MULTIVALENT T CELL ENGAGERS FOR THE TREATMENT OF PROSTATE CANCER

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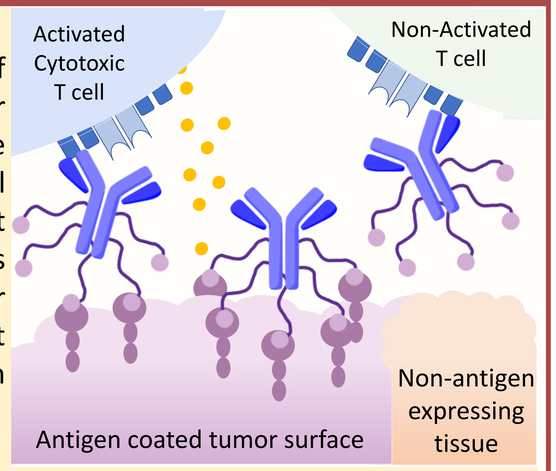
1. IMPROVING UPON BISPECIFIC T CELL ENGAGERS

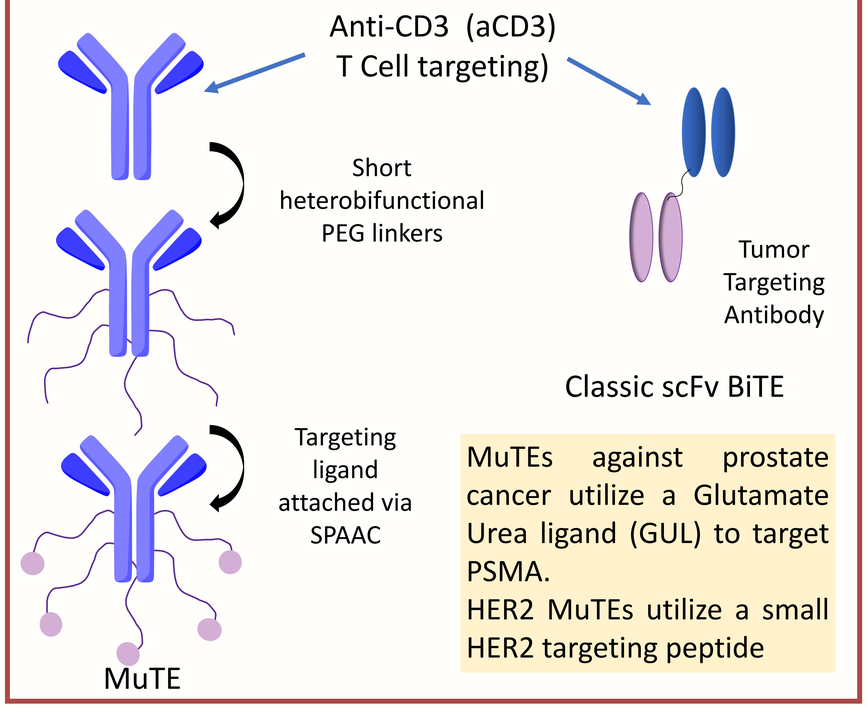
Immunotherapeutics are a growing field of research for cancer therapy. One example is the Bispecific T cell engagers (BiTEs) that simultaneously targets to T Cells and tumor antigens, to redirect the immune cells with MHC-independent activation.



Despite the success of BiTEs, they have limited efficacy in solid tumors due to their rapid clearance. As well, developing individual BiTEs requires complex production, making expansion of the BiTE time-consuming.

Here we developed a simple to synthesis, tumor targeting multivalent T cell engager (MuTE). Increased size and PEGylation help increase retention via an intratumoral injection or other local delivery, while simple synthesis via "click" reactions allows expansion to any targetable-cancer

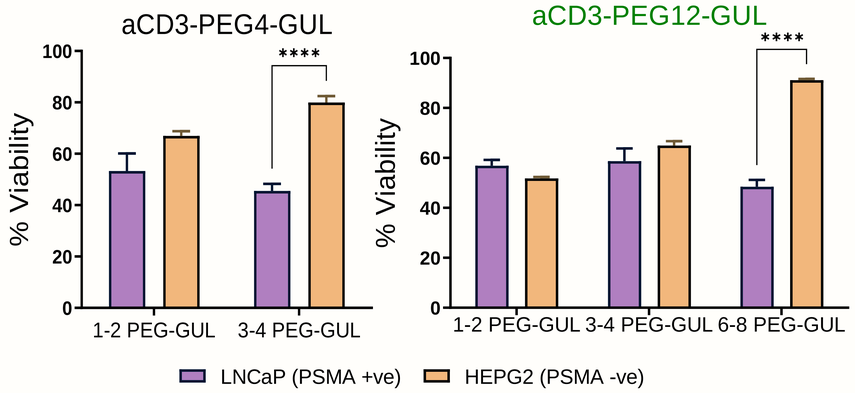
2. SIMPLE SYNTHESIS OF MULTIVALENT T CELL ENGAGER

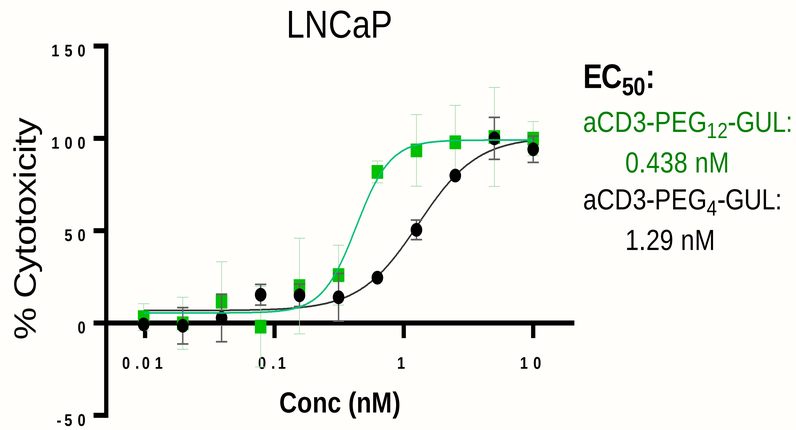


MuTEs against prostate cancer utilize a Glutamate Urea ligand (GUL) to target PSMA.

