We are thankful to both reviewers for thoughtful evaluation of the manuscript. Detailed below, we have addressed all concerns raised by the reviewers and we have added two new supplementary figures with robust data to address reviewer critiques.

**Review 1**

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>Can be improved</th>
<th>Must be improved</th>
<th>Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the introduction provide sufficient background and include all relevant references?</td>
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<td>Is the research design appropriate?</td>
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<td>Are the methods adequately described?</td>
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<td>Are the results clearly presented?</td>
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<td>Are the conclusions supported by the results?</td>
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</table>

**Reviewer 1:** Only one concentration of E64FC26 was used. Incubation time is not indicated. It will be important to see dose and incubation time course for E64FC26.

**Author Response:**

T cells are incubated in the presence of drug for 7 days during the peptide-mediated activation phase (3 days) and 4 more days of expansion in the presence of fresh drug. This is standard protocol for *in vitro* T cell expansion and we have clarified these details in the methods and Figure legends. We have included New Supplemental Figure 1 with % viability data from our initial 7 day activation and expansion experiments with E64FC26. T cells treated with 1uM of E64FC26 were not expanded after activation due to low cell yield and we have noted this in the New Supplemental Figure 1 legend.

**Reviewer 1:** Please quantify blots in Fig1E, 1J, 2C and 3A. In fig2C and 3A, it will be important to include a non-redox-responsive protein as a control.

**Author Response:**

We have included densitometry quantification normalized to tubulin or actin in the Figure Legends of Fig 1E, 1J, 2C and 3A. We have included Actin expression, a redox insensitive control protein in figs2C and 3A.

**Reviewer 1:** Fig.4B, it will be important to also examine the protein levels of these genes, as often gene and protein levels do not match.

**Author Response:**

We have included new western blotting data for Tcf7 and Hk2 protein expression in New Supplemental Figure 2. In the short time frame given for revisions we were unable to detect CPT1A by western blot; however, we probed phospho-Acetyl CoA Carboxylase as a surrogate for Cpt1a expression. p-ACC blocks restriction of CPT1A expression. P-ACC was increased in E64FC26-treated T cells (New Supplemental Figure 2).

**Reviewer 1:** Fig. 4E, all controls are used, but they are not clearly depicted the figure where particular inhibitors are added. It will also be interesting to look at the effect of E64FC26 on glycolysis, via measuring extracellular acid release using seahorse analyzer.

**Author Response:**

We have included injection markers and labels in Fig. 4E to indicate seahorse additions.
In New Supplemental Figure 2, we have added quantification of glycolytic capacity using Seahorse Bioanalysis in E64FC26 T cells.

**Reviewer 1:** Fig5, it will be important to compare the effect of E64FC26 with IL-15 priming.  
**Author Response:** Multiple publications have already established the phenomenon of IL-15 primed T cells to induce superior tumor control relative to IL-2 treated cells (PMID: 22206904, 30842774). Throughout the paper we use IL-15 primed T cells as a standard of memory-like T cells to show that inhibition of PDI using E64FC26 induces a memory-like T cell phenotype.  
This article was invited and prepared for a special issue focused on intraorganellar crosstalk and our finding that PDI inhibition in the endoplasmic reticulum shapes metabolism and tumor control in T cells is novel. Addition of IL-15-primed adoptive T cell therapy of tumors in Fig. 5 would detract from the central message of our paper. We have made sure to cite previous publications that establish the phenomenon of IL-15-primed memory-like T cells to improve T cell-mediated tumor control.

**Reviewer 1:** Minor concern: x-axis for Fig5B, "Days" is missing.  
**Author Response:** We have amended the figure label.