CNR
Istituto di Farmacologia Traslazionale
Laboratorio di Immunologia dei Tumori ed Immunoterapia

Combinazioni tra mAbs e molecole Fcγ chimeriche: nuove strategie di targeting tumorale in oncoematologia

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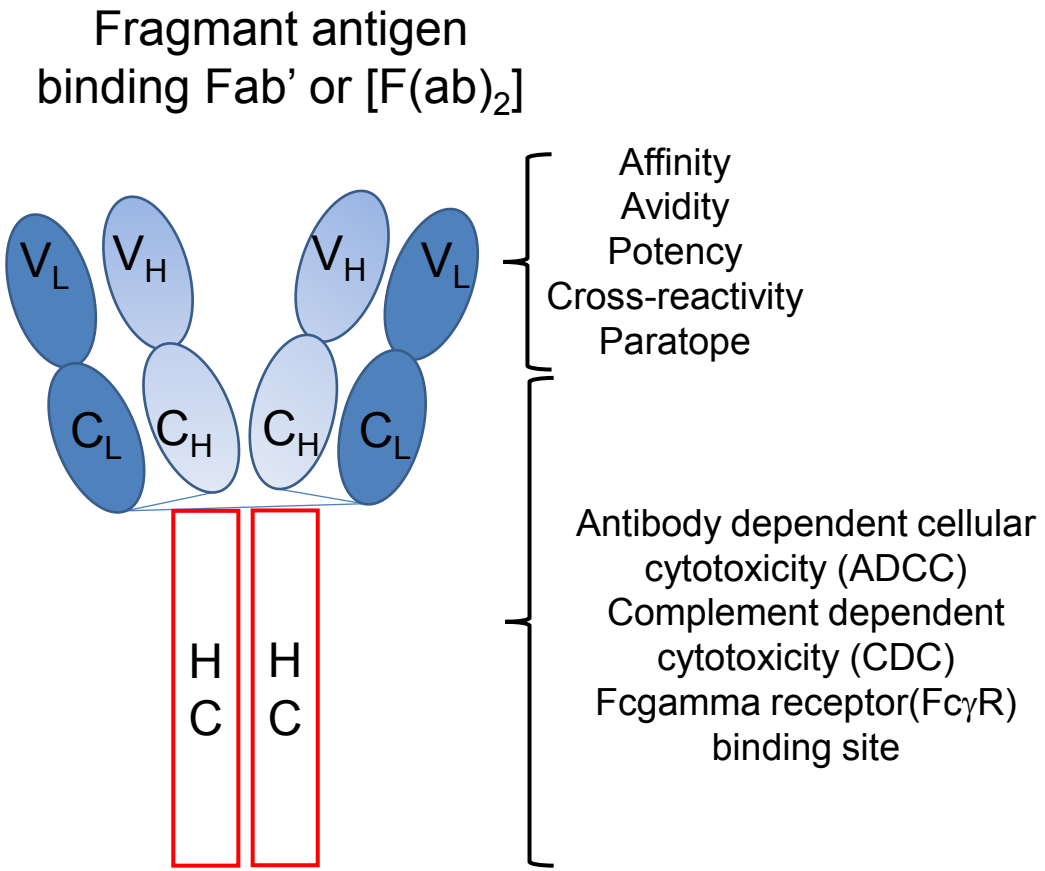
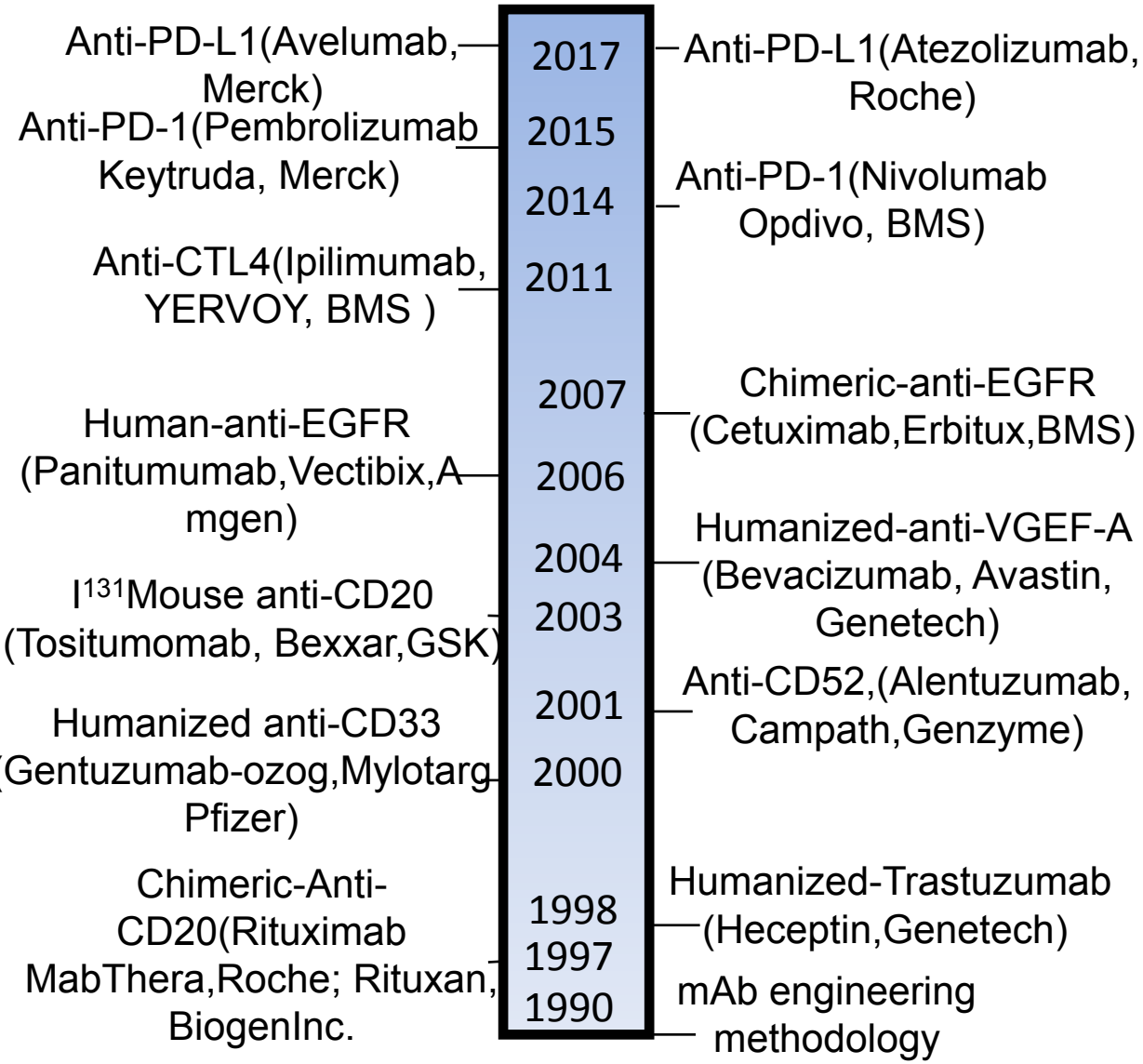
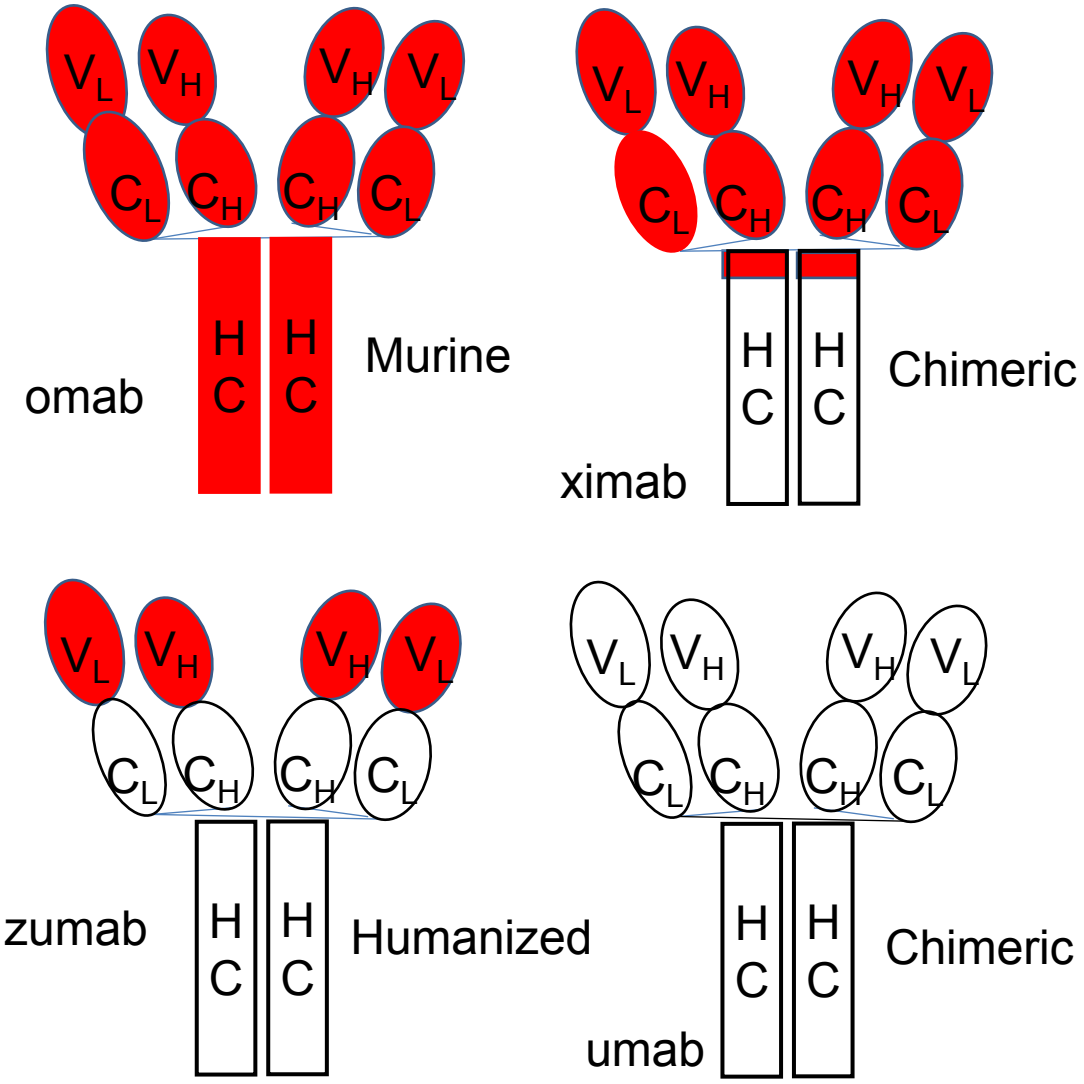
Immunoglobulins (IgGs)



