Cancer Immunotherapy

TREATMENTS FOR CANCER THERAPY

- Surgery
- Radio-therapy
- Chemo-therapy

Advantages of immunotherapy

- Specific action
- low side effects
- Independent from genetic background of tumor cells

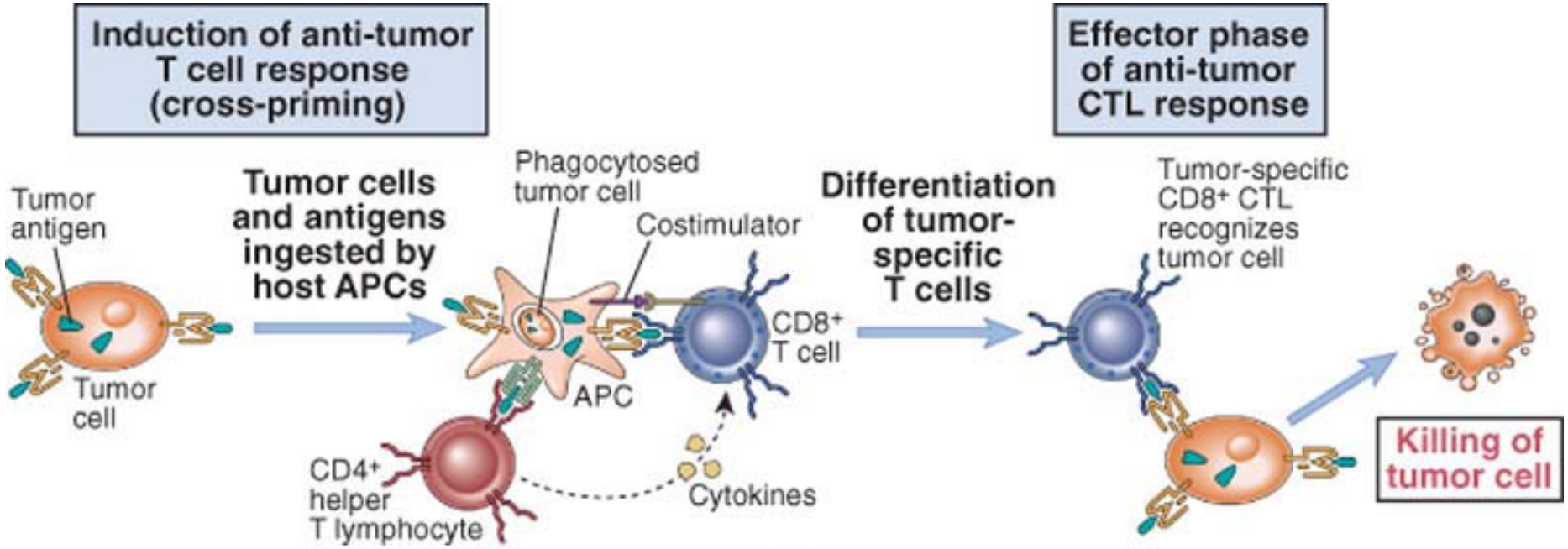
Immune response against tumor cells

- Innate immunity
  - NK cells
  - Macrophages
  - Complement system
- Adaptive immunity
  - Cytotoxic T-lymphocytes
  - Antibodies

CANCER IMMUNOTHERAPY

1. Enhancement of patient' immune response to cancer cells

Induction of a T-response against tumor



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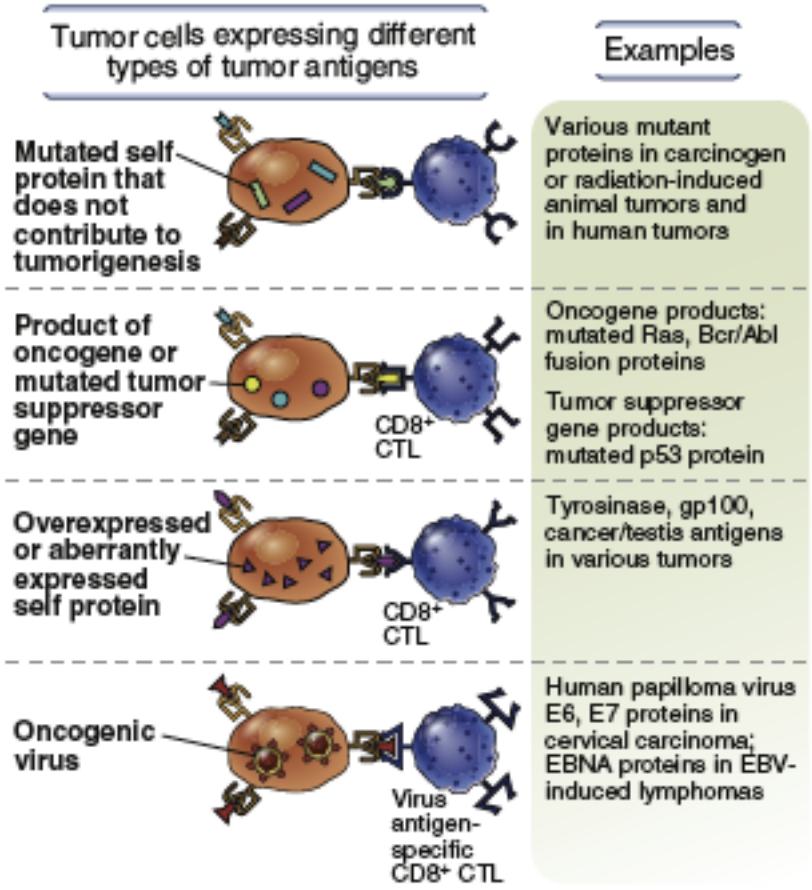
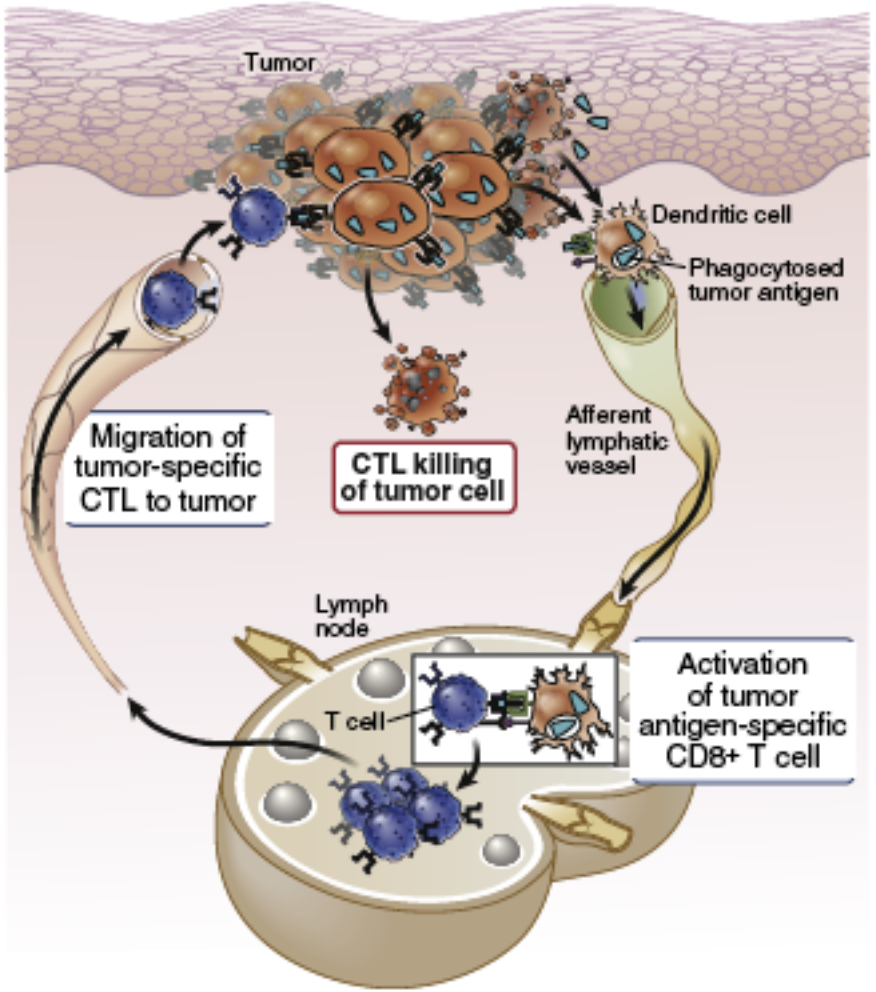
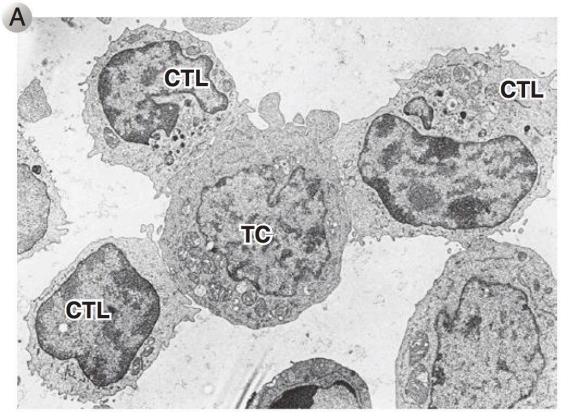
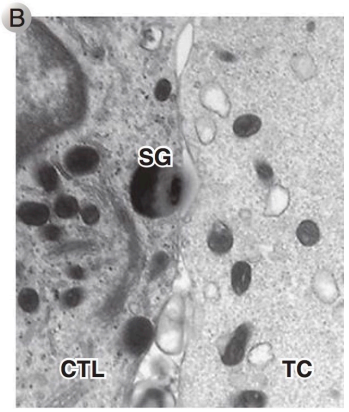
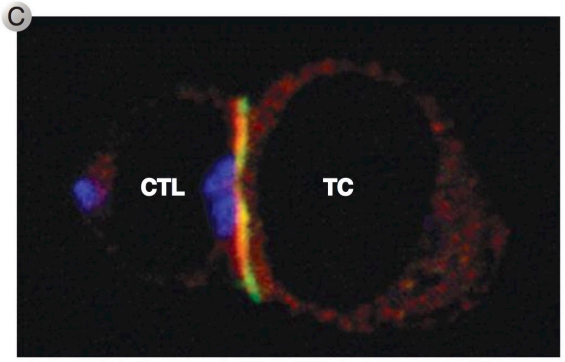




