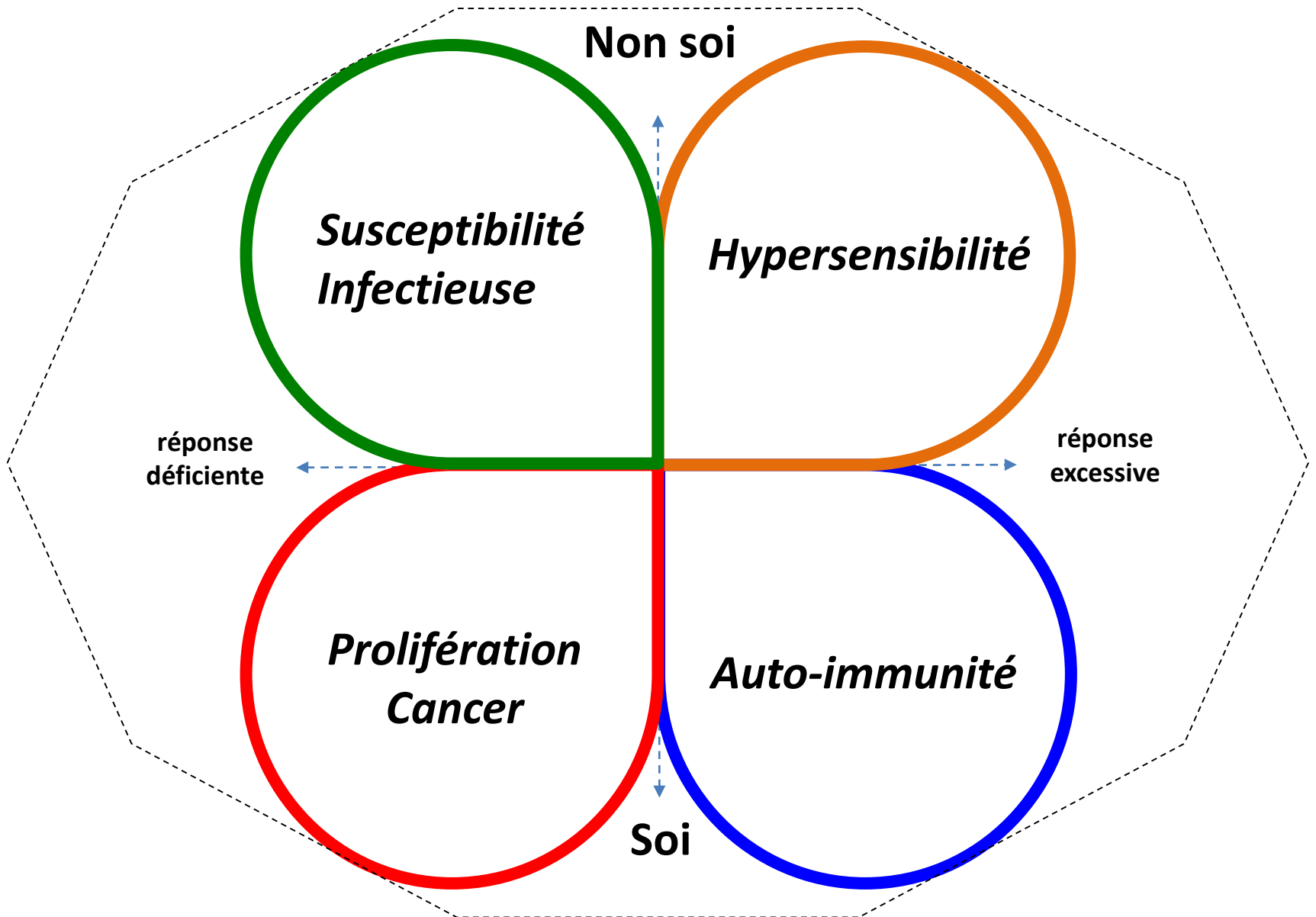




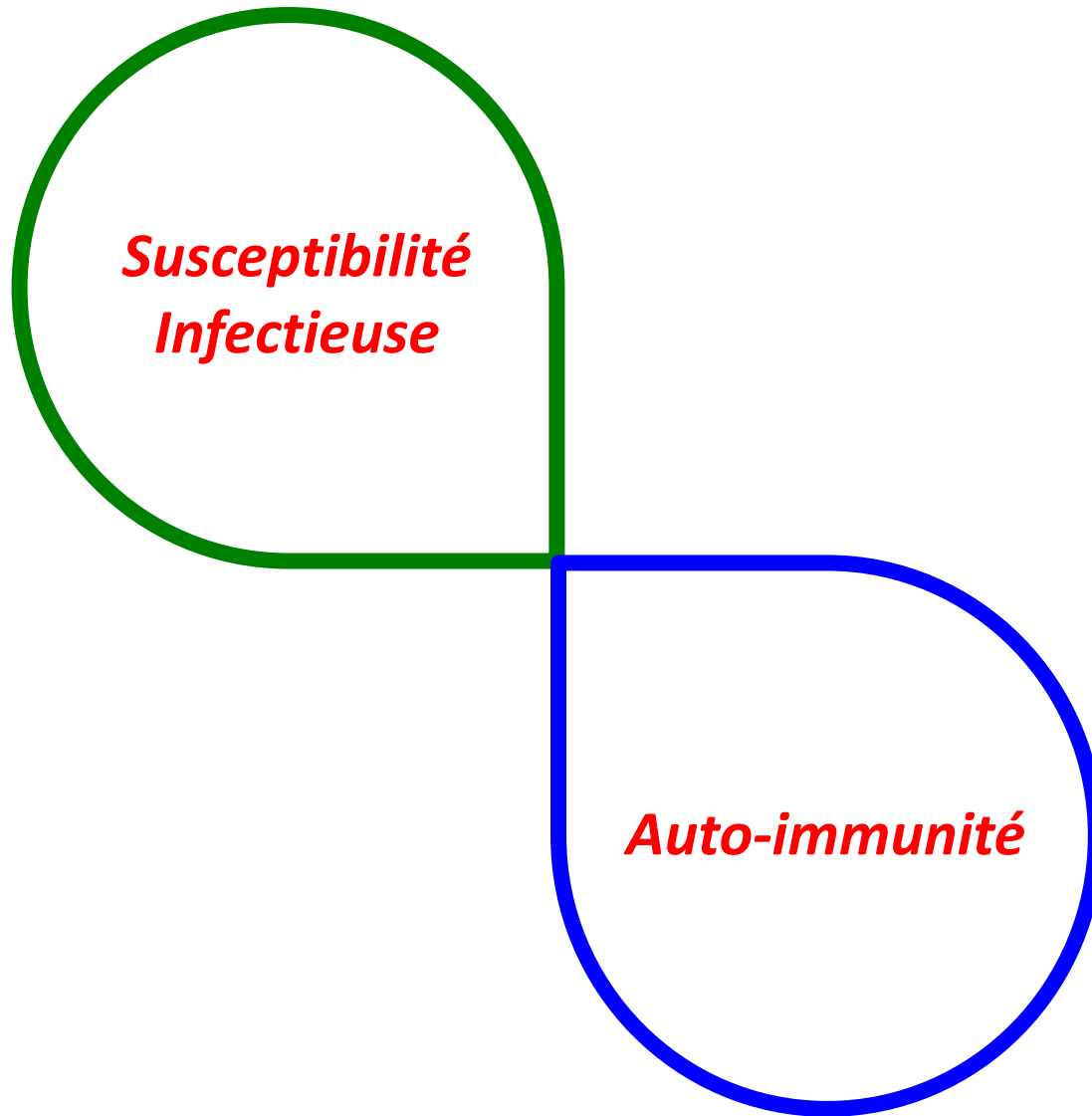
#Whatsup_ImmunoClinique

Dr Antoine Néel, PH, Médecine Interne, CHU de NANTES

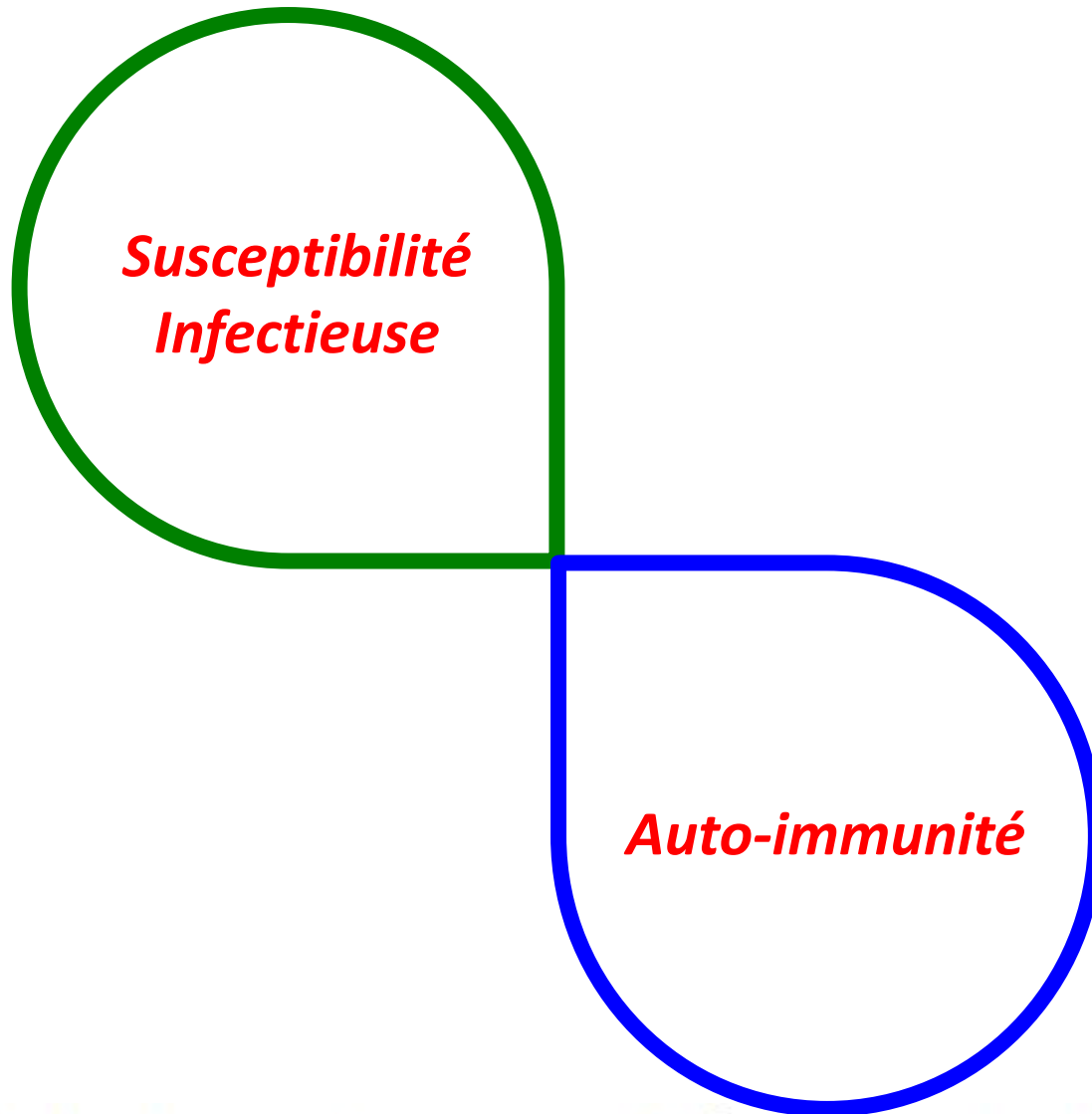
ImmunoClinique



Déficit Immunitaire



Déficit Immunitaire ... auto-immun



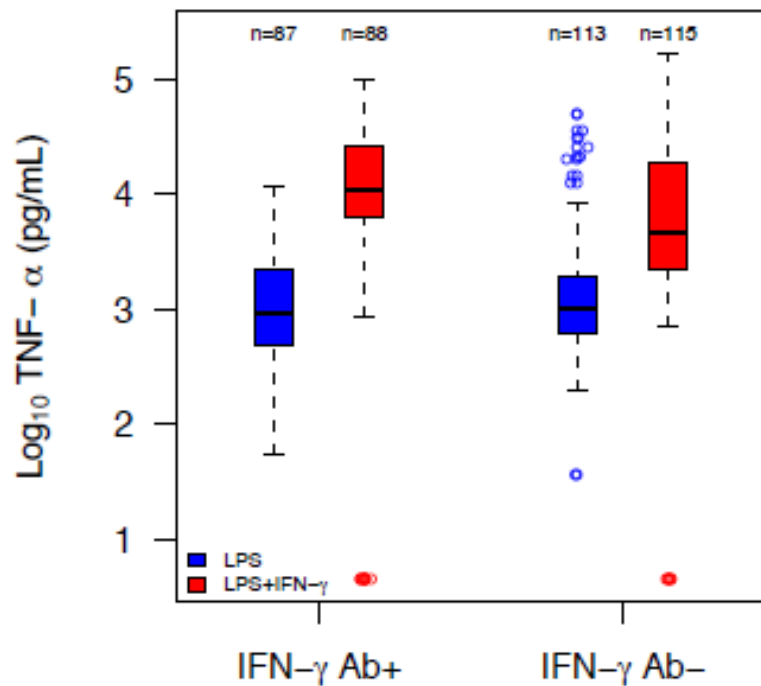
Adult-Onset Immunodeficiency in Thailand
and Taiwan

Browne SK. NEJM 2012

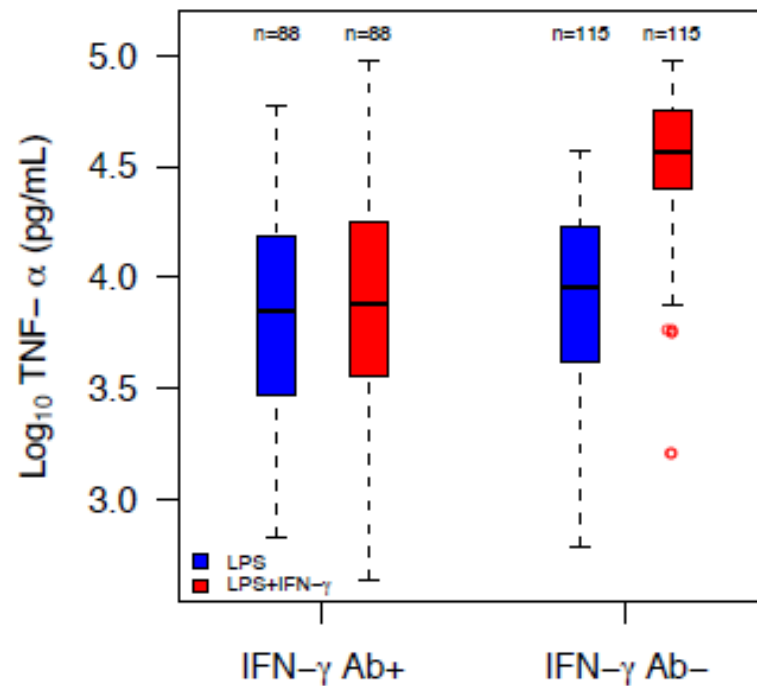
Variable	Group 1 (N=52)	Group 2 (N=45)
Organisms isolated (no./patient)		
Median	1	2
Range	1-4	1-5
Mycobacteria (no. of patients)		
Rapidly growing	36	39
Slowly growing	15	8
Nontuberculous mycobacteria, not specified	5	2
<i>Mycobacterium tuberculosis</i>	4*	10†
Total	60	59
Bacteria (no. of patients)		
Salmonella species		25
<i>Burkholderia pseudomallei</i>		4
Other		9
Fungi (no. of patients)		
<i>Cryptococcus neoformans</i>		10
<i>Histoplasma capsulatum</i>		7
<i>Penicillium marneffeii</i>		7
Varicella-zoster virus (no. of patients)		
Disseminated		3
Local	5	10
Parasites (no. of patients)		
<i>Strongyloides stercoralis</i>		1

+ Dermatose neutrophilique

Subject PBMC in fetal calf serum



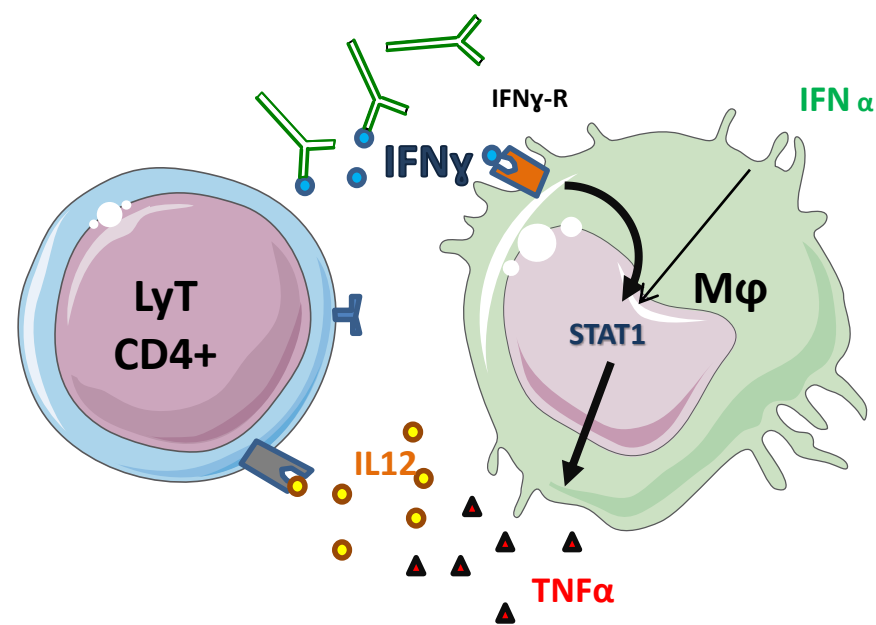
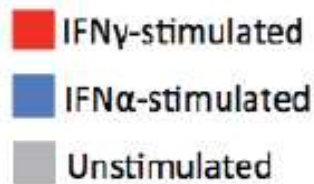
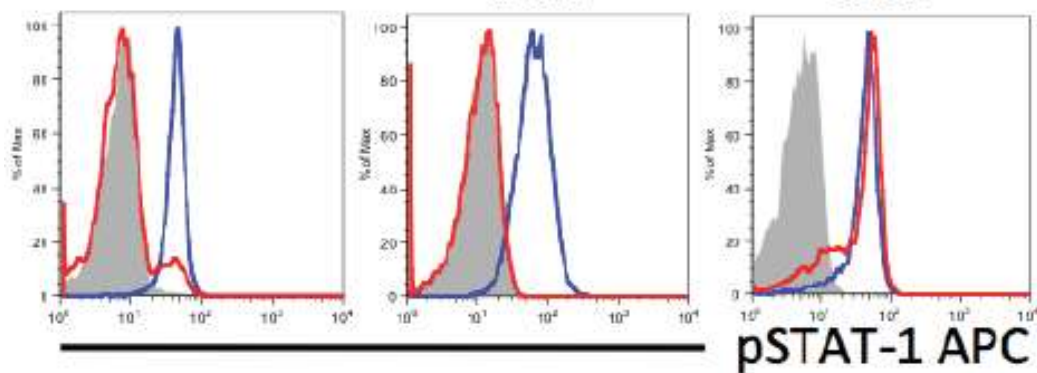
Normal PBMC in subject plasma



