

Revolutionary therapies for cancer

Programme & Abstracts



Revolutionary therapies for cancer

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Programme & Abstracts

Speakers & Chairmen

Andrea Alimonti

Institute of Oncology Research (IOR), Bellinzona, Switzerland; Università della Svizzera italiana (USI), Lugano, Switzerland; Department of Medicine, University of Padua, Padua, Italy; Veneto Institute of Molecular Medicine (VIMM), Padua, Italy

Franco Cavalli

Foundation for the Institute of Oncology Research (IOR), Bellinzona, Switzerland

Michael N. Hall

Biozentrum, University of Basel, Basel, Switzerland

Carl H. June

Perelman School of Medicine, University of Pennsylvania, Philadelphia, United States of America

Alberto Mantovani

Istituto Clinico Humanitas, Humanitas University, Milan, Italy; William Harvey Research Institute, London, United Kingdom

Solange Peters

Centre Hospitalier Universitaire Vaudois, University of Lausanne, Lausanne, Switzerland

Scientific Committee

Andrea Alimonti

Institute of Oncology Research (IOR), Bellinzona, Switzerland; Università della Svizzera italiana (USI), Lugano, Switzerland; Department of Medicine, University of Padua, Padua, Italy; Veneto Institute of Molecular Medicine (VIMM), Padua, Italy

Franco Cavalli

Foundation for the Institute of Oncology Research (IOR), Bellinzona, Switzerland

Silvia Misiti

Head of IBSA Foundation for scientific research, Lugano, Switzerland

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Presentation

Silvia Misiti

Head of IBSA Foundation for scientific research

The mission of the IBSA Foundation is to promote a science culture and to serve as a meeting point between the scientific world and the general public.

In order to achieve this goal, IBSA Foundation focuses on a range of activities, the most important of which is the organization of international Forums: these are one-day meetings that cover different and evolving aspects of new frontiers of life-science-related subject areas and bring a global network of scientists together to discuss the latest pre-publication research in their fields.

IBSA Forums – always organized in collaboration with the academic world, institutions, and leading research centres – represent a chance for speakers to compare and contrast ideas, as well as to exchange information and ideas on forward-looking topics and new developments in scientific research.

They also represent an opportunity for students, experts, and all participants to discuss issues, share insights and learn: a process of exchange that provides valuable input for further research and drives advancements in knowledge.

In each Forum prominent experts from the international scientific community focus on a significant topic in the field of biology or medicine that has a great impact on people's health and quality of life, describing state-of-art and future challenges.

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Introduction

Andrea Alimonti

IBSA Foundation Scientific Board

Although the first notion of immuno-oncology dates back to the end of the XIXth century, the field has only gained the general community's attentions in the last two decades.

Its efficacy is based on the use of the body's own immune system for the elimination of cancer cells. In the last decade, several treatments have been approved for their use in clinics, and the discovery of checkpoint inhibitor-based therapies has been awarded the 2018 Nobel Prize in Medicine.

Despite the initial enthusiasm, years of failures have taught us that tumors have the ability to evade and even exploit the immune response.

Ultimately, new exciting immunotherapies have been developed, which have demonstrated to be effective strategies against different type of malignancies: adoptive T cell therapy and immune checkpoint inhibitors are among the most relevant.

Cancer immunotherapy

Sara Zumerle¹, Andrea Alimonti²

¹ Department of Medicine, University of Padua, Padua, Italy; Veneto Institute of Molecular Medicine (VIMM), Padua, Italy

² Institute of Oncology Research (IOR), Bellinzona, Switzerland; Università della Svizzera italiana (USI), Lugano, Switzerland; Department of Medicine, University of Padua, Padua, Italy; Veneto Institute of Molecular Medicine (VIMM), Padua, Italy

Cancer immunotherapy is one of the most effective therapeutic strategies to fight different types of tumors. Its efficacy is based on the use of the body's own immune system to eliminate cancer cells.

Among the different types of immunotherapies, the most recent discoveries have focused on adoptive T cell therapy and immune checkpoint inhibitors.

Adoptive T cell transfer

Adoptive T cell therapy consists of the *ex vivo* expansion of patient-derived tumor-reactive T lymphocytes, and their reinfusion into the patient, with the aim of specifically recognizing and eliminating cancer cells. T lymphocytes may be derived from the tumor tissue (tumor-infiltrating lymphocytes, TILs), or from the patient's peripheral blood. To increase their ability of eliminating the tumor, T cells can be genetically engineered to express antigen-specific T cell receptors (TCR) or chimeric antigen receptors (CAR) [1].

CAR-T cells represent the most recent and exciting type of adoptive T cell therapy; the topic will be highlighted by Prof. Carl June, the discover of this approach. They are characterized by the expression of a chimeric receptor, combining a single chain variable fragment domain (scFv), with antibody-like features, with the signaling domain of CD3 linked to a costimulatory domain. Compared to engineered TCRs, CARs have the potential of recognizing the target antigen even in a major histocompatibility complex (MHC-unrestricted manner [1].

