IPH5201, a blocking antibody targeting the CD39 immunosuppressive pathway, unleashes immune responses in combination with cancer therapies

Poster # P488

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Background

CD39 is an extracellular ectonucleotidase highly expressed in the tumor microenvironment, by stromal cells and some immune infiltrating cells. CD39 contributes to the production of adenosine, an inhibitor of immune response, via sequential hydrolysis of adenosine triphosphate (ATP) and adenosine diphosphate (ADP) into adenosine monophosphate (AMP), which then is degraded into adenosine by CD73 enzyme.

In contrast, ATP has immune-stimulatory activity through promoting dendritic cell (DC) maturation. Blockade of CD39-mediated degradation of ATP may therefore stimulate anti-tumor immunity across a wide range of tumors by preventing production of immunosuppressive adenosine and by promoting accumulation of immunostimulatory ATP in the tumor microenvironment. IPH5201 is a humanized monoclonal antibody that selectively binds to and inhibits the activity of both membrane-bound and soluble human CD39.

Here, we explored the efficacy of IPH5201 *in vitro* and *in vivo* in immunocompetent human CD39 knock-in (huCD39KI) mouse model in combination with PD1/PDL1 immune checkpoint inhibitor.

Mechanism of action

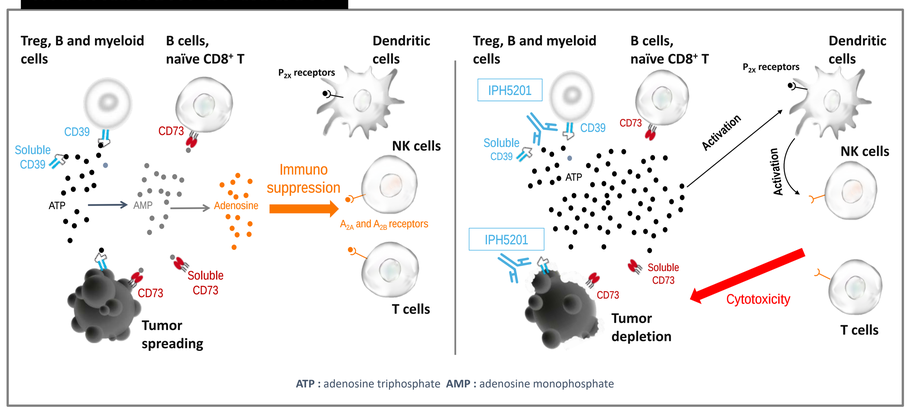
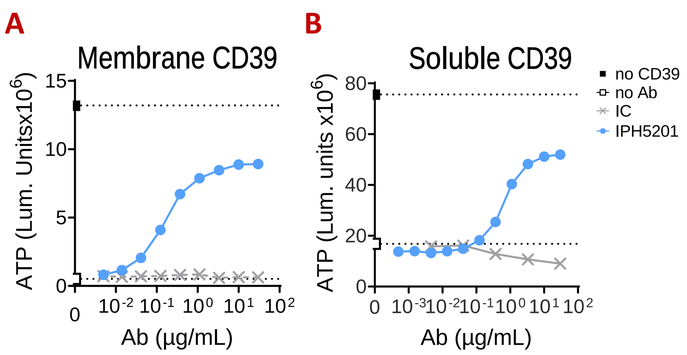


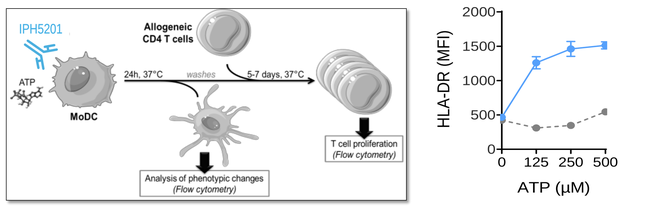
Figure 1: IPH5201 efficiently blocks soluble and membrane-bound CD39 enzyme activity

