Avancées pathogéniques dans l'HL

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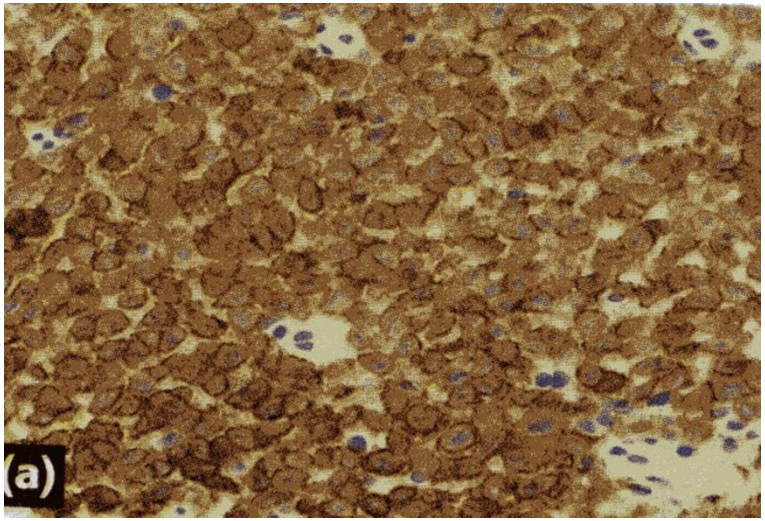
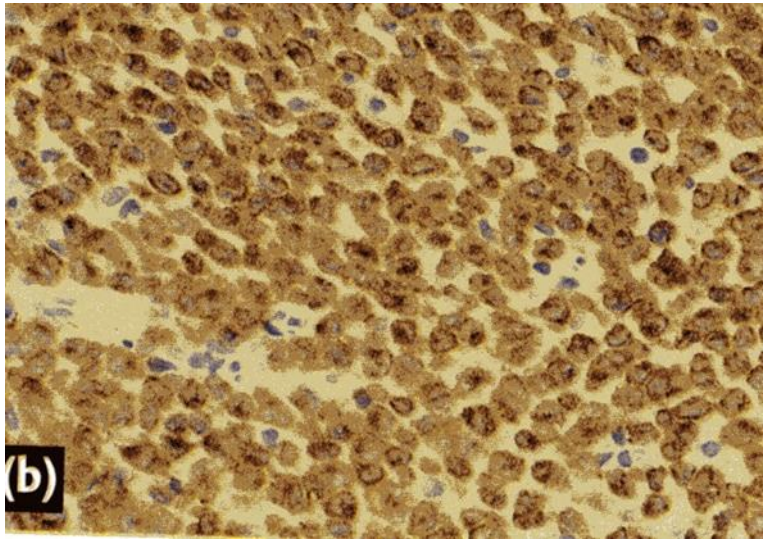
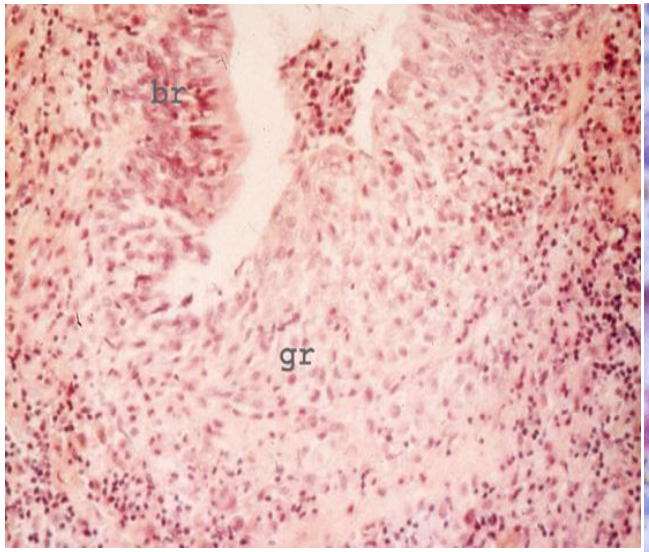
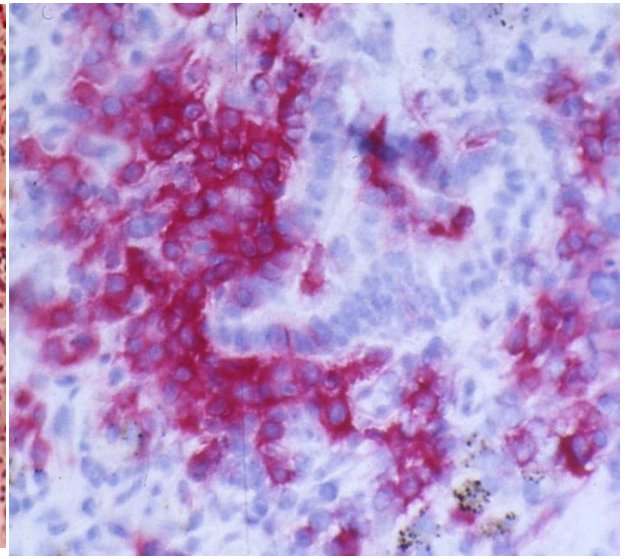
CD1a

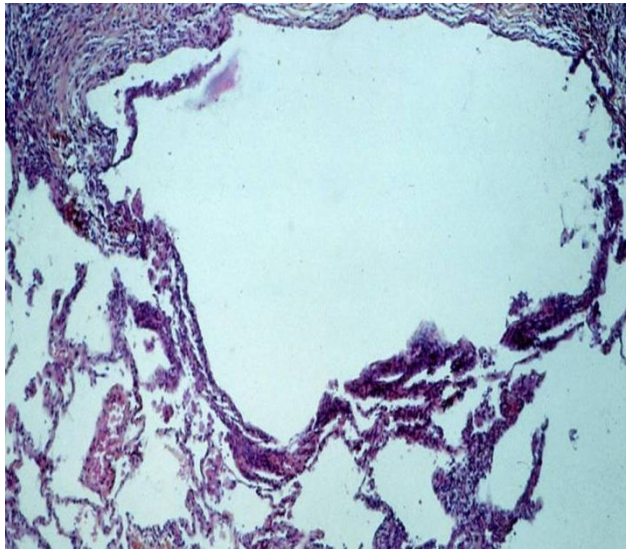
Langerine
CD207

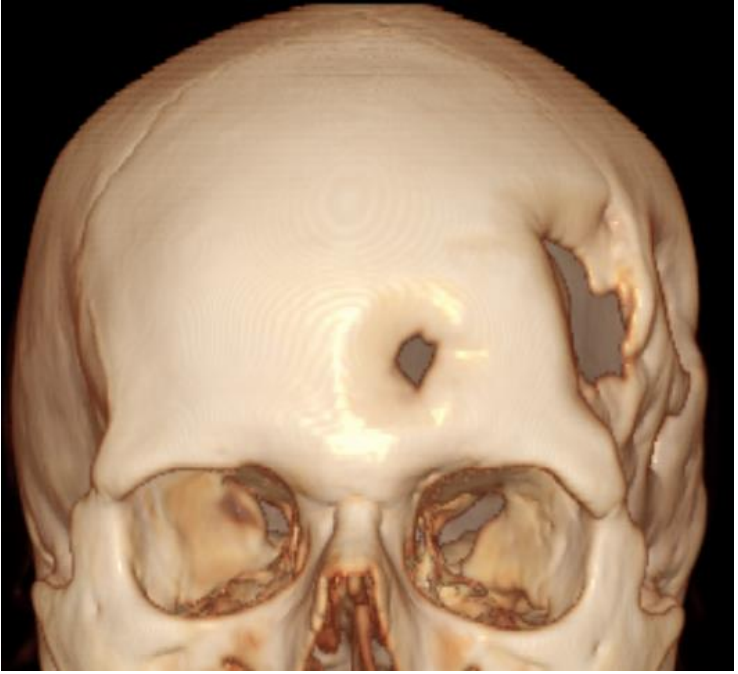


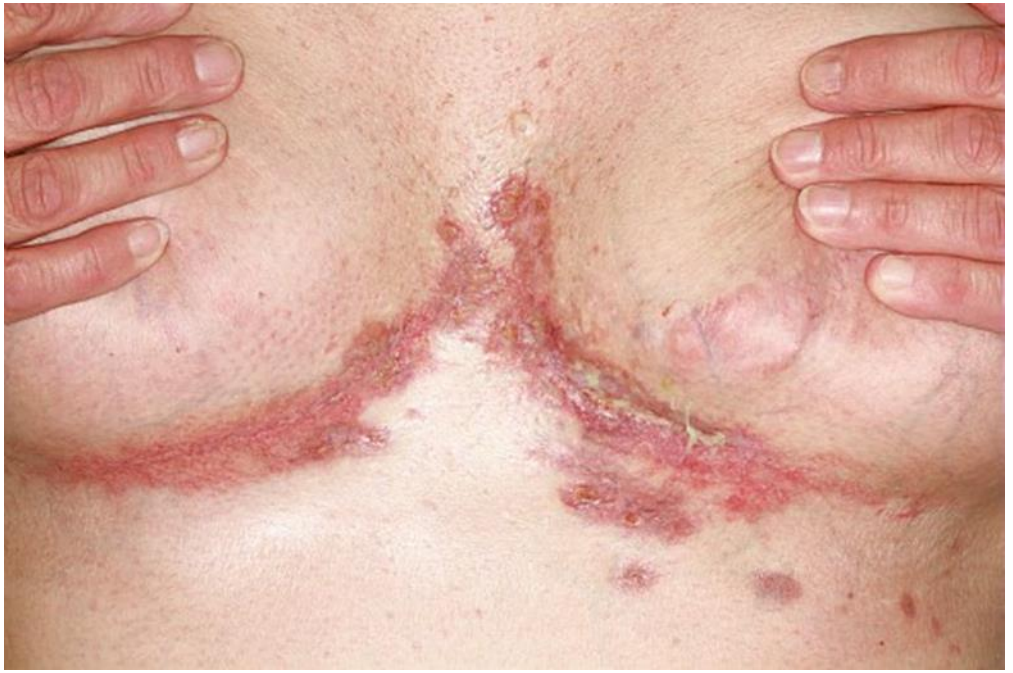


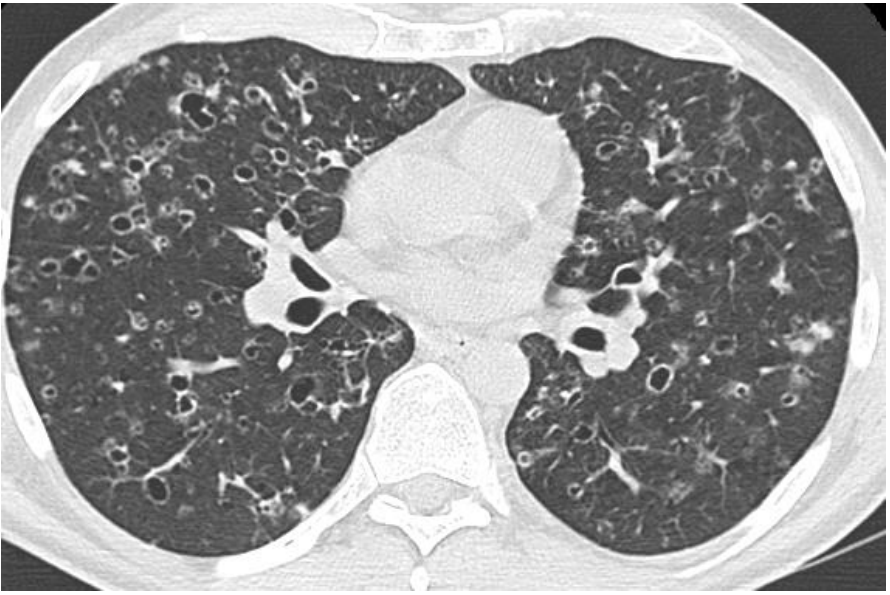


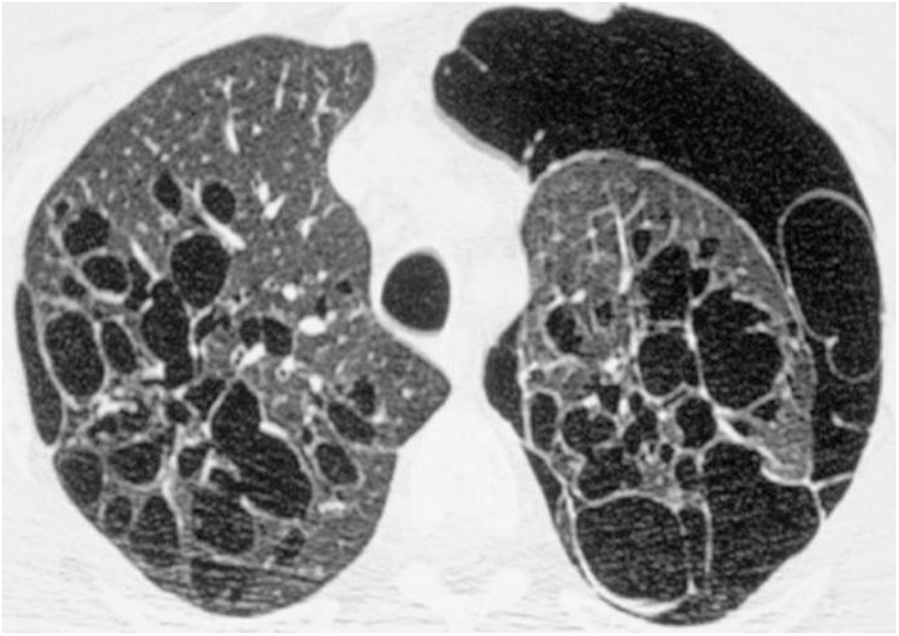








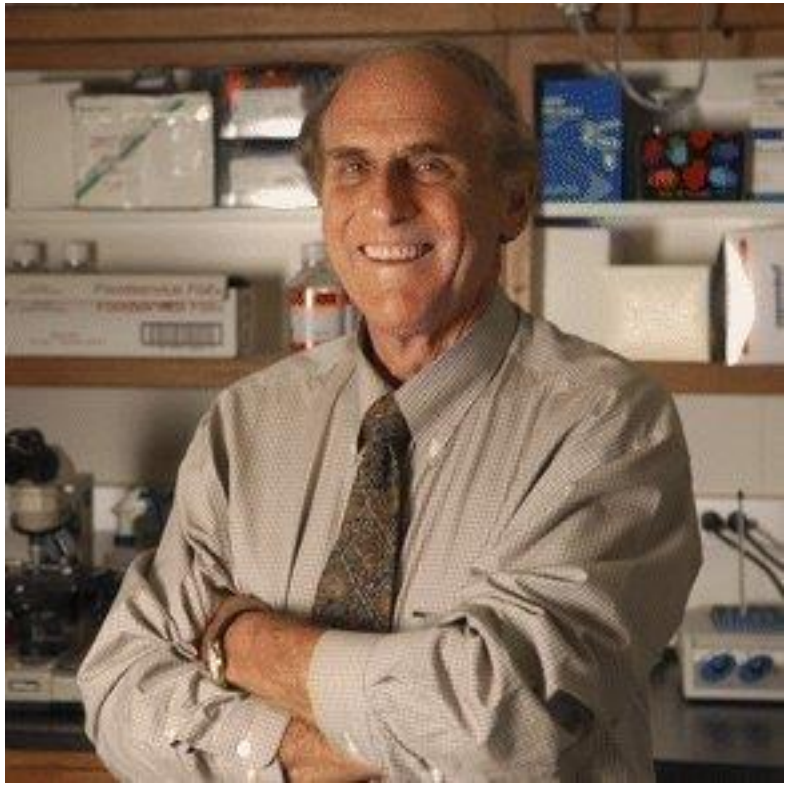




Plan

- Bref rappel sur la biologie des cellules dendritiques
- Accumulation des cellules de l'HL dans différents organes/tissus
- Caractère destructeur des lésions: lyse osseuse, cavité pulmonaire..
- Origine des cellules CD1a+ de l'HL?
- Variabilité de la maladie
  - Spectre clinique
  - Evolution variable des lésions et de la maladie (régression spontanée)
- Tabac et atteinte pulmonaire de l'adulte
- Etiologie (s)?
- Synthèse

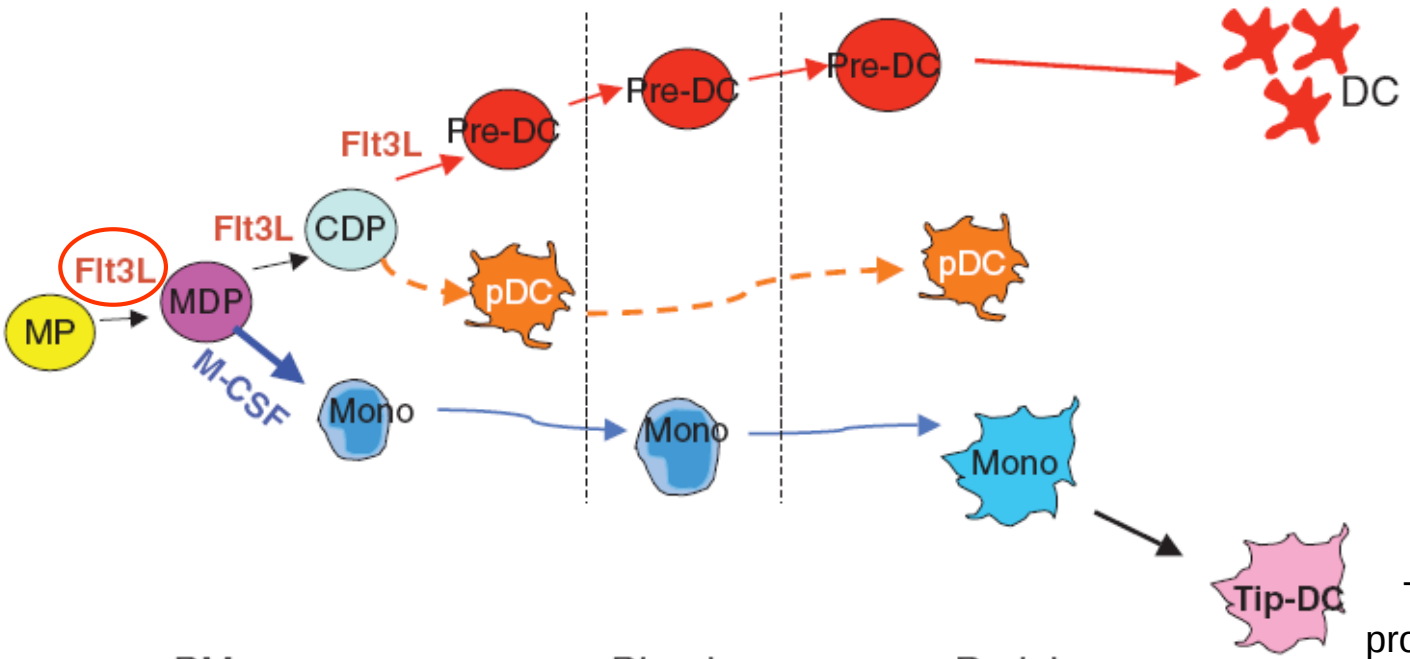
Ralph Steinman



Prix Nobel Médecine 2011

Kang Liu
Michel C. Nussenzweig

Origin and development of dendritic cells



Immunological Reviews 2010

Cellules Dendritiques

- Origine médullaire
- Puissantes cellules présentatrices d'antigènes
- Fonction de:
  - cellules sentinelles
  - cellules migratrices
  - cellules immunitaires afférentes
  - influent aussi sur les cellules effectrices
- Lien entre immunités innée et acquise

Cellules dendritiques (2)

- De façon schématique:
  - DC conventionnelles (cDC)
  - DC plasmacytoïdes (pDC)

- pDC
  - Production rapide et importante d'IFNα

- cDC
  - Résidentes dans organes lymphoïdes
  - Migratrices à partir des organes périphériques
  - Hétérogénéité ++
  - Capacités de capture, « processing », présentation antigénique, activation lymphocytaire T variables (microenvironnement)
  - Immatures à l'état basal

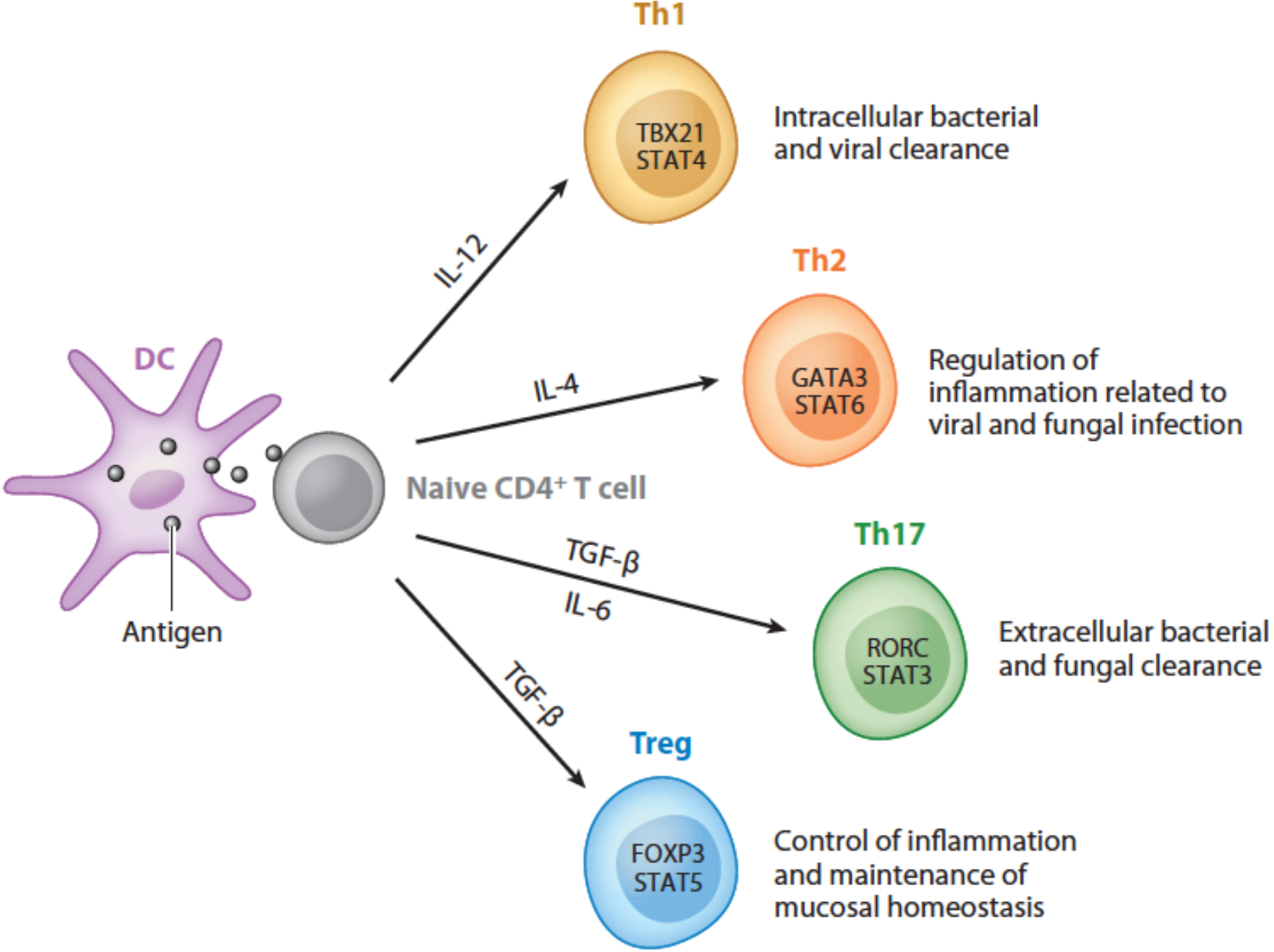
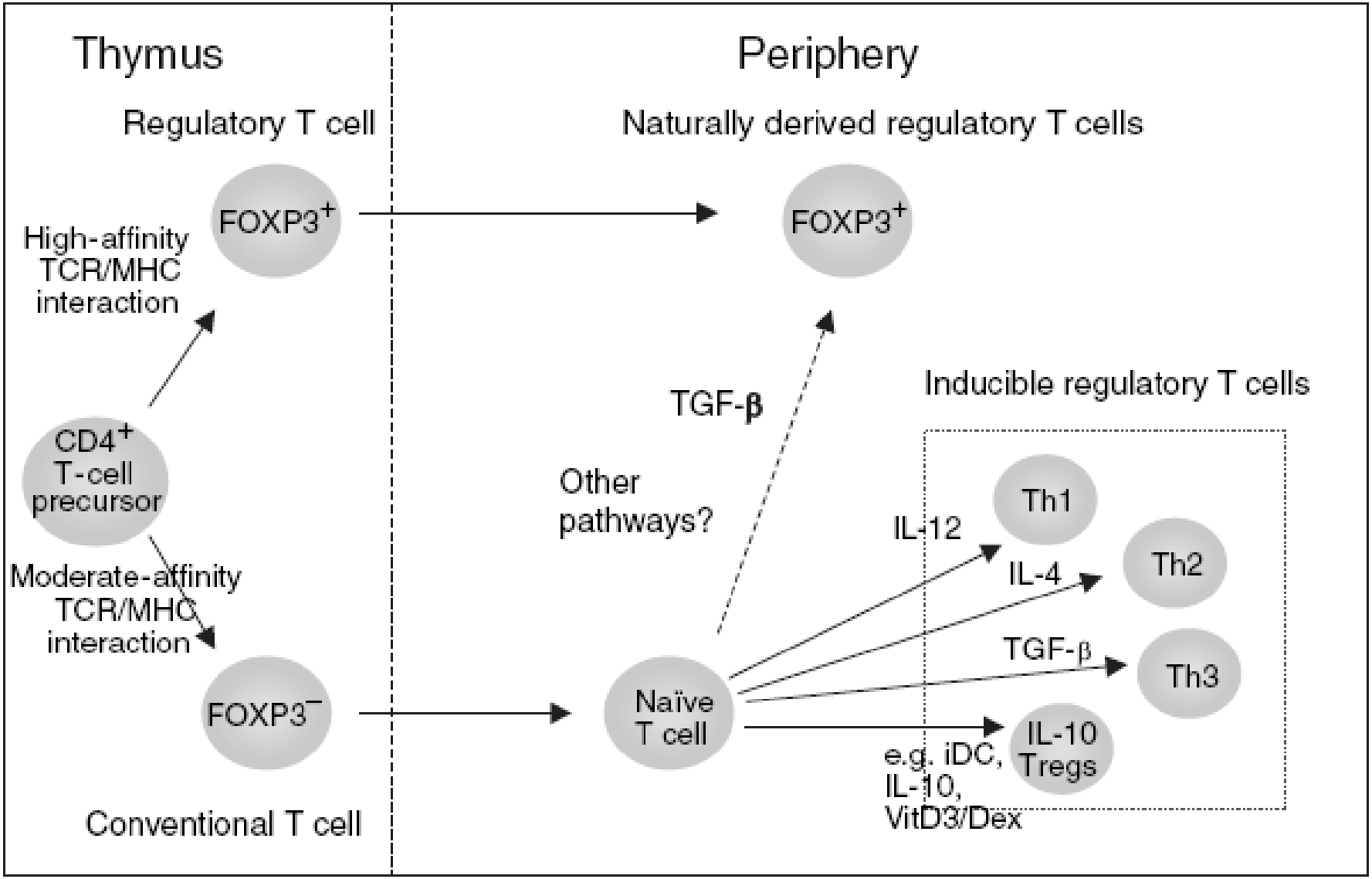


