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A Personalized Approach to Immune Therapies for Cancer: One drug, one patient

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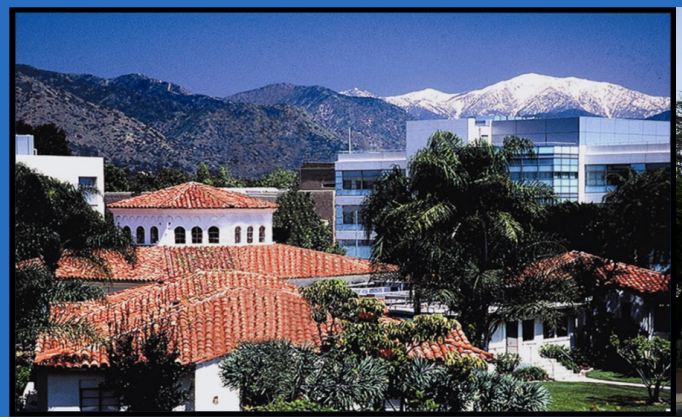
Dr. Michael Friedman Professor in Translational Medicine



Disclosure Information

Larry W. Kwak, MD PhD

I have the following financial relationships to disclose:

- Pepromene Bio *(founder equity, consultant, research funding)*
- InnoLifes *(founder equity, consultant, research funding)*

- *Theratest, Inc. (equity)*
- *SELLAS Life Sciences Group (consultant)*
- *Enzychem LifeSciences (consultant)*


A sobering view of our energy future p. 1330
Maternal care alters newborn mouse genomes pp. 1330 & 1387
Wet route to phosphorus fine chemicals pp. 1333 & 1383
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Immunotherapy strategies

- Monoclonal antibodies (mAbs) directed against tumor targets*
- Checkpoint blockade with specific mAb*
- Cancer vaccines *
- Adoptive cell therapies
  [chimeric antigen receptor transduced (CAR) *T* cells] *

* FDA approved products

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JOURNAL OF CLINICAL ONCOLOGY

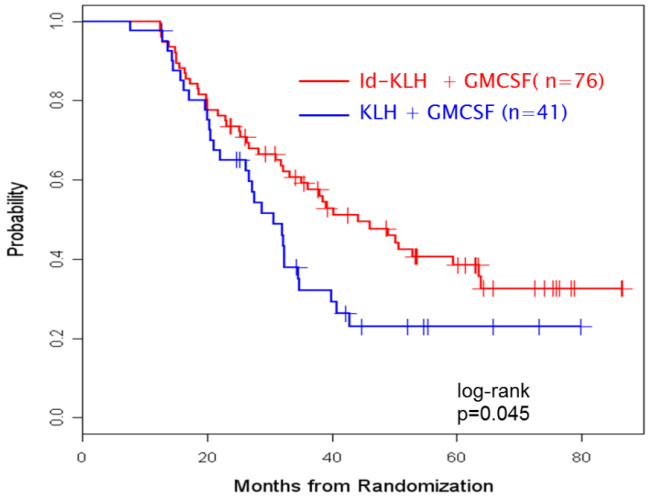
ORIGINAL REPORT

Stephen J. Schuster, Elise A. Chong, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; Sattva S. Neelapu, Donald A. Berry, Larry W. Kwak, The University of Texas MD Anderson Cancer Center, Houston, TX; Barry L. Gause, John E. Janik, Elaine S. Jaffe, Craig W. Reynolds, Center for Cancer Research, National Cancer Institute, National Institutes of

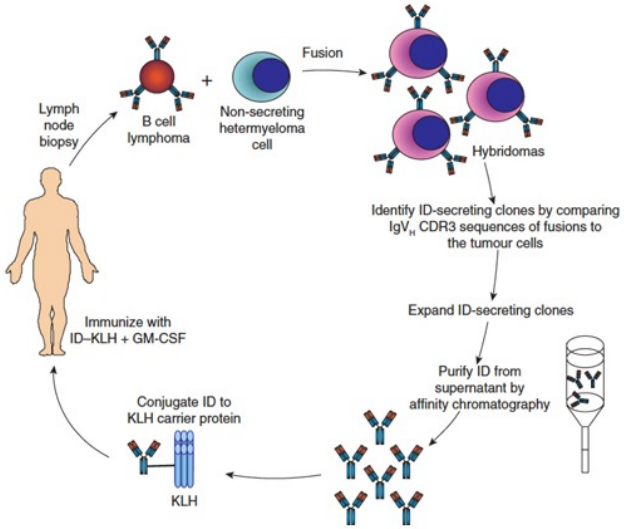
Vaccination With Patient-Specific Tumor-Derived Antigen in First Remission Improves Disease-Free Survival in Follicular Lymphoma

Stephen J. Schuster, Sattva S. Neelapu, Barry L. Gause, John E. Janik, Franco M. Muggia, Jon P. Gockerman, Jane N. Winter, Christopher R. Flowers, Daniel A. Nikcevich, Eduardo M. Sotomayor, Dean S. McGaughey, Elaine S. Jaffe, Elise A. Chong, Craig W. Reynolds, Donald A. Berry, Carlos F. Santos, Mihaela A. Popa, Amy M. McCord, and Larry W. Kwak

Kaplan-Meier disease-free survival



A personalized therapeutic



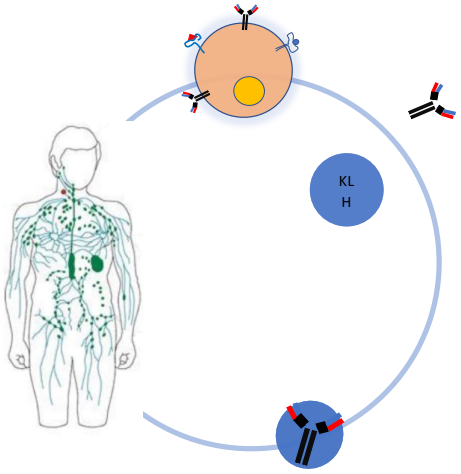
Challenges associated with personalized manufacturing

- Potential product variability
- Manufacturing may delay timely treatment
- Increased cost of goods
- No economy of scale

