

Utilisation of MHCII Variant Mice for Antibody Discovery

GSK is committed to the replacement, reduction and refinement of animal studies (3Rs). Non-animal models and alternative technologies are part of our strategy and employed where possible. When animals are required, application of robust study design principles and peer review minimises animal use, reduces harm and improves benefit in studies.

All animal studies were ethically reviewed and carried out in accordance with Animals (Scientific Procedures) Act 1986 and the GSK Policy on the Care, Welfare, and Treatment of Animals.

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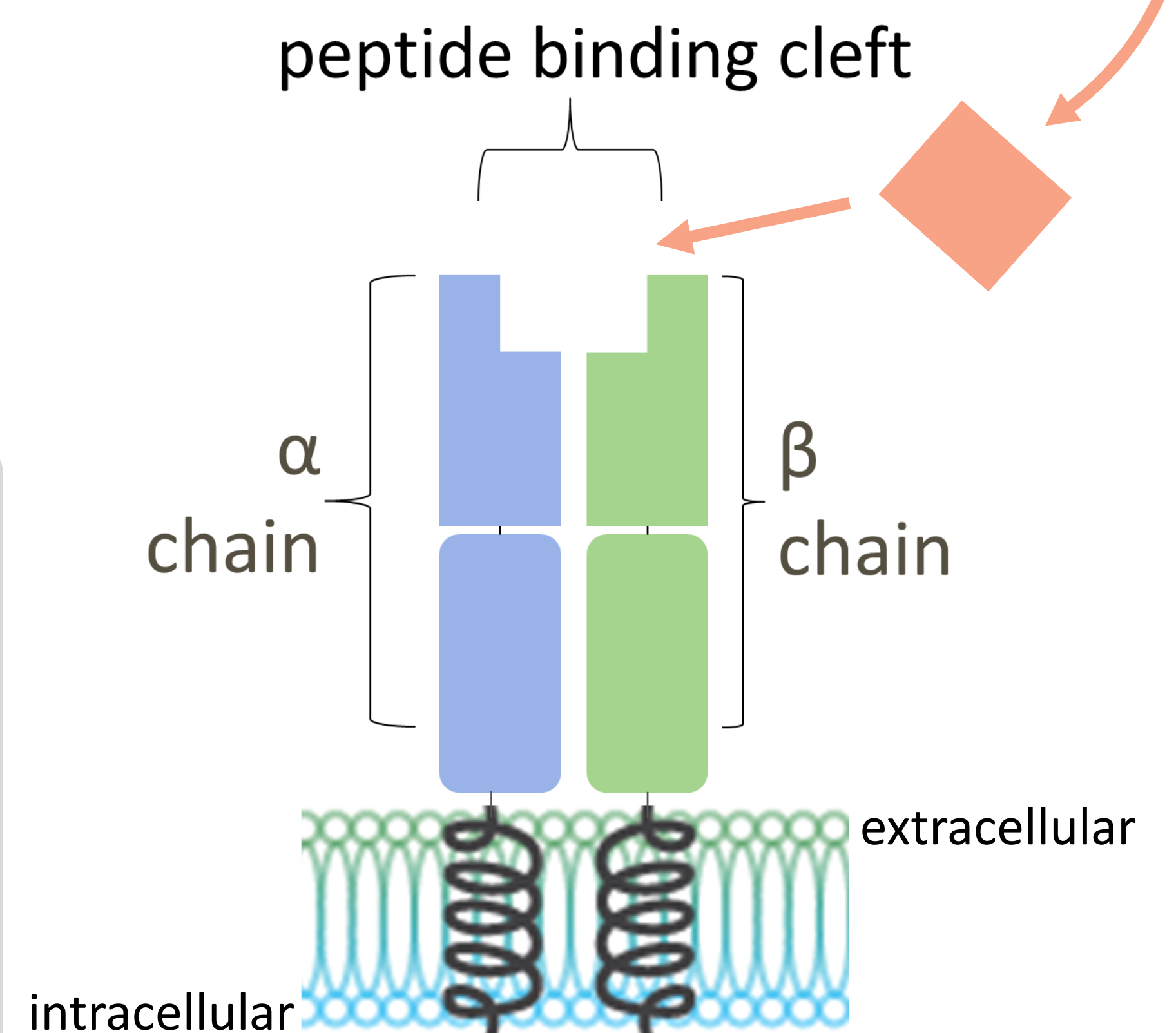
1. Purpose

- Identification of MHCII variants modulating antibody discovery in terms of:
 - Affinity
 - Epitope Diversity
 - Developability
- Investigation of *in-vivo* antibody discovery using mouse models



2. Major Histocompatibility Complex (MHC) II

- Expressed on the surface of **antigen presenting cells**
- **Activate T helper cells** by binding exogenous antigens
- **Critical** for induction of the **antibody response**
- **Many MHCII variants**
 - Mostly vary in the **peptide binding cleft**
 - Vary in their ability to bind peptides
 - Therefore, differ in ability to activate T-helper cells and the antibody response

