Neil Smith Memorial Lecture
A novel targeted immunotherapy for CTCL

Martine Bagot

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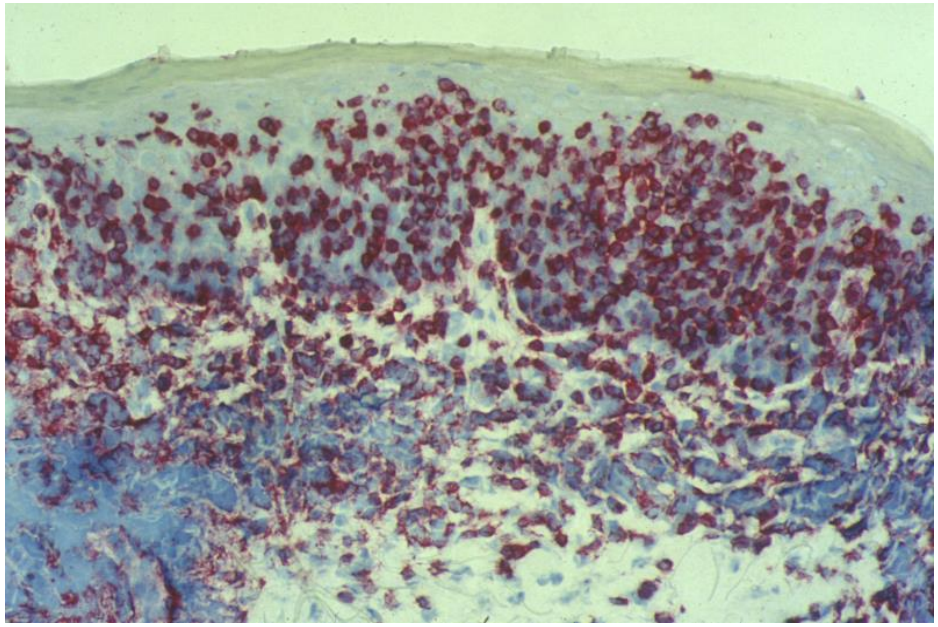
EORTC CLTF meeting, Torino, September 25-27, 2015

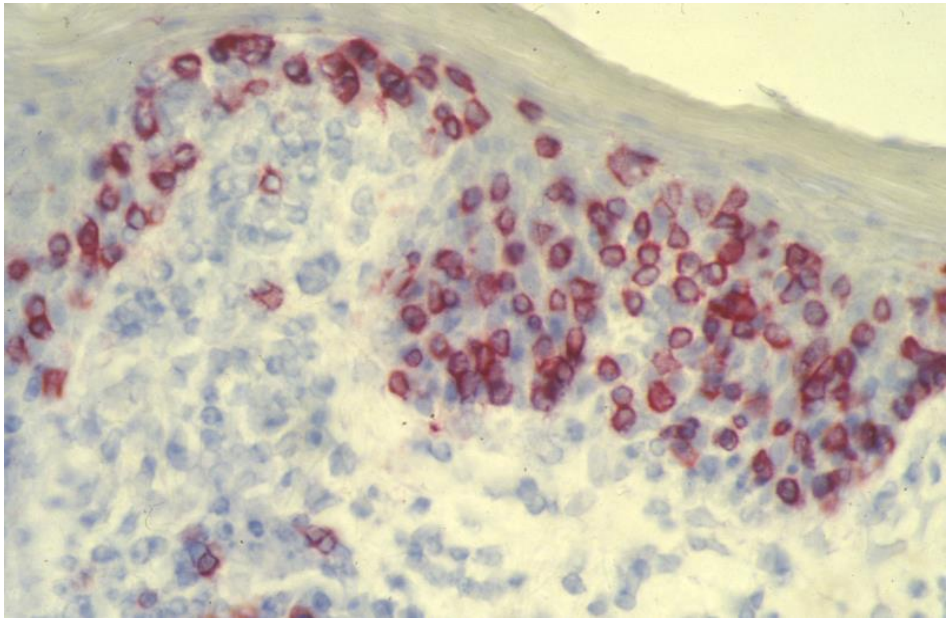
EORTC CLTF MEETING
TORINO 2015

How can we find new efficient treatments for CTCL patients ?

- Genomic studies to identify mutations and relevant targets within various signaling pathways
- Non specific immunotherapy: unleashing the immune system by releasing its negative regulatory checkpoints
- Specific immunotherapy: identifying tumor specific antigens to develop monoclonal antibodies specific for tumor antigens

Is it possible to separate reactive T cell clones from tumor T cell clones in CTCL skin and blood ?





Is there evidence for Tumor Infiltrating Lymphocytes in CTCL ?

blood 1998 91: 4331-4341

Isolation of Tumor-Specific Cytotoxic CD4$^+$ and CD4$^+$CD8dim$^+$ T-Cell Clones Infiltrating a Cutaneous T-Cell Lymphoma

Martine Bagot, Hamid Echchakir, Fathia Mami-Chouaib, Marie-Hélène Delfau-Larue, Dominique Charue, Alain Bernheim, Salem Chouaib, Laurence Boumsell and Armand Bensussan

British Journal of Dermatology 2003; **148:** 24–29.

Cutaneous Biology

Isolation of a CD8αα+ CD4– tumour T-cell clone with cytotoxic activity from a CD4+ CD8– cutaneous T-cell lymphoma

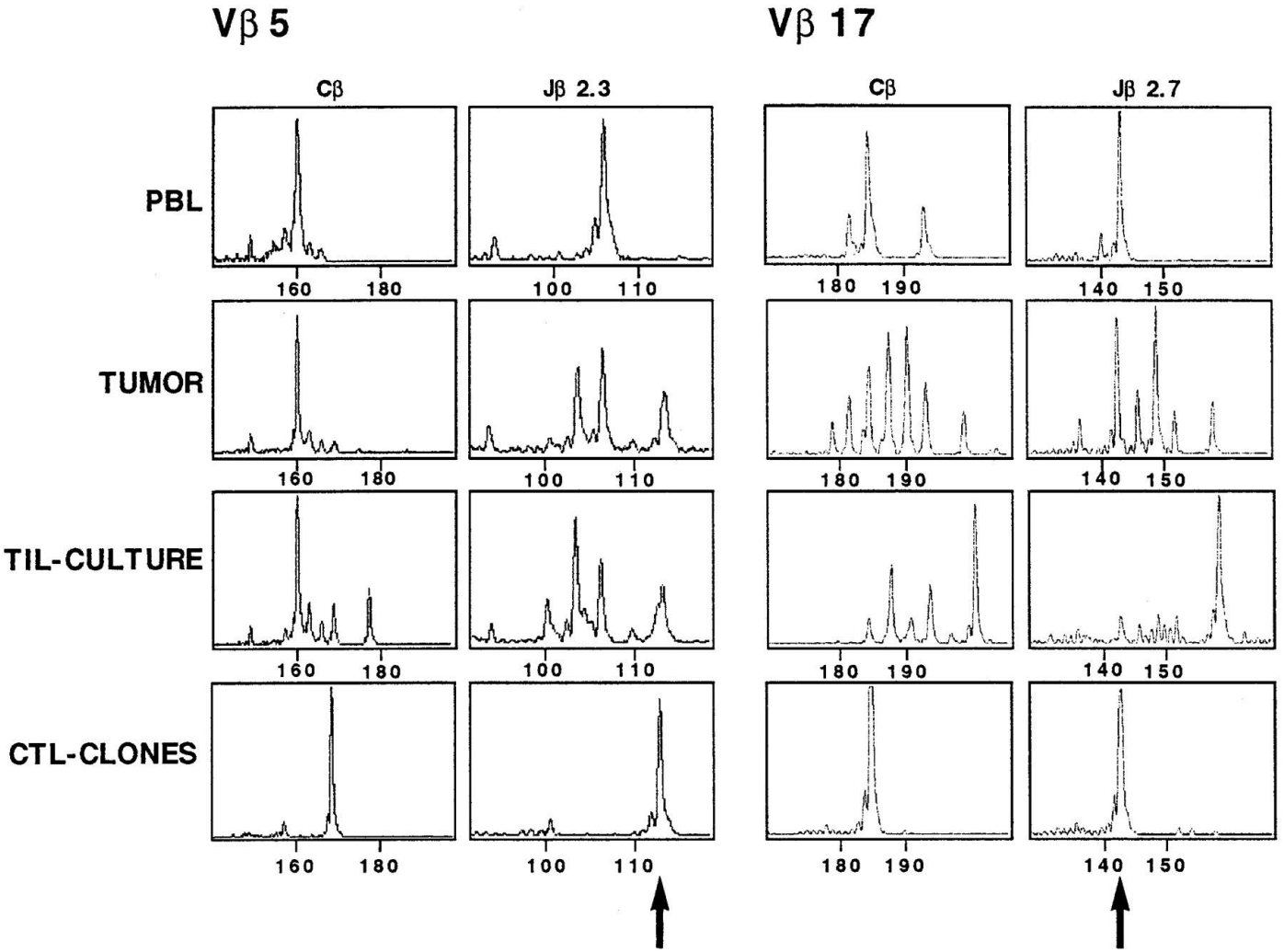
M.NIKOLOVA, H.ECHCHAKIR, J.WECHSLER,* L.BOUMSELL, A.BENSUSSAN AND M.BAGOT

INSERM U448, Department of Dermatology, Hôpital Henri Mondor, 94010 Créteil, France

**Department of Pathology, Hôpital Henri Mondor, 94010 Créteil, France*

Accepted for publication: 14 May 2002

Isolation of skin Tumor Infiltrating Lymphocytes in CTCL



Martine Bagot et al. Blood 1998;91:4331-4341

T cell clones isolated from CTCL may arise from tumor T lymphocytes but also from reactive T lymphocytes

Significance of circulating T-cell clones in Sézary syndrome

Nicolas Ortonne, Delphine Huet, Caroline Gaudez, Anne Marie-Cardine, Valérie Schiavon, Martine Bagot, Philippe Musette, and Armand Bensussan

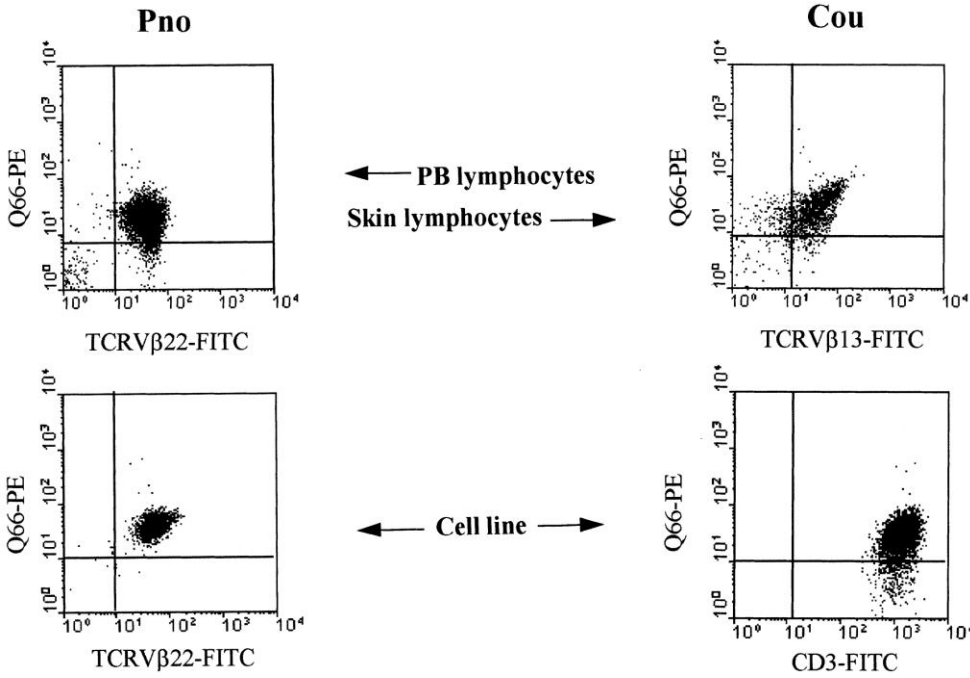
Identification of malignant Sézary cells by T-cell receptor (TCR) clonality studies is routinely used for the diagnosis of Sézary syndrome, but T-cell clones expressed in a single patient have never been accurately characterized. We previously reported that CD158k expression delineates Sézary syndrome malignant cells, and, more recently, we identified vimentin at the surface membranes of Sézary cells and normal activated lymphocytes. In the present study, T-cell clones from 13 patients with Sézary syndrome were identified by immunoscopy and further characterized in the blood according to their TCR Vβ, CD158k, and vimentin cell-surface expression. We found in most patients a unique malignant T-cell clone that coexpressed CD158k and vimentin and that, when patients were tested, was also present in the skin. However, in some patients we detected the presence of a nonmalignant circulating clone expressing high amounts of vimentin and lacking CD158k. These results indicate that clonal expansion may originate from circulating malignant and nonmalignant $CD4^+$ T cell populations in patients with Sézary syndrome. Identification of the malignant cells in Sézary syndrome cannot be achieved by T-cell clonality studies or by TCR Vβ monoclonal antibody (mAb) analysis alone; it also relies on CD158k phenotyping. (Blood. 2006;107:4030-4038)

Establishment of CTCL-derived long-term T cell lines

Functional characterization of an IL-7–dependent $CD4^+CD8\alpha\alpha^+$ Th3-type malignant cell line derived from a patient with a cutaneous T-cell lymphoma

Eva Poszepczynska, Martine Bagot, Hamid Echchakir, Denis Martinvalet, Mohamed Ramez, Dominique Charue, Laurence Boumsell, and Armand Bensussan

CDR3 of the functional rearranged T-cell receptor variable β region (*TCR-Vβ*) transcript was sequenced in order to demonstrate for the first time the identity between a long-term cultured T-cell line derived from a cutaneous T-cell lymphoma (CTCL) patient and the malignant T-cell clone present in the blood. The patient's peripheral blood lymphocyte-derived cultured T-cell line had a $CD3^+V\beta22^+CD4^+CD8\alpha\alpha^+CD25^-$ phenotype. It was named Pno and had been cultured for more than 1 year. Both fresh and long-term–cultured tumor cells proliferated highly in response to interleukin-7 (IL-7), and exogeneous IL-7 prevented Pno lymphocytes from apoptosis and maintained high levels of Bcl-2 expression. This unique malignant cloned lymphocyte line was further used to carry out functional studies. The results indicated that the CD3/TCR structures expressed by the Pno lymphocytes were functional because an immobilized anti-CD3 monoclonal antibody (mAb) or the combination of a soluble anti-CD3 mAb with submitogenic doses of phorbol 12 β-myristate 13 α-acetate induced a proliferative response. Further, the CD2 and CD28 co-receptors were functional because they were able to induce a strong proliferative response upon their specific stimulation. Finally, the Pno T cell line had a Th3-type cytokine profile because it produced high amounts of the immunosuppressor cytokine tumor growth factor–β1 (TGF-β1). This high production of TGF-β1 may inhibit antitumor specific responses in CTCL. (Blood. 2000;96:1056-1063)



Armand Bensussan
Member of International Human Cell Differentiation Molecules Council (CD nomenclature)
Test of more than 300 mAbs evaluated during the CDs' workshops

blood
2001 97: 1388-1391
doi:10.1182/blood.V97.5.1388

CD4+ cutaneous T-cell lymphoma cells express the p140–killer cell immunoglobulin-like receptor

Martine Bagot, Alessandro Moretta, Simona Sivori, Roberto Biassoni, Claudia Cantoni, Cristina Bottino, Laurence Boumsell and Armand Bensussan

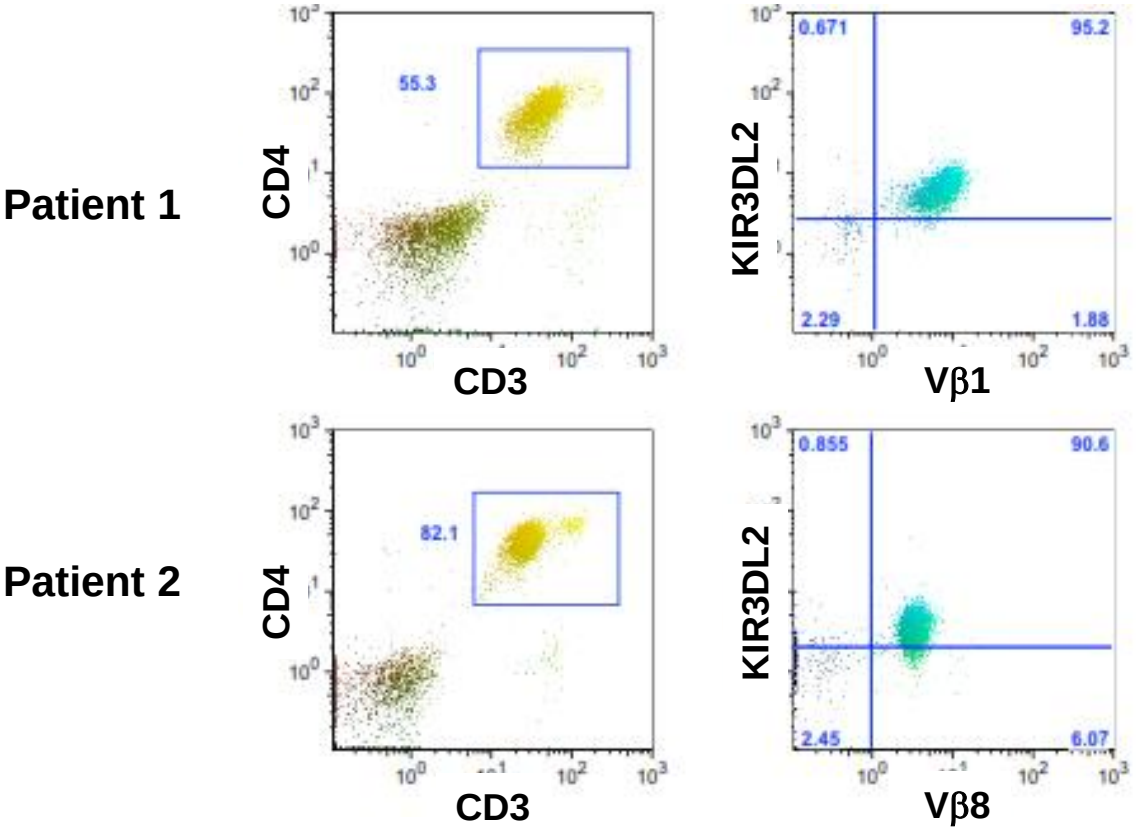
CD158k/KIR3DL2 Is a New Phenotypic Marker of Sezary Cells: Relevance for the Diagnosis and Follow-Up of Sezary Syndrome

Ewa Poszepczynska-Guigné,*† Valérie Schiavon,* Michel D'Incan,‡ Hamid Echchakir,* Philippe Musette,§ Nicolas Ortonne,* Laurence Boumsell,* Alessandro Moretta,¶ Armand Bensussan,*[1] and Martine Bagot*†[1]

*INSERM U448, Hôpital Henri Mondor, Créteil, France; †Department of Dermatology, Hôpital Henri Mondor, Créteil, France; ‡Department of Dermatology, Clermont-Ferrand, France; §Department of Dermatology, Rouen, France; ¶Dipartimento di Medicina Sperimentale, Università di Genova, Genova, Italy. French Cutaneous Lymphoma Study Group

J Invest Dermatol 122:820–823, 2004

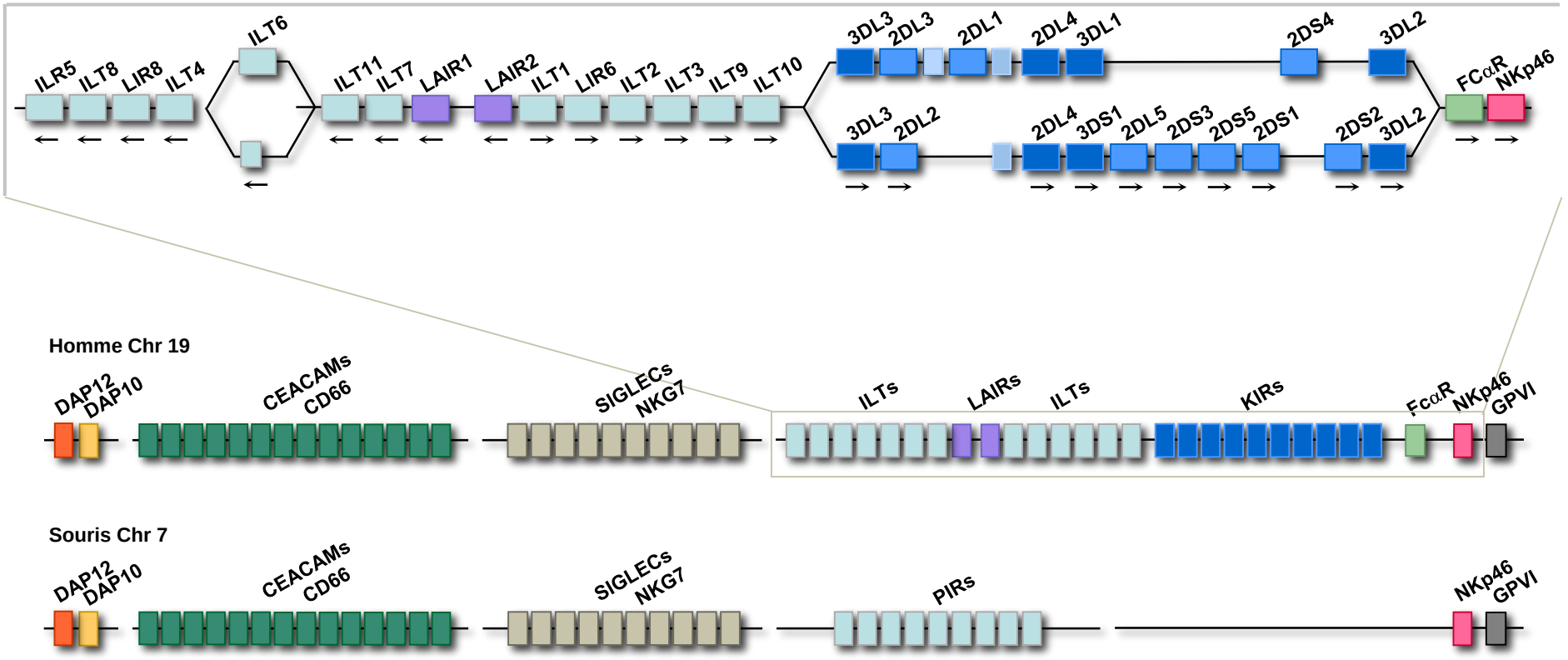
KIR3DL2 is a phenotypic marker for Sezary cells



