Elotuzumab has demonstrated clinical activity in relapsed/refractory MM and is currently in clinical trials as monotherapy or in combination with therapies such as lenalidomide and dexamethasone. It binds to the CS1 ligand on myeloma cells, triggering a signaling cascade that leads to the activation of NK cells and the induction of tumor cell apoptosis. Elotuzumab has been shown to enhance the activity of other therapies such as lenalidomide and dexamethasone, and in combination with lirilumab, a monoclonal antibody targeting the KIR2DL3 receptor, has shown promising results in preclinical studies.

**Methods**

- **Antibodies and recombinant proteins:** Humanized anti-human CS1 mAb, elotuzumab, and human anti-CD137 mAb, anti-CD137 (AeroCell, Bedminster, NJ), recombinant human IL-21 (Peprotech, Rocky Hill, NJ), recombinant human tumor necrosis factor (TNF) α (R&D Systems, Minneapolis, MN), recombinant human IFN-γ (R&D Systems), recombinant human IL-2 (Peprotech), recombinant human IL-12 (Peprotech), recombinant human IL-15 (Peprotech), recombinant human IL-18 (Peprotech), recombinant human GM-CSF (Peprotech), recombinant human TNF-α (R&D Systems), recombinant human IL-1β (Peprotech), recombinant human IL-6 (Peprotech), recombinant human IL-10 (Peprotech), recombinant human TNF-β (Peprotech), recombinant human IFN-β (R&D Systems), recombinant human IFN-γ (R&D Systems), recombinant human IL-12 (Peprotech), recombinant human IL-15 (Peprotech), recombinant human TNF-α (R&D Systems), recombinant human IL-1β (Peprotech), recombinant human IL-6 (Peprotech), recombinant human TNF-β (Peprotech), recombinant human IFN-β (R&D Systems), recombinant human IL-13 (Peprotech), recombinant human IL-18 (Peprotech), recombinant human TNF-α (R&D Systems), recombinant human IFN-β (R&D Systems), recombinant human GM-CSF (Peprotech), recombinant human IL-2 (Peprotech), recombinant human IL-12 (Peprotech), recombinant human IL-15 (Peprotech), recombinant human TNF-α (R&D Systems), recombinant human IFN-β (R&D Systems), and recombinant human IL-10 (Peprotech).

- **In vitro studies:** Cytotoxicity assays were performed in 96-well plates using the trypan blue dye exclusion method. The cytotoxicity of NK cells was measured by fluorescence-activated cell sorting analysis of CD107a expression.

- **In vivo studies:** Male severe combined immunodeficient SCID mice were inoculated subcutaneously with OPM-2 myeloma cells and treated with either elotuzumab or control antibody (lirilumab) alone or in combination with other therapeutic agents. Tumor growth was measured by Fowler Electronic Digital Caliper, and tumor volume was calculated using the formula: volume = length × width/2.

**Results**

- **IL-21 increases elotuzumab-mediated NK cell activation in vitro:** In mice with established OPM-2 xenograft tumors, elotuzumab activity was augmented when combined with IL-21 treatment, resulting in increased CD56+CD3– NK cell numbers and tumor cell apoptosis.

- **CD137 agonism increases elotuzumab activity in vitro:** In vitro co-culture experiments showed that elotuzumab-induced ADCC was enhanced by CD137 agonism, resulting in increased NK cell degranulation and tumor cell apoptosis.

- **CD137 agonism enhances elotuzumab activity in vivo:** In mice with established OPM-2 xenograft tumors, elotuzumab activity was augmented when combined with CD137 agonism, resulting in increased CD56+CD3– NK cell numbers and tumor cell apoptosis.

**Conclusions**

- **IL-21 increases elotuzumab-mediated NK cell activation and synergizes with other therapies:** IL-21 treatment enhances elotuzumab activity in vitro and in vivo, suggesting a synergistic effect.

- **CD137 agonism enhances elotuzumab activity in vivo:** CD137 agonism augments elotuzumab activity in vivo, potentially improving therapeutic outcomes.

**References**


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**Disclosures**

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