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Sixth Immunotherapy of Cancer conference (ITOC): advances and perspectives—a meeting report

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ABSTRACT

Immunotherapy has moved to the forefront of cancer treatment, illustrated by the accelerating pace of novel therapy approvals. In this complex environment, scientists rely on cutting edge conferences to stay informed. The Immunotherapy of Cancer (ITOC) conference was established jointly with the Society of the Immunotherapy of Cancer to bring the European researchers together. In its sixth edition, the ITOC conference has recently been held in Vienna, Austria.

PREFACE

The past years have seen an explosion in the number of indications approved for immunotherapeutic modalities and new clinical trials.[1 2] The present report highlights the novel aspects presented during the plenary sessions (figure 1). This year Immunotherapy of Cancer (ITOC) dedicated a lifetime award to *Alberto Mantovani* to recognize his input to the understanding of the mechanisms of innate immunity and inflammation in cancer.

MICROENVIRONMENT AND METABOLISM

Emanuel Donnadieu observed that T cells actively excluded from the tumor accumulate in the peritumoral region. Ex vivo microscopy revealed that $CD206^+$ macrophages reduce T cell motility, and dense matrix fibers prevent cell infiltration. However, ICAM1 expression on the tumor cells promoted CAR T cell infiltration.

Eduard Batlle observed that cancer-associated fibroblast cell programme is associated with prognosis in colorectal cancer (CRC) and driven by transforming growth factor-beta (TGF-β) signaling. Model of mouse CRC using organoids with Lgr5, APC, KRAS, Tgfbr2, and Trp53 mutations demonstrated therapeutic effects of TGF-β neutralization.

Bo Huang demonstrated that PCK1-mediated gluconeogenesis is essential for memory T cell formation and maintenance through the increase of reduced glutathione and decrease of reactive oxygen species (ROS). Moreover, cancer cells may mechanically resist cell lysis by myosin-based contraction.

While studying T cell metabolism, *Pedro Romero* revealed that memory T cells are essential for melanoma control. $VLA1^+$ tumor-infiltrating lymphocytes (TILs) controlled the tumor outgrowth and were found to coexpress CD69 and CD103, indicating a tissue-resident phenotype. Additionally, $TCF1^+CD8^+$ memory T cell frequency in patient samples correlated with a good prognosis.

Lisa Derosa identified that *Akkermansia muciniphila* and *Bacteroides salyersiae* present in the stool of non-small-cell lung carcinoma (NSCLC) and renal cell carcinoma patients are associated with favorable clinical responses to treatment. In murine models, these species reversed resistance to PD-1/CTLA-4 blockade after fecal transplantation from non-responder patients.

EMERGING CONCEPTS AND NEW AGENTS

Using single-cell RNA profiles, *Ana Anderson* found that checkpoint blockade therapy-induced transcriptional changes in Tim-3$^-$ PD-1$^-$CD8$^+$ TILs. Memory precursor subset of those TILs identified as CD62L$^-$Slamf-7^{hi}CX3CR1$^-$ the population is controlled by TCF1, and its loss limits the response to checkpoint blockade.

Paolo Ascierto showed that elevated expression of CD73 and its activity correlates with a low response rate to nivolumab and ipilimumab treatment. This concept was previously found valid for melanoma patients and is currently tested in prostate cancer.

Claudia Lengerke showed that chemotherapy-resistant LSCs lack NKG2D ligands that are necessary for NKG2D-mediated natural killer (NK) cell killing. PARP1 suppresses the expression of those ligands, and its inhibitors could be used as therapeutic agents to control leukemogenesis in acute myeloid leukemia.

