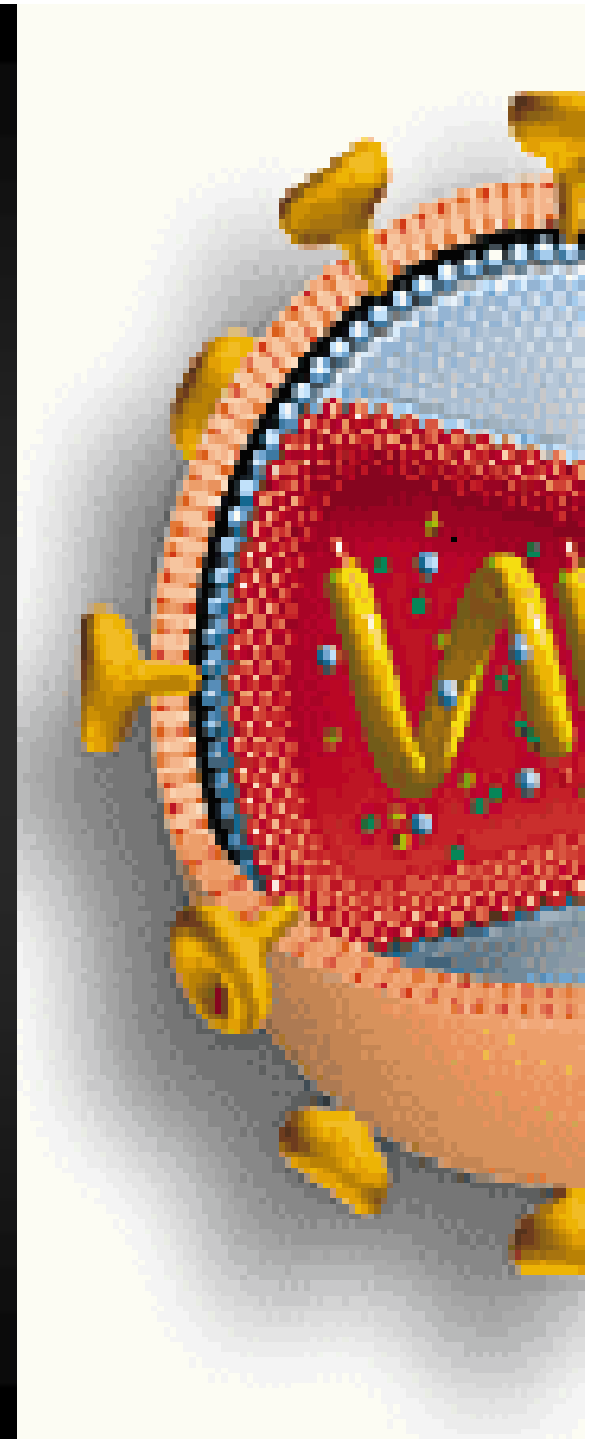


Antigenic mimicry of the HIV envelope by AIDS- associated pathogens.

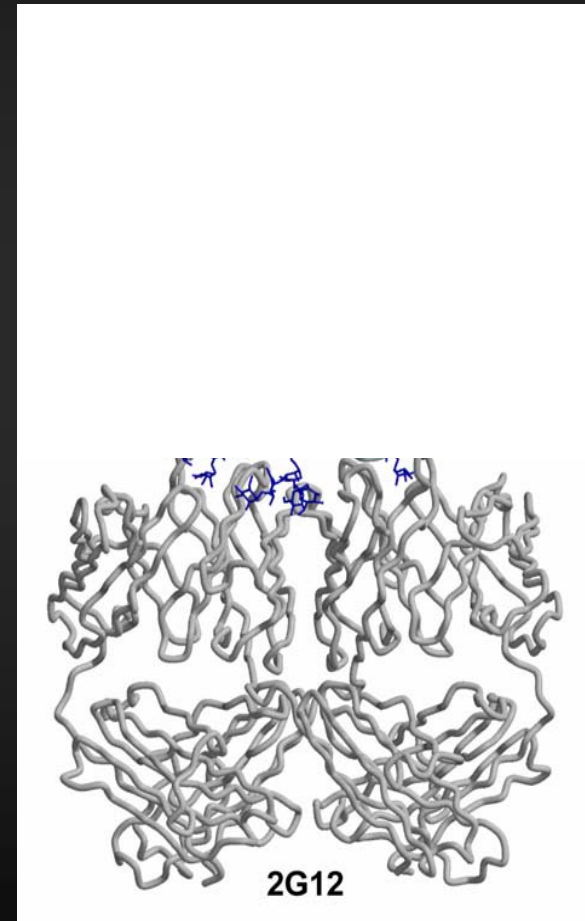
Wednesday 15th October,
2008

Cameron Dunlop
Oxford University



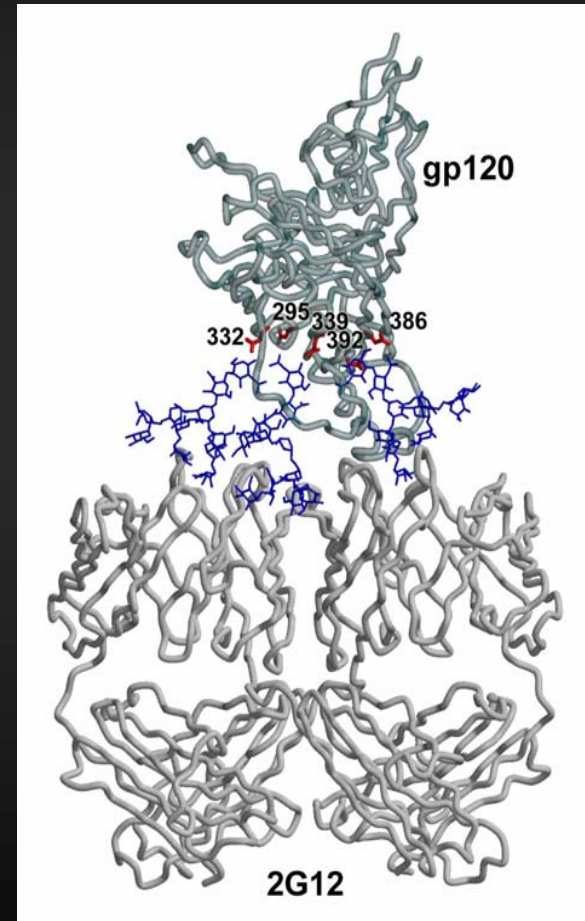
Project Background - 2G12

- 2G12, a broadly neutralising antibody, recognises an oligomannose cluster on gp120



