



Bristol-Myers Squibb



Elotuzumab (HuLuc63) Activates CD56^{dim} Natural Killer Cells and Monocytes Resulting in Secretion of IP-10 and MCP-1 Chemokines

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Elotuzumab (HuLuc63)

- A humanized monoclonal IgG1 antibody directed to human CS1 (CD2-subset 1, CRACC, SLAMF7, CD319)
- CS1
 - ◆ Highly expressed on multiple myeloma cells and normal plasma cells
 - ◆ Expressed at lower levels on NK and CD8+ T cells
- Mediates its effects via ADCC
- Eliminates or reduces xenograft tumors in MM mouse models *in vivo*
- Currently, elotuzumab is in clinical trials in relapsed MM subjects

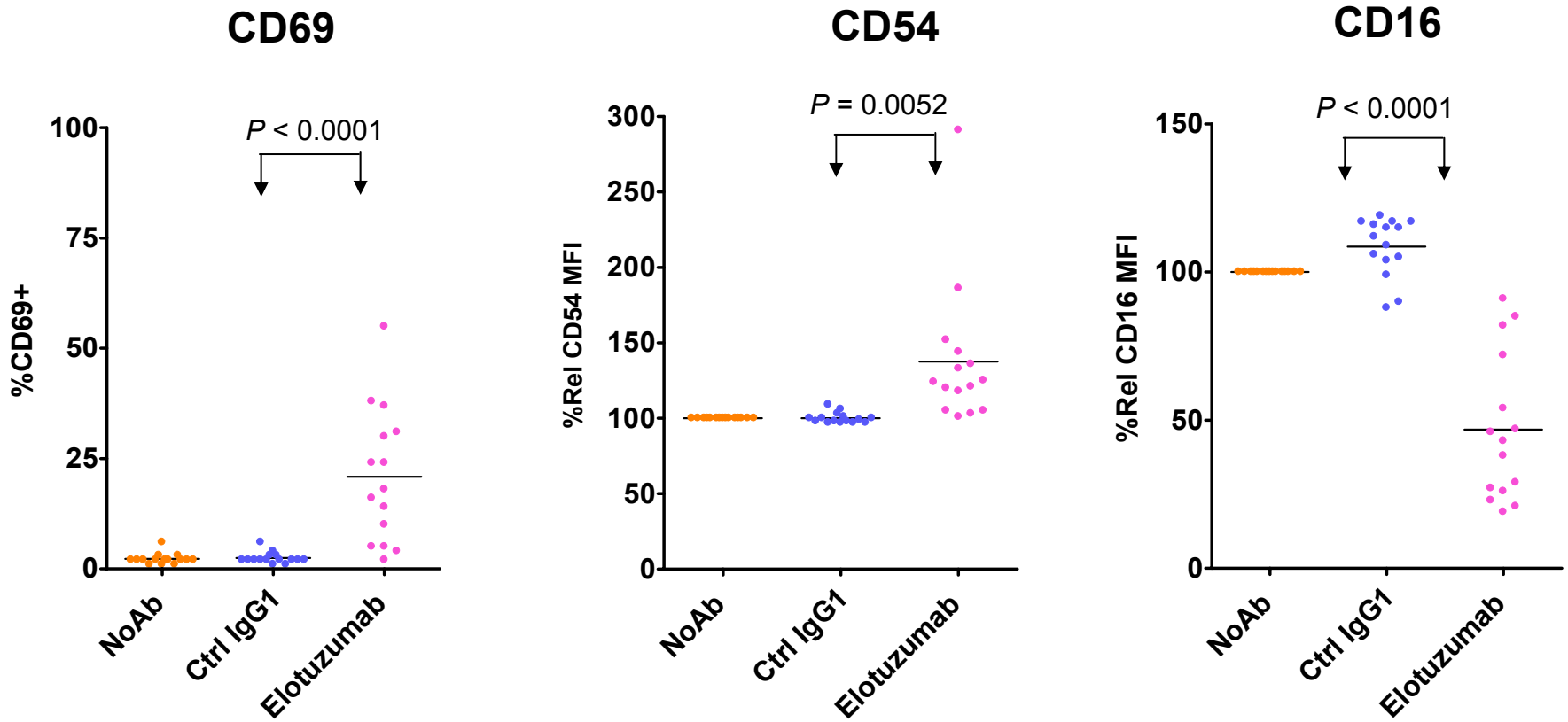


Objectives

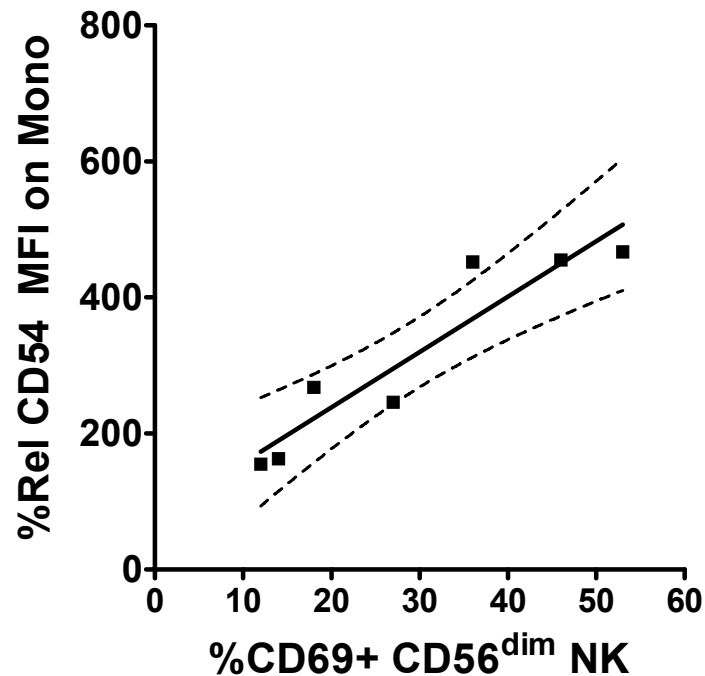
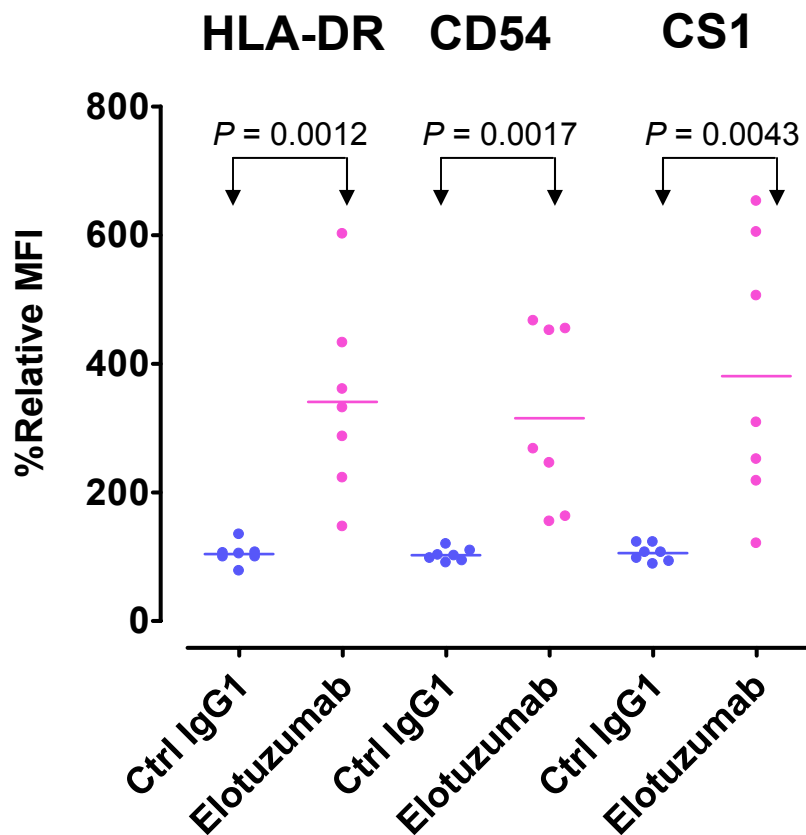
- Identify potential pharmacodynamic (PD) markers for elotuzumab activity
 - ◆ Evaluate elotuzumab effects on activation of immune subsets
 - ◆ Assess on cytokines/chemokine release *in vitro*
- Examine elotuzumab effects on NK function
 - ◆ ADCC activity of elotuzumab pre-exposed NK cells against OPM-2 tumor cells