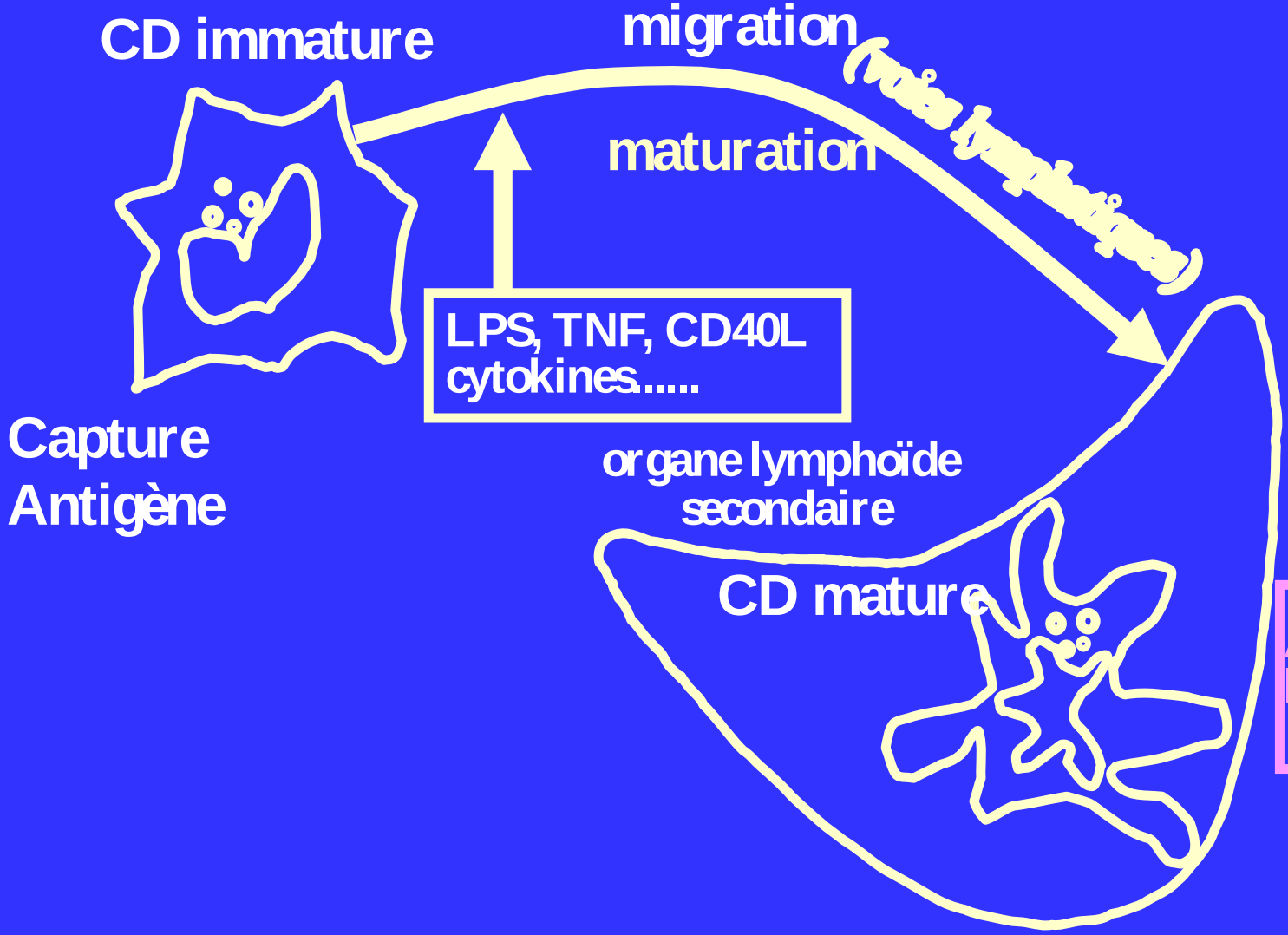
Figure 1

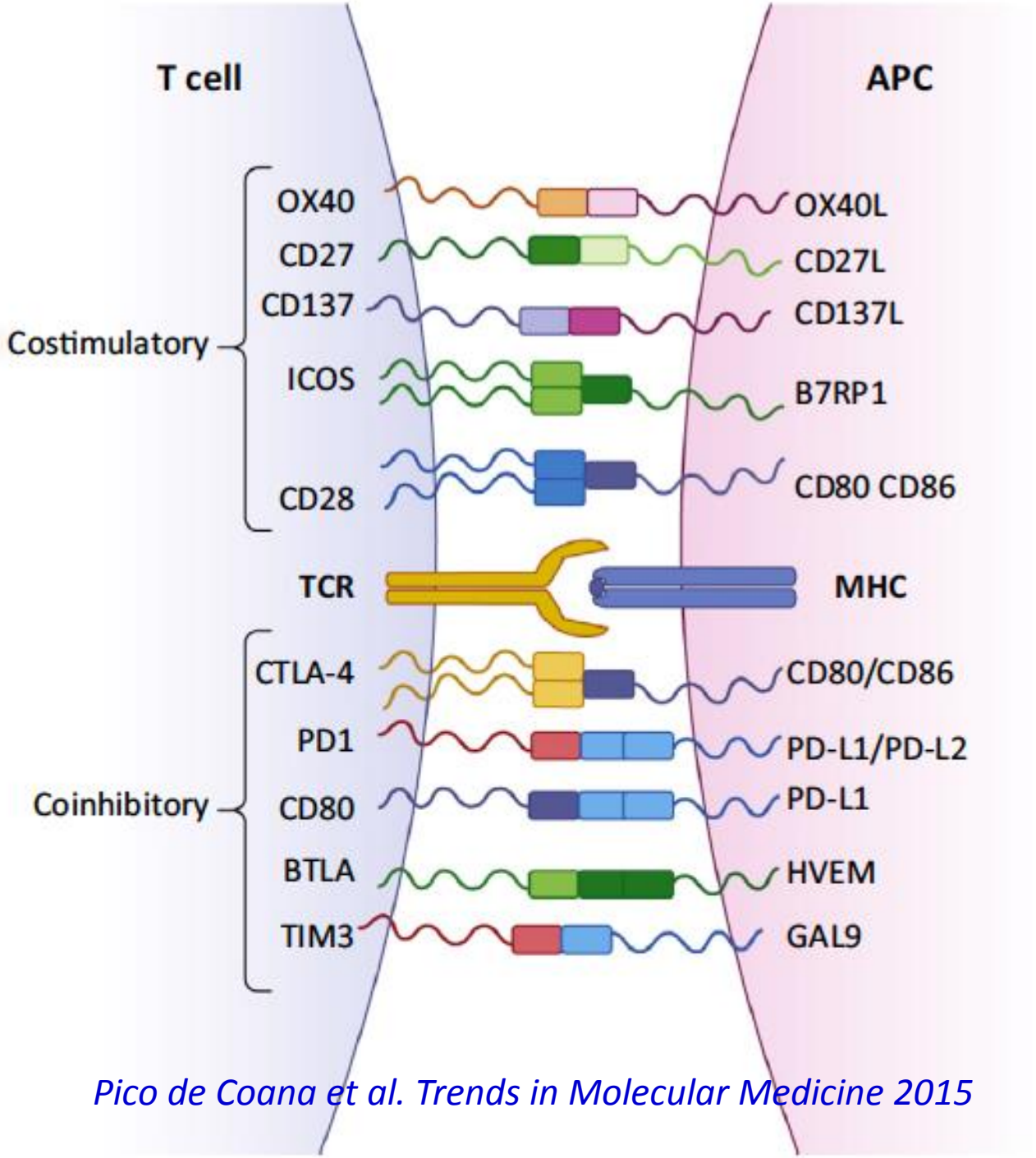
Chen et al Annu Rev Immunol 2013

Les lymphocytes T régulateurs



Maturation des Cellules Dendritiques





Pico de Coana et al. Trends in Molecular Medicine 2015

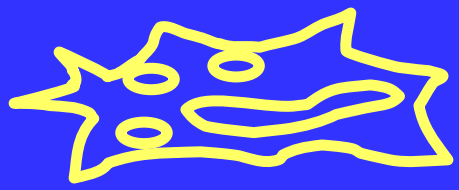
Chemokines et CD/CL

Récepteurs de chémokines

Chémokines

CD immature

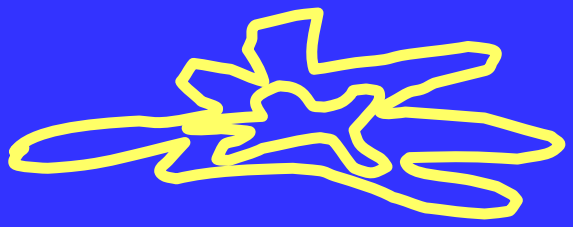
CCR1
CCR5
CCR6



CCL3 (MIP1- a)
CCL5 (RANTES)
CCL20 (MIP-3 a)

CD mature

CCR7



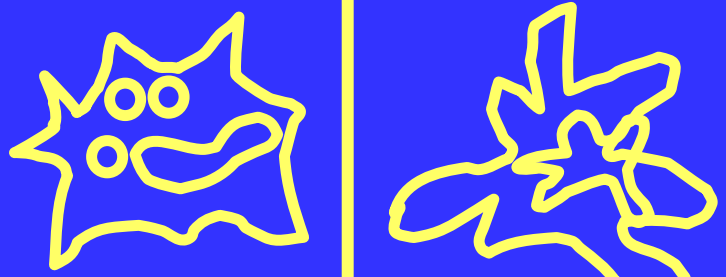
CCL19 (MIP- 3b)
CCL21 (SLC)

Caracterisation of DCs

Immature *DC*

Antigen processing
Intra-cellular MHC II
CD1a + (LC)
Langerin + (LC)
CD80-,CD86 +/-
CD40-
CCR6+

Inhibitory signals
(IL-10, TGF-b, VEGF..)



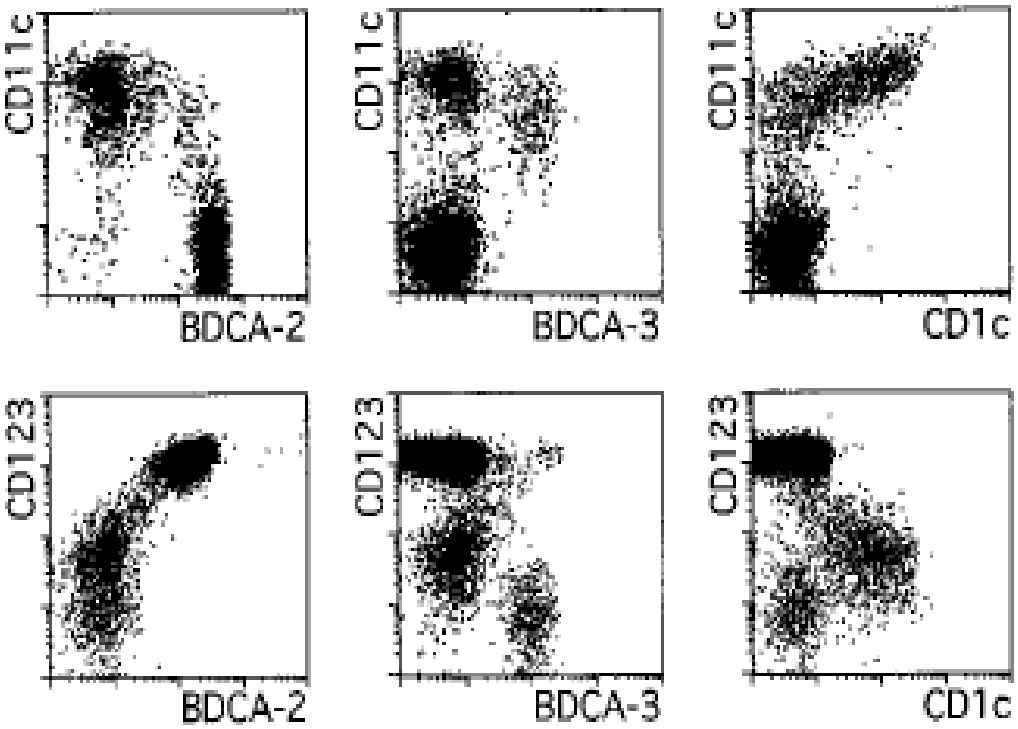
Mature DC

T cell activation
Surface MHC II
CD40 ++
CD80++ CD86++
CD83+, DC-LAMP+
CCR7+
IL-12+++

Activating signals
(IL-1b, TNF-a, CD40L..)

Microenvironment

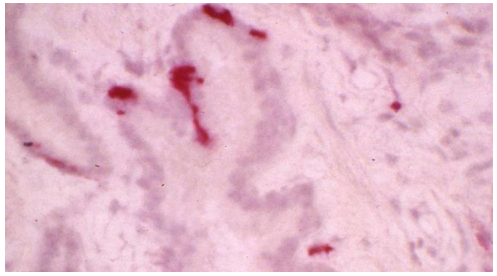
Les différentes sous-populations des CD du sang humain définies par les BDCA

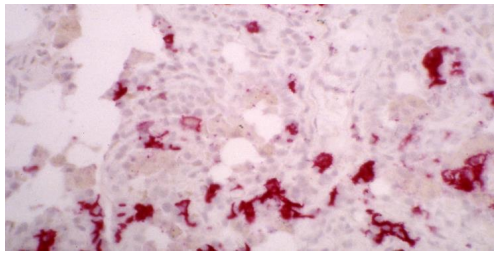


Dzionek et al JI 2000

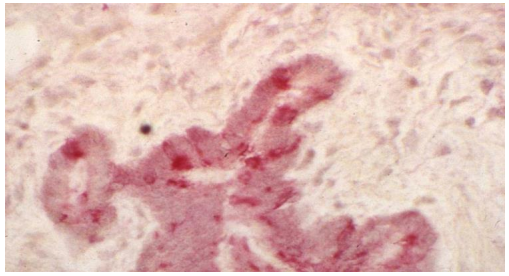
Accumulation des cellules de l'HL dans les lésions

