Manipulation of the immune response

PD Dr. Jürgen Knobloch

Chronic inflammatory diseases of the upper and lower airways

Asthma, COPD, CRS, and others

trigger

↓

chronic inflammation ⊣ **currently available therapies**

(to prevent progression)

e.g. local acting steroids, biologics

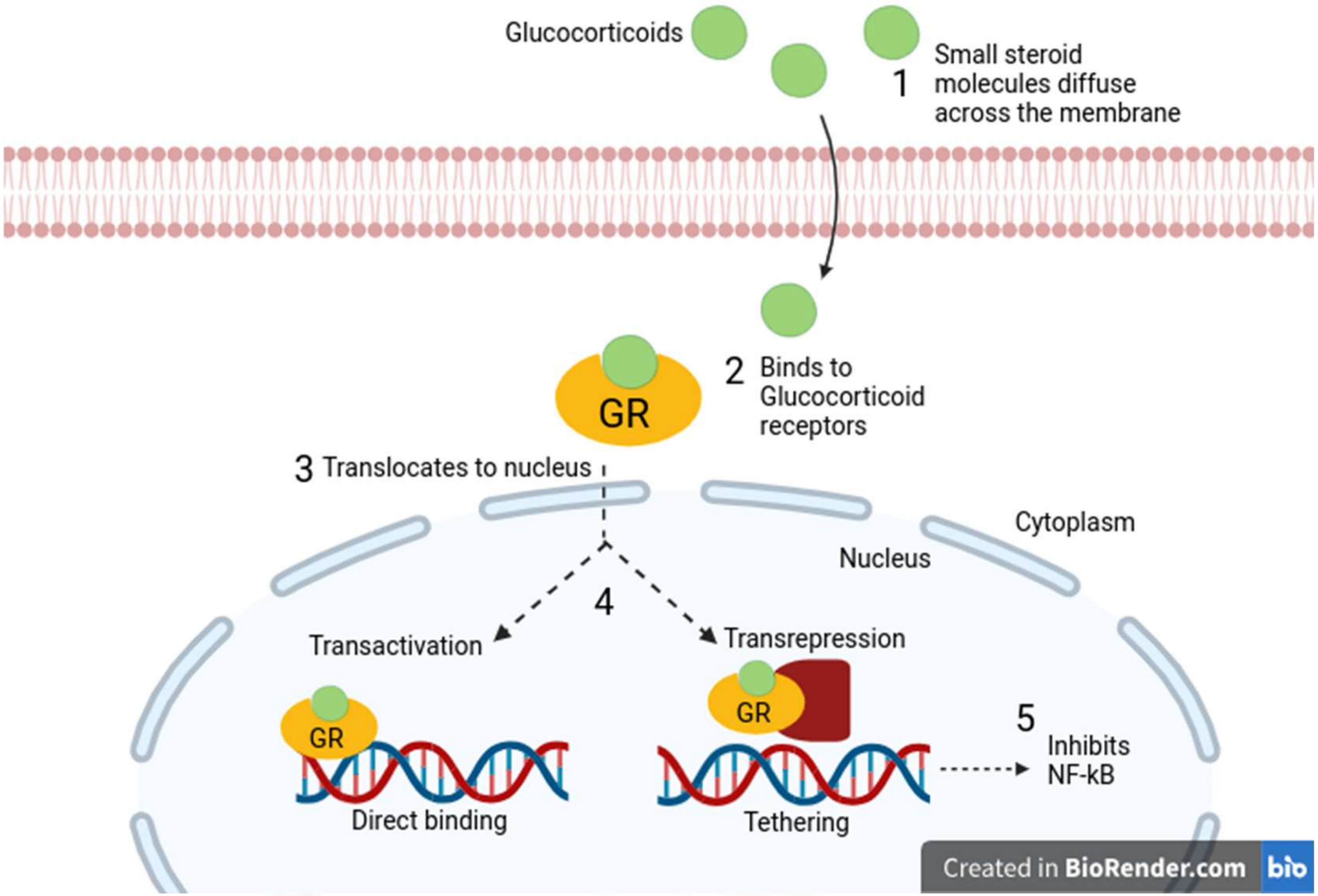
↓

airway remodeling
(destruction of functional tissue)

↓

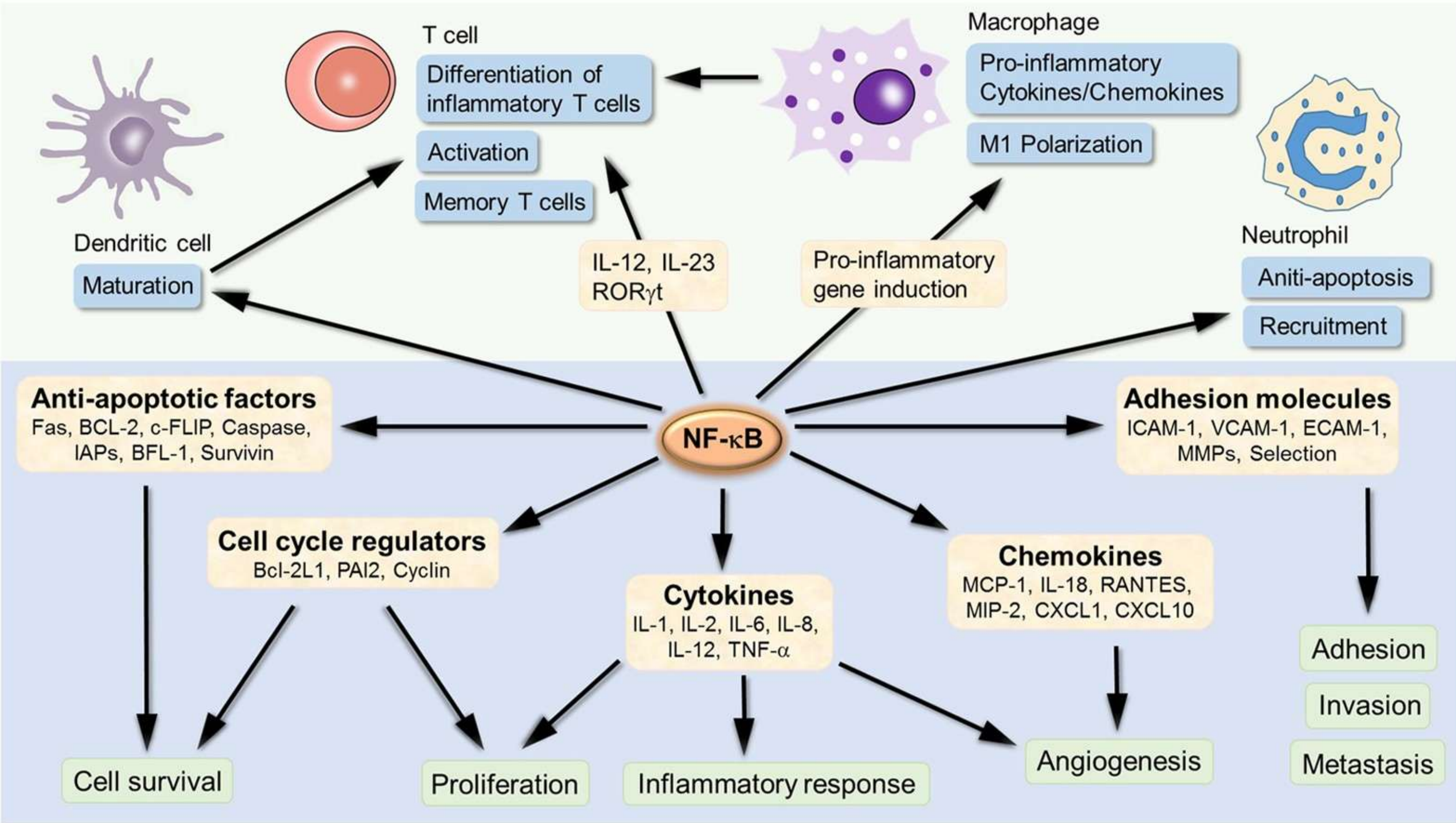
progression

Steroids/NF-κB blockade: mechanism of action



(2025-04-07) https://www.actionduchenne.org/vamorolone-and-corticosteroids-an-overview/

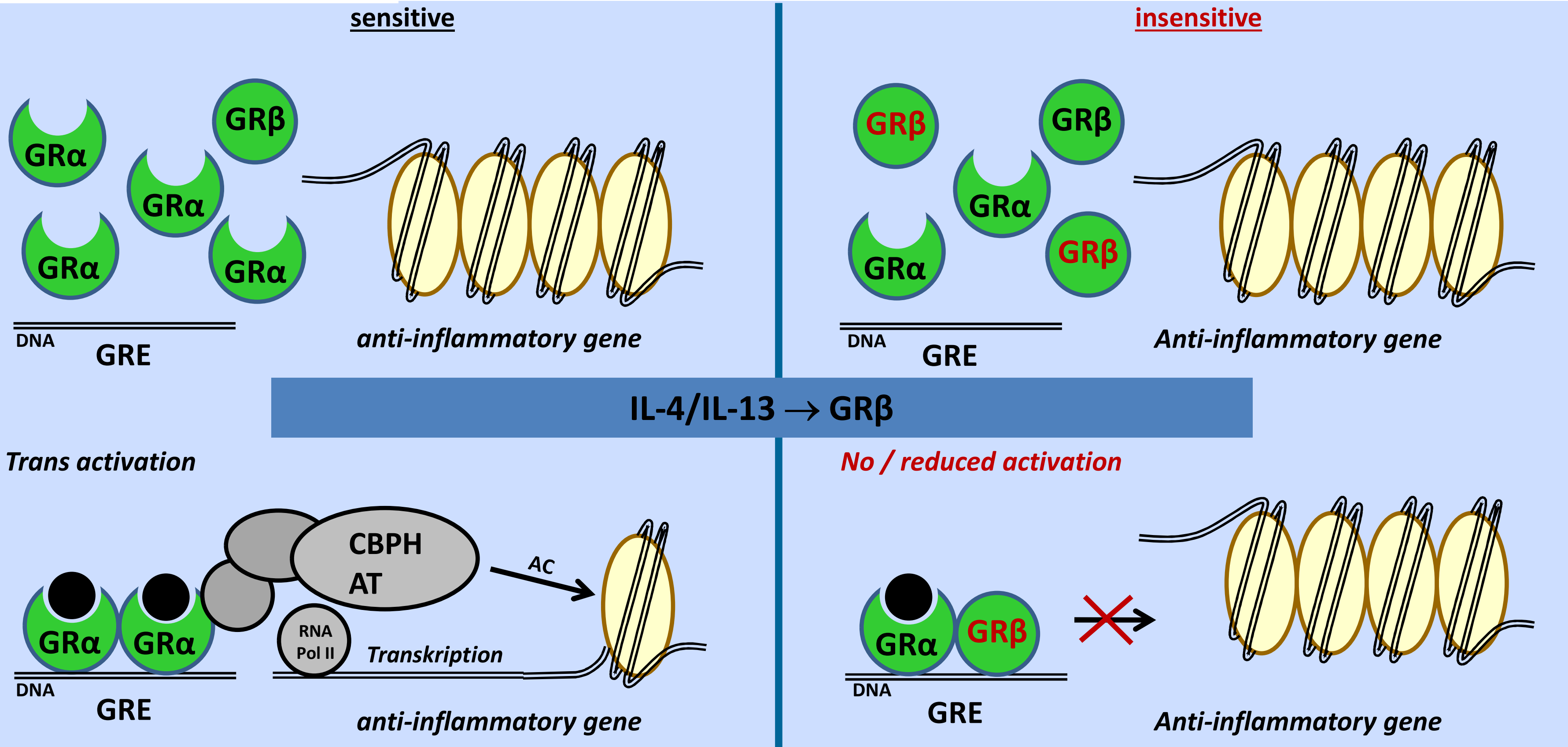
Steroids/NF-κB blockade: mechanism of action



doi.org/10.1038/sigtrans.2017.23

Mechanisms of steroid resistance

(in neutrophilic granulocytes)



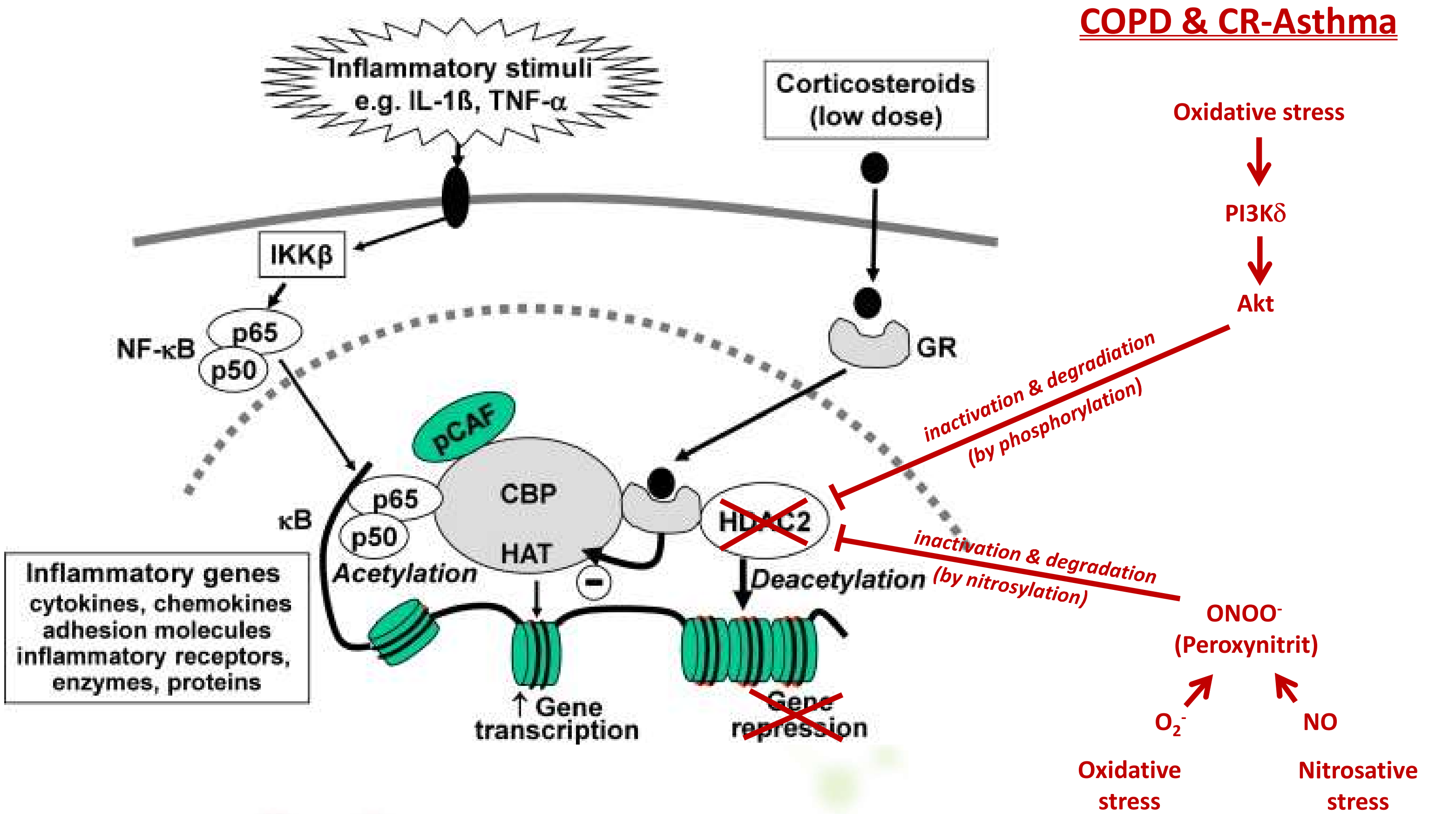
⇒ expression of GRα-regulated anti-inflammatory proteins

⇒ reduced expression of GRα-regulated anti-inflammatory proteins

nach Lewis-Tuffin/Cidlowski Ann N Y Acad Sci 2006 & Barnes JACI 2013

Mechanisms of steroid resistance: HDAC2 reduction

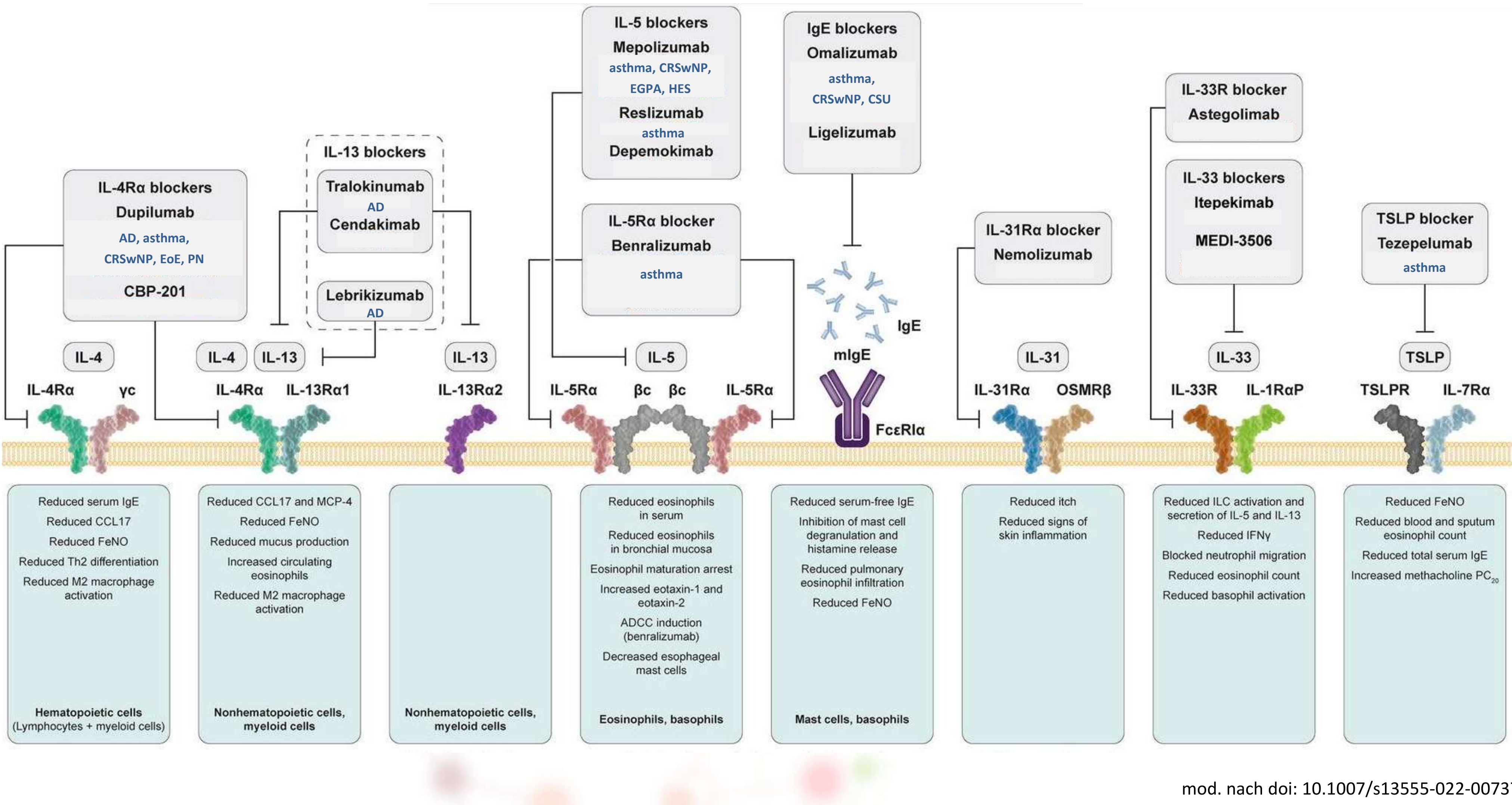
(in macrophages)



⇒ **reduced inhibition of inflammatory gene expression by steroids**

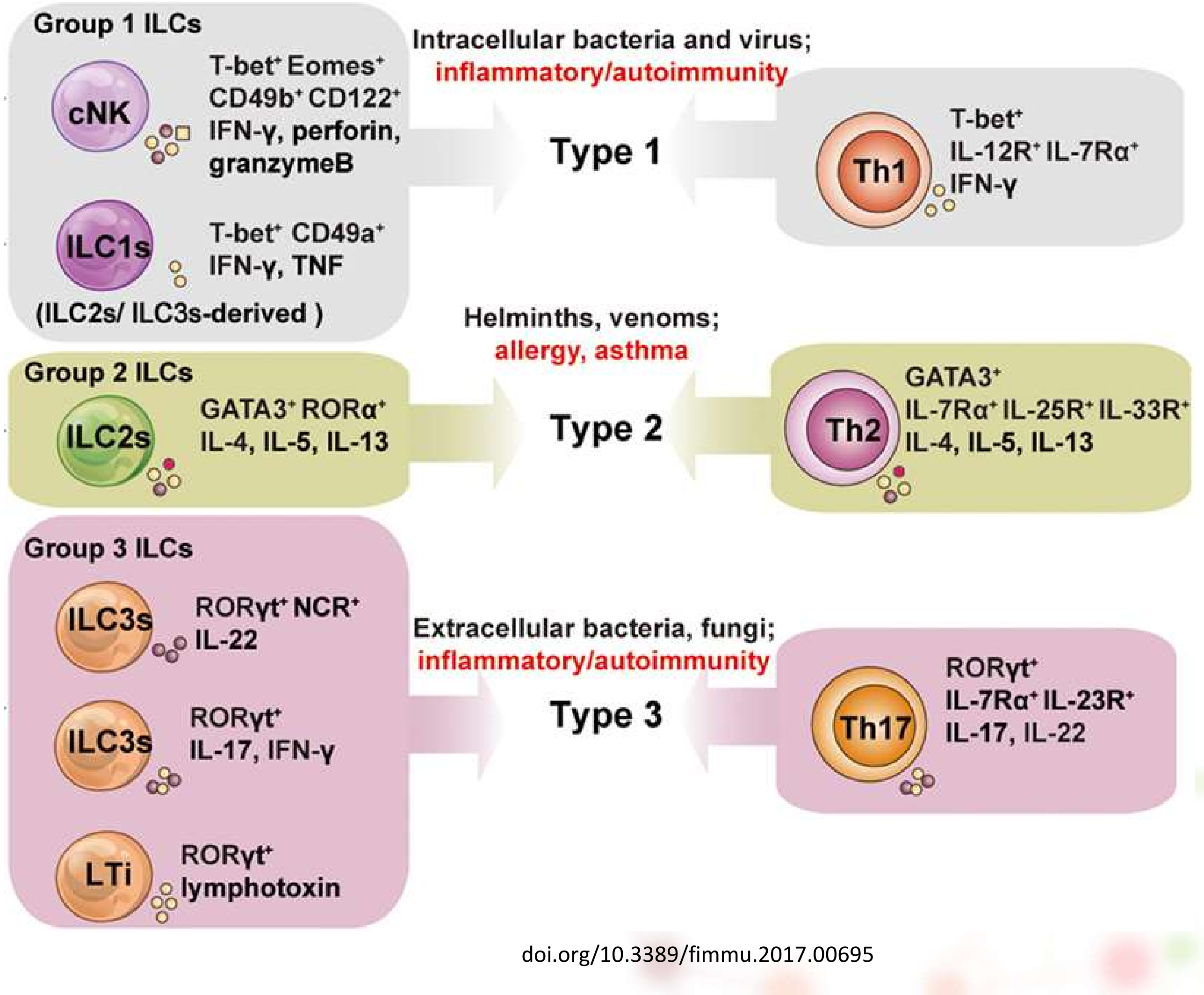
mod. According to Barnes, Steroid Biochem Mol Biol 2010

