

Expression of NK receptors by CTCL cells A new hope for targeted therapies

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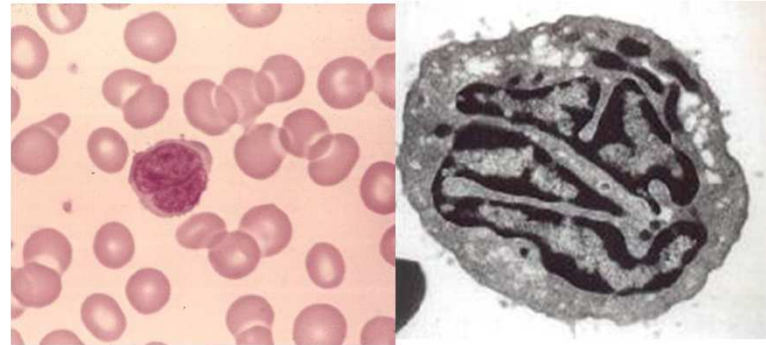


Sézary Syndrome

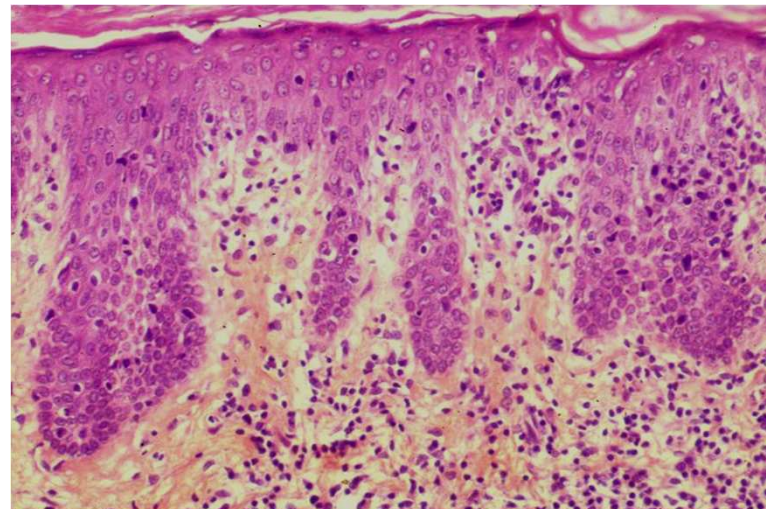


Albert Sézary

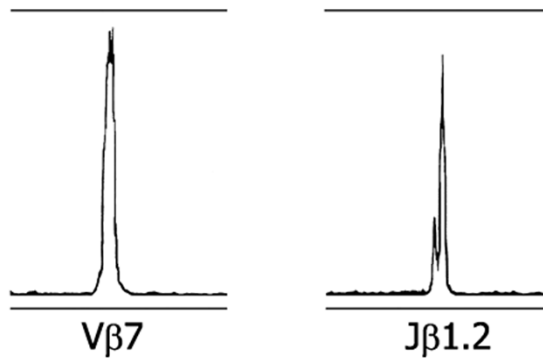
Blood...



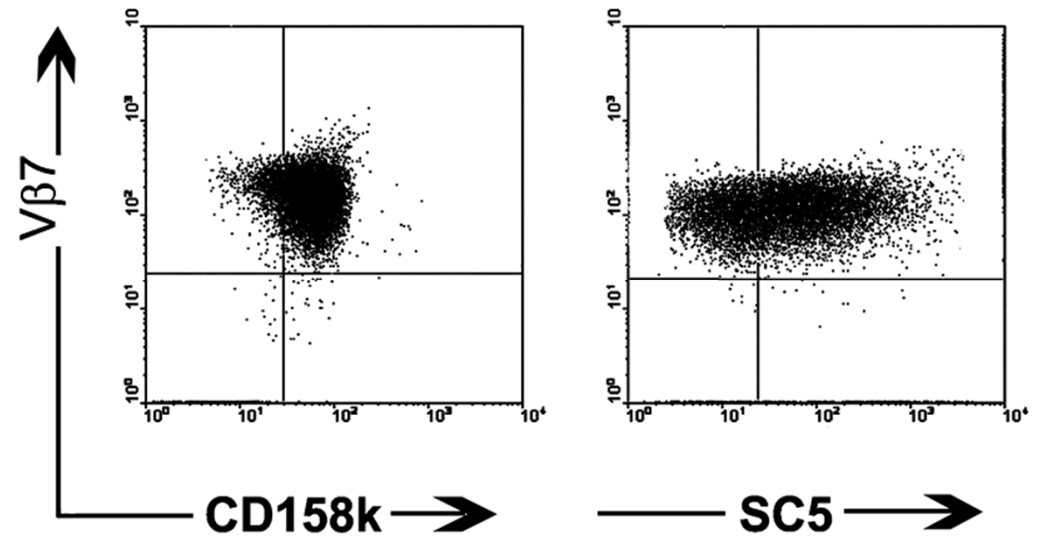
Skin...



CD158k (KIR3DL2): A new marker for malignant Sezary cells



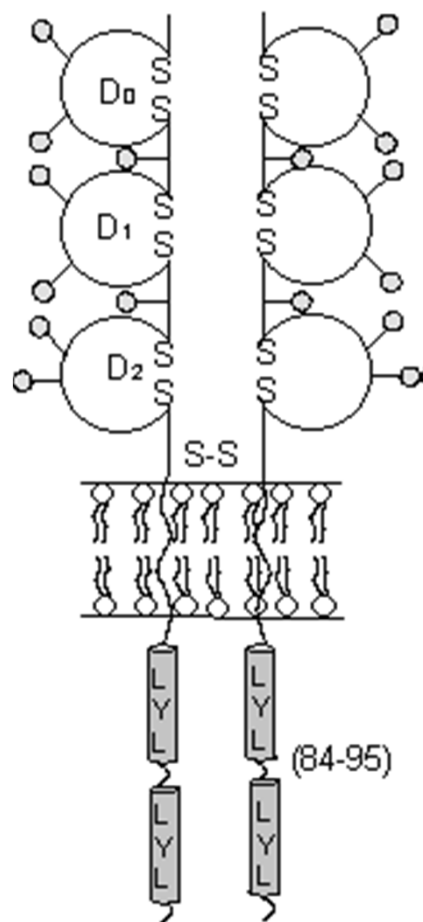
Vβ7.1 Framework			CDR3 loop					Jβ1.2 Framework					
TGC	GCC	AGC	AGC	CAA	CTC	AGG	GGA	GGA	GGC	TAC	ACC	TCC	GGT
Cys	Ala	Ser	Ser	Gln	Val	Arg	Gly	Gly	Gly	Tyr	Thr	Phe	Gly



