Meeting Report

Cancer Immunology Research

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

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Abstract

On September 30 to October 3, 2018, in New York City, the Fourth International Cancer Immunotherapy Conference (CICON) was hosted jointly by the Cancer Research Institute (CRI), the Association for Cancer Immunotherapy (CIMT), the European Academy of Tumor Immunology, and the American Association for Cancer Research (AACR). For the fourth straight year, more than 1,400 people attended the 4-day event, which covered the latest advances in cancer immunology and immunotherapy. This year's meeting also coincided with the announcement that the 2018 Nobel Prize in Physiology or Medicine would be awarded to one of CICON's attendees, James P. Allison.

Introduction

The Fourth Cancer Immunotherapy Conference (CICON) immersed experts from diverse backgrounds in the latest immunology and immunotherapy insights through more than 50 oral presentations and 400 posters that covered: T cells and the tumor microenvironment (TME), vaccines, biomarkers, and the microbiome, among other topics. This year's meeting, during which attendee James P. Allison was announced as the recipient of the 2018 Nobel Prize in Physiology or Medicine, endeavored to highlight approaches that, like the one developed by Allison, have the potential to "translate science into survival."

Dr. James P. Allison receives standing ovation upon Nobel Prize announcement (photo courtesy of CRI).

Regulating T Cells and Their Response to Cancer

Rafi Ahmed (Emory University) discussed PD-1$^+$TCF-1$^+$CD8$^+$ T cells with stem cell–like properties that are critical during chronic viral infection and showed that dual PD-1– and IL2-targeting immunotherapy promotes proliferation of a distinct subset of intratumoral T cells. In checkpoint blockade–responsive lung cancer patients, Christian Ottensmeier (University of Southampton, UK) revealed a subpopulation of tissue-resident memory (TRM) T cells characterized by TIM3 and PD-1 expression and the absence of IL7R. W. Nicholas Haining (Dana-Farber Cancer Institute) demonstrated that loss of ADAR (adenosine deaminase acting on RNA) sensitized tumors to immunotherapy by inhibiting double-stranded RNA (dsRNA) sensing, and that ADAR deletion could resensitize resistant tumors to PD-1 blockade. Nicholas Restifo (National Cancer Institute) clarified how potassium ion concentration ([K^+]) helps explain a "central paradox," wherein tumor-infiltrating lymphocytes (TIL) are inherently capable of stem cell–like behavior, despite being dysfunctional. To that end, elevated [K^+] preserved the stemness of memory-like CD8$^+$ TILs and epigenetically silenced effector functions. Roberta Zappasodi (Memorial Sloan Kettering Cancer Center, MSKCC) demonstrated that GITR agonism with TRX518 preferentially targeted GITR$^+$ effector regulatory T cells (Treg), both in peripheral blood and tumors, and announced a trial (NCT02628574) combining TRX518 and PD-1 blockade in advanced solid cancers. Jake O'Donnell (QIMR Berghofer Medical Research Institute, Australia) spoke about neoadjuvant immunotherapy's ability to enhance tumor-specific CD8$^+$ T-cell

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Dr. Phil Greenberg discusses the role of T cells in leukemia remissions (photo courtesy of CRI).

function, restore memory differentiation potential, and improve long-term survival in mice.

The 2018 William B. Coley Lecture

After the opening session, Padmanee Sharma (MD Anderson), this year's winner of the William B. Coley Award for Distinguished Research in Tumor Immunology, emphasized the importance of leveraging clinical samples in order to more deeply probe immunotherapy's effects in patients. She pointed to the discovery of ICOS's importance in the context of neoadjuvant CTLA-4 blockade in localized bladder cancer, and the ability of ipilimumab to turn "cold" prostate tumors "hot" in combination with androgen-deprivation therapy. Sharma also discussed the resistance to CTLA-4 blockade associated with interferon gamma (IFNγ) pathway copy-number alterations in melanoma cells and increased EZH2 expression in $CD4^+$ T cells, which are to be targeted in a proposed trial.

