Meeting Report

Cancer Immunology Research

Translating Science into Survival: Report on the Third International Cancer Immunotherapy Conference

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Abstract

On September 6 to 9, 2017, in Mainz, Germany, the Third International Cancer Immunotherapy Conference was hosted jointly by the Cancer Research Institute, the Association for Cancer Immunotherapy, the European Academy of Tumor Immunology, and the American Association for Cancer Research. For the third straight year, more than 1,400 people attended the four-day event, which covered the latest advances in cancer immunology and immunotherapy. This report provides an overview of the main topics discussed. *Cancer Immunol Res; 6(1); 10–13. ©2017 AACR.*

Introduction

Held in Europe for the first time, the Third International Cancer Immunotherapy Conference (CICON) immersed experts from academic, clinical, pharmaceutical, and regulatory backgrounds in the latest immunology and immunotherapy insights through 11 different sessions comprising 57 oral presentations and 500 posters. The specialized sessions had a clinically relevant focus that included neoantigens, biomarkers, adoptive cell therapies, combination strategies, microbiota, and oncolytic viruses, among others. This year's meeting endeavored to highlight approaches that have successfully "translated science into survival."

Neoantigens in Cancer Immunotherapy

Although genetic mutations fuel cancer, some of the mutated neoantigens that arise also offer valuable targets for personalized and often patient-specific immunotherapy approaches. Ugur Sahin (BioNTech) and Catherine Wu (Harvard Medical School and Dana-Farber Cancer Institute, Boston, MA) highlighted the therapeutic benefits of targeting these neoantigens with RNA-based (NCT02035956) and synthetic long peptide-based (NCT01970358) polytopic vaccines, respectively. Already, these approaches have produced complete responses (CR) in melanoma patients, both alone and in combination with PD-1 blockade. Meanwhile, sorting tumor-infiltrating lymphocytes (TILs) and enriching for those reactive against tumor-specific neoantigens enabled Stephen Schoenberger (University of California, San Diego, San Diego, CA) to improve the effectiveness of adoptive T-cell therapy in several preclinical models.

According to Ton Schumacher (Netherlands Cancer Institute, Amsterdam, the Netherlands), unbiased analysis of patients' intratumoral T-cell receptor (TCR) repertoires helps ensure that no tumor-reactive autologous T-cell clones get overlooked due to "exhaustion," although he also found that most exhausted $CD8^+$ TILs lacked tumor reactivity, which "may cap the value of efforts to revert intratumoral T-cell exhaustion." Using this analysis, Schumacher identified two correlations in patients, between the quantity of neoantigen-associated RNA and likelihood of immunogenicity, and between predicted neoepitope-binding affinity and the magnitude of neoantigen-specific T-cell responses. Céline Laumont (University of Montreal, Montreal, Canada), using a targeted k-mer profiling approach that is based on repetitive motifs in DNA segments, identified five tumor-specific antigens derived from noncoding genome regions in EL4 lymphoma cells and demonstrated the preclinical efficacy of targeting them with a prophylactic dendritic cell (DC)–based vaccine, whereas Timothy Chan (Memorial Sloan Kettering Cancer Center, New York, NY) revealed that 61% (11/18) of melanoma patients with mutations in either *SERPINB3* or *SERPINB4* experienced CRs after ipilimumab. Chan also observed that tumor genome "contraction" (i.e., a net loss of mutations) was associated with significantly increased overall and progression-free survival in nivolumab-treated melanoma patients. In long-term pancreatic cancer survivors, Vinod Balachandran (Memorial Sloan Kettering Cancer Center) observed increased numbers of intratumoral cytotoxic T cells, which were characterized by increased polyclonality.

