# Da Trieste a Boston: una storia di caso ed opportunità

MONICA GOSTISSA

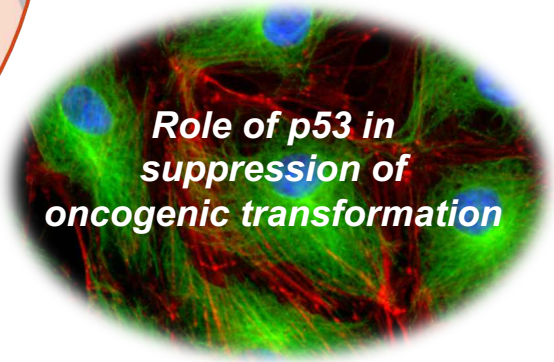
11 OTTOBRE 2024

# My journey

From Trieste to Boston…

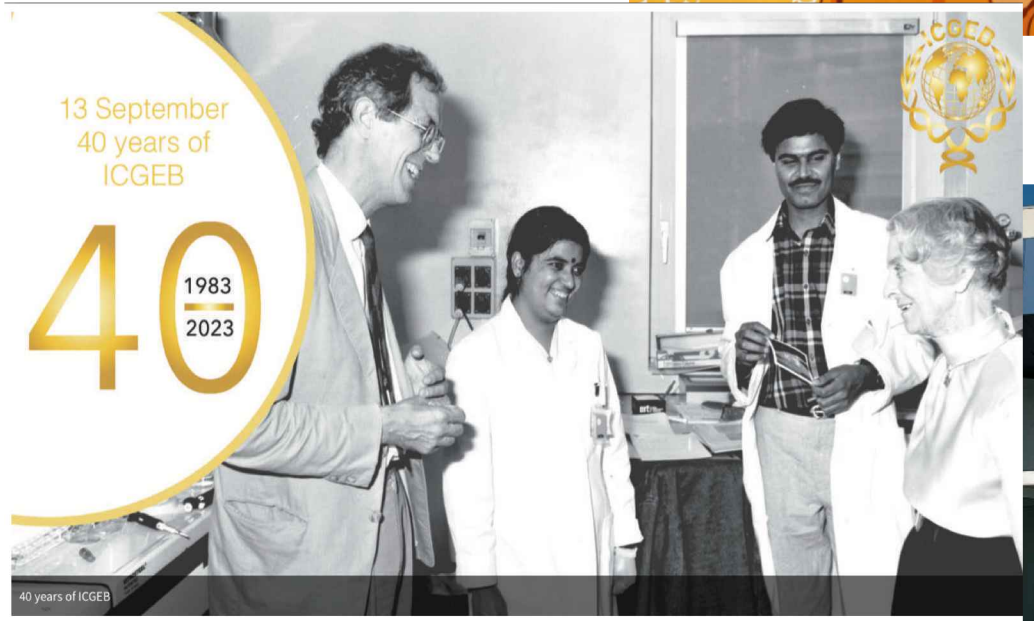
- Research fellow (2004-2010)
  Instructor (2010-2014)
  BCH/HMS

- PhD, Molecular Genetics
  SISSA/ISAS (2000)
- Research Fellow
  LNCIB (2000-2003)


- Head, Tumor Immunology and Imaging 121 Bio/Agenus (2014-2017)
- Director, In vivo and Ex vivo Science Jounce Therapeutics (2017-2023)
- Chief Scientific Officer
  Egle Therapeutics

… and from cells to mice to man!

