Cancer Immunology Research

The Sixth Annual AACR–CRI Lloyd J. Old Award in Cancer Immunology

Dr. Antoni Ribas

Established in 2013 in honor of Dr. Lloyd J. Old—the "father of modern tumor immunology" who served as the Cancer Research Institute's founding scientific and medical director—the American Association for Cancer Research and Cancer Research Institute (AACR–CRI) Lloyd J. Old Award in Cancer Immunology recognizes scientists whose work has significantly advanced the field of cancer immunology. On Tuesday April 17, 2018, at the annual AACR meeting in Chicago, the sixth annual Lloyd J. Old Award was presented to Dr. Antoni Ribas.

Dr. Ribas is currently the director of the tumor immunology program and a professor of medicine, surgery, and molecular and medical pharmacology at the Jonsson Comprehensive Cancer Center of the University of California, Los Angeles (UCLA). He was also a coleader of the SU2C-CRI Cancer Immunology Dream Team, the director of the Parker Institute for Cancer Immunotherapy Center at UCLA, and a member of the CRI Clinical Accelerator Clinical and Scientific Advisory Committee.

With his sights set on becoming an engineer, Ribas initially had no intention of practicing medicine—like his father, grandfather, and great-grandfather had—let alone curing cancer. Nonetheless, he has excelled in this endeavor, and the contributions he has made as both a physician and a researcher have improved our ability to treat cancer by utilizing patients' immune systems. He has even been able to incorporate a little engineering into his work along the way.

As a physician, Ribas has led several pivotal immunotherapy clinical trials involving checkpoint inhibitors. In a phase I/II trial, his team showed that the CTLA-4-targeting tremelimumab could provide durable benefit in patients with metastatic melanoma, and later demonstrated that the treatment increased the number of tumor-infiltrating T cells and broadened the diversity of patients' peripheral T-cell pools even in patients who did not experience a clinical response in terms of tumor regression.

Ribas was also instrumental in the early clinical development of pembrolizumab, which was the first anti–PD-1 checkpoint immunotherapy approved by the FDA and became the only cancer treatment of any type approved in a tissue-agnostic fashion when it was made available for patients with tumors characterized by high microsatellite instability (MSI-hi).

In addition to spearheading the clinical adoption of immune checkpoint blockade, his complementary research has shed light on the tumor-immune interactions responsible for the effectiveness of—and in some cases, resistance to—immunotherapy. His team found that the tumors of advanced melanoma patients who responded to PD-1 blockade were characterized, prior to treatment, by increased expression of CD8, PD-1, and PD-L1, by cells both within tumors and at the invasive margin, as well as a more clonal TCR repertoire, compared with nonresponding patients. Posttreatment, increased $CD8^+$ T-cell proliferation was also associated with therapeutic responses and correlated with the extent of tumor regression as determined by radiographic assessment. This led Ribas and his colleagues to the insight that PD-1 blockade–induced tumor regression requires preexisting "killer" T-cell activity that is negatively regulated by the PD-1/PD-L1 axis. He and his team then developed and validated a predictive model that could identify the patients most likely to benefit from this form of immunotherapy.

Later, the recognition that the majority of patients still do not experience long-term responses to PD-1 blockade spurred work by Ribas and others that deciphered mechanisms by which tumor cells can evade the immune system and become resistant to immunotherapy. First, in patients who initially responded to treatment but later relapsed, acquired resistance was linked with the emergence of loss-of-function mutations in pathways governing interferon-γ (IFNγ) activity and antigen presentation. Mutations in both the JAK1 and JAK2 pathways made cancer cells insensitive to IFNγ's antiproliferative effects as well as its impact on upregulating MHC class I expression, whereas mutations in β_2-microglobulin (β_2M) disrupted proper antigen presentation and interfered with the ability of T cells to recognize and target cancer cells. Subsequently, his group found that JAK1/2 loss-of-function mutations can also contribute to primary resistance in melanoma patients treated with anti-PD-1 immunotherapy.

With these findings, Ribas and colleagues helped define the factors that determine the success or failure of checkpoint blockade. In addition to enhancing our understanding of the dynamics at play in tumor microenvironments, these studies provided a foundation for the development of improved immunotherapy strategies.

One such strategy Ribas and his team have explored involves combining checkpoint immunotherapy with other immune-stimulating treatments. Most notably, a phase Ib trial evaluated the combination of pembrolizumab and talimogene

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laherparepvec (T-Vec), an oncolytic virus that is injected directly into melanoma tumors. Whereas a patient's odds of responding to pembrolizumab alone depended on baseline immune activity in and around the tumor, the combination treatment proved effective even in patients who lacked preexisting "killer" T-cell responses as a result of T-Vec's ability to remodel the tumor microenvironment into an inflamed state more conducive to PD-1 blockade–induced effector activity. Ultimately, he and his collaborators found that patient responses to the combination were still strongly associated with increases in $CD8^+$ T cells, PD-L1 expression, and IFNγ expression after oncolytic virus treatment.

Outside the clinic, the Ribas laboratory has also performed important studies with combinations involving checkpoint immunotherapy and adoptive T-cell immunotherapy. In 2012, he highlighted the synergistic effects of the BRAF inhibitor vemurafenib and genetically modified, tumor-targeting T cells in a $BRAF^{V600E}$-driven mouse model of melanoma. In 2015, using the same melanoma model, he showed that targeting the BRAF (via dabrafenib) and MEK pathways (via trametinib) improved the antitumor activity of both adoptive T-cell immunotherapy and PD-1 blockade.

Through other work in the $BRAF^{V600E}$ mouse melanoma model, Ribas has addressed the impact of immunosuppressive myeloid cells that are recruited to tumors through the CSF-1 pathway. Here, his team showed that adoptive T-cell immunotherapy became more effective when combined with PLX3397, a small molecule inhibitor of the CSF-1 receptor. Responses were associated with increases in tumor-infiltrating T cells, decreased accumulation of these tumor-protecting myeloid cells, and a shift from low MHC class II expression to high MHC class II expression in macrophages.

More recently, as discussed in his award acceptance speech at the AACR conference, Ribas developed a method to use peripheral blood stem cells to create T cells that are capable of targeting the NY-ESO-1 antigen commonly expressed by tumor cells. Importantly, this approach can modify these immune cell genomes without the use of a viral vector and has the potential to significantly speed up clinical translation of engineered T-cell immunotherapies, beginning with its evaluation in an upcoming phase I trial in combination with an IL2-activating immunotherapy for patients with advanced cancer.

Although his contributions thus far have made Ribas more than deserving of this career achievement award, his work is far from finished and he remains committed to improving immunotherapy's benefits through novel applications of immune-based strategies in the clinic as well as research that seeks to deepen our understanding of how the immune system interacts with cancer, with the aim of discovering new approaches that enable us to more consistently shift that tumor–immune balance in a direction that promotes patient survival.

Prior to receiving the Lloyd J. Old Award, Ribas received an AACR Richard and Hinda Rosenthal Award, a National Cancer Institute Outstanding Investigator Award, among others. He has also been elected to the American Society of Clinical Investigation.

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