So far, two CAR-T therapies have received approval from the Food and Drug Administration (FDA), both targeting the CD19 protein: tisagenlecleucel (Kymriah®), for the treatment of certain types of non-Hodgkin lymphoma and B cell acute lymphoblastic leukemia, and axicabtagene ciloleucel (Yescarta®), for certain types of non-Hodgkin lymphoma [2, 3] (● Table 1).

Moreover, CD19-CAR-T cells have shown promising results in the numerous clinical trials for hematologic malignancies, like acute lymphoblastic leukemia (ALL), diffuse large B cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL), and other B-cell non-Hodgkin lymphomas [4].

In solid tumors, CAR-T cell therapy has shown limited therapeutic efficacy. One major limitation is the identification of suitable antigens to be targeted, i.e. antigens whose expression is specific for and shared by the cancer cells [5]. Moreover, CAR-T cell recruitment and function in the tumor can be hindered by the suppressive tumor microenvironment.

● Table 1. FDA-approved immunotherapies

Treatment type	Drug	Target	FDA-approved application
CAR T-cells	Tisagenlecleucel (Kymriah®)	CD19	Non-Hodgkin lymphoma; B cell acute lymphoblastic leukemia
	Axicabtagene ciloleucel (Yescarta®)	CD19	Non-Hodgkin lymphoma
Immune checkpoint inhibitors	Ipilimumab (Yervoy®)	CTLA-4	Melanoma
	Atezolizumab (Tecentriq®)	PD-L1	Bladder and lung cancers
	Avelumab (Bavencio®)	PD-L1	Bladder and Merkel cell carcinoma
	Durvalumab (Imfinzi®)	PD-L1	Bladder and lung cancers
	Nivolumab (Opdivo®)	PD-1	Bladder, colorectal, head and neck, kidney, liver, and lung cancers, and melanoma
	Pembrolizumab (Keytruda®)	PD-1	Bladder, pediatric lymphoma, colorectal, esophageal, head and neck, and lung cancers as well as lymphoma and melanoma
	Ipilimumab + nivolumab	CTLA-4 and PD-1	Melanoma and kidney cancer

Immune checkpoint inhibitors

Another appealing immunotherapy approach aims to enhance the body's antitumor immune response by targeting inhibitory molecules that block T cell function, such as cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed cell death 1 (PD-1). This important discovery in the field of immunotherapy earned James P. Allison and Tasuku Honjo the Nobel Prize in Medicine.

CTLA-4 is expressed at the membrane of activated T lymphocytes, where it counteracts the action of the costimulatory molecule CD28. The idea of targeting CTLA-4 to boost antitumor immune response was theorized and tested by J. Allison [6] and it wasn't long before two anti-CTLA4 antibodies, ipilimumab and tremelimumab, entered clinical trials, demonstrating their clinical efficacy, in particular, in patients with advanced metastatic melanoma [7]. To date, one CTLA-4 inhibitor, ipilimumab (Yervoy®), has been approved by the FDA (in 2011) for the treatment of melanoma, and its action is being evaluated in different cancer types, together with other CTLA-4-targeting molecules.

PD-1 is expressed by T lymphocytes and binds to PD-L1, widely expressed by somatic cells, and PD-L2, mostly expressed by antigen-presenting cells. Upon ligand binding, PD-1 acts as an immune checkpoint of the TCR downstream signaling [8]. The expression of PD-L1 by tumor cells is induced by inflammatory mediators and results in PD-1-dependent T lymphocyte exhaustion. Nivolumab, the first PD-1-targeting antibody tested in clinical trials, showed consistent anti-tumor activity accompanied by limited toxicity [7].

Today, five treatments targeting the PD-1/PD-L1 axis have received FDA approval: atezolizumab (Tecentriq®) for the treatment of bladder and lung cancers; avelumab (Bavencio®) for the treatment of bladder and Merkel cell carcinoma; durvalumab (Imfinzi®) for the treatment of bladder and lung cancers; nivolumab (Opdivo®) for the treatment of bladder, colorectal, head and neck, kidney, liver, and lung cancers, and melanoma; and pembrolizumab (Keytruda®) for the treatment of bladder, pediatric lymphoma, colorectal, esophageal, head and neck, and lung cancers, as well as lymphoma and melanoma (• [Table 1](#)).