Elotuzumab activates CD56^{dim} NK cells (ADCC inducing) in whole blood cultures

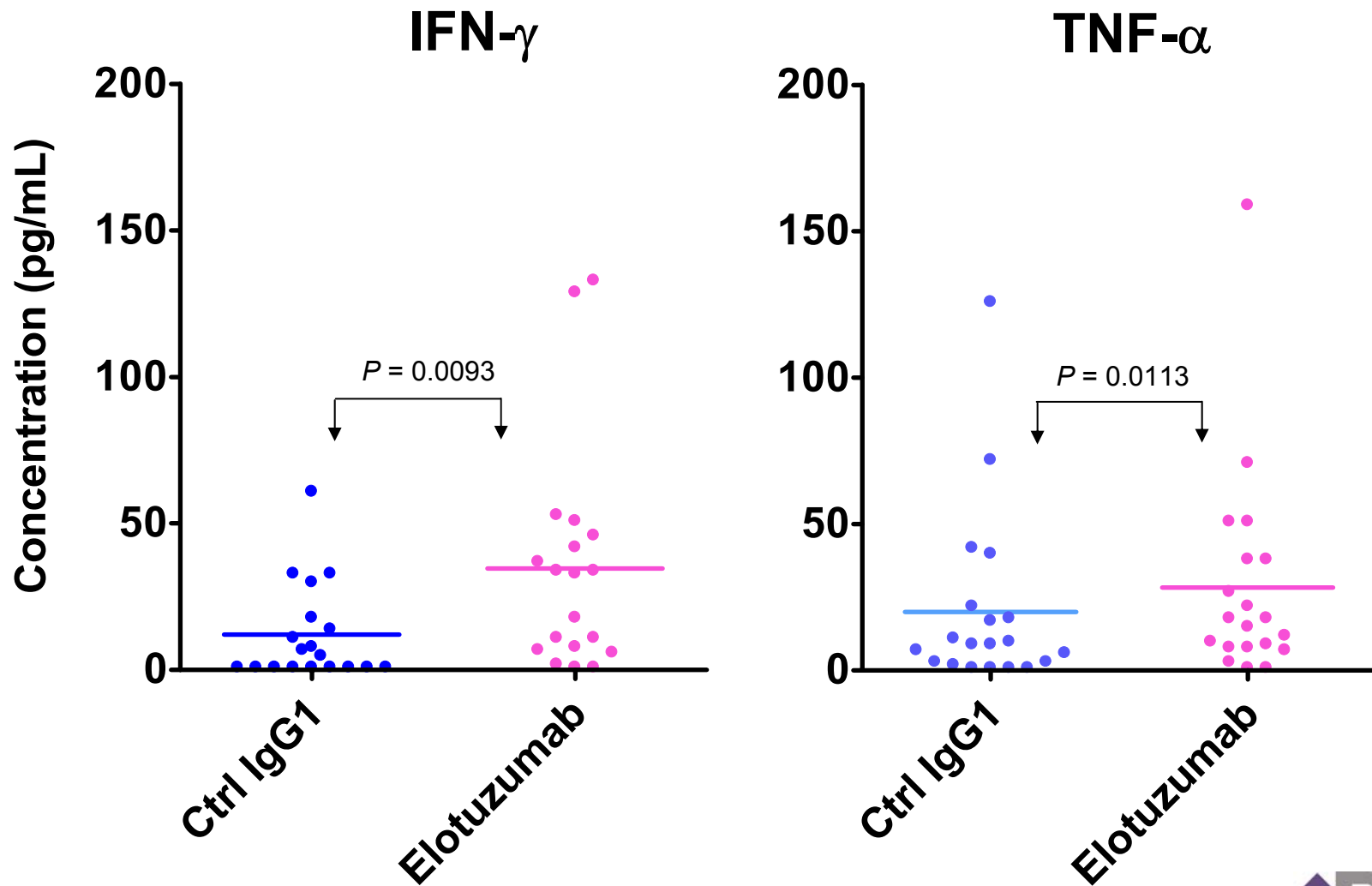


