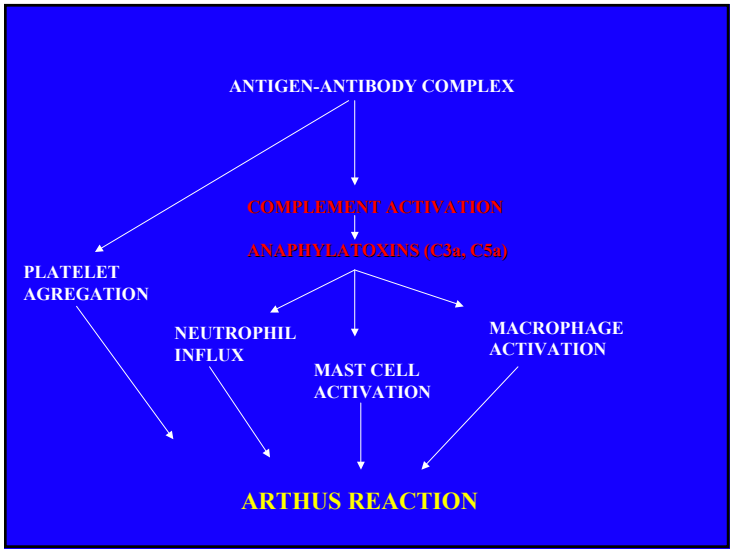
MAURICE ARTHUS 1903

«THE REPEATED INJECTIONS OF SOLUBLE FOREIGN ANTIGEN AT A UNIQUE SITE INTO RABBITS PRODUCES AN ERYTHEMATOUS AND EDEMATOUS «INFLAMMATORY» REACTION»

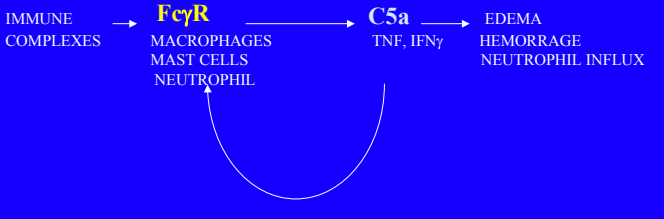


PARADOX

1994
Ravetch and col.

MICE DEFICIENT IN THE EARLY COMPONENTS OF COMPLEMENT (C1, C3) MOUNT A NORMAL INFLAMMATORY RESPONSE

INFLAMMATION IS CONTROLED BY FcγR AND C5a



FONCTIONS EFFECTRICES DES ANTICORPS

1. **NEUTRALISATION DES PATHOGÈNES : IgA (muqueuses)**
2. **ACTIVATION DU COMPLEMENT (IgM, IgG)**
3. **INTERNALISATION PAR PHAGOCYTOSE DANS LES MACROPHAGES ET LES NEUTROPHILES (IgG)**
4. **AUGMENTATION DE LA PRESENTATION DE L'ANTIGENE PAR LES CPA PAR ENDOCYTOSE(IgG)**
5. **ACTIVATION DE LA CYTOTOXICITE DES CELLULES NK (IgG), DES EOSINOPHILES ET BASOPHILES (IgE)**
6. **TRANSFERT**

LE TRANSPORT DES ANTICORPS A TRAVERS LES BARRIERES EPITHELIALES

TRANSPORT DES IgA SECRETOIRES (IgM)

- Via Poly IgR
- Intestin, bronches, glandes mammaires (lactation), salive, larmes