Biologics / monoclonal antibodies

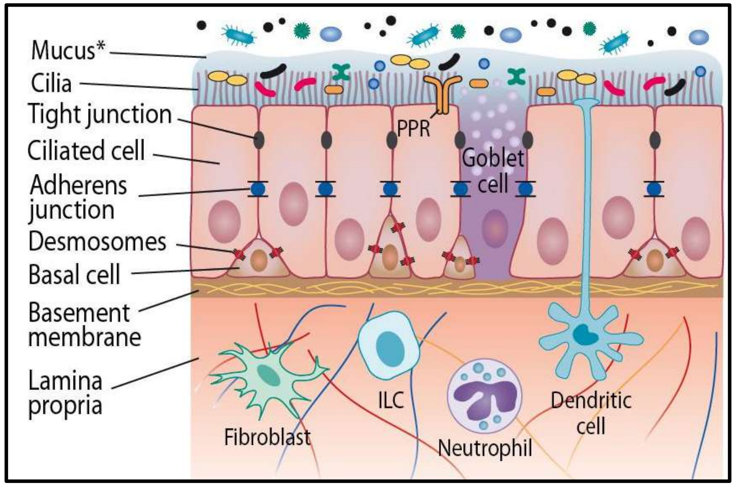


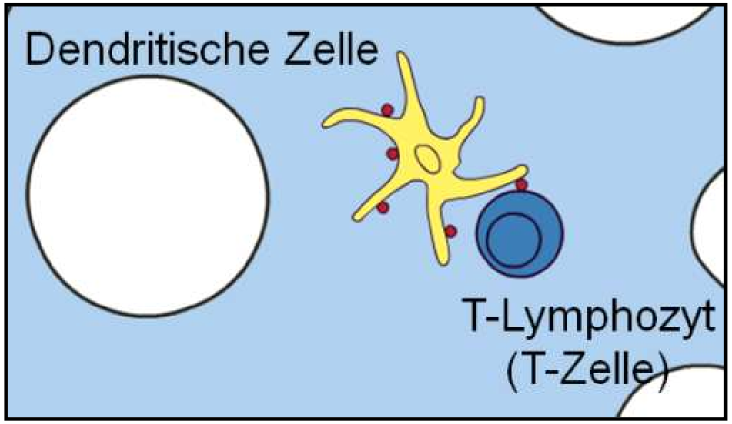
mod. nach doi: 10.1007/s13555-022-00737-7

Three types of inflammation

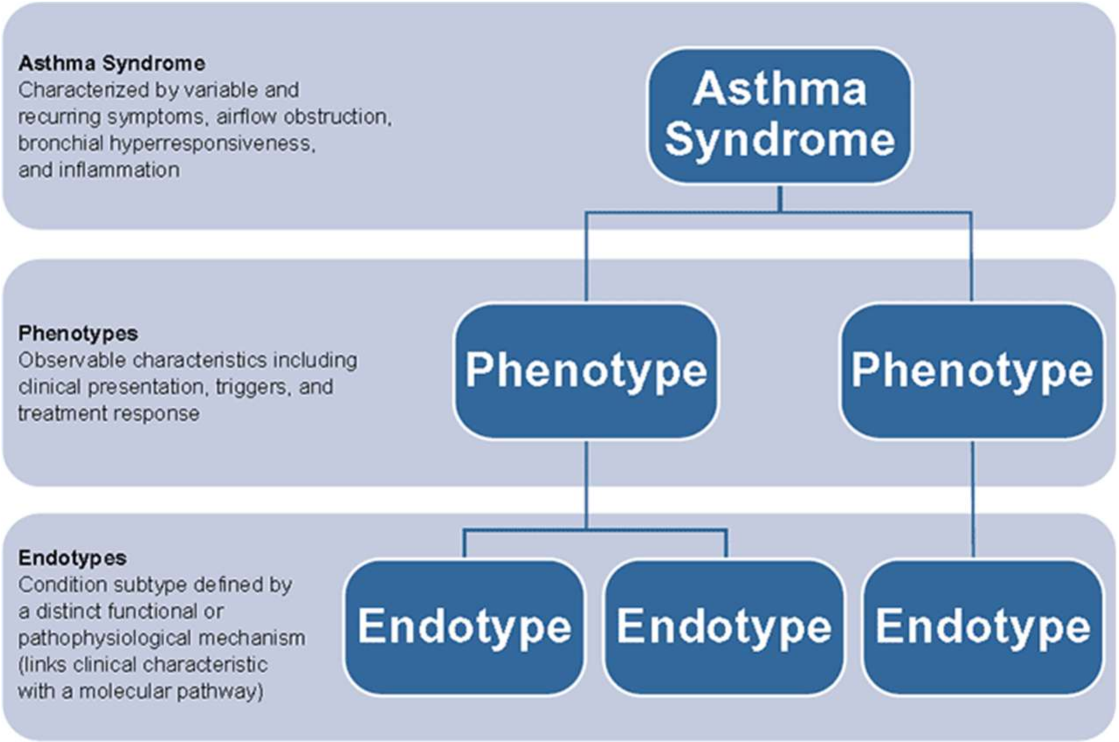


doi.org/10.3389/fimmu.2017.00695





Concept of phenotyping and endotyping a disease



⇒ endotypes are key for the individual success of a therapy / efficiency of a drug

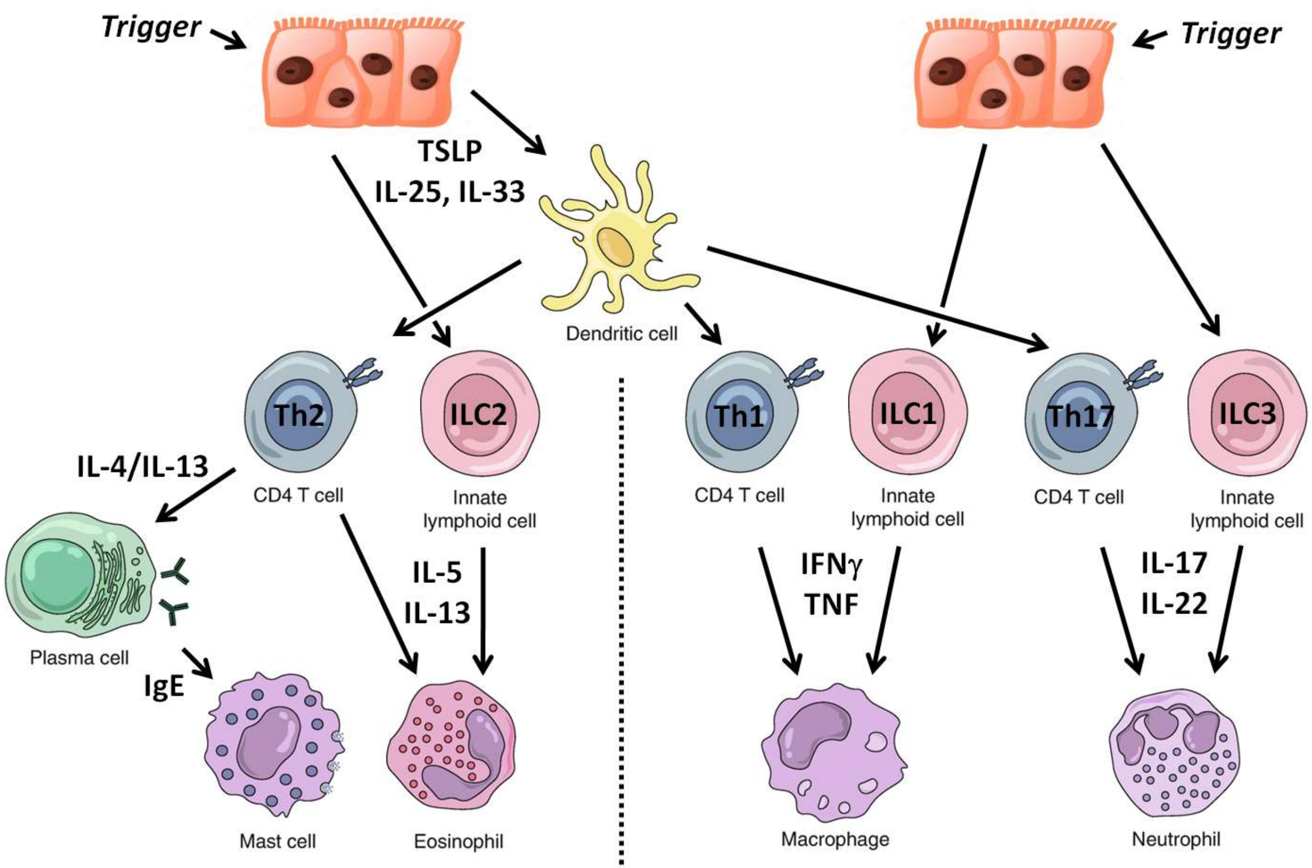
⇒ there are smooth transitions between the different endotypes

⇒ endotypes might change with age and disease progression

⇒ endotype reseach is the way to a personalized medicine – the ultimate goal to optimize individual therapy strategies

mod. according to Ortitz, 2014 http://advanceweb.com/web/**AstraZeneca**/focus_on_asthma_copd_issue10/Focus-on-Asthma-COPD-Issue-10-Asthma-Phenotypes.html

Inflammation endotypes T2 *versus* non-T2



Endotype: T2 = Type 2 = T2*high* Inflammation | T1+3 = non-Type 2 = T2*low* Inflammation

created/mod. according to
Brusselle et al. Nature Medicine 2013
doi.org/10.3389/fimmu.2017.00695
doi: 10.1007/s13555-022-00737-7
doi.org/10.3390/ijms22020910
doi.org/10.1016/j.anai.2022.04.020
doi.org/10.3390/ijms22094369
doi.org/10.1111/all.13760
doi: 10.1007/s13555-022-00737-7
doi.org/10.3390/biomedicines10102486

Biomarker

Severe Asthma:

Biomarker for inflammatory patterns

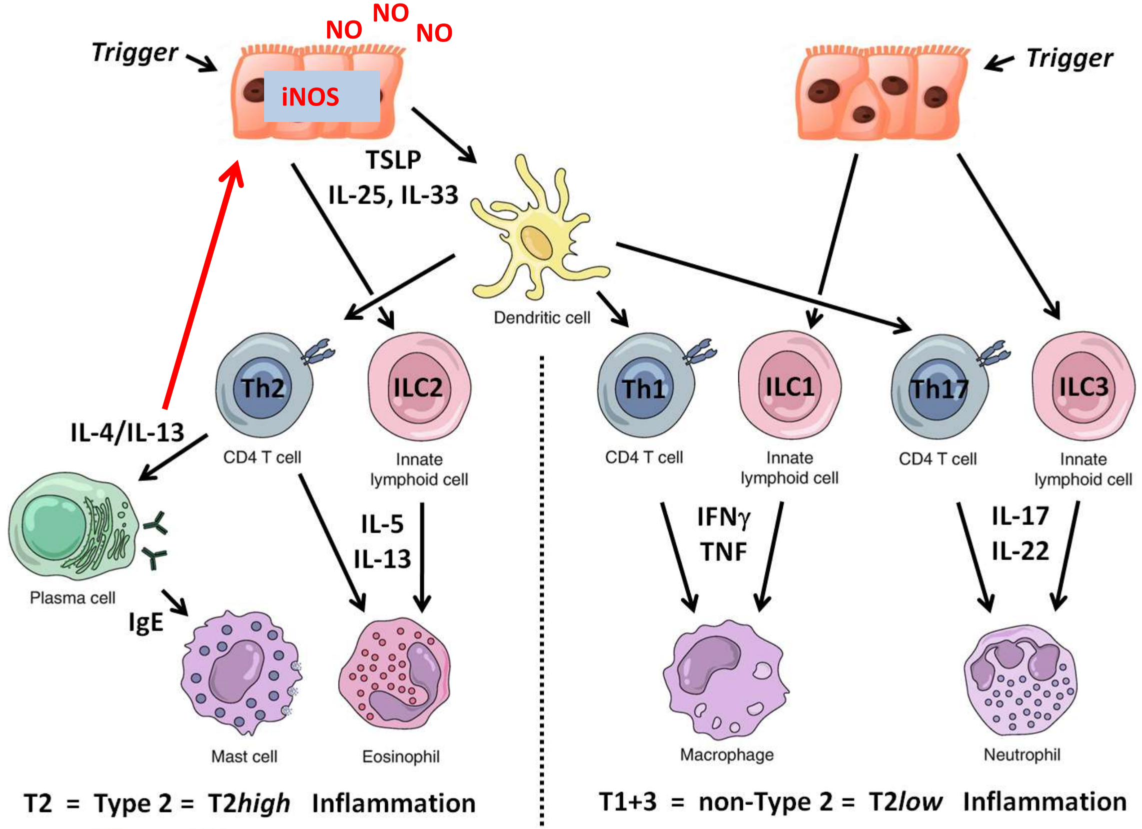
Serum-IgE: ≥76 IU/mL → T2 / allergic inflammation

Bluteosinophile: ≥150/300 Zellen/µL → T2 / eosinophilic inflammation

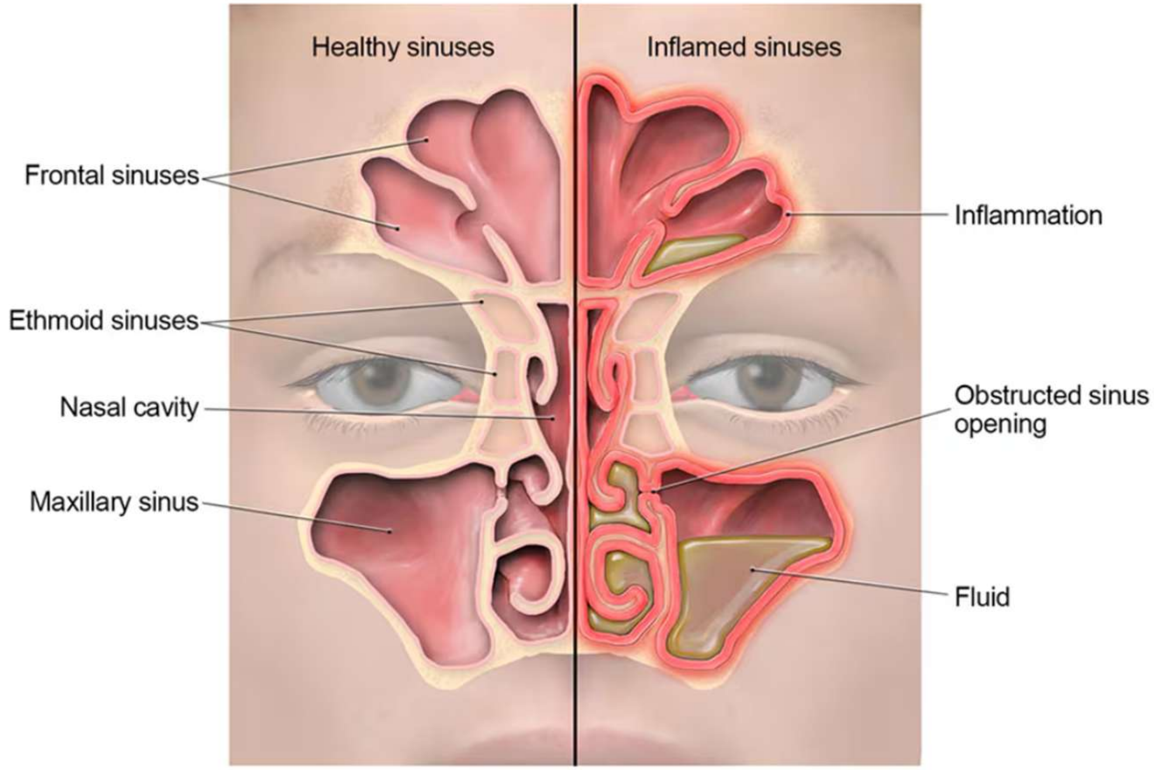
FeNO: ≤25 ppb → non-T2 / steroid-insensitive inflammation

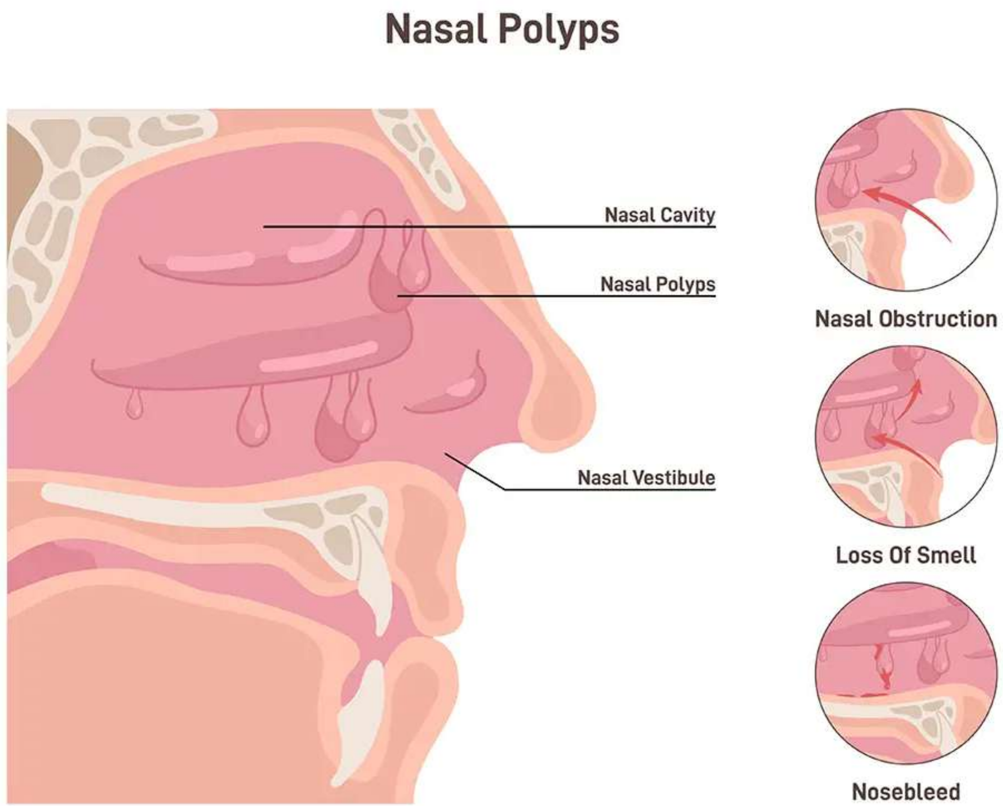
FeNO: ≥50 ppb → T2 / steroid-sensitive inflammation

doi.org/10.3389/fmed.2022.921967



Chronic Rhinosinusitis

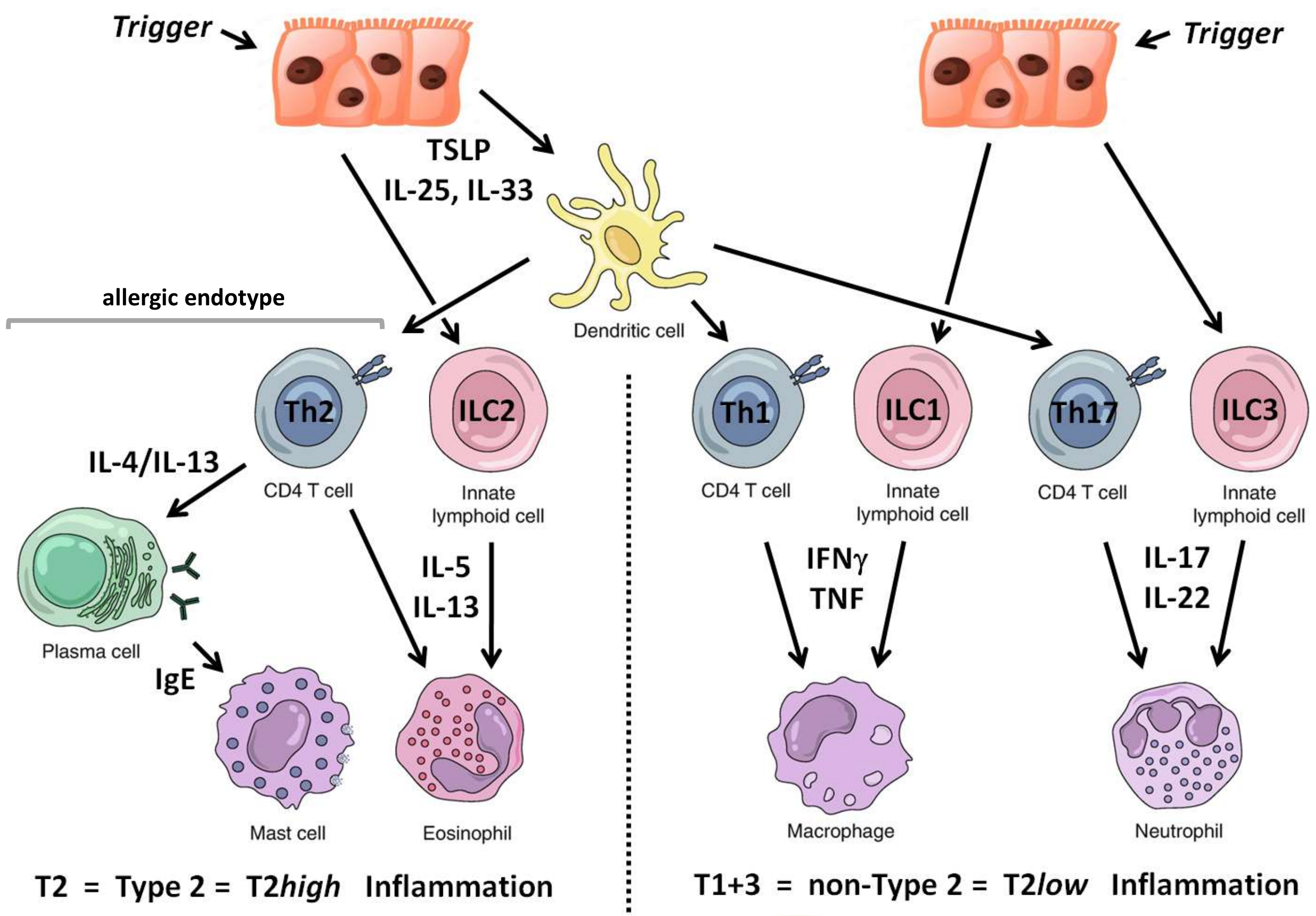




By Centers for Disease Control and Prevention - https://www.cdc.gov/sinus-infection/about/, Public Domain, https://commons.wikimedia.org/w/index.php?curid=155109646

