Glycopolymer Binding to SIGNR1, A Mouse Orthologue of Human DC-SIGN

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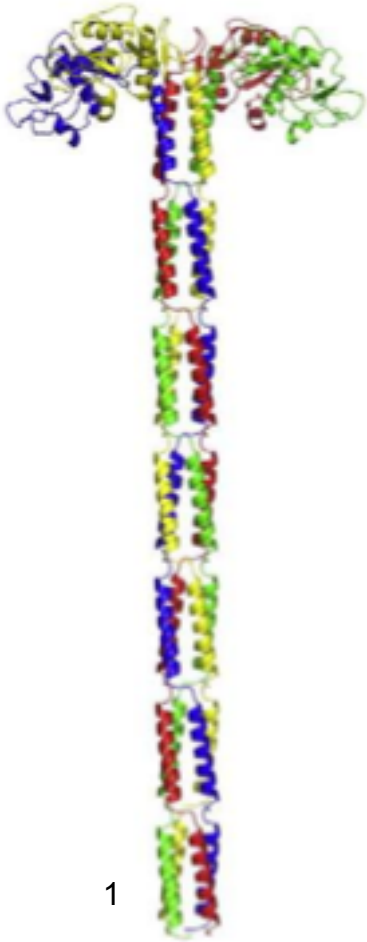
DC-SIGN

- Membrane protein found in dendritic cells and some types of macrophages.
- Receptor cells of this type traditionally bind to pathogens and present them to T-cells for destruction.
- DC-SIGN binds to HIV and presents that to T-cells, but instead of being digested the HIV infects the T-cell.



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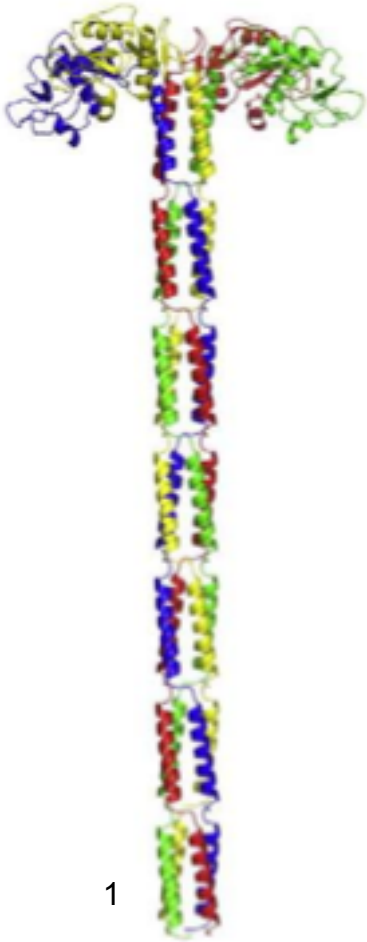
1. H. Feinberg *et al*., J. Mol. Biol., **394**, 613–620 (2009)

DC-SIGN

- C-type lectin; binds to mannose rich pathogens.
- GP120 in HIV envelope has mannose groups.
- Aim to design prophylactic treatment that binds to the carbohydrate recognition domain (CRD) and prevents GP120 from binding.
- One possible solution is glycopolymers.



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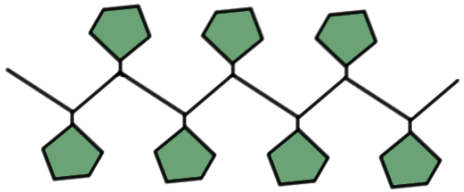
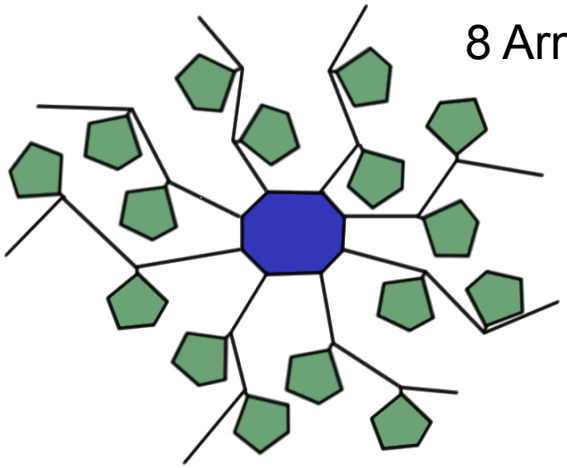
Glycopolymers

- Polymer chain with sugar groups attached.
- Used 3 different shape polymers each bound with multiple mannose groups.