Resistance to CAR-T cells and checkpoint inhibitors

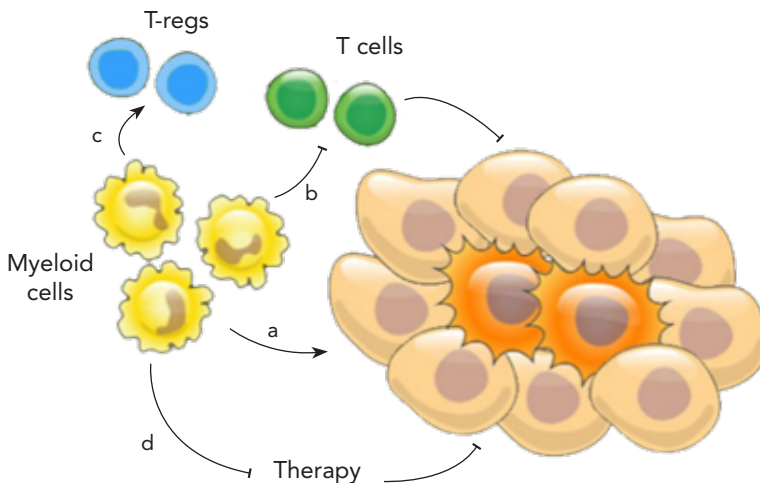
Despite the impressive durable response rates observed in subsets of cancer patients, cancer immunotherapies remain ineffective for the majority of patients, who are resistant to the treatment or relapse after a period of response. The

causes underlying cancer immunotherapy resistance can be multiple. For example, tumors can elude T cell recognition because they lack tumor antigens or they downregulate the antigen-presenting machinery. Alternatively, immunotherapy resistance can be driven by tumor-cell-extrinsic factors, such as the presence of immunosuppressive factors and immunosuppressive cells [9]. In this context, an important role is played by **myeloid cells**, which will be one the highlights of this Forum, with the speech of one of the main experts of the field, Prof. Alberto Mantovani.

Most solid tumors are characterized by a prominent myeloid infiltrate, constituted mostly of myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs) [10]. Tumor-associated myeloid cells have been correlated with poor prognosis and immunotherapy resistance [11, 12].

Tumor-associated myeloid cells are responsible for numerous tumor-promoting and immunosuppressive functions [13]: they can directly sustain tumor growth [14], they can suppress effector T cell function or migration [15], they can activate regulatory T cells [16], they can produce reactive oxygen and nitrogen species [17], they can induce angiogenesis [18], and they can drive resistance to therapy [19] (• Figure 1).

• **Figure 1.** Tumor-associated myeloid cells are responsible of numerous tumor-promoting and immunosuppressive functions: they can directly sustain tumor growth (a), they can suppress effector T cell function or migration (b), they can activate regulatory T cells (c), they can drive resistance to therapy (d)



For these reasons, targeting tumor-associated myeloid cells is a promising immunotherapeutic approach to counteract tumor growth and encouraging results have been achieved in pre-clinical and clinical research [20, 21]. Several strategies can be adopted to block tumor-promoting myeloid cells: *a)* depletion of existing cells; *b)* blockade of their generation; *c)* blockade of their recruitment to the tumor site; *d)* reprogramming of their immunosuppressive phenotype.

Importantly, targeting tumor-infiltrating myeloid cells can also synergize and improve the efficacy of other therapies. In Pten-null prostate tumors, blocking MDSC recruitment via a CXCR2 inhibitor improves the response to chemotherapy [14], while targeting MDSC-derived IL-23 restores sensitivity to androgen-deprivation therapy [19]. Moreover, depleting MDSCs in experimental models increases antitumor immune response and improves the efficacy of anti-PD-1 therapy [22]. Along the same line, TAM reprogramming by CSF1R blockade improves response to immune checkpoint inhibitors [23].

Finally, recent discoveries have identified the CD47-SIRP α axis as a potent immune checkpoint specific for macrophages: CD47 is expressed by several tumors and functions as a “don’t eat me” signal by binding to SIRP α on macrophages. Specific inhibitors are under investigation alone or in combination with other therapies to trigger immune response against cancer [24].

Altogether, these studies open the way to novel and complex types of immunotherapy, targeting both the adaptive and innate immune system.

References

- [1] June CH, Sadelain M. *Chimeric antigen receptor therapy*. N Engl J Med 2018 Jul 5;379(1):64-73.
- [2] Neelapu SS, Locke FL, Bartlett NL *et al*. *Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma*. N Engl J Med 2017 Dec 28;377(26):2531-44.
- [3] Prasad V. *Immunotherapy: Tisagenlecleucel – the first approved CAR-T-cell therapy: implications for payers and policy makers*. Nat Rev Clin Oncol 2018 Jan;15(1):11-2.
- [4] Hammerl D, Rieder D, Martens JWM *et al*. *Adoptive T cell therapy: new avenues leading to safe targets and powerful allies*. Trends Immunol 2018 Nov;39(11):921-36.