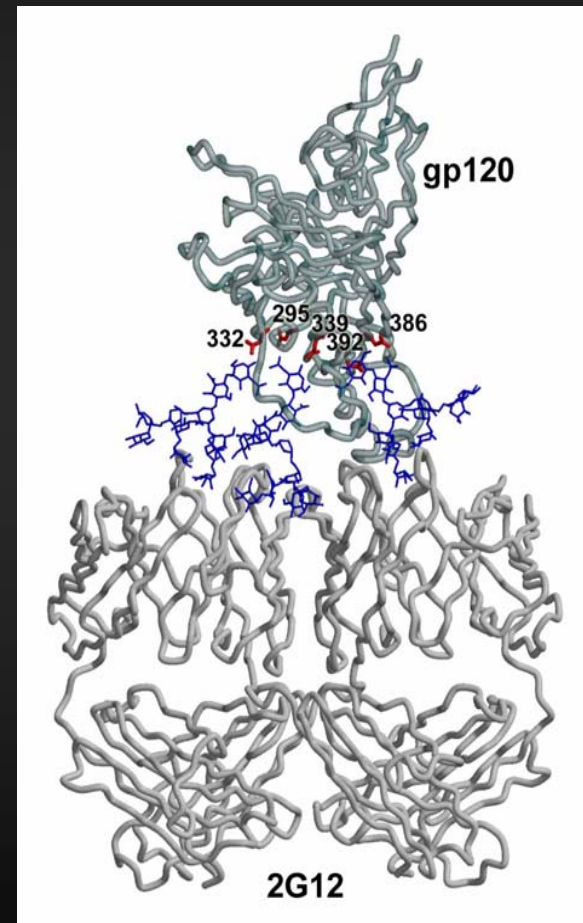
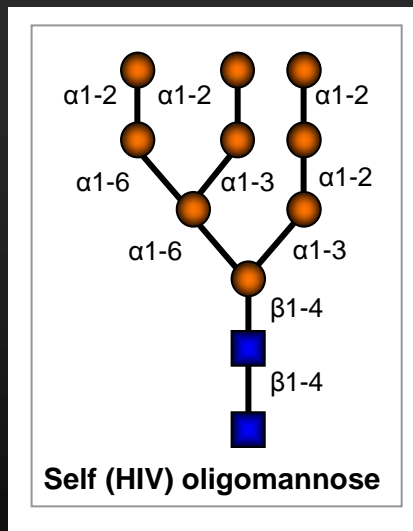
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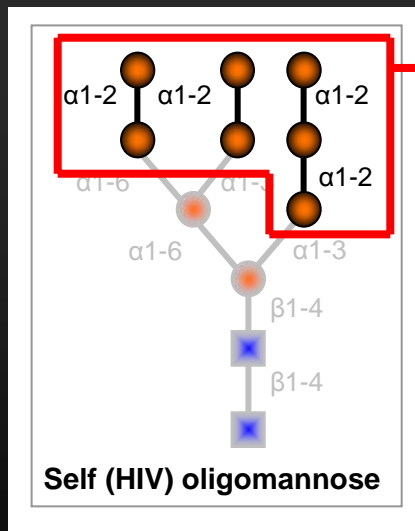
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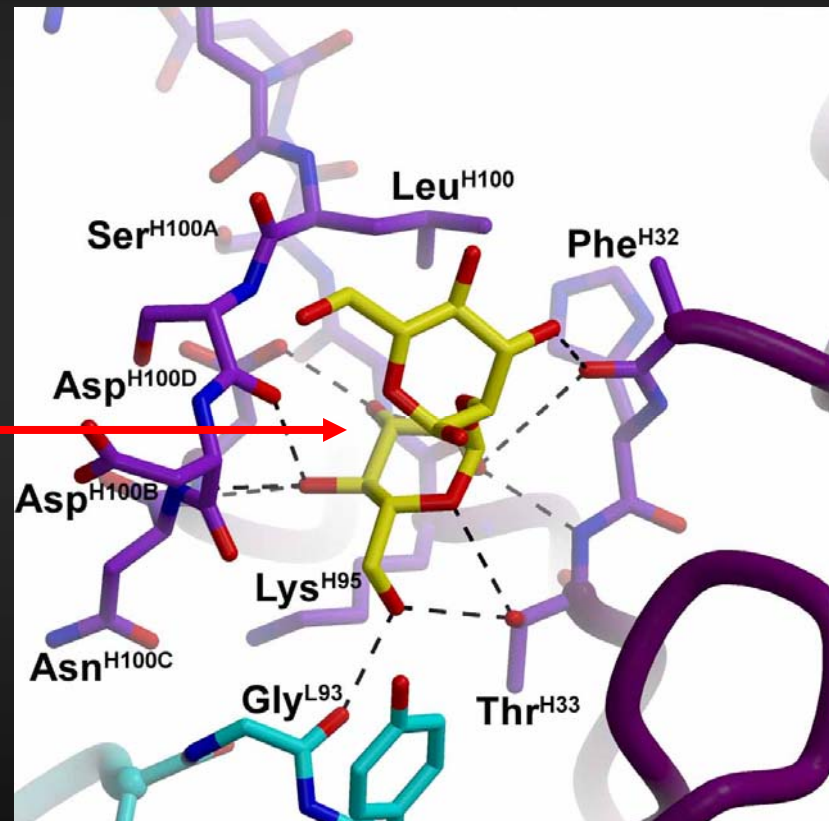


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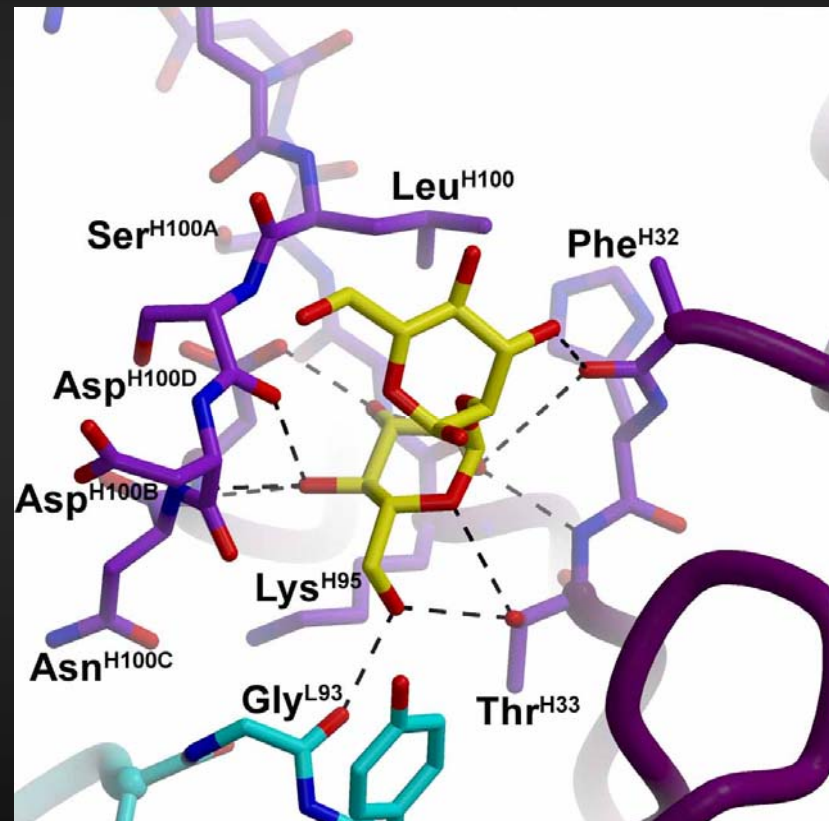


Man α 1-2Man



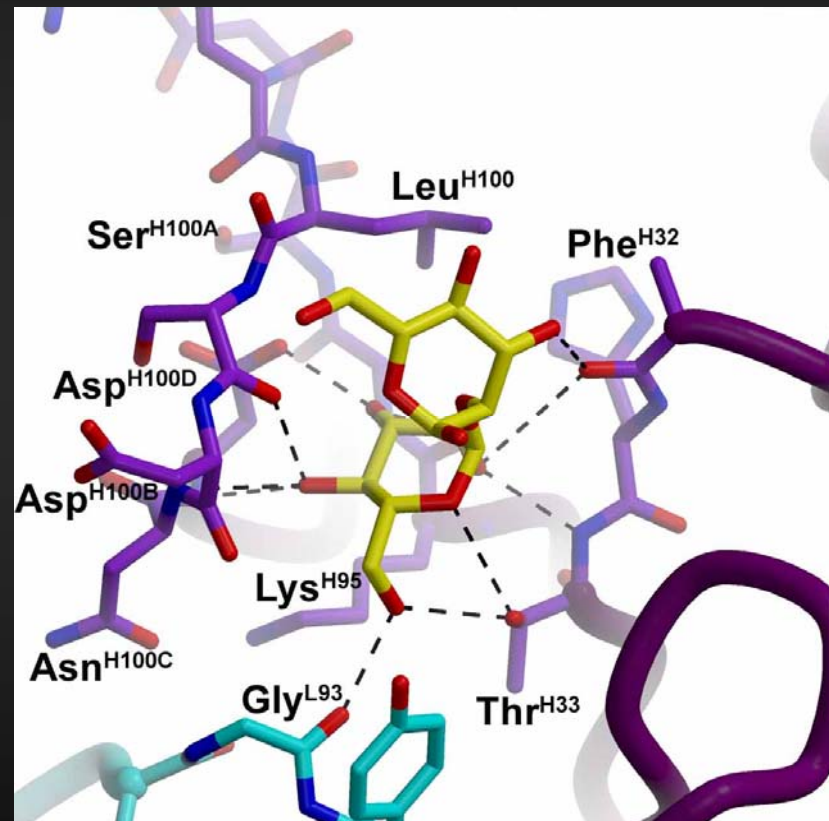
Project Background - 2G12

- 2G12, a broadly neutralising antibody, recognises an oligomannose cluster on gp120
- High avidity antibodies to oligomannose are not found in human sera