(2025-04-011) https://rockytop-ent.com/nose/nasal-polyps/

Chronische Rhinosinusitis : Endotypen



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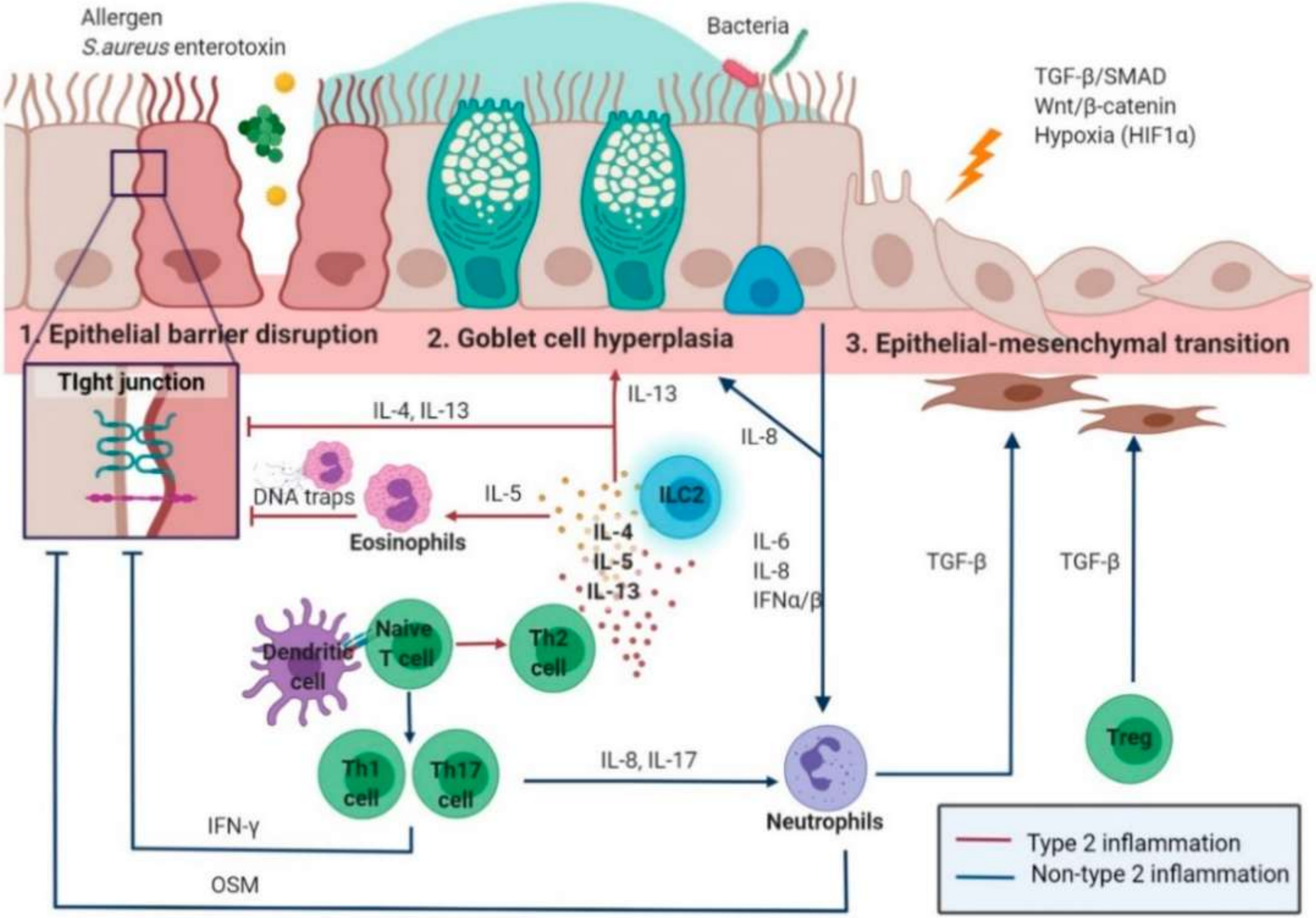
doi: 10.1007/s13555-022-00737-7
doi.org/10.3390/biomedicines10102486

CRS wNP sNP

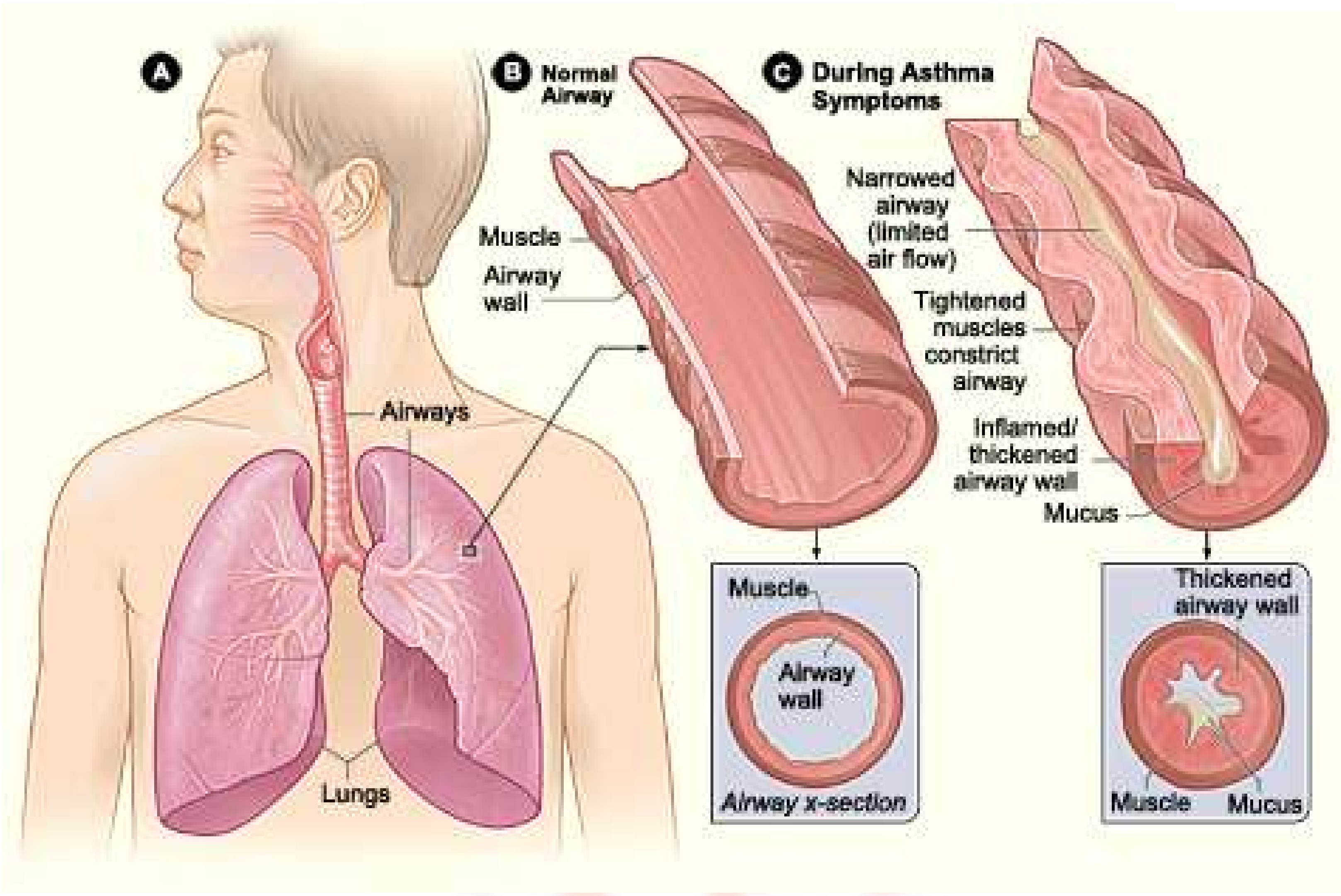
CRS wNP (major), sNP (30-55%) wNP (minor), sNP (asian: major)

Chronic Rhinosinusitis: pathophysiology



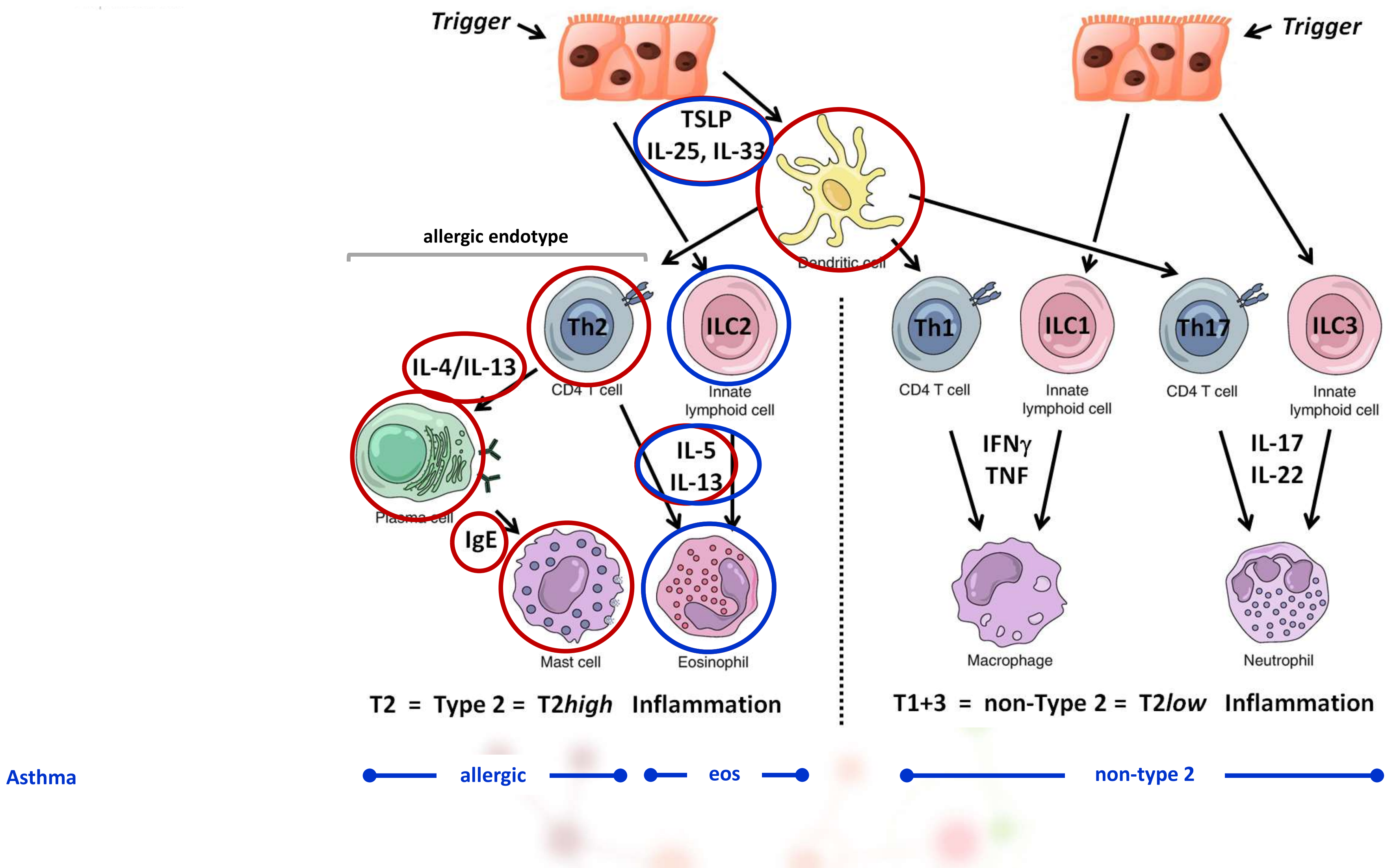
doi.org/10.3390/ijms22020910

Asthma



By United States-National Institute of Health: National Heart, Lung, Blood Institute - http://www.nhlbi.nih.gov/health/health-topics/topics/asthma/, Public Domain, https://commons.wikimedia.org/w/index.php?curid=24760677

Asthma: Endotypen



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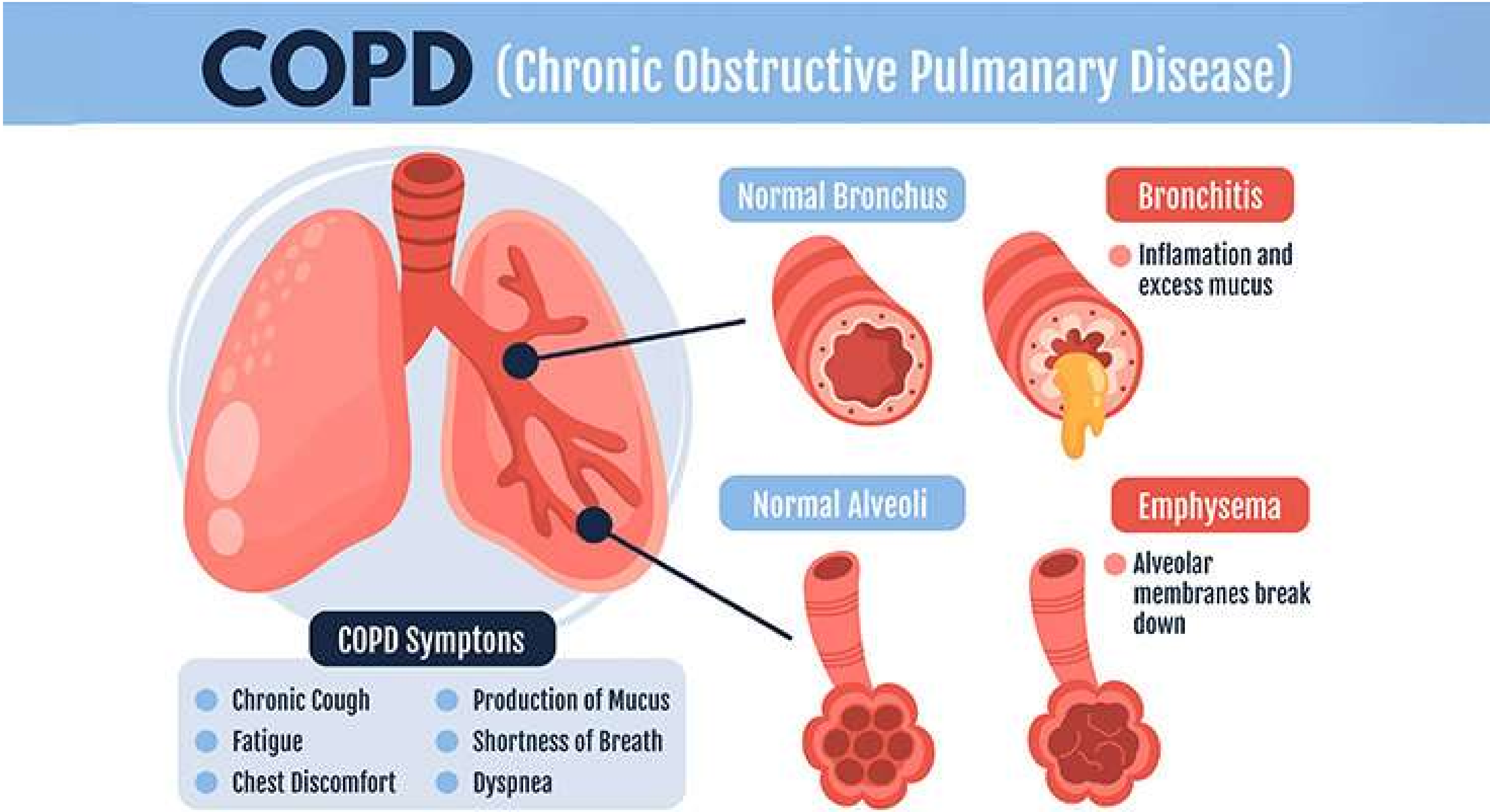
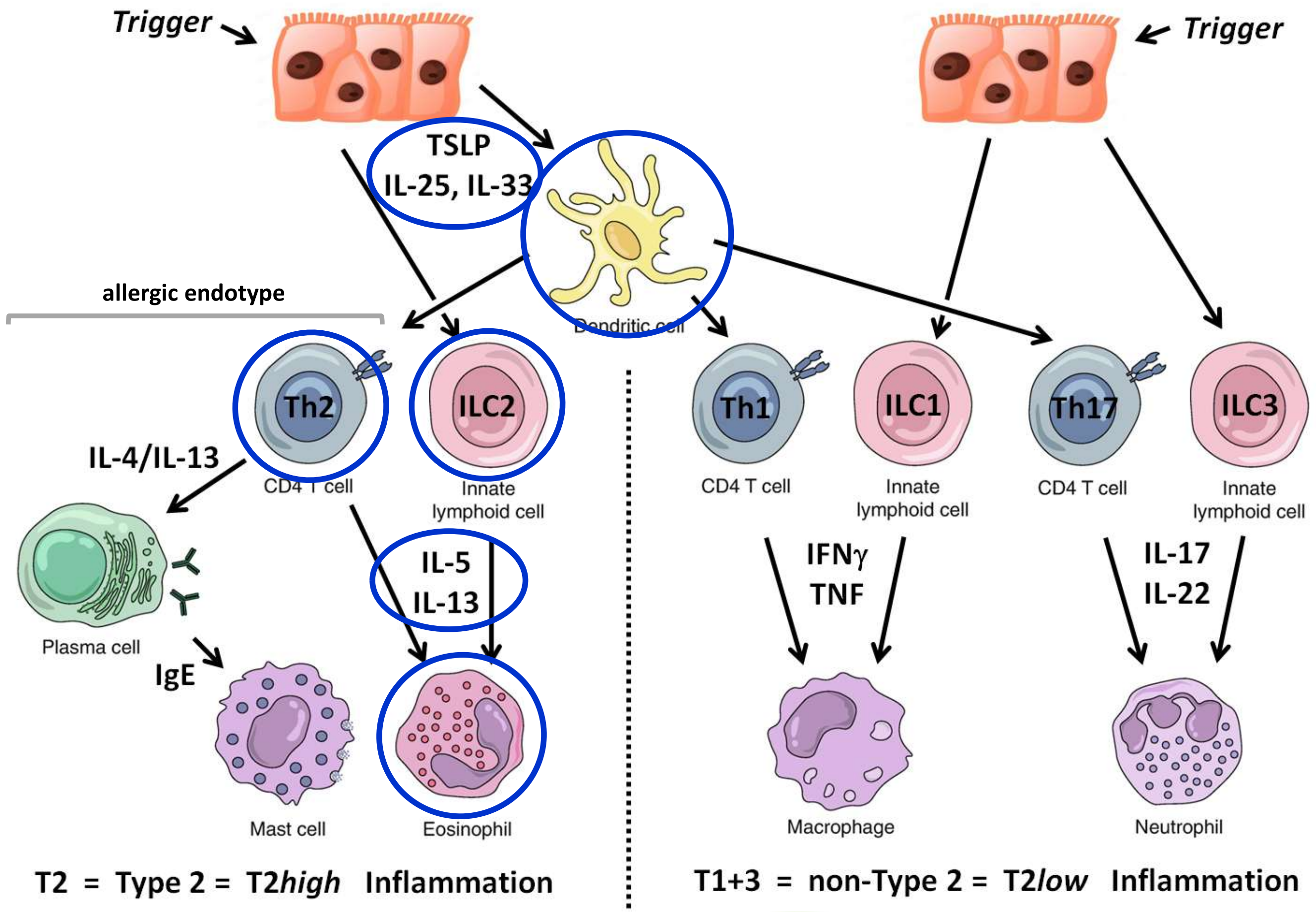


(2025-04-011) https://springfieldmedicalclinic.com/blogs/what-is-chronic-obstructive-pulmonary-disease-copd

COPD: Endotypen



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doi.org/10.3390/ijms22094369
doi.org/10.1111/all.13760
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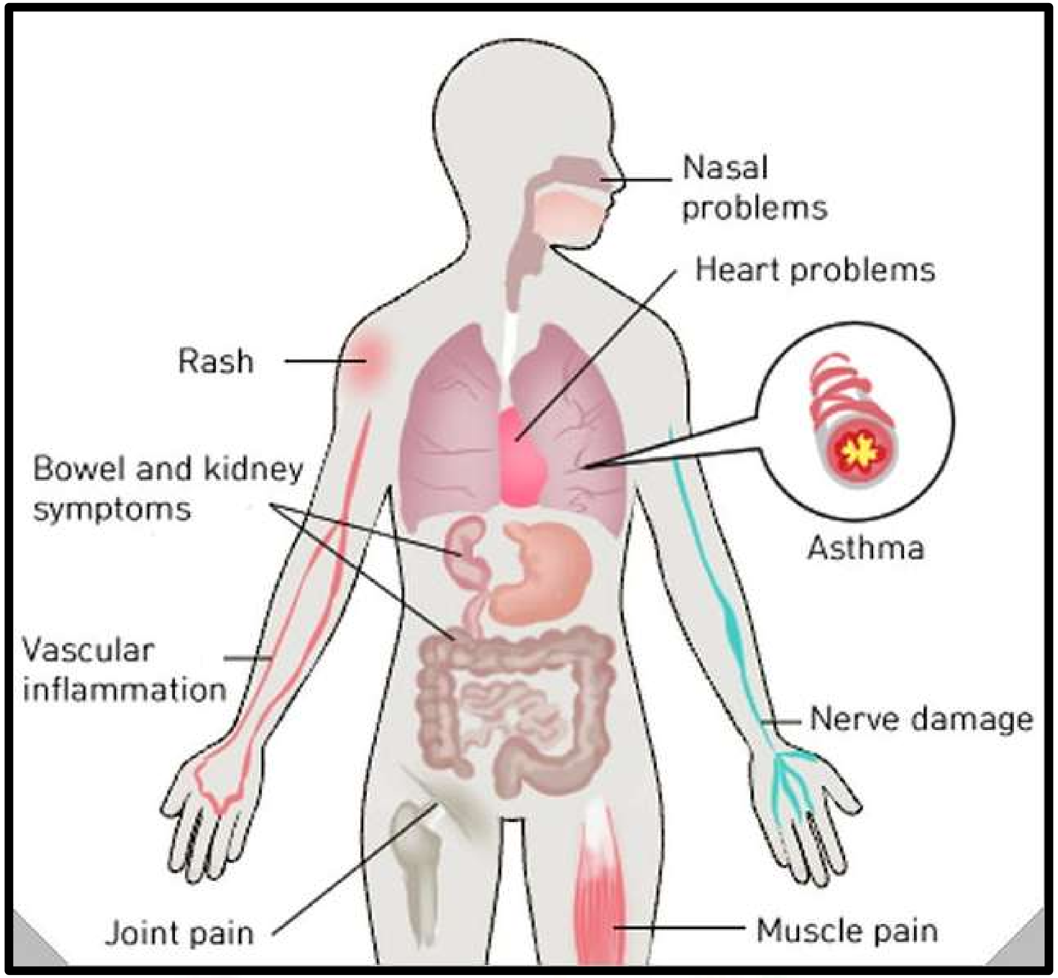
doi.org/10.3390/biomedicines10102486