Sezary patient with a TCRVβ7 tumor T cell clone

Ortonne et al. *Blood*, 2006

KIR3DL2/CD158k

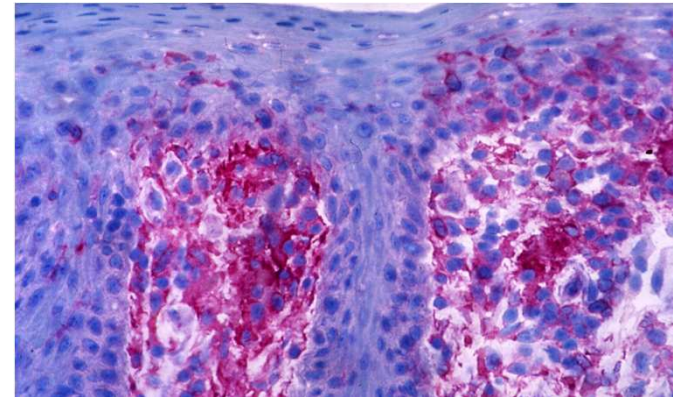
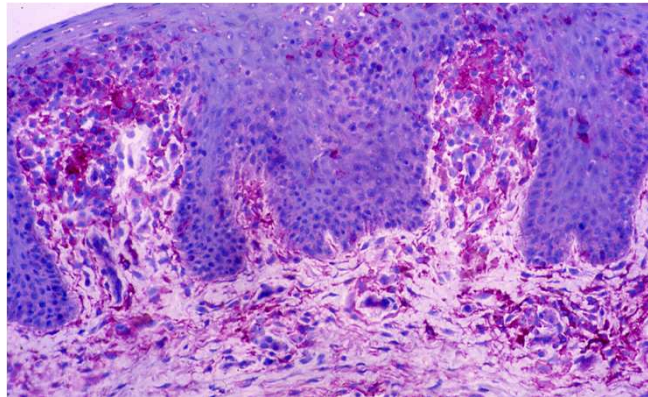


p140
(homodimer of p70)

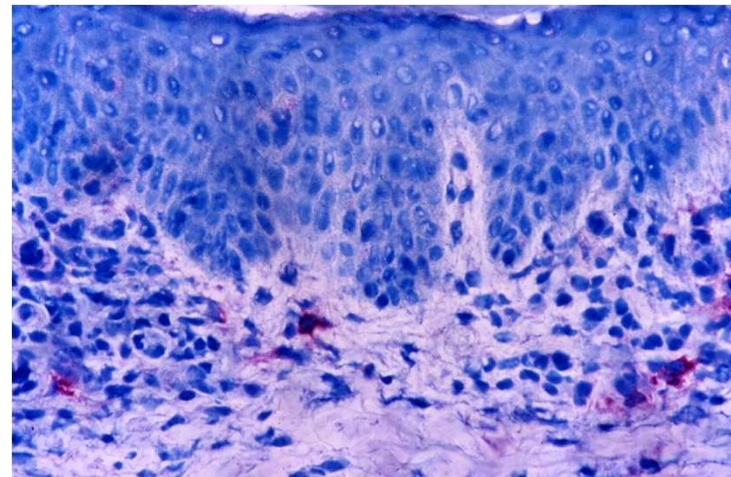
- **KIR: Killer Cell Immunoglobulin-like Receptor**
- **Family of genes located on chromosome 19q13.4**
- **Interaction with HLA- A3, -A11 and dimers of HLA-B27 heavy chains**
- **Expressed on lymphocyte subsets including Natural Killer and CD8⁺ T lymphocytes**
- **Provides inhibitory signals upon engagement**

