Diabète de types…

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CENTRE DE RECHERCHE
CENTRE AFFILIÉ À L'UNIVERSITÉ DE MONTRÉAL

Diabète Québec

Quand on pense au diabète…

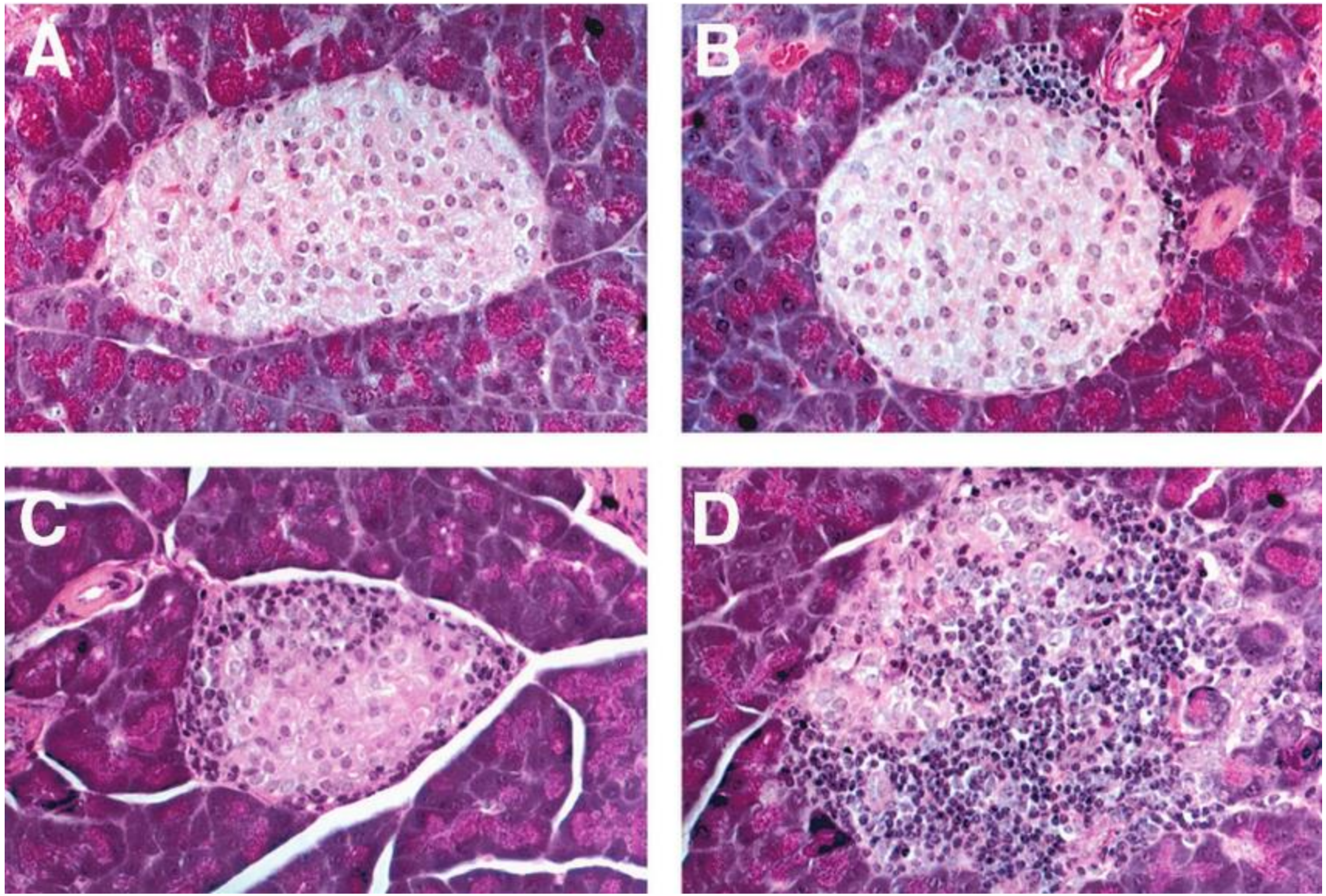
Diabète de type 1 **Diabète de type 2**

Le vrai visage du diabète

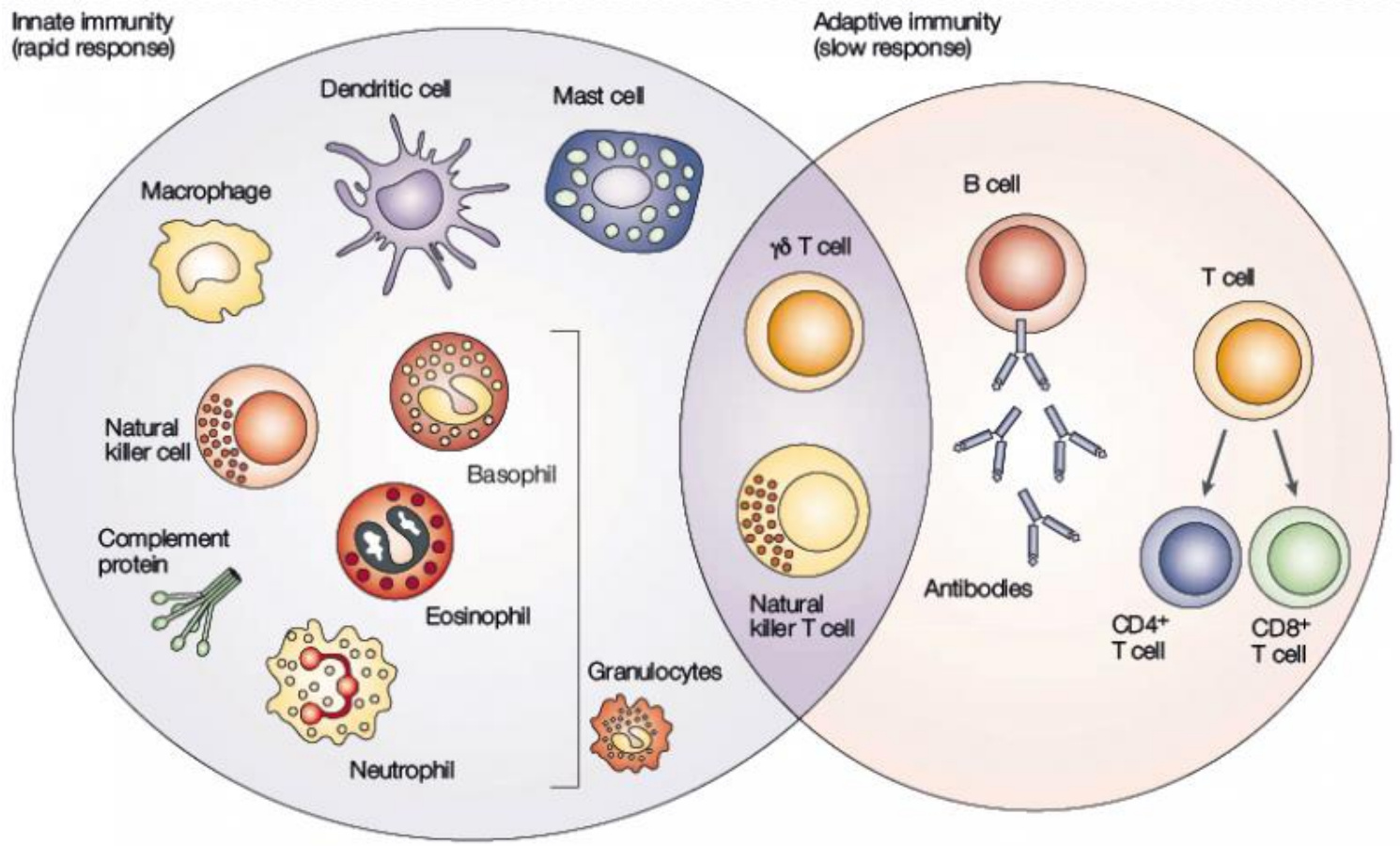
Le diabète: un ensemble de maladies

Contribution génétique:

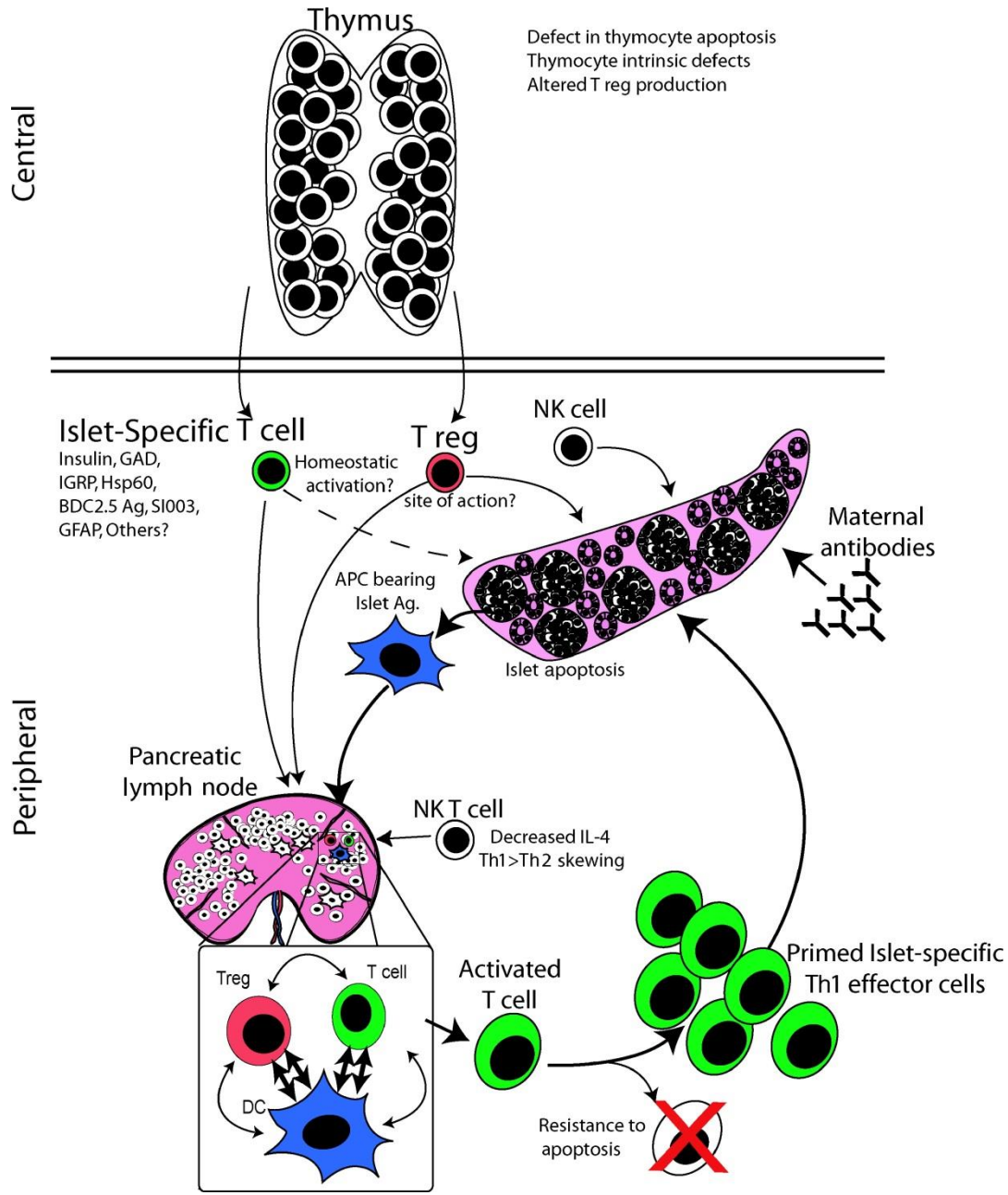
- D1T ~40% risque génétique
- D2T ~70% risque génétique
- Peu de gènes communs


A
B
C
D

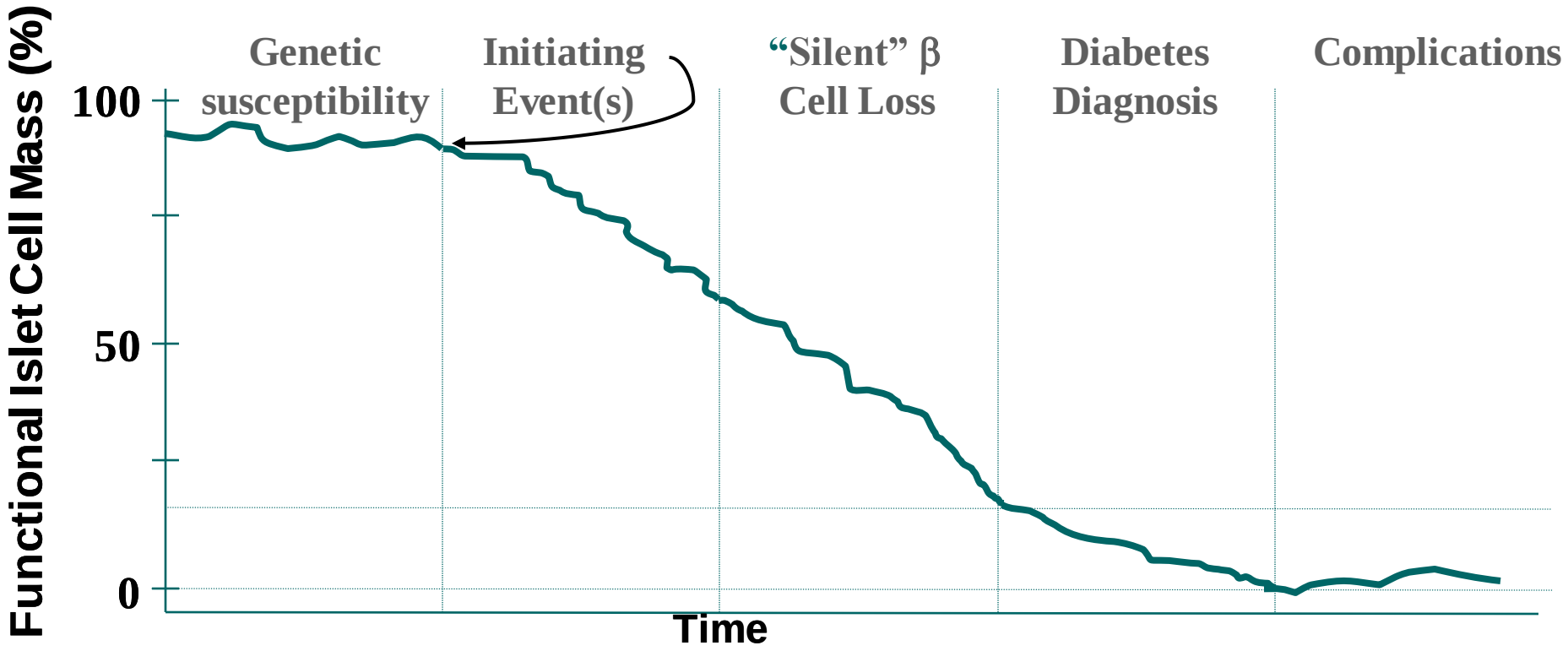
Les différentes cellules du système immunitaire