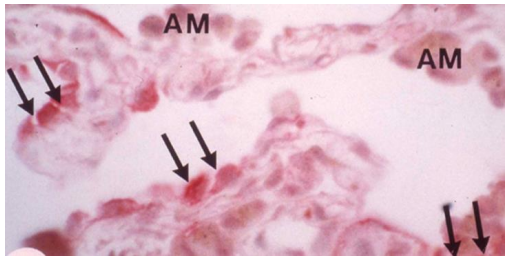
CD1a



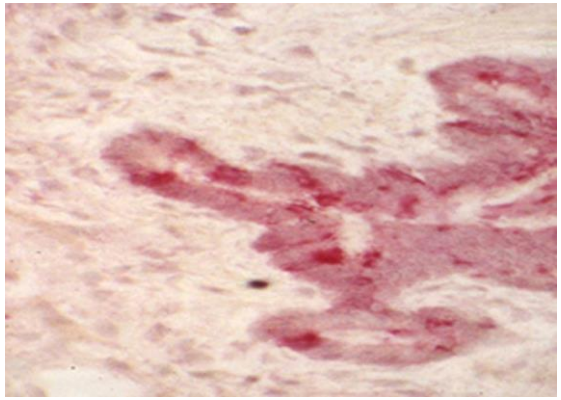


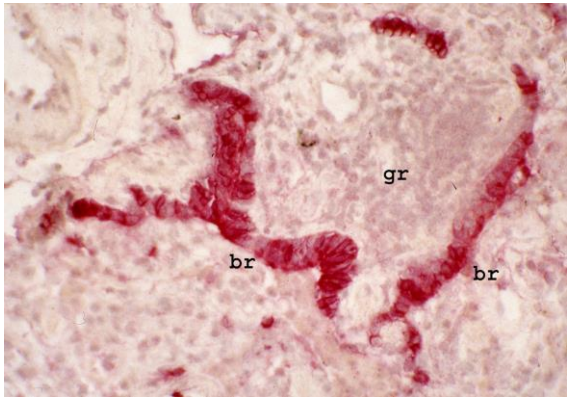
GM-CSF





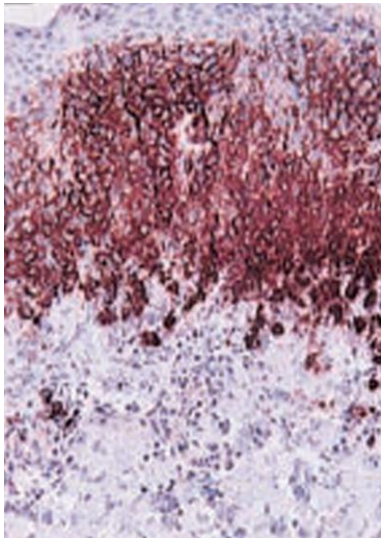
Tazi et al JCI 1993



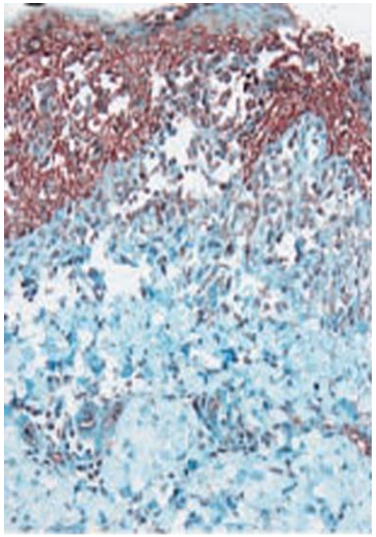


Tazi et al Thorax 1996

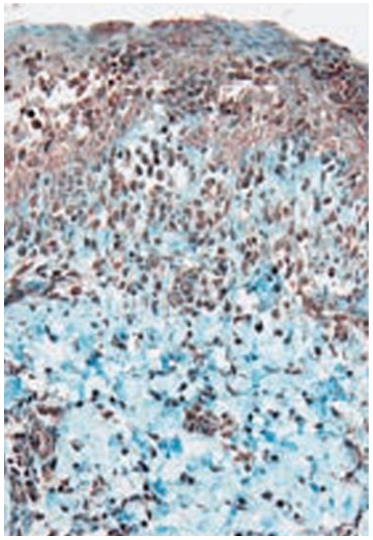
CD1a



CCR6



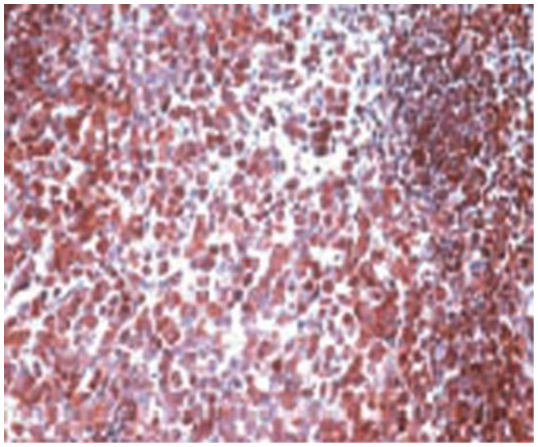
CCL20

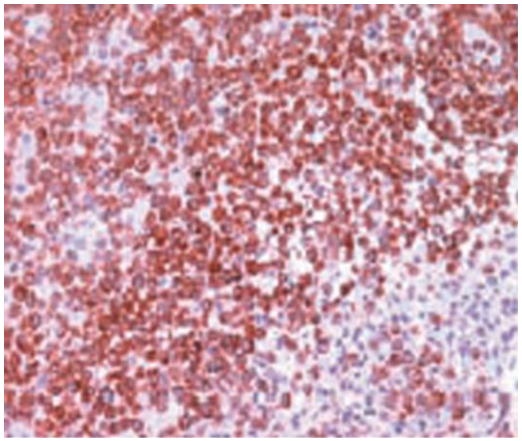


Fleming et al 2003

CCL20

LCH node



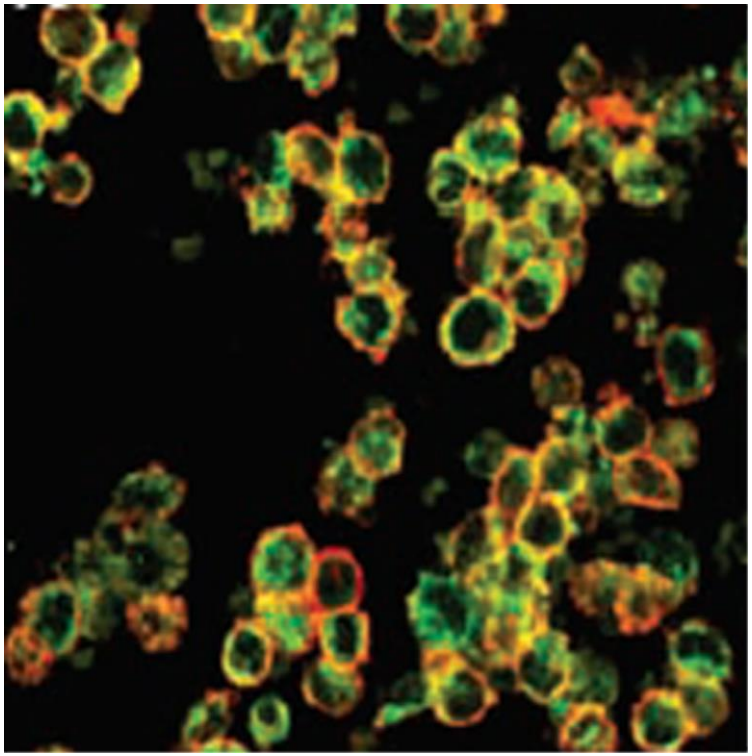


LCH bone

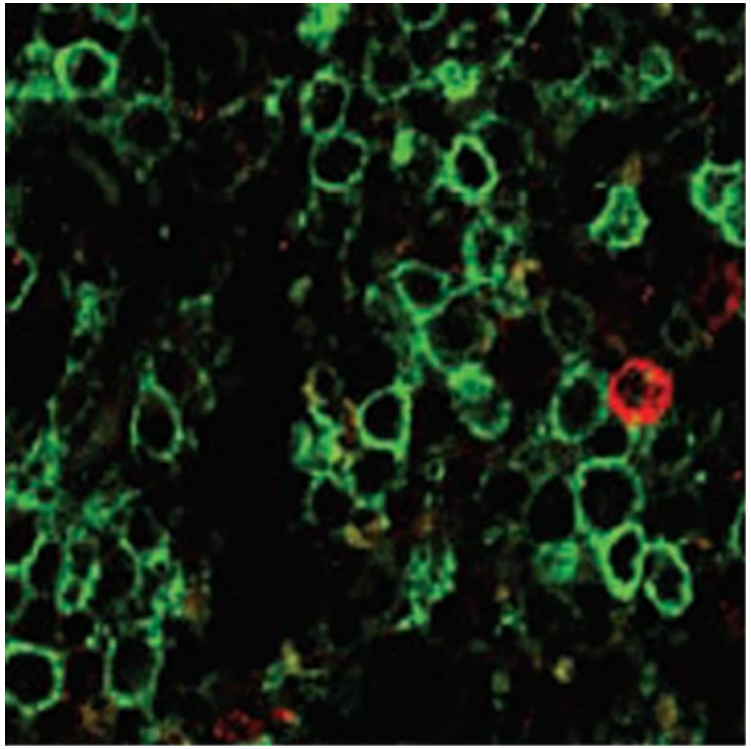
Annels et al 2003

Chemokine Receptor Expression
CD1 a+ cells in Bone LCH Lesions

CCR6

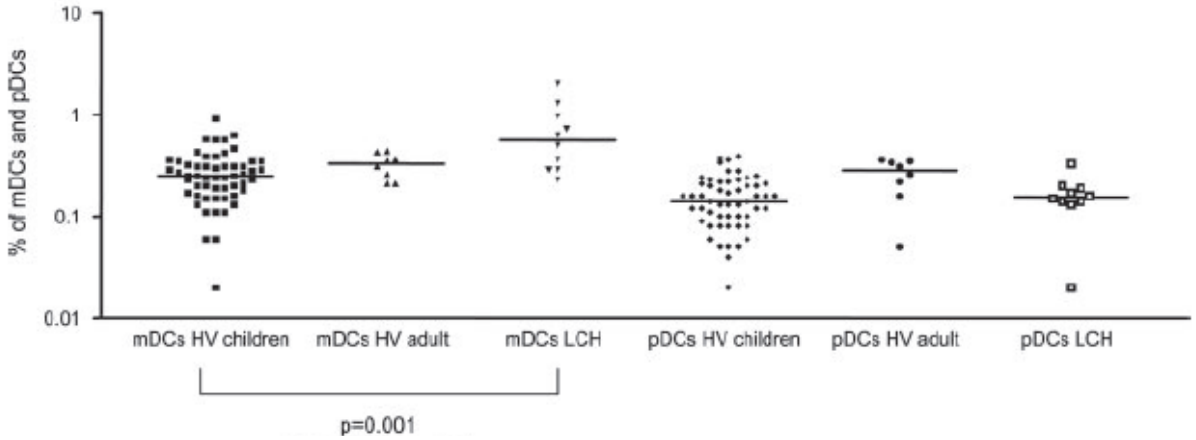


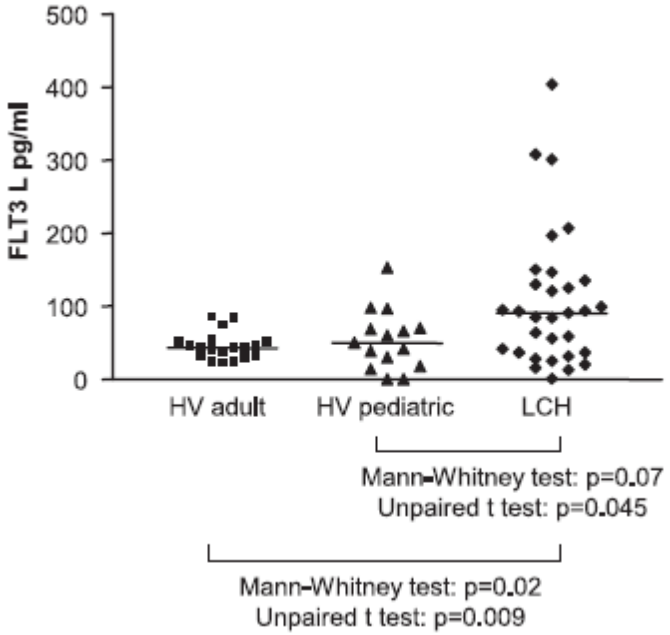
CCR7

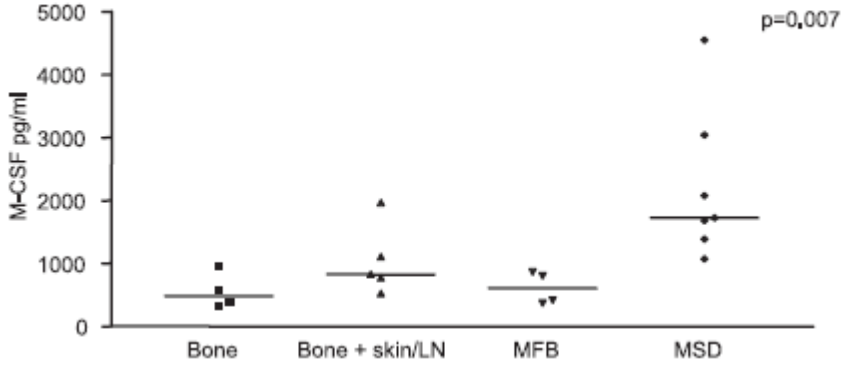


Annels et al 2003

Increased Blood Myeloid Dendritic Cells and Dendritic Cell-Poietins in Langerhans Cell Histiocytosis[1] *Rolland JI 2005*







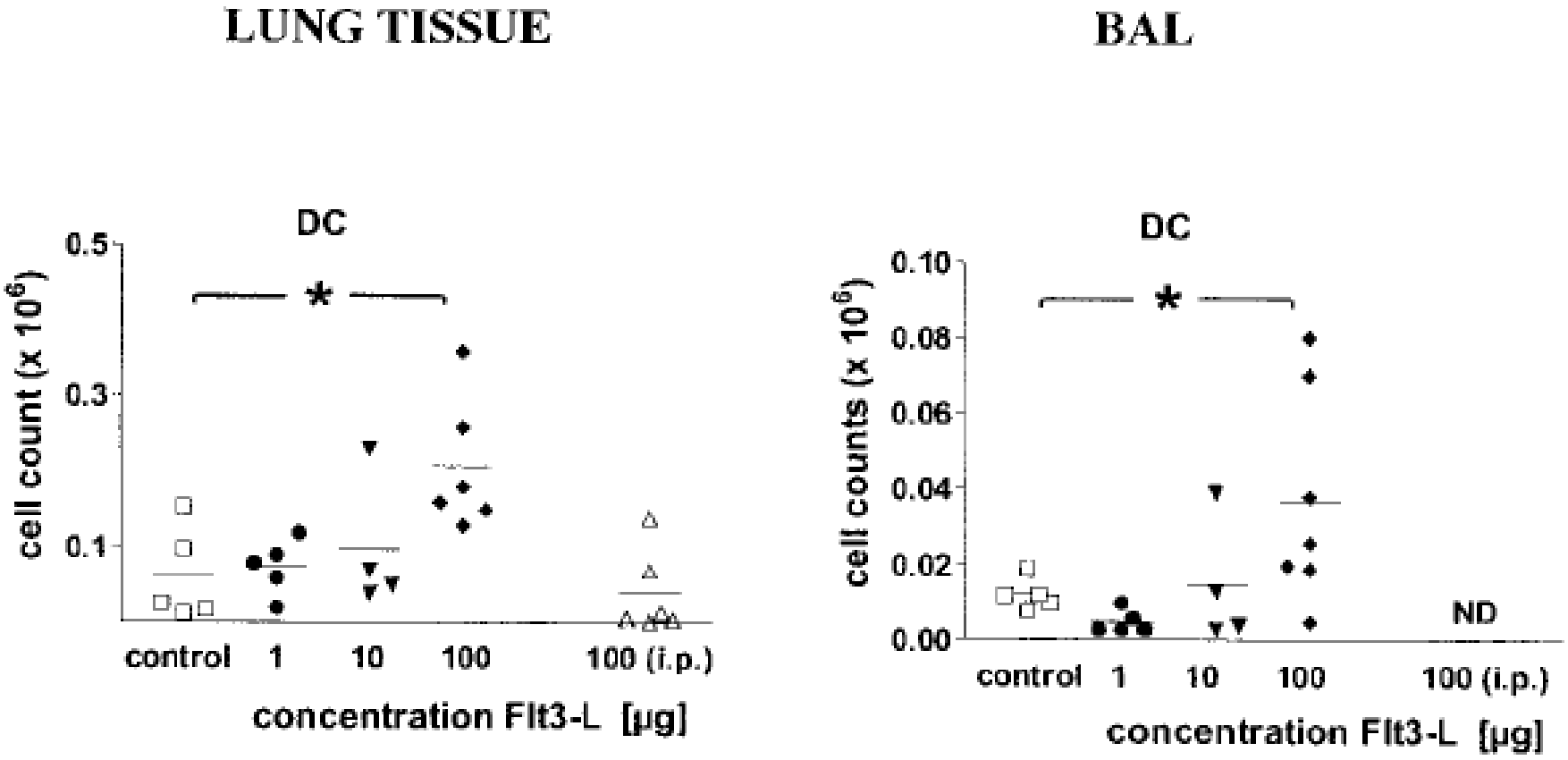
Recruitment of CD1a+ cells in LCH
Other Factors

- Neuropetides (bombesine-like)
- TGF-β
- Flt3-L

- Other chemokines

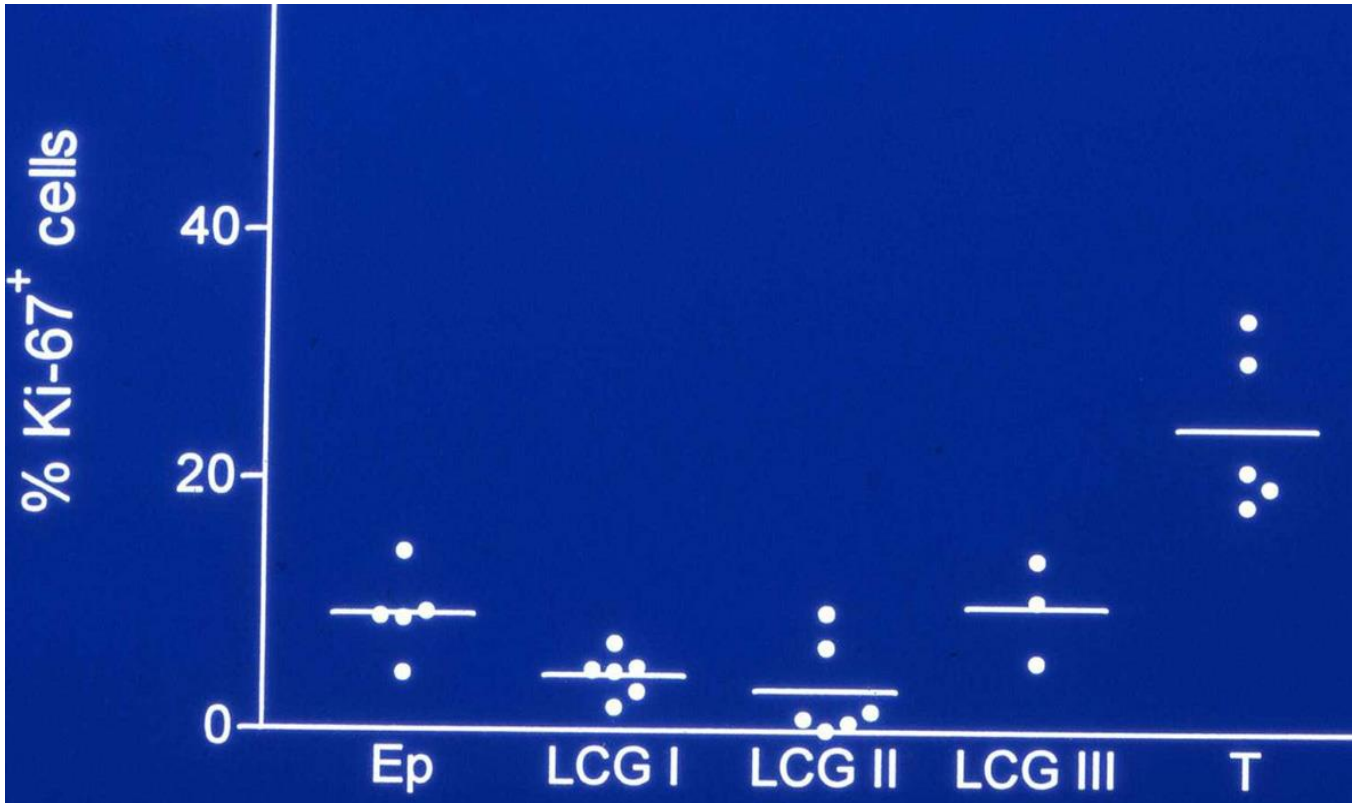
- Others
  - Homing molecules (E-cadherin)
  - Addressins
  - Adhesion molecules

Effets du Flt3-L sur le nombre des CD pulmonaires

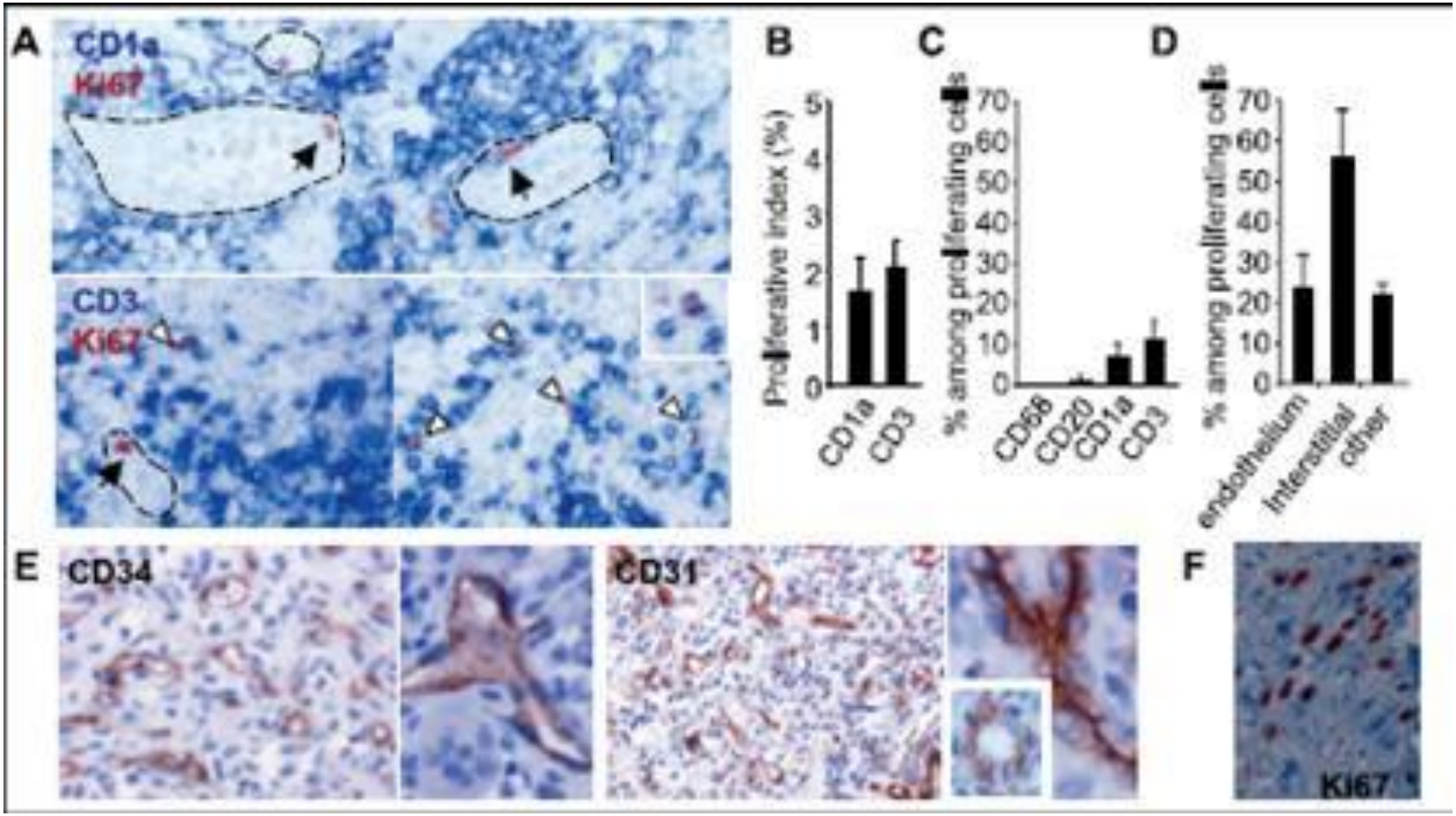


Pabst R et al JI 2003

CD1a+ cells Proliferation in LCH Lesions



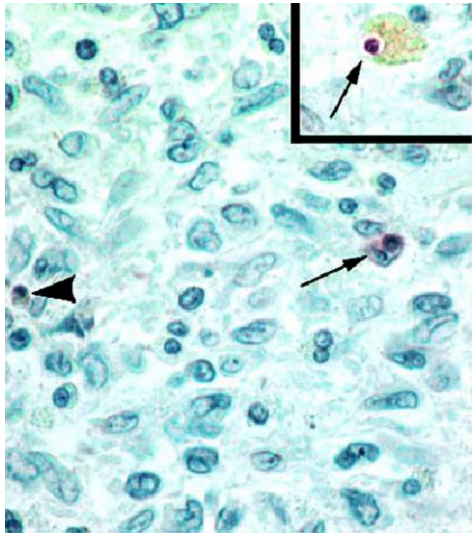
Brabencova et al 1998



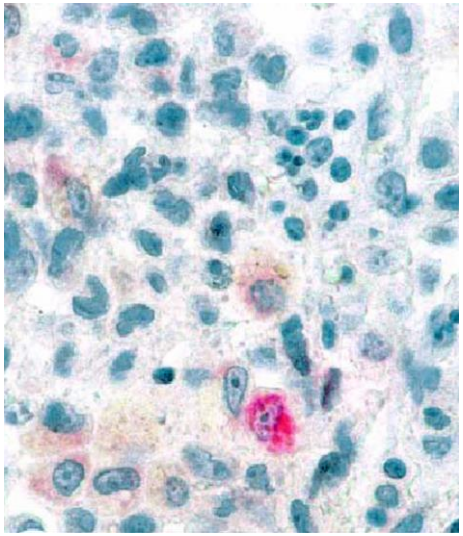
Senechal et al PloS Med 2007

CD1a+ cells Sensitivity to Apoptosis in Adult Pulmonary LCH Lesions

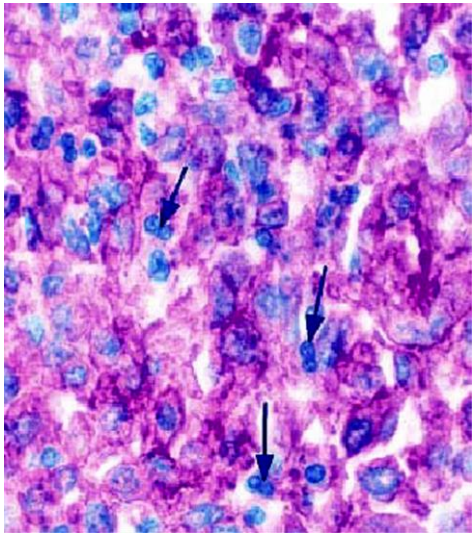
Tunel



Caspase-3



Bcl-X_L

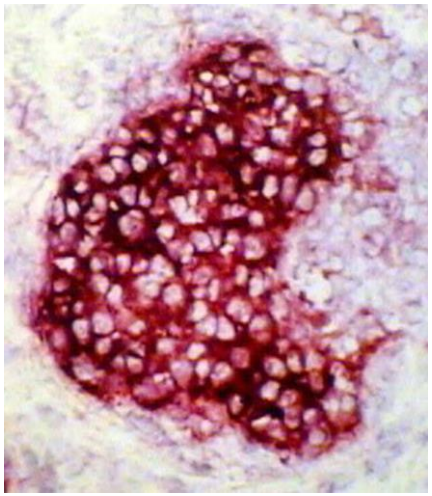
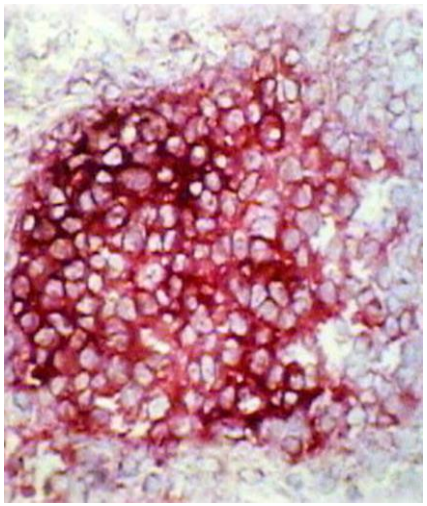
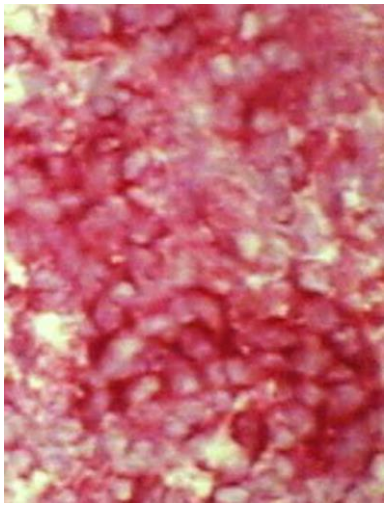
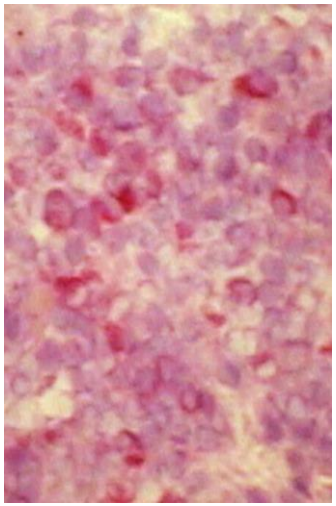


Marchal et al 2004

Etat d'activation des cellules CD1a+
dans les lésions d'HL?

