

NIH SAFETY SYMPOSIUM

GENE-MODIFIED T CELLS: CHALLENGES IN CLINICAL TRIAL DESIGN

CHIMERIC ANTIGEN RECEPTORS

Hematologic Antigens (CD19, CD20)

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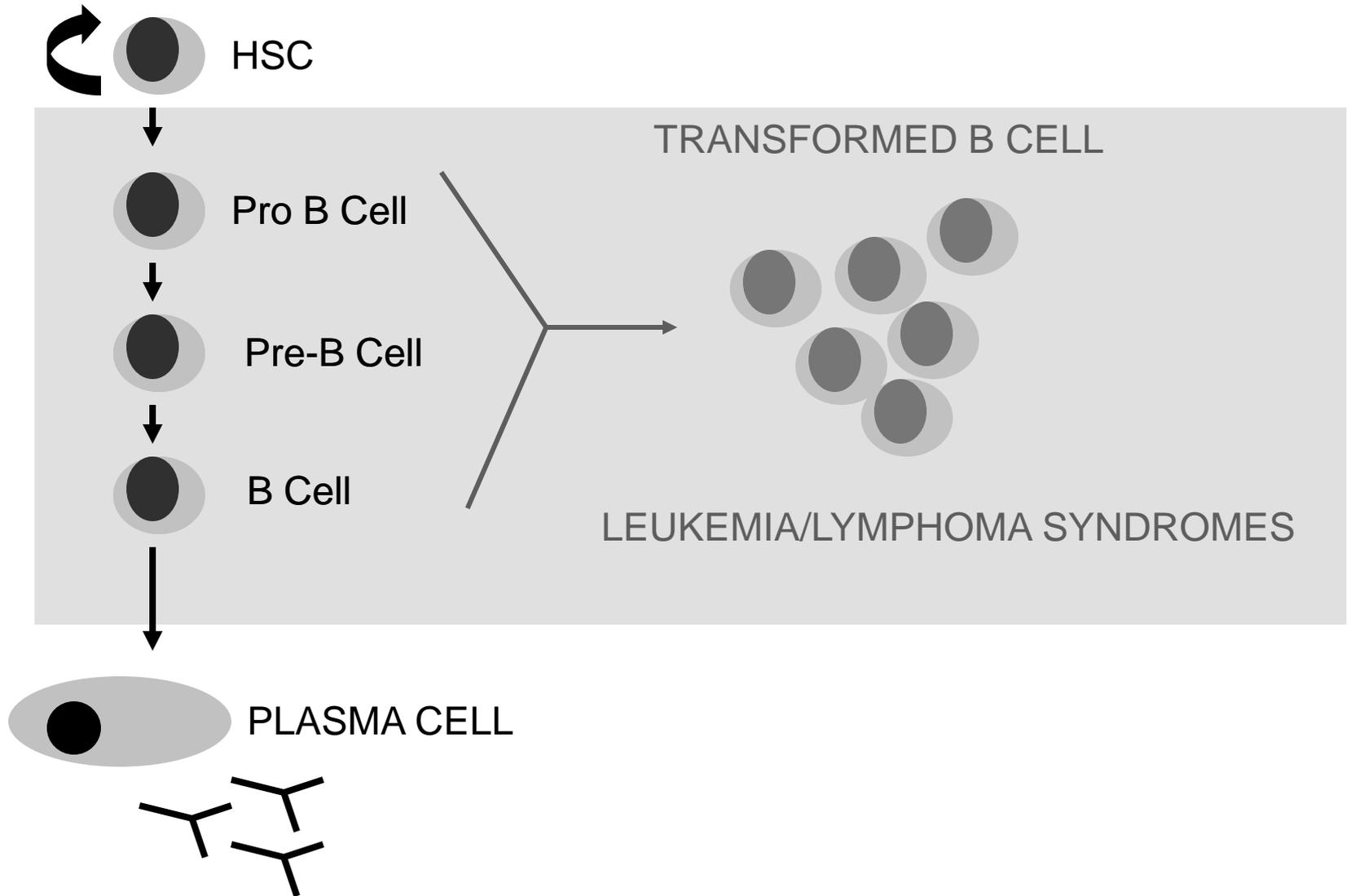
COI DISCLOSURE