This vaccine therapy was ahead of its time

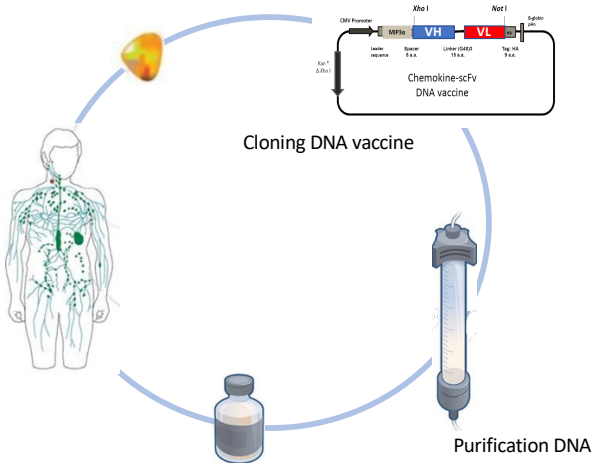
2nd generation DNA Vaccine Strategy

Original
Protein vaccine
6 months



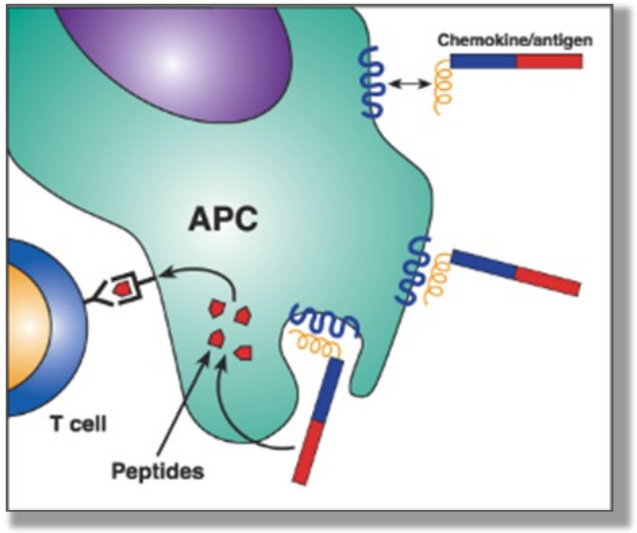
- **Expensive**
- **Time-consuming**

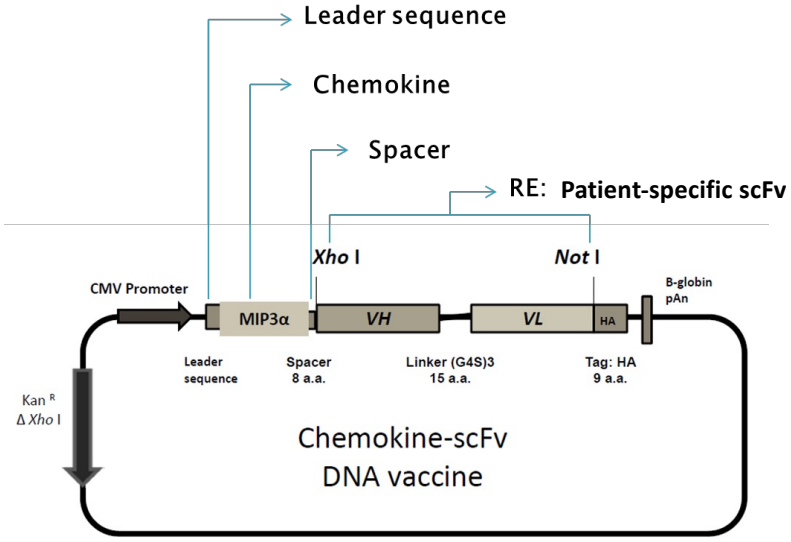
New
DNA vaccine
1.5 months



- **Targeted delivery**

2nd generation vaccines: targeting surface receptors on antigen presenting cells (APC) with genetic fusions





- Biragyn et al. [Kwak] *Nat Biotech* 1999
- Biragyn et al. [Kwak] *J Immunol* 2001
- Biragyn et al. [Kwak] *Science* 2002
- Ruffini et al. [Kwak] *J Leukoc Biol* 2004
- Biragyn et al. [Kwak] *Blood* 2004
- Qin et al. [Kwak] *Blood* 2009

Personalized Idiotype DNA vaccine for asymptomatic Lymphoplasmacytic lymphoma (LPL)

Current standard of care:

- No survival advantage to starting treatment early
- Follow asymptomatic patients on a program of observation.

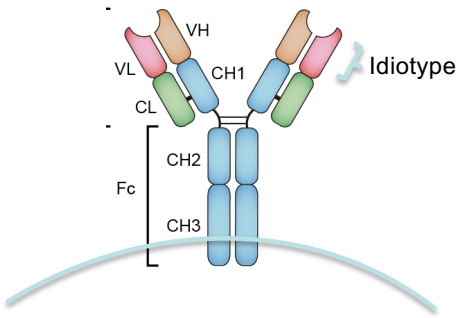
Potential objectives of early intervention:

- Lengthen interval before systemic therapies (e.g. chemotherapy) are required to maintain disease control.
- Without inducing cross resistance to available therapies

Appeal of a vaccine approach

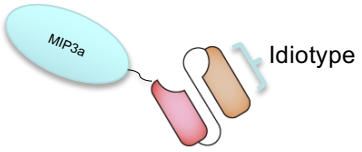
- Likely well tolerated
- Asymptomatic LPL patients are treatment-naïve

Structure of BCR receptor



B cell / Lymphoma cell

Structure of DNA- encoded Idiotype vaccine



scFv

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MD Anderson Cancer Center
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Personalized Idiotype DNA vaccine for asymptomatic LPL

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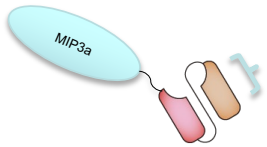
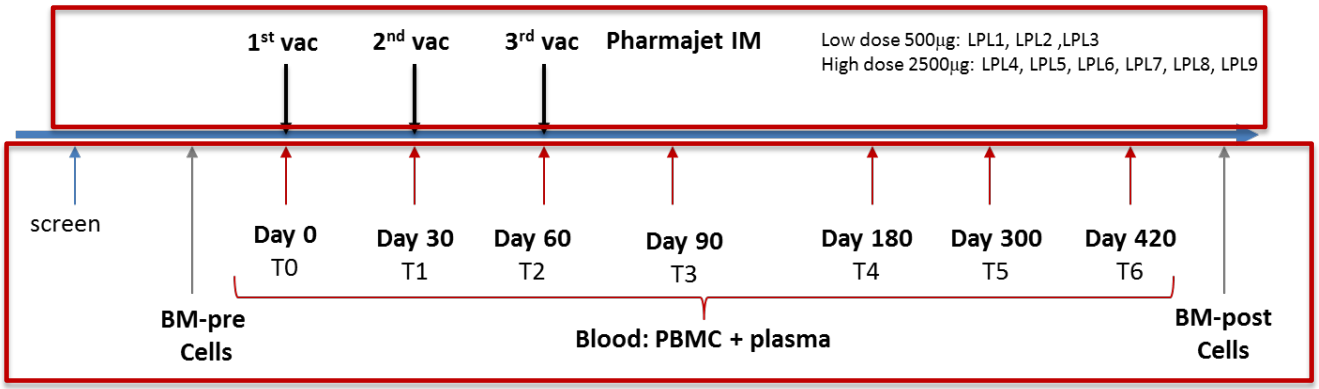
Approach

