

Optimización de la terapia celular: del laboratorio a la clínica

Alena Gros, PhD
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Disclosure

Consulting:

- SingulaBio (SAB)
- Achilles Therapeutics (SAB)
- InstilBio
- BioNTech (SAB)
- PactPharma

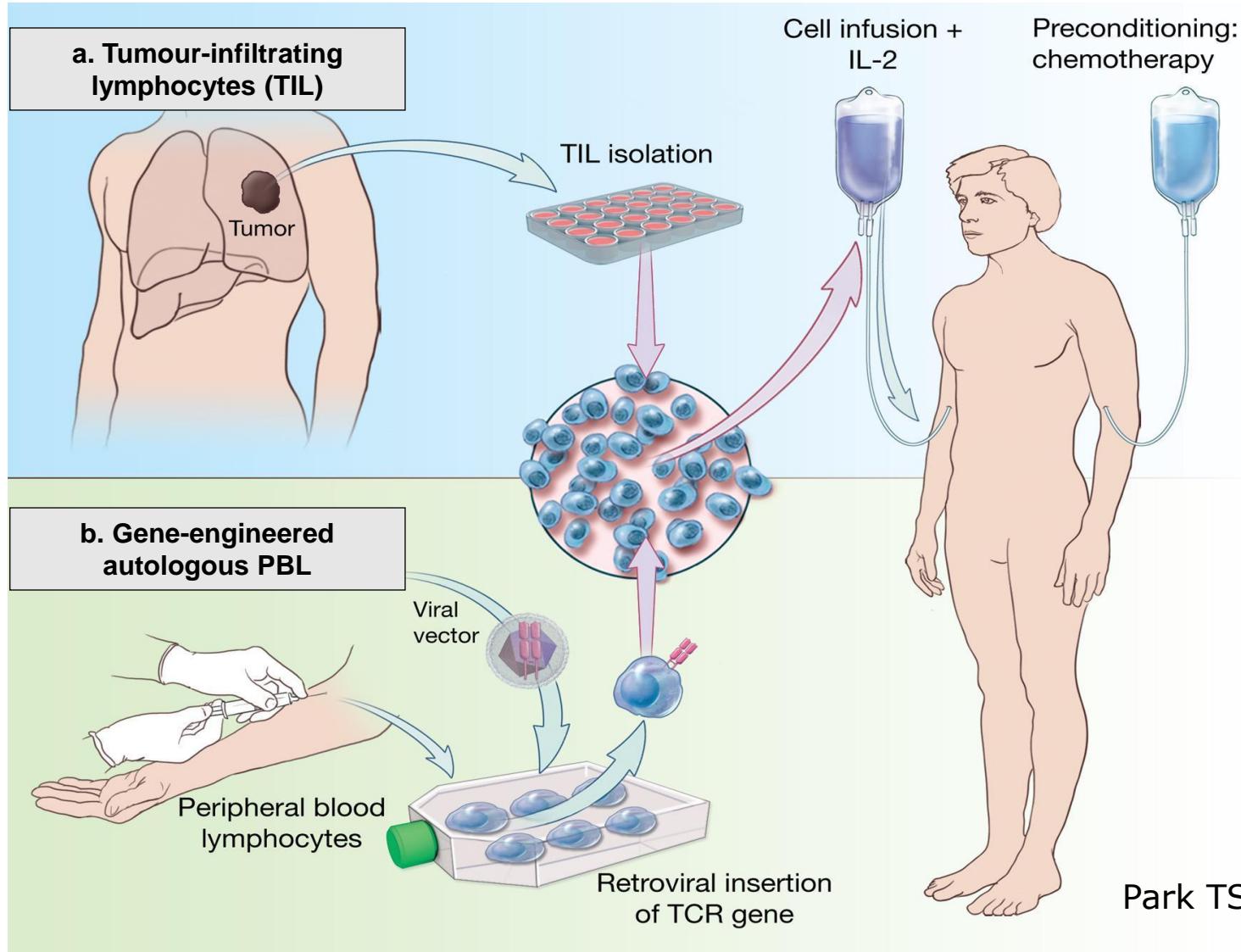
Funding:

- Novartis
- Roche
- Merck-Grant for Oncology Innovation

Patents:

Co-inventor in 4 patents describing methods for the isolation of tumor-reactive cells and TCRs from the tumor and blood

