Meccanismi dell'immunità

IMMUNITA' INNATA

Non specifica ma immediata

Senza "memoria"

Opera in tutti gli organismi

Barriere fische o chimiche (epiteli e mucose, pH gastrico)

Cellule con attività fagocitaria

Proteine specifiche,

RNAi

IMMUNITA' ADATTATIVA

Specifica ma lenta

Induce "memoria"

Limitata ai vertebrati

Risposte cellulari mediate da linfociti T

Risposte anticirpali mediate da linfociti B

Origine del sistema immunitario

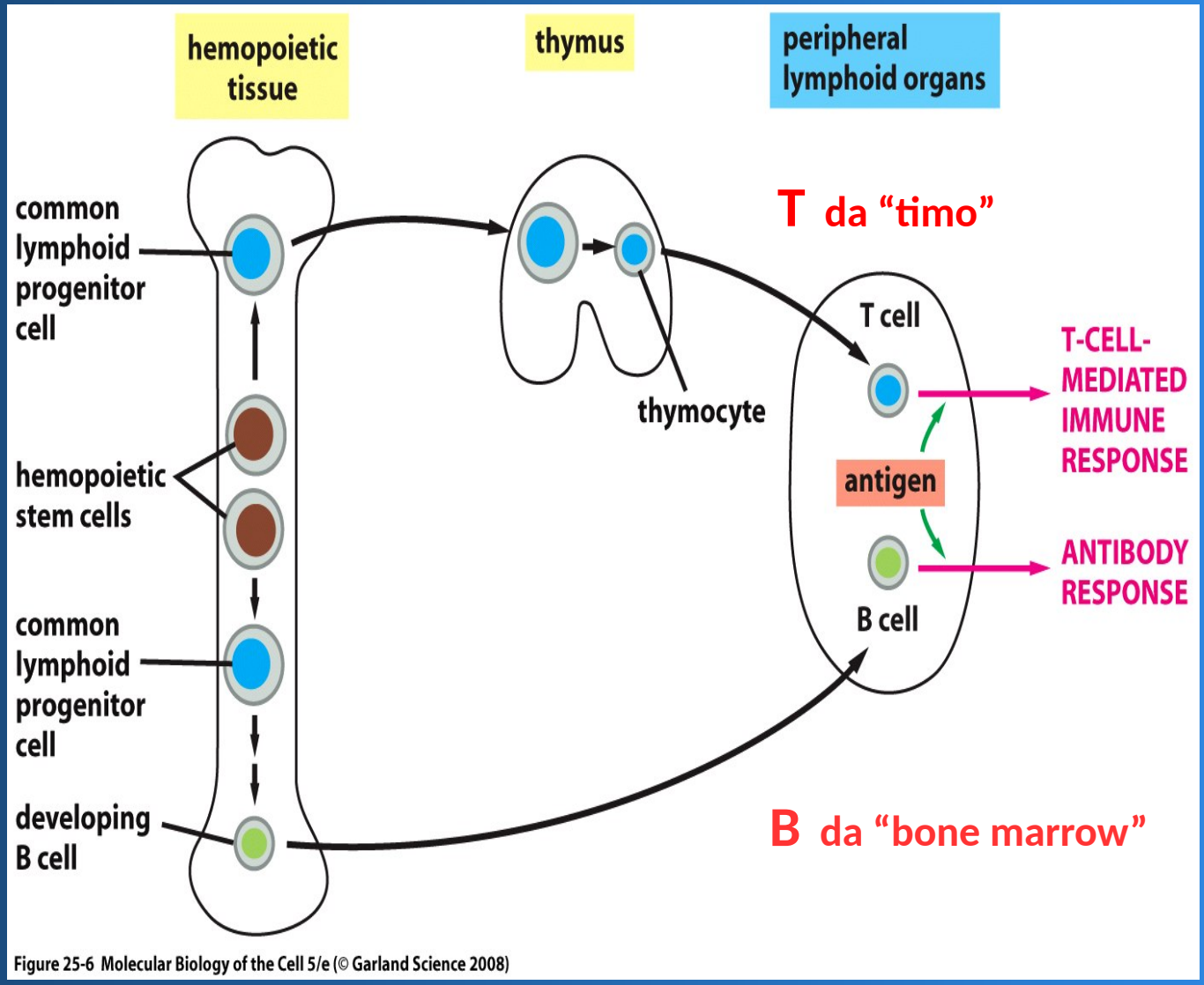
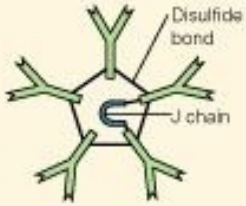
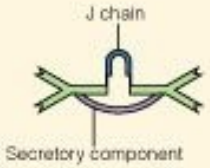
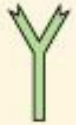


Figure 25-6 Molecular Biology of the Cell 5/e (© Garland Science 2008)

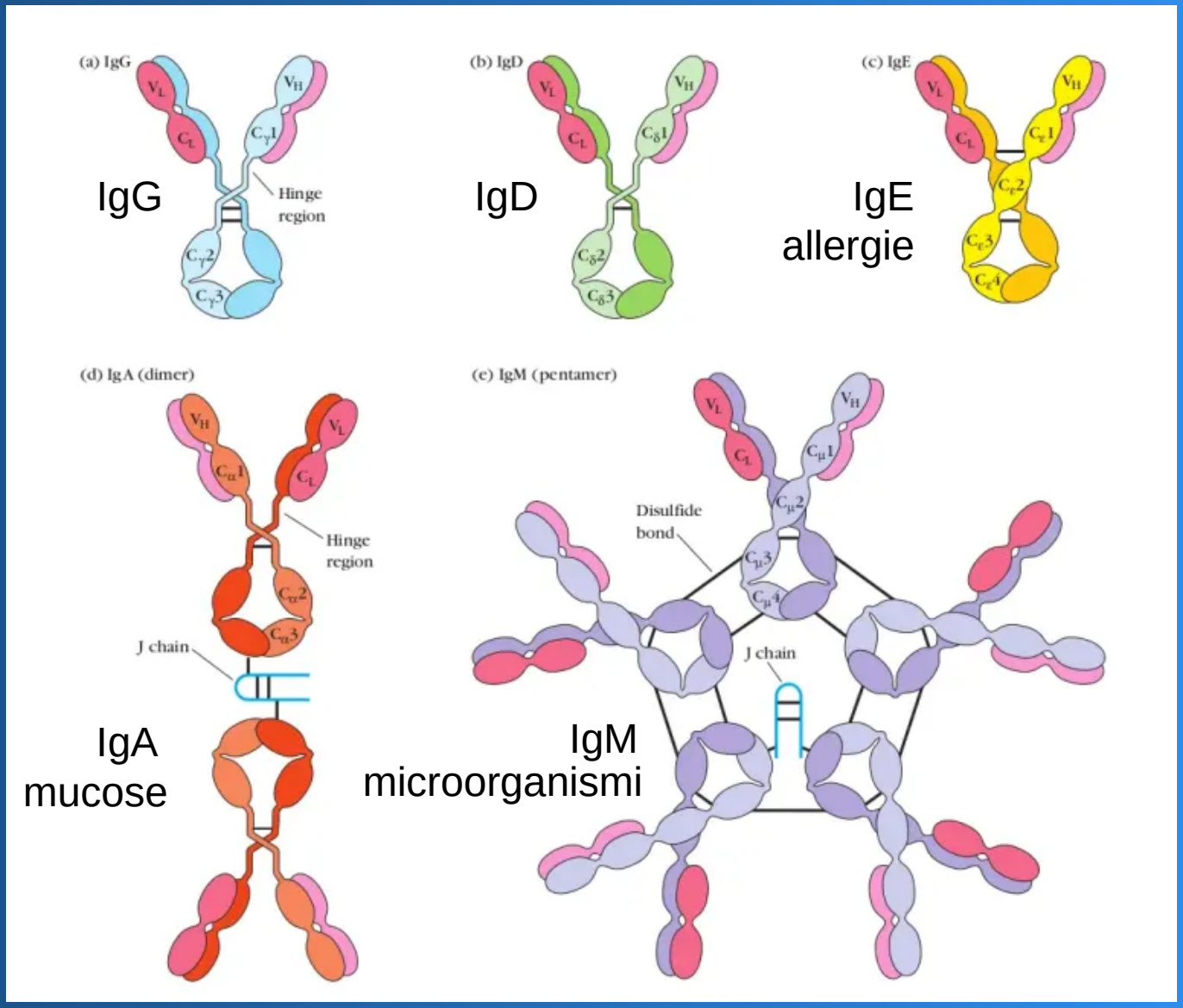
Risposta cellulare

Risposta Umorale
Immunoglobuline (anticorpi, Ab)