Dranoff G. Nat Rev Cancer 2004;4:11-22


Central
Peripheral
Thymus
Defect in thymocyte apoptosis
Thymocyte intrinsic defects
Altered T reg production
Islet-Specific T cell
Insulin, GAD,
IGRP, Hsp60,
BDC2.5 Ag, SI003,
GFAP, Others?
Homeostatic activation?
T reg
site of action?
NK cell
Maternal antibodies
APC bearing Islet Ag.
Islet apoptosis
Pancreatic lymph node
NK T cell
Decreased IL-4
Th1>Th2 skewing
Treg
T cell
DC
Activated T cell
Primed Islet-specific Th1 effector cells
Resistance to apoptosis

Progression du diabète de type 1



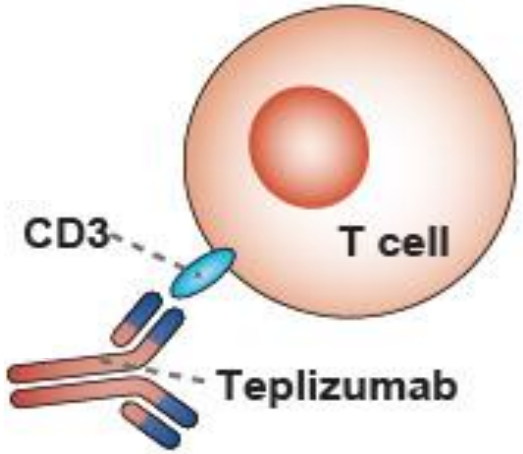
Découvertes canadiennes

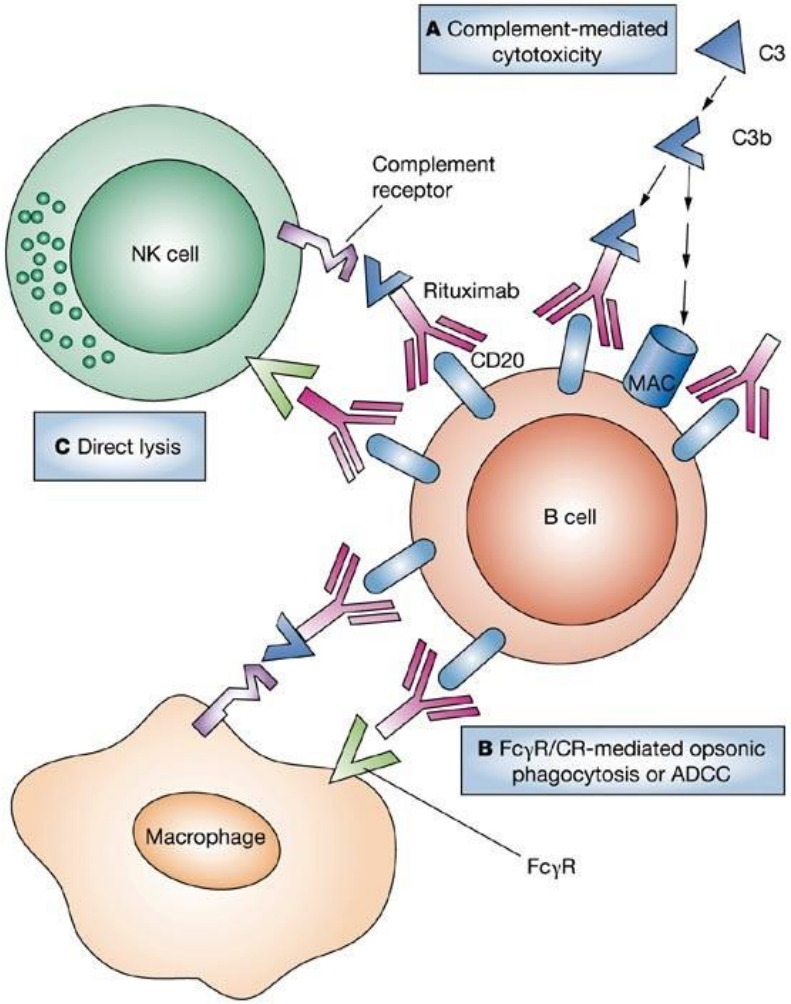
1921 Insuline
Banting et Best

1999 Edmonton protocol
Prof James Shapiro

Biologiques
Nouvelle generation de thérapies

Teplizumab
Depuis 2002

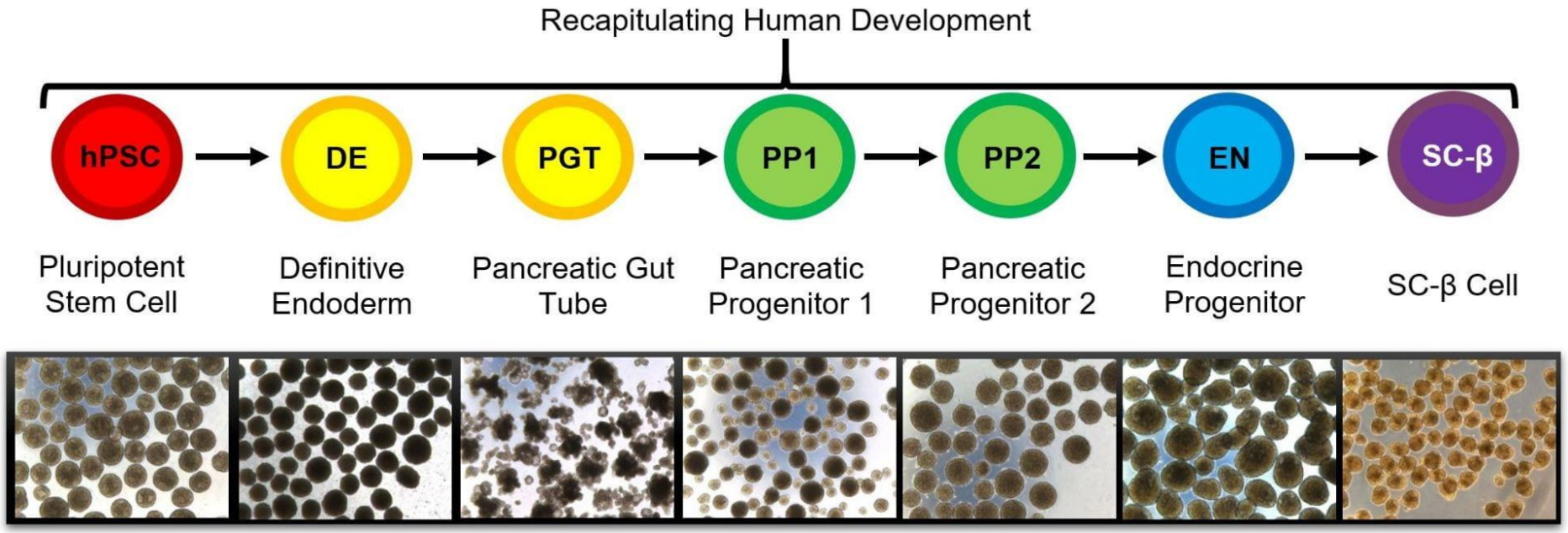




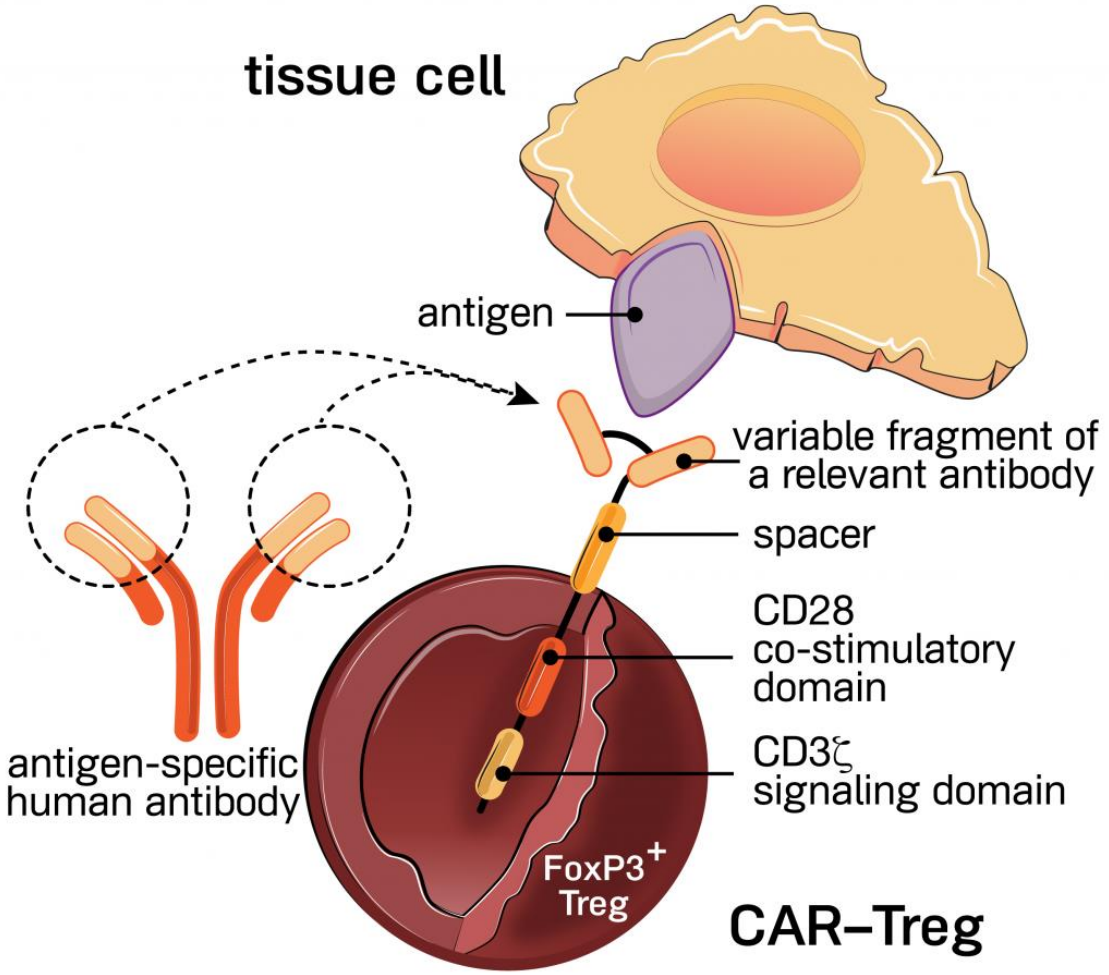
Rituximab
Depuis 2009

Le futur proche

Cellules souches – source de cellules beta



Le futur proche

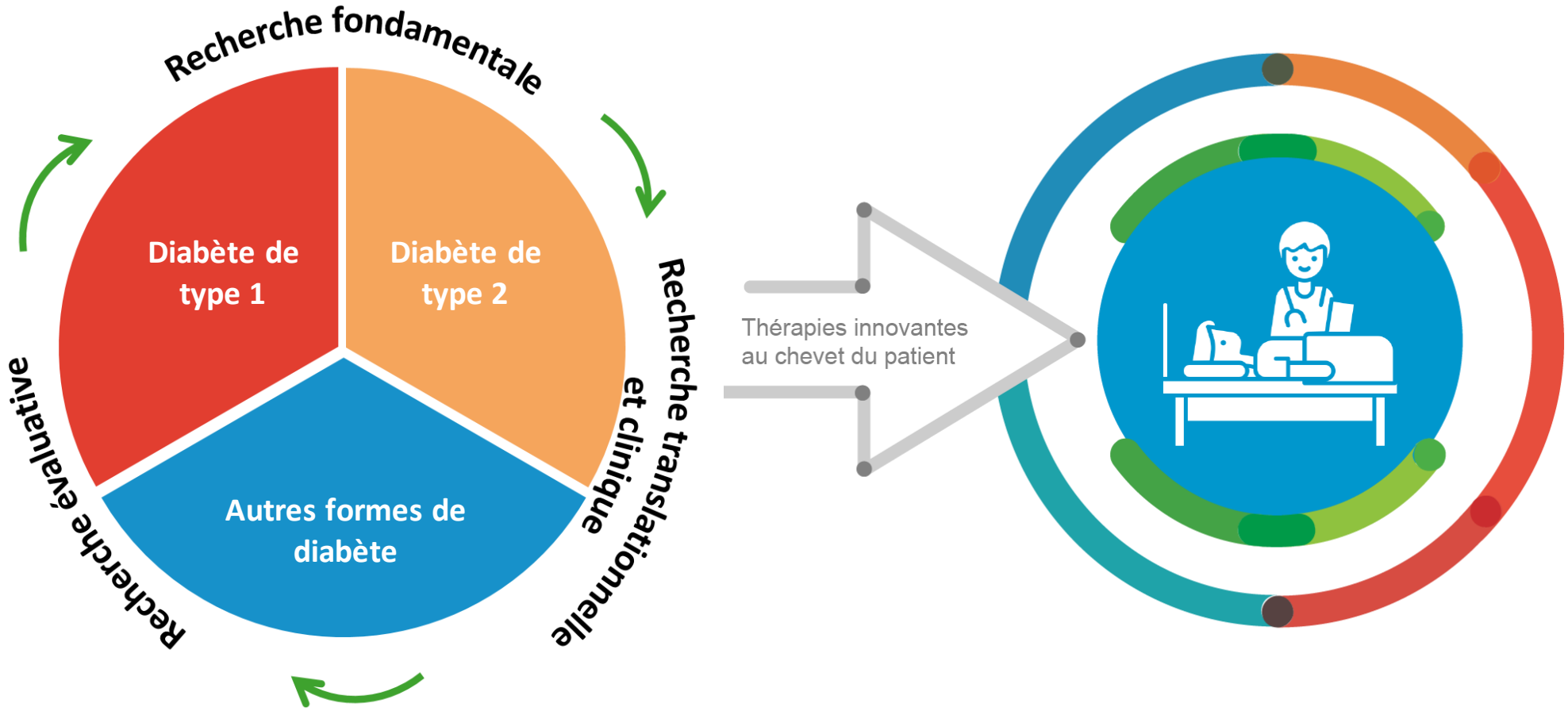


Immunosuppression spécifique

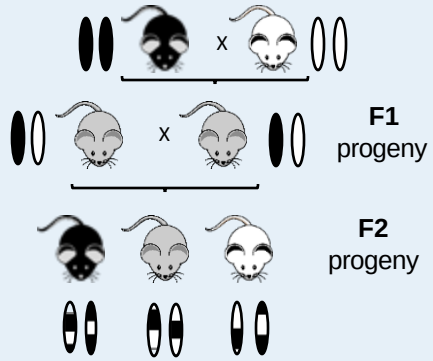
C’est quoi le futur proche?

C’est quoi le futur proche?
Pourquoi est-il si loin?

