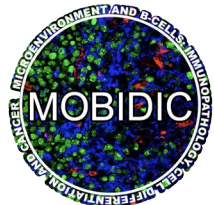
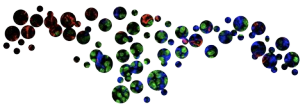
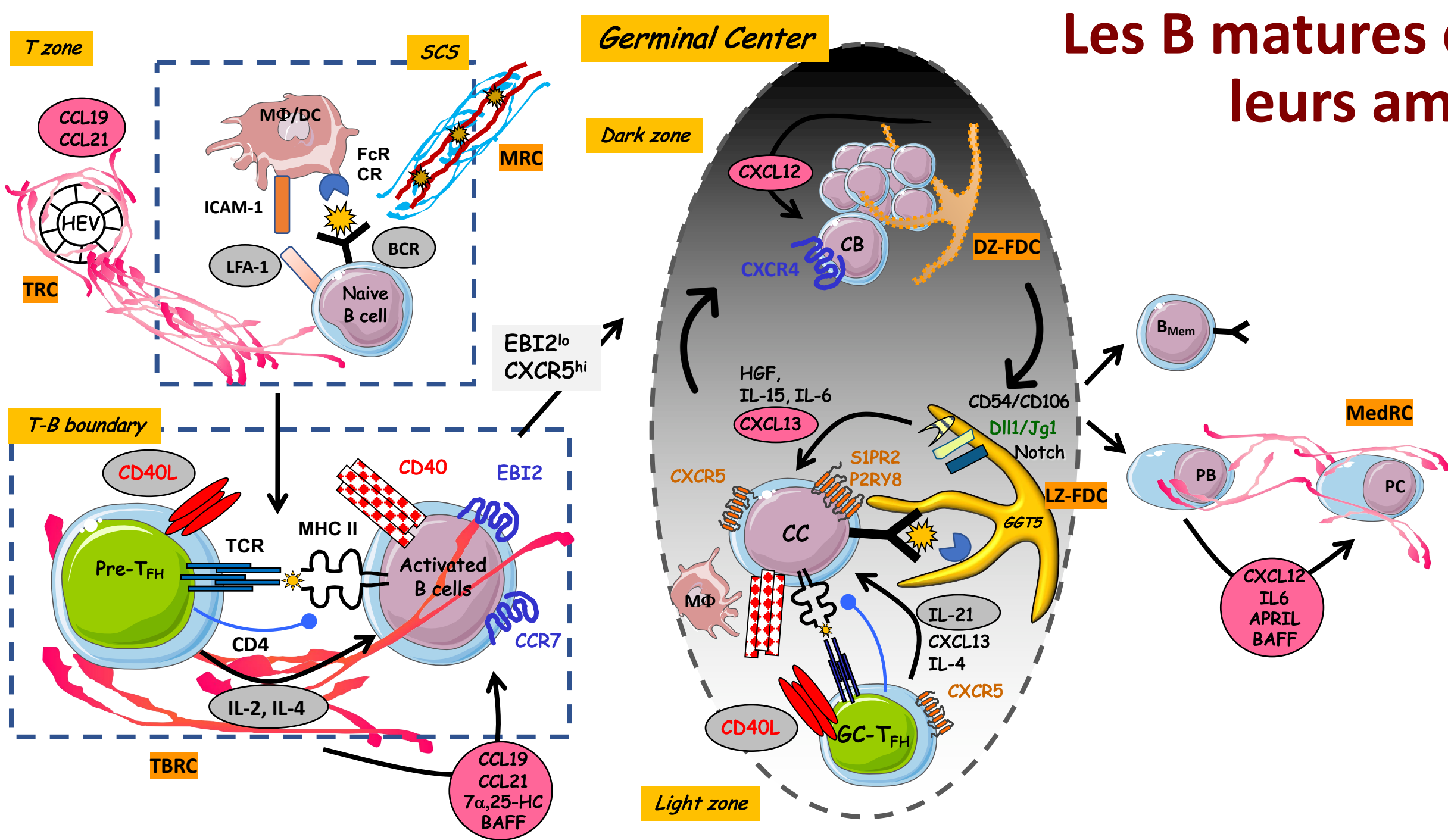


Microenvironnement et Lymphome Folliculaire

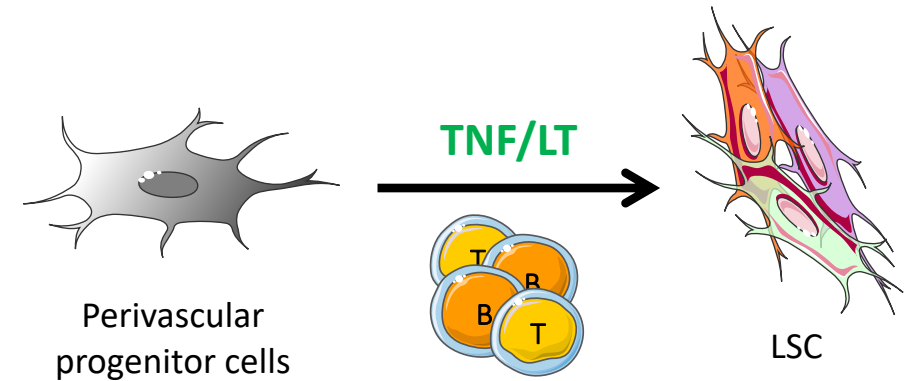
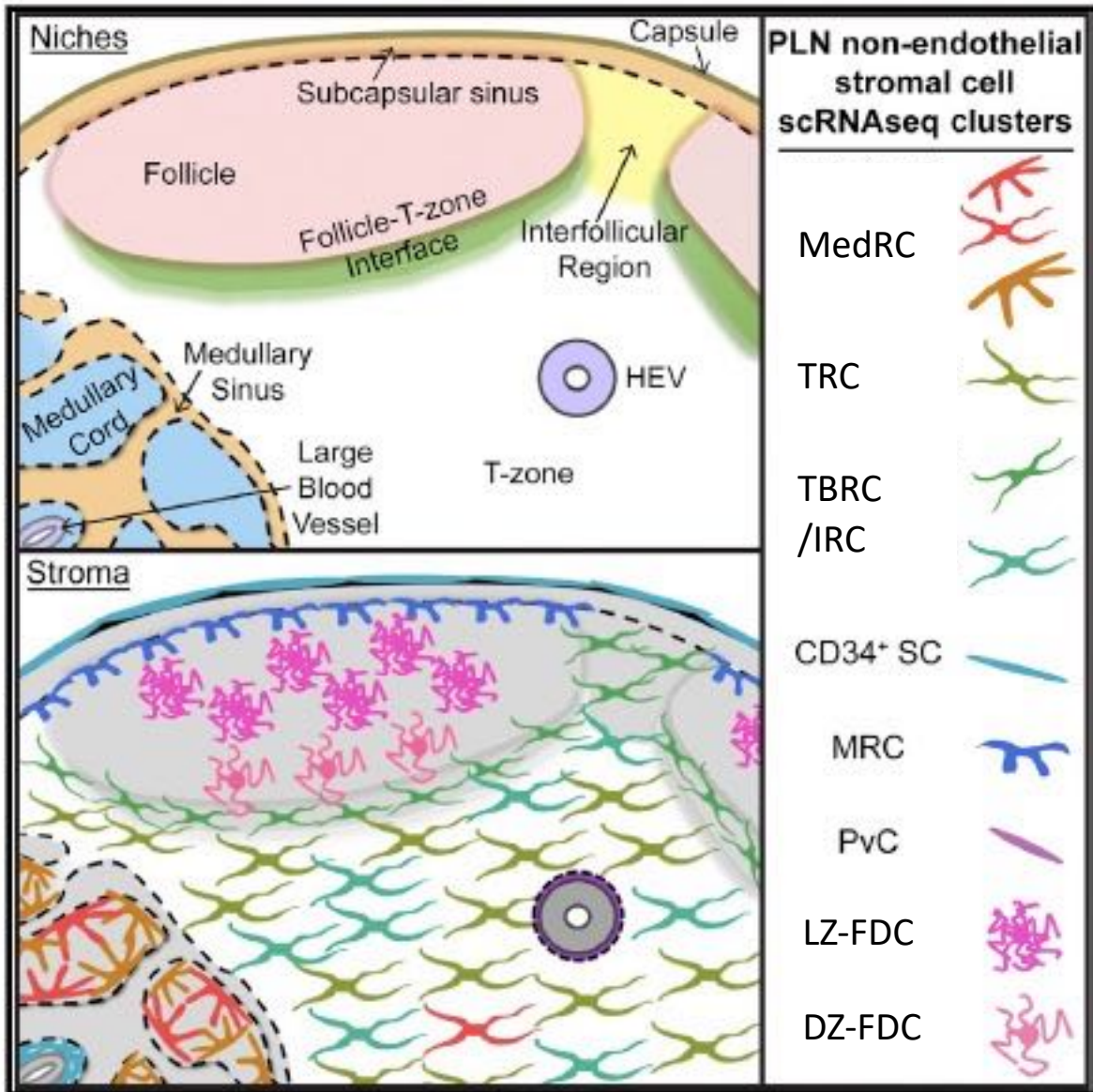
Une histoire de niche



