MERTK-Specific Antibodies That Have Therapeutic Antitumor Activity in Mice Disrupt the Integrity of the Retinal Pigmented Epithelium in Cytopathic Monolysosome

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Background

- MERTK, a receptor for the FGF (TGF alpha, HGF, ANGPT2) family of ligands, is an emerging cancer therapeutic target in cancers driven by RTK signaling.
- MERTK activation in human tumors is associated with poor survival.
- MERTK blocks retinal pigment epithelium (RPE) injury in vivo.
- MERTK inhibition provides antitumor activity in preclinical syngeneic models.

Antibody Binding and Inhibition

Antibody Binding and Inhibition

- In vitro, MERTK blocking antibodies:
  - Showed efficacy in syngeneic murine tumor models as monotherapies and in combination with anti-PD-L1.
  - Led to gene expression changes indicative of immune cell activation and monocyte infiltration.

MERTK Blockade and the Risk of Retinal Toxicity

- MERTK Cys Retinal Toxicity Study Findings:
  - Moderate elevation of MERTK levels leads to apoptosis in RPE cells and lens fiber.
  - Inhibition of MERTK using a small molecule inhibitor leads to changes in expression of the MERTK target genes.
  - The study revealed that the antibodies blocked expression of MERTK targets in RPE.
- Key Drug: SRF1, a selective MERTK antibody, led to toxicity in the retina.

Conclusions

- A panel of fully human MERTK blocking antibodies was developed.
- In vivo, MERTK blocking antibodies:
  - Inhibited GAS6/Axl tyrosine kinases phosphorylation and COX-2 upregulation in Kausen-2 cells.
  - Reduced primary human melanoma cell/macrophage effecotricy of apoptotic Jurkat cells.
- In vivo toxicity:
  - No evidence of retinal toxicity was observed.
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- A multidose study in cynomolgus monkeys revealed that MERTK therapeutic antibodies disrupted the integrity of the RPE.
- Because of observed treatment-related retinal disruption, further development of therapeutic MERTK antibodies was not pursued.
- Several therapies that block MERTK function are currently in preclinical development, although the evaluation of retinal toxicity is warranted.