→ *Rôle de protection au niveau des muqueuses chez l'adulte*

→ *Rôle de protection chez le nouveau-né*

TRANSPORT DES IgG

- Via FcR néonatal
- Sur le placenta

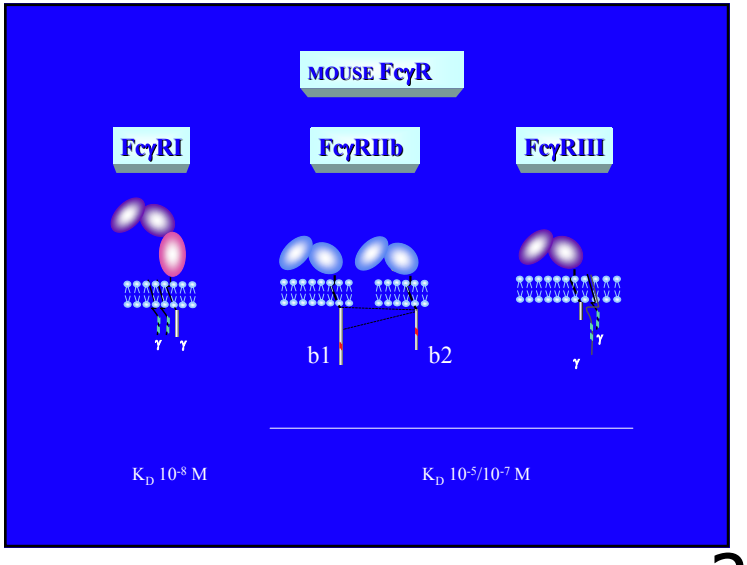
→ *Rôle de transport IgG mère – fœtus*

- Dans intestin, foie chez adulte (cellules endothéliales)

→ *Rôle régulateur du taux d'IgG sériques*

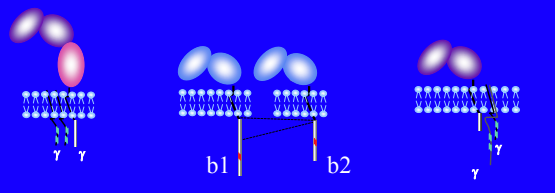
BIOLOGICAL ACTIVITIES OF Ag-Ab (IgG) COMPLEXES

- **Internalization**
  - **Phagocytosis**
  - **Endocytosis**
- **Cell activation :**
  - **Release of mediators**
  - **Perforin and granzyme release (ADCC)**
  - **Cytokine secretion**
- **Inhibition of Cell activation**



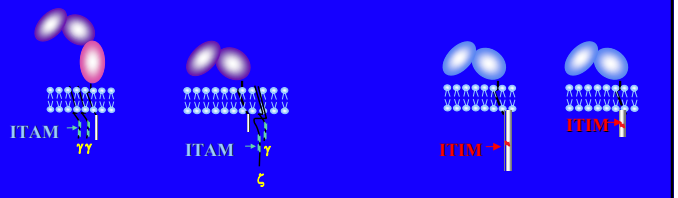
MOUSE FcγR

FcγRI	FcγRIIb	FcγRIII
K_D 10^{-8} M	K_D $10^{-5}/10^{-7}$ M	
Macrophages	B cells	Macrophages	NK cells
Neutrophils	Mast cells	Dendritic cells	Monocytes
Dendritic cells			Dendritic cells
			Mast cells



ACTIVATING RECEPTORS **INHIBITORY RECEPTORS**

FcγRI FcγRIII FcγRIIb1 FcγRIIb2



« Immunoreceptor tyrosine activation motif »

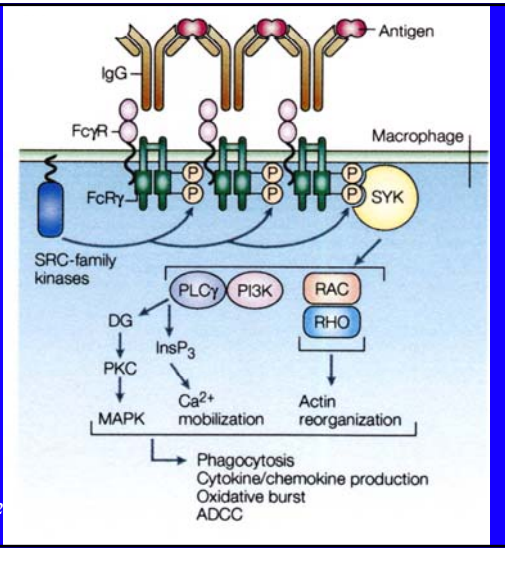
(YxxL)(X)n(YxxL)

