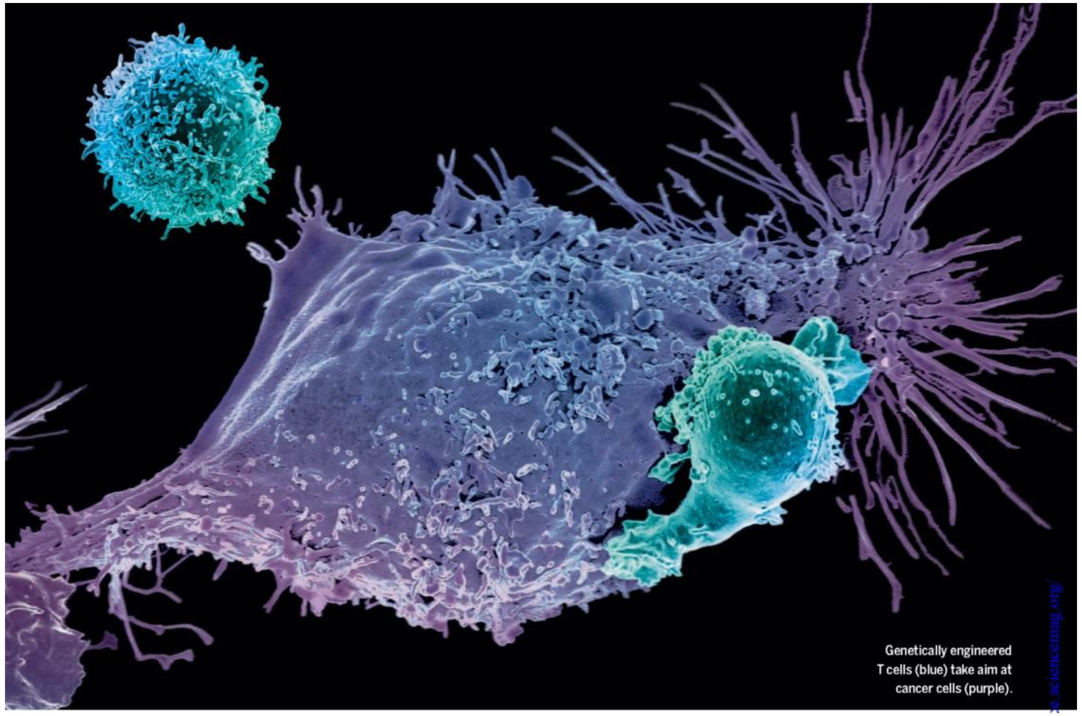
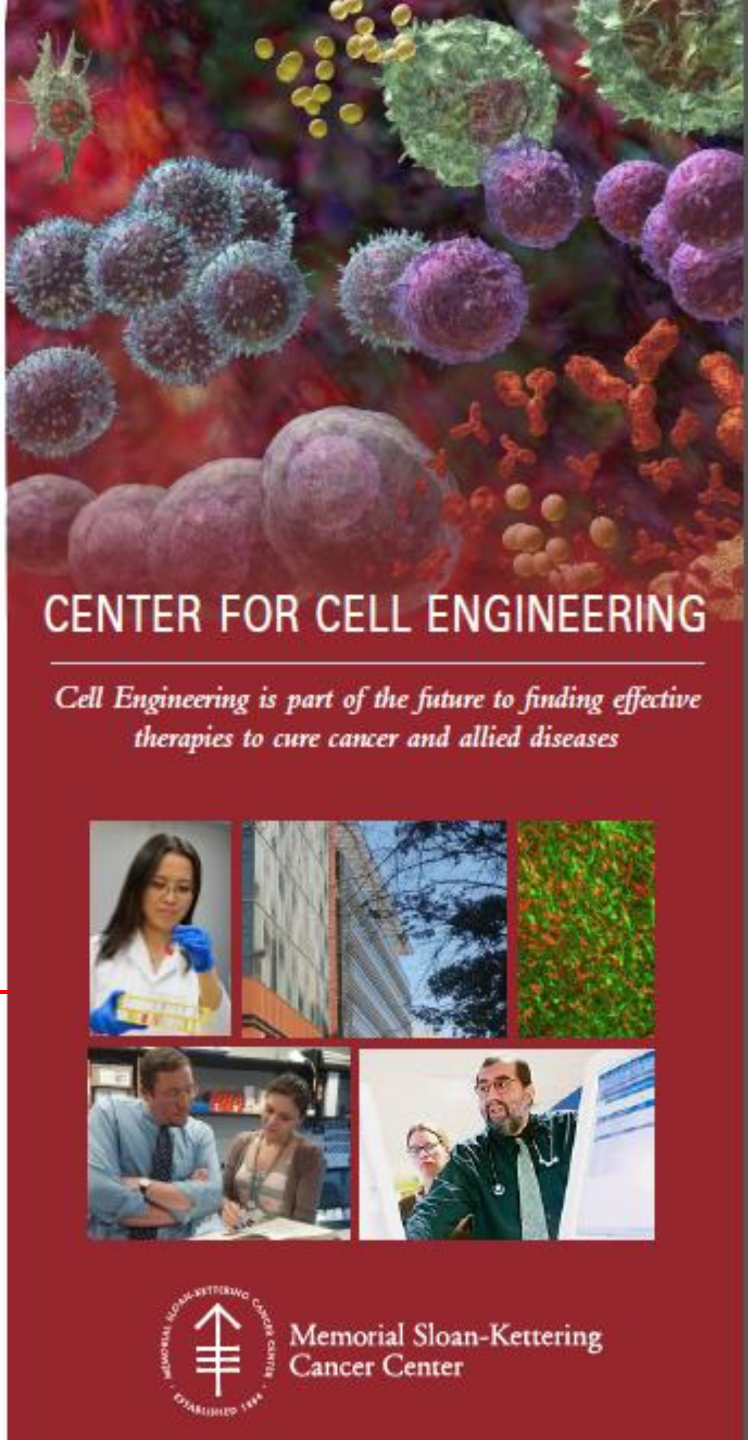
NAS Forum on Regenerative Medicine
Washington, DC, November3, 2021

Engineered Immunity as a Model for Regenerative Medicine



Michel Sadelain, MD, PhD
Director, Center for Cell Engineering
Immunology Program, Sloan Kettering Institute
Department of Medicine, Memorial Hospital
Memorial Sloan Kettering Cancer Center
New York, NY



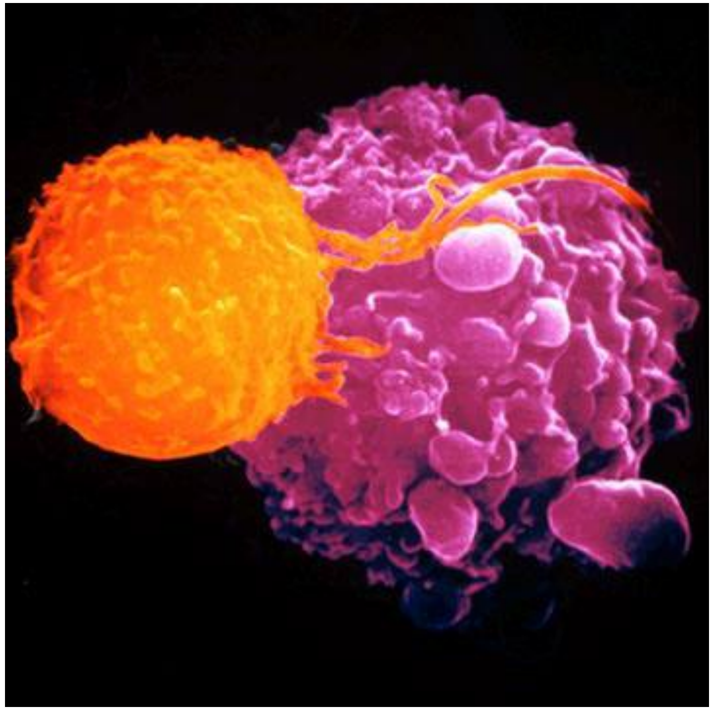
The rise of engineered T cells as cancer drugs

- Immunotherapy has curative potential
- Immunotherapy must harness T cell specificity, persistence and potency to achieve its goals

- Safety
- Efficacy

↕

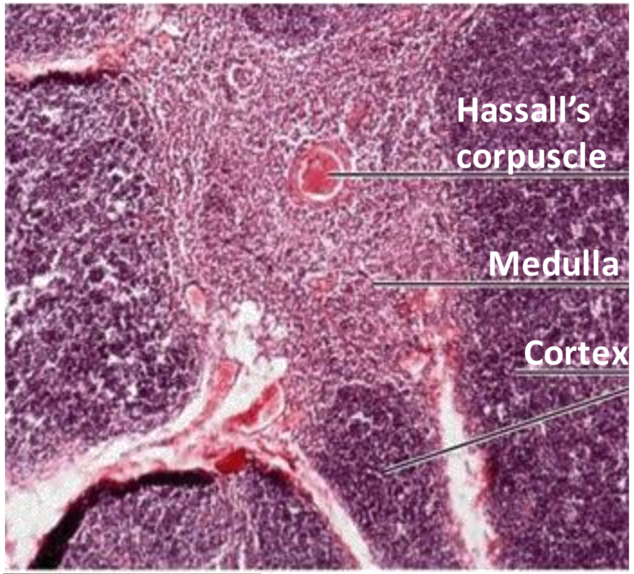
- Specificity
- Long-acting
- Potency

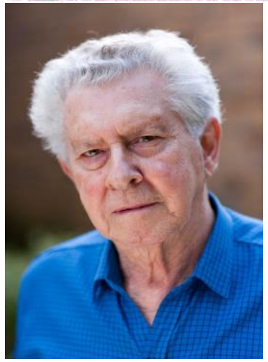


"CAR T cells are living drugs"

