Design of T Cell Receptors

(15 min)

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REVIEWS

Gene-engineered T cells for cancer therapy

Michael H. Kershaw[1,2], Jennifer A. Westwood[1] and Phillip K. Darcy[1,2]

NATURE REVIEWS | CANCER

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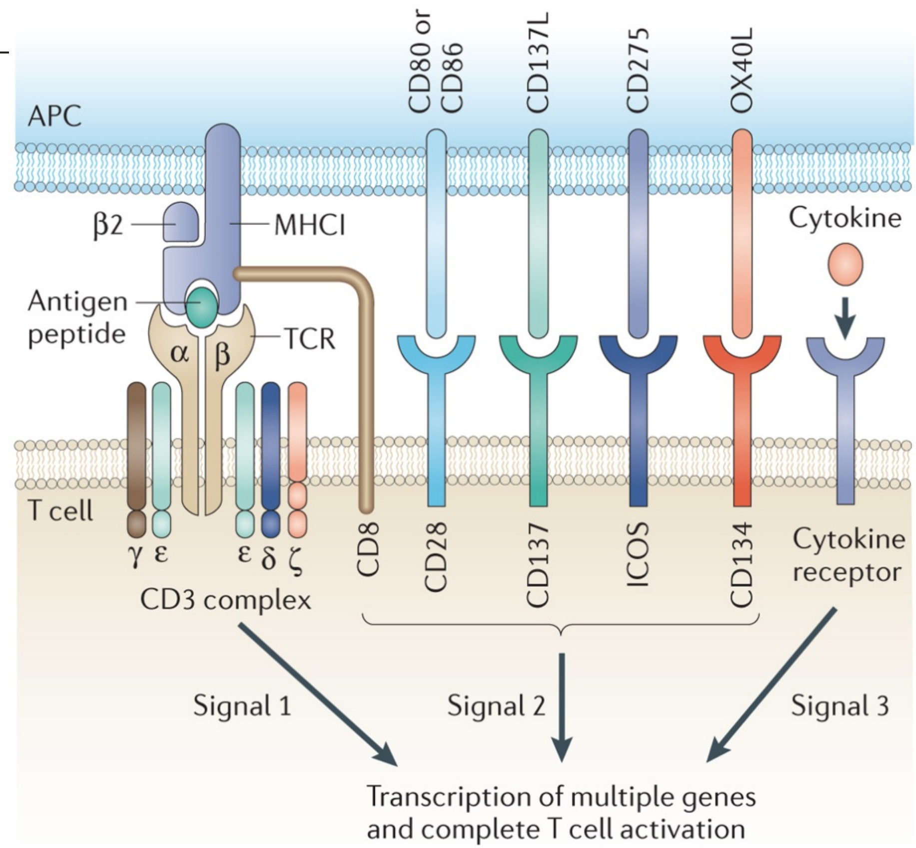
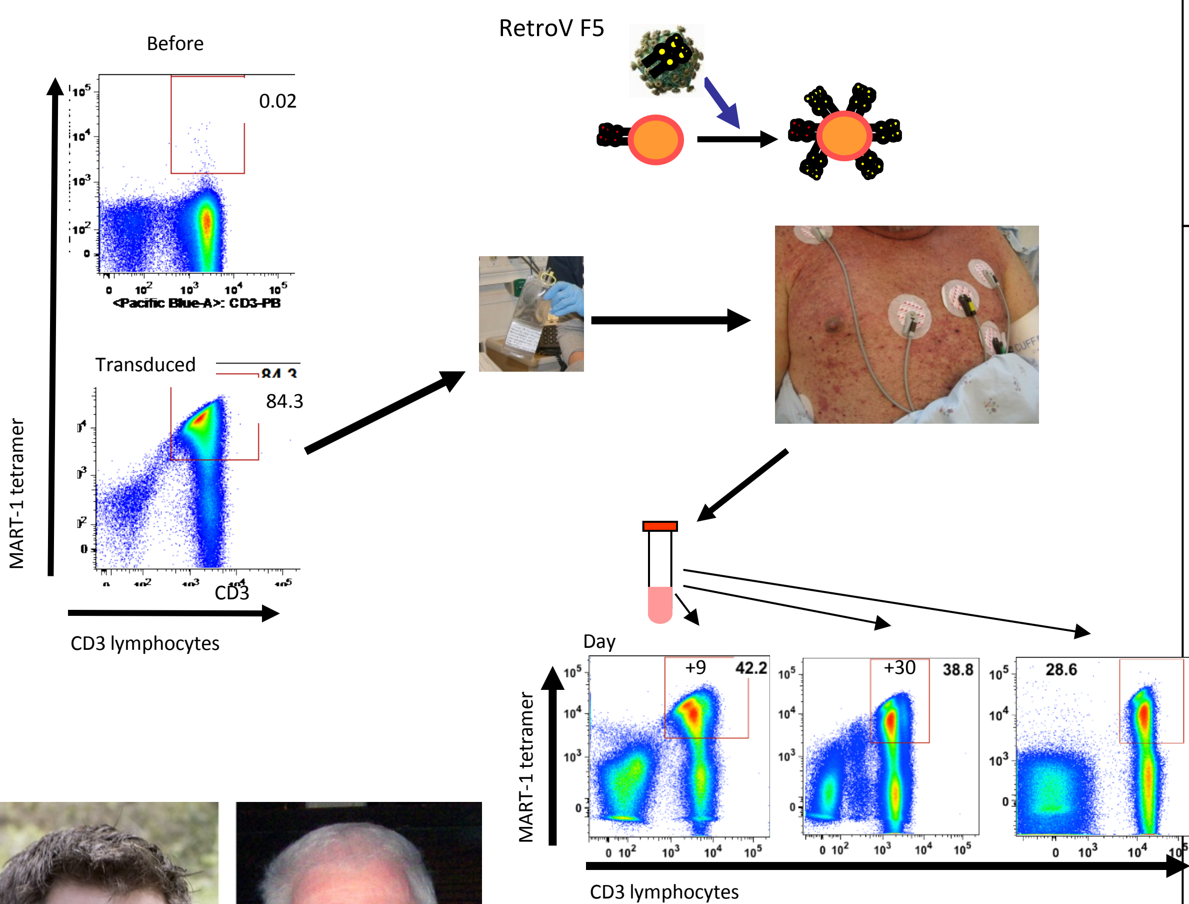
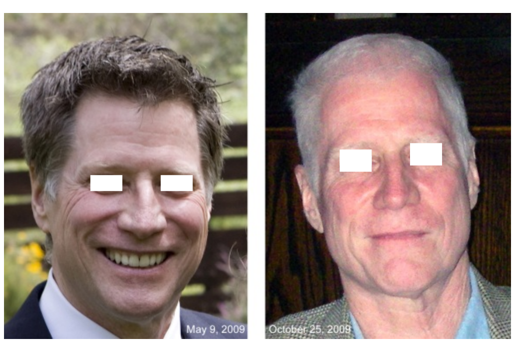
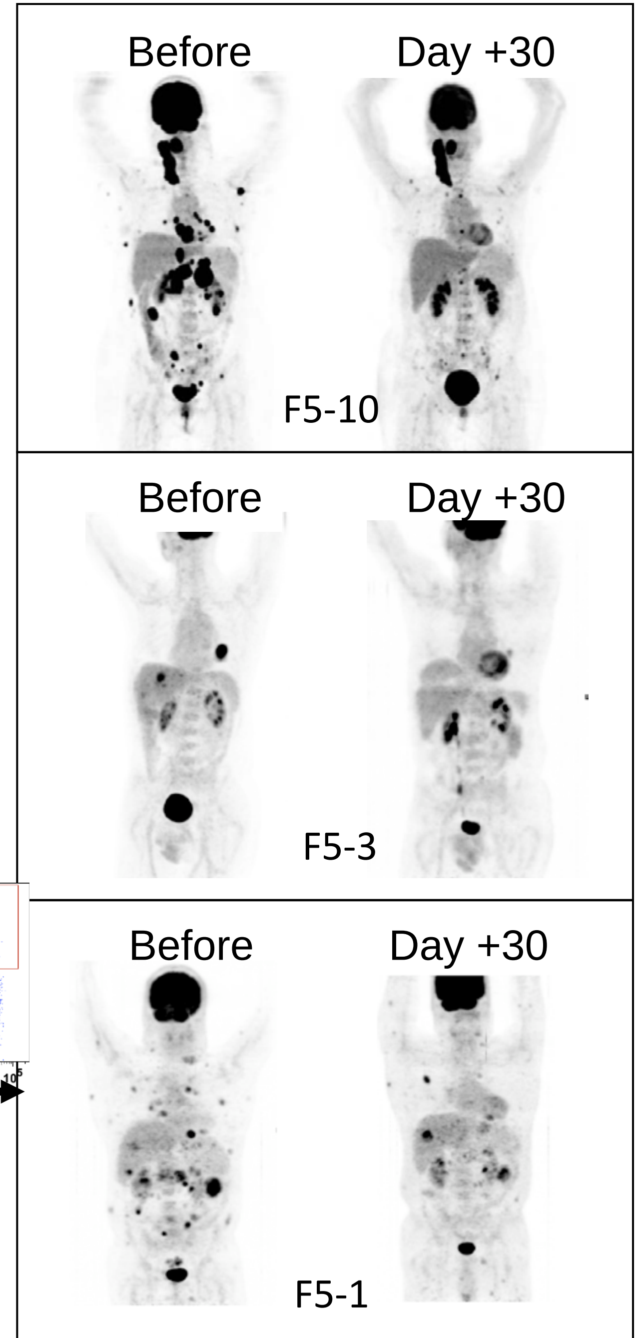


