Antikörpertherapie

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Endokrinologie /// Diabetologie /// Innere Medizin

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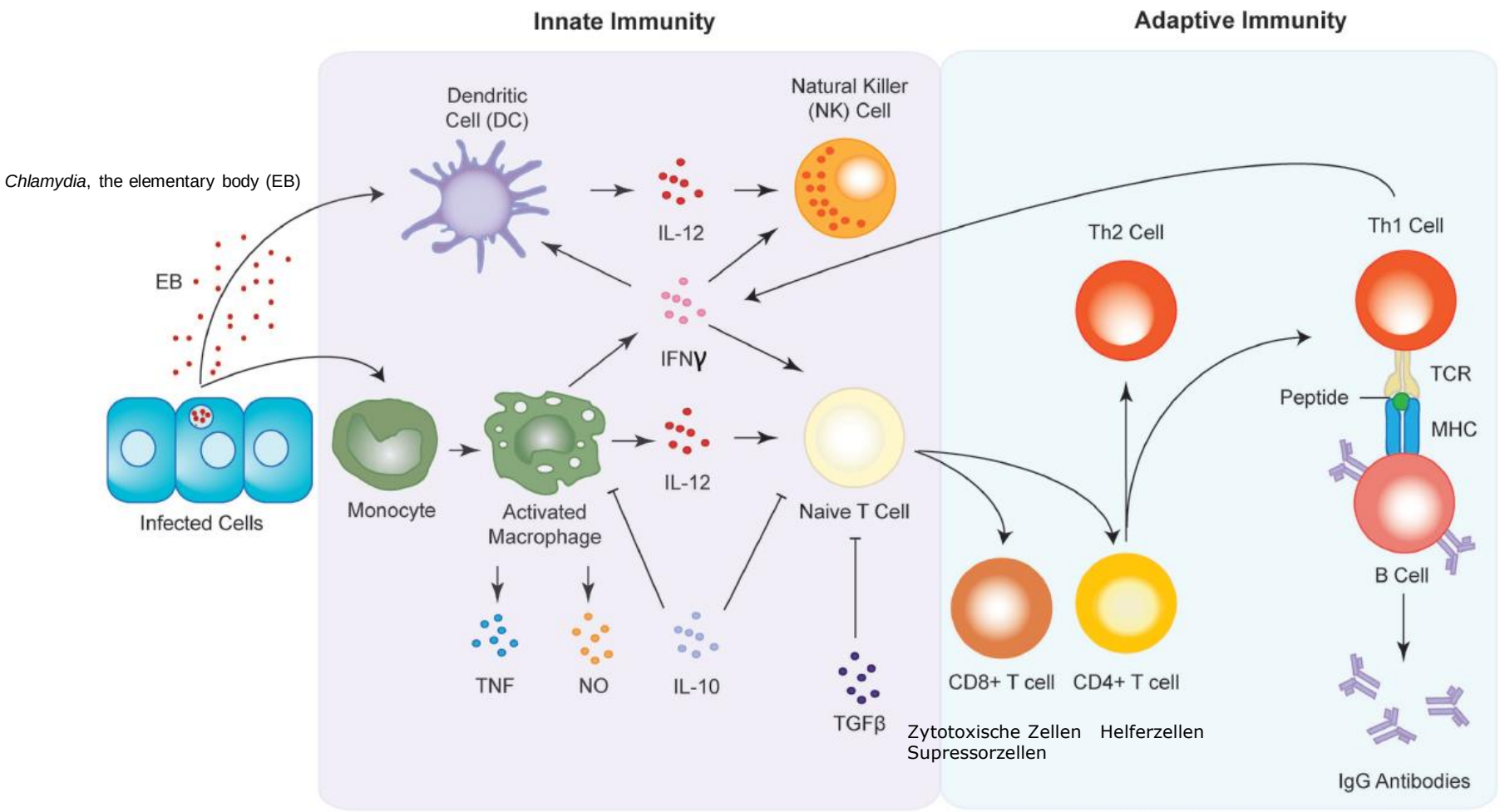
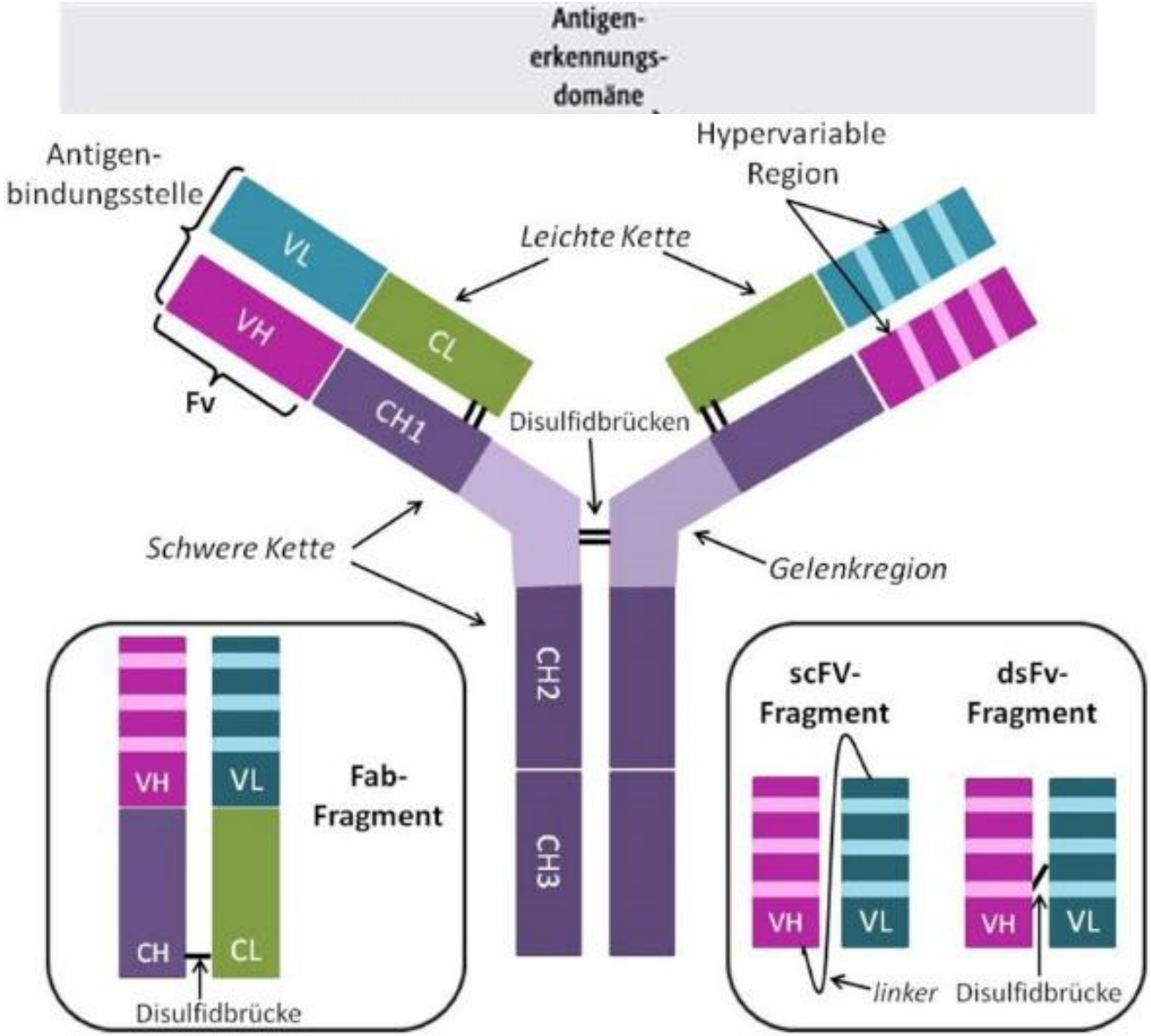
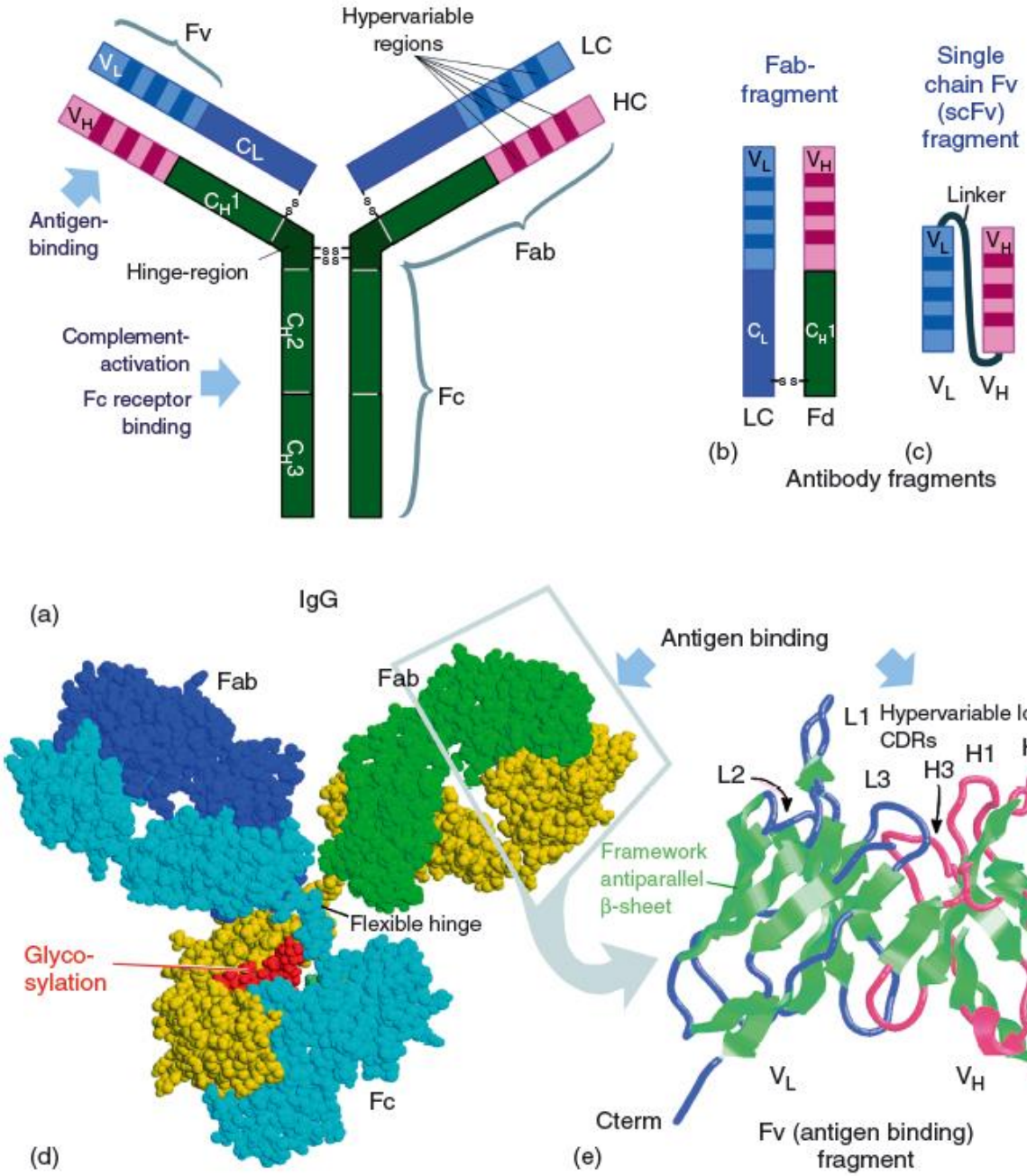
Immun-Antwort



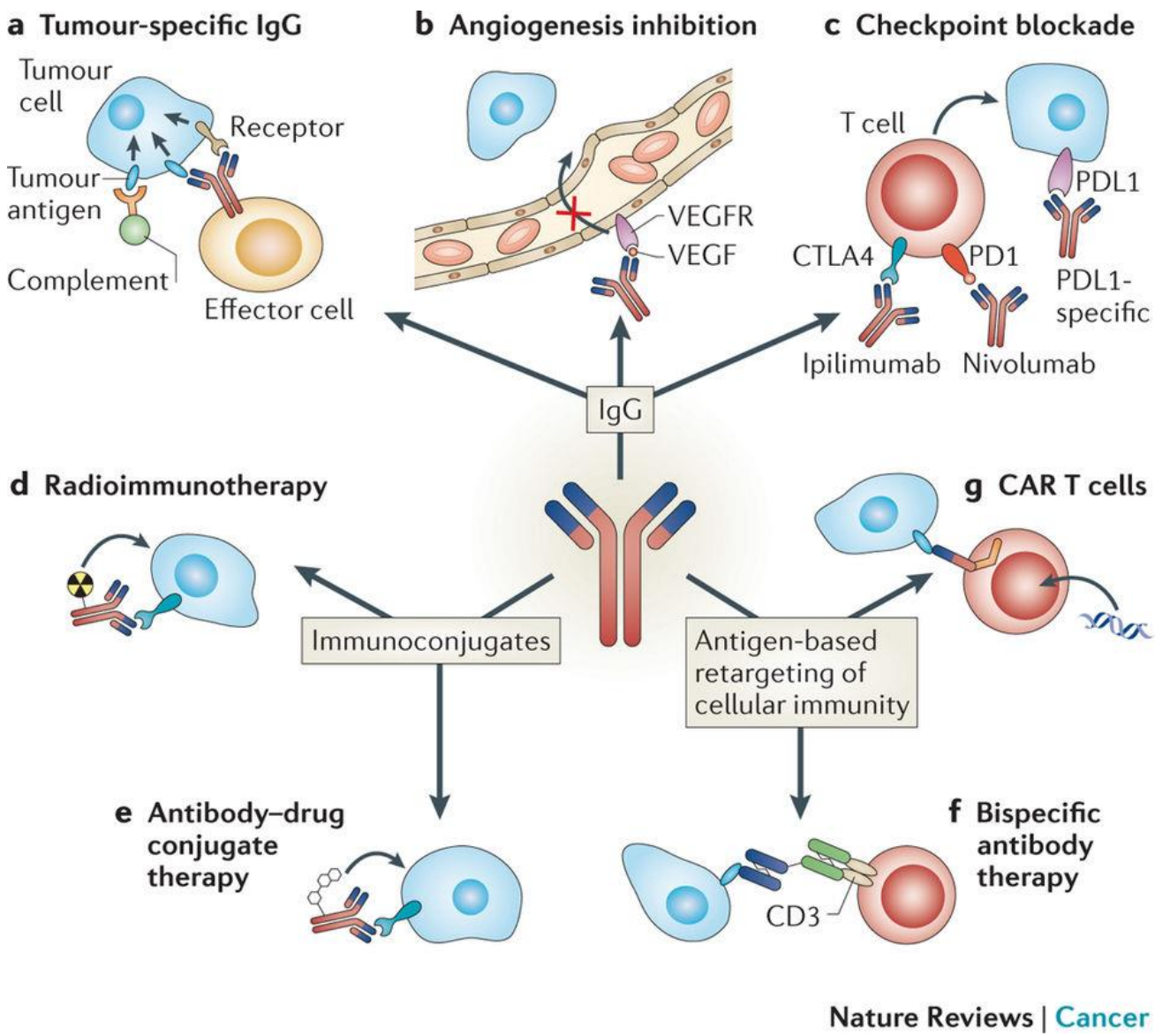
Innate and adaptive immune responses to Chlamydia infection. Upon infection, antigen presenting cells (APC) such as macrophages and dendritic cells are sequestered to the site of infection where they begin to release pro-inflammatory cytokines such as IFNγ and IL-12. The chemokines in turn activate natural killer (NK) cells and induce the maturation of T cells into either CD8+ or CD4+ T cells. CD4+ T cells go on to form either T-helper 1 (Th1) or T-helper 2 type (Th2) T cells. Th1 cell interact with B cells via the T cell receptor (TCR) and the major histocompatibility complex (MHC) to produce antibodies against the chlamydial infection.