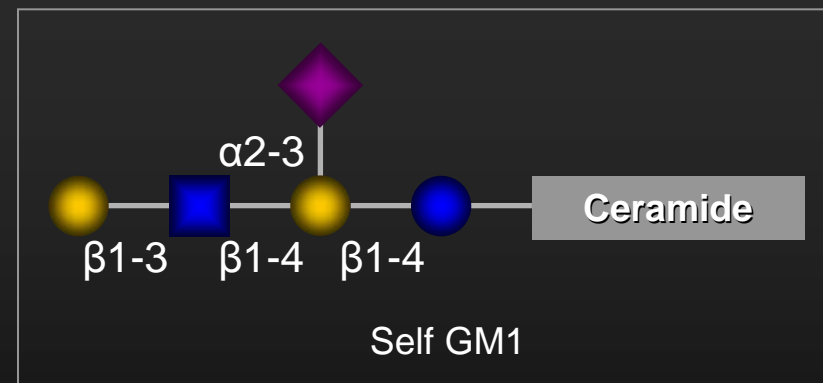
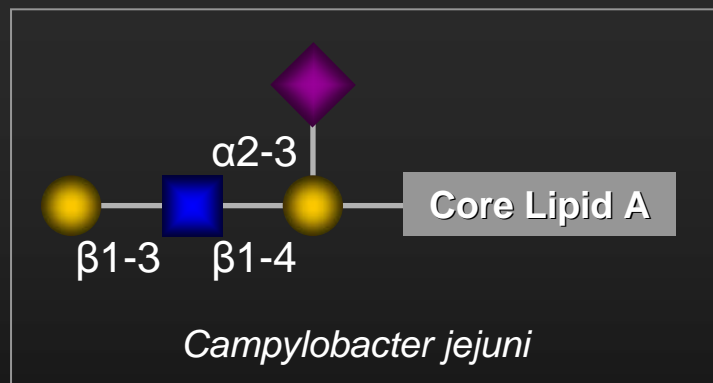
Project Background - 2G12

- How did 2G12 arise?



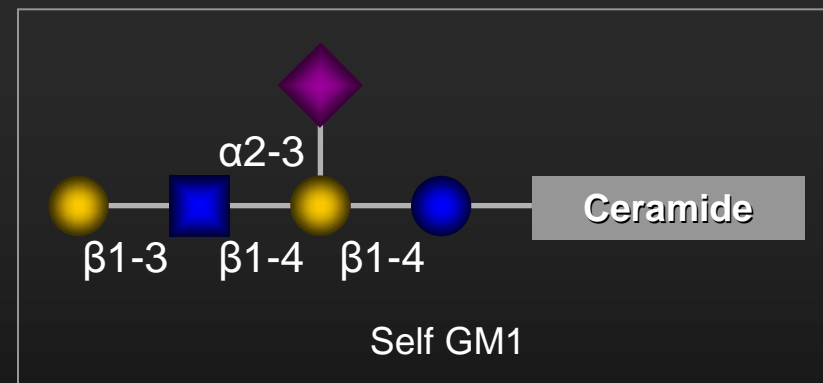
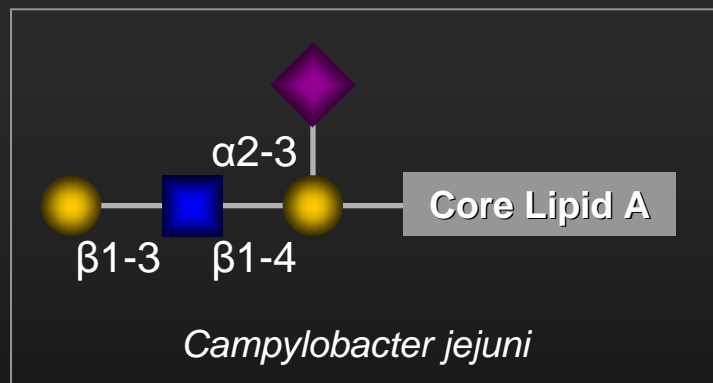
Antigenic mimicry

- Guillain-Barre syndrome.

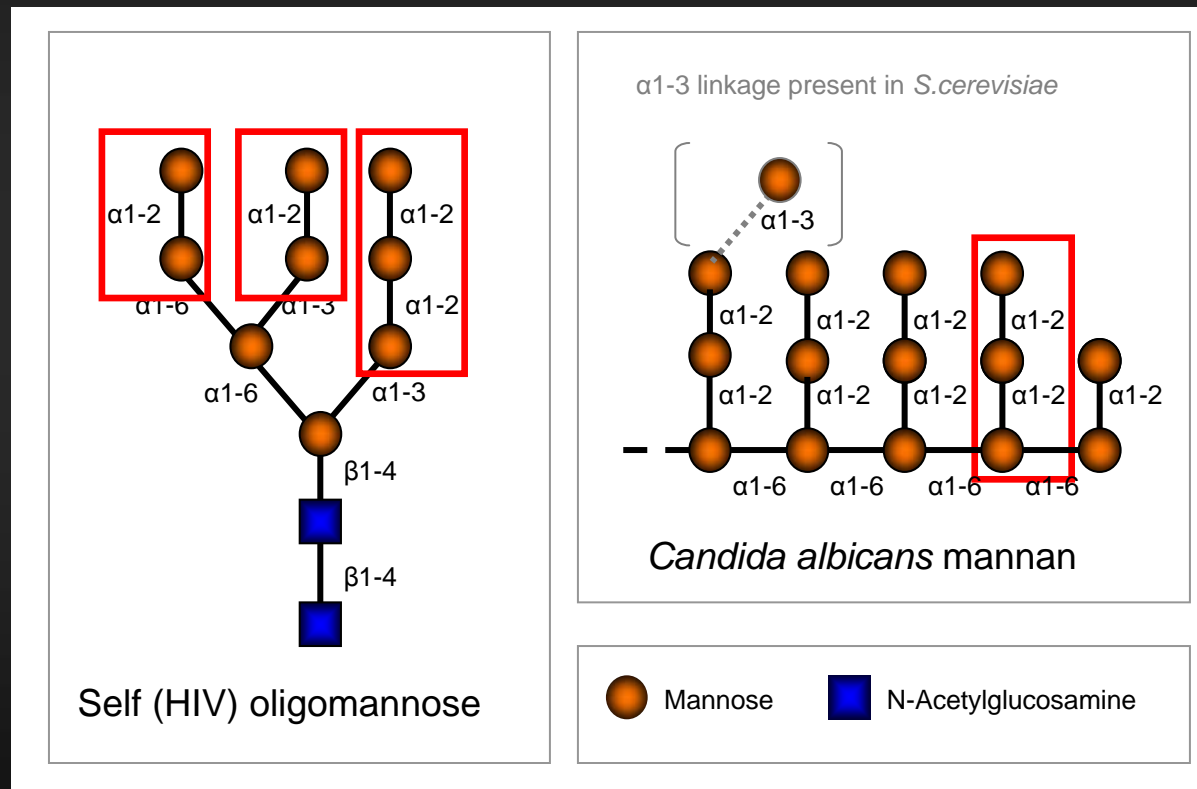


Antigenic mimicry

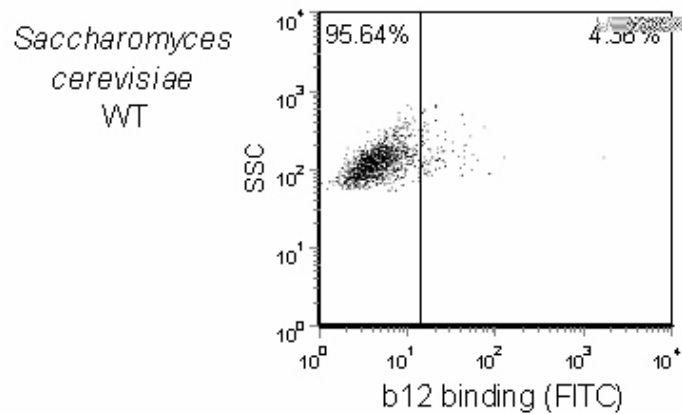
- Guillain-Barre syndrome.
- Antibodies against *Campylobacter jejuni* oligosaccharides cross-react with self-sugars on gangliosides leading to autoimmune disease.