TCR engineering uses a physiological recognition and (thus far) physiological control and signaling pathways

UCLA/Caltech Engineered Immunity Program
TCR engineered adoptive cell transfer therapy

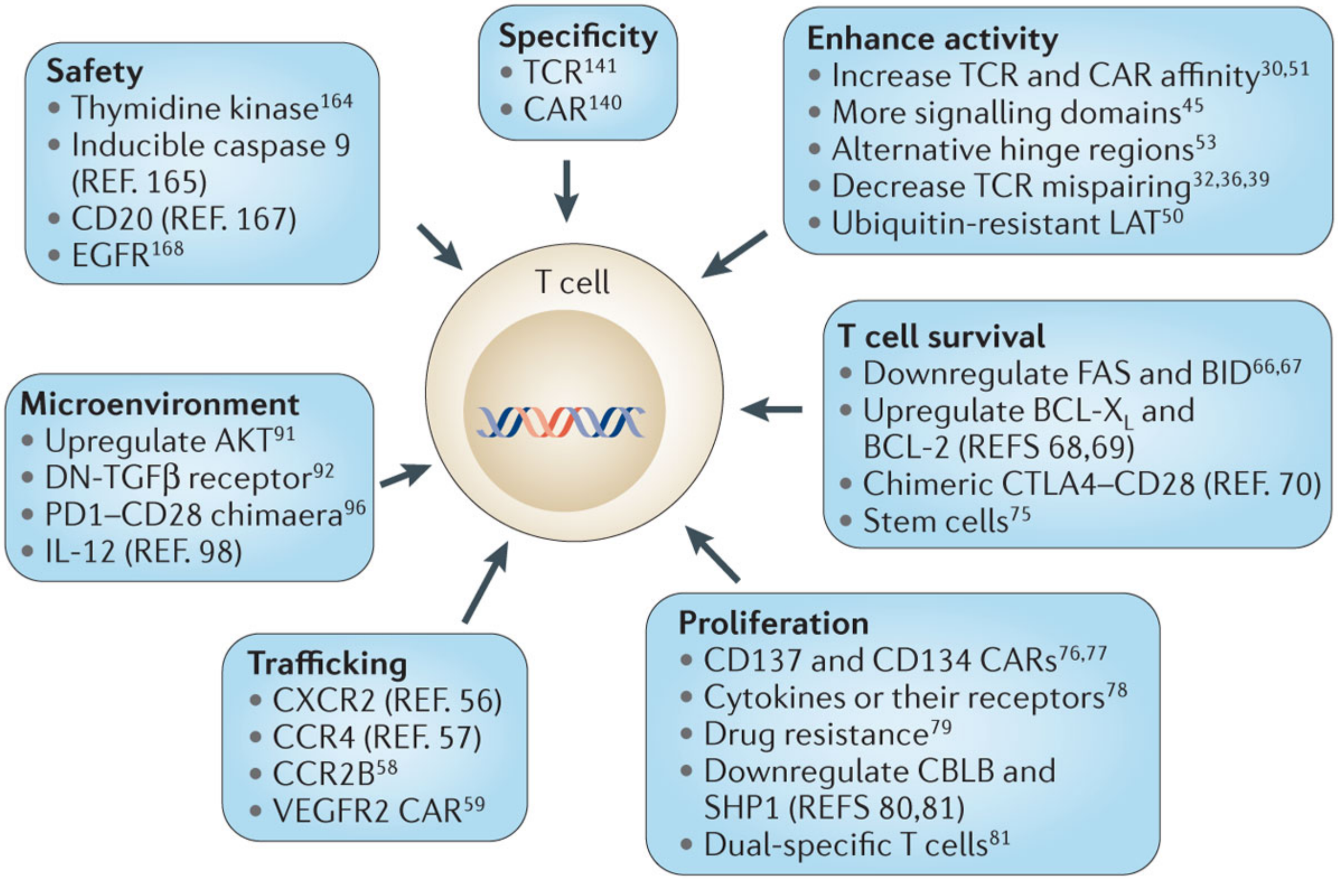






Chodon, Comin-Anduix, Koya, Economou, Kohn, Witte, Baltimore, Ribas

The promise: Further genetic engineering of TCR engineered T cells may broaden benefit in the clinic