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Novel Mechanisms of Immunosuppression and Immune Evasion

During his keynote lecture, Alberto Mantovani (Istituto Humanitas, Rozzano, Italy) discussed the roles of pentraxin-3 (PTX3) and IL1R8 in immune evasion. Evidence in both mice and humans linked PTX3 deficiency to increased cancer-related inflammation, whereas IL1R8-deficient mice were protected from hepatocellular carcinoma and sarcoma metastases. Deficiency in

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either MerTK or AXL, both TAM kinases, improved activation of natural killer (NK) cells, $CD4^+$ T cells, and $CD8^+$ T cells and aided antitumor immunity according to Yumeng Mao (AstraZeneca), whereas Nicholas Restifo (NCI, Rockville, MD) used a genome-wide CRISPR/Cas9 screen to identify several novel genes, including *BBS1*, *COL17A1*, *SOX10*, and *APLNR*, that appeared to be necessary for antitumor T-cell activity in humans. Restifo observed APLNR mutations in several immunotherapy-resistant patients, and Jesse Zaretsky (University of California, Los Angeles Medical Center, Los Angeles, CA) identified loss-of-function mutations in the JAK1, JAK2, and β2-microglobulin (β2M) genes in melanoma patients who became resistant to checkpoint immunotherapy.

Predictive Tissues Biomarkers

In colorectal cancer characterized by high microsatellite instability (MSI-hi), which is typically associated with $CD8^+$ TILs, Drew Pardoll (Johns Hopkins University, Baltimore, MD) demonstrated that T-cell responses comprised a broad repertoire of TCR specificities with no single dominant clone. Although $CD8^+$ TILs have positive prognostic value in colorectal cancer, Wolf Fridman (Cordeliers Research Centre at the University of Paris – Descartes, Paris, France) observed that $CD8^+$ T-cell infiltrate, as well as high C1q expression, were independent predictors of poor prognosis in renal cell carcinoma. Checkpoint immunotherapy-resistant melanoma patients have increased neutrophil-to-lymphocyte ratios, noted Thomas Tüting (University Hospital Magdeburg, Magdeburg, Germany), who showed that neutrophils recruited to mouse melanoma tumors adopt an immunosuppressive phenotype. With prior chemotherapy, Paola Nistico (Regina Elena National Cancer Institute, Rome, Italy) showed that peptide vaccination against Melan-A and gp100 generated much higher numbers of long-lasting, polyfunctional $CD8^+$ T cells.

Novel Immunotherapy Approaches

Promising approaches against several new targets were also unveiled. Ignacio Melero (Universidad de Navarra, Pamplona, Spain) highlighted agonist antibodies against 41BB, which enhanced PD-1 blockade and adoptive T-cell therapy efficacy, whereas A001421, a CD73 inhibitor showcased by Ulrike Schindler (Arcus Biosciences), reversed AMP-mediated immunosuppression and significantly reduced melanoma tumor growth when combined with PD-1 blockade in mice. Özlem Türeci (Ci3 Cluster for Individualized Immune Intervention) highlighted the benefits of two antibodies to claudin: IMAB362 (anti-CLDN18.2) improved overall survival in $CLDN18.2^+$ gastric cancer patients (NCT01630083), and 6PHU3, a T cell–engaging bispecific antibody to both CD3 and CLDN6, demonstrated preclinical efficacy. In addition, Türeci revealed the superior pharmacokinetics of CLDN6 RiboMAB, which delivers 6PHU3-encoding mRNA, in mice, compared with delivery of recombinant 6PHU3 protein. Patrick Baeuerle (TCR^2 Therapeutics) showcased the effectiveness of TRuC T cells, which possess entire TCRs equipped with tumor antigen–binding domains (i.e., antibody fragments) via recombinant fusion, against CD19- and mesothelin-expressing mouse cancer models, whereas Nicholas Huntington (Walter and Eliza Hall Institute, Parkville, Australia) showed that the absence of CIS, a negative NK-cell regulator, enhanced NK-cell cytotoxicity and protected mice against multiple tumor types.

