Beth Israel Deaconess Medical Center

A major teaching hospital of Harvard Medical School

Personalized Cancer Vaccines: A New Treatment Paradigm for Acute Myeloid Leukemia and Multiple Myeloma

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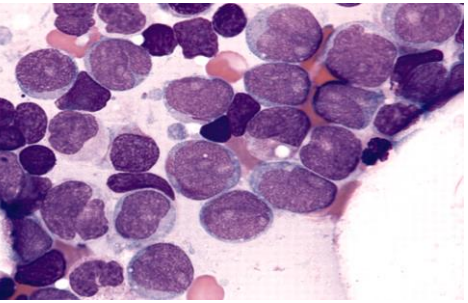
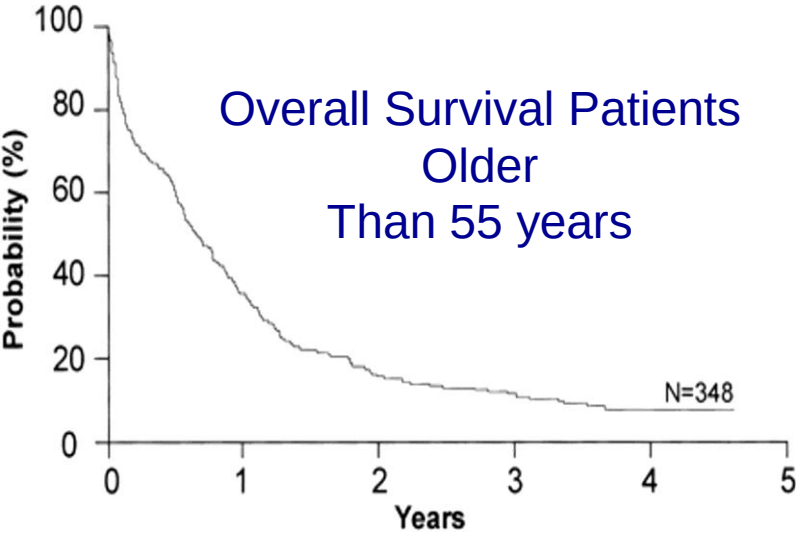


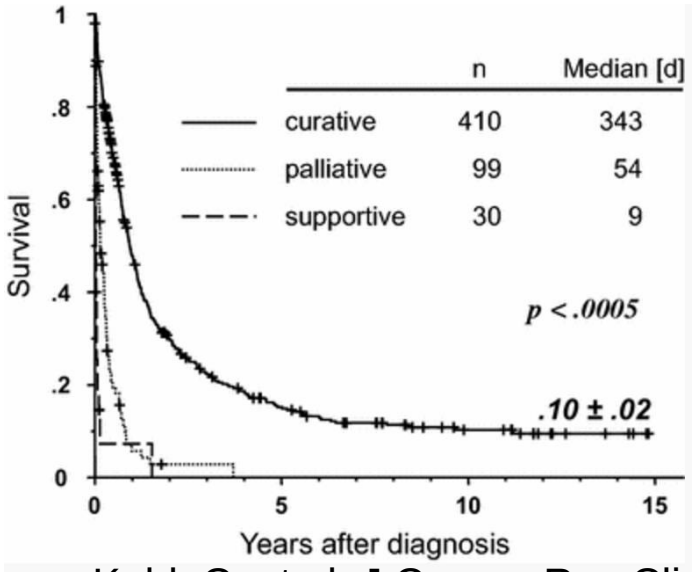
Acute Myeloid Leukemia

- >50% of patients achieve remission but chemotherapy is not curative for most patients
- Outcomes are poor for patients over age 60