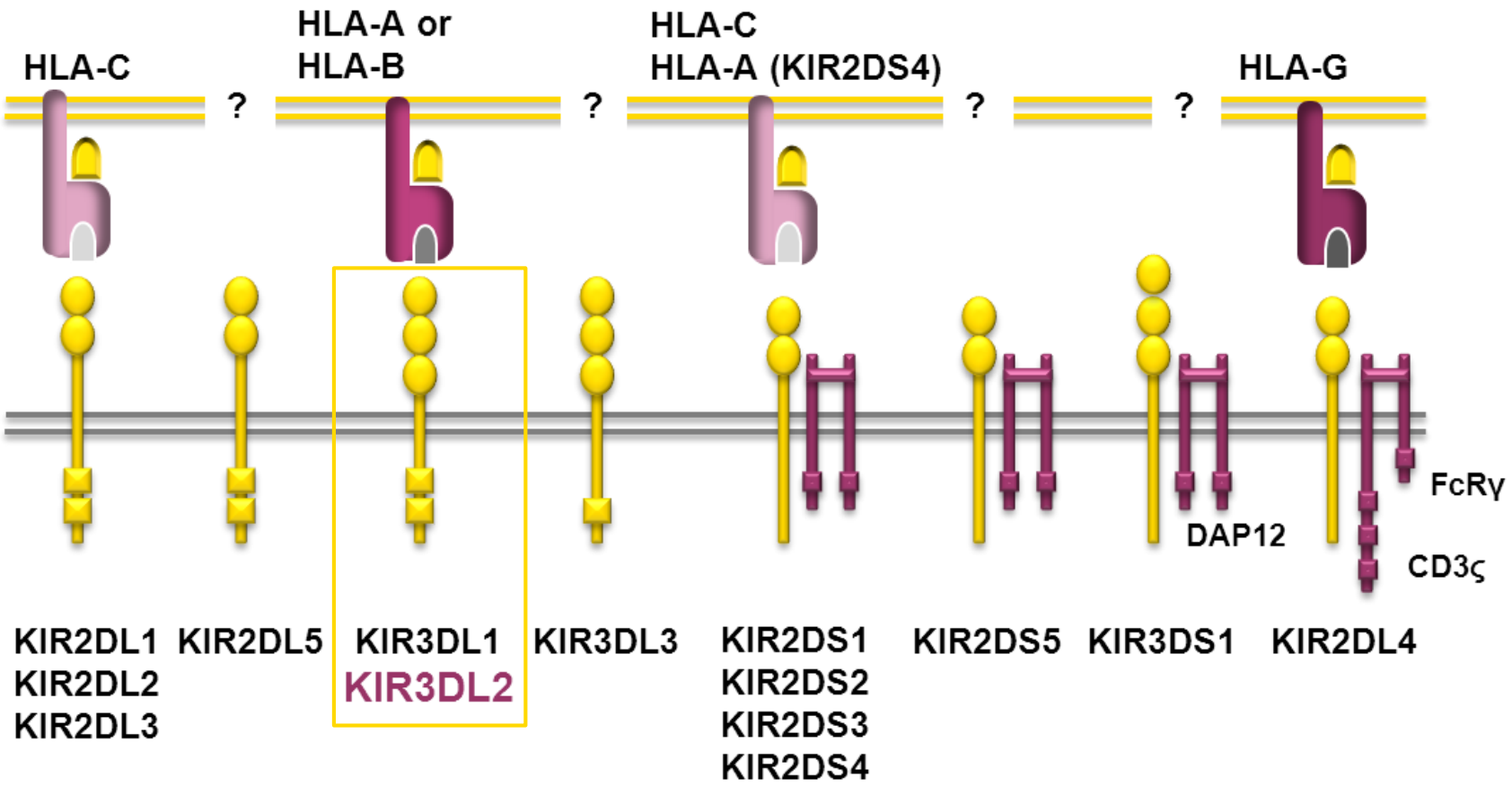
Clonal leukemic Sézary cells, defined by a single Vβ chain expression, are KIR3DL2^{+} in patient blood

Moins-Teisserenc H, J Invest Dermatol 2014

Leucocyte Receptor Cluster Organization

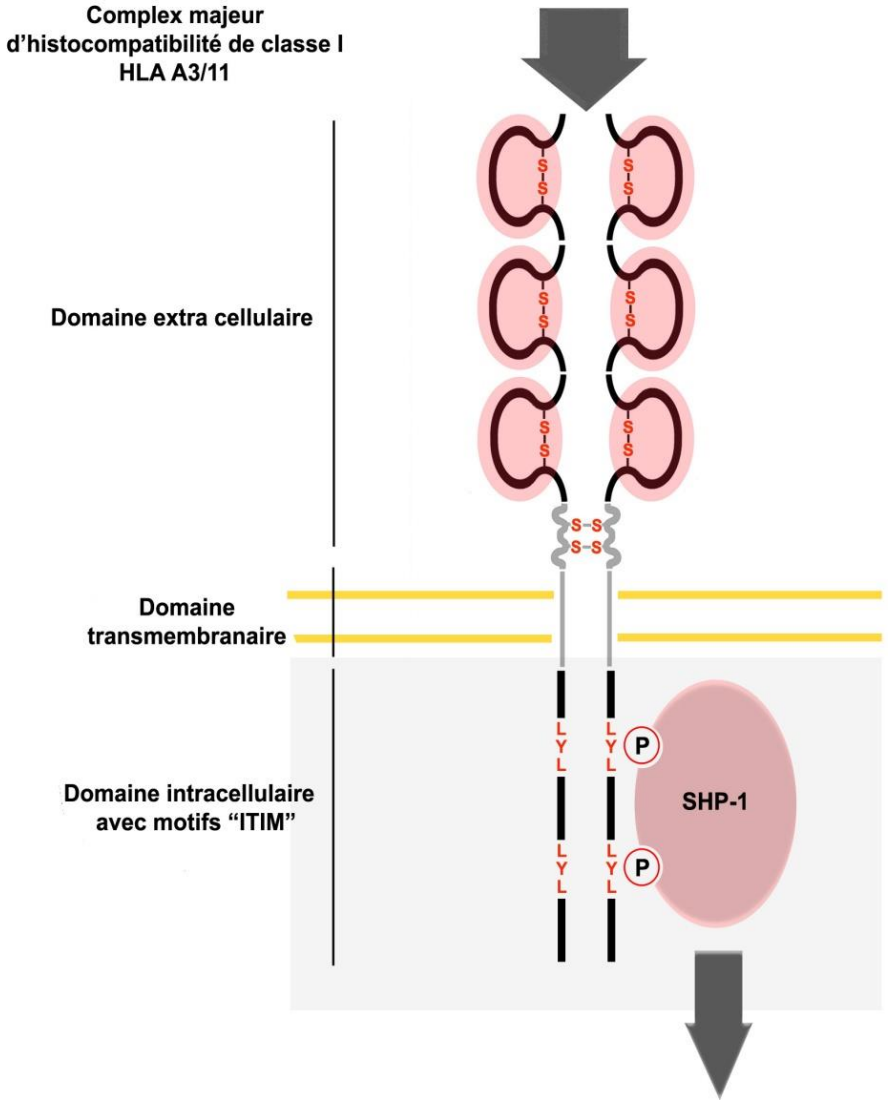


KIR Receptor Family

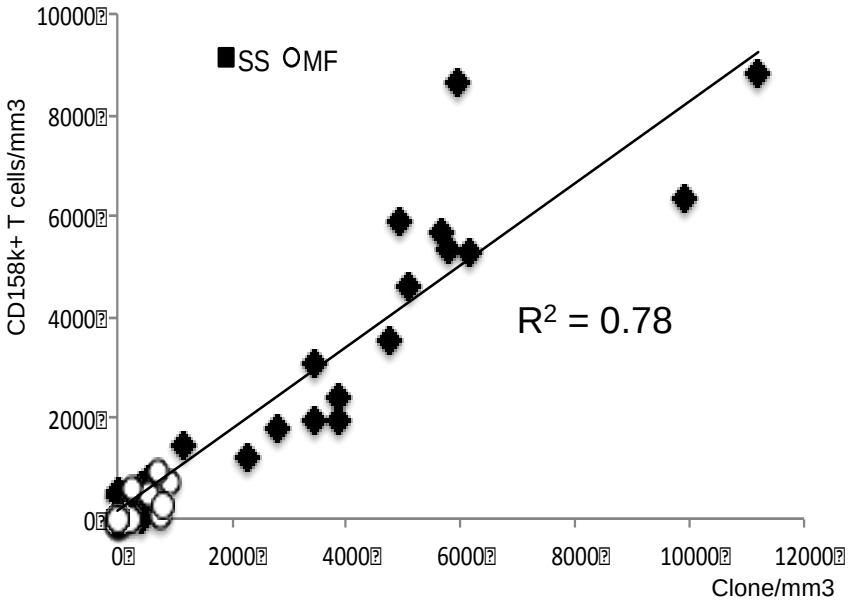


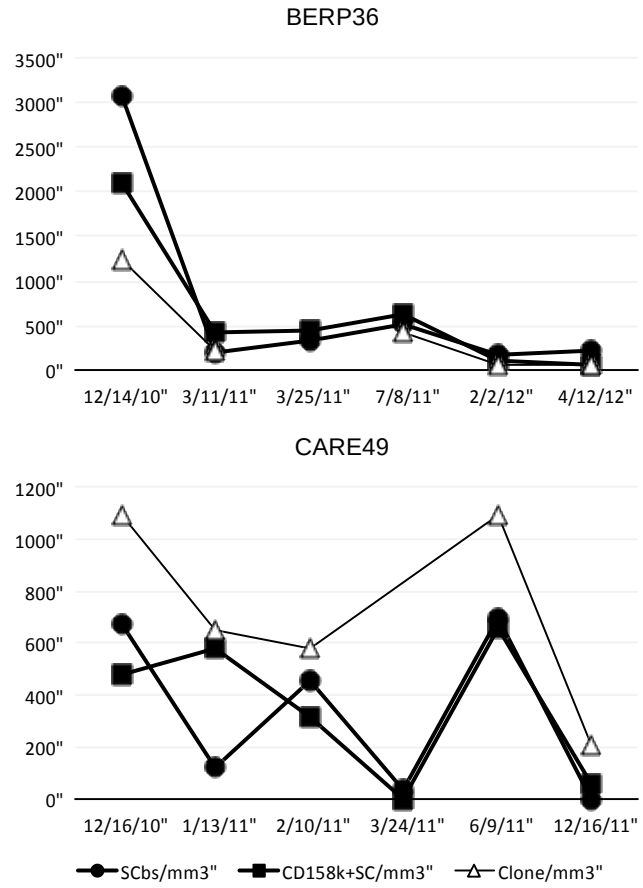
Adapted from Thielens et al., Curr Opin Immunol. 2012 Apr;24(2):239-45

The KIR3DL2/CD158k receptor



Identification of Sezary cells using either cytomorphology, flow-cytometry or TCR repertoire



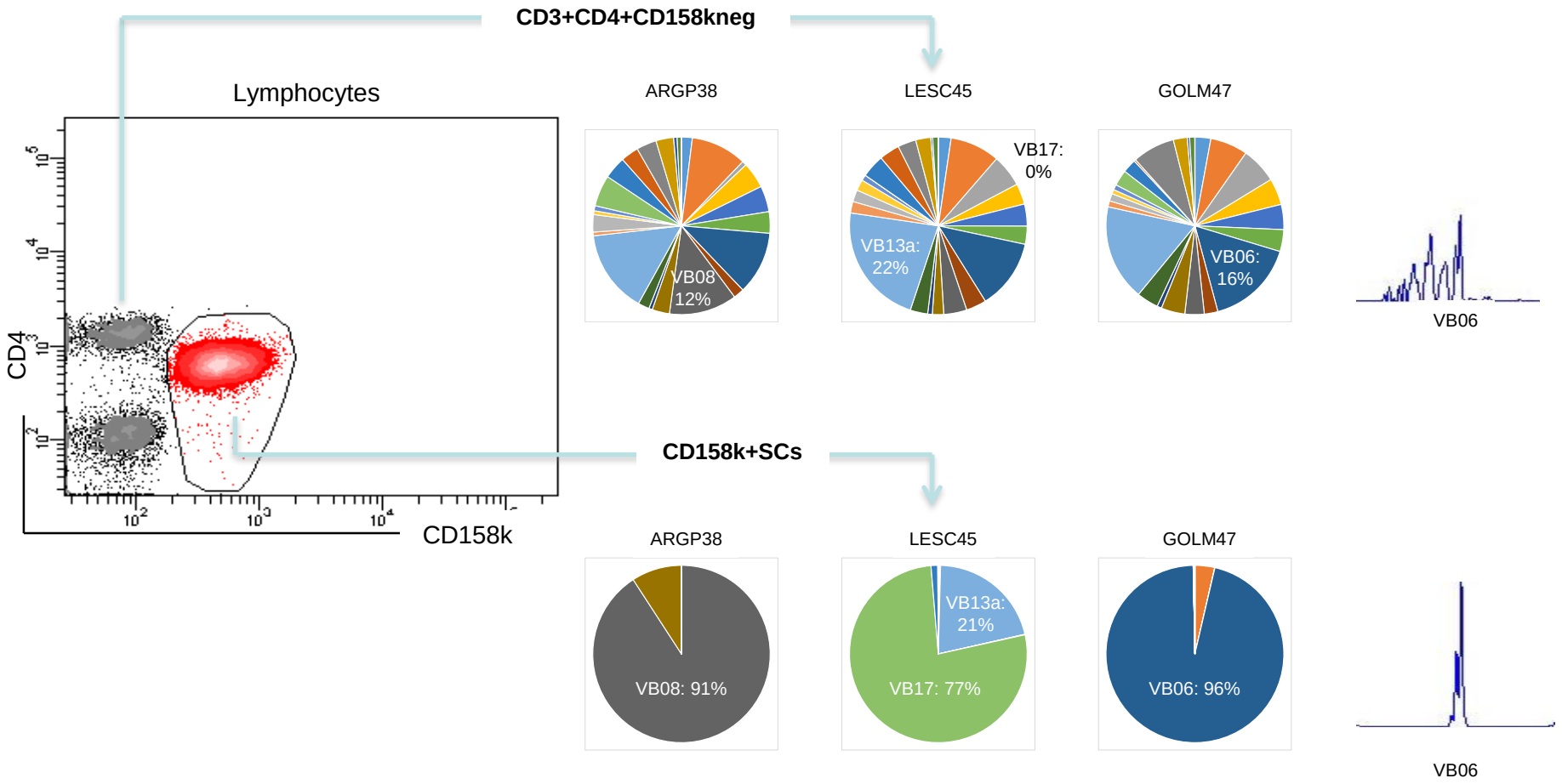


Longitudinal evolution over a period of 18 and 12 months

Moins-Tesserenc H, J Invest Dermatol 2014

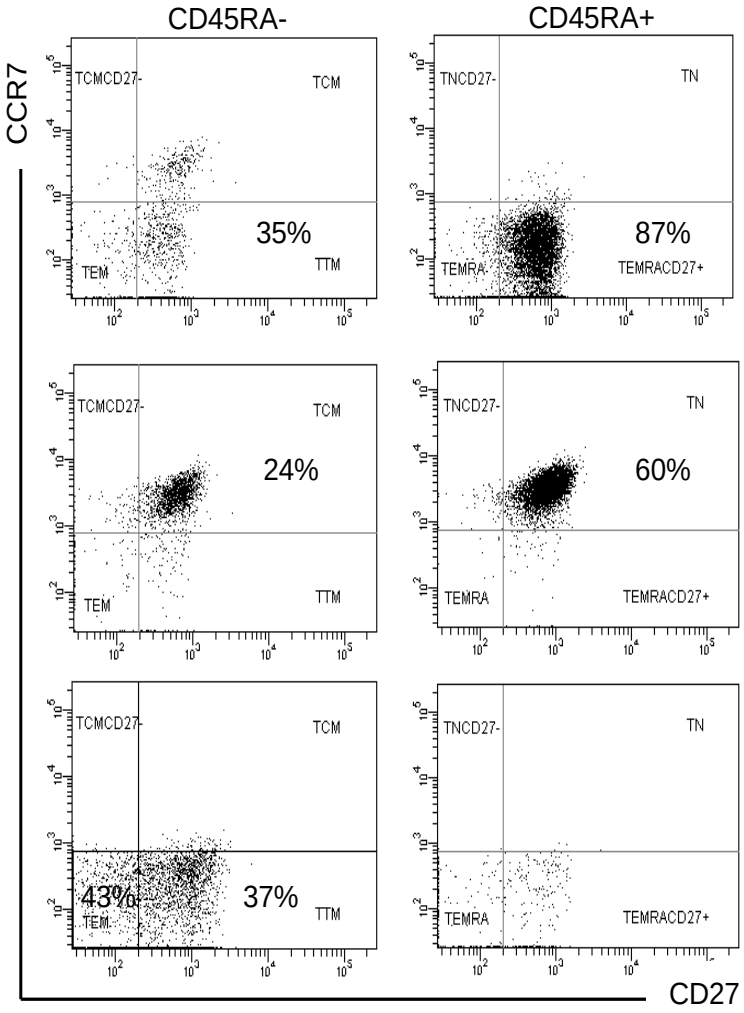
Analysis of CD158k+ T cells

Immunoscope analysis of Vβ families from CD158k+CD4+T cell and CD158k+T cells



Moins-Teisserenc et al, J Invest Dermatol, 2015

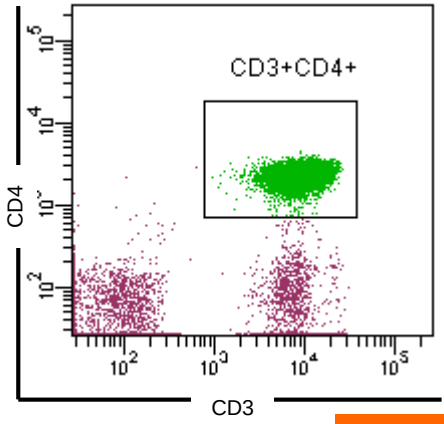
Phenotypic heterogeneity of CD158k+ T cells: memory and naive subsets



3 patients at initial diagnosis

Moins-Teisserenc et al, J Invest Dermatol, 2015

Phenotypic heterogeneity of T cells

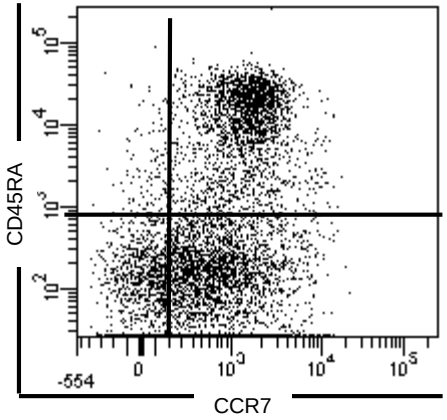


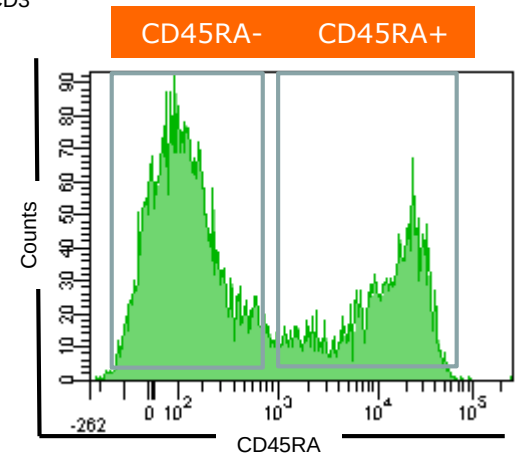
CD45RA+

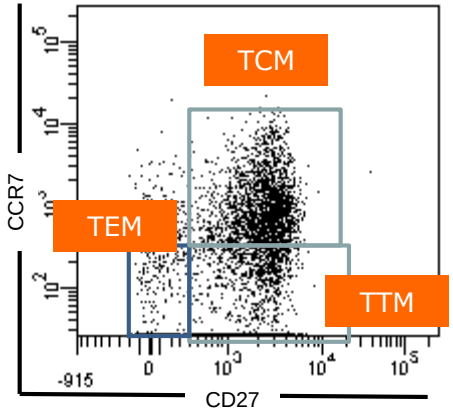
- CCR7+CD27= T Naive
- CCR7-CD27-= T Effector Terminal

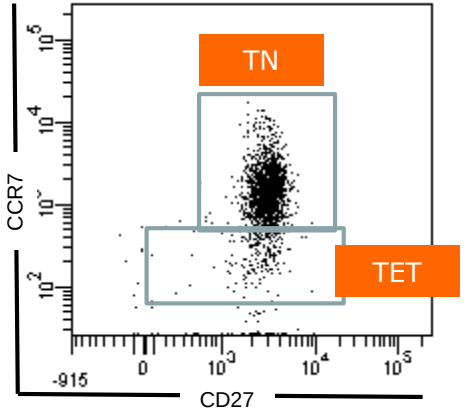
CD45RA-

- CCR7+CD27+= T Central Memory
- CCR7-CD27+= T Transitional Memory
- CCR7-CD27-= T Effector Memory









Phenotypic heterogeneity of CTCL

blood

2010 116: 767-771
Prepublished online May 18, 2010;
doi:10.1182/blood-2009-11-251926

Sézary syndrome and mycosis fungoides arise from distinct T-cell subsets: a biologic rationale for their distinct clinical behaviors