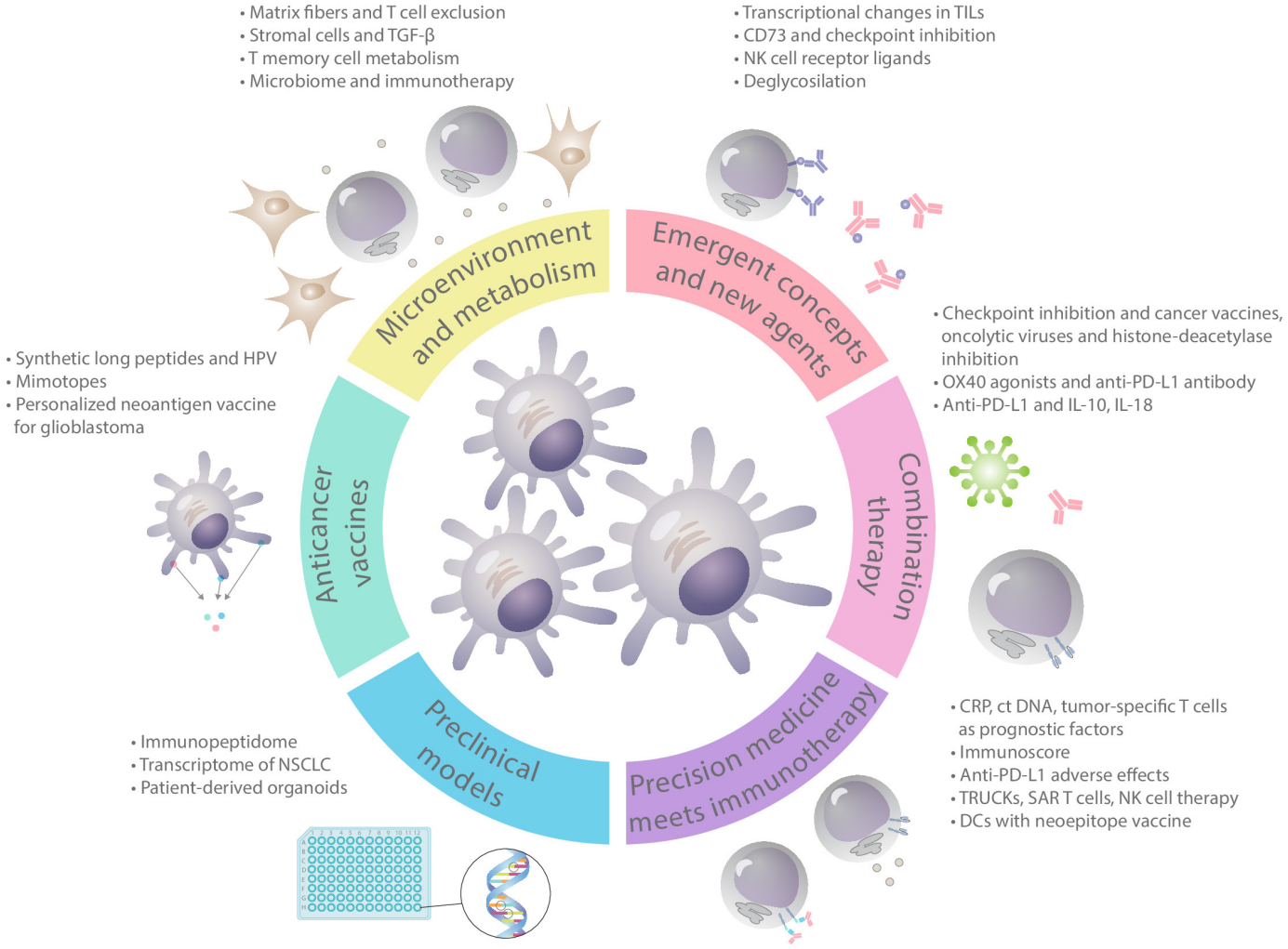

Figure 1 Summary of the sessions presented at the sixth Immunotherapy of Cancer conference. CRP, C-reactive protein; DC, dendritic cells; IL, interleukin; NK, natural killer; NSCLC, non-small-cell lung carcinoma; PD-L1, programmed death-ligand 1; RCC, renal cell carcinoma; SAR, synthetic agonist receptor; TGF-β, transforming growth factor-beta; TIL, tumor-infiltrating lymphocyte; TRUCKS, T cells redirected for antigen-unrestricted cytokine-initiated killing.

NKG2A, a receptor for HLA-E that suppresses NK cell function, is an attractive target for immunotherapy. *Stephanie Cornen* combined NKG2A blockade with cetuximab to target microsatellite stable colon cancer and head and neck squamous cell carcinoma.

Finally, glycosylation is shaping the interactions of cells with their microenvironment. Siglec-9 is a lectin that is upregulated in different tumor entities, which affect macrophage polarization. *Heinz Läubli* showed that tumor-specific antibodies coupled to sialidases are effective at delaying tumor growth.

COMBINATION THERAPY

Sjoerd van der Burg proposed to combine checkpoint inhibition with vaccines directed against human papillomavirus in oropharyngeal cancers. Moreover, the combination of carboplatin and paclitaxel depleted myeloid cells, which effectively induced strong and sustained T cell responses.

Samir Khleif highlighted that the combination of OX40 agonists and programmed death-ligand 1 (PD-L1) antibody therapy mutually inhibited each other. However, MEK inhibition decreases T cell exhaustion, which can potentially be used to enhance the therapeutic efficacy of OX40 agonists.

Efficacy of IL-18 therapy is hampered by IL18-BP, a soluble decoy receptor. *Aaron Ring* engineered a decoy-resistant interleukin 18 (IL-18) variant that showed efficacy as a single agent and in combination with anti-PD1 antibodies in several tumor models eliciting memory like $TCF1^+$ $CD8^+$ T cells.

IL-18 is also induced by PEGylated IL-10 (Peglio-decakin), which has been shown to enhance immune activation when combined with anti-PD-L1 therapy. *Aung Naing* presented data from a phase I trial supporting the observed effect, but side effects raise safety concerns.

Alan Melcher demonstrated that systemic administration of oncolytic reovirus induces immunogenic tumor cell death. It avoids neutralizing antibodies utilizing protective

cell carriage by monocytes, enhances their APC function, and improves the efficacy of checkpoint inhibitor blockade.

Alfred Budillon presented early phase clinical trials suggesting that epigenetic modifiers can potentiate the response to checkpoint inhibitors. Histone-deacetylase inhibitor therapy appears to be associated with an increase in immunogenic cell death, a decrease in Tregs, and downregulation of c-myc.