Phénotype des cellules CD1a+ dans l'HL pulmonaire

CD80 **CD86** **CD40** **CD40L**

Tazi et al. JI 1999

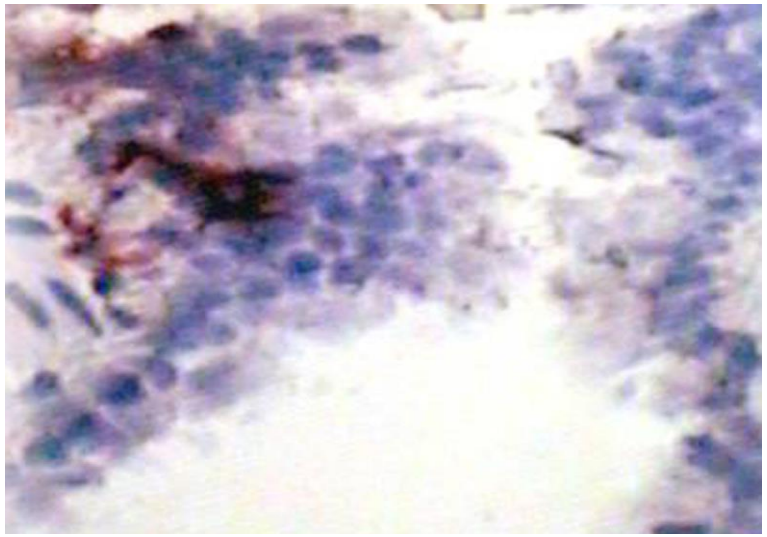
HL Pulmonaire de l'Adulte
Importance du Microenvironnement

	Hyperplasie alvéolaire	Carcinome	Granulome LC
CD80	-	-	+++
CD86	-	-	+++
CD40	-	-	+++
GM-CSF	+	+/++	+++
IL-1β	-	-	++
IL-10	++	++	-

Tazi et al. JI 1999

CD Phenotype in IL-10 K/O Mice

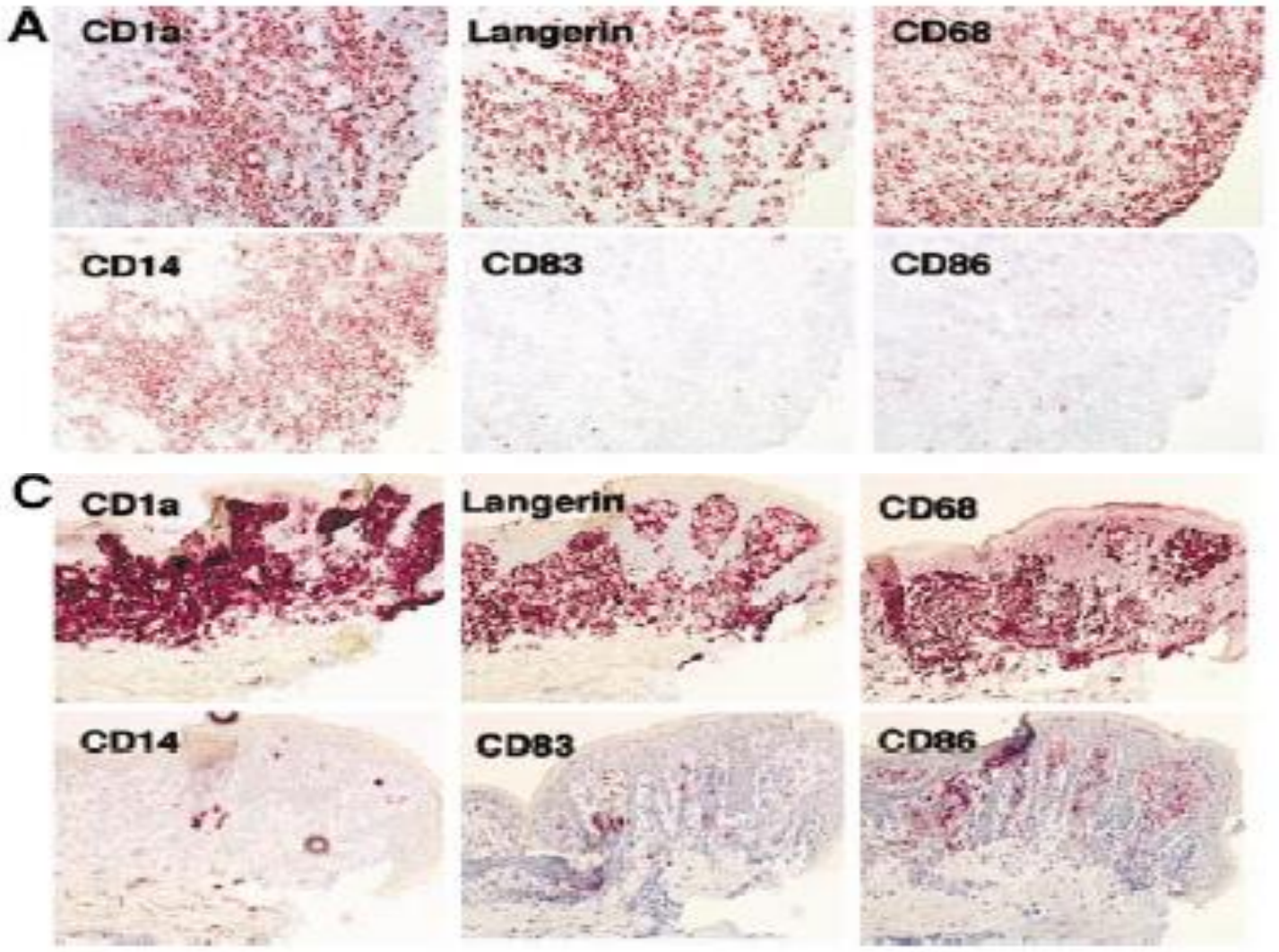
Class II



CD80

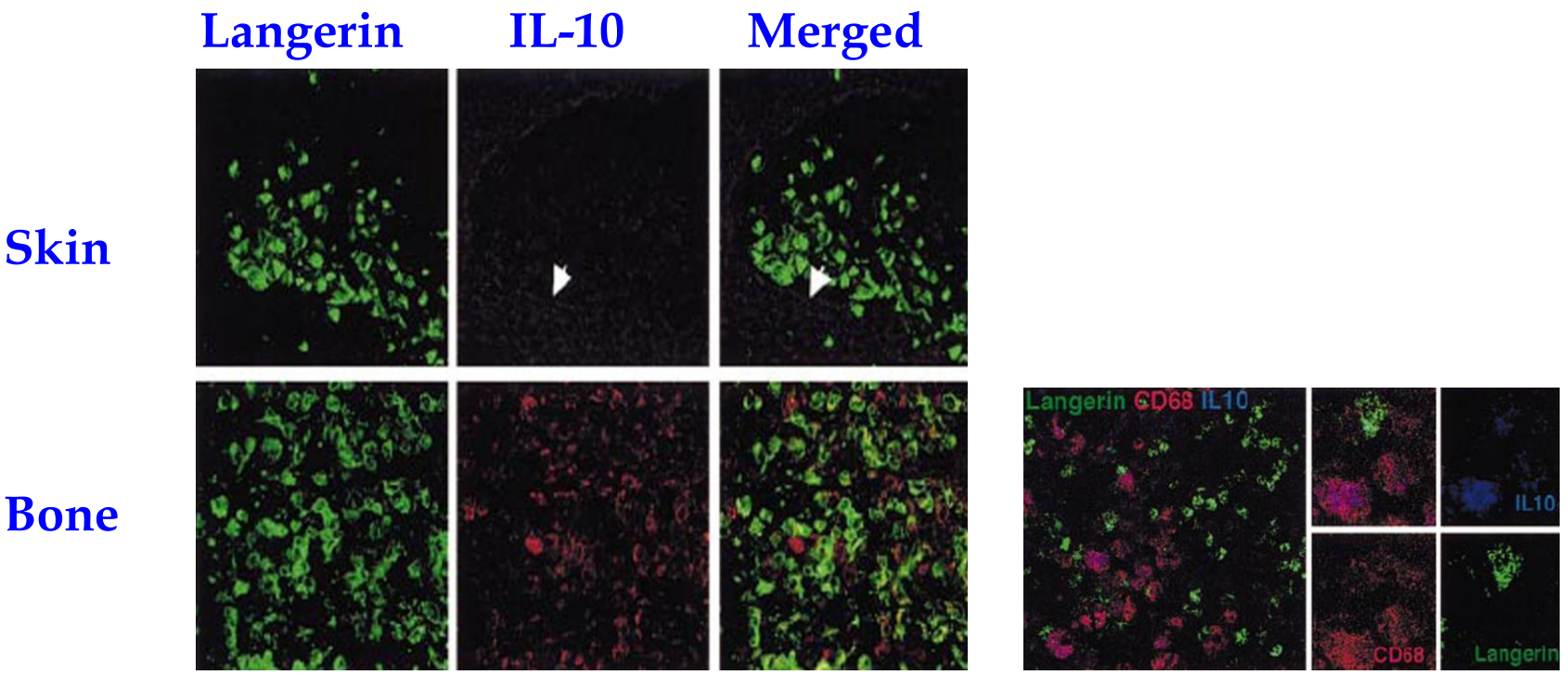
Tazi et al JI 1999

Phénotype des CL dans l'HL osseuse (A) et cutanée (C)



Geissmann et al Blood 2001

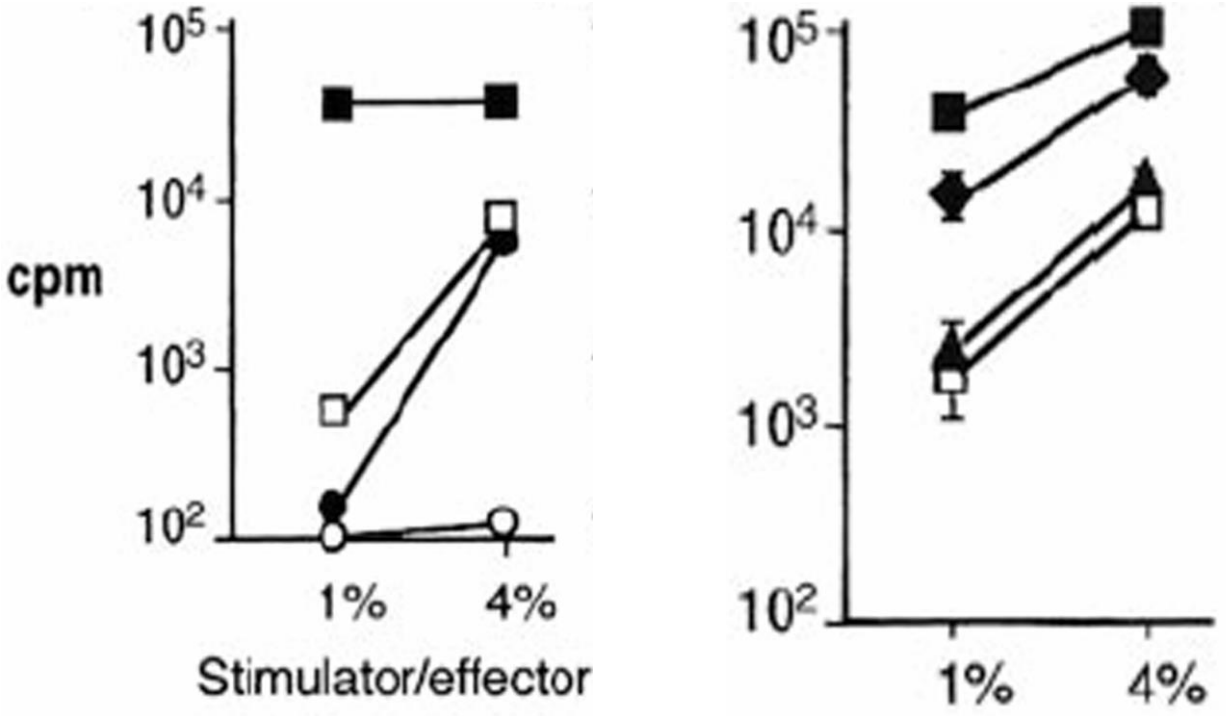
IL-10 Production in LCH Lesions



Geissmann et al Blood 2001

CD1a+ cells from Bone Granulomas
Functional Evaluation

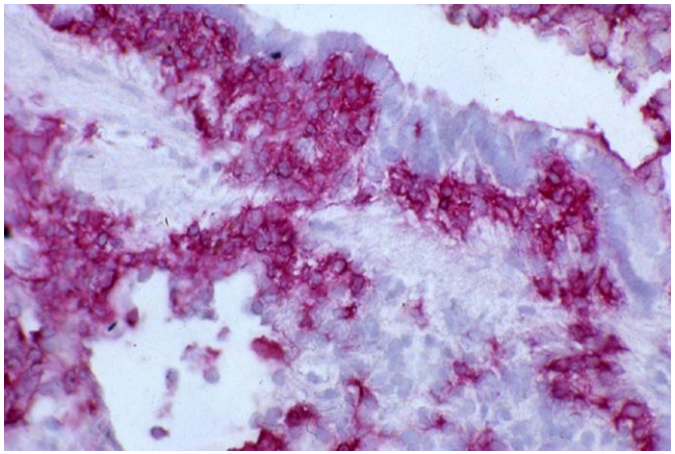
CD40-L



Geissmann et al Blood 2001

Destruction des bronchioles par les granulomes CL
Mécanismes?

- Effet direct des CD1a+ anormales?
- Production de metallo-proteinases?
- Cellules inflammatoires ?
- Cytokines: TGF-β, TNF…
- …..



Immature dendritic cell transdifferentiation into osteoclasts: a novel pathway sustained by the rheumatoid arthritis microenvironment

Aymeric Rivollier, Marlène Mazzorana, Jacques Tebib, Muriel Piperno, Tarik Aitsiselmi, Chantal Rabourdin-Combe, Pierre Jurdic, and Christine Servet-Delprat

Blood 2004

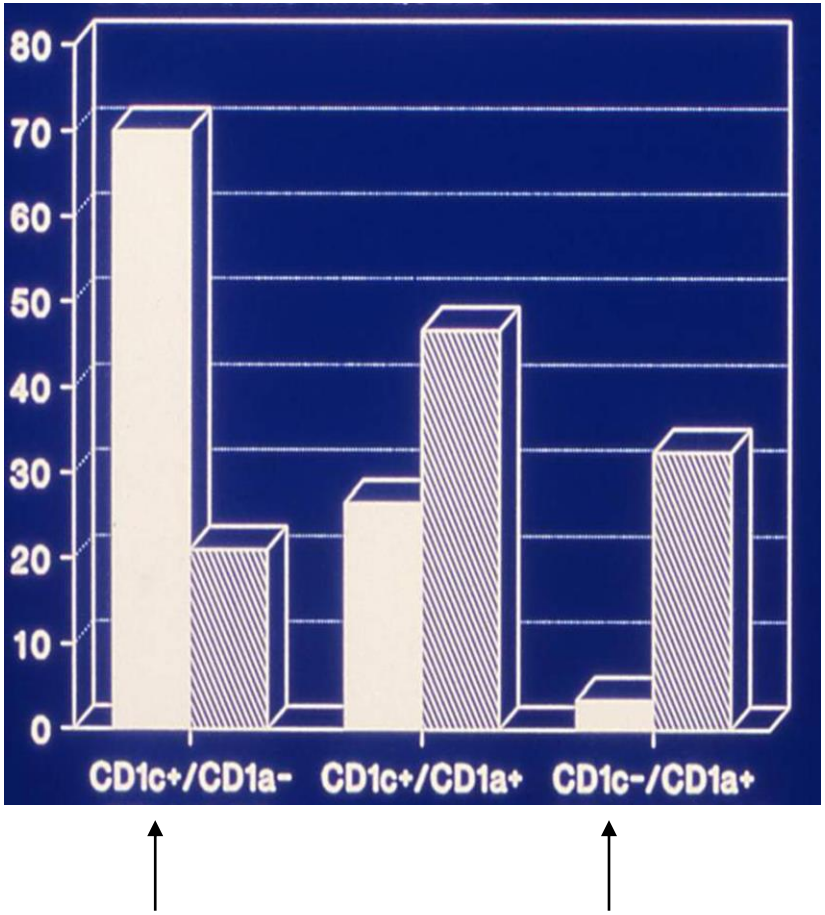
Tabagisme et atteinte pulmonaire de l'HL
Expérience pédiatrique

TABLE II. Characteristics of 41 LCH Patients With and Without Radiological Abnormalities of the Lungs at Follow-Up After ≥5 Years.

Pulmonary HRCT at follow-up	Age (years) at follow-up mean ± SD median (range)	Age (years) at diagnosis mean ± SD median (range)	Duration (years) from diagnosis to follow-up mean ± SD median (range)	Sex M/F	Organ involvement single/multiple	Pneumothorax yes/no	Chemotherapy yes/no	Radiotherapy to the thorax yes/no	Smoking yes/no
Normal	20.7 ± 7.7 19 (7–36)	5.2 ± 5.0 4 (0–17)	15.5 ± 7.0 15 (5–30)	20/11	21/10	0/31	10/21	3/28	3/28
Abnormal	36.7 ± 11.3 36 (13–54)	16.5 ± 15.0 16 (0–42)	20.2 ± 8.6 17 (12–33)	5/5	2/8	3/7	8/2	7/3	7/3
P-value between groups	< 0.0001	0.001	0.09	0.42	0.01	0.002	0.01	< 0.0001	< 0.0001

Bernstrand et al 1999

Les CD/CL du Parenchyme Pulmonaire

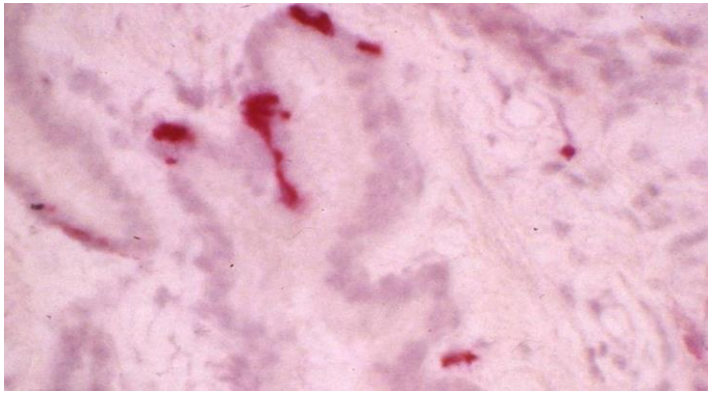


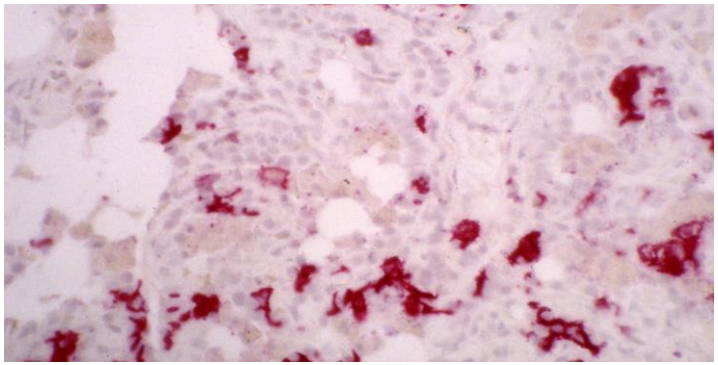
Non fumeurs

Fumeurs

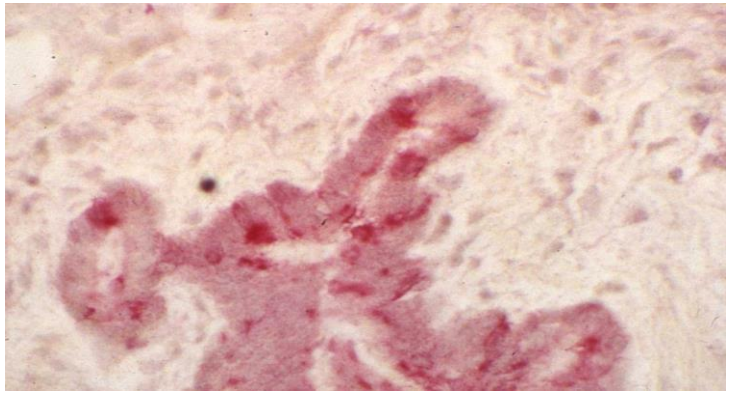
Soler et al AJRCCM 1989

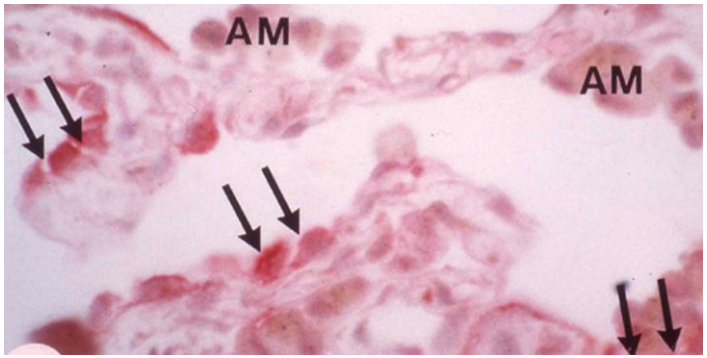
CD1a





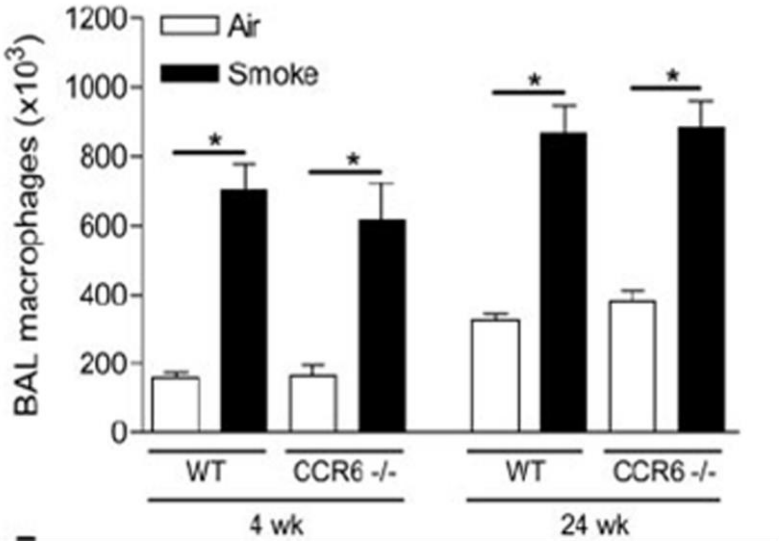
GM-CSF

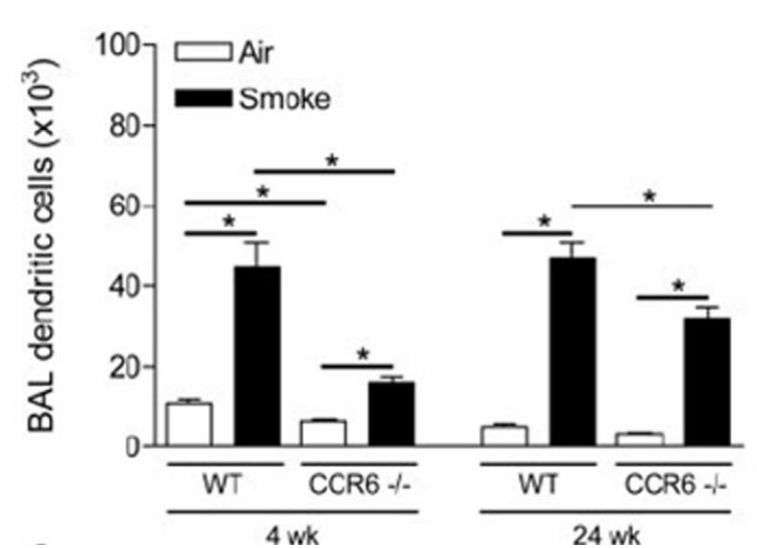




Tazi et al JCI 1993

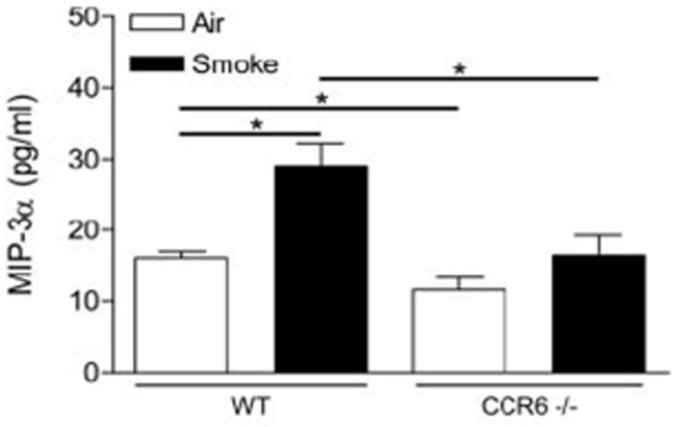
Cigarette Smoke-Induced Pulmonary Inflammation and Emphysema Are Attenuated in CCR6-Deficient Mice[1]