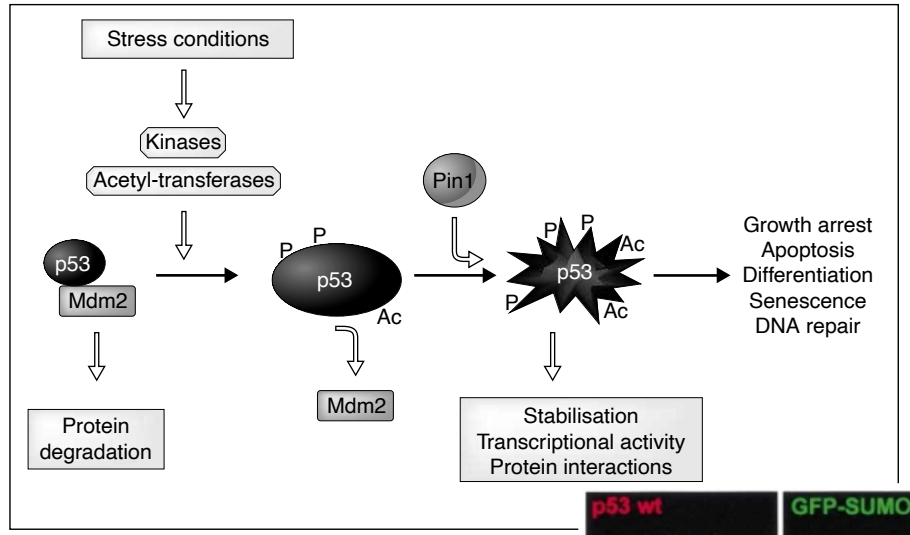



# Com’è cominciato (1983-1989)

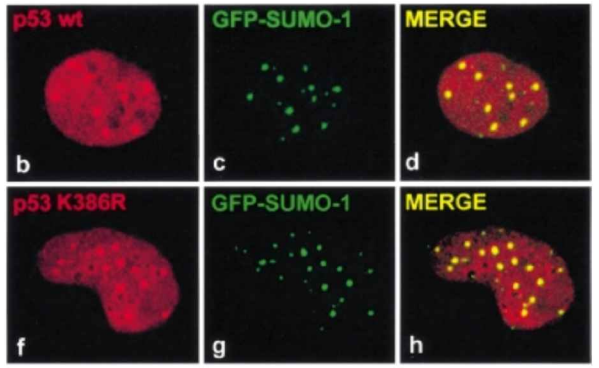
# I primi anni

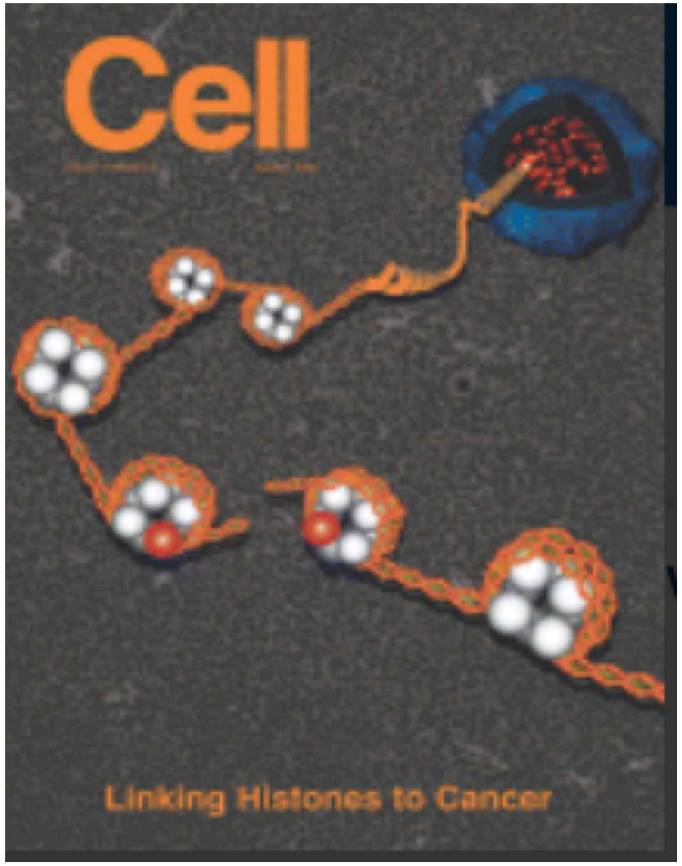
## Dipartimento BBCM

## Lab. Nazionale CIB



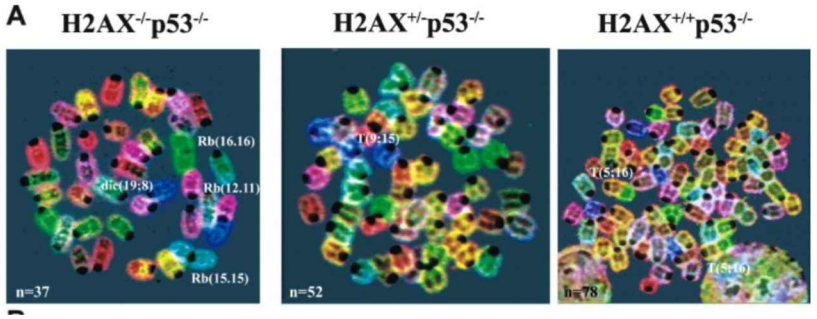

*Gostissa et al., 2003*

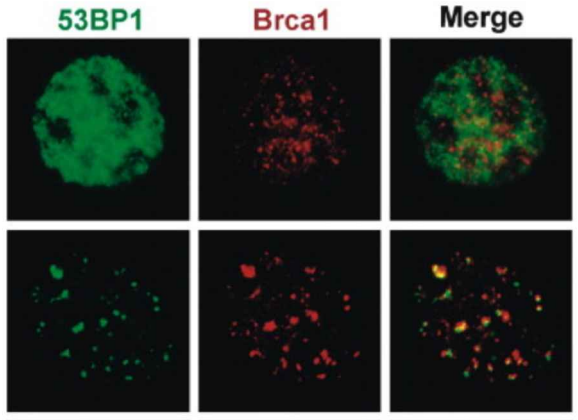





Cell, Vol. 114, 359–370, August 8, 2003, Copyright ©2003 by Cell Press

**Histone H2AX: A Dosage-Dependent Suppressor of Oncogenic Translocations and Tumors**

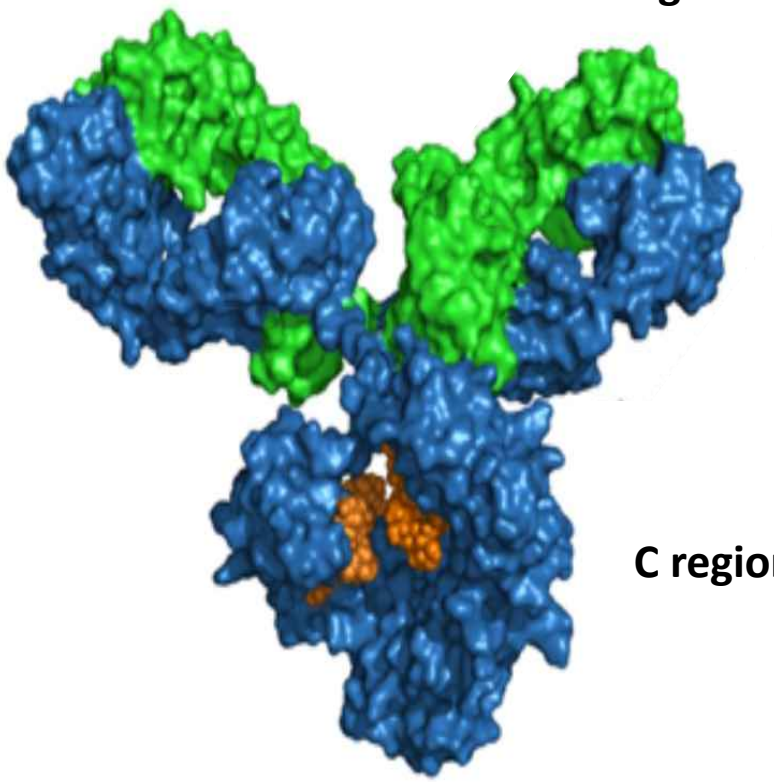


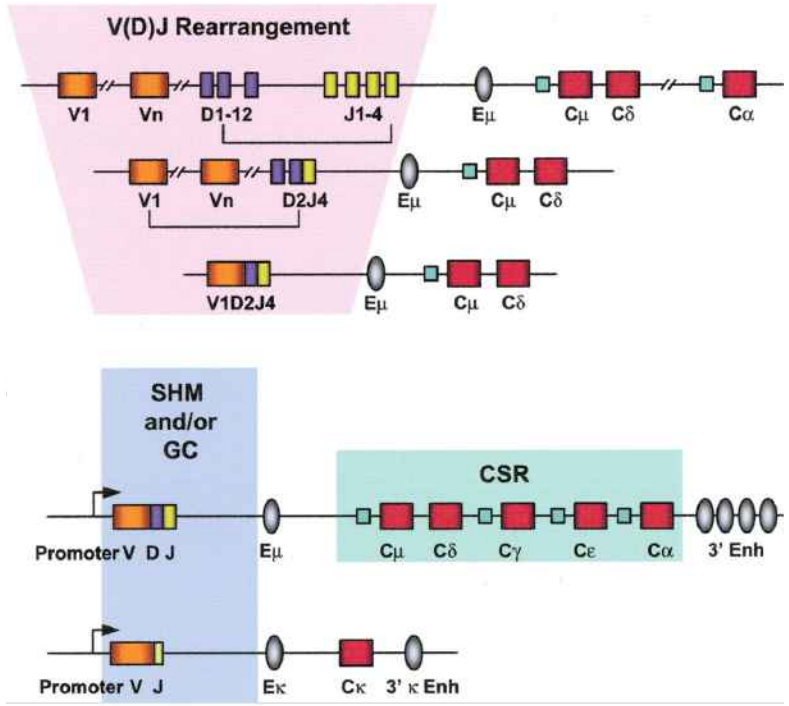



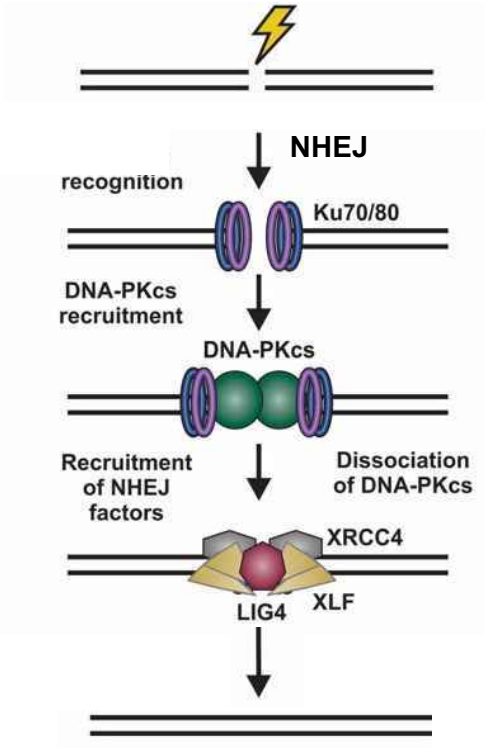

# Come sono arrivata a Boston

# Meccanismi alla base delle traslocazioni cromosomiche nei linfomi delle cellule B

- Antibody genes in B cells undergo a complex series of genomic rearrangements during development

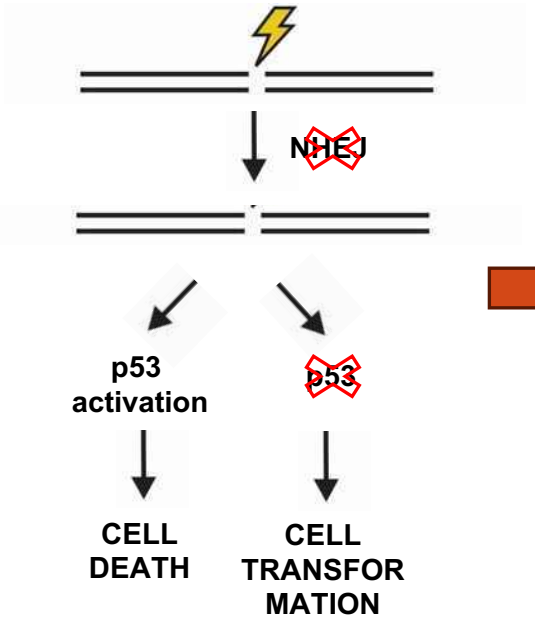


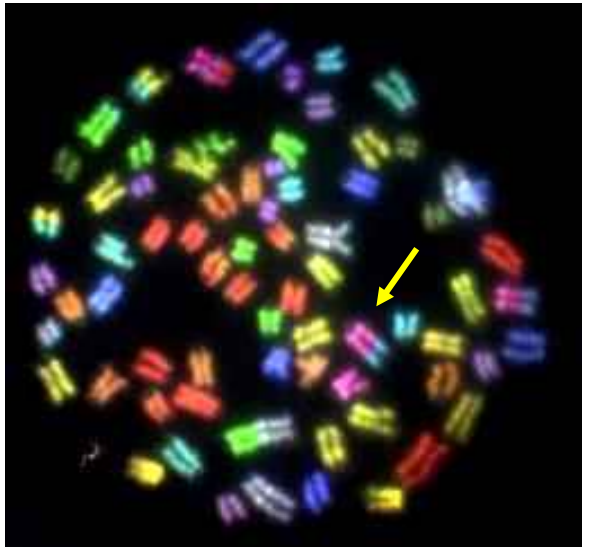



# Meccanismi alla base delle traslocazioni cromosomiche nei linfomi delle cellule B

- Mistakes in these programmed DNA rearrangements predispose B cell lymphomas to chromosomal translocations
- What other factors are responsible of facilitating these recurrent translocations?