I-142

II-094

III-045

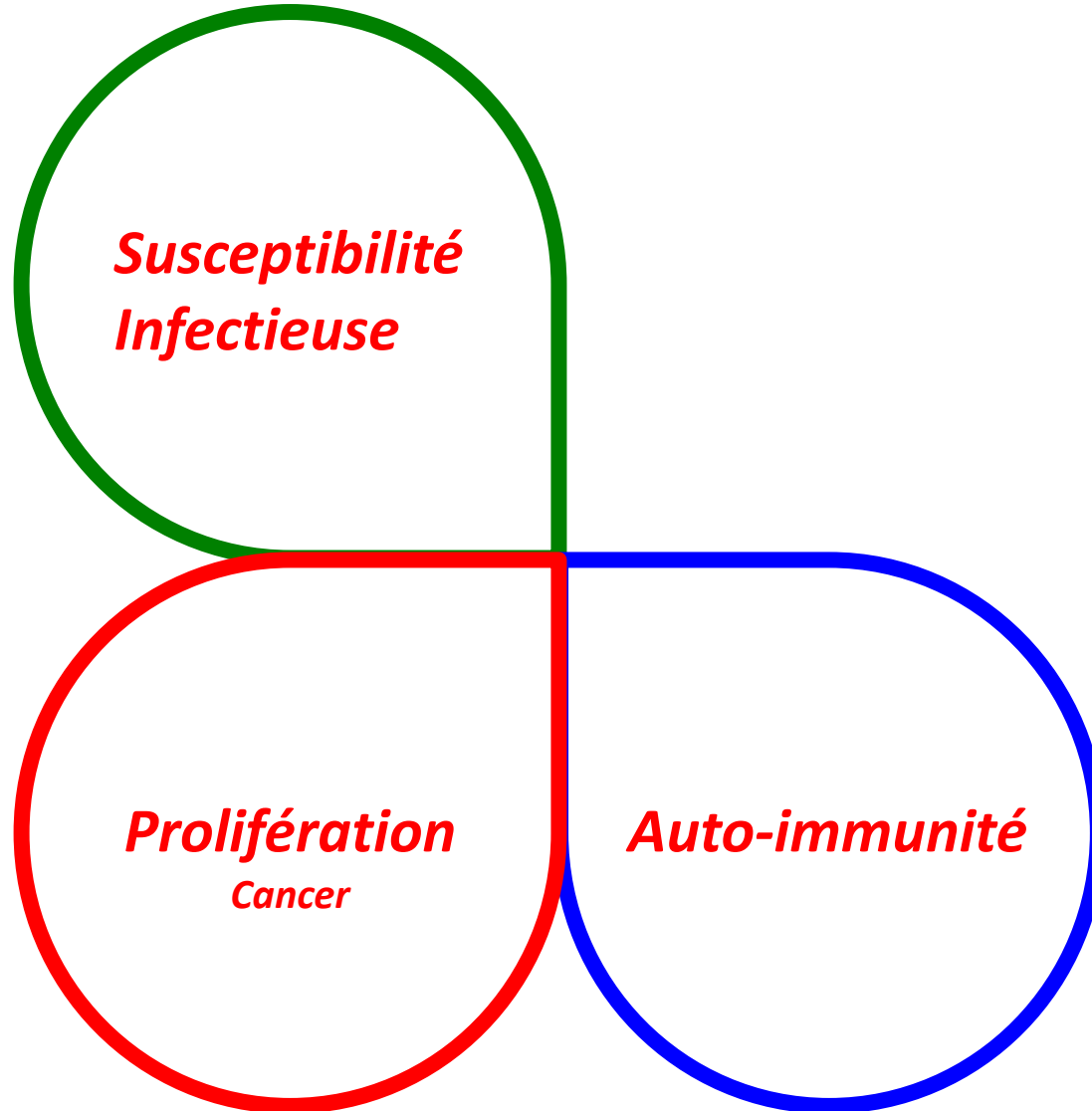


Auto-Ac anti-cytokines

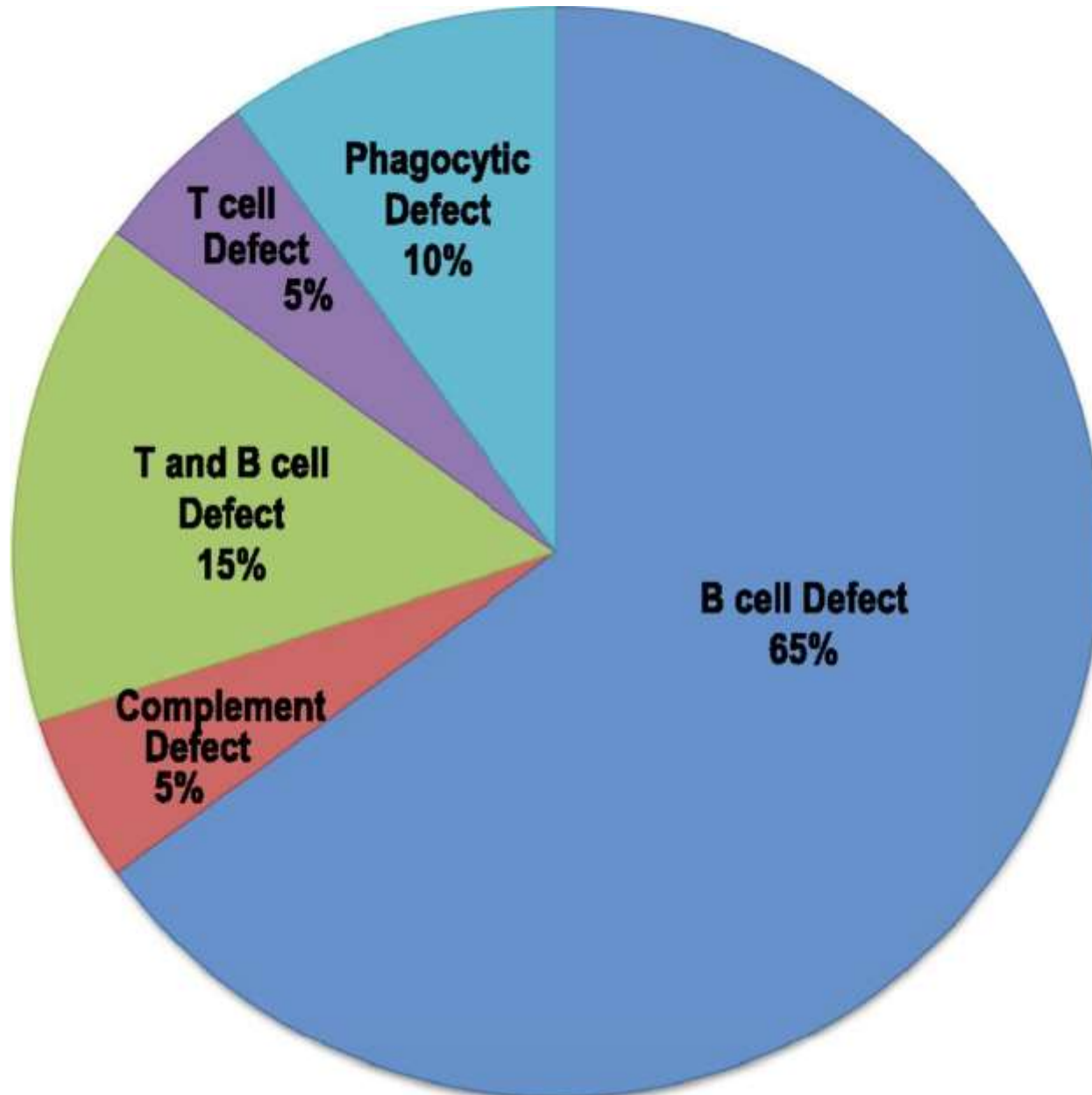
- **Ac anti-EPO** Erythroblastopénie
 - Ac anti-OPG Ostéoporose (1 cas)
 - Anti-IL6 Staphylococcie (1 cas)
 - Anti-G-CSF Felty, SLE ?
-
- **Ac anti-IL17/22** Candida // APECED / Thymome
-
- **Ac anti-GM-CSF** PAP, Cryptocoque, Nocardia

Rosen LB et al. J Immunol 2013
Rosen LB et al. Clin Infect Dis 2015

Génétique des Déficits Immunitaires Primitifs



Déficits Immunitaires Primitifs



Déficit Immunitaire Commun Variable

- **Hypo IgG** (<5g/L), +/- IgA, +/- IgM
Défaut de réponse vaccinale
Exclusion des autres causes

1^{er} Signes 19a → Diag 35a

- 1/30.000

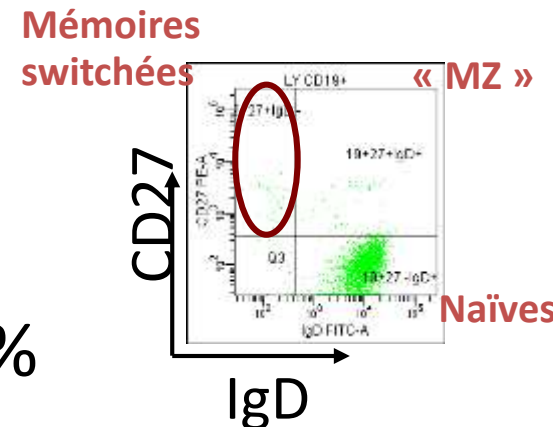
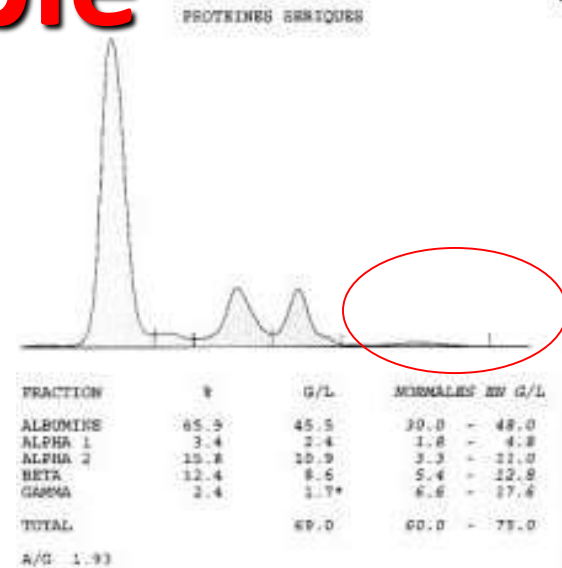
75-80% = sporadique

20% formes familiales → AD

<5% // mutation identifiée → AR

ICOS, CD19,

Mutation TACI hétérozygote: 11% vs 3%



DICV

- **Infection**

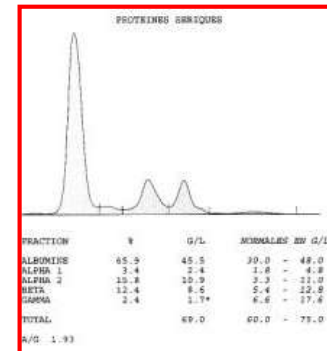
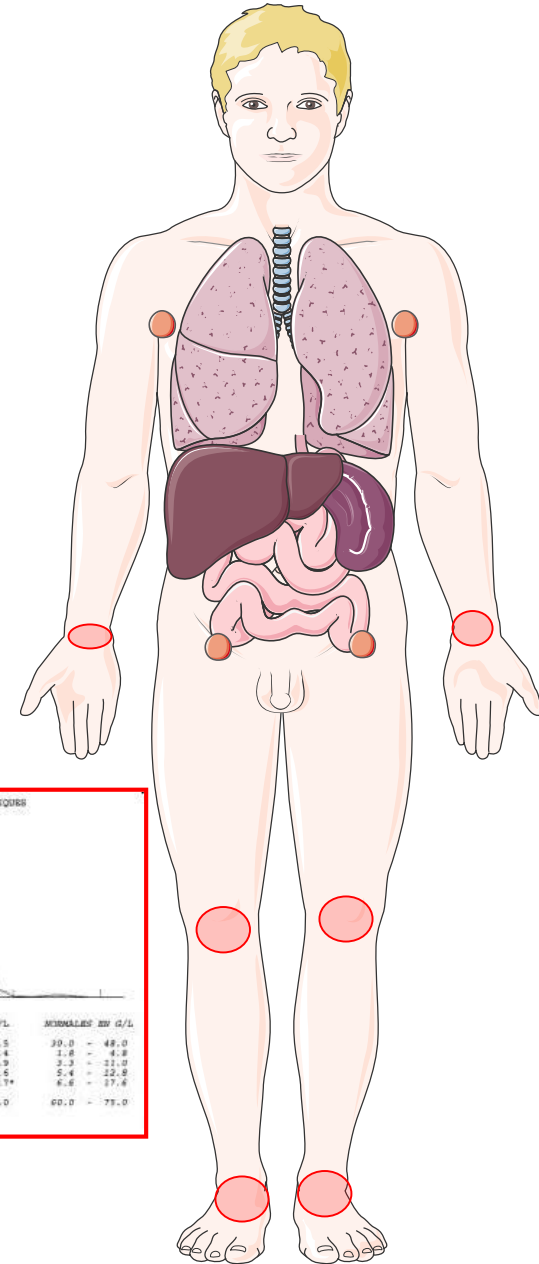
- Voies aériennes (ORL, Pnp, DDB)
- **Diarrhée** (inf°, atrophie villositaire, lymphoprolif°, pseudo-MICI)

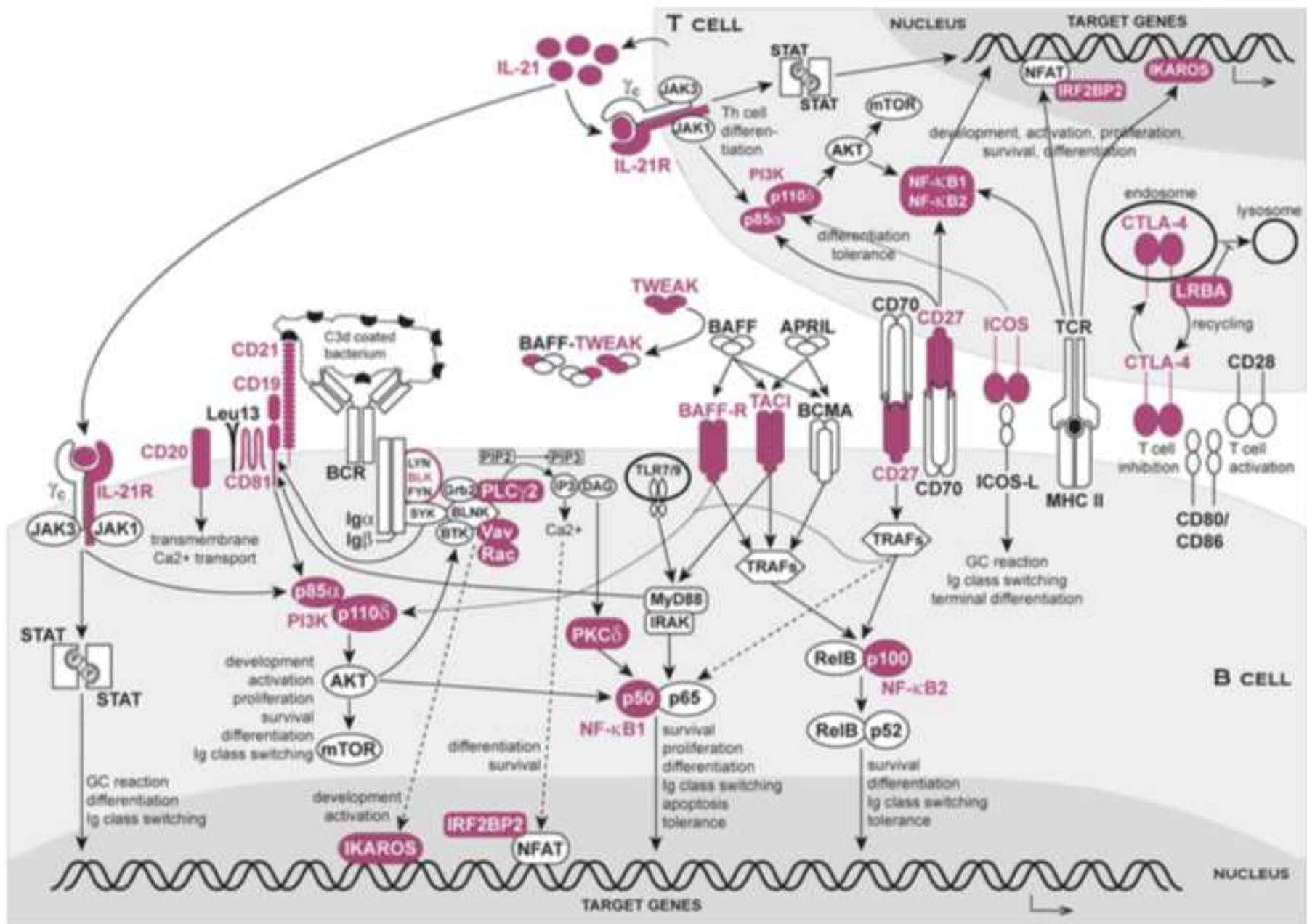
- **Prolifération**


- Proliférations lymphoïdes
- Granulomatose
- Cancer

- **Auto-immunité**

- Cytopénie AI : PTI AHAI
- Polyarthrite

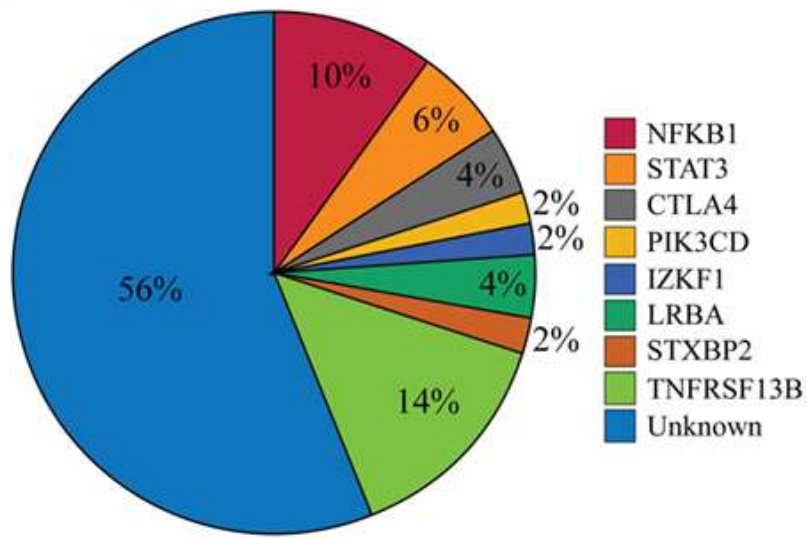
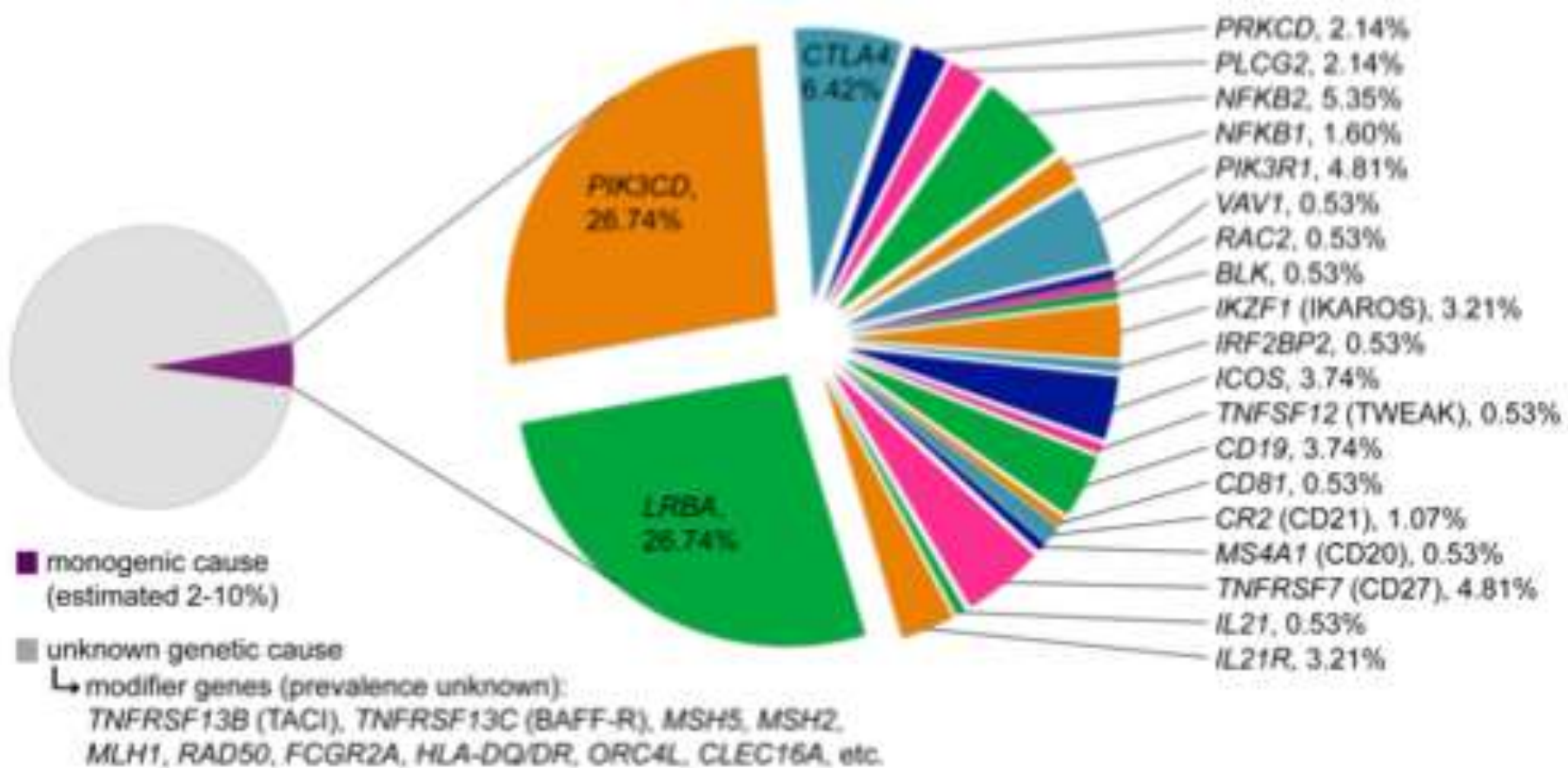




