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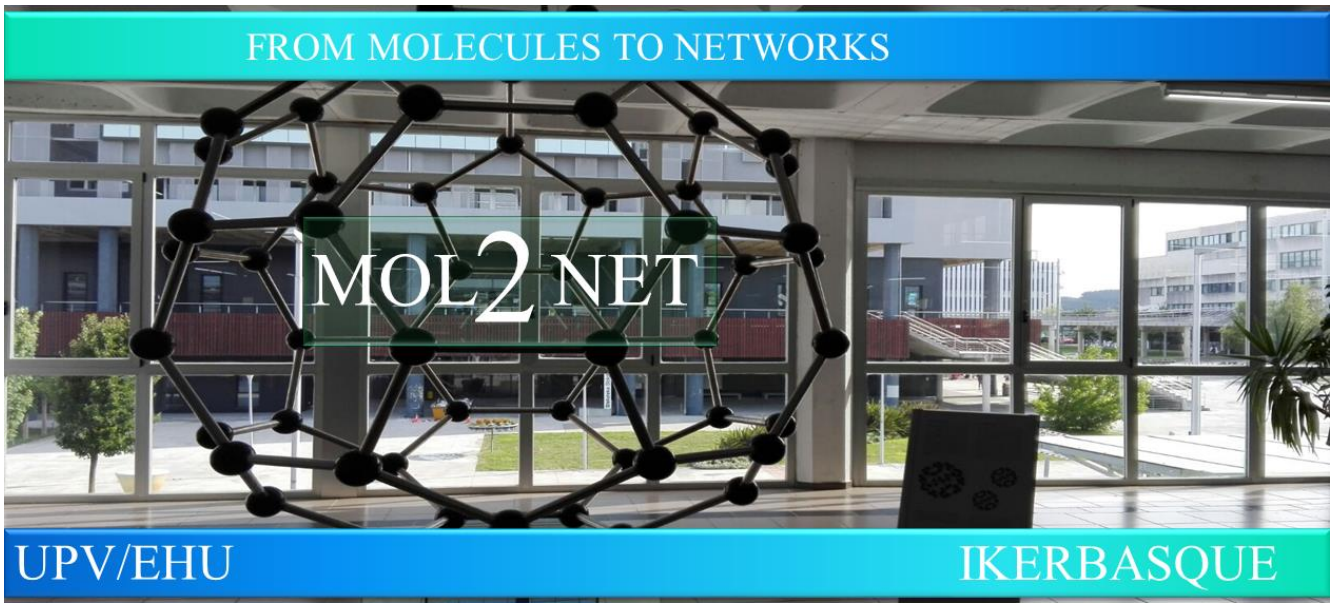
MOL2NET'22, Conference on Molecular, Biomedical & Computational Sciences and Engineering, 8th ed.



Role of the next-generation immune checkpoint LAG-3 in response and resistance to cancer immunotherapy

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Abstract.

Lymphocyte activation gene 3 (LAG-3) is a cell surface inhibitory receptor with multiple biological activities over T cell activation and effector functions. LAG-3 plays a regulatory role in immunity and emerged some time ago as an inhibitory immune checkpoint molecule comparable to PD-1 and CTLA-4 and a potential target for enhancing anti-cancer immune responses. LAG-3 is the third inhibitory receptor to be exploited in human anti-cancer immunotherapies, and considered a next-generation target in cancer immunotherapy, right next to PD-1 and CTLA-4. Unlike PD-1 and CTLA-4, the exact mechanisms of action of LAG-3 remain poorly understood. Indeed, PD-1/LAG-3 co-expression is a marker for exhausted T lymphocytes infiltrating tumors. This constitutes a high-risk signature, but also a clinical factor associated to overall survival. The lack of understanding of LAG-3 functions is partly caused by the presence of non-conventional signaling motifs in its intracellular domain, different from others present in classical immune checkpoints. Here we summarize the current understanding on LAG-3 and its role in response and resistance to cancer therapy, from its mechanisms of action to clinical applications (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: LAG-3, PD-1, immunotherapy, immune checkpoint

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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.