**NHEJ/p53 KO**




Vol 460|9 July 2009|doi:10.1038/nature08159 nature

**Mechanisms promoting translocations in editing and switching peripheral B cells**

Jing H. Wang[1,2,3,4]*, Monica Gostissa[1,2,3,4]*, Catherine T. Yan[1,2,3,4]*, Peter Goff[1,2,3,4], Thomas Hickernell[1,2,3,4], Erica Hansen[1,2,3,4], Simone Difilippantonio[5], Duane R. Wesemann[1,2,3,4,6], Ali A. Zarrin[1,2,3,4]†, Klaus Rajewsky[3], Andre Nussenzweig[5] & Frederick W. Alt[1,2,3,4]

Vol 462|10 December 2009|doi:10.1038/nature08633 nature

**Long-range oncogenic activation of *Igh–c-myc* translocations by the *Igh* 3′ regulatory region**

Monica Gostissa[1,2,3,4], Catherine T. Yan[1,2,3,4], Julia M. Bianco[1,2,3,4], Michel Cogné[5], Eric Pinaud[5] & Frederick W. Alt[1,2,3,4]

PNAS

**Chromosomal location targets different MYC family gene members for oncogenic translocations**

Monica Gostissa[1], Sheila Ranganath[1], Julia M. Bianco, and Frederick W. Alt[2]

The Howard Hughes Medical Institute, Children's Hospital Boston, Immune Disease Institute, and Department of Genetics, Harvard Medical School, 300 Longwood Avenue, Boston, MA 02115

Boston Children's Hospital

**Chromosomal context, transcriptional enhancers and selection**

# Meccanismi alla base delle traslocazioni cromosomiche nei linfomi delle cellule B

- What if we take oncogenic selection out of the picture?
- A new method for high-throughput and unbiased translocation cloning

**Genome-wide Translocation Sequencing Reveals Mechanisms of Chromosome Breaks and Rearrangements in B Cells**

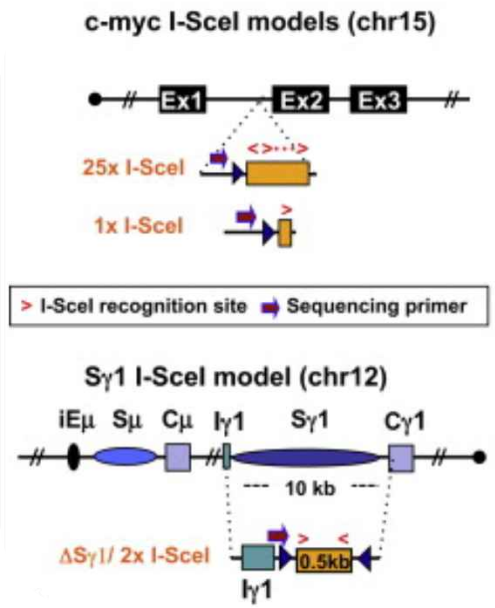
Cell

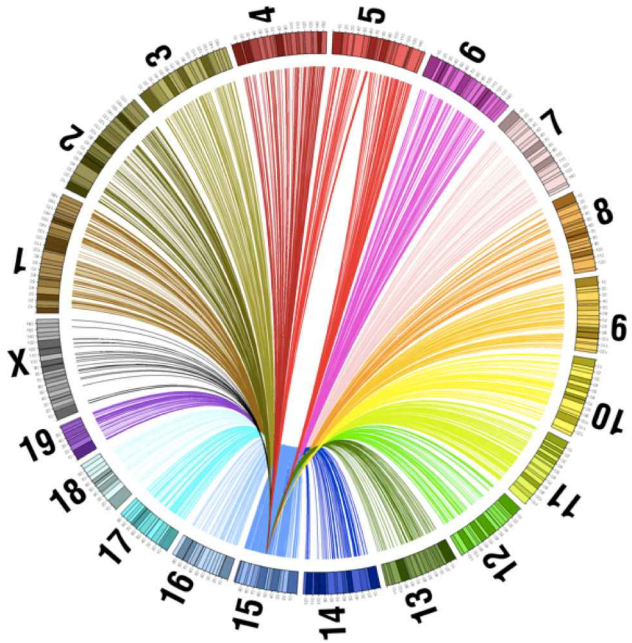
Roberto Chiarle,[1,2,7] Yu Zhang,[1,7,*] Richard L. Frock,[1,7] Susanna M. Lewis,[1,7] Benoit Molinie,[3] Yu-Jui Ho,[1] Darienne R. Myers,[1] Vivian W. Choi,[1] Mara Compagno,[1,2] Daniel J. Malkin,[1] Donna Neuberg,[4] Stefano Monti,[5,6] Cosmas C. Giallourakis,[3,*] Monica Gostissa,[1,*] and Frederick W. Alt[1,*]

**IgH class switching exploits a general property of two DNA breaks to be joined *in cis* over long chromosomal distances**

PNAS

Monica Gostissa[a,b,c,1], Bjoern Schwer[a,b,c,1], Amelia Chang[a,b,c], Junchao Dong[a,b,c], Robin M. Meyers[a,b,c], Gregory T. Marecki[a,b,c], Vivian W. Choi[a,b,c,2], Roberto Chiarle[a,b,c,3], Ali A. Zarrin[a,b,c,4], and Frederick W. Alt[a,b,c,5]



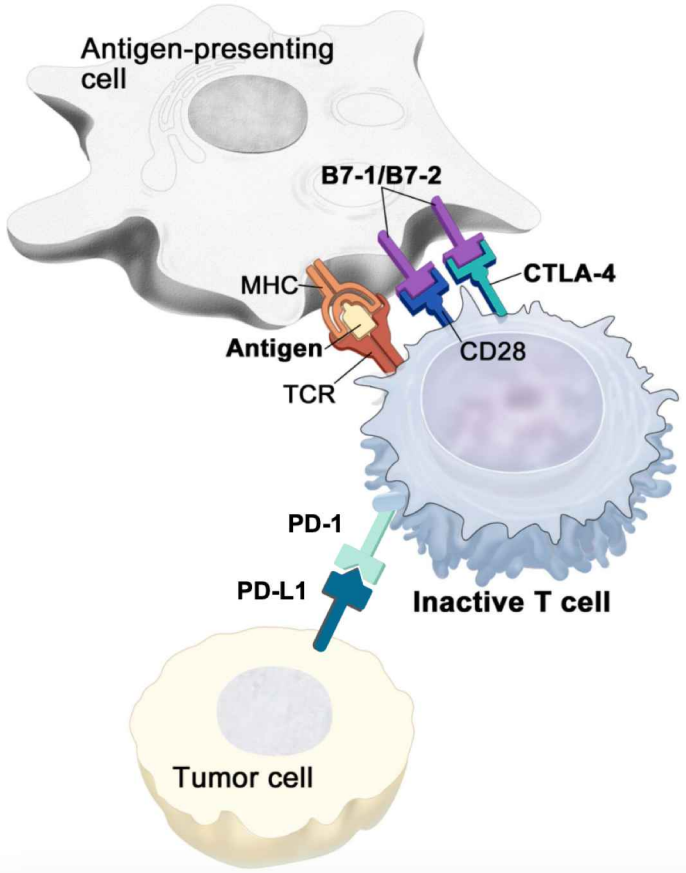

**Mechanistic factors:**
**spatial proximity and frequency of DNA breaks**

Boston Children's Hospital

VE RI TAS

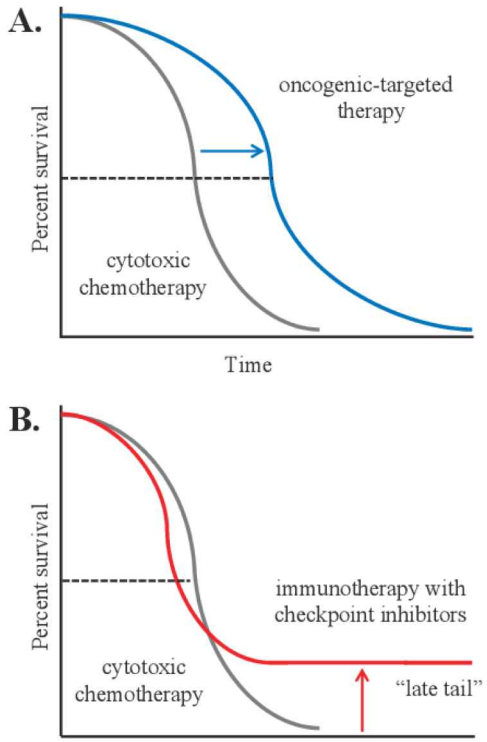
# 2011-2017: la rivoluzione dell'immunoterapia

- Identification of immune checkpoint mechanisms at the basis of tumor immune escape