**CD158k is expressed *in situ* in Sezary syndrome
but not in early Mycosis Fungoides**

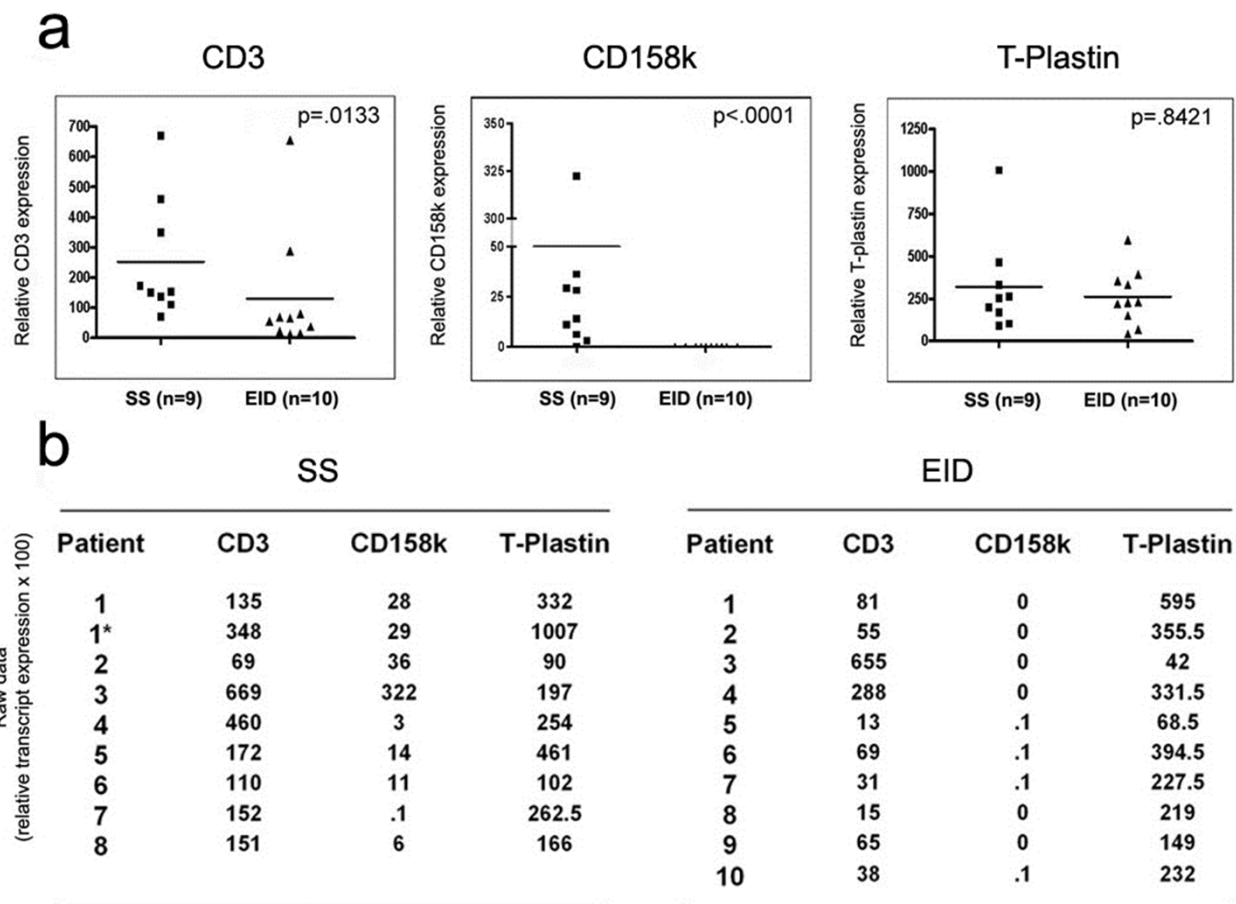
**Sézary
Syndrome**



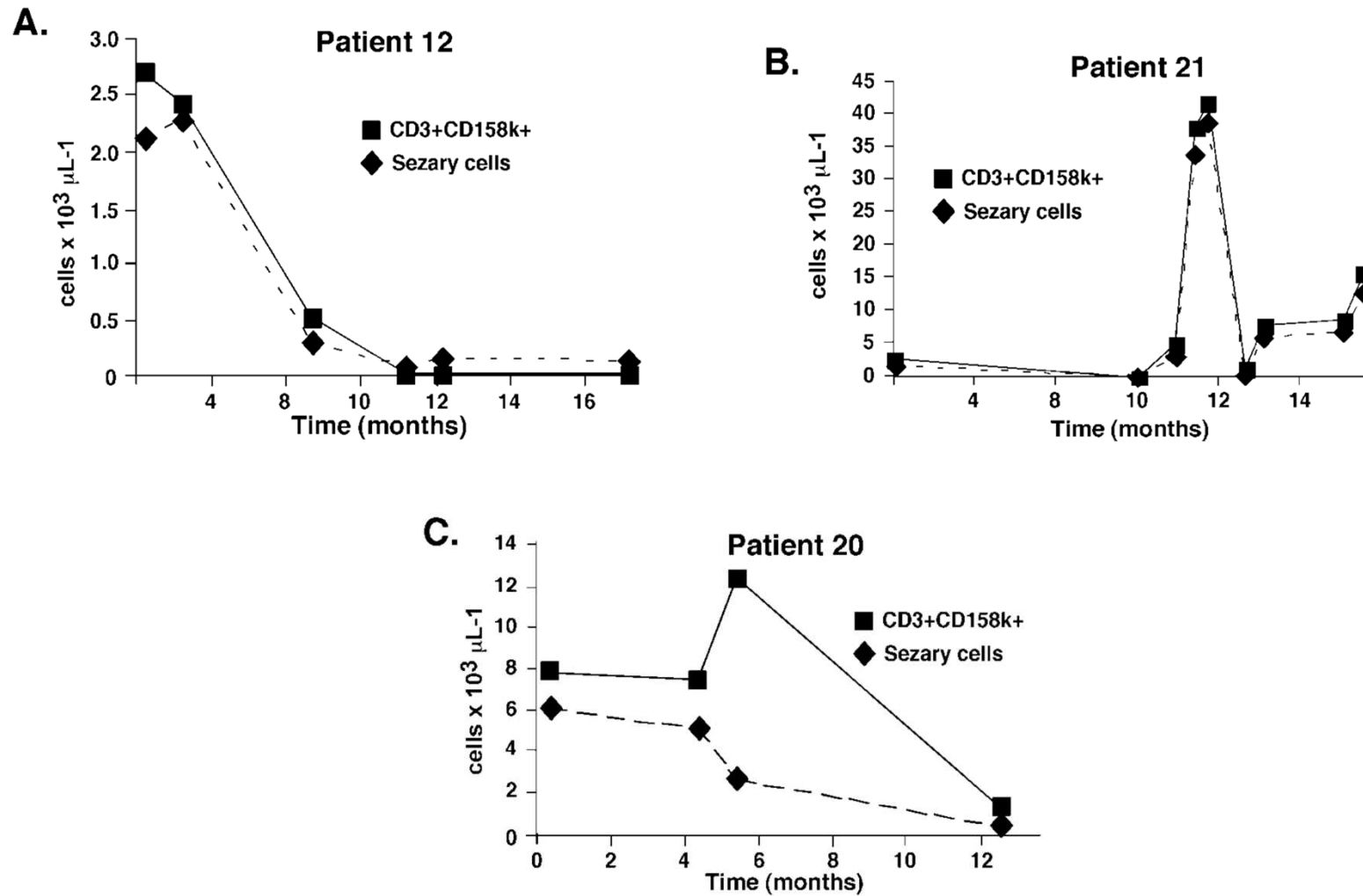
**Mycosis
Fungoides**



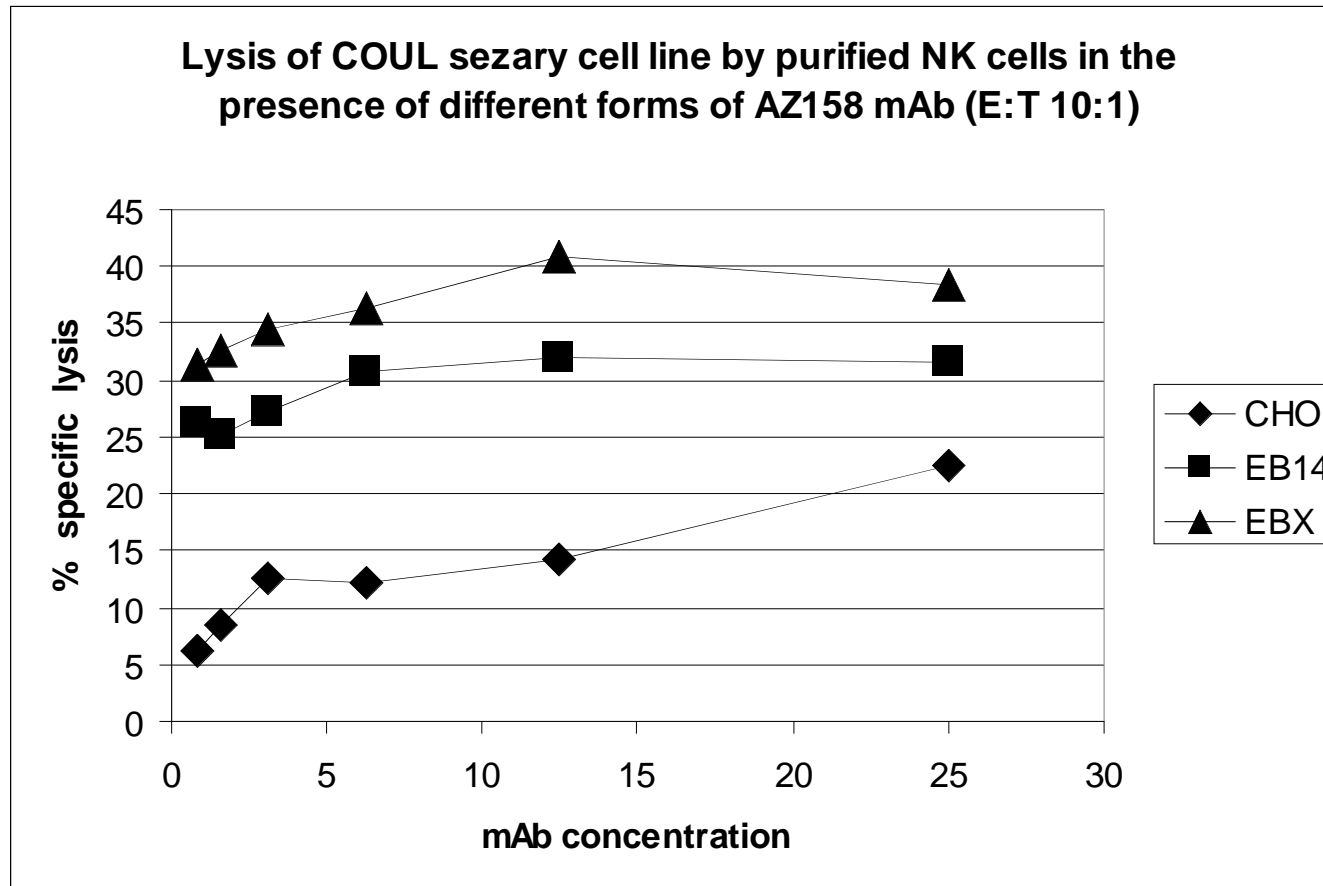
KIR3DL2 expression in the skin: a molecular diagnostic marker