Schematische Darstellung eines IgG-Antikörpers: Die Bindung eines Antikörpers an sein Antigen erfolgt nur über die sehr variablen complementarity determining regions (CDR) innerhalb der variablen Region. Zwischen diesen Bereichen befinden sich strukturgebende Proteinregionen, die als framework regions (FR) bezeichnet werden. Auch ein Teilstück des Antikörpers, das Fab-Fragment, ist in der Lage, ein Antigen spezifisch zu binden. Für eine Interaktion der Antikörper mit Zellen des Immunsystems oder mit Proteinen des Komplementsystems sorgt der jeweilige konstante Teil (Fc) des Antikörpers.


Fv
Hypervariable regions
LC
HC
V_L
V_H
C_L
C_H1
Antigen-binding
Hinge-region
Fab
C_H2
C_H3
Complement-activation
Fc receptor binding
Fc
(a)
Fab-fragment
Single chain Fv (scFv) fragment
Linker
LC
Fd
(b)
(c)
Antibody fragments
IgG
Fab
Fab
Flexible hinge
Glyco-sylation
Fc
(d)
Antigen binding
L1
Hypervariable loops
CDRs
H1
H2
L2
L3
H3
Framework antiparallel β-sheet
Cterm
Cterm
Fv (antigen binding) fragment
(e)

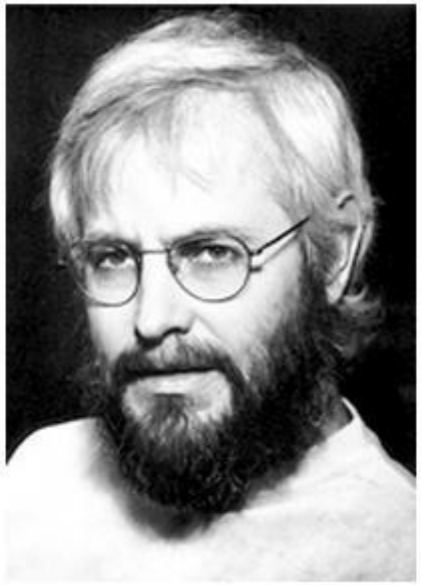
Möglichkeiten der Antikörpertherapie



Herstellung monoklonaler Antikörper

1975 [1]

Niels K. Jerne

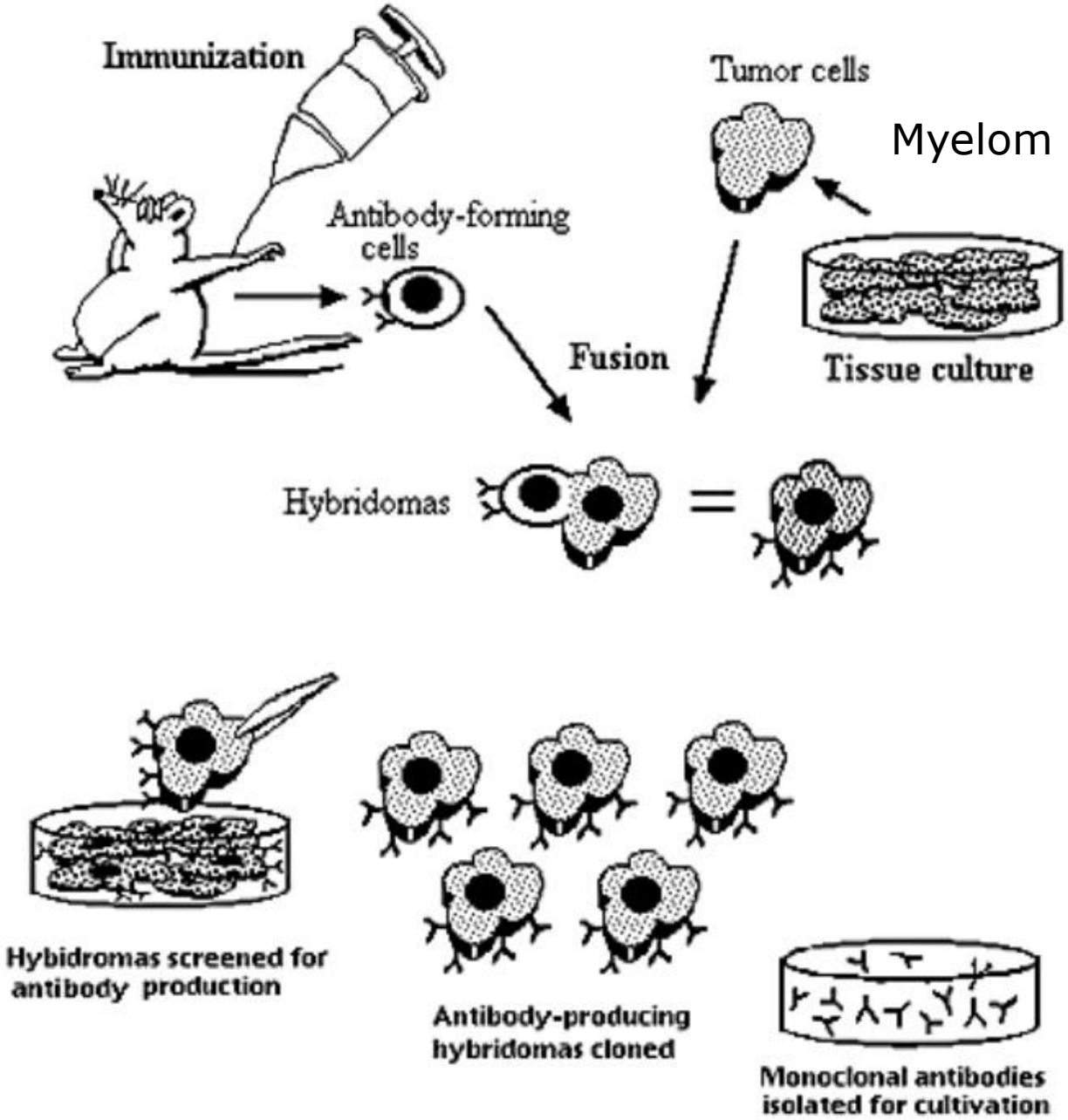


Georges J.F. Köhler

César Milstein

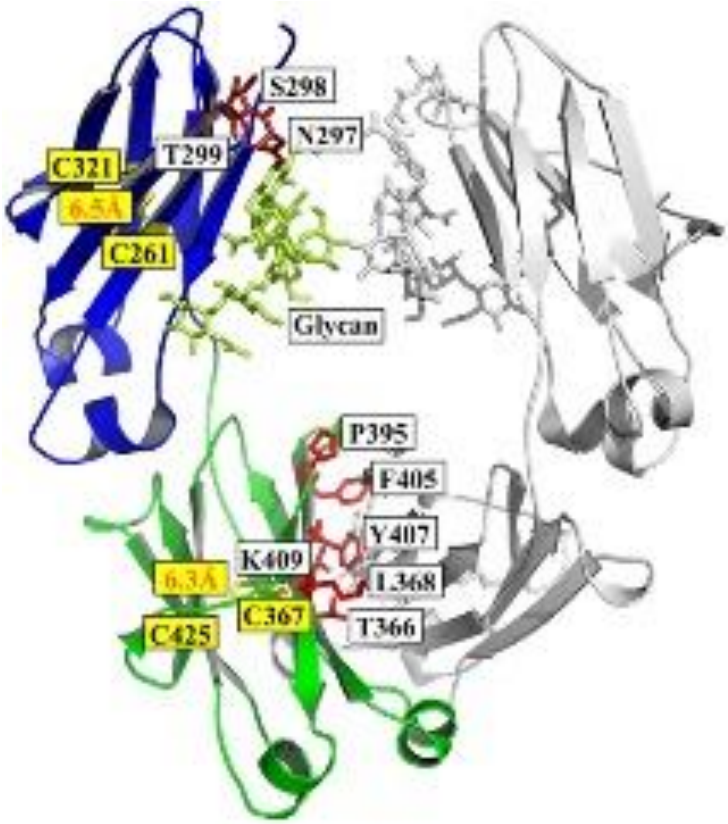
Nobel-Preis für Physiologie und Medizin 1984

(1) G. Köhler, C. Milstein: *Continuous cultures of fused cells secreting antibody of predefined specificity.* In: *Nature.* Bd. 256, 1975, S. 495–497.



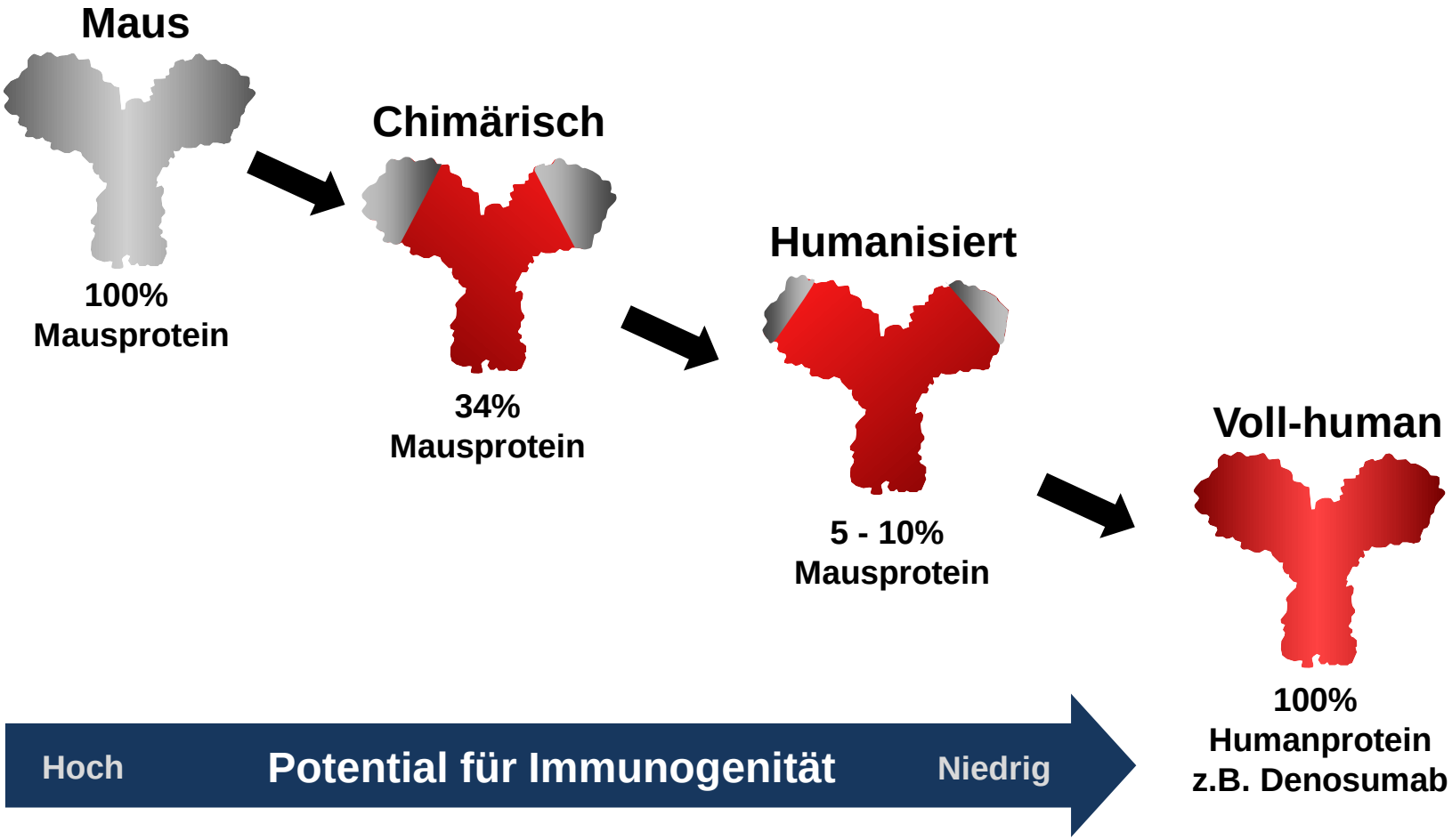
Monoclonal Antibody Production

Der erste therapeutische monoklonale Antikörper wurde im Jahr 1986 zugelassen. Muromonab-CD-23(Orthoclone OKT3®) ....

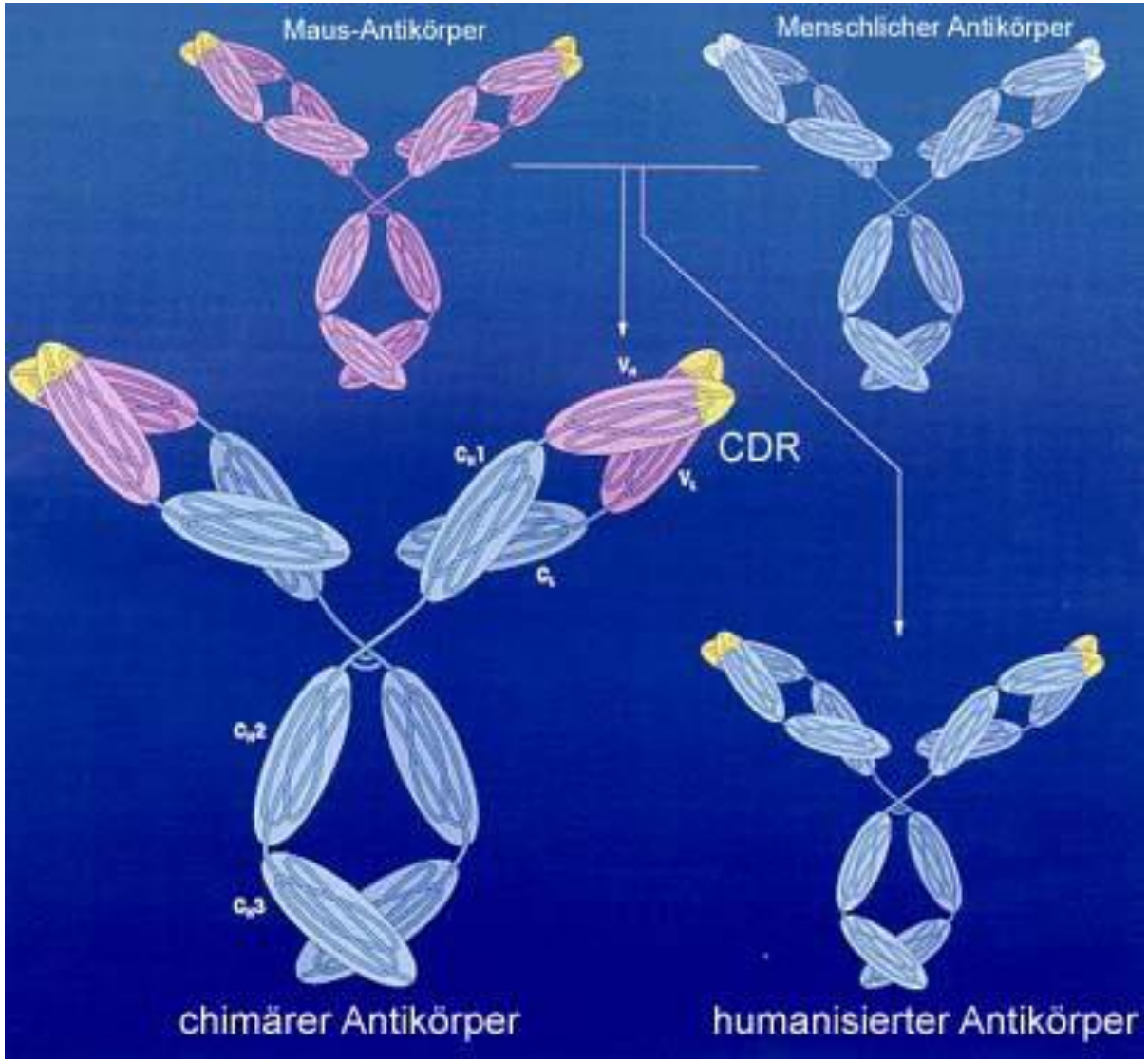


... bindet an den CD3-Rezeptor auf T-Zellen und wurde in der Transplantationsmedizin verwendet.

