



Immune landscape of rhabdoid tumors: non-genetic mechanisms of tumor immunogenicity

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Tumor Immune Microenvironment: A Holistic Approach

Workshop Schedule

Session III: Pediatric Tumors

21st April 2022, San Diego



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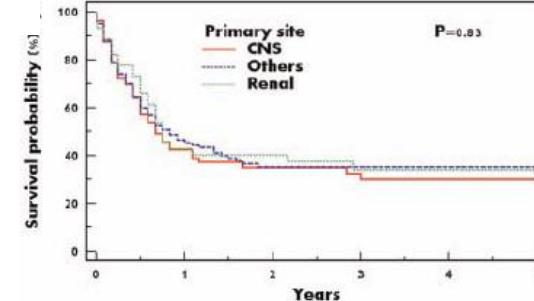
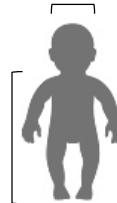
Name as typed: eliane piaggio

There will be discussion about the use of products for non-FDA approved indications in this presentations

Rhabdoid tumors (RTs)

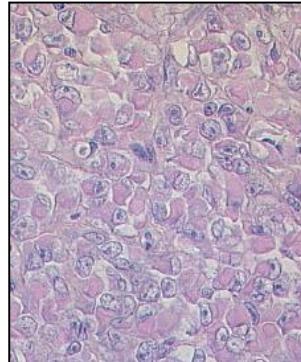
Atypical Teratoid/Rhabdoid tumor (AT/RT)

Extracranial rhabdoid tumors (ECRT)

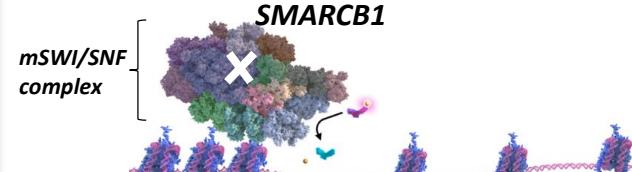
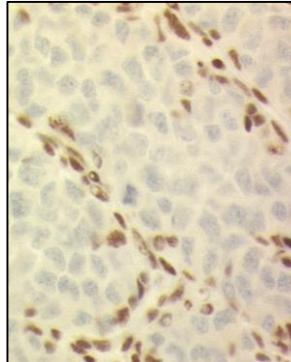


Sultan et al, Pediatr Blood Cancer 2010

HES



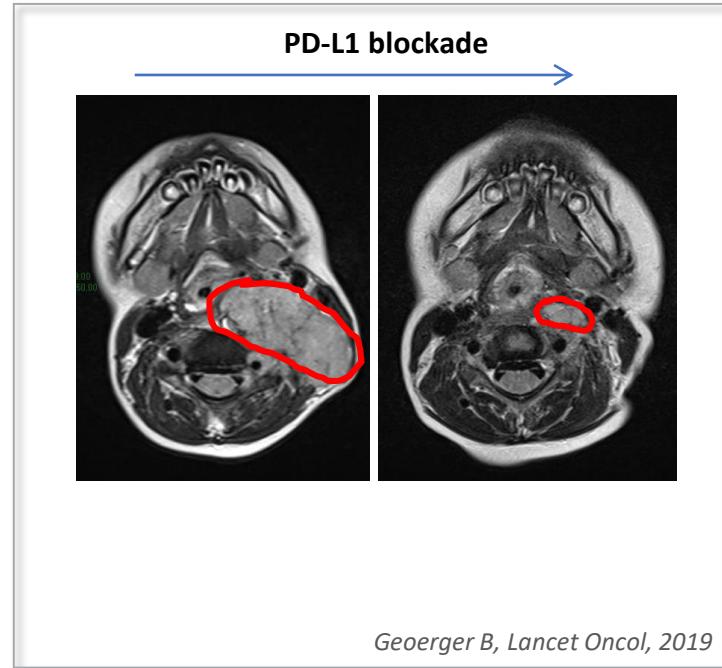
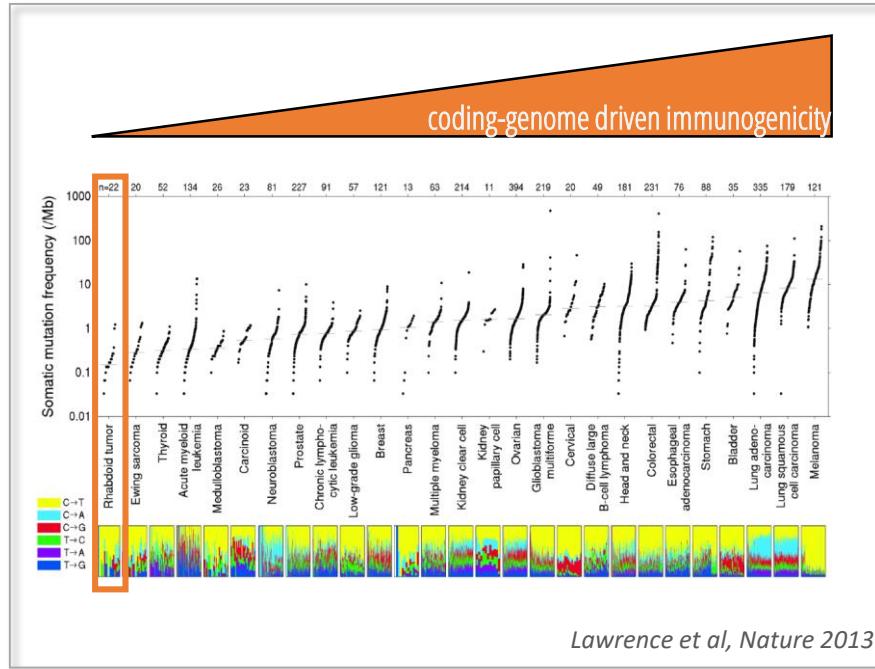
IHC SMARCB1



