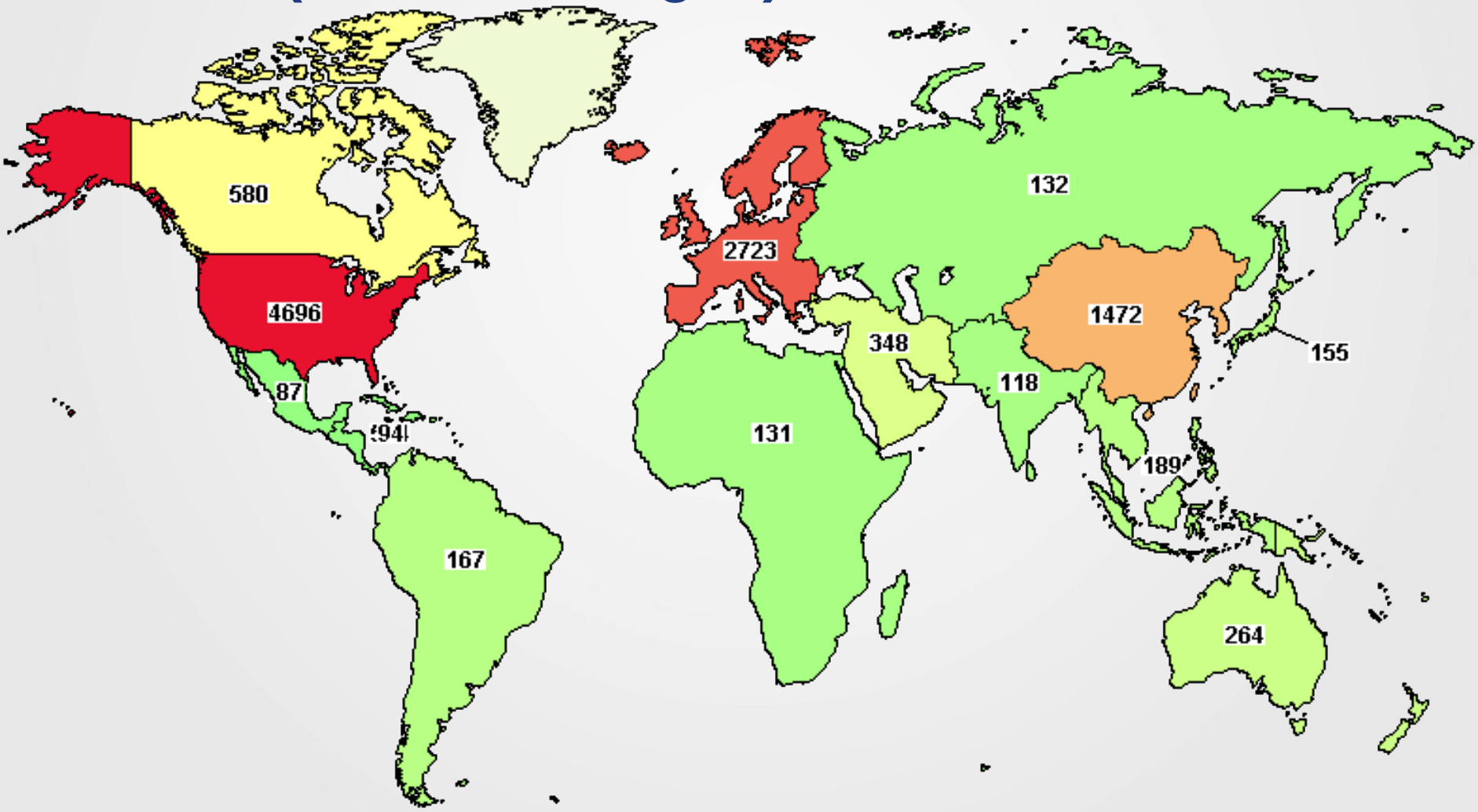
Cell and Gene Therapy (comes of age)

Chiara Bonini

Valencia, April 4th, 2016

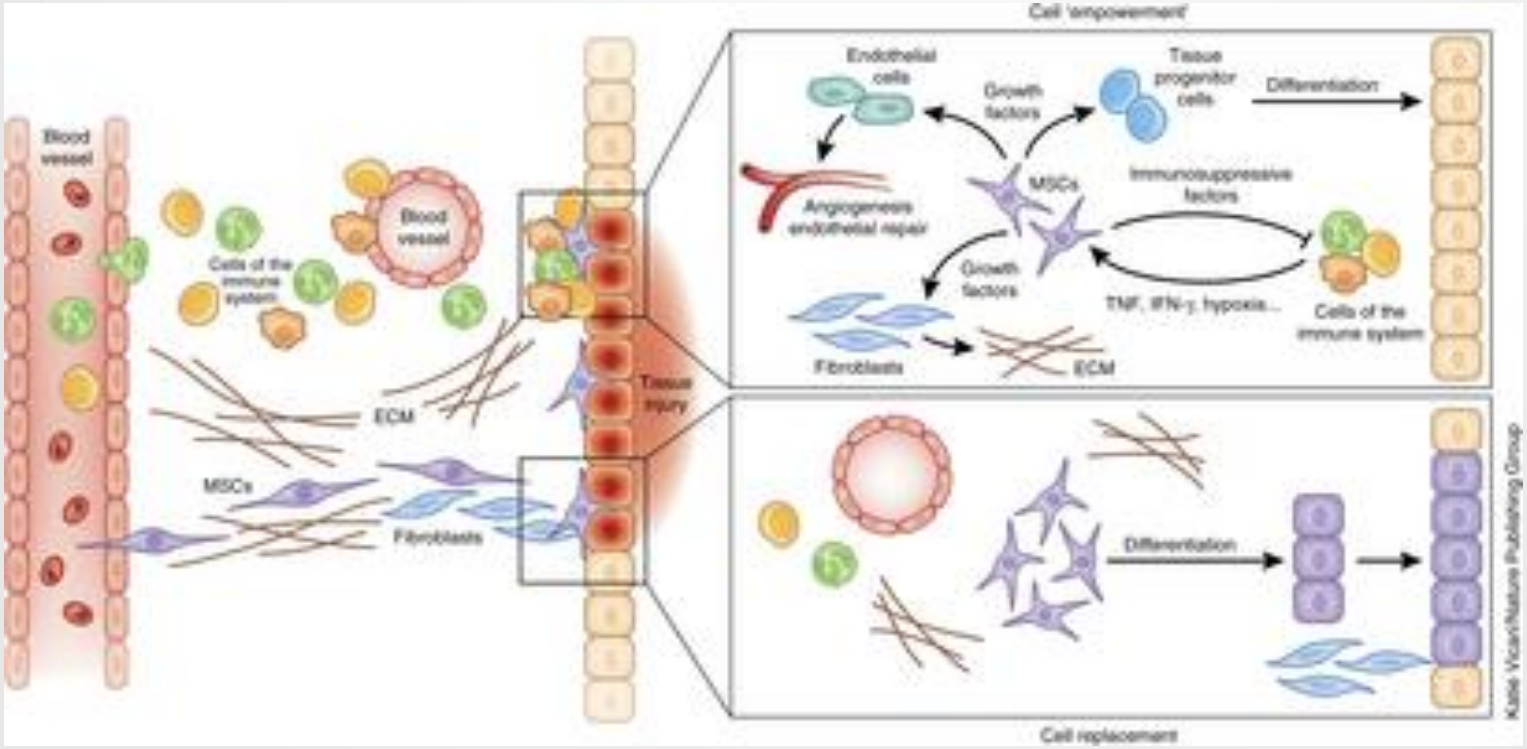
- Why EBMT is interested in cell and gene therapy?
- Why should we register patients undergoing cell and gene therapy?
- How should we proceed?

Cell Therapy: n. of active studies (clinicaltrials.gov)



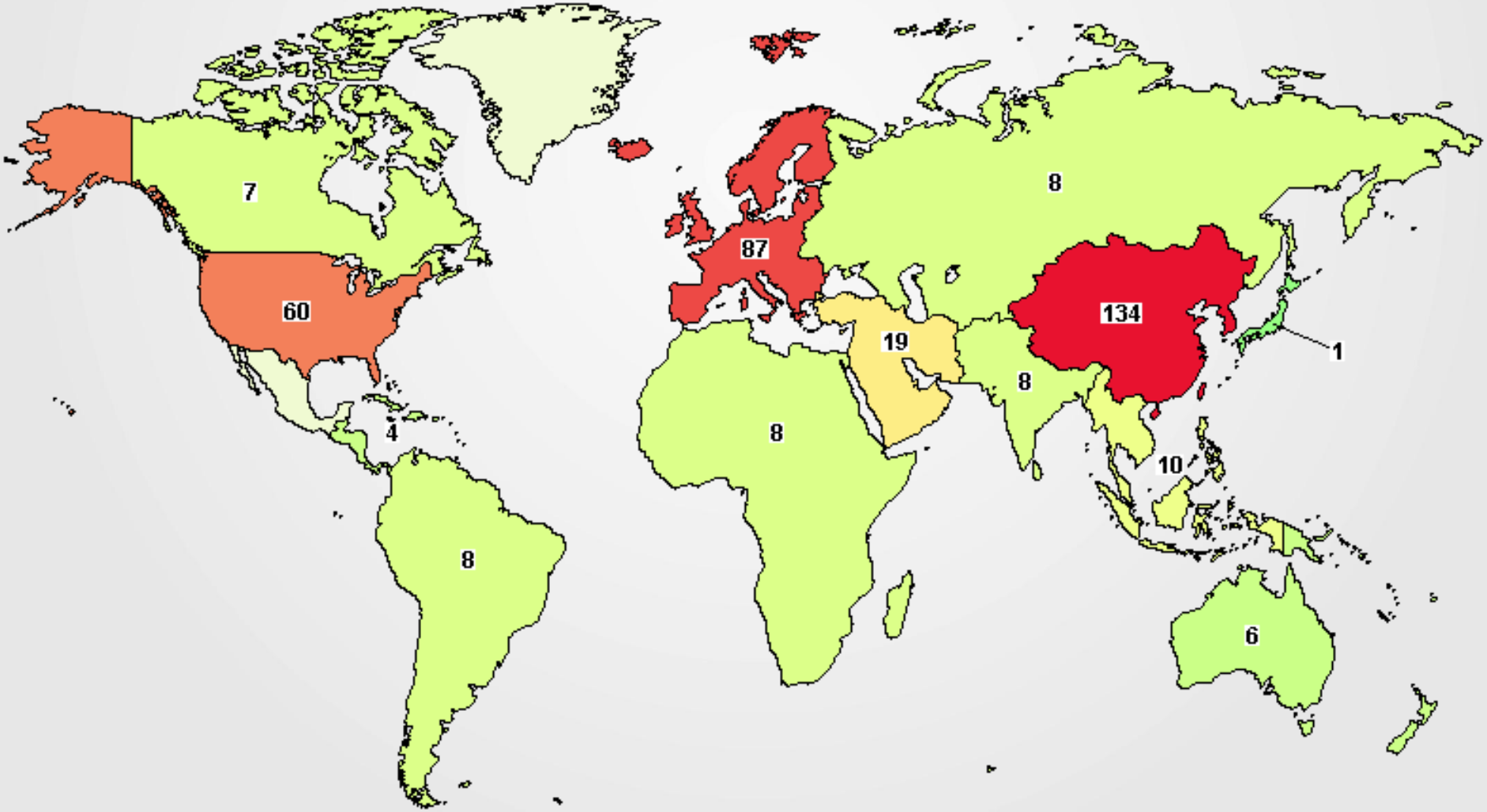
Example of Cell Therapy:

MSC-based therapy: cell replacement versus cell 'empowerment'.



