Lymphocytes T et cytokines

D.U. MALADIES SYSTEMIQUES ET MALADIES AUTOIMMUNES

Année universitaire 2016 – 2017

Autoimmunité: bases fondamentales

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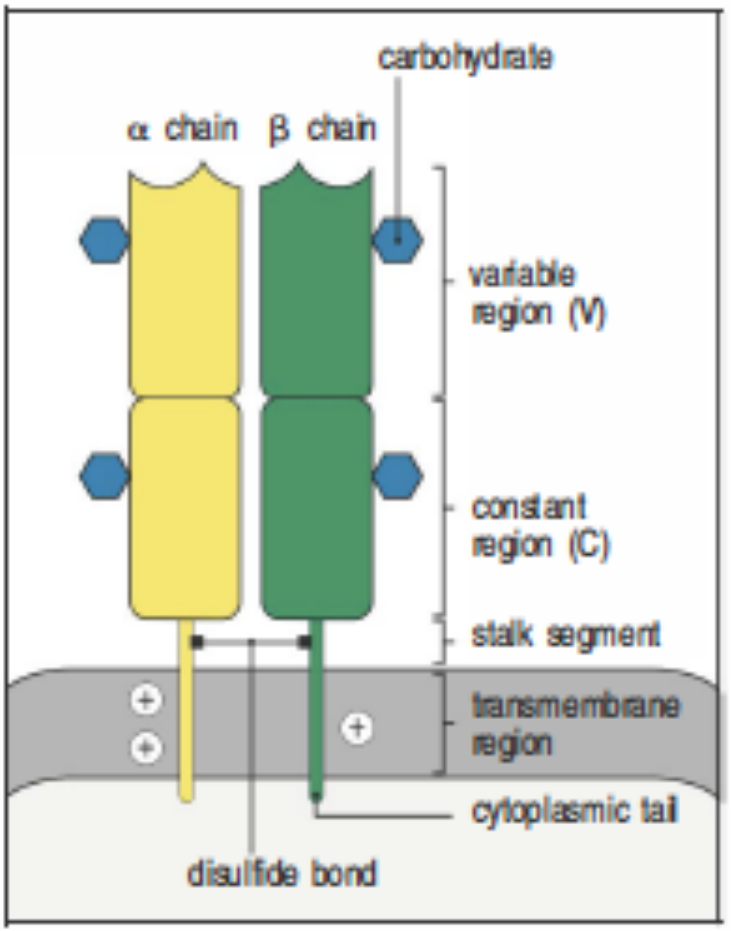
Lymphocytes T

Généralités

- Le Lymphocyte T:
  - Immunité à médiation cellulaire
    - Agents infectieux: bactéries – virus
    - Rejet de greffe
    - Rejet de tumeur
    - Hypersensibilité retardée
  - Différentes populations
    - CD8 cytotoxiques
    - CD4: auxiliaires, régulateurs,
    - Autres populations: Tγδ, NKT, MAIT.
  - Production 10^8/jour

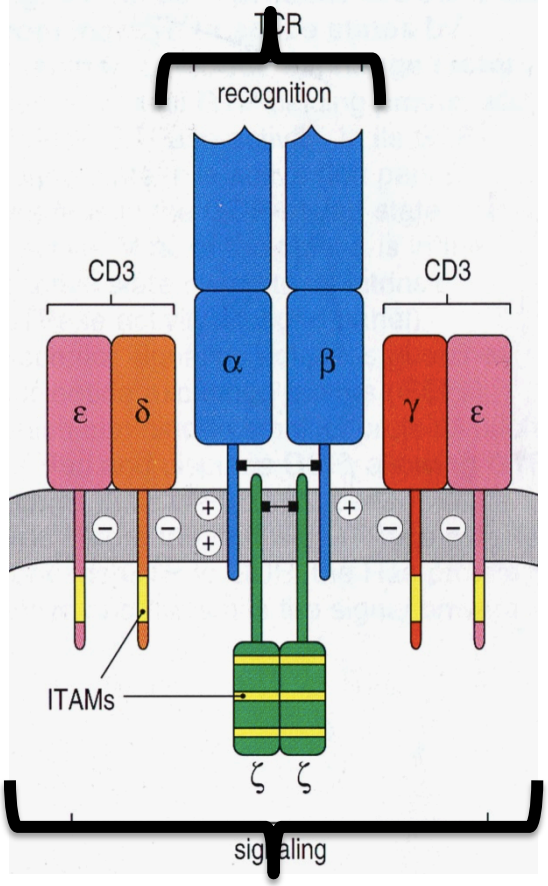
Le récepteur des lymphocytes T (TCR)

- 10^5 par lymphocyte T
- 2 chaines polypeptidiques unies par un pont disulfure:
  - Chaine α
  - Chaine β
- Un seul site de reconnaissance
- Obtenu par réarrangement génique
- Non sécrété
- Associé à des corécepteurs CD3, CD4 ou CD8…
- TCR αβ et TCR γδ



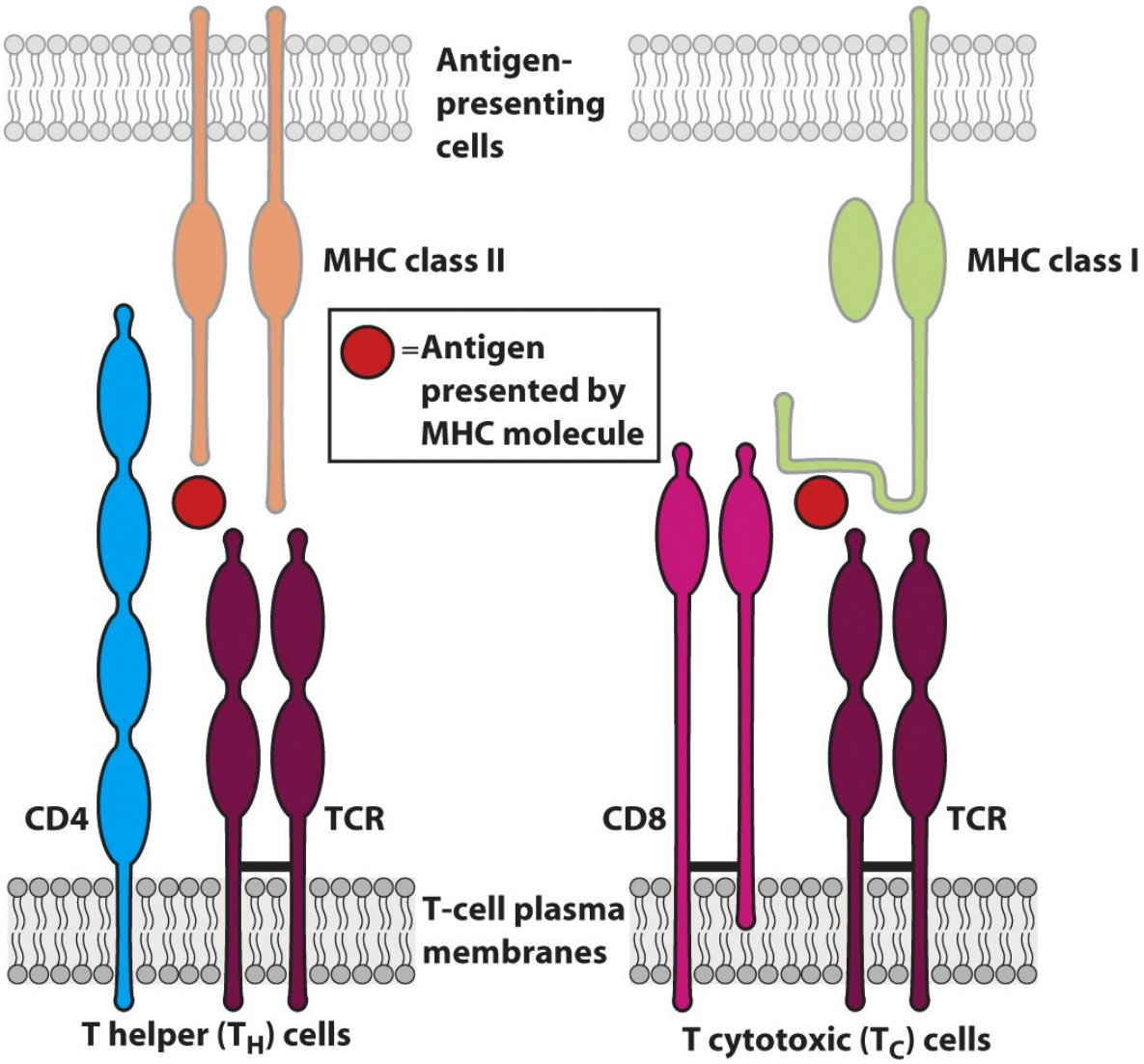
Le récepteur des lymphocytes T (TCR)