Verstege et al, Nature 1998
adapted from Kadoc et al, Biochemistry, 2016

Immunogenicity of tumor cells

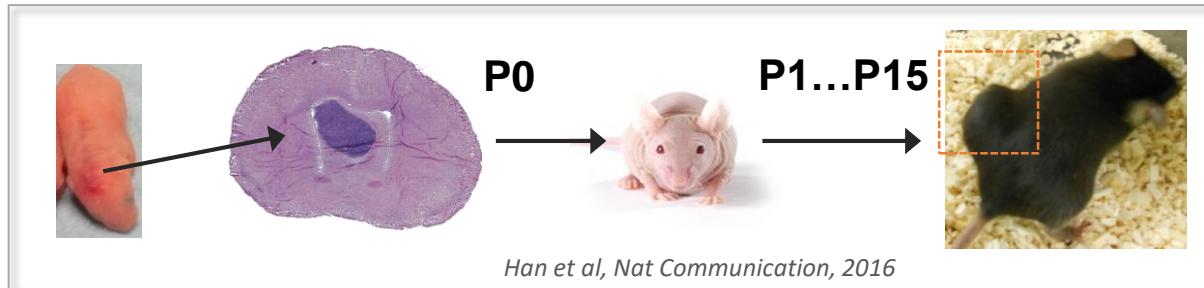
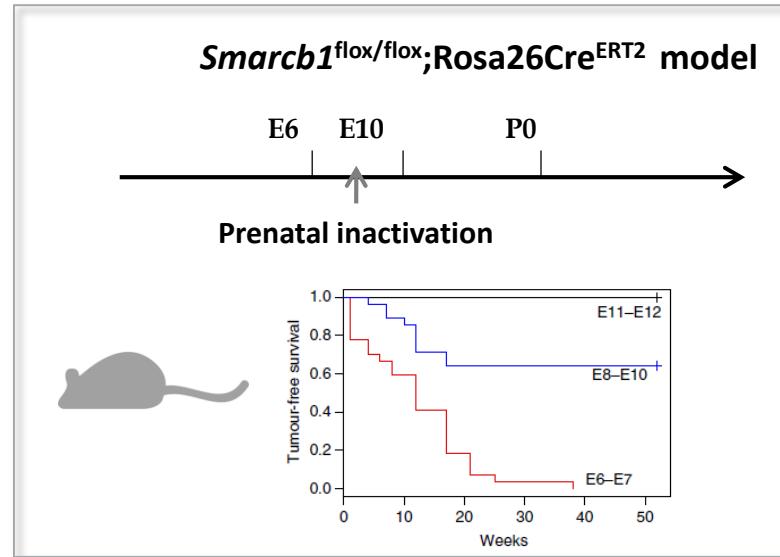
Current paradigm from adult cancers



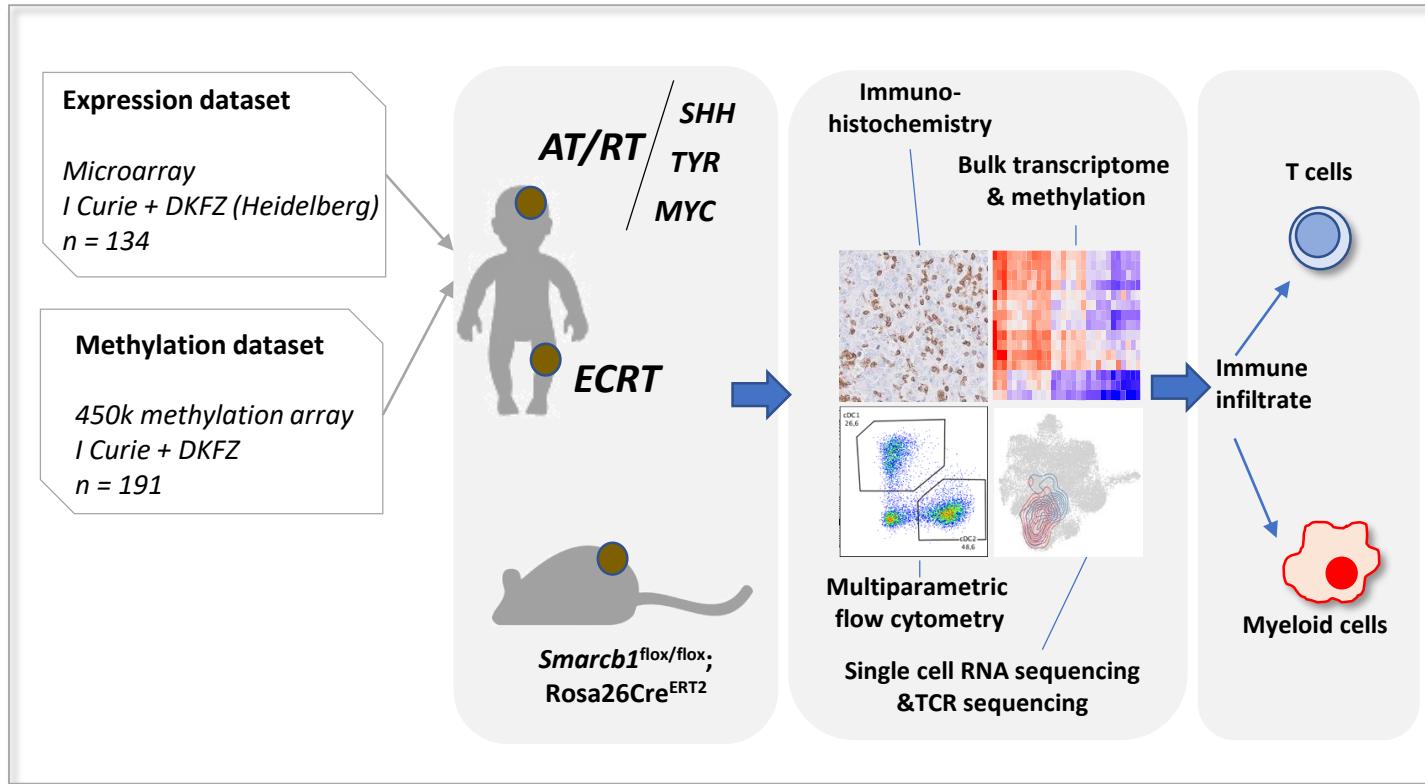
Georger B, Lancet Oncol, 2019

Can rhabdoid tumors be immunogenic despite their low mutational burden?