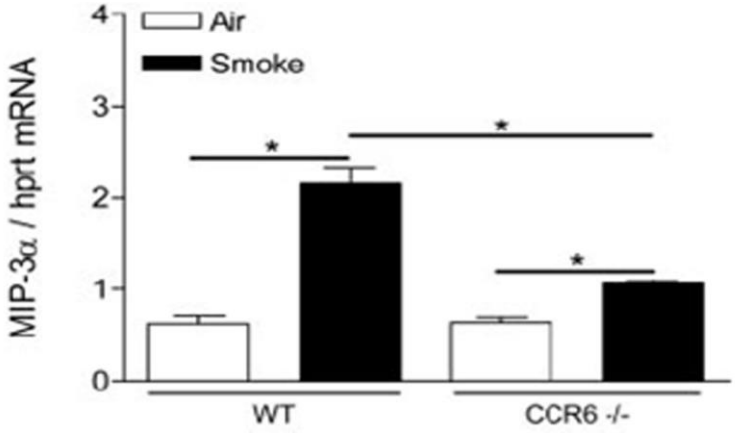




Bracke et al JI 2006

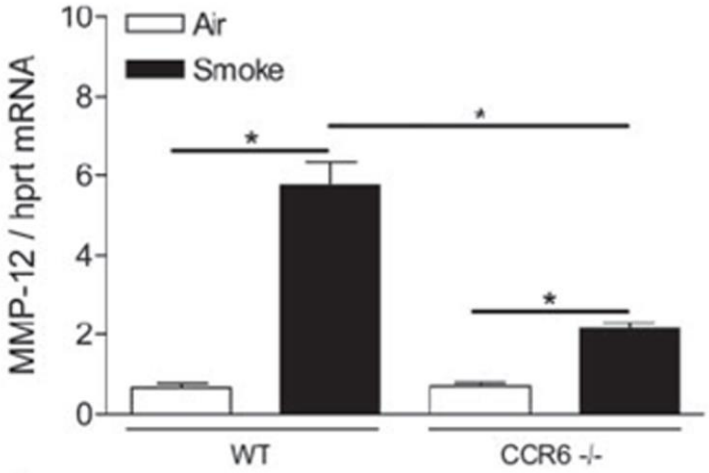
Cigarette Smoke-Induced Pulmonary Inflammation and Emphysema Are Attenuated in CCR6-Deficient Mice[1]

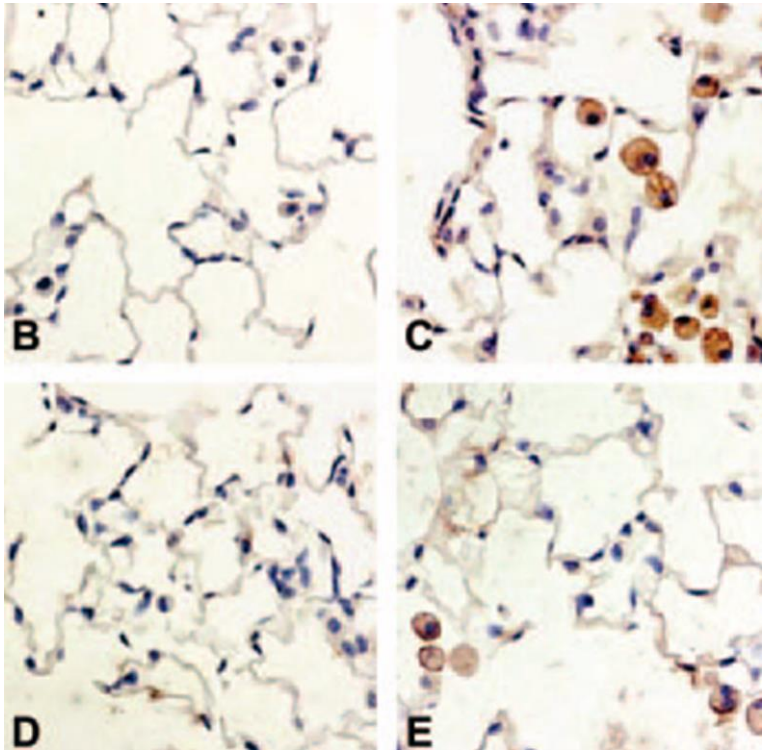




Bracke et al JI 2006

Cigarette Smoke-Induced Pulmonary Inflammation and Emphysema Are Attenuated in CCR6-Deficient Mice[1]



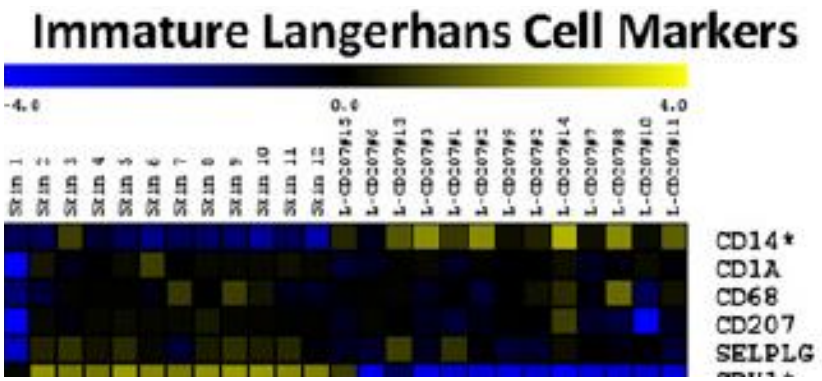


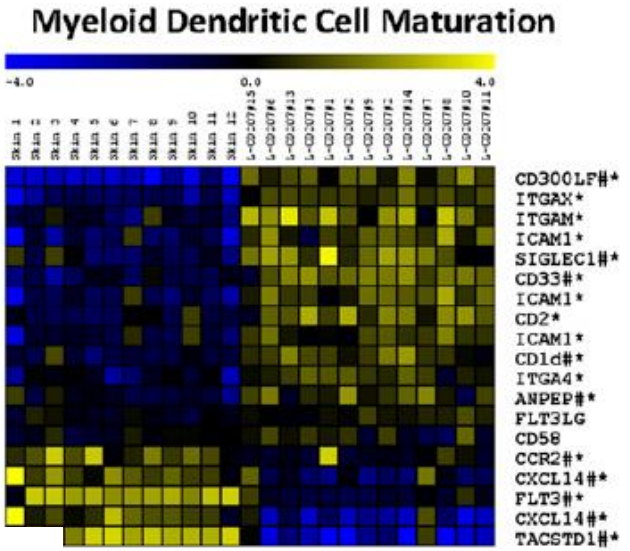
Bracke et al JI 2006

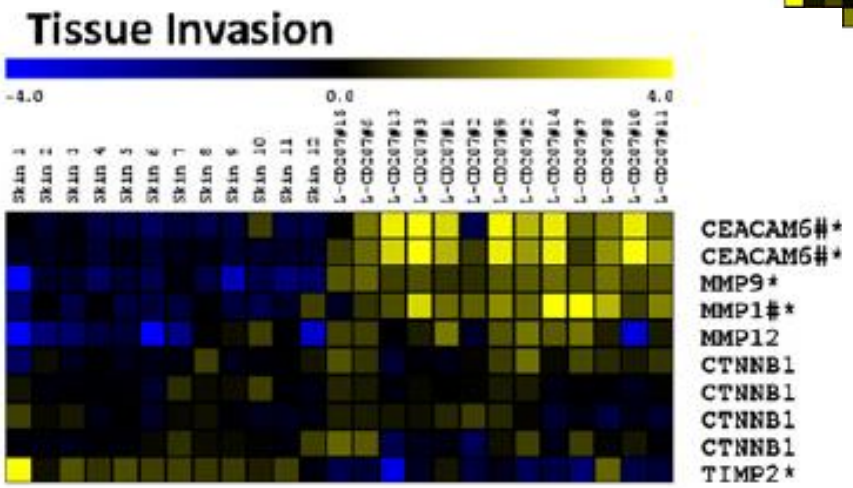
Origine des cellules de l'HL

Cell-Specific Gene Expression in Langerhans Cell Histiocytosis Lesions Reveals a Distinct Profile Compared With Epidermal Langerhans Cells

Allen et al JI 2010

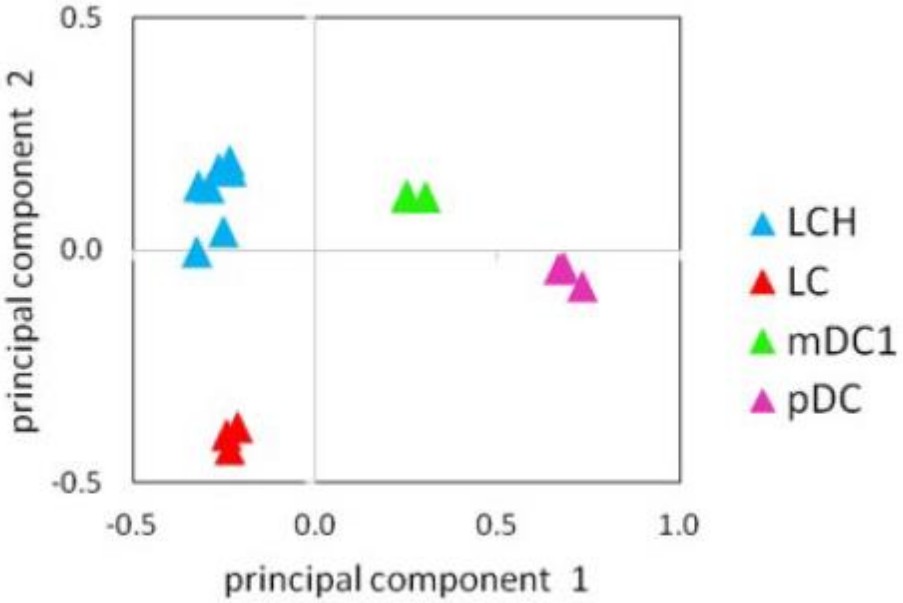


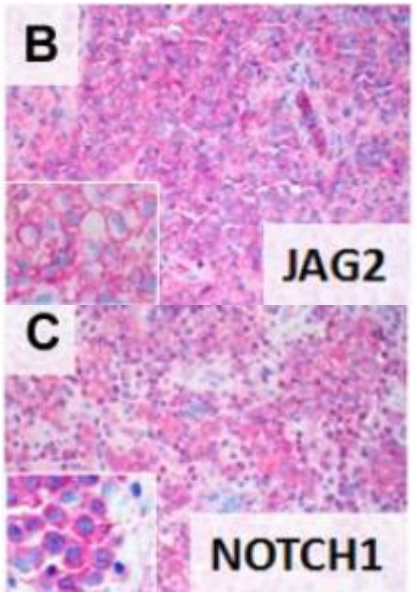


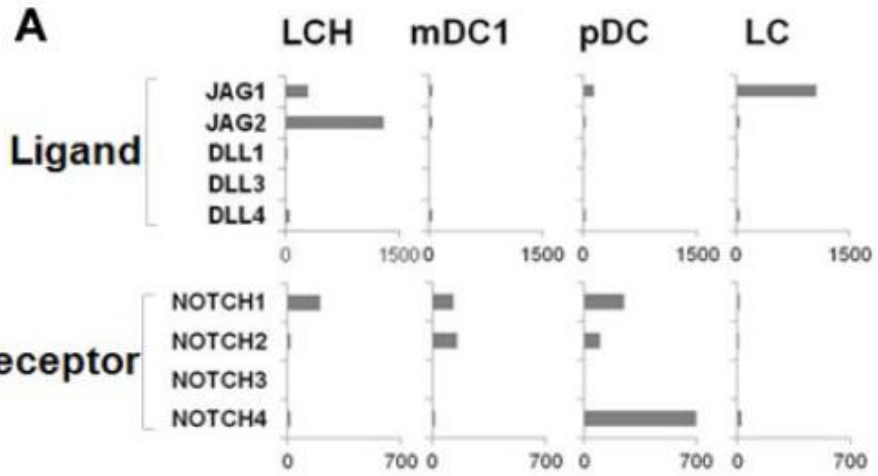


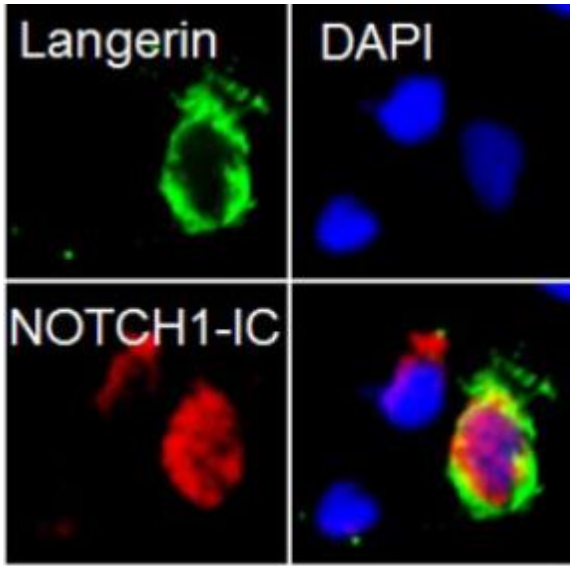
Notch is active in Langerhans cell histiocytosis and confers pathognomonic features on dendritic cells

Hutter et al Blood 2012









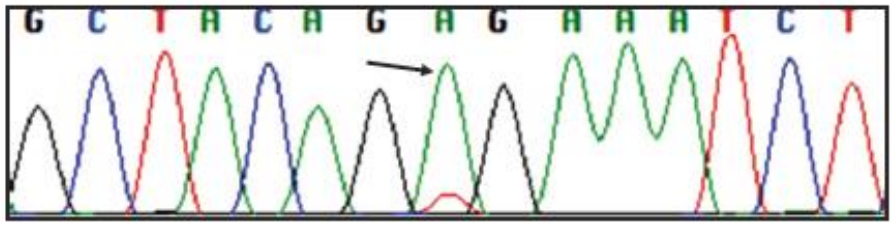
Brief report

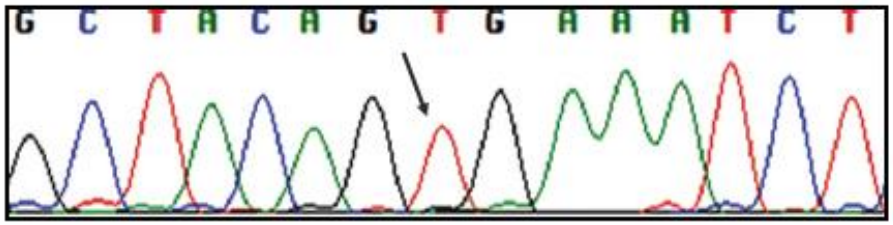
Recurrent *BRAF* mutations in Langerhans cell histiocytosis

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. Rollins[1-3]

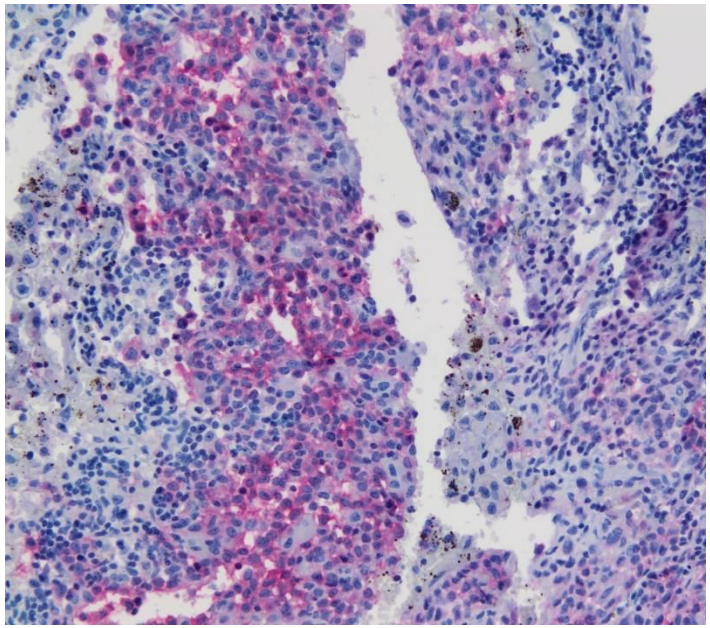
BLOOD, 16 SEPTEMBER 2010 • VOLUME 116, NUMBER 11

