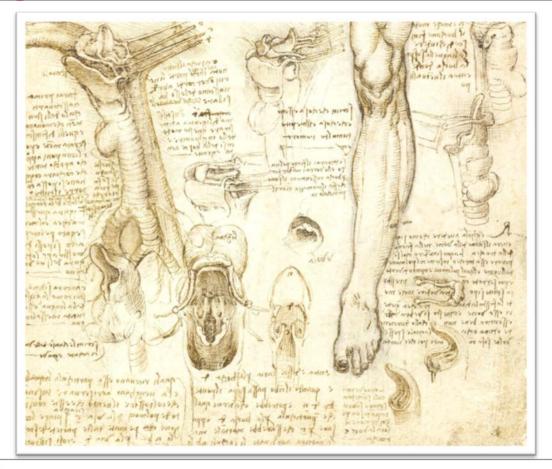
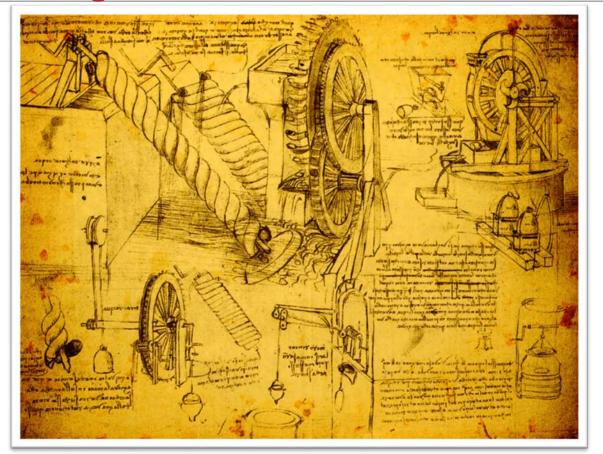


Understanding the structure and function of the body...



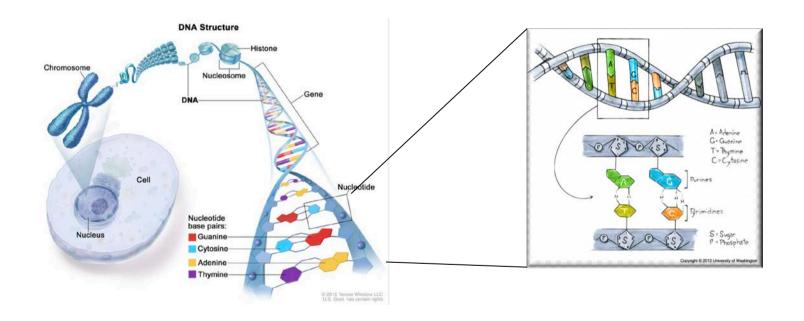
... allows us to design around its flaws



This is called SYNTHETIC BIOLOGY

and can be brought about by using the tools of GENETIC ENGINEERING

Genetic engineering



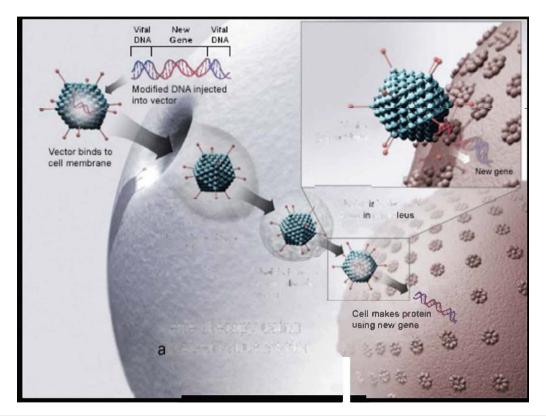
Gene therapy uses genetic engineering to make a treatment for disease

Therapeutic delivery of DNA into a patient's cells as a drug to treat disease

- DNA → RNA → protein
- replacement of absent function
- correction of defective function
- → production of novel function

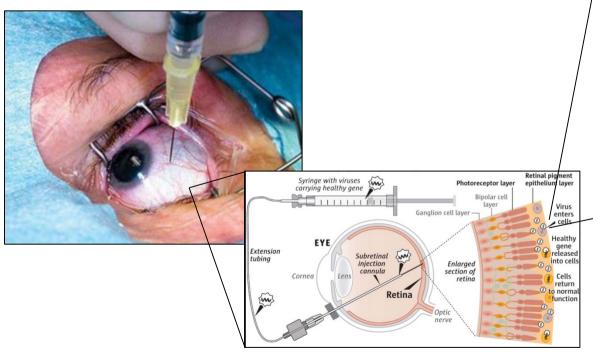
DNA is delivered into cells using a vector