Elotuzumab treatment of WB cultures results in activation of monocytes

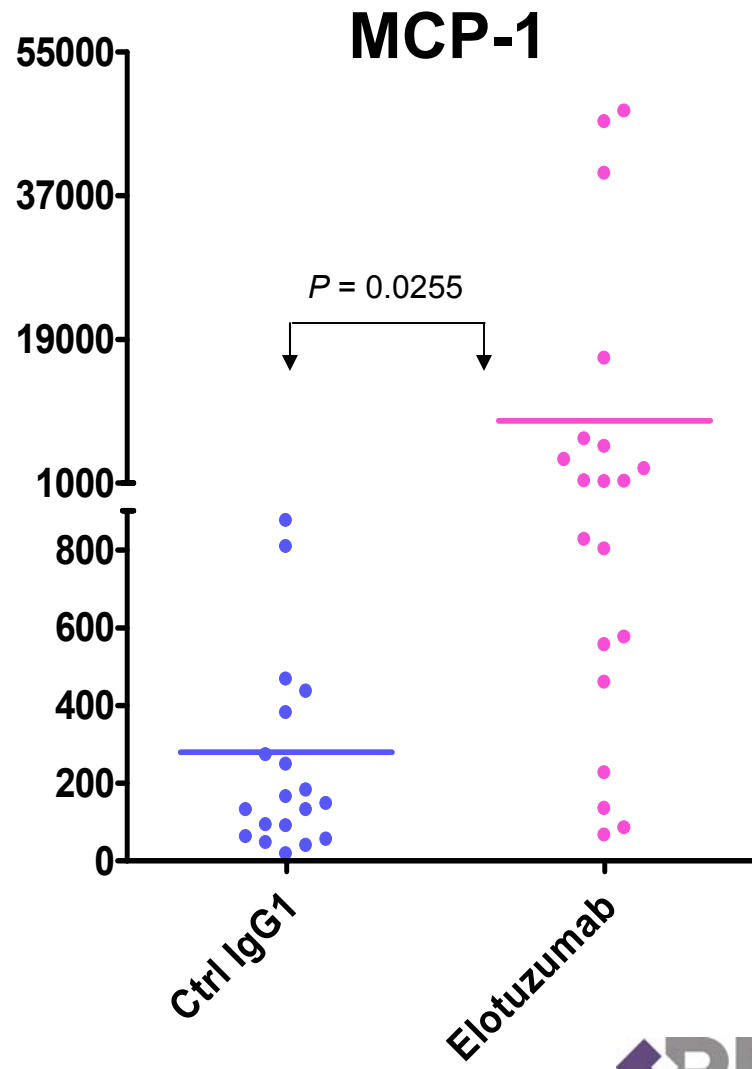
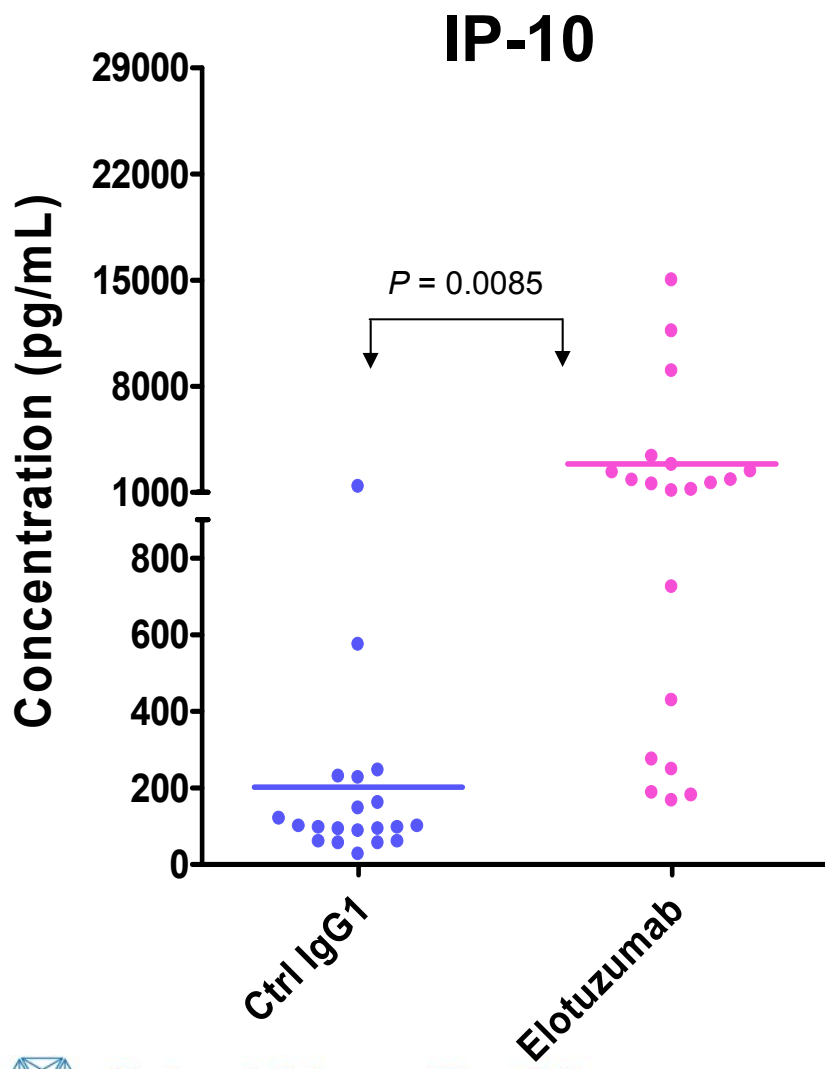