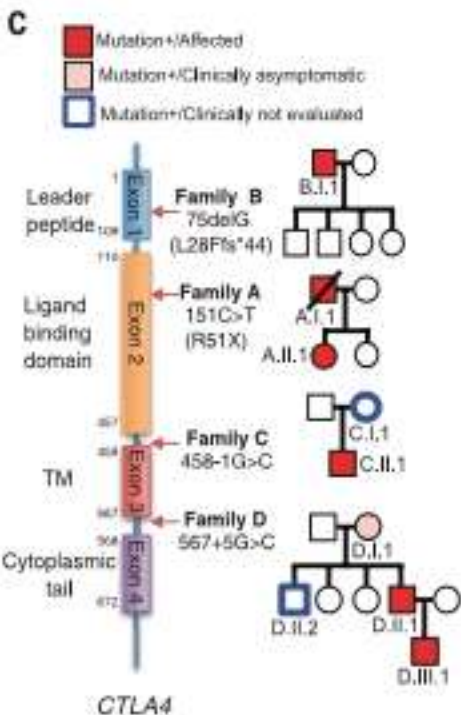
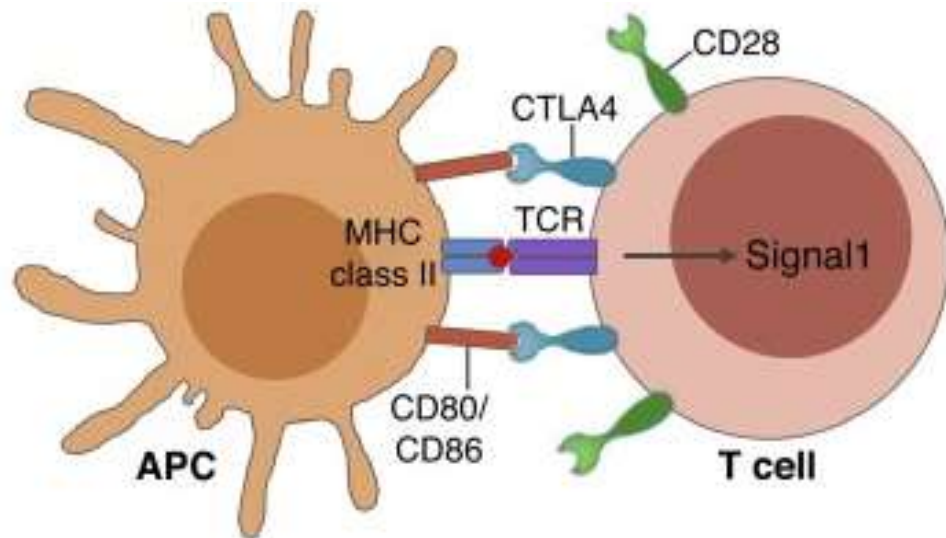
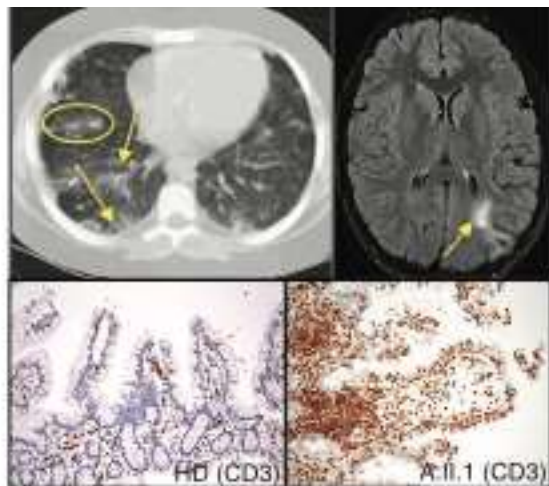
- 
- **Autosomique dominant** : déficit CTLA-4
 - Mutations **Activatrices** : PI3K, STAT-1, STAT-3...

 - **Expressivité variable**
 - **Auto-immunité et Lymphoprolifération**

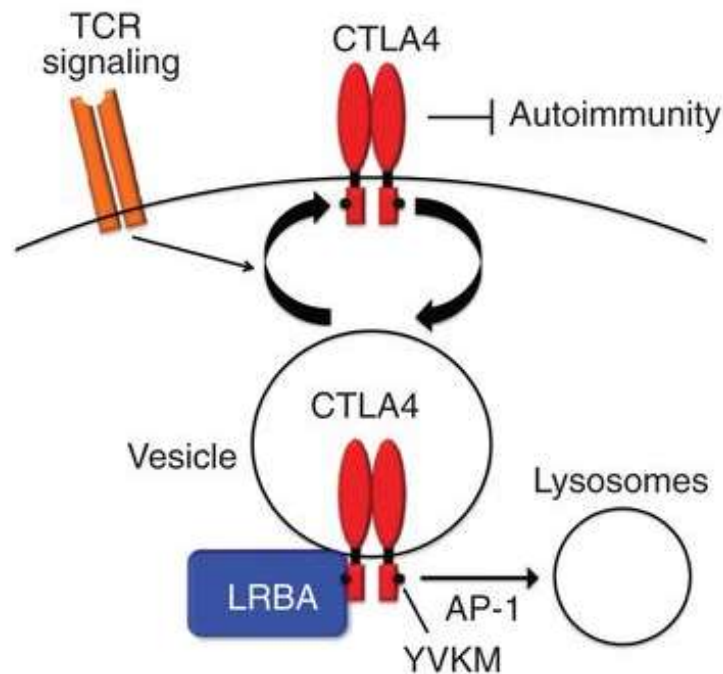
 - Pas si rares
 - Piste de **thérapie ciblée**... immunosuppressives



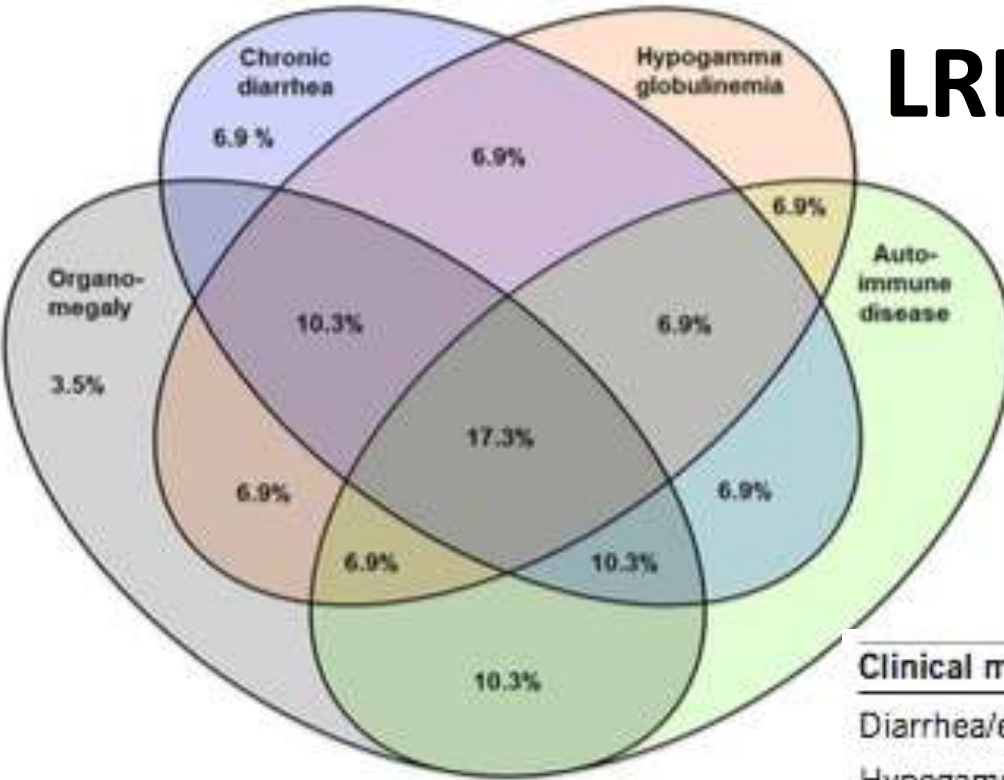
CTLA4 et LRBA



Patient	Autoimmune Features			
	Brain	Lung	Gut	Cytopenia
B.I.1				
A.I.1				
A.II.1				
C.I.1				
C.II.1				
D.I.1				
D.II.1				
D.II.2				
D.III.1				



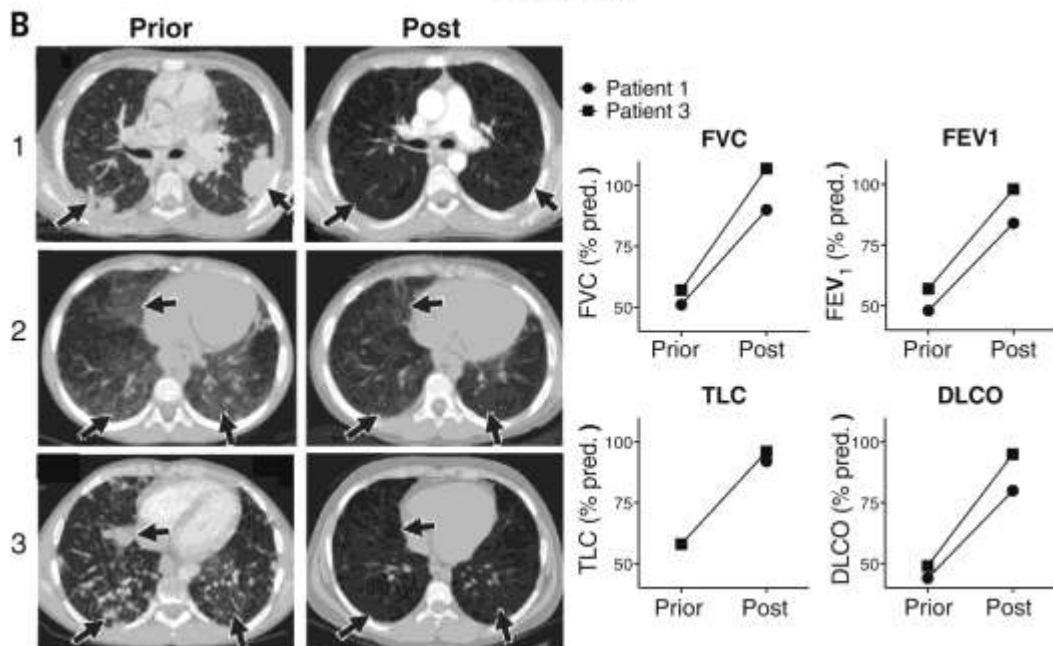
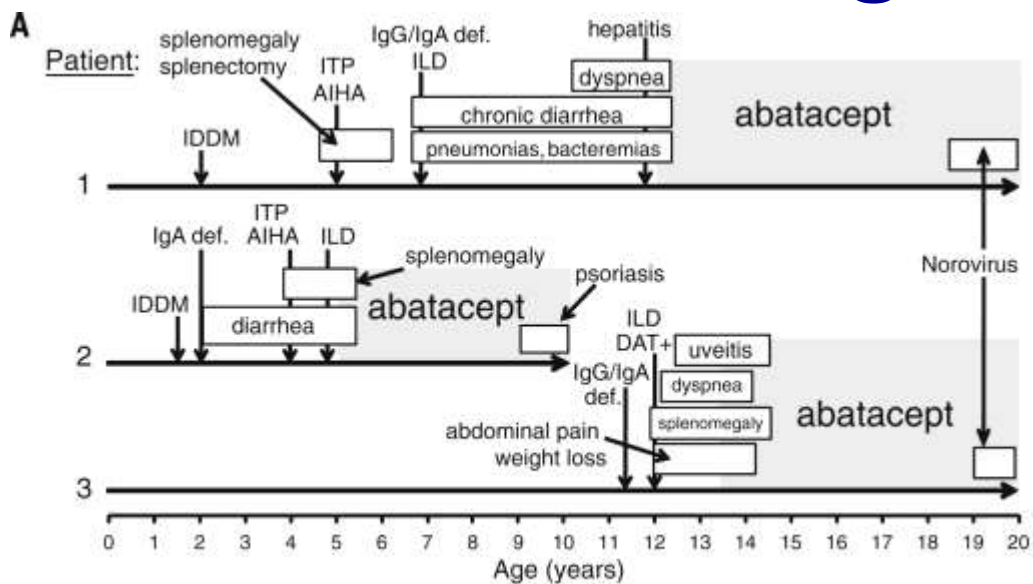
LRBA



CTLA-4

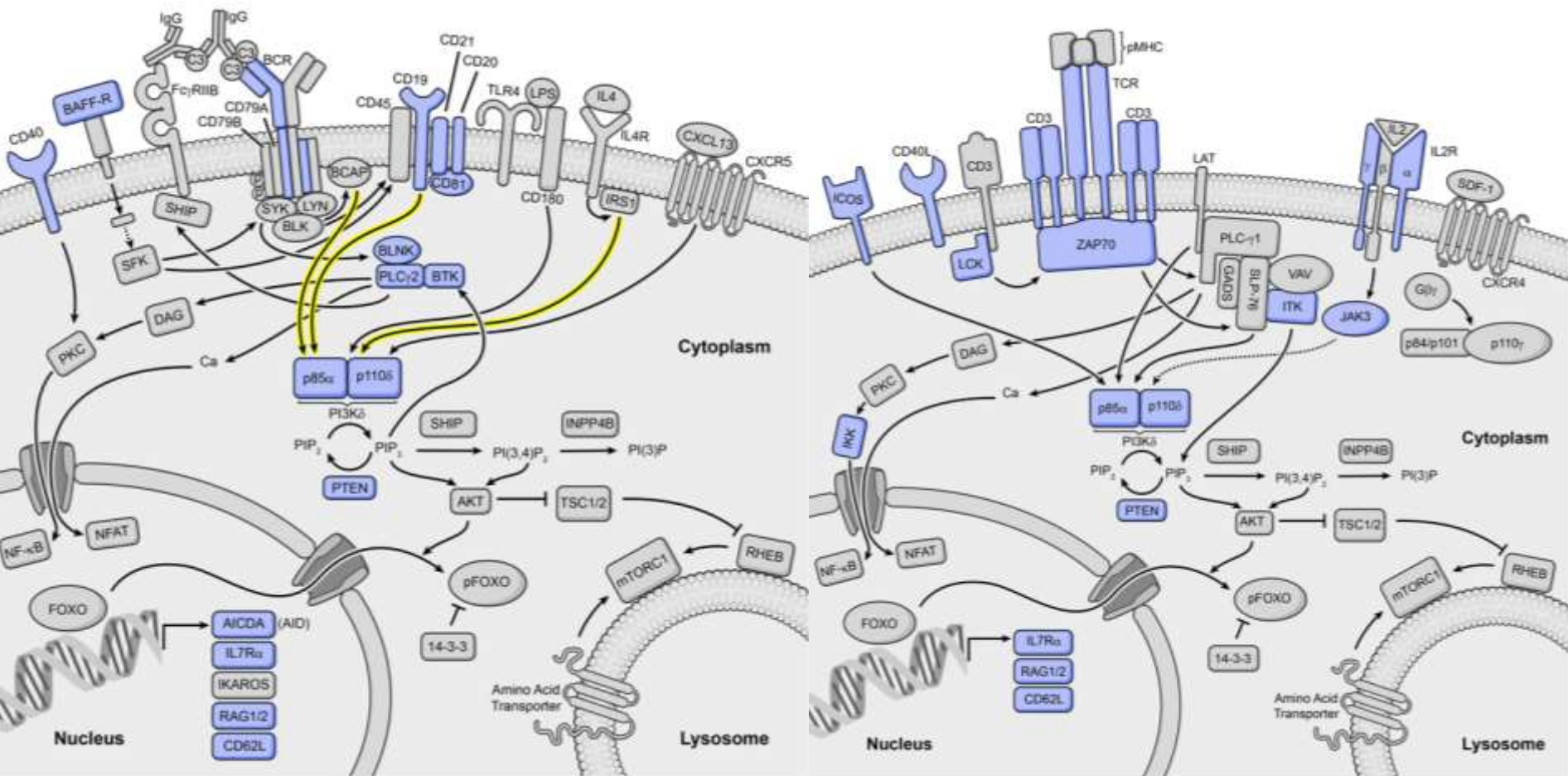
Clinical manifestations	Frequency
Diarrhea/enteropathy	11/14 (78%)
Hypogammaglobulinemia	10/13 (76%)
Granulomatous lymphocytic interstitial lung disease	8/12 (66%)
Respiratory infections ^a	8/14 (57%)
Organ infiltration (bone marrow, kidney, brain, liver)	7/14 (50%)
Splenomegaly	6/12 (50%)
Autoimmune thrombocytopenia	5/14 (35%)
Autoimmune hemolytic anemia	4/14 (28%)
Lymphadenopathy	4/14 (28%)
Psoriasis and other skin diseases ^b	3/14 (21%)
Autoimmune thyroiditis	2/13 (15%)
Autoimmune arthritis	2/14 (14%)
Solid cancer	1/14 (7%)

CTLA4-Ig



PI3 kinase APDS

Mutation activatrice => Prolif, AI et DIP



Rapamycin ?

Idelalisib ?