Adoptive Cell Therapies

Better insight into the mechanisms of cell-based immunotherapies will be crucial to improving their effectiveness. To that end, Hyam Levitsky (Juno Therapeutics) demonstrated that CAR T-cell constructs containing prostate-specific membrane antigen fragments enabled whole-body pharmacokinetic analysis in mice (via PET imaging) without sacrificing antitumor activity. Through barcoding that links specific TCR sequences to global RNA expression profiles, T-cell clonality could potentially be tracked during manufacturing and *in vivo* after treatment. Michael Jensen (University of Washington, Seattle, WA) highlighted a series of trials with defined anti-CD19 CAR T-cell products. Although 93% (40/43) of pediatric patients with acute lymphoblastic leukemia (ALL) experienced minimal residual disease–negative remission (NCT01683279), those with declining circulating CAR T cells could receive additional CAR T cells and T-cell antigen-presenting cells (CD19t T-APC) to enhance CAR T-cell persistence and reduce relapse (NCT03186118). Future trials will utilize both anti-CD22 CAR T cells (against antigen escape ALL variants; NCT03244306) and bispecific (CD19- and CD22-targeting) CAR T cells. Dirk Busch (Technical University Munich, Munich, Germany) demonstrated the effectiveness of donor-derived cytomegalovirus-specific $CD8^+$ T cells for patients with persistent post-hematopoietic stem cell transplantation (HSCT) infections and discussed promising preliminary results with prophylactic post-HSCT administration of donor-derived central memory cells (NCT02758223). In the first longitudinal microscopy study of CAR T cells (NCT02631044), Busch revealed the long-term (100+ days) persistence of CD19-targeting CAR T cells that stabilized a patient with CNS diffuse large B-cell lymphoma. Anja Feldman (Helmholtz-Zentrum Dresden-Rossendorf, Dresden, Germany) highlighted an alternative CAR T system called UniCAR, to which various modules can easily be attached to the UniCAR element, potentially allowing for simultaneous (or sequential) targeting of different antigens and improved safety. As engineered T-cell applications increase, innovative supply chain solutions will be needed to meet future manufacturing demands. According to Cedrik Britten (GlaxoSmithKline), it will be crucial to improve scalability, via disposable platforms with suspension-grown cells, for example, and to develop automated systems integrating quality control testing and point-of-care cell processing. Beyond T cells, Andrew Sikora (Baylor College of Medicine, Houston, TX) showed that human myeloid-derived suppressor cells (hMDSC) exposed to TGF-β1 became less immunosuppressive and (via SMAD2 signaling) gained FAS-dependent tumoricidal abilities.

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Combination Immunotherapy Strategies

According to Ira Mellman (Genentech), the PD-1/PD-L1 pathway may regulate T-cell activity primarily through inactivation of CD28, which the activated PD-1/Shp2 complex preferred compared with CD3ζ. Mellman also revealed that PD-L1 blockade with MEK inhibition increased $CD8^+$ T-cell

infiltration into colorectal cancer patients' tumors. Michael Curran (MD Anderson Cancer Center, Houston, TX) targeted hypoxia, which is associated with T-cell excluded, MDSC-rich, and immunotherapy-resistant tumors. Combined with both PD-1 and CTLA-4 blockade, hypoxia elimination reduced MDSCs, promoted T-cell infiltration and proliferation, and improved survival in models of pancreatic and head and neck cancer. Combinations to enhance T-cell mitochondrial activity were showcased by Partha Sarathi Chowdhury (Kyoto University, Kyoto, Japan). When individually combined with PD-1 blockade, both a radical oxygen species activator and chemical uncouplers enhanced antitumor immunity and survival in a mouse colorectal cancer model. Liang Deng (Memorial Sloan Kettering Cancer Center) showed that a heat-inactivated modified

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vaccinia virus Ankara (heat-iMVA) could, in a STING$^-$ and Batf3$^+$ DC-dependent fashion, turn "cold" tumors "hot" and, partly through the abscopal effect, sensitize preclinical melanoma and colon adenocarcinoma models to checkpoint blockade. Sjoerd van der Burg (Leiden University Medical Center, Leiden, the Netherlands) revealed that combining chemotherapy, which alone normalized CD14$^+$ myeloid cell levels in cervical cancer patients and augmented immune responses against recall antigens, with a long-peptide vaccine significantly strengthened T-cell immunity in an HPV16-specific model.

