A multi-center clinical consortium to investigate the biology and clinical efficacy of autologous T cells genetically targeted to the CD19 antigen in patients with B cell malignancies

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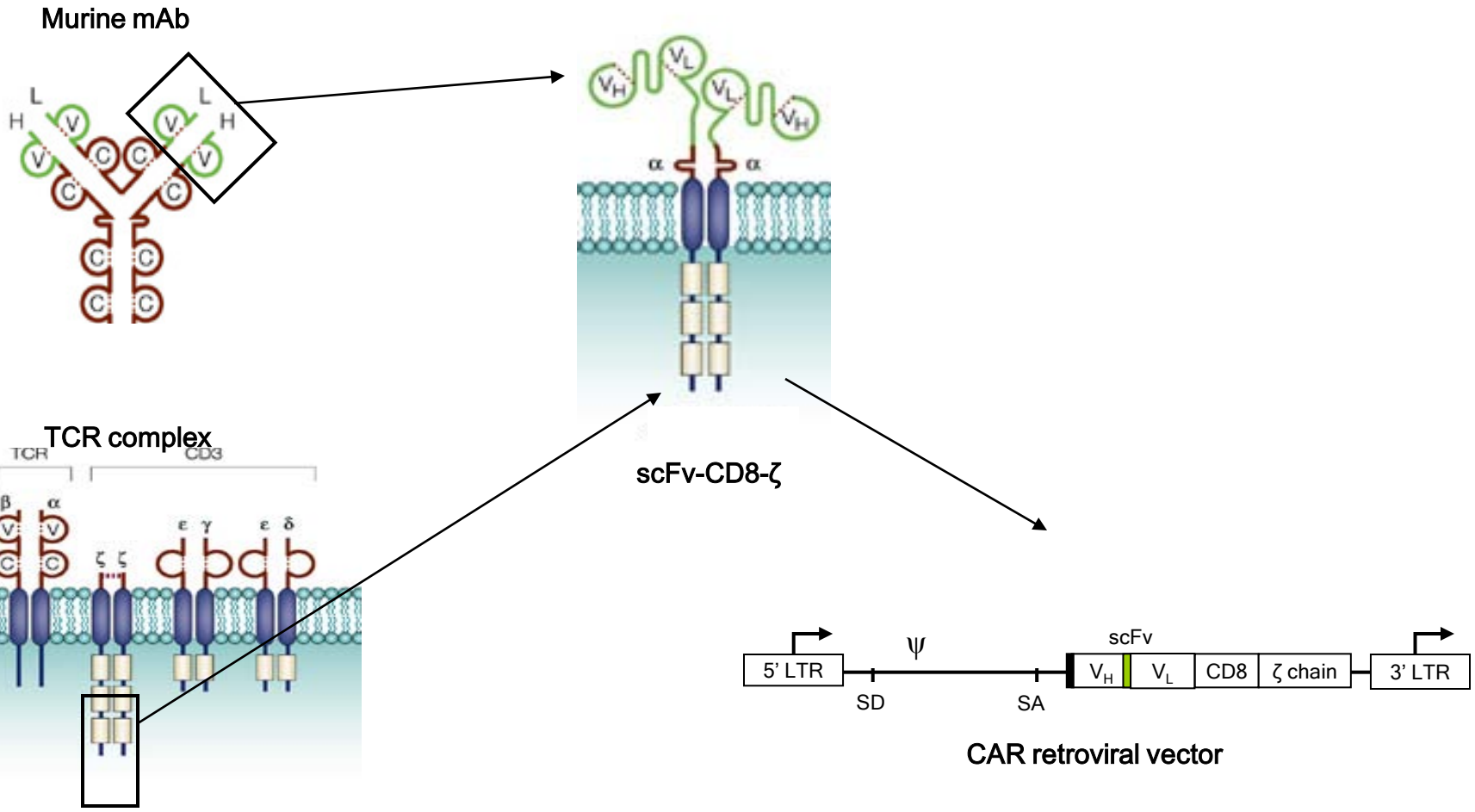
The Approach