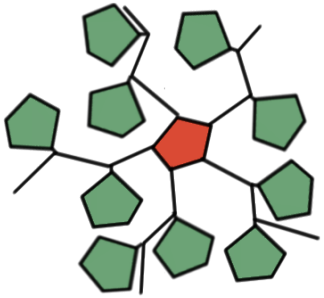
Straight Chain (DP60)



8 Arm



5 Arm

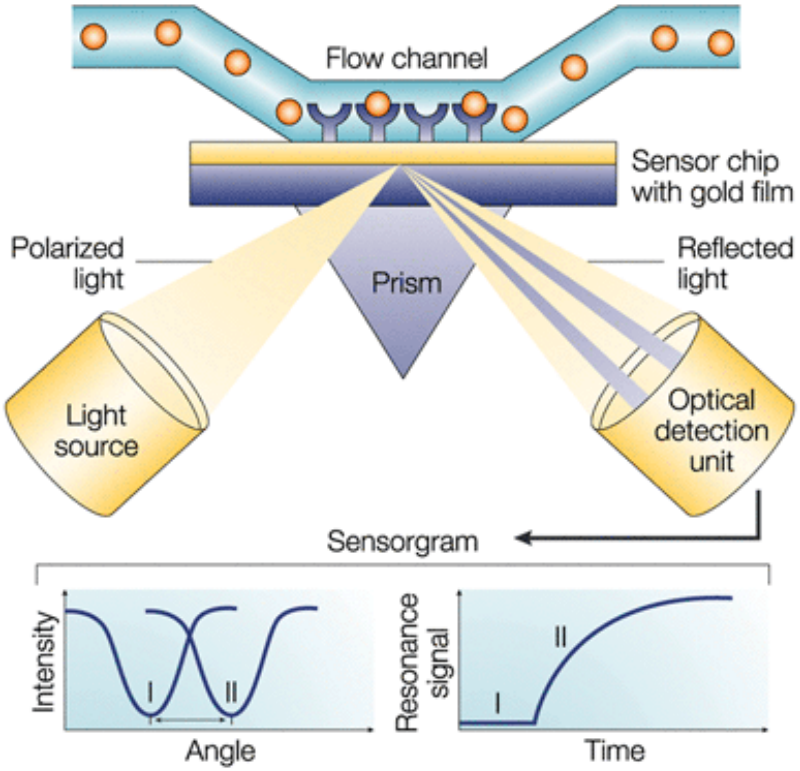


Why Use SIGNR1?

- Mouse orthologue of DC-SIGN.
- Test to see if experiments on mice would be relevant to research for human treatment.
- Would allow research without using human tissue; much easier to carry out.
- Need to test to see if binding of glycopolymers is comparable both in-vitro and in-vivo.

Surface Plasmon Resonance

- Method of detecting binding to a thin gold surface as refractive index changes.