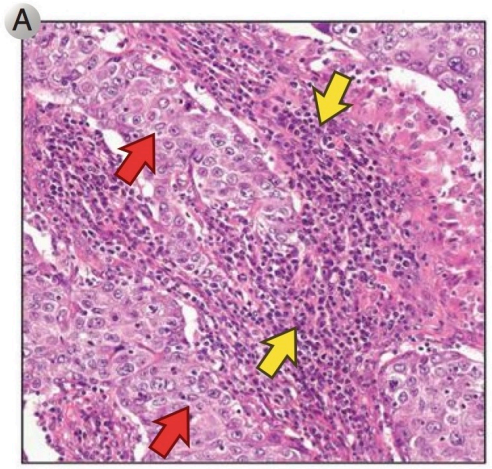
Induction of a T-response against tumor

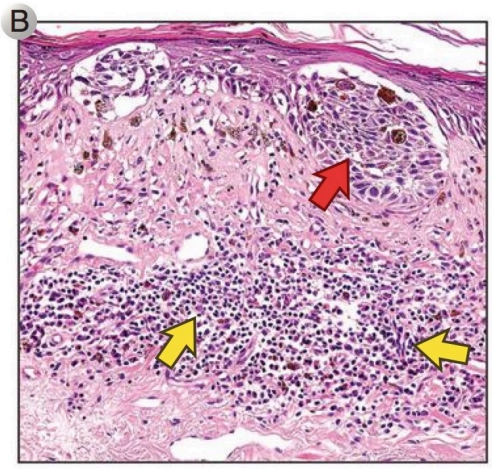


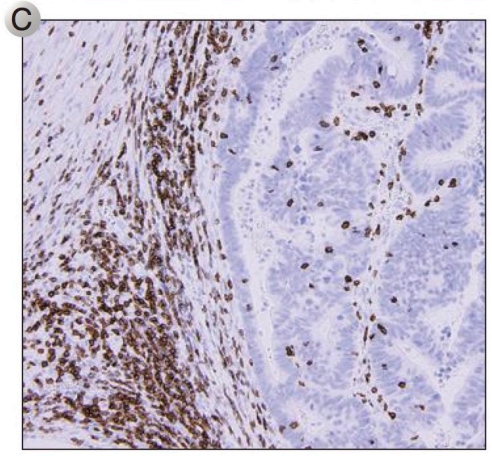


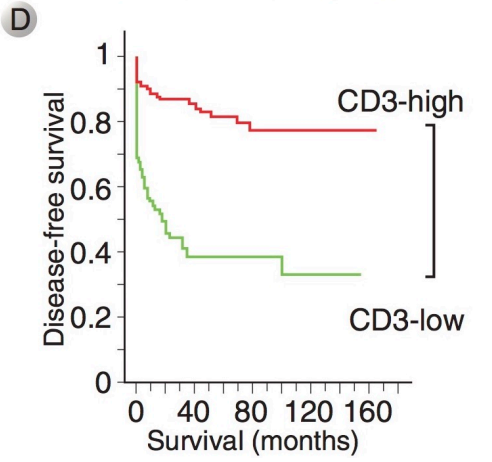


Cathepsins (blue) LFA-1 (green) Talin (red)

