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MEETING REPORT

9th Immunotherapy of Cancer conference (ITOC): A meeting report

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ABSTRACT

The Immunotherapy of Cancer conference (ITOC) is an European meeting providing a global platform for discussions where all those dedicated to the immunotherapy of cancer can exchange their knowledge and the latest findings about immuno-oncology. The 9th ITOC was held in Munich in September 2022. Major highlights of the 2022 edition included the key note address and life time achievement to Laurence Zitvogel on her contributions on the understanding of the role of microbiota in cancer development and therapy resistance. Her research has paved the way for therapeutic exploitation of the microbiome.

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Introduction

In the past decade, cancer immunotherapy has emerged as an essential pillar of cancer treatment and care.[1] Major advances in basic and translational cancer immunology have established the immune system as an essential contributor to cancer control but also eventually progression, setting the rationale for therapeutic interventions.[2] Today, a growing number of approaches is approved and an ever-blooming body of novel strategies are being investigated clinically and preclinically.[3] On the EMA- and FDA-approved drugs, a specific type of immune cells, so-called T cells, take a center stage: these can be differentiated in drugs directly targeting T cells (so-called check point inhibitors), drugs recruiting T cells to cancer cells by dually targeting both cell types (bispecific antibodies) and the direct therapeutic use of T cells, where the later are genetically engineered with a chimeric antigen receptor (CAR) for cancer cell engagement.[2,4] Especially check point inhibitors are occupying a growing space in solid oncology both in terms of indications covered and number of patients treated.[5] In any case, CAR-T cells and bispecific antibodies also represent a growing market, although their pace in somewhat slower because of the frequency of target indications (hematologic cancers).[6] All of these approvals were based on substantial prolongation of overall survival in otherwise many times refractory patients and with clear advantages over the standard of care.[5,6] In spite of these advances, many if not most patient treated will either not respond or relapse after an initial response.[5] This major issue roots both in innate or acquired resistance to immune treatment with common but also distinct causes depending on the treatment approach.

Overall, the landscape of novel advances and developments to tackle and overcome these problems is moving with an incredible pace and diversity, rendering it incredibly difficult to both clinicians and scientists to keep up. The ITOC meetings have been established to address this growing need. The 9th edition took place from September 22th to September 24th, 2022 in Munich Germany. Scientists from 4 continents and 27 different countries have attended the conference with a total of 262 participants, who had the opportunity to attend a cutting edge program on the most pressing and innovative advances in immune-oncology, structured in 12 sessions as follows:

Emerging concepts/new agents (including immunometabolism)

Daniela Thommen opened the Emerging Concepts/New Agents (including Immunometabolism) session. She gave an overview on her patient-derived tumor fragment (PDTF) platform that she used to evaluate response to anti-PD1 blockade in different cancer types in human *ex-vivo* tumor models. She found that treatment with anti-PD1 blockade can reactivate intra-tumoral T cells at the tumor site with an intra-tumoral heterogeneity in the capacity to respond to anti-PD1 blockade. In lung cancer, T cells expressing high levels of PD1 are impaired in the production of classical effector cytokines with the secretion of the chemokine CXCL13, which is normally not expressed by CD8 T cells but is critical for the formation and the maintenance of tertiary lymphoid structures.

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Maria Rescigno showed that increased levels of PV-1, a marker of impaired gut vascular barrier (GVB) in patients with colorectal cancer (CRC) is implicated in the migration of intra-tumoral microbiota from the primary tumor into the liver. Thereby, a premetastatic niche is formed that favors the recruitment of metastatic cells into the liver. In mice, metastasis of tumor cells is correlated with high level of chitinase 3-like 1 (CH13L1: a new checkpoint induced by microbiota) expression. In breast cancer, CHI3L1 is capable to inhibit ADCC and impair innate NK cell cytotoxicity by limiting the polarization of lytic granules, which opens an avenue for therapeutic interventions.

Xavier Catena observed in a melanoma mouse model that high levels of the growth factor MIDKINE affects dendritic cell (DC) maturation and reduces the number of common dendritic precursors in the bone marrow and thus intra-tumoral DC infiltration. Using RNA sequencing in melanoma patients, *Xavier Catena* showed that patients with high level of MIDKINE signature have less infiltrating dendritic cells and reduced expression of activation genes. MIDKINE also impairs phagocytic activity and the function of DC but also reduces the ability of DC to prime CD8+ T cells.

