Clinical Landscape of LAG-3-Targeted Therapy

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Background
The lymphocyte-activating gene-3 (LAG-3) is a cell surface inhibitory receptor with multiple biological effectors over T cell activation and effector functions. LAG-3 is the third inhibitory receptor to be exploited in human anti-cancer immunotherapies, and it is considered a potential neoadjuvant cancer immunotherapy target in human therapy. To date, few clinical trials have been conducted in the LAG-3 field. Here we summarize the current understanding of LAG-3 clinical applications.

Methods
Several LAG-3 blockade immunotherapeutic models are being pursued at various stages of clinical and pre-clinical development. An extensive bibliographic research was performed using Pubmed and Clinicaltrials.gov databases to study all the LAG-3 preclinical and clinical trials conducted up to date. We also summarize the current understanding of LAG-3 clinical applications.

Results
LAG-3 was first tested in clinical trials in 2008 as a LAG-3-Ig fusion protein to take advantage of its immune-stimulating activities as a soluble protein. Nowadays, there are several LAG-3-antagonist immunotherapeutic models at various stages of clinical and pre-clinical development. In addition, combinations blocking LAG-3 together with other immune checkpoints are also being studied. A new generation of bispecific PD-L1-LAG-3 blocking agents have shown strong capacities to specifically target PD-L1-LAG-3 highly dysregulated T cells and enhance their proliferation and effector activities.

Conclusions
LAG-3 is a key regulator of immune homeostasis and is a highly important next-generation immunity checkpoint. Anti-LAG-3 antibodies and combinations are being evaluated at the preclinical and clinical levels. Indeed, the blockade of LAG-3 with PD-1 is showing encouraging results. A deeper understanding of the mechanisms underlying LAG-3 immunological signaling will provide insight for further development of novel strategies for cancer targeted treatment.

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