James J. Campbell, Rachael A. Clark, Rei Watanabe and Thomas S. Kupper

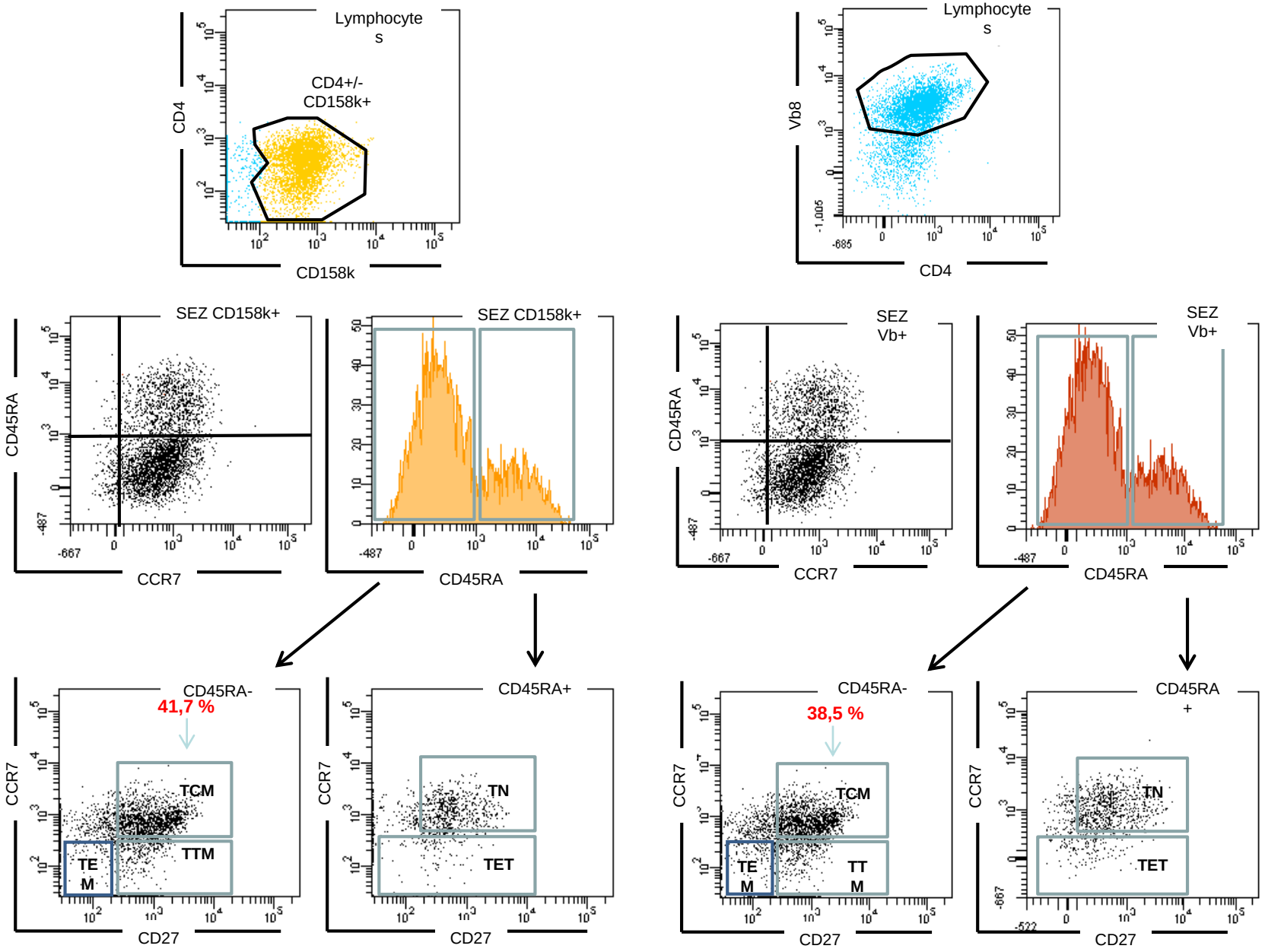
- Sezary patients:
  Central memory T-cells
  CD45RA-CCR7+CD27+

Published in final edited form as:
Sci Transl Med. 2012 January 18; 4(117): 117ra7. doi:10.1126/scitranslmed.3003008.

Skin effector memory T cells do not recirculate and provide immune protection in alemtuzumab-treated CTCL patients

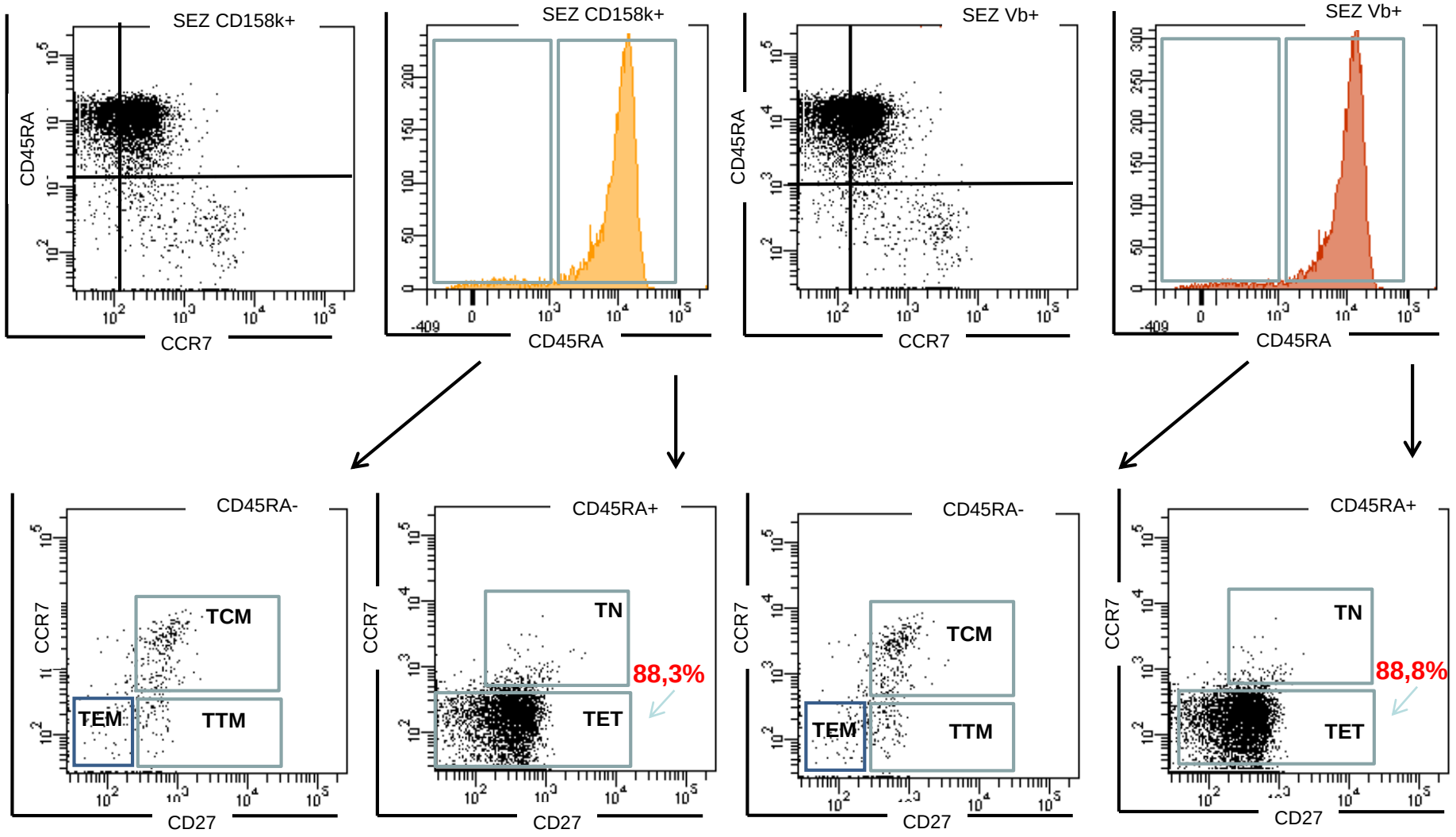
Rachael A. Clark[1,2,3,5], **Rei Watanabe**[1,2], **Jessica E. Teague**[1], **Christoph Schlapbach**[1], **Marianne C. Tawa**[3], **Natalie Adams**[3], **Andrew A. Dorosario**[3], **Keri S. Chaney**[1], **Corey S. Cutler**[3], **Nicole R. LeBoeuf**[1], **Joi B. Carter**[4], **David C. Fisher**[3], and **Thomas S. Kupper**[1,3,5]
[1]Department of Dermatology, Brigham and Women's Hospital and Harvard Medical School, Boston MA

- Mycosis fungoides:
  Effector memory T cells
  CD45RA-CCR7-CD27-

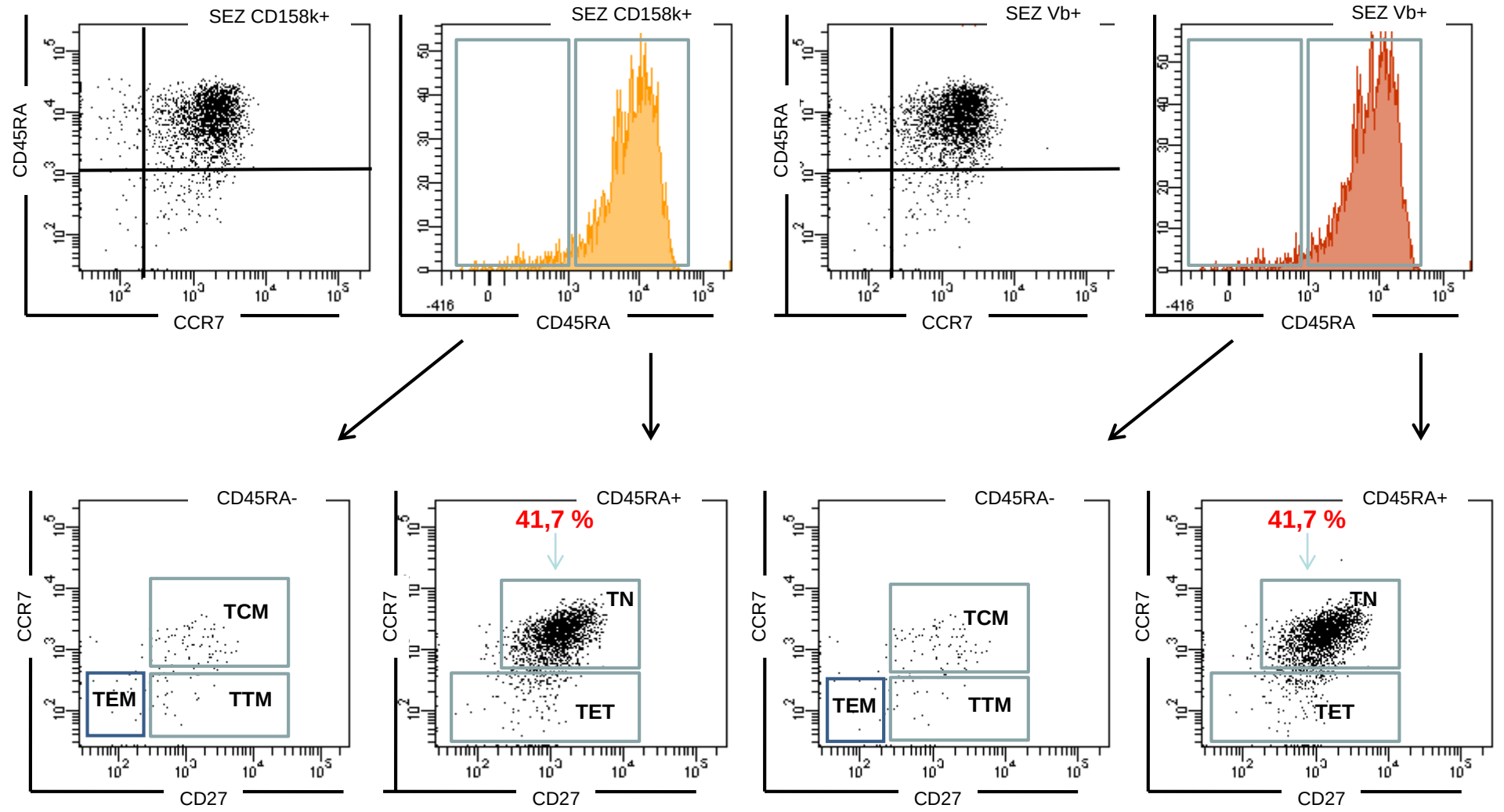


Phenotype: Central memory : CD45RA-CCR7+CD27+

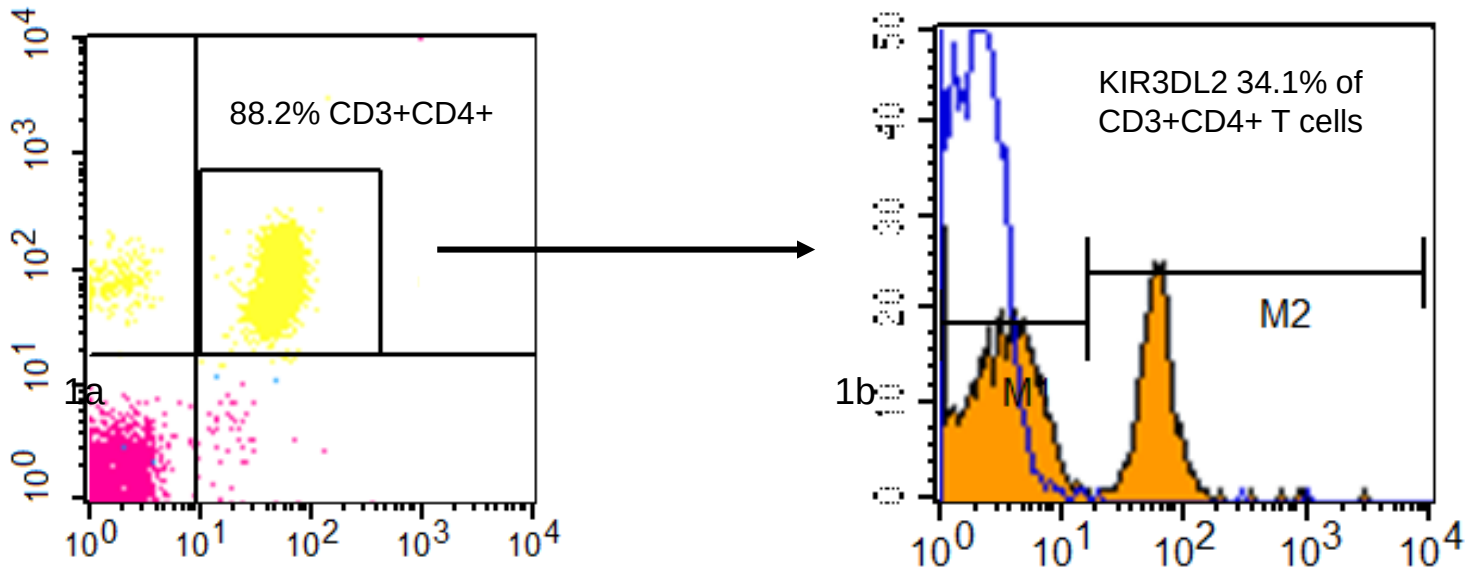
Phenotype Effector Terminal : CD45RA+CCR7-CD27-



Naive Phenotype : CD45RA+CCR7+CD27+

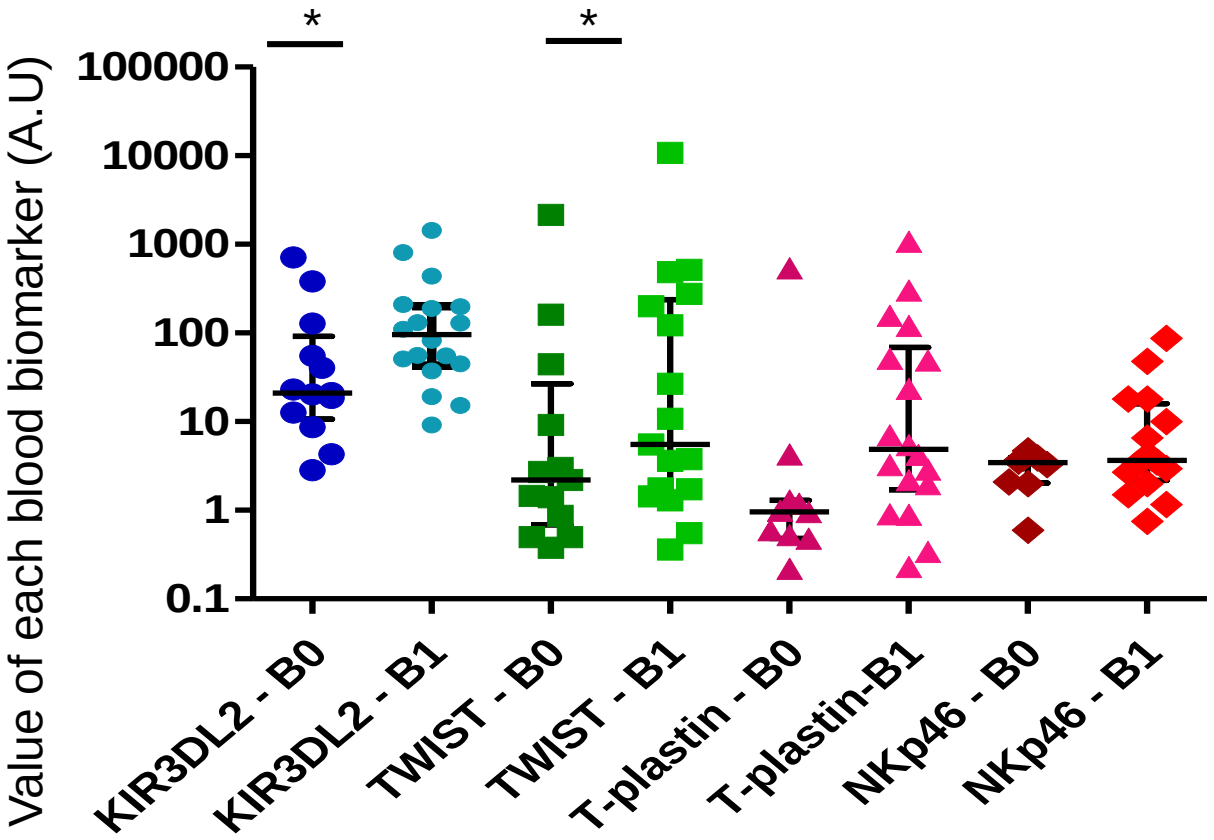


Flow cytometric analysis of CD3+CD4+KIR3DL2+ cells in a B1 erythrodermic mycosis fungoides



Hurabielle, J Invest Dermatol, 2015

Blood biomarkers in B0 and B1 Erythrodermic MF patients



Hurabielle, J Invest Dermatol, 2015

Sezary cells also express activating Killer cell Ig-like Receptors

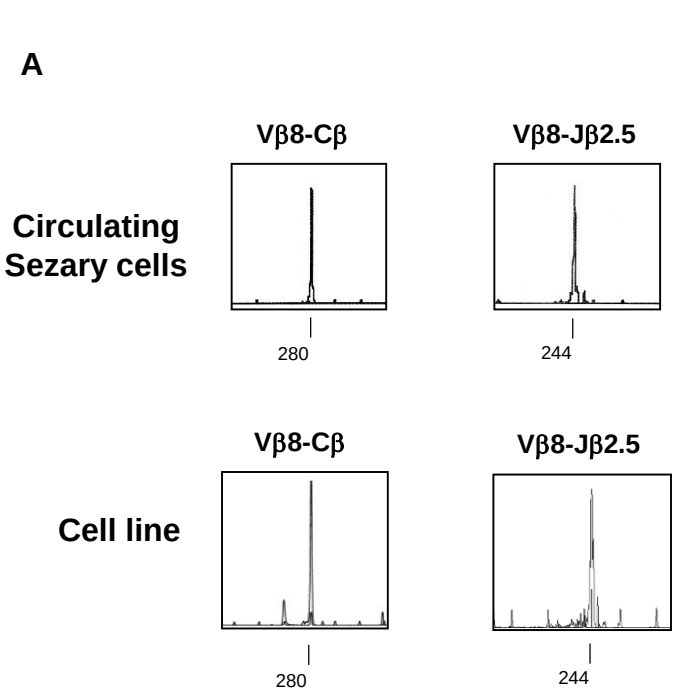
blood

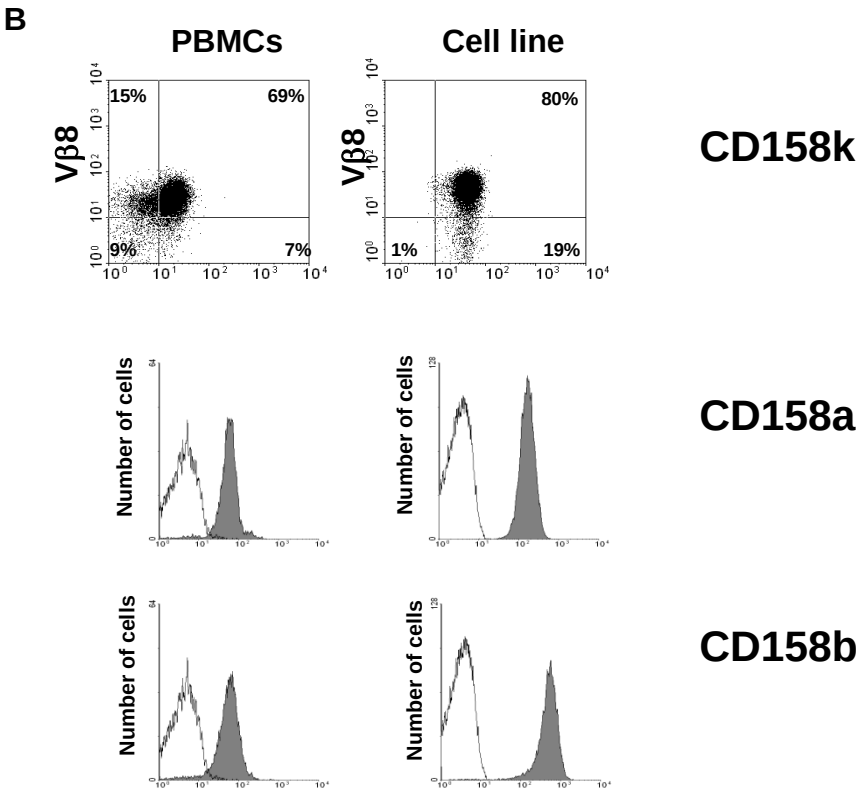
2007 109: 5064-5065
doi:10.1182/blood-2007-02-071993