Overall Survival Patients Older Than 55 years

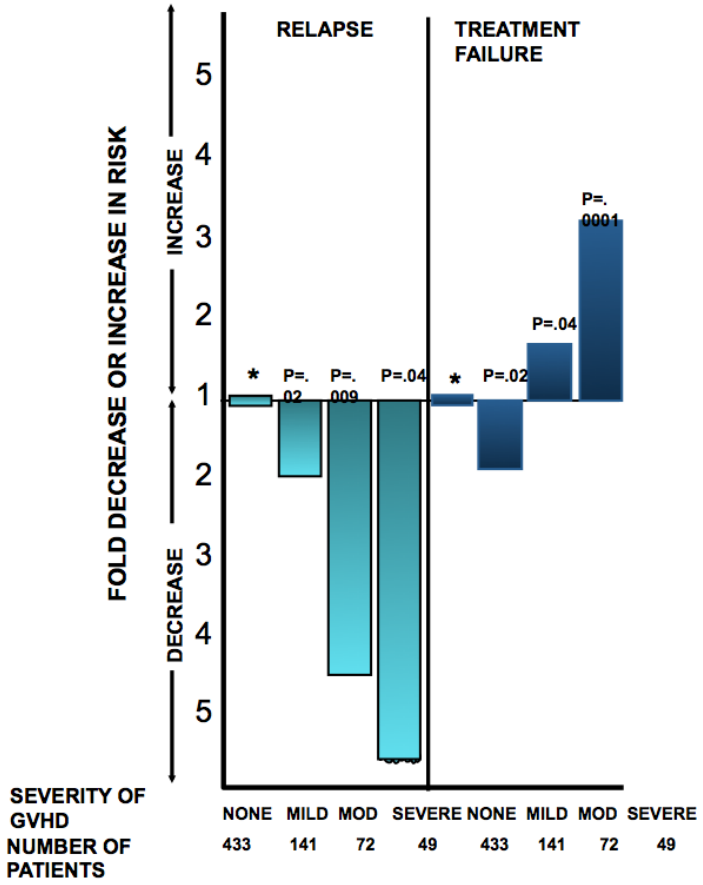
Forman, S. J. Hematology 2009:406-413



Kahl, C. et al. J Cancer Res Clin Oncol (2016)142: 305.

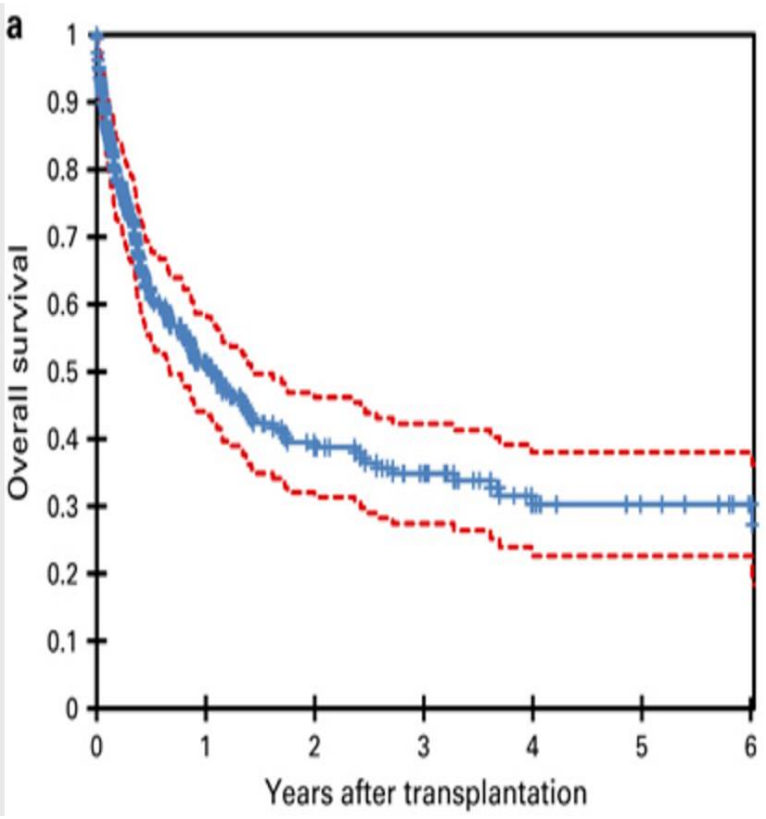
Potency of Immune Based Therapy for AML Lessons from Allogeneic Transplantation