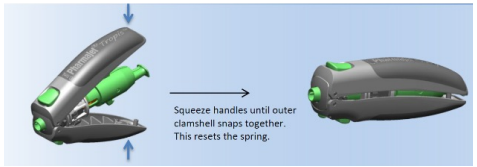
- Phase I clinical trial: 9 patients
- 3 intradermal injections of plasmid DNA vaccine 30 days apart (prime + boost)
- 2 doses of vaccine: low (500µg) and high (2500µg)
- Samples for collection: BM pre and post, PBMC + plasma at different time points

DNA-encoded Idiotype vaccine



Timeline of clinical trial





Principal Investigator: Sheeba Thomas, MD

Thomas ST et al. [Kwak] *BMC Cancer* 2018 Feb 13;18(1):187
doi: 10.1186/s12885-018-4094-2

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Response to Therapy

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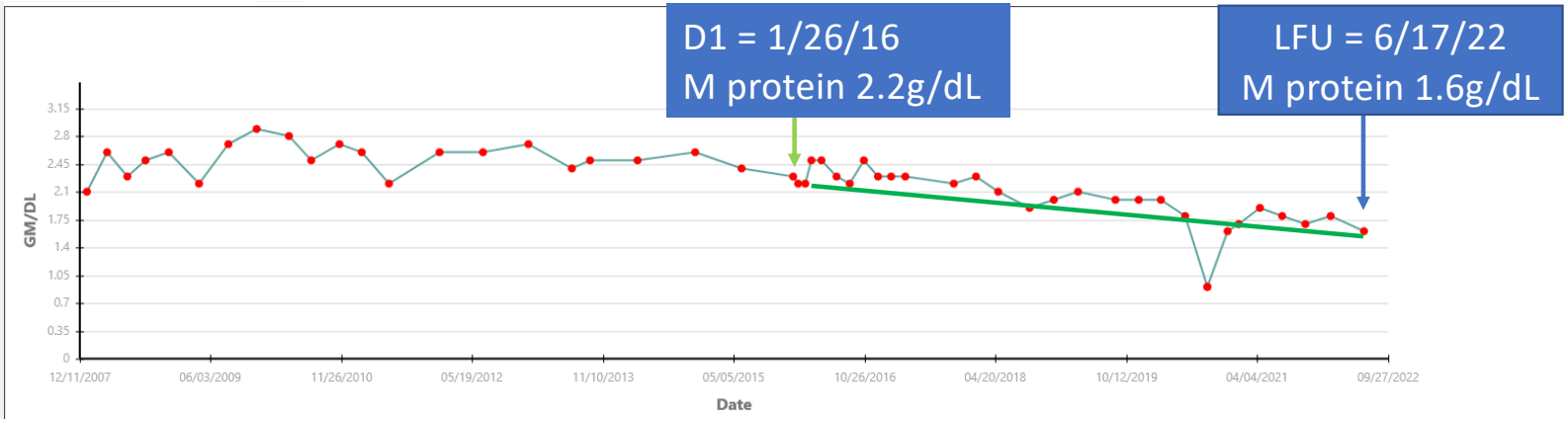
Dose Level	500µg (n=3)	2500µg (n=6)
Median Length of Follow Up after 1st vaccination (mos.)	78 (77-80)	53 (9-69)
Best Response	MR (1) SD (2)	SD (6)
Response at time of post vaccine bone marrow sampling	SD (3)	SD (5)*
Median Duration of SD (mos.)	78 (77-80)	30 (8-69)
Median Time to Symptomatic LPL/WM (mos.)	NR	27 (8-32); n=4

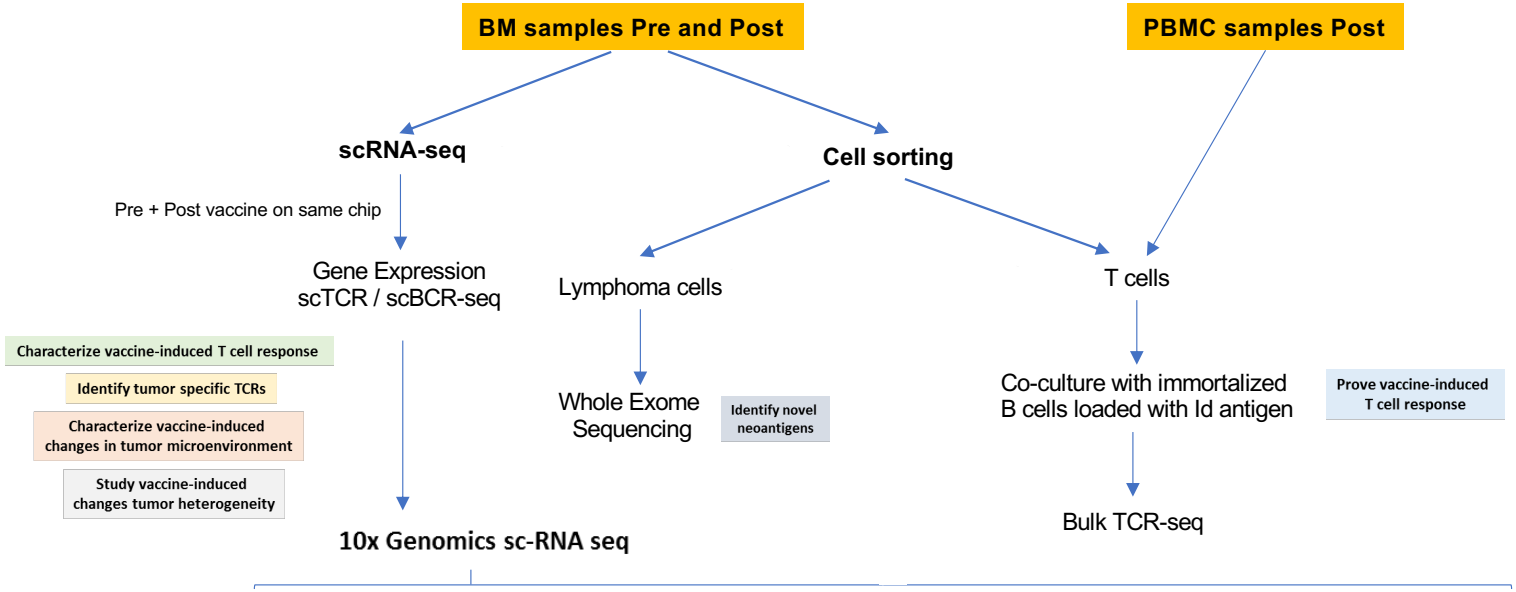
- No dose-limiting toxicity was observed and no serious adverse events reported