Die Entwicklung therapeutischer Antikörper



Lonberg N. *Nat Biotechnol*. 2005;23:1117-1125.
Ternant D, et al. *Expert Opin Biol Ther*. 2005;5(Suppl 1):S37-S47.
Yang X-D, et al. *Crit Rev Oncol Hematol*. 2001;38:17-23.
Weiner LM. *J Immunother*. 2006;29:1-9.



Um diese Nachteile zu vermeiden, werden mit gentechnischen Methoden große Bereiche der Maus-Antikörper, die sogenannten konstanten Regionen, durch entsprechende Fragmente humaner Antikörper ausgetauscht. Die konstanten Regionen spielen für die Spezifität der Antikörper praktisch keine Rolle. Je nach Gehalt an menschlichen Aminosäuresequenzen spricht man dann von chimärisierten oder humanisierten Antikörpern (siehe Abb.).

Die Herkunft ist am Suffix erkennbar (allgemein: -mab):

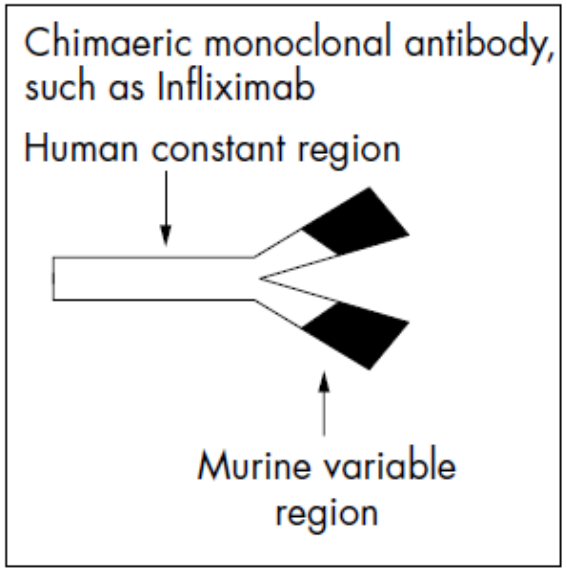
- **-ximab: chimäre Antikörper (murine und humane Komponenten, etwa 75% human), 1. Vertreter Abciximab (RheoPro®: Glyk. IIb/IIIa-AK: Rheologicum bei akuter kardialer Ischämie)**

- **-zumab: humanisierte Antikörper (85% human), 1. Vertreter Daclizumab (Zinbryta®: Interleukin-2-Rezep.-AK, bei akute Abstoßung nach NTX und MS, hepatotoxisch 2016 vom Markt weltweit)**

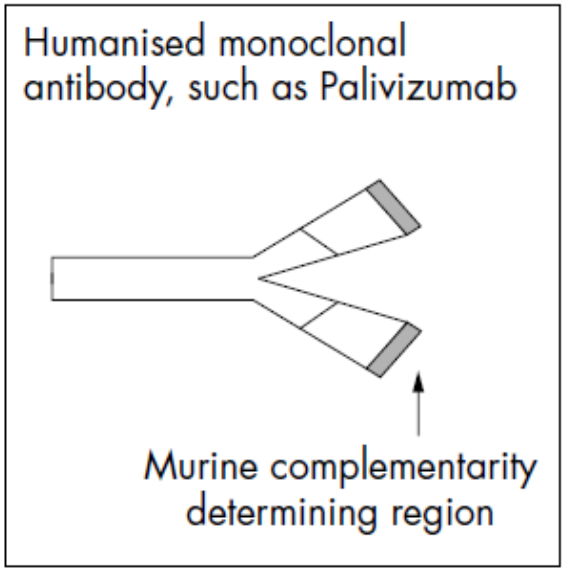
- **-umab: humane Antikörper (100% human), 1. Vertreter Adalimumab (Humira® und Amgevita ®: TNF-alpha-Ak; RA, Psoriasis-Arthritis, Spondylarthritis; Morbus Crohn, Colitis ulzerosa)**

4 Typen der monoklonalen Antikörper

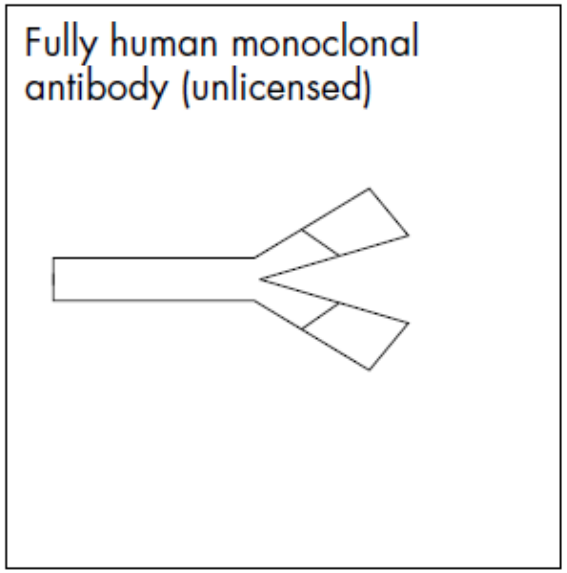
Chimaeric



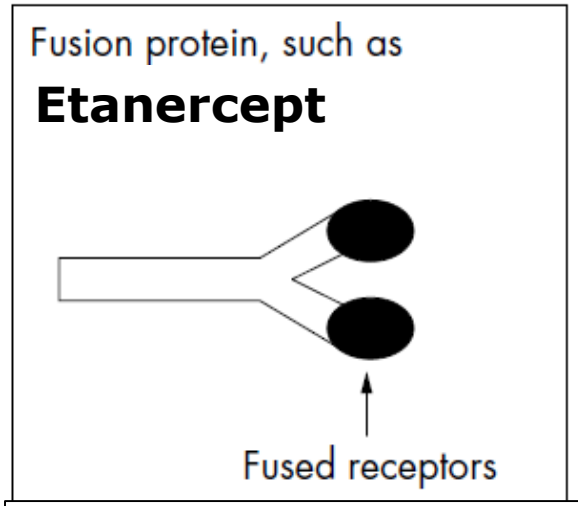
Humanised



Fully human



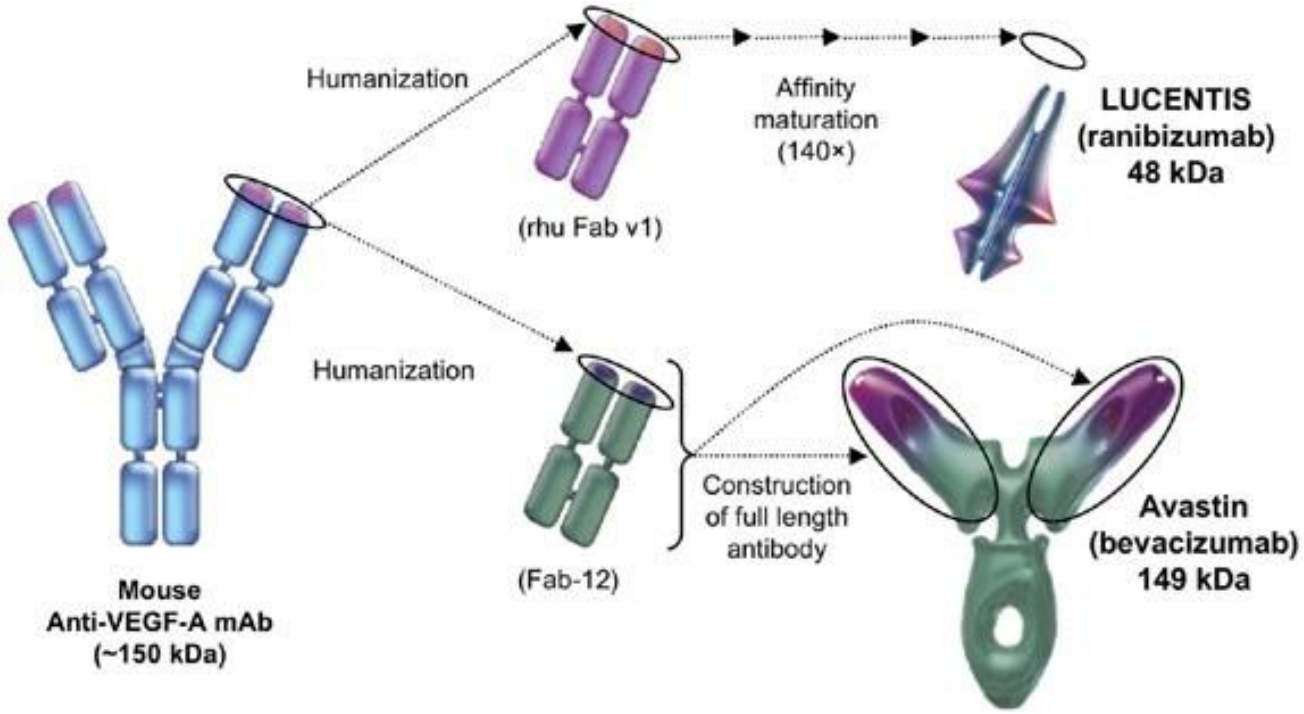
Fusion protein



Ligandenbindungsdomäne des humen TNF-alpha-Rezep.-2

J Clin Pathol 2002;**55**:81–85

Es wurden auch **Antikörperfragmente** entwickelt, die **nur aus** dem antigenbindenden **Fab-Fragment bestehen**. Ein solcher Wirkstoff ist beispielsweise Ranibizumab (Lucentis®). Die Fragmente verteilen sich **besser**, weil sie **kleiner** sind. Sie interagieren zudem weniger mit dem Immunsystem, weil das Fc-Fragment fehlt.



Name	Handelsname	Typ	Zielstruktur	Anwendungsgebiet
Hämatologie, Onkologie				
Alemtuzumab5	MabCampath	humanisiert	CD52-Antigen auf Lymphozyten	Chronische lymphatische Leukämie, T-Zell-Lymphome[2], akute lymphatische Leukämie[2]
Apolizumab1,2	Remitogen	humanisiert	HLA-DR-Antigen auf B-Lymphozyten	Solide Tumoren, akute lymphatische Leukämie, chronische lymphatische Leukämie, Non-Hodgkin-Lymphome
Atezolizumab (MPDL3280A)[1,2]	Tecentriq (Roche)	humanisiert	PD-L1	Blasenkrebs (zugelassen in USA)[3] In EU positive CHMP Empfehlung.[4]
Avelumab (MSB0010718C)[2]	Bavencio (Merck / Pfizer)	human	PD-L1	Blasenkrebs, Nichtkleinzelliges Bronchialkarzinom (NSCLC)[5], Merkelzellkarzinom[6]
Bevacizumab	**Avastin** (Roche)	humanisiert	VEGF (Vascular Endothelial Growth Factor)	Darmkrebs, Brustkrebs, nichtkleinzelliges Bronchialkarzinom, feuchte, altersbedingte Makuladegeneration (Off-Label-Use)[2]
Blinatumomab	**Blincyto** (Amgen)	murin, bispezifisch	CD-19	ALL
Catumaxomab	Removab (Neovii Biotech)	murin (Ratte/Maus), trifunktional	EpCAM-Antigen auf Tumorzellen, CD3-Rezeptor auf T-Lymphozyten	maligner Aszites aufgrund von EpCAM-positiven Karzinomen
Cemiplimab1,2 (REGN2810)	N.N., (Sanofi / Regeneron)	vom Primaten	PD-1	Plattenepithelkarzinom[7]
Cetuximab	Erbitux (BMS / Merck)	chimär	EGF-Rezeptor (Epidermal Growth Factor Receptor)	Darmkrebs, Kopf- und Halstumoren
Daratumumab1,2	Darzalex (Genmab / Janssen Biotech)	human	CD38	Multiples Myelom, in den USA und der EU bereits zugelassen[8][9]

Autoimmunerkrankungen, Transplantatabstoßung, Schmerz

Adalimumab	**Humira**	human	TNF-α (Tumor Necrosis Factor α)	Rheumatoide Arthritis, Psoriasis-Arthritis, Morbus Bechterew, Morbus Crohn
Alemtuzumab5	Lemtrada	humanisiert	CD52-Antigen auf Lymphozyten	Multiple Sklerose
Anifrolumab1,2 (MEDI-546)	N.N.	human	anti-type-I IFN	Lupus erythematodes
Basiliximab	Simulect	chimär	CD25-Antigen (Interleukin-2-Rezeptor)	Prophylaxe der akuten Abstoßungsreaktion bei Nierentransplantation
Belimumab	Benlysta	human	BLys (B-Lymphozyten-Stimulator, ein Zytokin der TNF-Superfamilie)	Lupus erythematodes
Brodalumab1,2	N.N. (AstraZeneca)	human	Interleukin-17-Rezeptor	Psoriasis, Psoriasis-Arthritis, Asthma
Canakinumab	Ilaris	human	Interleukin-1-beta-Rezeptor	Periodische Fiebersyndrome (CAPS, TRAPS, HIDS/MKD, FMF), Systemische juvenile idiopathische Arthritis (SJIA), Gichtarthritis
Certolizumab	Cimzia	humanisiert	TNF-α (Tumor Necrosis Factor α)	Rheumatoide Arthritis, Morbus Crohn
Clazakizumab1,2	N.N. (BMS)	humanisiert	Interleukin-6-Rezeptor	Rheumatoide Arthritis
Daclizumab	Zenapax (a.H.); Zinbryta (a.H.)	humanisiert	CD25-Antigen (Interleukin-2-Rezeptor)	Multiple Sklerose, aber aus dem Handel (a.H.) genommen[14]
Epratuzumab1,2	LymphoCide	humanisiert	CD22-Antigen	Autoimmunerkrankungen, Non-Hodgkin-Lymphome,
Fasinumab1,2	N.N. (Regeneron)	human	Nerve Growth Factor (NGF)	Schmerz bei Osteoarthritis
Guselkumab1,2	Tremfya (Janssen)	human	Anti-Interleukin-23	Psoriasis, Rheumatoide Arthritis
Golimumab	Simponi	human	TNF-α (Tumor Necrosis Factor α)	Colitis ulcerosa, Rheumatoide Arthritis, Psoriasis-Arthritis, Morbus Bechterew
Infliximab	**Remicade**	chimär	TNF-α (Tumor Necrosis Factor α)	Morbus Crohn, Rheumatoide Arthritis, Morbus Bechterew, Psoriasis-Arthritis, Colitis ulcerosa
Ixekizumab	Taltz	humanisiert	Interleukin-17A-Rezeptor (IL-17A)	Psoriasis, Psoriasis-Arthritis
Mavrilimumab (CAM-3001)1,2	N.N. (AstraZeneca)	human		Rheumatoide Arthritis
Muromonab-CD3	Orthoclon OKT3	murin	CD3-Rezeptor auf T-Lymphozyten	Behandlung der akuten Abstoßungsreaktion bei Nieren-, Herz- und Lebertransplantationen
Natalizumab3	Tysabri	humanisiert	CD49d (α4-Integrin)	Multiple Sklerose
Risankizumab1,2	N.N. (AbbVie)	humanisiert	Interleukin-23-Rezeptor	Psoriasis, Psoriasis-Arthritis, Morbus Crohn
Rituximab	MabThera	chimär	CD20-Antigen auf B-Lymphozyten	Rheumatoide Arthritis
Sarilumab	Kevzara	human	Interleukin-6 Rezeptor (IL-6R)	Rheumatoide Arthritis
Secukinumab	Cosentyx (Novartis)	human	Interleukin-17A-Rezeptor	Psoriasis, Psoriasis-Arthritis, Morbus Bechterew