IBMTR Analysis of Graft vs Leukemia Effect



Horowitz, Blood 1990;75:555

Outcome of allogeneic transplantation for AML in patients ≥ 60 years

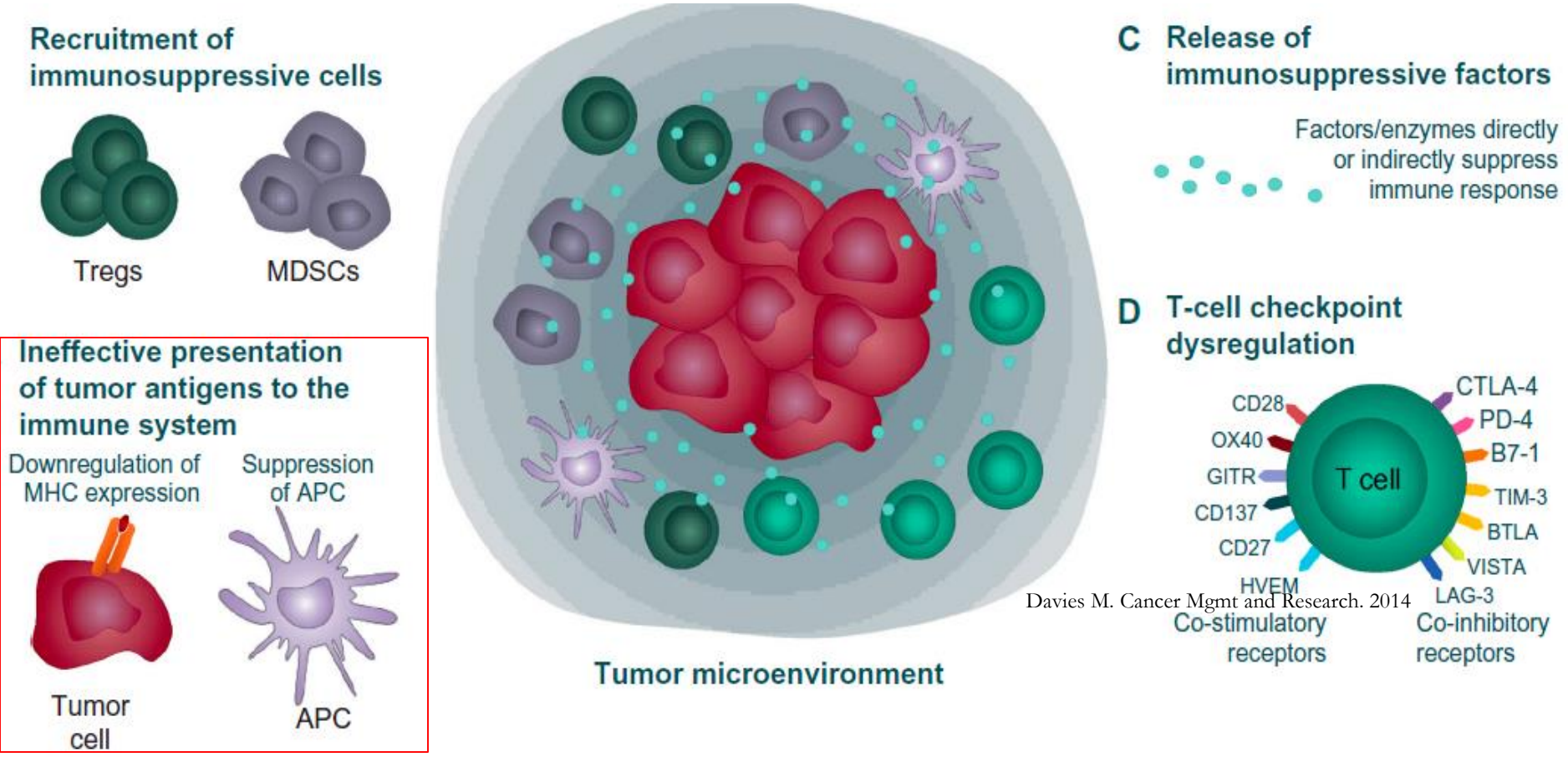


Pohlen et al. Bone Marrow Transplantation (2016) 51, 1441–1448

Can a Tumor Vaccine Induce Tumor Specific Immunity that Translates in Clinically Meaningful Outcomes?