Cell(s) of origin of RTs: time-dependency of Smarcb1 inactivation in early embryo



Study design



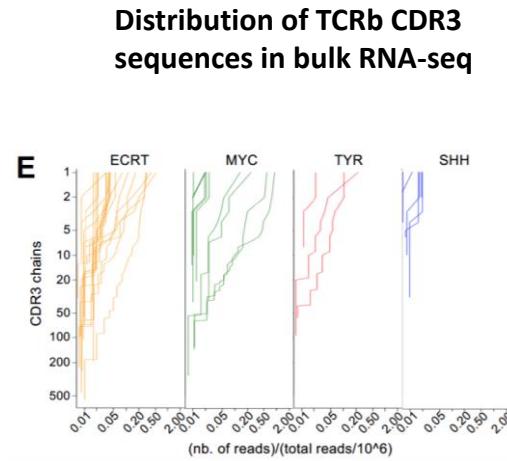
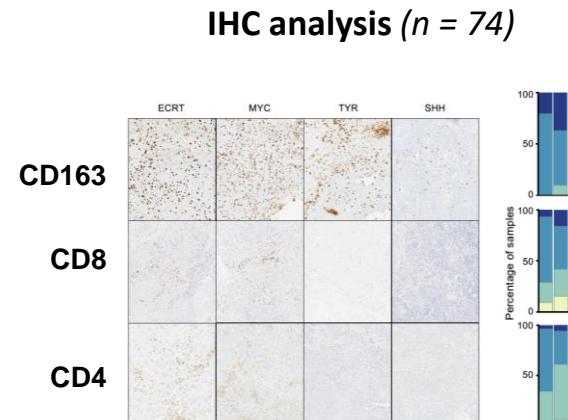
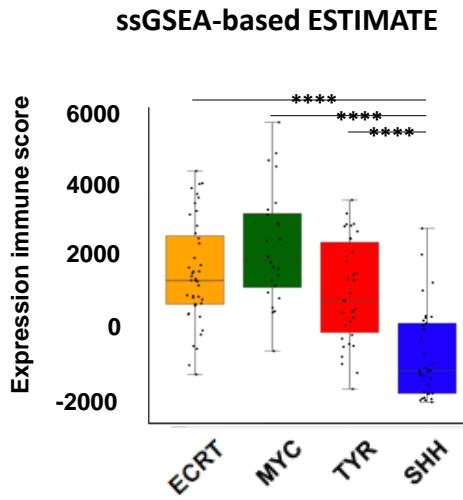
Leruste et al., Cancer Cell, 2019

Are rhabdoid tumors infiltrated by immune cells?

Analysis of Immune infiltration of human RT according to RT subgroups

RT are infiltrated by immune cells)

In silico analysis



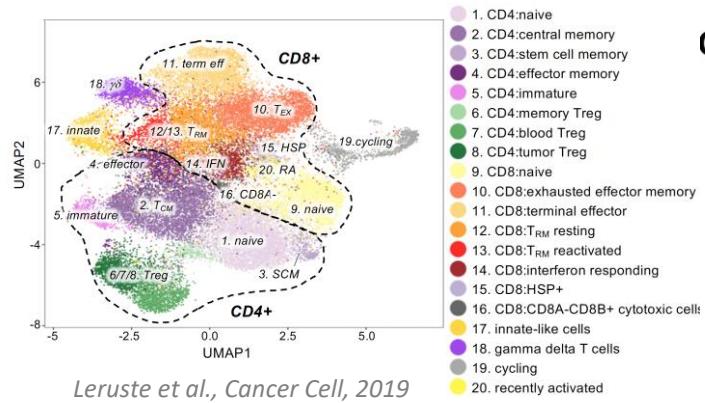
* RTs molecular subgroups are defined by transcriptomic and epigenetic characteristics

T cell heterogeneity and clonality characterization by scRNASeq

Human T cells

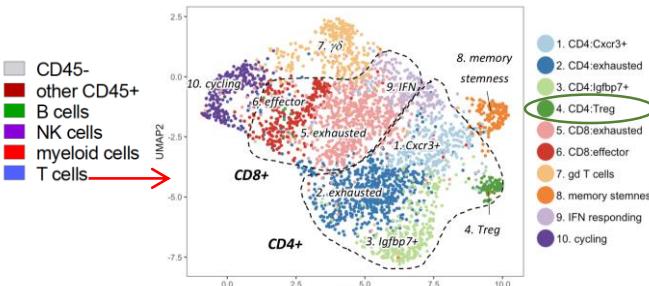
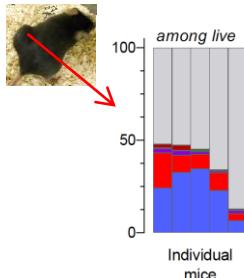
6 RT samples: blood + tumor

ID	Timepoint	Subtype	Tissue	T cells
INI254	diagnosis	SHH	Tumor	1,241
			PBMC	4,740
INI255	diagnosis	SHH	Tumor	1,273
			PBMC	3,215
INI256.1	diagnosis	MYC	Tumor	3,367
			PBMC	1,991
INI256.2	progression	MYC	Tumor	1,915
			PBMC	1,651
INI287	progression	MYC	Tumor	5,102
			PBMC	7,688
INI262	diagnosis	ECRT	Tumor	1,050
Total				33,233