Unité de reconnaissance αβ

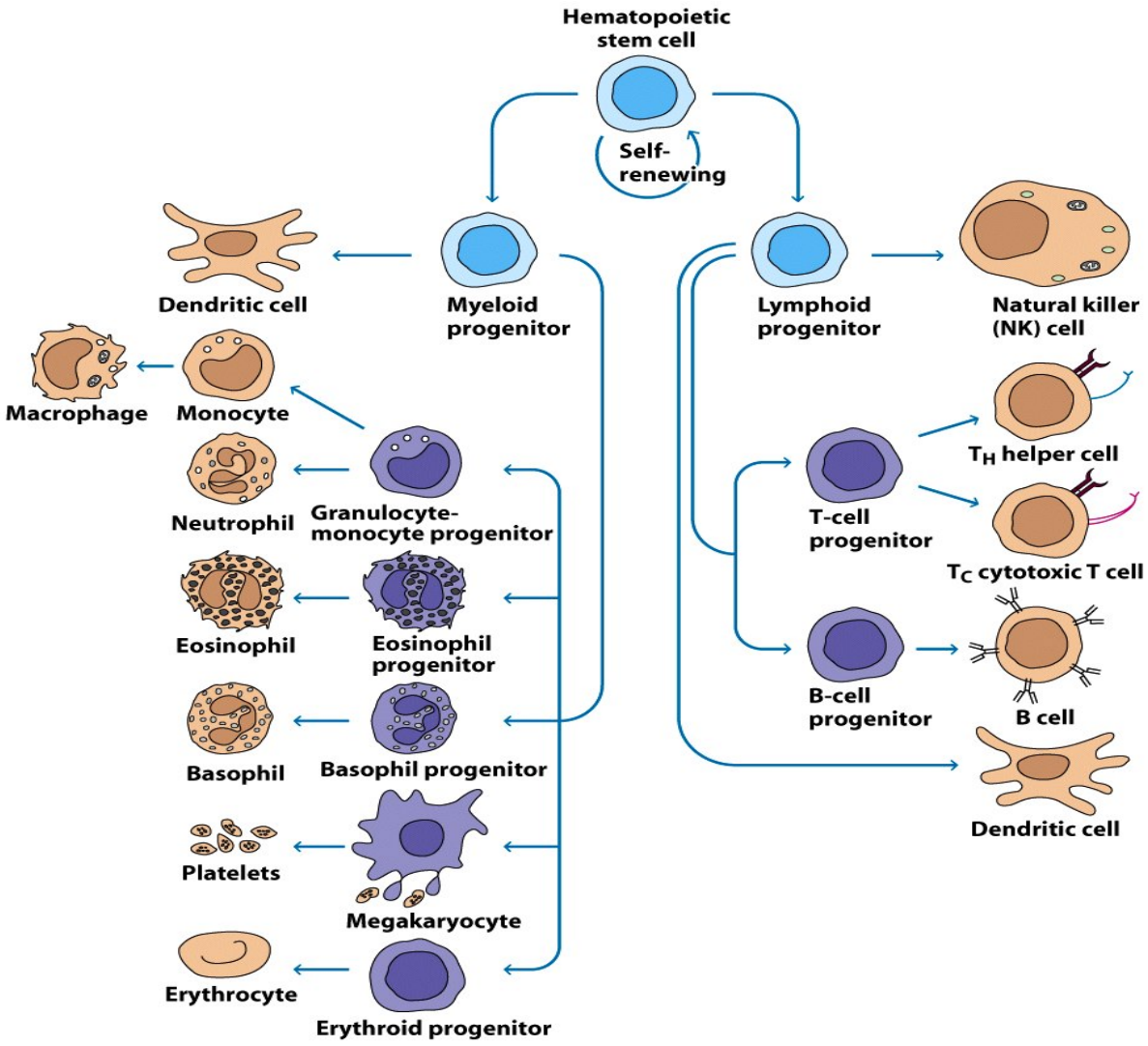


Unité de transduction du signal : CD3

Le récepteur des lymphocytes T (TCR): co-récepteurs CD4 ou CD8



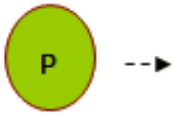
Lymphopoiësе T



Lymphopoïëse T: le thymus

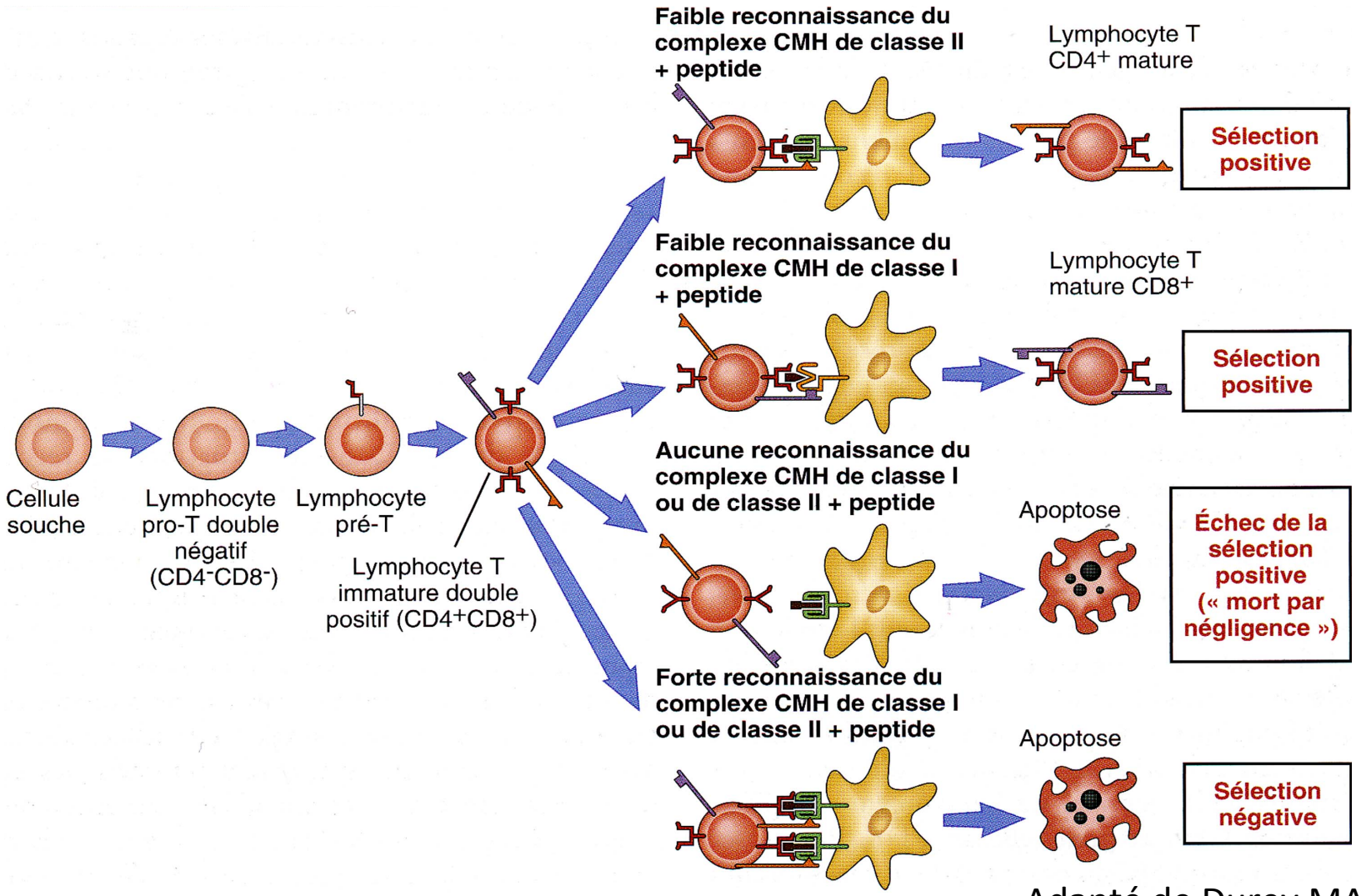
- 1960 Jacques Miller
- Thymus provient de la 3^{e} poche pharyngée de l'endoderme
- Organe impair médian bilobé thoracique organisé en unités fonctionnelles (lobules) séparés par des invaginations (trabécules)
- Souris thymectomisées à J1 de vie:
  - déficit majeur en lymphocytes circulants + aires ganglionnaires + rate
  - correction par greffe de thymus

Les étapes de la lymphopoièse T



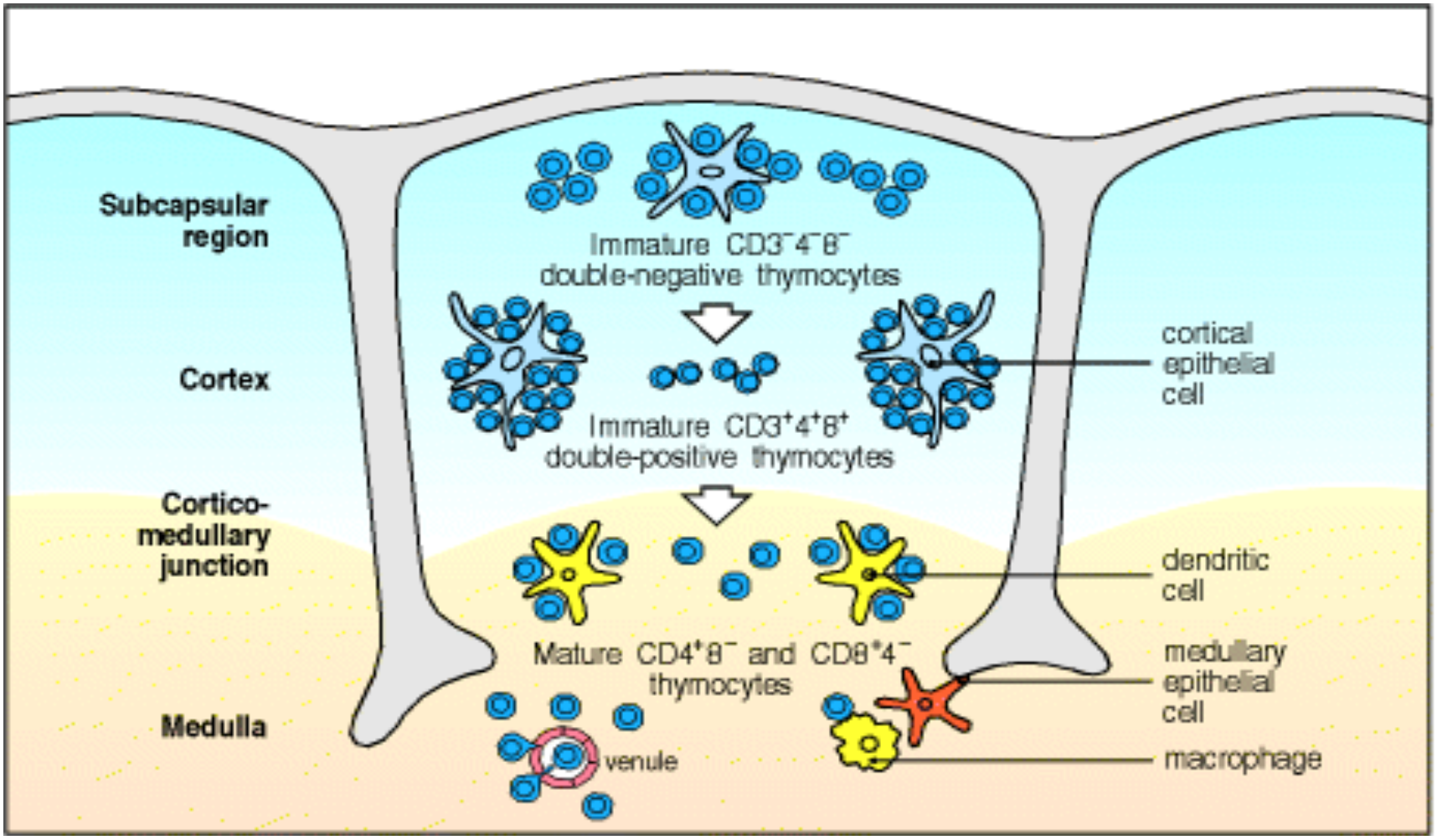
ç pluripotente

Lymphopoïèse T



Adapté de Durey MA 2012

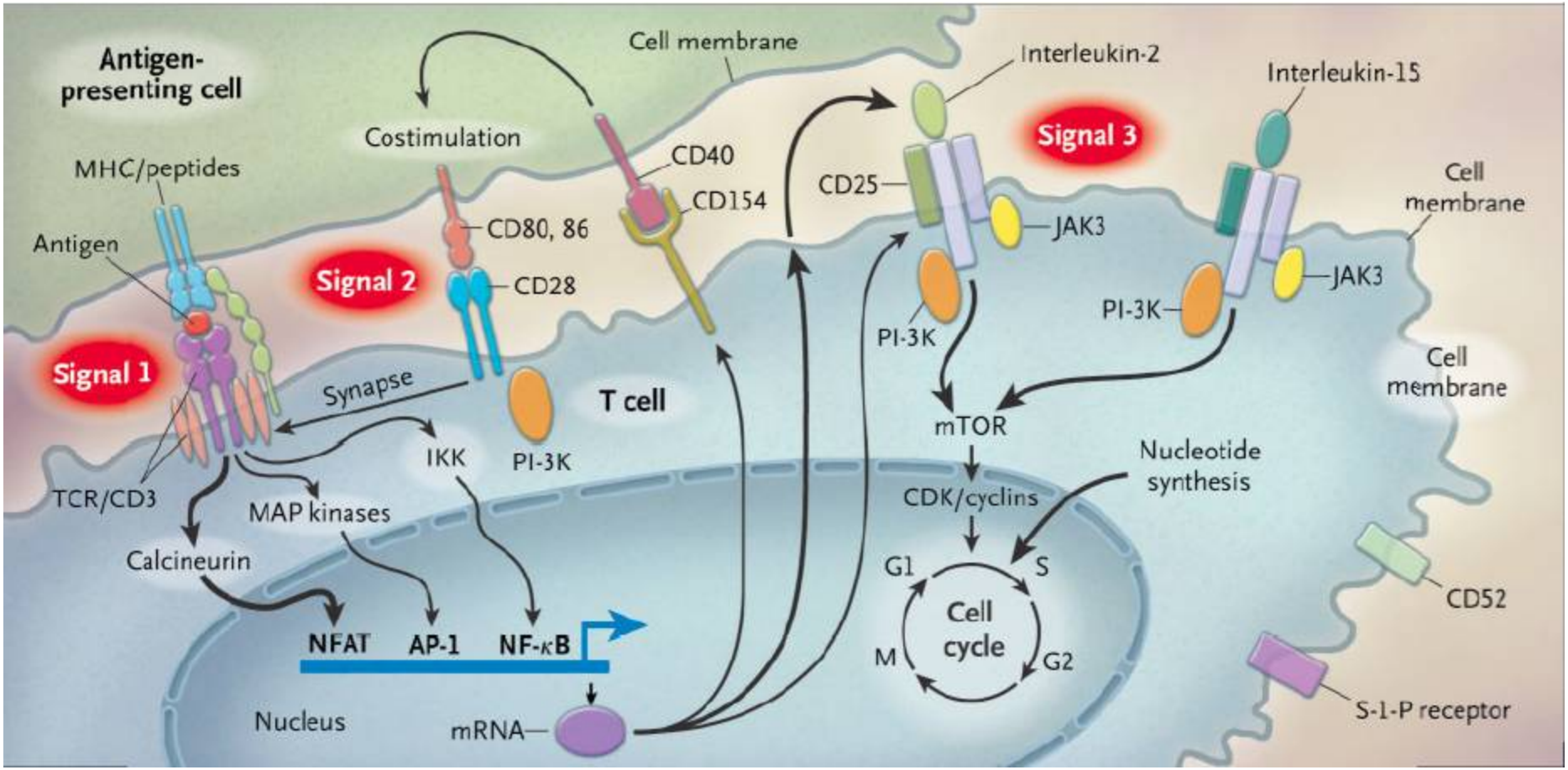
Lymphopoiëse T



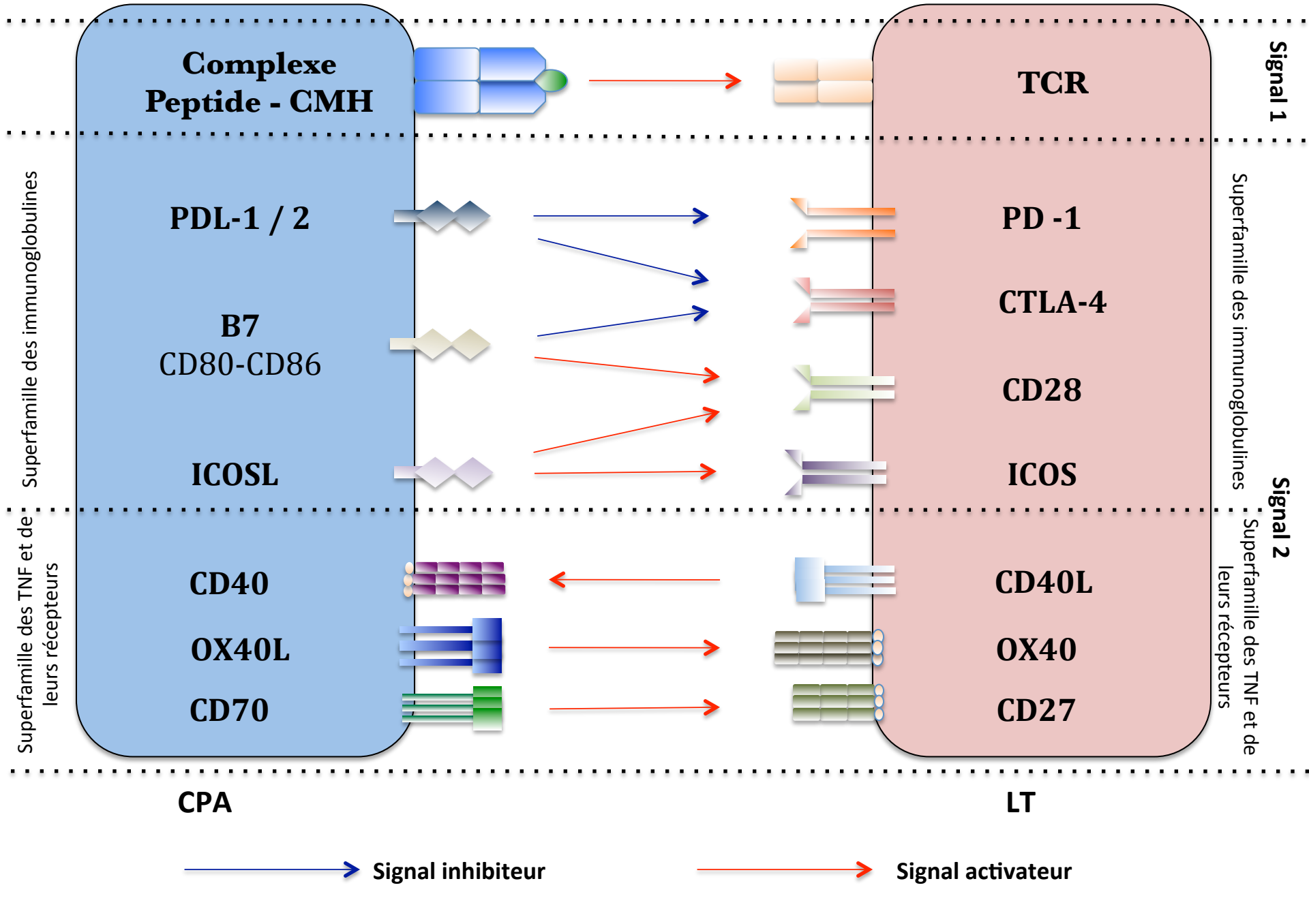
Activation des lymphocytes T

- Se fait par induction de récepteur à la surface des lymphocytes T
- Conséquences:
  - Prolifération ou différentiation
  - Non-réponse ou anergie
  - Maturation ou interruption de maturation
  - Auto-destruction: apoptose (activation induced cell death)