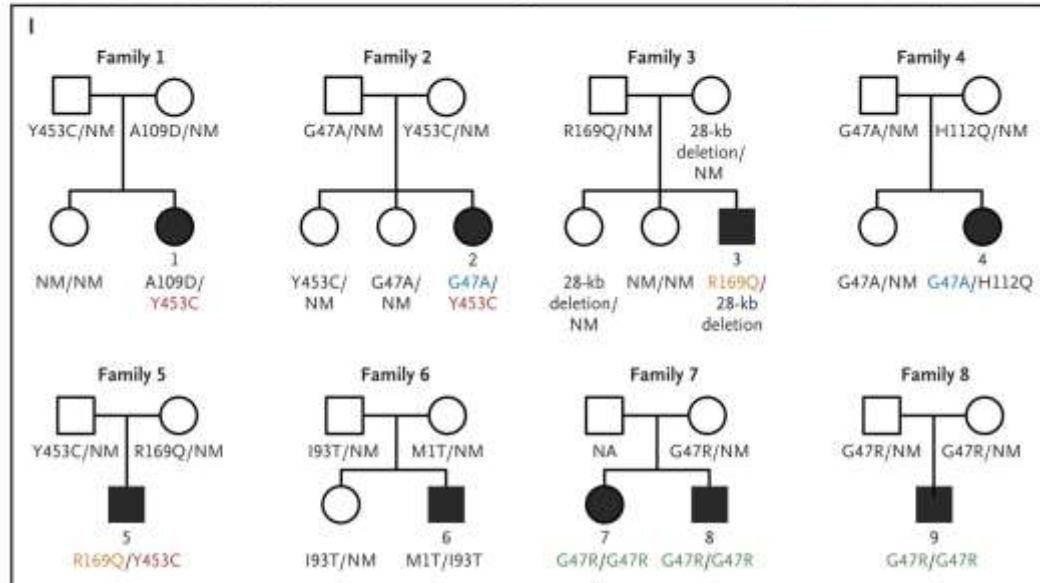
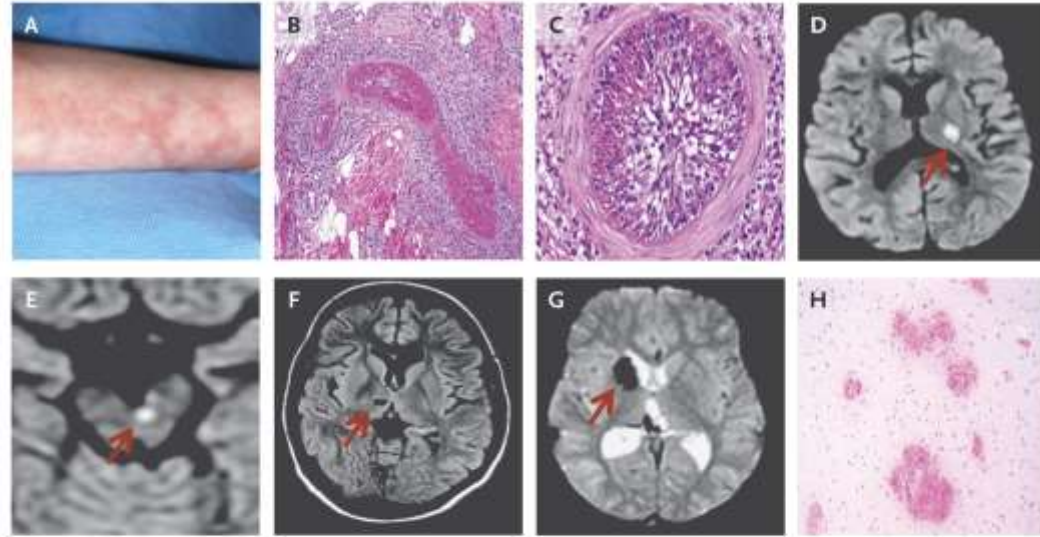
Déficit en ADA2

Table 1. Clinical and Laboratory Manifestations in Patients with Deficiency of Adenosine Deaminase 2.

Clinical Manifestation	Patients <i>no./total no.</i>
Fever	9/9
Ischemic stroke	8/9
Hemorrhagic stroke	3/9
Ophthalmologic involvement*	5/9
Livedo racemosa	8/9
Hepatosplenomegaly	6/7
Documented vasculitis†	4/9
Polyarteritis nodosa	2/9
Antinuclear antibody	3/9
Antineutrophil cytoplasmic antibody	0/9
Low serum IgM	5/5

* The ophthalmologic manifestations included central retinal artery occlusion in one patient, optic nerve atrophy in one, diplopia with irregular enhancement of the medial rectus muscle (as observed on magnetic resonance imaging) in one, third cranial nerve palsy in one, and strabismus in two. Patients could have more than one ophthalmologic disorder.

† The diagnosis of vasculitis included polyarteritis nodosa.

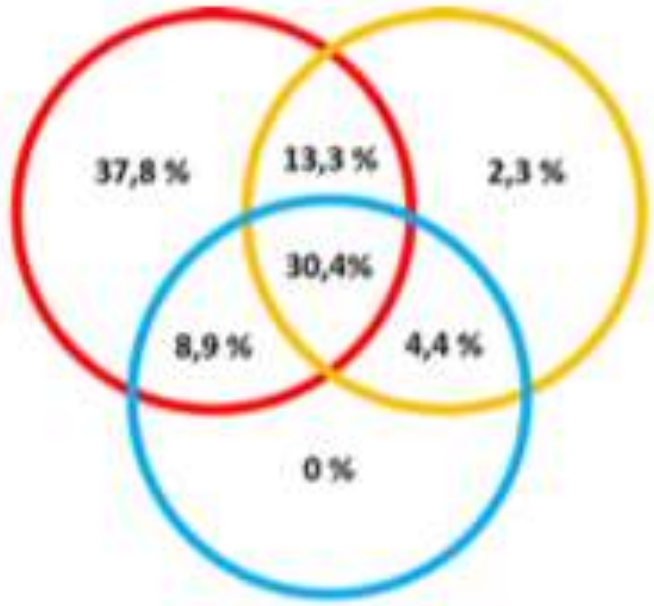


Déficit en ADA2

2017
135 cas

Vasculaire
inflammatoire

Hématologique



Déficit immunitaire



Fièvre
(76%)

Manifestations cutanées
Livedo 55,6 %
Ulcères / nécrose 17,8 %

Manifestations rhumatologiques
Arthralgies 23,7 %
Arthrites 15,6 %

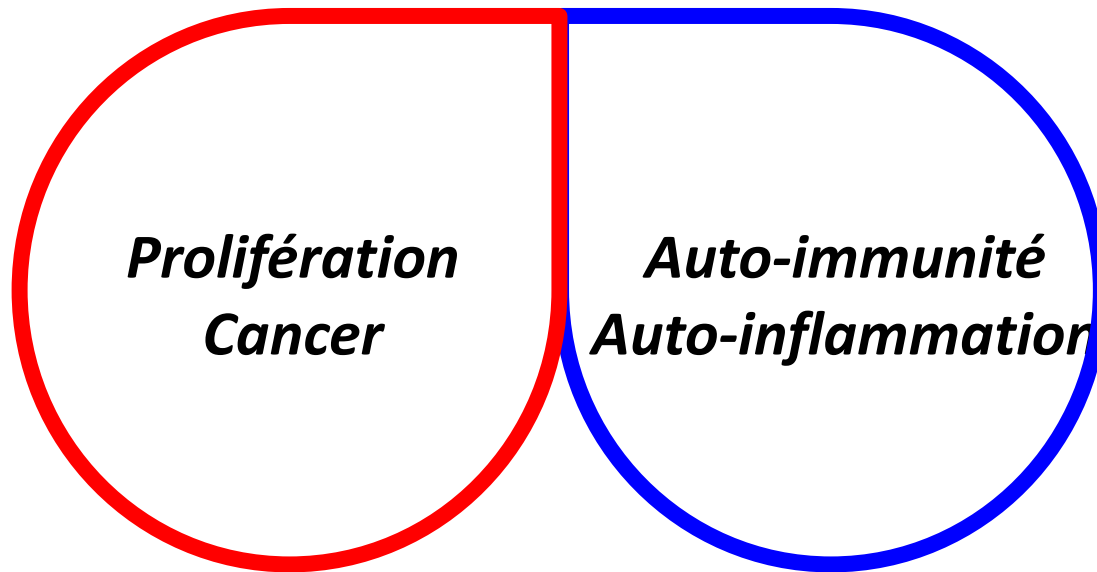


Manifestations neurologiques
AVC-i / AIT 41,5 %
AVC-h 11,9 %

Splénomégalie 32,6%

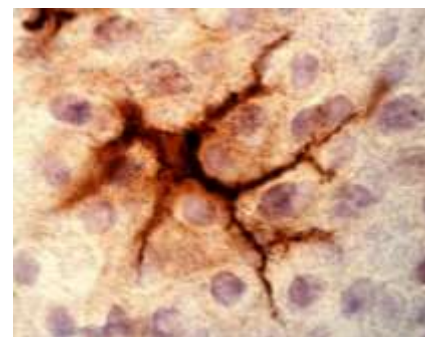
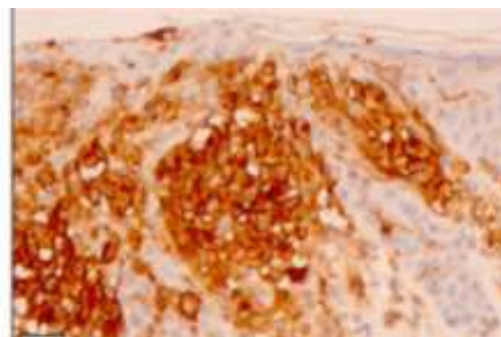
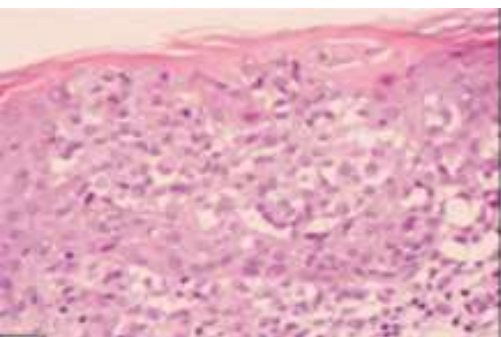
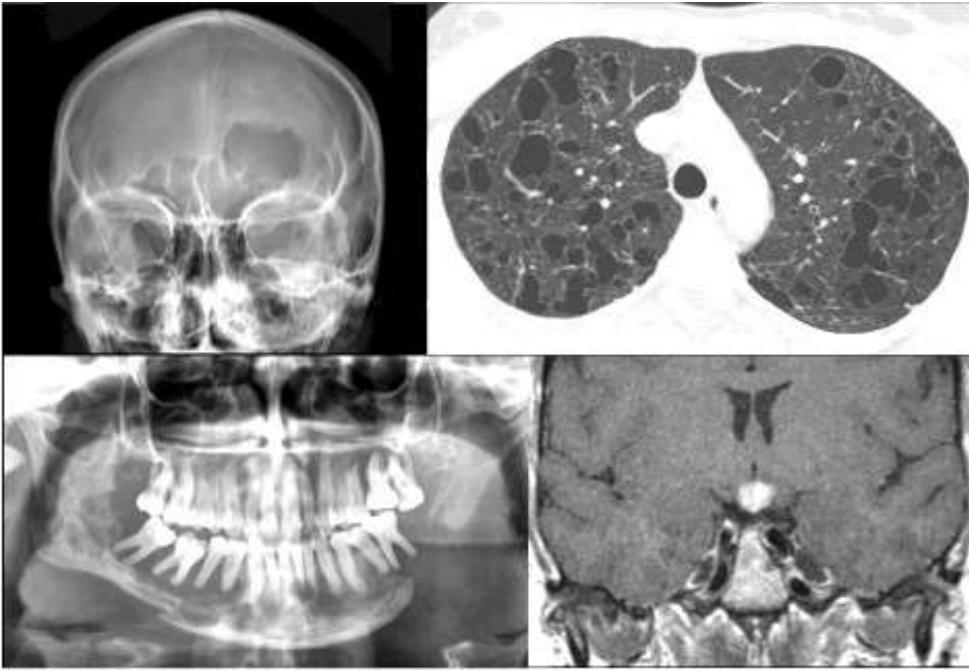
Manifestations digestives
Douleur abdominale / diarrhées 19,3%
Atteinte grave :
- Type MICI : 6,7%
- Vascularite : 3,0%

Cancer et/ou Maladie dysimmunitaire



Maladie de Letterer Sive,
Hand Schuller Christian
Granulome Eosinophile Osseux

Histiocytose (X)



Histiocytose
Langerhansienne

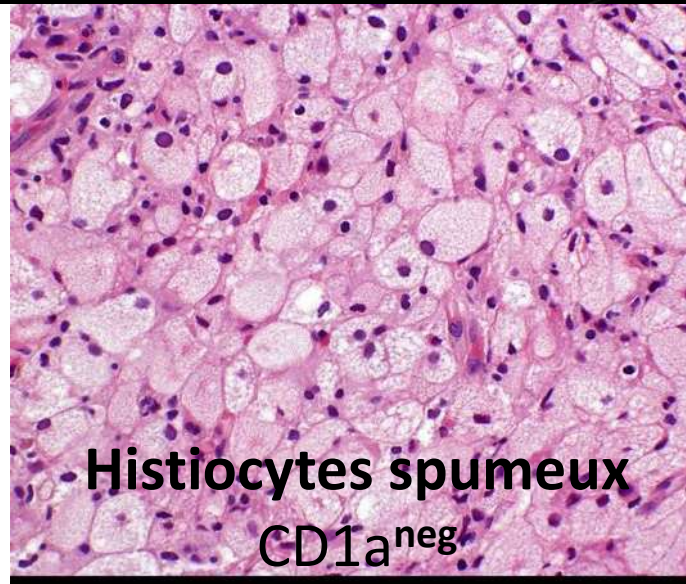
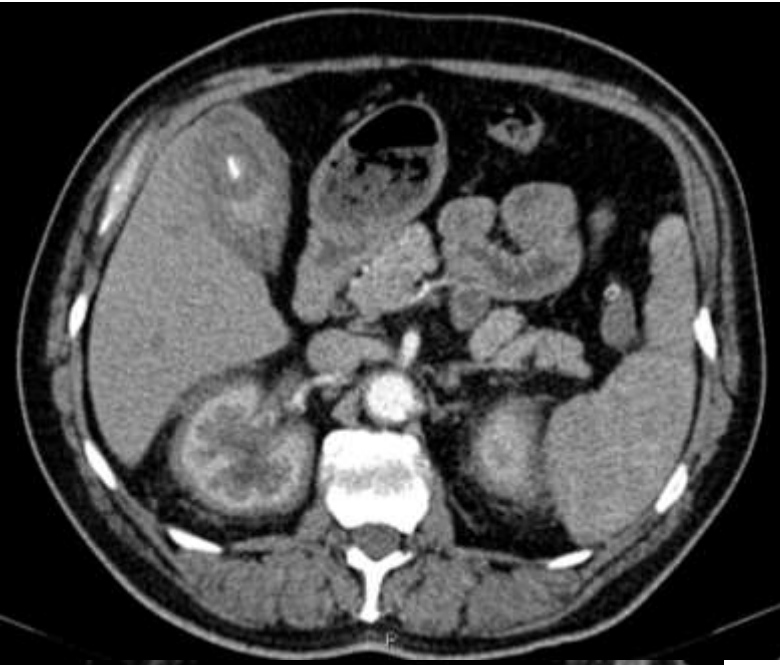
Histiocytes

CD1a^{pos}

Histiocytose

Langerhansienne vs non Langerhansienne

Maladie d'Erdheim-Chester



Brief report

Recurrent *BRAF* mutations in Langerhans cell histiocytosis

Gayane Badalian-Very,¹⁻³ Jo-Anne Vergilio,^{4,5} Barbara A. Degar,⁶⁻⁸ Laura E. MacConaill,⁹ Barbara Brandner,¹⁻³ Monica L. Calicchio,⁴ Frank C. Kuo,^{5,10} Azra H. Ligon,^{5,10,11} Kristen E. Stevenson,¹² Sarah M. Kehoe,⁹ Levi A. Garraway,^{1-3,9,13} William C. Hahn,^{1-3,9,13} Matthew Meyerson,^{1,2,9,13} Mark D. Fleming,^{4,5} and Barrett J. Rollins¹⁻³

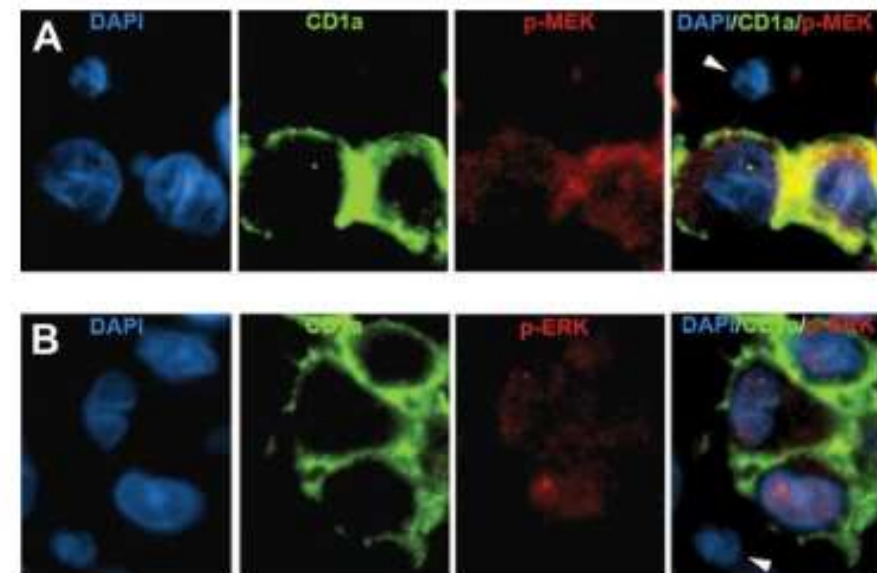
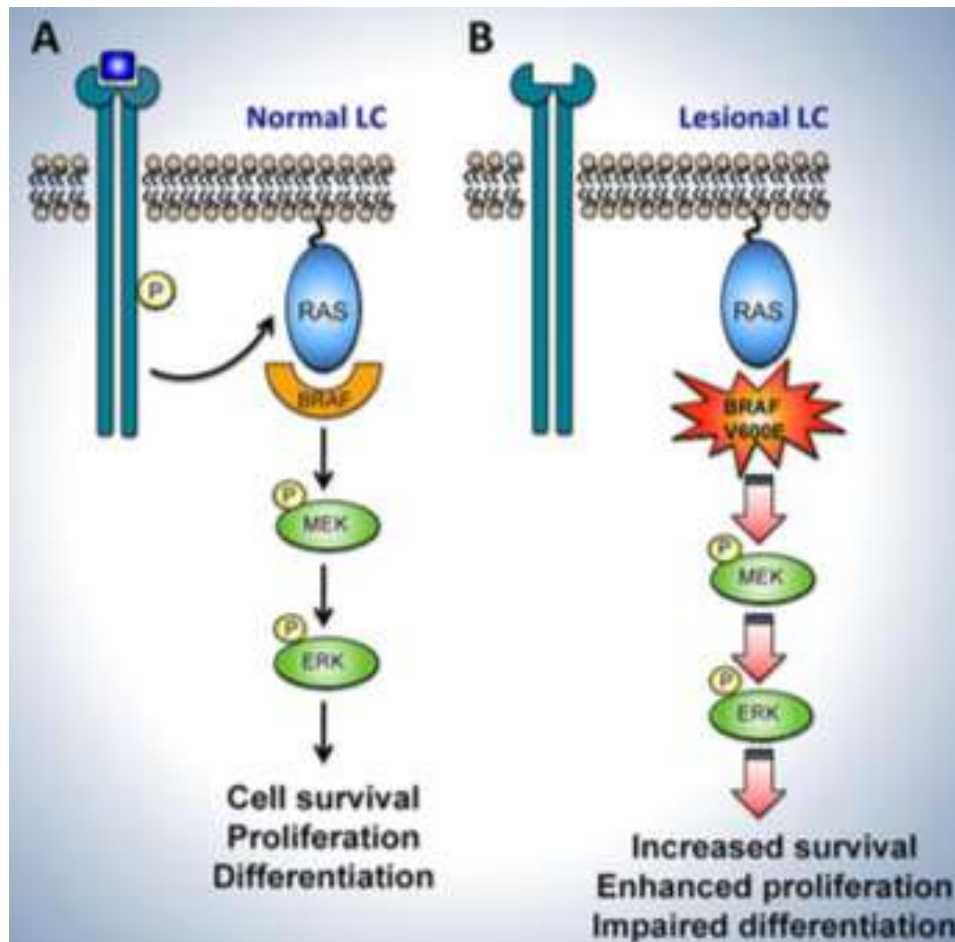


Figure 1. Immunofluorescence analysis of BRAF pathway activation in LCH. (A) LCH sample stained with DAPI (blue), anti-CD1a (green), antiphospho-MEK (red), and a merged image of all 3 stains. (B) LCH sample stained with DAPI (blue), anti-CD1a (green), antiphospho-ERK (red), and a merged image of all 3 stains. Arrowheads indicate CD1a-negative cells that are also negative for phospho-MEK and phospho-ERK. (Technical details described in supplemental Methods.)