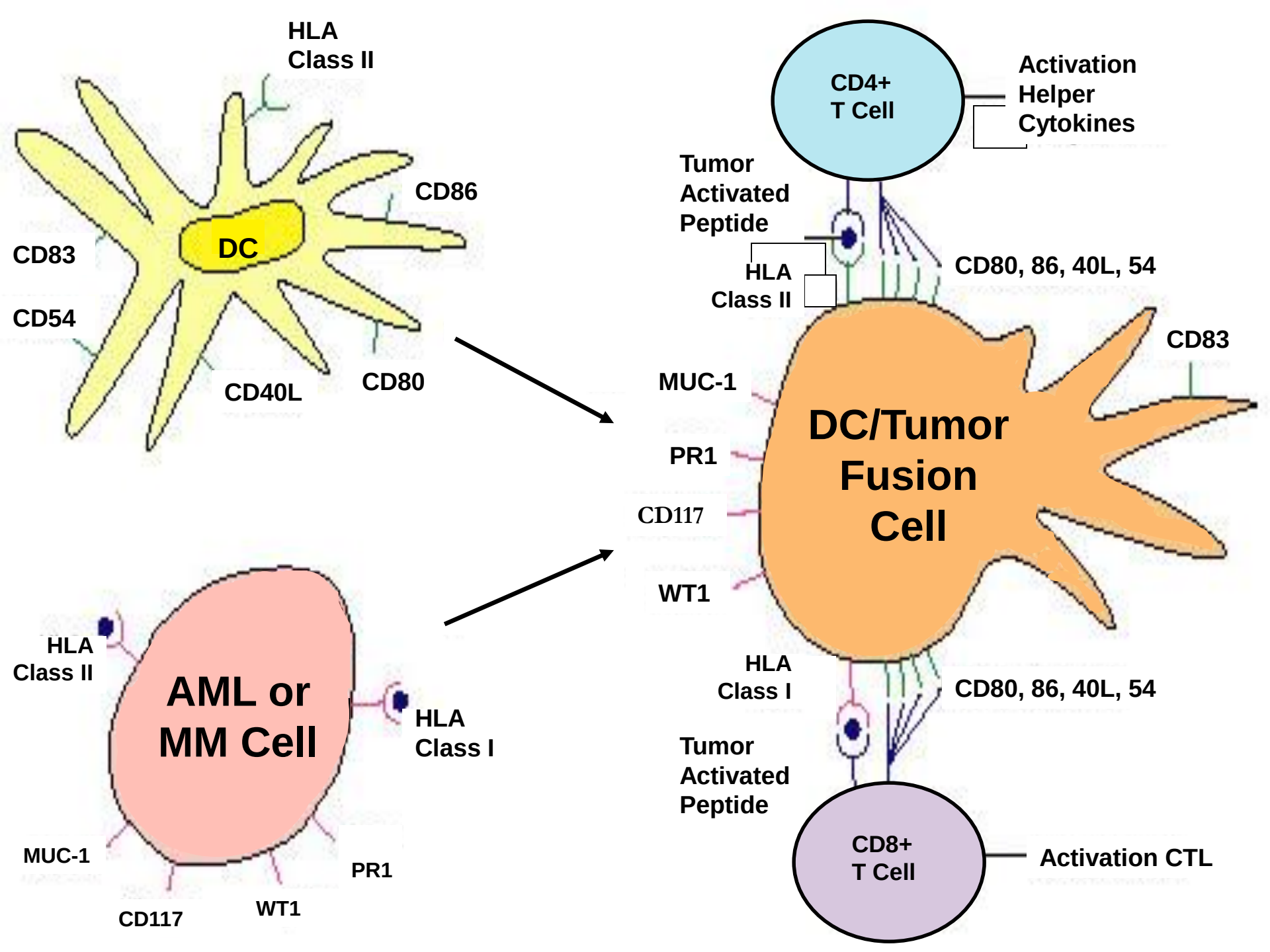
- Expansion of immune effector cells to selectively target malignant cells
- A broad anti-tumor immune response has the potential to target tumor heterogeneity, including malignant stem cell populations
- Immune response provides the potential for memory and long term surveillance

Cancer and Immune Escape : Role of the Tumor Microenvironment



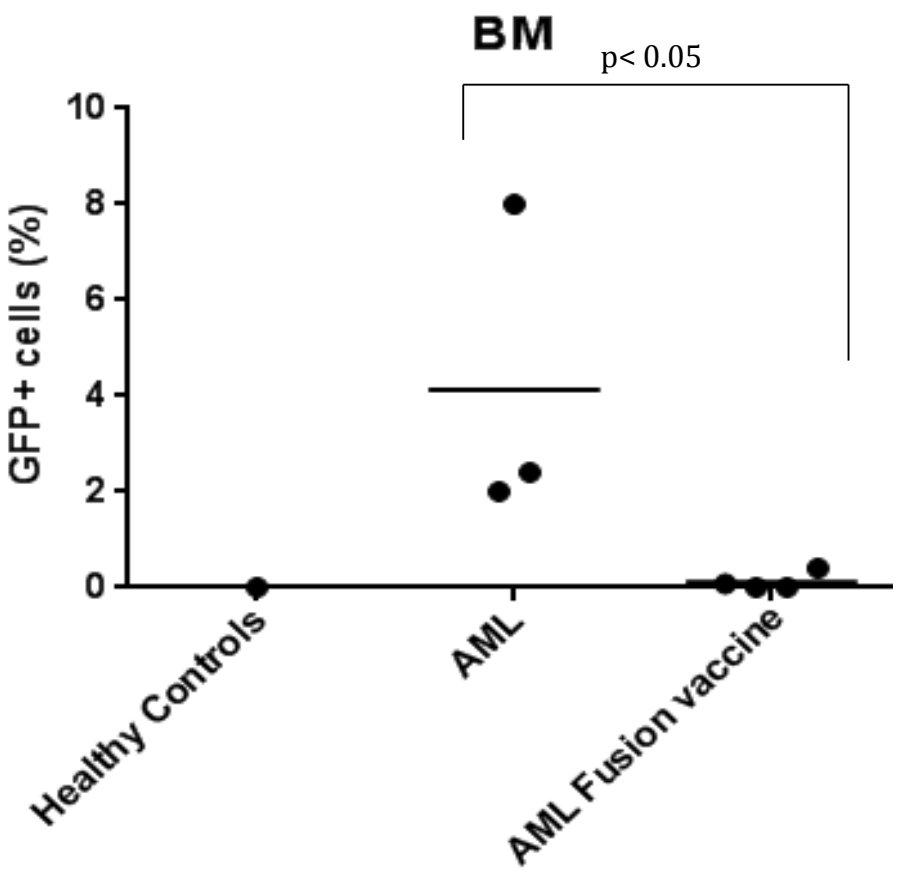
Davies M. Cancer Mgmt and Research. 2014