Overcoming Checkpoint Immunotherapy Resistance

Although ovarian cancer is largely resistant to checkpoint immunotherapy, George Coukos [(Ludwig Institute for Cancer Research (New York, NY) and University of Lausanne (Lausanne, Switzerland)] revealed that intranodal administration of a DC-based whole tumor vaccine enhanced the activity and frequency of preexisting neoepitope-specific T cells and generated polyfunctional, neoepitope-specific T cells *de novo* in ovarian cancer patients. Focusing on regulatory T cells (Treg), Alexander Rudensky (Memorial Sloan Kettering Cancer Center) demonstrated that impairing Treg proliferation via *CNS2* knockout reduced growth and metastasis in a mouse lung cancer model. With respect to Treg-targeting antibodies, naturally occurring FcR polymorphisms influence their activity, so Sergio Quezada (University College London Cancer Institute, London, United Kingdom) engineered a CTLA-4–targeting antibody with mutant IgG1 that more effectively depleted Tregs, and controlled cancer, in a humanized mouse model. In addition, although CD25-targeting antibodies promoted FcγRIII-dependent Treg depletion, Quezada found that FcγRIIB prevented intratumoral Treg depletion. In a preclinical melanoma model, Simon Heidegger (Technical University Munich) showed that the efficacy of CTLA-4 antibodies depended on signaling through RIG-I, a DNA/RNA–sensing receptor that promotes immunogenic, caspase-3–mediated tumor cell death, and enhances antigen cross-presentation by CD103$^+$ DCs. Therapeutically, the RIG-I agonist 3pRNA further enhanced the effectiveness of CTLA-4 blockade. Finally, Matthias Kloor (University Hospital Heidelberg, Heidelberg, Germany) pointed out that roughly 70% of MSI-hi colorectal cancer patients have mutations in genes governing antigen processing and presentation, including 30% with deactivating β2M mutations. Although these patients have a comparably positive prognosis, vaccinating against precancerous lesions in at-risk Lynch syndrome patients could potentially improve survival even further.

Other Checkpoint Inhibitory and Immunomodulatory Antibodies

Moving beyond PD-1/PD-L1 blockade, Charles Drake (Columbia University Medical Center, New York, NY) revealed that Treg-depleting antibodies against CTLA-4 synergized with other treatments to enhance survival in a preclinical prostate cancer model. Martin Glennie (University of Southampton, Southampton, United Kingdom) highlighted agonist antibodies against CD27 that, when combined with CD20-targeting antibodies, resulted in myeloid effector cell–mediated clearance of antibody-coated B cells in several difficult-to-treat models. Ana Anderson (Harvard Medical School, Boston, MA) identified genes upstream of metallothionein (MT) associated with T-cell "dysfunction," showing that after MT deletion, the relevant TIL populations were no longer dysfunctional, whereas Ofer Levy (Compugen Ltd.) identified CGEN-15032 by analyzing gene structures and found that its deletion inhibited mouse tumor growth, both alone and in combination with PD-L1 blockade.

The Impact of the Microbiota

The microbiota can also impact tumorigenesis and antitumor immunity. The microbiota of IL18R-deficient mice promotes tumor development, according to Giorgio Trinchieri (NIH, Bethesda, MD) who, through fecal metagenomic analysis, identified bacterial species associated with polyp formation as well as others associated with prevention. After first, noting that patients with advanced cancer who received antibiotics experienced decreased survival after PD-1/PD-L1 blockade, Laurence Zitvogel (Gustave Roussy Cancer Institute, Villejuif, France) showed that intestinal fecal transplants from "responder" patients synergized with PD-1 blockade and shrunk tumors in mice. Furthermore, she identified two bacterial species, *A. muciniphila* and *E. hirae*, that activated CCR9$^+$CXCR3$^+$CD4$^+$ mesenteric T cells and rescued mice from antibiotic-induced dysbiosis while restoring the efficacy of PD-1/PD-L1 blockade. In an orthotopic xenograft model, Eleonora Cremonesi (University of Basel, Basel, Switzerland) confirmed an association between infiltration of beneficial T-cell populations and expression of the CCL5, CCL17, CCL22, CXCL9, CXCL10, and CXCL12 chemokines by tumor cells exposed to gut bacteria–derived stimuli.

