Engineered Toxin Bodies (ETBs): Clinical stage immunotoxins with a safer and differentiated profile

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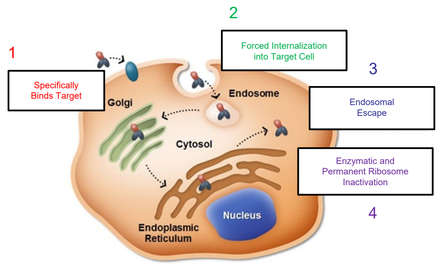
MOLECULAR TEMPLATES

ETBs represent a wholly differentiated approach for targeted therapies

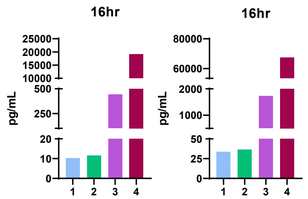
Engineered Toxin Bodies (ETBs) are fusion proteins consisting of an antibody fragment fused to a genetically engineered (de-immunized (DI)) form of the Shiga-like toxin A subunit (SLTA) capable of triggering receptor internalization and killing of target cells. ETBs can perform **"forced internalization"** of typically non-internalizing receptors opening completely novel target classes. In addition, CMV peptide antigen is included to leverage host antiviral cytotoxic T cell responses as a second mechanism of target cell killing, **"Antigen Seeding Technology" (AST). ETBs are clinically proven to target novel cell types resulting in phase 1 clinical responses**



First ever immunotoxin with an engineered de-immunized toxin body exhibiting no clinical innate immune activation or CLS

Second Generation ETBs exhibit superior safety profile to other immunotoxins

Next-gen (de-immunized) SLTA exhibits no innate immune activation

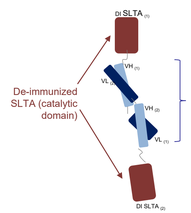


1. PBS
2. 2nd Gen
3. 1st Gen
4. LPS

- ***In 95+ patients treated to date with next-gen ETBs, there has not been a single case of capillary leak syndrome (CLS)***
- ***Historic immunotoxin CLS incidence is 33-55%***
- ***Dosing with next-gen ETBs is higher than what has been seen with historic immunotoxins, allowing for activity in solid tumor settings***

Forced internalization of CD38 exhibits clinical response in MM patient (MT-0169)

MT-0169



- **CD38 receptor does not naturally internalize**
- **MT-0169 is an extremely potent (sub-pM) CD38 targeting ETB that induces CD38 internalization**

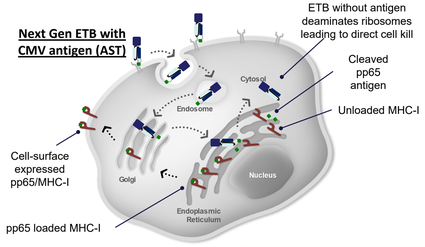
- **Stringent CR**: A 54-year-old male patient with relapsed Multiple Myeloma of IgA lambda type
- Five previous lines of therapy including progression on previous CD38 antibody therapy, proteasome inhibitors, IMiDs, and a BCMA bispecific
- Extramedullary Disease
- Follow-up PET/CT performed compared with background, consistent with stringent Complete Response (sCR)

One of four patients treated at lowest dose (5mcg/kg) qualifies as a stringent CR and currently continues therapy (cycle 8)

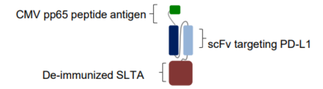
Delivering antigen seeding technology (AST) to the clinic (MT-6402: PD-L1 targeting)

Altering tumor immunophenotype to redirect CMV specific T cells

MT-6402 contains an HLA:A*02 restricted antigen from human Cytomegalovirus (CMV). MT-6402 "seeds" CMV-restricted MHC-I peptide response for redirection of endogenous CMV-specific CD8+ cytotoxic T cells against tumor cells



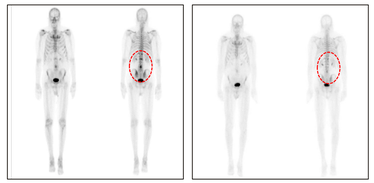
MT-6402
Next Gen ETB with Antigen Seeding Technology (AST)



PD-L1 targeted ETBs provide distinct benefits for overcoming clinical challenges of checkpoint non-responsive tumors
- Fundamentally alter the tumor microenvironment through direct depletion (not just blocking) of PD-L1 positive immunosuppressive cellular infiltrates (eg, MDSCs)
- Direct killing of PD-L1 expressing tumor cells through irreversible ribosomal inhibition
- Delivery of CMV antigen to HLA compatible tumors thereby leveraging host anti-viral immunity through redirection and expansion of circulating memory cytotoxic T cells to the TME

Reduction in metastasis in tumor PD-L1^{high}, AST engaged patient

Metastatic uptake: T11 and L1 vertebral bodies. Left 5th and 11th rib, right ischial tuberosity.

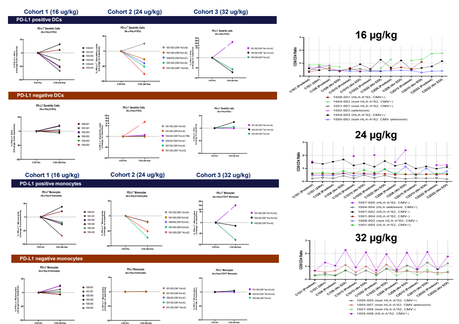


Interval decrease of T11 and L1 has mostly resolved. Left 5th rib and left 11th rib lesions have resolved.