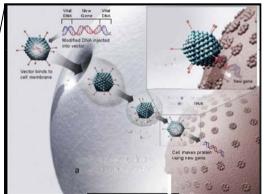
(Viral) vector mechanism of action



In vivo gene therapy (directly in the body)

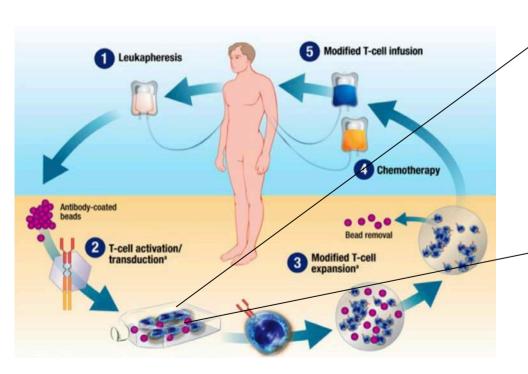
Luxturna

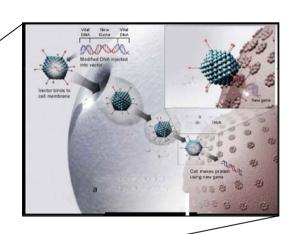


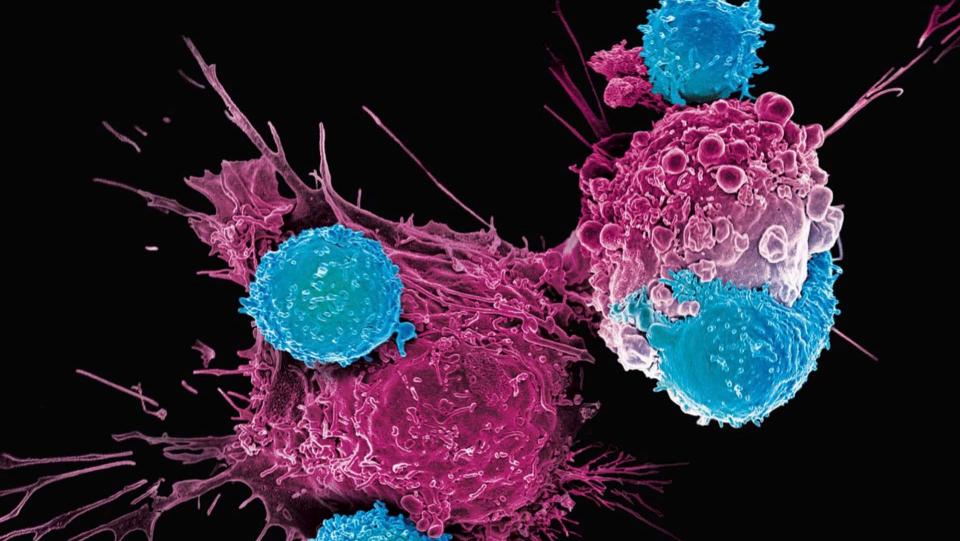


Ex vivo gene therapy (done outside the body)

CAR T cells







CAR T cells: a patient's journey













FDA approvals of CAR T cells for cancer

CART-19 for pediatric ALL (Novartis): approved 2017

CART-19 for NHL (Kite): approved 2017

CART-19 for NHL (Novartis): approved 2018

WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGICAL TOXICITIES

See full prescribing information for complete boxed warning.

- Cytokine Release Syndrome (CRS) including fatal or life-threatening reactions, occurred in patients receiving KYMRIAH. Do not administer KYMRIAH to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab. (2.2, 2.3, 5.1)
- Neurological toxicities, which may be severe or life-threatening, can occur following treatment with KYMRIAH, including concurrently with CRS. Monitor for neurological events after treatment with KYMRIAH. Provide supportive care as needed. (5.2)
- KYMRIAH is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAH REMS. (5.3)



-----INDICATIONS AND USAGE-----

KYMRIAH is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. (1)