Killer cell Ig-like receptors CD158a and CD158b display a coactivatory function, involving the c-Jun NH_2-terminal protein kinase signaling pathway, when expressed on malignant $CD4^+$ T cells from a patient with Sézary syndrome

Anne Marie-Cardine, Delphine Huet, Nicolas Ortonne, Natacha Remtoula, Sabine Le Gouvello, Martine Bagot and Armand Bensussan

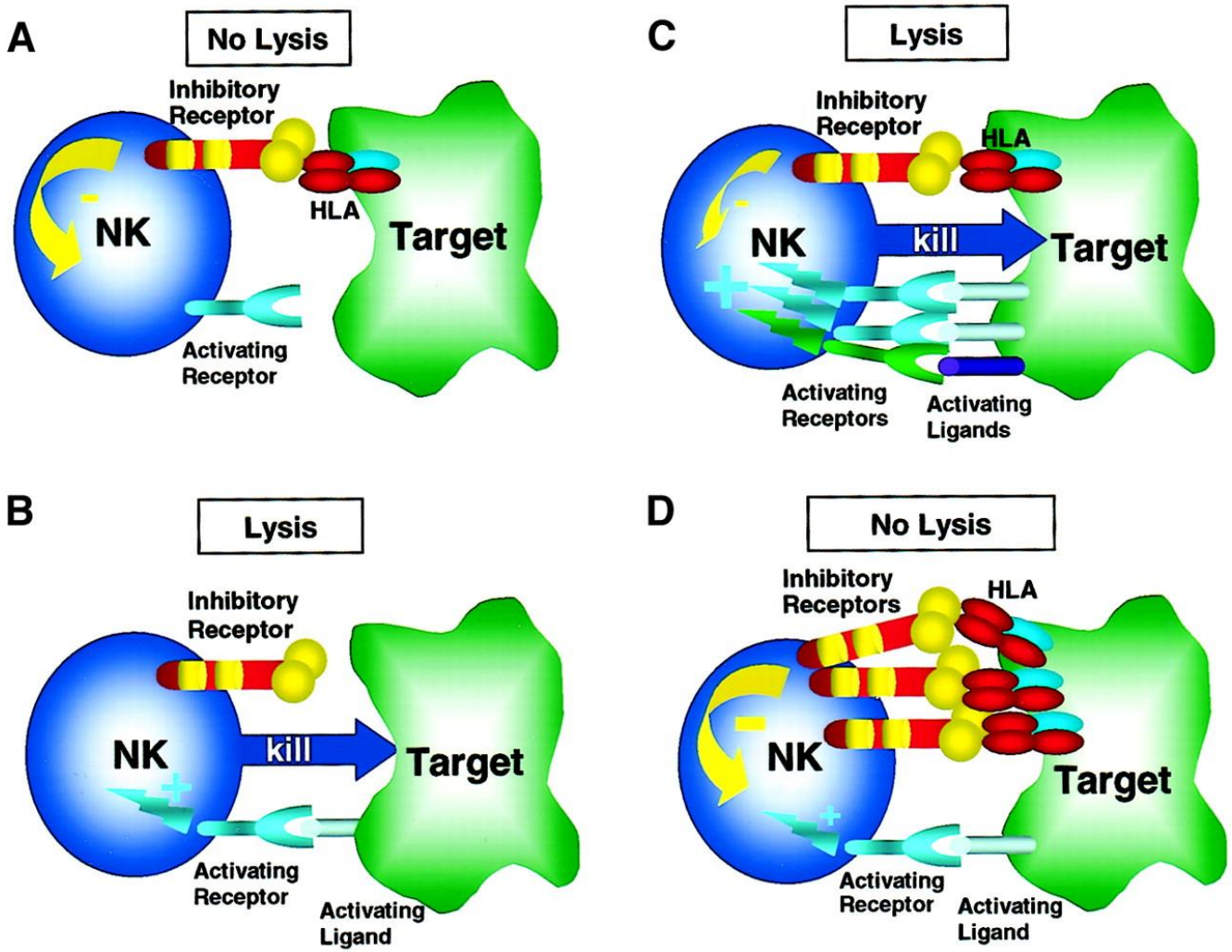
Expression of other KIRs by Sezary cells





Marie-Cardine, Blood 2007

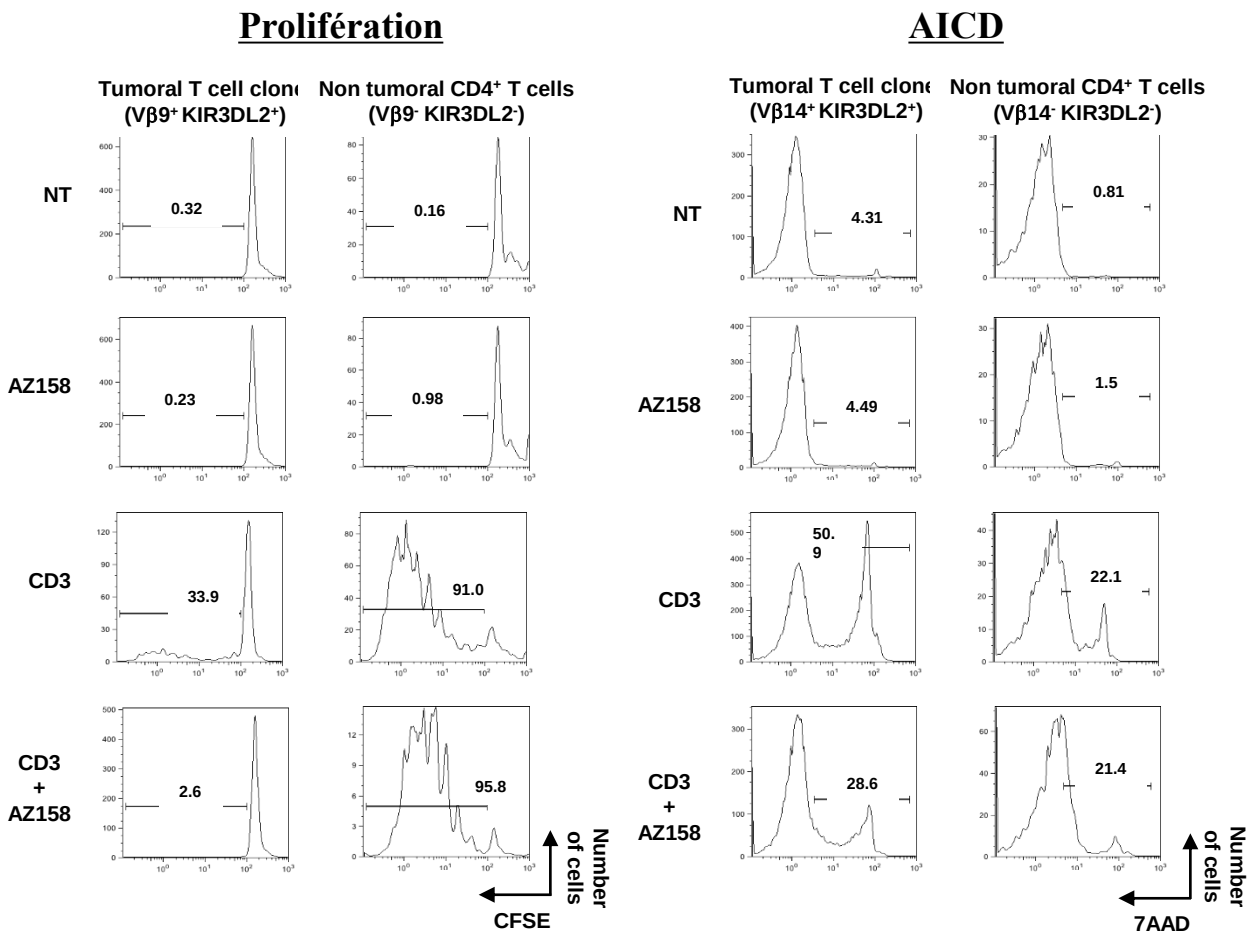
What is the function of CD158k/KIR3DL2 on CTCL cells ?


A
No Lysis
Inhibitory Receptor
HLA
NK
Target
Activating Receptor
C
Lysis
Inhibitory Receptor
HLA
NK
kill
Target
Activating Receptors
Activating Ligands
B
Lysis
Inhibitory Receptor
NK
kill
Target
Activating Receptor
Activating Ligand
D
No Lysis
Inhibitory Receptors
HLA
NK
Target
Activating Receptor
Activating Ligand

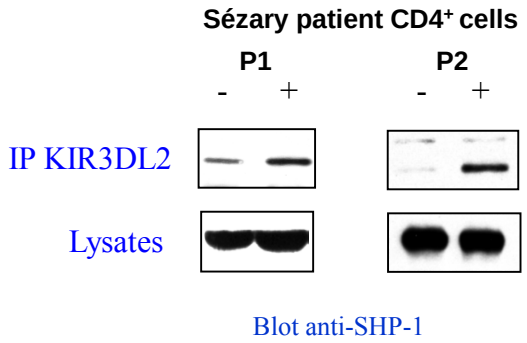
blood
2014 124: 3330-3332
doi:10.1182/blood-2014-09-598995

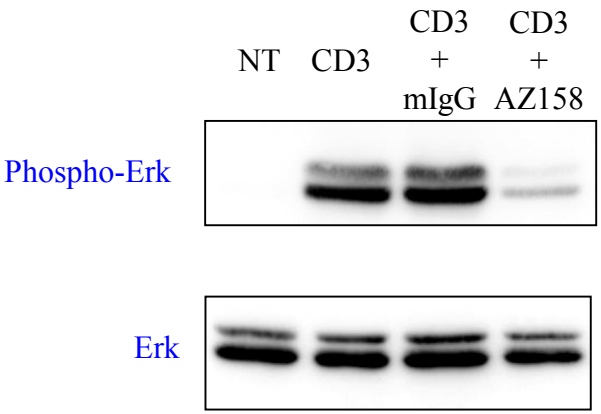
KIR3DL2 is a coinhibitory receptor on Sézary syndrome malignant T cells that promotes resistance to activation-induced cell death

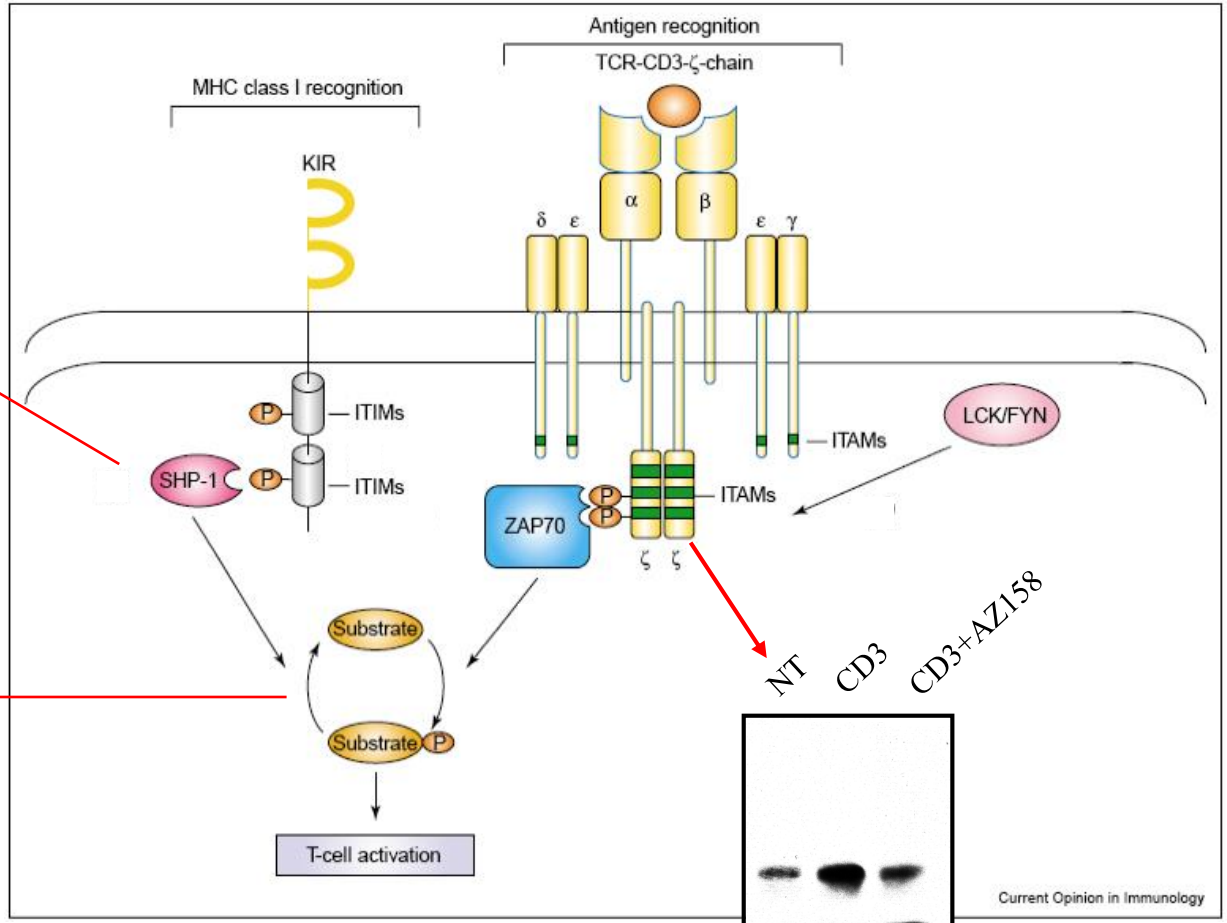
Nicolas Thonnart, Anne Caudron, Isabel Legaz, Martine Bagot, Armand Bensussan and Anne Marie-Cardine



Inhibition of the CD3-mediated activation upon CD158k recruitment



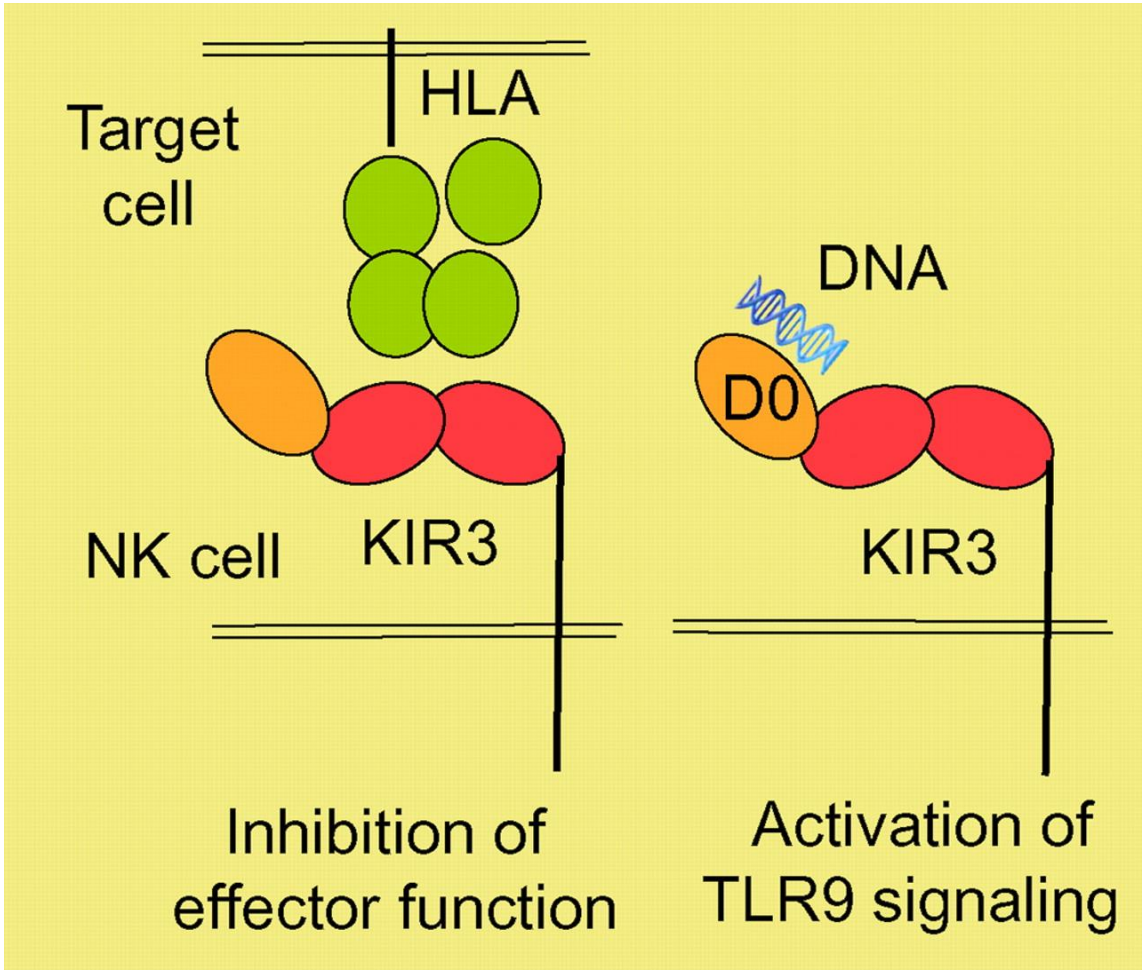




Phospho-ζ

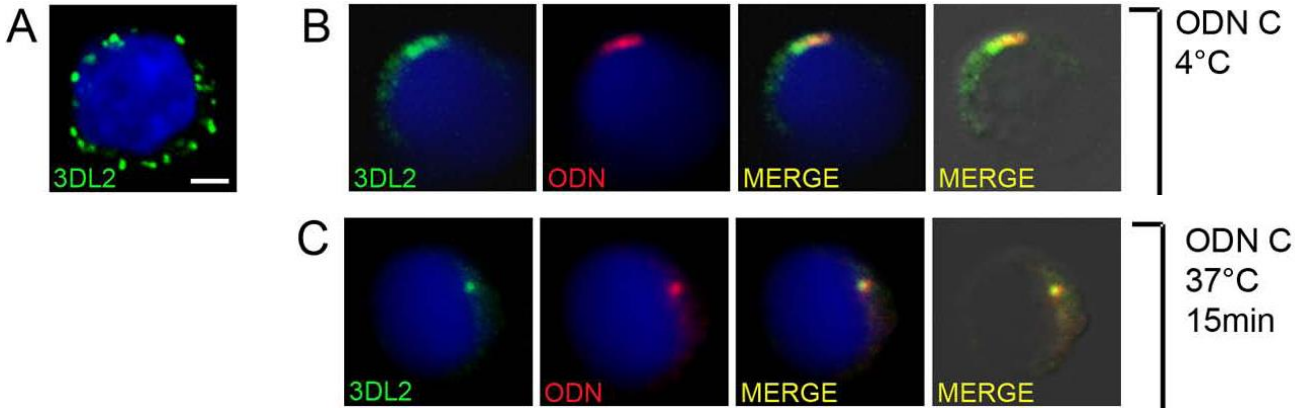
Co-inhibitory receptor

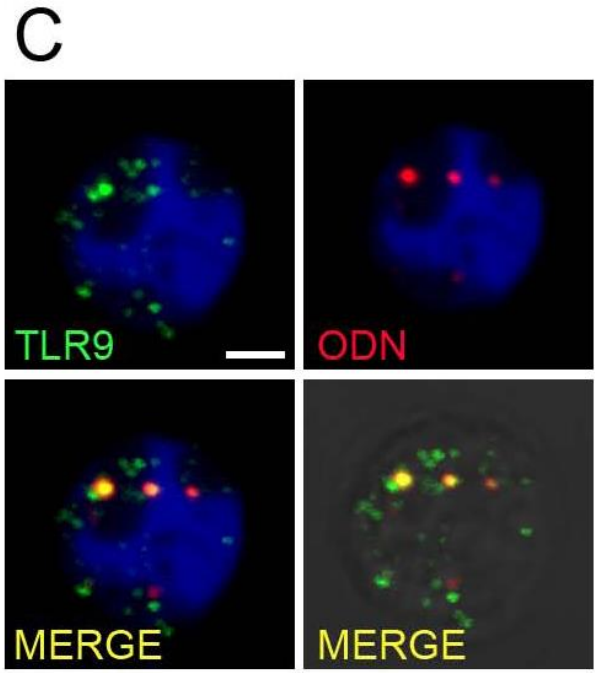
A novel KIR-associated function:evidence that CpG DNA uptake and shuttling to early endosomes is mediated by KIR3DL2



Sivori et al, Blood 2010

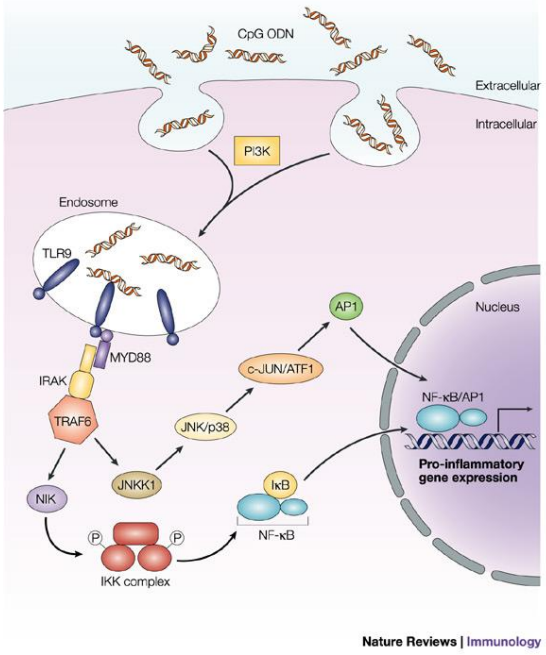
Visualisation of KIR3DL2-ODN interactions by confocal microscopy





