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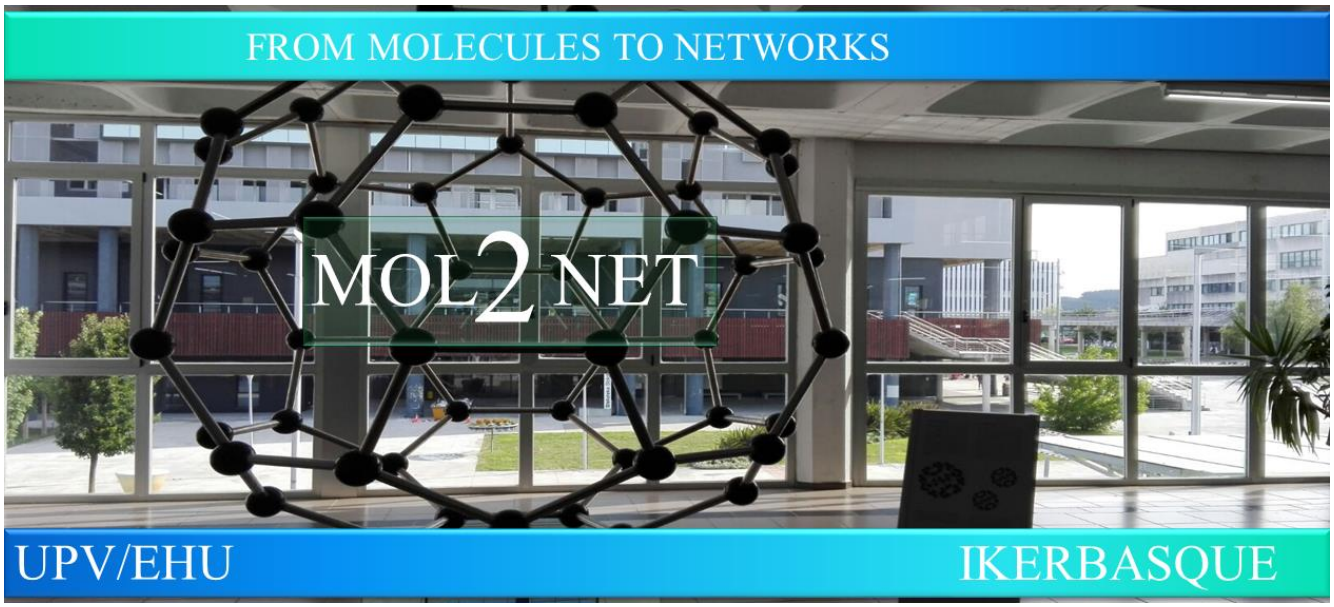
MOL2NET'22, Conference on Molecular, Biomedical & Computational Sciences and Engineering, 8th ed.



PD-L1/PD-1 Blockade Immunotherapy: Mechanism of response and resistance

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Abstract.

Cancer immunotherapies targeting the PD-L1/PD-1 axis are revolutionizing cancer treatment and transforming the practice of medical oncology. Despite the recent successes, most patients are refractory and present intrinsic or acquired resistance. This is one of the most significant challenges in oncology. However, the mechanisms leading to resistance are still poorly understood. Here, we discuss some of the major molecular mechanisms of resistance to PD-L1/PD-1 blockade. We also argue whether tumor intrinsic or extrinsic factors constitute main determinants of response and resistance. Primary and acquired resistances are important barriers in terms of benefit to the patient. Among others, tumor-intrinsic factors include poor tumor antigenicity, DNA repair mutational load, alterations in the regulation of oncogenic pathways, defects in IFN signal transduction and PD-L1 expression. On the other hand, tumor-extrinsic factors include T cell exhaustion, expression of additional immune checkpoint molecules, differentiation and expansion of immunosuppressive cell populations, and release of immunosuppressive cytokines and metabolites. The relative contribution of tumor cell intrinsic and extrinsic factors to primary, adaptive, and acquired resistance is yet unclear. Our group recently found that NSCLC patients that failed to respond to PD-1/PD-L1 inhibitors had systemic CD4 dysfunctionality, characterized by increased PD-1/LAG-3 co-expression in T cells. These results highlighted dysfunctional CD4 T cells as main contributors to treatment failure. A deeper understanding of the basic mechanisms underlying resistance will provide insight for further development of better therapeutic strategies by overcoming treatment failure. The development of new approaches to improve CD4 responses before immunotherapy could be a solution to overcome resistance (Zuazo et al, EMBO Mol Med 2019; Zuazo et al, EMBO Mol Med 2020; Chocarro de Erauso L et al, Front. Pharmacol. 2020; Zuazo et al, Font Immunol 2020; Bocanegra et al, Int J Mol Sci 2020; Hernández et al, Int J Mol Sci 2020; Arasanz et al, Cancers 2020; Chocarro et al, Int J Mol Sci 2021)

Keywords: *PD-1, PD-L1, immunotherapy, treatment response, resistance mechanisms*

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Funding

The OncoImmunology group is funded by the Spanish Association against Cancer (AECC, PROYE16001ESCO); Instituto de Salud Carlos III (ISCIII)-FEDER project grants (FIS PI17/02119, FIS PI20/00010, COV20/00000, and TRANSPOCART ICI19/00069); a Biomedicine Project grant from the Department of Health of the Government of Navarre (BMED 050-2019); Strategic projects from the Department of Industry, Government of Navarre (AGATA, Ref 0011-1411-2020-000013; LINTERNA, Ref. 0011-1411-2020-000033; DESCARTHES, 0011-1411-2019-000058); European Project Horizon 2020 Improved Vaccination for Older Adults (ISOLDA; ID: 848166); Crescendo Biologics Ltd. supported the OncoImmunology group for the development and testing of PD-1 and LAG-3 bispecifics.