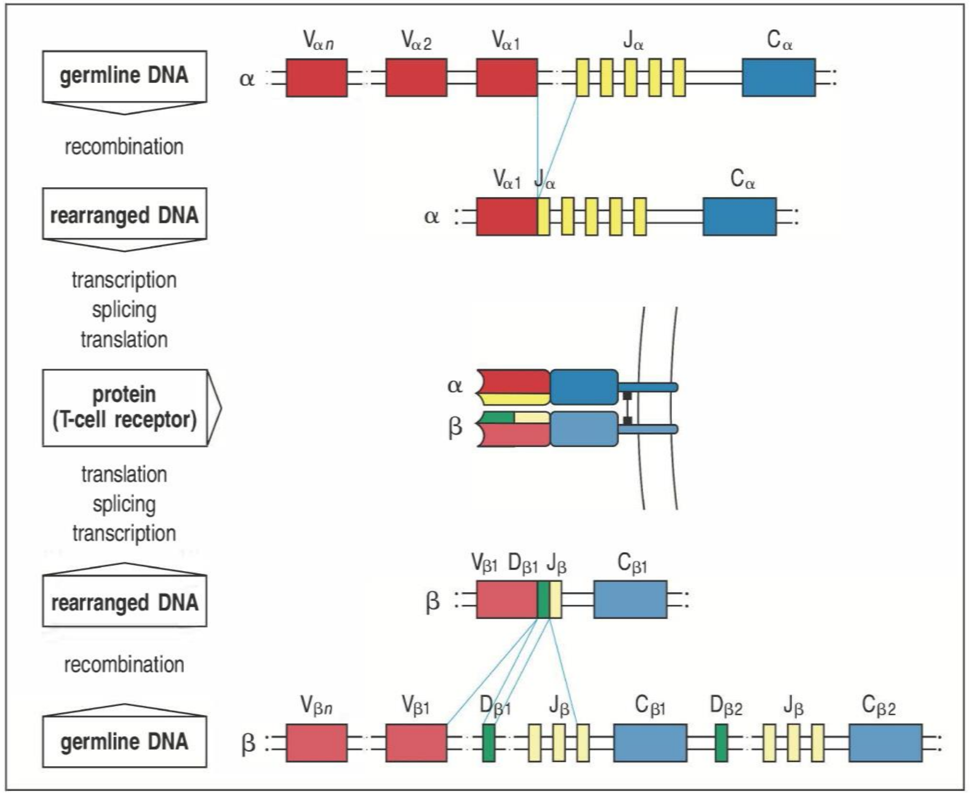
Sadelain, New York Times, 2012

T lymphocytes: thymic origin, VDJ recombination and clonal selection





Jacques Miller



Immunobiology: The Immune System in Health and Disease. 5th edition. Janeway CA Jr, Travers P, Walport M, et al. New York: Garland Science; 2001.

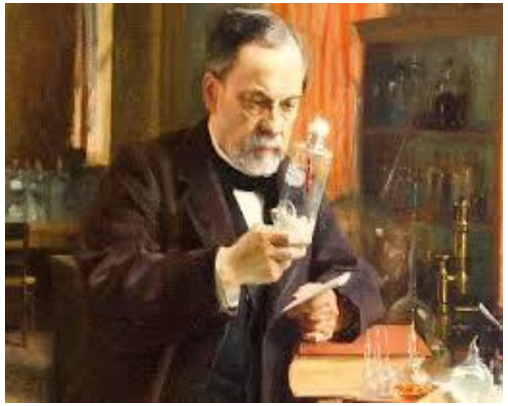
The clonal selection theory

•Each lymphocyte bears a single receptor with a unique specifity. • Interaction between a foreign molecule and a lymphocyte receptor capable of binding that molecule with a high affinity leads to lymphocyte activation and clonal expansion. • Lymphocytes bearing receptors specific for ubiquitous self molecules are deleted at an early stage in lymphoid cell development and are therefore absent from the repertoire of mature lymphoctyes.

F. Macfarlane Burnet

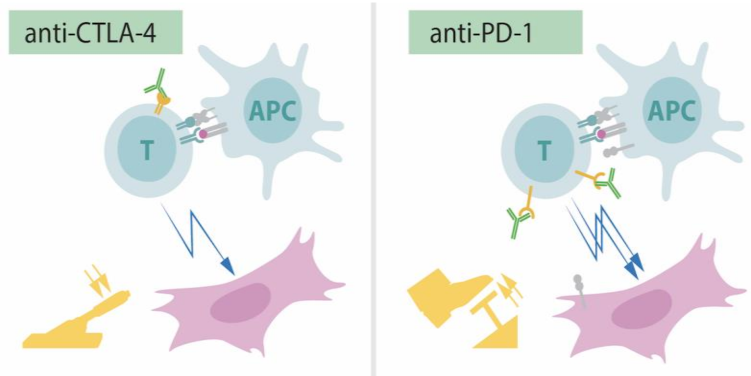
Mastering T cell responses: induce, derepress, instruct

Active immunization



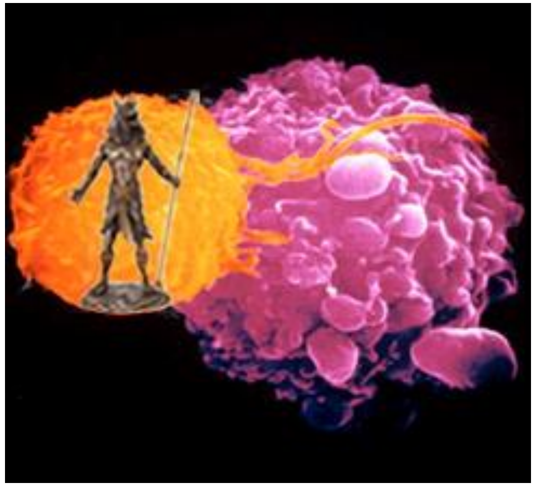
Active immunization induces protective natural responses

Inhibition of negative regulation



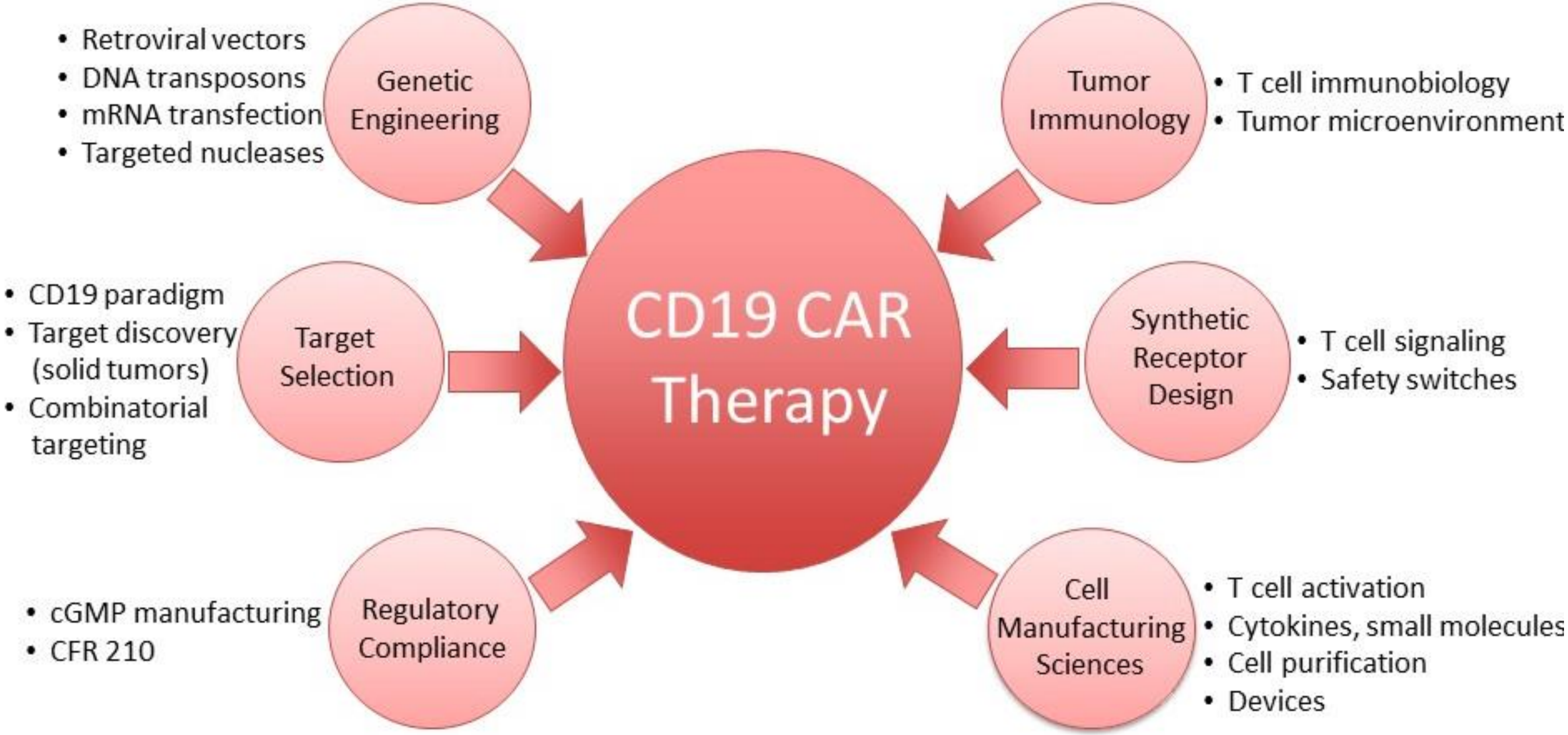
Antibodies against CTLA-4 or PD-1 block the brake function leading to activation of latent anti-tumor responses

