Cancer immunotherapy by promoting inflammasomes in dendritic cells.

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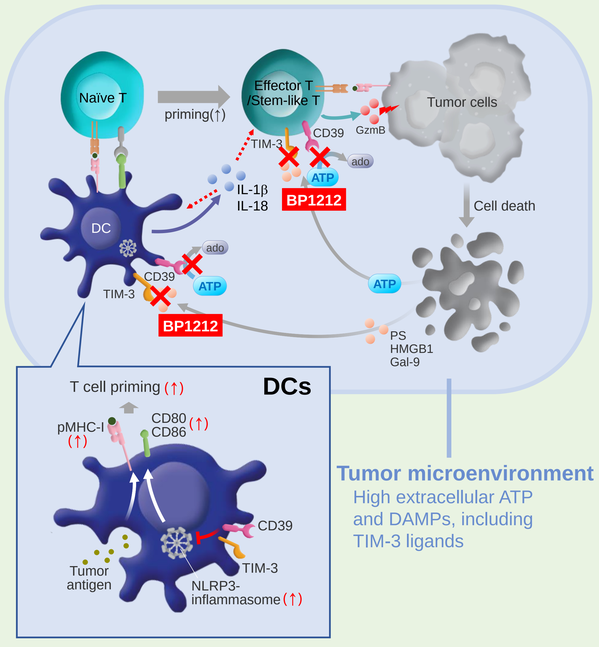
Background

The inflammasome is a key molecular complex in innate immunity that detects cellular stress and initiates inflammation. Despite its potential, strategies targeting the inflammasome remain underexplored in cancer immunotherapy.

Among the mechanisms controlling inflammasome activation, TIM-3 and CD39 have emerged as critical regulators. TIM-3 suppresses inflammasome activation in DCs, while CD39 degrades extracellular ATP, thereby dampening NLRP3 inflammasome activation. It remained unclear whether dual blockade of these molecules, together with NLRP3 activation, unleash the full potential of innate immunity and overcome resistance to current existing immunotherapies.

MoA of BP1212 (anti-huTIM-3/ huCD39 bispecific antibody)



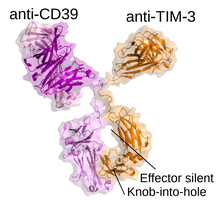
Tumor microenvironment
High extracellular ATP and DAMPs, including TIM-3 ligands

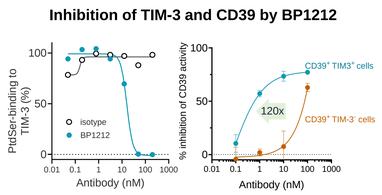
MoA on DCs
- Inhibit CD39-mediated ATP degradation.
- Relieve TIM-3-mediated suppression of inflammasomes.

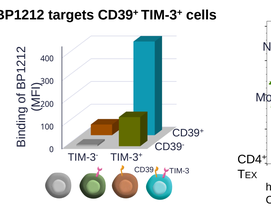
MoA on CTLs
- Inhibit adenosine production which attenuates T cells.
- Prevent T cell dysfunction by blocking TIM-3 signaling.

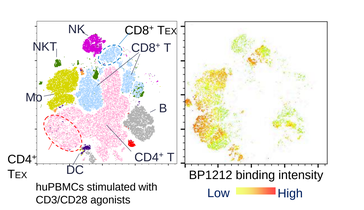
Research Strategy

To target the NLRP3 inflammasome, we developed a bispecific antibody (**BP1212**), that blocks the functions of TIM-3 and CD39, both of which are negative regulators of NLRP3 inflammasome. This bispecific antibody is humanized and is designed to be clinically applicable - suitable for pharmaceutical development, manufacturing, and therapeutic use. The generated antibody was subjected to in vitro evaluation, syngeneic antitumor studies using huTIM-3/huCD39 double knock-in (dKI-) mice, and safety and pharmacokinetic studies using cynomolgus monkeys.





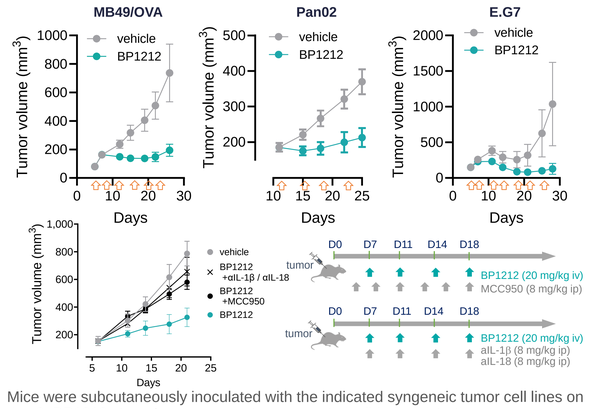




- BP1212 is a humanized, bispecific antibody with knob-into-hole format and effector-silent IgG_1(top-left). BP1212 preferentially binds to $CD39^+$ $TIM\text{-}3^+$ cells (bottom-left) and strongly inhibits CD39 ATPase activity as well as ligand binding to TIM-3 (top-right).
- BP1212 selectively binds DCs and activated T cells that express both TIM-3 and CD39 (bottom-right).