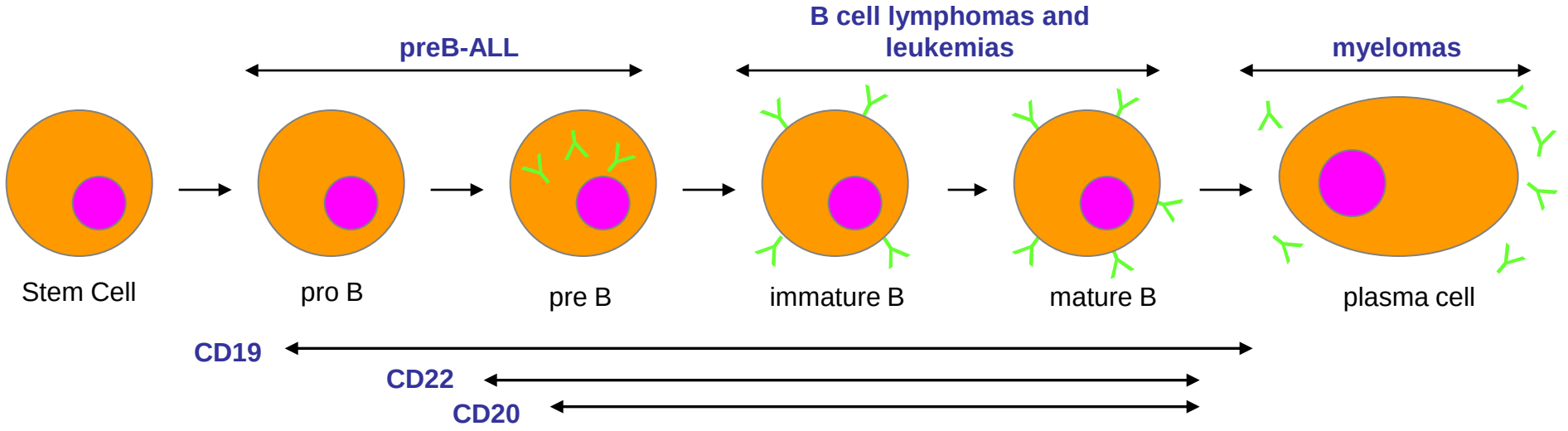
Utilization of a patient's own T-cells, genetically modified in the laboratory to recognize their tumor cells as a novel approach to treat patients with B cell malignancies

Generation of an antigen specific chimeric antigen receptor (CAR)

