Regulation of Mast Cell Activity by KTN0158, a Humanized anti-KIT Monoclonal Antibody

Introduction

- KTN0158 is a humanized immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) that specifically binds KIT (c-KIT; mast/stem cell factor growth factor; CD117).
- Mast cells have been implicated in a variety of allergic and inflammatory diseases such as asthma and rheumatoid arthritis as well as fibrosis (Metcalfe et al., 1997).
- Mast cell infiltrates are associated with tumors and may have roles in tumor promotion or rejection depending on the setting (Theoharides and Conti, 2004).
- KIT signaling in mast cells appears to play an important role in the development of plexiform neurofibromas in neurofibromatosis type 1 (NF1; Staser et al., 2012).



KTN0158 blocks KIT dimerization and partially blocks SCF binding

Effects of Imatinib on a Highly Morbid Neurofibroma in a Pediatric Patient





After 3 months on Imatinik Yang et al., Cell 135:437-448.

Inhibition of KIT may provide benefit in treatment of plexiform neurofibromas



Analysis of KIT Phosphorylation by ELISA

Chinese Hamster Ovary (CHO) cells expressing wild-type human KIT were starved, pre-treated for two hours with KTN0158 or precursor antibodies to KTN0158 and stimulated for 10 minutes with SCF ligand. KIT phosphorylation was measured by ELISA using a capture antibody to total KIT and an anti-phospho-tyrosine capture antibody.

Analysis of Degranulation and Cytokine Production in LAD2 Cells

LAD2 cells were incubated with biotinylated human myeloma IgE overnight. Cells were pretreated with KTN0158 or control IgG1 followed by addition of SCF and then streptavidin to crosslink IgE. Percent β-hexosaminidase release was determined by measurement of βhexosaminidase in the media compared to the total β hexosaminidase in the media and lysed cells. TNF α and GM-CSF release was measured in supernatants using multiplexed capture immunoassays with detection by ECL (Meso Scale Discovery, Gaithersburg, MD).

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Results



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