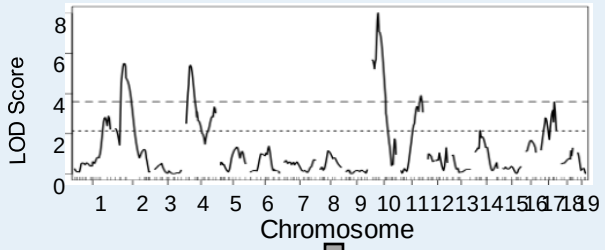
De la recherche fondamentale jusqu'aux soins



Immunogenetics



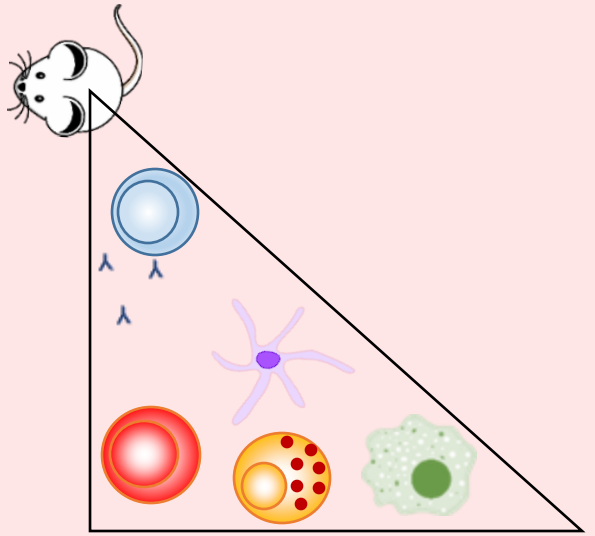
Phenotype vs Genetic Regions for F2 mice



Candidate genes

Validation

Cellular Immunology



In vitro and in vivo experiments to understand…

- **Cell phenotype**
- **Cell function**
- **Cell numbers**
- **Role in disease**

Translational Immunology

Identification of susceptibility genes → Identification of patient susceptibility to disease

At-risk patients + Curative cells → Treatment of disease

Immunogénétique

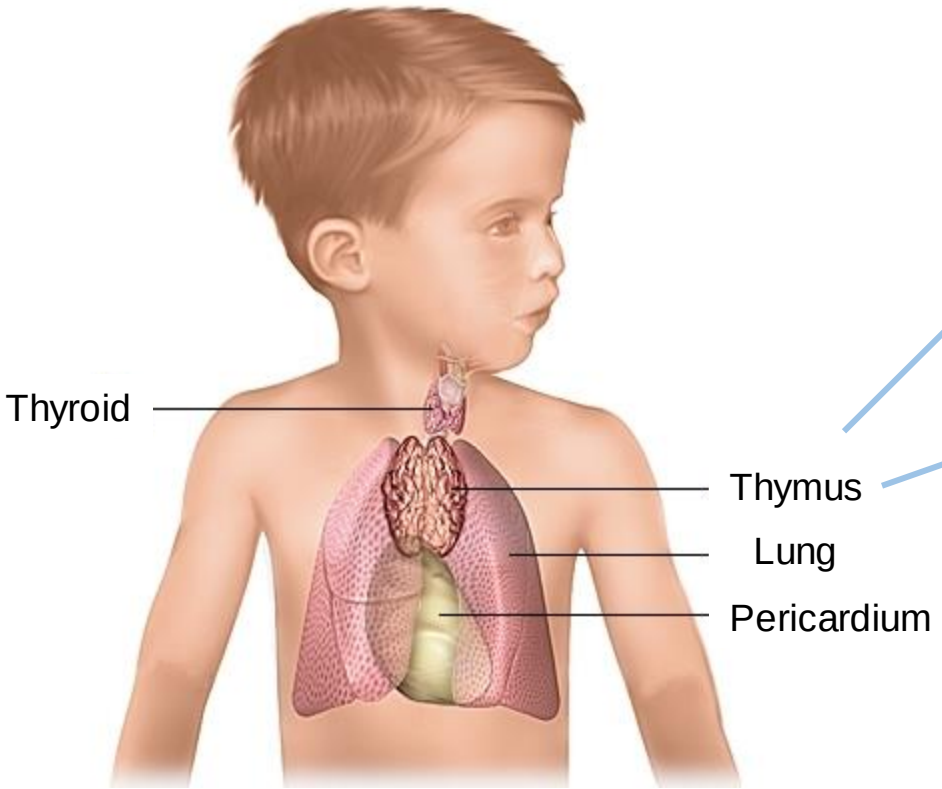
Cellules DN T

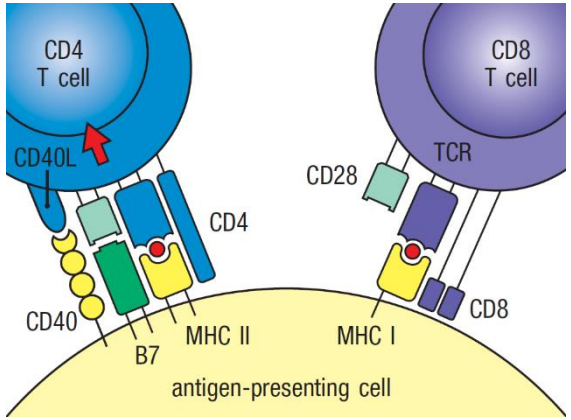
Cellules NK

Cellules dendritiques

LABO LESAGE

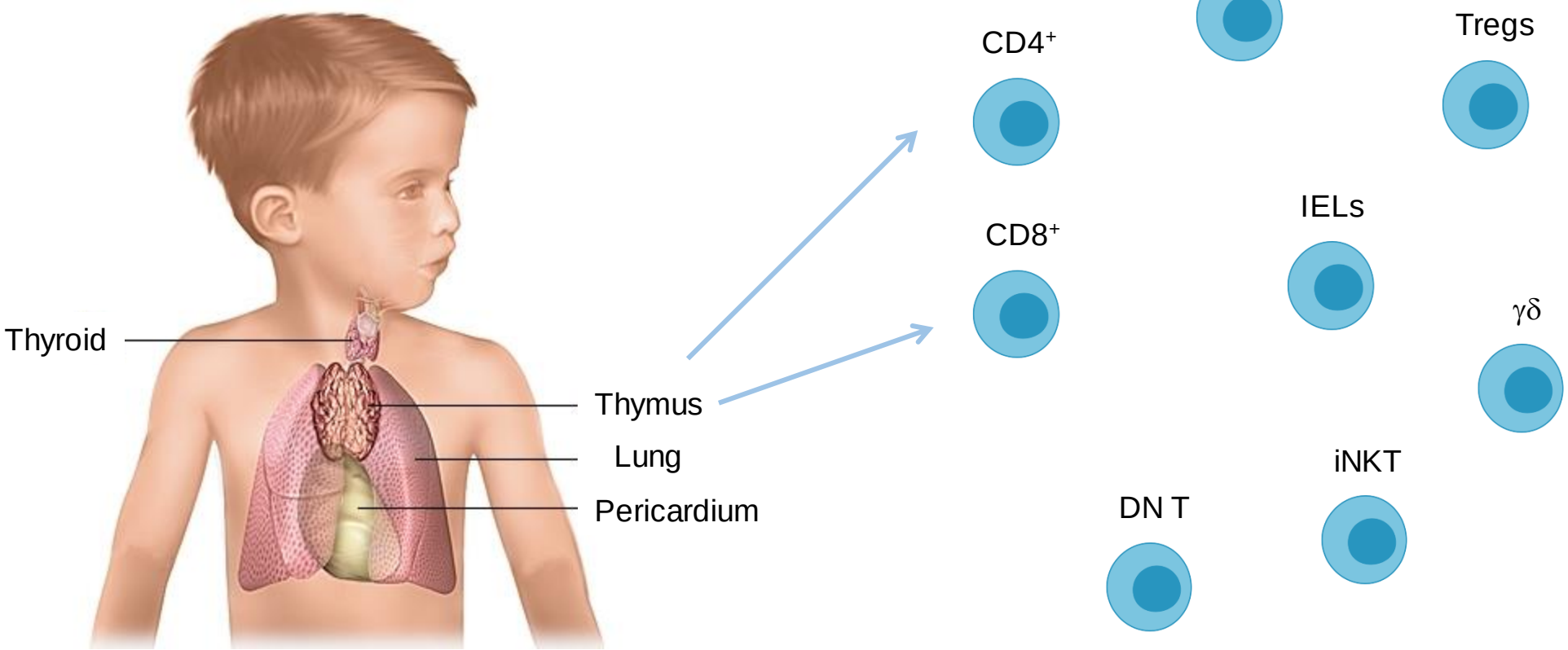
Thymus





Modified from Archives Larousse
(Michel Saemann)

Thymus



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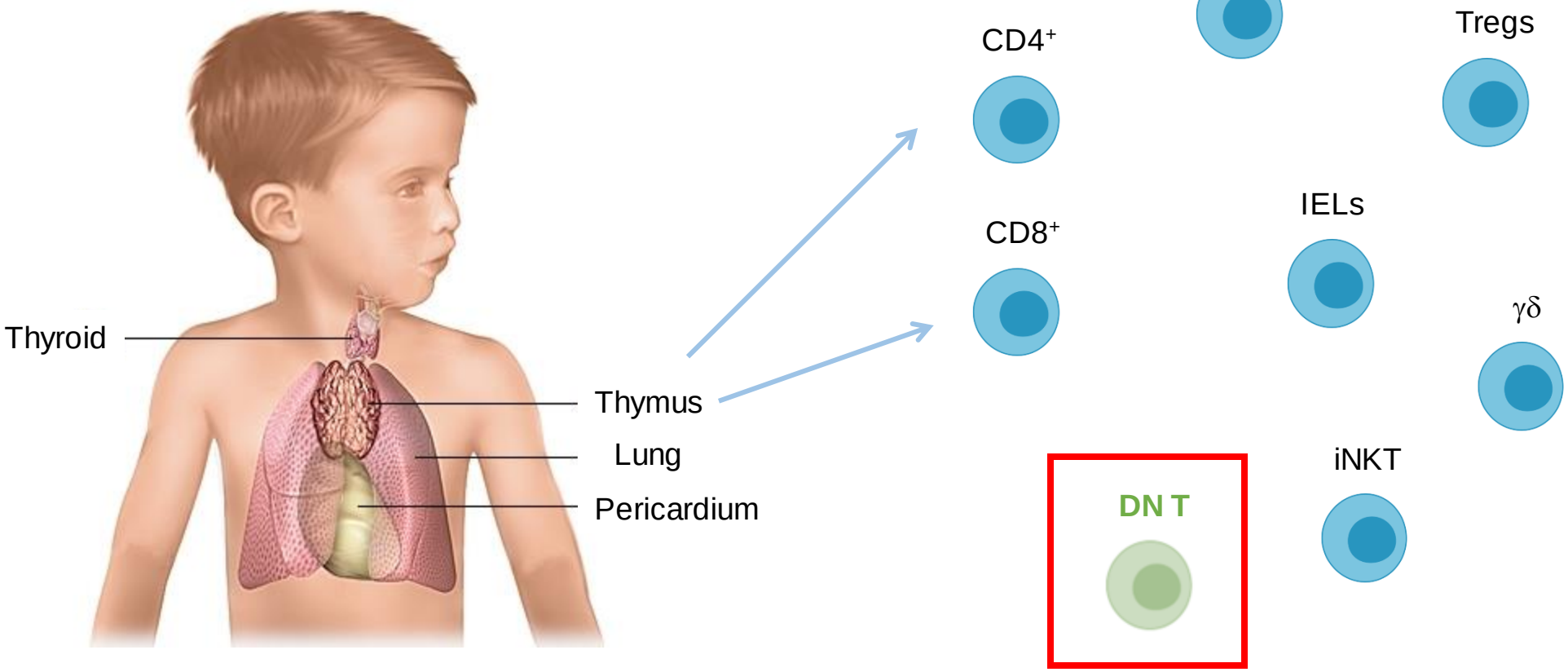


Modified from Archives Larousse
(Michel Saemann)

La souris NOD

Modèle de diabète autoimmun

Souris résistante au diabète

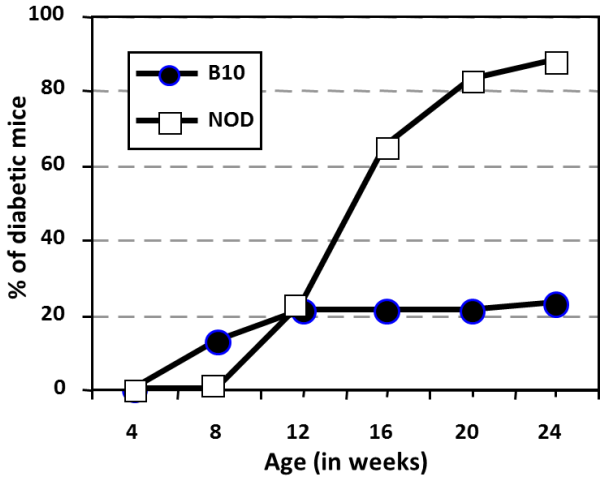
3A9 TCR transgénique

3A9 TCR: Specific for hen egg lysozyme (HEL) peptide 48–62:I-A^k + insHEL : Hel protein expressed under the rat insulin promoter