Nature Reviews | Cancer

Limiting step: Paucity of widely expressed MHC-antigen complexes to target

Cancer	Antigens targeted by CARs	Antigens targeted by TCR
Breast cancer	ERBB2 and MUC1	–
Cervical carcinoma	CD44v6, CD44v7 and CD44v8 (REF. 142)	HPV16-specific[14]
Gastrointestinal cancers	CEA, EPCAM (also known as EGP2 and EGP40), TAG72 and KIT[143]	CEA
Glioblastoma	IL-13Rα2 and EGFR[29]	–
Hepatocarcinoma	–	HBV-specific[13]
Lymphomas and leukaemias	CD19, CD20, CD22, CD30, CD33, κ-LC, ROR1 (REF. 144), CD38 (REF. 145) and NKG2D ligands[146]	WT1 (REF. 9), AURKA[147], HA1 (REF. 148), HA2 (REF. 149) and HMMR[150]
Melanoma	GD3, HMW-MAA[151], MAGE1 (REF. 152) and MAGEA3 (REF. 125)	MART1, GP100, NYESO1, tyrosinase[153], MAGEA3 (REF. 154) and MAGEA1 (REF. 155)
Neuroblastoma	GD2, CD171 (also known as L1CAM) and NCAM	–
Osteosarcoma	IL-11Rα[20]	–
Ovarian cancer	αFR[156] and MUC1 (REF. 3)	–
Pancreatic cancer	CEA	–
Prostate cancer	PSCA, PSMA and TARP[157]	–
Rhabdomyosarcoma	Fetal acetylcholine receptor	–
Renal cancer	CAIX	RCC antigen[158]
Tumour vasculature	VEGFR2 (REFS 59,159) and PSMA	–
Universal	BBIR[136] and FITC[135]	–
Various tumours	TAG72, mesothelin, LeY[28], 5T4 oncofetal antigen[53], ERBB3, ERBB4 and GP58 (REF. 160)	Survivin[161], MDM2 (REF. 11), MAGEA4 (REF. 162), NYESO1 and p53 (REF. 37)

αFR, α-folate receptor; AURKA, aurora kinase A; BBIR, biotin-binding immune receptor; CAIX, carbonic anhydrase IX; CEA, carcinoembryonic antigen; EGFR, epidermal growth factor receptor; FITC, fluorescein isothiocyanate; HA, minor histocompatibility antigen; HBV, hepatitis B virus; HMMR, hyaluronan-mediated motility receptor; HMW-MAA, high-molecular-weight-melanoma-associated antigen; HPV, human papillomavirus; IL-11Rα, interleukin-11 receptor-α; IL-13Rα2, interleukin-13 receptor-α2; κ-LC, κ-light chain; LeY, Lewis Y; MAGE, melanoma antigen; MART1, melanoma antigen recognized by T cells 1; NCAM, neural cell adhesion molecule 1; PSCA, prostate stem cell antigen; PSMA, prostate-specific membrane antigen; RCC, renal cell carcinoma; ROR1, receptor tyrosine kinase-like orphan receptor 1; TAG72, tumour-associated glycoprotein 72; TARP, TCRγ alternate reading frame protein; VEGFR2, vascular endothelial growth factor receptor 2; WT1, Wilm's tumour 1.

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Means to attempt to improve safety

Safety strategy	Methods	Refs
HSV-TK	T cells sensitive to gancyclovir	163,164
Inducible caspase 9 or FAS	Dimerization using AP1903 induces the apoptosis of T cells	165,166
CD20	Eliminate T cells using rituximab	167
EGFR (truncated)	Eliminate T cells using cetuximab	168
MYC tag in CAR	Deplete T cells using MYC-specific antibody	169
Reduce TCR mispairing	Various, including disulphide bonds and zinc finger nucleases	32,33,39
Decrease risk of oncogene activation	Use alternative vectors, such as lentivirus, transposons or RNA	118, 170,171
Inducible promoters	Tetracycline to switch transgene expression off	172
Target 2 antigens	Manipulate expression of two CARs such that effective response is only elicited by two antigens	173
Combinatorial signalling	Separate signal 1 and signal 2 into two CARs such that effective response needs engagement of two antigens	174,175

CAR, chimeric antigen receptor; EGFR, epidermal growth factor receptor.