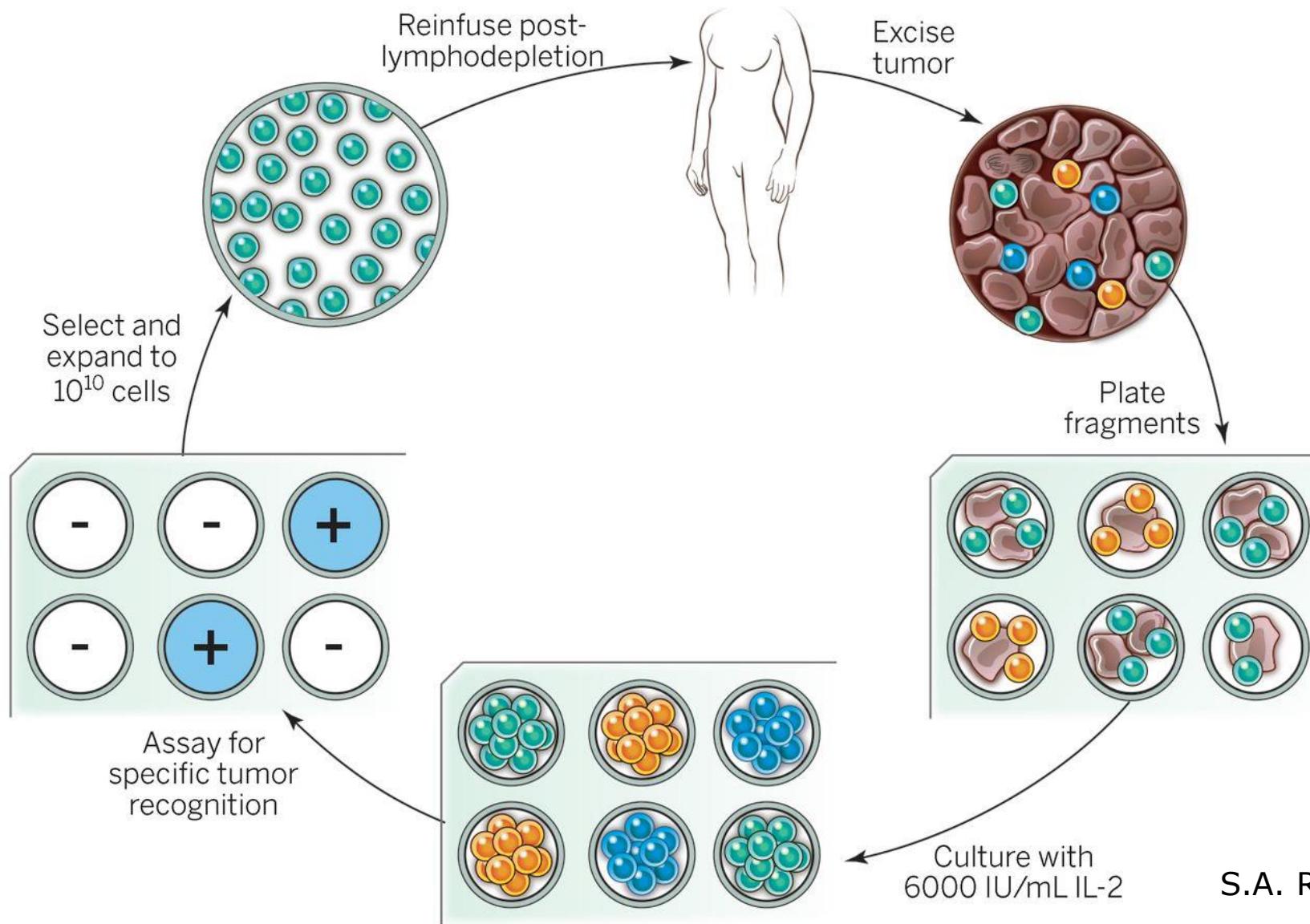
Adoptive T-cell therapies



Park TS, et al. Trends Biotechnol 2011

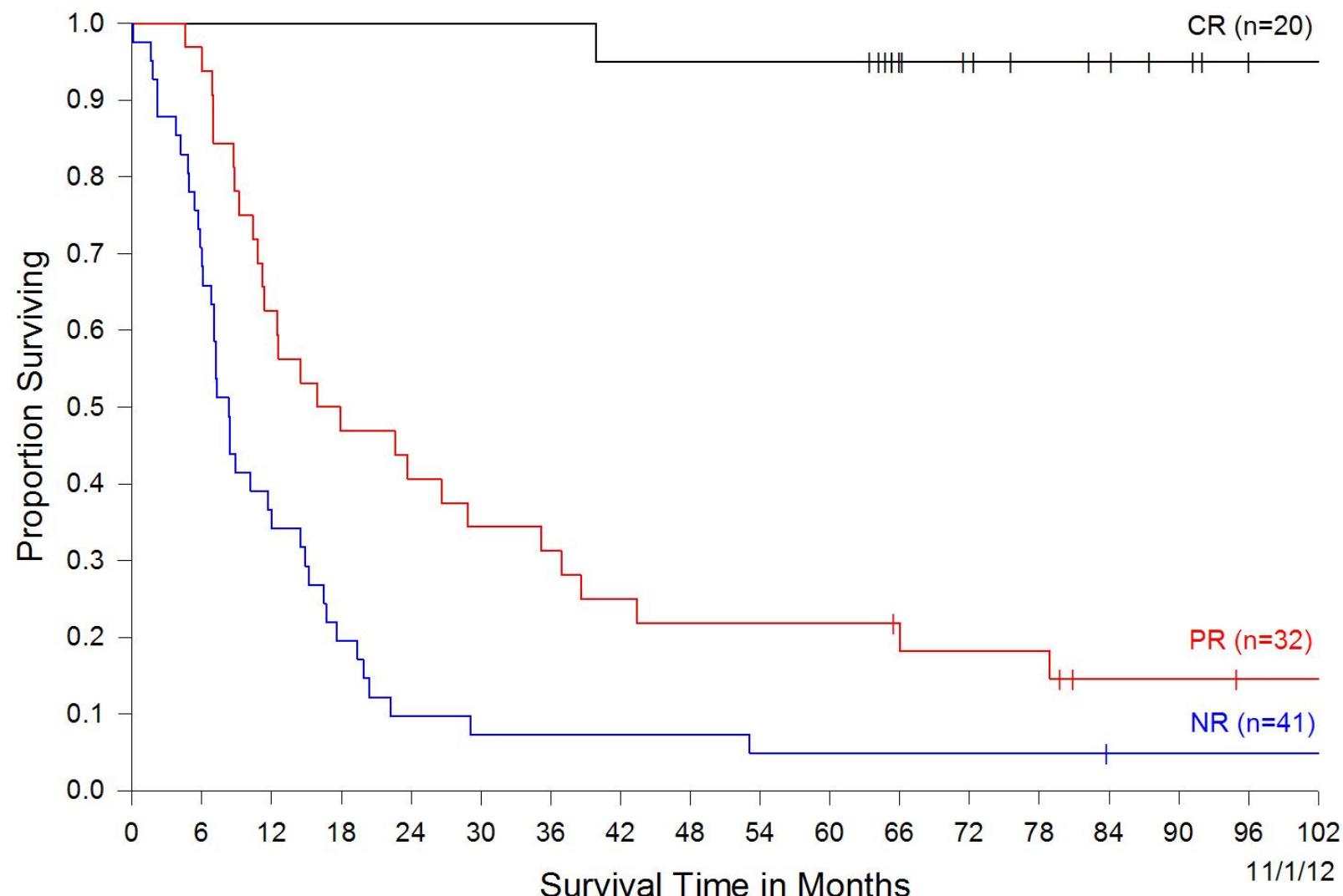
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TIL therapy leverages tumor-reactive lymphocytes that naturally infiltrate tumors

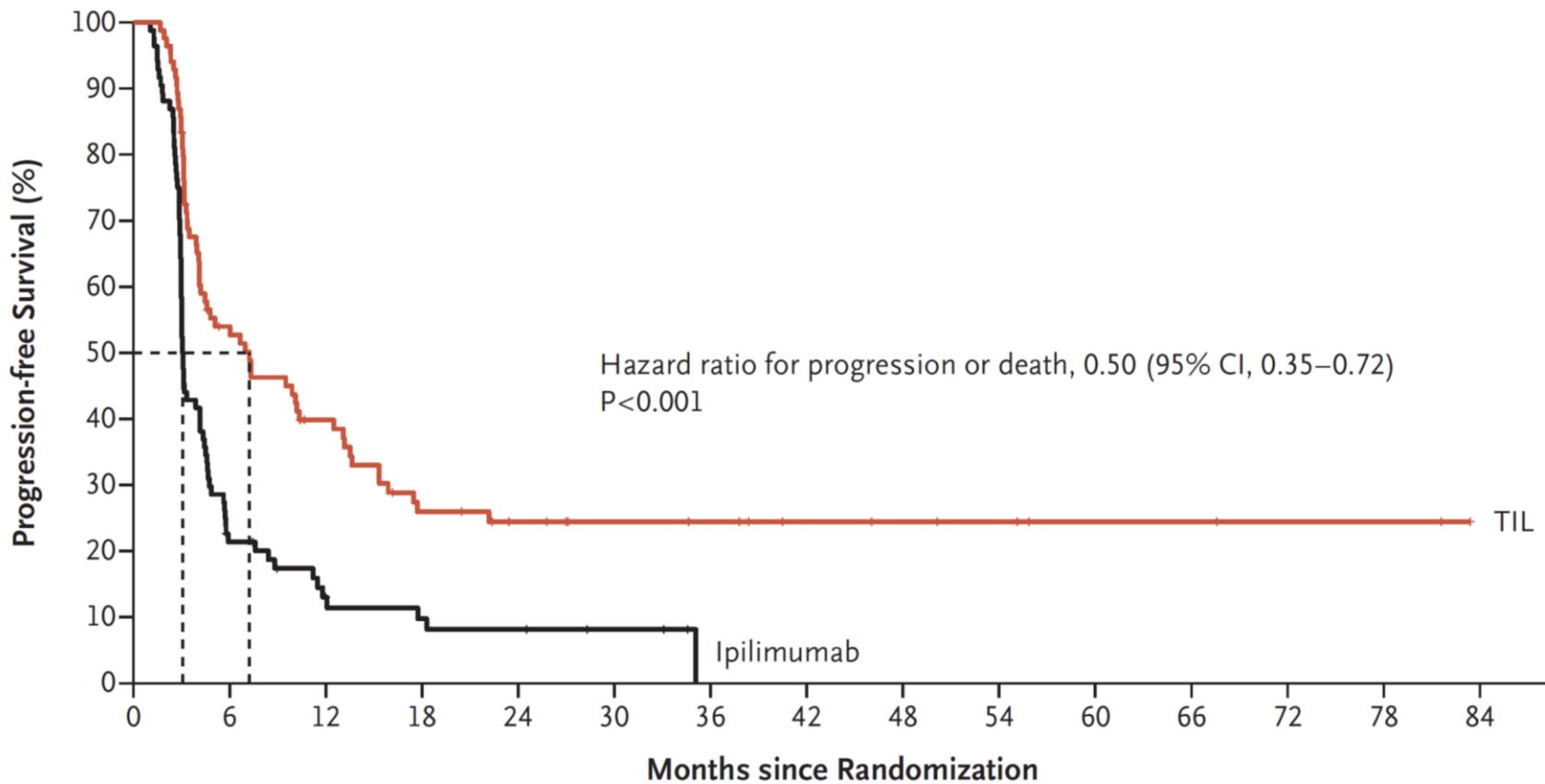


S.A. Rosenberg, Science 2015
'Hebron Institute of Oncology (VHIO)