- [5] Knochelmann HM, Smith AS, Dwyer CJ *et al.* *CAR T cells in solid tumors: blueprints for building effective therapies.* Front Immunol 2018 Jul 27;9:1740.
- [6] Leach DR, Krummel MF, Allison JP. *Enhancement of antitumor immunity by CTLA-4 blockade.* Science 1996 Mar 22;271(5256):1734-6.
- [7] Ribas A, Wolchok JD. *Cancer immunotherapy using checkpoint blockade.* Science 2018 Mar 23;359(6382):1350-5.
- [8] Ishida Y, Agata Y, Shibahara K, Honjo T. *Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death.* EMBO J 1992 Nov;11(11):3887-95.
- [9] Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. *Primary, adaptive, and acquired resistance to cancer immunotherapy.* Cell 2017 Feb 9;168(4):707-23.
- [10] Porta C, Sica A, Riboldi E. *Tumor-associated myeloid cells: new understandings on their metabolic regulation and their influence in cancer immunotherapy.* FEBS J 2018 Feb;285(4):717-33.
- [11] Bjoern J, Juul Nitschke N, Zeeberg Iversen T *et al.* *Immunological correlates of treatment and response in stage IV malignant melanoma patients treated with Ipilimumab.* Oncoimmunology 2015 Nov 25;5(4):e1100788.
- [12] Meyer C, Cagnon L, Costa-Nunes CM *et al.* *Frequencies of circulating MDSC correlate with clinical outcome of melanoma patients treated with ipilimumab.* Cancer Immunol Immunother 2014 Mar;63(3):247-57.
- [13] Dougan M, Dranoff G, Dougan SK. *Cancer immunotherapy: beyond checkpoint blockade.* Annu Rev Cancer Biol 2019;3:55-75.
- [14] Di Mitri D, Toso A, Chen JJ *et al.* *Tumour-infiltrating Gr-1+ myeloid cells antagonize senescence in cancer.* Nature. 2014 Nov 6;515(7525):134-7.
- [15] Molon B, Ugel S, Del Pozzo F *et al.* *Chemokine nitration prevents intratumoral infiltration of antigen-specific T cells.* J Exp Med 2011;208:1949-62.
- [16] Zoso A, Mazza EM, Bicciato S *et al.* *Human fibrocytic myeloid-derived suppressor cells express IDO and promote tolerance via Treg-cell expansion.* Eur J Immunol 2014 Nov;44(11):3307-19.
- [17] Nagaraj S, Gupta K, Pisarev V *et al.* *Altered recognition of antigen is a mechanism of CD8+ T cell tolerance in cancer.* Nat Med 2007 Jul;13(7):828-35.

- [18] Yang L, DeBusk LM, Fukuda K *et al.* *Expansion of myeloid immune suppressor Gr+CD11b+ cells in tumor-bearing host directly promotes tumor angiogenesis.* Cancer Cell 2004 Oct;6(4):409-21.
- [19] Calcinotto A, Spataro C, Zagato E *et al.* *IL-23 secreted by myeloid cells drives castration-resistant prostate cancer.* Nature 2018 Jul;559(7714):363-9.
- [20] Mantovani A, Marchesi F, Malesci A *et al.* *Tumour-associated macrophages as treatment targets in oncology.* Nat Rev Clin Oncol 2017 Jul;14(7):399-416.
- [21] Tobin RP, Davis D, Jordan KR, McCarter MD. *The clinical evidence for targeting human myeloid-derived suppressor cells in cancer patients.* J Leukoc Biol 2017 Aug;102(2):381-91.
- [22] Highfill SL, Cui Y, Giles AJ *et al.* *Disruption of CXCR2-mediated MDSC tumor trafficking enhances anti-PD1 efficacy.* Sci Transl Med 2014 May 21;6(237):237ra67.
- [23] Zhu Y, Knolhoff BL, Meyer MA *et al.* *CSF1/CSF1R blockade reprograms tumor-infiltrating macrophages and improves response to T-cell checkpoint immunotherapy in pancreatic cancer models.* Cancer Res 2014 Sep 15;74(18):5057-69.
- [24] Veillette A, Chen J. *SIRP α -CD47 immune checkpoint blockade in anticancer therapy.* Trends Immunol 2018 Mar;39(3):173-84.

ABSTRACTS

mTOR signaling in growth and metabolism

Michael N. Hall

Biozentrum, University of Basel, Basel, Switzerland

TOR (target of rapamycin) is a highly conserved serine/threonine kinase that controls cell growth and metabolism in response to nutrients, growth factors, and cellular energy. TOR was originally discovered in yeast but is conserved in all eukaryotes including plants, worms, flies, and mammals.

TOR is found in two structurally and functionally distinct multiprotein complexes termed TORC1 and TORC2. The two TOR complexes, like TOR itself, are highly conserved. Thus, the two TOR complexes constitute an ancestral signaling network conserved throughout eukaryotic evolution to control the fundamental process of cell growth. As a central controller of cell growth, TOR plays a key role in development and aging, and is implicated in disorders such as cancer, cardiovascular disease, obesity, and diabetes.

While the role of TOR in controlling growth of single cells is relatively well understood, the challenge now is to understand the role of TOR signaling in disease and in coordinating and integrating overall body growth and metabolism in multicellular organisms. This will require elucidating the role of TOR signaling in individual tissues.