Co-internalisation of KIR3DL2 and CpG-ODN in endosomes where TLR9 is located

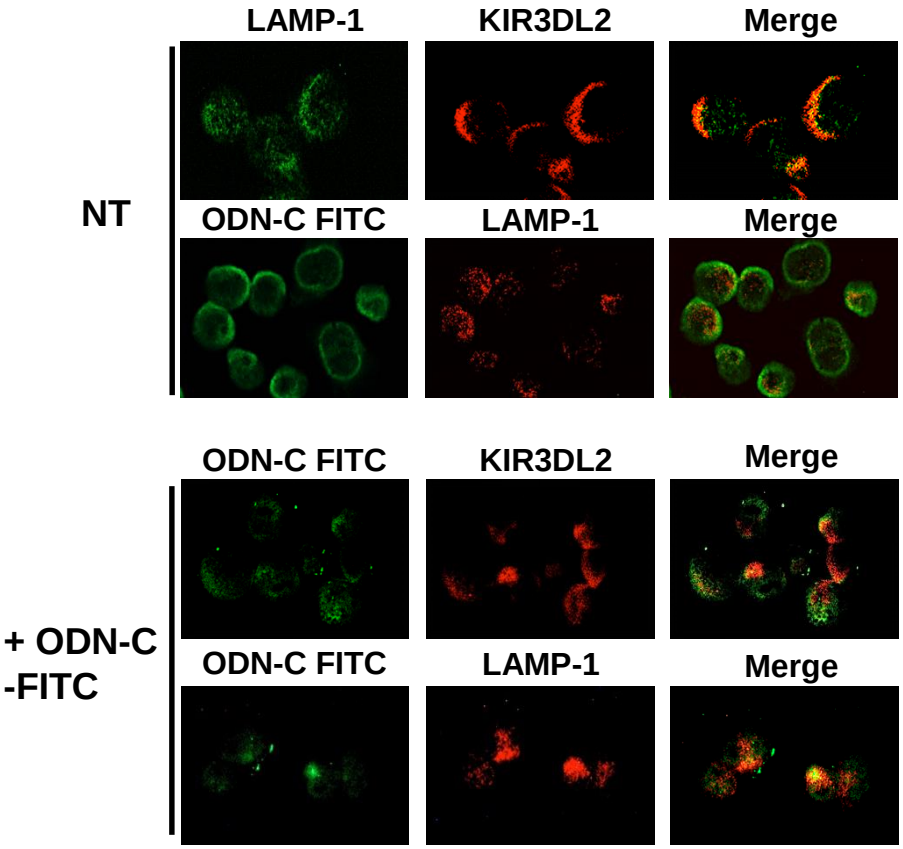
Sivori et al, Blood 2010

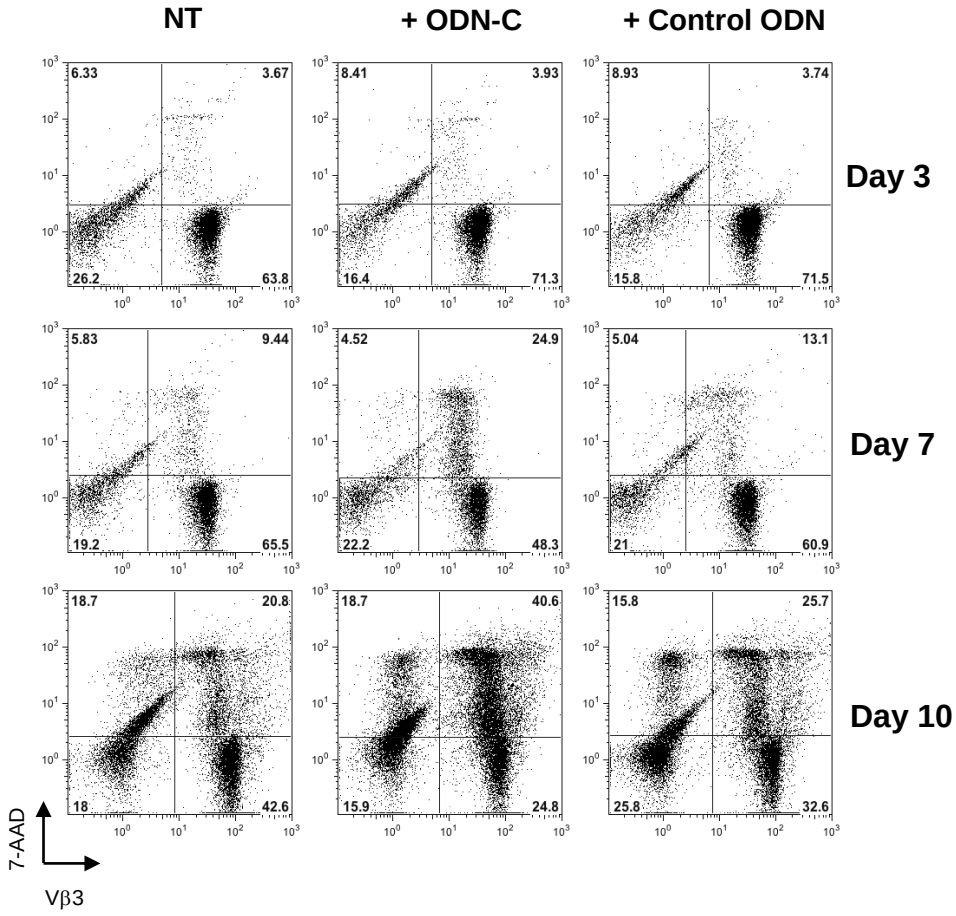


KIR3DL2/CpG ODN Interaction Mediates Sézary Syndrome Malignant T Cell Apoptosis

Bouchra Ghazi[1], Nicolas Thonnart[1,2], Martine Bagot[1,2,3], Armand Bensussan[1,2,3] and Anne Marie-Cardine[1,2]

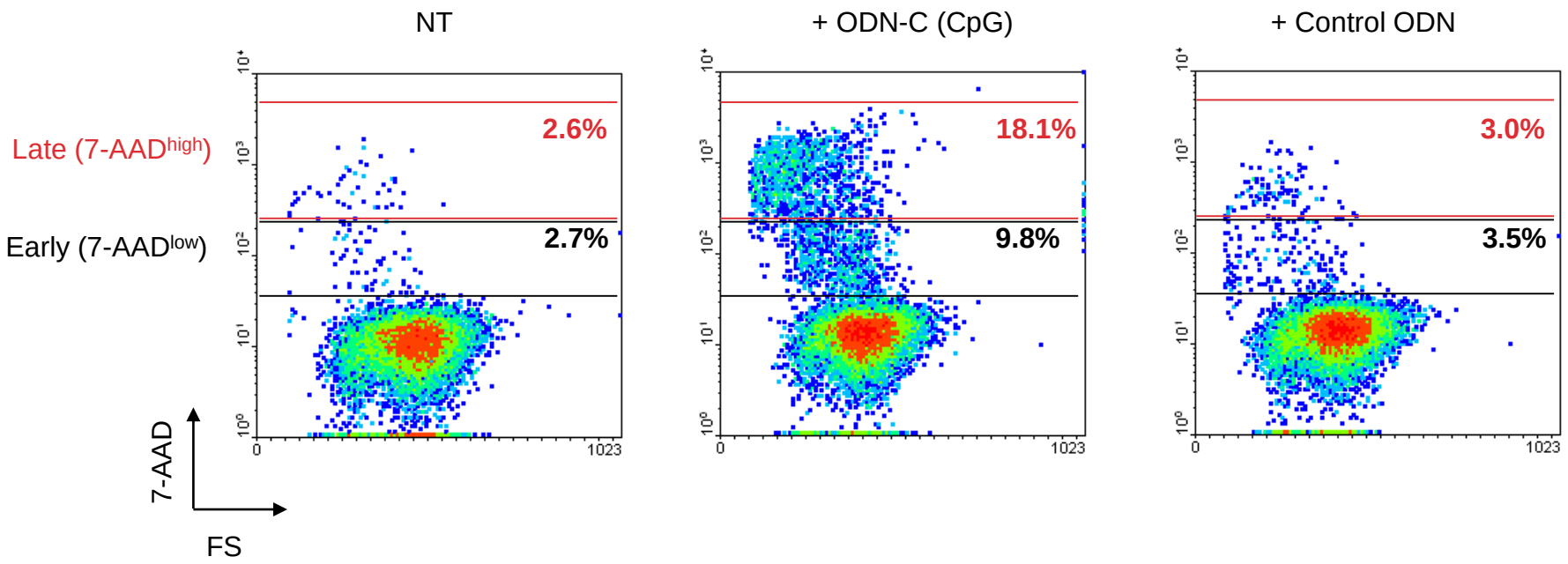
Journal of Investigative Dermatology advance online publication, 14 August 2014; doi:10.1038/jid.2014.286





KIR3DL2-CpG ODN interactions induces Sézary cell death

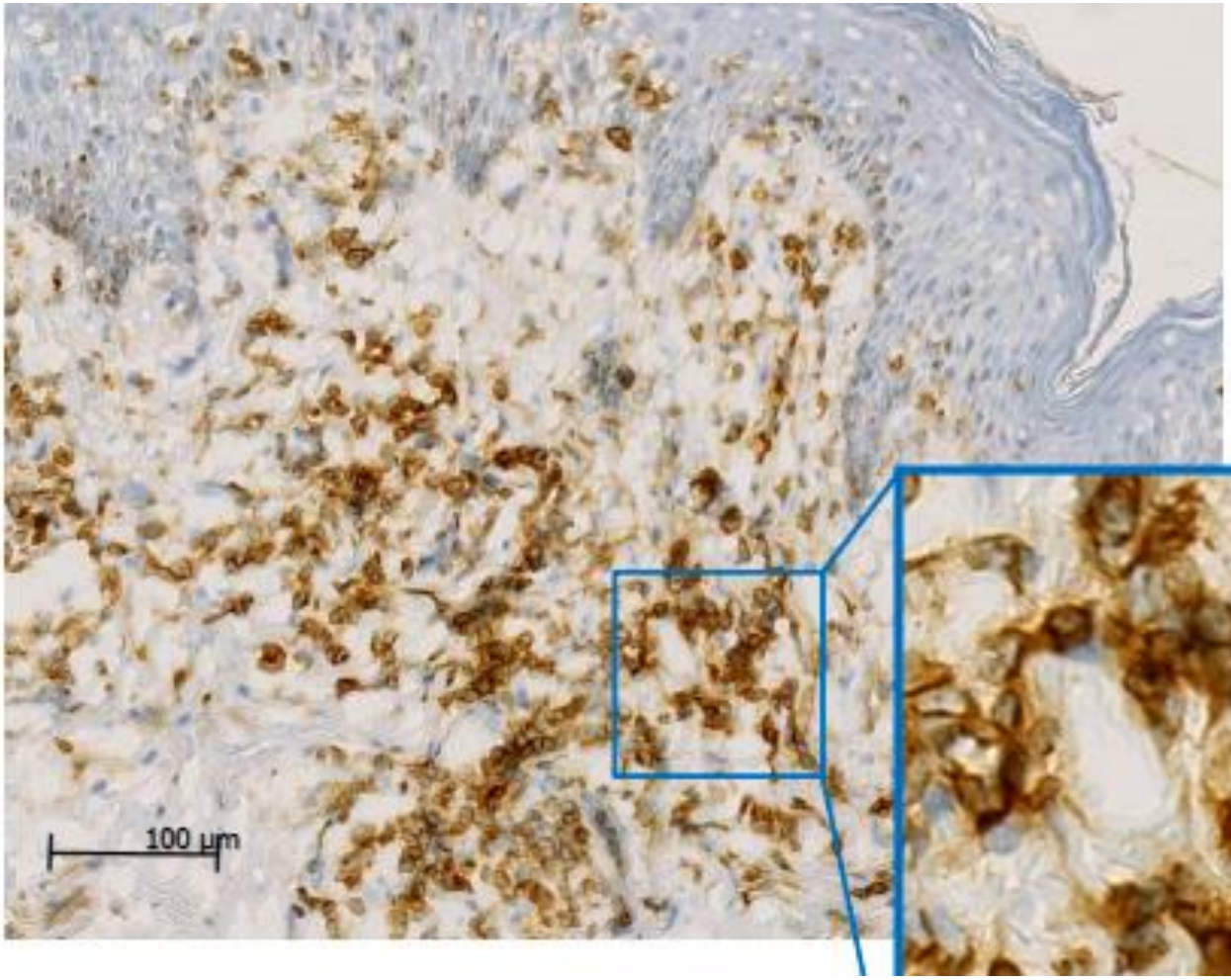
Sézary Patient
Gate: TCRVβ8^{+} CD4^{+}

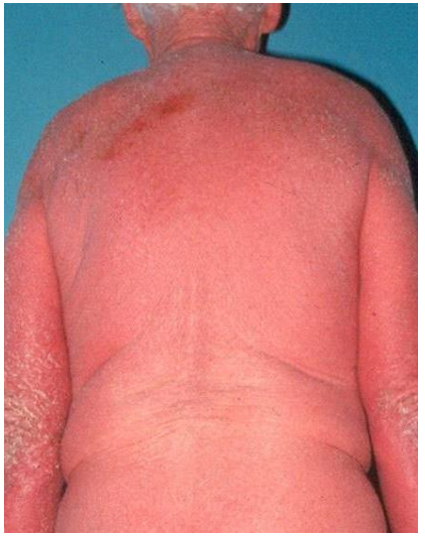


Ghazi et al, J Invest Dermatol, 2014

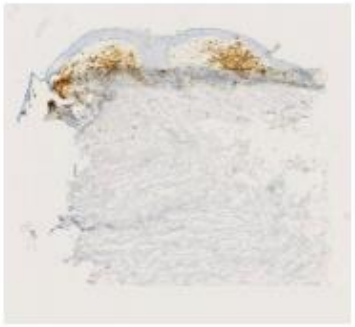
What is the distribution of CD158k/KIR3DL2 ?

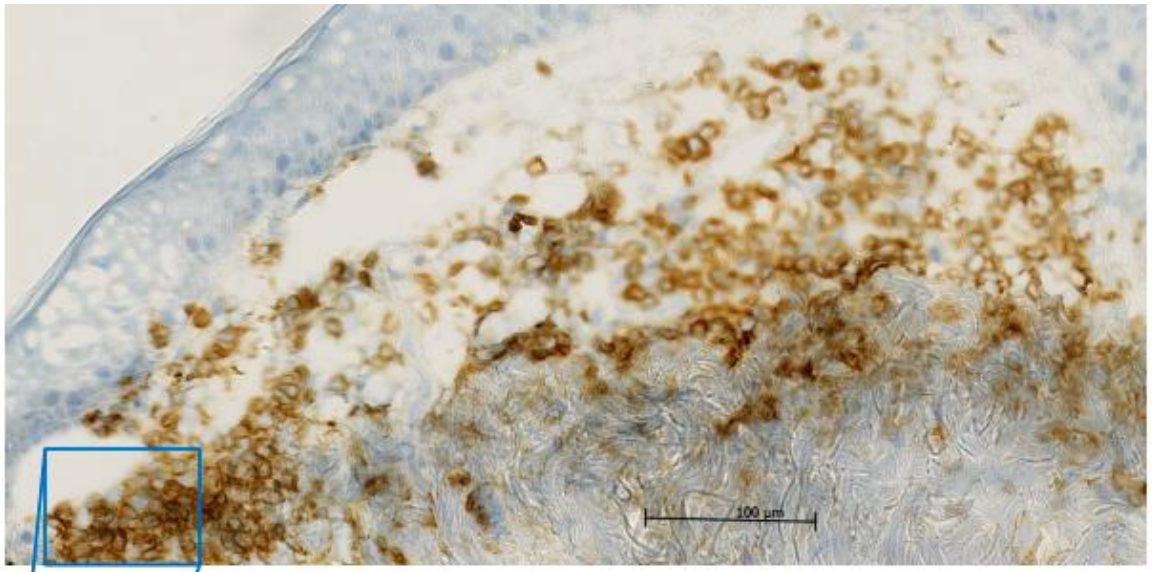
Sezary Syndrome

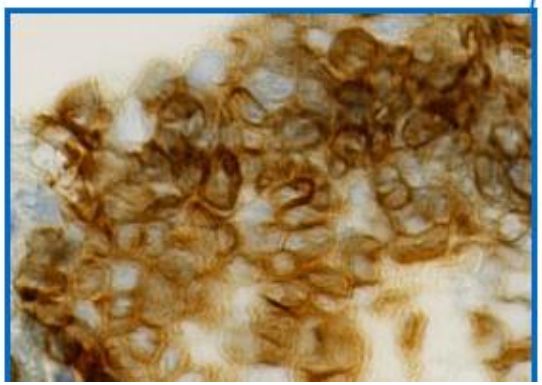


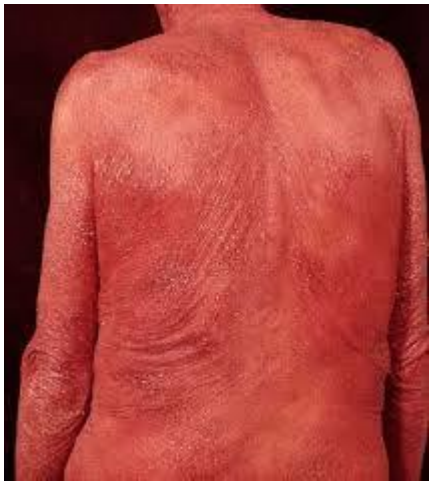


Sezary Syndrome

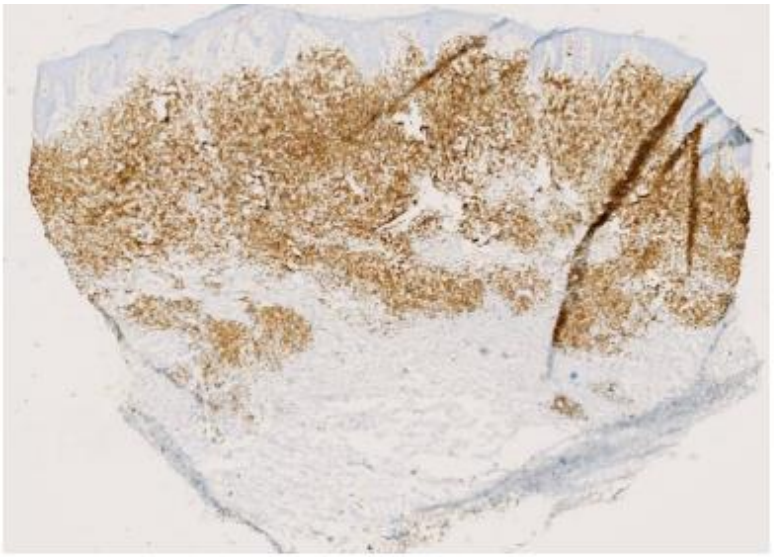


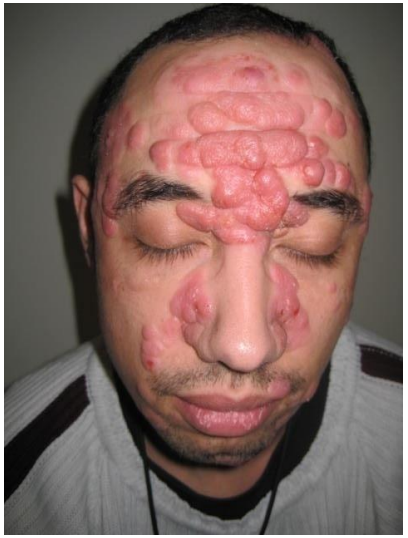


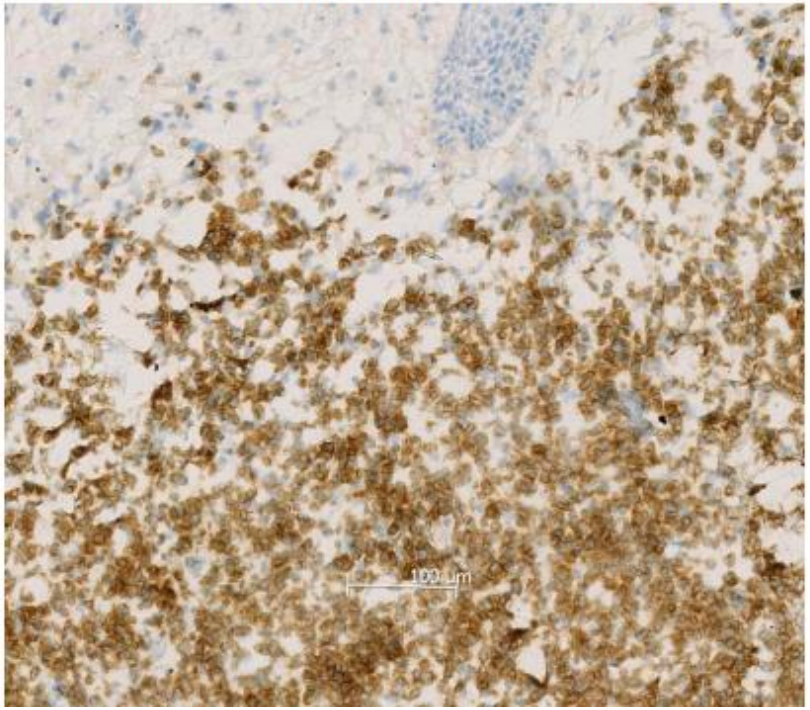




Transformed mycosis fungoides







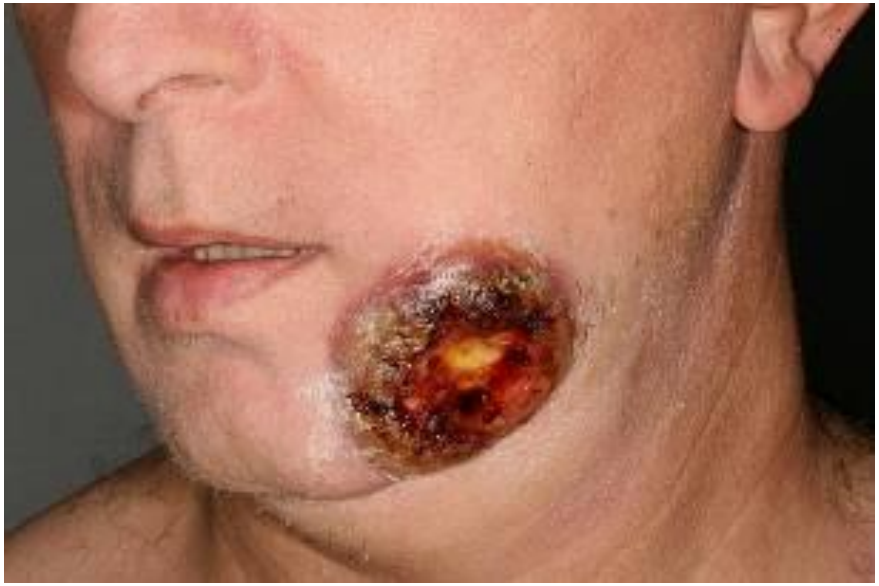
CTCL landscape
KIR3DL2 expression by WHO-EORTC subtype