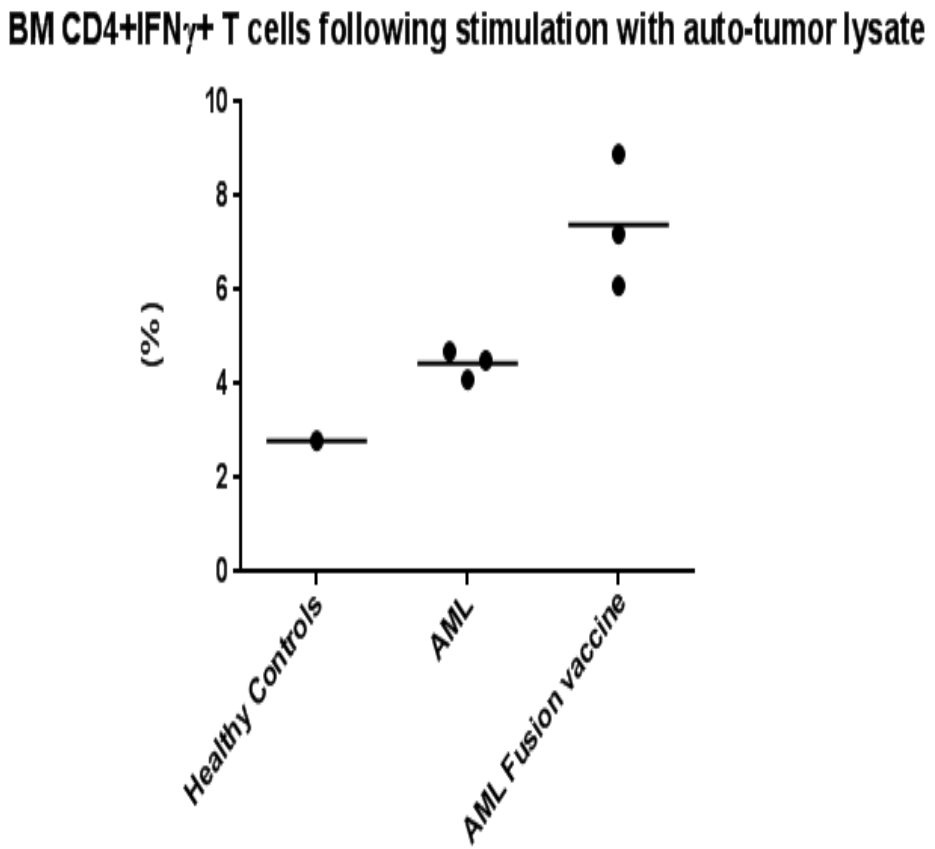
Davies M. Cancer Mgmt and Research. 2014