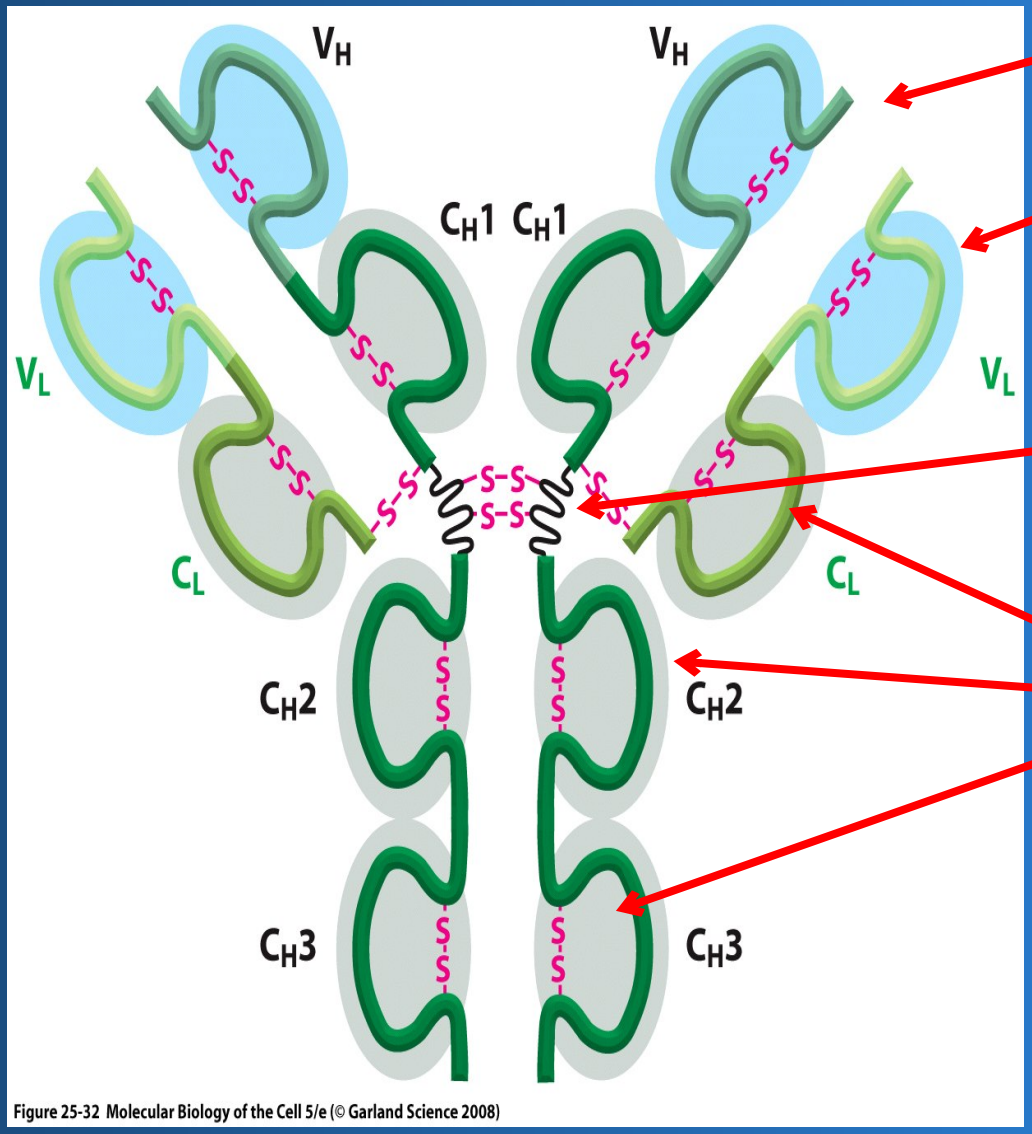
Classi di immunoglobuline (Ig)

Characteristics	IgG	IgM	IgA	IgD	IgE
					
Structure	Monomer	Pentamer	Dimer (with secretory component)	Monomer	Monomer
Percentage of total serum antibody	80%	5–10%	10–15%*	0.2%	0.002%
Location	Blood, lymph, intestine	Blood, lymph, B cell surface (as monomer)	Secretions (tears, saliva, mucus, intestine, milk), blood lymph	B cell surface, blood, lymph	Bound to mast and basophil cells throughout body, blood
Molecular weight	150,000	970,000	405,000	175,000	190,000
Half-life in serum	23 days	5 days	6 days	3 days	2 days
Complement fixation	Yes	Yes	No†	No	No
Placental transfer	Yes	No	No	No	No
Known functions	Enhances phagocytosis; neutralizes toxins and viruses; protects fetus and newborn	Especially effective against microorganisms and agglutinating antigens; first antibodies produced in response to initial infection	Localized protection on mucosal surfaces	Serum function not known; presence on B cells functions in initiation of immune response	Allergic reactions; possibly lysis of parasitic worms

Classi di immunoglobuline (Ig)



Immunoglobuline



Catena pesante

Catena leggera

Zone "cerniera"

Domini "IMMUNOGLOBULIN LIKE" di circa 100 aa

Immunoglobuline

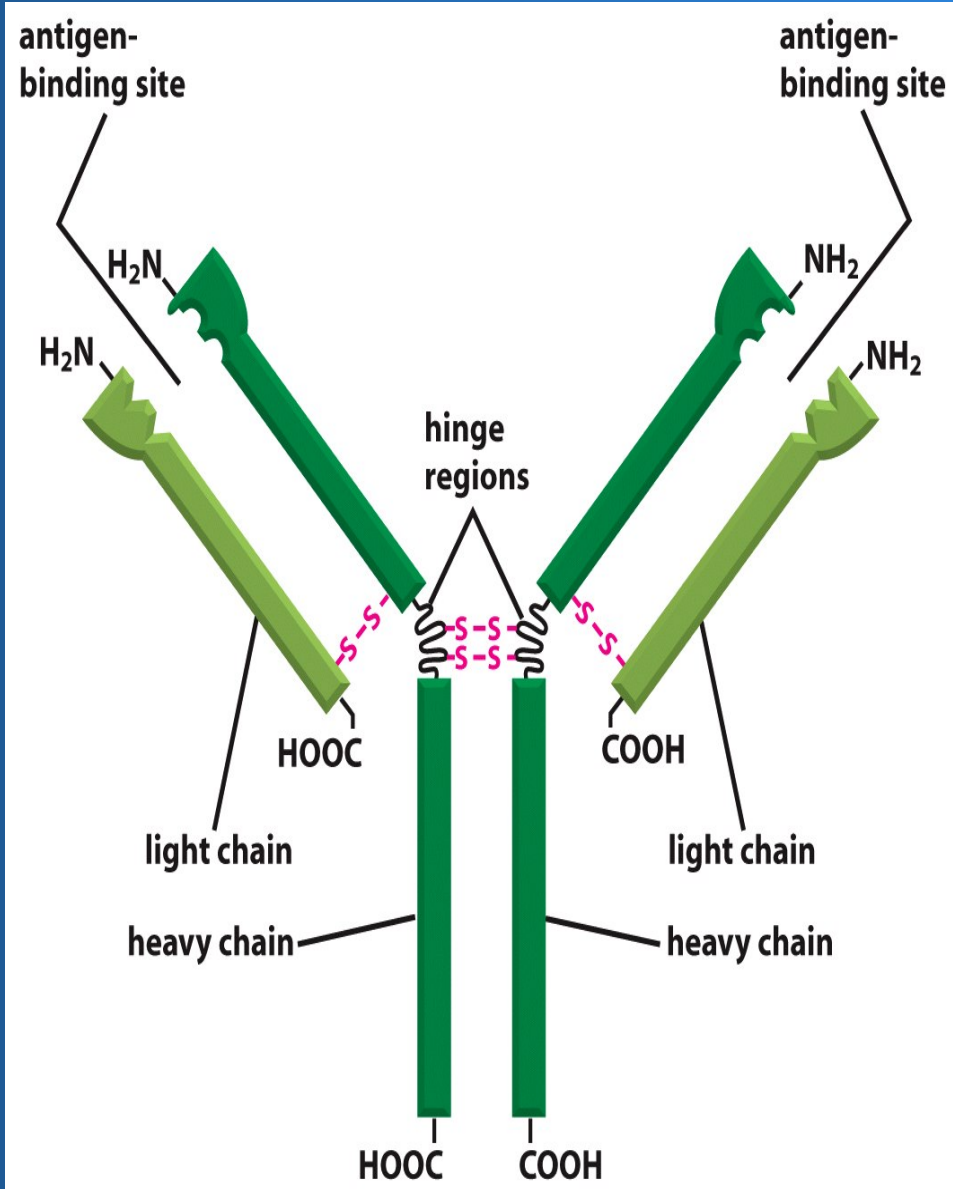
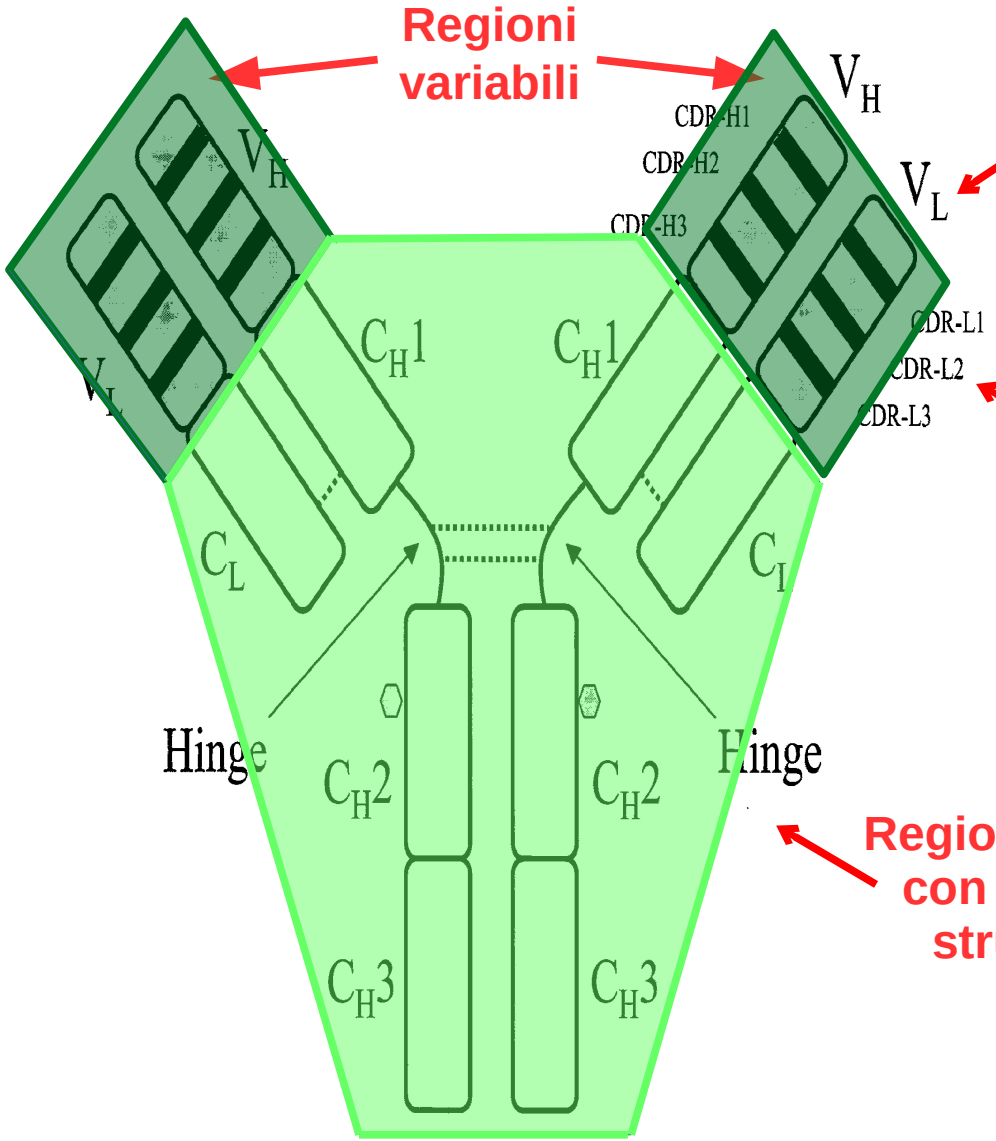