CAR T cell engineering



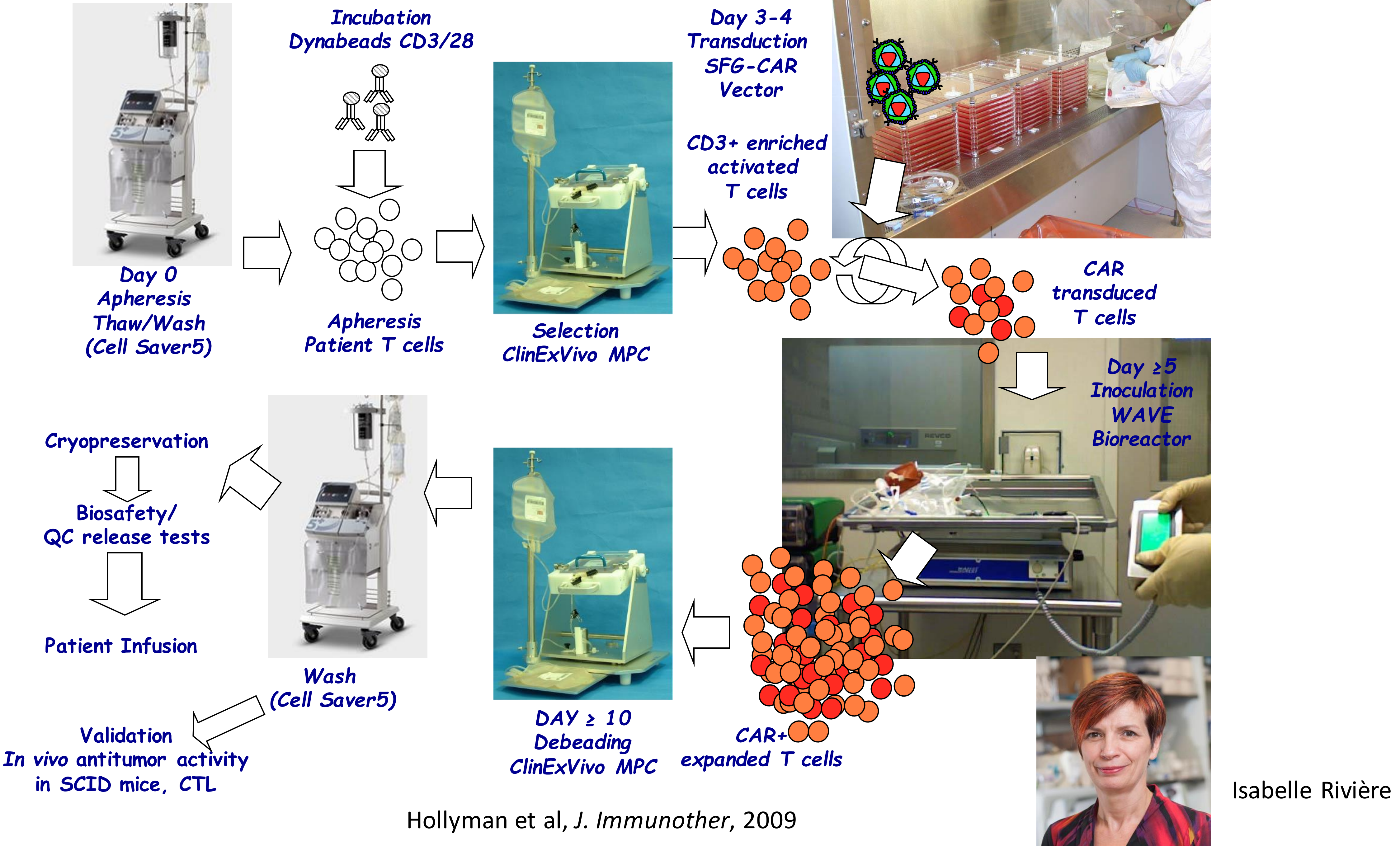
Synthetic receptors instruct supra-physiological immunity

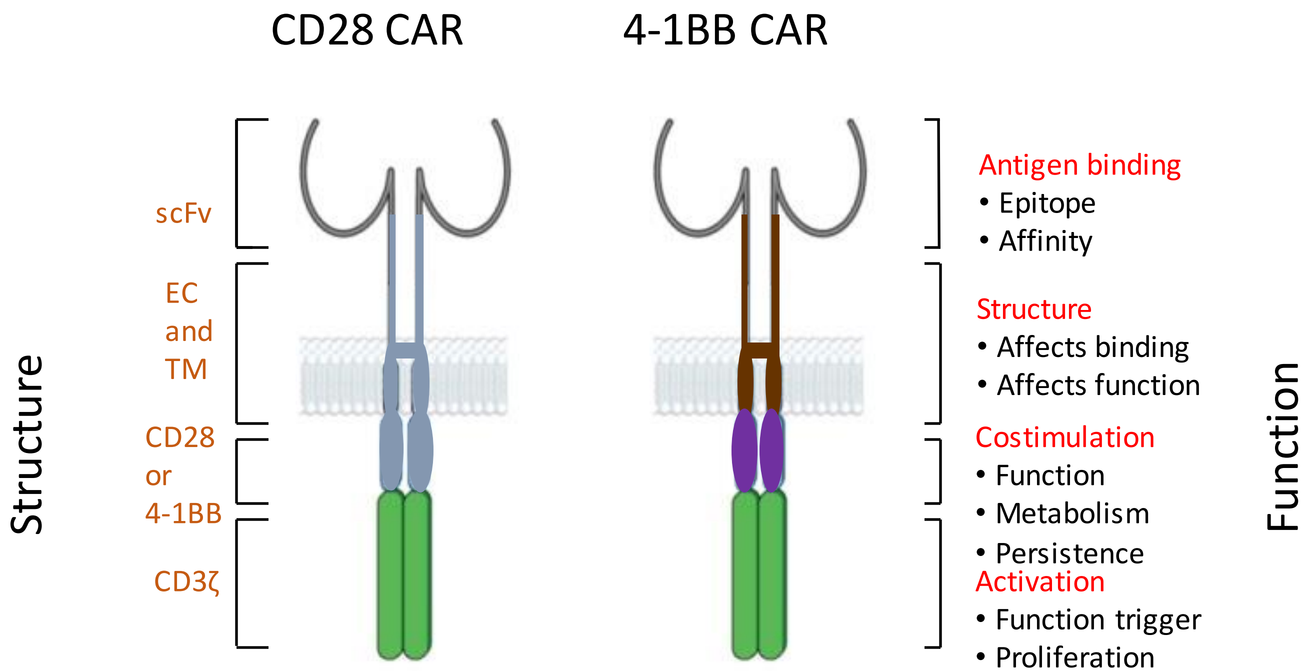
Assembling CARs for cell therapy



Rivière & Sadelain, *Mol Ther*, 2017

CAR T cell Manufacturing Flow



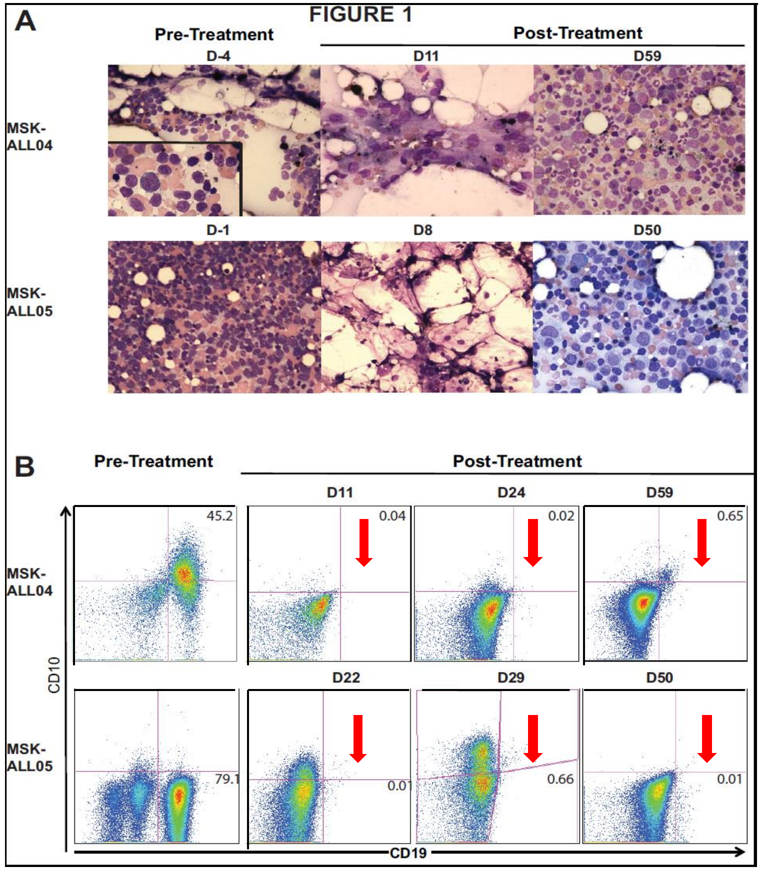


FDA approved in 2017

Axicabtagene Ciloleucel (Yescarta)	Tisagenlecleucel (Kymriah)