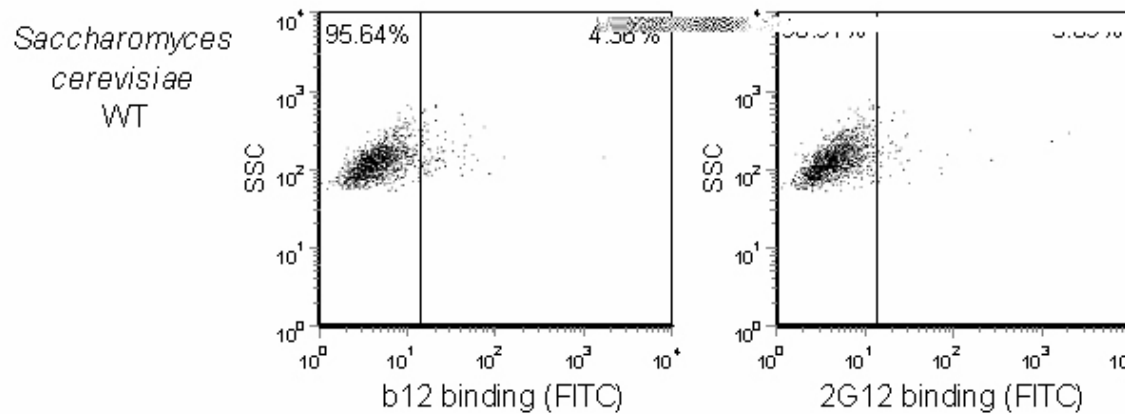
Could 2G12 be a response to something other than HIV-1?



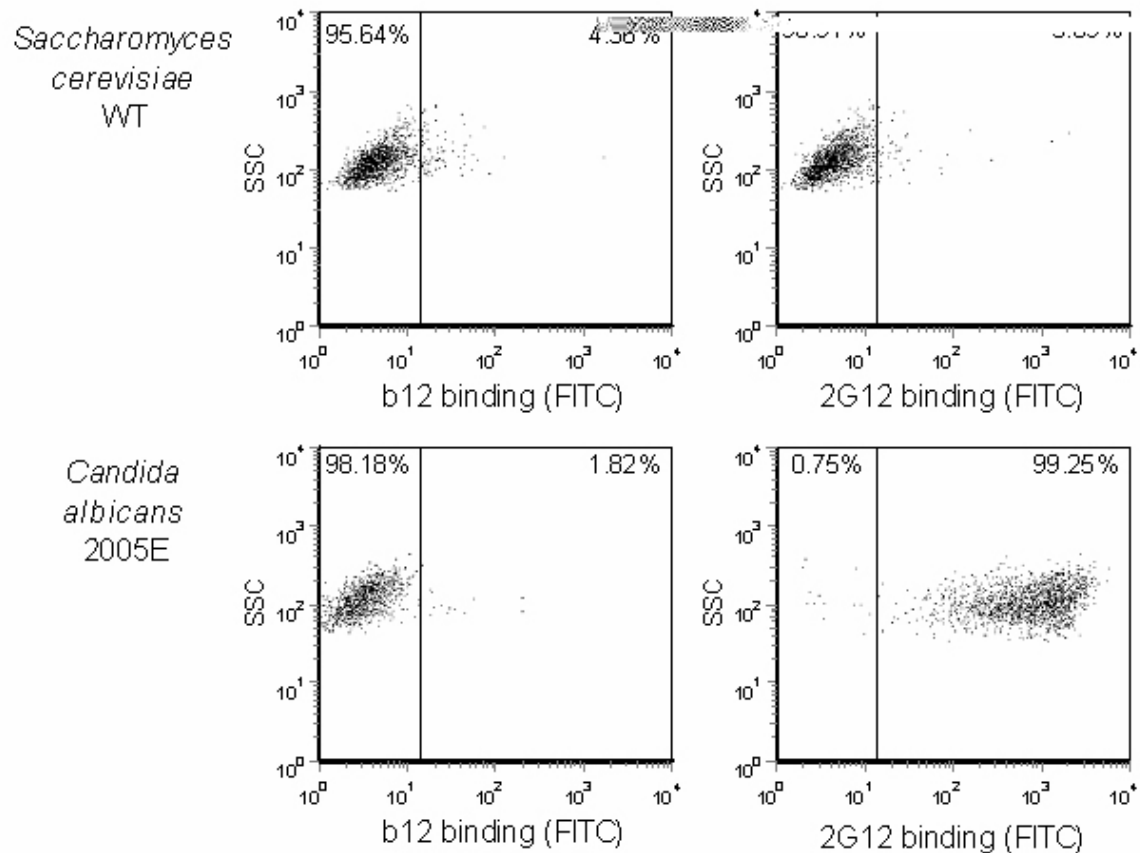
2G12 can bind to WT *Candida albicans*, but not WT *Saccharomyces cerevisiae*



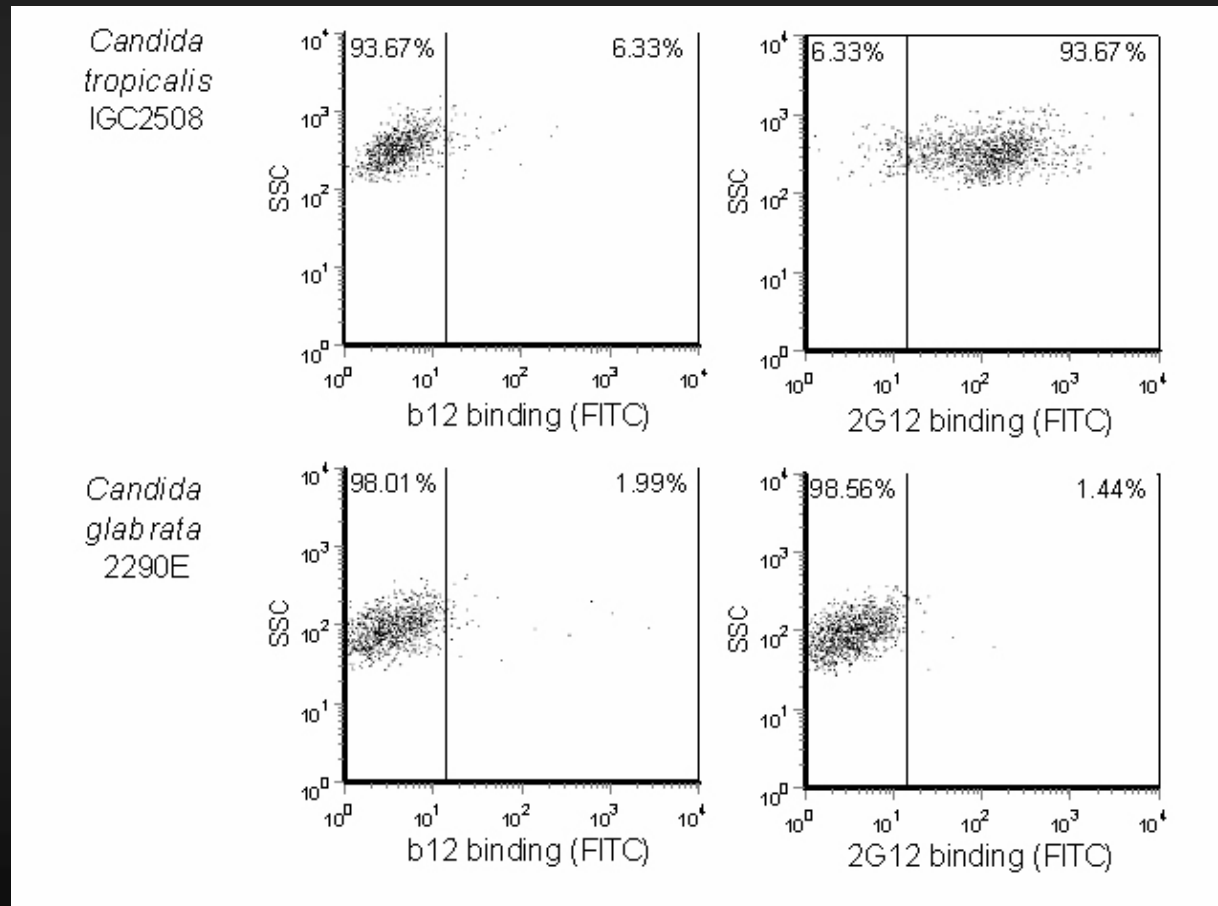
2G12 can bind to WT *Candida albicans*, but not WT *Saccharomyces cerevisiae*



