A Polymer-Associated Human IL-15 (NKTR-255) with Optimized Biological Activity and Unique Mechanisms of Action on CD8 T Cells and NK Cells

Tanya O Robinson¹, Shweta M Hegde¹, Achintyan Gangadharan¹, Takahiro Miyazaki² and Kimberly S Schluns¹

¹Department of Immunology, University of Texas MD Anderson Cancer Center, Houston, TX, USA,
²Nektar Therapeutics, San Francisco, CA, USA

Abstract
IL-15 has anti-tumor activity but with limited efficacy due to its unfavorable pharmacokinetic properties and tolerability. Nektar Therapeutics has developed a polymer-conjugated human IL-15 (NKTR-255) that exhibits a prolonged in vivo half-life and enhanced potency, which is currently being examined as a potential cancer immunotherapeutic agent. Since responses by IL-15 can be mediated by trans-presentation via the IL-15Ra, as soluble IL-15/IL-15Rα complexes, or by cis-presentation, we investigated the role of IL-15Ra in driving NKTR-255 responses by naïve and memory CD8 T cells and NK cells in mice. The effects of NKTR-255 were examined by the adoptive transfer of CFSE-labeled naïve ovalbumin-specific CD8 T cells (OT-I) or established memory OT-I T cells followed by systemic administration of NKTR-255. To assess responses by central and effector memory T cell subsets, sorted CD44hi memory phenotype CD8 T cells were transferred in wild-type (WT) recipients followed by NKTR-255 treatment. Additionally, NK cell responses to NKTR-255 were analyzed in IL-15Ra bone marrow (BM) chimeras by BrdU incorporation. Naïve CD8 OT-I T cells transferred into WT and IL-15Ra-/- mice proliferated at similar levels and acquired a central memory phenotype in response to NKTR-255. Interestingly, naïve IL-15Ra-/- OT-I T cells had a deficient response to NKTR-255 but not to rIL-15 or soluble IL-15 complexes. Additionally, proliferation by memory IL-15Ra-/- OT-I T cells in response to NKTR-255 was partially impaired compared to WT OT-I cells. Sorted memory CD8 T cells maintained their proportion of CD62Lhi and -subsets after NKTR-255-stimulated proliferation. Since IL-15Ra expression is essential for NK cell development, BM chimeras were generated with either IL-15Ra-/- or WT BM in WT recipients. In this model system, similar levels of BrdU were incorporated into IL-15Ra-/- and WT NK cells after treatment with NKTR-255. These findings suggest naïve CD8 T cells are critically dependent on cis-presentation of NKTR-255, while memory CD8 T cells are only partially dependent. For both naïve or memory CD8 T cells, trans-presentation of NKTR-255 was not required. In contrast to CD8 T cells, NK cell responses to NKTR-255 are not dependent on cis-presentation. Overall, these findings highlight the potential of polymerized IL-15 to modulate IL-15Ra dependency leading to different mechanisms of action on CD8 T cells and NK cells and unique therapeutic effects.

Background
Endogenous IL-15 Expression and Mechanisms of Action

IL-15 stimulates the proliferation and cytotoxic functions of CD8 T cells and NK cells leading to enhanced anti-tumor responses [1,2,3].

Endogenous IL-15 responses by lymphocytes do not require self expression of IL-15Ra but rather require trans-presentation [1,4,5].

The efficacy of rIL-15 as a cancer immunotherapeutic agent has been limited due to its short in vivo half-life [6]. Nektar Therapeutics has developed a polymer-associated human IL-15 (NKTR-255) that exhibits a sustained pharmacodynamics and enhanced in vivo responses.

NKTR-255 binds both mouse and human IL-15Ra.

Objective
Investigate the role of IL-15Ra in driving NKTR-255 responses by naïve and memory CD8 T cells and NK cells in mice.

References
6) Robinson, T. and Schluns, K. 2017. Immunology Letters. 190:159-168