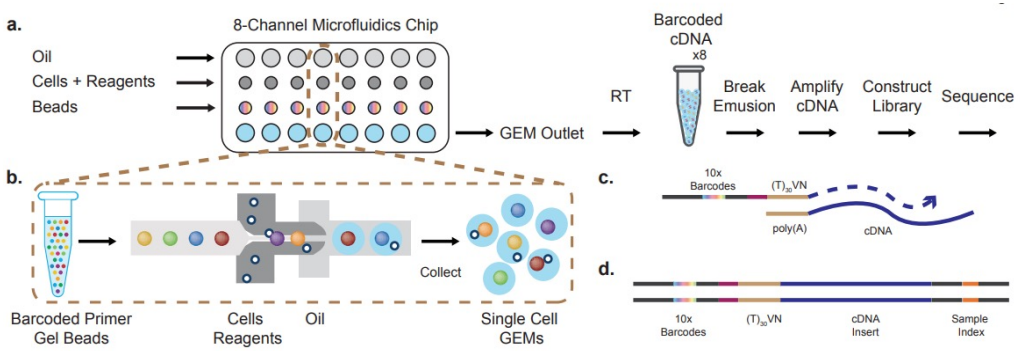
* 1 patient did not follow up for post vaccination bone marrow sampling

Patient 3 (LPL-003)
Dose = 500µg

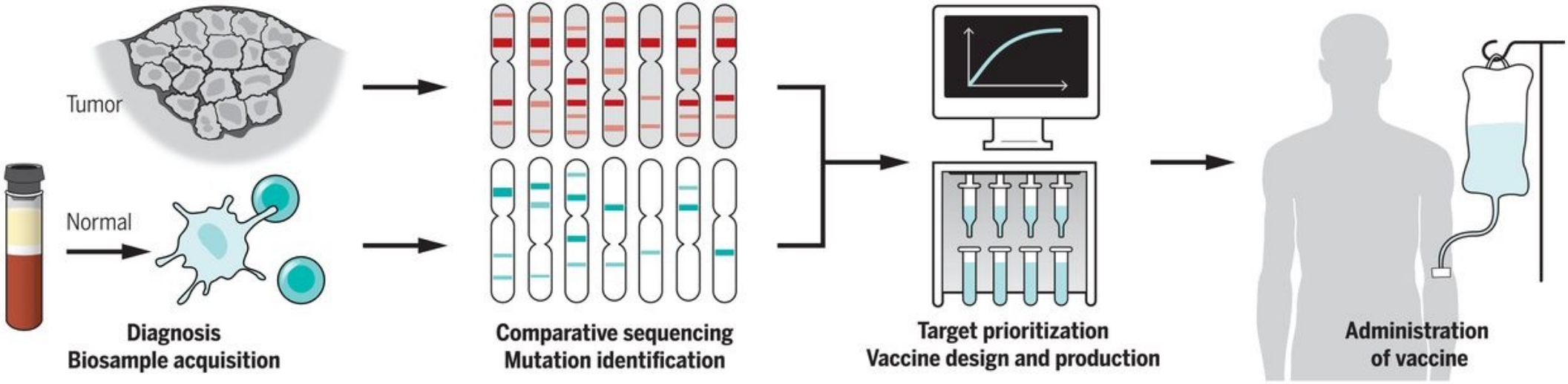


Workflow: Processing of Patient Samples





Development of *personalized neo-antigen* cancer vaccines

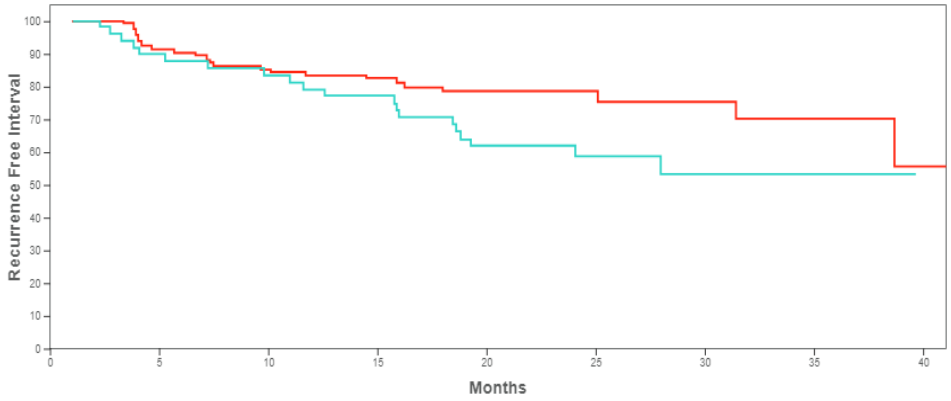


Mutation discovery/Neo-epitope identification

Adapted from Sahin et al., *Science* 359, 1355-1360 (2018)

An Efficacy Study of Adjuvant Treatment with the Personalized Cancer Vaccine mRNA-4157 and Pembrolizumab in Participants with High-Risk Melanoma (KEYNOTE-942)

Recurrence-free survival



Curves	N
mRNA-4157 (V940) + Pembrolizumab	107
Pembrolizumab	50

	HR (95% CI)	P-value
mRNA-4157 (V940) + Pembrolizumab vs Pembrolizumab	0.56 (0.31 - 1.02)	0.0266

