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

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ABSTRACT

From September 25 to 28, 2019, in Paris, France, the Fifth 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. This year, roughly 1,300 people attended the 4-day event, which covered the latest advances in cancer immunology and immunotherapy.

Introduction

The Fifth Cancer Immunotherapy Conference (CICON) immersed experts from diverse backgrounds in the latest immunology and immunotherapy findings through more than 50 oral presentations and 450 posters that covered T cells and the tumor microenvironment (TME), vaccines and neoantigens, metabolism and the microbiome, and new targets and technologies, among other topics. Overall, this year's meeting endeavored to highlight approaches that have the potential to "translate science into survival."

Keynote and William B. Coley Lectures

In the keynote lecture, Ton Schumacher (Netherlands Cancer Institute, Amsterdam, the Netherlands) showed that early immune responses in tumors, including T-cell infiltration and production of CXCL5, CXCL10, and CXCL13, can predict clinical responses in immunotherapy-treated patients. Schumacher also identified "quiescent" tumors that, even with T-cell infiltration, do not produce these chemokines and do not respond to PD-1 blockade. At least some of these immunotherapy-resistant tumors were characterized by dysfunctional pools of "stem-like" (TCF-1^{+}) T cells.

In the William B. Coley lecture, Elizabeth Jaffee (Johns Hopkins University, Baltimore, MD) noted how checkpoint immunotherapy has transformed the treatment landscape before highlighting how cutting-edge strategies like neoantigen vaccines and cellular immunotherapies represent the field's potentially bright future. To get there, Jaffee emphasized the need for more clinically valuable biomarkers and a deeper understanding of immunotherapy resistance mechanisms.

Jill O'Donnell-Tormey and Guido Kroemer with Elizbeth Jaffee (center), winner of the William B. Coley Award, at CICON 2019.

Cancer Prevention and Lifestyle Factors in Oncoimmunology

Olivera J. Finn (University of Pittsburgh, Pittsburgh, PA) proposed harnessing shared nonmutated neoantigens, showing that a MUC1-targeting vaccine was safe and effective in patients with colorectal cancer and showcasing the potential of such vaccines in the prophylactic setting. Guido Kroemer (Centre de Recherche des Cordeliers, Paris, France) showed that caloric restriction mimetics (CRM), similar to fasting, improved chemotherapy's effectiveness through the induction of protective autophagy and revealed that a tri-therapy combining a CRM with chemotherapy and PD-1 blockade demonstrated curative benefits. Pavel Hanc (Harvard Medical School, Boston, MA) demonstrated that nociceptors increase cytokine production by dendritic cells (DC), linking pain-sensitive neurons with DC-mediated immunity.

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Mental stress can also impact anticancer immunity, according to Yuting Ma (Suzhou Institute of Systems Medicine, Suzhou, China), whose stress-inducing social defeat model compromised the efficacy of PD-1 blockade and vaccination via the stress glucocorticoid TSC22D3.

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Blocking the glucocorticoid receptor reversed the negative impact of stress or glucocorticoids.

Combination Therapies with Immune Checkpoint Blockers

Alexander Eggermont (Gustave Roussy Cancer Center, Paris, France) highlighted how combinations involving PD-1 blockade have produced the highest success rates in melanoma. Arnab Ghosh (Memorial Sloan Kettering Cancer Center, New York, NY) demonstrated that increasing tumor p53 activity, alone or in combination with checkpoint blockade, delayed tumor growth and improved survival in mice. Cornelis "Kees" Melief (Leiden University Medical Center, Leiden, the Netherlands and ISA Pharmaceuticals BV, Leiden, the Netherlands) discussed a synthetic long peptide vaccine approach that doubled the response rate in patients with incurable HPV16$^+$ oropharyngeal cancer when combined with PD-1 blockade. Combined with chemotherapy, this vaccine induced HPV16-specific T-cell responses in patients with HPV16$^+$ metastatic cervical cancer.

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Eric Vivier (Innate Pharma, Marseille, France) introduced an NKG2A-blocking antibody that synergized with PD-L1 blockade, potentiated natural killer cell–mediated antibody-dependent cellular cytotoxicity and showed promising overall survival in combination with EGFR inhibition in patients with squamous cell carcinoma of the head and neck.