Data on the role of mammalian TORC1 (mTORC1) and mTORC2 in controlling cellular processes and in specific tissues will be presented.

Innate immunity, inflammation and cancer: from bench to bedside

Alberto Mantovani

Istituto Clinico Humanitas, Humanitas University, Milan, Italy;
William Harvey Research Institute, London, United Kingdom

Innate immunity consists of a cellular and a humoral arm. Tumor-associated macrophages are a key component of tumor-promoting inflammation. The long pentraxin PTX3 as originally cloned (cDNA and genomics, mouse and human) as an IL-1 inducible gene. We have used the long pentraxin PTX3 as a paradigm for the humoral arm of innate immunity and its interplay with cells. Components of humoral innate immunity including PTX3 and complement are a key component of the tumor microenvironment. Moreover, the evidence on the role of complement in macrophage recruitment and functional skewing of macrophages will be discussed.

In addition we recently discovered that IL-1R8, which we cloned as TIR8 and also identified as SIGIRR, serves as a checkpoint restraining NK cell mediated resistance against carcinogenesis and metastasis.

In the same vein, we originally identified a tetraspan-like molecule (MS4A4A) in polarized M2 and M2-like macrophages. The function of this molecule and its role in the interplay with NK cells in resistance to metastasis will be discussed. Thus macrophages engage in a complex interaction with innate lymphoid cells which plays a key role in tumor immunity.

References

- Bonavita E, Gentile S, Rubino M *et al.* *PTX3 is an extrinsic oncosuppressor regulating complement-dependent inflammation in cancer.* Cell 2015;160:700-14.
- Locati M, Curtale G, Mantovani A. *Diversity, mechanisms and significance of macrophage plasticity.* Annu Rev Pathol, *in press.*
- Mantovani A, Marchesi F, Laghi L *et al.* *Tumor-associated macrophages as treatment targets in oncology.* Nature Rev Clin Oncol 2017;14(7):399-416.
- Mantovani A, Dinarello CA, Molgora M, Garlanda C. *IL-1 and related cytokines in innate and adaptive immunity in health and disease.* Immunity 2019;50(4):778-95.
- Mattiola I, Tomay F, De Pizzol M *et al.* *The interplay of the macrophage tetraspan MS444A with Dectin-1 and its role in NK cell-mediated resistance to metastasis.* Nature Immunol, *in press.*
- Molgora M, Bonavita E, Ponzetta A *et al.* *IL-1R8 is a checkpoint in NK cells regulating anti-tumor and anti-viral activity.* Nature 2017;551:110-4.
- Ponzetta A, Carriero R, Carnevale S, Barbagallo ML, Molgora M, Perucchini C *et al.* *Neutrophils driving unconventional T cells mediate resistance against murine sarcomas and selected human tumors.* Cell, *in press.*

Building the next generation of CAR-T cells

Carl H. June

Center for Cellular Immunotherapies, Perelman School of Medicine, University of Pennsylvania, Philadelphia, United States of America

Immunotherapy is the latest breakthrough in cancer therapy, thanks to the remarkable clinical results of checkpoint inhibitors [1] and chimeric antigen receptor (CAR) T cells [2]. The US Food and Drug Administration (FDA) approval in 2017 of two CAR-T cell therapies for the treatment of B cell malignancies in pediatric and adult patients is a landmark for cancer immunotherapies. In 2018, these therapies were also approved in the European Union, the United Kingdom, and Canada.

The emergence of immune-oncology as the first broadly successful strategy for metastatic cancer will require clinicians to integrate this new pillar of medicine with the pillars of chemotherapy, radiation and targeted small molecule compounds. CAR-T cells have proven that engineered immune cells can serve as a powerful new class of cancer therapeutics. Adoptive immunotherapy retargeting T cells to CD19 via a chimeric antigen receptor is an investigational treatment capable of inducing complete tumor regression of B-cell malignancies when there is sustained survival of infused cells.

Clinical experience has helped to define the major challenges that must be met to make engineered T cells a reliable, safe, and effective platform that can be deployed against a broad range of tumors. The emergence of synthetic biology approaches for cellular engineering provides the field with a broadly expanded set of tools for programming immune cells [3]. In this presentation, I will discuss how these tools could be used to design the next generation of smart T cell precision therapeutics.

In solid tumors, we have observed antitumor activity in patients with ovarian cancer, pancreatic ductal adenocarcinoma, pleural mesothelioma and glioblastoma following infusion of CAR-T cells expressing scFv specific for mesothelin or EGFRvIII [4, 5]. However, this approach has not yet resulted in complete tumor eradication. Using genome edited T cells, it may be possible to enhance and prolong the activity of T cells that have disrupted immune and metabolic checkpoints [6]. In preclinical studies, we show that TCR-specific T cells have enhanced antitumor activity following disruption of TCR alpha and beta genes and the PD-1 gene using CRISPR/Cas9. This approach is just entering a clinical trial. These findings provide insights into the immunobiology of effector T cells and demonstrate the potential of multiplexed CRISPR/Cas9 genome editing to synthetically enhance the efficacy of immunotherapy.