Leruste et al., Cancer Cell, 2019

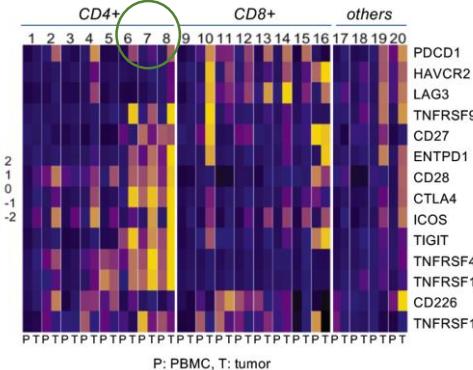
Mouse T cells



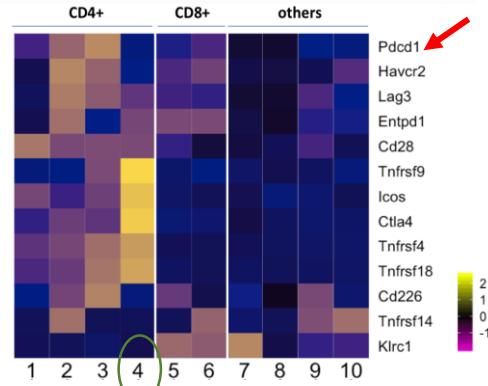
Unpublished data-don not post

immune checkpoint receptors

G

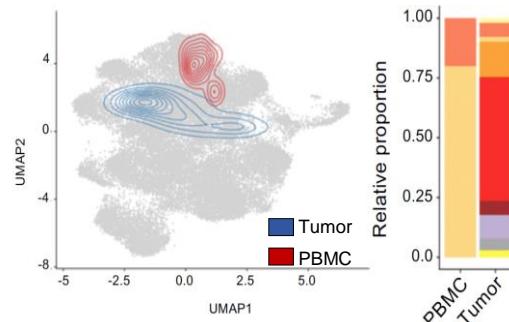
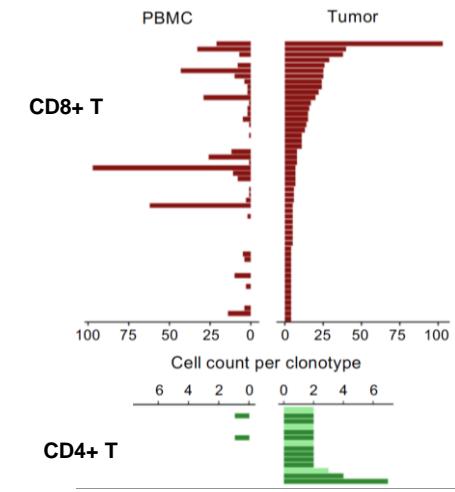
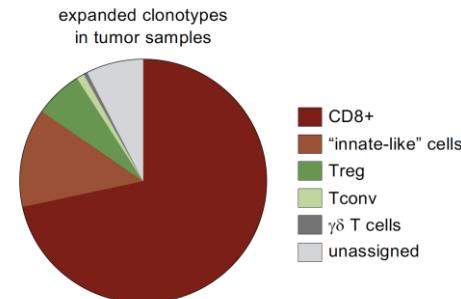
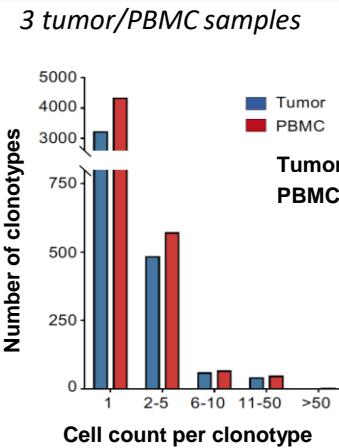


P: PBMC, T: tumor



Single-cell paired transcriptome and TCR

10X Genomics
Full length
TCR ($\alpha\beta$)



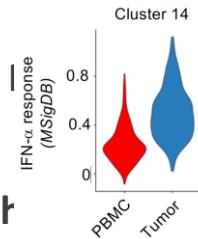
- 9. CD8:naive
- 10. CD8:exhausted effector memory
- 11. CD8:terminal effector
- 12. CD8:T_{RM} resting
- 13. CD8:T_{RM} reactivated
- 17. innate-like cells
- 19. cycling
- 20. recently activated

Tissue Resident and exhausted memory CD8+ T cells are highly expanded at the tumor site

Could the epigenetic dysregulations of RTs be a source of immunogenicity?

- Our scRNA-seq data identified IFN- α -responding T and myeloid cells in [REDACTED]
- IFN-regulated genes anticorrelate with SWI/SNF expression in TCGA cohort

Canadas et al., 2018

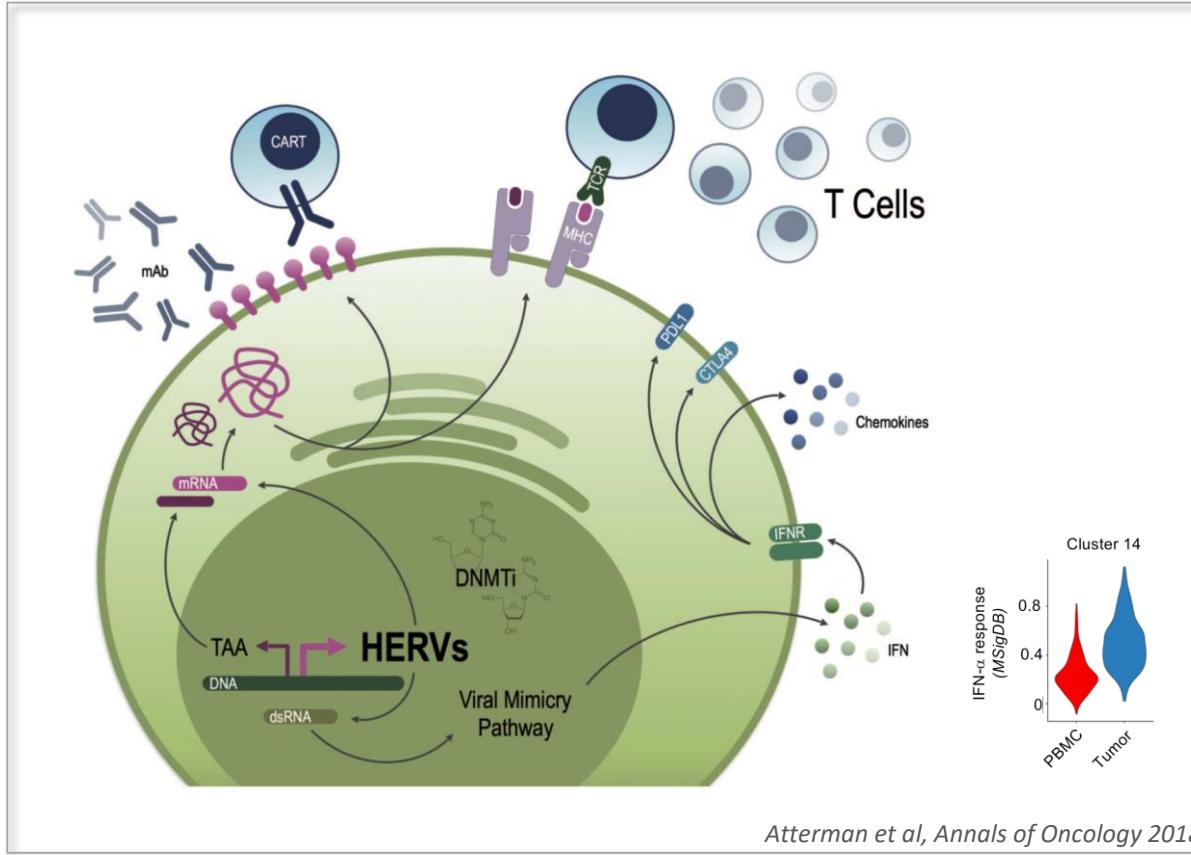


- Epigenetic changes modulate the expression of transposable elements, particularly ERVs, activating IFN-signaling in tumor cells