Tackling the TME

Manipulating other cells in the TME can also augment antitumor immune responses. Shannon Turley (Genentech) discussed how dual TGFβ and PD-L1 blockade inflamed immune-excluded tumors by altering stromal architecture, whereas Jeffrey Hubbell (University of Chicago) showed that conjugating antibodies—against PD-1, CTLA-4, IL2, and CCL4—with a collagen-binding domain increased the effector $CD8^+$ T-cell/Treg ratio, decreased intratumoral myeloid-derived suppressor cells (MDSC) and slowed tumor growth. Miriam Merad (Icahn School of Medicine at Mount Sinai) demonstrated that tumor tissue–resident embryonic macrophages induced Tregs and promoted tumor growth and invasiveness by inducing epithelial-to-mesenchymal transition (EMT). Leonid Metelitsa (Baylor College of Medicine) constructed anti-GD2 chimeric antigen receptor (CAR) natural killer T (NKT) cells that target both $GD2^+$ neuroblastoma cells and $CD1d^+$ M2 macrophages. In mice, and one human, these CAR NKTs localized to tumors without mediating graft-versus-host disease. Dmitry Gabrilovich (The Wistar Institute) discussed two types of tumor-associated neutrophils. Polymorphonuclear MDSCs (PMN-MDSC) are found in late-stage tumors and promote growth in primary and metastatic sites. In contrast, PMN-MDSC–like cells are found in early-stage tumors, where they alter metabolism and promote metastatic niche formation via EMT. Wei-Wu Tom Chen (National Taiwan University Hospital) classified common soft-tissue sarcomas into three immune-based clusters: cluster A comprises "cold," immune-desert tumors; cluster B tumors have high endothelial cell infiltration; cluster C—which was associated with the longest overall survival—comprises "hot" tumors. In melanoma, Kevin Barry (University of California, San Francisco) showed that an abundance of intratumoral stimulatory dendritic cells (SDC) correlated with immunotherapy response and predicted patient survival. NK cells also clustered with SDCs, suggesting the NK cell–SDC axis defines an immunotherapy-responsive microenvironment.

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Keynote Lecture

Keynote speaker Ignacio Melero (Universidad de Navarra, Spain) spoke about targeting IL8, high concentrations of which negatively affect survival after immunotherapy in several cancers, and a current trial (NCT03400332) evaluating dual IL8 and PD-1 blockade for advanced cancer patients with high IL8. Melero also discussed targeting CD137, showing that CD137 agonism could reinvigorate the mitochondria of tumor-reactive T cells and durably enhance their activity.

Genetically Engineered T Cells

In diffuse large B-cell lymphoma, James Kochenderfer (National Cancer Institute) noted that equipping CD19-targeting CAR T cells with a human CD8α hinge and transmembrane domain reduced neurotoxicity and led to a 55% complete remission rate (NCT02659943). Crystal Mackall (Stanford University School of Medicine) discussed targeting the AP-1/IRF family of proteins to overcome CAR T-cell exhaustion by lowering the activation threshold, which enhanced activity against leukemia cells with low antigen density. Steven Rosenberg (National Cancer Institute) demonstrated the viability of treating solid tumors with neoantigen-targeting, TCR-transduced T cells, whereas Christine Brown (City of Hope National Medical Center) showcased CAR T cells targeting IL13Rα2 in glioblastoma (NCT02208362). Michel Sadelain (MSKCC) showed how induced pluripotent stem cells (iPSC) could provide a scalable, self-renewing source for histocompatible CAR T cells. Philip Greenberg (Fred Hutchinson Cancer Research Center and University of Washington School of Medicine) highlighted the use of TCR-transduced T cells targeting WT1 to prevent and treat acute myeloid leukemia relapse. Both Greenberg and Christopher Klebanoff (MSKCC) proposed strategies to mitigate Fas pathway–mediated T-cell death. Clare Slaney (Peter MacCallum Cancer Centre, Australia) showed that dual HER2- and gp100-targeting CAR T cells are effective preclinically against HER2-positive breast cancer when combined with a gp100-expressing vaccinia virus and are currently in clinical development.

Maintenance of Immune Balance: Effects of Targeted and Immune Therapies

To promote CAR T-cell expansion, David Porter (University of Pennsylvania) discussed a pilot trial (NCT02640209) combining CD19-targeting CAR T cells with ibrutinib for relapsed or refractory chronic lymphocytic leukemia. Given immunotherapy's effectiveness in defective mismatch-repair (dMMR) tumors, Alberto Bardelli (University of Turin, Italy) showed that silencing the *MLH1* DNA-repair gene enabled spontaneous tumor rejection and improved survival in mice, and synergized with dual checkpoint blockade. Proposing a link between cancer and autoimmunity, Antony Rosen (Johns Hopkins University School of Medicine) suggested that initial responses against tumor neoantigens might subsequently spread to wild-type antigens. In addition to unusual diagnostic clustering in people with both diseases, he referenced several patients with autoimmune antibodies against RNA polymerase III subunit A (POLR3A), as well as POLR3A genetic abnormalities. Patrick Hwu (MD Anderson) identified RNA editing–derived neoepitopes in melanoma patients and showed that T cells could recognize cancer cells expressing mutated cyclin-1, but not those expressing the wild-type form. In triple-negative breast cancer, Peter Savas (Peter MacCalum Cancer Centre, Australia) revealed a high correlation between TILs and improved overall survival, and noted that the TRM signature was even more prognostic for overall survival than CD8 alone. Arabella Young (University of California, San Francisco) highlighted a strategy to prevent PD-1 blockade–induced type-1 diabetes (T1D). Equipping mice with a specific variant of the *IDD* gene protected against T1D without sacrificing PD-1 blockade's antitumor benefits. After noting the negative influence, the TCR and PD-1/PD-L1 pathways appear to have on each other's binding and signaling activity, Michelle Krogsgaard (New York University School of Medicine) demonstrated that Shp2 inhibition uncouples that relationship and prevents PD-1–induced dampening of TCR signaling.