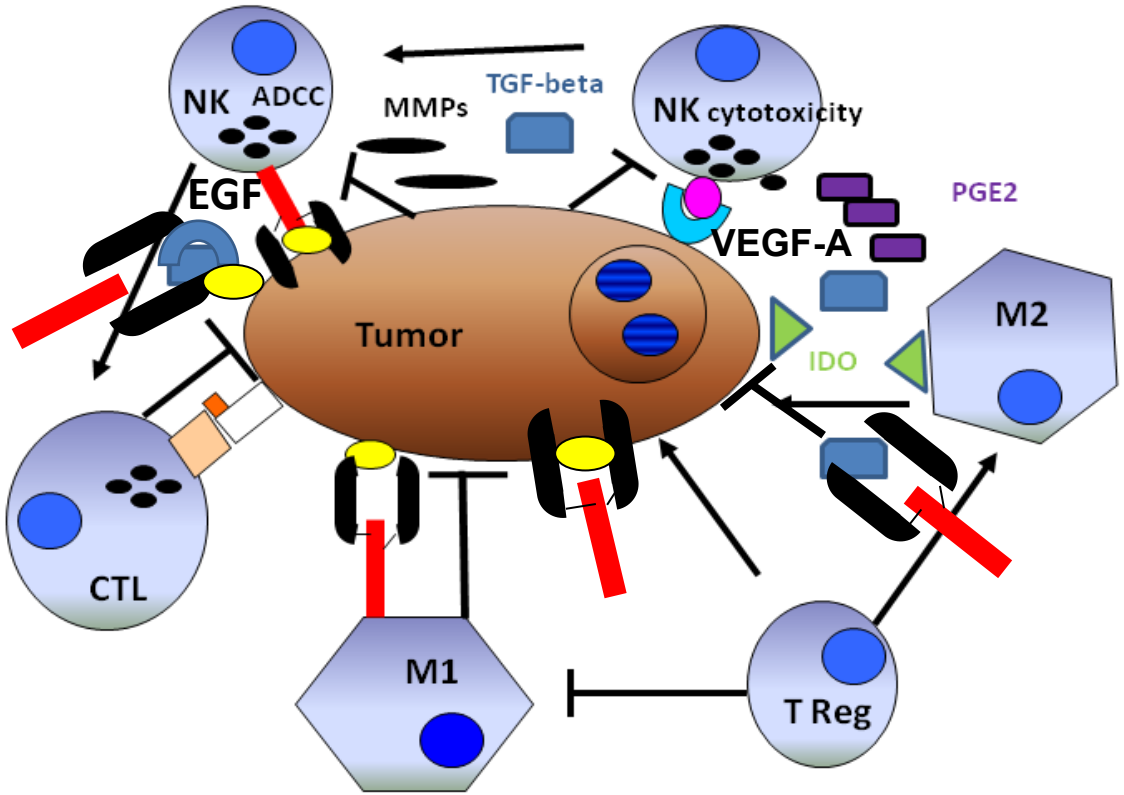
Features	IgG1	IgG2	IgG3	IgG4
Molecular Weight (kDa)	150	150	170	150
Amino acid hinge region	2	4	11	2
Half life (days)	14-21	14-21	7	14-21
Mean serum level (g/l)	6.98	3.8	0.51	0.56
Relative abundance (%)	60	32	4	4