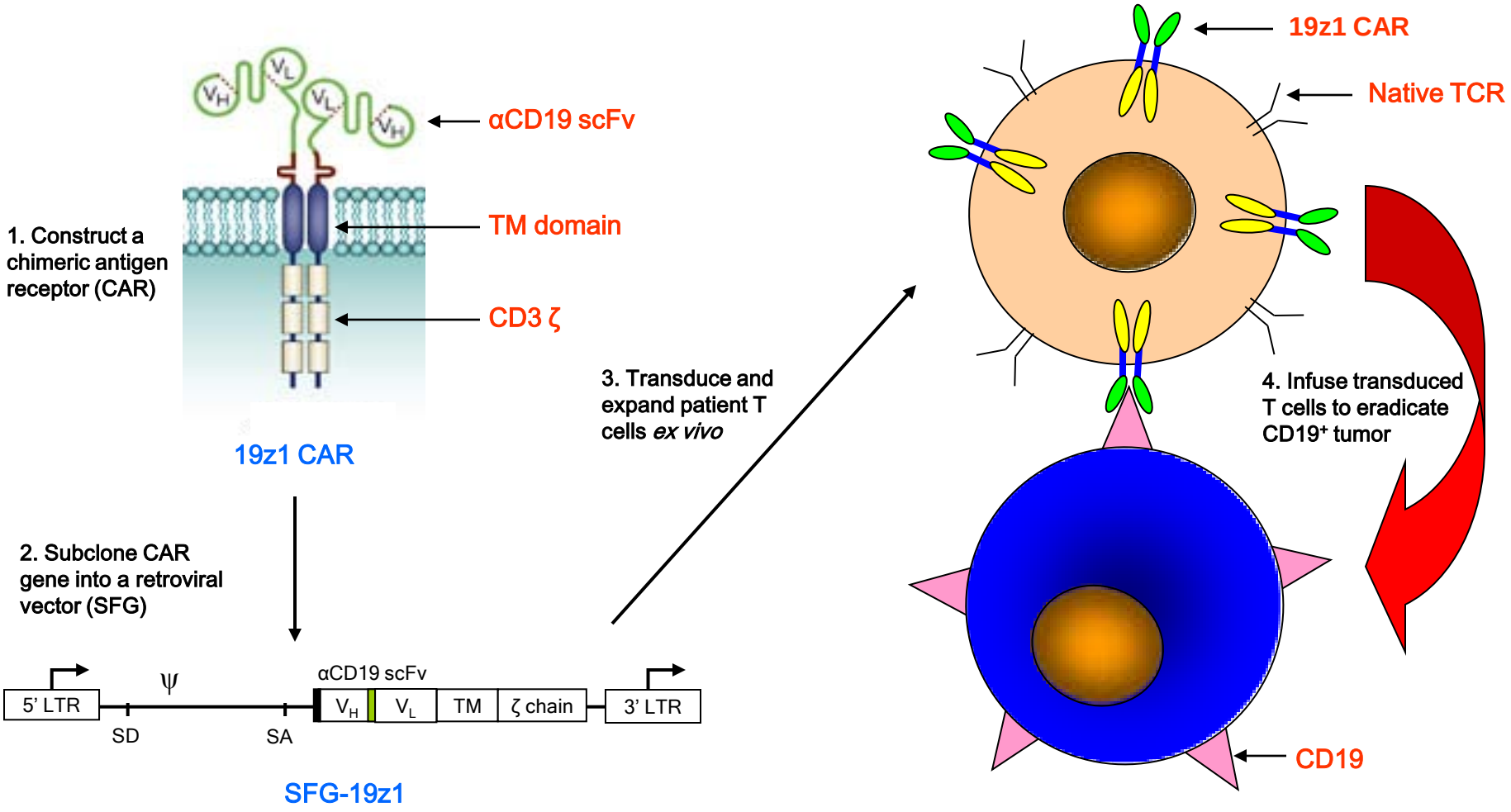


CD19

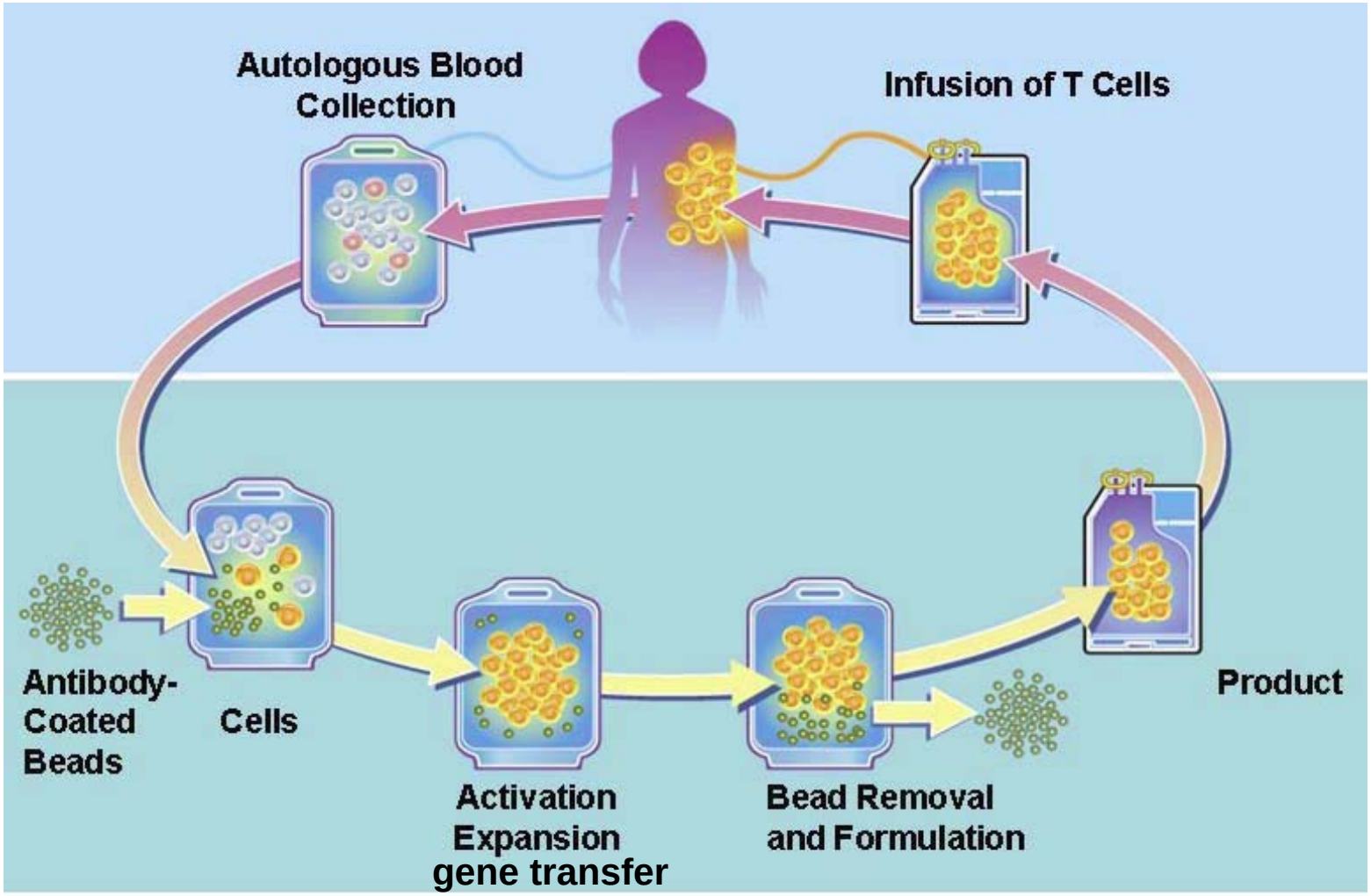
- CD19 expression is restricted to B cells and possibly follicular dendritic cells
- CD19 is not expressed on pluripotent bone marrow stem cells
- CD19 is expressed on the surface of most B cell malignancies
- Antibodies against CD19 inhibit growth of tumor cells