COPD *zusätzlich* + eos

Eosinophile Granulomatose mit Polyangiitis (EGPA): Endotypen



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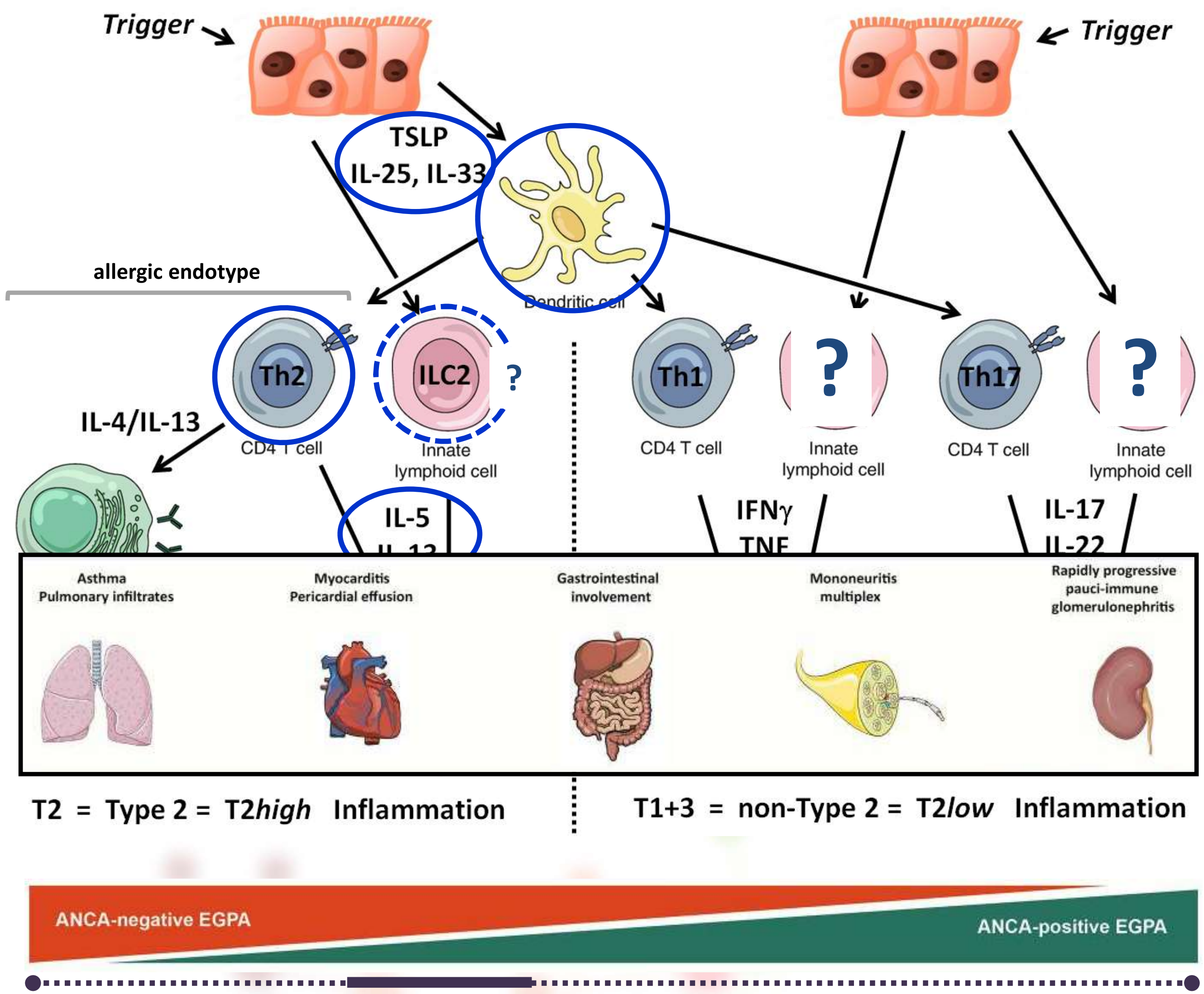
doi.org/10.1111/all.13760
doi: 10.1007/s13555-022-00737-7
doi.org/10.3390/biomedicines10102486
doi: 10.3389/fmed.2021.627776
doi:: 10.1038/s41584-022-00819-y

Eosinophile Granulomatose mit Polyangiitis (E



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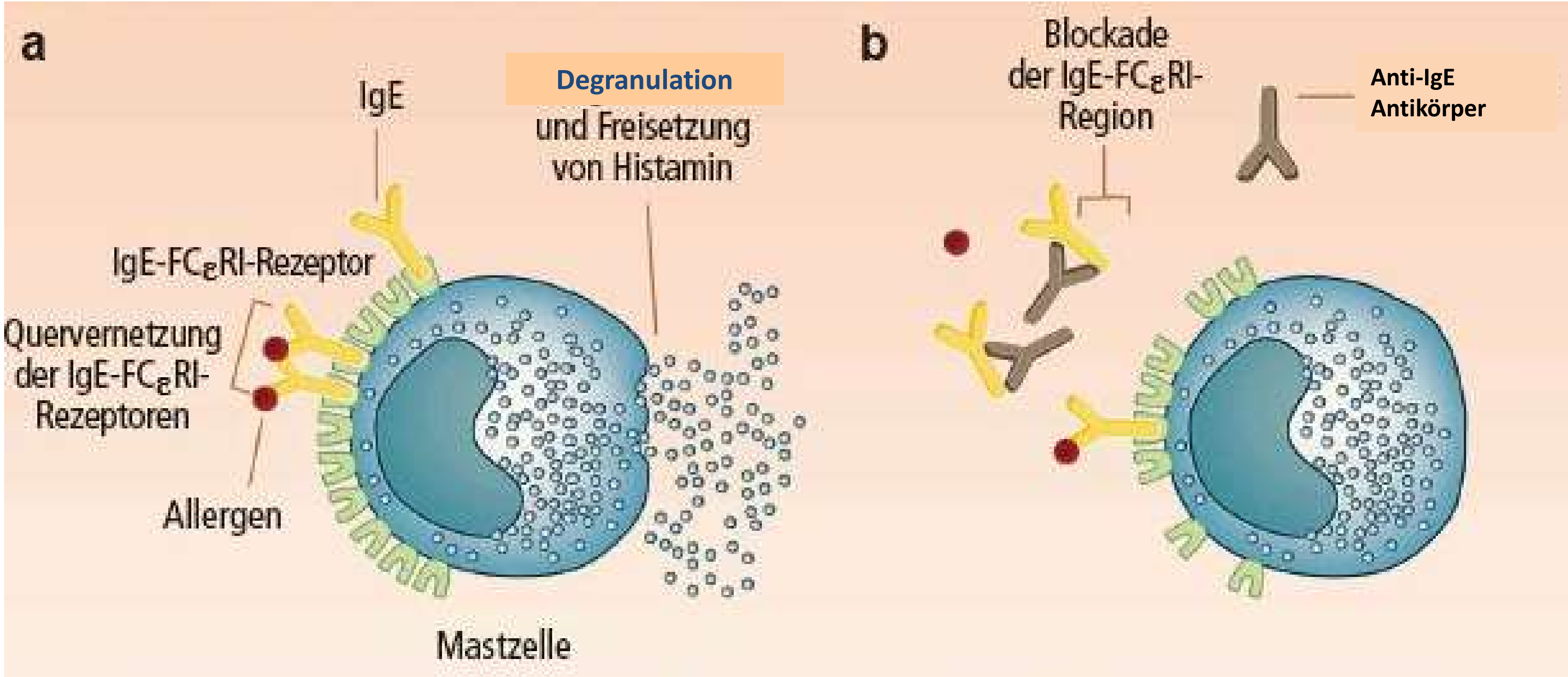
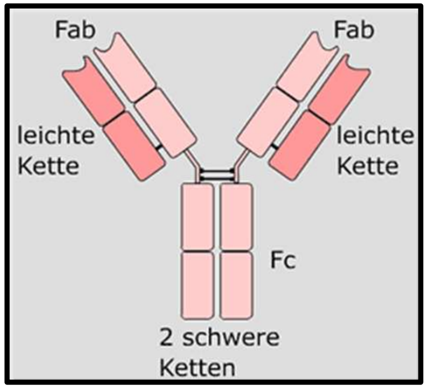
doi: 10.3389/fmed.2021.627776

Mechanisms of biologic drugs: anti-IgE antibody (Omalizumab)



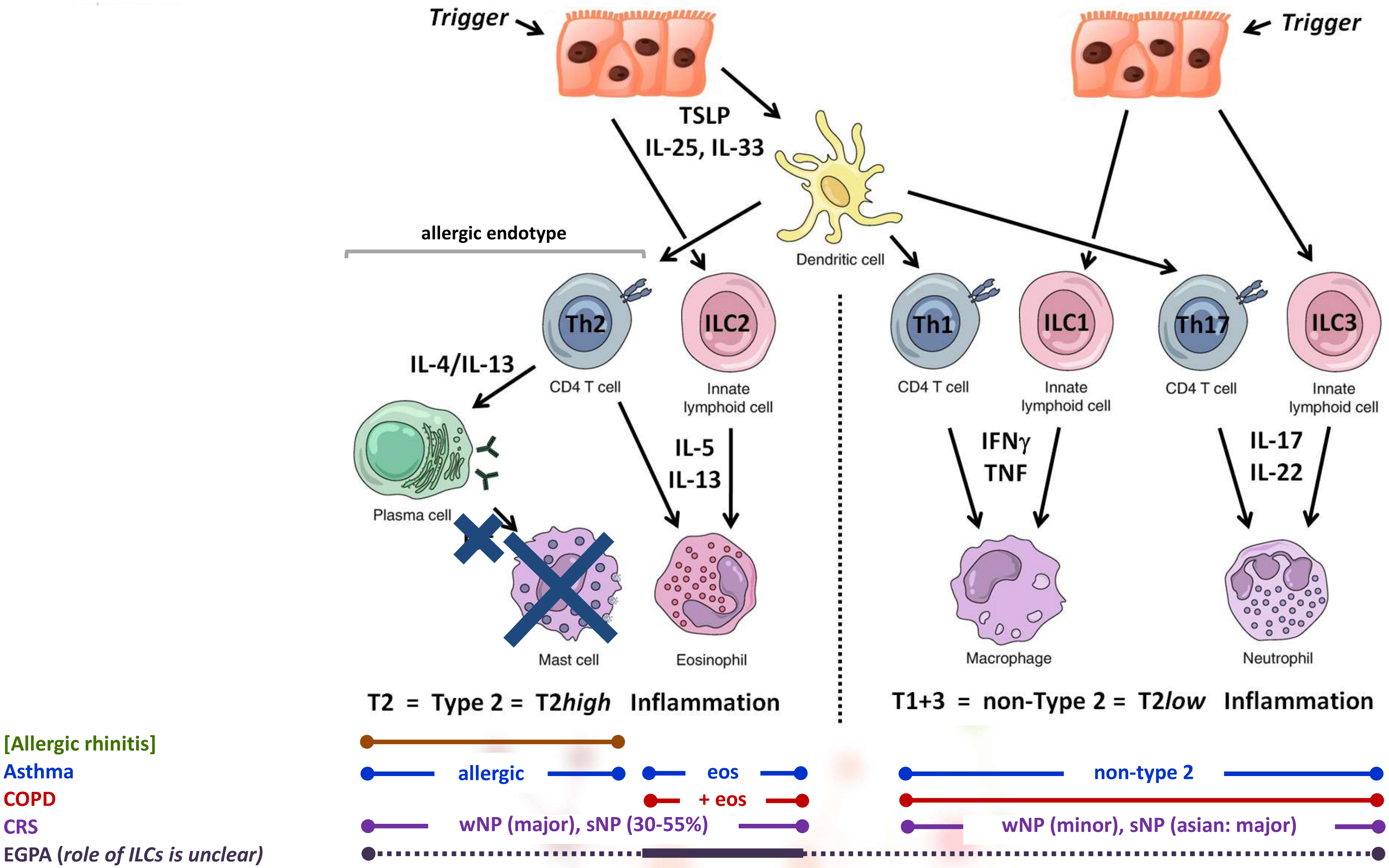


mod. nach Boushey, JACI, 2007

- der <u>anti-IgE</u> Antikörper bindet an die konstante Fc Region des IgE Antikörpers
- dadurch kann der IgE Antikörper nicht an die Mastzellen binden
- dadurch können die Mastzellen nicht durch das Allergen aktiviert werden

mod. nach http://www.infektionsbiologie.ch

Mechanisms of biologic drugs: anti-IgE antibody (Omalizumab)



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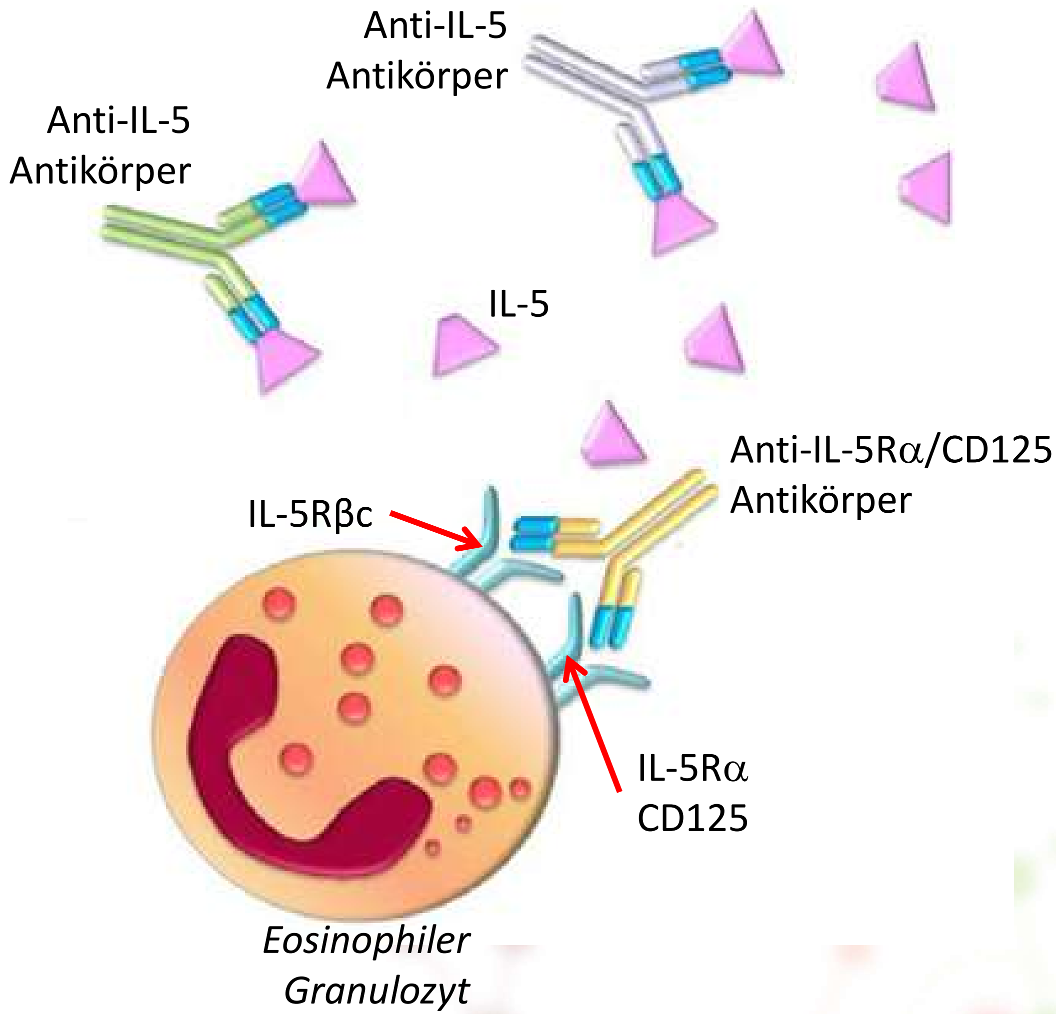
doi.org/10.1111/all.13760
doi: 10.1007/s13555-022-00737-7
doi.org/10.3390/biomedicines10102486

Mechanisms of biologic drugs: anti-IL-5 und anti-IL-5Rα/CD125 antibody (Mepolizumab, Reslizumab, Benralizumab)

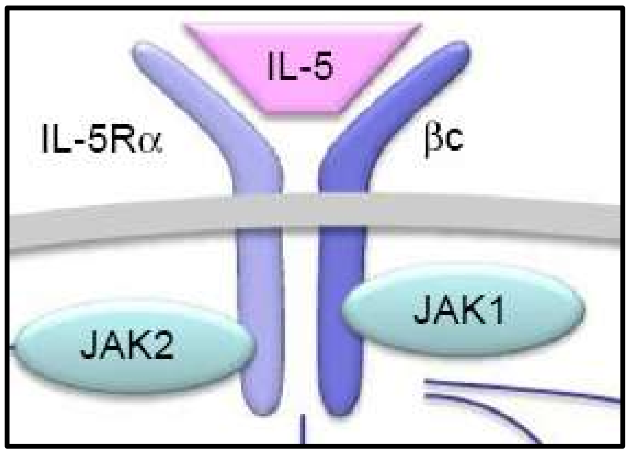


- anti-IL-5 Antikörper binden an IL-5
- anti-IL5Rα Antikörper binden an und blockieren den IL-5 Rezeptor auf den Eosinophilen

⇒ IL-5 kann nicht an den IL-5 Rezeptor auf den Eosinophilen binden

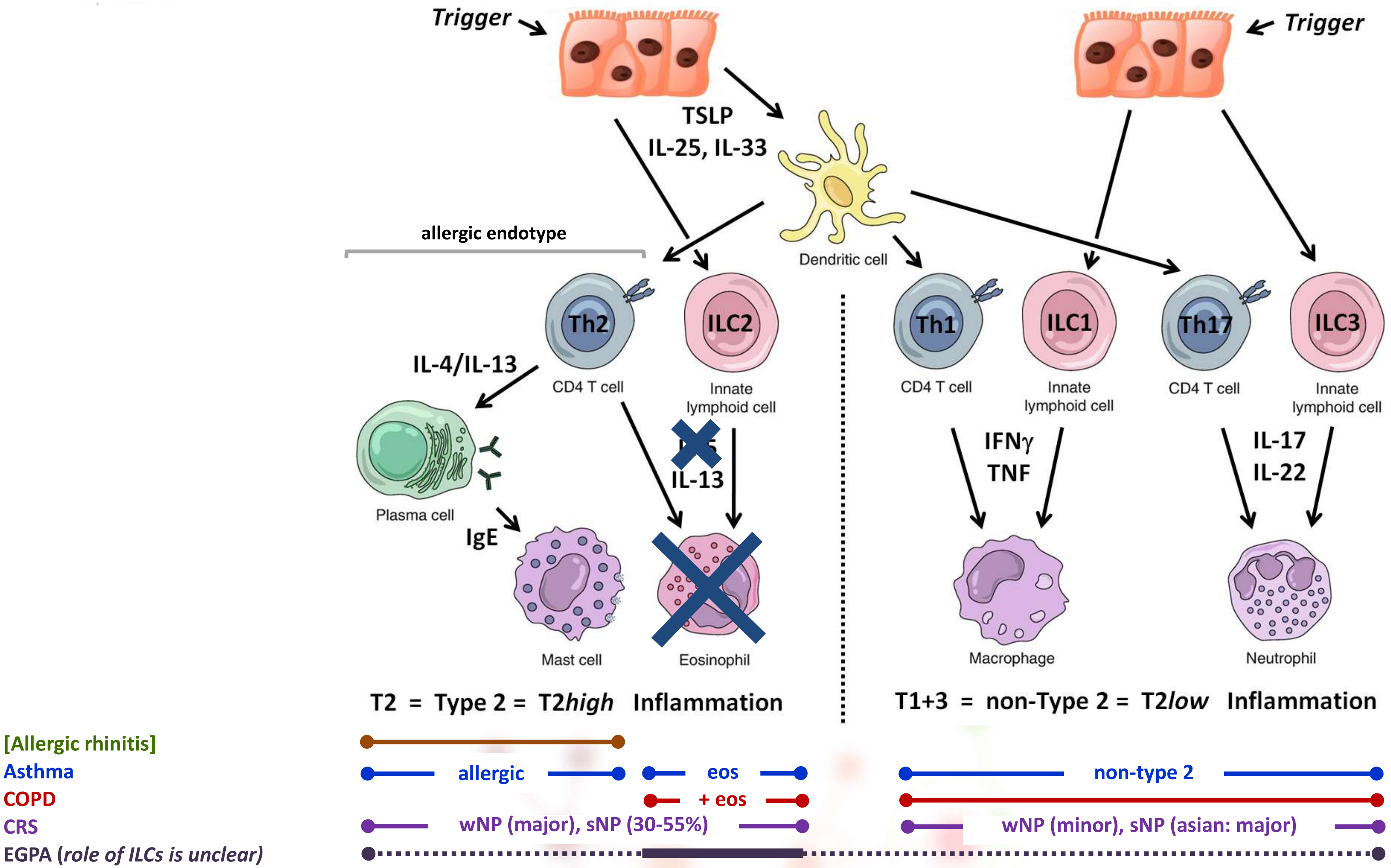
⇒ die Eosinophilen werden nicht aktiviert

⇒ die Eosinophilen gehen in den Zelltod



mod. nach Pelaia et al., Therapeutics and Clinical Risk Management, 2016, 12

Mechanisms of biologic drugs: anti-IL-5 und anti-IL-5Rα/CD125 antibody (Mepolizumab, Reslizumab, Benralizumab)



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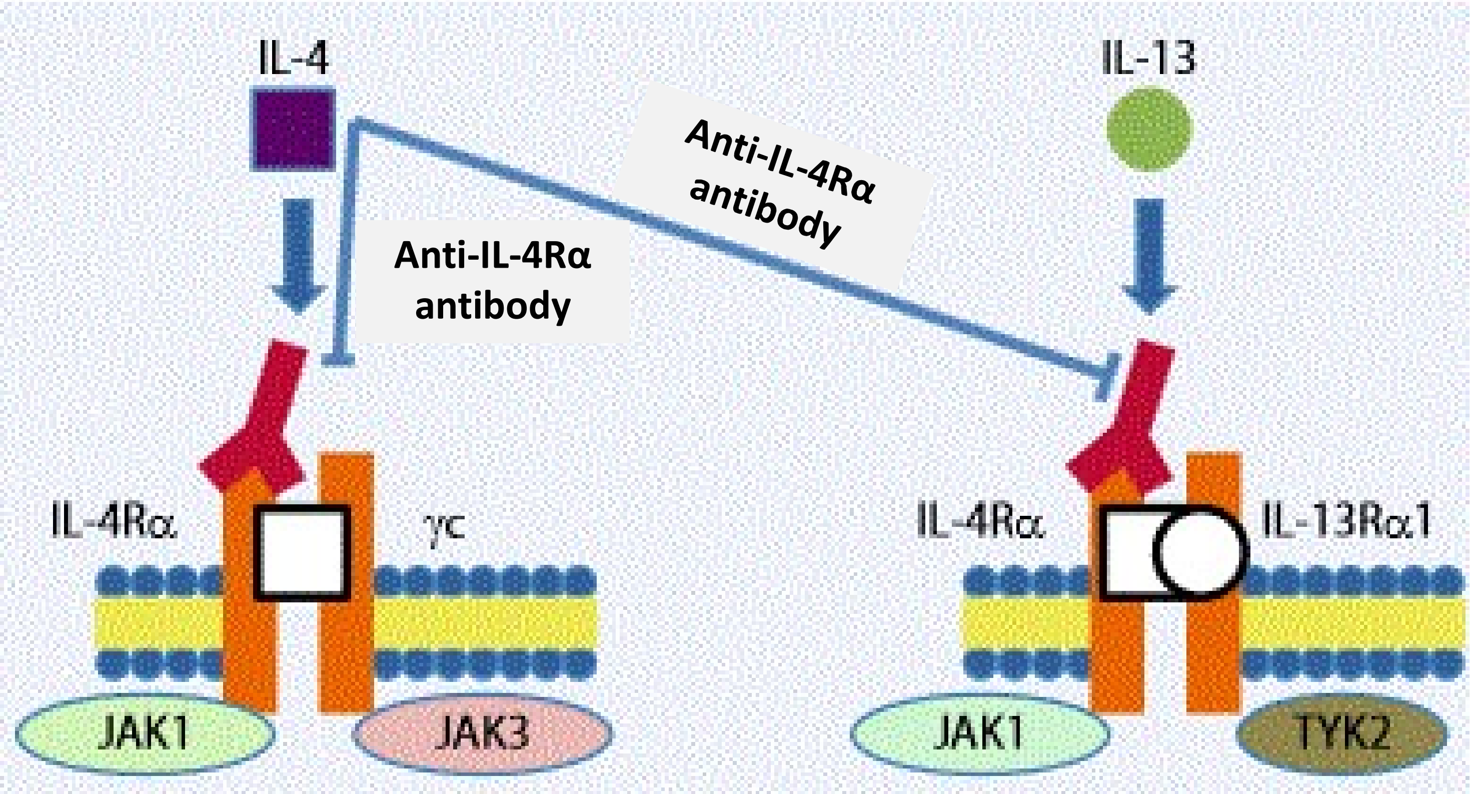
doi.org/10.3390/ijms22094369
doi.org/10.1111/all.13760
doi: 10.1007/s13555-022-00737-7
doi.org/10.3390/biomedicines10102486