- Wang Nat. Immunol 2014

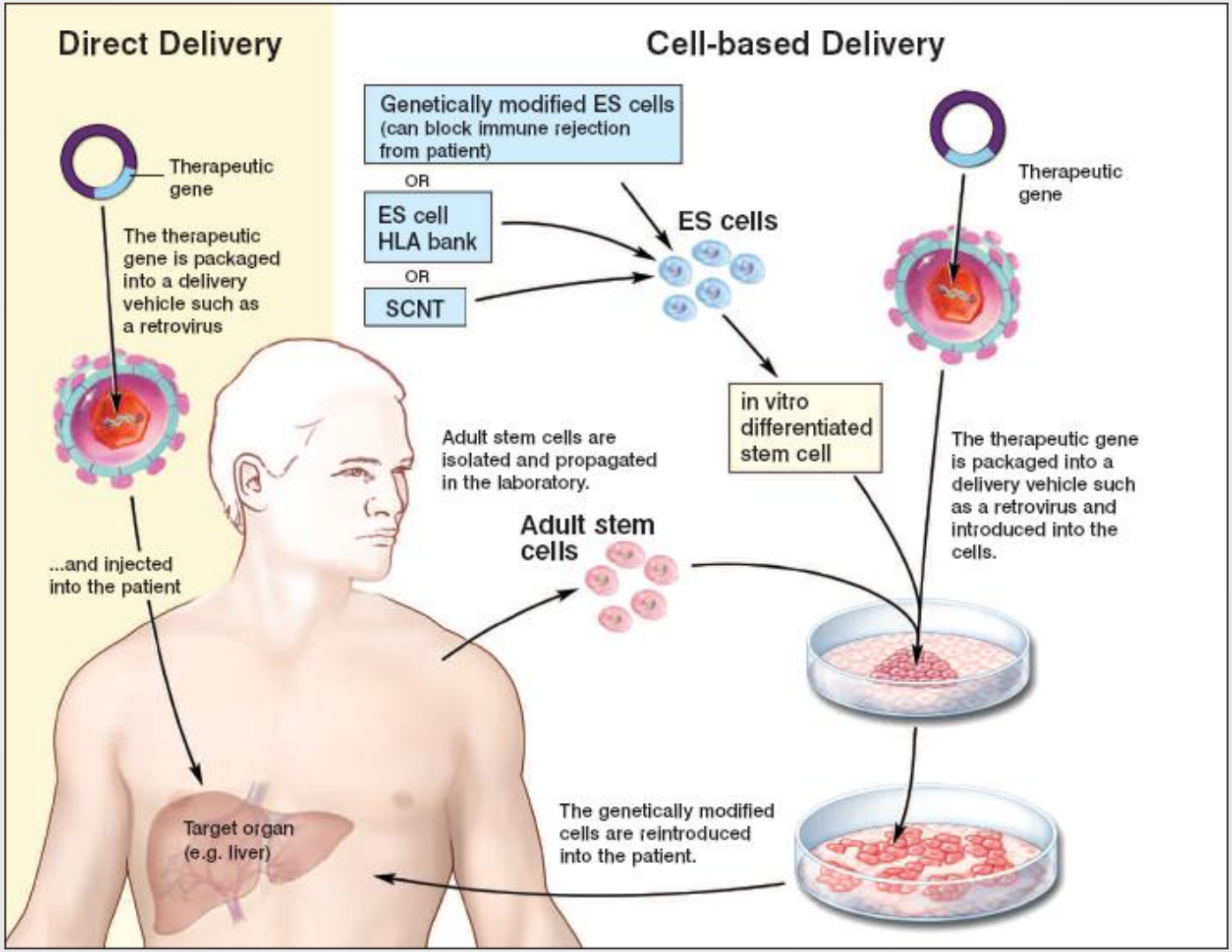
Mesenchymal stromal cells: n. of active studies (clinicaltrials.gov)



Gene transfer: is the process of transferring genetic material (DNA or RNA) into a cell to gain a missing function

Cell Based Gene therapy: is the use of gene-modified cells or vectors for therapeutic purposes

Gene Therapy

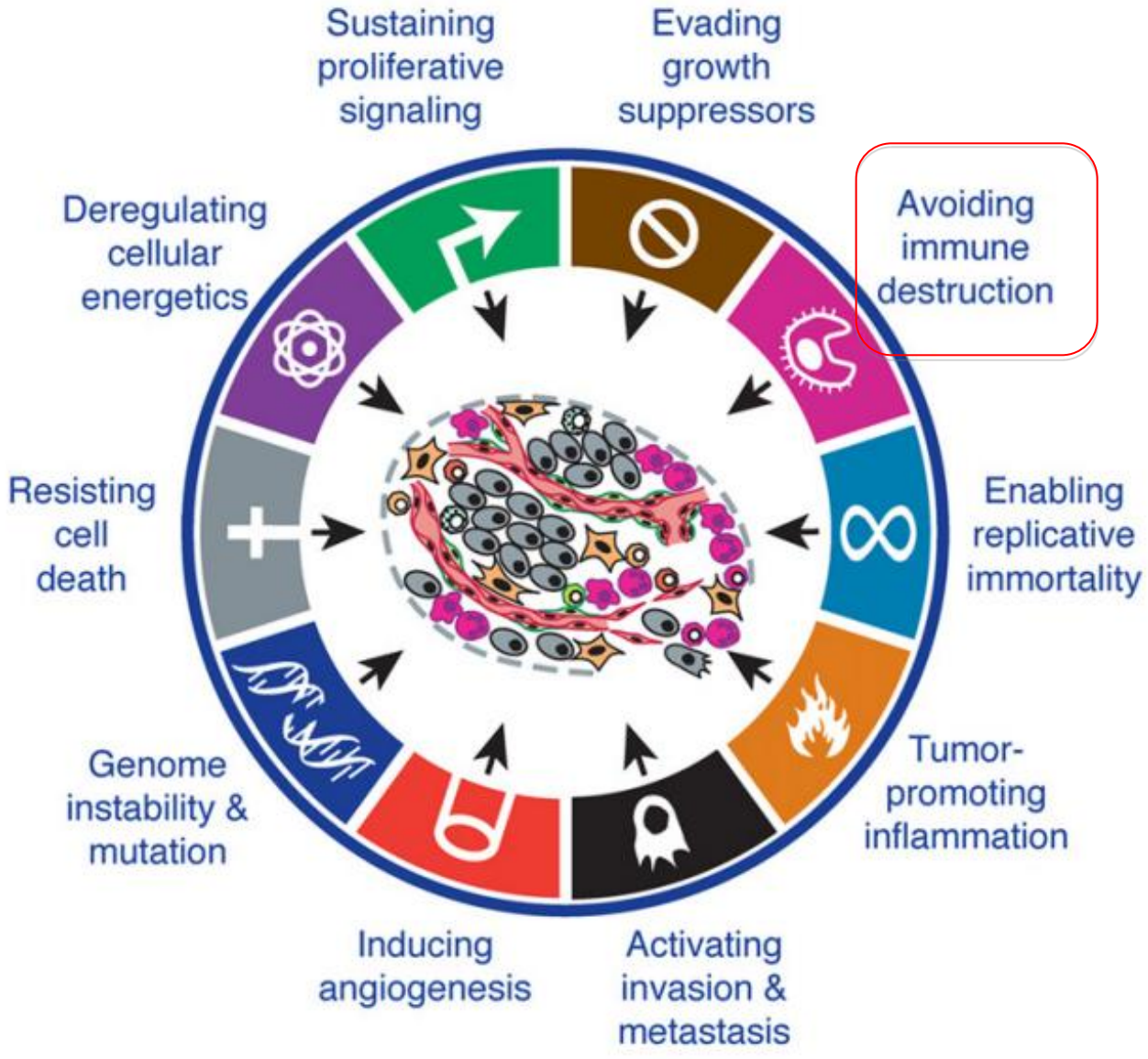


Cell based gene therapy (excluding cancer)

CELLS	DISEASE	GENE	VECTOR	Reference
T-lymphocytes	ADA-SCID	ADA	Gammaretroviral	Blaese et al (1995)
HSC	ADA-SCID	ADA	Gammaretroviral	Bordignon (1995)
				Aiuti et al (2002)
				Cavazzana-Calvo
2000				
				Boztug et al (2010)
				Aiuti et al (2013)
HSC				Ott et al (2006)
HSC				Cavazzana-Calvo 2010
HSC				Cartier et al (2009)
HSC				Biffi et al (2013)
HSC/T cells and	HIV	ZFNs targeting	Adenoviral	Burnett et al (2012)
		CCR5 (knock out)		Lee et al (2013)
Hepatocytes (1994)	Familial hypercholesterinemia	LDL receptor	Gammaretroviral	Grossman et al
Keratinocytes	Epidermolysis bullosa	laminin 5 b3	Gammaretroviral	Mavilio et al (2006)

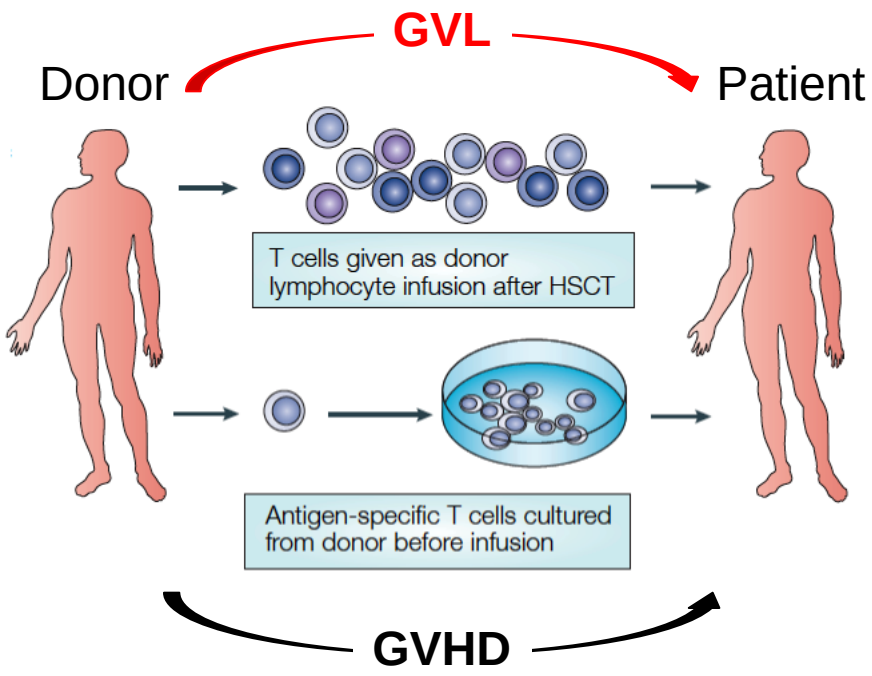
Approximately 60% of patients treated with gene therapy are affected by cancer

Hallmarks of cancer (and consequences for target selection)