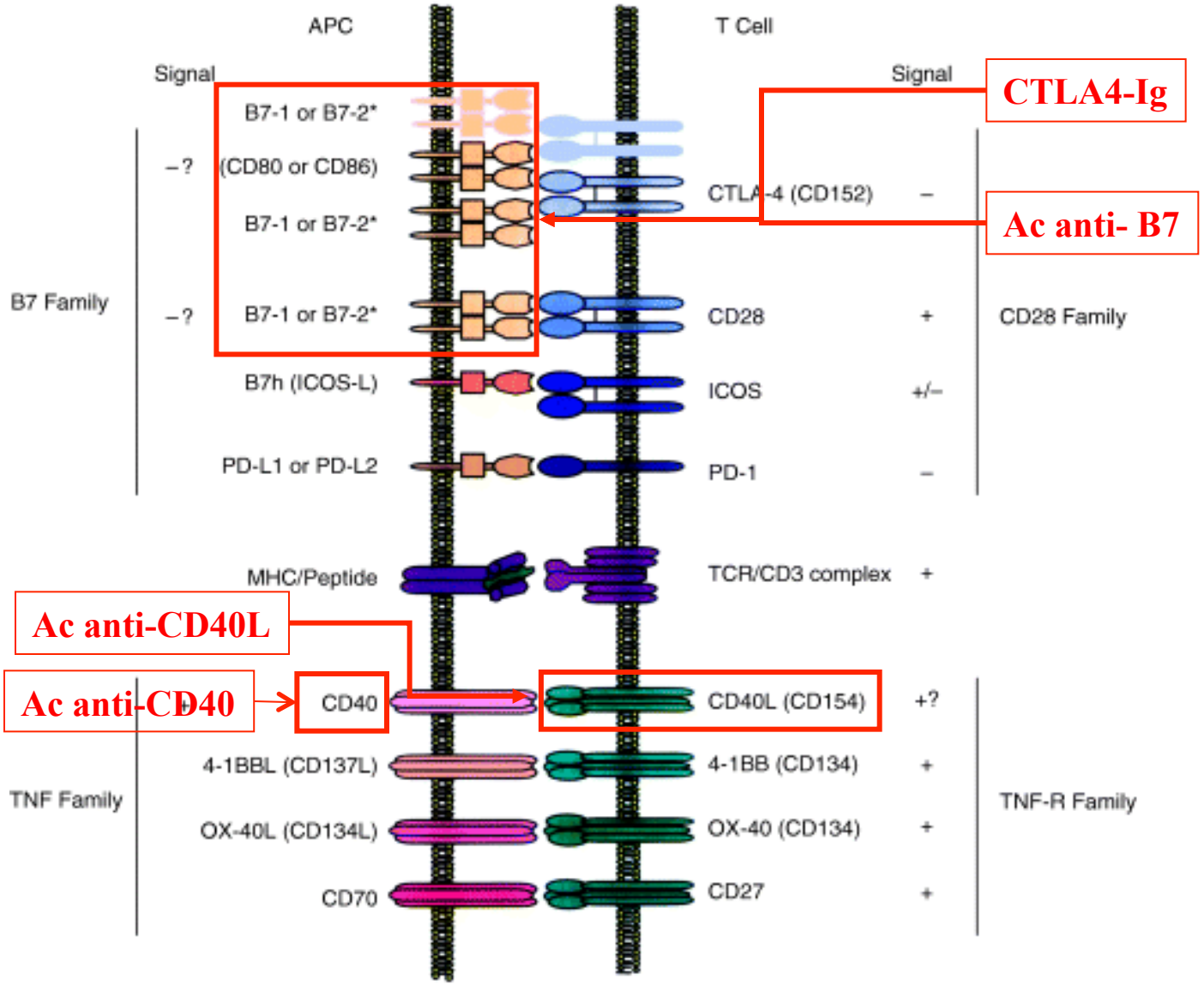
Activation des lymphocytes T: les 3 signaux d'activation



Halloran N Engl J Med, 351: 2715-2729


Complexe Peptide - CMH
TCR
Signal 1
Superfamille des immunoglobulines
PDL-1 / 2
B7
CD80-CD86
ICOSL
PD -1
CTLA-4
CD28
ICOS
Superfamille des immunoglobulines
Signal 2
Superfamille des TNF et de leurs récepteurs
CD40
OX40L
CD70
CD40L
OX40
CD27
Superfamille des TNF et de leurs récepteurs
CPA
LT
Signal inhibiteur
Signal activateur

Activation des lymphocytes T: intérêt clinique



Rothstein Immunological Reviews, 196, 2003

Fonctions des lymphocytes T

- T CD8: **T cytotoxiques**

  Peptide antigénique présenté par une CPA via un complexe p-CMH classe I

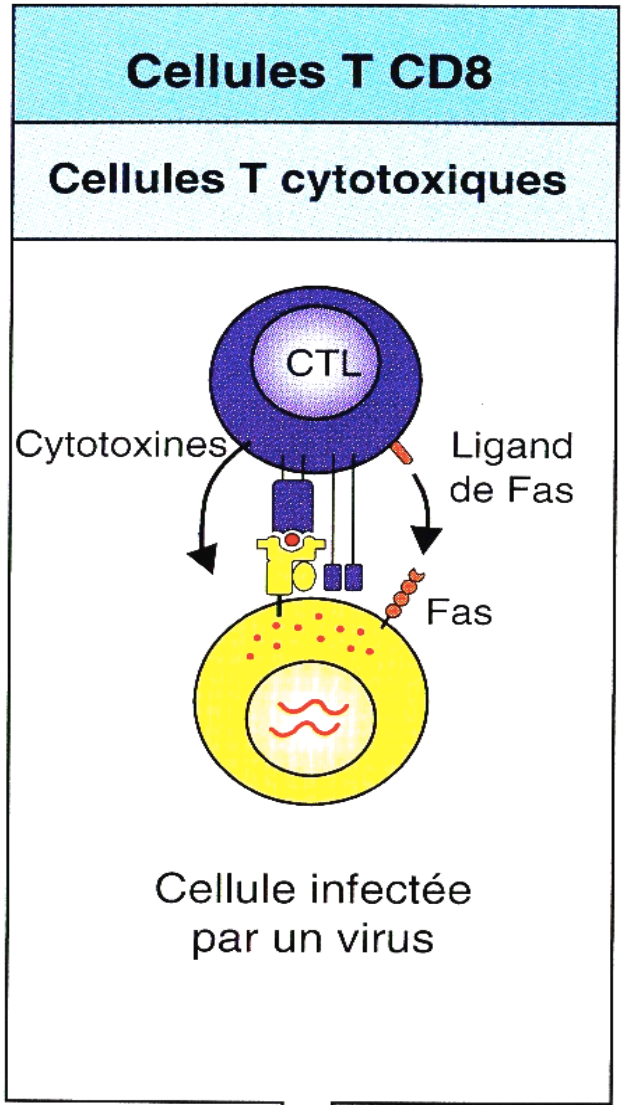
  – Immunité anti-infectieuse (virale, pathogène intra-cellulaire)
  – Immunité anti-tumorale
  – Allogreffe

Fonctions des lymphocytes T

- T CD8: **T cytotoxiques**

Cytotoxines sécrétées	Cytokines
Perforine Granzymes	Ligand de Fas IFN-γ TNF-β TNF-α

Protein in lytic granules of cytotoxic T cells	Actions on target cells
Perforin	Polymerizes to form a pore in target membrane
Granzymes	Serine proteases, which activate apoptosis once in the cytoplasm of the target cell



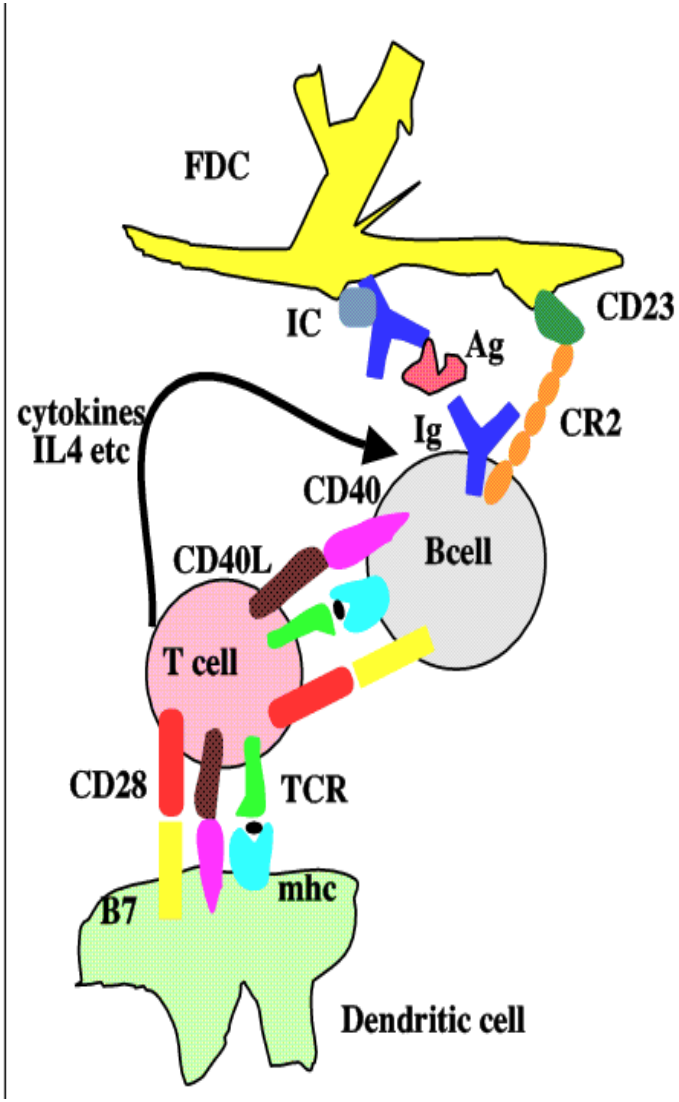
Fonctions des lymphocytes T

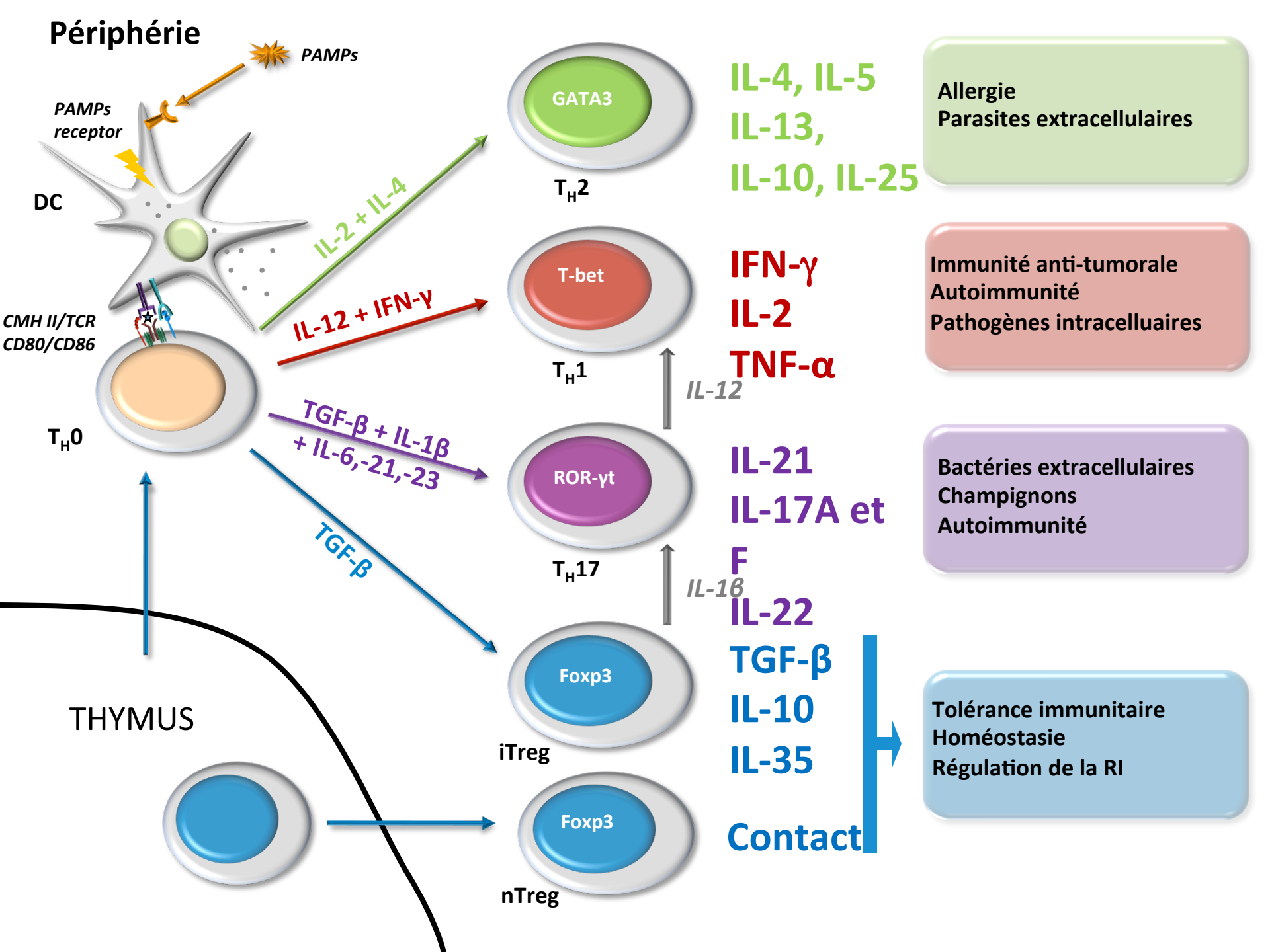
- T CD4: **T helper (Th) et T régulateurs (Treg)**