Mechanisms of biologic drugs: anti-IL-4Rα antibody (Dupilumab)



mod. according tohttp://www.springermedizin.at/artikel/50157

• IL-4- and IL-13-receptors each are heterodimers

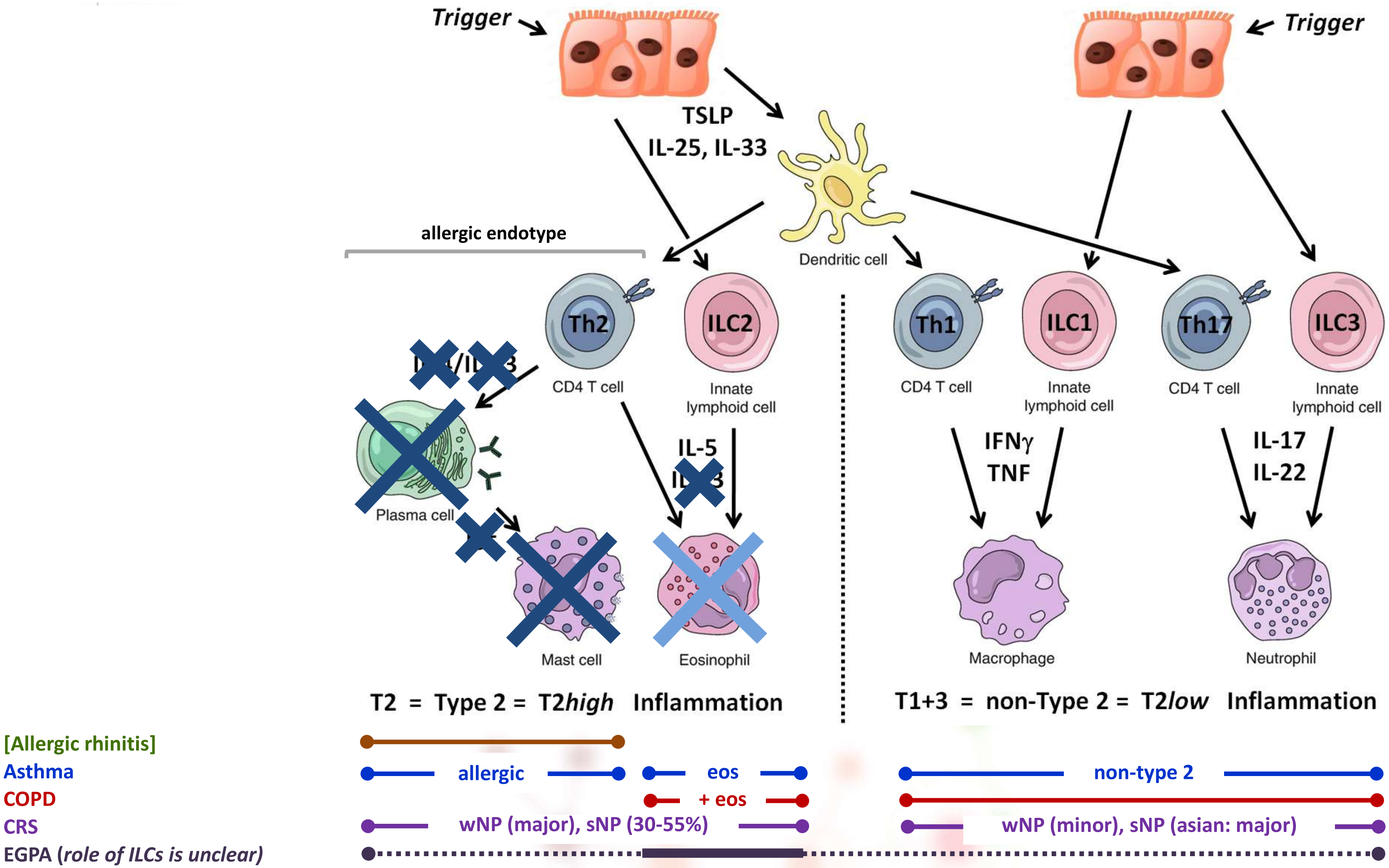
• both receptors contain IL-4Rα

⇒ anti-IL4Rα antibody binds and blocks both IL-4 and IL-13 receptors

⇒ B cells are not activated by IL-4 and IL-13 to produce IgE antibodies

⇒ this concepts evades the redundant functions of IL-4 and IL-13

Mechanisms of biologic drugs: anti-IL-4Rα antibody (Dupilumab)



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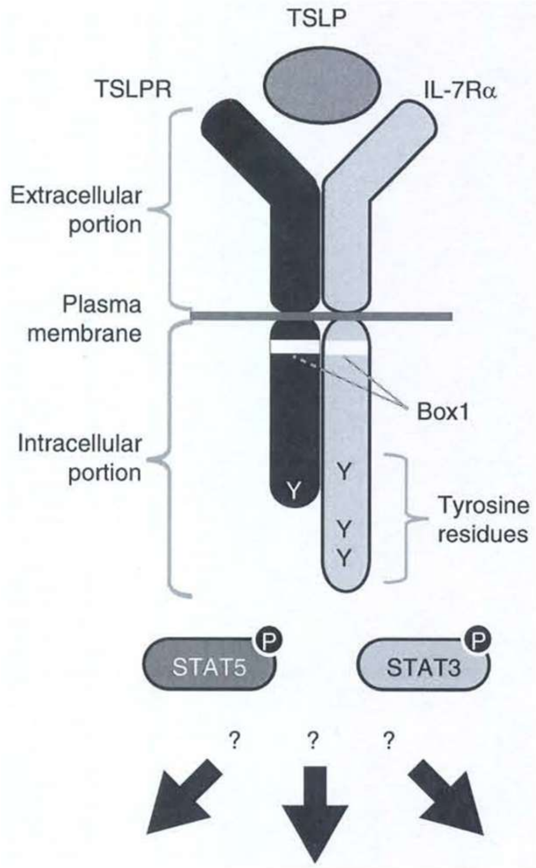
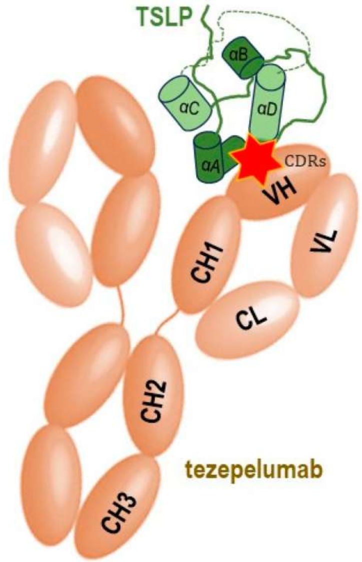
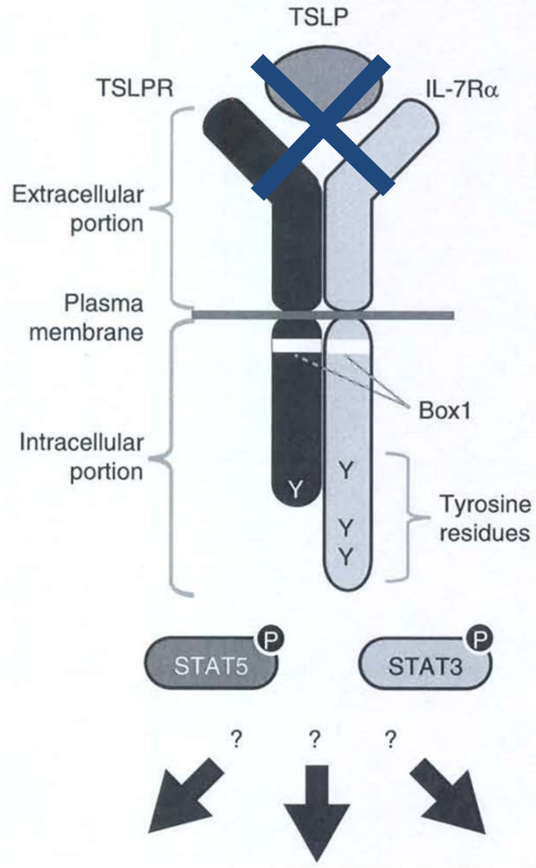
doi: 10.1007/s13555-022-00737-7
doi.org/10.3390/biomedicines10102486

Mechanisms of biologic drugs: anti-TSLP antibody (Tezepelumab)



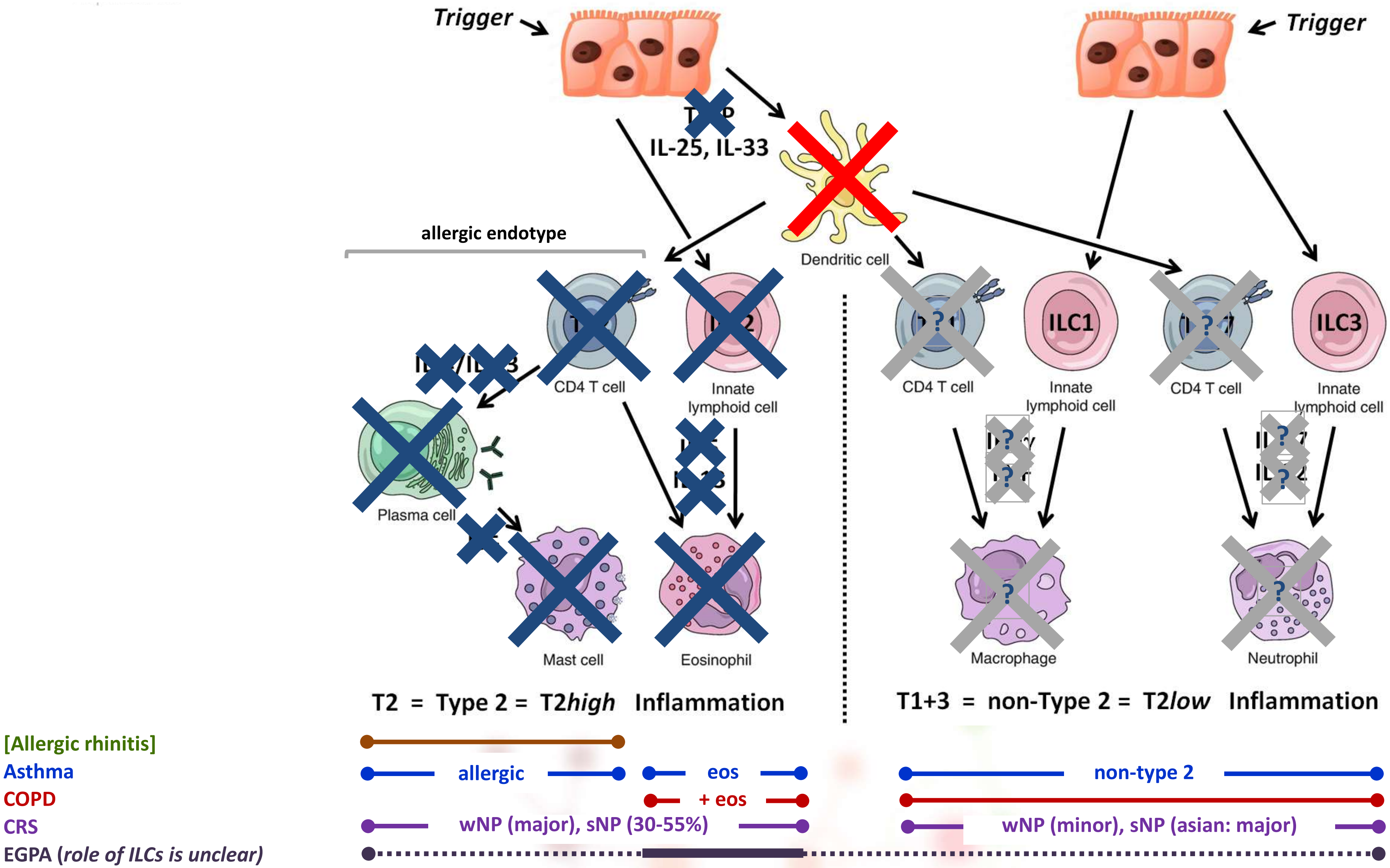




https://www.creativebiolabs.net/tezepelumab-overview.htm

DOI: 10.2332/allergolint.11-RAI-0376

Mechanisms of biologic drugs: anti-TSLP antibody (Tezepelumab)



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doi.org/10.3390/ijms22094369
doi.org/10.1111/all.13760
doi: 10.1007/s13555-022-00737-7
doi.org/10.3390/biomedicines10102486

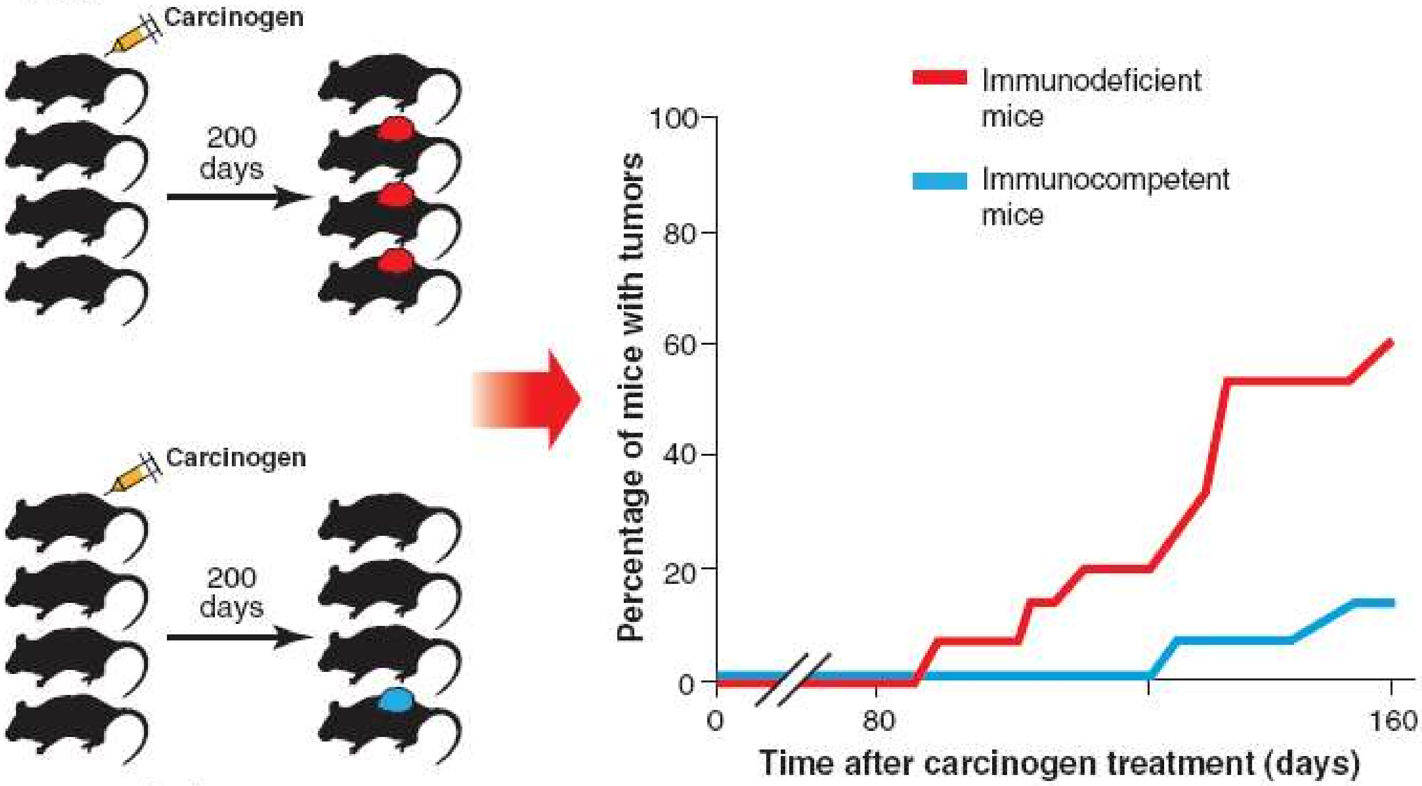
NUCALA
mepolizumab

nexus

GSK

Animal experimental evidence of the "immunosurveillance Theory" by Burnet (1957)

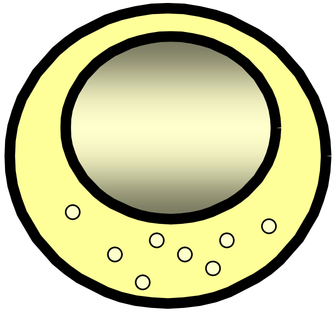
RAG2-deficient mice



immunocompetent mice

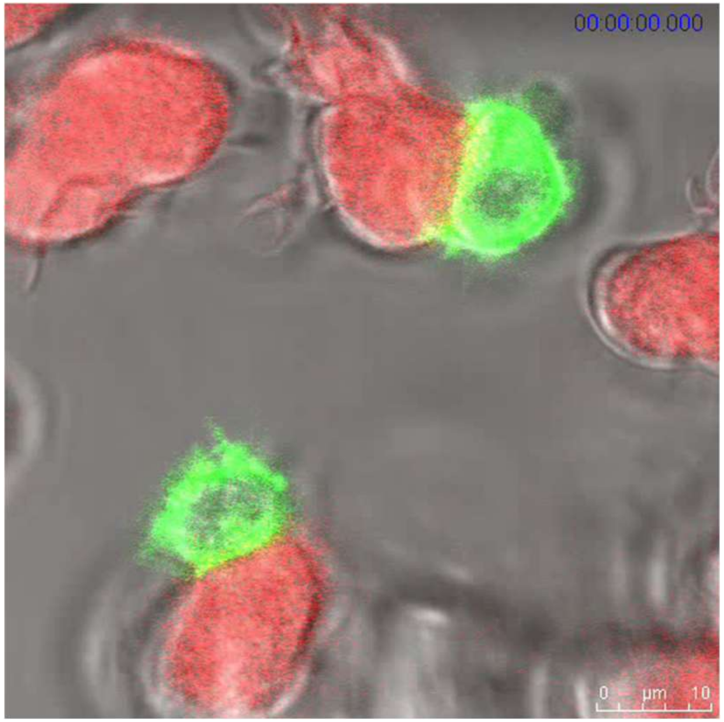
"Immunosurveillance" by natural killer cells of the innate immune system

Natural Killer Cells (NK-cells)