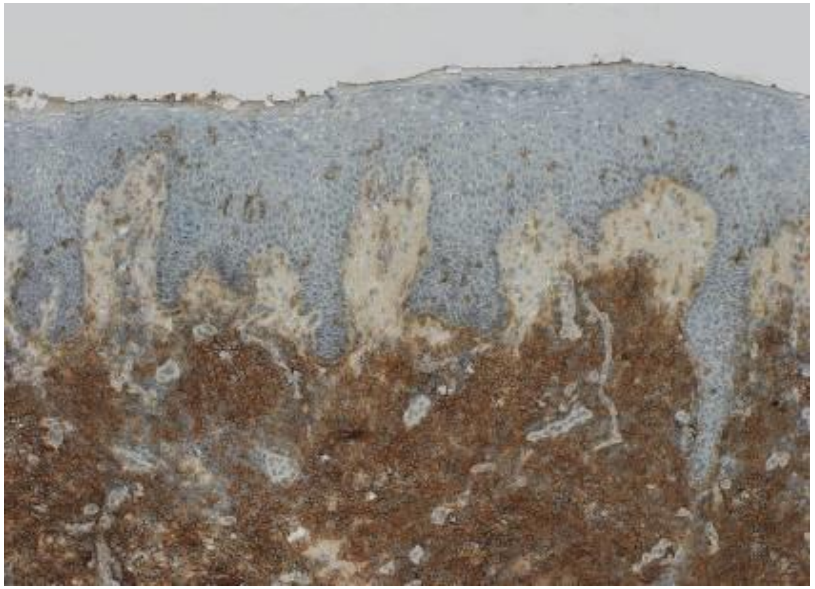
CTCL subtypes per WHO-EORTC classification

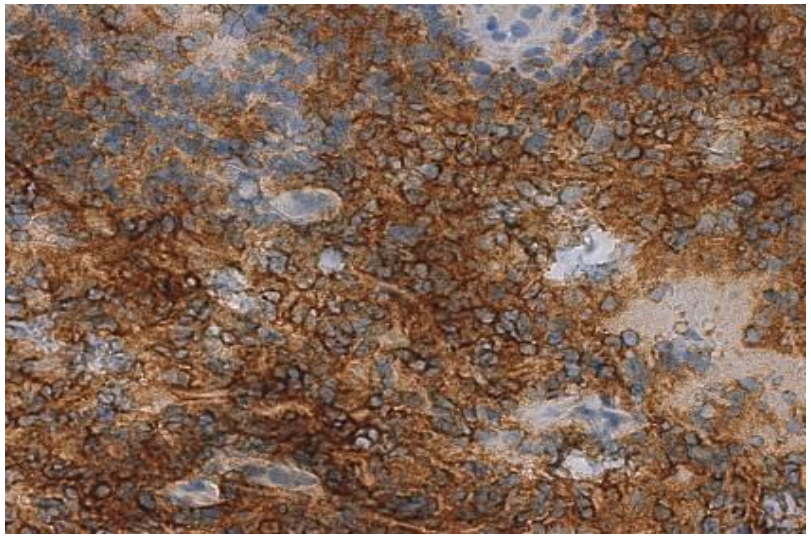
	%KIR3DL2$^+$ skin biopsies (n = 107 CTCL patients)
Mycosis Fungoïdes (MF)	~45%
transformed MF	>80%
CD30$^+$LPD (ALCL subtype)	100%
Sézary Syndrome	>85%
Others (ATL, NK/T, γδ,…)	~35% to 100%

KIR3DL2 is expressed in ~65% of all CTCL, irrespectively of disease subtype. Expression is more prominent in Sézary syndrome, transformed mycosis fungoides and CD30+ LPD (ALCL subtype)

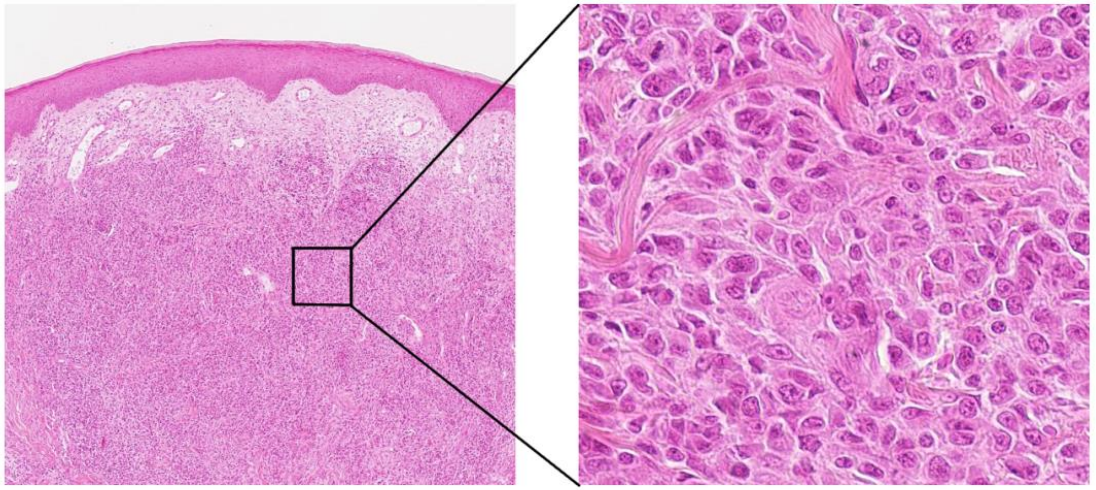
Primary cutaneous anaplastic large cell lymphoma

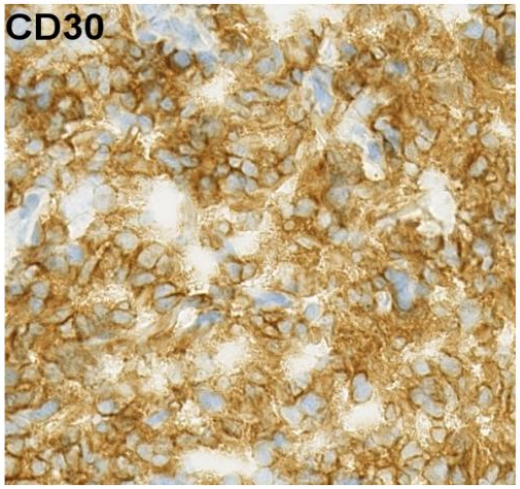


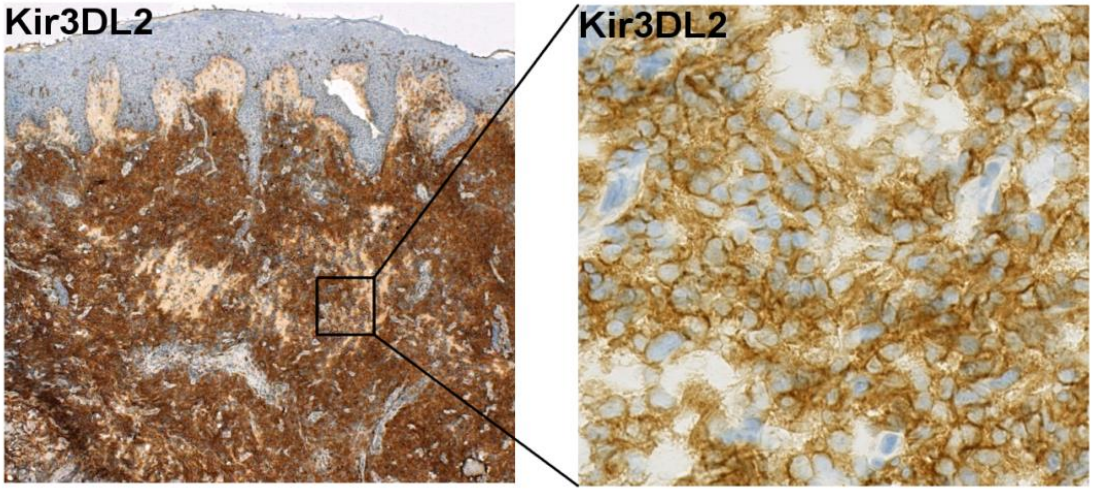


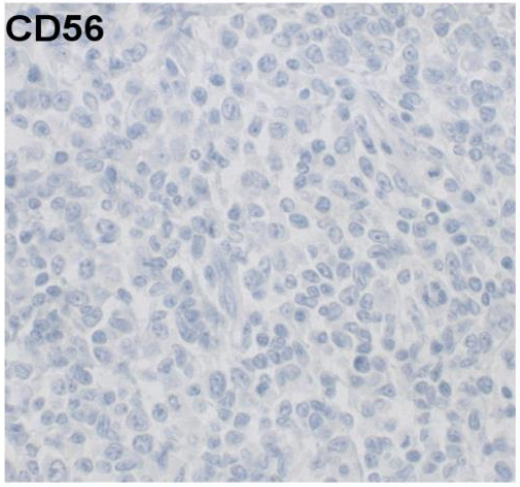


KIR3DL2 expression in primary cutaneous anaplastic large-cell lymphoma

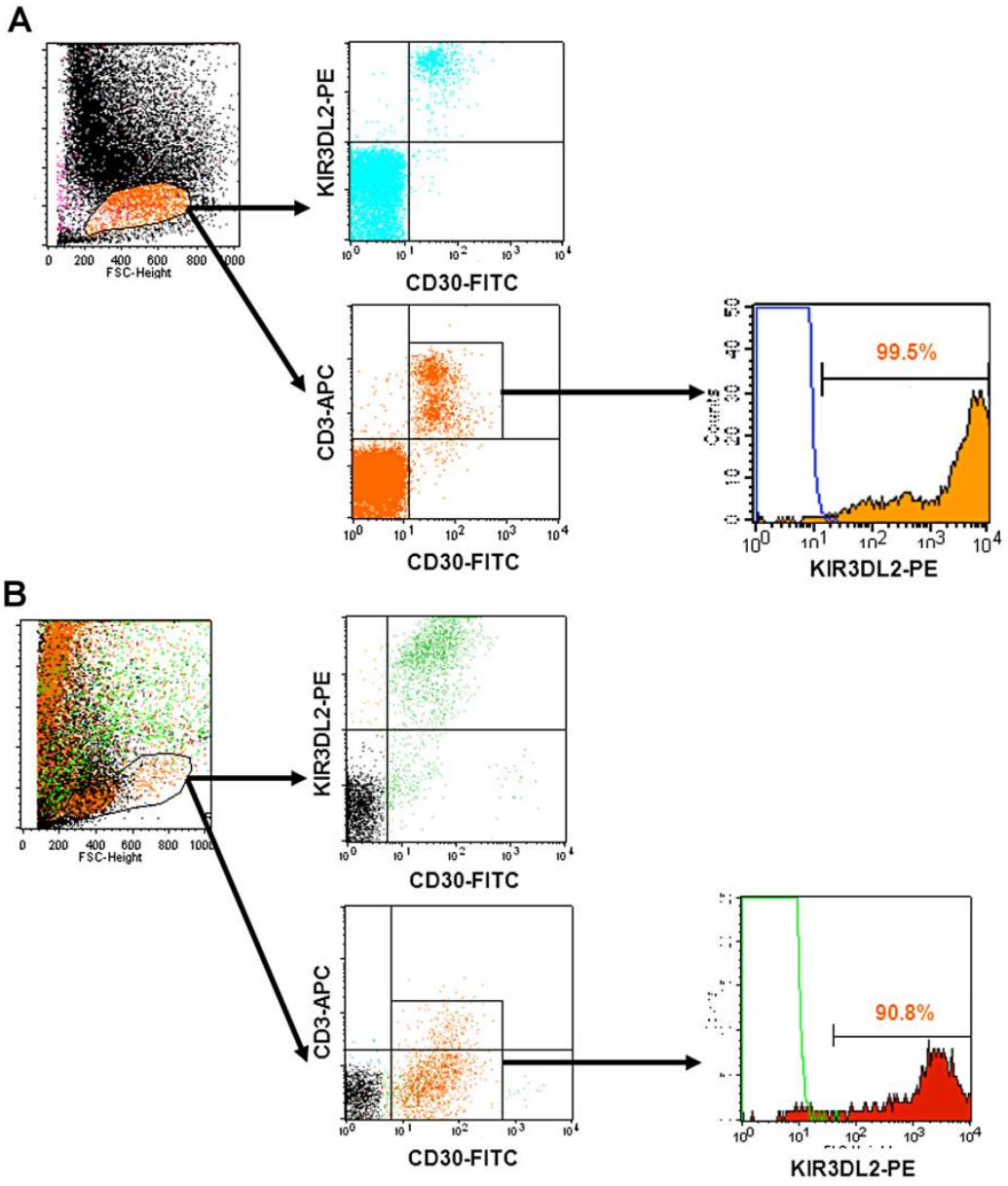








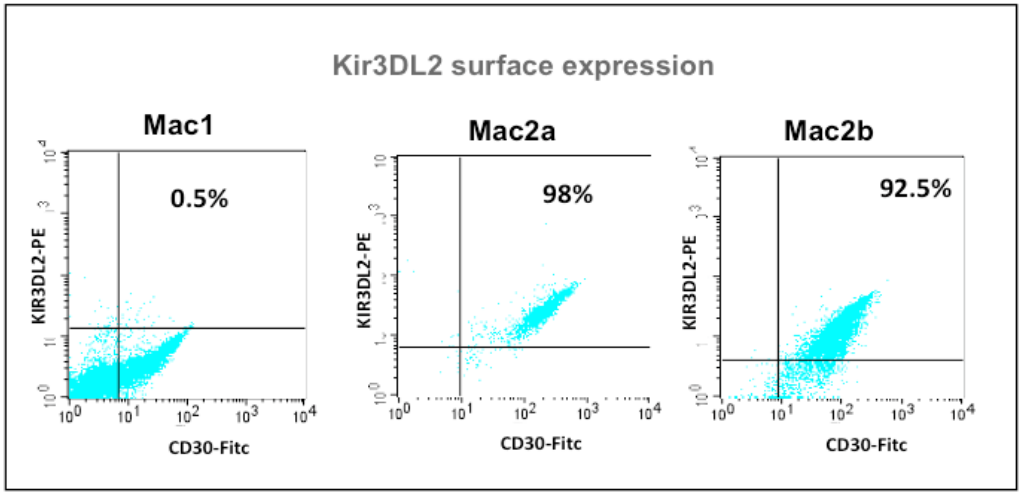
Strong KIR3DL2 expression by skin-infiltrating lymphocytes in pcALCL



KIR3DL2 is expressed by Mac2a and Mac2b ALCL lines

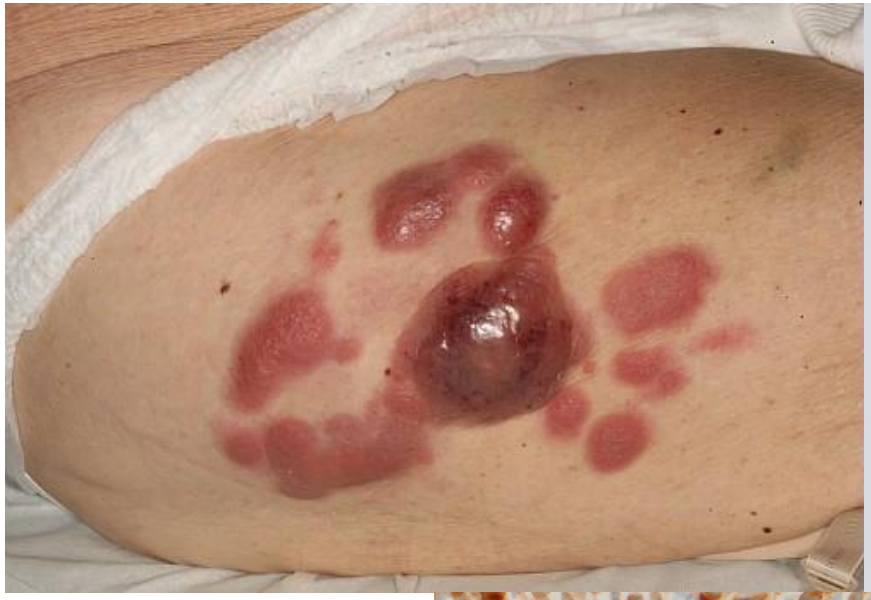
a

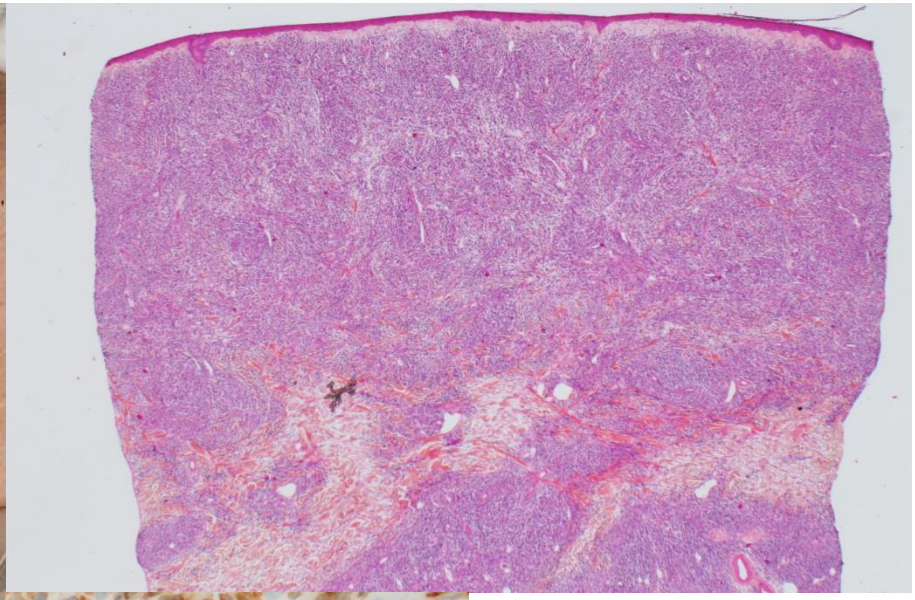
b

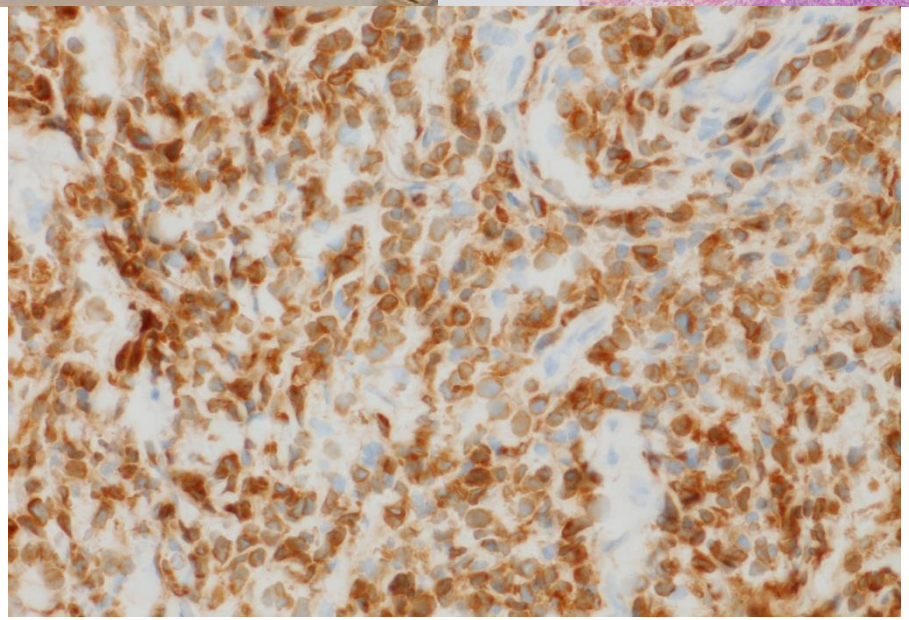


- Mac2a and Mac2b cell lines were derived from separate, rapidly growing skin tumors during disease progression, in a pcALCL patient
- Mac1 was derived from circulating tumor cells in the blood of the same patient during an earlier indolent course of the disease