Hypercholesterinämie				
Alirocumab	Praluent (Sanofi)	human	PCSK9 (darüber indirekt: LDL Rezeptor)	Hypercholesterinämie (Prävention kardiovaskulärer Ereignisse einschl. Schlaganfall)
Evinacumab (REGN1500)[1,2]	NN (Regeneron / Sanofi)	human	PCSK9	Homozygote familiäre Hypercholesterinämie
Evolocumab (AMG-145)	Repatha (Amgen)	human	PCSK9 (darüber indirekt: LDL Rezeptor)	Hypercholesterinämie (Prävention kardiovaskulärer Ereignisse einschl. Schlaganfall)
Kardiovaskuläre Erkrankungen				
Abciximab	ReoPro	chimär, Fab-Fragment	GPIIb/IIIa auf Thrombozyten	Verhinderung eines Gefäßverschlusses nach PTCA
Spezielle Therapieformen				
Idarucizumab	Praxbind	humanisiert	Antikörperfragment (Fab), das mit sehr hoher Affinität an Dabigatran bindet.	Antidot zur raschen und spezifischen Aufhebung der durch Dabigatran bedingten Gerinnungshemmung[17]
Infektionskrankheiten				
Bezlotoxumab1,2	Zinplava (MSD)	human	Clostridium difficile Toxin B	Clostridium difficile-Infektion (CDI)[18]
Motavizumab[4][19][20]	Numax	chimär	Bestandteil des Respiratory Syncytial Virus (RSV)	Prophylaxe der RSV (respiratory syncytial virus)-Pneumonie bei Frühgeborenen, ELBW (Extrem Low Birth Weight Preterm) und VLBW (Very Low Birth Weight Preterm)
Palivizumab	Synagis	humanisiert	Bestandteil des Respiratory Syncytial Virus (RSV)	Prophylaxe der RSV-Pneumonie bei Frühgeborenen
Ibalizumab-uiyk	Trogarzo	humanisiert	CD4-T-Zellrezeptor	AIDS
Neurologische Erkrankungen				
Aducanumab1,2	N.N. (Biogen)	human	tbd.	Alzheimer
Eptinezumab	N.N.	humanisiert	Calcitonin Gene-Related Peptide (CGRP)	Migräne[21][22]
Erenumab	Aimovig (Amgen)	human	Calcitonin Gene-Related Peptide (CGRP) receptor	Migräne[23][24][25]

Augenheilkunde				
Ranibizumab	**Lucentis**	humanisiert, Fab-Fragment	VEGF-A (Vascular Endothelial Growth Factor A)	Feuchte Makuladegeneration
Dermatologie				
Adalimumab	**Humira**	human	TNF-α (Tumor Necrosis Factor α)	Psoriasis
Dupilumab	Dupixent (Sanofi)	human	Interleukin 4/13	Atopisches Ekzem[30][31][32][33] Sinusitis
Efalizumab	Raptiva	humanisiert	CD11a-Antigen	Psoriasis
Infliximab	Remicade	chimär	TNF-α (Tumor Necrosis Factor α)	Psoriasis
Nemolizumab1,2	N.N. (Chugai)	humanisiert	Interleukin 31	Atopisches Ekzem
Ustekinumab	**Stelara**	human	Interleukin 12/23	Plaque-Psoriasis
Allergische Erkrankungen				
Benralizumab	Fasenra (AstraZeneca)	humanisiert	Alpha-Untereinheit des IL-5-Rezeptors (IL-5Rα)	Asthma; in COPD bisher zwar geprüft, aber nicht erfolgreich[34]
Mepolizumab	Nucala (GSK)	humanisiert	Interleukin-5	Asthma, COPD, Hypereosinophilie-Syndrom, Eosinophile Granulomatose mit Polyangiitis
Omalizumab	**Xolair**	humanisiert	IgE (Fc-Teil)	Schweres Asthma bronchiale, chronische idiopathische Urtikaria (Nesselsucht)
Reslizumab	Cinqaero (Teva)	humanisiert	Interleukin-5	Asthma
Tralokinumab1,2	N.N. (AstraZeneca / Medimmune)	humanisiert	IL-13	Schweres Asthma bronchiale, Atopisches Ekzem
Zahnheilkunde				
(plantibody)1,2	CaroRx	rekombinant in Pflanzen hergestellt („plantibody“)	spezifische Bindung an Streptococcus mutans (Leitkeim der Zahnkaries)	als Mundspülung gegen Zahnkaries; Beseitigung von S. mutans aus der Mundflora[35]
Osteologie				
Denosumab	**Prolia**, XGEVA	human	RANK Ligand (Rezeptoraktivator des NF-κB Liganden, RANKL)	Osteoporose; Knochenmetastasen
Romosozumab1,2 (AMG 785 / CDP7851)	N.N. (Amgen / UCB)	human	Sclerostin	postmen

Monoclonal antibodies: the new magic bullets for ALLERGY

TARGETS	
GPCRs[a]	**Catalytic receptors**[b]
CCR3	GM-CSF receptor
CXCR2	IL-1 receptor-like 1 (ST2)
NPSR1	IL-4 α receptor
Enzymes[c]	IL-9 receptor
ADAM33	IL-13 α 1 receptor
Carboxypeptidase A3	IL-17A receptor
	IL-31 β receptor
	TSLP receptor

LIGANDS		
Benralizumab	IL-12	Lebrikizumab
Brodalumab	IL-13	Mepolizumab
Dupilumab	IL-17A	Nitric oxide (NO)
Eotaxin (CCL11)	IL-17F	Omalizumab
GM-CSF	IL-22	Pascolizumab
IL-1β	IL-23	Reslizumab
IL-4	IL-25	Secukinumab
IL-5	IL-31	TSLP
IL-9	IL-33	Ustekinumab

British Journal of Pharmacology (2016) 173 793–803

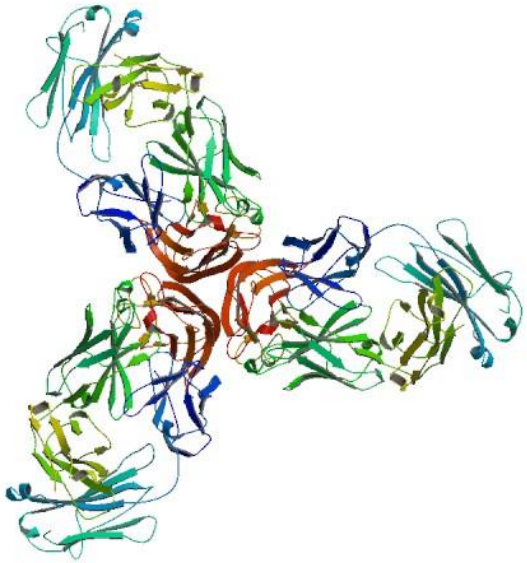
Name of the mAb	Trade name/company	Target of the mAb	Status/Effective	Indicaton
Omalizumab	Xolair (Genetech/Novartis)	IgE (Cε3 domain)	Commercially available	severe, persistent allergic asthma* chronic idiopathic urticaria§
QGE031 (ligelizumab)	Tanox/Novartis	IgE (Cε3 domain)	Phase II	allergic asthma (NCT01703312)¶ AD (NCT01552629)¶ chronic spontaneous urticaria (NCT02477332)¶
Dupilumab	Regeneron Pharmaceuticals/Sanofi-Aventis	IL-4 α receptor	Phase III	allergic asthma (NCT02414854)¶ AD (NCT02277769)¶
Pascolizumab	GlaxoSmithLKline	IL-4	Phase II	symptomatic steriod-naive asthma (NCT00024544)¶
Tralokinumab	Cambridge Antibody Technology/MedImmune	IL-13	Phase III Phase II	Uncontrolled asthma (NCT02161757)¶ AD (NCT02347176)¶
Lebrikizumab	Tanox/Chugai Pharmaceutical	IL-13	Phase III Phase II	Uncontrolled asthma (NCT01987492)¶ AD (NCT02340234)¶
Mepolizumab	Nucala (GlaxoSmithKline)	IL-5	Phase III terminated	Uncontrolled eosinophilic asthma (Mukherjee et al., 2014) (NCT01691521)¶
Reslizumab	Cinquil (Celltech R& D/Teva Pharmaceutical Industries)	IL-5	Phase III terminated	Uncontrolled eosinophilic asthma (NCT01285323)¶
Benralizumab	Kyowa Hakko/AstraZeneca; BioWa; MedImmune	IL-5 α receptor	Phase III	Eosinophilic asthma (NCT02322775)¶
KB003	KaloBios Pharmaceuticals	GM-CSF	Phase II	Moderate-to-severe asthma (NCT01603277)¶
MEDI-528	Genaera Corporation; Ludwig Institute for Cancer Research/MedImmune	IL-9	Phase II	Uncontrolled asthma (Oh et al., 2013).
Brodalumab	Amgen Inc.; AstraZeneca/MedImmune	IL-17A receptor	Phase II	Moderate-to-severe asthma (Busse et al., 2013) (NCT01199289)¶
AIN457 (secukinumab)	Novartis	IL-17A	Phase II	Uncontrolled asthma (NCT01478360)¶
Ustekinumab	Centocor/Janssen-Cilag	p40 submit of both IL-12/IL-23	Phase II	AD (NCT01806662)¶
ILV-094	Pfizer/Wyeth	IL-22	Phase II	AD (NCT01941537)¶
BMS-981164	Bristol-Myers Squibb; ZymoGenetics	IL-31	Phase I	AD (NCT01614756)¶
AMG282	Amgen	IL-33	Phase I	Mild atopic asthma (NCT01928368)¶
AMG157	Amgen/AstraZeneca	TSLP	Phase II Phase I	Uncontrolled asthma (NCT02054130)¶ AD (NCT0075042)¶

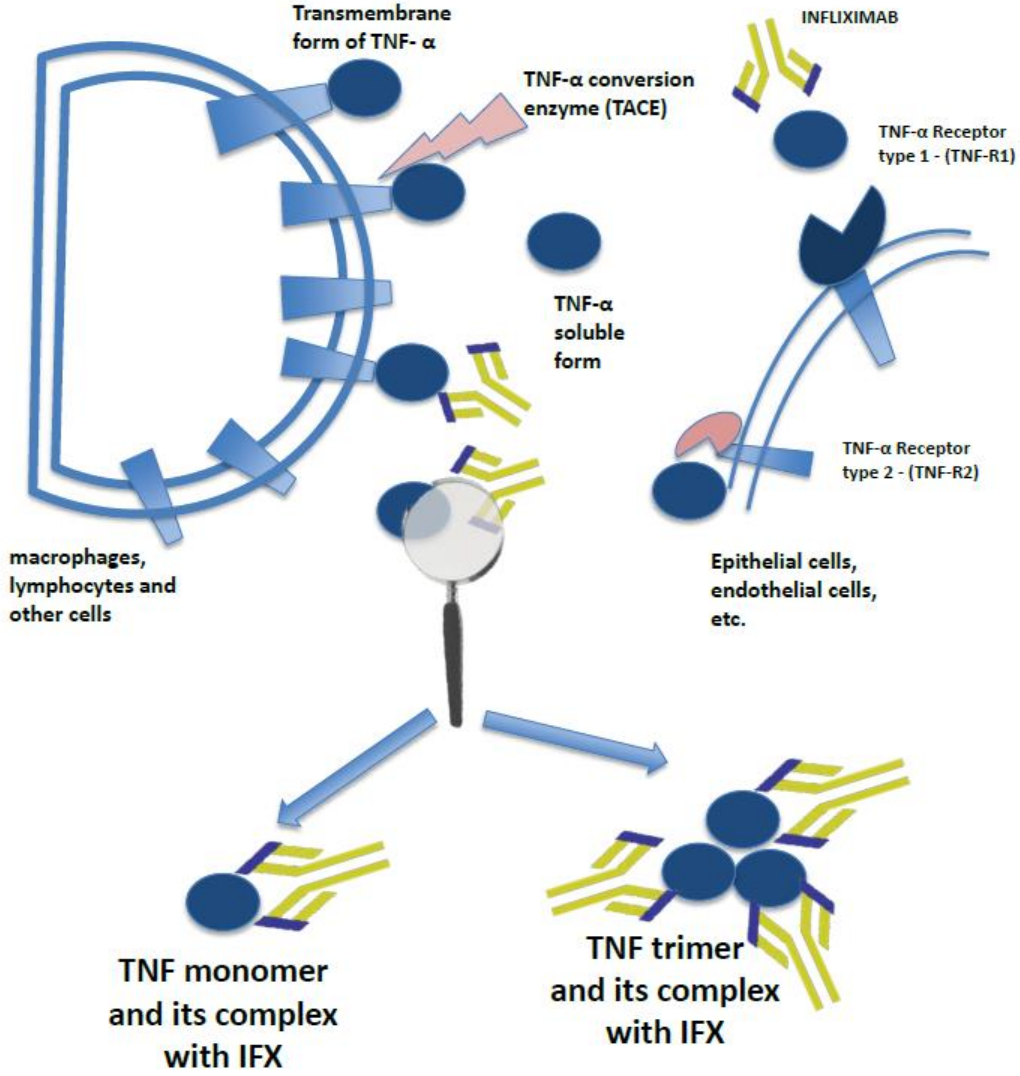
Zugelassene Antikörper 2018

Abciximab (ReoPro®)	Infliximab (Remicade®)
Adalimumab (Humira®)	Ixekizumab (Taltz®)
Alemtuzumab (Lemtrada®)	Lokivetmab (Tierarzneimittel)
Alirocumab (Praluent®)	Mepolizumab (Nucala®)
Atezolizumab (Tecentriq®)	Muromonab-CD3 (Orthoclone OKT® 3)
Avelumab (Bavencio®)	Natalizumab (Tysabri®)
Basiliximab (Simulect®)	Necitumumab (Portrazza®)
Belimumab (Benlysta®)	Nivolumab (Opdivo®)
Benralizumab (Fasenra®)	Obiltoxaximab (Anthim®)
Bevacizumab (Avastin®)	Obinutuzumab (Gazyvaro®)
Bezlotoxumab (Zinplava®)	Ocrelizumab (Ocrevus®)
Bimagrumab	Ofatumumab (Arzerra®)
Blinatumomab (Blincyto®)	Olaratumab (Lartruvo®)
Brentuximab vedotin (Adcetris)	Omalizumab (Xolair®)
Canakinumab (Ilaris®)	Palivizumab (Synagis®)
Certolizumab (Cimzia®)	Panitumumab (Vectibix®)
Cetuximab (Erbitux®)	Pembrolizumab (Keytruda®)
Daclizumab (Zinbryta®)	Pertuzumab (Perjeta®)
Denosumab (Prolia®)	Ramucirumab (Cyramza®)
Dupilumab (Dupixent®)	Ranibizumab (Lucentis®)
Eculizumab (Soliris®)	Reslizumab (Cinqair®)
Efalizumab (Raptiva®)	Rituximab (MabThera®)
Elotuzumab (Empliciti®)	Secukinumab (Cosentyx®)
Evolocumab (Repatha®)	Siltuximab (Sylvant®)
Golimumab (Simponi®)	Tocilizumab (Actemra®)
Guselkumab (Tremfya®)	Trastuzumab (Herceptin®)
Ipilimumab (Yervoy®)	Ustekinumab (Stelara®)
	Vedolizumab (Entyvio®)

NW

Infliximab, the **first anti-TNF-α agent** for IBD, is a **chimeric** monoclonal antibody directed against tumor necrosis factor-α (TNF-α).