NOD.$H2^k$ TCR 3A9 : insHEL

↓

Diabetes-prone



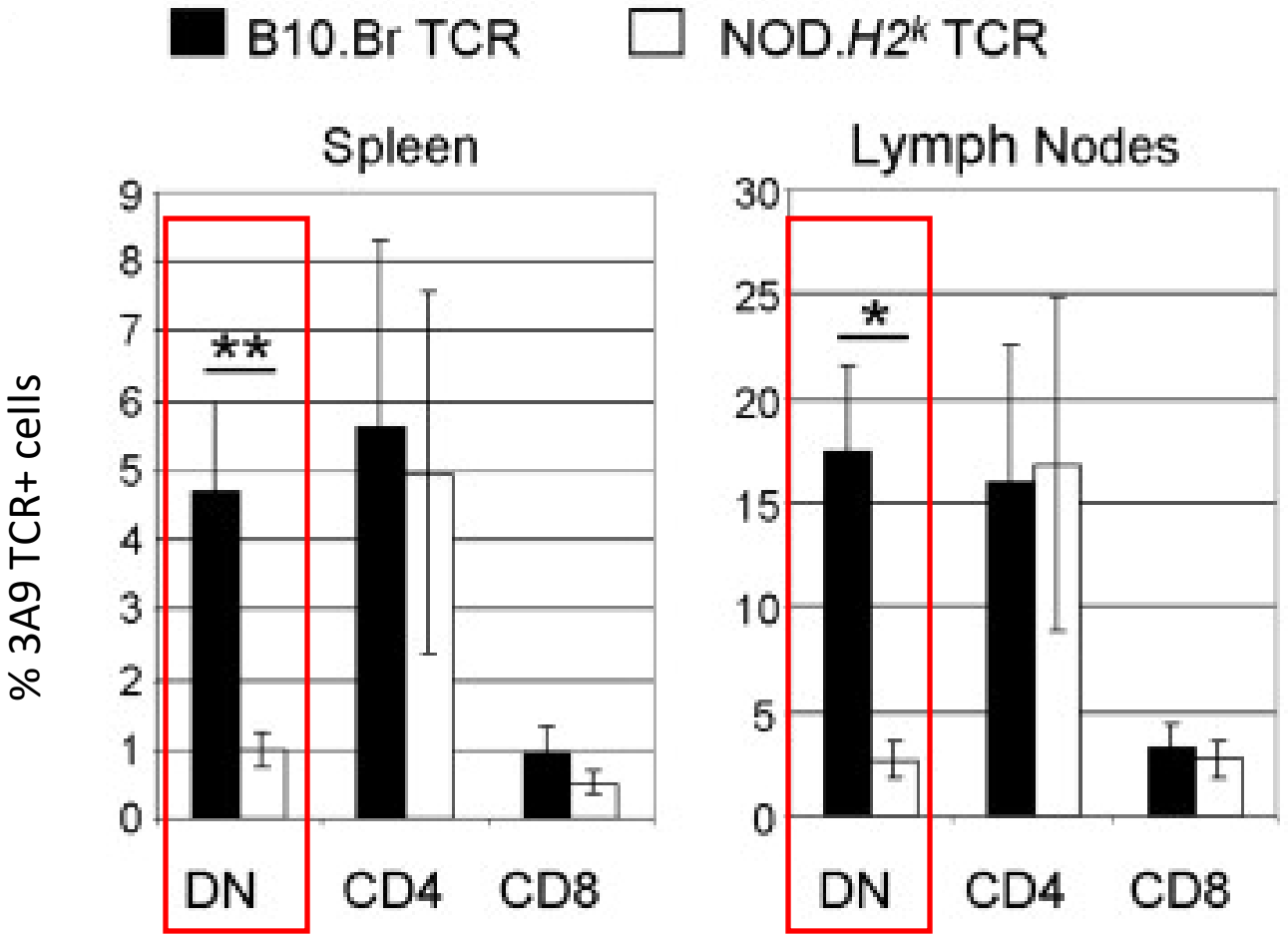
B10.BR TCR 3A9 : insHEL

↓

Diabetes-resistant

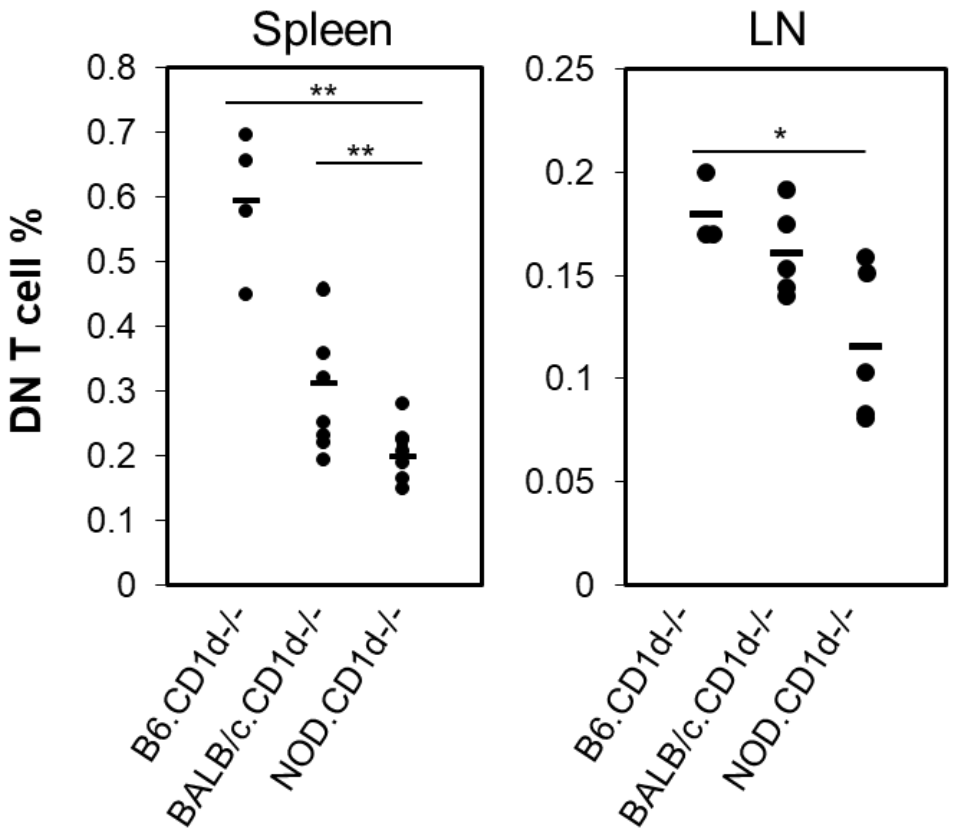
Lesage, S. *et al J Exp Med* **196**, 1175-1188 (2002).

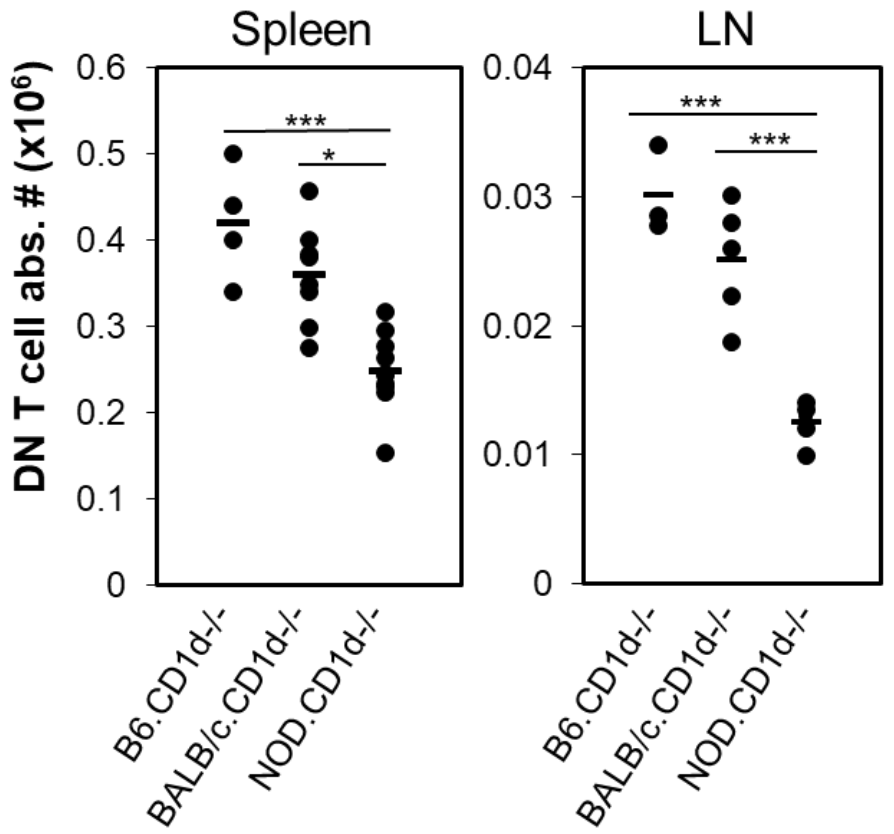
Les souris NOD ont peu de cellules DN T



Dugas, V. *et al. J Autoimmun* **35**, 23-32

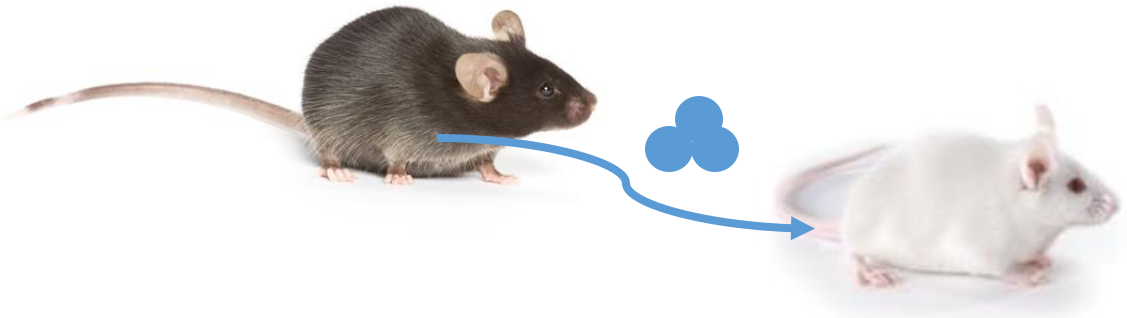
Faible nombre de cellules DN T





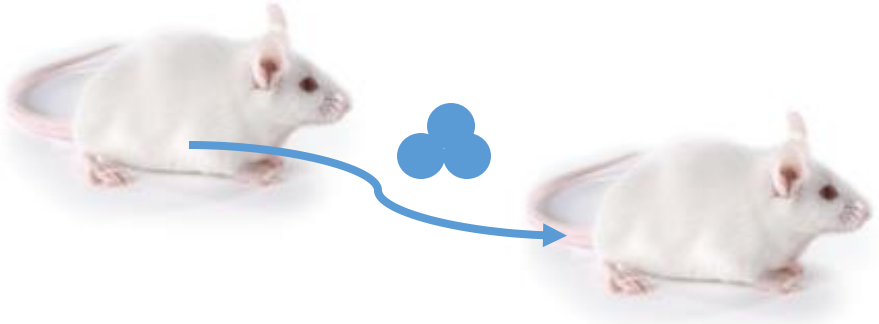
Unpublished Hillhouse

Beaucoup de
cellules DN T



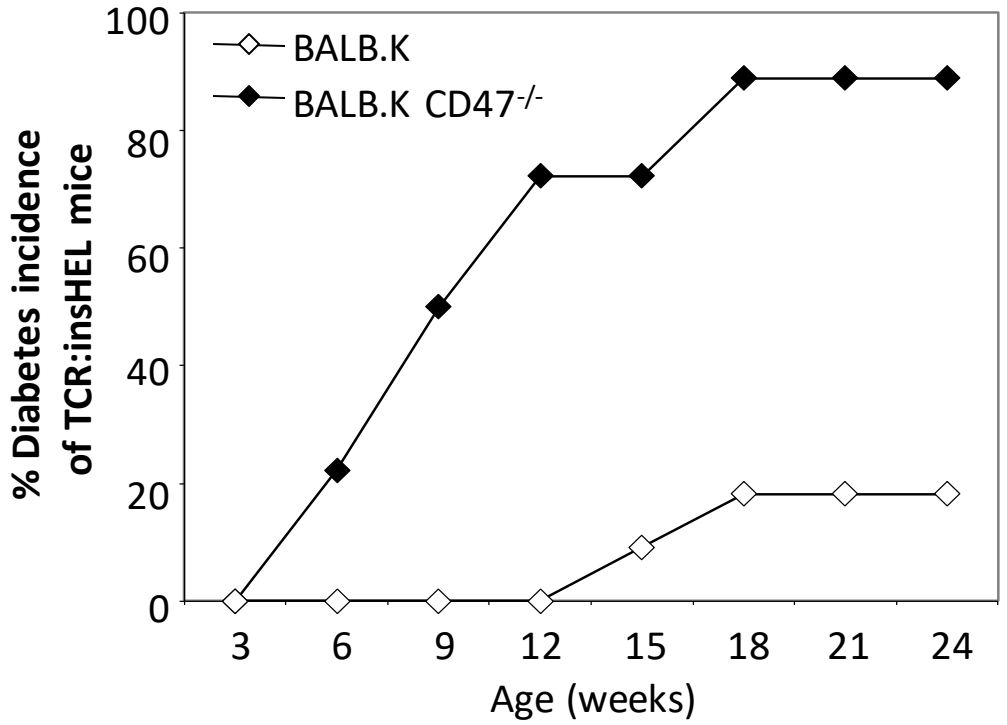
Prévenir ou
traiter le diabète?

Beaucoup de
cellules DN T



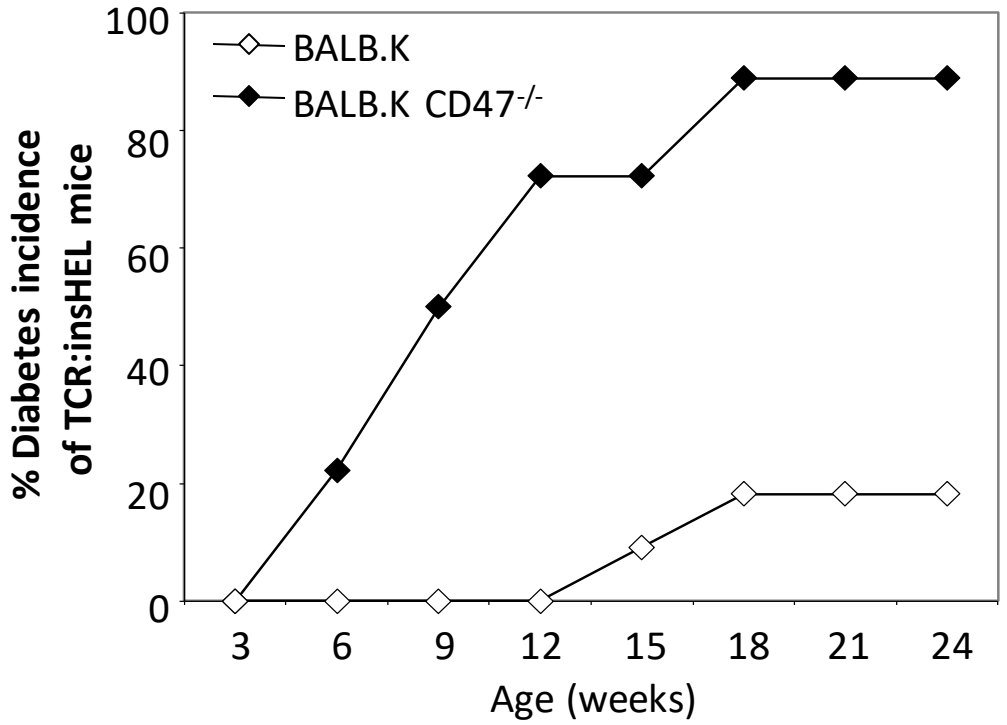
Prévenir ou
traiter le diabète?