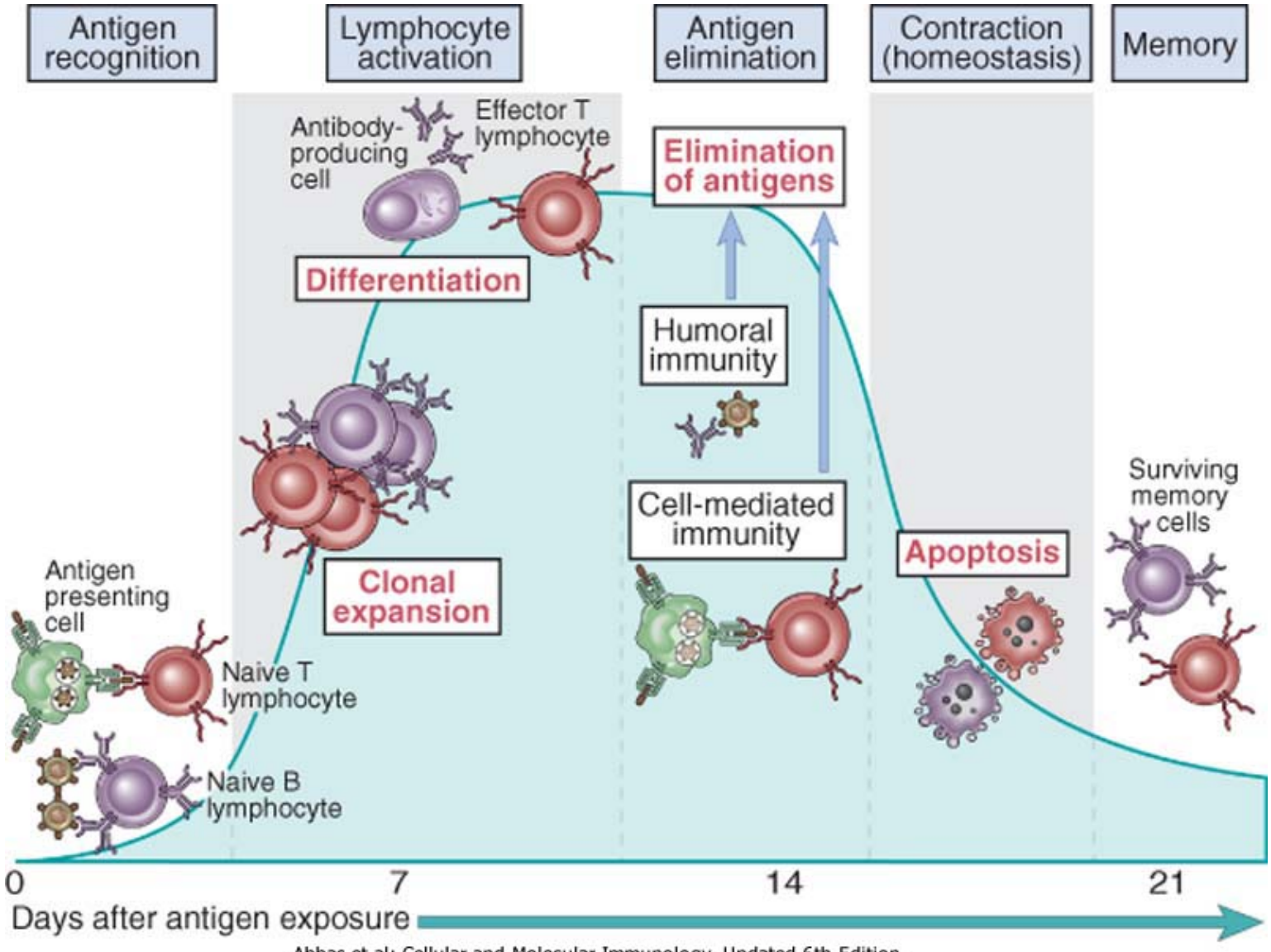


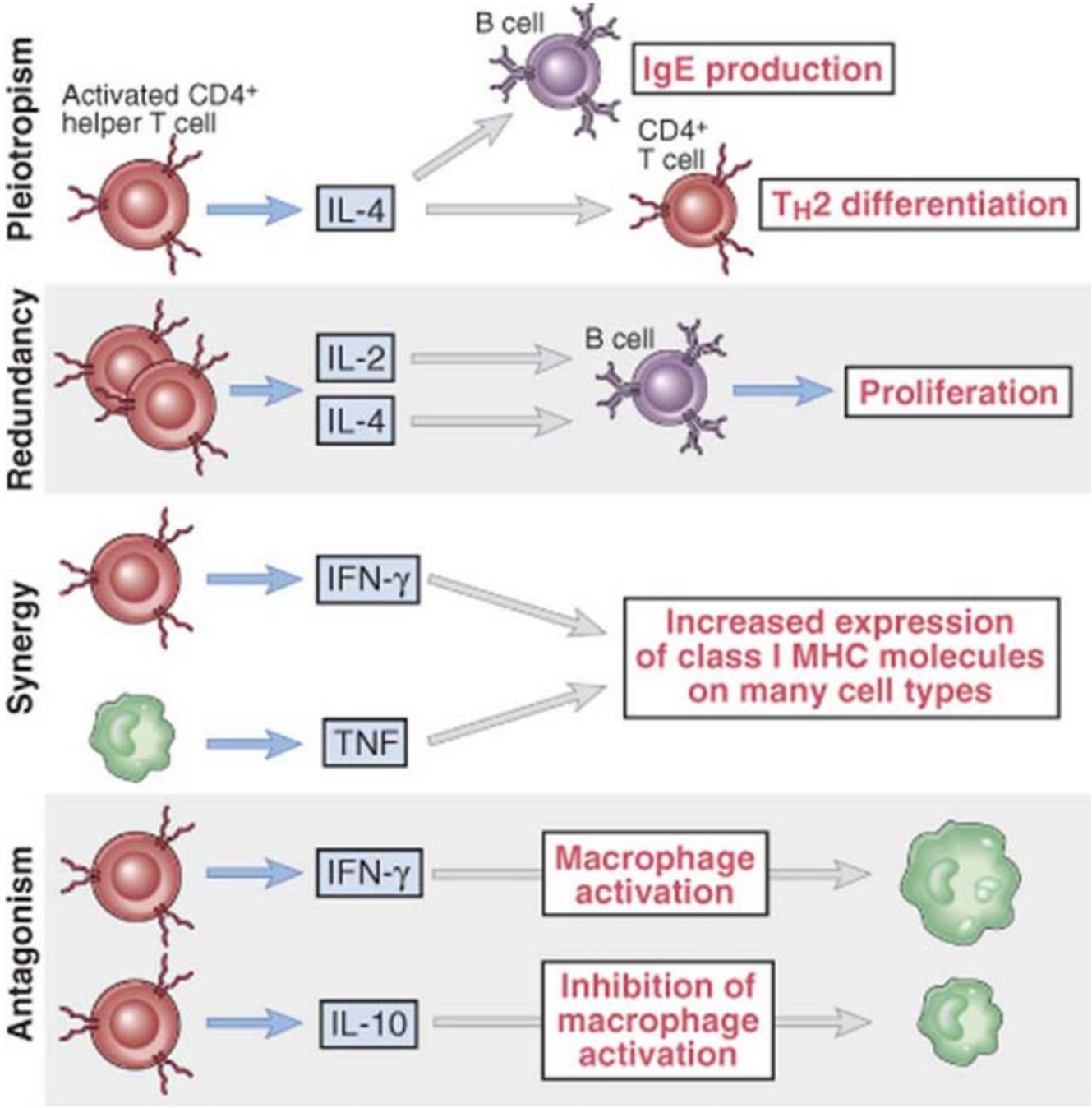






Phases of adaptive immune response

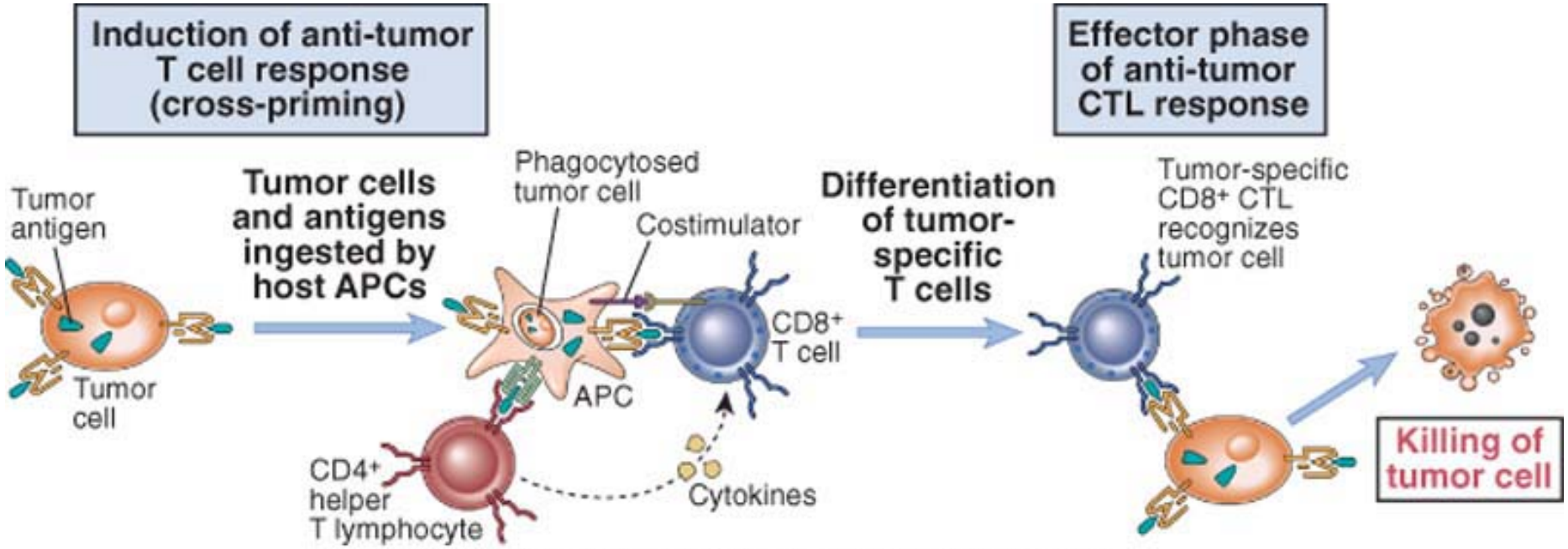




Systemic immunotherapy using cytokines and growth factors

Cytokine	Reject in animal models	Clinical studies	Toxicity
IL-2	yes	Melanoma, Renal and Colon carcinoma (response rate < 15%)	Vascular permeability, Shock, edema
IFN-gamma	No	Approved for melanoma	Fever
TNF	only after local administration	Sarcoma, melanoma (in local perfusion)	Septic shock syndrome
IL-12	Variable	Melanoma	Epatic Toxicity
GM-CSF	No	Bone marrow recovery	Bone pain

Induction of a T-response against tumor



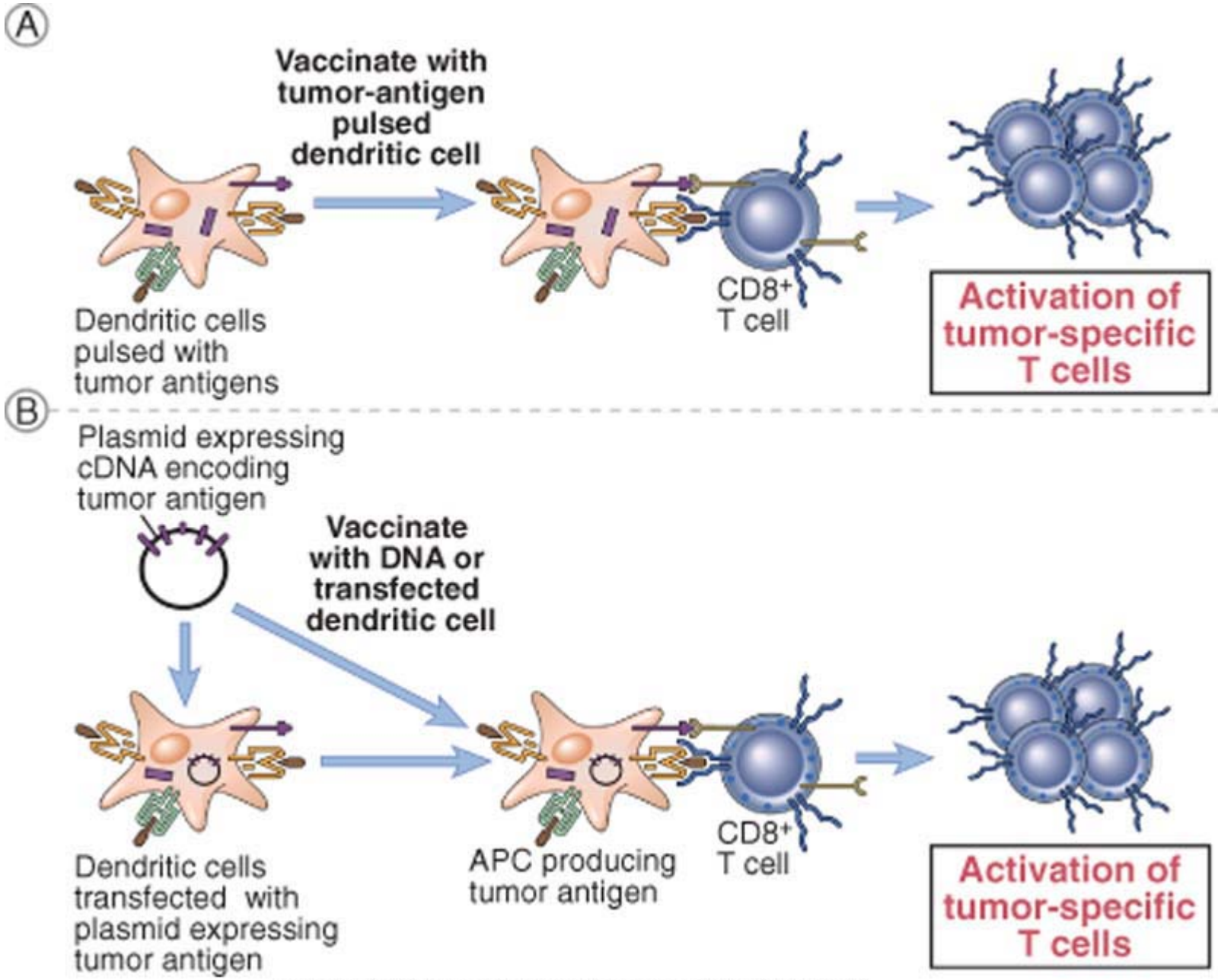
CANCER IMMUNOTHERAPY

1. Enhancement of patient' immune response to cancer cells

(VACCINATION)

Antitumoral Vaccination

Type of vaccination	Vaccine preparation	Animal models	Clinical studies
Died cancer cells	a) Tumor cells + adjuvants. b) lyseted tumor cells + adjuvants	Melanoma, Colon carcinoma. Sarcomas	Melanoma, Colon carcinoma. Melanoma
Purified tumor antigens	a) Melanoma Ags b) Heat Shock Protein	Melanoma several different models	Melanoma. Melanoma, Renal carcinoma, Sarcomas
APC-Based vaccines	a) TAA primed DC b) transfected DC (TAA-encoding vectors)	Melanoma, B linfoma, sarcoma Melanoma, Colon carcinoma	Melanoma, Non-Hodgkin linfoma, others Carcinomas



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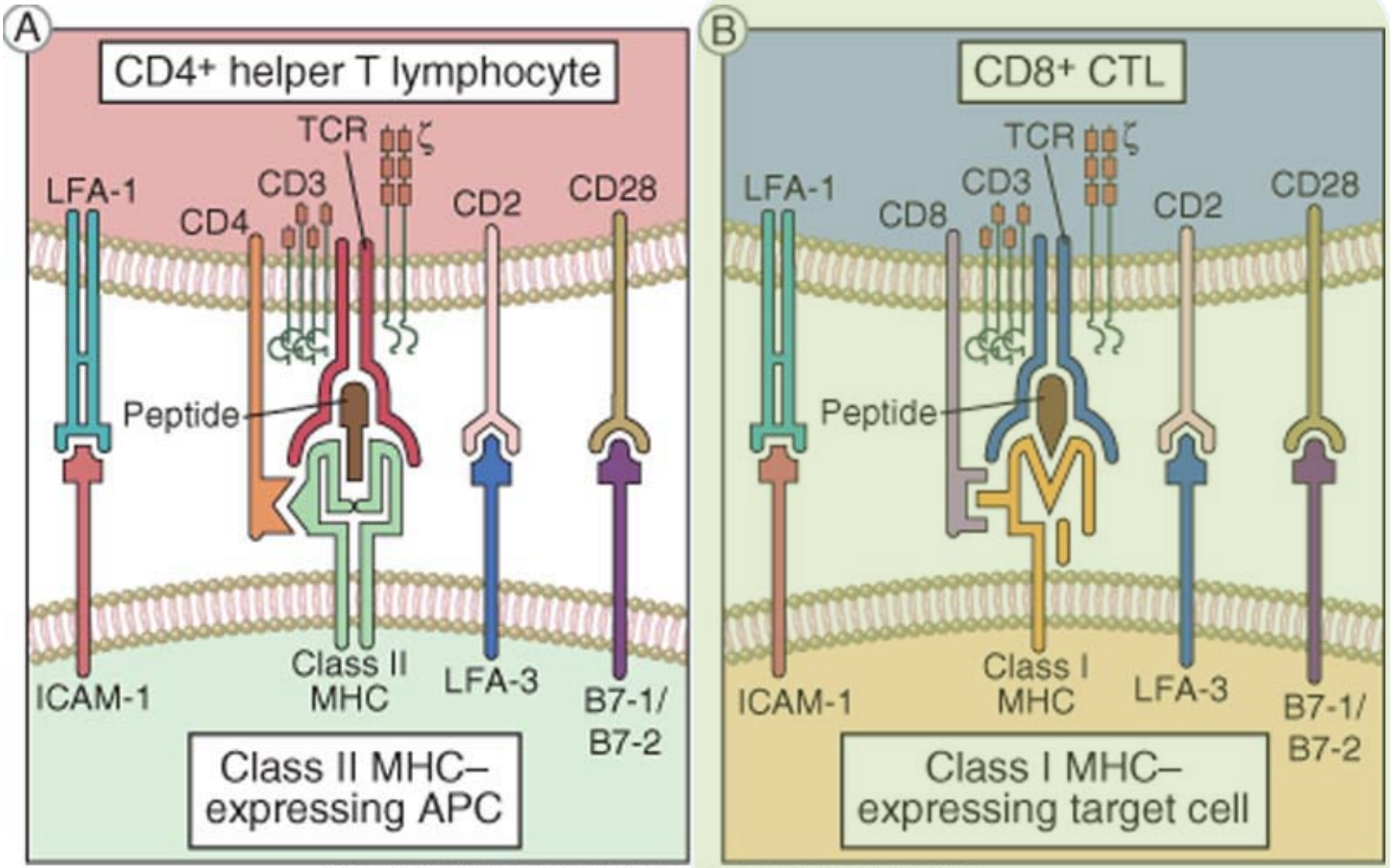
Vaccination enhanced by cytokines of co-stimulatory molecules	a) Transfected tumor cells (vector encoding cytokines or B7) b) Transfected tumor cells (vector encoding cytokines or B7) and pulsed with TAA	Renal and pulmonary Carcinomas, Sarcomas, B-leukemies	Melanoma, sarcomas Melanoma, Renal carcinoma