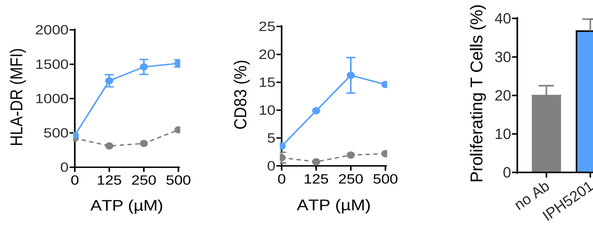


The CD39 expressing WIL2-NS human B-cell line (A) or recombinant human CD39 protein (B) was incubated with ATP in the presence or absence of IPH5201 or isotype control Ab (IC) over a range of concentrations. After 1 h, the remaining ATP was quantified in the supernatant.

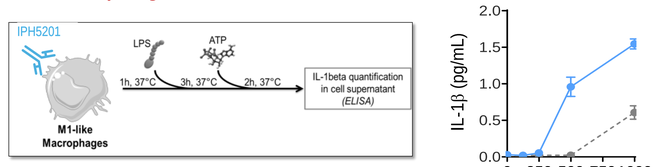
Figure 2: IPH5201 promotes the activation of immune cells, in presence of ATP

A : MoDC activation

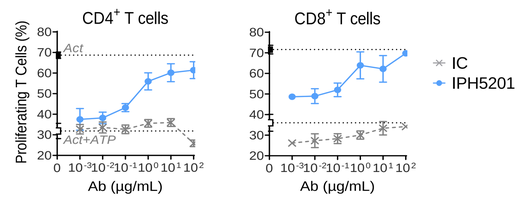




B : Macrophage activation



C: T cell proliferation

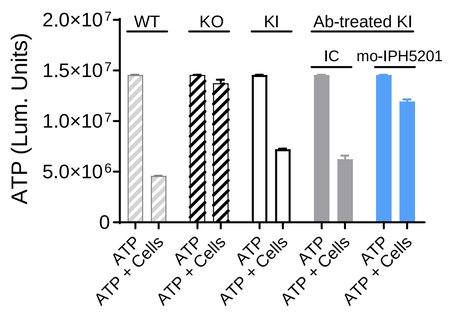


(A) Monocytes-derived dendritic cells (MoDCs) were incubated with (blue lines) or without (grey dotted lines) IPH5201 and stimulated with ATP. Median of fluorescence intensity (MFI) of HLA-DR-positive cells (left panel) and percentage of cells expressing CD83 (middle panel) were assessed by flow cytometry. T-cell proliferation was measured (right panel) after culture of ATP-stimulated MoDCs with allogeneic CD4+ T cells.
(B) Monocytes-derived M1-like macrophages were incubated with or without IPH5201 and stimulated with LPS and then with ATP. IL-1β production was determined.
(C) Human lymphocyte-enriched peripheral blood cells were activated with anti-CD3/anti-CD28 antibody-coated beads in the presence of ATP and IPH5201 or isotype control Ab. T-cell proliferation was assessed by flow cytometry.

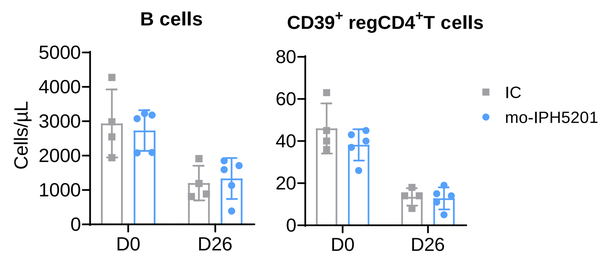
- IPH5201 preserved extra-cellular ATP, thereby promoting the activation of DCs and macrophages, and prevented adenosine accumulation by blocking ATP degradation, limiting its immunosuppressive effect on T cells *in vitro*.
- Together the *in vitro* and *in vivo* data presented indicate that blocking CD39 in conjunction with PD-1/PD-L1 checkpoint inhibitors provides increased anti-tumor efficacy and support the rationale for assessing this combination in clinical trials.