TIL therapy can mediate tumor regression in patients with metastatic melanoma



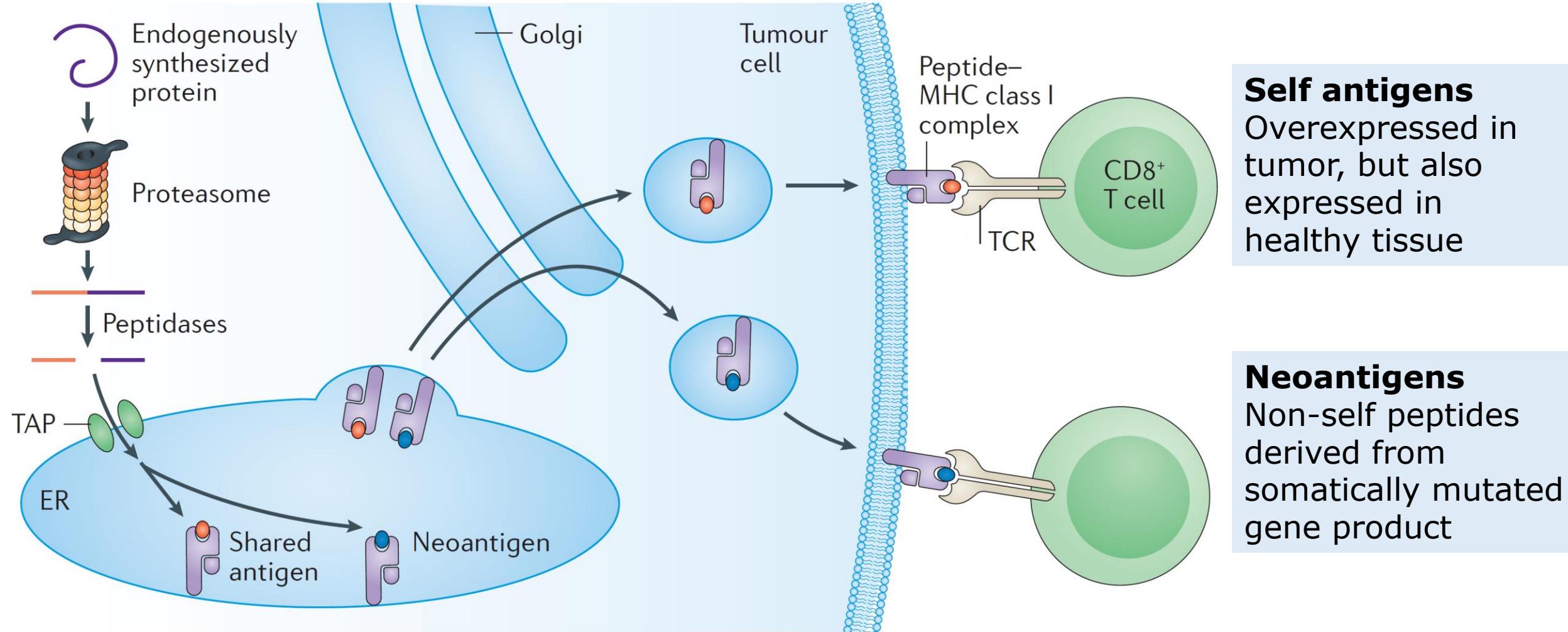
TIL therapy in second line treatment for metastatic melanoma



No. at Risk

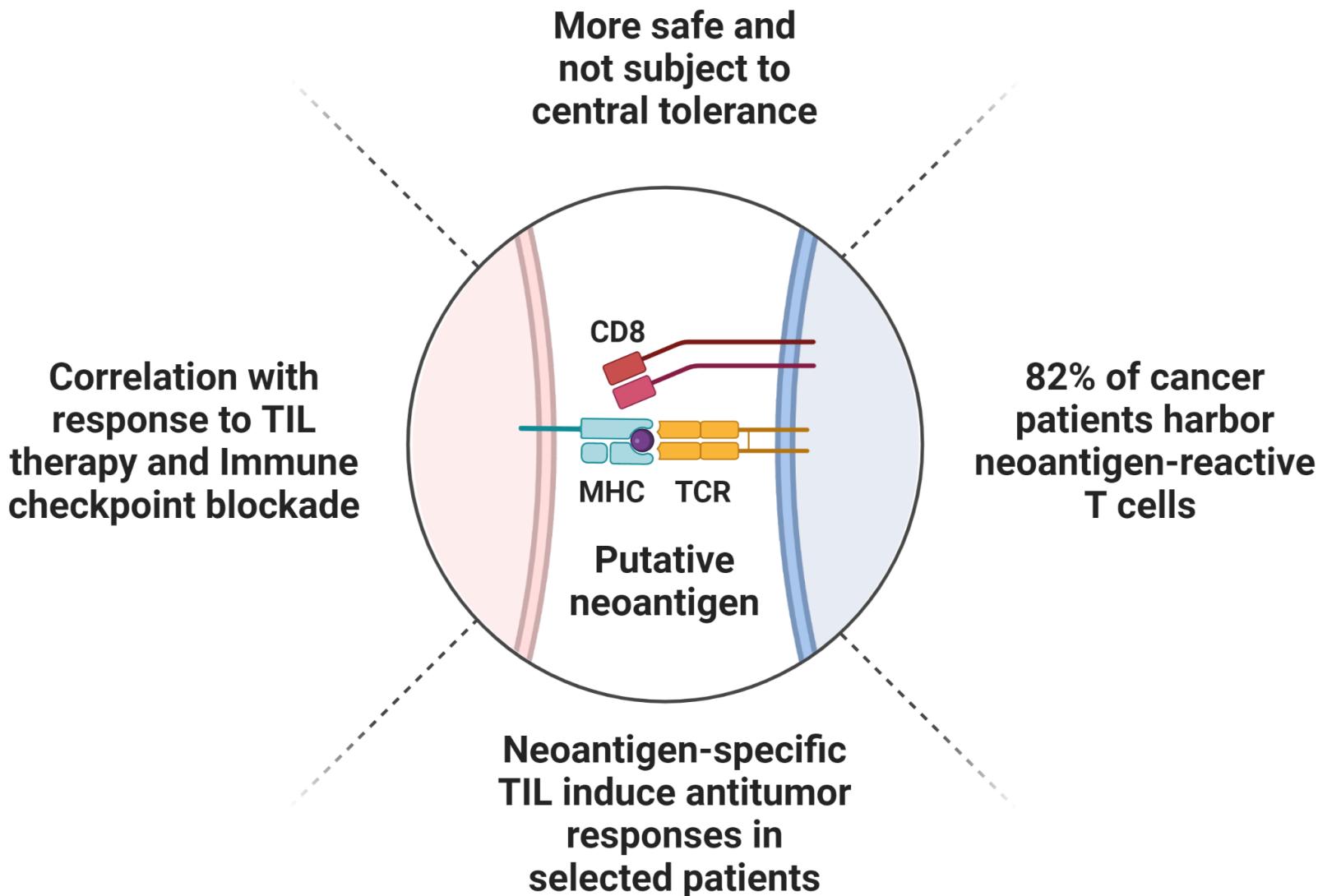
TIL	84	41	29	18	14	11	10	7	6	5	3	3	2	2	0
Ipilimumab	84	17	8	6	5	3	0	0	0	0	0	0	0	0	0