AACR 2023 (14-03-2023)

https://www.abstractsonline.com/pp8/#!/10828/presentation/10243

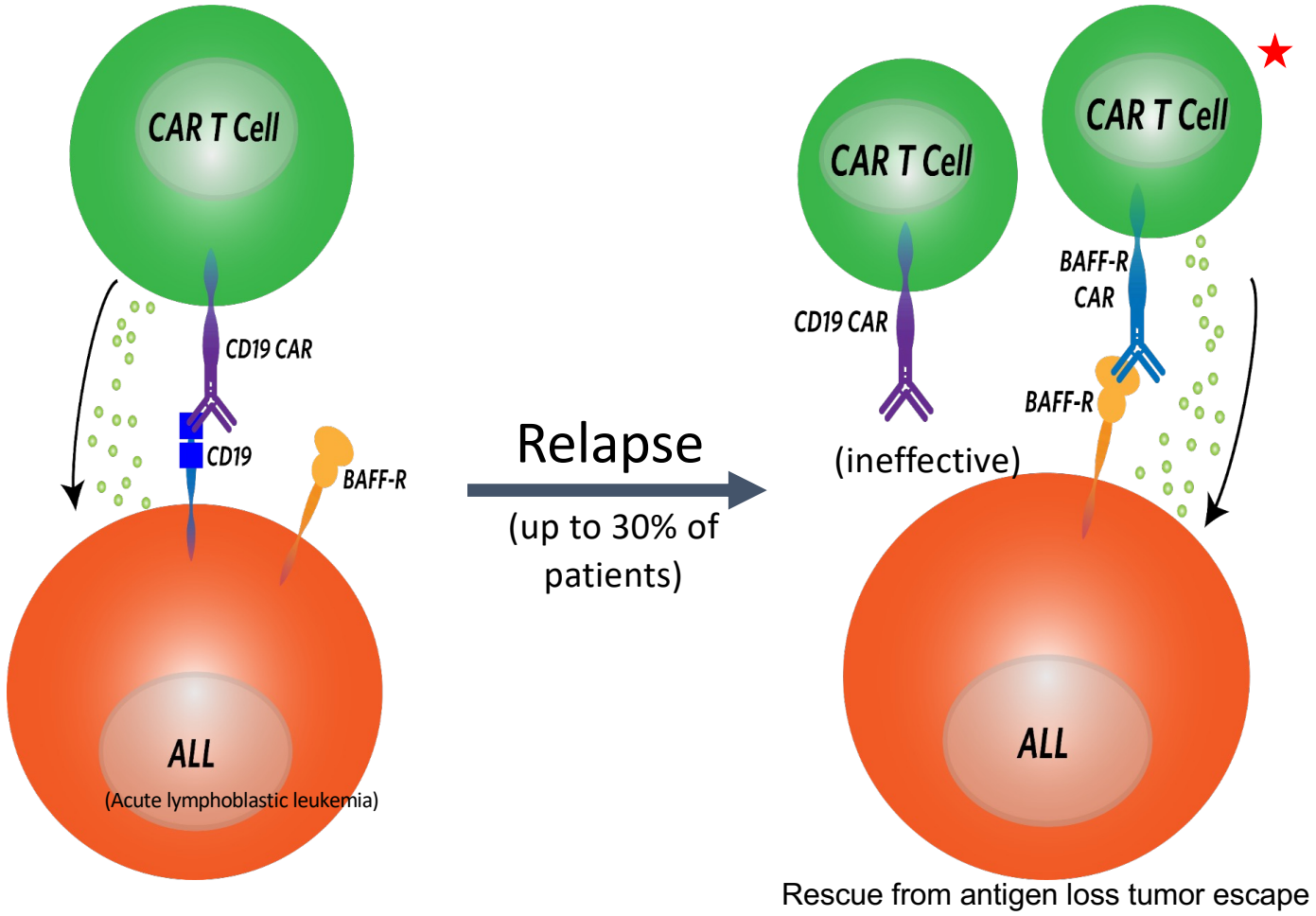
Kaplan-Meier Curve

Redrawn from digitized graphs
For more information on subscription to LARVOL CLIN, contact clin@larvol.com

Conclusions: A comeback for cancer vaccines

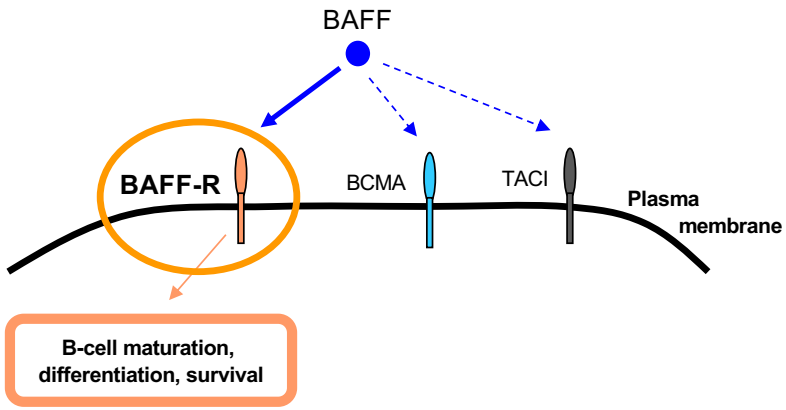
- At least 3 positive, controlled, randomized cancer vaccine clinical trials demonstrate that such therapeutic vaccines can work
  - Sipuleucel-T (FDA approved, prostate cancer) *NEJM* 2010
  - gp100 peptide (melanoma) *NEJM* 2010
  - B-cell idiotype protein (lymphoma) *J Clin Oncol* 2011
- Cancer vaccines appear to be safe
- Future cancer vaccines will be based on personalized neoantigens
- Future strategies will combine cancer vaccines with reversal of immune suppression by T-cell and/or myeloid checkpoint blockade

Urgent development of CAR T-cell therapy against novel targets



BAFF Receptor: A target for mAb or CAR T therapies against B-cell malignancies

BAFF (B-cell activating factor), a cytokine expressed by B cells for their proliferation and differentiation



BAFF-R Expressed on Plasma membrane of B cells	
Immature	++
Mature	+++
Activated	++++
Memory	++++
Plasma	+/-

BAFF-R expression by lymphoproliferative disorders

Lymphoproliferative disorder	*Total BAFF-R–positive (%)*
Pre–B lymphoblastic leukemia/lymphoma	0/8 (0)
Hairy cell leukemia	10/10 (100)
Chronic lymphocytic leukemia	21/21 (100)
Mantle cell lymphoma	7/7 (100)
Follicular lymphoma	13/16 (81)
Diffuse large B-cell lymphoma	14/18 (78)
Marginal zone lymphoma	10/11 (91)

Schneider, P., *et al., The Journal of experimental medicine* (1999).
Thompson, J. S., *et al. Science* (2001).
Rodig, S. J., *et al.*, *Human Pathology* (2005).

