Angioimmunoblastic T-cell lymphoma (AITL) and other Follicular Helper cell (TFH)-related PTCL

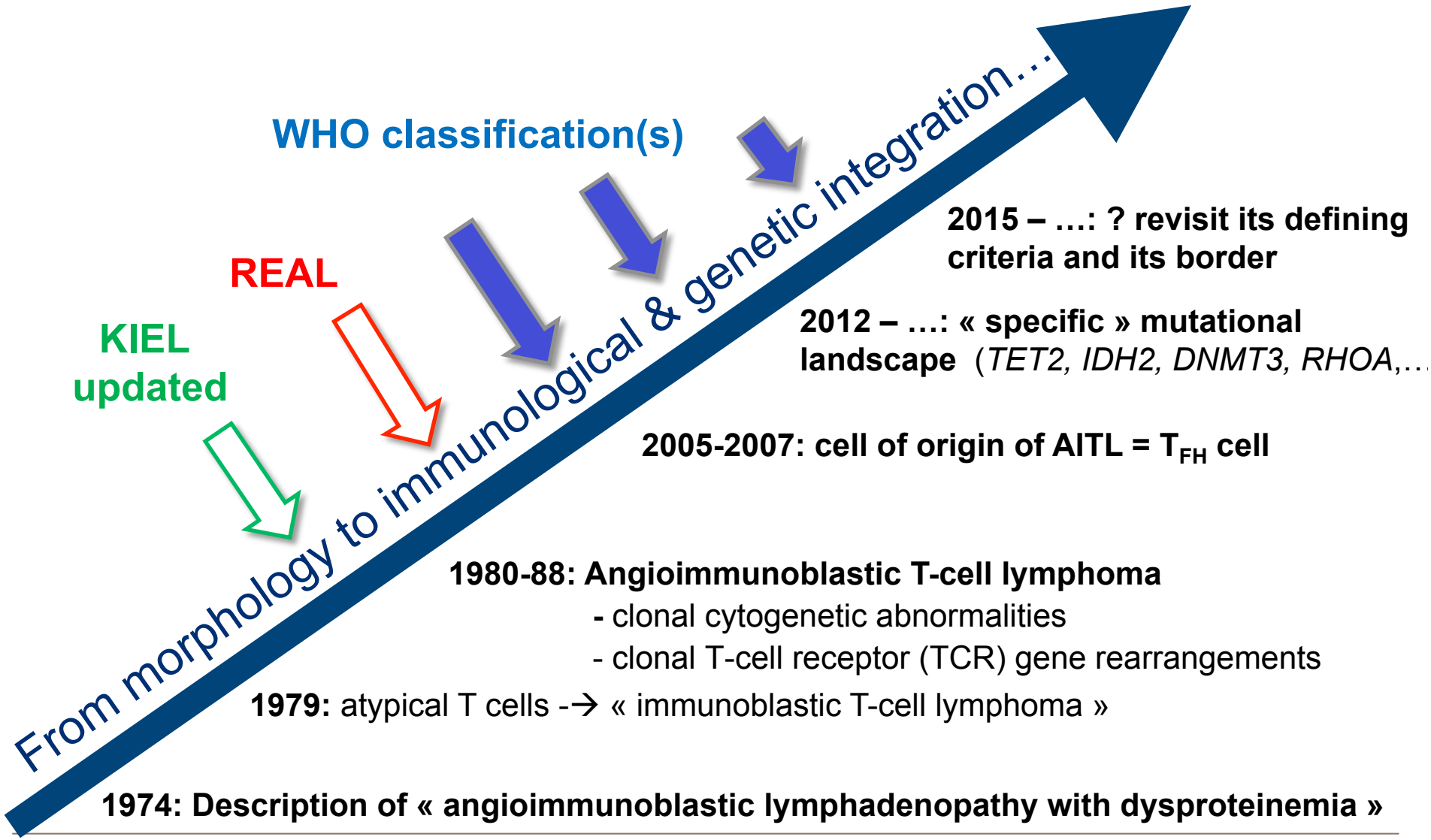
Bologna
April 27-29, 2015

Philippe Gaulard
Département de Pathologie & Inserm U955
Hôpital Henri Mondor, Créteil, France

Impossibile visualizzare l'immagine. La memoria del computer potrebbe essere insufficiente per aprire l'immagine oppure l'immagine potrebbe essere danneggiata. Riavviare il computer e aprire di nuovo il file. Se viene visualizzata di nuovo la x rossa, potrebbe essere necessario eliminare l'immagine e inserirla di nuovo.

Impossibile visualizzare l'immagine. La memoria del computer potrebbe essere insufficiente per aprire l'immagine oppure l'immagine potrebbe essere danneggiata. Riavviare il computer e aprire di nuovo il file. Se viene visualizzata di nuovo la x rossa, potrebbe essere necessario eliminare l'immagine e inserirla di nuovo.

From angioimmunoblastic lymphadenopathy to angioimmunoblastic T-cell lymphoma…!



Angioimmunoblastic T-cell lymphoma (AITL) : empiric therapies are not working…!

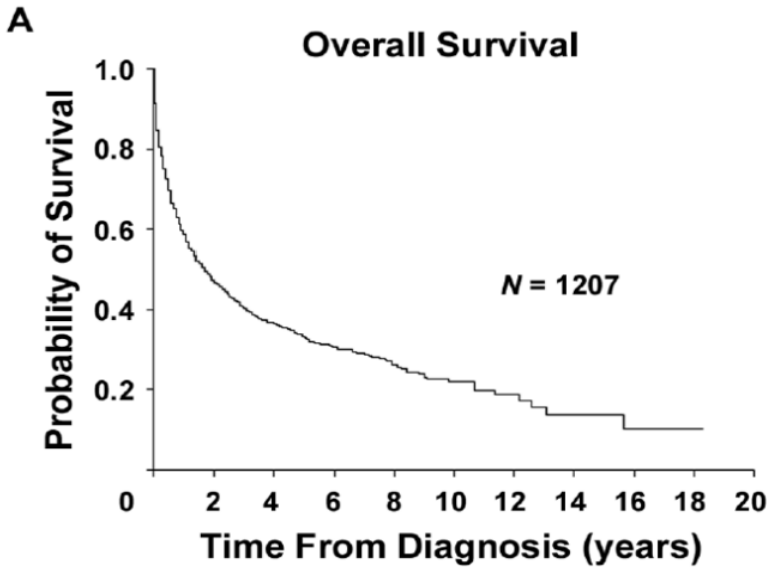
OPEN ACCESS Freely available online

PLOS | ONE

No Survival Improvement for Patients with Angioimmunoblastic T-Cell Lymphoma over the Past Two Decades: A Population-Based Study of 1207 Cases

Bei Xu[1], Peng Liu[2]*

1 Department of Medical Oncology, the First Affiliated Hospital of Nanjing Medical University, Nanjing, PR China, **2** Department of Hematology, the First Affiliated Hospital of Nanjing Medical University, Nanjing, PR China



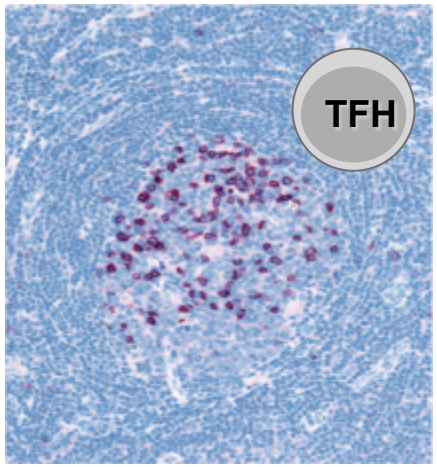
5 periods studied
1992-1998
1999-2001
2002-2004
2005-2007
2008-2010

« No survival differences overtime (1992 – 2010).. »

The good, the bad and the ugly — T_{FH} cells in human health and disease

Stuart G. Tangye[1,2], Cindy S. Ma[1,2], Robert Brink[1,2] and Elissa K. Deenick[1,2]