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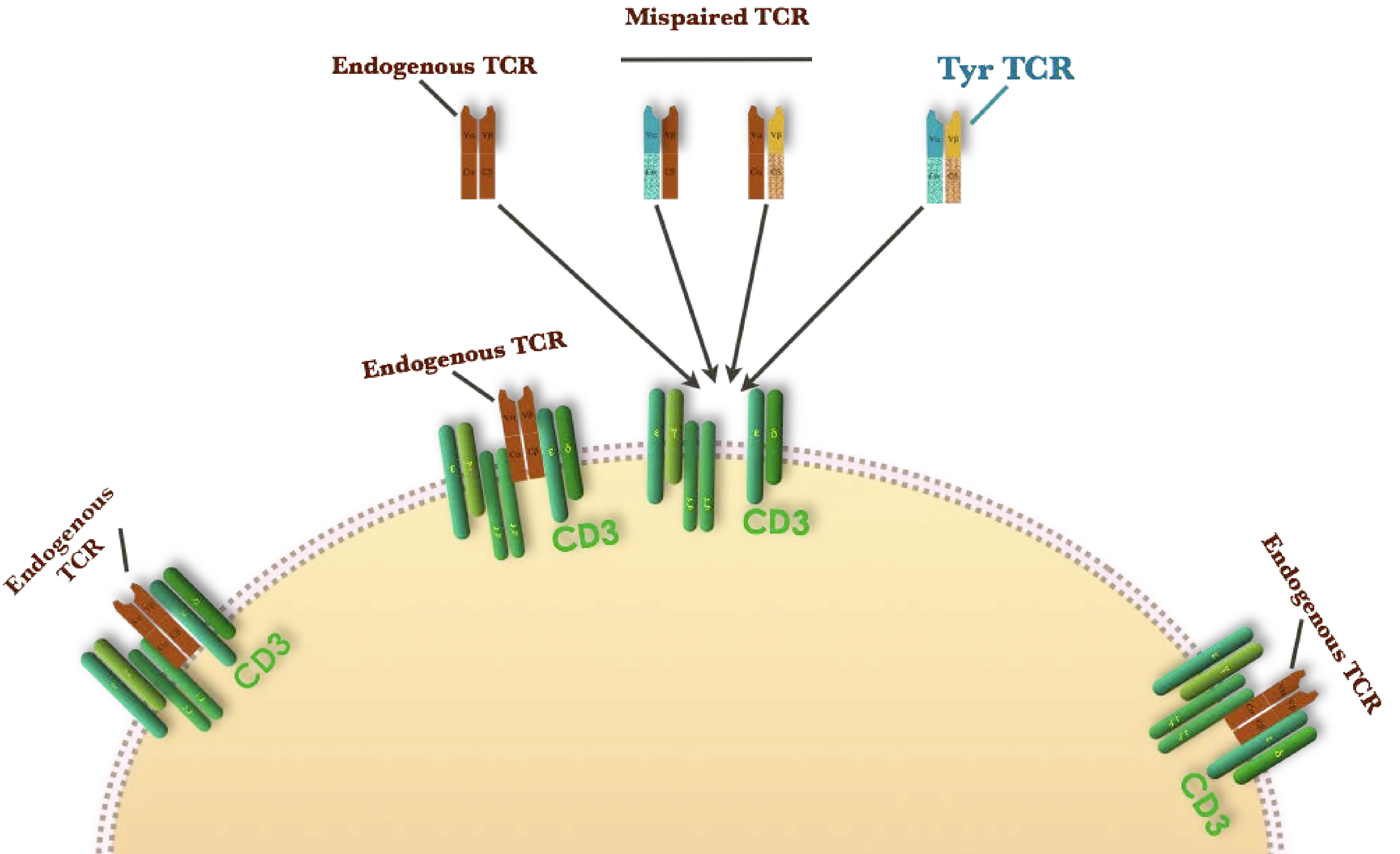
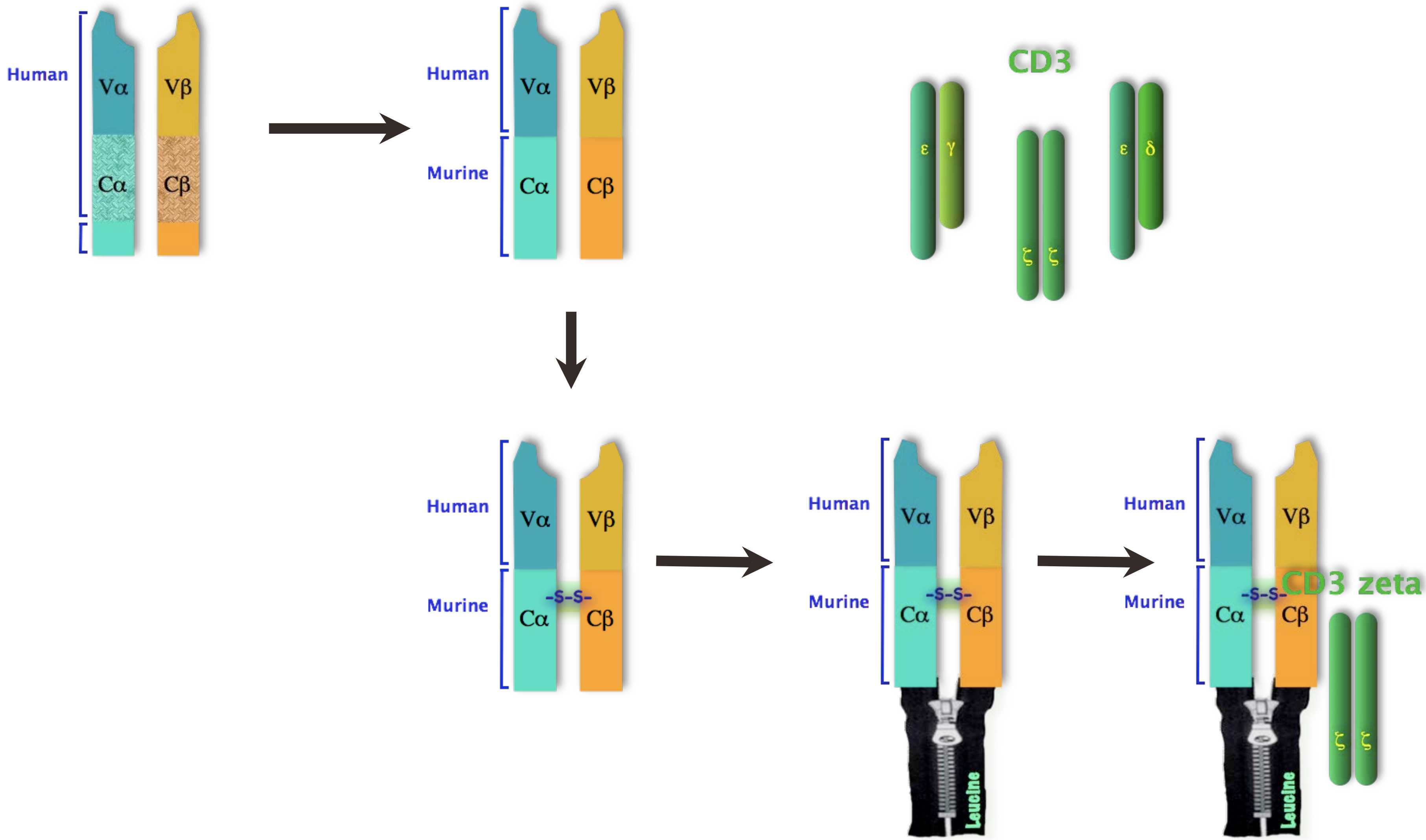
