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Translational Development of Novel Immunotherapies for Hematologic Cancers

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Presenter Disclosure Information

Larry W. Kwak, M.D., Ph.D.

The following relationships exist related to this presentation:

Xeme BioPharma, Inc. (founder equity, consultant)
Sellas (consultant)
Celltrion (consultant)
Antigenics/Agenus (equity)

Positive controlled Phase III cancer vaccine clinical trials

- Sipuleucel-T (prostate cancer) *
  NEJM July 2010
- gp100 peptide (melanoma)
  NEJM June 2011
- B-cell idiotype protein (lymphoma)
  J Clin Oncol July 2011

* FDA approved

Personalized vaccines based on individual lymphoma idiotypes

Cancer vaccine strategy

Lymphoma Tumor

Preclinical

• Addition of GM-CSF Adjuvant improves vaccine potency

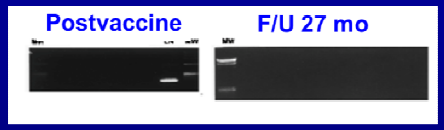
(*Proc Natl Acad Sci* 1996)

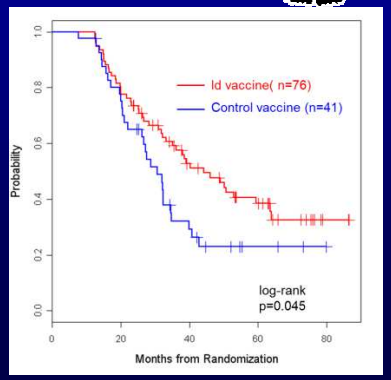
"Idiotype" protein

Phase I/II Clinical Trial

(*Nat Med* 1999):

• Vaccine induces molecular remissions





CD8+

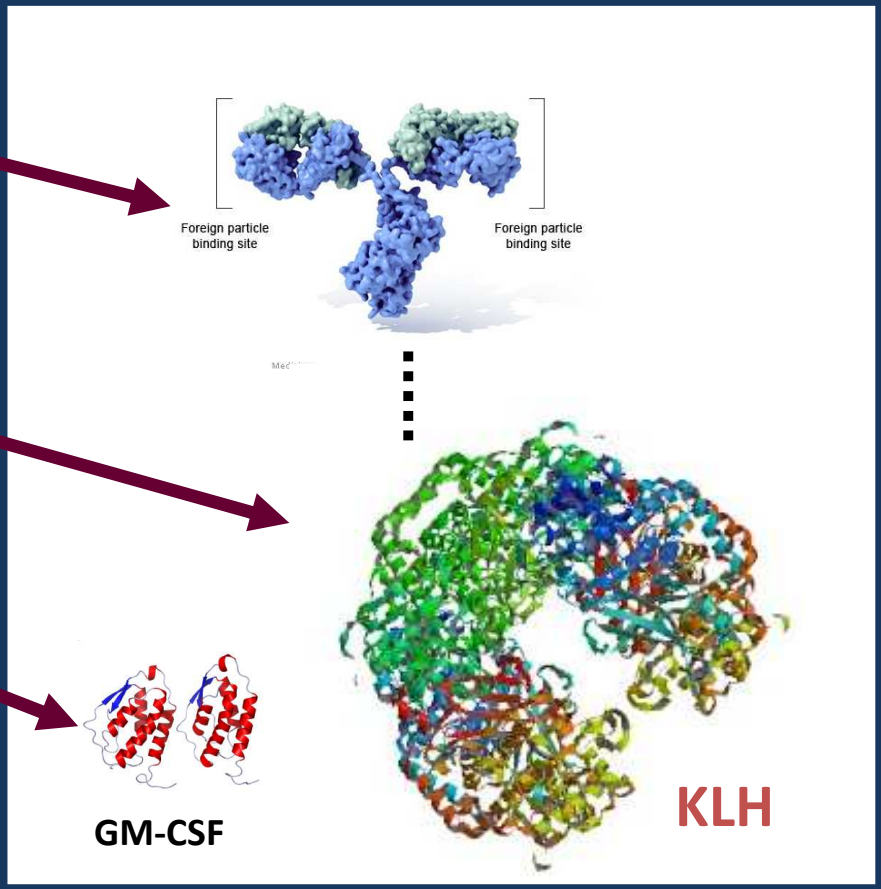
Phase III Controlled Clinical Trial

(*J Clin Oncol* 2011)

• Vaccine prolongs DFS in patients in a chemotherapy-induced remission (n=117, p=0.045)

1st generation vaccine components

- Idiotype of the Ig antigen of a B-cell lymphoma can be used as a tumor-specific immunogen
- Keyhole lympet hemocyanin (KLH) carrier serves as an immune stimulant
- GM-CSF administered concurrently at site of injection as an adjuvant



Conclusions

- As a controlled clinical experiment, this *positive* Phase IIII lymphoma vaccine randomized trial has scientific value for its validation of the cancer vaccine concept
- Long-term clinical experience with the vaccine demonstrates low toxicity, making it ideal for consolidation or maintenance therapy (standard of care)

Future directions

- Regulatory approvals were sought in Europe and Canada (BiovaxID)
- Additional clinical trials combining this vaccine with anti-CD20 mAb (rituximab)-containing chemotherapy regimens in the U.S.