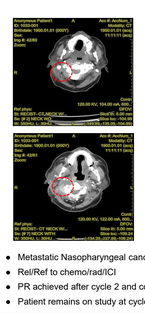
Patient had PD-L1 TPS 80%, HLA-A*02, and CMV positive. This patient remained on treatment for approximately 8 months. MT-6402 expansion to include a cohort of TPS >50%

MT-6402 offers a unique ability to also dismantle the tumor microenvironment

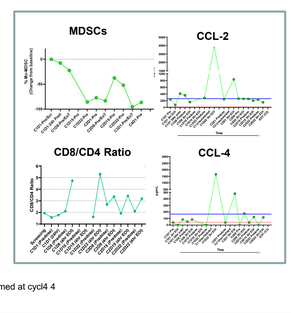
MT-6402 depletes PD-L1+ immune cells and activates CD8 T-cells; Cytokines associated with TME disruption upregulated



PD-L1+ immune cells are depleted in the periphery of patients with MT-6402 removing immunosuppression and activating an effector T-cell profile (increased CD8/CD4 ratio).



- Metastatic Nasopharyngeal cancer
- Rel/Ref to chemo/rad/ICI
- PR achieved after cycle 2 and confirmed at cycl4 4
- Patient remains on study at cycle 6

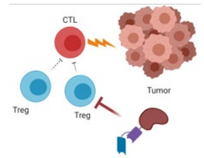


Metastatic nasopharyngeal cancer patient treated at 63 mcg/kg after progression on chemo, radiation, and checkpoint therapy. Patient had 2% TPS and was not HLA-A*02 (Not AST engaged). Partial response observed even though PD-L1 was low, suggesting MT-6402 cellular changes in the TME (dismantling) contribute to improved clinical outcomes. Increases in CCL2 and CCL4 suggest tumor's attempt to compensate for cleared immune cells.

MT-8421 removes immunosuppressive CTLA-4+ Tregs in the TME

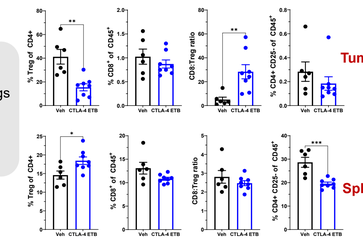
MT-8421 preferentially depletes tumor resident Tregs in mice

MT-8421 MOA



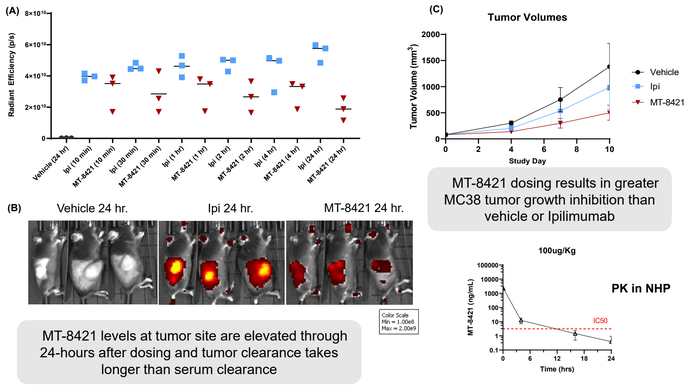
MT-8421 selectively depletes Tregs in TME of syngeneic humanized mice

MT-8421 characteristics	
CTLA-4 affinity	Sub-nM
Treg Potency	Sub-nM
Size	55 kD
In vivo half-life	~3 hrs



Human CTLA-4 knock-in HuGEMM mice (Biocytogen) were inoculated with MC38 tumors. ETB was dosed at 3 mg/kg for 3 consecutive days. On day 4, the tumors and spleens were harvested and processed for immunophenotyping

IV administration of MT-8421 sustains exposure and decreases MC38 tumor growth



MT-8421 dosing results in greater MC38 tumor growth inhibition than vehicle or Ipilimumab

MT-8421 levels at tumor site are elevated through 24-hours after dosing and tumor clearance takes longer than serum clearance

MC38 tumor bearing C57BL/6-hCTLA-4 mice dosed IV, q3dx3, with Vehicle or 3 mg/kg MT-8421 or Ipilimumab (Ipi)
(A) Fluorescence levels of Vehicle or VivoTag680 tagged Ipi or MT-8421 following three q3d doses
(B) Fluorescence imaging of C57BL/6-hCTLA-4 mice 24 hours after a 3rd, q3d, dose of Vehicle, Ipi, or MT-8421
(C) Subcutaneous MC38 tumor growth through dosing of Vehicle or VivoTag680 tagged Ipi or MT-8421

CONCLUSIONS

- Next gen ETBs with de-immunized SLTA do not activate innate immunity and do not induce capillary leak syndrome. This is the first engineered immunotoxin achieving clinical efficacious doses with no CLS cases.
- MT-0169, CD38 targeted ETB has shown evidence of monotherapy activity (stringent CR at cycle 8) in a penta-refractory patient with extramedullary IgA myeloma. This patient remains on study.
- MT-6402, PD-L1 targeted ETB has shown evidence of monotherapy activity in the clinic through two separate mechanisms of action unique to immuno-oncology: the alteration of tumor immunophenotype and the dismantling of the TME that differs from traditional mAbs and ADCs.
- CTLA-4 targeted ETB, MT-8421 is designed to eliminate preferentially target Tregs in the TME, while sparring CD8+ peripheral T cells thought to drive ipilimumab toxicity. MT-8421 IND has been approved for first-in-human phase I study by mid-year 2023.

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