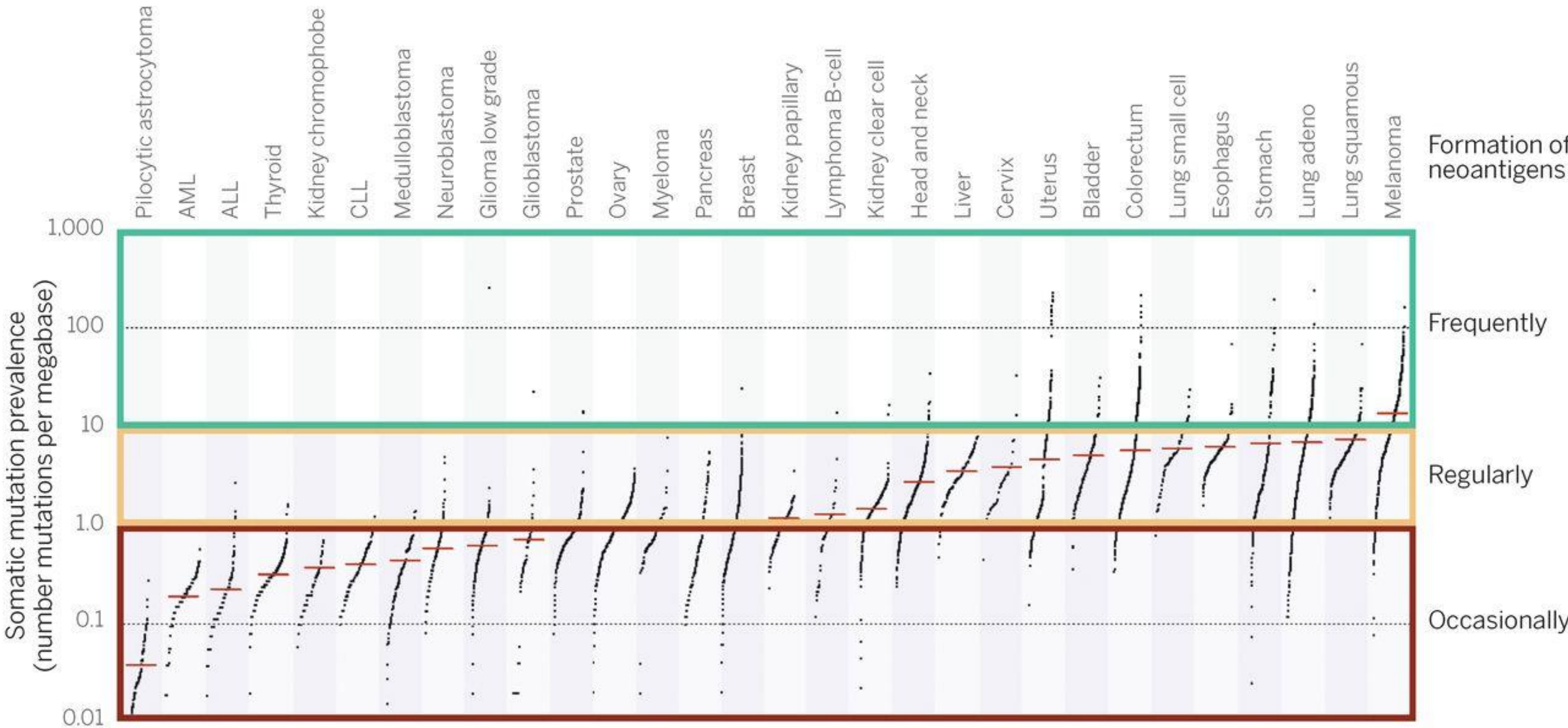
Immunotherapy:
Harnessing the immune system to fight cancer

The concept of immunological surveillance

" In large long-lived animals, inheritable changes must be common in somatic cells and a proportion of these changes will represent a step towards malignancy. It is an evolutionary necessity that there should be some mechanism for eliminating or inactivating such potentially dangerous cells and it is postulated that this mechanism is of immunological character."

F.M. Burnet, Prog. Exp. Tumor Res. Vol 13, p1-27, 1970.

Somatic mutations in tumors creates a neoantigen repertoire

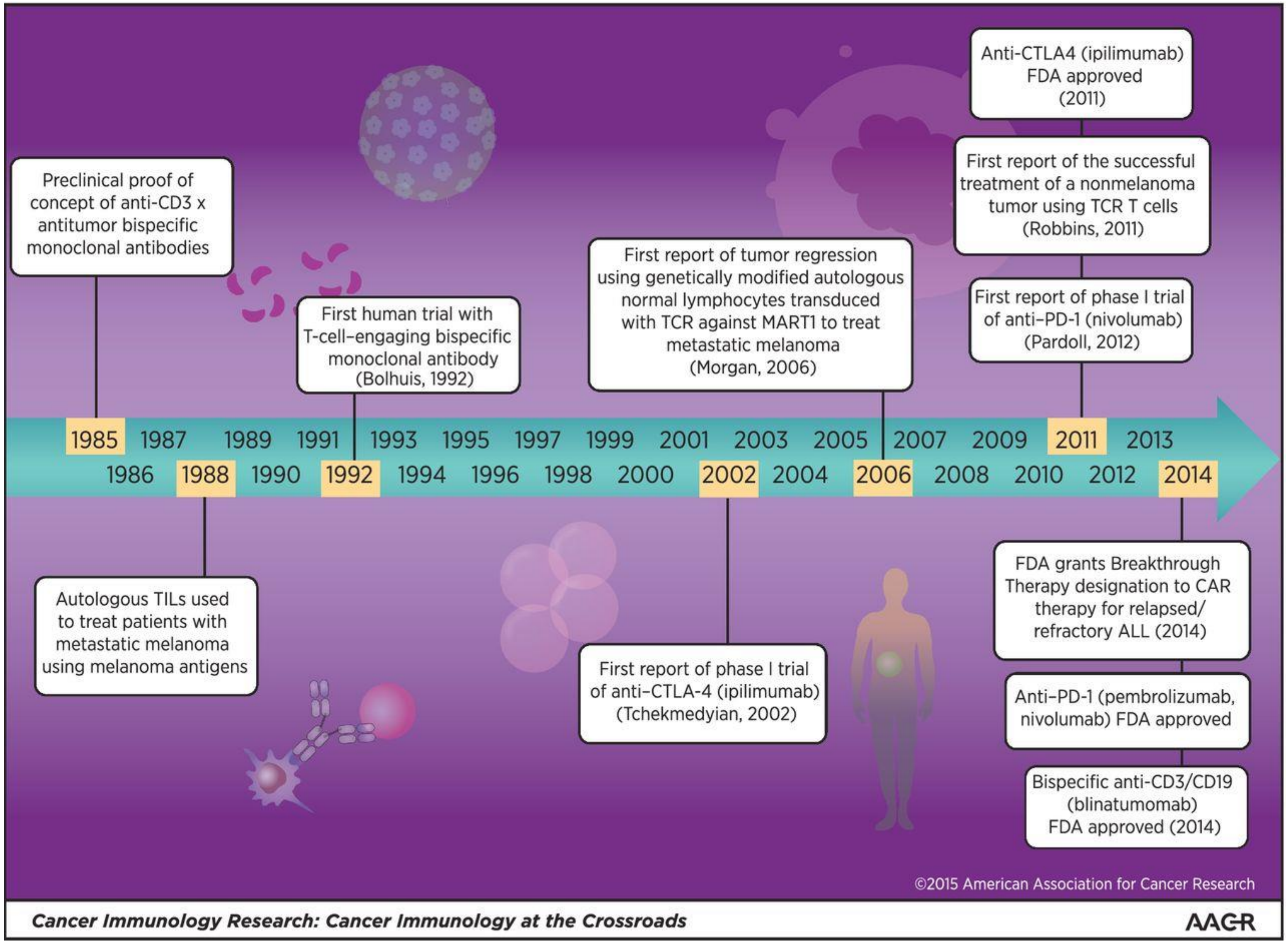


Value of 10/Mb:

150 nonsynonymous mutations within expressed genes

Schreiber and Schumacher, 2015

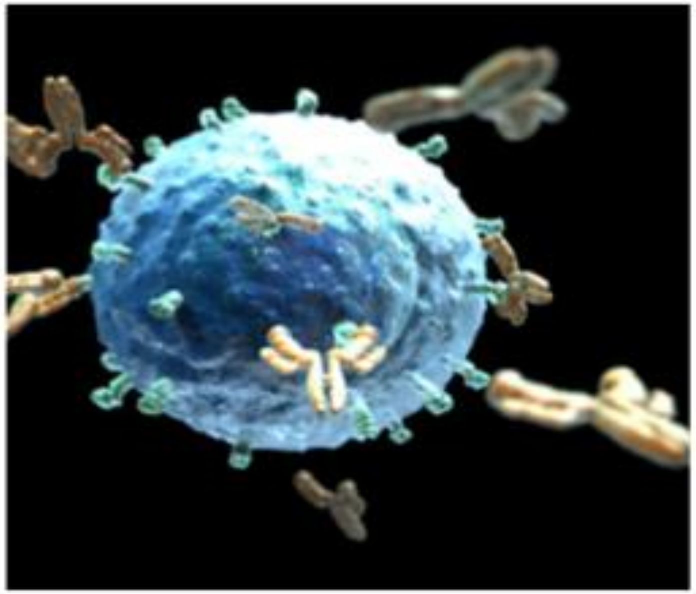
History of T-cell therapy in cancer.



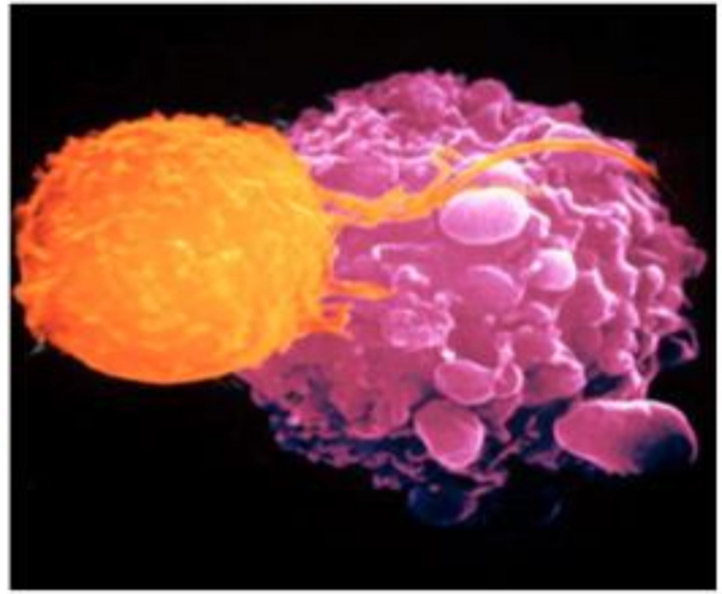
Roch Houot et al. Cancer Immunol Res 2015;3:1115-1122

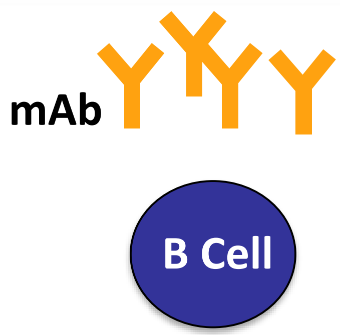
Targeted therapy:
Monoclonal Antibodies & T cell based