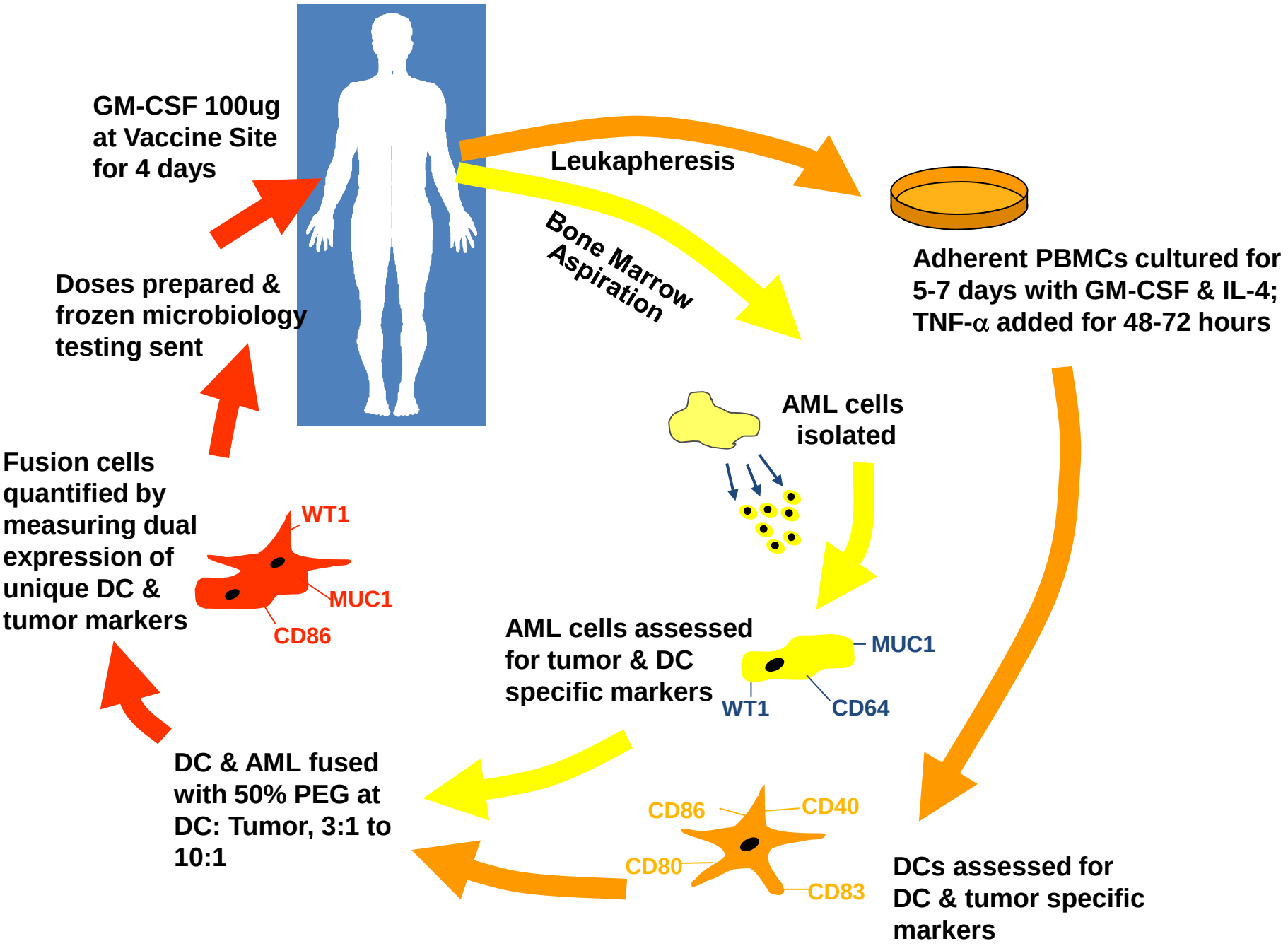

HLA
Class II
CD86
DC
CD83
CD54
CD40L
CD80
CD4+
T Cell
Activation
Helper
Cytokines
Tumor
Activated
Peptide
HLA
Class II
CD80, 86, 40L, 54
CD83
MUC-1
PR1
CD117
WT1
DC/Tumor
Fusion
Cell
HLA
Class II
AML or
MM Cell
HLA
Class I
MUC-1
PR1
CD117
WT1
HLA
Class I
CD80, 86, 40L, 54
Tumor
Activated
Peptide
CD8+
T Cell
Activation CTL

