FARMACI BIOLOGICI

Prof. Sergio Scaccianoce

Definizione

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biological drug (BY-oh-LAH-jih-kul...)

A substance that is made from a living organism or its products and is used in the prevention, diagnosis, or treatment of cancer and other diseases. Biological drugs include antibodies, interleukins, and vaccines. Also called biologic agent and biological agent.

Una classe in costante sviluppo. Esempio: anticorpi.

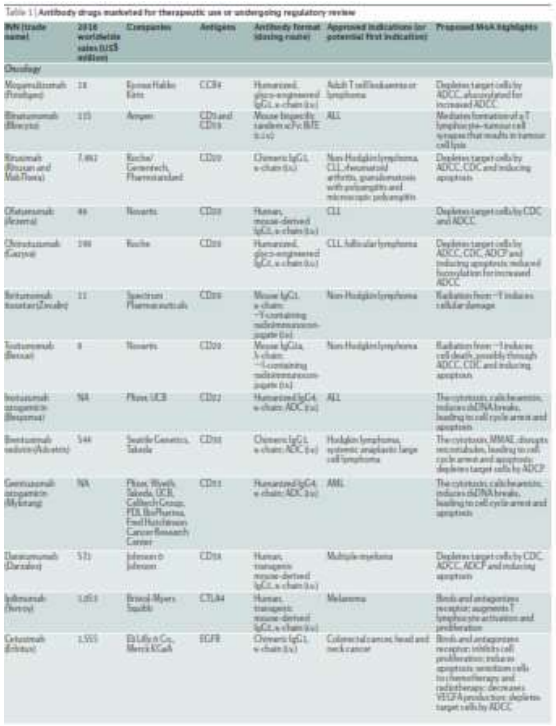


Table 1 | Antibody drugs marketed for therapeutic use or undergoing regulatory review

INN (trade name)	2016 worldwide sales (US$ million)	Companies	Antigens	Antibody format (dosing route)	Approved indications (or potential first indication)	Proposed MoA highlights
Oncology						
Mogamulizumab (Poteligeo)	38	Kyowa Hakko Kirin	CCR4	Humanized, glyco-engineered IgG1 κ chain (Lc)	Adult T cell leukaemia or lymphoma	Depletes target cells by ADCC, afucosylated for increased ADCC
Blinatumomab (Blincyto)	115	Amgen	CD3 and CD19	Mouse bispecific tandem scFv; BiTE (Lc)	ALL	Mediates formation of a T lymphocyte–tumour cell synapse that results in tumour cell lysis
Rituximab (Rituxan and MabThera)	7,461	Roche/ Genentech, Pharmstandard	CD20	Chimeric IgG1 κ chain (Lc)	Non-Hodgkin lymphoma, CLL, rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis	Depletes target cells by ADCC, CDC, and inducing apoptosis
Ofatumumab (Arzerra)	46	Novartis	CD20	Human, mouse-derived IgG1 κ chain (Lc)	CLL	Depletes target cells by CDC and ADCC
Obinutuzumab (Gazyva)	198	Roche	CD20	Humanized, glyco-engineered IgG1 κ chain (Lc)	CLL, follicular lymphoma	Depletes target cells by ADCC, CDC, ADCP and inducing apoptosis; reduced fucosylation for increased ADCC
Ibritumomab tiuxetan (Zevalin)	11	Spectrum Pharmaceuticals	CD20	Mouse IgG1 κ chain; –Y-containing radioimmunoconjugate (Lc)	Non-Hodgkin lymphoma	Radiation from –Y induces cellular damage
Ivuitumomab (Bexxar)	0	Novartis	CD20	Mouse IgG1κ, λ chain; –I-containing radioimmunoconjugate (Lc)	Non-Hodgkin lymphoma	Radiation from –I induces cell death, possibly through ADCC, CDC, and inducing apoptosis
Inotuzumab ozogamicin (Besponsa)	NA	Pfizer, UCB	CD22	Humanized IgG4 κ chain; ADC (Lc)	ALL	The cytotoxic calicheamicin, induces dsDNA breaks, leading to cell cycle arrest and apoptosis
Brentuximab vedotin (Adcetris)	544	Seattle Genetics, Takeda	CD30	Chimeric IgG1 κ chain; ADC (Lc)	Hodgkin lymphoma, systemic anaplastic large cell lymphoma	The cytotoxic, MMAE, disrupts microtubules, leading to cell cycle arrest and apoptosis; depletes target cells by ADCP
Gemtuzumab ozogamicin (Mylotarg)	NA	Pfizer, Wyeth, Takeda, UCB, Caltech Group, PDL BioPharma, Fred Hutchinson Cancer Research Center	CD33	Humanized IgG4 κ chain; ADC (Lc)	AML	The cytotoxic calicheamicin, induces dsDNA breaks, leading to cell cycle arrest and apoptosis
Daratumumab (Darzalex)	531	Johnson & Johnson	CD38	Human, transgenic mouse-derived IgG1 κ chain (Lc)	Multiple myeloma	Depletes target cells by CDC, ADCC, ADCP and inducing apoptosis
Ipilimumab (Yervoy)	1,053	Bristol-Myers Squibb	CTLA4	Human, transgenic mouse-derived IgG1 κ chain (Lc)	Melanoma	Binds and antagonizes receptor; augments T lymphocyte activation and proliferation
Cetuximab (Erbitux)	1,555	Eli Lilly & Co., Merck KGaA	EGFR	Chimeric IgG1 κ chain (Lc)	Colorectal cancer, head and neck cancer	Binds and antagonizes receptor; inhibits cell proliferation; induces apoptosis; sensitizes cells to chemotherapy and radiotherapy; decreases VEGFA production; depletes target cells by ADCC

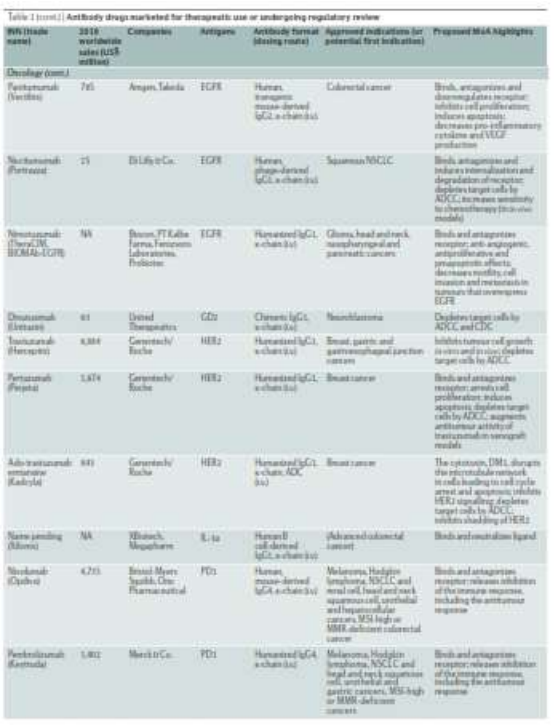
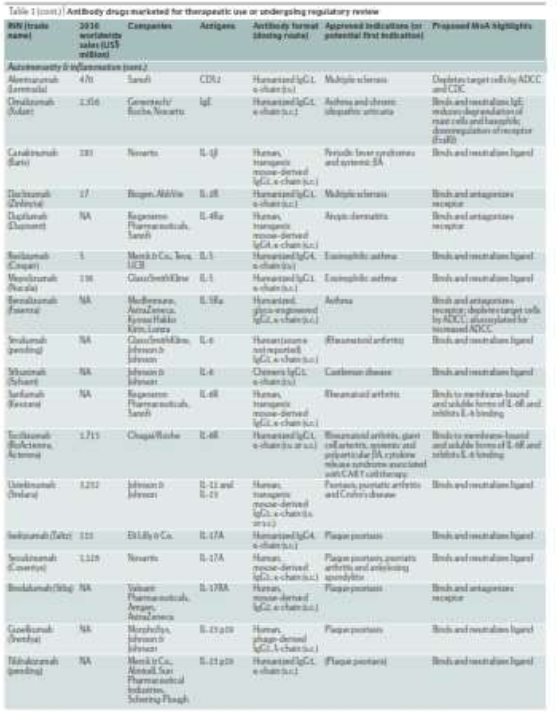


Table 1 (cont.) | Antibody drugs marketed for therapeutic use or undergoing regulatory review

INN (trade name)	2016 worldwide sales (US$ million)	Companies	Antigens	Antibody format (dosing route)	Approved indications (or potential first indication)	Proposed MoA highlights
Oncology (cont.)						
Panitumumab (Vectibix)	765	Amgen, Takeda	EGFR	Human, transgenic mouse-derived IgG2 κ chain (Lc)	Colorectal cancer	Binds, antagonizes and downregulates receptor; inhibits cell proliferation; induces apoptosis; decreases pro-inflammatory cytokine and VEGF production
Nimotuzumab (Theracim, THERACIM, BIOMAb EGFR)	NA	Biocon, PT Kalbe Farma, Ferrosan Laboratories, Probiotec	EGFR	Humanized IgG1 κ chain (Lc)	Glioma, head and neck, nasopharyngeal and pancreatic cancers	Binds and antagonizes receptor; anti-angiogenic, antiproliferative and proapoptotic effects; decreases motility, cell invasion and metastasis in tumours that overexpress EGFR
Dinutuximab (Unituxin)	61	United Therapeutics	GD2	Chimeric IgG1 κ chain (Lc)	Neuroblastoma	Depletes target cells by ADCC and CDC
Trastuzumab (Herceptin)	6,384	Genentech/ Roche	HER2	Humanized IgG1 κ chain (Lc)	Breast, gastric and gastroesophageal junction cancers	Inhibits tumour cell growth in vitro and in vivo; depletes target cells by ADCC
Pertuzumab (Perjeta)	1,674	Genentech/ Roche	HER2	Humanized IgG1 κ chain (Lc)	Breast cancer	Binds and antagonizes receptor; arrests cell proliferation; induces apoptosis; depletes target cells by ADCC; augments antitumour activity of trastuzumab in xenograft models
Ado-trastuzumab emtansine (Kadcyla)	841	Genentech/ Roche	HER2	Humanized IgG1 κ chain; ADC (Lc)	Breast cancer	The cytotoxin, DM1, disrupts the microtubular network in cells leading to cell cycle arrest and apoptosis; inhibits HER2 signalling; depletes target cells by ADCC; inhibits shedding of HER2
Naxitamab (Hu3F8)	NA	Y-mAbs Therapeutics, Memorial Sloan Kettering Cancer Center	IL-1α	Humanized IgG1 κ chain (Lc)	(Advanced colorectal cancer)	Binds and neutralizes ligand
Nivolumab (Opdivo)	4,755	Bristol-Myers Squibb, Ono Pharmaceutical	PD1	Human, mouse-derived IgG4 κ chain (Lc)	Melanoma, Hodgkin lymphoma, NSCLC, and renal cell, head and neck, squamous cell, urothelial and hepatocellular cancers, MSI-high or MMR-deficient colorectal cancer	Binds and antagonizes receptor; releases inhibition of the immune response, including the antitumour response
Pembrolizumab (Keytruda)	1,402	Merck & Co.	PD1	Humanized IgG4 κ chain (Lc)	Melanoma, Hodgkin lymphoma, NSCLC and head and neck squamous cell, urothelial and gastric cancers, MSI-high or MMR-deficient cancers	Binds and antagonizes receptor; releases inhibition of the immune response, including the antitumour response

Table 1 (cont.) | Antibody drugs marketed for therapeutic use or undergoing regulatory review

INN (trade name)	2016 worldwide sales (US$ million)	Companies	Antigens	Antibody format (dosing route)	Approved indications (or potential first indication)	Proposed MoA highlights
Oncology (cont.)						
Atezolizumab (Tecentriq)	256	Genentech/ Roche	PDL1	Human, phage-derived, aglycosylated IgG1 κ chain (Lc)	Urothelial cancer and NSCLC	Binds and neutralizes ligand; releases inhibition of the immune response, including the antitumour response; without inducing ADCC
Avelumab (Bavencio)	NA	Pfizer, Merck KGaA, Shire	PDL1	Human, phage-derived IgG1 κ chain (Lc)	Merkel cell and urothelial cancers	Binds and neutralizes ligand; releases inhibition of the immune response, including the antitumour immune response; depletes target cells by ADCC
Durvalumab (Imfinzi)	NA	AstraZeneca	PDL1	Human, transgenic mouse-derived IgG1 κ chain (Lc)	Urothelial cancer	Binds and neutralizes ligand; releases inhibition of immune response; Fc engineered to attenuate effector functions
Olaratumab (Lartruvo)	12	Eli Lilly & Co.	PDGFRα	Human, transgenic mouse-derived IgG1 κ chain (Lc)	Soft tissue sarcoma	Binds and antagonizes receptor; in vitro and in vivo antitumour activity
Denosumab (Prolia, Praia, Xgeva, Ranmark)	3,456	Amgen; Daiichi Sankyo	RANKL	Human, transgenic mouse-derived IgG2 κ chain (Lc)	Skeletal events in patients with bone metastases from solid tumours; patients with osteoporosis at high risk of bone fracture	Binds and neutralizes ligand; decreases bone resorption and increases mass and strength of cortic bones
Elotuzumab (Empliciti)	150	Bristol-Myers Squibb	SLAMF7	Humanized IgG1 κ chain (Lc)	Multiple myeloma	Activates NK cells through SLAMF7 pathway and Fc receptors; depletes target cells by ADCC
Bevacizumab (Avastin)	6,005	Genentech/ Roche	VEGFA	Humanized IgG1 κ chain (Lc)	Non-squamous NSCLC and colorectal, renal cell, cervical ovarian, fallopian tube and peritoneal cancers and glioblastoma	Binds and neutralizes ligand; reduces microvascular growth and inhibits metastatic disease progression in mouse xenografts
Ramucirumab (Cyramza)	414	Eli Lilly & Co.	VEGFR2	Human, phage-derived IgG1 κ chain (Lc)	NSCLC and gastric and colorectal cancers	Binds and antagonizes receptor; inhibits ligand-induced proliferation and endothelial cell migration; inhibits angiogenesis in an animal model
Autoimmunity & inflammation						
Natalizumab (Tysabri)	1,084	Biogen	α4 β1 and α4 β7 integrins	Humanized IgG4 κ chain (Lc)	Multiple sclerosis and Crohn's disease	Binds and antagonizes receptor; inhibits leukocyte adhesion
Vedolizumab (Entyvio)	1,324	Takeda	α4 β7 integrin	Humanized IgG1 κ chain (Lc)	Ulcerative colitis and Crohn's disease	Binds and antagonizes receptor; inhibits leukocyte adhesion
Belimumab (Benlysta)	414	GlaxoSmithKline	BAFF	Human, phage-derived IgG1 λ chain (Lc)	Systemic lupus erythematosus	Binds and neutralizes ligand; inhibits survival of B lymphocytes
Ixekizumab (Taltz)	Unknown; not reported	Eli Lilly & Co.	IL-17A	Humanized IgG4 κ chain (Lc)	Plaque psoriasis	Binds and neutralizes ligand
Ocrelizumab (Ocrevus)	NA	Genentech/ Roche, Biogen, PDL BioPharma	CD20	Humanized IgG1 κ chain (Lc)	Multiple sclerosis	Depletes B lymphocytes by ADCC and CDC



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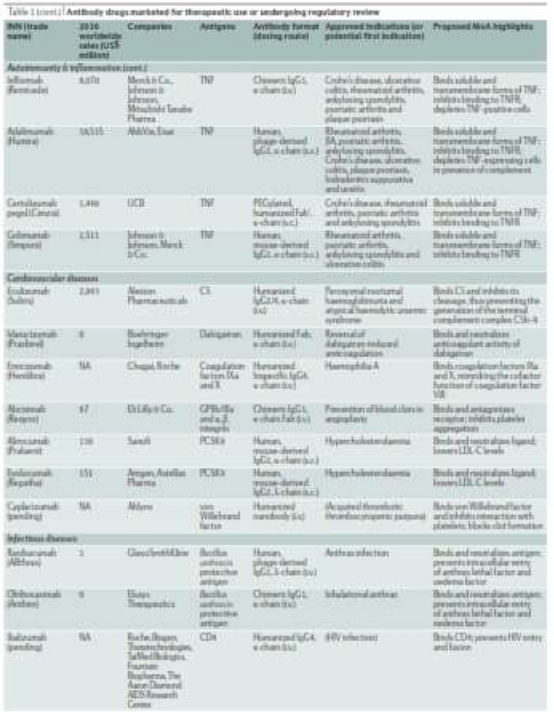
INN (trade name)	2016 worldwide sales (US$ million)	Companies	Antigens	Antibody format (dosing route)	Approved indications (or potential first indication)	Proposed MoA highlights
Autoimmunity & inflammation (cont.)						
Alemtuzumab (Lemtrada)	470	Sanofi	CD52	Humanized IgG1 κ chain (Lc)	Multiple sclerosis	Depletes target cells by ADCC and CDC
Omalizumab (Xolair)	1,356	Genentech/ Roche, Novartis	IgE	Humanized IgG1 κ chain (Lc)	Asthma and chronic idiopathic urticaria	Binds and neutralizes IgE; reduces degranulation of mast cells basophils; downregulation of receptor (FcεRI)
Canakinumab (Ilaris)	283	Novartis	IL-1β	Human, transgenic mouse-derived IgG1 κ chain (Lc)	Periodic fever syndromes and systemic JIA	Binds and neutralizes ligand
Daclizumab (Zinbryta)	17	Biogen, AbbVie	IL-2Rα	Humanized IgG1 κ chain (Lc)	Multiple sclerosis	Binds and antagonizes receptor
Dupilumab (Dupixent)	NA	Regeneron Pharmaceuticals, Sanofi	IL-4Rα	Human, transgenic mouse-derived IgG4 κ chain (Lc)	Atopic dermatitis	Binds and antagonizes receptor
Reslizumab (Cinqair)	5	Merck & Co., Teva, UCB	IL-5	Humanized IgG4 κ chain (Lc)	Eosinophilic asthma	Binds and neutralizes ligand
Mepolizumab (Nucala)	136	GlaxoSmithKline	IL-5	Humanized IgG1 κ chain (Lc)	Eosinophilic asthma	Binds and neutralizes ligand
Benralizumab (Fasenra)	NA	MedImmune, AstraZeneca, Kyowa Hakko Kirin, Lonza	IL-5Rα	Humanized, glyco-engineered IgG1 κ chain (Lc)	Asthma	Binds and antagonizes receptor; depletes target cells by ADCC; afucosylated for increased ADCC
Sirukumab (pending)	NA	GlaxoSmithKline, Johnson & Johnson	IL-6	Human (source not reported) IgG1 κ chain (Lc)	(Rheumatoid arthritis)	Binds and neutralizes ligand
Siltuximab (Sylvant)	NA	Johnson & Johnson	IL-6	Chimeric IgG1 κ chain (Lc)	Castleman disease	Binds and neutralizes ligand
Sarilumab (Kevzara)	NA	Regeneron Pharmaceuticals, Sanofi	IL-6R	Human, transgenic mouse-derived IgG1 κ chain (Lc)	Rheumatoid arthritis	Binds to membrane-bound and soluble forms of IL-6R and inhibits IL-6 binding
Tocilizumab (Roche/actemra, Actemra)	1,715	Chugai/Roche	IL-6R	Humanized IgG1 κ chain (Lc; or Lc)	Rheumatoid arthritis, giant cell arteritis, systemic and polyarticular JIA; cytokine release syndrome associated with CAR T cell therapy	Binds to membrane-bound and soluble forms of IL-6R and inhibits IL-6 binding
Ustekinumab (Stelara)	3,292	Johnson & Johnson	IL-12 and IL-23	Human, transgenic mouse-derived IgG1 κ chain (Lc; or Lc)	Psoriasis, psoriatic arthritis and Crohn's disease	Binds and neutralizes ligand
Ixekizumab (Taltz)	333	Eli Lilly & Co.	IL-17A	Humanized IgG4 κ chain (Lc)	Plaque psoriasis	Binds and neutralizes ligand
Secukinumab (Cosentyx)	1,328	Novartis	IL-17A	Human, mouse-derived IgG1 κ chain (Lc)	Plaque psoriasis, psoriatic arthritis and ankylosing spondylitis	Binds and neutralizes ligand
Brodalumab (Siliq)	NA	Valeant Pharmaceuticals, Amgen, AstraZeneca	IL-17RA	Human, mouse-derived IgG2 κ chain (Lc)	Plaque psoriasis	Binds and antagonizes receptor
Guselkumab (Tremfya)	NA	Morphosys, Johnson & Johnson	IL-23 p19	Human, phage-derived IgG1 λ chain (Lc)	Plaque psoriasis	Binds and neutralizes ligand
Tildrakizumab (pending)	NA	Merck & Co., Almirall, Sun Pharmaceutical Industries, Schering Plough	IL-23 p19	Humanized IgG1 κ chain (Lc)	(Plaque psoriasis)	Binds and neutralizes ligand



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Autoimmunity & inflammation (cont.)						
Infliximab (Remicade)	8,070	Merck & Co., Johnson & Johnson, Mitsubishi Tanabe Pharma	TNF	Chimeric IgG1 κ chain (Lc)	Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis	Binds soluble and transmembrane forms of TNF; inhibits binding to TNFR; depletes TNF-positive cells
Adalimumab (Humira)	14,515	AbbVie, Eisai	TNF	Human, phage-derived IgG1 κ chain (Lc)	Rheumatoid arthritis, JIA, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, plaque psoriasis, hidradenitis suppurativa and uveitis	Binds soluble and transmembrane forms of TNF; inhibits binding to TNFR; depletes TNF-expressing cells in presence of complement
Certolizumab pegol (Cimzia)	1,446	UCB	TNF	PEGylated, humanized Fab' κ chain (Lc)	Crohn's disease, rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis	Binds soluble and transmembrane forms of TNF; inhibits binding to TNFR
Golimumab (Simponi)	2,311	Johnson & Johnson, Merck & Co.	TNF	Human, mouse-derived IgG1 κ chain (Lc)	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and ulcerative colitis	Binds soluble and transmembrane forms of TNF; inhibits binding to TNFR
Cardiovascular disease						
Eculizumab (Soliris)	2,843	Alexion Pharmaceuticals	C5	Humanized IgG2/4 κ chain (Lc)	Paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome	Binds C5 and inhibits its cleavage, thus preventing the generation of the terminal complement complex C5b–9
Idarucizumab (Praxbind)	0	Boehringer Ingelheim	Dabigatran	Humanized Fab κ chain (Lc)	Reversal of dabigatran-induced anticoagulation	Binds and neutralizes anticoagulant activity of dabigatran
Emicizumab (Hemlibra)	NA	Chugai, Roche	Coagulation factors IXa and X	Humanized bispecific IgG4 κ chain (Lc)	Haemophilia A	Binds coagulation factors IXa and X, mimicking the cofactor function of coagulation factor VIII
Abciximab (Reopro)	87	Eli Lilly & Co.	GPIIb/IIIa and αv β3 integrin	Chimeric IgG1 κ chain Fab (Lc)	Prevention of blood clots in angioplasty	Binds and antagonizes receptor; inhibits platelet aggregation
Alirocumab (Praluent)	118	Sanofi	PCSK9	Human, mouse-derived IgG1 κ chain (Lc)	Hypercholesterolaemia	Binds and neutralizes ligand; lowers LDL-C levels
Evolocumab (Repatha)	151	Amgen, Astellas Pharma	PCSK9	Human, mouse-derived IgG2 κ chain (Lc)	Hypercholesterolaemia	Binds and neutralizes ligand; lowers LDL-C levels
Caplacizumab (pending)	NA	Ablynx	von Willebrand factor	Humanized nanobody (Lc)	(Acquired thrombotic thrombocytopenic purpura)	Binds von Willebrand factor and inhibits interaction with platelets; blocks clot formation
Infectious diseases						
Raxibacumab (Abthrax)	1	GlaxoSmithKline	Bacillus anthracis protective antigen	Human, phage-derived IgG1 λ chain (Lc)	Anthrax infection	Binds and neutralizes antigen; prevents intracellular entry of anthrax lethal factor and oedema factor
Obiltoxaximab (Anthim)	0	Elusys Therapeutics	Bacillus anthracis protective antigen	Chimeric IgG1 κ chain (Lc)	Inhalational anthrax	Binds and neutralizes antigen; prevents intracellular entry of anthrax lethal factor and oedema factor
Ibalizumab (pending)	NA	Roche, Biogen, Theravectys, TaiMed Biologics, Fountain Biopharma, The Aaron Diamond AIDS Research Center	CD4	Humanized IgG4 κ chain (Lc)	(HIV infection)	Binds CD4; prevents HIV entry and fusion

Table 1 (cont.) | Antibody drugs marketed for therapeutic use or undergoing regulatory review

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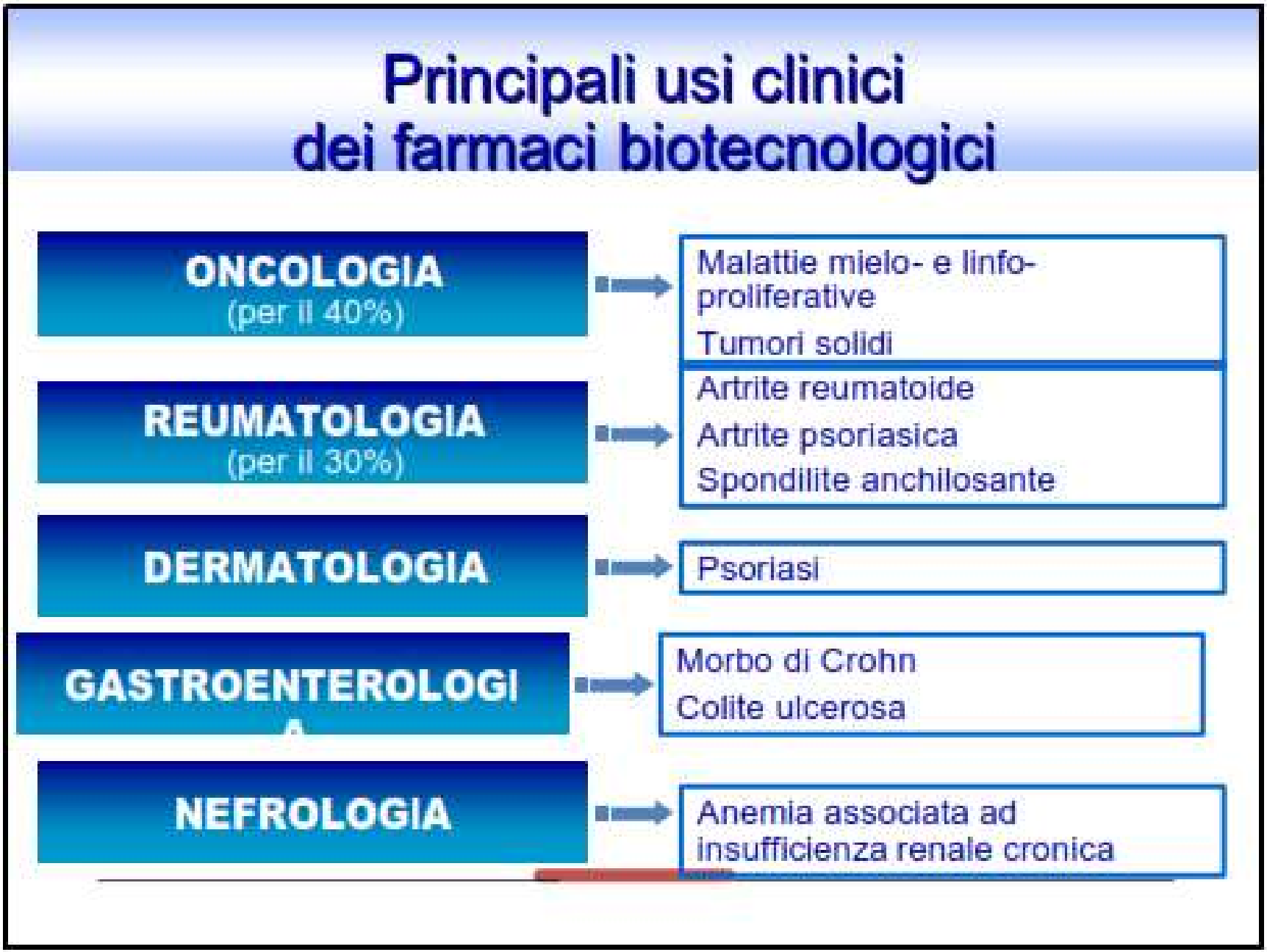
Infectious diseases (cont.)						
Bezlotoxumab (Zinplava)	NA	Merck & Co., Bristol-Myers Squibb, University of Massachusetts	Clostridium difficile toxin B	Human, mouse-derived IgG1 κ chain (Lc)	Reduce recurrence of C. difficile infection	Binds and neutralizes toxin B
Rmab (Rabishield)	Unknown; not reported	Serum Institute of India, Mandibooja (University of Manitoba/Rabies Medical Schools)	Rabies virus G glycoprotein	Human IgG1 (Lc and Lc)	Post-exposure prophylaxis of rabies	Binds to a conformational epitope of G glycoprotein of rabies virus
Palivizumab (Synagis)	1,055	Astra Zeneca, AbbVie	RSV gpF	Humanized IgG1 κ chain (Lm)	Prevention of RSV infection	Binds and neutralizes RSV; inhibits viral fusion and replication
Ophthalmology						
Ranibizumab (Lucentis)	1,261	Roche/ Genentech, Novartis	VEGF	Humanized IgG1 κ chain, Fab (Lc)	Neovascular (wet) age-related macular degeneration, macular oedema following retinal vein occlusion, diabetic macular oedema, diabetic retinopathy and myopic choroidal neovascularization	Binds and neutralizes ligand; reduces endothelial cell proliferation, vascular leakage and new blood vessel formation
Transplantation						
Muromonab-CD3 (Orthoclone OKT3)	46	Johnson & Johnson	CD3	Mouse IgG2a κ chain (Lc)	Prophylaxis of acute kidney-transplant rejection	Blocks function of T cell-expressed CD3; reverses graft rejection
Basiliximab (Simulect)	118	Novartis	IL-2Rα	Chimeric IgG1 κ chain (Lc)	Prevention of kidney transplant rejection	Binds and antagonizes receptor
Osteoporosis						
Romosozumab (Evenity)	NA	Amgen, UCB, Astellas Pharma	Sclerostin	Humanized IgG2 κ chain (Lc)	(Osteoporosis in postmenopausal women at increased risk of fracture)	Binds and neutralizes ligand; increases bone mineral density and bone formation and reduces bone resorption
Miscellaneous						
Eremezumab (Aimovig)	NA	Amgen, Astellas Ph	CGRPR	Human,	(Migraine prevention)	Binds and neutralizes ligand
Barnizumab (pending)	NA	K Pharmaceutical		mouse-derived IgG1 κ chain (Lc)		

Principali usi clinici dei farmaci biotecnologici



da: convegno SIF marzo 2012

Processo produttivo

Cinque fasi principali altamente variabili

1. CLONAZIONE e SCREENING: identificazione della sequenza genica della proteina da produrre e inserimento di tale DNA in un vettore plasmidico.

2. BANCA DI CELLULE MASTER: inserimento in linee cellulari per la costituzione di un'unica banca master capace di riprodurre in quantità la proteina.

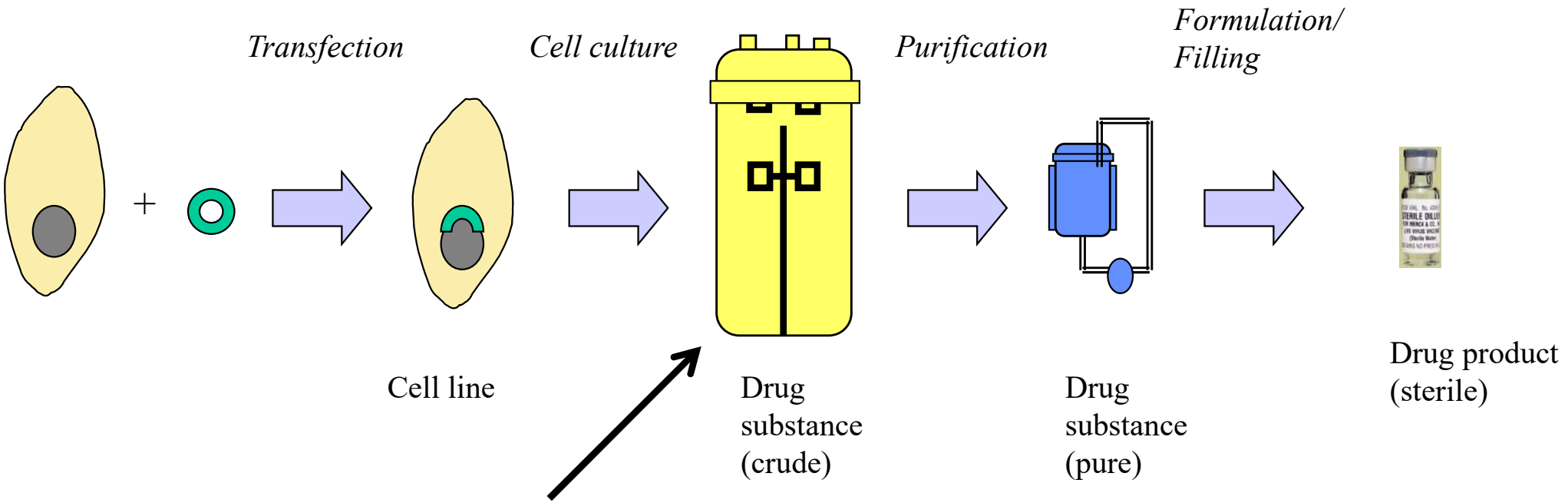
3. FERMENTAZIONE: si espande il volume della coltura cellulare fino a migliaia di litri e le cellule producono la sostanza desiderata in un medium.