- Making further improvements in the vaccine product (e.g. 2nd generation DNA fusion vaccines)

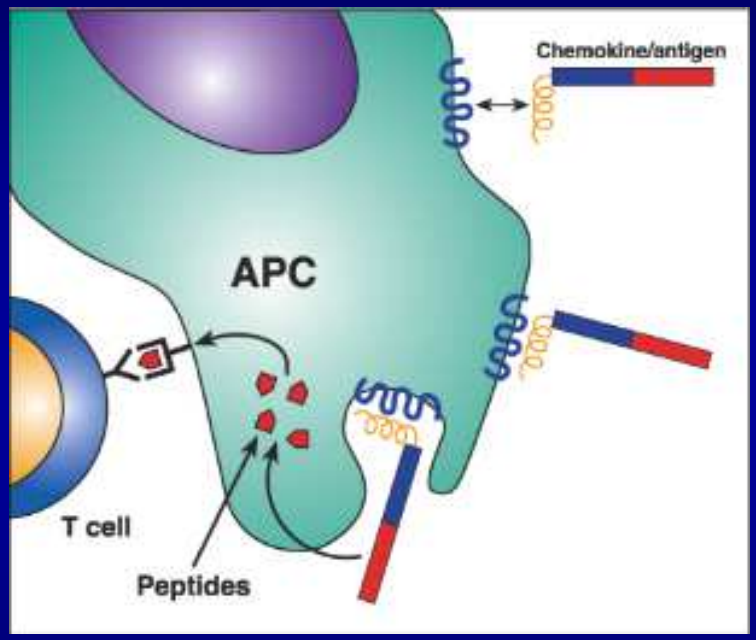
- Combine lymphoma vaccines with strategies to reverse immune suppression (e.g. use vaccines to convert PD-1 Ab non-responders)

2nd generation DNA Vaccine Strategy

- Maintain or improve efficacy

- Reduce Manufacturing Time
  - For Protein Vaccines: 3-6 months
  - For DNA Vaccines: 4-5 weeks

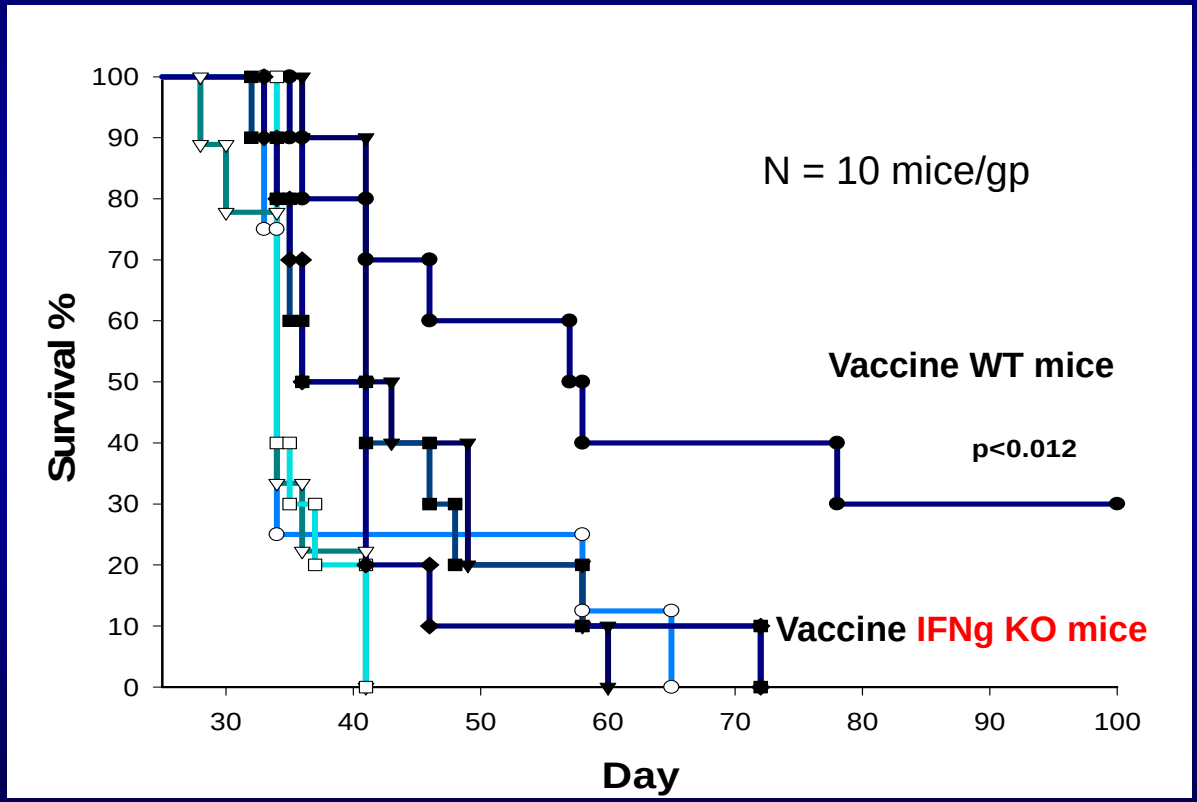
Next generation vaccines: targeting dendritic cells with genetic fusions



Antigen Presenting Cell (APC) Receptor Targeting

Biragyn et al. [Kwak] *Nature Biotech* 1999

Therapeutic anti-lymphoma immunity elicited by chemokine-idiotype fusion DNA vaccines



Biragyn et al. [Kwak] *Science* 2002

Phase I Study of an Active Immunotherapy for Asymptomatic Phase Lymphoplasmacytic Lymphoma with DNA Vaccines Encoding Antigen-Chemokine Fusion (activated March 2015)

- Formulation and Administration:
  - 0.5ml intramuscular injection rotated between thighs

- Dosing Cohorts:
  - Cohort 1: 500 μg
  - Cohort 2: 2500 μg

- Schedule of Administration:

Chemokine-antigen fusion DNA as a general vaccine delivery platform

Preclinical studies: 12 publications

Peer-reviewed grant support:
NCI Lymphoma SPORE,
NCI Myeloma SPORE
DoD, TRP, CPRIT, SCOR,

IND Approval: 01/23/2015
* Preclinical safety studies
* manufacturing SOPs
* Clinical study protocol

Kasturi SP, **Qin H (equal contribution)**, Thomson KS, El-Bereir S, Cha SC, Neelapu SS, Kwak LW, Roy K. Prophylactic anti-tumor effects in a B cell lymphoma model with DNA vaccines delivered on polyethylenimine (PEI) functionalized PLGA microparticles. J Control Release 113(3):261-70, 7/2006.

