

IPH5201

IPH5201 This program aims at developing an anti-CD39 antibody for immuno-oncology. By targeting the adenosine immunosuppressive pathway, it has the potential to promote anti-tumor immune responses across a wide range of tumors.

CD39 is a membrane-bound extracellular enzyme overexpressed on both regulatory T cells and several cancer types. It plays a major role in promoting immunosuppression through the pathway degrading adenosine triphosphate (ATP) into adenosine. Within the tumor microenvironment, ATP promotes immune cell-mediated killing of cancer cells. In contrast, adenosine accumulation causes immune suppression and dysregulation of immune cell infiltrates resulting in tumor spreading. Blockade of CD39 may therefore stimulate anti-tumor immunity across a wide range of tumors (including kidney, lung, ovarian, pancreatic, thyroid, testicular, endometrial, and prostate tumors, as well as in lymphoma and melanoma) by preventing the production of immunosuppressive adenosine and by promoting the accumulation of ATP in the tumor microenvironment.

Innate Pharma has selected the lead candidate, IPH5201, a CD39-blocking antibody aiming at restoring a pro-inflammatory microenvironment, currently in preclinical development.

The ectonucleotidases CD39 and CD73 hydrolyze extracellular adenosine triphosphate (ATP) and adenosine diphosphate (ADP) to generate adenosine, which binds to adenosine receptors and inhibits T-cell and natural killer (NK)-cell responses, thereby suppressing the immune system. The generation of adenosine via the CD39/CD73 pathway is recognized as a major mechanism of regulatory T cell (Treg) immunosuppressive function. The number of CD39⁺ Tregs is increased in some human cancers, and the importance of CD39⁺ Tregs in promoting tumor growth and metastasis has been demonstrated using several *in vivo* models. Here, we addressed whether CD39 is expressed by tumor cells and whether CD39⁺ tumor cells mediate immunosuppression via the adenosine pathway. Immunohistochemical staining of normal and tumor tissues revealed that CD39 expression is significantly higher in several types of human cancer than in normal tissues. In cancer specimens, CD39 is expressed by infiltrating lymphocytes, the tumor stroma, and tumor cells. Furthermore, the expression of CD39 at the cell surface of tumor cells was directly demonstrated via flow cytometry of human cancer cell lines. CD39 in cancer cells displays ATPase activity and, together with CD73, generates adenosine. CD39⁺CD73⁺ cancer cells inhibited the proliferation of CD4 and CD8 T cells and the generation of cytotoxic effector CD8 T cells (CTL) in a CD39- and adenosine-dependent manner. Treatment with a CD39 inhibitor or blocking antibody alleviated the tumor-induced inhibition of CD4 and CD8 T-cell proliferation and increased CTL- and NK cell-mediated cytotoxicity. In conclusion, interfering with the CD39-adenosine pathway may represent a novel immunotherapeutic strategy for inhibiting tumor cell-mediated immunosuppression.