- M. JENSEN IS AN INVENTOR ON PATENTS HELD BY CITY OF HOPE COVERING CD20- AND CD19-SPECIFIC CHIMERIC ANTIGEN RECEPTORS AND PER INSTITUTIONAL POLICY IS THE RECIPIENT OF A PORTION OF PROCEEDS FROM LICENSING AGREEMENTS.
- M. JENSEN IS A CO-FOUNDER AND EQUITY HOLDER IN ZETARX, LLC

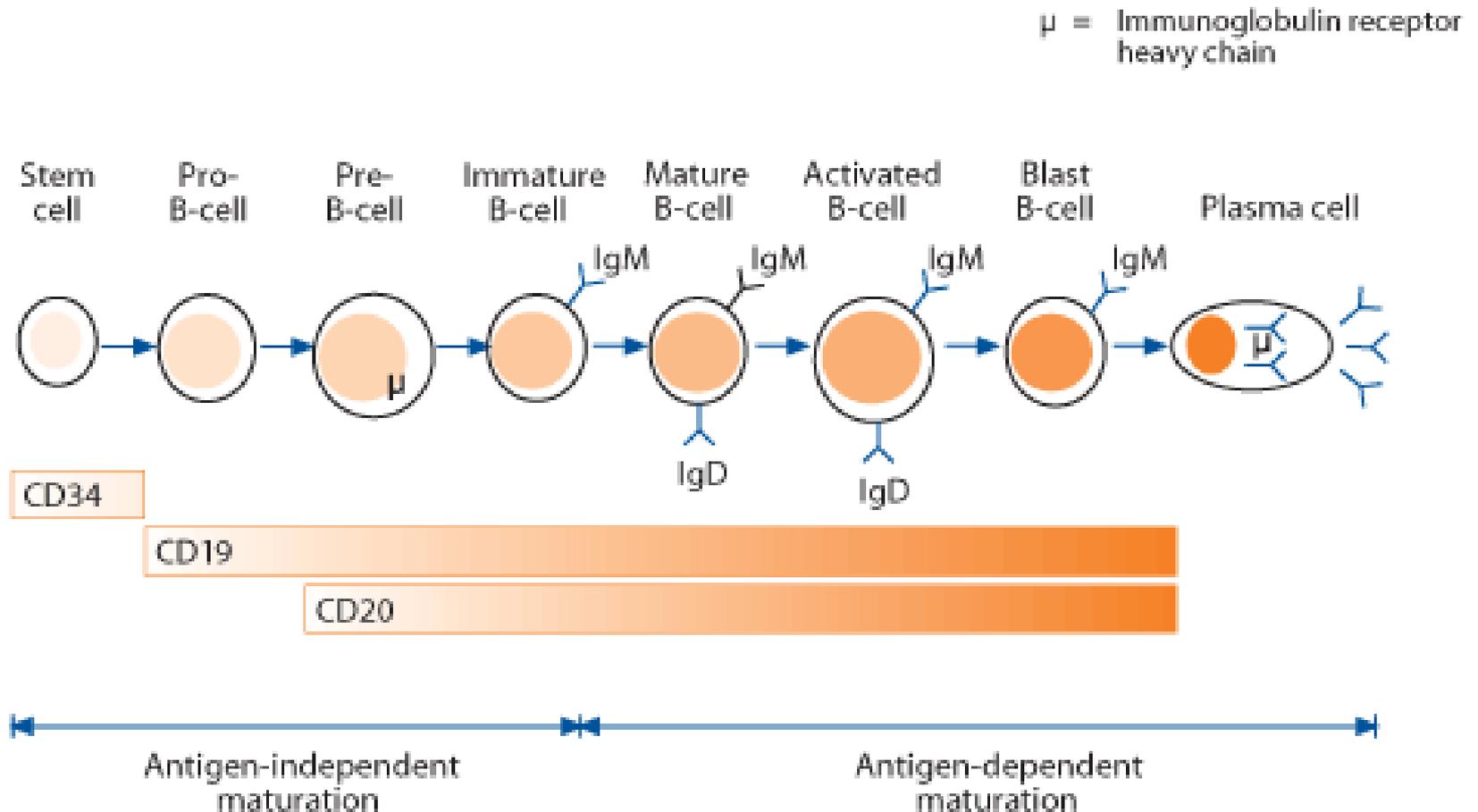
INTRODUCTION

- B CELL LINEAGE SPECIFIC TARGETS
- RATIONALE FOR APPLICATIONS TO HEMATOLOGIC MALIGNANCIES
- DISEASE SPECIFIC INDICATIONS
- PORTFOLIO OF PROTOCOLS IN DEVELOPMENT/FIRST-IN-MAN TRIALS
- UNIQUE ASPECTS/CONSIDERATIONS

CONCEPTUAL OVERVIEW:

