Monoclonal antibodies and the T-genero case

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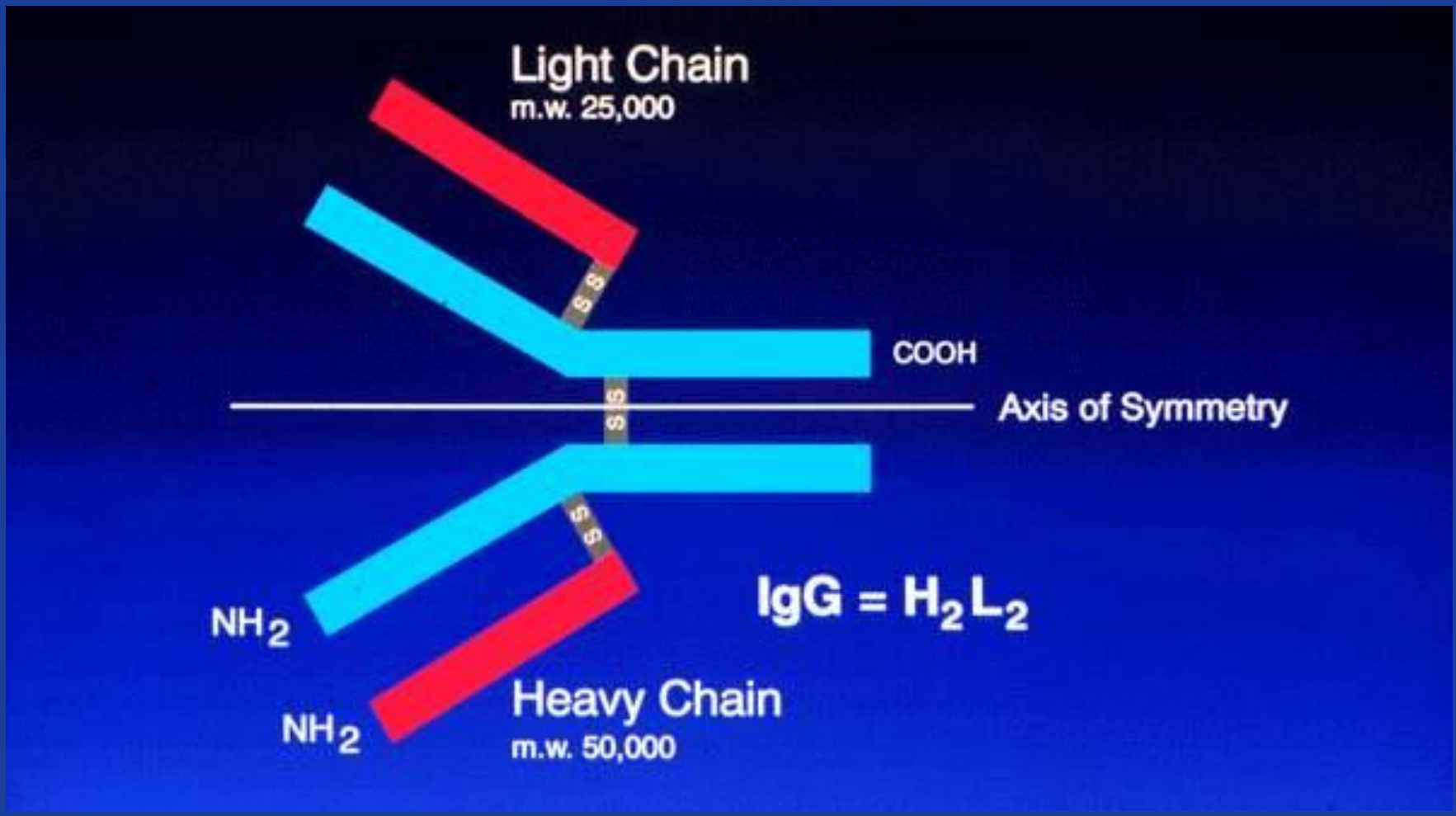
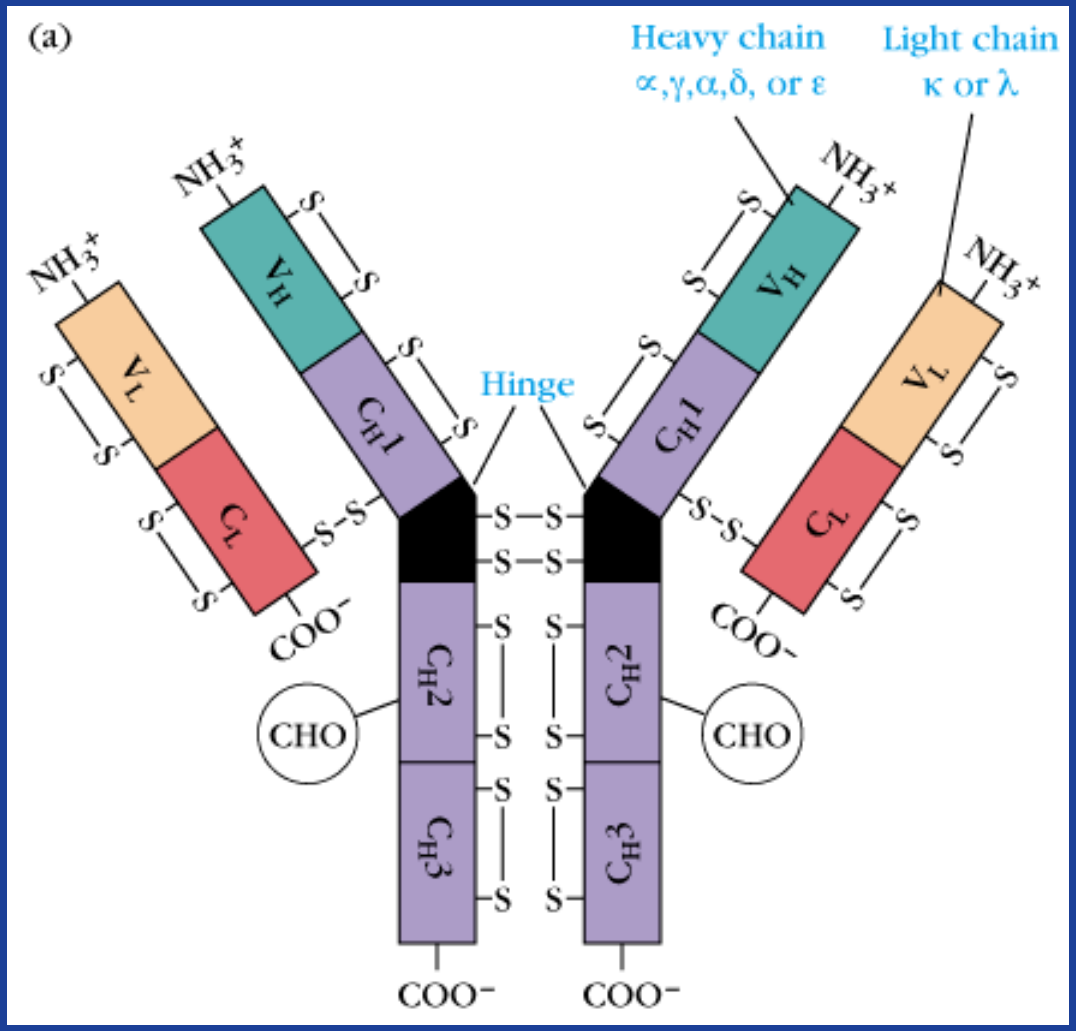
Four chain structure of IgG