Syndromes myéloprolifératifs

Cellules	Maladie	oncogene
Globule rouge	Polyglobulie de Vaquez	JAK2
Plaquettes	Thrombocythémie ess.	JAK2, CaIR, MPL
Neutrophiles	LMC	BCR-ABL / Chr Phi
Monocytes	LMMC	ASXL1-TET2-SRSF2
Mastocytes	Mastocytose	c-Kit
Eosinophiles	SHEm / LCE	FIP1L1-PDGFRa
Macrophages/DC	Histiocytoses LCH/ECD	BRAF, MAP2K1

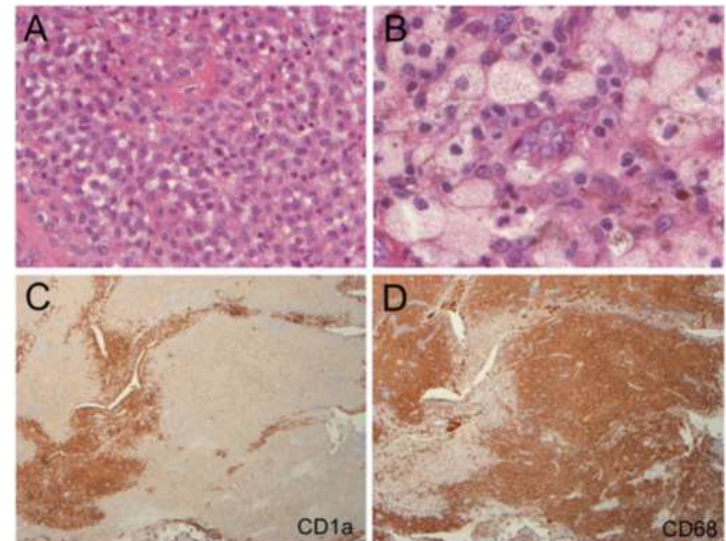
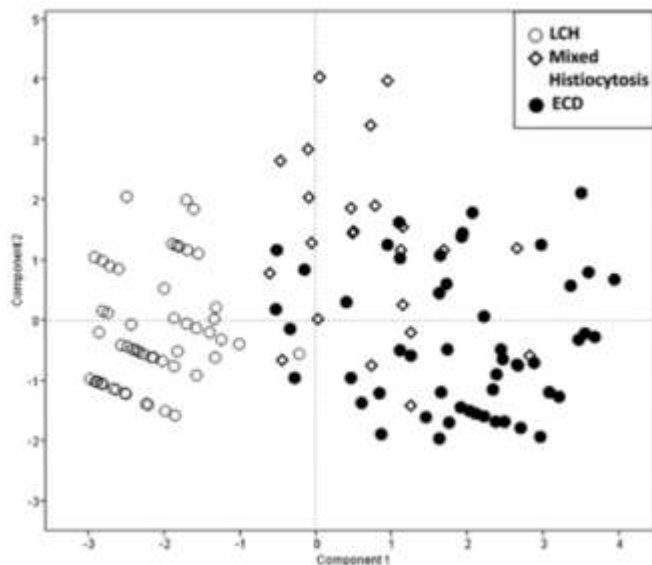
High prevalence of *BRAF V600E* mutations in Erdheim-Chester disease but not in other non-Langerhans cell histiocytoses

Haroche J et al. Blood 2012

	LCH	ECD	RDD	JXG	HS	XD	IDC S	N X
n	29	24	23	12	3	2	1	1
BRAF	38%	54%	0	0	0	0	0	0

Association of both Langerhans cell histiocytosis and Erdheim-Chester disease linked to the *BRAF V600E* mutation

Hervier B et al. Blood 2014



Vemurafenib

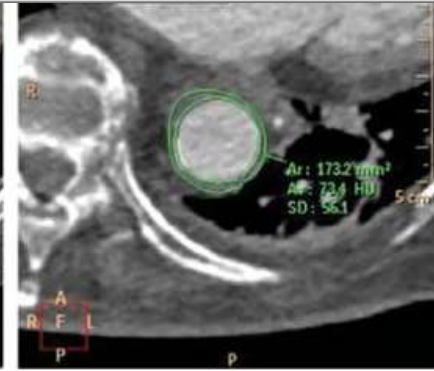


Before

M12



Before



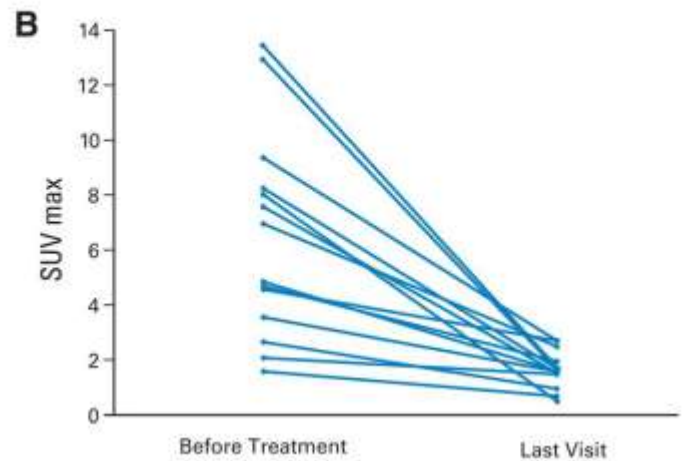
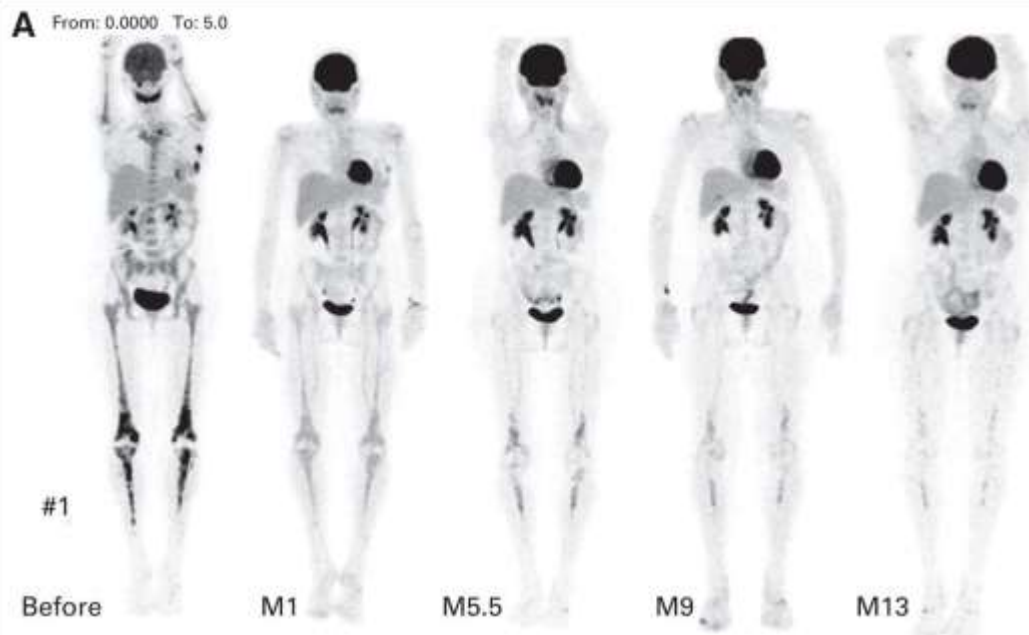
M6



Before



M13



Oncogenèse et auto-immunité

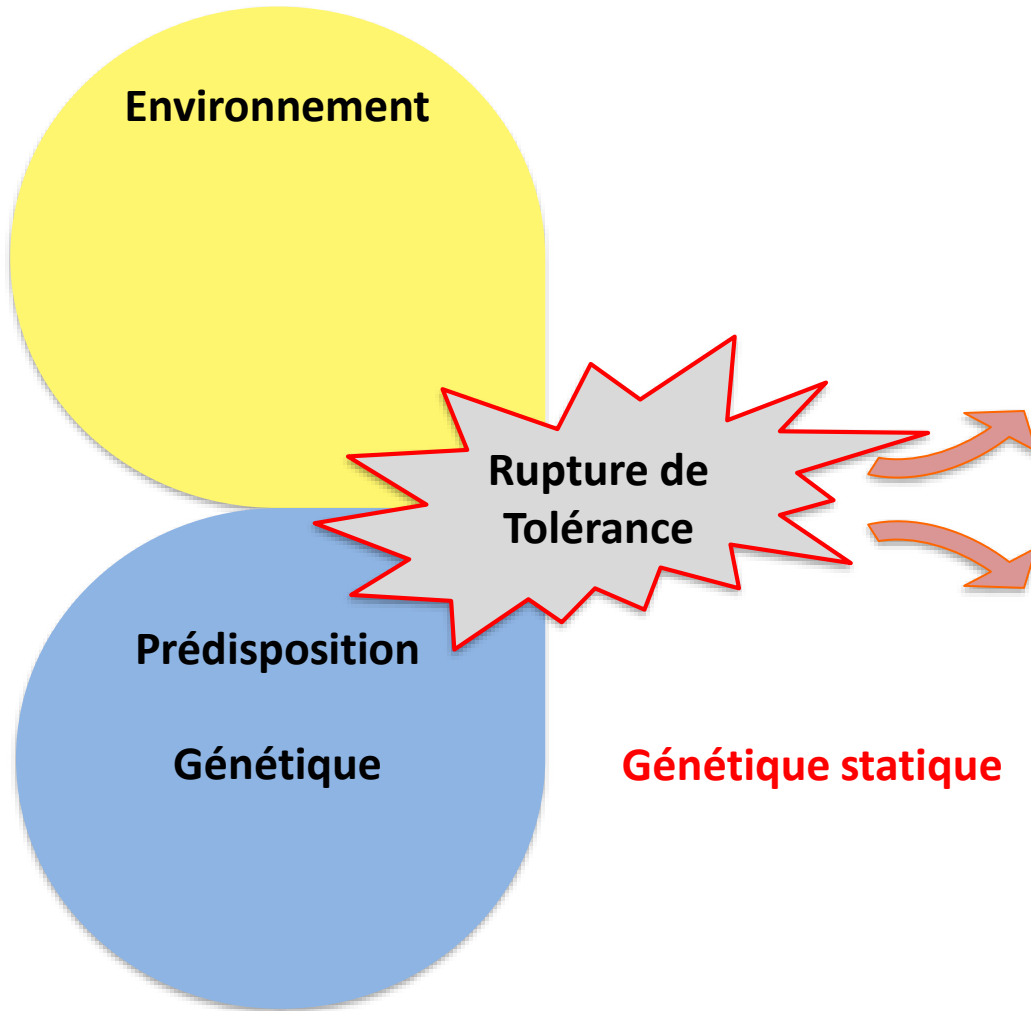
Physiopathologie des MAI



Prédisposition

Génétique

Physiopathologie des MAI



Physiopathologie des cancers



The diagram consists of two overlapping rounded rectangular shapes. The top shape is light orange and contains the text 'Environnement' and 'Carcinogènes'. The bottom shape is blue and contains the text 'Prédisposition génétique'. The shapes overlap in the middle, with the orange shape on top and the blue shape on the bottom.

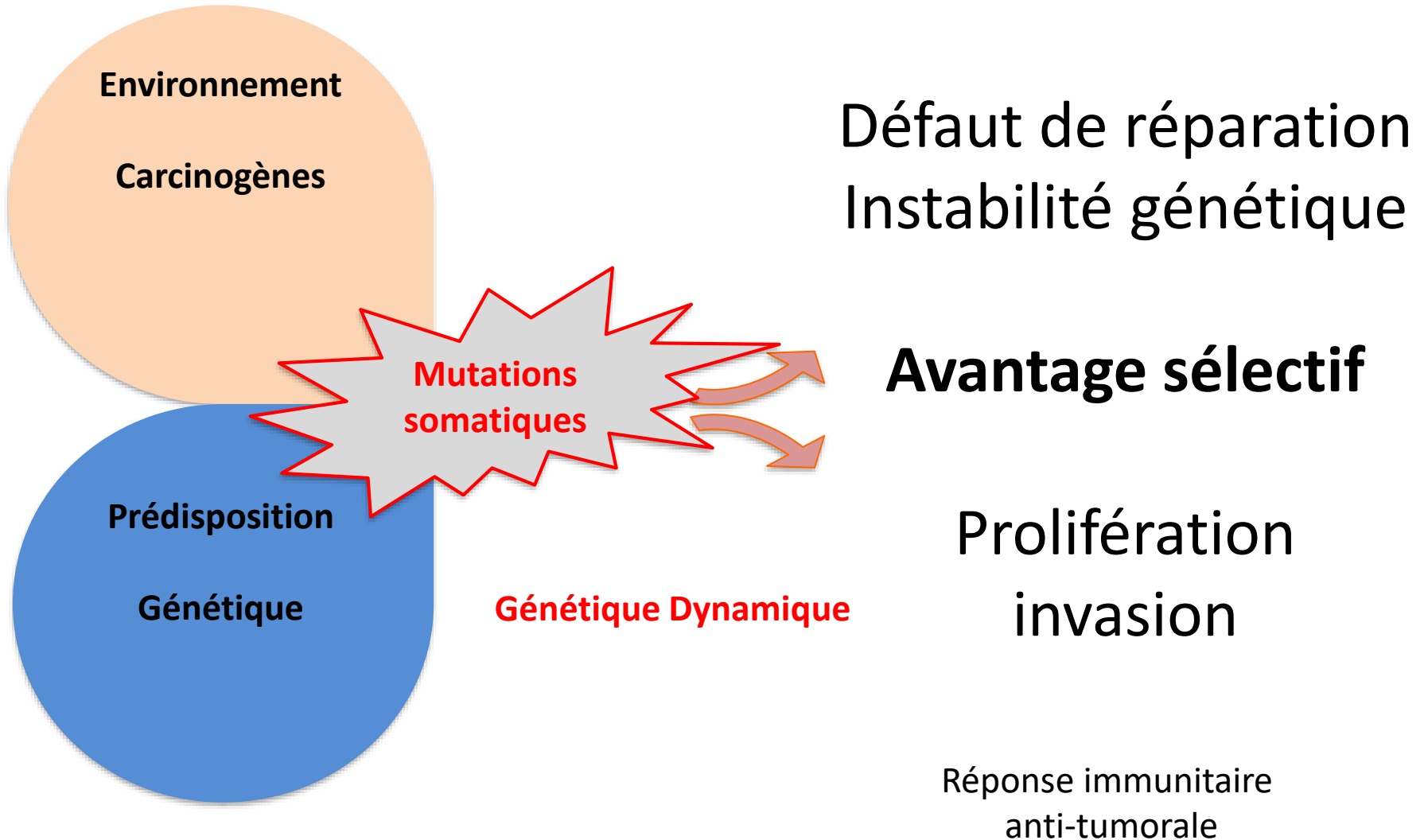
Environnement

Carcinogènes

Prédisposition

génétique

Physiopathologie des cancers





STAR WARS
EPISODE II

L'ATTAQUE DES CLONES

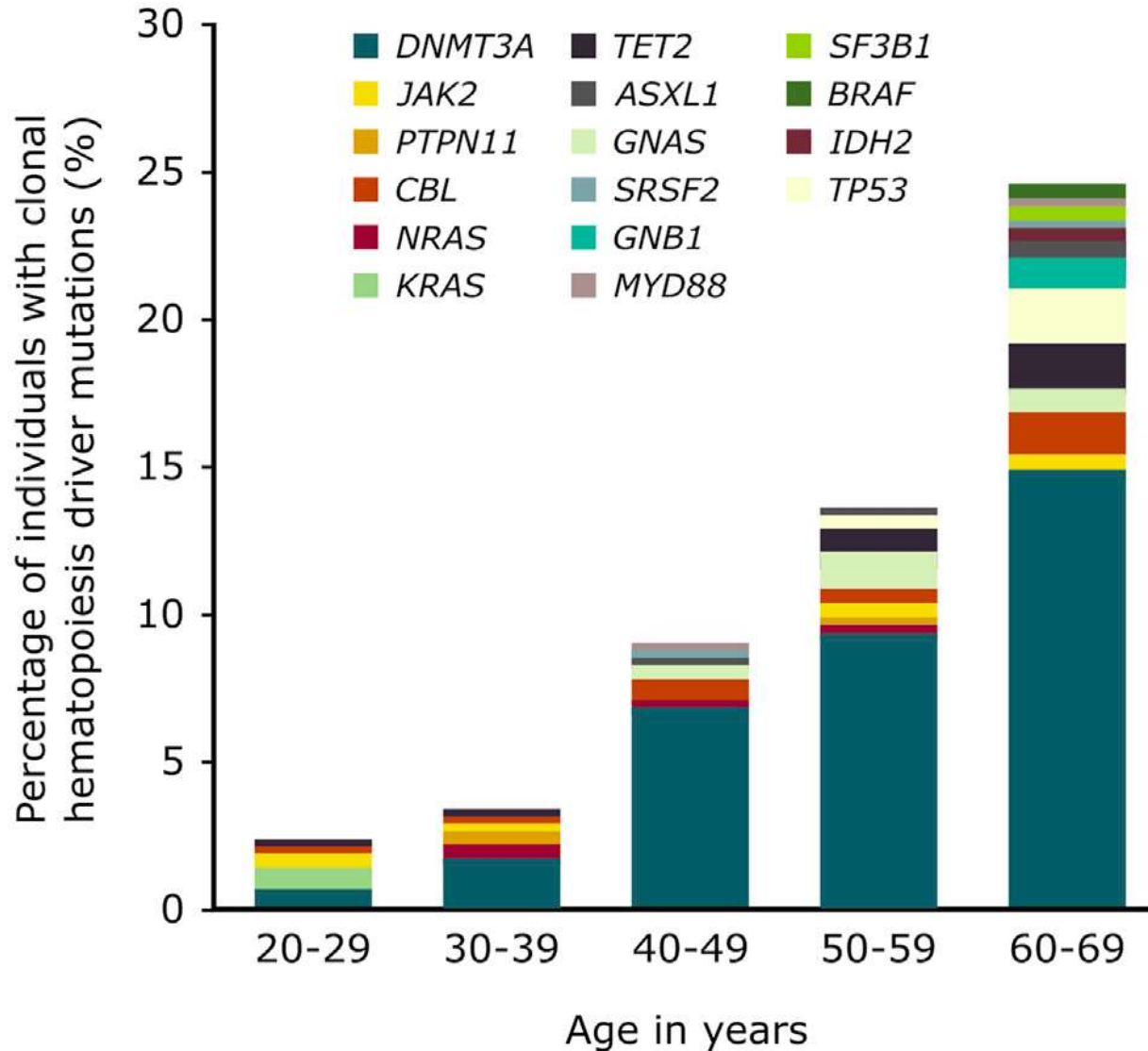
avec EWAN MCGREGOR NATALIE PORTMAN HAYDEN CHRISTENSEN
IAN MCDIARMID SAMUEL L. JACKSON CHRISTOPHER LEE
MUSIQUE DE JOHN WILLIAMS COSTUME DESIGNER RICK MCCALLUM
MONTAGE DE GEORGE LUCAS EDITEUR JONATHAN HALES
RÉALISÉ PAR GEORGE LUCAS