Generation of CD19-targeted T cells for treatment of B cell malignancies



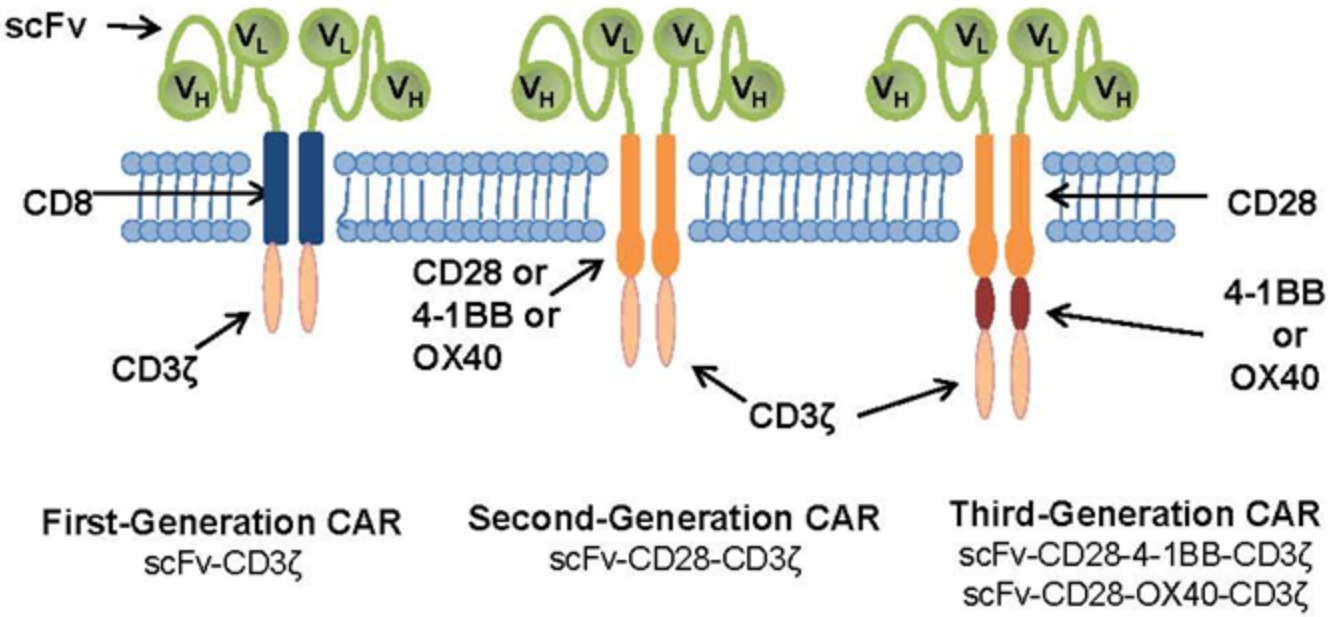
Clinical trial overview



The Problem

- There are many current ongoing phase I clinical trials targeting CD19 with many clinically relevant variables:
  - CAR gene transfer
    - Retrovirus
    - Lentivirus
    - Transposons
    - Electroporation
  - Targeted disease
    - Leukemia (CLL AML)
    - Lymphoma (NHL)
  - Patient population
    - Pediatric
    - Adult
  - Prior lymphodepletion (+/-)
  - CAR design
    - First generation CARs
    - Second and third generation CARs

Variables in CAR design



The Result

Center	Disease	CAR Endodomain	Vector to Express CAR	Conditioning Regimen	Target	Status	ClinicalTrials.Gov
MSKCC	CLL –refractory	Zeta/28	RV	Cyclophosphamide	CD3-selected	Open. 6 treated	NCT00466531
MSKCC	B ALL-relapsed	Zeta/28	RV	Cyclophosphamide	CD3-selected	Open. 1 treated	NCT01044069
BCM	B NHL and CLL	Zeta/28 vs. Zeta	RV	NA	PBMC (OKT3 and IL-2)	Open. 5 treated: 4 DLBCL 1 B-CLL	NCT00586391
BCM	B NHL and CLL	Zeta/28 vs. Zeta-EBV	RV	NA	PBMC and EBV CTL	2 treated	NCT00608270
BCM	B ALL, S/P HSCT	Zeta/28	RV	+30 days after allo-HSCT	Multi-virus CTL	open	NCT00709033
NCI	Lymphoma, CLL	Zeta/28	RV	Fludarabine and Cyclophosphamide	PBMC (anti-CD3 + REP)	Open. 4 treated	NCT00924326
U Penn	Refractory B Leukemia/ Lymphoma	Zeta/41BB vs. Zeta	LV	Variable	Auto PBMC (CD3/CD28 beads)	To open	NCT00891215
U Penn	Relapsed ALL, S/P HSCT	Zeta/41BB	LV	Variable	Allo DLI	To open	
MDACC	B-NHL, S/P autologous HSCT	Zeta/CD28	Electroporation/ SB plasmids	BEAM-R	Auto PBMC (+/- IL-2)	To open	NCT00968760
MDACC	B-lineage malignancy, S/P allogeneic HSCT	Zeta/CD28	Electroporation/ SB plasmids	Conditioning regimen for HSCT	Allogeneic PBMC or umbilical cord blood	To open	
COH		Zeta	Plasmid	Fludarabine or +28 days S/P HSCT	PBMC	Closed. 3 treated	NCT00182650
COH/ FHCRC	Recurrent LCL/MCL, S/P Autologous HSCT	Zeta	LV		Tcm: CD8+/CD4-/ CD45RA-/CD62+	To open	

Kohn et al Mol Ther (in press)