« Immunoreceptor tyrosine inhibition motif »

ITYSLL

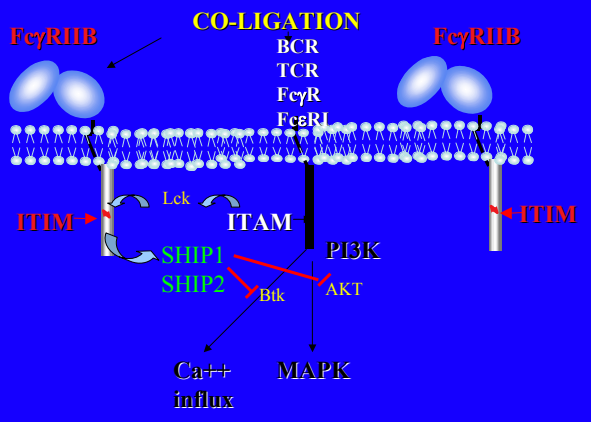
	ACTIVATING FcγR	INHIBITORY FcγR
Dendritic Cells	+	+
Macrophages	+	+
Neutrophils	+	+
Mast cells	+	+
NK cells	+	-
B cells	-	+

ACTIVATING RECEPTORS



T. Takaï, Nature Rev 2002

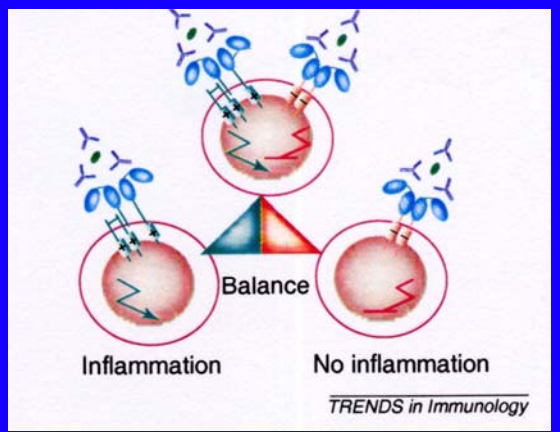
INHIBITORY FcγRECEPTORS DOWN REGULATE ITAM-DEPENDENT RESPONSES



MICE DEFICIENT IN ACTIVATING FcγR III DO NOT MOUNT IC-MEDIATED INFLAMMATORY RESPONSE

MICE DEFICIENT IN INHIBITORY FcγRII HAVE ENHANCED IC-MEDIATED INFLAMMATORY RESPONSE

FcγR CONTROL INFAMMATORY RESPONSES



PHENOTYPE OF MICE DEFICIENT IN ACTIVATING RECEPTORS

DELETED GENE PRODUCT	IN VITRO	IN VIVO
FcRγCHAIN or FcγRI or FcγRII	**IMPAIRED :** PHAGOCYTOSIS ADCC Ag PRESENTATION CYTOKINE RELEASE MAST CELL ACTIVATION (IgE, IgG)	**IMPAIRED :** HYPERSENSITIVITY REACTIONS ANAPHYLAXIS (IgG,IgE) **RESISTANT TO AUTOIMMUNE DISEASES :** • SPONTANEOUS (NZB/W) • INDUCED BY - COLLAGEN (DBA1) - ANTIBODIES - GLOMERULONEPHRITIS - VASCULATIS - ALVEOLITIS - ITP - AIHA **BACTERIAL INFECTIONS (FcγRI)**