Finally, advances in T cell engineering, genetic editing, the selection of optimal lymphocytes, and cell manufacturing have the potential to broaden T cell-based therapies and foster new applications beyond oncology, in infectious diseases, organ transplantation, and autoimmunity.

References

- [1] Ribas A, Wolchok JD. *Cancer immunotherapy using checkpoint blockade*. Science 2018;359(6382):1350-5.
- [2] June CH, Sadelain M. *Chimeric antigen receptor therapy*. N Engl J Med 2018;379(1):64-73.
- [3] Lim WA, June CH. *The principles of engineering immune cells to treat cancer*. Cell 2017;168(4):724-40.
- [4] Beatty GL, O'Hara MH, Lacey SF *et al*. *Activity of mesothelin-specific chimeric antigen receptor T cells against pancreatic carcinoma metastases in a phase I trial*. Gastroenterology 2018;155(1):29-32.
- [5] O'Rourke DM, Nasrallah MP, Desai A *et al*. *A single dose of peripherally infused EGFRvIII-directed CAR T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastoma*. Sci Transl Med 2017;9:(399). pii: eaaa0984.
- [6] Fraietta JA, Nobles CL, Sammons MA *et al*. *Disruption of TET2 promotes the therapeutic efficacy of CD19-targeted T cells*. Nature 2018;558(7709):307-12.

From molecular addiction to immune activation: reinventing therapies for cancer. Lung cancer as an illustration

Solange Peters

Oncology Department, Centre Hospitalier Universitaire Vaudois, University of Lausanne, Lausanne, Switzerland

Precision medicine based on detailed genomic analysis is of major therapeutic significance in cancer care, with the recent emergence of several targeted therapies across malignancies. In parallel, there has been remarkable success in treating certain malignancies by enhancing the immune response by preventing inhibition of the immune response by tumor cells. Immunotherapy is strikingly successful in a small fraction of tumors but remarkably unsuccessful in many tumors.

The paradigm of lung cancer has rapidly changed in the last ten years thanks to the introduction of molecularly tailored drugs, as well as cancer immunotherapy.

The development of low-cost high-throughput nucleic acid sequencing has had transformative effects on multiple aspects of biological science and medicine. In 2004 the discovery of the epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer (NSCLC) and their predictive value for therapy with the EGFR tyrosine kinase inhibitors (TKIs) opened the way to an intense program of research on lung cancer, aiming at identifying other genomic or protein alterations that could be used as target for treatment. Thus, genetic rearrangements of anaplastic lymphoma kinase (ALK) gene in lung cancer and its oncogenic features were discovered in 2007.

The impressive clinical results obtained with the inhibition of ALK and EGFR kinases compared to classical chemotherapy further supported the hypothesis that targeting signaling pathways aberrantly active in cancer cells might lead to a better outcome of therapy for lung cancer patients. Studies on molecular alter-

ations of lung tumors highlighted peculiar differences of biomarkers expression and role in the several subtypes of lung cancer. To date, a targetable and potentially actionable alteration may be recognized in 50-60% of adenocarcinomas.

The etiologic association with exposure to tobacco carcinogens is of particular relevance for cancer immunotherapy. Blockade of the programmed cell death protein 1 (PD-1)-PD-1 ligand 1 (PD-L1) receptor-ligand pair, a dominant mediator of immune resistance in the tumor microenvironment (TME), currently represents the mainstay of current immunotherapy of NSCLC. Current approaches targeting immune checkpoints exhibit increased responses in tumors with a high number of somatic mutations such as smoking-induced NSCLC.

In this landscape, the recent development since 2015 and approval of several monoclonal antibodies targeting programmed death 1 (PD-1) or its ligand programmed death ligand 1 (PD-L1) has revolutionized the treatment of and outlook for patients with newly diagnosed, locally advanced or metastatic NSCLC. The efficacies of current immunotherapy drugs vary considerably from patient to patient, highlighting the importance of identifying personalized biomarkers, and improving personalized immunotherapy strategies and deciphering resistance mechanisms.

BIOGRAPHIES



Andrea Alimonti

Andrea Alimonti, graduated at Sapienza University of Rome, has completed his studies in clinical oncology at the Regina Elena National Cancer Institute, in Rome. He continued his education in the United States, first at the Memorial Sloan-Kettering Cancer Center in New York and then at the Harvard Medical School in Boston, where he worked at the Pandolfi Laboratory, a cutting edge cancer research institute. He is currently Head of Molecular Oncology at Institute of Oncology Research (IOR), a research division of the Oncology Institute of Southern Switzerland (IOSI) in Bellinzona and Professor of Biomedical Science at Università della Svizzera italiana (USI) in Lugano. His research is focused on the characterization of a novel type of cellular senescence response which is elicited by complete loss of the tumour suppressor PTEN, and on the identification of novel compounds with pro-senescence activity. His final aim is to develop the concept of pro-senescence therapy for cancer, from experimental evidences to clinic, investigating the efficacy of “pro-senescence” compounds in phase I clinical trials. This will also allow for the identification of senescence markers in human tumour samples to be used in clinic.