LUCASFILM THX JBL DIGITAL DOLBY DIGITAL DOLBY DIGITAL EXCELLENCE
www.starwars.com

Le système immunitaire est une machine à clones

- **Immunité adaptative** : évident
 - Clone Proliférant => Leucémie / Lymphome
 - Clones Auto-réactifs => Maladie Auto-immune
- **Immunité innée / cellules myéloïdes**:
 - Clone Proliférant => Syndrome myéloprolifératif
 - Clones *Auto-inflammatoire ?..*

Hématopoïèse Clonale (CHIP)

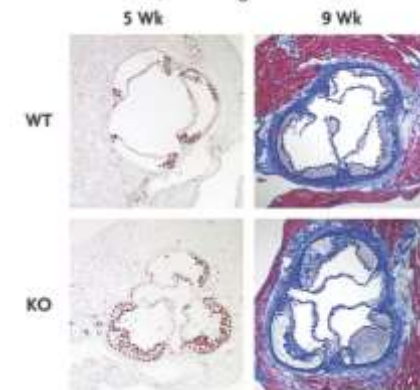


Les Clones Myéloïdes eux aussi savent être auto-pathogènes hors cancer

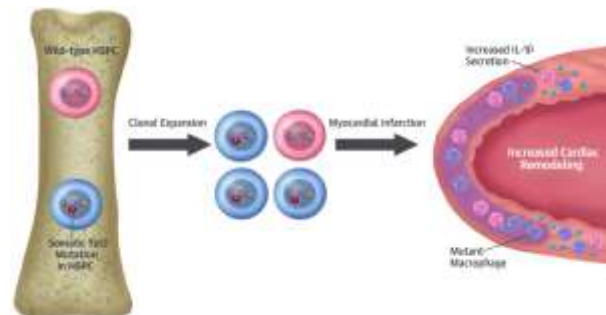
Jaiswal S, et al. Clonal hematopoiesis and Risk of Atherosclerosis. NEJM 2017

ATVB and PROMIS	No. of Participants with Myocardial Infarction/ No. at Risk	Odds Ratio (95% CI)	P Value
<i>DNMT3A</i>	31/46	1.4 (0.7–2.8)	0.29
<i>TET2</i>	12/13	8.3 (1.2–357.5)	0.02
<i>ASXL1</i>	8/8	Undefined	0.02
<i>JAK2</i>	16/16	Undefined	<0.001
Other	20/22	6.9 (1.7–61.6)	0.001

Aortic-Root Sections, According to Tet2 Status



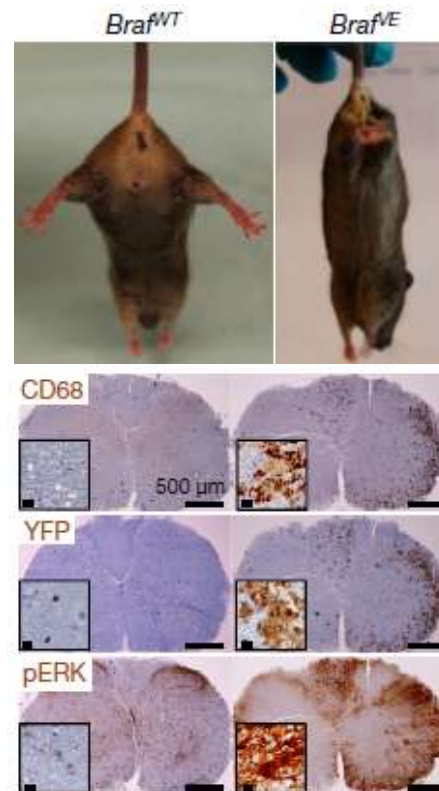
Sano S, et al. Tet2-Mediated Clonal Hematopoiesis Accelerates Heart Failure Through [...] the IL1 β /NLRP3 Inflammasome. JACC 2018



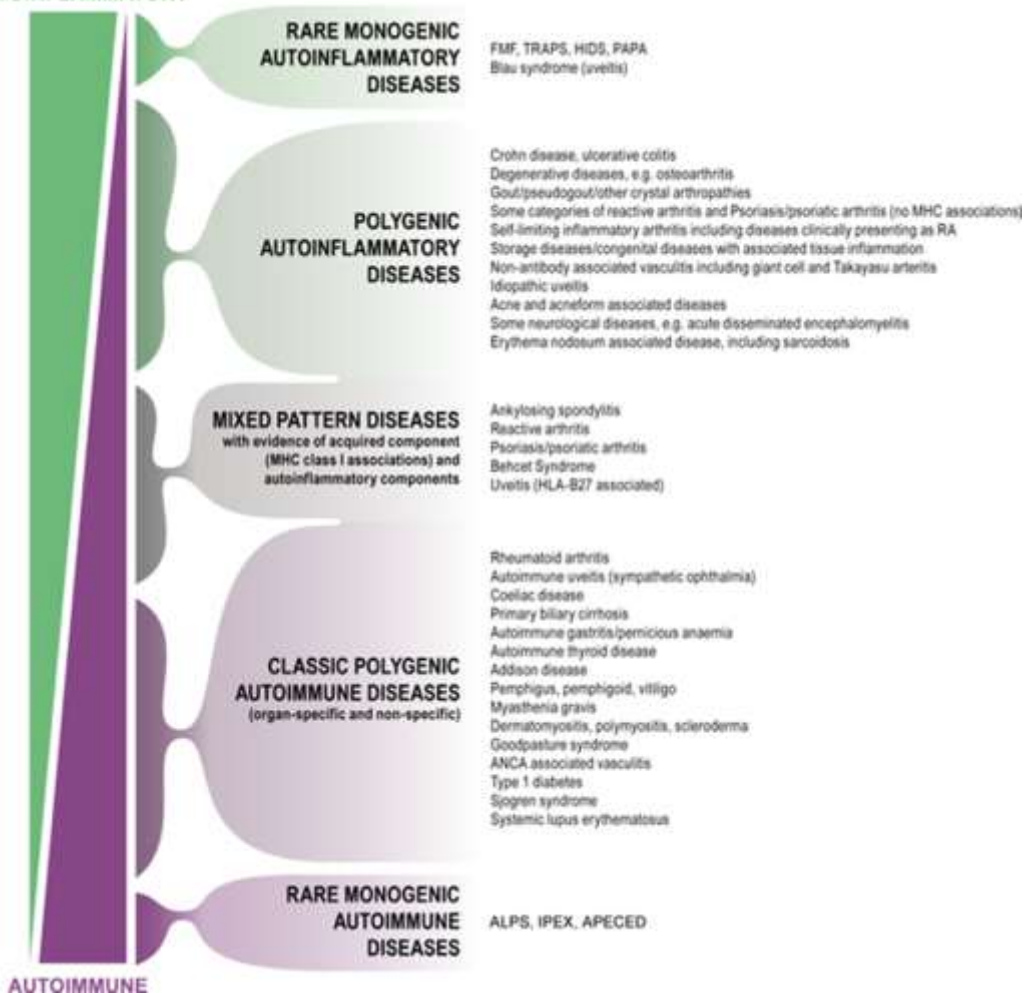
Les Clones Myéloïdes eux aussi savent être auto-pathogènes hors cancer

Mass E, et al. **A somatic mutation in erythro-myeloid progenitors causes neurodegenerative disease.**

Nature 2017



AUTOINFLAMMATORY

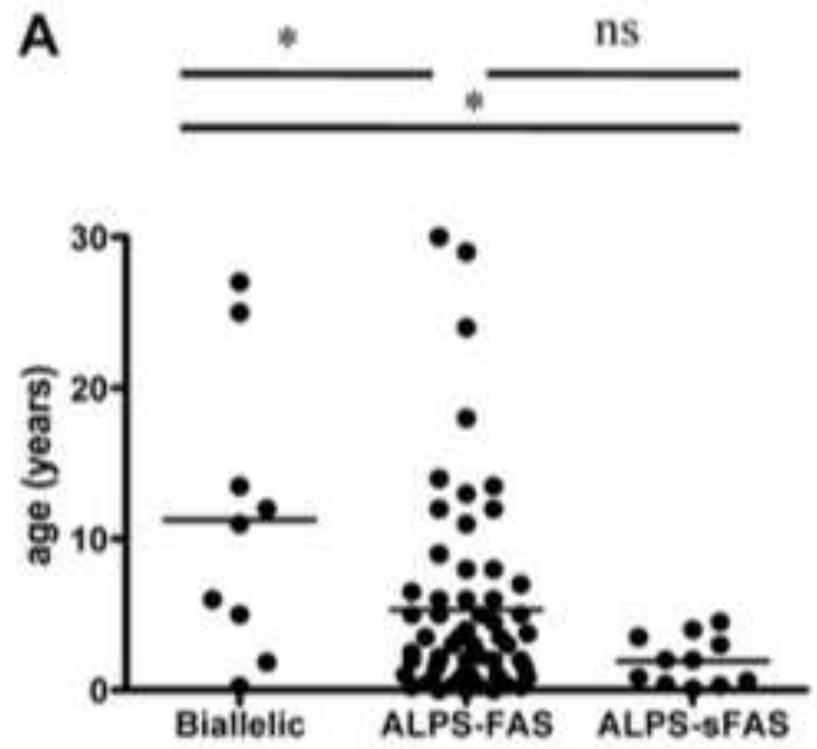
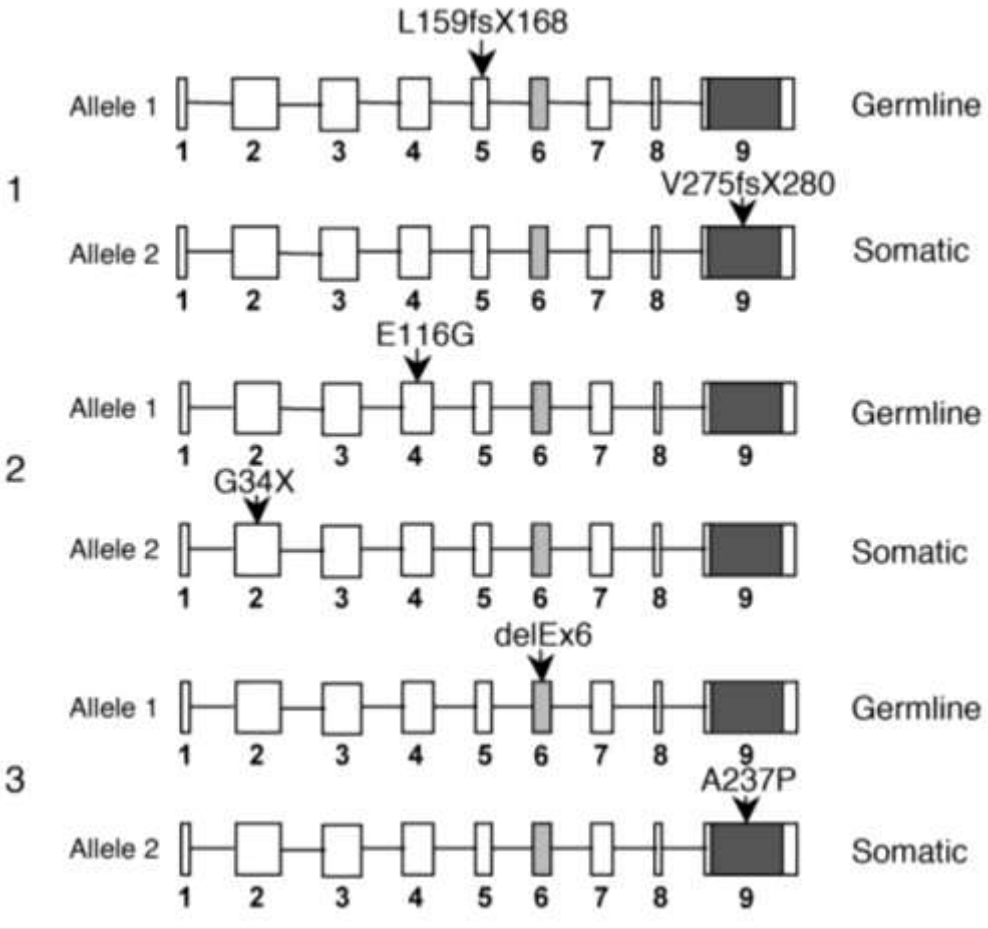


**Mutations somatiques
dans les cellules effectrices
des « IMIDs » ?**

ALPS

- Lympho-prolifération non maligne
- Auto-immunité (++) PTI, AHAI..)
- Ly T Double négatifs : $CD3^+ TCR\alpha\beta^+ CD4^- CD8^-$
 ↑FasL ↑IL10
- Mutation voie FAS

Type 0	ALPS-FAS	Germline homozygous mutations in <i>FAS</i>	
Type Ia	ALPS-FAS	Germ-line heterozygous mutations in <i>FAS</i>	65–70%
Type Im	ALPS sFAS	Somatic mutation in <i>FAS</i>	15–20%
Type Ib	ALPS-FASLG	Germline mutations in <i>FASL</i> (<i>TNFSF6</i>)	<1%
Type IIa	ALPS caspase 10	Germline mutation in <i>CASP10</i>	3–6%
Type III	ALPS-U	No identifiable mutation	20%



Cryopyrinopathies

CINCA/NOMID

Atteinte SNC, Urticaire, Arthropathie
Surdité, att oculaire

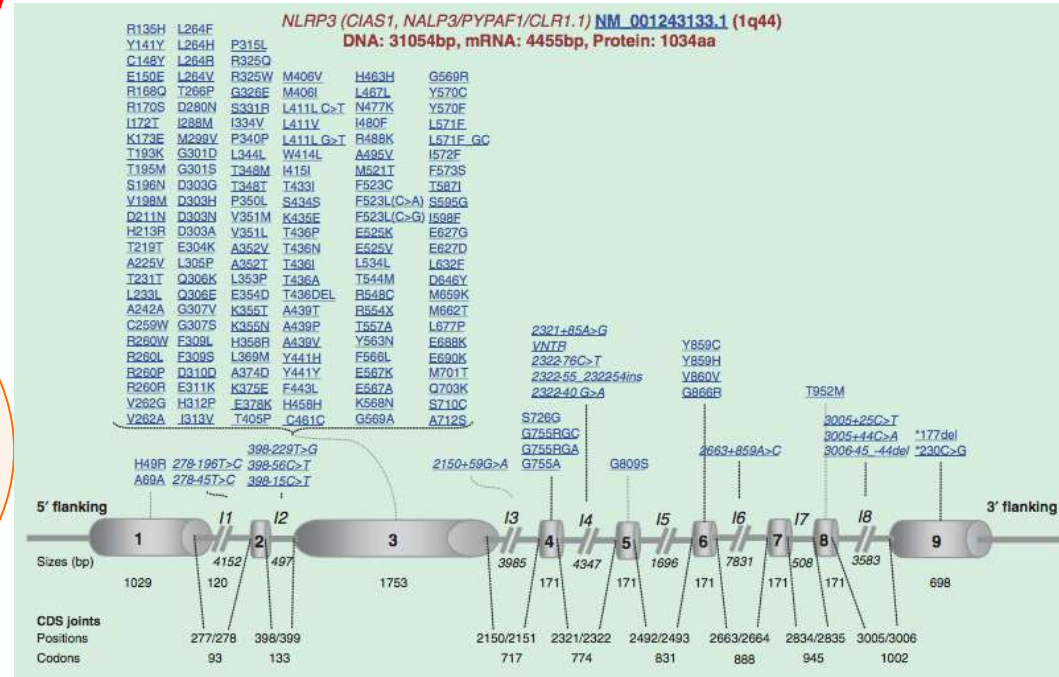


Muckle Wells

Urticaire, Fièvre, Arthralgies,
Céphalée, conjonctivite*
1-3j

Surdité progressive
Amylose AA

Urticaire familial au froid
fièvre, conjonctivite, arthralgies
12-24h



NLRP3

Anti-IL1 ++

CAPS – mutations NLRP3

- Mosaïcisme somatique NLRP3 et CINCA
- Mosaïcisme somatique NLRP3 et MWS (n=7) Nakagawa ARD 2013
- Mosaïcisme myéloïde et CAPS sporadique tardif Zhou AR 2015, Mensa-Vilaro AR 2016
- Mosaïcisme myéloïde et variant SchS (IgGk transitoire !) De Koenig JACI 2014 (n=2)

Mutations NLRP3
Parentale ou Pré-natale

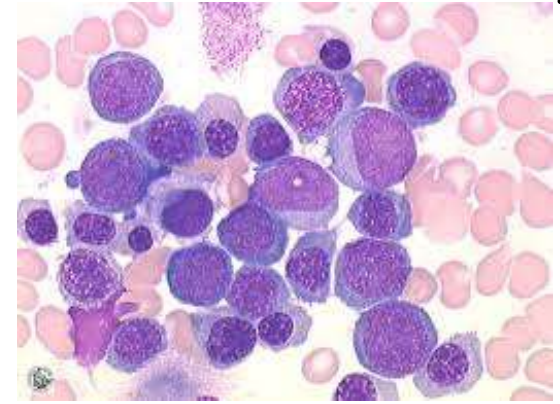
Mutations NLRP3 ou autres
acquise



Mutation héritée
ou de novo



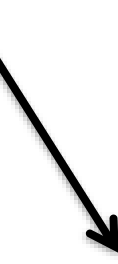
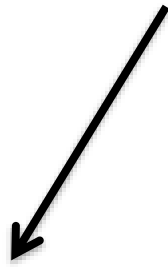
Mosaïcisme



Mutation acquise ?