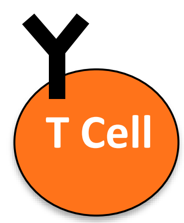
Antibody Targeting of Cancer



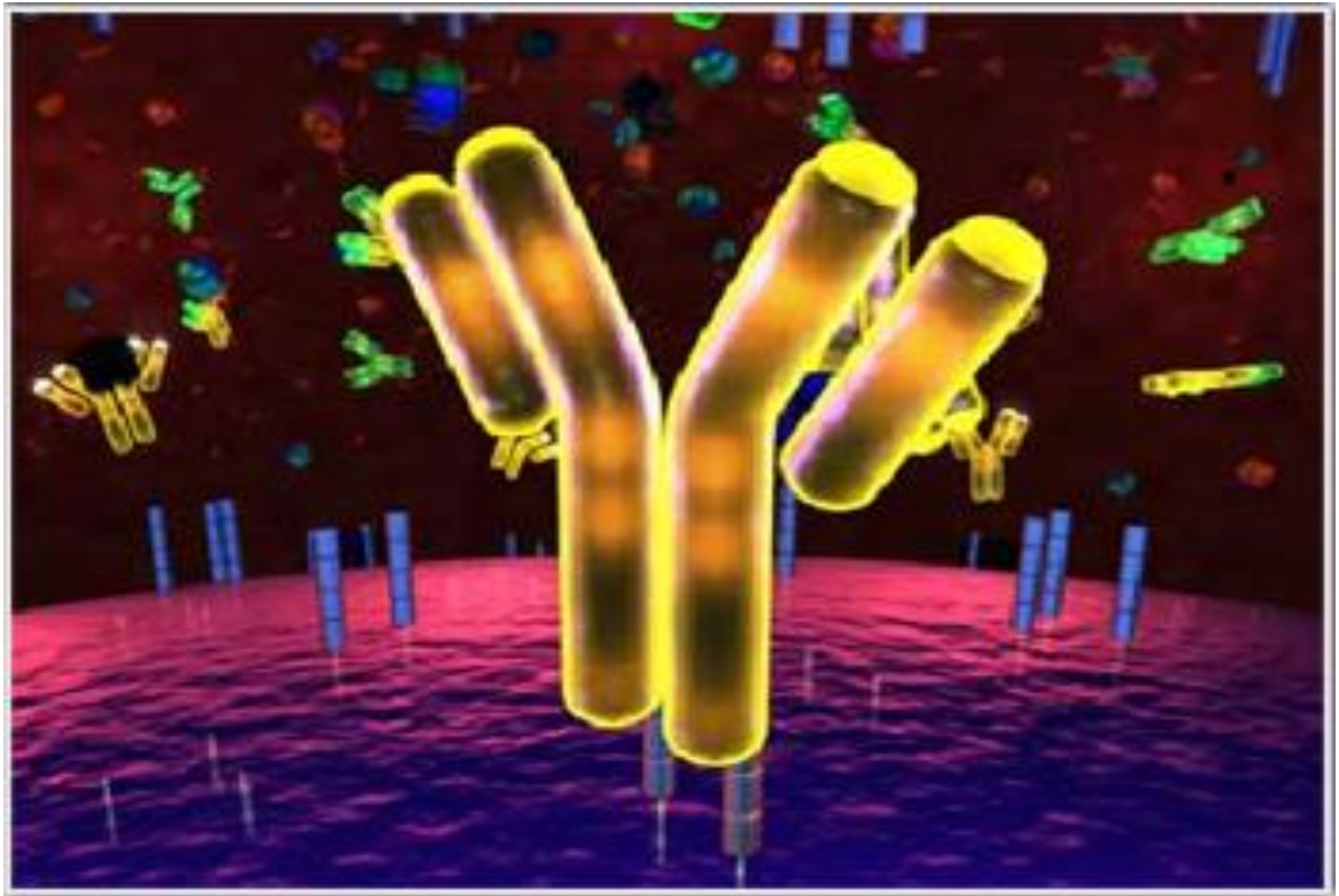
T Cell Targeting of Cancer







Immunotherapy with Antibodies



Antibodies to modulate immunity and cancers

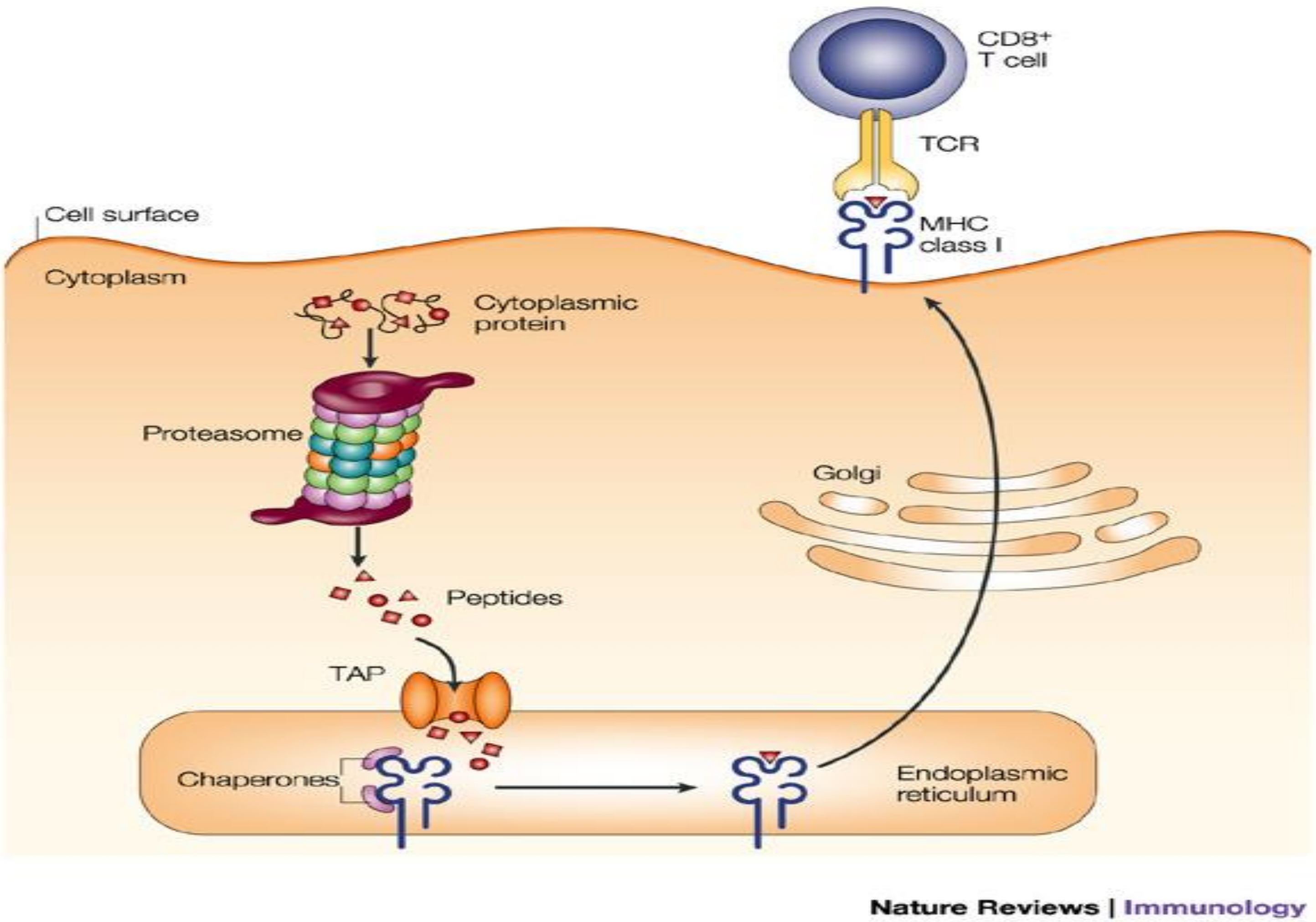
- **Anti-cytokine antibodies in autoimmunity (e.g. anti-TNF; 2.5 billion/yr)**

- **Herceptin; 1.6 billion/yr**

- **Blocking of T cell inhibition in cancer (e.g. anti-CTLA-4, anti-PD1)**

Prophylactic cancer vaccines:
Liver cancer: HBV vaccine
Cervical cancer: HPV vaccines (Gardasil and Cervarix)

Most cancer antigens are intracellular proteins: they are recognized by TCR and not by antibodies



Adoptive Immunotherapy: Melanoma

- 1988: 5/85 (34%) complete responses (CR)

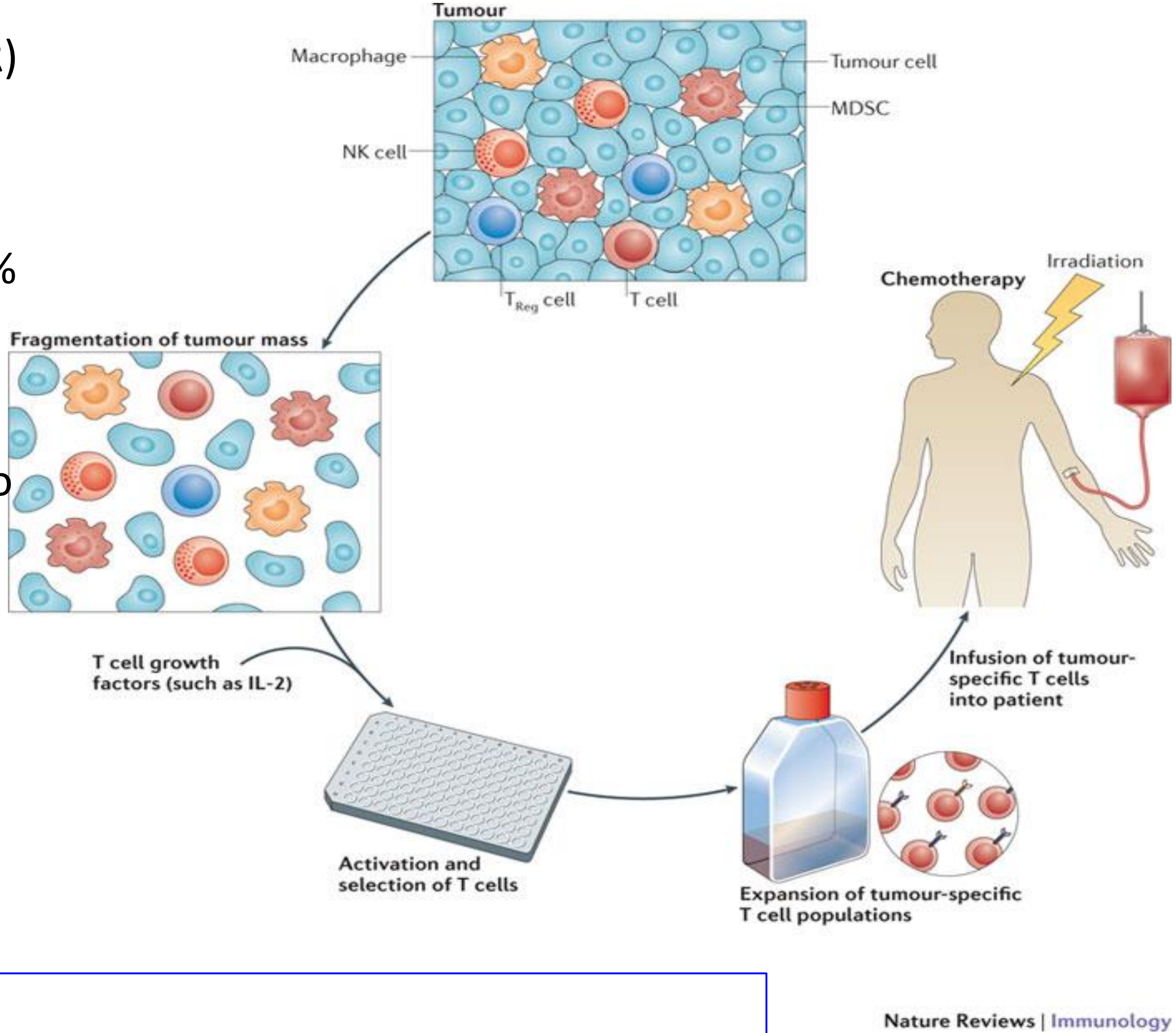
  (Rosenberg *et al* *N Engl J Med* 1988)

- 2002: TIL + chemo achieving OR up to 47%

  (Dudley *et al* *Science* 2002)

- 2008: TIL + TBI + nonmyeloablative chemo achieving OR up to 72%

  (Dudley *et al* J Clin Oncol 2008)

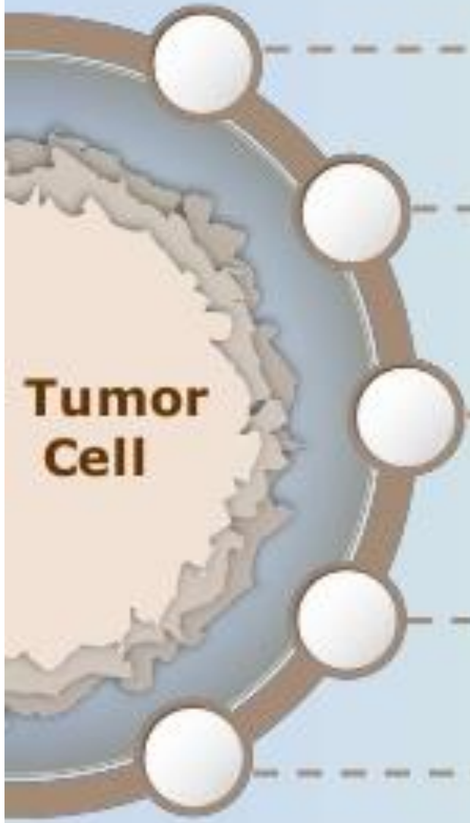


Only really successful in melanoma.