Figure 3: IPH5201 blocks CD39 activity in HuCD39KI mice without inducing cell depletion

A



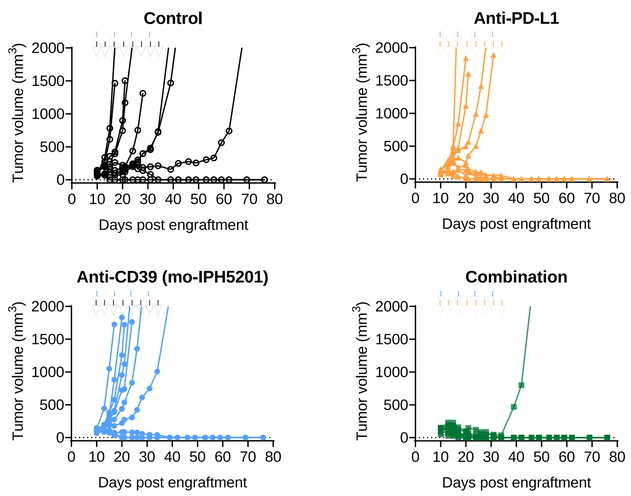
B



(A) Human CD39KI mice were injected with mo-IPH5201 (non-depleting mousified version of IPH5201) or isotype control (IC) Ab. 20 hours later, isolated spleen cells were incubated with 20 µM ATP. Residual ATP was quantified in the supernatant. WT=C57/BL6, KO=moCD39KO, KI=HuCD39KI mice.
(B) Peripheral blood concentrations of B cells (100% CD39+) and CD39+ RegCD4+ T cells after iv injection, twice a week for 3 weeks, of mo-IPH5201 or IC Ab into huCD39KI mice. The analysis was performed by flow cytometry before (D0) and 26 days (D26) after first treatment. Each dot corresponds to one mouse. Bar represents mean +/-SD. N=4-5. Sidak's multiple comparison test, non significant.

Figure 4: IPH5201 synergizes with anti-PD-L1 Ab therapy to promote anti-tumor immunity

A



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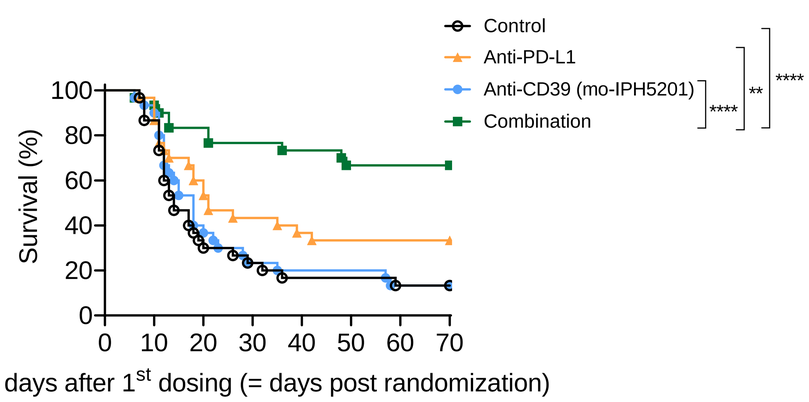

		Control	a-PD-L1	a-CD39	Combination
Complete Regression	n	2/10	5/10	3/10	9/10
	%	20	50	30	90

	Control	a-PD-L1	a-CD39	Combination
Median Survival (days)	14	21	18	undefined
Survival proportion (%)	13	33	13	67

(A) RMA-Rae-1β-tumor bearing huCD39KI mice were randomized on day 10 and then were treated as indicated with either anti-human CD39 Ab (i.v., mo-IPH5201, blue arrows) or isotype control Ab (grey arrows) and with either anti-mouse PD-L1 Ab (i.p., AB740080, orange arrows) or isotype control Ab (black arrows). Graphs show tumor growth in each individual (n=10/group) of one representative experiment out of three.
(B) Survival curves of the pool of three independent experiments (n=30 /group). Log rank test, **p=0.0072, ****p<0.0001. Undefined: not calculated as more than half of the mice are still alive at the end of the experiment.

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