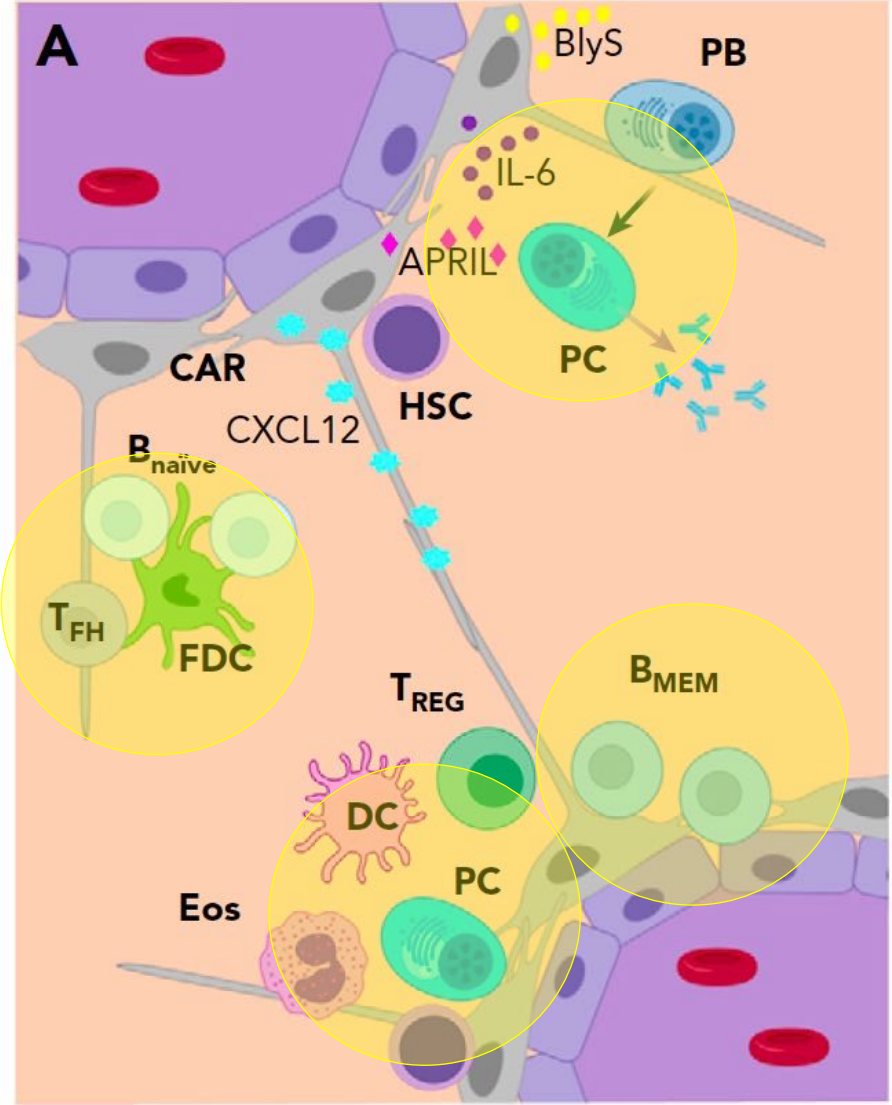
Les B matures et leurs amis



Les cellules stromales lymphoïdes

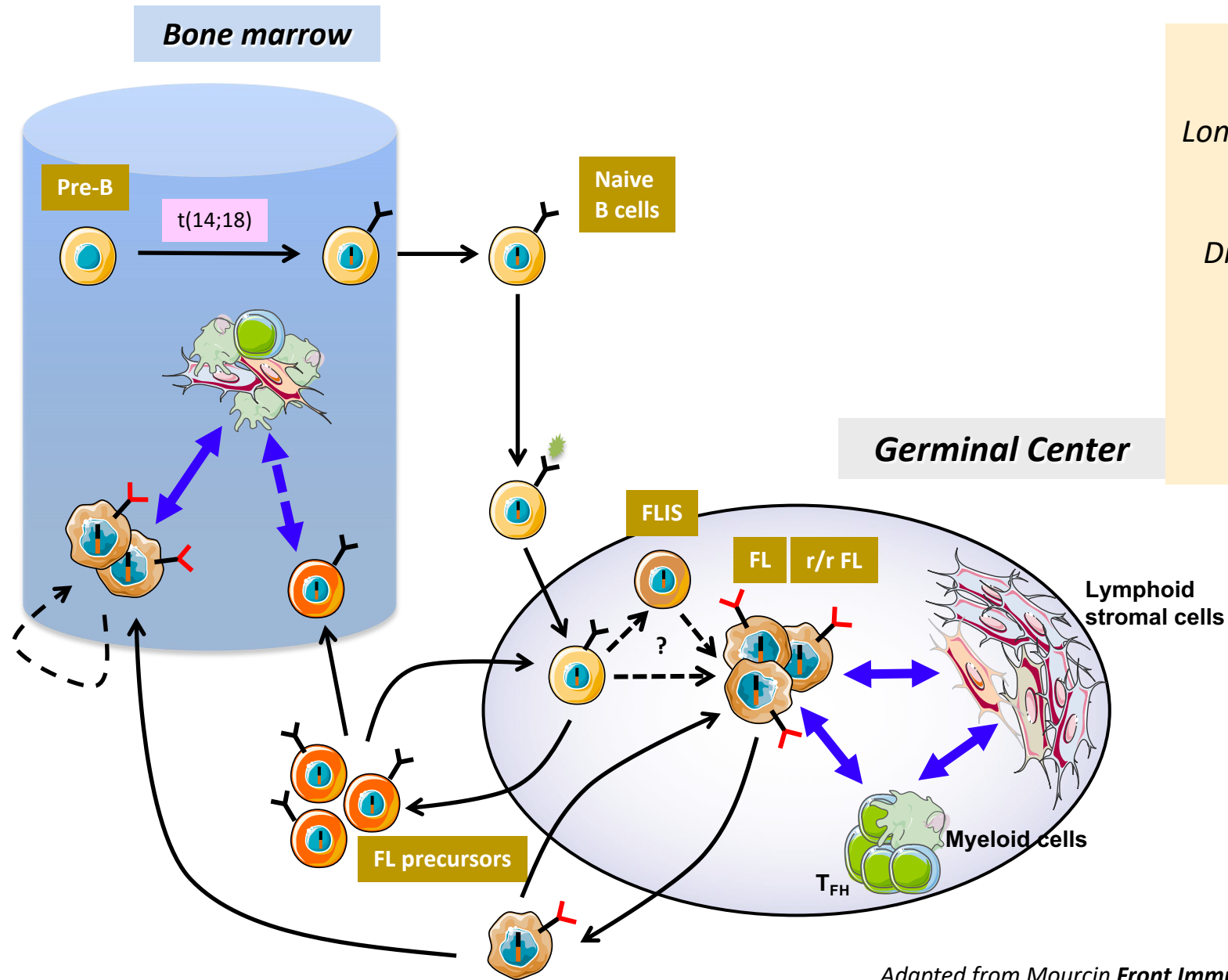


....et dans la MO?



Adapted from Schürch *Blood* 2021; 137: 3015-26

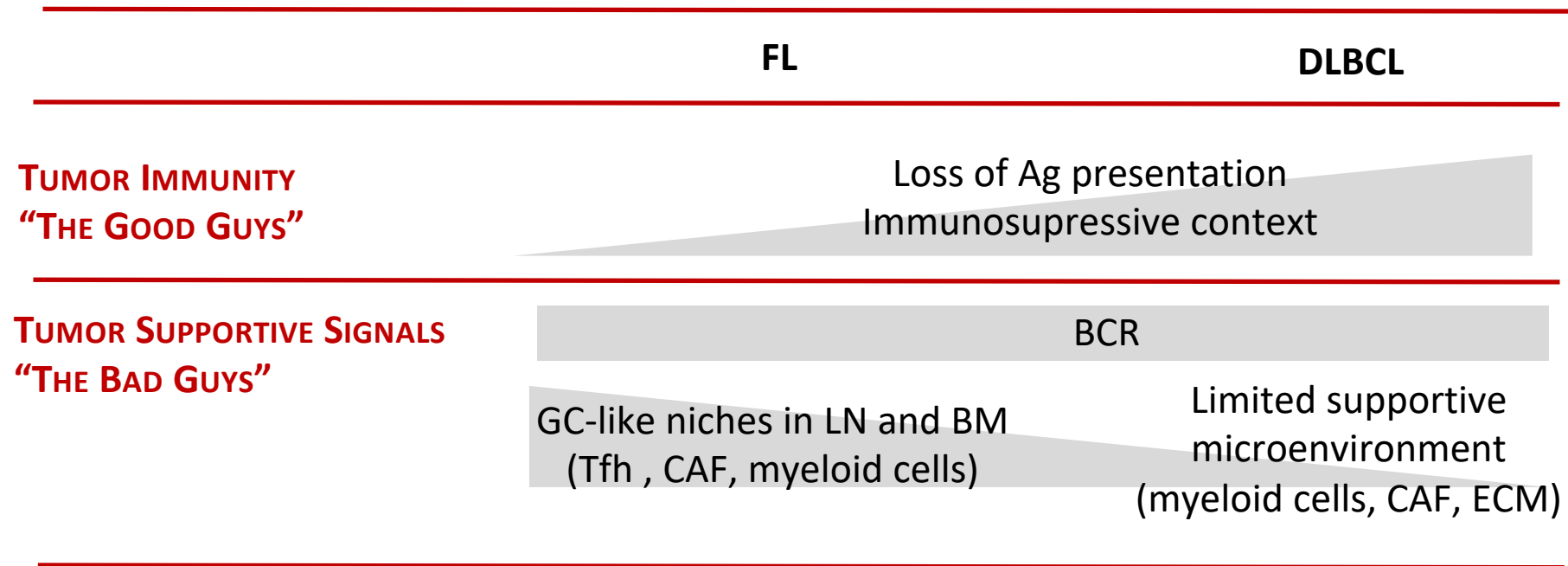
Follicular lymphoma



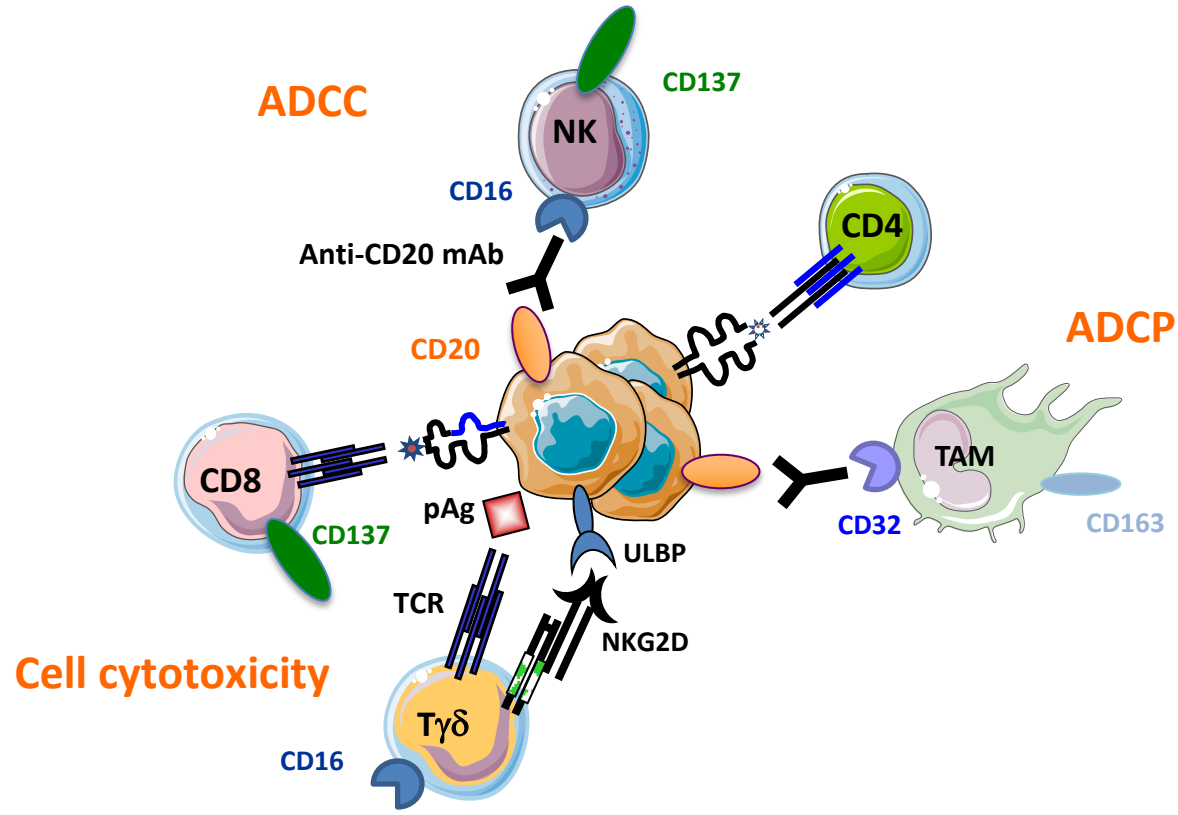
Most frequent indolent lymphoma
Incurable disease
Long-lasting preclinical course with iterative GC transit of
FL precursor cells
Late relapse and transformation
Disseminated disease with BM involvement (70% cases)

Ectopic lymphoid-like TME in invaded BM
Specific B-cell features in LN vs BM
Most FL-like mouse models rely on non B-cell specific
Bcl2 deregulation