Prototypic CD19 CARs

Rapid and complete eradication of refractory leukemia by 19-28z CAR T cells



Brentjens, Davila, Rivière *et al*,
Science Transl Med, March 2013

Breakthrough of the year
Science, December 2013

Table 1. Reponses to CAR T-Cell Therapy.*

Disease	Response Rate	Comments	Reference
	percent		
Leukemia			
B-cell acute lymphoblastic leukemia (in adults)	83–93	High initial remission rates; unresolved issue is whether CAR T-cell therapy is definitive therapy or should be followed by allogeneic hematopoietic stem-cell therapy	Park et al.,[35] Davila et al.,[36] Turtle et al.[37]
B-cell acute lymphoblastic leukemia (in children)	68–90	Approximately 25% of patients reported to have a relapse with CD19-negative or CD19-low leukemia; CD22 CAR T cells may improve survival among some patients with CD19 relapses	Maude et al.,[34] Maude et al.,[38] Fry et al.,[39] Lee et al.[40]
Chronic lymphocytic leukemia	57–71	Relapse is rare in patients who have a complete response; ibrutinib appears to increase response rates	Porter et al.,[41] Turtle et al.[42]
Lymphoma			
Diffuse large B-cell lymphoma	64–86	Approximately 40–50% of patients reported to have a durable complete response	Turtle et al.,[43] Kochenderfer et al.,[44] Schuster et al.,[45] Neelapu et al.[46]
Follicular lymphoma	71	At a median follow-up of 28.6 mo, the response was maintained in 89% of patients who had a response	Schuster et al.[45]
Transformed follicular lymphoma	70–83	A total of 3 of 3 patients with transformed follicular lymphoma had a complete response	Turtle et al.,[43] Schuster et al.,[45]Neelapu et al.[46]
Refractory multiple myeloma	25–100	B-cell maturation antigen CAR T cells; stringent complete response in approximately 25% of patients	Ali et al.,[47] Fan et al.,[48] Berdeja et al.[49]
Solid tumors			
Glioblastoma	ND	{q4}In case report from phase 2 study, complete response on magnetic resonance imaging after intravenous and cerebrospinal fluid administration of CAR T cells; complete response lasted 7.5 mo	Brown et al.[50]
Pancreatic ductal adenocarcinoma	17	In one patient with liver metastasis, CAR T-cell treatment produced a complete metabolic response in the liver but was ineffective against the primary pancreatic tumor	Beatty et al.[51]

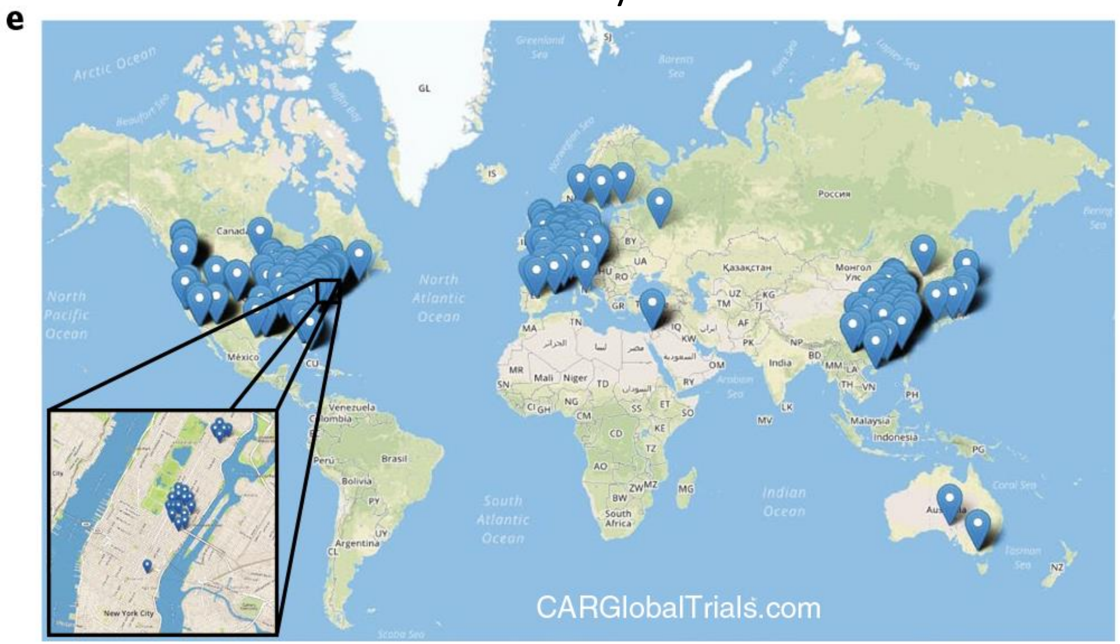
* ND denotes not determined.

June and Sadelain,
N Engl J Med, 2018

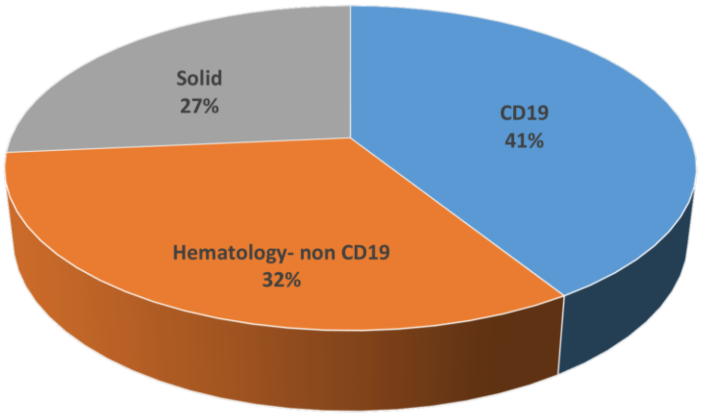
Impact of CD19 CAR therapy

- Good news for patients with relapsed B cell malignancies
- First gene therapy to be approved in the US
- First engineered T cell to be approved worldwide
- Ushers "synthetic biology" in the clinical arena (chimeric proteins, circuits)
- Convinced big pharma to manufacture cells as medicines ("living drugs")
- Obliges to rethink drug manufacturing, distribution and reimbursement
- Poised to extend to other cancers and beyond cancer
- Paves the way for other cell and gene therapies

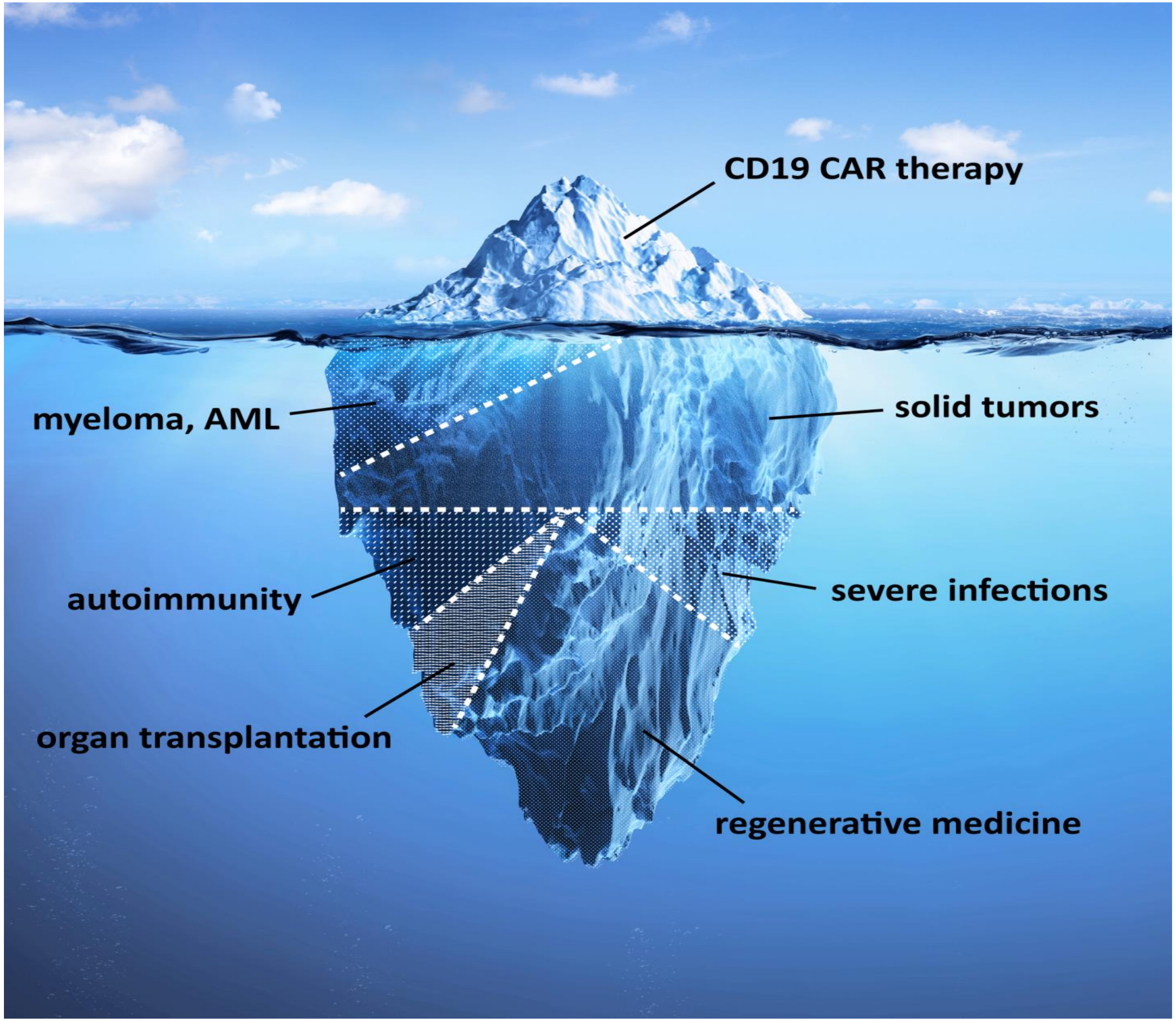
Interventional CAR clinical trials by country
Matthew MacKay et al. *Nat Biotechnol*. 2020



CD19 CAR trials account for 41% of 700 CAR trials listed at clinical trials.gov (March 2021), Globerson-Levin et al., *Eur J Immunol*, 2021