Currently open clinical trials of CD-19 targeted T cells: MSKCC, UPenn, and CHOP

MSKCC Clinical Trials:

IRB 06-138: A Phase I Trial for the Treatment of Purine Analog-Refractory Chronic Lymphocytic Leukemia using Autologous T cells Genetically Targeted to the B cell Specific Antigen CD19

Adult patients with CLL, 1928z retroviral vector, prior lymphodepletion (8 enrolled, 7 treated)

IRB 09-114: A Phase I Trial of B Cell Acute Lymphoblastic Leukemia (B-ALL) Treated with Autologous T cells Gene Targeted to the to the B cell Antigen CD19.

Adult patients with ALL, 19-28z retroviral vector, prior lymohodepletion (3 enrolled, 1 treated)

UPenn Clinical Trial:

UPCC 04409: Pilot Study of Redirected Autologous T Cells Engineered To Contain Anti-CD19 Attached To TCR And 4-1BB Signaling Domains in Patients with Chemotherapy Resistant or Refractory $CD19^{+}$ Leukemia and Lymphoma.

Adult patients with refractory leukemia and lymphoma, 19-41BB lentiviral vector, prior lymophodepletion (3 enrolled, 3 treated)

CHOP Clinical Trial:

CHP-959: Phase 2A Study of Redirected Autologous T cells Engineered to Contain anti-CD19 attached to TCR and Co-stimulatory Signaling Domains in Patients with Chemotherapy Resistant or Refractory $CD19^{+}$ Leukemia and Lymphoma.

Pediatric patients with refractory leukemia and lymphoma, 19-41BB lentiviral vector, prior lymophodepletion

A Solution (with Multiple Endpoints)

To generate a multi-center consortium utilizing harmonized pre-existing ongoing clinical trials to address variables in gene transfer and CAR design, as well as validate this therapeutic approach in larger multi-center clinical trials. To directly compare retrovial and lentiviral vectors for gene transfer of CARs into patient T cells.

1) To directly compare *in vivo* persistence and anti-tumor efficacy of second generation CD19 targeted CARs containing either the CD28 or 4-1BB co-stimulatory domains.

2) To more rapidly generate statistically relevant data regarding these variables.

3) To further demonstrate the “exportability” of this technology between academic institutions suitably endowed with requisite GMP facilities validating the feasibility of conducting future planned phase II-III clinical trials utilizing this technology.

PLAN: Harmonizing currently open clinical trials of CD-19 targeted T cells at MSKCC, UPenn, and CHOP

1) Protocols for both retroviral and lentiviral gene transfer will be harmonized between MSKCC, UPenn, and CHOP.

2) UPenn will provide MSKCC with 19-41BBz lentiviral vector (BB-IND 13960) under cross reference to validate gene transfer in the clinical setting at MSKCC, while clinical grade retroviral 19-28z vector from MSKCC (BB-IND 13266) will be provided to UPenn for similar validation.

3) All clinical trials at MSKCC, UPenn, and CHOP will be modified to adhere to the planned harmonized protocol of treating all subsequent patients on these protocols with equal numbers of retrovirally transduced 19-28z T cells and lentivirally transduced 19-41BBz T cells, the sum of infused T cells being equal to the total of planned infused modified T cells as stipulated in the respective initial clinical trials.

4) Immune monitoring of modified T cells and endogenous immune effectors will be conducted in part through collaborative efforts by the immune monitoring cores at each center (Kalos UPenn, and Jianda MSKCC) (Aim 2).

5) Ideally, collated analyses of vector and CAR design in these proposed studies will overcome variables including the targeted B cell malignancy and patient selection (adult versus pediatric patients) providing data to support recommendation of the better viral vector construct to generate the optimal number of tumor targeted T cells as well as the superior CD19 targeted CAR construct to induce optimal *in vivo* anti-tumor responses and modified T cell persistence.