HER2 MuTEs utilize a small HER2 targeting peptide

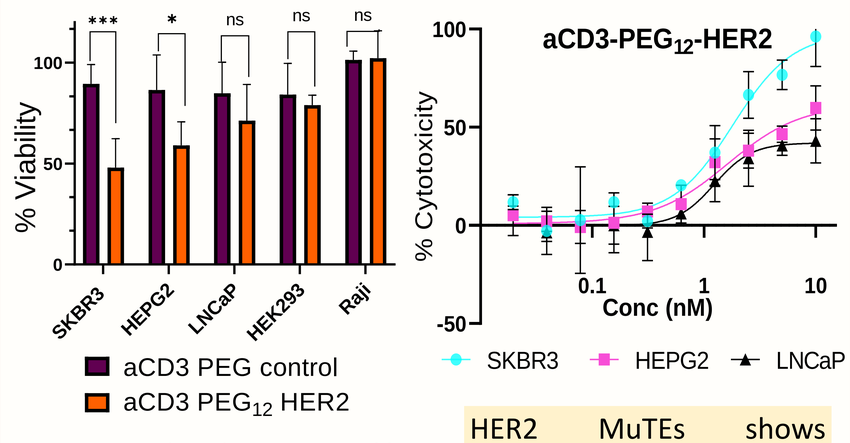
3. OPTIMIZING MuTE PLATFORM IN PROSTATE CANCER: improving targeted cytotoxicity





Co-culture of T cells and cancer cells (+ve and –ve) (at 5:1 E:T ratio) in the presence of PSMA targeting PEGylated MuTEs. Increasing PEG length decreases EC_{50} values.

5. EXPANDING THE MuTE PLATFORM HER-2 Expression-level dependent cytotoxicity

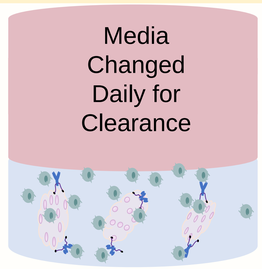


SKBR3 (+++) HEK293 (-)
HEPG2 (++) Raji (-)
LNCaP (+)

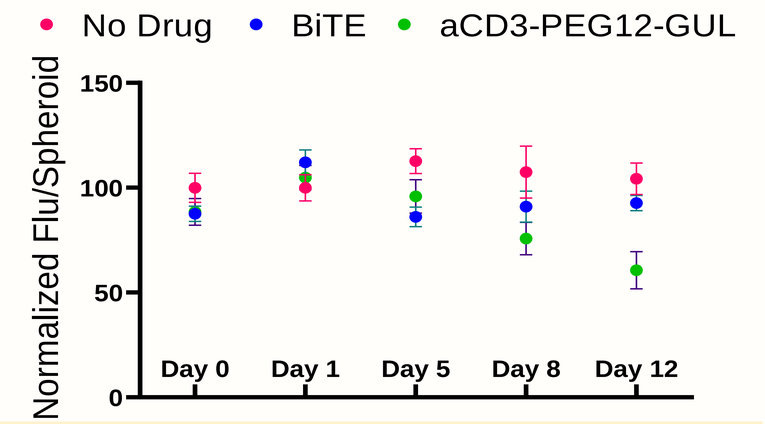
HER2 MuTEs shows potential for expression level dependent targeting.

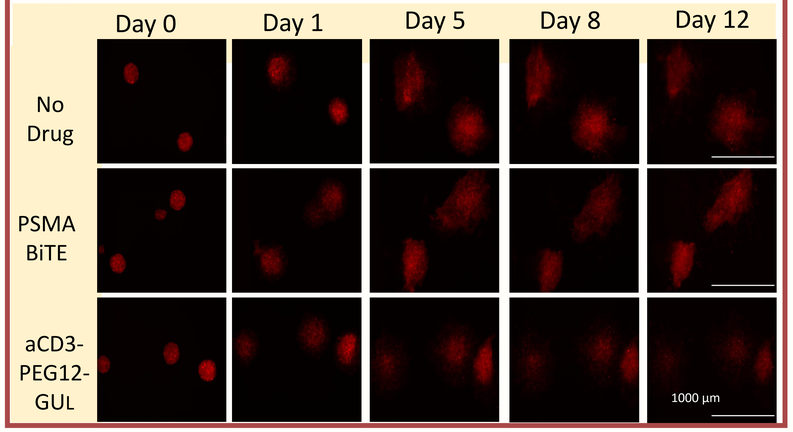
4. MuTEs IN A LOCAL DELIVERY MODEL have prolonged cell death and slower clearance

PSMA targeting MuTEs in a local delivery *in vitro* model showed strong cytotoxic effects against spheroids, lasting more than twice as long as the BiTE. Overall, the MuTEs in a 3D *in vitro* model show promise solid tumor efficacy in intratumoral or local delivery.



T Cells & Spheroids embedded in Collagen-HA gel with MuTE to mimic local delivery of drug to tumor site





6. The Future of the MuTE platform

The MuTE scaffold allows for the rapid development of new T cell engaging therapies and improves efficacy of tumor treatments; MuTEs may prove beneficial for local therapies. To further extend this platform, multiple cancer targets can be conjugated to overcome tumor heterogeneity and immune evasion.

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