CAPS classiques

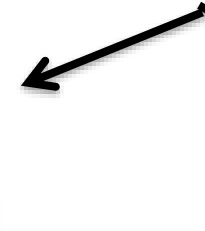


**CAPS tardifs
sporadiques**



Myéloïde

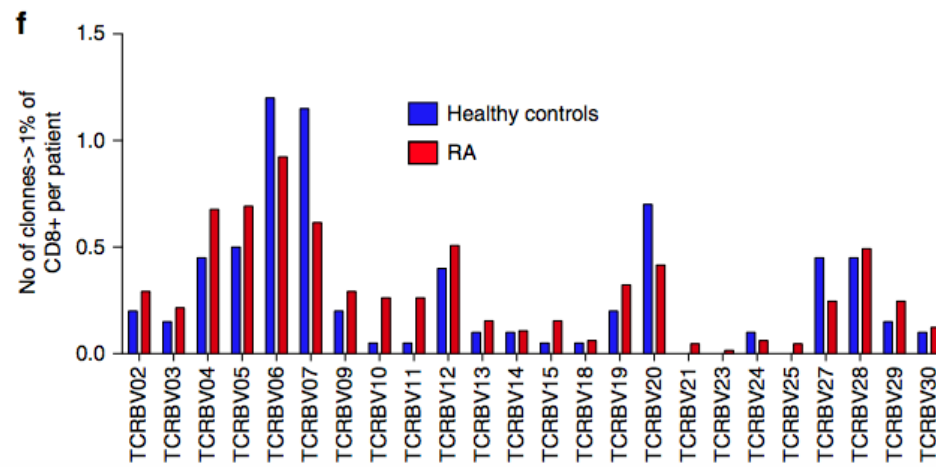
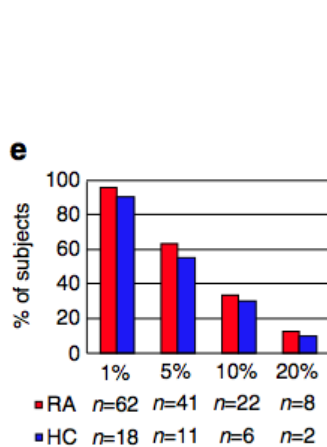
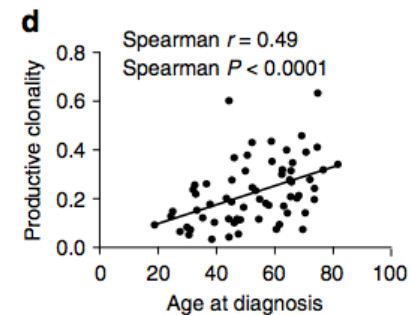
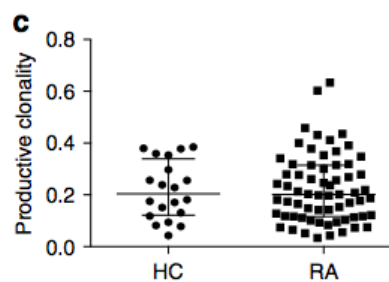
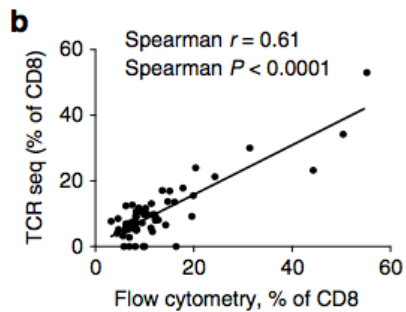
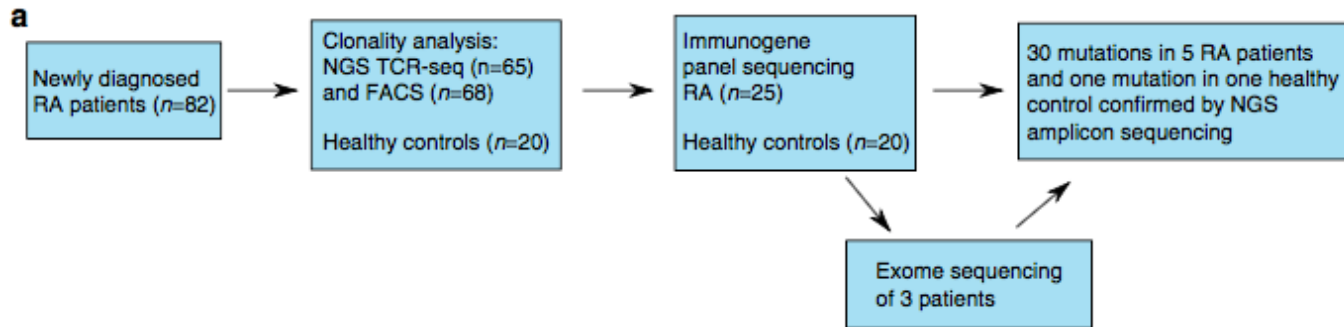
VarSchnitzler
IgG +/-

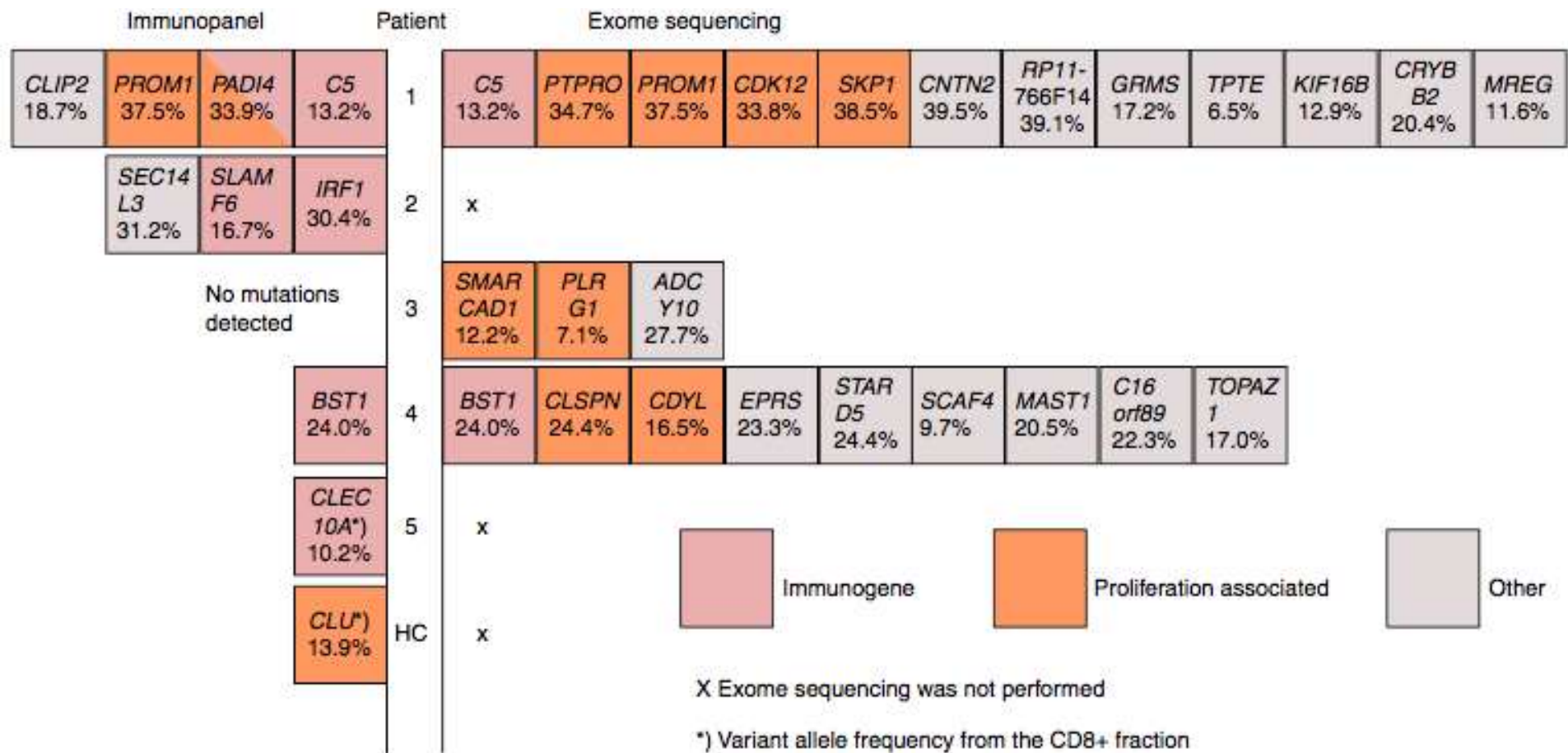


Ly B ?

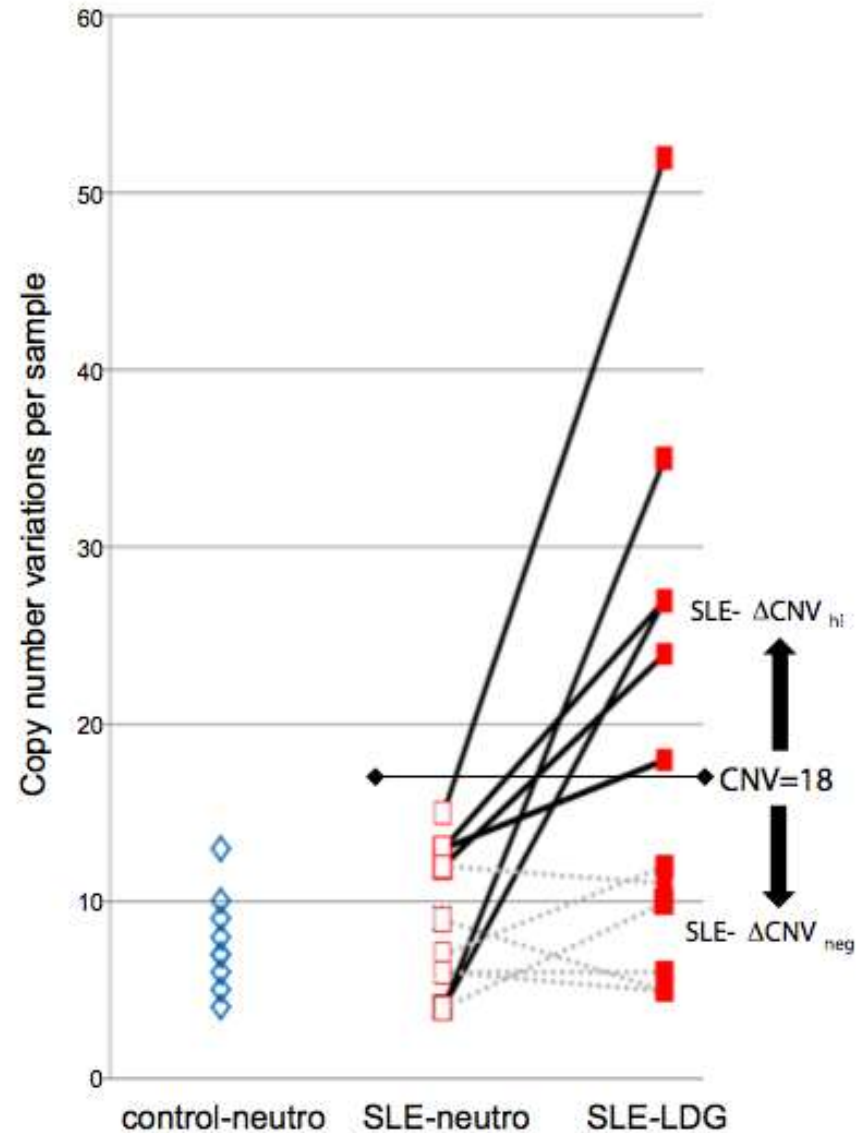
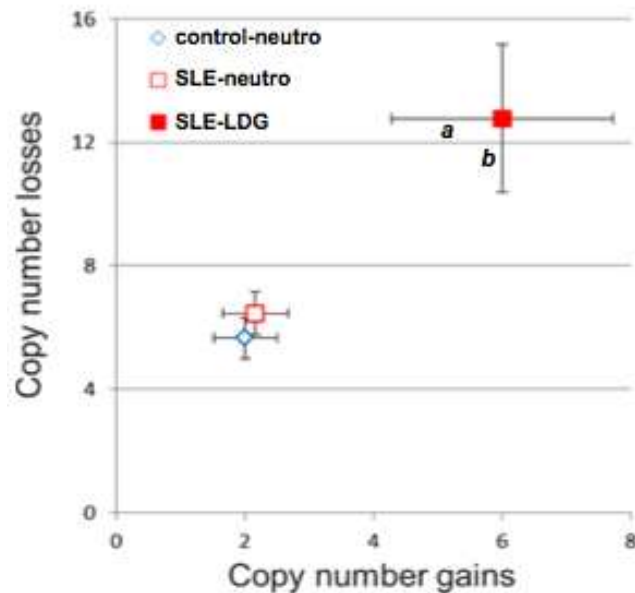
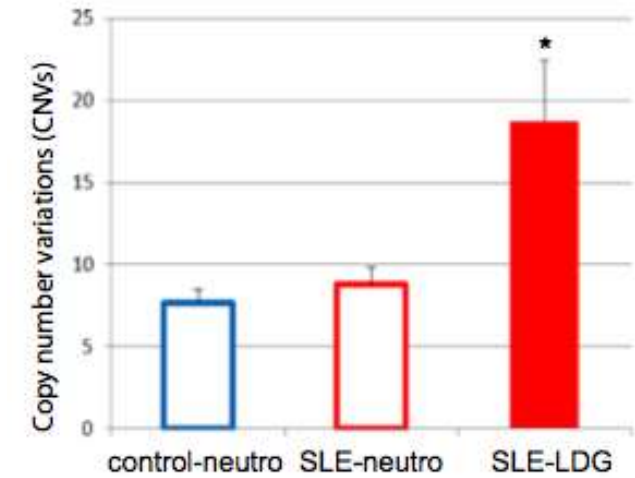
Schnitzler
IgM+ ?

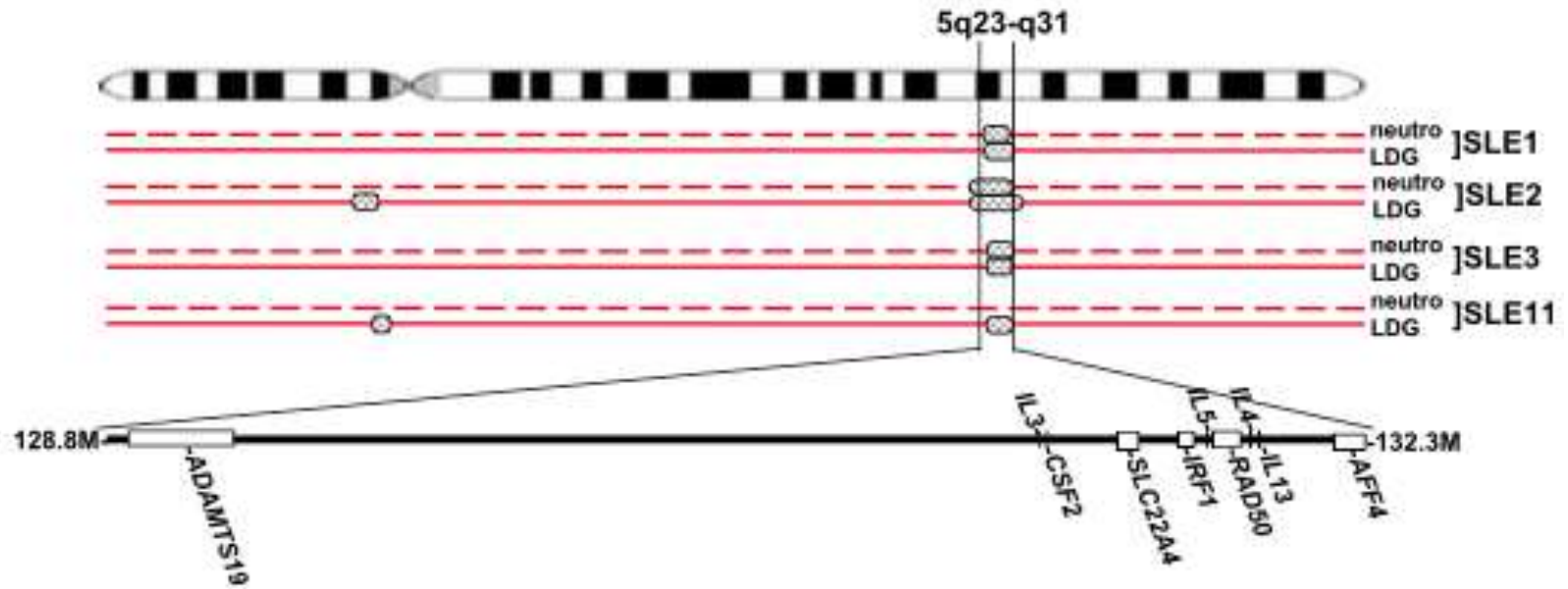
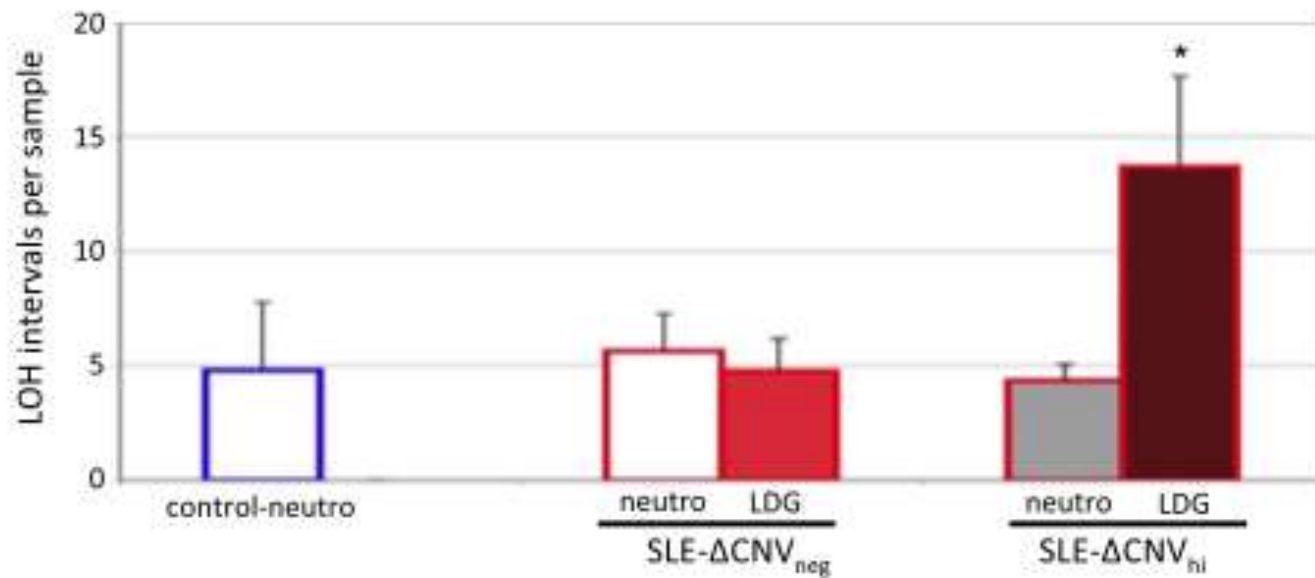






Low Density Granulocytes et Lupus





**Mutations somatique
de la cible antigénique ?**

La victime est le coupable

Les cibles des auto-Ag des maladies systémiques

- Acide Nucléique ++
- Cycle cellulaire ++

Auto-Ac et cancer

- Connectivites associées aux cancers
- Syndromes ParaNéo Auto-immuns (Neuro...)
- Cycle cellulaire : MSA, centromère F ...
- Anti-thyroglobuline et cancer de la Thyroïde

Coherent Somatic Mutation in Autoimmune Disease

Kenneth Andrew Ross*

Department of Computer Science, Columbia University, New York, New York, United States of America