Statistics
 Pearson r = 0.9376
 R squared = 0.8791
 p value = 0.0018

Elotuzumab induces low levels of IFN- γ and TNF- α in whole blood cultures

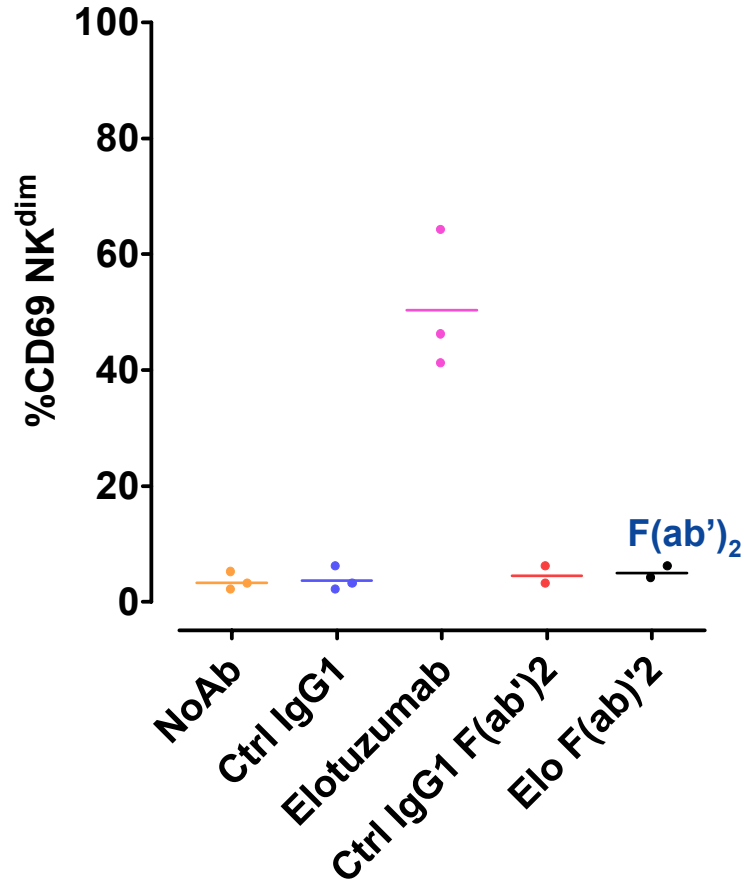


Elotuzumab induces high levels of IP-10 and MCP-1 in whole blood cultures

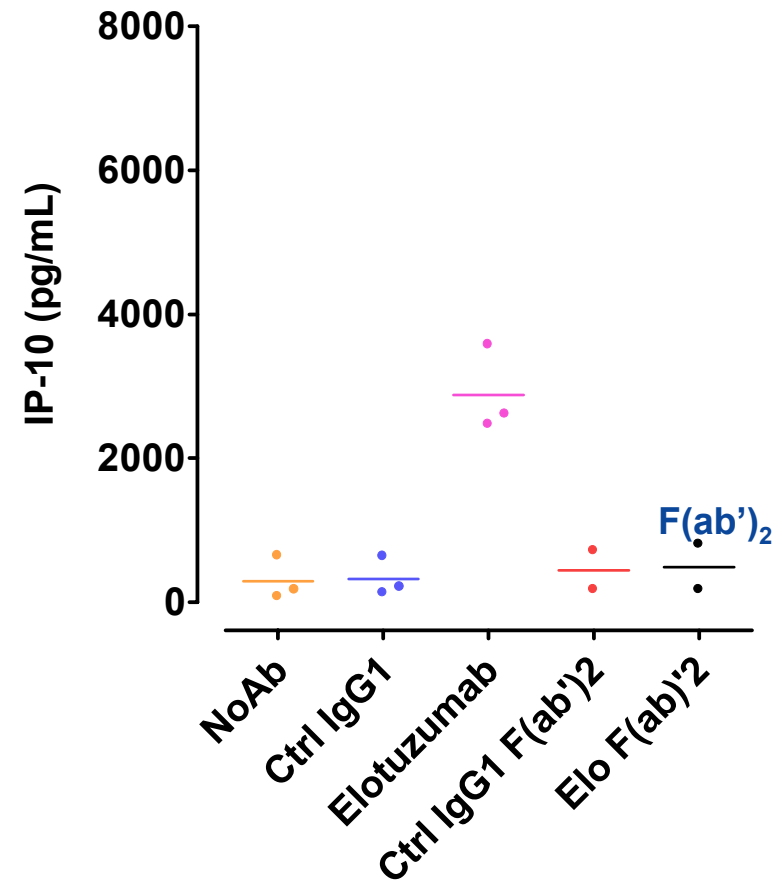