Biochem Pharmacol (Los Angel) 2016, 5:2

Infliximab (chimeric) - Morbus Crohn -

Table 4. Summary of Safety and Immunogenicity Analyses for All Patients Who Underwent Randomization.*

Variable	ACT 1 (through Week 54)				ACT 2 (through Week 30)			
	Placebo (N=121)	5 mg of Infliximab (N=121)	10 mg of Infliximab (N=122)	P Value†	Placebo (N=123)	5 mg of Infliximab (N=121)	10 mg of Infliximab (N=120)	P Value†
Mean duration of treatment — wk	24.2	34.8	33.3	ND	14.4	19.3	18.6	ND
Mean duration of follow-up — wk	36.2	44.9	44.2	ND	21.9	27.5	26.6	ND
Any adverse event — no. of patients (%)	103 (85.1)	106 (87.6)	111 (91.0)	0.31	90 (73.2)	99 (81.8)	96 (80.0)	0.11
Adverse events occurring in ≥10% of any treatment group — no. of patients (%)								
Worsening ulcerative colitis	40 (33.1)	23 (19.0)	26 (21.3)		20 (16.3)	11 (9.1)	12 (10.0)	
Abdominal pain	16 (13.2)	11 (9.1)	21 (17.2)		14 (11.4)	10 (8.3)	13 (10.8)	
Nausea	14 (11.6)	14 (11.6)	17 (13.9)		9 (7.3)	6 (5.0)	10 (8.3)	
Upper respiratory tract infection	28 (23.1)	20 (16.5)	29 (23.8)		14 (11.4)	16 (13.2)	14 (11.7)	
Pharyngitis	10 (8.3)	12 (9.9)	14 (11.5)		3 (2.4)	7 (5.8)	9 (7.5)	
Sinusitis	4 (3.3)	8 (6.6)	16 (13.1)		7 (5.7)	11 (9.1)	7 (5.8)	
Pain	19 (15.7)	14 (11.6)	14 (11.5)		11 (8.9)	9 (7.4)	12 (10.0)	
Rash	16 (13.2)	14 (11.6)	7 (5.7)		3 (2.4)	2 (1.7)	5 (4.2)	
Arthralgia	18 (14.9)	21 (17.4)	21 (17.2)		6 (4.9)	16 (13.2)	10 (8.3)	
Headache	27 (22.3)	22 (18.2)	18 (14.8)		18 (14.6)	19 (15.7)	26 (21.7)	
Fever	10 (8.3)	14 (11.6)	12 (9.8)		12 (9.8)	13 (10.7)	9 (7.5)	
Anemia	12 (9.9)	4 (3.3)	9 (7.4)		13 (10.6)	6 (5.0)	2 (1.7)	
Fatigue	11 (9.1)	14 (11.6)	14 (11.5)		6 (4.9)	6 (5.0)	14 (11.7)	
Adverse events of particular interest — no. of patients (%)								
Fungal dermatitis	8 (6.6)	1 (0.8)	3 (2.5)		0	0	1 (0.8)	
Pneumonia	0	2 (1.7)	4 (3.3)		0	0	2 (1.7)	
Varicella–zoster virus infection	1 (0.8)	1 (0.8)						
Herpes zoster	0	1 (0.8)						
Adverse events leading to discontinuation of study drug — no. of patients (%)	11 (9.1)	10 (8.3)						
Serious adverse events — no. of patients (%)	31 (25.6)	26 (21.5						
Infections — no. of patients (%)	47 (38.8)	53 (43.8						
Infections requiring antimicrobial treatment — no. of patients (%)	25 (20.7)	39 (32.2						
Earache	0	0	0		0	1 (0.8)	0	
Fever	0	0	1 (0.8)		0	1 (0.8)	0	
Vaginitis	0	0	0		0	0	1 (0.8)	
Appendicitis	0	1 (0.8)	0		0	0	0	
Colitis	0	0	1 (0.8)		0	0	0	
Surgical-wound infection	1 (0.8)	0	1 (0.8)		0	0	1 (0.8)	
Pancreatitis	0	1 (0.8)	0		0	0	0	
Pleurisy	0	0	1 (0.8)		0	0	0	
Sinusitis	1 (0.8)	0	0		0	0	0	
Acute infusion reaction (any adverse event occurring ≤2 hr after start of infusion) — no. of patients (%)	13 (10.7)	12 (9.9)	15 (12.3)	1.00	10 (8.1)	14 (11.6)	14 (11.7)	0.37
Possible delayed hypersensitivity reactions — no. of patients (%)	2 (1.7)	2 (1.7)	0	0.60	0	0	1 (0.8)	1.00
Antinuclear antibodies — no. of patients/total no. (%)‡	7/95 (7.4)	32/101 (31.7)	33/95 (34.7)	<0.001	6/82 (7.3)	23/88 (26.1)	22/78 (28.2)	<0.001
Antibodies against double-stranded DNA — no. of patients/total no. (%)‡	0/104	12/112 (10.7)	7/108 (6.5)	<0.001	0/93	5/102 (4.9)	6/100 (60.0)	0.02
Antibodies against infliximab during the study — no. of patients/total no. (%)§	—	9/116 (7.8)	5/113 (4.4)	—	—	9/95 (9.5)	3/93 (3.2)	—
Pharmacologic management at baseline — no. of patients/total no. (%)¶								
Corticosteroids or immunosuppressants	—	6/96 (6.2)	2/94 (2.1)		—	3/65 (4.6)	2/64 (3.1)	
Corticosteroids and immunosuppressants	—	0/34	1/30 (3.3)		—	0/24	0/48	
Corticosteroids without immunosuppressants	—	5/34 (14.7)	1/38 (2.6)		—	3/22 (13.6)	2/27 (7.4)	
Immunosuppressants without corticosteroids	—	1/28 (3.6)	0/26		—	0/19	0/13	
Neither corticosteroids nor immunosuppressants	—	3/20 (15.0)	3/19 (15.8)		—	6/30 (20.0)	1/29 (3.4)	

	ACT 1 (through Week 54)				ACT 2 (through Week 30)			
	Placebo (N=121)	5 mg of Infliximab (N=121)	10 mg of Infliximab (N=122)	P Value†	Placebo (N=123)	5 mg of Infliximab (N=121)	10 mg of Infliximab (N=120)	P Value†
Infections — no. of patients (%)	47 (38.8)	53 (43.8)	60 (49.2)	0.18	29 (23.6)	33 (27.3)	34 (28.3)	0.45
Infections requiring antimicrobial treatment — no. of patients (%)	25 (20.7)	39 (32.2)	43 (35.2)	0.01	15 (12.2)	18 (14.9)	17 (14.2)	0.63
Serious infections — no. of patients (%)	5 (4.1)	3 (2.5)	8 (6.6)	1.00	1 (0.8)	2 (1.7)	3 (2.5)	0.67

* ND denotes not done, and dashes not applicable.
† P values are based on Fisher's exact test for the comparison of the combined infliximab groups with the placebo group.
‡ Denominators represent patients with negative findings at baseline. Test results for antinuclear antibodies were considered positive if the titer was at least 1:40. Samples positive for antinuclear antibodies were tested for antibodies against double-stranded DNA . Test results for anti–double-stranded DNA were positive if the titer was at least 1:10 (according to a crithidia assay) and at least 5.4 IU (according to Farr radioimmunoassay).
§ Denominators represent patients with appropriate serum samples (i.e., patients with either antibodies against infliximab at some time after their first infusion or at least one sample obtained after their last infusion).
¶ Immunosuppressants include mercaptopurine and azathioprine.

N Engl J Med 2005; 353:2462-2476

Remicade (Infliximab) darf nicht angewendet werden, wenn:

• Sie **allergisch** gegen Infliximab (Wirkstoff in Remicade) oder einen der in Abschnitt 6. genannten sonstigen Bestandteile dieses Arzneimittels sind.

• Sie überempfindlich (allergisch) gegen Proteine sind, die von Mäusen stammen.

• Sie **Tuberkulose (Tbc)** oder eine andere **schwerwiegende Infektion**, wie z.B. Lungenentzündung oder Blutvergiftung haben.

• Sie eine Herzinsuffizienz haben, die mäßiggradig oder schwer ist.

Fachinformation: Remicade, infliximab - MSD Sharp & Dohme GmbH

Zugelassene Antikörper 2018

Abciximab (ReoPro®)	Infliximab (Remicade®)
Adalimumab (Humira®)	Ixekizumab (Taltz®)
Alemtuzumab (Lemtrada®)	Lokivetmab (Tierarzneimittel)
Alirocumab (Praluent®)	Mepolizumab (Nucala®)
Atezolizumab (Tecentriq®)	Muromonab-CD3 (Orthoclone OKT® 3)
Avelumab (Bavencio®)	Natalizumab (Tysabri®)
Basiliximab (Simulect®)	Necitumumab (Portrazza®)
Belimumab (Benlysta®)	Nivolumab (Opdivo®)
Benralizumab (Fasenra®)	Obiltoxaximab (Anthim®)
Bevacizumab (Avastin®)	Obinutuzumab (Gazyvaro®)
Bezlotoxumab (Zinplava®)	Ocrelizumab (Ocrevus®)
Bimagrumab	Ofatumumab (Arzerra®)
Blinatumomab (Blincyto®)	Olaratumab (Lartruvo®)
Brentuximab vedotin (Adcetris®)	Omalizumab (Xolair®)
Canakinumab (Ilaris®)	Palivizumab (Synagis®)
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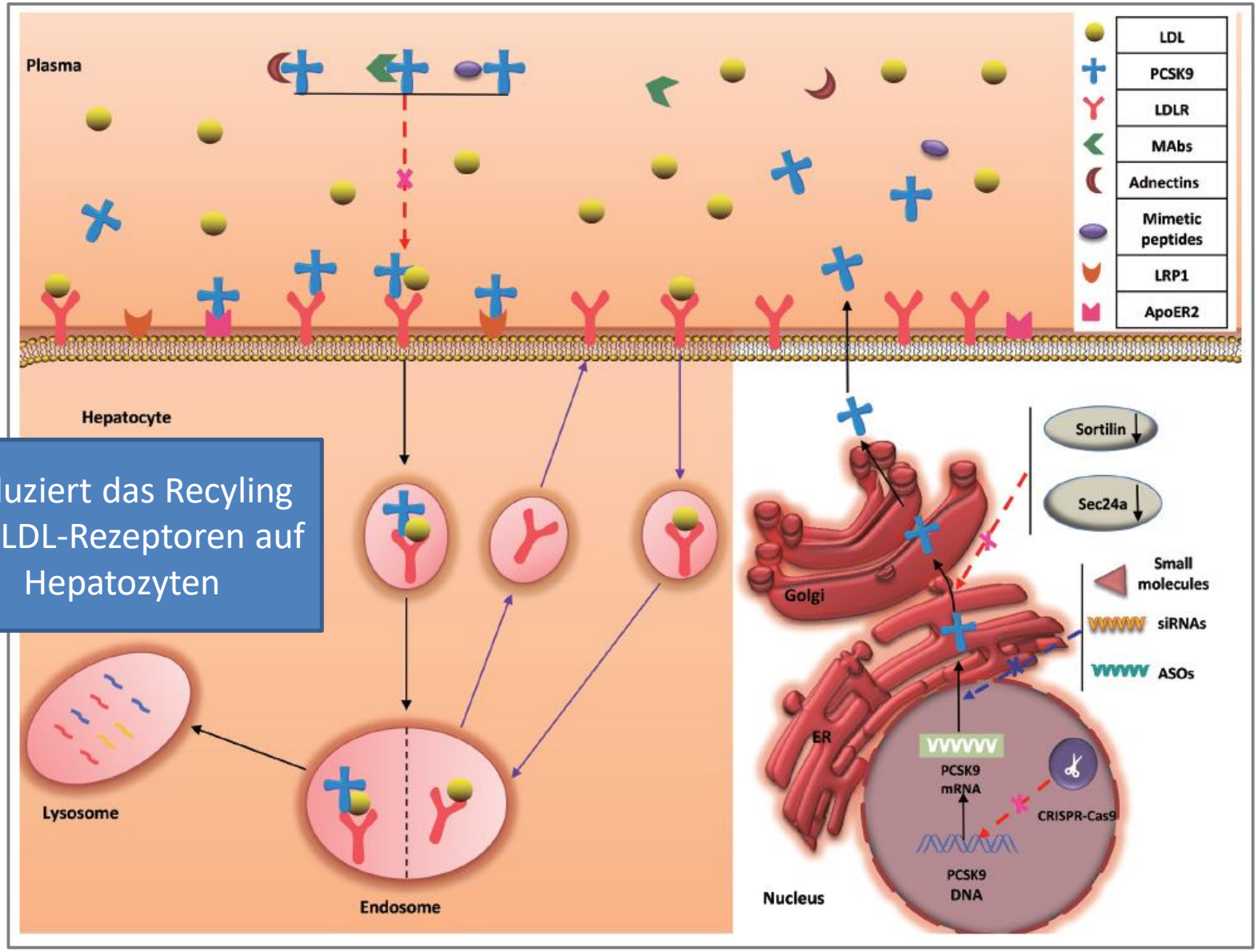
PCSK9-targeting drugs



reduziert das Recyling der LDL-Rezeptoren auf Hepatozyten

Steps in the LDLR metabolic pathway. After LDL binds to the LDLR at the cell membrane, the LDLR-LDL complex undergoes endocytosis. Within the endosome, LDL dissociates from the LDLR. The LDL then enters the lysosome where it is degraded, and the LDLR is recycled to the cell surface. The LDLR metabolic pathway under PCSK9 regulation. Secreted PCSK9 binds to the LDLR at the cell surface, and the PCSK9-LDLR complex is endocytosed, thereby promoting its lysosomal degradation. PCSK9-targeted therapies include mAbs, adnectins, and mimetic peptides (which block the interaction between PCSK9 and the LDLR), CRISPR/Cas9 genome editing technology, antisense oligonucleotides (ASOs), siRNAs and small molecules (which inhibit PCSK9 expression), and drugs that interfere with PCSK9 secretion from the ER.

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PCSK9-Wirkungsmechanismus

Mechanisms	Representative agents	References
Blocking the combination of PCSK9 and LDLR	Mimetic Peptides	[25, 35]; [57–60]
	Adnectins	[61]
	Monoclonal antibodies (alirocumab; evolocumab; bococizumab)	[62–75]
Inhibiting PCSK9 expression	CRISPR/Cas9 technology	[11]; [76–79]
	Small molecules (berberine; oleanoic acid)	[81–91]; [92–99]
	Antisense oligonucleotides	[100–102]
	Small interfering RNAs	[103, 104]; [58, 59]
Interfering PCSK9 secretion	Sortilin	[105, 106]
	Sec24a	

Evolocumab: 140 mg alle zwei Wochen oder 420 mg einmal monatlich s.c.