TIL can recognize self antigens and neoantigens

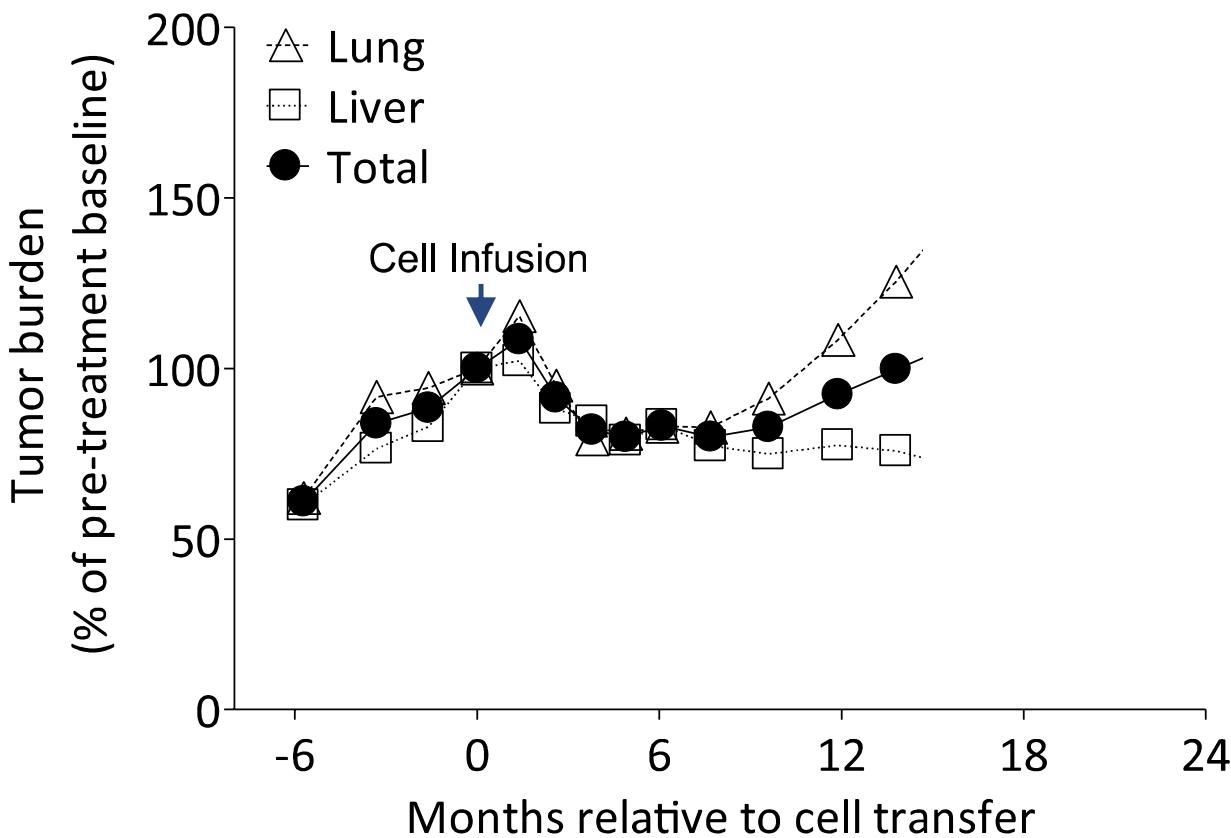


Adapted from M. Yarchoan et al. Nature Rev Cancer, 2017
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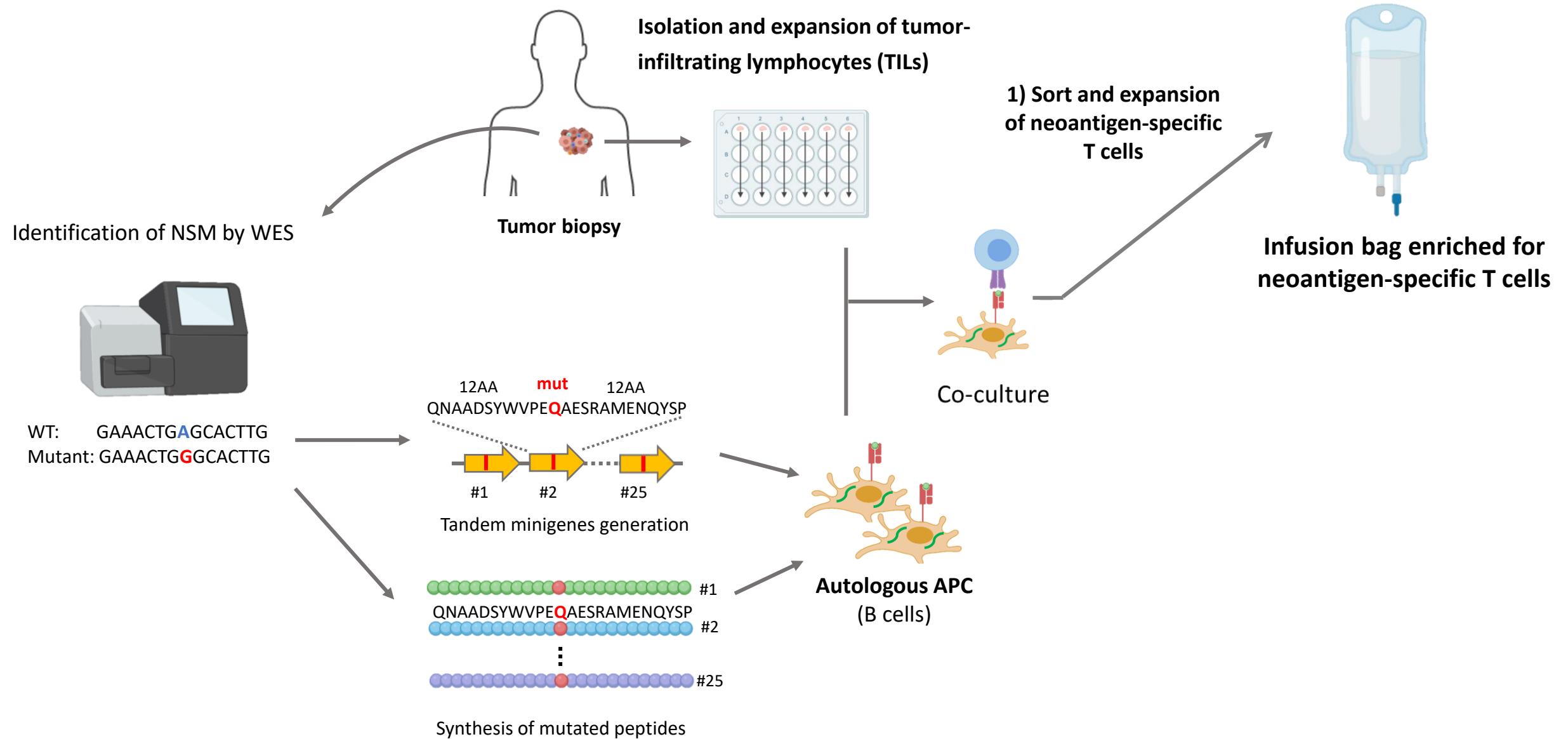
Neoantigens as optimal targets for cancer immunotherapy