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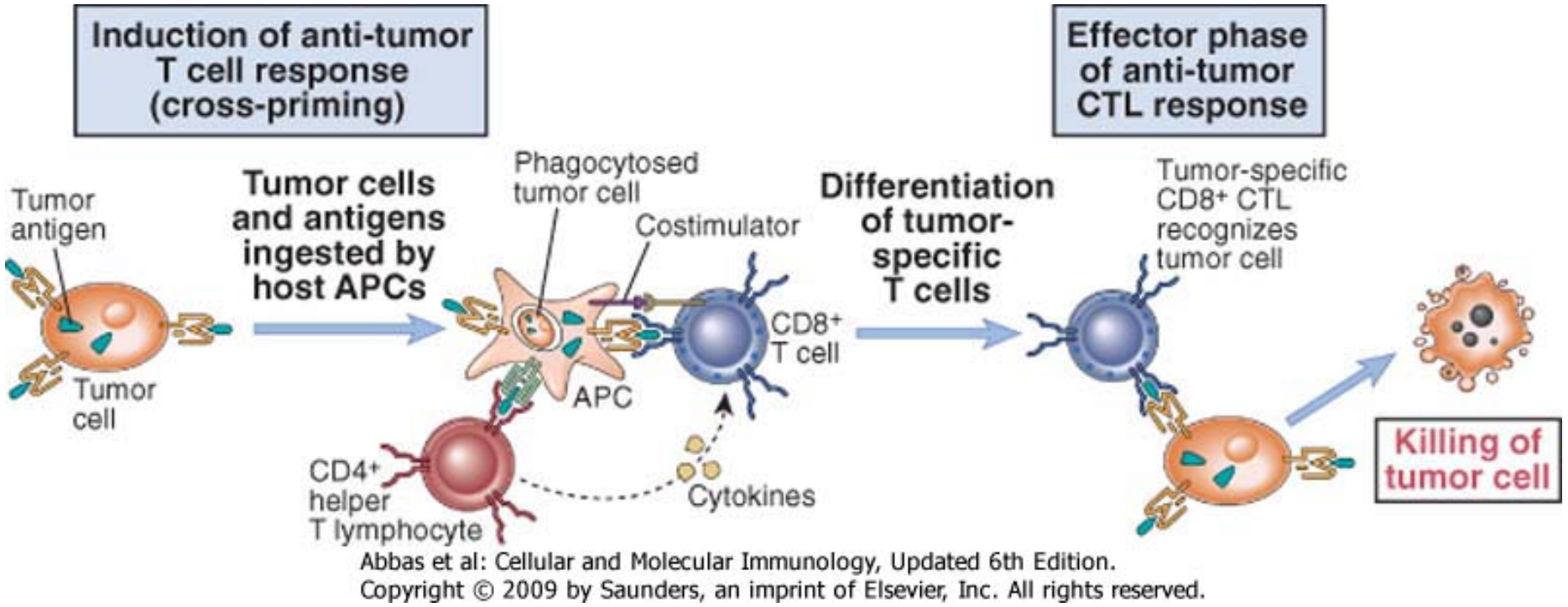


Phagocytosis of apoptotic cells

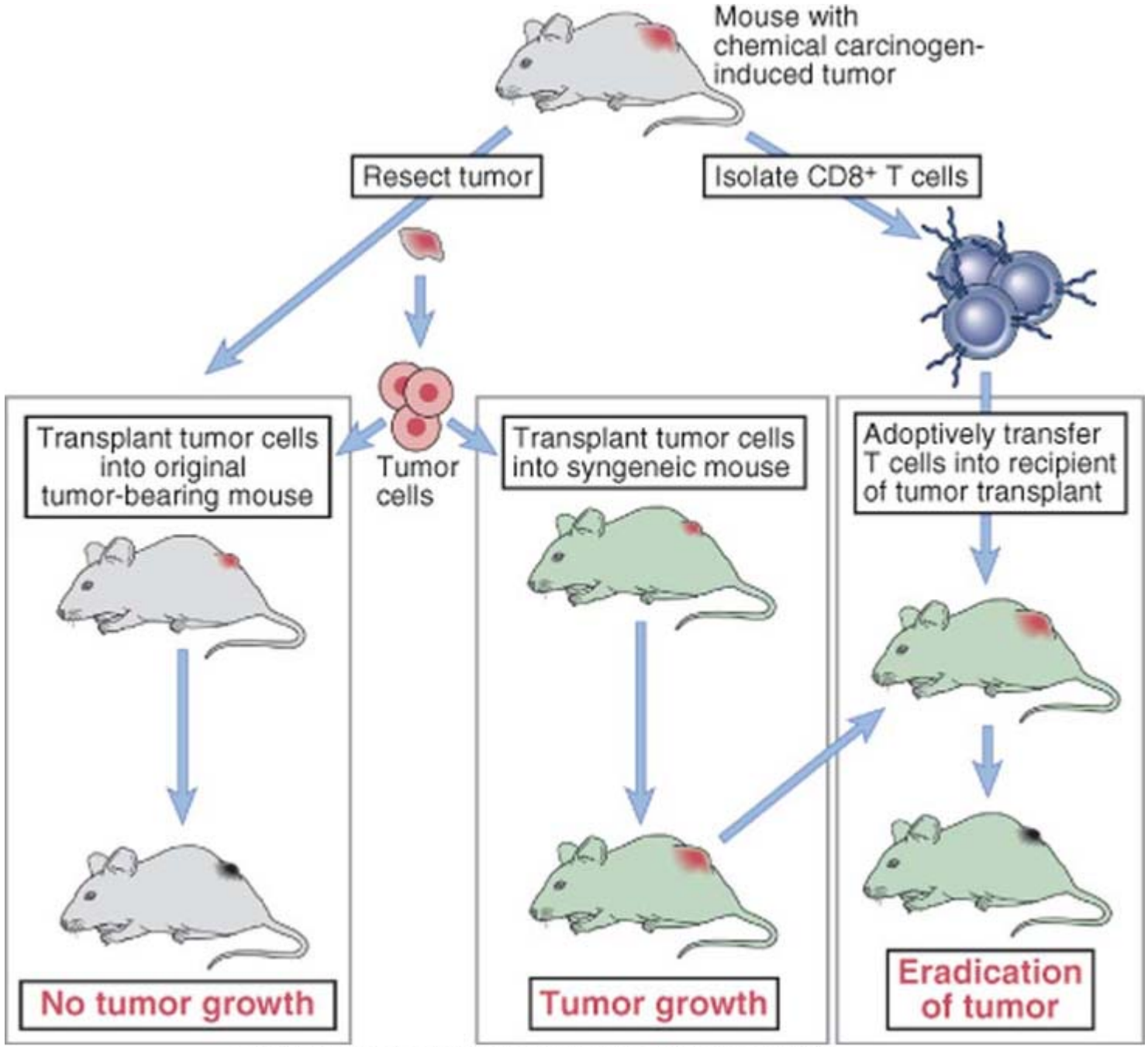
Antitumoral Vaccination

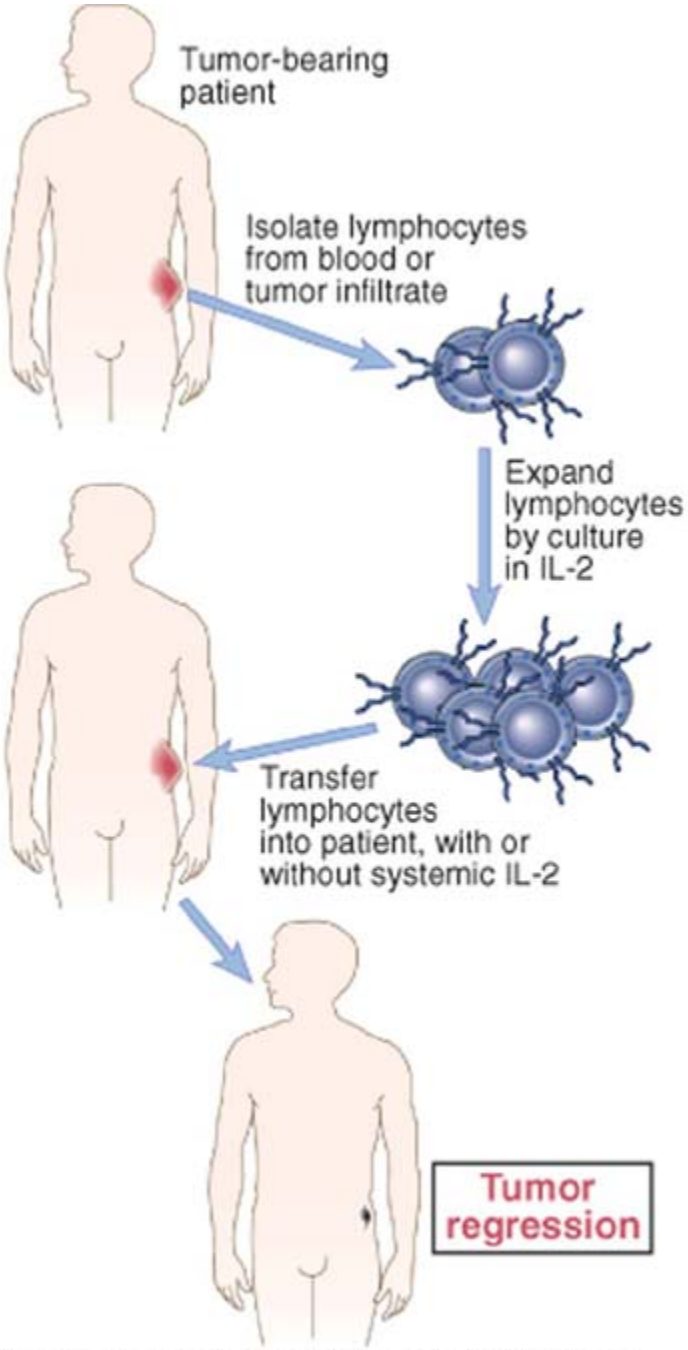
Type of vaccination	Vaccine preparation	Animal models	Clinical studies
Died cancer cells	a) Tumor cells + adjuvants. b) lyseted tumor cells + adjuvants	Melanoma, Colon carcinoma. Sarcomas	Melanoma, Colon carcinoma. Melanoma
Purified tumor antigens	a) Melanoma Ags b) Heat Shock Protein	Melanoma several different models	Melanoma. Melanoma, Renal carcinoma, Sarcomas
APC-Based vaccines	a) TAA primed DC b) transfected DC (TAA-encoding vectors)	Melanoma, B linfoma, sarcoma Melanoma, Colon carcinoma	Melanoma, Non-Hodgkin linfoma, others Carcinomas
Vaccination enhanced by cytokines of co-stimulatory molecules	a) Transfected tumor cells (vector encoding cytokines or B7) b) Transfected tumor cells (vector encoding cytokines or B7) and pulsed with TAA	Renal and pulmonary Carcinomas, Sarcomas, B-leukemies	Melanoma, sarcomas Melanoma, Renal carcinoma
DNA vaccination	Vectors encoding TAA	Melanoma	Melanoma
Viral vectors	Adenovirus encodingTAA + cytokines	Melanoma, sarcomas	Melanoma