Le microenvironnement dans les lymphomes du GC



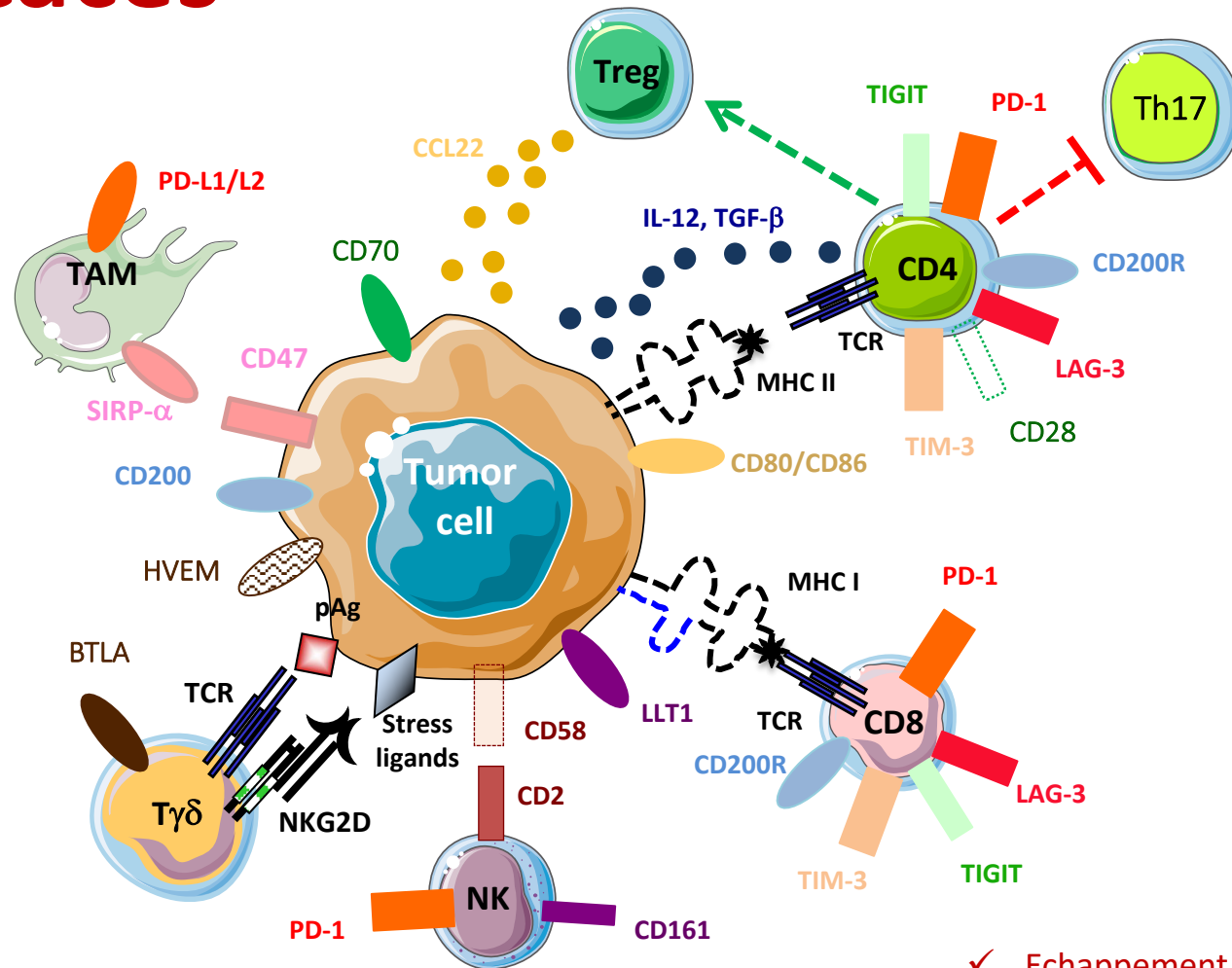
Les good guys...



ANTI-TUMORAL MICROENVIRONMENT

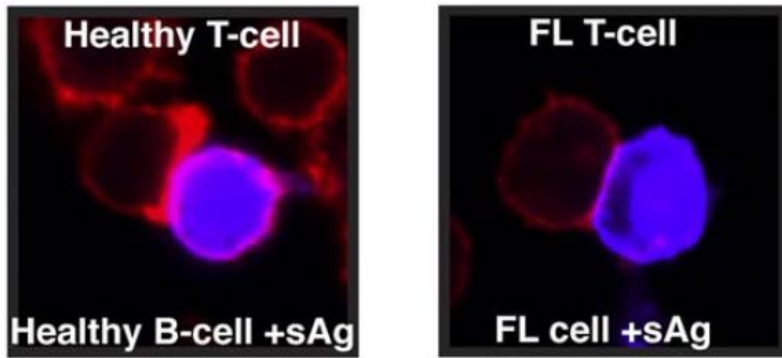
- ✓ Efficacy of immunotherapy-based strategies
- ✓ Identification of T cells targeting Ig-derived peptides
- ✓ Synergy between anti-CD20 and anti-CD137 Abs
- ✓ High immune infiltration is of good prognosis

...sont inefficaces

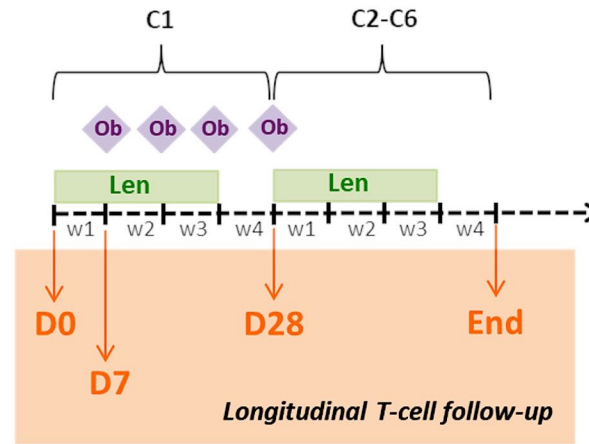


- ✓ Echappement à la reconnaissance par le SI
- ✓ Exhaustion T et inhibition NK
- ✓ Echappement à l'ADCP
- ✓ Amplification de Treg (peu de cellules myéloïdes suppressives / DLBCL)

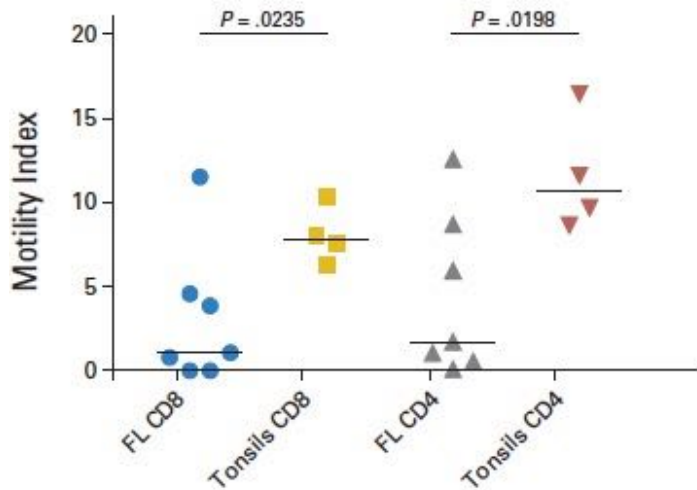
...sont inefficaces



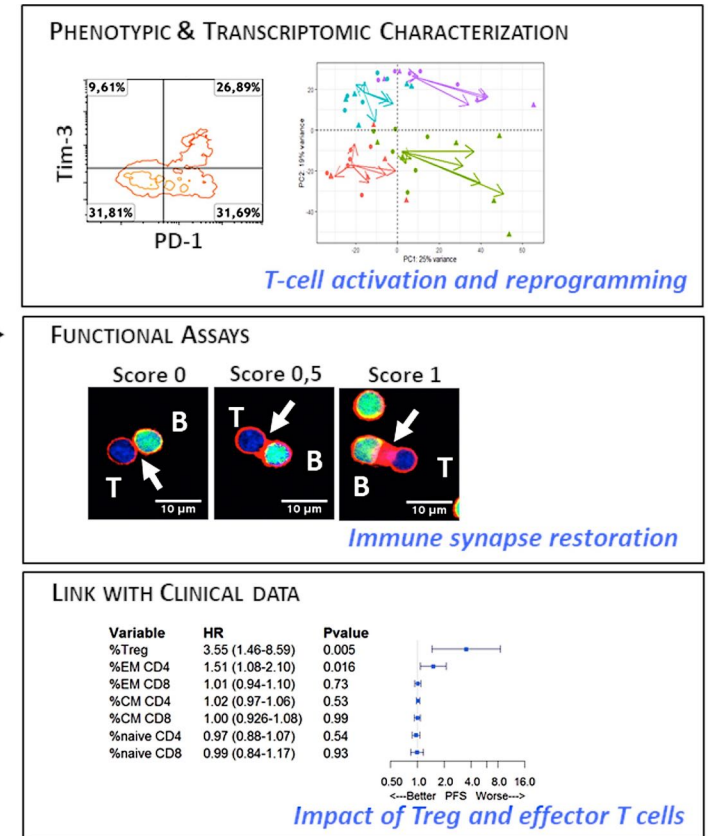
Ramsay *Blood* 2009



R/R and first-line FL
71 patients



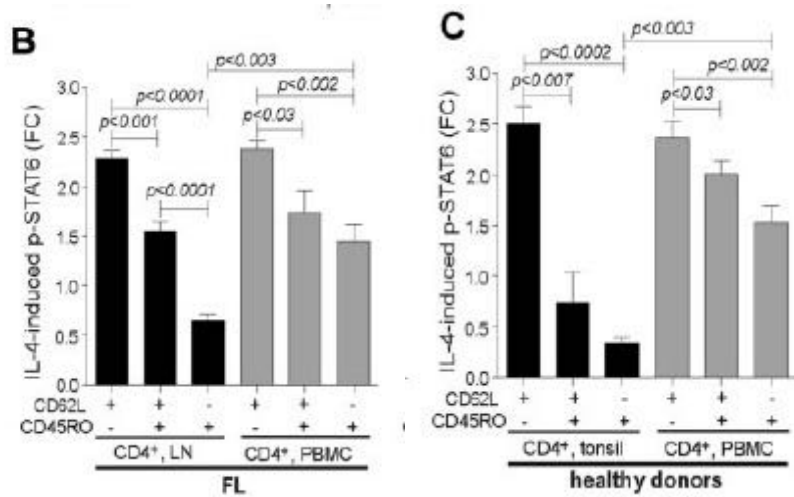
Kiaii *JCO* 2013



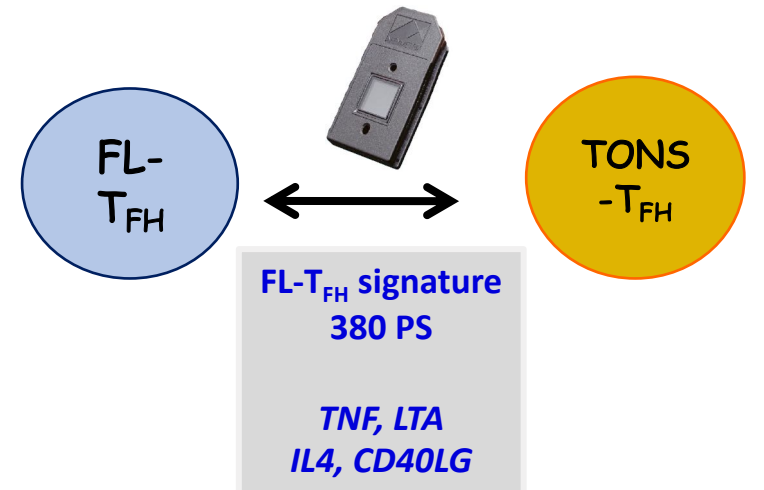
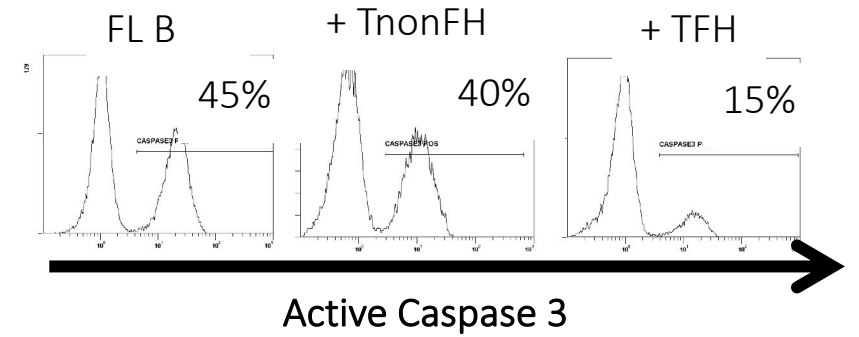
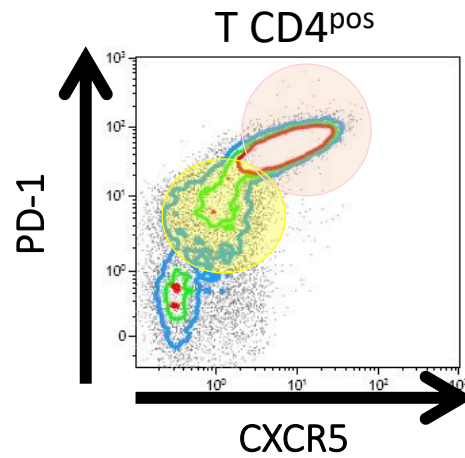
Ménard *Blood Adv* 2021

- ✓ Altération de la synapse B/T (reversible sous Len)
- ✓ Défauts intrinsèques de motilité T

Et les choses ne sont pas si simples!