The Fc portion of elotuzumab is required for NK activation and chemokine release

CD69



IP-10



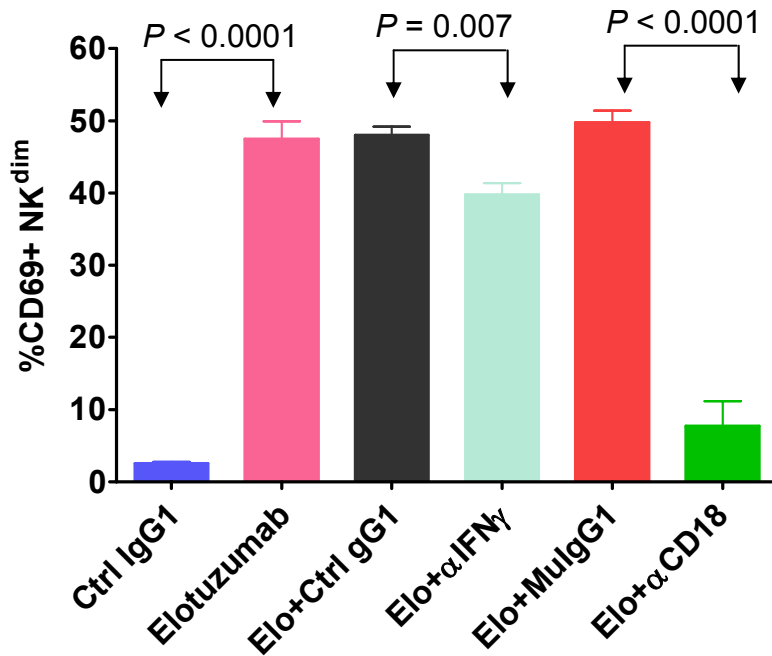
Monocytes but not NK cells secrete IP-10 and MCP-1 chemokines in elotuzumab treated cultures

	IFN- γ	TNF- α	MCP-1	IP-10
Whole Blood	+	+	+++	++++
PBMC	+	+	+++	++++
PBMC-CD3 T	+	+	+++	++++
PBMC-Monocytes	+	+	-	-
Purified NK	+	+	-	-