Absolute CD3⁺CD158k⁺ lymphocyte count is reliable and more sensitive than cytomorphology to evaluate blood tumour burden in Sezary syndrome

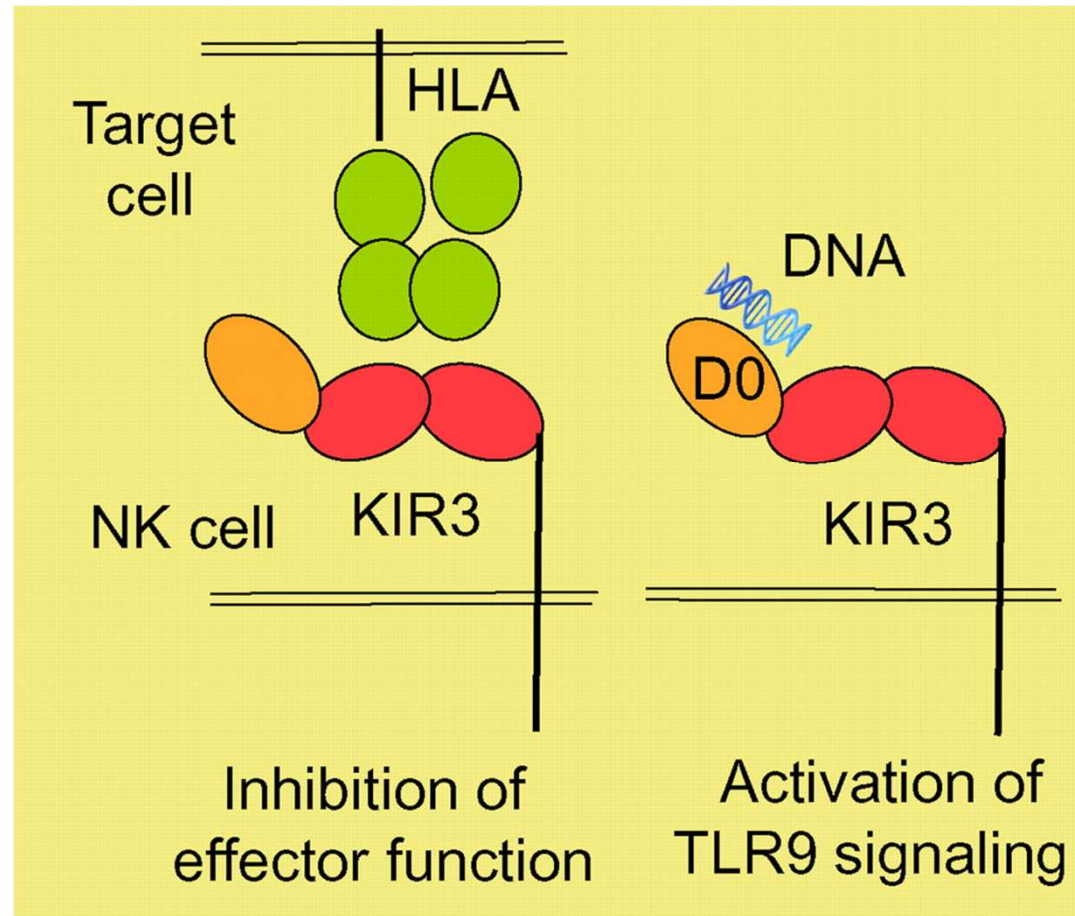


Low-fucosylated chimeric anti-KIR3DL2 mAb mobilizes PB-NK lymphocyte cytotoxic effector function against Sézary cell line