4. PURIFICAZIONE: rimozione, filtrazione di particelle e composti estranei.

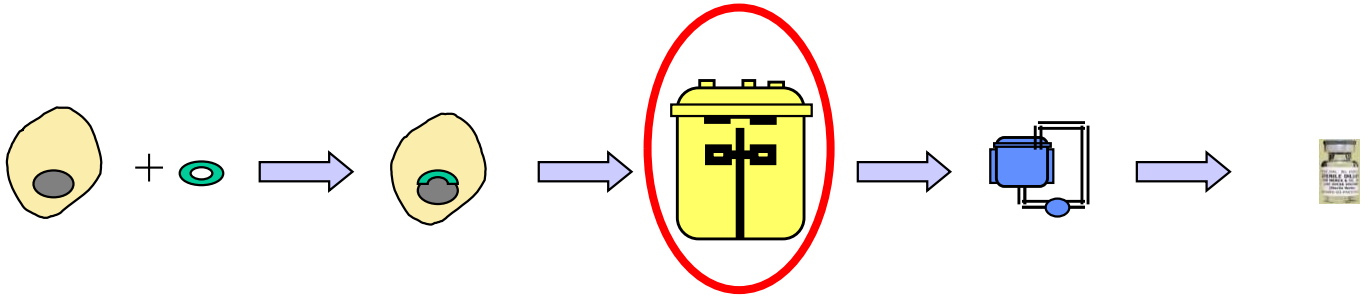
5. FORMULAZIONE E CONFEZIONAMENTO

Processo produttivo

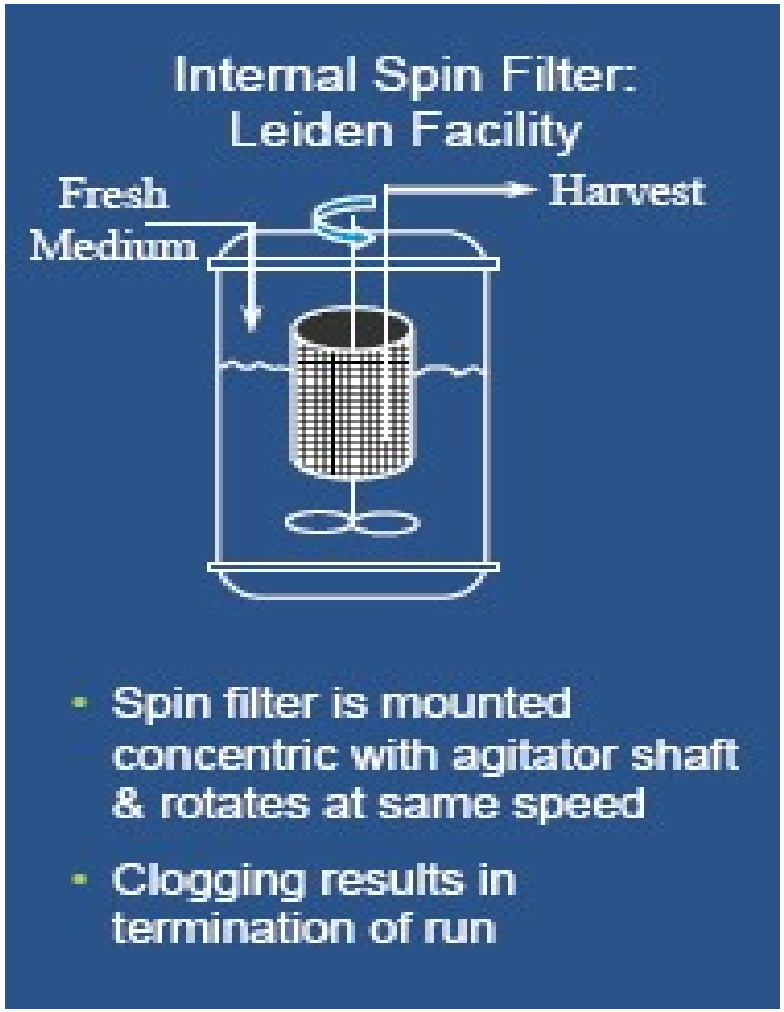
"il prodotto è il processo di produzione" (Karson KL., Nature Biotecnol, 2005).

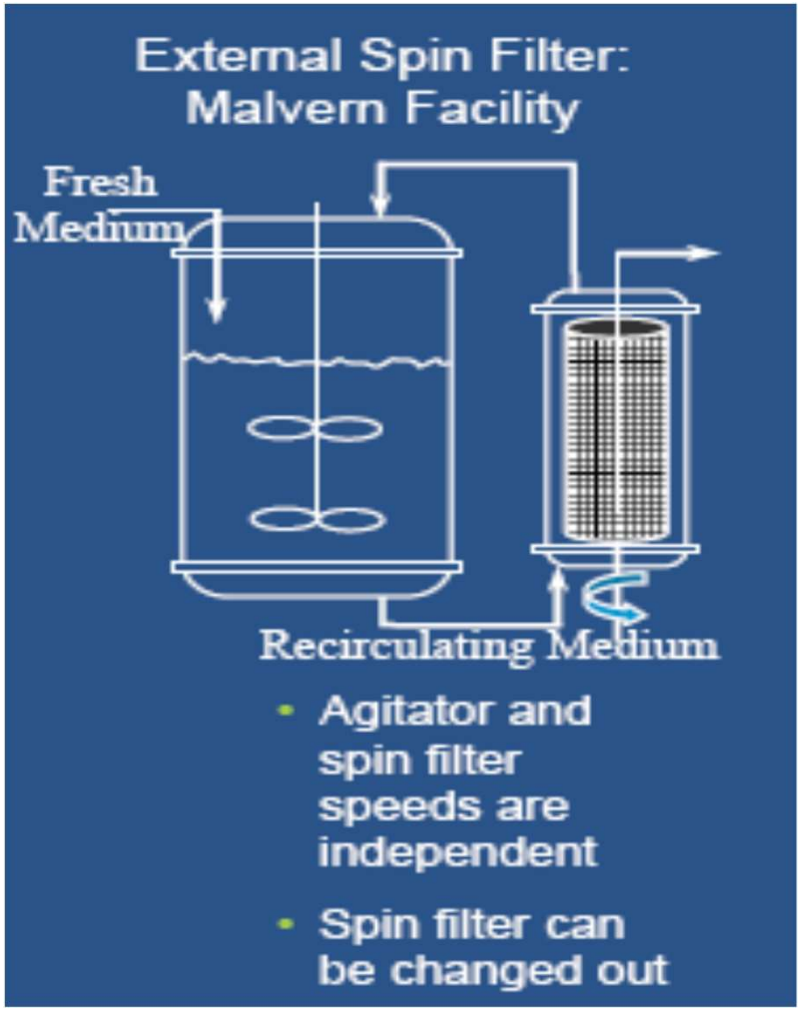


Processo di produzione



Bioreattore: un esempio di variabilità





Processo produttivo

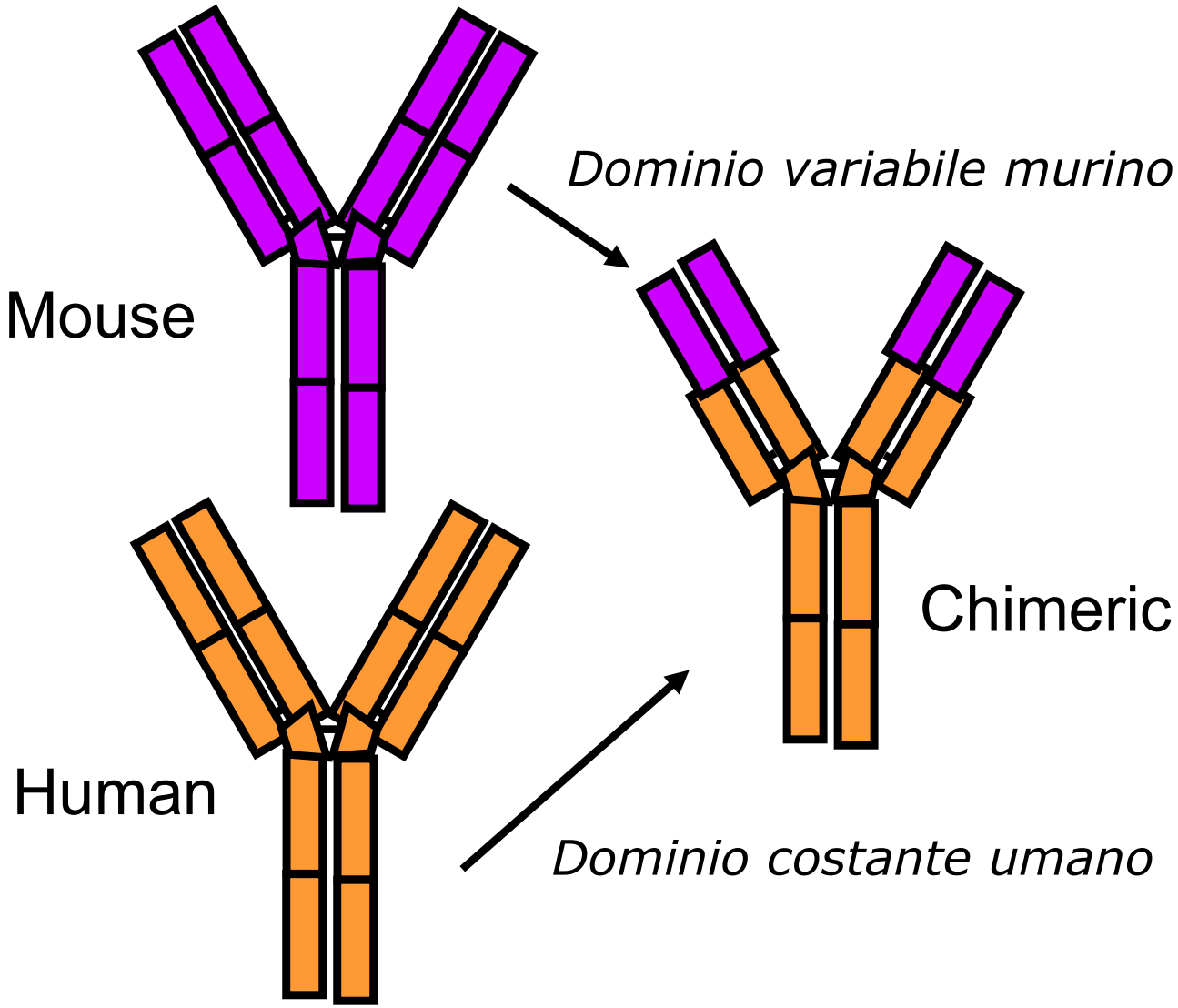
Example of a 1000 L Bioreactor with an external spin filter used in the production of Remicade® in Malvern, PA

Adattato da: T. Burkett, The Community College of Baltimore County

Difficoltà e strategie nella realizzazione

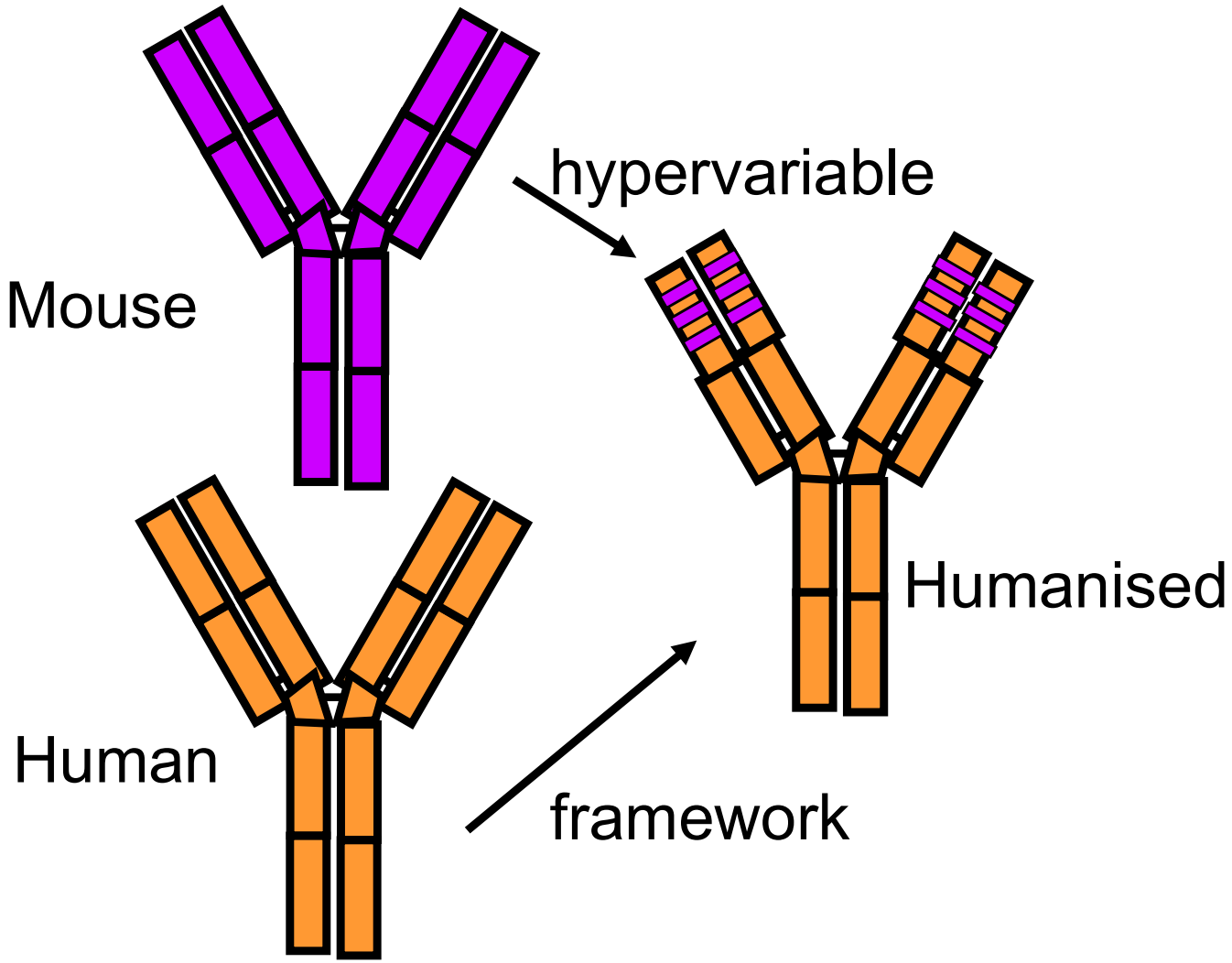
- Macromolecole in alcuni casi a struttura quaternaria.
- Generalmente caratterizzate da bassa biodisponibilità (di solito sono molto voluminosi).
- Trasporto sull'organo bersaglio.
- Eventuale comparsa di effetti collaterali per azione sistemica (es. sistema immunitario).

Difficoltà e strategie nella realizzazione



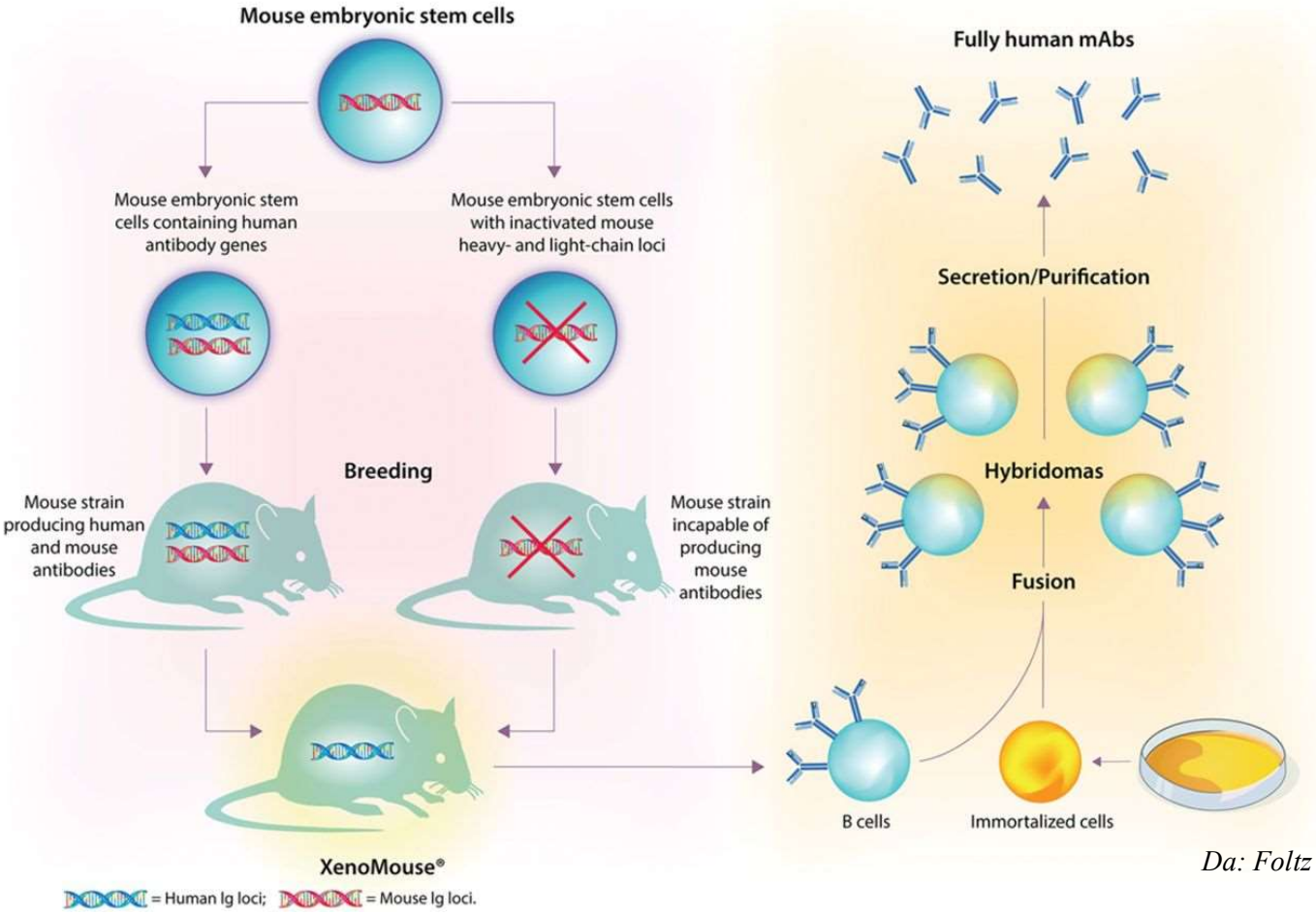
Un primo approccio per la riduzione della immunogeneticità è rappresentato dagli ***anticorpi chimerici****, nei quali il* ***dominio variabile murino*** *è* ***legato*** *al* ***dominio costante umano****. Esempi di anticorpi chimerici sono il ritu****ximab*** *e l'infli****ximab****.*

Difficoltà e strategie nella realizzazione



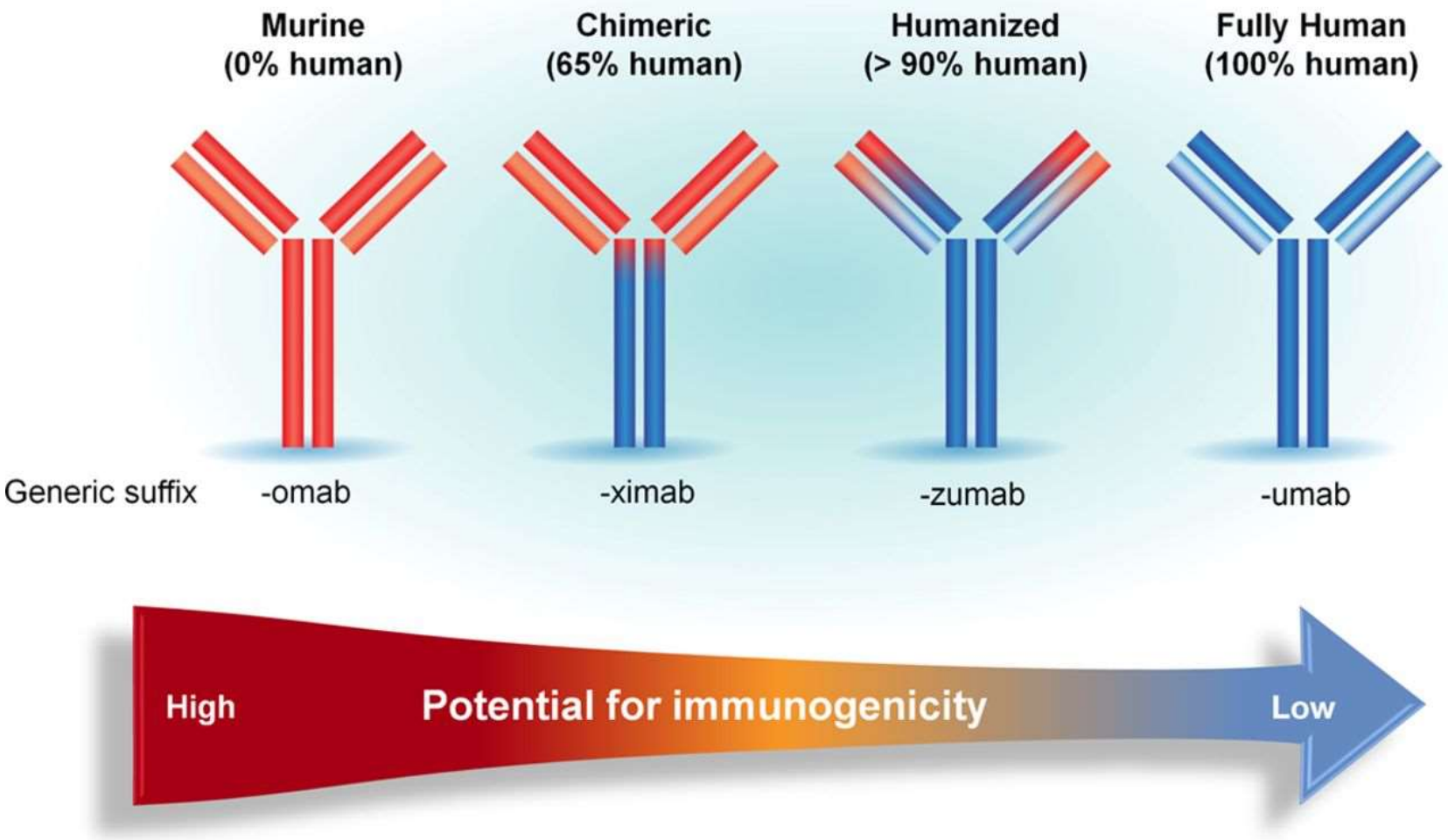
*Negli **anticorpi umanizzati**, la porzione **ipervariabile murina** è inserita in una Ig umana. L'anticorpo risultante ha le stesse caratteristiche di legame dell'anticorpo murino. Il primo anticorpo umanizzato è stato l'alemtu**zumab**.*

Difficoltà e strategie nella realizzazione



Da: Foltz IN et al. Circulation 2013

*Gli **anticorpi monoclonali umani** sono prodotti utilizzando topi transgenici o tramite la tecnica del phage display. L'adalim**umab** è un esempio di anticorpo monoclonale umano.*



Da: Foltz IN et al. Circulation 2013

Biosimilari

Agenzia Italiana del Farmaco

AIFA

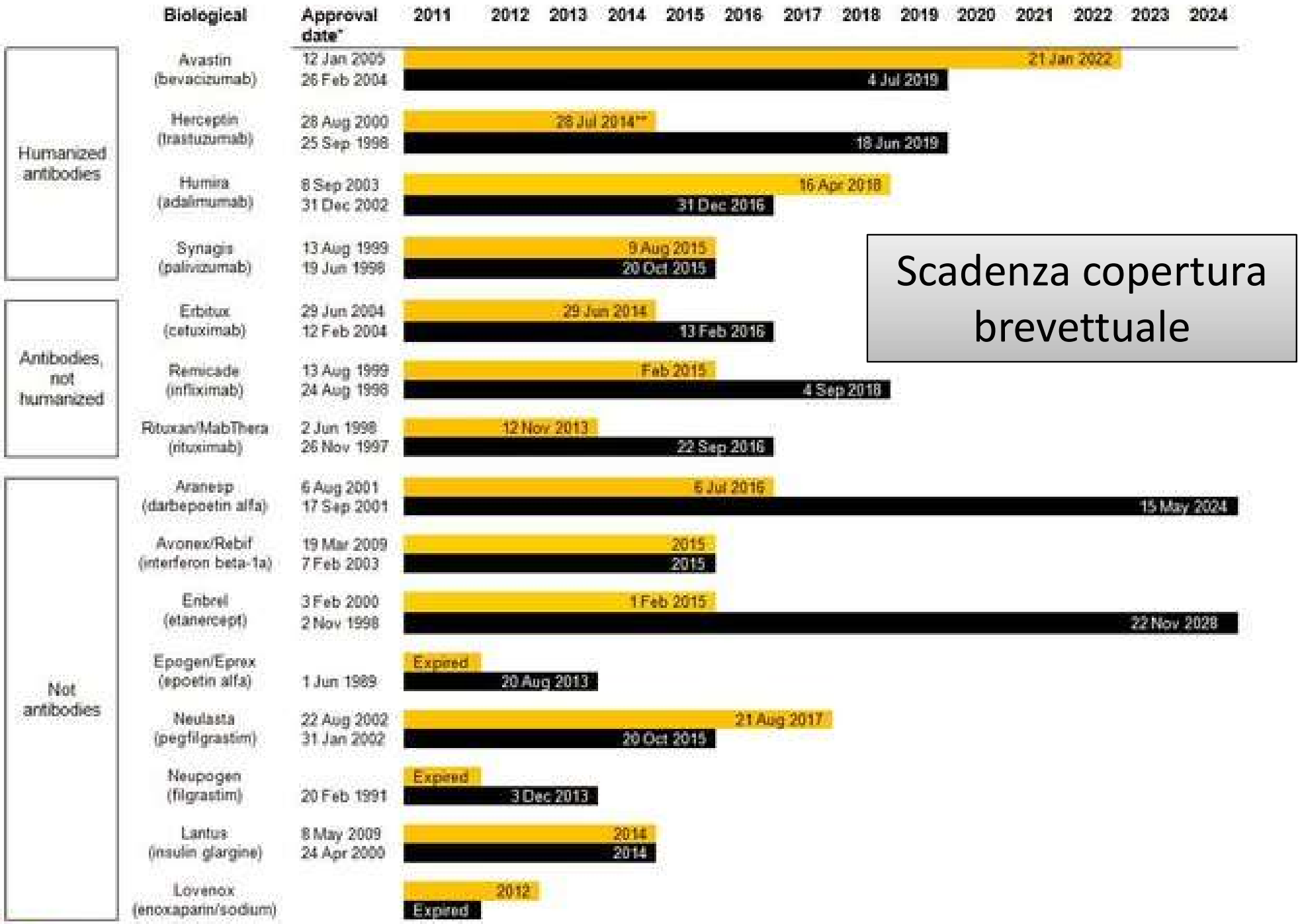
15 giugno 2016

SECONDO CONCEPT PAPER AIFA SUI FARMACI BIOSIMILARI

STATO ATTUALE

La **perdita** della **copertura brevettuale** permette l'entrata sulla scena terapeutica dei farmaci cosiddetti "**biosimilari", medicinali "simili" per qualità, efficacia e sicurezza ai prodotti biologici originatori di riferimento e non più soggetti a copertura brevettuale**.

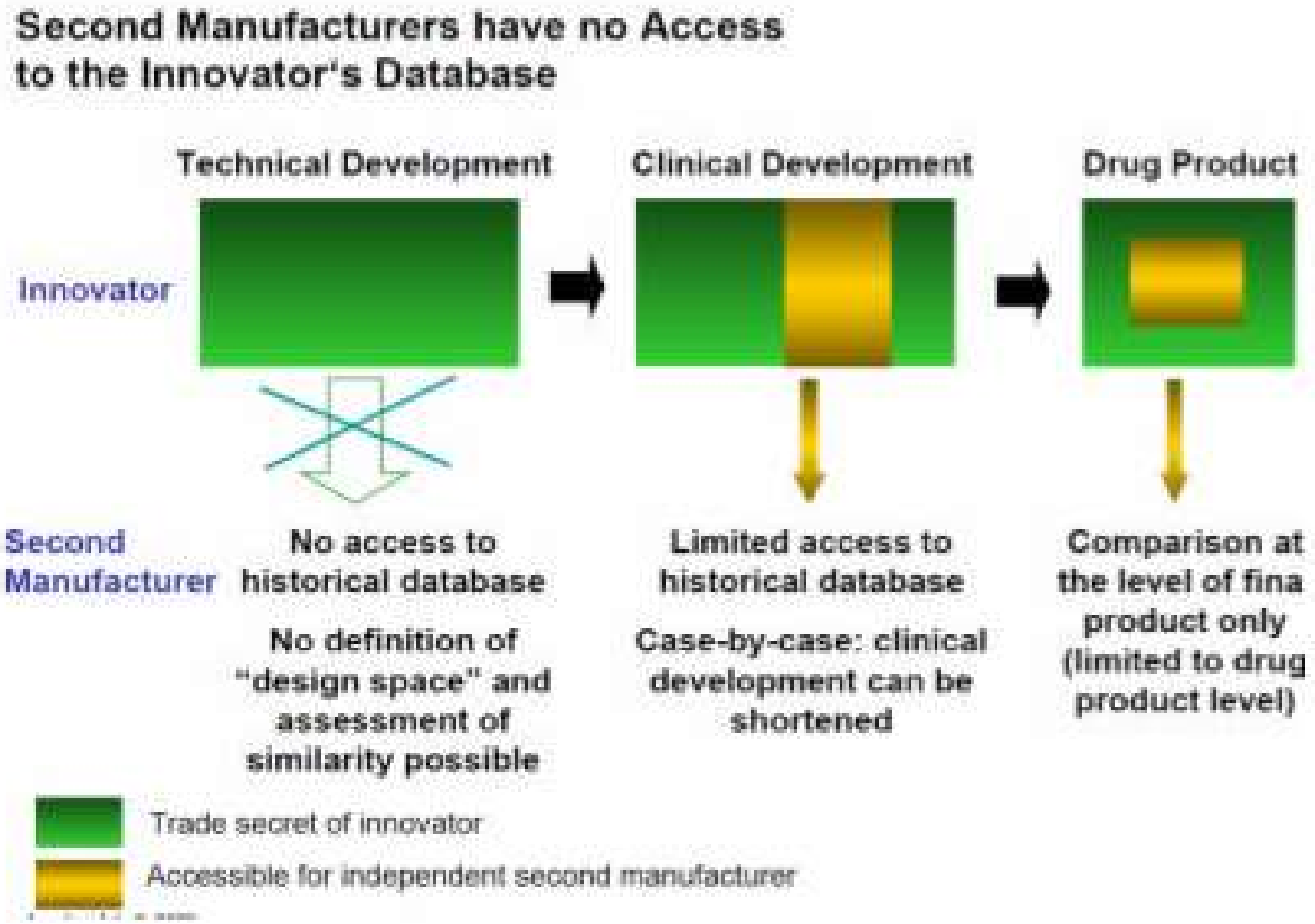
La disponibilità dei prodotti biosimilari genera una concorrenza rispetto ai prodotti originatori e rappresenta perciò un fattore importante per il **mantenimento** della **sostenibilità economica** dei **servizi sanitari** nel prossimo futuro.



Scadenza copertura brevettuale

* EU provides 10 years of data exclusivity, US BPCI Act provides 12 years exclusivity, ** In the UK. Other major EU markets follow on 28 August 2015.
Source: GaBI Online (www.gabionline.net), Sheppard et al. [1], Bernstein Research [2]
Notes: 1. Data updated on 17 January 2014, 2. Patent expiry dates are subject to change

...ma non scade il brevetto del processo produttivo.