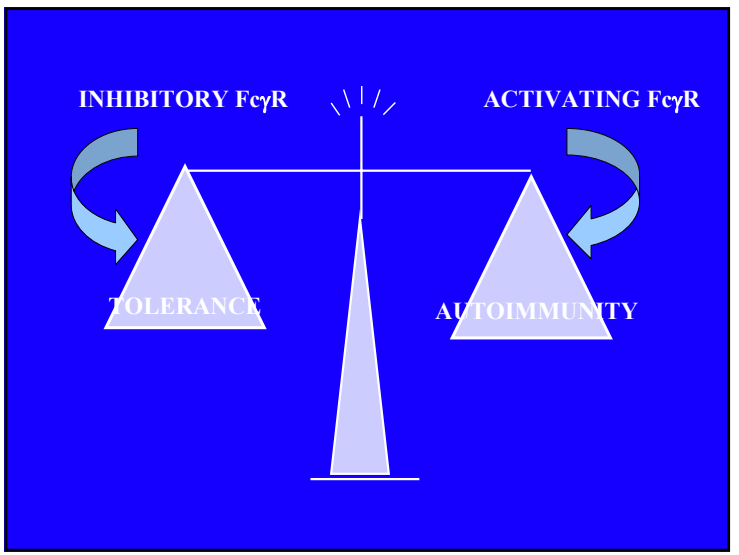
ACTIVATING RECEPTORS ARE REQUIRED FOR AUTOIMMUNITY

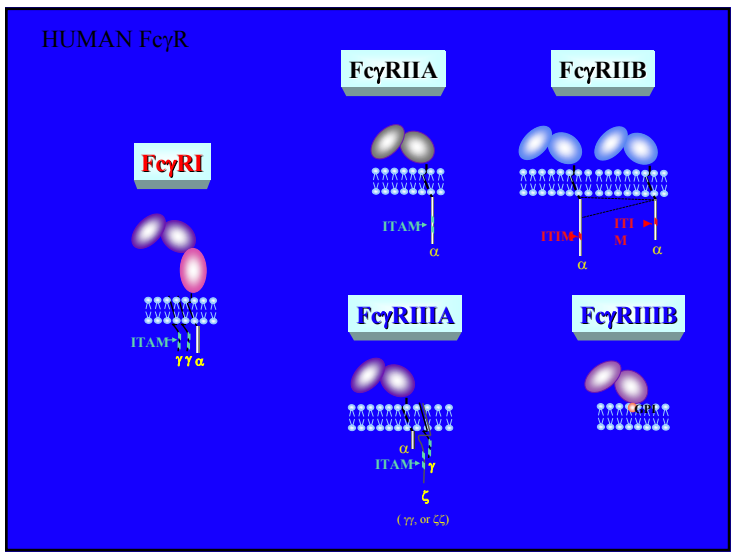
PHENOTYPE OF FcRγRIIB-DEFICIENT MICE

IN VITRO	IN VIVO
ENHANCED MACROPHAGE RESPONSE TO IC =	ENHANCED
- Ca ++	- TYPE I, II, III HYPERSENSITIVITY REACTIONS
- PHAGOCYTOSIS	-ARTHUS REACTION
	- ANTIBODY PRODUCTION
	INCREASED SUSCEPTIBILITY TO AUTOIMMUNE DISEASES
	• SPONTANEOUS = IN C57 BL/6 (GLOMERULONEPHRITIS)
	• INDUCED BY - COLLAGEN (DBA/1), MOG (EAE)
	- ANTIBODIES GLOMERULONEPHRITIS ALVEOLITIS

INHIBITORY RECEPTORS CONTROL PERIPHERAL TOLERANCE

MICE DEFICIENT IN	HYPERSENSITIVITY REACTIONS (II,III) ARTHUS REACTION	AUTOIMMUNE DISEASES (IgG DEPENDENT)
ACTIVATING FcγR	IMPAIRED	RESISTANT
INHIBITORY FcγR	ENHANCED	INCREASED SUSCEPTIBILITY