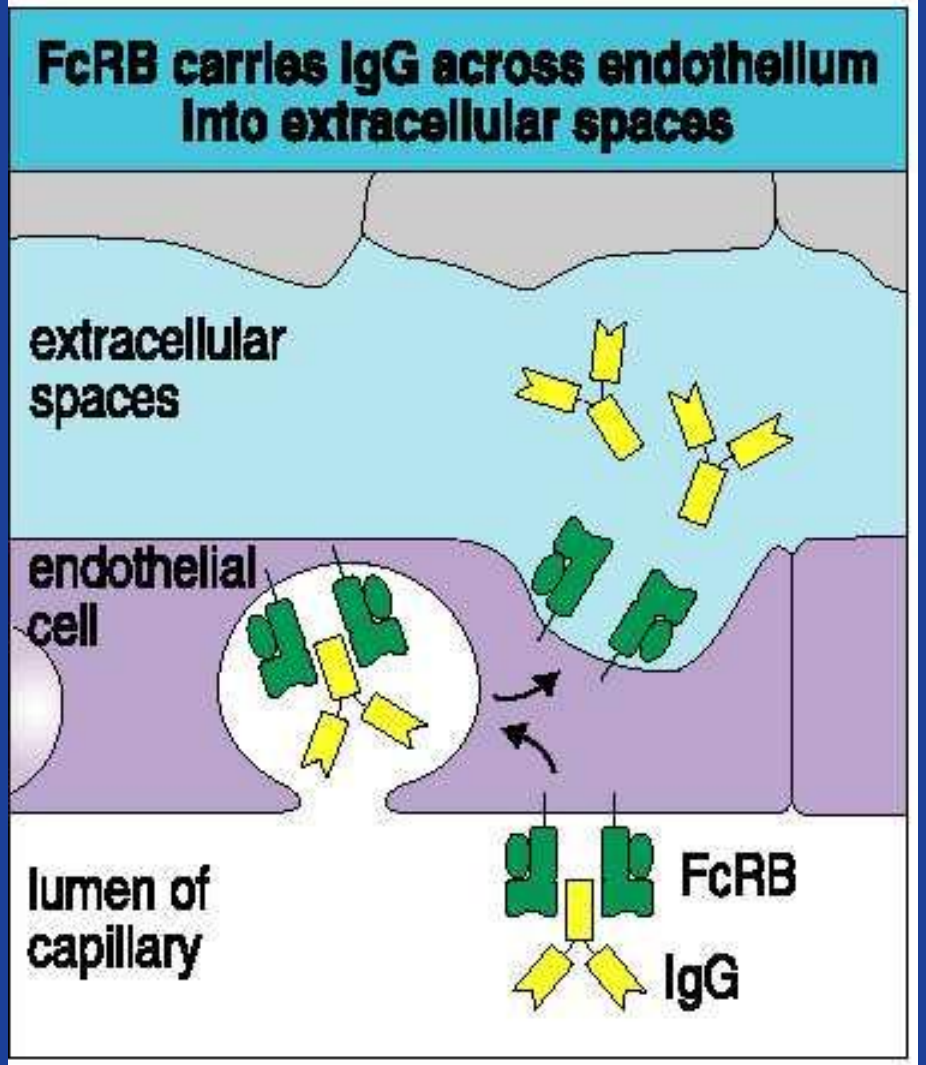


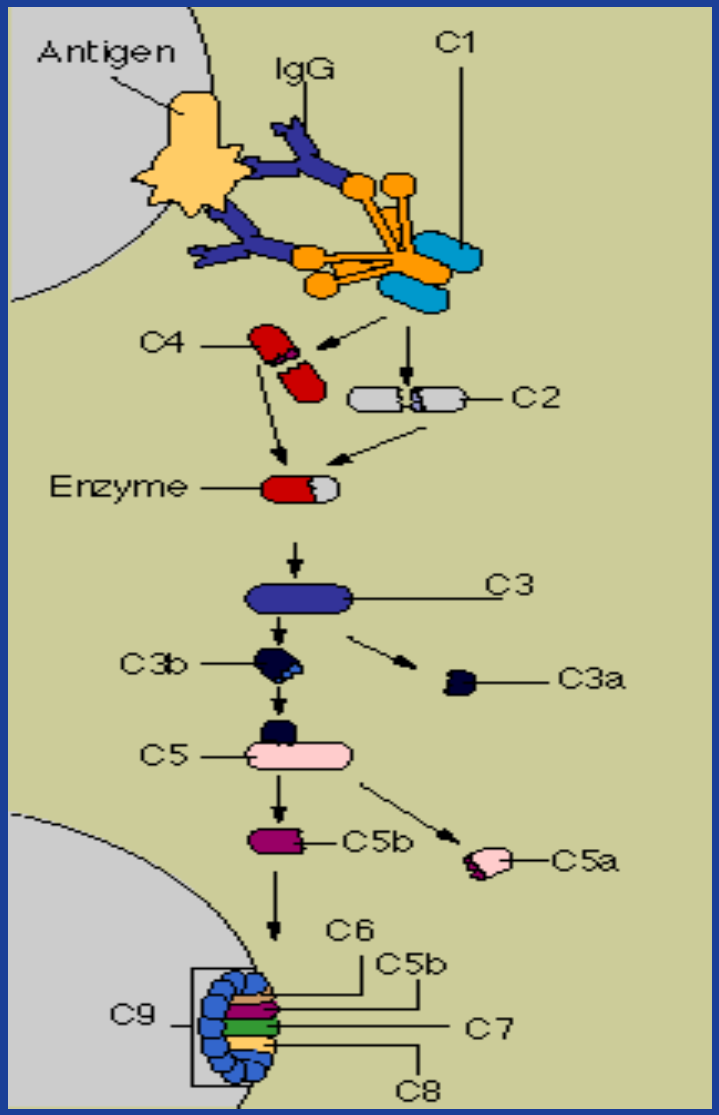

(a)
Heavy chain
α,γ,α,δ, or ε
Light chain
κ or λ
Hinge
NH_3^+
V_H
C_H1
V_L
C_L
C_H2
C_H3
CHO
COO^-

Some functions of Fc part

- Binds to Fc receptors