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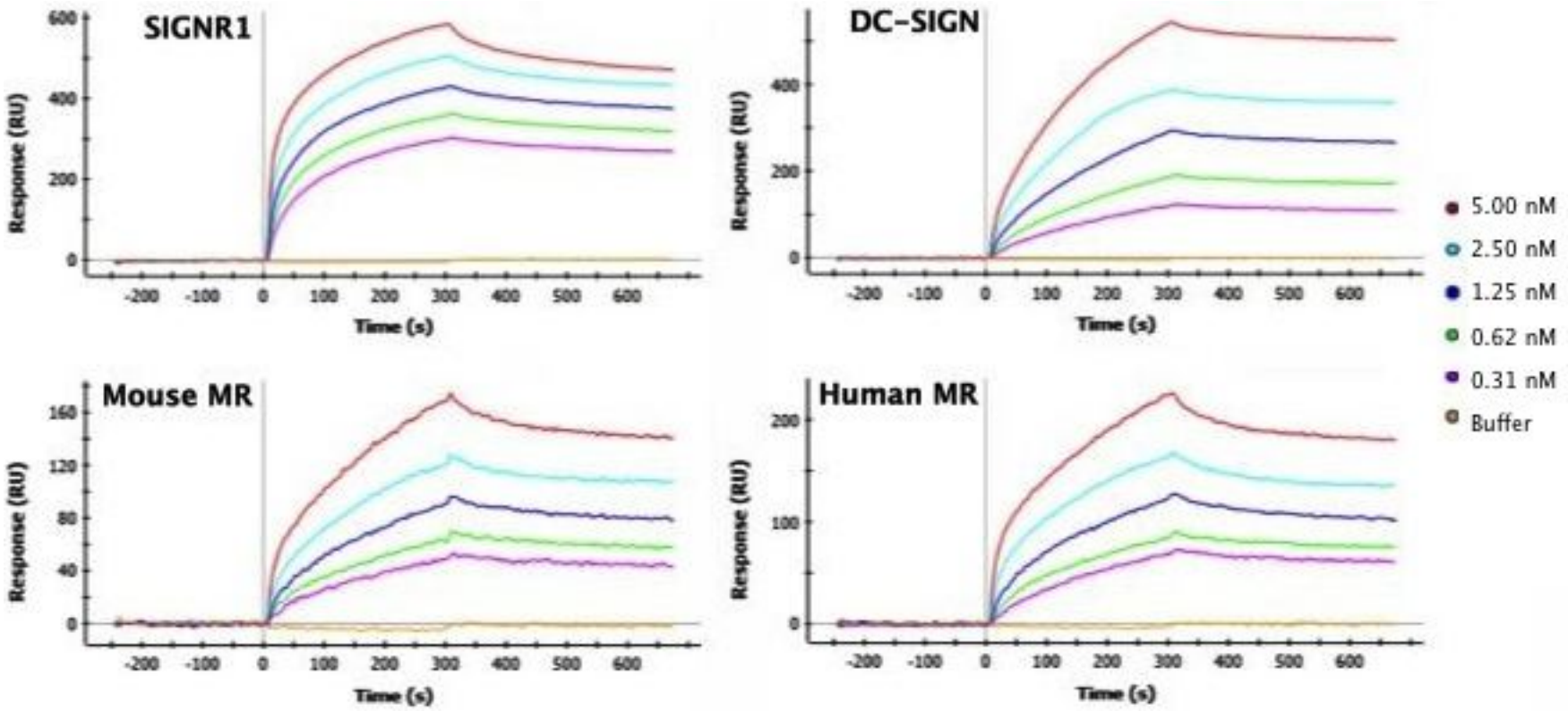
2. M. Cooper, Nature Reviews Drug Discovery **1**, 515-528 (2002)