Key Findings

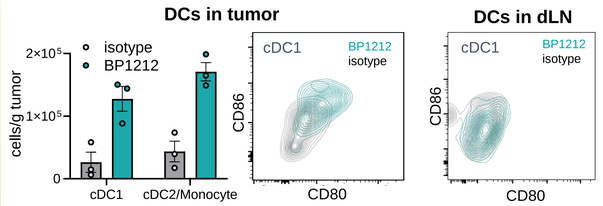
BP1212 suppresses tumor growth in vivo in an inflammasome-dependent manner



Mice were subcutaneously inoculated with the indicated syngeneic tumor cell lines on day 0. BP1212 strongly suppresses tumor growth by IV administration.

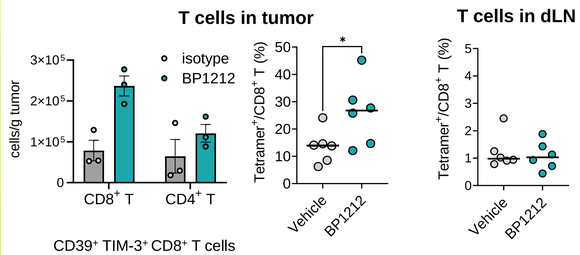
Antitumor effects of BP1212 is abolished by NLRP3 inflammasome inhibitor, MCC950 and IL-1β/IL-18 neutralizing antibodies.

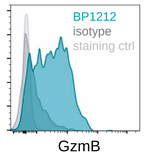
BP1212 induces the activated DCs in tumor and suppresses tumor cell growth



MB49 subcutaneous tumors or draining lymph nodes were resected from BP1212 treated mice. The tumor infiltrating DCs were analyzed by flow cytometry.

BP1212 increased the active and mature DCs in tumors (left) but not in dLNs (right).

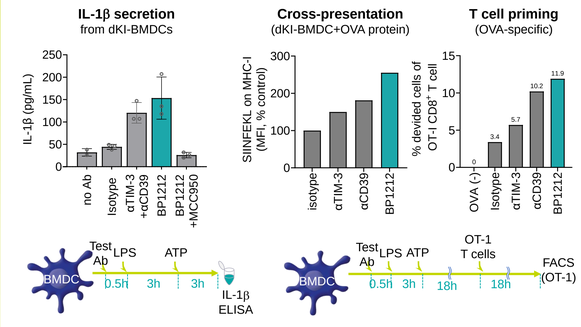




The number of T cells per tumor weight and the tumor-antigen-specific T cells (left) are significantly increased by BP1212 administration, but not in dLNs.

$CD39^+$ $TIM\text{-}3^+$ $CD8^+$ T cells to which BP1212 binds had significantly increased levels of intracellular granzyme B.

Inflammasome activation drives antigen-specific T cell priming by DCs.

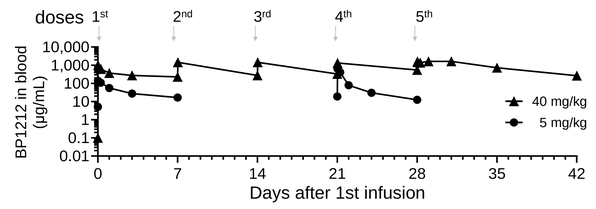


BP1212 induces IL-1β secretion from dKI-mouse BMDCs (left) via inflammasome activation.

BP1212 increases cross-presentation of OVA antigen (middle) and enhances OT-I T cell proliferation (right) in vitro.

Repeated BP1212 dosing in primates shows safety and sustained serum levels.

- BP1212 was administered to cynomolgus monkeys at up to 40 mg/kg. Repeat dosing (q1w x5) at 5 and 40 mg/kg is shown; single-dose data (1–40 mg/kg) not shown.
- No AEs were observed in general condition, body weight, food intake, hematology, or clinical chemistry.
- No detectable induction of inflammatory cytokine in the serum was observed after the doses.
- PK parameters were within the typical range for therapeutic antibodies in clinical use.



Conclusion

- $BP1212$ binds to $CD39^+$ $TIM3^+$ cells and potently inhibits TIM-3 and CD39 ATPase on the target cells.
- BP1212 promotes inflammasome activation in DCs, enhancing antigen cross-presentation and T cell priming.
- BP1212 increases the population of active and mature DCs in tumors, thereby recruiting highly cytotoxic CTLs and markedly suppressing tumor growth in vivo.
- The anti-tumor effect of BP1212 is dependent on inflammasome activation and is exerted in the tumor microenvironment.
- Pre-clinical studies suggest favorable safety and PK profile.
- BP1212 is structurally designed for clinical development and shows good stability and formulation characteristics.

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