function

Release of Perforin and Granzym which can kill tumor cells



NK cells recognise tumour cells: mechanism 1

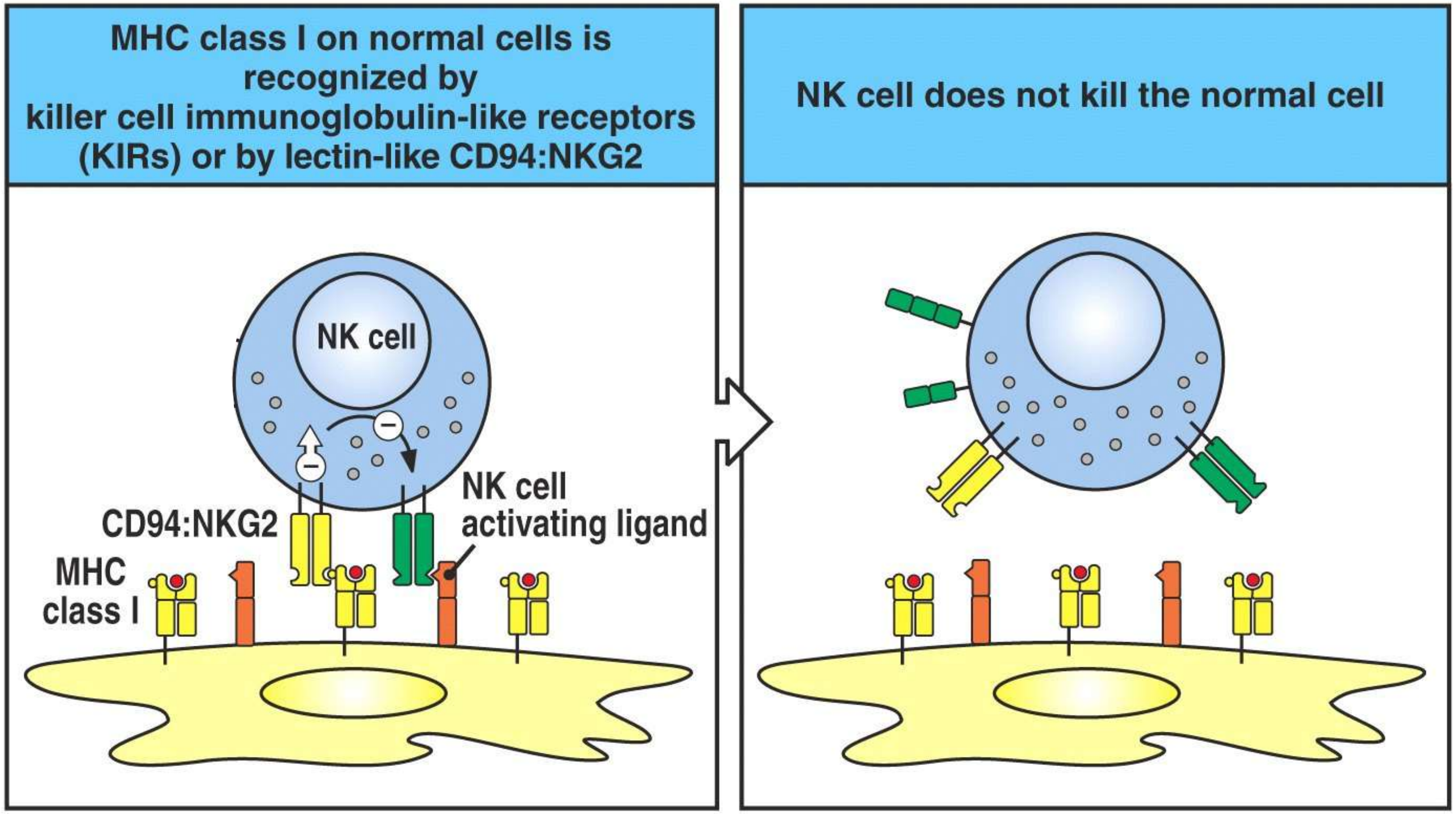


Figure 2-50 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

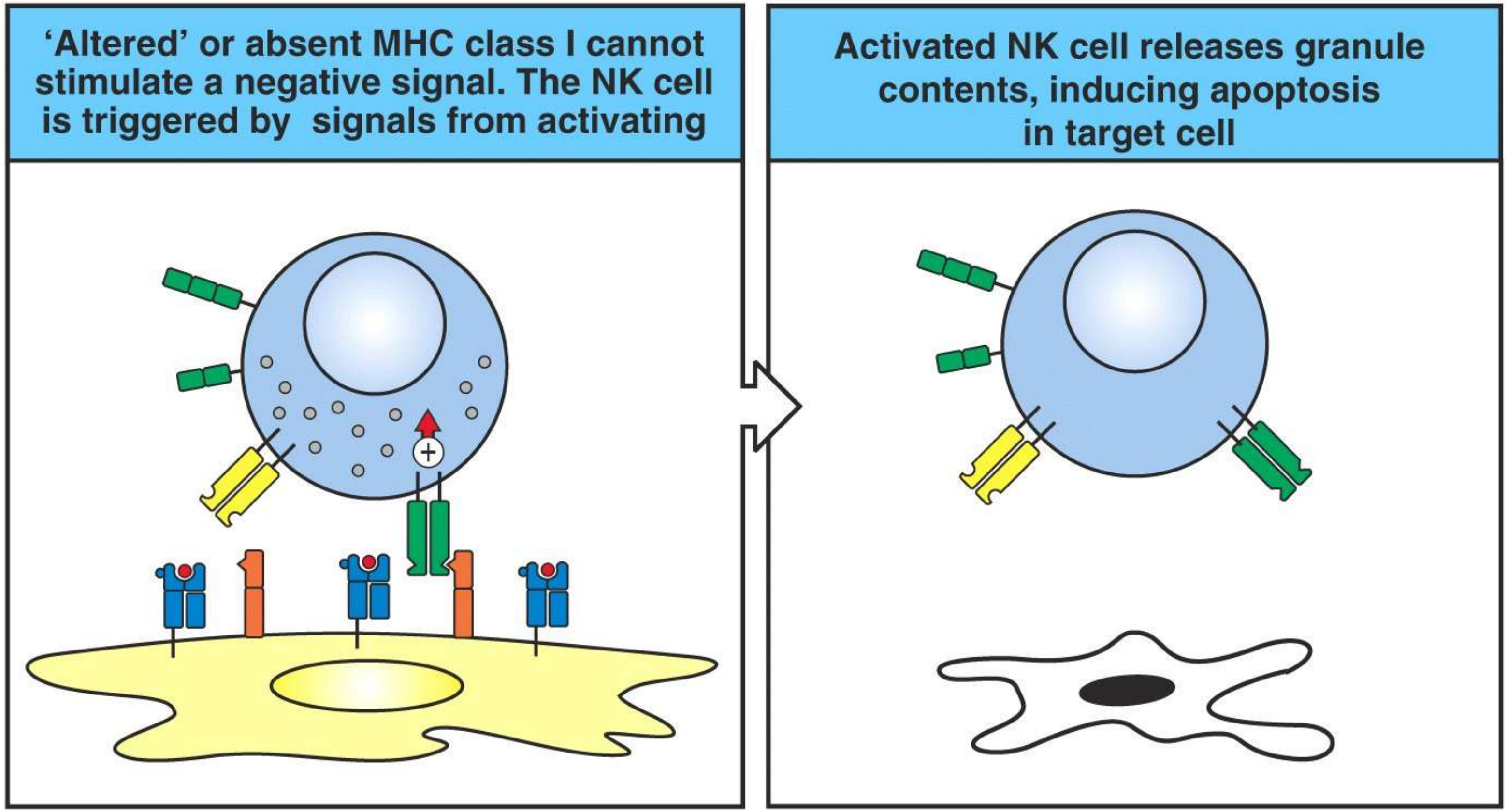


Figure 2-50 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Tumour antigens against which an adaptive immune response can evolve

Examples for the presentation of tumour antigens

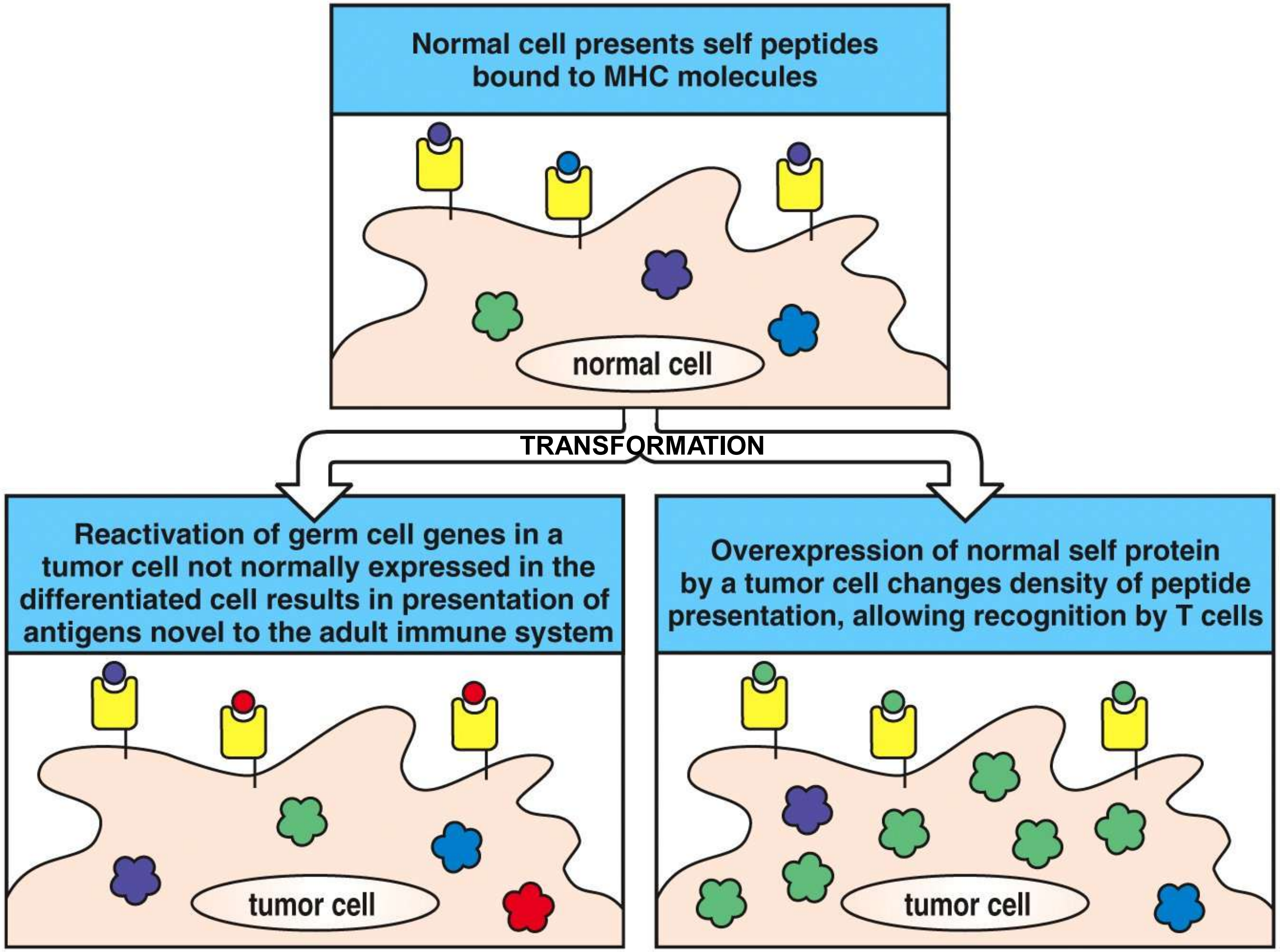


Figure 14-13 Immunobiology, 6/e. (© Garland Science 2005)

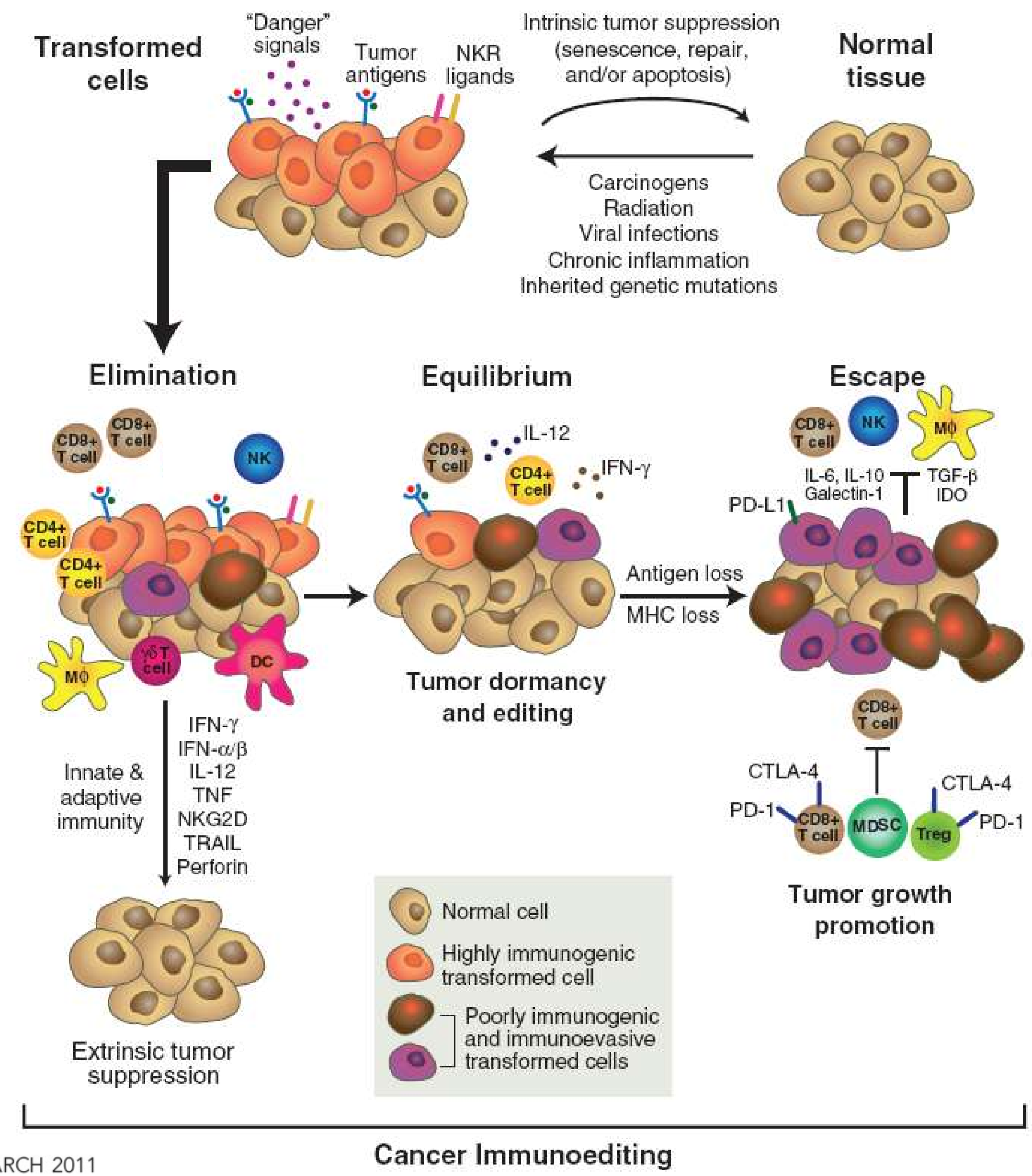
MAGE=melanoma-associated antigen

HER-2= Receptor tyrosine-protein kinase erbB-2

MUC= Mucin

Potential tumor rejection antigens have a variety of origins

Class of antigen	Antigen	Nature of antigen	Tumor type
Differentiation	Tyrosinase	Enzyme in pathway of melanin synthesis	Melanoma
	Surface Ig	Specific antibody after gene rearrangements in B-cell clone	Lymphoma
Abnormal gene expression	HER-2/neu	Receptor tyrosine kinase	Breast Ovary
Abnormal post-translational modification	MUC-1	Underglycosylated mucin	Breast Pancreas
Oncoviral protein	HPV type 16, E6 and E7 proteins	Viral transforming gene products	Cervical carcinoma
Tumor-specific mutated oncogene or tumor suppressor	Cyclin-dependent kinase 4	Cell-cycle regulator	Melanoma
	β-Catenin	Relay in signal transduction pathway	Melanoma
	Caspase-8	Regulator of apoptosis	Squamous cell carcinoma
Germ cell	MAGE-1 MAGE-3	Normal testicular proteins	Melanoma Breast Glioma



Transformed cells
"Danger" signals
Tumor antigens
NKR ligands
Intrinsic tumor suppression (senescence, repair, and/or apoptosis)
Normal tissue
Carcinogens
Radiation
Viral infections
Chronic inflammation
Inherited genetic mutations
Elimination
Equilibrium
Escape
CD8+ T cell
NK
CD4+ T cell
Mϕ
γδT cell
DC
IL-12
IFN-γ
IL-6, IL-10
Galectin-1
TGF-β
IDO
PD-L1
Antigen loss
MHC loss
Tumor dormancy and editing
IFN-γ
IFN-α/β
IL-12
TNF
NKG2D
TRAIL
Perforin
Innate & adaptive immunity
Extrinsic tumor suppression
Normal cell
Highly immunogenic transformed cell
Poorly immunogenic and immunoevasive transformed cells
CTLA-4
PD-1
MDSC
Treg
Tumor growth promotion
Cancer Immunoediting

Mechanisms involved in the immune escape of tumor cells

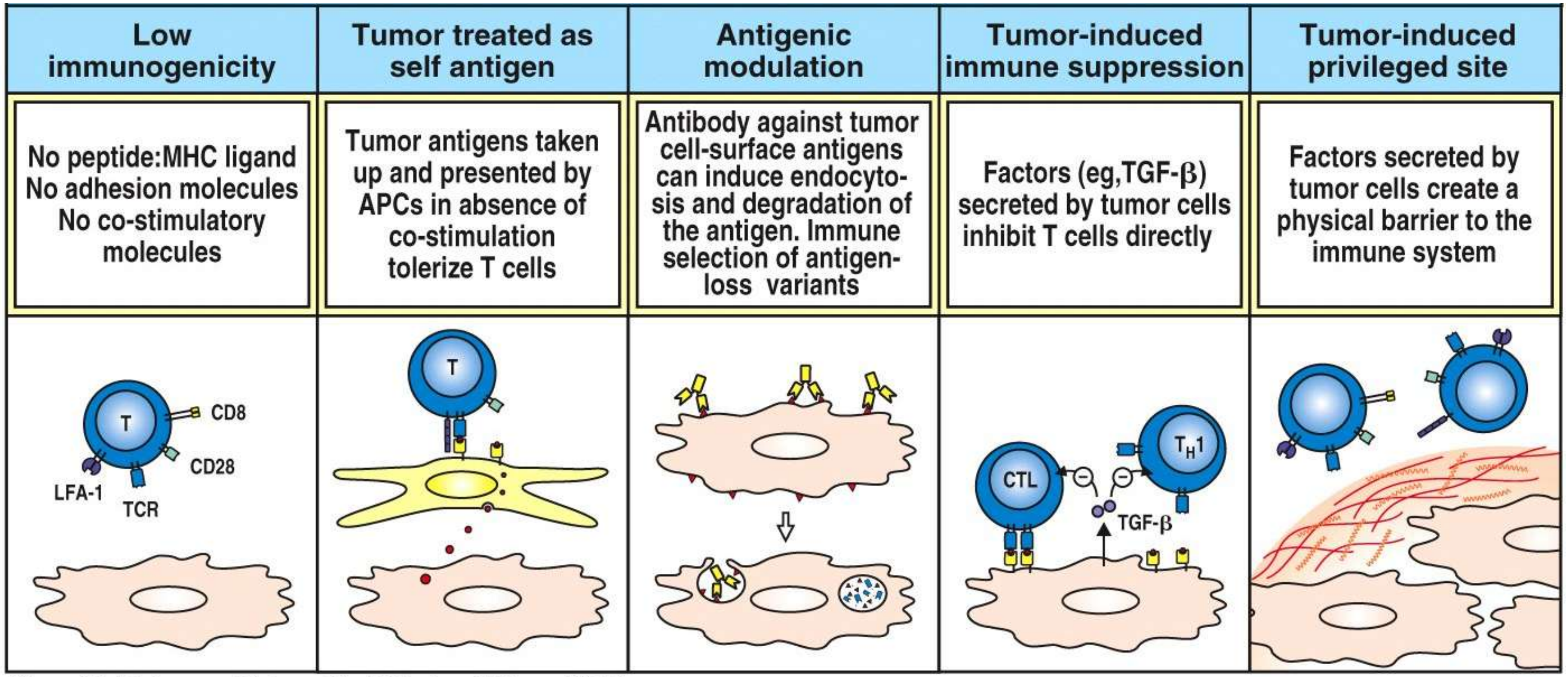
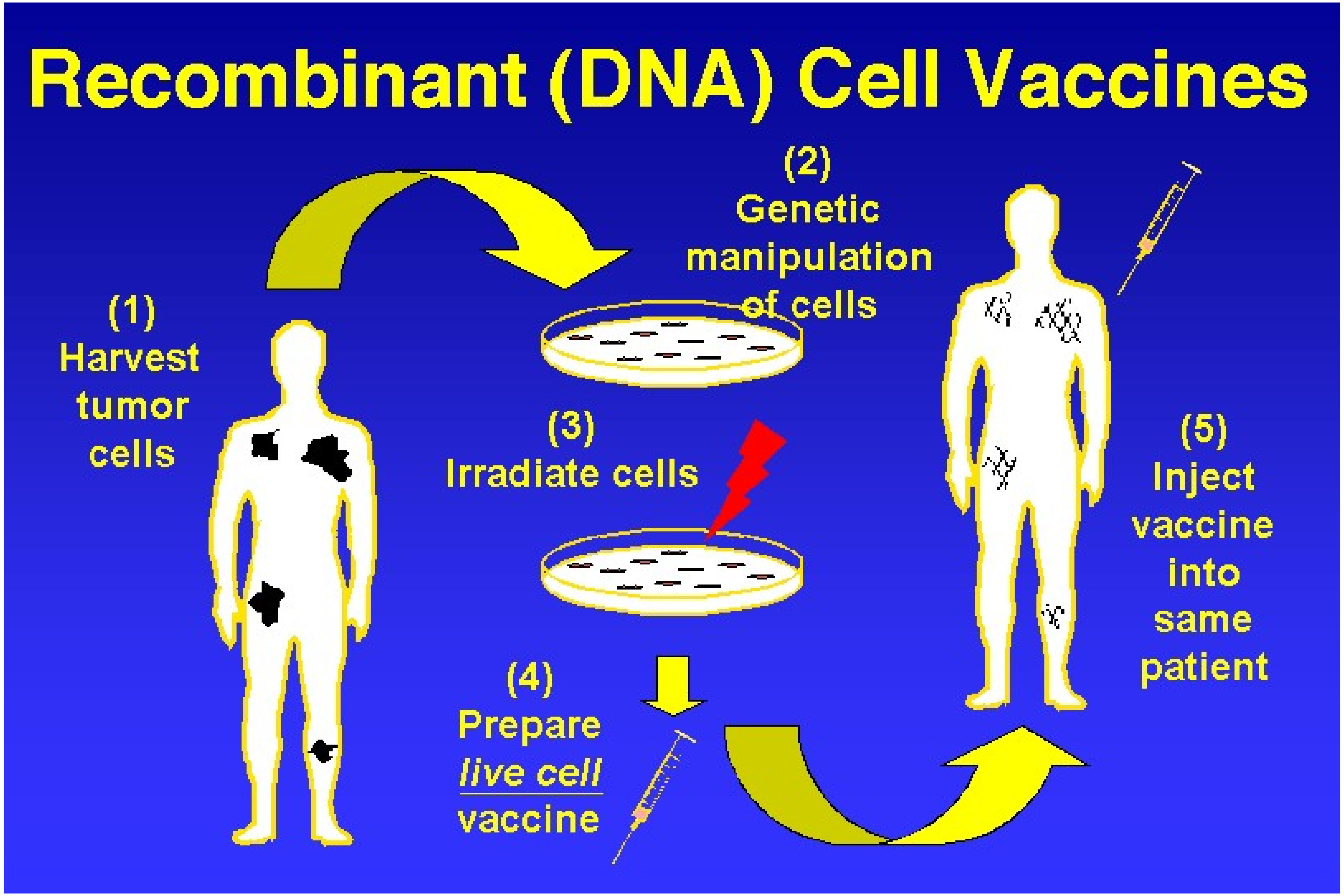


Figure 14-14 Immunobiology, 6/e. (© Garland Science 2005)

How can the immune system be activated so that it actively fights tumor cells?

Immunization with tumor antigens

Immunization with gene-transfected tumor cells



Naylor, M. F. (2000). Melanoma Vaccines. *Dermatology Online Journal*, 6(1).