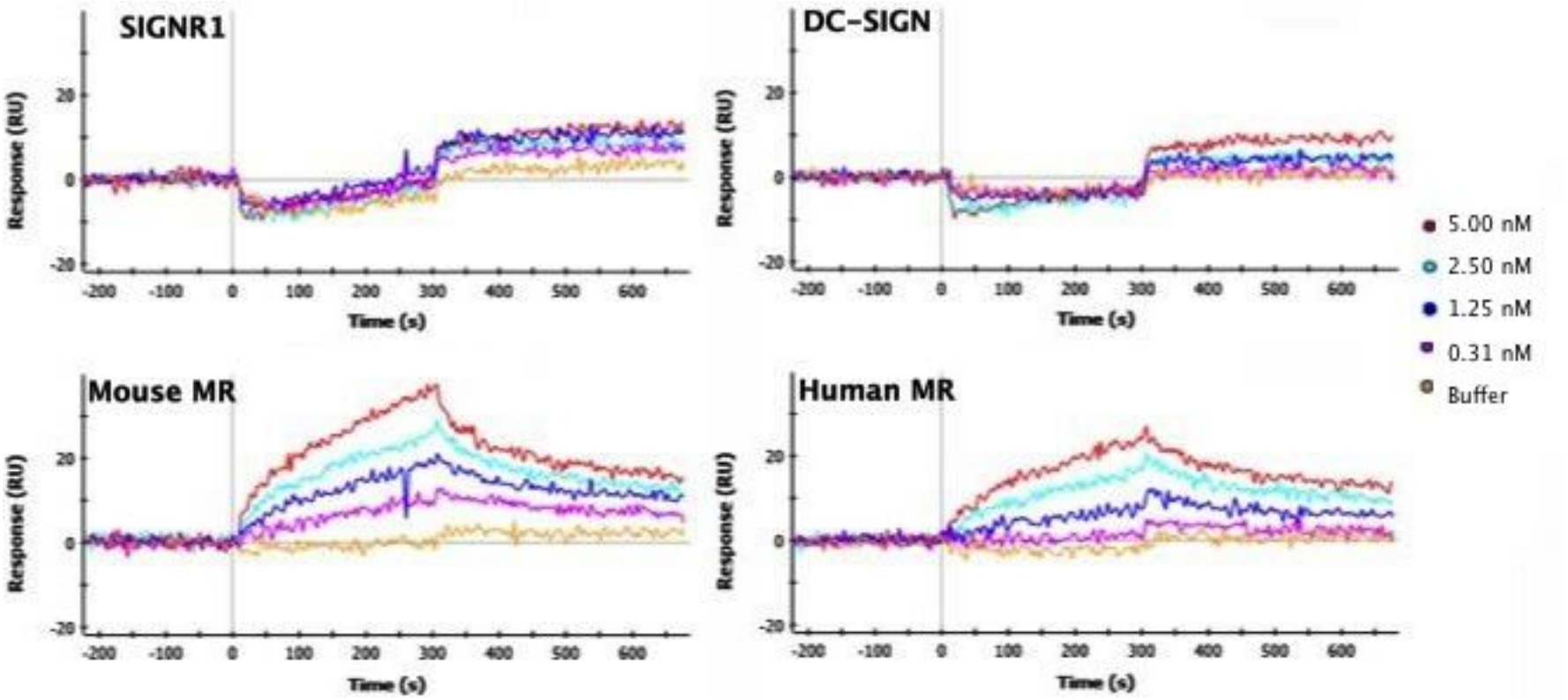
Results

- MAN DP60



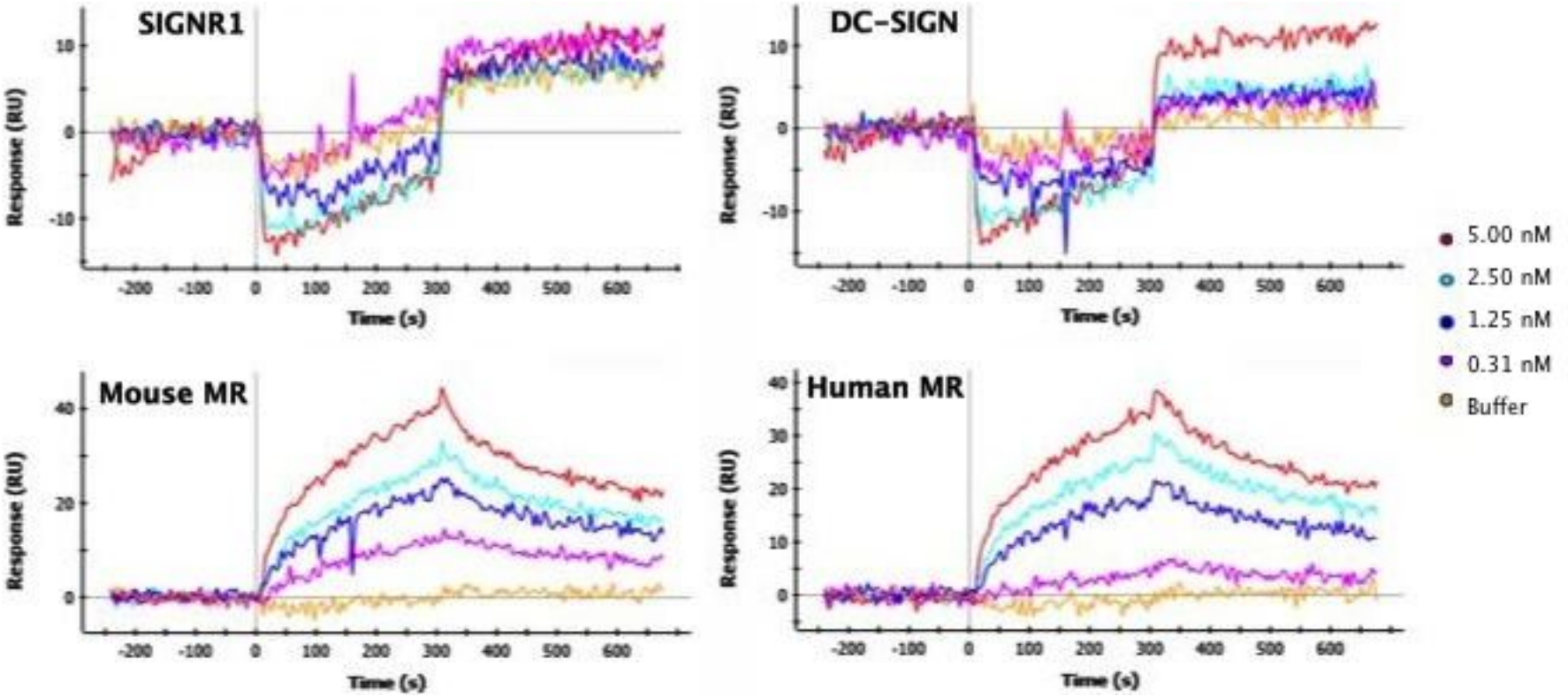
Results

- MAN-8ARM



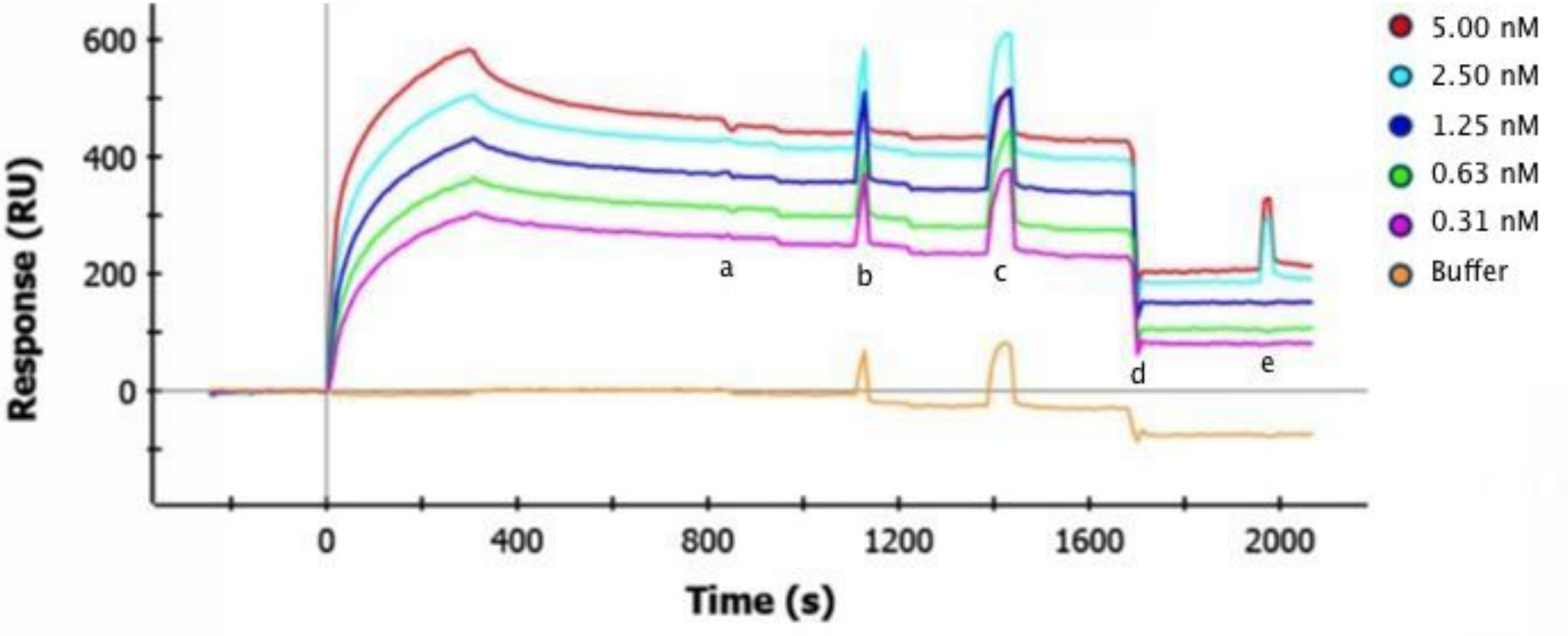
Results

- MAN-5ARM