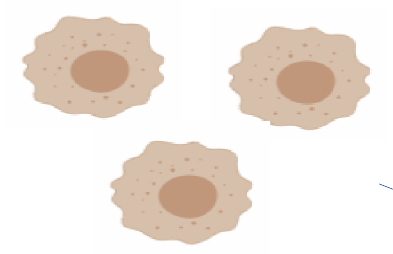



CD19 CAR therapy


CD19 CAR therapy
myeloma, AML
solid tumors
autoimmunity
severe infections
organ transplantation
regenerative medicine

Cellular senescence is a stress response program

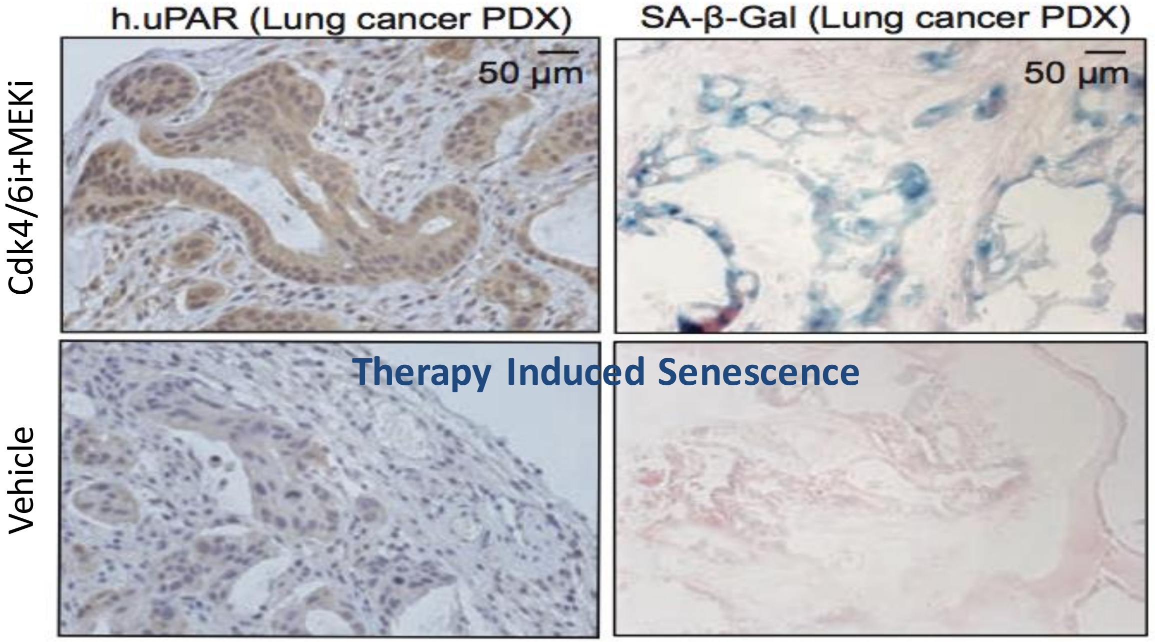
Proliferating cells



Stress triggers

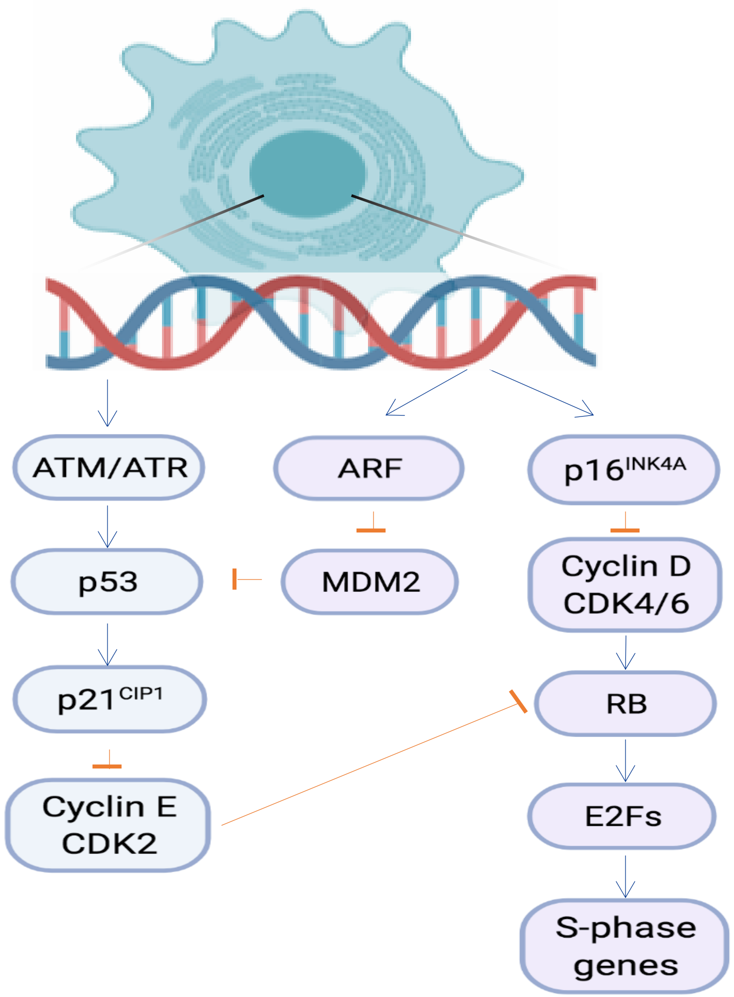
- DNA damage
- Oncogene activation
- Telomere erosion
- Lysosomal stress
- ROS

Hayflick; Moorhead. *Exp Cell Res.*; **25**; 585-621 (1961)
Harley *et al. Nature.*; **345**; 458-469 (1990)
Serrano et al. *Cell.*; **88**; 593-602 (1997)
Weinberg. *Cell.*; **88**; 573-575 (1997)
Gorgoulis et al. *Cell.* **179**; 813-827 (2019)



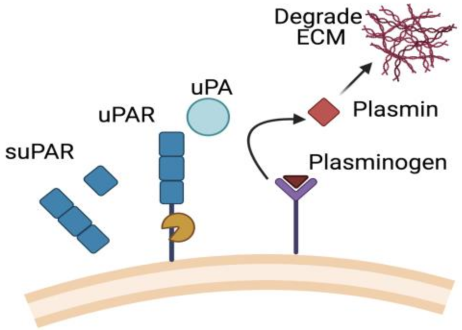
Therapy Induced Senescence

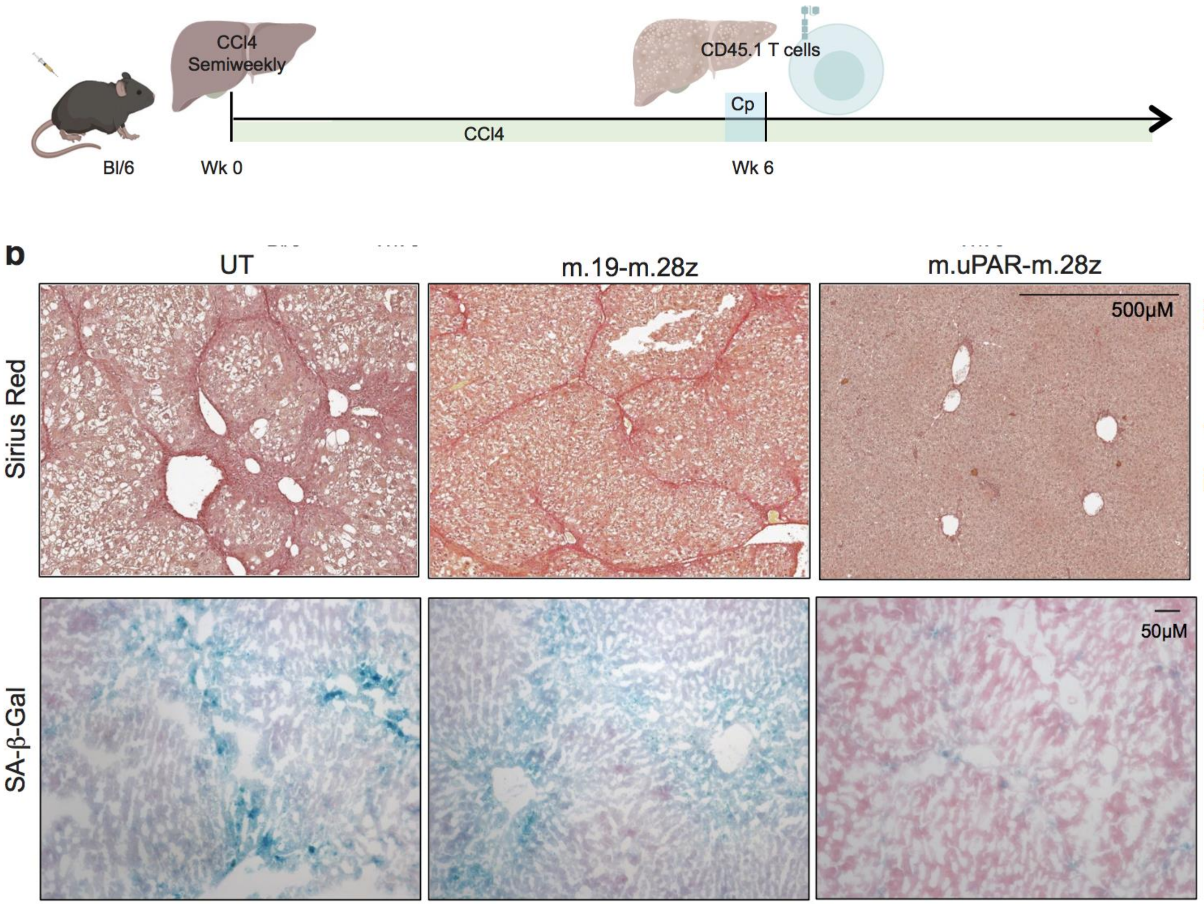
Stably arrested senescent cells



Senolytic uPAR CAR T cells restore tissue homeostasis in senescence-associated liver fibrosis

