MAIT Engagers: an efficacious novel modality in the field of T-cell engagers for the treatment of solid tumors.

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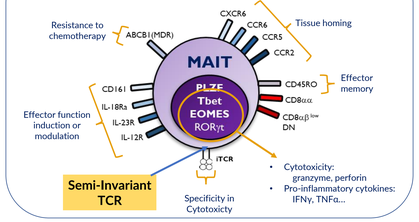
Introduction

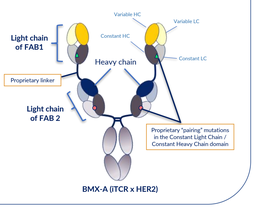
Mucosal-Associated Invariant T cells (MAITs) are an abundant subset of non-conventional T-cells with potent cytotoxic capacity (up to 20% of circulating T-cells) that are naturally resident in many tissues and solid tumors. They can be activated by a TCR-dependent and independent manner and exhibit a rapid, innate-like response to bacterial and viral infections. MAITs express a semi-invariant TCR and respond to microbial metabolites presented in the context of the MHC-like protein, MR1. They have potent cytotoxic potential and readily infiltrate inflamed tissues where their cytotoxic activity can be induced by TCR engagement or by IL-12/IL-18.

Mucosal Associated Invariant T cells.



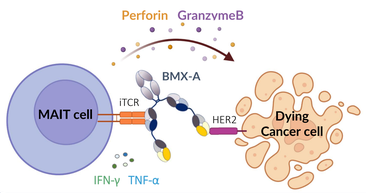
Features of the BiXAb® platform.

- Plug and Play format.
- Swap any 2 FABs.
- Bispecific
- Bivalent (for each target).
- Fc effector function competent or null.
- IgG1 or other.



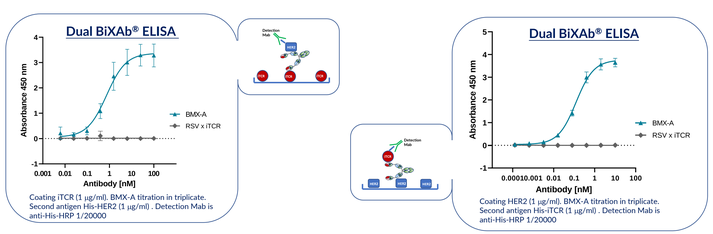
T-cell redirection is a clinically validated approach to treating haematological cancers but has had limited success so far in solid tumors. Classical T-cell engagers (TCE) bind the epsilon chain of the TCR leading to activation of all T-cells (Cytotoxic CD8s and all CD4 subsets including Tregs) which can lead to Cytokine Release Syndrome (CRS) and associated dose limiting toxicities. Activation of the Treg population in the tumor microenvironment by classical TCEs may also contribute to the reduced activity of this modality in solid tumors.

Biomunex Pharmaceuticals, using their proprietary BiXAb® technology, has developed a bispecific antibody to uniquely engage MAIT cells and redirect them to kill cancer cells by binding the invariant TCR (iTCR) expressed on MAIT cells and a tumor associated antigen (HER2). Given the significant abundance of MAIT cells and their propensity to infiltrate tissues and cancers, MAIT cell redirection is expected to significantly increase efficacy in solid tumors where there will be no activation of tumor resident Tregs with increased immunosuppression and no overt activation of all T-cell subsets leading to CRS.



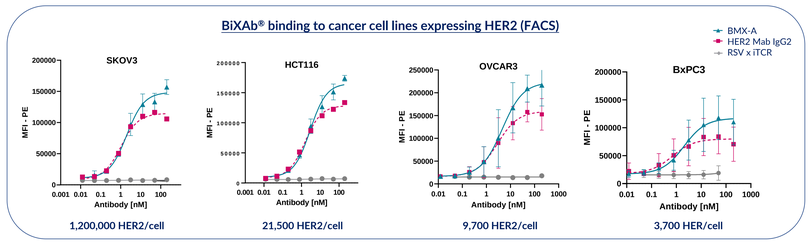
- The BiXAb® binds "in trans" to form an immunological synapse
- Activated/bridged MAIT cells directly kill the cancer cell.
- Local release of cytokines to induce secondary immune cell recruitment.

The BiXAb® MAIT Engager can bind both targets simultaneously (ELISA)



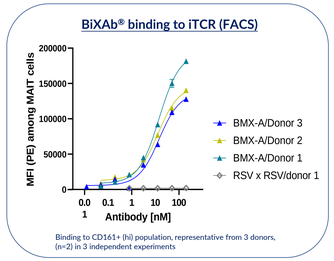
The BiXAb® BMX-A, targeting the MAIT iTCR and HER2 is able to bind both proteins simultaneously, as judged by dual ELISA (performed in both orientations).

The BiXAb® binds to HER2 on cancer cells lines as effectively as the parental Mab



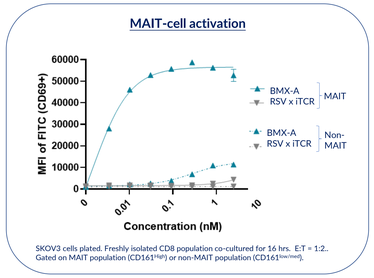
The iTCR x HER2 BiXAb® (BMX-A) is able to effectively bind HER2 expressed on cells over a wide range of receptor density. Note, at low receptor density (BxPC3) BMX-A binds with a higher "Y-max", compared to the parental Mab, due to the architecture of the BiXAb® format.