- Binds and activates complement
- Activates macrophages
- Induces Antibody Dependent Cellular Toxicity (ADCT)

Figure 7.16




Antigen
IgG
C1
C4
C2
Enzyme
C3
C3b
C3a
C5
C5b
C5a
C6
C5b
C9
C7
C8

Biological function IgG isotypes

	IgG1	IgG2	IgG3	IgG4
Complement binding	+	+/-	+	-
Phagocytosis/ADCC	+	-	+	+/-
Ig regulation	+	+/-	+	-
Half-life	long	long	short	long

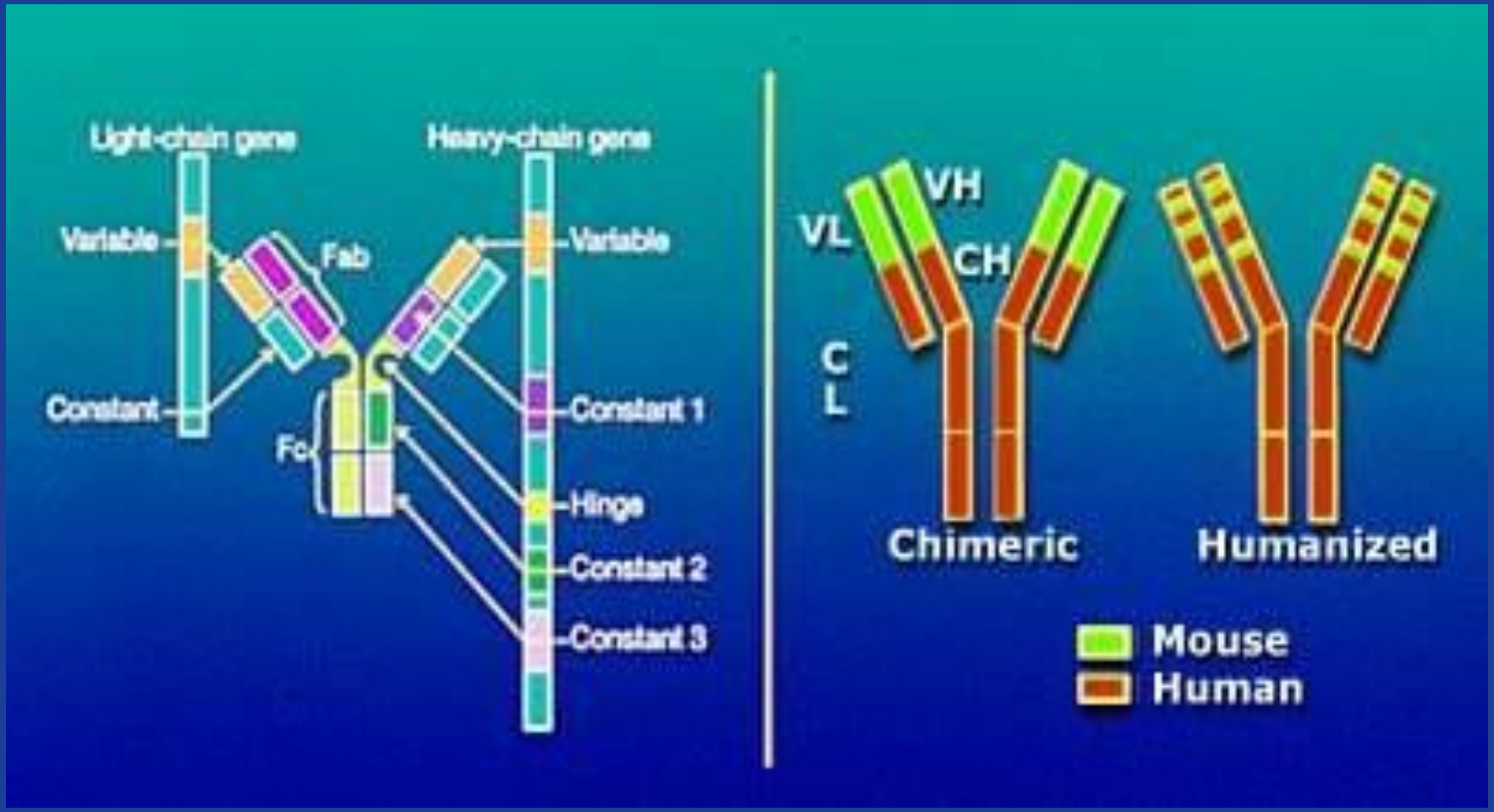
ADCC, antibody-dependant cellular toxicity