412 | JUNE 2013 | VOLUME 13 www.nature.com/reviews/immunol

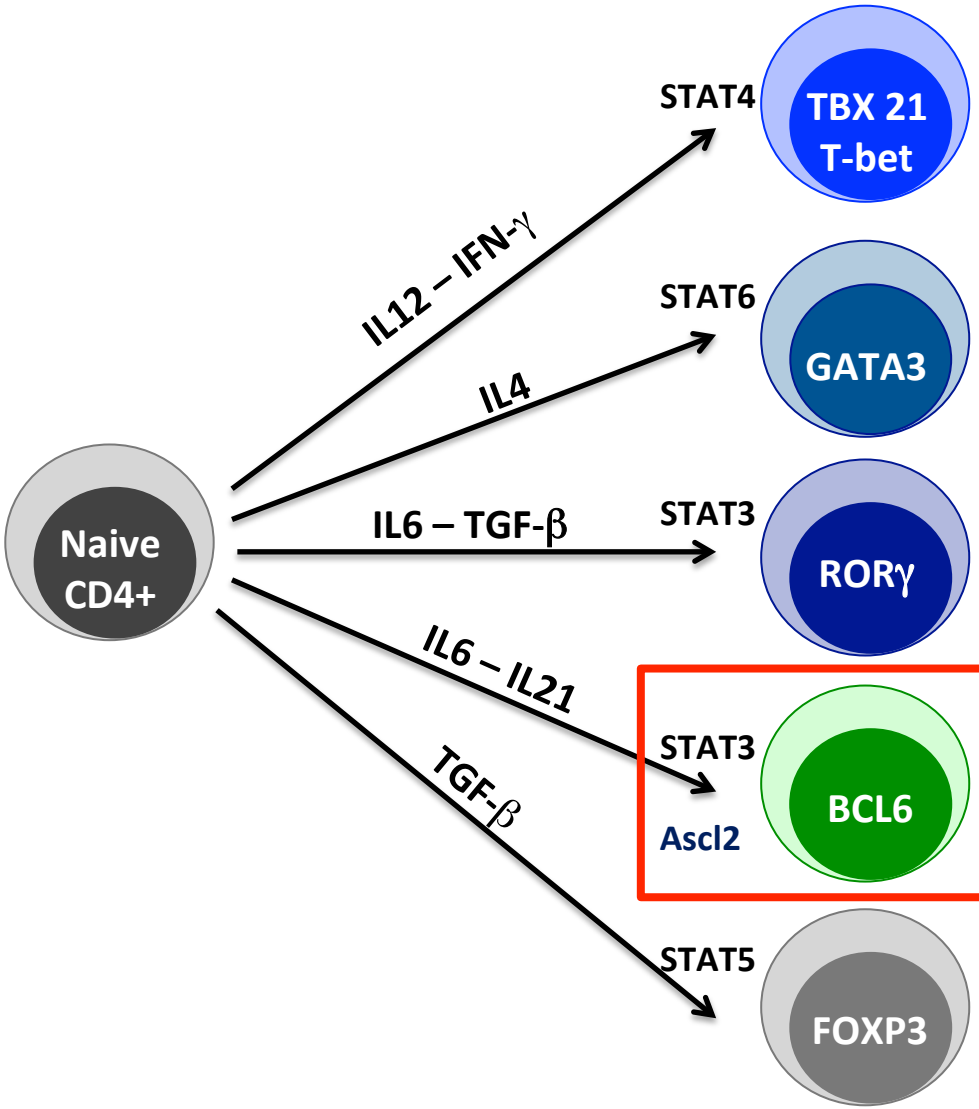


Germinal center B and follicular helper T cells: siblings, cousins or just good friends?

Stephen L Nutt[1,2] & David M Tarlinton[1,2]

VOLUME 12 NUMBER 6 JUNE 2011 NATURE IMMUNOLOGY

The main Th cell subsets



T_H1 cell -> IFN-γ
Intracellular bacteria

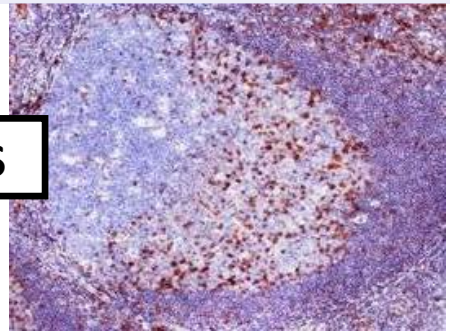
T_H2 cell -> IL4, IL5, IL13
Helminths

T_H17 cell -> IL17, IL21
Extracellular bacteria, fungi

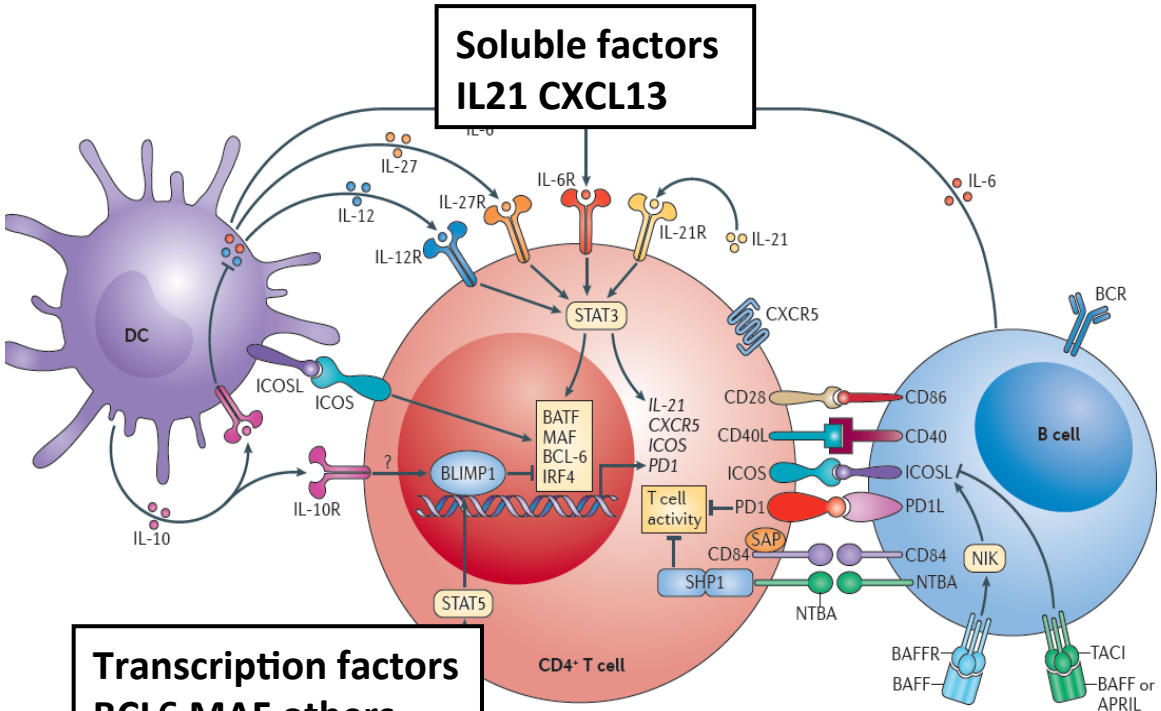
T_{FH} cell -> IL21
B-cell help

T_{reg}cell ->TGF-β, IL10
Regulatory function

T_{FH} cells: a unique T-cell subset



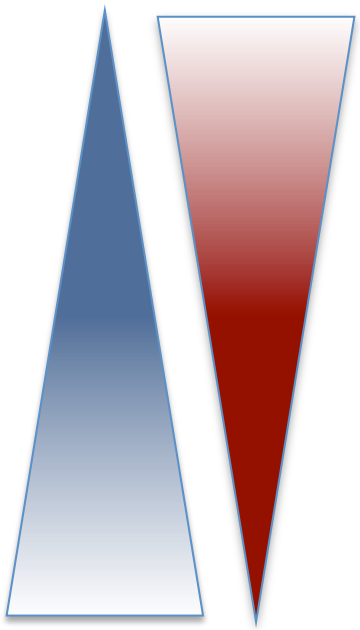
ICOS



- ✓ A specific function: interaction with B cells to provide help and allow antibody responses
- ✓ A unique transcriptional profile
- ✓ Express Bcl-6 and secrete IL-21
- ✓ CXCL13+, CXCR5^{high}, ICOS^{high}, PD1^{high} , low levels of T-bet, Gata-3, Rorγt and FoxP3
- ✓ Plasticity : Heterogeneous T_{FH} cell subsets …

Tangye SG et al, Nature Rev Immunol 2013

Criteria to postulate a T_{FH} derivation in a given tumor



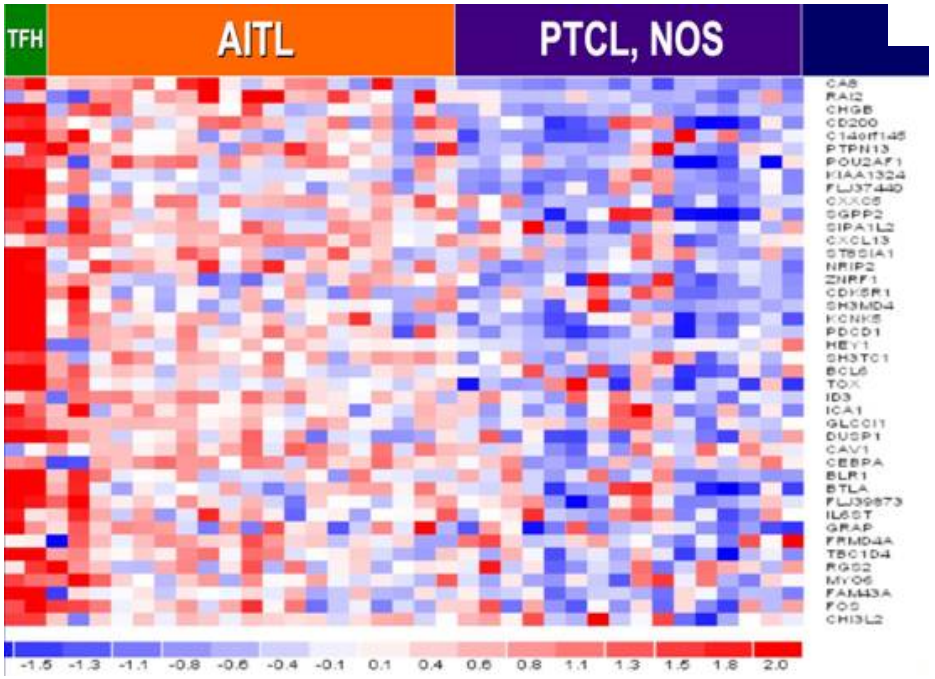
- ✓ No single marker is 100% sensitive, or 100% specific
- ✓ **ICOS and PD1 are sensitive but less specific and CXCL13 and CD10 more specific but less sensitive**
- ✓ CD10 stains only a proportion of tumor cells
- ✓ !! Some are expressed by other subtypes of PTCL (incl ALCL-ICOS, PD1/CD10 MF/SS)
- ✓ **A combination of several markers (at least 2 or 3?) to be recommanded (incl CD10)?**

Grogg et al 2005; Dupuis et al 2006; Grogg et al 2006; Dorfman et al 2006; Krenacs et al 2006; Roncador et al 2007; Ortonne et al 2007; Xerri et al 2008; Yu et al 2009; Rodriguez-Justo et al 2009; Marafioti et al 2009; Dorfman et al. 2011; Bisig B Histopathol 2011; Agostinelli C et al. Histopathol 2011, Attygalle Histopathology 2014; Ame-Thomas et al. Blood 2015