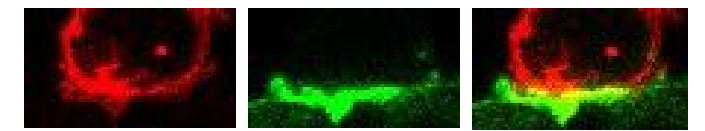
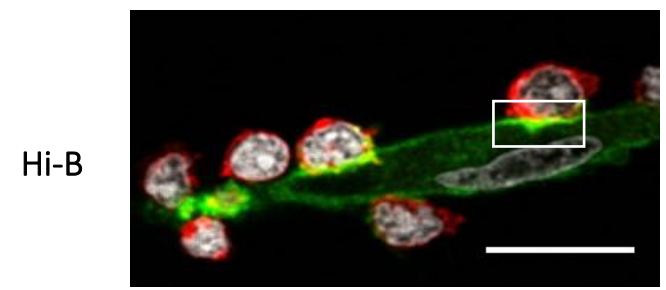
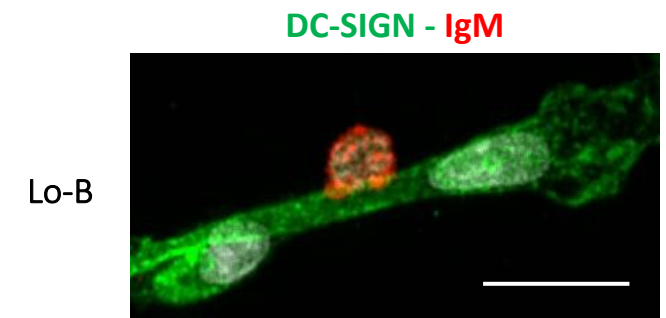
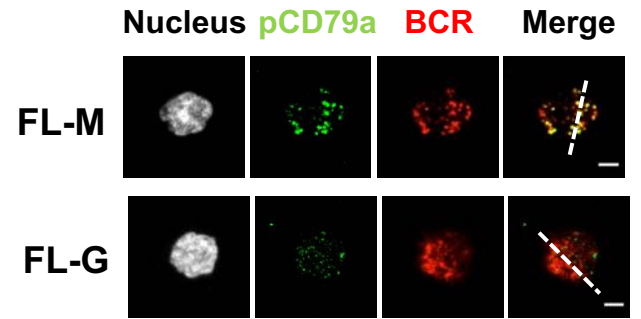
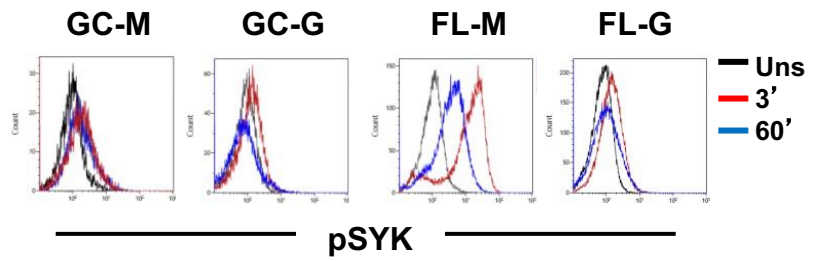
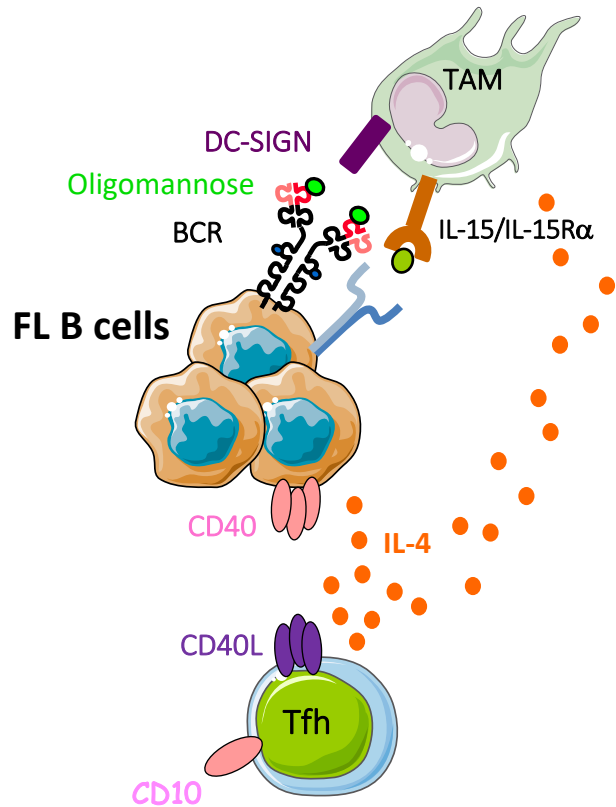


Myklebust Blood 2013; 121: 1367

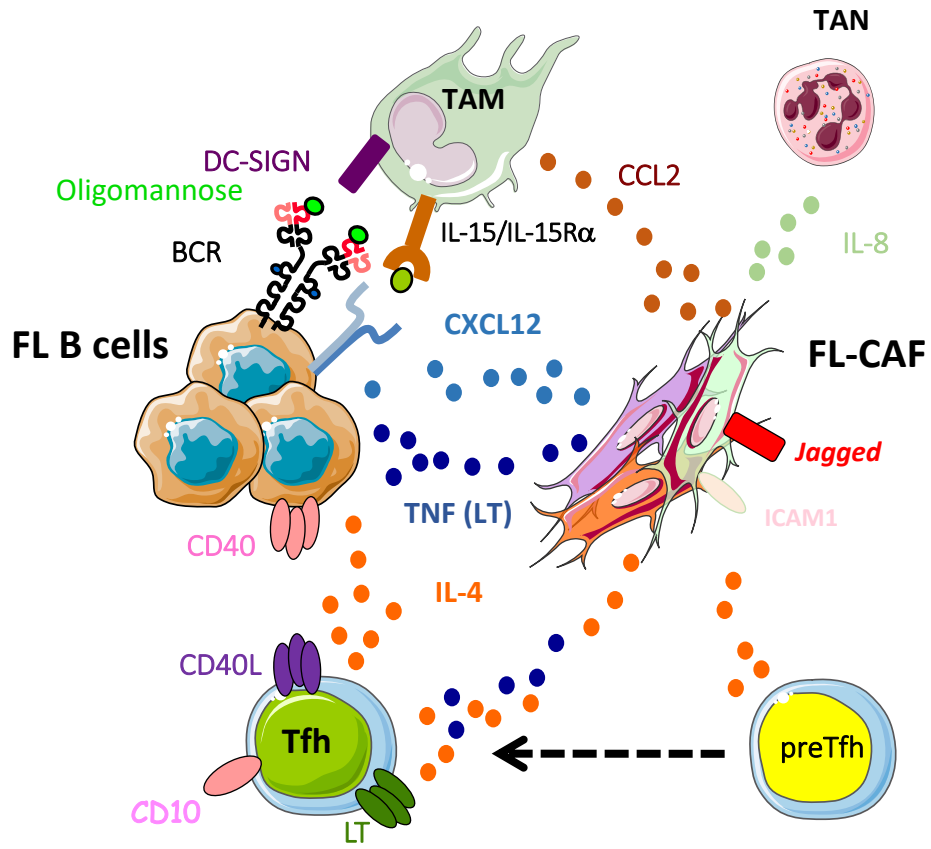


- ✓ Expansion d'un compartiment Tfh fonctionnel en plus de la dysfonction des TCD4nonFH et des TCD8
- ✓ FL-Tfh ont un GEP spécifique

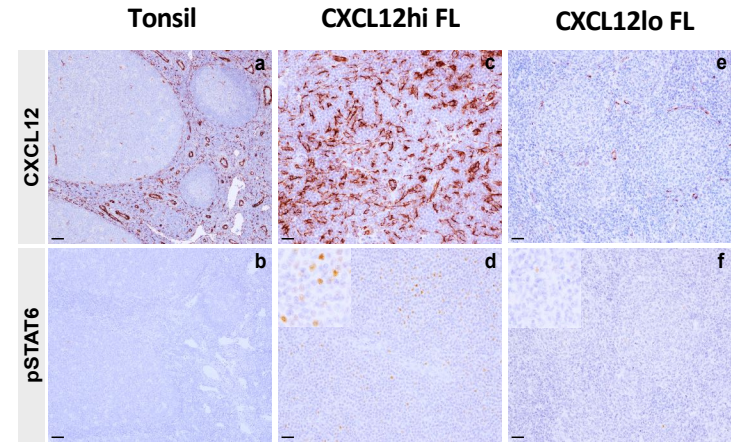
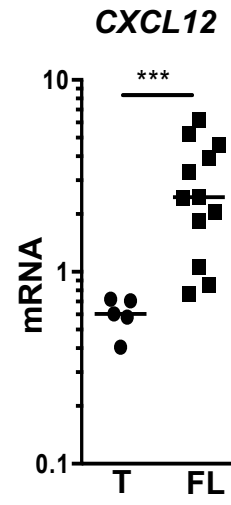
Les bad guys



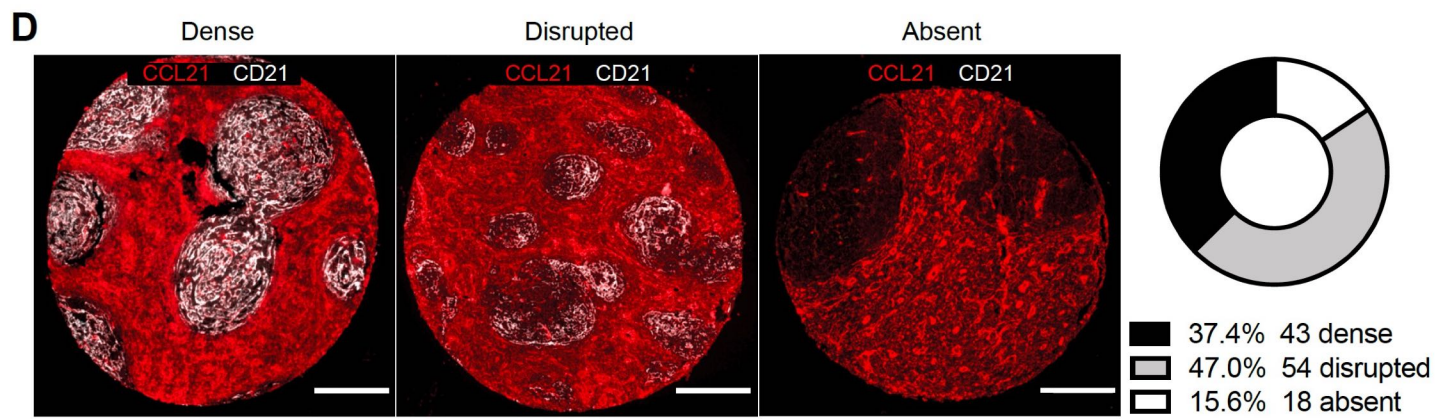
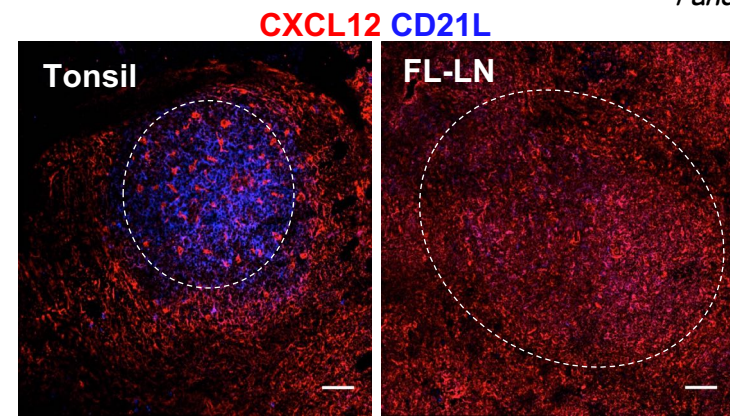
- ✓ **Signal 1: FL-Tfh (CD40/IL-4)**
- ✓ **Signal 2: BCR (oligomannose-DC-SIGN/IgM)**
- i) N-gly dans 85% des cas (précoce, conservé)-Macrophages
- ii) Pression de sélection pour le maintien d'une IgM de surface (?)