Evolution of Therapeutic monoclonal antibodies (mAbs)

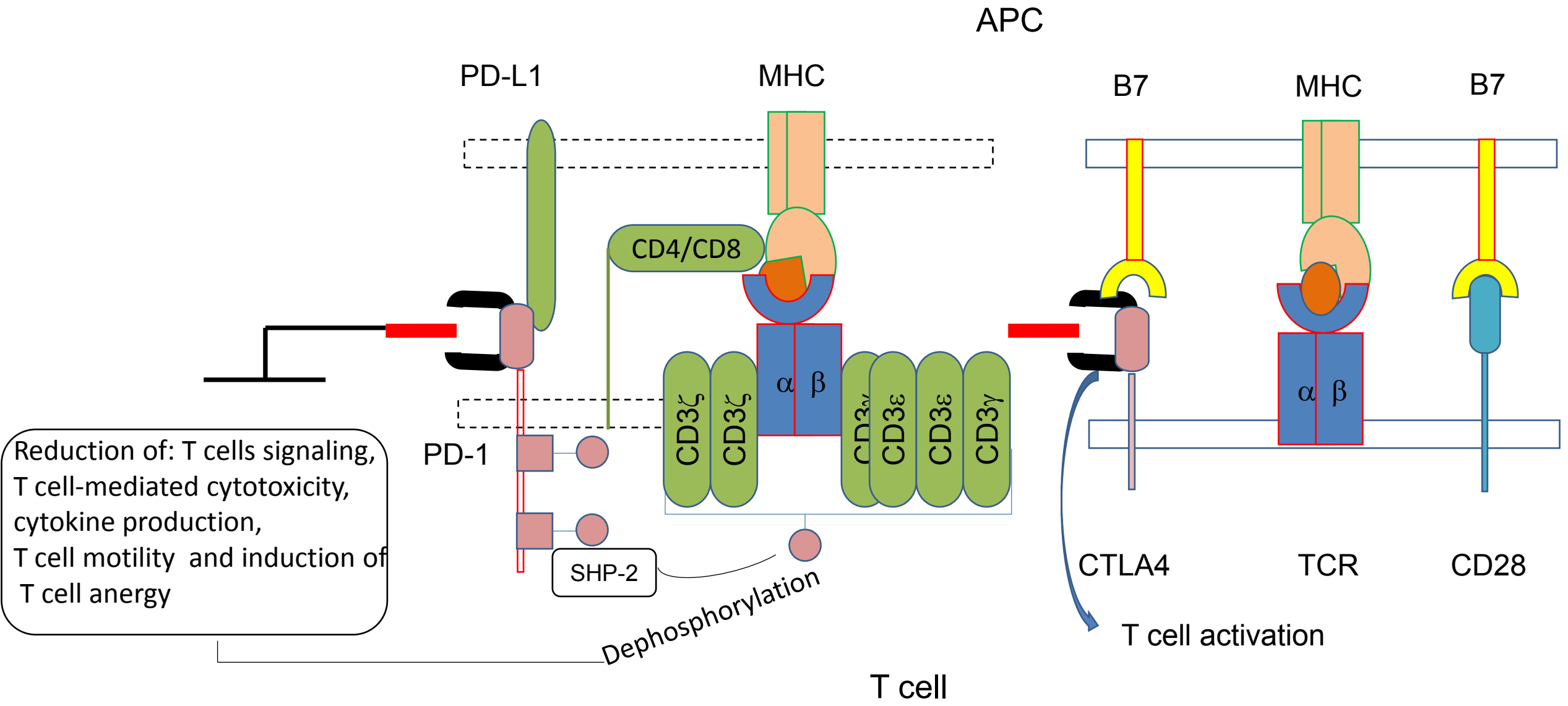




Types of anti-tumor activity of naked mAbs



The immune check point of T cell activation



Therapeutic mAbs improve the clinical course of solid and hematological malignancies

Therapeutic mAbs	Target	Therapeutic activity
Rituximab	CD20	Improves the clinical outcome of aggressive, indolent, low-grade B cell lymphomas and CLL
Cetuximab , panitumumab	EGFR	Benefits mCRC patients without KRAS and NRAS mutations. Cetuximab is also active in Head & Neck cancers
Trastuzumab	EGFR2 (HER2)	Early stage, metastatic and refractory BC and stomach cancer
Bevacizumab	VEGF-A	Useful in mCRC and recurrent GBM
Ipilimumab, and pembrolizumab and nivolumab	CTLA, and PD-1 respectively	Doubled the OS of mMelanoma patients and induced remission in refractory HL patients
Atezolizumab	PDL-1	Improves the OS in NSCLC patients. New treatment for advanced bladder cancer with 27% of response in a recent study
Pembrolizumab	PD-1	Improves OS in NSCLC patients. Since october 2016, iia the 1st line treatment of PDL-1+ NSCLC
Nivolumab	CTL4	Doubled the OS of patients with CHT resistant head & neck cancer

Limitations of therapeutic mAb-based immunotherapy

- Impairment of a direct anti-tumor activity of mAbs by KRAS and NRAS mutations involved in the signaling pathway of EGFRs.
- Lack of effective biomarkers indicating which subpopulation of cancer patients take advantage from check point inhibitor-based immunotherapy
- Inadequate success of check point inhibitor-based immunotherapy in patients without hypermutated cancers.