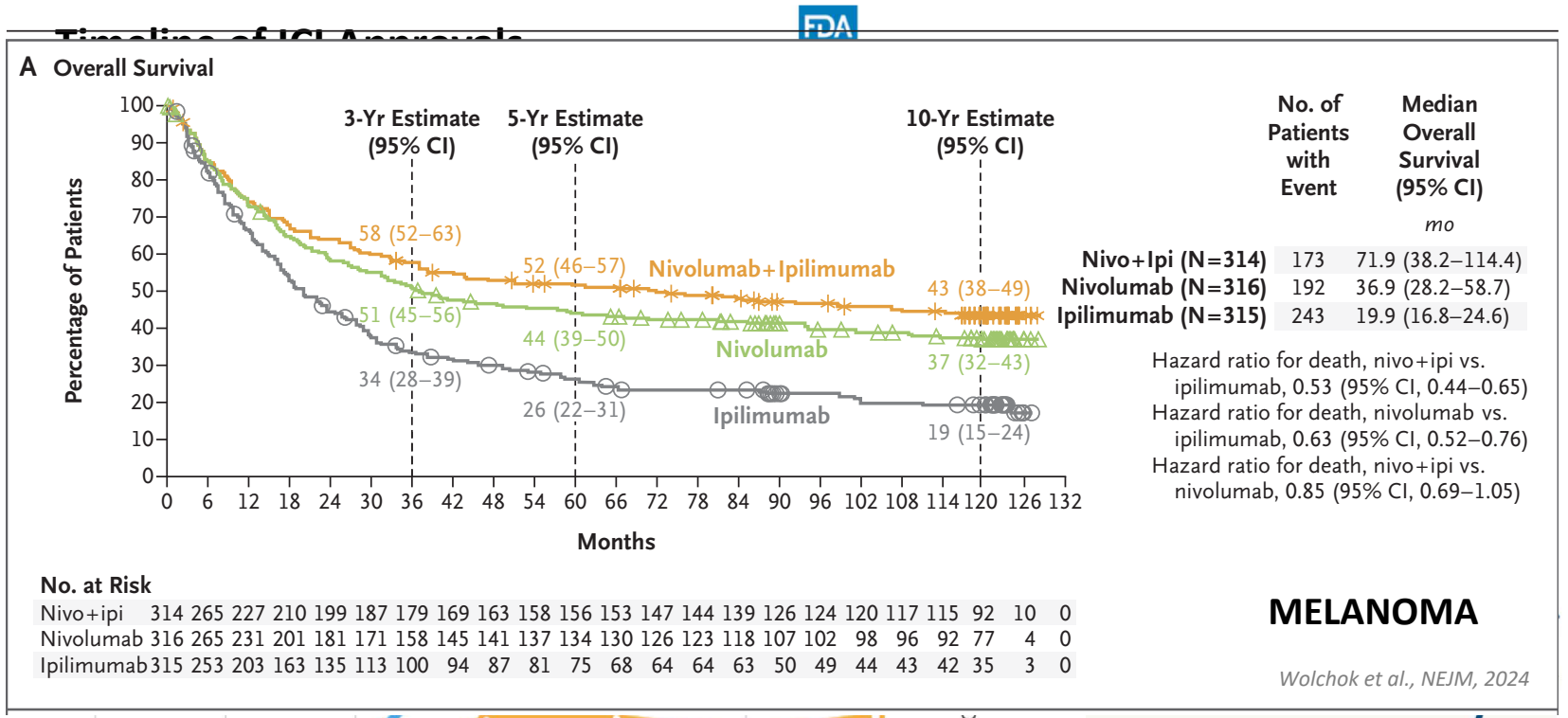



*Created in BioRender.com*

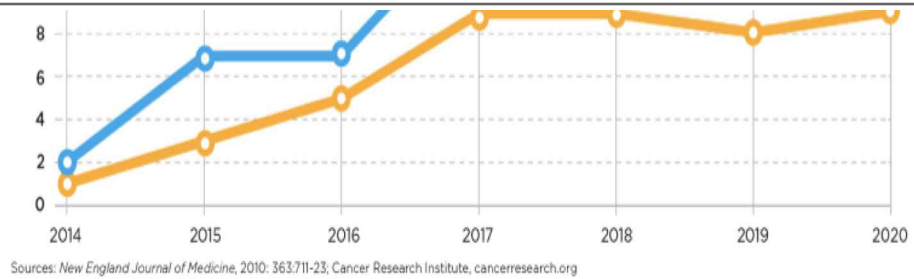
# 2011-2017: la rivoluzione dell'immunoterapia

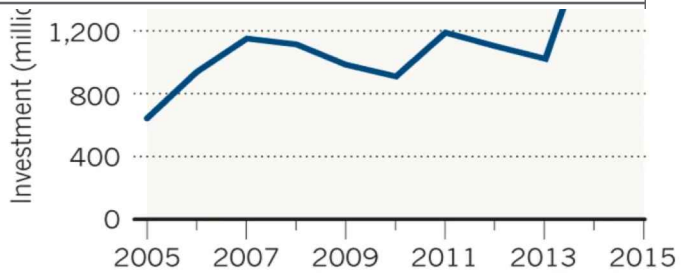



Yoneda et al 2018



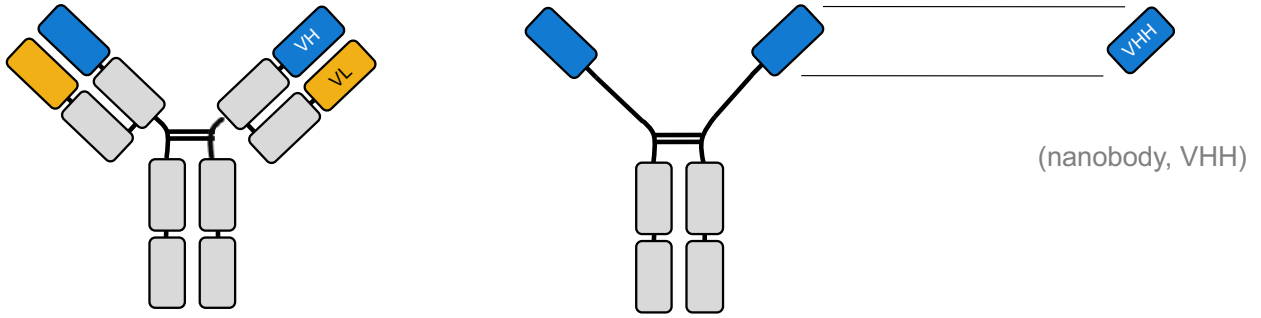

Wolchok et al., NEJM, 2024



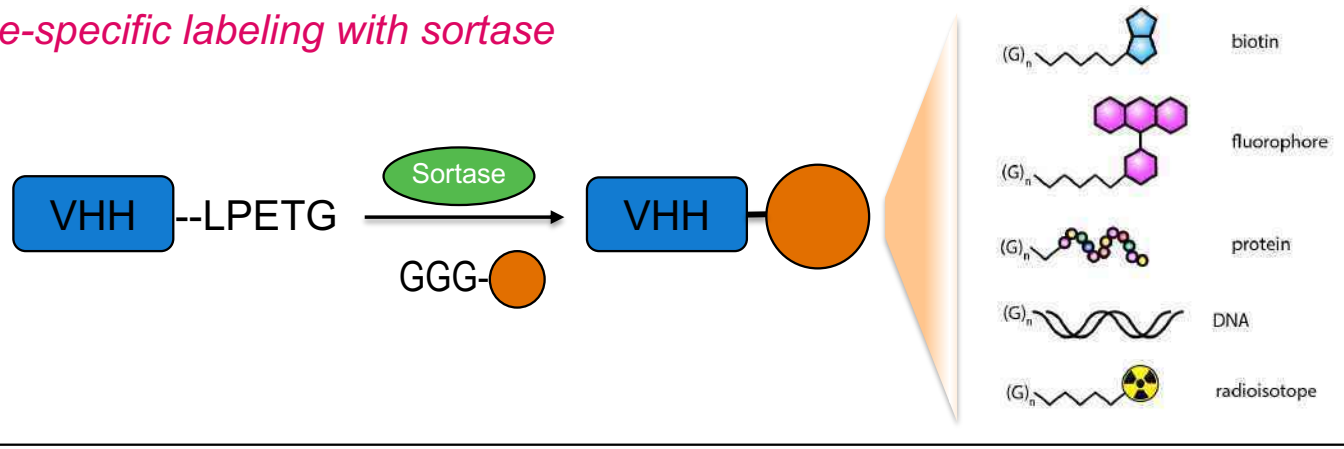



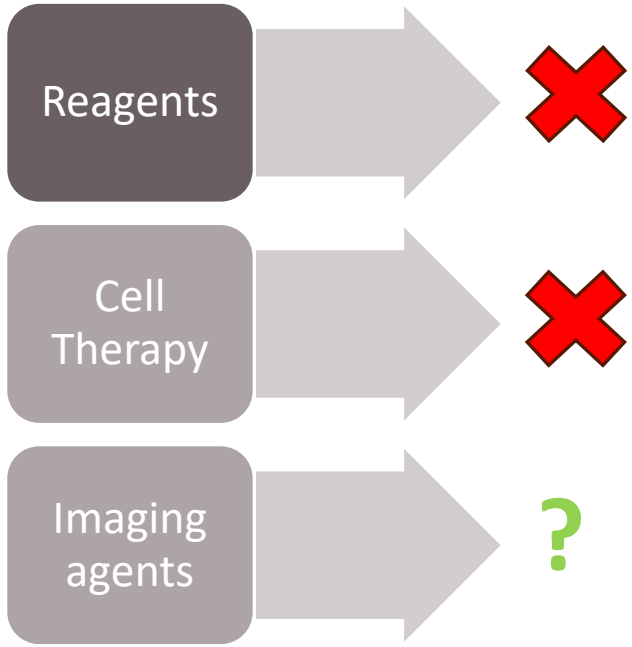
# 121Bio: una piattaforma tecnologica in cerca di

*Single-domain antibodies from camelids*



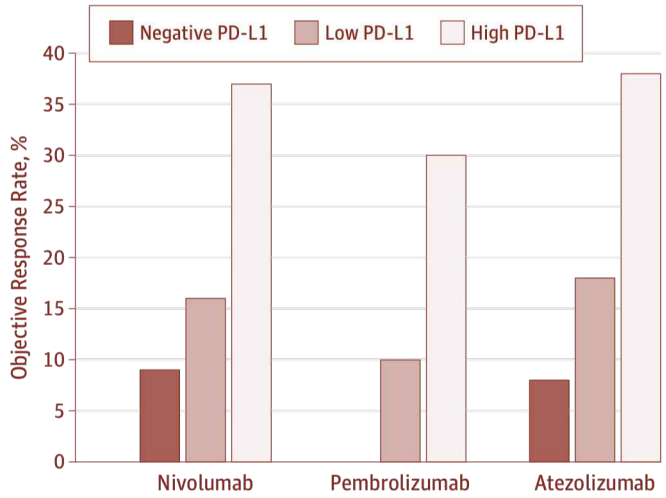

*Site-specific labeling with sortase*




121Bio

# “Raise the tail”: nuovi e piu’ efficaci biomarkers




*NSCLC; Saher and Gandhi, JAMA 2016*

## Imaging for biomarker evaluation

**BIOPSY**

single lesion

invasive

non-repeatable

non-standardized

**PET imaging**

whole-body

non-invasive

allows longitudinal studies

broadly applicable

*STANDARD OF CARE*

*121 Bio APPROACH*

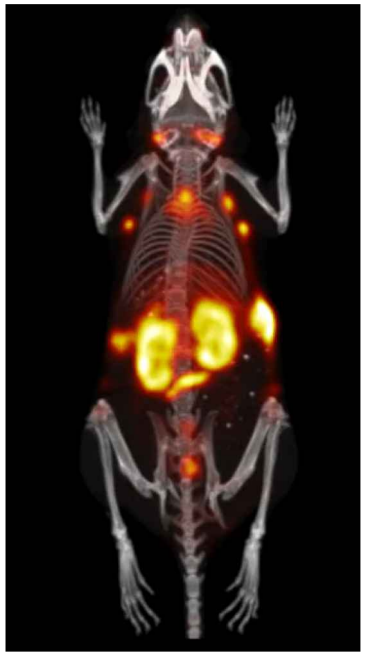
121Bio agenus

# CD8 nanobodies per visualizzare le cellule T nel

- Whole body and longitudinal imaging of T cell infiltration in tumors upon PD-1 treatment