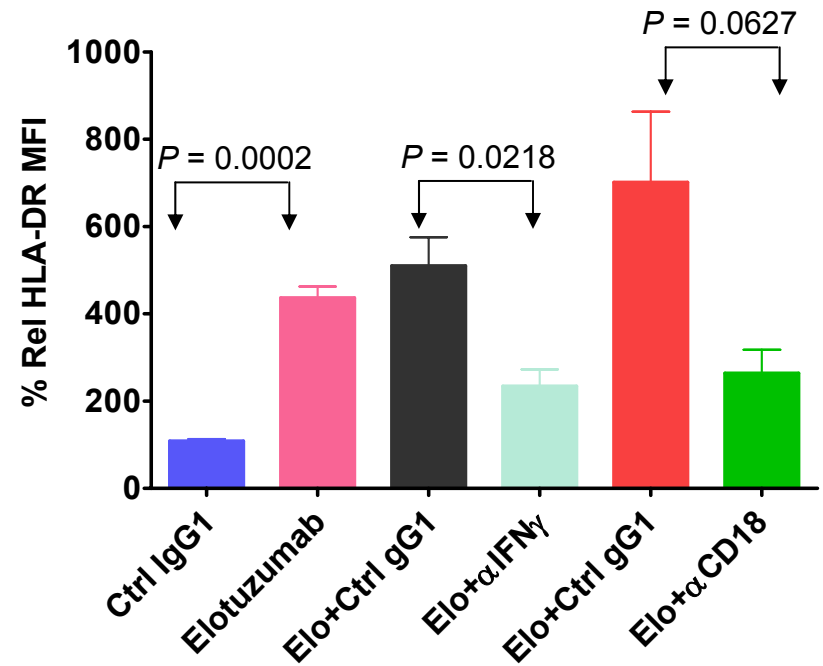
Cellular interactions and IFN- γ play a role in elotuzumab-induced activation

CD56^{dim} NK



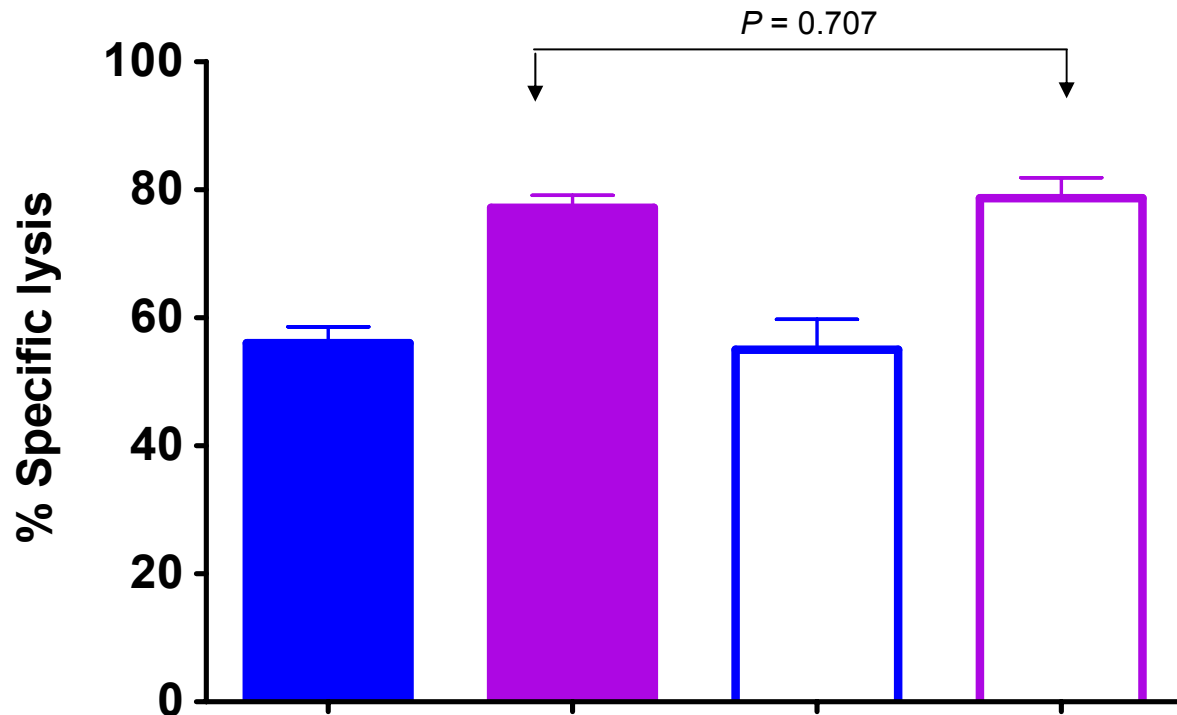
(n = 4)