Chiappinelli et al., 2015; Roulois et al., 2015

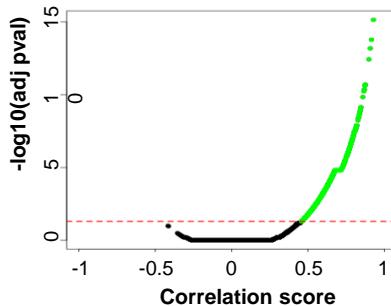


Endogenous retroviruses and anti-tumor immune response

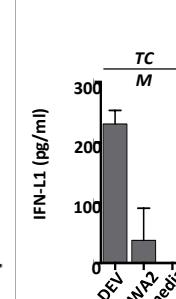
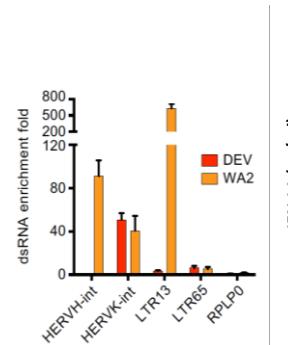
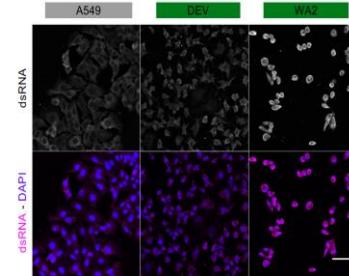


Endogenous retroviruses in RT samples: correlation with CYT score

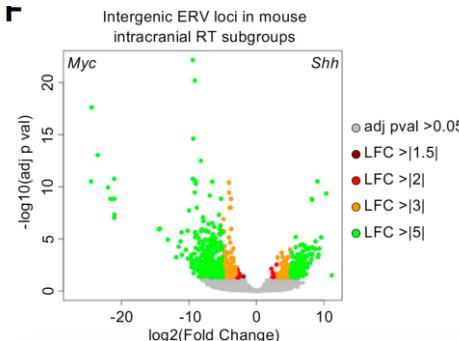
Correlation between CYT score and ERVs sense expression
mRNAseq, n=45



Human RT cell lines

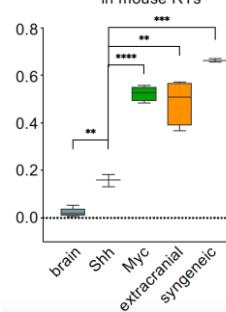


Mouse tumors



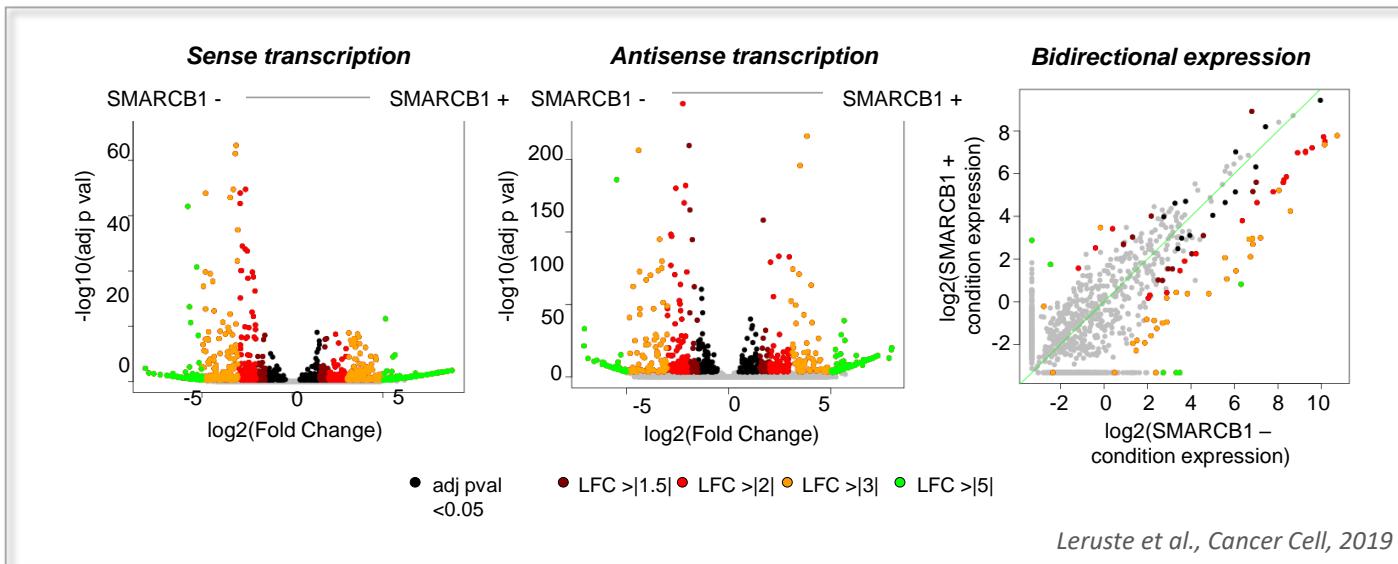
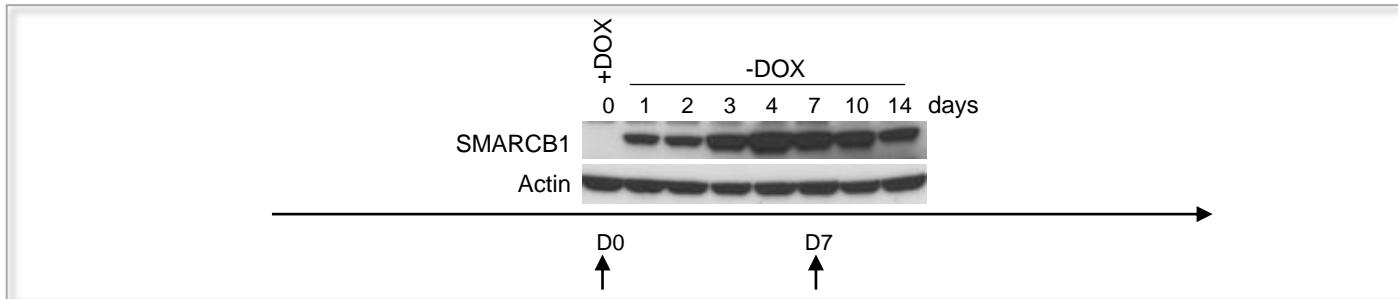
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IFN- α response in mouse RTs



dsRNA ERV expression (PAMPS?) could trigger IFN-signaling via dsRNA sensing pathways (PRR?)