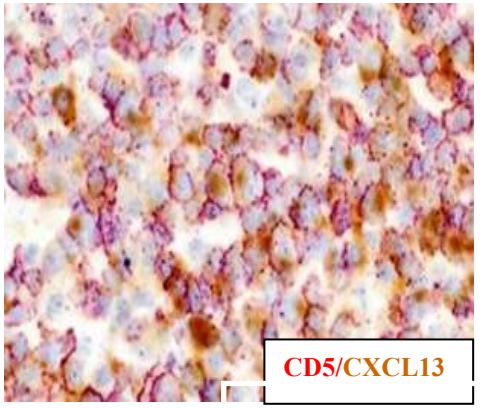
T_{FH} cells and human diseases

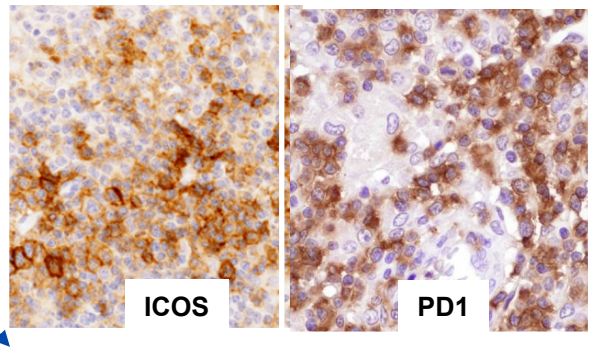
- **Immune deficiencies (Primary, HIV)**
- **Autoimmune diseases *(SLE, Sjogren's Sme, RA,..)***
- **Lymphoid neoplasms**
  - **B-cell neoplasms /Hodgkin lymphoma**
  - **Lymphomas derived from T_{FH} cells**

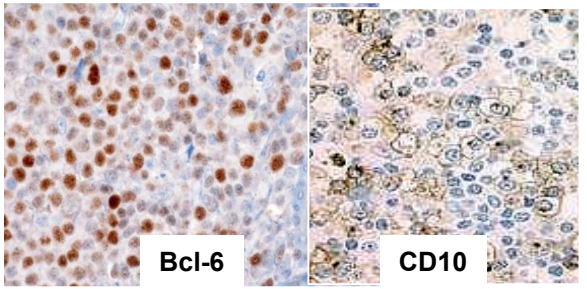
The cellular origin of AITL from follicular *helper* T cells (T_{FH})



de Leval et al. Blood, 2007

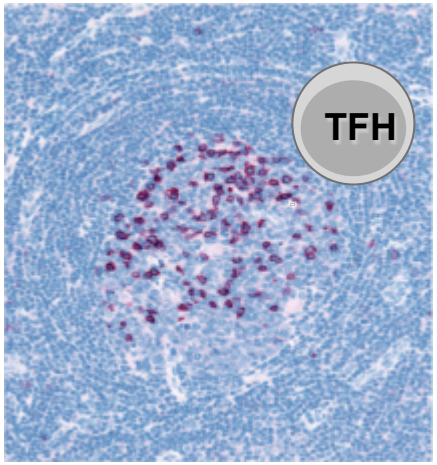


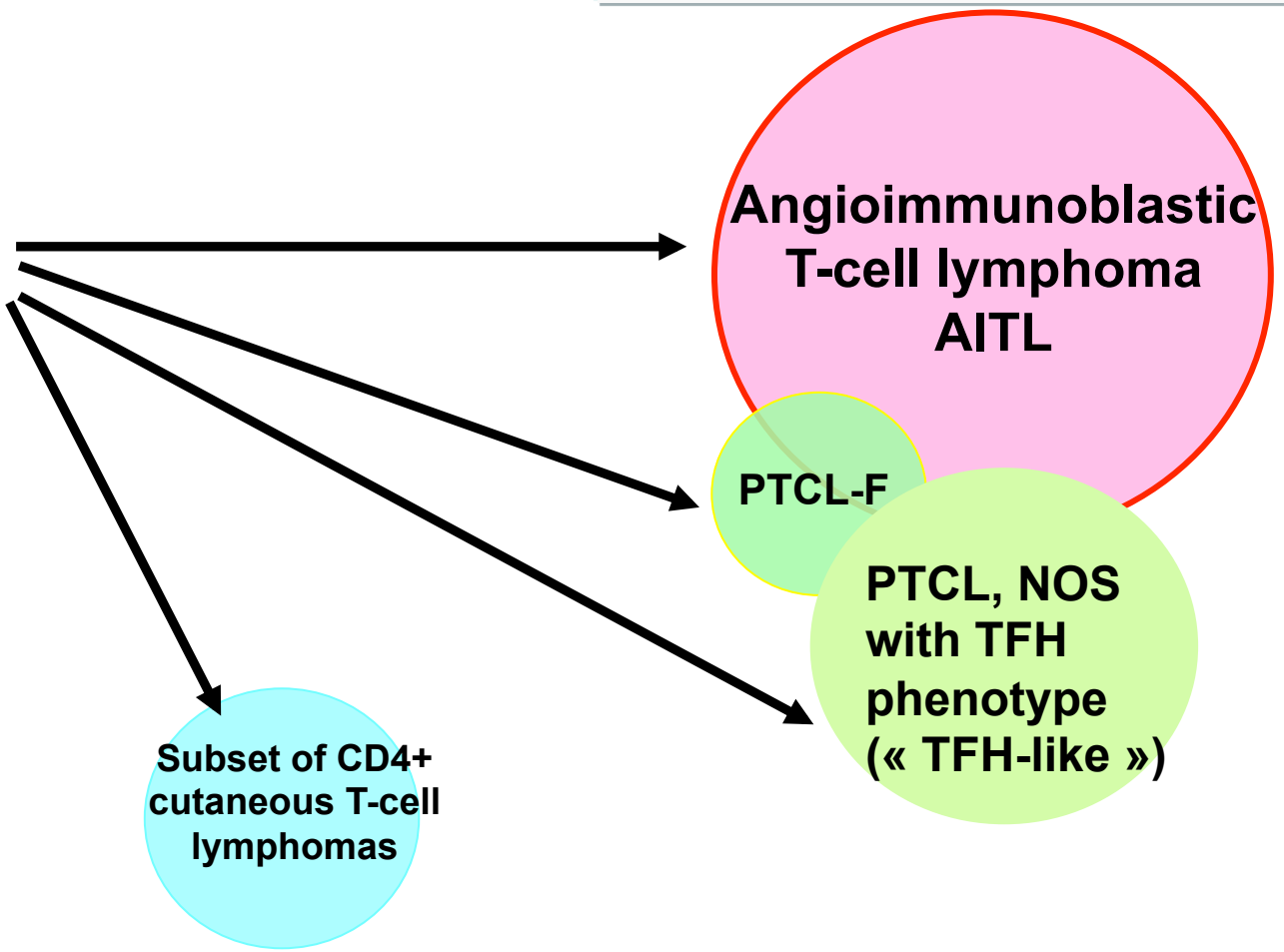




AITL: the prototype of T_{FH}-derived lymphoma

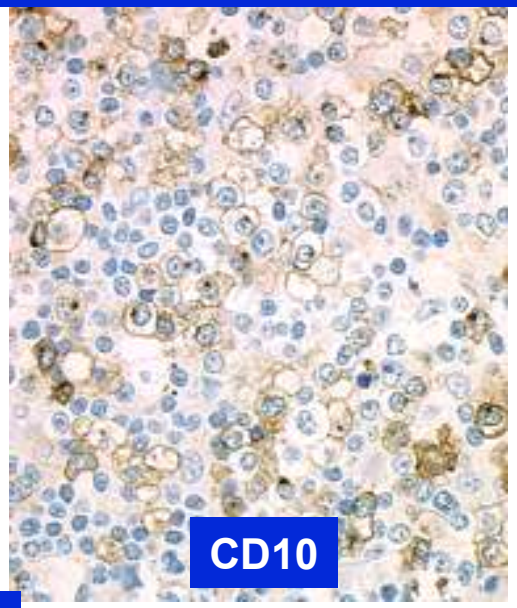
1. Described as a “dysimmune” non neoplastic condition
2. Distinctive clinical features, with immunologic abnormalities
3. Peculiar pathological aspects



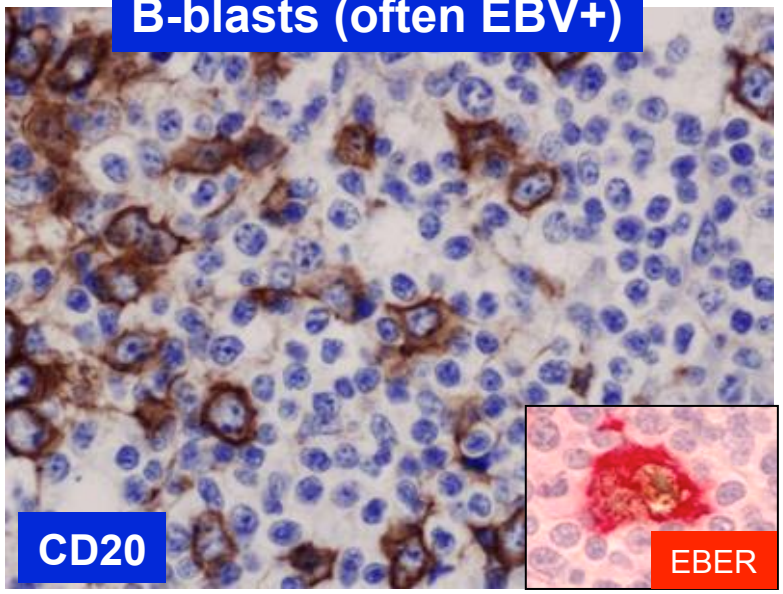


Pathological aspects of AITL

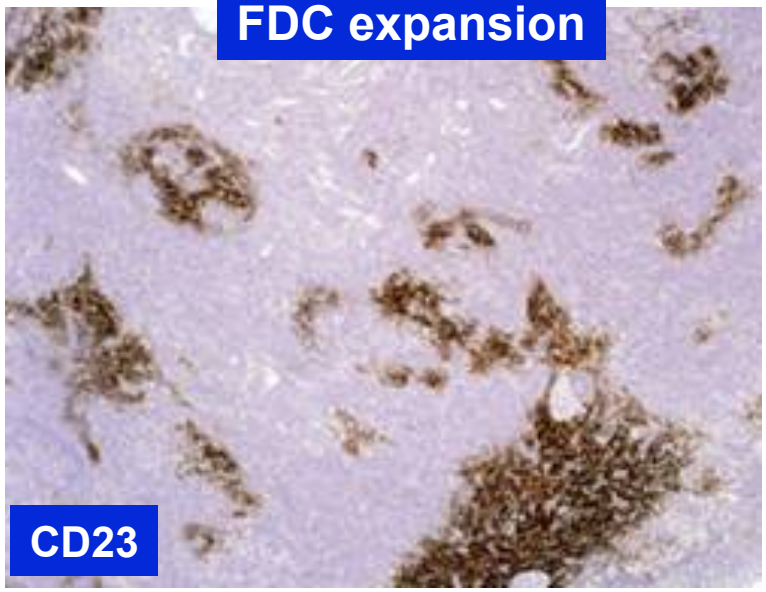
CD4+ αβT cells (T_{FH}), often CD10+



B-blasts (often EBV+)