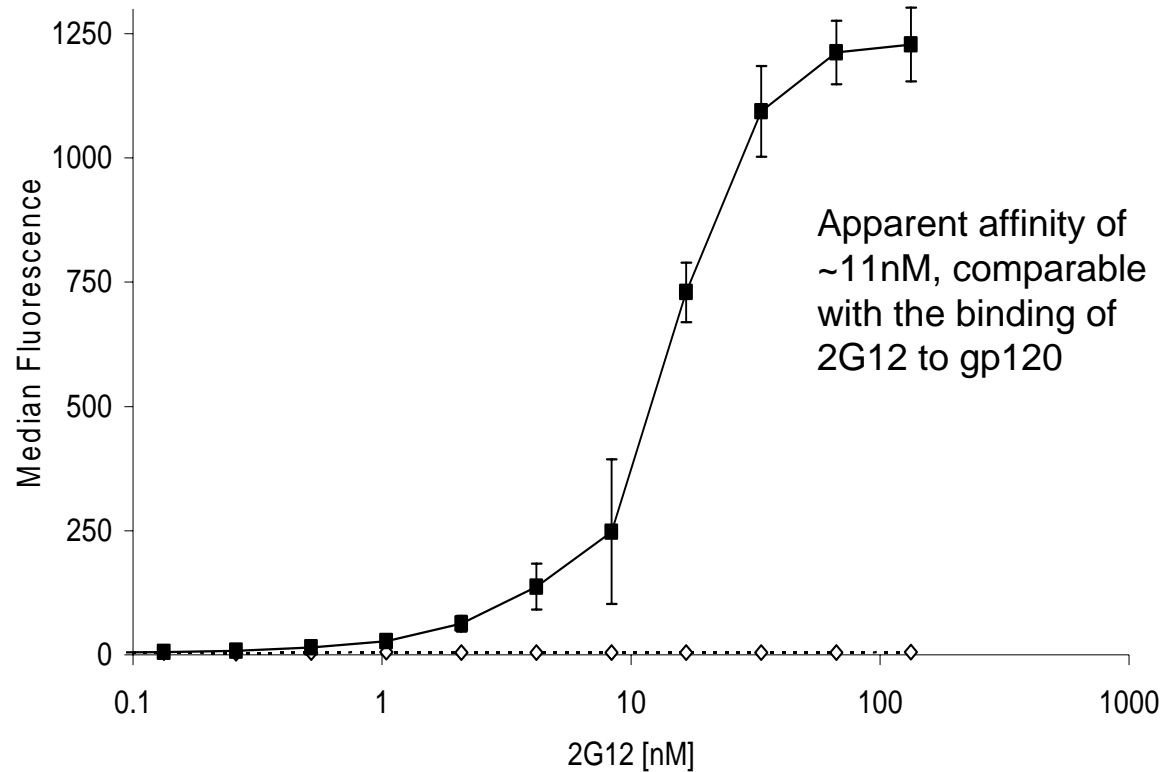
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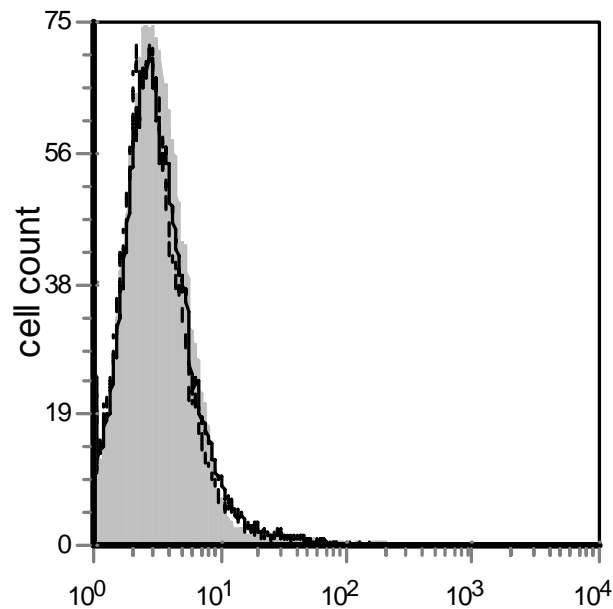
2G12 can also bind to *Candida tropicalis*, but *Candida glabrata*



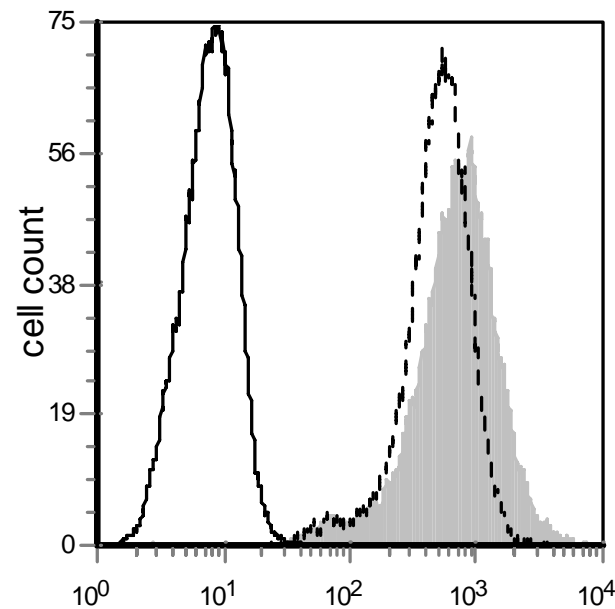
Affinity of 2G12 for the *C.albicans* surface



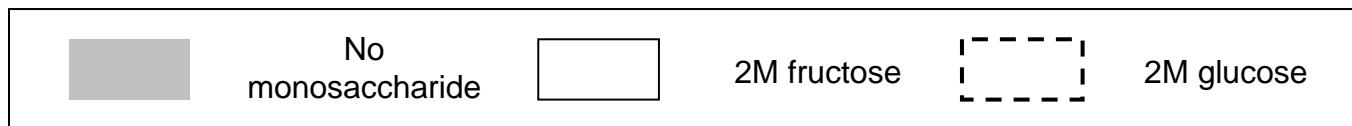
Carbohydrate recognition can explain antigenic mimicry between *C. albicans* and HIV-1 gp120.



