1097 MDK1654: A BRANCHED SYNTHETIC PEPTIDE THAT ACTIVATES BOTH THE IL-7 RECEPTOR AND THE βγC FORM OF THE IL-2/15 RECEPTOR

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Background Derivatives of IL-2, IL-15, and IL-7 are in clinical development as immuno-oncology agents. IL-2 and IL-15 stimulate proliferation and enhance the function of effector T cells and natural killer cells, whereas IL-7 acts on naïve and memory T cells and is crucial for persistent effector T cell generation. Combining these complementary effects on immune cells may offer benefits over either mechanism alone. We have previously described small synthetic peptidyl agonists (PEPTIKINES), unrelated to IL-2, IL-15, or IL-7, that selectively activate either IL-2/15Rβγc or IL-7Rαγc.

Methods Here we report the creation and pharmacology of a synthetic branched peptide, MDK1654, comprised of three peptide ligands binding to IL-7Rα, IL-2/15Rβ, and γc separately and linkers that are engineered to provide appropriate spatial orientation of the ligands. The *in vitro* pharmacology of MDK1654 was compared to non-alpha IL-2/15 or IL-7 mono-specific PEPTIKINES by signaling and immune cell proliferation.

Results MDK1654 can activate both IL-2/15Rβγc and IL-7Rαγc signaling pathways as measured by phosphorylation of STAT5 and showed full agonist activity for both receptors with EC50s <10 nM in naturally γc-expressing TF-1 cells engineered to overexpress either IL-2Rβ or IL-7Rα.

In *ex vivo* studies with PBMCs from 5 healthy donors, MDK1654 exhibited additive and complementary effects of IL-2/15Rβγc and IL-7Rαγc signaling among various lymphocyte subpopulations. The mono-specific non-alpha IL-2/15 and IL-7 PEPTIKINEs produced signaling patterns in lymphocyte subsets similar to those induced by IL-2v (a "non-alpha" mutant of IL-2) and IL-7, respectively. In the resting PBMCs, MDK1654 induced pSTAT5 and cell proliferation response profiles in CD8, CD4, and naïve and memory subpopulations similar to the IL-7 PEPTIKINE, including expansion of Tscm cells. In PBMCs activated with anti-CD3 antibody, a treatment known to increase IL-2/15Rβ expression, MDK1654 behaved similarly to the non-alpha IL-2/15 PEPTIKINE in most cell populations except for the Tscm population. NK cells were expanded by MDK1654 and the non-alpha IL-2/15 PEPTIKINE but not by the IL-7 PEPTIKINE.

Conclusions These data indicate that MDK1654 mimics the effect of the non-alpha binding form of IL-2/15 or IL-7, depending on the cell type. To our knowledge, this is the first demonstration of a synthetic peptide with agonist activity for two different cytokine receptors and offers an exciting new modality for cancer immunotherapy.

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