Figure 25-21 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Immunoglobuline



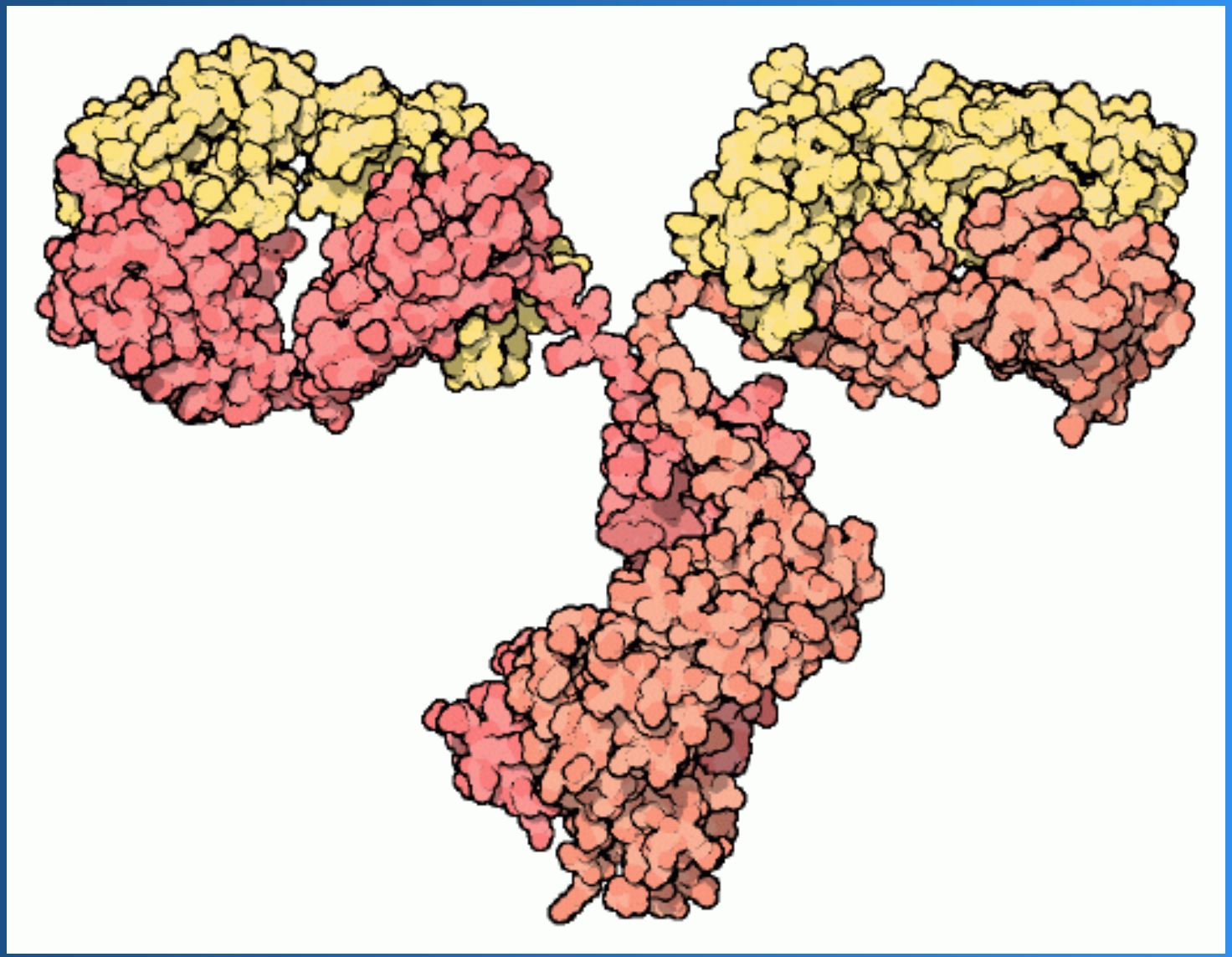
Regioni ipervariabili DIRETTAMENTE COINVOLTE NEL LEGAME