  Peptide antigénique présenté par une CPA via un complexe p-CMH classe II

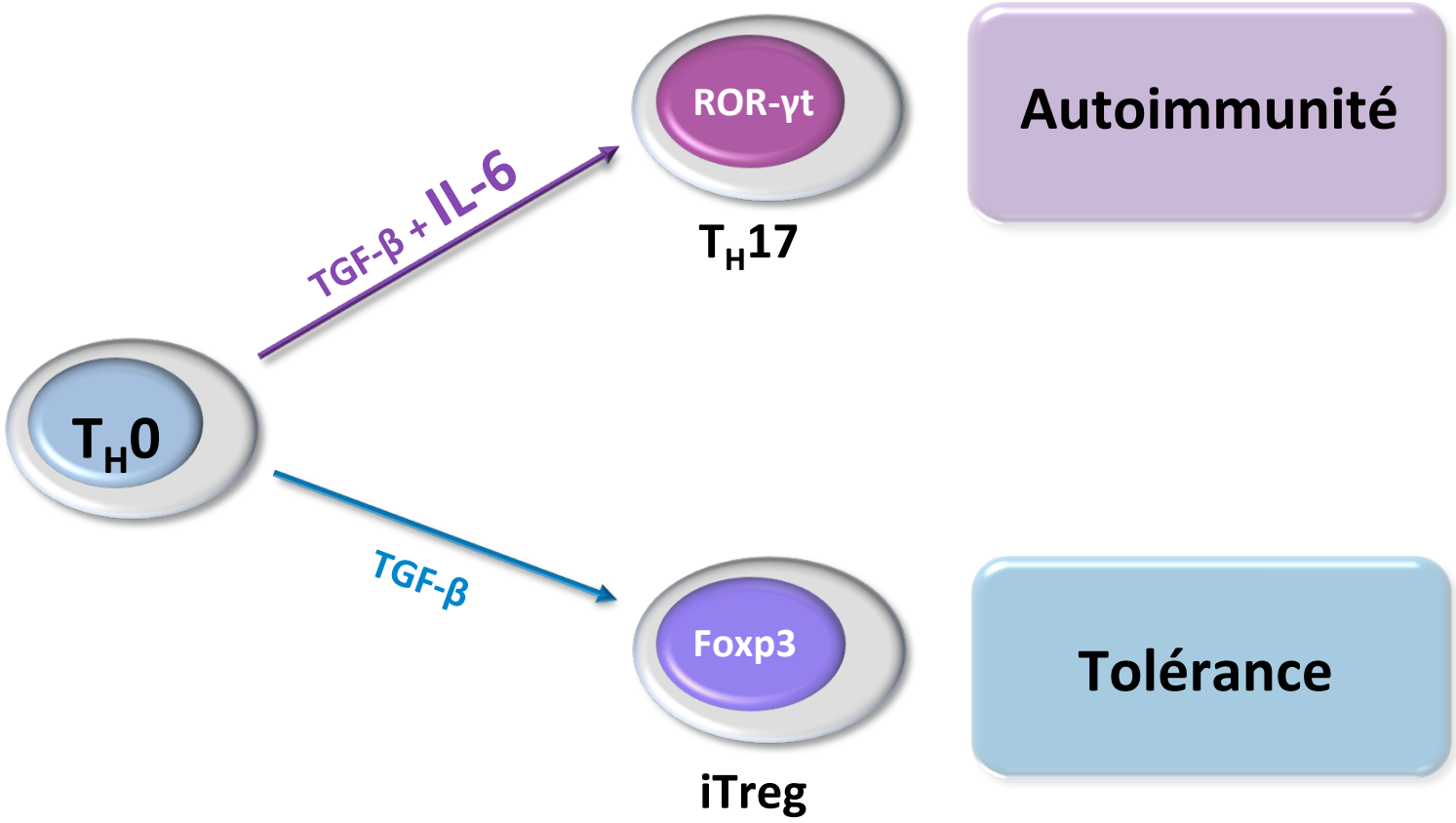
  - Coopération cellulaire
  - Production de cytokines
  - Coopération B/T
  - Sous-populations lymphocytaires T CD4

Fonctions des lymphocytes T



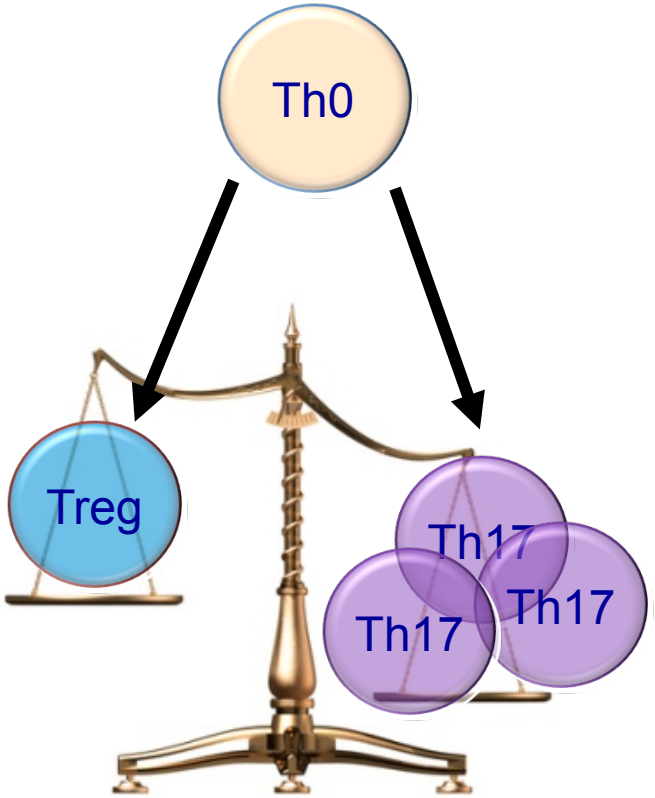

Périphérie
PAMPs
PAMPs receptor
DC
CMH II/TCR
CD80/CD86
T_H0
IL-2 + IL-4
IL-12 + IFN-γ
TGF-β + IL-1β + IL-6,-21,-23
TGF-β
GATA3
T_H2
T-bet
T_H1
ROR-γt
T_H17
Foxp3
iTreg
Foxp3
nTreg
IL-12
IL-1β
IL-4, IL-5
IL-13,
IL-10, IL-25
IFN-γ
IL-2
TNF-α
IL-21
IL-17A et F
IL-22
TGF-β
IL-10
IL-35
Contact
Allergie
Parasites extracellulaires
Immunité anti-tumorale
Autoimmunité
Pathogènes intracelluaires
Bactéries extracellulaires
Champignons
Autoimmunité
Tolérance immunitaire
Homéostasie
Régulation de la RI
THYMUS

Activation des CD4 : déséquilibre de la balance Th17/Treg



Bettelli, Nature, 2006

Balance Th17/Treg



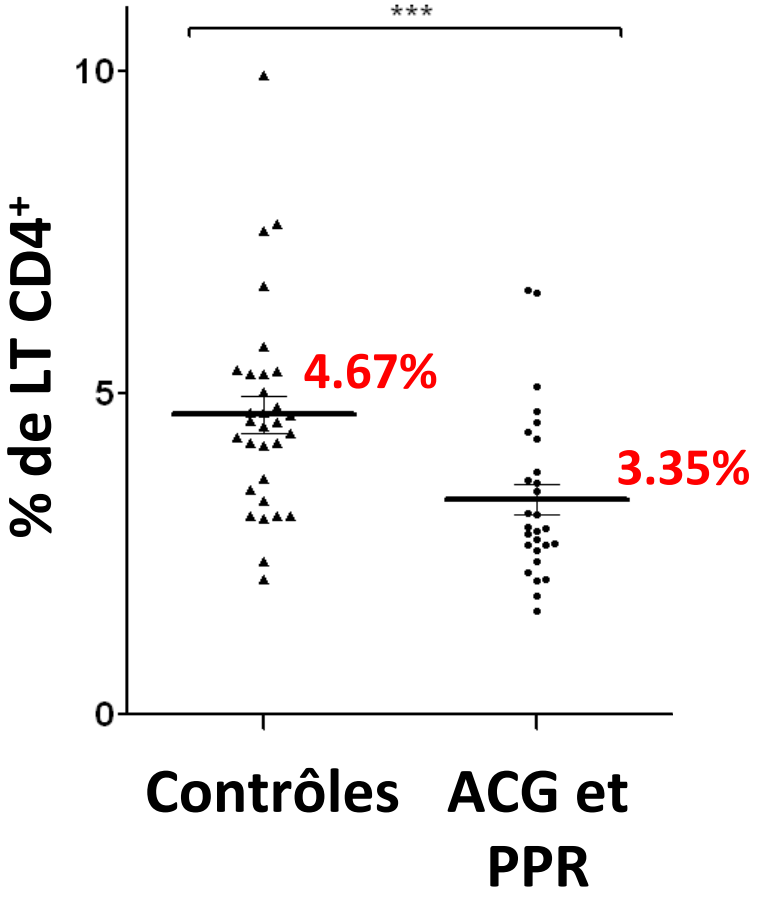
Maladies auto-immunes et auto-inflammatoires

Exemples de vascularites:

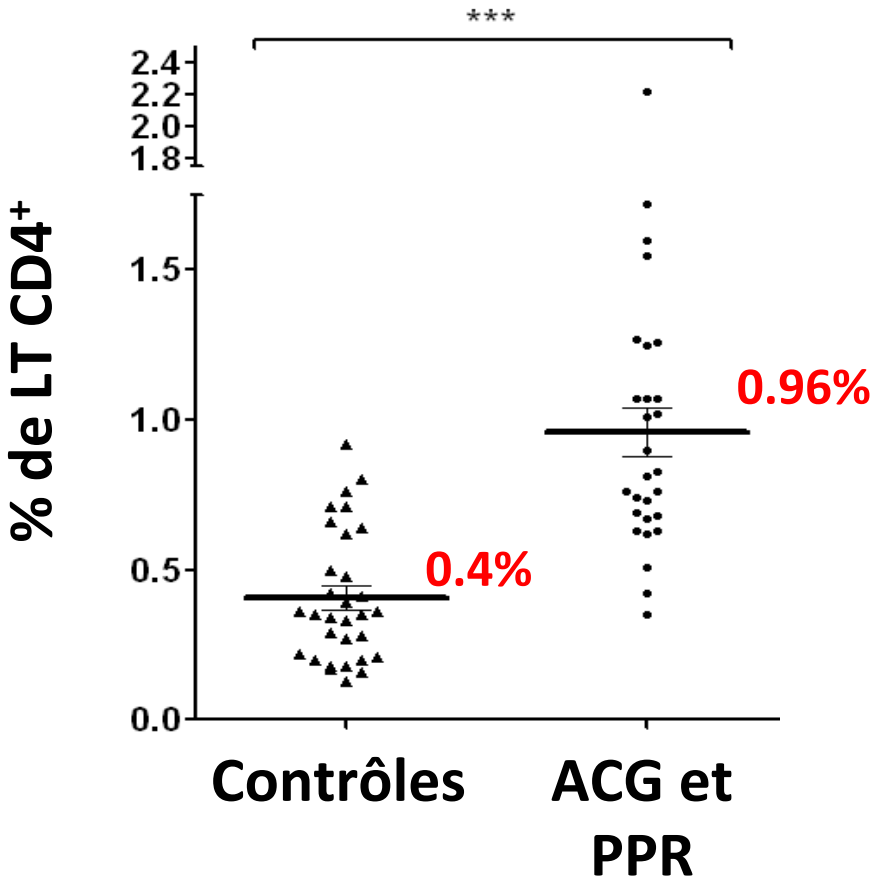
- Balance Th17/Treg dans l'artérite à cellules géantes (ACG) et pseudopolyarthrite rhizomélique (PPR)
- Distributions biaisées des lymphocytes T $CD4^+$ dans la granulomatose avec polyangéïte (GPA)
- Balance Th1-Th17/Treg dans la maladie de Behçet

Déséquilibre de la balance Th17/Treg

Diminution des Treg
($CD4^+$ $CD25^{high}$ $Foxp3^+$)



Augmentation des Th17
($CD4^+IL\text{-}17^+$)