T-cell Exhaustion: Resistance Mechanisms

W. Nicholas Haining (Merck, Boston, MA) identified PTPN2 as an important factor in exhaustion, and showed that its deletion increased the cancer-killing T-cell pool in mice and improved the efficacy of adoptive cell therapy. Another exhaustion-related factor is TOX, according to Dietmar Zehn (Technical University of Munich, Freising, Germany), who showed that the lack of TOX signaling reduced the functionality of effector T cells and decreased the size and fitness of the progenitor T-cell pool. In contrast, Ludovic Martinet (INSERM, Marseilles, France) showed that CD226 signaling appeared to be necessary for optimal T-cell activity, as its absence dampened T-cell receptor (TCR) signaling sensitivity and limited the efficacy of checkpoint blockade. Forced expression of CD226, meanwhile, restored the activity of cancer-killing T cells. David Brooks (Princess Margaret Cancer Centre, Toronto, Canada) revealed that naïve T cells strongly primed in the midst of infection gave rise to memory T cells and, subsequently, effector T cells that were less exhausted and more

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responsive to PD-1 blockade, suggesting that checkpoint immunotherapy acts predominantly on "already cycling" T cells as opposed to restoring the activity of dysfunctional ones. Turning to bispecific antibodies, Dimitris Skokos (Regeneron, New York, NY) highlighted a combination of potentially synergistic CD3xMUC16 and CD28xMUC16 agents that provide two signals for T-cell activation and bind to different regions of the MUC16 protein to prevent competition.

Immunotherapies, Non-Cell–Based

Ira Mellman (Genentech, San Francisco, CA) questioned whether PD-1/PD-L1 blockade reverses T-cell exhaustion and discussed a model of T-cell activation in which checkpoint blockade's efficacy relies on the CD28/B7 pathway. Katharina Reinhard (BioNTech AG, Mainz, Germany) presented the chimeric antigen receptor (CAR) T-cell amplifying RNA vaccine strategy, showing that systemic Claudin6 (CLDN6)-targeting vaccine delivery via liposomal RNA (RNA-LPX) enhanced CAR T-cell proliferation, which in turn facilitated tumor lysis *in vivo*. Given that the identification of immune targets, assessment of the immune milieu, and granular analysis of immunotherapeutic responses often rely on high-throughput data, Nikesh Kotecha (Parker Institute for Cancer Immunotherapy, San Francisco, CA) walked the audience through a systems immunology approach that covers deep immune profiling and informatics-driven analysis with respect to immunotherapy-related effects. Sumit Subudhi (The University of Texas MD Anderson Cancer Center, Houston, TX) reported on the limits of checkpoint blockade in patients with prostate cancer, before showing that targeting both CTLA-4 and TGFβ improves outcomes in a preclinical model of bone metastatic prostate tumors. Richard Vile (Mayo Clinic, Rochester, MN) discussed a possible "trap and ambush" approach after recognizing that tumor escape from a vesicular stomatitis virus–based oncolytic virotherapy was often associated with the APOBEC3-mediated emergence of mutant CSDE1, which could have value as a vaccine or cellular immunotherapy target.

Immunotherapies, Cell-Based

Carl Figdor (Radboud University, Nijmegen, the Netherlands) discussed three strategies in the realm of DC-based immunotherapy: loaded nanoparticles to stimulate immune responses *in vivo*, synthetic DCs made of polymer filaments that could home to lymph nodes, and synthetic injectable immune niches to mimic the function of lymph nodes and tertiary lymphoid structures. According to Laurie Menger (Curie Institute, Paris, France), the SOCS1 checkpoint negatively regulates the activity of CD4$^+$ memory T cells—when SOCS1 was knocked out, it restored CD4$^+$ T memory cell proliferation and their ability to infiltrate and aid the elimination of tumors. Engineered TCR T cells targeting antigens associated with the Epstein–Barr virus were

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discussed by Helen Heslop (Baylor College of Medicine, Houston, TX), as were CD30-targeting CAR T cells. Finally, Kole Roybal [University of California, San Francisco (UCSF), San Francisco, CA] touched on his work involving synNotch receptors that can sense environmental cues and then initiate specific, and customizable, cellular programs in response to those environmental cues.

New Targets and Concepts

Ellen Puré (University of Pennsylvania, Philadelphia, PA) spoke about the "stromagenic switch" that results in fibroblast activation protein (FAP)–expressing fibroblasts that aid tumor growth and provide protection. FAP-targeting CAR T cells were able to break down the associated fibrotic barrier and enhance the infiltration and activity of T cells. Thea Tlsty (UCSF, San Francisco, CA) observed that low CD36 expression is associated with this switch, and found that macrophages without CD36 were unable to perform phagocytosis and resolve tissue debris. In contrast, Susan Kaech (Salk Institute, La Jolla, CA) found that CD36 signaling detrimentally affected T cells by altering their metabolism. CD36-deficient T cells had superior cancer-killing activity and increased metabolic function, which correlated with patient responses to PD-1 blockade. According to Amira Barkal (Stanford University, Stanford, CA), cancer cells can also block phagocytosis through the expression of CD24, which binds Siglec-10 on macrophages

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and is associated with poor prognosis. When CD24 signaling was blocked, it enhanced phagocytic activity and tumor clearance.