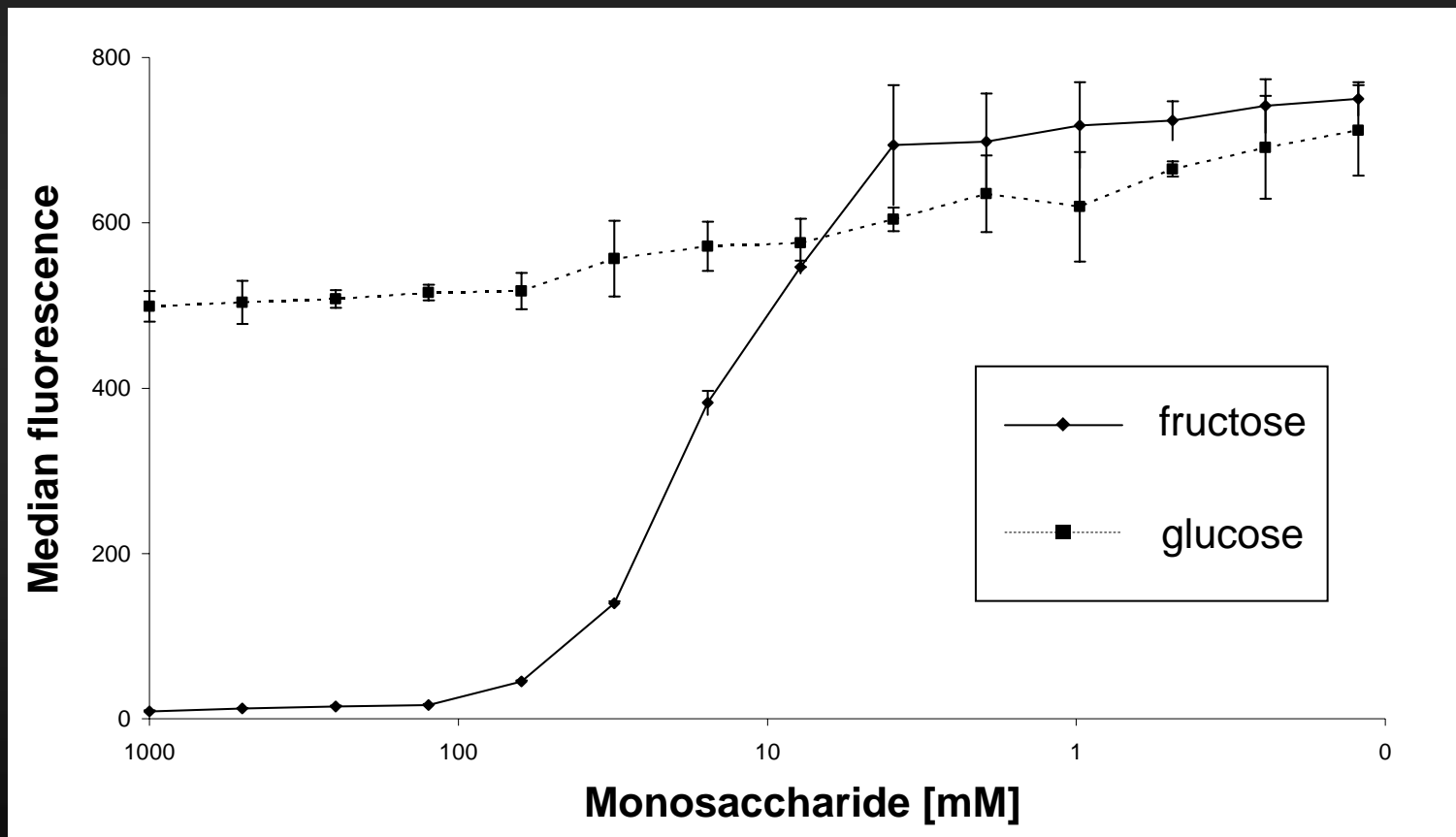
b12 binding (FITC)



2G12 binding (FITC)



Carbohydrate recognition can explain antigenic mimicry between *C. albicans* and HIV-1 gp120.



Carbohydrate recognition can explain antigenic mimicry between *C. albicans* and HIV-1 gp120.

- *Candida albicans* is a common opportunistic infectious agent in HIV +ve people.

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- Could maturation of B cells expressing anti-*Candida* antibodies in the presence of HIV lead to cross-reactive antibodies?

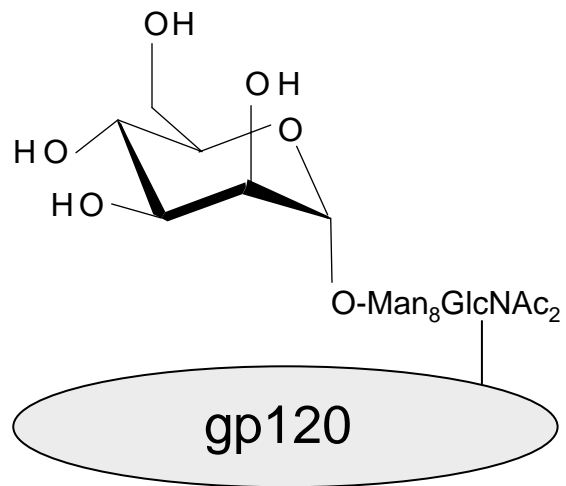
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- *Candida albicans* is a common opportunistic infectious agent in HIV +ve people.
- Could maturation of B cells expressing anti-*Candida* antibodies in the presence of HIV lead to cross-reactive antibodies?
- Immunisation trials in rabbits using various yeast species along with modified gp120 are underway.

Breaking tolerance

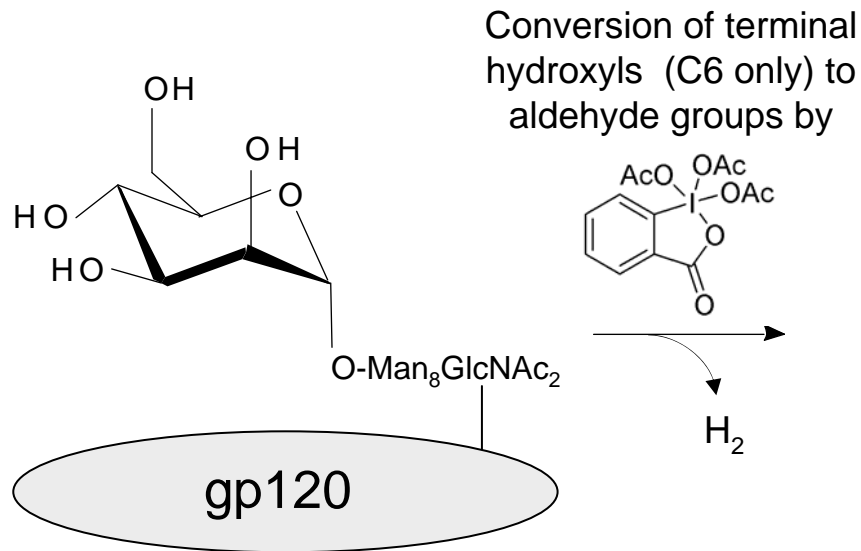
- Cross-reactivity as a method of overcoming self-tolerance is not a new concept – In 1965 Weigle *et al* were able to induce an immune response to a self protein by immunising with a chemically modified version.