FDC expansion



AITL: clinical & biological features

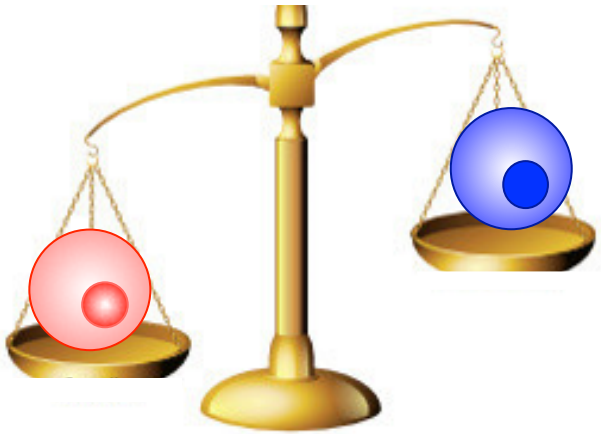
• Median age	57 - 68 yrs
• Advanced stage (III/IV)	68 – 94 %
• **B symptoms**	**52 – 86 %**
• Polyadenopathy	81 – 100%
• Skin rash	38 – 58 %
• Bulky mass	5 – 26 %
• **Hyperγglobulinemia**	**30 – 83 %**
• **Positive Coombs test**	**32 – 75 %**
• **Monoclonal gammopathy**	**10 – 20 %**

Manifestations of immune dysregulation are typical of AITL, but not universal and therefore not mandatory for the diagnosis

Reviewed in de Leval L et al, Br J Haematol 2010; Attygalle AD et al. Histopathology 2014; International T-cell Lymphoma Project, J Clin Oncol 2008; Parrens M et al. ASH proceedings 2012

Importance of the microenvironment in AITL

Microenvironment
(B-cells, FDC, macrophages, vessels, eosinophils, mast cells…)
(°)



Neoplastic T_{FH} cells

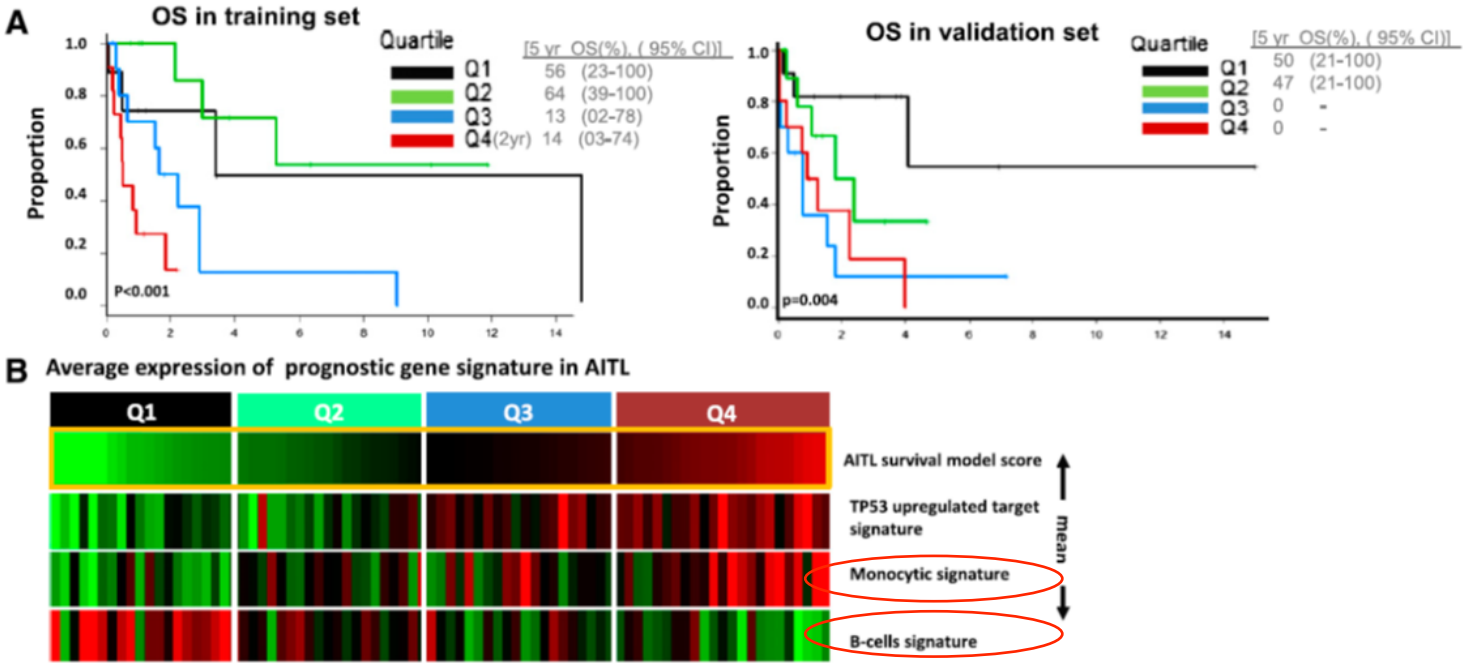
- **Variable morphology: wide spectrum+++**
- **Clinical presentation/outcome?**

(°) Critical in sustaining tumor cells (no cell lines)
(°) <u>May vary over time in a single case and from case to case</u>

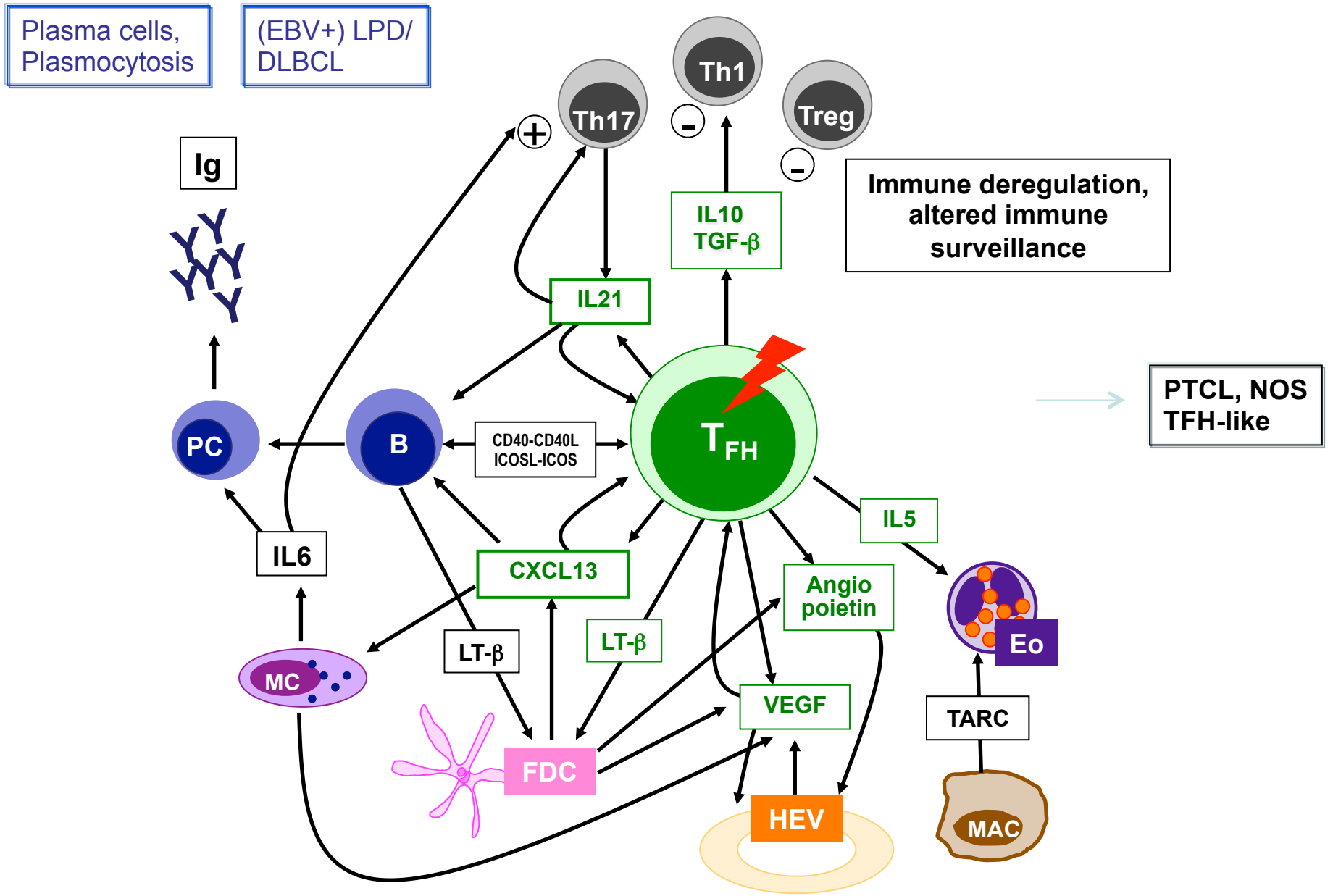
Microenvironment in AITL may have a prognostic impact