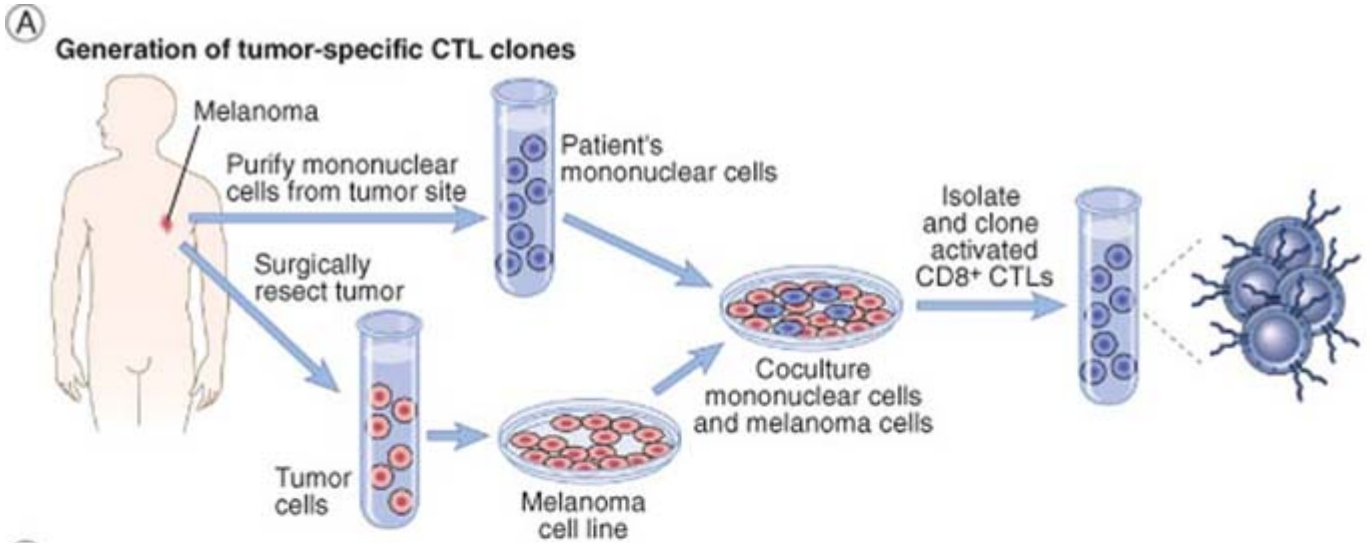
CANCER IMMUNOTHERAPY

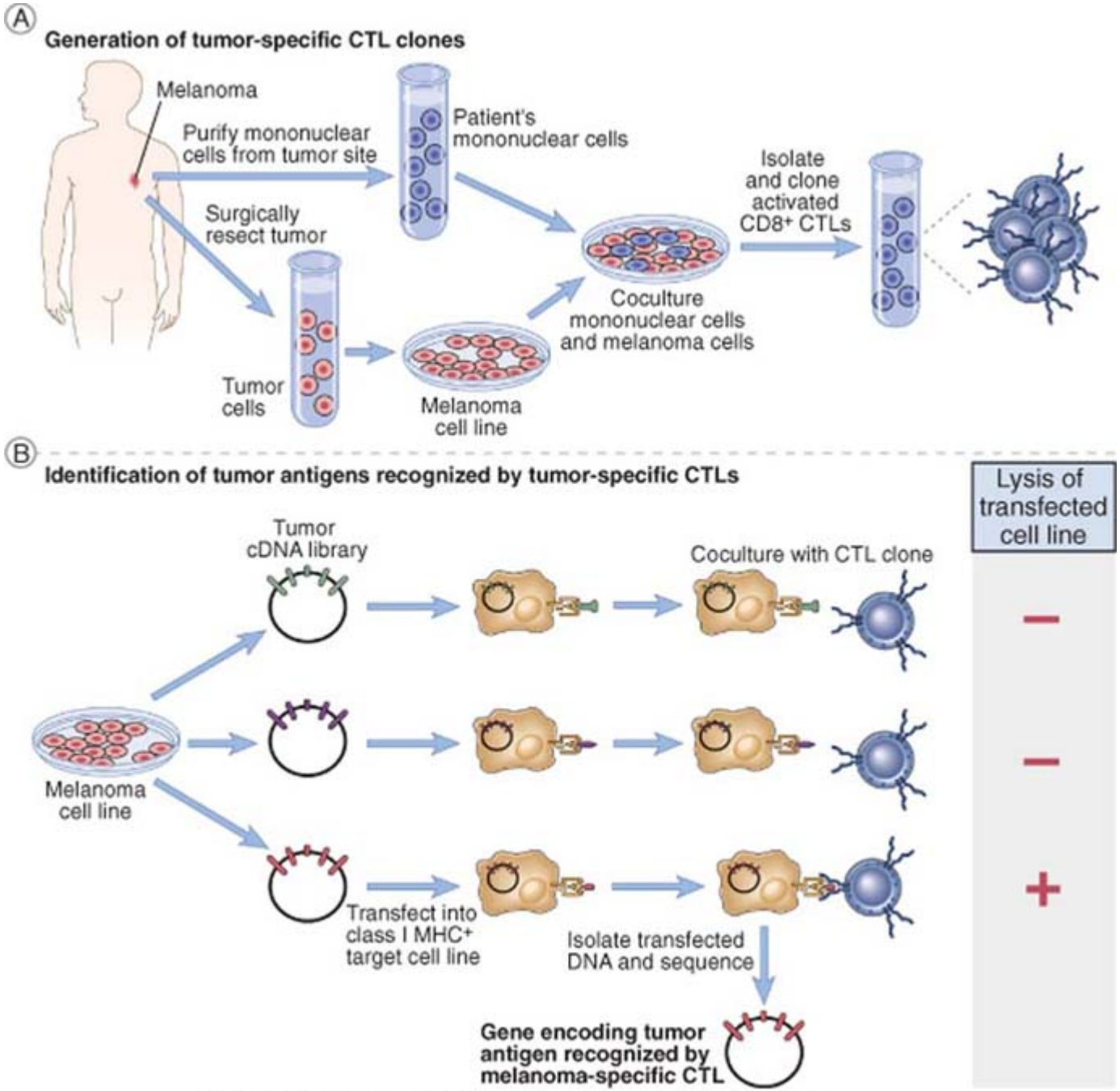
1. Enhancement of patient' immune response to cancer cells

2. Passive immunotherapy using T lymphocytes






A
Generation of tumor-specific CTL clones
Melanoma
Purify mononuclear cells from tumor site
Patient's mononuclear cells
Surgically resect tumor
Isolate and clone activated CD8+ CTLs
Coculture mononuclear cells and melanoma cells
Tumor cells
Melanoma cell line



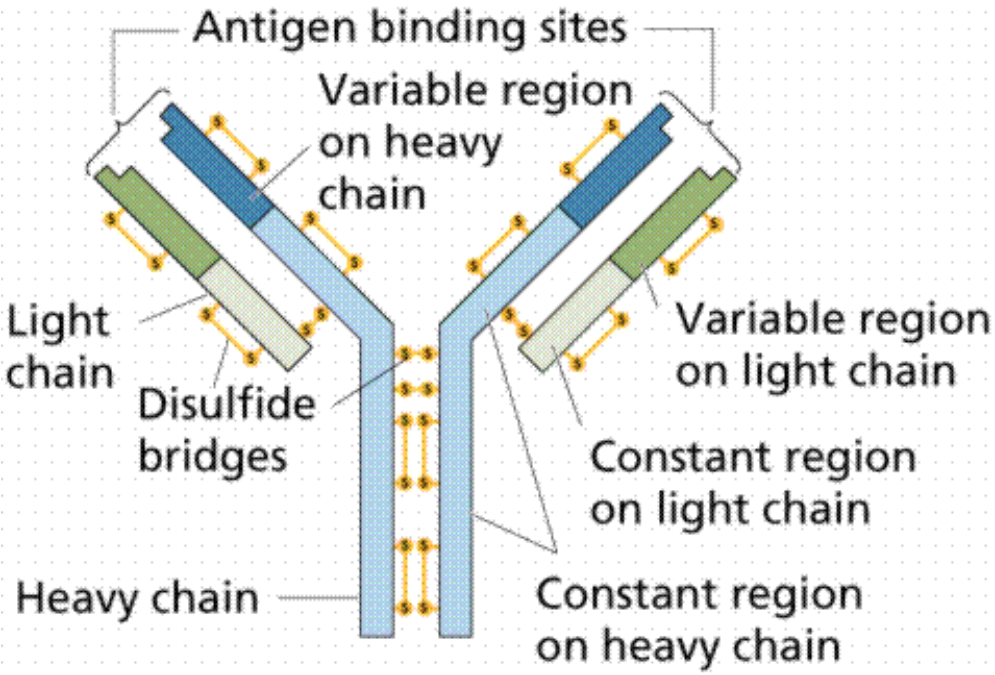
CANCER IMMUNOTHERAPY

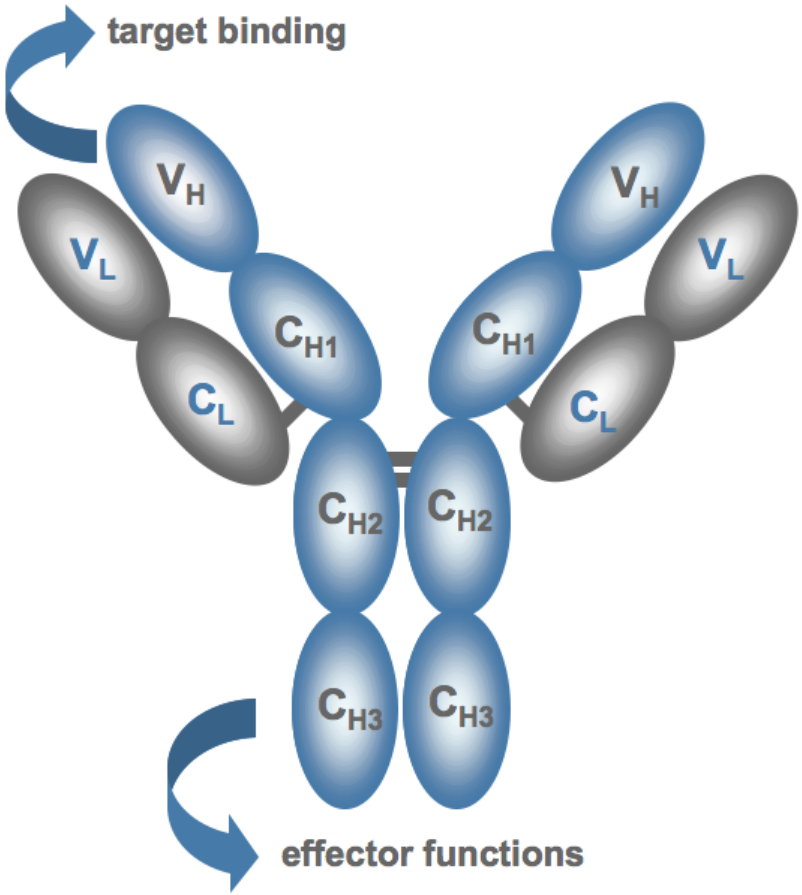
1. Enhancement of patient' immune response to cancer cells