**Imaging of CD8+ tumors**

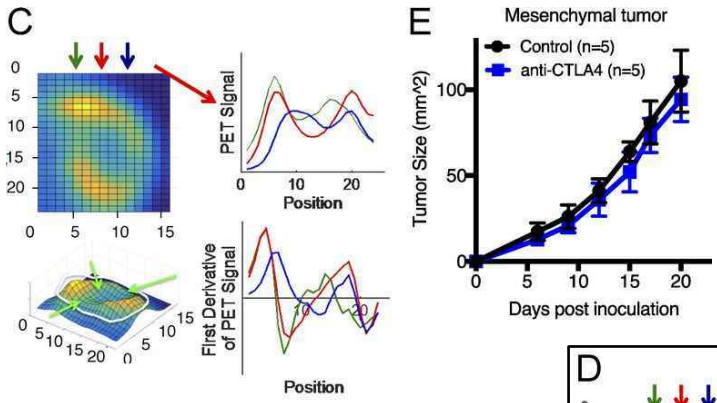

**Imaging of tumor T cell infiltrate**

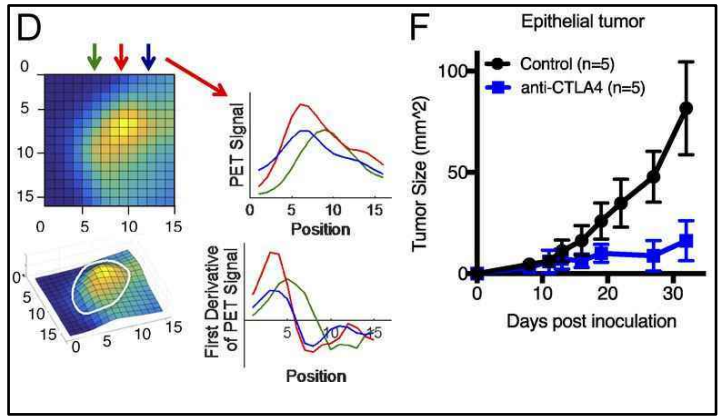


JEM Brief Definitive Report

Predicting the response to CTLA-4 blockade by longitudinal noninvasive monitoring of CD8 T cells

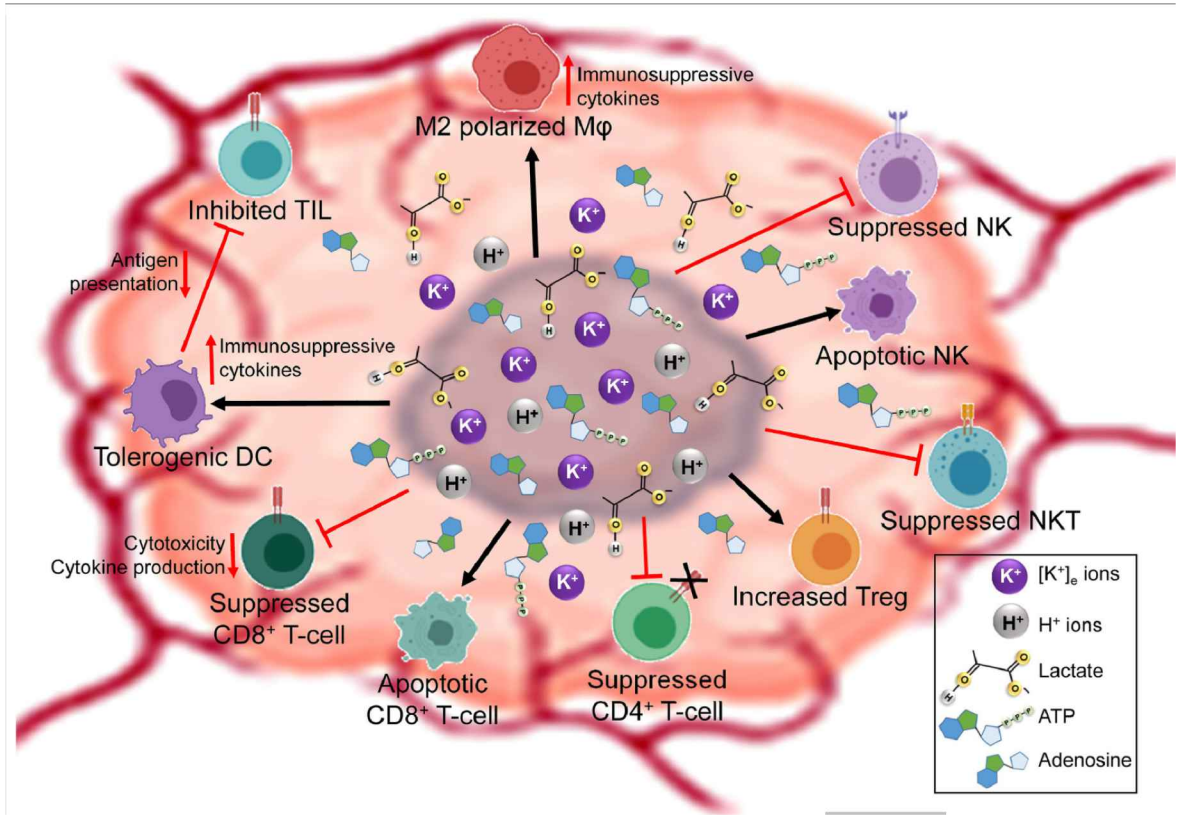
Mohammad Rashidian,[1*] Jessica R. Ingram,[1*] Michael Dougan,[1,2*] Anushka Dongre,[1,4] Katherine A. Whang,[1] Camille LeGall,[1] Juan J. Cragnolini,[5] Brian Bierie,[1] Monica Gostissa,[5] James Gorman,[5] Gijsbert M. Grotenbreg,[5] Atul Bhan,[3] Robert A. Weinberg,[1,4,6] and Hidde L. Ploegh[1,6]