Immunization with gene-transfected tumor cells

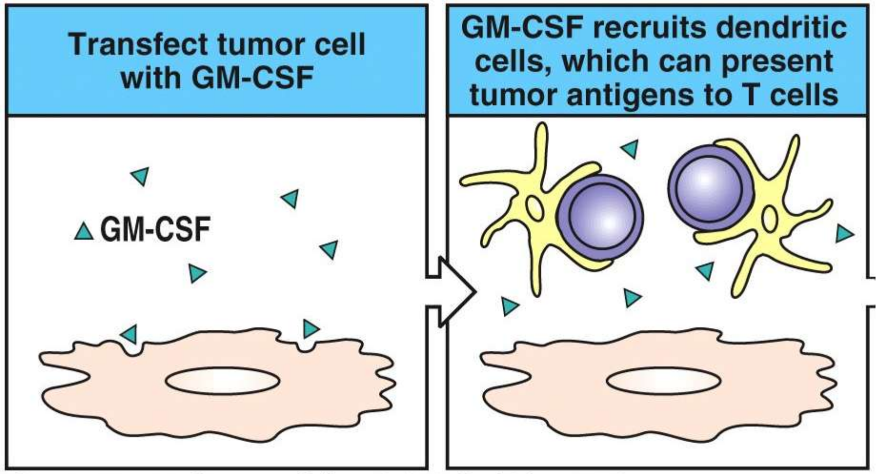


Figure 14-20 part 2 of 3 Immunobiology, 6/e. (© Garland Science 2005)

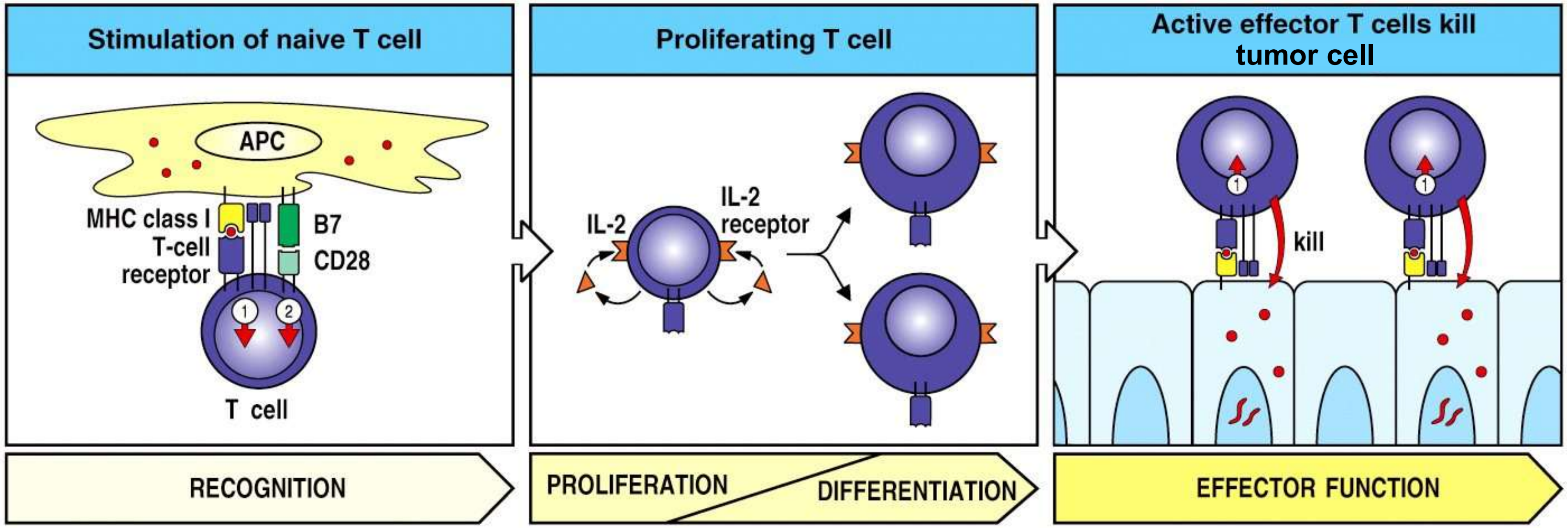
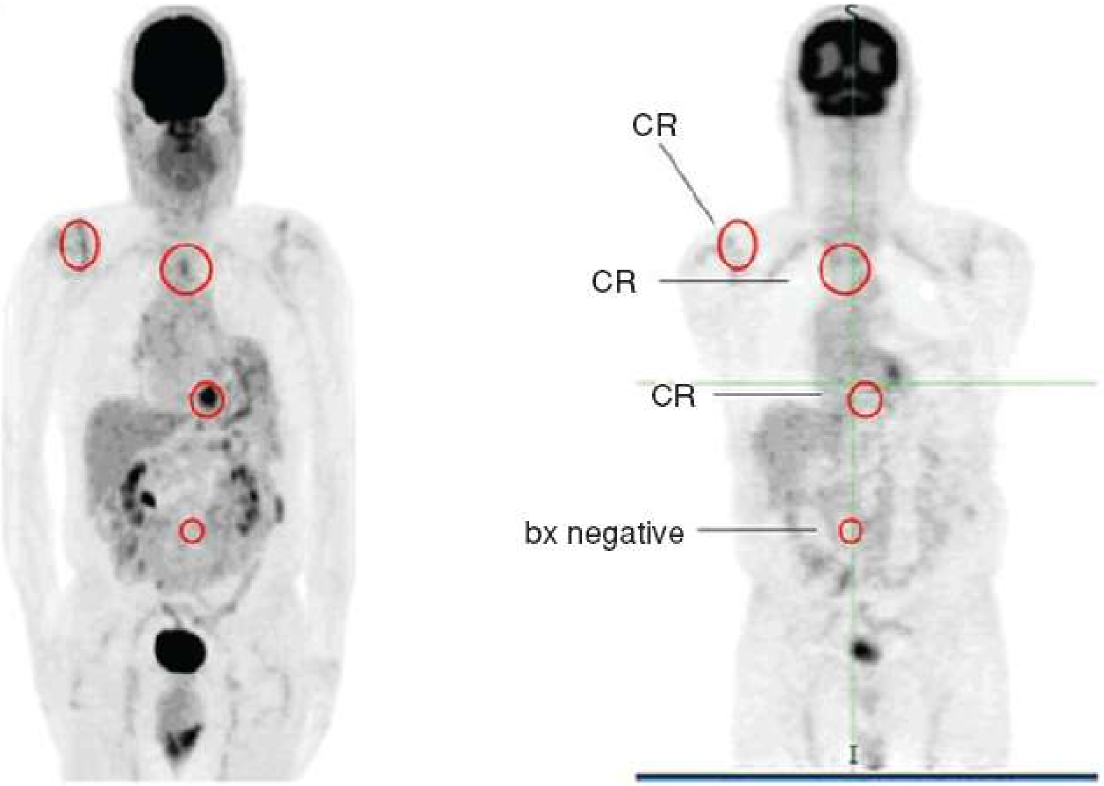


Figure 8-22 Immunobiology, 6/e. (© Garland Science 2005)

"Complete response" through vaccination in a melanoma patient



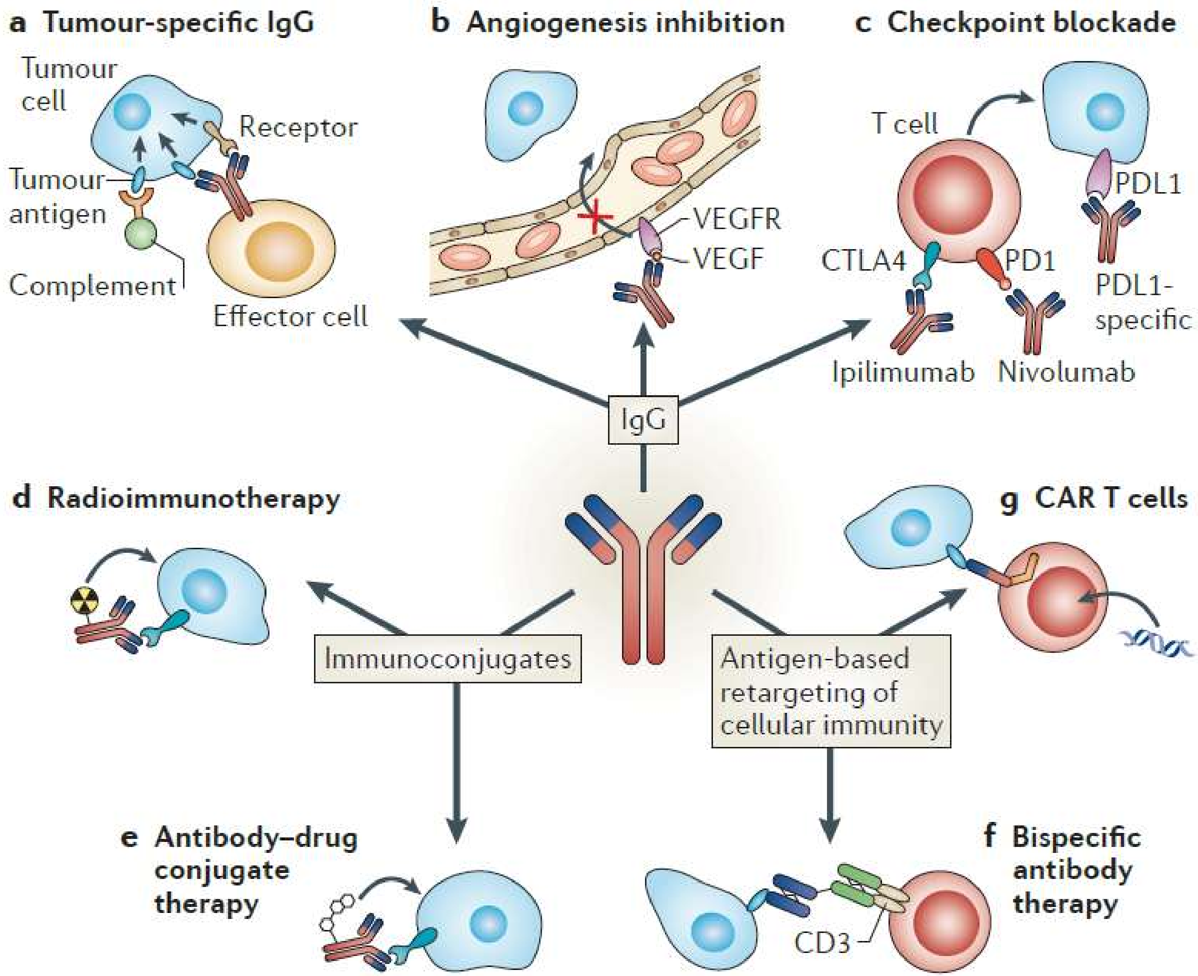
07/07/08

10/05/09

How can the immune system be activated so that it actively fights tumor cells?

Use of antibodies and tumor antigen specific immune cells

Use of antibodies (conjugates) for the treatment of tumors



NK cells recognise tumour cells: mechanism 2

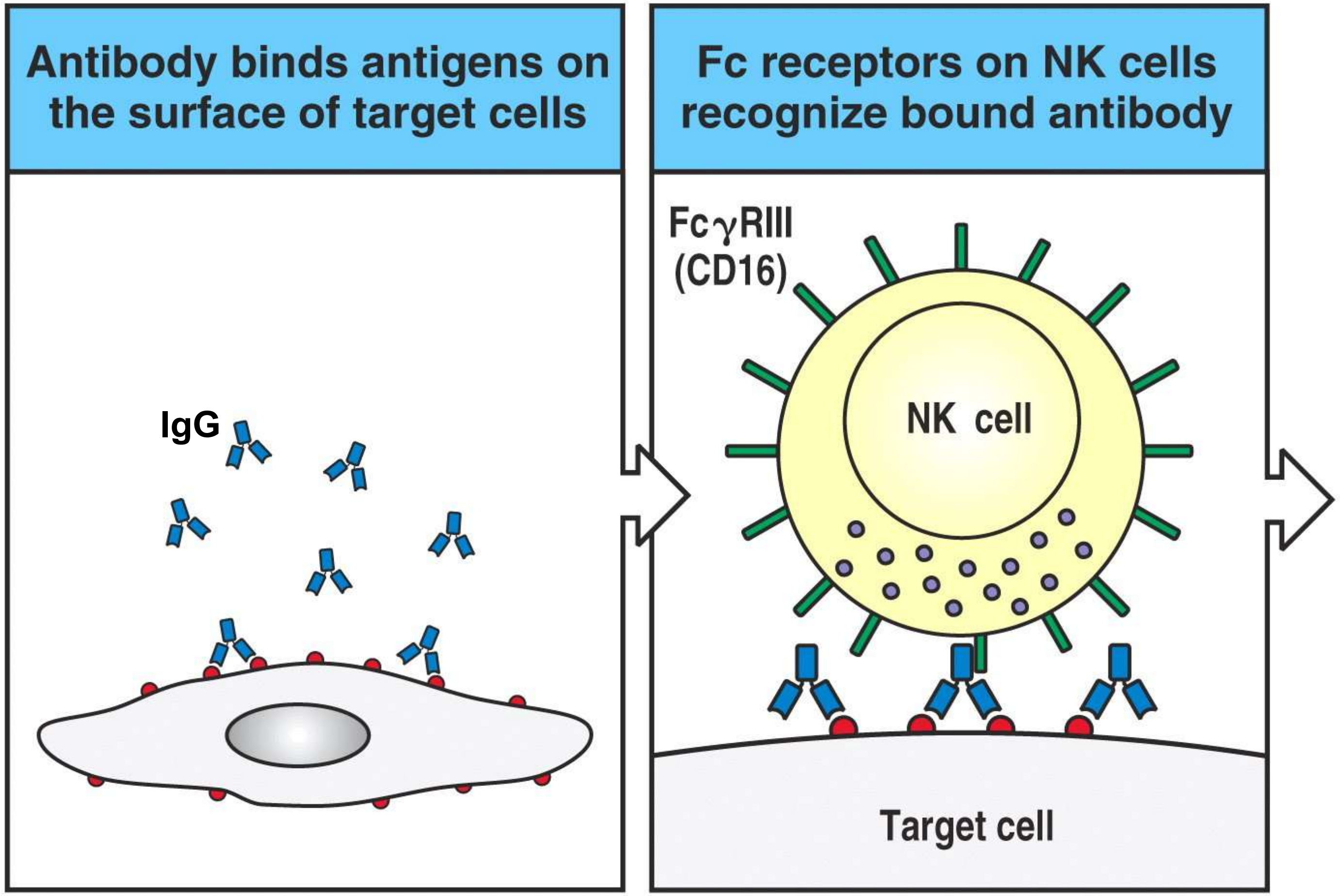


Figure 9-34 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

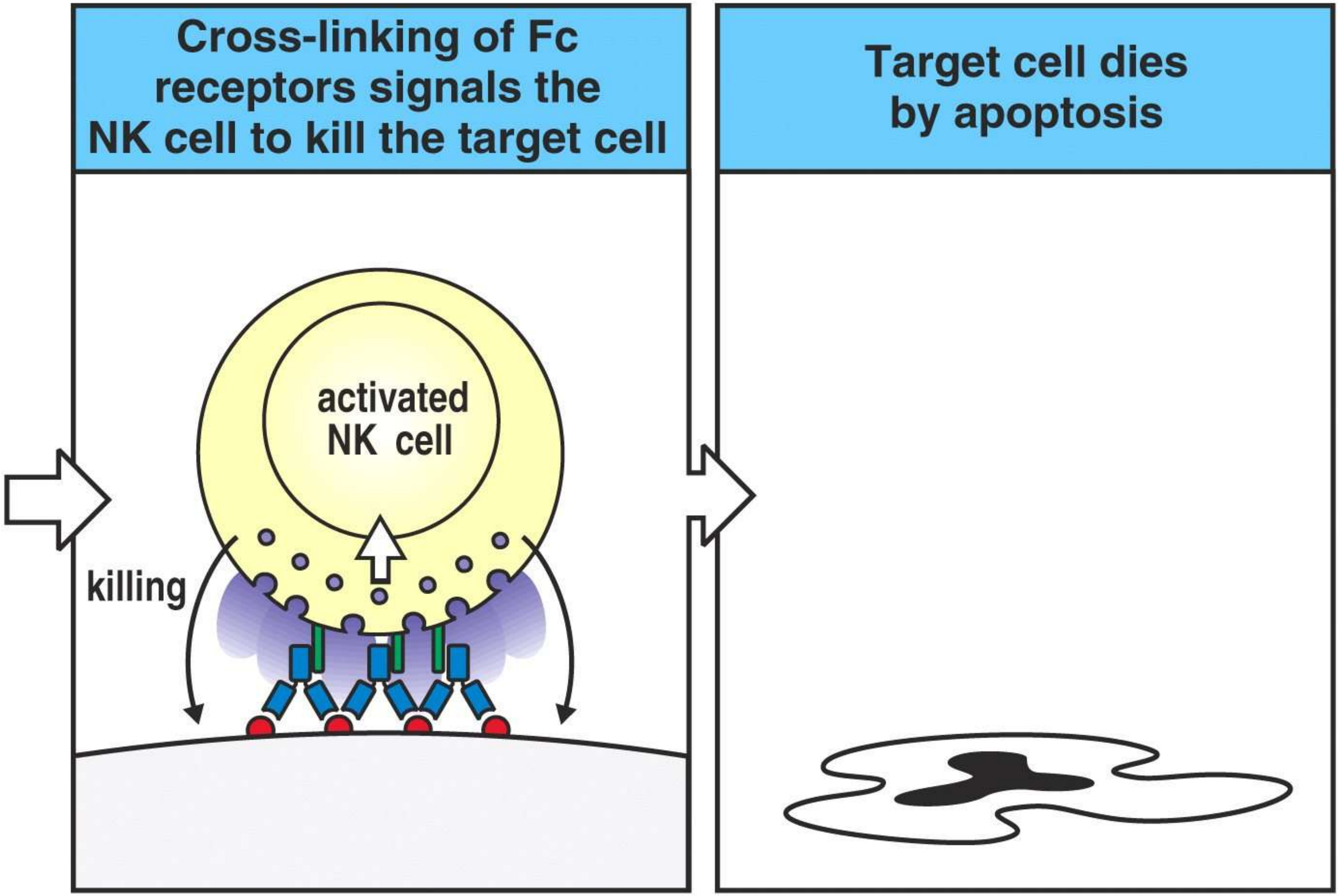
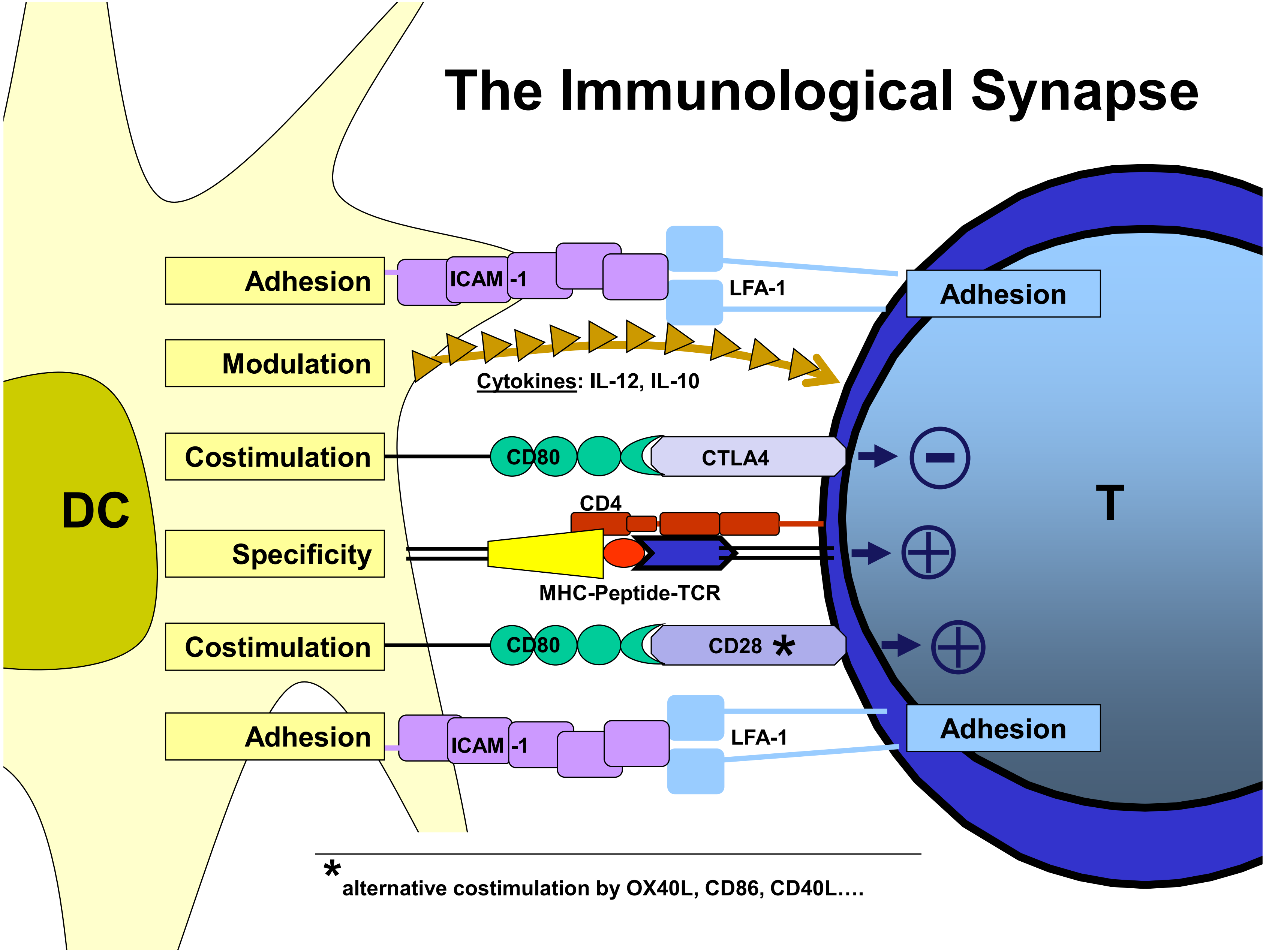


Figure 9-34 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Use of antibodies as
Checkpoint inhibitors

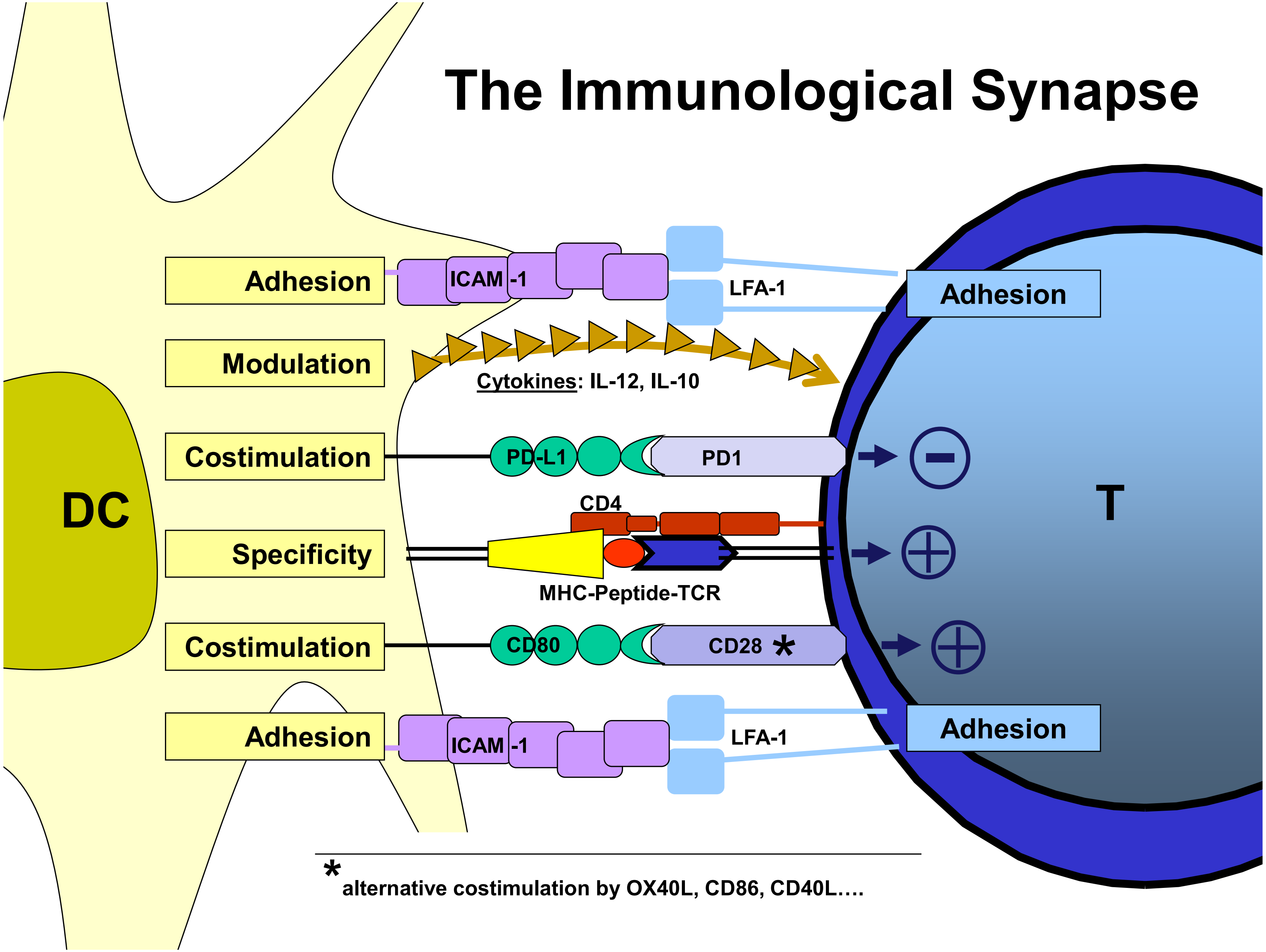
Blocking the interaction of:
CD80 --- CTLA4
PDL1 --- PD1