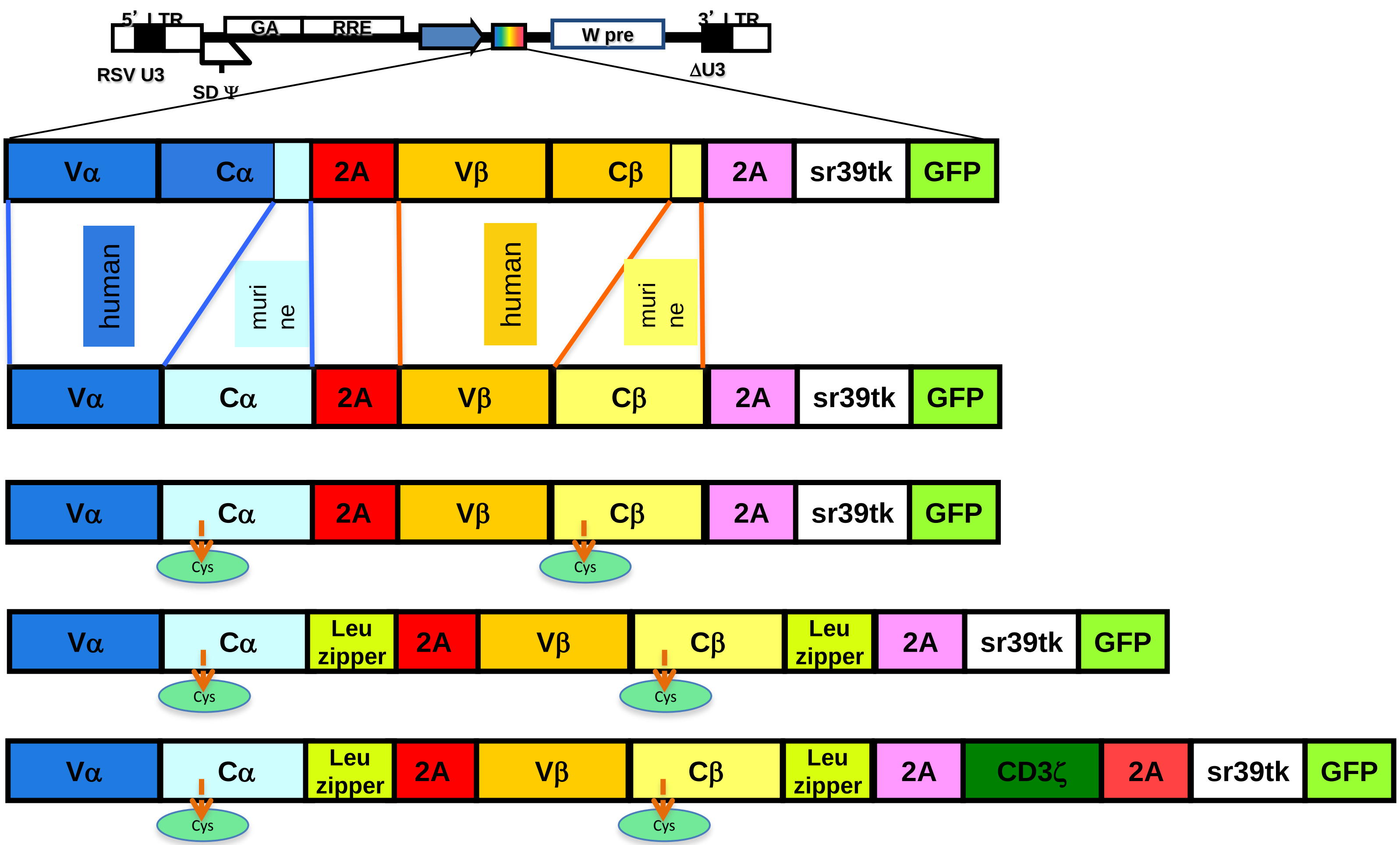
Mispairing of alpha and beta chains between endogenous and recombinant TCRs