Chemical modifications to oligomannose *in situ*



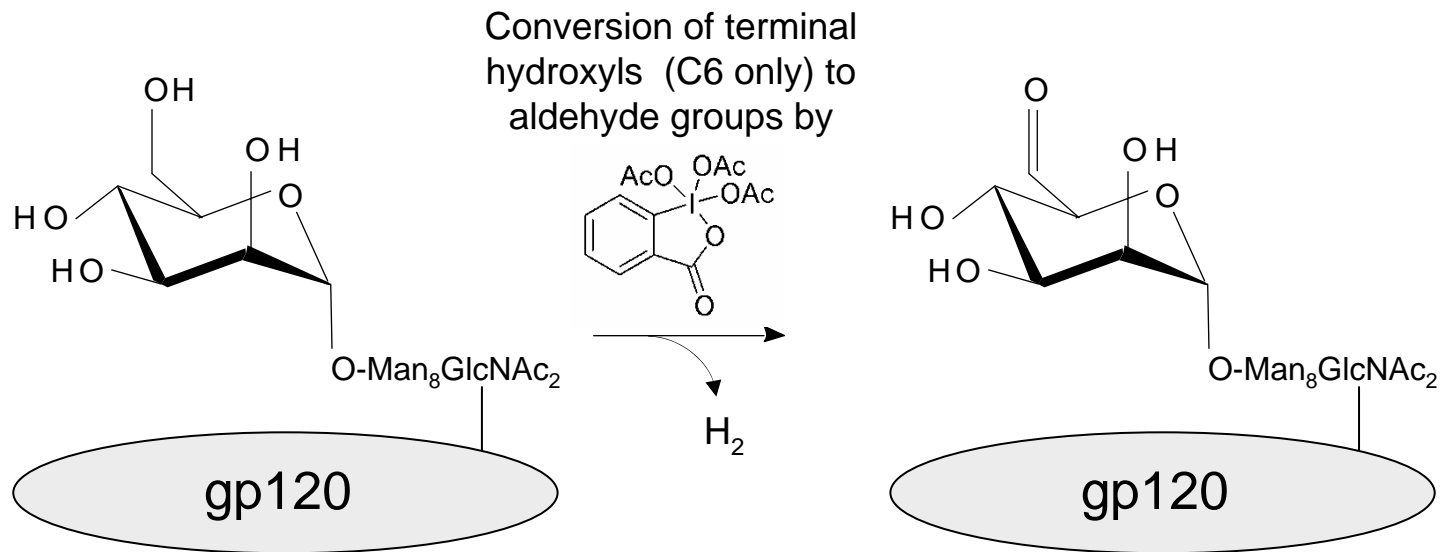
Oligomannose: not immunogenic

Chemical modifications to oligomannose *in situ*



Oligomannose: not immunogenic

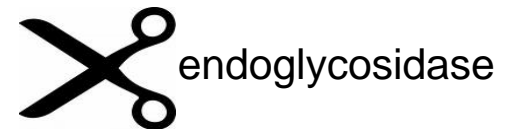
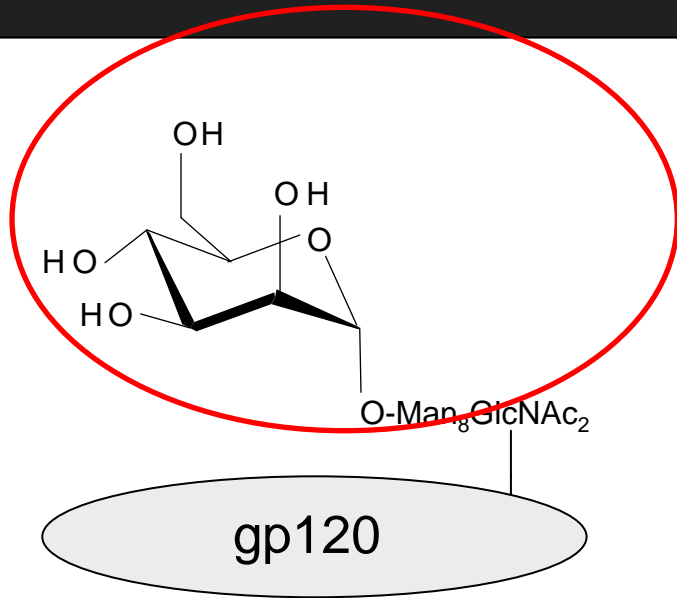
Chemical modifications to oligomannose *in situ*



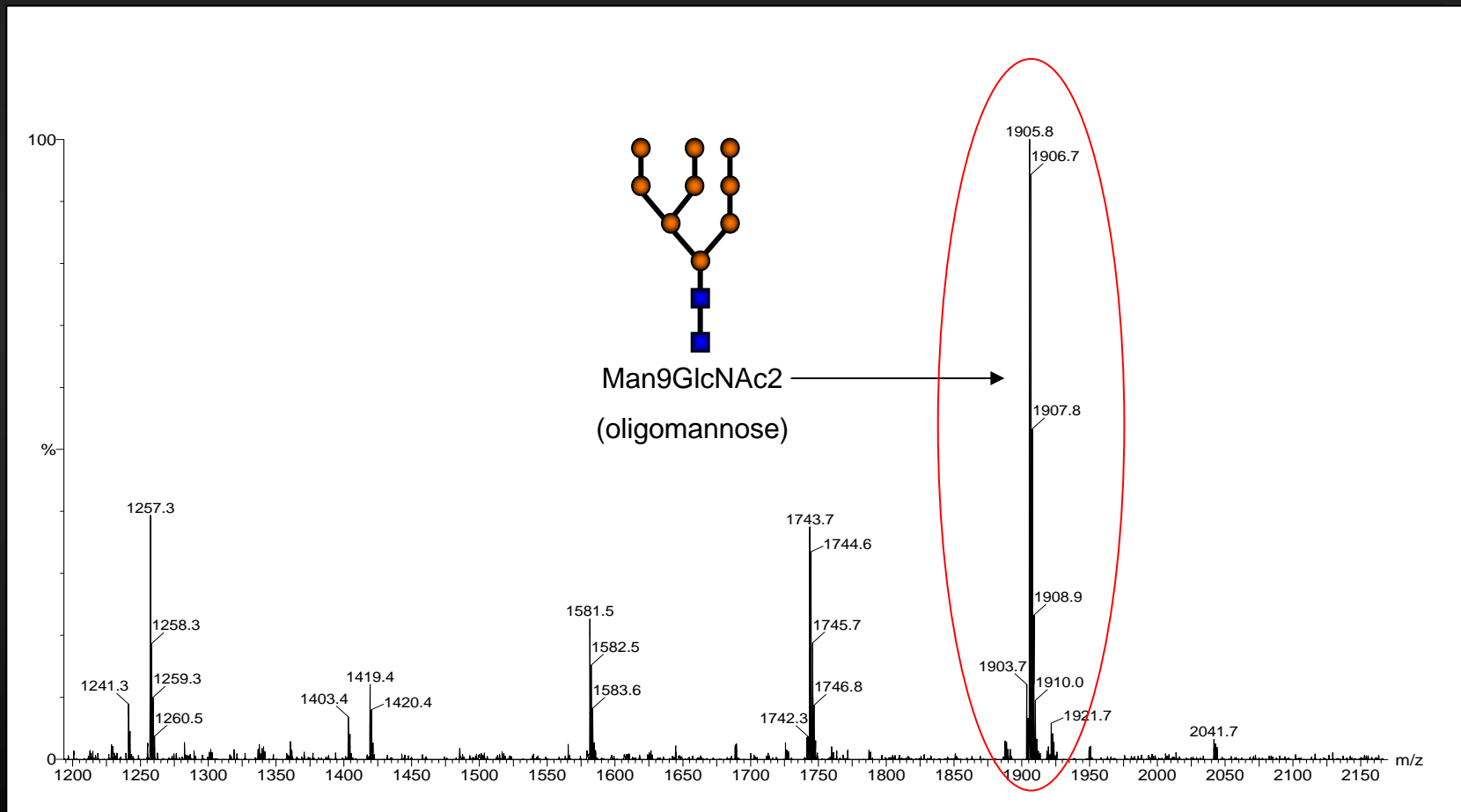
Oligomannose: not immunogenic

Oligomannose with aldehyde groups: structurally similar yet immunogenic?

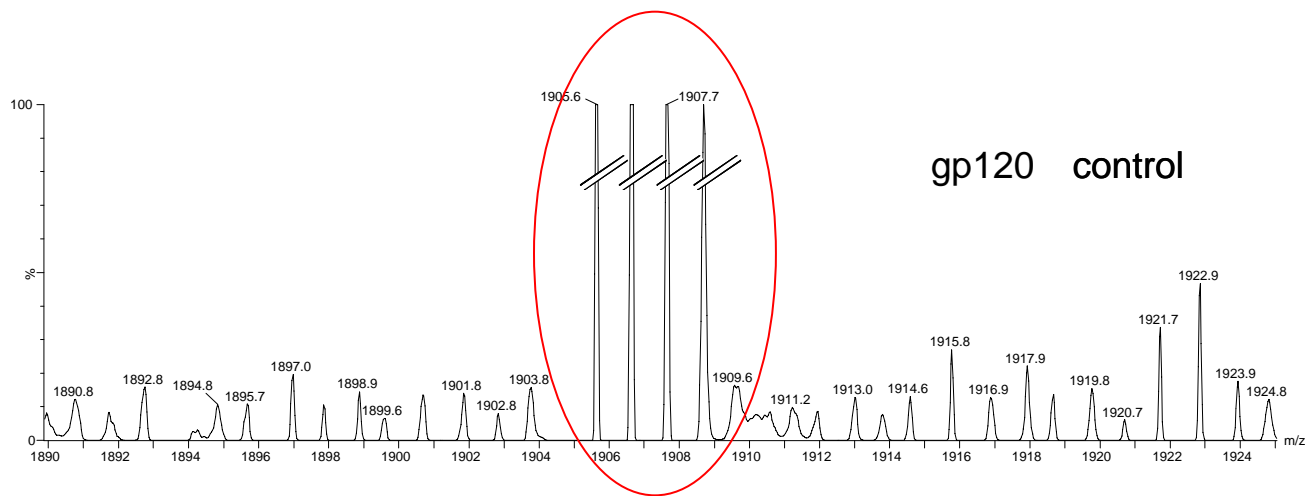
Chemical modifications to oligomannose *in situ*