PRECLINICAL MODELS

Krijn Dijkstra cocultured peripheral-blood-derived T cells with patient-derived organoids to enrich tumor-reactive T cells and analyze tumor-specific T cell responses to epithelial cancers. Such T cells showed no cross-reactivity with healthy tissue organoids as assessed by CD137 expression.

Using single-cell RNA sequencing, *Bernard Thienpont* presented the transcriptome clustering of cells that shape the microenvironment of NSCLC. He identified stromal cells as the major contributor that are further divided into 52 clusters. The comprehensive data array is also available for endothelial, epithelial, and immune cells in online (gbiomed.kuleuven.be/scRNAseq-NSCLC).

Angela Krackhardt used mass spectrometry to analyze the immunopeptidome from melanoma patients and identify neoepitopes. She showed that zirconium-89 labeled neoantigen-specific TCR transgenic T cells could be tracked by PET imaging in mice and humans.

Precision medicine meets immunotherapy

Jeffrey Weber has identified C-reactive protein (CRP) and IL-6 as negative prognostic factors shared among different malignancies. CRP has been shown to suppress T cell activation.

Francois-Clément Bidard proposed to assess tumor mutational burden analyzing ctDNA in plasma as compared with tissue biopsies with higher sensitivity and lower failure rate.

Han Si analyzed ctDNA in metastatic NSCLC patients treated with anti-PD-L1 and anti-CTLA4 therapies. He used the Guardant Health OMNI platform, a highly sensitive 500-gene sequencing test, to stratify patients according to their TMB score to predict checkpoint inhibition outcome.

High T-cell infiltration is a favorable prognostic factor in breast cancers, including triple-negative breast cancer (TNBC). *Barbara Seliger* combined PD-L1-blockade with chemotherapy, which promoted immune infiltration into TNBC.

Immune checkpoint inhibitors can induce life-threatening toxicity due to myocarditis. *Lei Zheng* used animal models to study and predict dilated cardiomyopathy due to PD-1, PD-L1/PD-L2 deletion, or anti-PD-L1 antibody treatment.

Jerome Galon utilized high-throughput methods to discover critical parameters of the immune response that together compose the immune contexture of tumors: nature, functional orientation, density, and localization of immune cell populations, which are combined as Immunoscore. It was used to identify CRC patients with a high risk of recurrence.

Alessandra Nardin performed analysis of PBMCs from patients treated with atezolizumab (PD-L1-blockade) in the POPLAR trial and revealed that the majority of unique neoantigen T cells were present in the patients that responded to treatment. Hence, tumor-specific T cells could be used as a prognostic marker of therapy outcome.

CELL THERAPY

Lisa Butterfield presented the current advancements in the development of next-generation cell therapies, including affinity-enhanced T cells (NY-ESO-1^{c259} TCR in metastatic synovial sarcoma, H3.3K27M-specific TCR in diffuse midline gliomas), combinatorial antigen recognition CAR T cells, dendritic cell-based personalized multipeptide neoepitope vaccines.

Hinrich Abken presented T cells redirected for antigen-unrestricted cytokine-initiated killing that secret CAR-inducible IL-12 or IL-18 and target CEA antigen in pancreatic cancer. They indirectly promote the killing of CEA$^-$ cancer cells. CAR T cells with the inducible secretion of IL-7 and an artificial IL-7R/IL-2Rβ can be rendered resistant to TGF-β-mediated immunosuppression.

Sebastian Kobold presented T cells bearing synthetic agonist receptor (SAR) as a new modular cellular therapy platform to overcome the issues of antigen restriction. Cross-linking bispecific antibody conditionally activates SAR T cells in the presence of tumor-specific antigens, which enables a large variety of antigens to be targeted by a single genetically modified T cell.

Ulrike Koehl gave insights into the current developments of NK cell-based therapies. Currently, multiple trials employ NK donor lymphocyte infusion (NK-DLI), autologous and allogeneic CAR NK cells (anti-CD19 and CD123 against leukemic cells), redirected "CAR" NK-92 cell line and additional IL-2 stimulation.

ANTI-CANCER VACCINES

Cornelis Melief proposed to use synthetic long peptides that stimulate CD4$^+$ and CD8$^+$ positive T cells to target human papilloma virus (HPV)-associated cancers and particularly in head and neck cancers, in combination with nivolumab and ipilimumab.

Ursula Wiedermann-Schmidt demonstrated that Her-2/neu specific mimotopes are efficient and safe for vaccination against breast cancer.

David Reardon presented results of a phase I study of a personalized neoantigen cancer vaccine for glioblastoma that is designed to overcome the effects of tumor evolution. However, this concept could still not overcome the immunosuppression generated by the tumor.

SUMMARY

While combinatorial treatments currently lead the pace of clinical development, novel strategies are still emerging.

Along with a growing understanding of the complexity of cancer and the immune system, we are looking forward to the new approaches in the field. The upcoming ITOC7 conference to be held in Munich from 2 April to 4 April 2020.

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