Tumor Antigens

Yardena Samuels (Weizmann Institute of Science, Rehovot, Israel) showed through a clever series of experiments that mutational load alone is not sufficient for stimulating immune responses. However, along with intratumoral heterogeneity, it can affect the degree of immune responses. Robert Schreiber (Washington University School of Medicine in St. Louis, St. Louis, MO) revealed that MHC class II–restricted neoantigens were required to render tumors susceptible to immunotherapy even if the tumors did not express MHC-II. Furthermore, MHC-II–restricted neoantigen-specific $CD4^+$ T cells augment tumor-specific $CD8^+$ T-cell priming and differentiation into cytotoxic T cells. Chloe Chong (Ludwig Institute for Cancer Research, Lausanne, Switzerland) developed a mass spectrometry–based antigen discovery platform to identify novel noncanonical human leukocyte antigen (HLA) peptides and possibly reveal a myriad of such unique as well as shared peptides in cancer.

> ***"Class II-restricted neoantigens were required. . .even if the tumors did not express MHC-II."***

Sjoerd van der Burg (Leiden University, Leiden, the Netherlands) characterized recurrent tumors upon a suboptimal vaccination protocol in a head and neck cancer model and found that these relapsed tumors develop secondary resistance that renders them inaccessible to tumor-reactive T cells. He also noted that such tumors are less efficient at attracting the inflammatory myeloid cells linked to the phenomenon. Lorenzo Galluzzi (Weill Cornell Medicine, New York, NY) focused on type I IFN–dependent abscopal responses observed upon radiotherapy and linked it to the ability of autophagy to limit type I IFN responses by decreasing the activity of the mitochondrial DNA–driven CGAS–STING pathway.

Vaccination Strategies

Sandra Demaria (Weill Cornell Medicine, New York, NY) also addressed the abscopal response upon radiotherapy in combination with CTLA-4 blockade, showing that radiotherapy exposes immunogenic neoantigens to the immune system and induces large dynamic changes in TCR repertoire that result in expansion of tumor-specific polyfunctional T-cell clones, in both preclinical clinical settings. Özlem Türeci (BioNTech AG, Mainz, Germany) highlighted the RNA–lipoplex platform that targets shared tumor-associated antigens in melanomas that do not possess significant numbers of mutations. This RNA–lipoplex platform may also pair well with local tumor radiotherapy, as discussed by Sebastian Kreiter (BioNTech AG, Mainz, Germany). Elizabeth Evans (Vaccinex, Bloomfield, NY) showed that a semphorin-4D–targeting antibody augmented immune cell infiltration into tumors, suppressed myeloid-derived suppressor cell activity, and could synergize with checkpoint inhibitor antibodies. By screening pediatric brain tumors, Michelle R. Brault (Fred Hutchison Cancer Research Center, Seattle, WA) identified novel immunogenic epitopes, including one derived from PDZ-binding kinase (PBK), a cancer–testis antigen, in addition to PBK-targeting T cells, suggesting it might be a good target for vaccination or cellular therapy in pediatric brain cancer. Tamara Ouspenskaia (Broad Institute, Cambridge, MA) developed a database of unannotated open reading frames (nuORF) across various tissues using ribosome profiling. She hypothesized that nuORFs could be a source for neoantigens either due to cancer-specific somatic mutations in translated nuORFs or by cancer-specific translation of unmutated nuORFs.

New Trends in Technology and Informatics

Hannah Carter (University of California, San Diego, CA) demonstrated that individual MHC allele combinations determine the oncogenic mutational landscape and that the presence of a high-affinity driver mutation correlates with benefit in checkpoint immunotherapy. E. John Wherry (University of Pennsylvania, Philadelphia, PA) discussed the reason for the limited durability of reinvigorated T-cell response and presented data on how the transcription factor TOX transcriptionally and epigenetically programs $CD8^+$ T-cell exhaustion. Michal Bassani-Sternberg (Lausanne University Hospital, Lausanne, Switzerland) discussed an approach to use HLA peptidomics for the development of personalized noncanonical HLA-based cancer immunotherapy, and Livnat Jerby (Broad Institute, Cambridge, MA) showed that the oncogene SS18-SSX can function as a negative regulator of cellular immunity in synovial sarcoma.