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Cha SC, **Qin H (equal contribution)**, Kannan S, Rawal S, Watkins LS, Baio FE, Wu W, Ong J, Wei J, Kwak B, Kim S, Popescu MS, Paick DS, Kim K, Luong A, Davis RE, Schroeder HW Jr, Kwak LW, Neelapu SS. Nonstereotyped lymphoma B cell receptors recognize vimentin as a shared autoantigen. J Immunol. 2013 May 1; 190(9): 4887-98.

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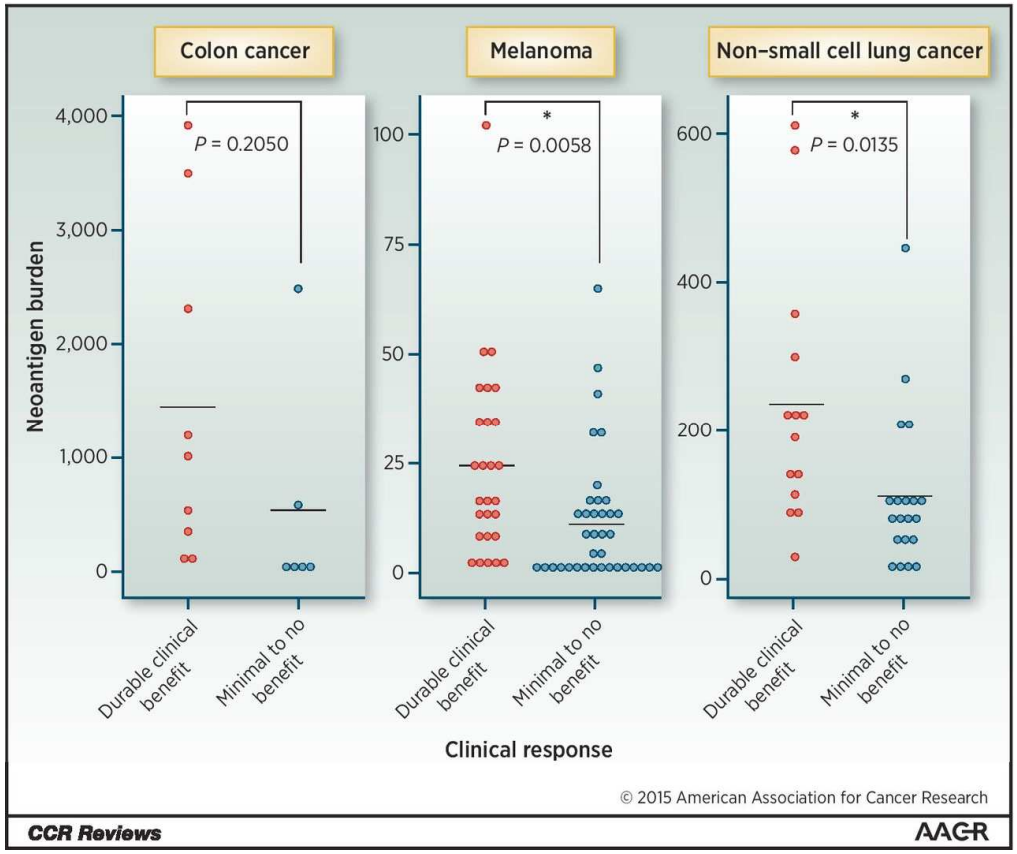
Qin H, Nehete PN, He H, Nehete B, Buchl S, Cha SC, Sastry JK, Kwak LW. Prime-boost vaccination using chemokine-fused gp120 DNA and HIV envelope peptides activates both immediate and long-term memory cellular responses in rhesus macaques. J Biomed Biotechnol. 2010:860160. 5/2010.

Park HJ, **Qin H** ‡ **(corresponding author & equal contribution)**, Cha SC, Sharma R, Chung YS, Neelapu SS, Overwijk WW, Hwu P. Kwak LW. Induction of TLR4-dependent $CD8^+$ T cell Immunity by murine β-defensin2 fusion protein vaccines. Vaccine. 18;29(18):3476-82, 4/2011.

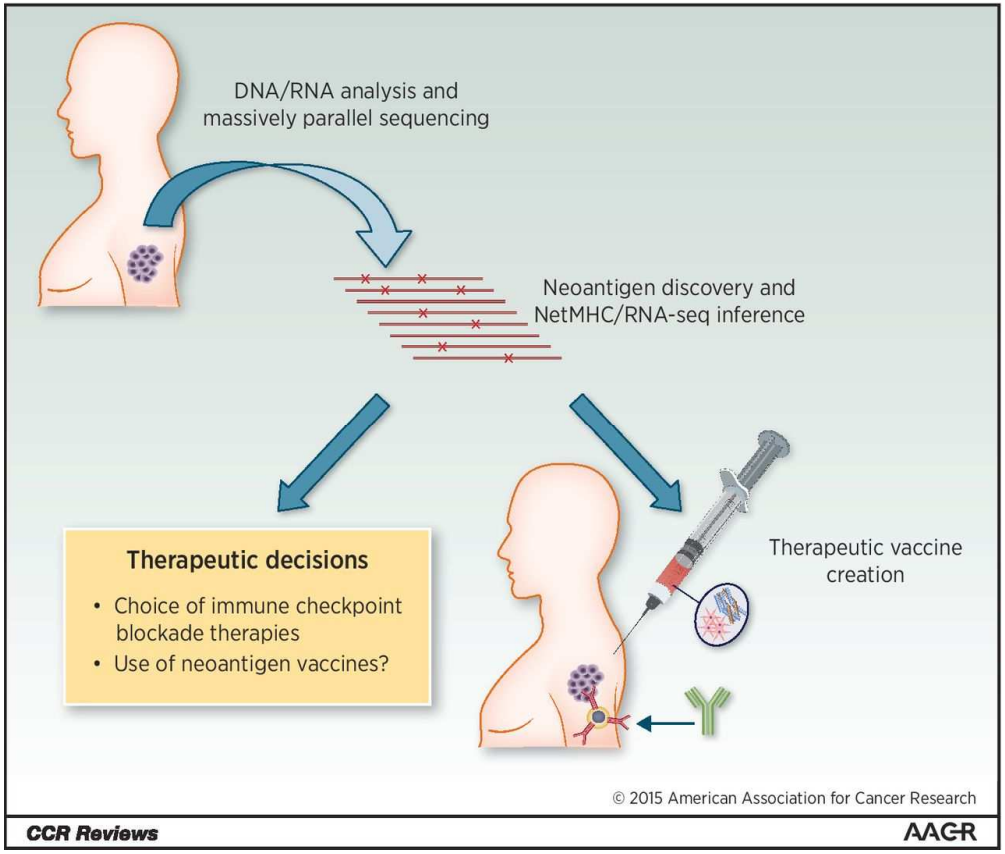
Neoantigen load correlates with clinical benefit to checkpoint blockade immunotherapy.