Tumor microenvironment

Amanda Lund found, in several mice models, that tumor-associated lymphatic vessels control T cell exit from the tumor microenvironment through the expression of the chemokine CXCL12. This chemokine recruits CXCR4+CD8+ T cells to the tumor periphery leading to a movement of these cells out of the tumor to the lymph nodes and thereby limiting tumor control. In addition, CXCR4 inhibition and loss of lymphatic-specific CXCL12 in CXCL12 *Knock-out* mice boosts T cell retention and enhances response to therapeutic immune checkpoint blockade.

Using single-cell RNA sequencing, *Thorsten Mempel* found that stem like- T cells (TCF1+ cells) upregulate the chemokine receptor CXCR6 in order to convert into effector-like Cytotoxic T lymphocytes (CTL) in the mouse melanoma model D4 M.3A-pOVA.

This receptor directs effectors CTL in the perivascular niche of the tumor stroma occupied by CCR7+ DCs expressing the CXCR6-ligand CXCL16 and the survival cytokine IL-15.

Using bulk RNA sequencing, *Simon Heidegger* found that tumor-intrinsic RIG-I mediated by 3pRNA induces the upregulation of genes related to extracellular vehicles (EVs) biogenesis in a B16.ova melanoma mouse model. These EVs are uptaken by dendritic cells via different mechanisms, leading to the release of INFα and can also induce T cell priming. Transcriptome of melanoma patients also showed that RIG-I induced tumor EVs have also a strong anti-tumor therapeutic potential and can render tumors susceptible to checkpoint inhibitors.

B cells in immunooncology

Marie-Caroline Dieu-Nosjean observed in several cohorts of patients with early, intermediate, advanced and metastatic stages of cancer that the presence of Tertiary Lymphoid Structures (TLS) is associated with better outcome and survival. B cells in TLS are correlated with the presence of plasma cells secreting antibodies that can bind tumor antigens. Using immunofluorescence, *Marie-Caroline Dieu-Nosjean* identified a close interaction between IgG and IgA plasma cells and CD8 + T cells in TLS stimulating the proliferation of CD8+ and supporting an anti- tumor immune response through potential improvement of the effector capacity of CD8+ T cells in tumors.

Nikhil Joshi used RNA splicing to develop iNversion INduced Joined neoAntigen (NINJA) to generate neoantigens enabling the study of endogenous antigen-specific T cells in several diseases. Injection of tumor cell lines induced with NINJA in mice triggers CD8 and CD4 T cells responses upon neoantigen induction, enhances anti-tumor immunity and bypasses central and peripheral tolerance mechanisms. In different studies, *Nikhil Joshi* also revealed turning PD1 on in the skin, remodels myeloid cell compartment and create tolerant CD8 T cells preventing them to reach pathogenic sites.

Adi Barzel demonstrated that B cells can be engineered by CRISPR/Cas9 to express anti-HIV neutralizing antibodies by targeting the J-C intron of the IgH locus. Such B cells are capable to migrate to the germinal center where they proliferate and differentiate into either memory B cells or antibody secreting plasma cells while also undergoing class switch recombination (CSR) and somatic hypermutation (SHM) after transfer into mice. Also, using single cell RNA sequencing, editing of human T cells with CRISPR-Cas9 and guide RNA targeting genes for TCR chains leads to a loss of chromosome 14, containing the TCRα locus and to aneuploidy. He showcases that aneuploidy and chromosomal truncations in CRISPR-Cas9 cleavage should be monitored in clinical protocols.

Fernanda Escobar-Riquelme uses vaccination to induce the production of autoantibodies targeting the tumor endothelial cell antigen Robo4 selectively expressed on tumor vascular endothelium but not on healthy vasculature. The injection of Robo4- conjugate vaccine increases NK cells, dendritic cells, CD4+ and CD8+ T cells in a lung Lewis carcinoma model.

Sina Bondza studied the binding mechanism and of three anti-CD20 monoclonal antibodies (Rituximab, Ofatumumab and Obinutuzumab) using real-time interaction analysis performed on cell lines and primary B-cells. *Sina Bondza* showed that Ofatumumab displayed the most stable binding to CD20 with bivalent target engagement, while Rituximab could overall engage more in bivalent binding compared to Ofatumumab. The binding of the first complement component C1q was more stable and most dominant for Ofatumumab.

Vaccine therapy

In a clinical trial study (NOA16), *Michael Platten* showed that an IDH1 (R132)-specific peptide vaccine induces immune responses and prolongate the survival of glioblastoma patients, compared to historical controls. However, patients without an immune response showed tumor progression. Single cell RNA and T cell receptor sequencing revealed tumor infiltration of CXCL13+ and CD40LG+ T helper cell dominated by a single

IDH1(R132 H)-reactive T cell receptor in patients with pseudo-progression.