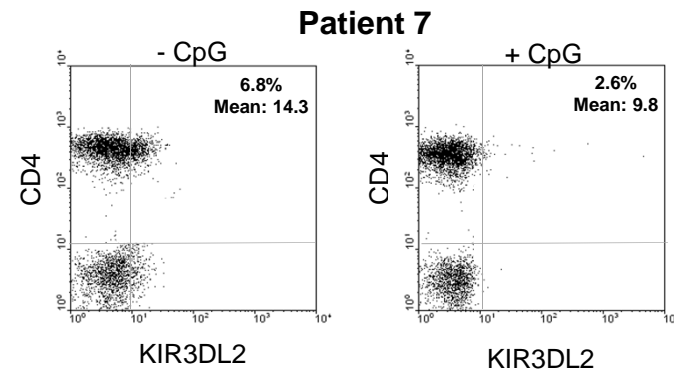
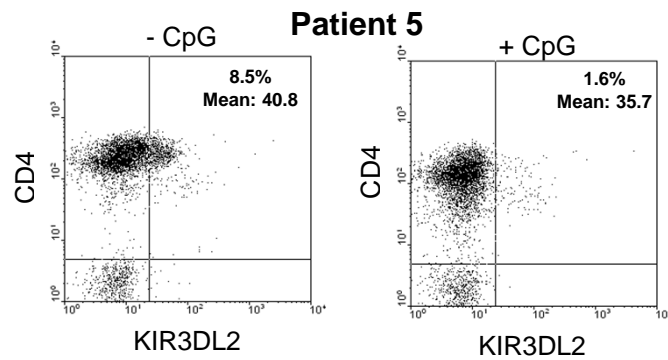
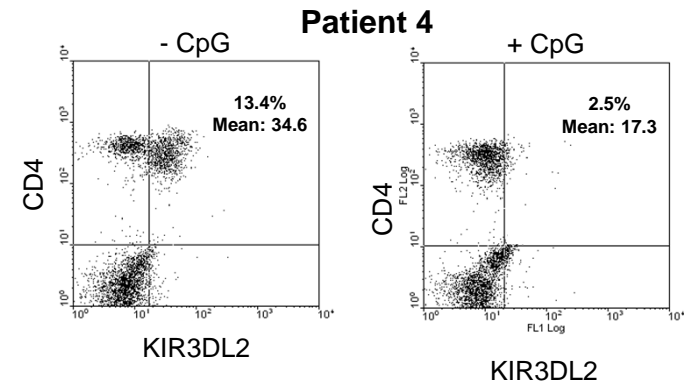
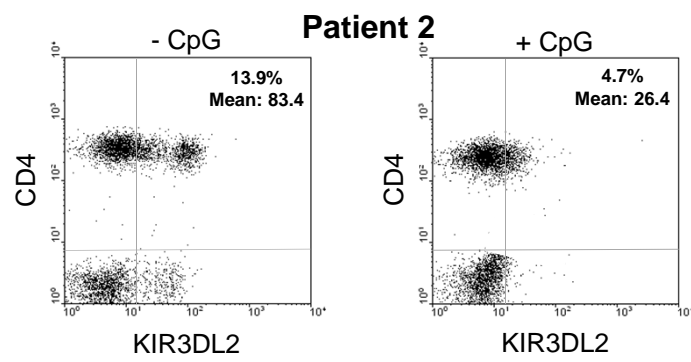


Collaboration with the Biotechnology Company Innate Pharma, Marseille, France

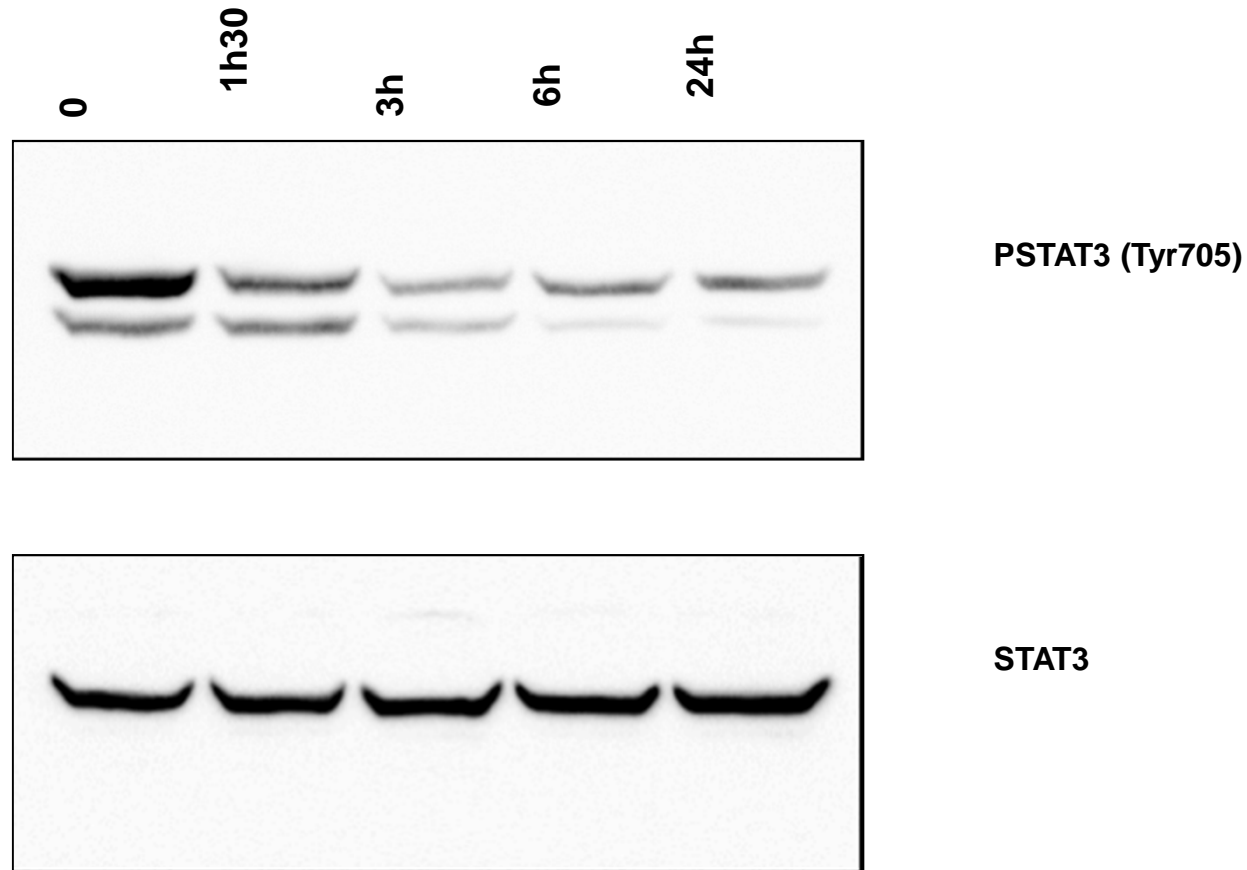
A novel KIR-associated function: evidence that CpG DNA uptake and shuttling to early endosomes is mediated by KIR3DL2