BRAF (codon 600): V E
GTG → GAG

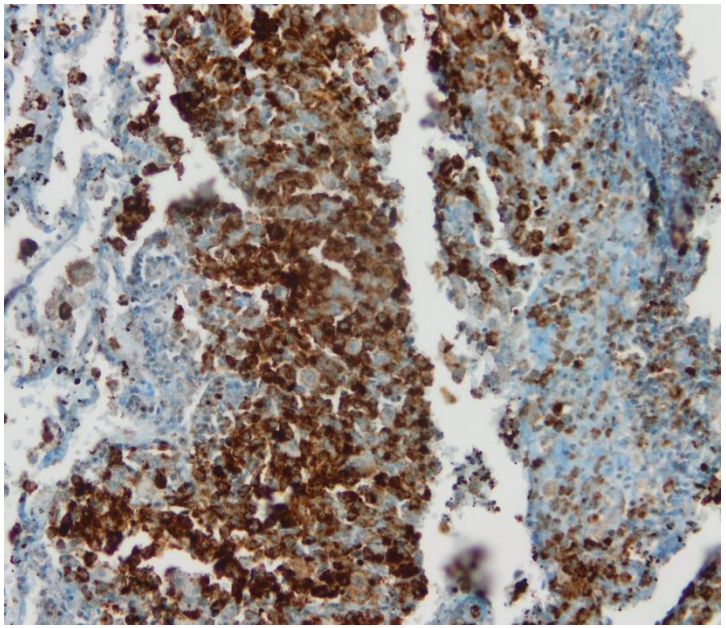


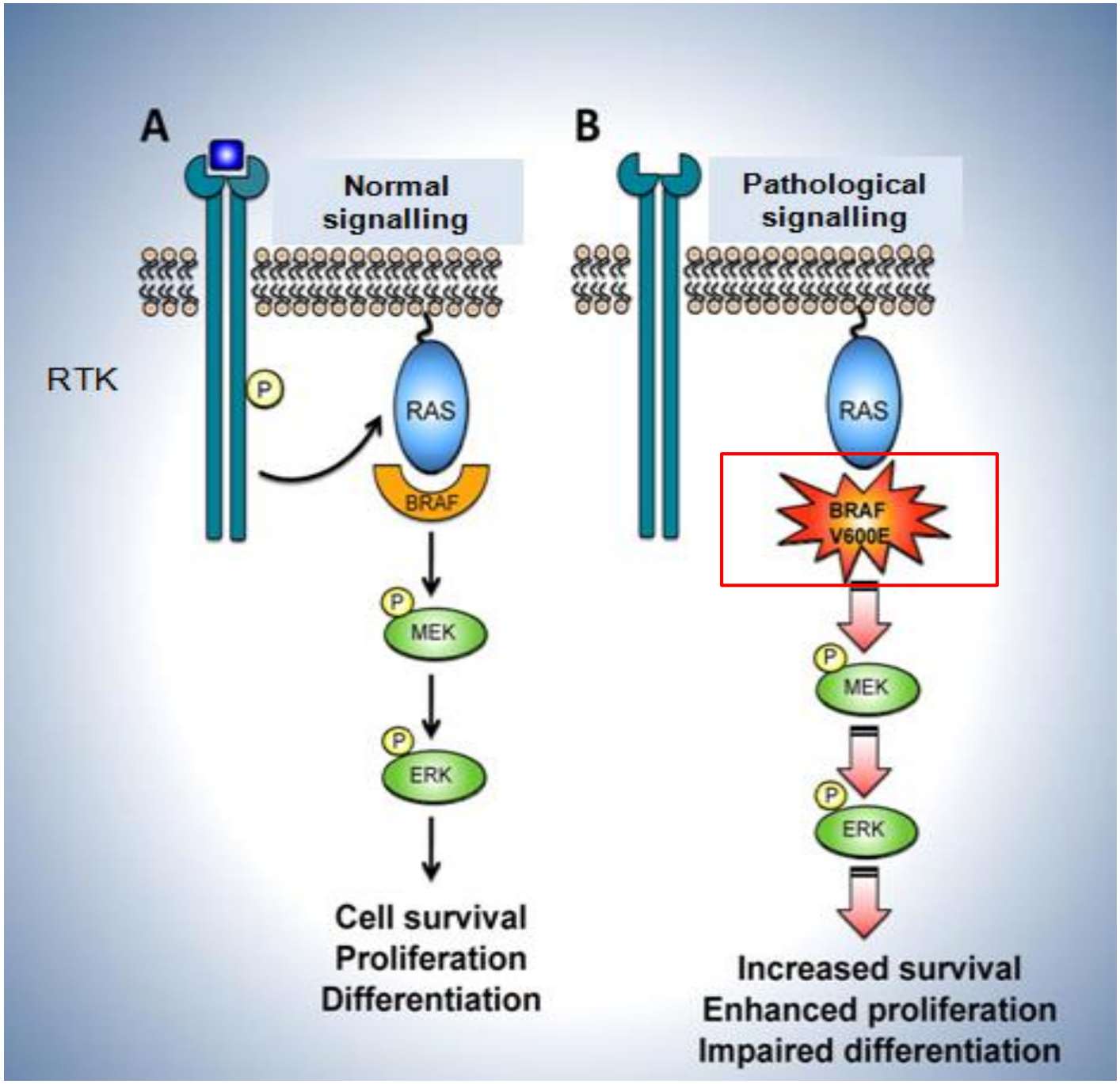


CD1a



VE1

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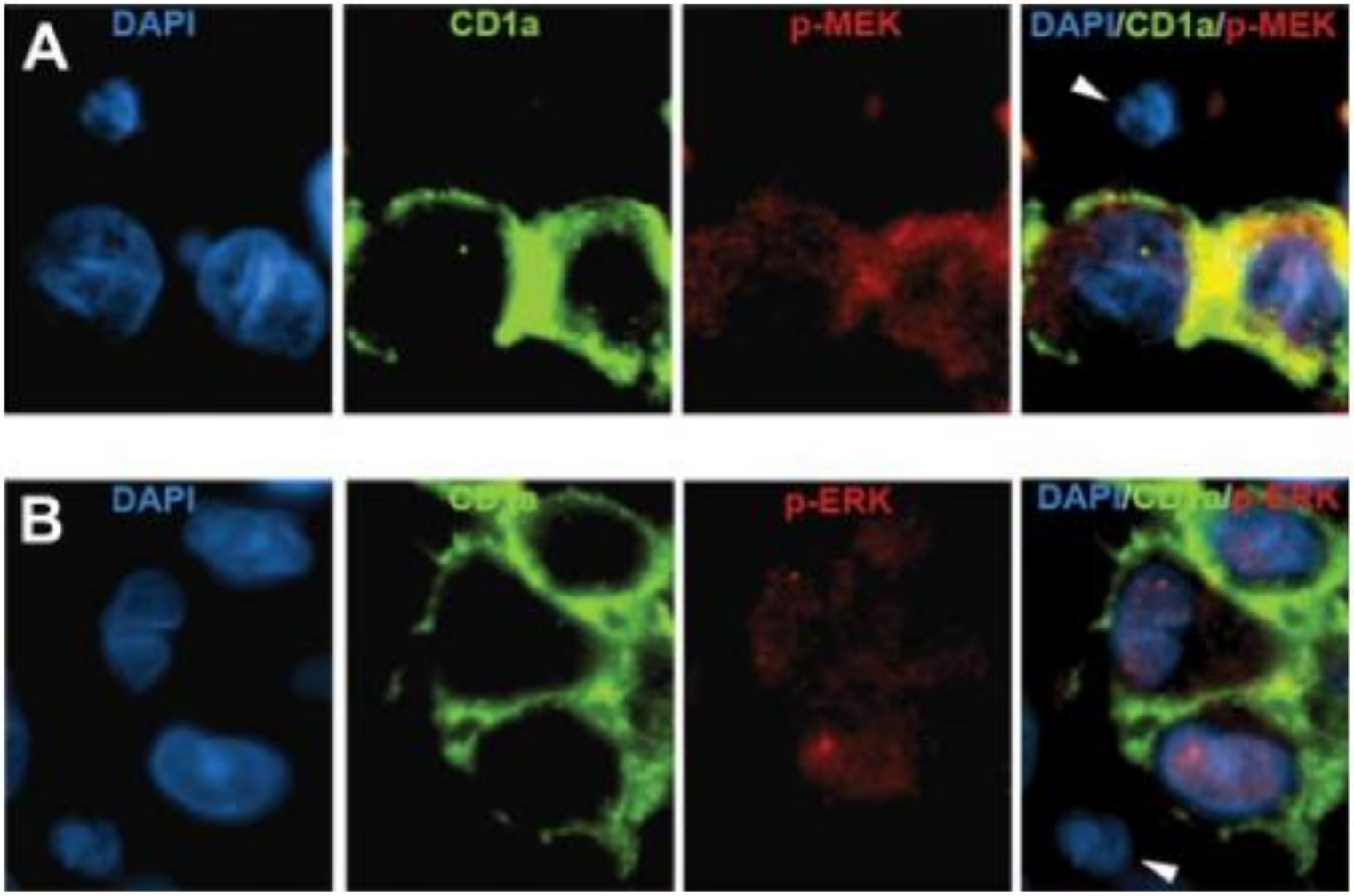
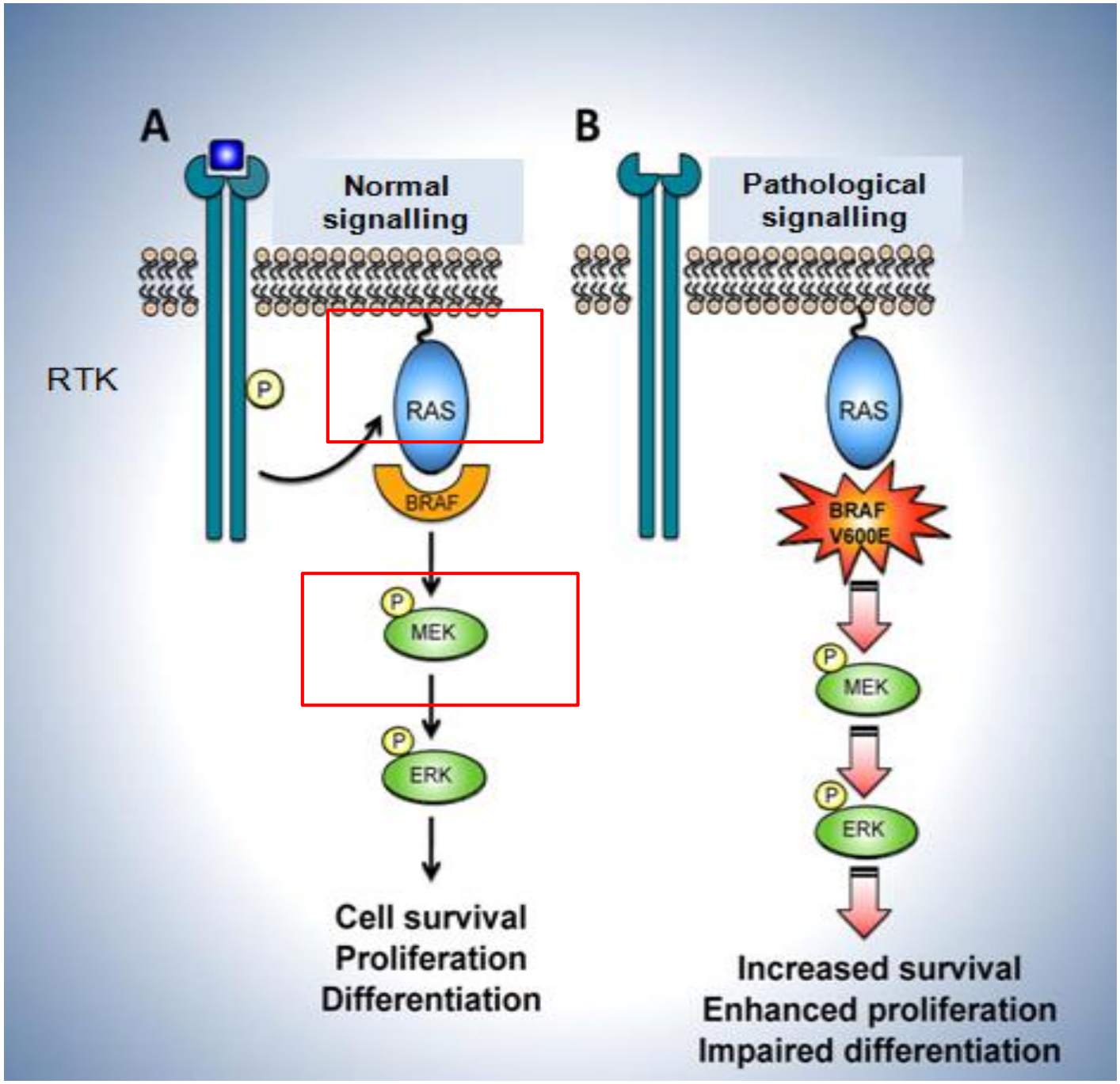
Normal signalling
RTK
P
RAS
BRAF
P
MEK
P
ERK
Cell survival
Proliferation
Differentiation
B
Pathological signalling
RAS
BRAF V600E
P
MEK
P
ERK
Increased survival
Enhanced proliferation
Impaired differentiation



Badalian-Very et al Blood 2010


A
Normal signalling
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P
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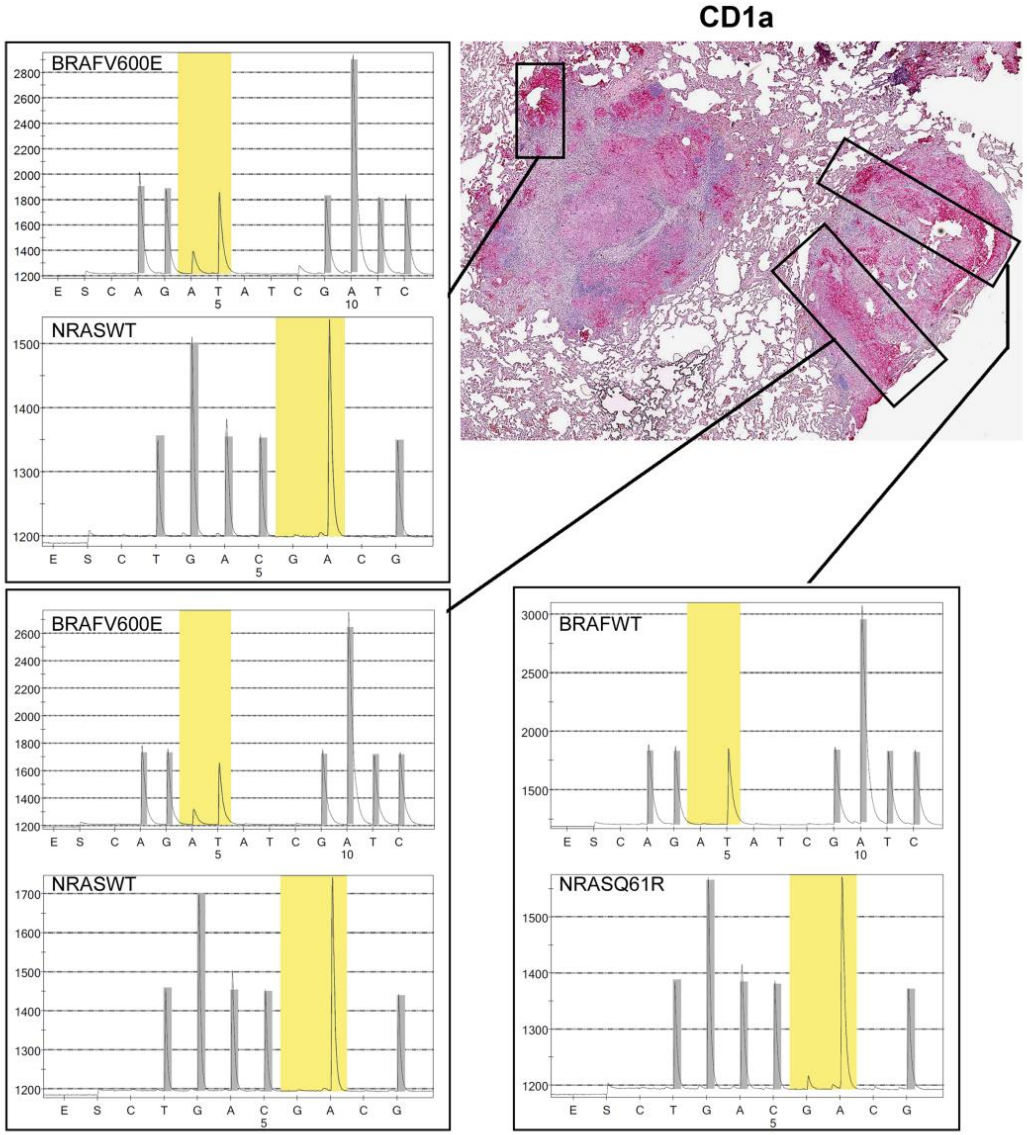
Increased survival
Enhanced proliferation
Impaired differentiation

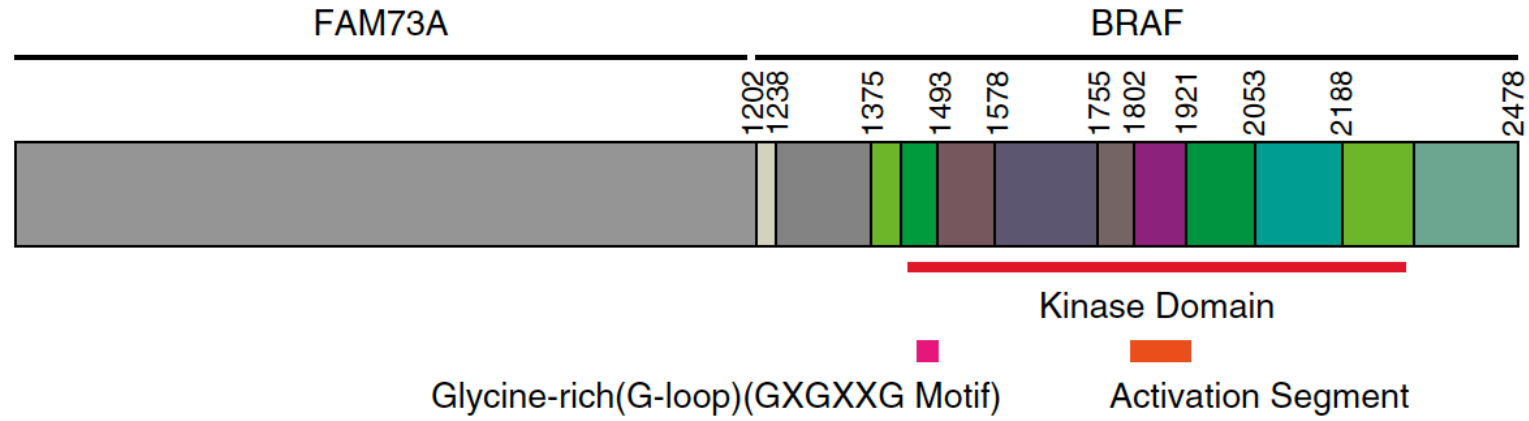
Recurrent *NRAS* mutations in pulmonary Langerhans cell histiocytosis

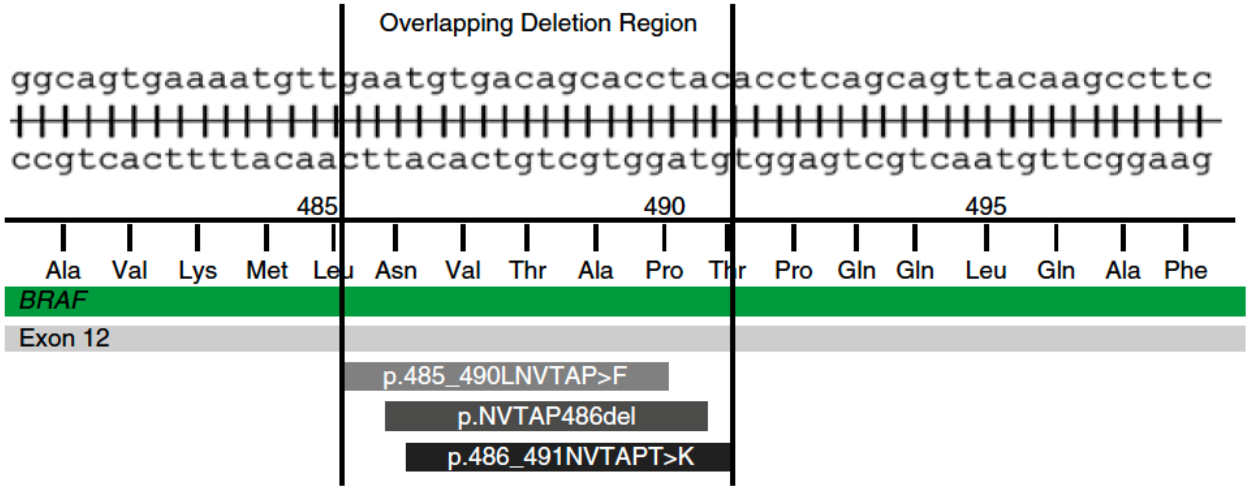


Mourah et al Eur Respir 2016

Alternative genetic mechanisms of BRAF activation in Langerhans cell histiocytosis

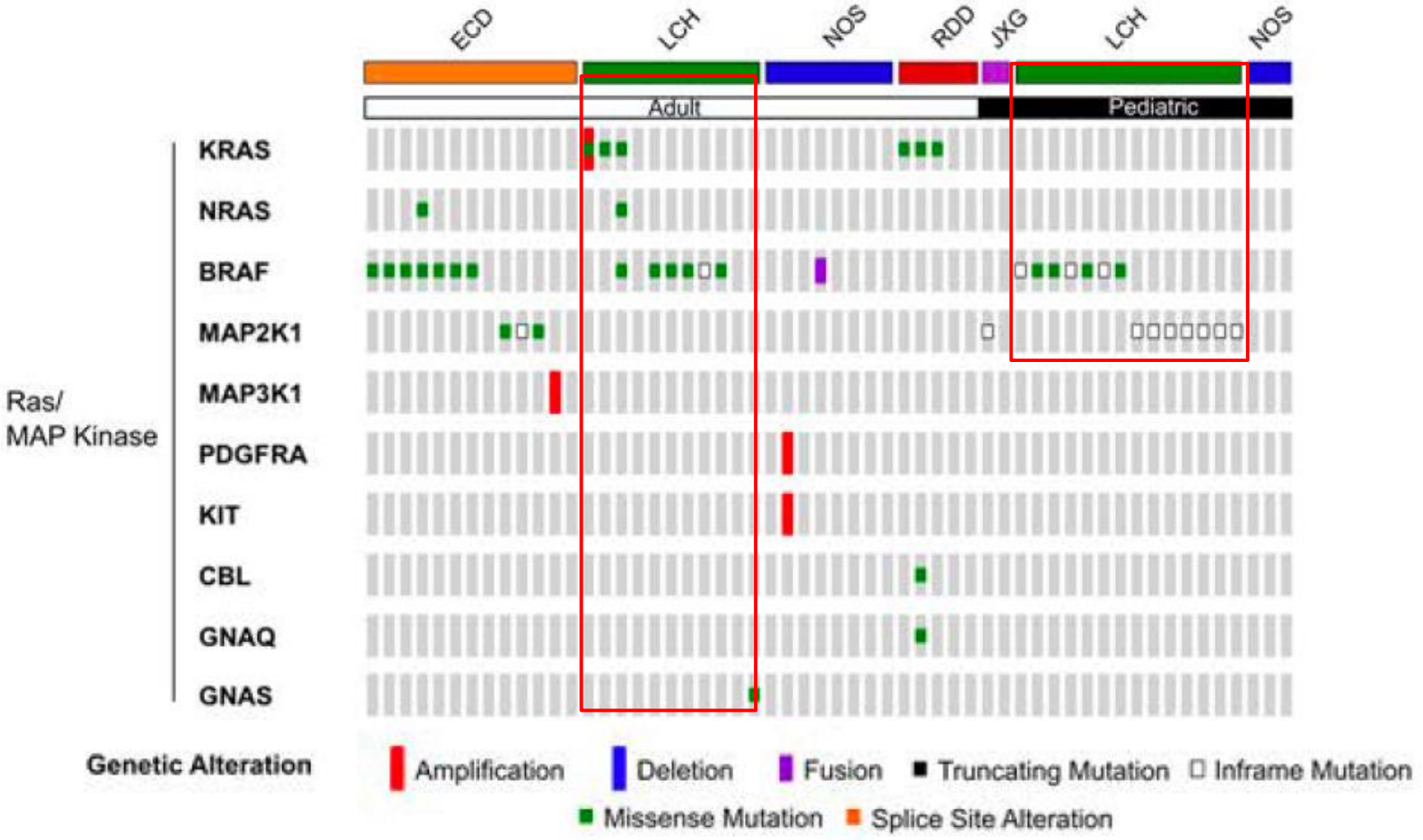
Chakraborty et al Blood 2016





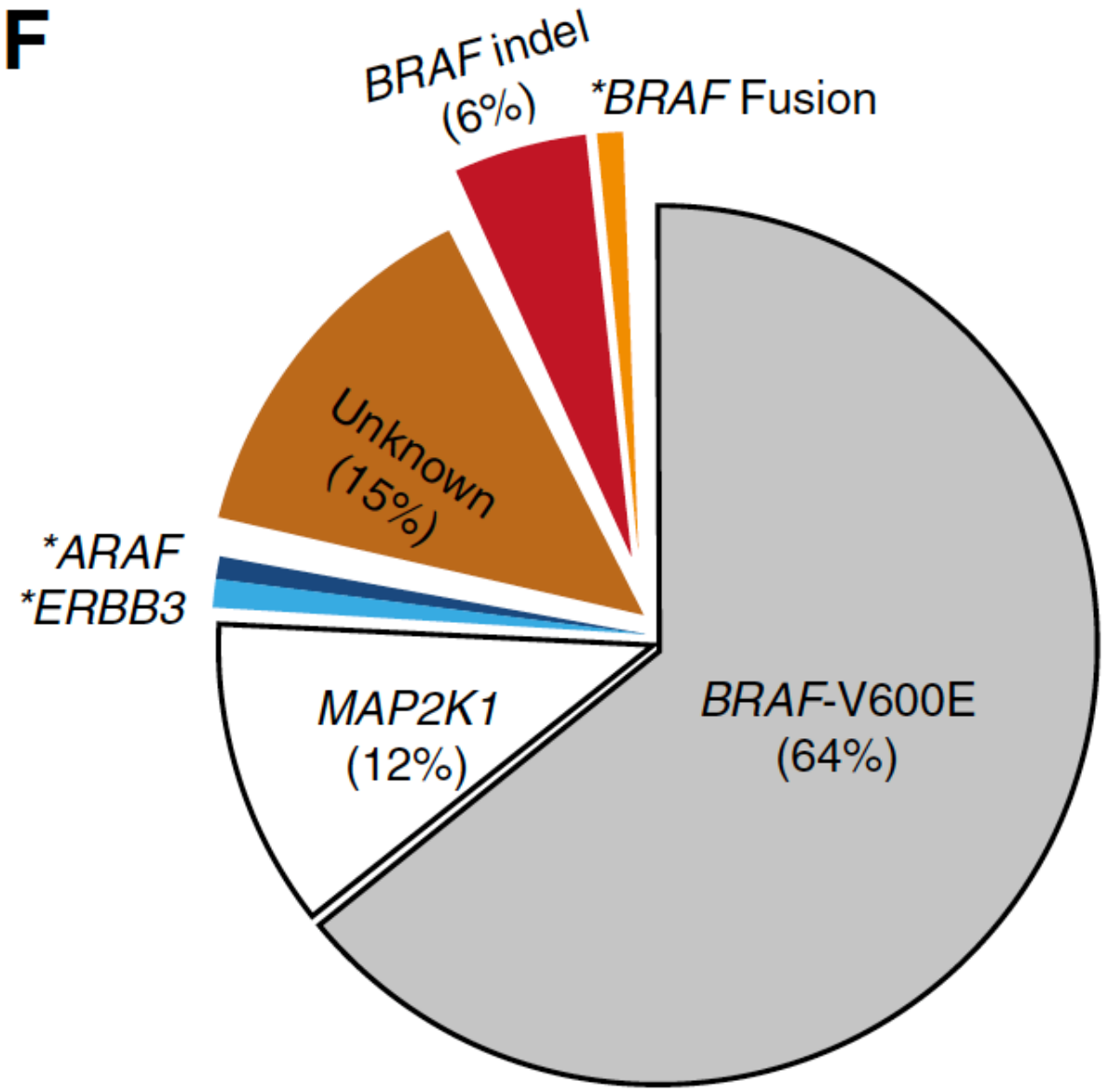
Real-time genomic profiling of histiocytoses identifies early-kinase domain BRAF alterations while improving treatment outcomes

Lee et al. JCI 2017



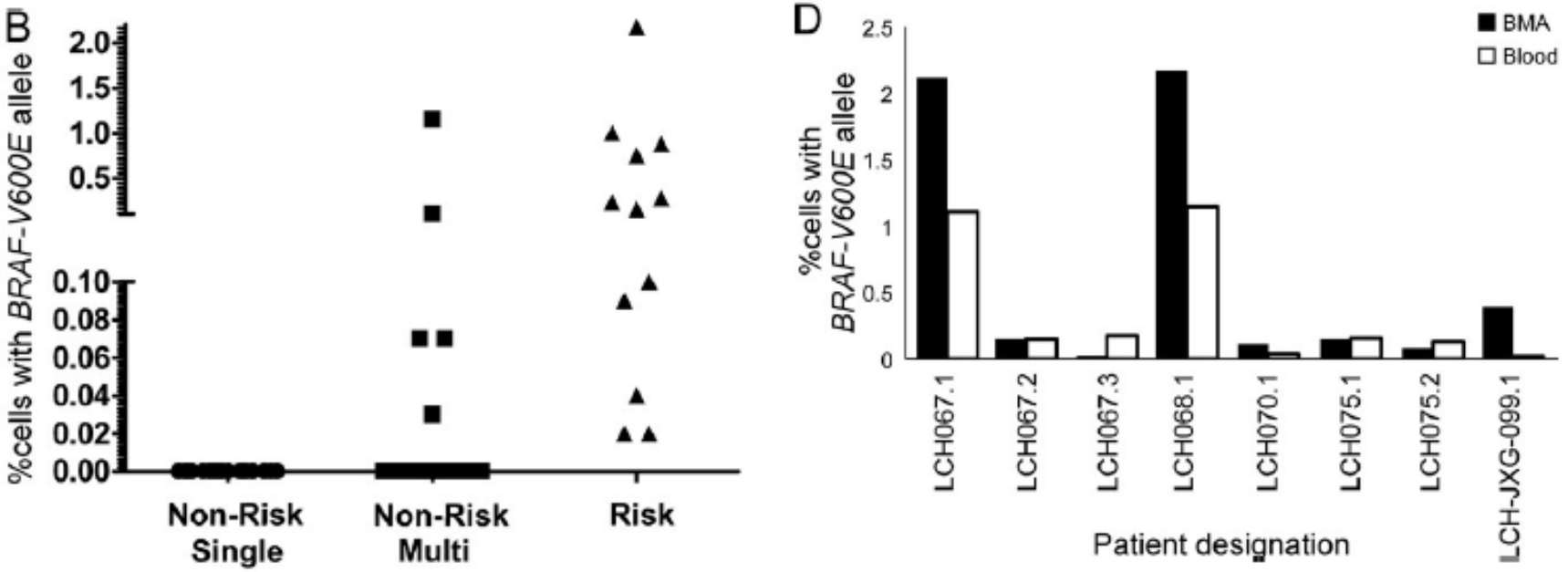
Supplementary Table 1: Demographics and clinical features of patient samples submitted for targeted sequencing with identified candidate driver mutations. Alterations represented as amino acid changes, except where indicated.