ERV re-expression in RTs is dependent on SMARCB1 deficiency



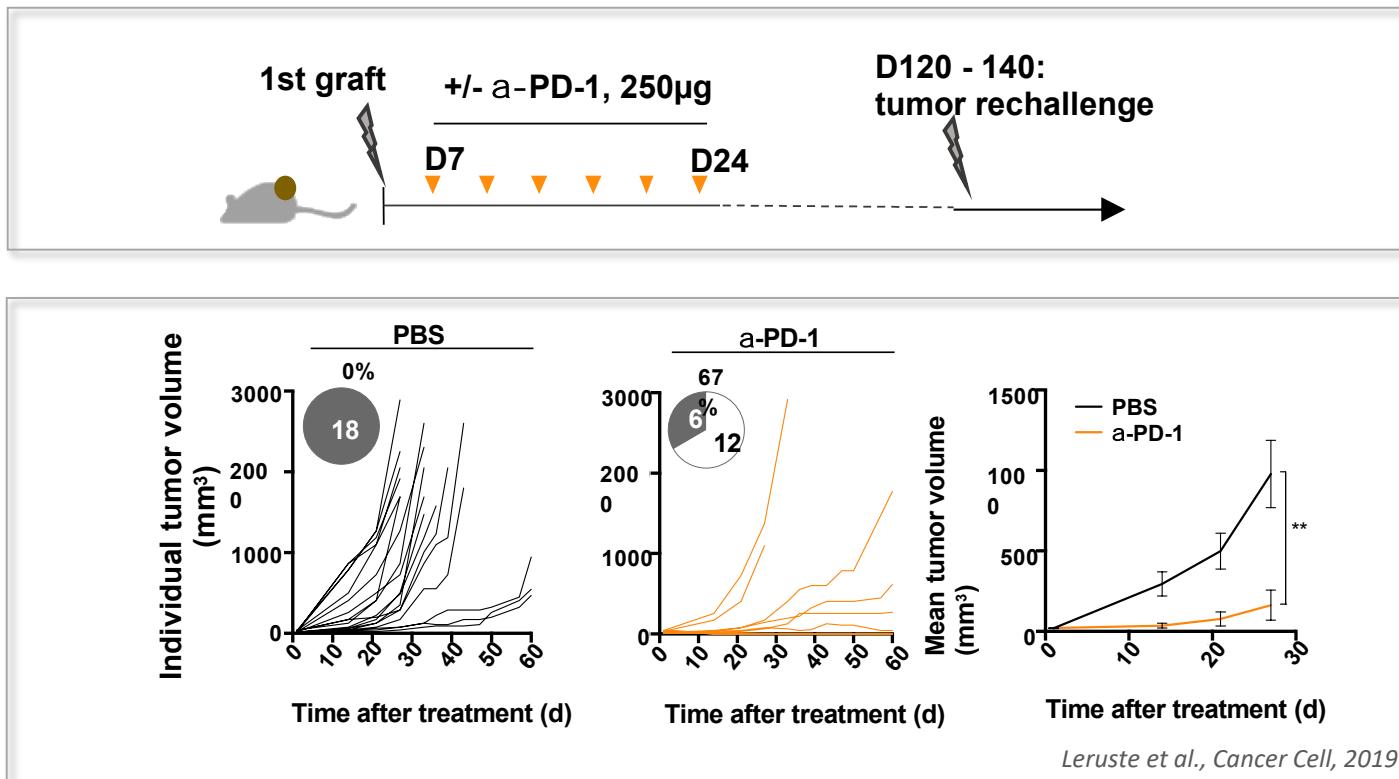
Is targeting of the immune infiltrate of clinical utility for RTs?

Preclinical evaluation of immunotherapy in RTs:

Targeting T and myeloid cells



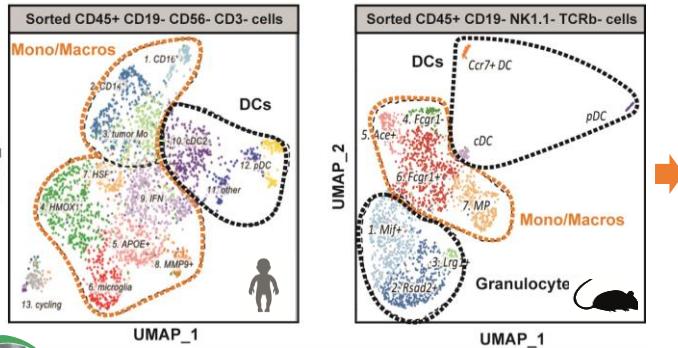
a-PD-1 blockade controls tumor growth



❖ How to improve the treatment and translate it to patients?

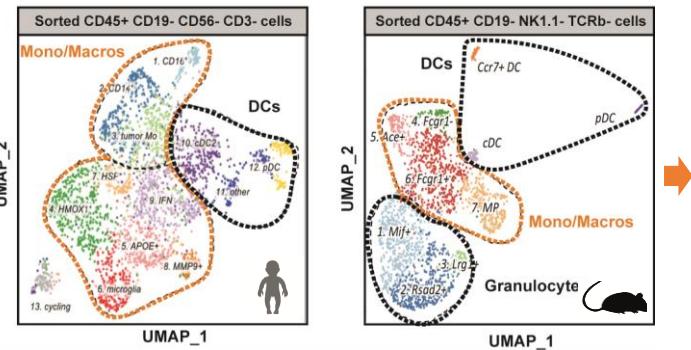
Targeting tumor-associated macrophages (TAMs) to enhance tumor immunotherapy