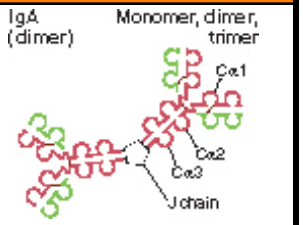
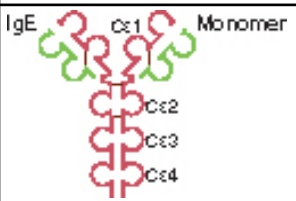
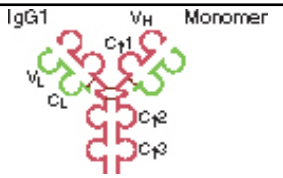
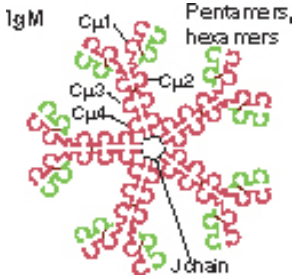
2. Passive immunotherapy using T lymphocytes

3. **Passive immunotherapy using antibodies**

Anticorpi


Antigen binding sites
Variable region on heavy chain
Light chain
Disulfide bridges
Variable region on light chain
Constant region on light chain
Heavy chain
Constant region on heavy chain


target binding
V_H
V_L
C_{H1}
C_L
C_{H2}
C_{H3}
effector functions

isotiopo	Sottotipo	Concentrazione nel siero (mg/ml)	Emivita nel siero (giorni)	Forma secreta
IgA	1,2	3,5	6	
IgD	-	-	3	-
IgE	-	0,05	2	
IgG	1-4	13,5	23	
IgM	-	1,5	5	

Antibody Isotope	Isotype-specific effector functions
IgG	- Opsonization of antigens for phagocytosis by macrophages and neutrophils - Activation of the classical pathway of complement - Antibody-dependent cell-mediated cytotoxicity mediated by natural killer cells - Neonatal immunity: transfer of maternal antibody across the placenta and gut - Feedback inhibition of B cell activation
IgM	- Activation of the classical pathway of complement - Antigen receptor of naive B lymphocytes
IgA	- Mucosal immunity: secretion of IgA into the lumens of the gastrointestinal and respiratory tracts - Activation of complement by the lectin pathway or by the alternative pathway
IgE	Mast cell degranulation (immediate hypersensitivity reactions)
IgD	Antigen receptor of naive B lymphocytes

FcR	Affinity for immunoglobulin	Cell Distribution	Function
Fc γ RI (CD64)	High (Kd ~ 10^{-9} M) binds IgG1 and IgG3	Macrophages, neutrophils; also eosinophils	Phagocytosis, activation of phagocytes
Fc γ RIIA (CD32)	Low (Kd > 10^{-7} M)	Macrophages, neutrophils; eosinophils, platelets	Phagocytosis; cell activation (inefficient)
Fc γ RIIB (CD32)	Low (Kd > 10^{-7} M)	B lymphocytes, dendritic cells, macrophages	Feedback inhibition of B cells, macrophages, dendritic cells
Fc γ RIIIA (CD16)	Low (Kd > 10^{-6} M)	NK cells	Antibody-dependent cell-mediated cytotoxicity
Fc γ RIIIB (CD16)	Low (Kd > 10^{-6} M) GPI-linked protein	Neutrophils, other cells	Phagocytosis (inefficient)
Fc ε RI	High (Kd > 10^{-10} M) binds monomeric IgE	Mast cells, basophils, eosinophils	Cell activation (degranulation)
Fc ε RII (CD23)	Low (Kd > 10^{-7} M)	B lymphocytes, eosinophils, Langerhans cells	Unknown
Fc α R (CD89)	Low (Kd > 10^{-6}M)	Neutrophils, eosinophils, monocytes	Cell activation?

Meccanismi d'azione degli anticorpi antitumorali

CITOTOSSICITA' CELLULARE ANTICORPO DIPENDENTE (ADCC)	Mediata in particolare dalle cellule NK, che tramite il recettore FcgRIII riconosce la porzione Fc dell'anticorpo. Liberazione del contenuto dei granuli citoplasmatici (perforine, granzimi).
OPSONIZZAZIONE E FAGOCITOSI	Gli anticorpi rivestono la cellula tumorale e ne favoriscono l'internalizzazione da parte dei fagociti che riconoscono la porzione Fc mediante i recettori per Fc.
APOPTOSI	Da aggregazione dell'antigene sulla superficie cellulare.
ATTIVAZIONE DELLA VIA CLASSICA DEL COMPLEMENTO	Legame di C1q all'Fc dell'anticorpo; lisi cellulare (CDC); i prodotti generati dall'attivazione del complemento (anafilotossine e opsonine) inducono flogosi e promuovono la fagocitosi.

Caratteristiche degli anticorpi

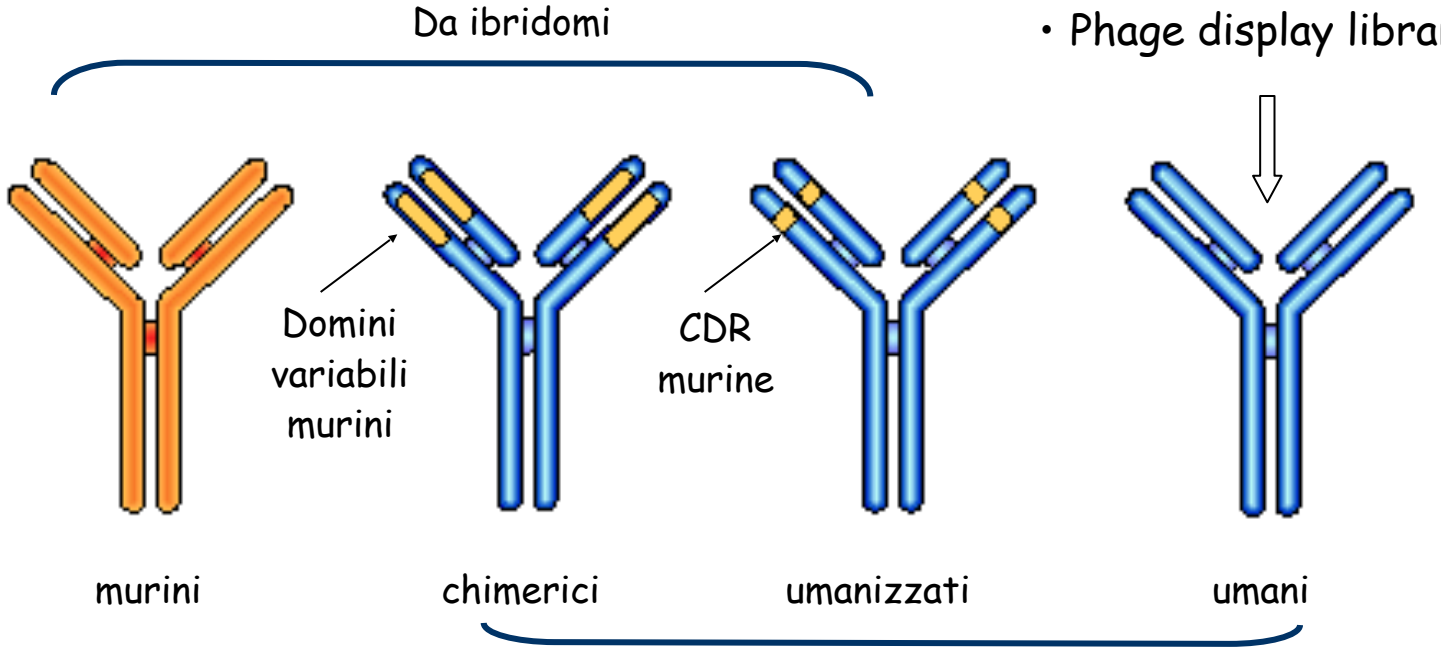
- Specificità d'azione

1. Attivazione del sistema immunitario

2. Biodistribuzione/tempo di permanenza in circolo

Ingegnerizzazione degli anticorpi

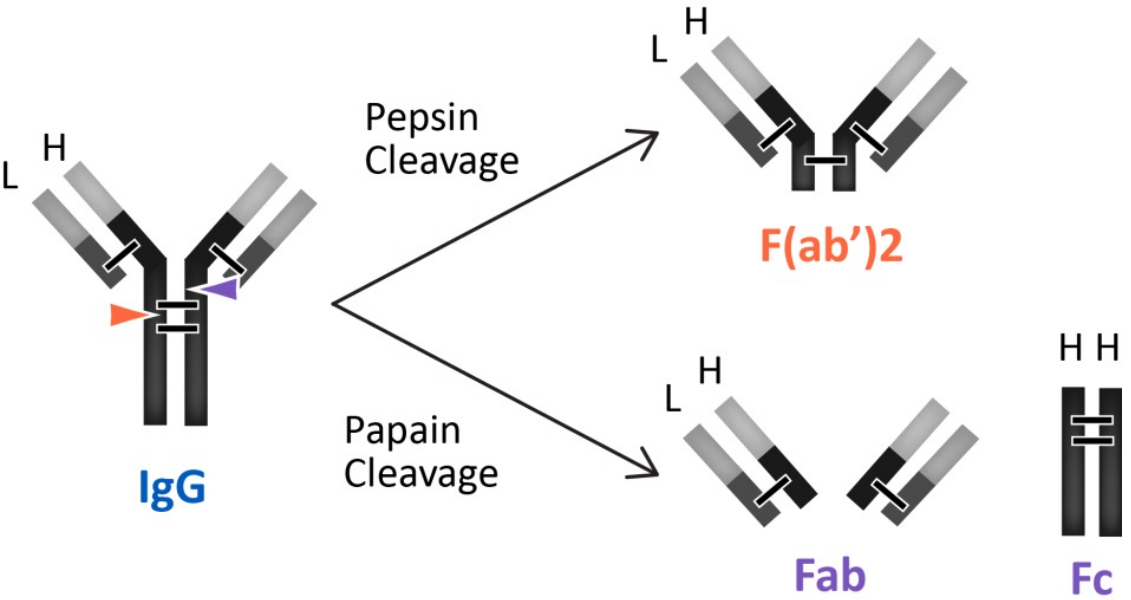
- Topi transgenici
- Phage display library