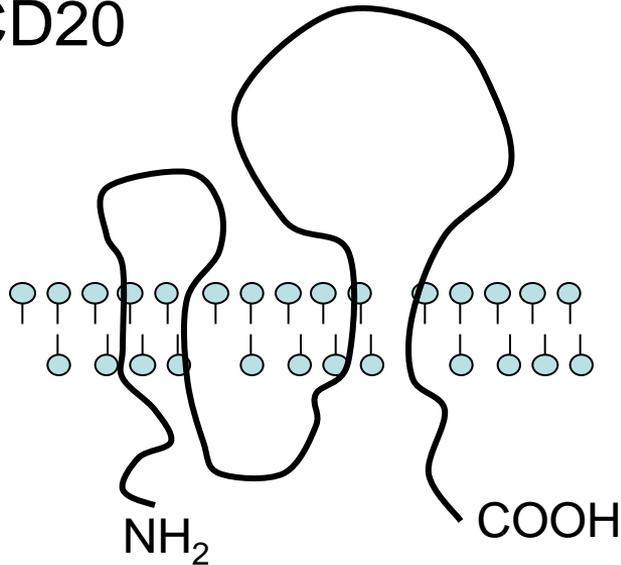


B-CELL ONTOGENY

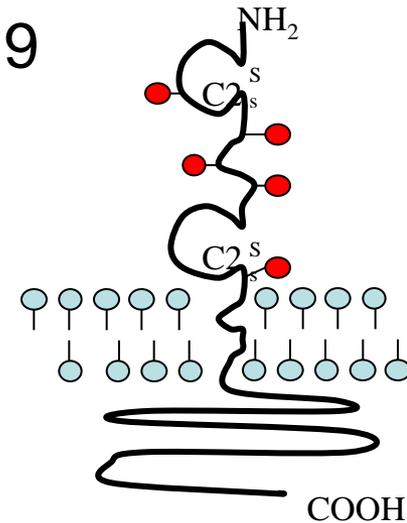


CD19 & CD20 AS TARGETS FOR CAR RE-DIRECTED T CELLS

CD20

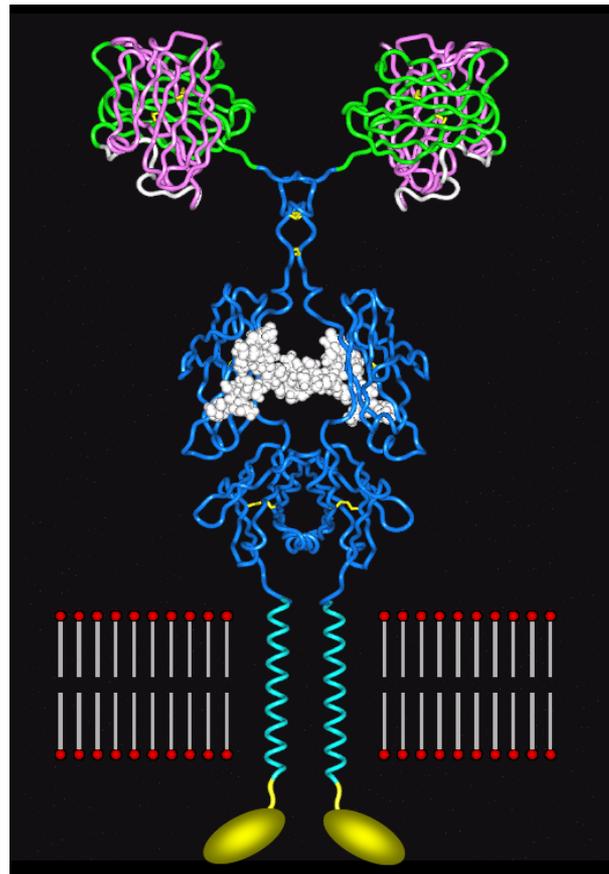


CD19



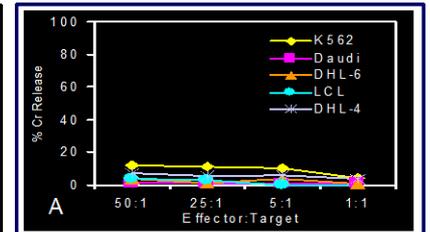
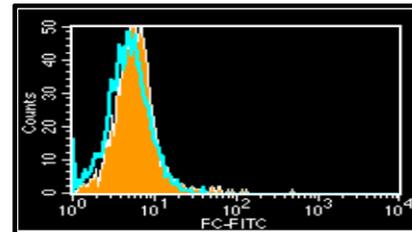
- B CELL SPECIFIC EXPRESSION