CpG ODN-C down-modulates the expression of KIR3DL2 on the surface of Sézary malignant cells



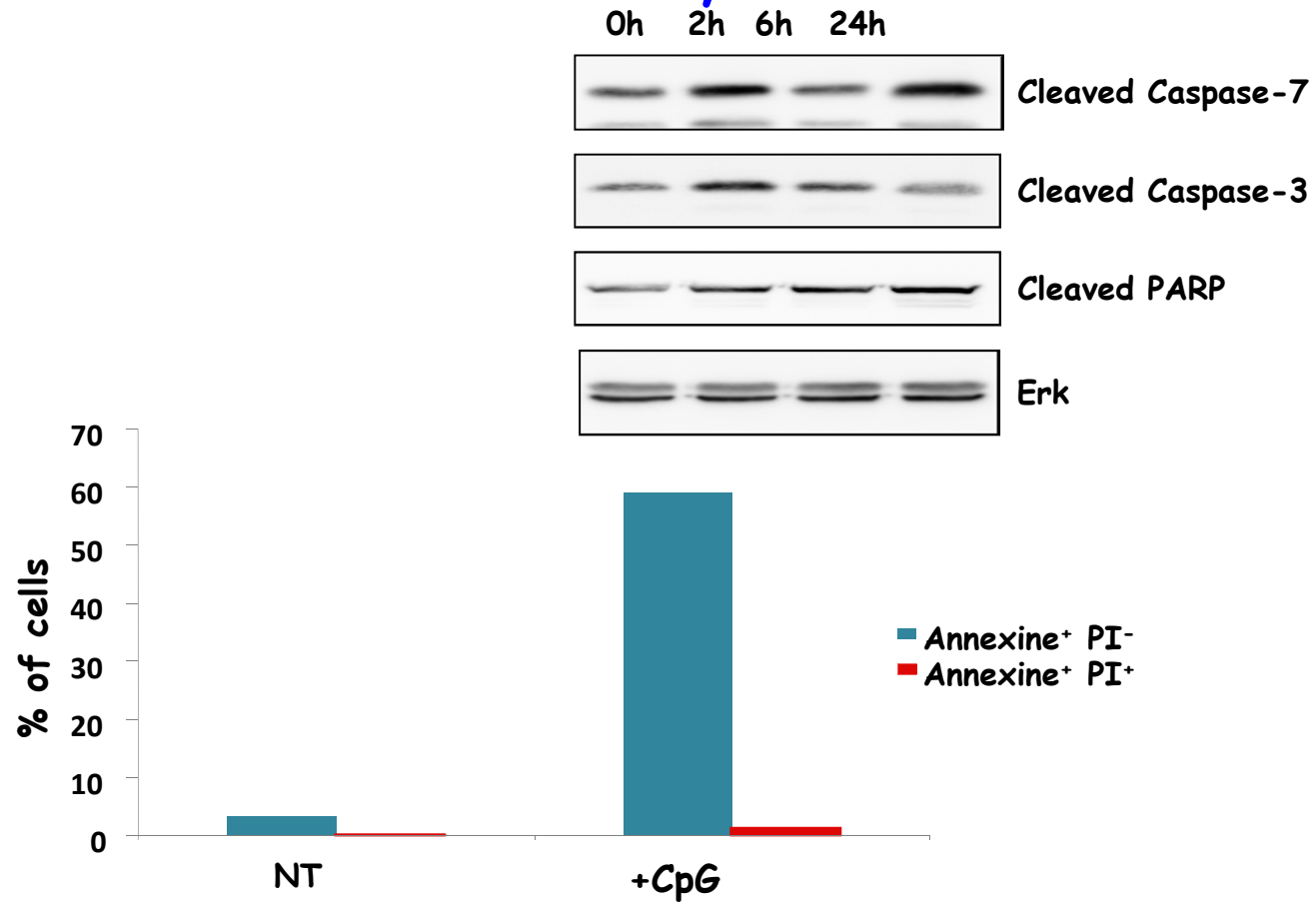
CpG ODN-C treatment of KIR3DL2 expressing Sezary cells results in STAT3 dephosphorylation



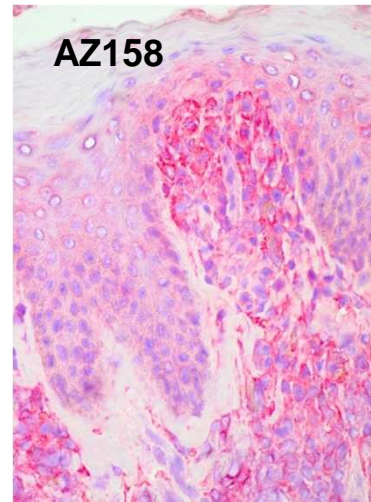
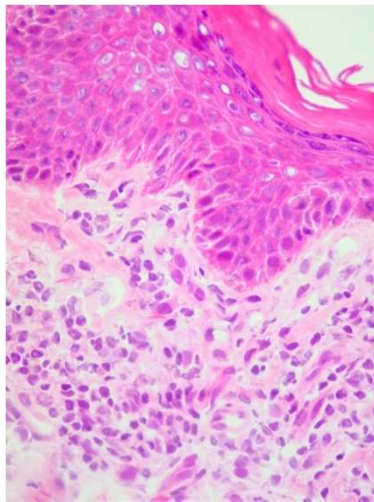
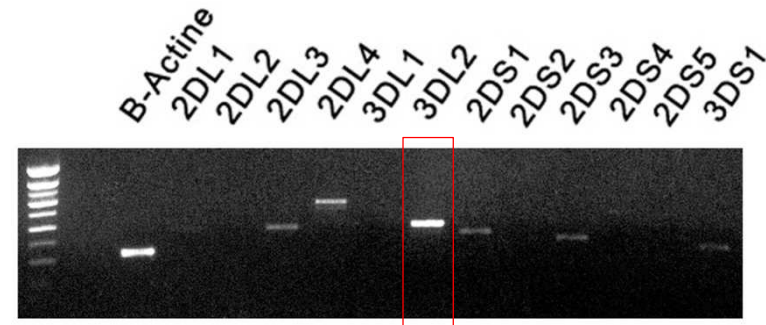
Activation of STAT3 signaling plays an essential part in malignant transformation of CTCL