The BiXAb® MAIT Engager is able to bind the iTCR on MAIT cells



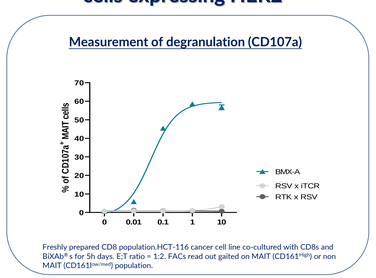
The BiXAb® (BMX-A) is able to bind to the iTCR on freshy isolated human MAIT cells .

Upon engagement with HER2-expressing cells, the BiXAb® binds and activates MAIT cells



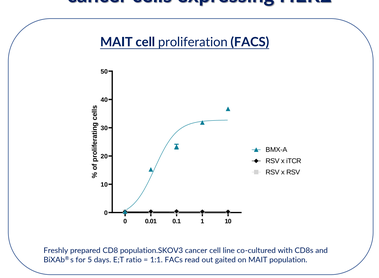
The BiXAb® (BMX-A) induces MAIT cell activation in the context of binding HER2+ cells. It does not activate the other CD8 cells present.

The BiXAb® can induce MAIT cell degranulation in co-culture with cancer cells expressing HER2



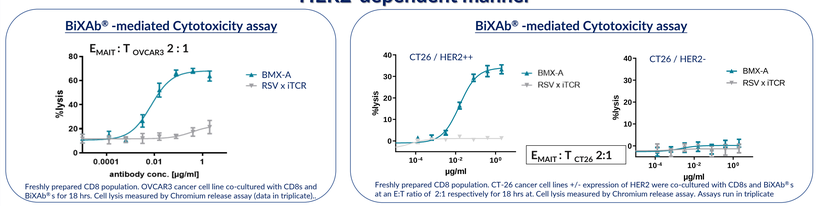
The BiXAb® (BMX-A) induces MAIT cell degranulation in the context of binding HER2+ cells. It does not impact other CD8 cells (data not shown).

The BiXAb® can induce MAIT cell proliferation when co-cultured with cancer cells expressing HER2



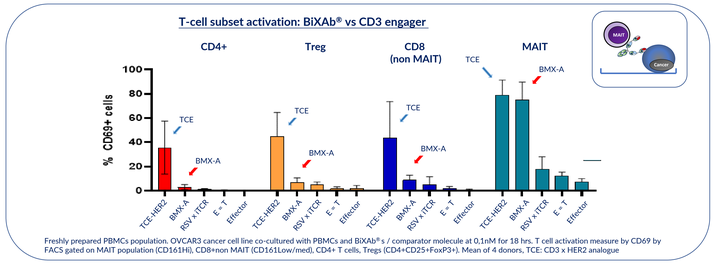
The BiXAb® (BMX-A) induces MAIT cell proliferation in the context of binding HER2+ cells. It does not impact other CD8 cells (data not shown).

The BiXAb® MAIT Engager can redirect MAIT cells to directly kill cancer cells in a HER2-dependent manner



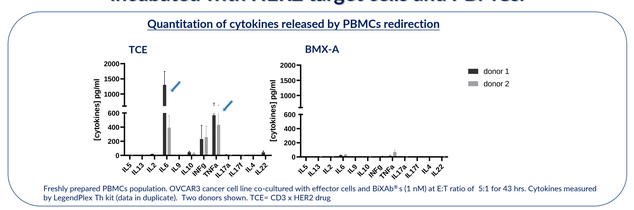
Even at low E:T ratio, the MAIT engager demonstrates potent cytotoxicity towards OVCAR3 cells expressing HER2 (ca 70% cytotoxicity in 18 hrs). Using an isogenic cell line CT26, depletion of HER2 prevents MAIT engager cytotoxicity and confirms the HER2 specificity of the BiXAb® -mediated MAIT cell redirection.

The BiXAb® MAIT Engager only activates MAIT cells whilst a classical HER2-directed TCE activates all T cells, including Tregs.



The MAIT engager only activates MAIT cells whilst the classical TCE activates all T cells. Treg activation could lead to increased immuno-suppression in the TME.

Minimal cytokines are released by a MAIT engager compared to a classical TCE when incubated with HER2 target cells and PBMCs.



In a PBMC mixture, the classical TCE induced the production of significant quantities of IL-6 and TNFα. The MAIT engager induced minimal cytokines, as expected

Discussion

- Biomunex Pharmaceuticals has developed a bispecific antibody platform (BiXAb®) that can effectively redirect MAIT cells to specifically kill cancer cells. The BiXAb® can:
  - Bind both the iTCR and HER2 simultaneously and bind HER2 on cancer cells over a wide [HER2] range
  - Activate MAIT cells, leading to degranulation, proliferation and direct cancer cell cytotoxicity.
- MAIT engagers have great therapeutic potential for the treatment of solid tumors:
  - Efficiently and specifically redirect MAIT cells to kill cancer cells (e.g. expressing the HER2).
  - Reduced cytokine storm due to the activation of a limited subset of T-cells.
  - Do not activate Tregs and therefore do not increase local immunosuppression in the TME.
  - From the above attributes, BiXAb® MAIT engagers should be efficacious in solid tumors
  - Can be designed to target any Tumor Associated Antigen.