Case ID	Age	Gender	Diagnosis	Genetic Alterations
A-LCH-32	72	Female	LCH	*KRAS* Q61H, *KRAS* amplification, *RBM10* E47*
A-LCH-44	65	Male	LCH	*TET2* H1904R
A-LCH-55	56	Female	LCH	*BRAF* G466R, *SRSF2* Y44H
A-LCH-56	34	Female	LCH	*BRAF* V600E
A-LCH-57	56	Female	LCH	*BRAF* V600E, *TET2* E1106fs*23, *TET2* H937fs*16
A-LCH-63	47	Female	LCH	*BRAF* N486_P490del, *DNMT3A* Y533C
A-LCH-64	78	Male	LCH	*BIRC3* S116*, *CDKN2A/B* loss, *FAS* loss, *KRAS* K117N, *SETD2* splice site 7431+2_7431+24del23
A-LCH-69	34	Male	LCH	*BRAF* V600E
A-LCH-71	57	Female	LCH	*BRAF* V600E, *KRAS* G13C, *NRAS* G12D
A-LCH-74	52	Female	LCH	*ETV3-NCOA2* rearrangement
A-LCH-82	50	Male	LCH	*GNAS* R201C



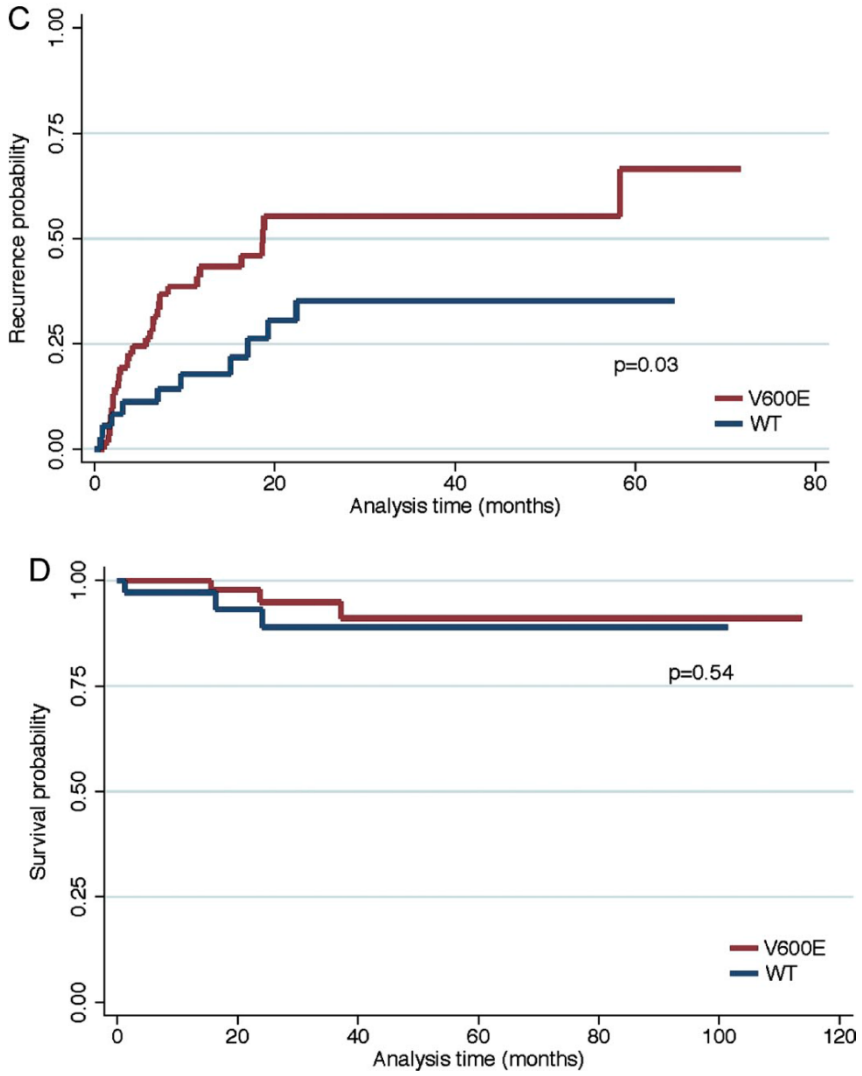
Chakraborty et al Blood 2016

BRAF-V600E expression in precursor versus differentiated dendritic cells defines clinically distinct LCH risk groups



Berres et al JEM 2014

BRAF-V600E expression in precursor versus differentiated dendritic cells defines clinically distinct LCH risk groups



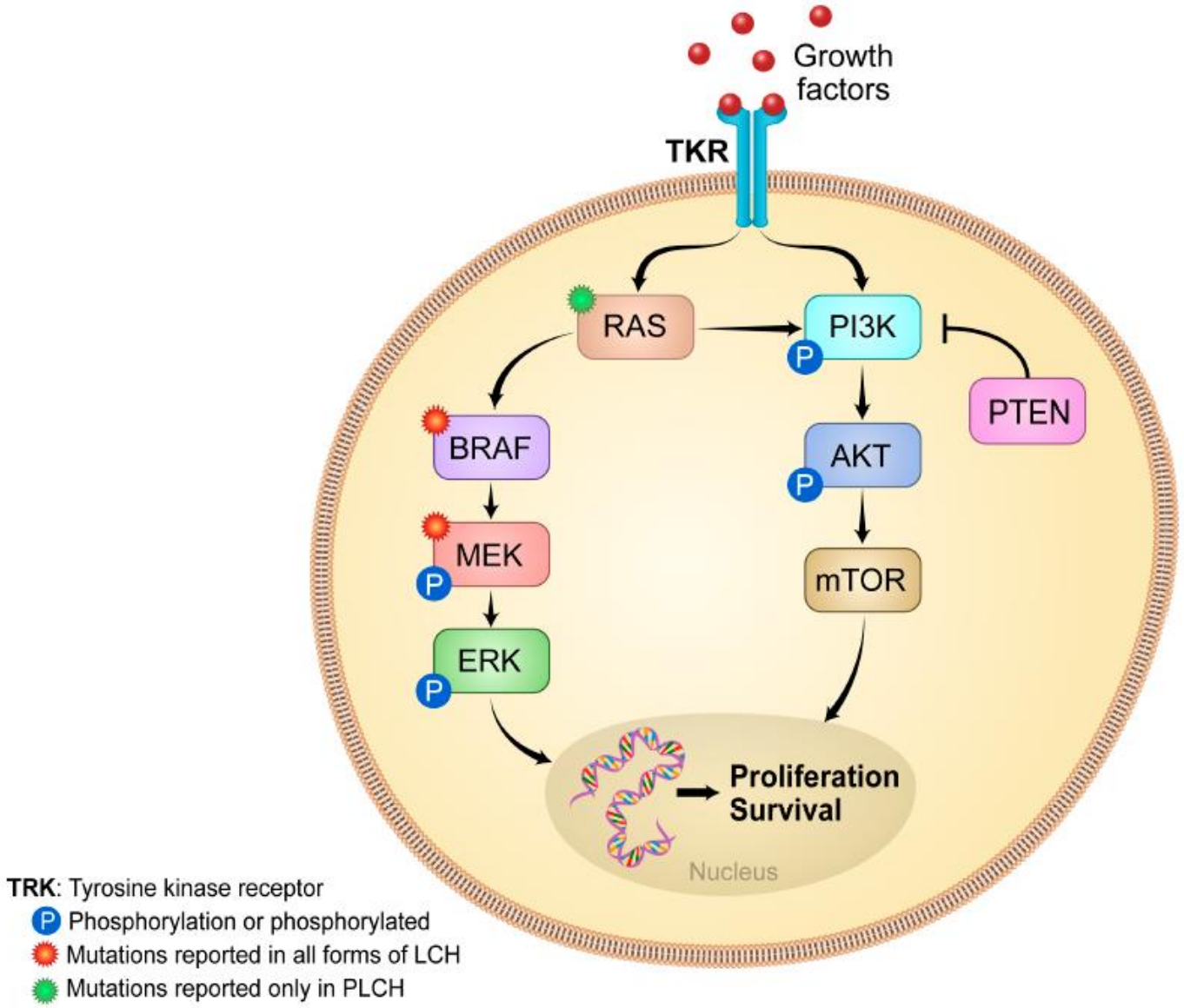
Berres et al JEM 2014

BRAF Mutation Correlates With High-Risk Langerhans Cell Histiocytosis and Increased Resistance to First-Line Therapy

Table 2. Logistic Regression Analyses of Associations Between *BRAF* Status and Independent Clinical Binary Covariates

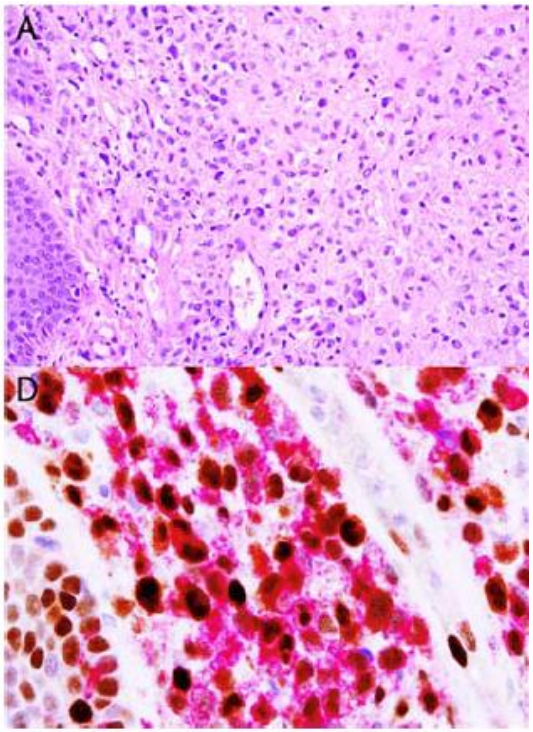
Variable	No.	OR (95% CI)	*P*
Age at diagnosis < 3 years	150	1.01 (0.57 to 1.81)	.96
Female sex	148	1.06 (0.65 to 1.75)	.80
Involvement			
Bone	262	1.52 (0.70 to 3.31)	.29
Skin	113	3.65 (1.81 to 7.35)	< .001
RO	49	6.35 (2.03 to 19.85)	.001
Pituitary	48	1.60 (0.63 to 4.08)	.32
Lung	37	0.63 (0.26 to 1.54)	.31
Lymph node	27	0.33 (0.11 to 1.01)	.05
CNS	24	1.30 (0.36 to 4.73)	.69

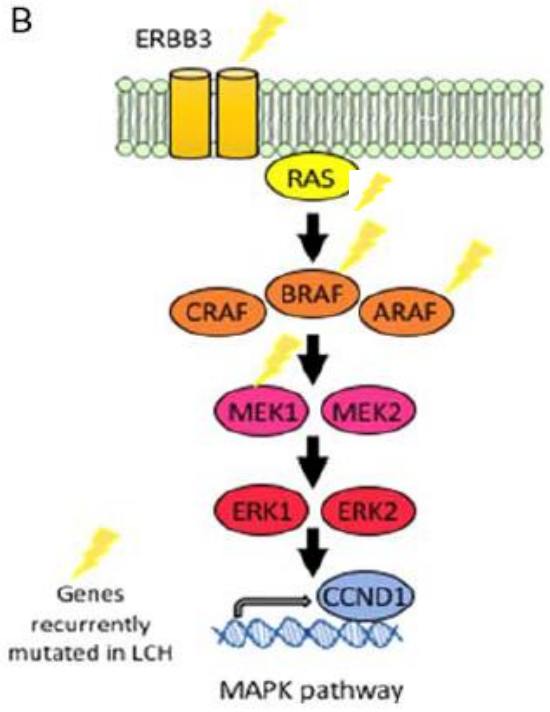
Heritier et al JCO 2016



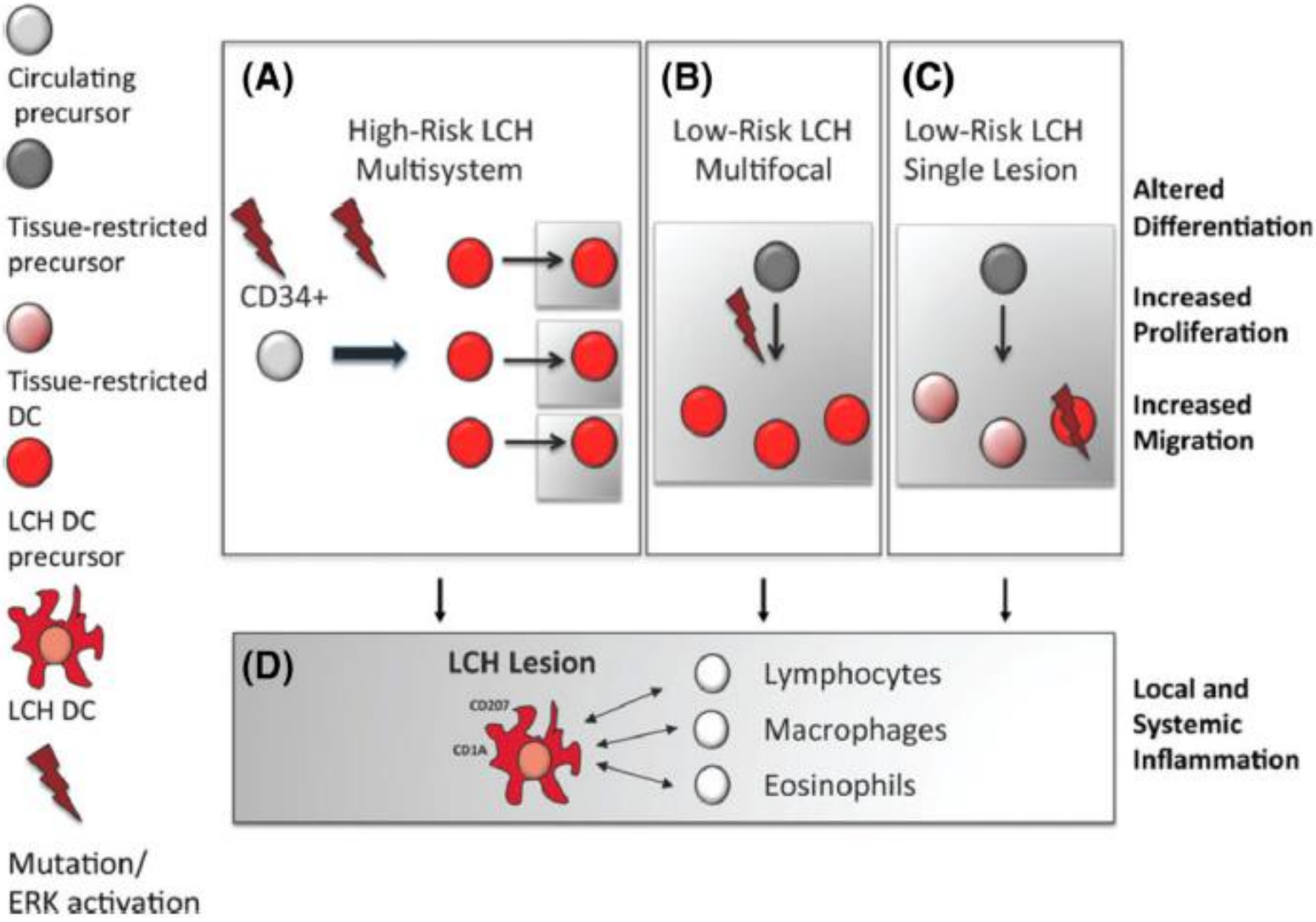
Vassallo R, Harari S, Tazi A. Thorax 2017

Cyclin D1 is Expressed in Neoplastic Cells of Langerhans Cell Histiocytosis but Not Reactive Langerhans Cell Proliferations





Shanmugam et al Am J Surg Pathol 2017



Berres ML, Merad M, Allen CE Br J Haematol 2015

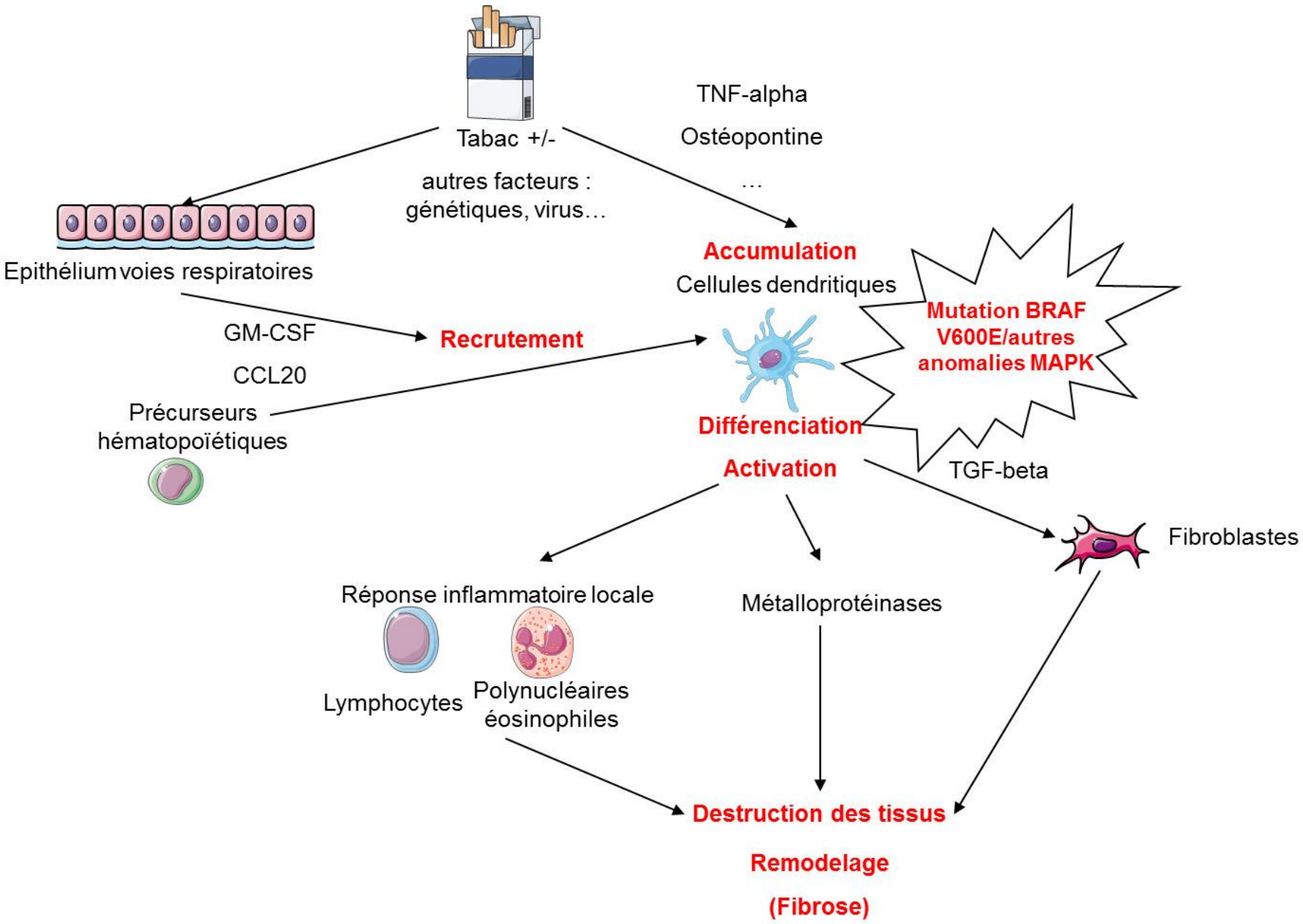
Lung Transplantation for Pulmonary Langerhans' Cell Histiocytosis: A Multicenter Analysis