TILs are rare to find and hard to isolate in other types of cancer

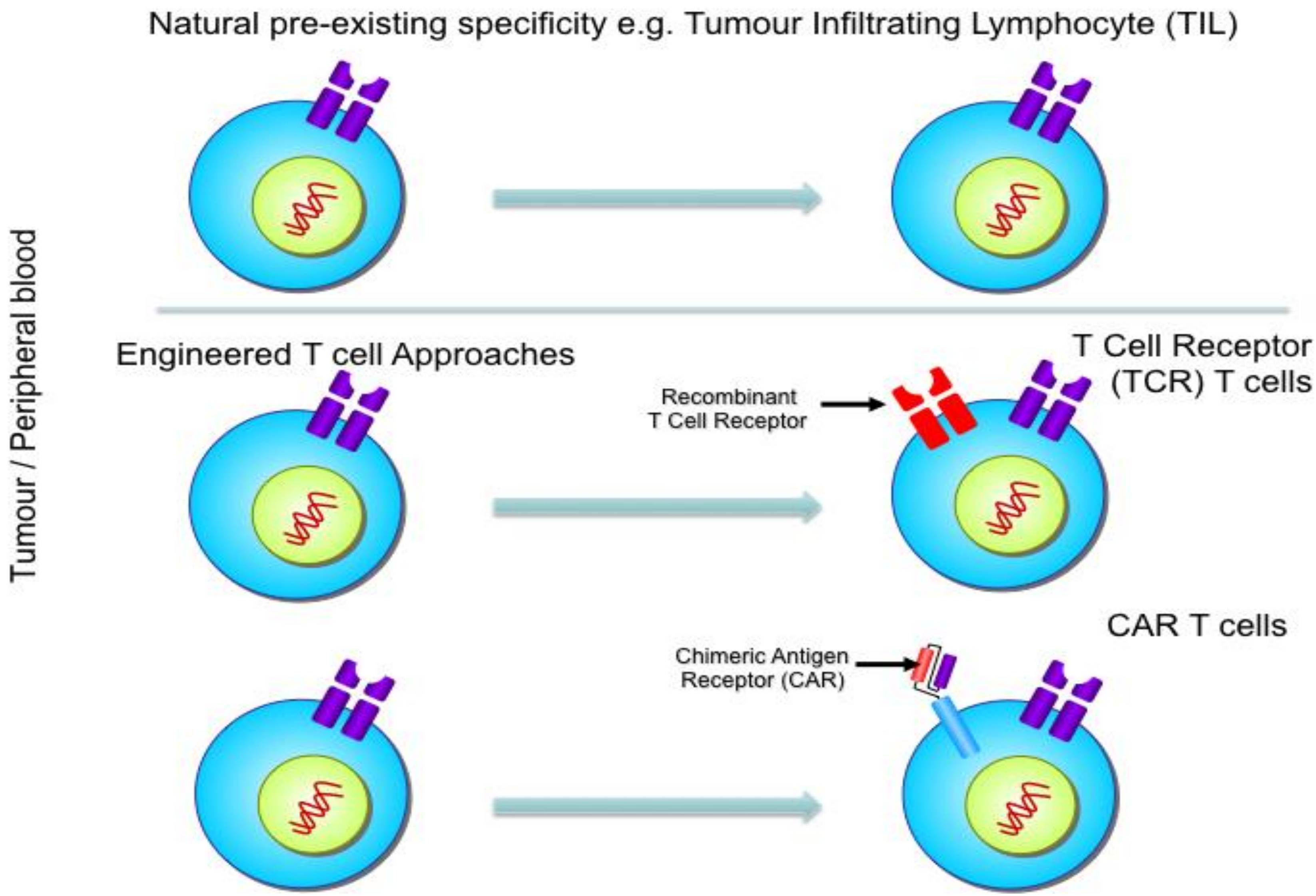
TUMOR IMMUNE ESCAPE

How dose tumor cell escape from immune system

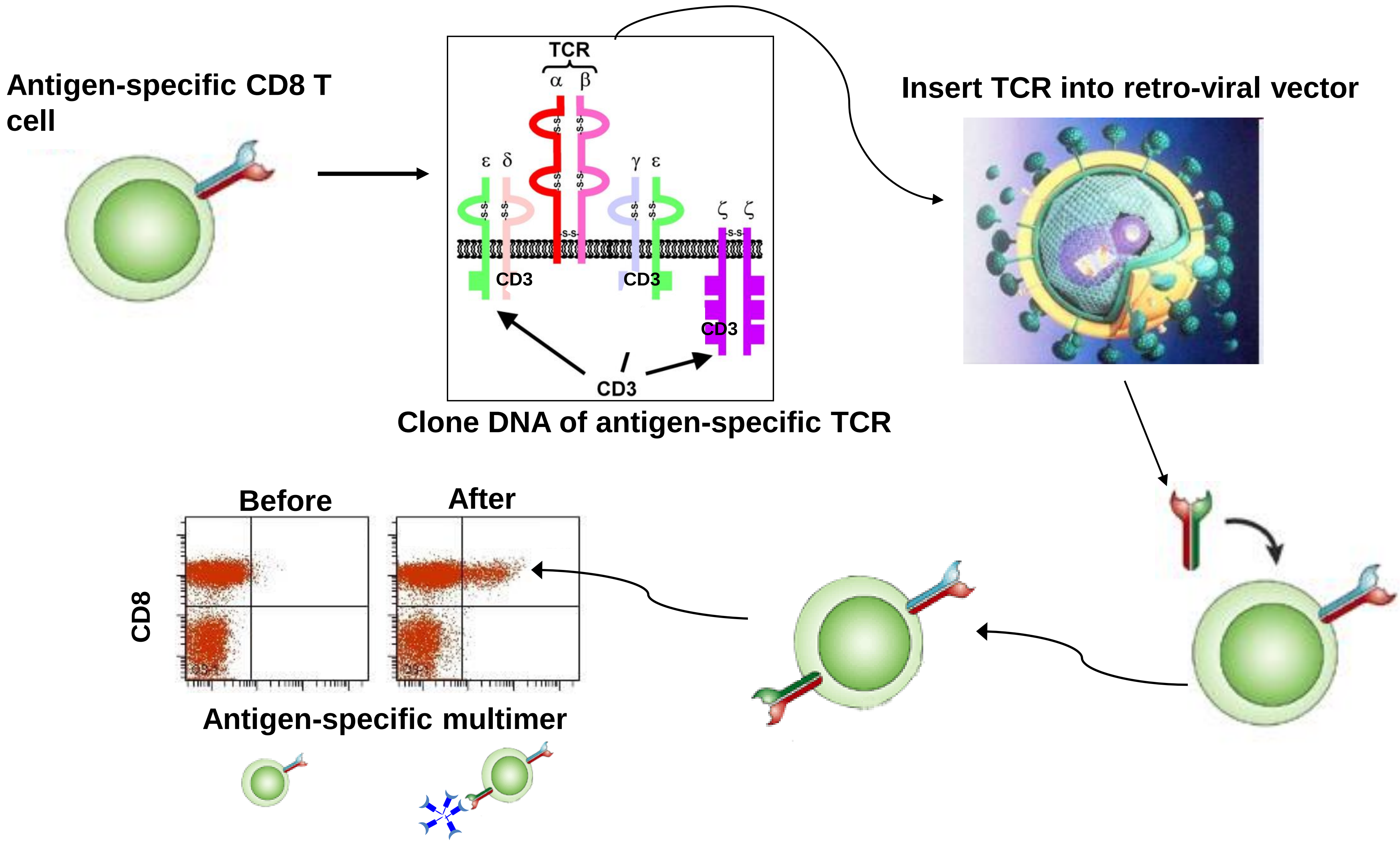


- **Down modulation of Tumor Antigen Presentation** — Genetic instability; Tumor marker mutation/deletion/ inactivation; MHC I pathway down regulation;
- **Tumor Micro-environment** — MDSC; T_{reg}; Immunosuppressive factor
- **Disable Antigen Presenting Cells** — Suppress DC cell maturation; immunosuppressive signaling
- **CD4 T-Cell Tolerance** — Deletion of autoreactive T cell, immunosuppressive signaling
- **CD8 T-Cell Dysfunction** — Chronic tumor antigen exposure cause CD8 T cell tolerance; Disable co-stimulation signaling

Potential Sources of T Cells for Therapy

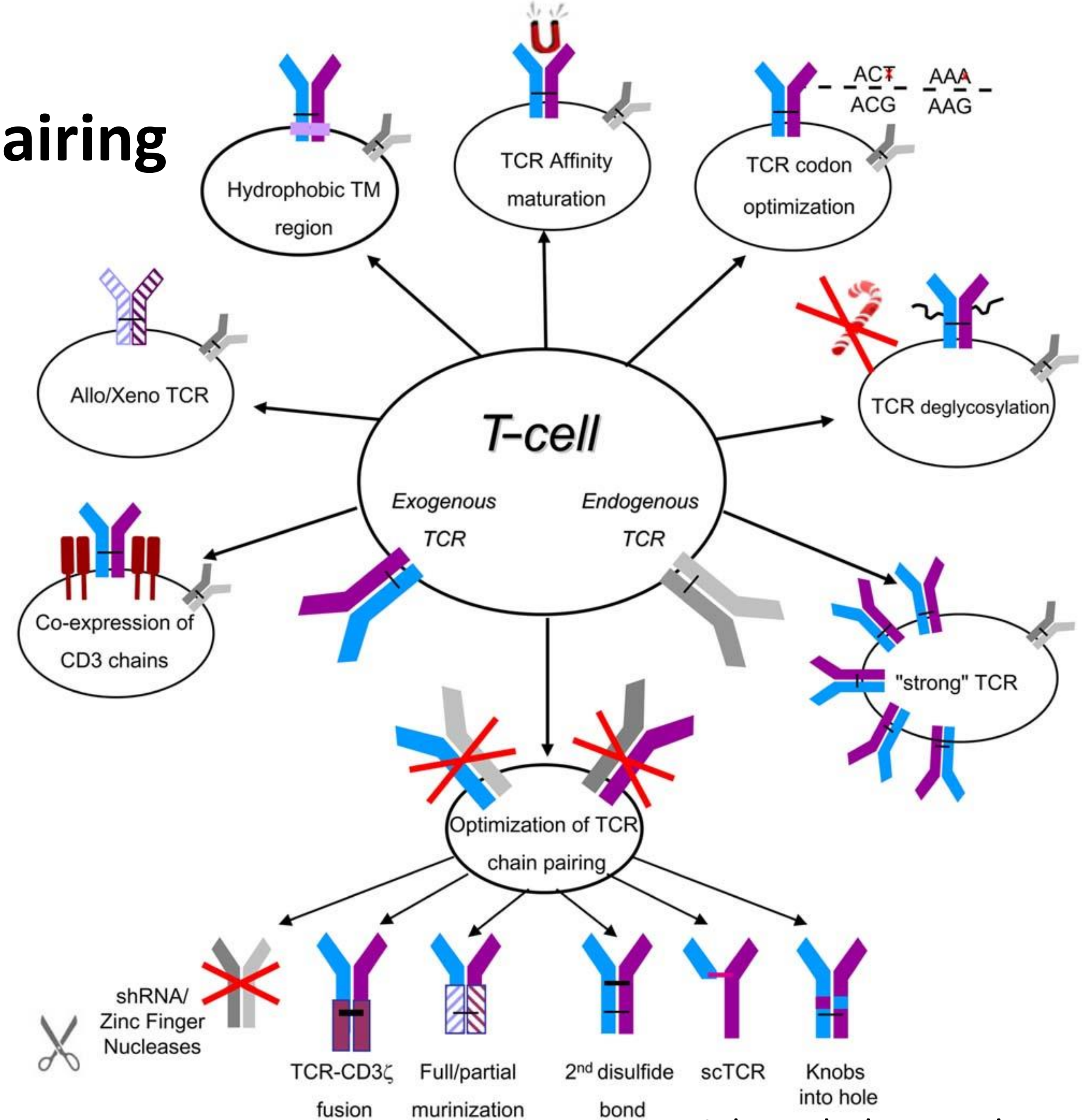


Introduction of a new/optimized TCR



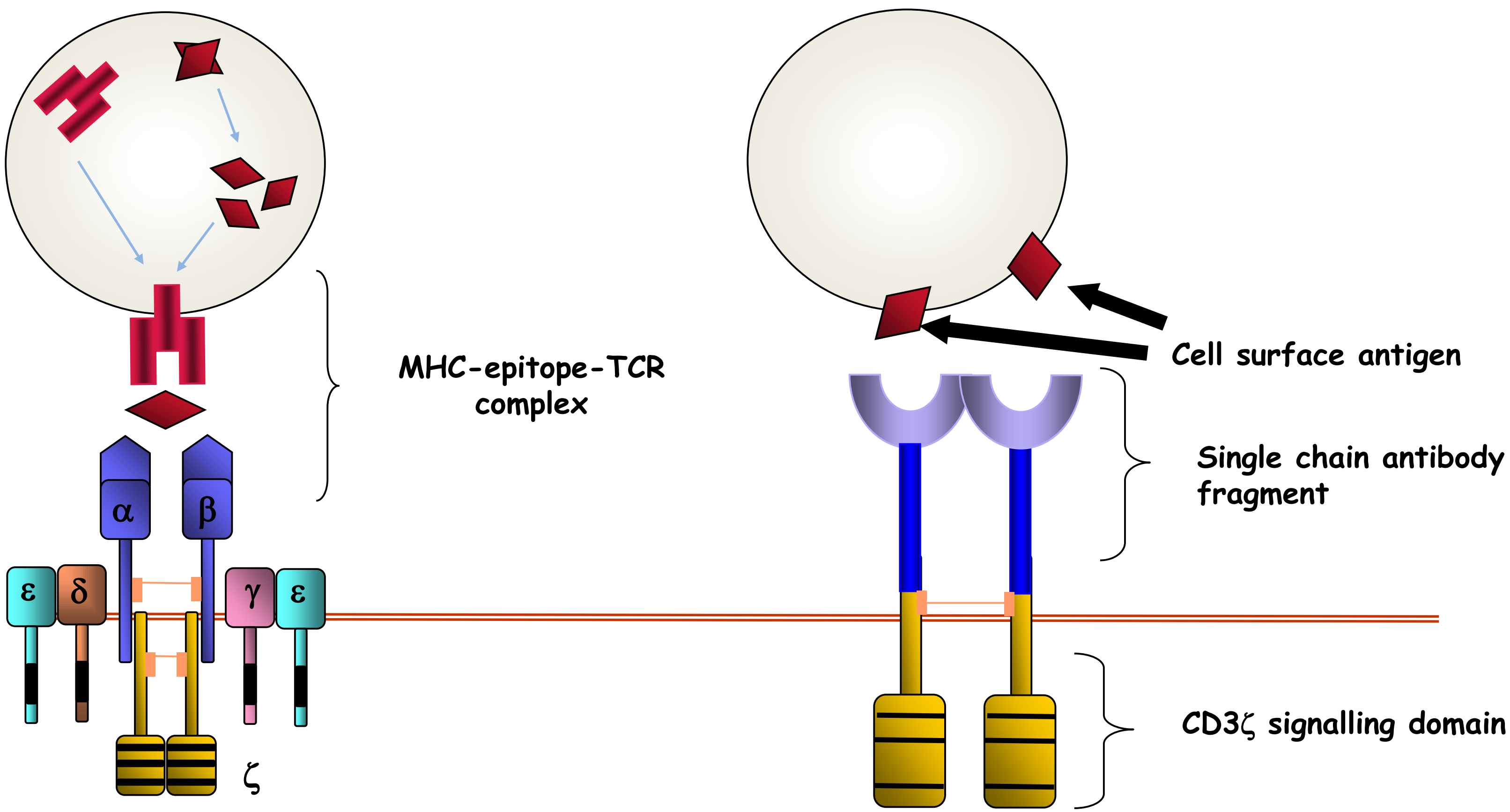
TCR gene transfer:
Problem of mispairing

Problem of "ethnicity"