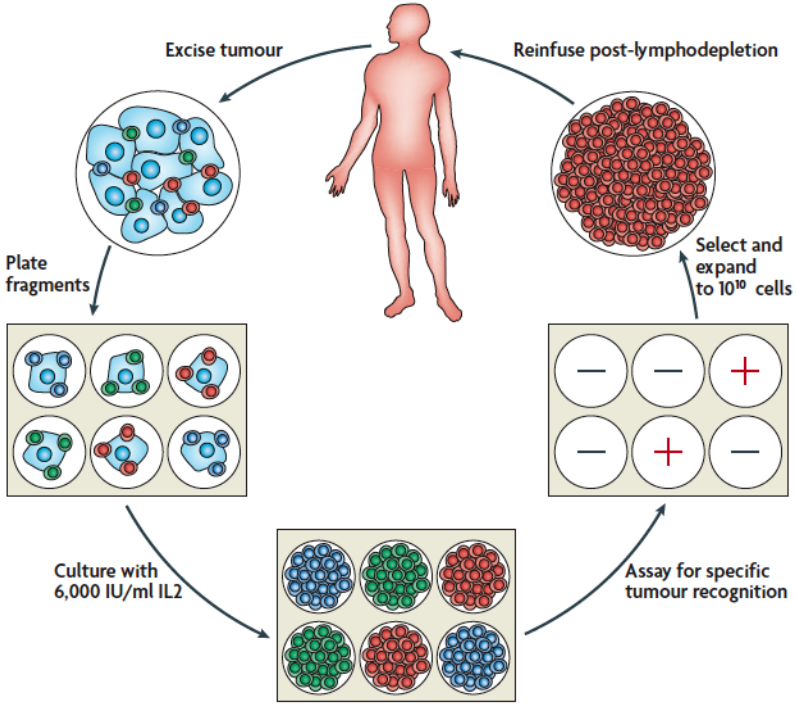
Adoptive T-cell therapy for cancer

Allogeneic ACT



Toxicity

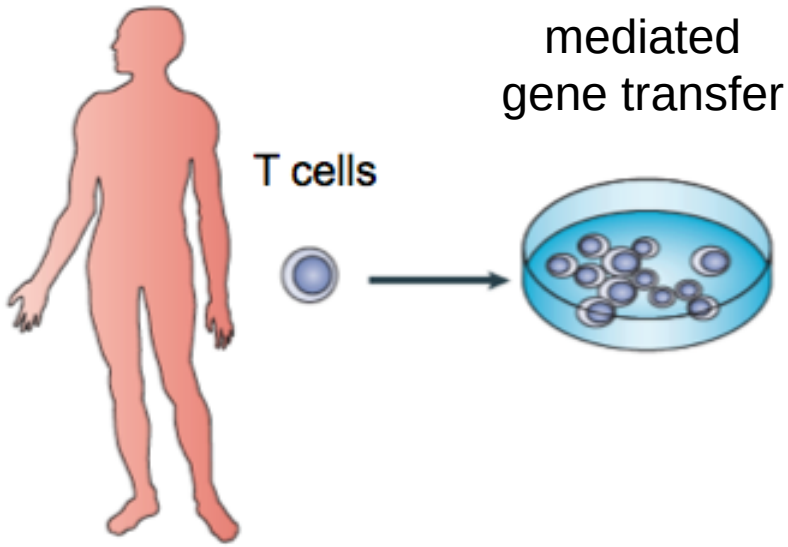
Autologous ACT

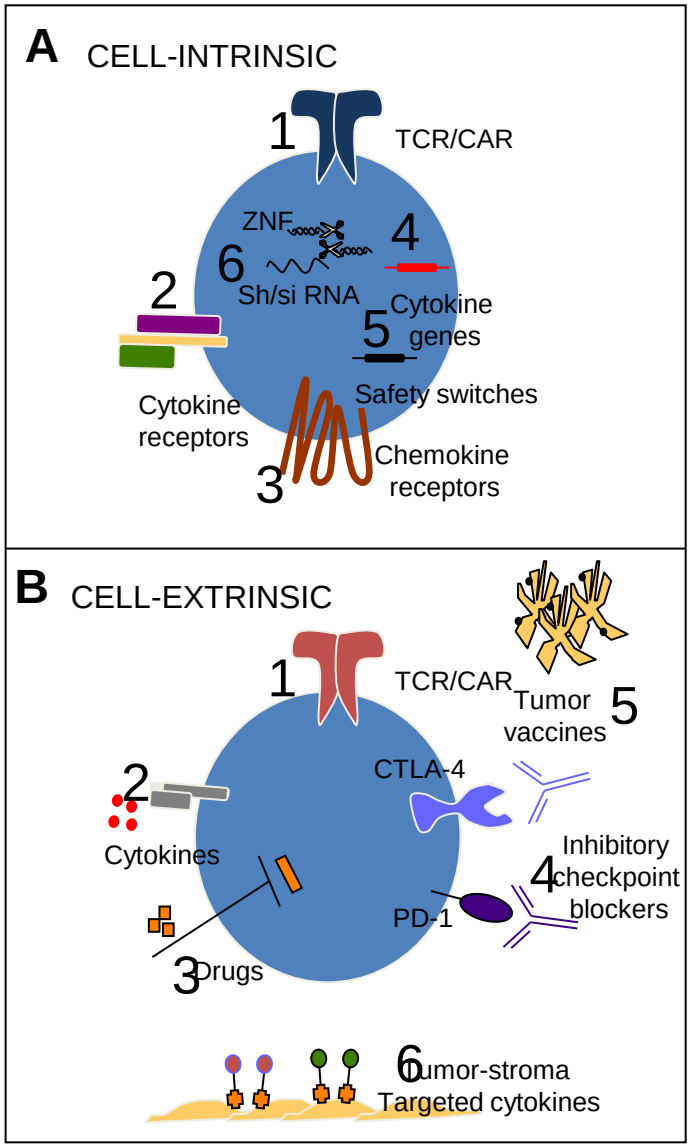


Limited applicability

Rosenberg, *Nature Reviews | Cancer,* 2008

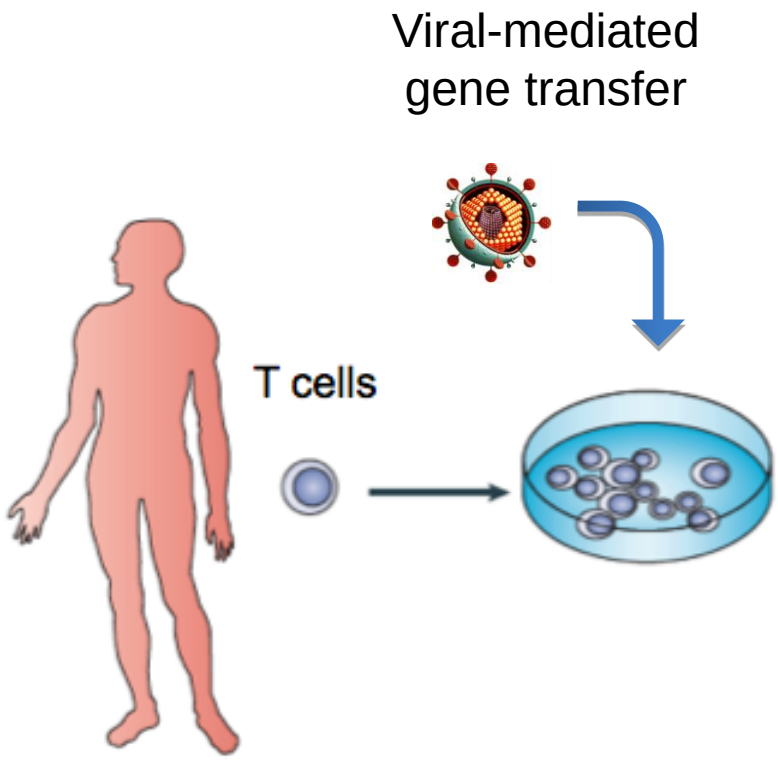
Adoptive T-cell therapy for cancer: The era of genetically engineered cells





Bonini and Mondino, Eur J Immunol. 2015 Sep;45(9)

Adoptive T-cell GENE therapy for cancer: Currently @ San Raffaele Scientific Institute



Suicide gene therapy in allo-HSCT

(Bonini et al., Science 1997; Bonini et al., Nat. Med. 2003; Bonini Ciceri et al., Lancet Oncol 2009; Vago et al., Blood 2012)

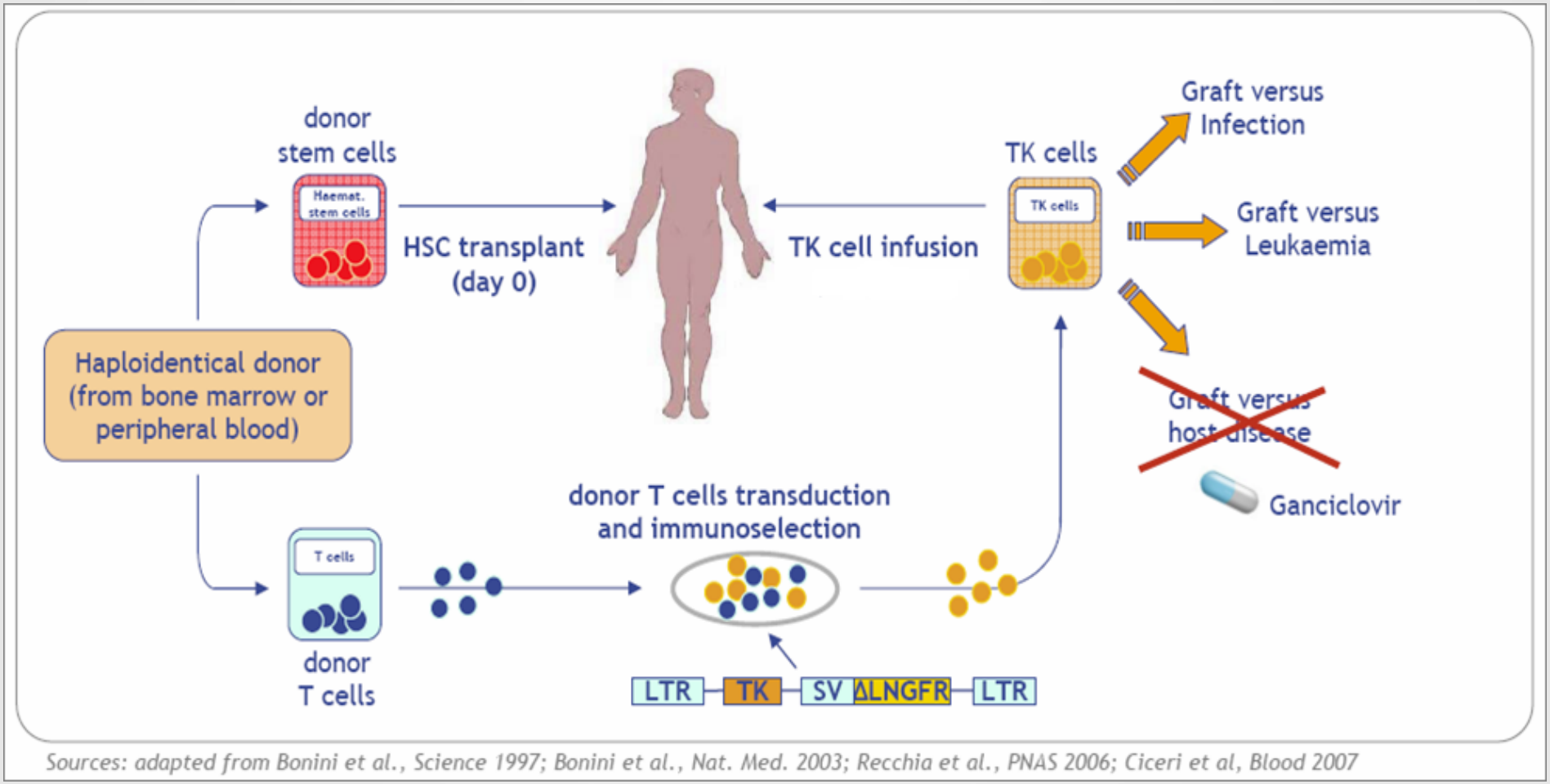
CAR-T cells redirected to CD44v6 to treat hematological malignancies and solid tumors