Urokinase Plaminogen Activator Receptor (uPAR)





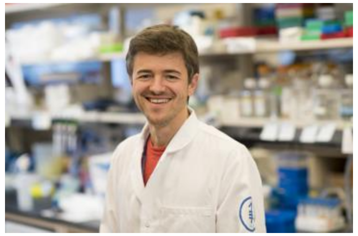
Amor, Feucht, Leibold. *Nature*.**538**; 127-132 (2020)

Senescence-associated pathologies

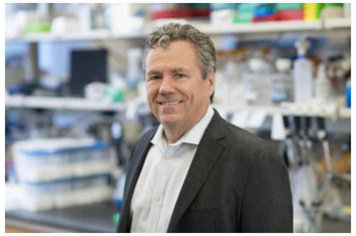
Senolytic CAR T cells
e.g., liver fibrosis, NASH

Judith C. Feucht

Corina A. Vegas Lowe Lab

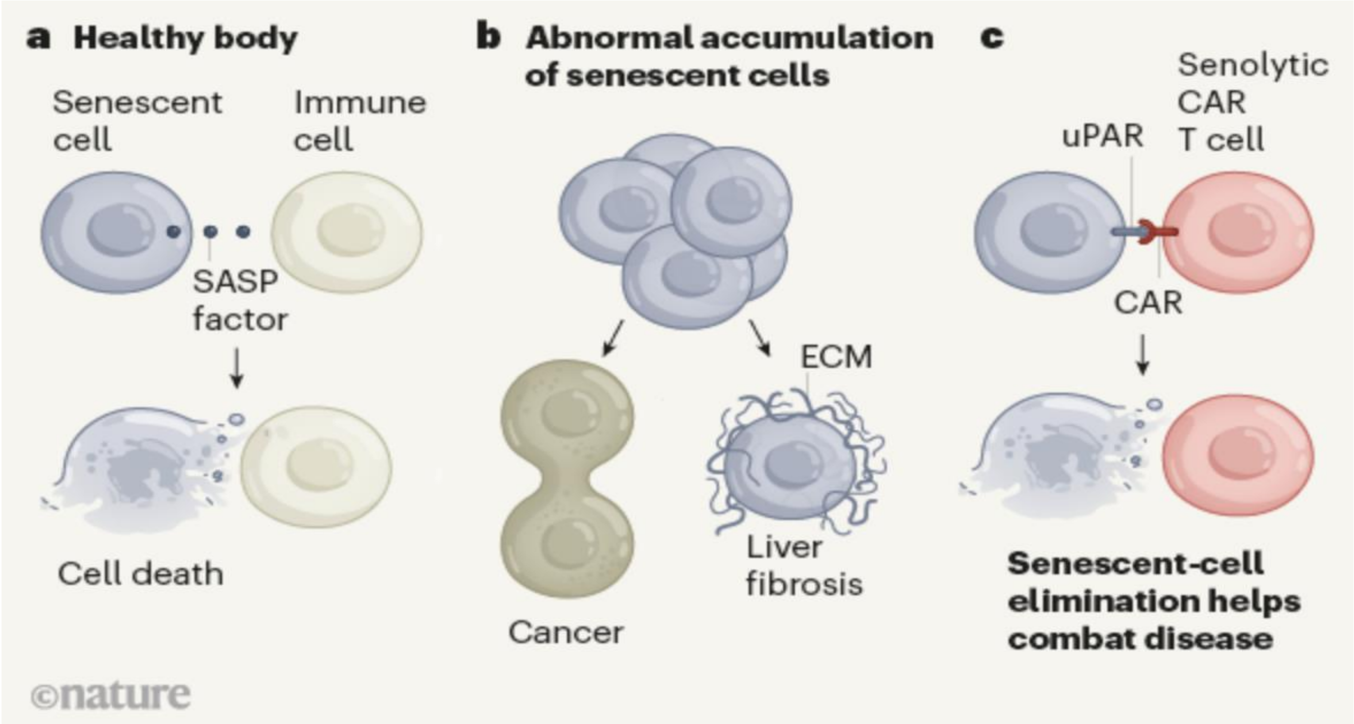


Josef Leibold Lowe Lab



Scott Lowe

Therapeutic potential of senolytic CAR T cells in regenerative medicine

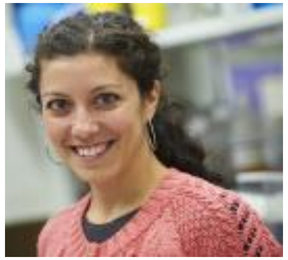


Wagner,V & Gil,J. *Nature*.**538**; 37-38 (2020)

uPAR and uPAR CAR T cells offer a platform to study and perturb senescence

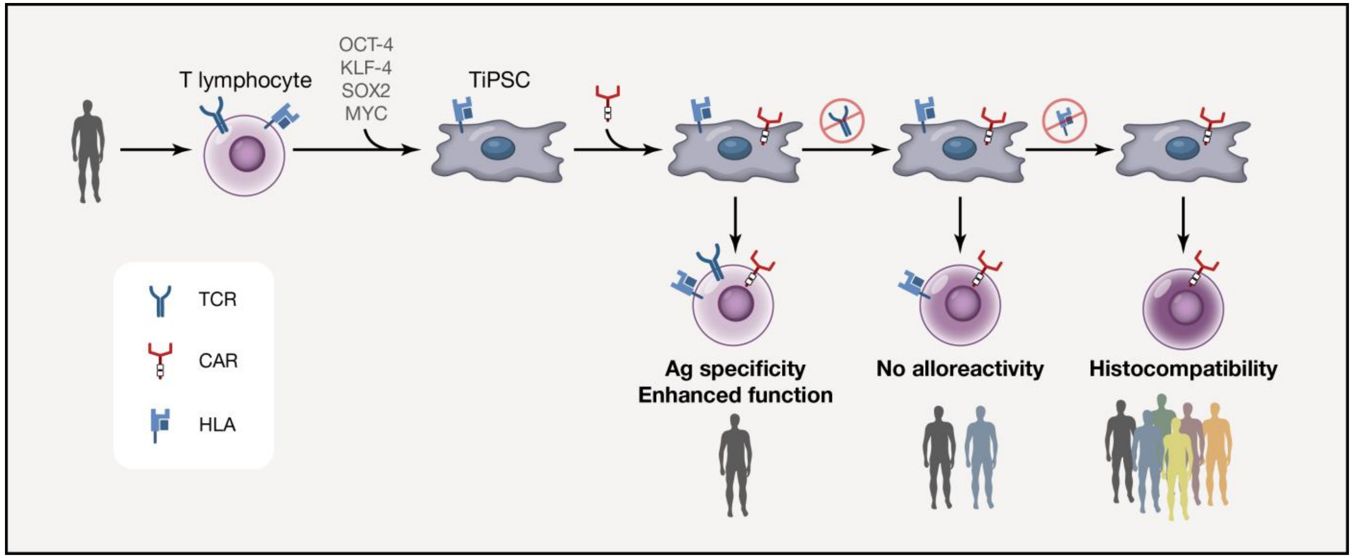
CAR T cell sources

• Autologous T cells	With TCR	– Bulk PBMCs
		– T cell subsets
• Allogeneic T cells	With TCR	– DLI
		– VSTs
		– $\gamma\delta$ T cells
		– iNKT cells
	Without TCR	– $\alpha\beta$-TCR$^{-/-}$ DLI
		– (NK cells)
• In vitro generated T cells	With/Without	– CB
		– ESC
		– TiPS



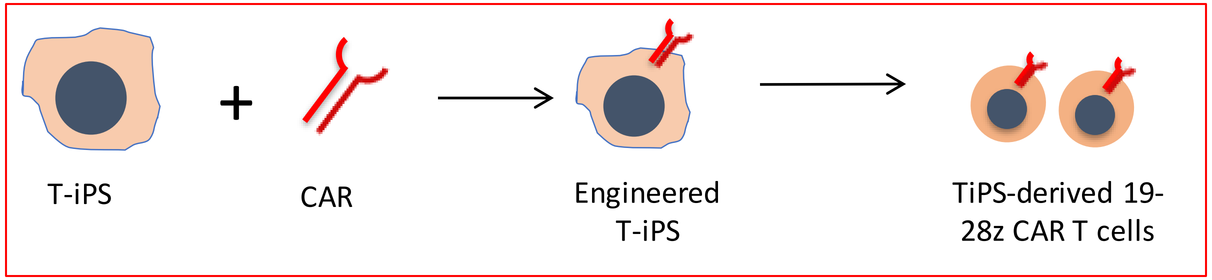
Maria Themeli

Sjoukje van der Stegen



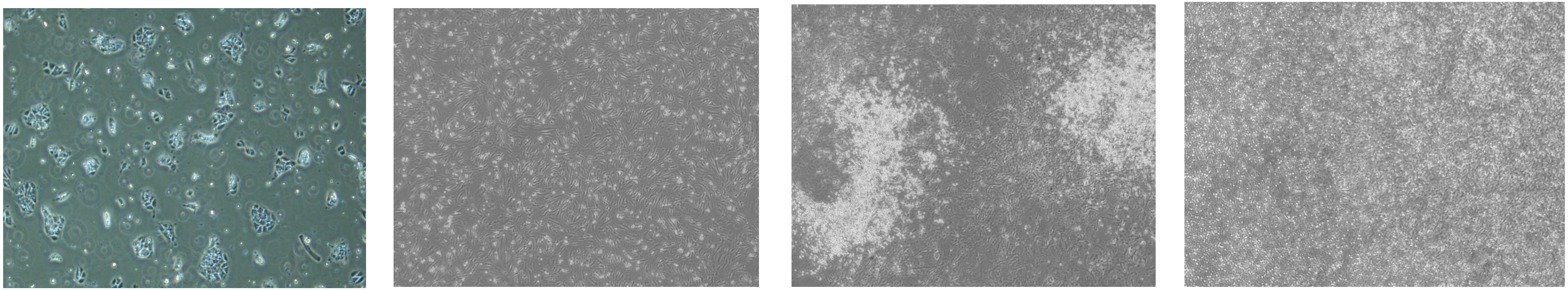
Themeli, Riviere & Sadelain, *Cell Stem Cells*, 2015