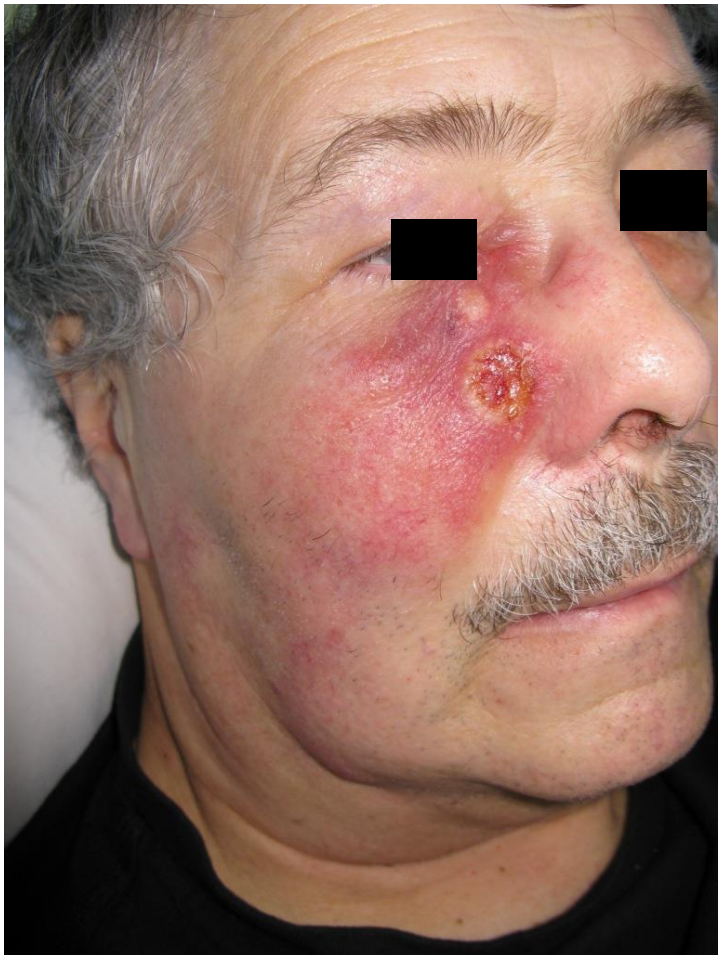
Cutaneous γ/δ T-cell lymphoma

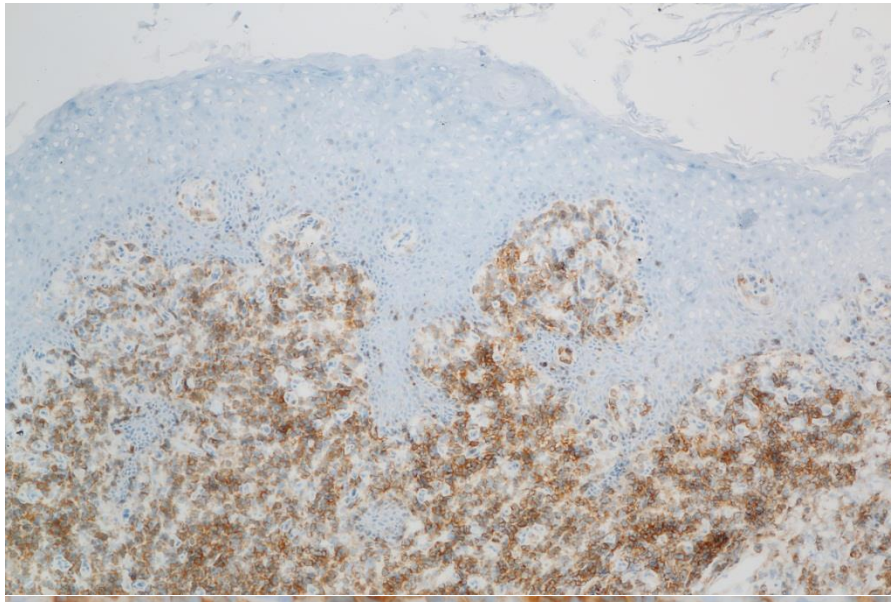


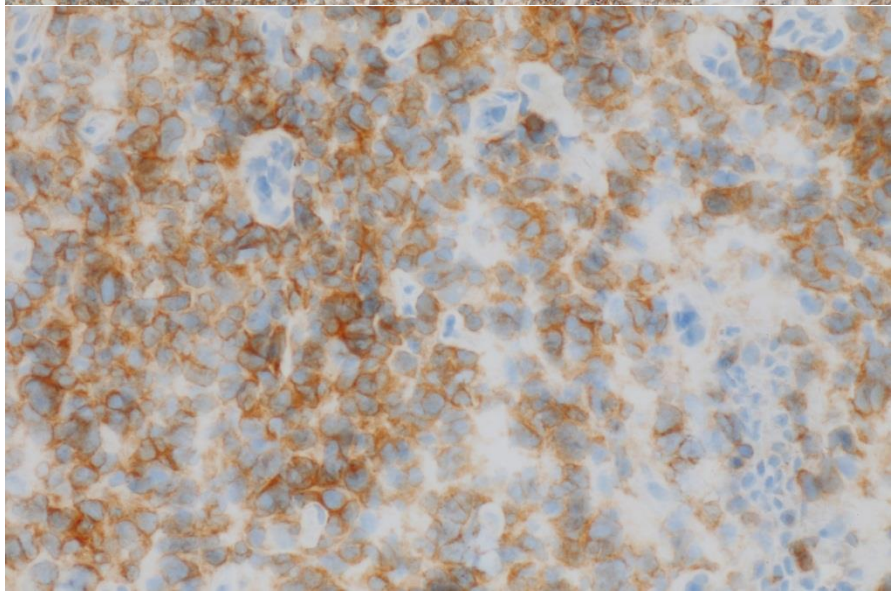




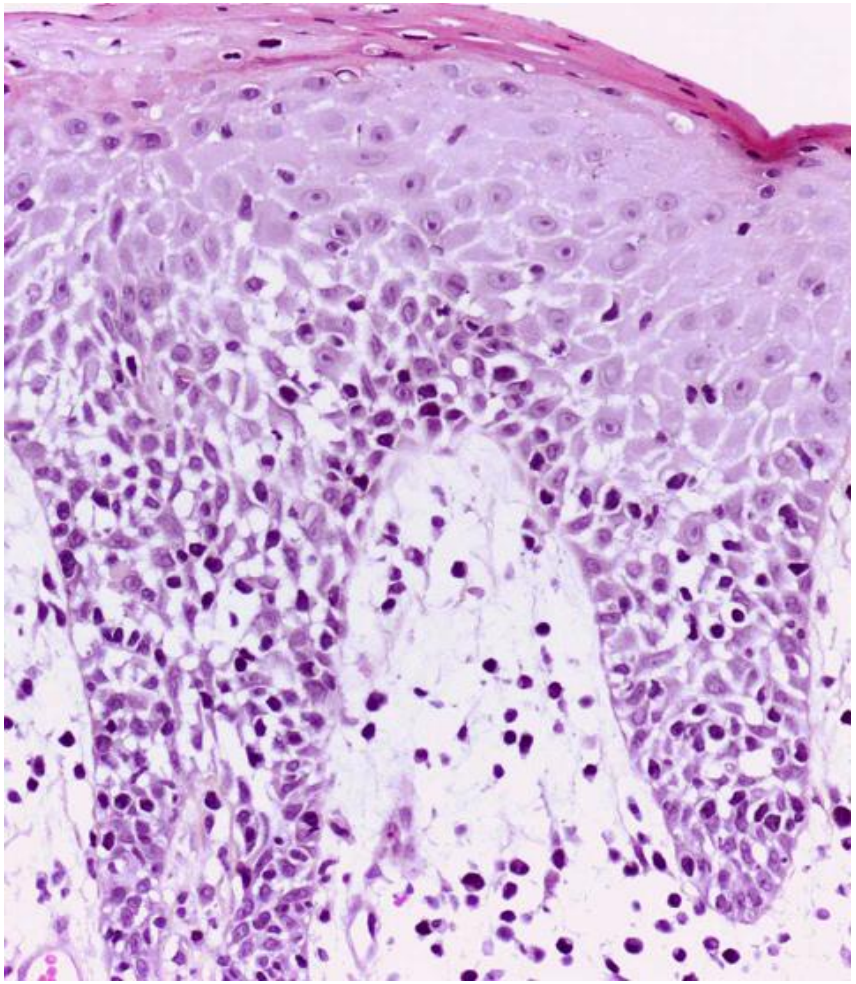
Extranodal NK/T lymphoma,nasal type

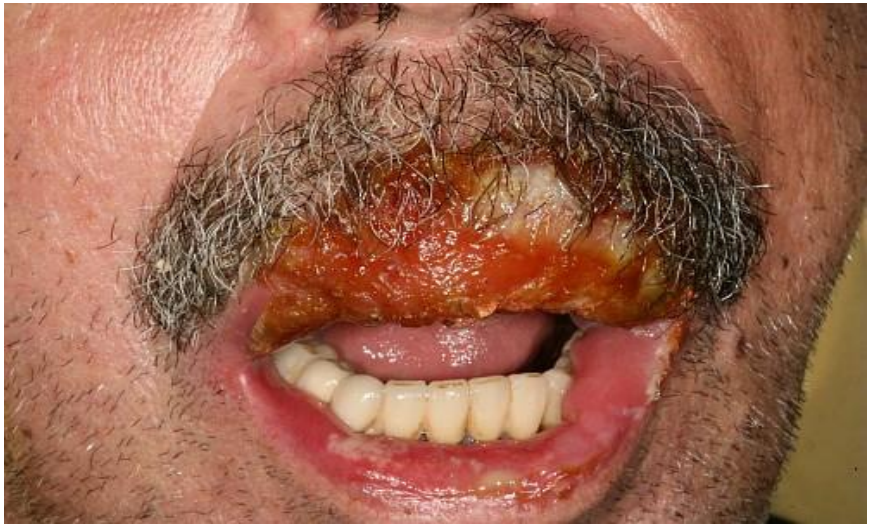


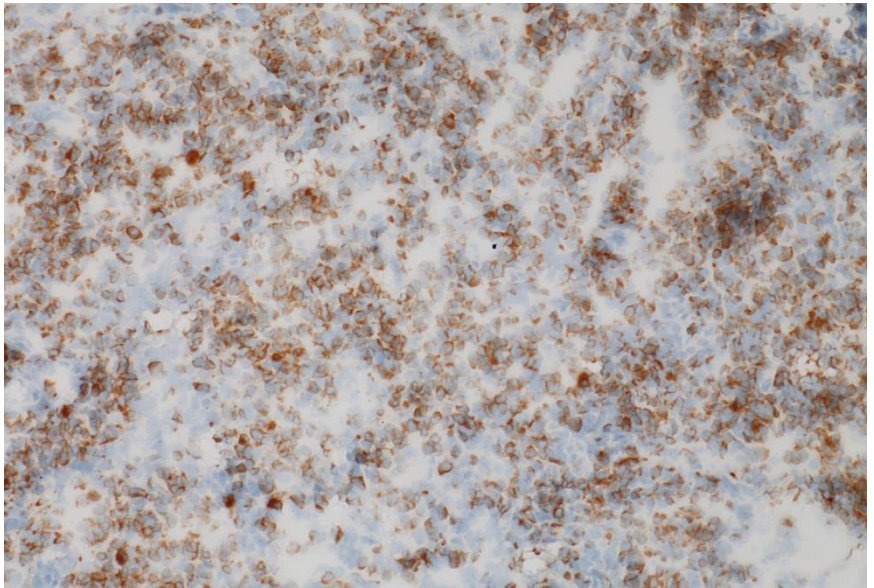




Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma







Is there a rationale to develop an anti-KIR3DL2 Immunotherapy ?

NK cells of Sezary patients are functional

Circulating Natural Killer Lymphocytes Are Potential Cytotoxic Effectors Against Autologous Malignant Cells in Sezary Syndrome Patients

Jean-David Bouaziz, Nicolas Ortonne, Jérôme Giustiniani, Valérie Schiavon, Delphine Huet, Martine Bagot, and Armand Bensussan*

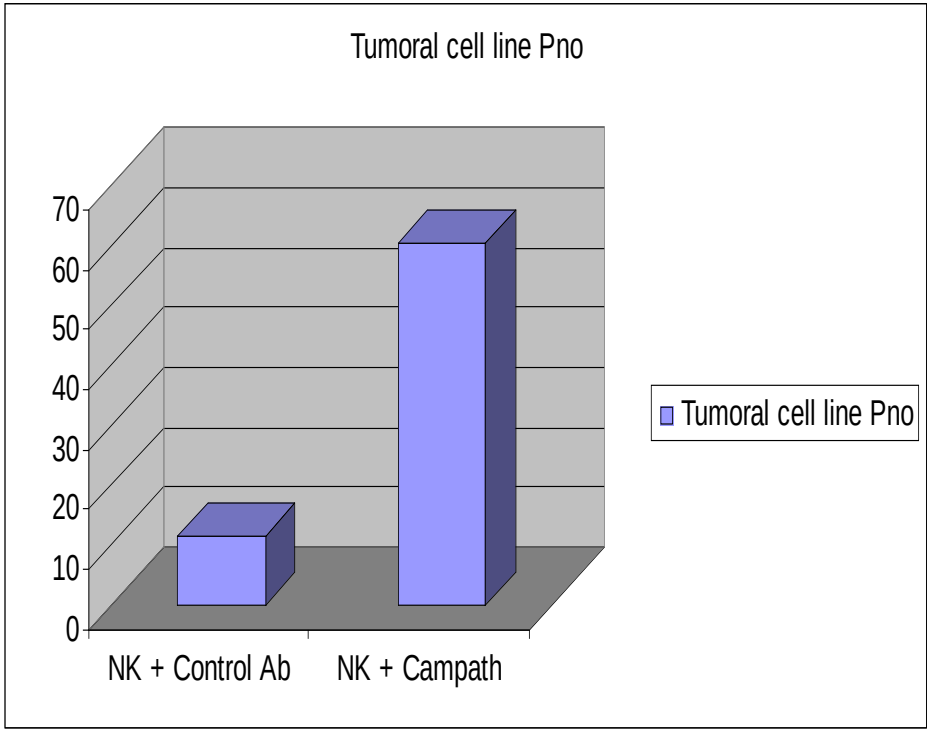
*INSERM 659, Faculté de Médecine de Créteil 8, rue de général Sarrail, Créteil, France

Patients with advanced cutaneous T cell lymphoma (CTCL) exhibit profound defects in cell-mediated immunity. Although it has been suggested that Sezary syndrome (SS) patients have a decreased natural killer (NK) lymphocyte activity, nothing has been reported concerning the sensitivity of Sezary cells to NK lymphocyte-mediated cytotoxicity. Peripheral blood NK cells from healthy donors were tested against Sezary tumoral cell lines as well as against freshly isolated Sezary cells. Further, we studied their ability to exhibit antibody -dependent cell-mediated cytotoxicity using either the murine anti-CD158k/KIR3DL2 monoclonal antibody (moAb) AZ158 that specifically recognizes Sezary cells, or the anti-CD52 monoclonal antibody alemtuzumab. The results show that Sezary cell lines are susceptible to NK lymphocyte lysis. More importantly, we found that freshly isolated malignant cells are killed either by IL-2 activated allogeneic NK lymphocytes or when the tumor lymphocyte targets are incubated with an anti-MHC class I F(ab)'2 antibody. Further, anti-KIR3DL2 and anti-CD52 moAb can enhance the NK lysis. Finally, we report that NK lymphocytes isolated from SS patients are potentially cytotoxic lymphocytes against autologous malignant Sezary cells. These findings indicate that antitumor-mediated NK lymphocyte cytotoxic activity can be triggered in patients with CTCL and raise the possibility of developing novel therapeutic strategies by stimulating their innate immunity.

Bouaziz et al, J Invest Dermatol, 2005

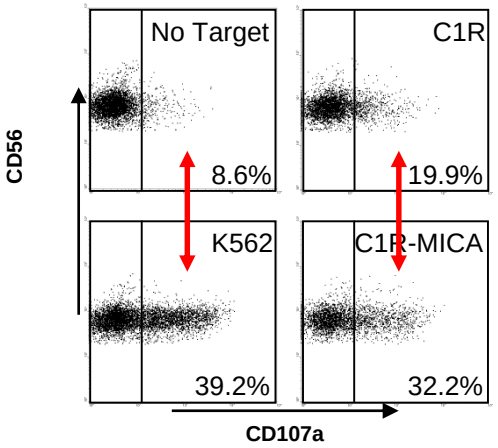
NK lysis of tumor cells is enhanced via an ADCC mechanism

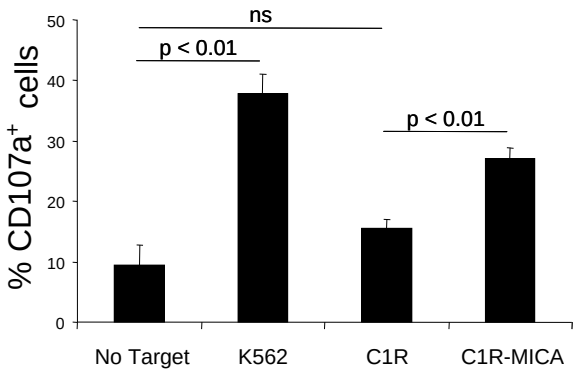
Alemtuzumab

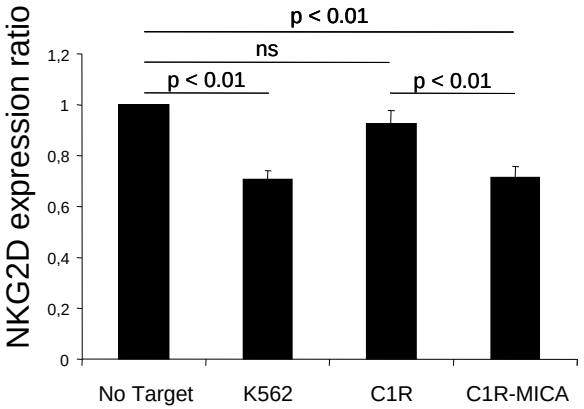


Bouaziz et al, J Invest Dermatol, 2005

Sezary patients NK cells are able to degranulate







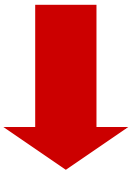
- Sezary NK cells are able to degranulate perforin and granzymes against a HLA-Cl.I-negative target.
- NKG2D activates Sezary NK cells.

⇨ Sezary patients NK cells are - fully functional
- ready to kill NKG2D-L$^+$ targets

Dulphy et al. J Invest Dermatol, 2009

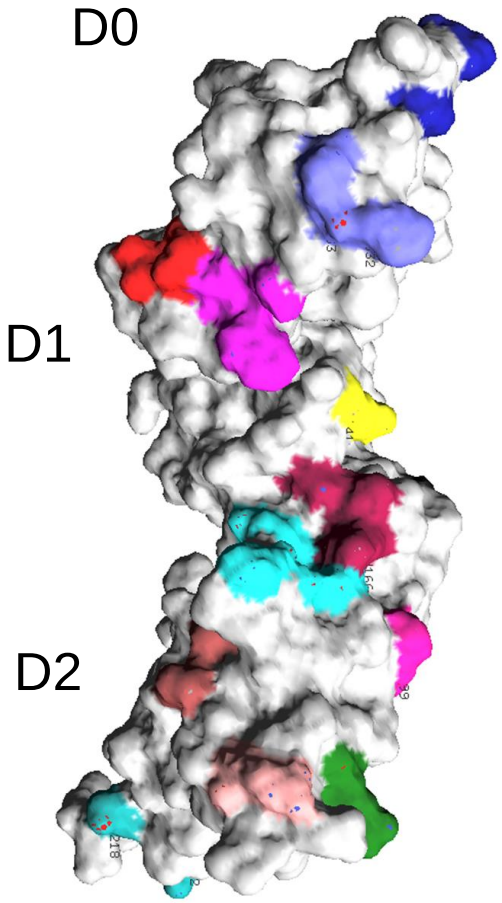
Is it possible to develop a specific anti-KIR3DL2 Immunotherapy ?