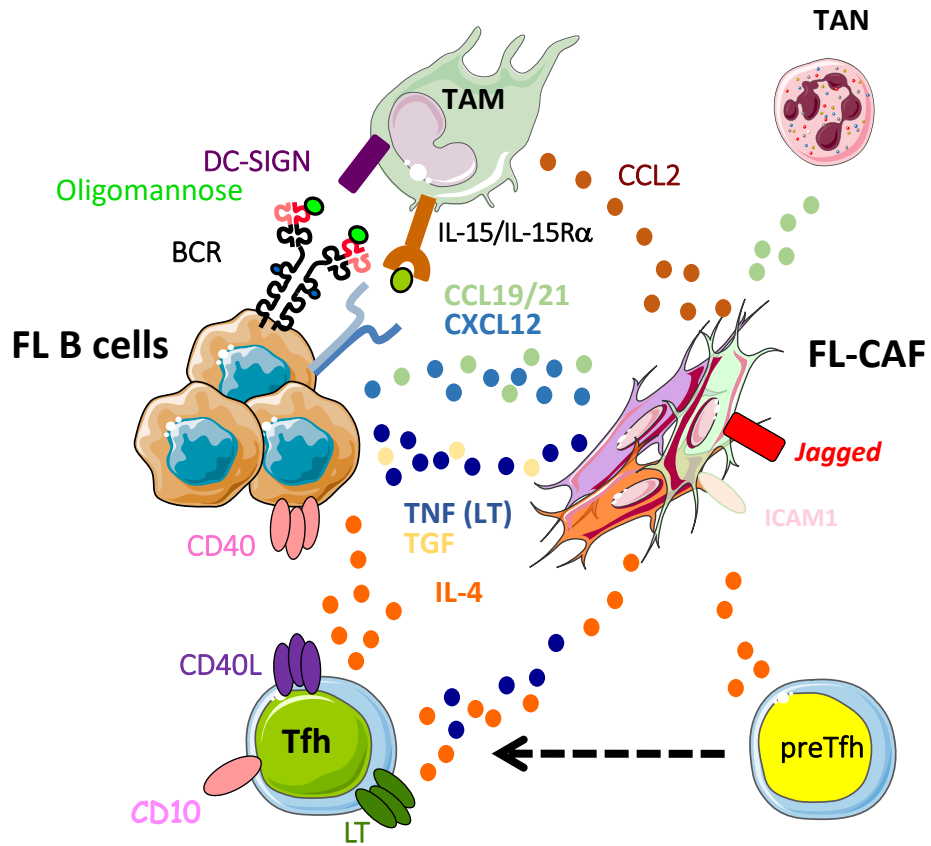
- ✓ **Signal 1: FL-Tfh (CD40/IL-4)**
- ✓ **Signal 2: BCR (oligomannose-DC-SIGN/IgM)**
- ✓ **Signal 3: CAF (CCL2/IL8/CXCL12)**



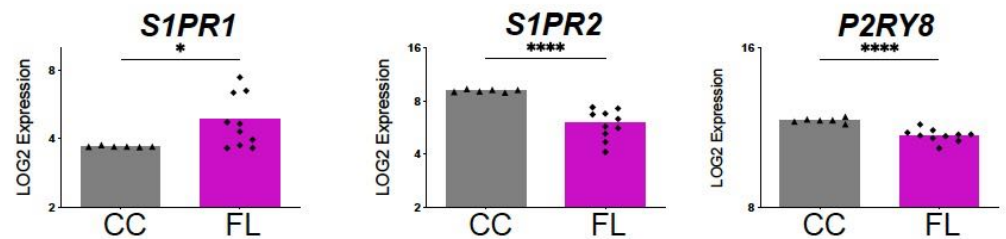
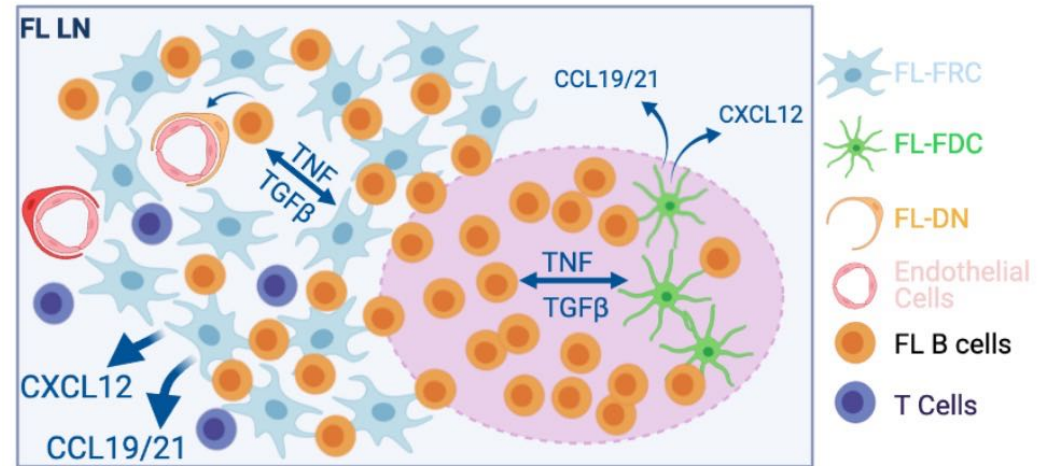
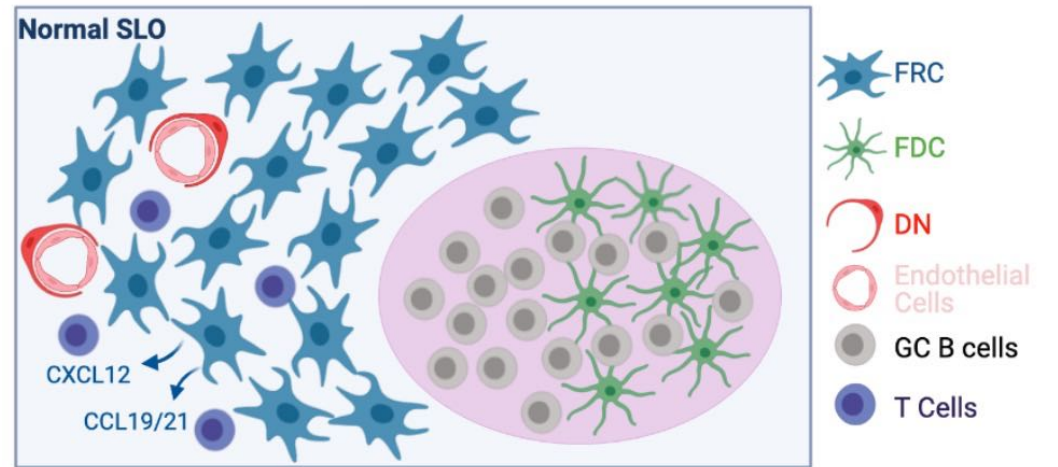
Pandey Blood 2017



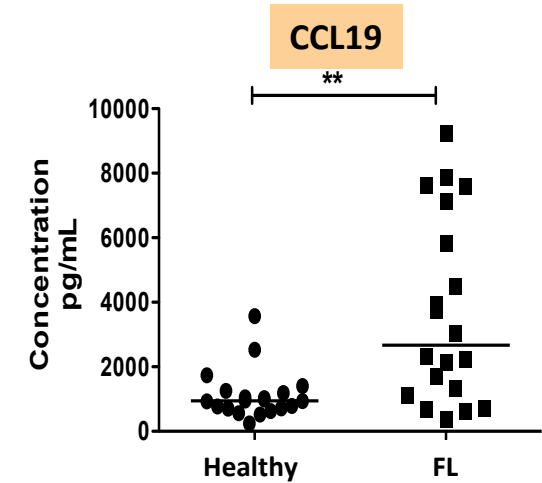
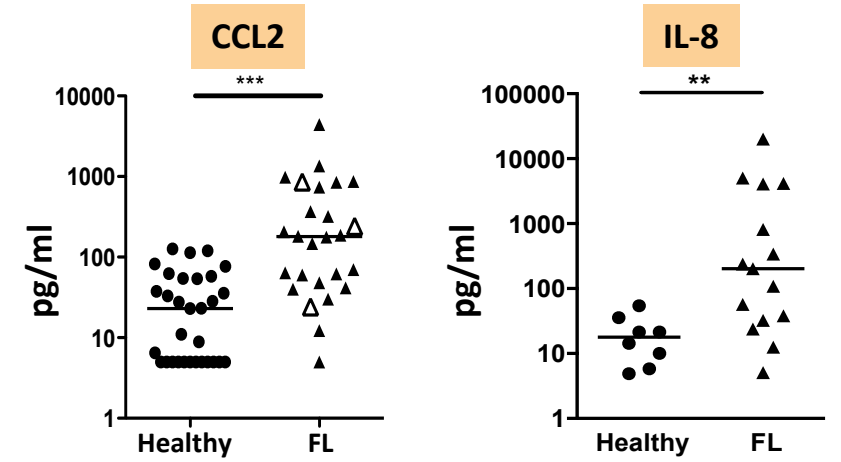
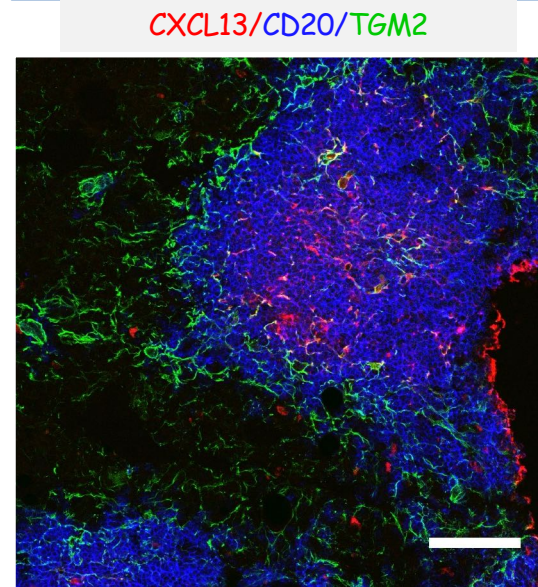
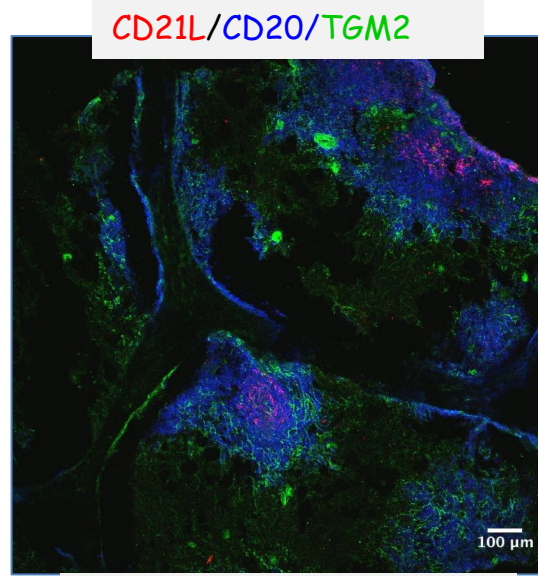
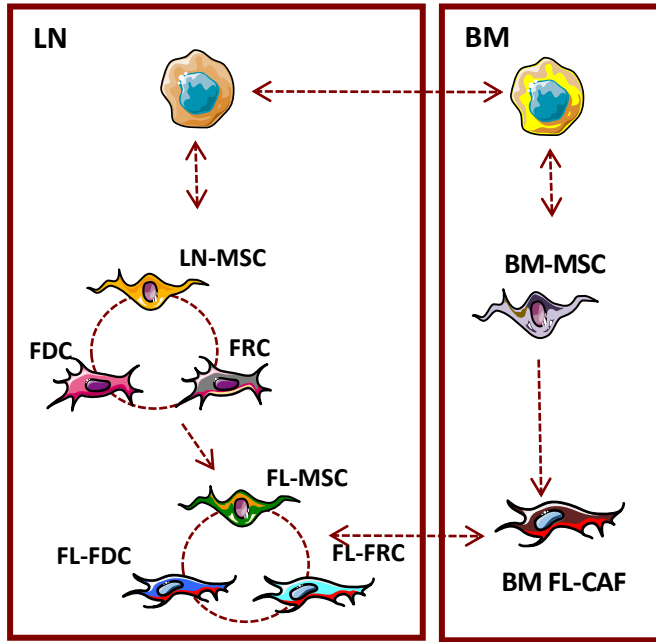
Mourcin Immunity 2021



- ✓ **Signal 1: FL-Tfh (CD40/IL-4)**
- ✓ **Signal 2: BCR (oligomannose-DC-SIGN/IgM)**
- ✓ **Signal 3: CAF (CCL2/IL-8/CXCL12/CCL21)**