The Immunological Synapse

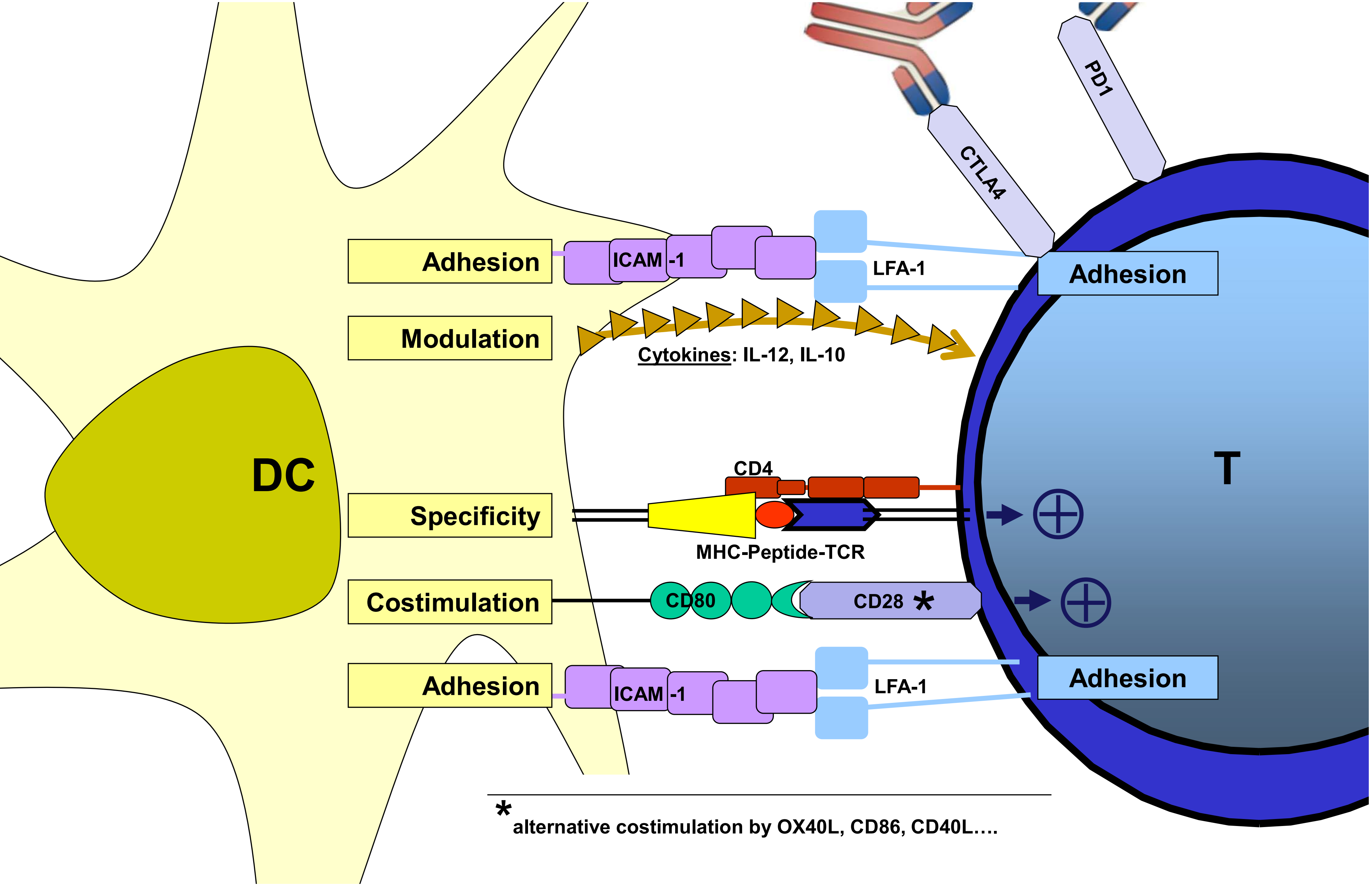


* alternative costimulation by OX40L, CD86, CD40L….

The Immunological Synapse



* alternative costimulation by OX40L, CD86, CD40L….



* alternative costimulation by OX40L, CD86, CD40L….

Treatment with anti-PD1 without anti-CTLA-4

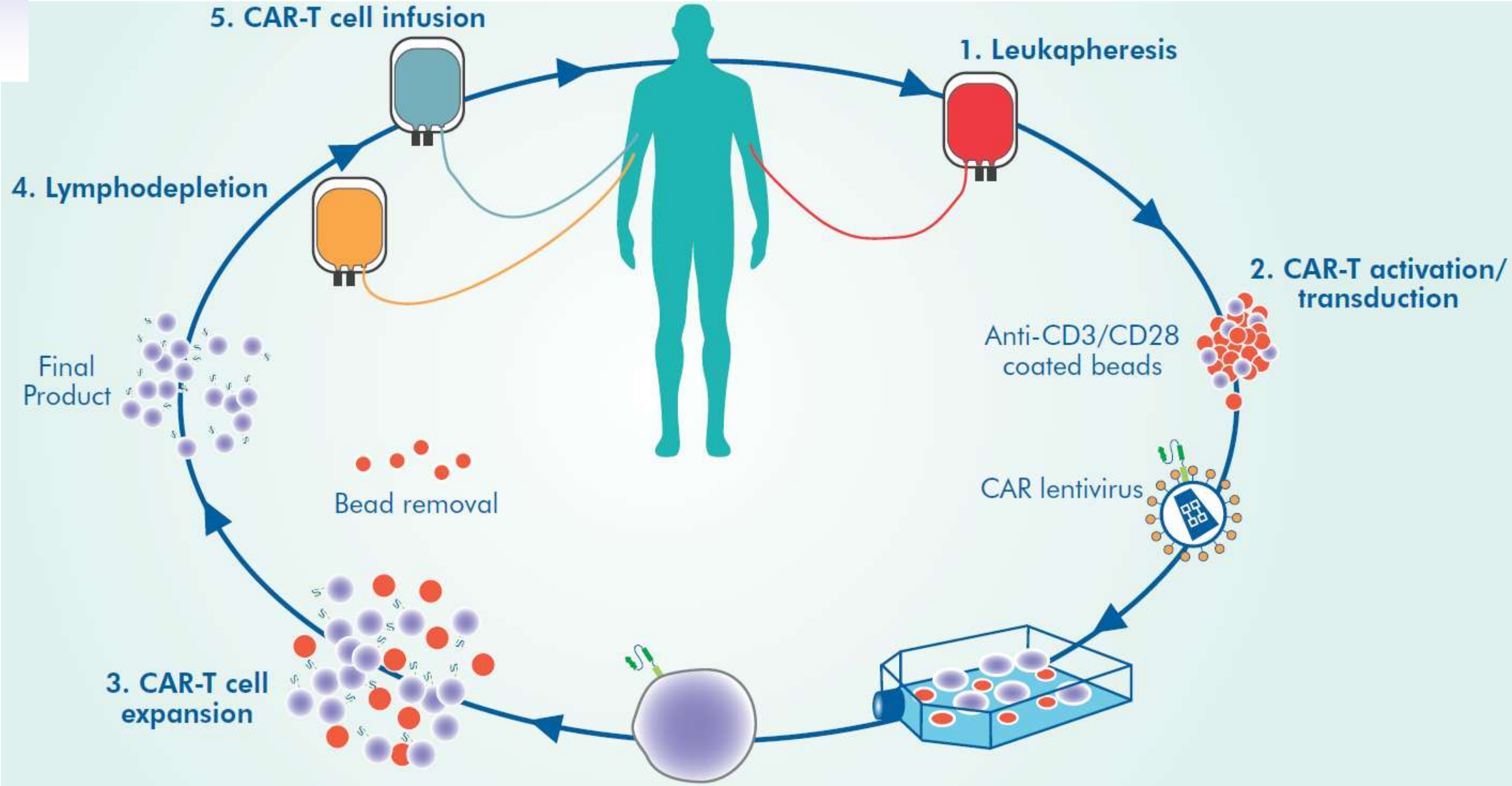
Drug	Condition	Treatment regimen	Treatment in control group	Objective response rate	Complete response rates	Overall survival (months)	Progression-free survival (months)	Grade 3–5 adverse events	Participants treated (and controls)
Nivolumab (IgG4a)	Melanoma (stage III/IV)	3 mg/kg/2 weeks	(*vs* combination therapy)	43.7%	8.9%	n/a	6.9	16.3%	316
	Renal cell carcinoma (metastatic)	3 mg/kg/2 weeks	10 mg/day Everolimus	25% (4% control)	1% (<1% control)	25.0 (19.6 control)	4.6 (4.4 control)	19% (27% control)	406 (397 control)
	Hodgkin's lymphoma (relapsed/refractory)	3 mg/kg/2 weeks	n/a	87%	17%	n/a	86% at 24 weeks	22%	23
	Squamous-cell carcinoma of the head and neck (recurrent)	3 mg/kg/2 weeks	Single-agent systemic therapy (methotrexate, docetaxel, or cetuximab)	13.3% (5.8% control)	2.5% (0.8% control)	36.0%/1 year (16.6% control)	19.7% at 6 months (9.9% control)	13.1% (35.1%)	240 (121 control)
	Non-small cell lung cancer	3 mg/kg/2 weeks	Docetaxel	19% (12% control)	1% (<1% control)	12.2 (9.4 control)	2.3 (4.2 control)	10% (54% control)	292 (290 control)
		3 mg/kg/2 weeks	Docetaxel	20% (9% control)	1% (0% control)	9.2 (6 control)	3.5 (2.8 control)	7% (55% control)	135 (137 control)
	Ovarian cancer (platinum-resistant)	1 or 3 mg/kg/2 weeks	n/a	15%	10%	20	3.5	40%	20
Pembrolizumab (IgG4a)	Melanoma (stage III/IV)	10 mg/2 weeks or 3 weeks	(*vs* ipilimumab)	33.7–32.9%	5.0–6.1%	n/a	5.5–4.1	13.3–10.1%	279–277
	Merkel cell carcinoma	2 mg/kg/3 weeks	n/a	56%	16%	n/a	65% at 6 months	15%	26
	Non-small cell lung cancer	2 mg/kg/3 weeks 10 mg/kg/3 weeks 10 mg/kg/2 weeks	n/a	19.4%	n/a	12	3.7	9.5%	495
		200 mg/2 weeks (PD-L1 + patients only)	Platinum-based chemotherapy	44.8 (27.8% control)	n/a	80.2% at 6 months (72.4% control)	10.3 (6 control)	26.6% (53.3% control)	154 (154 control)
		2 or 10 mg/kg/3 weeks (PD-L1 + patients only)	Docetaxel	18/18% (9% control)	0/0% (0% control)	10.4/12.7 (8.5 control)	3.9/4.0 (4.0 control)	13/16% (35% control)	345/346 (343 control)

Treatment with anti-CTLA4 +/- Anti PD1

	Drug	Condition	Treatment regimen	Treatment in control group	Objective response rate	Complete response rates	Overall survival (months)	Progression-free survival (months)	Grade 3–5 adverse events	Participants treated (and controls)
CTLA-4	Ipilimumab (IgG1)	Melanoma (stage III/IV)	10 mg/kg plus decarbazine	Decarbazine alone	15.2% (10.3% control)	1.6% (0.8% control)	11.2 (9.1 control)	n/a	56.3% (27.5%)	250 (252 control)
			3 mg/kg/3 weeks	(*vs* Pembrolizumab)	11.9%	1.4%	n/a	2.8	19.9%	278 315
			3 mg/kg/3 weeks	(*vs* combination with nivolumab)	19%	2.2%	n/a	2.9	27.3%	311
	Tremelimumab (IgG2)	Melanoma (stage III/IV)	15 mg/kg/90 days	chemotherapy (temozolomide or dacarbazine)	10.7% (9.8% control)	3% (2% control)	12.6% (10.7 control)	20.3% at 6 months (18.1% control)	52% (37% control)	328 (327 control)
CTLA4 +PD1	Nivolumab + Ipilimumab	Melanoma (stage III/IV)	3 mg/kg/2 weeks Nivolumab 3 mg/kg/3 weeks Ipilimumab	(*vs* single)	57.6%	11.5%	n/a	11.5	55%	314
		Non-small cell lung cancer	Nivo + Ipi: 1 + 3 or 3 + 1 mg/ml	Nivolumab alone	23/19% (10% control)	2/0% (0%)	7.7/6 (4.4)	2.6/1.4 (1.4 control)	30/19% (13% control)	61/54 (98 control)

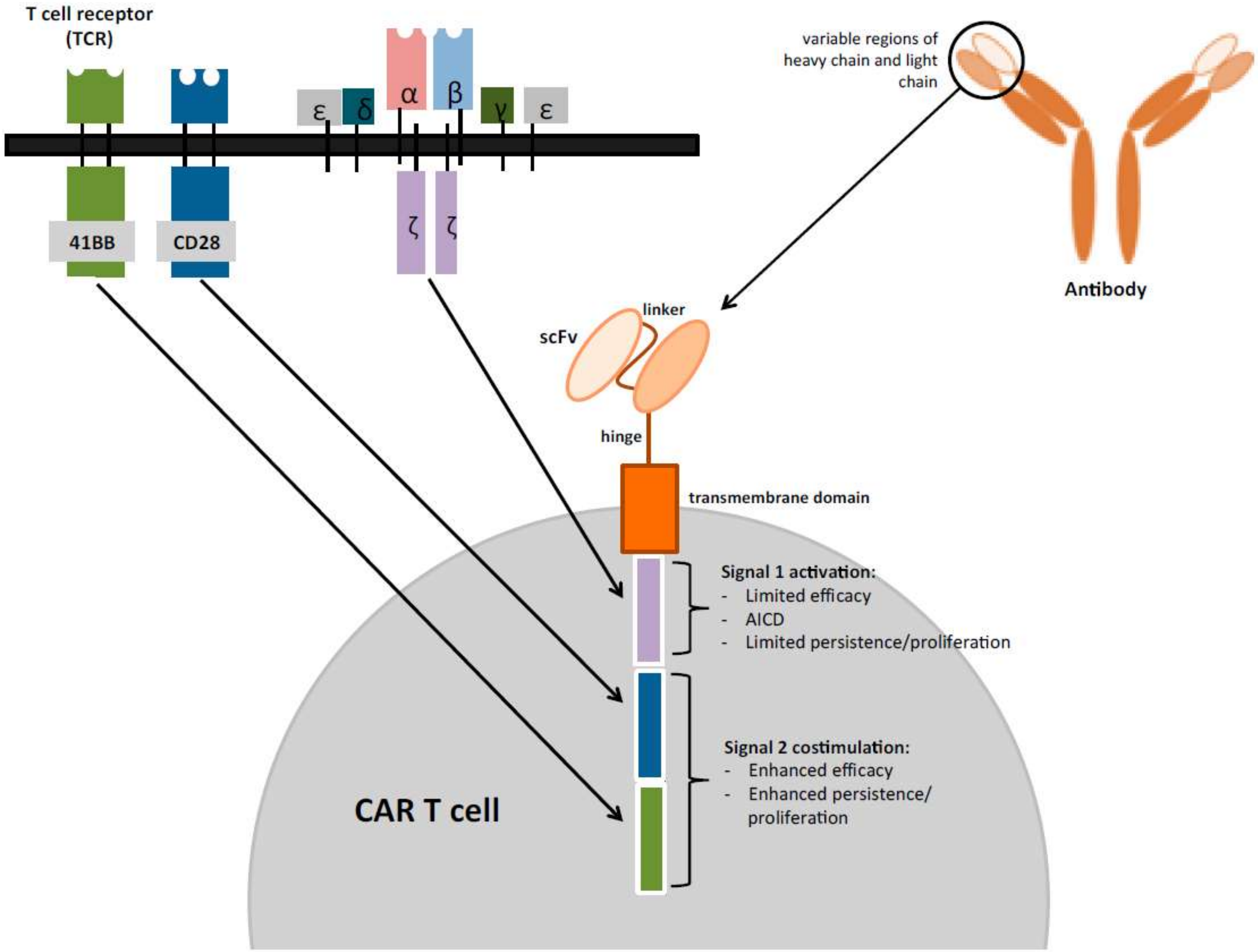
Chimeric Antigen Receptor (CAR)-T Cell Immunotherapy

Chimeric Antigen Receptor (CAR) T-cells



Marco Ruella, MD, University of Pennsylvania

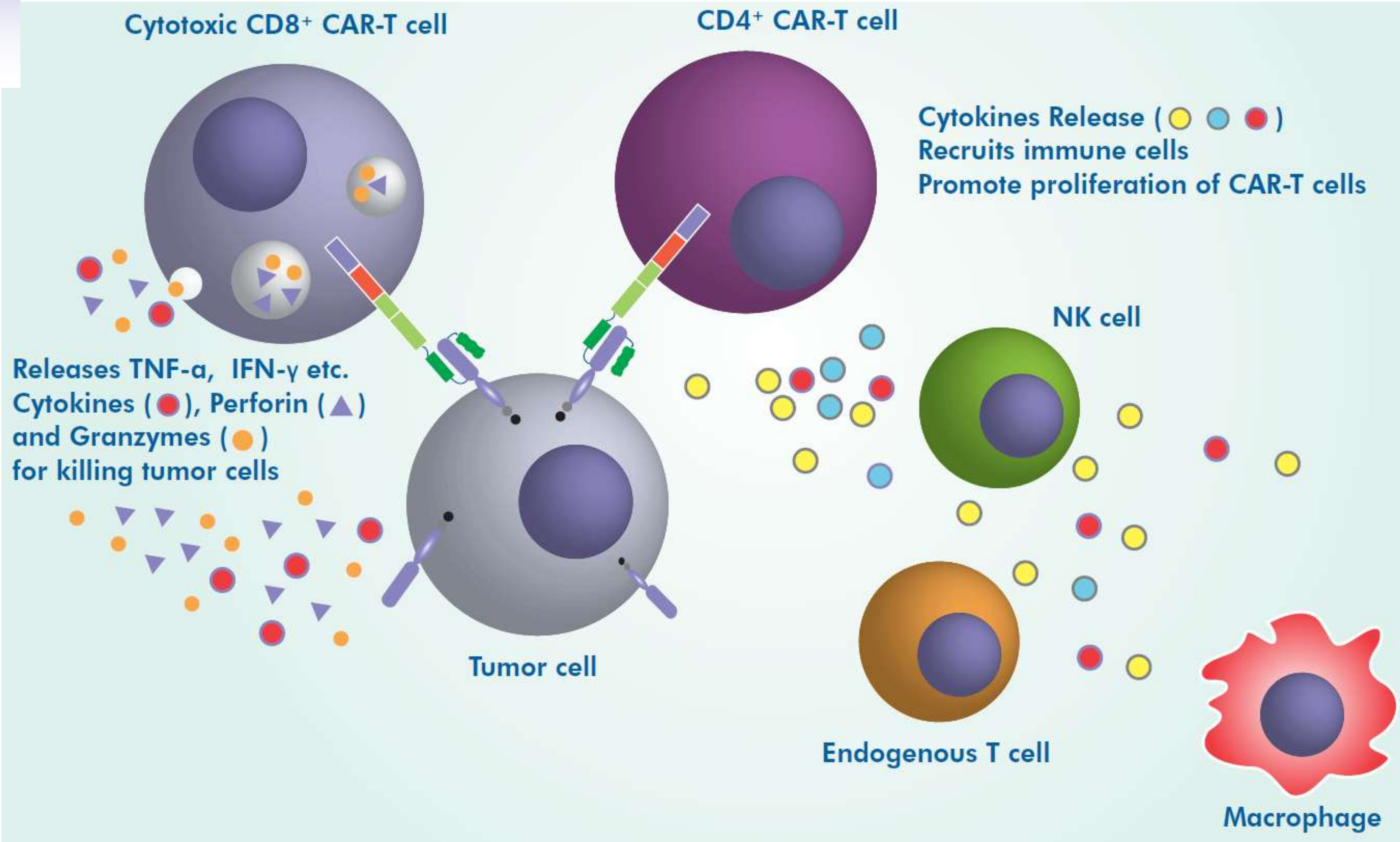
Chimeric Antigen Receptor (CAR) specific T-cells



scFV: single chain variable fragment

Cancers **2017**, *9*, 115; doi:10.3390/cancers9090115

Effector mechanism of CAR T-cells



Marco Ruella, MD, University of Pennsylvania

Key targets for CAR-T cell therapy and established clinical results

Disease	Target	Effector	Efficacy	Toxicity	Citation
B-cell Acute Leukemia (pediatric-young adult)	CD19	CTL019 (4-1BB)	CR 81% [61/75] RFS (12 months) 59%	CRS 77% Gr. 4 CRS 25% Neurotoxicity 40%	Maude *et. Al.*, 2018 [NEJM; PMID: 29385370]
B-cell Acute Leukemia (adult)	CD19	JCAR017 (CD4/CD8; 4-1BB)	CR 93% [27/29] RFS: n/a	CRS 83% Severe CRS (Doesn't Specify) 23% Neurotoxicity 50%	Turtle *et al*, 2017 [JCI; PMID: 27111235]
B-cell Lymphoma (DLBCL, FL)	CD19	CTL019 (4-1BB)	CR 57% [16/28] PFS (28.6 months) 57%	CRS 57% Severe CRS: (Grade 3 or higher): 18% Neurotoxicity 39%	Schuster *et al*, 2017 [NEJM; PMID: 9226764]
B-cell Chronic Leukemia	CD19	CTL019 (4-1BB)	CR 29% [4/14] PFS (18 months) 29%	CRS 64% Severe CRS 29% (43%) Neurotoxicity 37% [6/16]	Porter *et al*, 2015 [STM; PMID: 26333935]
B-cell Acute Leukemia (pediatric-young adult)	CD22	CAR-T-22 (4-1BB)	CR 57% [12/21] PFS (6 months) 50%	CRS 76% Severe CRS 0% Neurotoxicity 37% [6/16]	Fry *et al* 2017, [Nat Med; PMID: 29155426]
Multiple Myeloma	BCMA	BCMA-CAR-T (4-1BB)	ORR 100% [15/15] sCR+VGPR 73% [11/15]	CRS 78% [14/18] Severe CRS 11% [2/18]	Bergdeja *et al*, 2017 [ASH; Paper 107984, Session: 653]

CR = complete remission; PFS = progression-free survival; DFS = disease-free survival; CRS = cytokine release syndrome; n/a = not applicable sCR = stringent CR; VGPR = very good partial remission; ORR = overall response rate