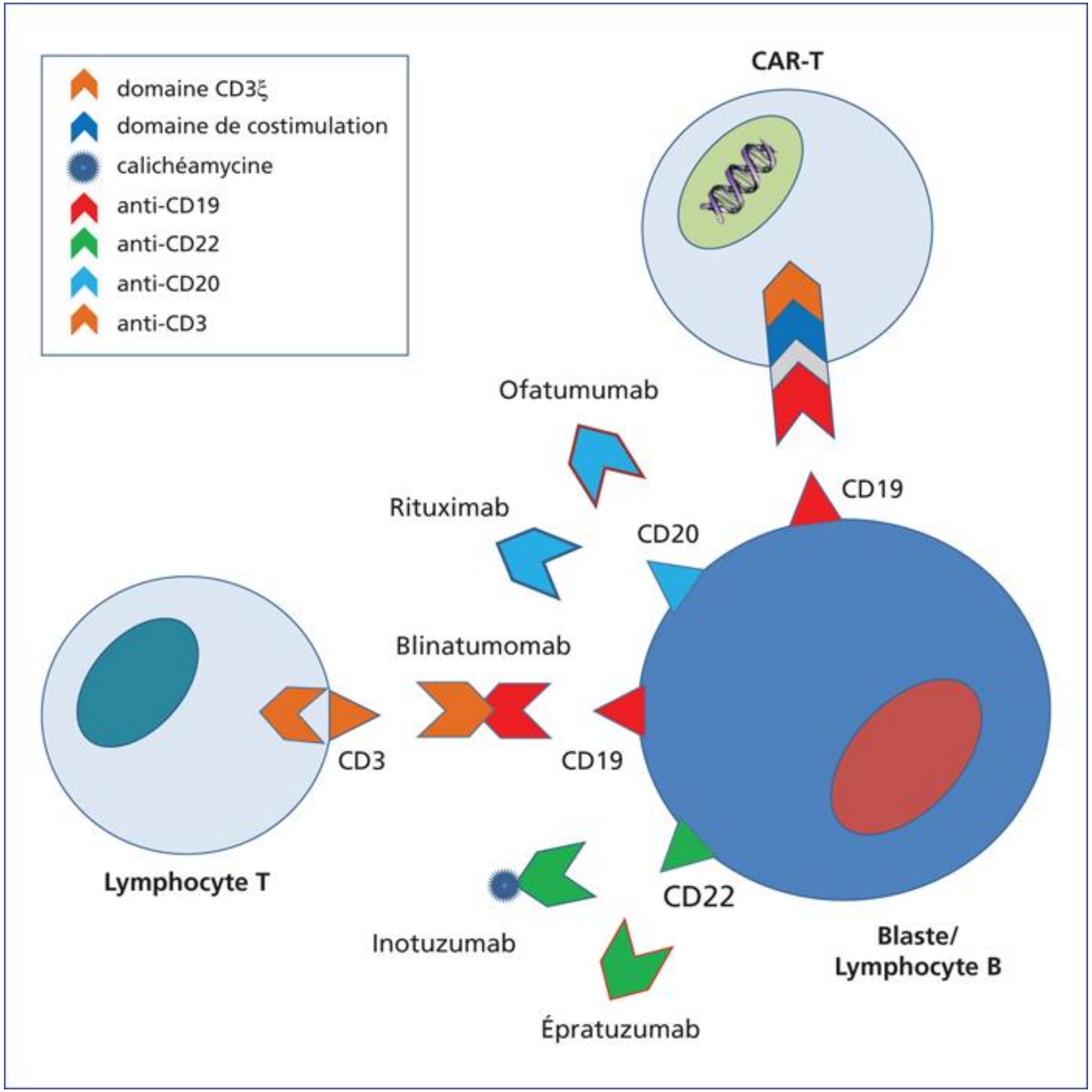


Daniel-Meshulam et al. 2012

CAR T cells: Avoidance of HLA restriction

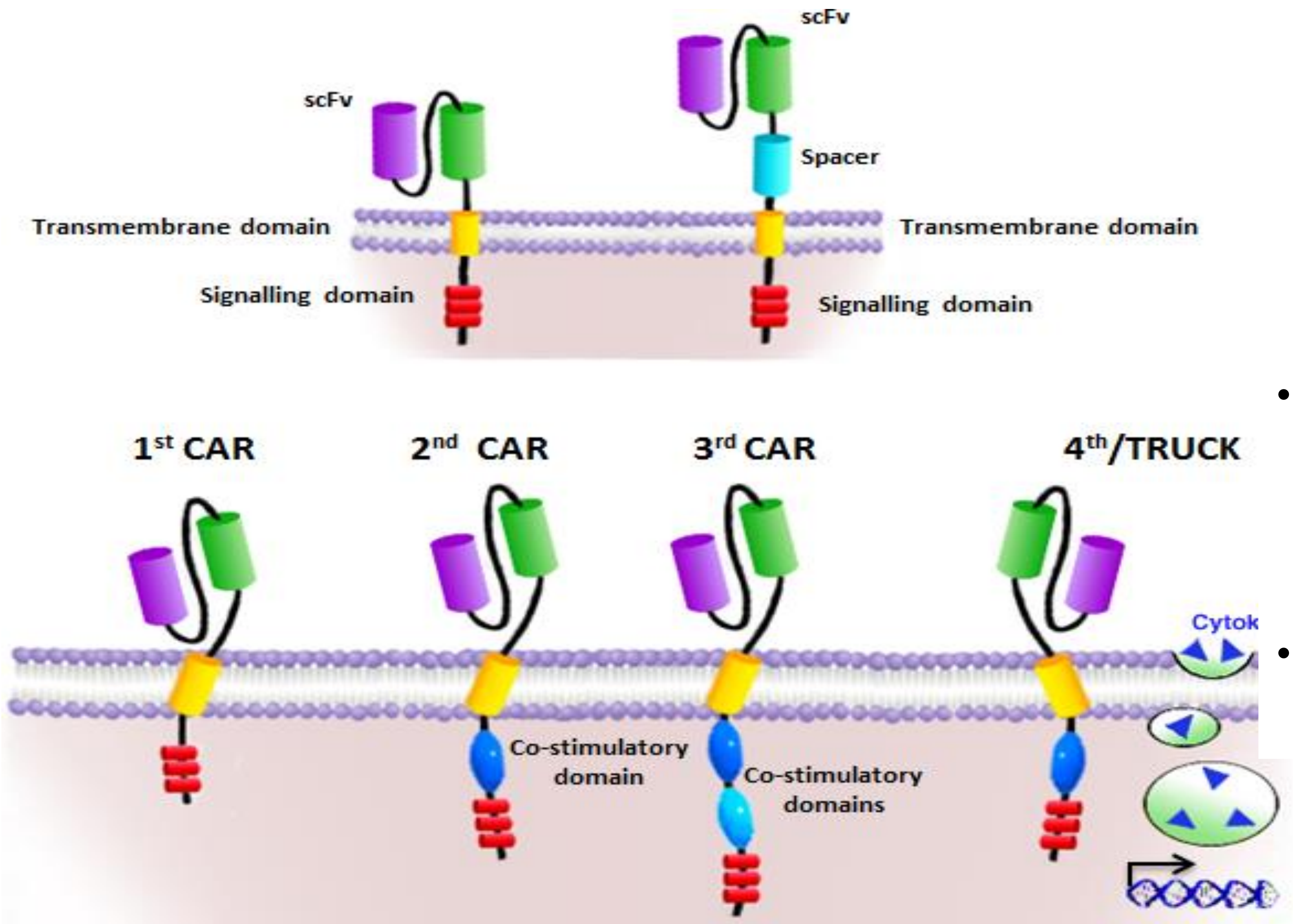


Antibody, BiTE and CAR tumor treatments



Cabannes-Hamy and Boissel, 2017

CAR Generations



- Extracellular single chain variable fragment (scFv) specific for a tumour associated antigen (TAA).
- Linked to intracellular signaling domains which facilitates T cell activation

Eleanor J. Cheadle, Hannah Gornall, Vania Baldan, Vivien Hanson, Robert E. Hawkins, David E. Gilham. Immunological reviews, Jan 2014

CARs in the clinic

CBS/AP / *July 12, 2017, 4:54 PM*

CAR-T gene therapy for leukemia clears FDA hurdle

https://www.cbsnews.com/news/car-t-leukemia-cancer-gene-therapy-fda/

Table 1 | **Examples of chimeric antigen receptor T cell clinical trials**

Target	Indication	Clinical trials and refs*
CD19- or CD20-directed trials		
CD19 or CD20	Leukaemia	NCT01860937, NCT02146924, NCT02228096, NCT02435849, NCT02028455, NCT02614066, NCT02625480, NCT01747486, NCT02030847, NCT02535364 and NCT01683279
		7,8,20,210–214
	Leukaemia or lymphoma	NCT02443831, NCT02529813, NCT02546739, NCT01430390, NCT01853631, NCT02050347, NCT02456350, NCT02081937, NCT02132624, NCT02349698, NCT01475058 and NCT02537977
		10,33,215–220
	Lymphoma	NCT02650999, NCT02431988, NCT02631044, NCT02445248, NCT02277522, NCT02624258, NCT01493453, NCT01840566, NCT02134262, NCT02247609, NCT02348216 and NCT02030834
		14,27,28,34,221–226
	Multiple myeloma	16,227
Additional targets for haematological CAR T cell trials		
CD22	B cell malignancy	NCT02588456 and NCT02315612
Igκ light chain	B cell malignancy	228
CD30	Lymphoma	NCT02259556 and NCT02274584
		229
CD138	Multiple myeloma	230
BCMA	Multiple myeloma	NCT02546167 and NCT02215967
CD33	Myeloid malignancies	231
CD123	Myeloid malignancies	NCT02623582 and NCT02159495
NKG2D ligands	Various haematological malignancies	NCT02203825
ROR1	Leukaemia	58
Solid tumour CAR T cell trials		
EGFR	EGFR^{+} solid tumours	NCT02331693
		232
EGFRvIII	Glioblastoma	NCT02209376
		74,75,124,233
GD2	Neuroblastoma, Ewing's sarcoma, osteosarcoma and melanoma	NCT01822652 and NCT02107963
IL13Rα2	Glioma	NCT02208362
HER2	HER2^{+} solid tumours	107,110
Mesothelin	Mesothelioma, pancreatic cancer and ovarian cancer	NCT02159716, NCT02414269, NCT01897415, NCT02580747 and NCT02465983
		99
PSMA	Prostate cancer	NCT01140373
		234
FAP	Malignant pleural mesothelioma	NCT01722149
GPC3	Hepatocellular carcinoma	NCT02395250
MET	Breast cancer	NCT01837602
MUC16	Ovarian cancer	NCT02498912
CEA	Various solid tumours	NCT02349724 and NCT01723306
Lewis-Y	Solid tumours and myeloid malignancies	NCT01716364
MUC1	Hepatocellular carcinoma, NSCLC, pancreatic carcinoma and triple-negative invasive breast carcinoma	NCT02617134 and NCT02587689

BCMA, B cell maturation antigen; CEA, carcinoembryonic antigen; EGFR, epidermal growth factor receptor; EGFRvIII, EGFR variant III; FAP, fibroblast activation protein; GPC3, glypican 3; HER2, human epidermal growth factor receptor 2; Ig, immunogloulin; IL13Rα2, interleukin 13 receptor α2 subunit; MUC, mucin; NSCLC, non-small cell lung carcinoma; ROR1, receptor tyrosine kinase-like orphan receptor. *Ongoing trials are indicated by NCT accession numbers and trials with published or presented results are denoted by references.

Levine *et al*. Nat Rev Cancer 2016

Science News *... from universities, journals, and other research organizations*

T-Cell Therapy Eradicates an Aggressive Leukemia in Two Children

Mar. 25, 2013 — Two children with an aggressive form of childhood leukemia had a complete

In Girl's Last Hope, Altered Immune Cells Beat Leukemia

Breakthroughs in Cancer Immunotherapy Webinar: Carl June, Engineering T Cells to Conquer Cancer

Dramatic success of CD19-CAR-T cells…..

CD19 CAR–T cells of defined $CD4^+$:$CD8^+$ composition in adult B cell ALL patients

Cameron J. Turtle,[1,2] Laïla-Aïcha Hanafi,[1] Carolina Berger,[1,2] Theodore A. Gooley,[1] Sindhu Cherian,[3] Michael Hudecek,[1] Daniel Sommermeyer,[1] Katherine Melville,[1] Barbara Pender,[1] Tanya M. Budiarto,[1] Emily Robinson,[1] Natalia N. Steevens,[1] Colette Chaney,[1] Lorinda Soma,[3] Xueyan Chen,[3] Cecilia Yeung,[3,4] Brent Wood,[3,4] Daniel Li,[5] Jianhong Cao,[1] Shelly Heimfeld,[1] Michael C. Jensen,[1,6] Stanley R. Riddell,[1,2,7] and David G. Maloney[1,2]

JCI, 2016

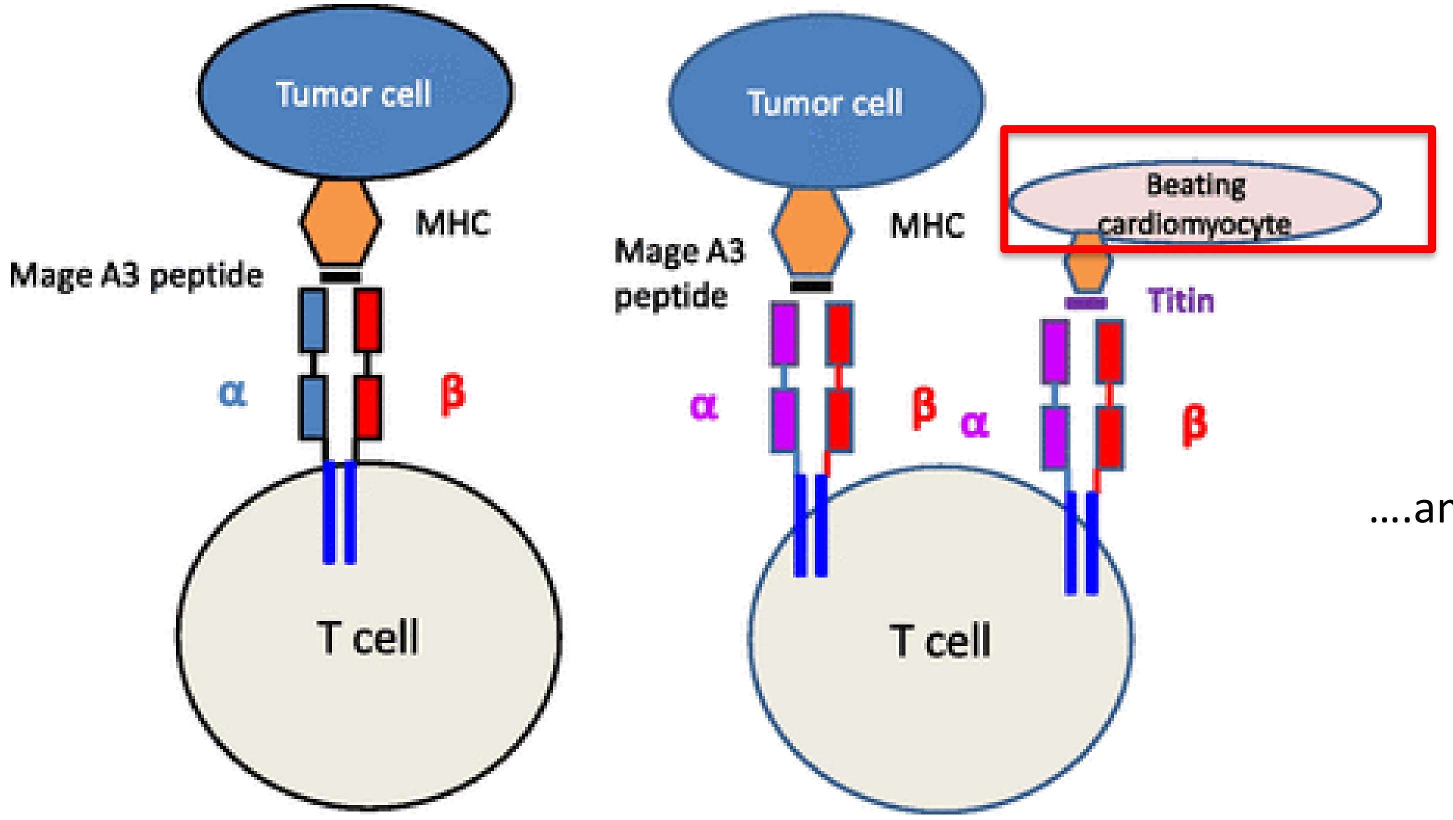
27 of 29 ALL patients went into remission: 93%

7 of 11 non-Hodgkin lymphoma patients treated with CAR T cells and improved chemotherapy went into complete remission: 64%

But there are problems….

Death of two patients treated with MAGE A3 TCRs died of cardiotoxicity

Cross-reactivity between the HLA A1-restricted MAGE A3 and Titin



….amino acid scanning approach

Cameron et al. Sci Transl. Med. 2013

Linnette et al. Blood 2013;

Heslop, Blood 2013;

Cameron et al Sci Transl Med 2013

-Many patients don't respond to immunotherapy

- -T cells are not active against tumor antigens
- -T cells don't persist

Issues….

? Why are CD19-CARs so much more potent than all other CARs…

- Optimal chemotherapy/
  TBI
- Type of T cells to transduce (naive/effector/memory/etc..)
- Optimizing Ex vivo culture conditions/selection to:
  Avoid exhaustion / Enhance effector functions?

Significant differences in CD19-CAR chemotherapy protocols….