- INTEGRAL MEMBRANE PROTEINS
- LIMITED SHEDDING
- HOMOGENOUSLY EXPRESSED
- LIMITED ANTIGEN ESCAPE

CD20/CD19-SPECIFIC scFv-CARs

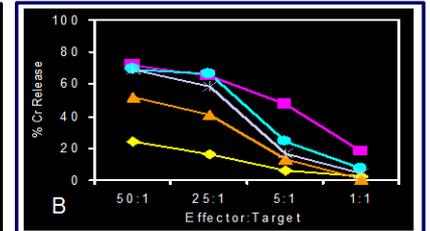
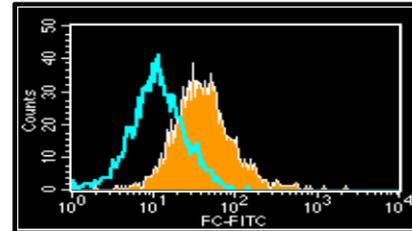


→ ANTI-CD20 LEU-16
 ANTI-CD19 FMC63

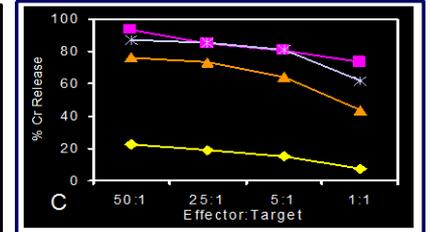
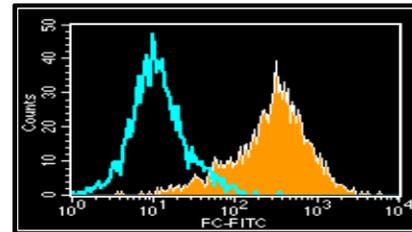
CAR⁻