CDR 5–10 AA

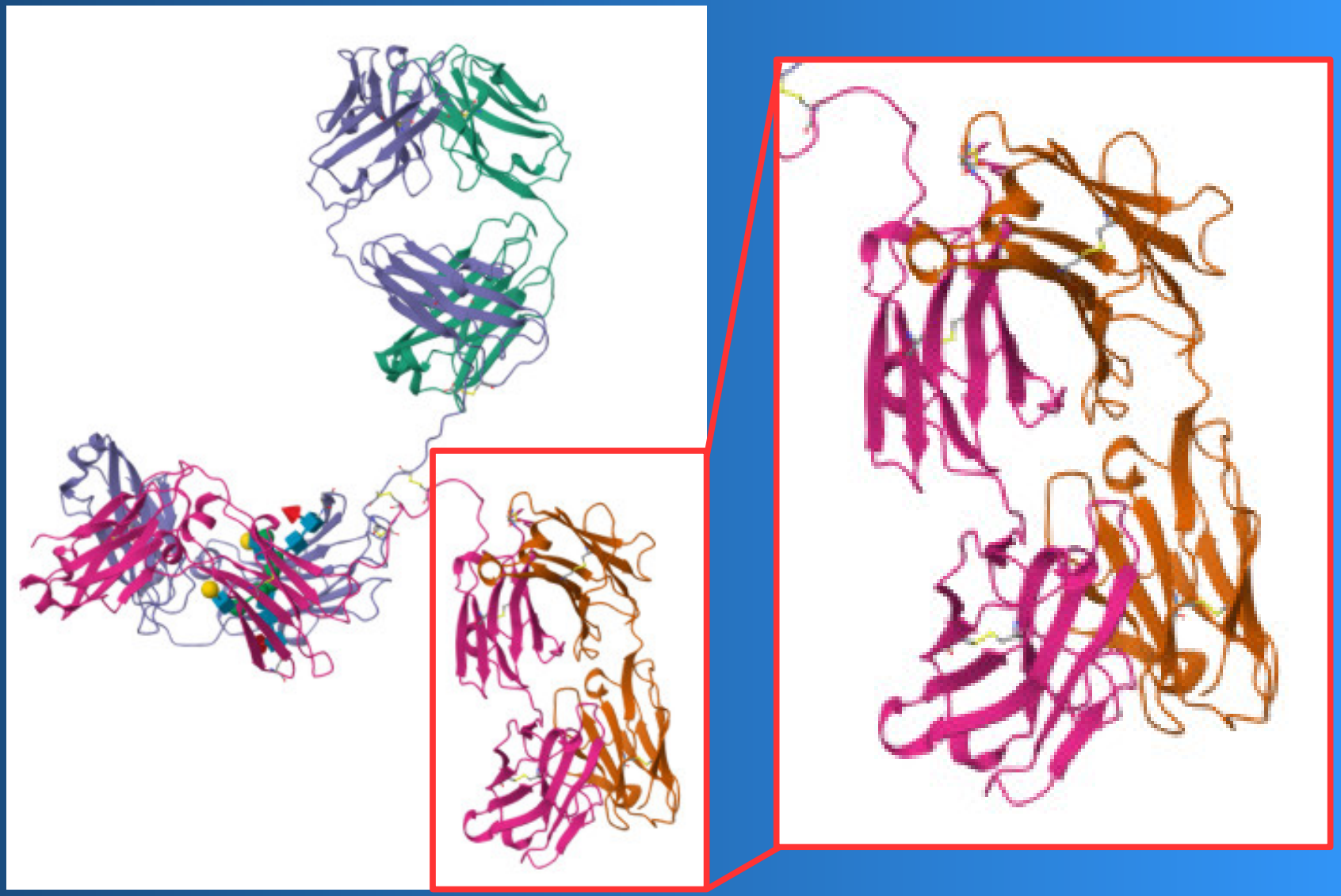
Complementarity Determining Regions

Regioni costanti con funzione strutturale

Immunoglobuline



Immunoglobuline



Immunoglobuline

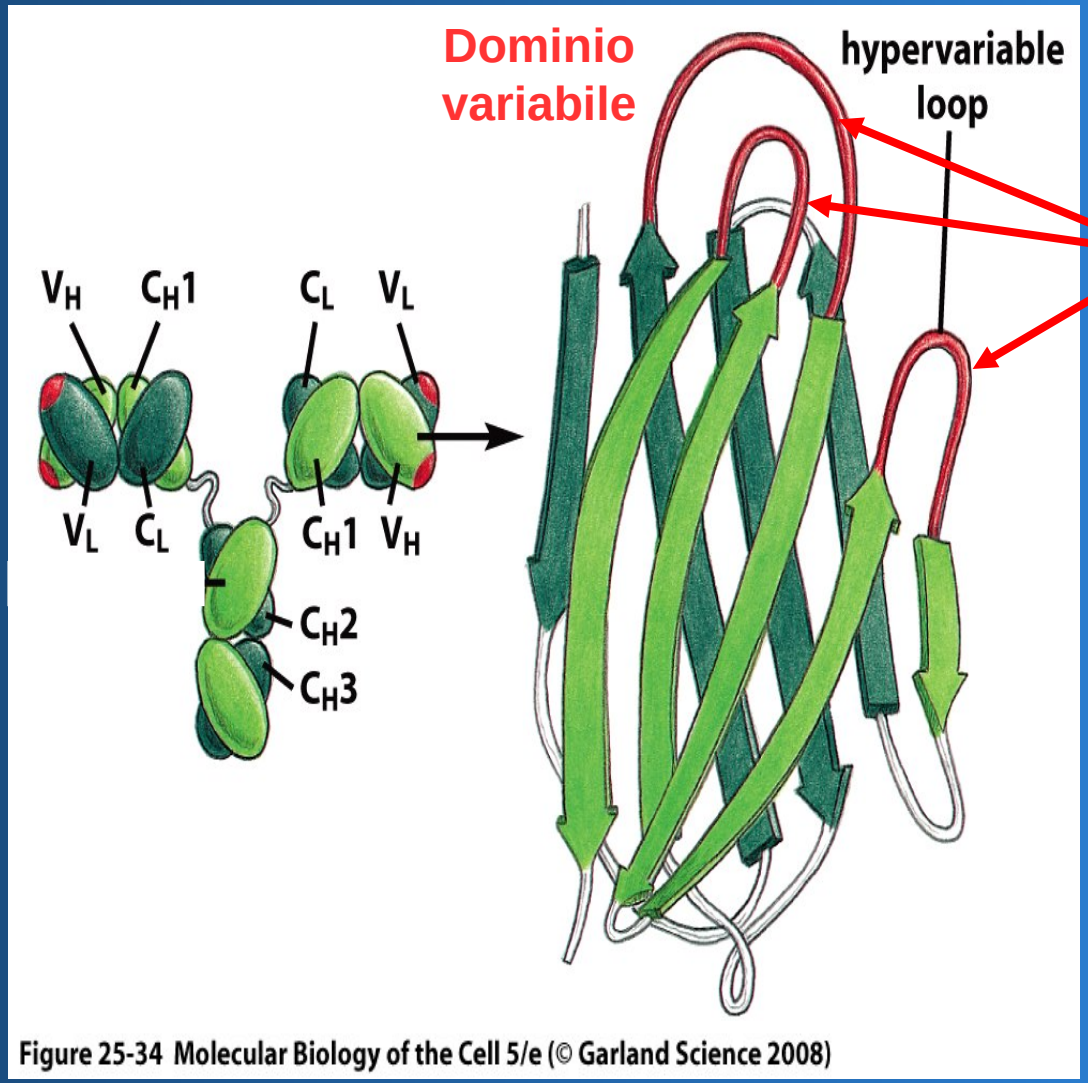


Figure 25-34 Molecular Biology of the Cell 5/e (© Garland Science 2008)

CDR

<u>Ipervariabili</u>

sono le zone più esposte

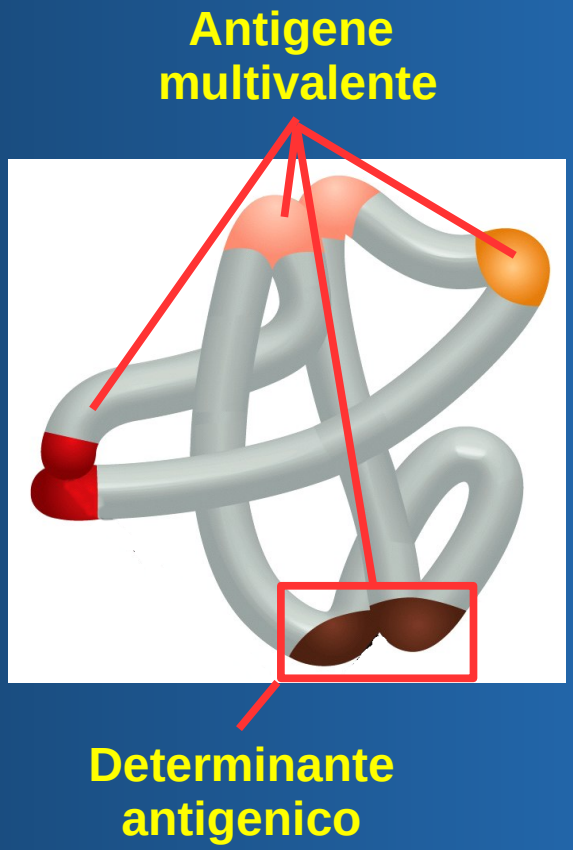
riconoscono gli antigeni

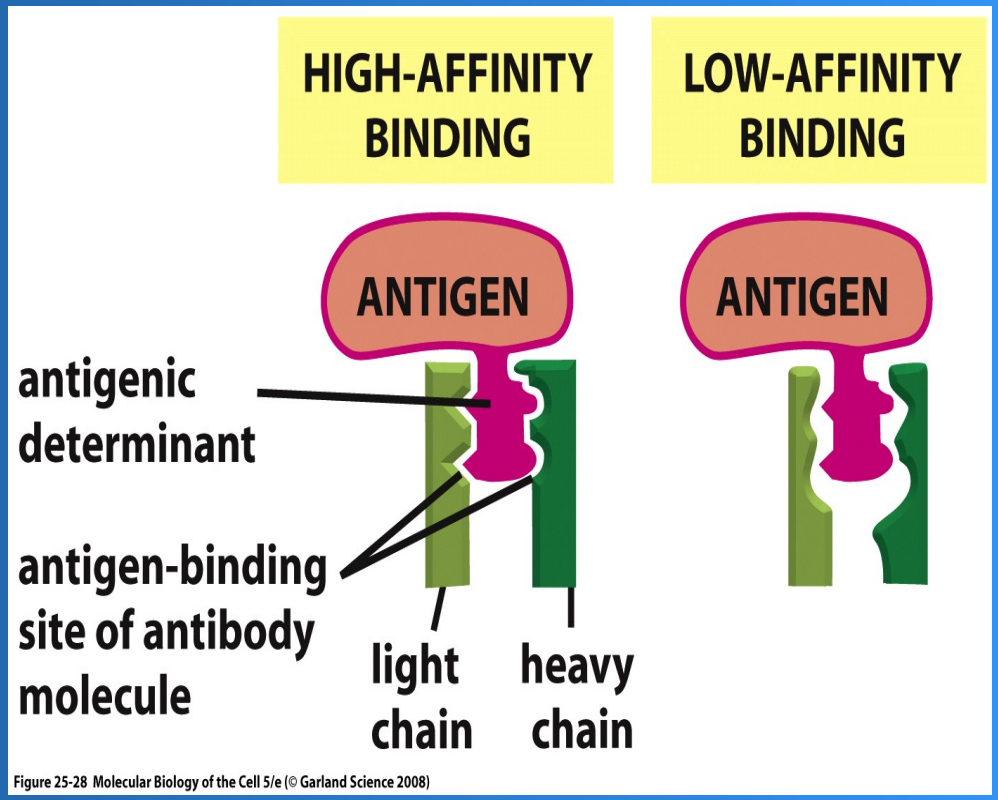
5 – 10 aminoacidi di lunghezza

Antigeni ed epitopi

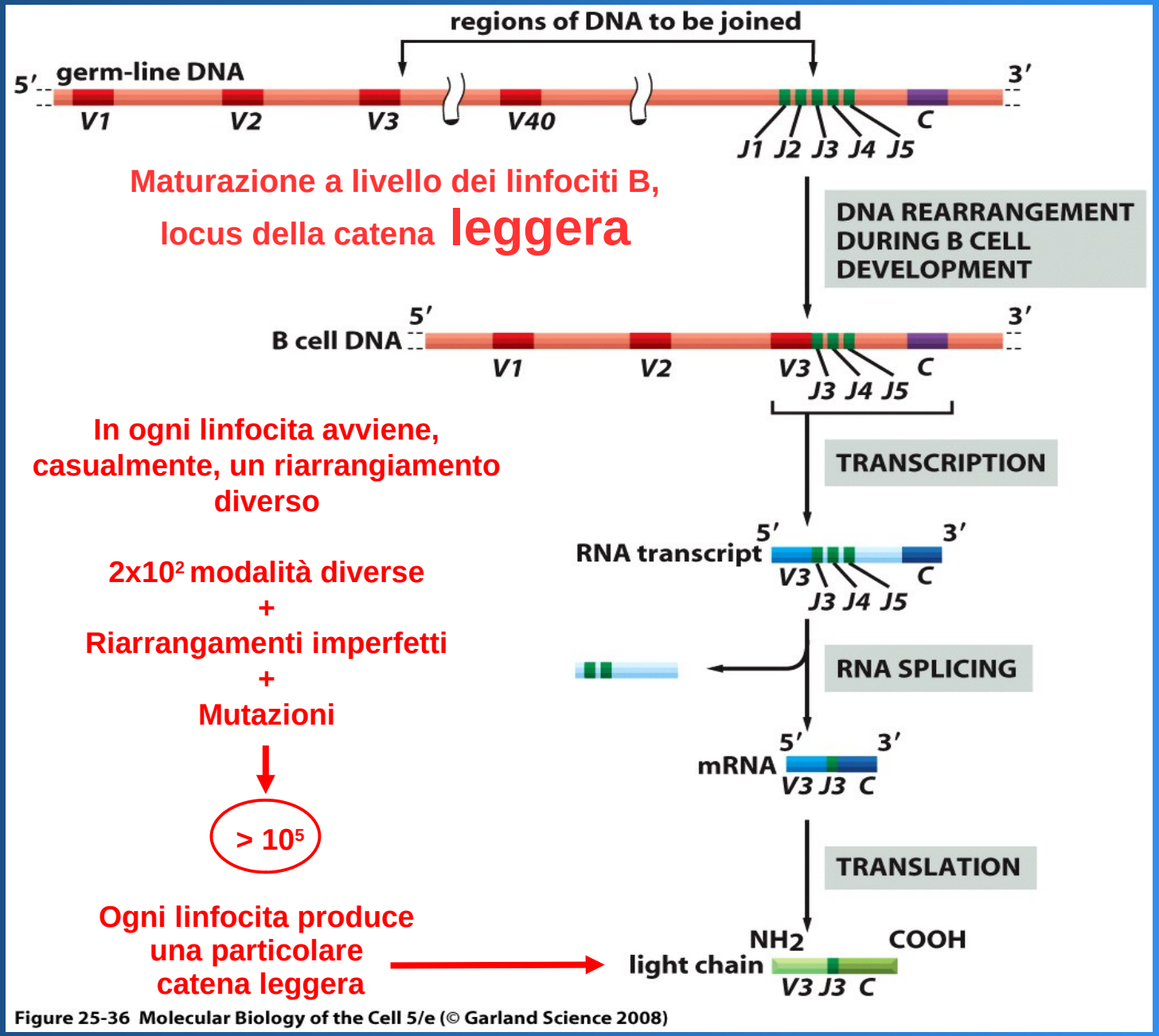
Un antigene può avere uno o più determinanti antigenici (epitopi).