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Published OnlineFirst November 27, 2017; DOI: 10.1158/1078-0432.CCR-17-1193

Cancer Therapy: Preclinical

Clinical Cancer Research

Novel BAFF-Receptor Antibody to Natively Folded Recombinant Protein Eliminates Drug-Resistant Human B-cell Malignancies *In Vivo*

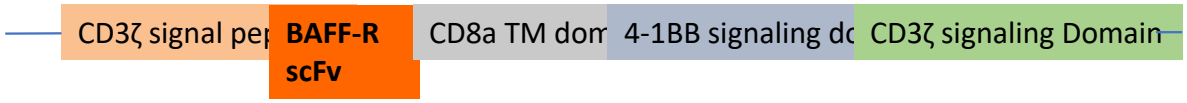
Hong Qin[1], Guowei Wei[1], Ippei Sakamaki[2], Zhenyuan Dong[1], Wesley A. Cheng[1], D. Lynne Smith[1], Feng Wen[1,3], Han Sun[1], Kunhwa Kim[4], Soungchul Cha[4], Laura Bover[5], Sattva S. Neelapu[4], and Larry W. Kwak[1]

- Previous attempts by several pharmaceutical companies yielded mAb which did not kill B-cell tumors
- These new antibodies target and deplete various B-cell malignancies by ADCC *in vitro* and *in vivo.*
- Humanization and translational development is ongoing

Anti-BAFF-R CAR

CAR Construct

Schematic Structure



Humanized BAFF-R scFv

2nd generation CAR containing 4-1BB and TCR signaling domains

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

CAR T cells targeting BAFF-R can overcome CD19 antigen loss in B cell malignancies

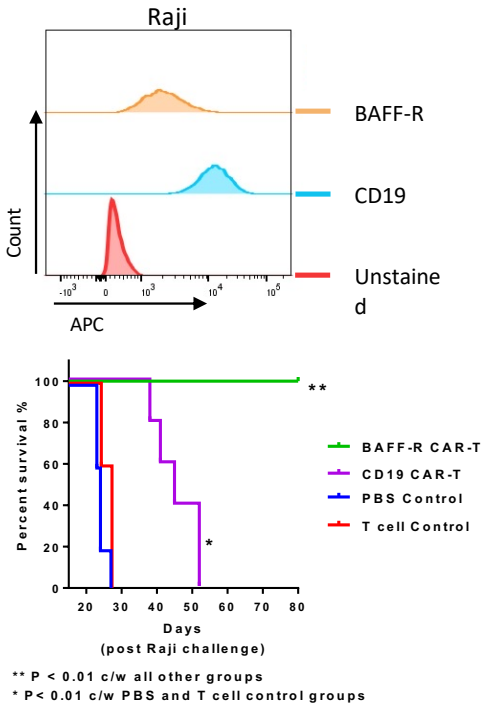
Hong Qin[1]*, Zhenyuan Dong[1]*, Xiuli Wang[2], Wesley A. Cheng[1], Feng Wen[1,3], Weili Xue[1,4], Han Sun[1], Miriam Walter[2], Guowei Wei[1], D. Lynne Smith[1], Xiuhua Sun[5], Fan Fei[6], Jianming Xie[6], Theano I. Panagopoulou[7], Chun-Wei Chen[7], Joo Y. Song[8], Ibrahim Aldoss[9], Clarisse Kayembe[10], Luisa Sarno[10], Markus Müschen[7], Giorgio G. Inghirami[10], Stephen J. Forman[2], Larry W. Kwak[1†]

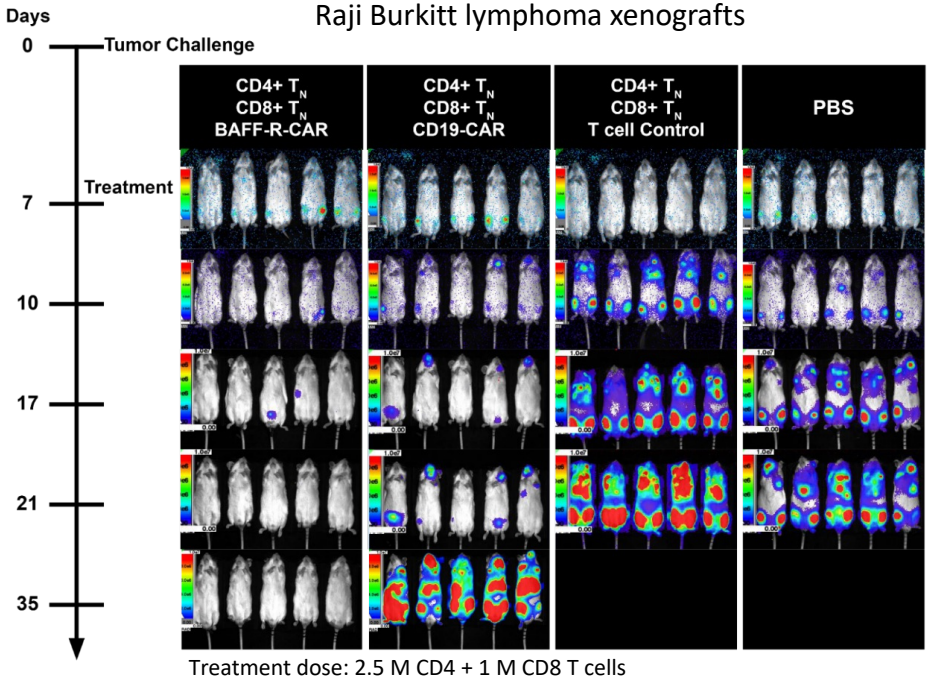
Sep 25, 2019, doi: 10.1126/scitranslmed.aaw9414

- CD19-negative primary ALL tumors (five paired samples) retained BAFF-R expression and activated BAFF-R, but not CD19-CAR T cells (in vitro)

- BAFF-R CAR T cells eradicated a CD19-negative B-ALL PDX model (in vivo)

BAFF-R CAR-T cells can outperform CD19 CAR-T cells





Key differentiating features of BAFF-R as a target

- BAFF-R antigen loss by tumor cells is unlikely, because BAFF-R signaling, which activates NF-kB, promotes normal B-cell proliferation and appears to be required for survival.