> "That initial responses against tumor neoantigens might subsequently spread to wild-type antigens."

Novel Vaccine Platforms and Combinations

Using high-dimensional analysis to better understand immunotherapy-induced changes, Matthew Gubin (Washington University in St. Louis) identified various myeloid cell populations within tumors that respond differently to checkpoint immunotherapy. Although an iNOS^{+} macrophage population expanded upon dual PD-1 and CTLA-4 blockade, this approach reduced CX3CR1^{+} macrophages. In melanoma, Ugur Sahin (TRON and BioNTech AG, Germany) showcased RNA-based vaccines that induced T-cell responses against at least 3 of the 10 mutations targeted in every patient, with an immunogenicity rate of 60% (NCT01684241). Nine of 9 patients remained free from metastatic recurrence at 19 to 33 months after vaccination. Catherine Wu (Dana-Farber Cancer Institute) focused on peptide-based vaccines. In addition to activity in melanoma, this vaccine approach induced infiltration of neoantigen-specific T cells in multiple glioblastoma patients. Cornelis Melief (ISA Pharmaceuticals, Netherlands) reported on targeting HPV16-related cancers with synthetic long peptides (SLP). In recurrent or metastatic cervical cancer (NCT02128126), this vaccine synergized with chemotherapy, increasing overall survival in responders, whereas in head and neck cancer (NCT03669718), the SLP vaccine combined with PD-1 blockade nearly doubled median overall survival compared with PD-1 monotherapy. Using a locally administered SLP vaccine, Robert Seder (Vaccine Research Center, National Institutes of Health) demonstrated the ability to improve a neoantigen's immunogenicity by increasing its solubility and showed that a self-assembling nanoparticle-based SLP vaccine, combined with TLR7/8 agonism, could increase the breadth and magnitude of CD8^{+} T-cell responses against a variety of murine cancer neoantigens. James Moon (University of Michigan Cancer Center) highlighted a synthetic high-density lipoprotein (sHDL) nanodisc-based vaccine system capable of improving antigen delivery, T-cell responses, and antitumor immunity in many preclinical models, both alone and in combination with checkpoint blockade. Turning to oncolytic viruses (OV), Alan Melcher (The Institute of Cancer Research, UK) intratumorally injected reovirus, which turned patients' "cold" brain tumors "hot" (NCT00528684) and, at least preclinically, enhanced checkpoint blockade. OV-infected tumor cell antigens also primed T cells against multiple tumor-associated antigens. *In vitro*, OVs also drove human monocytes toward a DC-like phenotype, linking innate and adaptive immunity.

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Mutational Analysis and Predicting Response to Immunotherapy

Tumor-infiltrating lymphocytes (TILs) offer one biomarker for predicting clinical outcomes with immunotherapy. To eliminate the impact of "exhaustion" when evaluating the reactivity of TILs, Ton Schumacher (Netherlands Cancer Institute) reconstituted the intratumoral TCR repertoire in healthy donor T cells. This unbiased analysis revealed that although the majority of TILs do not recognize autologous tumor, PD-1^{high} TILs were more likely to be tumor reactive and their presence correlated with immunotherapy's efficacy. Naiyer Rizvi (Columbia University Medical Center) revealed that high tumor mutational burden (TMB) and PD-L1 expression characterize those who benefit greatest from anti–PD-L1 monotherapy and noted that TMB estimation was both feasible and scalable, but must be refined through platform harmonization and incorporation of additional factors. Using MANAFEST (mutation-associated neoantigen functional expansion of T cells), Drew Pardoll (John Hopkins University) showed that MANA-specific T-cell responses evolve after PD-1 blockade and were even detected in low TMB cases, including a lung cancer complete responder with only 30 mutations. Focusing on pancreatic cancer, Vinod Balachandran (MSKCC) named an immune-stimulatory tumor environment, augmented T-cell activity, and a clonal intratumoral TCR repertoire as markers associated with long-term survival. In particular, the neoantigen quality determined was crucial, with T cells targeting high-quality neoantigens readily measurable in circulation up to 12 years after first detection. Benjamin Greenbaum (Icahn School of Medicine at Mount Sinai) spoke about an evolutionary framework for

understanding antigen-driven fitness that compared a neoantigen's MHC binding affinity to its wild-type counterpart in order to estimate the likelihood of neoantigen presentation and subsequent T-cell recognition. In this way, their model could predict survival in immunotherapy-treated patients.