Marie-Cardine et al, submitted

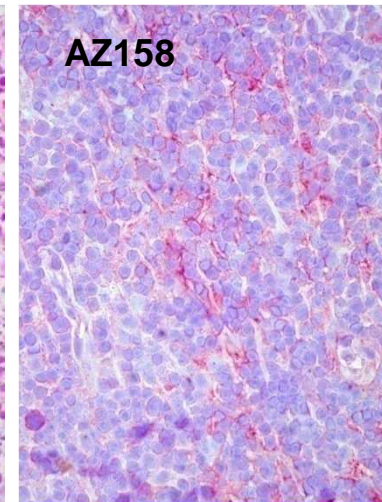
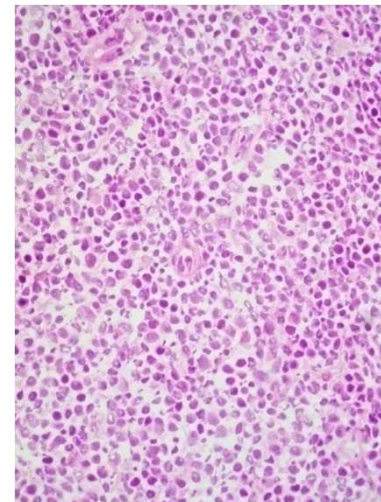
CpG-KIR3DL2 interactions induces apoptosis of Sezary cells



Expression of KIRs in Sezary (*Skin and node*)

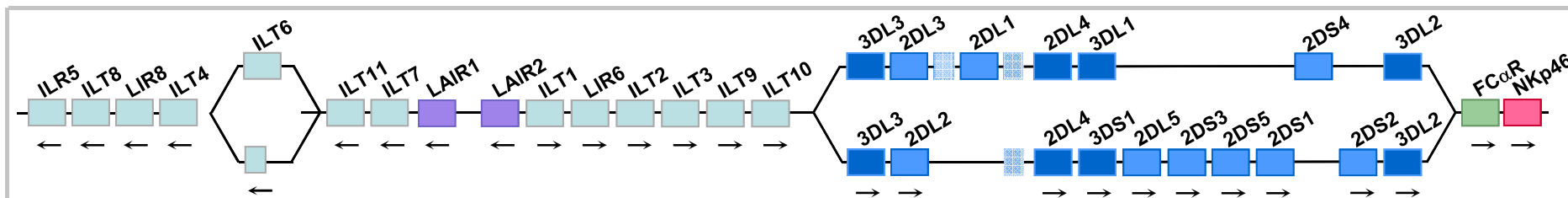


Plaque

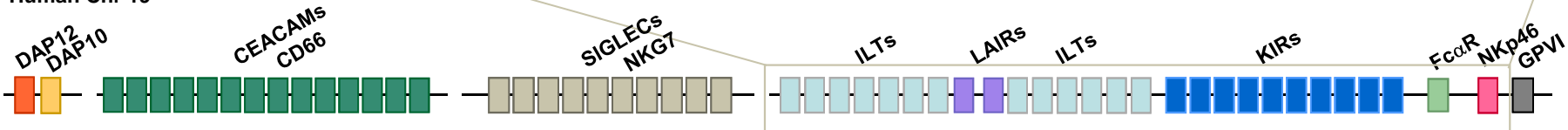


Lymph node

LEUCOCYTE RECEPTOR CLUSTER ORGANIZATION



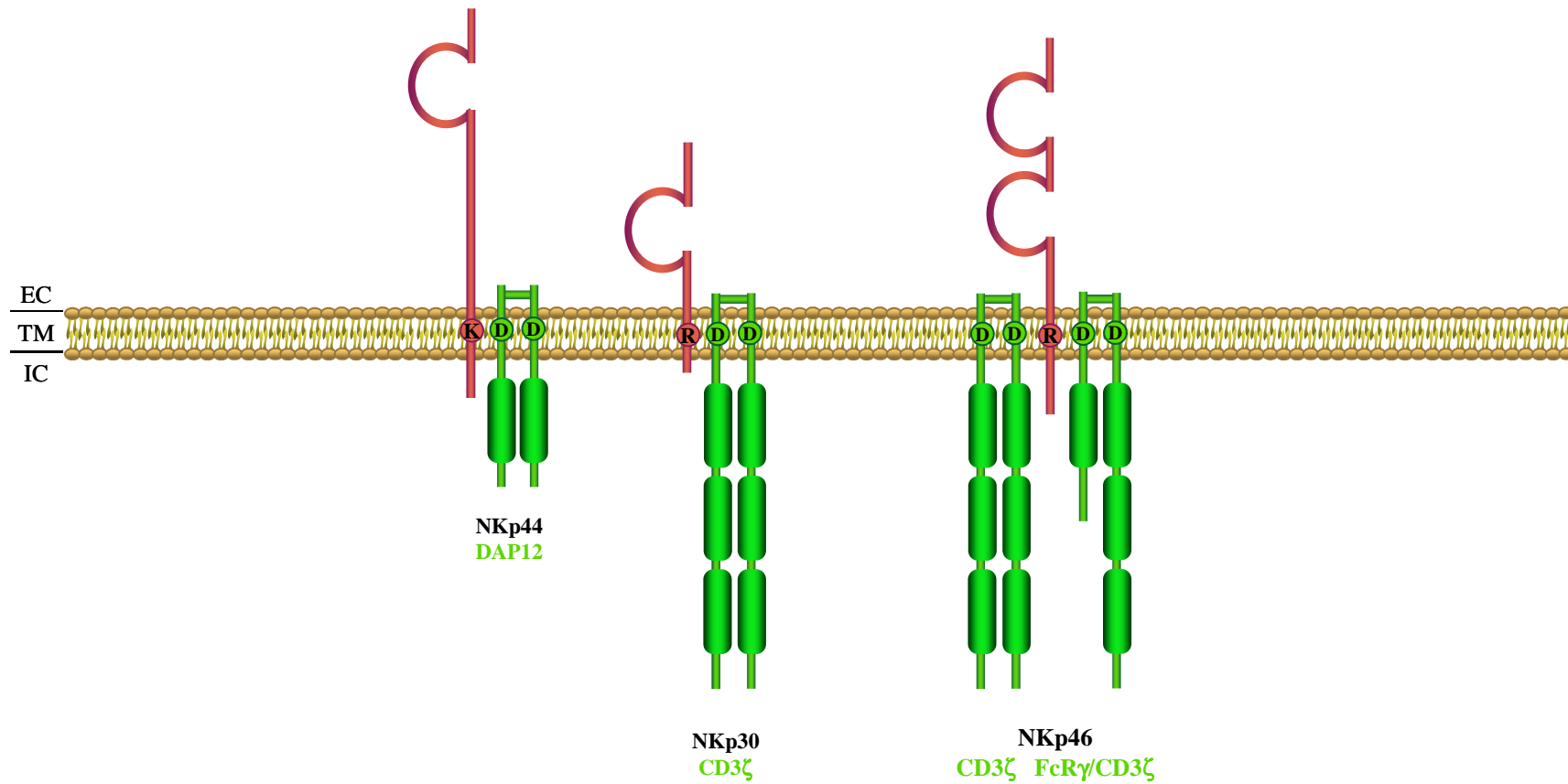
Human Chr 19



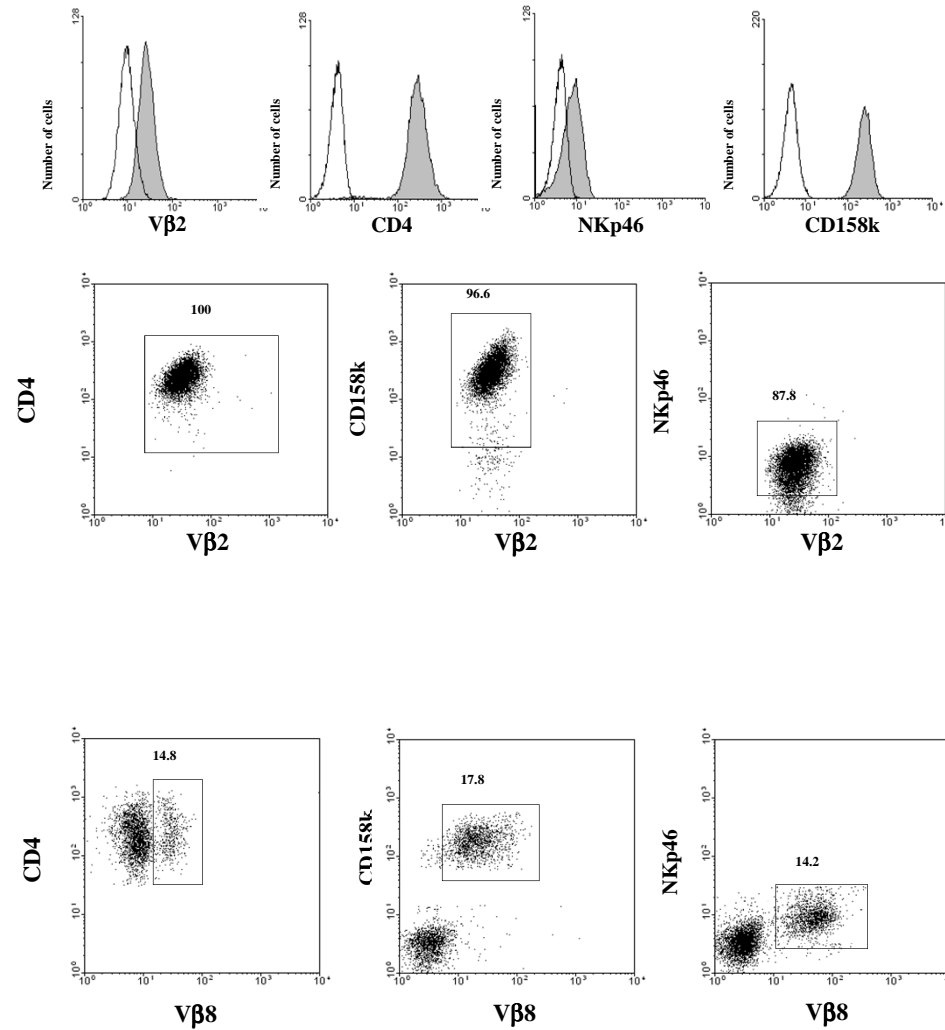
Mouse Chr 7



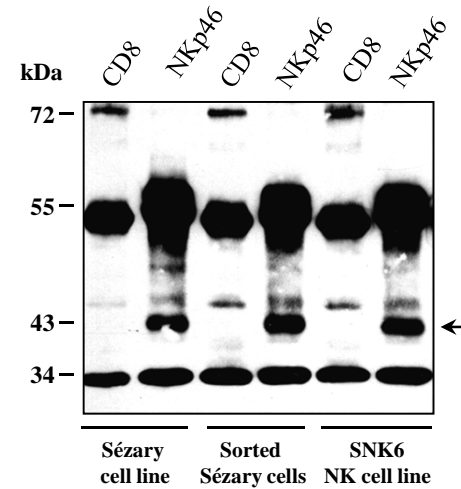
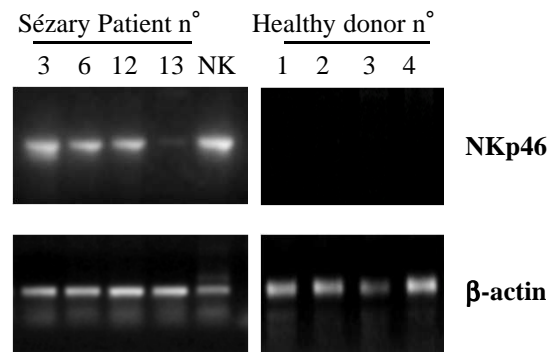
Natural Cytotoxic Receptors



The malignant Sézary syndrome T lymphocytes coexpressed NKp46 and KIR3DL2



NKp46 is specifically expressed by tumoral Sézary cells



Conclusions

- Cutaneous lymphoma T lymphocytes (CTCL) express a wide range of NK receptors which suggest a dedifferentiation of the malignant cells toward the NK cell lineage
- These receptors must be investigated as diagnostic and prognostic markers
- They are also potential therapeutic targets
- Their role in the pathophysiology of CTCL remains to be determined