- Specific expression of KIR3DL2 by malignant T lymphocytes
- Circulating Sézary patients NK lymphocyte are functional
- Sézary T cell clones are sensible to Perforin/GrB lysis



Development of a therapeutic monoclonal antibody (Innate Pharma)

Portfolio of anti-KIR3DL2 mAbs

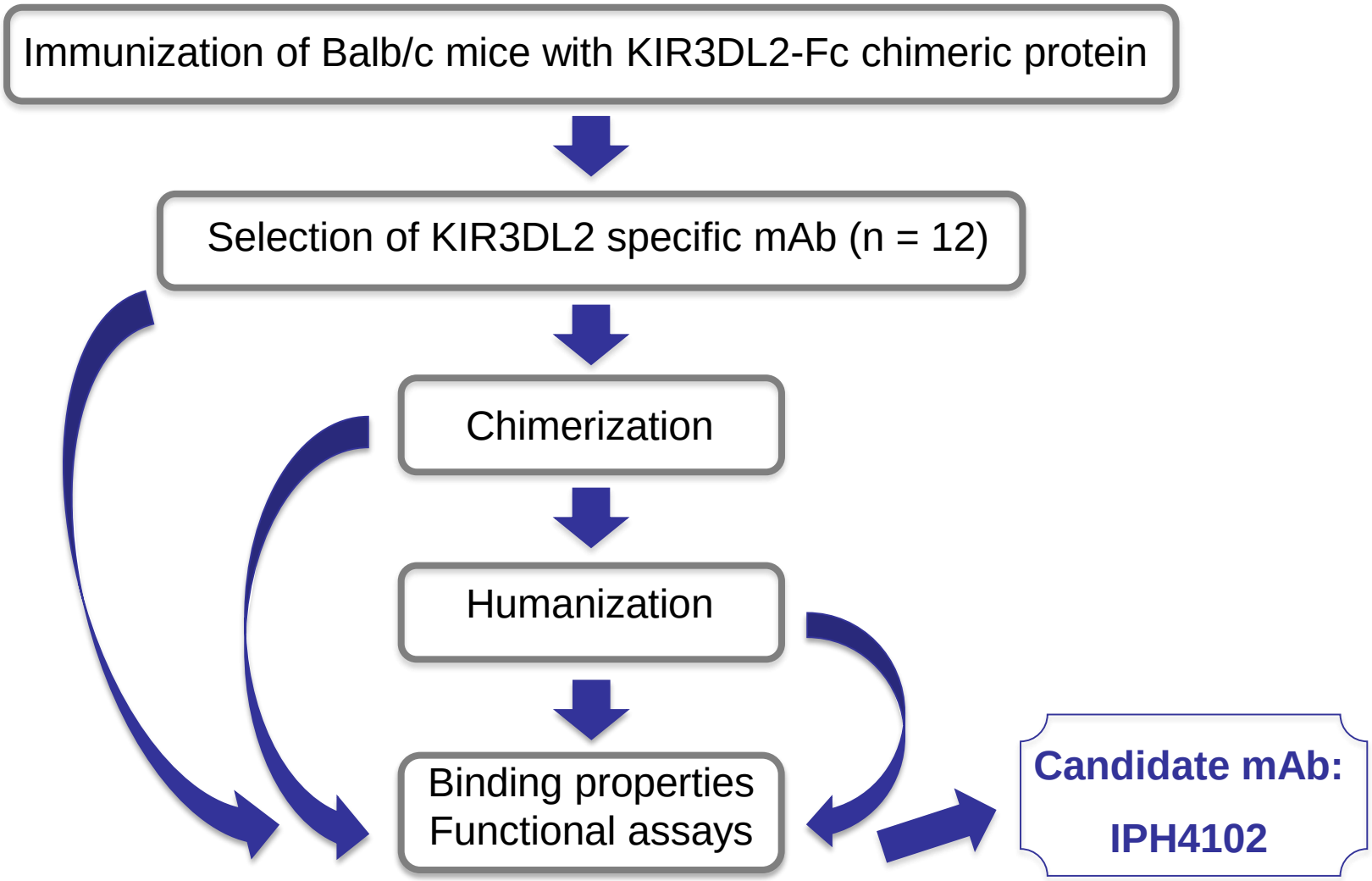


The 3 Ig domains of KIR3DL2 protein

- mAbs binding to epitopes on all 3 Ig domains of KIR3DL2 were generated and all their epitopes were identified
- Epitopes (colored AA) bound correlate with distinctive properties (efficient killing of KIR3DL2^{+} cells, internalization of the molecule, inhibition of binding to HLA-class 1…)
- Based on preliminary efficacy data, the 3 most promising candidates were humanized

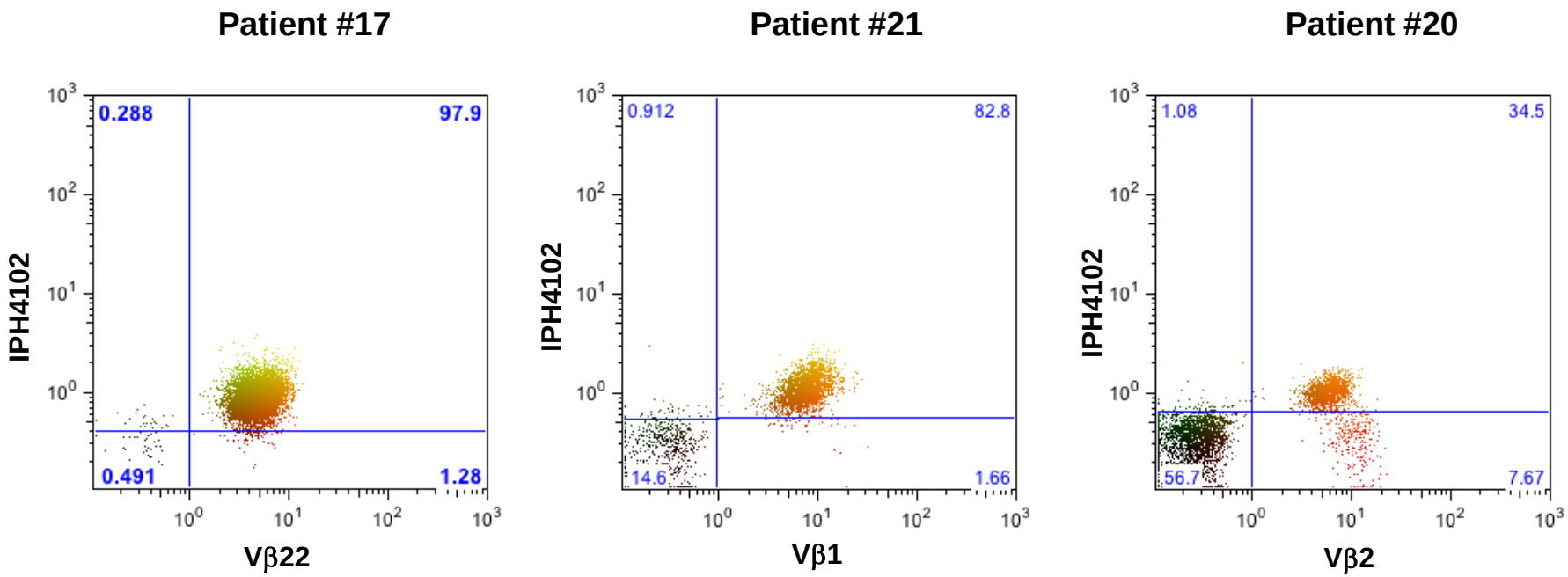
Marie-Cardine A, Cancer Research 2014

Strategy for the generation and testing of anti-KIR3DL2 therapeutic antibodies



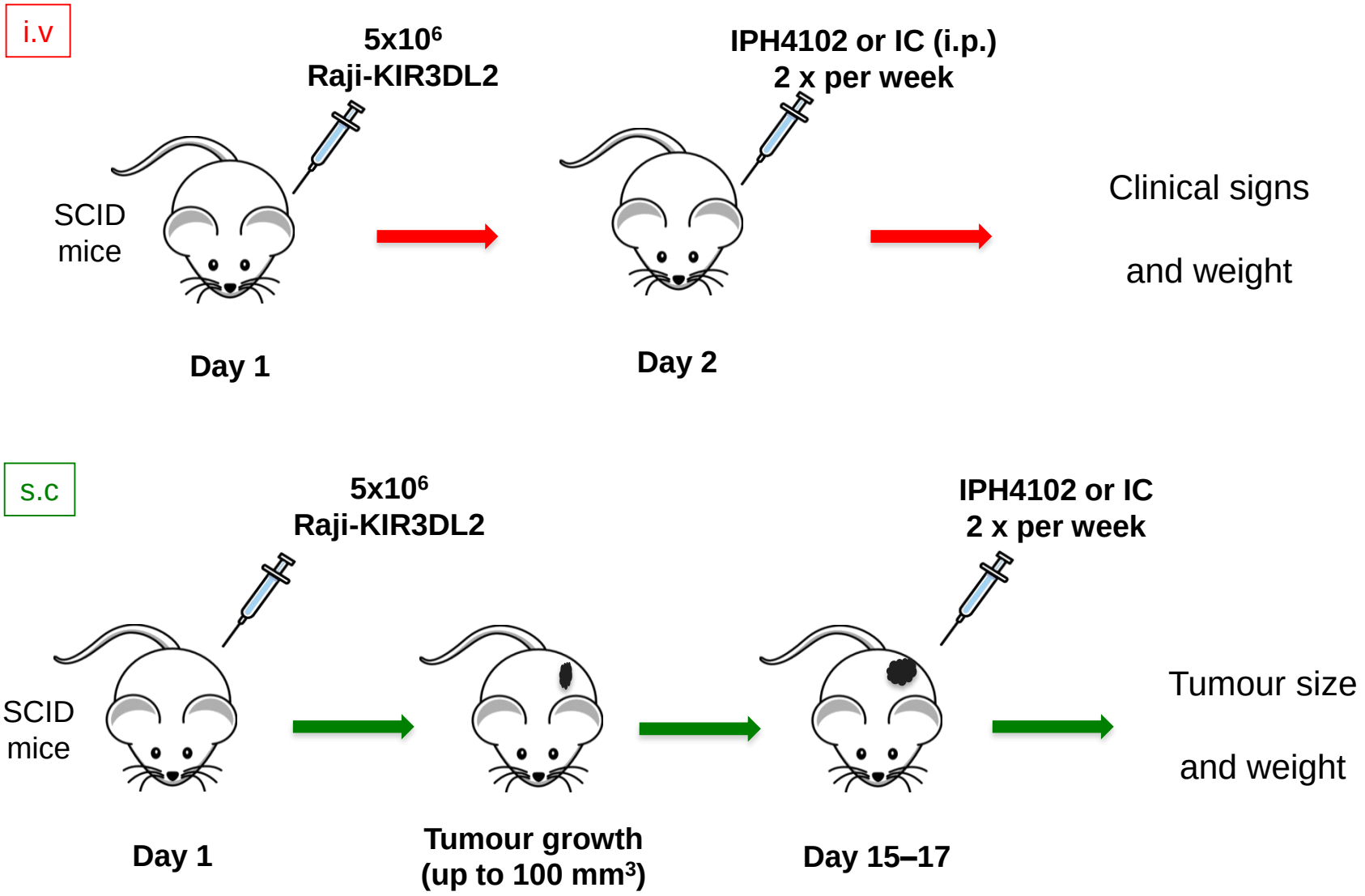
Marie-Cardine A, et al. Cancer Res. 2014;74:6060-70.

IPH4102 delineates Sézary cells



Marie-Cardine et al, Cancer Res, 2014

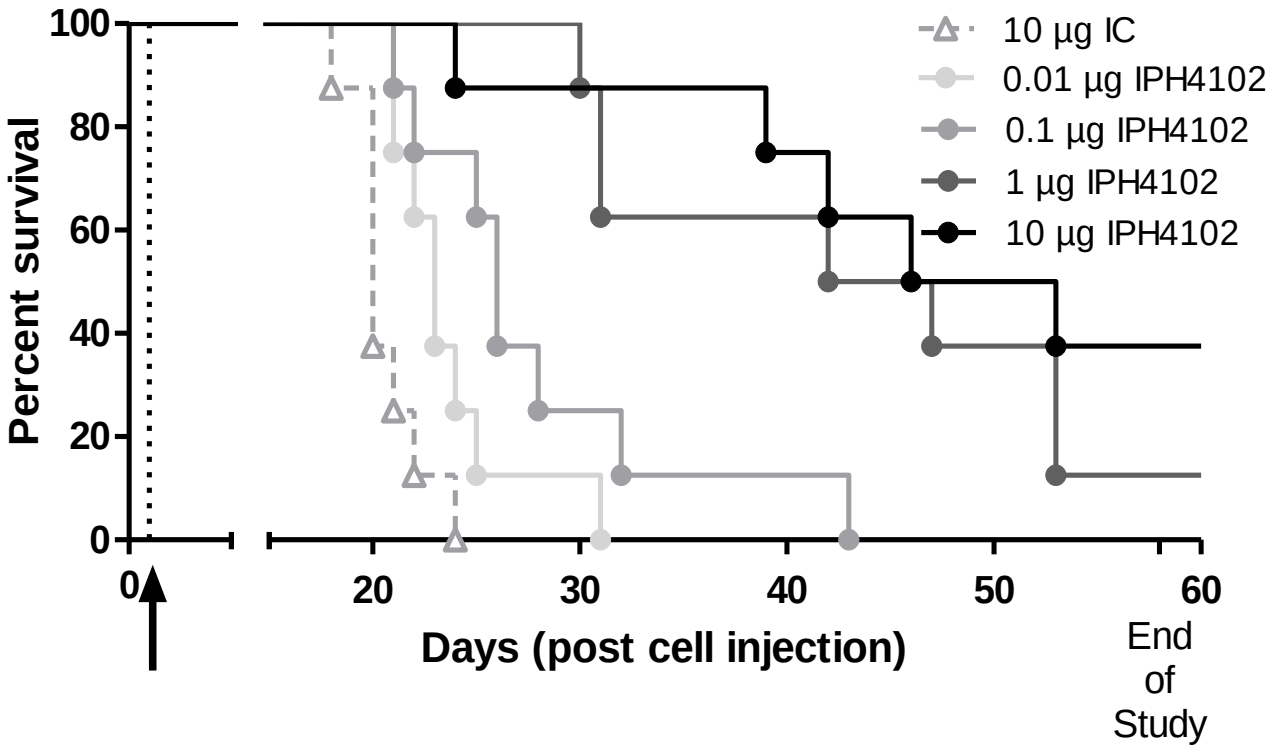
In vivo efficacy of IPH4102: experimental design



i.p., intraperitoneal; i.v., intravenous; s.c., subcutaneous; SCID, severe combined immunodeficiency.

Marie-Cardine A, et al. Cancer Res. 2014

IPH4102 promotes the survival of mice engrafted with KIR3DL2+ tumour cells

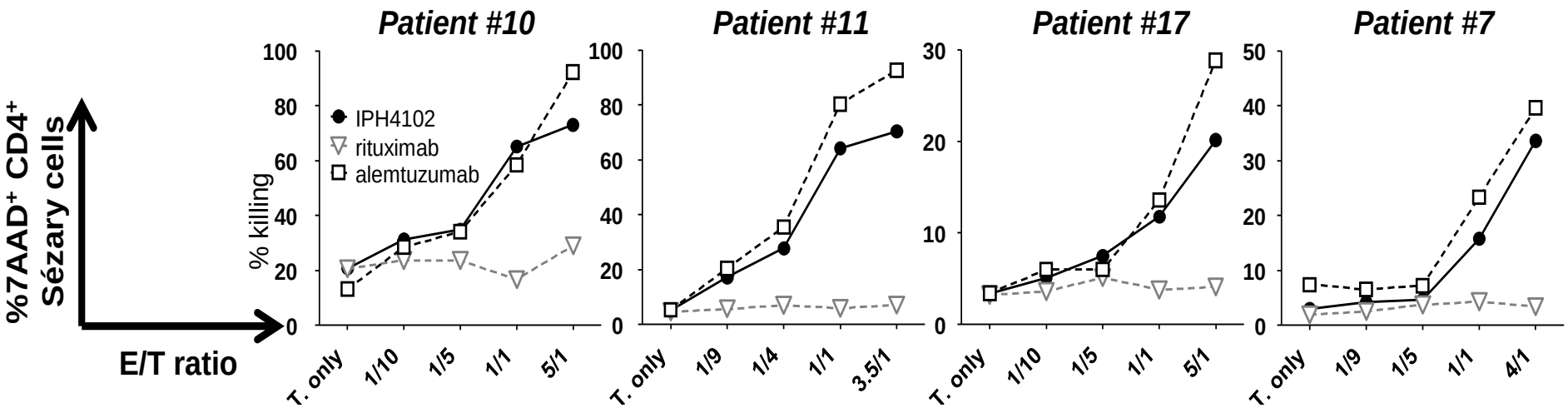


IPH4102 improves survival
in a dose-dependent manner

Mice: SCID (n = 8)
RAJI-KIR3DL2: 5 M IV at D0
IPH4102: single IV admin. at D1
Read-out: survival

IPH4102 Efficacy *ex vivo:* Autologous ADCC

Efficacy Results



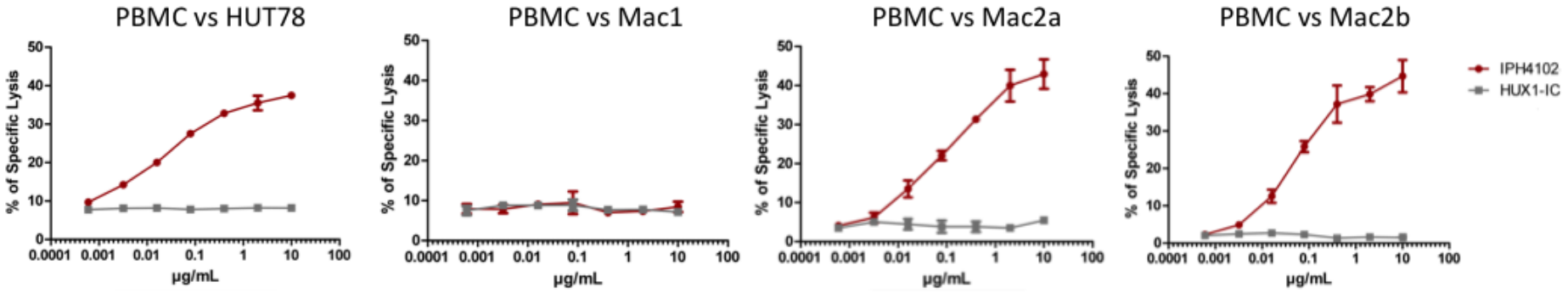
IPH4102 as potent as alemtuzumab in *ex vivo* autologous ADCC assays

mAb: 10 µg/mL
Incubation time: 4 – 6 hours
Read-out: 7AAD incorporation
KIR3DL2 sites per cell: 1,000 to 4,000
%KIR3DL2+ cells among CD4+ > 85%
Total n = 15 patients

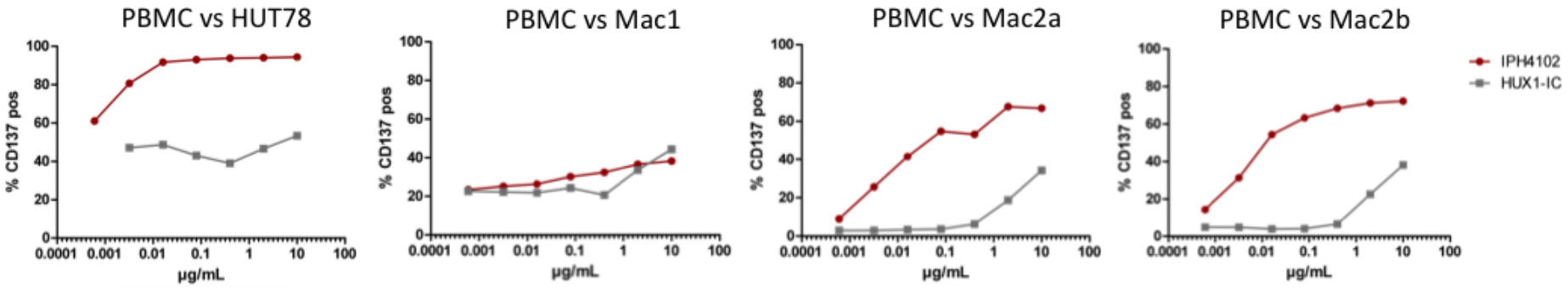
Marie-Cardine A. *et al*, Cancer Res. 2014

KIR3DL2+ Mac2a and Mac2b ALCL lines are sensitive to ADCC mediated by IPH4102

a. IPH4102-induced antitumor cytolytic activity



b. IPH4102-induced NK cell activation



IPH4102-101 FIH Development

- Sept 2013-Sept 2014: Preclinical studies
- August 2014: Orphan Drug designation in the European Union for the treatment of CTCL
- Sept 2014-Sept 2015: Regulatory process
- 5 August 2015: ANSM approval for phase I trial in France
- 11 Sept 2015: FDA approval
- 21 Sept 2015: French ethics committee approval

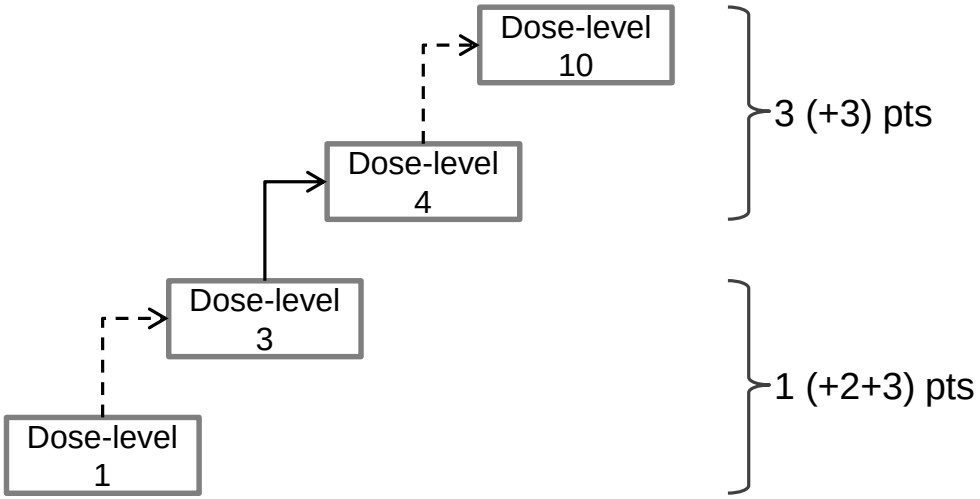
IPH4102-101 STUDY DESIGN

- First-in-Human Phase I study of IPH4102
- Two-portion study:
  - Dose-escalation portion – 10 dose-levels
  - Cohort expansion portion, at the recommended dose determined in the dose-escalation – 2 CTCL subtypes (SS and tMF)
- Patient profile:
  - Relapsed/refractory (≥ 2 previous lines of systemic therapy) CTCL patients
  - For MF/SS patients: grade ≥ IB
- Centrally assessed expression of KIR3DL2 on tumors:
  - KIR3DL2-positivity on skin biopsies (and/or blood $CD4^+$ T cells, if applicable), is required for eligibility

IPH4102-101 FIH Study Design Objectives

- Primary objective: to assess safety & tolerability of increasing IV doses of single agent IPH4102 by:
  - characterizing the dose-limiting toxicities (DLT) and (S)AEs
  - identifying the MTD or Recommended Ph 2 Dose (RP2D)
- Secondary objectives:
  - To explore antitumor activity
  - To assess pharmacokinetics (PK) and immunogenicity
- Translational objectives, biomarker exploration:
  - To monitor the fate of KIR3DL2-expression cells in skin lesions, blood and lymph nodes (pharmacodynamics)
  - To monitor immune cell activation in blood and explore NK cell and macrophage infiltration in skin lesions
  - To assess Minimal Residual Disease (clonal Vβ chain)
  - To assess cytokine release

IPH4102-101 FIH Study Design
Study Design



- **Cohort expansion Part:**
  same dose for all: RP2D
  pts with KIR3DL2+ tumors
  pre-selected CTCL subtypes

Recommended Phase II Dose (RP2D)

e.g. n = 10 tMF + 10 SS

The CTCL subtypes and number of pts will be adjusted based on the findings during the dose escalation phase

- **Dose-escalation Part:**
  accelerated 3+3 design
  pts with KIR3DL2+ tumors
  all CTCL subtypes eligible

IPH4102-101 FIH STUDY DESIGN
Participating sites

Clinical sites (dose-escalation part):

- St Louis Hospital, Paris (M. Bagot)
- UMC Leiden, the Netherlands (M. Vermeer)
- Guy's and St Thomas' Hospital, London UK (S. Whittaker)
- Stanford U., CA, US (Y. Kim)
- MD Anderson, Houston, TX, US (M. Duvic)
- OSU, Columbus, OH, US (P. Porcu)

Unit 976 (Paris, France)

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LARIBOISIÈRE
FERNAND-WIDAL

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H. Sicard
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M. Bléry
C. Bonnafous
C. Paturel
R. Joly
S. Chanteux
B. Rossi
L. Gauthier
K. Pilz
C. Paiva

Dept of Immunology

H. Moins-Teisserenc
A. Toubert

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