CAR^{low}



CAR^{high}



APPLICATIONS (1): SPECTRUM OF DISEASE INDICATIONS

LEUKEMIAS

ACUTE LYMPHOBLASTIC (CD19)
CHRONIC LYMPHOCYTIC (CD19/CD20)

NON-HODGKIN
LYMPHOMAS

LOW GRADE (CD19/CD20)
INTERMEDIATE GRADE (CD19/CD20)
HIGH GRADE (CD19/CD20)

MULTIPLE MYELOMA

? MM PROGENITOR (CD19)

APPLICATIONS (2): SPECTRUM OF THERAPEUTIC VENUES

STAND ALONE THERAPY +/- LYMPHODEPLETION

IN CONJUNCTION WITH MYELOABLATIVE HSCT

POST AUTO-HSCT (CONSOLIDATIVE VS SALVAGE)

--STANDARD OF CARE LYMPHOMA RX

POST ALLO-HSCT (CONSOLIDATIVE VS SALVAGE)

--STANDARD OF CARE FOR ACUTE LEUKEMIAS

SOME INDICATIONS FOR LYMPHOMA

APPLICATIONS (3): SPECTRUM OF DISEASE SITES

LEUKEMIAS

CIRCULATION, MARROW
+/- CNS/TESTIS/SKIN

NON-HODGKIN
LYMPHOMAS

LYMPH NODES +/- MARROW,
EXTRA NODAL SITES

NORMAL B CELL
COMPARTMENT

MARROW, CIRCULATION
LYMPH NODES/LYMPHATICS

PORTFOLIO OF APPLICATIONS IN DEVELOPMENT

CD20-specific CAR TRIALS

Title	Protocol # 330: Pilot Phase I Study to Evaluate the Safety of Cellular Immunotherapy Using Genetically Modified Autologous CD20-Specific CD8+ T Cell Clones for Patients with Recurrent/Refractory CD20+ Lymphoma Undergoing Autologous Peripheral Blood Stem Cell Transplantation
PI	Michael C.V. Jensen, M.D.
Vector and Signaling Moieties	Plasmid/CD3 Zeta

Title	Protocol # 491: A Phase I Study to Evaluate the Safety of Cellular Immunotherapy Using Genetically-Modified Autologous CD20-Specific T Cell Clones for Patients with Relapsed CD20+ Mantle Cell or Indolent Lymphomas
PI	Oliver W. Press, M.D., Ph.D.
Vector and Signaling Moieties	Plasmid/CD3 zeta

Title	Protocol # 863: A Pilot Study To Evaluate the Safety and Feasibility of Cellular Immunotherapy Using Genetically Modified Autologous CD20-Specific T cells for Patients with Relapsed or Refractory Mantle Cell and Indolent B Cell Lymphomas
PI	Oliver W. Press, M.D., Ph.D.
Vector and Signaling Moieties	Plasmid/CD3 zeta 4-1BB-CD28

CD19-specific CAR Protocols

Title	Protocol # 543: Phase I Study to Evaluate the Safety of Cellular Immunotherapy for CD19+ Follicular Lymphoma Using Autologous T Cell Cytolytic Clones Genetically Modified to be CD19-Specific and Express HyTK (1st generation)
PI	Laurence J. Cooper, M.D., Ph.D.
Vector and Signaling Moieties	Plasmid/CD3 Zeta

Title	Protocol # 721: 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
PI	Renier Brentjens, M.D., Ph.D.
Vector and Signaling Moieties	Retrovirus/CD28, CD3 zeta

Title	Protocol # 776: Phase I Study of CD19 Chimeric Receptor Expressing T Lymphocytes in B-Cell Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia
PI	Helen E. Heslop, M.D.
Vector and Signaling Moieties	Retrovirus/CD28, CD3 zeta

Title	Protocol # 793: Pilot Study of Redirected Autologous T Cells Engineered to Contain Anti-CD19 Attached to TCRζ and 4-1 BB Signaling Domains in Patients with Chemotherapy Resistant Or Refractory CD19+ Leukemia and Lymphoma
PI	David L. Porter, M.D.
Vector and Signaling Moieties	Lentivirus/CD3 zeta

CD19-specific CAR Protocols (cont.)