Ogni epitopo stimola cellule B differenti





Riarrangiamento delle catene leggere



Riarrangiamento delle catene pesanti

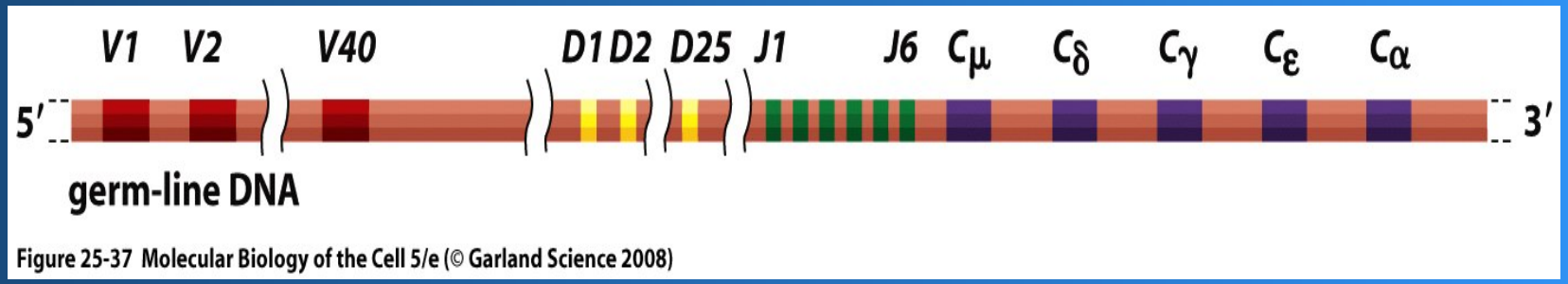


Figure 25-37 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Maturazione a livello dei linfociti B,

locus della catena pesante

In ogni linfocita avviene,
casualmente, un riarrangiamento diverso

$6x10^3$ modalità diverse
+
Riarrangamenti imperfetti
+
Mutazioni → **10^6 - 10^7**

Ogni linfocita produce una particolare catena pesante

Variabilità delle Ig

10^5 catene leggere diverse

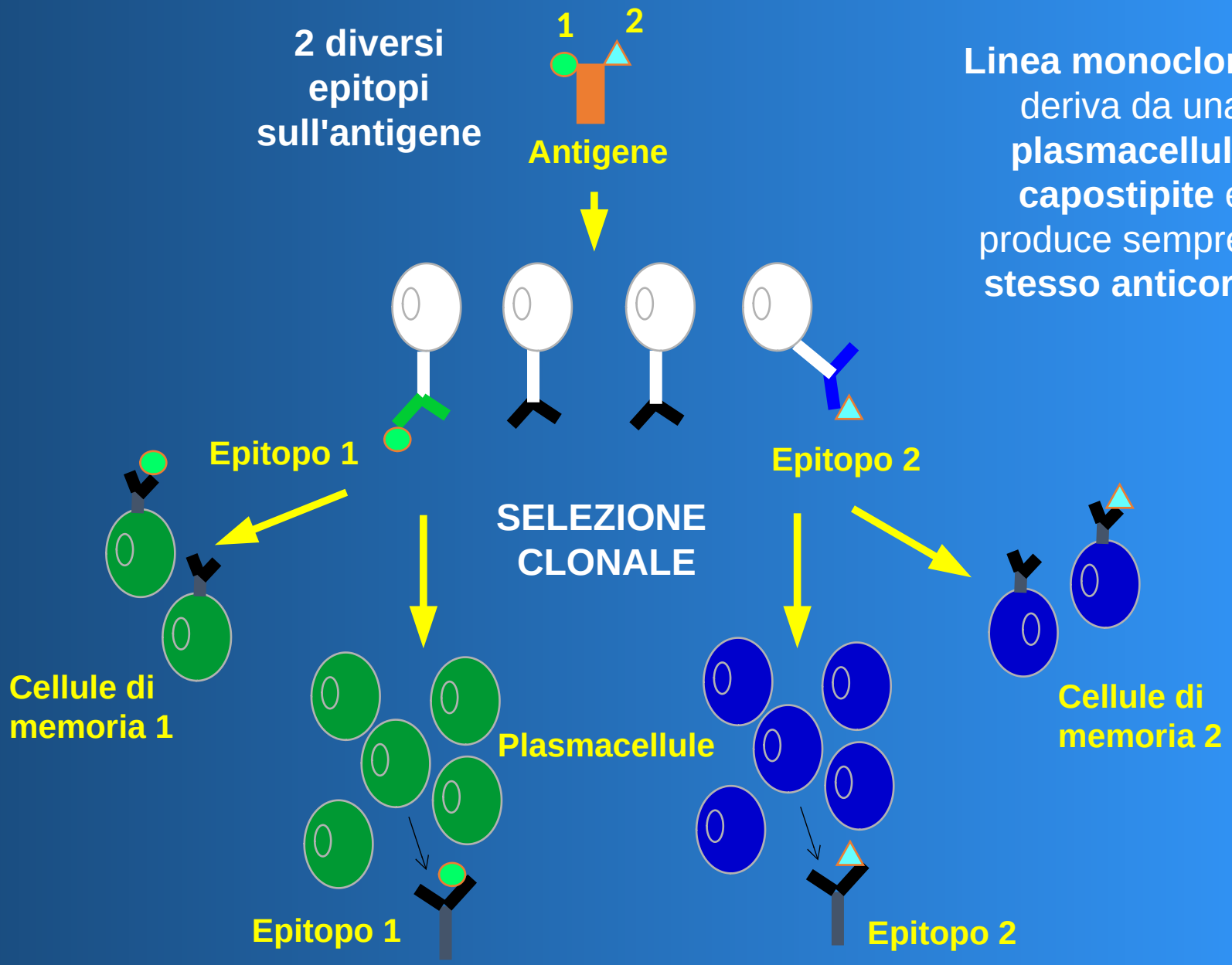
che si uniscono a

10^7 catene pesanti diverse

Diversificazione teorica degli anticorpi maturi circa 10^{12}

Molti eventi di ricombinazione non portano alla produzione di anticorpi funzionanti, ma la diversificazione reale è comunque maggiore di 10^{10}

Risposta policlonale ad un antigene



Risposta primaria e secondaria

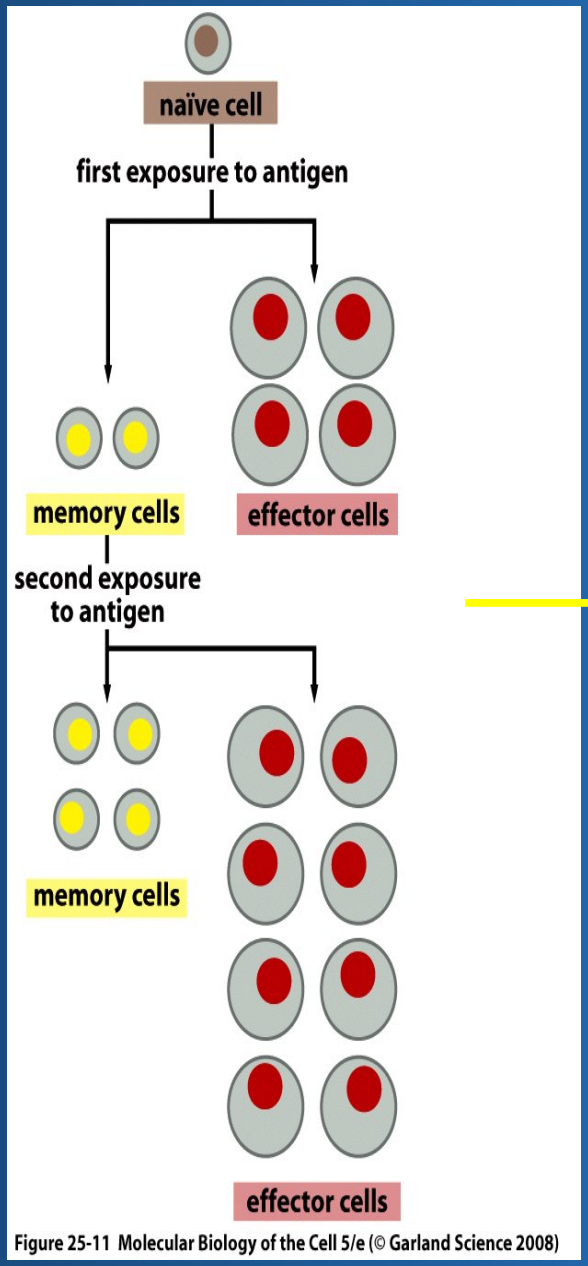


Figure 25-11 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Linfocita mai esposto all'antigene