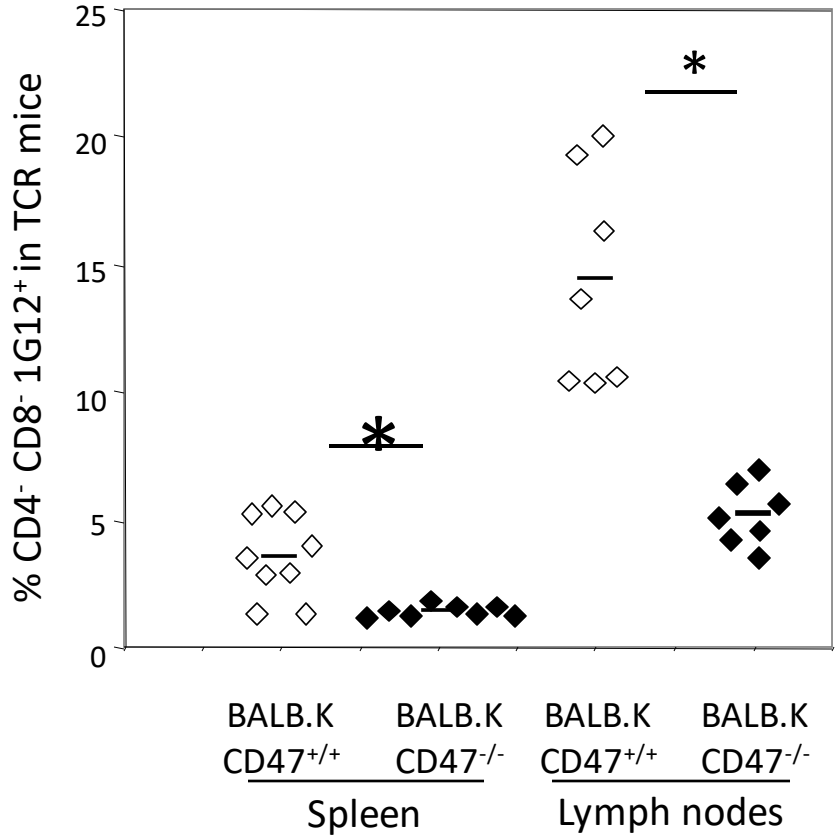
Un modèle syngénique



Dugas, V., et al. (2010). J Autoimmun 35(1): 23-32

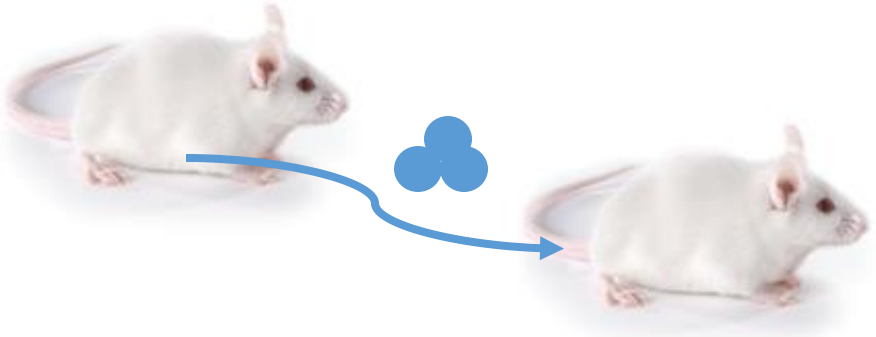
Un modèle syngénique
Plus de diabète et moins de cellules DN T





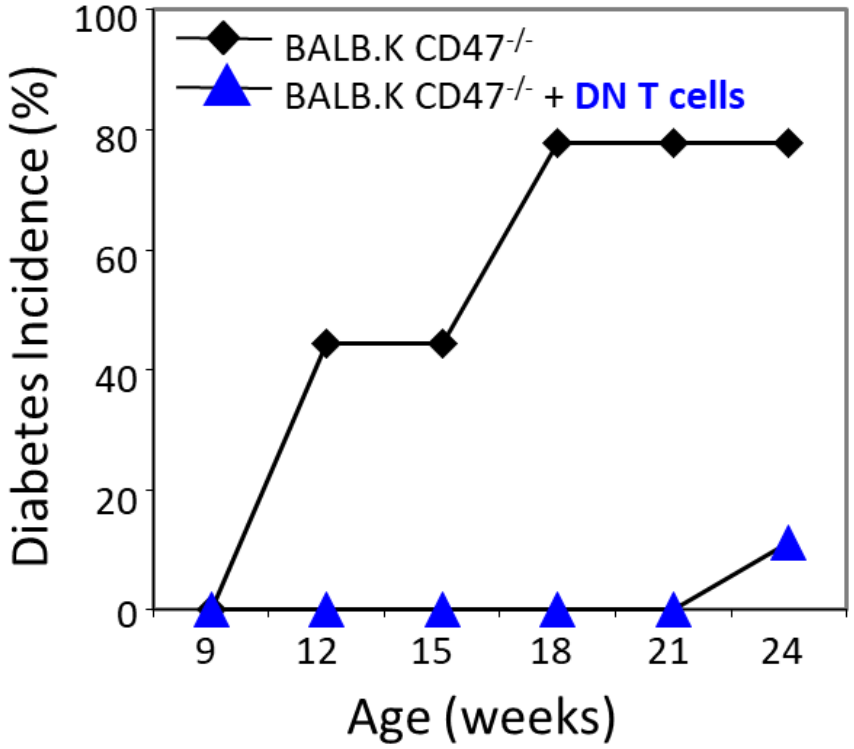
Dugas, V., et al. (2010). J Autoimmun 35(1): 23-32

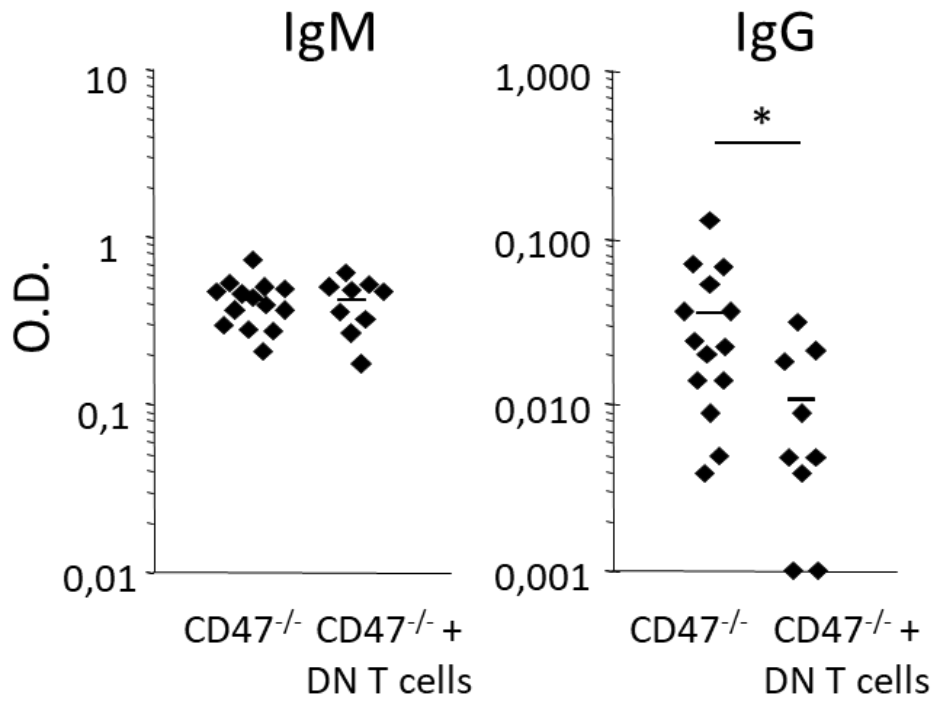
Beaucoup de
cellules DN T



Prévenir ou
traiter le diabète?

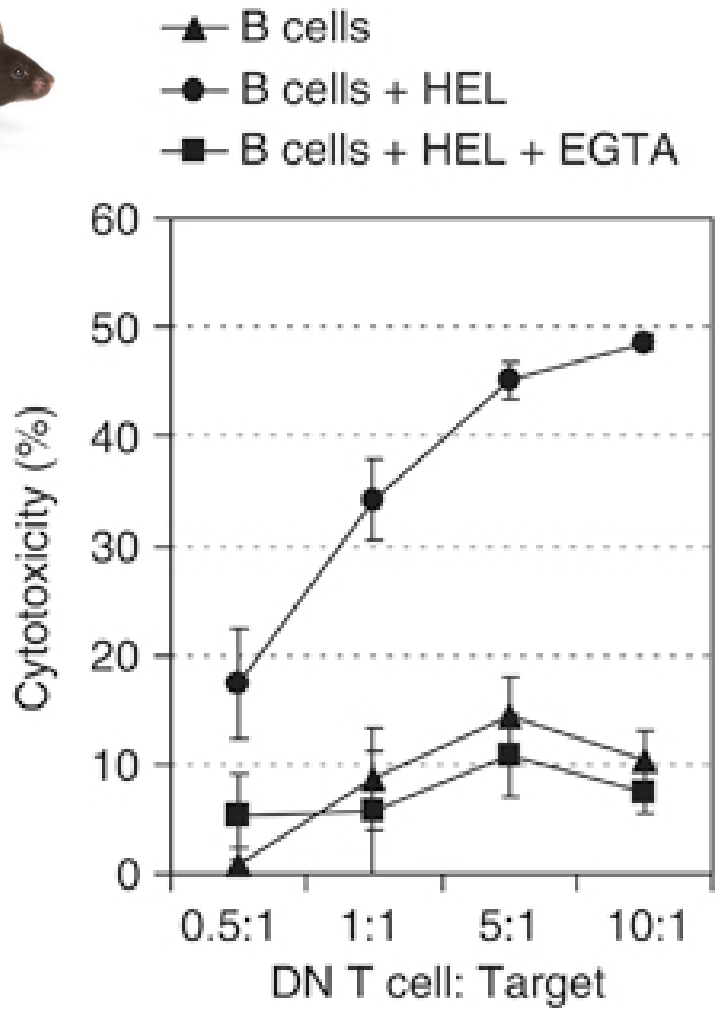
Les cellules DN T et le diabète

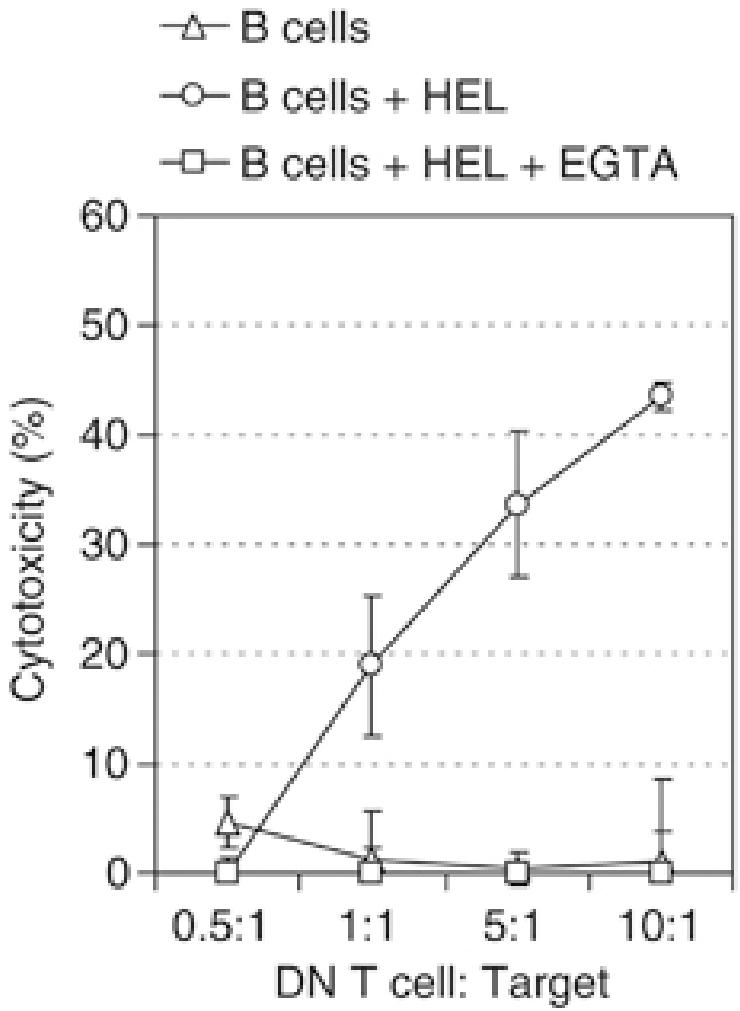




Dugas, V., et al. (2010). J Autoimmun 35(1): 23-32

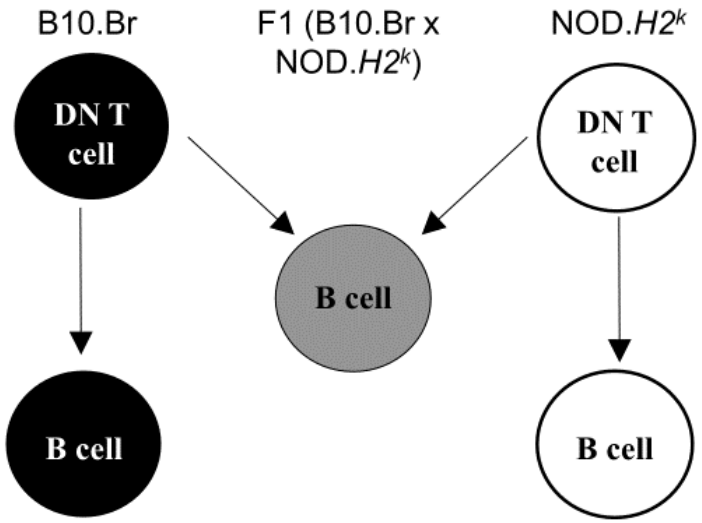
Les cellules DN T cells éliminent les cellules B

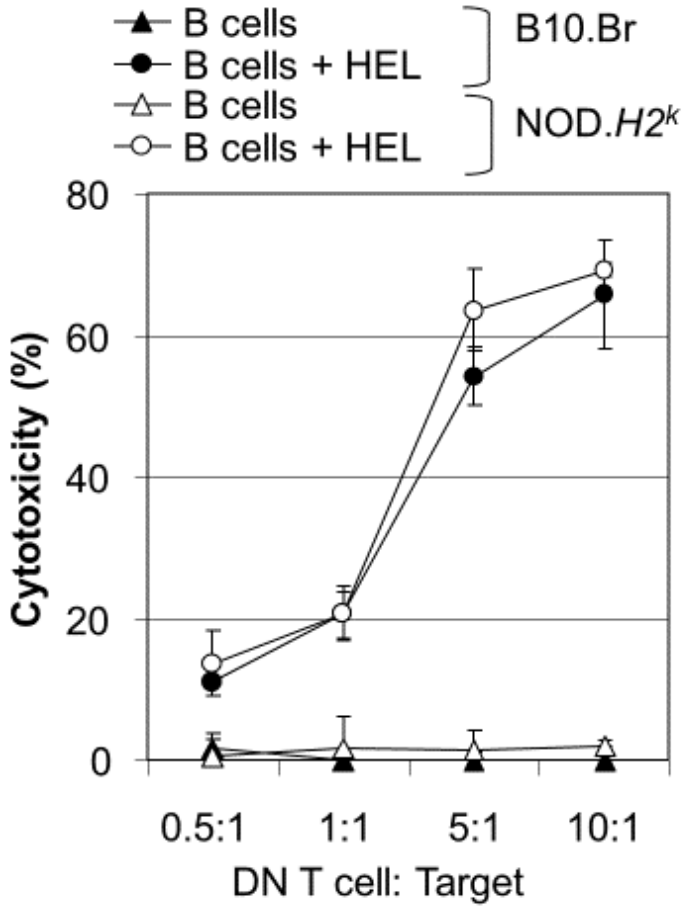




Hillhouse, EE *et al.*, *Immunol Cell Biol*, 2010 Nov-Dec;88(8):771-80.