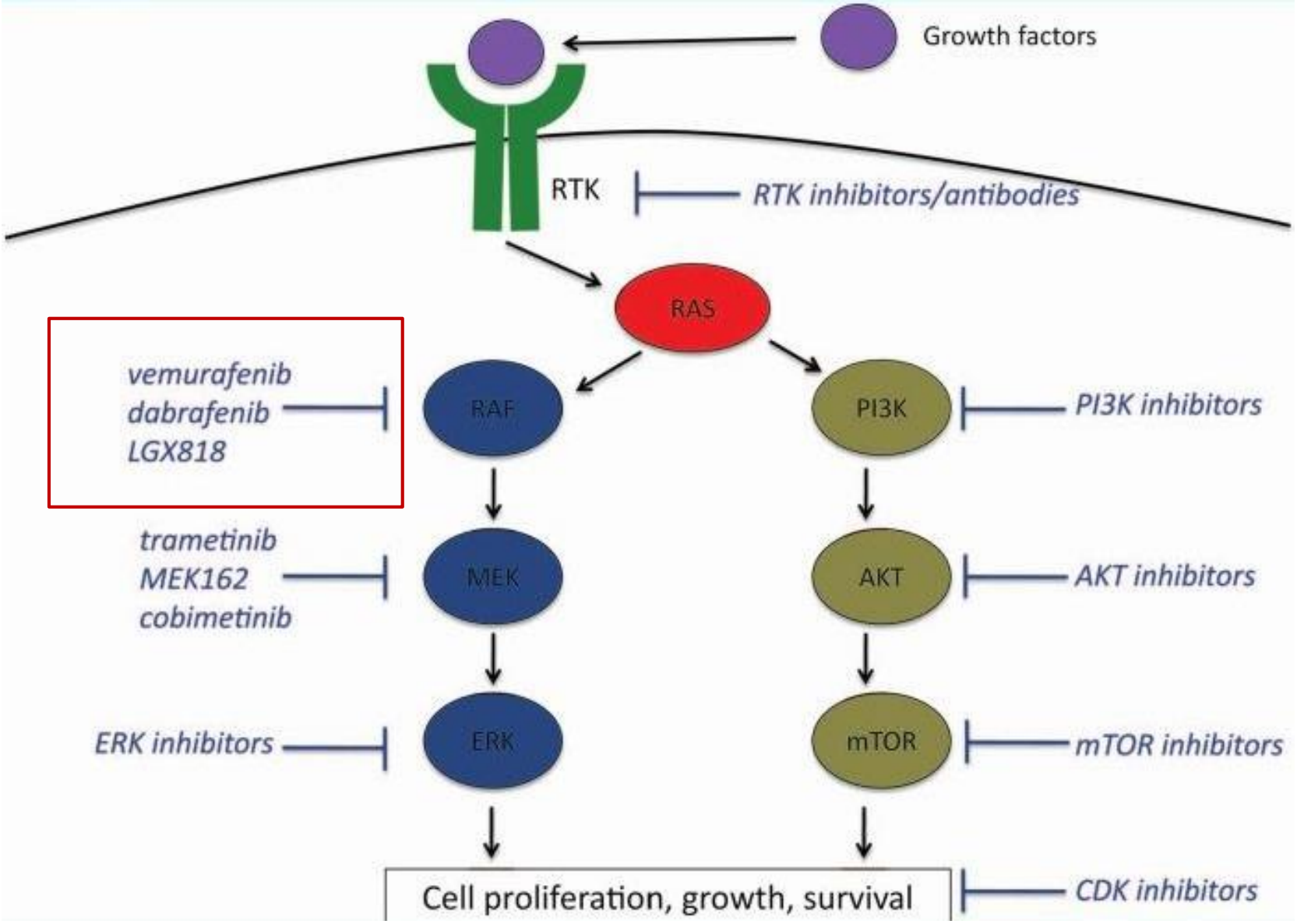
Gaëlle Dauriat,[1] Hervé Mal,[1,8] Gabriel Thabut,[1] Jean-François Mornex,[2] Michelle Bertocchi,[2] François Tronc,[2] François Leroy-Ladurie,[3] Philippe Dartevelle,[3] Martine Reynaud-Gaubert,[4] Pascal Thomas,[4] Christophe Pison,[5] Dominique Blin,[5] Marc Stern,[6] Pierre Bonnette,[6] Claire Dromer,[7] Jean-François Velly,[7] Olivier Brugière,[1] Guy Lesèche,[1] and Michel Fournier[1]

Transplantation 2006;81: 746–750

TABLE 4. Characteristics of the patients with recurrence of PLCH after lung transplantation

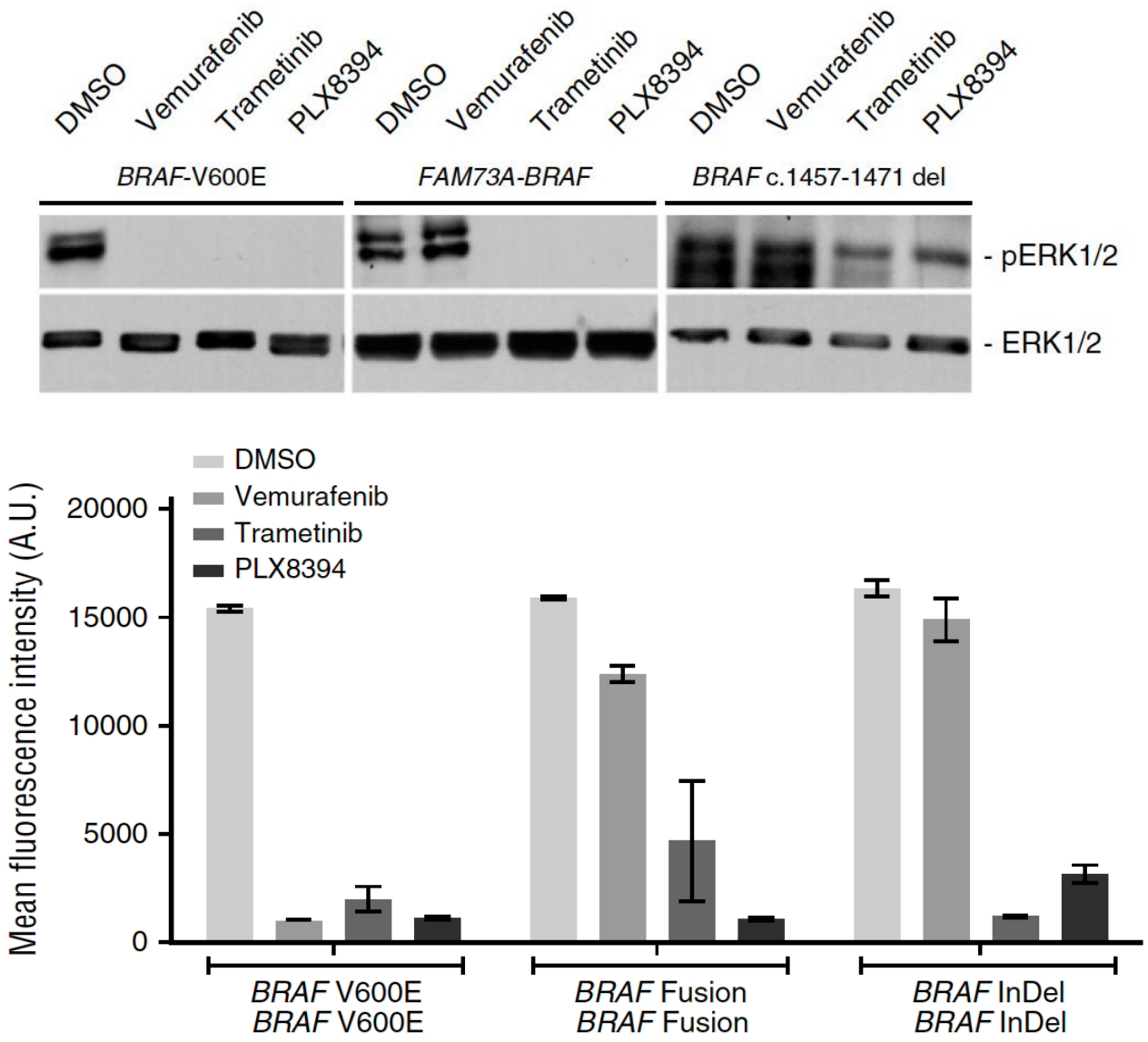
Patient	Sex	Age (years)	Smoking habit (pack-years)	Resumption of smoking	CT scan	Method of diagnosis	Interval between LT and recurrence (months)	Status at the last follow-up (etiology)	Interval between LT and last follow-up (months)
1	F	30	30	Yes	Nodules	CT scan	24	Dead (lung carcinoma)	50
2	F	45	10	No	Ground-glass opacities	Transbronchial biopsy	5	Dead (pneumonia)	24
3	M	29	5	No	Cysts	CT-scan	18	Alive	89
4	M	30	30	No	Nodules	CT-scan	48	Alive	92
5	M	21	3	No	Nodules	Transbronchial biopsy	48	Alive	85
6	M	21	3	Yes	Nodules + cysts	Surgical lung biopsy	13	Dead (morphine overdosage)	24
7	M	30	20	Yes	Nodules + cysts	Transbronchial biopsy	12	Dead (pneumonia)	17
8	M	42	30	No	Nodules + cysts	Transbronchial biopsy	60	Alive	71


Tabac +/-
autres facteurs :
génétiques, virus…
TNF-alpha
Ostéopontine
…
Epithélium voies respiratoires
Accumulation
Cellules dendritiques
Mutation BRAF
V600E/autres
anomalies MAPK
GM-CSF
CCL20
Recrutement
Précurseurs
hématopoïétiques
Différenciation
Activation
TGF-beta
Fibroblastes
Réponse inflammatoire locale
Lymphocytes
Polynucléaires
éosinophiles
Métalloprotéinases
Destruction des tissus
Remodelage
(Fibrose)


Growth factors
RTK
RTK inhibitors/antibodies
RAS
vemurafenib
dabrafenib
LGX818
RAF
PI3K
PI3K inhibitors
trametinib
MEK162
cobimetinib
MEK
AKT
AKT inhibitors
ERK inhibitors
ERK
mTOR
mTOR inhibitors
Cell proliferation, growth, survival
CDK inhibitors

Alternative genetic mechanisms of BRAF activation in Langerhans cell histiocytosis

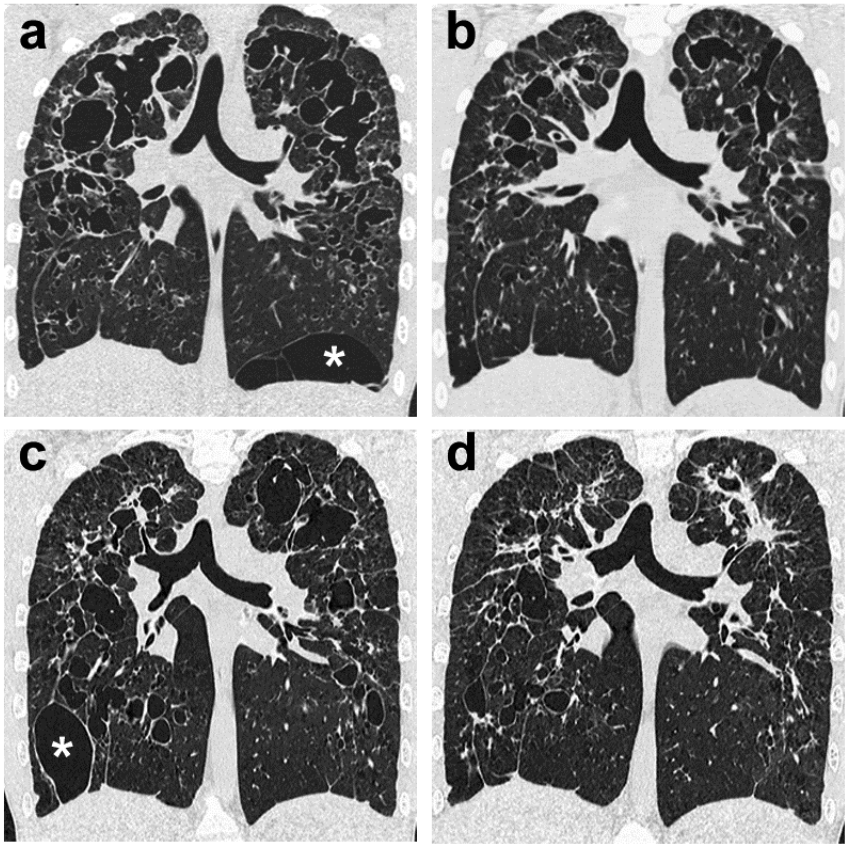
Chakraborty et al. Blood 2016



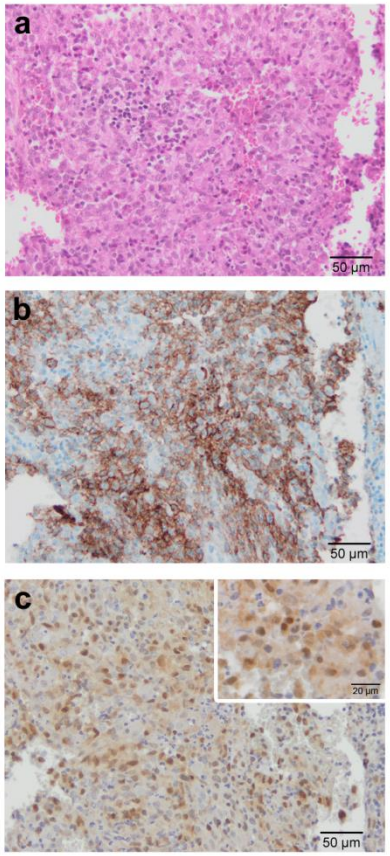
Response to Trametinib of a Pulmonary Langerhans cell Histiocytosis Harboring a MAP2K1 deletion

Lorillon et al AJRCCM 2018

cladribine



trametinib



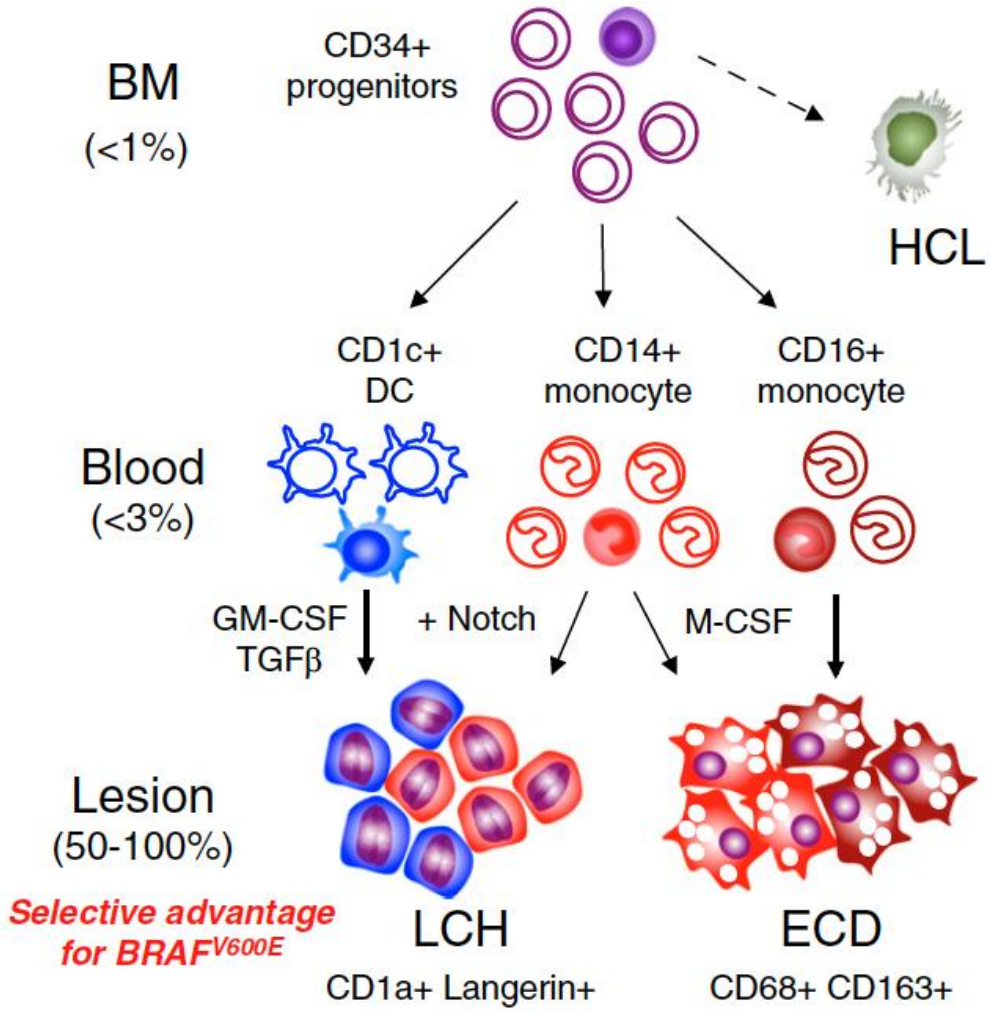
HES

CD1a

p-ERK1/2

Hematopoietic origin of Langerhans cell histiocytosis and Erdheim-Chester disease in adults

Mine et al Blood 2017



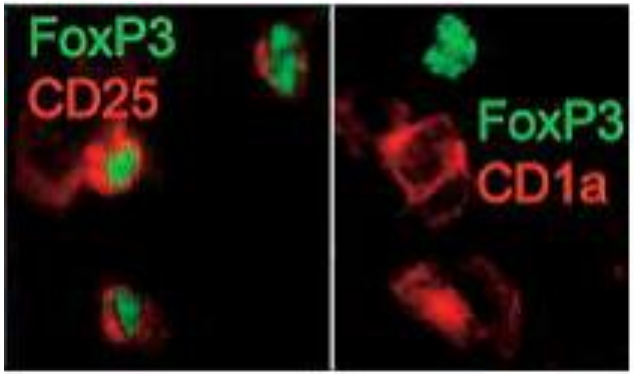
Disseminated histiocytoses biomarkers beyond BRAFV600E: frequent expression of PD-L1

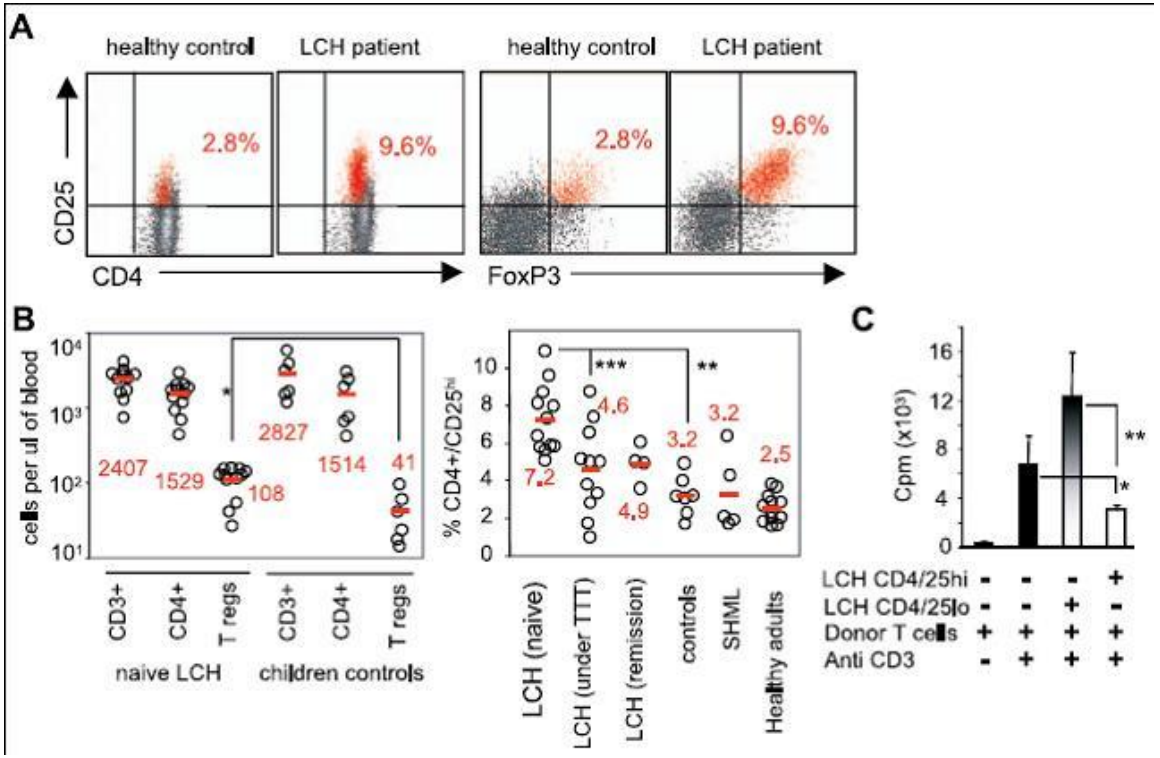
Gatalica et al Oncotarget 2015

BRAF V600E mutation correlates with suppressive tumor immune microenvironment and reduced disease-free survival in Langerhans cell histiocytosis

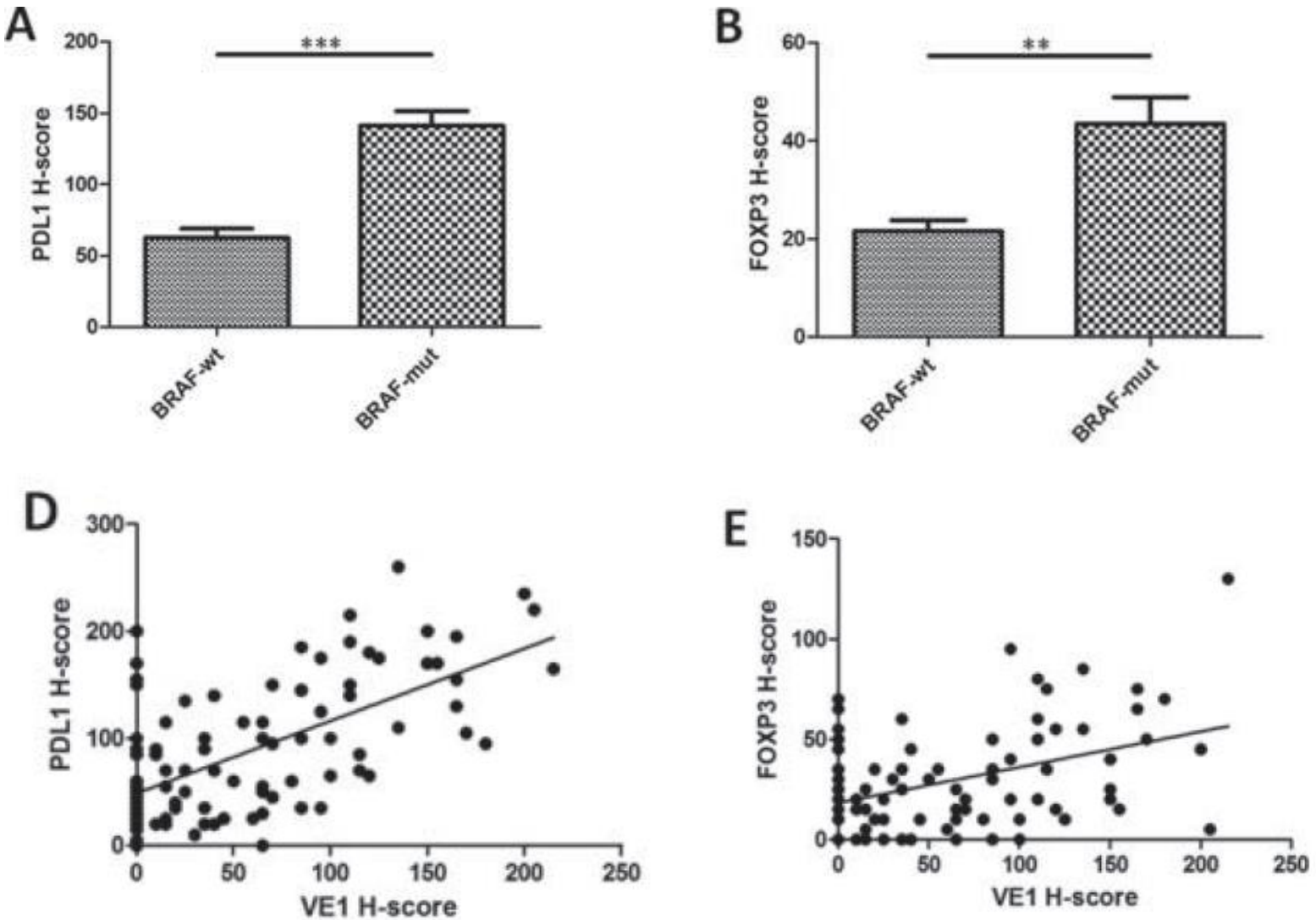
Zeng et al Oncoimmunol 2016

Regulatory T Cells in LCH





Senechal et al PloS Med 2007



Zeng et al Oncoimmunology 2016

Histiocytose Langerhansienne
Etiologies?

- Pas d'agent environnemental hormis lien avec tabac
- Origine infectieuse ?
  - Précession infection virale
  - Association vaccination
- Recherches jusqu'à présent négatives
  - (polyomavirus de Merkel?)

Conclusion

- Néoplasie myéloïde inflammatoire (à cellules dendritiques)
  - expression clinique variable
- Voie des MAPK++
  - *BRAF^{V600E}/MAP2K1*
  - autres anomalies génétiques (adulte)
- Nouvelles approches thérapeutiques
  - effets indésirables potentiels graves
  - recherche clinique++
- Organisation et prise en charge structurée
  - Filière MARIH
  - CRMR, CC, RCP pluridisciplinaire www.marih.fr www.histiocytose.org www.histiocytoses.fr
  - Caractérisation large des mutations (NGS)