Convergence of Technology and Cancer Immunotherapy

Through analysis of PD-1 blockade–treated melanoma patients, Nir Hacohen (Broad Institute) revealed distinct memory-like and exhausted-like states of $CD8^+$ T cells, identifying TIM3 and CD39 as markers enriched in nonresponders, which could be blocked to reduce melanoma growth in mice. In contrast, intratumoral memory-like $CD8^+$ T cells expressing TCF7 (also known as T-cell factor 1) could predict PD-1 blockade responsiveness and good prognosis. Exploiting the insertion ability of amphiphilic ligands into the membranes of antigen-presenting cells, Darrell Irvine (Massachusetts Institute of Technology) designed lymph node–targeting vaccines to boost CAR T-cell activity against targets of interest in mice, including an EGFR-associated neoantigen in glioblastoma. Dan Dongeun Huh (University of Pennsylvania) showcased his cutting-edge organ-on-a-chip technology that he has used to mimic the impact of smoking on lungs and of blinking on eyes and unveiled plans for a tumor-on-a-chip device to probe tumor immunology mechanisms and evaluate the safety and efficacy of various immunotherapies.

"Plans for a tumor-on-a-chip device to probe tumor immunology mechanisms and evaluate the safety and efficacy of various immunotherapies."

Microbiome and Metabolism

The gut microbiome also affects the immune system and immunotherapy's effectiveness. Hassane Zarour (University of Pittsburgh School of Medicine) noted bacterial species associated with PD-1 blockade responses in metastatic melanoma and highlighted a trial (NCT03341143) in which PD-1 blockade–resistant patients are being re-treated with PD-1 blockade and fecal microbiota transplants (FMT). Jennifer Wargo (MD Anderson), who also identified predictive gut microbiome signatures, found that responders possessed more diverse gut microbiomes and identified bacteria that could affect immunotherapy-induced toxicity. Healthy donor FMT resolved steroid-resistant colitis in one patient. Wargo also discussed a trial treating immunotherapy-resistant melanoma patients with FMTs from PD-1 blockade responders, which revealed an association between high fiber diets and increased microbiome diversity, whereas antibiotics or probiotics were linked with decreased diversity.

Moving to metabolism, Yasmine Belkaid (National Institute of Allergy and Infectious Diseases) discussed how immunologic memory is preserved during nutritional stress. Under 30% caloric restriction, memory T cells accumulated in mouse bone marrow, whereas spleen, blood, and lymph node T cells were reduced. If caloric restriction occurred after bacteria exposure, caloric restoration enabled stronger secondary immune responses. In glioma, Mirco Friedrich (German Cancer Research Center, DFKZ) showed that mutated isocitrate dehydrogenase (IDH) can promote immunosuppression through overproduction of R-2-hydroxyglutarate (R-2HG), which suppresses TCR signaling through the aryl hydrocarbon receptor (AhR). AhR blockade could improve PD-L1 blockade's efficacy, but only in gliomas possessing mutated IDH. Lastly, Michael Constantinides (National Institute of Allergy and Infectious Diseases) sought to determine the role that bacteria play in the development of mucosal-associated invariant T (MAIT) cells, which are enriched in barrier tissues like the skin, and found that mice lacking commensal bacteria had significantly lower levels of MAIT cells. The frequency of MAIT cells in adult mice was influenced by early-life exposure to certain bacteria, whereas topical application of commensal *Staphylococcus epidermis* could stimulate MAIT-cell proliferation, which also required antigen presentation via MR1.

"An association between high fiber diets and increased microbiome diversity, whereas antibiotics or probiotics were linked with decreased diversity."

Conclusion

Highlighted by James P. Allison's Nobel Prize announcement, the fourth CICON showcased the latest immunotherapy advances, including strategies to improve current immunotherapies as well as efforts to translate basic discoveries into the next-generation immune-based approaches to provide even greater benefits to patients. The fifth CICON will be held on September 25–28, 2019, in Paris, France.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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