Brian Lichty demonstrated that vaccinia virus is able to impair c-GAS/c-GAMP/Sting signaling pathway but it is unable to impair bacterial dinucleotide cyclases and alternative dinucleotide cyclases. Cyclase-vaccinia viruses can strongly activate immunostimulatory genes that can enhance the survival of mice when combined with anti PD-1 therapy in a MC38 colon adenocarcinoma model. Exocyclase carrying multimeric fusion protein with various cargos that are used to program exosome provides constitutively active STING agonist that can be directed to DC and macrophages in order the improve immune responses.

Pro & contra sessions for critical topics

Mascha Binder observed by studying patients suffering from several types of cancer treated with chemotherapy and Immuno-Oncology agents (IO) that the most striking effect of IO are in combination with chemotherapy or as sequential approach (chemotherapy followed by IO). However, the clinical success of these combination has not generated deep mechanisms insight and need more caution and optimization of doses.

Stéphane Champiat demonstrated that IO monotherapy is sufficient in some patients. However, certain patients do not at all benefit from IO due to several severe side effects. The addition of chemotherapy should be based on unfavorable biomarkers such as PD-L1 status and the tumor burden, which is why negative predictive markers for IO are crucially needed.

Precision medicine meets immunotherapy (immuno-monitoring)

Maya Saleh performed ScRNA-seq performed on CD45+ PanTCRαβ CD19- cells isolated from tumors or adjacent non-tumoral livers of hepatocellular carcinoma (HCC) patients with different etiologies (NASH and cirrhosis). She identified three main subsets of MDSCs; a monocytic MDSC (M-MDSC), a granulocytic MDSC (G-MDSC) and early MDSC (e-MDSC) that express the inflammatory receptor TREM-1. TREM-1+ e-MDSC coordinate pro-fibrotic immune-excluded desmoplastic lesions and immunosuppression in HCC. In glioblastoma (GB), ScRNA-seq on tissue isolated from WT and inflammasome deficient ($Ice^{-/-}$) mice after orthotopic injection of GL-261-GFP-Gluc cell line showed an increase of monocytes, DC and Treg subsets. This was found in the adjacent non-tumoral tissue in WT but not in $Ice^{-/-}$ mice and associated with faster tumor regrowth and decreased survival rate in WT mice.

Elisabeth de Vries radiolabeled trastuzumab targeting HER2 with ^{89}Z that can be internalized after binding to its receptor leading to the degradation of HER2+ tumor cells and the release of ^{89}Z allowing a better imaging in positron emission tomography (PET). ^{89}Z labeled PDL-1 antibody showed a better uptake in the tumor and a modest uptake in the spleen in breast cancer patients. In melanoma and non-small lung cancer, ^{89}Z labeled PDL-1 antibody uptake is related to the lesion site with lymph node metastases showing the highest uptake, while a low uptake was observed in brain metastases.

Judith Wienke demonstrated by single□cell RNA sequencing of neuroblastoma samples an infiltration of NK cells with reduced cytotoxicity, while T cells had a dysfunctional profile. The interaction analysis could identify NECTIN2-TIGIT as an important immune checkpoint that can affect T and NK cell function. She also observed that blocking TIGIT and PD-L1 improved survival *in-vivo* and adding TIGIT blockade to the standard treatment in a chemotherapy-resistant syngeneic model can improve the survival of mice.

Using advanced functional genomics on 9,000 human tumors and single cell RNA sequencing, *Niroshana Anandasabapathy* showed an enrichment of memory – resident T cells in solid tumors. In melanoma, a high fraction of CD8+ TILs is observed in anti-PD1 responders that expand after therapy. Memory-persistence signatures can positively stratify melanoma survival and are correlated with DC maturation-migration and INFγ programming.

Lifetime achievement award awarded to Prof. Laurence Zitvogel

Laurence Zitvogel showed that fecal microbiota transplantation (FMT) from patients who responded to Immune checkpoint inhibitor (ICI) into germ-free or antibiotic-treated mice ameliorated the anti-tumoral effects of PD-1 blockade. In non-small-cell lung cancer (NLSC), Akkermansia muciniphila (Akk) is associated with clinical benefit with an increase of overall survival of patients after PD1 blockade. FMT depleted of AKK from NLSC patients to MCA-205 tumor bearing C57BL/6 mice transferred resistance to PD1 blockade. This phenotype was restored after transfer of AKK. *Laurence Zitvogel* also showed that blockade of β-adrenergic receptors or genetic deficiency in *Adrb2* gene prevented cancer-induced ileopathy associated with increased gut permeability dominated by Gram-positive *Clostridium* bacteria. In bladder cancer, patients treated with pembrolizumab, *E. coli*–specific CXCL13 producing T_{FH} and IgG constitute biomarkers that predict clinical benefit.