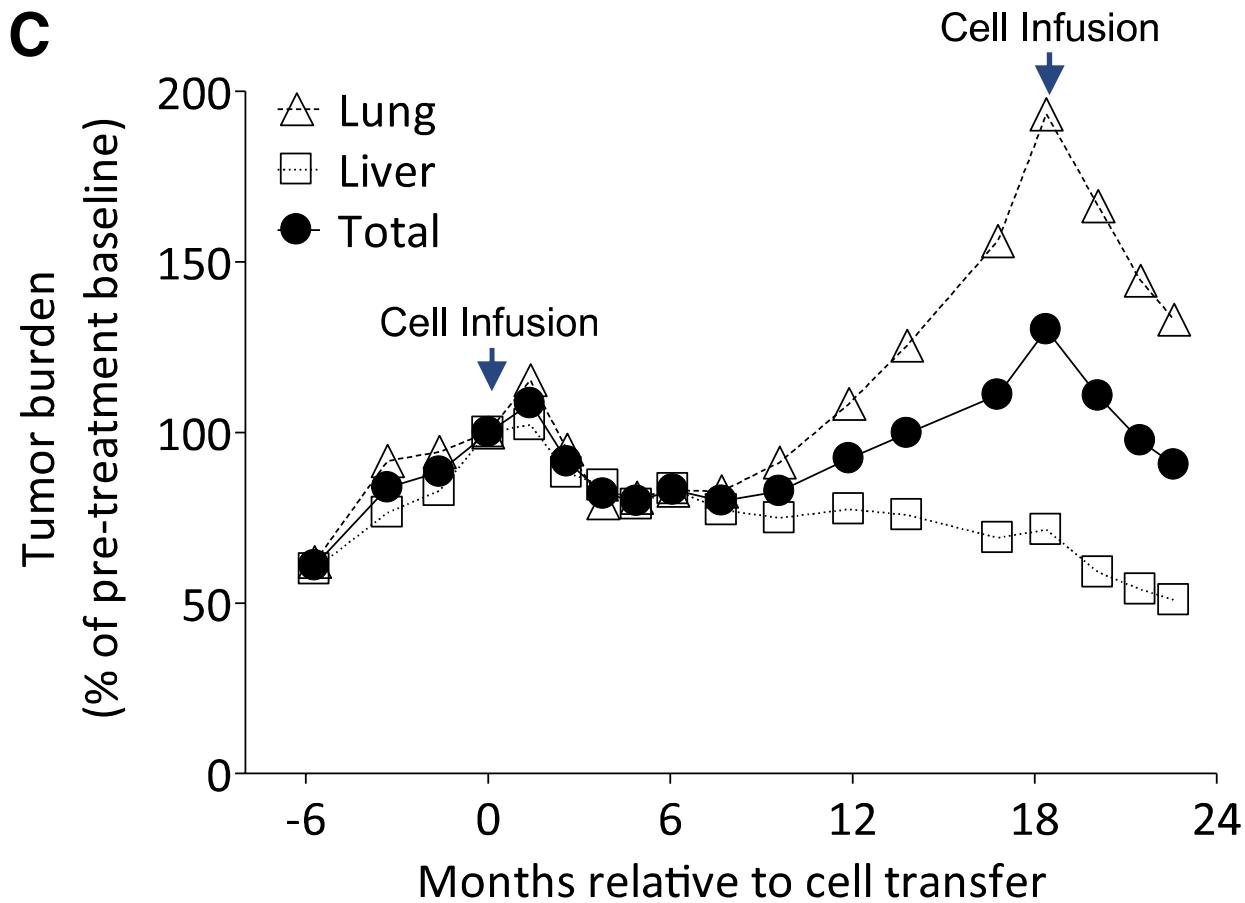
TIL therapy induced transient stabilization of tumor growth in patient with cholangiocarcinoma



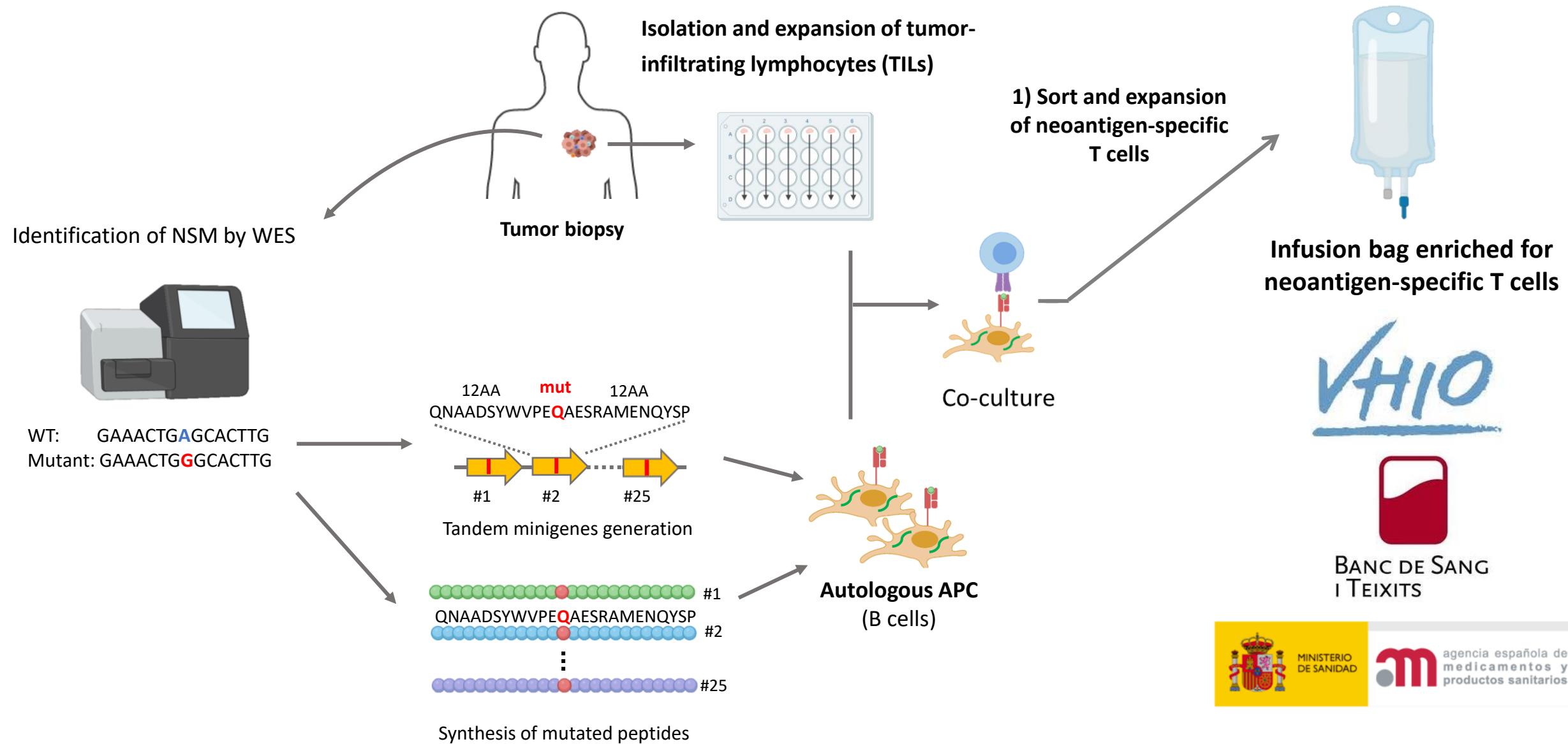
Systematic identification of neoantigen-reactive TILs



CD4+ TILs enriched for neoantigen recognition mediated durable tumor regression



Ongoing clinical trial at VHIo – recruiting patients

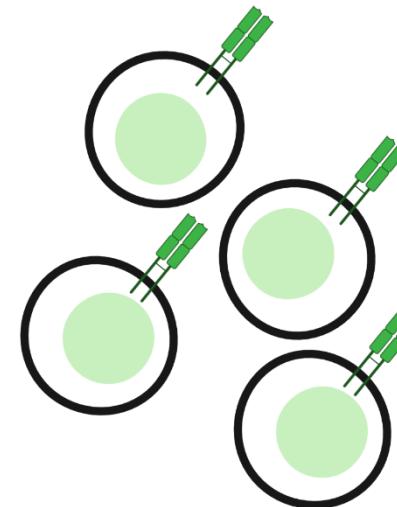


Towards selected tumor-reactive T-cell products

From serendipity...



... to generalizability

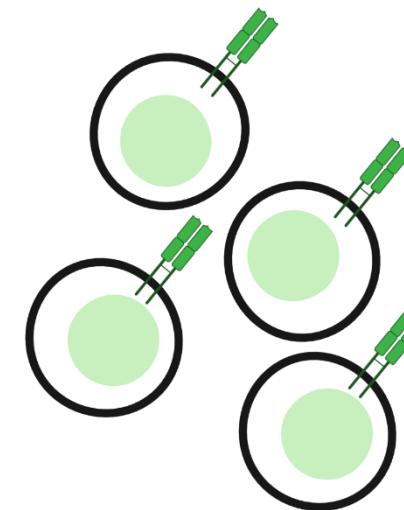


Towards selected tumor-reactive T-cell products

From serendipity...