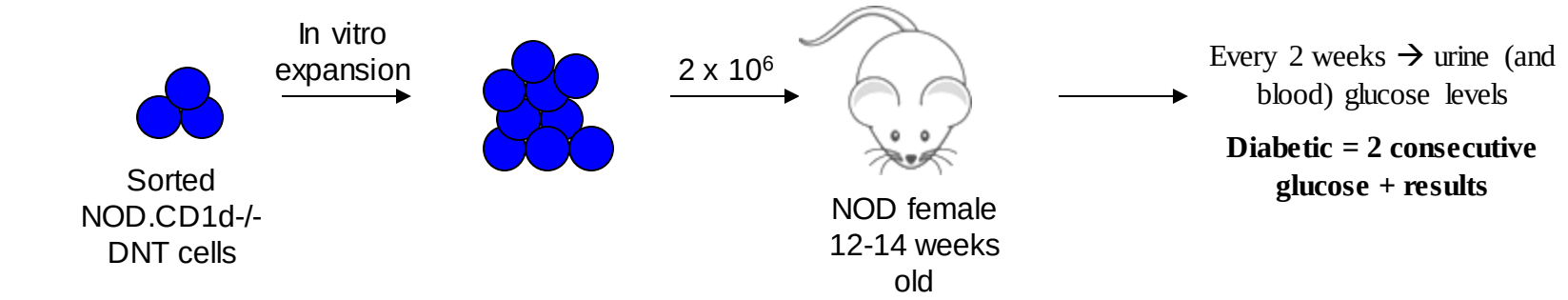
Les cellules DN T sont fonctionnelles

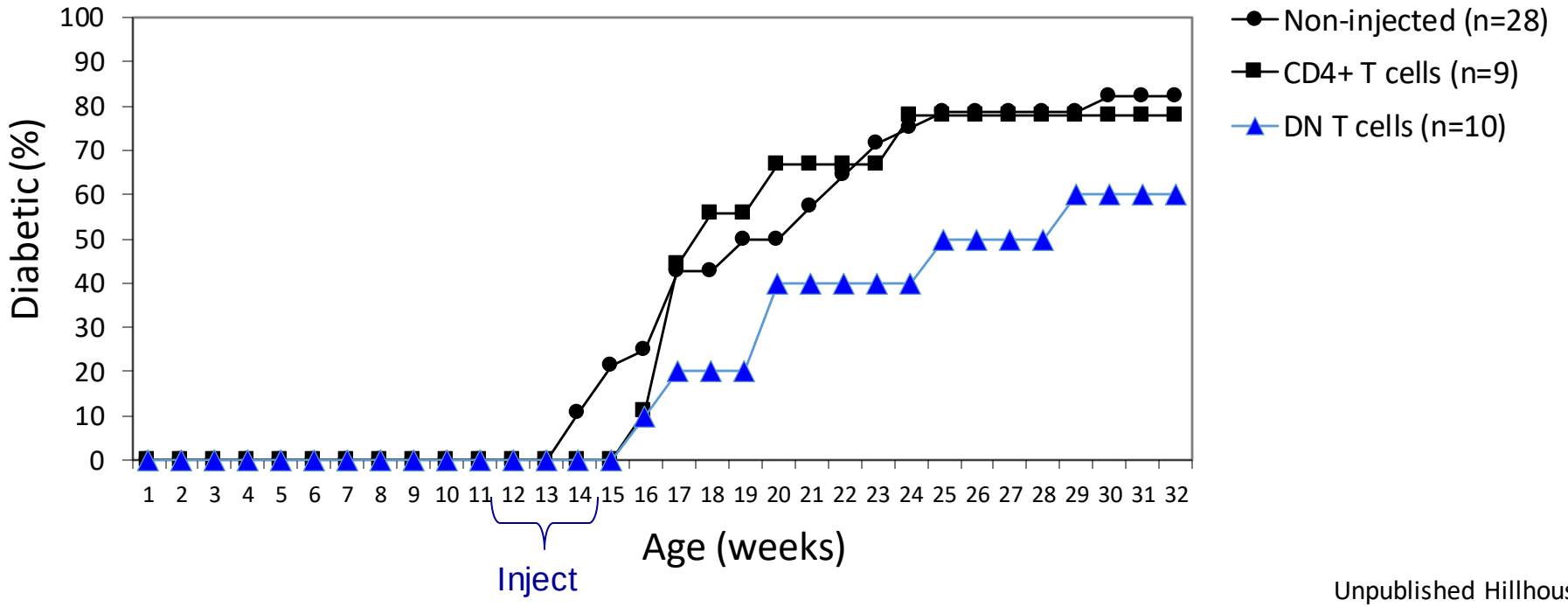




Hillhouse, EE *et al*., *Immunol Cell Biol*, 2010 Nov-Dec;88(8):771-80.

Une injection de cellules DN T réduit l'incidence de diabète





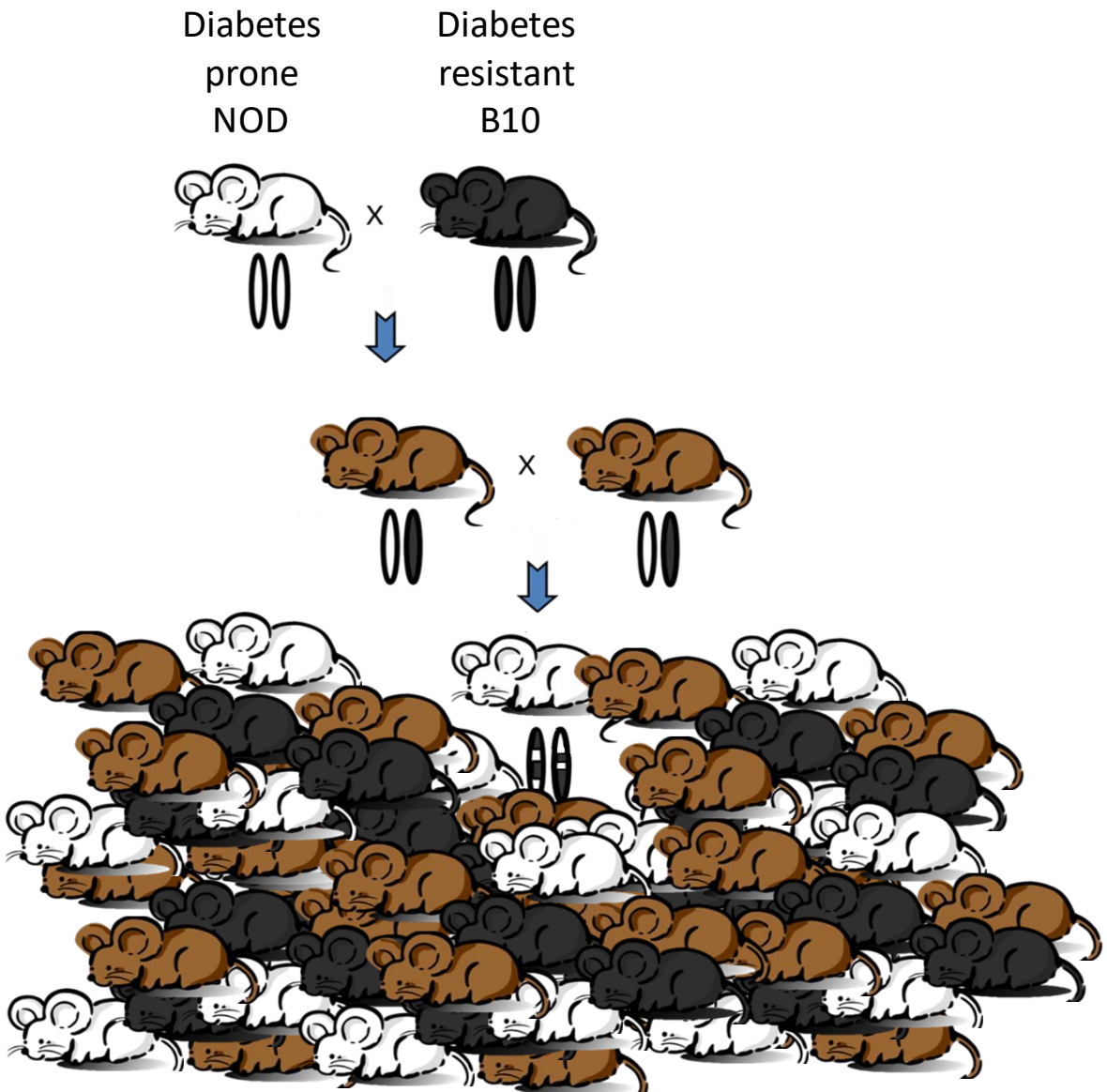
Unpublished Hillhouse

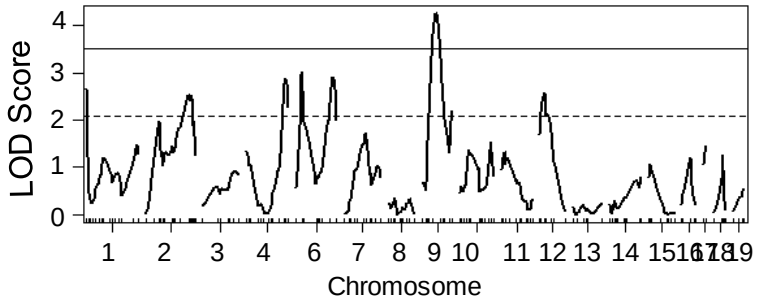
Génétique des cellules DN T

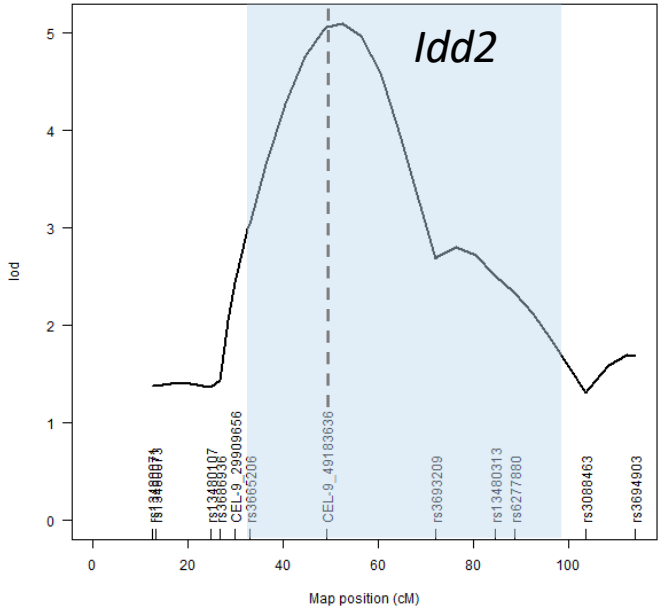
Souris prédisposée
au diabète - NOD

Collin et al. J. Immunol. 2014

Idd2 est lié à la proportion de cellules DN T







Collin et al. J. Immunol. 2014

Génétique classique

	Mouse strains	Loci	Candidate gene validation
NK cell functional maturation	B6.Rag1$^{-/-}$ vs NOD.Rag1$^{-/-}$	6 loci, none *Idd* related	**TRP53**
Pre-mNK cells	B6.Rag1$^{-/-}$ vs NOD.Rag1$^{-/-}$	Distal chromosome 7	(>500 candidates)
NK cells	B6.Rag1$^{-/-}$ vs NOD.Rag1$^{-/-}$	3 loci (Chr. 8, 9 and 17)	(IL-15 on chr 8, not us)
CD4-CD8- TCR αβ+ immunoregulatory T cells	3A9 TCR transgenic B10.BR vs NOD.*H2*^{k}	*Idd2* and *Idd13*	**RAD51 (*Idd13*)**
Thymic selection	3A9 TCR transgenic B10.BR vs NOD.*H2*^{k}	Distal chromosome 7, *Idd5, Idd8, Idd13, Idd14*	**BIM (*Idd13*)**
Antibody affinity maturation	3A9 TCR transgenic B10.BR vs NOD.*H2*^{k}	Chromosome 12	(~30 candidates)
Pancreatic beta cells	insHEL transgenic.Rag1$^{-/-}$ B10.BR vs NOD.*H2*^{k}	3 loci (chr. 13 (2), chr. 19)	**XRCC4 (Chr 13), GLIS3 (Chr 19)**
Plasmacytoid dendritic cells	B6.Rag1$^{-/-}$ vs NOD.Rag1$^{-/-}$	Chromosome 7	(>1000 candidates)
Merocytic dendritic cells	B6.Rag1$^{-/-}$ vs NOD.Rag1$^{-/-}$	*Idd13*	**BIM**