"Lost in translation"

Tanja de Gruijl observed by flow cytometry that tumor ablation through irreversible electroporation (IRE) decreases regulatory T cells rates and increases PD-1 expression in CD8+ and CD4+ T cells in patients with pancreatic cancer. In addition, the combination of IRE with CpG and PD-1 blockade in metastatic pancreatic cancer can activate the immune system and specifically dendritic cells. *Tanja de Gruijl* also showed that suppression of LN-resident DC subsets leads to spread and dissemination of melanoma to distant sites.

Injection of TLR9 ligand (CpG) locally activated LN-resident DC inducing T cell responses both in the lymph nodes and the peripheral blood and improved recurrence-free survival.

Sine Reker Hadrup demonstrated that neoantigen-reactive CD8+ T cell (NART) populations increase in patients with

controlled disease in comparison to patients with progressive disease in metastatic urothelial carcinoma. These NART enrich for Ki67 positivity and acquire PD-1-expression after 3 weeks of treatment with immune checkpoint blockade (ICB). In metastatic melanoma patients, NART derived from tumor-infiltrating lymphocytes (TILs) is correlated with increased survival of patients. *Sine Rekers Hadrup* also develops a new technology that can expand and activate antigen-specific CD8 T cells by using a peptide-MHC assembled to a dextran-based polysaccharide backbone in a combination with cytokines and co-stimulatory molecules (Ag-Scaffold).

Yogesh Basavaraju evaluated 653 peptides derived from clonotypic B-cell receptor immunoglobulins (BcR IGs) of 25 Chronic lymphocytic leukemia (CLL) patients using DNA-barcoded multimers of peptide-major histocompatibility complexes (MHC) to determine the presence of neoepitope reactive T cells. Among the 25 patients, they observed the reactivity of T cells toward 3 peptide-MHC specificities demonstrating that cancer-specific somatic hypermutation in the BCR IG can be a potential target of T cell recognition in CLL.

Young researcher session

Thaddäus Strzalkowski observed that the expression of C-C chemokine receptor 8 (CCR8) enhances the migration of CAR-T cells *in-vitro* and redirect CAR-T cells targeting HER2 to the tumor site, while the expression of the dominant-negative TGF-β receptor 2 (DNR) can prevent the immunosuppressive tumor microenvironment. Equipment of CAR T cells with both CCR8 and DNR enhances the anti-tumor activity of CAR-T cells in pancreatic and colorectal mouse tumor models and also protects against relapse in an ovarian cancer model.

Florian Märkl proposed arming T cells with EGFRvIII synthetic agonistic receptors (E3 SARto selectively activate such T cells by cross-linking bispecific antibodies (BiAb). In such case, BiAb specific for both SAR T cells and melanoma-associated antigens TYRP1 and MCSP induce the proliferation of E3 SAR T cells leading to tumor cell lysis and an enhancement of tumor-free survival in several melanoma xenograft models.

Kateryna Onyshchenko reported in mouse tumor models that combination of radiation (RT) with anti-PD1 and CD122-directed IL-2/anti-IL2 complex (IL-2c) increases the abscopal effects in comparison to mice treated with either agent and enhanced survival of mice. An increased expression of CXCR3+ on tumor specific CD8+ T cells induced by IL-2c was also observed. Anti-tumoral effects of the triple treatment were associated with the expansion of tumor specific CD8+ T cells with stem- and effector-like phenotypes.

Using single-cell RNA sequencing and flow cytometry, *Chen Qing* showed that the combination of an anti-CD25 used for the depletion of regulatory T cells with a B16 tumor vaccine (GVAX) is effective in a poorly infiltrated B16 mouse model. Most mice that achieve a partial response relapse due to deactivation and death of activated infiltrating effector T cells.