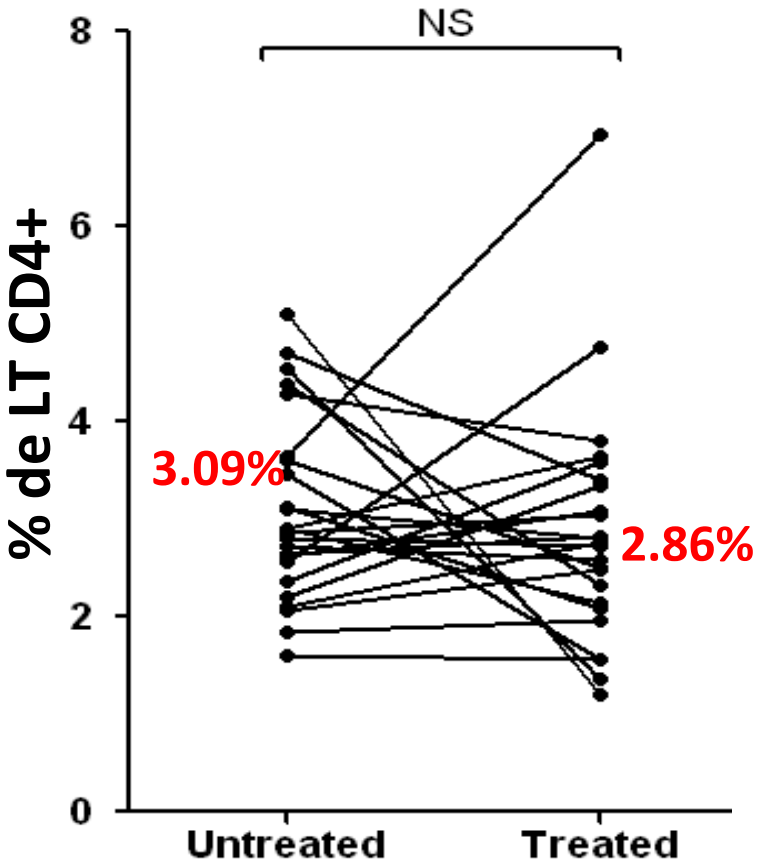
Samson et al. Arthritis Rheum 2012

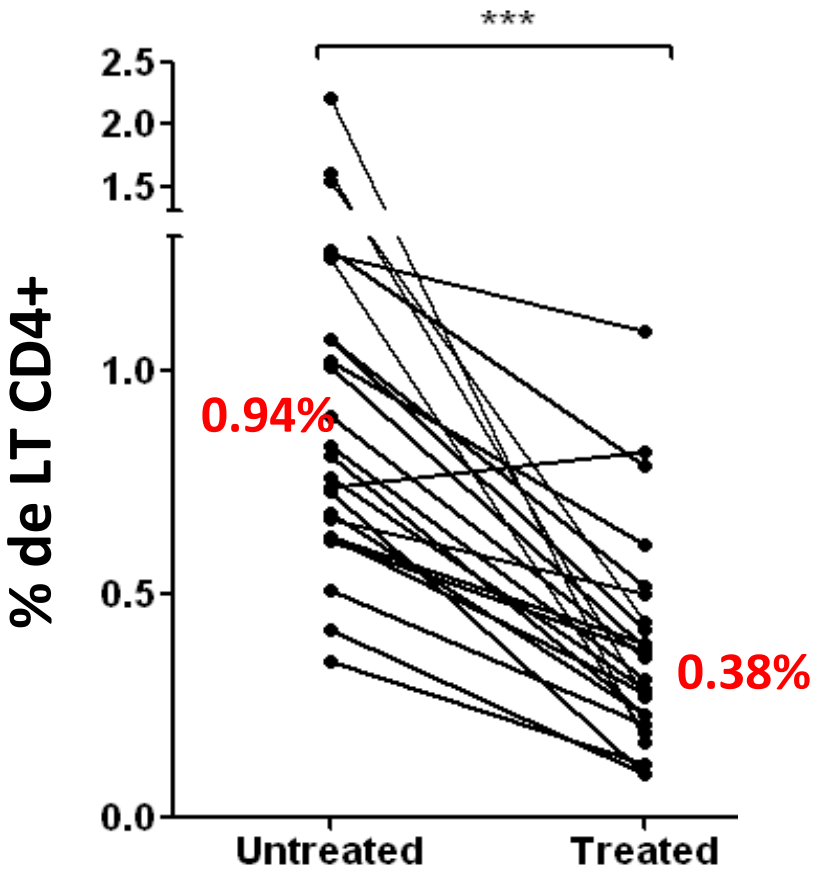
Effets de la corticothérapie

=

Treg

Th17 ↓





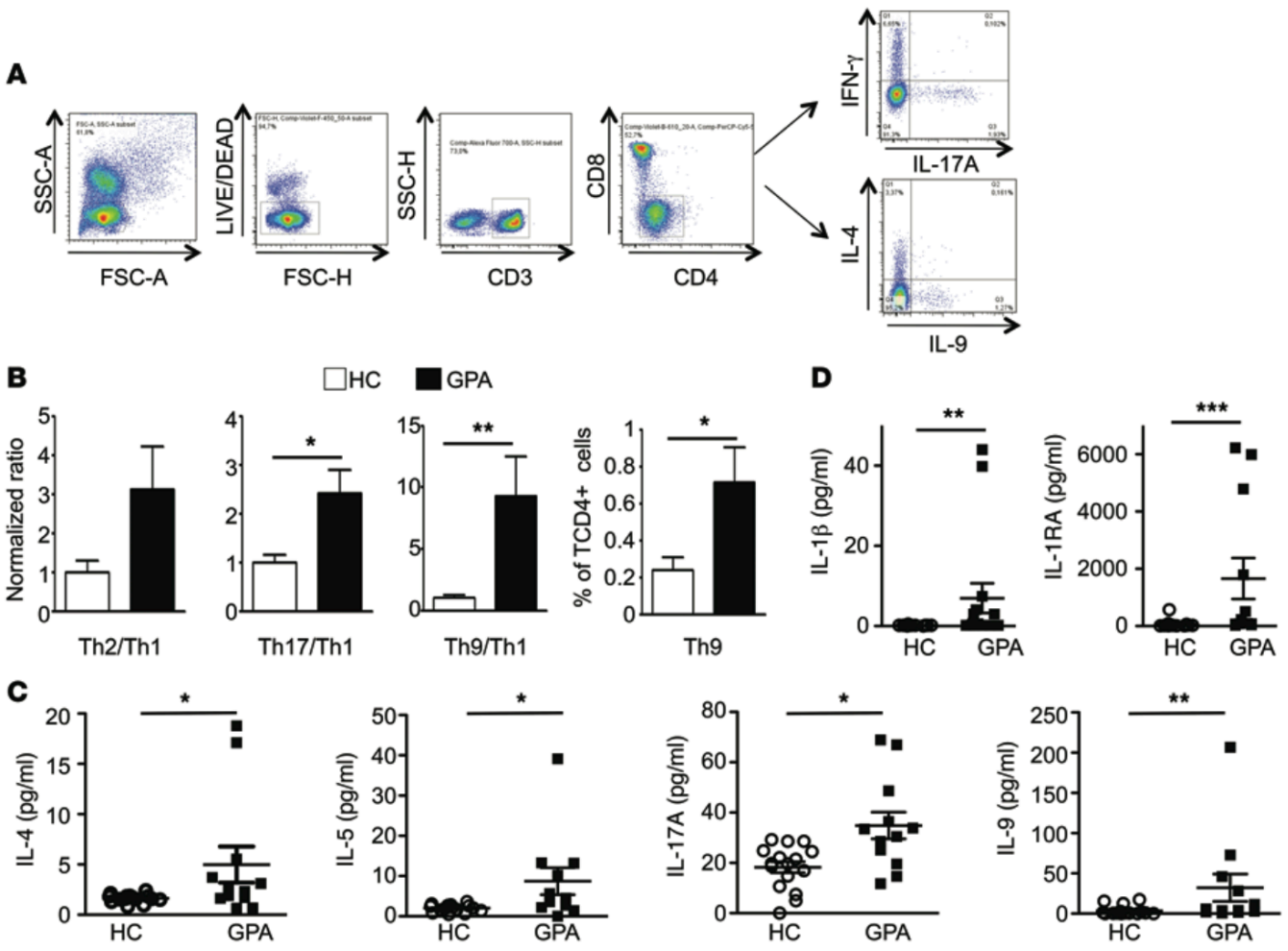
Samson et al. Arthritis Rheum 2012

Biphasic course of WG due to TH1 and TH2 responses

Csernok E, Gross W 1998

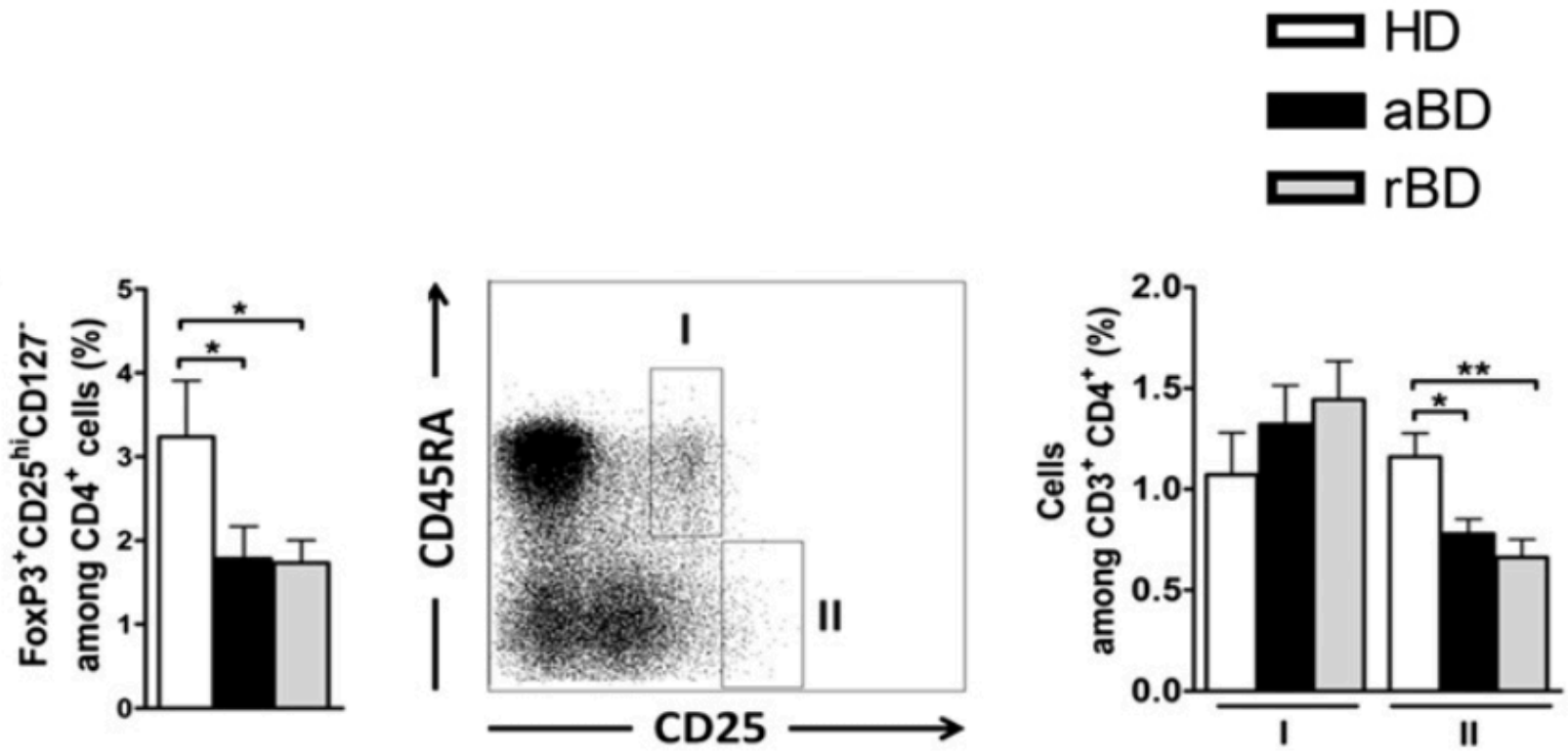
	Granulomatous phase	Vasculitis phase
Clinic	limited	severe
Biopsy	granuloma	vasculitis
Immun.	TH1 (IFNγ)	TH2 (IL4)

CD4 T cells from GPA patients have a skewed distribution of Th2/Th9/Th17



Millet A. J Clin Invest 2014

Perturbation de la balance T reg/Teff



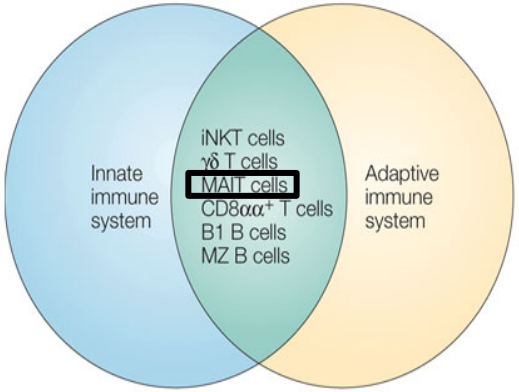
Différenciation lymphocytaire T CD4+ au profit des T effecteurs Th1 et Th17 au détriment des T régulateurs