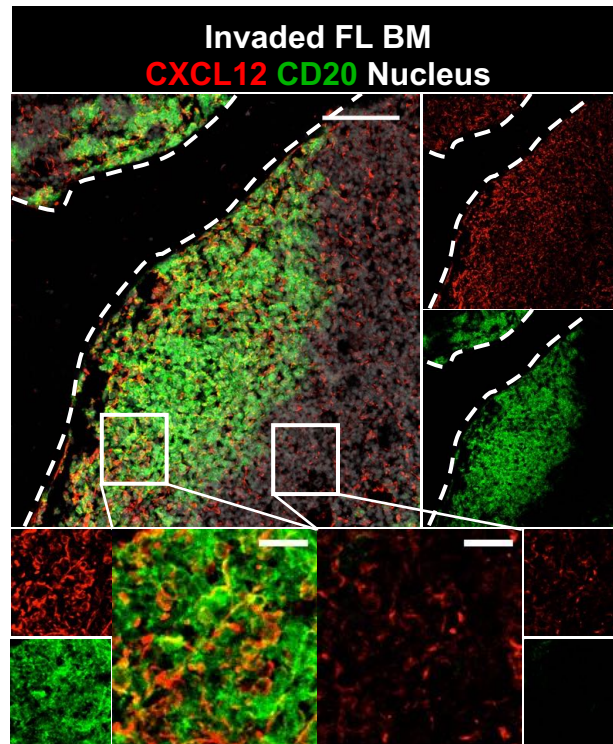
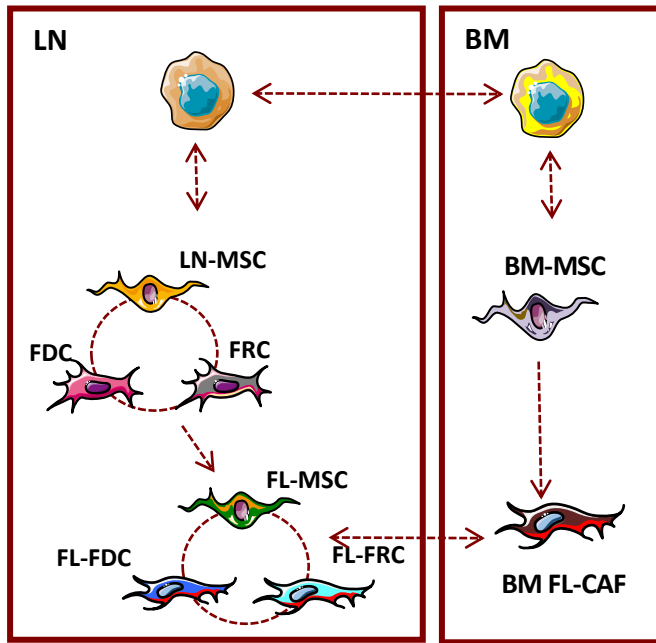


...et dans la MO?

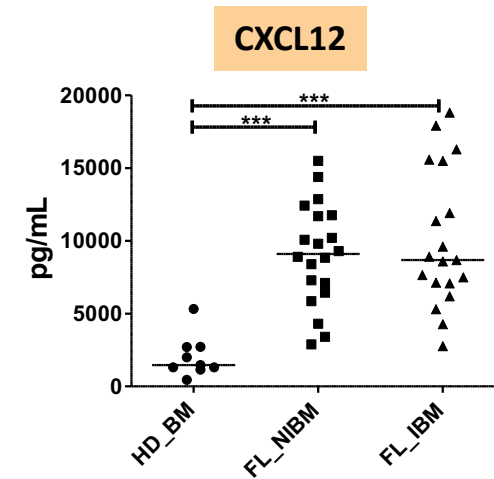


- ✓ **Signal 1: Ectopic Tfh-like cells?**
- ✓ **Signal 2: BCR ?**
- ✓ **Signal 3: CAF (CCL2/IL8//CCL21)**

...et dans la MO?



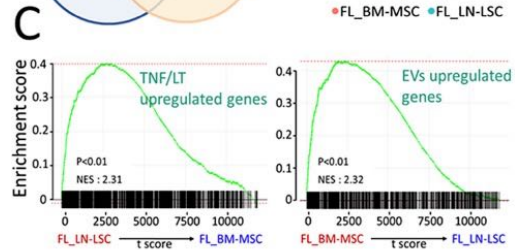
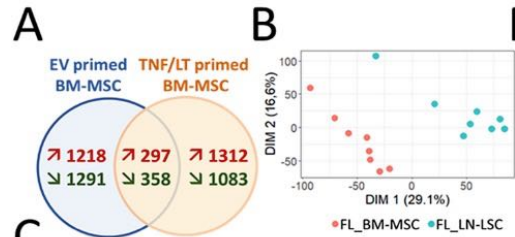
Pandey *Blood* 2017



- ✓ **Signal 1: Ectopic Tfh-like cells?**
- ✓ **Signal 2: BCR ?**
- ✓ **Signal 3: CAF (CCL2/IL8/CCL21/CXCL12)**

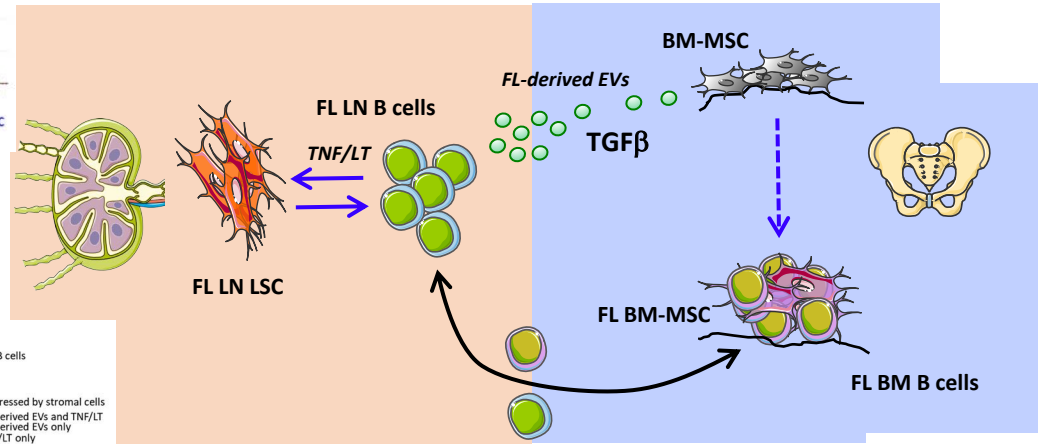
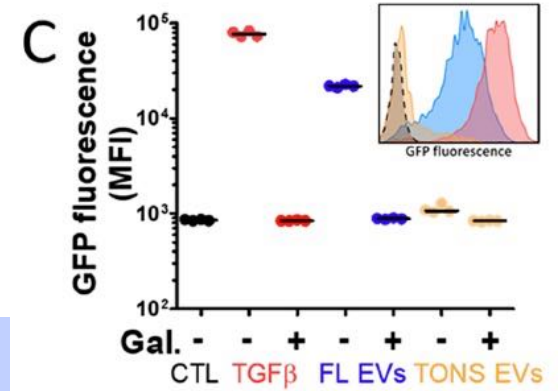
- ✓ **Le stroma de la MO est-il équivalent à celui des ganglions?**
- ✓ **Mécanismes d'induction?**

...et dans la MO?

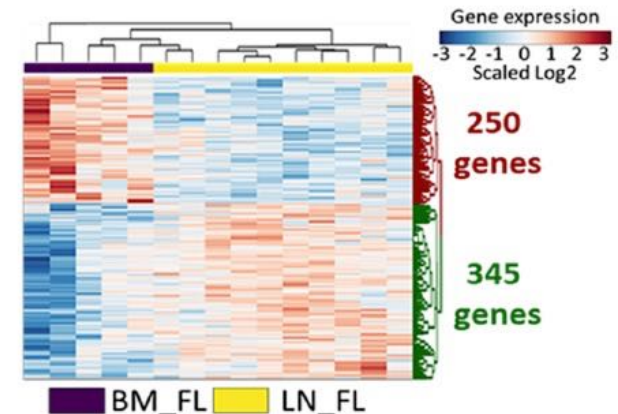
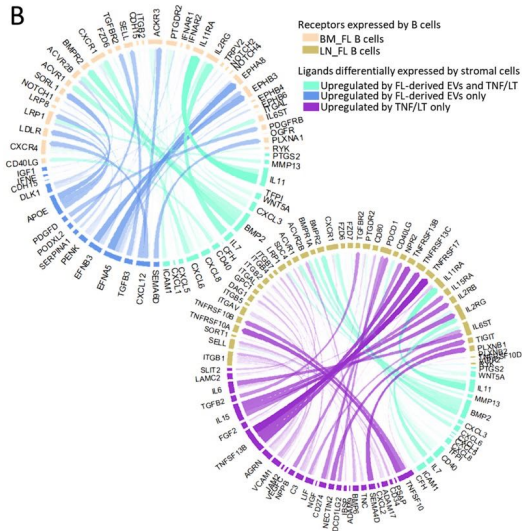


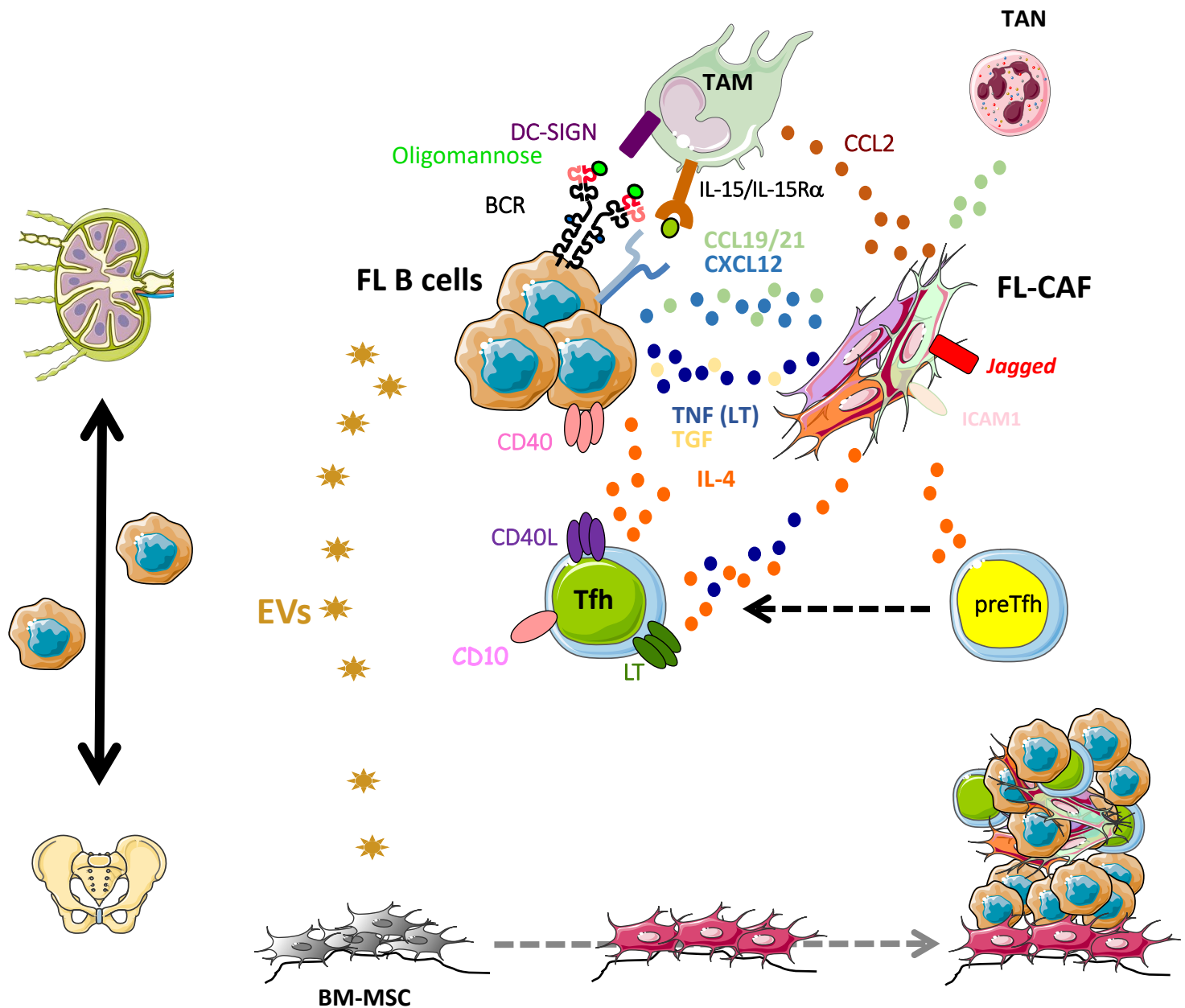
EV signature

RANK	MOTIF	SYMBOL	P-VALUE
1	CCATTGTTT	SOX6	1,00E-04
2	CCATTGTTT	SOX2	1,00E-03
3	CCATTGTTT	SOX21	1,00E-03
4	CCATTGTTT	SOX4	1,00E-03
5	CCATTGTTT	SOX10	1,00E-03