  - Mouse strains expressing a mutant BAFF-R exhibited decreased B-cell life spans and a dramatically reduced peripheral B-cell compartment (*Eur J Immunol* 21:1123, 1991)

  - BAFF-R null mice exhibited greatly reduced B-cell numbers and are essentially devoid of marginal zone B cells (*J Immunol* 173:2245, 2004)

- Unlike CD19 CAR T-cells, BAFFR-CAR T cells may produce less severe B-cell aplasia because BAFFR are not expressed by early-stage B-cells.

- The BAFF-R target is expressed on all subtypes of B-cell non-Hodgkin's lymphomas.

- Head-to-head comparisons against CD19 CAR T cells in preclinical models suggested superior efficacy with BAFFR CAR T cells.

A Phase 1 (First in human) Study Evaluating BAFFR-targeting CAR T cells for Patients with Relapsed or Refractory B-NHL (PMB-102)

Study Detail	
Population/Indication(s):	Adult patients with Relapsed/refractory (r/r) mantle cell lymphoma (MCL)
Phase:	1
Sample Size:	18 evaluable participants
Estimated Accrual Duration:	2 years
Estimated Study Duration	3 years
Participant Duration:	1 year short term follow-up & Up to 15 years long term follow-up
Participating Sites	City of Hope Duarte, CA
Sponsor:	Pepromene Bio, Inc.

Objectives

Primary Objective(s)

Safety and MTD/RP2D

Secondary Objective(s)

- Clinical efficacy including complete response (CR)
- Level of residual disease
- Duration of B cell aplasia
- Progression-free survival (PFS) and overall survival (OS)

Cell Therapy Production Center, City of Hope

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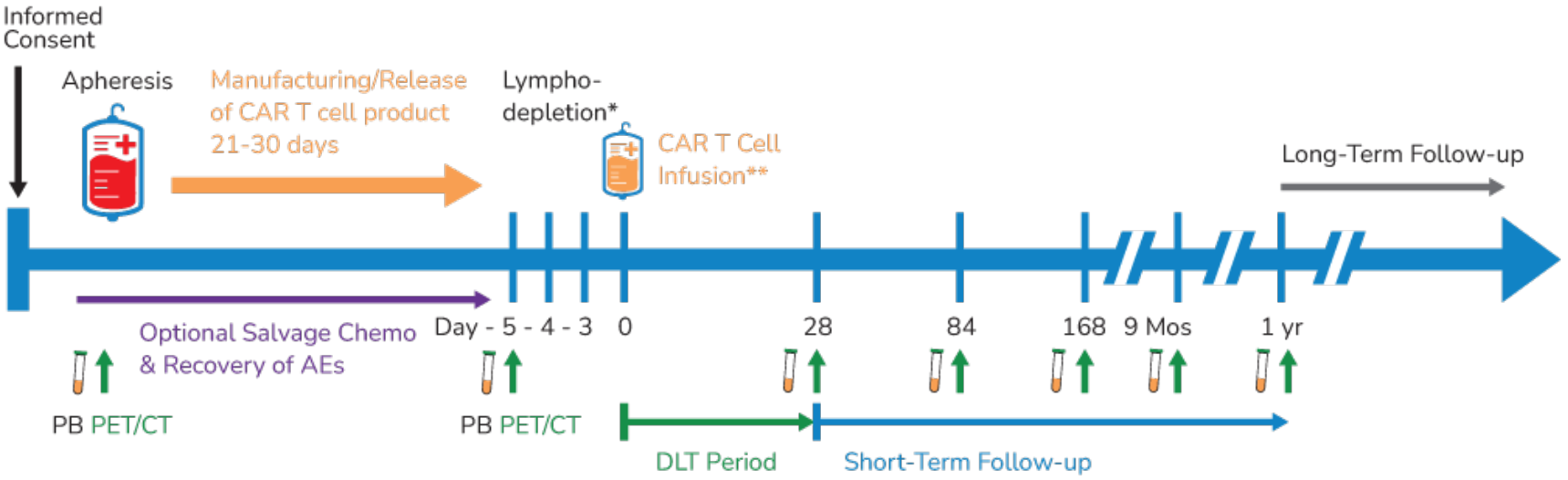
Study schema

Principal Investigators: Elizabeth Budde, MD (NHL)
Ibrahim Aldoss, MD (B-ALL)



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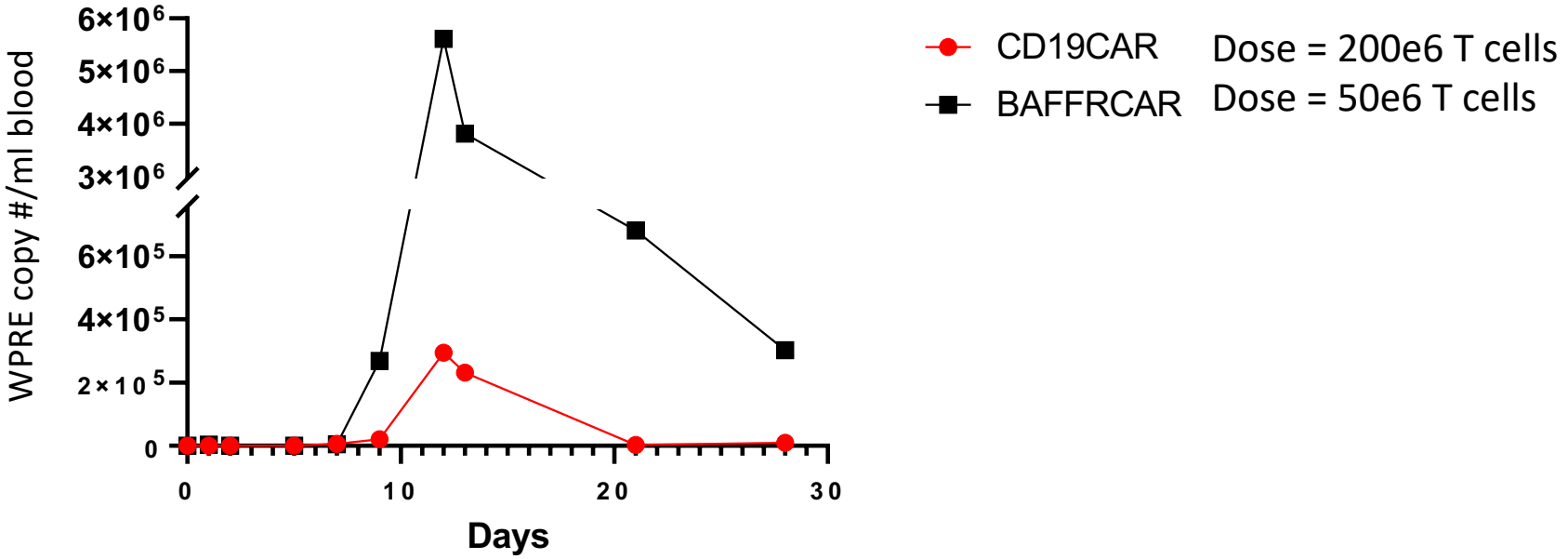
PMB-102 B-NHL Clinical Trial Update