Geri, JACI, 2011

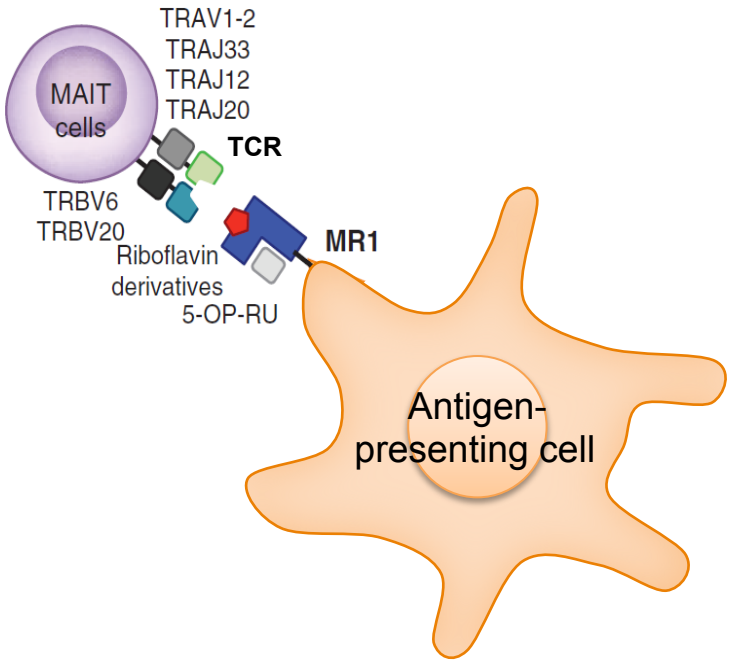
Lymphocytes T γδ, NKT, MAIT

- Lymphocyte T γδ:
  - Majorité DN ou SP CD8+, rares SP CD4+
  - Différence d'ontogénie
  - Répartition tissulaire différente: muqueuses, peau
  - TCR moins diversifés
  - Reconnaissent des épitopes conservés au sein des pathogènes
  - Immunité Innée
- NKT
  - TCR + CD3 + CD56 + CD16
  - TCR quasi invariant
    - Chaîne α = Vα 14 et Jα 18
  - Reconnaissent des lipides et glycolipides présentés par C1d
  - 0.001 à 3% des lymphocytes circulant
- MAIT

Mucosal Associated Invariant T (MAIT) cells



- Abundant population (1 - 10% of T cells in human blood, also present in human liver and mucosal tissues)
- **Non conventional T cells**: do not recognize classical peptides antigens, invariant TCRα chain consisting of TRAV1-2 (**Vα7.2⁺)** joined to TRAJ33
- Role in **host defense against bacteria**
- Target: **MR1** (non-polymorphic MHC class I like protein) presenting **bacterial-derived vitamin B** (riboflavin, folate) **derivatives**



Adapted from Godfrey et al., Nat Immunol 2015

Cytokines

Généralités

- **Définition**: petites protéines cellulaires solubles sécrétées qui ont la capacité de modifier le comportement ou les propriétés de la cellule sécrétrice ou d'une autre cellule.
- **Rôles:** communication intercellulaire et médiation soluble

- **Caractéristiques communes :**
- Faible masse moléculaire (10-25 kDa), et glycosylation variable
- Production spontanée relativement réduite
- Essentiellement mise en jeu lors d'une activation cellulaire
- Action de courte durée, à très faible concentration (pg/ml)
- **Applications cliniques:** dosages, cibles thérapeutiques

CYTOKINES

Facteur de croissance

GM-CSF
G-CSF
M-CSF
EPO, TPO, …

Interleukines

IL-1 → **IL-38….**

TNFs *parenté structurale*
IFNs *activité anti-virale*

Chimiokines

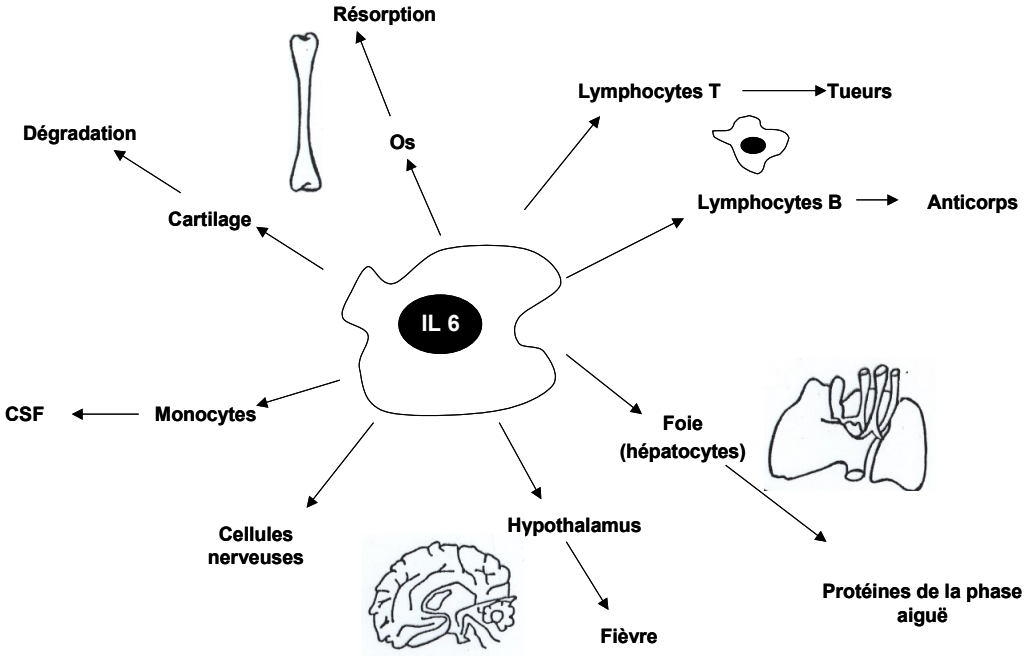
Famille Cys-Cys

Famille Cys-X-Cys

propriétés chémoattractantes

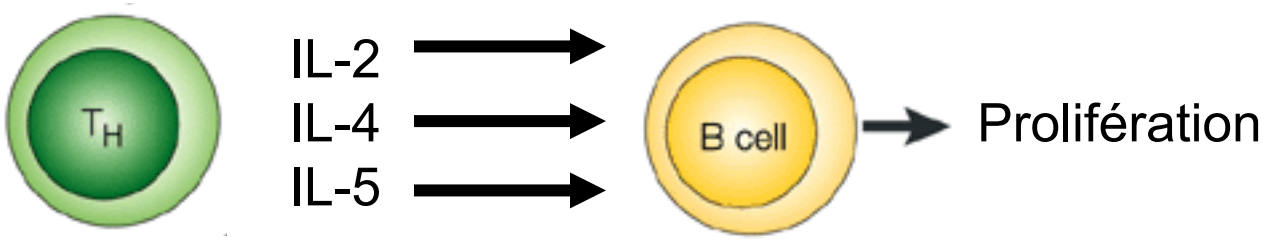
Propriétés des cytokines

- Pléiotropie: capacité à induire des effets différents sur des cibles cellulaires diverses



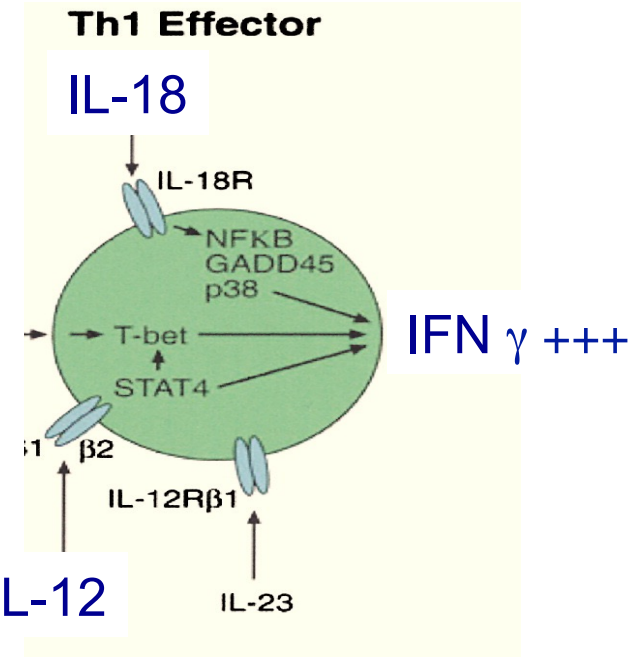
Propriétés des cytokines

- Pléiotropie
- Redondance:



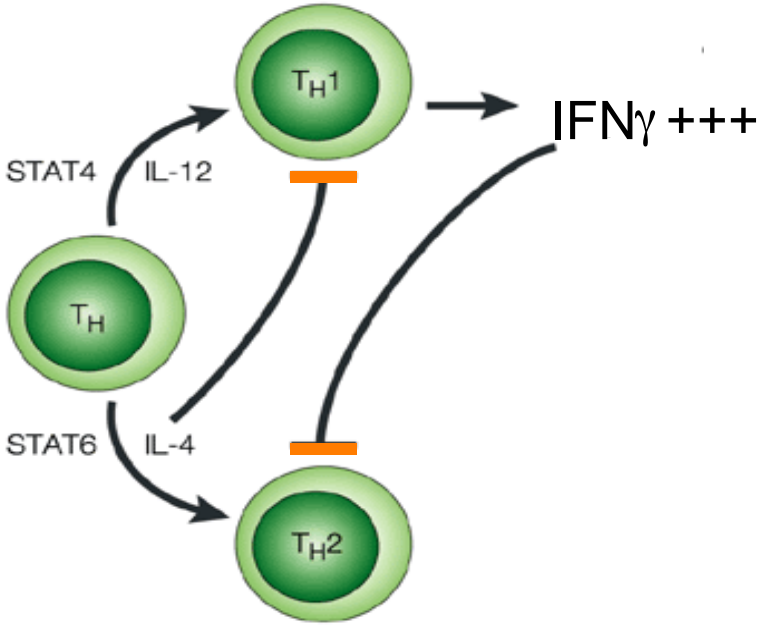
Propriétés des cytokines

- Pléiotropie
- Redondance
- Synergie:



Propriétés des cytokines

- Pléiotropie
- Redondance
- Synergie
- Antagonisme:



