## Targeting Immune Checkpoints

Immune Checkpoints regulation and activation of T lymphocytes depend on signaling by the T cell receptor (TCr) and also by cosignaling receptors that deliver negative (—) or positive (+) signals. The amplitude and quality of the immune response of T cells is controlled by an equilibrium between costimulatory and inhibitory signals, called immune checkpoints. Under normal physiological conditions, immune checkpoints are crucial for the maintenance of self-tolerance and to protect tissues from damage during pathogenic infection. Manipulations of the inhibitory immune checkpoints using monoclonal antibodies or soluble receptors may provide therapeutic strategies for autoimmune diseases, tumor growth, infectious diseases and transplantation by enhancing T cell activity.

Some immune checkpoints have been actively studied for clinical immunotherapies:

- **CTLA-4** (Cytotoxic T Lymphocyte Antigen-4) shares sequence homology and ligands (CD80/B7-1 or CD86/B7-2) with the costimulatory molecule CD28, but differs by delivering inhibitory signals to the T cells on which it is expressed as a receptor.

- **PD-1** (Programmed Cell Death Protein-1) is a negative costimulatory molecule with two ligands, PD-L1 (also known as B7-H1; CD274) and PD-L2 (B7-DC; CD273). Antagonistic monoclonal antibodies to CTLA-4 or PD-1 and soluble CTLA-4 or PD-1 receptors fused to the Fc region of immunoglobulin (Ig) are used for the enhancement of T cell cytotoxicity against tumor cells.

- **LAG-3** (Lymphocyte Activation Gene-3 Protein) is a CD4-like negative regulatory protein with a high affinity binding to MHC Class II that leads to tolerance of T cell proliferation and homeostasis. Blockade of the LAG-3/Class II interaction using a LAG-3-Ig fusion protein enhances antitumor immune responses. Combinatorial blockade of PD-1 and LAG-3 synergistically reduces the growth of established tumors.

In addition, blockade of other inhibitory receptors, such as **BTLA** (B- and T-lymphocyte attenuator), **KIR** (killer immunoglobulin-like receptors), **TIM-3** (T cell immunoglobulin and mucin domain-containing protein 3), **A2aR** (adenosine 2A receptor), **B7-H3 or H4** (B7 family members) either alone or in combination with a second immune checkpoint inhibitor has also been shown to enhance antitumor immunity.

Costimulatory signaling proteins such as **ICOS** (inducible T cell costimulator), **CD28** or the TNF family members **4-1BB** (CD137), **OX40**, **CD27** or **CD40** have been shown to be involved in allergy, autoimmune or inflammatory diseases.

### References

- Combinatorial immunotherapy: PD-1 may not be LAG-ering behind any more: ME. Turnis, et al.; Onc Immunology 1, 1172 (2012)

Adapted from D.M. Pardoll; Nat. Rev. Canc. 12, 253 (2012)