FcγR POLYMORPHISMS IN HUMAN AUTOIMMUNE DISEASES

INCREASED SUSCEPTIBILITY TO	FcγRIIa	FcγRIIB	FcγRIIIA	FcγRIIIB
SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)	131 Arg	232 Thr*	158 Phe	NA2
RHUMATOID ARTHRITIS (RA)			158 Phe	
WEGENER GRANULOMATOSIS				NA1
GUILLAIN BARRE SYNDROME	131Arg			NA2
MULTIPLE SCLEROSIS	131 Arg			NA2

FcγR CONTROL AUTOIMMUNITY VIA

1 - DENDRITIC CELLS =

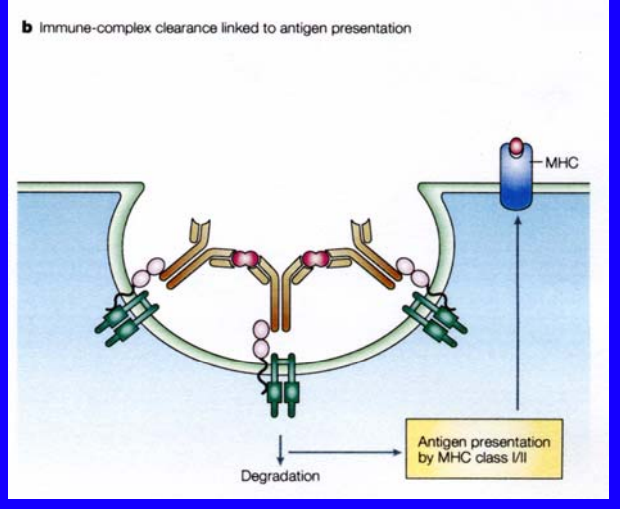
FcγR REGULATE ANTIGEN PRESENTATION

2 - B CELLS =

FcγR DOWN REGULATE AUTO ANTIBODY PRODUCTION

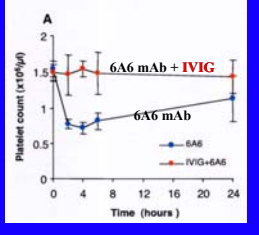
3 - MACROPHAGES =

FcγR CONTROL
PRODUCTION OF INFLAMMATORY CYTOKINES
CLEARANCE OF IMMUNE COMPLEXES (LIVER)