Kalos et al 2011
- Bendamustine
- Bendamustine/Rituximab
- Pentostatine/Cyclophosphamide

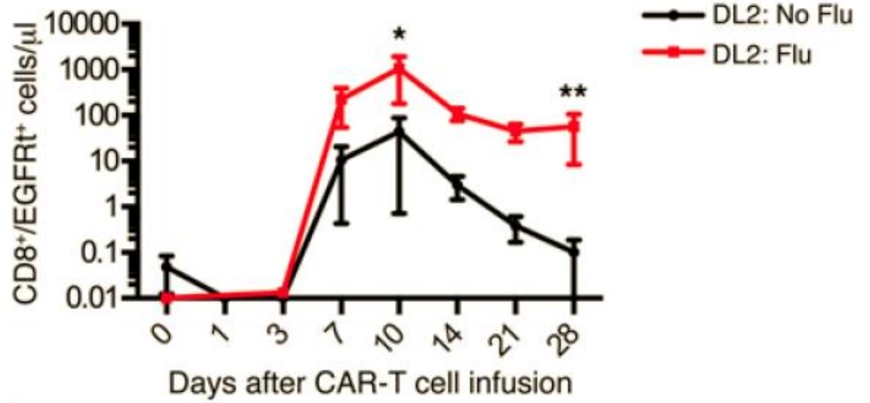
Lee et al 2014
- Cyclophosphamide

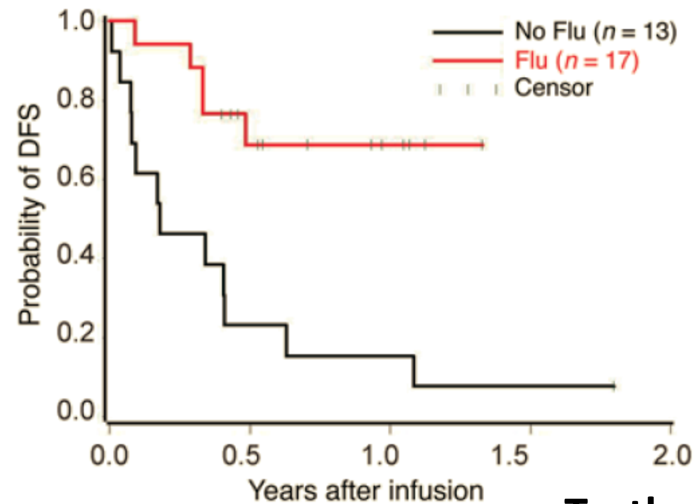
Porter et al 2011
- Pentostatine/cyclophosphamide

Brentjens et al 2011
- None
- Cyclophosphamide

Turtle et al 2016
- Cyclophosphamide
- Fludarabine/Cyclophosphamide

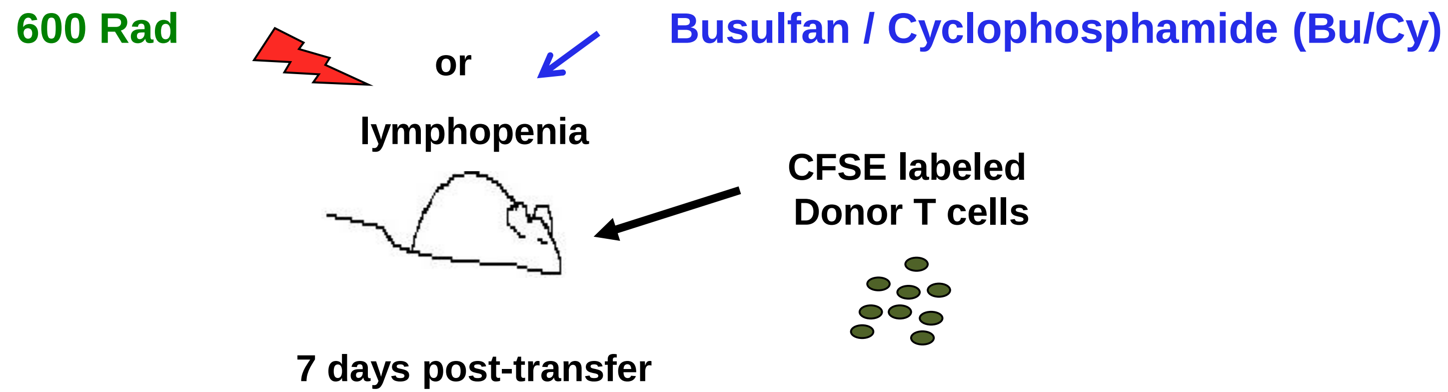
Grupp et al 2013
- None
- Etoposide/ Cyclophosphamide

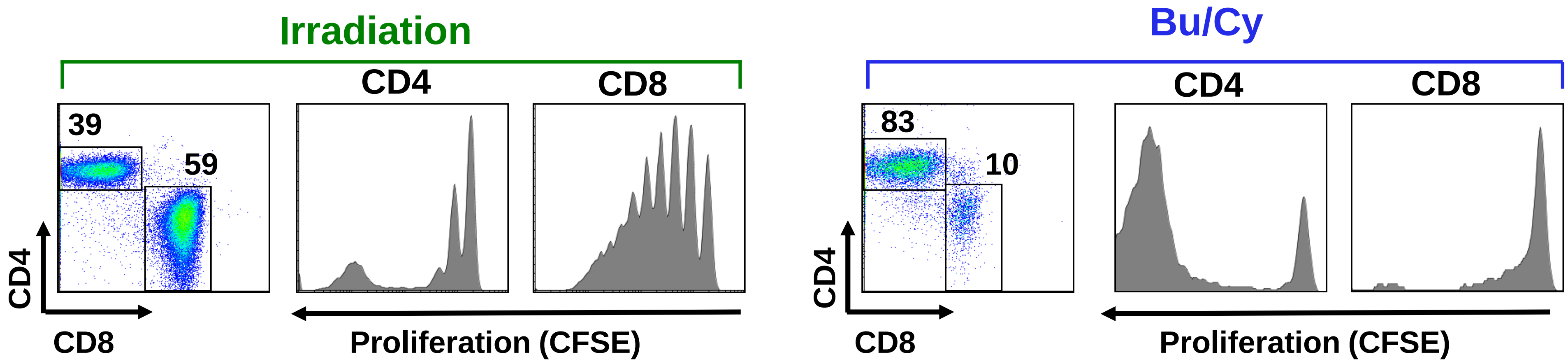




Turtle et al 2016

Conditioning regimens differentially affect T cell proliferation





Homeostatic CD8 proliferation

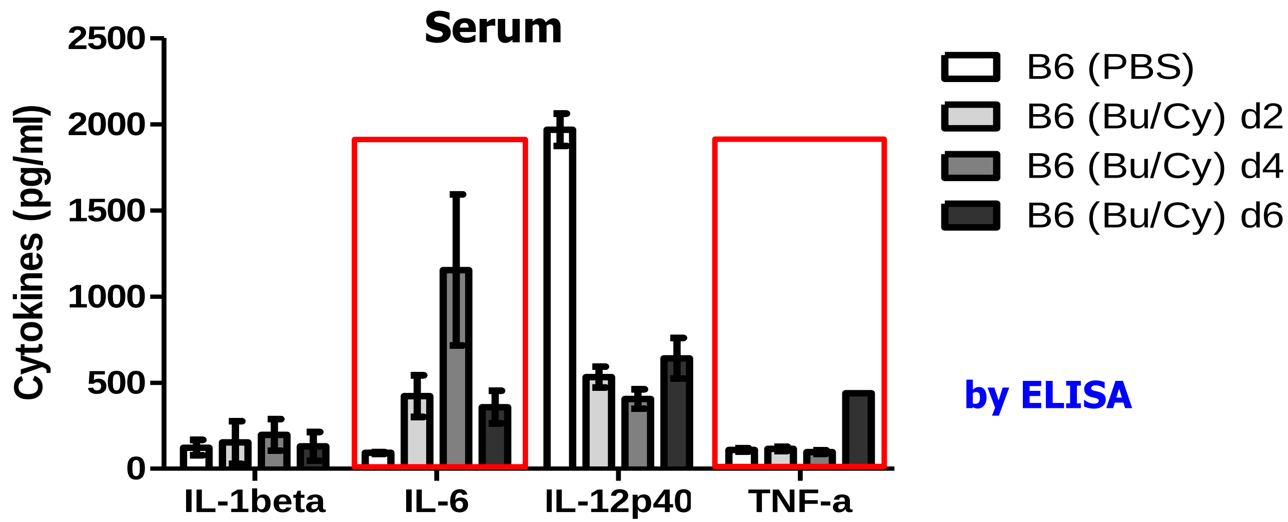
Extensive rapid CD4 proliferation

Significant induction of IL-6 and TNF-a in Bu/Cy-conditioned mice

D-4
D-3 BuCy
D-2

D 0

D 2
D 4 Analysis (serum)
D 6

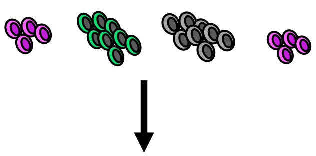


by ELISA

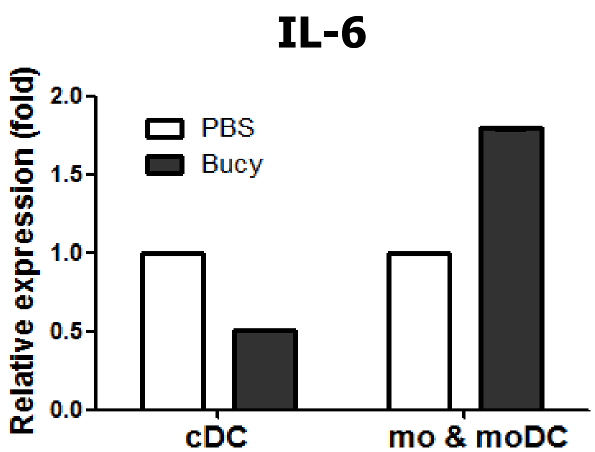
D-4
D-3 BuCy
D-2

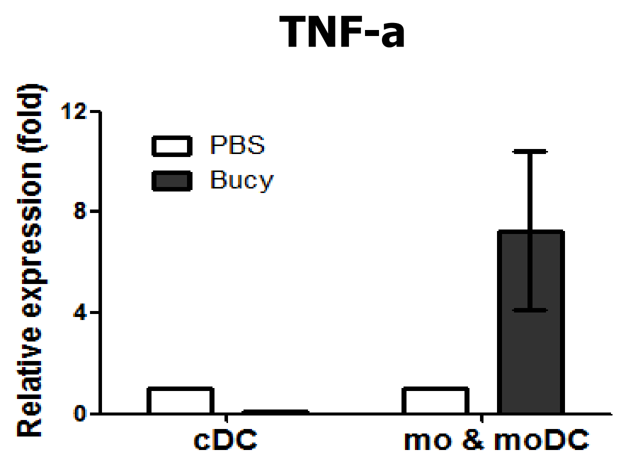
D 0

D 3 **Sort** (SPL cells)



Measure the mRNA





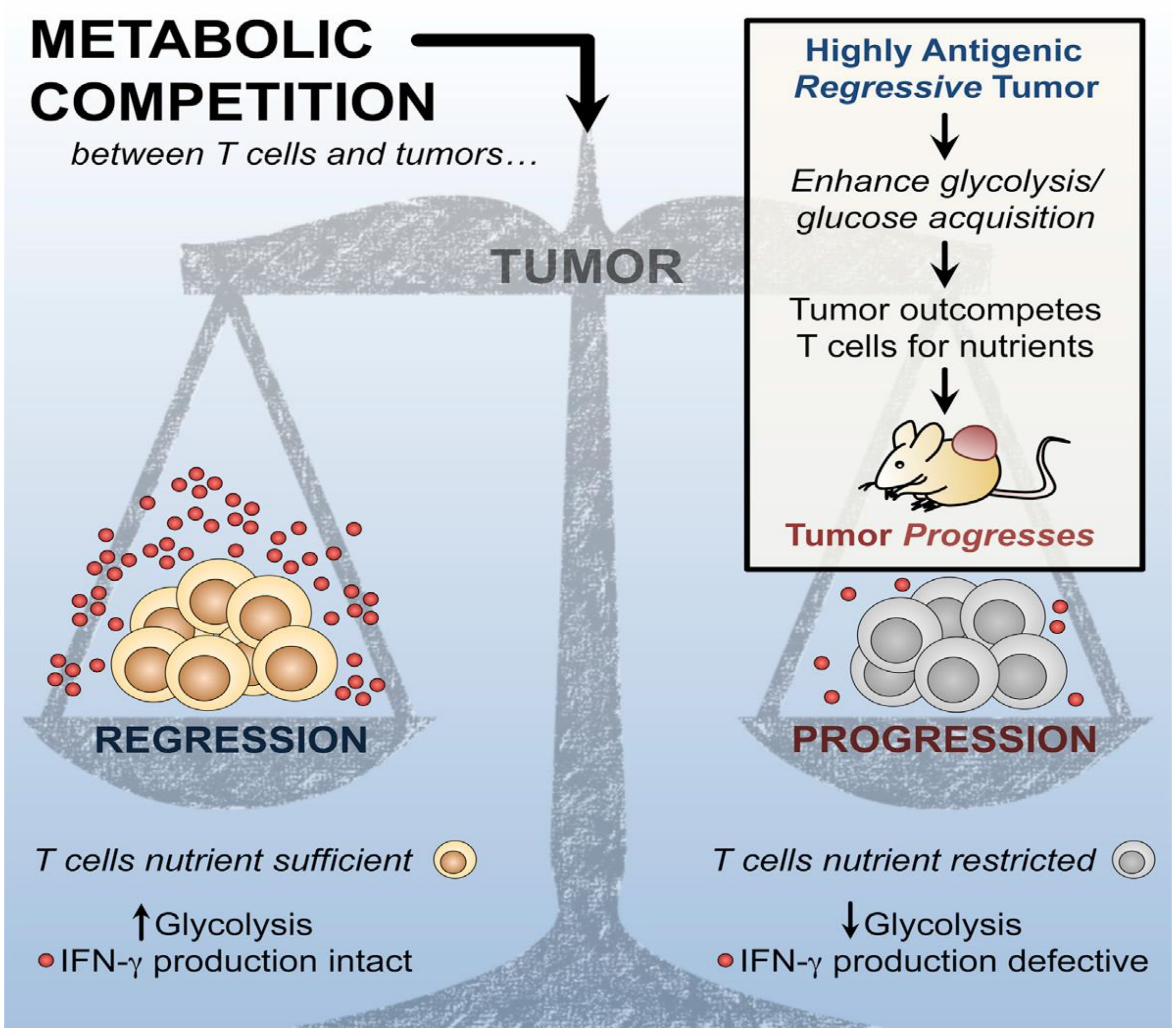
by RT-PCR

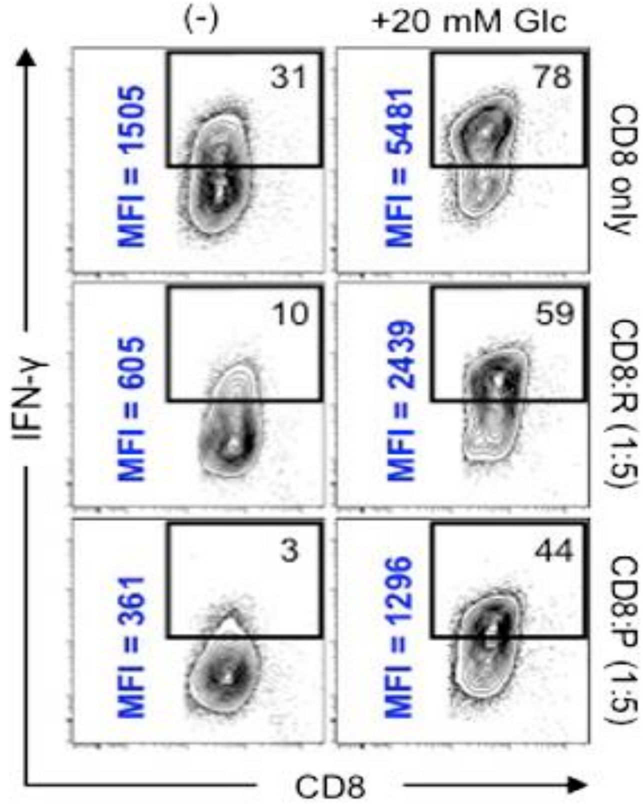
Modulation of T cell fate by…

stromal and cytokine micro-environment following chemotherapy and irradation

Role of metabolism…

Tumor and T cells compete for glucose and other nutrient resources….