7 DRUG INTERACTIONS

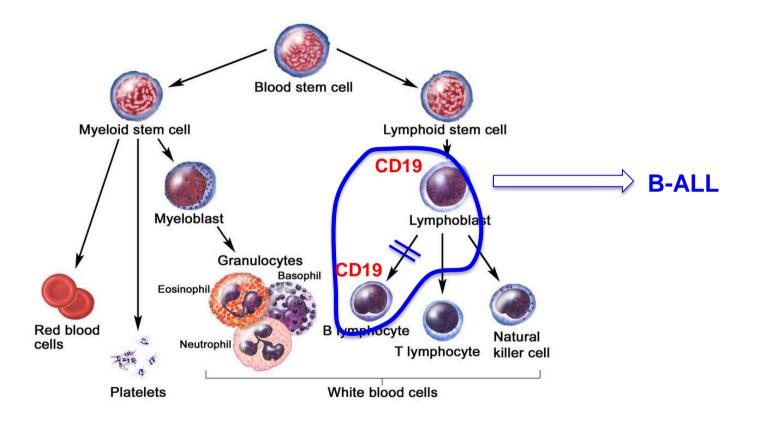
HIV and the lentivirus used to make KYMRIAH have limited, short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid test (NAT) tests may yield false-positive results in patients who have received KYMRIAH.

CAR T cell therapy of leukemia

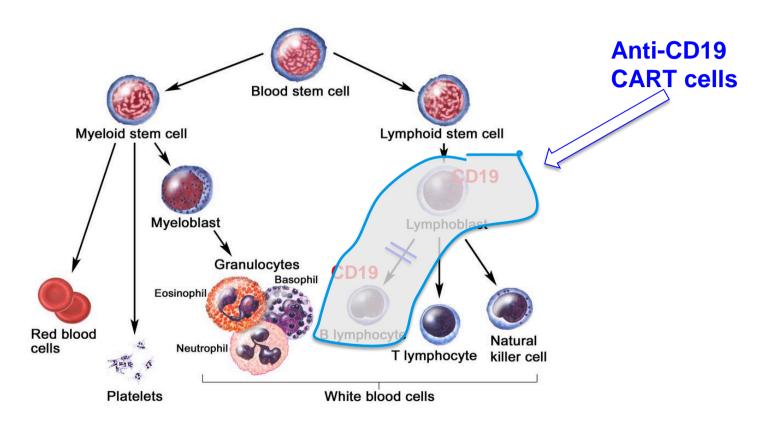
- Complete responses in 90% of children and young adults whose disease relapsed despite multiple prior types of chemotherapy (Philadelphia)¹
- Complete responses in 70% of patients (National Institutes of Health)²
- Complete responses in 88% of adult (Sloan-Kettering, New York)³
- Similar efficacy in preliminary data from US multi-center⁴ and global multicenter phase 2 trial⁵

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1 Maude SL et al, NEJM 2014
2 Lee DW et al, Lancet 2015
3 Davilla ML et al, STM 2014
4 Maude SL et al, Blood 2016
5 Grupp SA et al, Blood 2016
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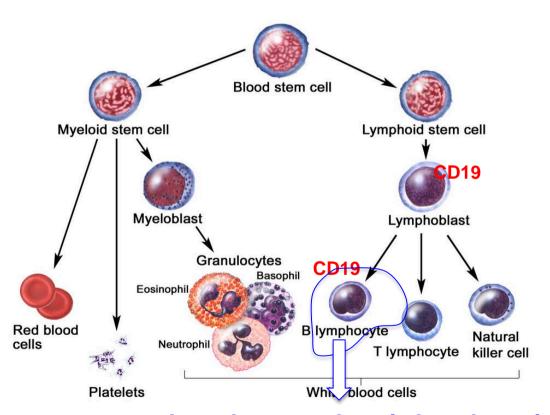
CAR T cell therapy of B-cell acute lymphoid leukemia



CAR T cell therapy of B-cell acute lymphoid leukemia

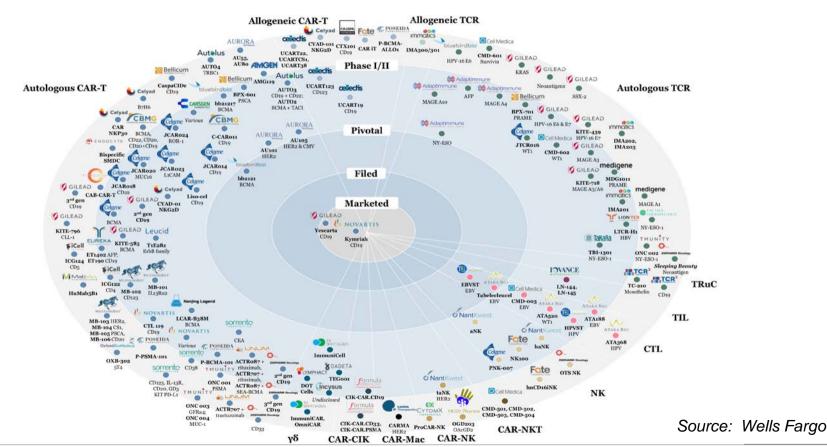


CAR T cell therapy: Beyond A.L.L.