Souches de souris communes

A/J

B6

129S

NOD

NZO

PWK

CAST

WSB

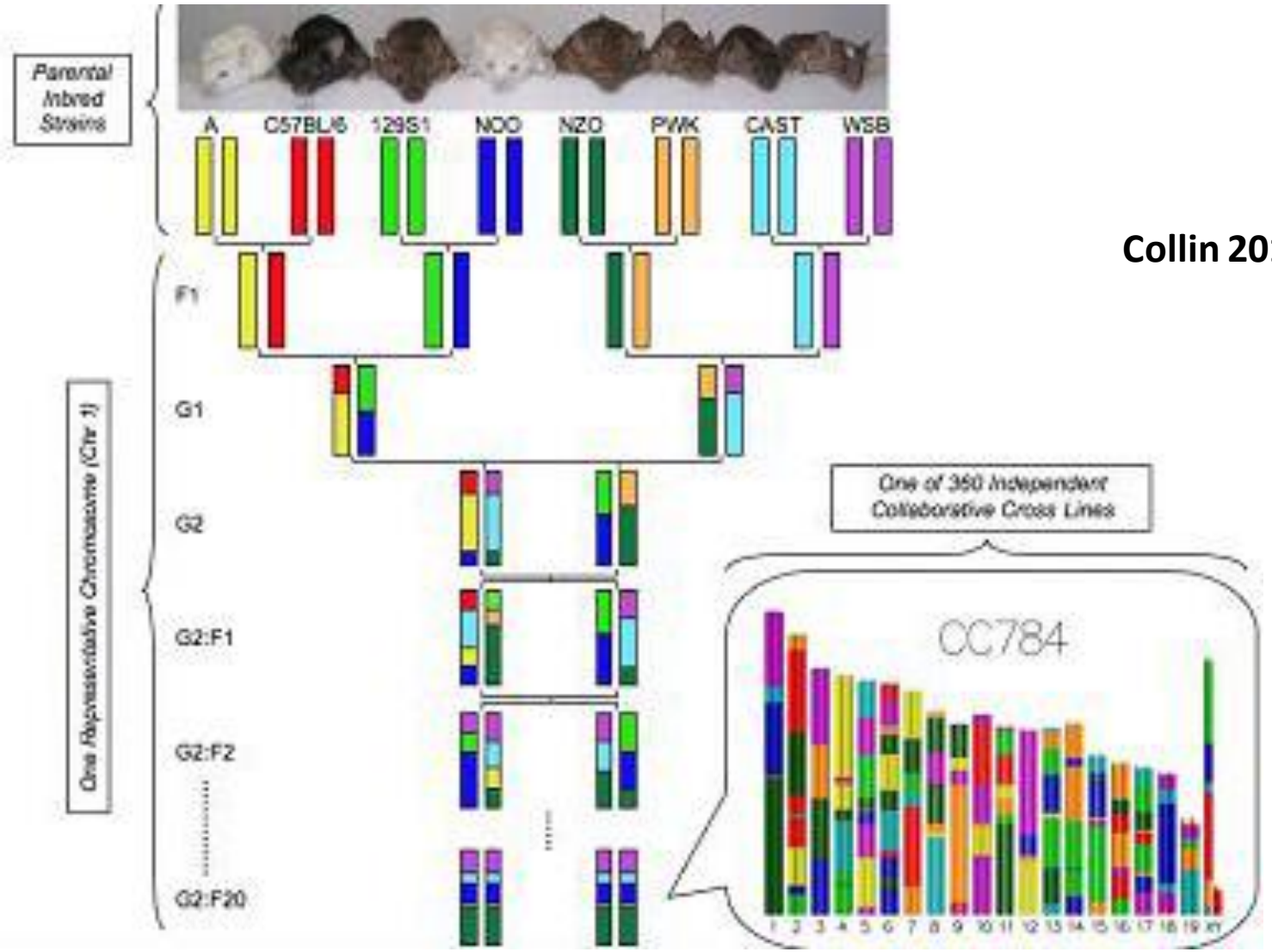
C3H

BALB/c

NOR

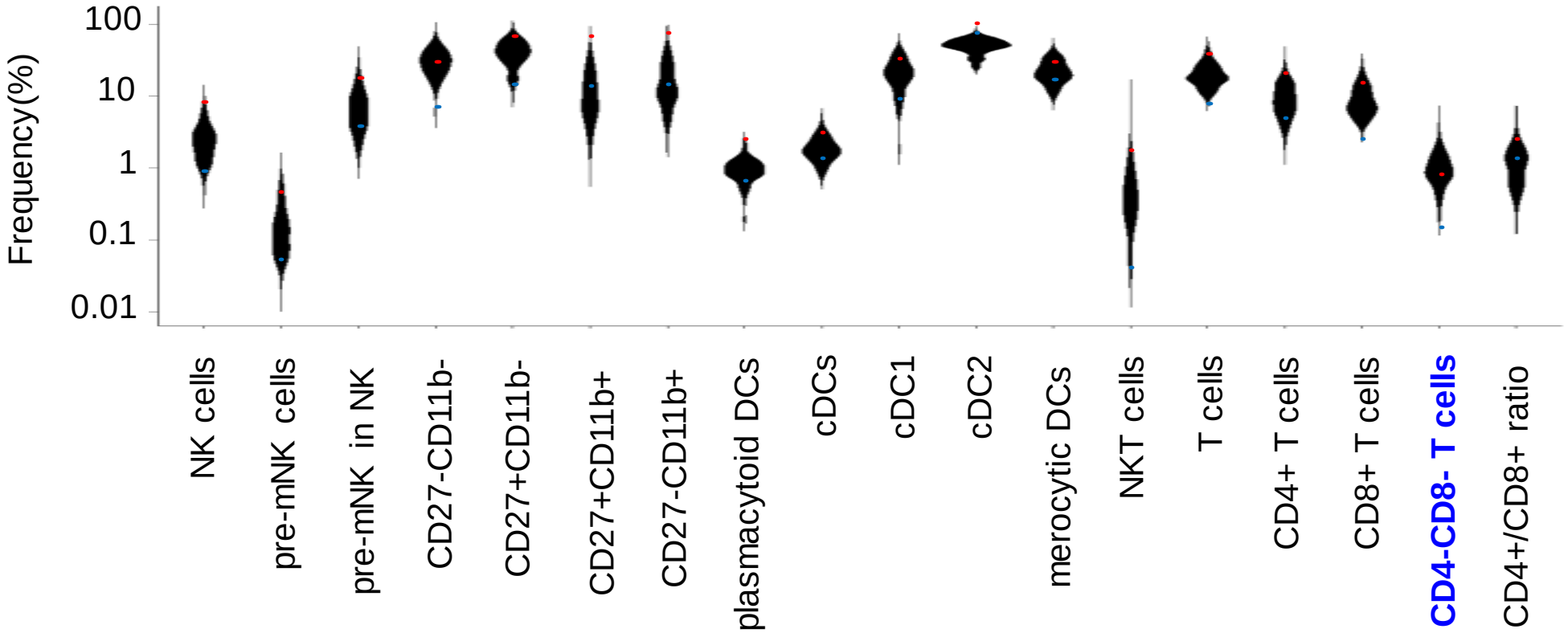
FVB

The Collaborative Cross



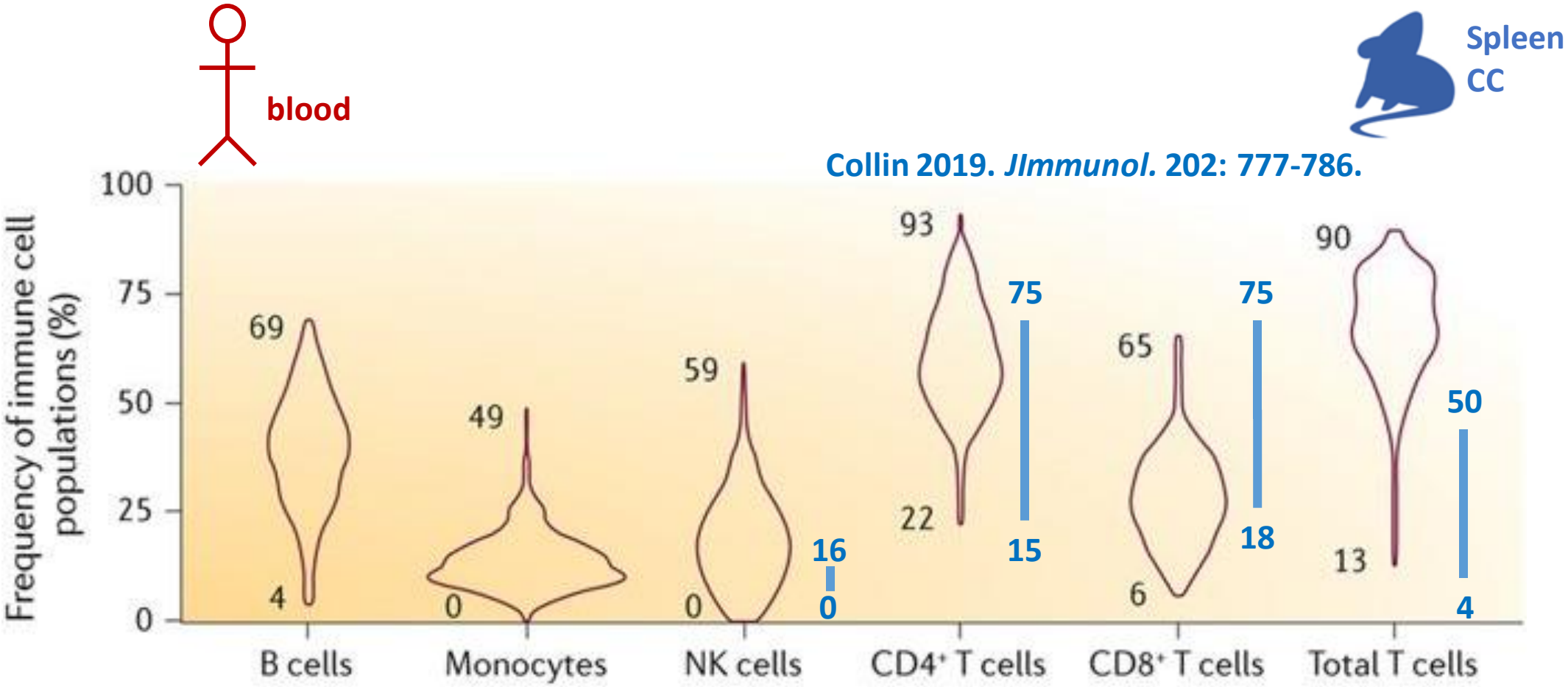
Collin 2019. *JImmunol*. 202: 777-786.

Variation dans la distribution des cellules immunitaires



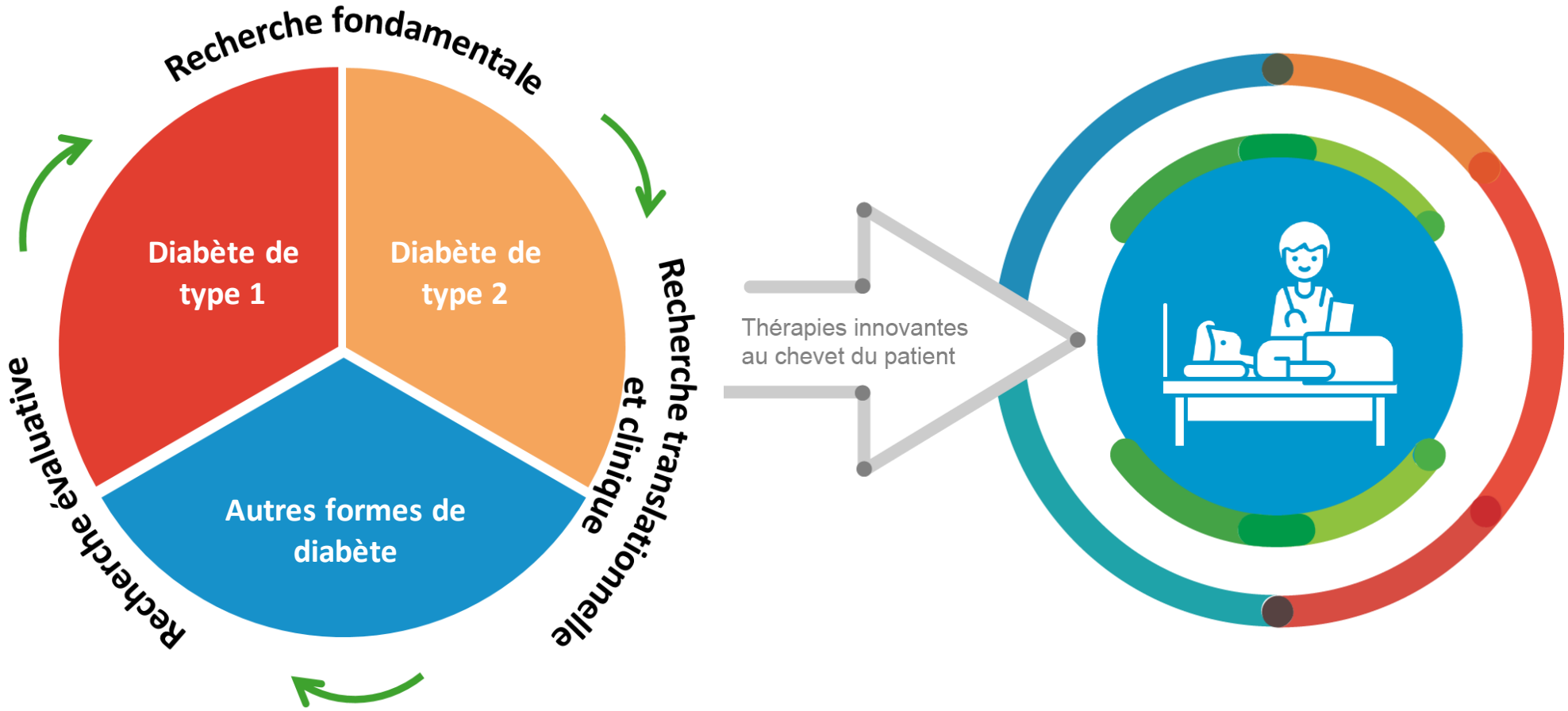
Collin, R. *et al. J Immunol*. 2019

Variation dans la distribution des cellules immunitaires

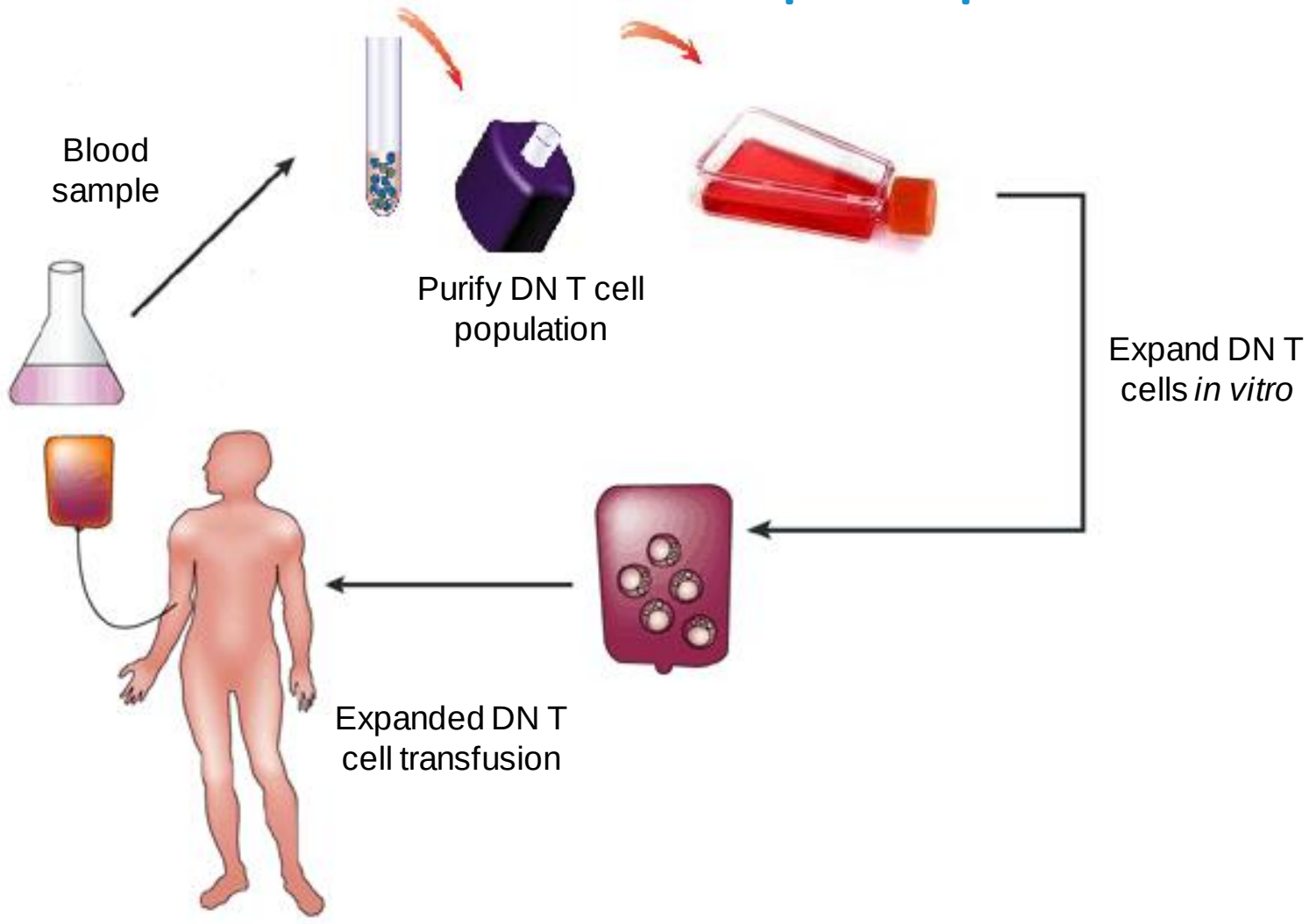


Nature Reviews Immunology **volume17**, pages21–29 (2017)

De la recherche fondamentale jusqu'aux soins



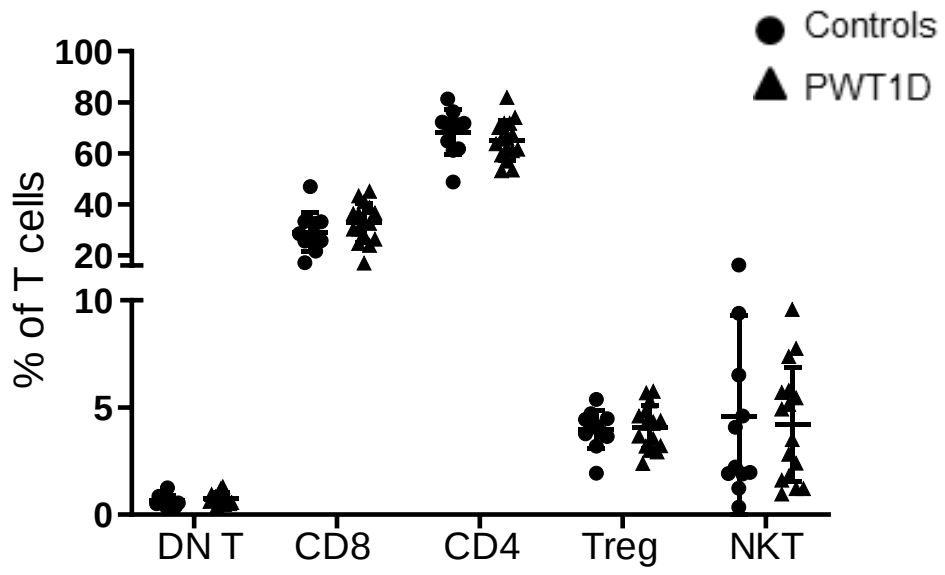
Objectif:
Augmenter le nombre de cellules DN T pour prévenir le diabète