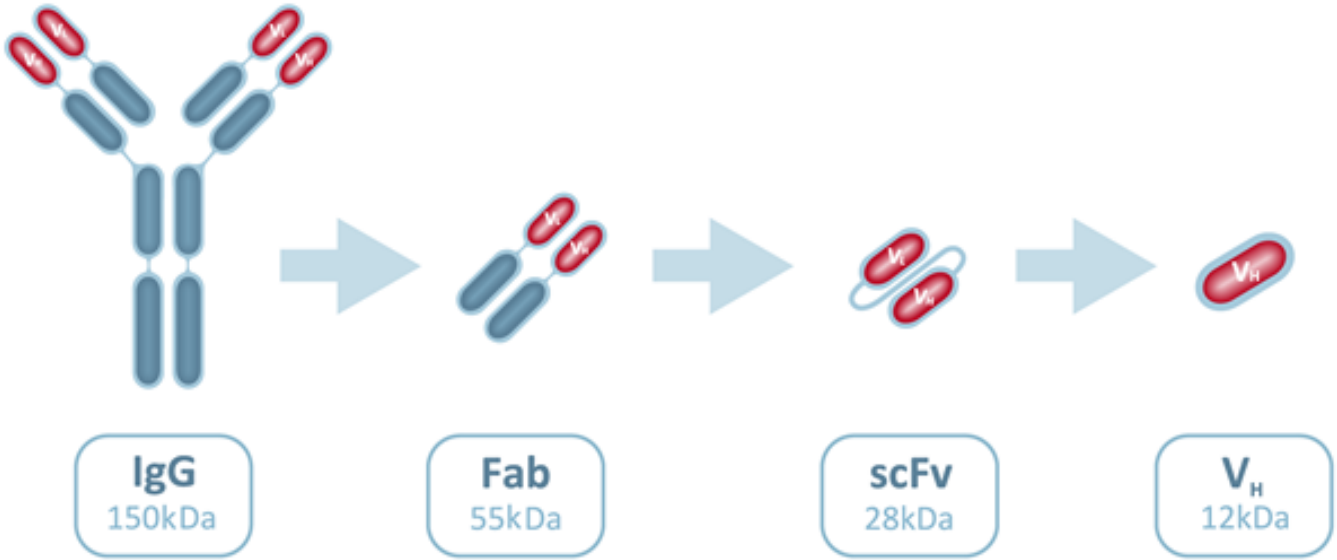


Immunogeni; breve emivita; regione Fc murina è debole attivatore delle funzioni immunitarie umane

Meno immunogeni; prolungata emivita sierica; permettono l'attivazione delle funzioni effettrici mediate dall'Fc

Frammenti anticorpali





Frammenti anticorpali

IgG
(150 kDa)

Fab
(50 kDa)

$F(ab')_2$
(50 kDa)

Monospecific
Fab_2 (50 kDa)

Bispecific Fab_2
(50 kDa)

Trispecific
Fab_3 (150 kDa)

Monovalent
IgG (75kDa)

scFv
(25 kDa)

Bispecific
Diabody
(50 kDa)

Trispecific
Triabody
(75 kDa)

scFv-Fc
(100 kDa)

Minibody
(75 kDa)

IgNAR
(175 kDa)

V-NAR
(15 kDa)

hcIgG
(75 kDa)

VhH
(15 kDa)

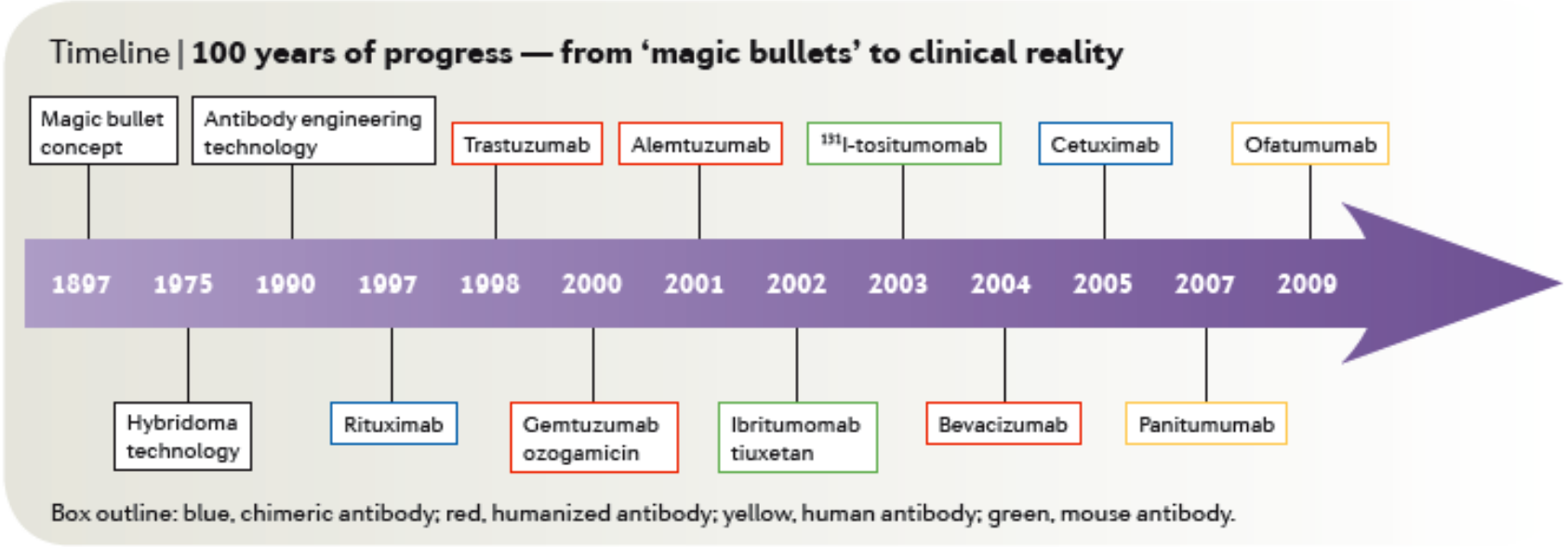
Mercato degli anticorpi anti-tumorali

Generic name (trade name; sponsoring companies)	Target	Antibody Format	Cancer Indication	Refs
Unconjugated antibodies				
Rituximab (Rituxan/Mabthera; Genentech/Roche/Biogen Idec)	CD20	Chimeric IgG1	Non-Hodgkin lymphoma	74,105
Trastuzumab (Herceptin; Genentech/ Roche)	HER2	Humanized IgG1	Breast cancer	19,72
Alemtuzumab (Campath/ MabCampath; Genzyme/Bayer)	CD52	Humanized IgG1	Chronic lymphocytic leukaemia	58
Cetuximab (Erbitux; ImClone Systems/Bristol–Myers Squibb)	EGFR	Chimeric IgG1	Colorectal cancer	13,106
Bevacizumab (Avastin; Genentech)	VEGFA	Humanized IgG1	Colorectal, breast and lung cancer	71, 107,108
Panitumumab (Vectibix; Amgen)	EGFR	Human IgG2	Colorectal cancer	109
Ofatumumab (Arzerra; Genmab/ GlaxoSmithKline)	CD20	Human IgG1	Chronic lymphocytic leuakemia	110
Immunoconjugates				
Gemtuzumab ozogamicin (Mylotarg; Pfizer)	CD33	Humanized IgG4	Acute myelogenous leukaemia	111
^{90}Y-Ibritumomab tiuxetan (Zevalin; Biogen Idec)	CD20	Mouse	Lymphoma	112
Tositumomab and ^{131}I-tositumomab (Bexxar; GlaxoSmithKline)	CD20	Mouse	Lymphoma	113

EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; VEGF, vascular endothelial growth factor.

Weiner et al, Nature Review, 2010

Terapia con anticorpi (ambito tumorale)



4082 studies found for: antibody and cancer

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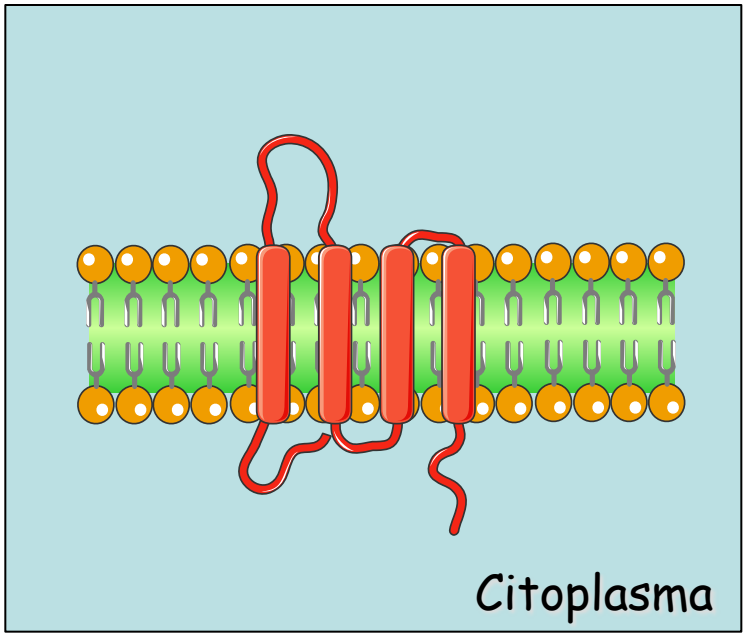
Rank	Status	Study
1	Active, not recruiting	**Safety Study of Radio-labeled huA33 Antibody in Colorectal Cancer** **Conditions:** Colorectal Neoplasms; Colorectal Cancer; Colorectal Tumor; COlorectal Carcinoma **Intervention:** Drug: Iodine-124 labeled humanized A33 (antibody)
2	Recruiting	**Copper Cu 64 Anti-CEA Monoclonal Antibody M5A PET in Diagnosing Patients With CEA Positive Cancer** **Conditions:** Breast Cancer; Colon Cancer; Extrahepatic Bile Duct Cancer; Gallbladder Cancer; Gastrointestinal Cancer; Liver and Intrahepatic Biliary Tract Cancer; Lung Cancer; Metastatic Cancer; Pancreatic Cancer; Rectal Cancer; Thyroid Gland Medullary Carcinoma; Unspecified Adult Solid Tumor, Protocol Specific **Interventions:** Procedure: radionuclide imaging; Procedure: positron emission tomography; Other: laboratory biomarker analysis; Other: pharmacological study; Drug: Cu 64 anti-CEA monoclonal antibody M5A IV