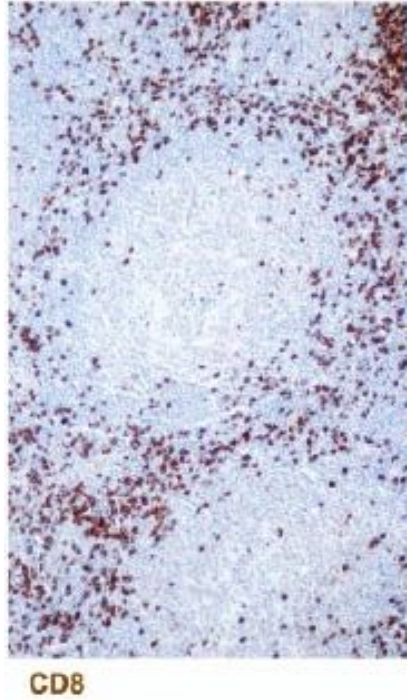
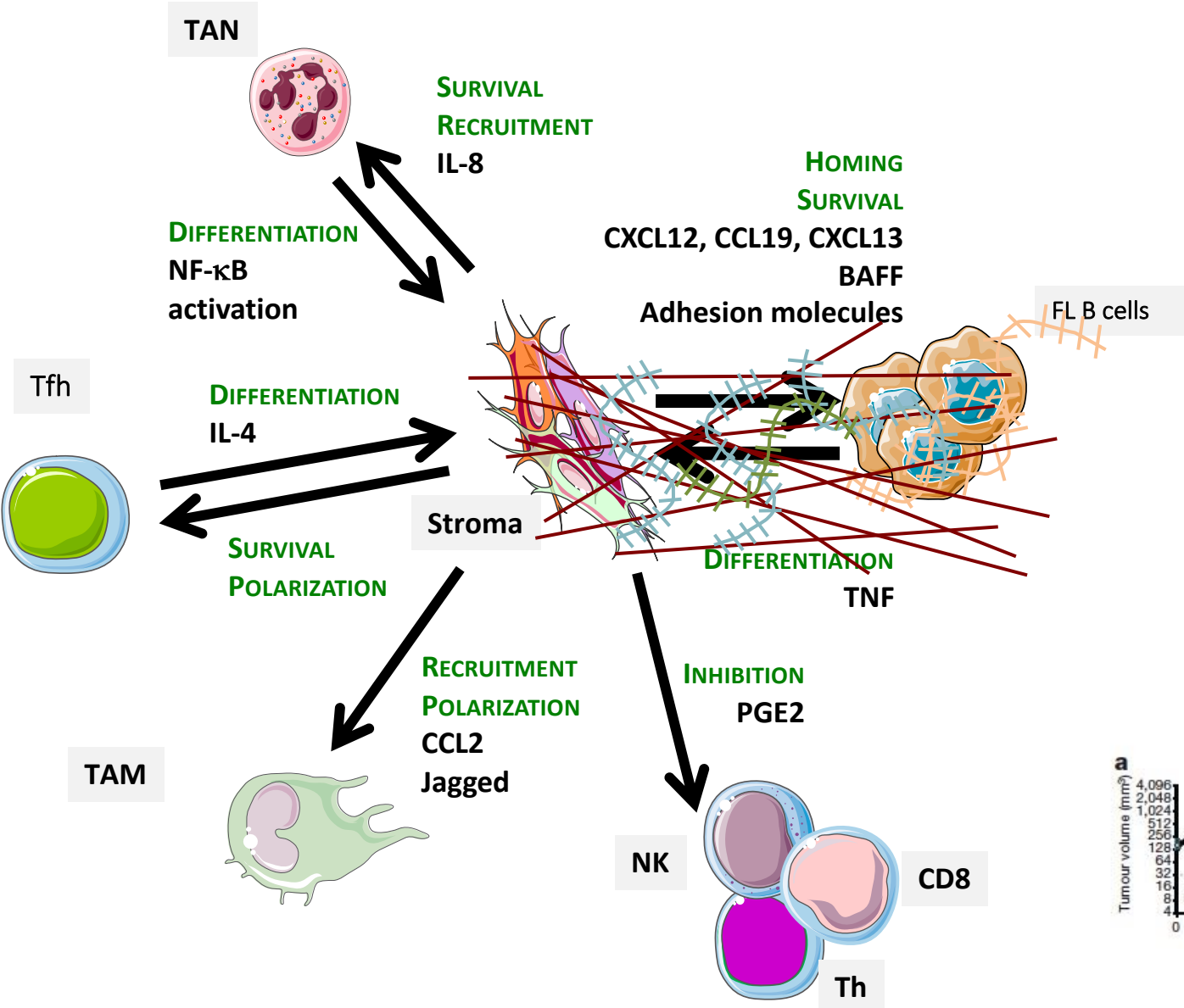


Dumontet Blood 2021



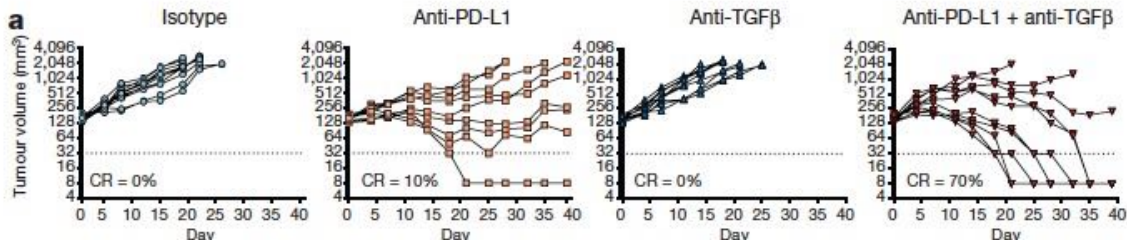


Q1: Matrice extracellulaire, forces biomécaniques?



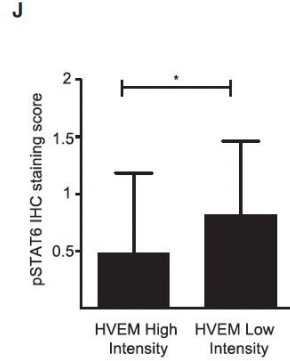
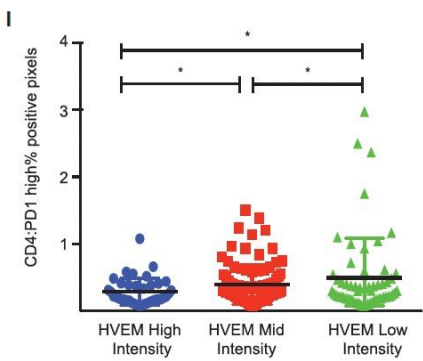
Laurent Blood 2011; 118:5371

Importance en immunothérapie?



Mariathanas Nature 2018 554:544

Q2: Impact de l'hétérogénéité génétique?

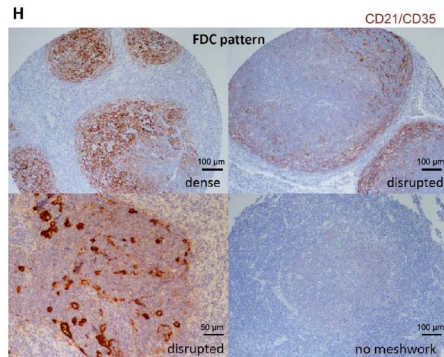
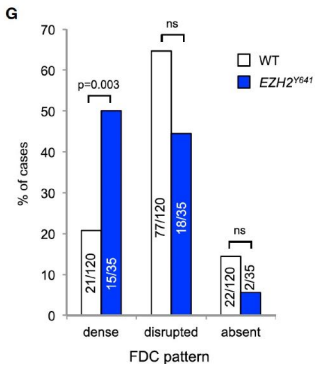
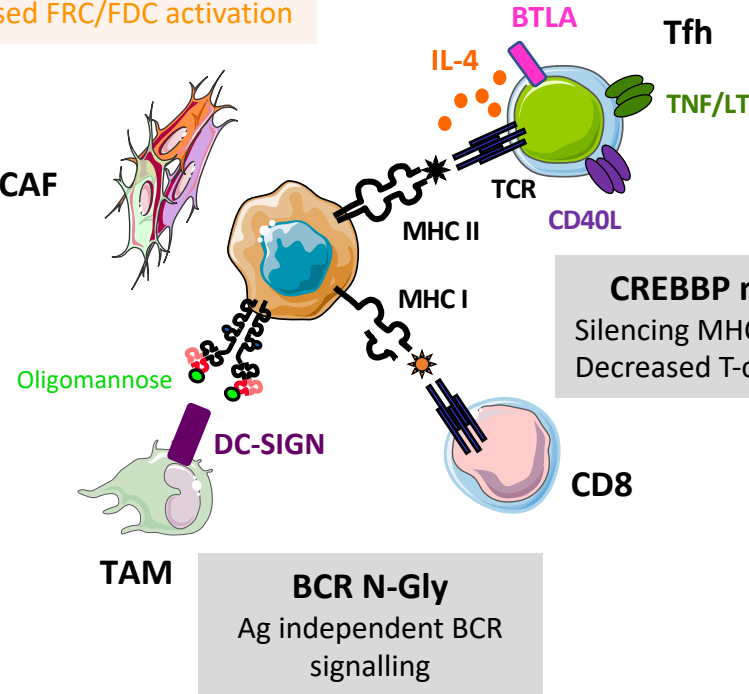


HVEM mutations
 Increased Tfh activation
 Increased FRC/FDC activation

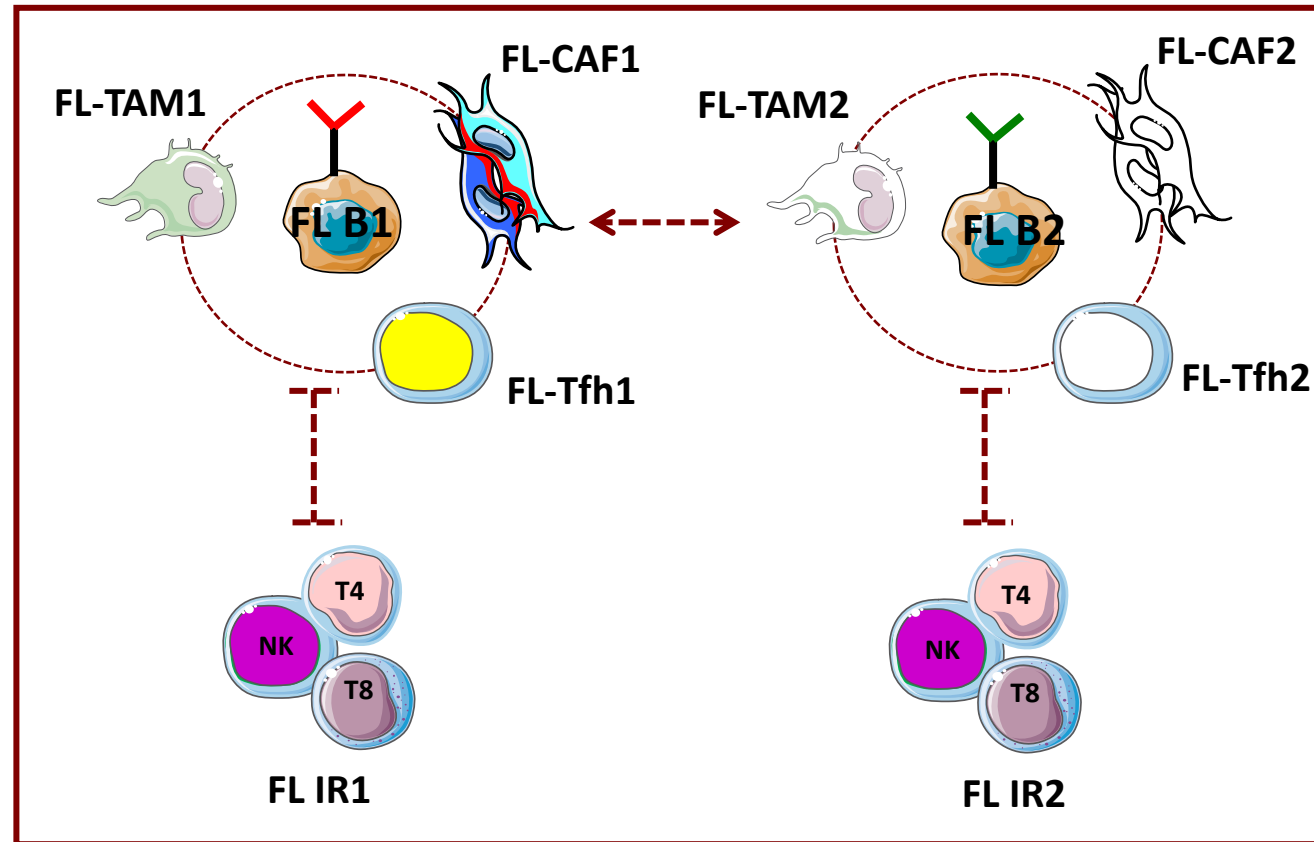
CTSS mutations
 Enhanced MHC II Ag presentation
 Increased Tfh infiltration
 Decreased CD8 infiltration

