IPH4301, an antibody targeting MICA and MICB, exhibits potent cytotoxic activity and immunomodulatory properties for the treatment of cancer

**Introduction**

We have generated an anti-MICA/B antibody that neutralizes MICA/B on target cells. Chronic exposure upregulates MICA/B expression by some chemotherapies, radiotherapy and cytokines. Recently, MICA/B expression was described on non-associated immunosuppressive macrophages. Chronic exposure to membrane-bound MICA/B activates M2 macrophages (M2).

**Mechanism of Action**

1. **MICA-B cell MAb** has high affinity and crossreactivity to MICA and MICB allotypes
2. **MCMA-B expression is induced in numerous tumor types**
3. **Prevalence of MICA/B expression across tumor types**
4. **In vitro cytotoxicity**
   - IPH4301 mediates potent ADCC by reacting primary human NK cells
   - IPH4301 overcomes M2 macrophage suppression of NK cell activity
5. **In vitro immunomodulation**
   - IPH4301 blocks MICA/B-induced downmodulation of NKG2D on NK and CD8+ T cells and promotes their activation

**Preclinical Evaluation**

**In vivo efficacy – TRAMP/Cb mouse model**

- IPH4301 blocks MICA/B-induced downmodulation of NKG2D on NK and CD8+ T cells and promotes ADCC-mediated tumor cell lysis

**Conclusion**

- We have generated and characterized a pan-allocreactive anti-MICA/B antibody, IPH4301.
- IPH4301 efficiently mediates ADCC towards tumor target expressing various alleles of MICA or MICB.
- IPH4301-based ADCC overcomes M2 macrophage-induced NK cell and T cell suppression.
- MICA/B downregulation by chronic exposure to MICA/B is induced by primary non-associated macrophages. In addition, IPH4301 efficiently mediates ADCC towards M2 macrophages and induces ADCC-mediated tumor cell lysis.
- IPH4301 shows in vivo efficacy in immunodepressed mice. IPH4301-resistant tumors exhibit spontaneous anti-tumor immunity and primary mouse xenografts in TANMAME immunocompromised mice. IPH4301 eliminates slow tumor growth in syngeneic primary tumors. The development of a monoclonal antibody with immune regulation properties will be the subject of future studies.

**References**

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