Optimizing expression of engineered TCR

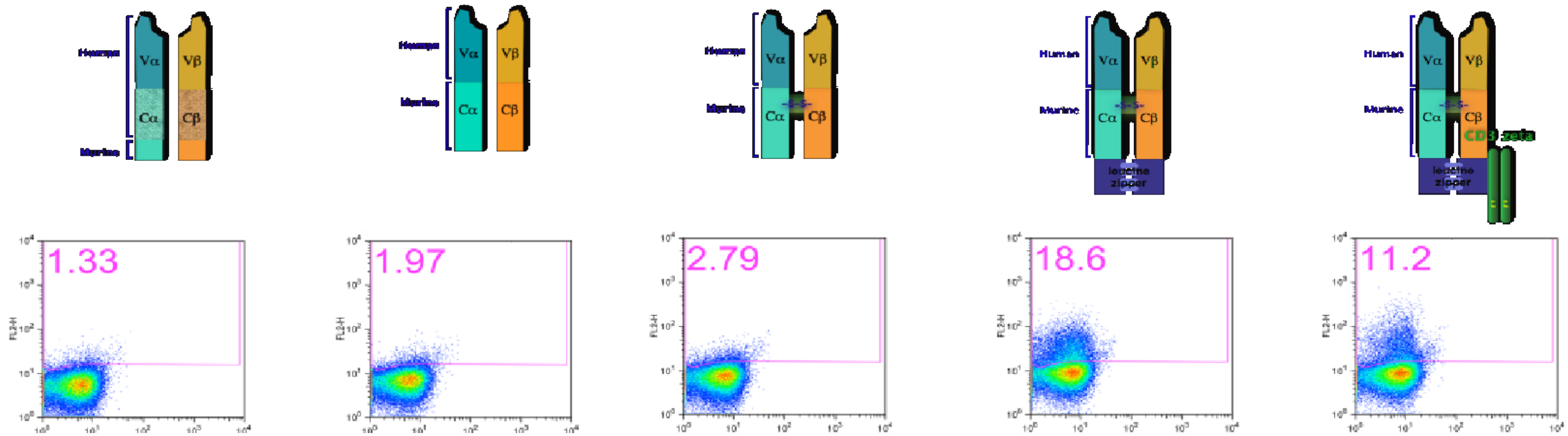


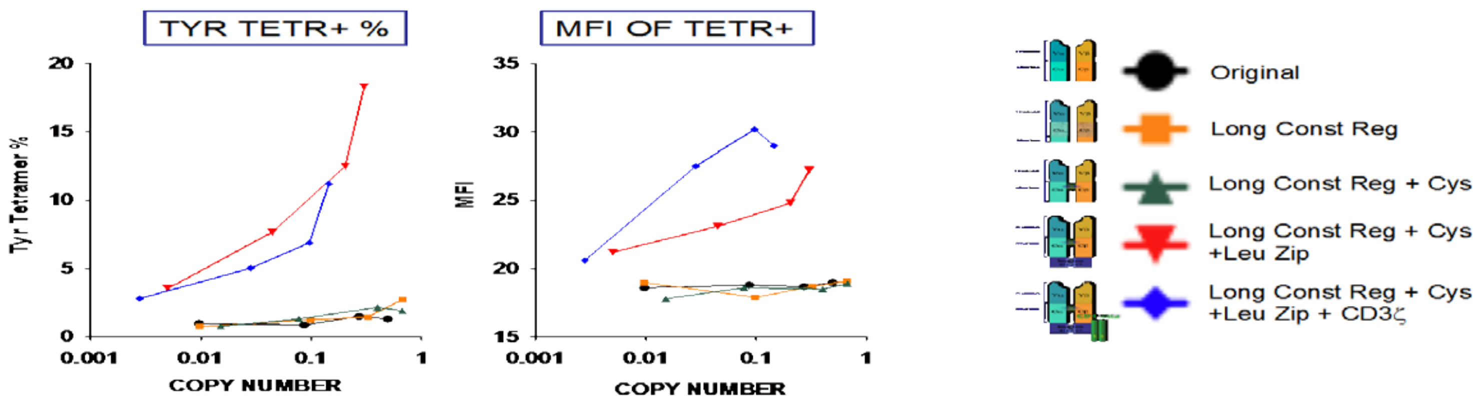
Retroviral vectors to test modifications to improve TCR pairing and expression