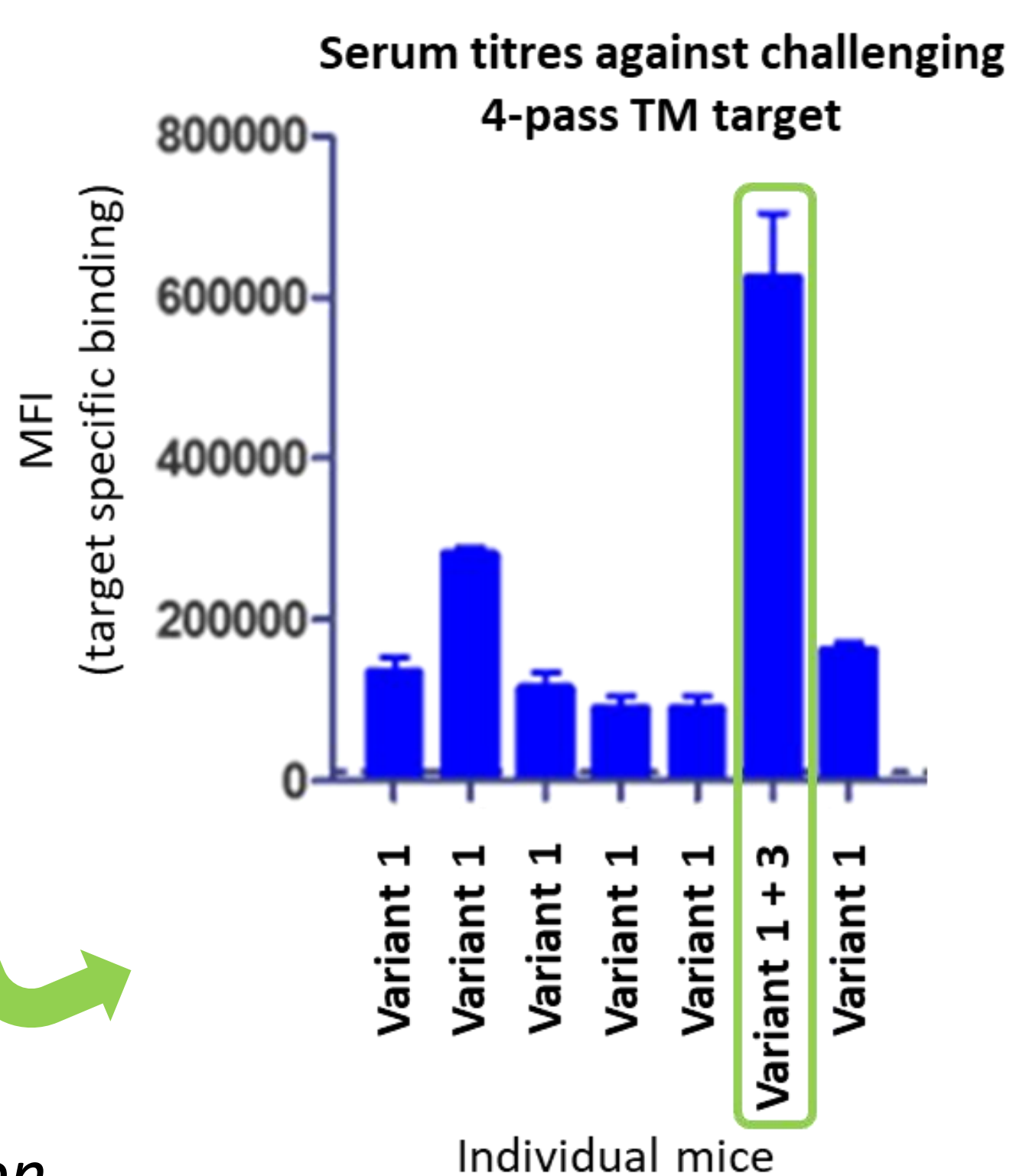


3. MHCII Haplotype Mice

- Immunisation of Next Generation **Transgenic** Mice expressing humanised antibodies for antibody discovery
- Mice generated expressing **humanised antibodies AND differing MHCII variants**: 'Variants 1-3'
- Compensate for MHCII variation in antibody discovery

4. Serum Titres

- **Serum titres demonstrate MHCII variant modulation of antibody responses**



- Variant 3 enhances target specific serum titres

- *N=1 observation*
- *MHCII heterozygous mice utilised for availability*

5. MHCII Variant Sequences

- **Peptide**
 - 2 amino acid **deletion** in *variant 3* β chain
 - Numerous amino acid **substitutions** across both chains
 - Substitutions for amino acids with substantially **different characteristics**

MHCII variant β chain	Variant 1	Variant 2	Variant 3
Variant 1		90.2	84.3
Variant 2	90.2		84.3
Variant 3	84.3	84.3	

- Variations likely **modulate antigen binding**

6. To conclude,

- MHCII is critical for activation of the antibody response
 - Modulation by MHCII variation
- MHCII haplotype mice incorporate MHCII variation
- Positive observations are already being made

More to come!