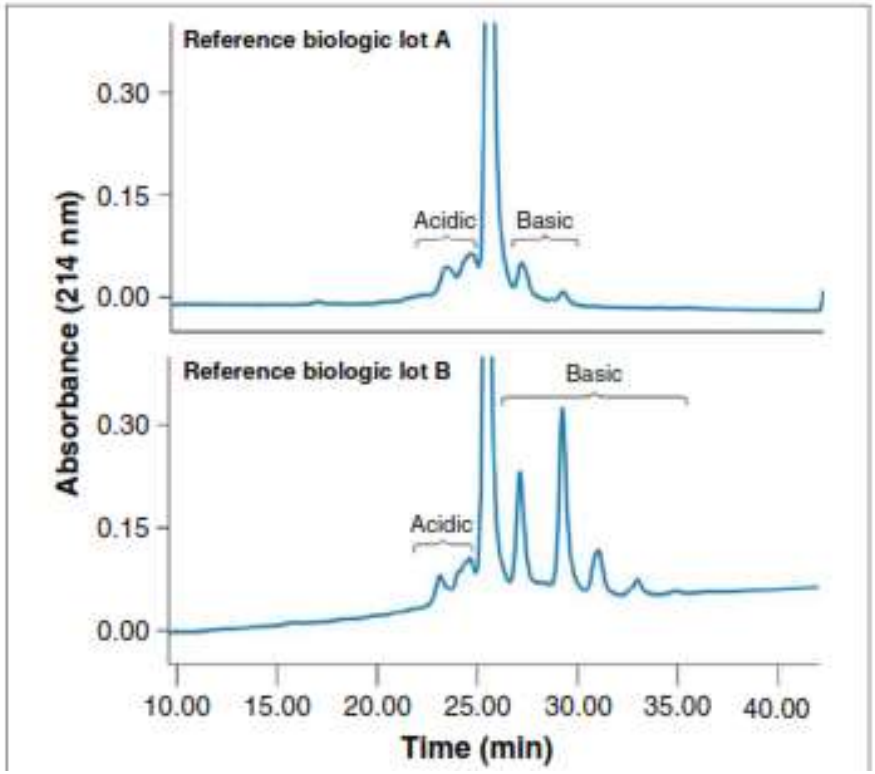
Definizione Biosimilare

Medicinale, autorizzato dopo procedura registrativa in Europa, simile a un prodotto biologico di riferimento per il quale sia scaduta la copertura brevettuale.

Problematiche nella **realizzazione** (pre-clinica):

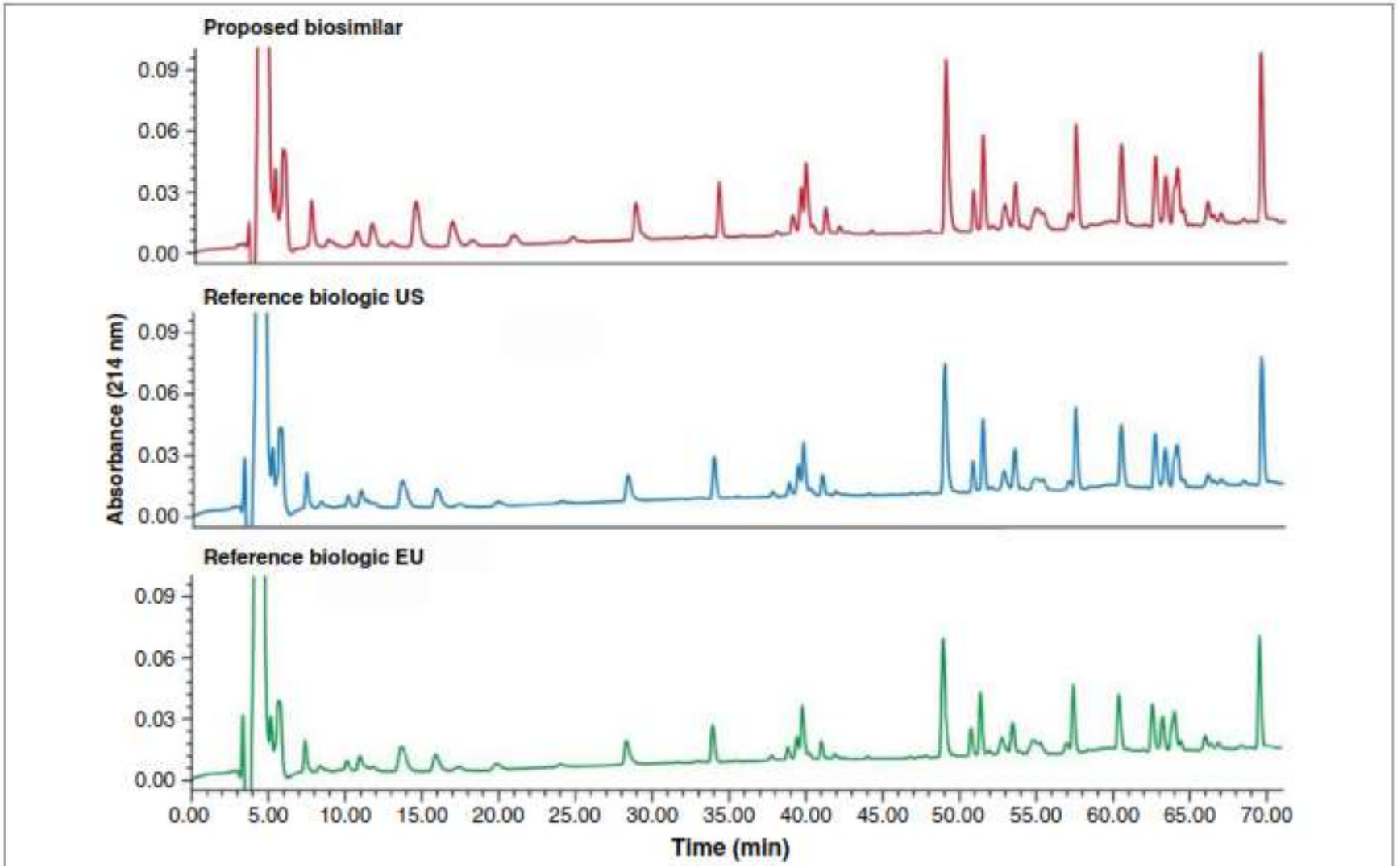
1) **Identificazione** dei **bersagli qualitativi caratterizzanti** del prodotto biologico di riferimento;

1.1) Problema: devo usare diversi lotti del riferimento…



Problematiche nella realizzazione (pre-clinica):

2) Composizione **sequenza aminoacidica**:



Problematiche nella realizzazione (pre-clinica):

3) **Saggi funzionali** (esempio, inibizione crescita cellulare):

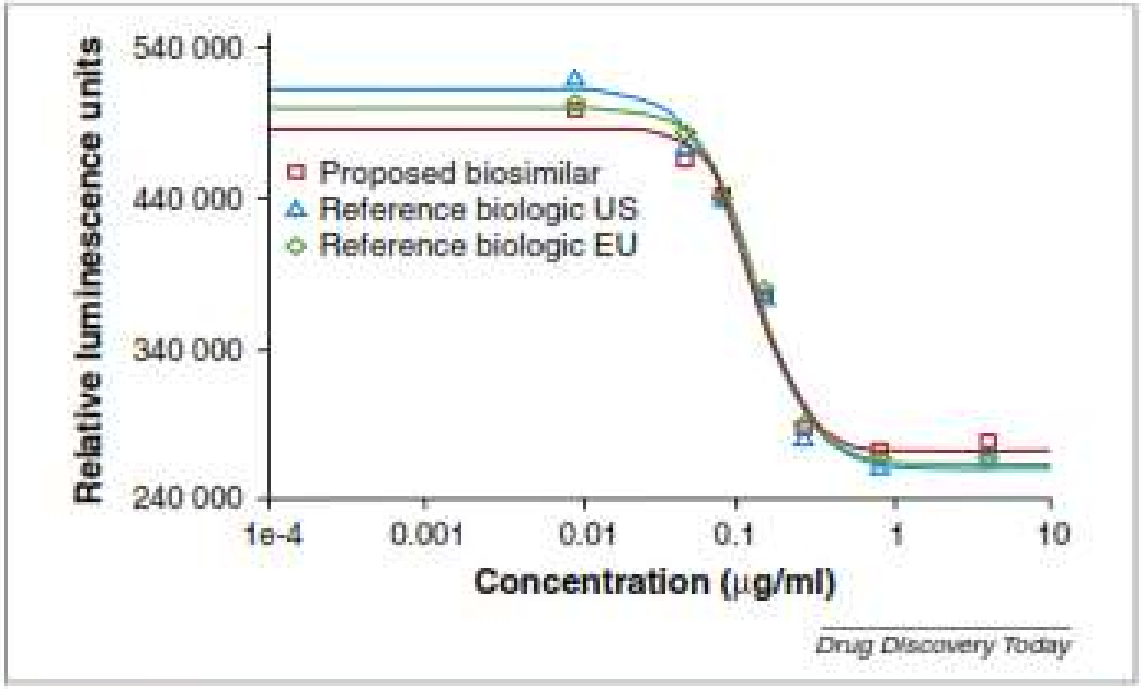


FIGURE 7

Example of a functional assay: inhibition of cell growth with a proposed biosimilar and its reference biologic products. A proposed biosimilar and its reference biologic products from the EU and the USA were evaluated for activity in a cell growth inhibition assay. As can be interpreted from the curves, the effective concentration (EC) required to inhibit growth by 50% (EC_{50}) of the cell population is similar between the proposed biosimilar and the EU and US reference biologic products [30].

Problematiche nella realizzazione (pre-clinica):

4) **farmacocinetica**:

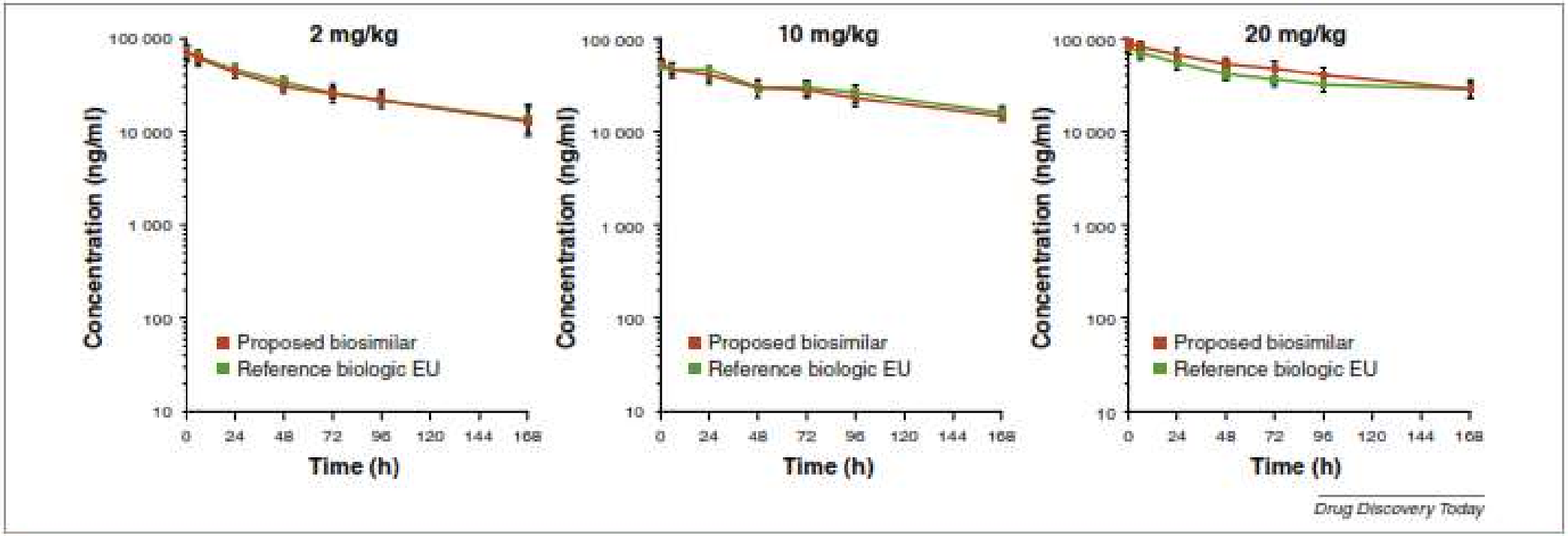


FIGURE 8

Preclinical pharmacokinetic (PK) comparison: serum concentration–time profile for a biosimilar mAb and its reference biologic product (AUC curves). The serum concentration–time profiles for a proposed biosimilar mAb and a reference biologic mAb are shown at three different doses (2 mg/kg, 10 mg/kg, 20 mg/kg) 168 h post-dose. As can be seen from the curves, the PK profiles are comparable between the proposed biosimilar and the reference biologic at all doses tested [34].

Problematiche nella realizzazione (pre-clinica):

5) **Immunogenocità** *in vivo*:

The preclinical in vivo *program: immunogenicity assessments*

Unlike small-molecule drugs, biologics (including biosimilars) are large protein molecules that can be capable of evoking an immune response. Several factors can influence immunogenicity of biologics (including biosimilars) including [33]:

- nature of the biosimilar (e.g. B cell depletion can decrease ADA production);
- presence of process-related impurities;
- route of administration (subcutaneous *versus* intravenous);
- patient population in question, patient-specific factors include:
  - disease-related immunosuppression;
  - concomitantly administered immunosuppressive drugs.

ADA: antidrug antiboby

Sviluppo clinico (esempio: Ab monoclonali)

Aspetti regolatori per i MAb biosimilari

18 November 2010
EMA/CHMP/BMWP/403543/2010
Committee for Medicinal Products for Human Use (CHMP)

Guideline on similar biological medicinal products containing monoclonal antibodies

Draft

- **Sviluppo clinico:** dimostrazione che **efficacia e sicurezza** del farmaco sono **simili** all'*originator* in popolazioni omogenee di pazienti
- **Processo di sviluppo e registrazione**
- **Tipologia dei trials clinici** necessari e **quali patologie** potranno essere trattate con lo stesso MAb
- L'**estrapolazione** dell'efficacia clinica e dei dati di sicurezza **ad altre indicazioni approvate per il MAb *originator*** non specificamente studiate per il MAb biosimilare è possibile sulla base dell'**evidenza clinica globale** fornita dal biosimilare e dopo **adeguata giustificazione tecnica**
- **Quando il MAb *originator* è approvato in due indicazioni**, ampiamente **differenti** tra loro, l'estrapolazione dei dati al biosimilare costituisca una sfida maggiore (i.e. **in questi casi potrebbero essere necessari nuovi studi**)

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/11/WC500099361.pdf

Secondo Position Paper AIFA sui Farmaci Biosimilari

Come dimostrato dal processo regolatorio di autorizzazione, il rapporto rischio-beneficio dei biosimilari è il medesimo di quello degli originatori di riferimento. Per tale motivo, l'AIFA considera i biosimilari come prodotti intercambiabili con i corrispondenti originatori di riferimento. Tale considerazione vale tanto per i pazienti *naïve* quanto per i pazienti già in cura.

Marzo 2018

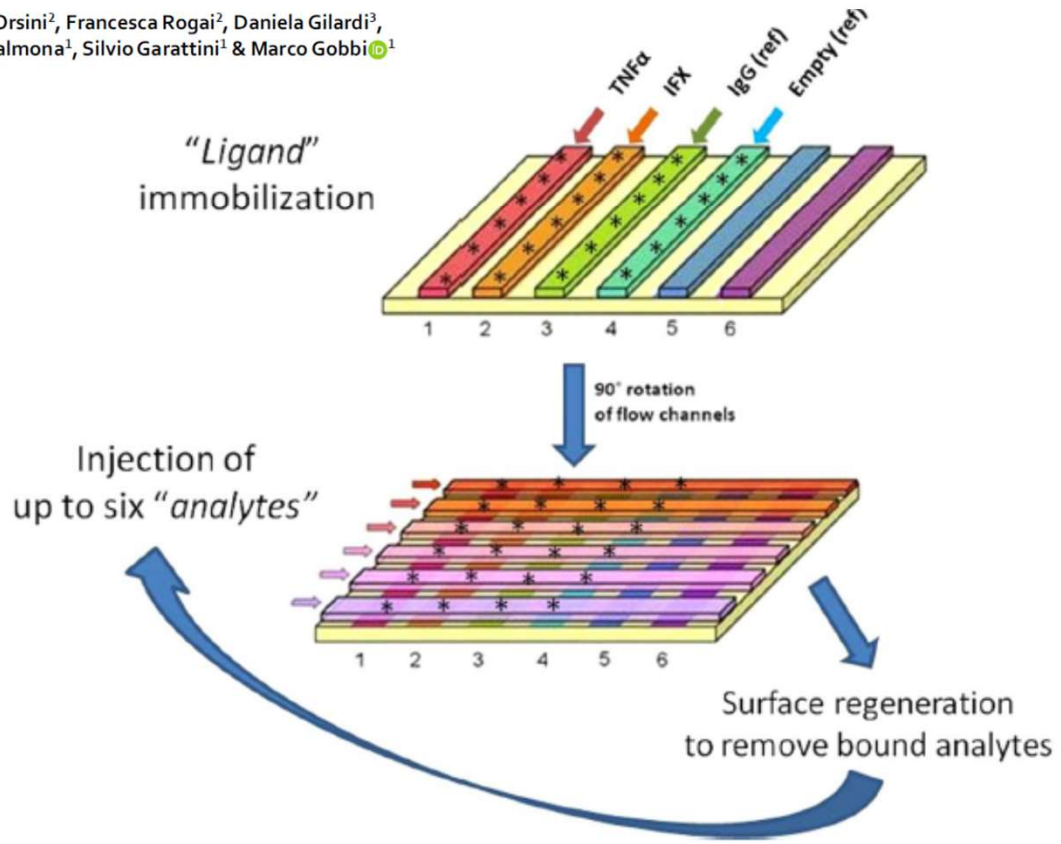
SCIENTIFIC REPORTS

OPEN

3 September 2018
17 December 2018
online: 14 February 2019

A Surface Plasmon Resonance-based assay to measure serum concentrations of therapeutic antibodies and anti-drug antibodies

Marten Beeg[1], Alessandro Nobili[1], Barbara Orsini[2], Francesca Rogai[2], Daniela Gilardi[3], Gionata Fiorino[3,4], Silvio Danese[3,4], Mario Salmona[1], Silvio Garattini[1] & Marco Gobbi[1]



Permette la misurazione delle concentrazioni sieriche di infliximab e degli anticorpi anti-infliximab in pochi minuti

Target: VEGF

"In assenza di vascolarizzazione,i tumori solidi rimangono dormienti e hanno una dimensione di 2-3 mm^3, con dimensioni limitate dalla capacità dell'ossigeno e dei nutrienti di diffondersi nel tumore"

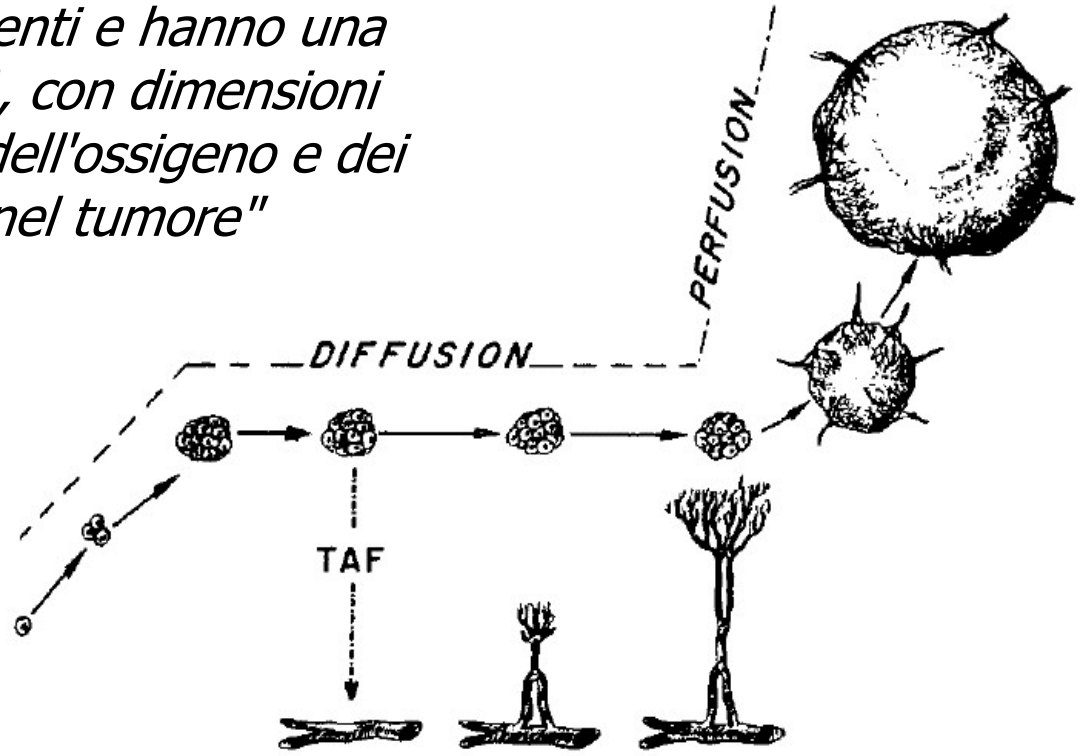


Figure 2. Illustration of the Concept That Most Solid Tumors May Exist Early as Tiny Cell Populations Living by Simple Diffusion in the Extracellular Space (Further Growth Requires Vascularization, and the Tumor Then Maintains Itself by Perfusion).

Tumor-angiogenesis factor (TAF) may be the mediator of neovascularization.

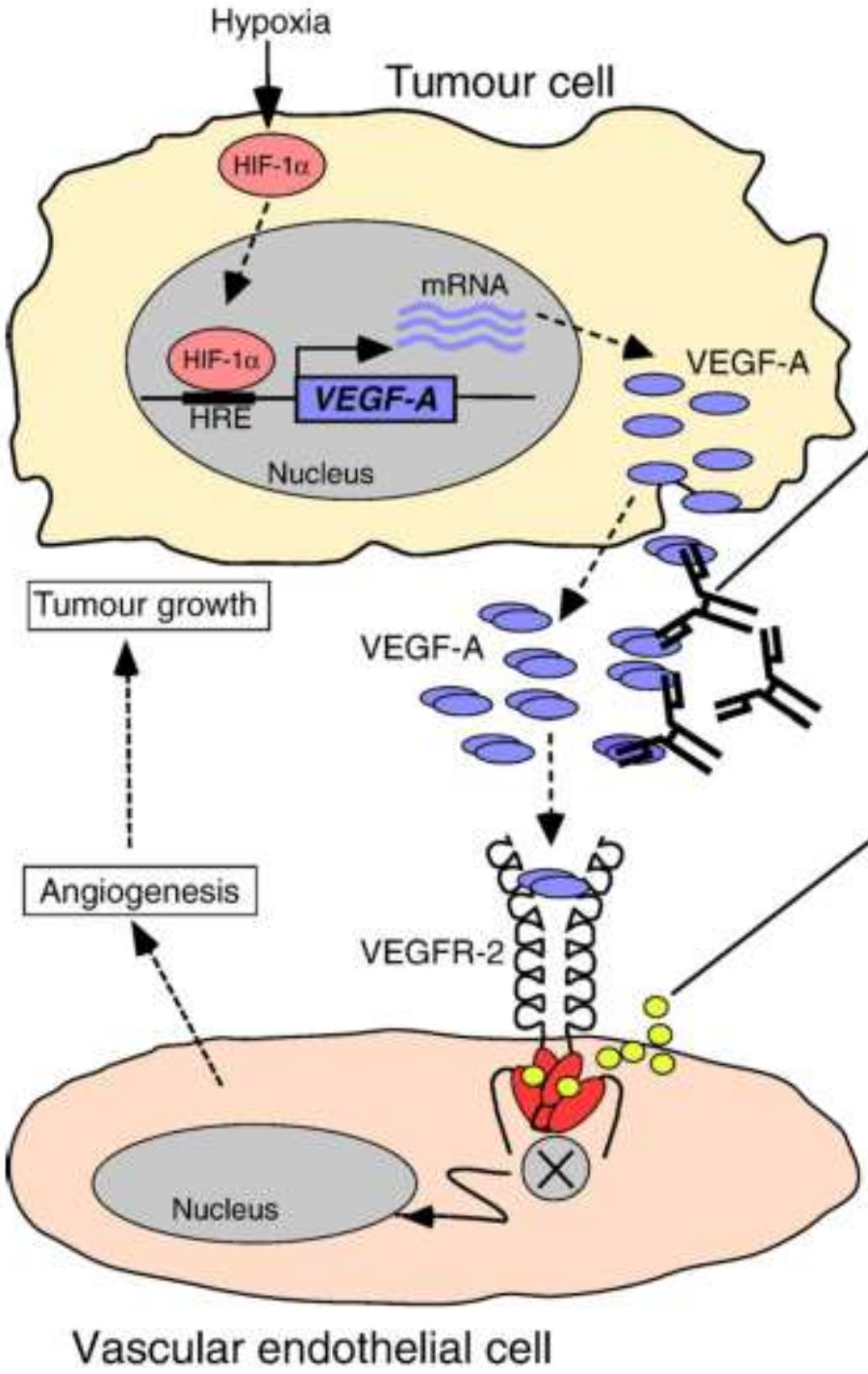
Folkman J. N Engl J Med 1971

Available online at www.sciencedirect.com
ScienceDirect
Cellular Signalling 19 (2007) 2003–2012
CELLULAR SIGNALLING
www.elsevier.com/locate/cellsig

Review

Vascular endothelial growth factor receptor-2: Structure, function, intracellular signalling and therapeutic inhibition

Katherine Holmes, Owain Ll Roberts, Angharad M. Thomas, Michael J. Cross *



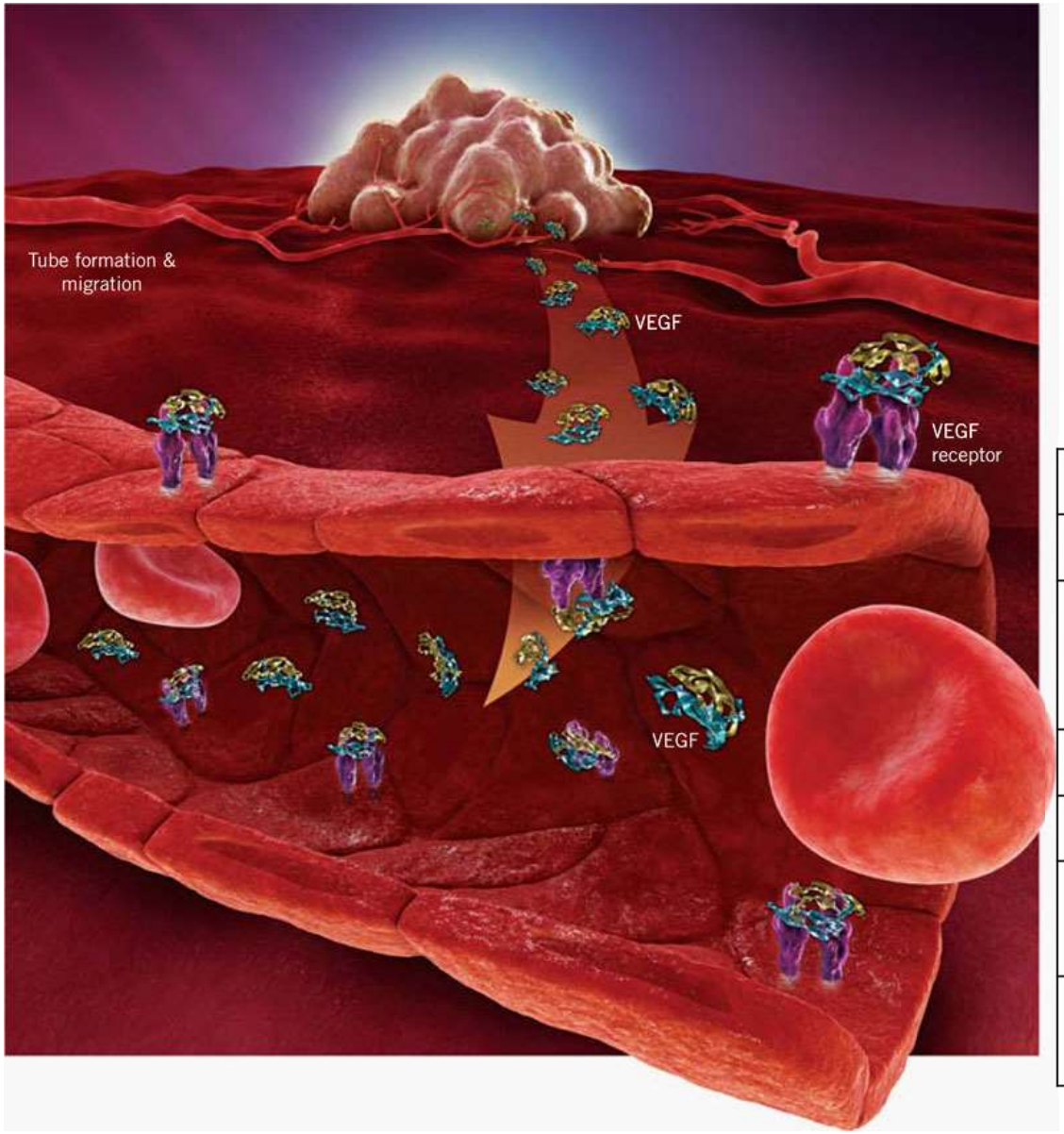
Agent	Mechanism of action	Phase
Bevacizumab (Avastin®)	Humanised monoclonal anti-VEGF-A antibody	FDA approved for advanced colorectal cancer in combination with chemotherapy

Tyrosine Kinase Inhibitors

Agent	Target	IC_{50} (μM)	Phase
SU11248 (Sunitinib/ Sutent®)	**VEGFR-2**	**0.01**	FDA approved for renal cell carcinoma and gastrointestinal stromal tumour
	PDGFR-β	0.01	
BAY 43-9006 (Sorafenib/ Nexavar®)	Raf-1	0.006	FDA approved for renal cell carcinoma
	VEGFR-3	0.020	
	PDGFR-β	0.057	
	c-Kit	0.068	
	VEGFR-2	**0.090**	
PTK787/ZK222584 (Vatalanib)	**VEGFR-2**	**0.039**	III
	VEGFR-1	0.054	
	c-Kit	0.364	
	PDGFR-β	0.567	
	c-fms	0.600	
ZD 6474 (Vandetanib/ Zactima®)	**VEGFR-2**	**0.04**	III
	VEGFR-3	0.11	
	EGFR	0.50	
AZD2171 (Recentin®)	**VEGFR-2**	**<0.001**	III
	c-Kit	0.002	
	VEGFR-3	0.003	
	VEGFR-1	0.005	
	PDGFR-β	0.05	

…al 2007.