Richard C. Koya

The inclusion of a leucine zipper markedly increases surface TCR expression by tetramer assay





Increased vector copy number resulted in increased surface TCR expression only when using leucine zippers

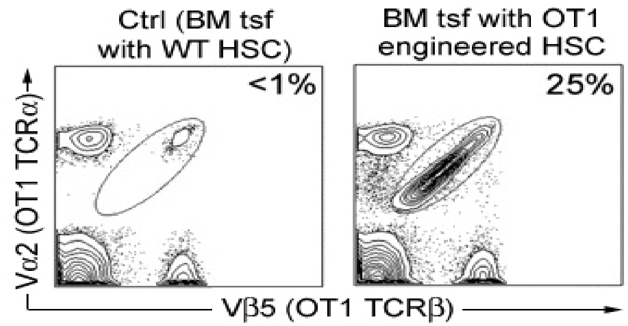
Continuous endogenous generation of TCR transgenic T cells by hematopoietic stem cells

Long-term *in vivo* provision of antigen-specific T cell immunity by programming hematopoietic stem cells

Lili Yang and David Baltimore*

PNAS | March 22, 2005 | vol. 102 | no. 12

PNAS 2002; 99 (9): 6204-9.
PNAS 2005; 102 (12): 4518-23.



Antitumor activity from antigen-specific CD8 T cells generated in vivo from genetically engineered human hematopoietic stem cells

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PNAS 2011; 108 (51): E1408-16.

Allelic Exclusion and Peripheral Reconstitution by TCR Transgenic T Cells Arising From Transduced Human Hematopoietic Stem/Progenitor Cells

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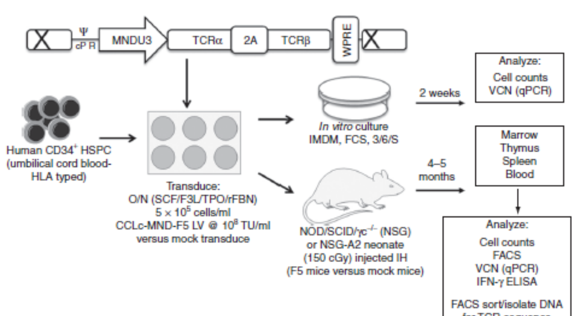

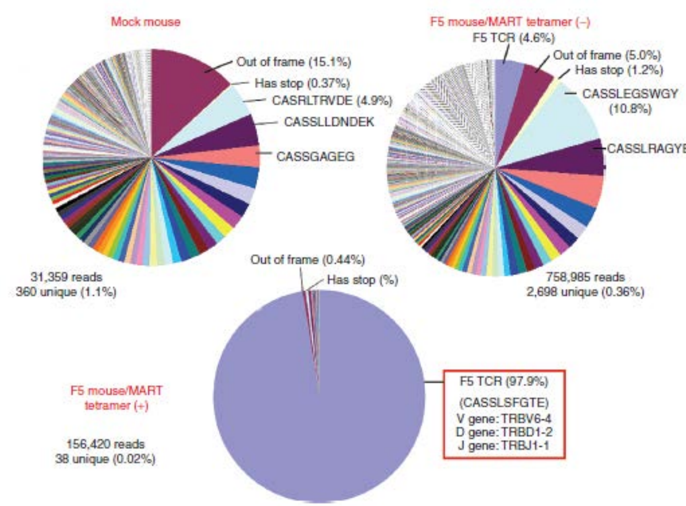

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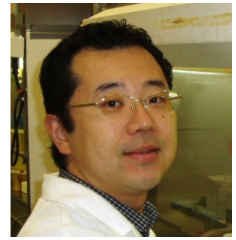

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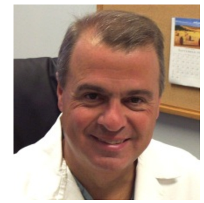

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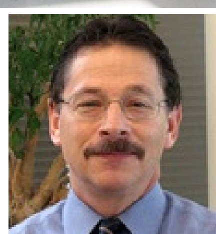

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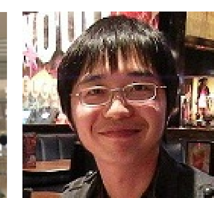

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