B-NHL trial

- **PMB-102-0001**:
  - 56-y MCL patient refractory to several prior lines of treatment (Chemoimmunotherapy, BTK inhibitor, Venetoclax and CD19-CAR T therapy)
  - Received PMB-CT01 treatment in November 2022
  - Good safety profile (max CRS grade 1, no neurotoxicity)
  - Complete Response at 1 month, 3-month disease assessment (CR with no BM involvement and negative MRD)

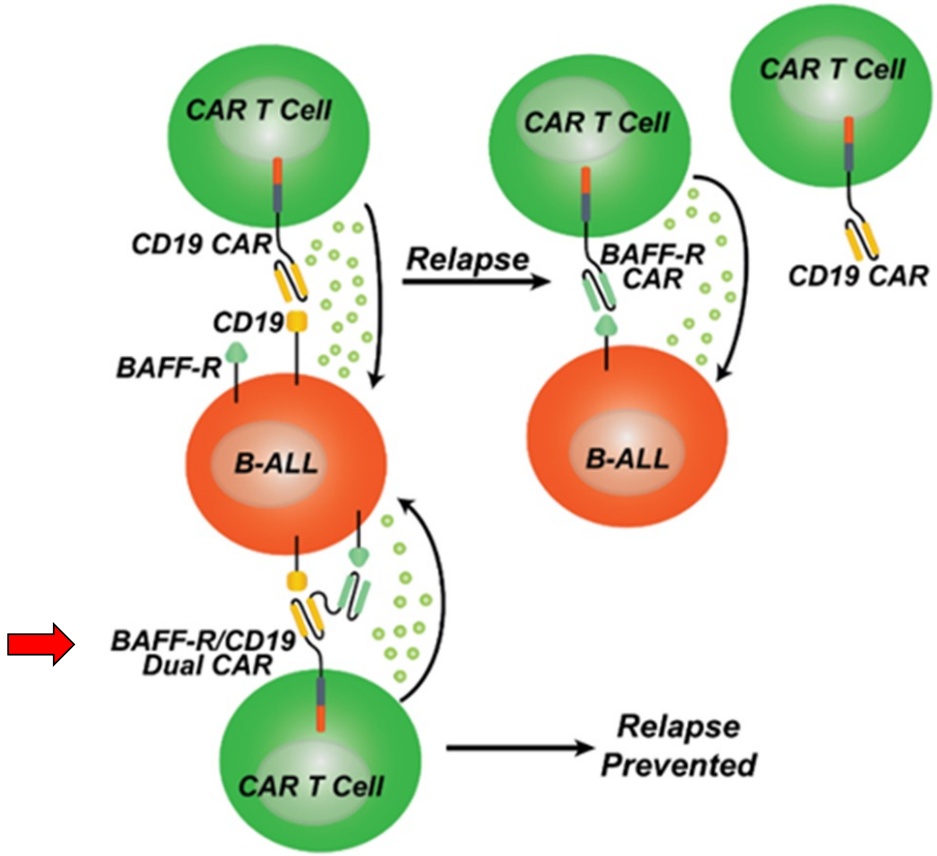
- **PMB-102-0002**:
  - 75-y MCL patient relapsed to several prior lines of treatment (Chemoimmunotherapies, BTK inhibitor, Venetoclax, Copanlisib, investigational drugs and CD19 CAR T)
  - Received PMB-CT01 treatment in March 2023
  - Good safety profile (max CRS grade 1, neurotoxicity grade 1)
  - Complete Response at 1 month (CR with no BM involvement and negative MRD)

CD19- vs. BAFF-R- CAR T cell expansion in a single patient



- Woodchuck Hepatitis virus post-transcriptional regulatory element (WPRE) used in both CAR constructs
- Same clinical-grade lentiviral vectors/manufacturing platforms

Future direction: BAFF-R/CD19 dual CAR T cells to prevent relapse



Wang et al. *Leukemia*. 2022 Apr;36(4):1015-1024

Kwak laboratory– Past trainees
(NCI, MD Anderson Cancer Center, City of Hope)

Fellow	Current institution
Sattva Neelapu, MD	MD Anderson
Arya Biragyn, PhD	Natl. Inst. on Aging
M. Bendandi, MD	Univ. Navarra (Spain)
P. Ruffini, MD	Univ. Milan (Italy)
L. Sternas, MD, PhD	Celgene Corp.
Miriam Foglietta, MD	Univ. of Cuneo (Italy)
S. Weeks, PhD	U.S. Army medical research
Sung-Bae Kim, MD, PhD	Asan Medical Center
Soung-Chul Cha, PhD	City of Hope
J. Kim, PhD	LG Chem
H. Goto, MD	Univ. Tokushima (Japan)
C. Kobrin, PhD	NCI research contractor
R. Hornung, PhD	NCI research contractor
M. Dar, MD	Medimmune, Inc.
Ippei Sakamaki, MD , PhD	Fukui Medical University
Seung-Tae Lee, MD	Univ. of Maryland
Keon Uk Park, MD	Keimyung University
Hong Qin, PhD	Mayo Clinic
Sung Doo Kim, MD (*dec.*)	Asan Medical Center
Kun Hwa Kim, MD	Einstein Medical Center
Zhenyuan Dong, PhD	City of Hope
Zhe Wang, PhD	City of Hope
Szymon Symura, PhD	City of Hope
Tiantian Zhang, PhD	City of Hope
Lin Wang, PhD	City of Hope

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- Leukemia & Lymphoma Society (TRP, SCOR)
- IWMF/LLS Roadmap
- DoD Idea Award