Lymphomas, chronic lymphocytic leukemia

Where is CAR T cell therapy in early 2019?



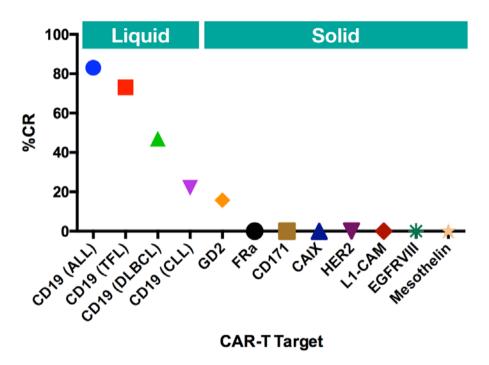
currently recruiting trials n=236; ~ 50% solid

Target	Effector Cell	Country	Tissue
Epcam	αβ T cells	China	Lung
Muc1	NK cells	USA	NPC
CEA		UK	liver
HER2		Europe	GI
Mesothelin			Cervical
PSMA			Pancreas
EGFR			Renal
NKG2DL			Prostate
ROR1			Breast
CD133			GBM
Glypican 3			Head & neck
GD2			Melanoma
cMet			
EGFRVIII			
IL13Ra2			
FAP			

Solid tumors: what are the problems?

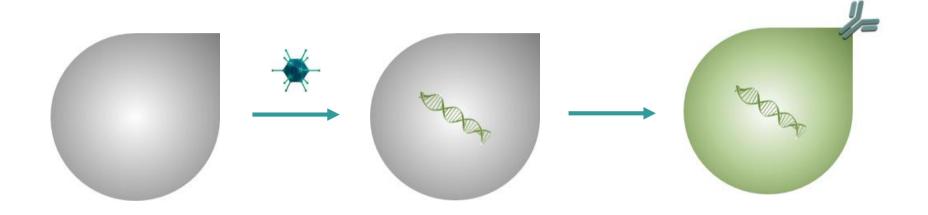
- Target selection
- Histology (type of tumor)
- Immunosuppressive (unfavorable) microenvironment
- Intrinsic resistance to T cells?
- Effector cell type (T cells vs other)

CAR T cells in "liquid" vs "solid" tumors



GD2 = neuroblastoma, Fra = ovarian cancer, CD171=neuroblastoma; CAIX = renal cell cancer; HER2 = sarcoma L1-CAM = neuroblastoma; mesothelin = various (pancreatic, ovarian, mesothelial)

Solid tumors effector cell type: macrophages



Macrophage

Engineered with a viral vector to express a chimeric antigen receptor

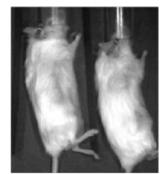
CAR Macrophage Targeted and activated

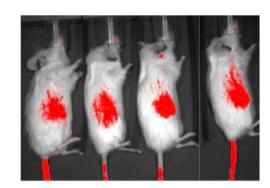
Macrophages actively recruited to solid tumor

Untreated

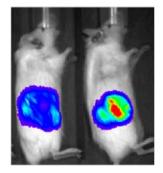
5e6 Macrophages I.V.