Primo contatto con l'antigene

↓

Proliferazione e differenziamento

↓

a partire da una cellula

Poche cellule, risposta lenta

Seconda esposizione allo stesso antigene

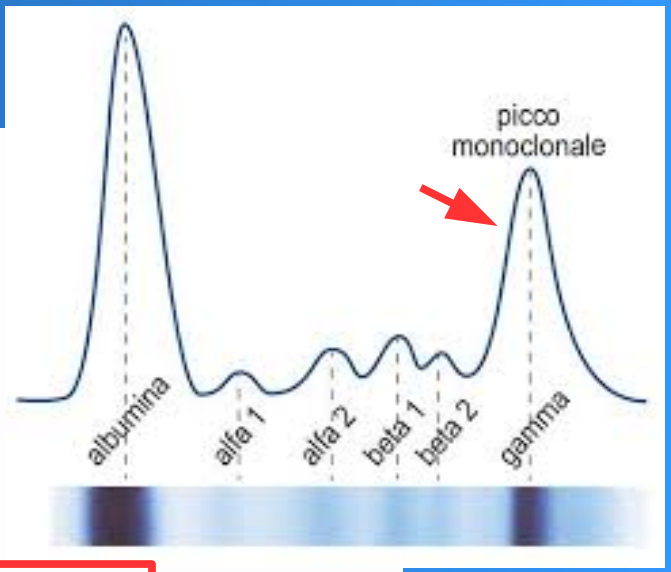
↓

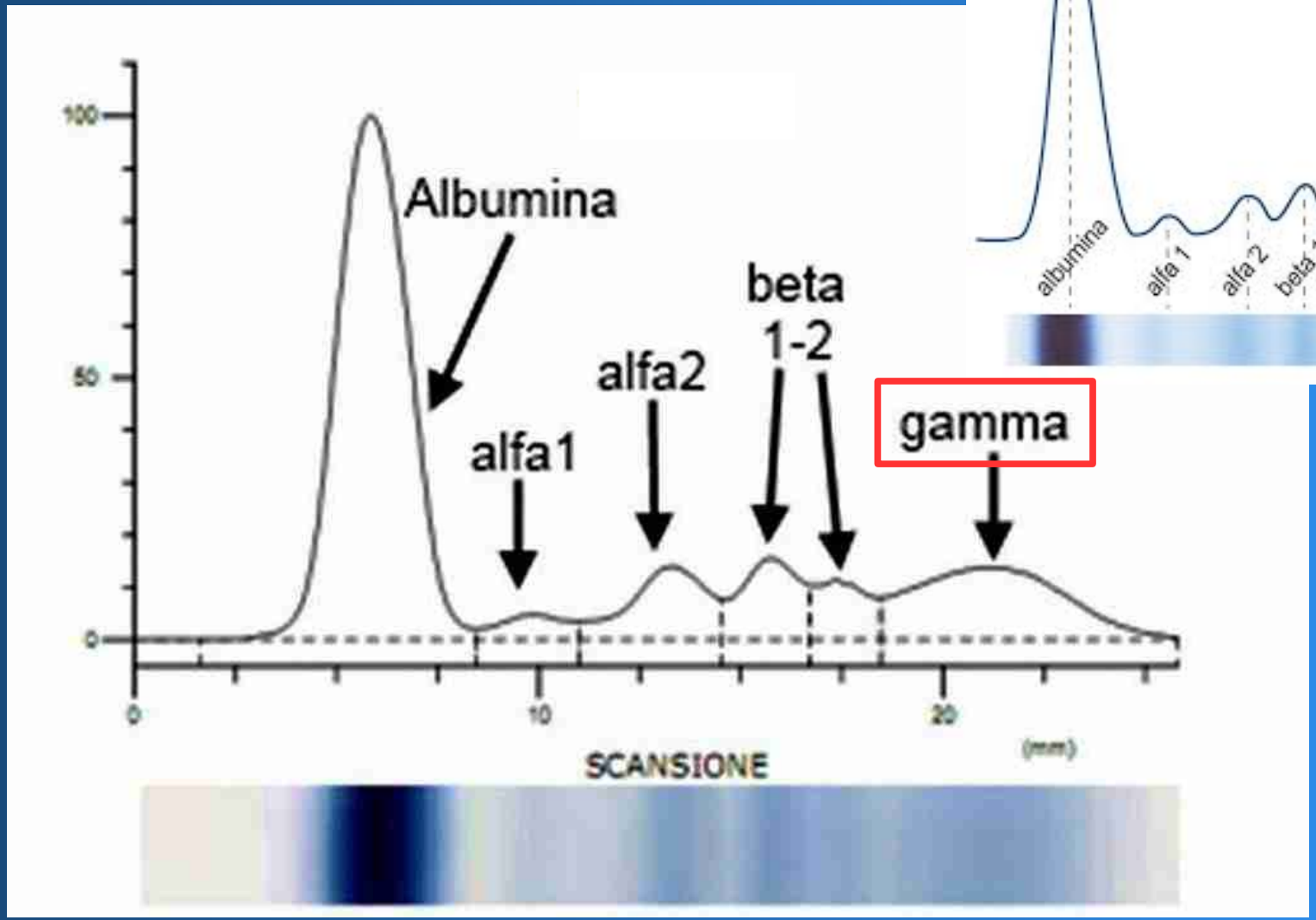
Proliferazione e differenziamento di molte cellule-memoria