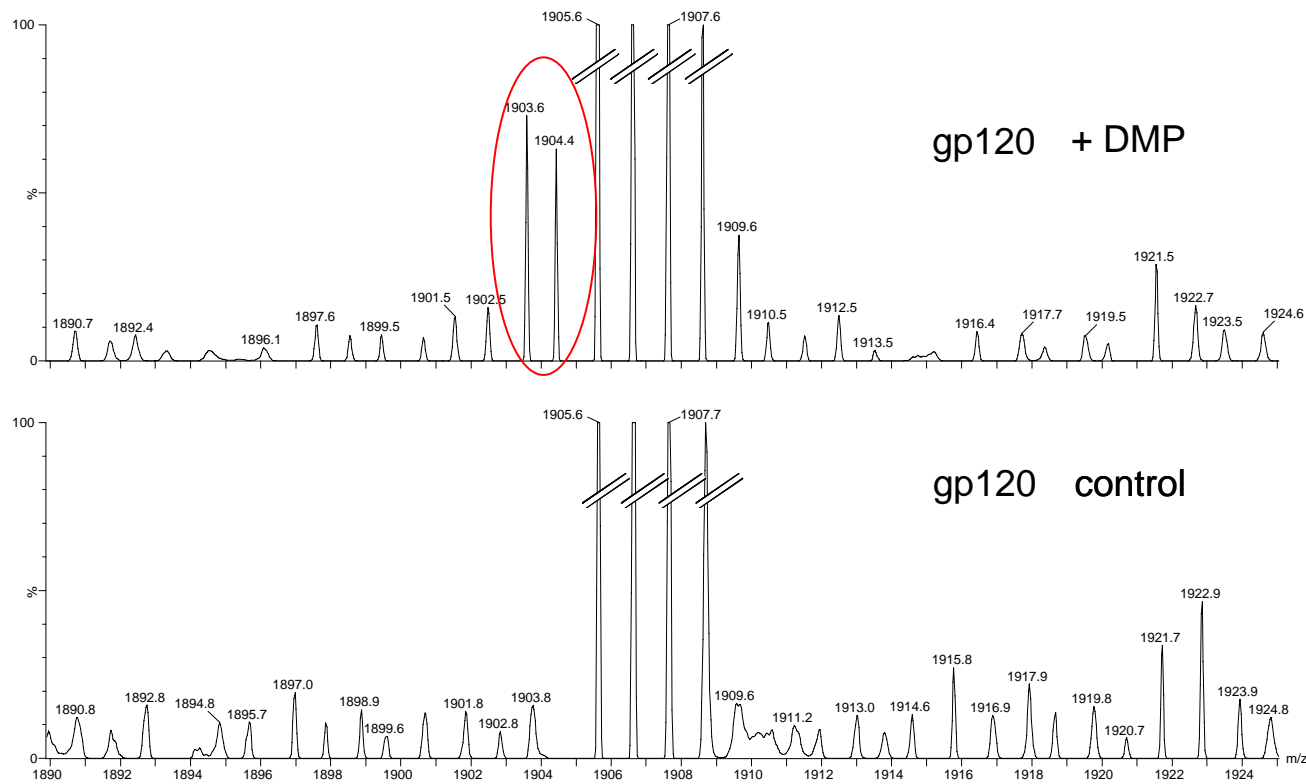
MS of gp120 control



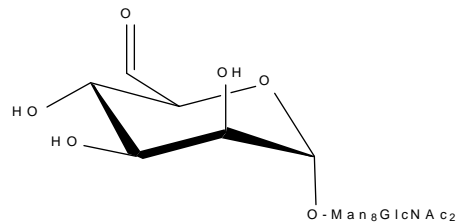
MS of gp120 control (focus on $\text{Man}_9\text{GlcNAc}_2$ peak)



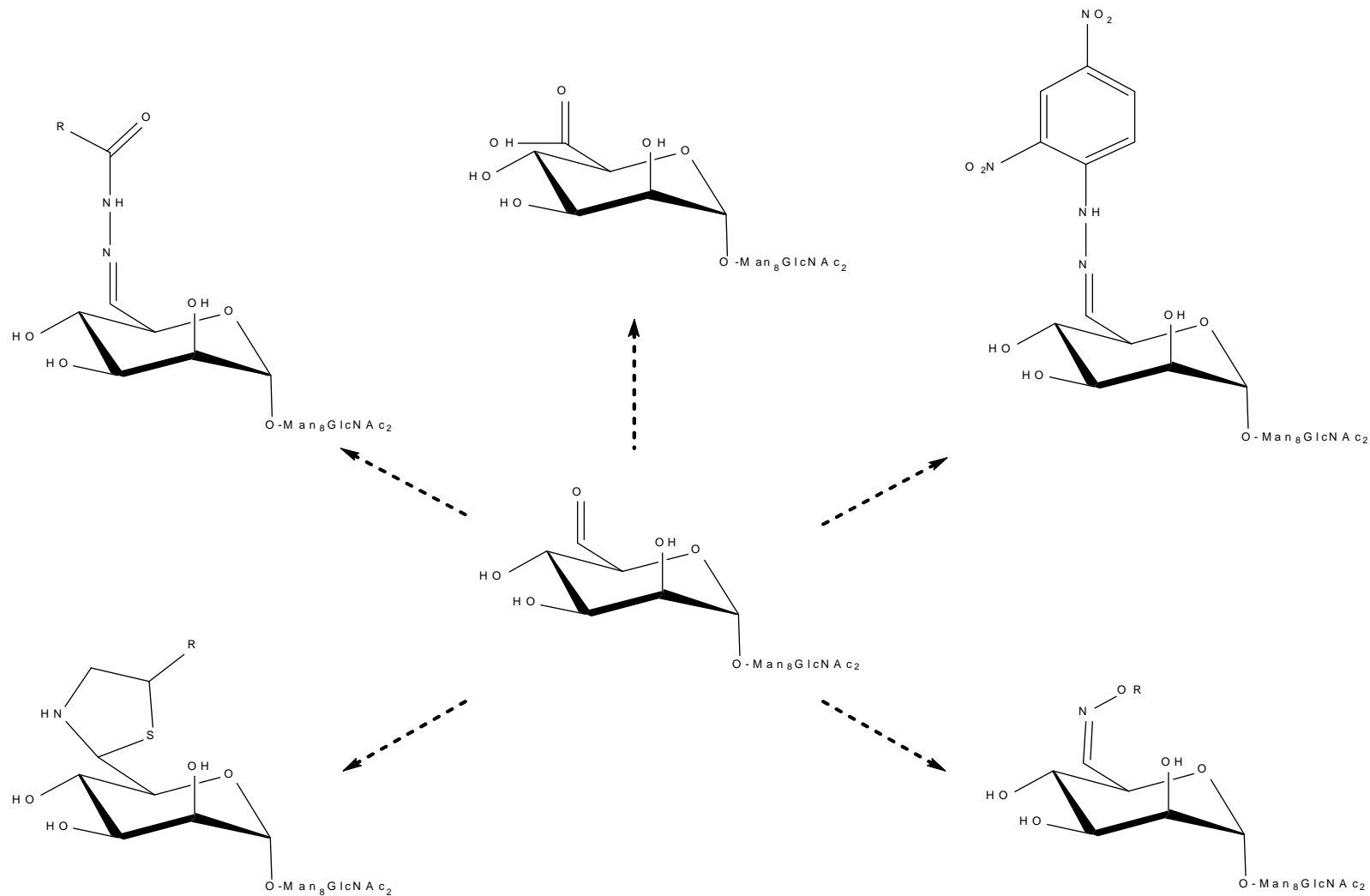
DMP-modified kifunensine treated gp120 and control (focus on $\text{Man}_9\text{GlcNAc}_2$ peak)



Selective oxidation as a scaffold for immunogen diversification



Selective oxidation as a scaffold for immunogen diversification



Ongoing work

- Increase the efficiency of the aldehyde formation reaction on gp120's glycans.
- Immunise directly with this, to investigate methods of overcoming tolerance... in addition to using the aldehyde groups as attachment points for other immunogenic chemical groups.

Acknowledgements



Chris Scanlan
Nicole Zitzmann
Raymond Dwek
John Offer
Fatma Mansab
Dave Harvey
Mark Wormald
...and everyone in
the Zitzmann lab



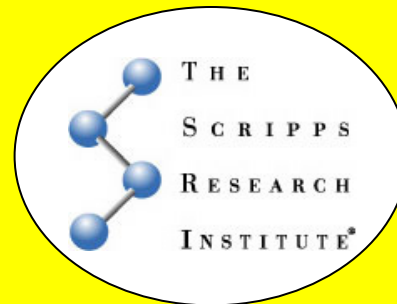
Dennis Burton
Ian Wilson
Dan Calarese
Ola Blixt
Rena Astronomo





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Dave Harvey
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Ian Wilson
Dan Calarese
Ola Blixt
Rena Astronomo

welcome trust

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