(Casucci et al., Blood 2013)

TCR gene editing to treat hematological malignancies

(Provasi, Genovese et al., Nat. Med 2012; Mastaglio et al., in preparation)

HSV-TK cells approach



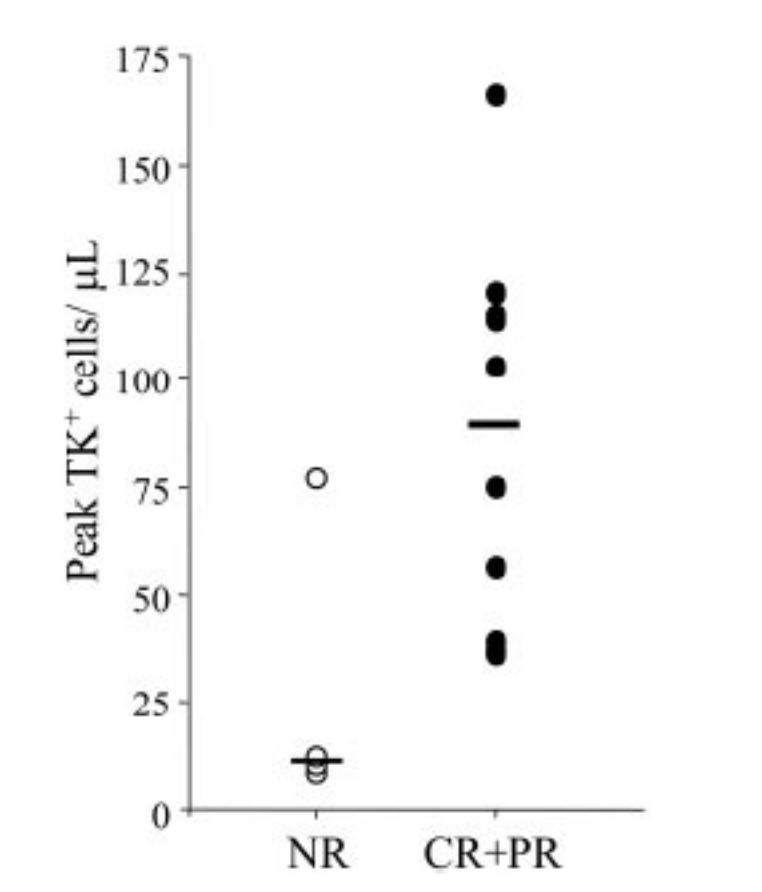
Sources: adapted from Bonini et al., Science 1997; Bonini et al., Nat. Med. 2003; Recchia et al., PNAS 2006; Ciceri et al, Blood 2007

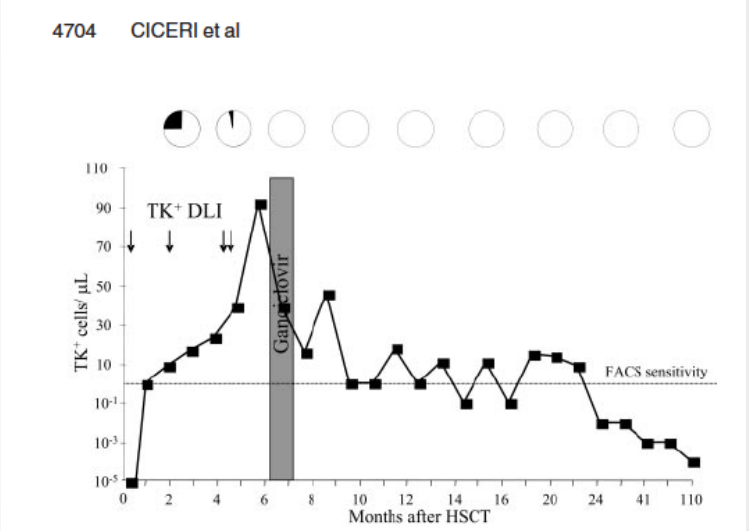
13

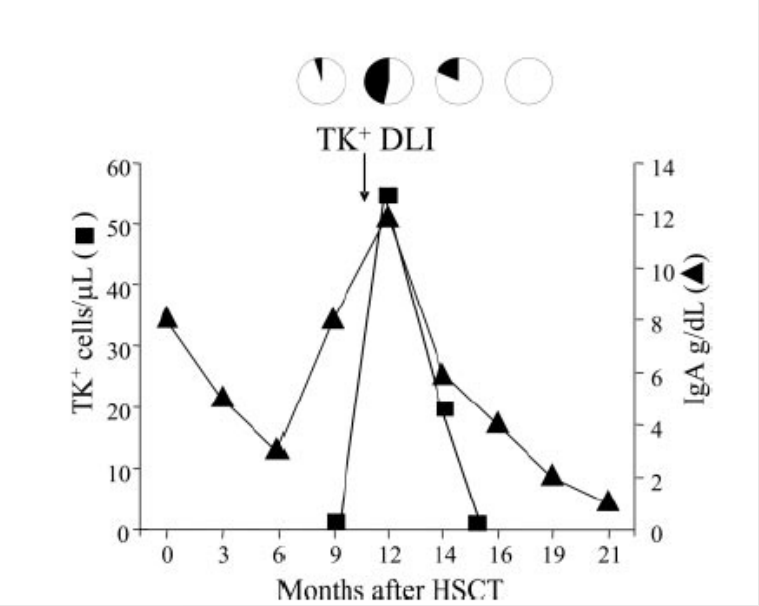
TK cells show in vivo anti-tumor effect

Ciceri et al, Blood 2007

TK-DLI in 23 relapsed pts







TK cells clinical development in haploidentical SCT

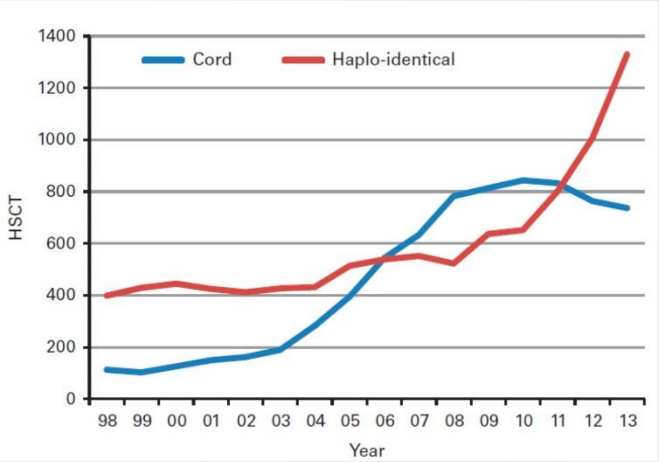
- **Haploidentical transplant is a lifesaving procedure for many patients with hematologic malignancies**

✓ ***Ex vivo*** **T-cell depleted haplo grafts without any donor cell therapy**

- **delayed immune recovery and increased non-relapse mortality**

✓ **T-cell replete haplo grafts followed by *in vivo* T-cell depletion and immunosuppression**

- **increased GvHD and relapse risks**



Passweg 2015

Numbers of haploidentical transplants doubled since 2010 for all the indications*

TK cells clinical trials

Phase I-II TK007

NCT00914628

Ciceri, Bonini et al, Lancet Oncol 2009

Haplo-HSCT* plus TK cells

*T-depleted (T cells, 1x10^4/Kg)

Dose of TK cells (1-x10^6/Kg - 1x10^7/Kg)
Up to 4 monthly doses up to IR (CD3+ cell count >/= 100/mcl)
Starting 21 to 49 days after HSCT in absence of IR and/or GvHD

Phase III TK008

MOLMED

NCT00914628

R (3:1)

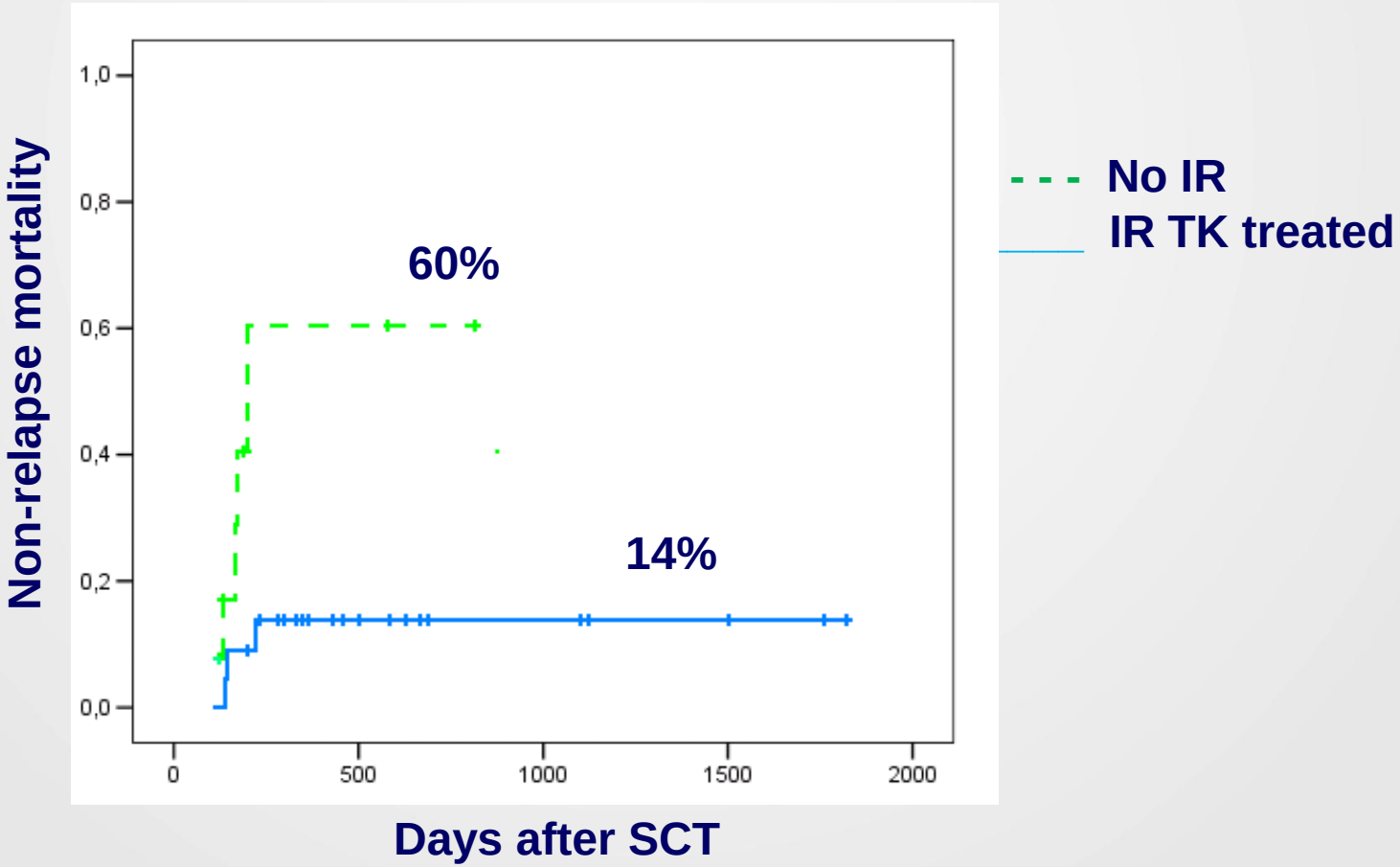
- **Haplo-HSCT* plus TK cells**
- **Haplo-HSCT****