Overcoming mAb limitations transfering ADCC function from NK cells to T cells

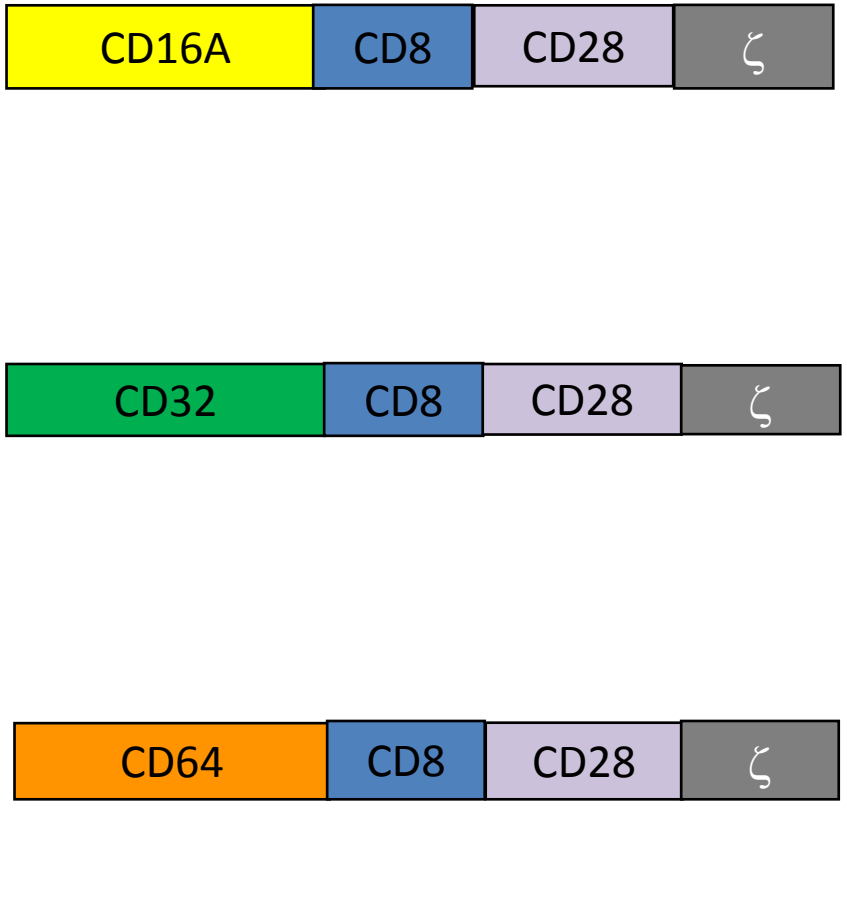
- NK cells armed with anti-EGFR mAbs kill KRAS mutated cancer cells
- The presence of specific FcγRIII polymorphisms on NK cells predict favorable in patients with EGFR + malignancies.

- Leukemia and solid tumor cells induce NK cell damage
- NK cells barely infiltrate the tumor microenvironment

- CD8+ T cells are significantly present in colorectal lesions, and their infiltration is associated with a favorable prognosis

We and other investigators propose to enhance the anti-tumor potential of mAbs by engineering cytotoxic T cells with FcγRs

Fcγ Chimeric Receptors (Fcγ-CR)