Target: VEGF

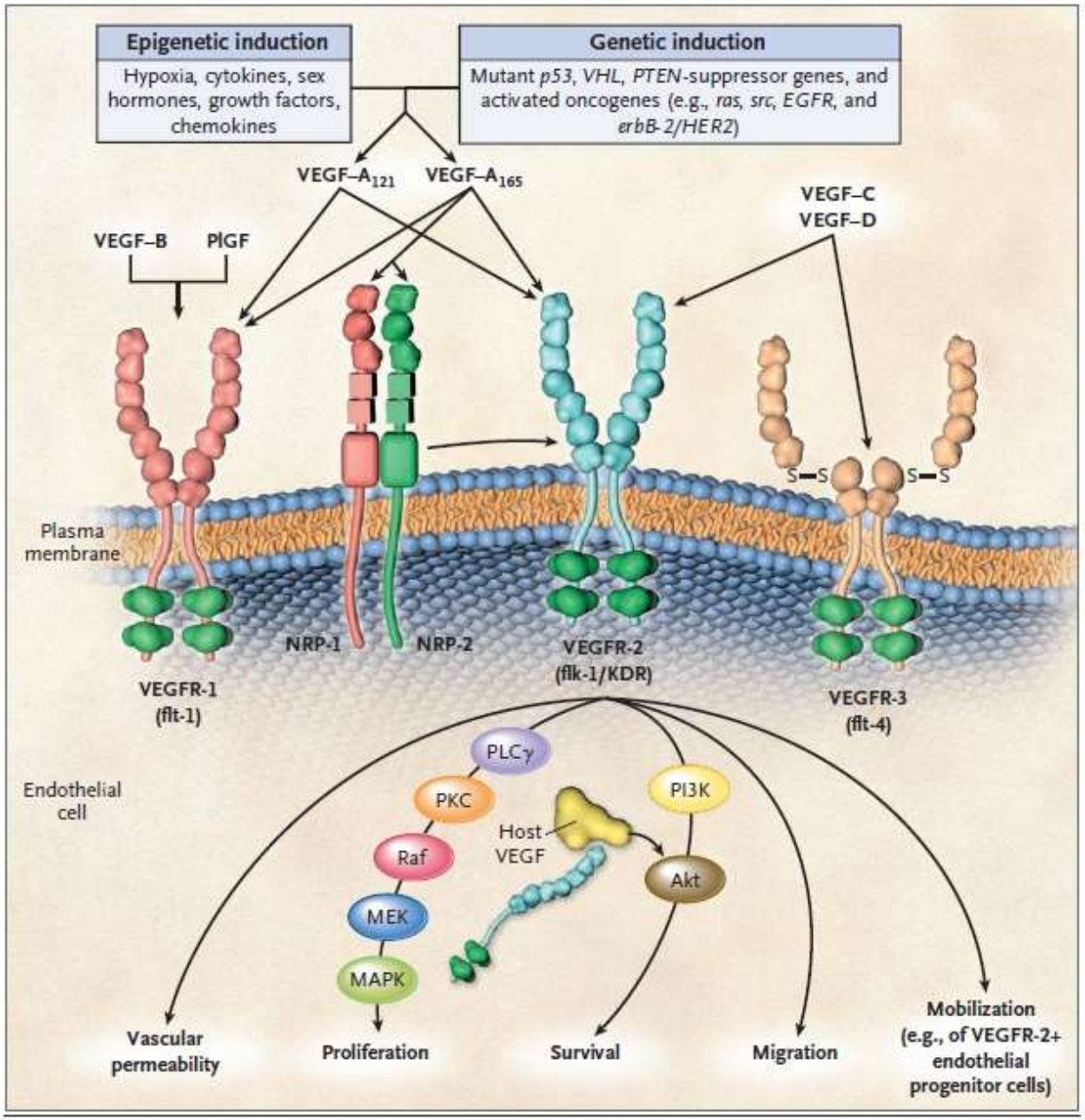


Il *Vascular Endothelial Growth Factor* (VEGF) è il principale fattore coinvolto nell'angiogenesi. La tabella indica i principali effetti esercitati dal VEGF.

Function[1,2]	**Mechanism**
Proliferation	Activation of mitogen-activated protein kinases
Permeability	Vesicovascular organelles Endothelial fenestrations Opening of junctions between adjacent endothelial cells
Invasion	Induction of metalloproteinases uPA, uPAR, TTPA
Migration	Activation of FAK, p38, nitric oxide
Survival	Induction of PI3K/Akt, Bcl2, A1, survivin, XIAP, or FAK Inhibition of caspases
Activation	Upregulation of integrin expression Alteration of cell cytoskeleton

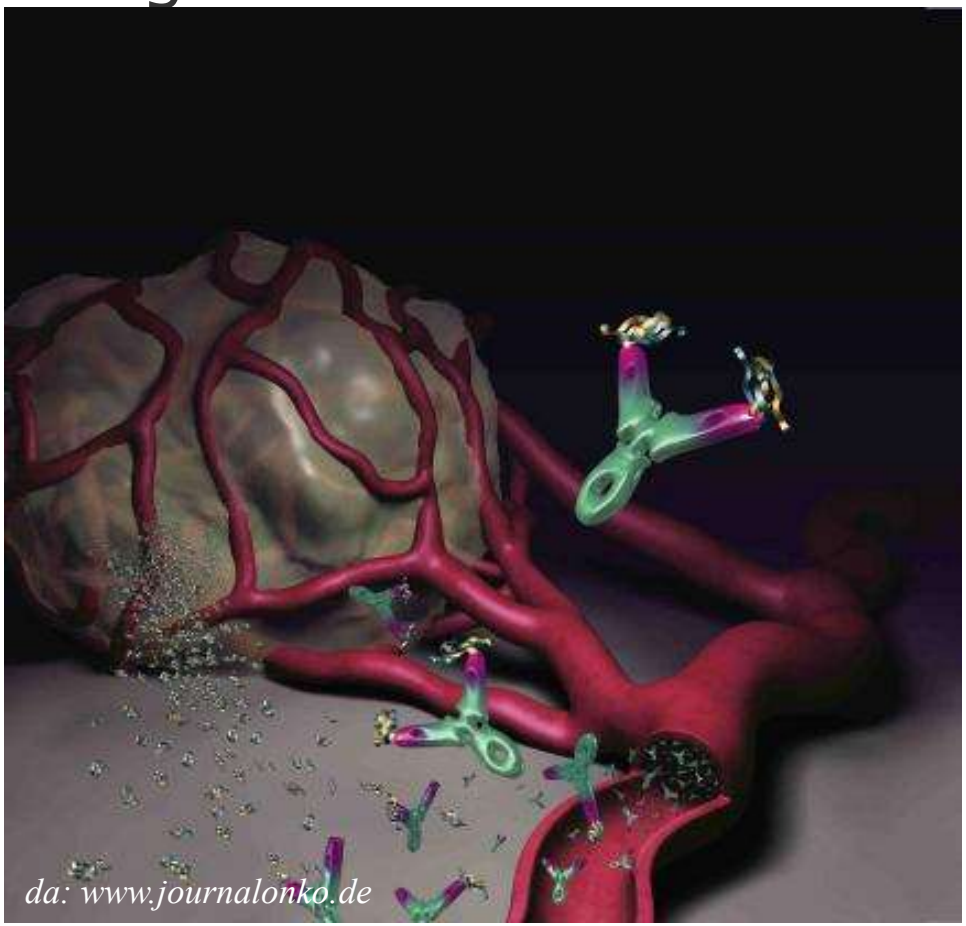
1. Ferrara N. et al. *Nature*. 1996 **2.** Carmeliet P. et al. *Nature.*1996

Target: VEGF

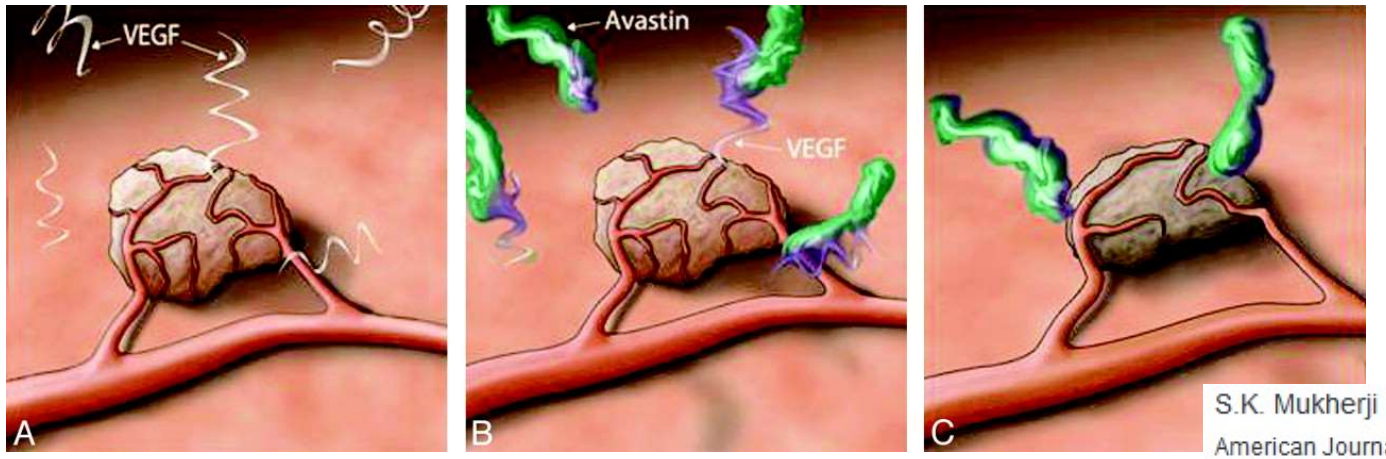


I VEGF esiste in 4 forme distinte (A,B, C e D). Il mediatore basilare dell'angiogenesi è il VEGF-A (isoforme 121 e 165) che interagisce principalmente con il recettore 2 (VEGFR-2). Benché il VEGF leghi il VEGFR-1 con un'affinità superiore (10x) al VEGFR-2, il suo ruolo nell'angiogenesi non è chiaro.

Target: VEGF



Bevacizumab è un anticorpo monoclonale umanizzato prodotto mediante la tecnica del DNA ricombinante in cellule ovariche murine. Utilizzato (in associazione) nel carcinoma del colon/retto, mammario, polmonare e renale. E' impiegato (somm. intravitreo) anche nella degenerazione maculare senile.



S.K. Mukherji
American Journal of Neuroradiology February 2010,

Target: VEGF

CLINICAL AND EXPERIMENTAL
OPTOMETRY

REVIEW

Inhibitors of vascular endothelial growth factor (VEGF) in the management of neovascular age-related macular degeneration: a review of current practice

Clin Exp Optom 2008; 91: 5: 427–437

van Wijngaarden P. and Qureshi SH.

"It remains to be seen whether this therapy will have long-term adverse effects on retinal function. Further research is required to clarify the comparative efficacy and safety of the commonly used anti-VEGF agents."

Anti-VEGF in oftalmologia

Indicazioni terapeutiche

Lucentis® (ranibizumab)

registrato e indicato nelle seguenti patologie maculari:

- degenerazione maculare legata all'età essudativa (rimborsato SSN)
- edema maculare secondario a retinopatia diabetica (rimborsato SSN)
- edema maculare secondario occlusione venosa retinica (rimborsato SSN)
- miopia patologica (maculopatia miopica con neovascolarizzazione coroideale) (rimborsato SSN)

Avastin nella lista dei farmaci di uso consolidato per la degenerazione maculare senile

10/06/2014

La Commissione Tecnico Scientifica (CTS) dell'AIFA, nel corso nella seduta del 9 e 10 giugno, si è espressa a favore dell'inserimento di bevacizumab (Avastin) nell'elenco dei farmaci erogabili a totale carico del Servizio Sanitario Nazionale (SSN), ai sensi della legge 648/96, per il trattamento della degenerazione maculare legata all'età (AMD).

Il parere della CTS dell'AIFA è stato espresso alla luce delle richieste avanzate dalle Regioni Veneto ed Emilia Romagna per l'inserimento di bevacizumab nella lista della legge 648/96 (lista classica) per la degenerazione maculare legata all'età, visto il parere del Consiglio Superiore di Sanità (CSS) in merito al profilo di sicurezza e di efficacia dei farmaci Avastin e Lucentis (sezione V seduta del 15 aprile 2014) e la nuova regolamentazione sull'uso off-label dei farmaci (DL 20 marzo 2014 convertito in Legge n. 79 del 16 maggio 2014).

La CTS ha accolto la richiesta per l'utilizzo del farmaco nell'indicazione non registrata, individuando all'unanimità una serie di condizioni indispensabili a tutela della salute dei pazienti:

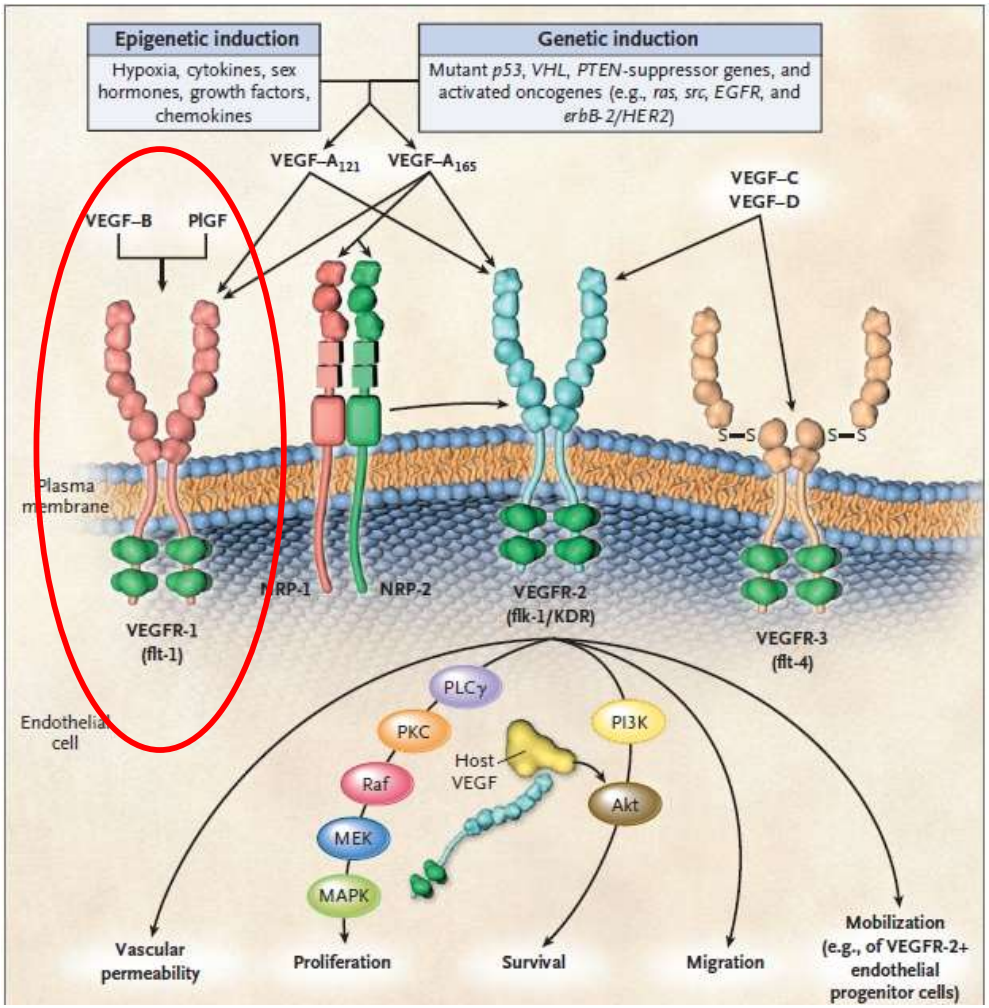
- il confezionamento in monodose del farmaco bevacizumab per l'uso intravitreale dovrà essere effettuato, per garantirne la sterilità, esclusivamente dalle farmacie ospedaliere in possesso dei requisiti necessari, nel rispetto delle Norme di Buona Preparazione;
- la somministrazione di bevacizumab per uso intravitreale dovrà essere riservata a centri oculistici ad alta specializzazione presso ospedali pubblici individuati dalle Regioni;
- la somministrazione del farmaco potrà avvenire solo previa sottoscrizione da parte del paziente del consenso informato, che contenga le motivazioni scientifiche accompagnate da adeguate informazioni sull'esistenza di alternative terapeutiche approvate, seppure ad un costo più elevato a carico del SSN;
- l'attivazione di un registro di monitoraggio a cui sia allegata la scheda di segnalazione delle reazioni avverse.

La CTS si riserva di assumere ogni diversa valutazione a seguito dell'analisi dei dati raccolti attraverso gli strumenti di monitoraggio attivati o di ogni ulteriore evidenza scientifica che dovesse rendersi disponibile.

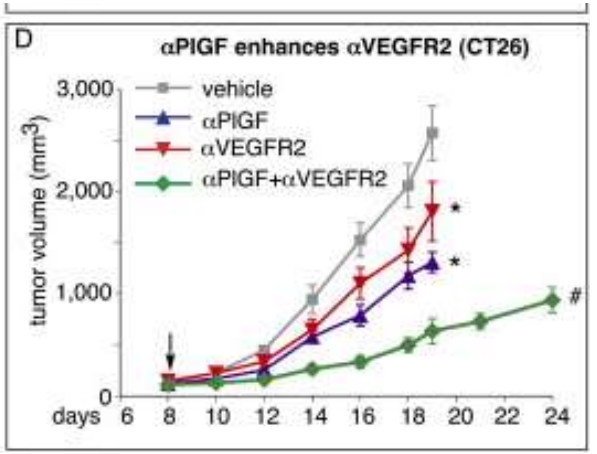
Target: PlGF

Anti-PlGF Inhibits Growth of VEGF(R)-Inhibitor-Resistant Tumors without Affecting Healthy Vessels

Fischer et al. Cell, 2007



*"Placental growth factor (PlGF) levels in plasma and tumors correlate with tumor stage, vascularity, recurrence, metastasis, and survival...*and*...is upregulated in cancer patients treated with $VEGF^{R}I$ ... suggesting a key role of PlGF in the angiogenic rescue"*



Meccanismi molecolari del PlGF

Precisazioni sulla nomenclatura:

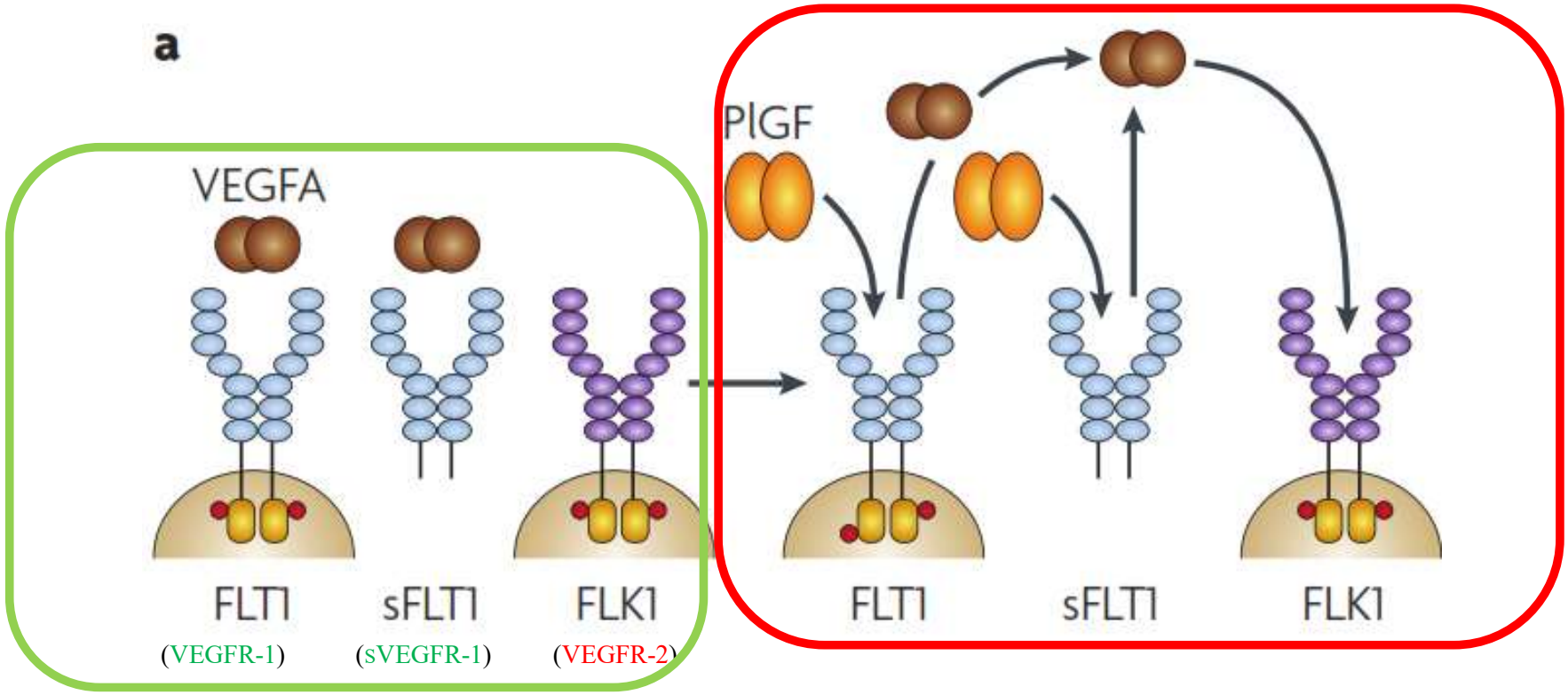
VEGFR-1 = FLT1

VEGFR-2 = FLK1.

Ruolo nell'angiogenesi:

VEGFR-2 (FLK1)>>VEGFR-1(FLT1)

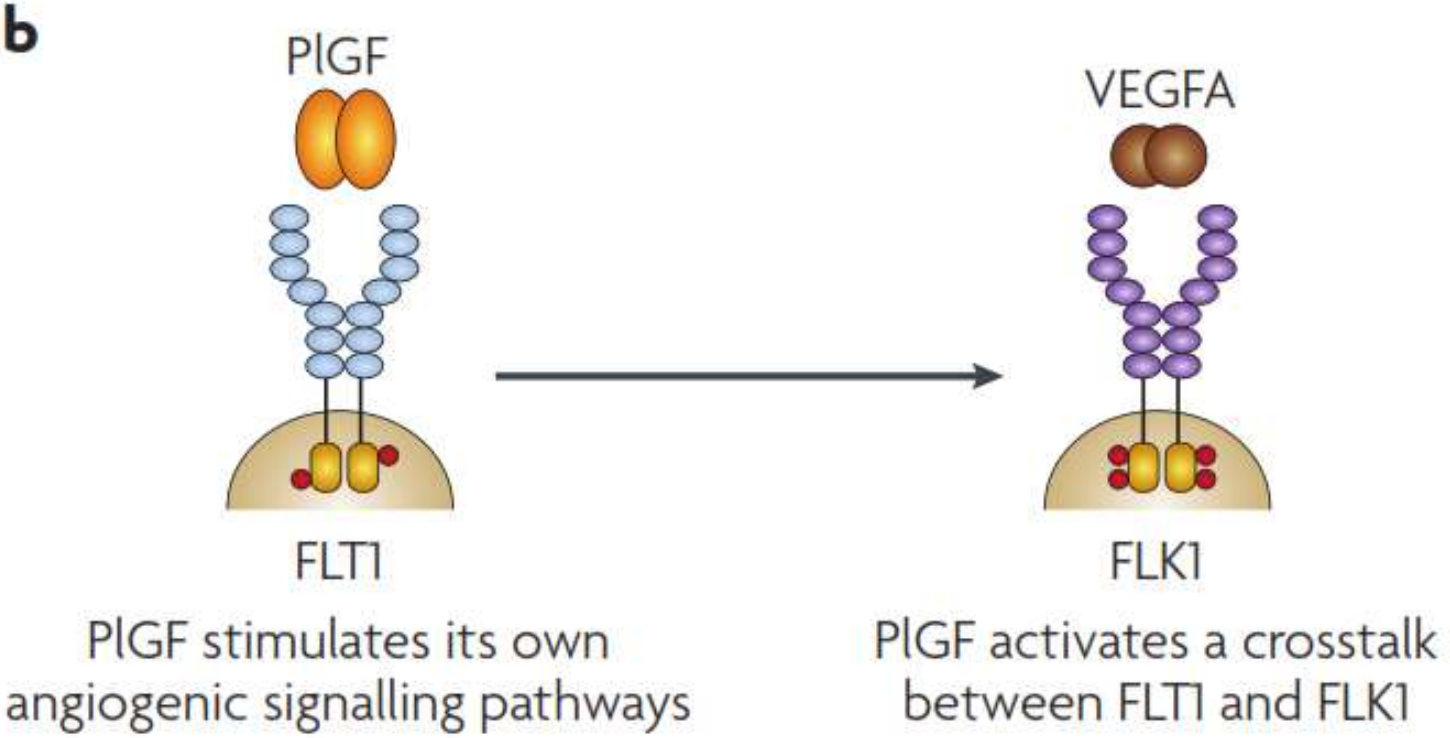
Meccanismi molecolari del PlGF



In condizioni fisiologiche PlGF è assente. VEGFA lega FLT1 e FLT1 solubile (sFLT1) con maggiore affinità rispetto a FLK1.

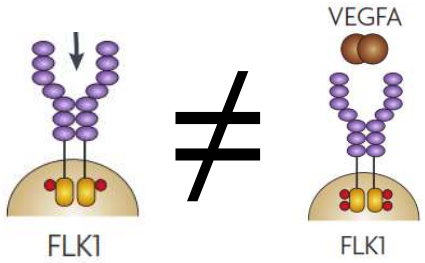
La condizione patologica up-regola PlGF; questo spiazza VEGFA da FLT1 e sFLT1 e lo ″indirizza″ verso FLK1 →Angiogenesi.

Meccanismi molecolari del PlGF



PlGF lega FLT1 attivando la propria risposta angiogenica.

L'attivazione di FLT1 indotta da PlGF induce un *crosstalk* tra FLT1 e FLK1 amplificando la risposta di VEGFA FLK1-mediata.



Neuro-Oncology

Neuro-Oncology 17(7), 1007–1015, 2015
doi:10.1093/neuonc/nov019
Advance Access date 9 February 2015

Phase 1 dose-escalation study of the antiplacental growth factor monoclonal antibody RO5323441 combined with bevacizumab in patients with recurrent glioblastoma

Ulrik Lassen, Olivier L. Chinot, Catherine McBain, Morten Mau-Sørensen, Vibeke Andrée Larsen, Maryline Barrie, Patrick Roth, Oliver Krieter, Ka Wang, Kai Habben, Jean Tessier, Angelika Lahr, and Michael Weller

British Journal of Cancer (2012), 1–7

www.bjcancer.com

Short Communication

A phase I, dose-escalation study of TB-403, a monoclonal antibody directed against PlGF, in patients with advanced solid tumours

U Lassen[*,1], DL Nielsen[2], M Sørensen[1], L Winstedt[3], T Niskanen[3], Y Stenberg[3], S Pakola[4], J-M Stassen[4] and S Glazer[3]

Anti PlGF nell'edema maculare diabetico

OXURION®

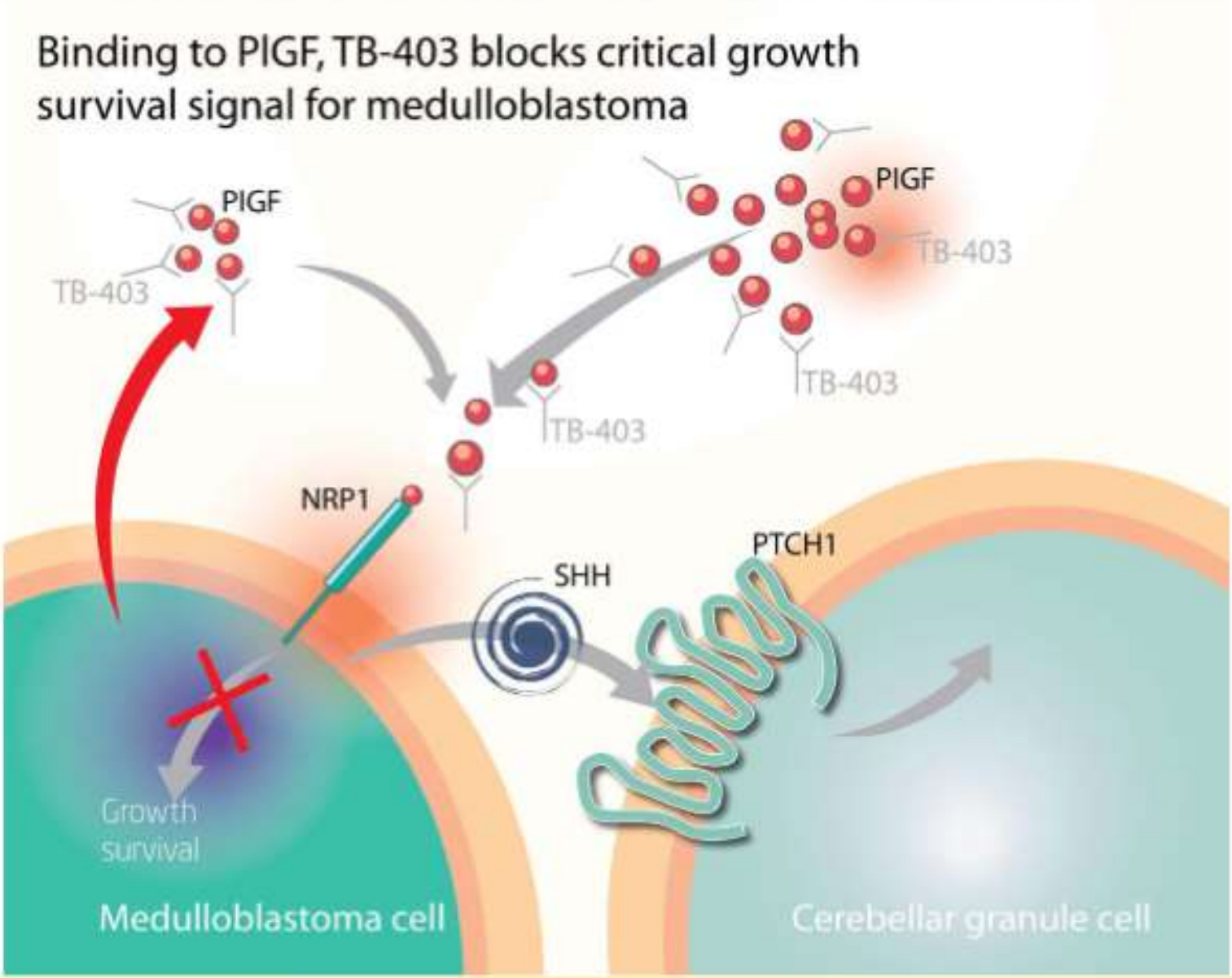
ADVANCING SCIENCE. ENHANCING VISION

PRESS RELEASE

Oxurion NV - Data from a Phase 1/2 Clinical Study evaluating THR-317 (anti-PlGF) for DME presented at 2019 FLORetina Meeting

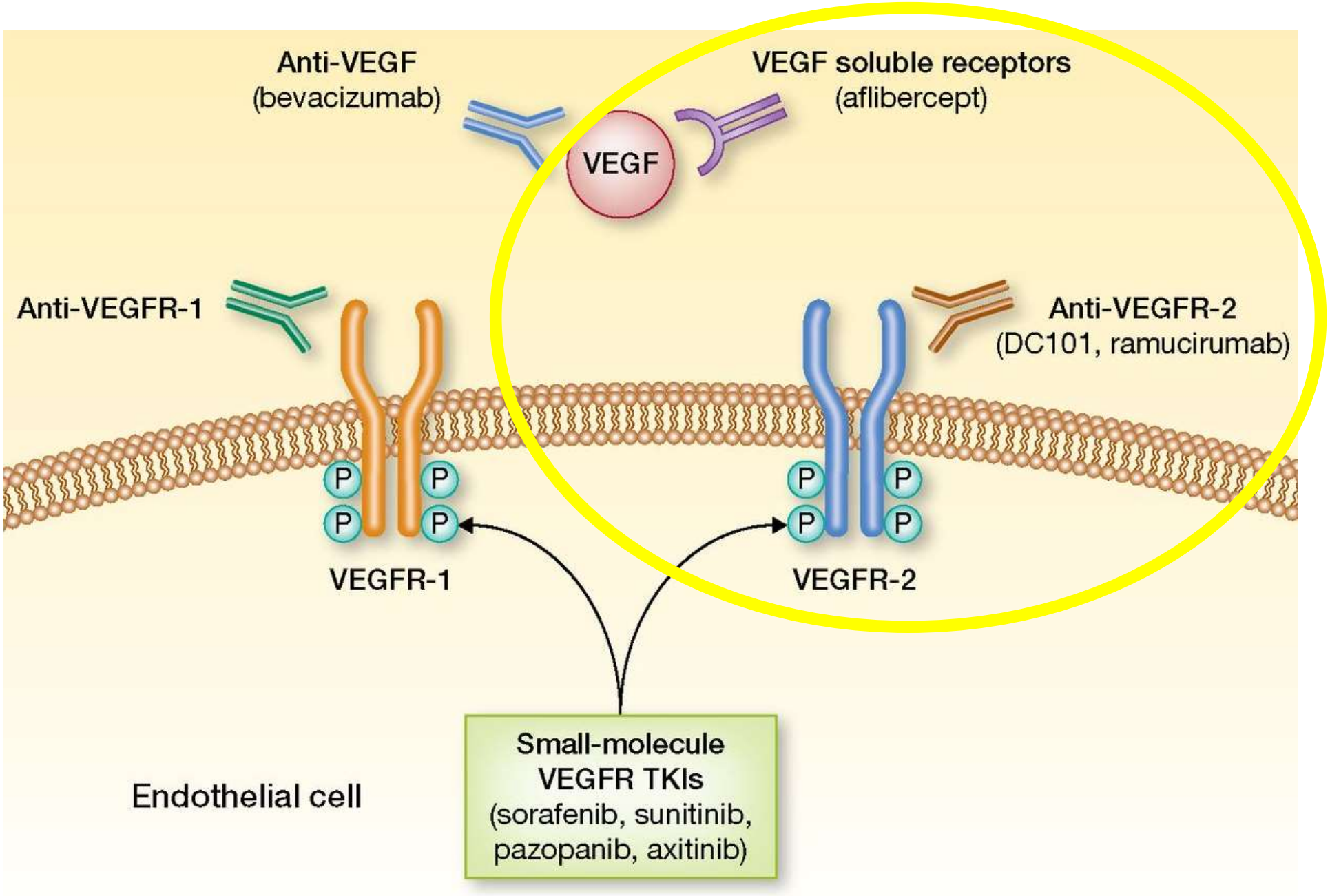
Leuven, Belgium, 6th June 2019 – *7 PM CET* – Oxurion NV (Euronext Brussels: OXUR), a biopharmaceutical company developing innovative treatments to preserve vision in patients with diabetic eye disease, announced that today clinical-stage data from a Phase 1/2 study evaluating its anti-placental growth factor candidate THR-317 for the treatment of diabetic macular edema (DME) were presented at the biannual Retina Meeting (FLORetina 2019) in Florence, Italy. THR-317 (anti-PlGF) is a recombinant humanized monoclonal antibody directed against the receptor-binding site of human placental growth factor (PlGF).