↓

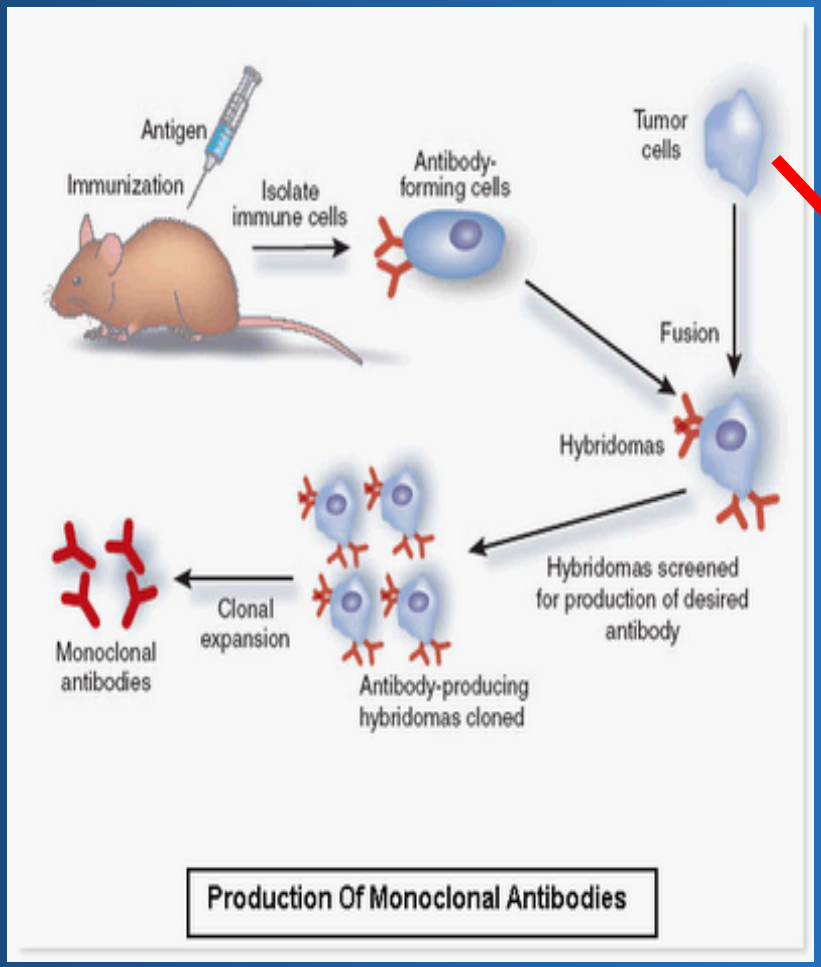
Molte cellule, risposta veloce

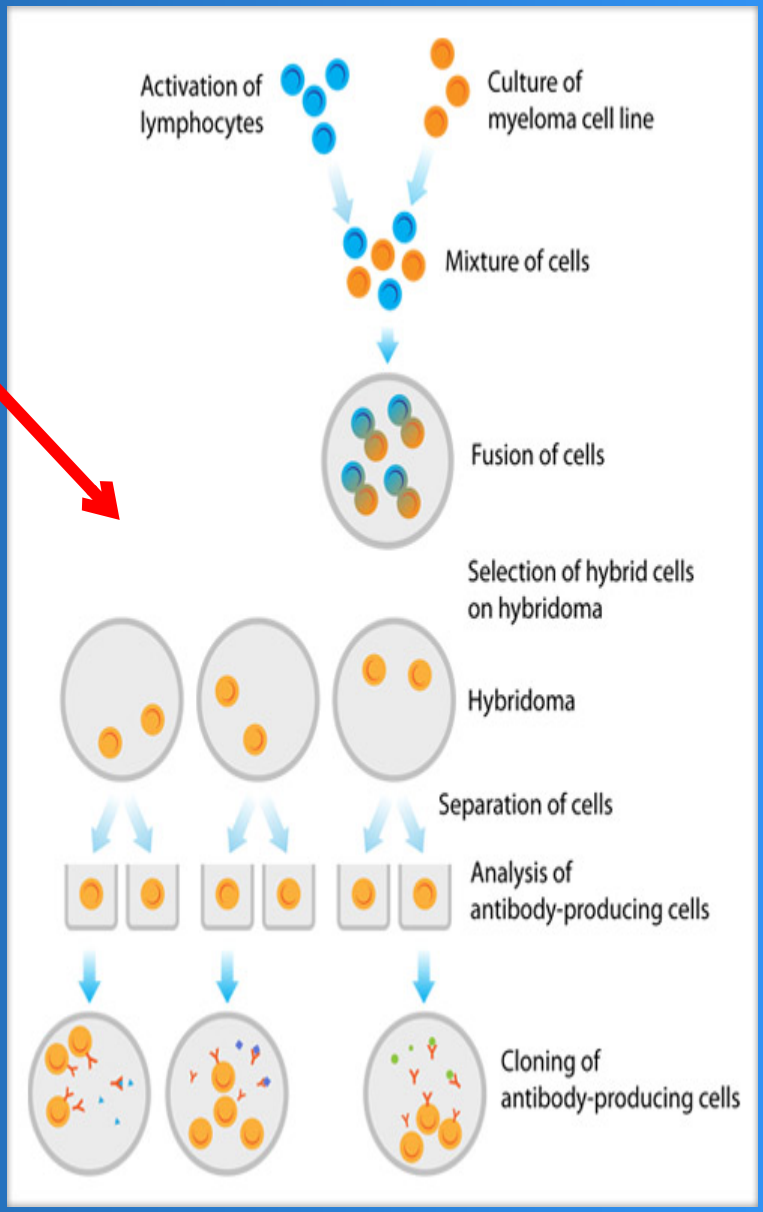
Tracciato elettroforetico



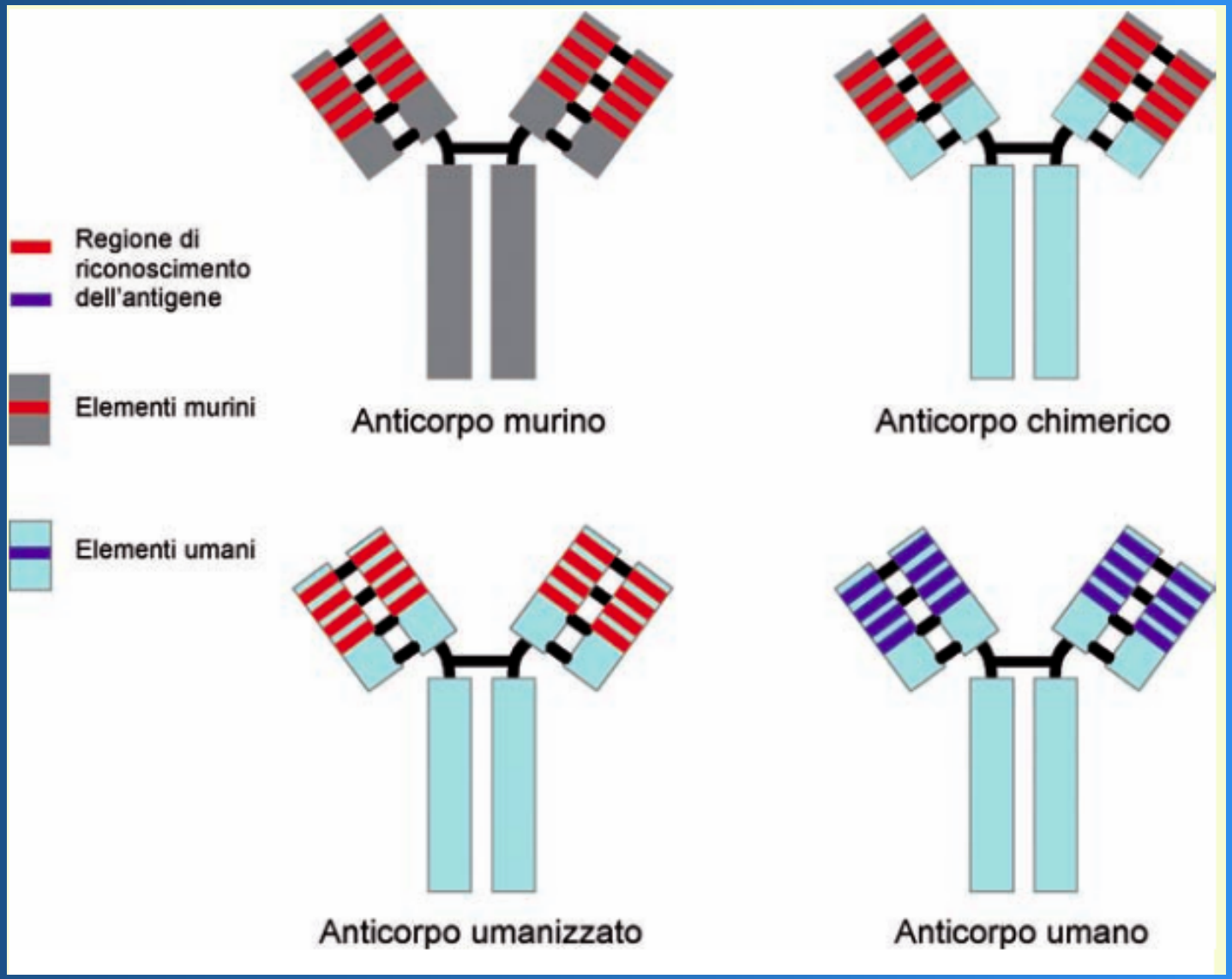


Anticorpi monoclonali





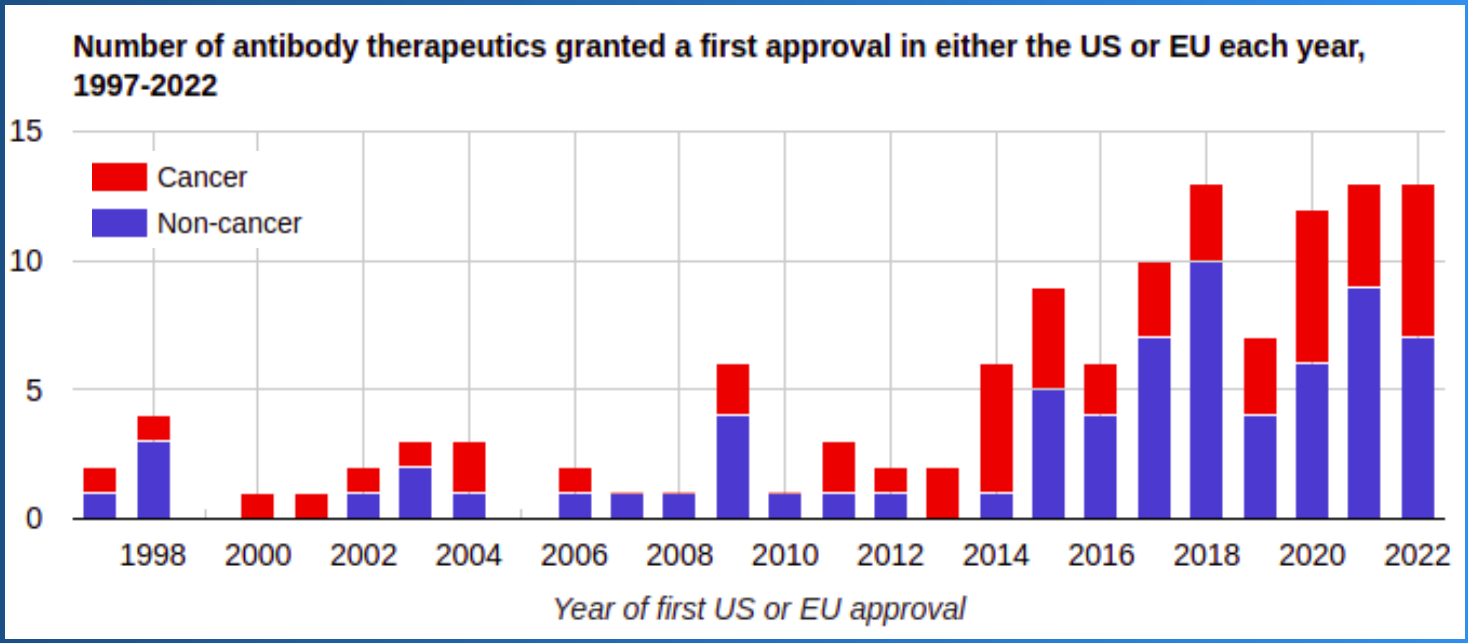
Umanizzazione degli anticorpi



Uso degli anticorpi in terapia

- ✔ **Blocco di interazioni ligando-recettore**
- ✔ **Blocco di funzioni proteiche**
- ✔ ***Utilizzati soprattutto nelle terapie antitumorali ed in quelle di tipo infiammatorio.***
- ✔ ***Usati anche per alcune malattie infettive emergenti***