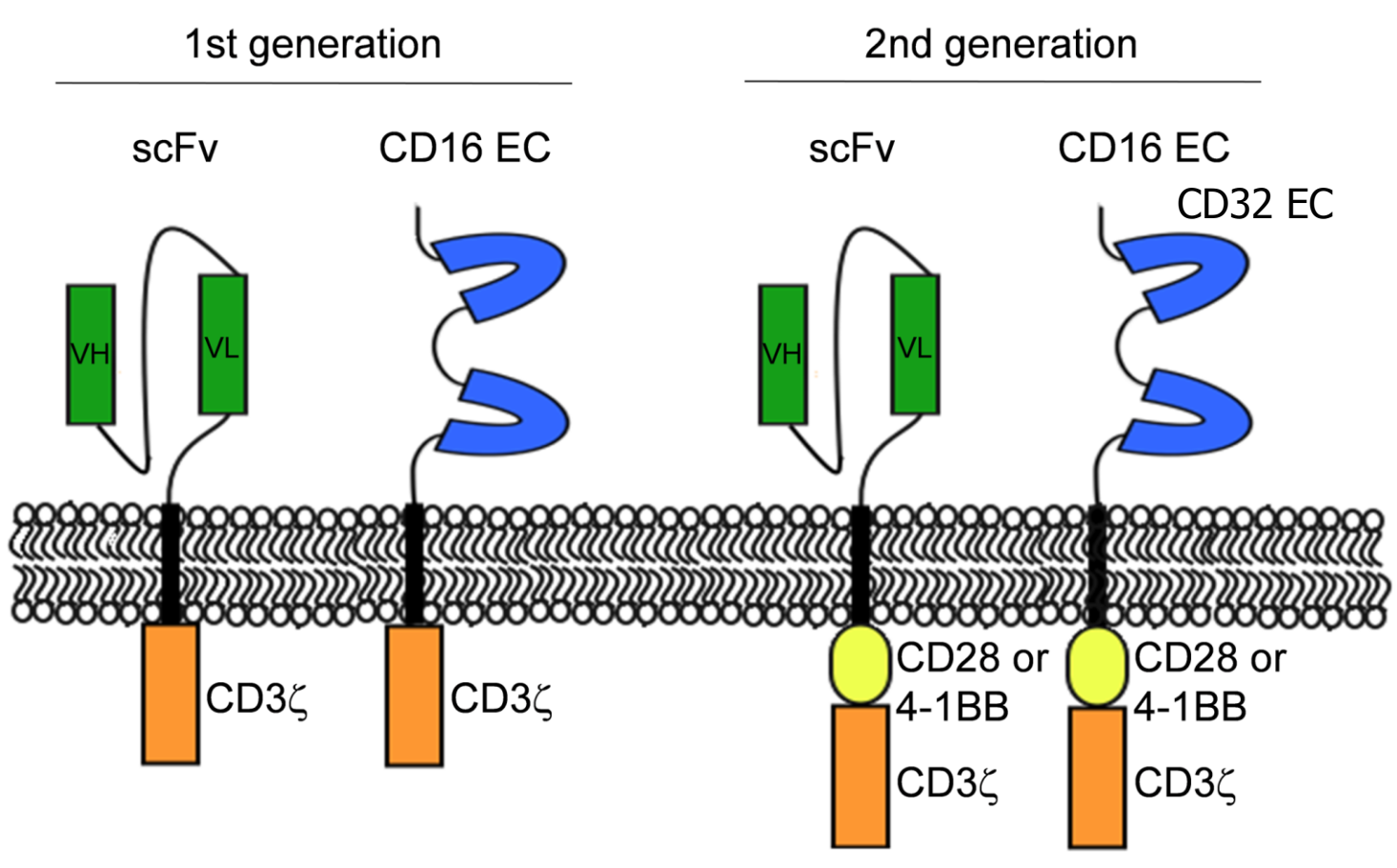


CD16-CR

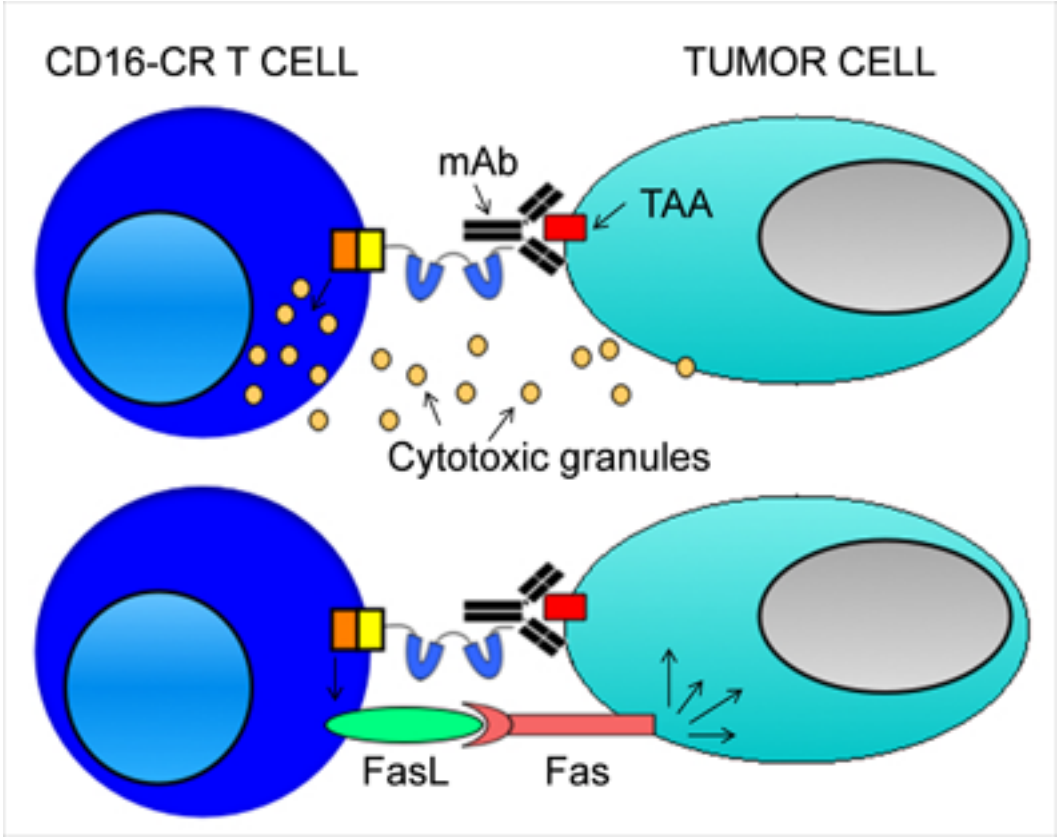
CD32-CR

CD64-CR

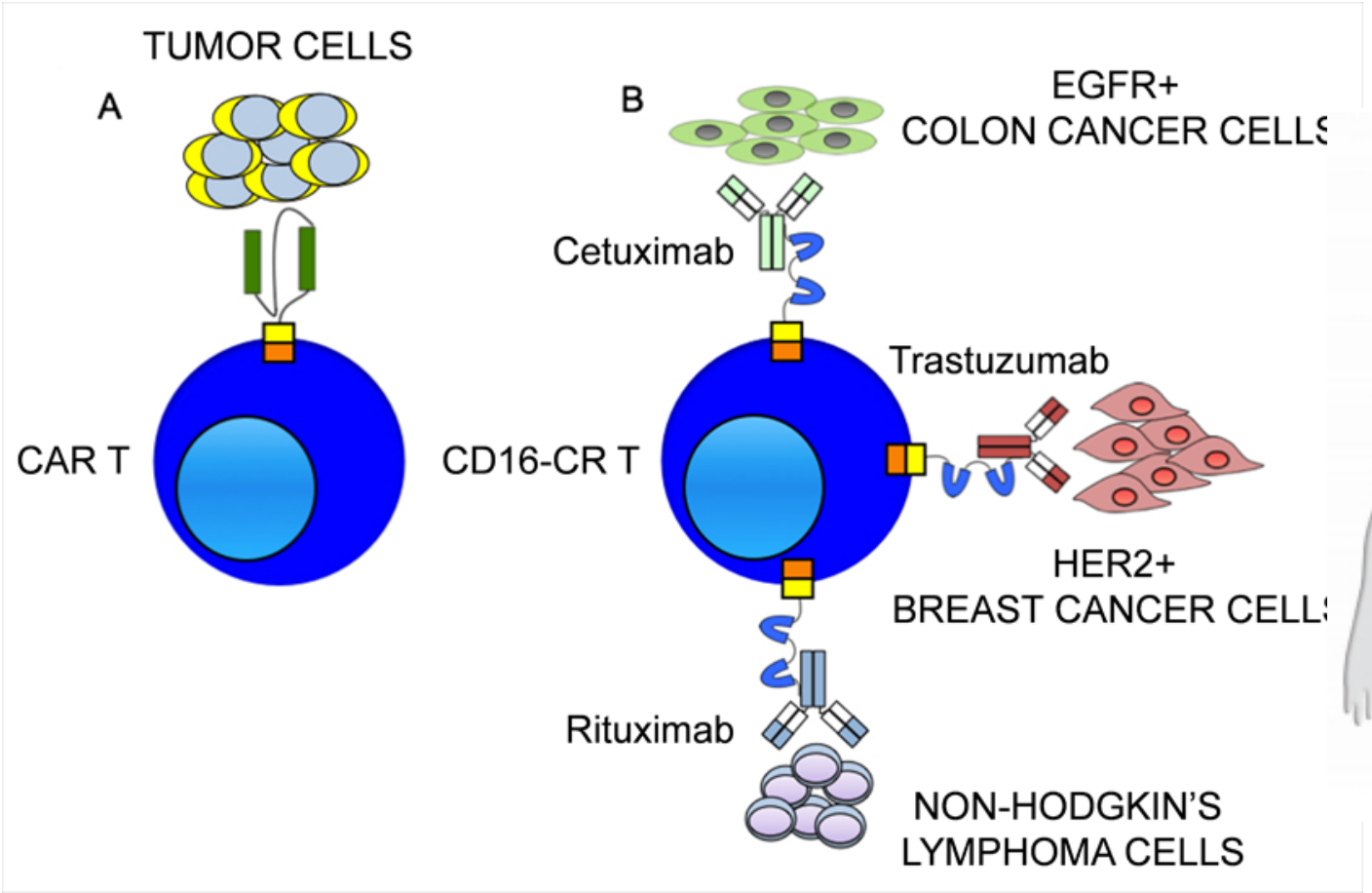
Therapeutic mAbs confear multiple tumor specificity to Fcγ–CR-engineered T cells