*T-depleted (T cells, 1x10^4/Kg)

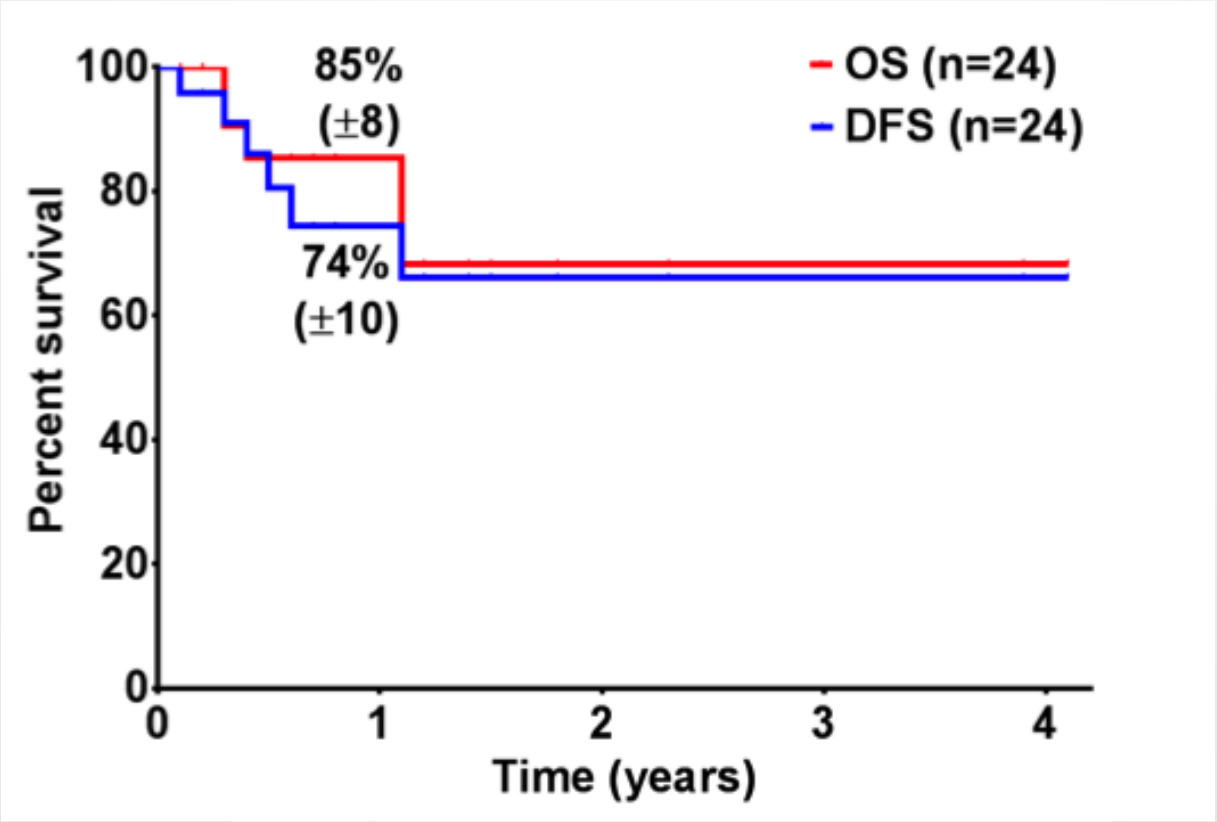
**T-depleted (T cells, 1x10^4/Kg)
or
** unmanipulated BMT/PB + HD CTX

Dose of TK cells (1x10^7/Kg)
Up to 4 monthly doses up to IR (CD3+ cell count >/= 100/mcl)
Starting 21 to 49 days after HSCT in absence of IR and/or GvHD

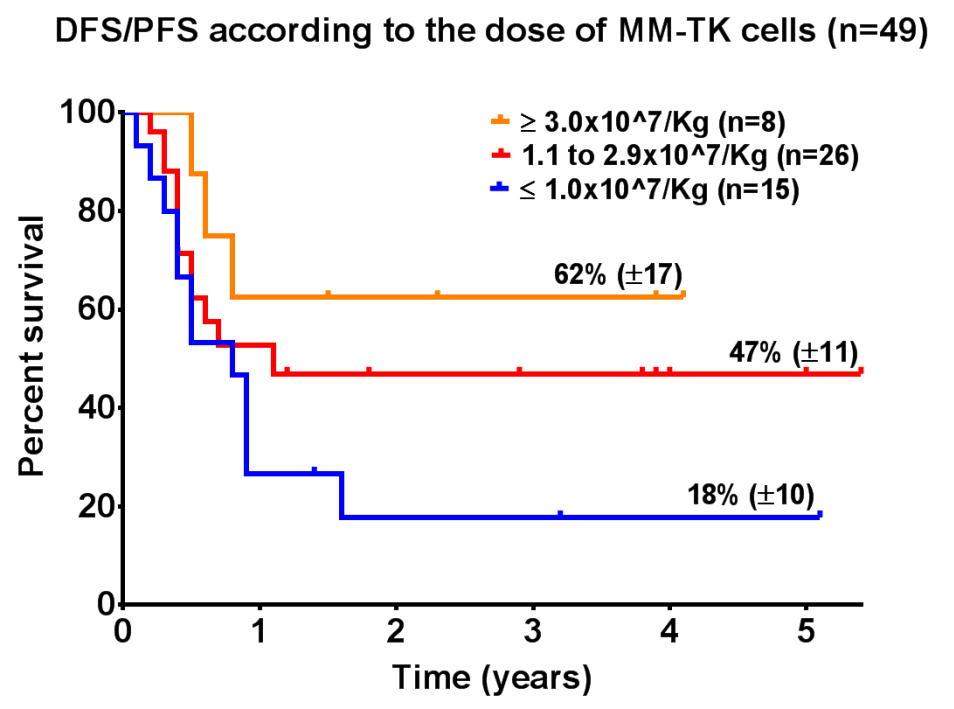
TK007 phase II trial: very low infectious mortality after TK-cells

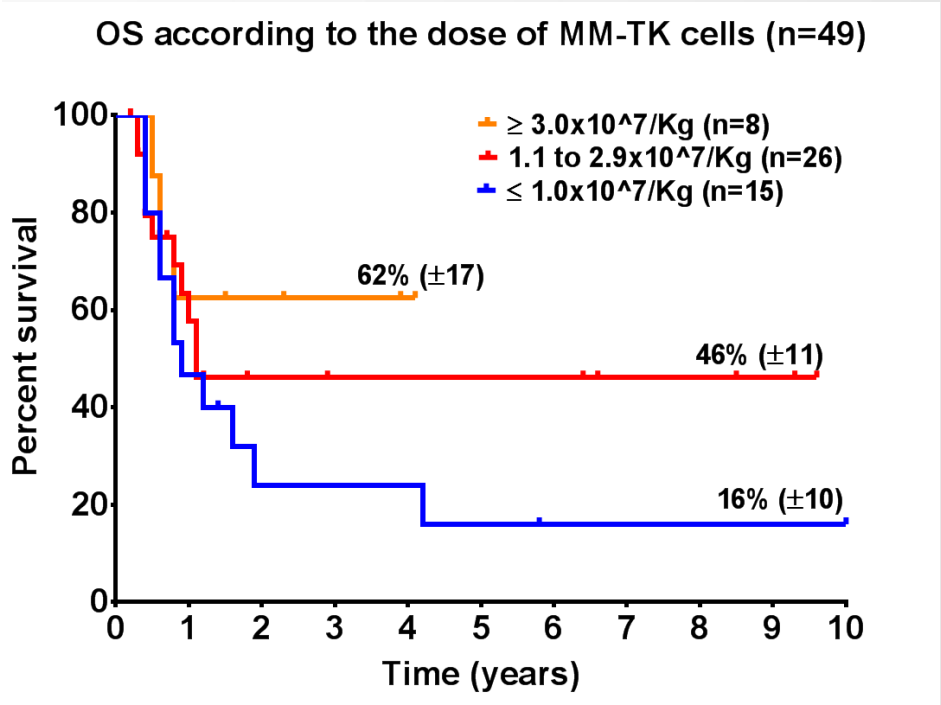


GvHD-free survival: TK008 experimental arm



TK008 & TK007 (pooled analysis): Impact on survival rates of TK-cell doses

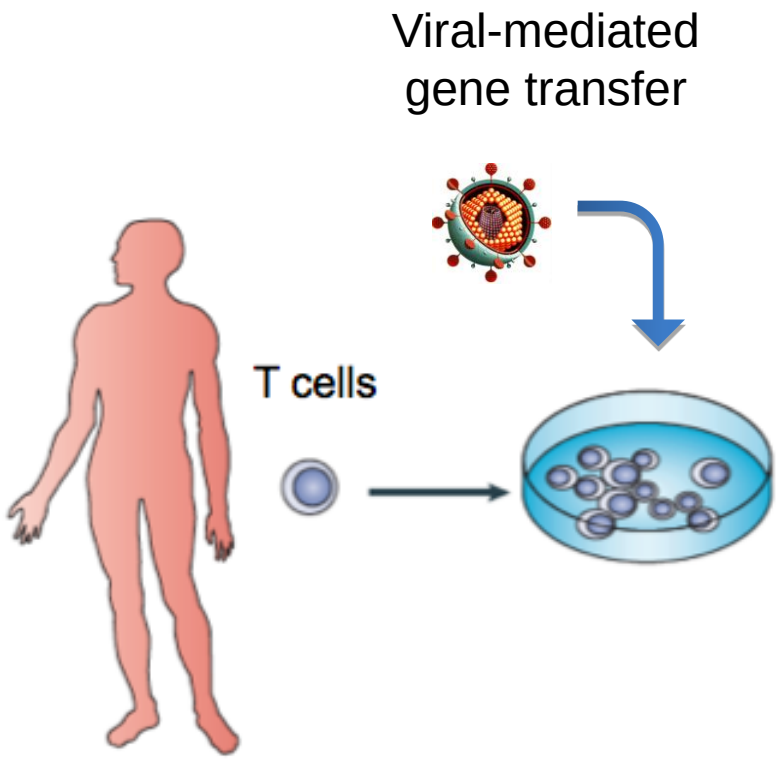




TK008 Participating Institutions

Fabio Ciceri, Arnon Nagler, Evangelia Yannaki, Maria Teresa Lupo Stanghellini, Attilio Bondanza, Giacomo Oliveira, Raffaella Greco, Eduardo Olavarria, Eva M Weissinger, Michael Stadler, Donald Bunjes, Dietger Niederwieser, Lutz Uharek, Wolfgang Bethge, John DiPersio, Michele Donato, Andrew Pecora, Antonio Lambiase, Claudio Bordignon