✓M2 macrophages, Th17/mast cells, VEGF expression or vascular density, plasma EBV DNA (B Cells) related with prognosis *(Niino et al. Pathol Intern 2010; Tripodo. Am J Pathol 2012; Zhao et al. Lab Invest 2004; Ganjoo et al. Leuk Lymphoma 2014; Au et al. Blood 2014)*

✓ **Molecular prognosticator** in AITL



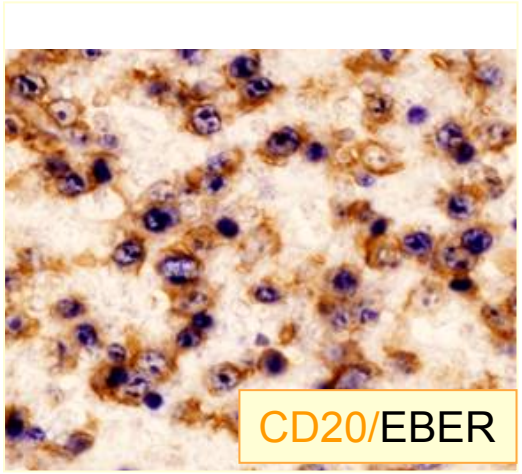
Iqbal et al. Blood 2010
Iqbal et al. Blood 2014

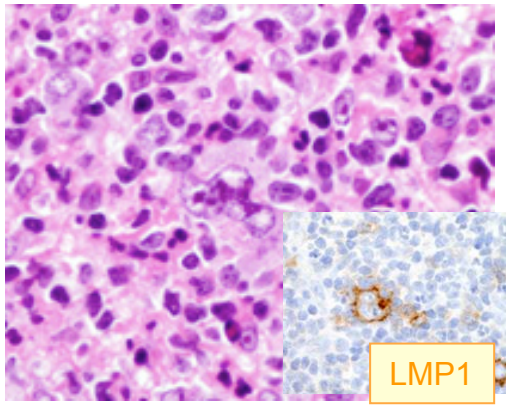


Gaulard P, de Leval L, Semin Cancer Biology 2014

Spectrum of B-cell proliferations is broad in AITL

1. From scattered to “increased” B blasts to DLBCL–like
2. HRS-like cells may be seen; should not be misdiagnosed as cHL or composite !
3. EBV positive (more often) or EBV negative
4. Plasma cell proliferation (monotypic or not)
5. Up to one third of AITL show clonal B-cell population : clonality analysis may be misleading!
6. Mechanisms:
   - favoured by T_{FH} help and decreased immune surveillance
   - Hypermutated Ig genes with destructive mutations





Brauninger J Exp Med 2001; Lome-Maldonado Leukemia 2002; Willenbrock BJH 2007; Attygalle AJSP 2007; Nicolae AJSP 2013; Attygalle Histopathology 2014

Targeting intratumoral B cells with rituximab in addition to CHOP in angioimmunoblastic T-cell lymphoma. A clinicobiological study of the GELA

Marie-Hélène Delfau-Larue,[1,2,3] Laurence de Leval,[4*] Bertrand Joly,[5*] Anne Plonquet,[1,2,3] Dominique Challine,[1,6] Marie Parrens,[7] Alain Delmer,[8] Gilles Salles,[9] Franck Morschhauser,[10] Richard Delarue,[11] Pauline Brice,[12] Reda Bouabdallah,[13] Olivier Casasnovas,[14] Hervé Tilly,[15] Philippe Gaulard,[1,2,16] and Corinne Haioun[1,17]

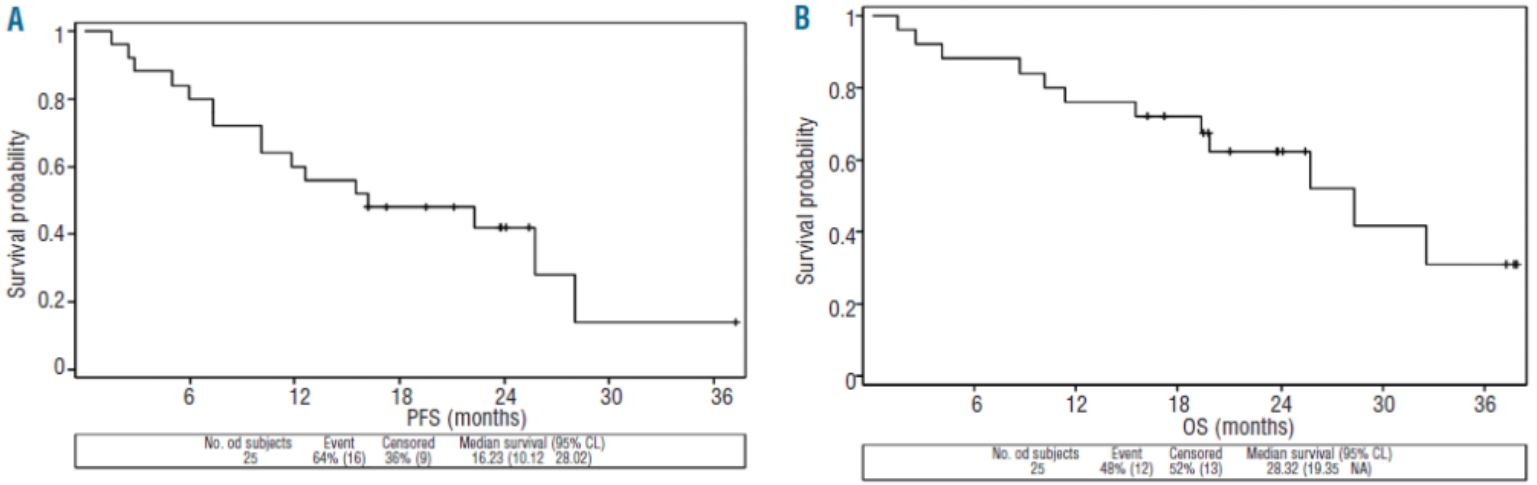
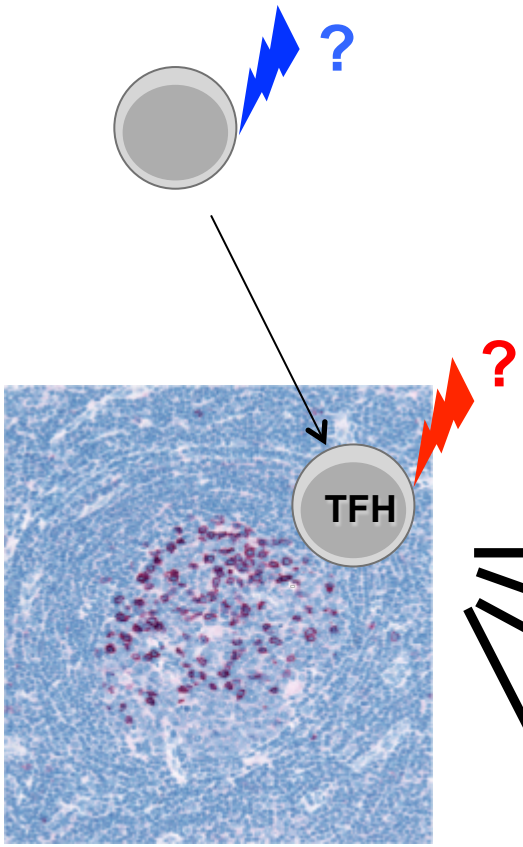


Figure 5. Clinical outcome. (A) Progression-free survival (PFS). (B) Overall survival (OS).

MH Delfau-Larue et al. Haematologica 2012

Oncogenic pathways…?

1. No recurrent translocation
2. Gains and losses
3. No « true » mouse model (SANROQUE, cMAF)



?

?

?

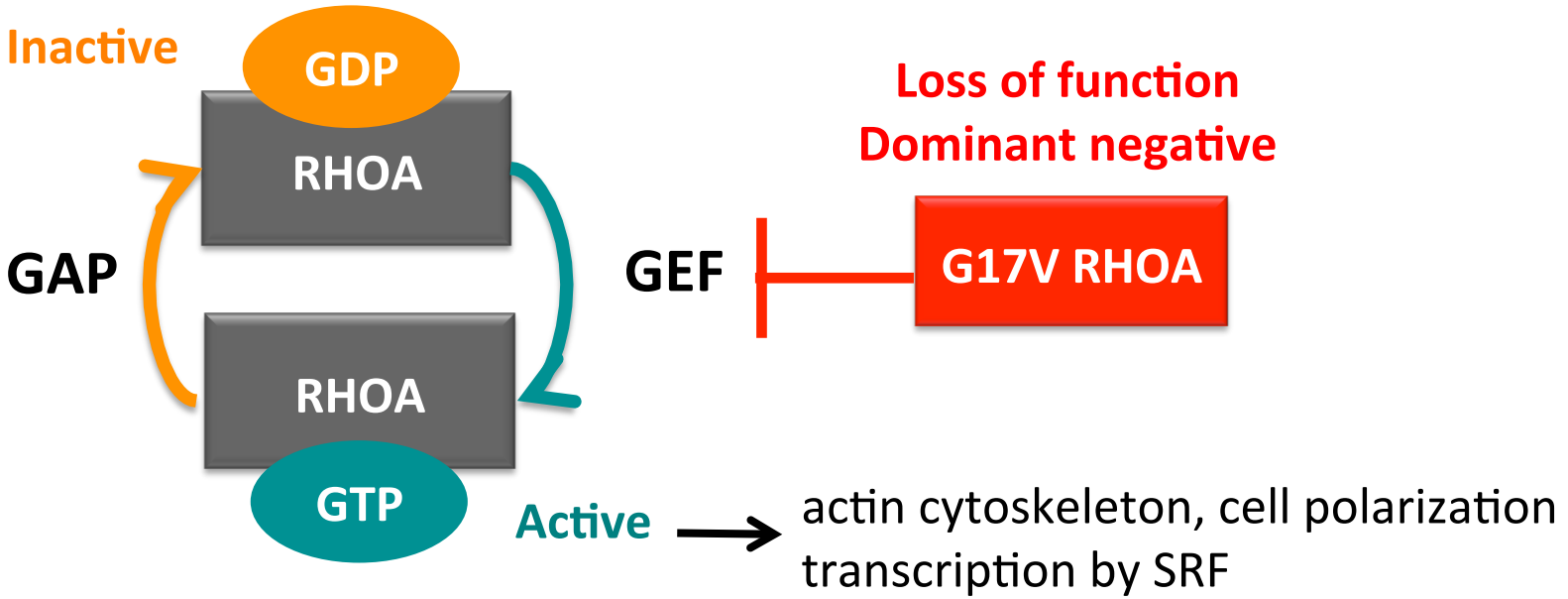
Angioimmunoblastic T-cell lymphoma AITL

PTCL-F

PTCL, NOS with TFH phenotype (« TFH-like »)