Meeting Criteria for IRM STRAP Funding: Development over Discovery

- Is this a clinically significant translational cancer research opportunity that should be accelerated?
  - **Yes. Preclinical and clinical data generated at our institutions as well as others demonstrate that adoptive therapy with genetically targeted tumor specific T cells have significant clinical promise worthy of accelerated development.**
- Does the proposal address one of the four prioritized areas in the Notice?
  - **Yes. This proposal addresses both adoptive therapy and "T body" or CAR therapy.**
- Is this an opportunity that would be difficult to accomplish through other available funding approaches?
  - **Yes. Significant funding for clinical development in the form of clinical trials, especially in a multi-center format, is difficult to obtain through other currently available RFAs.**
- Does the research plan address the developmental requirements of an IRM STRAP with components such as a well-described plan, reasonable timeframe/milestones, defined collaboration responsibilities, etc.?
  - **Yes. The proposal is a first of its kind multi-institutional collaborative effort designed to accelerate clinical development of adoptive T cell therapy of cancer with a uniquely reasonable time frame to begin accrual and therapy.**
- Is there a reasonable likelihood that the proposed research can reach IND status and clinical testing?
  - **Yes. INDs are already in place, and initiation of planned clinical trials will only require cross reference of INDs and IRB and FDA approval of modified/harmonized pre-existing clinical trials.**
- Does the proposed Research Team have the appropriate expertise and experience to accomplish the IRM STRAP?
  - **Yes. Investigators at MSKCC, UPenn, and CHOP have previously demonstrated expertise the conduct of adoptive T cell therapy trials, as well all investigators have demonstrated prior proficiency in navigating clinical trials through both institutional committees as well as federal agencies.**

Milestones and (modified) Timeline

- 6-9 months: Obtain IRB approvals for harmonized/ modified clinical trials and FDA approval for cross-referencing of existing INDs.
- 6-12 months: Initiate enrollment on modified protocols.
- 12-24 months: Completion of preclinical comparative CAR and vector studies as described in Aim 3.
- 24-30 months: Complete enrollment of 24 patients on collective clinical trials.
- 24-36 months: Complete analyses of clinical and correlative data (Aim 2) from enrolled and treated patients on the collective clinical trials.

Progress to Date: Harmonizing Gene Transfer Protocols

TASK	MSKCC	UPenn	CHOP
MTAs for vector exchange	✓	✓	✓
Transfer of viral stocks	✓	✓	✓
Harmonizing of retroviral and lentiviral gene transfer protocols	Pend	Pend	Pend
Validation of gene transfer protocols	Pend	Pend	Pend

Progress to Date: Harmonizing Clinical Trials

TASK	MSKCC	UPenn	CHOP
Modification of existing clinical trials	✓	✓	✓
Submission to IRB	**Pend**	**Pend**	**Pend**
IND cross reference and FDA submission	**Pend**	**Pend**	**Pend**
Initiate enrollment of patients on modified trials	**Pend**	**Pend**	**Pend**

Relevance of IRM STRAP Award to Parent RO1 Award

- NIH-R01 Award (CA138738-01): Adoptive Immunotherapy of Cancer with IL-12 Secreting Tumor-Targeted T cells
  - The aims of this application are to investigate the enhanced in vivo anti-tumor potential of CD19 targeted T cells further modified to secrete the IL-12 cytokine.
  - The ultimate goal of this work is to translate this approach to the clinical setting.
  - Accelerated enrolment and analyses of patients treated on the “first generation” clinical protocols presented in this STRAP award will more rapidly provide much needed insight into the clinical *in vivo* biology and limitations of CAR modified T cells.
  - As well, the studies funded by the STRAP award, will likely therefore provide the rationale for “second generation” trials utilizing IL-12 secreting, CD19 targeted T cells with predicted enhanced anti-tumor efficacy and persistence