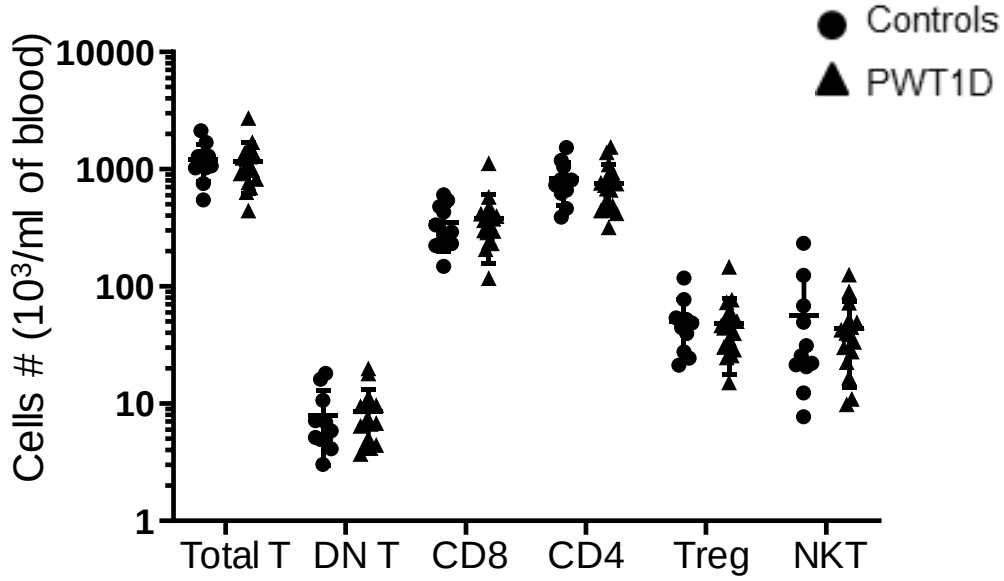


Modified from **Nature Reviews** | Cancer

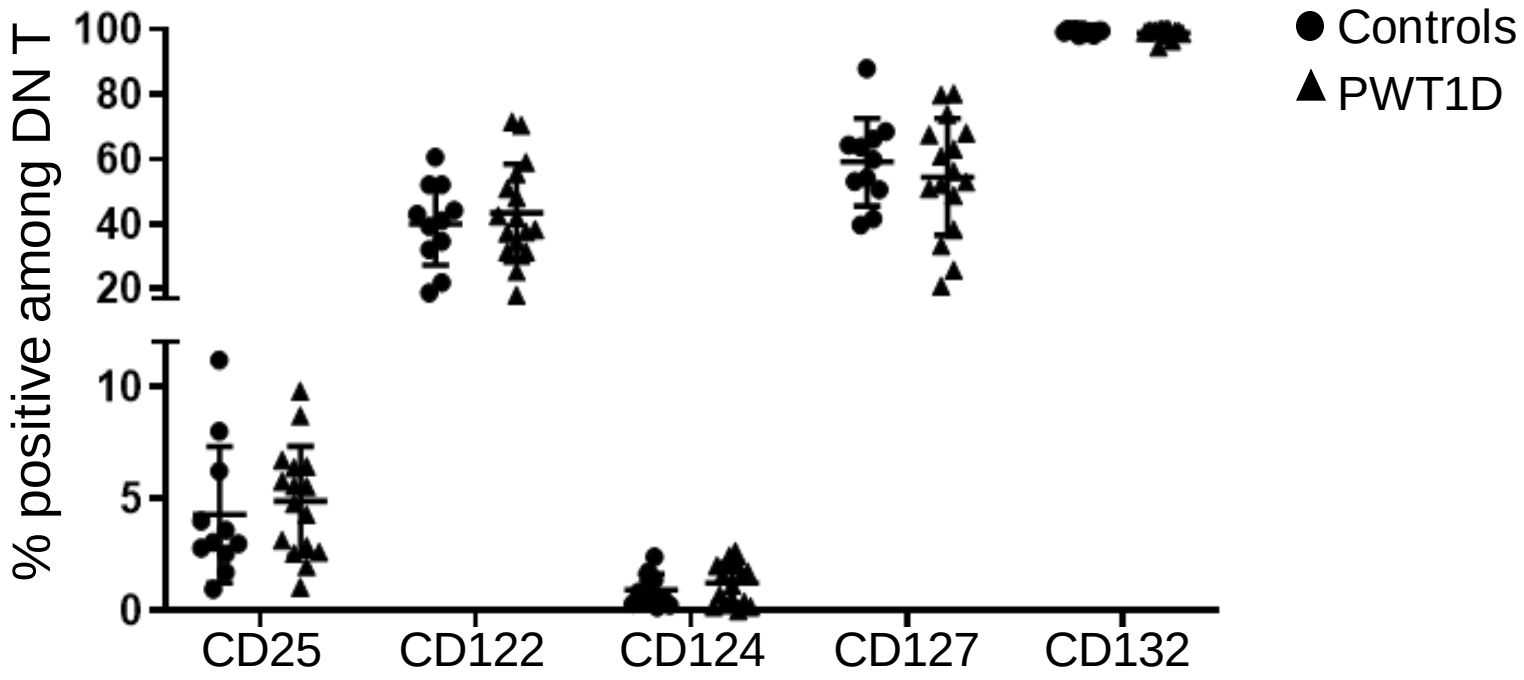
		Controls	T1D
	Sample size	11	16
Age	**Median**	31	22
	Mean	31	24
	Range	26-36	18-37
	p (mean)	0.0012	
Sex	**F (%)**	5 (45)	6 (38)
	M (%)	6 (55)	10 (62)
	p (sex)	0.6794	
	Smokers (%)	1 (9)	3 (19)
HbA1c (%)	**≥8 (%)**	NA	6 (38)
	<8 (%)	NA	8 (50)
	unknown	NA	2 (12)
Ethnicity	**Caucasian (%)**	10 (91)	12 (75)
	Hispanic (%)	1(9)	0
	Afro Caribbean (Haitian) (%)	0	1 (6)
	North African (%)	0	3 (19)

Distribution normale des cellules T

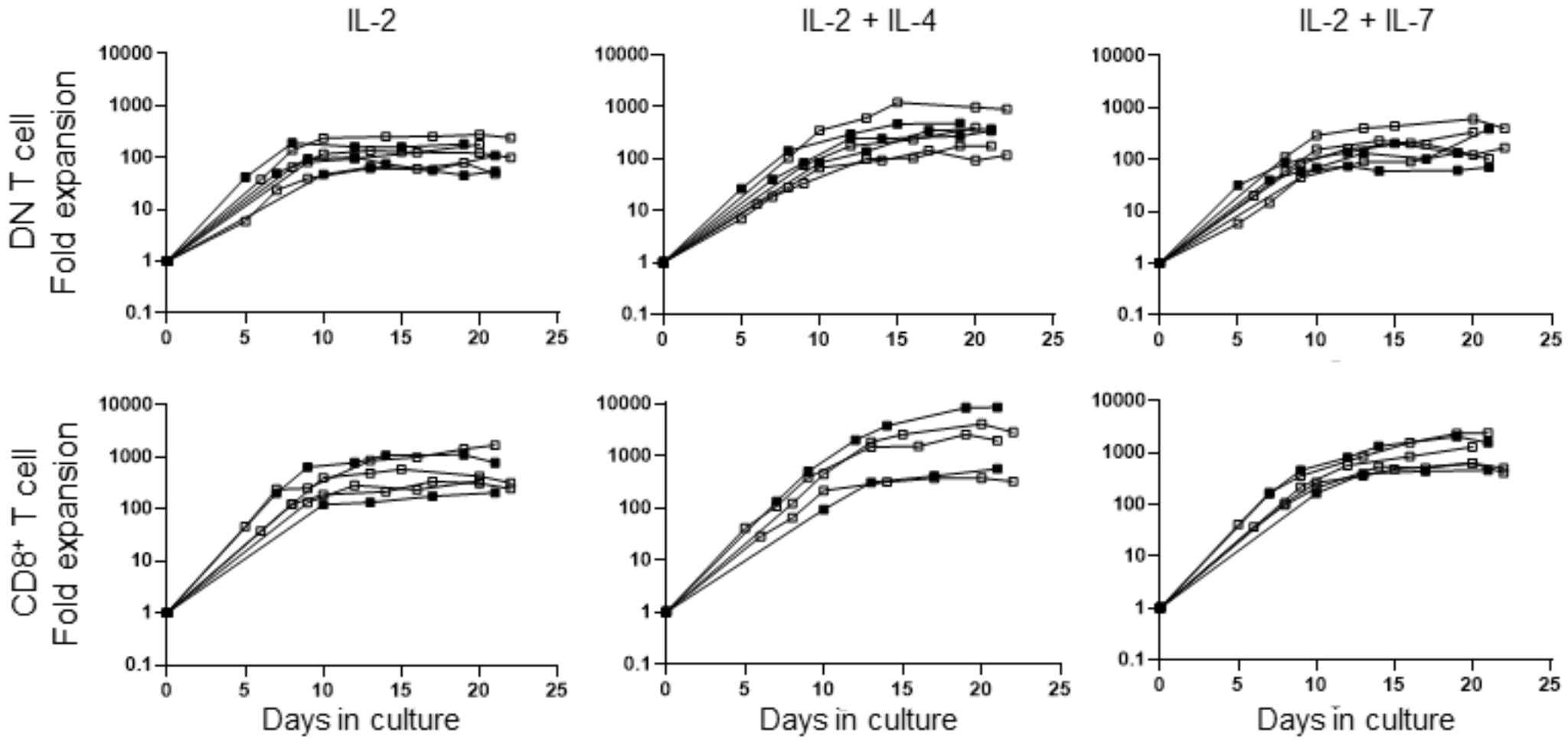




Expression des récepteurs de cytokines



Augmentation de 100 à 500 fois en 10 jours



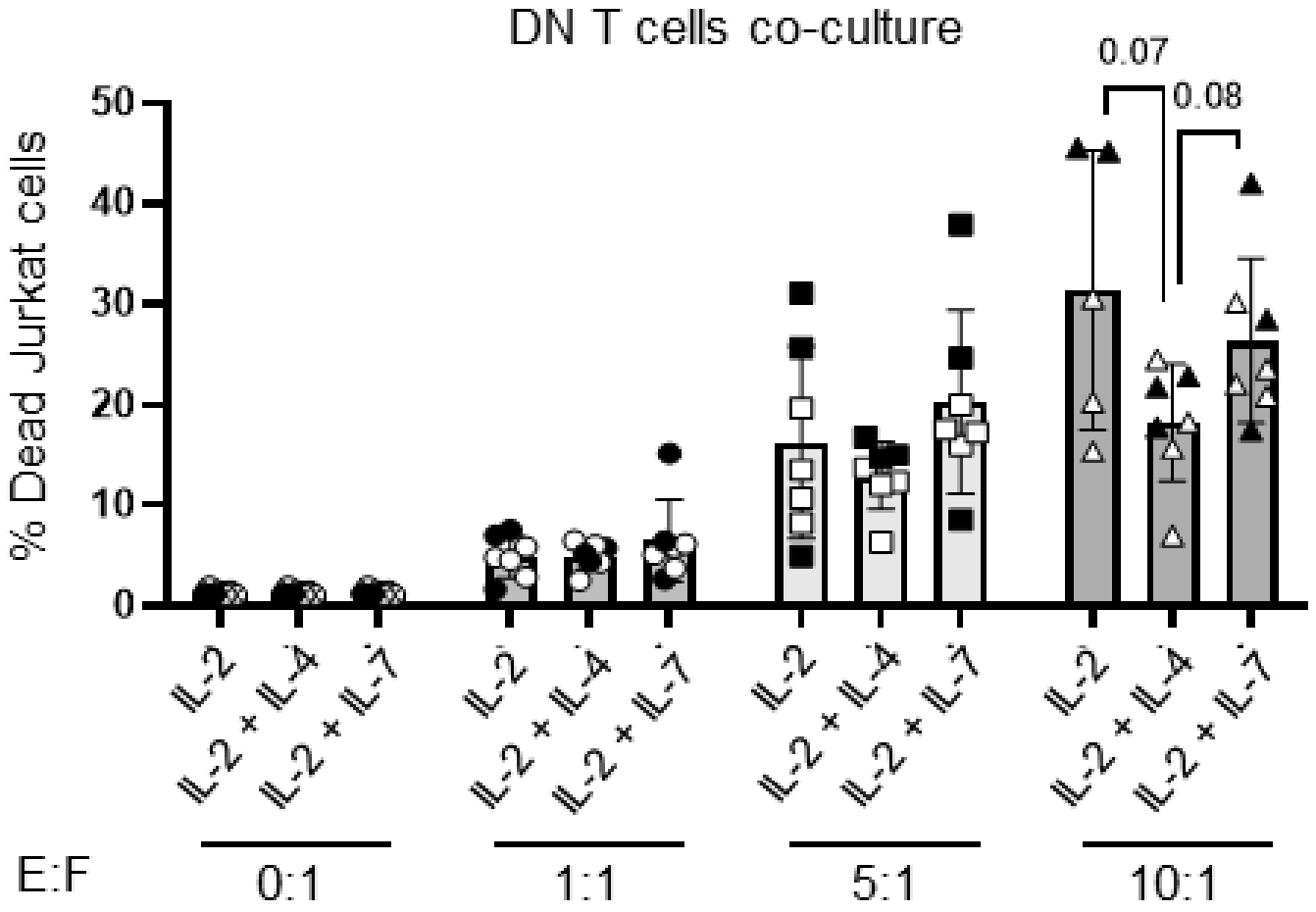
Augmentation de 500 fois en 10 jours

De 2 000$ à 1 000 000$ en 10 jours

Chaque condition impose des différences

	IL-2		IL-2 + IL-4			IL-2 + IL-7		
	Control	T1D	Control	T1D	*P*-value vs. IL-2	Control	T1D	*P*-value vs. IL-2
2B4+	26	30	28	31	NS	28	31	NS
CD57+	25	24	25	23	NS	19	18	*
FAS MFI	1853	1594	1570	1433	*	1954	1716	**
KLRG1+	14,1	18,0	11,3	10,9	NS	9,2	13,9	NS
LAG-3 MFI	1770	1810	1567	1423	NS	2159	2372	*
PD-1+	13,6	12,7	13,2	13,5	NS	13,6	13,5	NS
TIM-3 MFI	5021	4550	3636	3301	***	6978	6497	***
CCR7+	78	76	87	88	***	79	73	NS
CD45RA+	67	66	49	56	***	65	67	NS
CD45RO+	69	62	80	72	***	72	66	NS

Les cellules DN T demeurent fonctionnelles peu importe la condition de culture



Conclusions

- Plusieurs types de diabète
- Une variété de thérapies en différentes phases de développement
- Le système immunitaire est une composante centrale (T1D)
- Comprendre le système immunitaire et la génétique pour mieux les manipuler
- Les cellules DN T seront peut-être la prochaine thérapie!

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