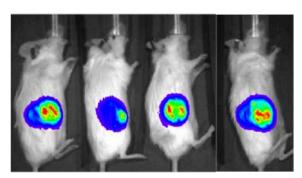




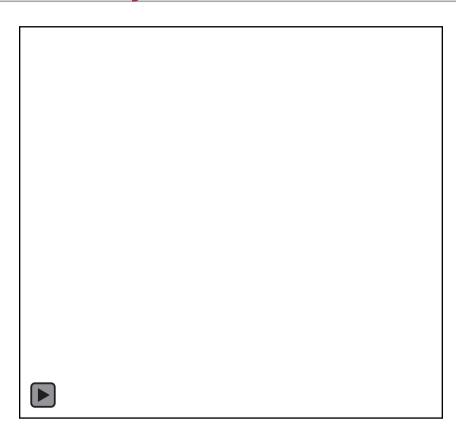


Tumor

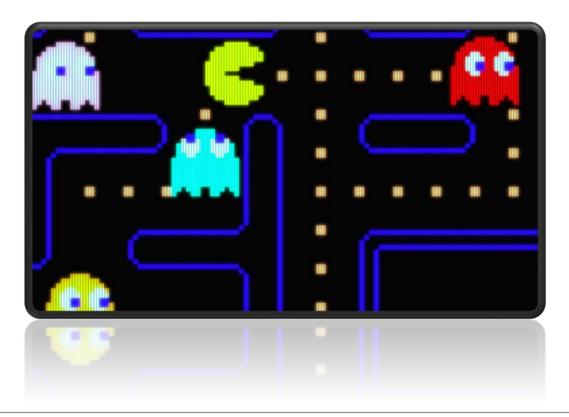




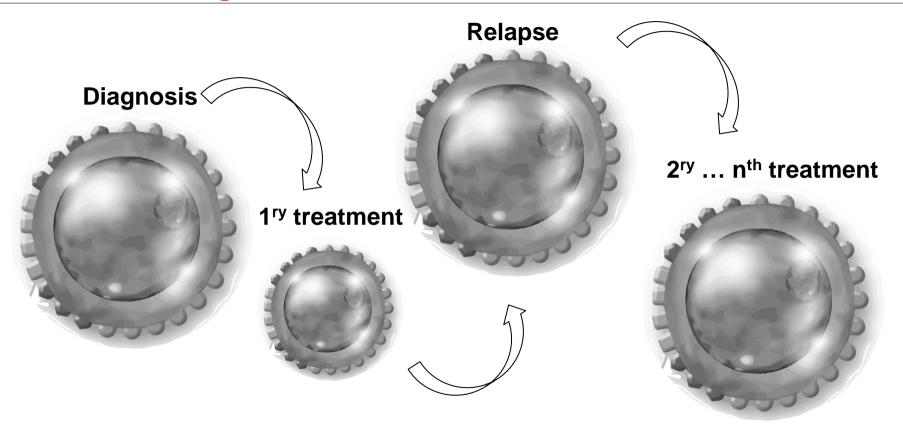
Macrophages selectively eat cancer cells



Macrophages selectively eat cancer cells



What is our goal?



What is our goal?

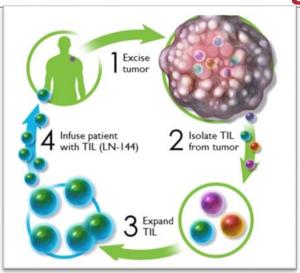




Rosenberg et al. Current Opinion in Immunology 2009

Dudley et al. Clinical Cancer Research 2010

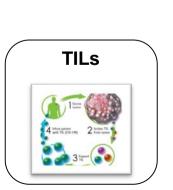
Tumor-infiltrating lymphocytes

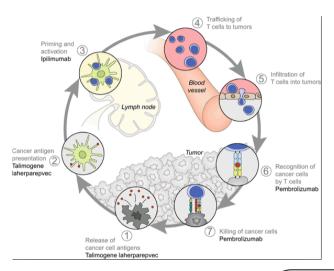


	INDICATION	REGIMEN	N	PARTNER	PRECLINICAL	PHASE I		PHASE 2
	Melanoma	Combination TIL ± TBI	101	NIH NATIONAL CANCER INSTITUTE				Trial completed, 56% ORR, 24% CR
Lion (lovance) Biotechnologies	Melanoma	Combination TIL + ipi		MOFFITT (M)		\rangle		Trial completed, publishing results soon
	Melanoma	Combination TIL + Keytruda	170	NIH CANCER INSTITUTE		\rangle		Enrolling
	Melanoma	Combination TIL + Opdivo	12	MOFFITT			Enrolling	
	Ocular (Uveal) Melanoma	TIL	23	NIH NATIONAL CANCER INSTITUTE		\rangle		Not enrolling
	Melanoma	TIL LN-144	60	-	1	\rangle		Enrolling

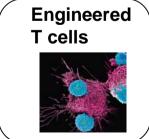
Putting it all together: how to stimulate the immune system in the fight against cancer











Conclusions and thoughts about the future

- Understanding the interaction of cancer with the immune system allows us to design treatment that capitalizes on vulnerabilities (chinks in the armor)
- Examples already exist: checkpoint inhibiting antibodies, TILs
- We need to find synergies between existing therapies and to develop new approaches