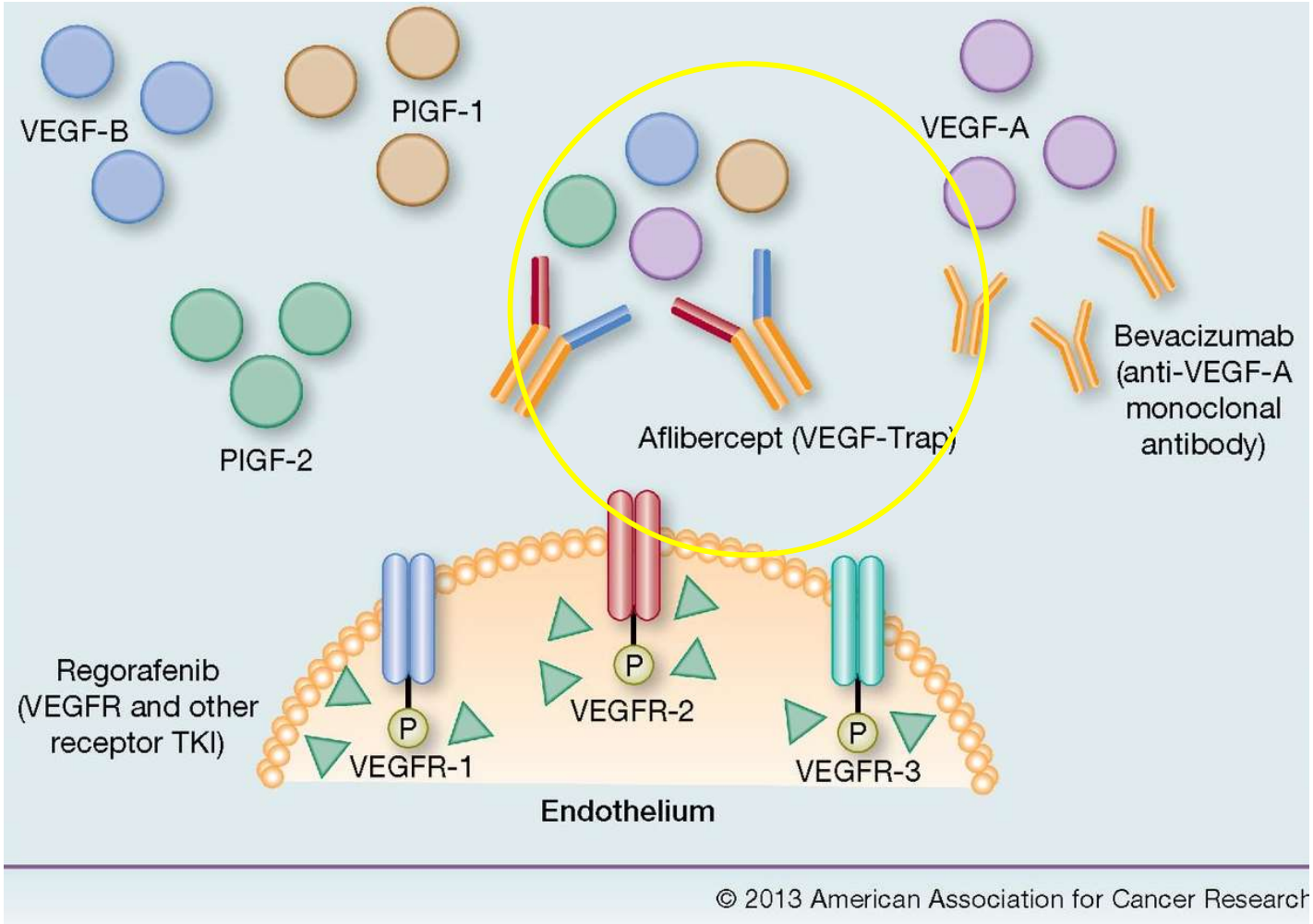
PlGF: an undesired overactive growthfactor



Oncurious

Ulteriori strategie dirette verso il VEGF





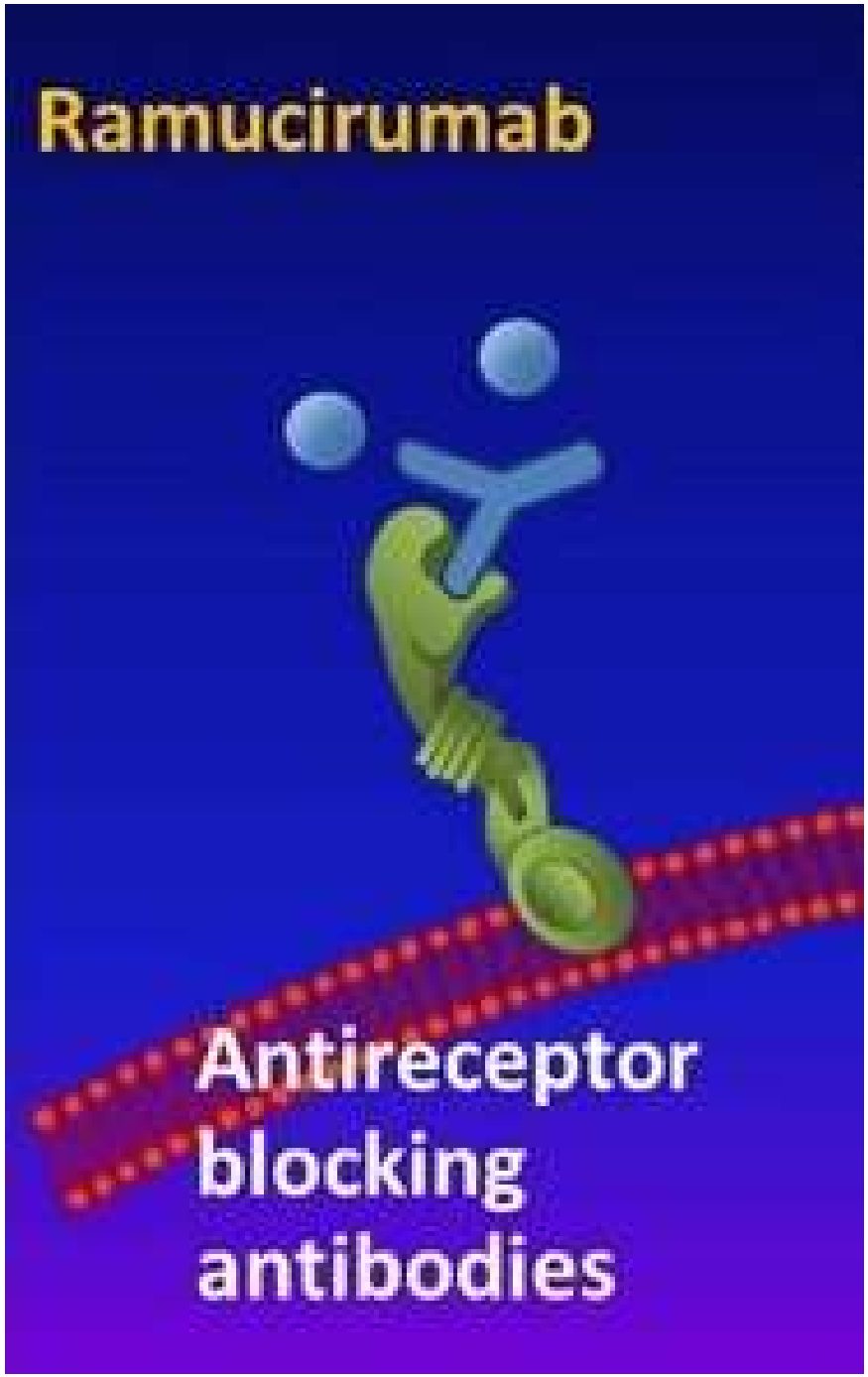
Aflibercept è un esempio di **VEGF-Trap.** Funge da recettore solubile di captazione che lega, **con un'affinità maggiore di quella dei recettori nativi**, il VEGF-A il PlGF e il VEGF-B. Approvato il combinazione con chemioterapia nel carcinoma colorettale metastatico

Aflibercept in oftalmologia

Eylea® (aflibercept)

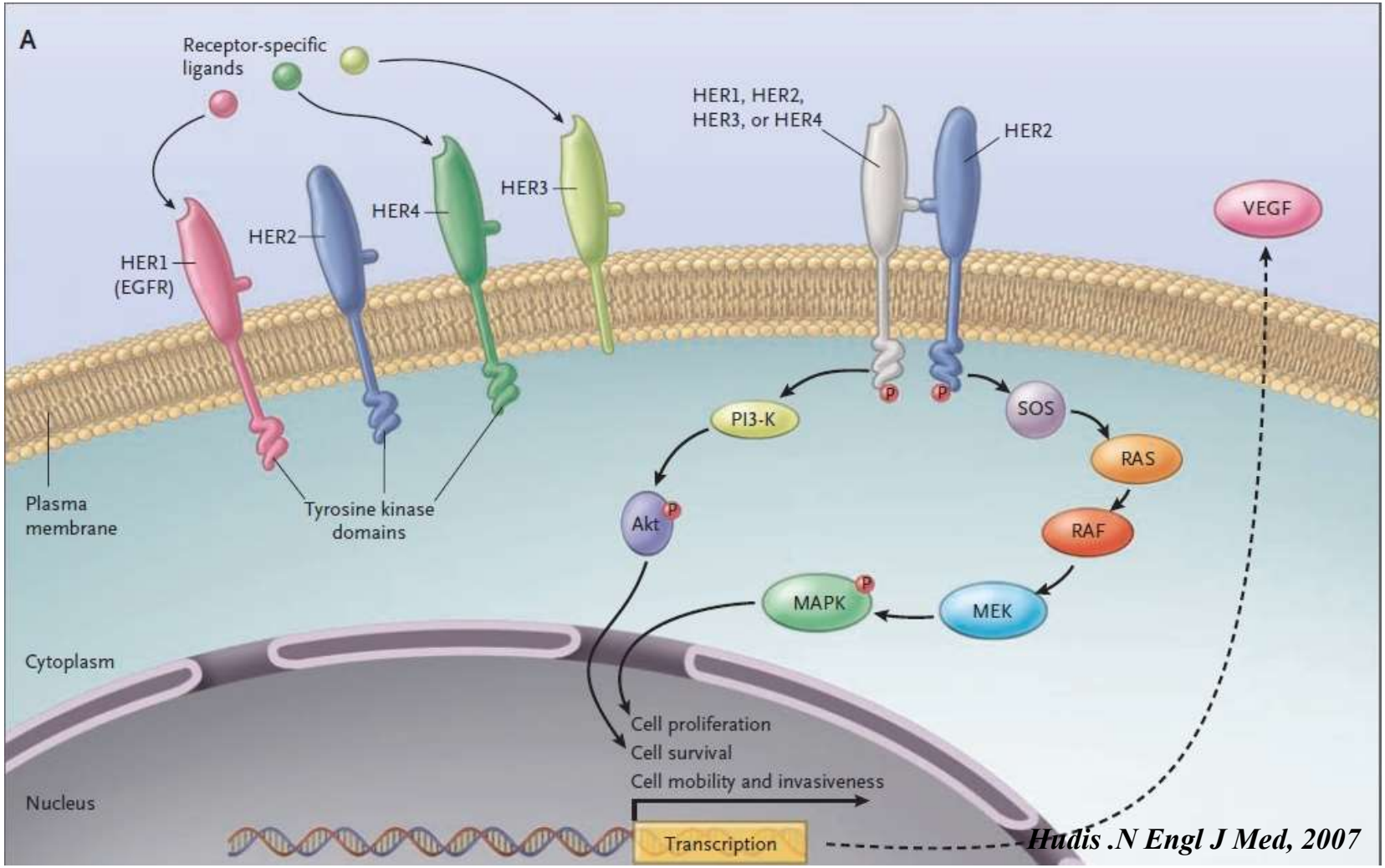
registrato e indicato nelle seguenti patologie maculari:

- degenerazione maculare legata all'età essudativa (rimborsato SSN)
- edema maculare secondario occlusione della vena centrale della retina (rimborsato SSN)
- edema maculare secondario a retinopatia diabetica (non rimborsato dal SSN)



Ramucirumab: anticorpo umano diretto contro
VEGFR-2 (FLK1).
Indicazioni: in associazione con chemioterapici nel trattamento del carcinoma gastrico o adenocarcinoma della giunzione gastro-esofagea.

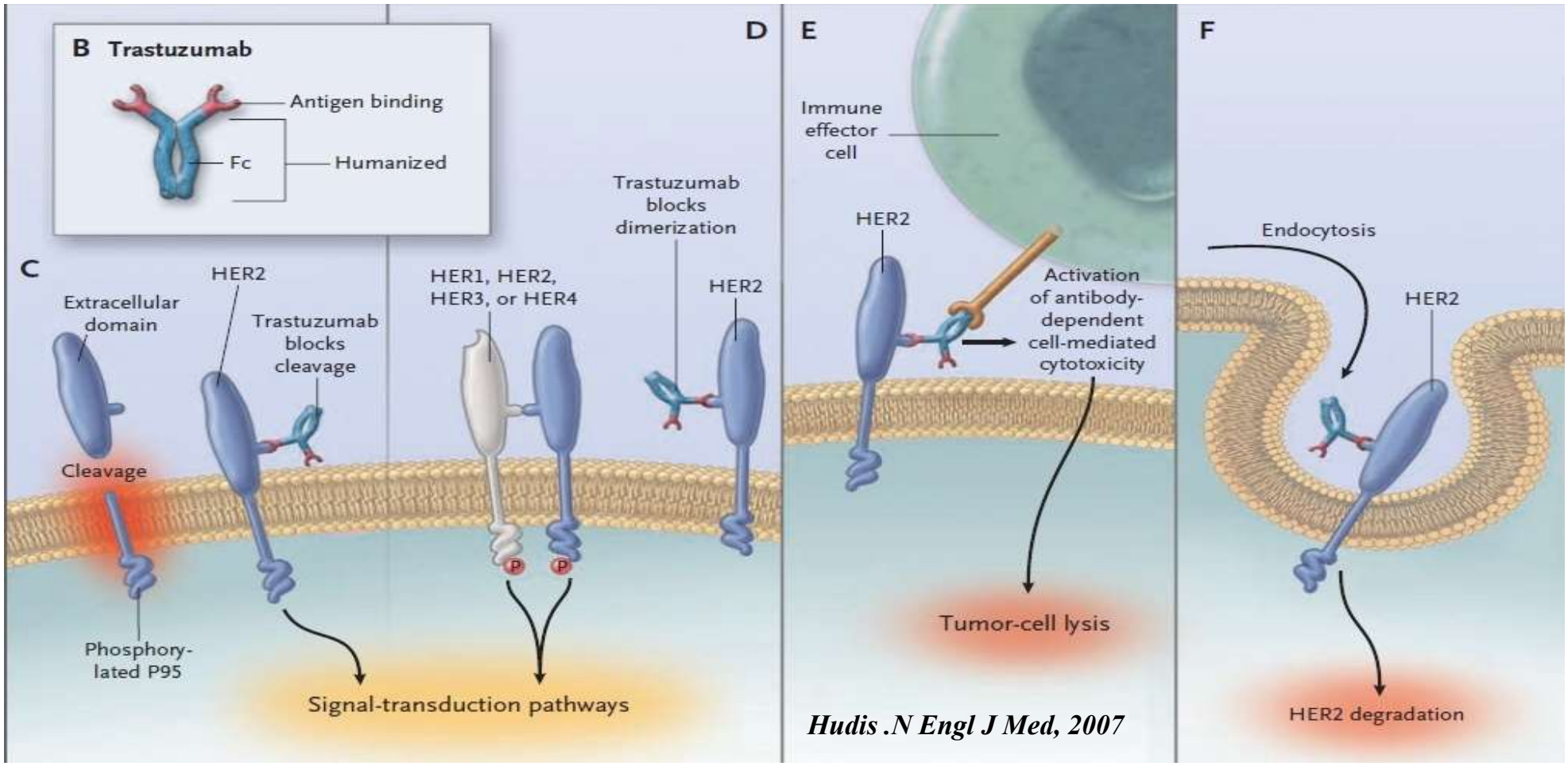
Target: HER2



Lo *human epidermal growth factor receptor type 2* (HER2), è sovraespresso nel 20-30% dei tumori mammari.

Dopo omo- o etero-dimerizzazione, si osserva la fosforilazione del dominio intracellulare tirosin-chinasico che provoca l'attivazione di un segnale di attivazione per diversi geni coinvolti nella proliferazione e crescita cellulare.

Target: HER2



Il **trastuzumab** è un anticorpo monoclonale ricombinante umanizzato, con elevata affinità di legame per la proteina HER2.

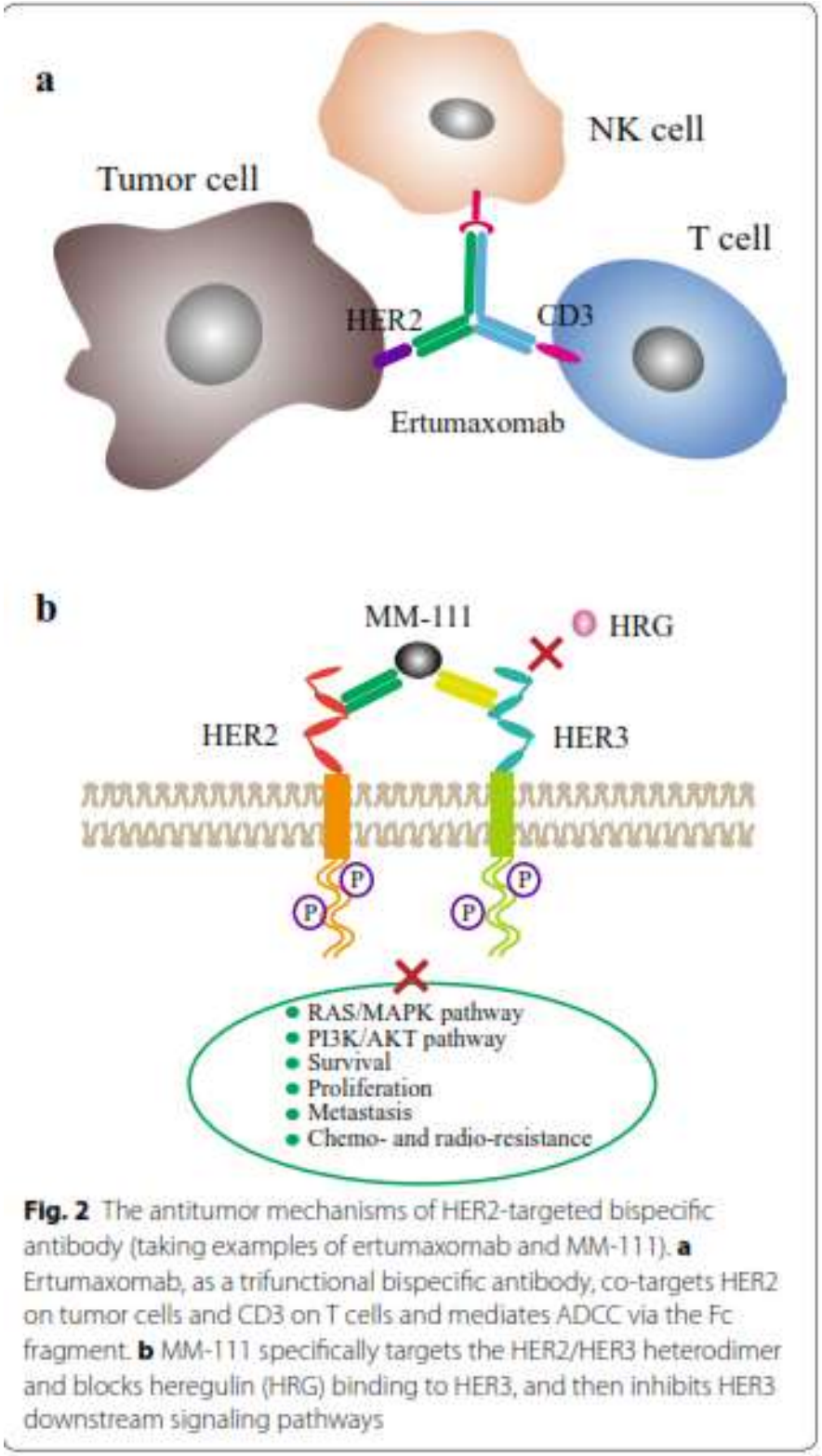


Fig. 2 The antitumor mechanisms of HER2-targeted bispecific antibody (taking examples of ertumaxomab and MM-111). **a** Ertumaxomab, as a trifunctional bispecific antibody, co-targets HER2 on tumor cells and CD3 on T cells and mediates ADCC via the Fc fragment. **b** MM-111 specifically targets the HER2/HER3 heterodimer and blocks heregulin (HRG) binding to HER3, and then inhibits HER3 downstream signaling pathways

Target: HER2

Ertumaxomab: anticorpo tri-funzionale. Collega le cellule T, i macrofagi e le cellule cancerose (interrotto).

MM-111: anticorpo bispecifico per HER2/HER3 che interferisce con la loro interazione (studi clinici in corso).

Inibitori tirosin chinasi

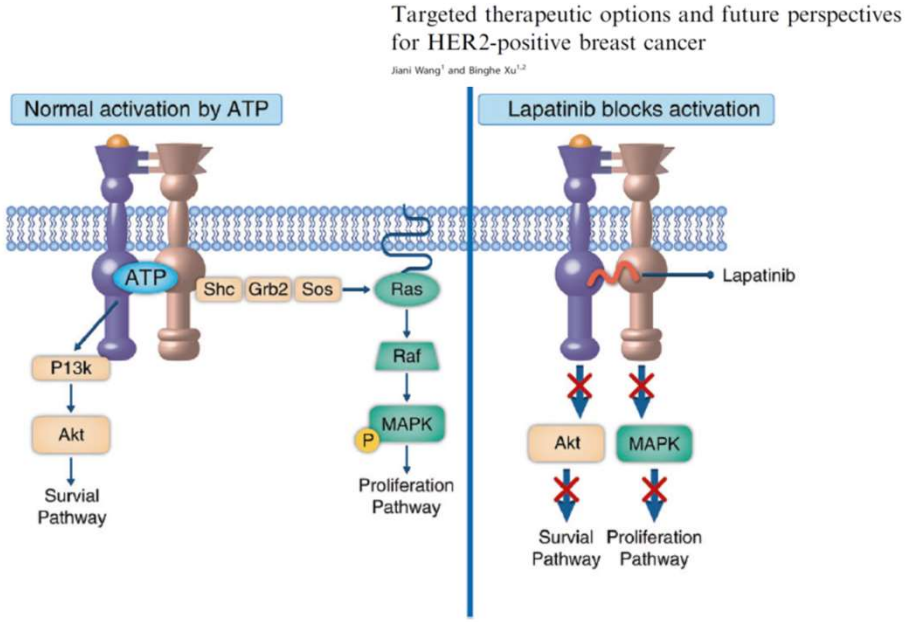
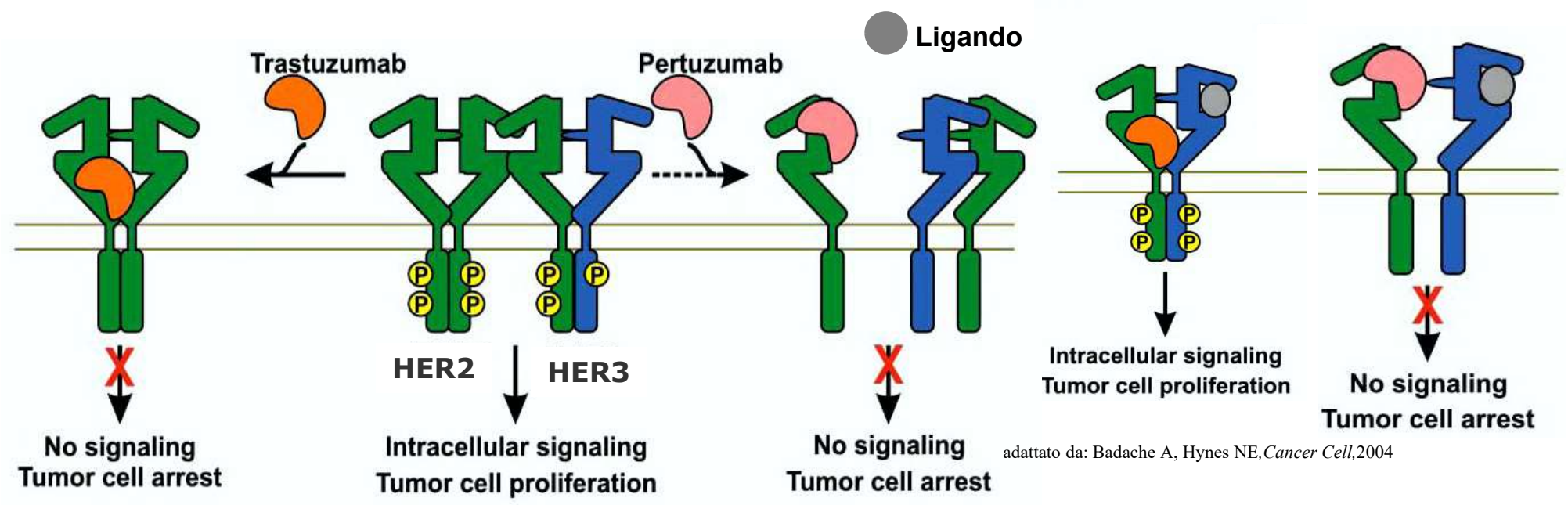


Fig. 3 Mechanism of lapatinib action. By competing with ATP, small-molecule TKI Lapatinib blocks HER2 signaling, preventing auto phosphorylation and subsequent downstream signaling events

Target: HER2. **Pertuzumab**



adattato da: Badache A, Hynes NE, *Cancer Cell*, 2004

A Phase I Study of the Safety and Pharmacokinetics of the Combination of Pertuzumab (rhuMab 2C4) and Capecitabine in Patients with Advanced Solid Tumors

Joan Albanell,[1] Clara Montagut,[1] Eileen T. Jones,[2] Linda Pronk,[3] Begoña Mellado,[1] Janette Beech,[2] Pere Gascon,[1] Gerhard Zugmaier,[3] Michael Brewster,[3] Mark P. Saunders,[2] and Juan W. Valle[2]

Clinical Cancer Research, 2008.

Conclusions: *Pertuzumab and capecitabine were well tolerated at all dose levels... In conclusion, this combination is ready for phase II testing.*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 14, 2019 VOL. 380 NO. 7

Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer

G. von Minckwitz, C.-S. Huang, M.S. Mano, S. Loibl, E.P. Mamounas, M. Untch, N. Wolmark, P. Rastogi, A. Schneeweiss, A. Redondo, H.H. Fischer, W. Jacot, A.K. Conlin, C. Arce-Salinas, I.L. Wapnir, C. Jackisch, M.P. DiGiovanna, P.A. Fasching, J.P. Crown, P. Wülfing, Z. Shao, E. Rota Caremoli, H. Wu, L.H. Lam, D. Tesarowski, M. Smitt, H. Douthwaite, S.M. Singel, and C.E. Geyer, Jr., for the KATHERINE Investigators*

ABSTRACT

BACKGROUND

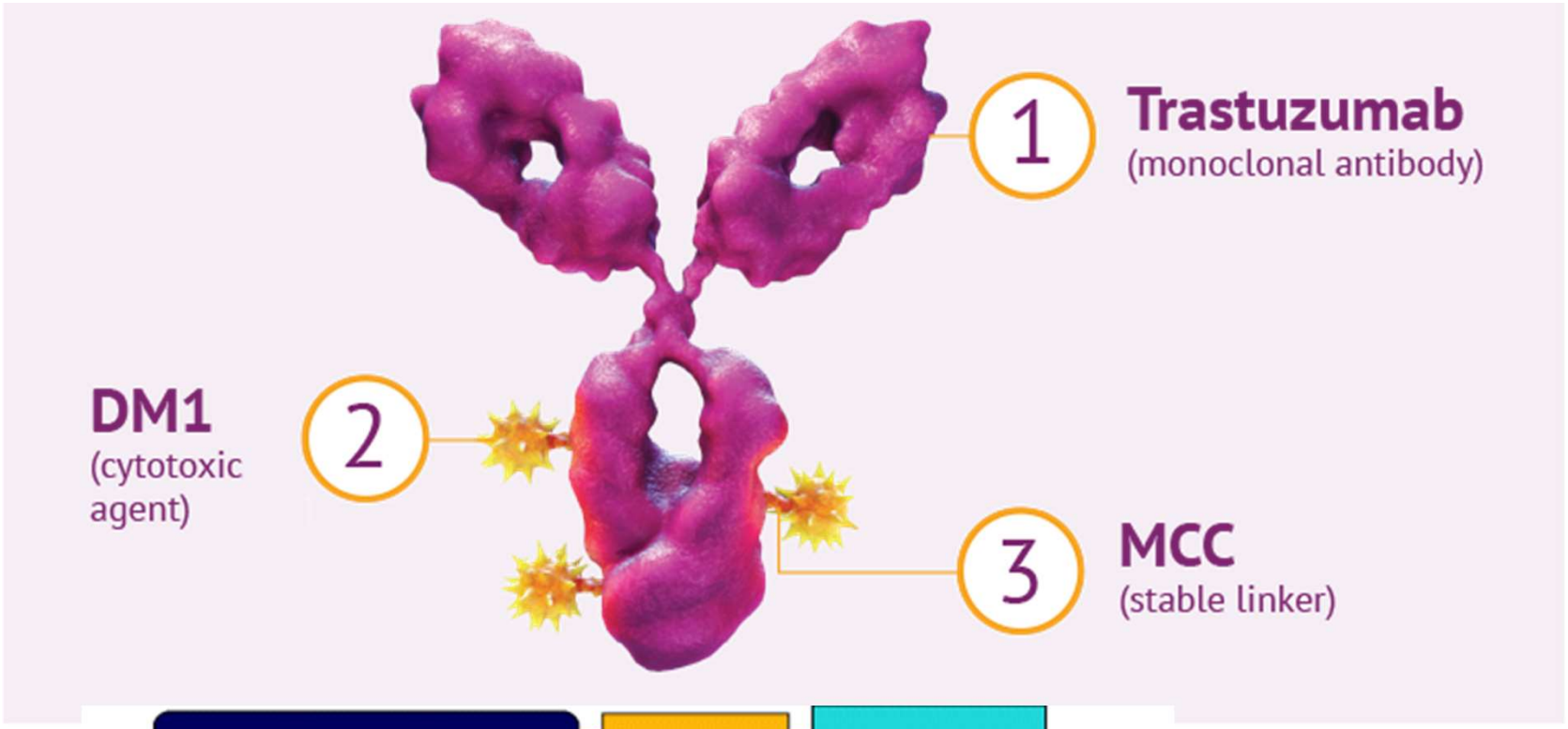
Patients who have residual invasive breast cancer after receiving neoadjuvant chemotherapy plus human epidermal growth factor receptor 2 (HER2)–targeted therapy have a worse prognosis than those who have no residual cancer. Trastuzumab emtansine (T-DM1), an antibody–drug conjugate of trastuzumab and the cytotoxic agent emtansine (DM1), a maytansine derivative and microtubule inhibitor, provides benefit in patients with metastatic breast cancer that was previously treated with chemotherapy plus HER2-targeted therapy.