Adoptive T-cell GENE therapy for cancer: Currently @ San Raffaele Scientific Institute



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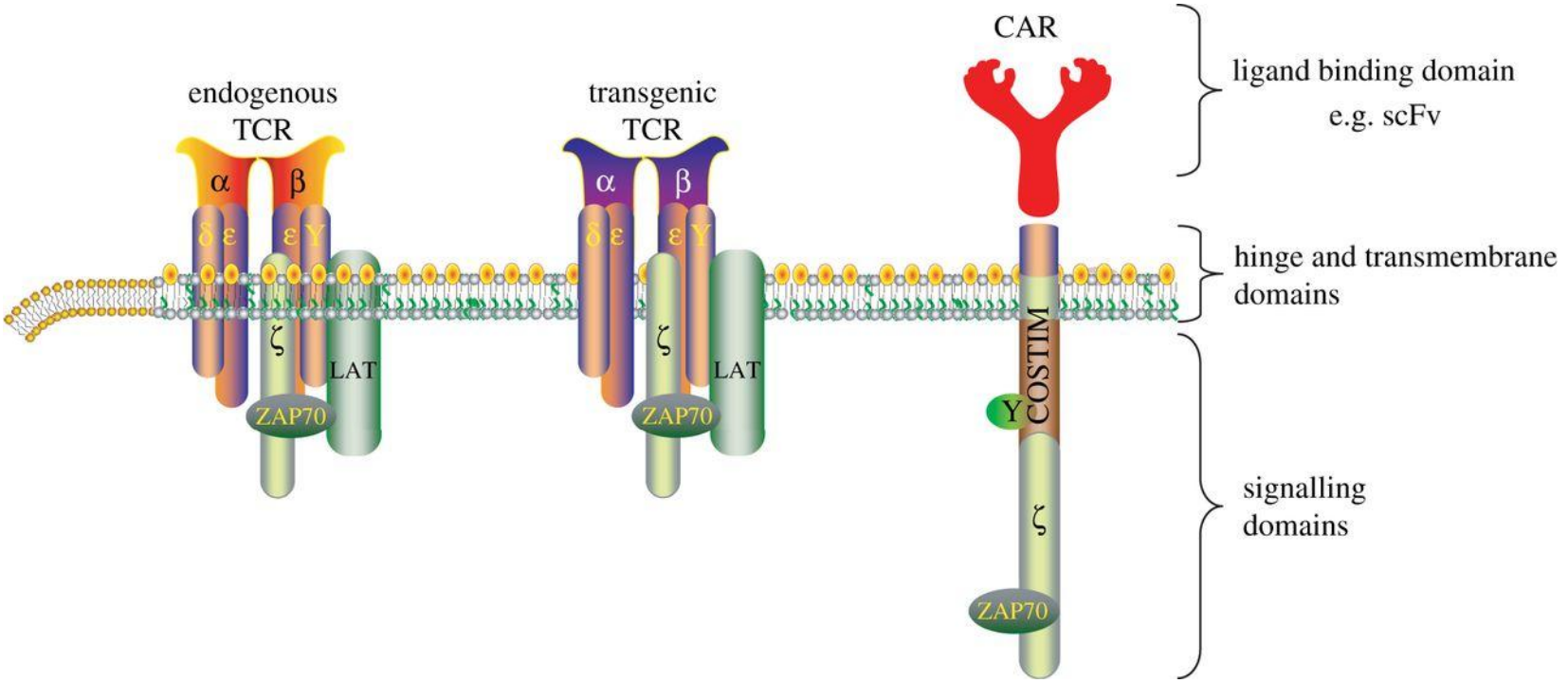
T cells can be engineered to have retargeted specificity for tumours.



Carl H. June, and Bruce L. Levine Phil. Trans. R. Soc. B 2015;370:20140374

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

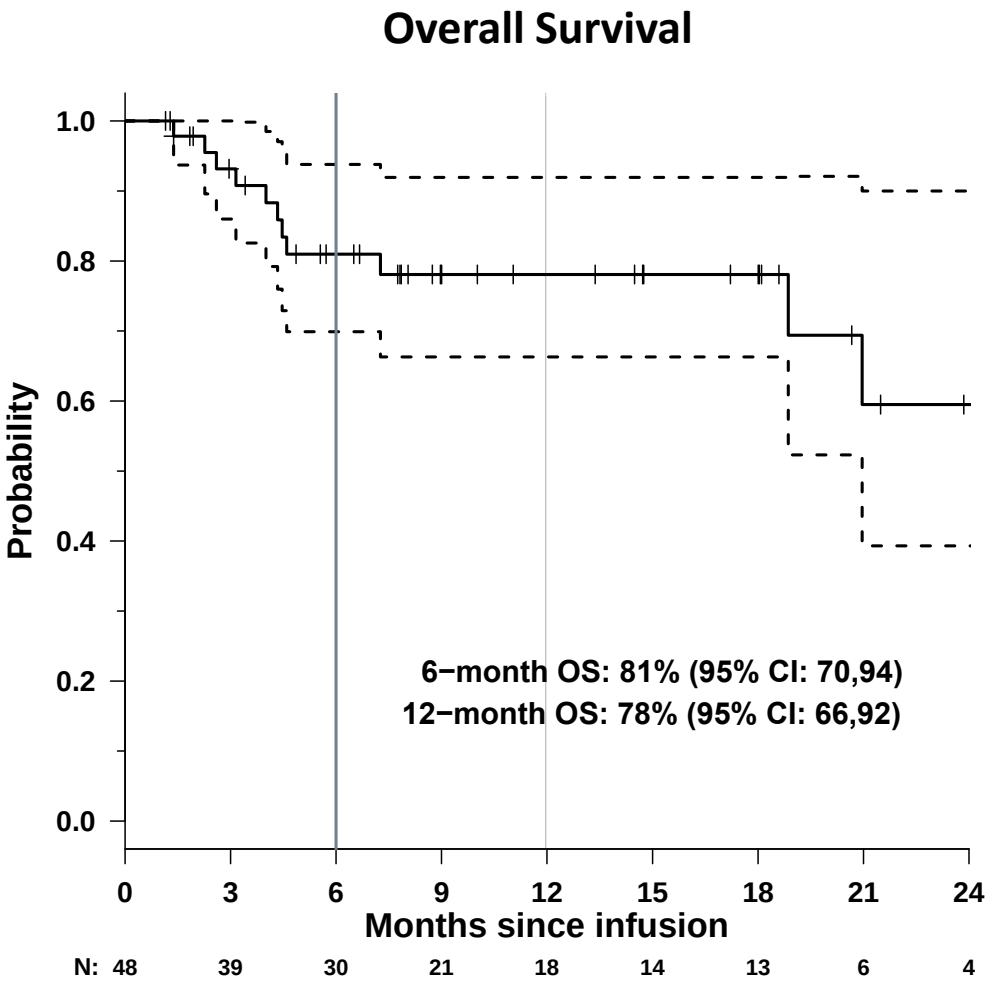
Pros and cons of adoptive immunotherapeutic tools

	mAb	TCR	CAR
MHC restriction	-	+	**-**
Antigen processing	-	+	**-**
Lipid/sugar antigens	**+**	**-**	**+**
Biodistribution	+/-	+	**+**
Persistance	-	+	**+/-**
Safety factors	-	+	**+**
Intracellular antigens	-	+	**-**
Costimulation	/	+	**+/-**

94% CR rate for r/r ALL after CTL019

175 patients with CLL, ALL, NHL, MM have gotten CTL019

- 48 r/r pediatric ALL pts: 45 in CR at 1 mo (94%)
- 5 went to subsequent transplant
- 6-month DOR: 76%
- 18 patients out ≥1 year
- No relapses past 1 year
- 13 patients in remission ≥1 year, 10 without further therapy



Kindly provided by S. Grupp

2G CAR efficacy

Cancer	Target	Gene-Vector	Pts	Results	Reference
CLL	CD19	2G CAR-LTV 4-1BB (beads)	24	5 CR, 7 PR **OR rate 50%**	Porter, *NEJM* 2011 Kalos ASH 2013
ALL	CD19	2G CAR-LTV 4-1BB (beads)	17	11 CR **OR rate 64%**	Grupp, *NEJM* 2012 Kalos, *ASH* 2013
MCL, CLL, DLBCL	CD19	2G CAR-RTV	10	2 PR, 6 SD	Kochenderfer, *Blood* 2013
DLBCL	CD19	2G CAR-RTV CD28 (OKT3)	15	8 CR, 4 PR **OR rate 80%**	Kochenderfer, *JCO 2014*
ALL	CD19	2G CAR-RTV CD28 (beads)	16	14 CR, 2 cCR **OR rate 88%**	Davila, *Sci Transl Med 2014*
ALL	CD19	2G CAR-LTV 4-1BB (beads)	30	27 CR **CR rate 90%**	Maude, *NEJM* 2014

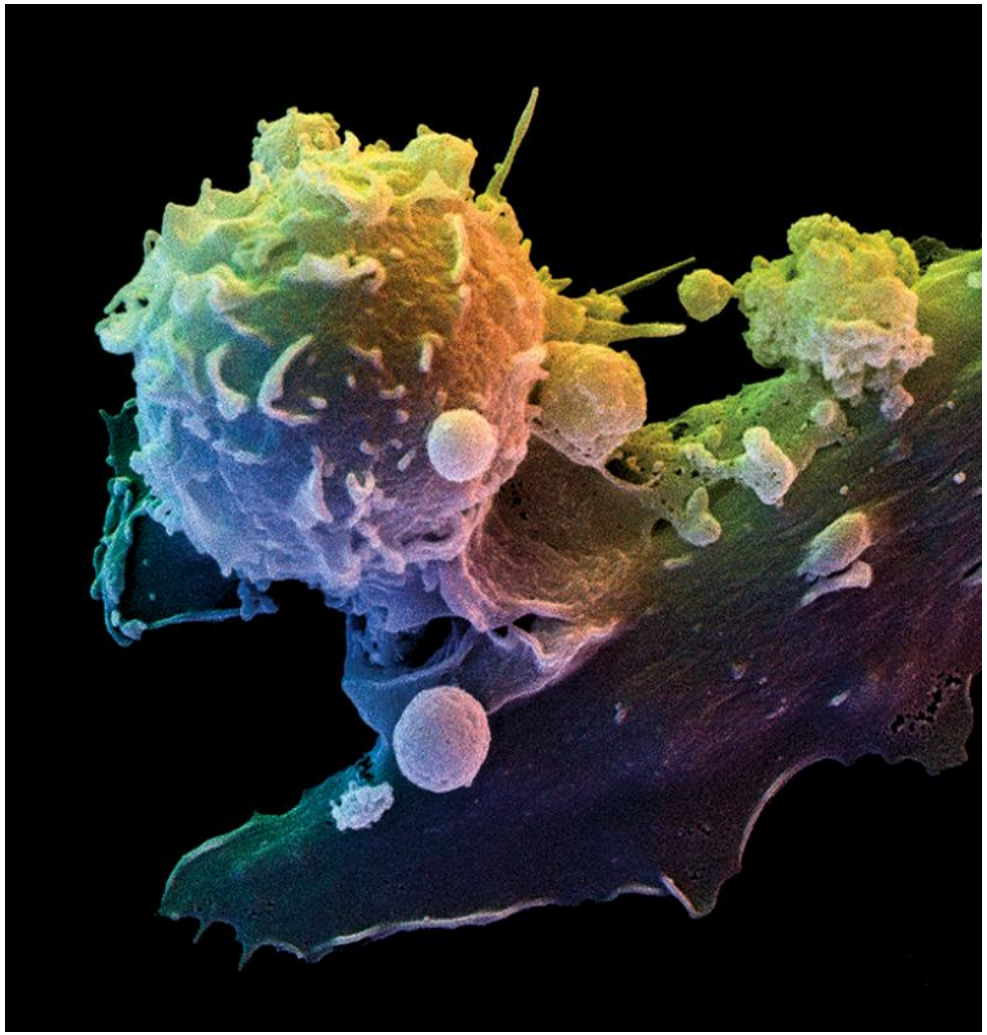
updated from Bondanza et al, *ASGCT newsletter* 2012