Antigeni associati al Linfoma contro cui sono stati isolati anticorpi

CD19	Hekman, Cancer Immunol Immunother, 1991
CD20	Davis, Clin Cancer Res, 1999
CD22	Leonard, J Clin Oncol, 2003
CD52	Dyer, Blood, 1989
Idiotipo	Kwak, N England J Med, 1992

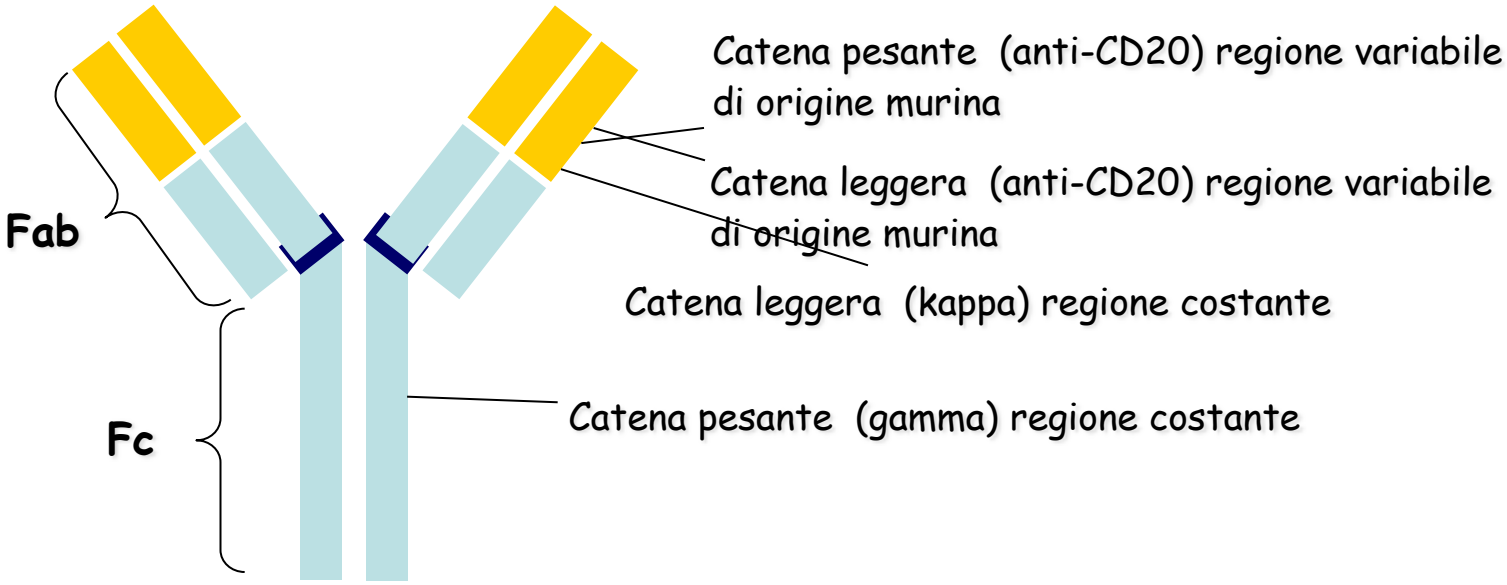
CD20

- Fosfoproteina transmembrana
- Dominio unico extracellulare
- Ligando naturale non identificato
- Funzione biologica ipotizzata: canale ionico al Ca^{++}
- Resistente ad internalizzazione e secrezione



Rituximab (IDEC-C2B8; Rituxan®; MabThera®)

Proprietà molecolari

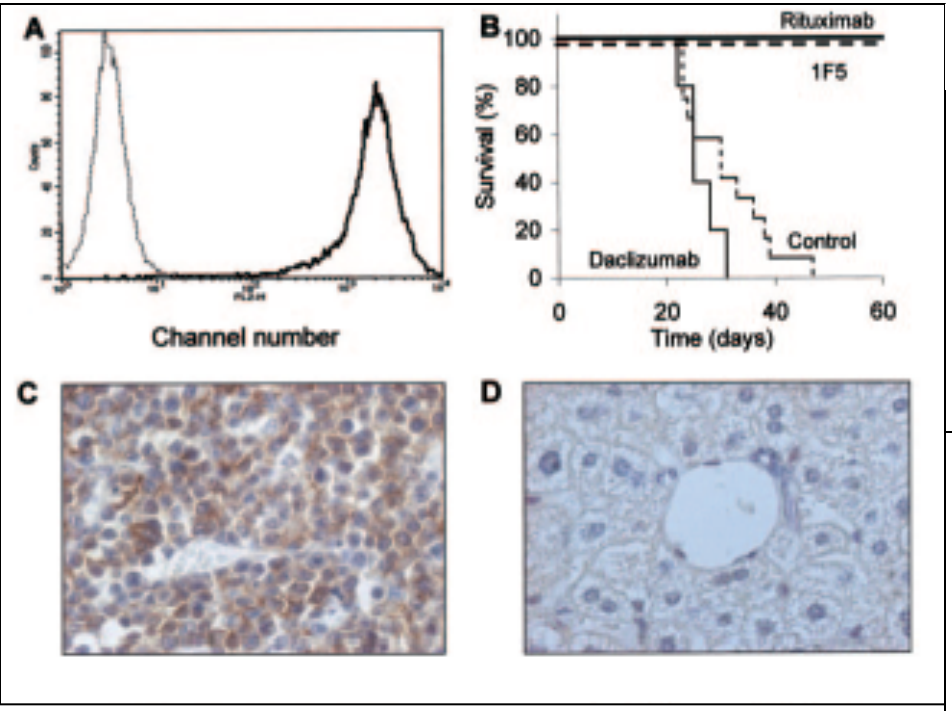


Anticorpo monoclonale anti CD20

Anticorpo chimerico:

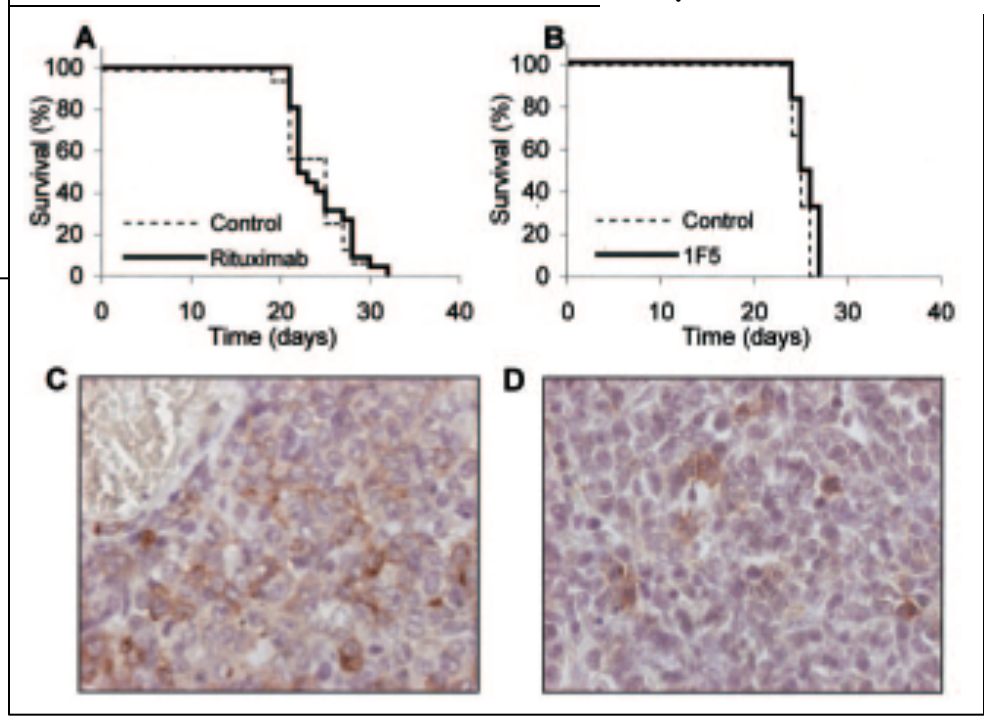
Sito di legame antigenico di origine murina fuso a regioni costanti della catena pesante (H) umana IgG1k e della catena leggera (L) umana k.

Effetto del Rituximab in un modello in vivo di linfoma non-Hodgkin's



C57BL/6

$C1q^{-/-}$ (C57BL/6)



Di Gaetano et al. J. Immunol, 2003

Associazione Rituximab-chemioterapia

Rituximab + Fludarabine	Di Gaetano, Br J Haematol, 2001
Rituximab + Fludarabine	Byrd, Blood, 2003
Rituximab + CHOP (insieme o come mantenimento)	Habermann, Blood, 2004
Rituximab + FND	McLaughlin, Ann Oncol, 2005

VALUTAZIONE FARMACOECONOMICA

	CHOP	R-CHOP	Differenza
Indice di Risposta	62,1%	75,4%	13,3%
Sopravvivenza in anni			
Libera da malattia	2,93	4,71	1,77
Complessiva	5,25	6,43	1,19
Post-progressione	2,10	1,54	-0,57
Sopravvivenza complessiva media	4,85	5,93	1,08
QALYs	3,08	4,23	1,15
Costi Terapia			
Rituximab		€13.631	€13.631
CHOP	€977	€1.033*	€56
Follow-up	€ 3.612	€4.764*	€1.151
Totale	€ 4.589	€19.427	€14.838
Costo/Eff			
Per Life Years guadagnata			€13.732
Per QALY guadagnata			€12.879

Costi dell'immunoterapia con Rituximab

- Un ciclo di terapia con Rituximab costa circa 15.000 euro a paziente con linfoma Non-Hodgkin
- In Italia si spendono all'anno 200 milioni di euro solo per Rituximab

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Adding fresh frozen plasma to rituximab for the treatment of patients with refractory advanced CLL

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Summary

Background: Many patients with chronic lymphocytic leukaemia (CLL) develop progressive, treatment-resistant disease. Rituximab (RTX), a monoclonal antibody targeting CD20 on B lymphocytes and widely used in other indolent B cell neoplasms is less efficacious in CLL, possibly due to associated complement deficiencies.

Objective: To examine in open trial whether providing complement by concurrent administration of fresh frozen plasma (FFP) will enhance the effect of RTX in CLL.

Setting: Outpatient haematology clinics in Israel and Greece.

Patients: Five patients with severe treatment-resistant CLL. All had been previously treated with fludarabine and three also failed treatment with RTX.

Intervention: Two units of FFP followed with RTX 375 mg/m^2 as a single agent, repeated every 1–2 weeks, as needed.

Results: A rapid and dramatic clinical and laboratory response was achieved in all patients. Lymphocyte counts dropped markedly followed by shrinkage of lymph nodes and spleen and improvement of the anaemia and thrombocytopenia. This could be maintained over 8 months (median) with additional cycles if necessary. Treatment was well tolerated in all cases.

Conclusion: Adding FFP to RTX may provide a useful therapeutic option in patients with advanced CLL resistant to treatment.