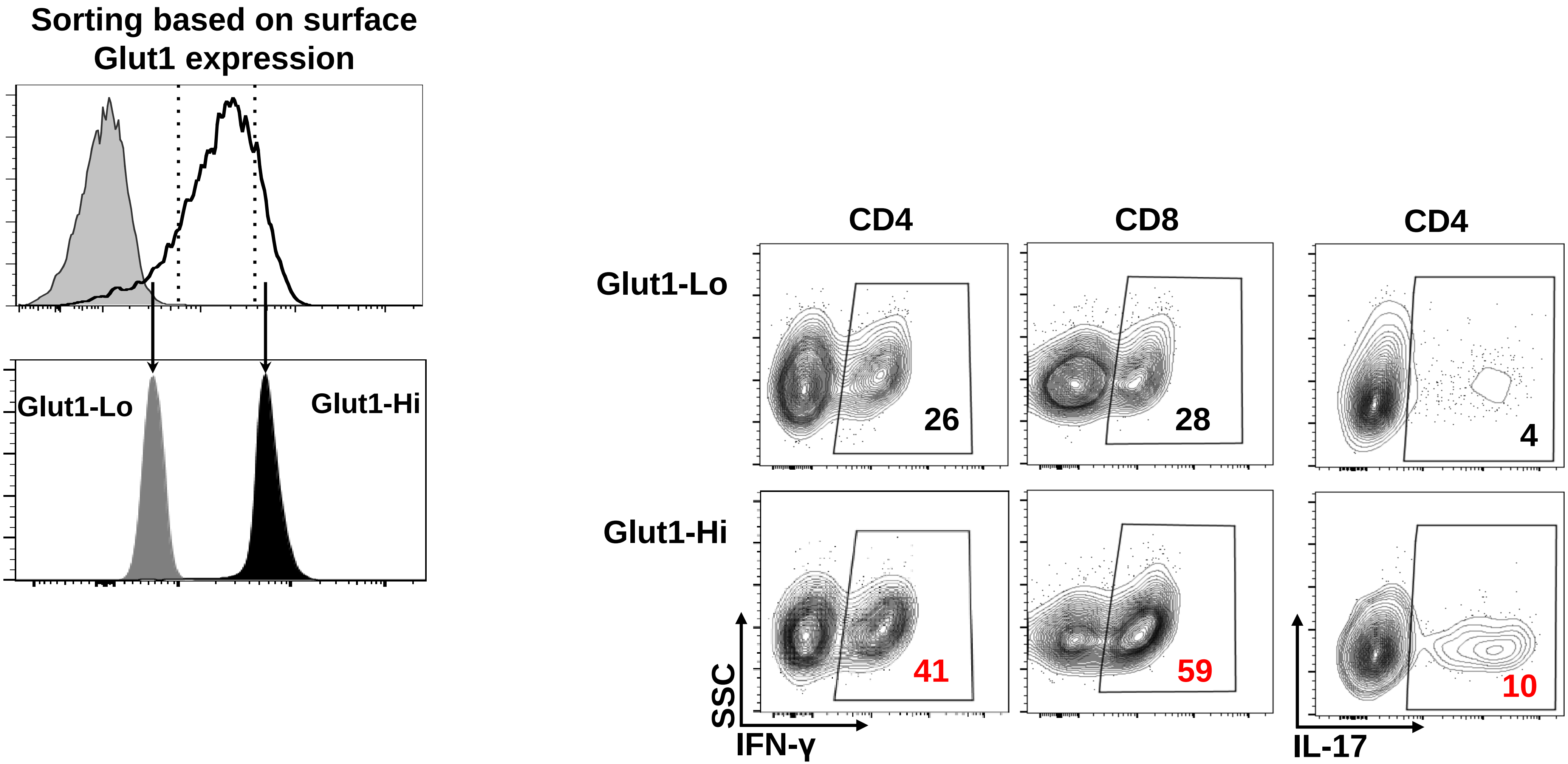




Erika Pearce and colleauges, Cell 2015

Can expression of the Glut1 glucose transporter be used to select T cell subsets with distinct effector functions?

Glut1-Hi T cells exhibit high cytokine production capacity



Cretenet et al., *Sci Reports* 2016

Problems with CAR T cell therapy

IMMUNOTHERAPY, VOL. 7, NO. 5 | REVIEW

Adoptive therapy with CAR redirected T cells: the challenges in targeting solid tumors

Hinrich Abken

CAR T-cell therapy of solid tumors

Carmen S M Yong[1,2], Valerie Dardalhon[2], Christel Devaud[3], Naomi Taylor[2], Phillip K Darcy[1,4] and Michael H Kershaw[1,4]

Contents lists available at ScienceDirect

Cytokine & Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

ELSEVIER

Targeting the tumor and its associated stroma: One and one can make three in adoptive T cell therapy of solid tumors

Anna Mondino*, Gerlanda Vella, Laura Icardi

and Maus *Journal for ImmunoTherapy of Cancer* (2017) 5:28
1186/s40425-017-0230-9

Journal for ImmunoTherapy of Cancer

VIEW Open Access

CrossMark

Current approaches to increase CAR T cell potency in solid tumors: targeting the tumor microenvironment

Irene Scarfò and Marcela V. Maus*

Enhancing CD8+ T cell immunotherapy: Preclinical studies

Cancer Cell
Article

Low-Dose Irradiation Programs Macrophage Differentiation to an iNOS+/M1 Phenotype that Orchestrates Effective T Cell Immunotherapy

Felix Klug,[1,11] Hridayesh Prakash,[1,2,4,11] Peter E. Huber,[5,11,*] Tobias Seibel,[1,11] Noemi Bender,[1] Niels Halama,[6] Christina Pfirschke,[1] Ralf Holger Voss,[7] Carmen Timke,[5] Ludmila Umansky,[1] Kay Klapproth,[8] Knut Schäkel,[2] Natalio Garbi,[9,10] Dirk Jäger,[6] Jürgen Weitz,[3] Hubertus Schmitz-Winnenthal,[3] Günter J. Hämmerling,[8] and Philipp Beckhove[1,*]

Cancer Research

IL-12 Release by Engineered T Cells Expressing Chimeric Antigen Receptors Can Effectively Muster an Antigen-Independent Macrophage Response on Tumor Cells That Have Shut Down Tumor Antigen Expression

Markus Chmielewski, Caroline Kopecky, Andreas A. Hombach, et al.

Tumor-specific IL-9–producing CD8+ Tc9 cells are superior effector than type-I cytotoxic Tc1 cells for adoptive immunotherapy of cancers

Yong Lu[a], Bangxing Hong[a], Haiyan Li[a], Yuhuan Zheng[a], Mingjun Zhang[a], Siqing Wang[b], Jianfei Qian[a], and Qing Yi[a,1]

[a]Department of Cancer Biology, Lerner Research Institute, Cleveland Clinic, Cleveland, OH 44195; and [b]Institute of Translational Medicine, The First Hospital, Jilin University, Changchun 130061, China

Edited by James P. Allison, MD Anderson Cancer Center, University of Texas, Houston, TX, and approved January 9, 2014 (received for review

Redirected Primary Human Chimeric Antigen Receptor Natural Killer Cells As an "Off-the-Shelf Immunotherapy" for Improvement in Cancer Treatment

*Olaf Oberschmidt, Stephan Kloess and Ulrike Koehl**

Th17 cells promote cytotoxic T cell activation in tumor immunity

Natalia Martin-Orozco[1], Pawel Muranski[4], Yeonseok Chung[1], Xuexian O. Yang[1], Tomohide Yamazaki[1], Sijie Lu[2], Patrick Hwu[3], Nicholas P. Restifo[4], Willem W. Overwijk[3], and Chen Dong[1]

[1] Department of Immunology, MD Anderson Cancer Center, Houston, TX 77030

[2] Department of Stem Cell Transplantation and Cell Therapy, MD Anderson Cancer Center, Houston, TX 77030

[3] Department of Melanoma Medical Oncology, MD Anderson Cancer Center, Houston, TX 77030

[4] National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA

Antigen-Specific Cytolysis by Neutrophils and NK Cells Expressing Chimeric Immune Receptors Bearing ζ or γ Signaling Domains

Margo R. Roberts, Keegan S. Cooke, Annie-Chen Tran, Kent A. Smith, Wei Yu Lin, Martin Wang, Thomas J. Dull, Deborah Farson, Krisztina M. Zsebo and Mitchell H. Finer

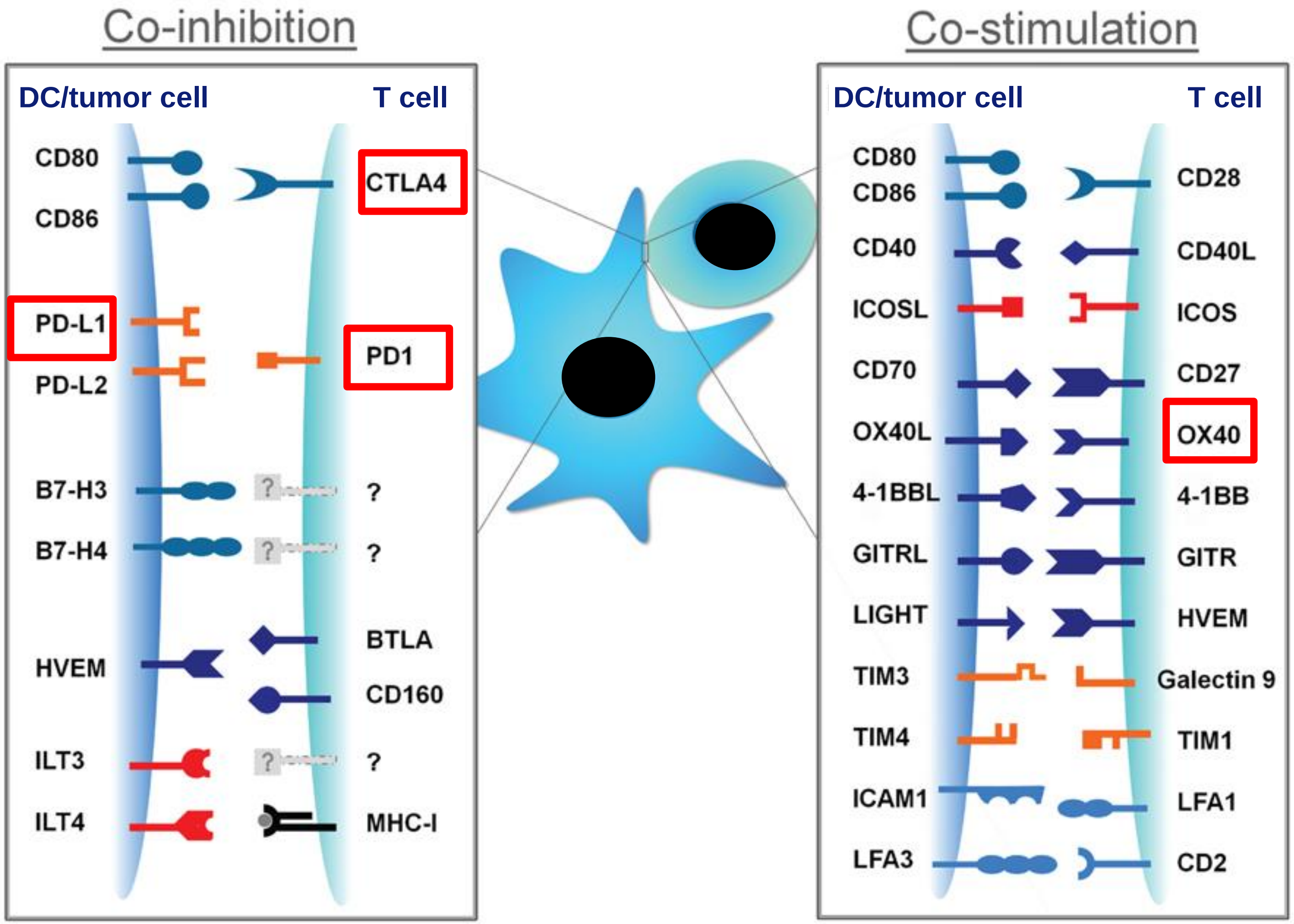
J Immunol 1998; 161:375-384; ;
http://www.jimmunol.org/content/161/1/375