CAR T cells can be differentiated from from TiPS (T cells reprogrammed to pluripotency)



Themeli et al, *Nature Biotechnol*, 2013

D0 → Hematopoietic specification → D10 → Lymphoid commitment → D20 → T cell differentiation → D35



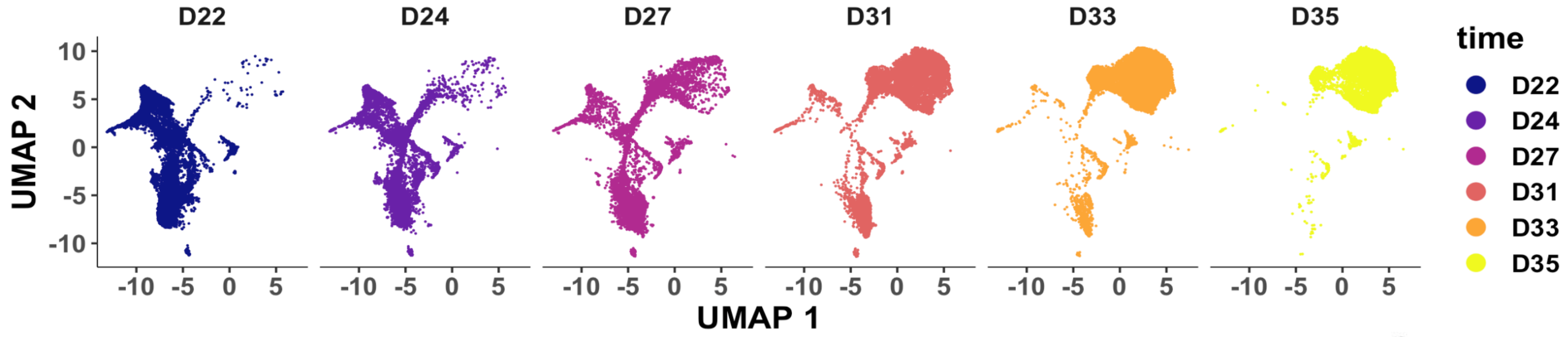
BMP4, bFGF, VEGF, SCF, Flt3L,IL-3, IL-6, IL-11, TPO