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Targeting the Tumor Microenvironment

In the annual William B. Coley lecture, this year's award recipient, Thomas Gajewski (University of Chicago, Chicago, IL), demonstrated the effectiveness of anti-LAG3 and anti-41BB antibodies against established melanoma tumors in mice, and that

type I IFN-activating STING agonists, by enhancing Batf3$^+$ DC-mediated cross-priming of CD8$^+$ T cells, led to profound therapeutic effects even in noninflamed, β-catenin–expressing tumors associated with defective CD8$^+$ T-cell priming and recruitment. Dmitry Gabrilovich (Wistar Institute, Philadelphia, PA) revealed an inverse correlation between CSF1 concentrations and intratumoral infiltration of polymorphonuclear (PMN)-MDSCs in patients and then demonstrated that CSF-1R inhibition proportionally increased tumor (PMN)-MDSCs and CXCL1 expression in cancer-associated fibroblasts (CAF). Roberta Melchionna (Regina Elena National Cancer Institute) revealed the importance of the hMENAΔv6 isoform in the function and tumor-mediated activation of CAFs. While Serge Fuchs (University of Pennsylvania, Philadelphia, PA) observed IFNAR1 downregulation, and a corresponding decrease in the viability and efficacy of adoptively transferred T cells, in both human and mouse colorectal cancer, genetic stabilization improved immunotherapy's efficacy and pharmacologic stabilization (via PDK2/p38 inhibitors) enhanced tumor growth control. Yousef Zakharia (University of Iowa, Iowa, IA) combined indoximod, an inhibitor of the indoleamine 2,3-dioxygenase pathway, and PD-1 blockade, which resulted in an 80% disease control rate (and 20% CR rate) in patients with metastatic melanoma without additional toxicity compared with PD-1 blockade alone (NCT02073123). In pulmonary osteosarcoma, Alex Huang (Case Western Reserve University School of Medicine, Cleveland, OH) targeted the VCAM-1/VLA4 signaling axis that promotes the M2-like macrophage phenotype. Depleting these M2 macrophages reduced pulmonary osteosarcoma incidence in mice, whereas disruption via anti-VCAM1 peptide or antibodies against the α4β1/7 integrin ameliorated established pulmonary osteosarcoma.

Oncolytic Viruses

According to John Bell (Ottawa Hospital Research Institute, Ottawa, Canada), the Maraba MG1 oncolytic virus extended survival in several preclinical models, whereas a MAGE-A3–expressing Maraba MG1 virus (MG1-MAGEA3) remodeled the microenvironment of MAGE-A3$^+$ solid tumors (NCT02285816). When combined with CTLA-4 blockade, the herpes-based Talimogene laherparepvec (T-Vec) clinically benefitted melanoma patients (NCT01740297) and significantly improved the contralateral tumor rejection rate in preclinical lymphoma and colorectal cancer models, according to Pedro Beltran (Amgen), whereas the combination of T-Vec and pembrolizumab was also effective in advanced melanoma patients (NCT02263508). Stephen Russell (Mayo Clinic) highlighted vesicular stomatitis virus (VSV)–based oncolytic platforms. VSV-IFNβ-NIS has already produced clinical responses in hepatocellular carcinoma patients and is also being evaluated in leukemia, lymphoma, and myeloma (NCT03017820) and endometrial cancer (NCT03120624), while the measles-based MV-NIS platform, adapted for CD46-targeted fusion, has led to one CR in multiple myeloma (NCT00450814) and increased survival in ovarian cancer patients who received MV-NIS–infected mesenchymal stem cells. Tala Shekarian (Leon Berard Cancer Research Center, Lyon, France) revealed that the oncolytic Rotavirus vaccine, in combination with CTLA-4 blockade, produced complete tumor regression as well as immune memory in mice with either neuroblastoma or lymphoma.

Conclusion

The third CICON showcased the latest insights in cancer immunology and also highlighted how these advances are being translated into the clinic, where they can provide meaningful, even life-saving benefits for patients. The fourth CICON will be held on September 30–October 3, 2018, in New York City.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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