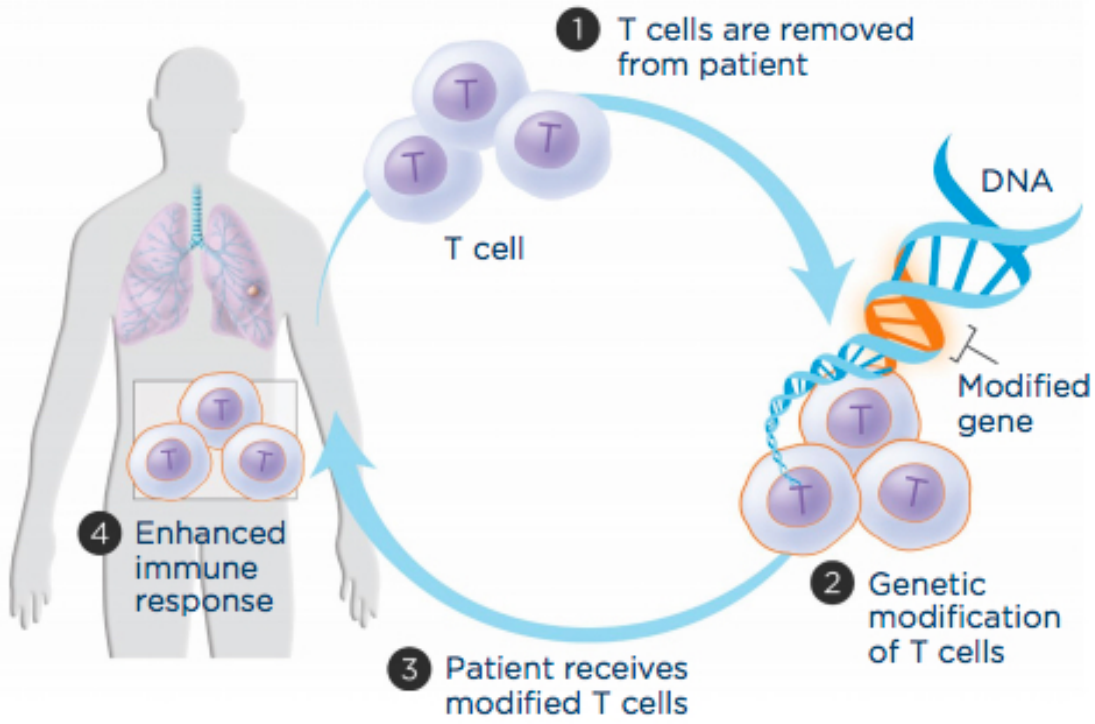


Mechanisms of Fcγ–CR T cell anti-tumor activity



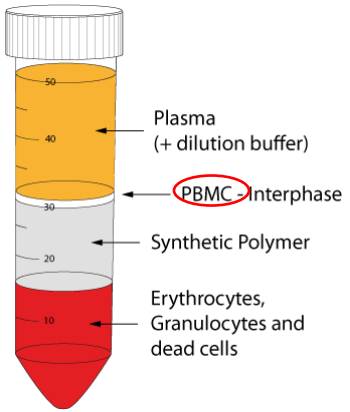
Therapeutic mAbs confear multiple tumor specificity to Fcγ–CR-engineered T cells





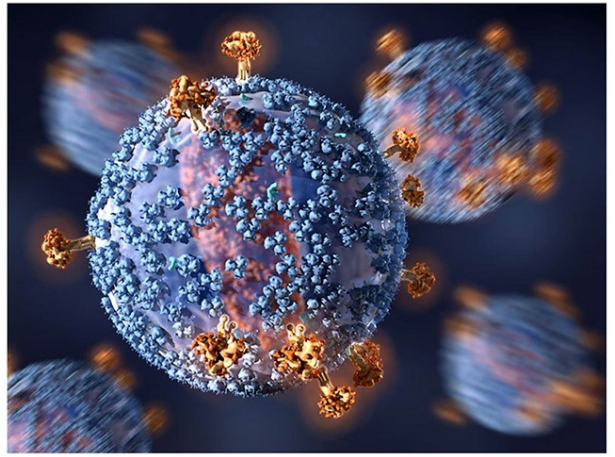
Gene transfer technology used to engineer T cells to express Fcγ-CR