Monocytes



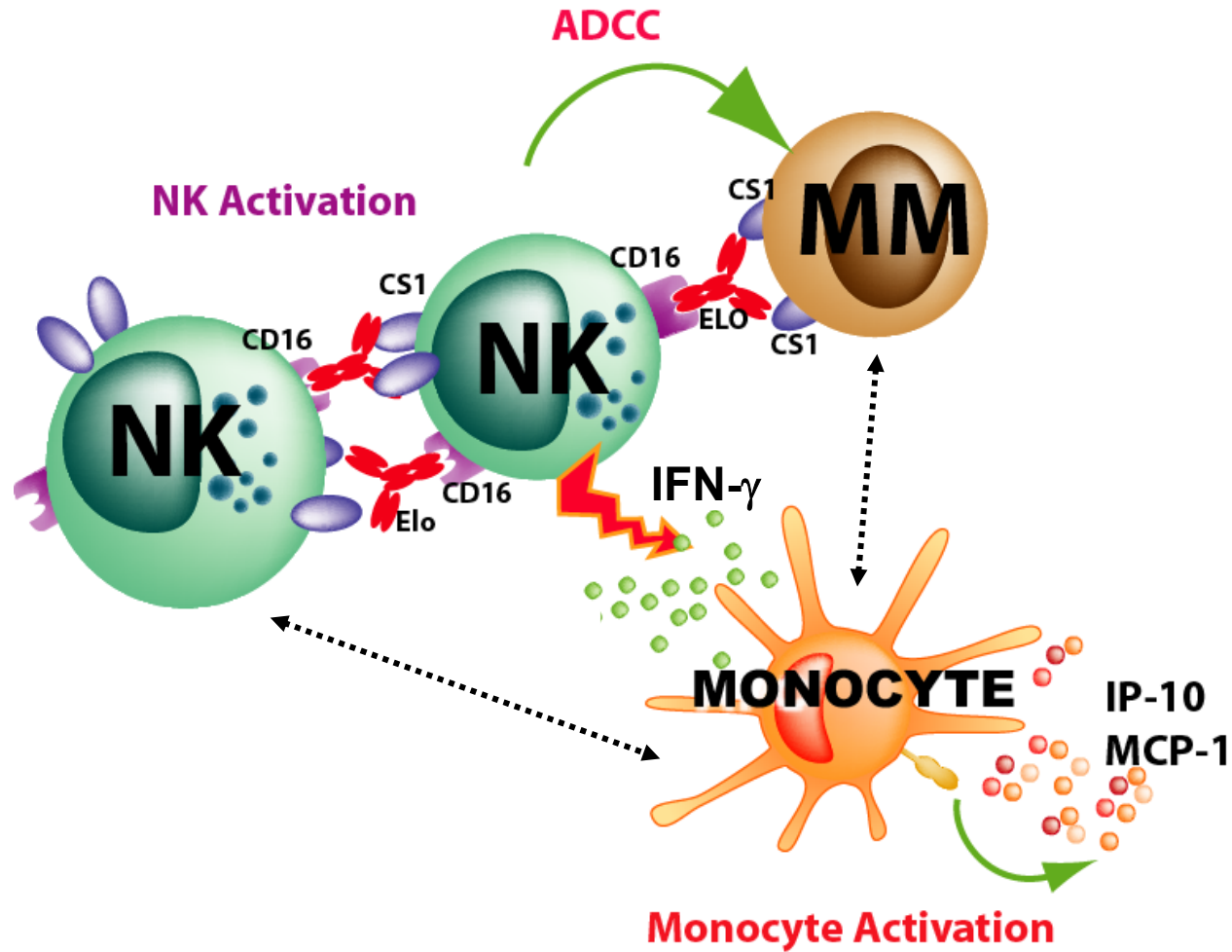
(n = 3)

NK cells pre-exposed to elotuzumab remain fully competent to mediate ADCC



NK cells Pre-exposed: Ctrl IgG1 Ctrl IgG1 Elo Elo
OPM-2 incubated with: Ctrl IgG1 Elo Ctrl IgG1 Elo

Elotuzumab: Mechanism of action



Summary

- Elotuzumab, via bridging CS1 and CD16, directly induces NK cell activation and indirectly monocyte activation
- Subsequently induces secretion of cytokines/chemokines
- Elo pre-exposed NK cells are fully competent to mediate ADCC
- NK activation markers, cytokines/chemokines and ADCC will be followed during the elotuzumab clinical trials