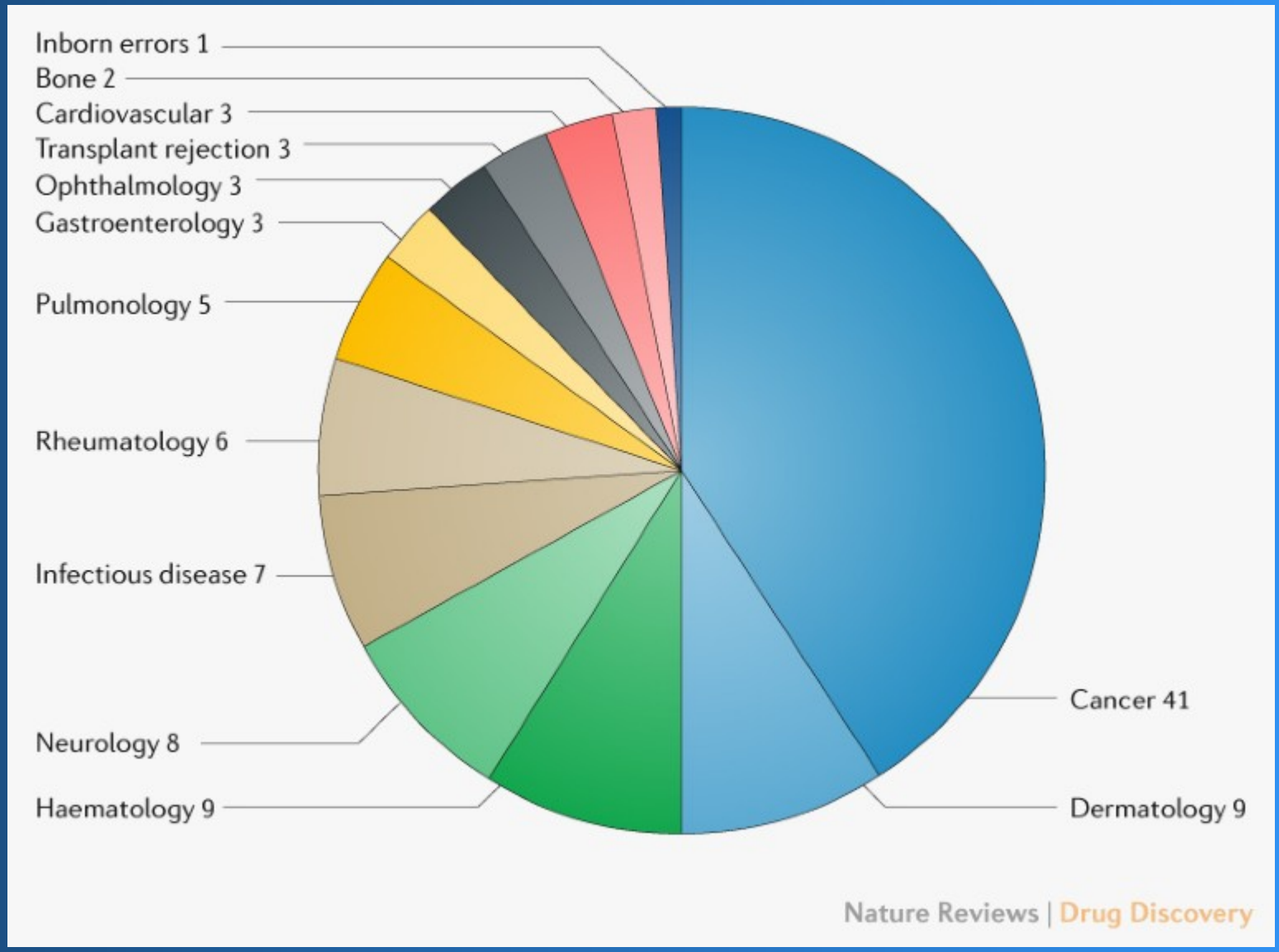
Anticorpi terapeutici



lista completa aggiornata qui

https://www.antibodysociety.org/antibody-therapeutics-product-data/

Anticorpi terapeutici



Anticorpi terapeutici

Table 1. Approved therapeutic antibodies.

Year (FDA)	Trade name (Generic)	Type of antibody (Target antigen)	Disease indication	Company
1986	OKT 3 (muromanab-CD3)	Murine (CD3)	Allograft rejection	Ortho Biotech
1994	ReoPro (abciximab)	Chimeric Fab (GPIIb/IIIa)	Adjunct to PTCA	Centocor
1995	Panorex (edrecolomab)	Chimeric (CA17-1A)	Colorectal cancer	GSK/Centocor
1997	Rituxan (rituximab)	Chimeric (CD20)	Non-Hodgkins lymphoma	IDEC
1997	Zenapax (daclizumab)	Humanized (IL2R)	Prevention of kidney transplant rejection	PDL
1998	Herceptin (trastuzumab)	Humanized (Her2/neu)	Metastatic breast cancer	Genentech
1998	Synagis (palivizumab)	Humanized (RSV F)	RSV propylaxis	MedImmune
1998	Simulect (basiliximab)	Chimeric (IL2R)	Prevention of kidney transplant rejection	Norvatis
1998	Remicade (infliximab)	Chimeric (TNF-α)	Rheumatoid arthritis, Crohn's disease	Centocor
2000	Mylotarg (gemtuzumab ozogamicin)	Humanized-calicheamicin(CD33)	CD33-acute myeloid leukemia	Celltech
2001	Campath (alemtuzumab)	Humanized (CD52)	B-cell Chronic Lymphocytic Leukemia	Millennium
2002	Zevalin (ibritumomab tiuxetan)	Murine-Y-90 (CD20)	Non-Hodgkins lymphoma	IDEC
2002	Humira (adalimumab)	Human (TNF-α)	Crohn's disease, RA	CAT/BASF
2003	Xolair(omalizumab)	Humanized (IgE)	Asthma	Tanox/Genentech/ Novartis
2003	Raptiva (efalizumab)	Humanized (CD11a)	Psorisis	Xoma/Genentech
2003	Bexxar (tositumomab)	Murine-I-131 (CD20)	Non-Hodgkins lymphoma	Corixa/GSK
2004	Erbitux (cetuximab)	Chimeric (EGFR)	Colorectal cancer	Imclone
2004	Avastin (bevacizumab)	Humanized (VEGF)	CRC, breast, renal, NSCL cancer	Genentech

Anticorpi terapeutici

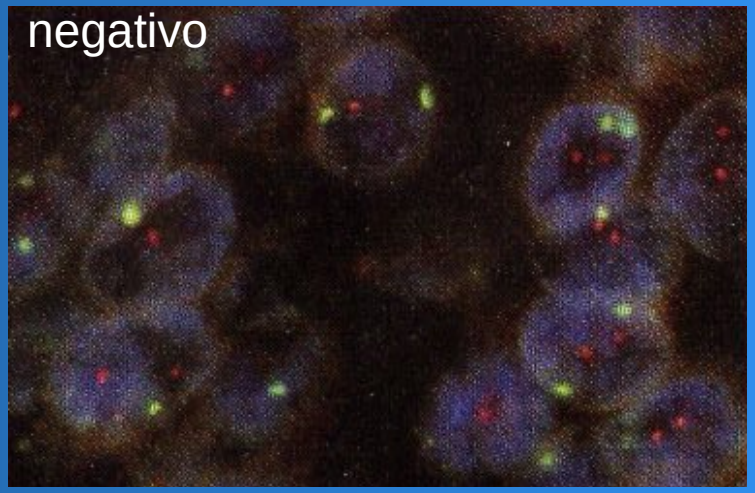
anti TNFalpha,
umanizzato
per malattie autoimmuni

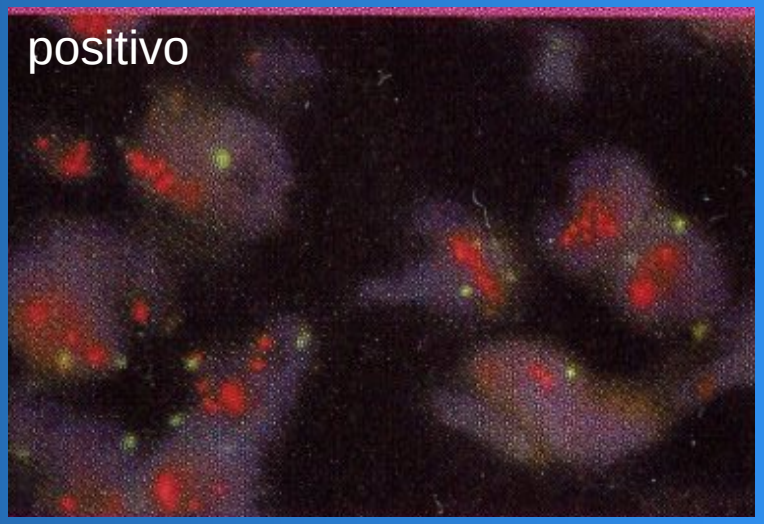
anti HER2,
umanizzato
per tumore al seno

anti VEGF-A
umanizzato
per tumori metastatici

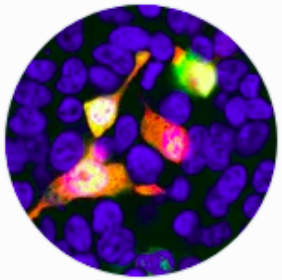
Anticorpi diagnostici

Un gene che codifica per il recettore del fattore di crescita HER2 viene contrassegnato con un marcatore rosso fluorescente in cellule di tumore al seno (*sopra*). Nelle cellule cancerose positive per HER2 (*sotto*) il gene è duplicato moltissime volte, causando la sovrapproduzione di proteine HER2 che provoca un'eccessiva ricezione di segnali di crescita da parte delle cellule.

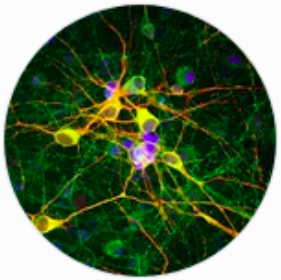




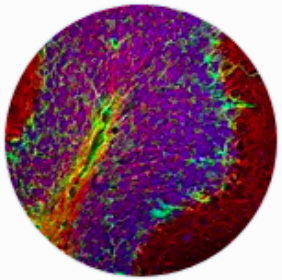
Anticorpi come strumenti per la ricerca



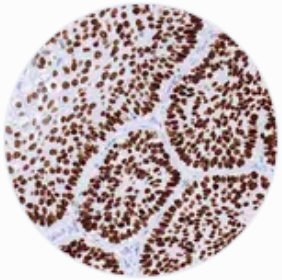
Anticorpi Coniugati



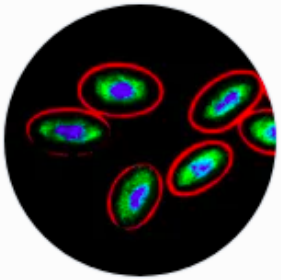
Anticorpi di Dimensione di Prova



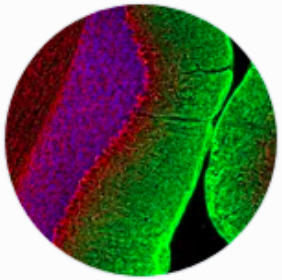
Anticorpi ICC/IF



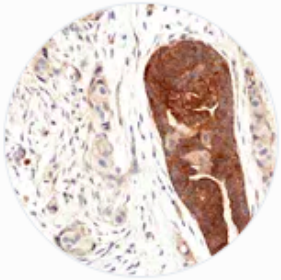
Anticorpi IHC



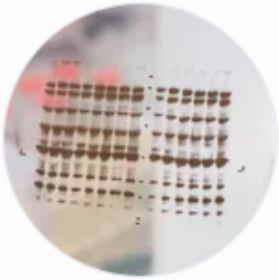
Anticorpi Monoclonali



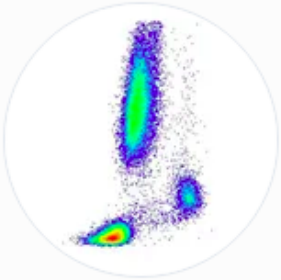
Anticorpi Policlonali



Anticorpi Ricombinanti



Anticorpi Western Blot



Citometria a Flusso