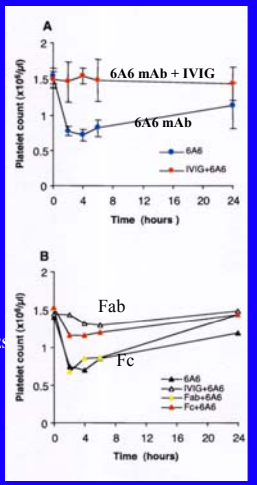
IVIG PROTECT MICE FROM Ab- INDUCED ITP

Samuelson et al, Science 2001



IVIG
Anti-platelet mAb 6A6 → MOUSE
Measure platelet counts

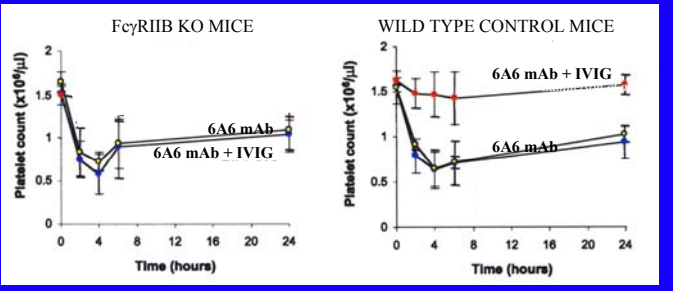
IVIG PROTECT MICE FROM Ab- INDUCED ITP



Samuelson et al, Science 2001

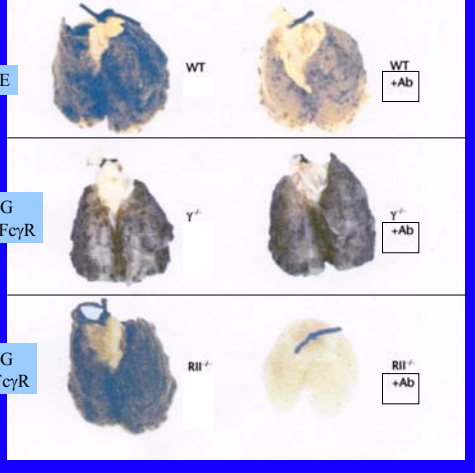
IVIG PROTECTION REQUIRES THE CONSTANT BUT NOT THE VARIABLE REGION OF IVIG

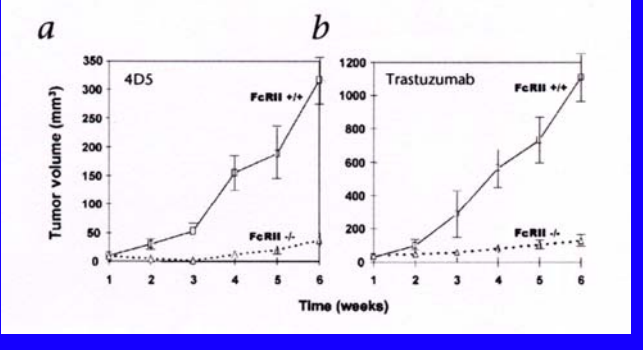
PROTECTION BY IVIG REQUIRES INHIBITORY FcγR