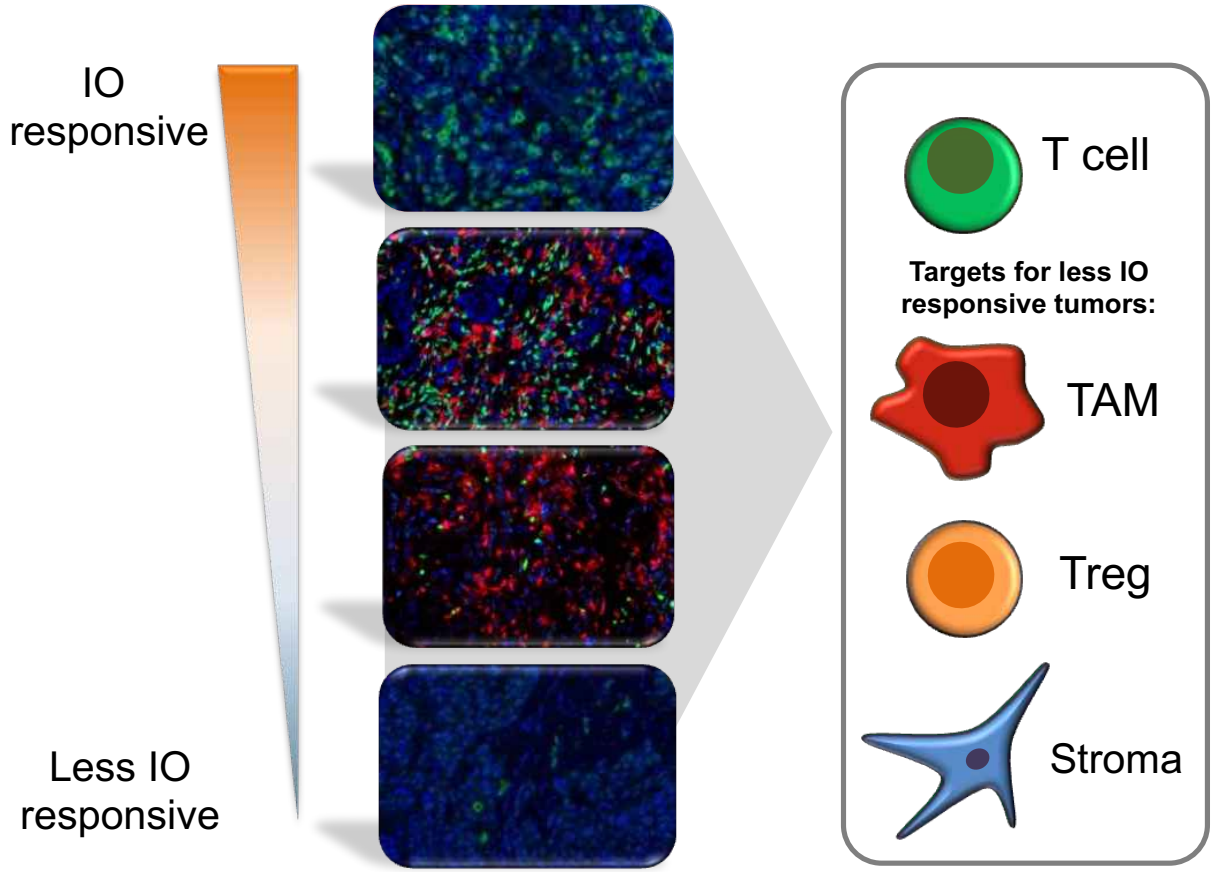




121Bio agenus

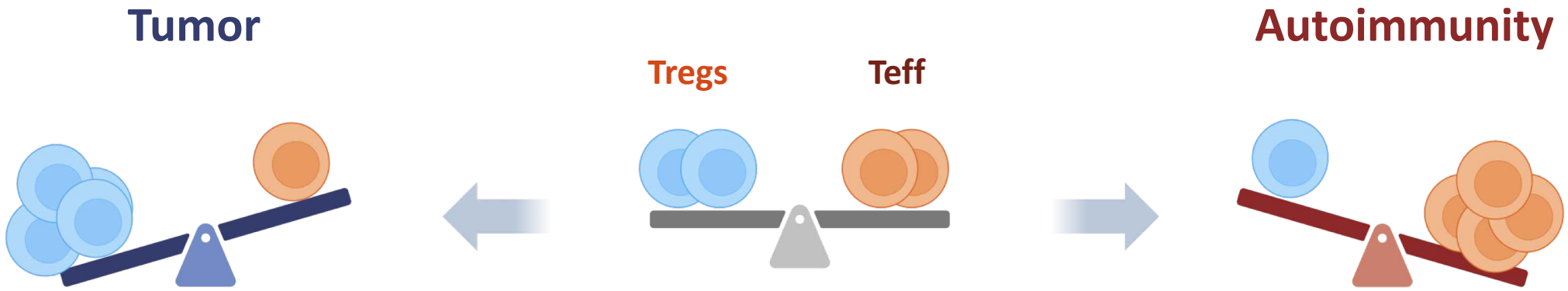
# ”Raise the tail”: colpire cellule immunosuppressive nel microambiente tumorale

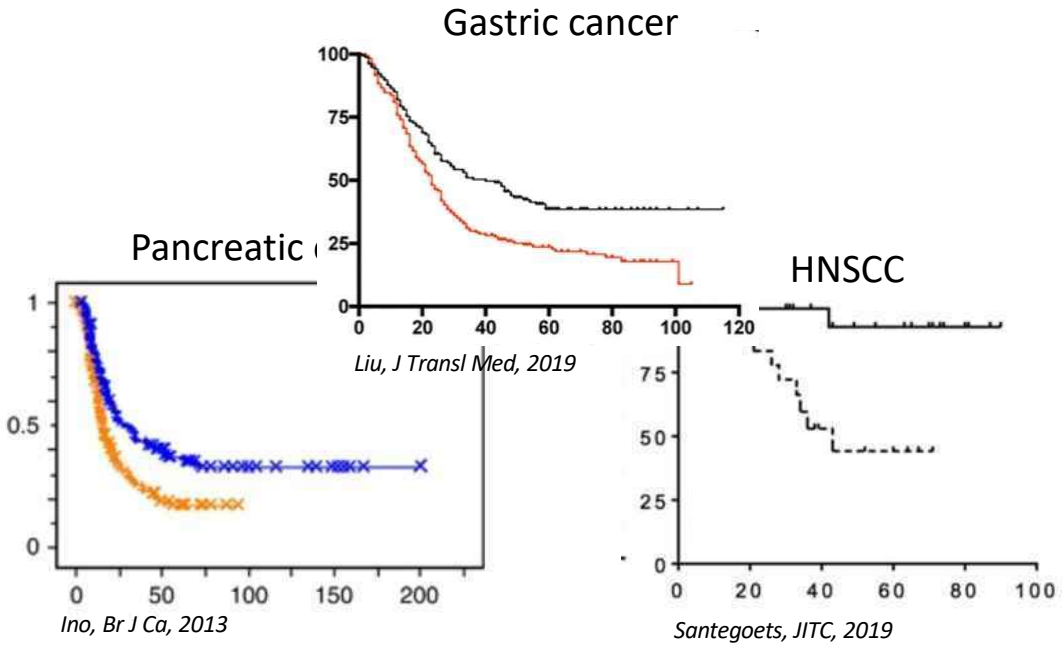


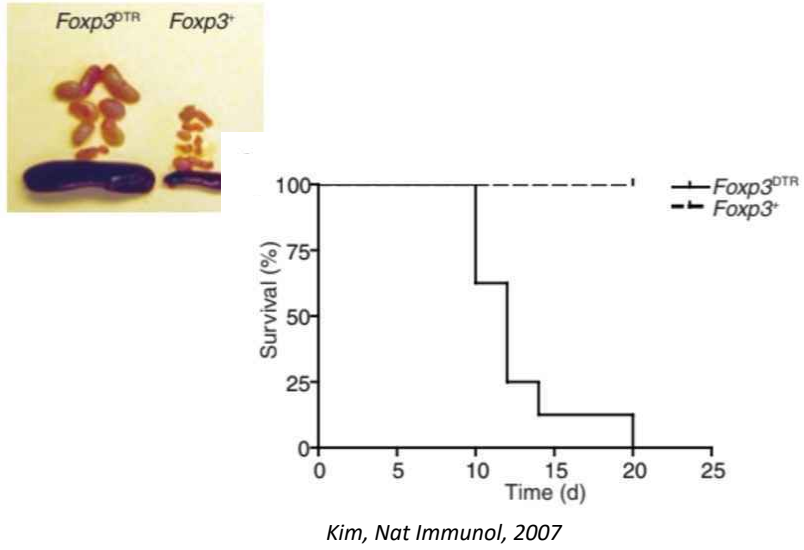

*Verma et al, 2022*



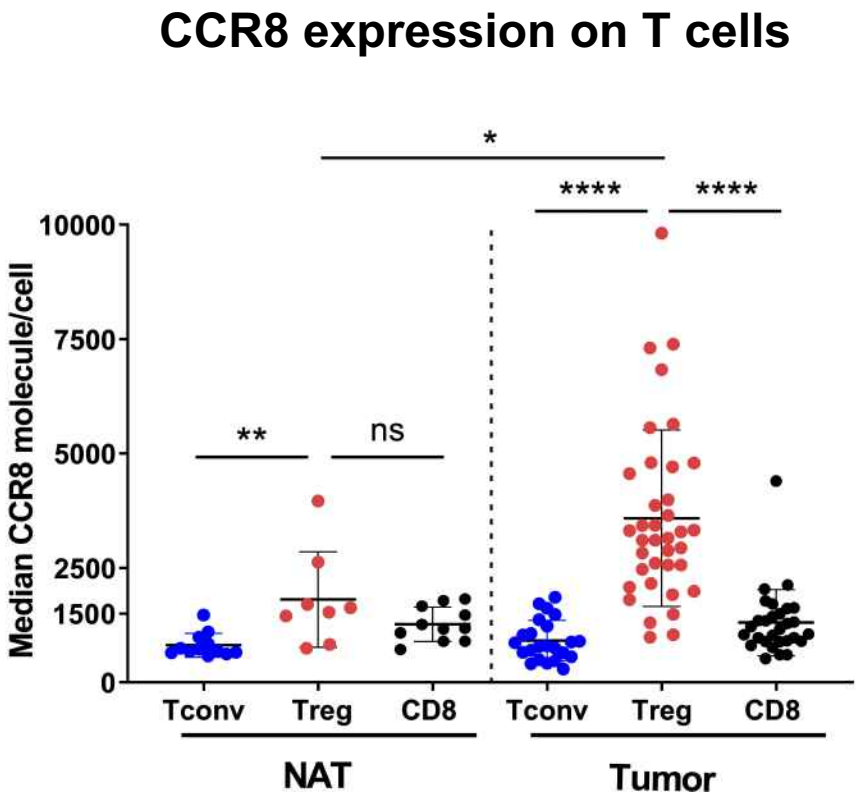
# L’equilibrio Treg/Teff e’ alterato nel cancro e nelle malattie autoimmuni