Title	Protocol # 915: Phase I Study of the Administration of Peripheral Blood T Cells or EBV Specific CTLs Expressing CD19 Chimeric Chronic Lymphocytic Leukemia Receptors for Advanced B-Cell Non Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia
PI	Helen E. Heslop, M.D.
Vector and Signaling Moieties	Retrovirus/CD28, CD3 zeta

Title	Protocol # 940: Treatment of B Cell Malignancies with T Cells Expressing an Anti-CD19 Chimeric Receptor: Assessment of the Impact of Lymphocyte Depletion Prior to T Cell Transfer
PI	Steven A. Rosenberg, M.D., Ph.D.
Vector and Signaling Moieties	Retrovirus/CD28, CD3 zeta

Title	Protocol # 945: Phase I/II Study of the Administration of Multi-virus-specific Cytotoxic T Lymphocytes (CTLs) Expressing CD19 Chimeric Receptors for Prophylaxis or Therapy of Relapse of Acute Lymphoblastic Leukemia Post Hematopoietic Stem Cell Transplantation (MultiPRAT)
PI	Catherine Bollard, M.D.
Vector and Signaling Moieties	Retrovirus/CD28, CD3 zeta

KEY ISSUES IN CONSIDERING CLINICAL EFFICACY/SAFETY (1)

1. IMPACT OF NORMAL B CELLS:

- CIRCULATING B CELLS AND SYNCHRONOUS INTRAVASCULAR ACTIVATION OF INFUSED T CELLS
- EFFECT OF CONTINUOUS SOURCE OF ANTIGEN GENERATED FROM HSC PROGENITORS
- TOLERIZING EFFECT OF RESTING B CELLS

KEY ISSUES IN CONSIDERING CLINICAL EFFICACY/SAFETY (2)

2. IMPACT ON NORMAL B CELLS:

- EXACERBATION OF B CELL LYMPHOPENIA (MAGNITUDE AND DURATION)

? WILL DURATION OF EFFECT OF AT BE SELF LIMITED BASED ON REPLICATIVE SENESENCE OF INFUSED PRODUCT

? WILL OTHER STRATEGIES BE NEEDED TO ATTENUATE ANTI-B CELL RESPONSE

VENUE OF HEMATOLOGIC MALIGNANCIES FOR NEW TECHNOLOGY CLINICAL TESTING

- **VECTORS:**
 - NAKED DNA
 - RETROVIRUS
 - LENTIVIRUS
 - SLEEPING BEAUTY SYSTEM
- **SECOND/THIRD GENERATION CARS**
- **BISPECIFIC T CELL PRODUCTS (VIRUSXCAR)**
- **DEFINED T CELL POPULATIONS (PURIFIED CENTRAL MEMORY VS NAÏVE T CELL DERIVED PRODUCTS)**
- **COMBINATION PRODUCTS (T CELLS + IL-15, +VACCINE, +IMMUNOCYTOKINES, +CHECKPOINT BLOCKAIDE)**
- **VENUE FOR MULTI-INSTITUTIONAL TRIALS (PHASE II)**

? COMMON APPROACH TO ADDRESSING SAFETY IN CLINICAL TRIALS USING CD20/CD19 CARs IN HEMATOLOGIC MALIGNANCIES

- DOSE ESCALATION (BY COHORT FOR SINGLE INFUSION, INTRAPATIENT FOR MULTIPLE DOSING)
- DEPLETION OF CIRCULATING NORMAL B CELLS PRIOR TO AT (RITUXIMAB)
- DESIGN TRIALS TO TREAT WHEN PATIENTS HAVE MINIMAL/LIMITED DISEASE BURDEN