

The "Smart" Cancer Drug: Targeting Cancer's Achilles Heel with Novel CRISPR/Cas9

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Development of cancer-specific drugs is critical to improve quality of life and survival of cancer patients. This integrative research demonstrates a novel concept to improve specificity of cancer treatments by targeting Warburg Effect using conditional, or cell type-specific, CRISPR/Cas9. Cancer cells heavily depend on glycolysis (Warburg Effect); thus, blocking glycolysis may preferentially kill cancer cells, sparing normal cells. Warburg Effect can be targeted by disrupting key glycolysis gene, ENO1, using state-of-the-art gene editing technology, CRISPR/Cas9. Therefore, knocking out ENO1 by CRISPR/Cas9 activated in a cancer-specific manner is hypothesized to selectively kill cancer cells. Here, HEK293 and A549 cells were used as a model system to determine if conditional CRISPR/Cas9-mediated inactivation of ENO1 leads to cell type-specific toxicity. Bioinformatics analysis revealed highly expressed genes in HEK293 or A549. Subsequently, promoters of those genes were used to create HEK293- and A549-specific CRISPR/Cas9 vectors designed to inactivate ENO1 in a cell type-specific manner. Indeed, MiSeq sequence analysis revealed that HEK293- and A549-specific CRISPR/Cas9 preferentially generated knockout mutations in ENO1. Furthermore, conditional CRISPR/Cas9 induced significant and selective toxicity in HEK293 and A549 as evidenced by MTS and trypan blue assays ($p < 0.05$). Significant reduction of ENO1 protein, lactic acid, and ATP production in a cell type-specific fashion were also observed, providing molecular insights into conditional CRISPR/Cas9-generated cell type-specific toxicity. Taken together, these data unequivocally demonstrate the power of the novel strategy of cancer-specific CRISPR/Cas9 to significantly increase the selectivity of cancer therapeutics.

Awards Won:

Intel ISEF Best of Category Award of \$5,000

First Award of \$5,000