- 16 Sclérodémie avec Cancer

8 anti-CenpB ou Topo1

K tardif

8 anti-RNAPol3 +

K synchrone

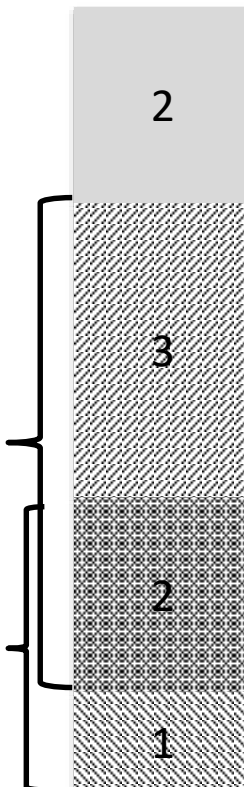
Gene RNAPol3 de la tumeur



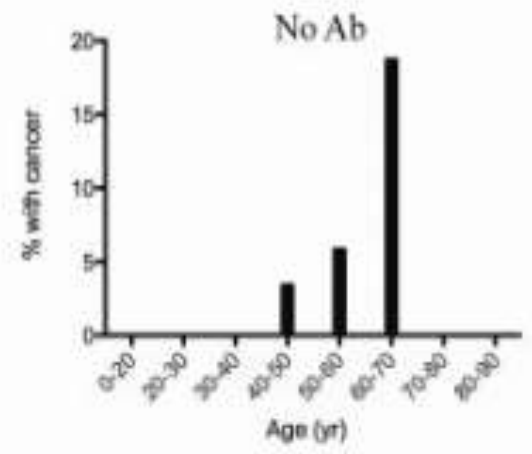
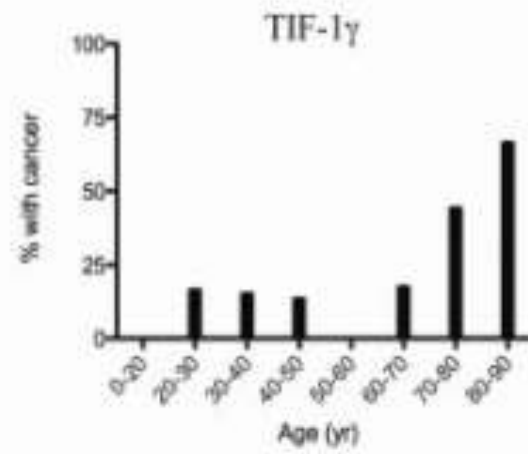
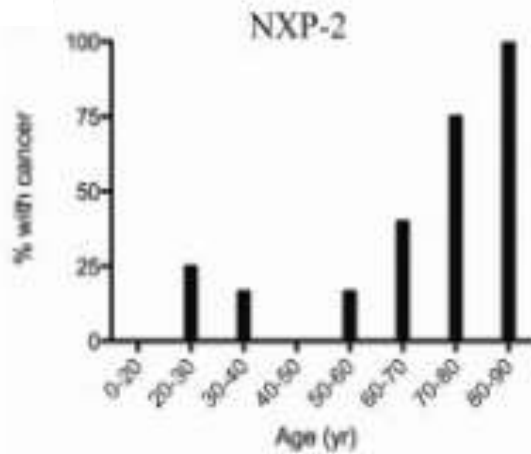
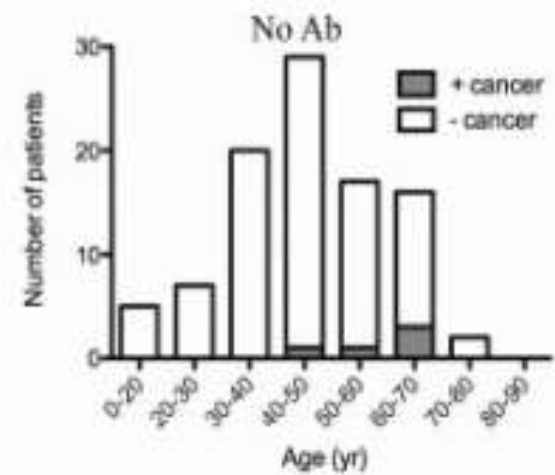
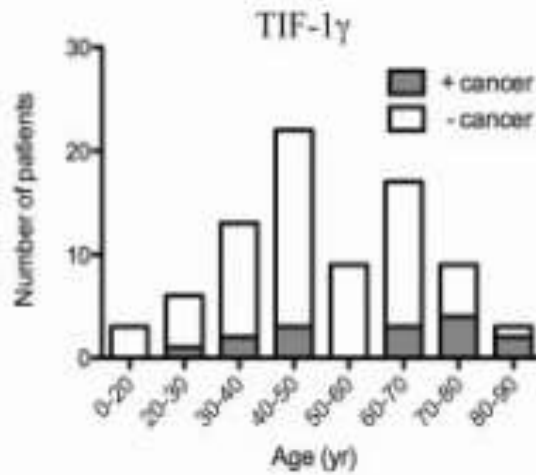
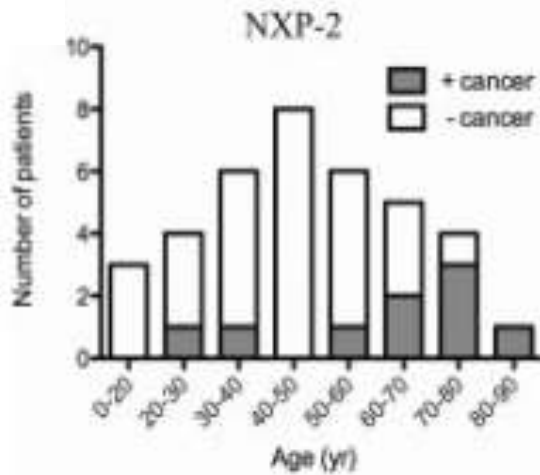
Perte d'hétérozygotie

2/3 : CD4 anti-RNAPol3

mutation somatique subclonale



Dermatomyosite ?



NXP2 = MORC3

TIF-1 γ = TRIM33

STAR

THE

CLONE

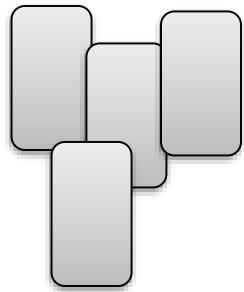
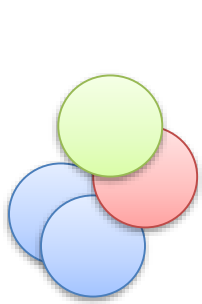
WARS

WARS

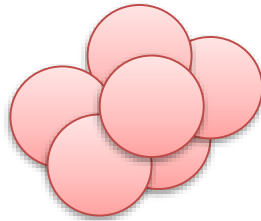
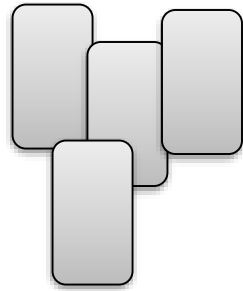
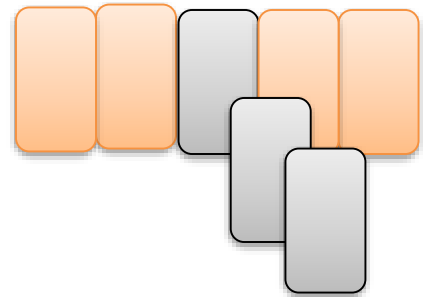
Carcinome

Cell effectrices

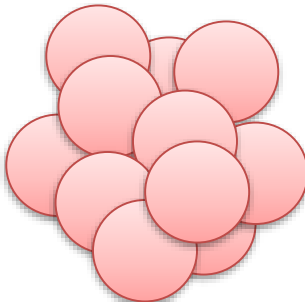
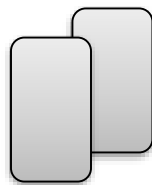
Cell Régulatrices



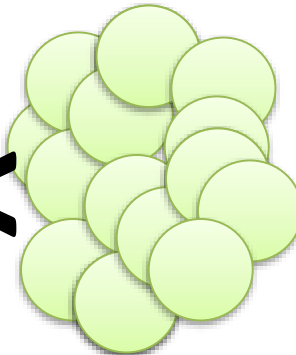
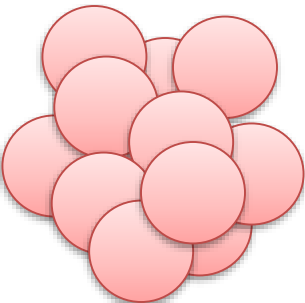
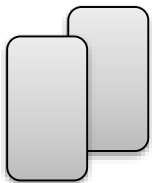
Cancer



**MAI Ac+
Cancer**



**MAI Ac+
Sans Cancer**

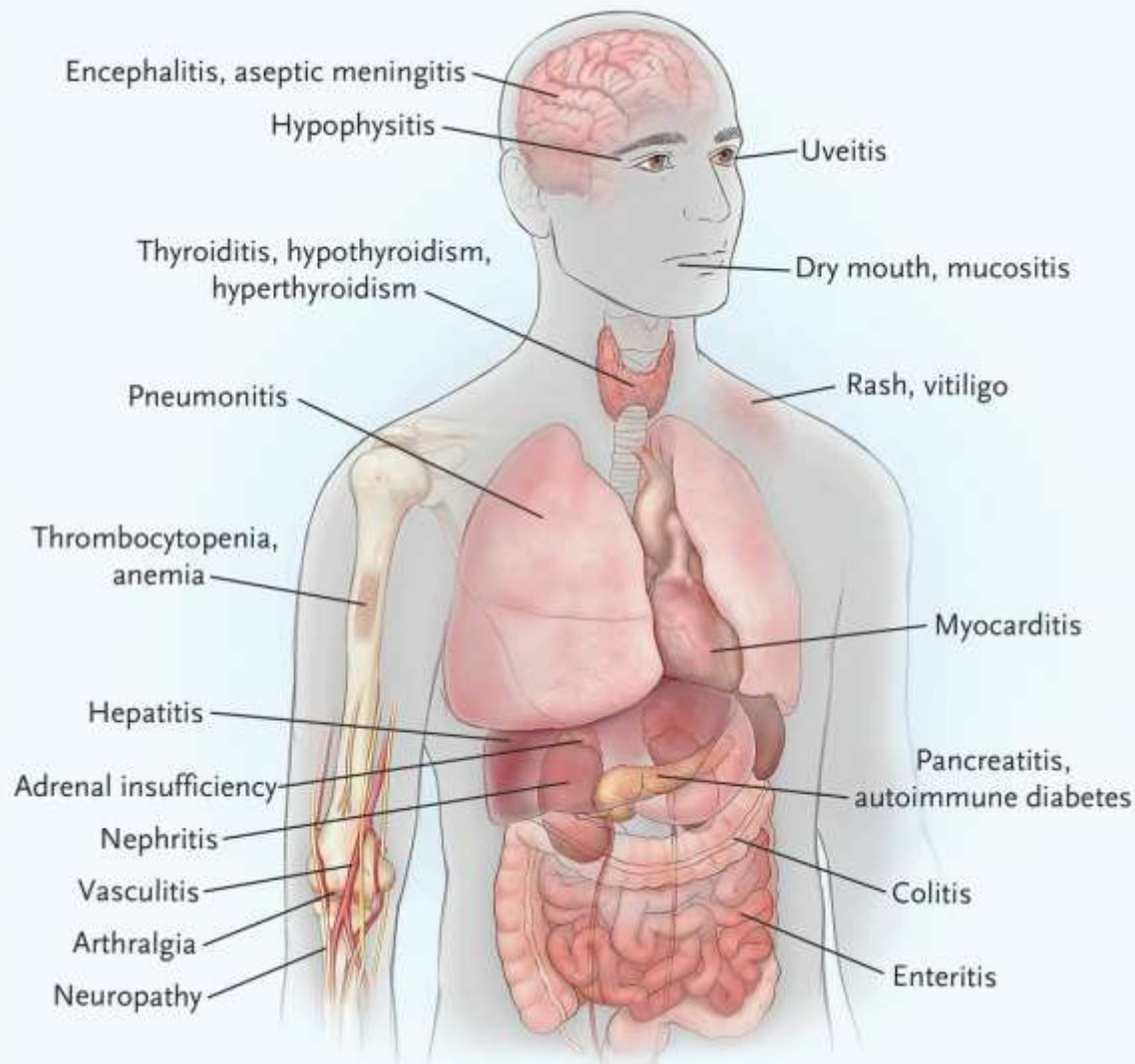


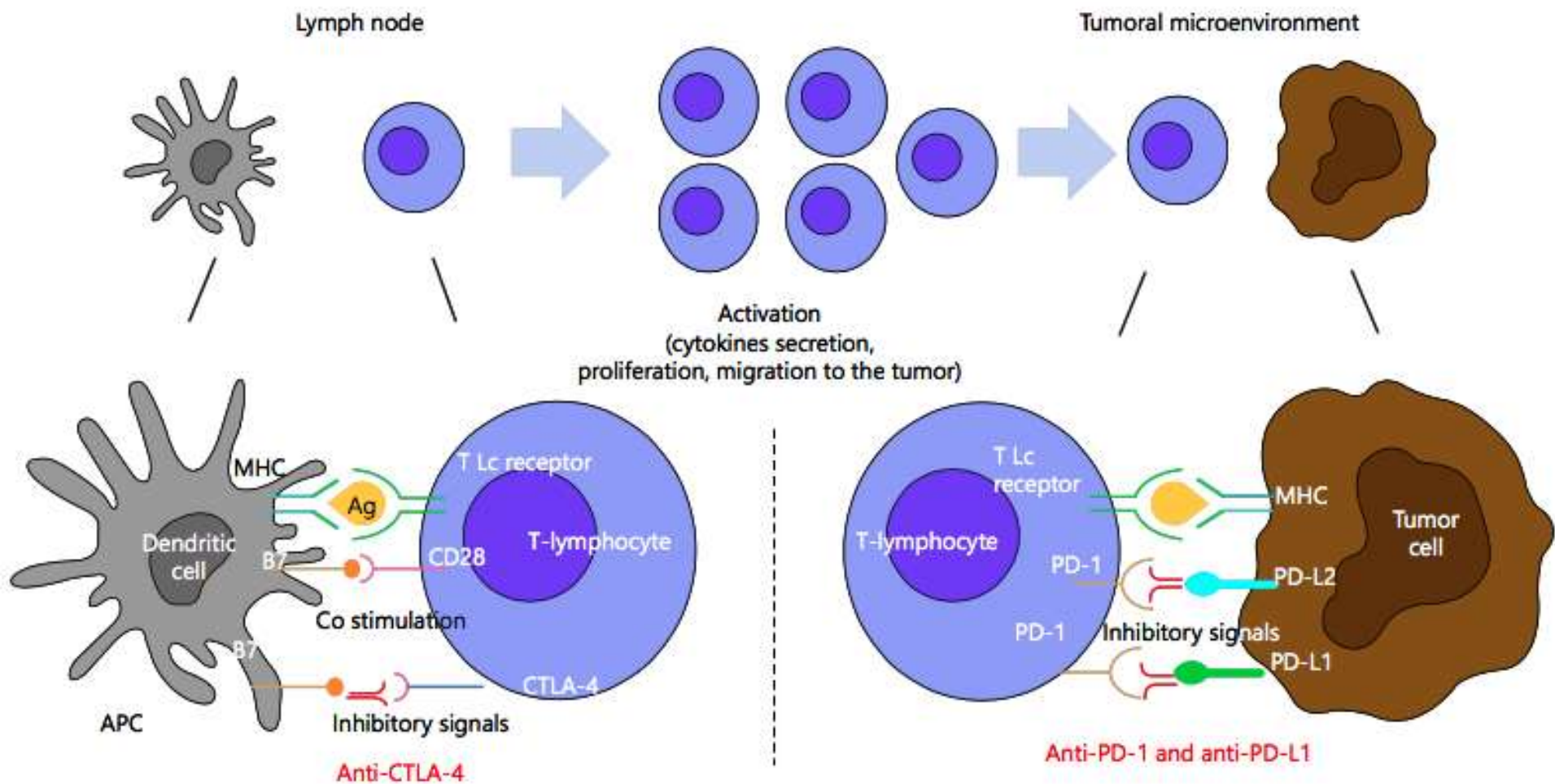
Rien

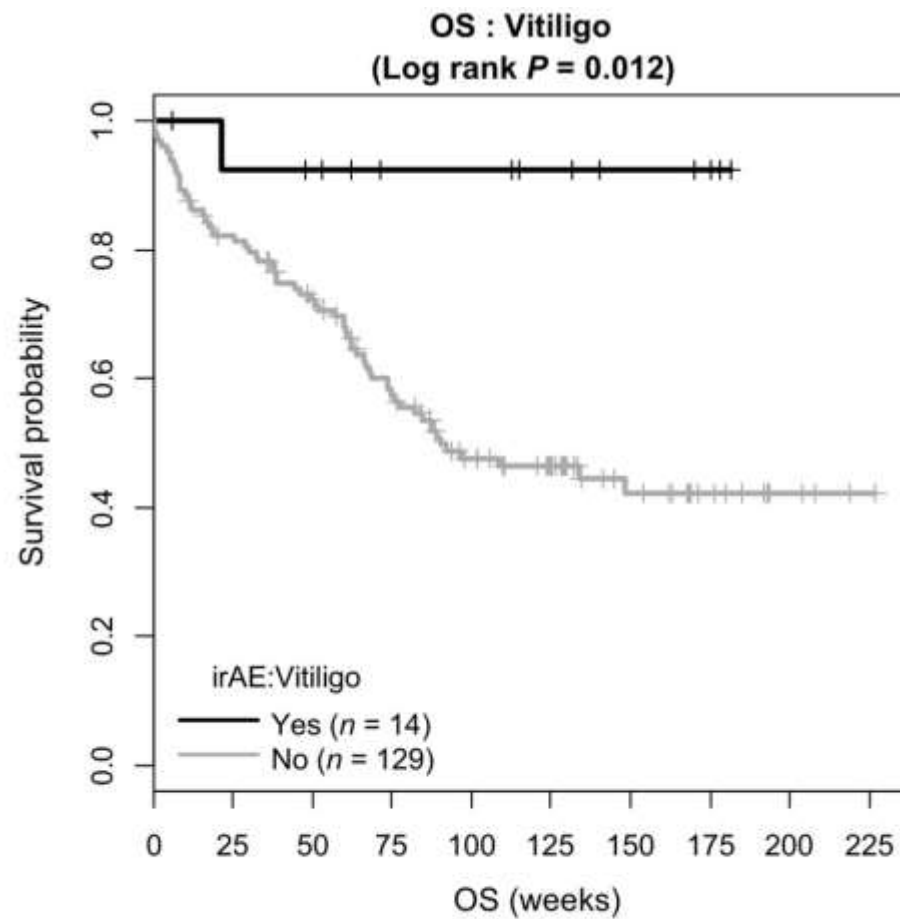
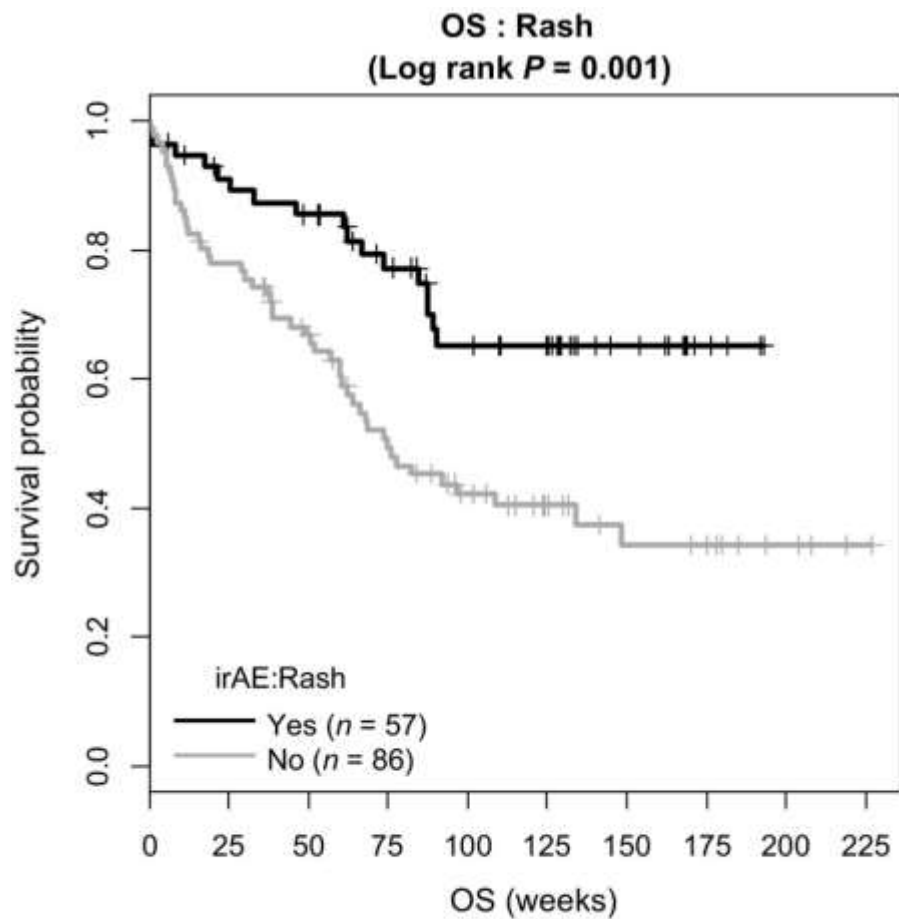
Immune related Adverse Events (irAEs)

Inhibiteurs de Checkpoint

Drug	Target
Ipilimumab	CTLA-4
Nivolumab	PD-1
Pembrolizumab	PD-1
Atezolizumab	PD-L1
Avelumab	PD-L1
Durvalumab	PD-L1







Group	0	25	50	75	100	125	150	175	200	225
Yes	57	49	45	36	27	23	11	4	4	4
No	86	66	52	36	26	17	11	10	4	1

Group	0	25	50	75	100	125	150	175	200	225
Yes	14	12	11	8	8	6	4	3	3	3
No	129	103	86	64	45	34	18	11	4	1

L'auto-immunité est-elle le prix à payer ?



FIN