ORIGINAL ARTICLE

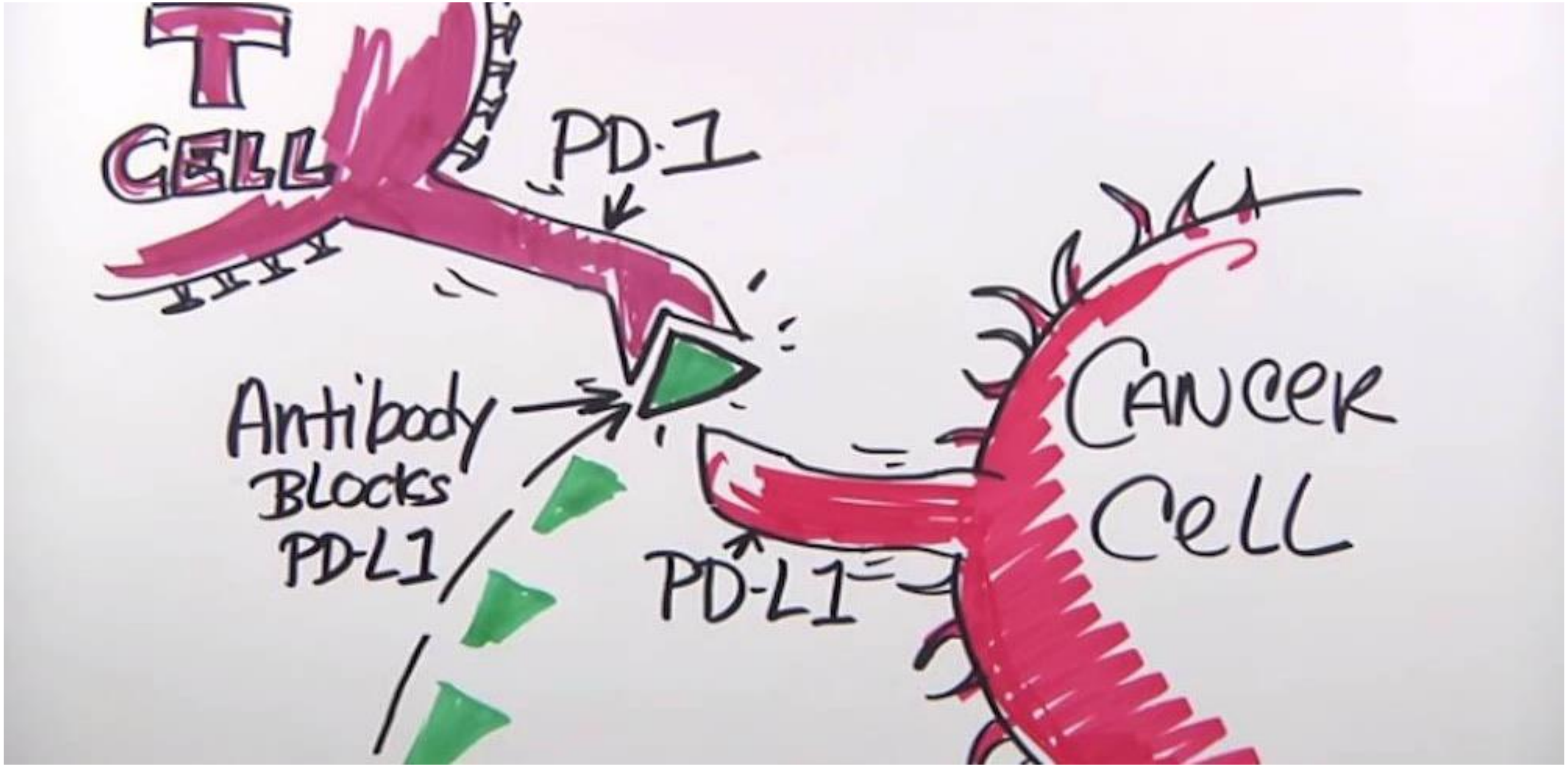
CS1-specific chimeric antigen receptor (CAR)-engineered natural killer cells enhance *in vitro* and *in vivo* antitumor activity against human multiple myeloma

[1,2,9], Y Deng[1,3,9], DM Benson[1,2], S He[2], T Hughes[2], J Zhang[4], Y Peng[2], H Mao[2], L Yi[2], K Ghoshal[2,5], X He[2,6], SM Devine[1,2,7], X Zhang[8], Caligiuri[1,2], CC Hofmeister[1,2] and J Yu[1,2,7]

T cell co-signaling: an extended family of receptors and ligands



Checkpoint inhibitors keep T cells in 'check'
so they do not attack normal tissue



Dana Farber Cancer Institute

T cell co-signaling: like people’s hugs

‘The no hug

Harmless or not?

‘The inhibitory hug’

PD-1

CTLA-4

No comment

‘The stimulatory hug’

OX40

4-1BB

One hug...two happy people

SOME “FIRST” CHECKPOINT INHIBITOR TRIALS

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

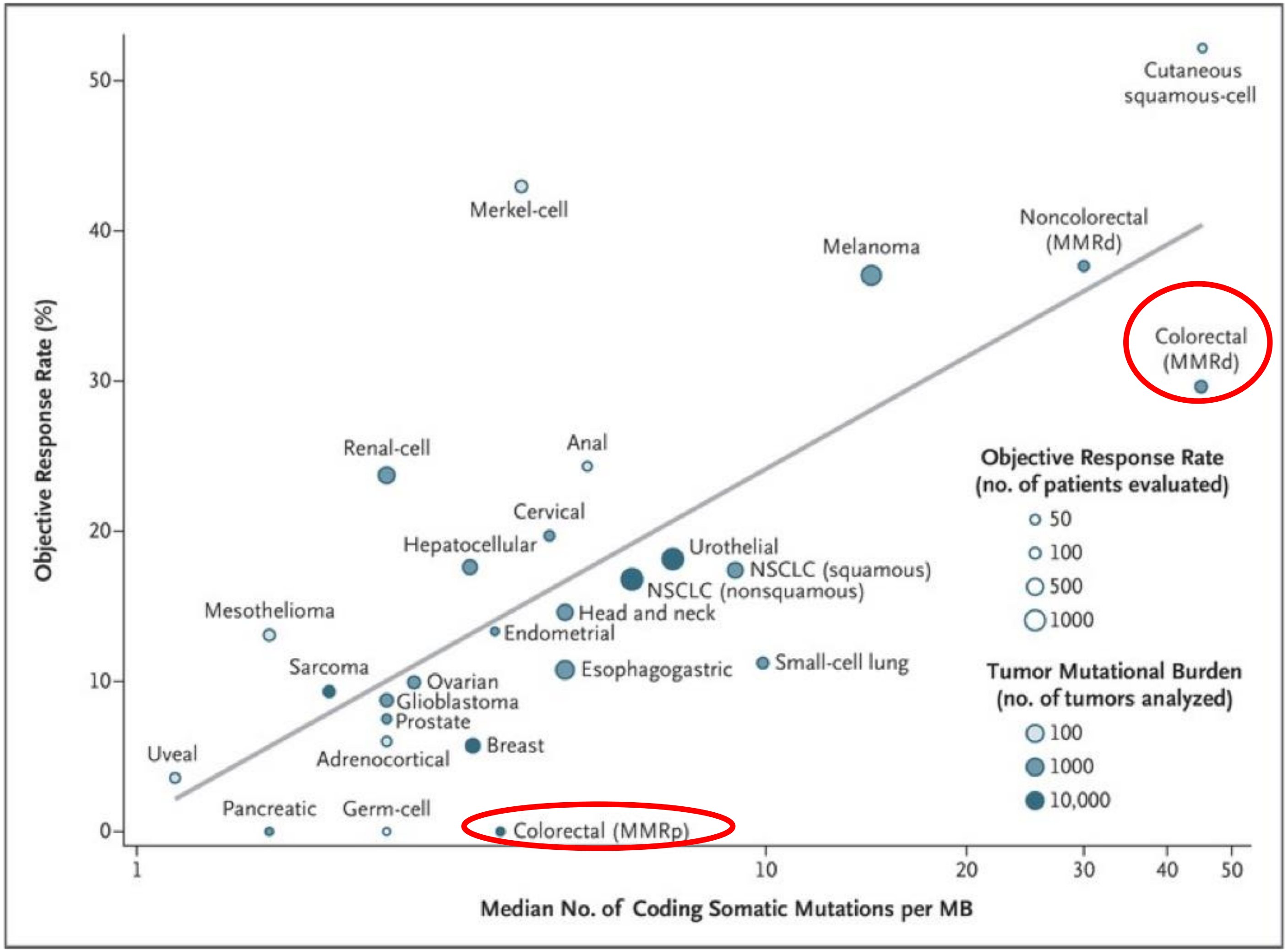
N Engl J Med. 2010, 363:711

Safety, activity, and immune correlates of anti-PD-1 antibody in cancer

N Engl J Med. 2012 Jun 28;366(26):2443-54

Challenge: Autoimmune side effects due to ‘global’ T cell activation

Efficacy of PD1 inhibitors correlates with tumor mutational status



Yarchoan *et al. NEJM*, 2017

T cells induce inflammation even if target antigen is expressed in minute quantities on healthy cells

T cell co-signaling antibodies

Ipilimumab or Nivolumab: Grade 3-4 SAE in 15-25% of pts, deaths in up to 2% of pts
Ipilumimab+Nivolumab: Grade 3-4 SAE in 50% of pts
Pembrolizumab: Grade 3-4 SAE in 20% of pts

Grade 3-4 SAE are mostly inflammation of skin and/or gastrointestinal tract, and liver enzyme abnormalities

Adoptively transferred T cells

TILs: Vitiligo and uveitis in 35 and 15% of pts, respectively
CAR T cells: B-cell anaplasia and cytokine release syndrome in responding pts (*CD19 target*)
Liver enzyme abnormalities in 50% of pts (*CAIX – Rotterdam study*)[1]
Respiratory distress and death of pt (*ERBB2*)
TCR T cells: Severe melanocyte destruction of skin, eyes and ears in 25% of pts (*MARTI/HLA-A2; gp100/HLA-A2*)
Inflammation of colon in responding pts (*CEA/HLA-A2*)
Neurological toxicity in 33% of pts (2 out of 3 pts died) (*MAGE-A3/HLA-A2, shared epitope*)
Cardiac toxicity and death in 2 pts (*MAGE-A3/HLA-A1, recognition of similar epitope*)

PD1 inhibitors

Meta-analysis-6360 patients, 16 studies — 2.9% incidence of pneumonitis*

[1]*Lamers, JCO, 2006; Lamers, Mol Ther, 2013*

*Wu et al. *Scientific Reports* 2017

And dangers of activating T cells by PD-1 inhibition…

Rapid Progression of Adult T-Cell Leukemia–Lymphoma after PD-1 Inhibitor Therapy

Table 1. Laboratory Data.*

Variable	Baseline Value	Peak Value after Nivolumab Treatment†		
	All Patients	Patient 1, Chronic ATLL‡	Patient 2, Smoldering ATLL§	Patient 3, Acute ATLL¶
PD-L1 expression on ATLL cells (%)‖		<1	<1	5
Creatinine (mg/dl)	<1.1	1.4	2.5	1.7
Calcium (mg/dl)	<10.0	12.2	13.3	11.8
Lactate dehydrogenase (U/liter)	<320	1335	351	3520
White-cell count (per mm^3)	<12.0	40.6	17.0	41.2
Factor increase in absolute lymphocyte count		11.7	1.5	10.6
Atypical lymphocytes (%)	≤5	24	NA	30
Bilirubin (mg/dl)	<1.0	2.5	0.6	21.7
Factor increase in HTLV-1 DNA**		63.0	NA	2.4

Clinical trial NCT02631746 (nivolumab)- STOPPED after 3 patients

***Ratner et al. *NEJM, May* 2018**

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

2016

T-Cell Therapy Using Interleukin-21–Primed Cytotoxic T-Cell Lymphocytes Combined With Cytotoxic T-Cell Lymphocyte Antigen-4 Blockade Results in Long-Term Cell Persistence and Durable Tumor Regression

Aude G. Chapuis, Ilana M. Roberts, John A. Thompson, Kim A. Margolin, Shailender Bhatia, Sylvia M. Lee, Heather L. Sloan, Ivy P. Lai, Erik A. Farrar, Felecia Wagener, Kendall C. Shibuya, Jianhong Cao, Jedd D. Wolchok, Philip D. Greenberg, and Cassian Yee

MART1-specific CTLs

How to test/control for combined therapies…

Gaspard Cretent
Dorota Klysz
Daouda Abba Moussa
Maria Mathias
Carmen Yong
Marco Craveiro
Cedric Mongellaz
Valérie Dardalhon

Marie Pouzolles
Alice Machado
Sarah Gailhac

Leal Oburoglu
Manuela Romano
Marie Daumur
Sandrina Kinet

Naomi Taylor
Valérie Zimmermann

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cnrs dépasser les frontières

Contre le Cancer La Ligue 101 comités pour la vie

Association pour la Recherche sur le Cancer

Projet financé par l'ANR - Project funded by ANR

ATTACK Adoptive engineered T-cell targeting to activate cancer killing

AFMTÉLÉTHON INNOVER POUR GUÉRIR

Marie Curie Actions

Université Montpellier

Seventh Framework Programme

Laboratory of Excellence GR-Ex The red blood cell: from genesis to death

National Institutes of Health The Nation's Medical Research Agency

Use of bispecific CAR-T cells

Cancer Cell
Article

Low-Dose Irradiation Programs Macrophage Differentiation to an iNOS$^+$/M1 Phenotype that Orchestrates Effective T Cell Immunotherapy

Felix Klug,[1,11] Hridayesh Prakash,[1,2,4,11] Peter E. Huber,[5,11,*] Tobias Seibel,[1,11] Noemi Bender,[1] Niels Halama,[6] Christina Pfirschke,[1] Ralf Holger Voss,[7] Carmen Timke,[5] Ludmila Umansky,[1] Kay Klapproth,[8] Knut Schäkel,[2] Natalio Garbi,[9,10] Dirk Jäger,[6] Jürgen Weitz,[3] Hubertus Schmitz-Winnenthal,[3] Günter J. Hämmerling,[8] and Philipp Beckhove[1,*]

Cancer Research

IL-12 Release by Engineered T Cells Expressing Chimeric Antigen Receptors Can Effectively Muster an Antigen-Independent Macrophage Response on Tumor Cells That Have Shut Down Tumor Antigen Expression

Markus Chmielewski, Caroline Kopecky, Andreas A. Hombach, et al.