Alexis Desrichard et al. Clin Cancer Res 2016;22:807-812

Clinical Cancer Research
AACR American Association for Cancer Research

Development of other *personalized* cancer vaccines

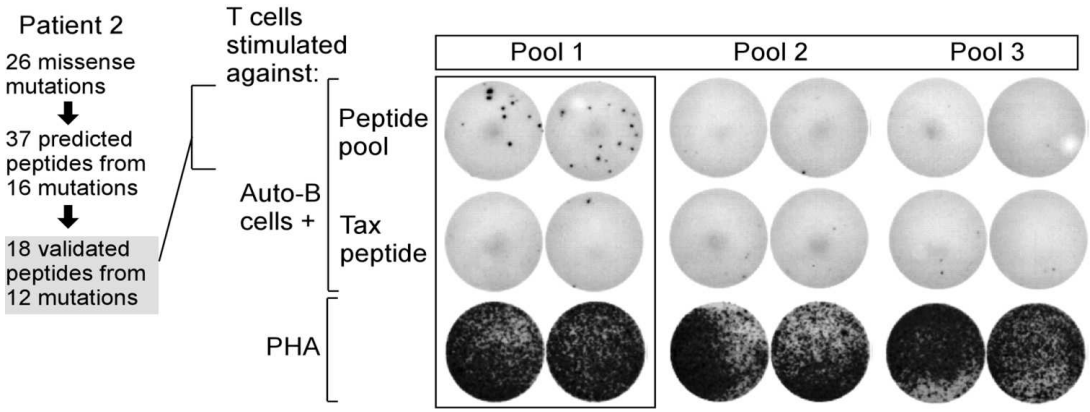


Alexis Desrichard et al. Clin Cancer Res 2016;22:807-812

Identification of personal tumor-specific neoantigen responses after autologous whole CLL vaccines/HSCT