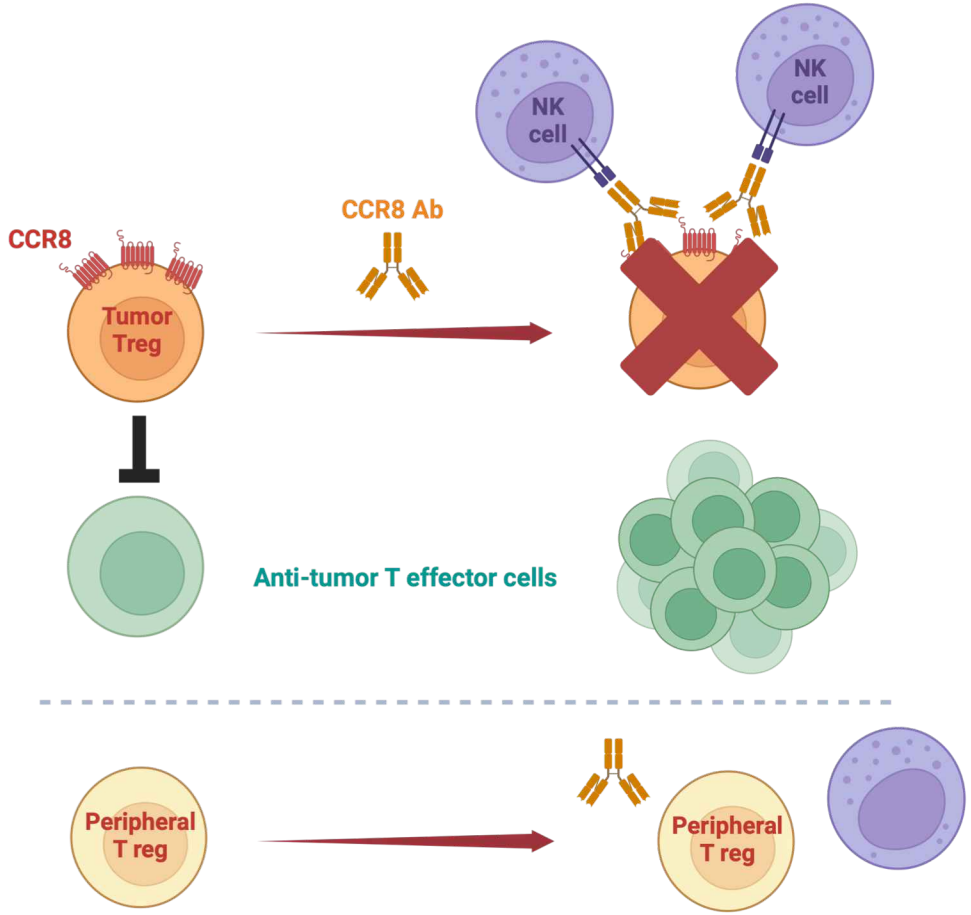


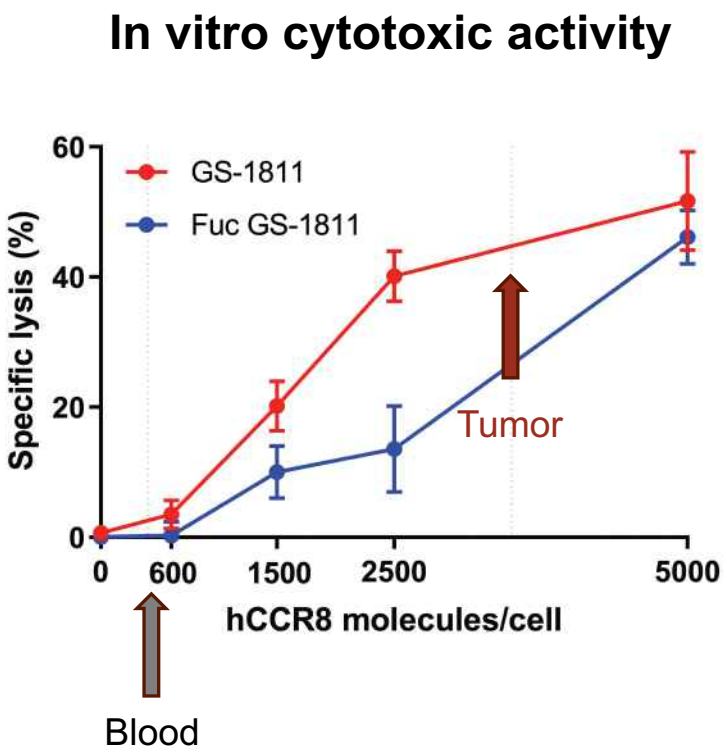



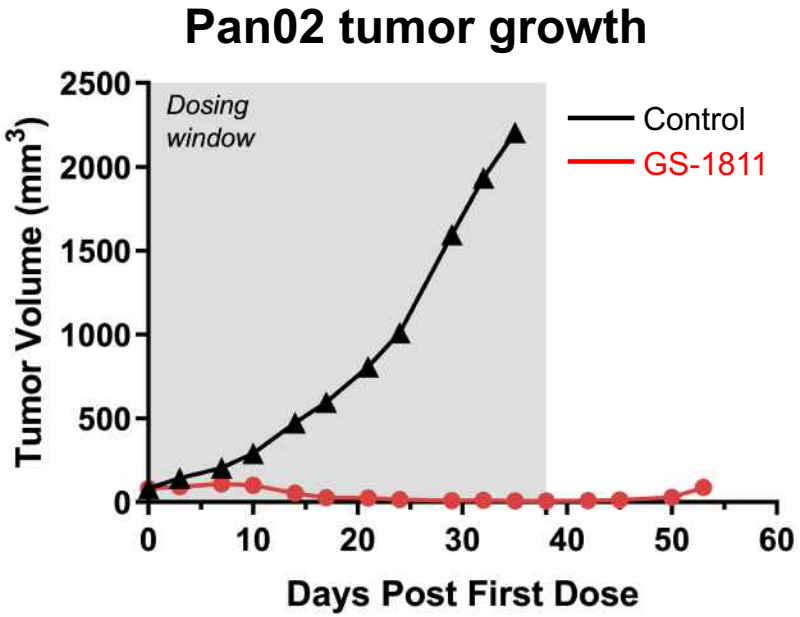
# CCR8: un marker altamente specifico delle cellule Treg nei tumori