On-target toxicities

Cancer	Target	Gene-Vector	Pts	Results	Reference
CLL/B-ALL	CD19	2G CAR-RTV CD28 (beads)	8	**B-cell aplasia** **CRS**	Brentjens, *Blood* 2011
CLL	CD19	2G CAR-LTV 4-1BB (beads)	24	**B-cell aplasia** **CRS**	Porter, *NEJM* 2011 Kalos, *ASH* 2013
ALL	CD19	2G CAR-LTV 4-1BB (beads)	17	**B-cell aplasia** **CRS**	Grupp, *NEJM* 2012 Kalos, *ASH* 2013
MCL, CLL, DLBCL	CD19	2G CAR-RTV	10	**B-cell aplasia** **CRS**	Kochenderfer, Blood 2013
ALL	CD19	2G CAR-RTV CD28 (beads)	16	**B-cell aplasia** **CRS**	Davila, *Sci Transl Med 2014*
DLBCL	CD19	2G CAR-RTV CD28 (OKT3)	15	**B-cell aplasia** **CRS**	Kochenderfer, *JCO 2014*

2013

Combination therapies that help harness T cells and other immune cells in the cancer fight are a key area to watch.

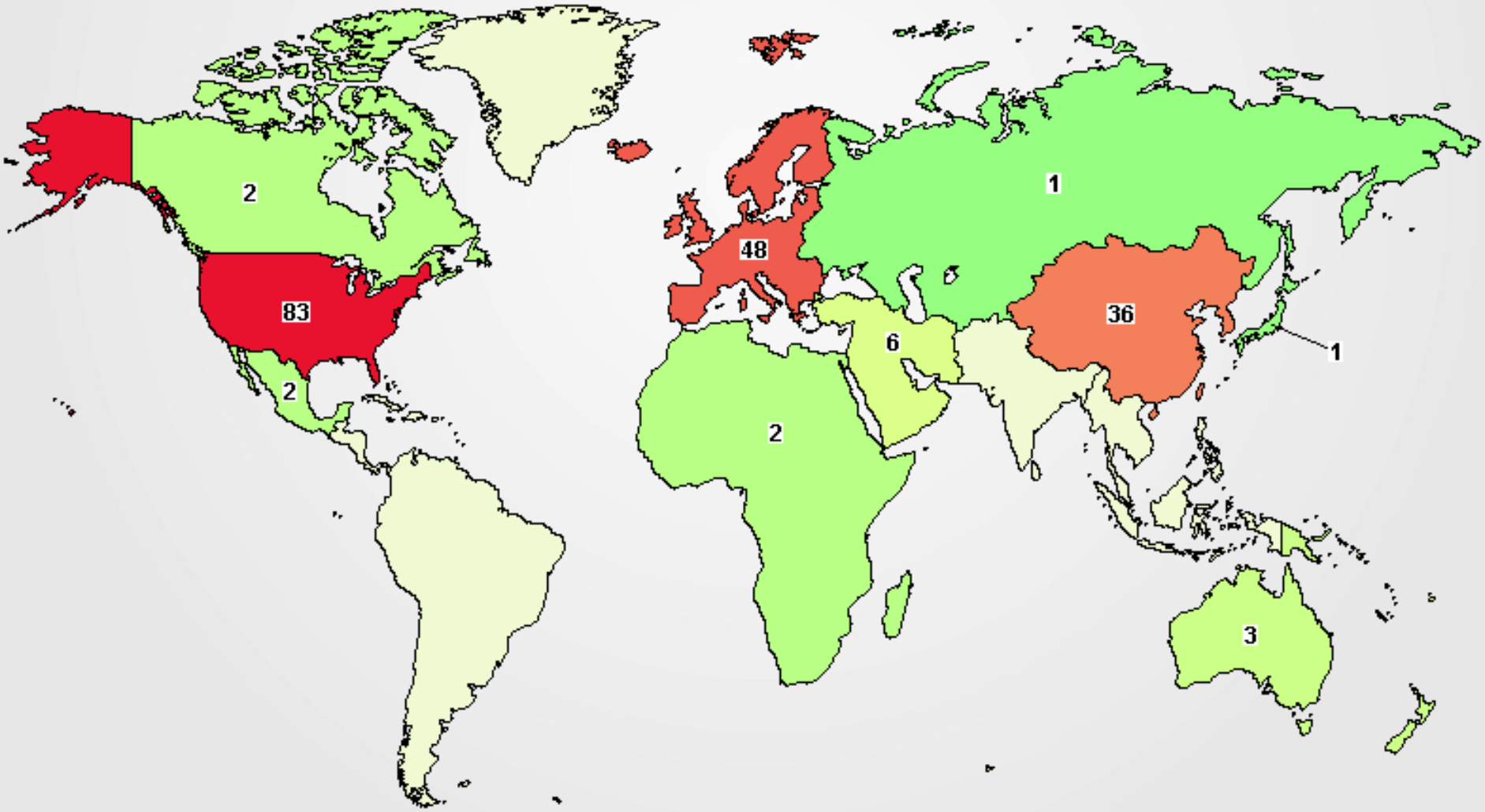


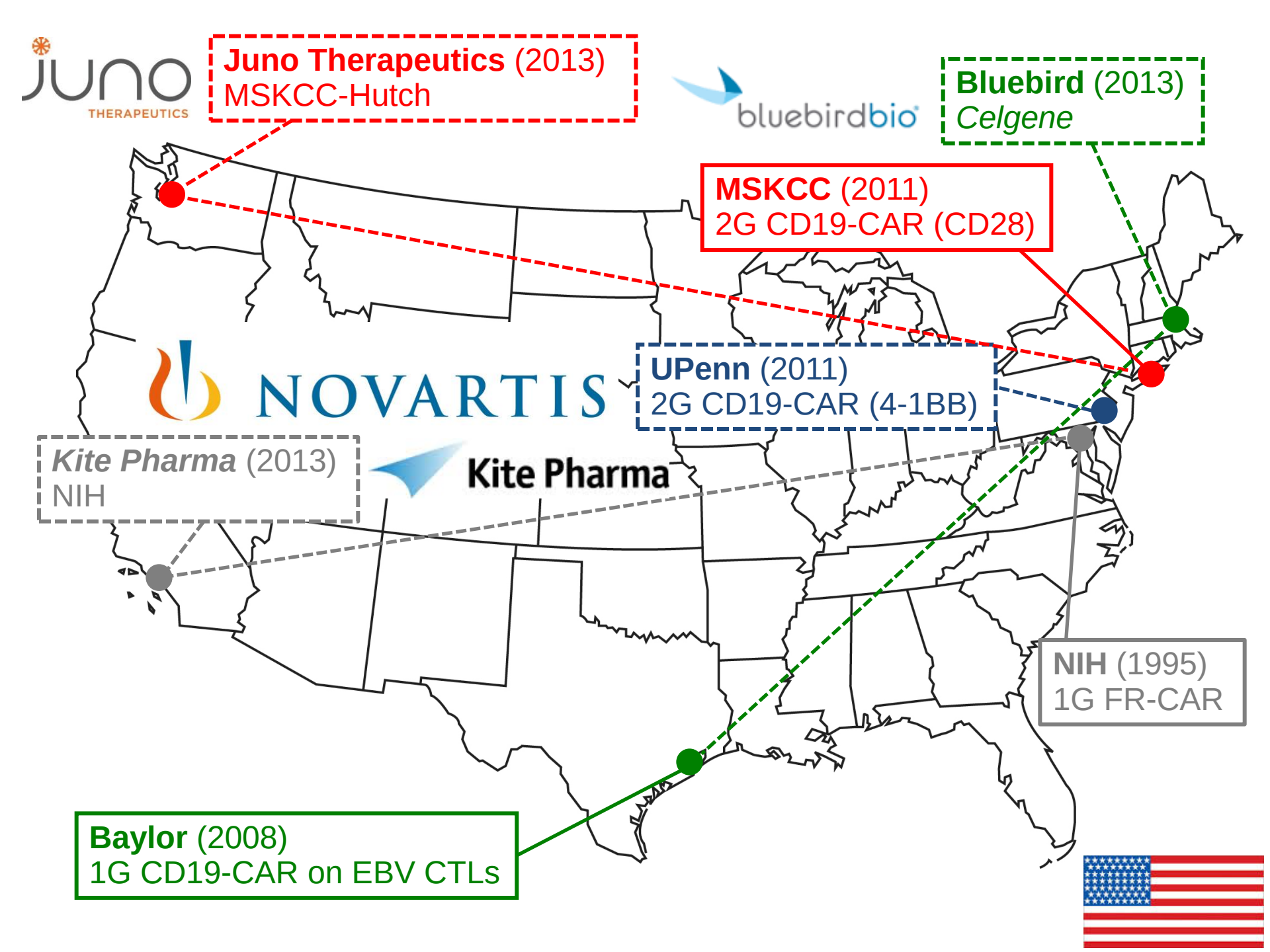
American Association for the Advancement of Science Science 2014;346:1450
Published by AAAS

