**Background & Rationale**

Adoptive cell therapy with tumor-infiltrating lymphocytes (TILs) has demonstrated promise in clinical trials for patients with solid tumors. Currently, TIL therapy requires IL-2 administration to support TIL expansion and survival, but this cytokine is associated with T cell exhaustion and can result in severe toxicities that limit patient eligibility.

To this end, we genetically engineered TILs to express membrane-bound IL-15 (mIL-15) under the control of Obsidian’s cytoDRIVE® technology (cytoTIL15™), which allows regulation of protein expression via a drug-responsive domain (DRD) upon acetazolamide (ACZ) administration. IL-15 is a preferred cytokine over IL-2 to mediate TIL activation and expansion because it does not result in CD8 T cell exhaustion or stimulation of regulatory CD4 T cells but supports homoeostatic proliferation of memory T cells. We have previously demonstrated IL-15 independent, 3-6-fold increased cytoTIL15 cell persistence in an antigen-independent, in vivo setting relative to unengineered TIL therapy (uTIL) with IL-2.

Since generating autologous tumor/TIL-matched pairs poses multiple challenges, we developed an allogeneic, HLA-matched, patient-derived xenograft (PDX) model which allows antigen-specific comparison of cytoTIL15 anti-tumor efficacy across multiple donors.

**Primary melanoma PDX model developed to assess TIL efficacy**

- Melanoma biopsied & implanted into NGS mice within 24 hours
- Initial tumor take
  - Sera and passage, tissue- and cryopreserved
- Confirm epithelial histology

**PDX tumor expresses conserved melanoma antigens**

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<th>Human melanoma cell line</th>
<th>Melanoma PDX</th>
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<td>Melanoma PDX</td>
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**HLA-matched TIL donors demonstrate reactivity to PDX tumor**

- HLA-A/02 selected melanoma TIL donors
- TIL-PDX reactivity assay (IFNγ levels)
- MART1 + gp100 TCR expression

**Cells engineered with cytoDRIVE® technology to enable regulation of fusion proteins via drug responsive domains**

- PDX Growth Kinetics Study
  - Growth Kinetics: 100 mg tumor
  - Growth Kinetics: 30 mg tumor

**Conclusions**

- In this report of its kind, these data demonstrate the feasibility of comparing multiple TIL donors in a standardized, allogeneic, HLA-matched PDX tumor efficacy model rather than evaluating each in the traditional autoologous format. Evaluation of three donors in the model showed:
  - Significantly greater anti-tumor activity of ACZ-regulated cytoTIL15 cells compared to TIL plus IL-2, including complete responses.
  - Significantly increased persistence of ACZ-regulated cytoTIL15 cells compared to TIL plus IL-2.
  - Significantly 8-10-fold increased tumor infiltration of regulated cytoTIL15 cells, including MART1-specific TIL.

**References**

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