Cell therapy in solid tumors

To overcome the main limitations of CAR-T cell therapy in solid tumors, *Sebastian Kobold* showed that the addition of the chemokine receptors CCR8 and CXCR6 into CAR-T cells enhances the trafficking of CAR-T cells into the tumor site. Using CAR-T cells targeting the P329 G mutation combined with antigen-binding human IgG1 antibodies containing the P329 G Fc mutation can overcome antigen heterogeneity. On the other hand, inhibition of the adenosine receptor protects CAR-T cells from immunosuppressive signaling in response to adenosine. To identify specific tumor antigens, *Sebastian Kobold* used single cell RNA sequencing to reveal unrecognized targets for cancer therapy.

Prasad Adusumilli showed that mesothelin-targeted CAR-T cell immunotherapy combined with anti-PD1 blockade enhance CAR-T cell function in mice and prolongate overall survival in patients. In a clinical trial study, Prasad Adusumilli also showed that equipment of CAR-T with a PD-1 dominant negative receptor (PD1DNR) that provides T-cell intrinsic checkpoint blockade is associated with a better persistence of CAR-T cells in the peripheral blood.

Cell therapy in hematologic diseases

Using a single cell RNA sequencing approach, *Caleb Lareau* could identify a rare population of CD19 expressing mural cells, which normally wrap and support the vasculature in the human brain. The depletion of these mural cells during the treatment of hematological malignancies with anti-CD19 CAR-T cells increases the possibility of blood brain leakiness and potentially leads to neurotoxicity. In a different study, *Caleb Lareau* showed that the Human Herpesvirus 6 (HHV-6) can be reactivated in standard T cell cultures during the process of CAR-T cells generation potentially leading to encephalitis in patients treated with CAR-T cells.

Andrea Schmidts developed a TriPRIL CAR that can target both BCMA and TACI antigens expressed on myeloma cells in-vitro and in-vivo. This TriPRIL CAR carries three copies of APRIL ligand (ligand for both BCMA and TACI) in order to mimic the natural trimeric structure of APRIL. This TriPRIL CAR showed an enhancement in the clearance of myeloma in-vivo after the injection of MM1S cell line in NSG and BCMA KO mice showing a good efficacy of the TriPRIL CAR against BCMA-negative Myeloma.

Johanna Olweus observed that T cells that express a T-cell receptor (TCR) specific for the terminal deoxynucleotidyl transferase (TdT) enzyme in the context of HLA-A *02:01 can efficiently eliminate primary acute lymphoblastic leukemia (B-ALL and T-ALL). By contrast, TdT TCR T cell therapy does not affect normal human thymocytes or normal hematopoiesis in humanized mice.

Combination therapy (with a special focus on local IO)

Chong-Xian Pan observed that targeting the PI3K pathway in bladder patient-derived xenografts models (PDX) with a combination of Copanlisib and anti-PD1 alters tumor immune microenvironment by increasing CD8 T cell infiltration and decreasing FOXP3 Treg cell. This combination therapy also promotes DC migration into tumor draining lymph nodes and downregulates the TGFβ pathway via PI3K inhibition.

Gosse Adema demonstrated that a combination treatment of cryoablation plus TLR9 stimulation via CpG-oligodeoxynucleotides in mice is more effective in the eradication of tumors than either treatment modality alone. This combination therapy results in increased DC maturation and cytotoxic T lymphocytes induction leading to tumor eradication. *Gosse Adema* also showed that Saponin-based adjuvants (SBAs) induces lipid bodies (LB) that facilitate cross-presentation by DC and has a specific effect on migratory/inflammatory $CD11^{high}$CD8a- cells but not on CD8+, BAtf3+ DC. SBA combined with tumor ablation enhances DC presentation and activation and induces CD8+ T cells expansion.

Maria Sasso demonstrated in multiple *in-vitro* human cell culture models that the Tumor Specific Immuno-Gene (T-SIGn) viruses encoding multiple immunostimulatory mediators can reprogram the tumor microenvironment. TSIGn lead to an efficient expression of CD19 antigen on tumor cell surface and so re-directing CAR-T cells to act against tumor cells.

Fabian Schuurmans aimed to improve anti-GD2 immunotherapy in Neuroblastoma by using bifunctional antibodies that can recognize GD2 but are also able to block CD47 overexpressed on tumor cells and ligand for SIRPα receptor expressed on myeloid cells. These bifunctional antibodies are able to bind and block CD47 in a GD2 dependent manner but also increase the phagocytosis of GD2 expressing cell lines in a dose dependent manner.

Conclusion

This year the ITOC dedicated the lifetime achievement award to Professor Laurence Zitvogel from France to recognize her work on Microbiota-centered interventions to circumvent primary resistance to I-O. The upcoming ITOC10 conference will be held from 21 to 23 March 2024 in Munich in Germany.

Disclosure statement

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