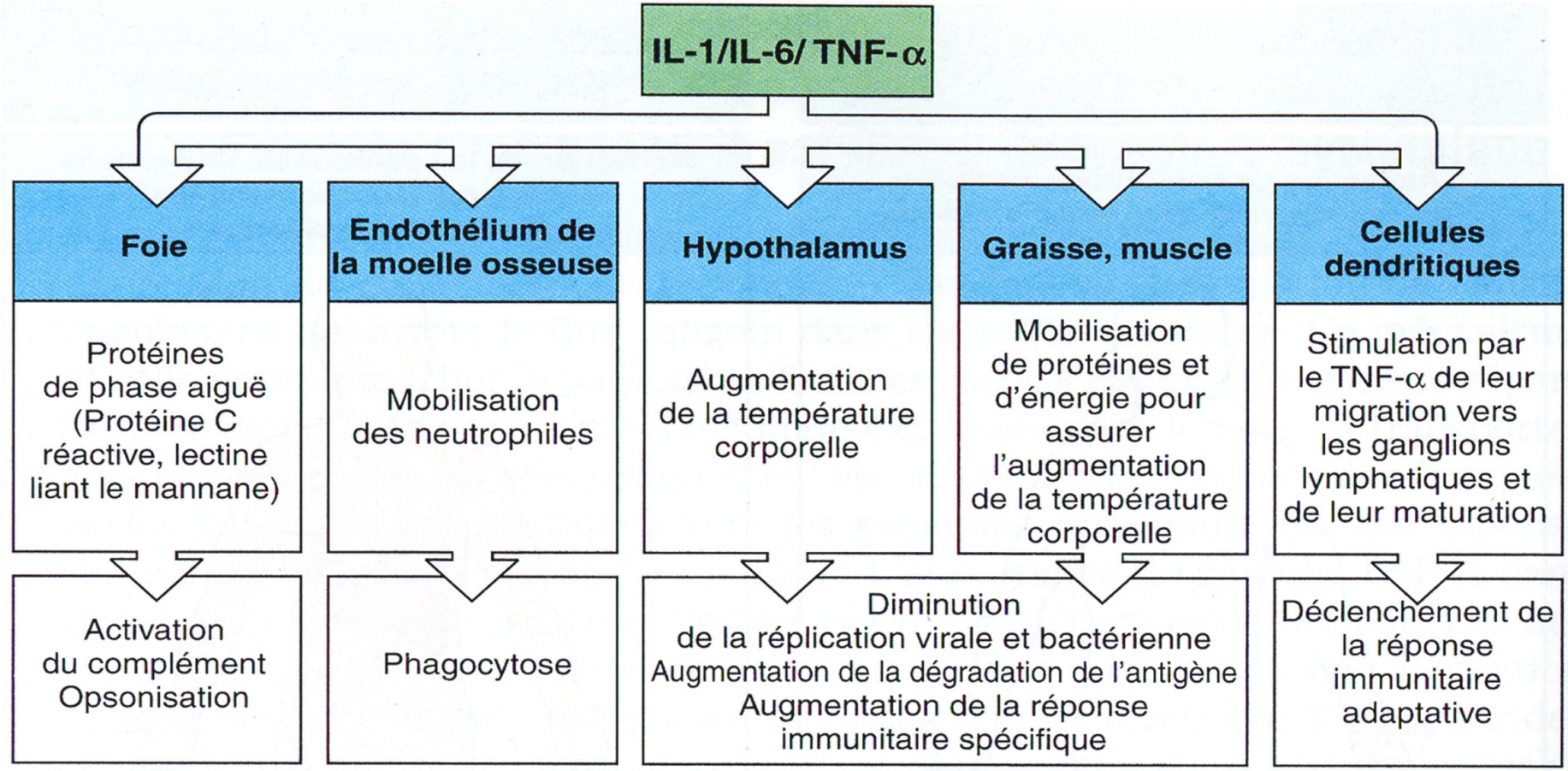
Propriétés des cytokines

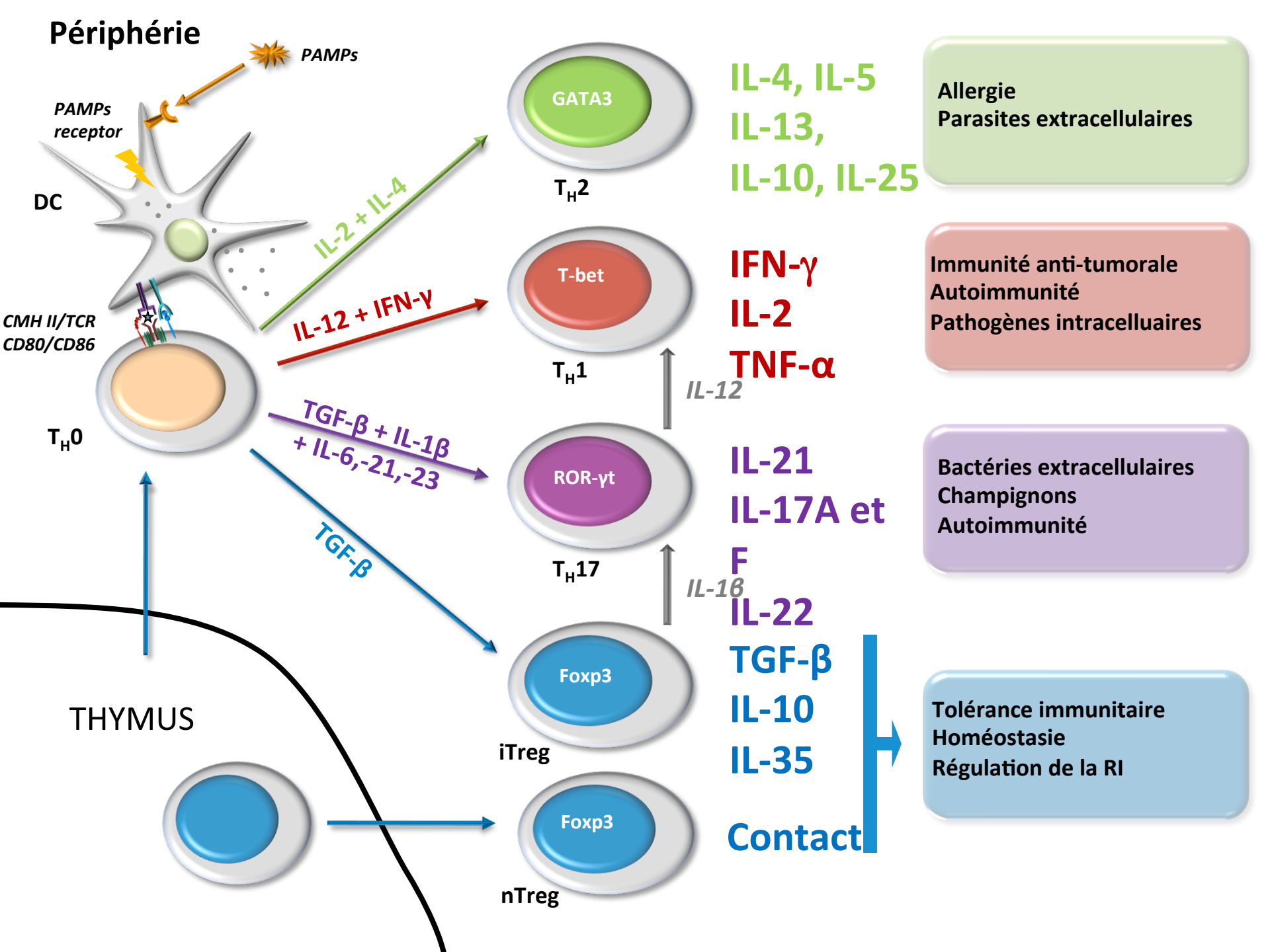
- Pléiotropie
- Redondance
- Synergie
- Antagonisme
- Induction de cascades

Fonctions

Cytokine	T-cell source	Effects on					Effect of gene knockout
		B cells	T cells	Macrophages	Hematopoietic cells	Other tissue cells	
Interleukin-2 (IL-2)	Naive, T_H1, some CD8	Stimulates growth and J-chain synthesis	Growth	–	Stimulates NK cell growth	–	↓T-cell responses IBD
Interferon-γ (IFN-γ)	T_H1, CTL	Differentiation IgG2a synthesis (mouse)	Inhibits T_H2 cell growth	Activation, ↑MHC class I and class II	Activates NK cells	Antiviral ↑MHC class I and class II	Susceptible to mycobacteria, some viruses
Lymphotoxin-α (LT-α, TNF-β)	T_H1, some CTL	Inhibits	Kills	Activates, induces NO production	Activates neutrophils	Kills fibroblasts and tumor cells	Absence of lymph nodes Disorganized spleen
Interleukin-4 (IL-4)	T_H2	Activation, growth IgG1, IgE ↑MHC class II induction	Growth, survival	Inhibits macrophage activation	↑Growth of mast cells	–	No T_H2
Interleukin-5 (IL-5)	T_H2	Mouse: Differentiation IgA synthesis	–	–	↑Eosinophil growth and differentiation	–	Reduced eosinophilia
Interleukin-10 (IL-10)	T_H2 (human: some T_H1), T_{reg}	↑MHC class II	Inhibits T_H1	Inhibits cytokine release	Co-stimulates mast cell growth	–	IBD
Interleukin-3 (IL-3)	T_H1, T_H2, some CTL	–	–	–	Growth factor for progenitor hematopoietic cells (multi-CSF)	–	–
Tumor necrosis factor-α (TNF-α)	T_H1, some T_H2, some CTL	–	–	Activates, induces NO production	–	Activates microvascular endothelium	Susceptibility to Gram –ve sepsis
Granulocyte-macrophage colony-stimulating factor (GM-CSF)	T_H1, some T_H2, some CTL	Differentiation	Inhibits growth?	Activation Differentiation to dendritic cells	↑Production of granulocytes and macrophages (myelopoiesis) and dendritic cells	–	–
Transforming growth factor-β (TGF-β)	CD4 T cells (T_{reg})	Inhibits growth IgA switch factor	Inhibits growth, promotes survival	Inhibits activation	Activates neutrophils	Inhibits/ stimulates cell growth	Death at ~10 weeks
Interleukin-17 (IL-17)	CD4 T cells (T_H17), macrophages	–	–	–	Stimulates neutrophil recruitment	Stimulates fibroblasts and epithelial cells to secrete chemokines	–

Cytokines pro-inflammatoires




Périphérie
PAMPs
PAMPs receptor
DC
CMH II/TCR
CD80/CD86
T_H0
IL-2 + IL-4
IL-12 + IFN-γ
TGF-β + IL-1β + IL-6,-21,-23
TGF-β
GATA3
T_H2
T-bet
T_H1
ROR-γt
T_H17
Foxp3
iTreg
Foxp3
nTreg
IL-12
IL-1β
IL-4, IL-5
IL-13,
IL-10, IL-25
IFN-γ
IL-2
TNF-α
IL-21
IL-17A et F
IL-22
TGF-β
IL-10
IL-35
Contact
Allergie
Parasites extracellulaires
Immunité anti-tumorale
Autoimmunité
Pathogènes intracelluaires
Bactéries extracellulaires
Champignons
Autoimmunité
Tolérance immunitaire
Homéostasie
Régulation de la RI
THYMUS

Quelques exemples …

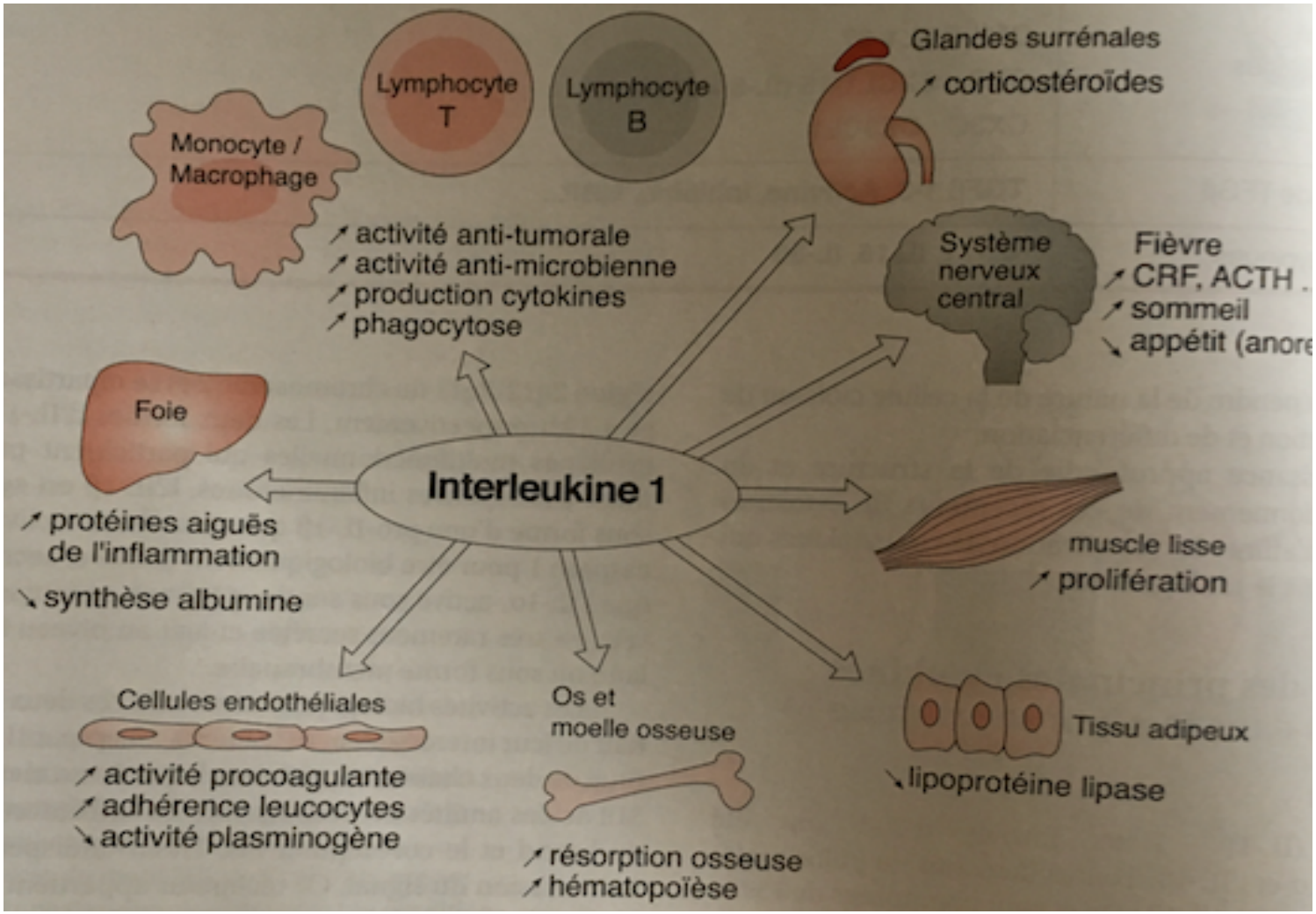
TNF-α

- Gène: chr 6, 4 exons 3 introns
- Cellules porteuses du gène: macrophages, LT, LB, mastocytes, granulocytes, cellules NK, fibroblastes, neurones, kératinocytes, cellules musculaires lisses
- 233 AA (27kDA) d'abord membranaire puis clivée en TNF-α soluble
- Forme active (soluble ou membranaire)= homotrimère
- 2 récepteurs : R1 (p55) et R2(p75)
- Actions:
  - Facteur de transcription de cytokines pro-inflammatoires, GM-CSF …
  - Synthèse de protéines de l'inflammation
  - Thermorégulateur (fièvre)
  - Recrutement de molécules sur site de l'inflammation
  - Activation des monocytes et des macrophages
  - Libération de molécules de défense immédiate
  - Relargage acide arachidonique et protaglandine PGE2
  - Induction de l'apoptose de cellules infectées
  - Mitogène des fibroblastes
  - Stimule le système immunitaire adaptatif
- Inhibiteurs commercialisés: infliximab, adalimumab, golimumab, certolizumab pegol, etanercept

IL-1

- Famille des IL-1/TLR: 11 membres -> 7 pro-inflammatoires, 4 antagonistes
- Activatrice ou freinatrice de l'inflammation
- Sécrétées sous frome d'un précurseur (sauf IL-1Ra)
- Rôles pro-inflammatoires:
  - Induction de l'expression du gène et synthèse CO2, phospholipase A2 et synthèse d'oxyde nitrique.
  - Augmentent expression des molécules d'adhésion endothéliale
  - Angiogénèse
  - Ostéoclastogénese
  - Différentiation Th17
  - Développement des Breg producteurs Il-10
- Inhibiteurs:
  - Anakinra: anti-récepteur des IL-1α et β
  - Canakinumab: anti IL-1β
  - Rilonacept: anti-IL-1
  - Gevokinumab: anti-IL-1β

IL-1



Bach et Chatenoud Immunologie
6ème édition

IL-6

- Glycoprotéine homodimérique de 19-26kD
- Famille des IL-6: MIF, oncostatine, cardiotrophine…
- Récepteur: chaîne α gp80 (membranaire ou soluble activatrice via le trans-signalling) et chaîne β gp130 (voie JAK-STAT)
- Roles:
  - Phase aigue de l'inflammation
  - Migration et activation leucocytaire
  - Différentiation, activation, survie LT
  - Différentiation LB
  - Osteoclastogènèse, résorption osseuse
  - Néoangiogénèse in vivo
  - Prolifération de fibroblastes
  - Dégradation cartilagineuse
  - …
- Prinicpal inhibiteur: tocilizumab (anti-IL6-Rα)

Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial

Dinesh Khanna, Christopher P Denton, Angelika Jahreis, Jacob M van Laar, Tracy M Frech, Marina E Anderson, Murray Baron, Lorinda Chung, Gerhard Fierlbeck, Santhanam Lakshminarayanan, Yannick Allanore, Janet E Pope, Gabriela Riemekasten, Virginia Steen, Ulf Müller-Ladner, Robert Lafyatis, Giuseppina Stifano, Helen Spotswood, Haiyin Chen-Harris, Sebastian Dziadek, Alyssa Morimoto, Thierry Sornasse, Jeffrey Siegel, Daniel E Furst

Lancet 2016; 387: 2630–40

Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial

Peter M Villiger, Sabine Adler*, Stefan Kuchen, Felix Wermelinger, Diana Dan, Veronika Fiege, Lukas Bütikofer, Michael Seitz, Stephan Reichenbach*

Lancet 2016; 387: 1921–27

J Rheumatol. 2016 Aug;43(8):1547-52. doi: 10.3899/jrheum.151252. Epub 2016 May 15.