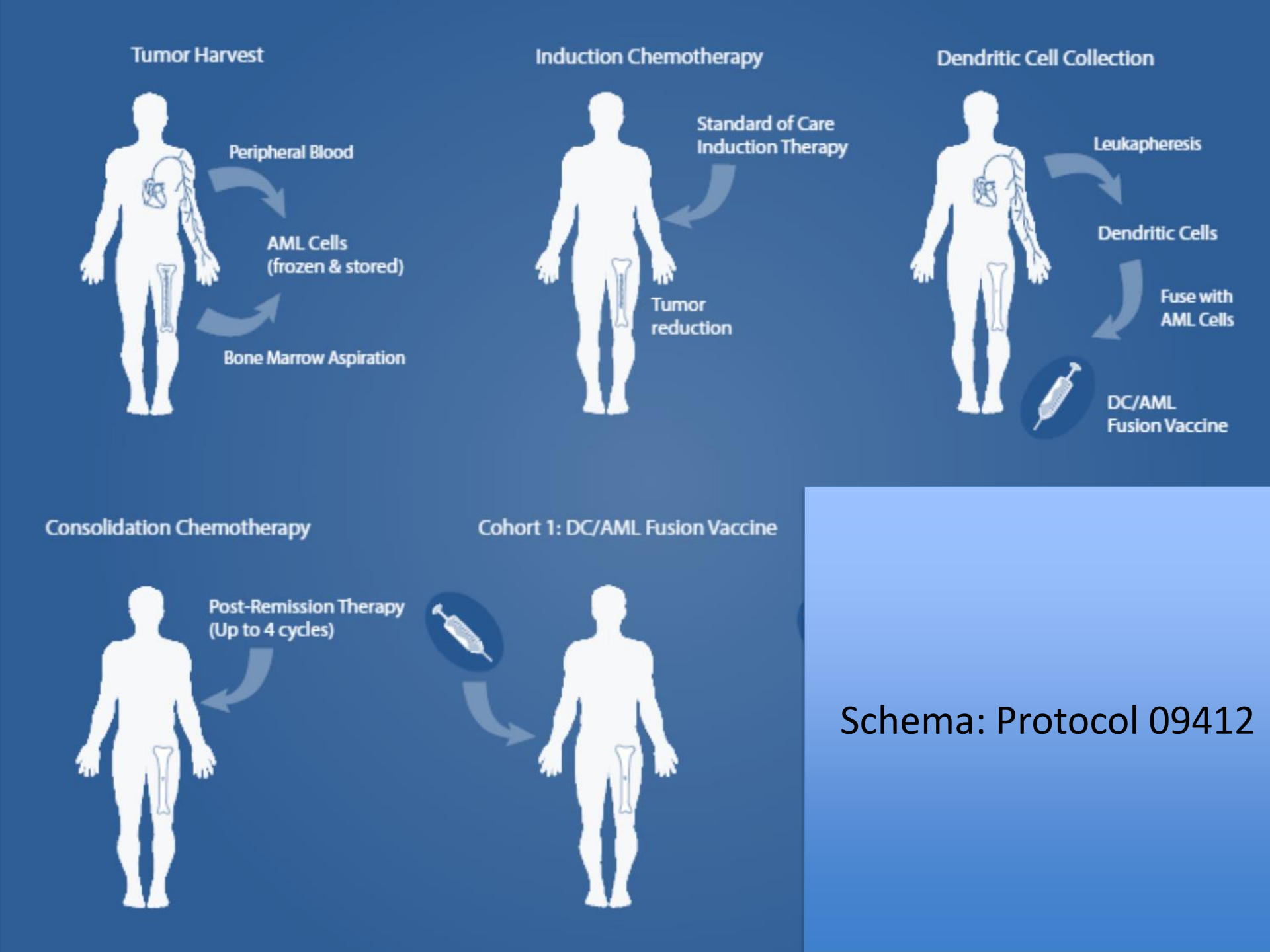
DC/AML Fusion Vaccine: Immunocompetent Murine Model:

C57BL/6J mice inoculated with GFP+ TIB-49 AML cells






GM-CSF 100ug at Vaccine Site for 4 days
Leukapheresis
Bone Marrow Aspiration
Adherent PBMCs cultured for 5-7 days with GM-CSF & IL-4; TNF-α added for 48-72 hours
AML cells isolated
Doses prepared & frozen microbiology testing sent
Fusion cells quantified by measuring dual expression of unique DC & tumor markers
WT1
MUC1
CD86
AML cells assessed for tumor & DC specific markers
MUC1
WT1
CD64
DC & AML fused with 50% PEG at DC: Tumor, 3:1 to 10:1
CD86
CD40
CD80
CD83
DCs assessed for DC & tumor specific markers



Schema: Protocol 09412

Characteristics of 19 patients who completed vaccine generation

- Median age was **63 years**
- 11 patients had **intermediate or high risk** disease
- 2 patients completed vaccine generation, but did not receive any vaccination:
  - relapsed AML (n=1)
  - ongoing chemotherapy toxicity (n=1).

- **17 patients initiated vaccination**:
  - 16 patients received at least 2 vaccines
  - 1 patient relapsed after 1 dose of vaccine

- Median time from completing chemotherapy to initiating vaccination was 56 days (range 38-118 days)

Sci Transl Med. 2016 Dec 7;8(368):368ra171.

