The enLIGHTEN™ Discovery Platform

Programmable vectors
Artificial intelligence-driven payload selection
Multimodal therapies by design

- enLIGHTEN™ enables the generation of multimodal agents able to overcome barriers in the tumor microenvironment and improve response in immunotherapy-resistant patients.
- Vectors are generated with programmable features engineered through the combinations of vector genome, donor-recipient, and gene insertion of synthetic, non-encodable elements.
- In silico predicted payload combinations are encoded in single gene minivectors, and tested in vivo and in vitro assays.

Figure 1: Gene Set Enrichment Analysis (GSEA) of RNAseq data from patients treated with ICI in the advanced setting compared to Alpha-201 infected patients. A. Normalized enrichment score (NES) for all statistically significant hallmark GSEA pathways from RNAseq data comparing ICI responder to non-responder patients reported by Real et al (8). B. Normalized enrichment scores (NES) for all statistically significant hallmark GSEA pathways from RNAseq data obtained from H677T cells infected with Alpha-201 encoding GFP (10 PFU/cell). C. Correlation analysis for all pathway ranks: Rank-NESS(\log 10 (p value)).

Figure 2: Validation of minivectors. A. H677T cells were infected with Alpha-201 vectors (3 or 10 PFU/cell), and then conditioned medium was collected every 2 days for quantification of payload production rates. B. Cell viability was measured with Real-time-Glo 6 days after infection. ANOVA with Tukey’s correction, *p < 0.05, **p < 0.01, ***p < 0.001.

Figure 3: TLS induction by programmable vector-mediated delivery of in silico predicted payload combinations

The ability of minivector combinations to induce TLS was tested in murine salivary glands, a tissue highly permissive to TLS formation. Alone, Alpha-201-GFP infection enhanced immune infiltration into infected glands (Fig 3). The delivery of a combination of minivectors, encoding in silico predicted payloads, was able to induce TLS that were organized in number, size, and organization as compared to control vector (Fig 4). Induced TLS also yield mature fibroblastic reticular cell networks and de novo expression of CCL21 (Fig 5).

Figure 4: TLS formation after treatment with Multiplex 1. A. Immunofluorescent images of salivary glands obtained 15 days after Alpha-201-GFP administration. B. Immunofluorescent images of salivary glands obtained 15 days after administration of Multiplex 1. Dendritic cells (CD11c, red), CD4+ T-cells (CD4, blue), B-cells (B220, green), and nuclei (DAPI, white) are visualized.

Figure 5: Mature fibroblastic reticular cell network and de novo CCL21 expression in TLS induced by Multiplex 1. A. Immunofluorescent images of salivary glands 15 days after administration of Multiplex 1. CCL21 (red) and fibroblastic reticular cell (FPR, green) are co-localized with CD4+ T-cells (CD4, blue). CCL21 (red) and fibroblastic reticular cell (FPR, green) are co-localized with B-cells (B220, green). Nuclei (DAPI, white), 40X magnification.

Conclusions
• Here we present data on two new experimental agents that induce TLS in a permissive tissue and have robust anti-tumor activity in a model of breast cancer through a combination of vector- and payload-dependent effects.
• Combination of Alpha-201 minivectors with anti-PD-1 therapy increased the number of long-term survivors.
• Together, these data demonstrate the ability of enLIGHTEN™ to design multimodal specific therapeutics resulting in the development of a first-in-class immunotherapeutic for TLS induction and anti-tumor activity in solid tumors.

Contact email: info@caneldxs.com

References: