STK-012, a First-in-Class α/β IL-2 Receptor Biased Partial Agonist Enhances the Anti-Tumor Efficacy of Bispecific Antibodies

Inyoung Jung, Daniel Park, Deepti Rokkam, Somya Singh, Bhargavi Jayaraman, Deepti Chaturvedi, Marie Semana, Michele Bauer, Mohammed Ali, Patrick Lupardus, Martin Oft, and Paul-Joseph Aspuria

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ABSTRACT #682

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Background

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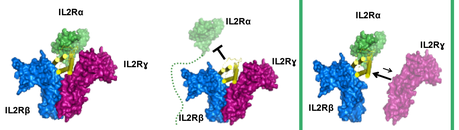
Interleukin-2 (IL-2) promotes the proliferation and effector function of T cells. High-dose IL-2 monotherapy can induce complete responses in cancer patients, but its clinical application is severely limited by acute vascular toxicities , notably capillary leak syndrome and severe hypotension via the systemic activation of lymphocytes and natural killer (NK) cells. IL-2 activates lymphocytes and NK cells through the intermediate-affinity dimeric IL-2 receptor (IL-2Rβγ, composed of CD122/CD132). In contrast, certain lymphocytes such as antigen-activated T-cells exhibit increased sensitivity to IL-2 due to their expression of the high-affinity trimeric IL-2 receptor (IL-2Rabg, composed of CD25/CD122/CD132). To avoid systemic lymphocyte and NK cell activation, but maintain anti-tumor efficacy, we have developed a novel pegylated, α/β-IL-2 agonist (STK-012) engineered for preferential binding to the IL-2Rαβγ receptor, which is highly upregulated on antigen-activated T-cells.

Methods and Results

We show that the murine surrogate of STK-012, mSTK-012, is effective in various syngeneic solid tumor models without inducing acute vascular toxicities. mSTK-012 led to enhanced expansion of tumor antigen-specific CD25⁺PD-1⁺CD8⁺ T cells both systemically and within the tumor microenvironment, resulting in complete responses and durable tumor immune memory with mSTK-012 monotherapy.

Furthermore, a mouse tumor model resistant to CD19 targeting TCEs was developed. We demonstrate that STK-012, in combination with an anti-CD3/CD19 TCE, rescued suboptimal TCE anti-tumor efficacy.

STK-012: Pegylated α/β-biased IL-2 partial agonist



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IL-2R Bias	Trimeric >> dimeric IL-2R	Dimeric IL-2 receptor	Trimeric IL-2 receptor
IL-2R Subunit Sparing	None	**Reduced binding IL-2Rα**	**Reduced binding to IL-2Rγ**
Cell Selectivity	Act T cells > Tregs > NK > resting lymphocytes	Act T cells = Tregs = NK = resting lymphocytes	Act T cells >> Tregs >>> NK cells and resting lymphocytes
	Deep, durable responses in certain patients but limited use given toxicity	*Avoids Tregs for enhanced anti-tumor function. Avoids eosinophils / endothelial cells?*	*Avoids NK cells (toxicity). Targets Activated T cells / Tregs*
Human molecules	**hIL-2/WT-hIL-2-PEG**	**Non-α-IL-2-PEG**	**STK-012 (α/β-hIL-2-PEG)**
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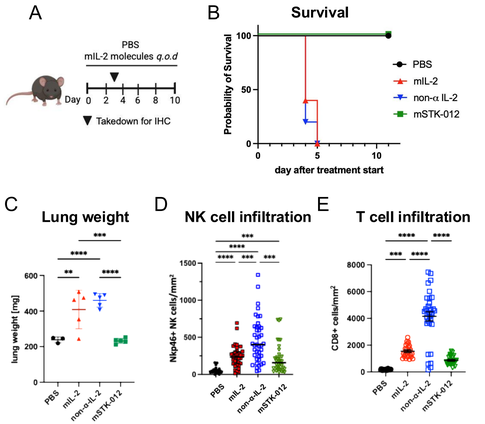

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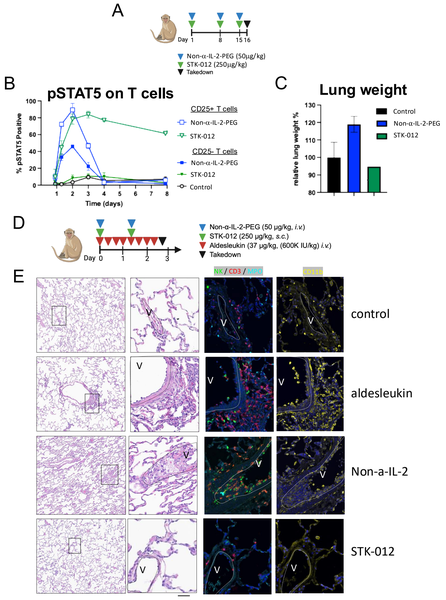

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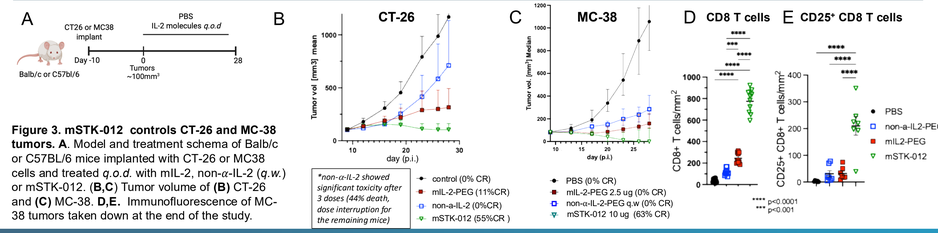

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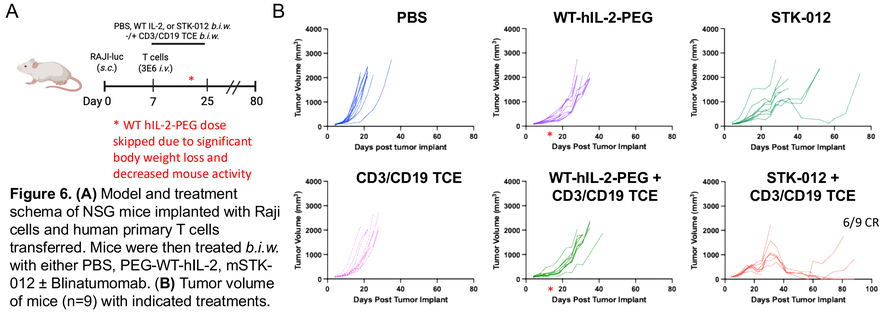

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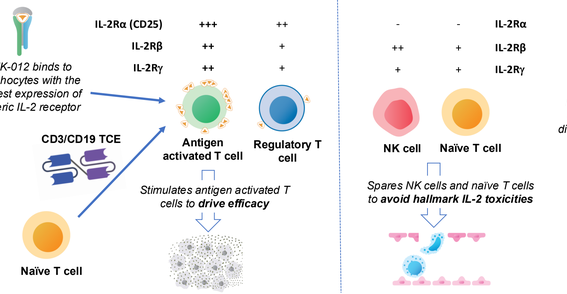
STK-012 + CD3/CD19 bispecific T cell engager mechanism of action



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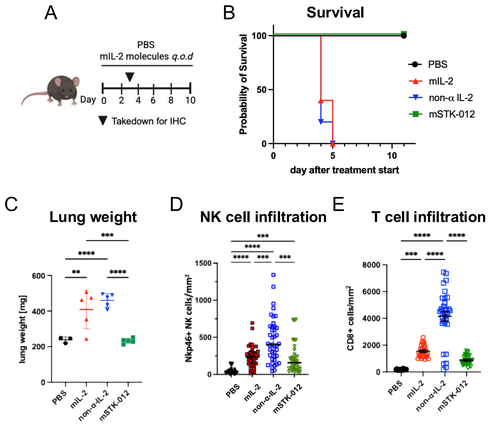

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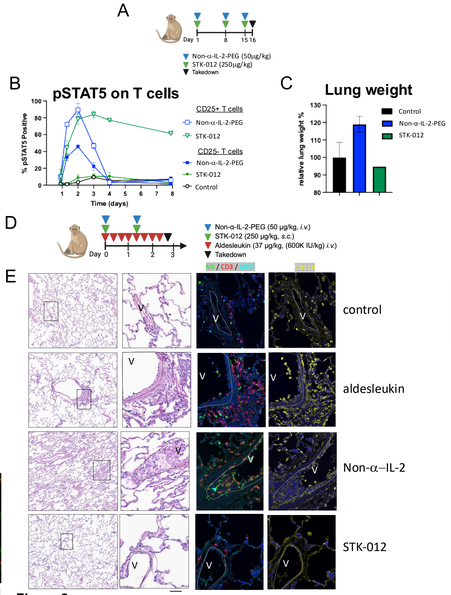

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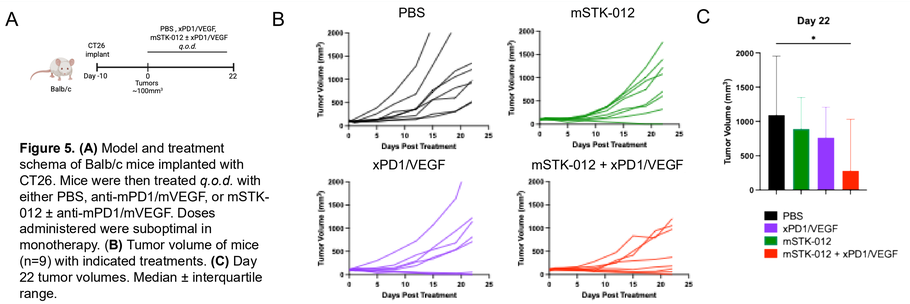

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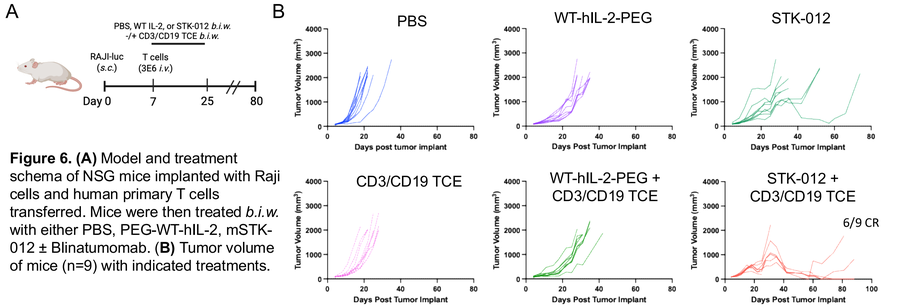

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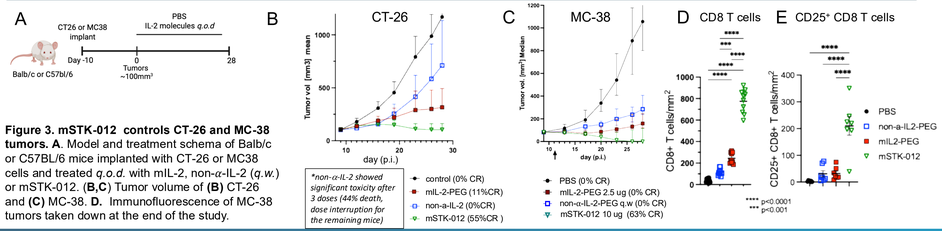

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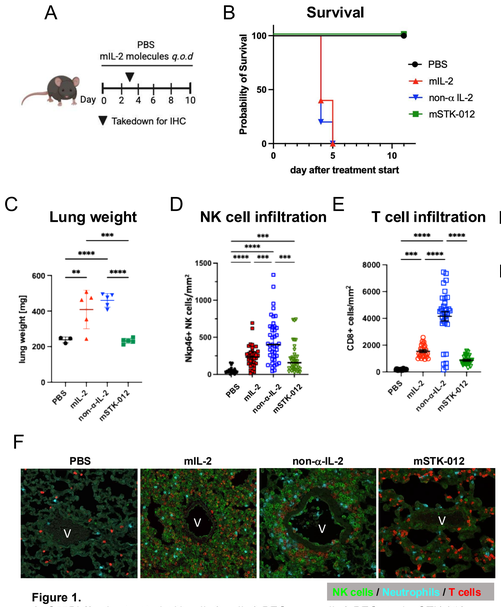

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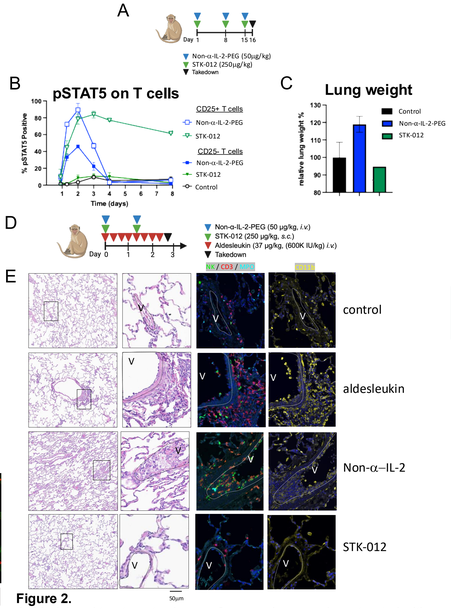

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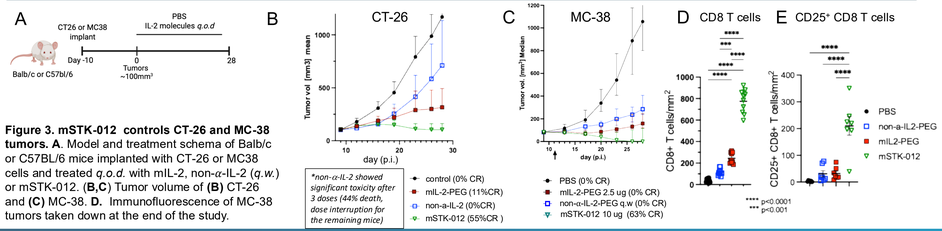

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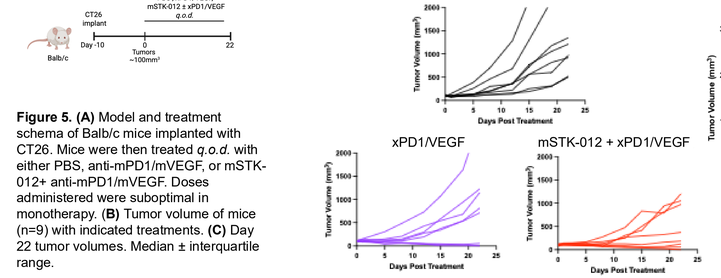

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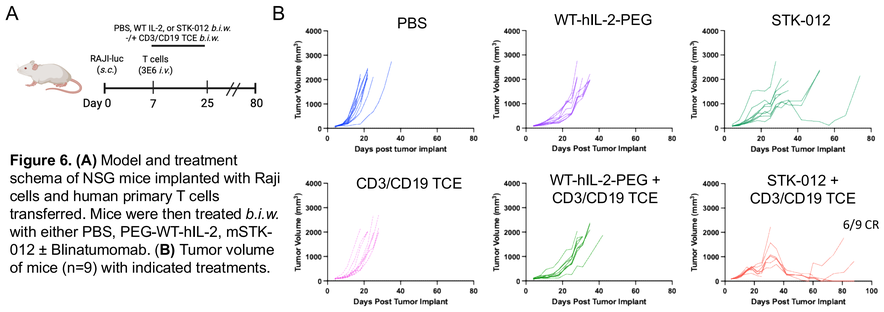

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Abstract #1345: Initial Phase 1a/1b Results of STK-012, an α/β IL-2 Receptor Biased Partial Agonist, with Pembrolizumab, Pemetrexed, and Carboplatin in 1L PD-L1 Negative Non-Squamous NSCLC