Samuelson et al, Science 2001

Fcγ RECEPTORS CONTROL ANTIBODY THERAPY TO METASTATIC MELANOMA





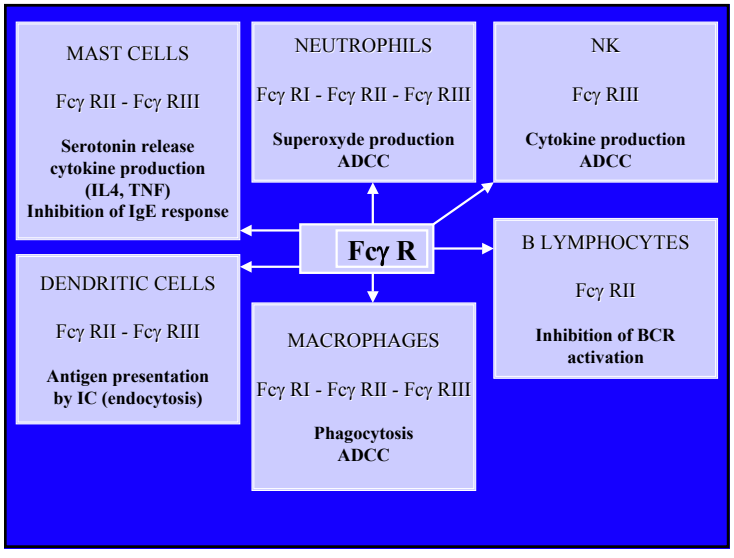
CONCLUSIONS

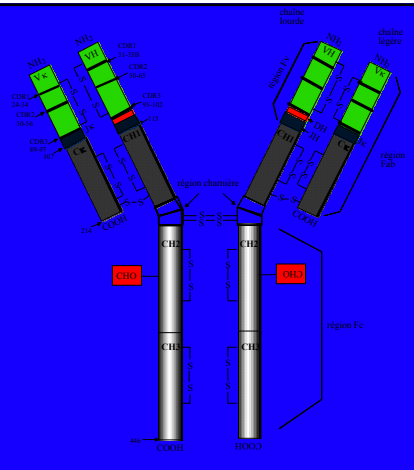
FcγR CONTROL

1-INFLAMMATION

2-PERIPHERAL TOLERANCE

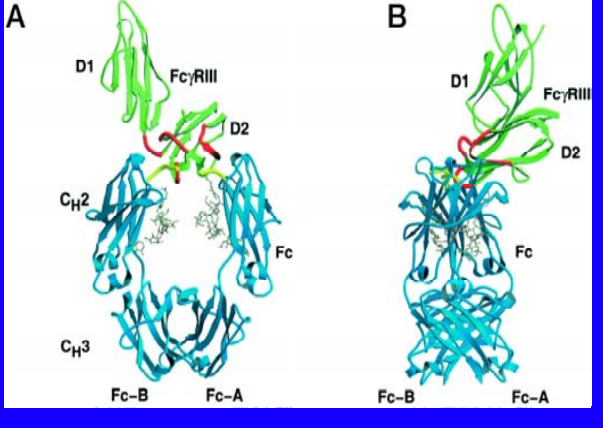
3-RESPONSE TO ANTIBODY-MEDIATED THERAPIES OF AUTOIMMUNE DISEASES AND CANCER

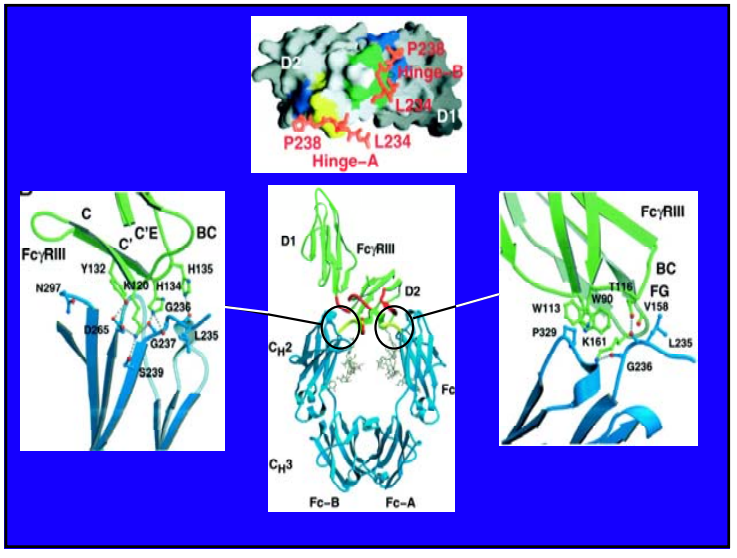


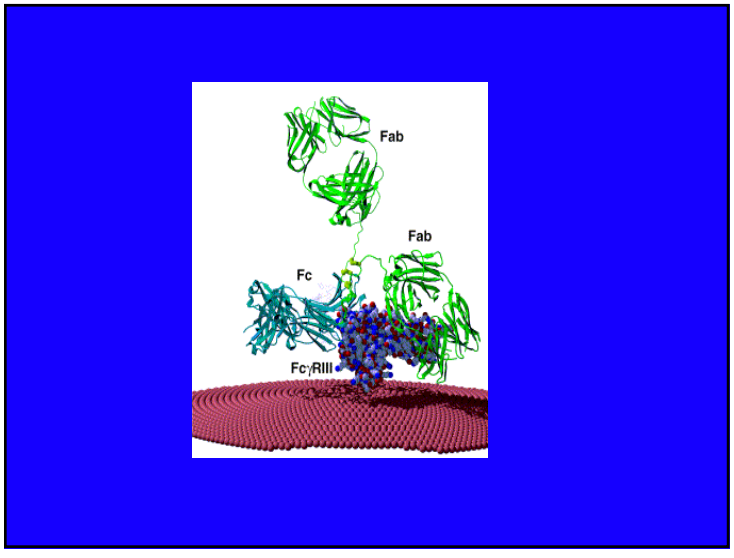


HOW TO AVOID PERMANENT ACTIVATION OF THE IMMUNE SYSTEM ?

ONE IgG BINDS ONE FcγR
(Coll K. Kato et al, and P. Sun et al)







CONCLUSION 2

ONE FcγR MOLECULE BIND ONE IgG MOLECULE

THIS STOICHIOMETRY AVOIDS THE DELETERIOUS EFFECTS THAT IgG ANTIBODIES MAY EXERT VIA ACTIVATING FcγR

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