... to generalizability



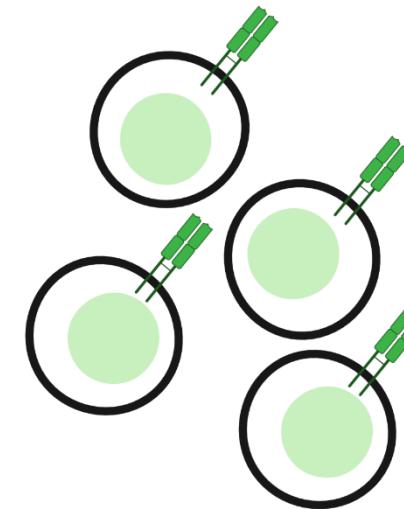
Discovery of biomarkers expressed on
tumor-reactive TIL or PBL

Towards selected tumor-reactive T-cell products

From serendipity...

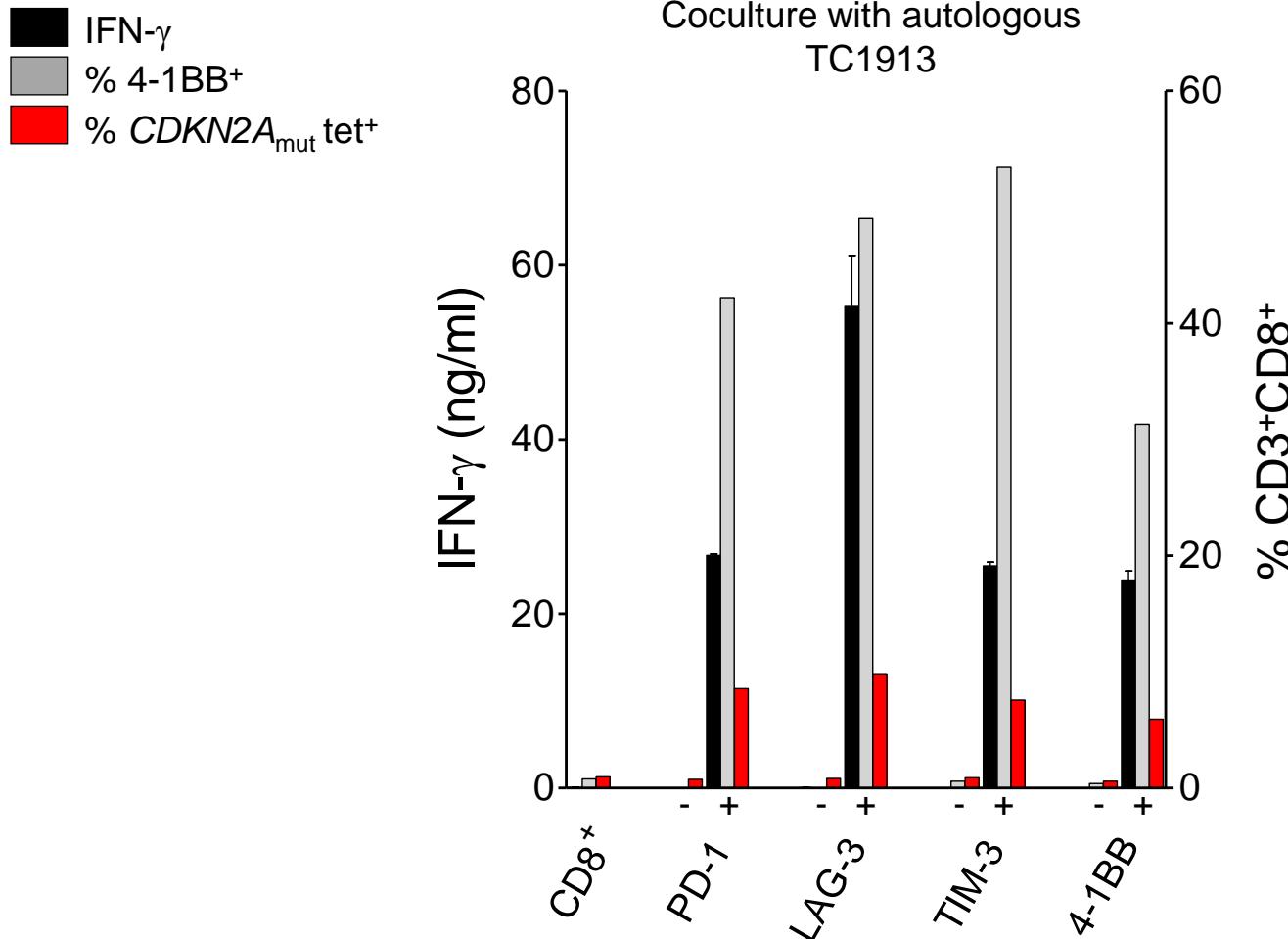


... to generalizability



Discovery of biomarkers expressed on
tumor-reactive TIL or PBL
PD-1, TIM-3, CD103+/CD39+...

CD8+ melanoma TIL co-express PD-1 LAG-3 and TIM-3 and cells expressing these receptors are enriched in tumor-reactive T cells



Biomarkers reported to enrich for tumor-reactive TIL

CD103+

PD-1+

TIM-3+, LAG-3+

4-1BB+

CD103+CD39+

CD39+

PD-1hi CD39+

CD8+ TIL

Webb JR et al. Gynecol.
Oncol 2010

Inozume T et al.
J. Immunotherapy 2010

Gros A et al.
J Clin Invest 2014

Ye Q et al.
Clin Cancer Res 2014

Duhen et al.
J. Immunotherapy 2010

Simoni Y et al.
Nature 2018

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CD4+ TIL

Not expressed

-

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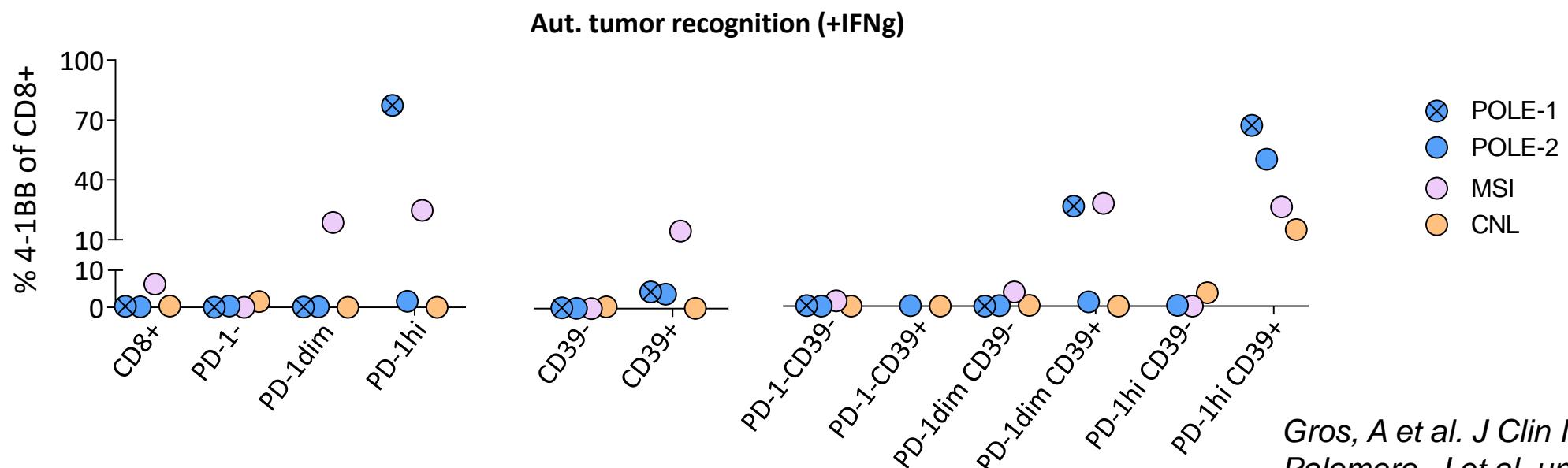
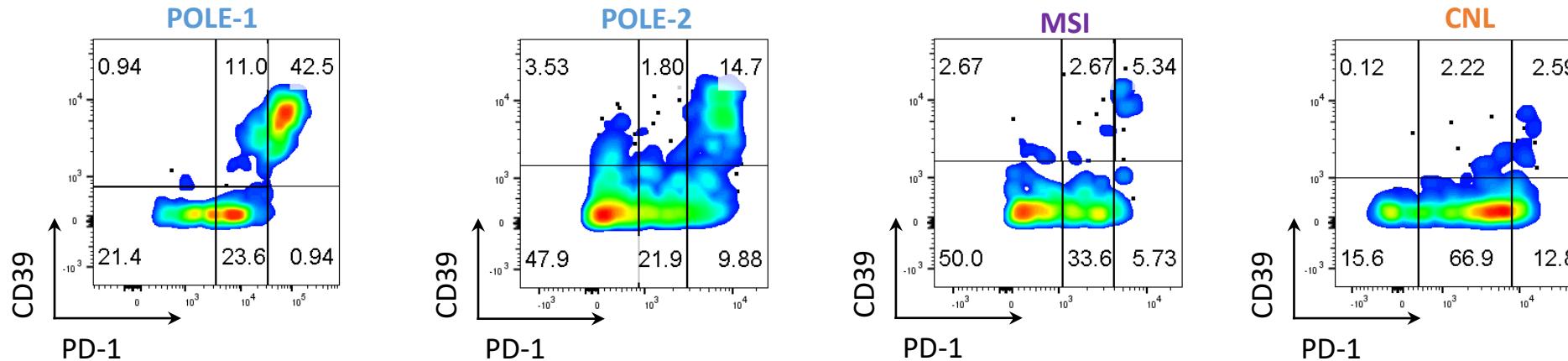
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Kortekaas KE et al.
Cancer Immunol Res 2020