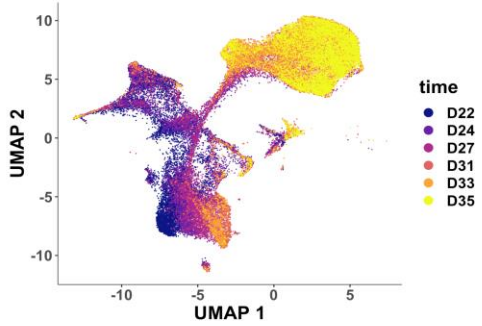
Flt3L, IL-7, SCF, TPO, IL-3

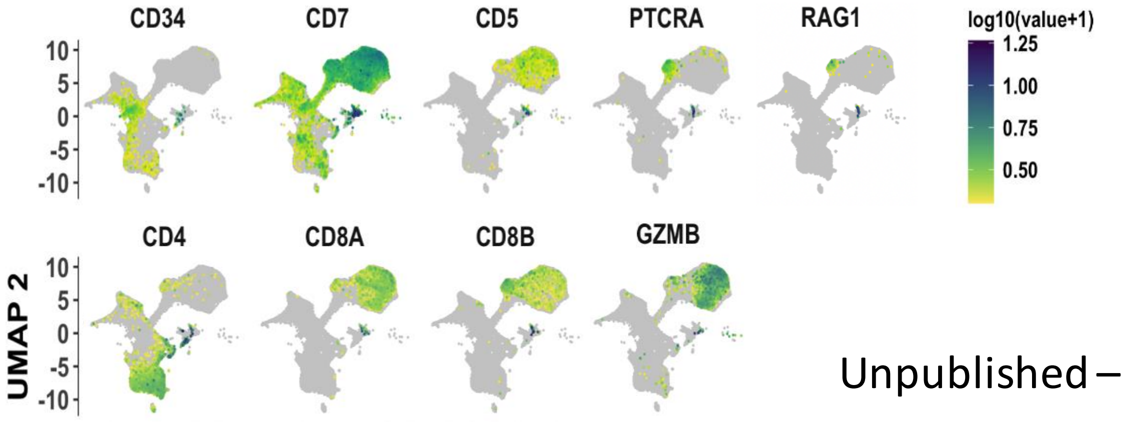
Flt3L, IL-7, SCF

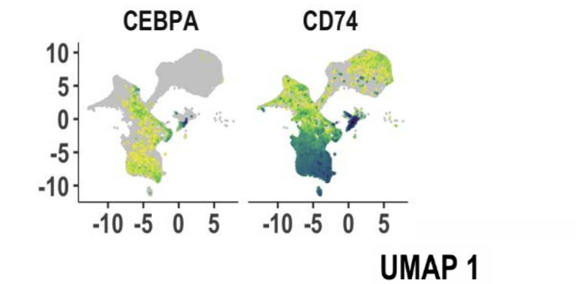
Understanding T cell genesis in a dish

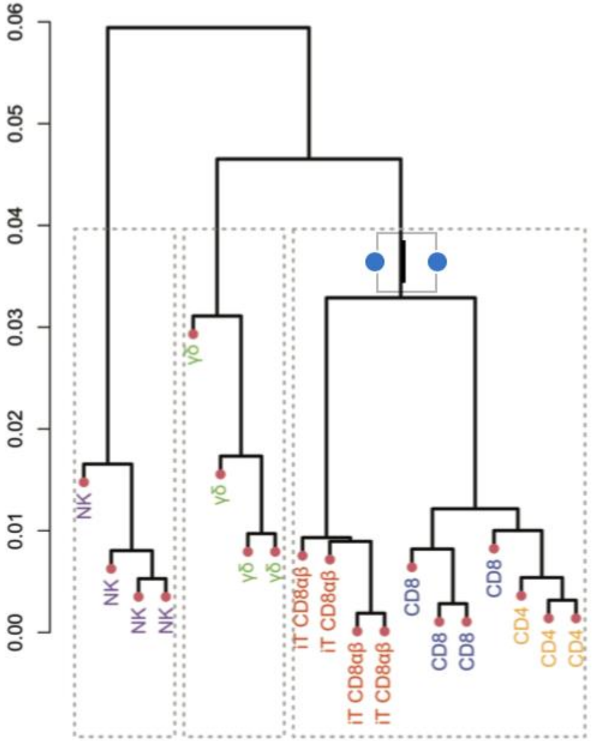
iPSC





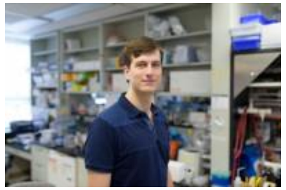






Unpublished – do not post

Hongyao Xie

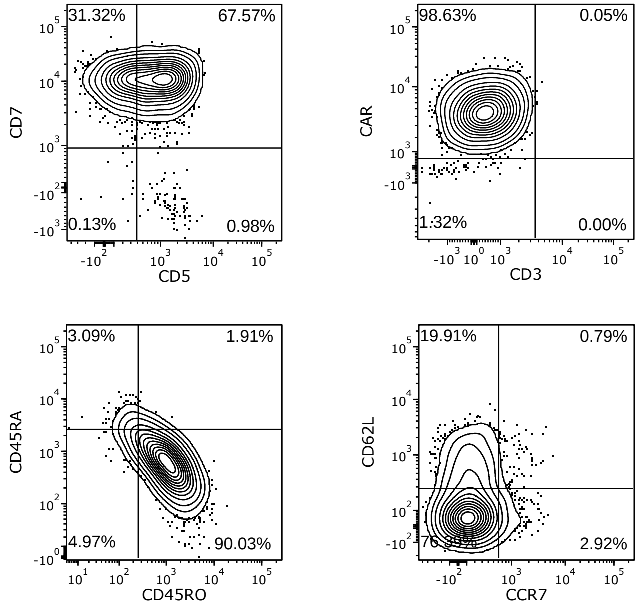


Pieter Lindenbergh

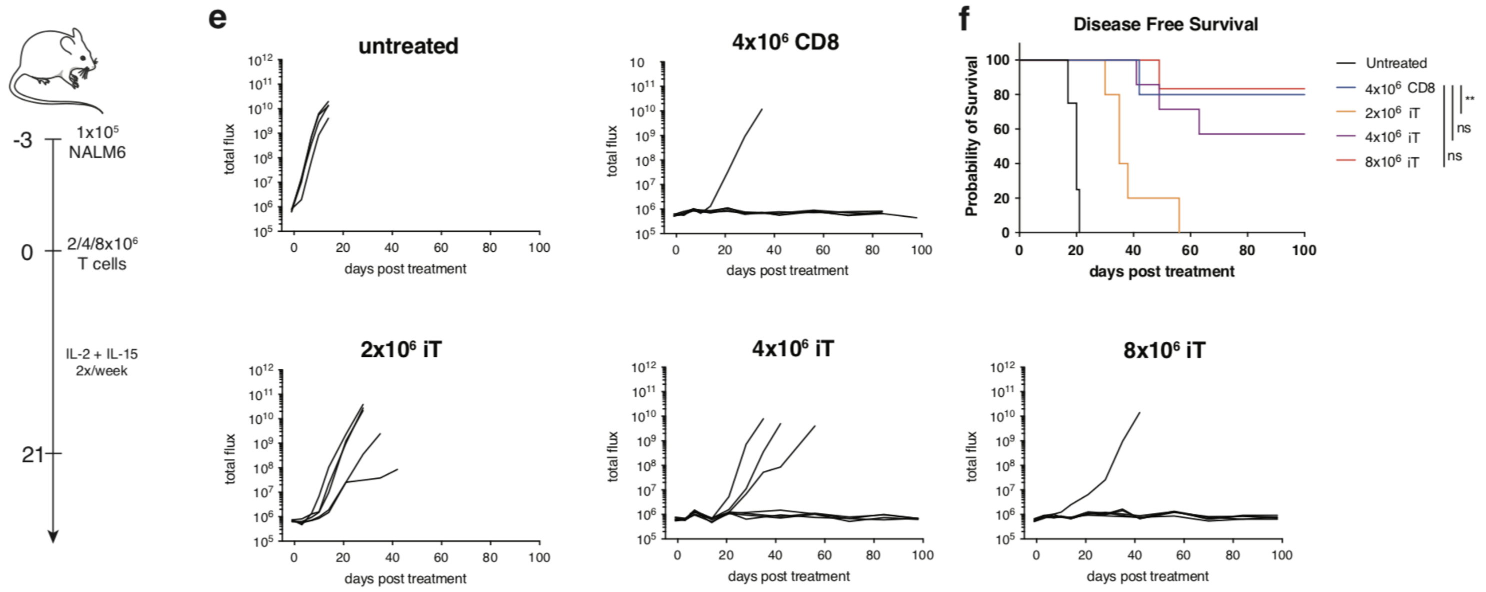
Sjoukje van der Stegen

CD19 1XX-CAR T cells derived from TiPS are efficacious against systemic B-ALL in mice

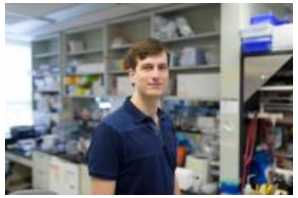
Day 42 EOP for infusion



CD19 1XX CAR iT cell therapy in the NALM/6 ALL model in NSG mice



Sjoukje van der Stegen

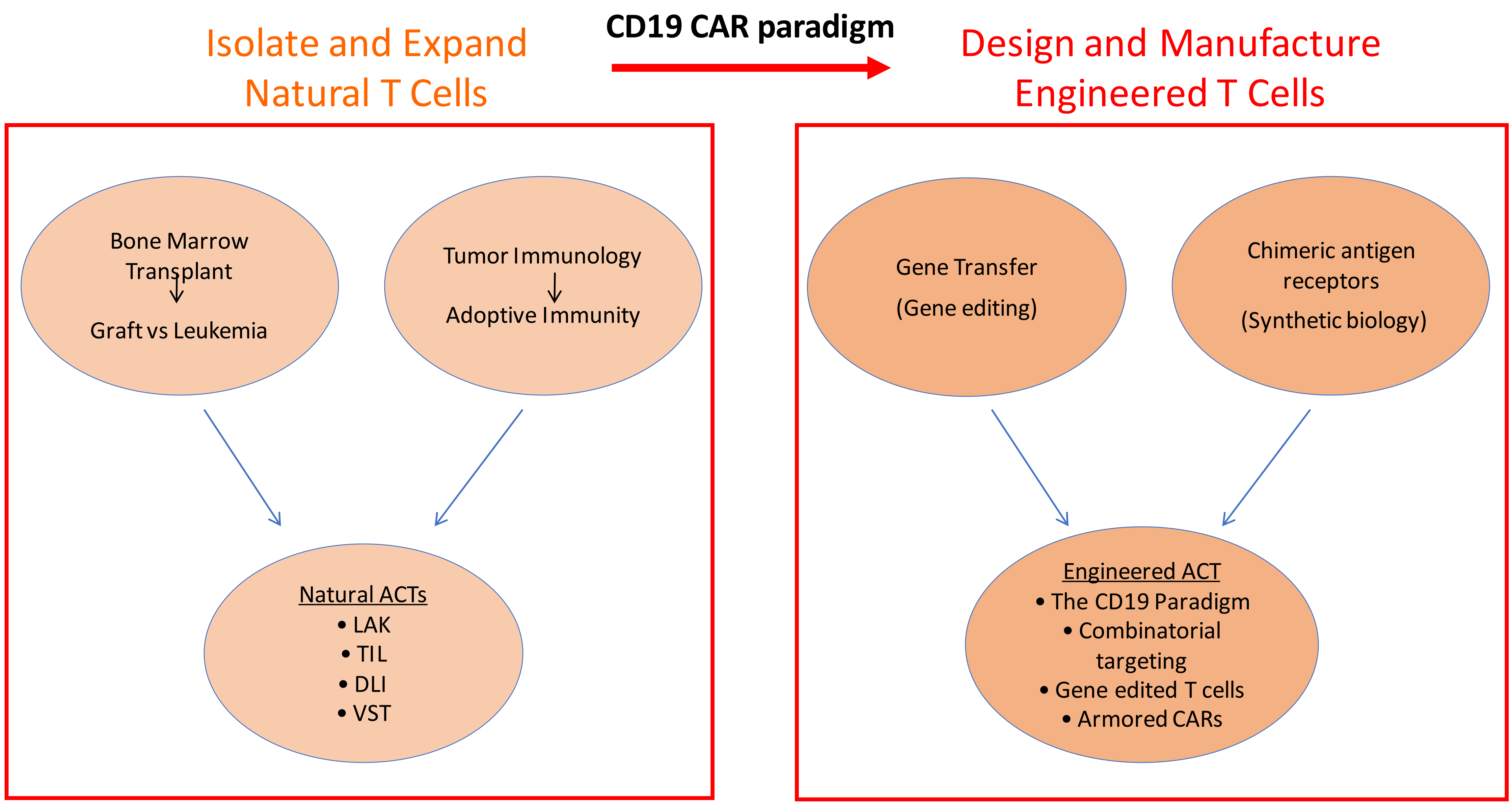


Pieter Lindenbergh

Mame Diop

Vera Alexeeva

Unpublished
Please do not post



Sadelain. CARs: driving immunology toward synthetic biology, *Curr Opin Immunol*, 2016

Lab members and visitors

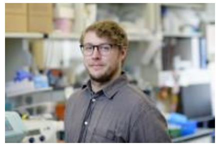

Vera Alexeeva


Annalisa Cabriolu


Dorine De Jong


Mame Diop


Anton Dobrin


Tyler Edwards


Judith C. Feucht


Andreina Garcia Angus


Gertrude Gunset


Mohamad Hamieh

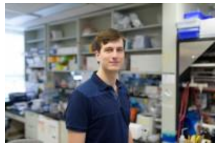

Sophie Hanina


Sascha Haubner


Archana Iyer

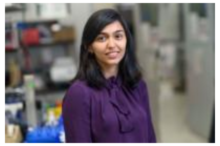

Nayan Jain


Ivan Kotchetkov


Pieter Lindenbergh

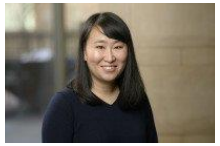

Michael A. Lopez

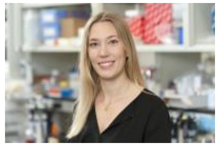

Jorge Mansilla-Soto


Ashlesha Odak

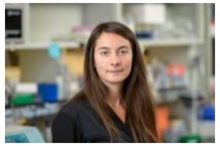

Karlo Perica


Michelle Saetersmoen


Yuzhe Shi


Maria Lemdal Sjostrand


Sjoukje van der Stegen


Ophelie L. Vivier

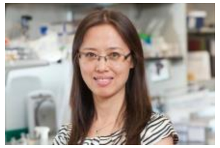

Zeguo Zhao

Not pictured
Friederike Kogel
Roseanna Petrovic

Long time collaborators


Isabelle Rivière


Renier J. Brentjens


Xiuyan Wang


Prasad S. Adusumilli

Memorial Sloan Kettering Cancer Center

Acknowledgements

Cell Therapy and Cell Engineering Facility: Isabelle Rivière, PhD

R&D/Manufacturing:* Xiuyan Wang, PhD,** Oriana A. Borquez-Ojeda, Jolanta Stefanski, Fang Du, Jagrutiben Chaudhari, Keyur Thummar, Melanie Hall, Juan Zhen, Mingzhu Zhu, Ling-Bo Shen, Paridhi Gautam Joe Powers ***QA/Operations Unit:* Devanjan Sikder, PhD,** Brent J. Safford, Nicholas J. Yeomans, Lissa Rojas, Nidhi Radia, James Hosey, Willard Joseph, Tasmin Farzana, Maria Scaringi, Nahian Rahman, Venky Gajjela ***QC and immune monitoring:* Brigitte Senechal, PhD**; Jinrong Qu, Yanjie Sun, Renise Baptiste ***Project Management: Vladimir Bermudez

Cell Therapy Center: Renier Brentjens, MD, PhD
CD19 CAR trials - **Jae Park, MD**, Kevin Curran, MD, Craig Sauter, MD
Mesothelin CAR trials - **Prasad Adusumilli, MD**

Proteomics Core: Ron Hendrickson
Immunology: Morgan Huse
Dasatinib CRS: Michael Hudecek
Safe harbors: Christina Leslie

Research support

NCI; NIAID; Mr. and Mrs. Goodwin and the Commonwealth Foundation for Research; The Lake Road Foundation; NY Stem Cell Foundation; The Leukemia and Lymphoma Society; Pasteur-Weizman/Servier award; Paul Griffuel awardCollaborative research agreements with Atara Biotherapeutics, Fate Therapeutics and Takeda Pharmaceuticals

We thank Fate THERAPEUTICS for their collaborative support on T-iPS studies.