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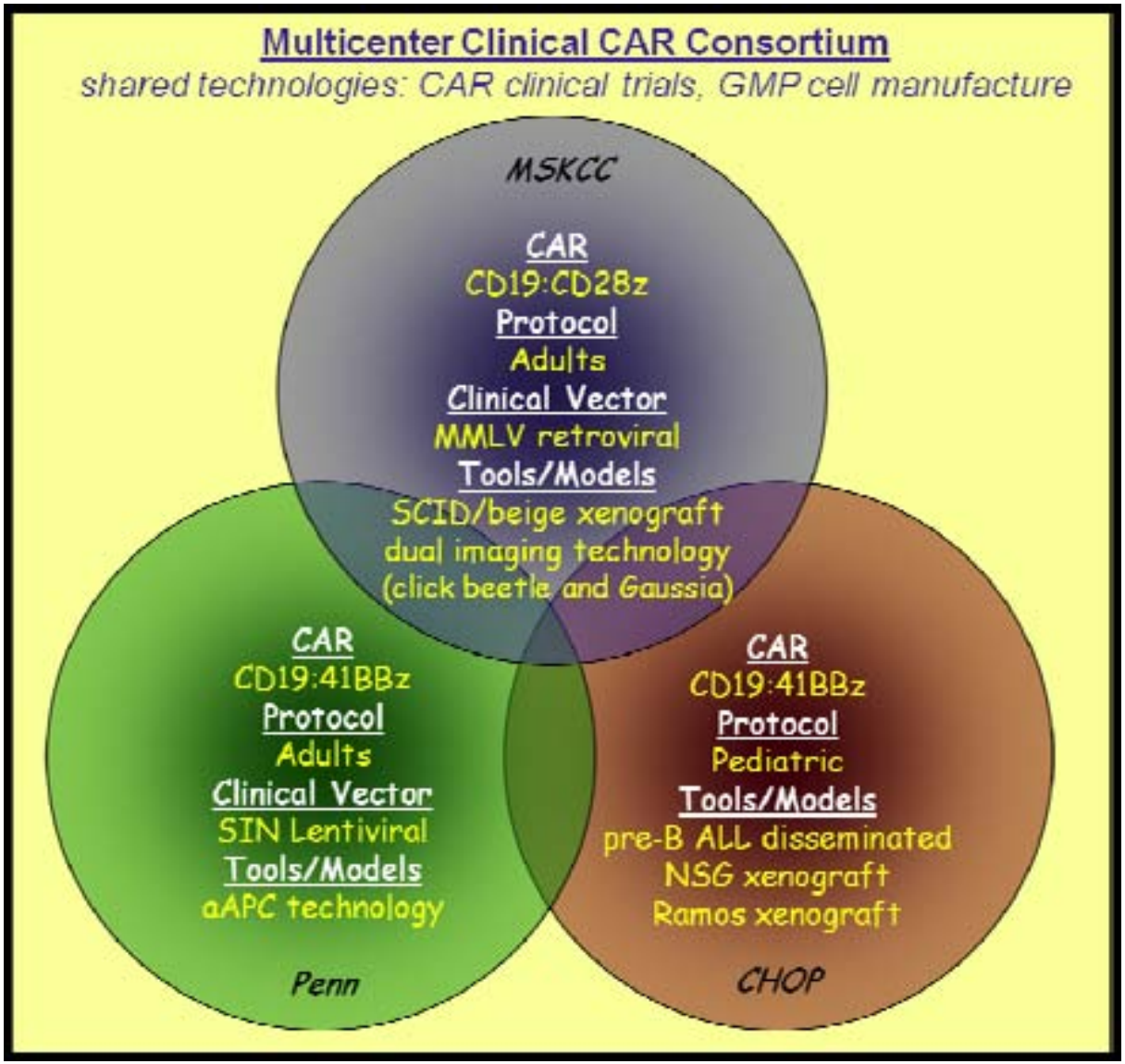
Multicenter Clinical CAR Consortium
shared technologies: CAR clinical trials, GMP cell manufacture
MSKCC
CAR
CD19:CD28z
Protocol
Adults
Clinical Vector
MMLV retroviral
Tools/Models
SCID/beige xenograft
dual imaging technology
(click beetle and Gaussia)
CAR
CD19:41BBz
Protocol
Adults
Clinical Vector
SIN Lentiviral
Tools/Models
aAPC technology
Penn
CAR
CD19:41BBz
Protocol
Pediatric
Tools/Models
pre-B ALL disseminated
NSG xenograft
Ramos xenograft
CHOP