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

Chris Moore, Swati Khanna, Lee Robinson, Garrett Cornelison, Joseph Dekker, Roger Waltzman, John Majercak, Joseph Phillips, Jay Zhao, Jason Kim, Eric Poma

Molecular Templates Inc., Austin, TX

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 toxin (GEMIST) form of the Stage-1 toxin in a rodent (GSTA) capable of triggering receptor internalization and killing of target cells. ETBs can perform “forced internalization” of typically non-internalizing receptors opening a novel target cleavage site. In addition, CMV peptide antigen is included to leverage hetero-antigen 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

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

MT-6402 contains an HLA:A*02 restricted antigen from human Cytomegalovirus (CMV). MT-6402 “loads” CMV restricted MHC-I peptide response for reactivation of endogenous CMV specific CD8+ cytotoxic T cells against target cells

Second Generation ETBs exhibit superior safety profile to other immunotoxins

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

• In >5% 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)

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 (sg lambda) type
• Five previous lines of therapy including progression on previous CD38 antibody therapy, proteasome inhibitors, IMIDs, and a BCMA targeted therapy
• Extraordinary response
• 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)

MT-6402 preferentially depletes tumor resident Tregs in mice

Patient had PD-L1 TPS 80%, HLA-A*02, and CMV positive. This patient remained on treatment for approximately 6 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

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

MT-6402 targets ETBs provide distinct benefit for overcoming clinical challenges at checkpoint non-responsive tumors

• Fundamentally alter the tumor microenvironment through direct depletion and up-regulating killing of PD-L1+ tumor cells through multiple mechanisms of action
• Redirecting of PD-L1+ expressing tumor cells through reversible immunostimulatory cytokine secretion
• Delivery of CMV antigen to HLA compatible tumors thereby leveraging forgiving innate and adaptive immunity through transcription and expansion of occurring memory updates T cells to the TME

MT-6402 expands in a cohort of patients with PD-L1+ immune cells are depleted in the periphery of patients with MT-6402 removing immunosuppression and activating an effective T cell profile (increased CD8:CD4 ratios)

Metastatic nasopharyngeal cancer patient treated at 53 mcg/kg after progression on chemotheraphy, radiation, and checkpoint therapy. Patient had 2% TPS and was naïve to AST and Ipi. Partial response observed even though PD-L1 was low, suggesting MT-6402 cellular changes in the TME (dynambing) contribute to improved clinical outcomes. Increases in CD8 and CD4 favor suggest tumor's attempt to compensate for shored immunity.

CTLA-4 targeted ETBs, MT-6421 is designed to eliminate preferentially target Tregs in the TME, while sparing CD8+ peripheral T cells thought to drive clinical efficacy. MT-6421 IND has been approved for first-in-human phase 1 study mid year 2023.

www.mtem.com; Contact: bd@mtem.com, chris.moore@mtem.com

Abstract Number 2661

AACR Annual Meeting 2023

CONCLUSIONS

MT-6421 restores immunosuppressive CTLA-4+ Tregs in the TME

MT-0169, CD38 targeted ETB has shown evidence of microtubule activity (stringent CR at cycle 8) in a heavily pre-treated patient with extramedullary lg lambda 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 immunotoxins: the alteration of tumor immunophenotype and the dismantling of the TME that differs from traditional mAbs and ADCs.

MC38 tumor bearing C57BL/6-hCTLA-4 mice dosed i.p. with Vehicle or 3 mg/kg MT-6421 or ipilimumab (Ipi)

MT-6421 doses of 100ug/Kg or Vehicle significantly target the MC38 tumor burden more than 100% (p<0.05) compared to Vehicle control (p<0.0001)

MT-6421 levels at tumor site are elevated through 24 hours after a single exposure leading to TME disruption longer than with control treatment

MC38 tumor bearing C57BL/6-hCTLA-4+ mouse dosed i.p, withVehicle or 3 mg/kg MT-6421 or ipilimumab (Ipi)

MT-6421 closing results in greater MC38 tumor growth inhibition than vehicle or ipilimumab control (p<0.05)

MC38 tumor bearing C57BL/6-hCTLA-4 mice dosed i.p, with Vehicle or 3 mg/kg MT-6421 or ipilimumab (Ipi)

MT-8421 preferentially depletes tumor resident Tregs in mice

MT-8421 levels at tumor site are elevated through 24 hours after a single exposure leading to TME disruption longer than with control treatment

Next gen ETBs with do-imunized SLTA do not activate innate immunity and do not induce capillary leak syndrome

MT-8421 dosing results in greater MC38 tumor growth inhibition than vehicle or ipilimumab control (p<0.05)

MT-8421 levels at tumor site are elevated through 24 hours after a single exposure leading to TME disruption longer than with control treatment

Metastatic breast cancer (BC) patient treated at 53 mcg/kg after progression on chemotheraphy, radiation, and checkpoint therapy. Patient had 2% TPS and was naïve to AST and Ipi. Partial response observed even though PD-L1 was low, suggesting MT-6402 cellular changes in the TME (dynambing) contribute to improved clinical outcomes. Increases in CD8 and CD4 favor suggest tumor's attempt to compensate for shored immunity.

MT-6421 dosing results in greater MC38 tumor growth inhibition than vehicle or ipilimumab control (p<0.05)

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Next gen ETBs with de-imunized SLTA do not activate innate immunity and do not induce capillary leak syndrome

MT-0169, CD38 targeted ETB has shown evidence of microtubule activity (stringent CR at cycle 8) in a heavily pre-treated patient with extramedullary lg lambda myeloma. This patient remains on study.

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