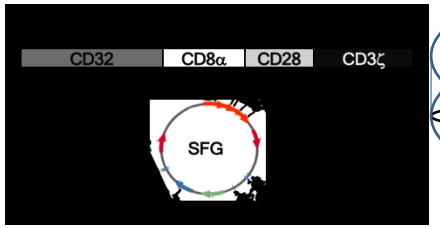
Ficoll

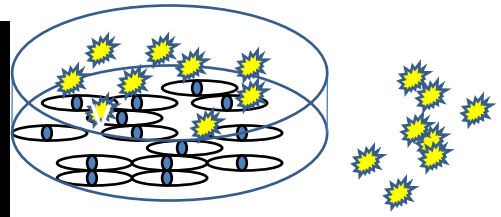


T cell activation with **anti-CD3+anti-CD28 mAbs**

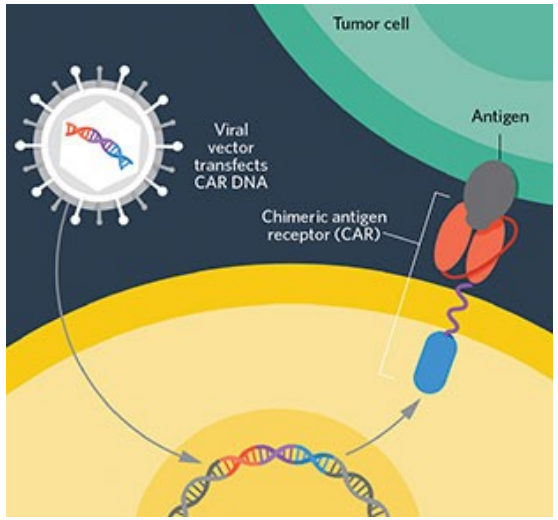
Fcγ-CR T cells



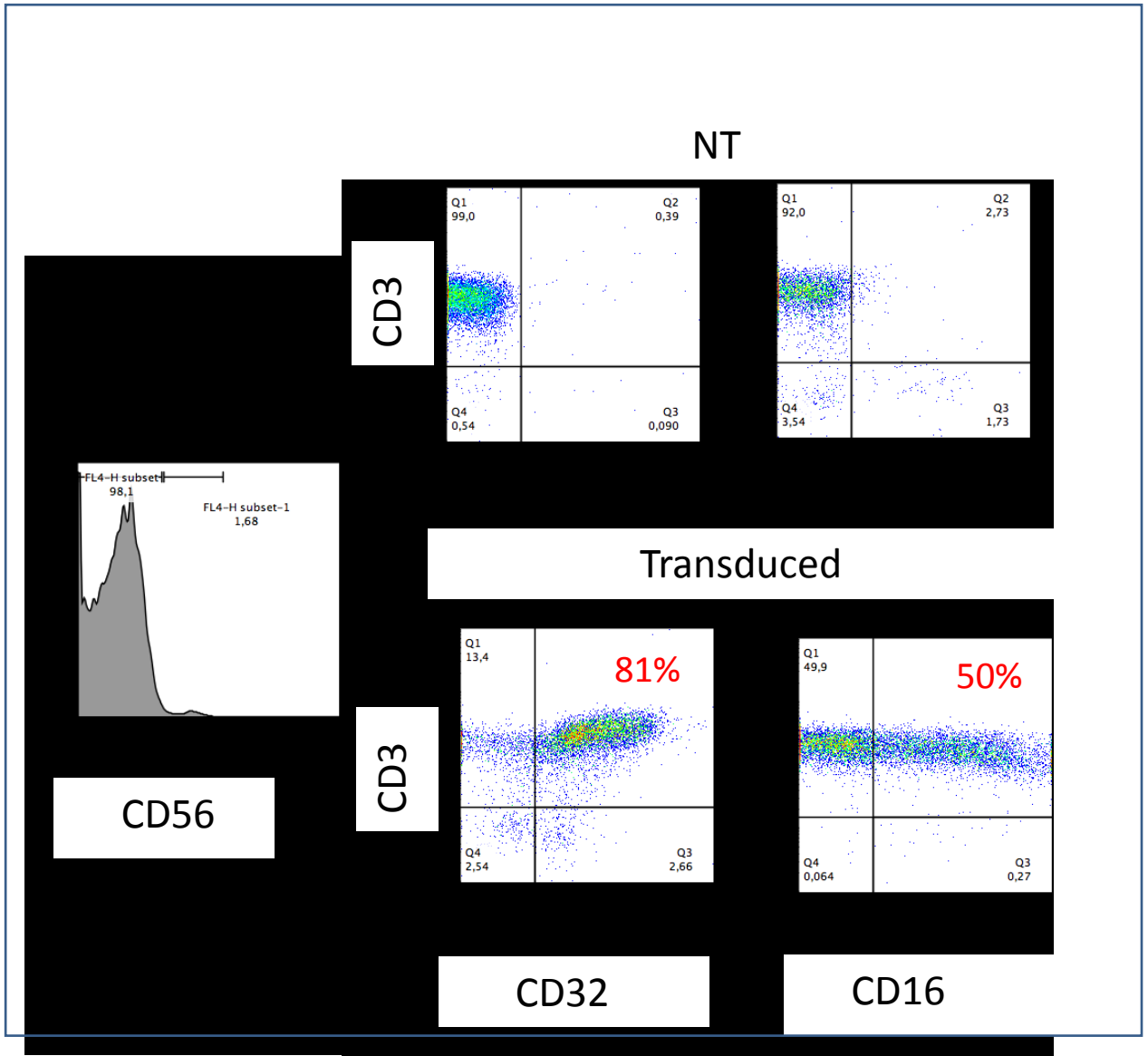


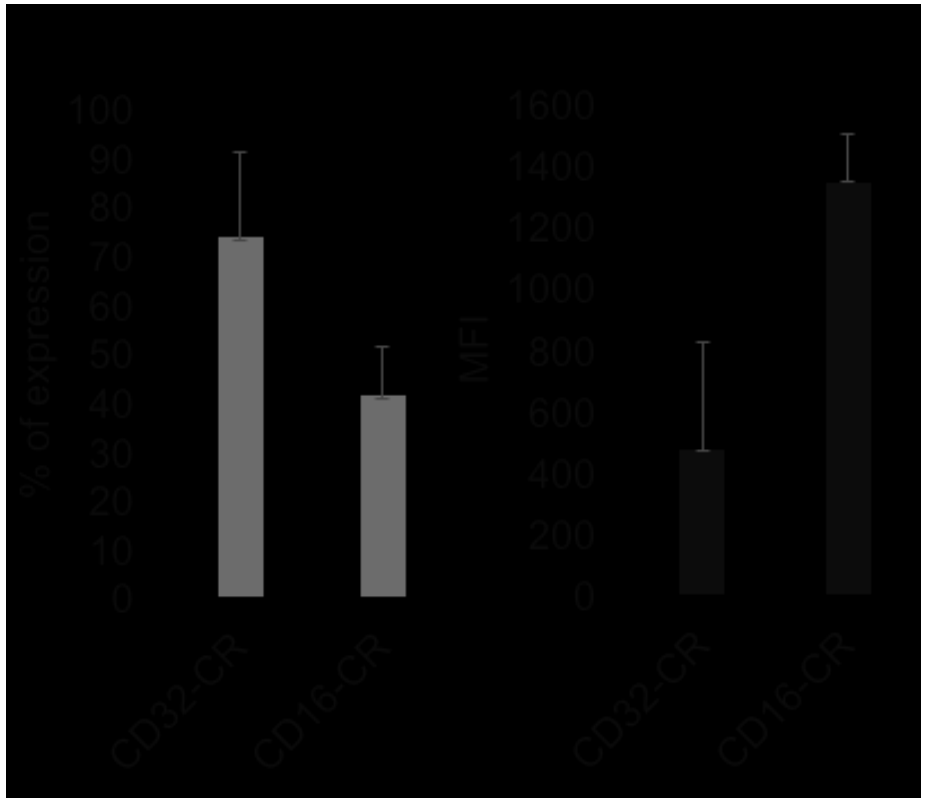


Retrovirus production

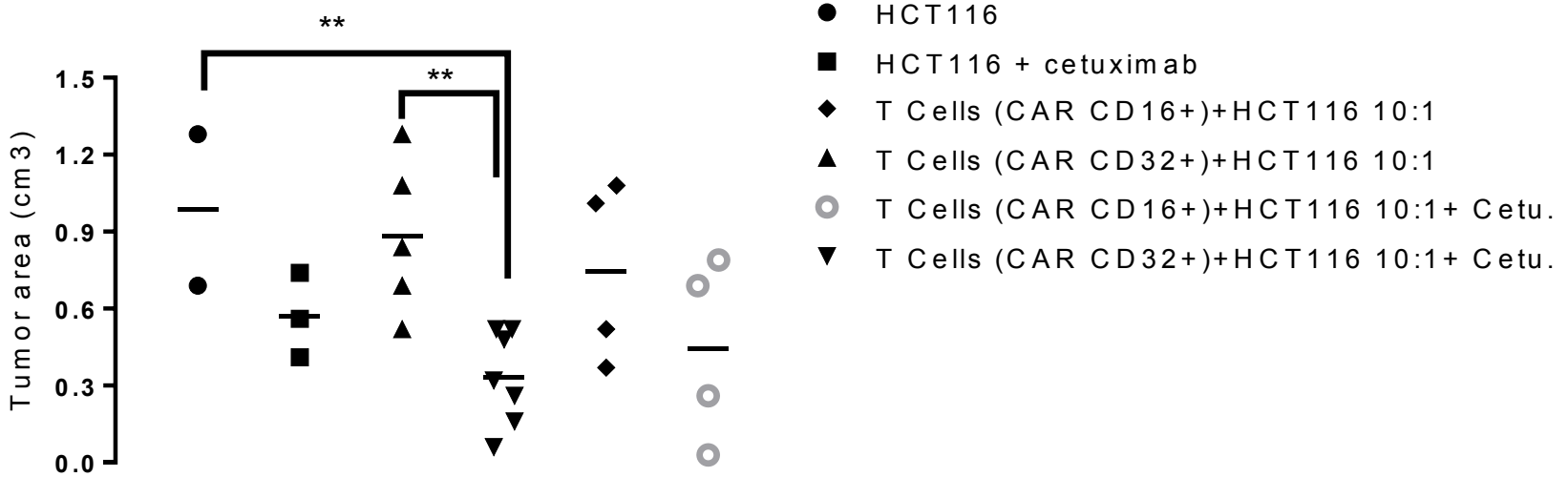


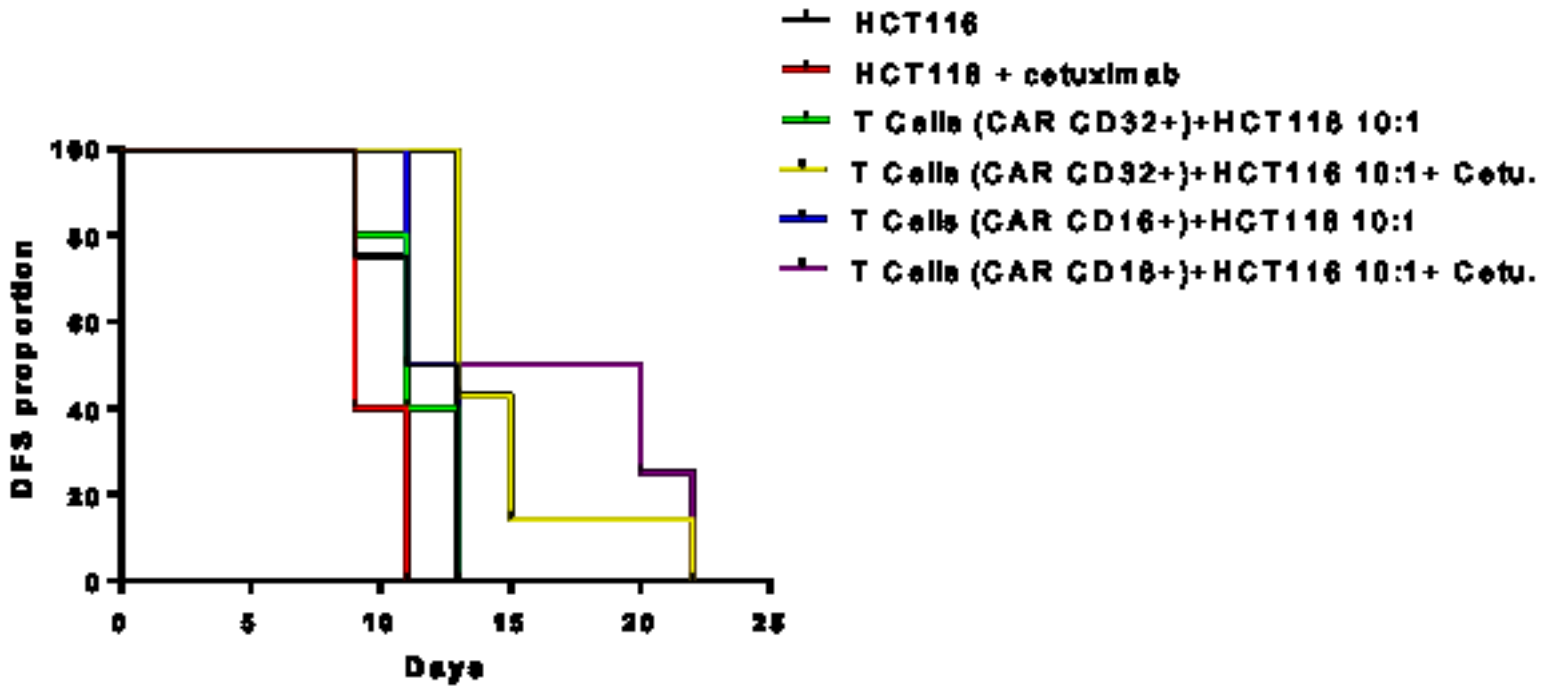
CD32-CR and CD16-CR are differently expressed on T cells





Fcγ-CR-engineered T cells damaged KRAS-Mutaded cancer cells



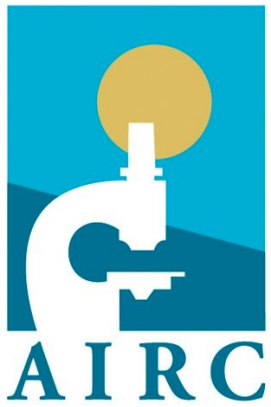


Future perspectives

- ✓Optimizing of CD64-CR
- ✓Improving CD16- and CD32-CRs affinity for IgG isotypes (point mutation $CD16^{V158}$/$CD32^{H131}$)

- ✓Testing the Fcγ-CR T cells anti-cancer activity against different EGFR+++/KrasM tumors in vitro and in vivo (es. NSCLC)
- ✓Testing Fcγ-CR toxicity in non-immunodeficient mice bearing a spontaneous or engrafted CRC.

Acknowledgments



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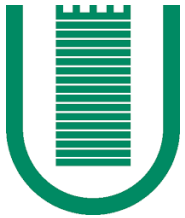

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