, Head Molecular Oncology at IOR/IOSI), whose research has provided important contribution in cancer research, focusing on the characterization and stimulation of novel cellular senescence response.

Ronald Levy, Director of the Oncology Division of the Stanford University School of Medicine (USA), provided an overall overview on the past and present approaches in fighting lymphoma, from the immunotherapy introduction to the utilization of Drop-seq technology to specifically target tumor cells. Guido Kroemer, Professor at the University Paris Descartes and author of important publications on cellular suicide (apoptosis), for which he has been rewarded the Nobel prize, focused on the immunogenic cell death, a process which revealed to be crucial in chemotherapy efficacy. An interesting overview has been made on the additional strategies that can be implemented to improve chemotherapy success, with a particular attention on the caloric restriction mimetics (CRMs), which enclosed the ability to enhance cancer immunosurveillance.

Federico Caligaris Cappio, Scientific Director of the Italian Association for Cancer Research (AIRC) and expert on new techniques called “CAR-T cells”, moved to the basic mechanisms of cancer immunotherapy, focusing on the inadequacy of the immune response in lymphoma. From this point of view, the most conceivable strategies appear to be the blockade of receptors inhibiting the immune response or the utilization of the genetically modified chimeric antigen receptor (CAR)-T-cells.

Finally, Bruno Amati, a Swiss and Italian citizen, Division Director at the European Institute of Oncology (IEO) and Director of Center for Genomic Science of the Italian Institute of Technology (IIT) in Milan, moved to novel combinatorial therapies against Myc/Bcl2 double-hit lymphoma, showing very recent data on the topic.

The debate was intense and in-depth, since different novel issues were discussed. In conclusion every participant understood that research is hardly working to bypass the limitations in antibody based therapy in lymphoma, and that studies are giving promising results.





In the last years cancer immunotherapy has achieved remarkable results and represents today the most promising new cancer treatment. Thanks to this revolutionary treatment now it is possible to manage in a more successful manner tumors which until recently were difficult to treat with classic therapies.

The Special Forum “Basic mechanisms of cancer immunotherapy” was organized within the context of the 14-ICML (International Congress on Malignant Lymphoma), the most important international meeting devoted to the study and treatment of lymphoid neoplasms.