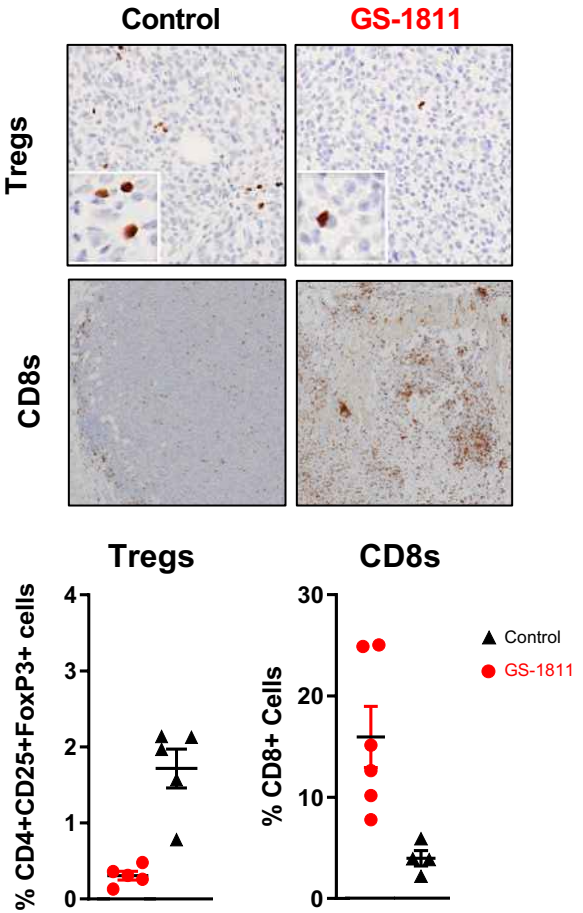


# GS-1811: un anticorpo ingegnierizzato per ridurre le Tregs nei tumori

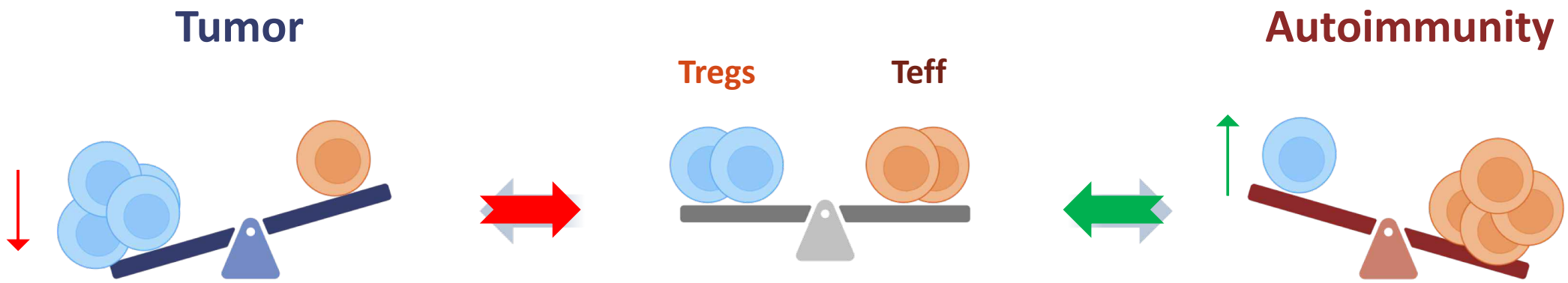


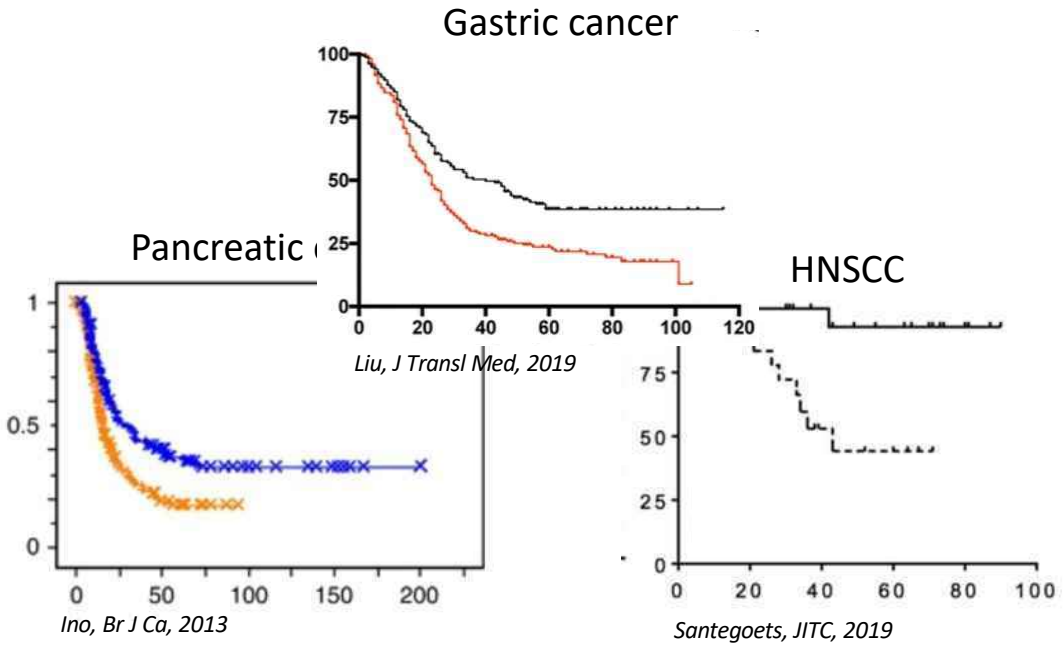



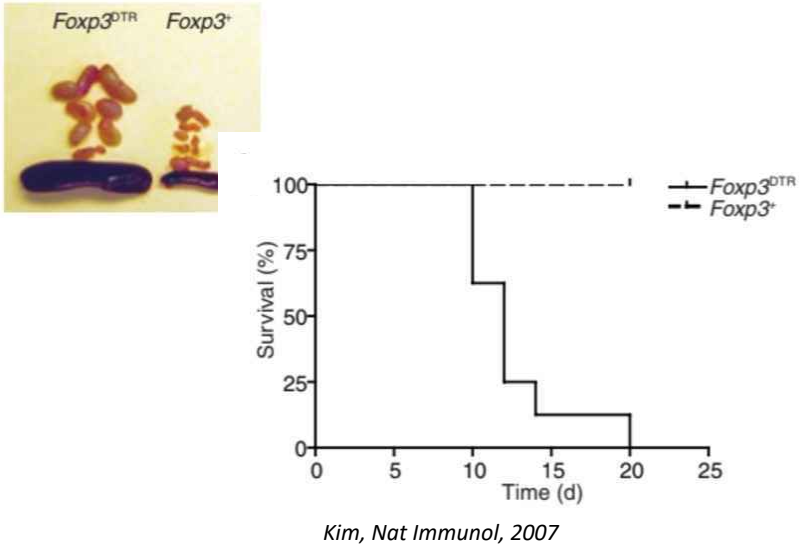




- GS-1811 e' attualmente in sperimentazione clinica (Ph2) con Gilead Sciences (NCT05007782)

# IL-2 muteine Treg-specifiche: ri-bilanciare

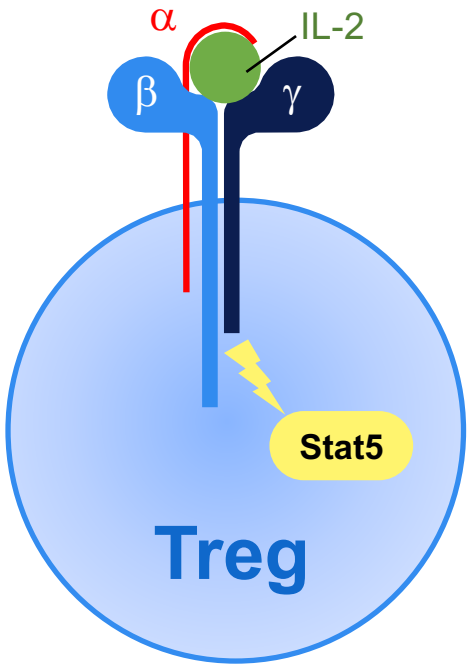


# IL-2 muteine Treg-specifiche: ri-bilanciare

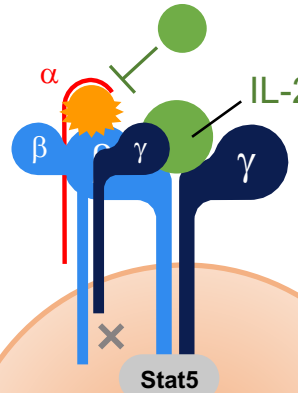
## Regulatory T cells




- Express high affinity α/β/γ IL-2 receptor
- Depend on IL-2 for function and survival

**Egle Tx:**
**IL-2Rα (CD25) - selective IL-2 muteins**

**IMMUNO-ONCOLOGY:** Treg "starver"

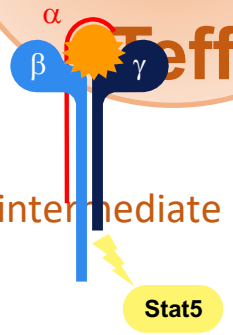



**Treg-selective IL-2 antagonist**

- Blocks IL-2 signaling in Tregs
- Does not affect effector T cells

→ **Treg inhibition and death**

**AUTOIMMUNITY:** Treg "engager"




- Express intermediate affinity β/γ IL-2 receptor

**Treg-selective IL-2 agonist**

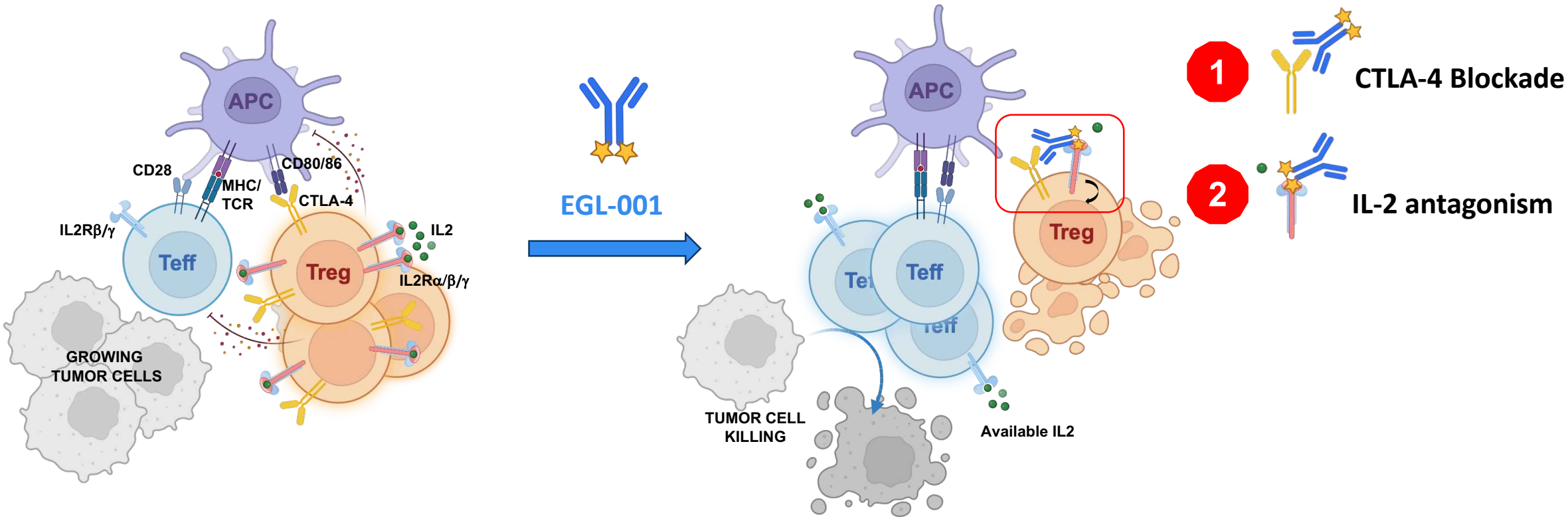
- Activates IL-2 signaling in Tregs
- Reduced affinity for effector T cells

→ **Treg expansion**

egle Tx

Institut Pasteur institutCurie

# EGL-001: CTLA-4 targeted Treg starver for I/O




- EGL-001 entrera' in sperimentazione clinica nelle prossime settimane! (NCT06622486)

# Per concludere…

L’impegno paga! Assieme ad entusiasmo, curiosita’ e capacita’ di crescere (anche in situazioni non ideali)

Le opportunita’ migliori a volte si presentano per caso e bisogna avere il coraggio di coglierle

Science is science. Nuove nozioni e tecniche sono facili da apprendere, ma sviluppare un solido senso critico e metodo scientifico e’ fondamentale

Scegliete bene i vostri mentori!

Work is life, but there’s more to life than work!