scRNASeq of myeloid cells

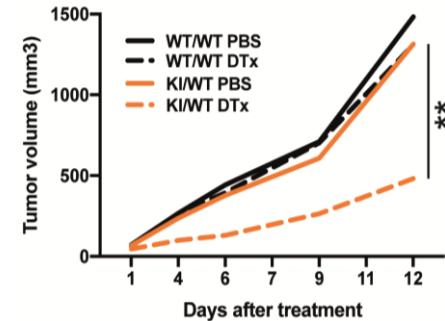


Targeting tumor-associated macrophages (TAMs) to enhance tumor immunotherapy

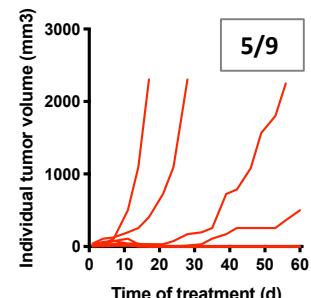
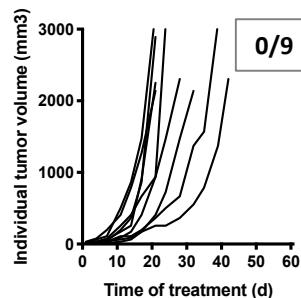
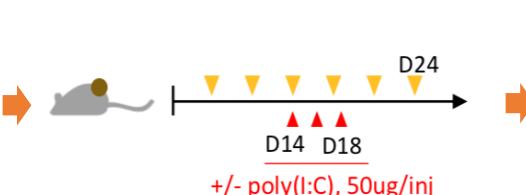
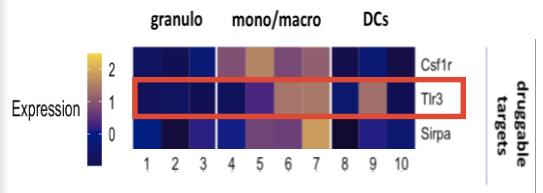
scRNASeq of myeloid cells



Depletion of macrophages?



Immune modulation of macrophages?

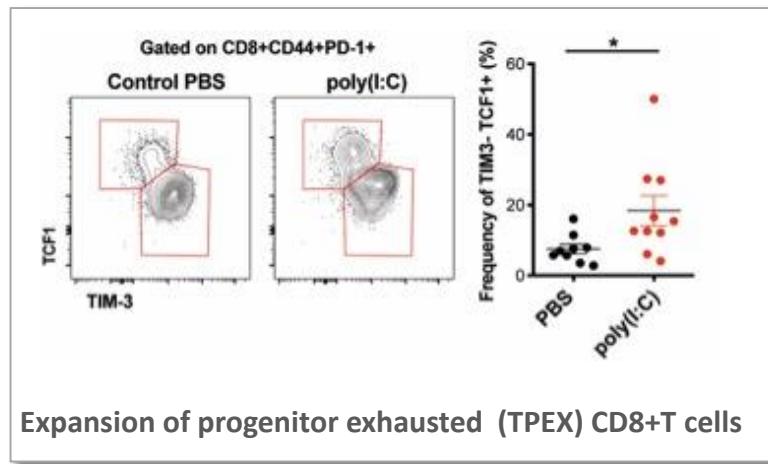
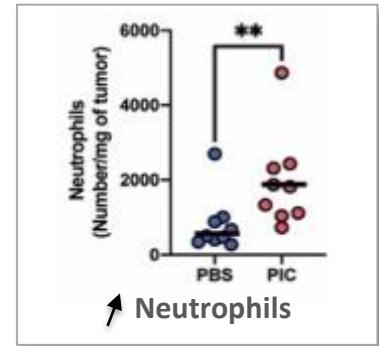
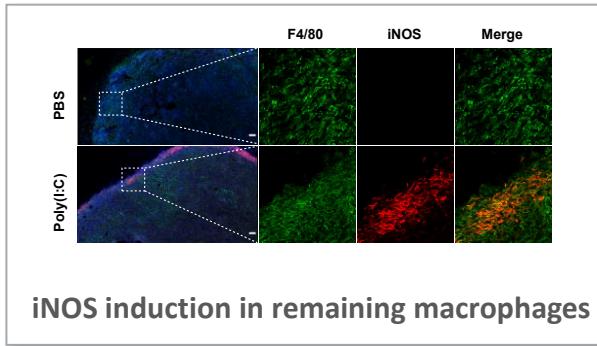
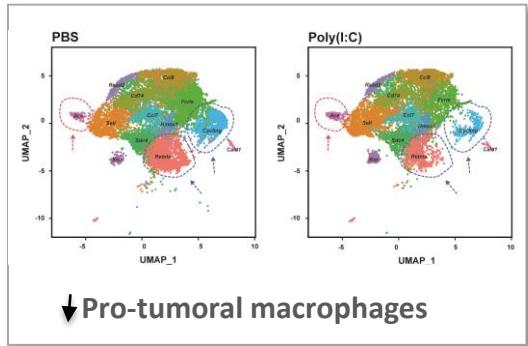


❖ Poly(I:C) induces partial tumor control

Unpublished data-don not post

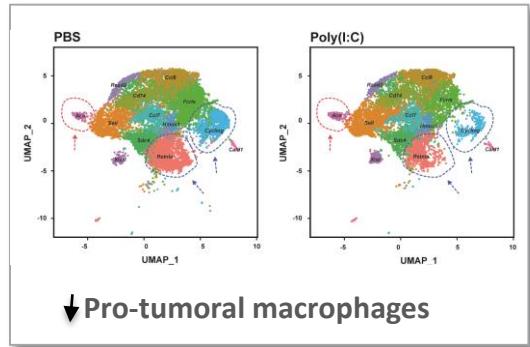


Poly (I:C) induces a global remodeling of the TME

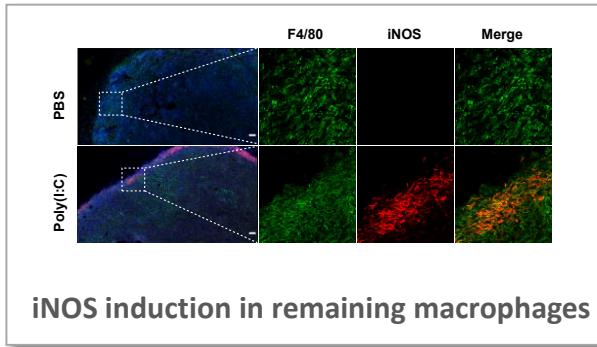


Expansion of progenitor exhausted (TPEX) CD8+T cells

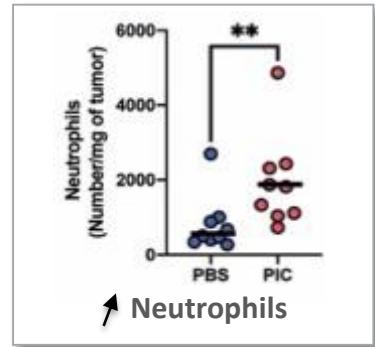
Poly (I:C) induces a global remodeling of the TME