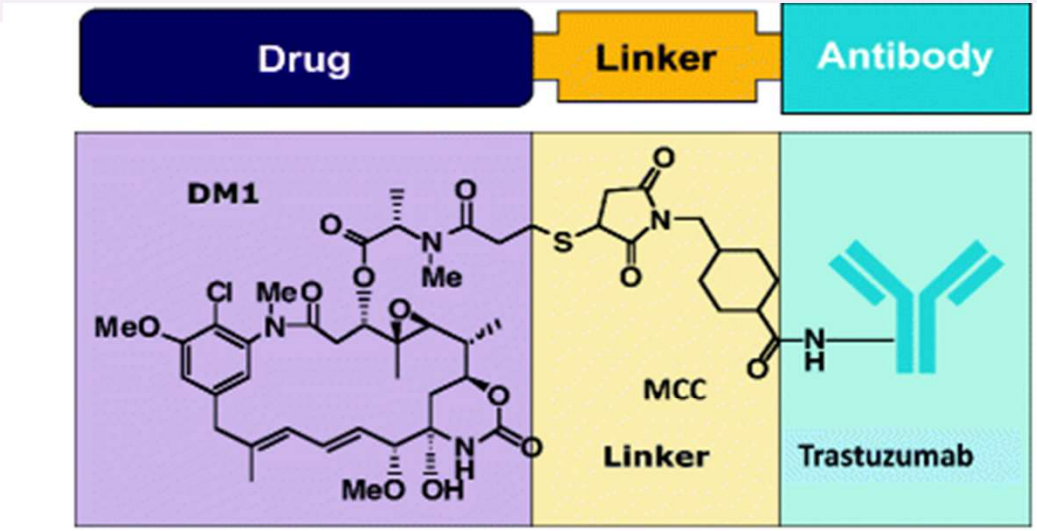
METHODS

We conducted a phase 3, open-label trial involving patients with HER2-positive early-

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. von Minckwitz at the German Breast Group, GBG Forschungs, Martin-Behaim-Str. 12, 63263 Neu-Isenburg, Germany, or at vonminckwitz@gbg.de.

*A complete list of the KATHERINE Investigators is provided in the Supplementary Appendix, available at NEJM.org.





MW:	738	238	~150,000
Ratio:	3.5	3.5	1

DM1 = Derivative of Maytansine, a microtubule destablizing agent
MCC = [maleimidomethyl] cyclohexane-1-carboxylate, a nonreducible thioether linkage
Trastuzumab (Herceptin) = Monoclonal antibody directed against HER2

Indicazioni terapeutiche

Tumore mammario in stadio iniziale e metastatico

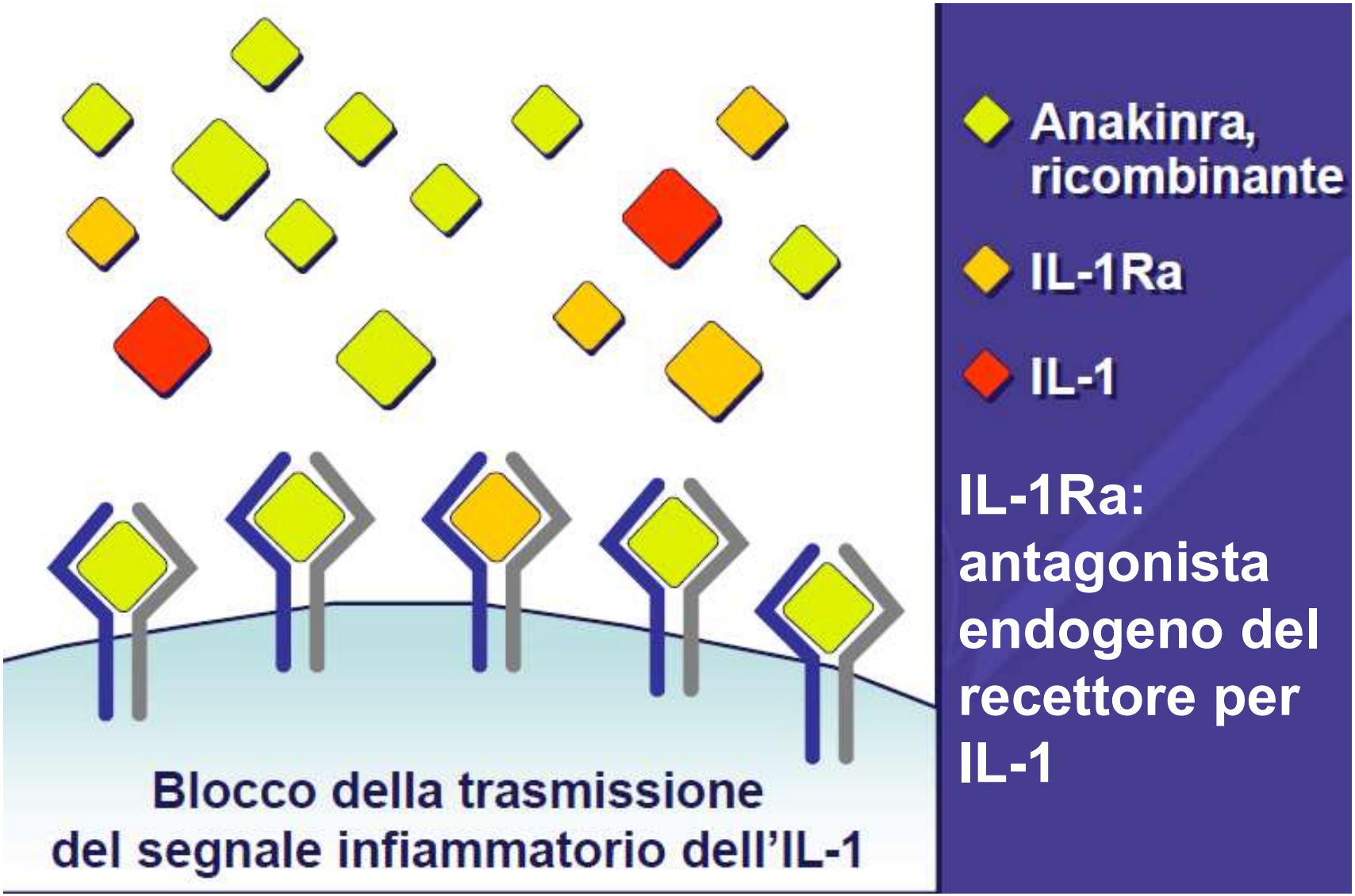
Target: recettore IL-1

Anakinra

Anakinra è una forma ricombinante dell'**antagonista del recettore per l'interleuchina-1** (IL-1Ra) **endogeno**, ottenuta tramite DNA ricombinante.

Parametri farmacocinetici:
Biodisponibilità: 95%
Emivita: 4-6 ore

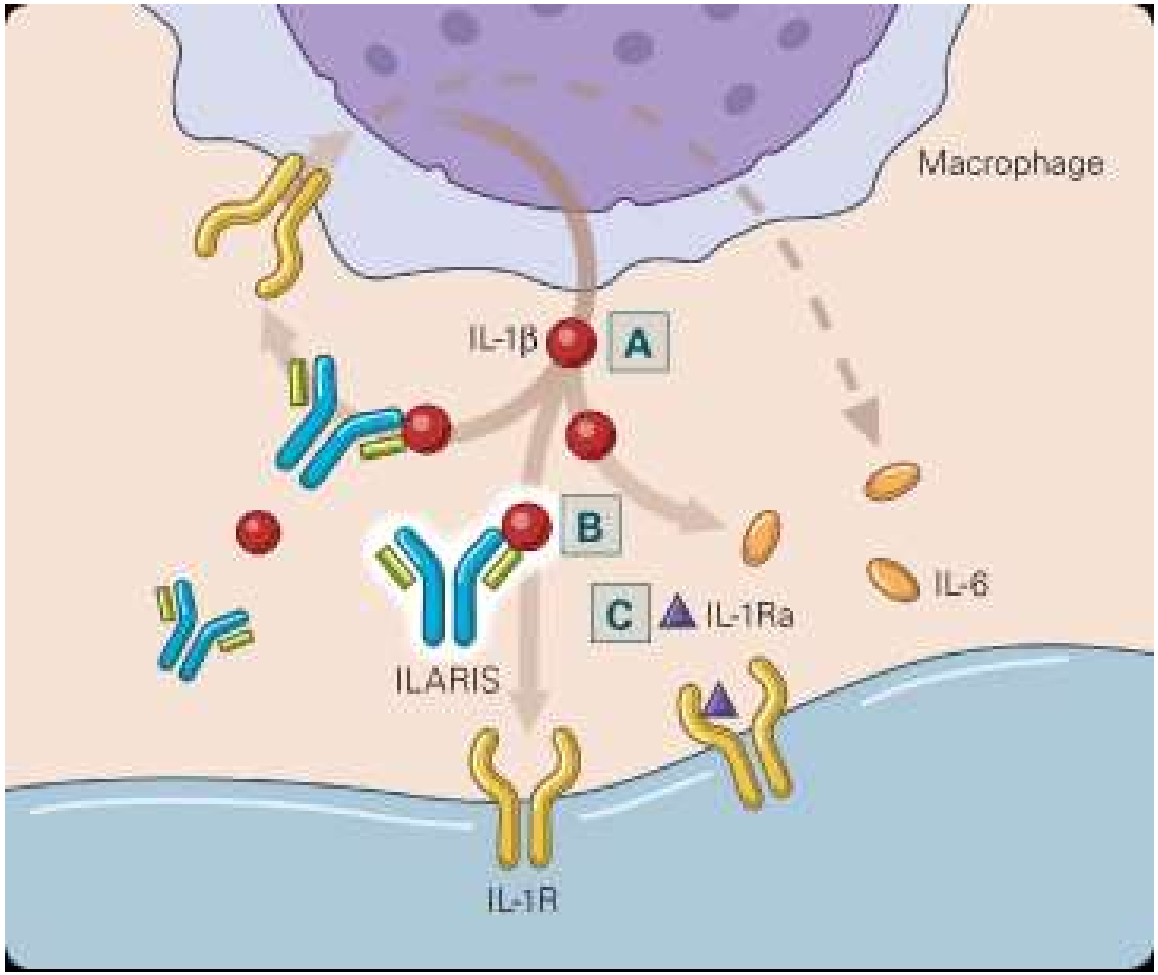
Target: recettore IL-1



Nature Reviews Drug Discovery | Published online 29 Sep 2017; doi:10.1038/nrd.2017.186

Anti-inflammatory drug cuts risk of heart disease — and cancer

Results from Novartis's huge trial of the interleukin-1β blocker canakinumab could revitalize efforts to target inflammation in atherosclerosis, and have demonstrated unanticipated activity in lung cancer.



Canakinumab (Ilaris) lega IL-1β.

Indicazioni terapeutiche:

- Sindromi da febbre periodica
- Sindromi Periodiche Associate a Criopirina
- Sindrome di Muckle-Wells
- Sindrome periodica associata al recettore del fattore di necrosi tumorale
- Sindrome da iperimmunoglobulinemia D/deficit di mevalonato chinasi
- Febbre Mediterranea Familiare
- Malattia di Still
- Artrite gottosa

Target: TNF

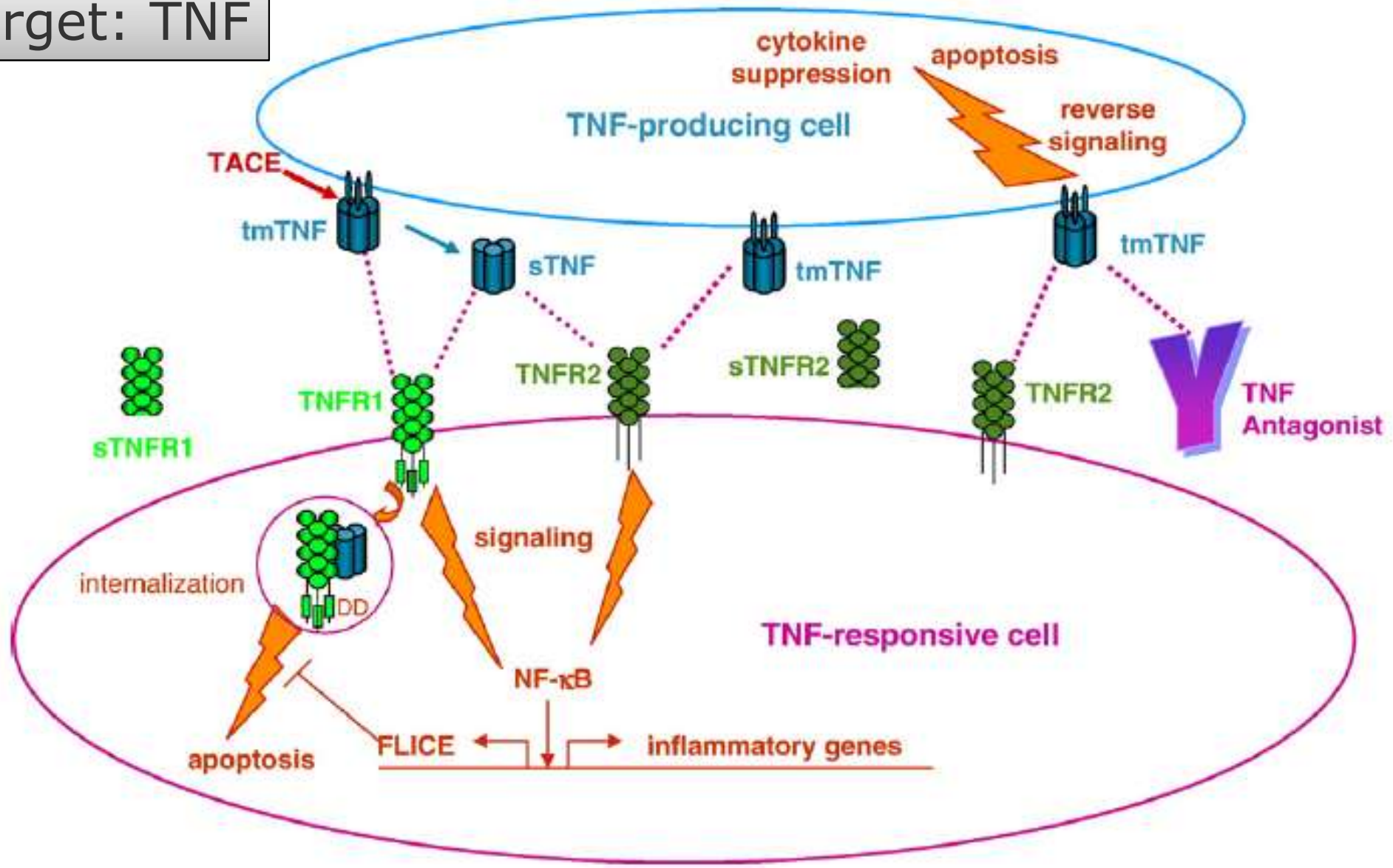
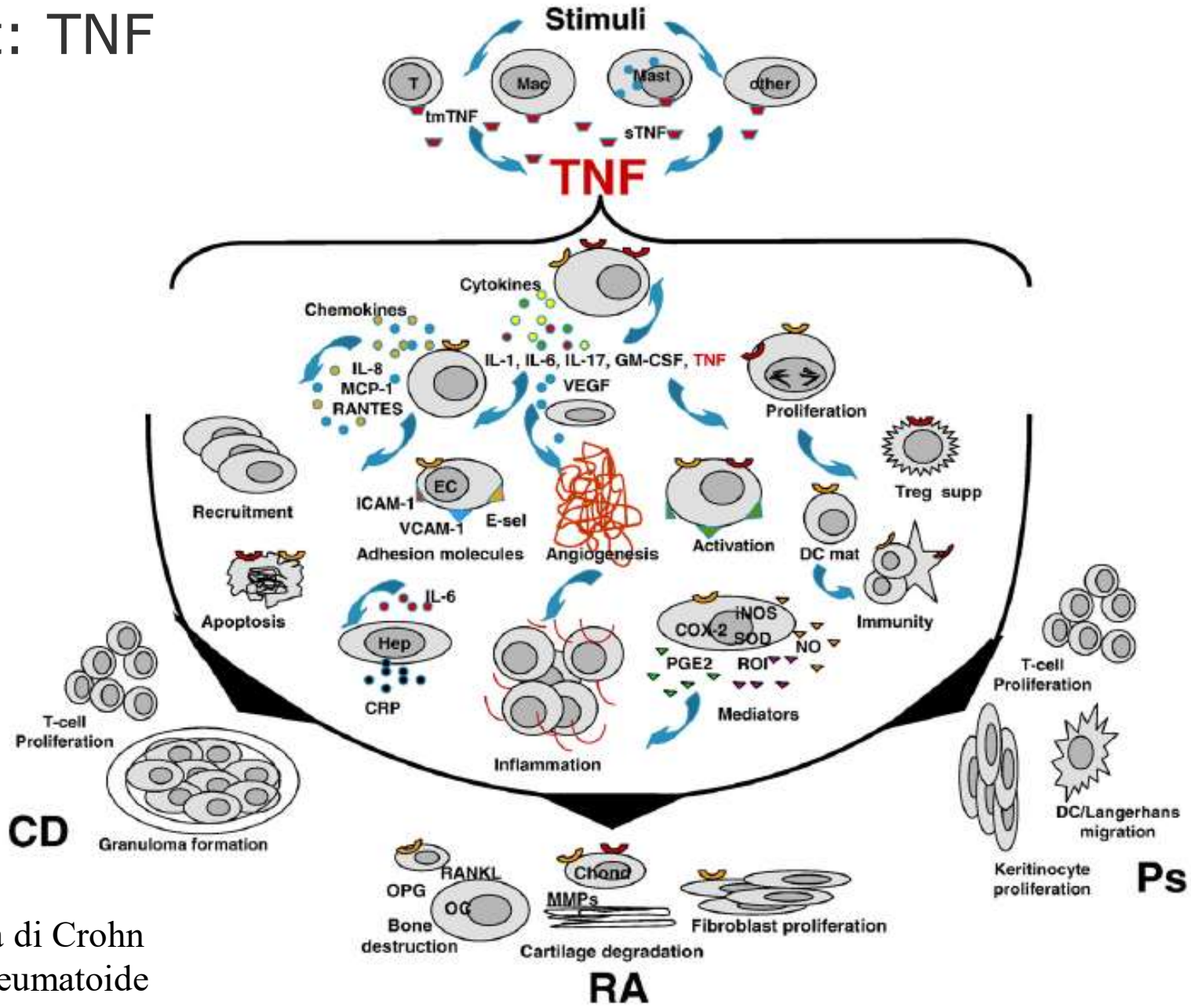


Fig. 1. Biology of TNF production, receptor interaction and signaling. Stimulation of a TNF-producing cell (top) results in cell surface expression of tmTNF trimers and enzymatic cleavage by TACE to release sTNF. Both tmTNF and sTNF can bind to cell surface TNFR1 or TNFR2 on a TNF-responsive cell (bottom), initiating signaling pathways that lead to apoptosis or NF-κB activation and inflammatory gene activation. The induction of apoptosis by sTNF via TNFR1 involves internalization of the ligand–receptor complex and association of death domains (DD) in the cytoplasmic tail of TNFR1 with adapter proteins and is normally blocked by FADD-like IL-1β–converting enzyme (FLICE). Reverse signaling can be initiated by TNFR2 or TNF antagonist binding to cell surface tmTNF, resulting in cytokine suppression or apoptosis. Soluble TNF receptors (sTNFR1 and sTNFR2) can be released from a TNF-responsive cell following enzymatic cleavage.

D. Tracey et al. / Pharmacology & Therapeutics 117 (2008)

Target: TNF



CD: malattia di Crohn
RA: artrite reumatoide
Ps: psoriasi

Fig. 3. In the pathophysiology of RA, Crohn's disease and psoriasis, TNF is produced at high concentrations by a variety of cell types, presumably induced by endogenous or microbial stimuli. A cascade and network of cellular responses mediated by TNF that are common to these 3 diseases are shown in the enclosed area in the center of the diagram. Mechanisms and cellular features restricted to a particular disease are shown outside of the enclosed area.

D. Tracey et al. / Pharmacology & Therapeutics 117 (2008)

Target: TNF

Razionale: l'esempio dell'artrite reumatoide (AR)

1982[a]: IL-1 nel liquido sinoviale (LS) pz. AR;

1988[b]: TNF, IL-6, IL-2, GM-CSF (granulocyte-macrophage colony-stimulating factor) in colture di LS pz. AR;

1989[c]: Ab-anti TNF blocca produzione IL-1

Preliminary Communication

INHIBITORY EFFECT OF TNFα ANTIBODIES ON SYNOVIAL CELL INTERLEUKIN-1 PRODUCTION IN RHEUMATOID ARTHRITIS

FIONULA M. BRENNAN DAVID CHANTRY
ANDREW JACKSON RAVINDER MAINI
MARC FELDMANN

Charing Cross Sunley Research Centre, and Kennedy Institute of Rheumatology, Hammersmith, London W6 8LW

Summary The effect of tumour necrosis factor (TNFα) antibodies on synovial cell interleukin-1 (IL-1) production was investigated in 7 patients with rheumatoid arthritis and in 7 with osteoarthritis. Synovial cell IL-1 production was significantly reduced by anti-TNFα antibody in cultures from patients with rheumatoid arthritis, but anti-lymphotoxin antibody did not have this effect (except in 1 culture). In cultures from patients with osteoarthritis spontaneous IL-1 production was low, despite high concentrations of TNFα, and IL-1 production was not inhibited by anti-TNFα antibody. In rheumatoid arthritis, TNFα may be the main inducer of IL-1, and anti-TNFα agents may be useful in treatment.

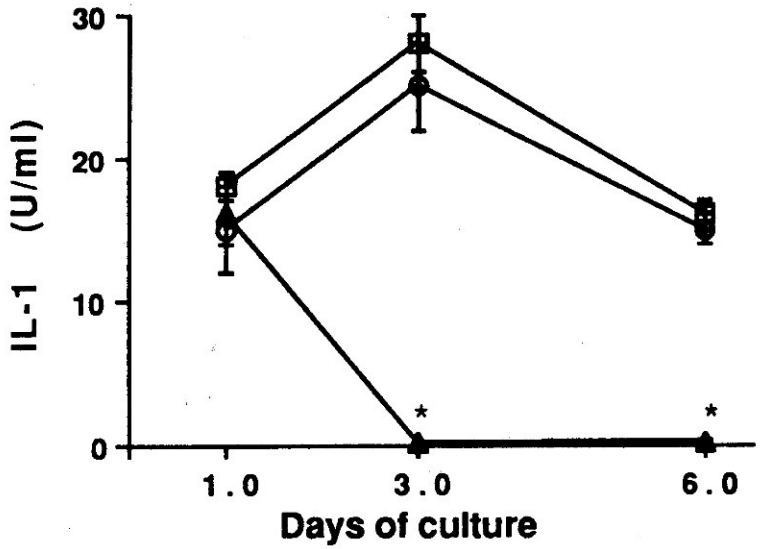


Fig 1—Culture of rheumatoid arthritis synovial membrane cells with polyclonal antibodies to TNFα (▲), polyclonal antibodies to lymphotoxin (○), or equivalent amount of control rabbit IgG (□).

1992[d]: modelli animali.

a: Fontana A et al., *Rheumatol. Int.* 1982
b: Buchan G et al., *Clin. Exp. Immunol.* 1988
c: Brennan FM et al., *Lancet* 1989
d: Williams RO et al., *Proc. Natl. Acad. Sci. USA* 1992

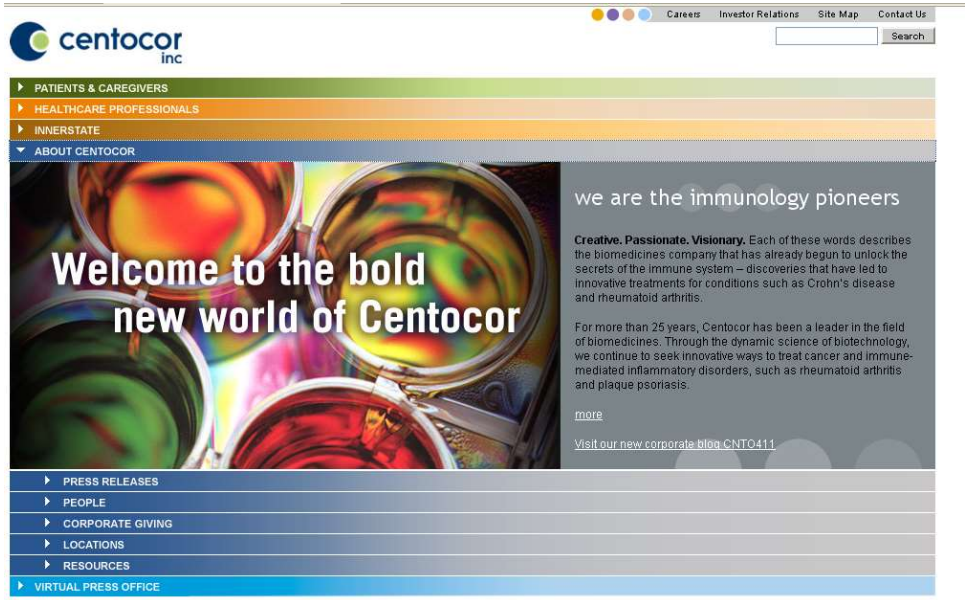
Target: TNF

Table 4. Some milestones in the development of TNF-blocking agents (1985–1999)[a]

Year	Progress	Refs
1985	Polyclonal antibody to TNF shown to protect mice from bacterial sepsis	[14]
1989	Anti-TNF antibody shown to abrogate IL-1 production in synovial cell cultures from RA joints	[58]
1988–1989	Murine anti-TNF monoclonal antibody A2 generated at New York University	[b]
1990–1991	Generation of chimeric anti-TNF monoclonal antibody cA2 from A2 and its preclinical development at Centocor and NYU	[51,52]
1990–1992	Anti-TNF antibodies shown to be effective in mouse models of arthritis	[67–70]
1991–1992	Clinical trial with cA2 antibody in sepsis patients sponsored by Centocor; no significant benefit seen	[c]
1992	cA2 antibody found to be effective in small, open-label clinical trial in RA at Charing Cross Hospital	[19]
1993	cA2 antibody found to be effective in a patient with Crohn's disease	[88]
1993	Formal proof of efficacy of cA2 antibody in RA in a placebo-controlled study	[71]
1993–1998	Phase I/II trials of cA2 in Crohn's disease, which led to FDA approval of Remicade® (infliximab) in 1998	[20]
1993–1998	Clinical trials of the p75 TNF receptor–IgG fusion protein [Enbrel® (etanercept)] in RA, which led to FDA approval in 1998	[21]
1993–1999	Phase II/III trials of cA2 in RA, which led to FDA approval of Remicade® in 1999	[74–76]

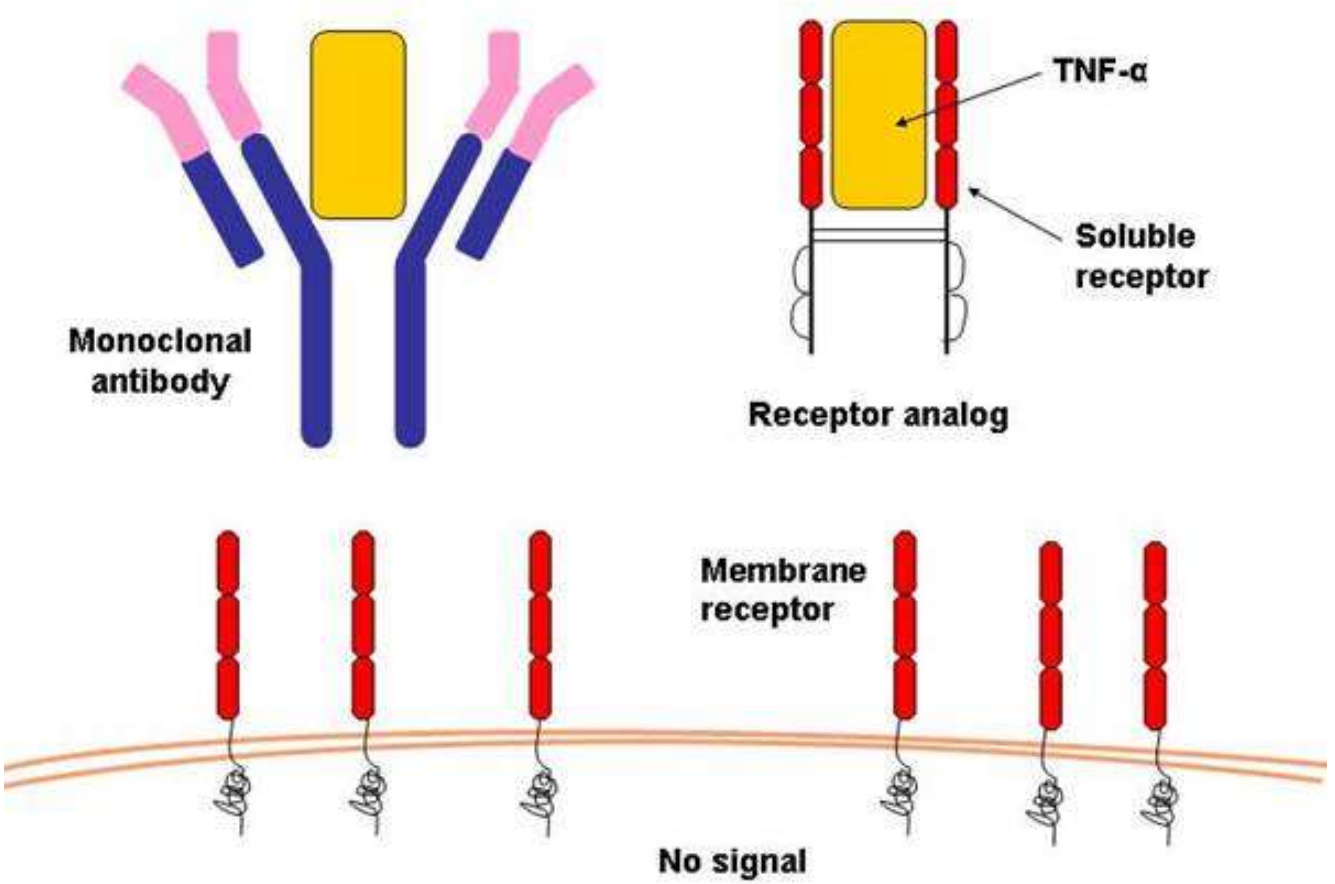
[a]Abbreviations: FDA, Food and Drug Administration; IL, interleukin; NYU, New York University; RA, rheumatoid arthritis; TNF, tumor necrosis factor.
[b]J. Le and J. Vilcek, unpublished.
[c]Unpublished.

Vilček J and Feldmann M, *TIPS* 2004



Target: TNF

Strategie



Target: TNF

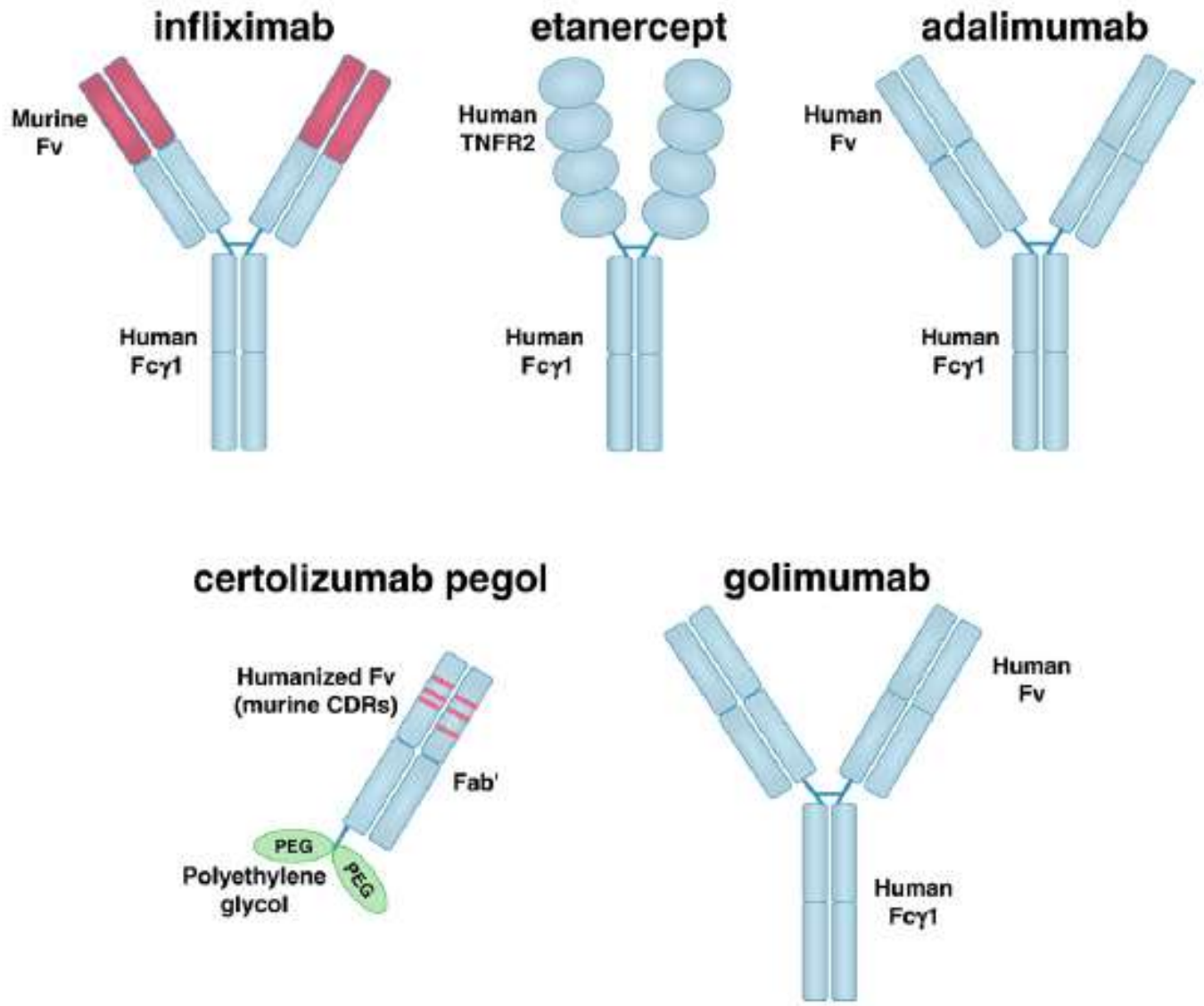


Fig. 4. Simplified diagrams of the molecular structures of 5 TNF antagonists. Infliximab is a mouse/human chimeric monoclonal anti-TNFantibody of IgG1 isotype. Adalimumab and golimumab are fully human IgG1 monoclonal anti-TNF antibodies. Etanercept is a fusion protein of TNFR2 (p75) and the Fc region of human IgG1. Certolizumab is a PEGylated Fab' fragment of a humanized IgG1 monoclonal anti-TNF antibody.