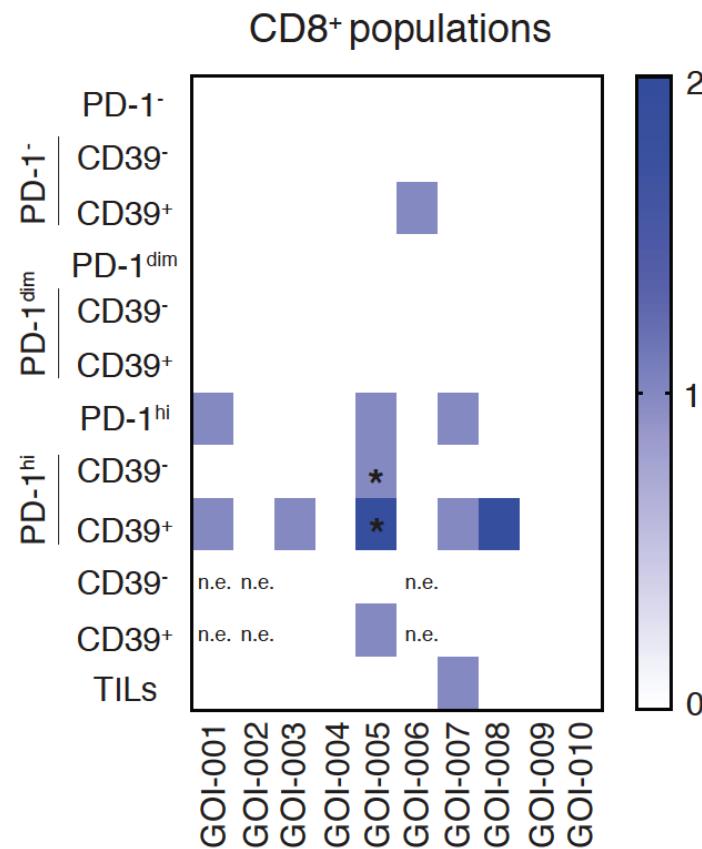
Balança CC et al.
J Clin Invest 2020

CD8+CD39+ TIL accumulate the majority of tumor- and neoantigen-reactive lymphocytes



Gros, A et al. J Clin Invest 2014
Palomero, J et al. under revision
© Vall d'Hebron Institute of Oncology (VHIO)

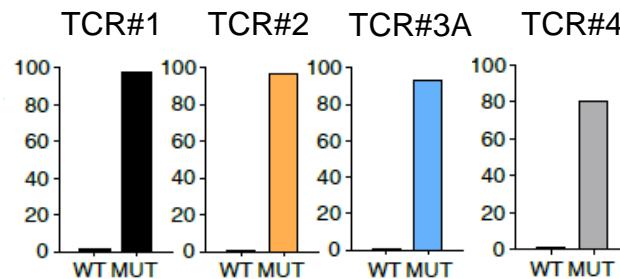
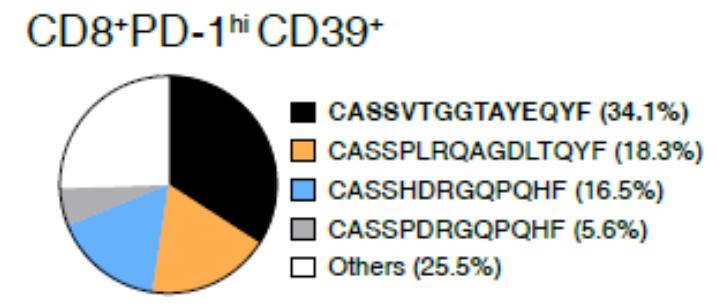
CD8+PD-1^{hi}CD39+ circulating lymphocytes are enriched in tumor- and neoantigen-reactive T cells in cancer patients



N=10, 5 tumor types

2 Breast
2 H&N
1 Ovarian
2 MSI CRC
1 MSS CRC
2 Chordomas

**Reactivities identified
in 8 of 10 patients**
**16 neoantigen-reactive
3 CG antigen-reactive**

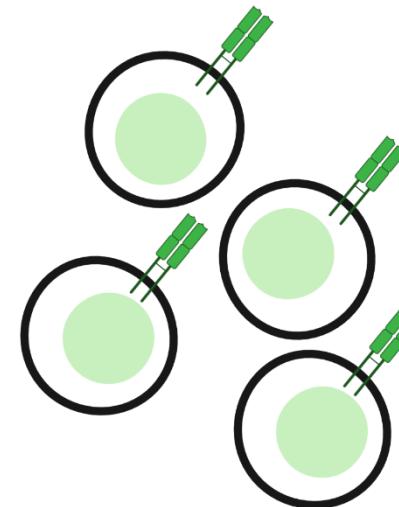


Towards tumor-reactive T-cell products

From serendipity...



