

## IMPROVED ANTIBODY Fc DOMAINS

A team led by Dr Mike Clark and Dr Lorna Williamson have engineered human Fc domains to obtain ideal immunological profiles including reduced activation of the immune system that causes destructive inflammatory responses and unwanted cytotoxicity.

### Key benefits:

- Cytotoxic effects can be reduced while maintaining antibody half-life
- Side effects limited, allowing for a higher therapeutic dose
- Optimal performance in **blocking antibodies**, **soluble receptors** or **fusion proteins**

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## Background

The majority of monoclonal antibodies (mAbs) under development are directed towards autoimmunity and immunosuppression and act by blocking or modulating immune responses. Ideally, these mAbs will have constant regions that have minimal effector functions which do not cause destructive inflammatory responses.

At present, IgG1 and IgG4 constant regions are commonly used. However, these Fc domains retain binding to the receptors FcγRI, FcγRII, FcγRIII and C1q, which are responsible for toxicity and can generate side effects that are potentially limiting in determining therapeutic dose.

## Technology

Novel Fc domains have been systematically created and studied to obtain the optimal immunologic profile—retaining FcRn binding necessary for long half-life but massively reducing binding to FcγR1, FcγRII, FcγRIII and C1q.

Use of these modified antibodies almost completely abrogates *in vitro* cellular activation, and can completely inhibit cellular responses triggered by unmodified antibodies of the same specificity.

Some binding to the inhibitory FcγRIIb receptor is

still retained, creating the potential for specific down-regulation of cellular responses including autoantibody synthesis. Gm allotypes are also eliminated from these improved Fc regions, reducing the potential for unwanted allotypic responses to the therapeutic agent.

## Commercialisation

These novel Fc domains can be combined with the variable region genes or receptor domains of your choice to produce antibodies or fusion proteins of any desired specificity.

Such therapeutic agents would be capable of blocking ligand-receptor or auto-antibody-receptor interactions. These Fc regions could have valuable applications in autoimmunity, inflammation, allergy, asthma, cardiovascular disease and cancer.

These Fc domains are already in commercial development for antibody products targeted at autoimmunity and neurological disorders.

## Patent and Publications

This technology is protected by an international patent application WO9958572 which has been **granted** in a number of territories.

Armour *et al.*, Blood, 2006. 107(6): 2619-2626

Kirton *et al*, Eur J Immunol. 2005. 35: 3119–3130

**Table 1:** Binding and functional activities of wild-type IgG molecules and CH2 variants

Binding to	Mutants of...	Activity Level										
		G1			G2			G4				
		wt	Δa	Δb	Δc	Δab	Δac	wt	Δa	wt	Δb	Δc
FcγRI		100	100	0	5	0	5	5	0	80	0	5
FcγRIIIa R/R		100	80	10	10	15	10	35	40	20	10	5
FcγRIIIa H/H		100	50	10	5	10	5	100	60	5	5	0
FcγRIIb 1		100	90	25	25	30	35	50	60	70	20	15
FcγRIIIb NA1		100	35	0	15	0	0	0	0	5	0	0
FcγRIIIb NA2		100	25	0	5	0	0	0	0	0	0	0
Monocyte activation		100	90	0	10	0	5	0	0	50	0	5
Complement lysis		100	5	0	0	0	0	80	0	0	0	0
ADCC		100	45	5	10	0	0	5	0	10	0	0