Acta Pharmacologica Sinica *(2017) 38: 301–311*

Nebenwirkungen PCSK9 mAbs

Side effect profiles	Description		
	Symptoms	Occurence	
		Alirocumab vs placebo (%)	Evolocumab vs placebo (%)
Neurocognitive adverse effects	Amnesia mental impairment	0.8 vs 0.7	No
	Injection site reactions	7.2 vs 5.1	5.7 vs 5.0
	Nasopharyngitis	11.3 vs 11.1	10.5 vs 9.6
	Influenza	5.7 vs 4.6	7.5 vs 6.3
	Urinary tract infections	4.8 vs 4.6	4.5 vs 3.6
	Cough	2.5 vs 2.3	4.5 vs 3.6
	Myalgia	4.2 vs 3.4	4.0 vs 3.0
	Sinusitis	3.0 vs 2.7	4.2 vs 3.0
Other adverse events in clinical trials of PCSK9 mAbs	Musculoskeletal pain	2.1 vs 1.6	3.3 vs 3.0
	Bronchitis	4.3 vs 3.8	
	Diarrhea	4.7 vs 4.4	3.0 vs 2.6
	Upper respiratory tract infections	3.1 vs 2.4	9.3 vs 6.3
	Back pain		
	Headache		6.2 vs 5.6
	Dizziness		4.0 vs 3.6
	Hypertension		3.7 vs 2.6
	Gastroenteritis		3.2 vs 2.3
			3.0 vs 2.0

Acta Pharmacologica Sinica *(2017) 38: 301–311*

Zugelassene Antikörper 2018

Abciximab (ReoPro®)	Infliximab (Remicade®)
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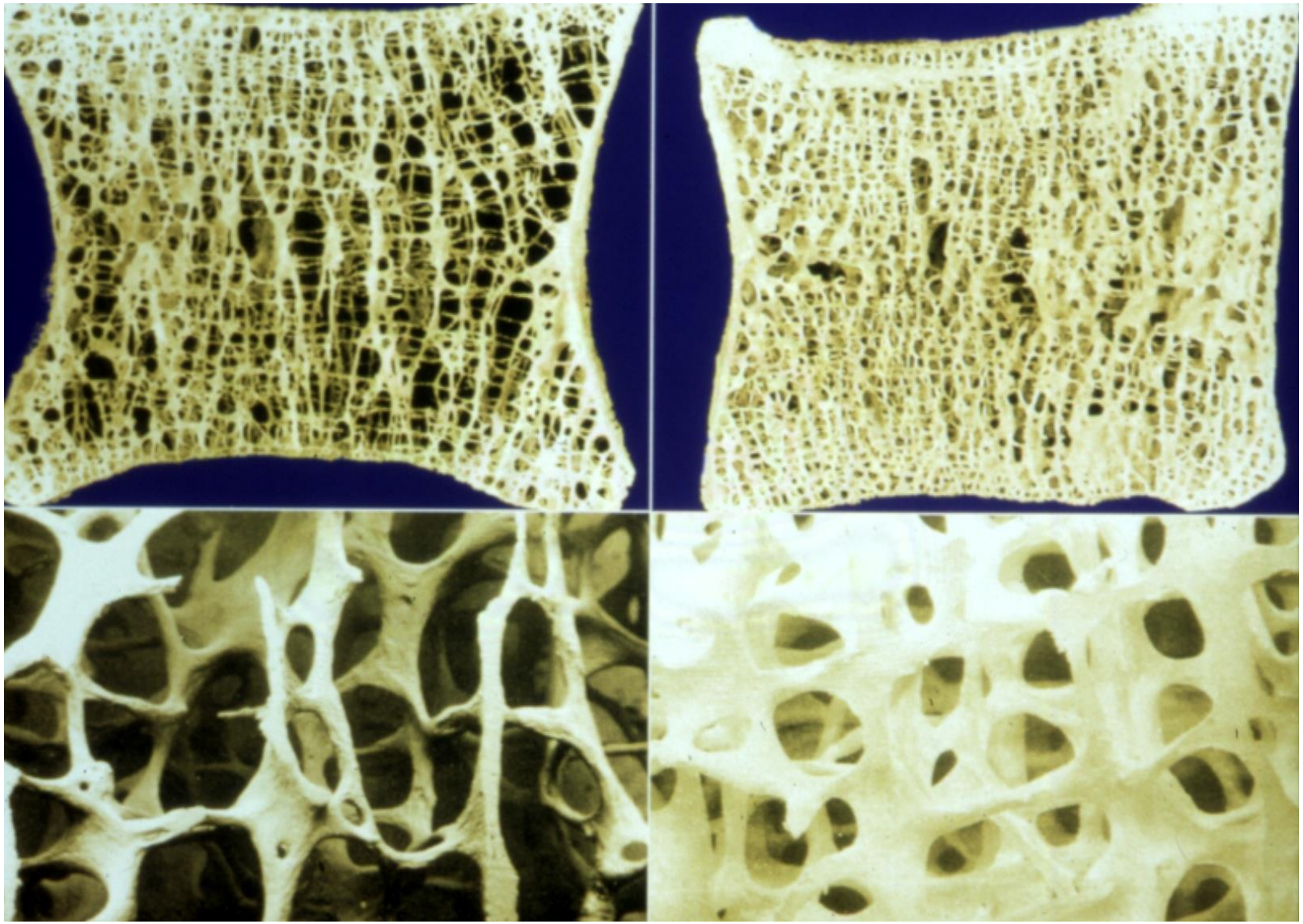
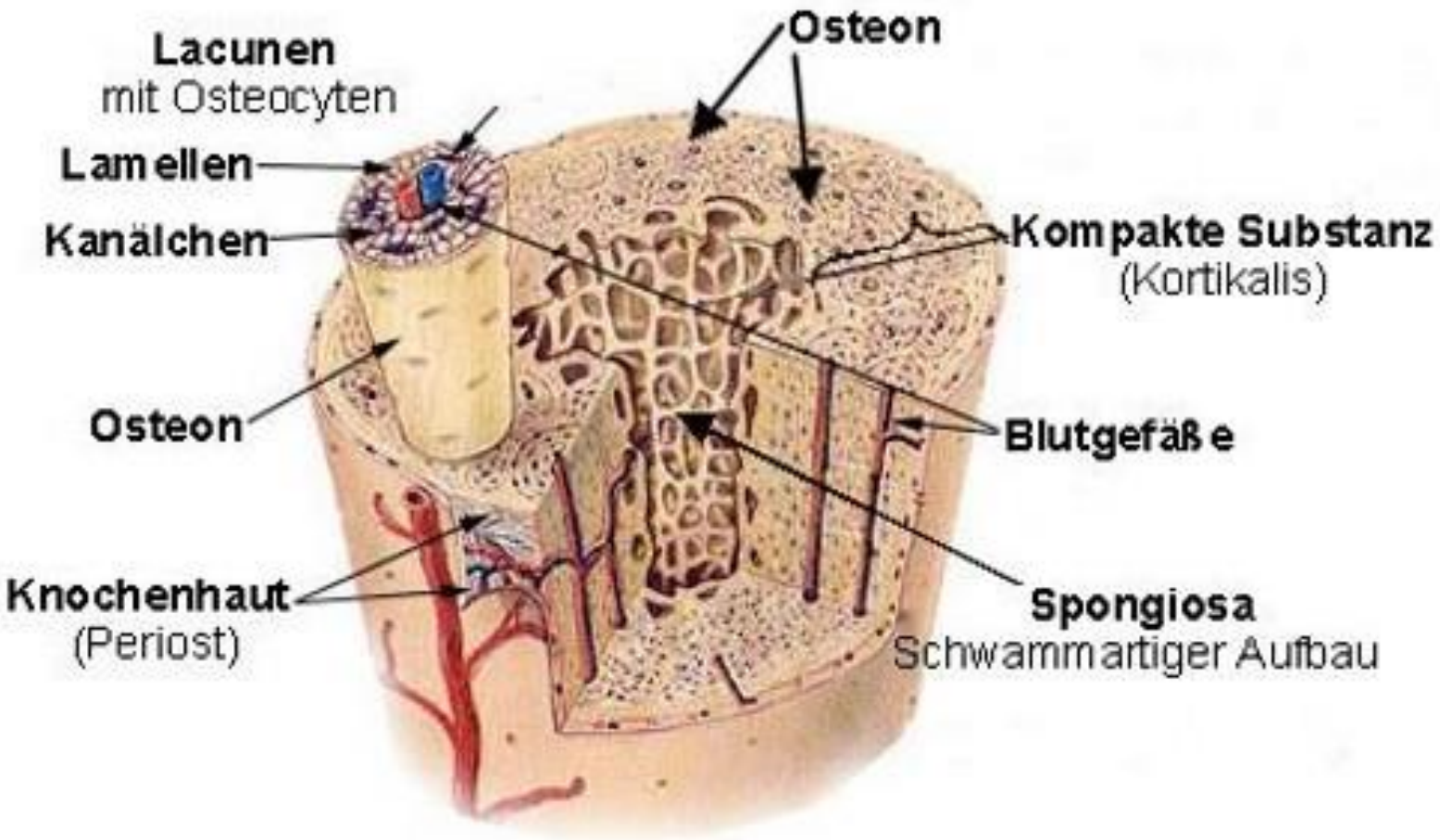
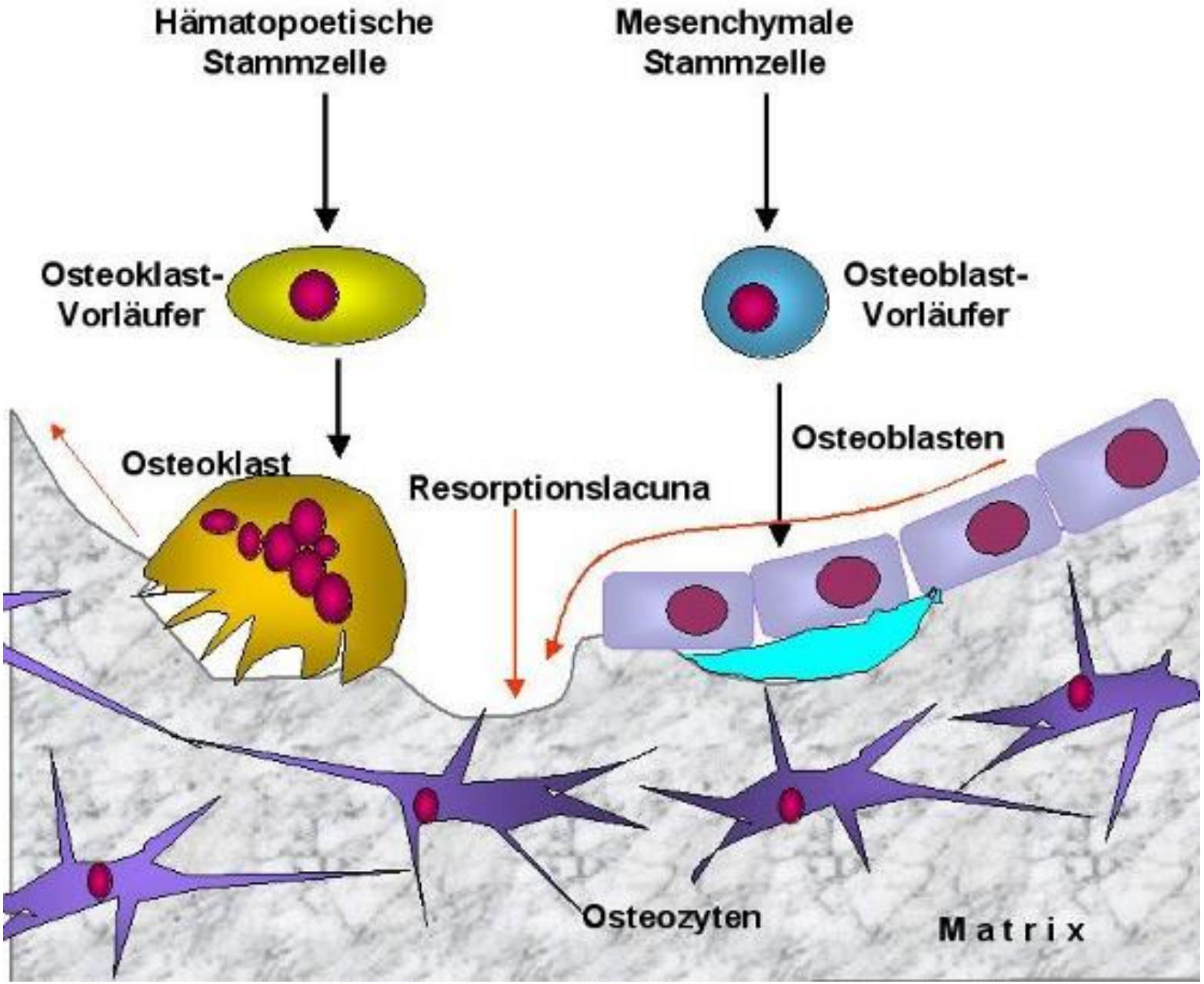
	Vedolizumab (Entyvio®)

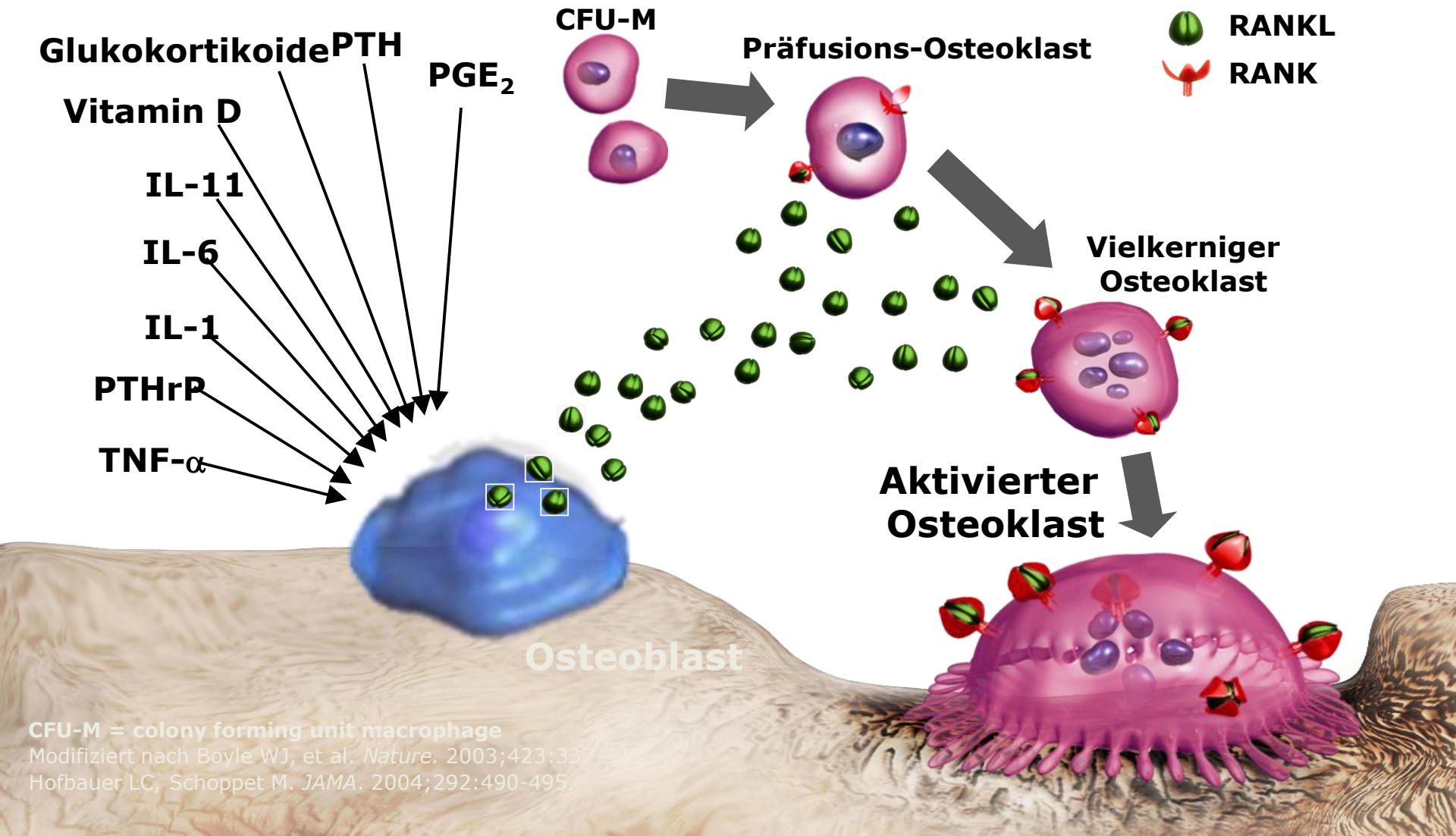
Knochenstoffwechsel - Osteoporose




Lacunen
mit Osteocyten
Lamellen
Kanälchen
Osteon
Osteon
Kompakte Substanz
(Kortikalis)
Blutgefäße
Knochenhaut
(Periost)
Spongiosa
Schwammartiger Aufbau