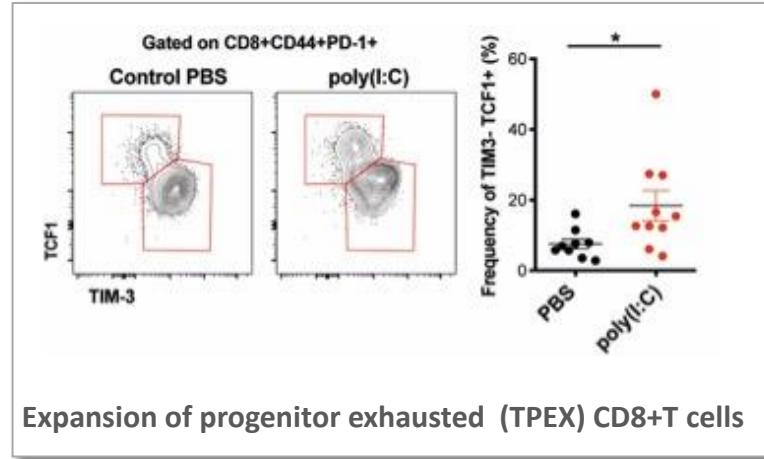
↓ Pro-tumoral macrophages



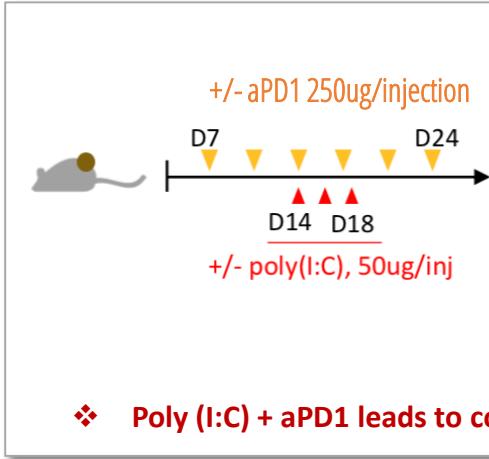
iNOS induction in remaining macrophages



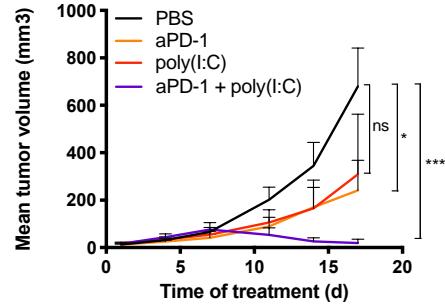
↑ Neutrophils



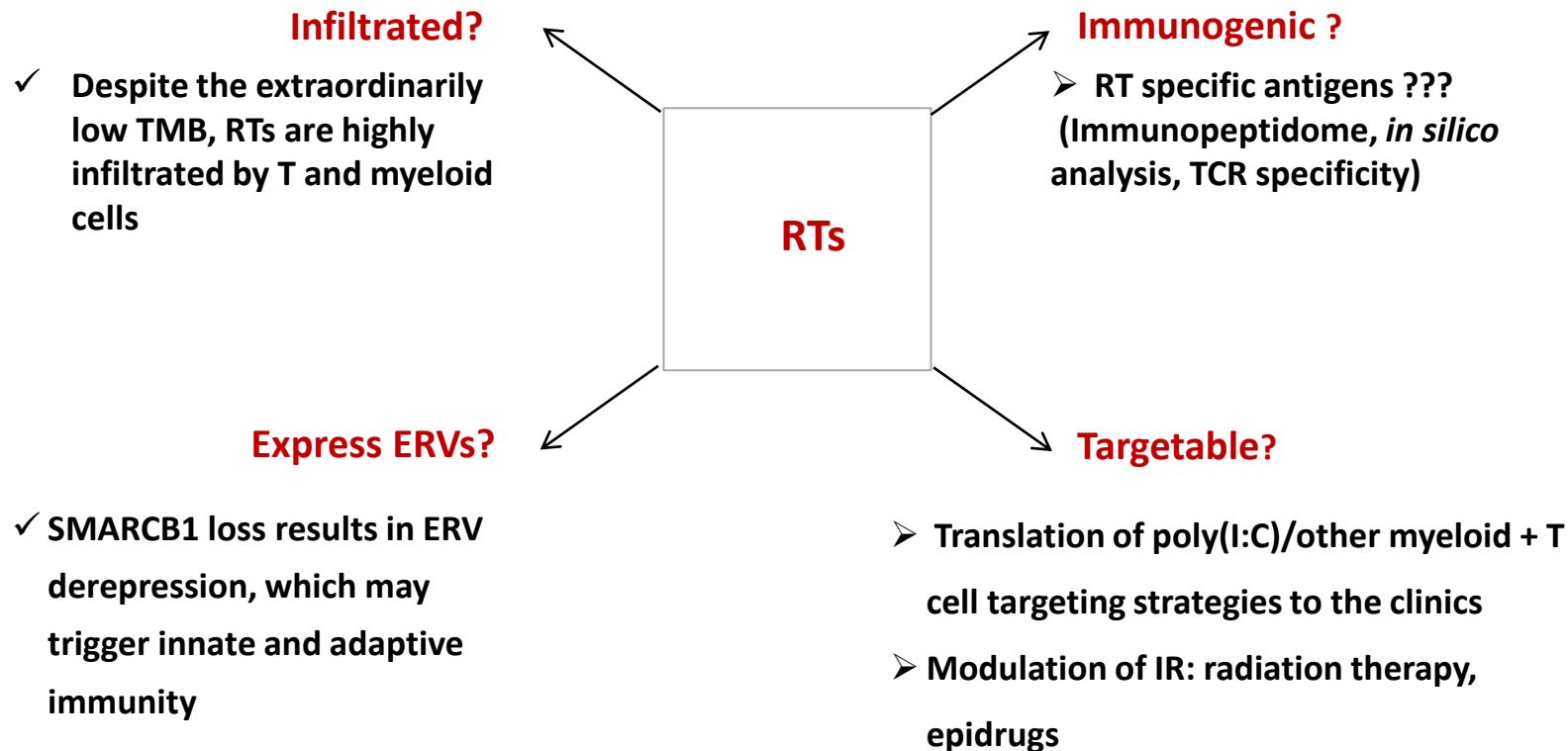
Expansion of progenitor exhausted (TPEX) CD8+T cells



❖ Poly (I:C) + aPD1 leads to complete tumor rejection



Take home messages & perspectives



Acknowledgments

Translm team:

- Eliane Piaggio
- Julie Helft
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- Céline Chauvin
- Irene Jimenez
- Mathieu Chicard
- Adrien Danzon...

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- Kevin Beccaria

NGS plateform

- Sylvain Bolande
- Mylène Bohec
- Sonia Lameiras



Janssen
Horizon