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Franco Cavalli

Franco Cavalli was Scientific Director of the Oncology Institute of Southern Switzerland (IOSI) in Bellinzona until 2017. He created this institute, which encompasses medical oncology, radio-oncology, nuclear medicine, palliative care, hematology and an important research division. He is currently President of the Foundation, which manages the Institute of Oncology Research (IOR), located in Bellinzona. Professor of Medical Oncology at the Medical Faculty in Bern, he has an international reputation for the treatment of and research into malignant lymphoma and

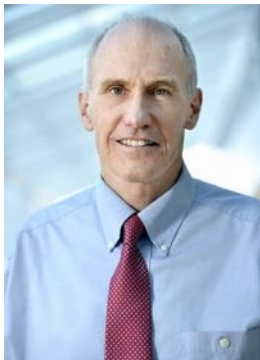
new drugs. Every second year he organizes the ICML (International Conference on Malignant Lymphoma) in Lugano. ICML is the most important congress on this topic worldwide. The quality of his work has been recognized by the award of 24 national and international prizes, including the Petzcoller Award for special dedication to oncology and the ESMO Lifetime Achievement Award. He has published more than 600 articles in peer-reviewed journals and has contributed to many books on cancer, including the Textbook of Medical Oncology, edited together with S. Kaye, H. H. Hansen and D. Armitage. He has been President of the Swiss Cancer League and of the International Union Against Cancer (UICC).

He is Chairman of the Scientific Committee of the European School of Oncology (ESO) and of the World Oncology Forum (WOF). He is member of World Health Organization (WHO) Committee of selection of essential medicines for cancers since 2015.



Michael N. Hall

Michael N. Hall, born in Puerto Rico, grew up in Venezuela and Peru. He received his Ph.D. from Harvard University and was a postdoctoral fellow at the Pasteur Institute in Paris and the University of California, San Francisco. In 1987 he joined the Biozentrum of the University of Basel, where he is currently Professor and former Chair of Biochemistry. He is a pioneer in the fields of TOR signaling and cell growth control. In 1991, Hall and colleagues discovered TOR and subsequently elucidated its role as a central controller of cell growth and metabolism. This discovery led to a fundamental change in how one thinks of cell growth. It is not a spontaneous process that just happens when building blocks (nutrients) are available, but rather a highly regulated, plastic process controlled by TOR-dependent signaling pathways. As a central controller of cell growth and metabolism, TOR plays a key role in development and aging, and is implicated in disorders such as cancer, cardiovascular disease, diabetes, and obesity. Member of the US National Academy of Sciences, he received numerous awards, including the Louis-Jeantet Prize for Medicine (2009), the Marcel Benoist Prize for Sciences or Humanities (2012), the Breakthrough Prize in Life Sciences (2014), the Canada Gairdner International Award (2015), and the Albert Lasker Award (2017). He has served on several editorial and scientific advisory boards.



Carl H. June

Carl H. June is the Director of the Center for Cellular Immunotherapies at the Perelman School of Medicine, and of the Parker Institute for Cancer Immunotherapy at the University of Pennsylvania. He maintains a research laboratory that studies various mechanisms of lymphocyte activation that relate to immune tolerance and adoptive immunotherapy for cancer and chronic infection. In 2011, his research team published findings detailing a new therapy in which patients with refractory and relapsed chronic lymphocytic leukemia were treated with genetically engineered versions of their own T cells. The treatment has also now also been used with promising results to treat children with refractory acute lymphoblastic leukemia, and adults with re-

fractory lymphoma. CTL019, the CAR-T cell developed in the June laboratory, was the first gene therapy to be approved by the US FDA in August 2017. He has published more than 400 manuscripts and is the recipient of numerous prizes and honors, including election to the Institute of Medicine in 2012 and the American Academy of Arts and Sciences in 2014, the Paul Ehrlich and Ludwig Darmstaedter Prize (shared with J. Allison), the Novartis Prize in Immunology (shared with Z. Eshhar and S. Rosenberg), the Karl Landsteiner Memorial award, the Karnofsky Prize from the American Society of Clinical Oncology, the Albany Medical Prize and a lifetime achievement award from the Leukemia and Lymphoma Society.