EZH2 mutations
 Decreased dependency on Tfh
 Increased dependency on FDC

CREBBP mutations
 Silencing MHC II
 Decreased T-cell infiltration

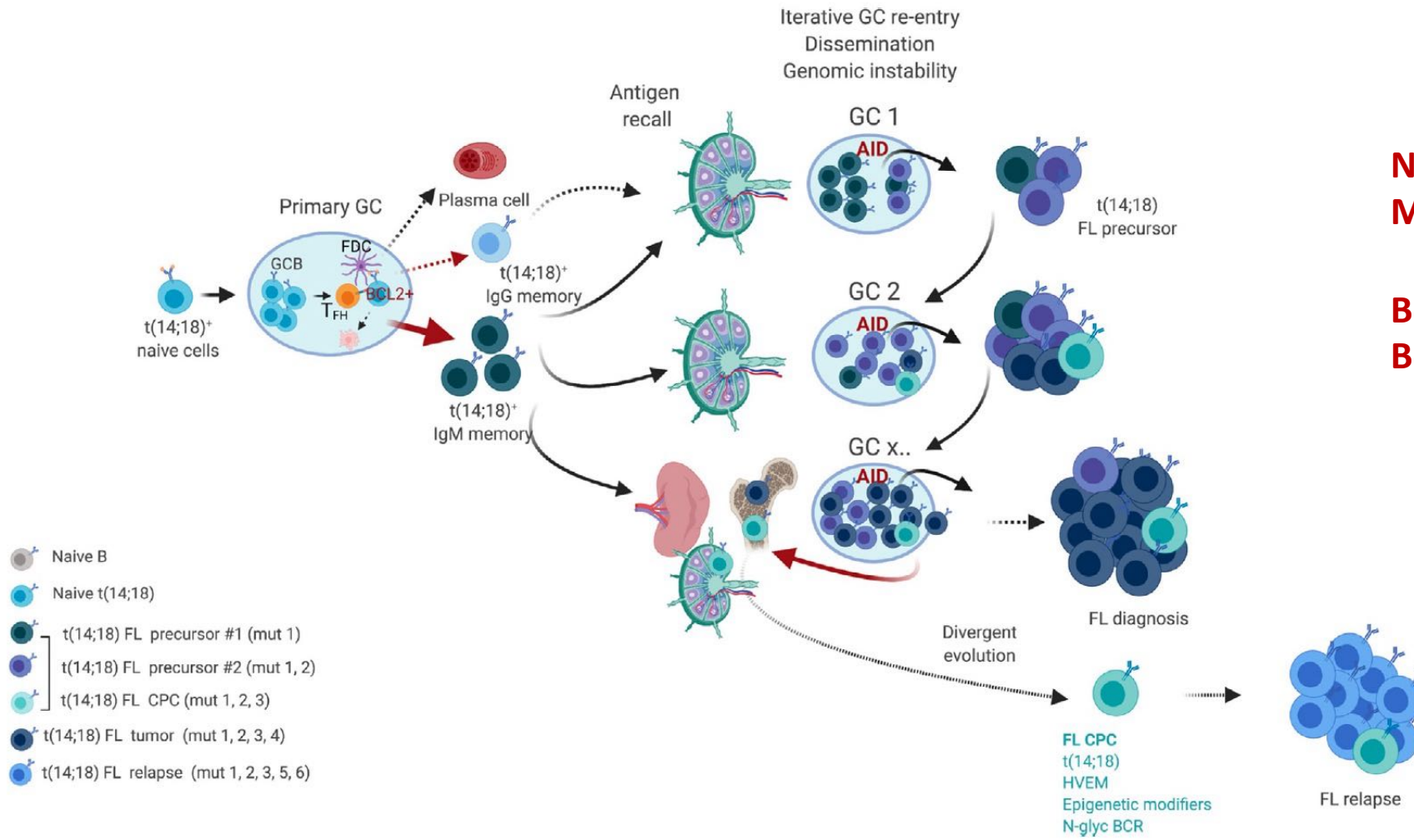


Q2: Impact de l'hétérogénéité génétique?



Répercussions au stade FL?
Besoin de modèles (souris Tg)

Q3: Impact de l'hétérogénéité cinétique?



**Niche des CPC (initiation, MRD)?
Modifications post-traitement?**

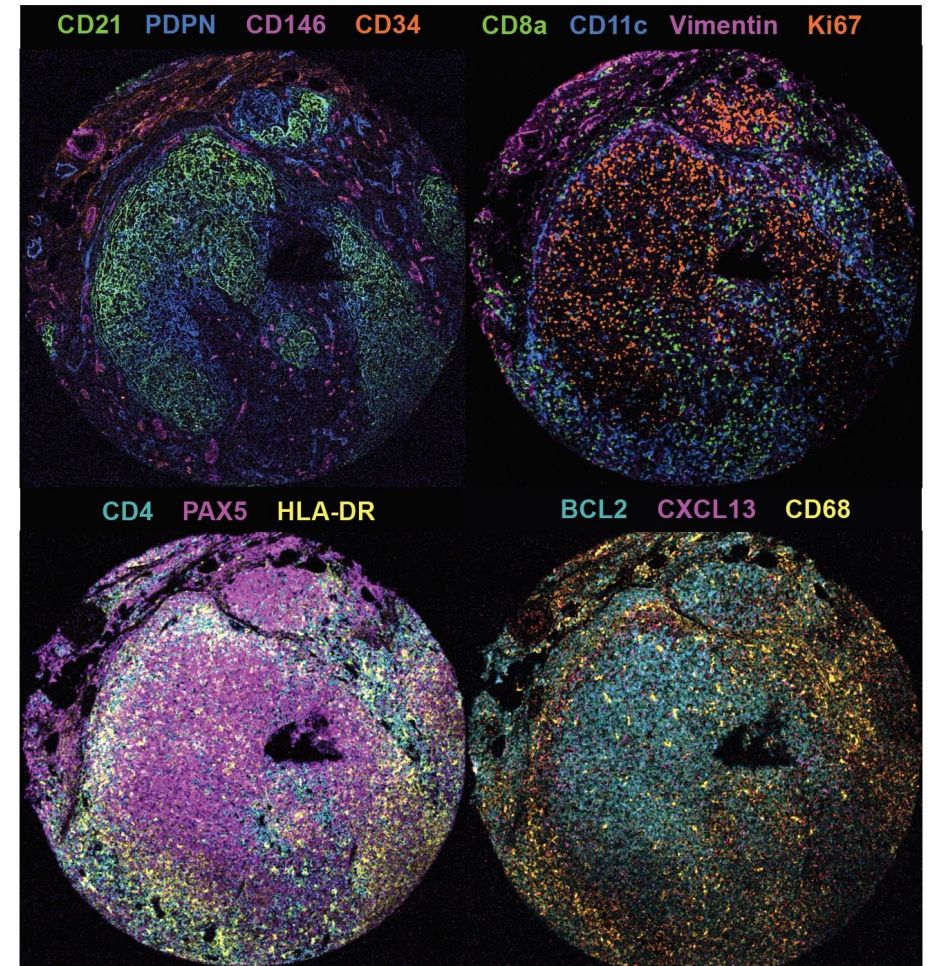
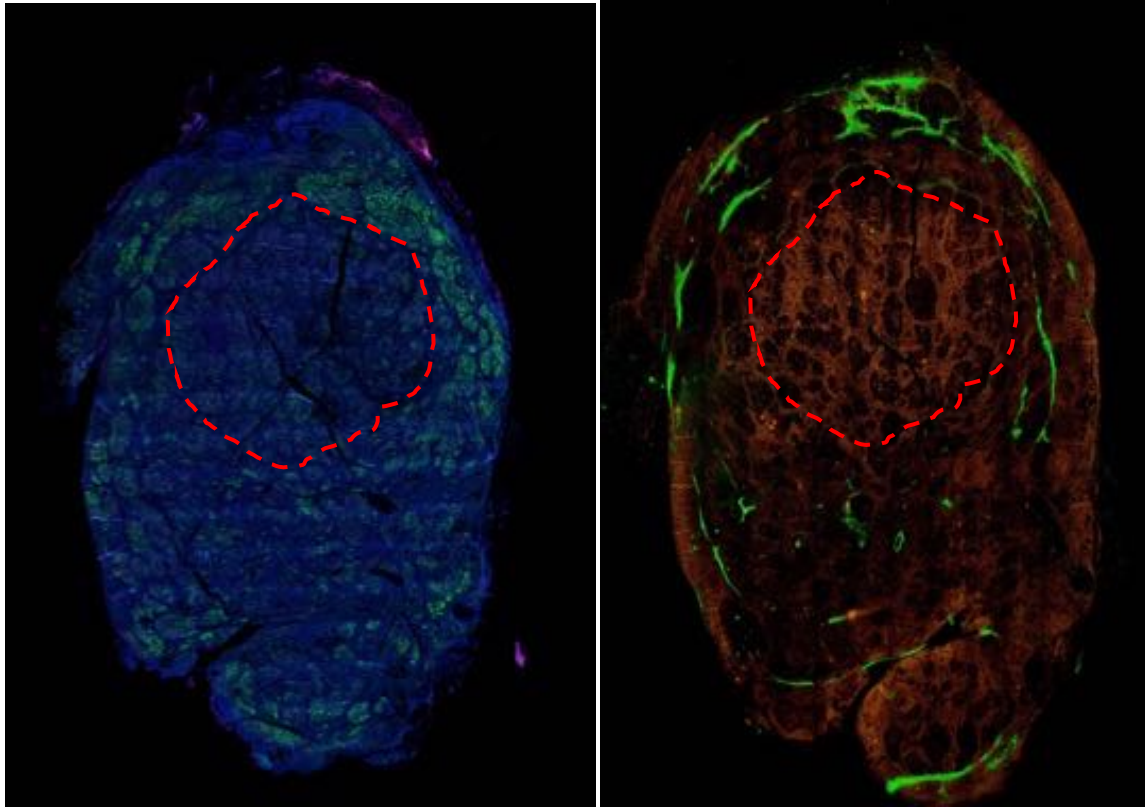
**Besoin de modèles +++
Besoin de prélèvements itératifs**

Q4: Impact de l'hétérogénéité spatiale?

Dylan Richard Mc Nally

Pax5Podoplanin

CCL21Periostin



Besoin d'approches in situ ++

Take-home messages

- Microenvironnement dans le FL est complexe, hétérogène et dynamique
- Constitué d'un réseau interconnecté de cellules antitumorales et protumorales
- Lien fort avec la génétique
- Intérêt clinique: biomarqueurs, nouvelles stratégies ?
- Off-target de thérapies ciblées?
- Besoin de nouvelles approches technologiques....et d'un lien fort avec les cliniciens !!!!