Hämatopoetische Stammzelle
Mesenchymale Stammzelle
Osteoklast-Vorläufer
Osteoblast-Vorläufer
Osteoblasten
Osteoklast
Resorptionslacuna
Osteozyten
Matrix

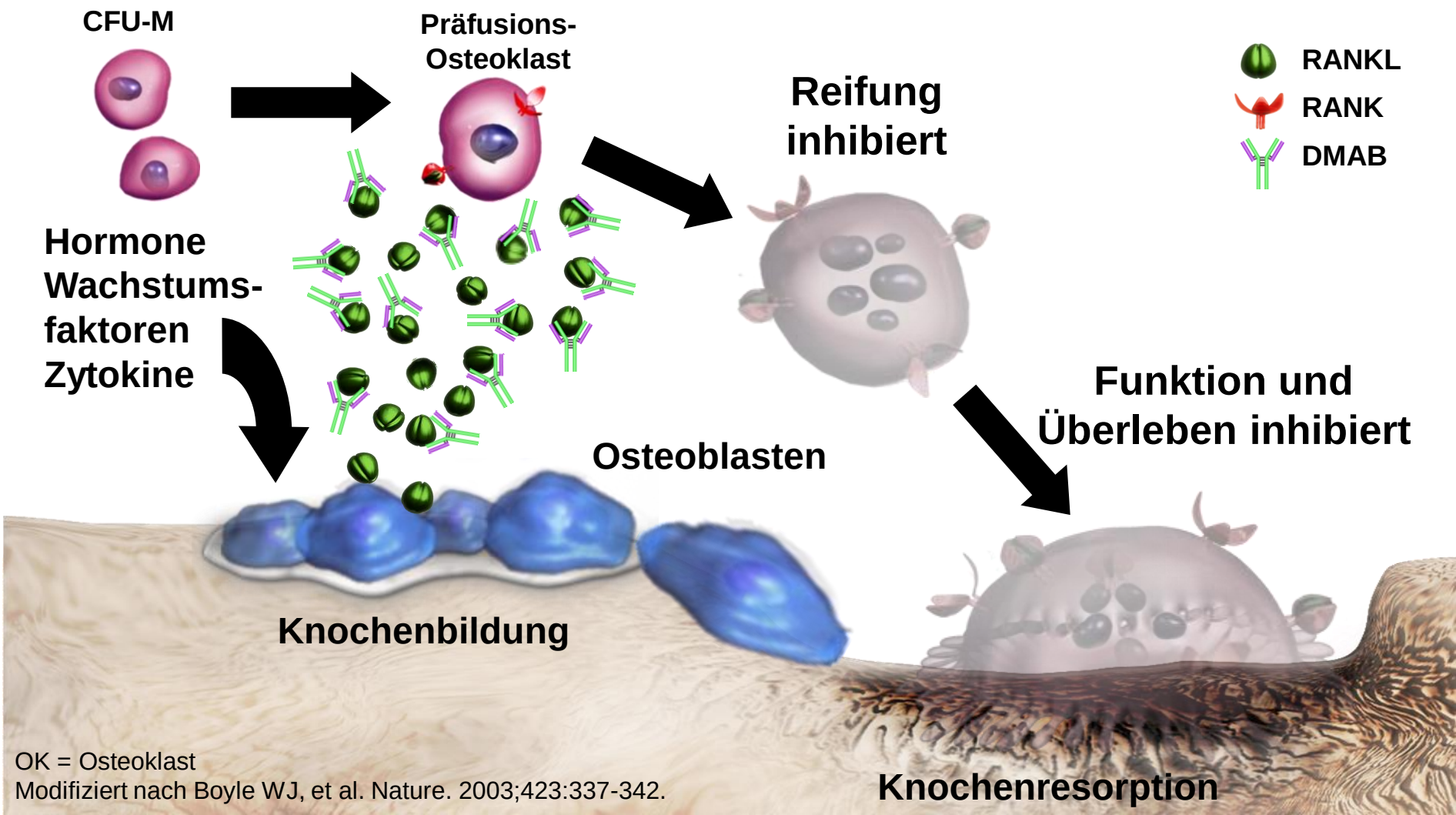
Interaktion Osteoblast und Osteoclast



CFU-M = colony forming unit macrophage

Modifiziert nach Boyle WJ, et al. *Nature*. 2003;423:337-342.
Hofbauer LC, Schoppet M. *JAMA*. 2004;292:490-495.

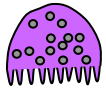
Denosumab ist ein vollhumaner monoklonaler Antikörper und verhindert die Bindung von RANK-Ligand an RANK



OK = Osteoklast
Modifiziert nach Boyle WJ, et al. Nature. 2003;423:337-342.

OPG/RANK/RANKL

Wildtyp



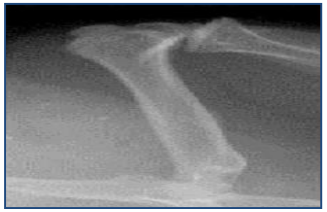
Normale BMD

RANK or RANKL Knock-Out[1,2]

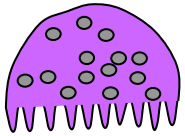
Erhöhte BMD ↑

OPG Überexpression[3]

Erhöhte BMD ↑



OPG-Knock-Out[3]



Niedrige BMD ↓

1 Kong YY *et al.* Nature 1999; 397: 315–323; 2 Li J *et al.* Proc Natl Acad Sci USA 2000; 97: 1566–1571;
3 Bolon B, et al. *Arthritis Rheum.* 2002;46:3121-3135

Nomenklatur monoklonaler Antikörper (MABs)

Prefix	Ziel oder Zustand		Quelle		Suffix
variabel	*-o(s)-*	bone	*-u-*	human	*-mab*
	-vi(r)-	viral	*-o-*	mouse	
	-ba(c)-	bacterial	*-a-*	rat	
	-li(m)-	immune	*-e-*	Hamster	
	-le(s)-	infectious lesions	*-i-*	Primate	
	-ci(r)-	cardiovascular	*-xi-*	Chimeric	
	-mu(l)-	musculoskeletal	*-zu-*	Humanized	
	-ki(n)-	interleukins	*-axo-*	rat/murine hybrid	
	-co(l)-	colonic tumor			
	-me(l)-	melanoma			
	-ma(r)-	mammary tumor			
	-go(t)-	testicular tumor			
	-go(v)-	ovarian tumor			
	-pr(o)-	prostate tumor			
	-tu(m)-	miscellaneous tumor			
	-ne(r)-	nervous system			
	-tox(a)-	toxin as target			
	-fu(ng)-	fungal			

Beispiel:

Den/ os / u / mab

Prefix: variabel

Ziel: Knochen

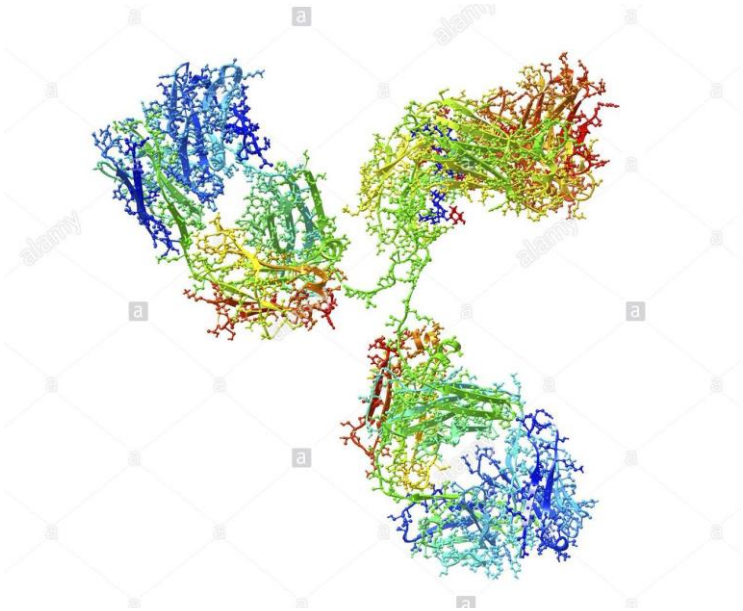
Quelle: human

Suffix: Monoclonal antibody

Available at: www.ama-assn.org/ama/pub/category/13280.html. Accessed August 10, 2007.

Pharmakologische Eigenschaften von Denosumab

- IgG_2 Immunoglobulin Isotyp
- Vollhumaner monoklonaler Ak
- Hohe Affinität zu humanem RANK-Ligand
- Hohe Spezifität für RANK-Ligand
  - Keine Bindung an TNFα, TNFβ, TRAIL, oder CD40L
- Keine neutralisierenden Antikörper in klinischen Studien bisher nachweisbar
- Effekt auf die Knochenresorption ist reversibel



TNF = tumor necrosis factor; TRAIL = TNFα-related apoptosis-inducing Ligand.

Bekker PJ, et al. *J Bone Miner Res.* 2004;19:1059-1066.
Elliott R, et al. *Osteoporos Int.* 2007;18:S54. Abstract P149.
McClung MR, et al. *New Engl J Med*. 2006;354:821-31.

Frakturverhinderung

Normaler Wirbelkörper
(Grad 0)

Milde Deformität
(Grad 1, 20–25%)

Moderate Deformität
(Grad 2, 25–40%)

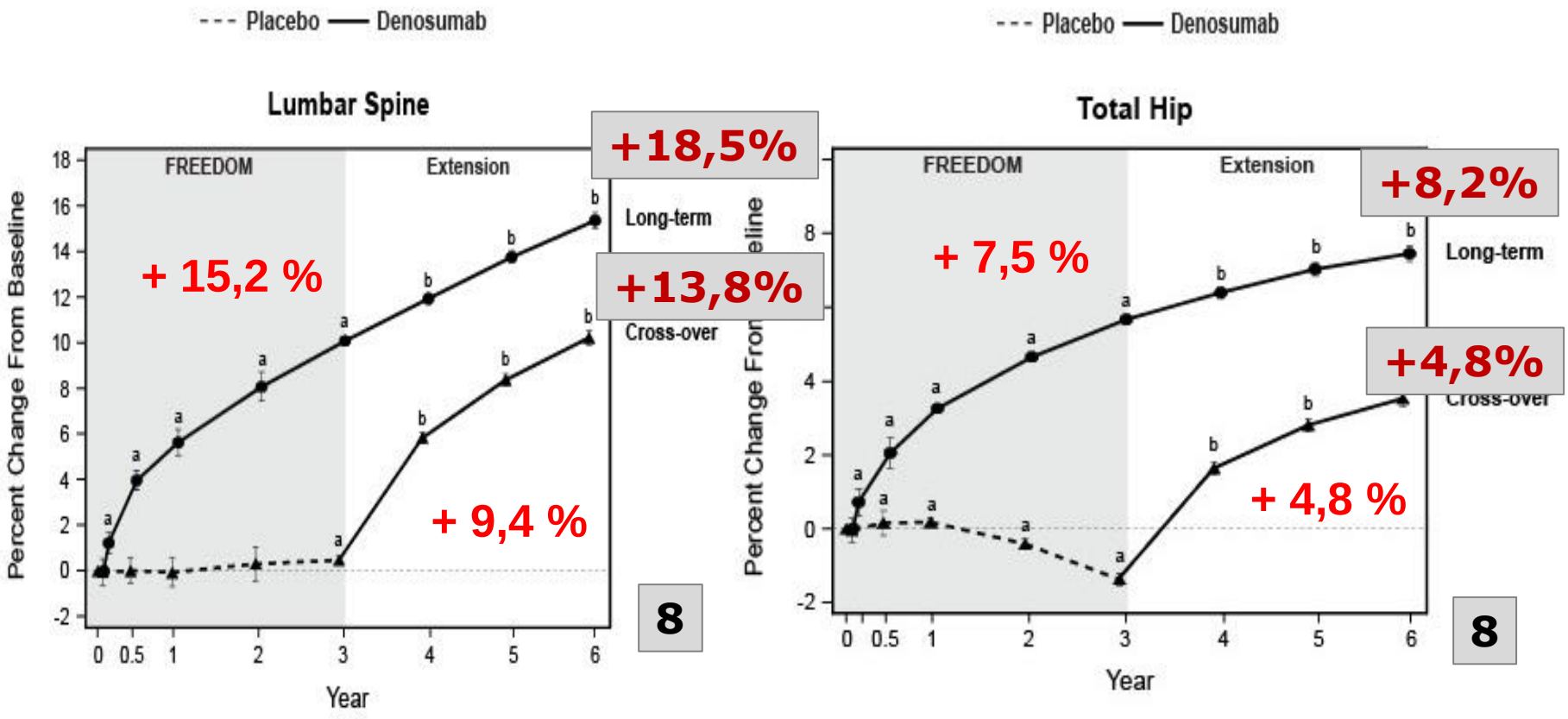
Schwere Deformität
(Grad 3, >40%)

Keil-(„Wedge"-)
Deformation

Biconcave
Deformation

Kompressions-
(„Crush-)Deformation

FREEDOM Extension: 6 (8)-Jahresdaten BMD



[a]$P < 0.05$ compared with FREEDOM baseline.
[b]$P < 0.05$ compared with FREEDOM baseline and Extension baseline.

Brown JP et al., ACR Scientific Meeting, Chicago/IL 2011 (# L8).

Mortalitätsdaten

Substanz	Population	Studienart	Effekt	P-Wert
Zoledronat vs. Placebo[1] (HORIZON-RFT)	Prävalente Femurfraktur	RCT	9,6% vs. 13,3%	$p < 0,01$
Alendronat / Risedronat vs. no treatment[2]	Frauen (+ Männer) ≥ 60 J.	Prospektive Kohortenstudie	9,8% vs. 43,1%	$p < 0,0001$
Raloxifen[3] (MORE/CORE/ RUTH)	MORE/CORE: PMO	RCTs: MORE/CORE	1,8% vs. 2,5%	$p = 0,04$
	RUTH: KHK	MORE/CORE/ RUTH	7,9% vs. 8,7%	$p = 0,05$
Denosumab[4,5] vs. Placebo (FREEDOM)	Gesamtpopulation	RCT	1,8% vs. 2,3%	$p = 0,08$
	≥ 2 vert. Fx SQ1 oder ≥1 Fx ≥ SQ2	Post hoc	1,8% vs. 4,9%	$p = 0,02$
	≥ 2 vert. Fx SQ1 oder ≥ 1 Fx ≥ SQ2 + SH-T-Wert ≤ -2,5	Post hoc	1,6% vs. 7,1%	$p = 0,01$ $p_{interaktion} = 0,03$

*p-Wert für Interaktion vs. niedriges Risiko: p = 0,03; PMO: Postmenopausale Osteoporose ;
KHK: Koronare Herzkrankheit; Vert. Fx: vertebrale Fraktur; SQ1/SQ2: Grad 1 nach Genant; SH: Schenkelhals

1. Lyles et al., **N Engl J Med** 2007;357:1799-809; 2. Center et al., **J Clin Endocrinol Metab** 2011; 96: 1006–1014;
3. Grady et al., **Am J Med** 2010: 123, 469.e1-469.e7; 4. Cummings et al., **N Engl J Med** 2009;361:756-65;
5. Boonen et al., **J Clin Endocrinol Metab** 2011; 96:1727–1736

Empfehlungsgrad DVO-Leitlinie 2017

Substanz	Mortalität	Vertebrale Frakturen	Nonvertebrale Frakturen	Hüftfrakturen
Alendronat	B	A	A	A
Bazedoxifen		A	B	
Denosumab	B	A	A	A
Östrogene		A	A	A
Ibandronat		A	B	
PTH (1-34)		A	B	
PTH (1-84)		A		
Raloxifen	C	A		
Risedronat	B	A	A	A
Zoledronat	B	A	A	A

Denosumab: Nebenwirkungen

NW, *n* (%)	Placebo (*n* = 3,876)	Denosumab 60 mg Q6M (*n* = 3,886)
Unerwünschte Ereignisse		
Infektionen	2,108 (54.4)	2,055 (52.9)
Malignitäten	166 (4.3)	187 (4.8)
Hautreaktionen an der Injektionsstelle	26 (0.7)	33 (0.8)
Hypocalcämie	3 (0.1)	0 (0)
Verzögerte Frakturheilung	4 (0.1)	2 (0.05)
Subtrochantäre Femurfrakturen	3 (0.1)	0 (0)
Nicht-heilende Humerusfrakturen	1 (0.03)	0 (0)
Osteokiefernekrosen	0 (0)	0 (0)
Unerwünschte Ereignisse mit einer Inzidenz ≥ 2% und *P* ≤ 0.05		
Ekzeme	65 (1.7)	118 (3.0)
Stürze*	219 (5.7)	175 (4.5)
Flatulenz	53 (1.4)	84 (2.2)

*Ausgeschlossen waren Stürze, die sich am selben Tag einer Fraktur ereigneten.
Adaptiert nach: Cummings SR, et al. N Engl J Med. 2009 Aug 20;361(8):756-65.