Alberto Mantovani

Alberto Mantovani is Professor of Pathology at the Humanitas University in Milan, and Scientific Director of the Istituto Clinico Humanitas. His attention has been focused on molecular mechanisms of innate immunity and inflammation. He has contributed to the advancement of knowledge in the field of Immunology formulating new paradigms and identifying new molecules and functions. For his research activity he has received several national and international awards, such as the Triennial OECI Award from the Organization of the European Cancer Institutes, the

Robert Koch Award for his contribution to tumor immunology and immunotherapy, the AICF Prize for Excellence in Medicine and, most recent, the American Association for Cancer Research International Pezcoller Award for Extraordinary Achievement in Cancer Research. The broad impact of his contributions is testified by citations. As of January 2019 he has over 111,000 (Scopus), 80,000 (Web of Science) or 160,000 (Google Scholar) citations and an H-index of 161 (Scopus), 125 (Web of Science) or 185 (Google Scholar).



Silvia Misiti

Silvia Misiti, MD Ph.D. In 2001 she started working for Sapienza University of Rome as a researcher in Endocrinology. In 2012 she moved to Lugano, where she lives and directs the IBSA Foundation for scientific research, a non profit organization founded by the pharmaceutical company IBSA, Institut Biochimique SA. Her mission is to combine her great passion in scientific research with the promotion of different activities focused on innovation, education and dissemination, by collaborating with cultural and academic institutions. She is also

Head of Corporate Communication & CSR for IBSA.



Solange Peters

Solange Peters is Professor and Chair of Medical Oncology as well as the Thoracic Malignancies Programme in the Department of Oncology at the University Hospital of Lausanne, Switzerland. She received both her doctorate in medicine and PhD from the University Hospital of Lausanne. After completing her clinical education in medical oncology and molecular biology in Switzerland and Italy, Peters has specialized in thoracic tumors, lung cancer, and pleural tumors. She is currently in charge of teaching and patient care in the area of thoracic malignancies in

the Department of Oncology of Lausanne University, where she is building a translational program in collaboration with the Molecular Oncology Laboratory directed by Dr Hanahan at the Swiss Federal Institute of Technology in Lausanne and the Ludwig Institute. Peters' main fields of interest are new biomarkers discovery and validation in preclinical and clinical settings, multimodality strategies for locally advanced non-small cell lung cancer (NSCLC), as well as cancer immunotherapy. Peters' current research projects are focused on multimodality stage III NSCLC treatment strategies, immunotherapy in limited small cell lung cancer and advanced NSCLC and thymic malignancies, ALK inhibitors, HER2 inhibitors, as well as innovative immunotherapy combinations and new immunomodulating treatments across thoracic malignancies. She acts as the local Principal Investigator (PI) for lung trials opened at Lausanne Cancer Centre, focused on phase I predictive biomarkers and thoracic malignancies immunotherapy, and is a co-PI of several other trials. Additionally, she acts as the scientific coordinator and Foundation Council member of the European Thoracic Oncology Platform. Solange Peters has authored numerous peer-reviewed manuscripts and book chapters, and serves as deputy editor of the *Journal of Thoracic Oncology*, and on the editorial board of several other oncology journals. She is active in the educational programs of the ESMO and IASLC, notably working as the current editor of the ESMO lung cancer clinical practice guidelines. She is the Chair of ESMO Women for Oncology Committee, and she is the youngest ESMO President-elect ever, for a mandate in 2020-2021. She was also a member of the IASLC board of directors, and acts as vice president of the Swiss Group for Clinical Cancer Research lung group.

IBSA Foundation Papers

- 1** *Treatment of subclinical hypothyroidism in children, in women, and in adults*
10-12 May 2013, Baveno-Stresa (available also in Italian)
- 2** *News for hypothyroidism*
27-29 September 2013, Gubbio (available also in Italian)
- 3** *Stem cell therapy: hype or hope?*
29 March 2014, Lugano
- 4** *Metabolic diseases and tendinopathies: the missing link*
21 June 2014, Lugano
- 5** *Aging: is it a disease?*
27 September 2014, Frankfurt am Main
- 6** *Sexual health and sexual ecology*
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3 July 2015, Siena
- 8** *Cancer immunology makes it to clinic: how cancer will be treated in the coming years*
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15 April 2016, Naples
- 10** *New technologies to treat neurodisorders: neuroprosthetics*
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- 12** *Female healthy aging*
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- 13** *The new nutrition era: from molecular mechanisms to human health*
12 April 2018, Milan
- 14** *Sguardi scientifici sulle migrazioni/Scientific views on migrations*
13 October 2018, Lugano (bilingual Italian/English)

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Over the years cancer immunotherapy has shown very promising results in the treatment of multiple cancers and represents today one of the most innovative strategies in the search for new tools for the fight against cancer. The latest progresses made in this area confirm the main role of this therapeutic modality in the treatment of pathologies that affect human health worldwide.

The “Revolutionary therapies for cancer” Special Forum is organized within the context of the 15-ICML (International Congress on Malignant Lymphoma). Since its first edition, the 15-ICML has become a must-attend event for the scientific community involved in the study and treatment of lymphoid neoplasms.