Tocilizumab in Giant Cell Arteritis: A Multicenter Retrospective Study of 34 Patients.

Régent A[1], Redeker S[1], Deroux A[1], Kieffer P[1], Ly KH[1], Dougados M[1], Liozon E[1], Larroche C[1], Guillevin L[1], Bouillet L[1], Espitia O[1], Costedoat-Chalumeau N[1], Soubrier M[1], Brihaye B[1], Lifermann F[1], Lefevre G[1], Puéchal X[1], Mouthon L[1], Toussirot E[1]; French Vasculitis Group, the Groupe Francais pour l'Etude de l'Artérite à Cellules Géantes, and the Club Rhumatismes et Inflammation.

⊕ **Author information**

Abstract

OBJECTIVE: To report the efficacy and safety of tocilizumab (TCZ) for giant cell arteritis (GCA).

METHODS: A retrospective multicenter study that included 34 patients receiving TCZ for GCA.

RESULTS: TCZ was effective in all but 6 patients, who still had mild symptoms. Mean glucocorticoid dose was tapered. One patient died and 3 patients had to stop TCZ therapy because of severe adverse events. Twenty-three patients stopped treatment; 8 of these experienced relapses after a mean of 3.5 ± 1.3 months.

CONCLUSION: TCZ is effective in GCA. However, side effects occur. Whether this treatment has only a suspensive effect remains to be determined.

IL-5

- Homodimère de 15 kDa
- Récepteur hétérodimérique partagé avec IL-3
- Agit sur éosinophiles, mastocytes, Treg, neutrophiles et monocytes
- Fonctions:
  - différentiation des cellules myéloïdes
  - stimulation de l'activité chémotactique des éosinophiles
  - stimulation de l'adhésion des éosinophiles
  - cicatrisation et remodelage

Principal inhibiteur: mepolizumab (mAb anti-IL-5)

Mepolizumab as a steroid-sparing treatment option in patients with Churg-Strauss syndrome

Sophia Kim, MD,[a] Gautham Marigowda, MD,[b] Eyal Oren, MD,[c] Elliot Israel, MD,[b] and Michael E. Wechsler, MD[b]

Boston, Mass

doi:10.1016/j.jaci.2010.03.028

TABLE II. Summary table of outcome variables in all 7 patients at different times throughout the study

Mean (range)	Week −4, enrollment	Week 0, treatment phase	Week 12, treatment phase	Week 16, washout phase	Week 20, washout phase	Week 28, safety-monitoring phase	Week 40, safety-monitoring phase
Prednisone dose (mg)	18.8	12.9	4.6	6.7	5.0	4.3	15.7
Eosinophil (%)	2.9 (0.2-7)	3.4 (0.1-10.8)	0.8 (0.5-1.7)	0.4 (0.1-1)	1.0 (0-2.8)	2.4 (0.4-6)	3.8 (0-9.9)
No. of exacerbations		2		4		14	
IL-5 (pg/mL)	8 (2-14)	12 (0-65)	7 (0-24)	5 (0-10)	Not collected at this visit	Not collected at this visit	6 (0-18)
FEV_1 (% predicted)	79 (60-101)	76 (59-98)	76 (49-102)	75 (47-99)	75 (52-99)	80 (47-111)	77 (47-98)
PEF	Not measured @ visit	410 (300-480)	432 (210-529)	404 (210-529)	413 (240-529)	421 (280-523)	443 (380-564)
ACQ score	1.74 (0-2.86)	1.57 (0-2.86)	1.22 (0.29-2)	1.02 (0-1.71)	1.36 (0-1.83)	1.65 (0-3.86)	1.14 (0.57-3.86)
FeNO	62.2 (15-153.4)	47.4 (11-141.7)	39.1 (9.3-101.1)	50.5 (9.7-163.7)	62.1 (20.5-98.6)	Not collected at this visit	49.9 (31.1-86)
BVAS score	10.5 (3-18)	6.9 (3-15)	6.1 (0-11)	6.4 (0-17)	7.4 (0-14)	9.3 (3-12)	8.0 (0-23)
CRP (mg/L)	6.2 (0.6-15.8)	3.9 (0.8-10.5)	6.1 (0.9-17.1)	4.2 (0.8-19.3)	7.5 (0.8-27.4)	3.1 (0.8-12.4)	6.5 (0.4-19.6)
ESR (mm/h)	8 (2-25)	7 (2-20)	10 (3-21)	9 (2-25)	11 (1-26)	4 (1-6)	7 (2-27)

There were no significant changes in markers of disease activity noted despite clinical stability and decreased overall prednisone dosing. Mean IL-5 levels did not change in response to mepolizumab therapy.

PEF, Peak expiratory flow.

Clin Exp Rheumatol. 2012 Jan-Feb;30(1 Suppl 70):S62-5. Epub 2012 May 10.

Extended follow-up after stopping mepolizumab in relapsing/refractory Churg-Strauss syndrome.

Herrmann K[1], Gross WL, Moosig F.

⊕ Author information

Abstract

OBJECTIVES: To report on the extended follow-up of relapsing/refractory CSS patients treated with mepolizumab with respect to relapse rates.

METHODS: The follow-up consisted of regular clinic visits of patients who received nine infusions of mepolizumab (750mg IV) and switched to methotrexate 0.3mg/kg for maintenance of remission. Glucocorticoids were maintained as low as possible. Disease activity was measured using the Birmingham Vasculitis Activity Score (BVAS). Disease states as remission or relapse were defined according to the EULAR/EUVAS recommendations. The serum eosinophil cationic protein (ECP) was measured regularly and concentrations were correlated with BVAS.

RESULTS: The follow-up of the study population under standard methotrexate maintenance therapy was extended to a median of 22 months. Three of nine patients were still in remission at the end of follow-up. During this time five major relapses in three and seven minor relapses in five out of the total nine patients were recognised. ECP levels were found to correlate stronger with the BVAS ($r=0.38$; $p<0.0001$) than other measures such as eosinophil counts.

CONCLUSIONS: After induction of remission with mepolizumab the majority of patients suffered relapses when switched to methotrexate maintenance therapy. These data suggest that patients with CSS may require long term treatment with mepolizumab. Future trials in CSS should use other doses or dosing intervals for patients in remission. ECP is a promising marker of disease activity in CSS.

PMID: 22512988

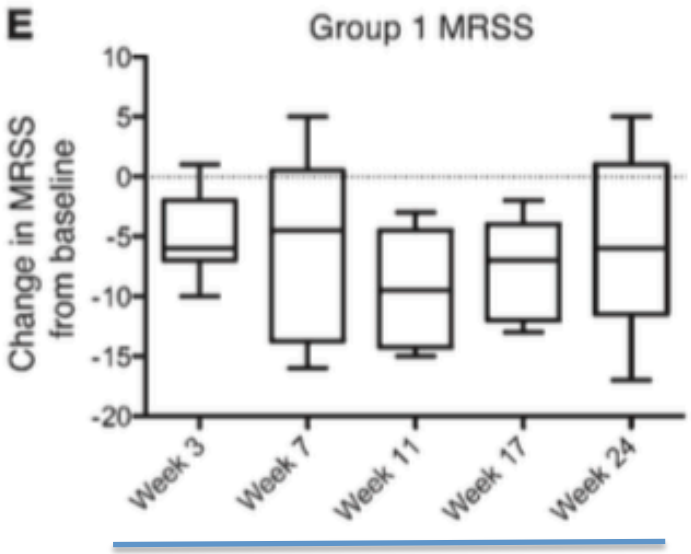
TGF-ß

- Superfamille TGF-ß: 3 isoformes homologues – homodimère 25kDa
- Formé d'un pro-domaine LAP (peptide associé à la latence) N-terminal inactif et le peptide C-terminal actif
- Fixation au récepteur nécessite: protéolyse, acidification, ROS, ou intégrines αV..
- Rôles: -balance inflammatoire (Treg)
  - dvt embryonnaire (squelette et système c-v)
  - transition mésenchymateuse des cellules épithéliales et endothéliales
  - dvt matrice extracellulaire
  - induction apoptose
  - inhibition de la prolifération
  - remodelage
- Inhibiteur: fresolimumab (mAb anti-TGF-ß3)

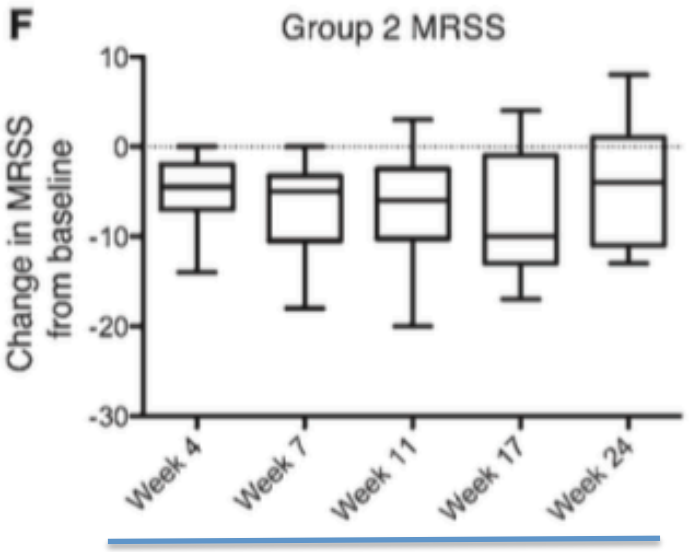
Fresolimumab treatment decreases biomarkers and improves clinical symptoms in systemic sclerosis patients

Lisa M. Rice,[1] Cristina M. Padilla,[1] Sarah R. McLaughlin,[1] Allison Mathes,[1] Jessica Ziemek,[1] Salma Goummih,[1] Sashidhar Nakerakanti,[1] Michael York,[1] Giuseppina Farina,[1] Michael L. Whitfield,[2] Robert F. Spiera,[3] Romy B. Christmann,[1] Jessica K. Gordon,[3] Janice Weinberg,[4] Robert W. Simms,[1] and Robert Lafyatis[1]

[1]Boston University School of Medicine, Department of Internal Medicine, Rheumatology Section, Boston, Massachusetts, USA. [2]Hospital for Special Surgery, New York, New York, USA. [3]Geisel School of Medicine at Dartmouth University Medical School, Hanover, New Hampshire, USA. [4]Boston University School of Public Health, Boston, Massachusetts, USA.



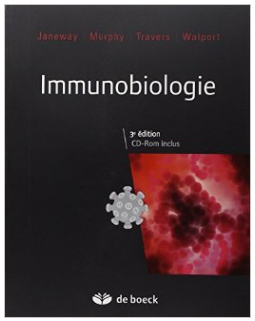
2*1mg/kg fresolimumab n=7

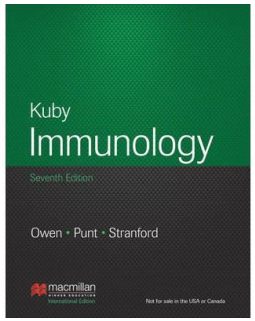


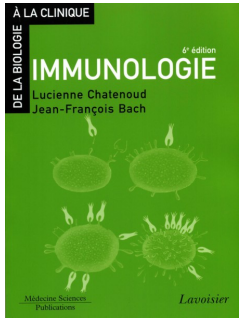
1*5mg/kg fresolimumab n=8

Pour en savoir plus…

- Text books:
  - Janeway, Murphy, Travers, Walport. Immunobiologie
  - Kuby. Immunology
  - Chatenoud L, Bach JF. Immunologie 6ème édition







Pour en savoir plus…

Fundamentals of allergy and immunology

Interleukins (from IL-1 to IL-38), interferons, transforming growth factor β, and TNF-α: Receptors, functions, and roles in diseases

Mübeccel Akdis, MD, PhD, Alar Aab, MSc, Can Altunbulakli, MSc, Kursat Azkur, DVM, Rita A. Costa, MSc, Reto Crameri, PhD, Su Duan, MD, Thomas Eiwegger, MD, Andrzej Eljaszewicz, PhD, Ruth Ferstl, PhD, Remo Frei, PhD, Mattia Garbani, PhD, Anna Globinska, MSc, Lena Hess, MD, Carly Huitema, PhD, Terufumi Kubo, MD, Zsolt Komlosi, MD, Patricia Konieczna, PhD, Nora Kovacs, MD, Umut C. Kucuksezer, PhD, Norbert Meyer, MD, Hideaki Morita, MD, Judith Olzhausen, PhD, Liam O'Mahony, PhD, Marija Pezer, PhD, Moira Prati, MSc, Ana Rebane, PhD, Claudio Rhyner, PhD, Arturo Rinaldi, MSc, Milena Sokolowska, MD, PhD, Barbara Stanic, PhD, Kazunari Sugita, MD, Angela Treis, PhD, Willem van de Veen, PhD, Kerstin Wanke, PhD, Marcin Wawrzyniak, PhD, Paulina Wawrzyniak, MSc, Oliver F. Wirz, MSc, Josefina Sierra Zakzuk, MD, and Cezmi A. Akdis, MD *Davos, Switzerland*

J Allergy Clin Immunol 2016 Aug