Tumor-specific IL-9–producing CD8$^+$ Tc9 cells are superior effector than type-I cytotoxic Tc1 cells for adoptive immunotherapy of cancers

Yong Lu[a], Bangxing Hong[a], Haiyan Li[a], Yuhuan Zheng[a], Mingjun Zhang[a], Siqing Wang[b], Jianfei Qian[a], and Qing Yi[a,1]

[a]Department of Cancer Biology, Lerner Research Institute, Cleveland Clinic, Cleveland, OH 44195; and [b]Institute of Translational Medicine, The First Hospital, Jilin University, Changchun 130061, China

Edited by James P. Allison, MD Anderson Cancer Center, University of Texas, Houston, TX, and approved January 9, 2014 (received for review

Redirected Primary Human Chimeric Antigen Receptor Natural Killer Cells As an "Off-the-Shelf Immunotherapy" for Improvement in Cancer Treatment

*Olaf Oberschmidt, Stephan Kloess and Ulrike Koehl**

Th17 cells promote cytotoxic T cell activation in tumor immunity

Natalia Martin-Orozco[1], Pawel Muranski[4], Yeonseok Chung[1], Xuexian O. Yang[1], Tomohide Yamazaki[1], Sijie Lu[2], Patrick Hwu[3], Nicholas P. Restifo[4], Willem W. Overwijk[3], and Chen Dong[1]

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Antigen-Specific Cytolysis by Neutrophils and NK Cells Expressing Chimeric Immune Receptors Bearing ζ or γ Signaling Domains

Margo R. Roberts, Keegan S. Cooke, Annie-Chen Tran, Kent A. Smith, Wei Yu Lin, Martin Wang, Thomas J. Dull, Deborah Farson, Krisztina M. Zsebo and Mitchell H. Finer

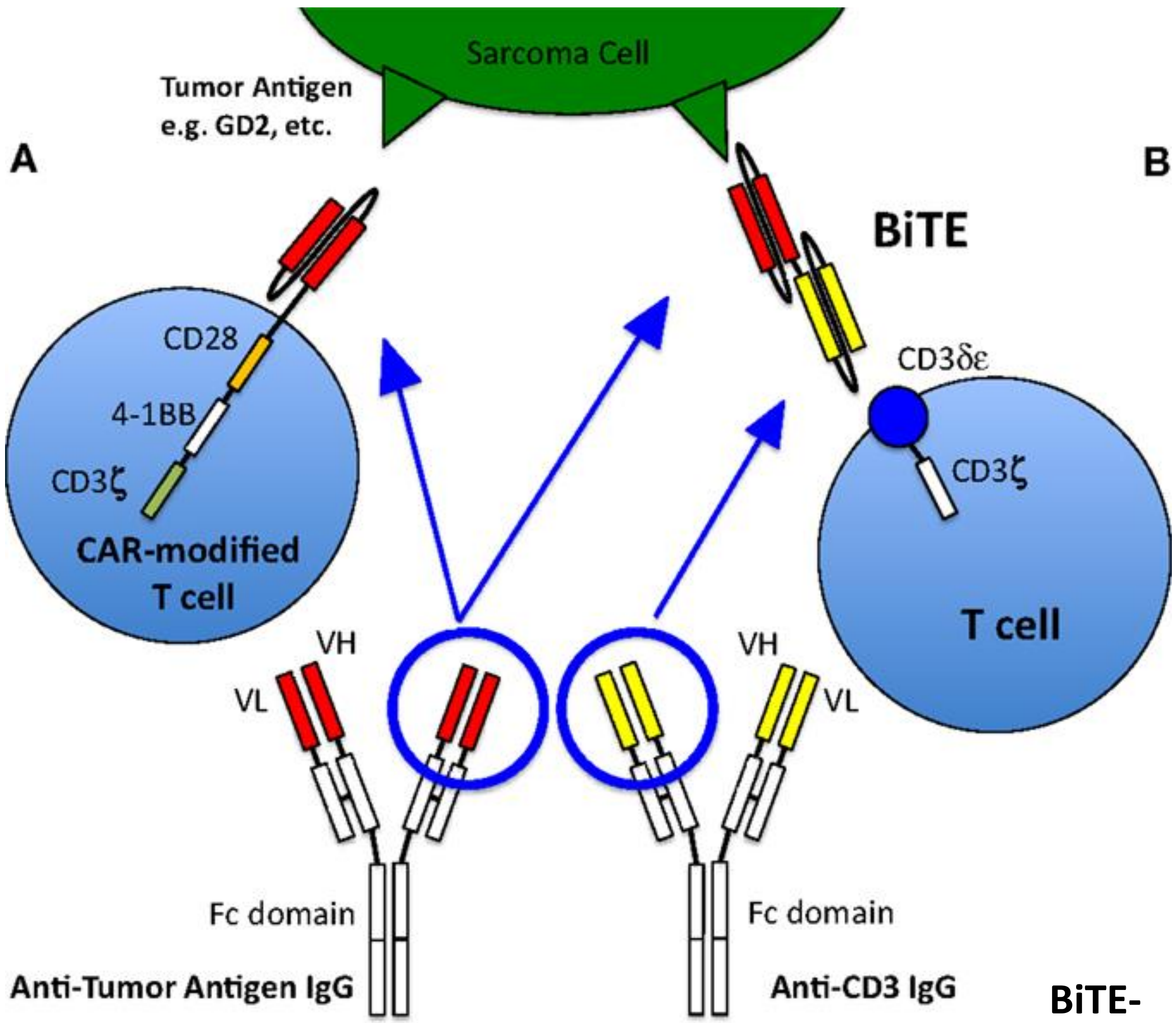
J Immunol 1998; 161:375-384; ;
http://www.jimmunol.org/content/161/1/375

ORIGINAL ARTICLE

CS1-specific chimeric antigen receptor (CAR)-engineered natural killer cells enhance *in vitro* and *in vivo* antitumor activity against human multiple myeloma

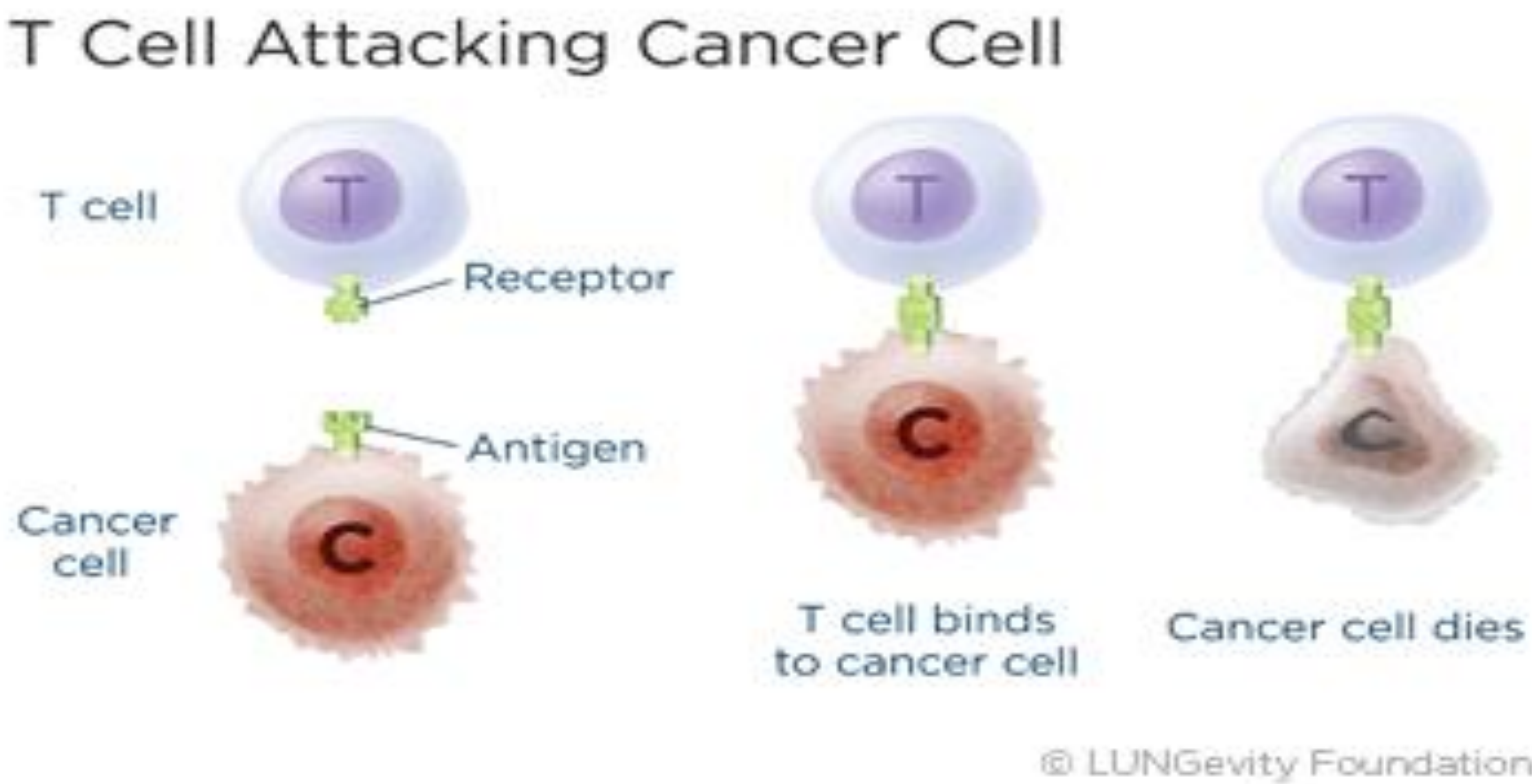
ı[1,2,9], Y Deng[1,3,9], DM Benson[1,2], S He[2], T Hughes[2], J Zhang[4], Y Peng[2], H Mao[2], L Yi[2], K Ghoshal[2,5], X He[2,6], SM Devine[1,2,7], X Zhang[8], :aligiuri[1,2], CC Hofmeister[1,2] and J Yu[1,2,7]

Potential for bispecific antibodies: Bringing tumor antigens and T cells "together"

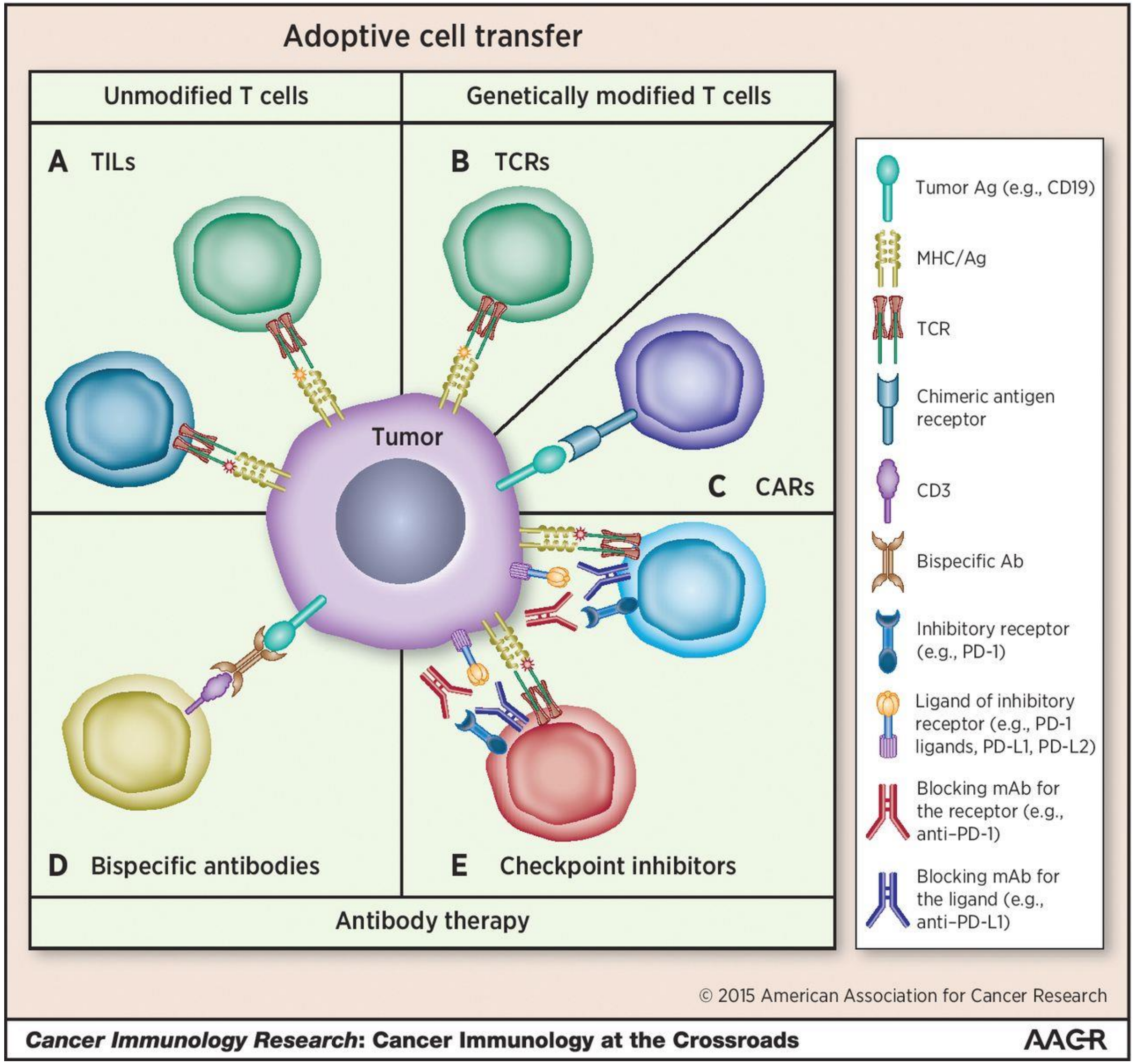


BiTE-
Bispecific T-cell engagers

T-cell Therapy



Multiple strategies are being used to optimize T-cell therapies for cancer….



Roch Houot et al. Cancer Immunol Res 2015;3:1115-1122

T cell co-signaling: clinical studies

Anti-CTLA4 mAb (Ipilimumab, BMS)

Phase III trial with vaccination, 137 melanoma pts:	**OR: 28%; CR: 2% *(Hodi, NEJM, 2010)***
Phase III trial with dacarbazine, 252 melanoma pts:	**OR: 14%; CR: 10% *(Robert, NEJM, 2011)***

Anti-PD1 mAb (Nivolumab, BMS)

Phase I trial, 94 melanoma pts:	**OR: 28%; CR: nr *(Topalian, NEJM, 2012)***
33 renal cell carcinoma pts:	**OR: 27%; CR: nr *(Topalian, NEJM, 2010)***
76 NSCLC pts:	**OR: 18%; CR: nr *(Topalian, NEJM, 2010)***
Phase III trial, 418 melanoma pts:	**OR 40%; CR: 8% *(Robert, NEJM, 2015)***

Anti-CTLA4 mAb (Ipilumimab)+anti-PD1 mAb (Nivolumab)

Phase I trial, 53 melanoma pts:	**OR: 40%; CR: 10% *(Wolchok, NEJM, 2013)***
Phase II, 142 melanoma pts:	**OR: 61%; CR: 22% *(Postow, NEJM, 2015)***

Anti-PD1 mAb (Pembrolizumab, Merck)

Phase I trial, 135 melanoma pts:	**OR: 38%; CR: nr *(Hamid, NEJM, 2013)***

Anti-PD1 therapy in

Melanoma

Renal Cell Carcinoma

Lung Cancer