Subset of CD4+ cutaneous T-cell lymphomas

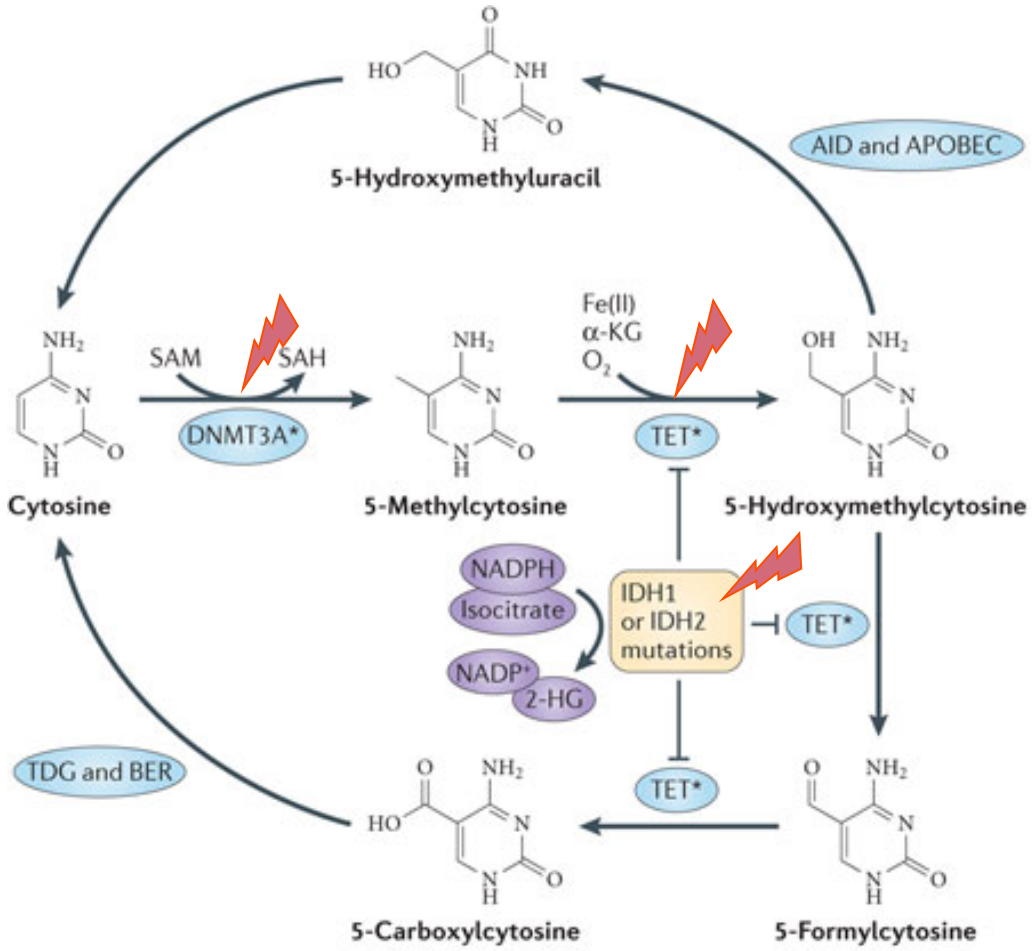
Recurrent *RHOA* mutations discovered by NGS



- **Up to 70% AITLs and a subset of PTCL, NOS with T_{FH} like features**
- Absent in myeloid, **confined to tumor cells**
- **RHOA G17V** in most cases, **association with *TET2* mutations**
- Inducibly expressed G17V RHOA does not affect the growth or cell cycle progression in Jurkat cells
- Could also act as a TSG in ATLL (*Sakata-Yanagimoto, 2014 EHA meeting*), gastric carcinoma (*Wang, Nat Genet 2014, Kakiuchi, Nat Genet 2014)*) and Burkitt lymphoma (*Rhode, GCC, 2014)*

Palomero et al, Sakata-Yanagimoto et al, Yoo H-Y et al Nat Genetics 2014;
L de Leval & P Gaulard, unpublished [RHOA mut: AITL (65%, n=76); PTCL, TFH-like (46%, n=13)]

TET2, DNMT3A & *IDH2* are involved in DNA methylation

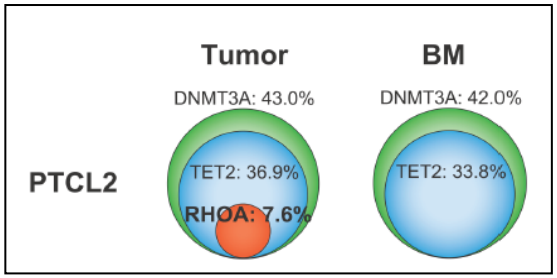


Adapted from Shih et al. Nat Rev Can.2012

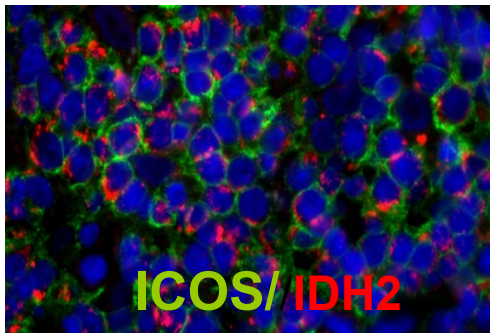
In AITL, the 3 mutations are commonly associated

Nature Reviews | Cancer

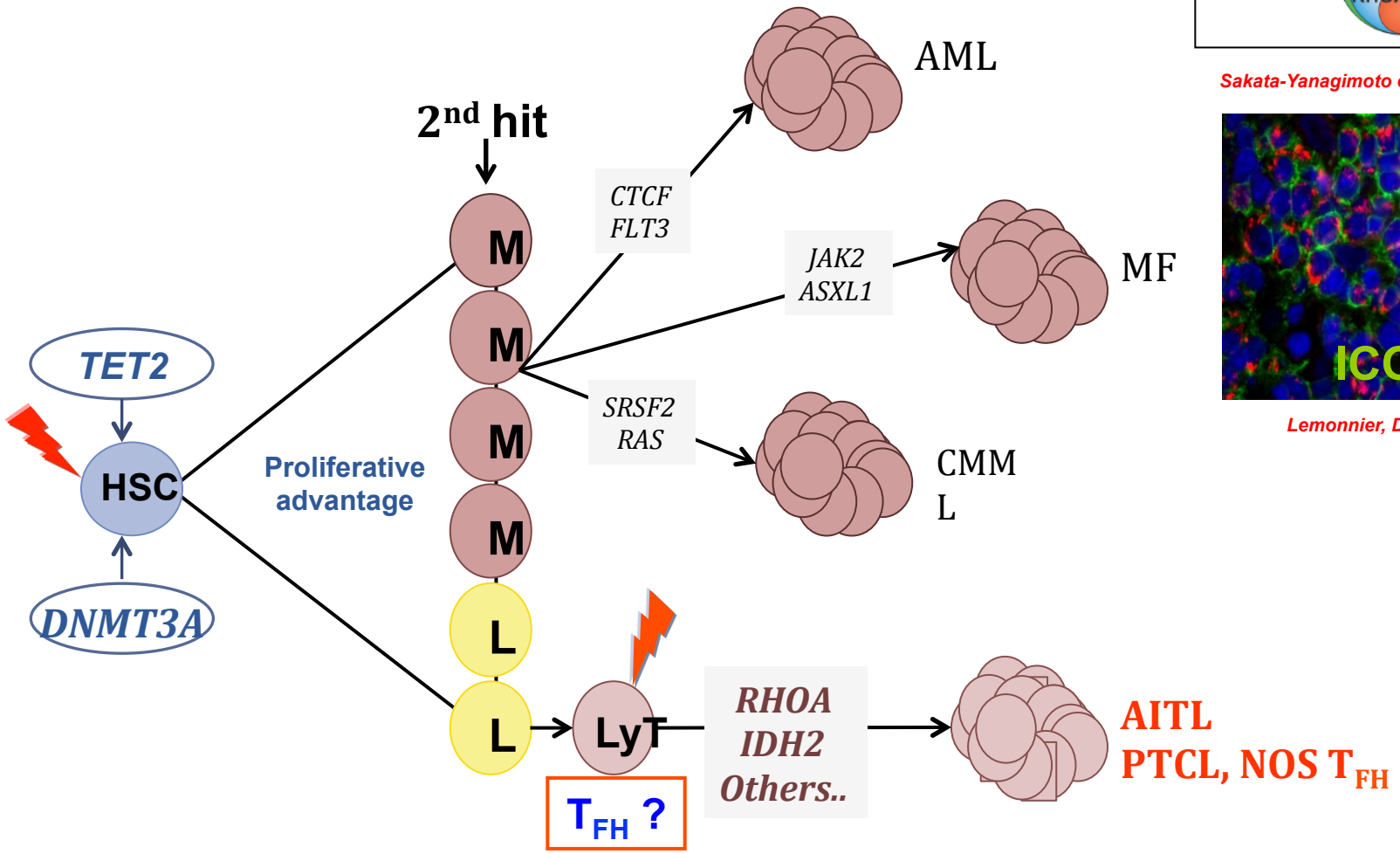
A peculiar model of lymphomagenesis….