Target: TNF

Clinical profile of TNF antagonists

	Infliximab	Etanercept	Adalimumab	Certolizumab	Golimumab
Brand name	REMICADE	ENBREL	HUMIRA	NA	NA
Synonyms/historical	cA2	p75TNFR-Fc	D2E7	CDP870	CNTO-148
EU registration	RA, PsA, AS, CD, UC, Ps	RA, PsA, AS, JIA, Ps	RA, PsA, AS, CD, Ps	NA	NA
US registration	RA, PsA, AS, CD, UC, Ps	RA, PsA, AS, JIA, Ps	RA, PsA, AS, CD	NA	NA
Efficacy in RA	+++	+++	+++	+++	+++
Efficacy in PsA	+++	+++	+++	ND	ND
Efficacy in AS	+++	+++	+++	ND	ND
Efficacy in CD	+++	–	+++	++	ND
Efficacy in UC	+++	ND	ND	ND	ND
Efficacy in Ps	+++	++	+++	ND	ND
Efficacy in JIA	++	++	ND	ND	ND
Efficacy in Wegener's granulomatosis	++	–	ND	ND	ND
Efficacy in sarcoidosis	++	–	ND	ND	ND
Administration	IV	SC	SC	SC	SC
Dosages	3–10 mg/kg q4–8w	25 mg biw; 50 mg qw	40 mg eow; 40 mg qw	100, 200 or 400 mg q4w	50 or 100 mg q2w or q4w
Pharmacokinetics					
Half-life (t ½)	8–10 days	4 days	10–20 days	~14 days	7–20 days
Volume of distribution (Vss)	4.3 +/−2.5 L [a]	8.0 L [b]	4.7–6.0 L [c]	ND	6.9 L [d]
Clearance (C_L)	11 mL/h [a]	72 +/−5 mL/h [e]	12 mL/h [c]	ND	16.7 mL/h [f]
Cmax	118 μg/mL [a]	1.1 +/−0.6 μg/mL [e]	4.7 +/−1.6 μg/mL [g]	ND	70.8 +/−18.9 μg/mL [h]
Immunogenicity					
RA monotherapy	+++	+	+	ND	ND
RA with MTX	+	+/–	+/–	ND	ND
CD monotherapy	+++	+	+	+	ND

Target: TNF

Biochemical and mechanistic profile of TNF antagonists

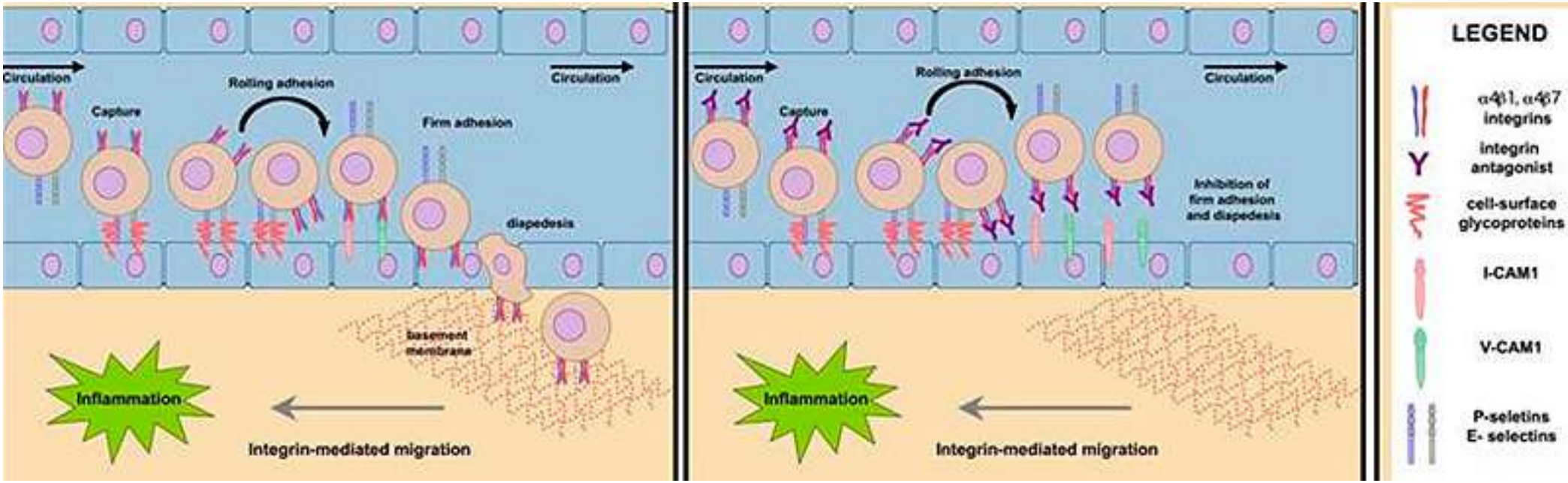
	Infliximab	Etanercept	Adalimumab	Certolizumab	Golimumab
Class	Monoclonal antibody	Fc-fusion protein	Monoclonal antibody	Monoclonal antibody fragment	Monoclonal antibody
Structure	Mo/Hu chimeric IgG1κ	Hu sTNFR2-Fcγ1	Hu IgG1κ	PEG-Hu IgG1κ Fab[1]	Hu IgG1κ
Molecular weight (kDa)	150	150	150	~95	150
Specificity	TNF	TNF/LT	TNF	TNF	TNF
TNF ligands	sTNF, tmTNF	sTNF, tmTNF,	sTNF, tmTNF	sTNF, tmTNF	sTNF, tmTNF
LT ligands	–	LTα3, LTα2β1	–	–	–
Neutralization potency					
sTNF (low conc)	++	+++	++	ND	ND
sTNF (high conc)	+++	+++	+++	+++	ND
tmTNF binding	+++	++	+++	+++	ND
tmTNF neutralization	+++	++	+++	+++	ND
Reverse signaling (apoptosis)	+++	++/–	+++	–	ND
Reverse signaling (cytokine suppression)	+++	++/–	+++	+++	ND
FcγR binding					
Drug–TNF complexes 1:1 ratio	++	–	++	ND	ND
Drug–TNF complexes >10:1 ratio	–	–	–	ND	ND
CDC	+++	++/–	+++	–	ND
ADCC	+++	++/–	+++	–	ND

Malattie infiammatorie Croniche Intestinali
Morbo di Crohn e Colite Ulcerosa

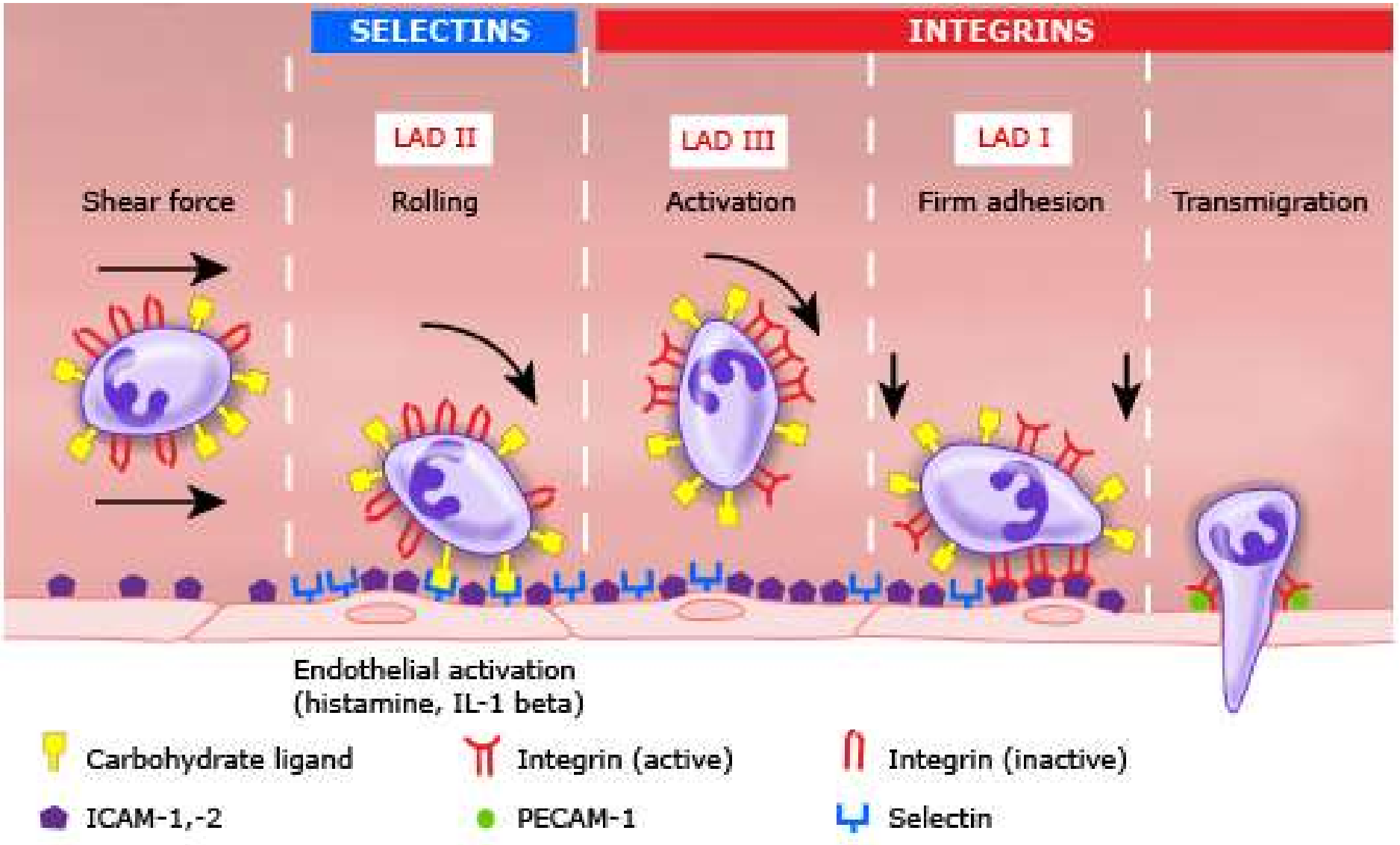
Aspetti chiave:

1) Reclutamento e ritenzione dei leucociti: determinante della risposta infiammatoria;

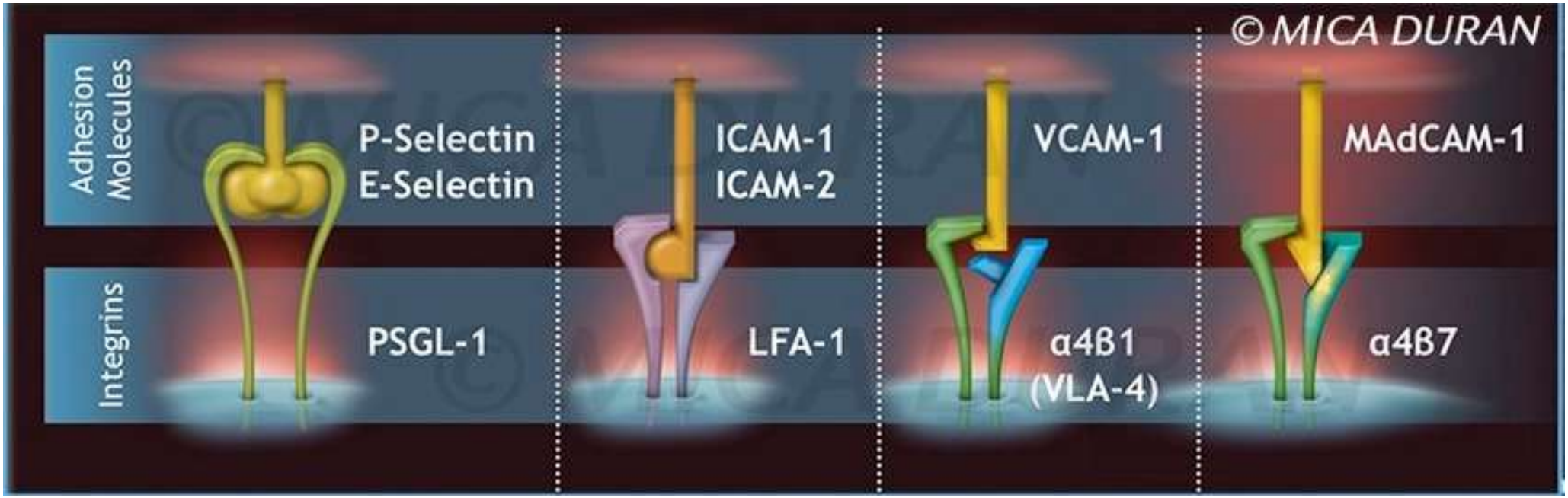
2) Razionale: *target* potenziali; integrine, molecole di adesione (MAdCAM-1, ICAM-1, VCAM-1), recettori per le chemochine e chemochine.



MAdCAM-1: Mucosal Addressin Cellular Adhesion Molecule 1, ICAM-1: Intercellular Cell Adhesion Molecule, VCAM-1: Vascular Cell Adhesion Molecule



- Attivazione endotelio → espressione selectine (P e E).
- Attivazione integrine.
- Adesione stabile tramite MAdCAM-1, ICAM -1 e VCAM-1.
- Trasmigrazione (diapedesi leucocitaria).



Molecole *anti-adesione*
Anticorpi diretti verso specifiche porzioni della struttura delle integrine.

- **Natalizumab**: blocco α4 (VCAM-1 e MAdCAM-1).

- **Vedolizumab:** inibisce specificatamente α4β7 prevenendo legame di MAdCAM-1 (presente specificatamente nell'intestino).

Vedolizumab: A Humanized, Monoclonal Antibody (mAb) Against α4β7 Integrins

Infusione iv in 30 – 60 minuti.

Approvato per colite ulcerosa e malattia di Crohn nei pazienti che hanno avuto una perdita di risposta o sono risultati intolleranti alla terapia convenzionale o alla somministrazione di un antagonista del TNFα.

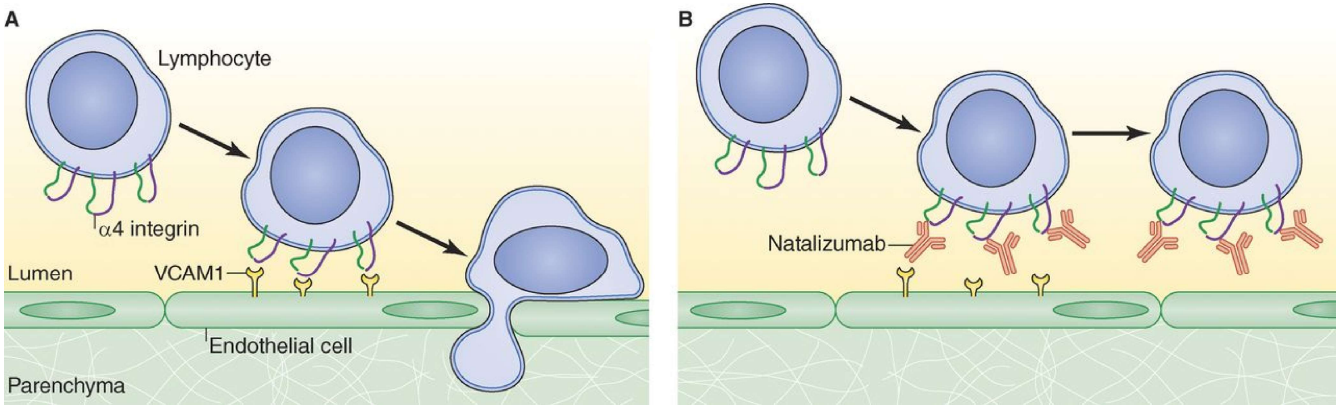
Natalizumab (blocco α4) nella sclerosi multipla

Segnalati (2008) due casi di **leucoencefalopatia multifocale progressiva** (PML) in pazienti con sclerosi multipla in trattamento con natalizumab.

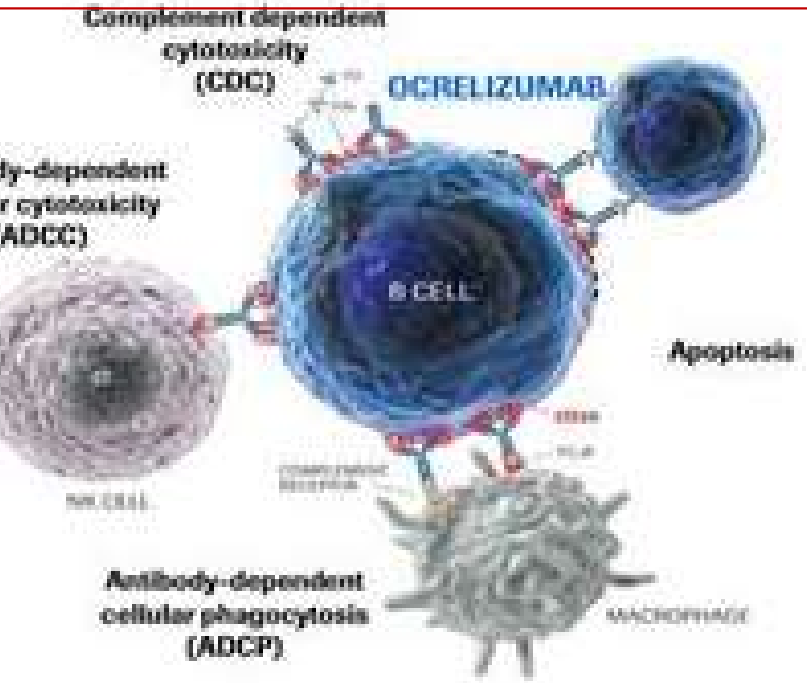
La PML è associata a un aumento incontrollato del virus JC nel cervello.
Il virus JC è un virus comune che infetta molte persone senza però provocare normalmente malattie osservabili.
Fondamentale effettuare un esame del sangue per controllare se presenti anticorpi anti virus JC.

Il rischio di sviluppare la PML con natalizumab è più elevato:
- se nel sangue sono presenti anticorpi anti virus JC.
- se il trattamento si prolunga, specialmente oltre i due anni.
- se in precedenza ha assunto immunosoppressori.

Se presenti tutti e tre i fattori di rischio elencati sopra, la probabilità che sviluppi una PML è più elevata.



Ocrelizumab: anticorpo monoclonale umanizzato diretto contro cellule B CD20+ responsabili del danno alla mielina e all'assone che si osserva nella **sclerosi multipla**.



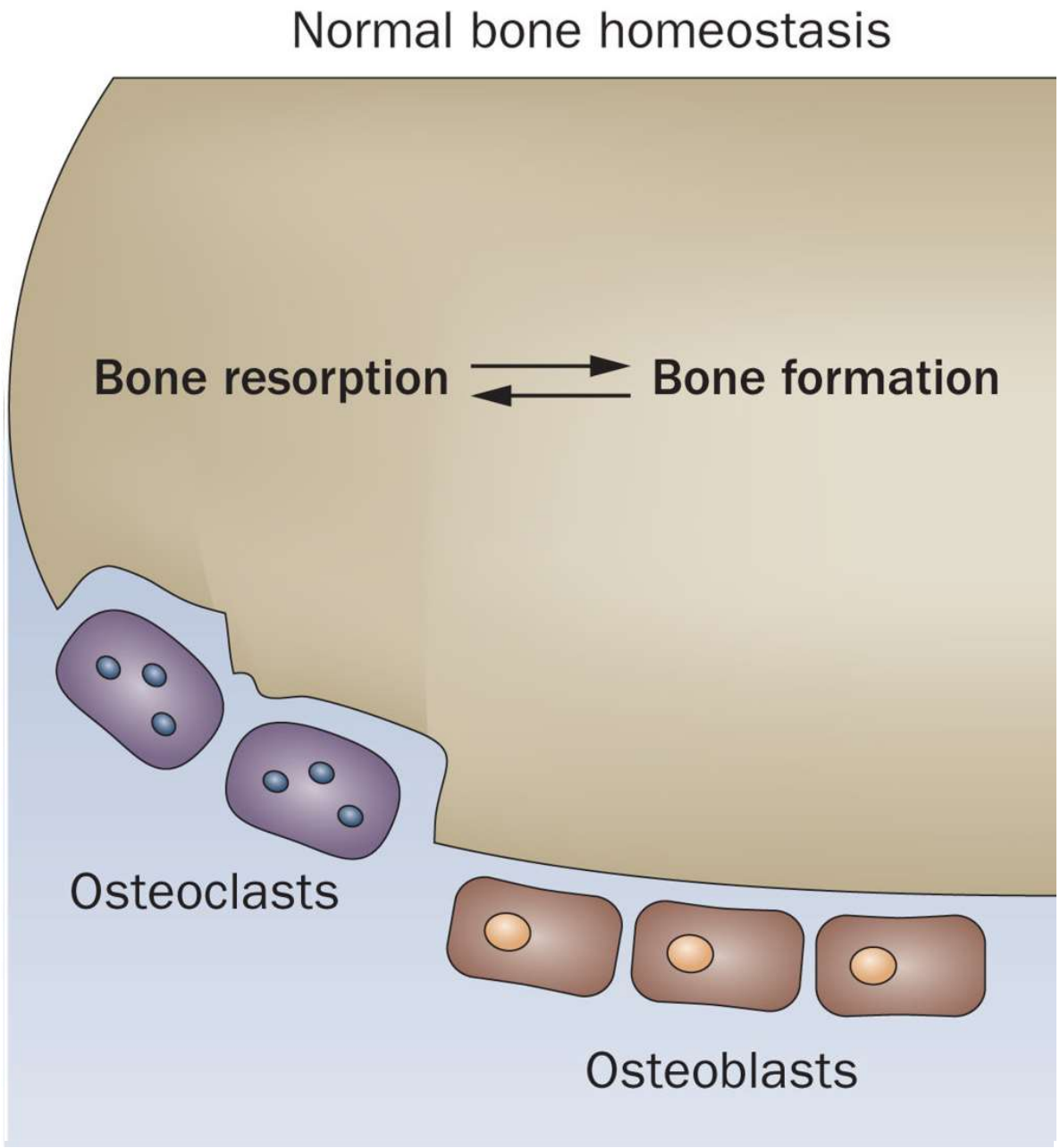
Sclerosi multipla: ocrelizumab sarà erogato dal servizio Sanitario Nazionale in ambito ospedaliero

04/09/2018

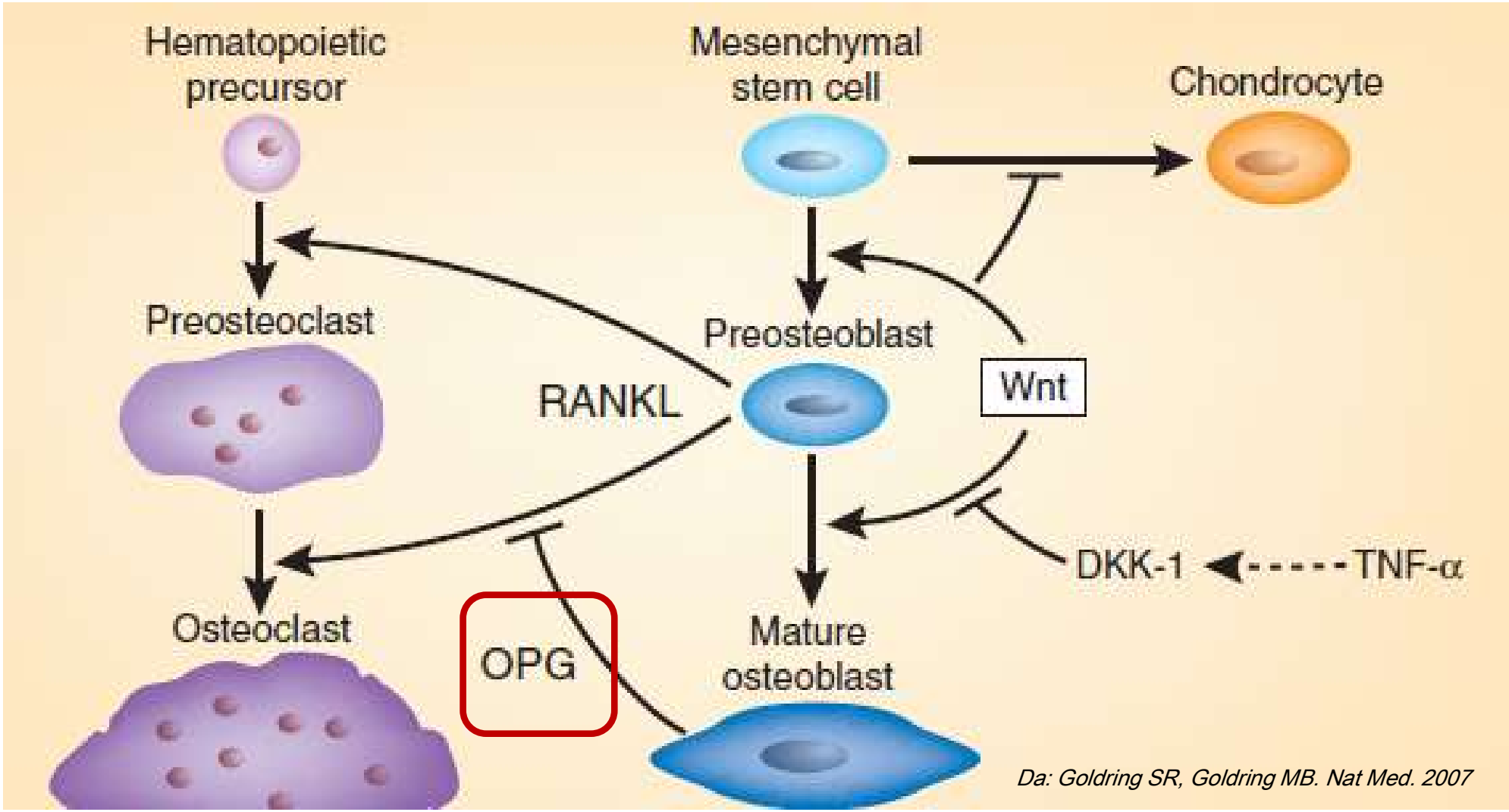
Targeted product profile

- Humanized antibody targeting CD20+ B cells
- Selective depletion of a subset of B cells leaving the ability to generate new B cells intact
- Administered by IV twice yearly

Farmaci biologici nell'artrite reumatoide

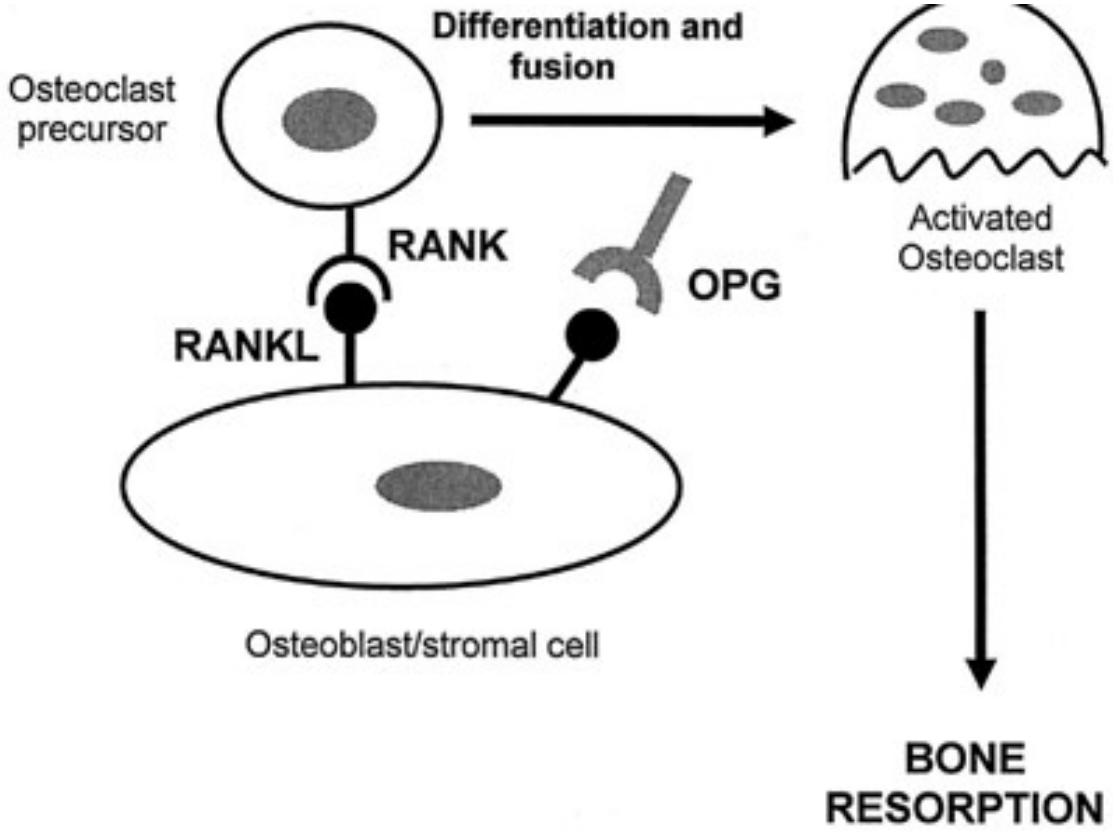


da: Choi Y, Arron JR, Townsend MJ. Nat Rev Rheumatol. 2009



I pre-osteoblasti secernono Wnt ed esprimono RANKL.
Wnt indirizza alla formazione di osteoblasti e regola negativamente la formazione di condrociti.
I pre-osteoblasti indirizzano verso il riassorbimento tramite l'espressione di RANKL.
L'attivazione di Wnt up-regola l'espressione di OPG che impedisce il legame RANK-RANKL

RANK(L): Receptor Activator for Nuclear Factor κ B (Ligand), OPG: (Osteoprotegerina), Dkk-1: Dickkopf-1



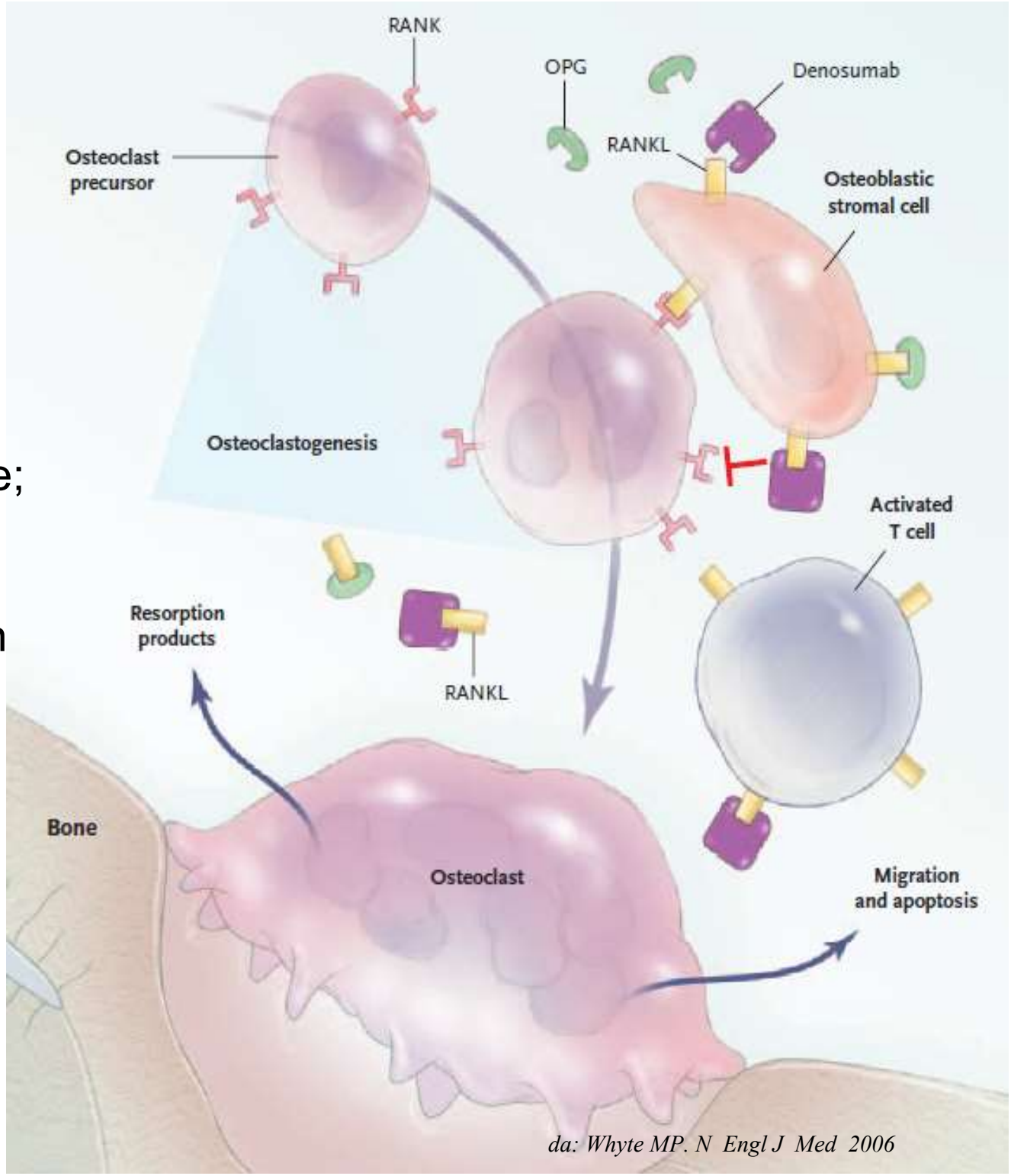
La osteoprotegerina (OPG) è una glicoproteina inibitrice del riassorbimento osseo coinvolta nella regolazione della degradazione ossea. OPG si lega come *recettore "esca"* al RANKL e ne diminuisce la disponibilità per il recettore.