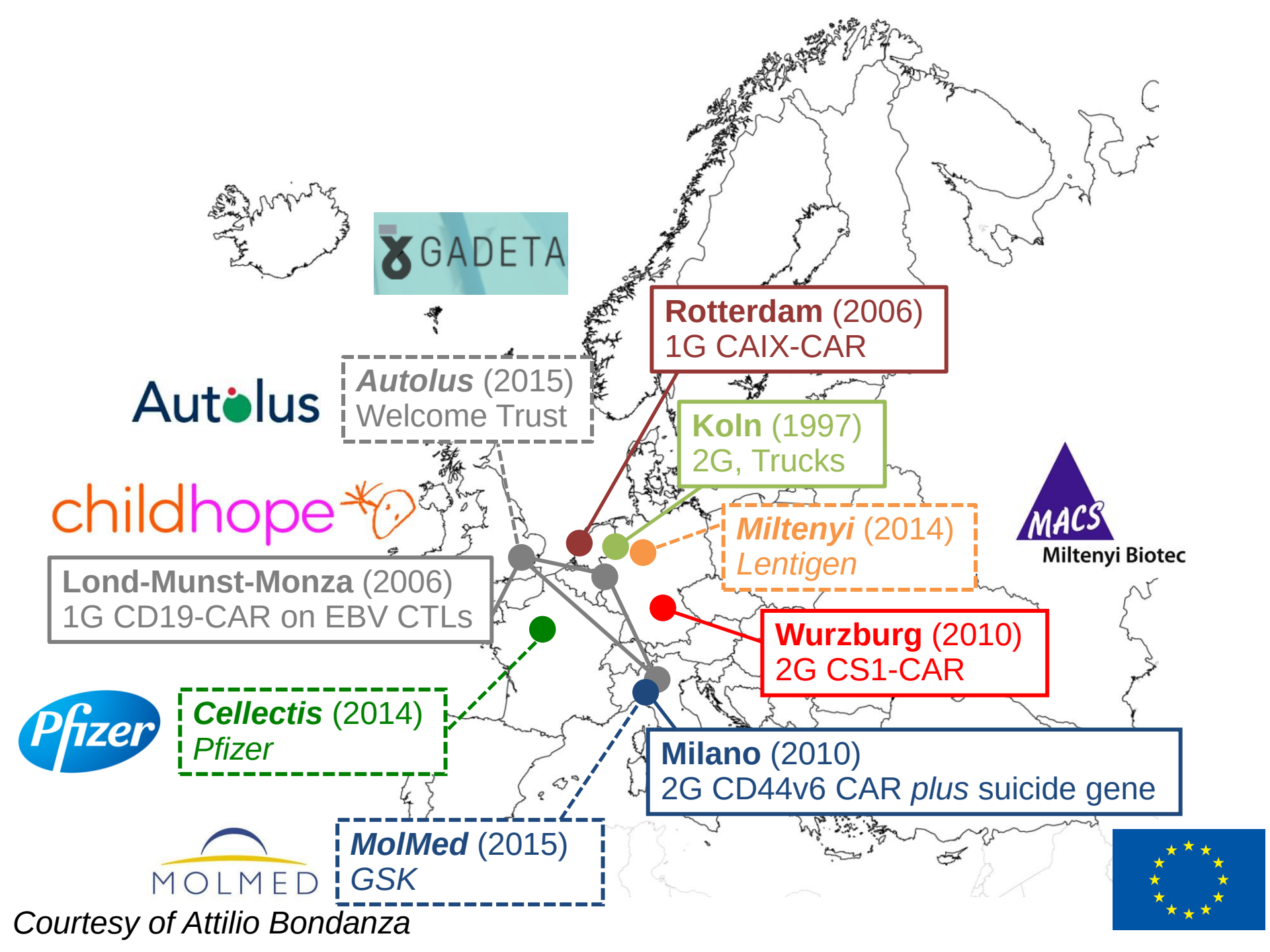
Science
AAAS

2014

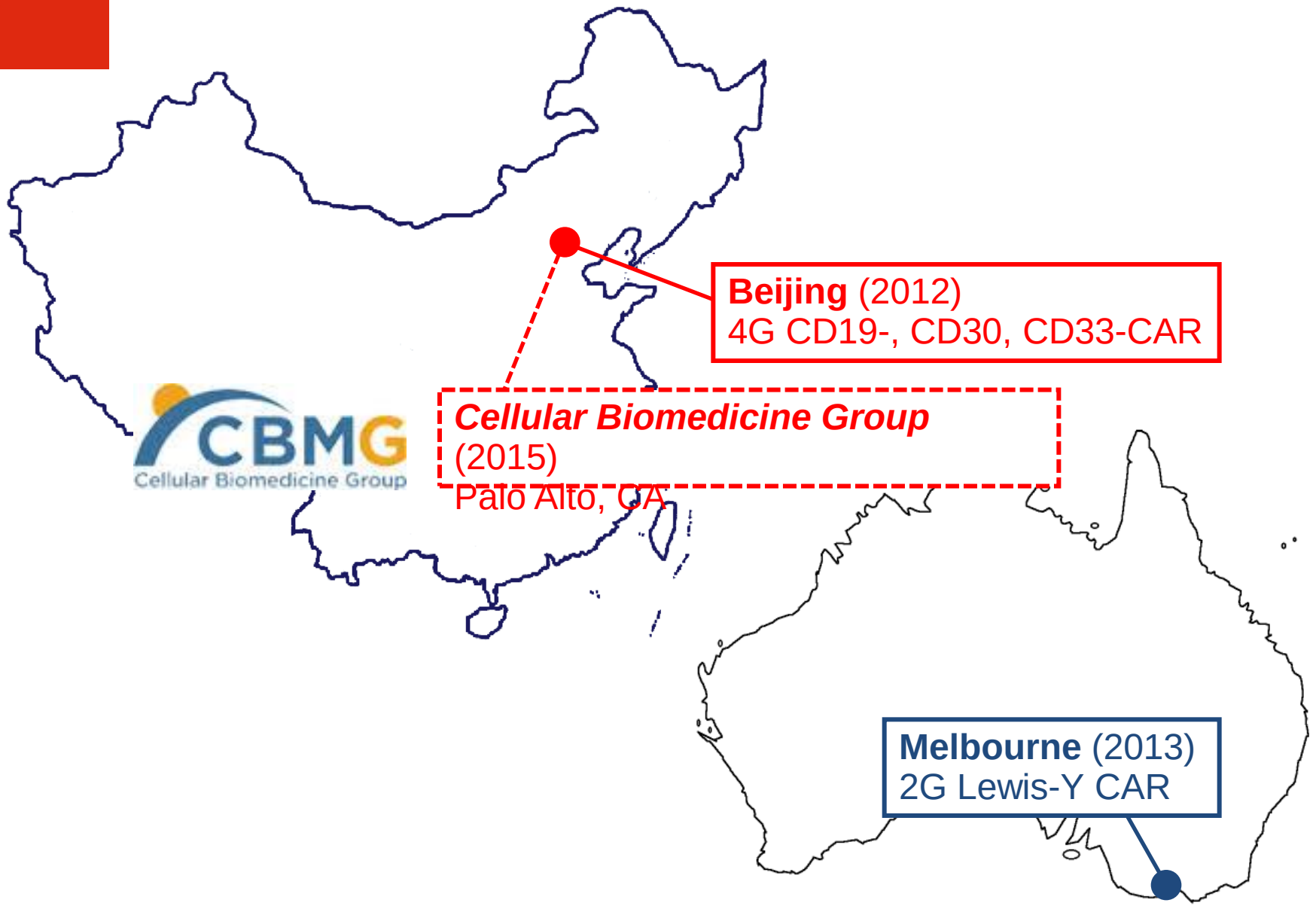
CAR active trials (clinicaltrials.gov)




Juno Therapeutics (2013)
MSKCC-Hutch
bluebirdbio
Bluebird (2013)
Celgene
MSKCC (2011)
2G CD19-CAR (CD28)
NOVARTIS
UPenn (2011)
2G CD19-CAR (4-1BB)
Kite Pharma (2013)
NIH
Kite Pharma
NIH (1995)
1G FR-CAR
Baylor (2008)
1G CD19-CAR on EBV CTLs



Courtesy of Attilio Bondanza


Beijing (2012)
4G CD19-, CD30, CD33-CAR
Cellular Biomedicine Group
(2015)
Palo Alto, CA
CBMG
Cellular Biomedicine Group
Melbourne (2013)
2G Lewis-Y CAR

- Why EBMT is interested in cell and gene therapy?
- Why should we register patients undergoing cell and gene therapy?
- How should we proceed?

CTIWP: Mission and implementation

To improve EBMT Registry, with a **dedicated registry for cellular products, and clinical trials** of cell and cell-based gene therapy.

To promote **partnerships with the International and European Societies** of Cell/Gene Therapy and with **major investors** in the field.

To promote retrospective and prospective trials of cell/gene therapy under the EBMT shelter

To implement an **EBMT Cellular Repository** for Cell/gene therapy clinical trials

To map **GMP facilities** spread in Europe

Major Achievements 2015
CTIWP Studies and Surveys (2/2)

- An effort to upgrade the **EBMT registry** forms and improve the EBMT ability to collect additional and high-quality clinical and biological information from patients receiveing **innovative cellular therapy and cell-based gene therapy**. (Joined effort with STWP, ADWP, IEWP)

- An upgrade of **the EBMT Annual activity Survey** to include Cellular therapy and Gene therapy (Baldomero & Passweg)

- A survey on currently used practices for **minimally-manipulated cell products**, with a view to harmonized recommendations (Chabannon)

- A survey of high resolution typing in the EBMT database regarding the use **unrelated donors** (Rocha & Fleischhauer)

- A survey on **mesenchymal stem cell manufacture harmonization**. (Dazzi, Bernardo)

2015 EBMT SURVEY: FOCUS ON CELLULAR THERAPY

Table 2: Cellular therapies using manipulated or selected cells

Non HSCT Cellular Therapy	Indication for treatment (Number of patients)	MSC		Selected T cells (non DLI)		Regulatory T cells (TREGS)		NK cells		Expanded CD34		Genetically modified T cells (CAR/TCR)		Genetically modified T cells (suicide gene)		Genetically modified CD34		Other	
		Allo	Auto	Allo	Auto	Allo	Auto	Allo	Auto	Allo	Auto	Allo	Auto	Allo	Auto	Allo	Auto	Allo	Auto
	GvHD after HSCT																		
	Graft enhancement																		
	Autoimmune disease																		
	Genetic disease																		
	Infection																		
	Malignancy																		

CTIWP: A dedicated registry

To improve EBMT Registry, with a **dedicated registry for cellular products, and clinical trials** of cell and cell-based gene therapy.

Joined effort with ADWP, STWP, IEWP of EBMT
Possible partnership with ESGCT, AGORA, ISCT, other Scientific Societies

→ A Cellular Therapy Registry Committee

PROPOSAL for a Cellular Therapy Registry Committee (CTIWP-ADWP-STWP-IEWP)

- Chiara Bonini (CTIWP)
- Christian Chabannon (CTIWP)
- Carmen Ruiz (EBMT Registry)
- Steffie van der Werf, EBMT
- Fabio Ciceri (CTIWP)
- Alessandro Aiuti (IEWP, ESGCT)
- Maria Pia Cicalese (IEWP)
- Maria Ester Bernardo (CTIWP)
- Marina Cavazzana Calvo (IEWP, ESGCT)
- Alessandra Magnani (IEWP)
- Elisa Magrin (IEWP)
- Fabien Touzot (IEWP)
- Attilio Bondanza (CTIWP)
- Eliane Gluckman (CTIWP, Eurocord)
- Dominque Farge-Bancel (ADWP)
- John Snowden (ADWP)
- Francesco Lanza (STWP)
- Paolo Pedrazzoli (STWP)
- Patrizia Comoli (STWP)
- Francesco Dazzi, (CTIWP)
- Martin Bonhauser (CTIWP)
- Hans-Jochem Kolb (CTIWP)
- Jakob Passweg (CTIWP)
- Helen Baldomero (CTIWP)
- Andrea Velardi (CTIWP)
- Loredana Ruggeri (CTIWP)
- Katarina LeBlanc (ADWP, CTIWP)

Cell Therapy

-MED – A Registration to day 100

-MED – A Annual Follow-up

-Manual

Registry for Cellular Therapy: Roadmap

- The **new MED/A + manual are ready**, and shall be presented during the CTIWP business meeting.
- Registration shall be **implemented** in the **summer**,
- **validated** by the Cellular Therapy Registry Committee Members in the **fall**,
- **ready for all the Centers by the end of 2016**.

Cellular Therapy & Immunobiology
Working Party (CTIWP) - 1

Coming soon

Registry for Cellular Therapy

In order to collect pertinent and good quality clinical data, please register all your cellular therapies in this registry in a timely manner via the Cell Therapy Registry MED A form

More Information ➡ contact CTIWPebmt@lumc.nl

Cell Therapy Registry – Med-A