TME Analysis

Wolf Hervé Fridman (Centre de Recherche des Cordeliers, Paris, France) provided insight on the role of B cells in the TME, showing that they can produce tumor-specific antibodies and present tumor antigens to T cells in tertiary lymphoid structures, but can also produce complement-related antibodies that lead to tumor-promoting inflammation and angiogenesis. Nir Hacohen (Massachusetts General Hospital, Boston, MA and Broad Institute, Cambridge, MA) introduced novel methods, such as single-allele HLA peptide sequencing by mass spectrometry, for better prediction of processed and presented epitopes and added that other factors like proteasomal processing and expression of the target gene may also play a role in the

predictive power of such methods. Miriam Merad (Icahn School of Medicine at Mount Sinai, New York, NY) defined macrophages as an untapped source of therapeutic targets. Tissue-resident macrophages are involved in invasiveness during early tumor stages, suggesting that targeting them might help disrupt tumor progression. In contrast, monocyte-derived macrophages dampen immunity in established tumors, an effect that could be alleviated by reducing the number of circulating and tumor-associated monocytes. Barbara B. Maier (Icahn School of Medicine at Mount Sinai, New York, NY) focused on mature DCs enriched in regulatory molecules, which are induced by tumor antigen uptake, further triggered by IL4 signaling, and can result in suboptimal T-cell priming that allows for tumor growth.

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Immuno-oncology Cross-talk and Metabolism

Greg Delgoffe (University of Pittsburgh, Pittsburgh, PA) revealed how hypoxia affects T-cell activity within tumors. Regulatory T cells flourish in low O_2 and preferentially utilize lactate, whereas antigen-stimulated $CD8^+$ T cells exhibit mitochondrial loss and dysfunction. This is associated with resistance to PD-1 blockade, which knockout studies showed was mediated by Blimp-1–mediated repression of PGC1α. PSGL-1 also negatively influences T-cell activity, according to Jennifer Hope (Sanford Burnham Prebys Medical Discovery Institute, San Diego, CA). The absence of PSGL-1 led to more polyfunctional $CD8^+$ T cells and effector $CD4^+$ T cells and better tumor control, whereas T cells lacking PSGL-1 exhibited increased glucose metabolism and TCR sensitivity. Ursula Grohmann (University of Perugia, Perugia, Italy) spoke about targeting the signaling activity of IDO1, as opposed to its enzymatic activity, through the use of VIS-128, which improved DC stimulatory capacity. James Reading (University College London, London, United Kingdom) revealed that as the number of tumor neoantigens increases, TCR diversity increases and the TCR repertoire becomes redistributed within the tumor, leading to a loss of early differentiated and memory T-cell pools associated with exhaustion. According to Chang-Suk Chae (Weill Cornell Medicine, New York, NY), endoplasmic reticulum stress can reprogram ovarian cancer cells via the IRE1α–XBP1 pathway and inhibit DC activity while increasing their production of prostaglandin-E2. Vaccination with XBP-1–deficient DCs resulted in more tumor-infiltrating T cells, both "killer" and "helper," and improved survival in a metastatic ovarian cancer model.

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Microbiota in Oncoimmunology

Laurence Zitvogel (Gustave Roussy Cancer Center, Villejuif, France) showed that the bacterium *Enterococcus hirae* is associated with anticancer immunity and prolonged survival in response to immunogenic chemotherapies like cyclophosphamide. Furthermore, Zitvogel identified the enterophage antigen tape measure protein as a relevant factor in the efficacy of PD-1 blockade. Giorgio Trinchieri (NCI, Bethesda, MD) explained how to use fecal microbiota transplants to improve gut microbiome composition in patients with melanoma refractory to PD-1 blockade, and briefly touched on how dietary fiber intake affects ICOS expression by $CD8^+$ T cells and PD-1 blockade responses. Jennifer A. Wargo (The University of Texas MD Anderson Cancer Center, Houston, TX) showed that diet and lifestyle factors influence the gut microbiome and in turn the efficacy or toxicity of immunotherapy. In addition, Wargo reported a gut microbiome "signature" that can serve as a biomarker for response to PD-1 blockade. Duncan R. McKenzie (The Francis Crick Institute, London, United Kingdom) showed that skin immunosurveillance by intraepithelial lymphocytes (IEL) involves the interaction between IELs and Skint1 on keratinocytes via the invariant Vγ5Vδ1 TCR, which regulates their sensitivity to stimulatory signaling. Chengcheng Jin (Massachusetts Institute of Technology, Cambridge, MA) showed that increased bacterial load and reduced bacterial diversity in the lung microbiome correlates with the activation of IL17-producing tissue-resident γδ T cells, which in turn fuels the progression of lung cancer in a preclinical model.

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Conclusion

The fifth CICON showcased the latest immunotherapy advances, including strategies to improve current treatments, as well as efforts to translate basic discoveries into next-generation immune-based approaches to provide even greater benefits to patients. The sixth CICON will be held from September 14 to 17, 2020, in New York City. To learn more, go to www.cancerimmunotherapyconference.org.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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