Sakata-Yanagimoto et al. Nat Genetics 2014

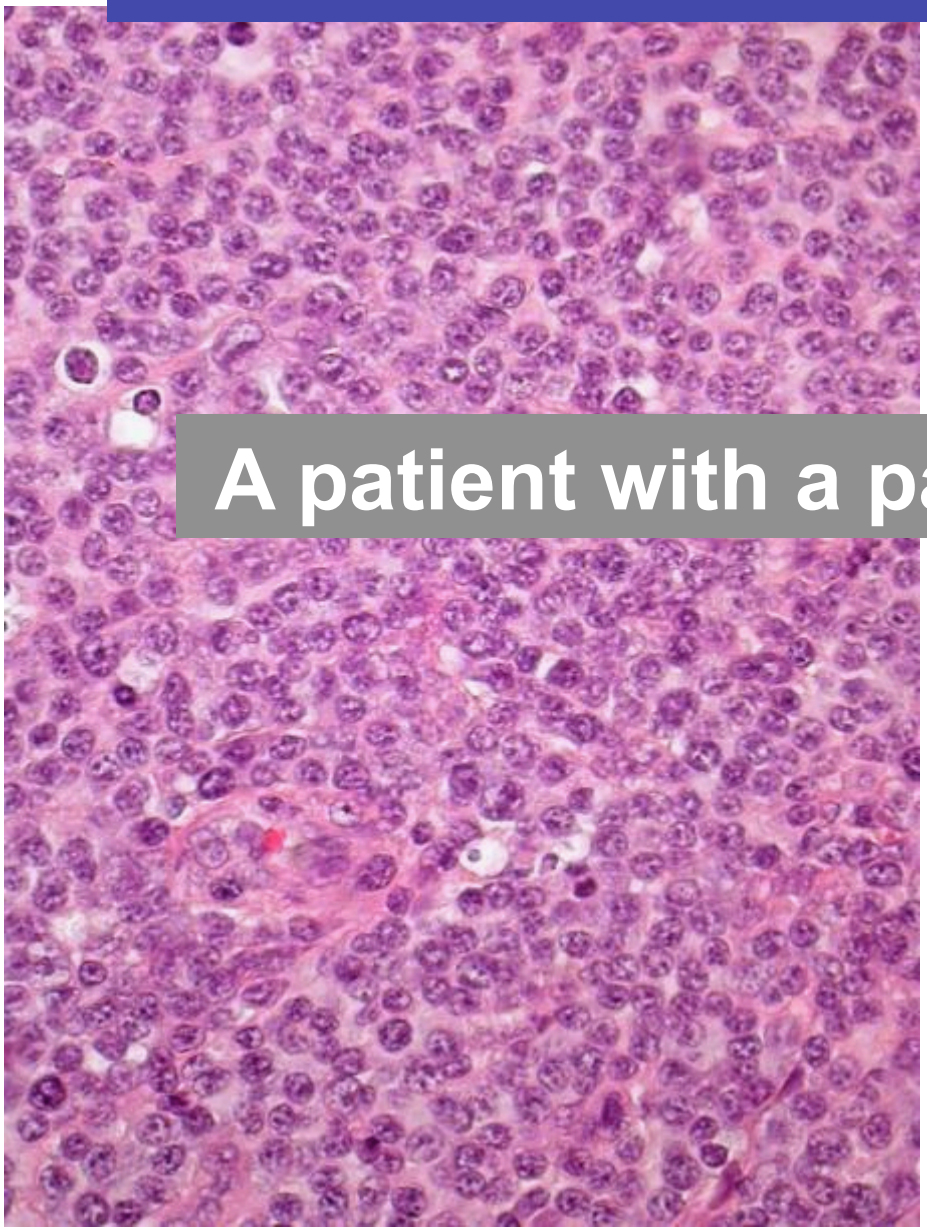


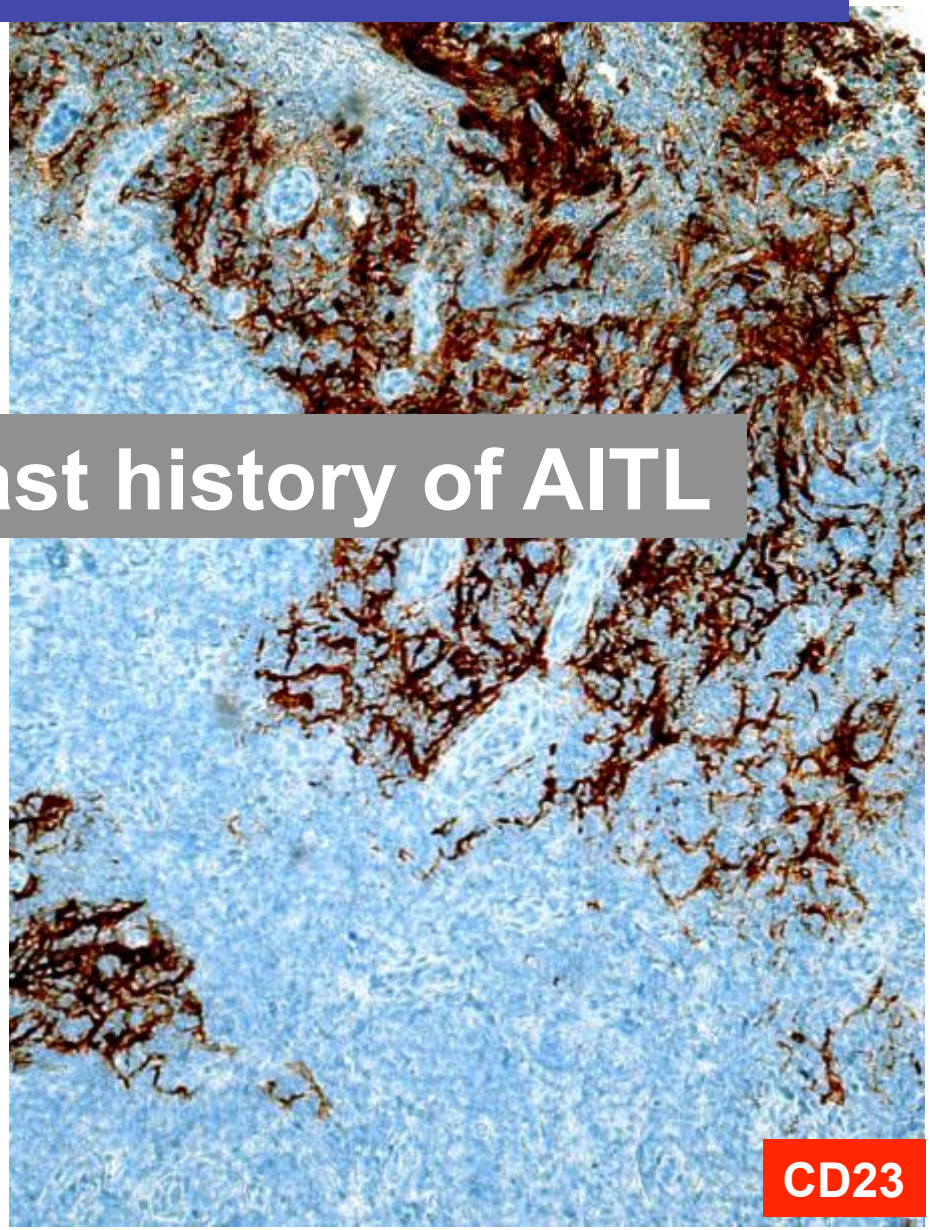
Lemonnier, Dupuy et al. unpublished



Quivoron, Couronné et al. Cancer Cell 2011
Sakata-Yanagimoto et al. Nat Genetics 2014

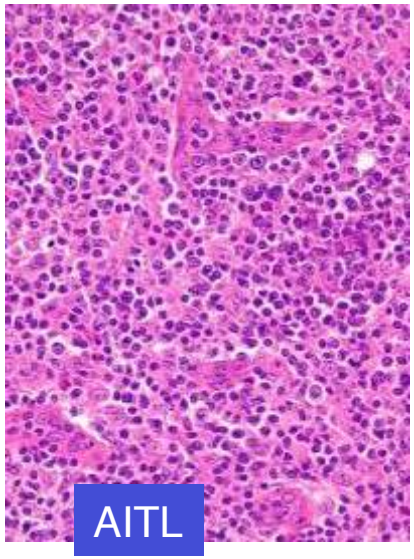
PTCL,NOS or AITL « tumour-cell rich ?



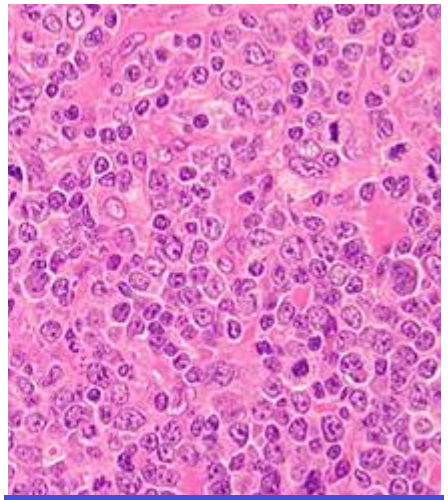


A patient with a past history of AITL

Revisit the diagnostic criteria of AITL ?