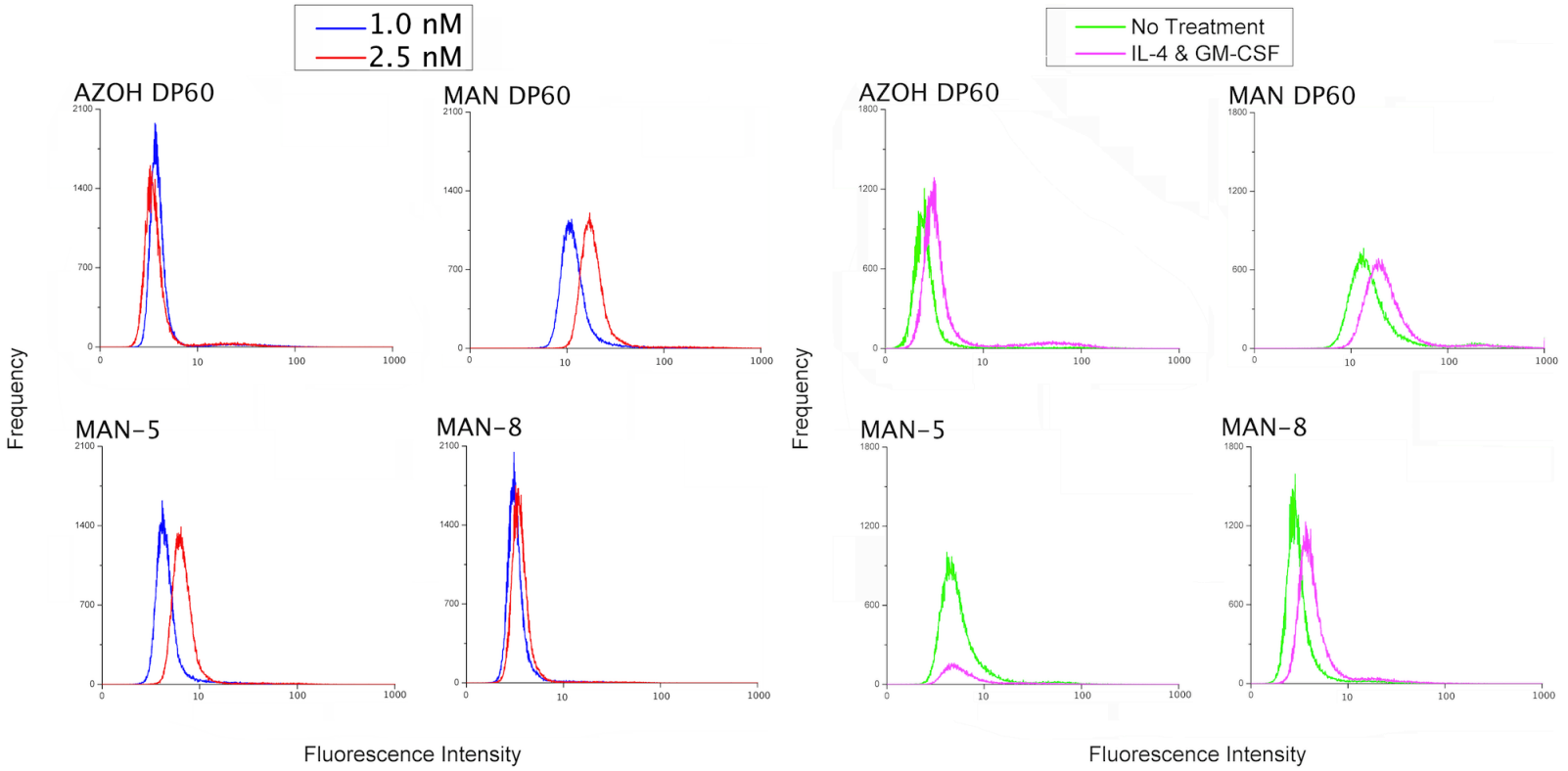
Results

- Regeneration



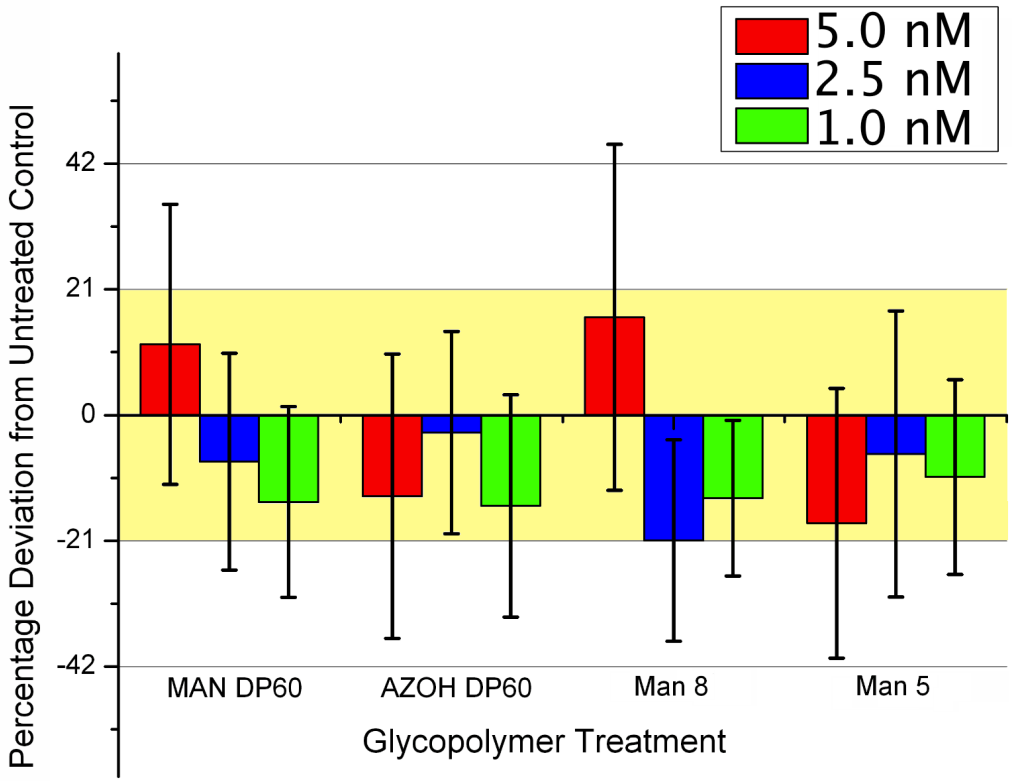
Results

- Flow Cytometry



Results

- Cytotoxicity



Summary

- MAN DP60 shown to bind well to DC-SIGN and SIGNR1.
- Further work needed for conclusive results of MAN-5ARM and MAN-8ARM.
- Demonstrated cytokines increase binding to cells.
- Shown that polymers are not toxic to cells in concentrations used.
- Binding profiles similar for SIGNR1 and DC-SIGN; mouse disease models can be used to develop human treatment.

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