	Abciximab (ReoPro®)	Infliximab (Remicade®)
	Adalimumab (Humira®)	Ixekizumab (Taltz®)
	Alemtuzumab (Lemtrada®)	Lokivetmab (Tierarzneimittel)
	Alirocumab (Praluent®)	Mepolizumab (Nucala®)
	Atezolizumab (Tecentriq®)	Muromonab-CD3 (Orthoclone OKT® 3, ausser Handel)
	Avelumab (Bavencio®)	Natalizumab (Tysabri®)
	Basiliximab (Simulect®)	Necitumumab (Portrazza®)
	Belimumab (Benlysta®)	Nivolumab (Opdivo®)
	Benralizumab (Fasenra®)	Obiltoxaximab (Anthim®)
	Bevacizumab (Avastin®)	Obinutuzumab (Gazyvaro®)
	Bezlotoxumab (Zinplava®)	Ocrelizumab (Ocrevus®)
	Bimagrumab	Ofatumumab (Arzerra®)
	Blinatumomab (Blincyto®)	Olaratumab (Lartruvo®)
	Brentuximab vedotin (Adcetris®)	Omalizumab (Xolair®)
	Canakinumab (Ilaris®)	Palivizumab (Synagis®)
	Certolizumab (Cimzia®)	Panitumumab (Vectibix®)
	Cetuximab (Erbitux®)	Pembrolizumab (Keytruda®)
	Daclizumab (Zinbryta®, ausser Handel)	Pertuzumab (Perjeta®)
	Denosumab (Prolia®)	Ramucirumab (Cyramza®)
	Dupilumab (Dupixent®)	Ranibizumab (Lucentis®)
	Eculizumab (Soliris®)	Reslizumab (Cinqair®)
	Efalizumab (Raptiva®, ausser Handel)	Rituximab (MabThera®)
	Elotuzumab (Empliciti®)	Secukinumab (Cosentyx®)
	Evolocumab (Repatha®)	Siltuximab (Sylvant®)
	Golimumab (Simponi®)	Tocilizumab (Actemra®)
	Guselkumab (Tremfya®)	Trastuzumab (Herceptin®)
	Ipilimumab (Yervoy®)	Ustekinumab (Stelara®)
		Vedolizumab (Entyvio®)

Antikörpertherapie

Prof. Dr. Burkhard L. Herrmann

Endokrinologie /// Diabetologie /// Innere Medizin

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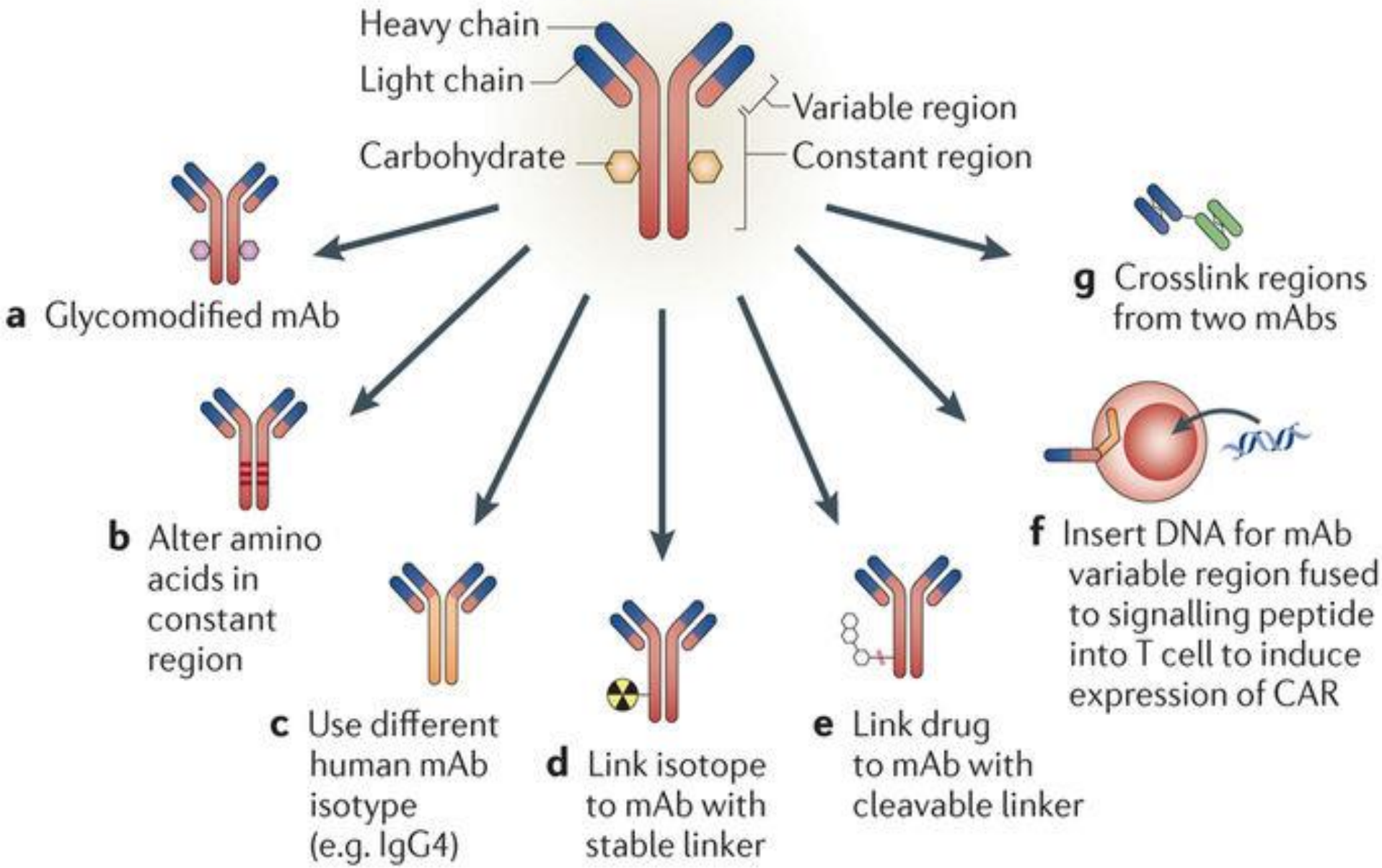
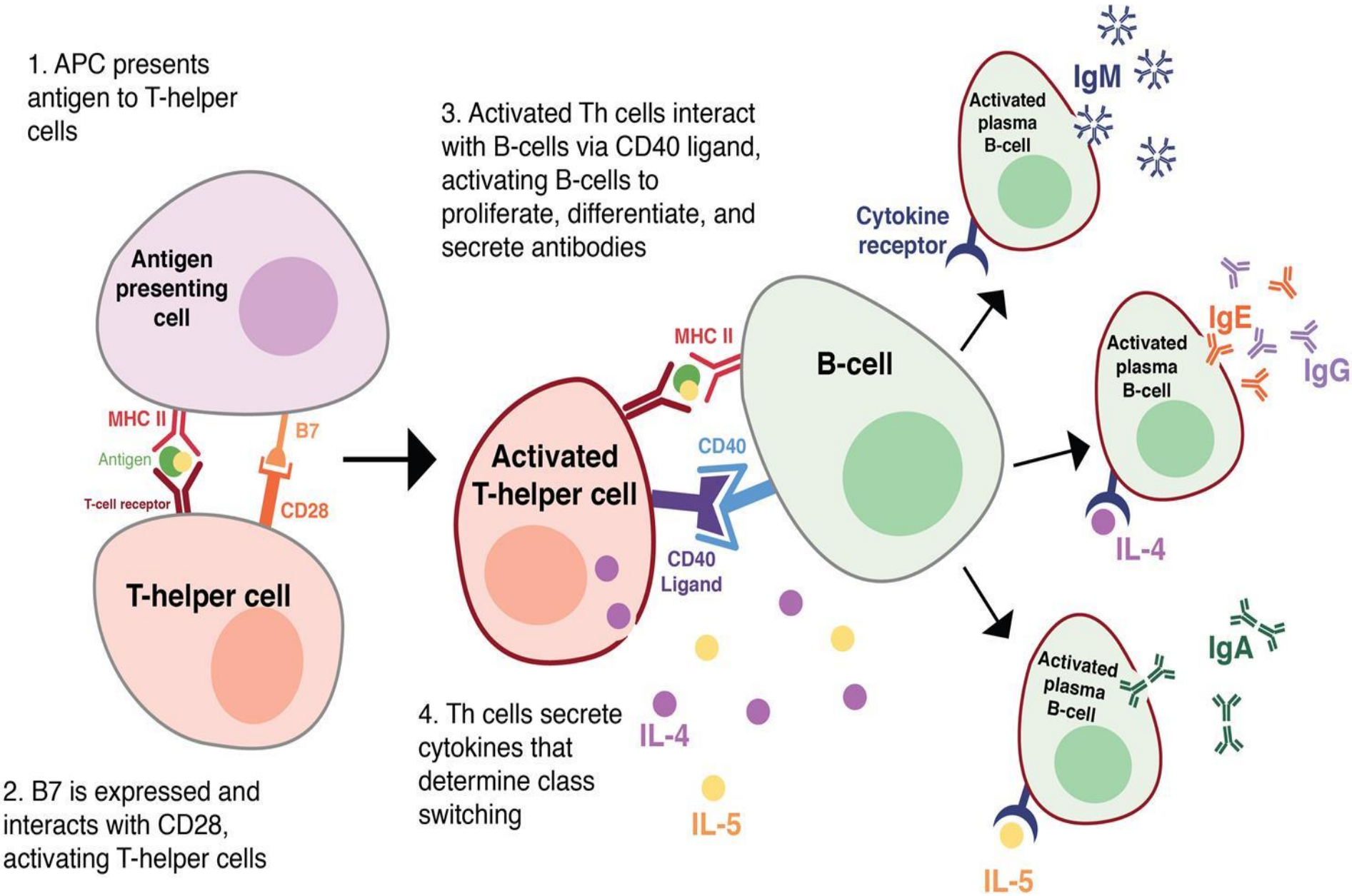

Heavy chain
Light chain
Carbohydrate
Variable region
Constant region
a Glycomodified mAb
b Alter amino acids in constant region
c Use different human mAb isotype (e.g. IgG4)
d Link isotope to mAb with stable linker
e Link drug to mAb with cleavable linker
f Insert DNA for mAb variable region fused to signalling peptide into T cell to induce expression of CAR
g Crosslink regions from two mAbs

Activation and Class-switching of B-cells



© Lineage

Lucy Liu

4 Typen der monoklonalen Antikörper

Table 1 UK licensed monoclonal antibodies

Name	Type of antibody	Target	Licensed indication
Infliximab (Remicade)	Human–mouse chimaera IgG1	TNF-α	Refractory Crohn's, Crohn's fistulas, refractory rheumatoid arthritis
Palivizumab (Synagis)	Humanised IgG1	F protein on RSV	Prophylaxis, RSV in premature infants or brochopulmonary dysplasia
Abciximab (ReoPro)	Human–mouse chimaera	Platelet glycoprotein IIb/IIIa	High risk coronary intervention
Rituximab (MabThera)	Human–mouse chimaera IgG1	CD20	Refractory low grade or follicular B cell lymphoma
Basiliximab (Simulect)	Human–mouse chimaera IgG1K	IL-2 receptor α chain	Prophylaxis of acute rejection in allogeneic renal transplantation
Daclizumab (Zenapax)	Humanised IgG1	IL-2 receptor α	As Basiliximab
Trastuzumab (Herceptin)	Humanised IgG1	HER 2 growth receptor	Relapsed HER2 (high) breast malignancy

IL-2, interleukin 2; TNF-α, tumour necrosis factor α; RSV, respiratory syncitial virus.

J Clin Pathol 2002;**55**:81–85

Selected examples of licensed therapeutic monoclonal antibodies

Name	Target	Year	Use	Manufacturer	Reference
Muronomab-CD3 (Orthoclone® OKT3)	CD3	1992	Transplant rejection	Centocor Ortho Biotech, Inc., Horsham, PA, USA	2
Rituximab (Rituxan)	CD20	1997	B cell non-Hodgkin lymphoma	Genentech Inc., San Francisco, CA, USA	3
Infliximab (Remicade)	TNF	1998	RA, ankylosing spondylitis, Crohn's disease, ulcerative colitis	Janssen Biotech, Inc., Horsham, PA, USA	4
Trastuzumab (Herceptin)	HER-2	1998	HER-2 positive breast cancer	Genentech Inc., San Francisco, CA, USA	5
Palivizumab (Synagis®)	RSV F protein	1998	Prevention of RSV infection in neonates	MedImmune, Gaithersburg, MD, USA	6
Alemtuzumab (Campath)	CD52	2001	B-CLL	Genzyme, Cambridge, MA, USA	7
Ibritumomab tiuxetan (Zevalin)	CD23	2002	Non-Hodgkin's lymphoma	Spectrum Pharmaceuticals, Irvine, CA, USA	8
Bevacizumab (Avastin)	VEGF	2004	Colorectal, lung, breast cancer	Genentech, San Francisco, SFO, USA	9
Panitumumab (Vectibix)	EGFR	2007	Colorectal cancer	Amgen Inc., Thousand Oaks, CA, USA	10
Ustekinumab (Stelara)	IL-12	2009	Plaque psoriasis	Janssen Biotech, Inc., Horsham, PA, USA	11
Mogamulizumab	CCR4	2012	Relapsed or refractory CCR4-positive T cell leukemia-lymphoma	Kyowa Hakko Kirin Co., Tokyo, Japan	12

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Selected examples of therapeutic **monoclonal antibodies** in **clinical development**

Name	Target	Phase	Use
CR6261/CR8020	Influenza HA type A	I	Influenza infection
Brentuximab vedotin	CD30	II	Germ cell cancer
Daratumumab	CD38	II	Multiple myeloma
Epratuzumab	CD22	II	B-cell acute lymphoblastic leukemia
MOR103	GM-CSF	II	Rheumatoid arthritis
Roledumab	Rhesus D	II	Prevention of Rhesus D alloimmunization
Evolocumab	PCSK-9	III	Hypercholesterolemia; hyperlipidemia
Gantenerumab	Amyloid-β	III	Alzheimer's disease
Ixekizumab	IL-17a	III	Psoriasis, psoriatic arthritis, plaque psoriasis
Tremelimumab	CTLA-4	III	Metastatic melanoma

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