DENOSUMAB

Approvato per:

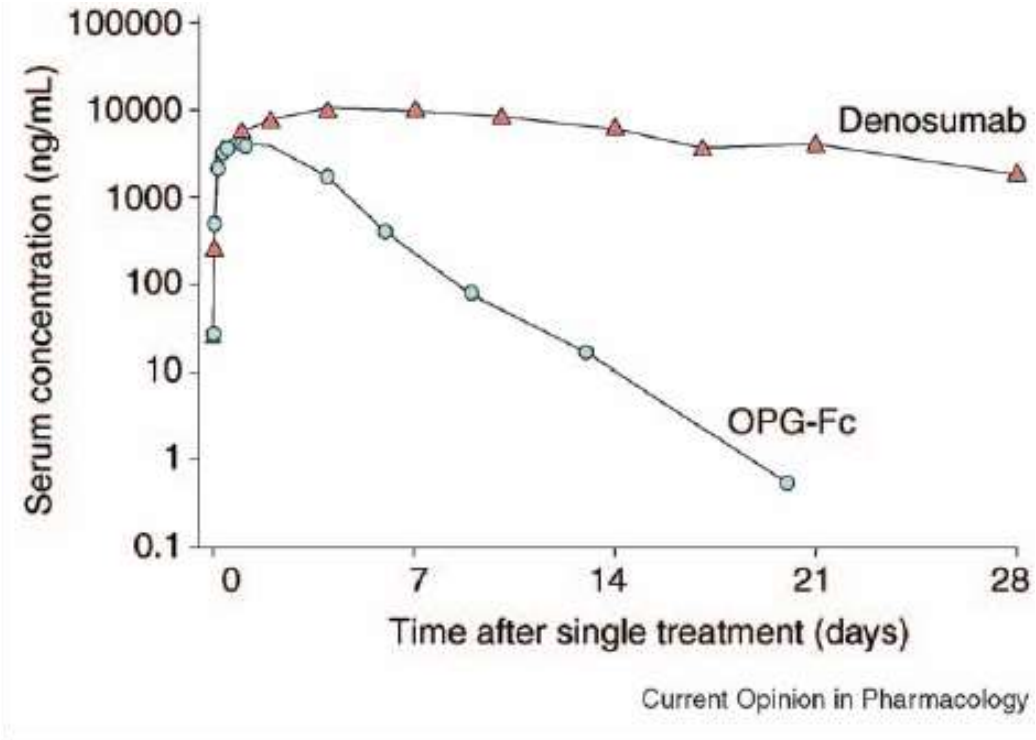
•osteoporosi post-menopausale in donne ad aumentato rischio di fratture;

•perdita ossea associata a terapia ormonale ablativa in uomini affetti da carcinoma prostatico.



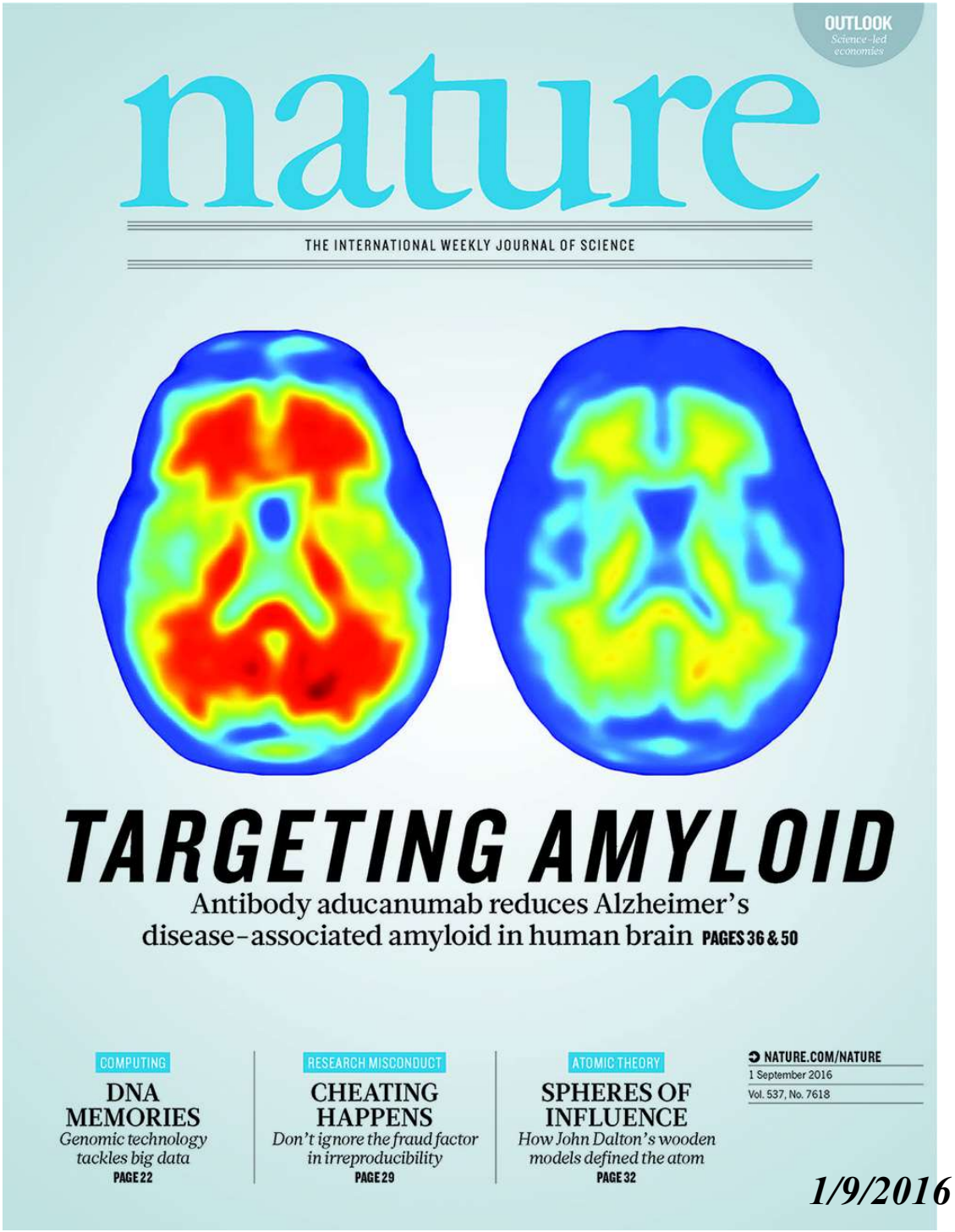
da: Whyte MP. N Engl J Med 2006

Limitazioni farmacocinetiche all'uso di osteoprotegerina (OPG)



Pharmacokinetic comparison between denosumab and OPG-Fc in cynomolgus monkeys. Drugs were injected once (subcutaneously) at 1 mg/kg and blood was drawn at regular intervals for measurement of drug levels. Serum levels of OPG-Fc were below detection limits after 21 days. Data represent the means of three animals per group.

da:Kostenuik PJ. Curr Opin Pharmacol. 2005



1/9/2016

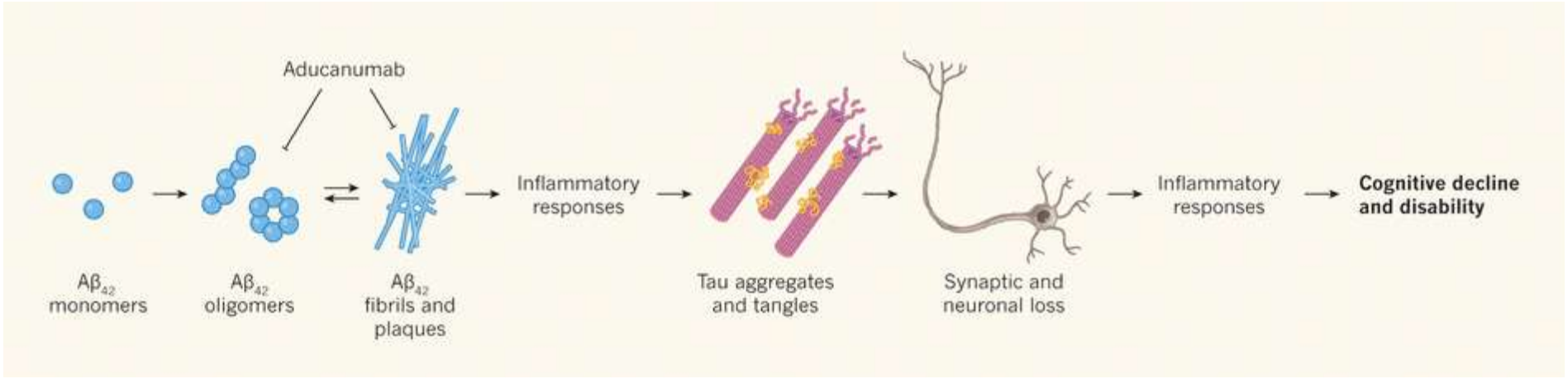
Aducanumab ha come bersaglio le forme aggregate di beta amiloide, compresi gli oligomeri solubili e le fibrille insolubili depositati nelle placche.

FDA ha concesso il *Fast Track status* nel settembre del 2016.
Ammesso al **programma PRIME** (PRIority MEdicines) dell'Agenzia europea per i medicinali (EMA).
Giappone *Fast Track status* in aprile 2017.

The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

Jeff Sevigny[1*], Ping Chiao[1*], Thierry Bussière[1*], Paul H. Weinreb[1*], Leslie Williams[1], Marcel Maier[2], Robert Dunstan[1], Stephen Salloway[3], Tianle Chen[1], Yan Ling[1], John O'Gorman[1], Fang Qian[1], Mahin Arastu[1], Mingwei Li[1], Sowmya Chollate[1], Melanie S. Brennan[1], Omar Quintero-Monzon[1], Robert H. Scannevin[1], H. Moore Arnold[1], Thomas Engber[1], Kenneth Rhodes[1], James Ferrero[1], Yaming Hang[1], Alvydas Mikulskis[1], Jan Grimm[2], Christoph Hock[2,4], Roger M. Nitsch[2,4]§ & Alfred Sandrock[1]§

NATURE | VOL 537 | 1 SEPTEMBER 2016



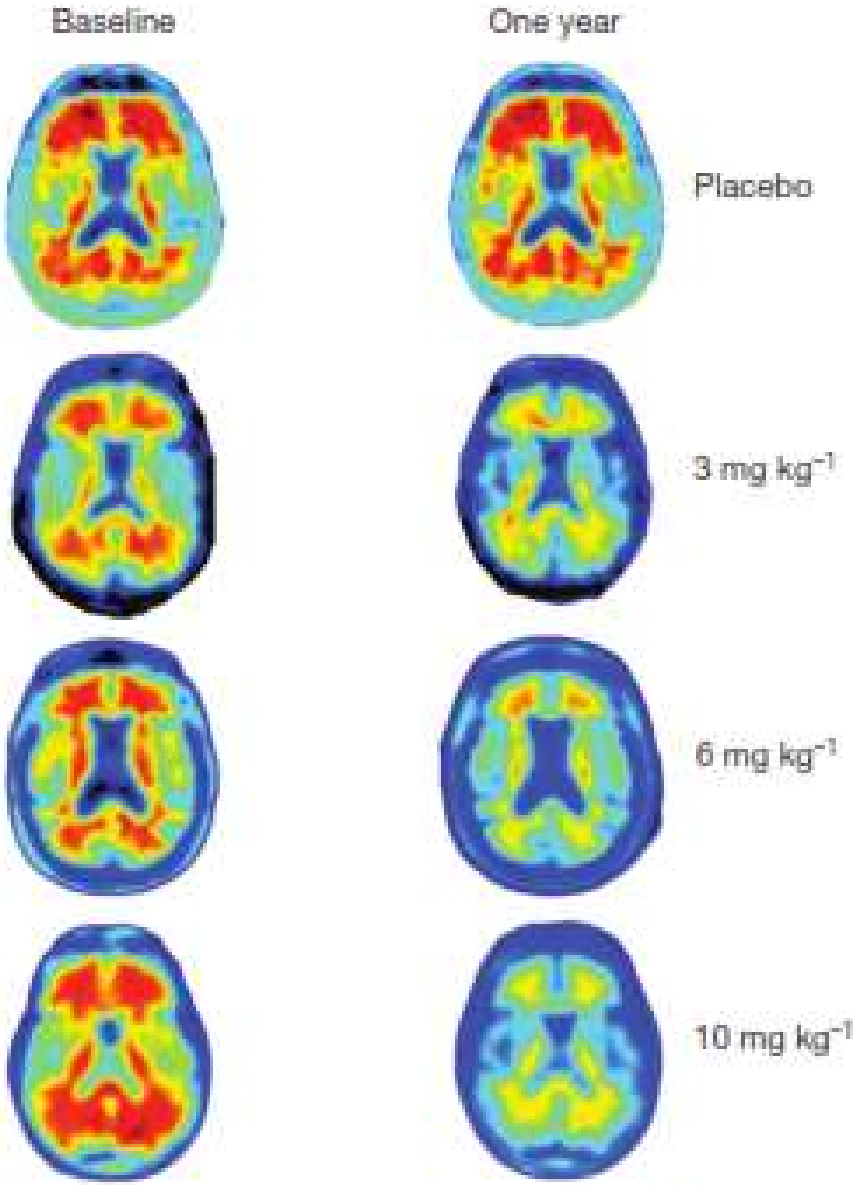


Figure 1 | Amyloid plaque reduction with aducanumab: example amyloid PET images at baseline and week 54. Individuals were chosen based on visual impression and SUVR change relative to average one-year response for each treatment group ($n = 40$, 32, 30 and 32, respectively). Axial slice shows anatomical regions in posterior brain putatively related to AD pathology. SUVR, standard uptake value ratio.

PHARMASTAR
il Giornale on-line sui Farmaci

Alzheimer, tonfo in borsa per Biogen per ridefinizione studio su aducanumab

Giovedi 15 Febbraio 2018 *Redazione*

L'azienda ha deciso di aggiungere 510 pazienti ai suoi due studi fondamentali per aducanumab al fine di contrastare la variabilità dei risultati osservata nei primi pazienti nel raggiungimento dell'end point primario del trial.

L'azienda si aspetta di completare l'arruolamento entro l'estate e poiché lo studio dura 18 mesi i risultati finali per la fine del 2019 e inizio del 2020.

PUBBLICATO IL 08-06-2021

FDA approva il primo farmaco della storia per l'Alzheimer. Rallenterebbe il declino cognitivo se somministrato nelle fasi precoci. Ma il condizionale, visti i trial clinici contrastanti, è d'obbligo

Fondazione Umberto Veronesi –per il progresso delle scienze

Un passo storico che però non rappresenta affatto la soluzione all'Alzheimer: approvato contro il volere del comitato indipendente dell'FDA, i trial clinici su cui si è basata l'immissione in commercio non hanno portato a risultati chiari sul ***reale beneficio*** *di aducanumab.*

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

AUGUST 26, 2021

Revisiting FDA Approval of Aducanumab

G. Caleb Alexander, M.D., David S. Knopman, M.D., Scott S. Emerson, M.D., Ph.D., Bruce Ovbiagele, M.D., Richard J. Kryscio, Ph.D., Joel S. Perlmutter, M.D., and Aaron S. Kesselheim, M.D., J.D.

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

An Appropriate Use of Accelerated Approval — Aducanumab for Alzheimer's Disease

Billy Dunn, M.D.
Peter Stein, M.D.
Robert Temple, M.D.
Patrizia Cavazzoni, M.D.
U.S. Food and Drug Administration
Silver Spring, MD

This letter was published on July 28, 2021, at NEJM.org

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 December 2021
EMA/750220/2021
EMEA/H/C/005558

Refusal of the marketing authorisation for Aduhelm (aducanumab)

What were the main reasons for refusing the marketing authorisation?

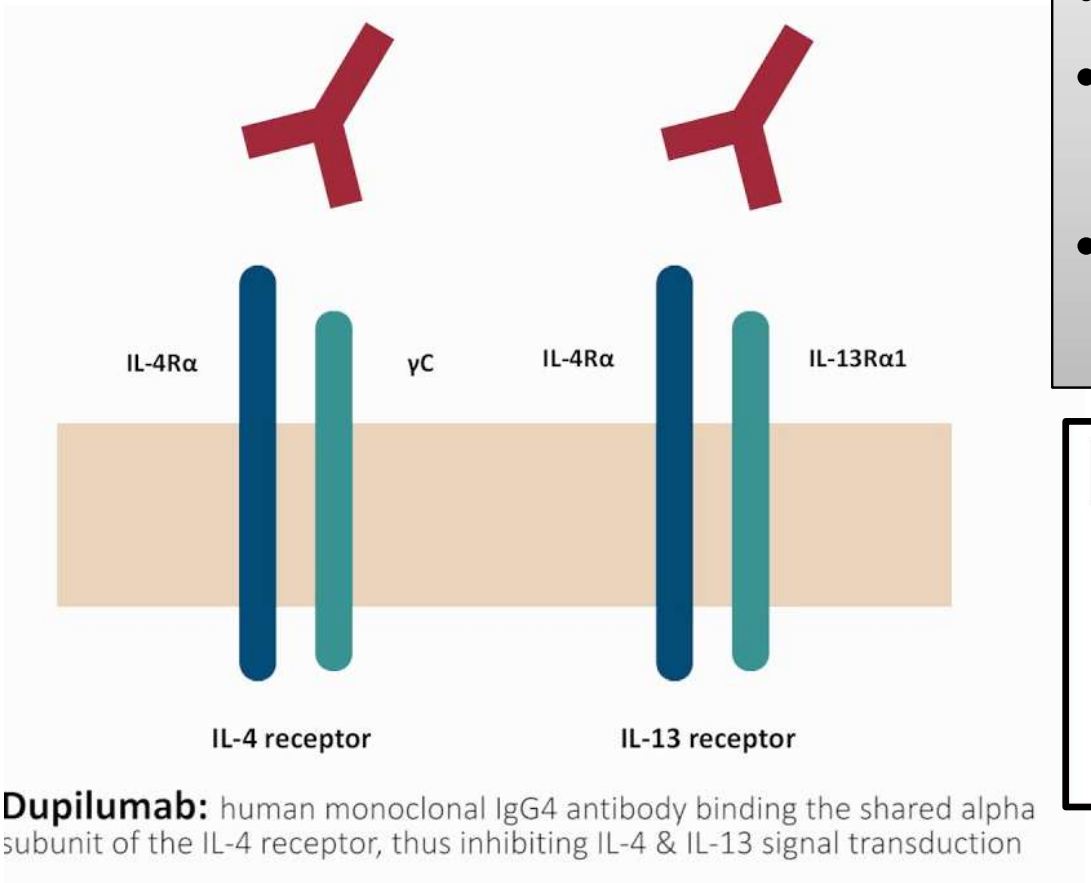
The European Medicines Agency noted that although Aduhelm reduces amyloid beta in the brain, the link between this effect and clinical improvement had not been established. Results from the main studies were conflicting and did not show overall that Aduhelm was effective at treating adults with early stage Alzheimer's disease.

In addition, the studies did not show that the medicine was sufficiently safe as images from brain scans of some patients showed abnormalities suggestive of swelling or bleeding, which could potentially cause harm. Furthermore, it is not clear that the abnormalities can be properly monitored and managed in clinical practice.

Therefore, the Agency's opinion was that the benefits of Aduhelm did not outweigh its risks and it recommended refusing marketing authorisation.

Target: subunità α dell'interleuchina(IL)-4.

Dupilumab: inibisce la trasmissione del segnale di IL-4/IL-13



Dupilumab: human monoclonal IgG4 antibody binding the shared alpha subunit of the IL-4 receptor, thus inhibiting IL-4 & IL-13 signal transduction

Approvato per:

- trattamento dermatite atopica;
- asma grave con infiammazione di tipo 2;
- rinosinusite cronica con poliposi nasale.

ORIGINAL ARTICLE

Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma

M. Castro, J. Corren, I.D. Pavord, J. Maspero, S. Wenzel, K.F. Rabe, W.W. Busse, L. Ford, L. Sher, J.M. FitzGerald, C. Katelaris, Y. Tohda, B. Zhang, H. Staudinger, G. Pirozzi, N. Amin, M. Ruddy, B. Akinlade, A. Khan, J. Chao, R. Martincova, N.M.H. Graham, J.D. Hamilton, B.N. Swanson, N. Stahl, G.D. Yancopoulos, and A. Teper

N ENGL J MED 378;26 NEJM.ORG JUNE 28, 2018

Agenti Stimolanti l'Eritropoiesi (ESA)

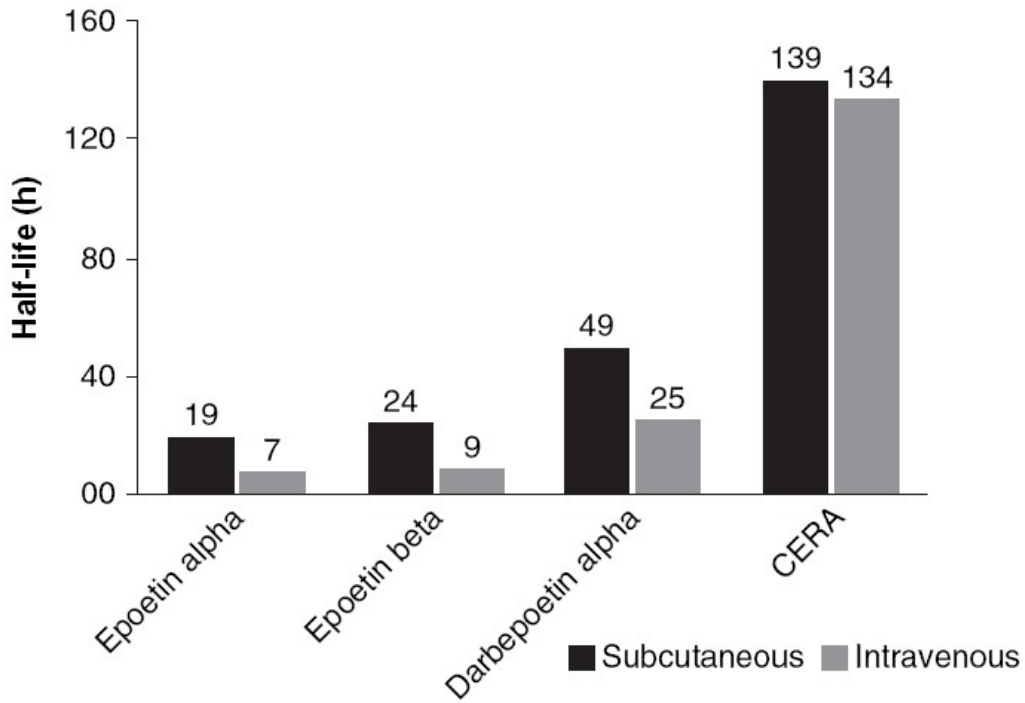
Proc. Natl. Acad. Sci. USA
Vol. 82, pp. 7580–7584, November 1985
Biochemistry

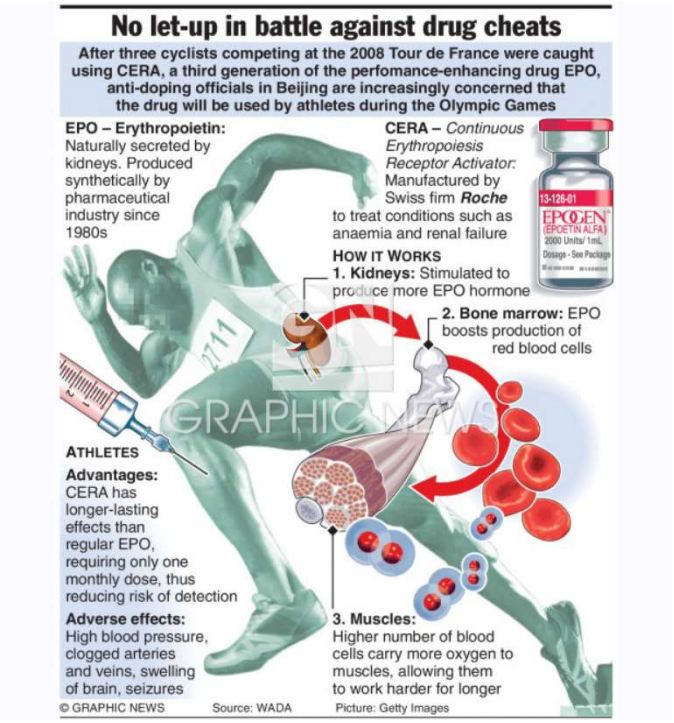
Cloning and expression of the human erythropoietin gene

(erythropoietic factor/glycoprotein hormone/mixed oligonucleotide probes/genomic screening)

FU-KUEN LIN*, SIDNEY SUGGS*, CHI-HWEI LIN*, JEFFREY K. BROWNE*, RALPH SMALLING*, JOAN C. EGRIE*, KENNETH K. CHEN*, GARY M. FOX*, FRANK MARTIN*, ZIPPORA STABINSKY*, SAYED M. BADRAWI*, POR-HSIUNG LAI*, AND EUGENE GOLDWASSER†

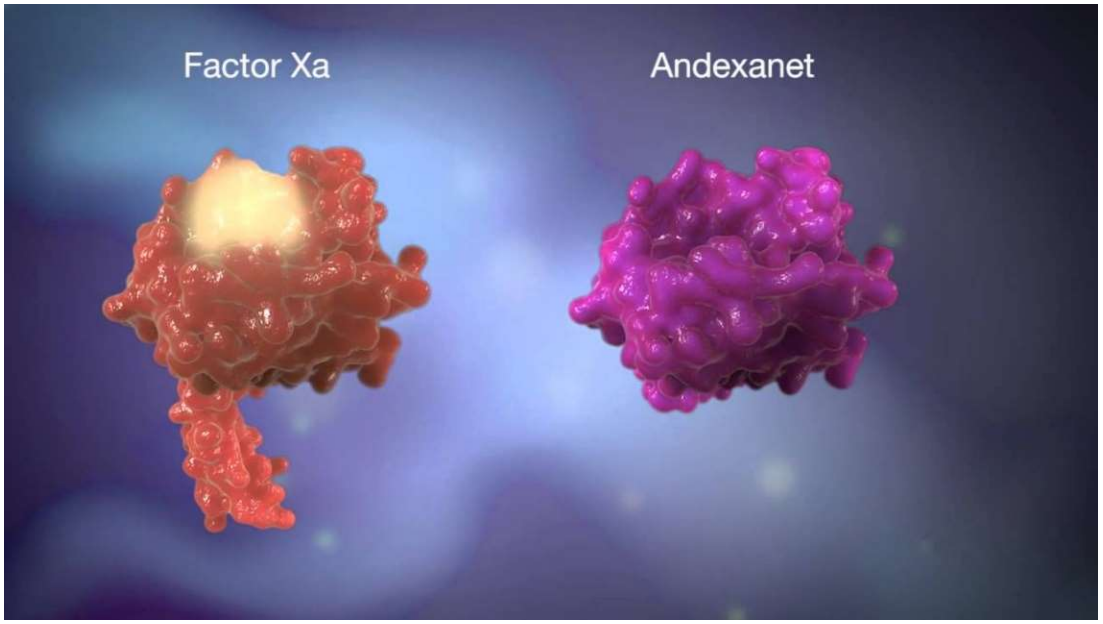
- Eritropoietina Alfa: breve durata d'azione somministrabile s.c. o e.v.
- Eritropoietina Beta: breve durata d'azione, somministrabile s.c. o e.v.
- Eritropoietina Teta: breve durata d'azione, somministrabile s.c. o e.v. solo ospedaliera
- Darbepoietina: intermedia durata d'azione; somministrabile s.c. o e.v.
- Eritropoietina beta–Pegilata (CERA *Continuous Erytropoiethin Receptors Activator*): lunga durata; somministrabile s.c. o e.v.





Andexanet alfa

- Derivato ricombinante modificato del FXa. Mutazione nella regione catalitica (manca azione pro-coagulante). Maggiore affinità del FXa nativo. Coda modificata previene interazione altri fattori coagulazione.



Rivaroxaban
Apixaban
Edoxaban
LMWH
Fondaparinux

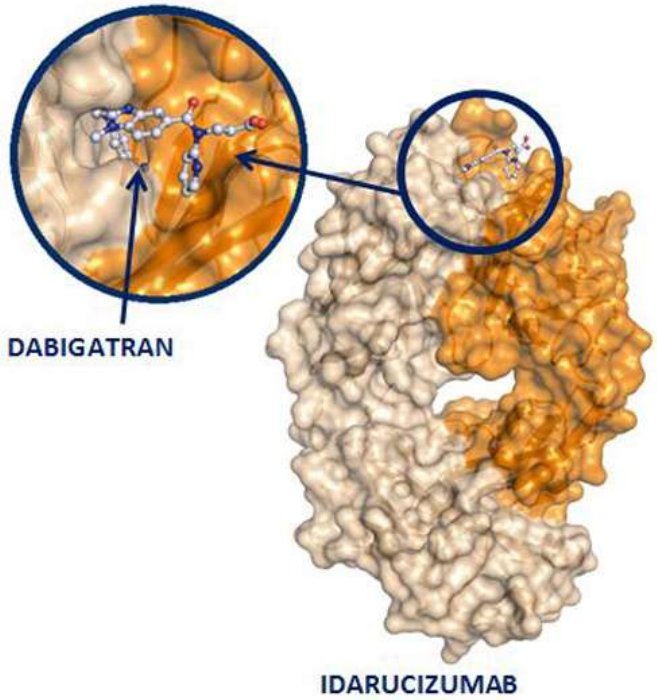
400 mg, IV, Bolus (30mg/min)
400 mg, IV, Bolus (30mg/min) the Infusion 4mg/min for 120min (480mg total)

Idarucizumab

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal



Anticorpo monoclonale (Fab o Humanized Antibody Fragment) disegnato come antidoto del Dabigatran Etexilato.
Approvato EMEA.

Patients received **5 g of intravenous idarucizumab**, which was administered as two 50-ml bolus infusions, each containing 2.5 g of idarucizumab, no more than 15 minutes apart. The 5-g dose was calculated to reverse the total body load of dabigatran that was associated with the 99th percentile of the dabigatran levels measured in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial.