Active STAT5 promotes long-lived cytotoxic CD8 T cells that induce regression of autochthonous mouse melanoma.

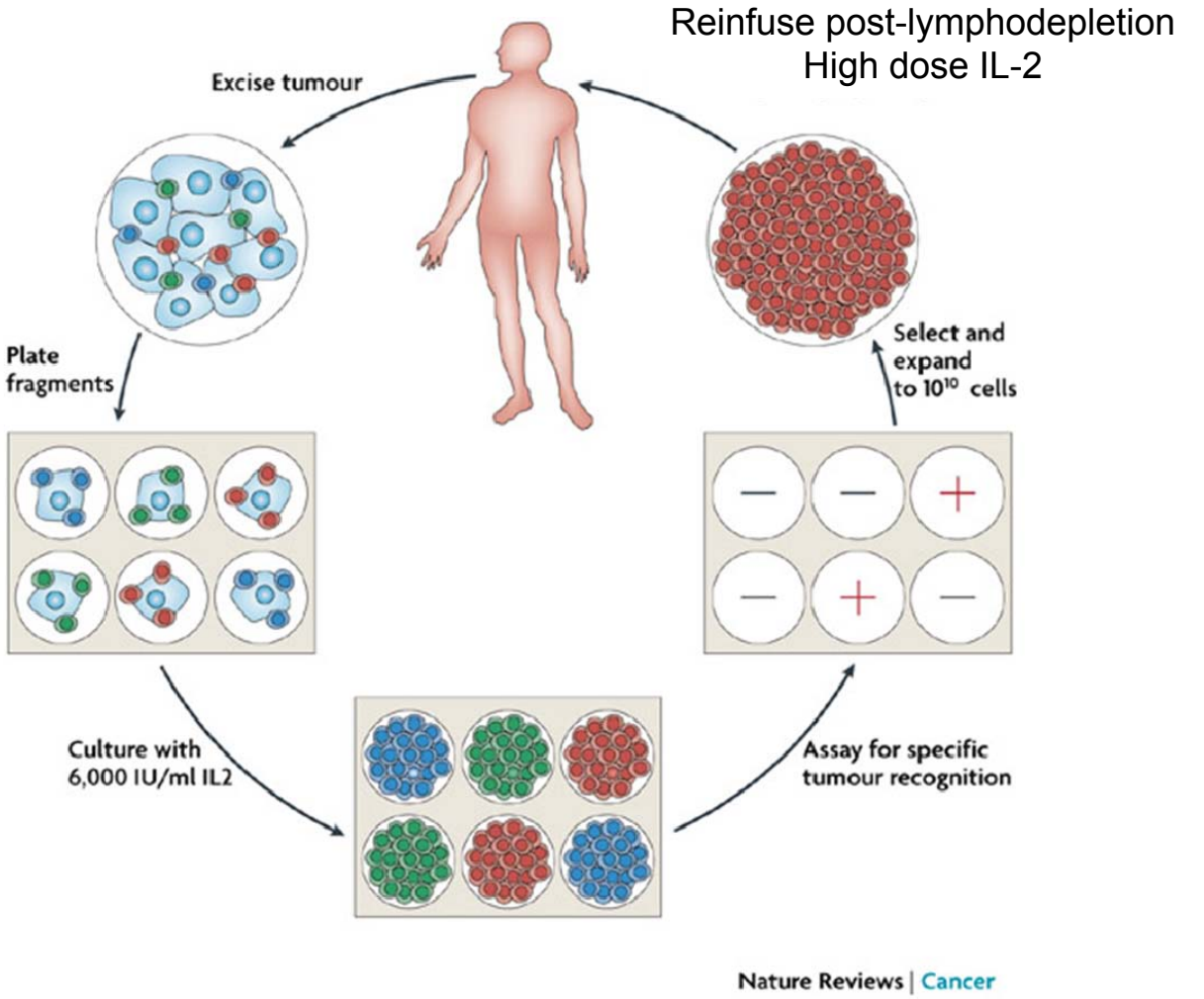
SITC 2011

Grégory Verdeil

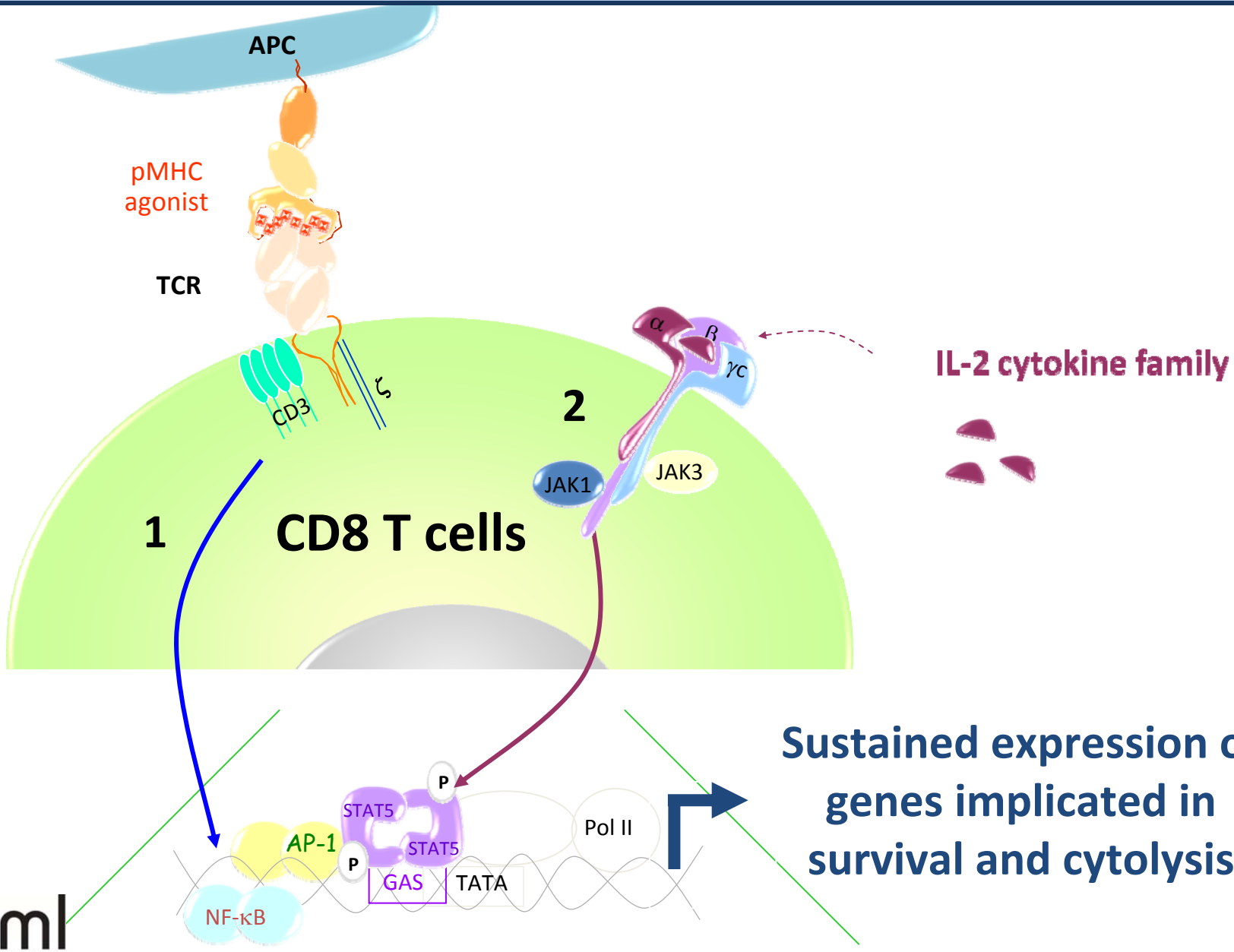
No relationships to disclose

T cell adoptive transfer for cancer immunotherapy

- Short-lived CD8 T cells, poor tissue infiltration
- High doses of IL-2 = systemic action of IL-2 (side effects)



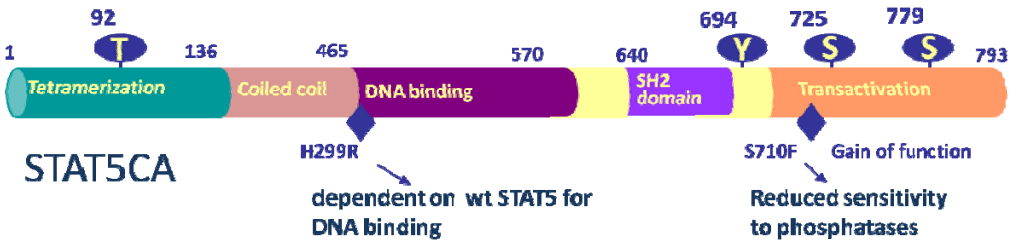
Activation of IL2/STAT5 sustains CD8 T cells effector functions

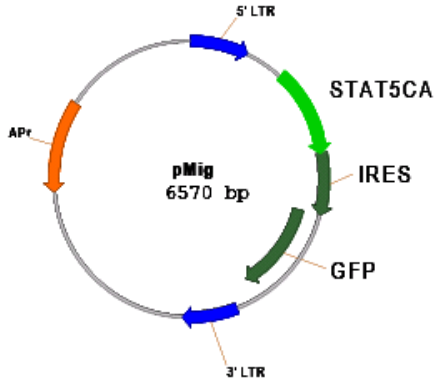


Ciml IMMUNOLOGY

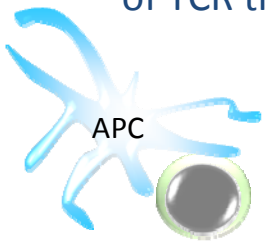
Verdeil et al. Journal of Immunology 2006

Use of STAT5CA to increase tumor elimination by CD8 T cells



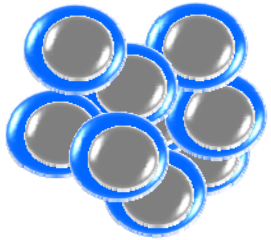


Retroviral transduction of TCR transgenic CD8 T cells



Naïve TCR transgenic CD8 T cell (TCRP1A)

Expansion / differentiation



Cytotoxic CD8 T cells

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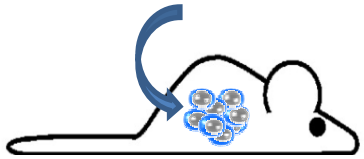
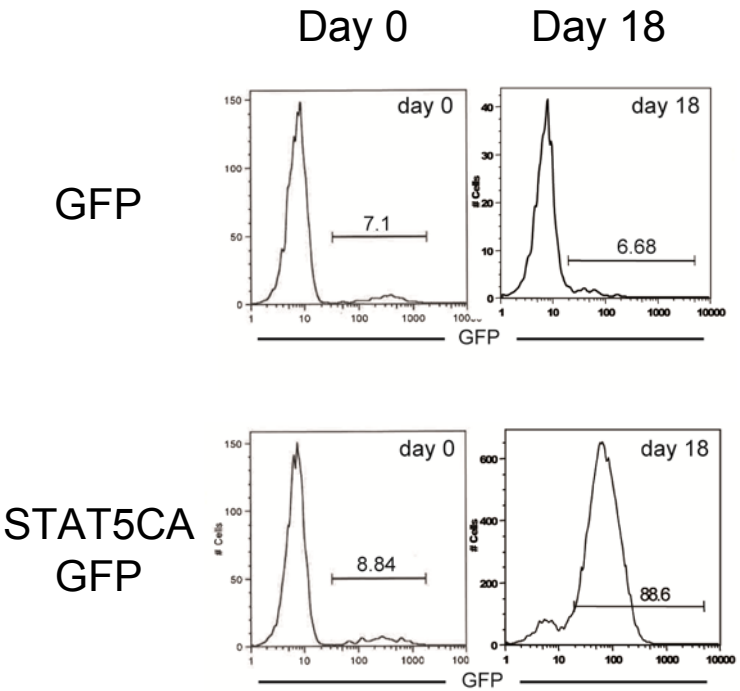
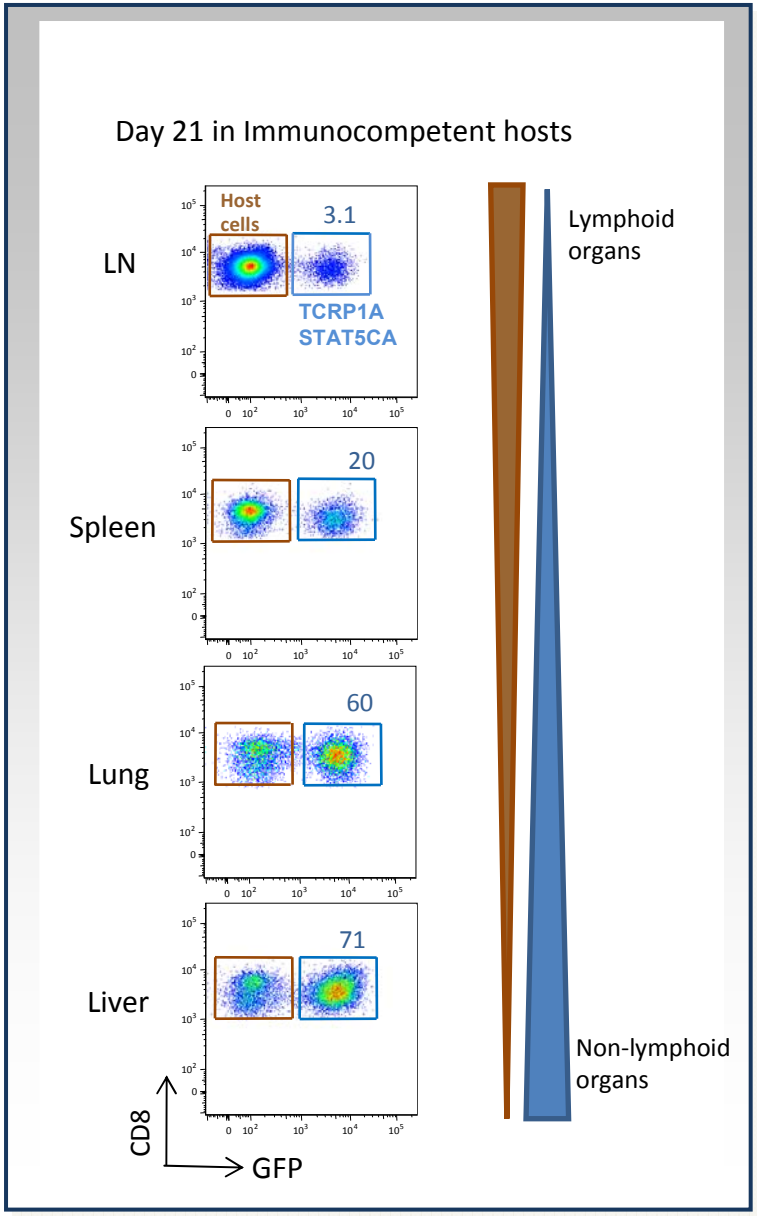
Preferential expansion and tissue-homing of STAT5CA -T cells

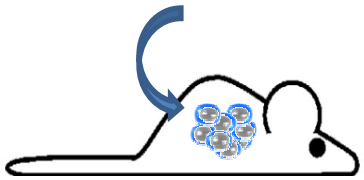


WT B10D2
(immunocompetent)

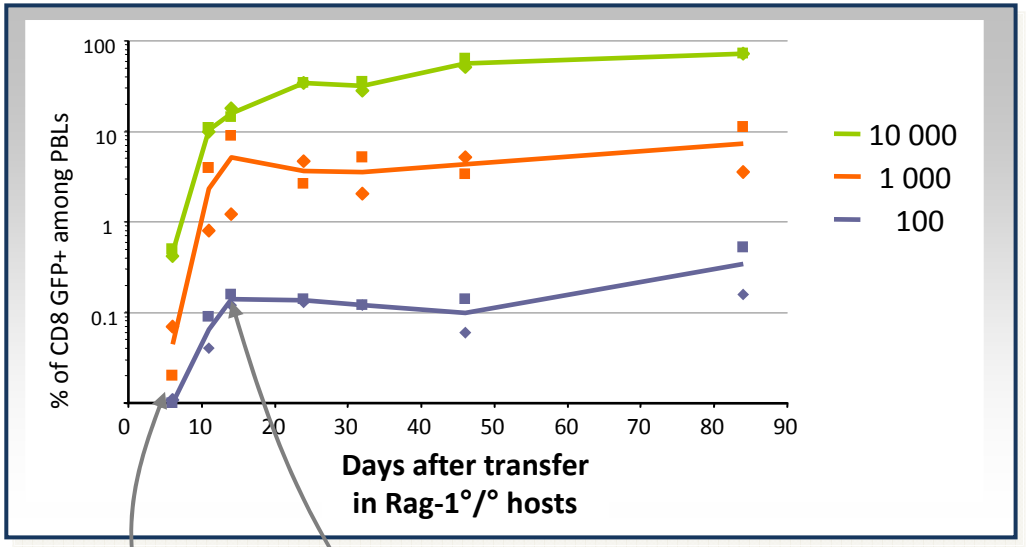


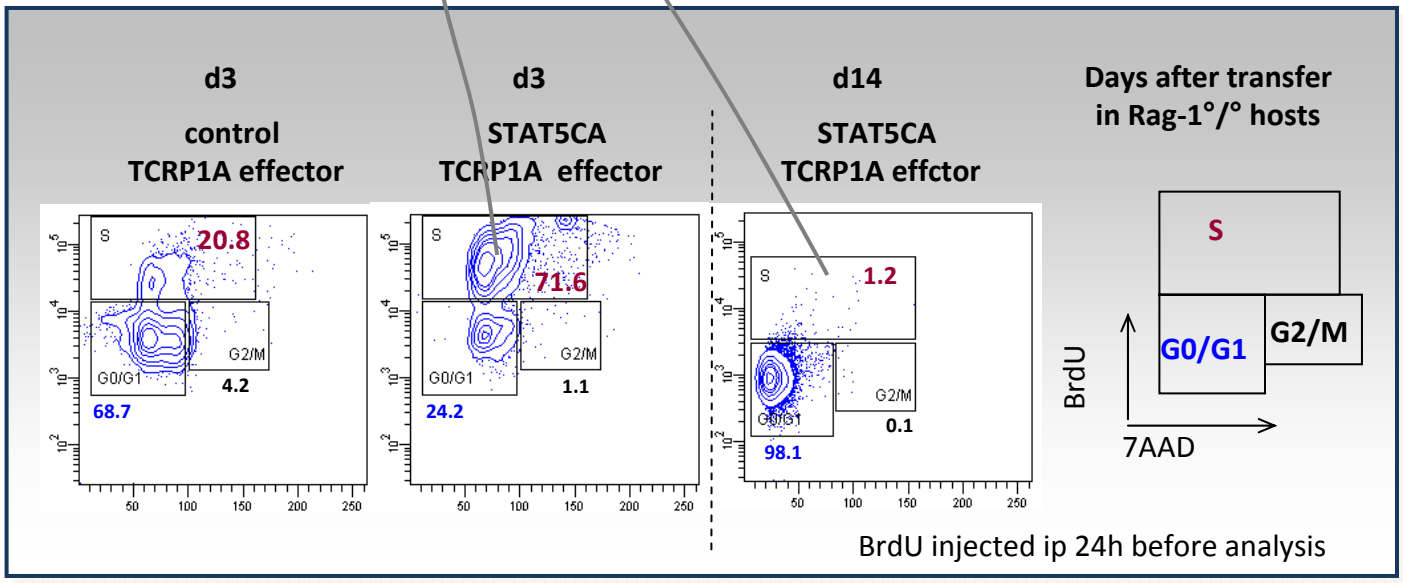


STAT5CA expressing T cells are maintained at a quiescent G0 state

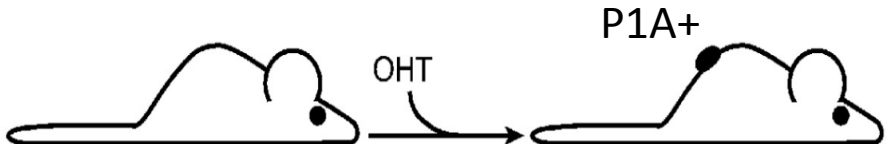


Rag-/-
(immunodeficient)





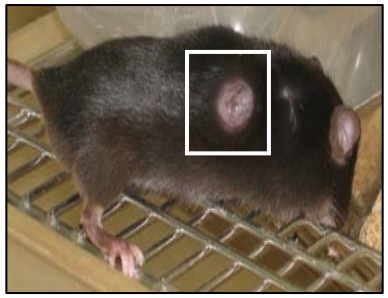
Inducible melanoma model (TIRP mice)



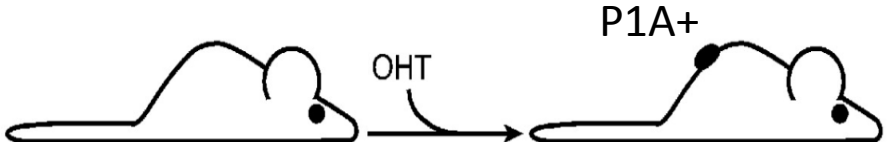
WT(immunocompetent)

In melanocytes
$HRas^{G12V}$ on
P1A cancer-germline Ag on
Ink4a/Arf off

36%
143 days of latency



Amela
Aggressive



Rag-/- (immunodeficient)

In melanocytes
$HRas^{G12V}$ on
P1A cancer-germline Ag on
Ink4a/Arf off

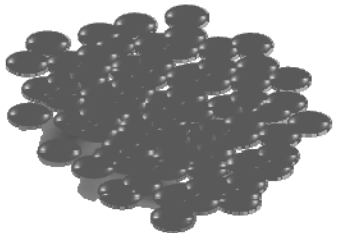
72%
82 days of latency

The adaptive immune system controls tumor growth in TIRP mice.

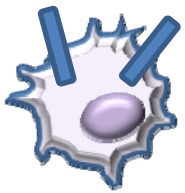
Ciml IMMUNOLOGY

Huijbers et al. Cancer research 2006;
Soudja et al. Cancer research 2010

Amela tumors are strongly immunosuppressive



VEGF
G-CSF
IL-10
IL-6

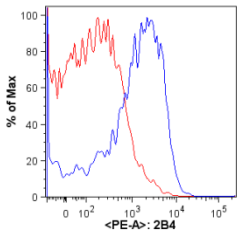


Arginase-1+
Cox-2+

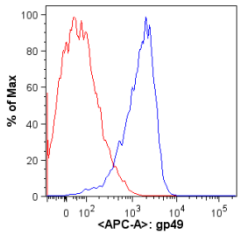
Myeloid **D**erived **S**uppressor **C**ells

Immunosuppressive environment

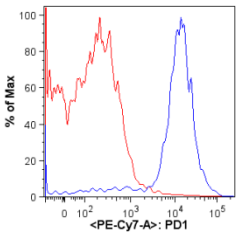
Expression of inhibitory receptors



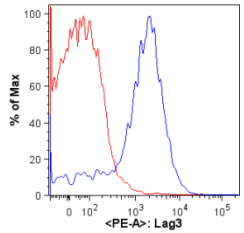
2B4



GP49



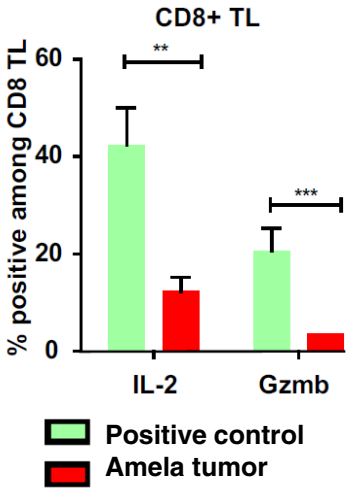
PD-1



lag3

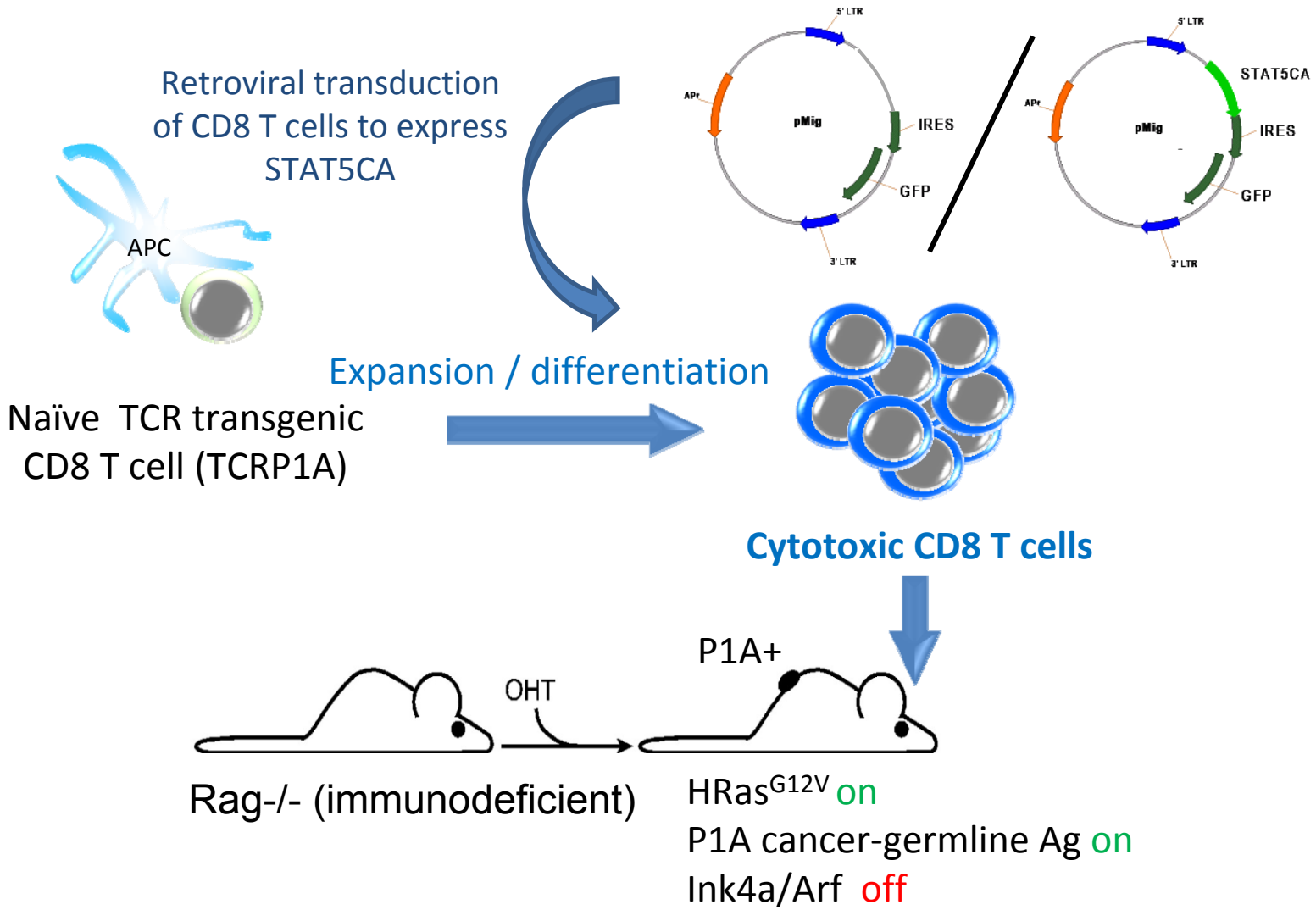
Endogenous CD8 T cells have an **exhausted** phenotype **Inside the tumor**

Loss of functionnal properties

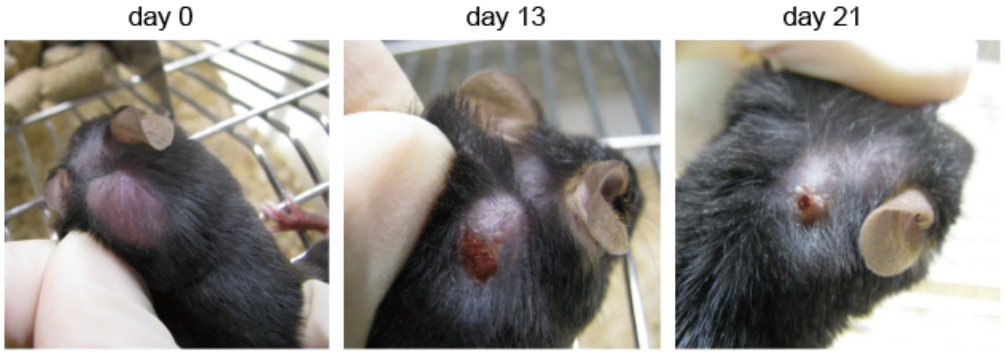


IMMUNOLOGY

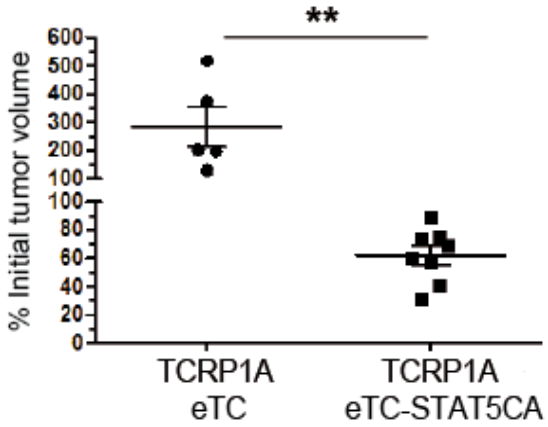
Use of STAT5CA to increase tumor elimination by CD8 T cells



STAT5CA expressing T cells induce melanoma regression in Rag-/- TiRP mice



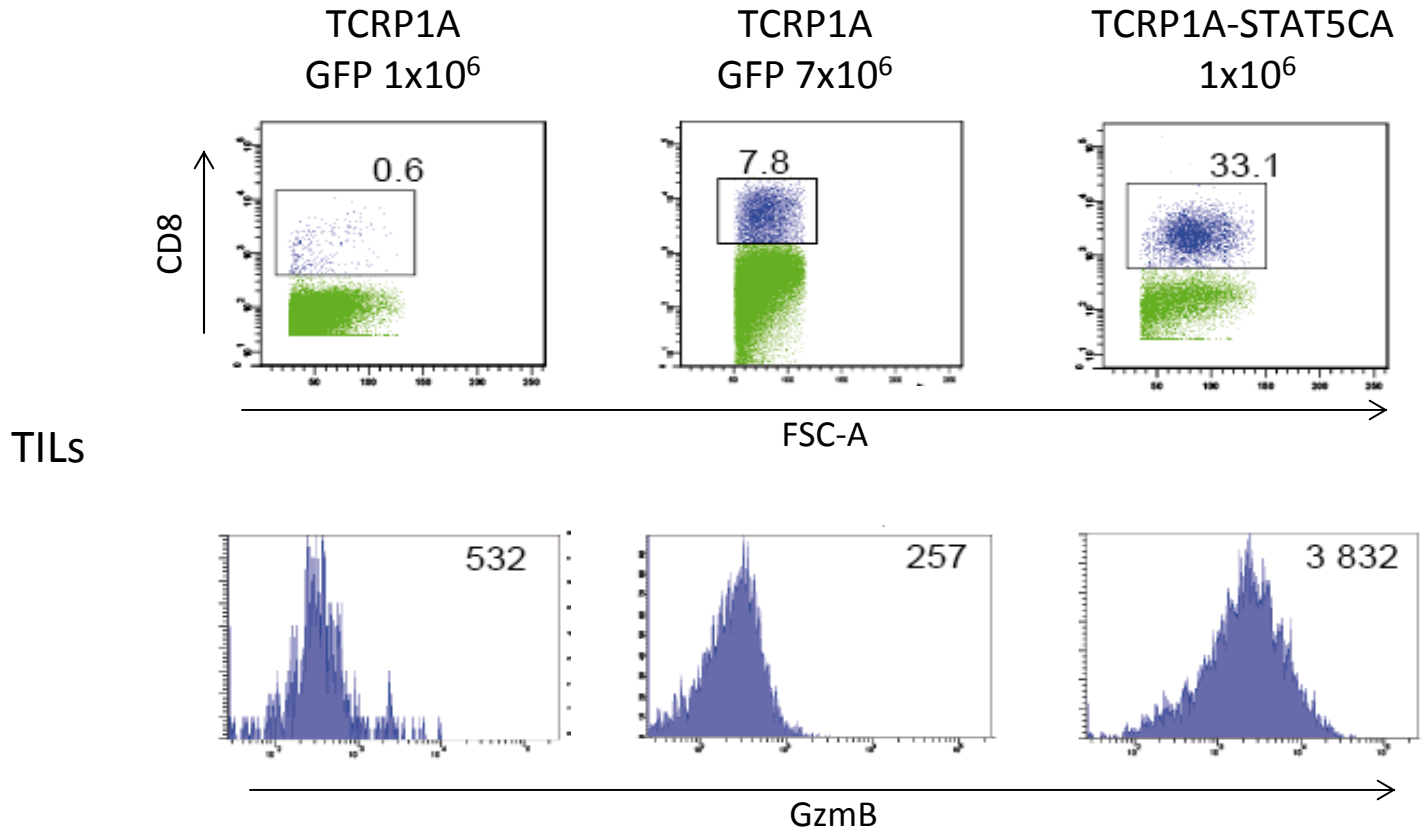
7 days post-treatment



Ciml IMMUNOLOGY

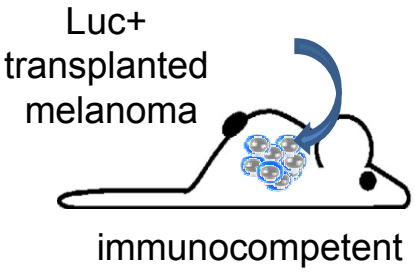
Grange et al. Cancer research in press

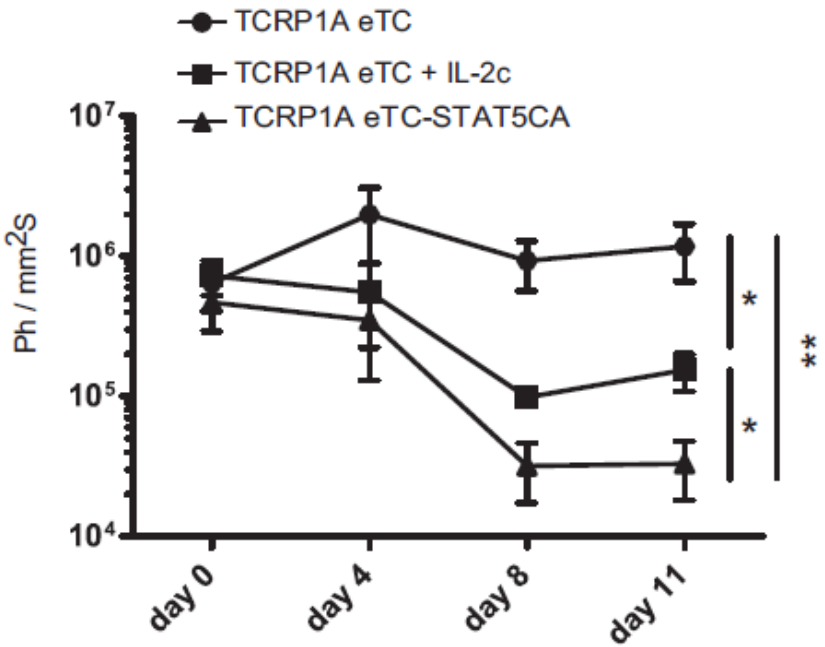
STAT5CA-T cells remain active in the melanoma immunosuppresive environment

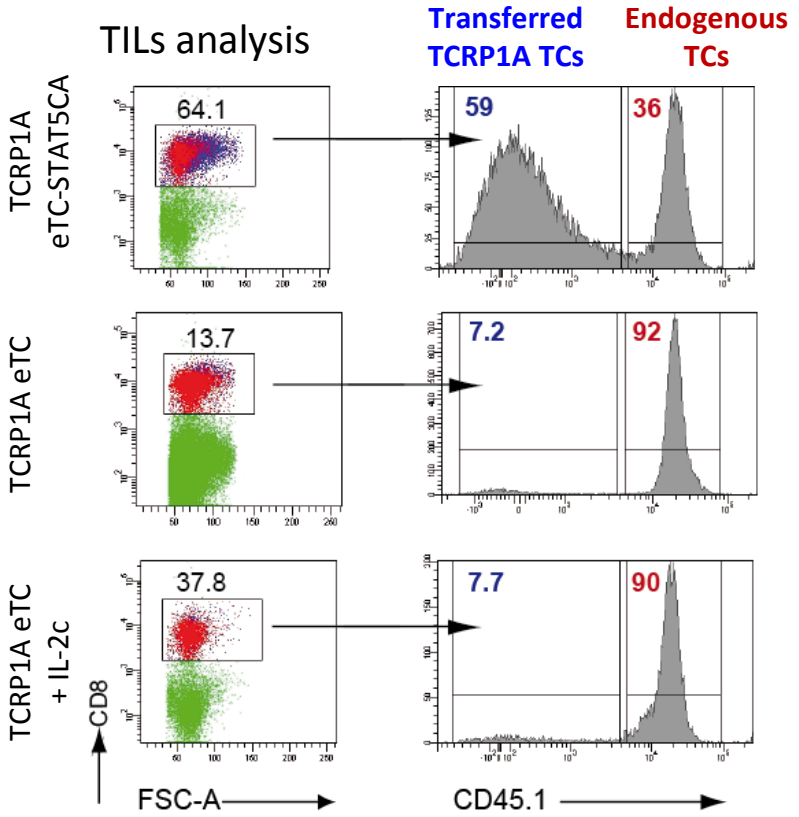


Grange et al. Cancer research in press

STAT5CA T cells are more efficient than IL-2 complexes to induce tumor regression







Grange et al. Cancer research in press

Conclusions

-STAT5CA transduced T cells show high cytolytic potential and capacity to migrate into tissues/tumors

- STAT5CA transduced T cells remain dependent on the presence of the antigen for restimulation

- STAT5CA transduced T cells induce strong regression of an autochthonous melanoma with high immunosuppressive properties

- What are the mechanisms involved in resistance of STAT5CA transduced T cells to immunosuppression?

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CIML
Anne-Marie Schmitt-Verhulst's Lab

Nathalie Auphan-Anezin
Magali Grange
Michel Buferne

Marielle Mello
Marilyn Giordano
Annick Guimezanes
Amandine Mas
Claude Boyer
Pierre Mouchacca

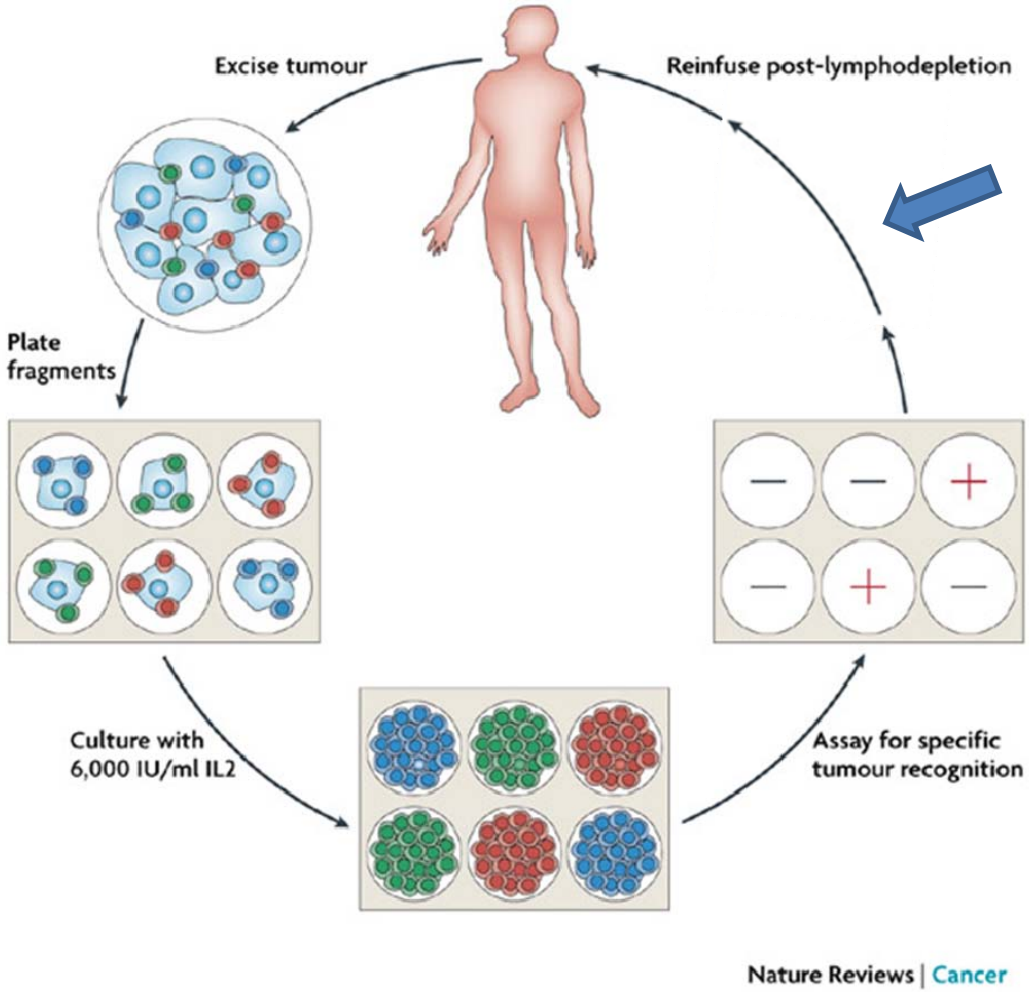
Saïdi M'homa Soudja
Maria Wehbe

Association pour la Recherche sur le Cancer

Institut National du Cancer

Agence Nationale de la Recherche ANR

T cell adoptive transfer for cancer immunotherapy



STAT5-CA ?

No need of IL-2 injections

= **Targeted action on CD8 Te**

Long-lived CD8 Te (>d140)

Tissue infiltration

For safety: coupling to a suicide gene

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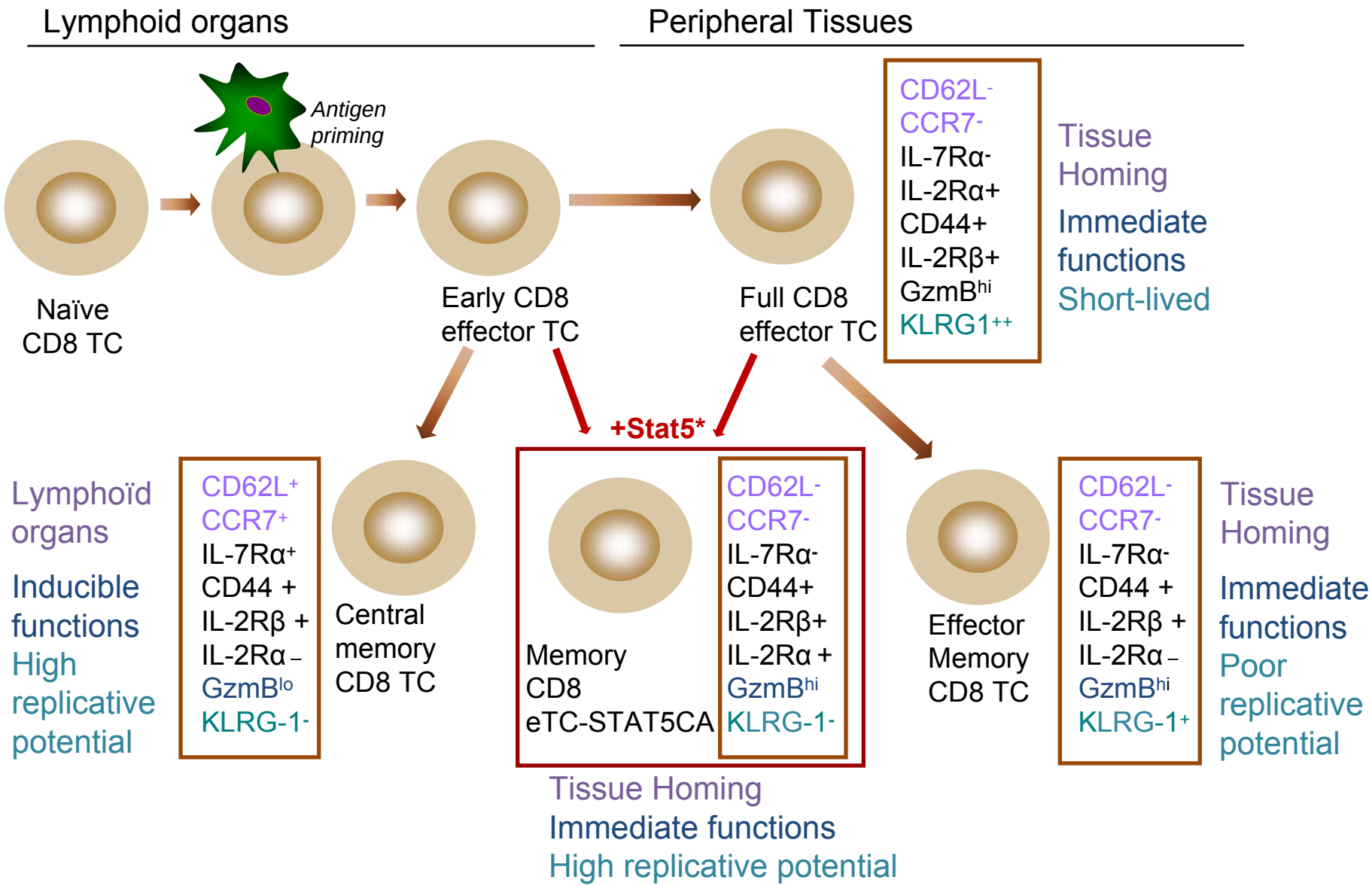
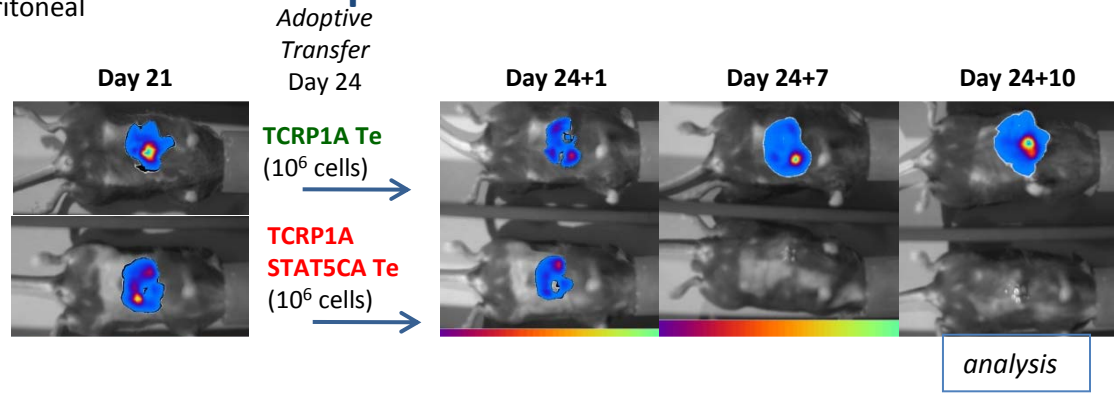

Lymphoid organs
Peripheral Tissues
Antigen priming
Naïve CD8 TC
Early CD8 effector TC
Full CD8 effector TC
CD62L-
CCR7-
IL-7Rα-
IL-2Rα+
CD44+
IL-2Rβ+
GzmBhi
KLRG1++
Tissue Homing
Immediate functions
Short-lived
+Stat5*
Lymphoïd organs
Inducible functions
High replicative potential
CD62L+
CCR7+
IL-7Rα+
CD44 +
IL-2Rβ +
IL-2Rα –
GzmBlo
KLRG-1-
Central memory CD8 TC
Memory CD8 eTC-STAT5CA
CD62L-
CCR7-
IL-7Rα-
CD44+
IL-2Rβ+
IL-2Rα +
GzmBhi
KLRG-1-
Tissue Homing
Immediate functions
High replicative potential
Effector Memory CD8 TC
CD62L-
CCR7-
IL-7Rα-
CD44 +
IL-2Rβ +
IL-2Rα –
GzmBhi
KLRG-1+
Tissue Homing
Immediate functions
Poor replicative potential

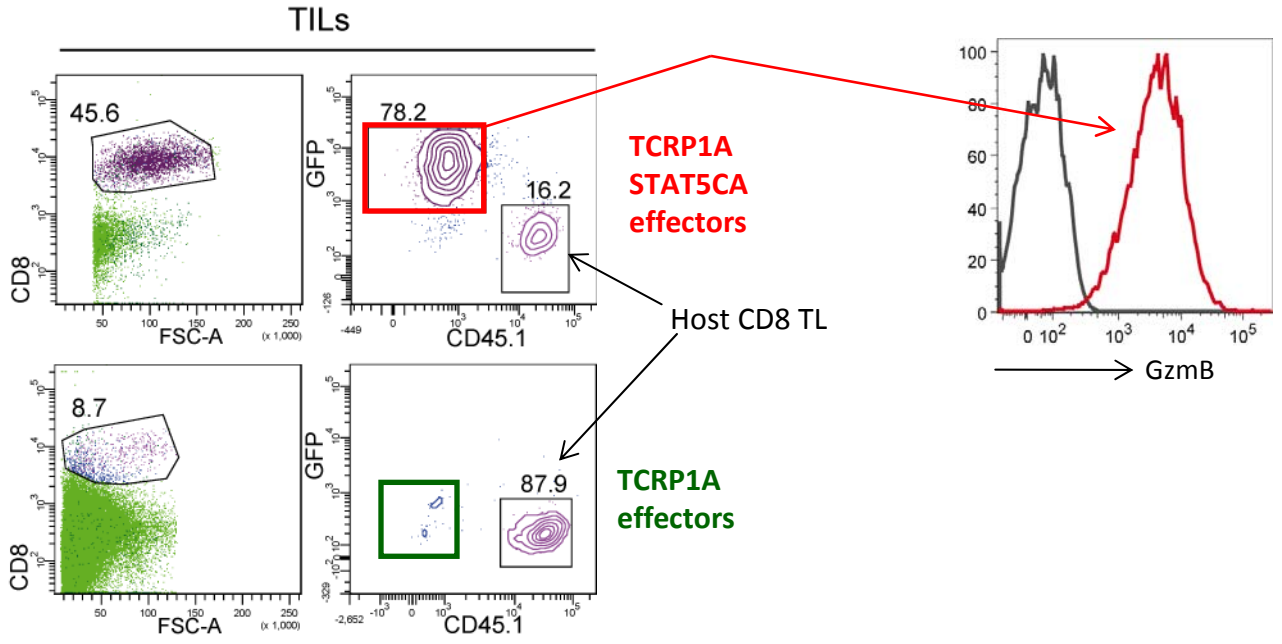
STAT5CA TCRP1A CD8 T cells also reject a P1A+ melanoma in immunocompetent hosts

STAT5CA expressing CD8 T cells show a higher expansion and tumor infiltration than non manipulated CD8 Te counterparts

Recipients = LysoM eGFP Ly5.1 B10.D2
D0: 10^6 T429-luc retro-peritoneal



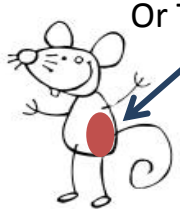
No Ph emission but small residual tumor



Adoptive therapy in mice bearing a transplanted melanoma

Day 0

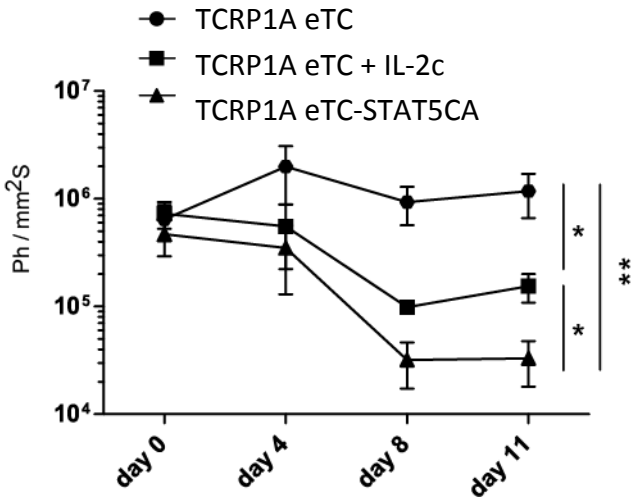
TCRP1A eTC-STAT5CA i.v.
Or TCRP1A eTC
Or TCRP1A eTC + IL-2c (day+1;+2;+3;+5;+7;+9)



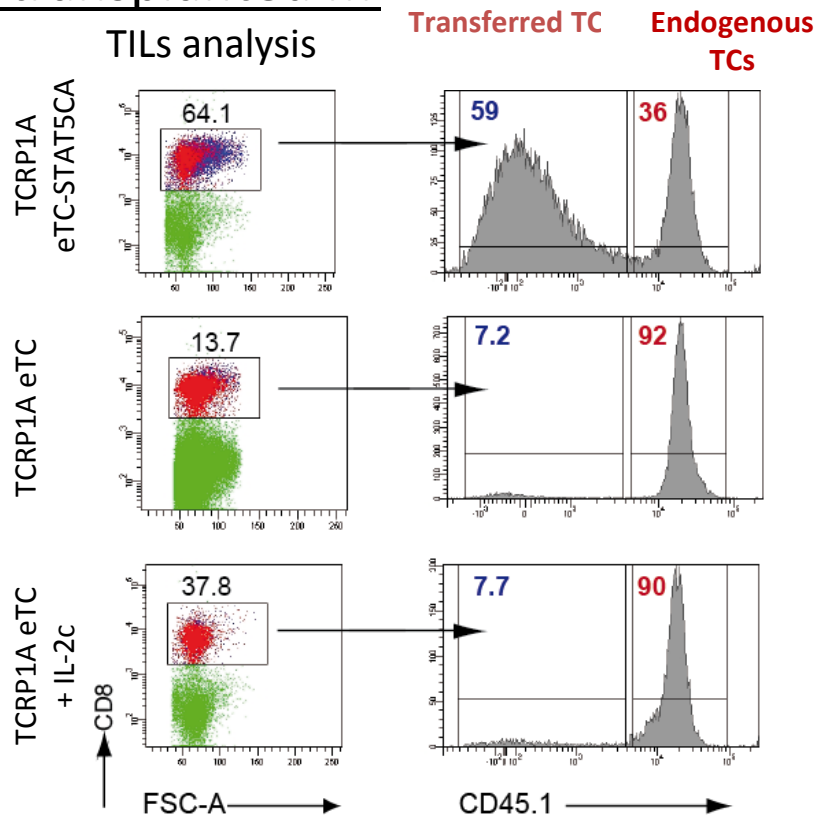
LysoM-eGFP
B10.D2

Monitoring of tumor growth by bioluminescence

Analysis day +11 post- adoptive transfer



TILs analysis



CRP1A CD8 eTC-STAT5CA
ıduce regression of a
1A+ transplanted melanoma in
uno-competent hosts

TCRP1A CD8 eTC-STAT5CA show a higher intra-tumor accumulation than non manipulated CD8 eTC, even when coupled to IL-2c infusions.

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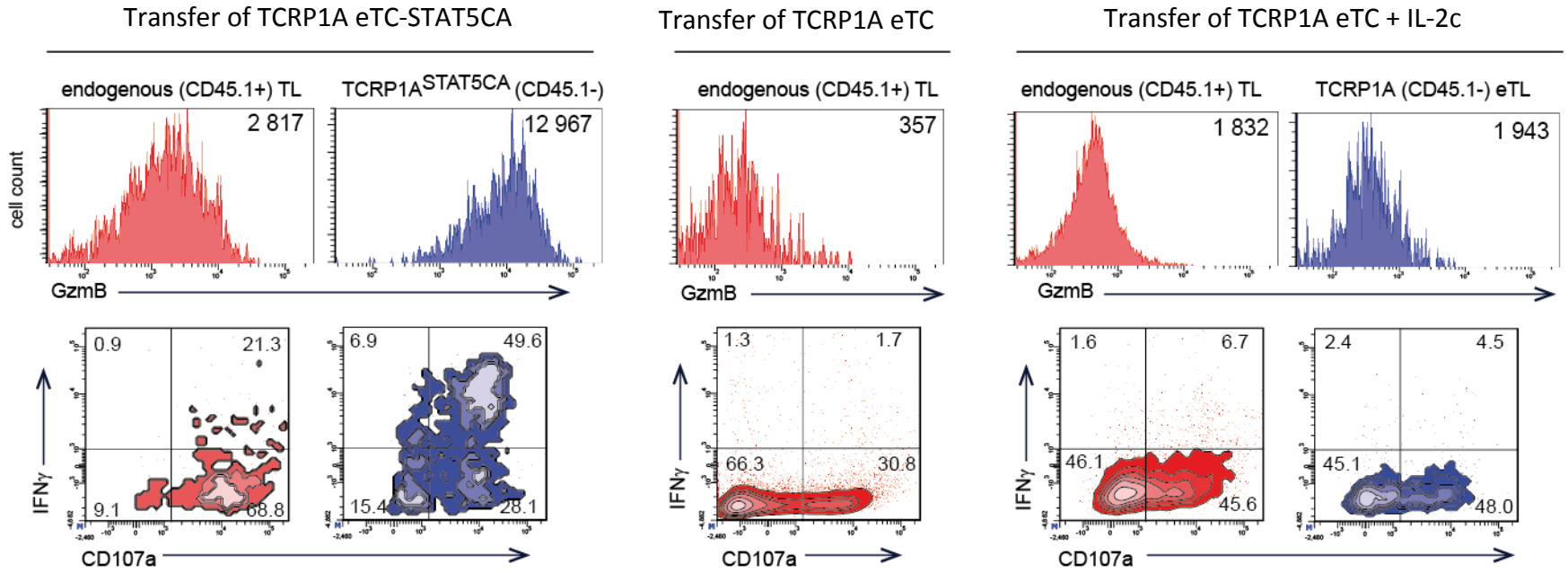

Compared to endogenous CD8 TILs, TCRP1A eTC-STAT5CA expressed higher levels of GzmB and responded efficiently to recall restimulation.

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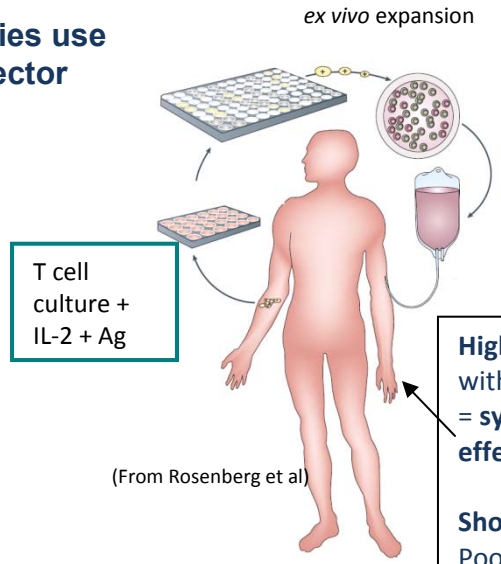
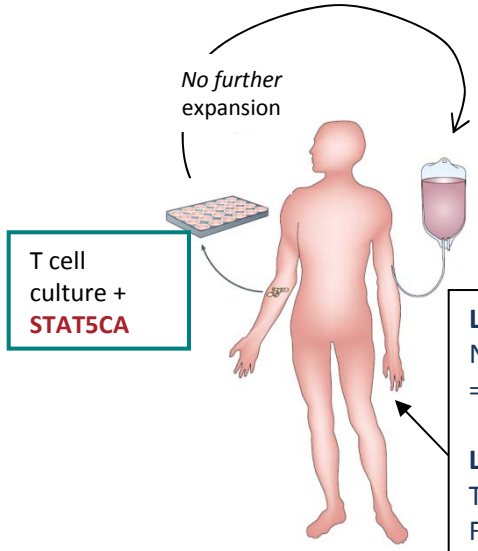
Current adoptive therapies use highly differentiated effector CD8 T cells



High number of T cells
with high doses of IL-2
= **systemic action of IL-2/dise effects** (including on **Tregs**)

Short-lived CD8 Te (up to d14)
Poor tissue infiltration

STAT5CA based adoptive therapies promote less-differentiated and long-lived effector CD8 T cells



Low number of T cells
No need of IL-2 injections
= **Targeted action on CD8 Te**

Long-lived CD8 Te (>d140)
Tissue infiltration
For safety: coupling to a suicide gene

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<YOUR NAME HERE>

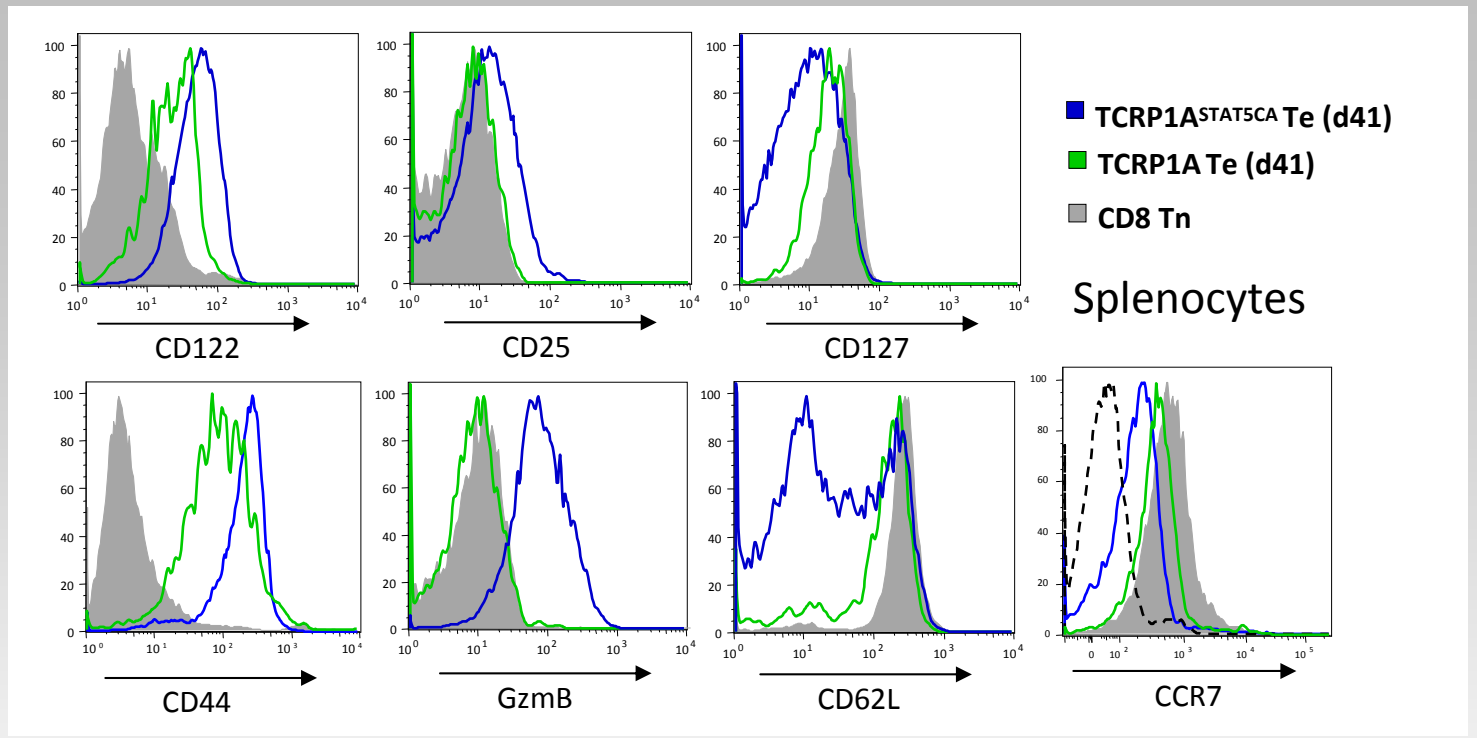
The following relationships exist related to this presentation:

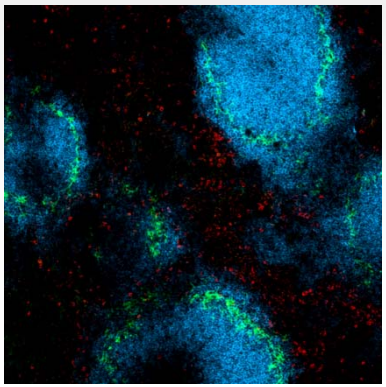
<No Relationships to Disclose>

<OR>

<COMPANY X, Received, Role (i.e. BMS, Honorarium, Speaker)>
<COMPANY Y, Received, Role (i.e. Pfizer, Salary, Employee)>

STAT5CA expressing CD8 T cells have a T effector memory phenotype





MOMA B220 GFP

In correlation with CCR7 down-modulation, STAT5CA transduced T cells are found in the red pulp

(d6 after transfer in B10D2 syngenic mice, spleen)

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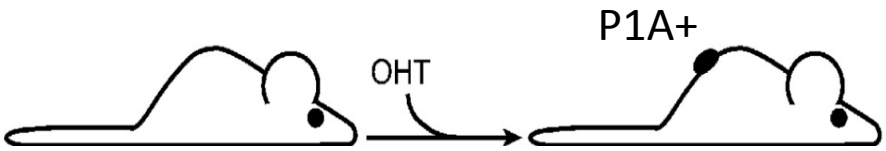
Inducible melanoma model (TiRP mice)

Inducible melanoma



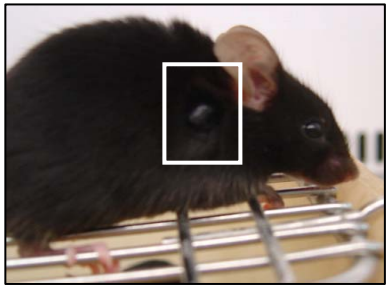
TiRP mice

$HRas^{G12V}$ on

P1A cancer-germline Ag on

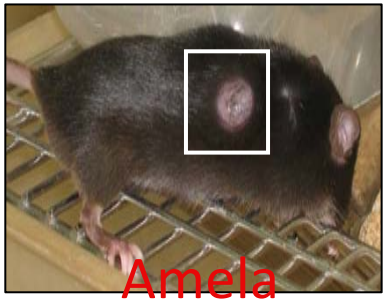
Ink4a/Arf off

	Mela (pigmented)	Amela (unpigmented)
Incidence *(Number/%)*	29 (8.0 %)	94 (26.0 %)
Latency *(days)*	159 ± 22	163 ± 17
Growth *(mm^3/day)*	12 ± 8	98 ± 19



Mela

Slow progressing



Amela

Aggressive

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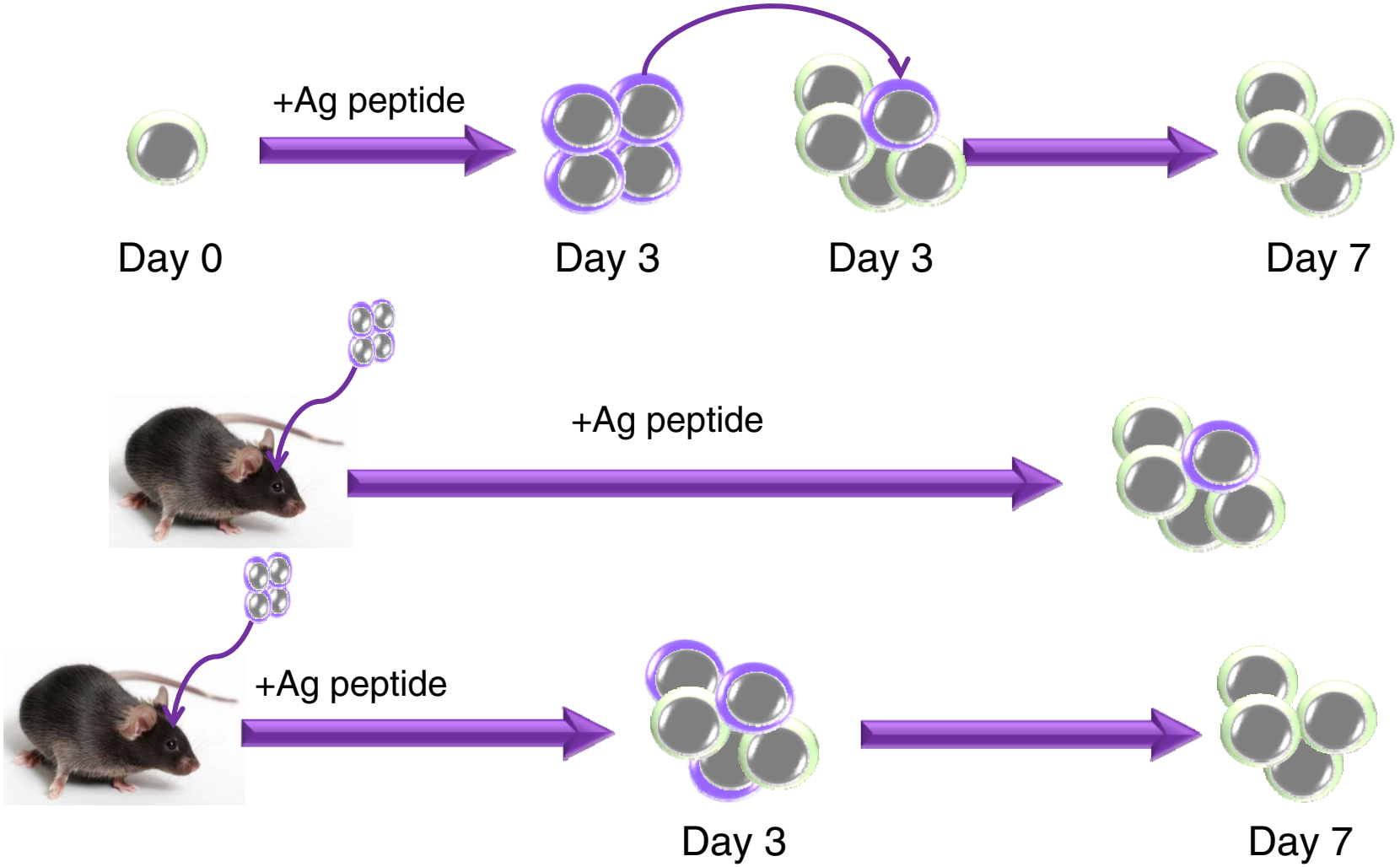
Huijbers et al.2006; Soudja et al. 2010

Effector function



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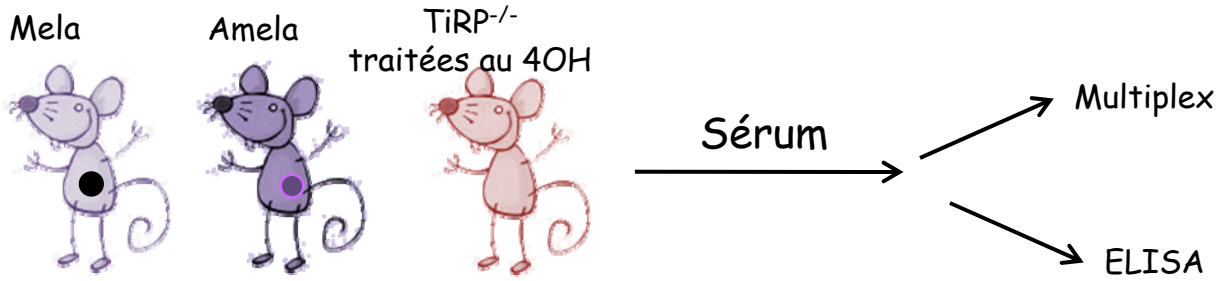
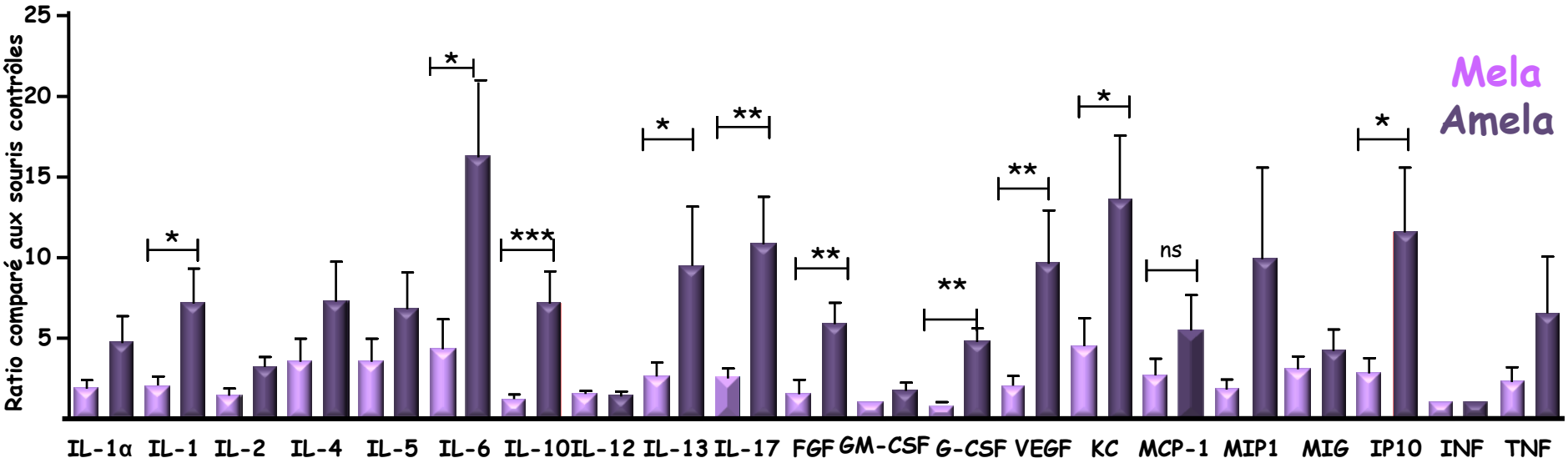
Les tumeurs Amela sont associées à l' inflammation





M'homa Soudja S. Wehbe M. Mas A. 2009

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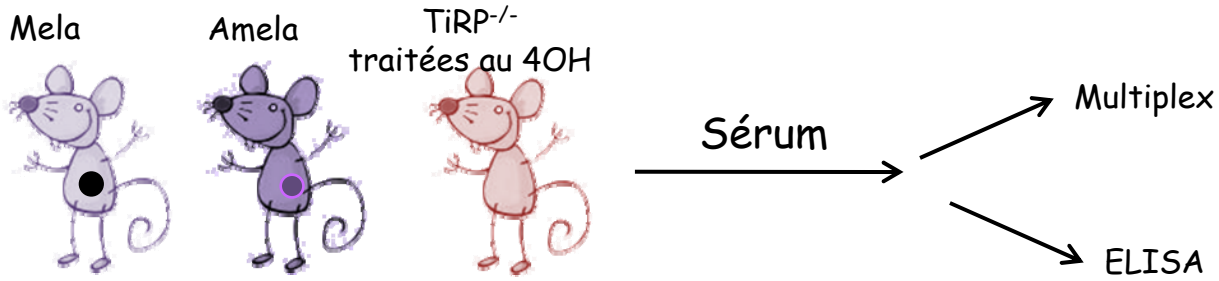

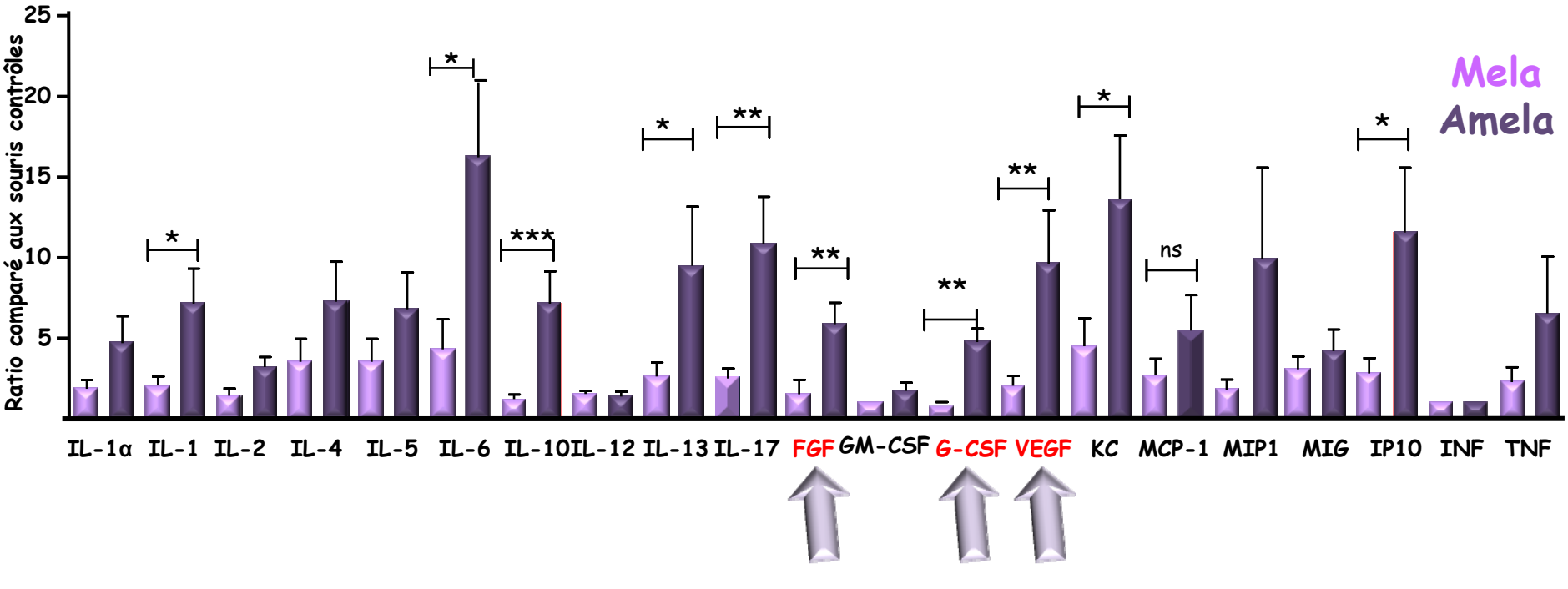

M'homa Soudja S. Wehbe M. Mas A. 2009

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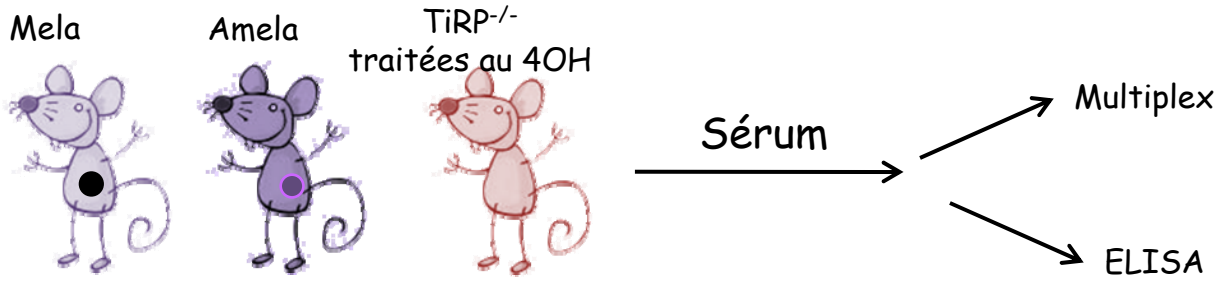

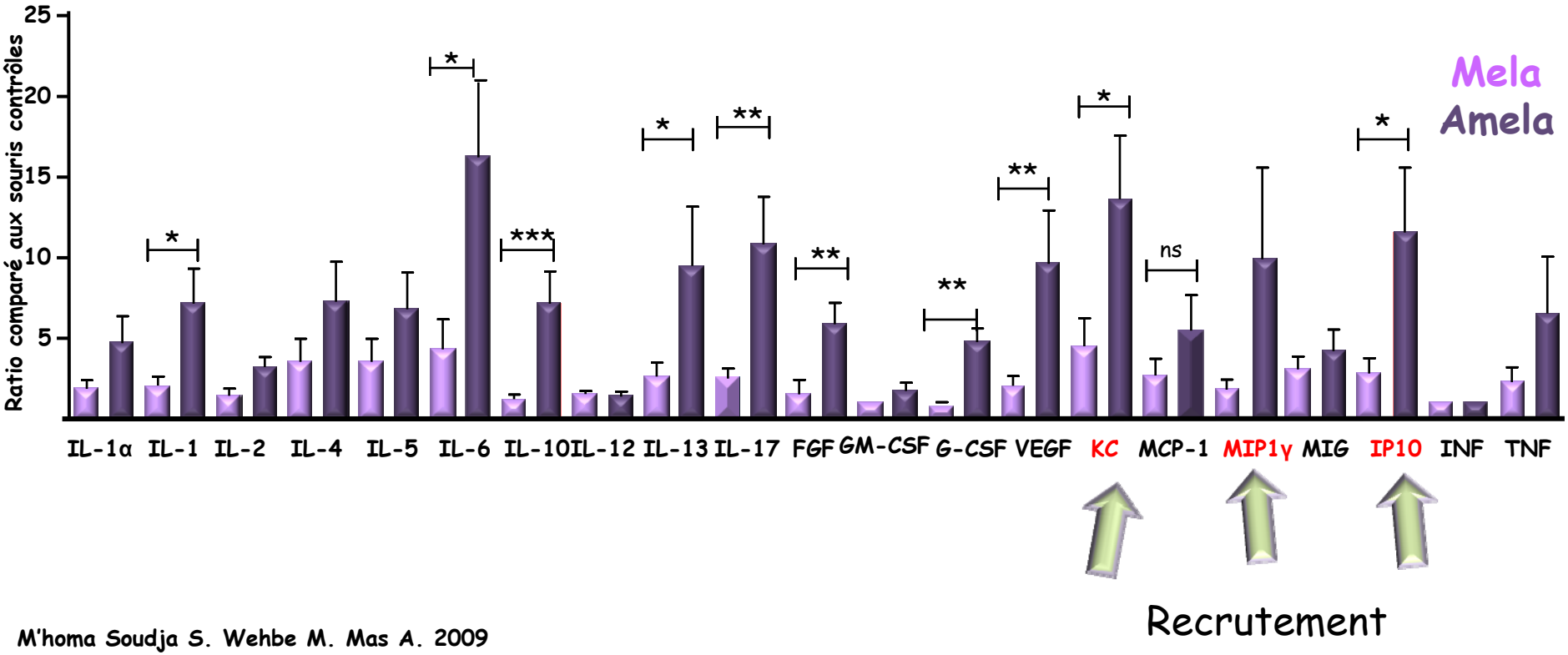

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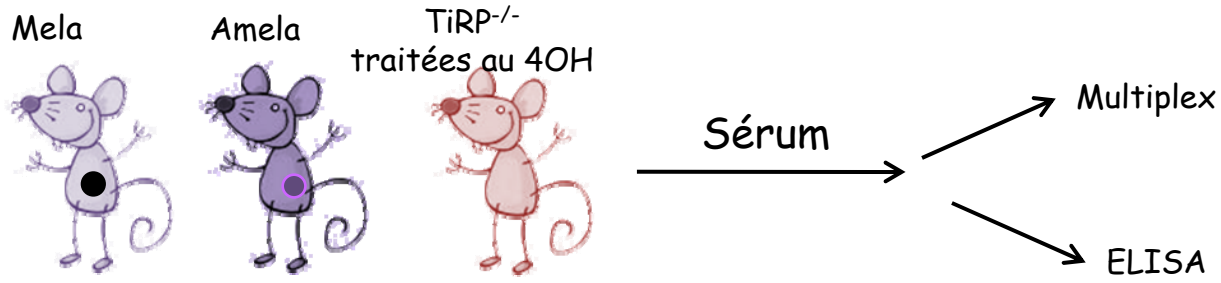
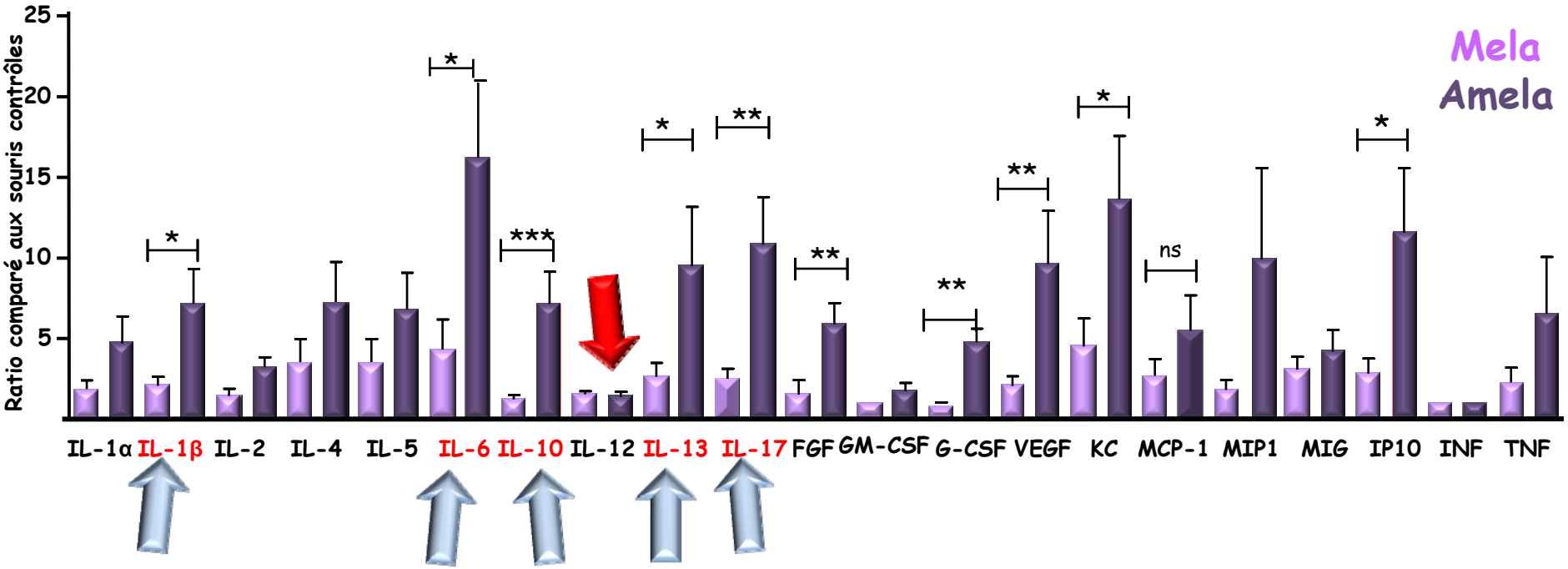
Les tumeurs Amela sont associées à l' inflammation





Polarisation de la réponse immunitaire (Th2/Th17)

M'homa Soudja S. Wehbe M. Mas A. 2009

Grégory Verdeil

Active STAT5 promotes long-lived cytotoxic CD8 T cells that induce regression of autochthonous mouse melanoma.

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No relationships to disclose