... to generalizability

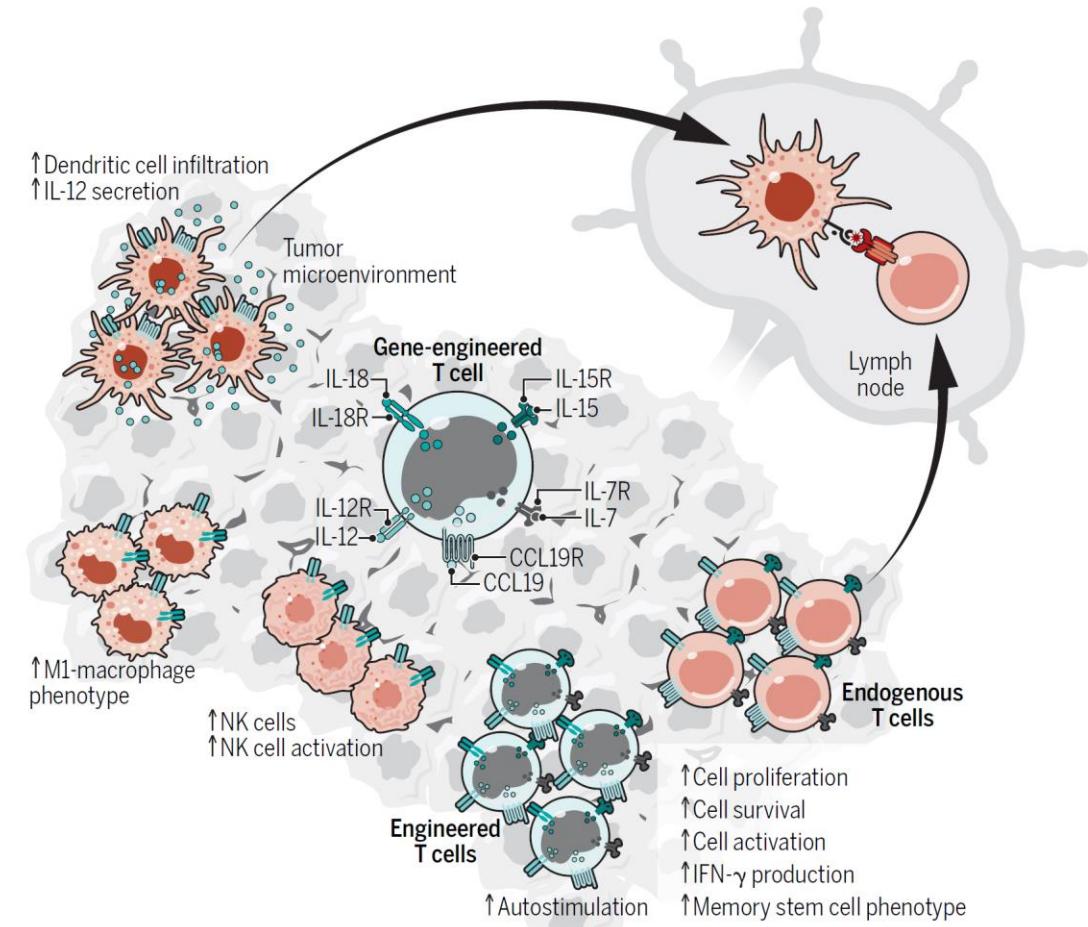
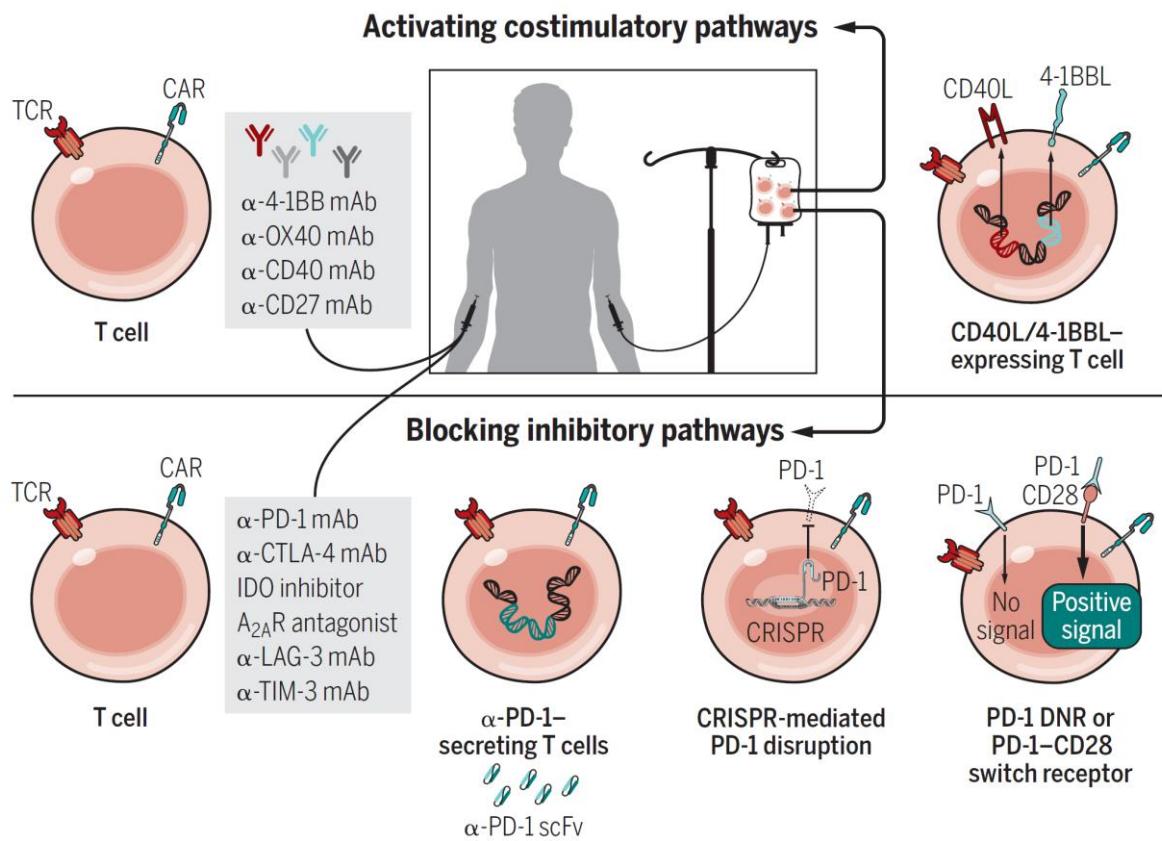


Discovery of biomarkers

Driving tumor antigen-specific proliferation – sensitization

TCR gene engineered lymphocytes

Rationale for combination of T cells with ICB and arming T cells to enhance antitumor efficacy

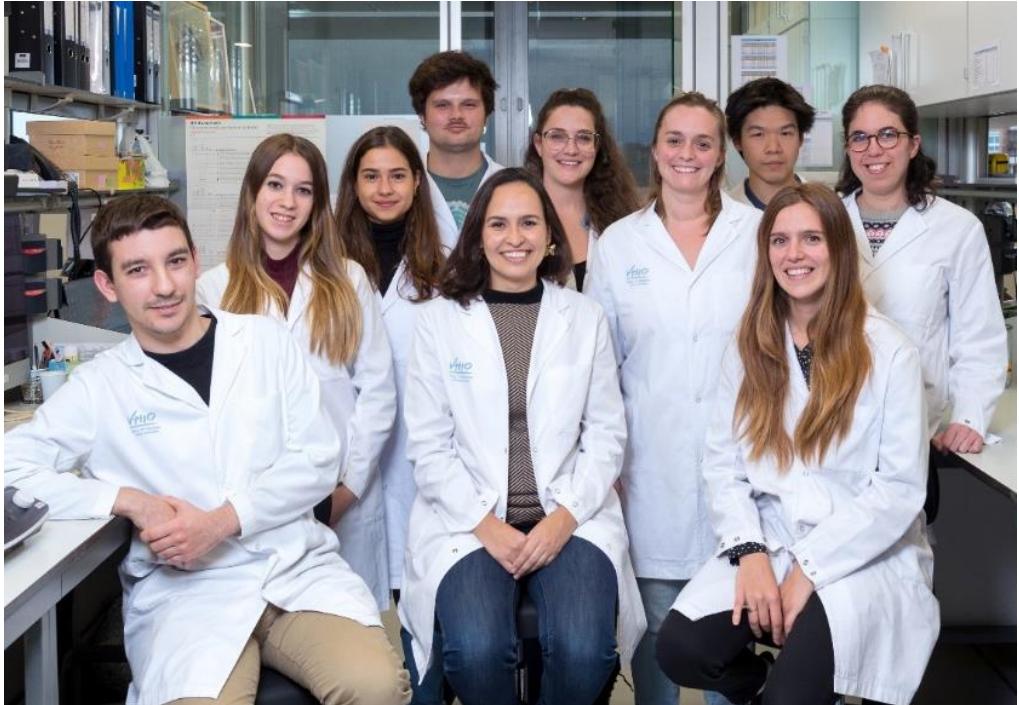


Take-home message

- 1- TIL therapy can induce antitumor responses in patients with metastatic melanoma and is being explored in other cancer types
- 2- Selected or enriched tumor and neoantigen-reactive TIL/PBL products can overcome some of the inconsistencies in the expansion of tumor-reactive TIL and could enhance clinical activity
- 3- TCR gene-engineered T-cell therapies have co-evolved with TIL therapy and have shown promising antitumor responses
- 4- Combination with other immunotherapies and arming of transferred T cells could further enhance clinical efficacy

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