AITL

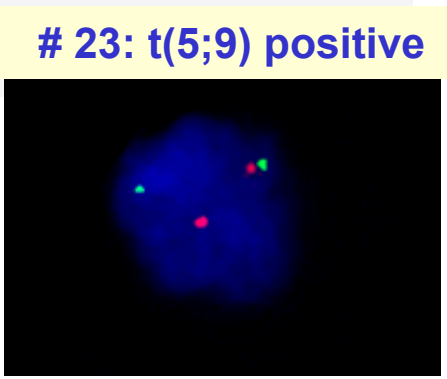


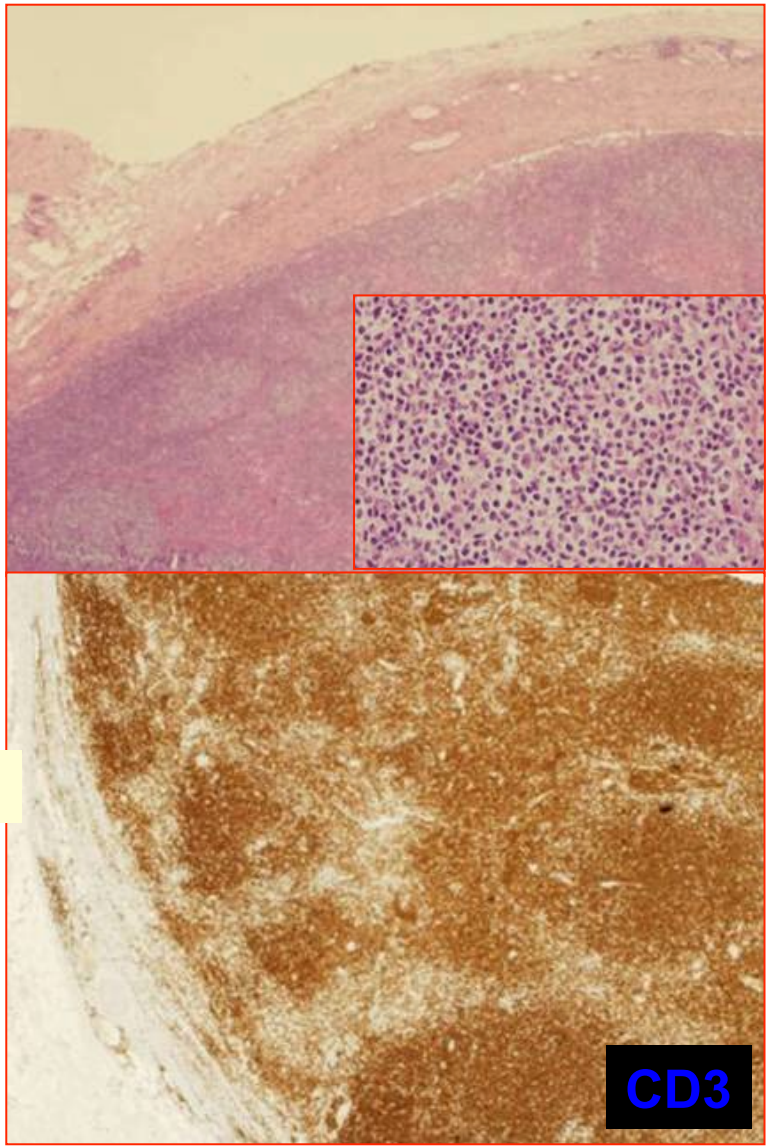
PTCL,NOS, TFH-like

- Loss of the microenvironment ↘ (inflammatory component↘ ↘vascularity, FDC)
- Enrichment in large neoplastic cells

Follicular PTCL

- Nodular growth pattern
- small/medium sized T cells
- CD4+, CD10±
- Expression of T_{FH} markers (BCL6, CXCL13, PD1, ICOS), CD57±
- **t(5;9) translocation (SYK-ITK fusion) in 20-30% of cases**
- *TET2* mutations
- Relationship to AITL?

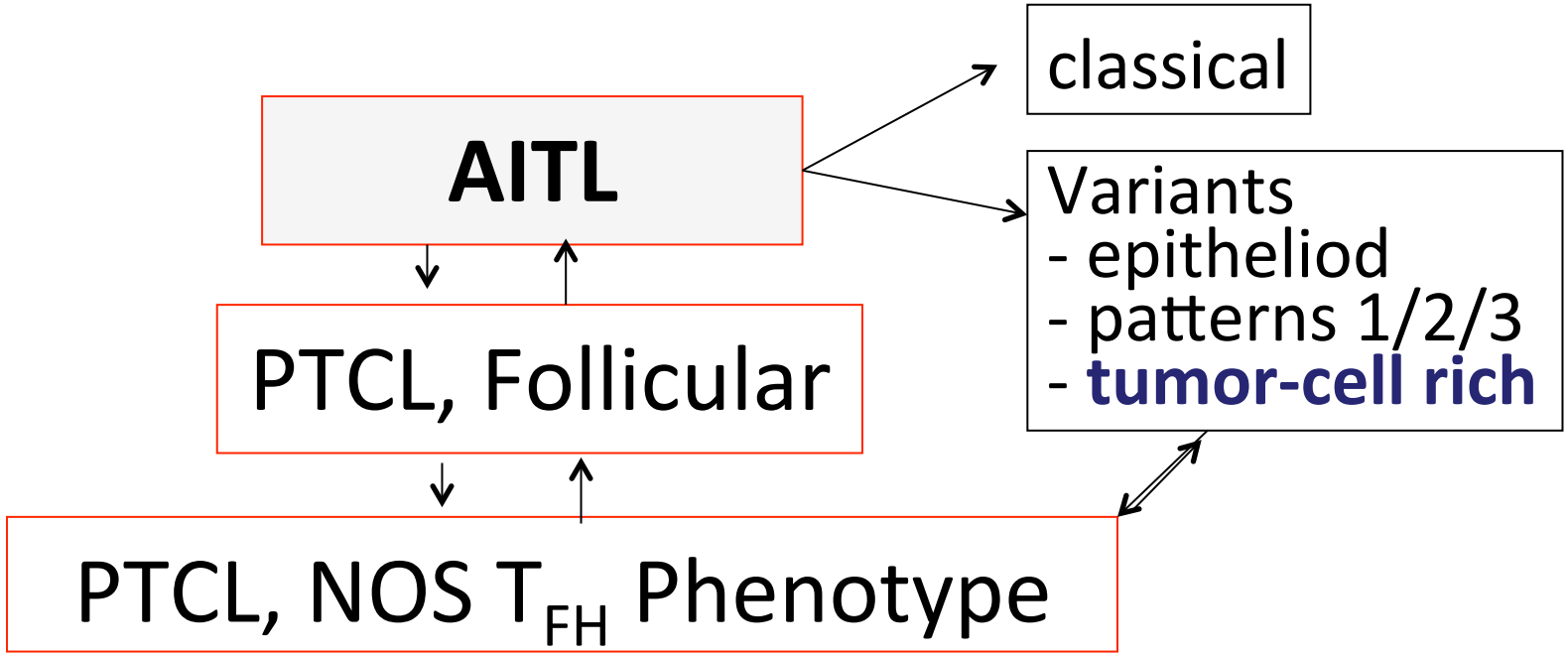




de Leval L et al. AJSP 2001; Streubel B et al. Leukemia 2006; Bacon C et al. Br J Haematol 2008; Qubaja M et al. Human Pathol 2008; Huang L et al. AJSP 2009

Courtesy: Louise Galmiche-Rolland

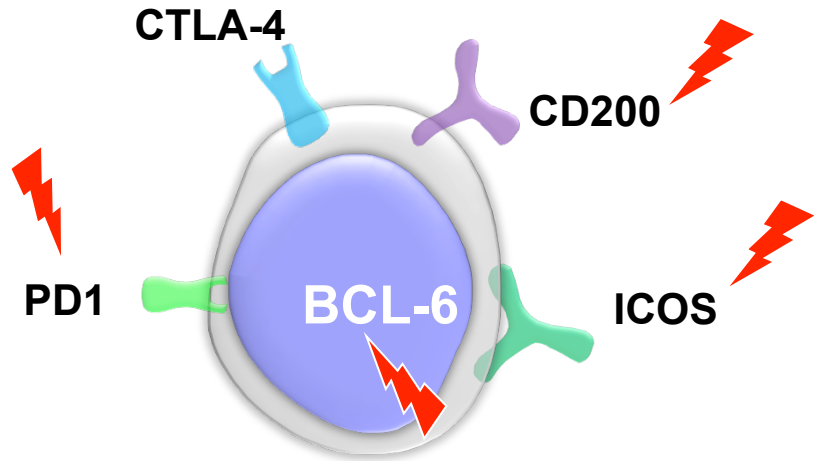
Nodal T_{FH}-related PTCL
Future evolutions of the WHO classification



- ✓ Despite a different morphology, share a similar TFH profile, likely similar genetic alterations and GEP
- ✓ Recommandation: extensively investigate any case of « PTCL, NOS » for FDC, CD10, T_{FH} markers, EBV…..
- ✓ In the next future, may influence the clinical management & therapy

Nodal T_{FH}-related PTCL : implications for therapy…?

- **Microenvironment:**
anti-angiogenic (thalidomide, anti-VEGF/Bevacizumab), macrophages ?, B-blasts (Rituximab),…
- **Immunomodulatory** compounds: IFNγ, cyclosporine, lenalinomide,…..
- **Neoplastic T_{FH} antigens** (campath, TFH antigens, cytokines (IL21, IL6), chemokines (CXCL13)
- **Specific pathways** (PDGFRA, SYK, IDH2 inhibitors, demethylating agents…)



TFH cell

Pathologically and biologically-oriented clinical trials…..

The lymphoma classification will continue to evolve!

2014 WHO CAC Meeting, Chicago