Problems with murine Mab's

- Inappropiate Fc functions
- Immunogenicity

Mab, monoclonal antibody

Chimerised and humanised antibodies

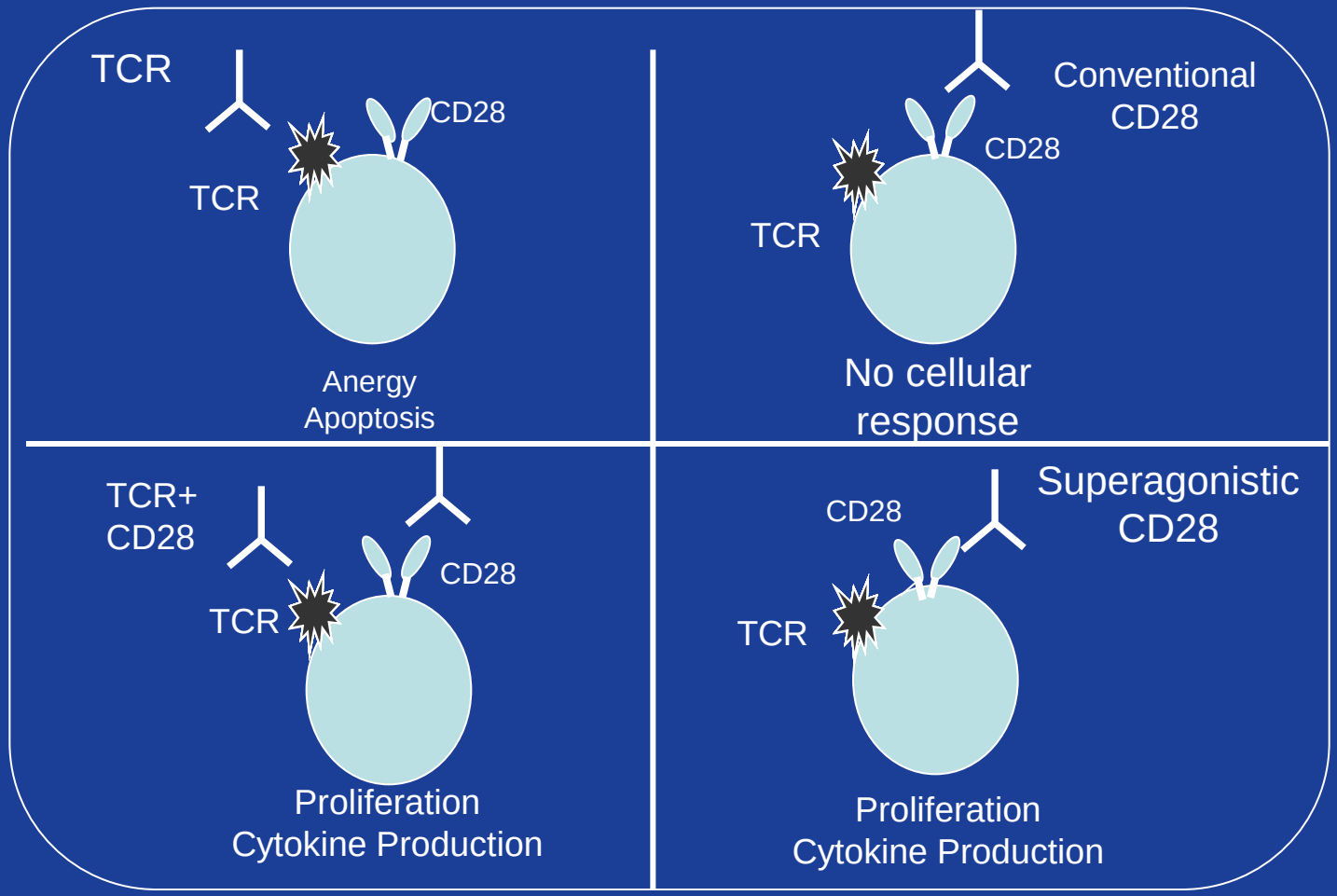


The TGN 1412 incident

- March 13, 2006 injection of 6 volunteers in a first-in-man trial
- Within 6 hours all volunteers in intensive care with severe inflammatory reactions and multi-organ failure

CD28

- Co-stimulatory receptor on CD4 T cells and most CD8 T cells
- Works in conjunction with the TCR
- Promotes the Th-1 and Th-2 cells


TCR
CD28
TCR
Anergy
Apoptosis
Conventional
CD28
CD28
TCR
No cellular
response
TCR+
CD28
CD28
TCR
Proliferation
Cytokine Production
Superagonistic
CD28
CD28
TCR
Proliferation
Cytokine Production

TGN 1412

- Developed for the treating of chronic inflammation and haematological malignancies
- Humanised MAb
- IgG 4
- Binds to C””D loop of CD28

In vitro activity TGN1412

- Binding to human, cynomolgus and rhesus monkey T cells
- Co-incubation with PBMC resulted in polyclonal T cell proliferation and cytokine production

PBMC, Peripheral Blood Mononuclear Cell

TGN 1412 in monkeys

- Expansion and activation of T cells in rhesus monkeys but no induction of cytokines
- Less active than IgG1 variant
- Also active in cynomolgus
- Half life of 8 days after IV injection
- No evidence for accumulation
- Loss of response after repeated administration

Toxicity studies with TGN1412

- Well tolerated in cynomolgus up to 50mg/kg/week for four weeks with no immune toxicity or major organ systems
- NOAEL was considered 50mg/kg
- Increase in T cells between day 13 and 17
- Moderate increase in some cytokines in some animals

NOAEL, no observe adverse events level

Volunteer trial

- Human equivalent dose was calculated to be 16 mg/kg
- Max recommended starting dose was estimated to be 1.6 mg/kg
- Company added safety margin and a starting dose of 0.1 mg/kg was proposed

Conduct of the trial

- Subjects aged 19–34
- Dosed between one hour
- Problems only in active drug group

Symptoms and timing

- Headache between 50–90 minutes
- All lumbar lumbagia
- Rigors bteween 58–120 minutes
- Fever between 2.5–6.5 hours
- Hypotension between 3.5–4.6 hours
- Tachycardia between 2.5–4.6 hours
- Nausea, vomiting, dyspnoea, bowel disturbances, amnesia

In addition extreme lymphopaenia between 8-16 hours