• Ex vivo stimulation of T cells with mutated peptides

•CD8+ T cell responses detected by IFN-γ ELISPOT assay

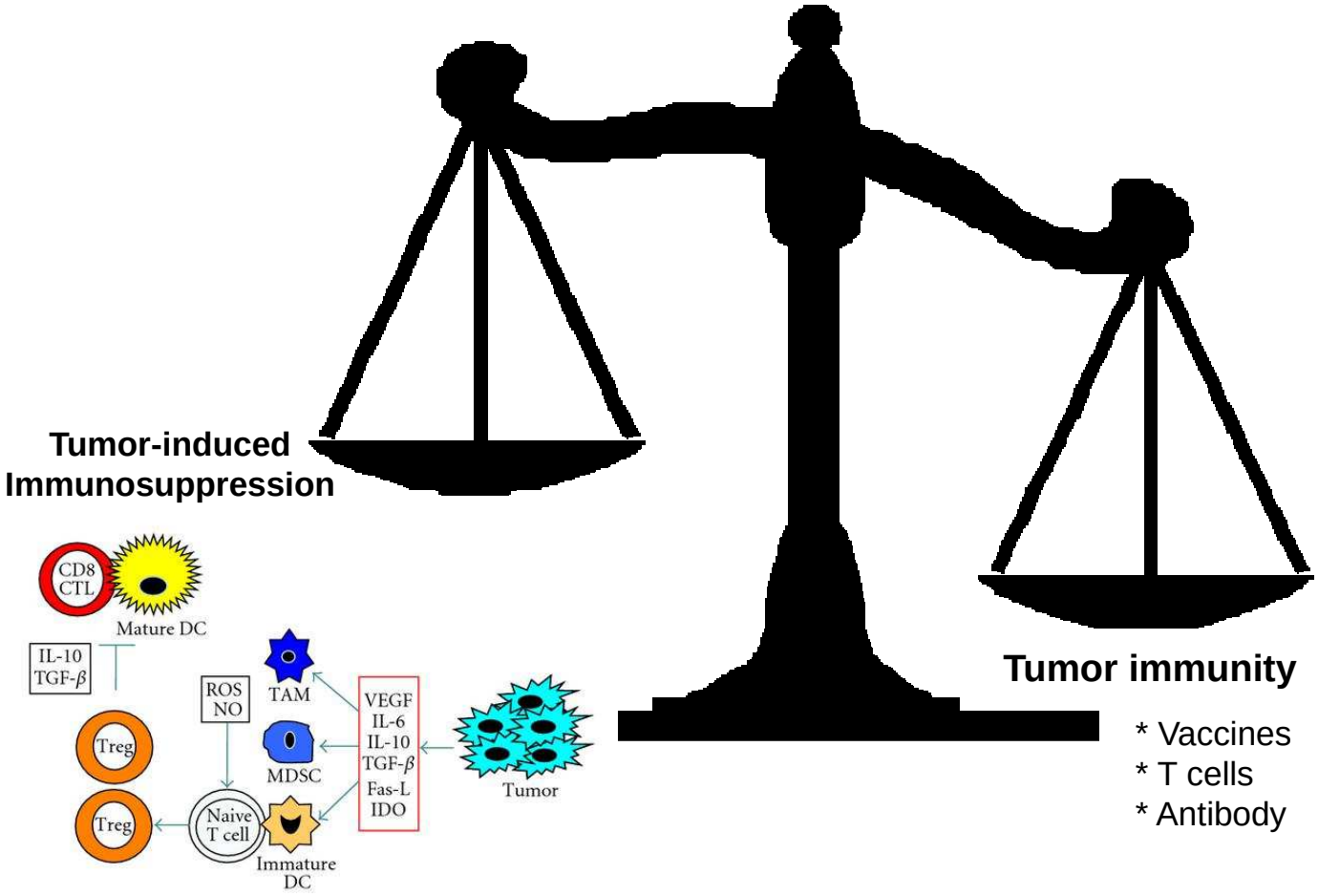


CLL patients in continuous remission following HSCT/GVAX

(Burkhardt [Wu] et al. *JCI* 2013)

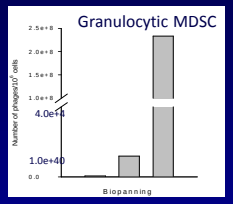
Attribution: C. Wu

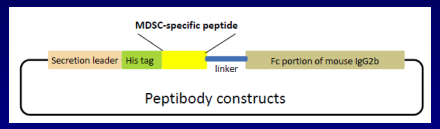
Future direction: Optimizing cancer vaccine therapy with combinations



Discovery of a novel marker for depletion of murine MDSC using a peptide phage display library platform

Hong Qin, Ph.D

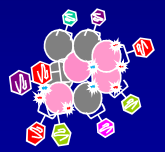




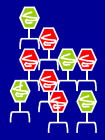
Total splenocytes from EL-4 tumor-bearing mice

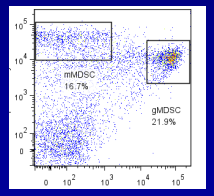
+ CD11B-APC
+ Gr1-FITC

Incubate with Randomized Phage Library

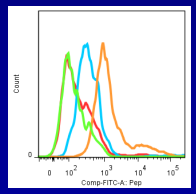


Sorting
Elute phage
Amplify
Enrich





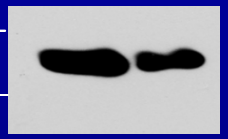
CD11b$^+$Ly6G$^+$Ly6C$^{int/low}$ granulocytic MDSC



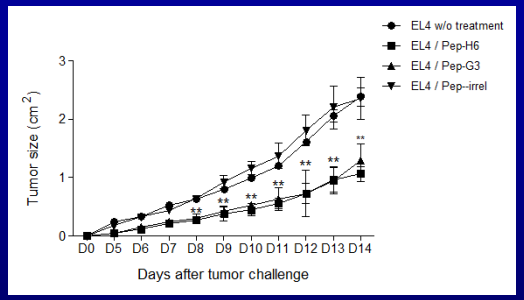
- No Pep
- Pep-irrel-FITC
- Pep-G3-FITC
- Pep-H6-FITC

MDSC lysate

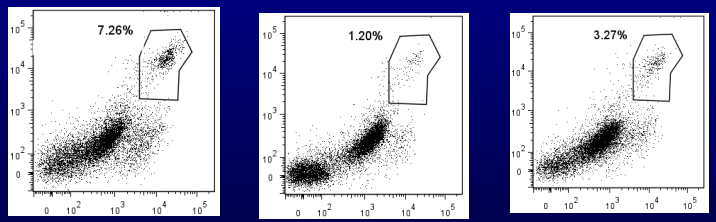
Pep	–	+
Prot A	–	+



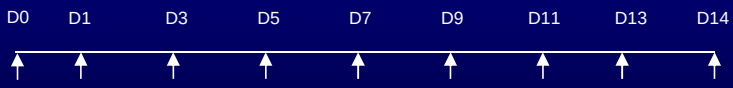
Blot: S100A9 Ab or S100A8 Ab



EG.7 / Pep-irrel | EG.7 / Pep-G3 | EG.7 / Pep-H6



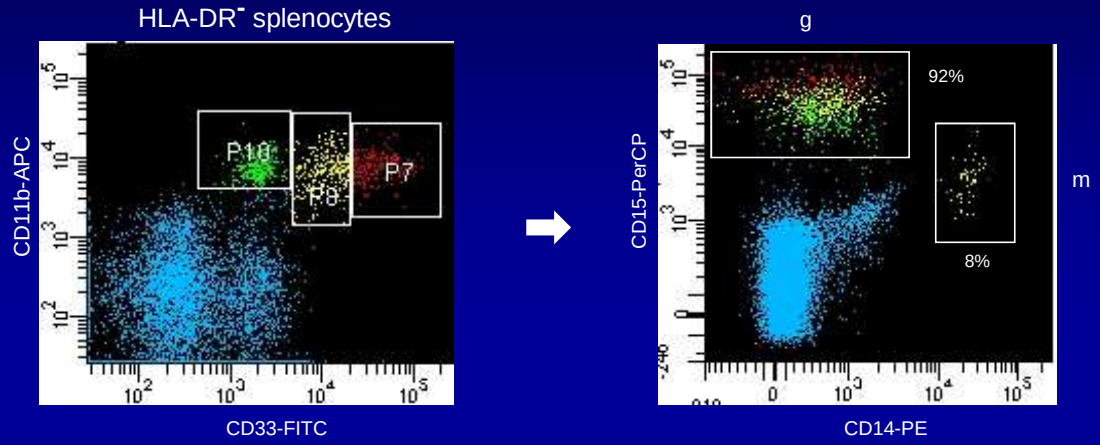
Intra-tumoral MDSC depletion

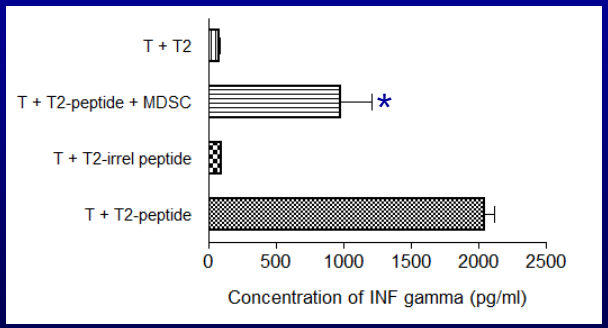


In vivo peptibody: 50 µg/mouse/day

Qin et al. [Kwak] *Nature Med* 20:676-81, 2014

Identification of tumor-infiltrated human MDSC in lymphoma patients





Unpublished

HLA-A2+ lymphoma idiotype-peptide specific T-cell clones were mixed with peptide-pulsed T2 cells, with or without HLA-DR-/CD11b+/CD33+ sorted human MDSC isolated from (A) at a 1:1 ratio. After 24h incubation, culture medium was collected and assayed for INFgamma by ELISA.

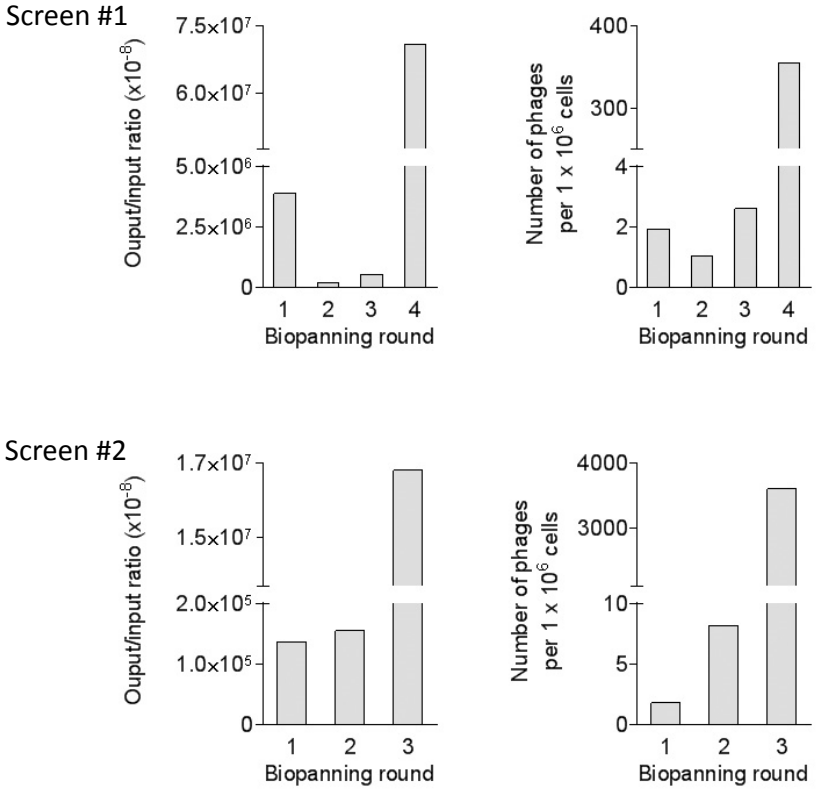


Figure 1: Discovery of antibody binding domains that recognize human tumor-infiltrating MDSC. HLA-DR/CD11b/CD33 labeled splenocytes from a patient with splenic marginal zone lymphoma were incubated with 2×10^{10} human antibody phage display library for 1h at 4°C. HLA/DR^{-}/CD11b^{+}/CD33^{+} MDSC were then sorted and their bound phage was eluted, titered and amplified for the next round of biopanning. Biopanning enrichment was expressed in either "Number of plaques/10^6 cells" (B) or phage "Output/Input ratio" ($\times10^{-8}$).

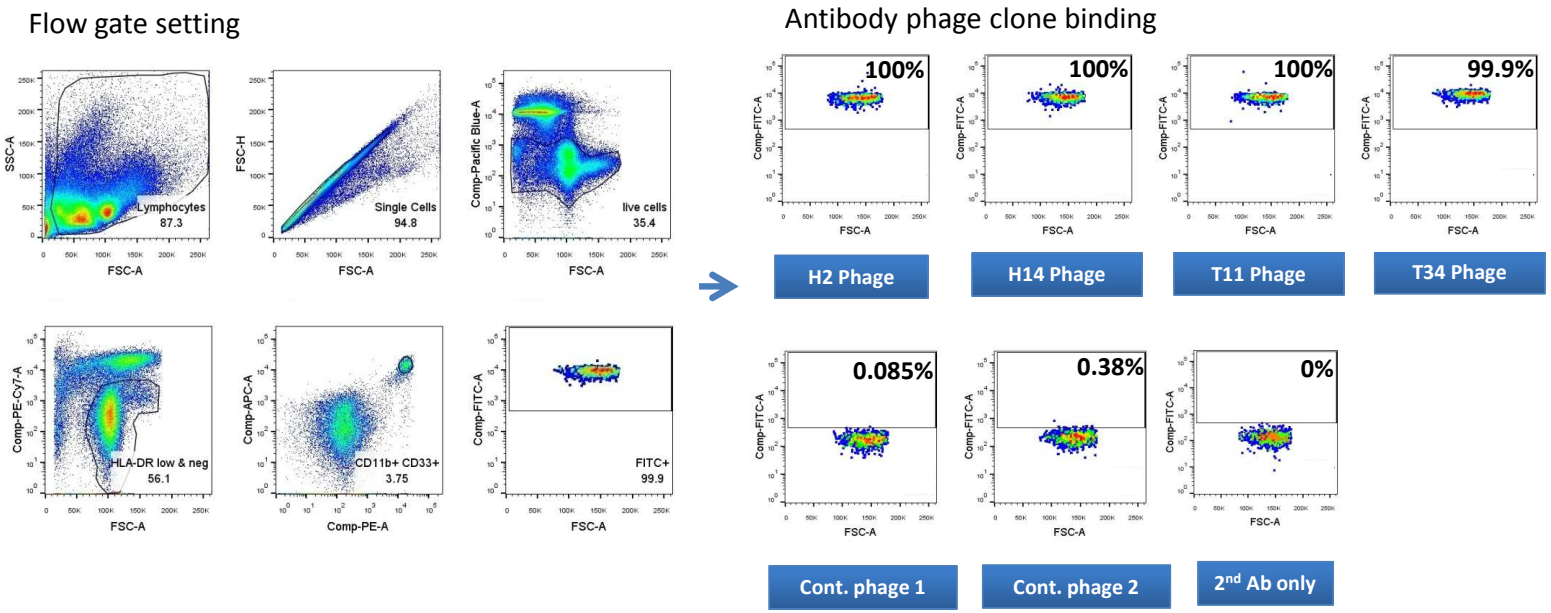
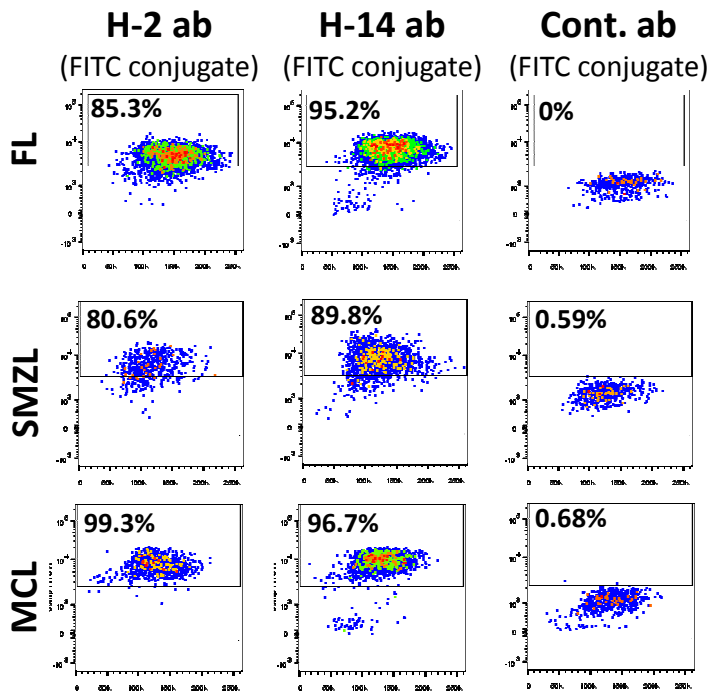


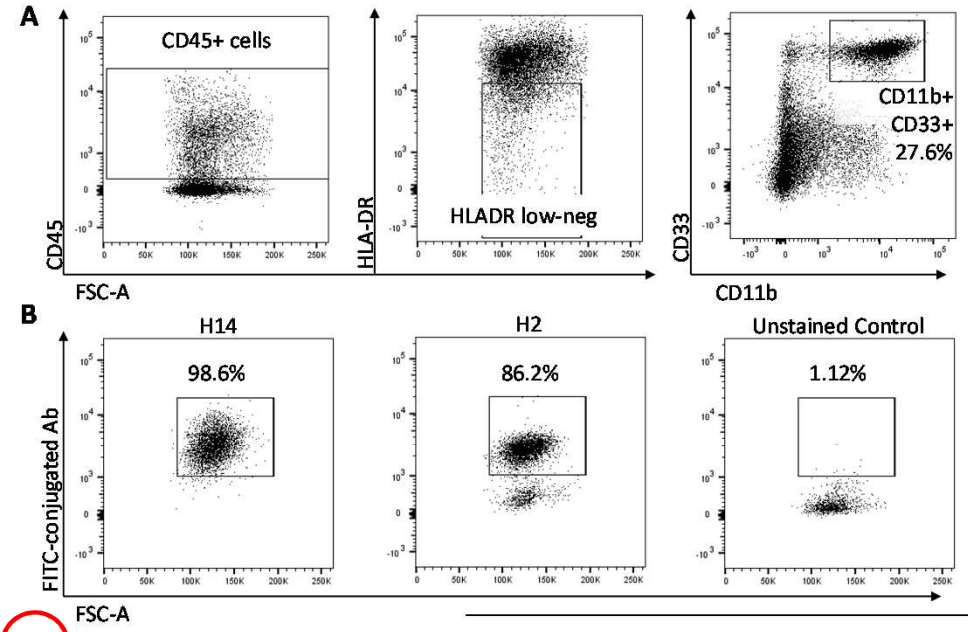
Figure 2: Enriched antibody phage clones bound with primary tumor-infiltrating MDSC. Splenocytes of a lymphoma patient were co-stained with anti-CD11b-APC, anti-CD33-PE, anti—HLA-DR-Cy7, and antibody phage clone plus ant-M13-FITC. Antibody binding was analyzed on $CD11b^{+}CD33^{+}HLA\text{-}DR^{-/low}$ gated tumor-infiltrating MDSC



MDSC binding % of H2 & H14 recombinant fully human antibodies			
Sample Id	**Diagnosis**	**H2**	**H14**
M051406	FL (tumor)	99.7	93.5
M054610	FL (tumor)	61.8	98.2
M053680	FL (tumor)	85.3	95.2
16028	SMZL (spleen)	100	100
10005	SMZL (spleen)	86.8	88.9
471772	SMZL (spleen)	80.6	89.8
10009	MCL (apheresis)	91.5	82.7
10016	MCL (apheresis)	99.3	96.7
		86.43	**93.13**

Figure 4: Development of MDSC-specific fully human antibodies: To determine the binding specificity of recombinant fully human antibodies (H2 and H14), primary tumor samples from three different types of lymphoma (FL, SMZL and MCL) were co-stained with anti-CD11b-APC, anti-CD33-PE, anti—HLA-DR-Cy7 and FITC-conjugated H2 or H14 antibodies. Antibody binding was analyzed on $CD11b^{+}CD33^{+}HLA\text{-}DR^{-/low}$ gated tumor-infiltrating MDSC . The antibodies were tested on a total of 8 patients' tumors.

Ab inhibition of potential human MDSC in vivo: NSG mice engrafted with CD34-enriched human hematopoietic stem and progenitor cells



Cohort	*MDSC Frequency(%)*					*Average Frequency (%)*
Untreated Control		27.6	24.1	28.3		26.4
Antibody Treated	9.82	12.4	12.7	10.7	16.4	11.3

Future directions

- Verify suppressive activity of human CD11b+CD33+ cells depleted in humanized mice

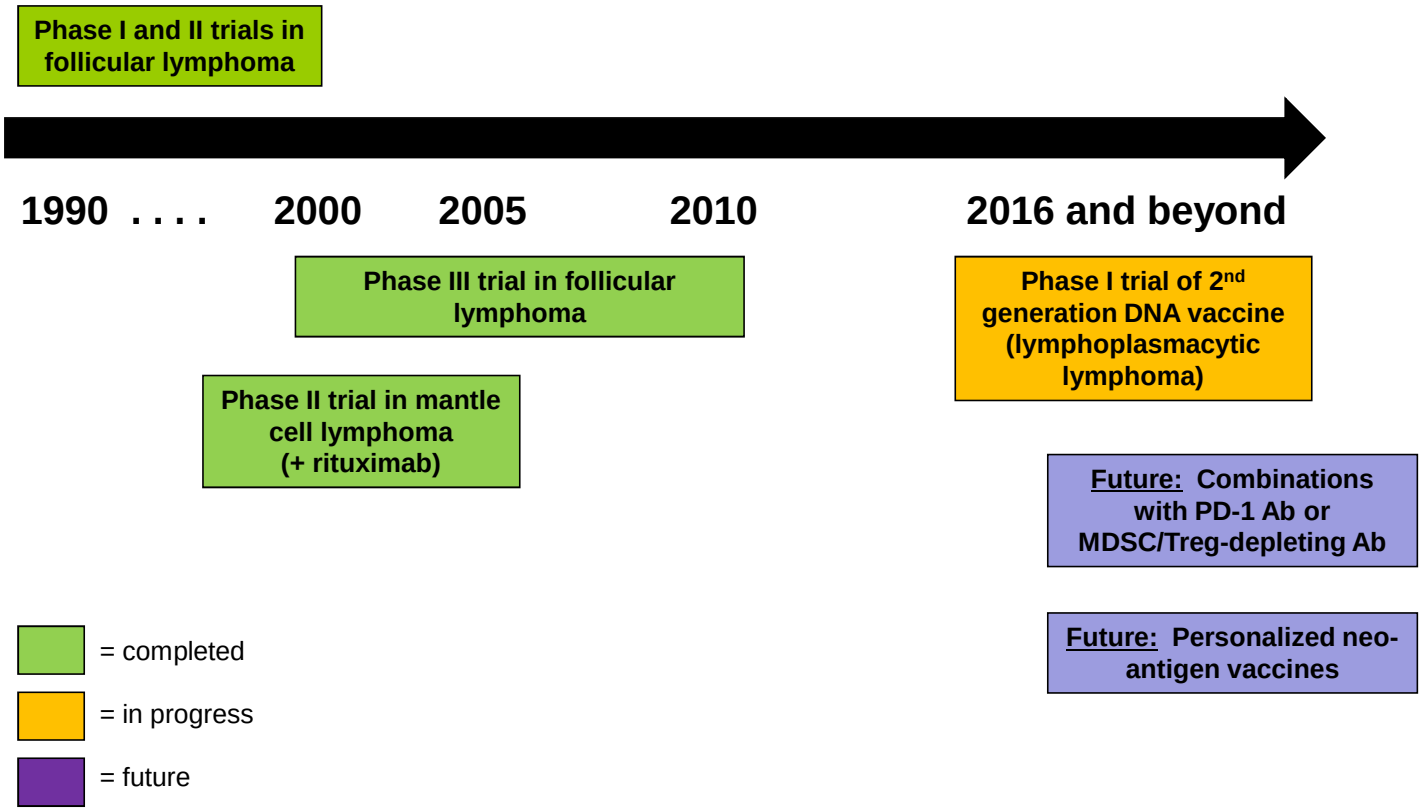
- Test mAb candidates for functional depletion in vivo

  (primary human tumor growth in NSG mice reconstituted with human stem/progenitor cells)

- Determine tissue specificity

- Identify the cell surface target of mAb candidates

Summary and Future Directions: Therapeutic cancer vaccine trials



Acknowledgements

Kwak Laboratory

- Hong Qin

- Soung-Chul Cha

mAb against novel lymphoma targets (e.g. BAFF-R)

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- Damian Gwak
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- Han Sun
- Feng Wen

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- Sapna Parshottam
- Karen C. Dwyer
- Roza Nurieva
- Yared Hailemichael

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- NCI Multiple Myeloma SPORE