Table 1. Patient Demographics

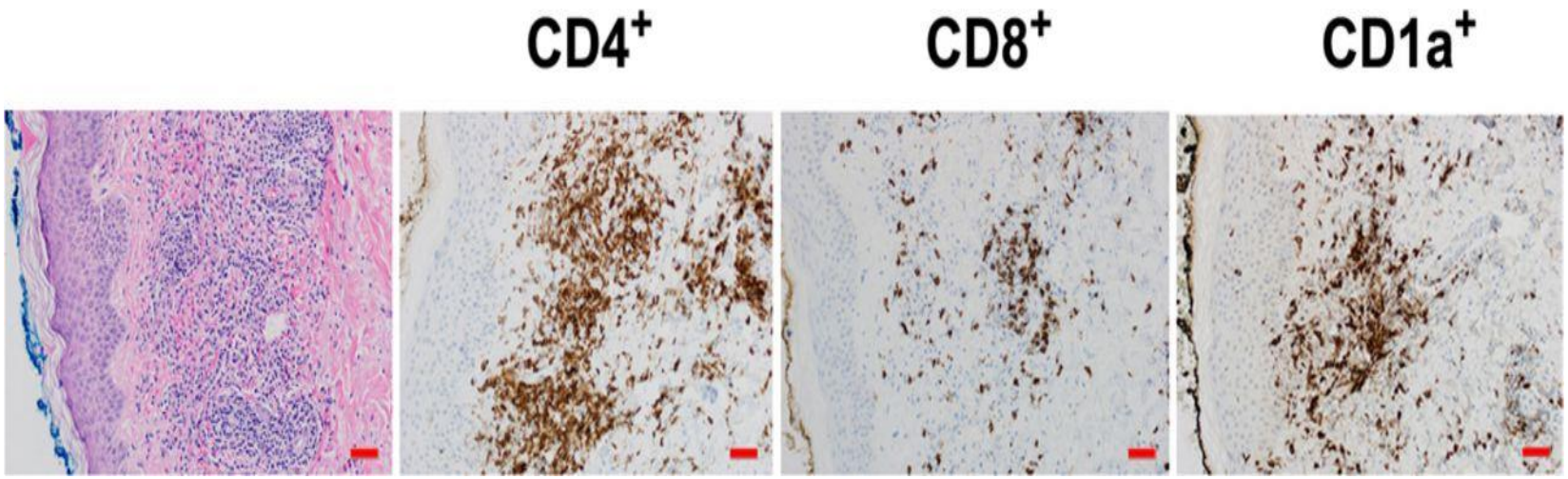
Study Number	Age	Gender	Disease Status at Presentation	WHO Classification	Induction Regimen(s)	Consolidation	Current Status	Time to Relapse (Months)	Duration of CR (Months)
PA2	37	F	Initial Diagnosis	Acute myelomonocytic leukemia	7+3	4 cycles of HiDAC	CR		71.6
PA3	76	M	Initial Diagnosis	AML with maturation	7+3	3 cycles of MiDAC	CR		71
PA5	69	M	Initial Diagnosis	Acute monocytic leukemia	7+3	3 cycles of MiDAC	CR		69.4
PA6	66	M	Initial Diagnosis	AML with minimal differentiation	7+3 and MEC	1 cycle HiDAC, 1 cycle MiDAC	Relapse	5.8	
PA8	32	M	Initial Diagnosis	Acute myelomonocytic leukemia	7+3	4 cycles of HiDAC	CR		68.2
PA9	54	F	Initial Diagnosis	Acute monocytic leukemia	7+3	4 cycles of HiDAC	Relapse	8.1	
PA10	56	F	Initial Diagnosis	t-AML	7+3	4 cycles of HiDAC	CR		58.3
PA11	77	F	1st Relapse (following remission of 1 year)	Acute myelomonocytic leukemia	MEC	1 cycle of MiDAC	CR		59.8
PA13	76	M	Initial Diagnosis	AML w/MDS-related changes	2 cycles of Decitabine	4 cycles of Decitabine	Relapse	9.1	
PA14	28	F	Initial Diagnosis	AML with maturation	7+3 and 5+2	4 cycles of HiDAC	Relapse	14	
PA16	64	M	Initial Diagnosis	AML with t(8;21)(q22;q22); RUNX1-RUNX1T1	7+3	4 cycles of HiDAC	CR		58.3
PA18	62	F	Initial Diagnosis	AML without maturation	7+3	3 cycles of HiDAC	CR		54.6
PA21	56	M	Initial Diagnosis	AML with t(8;21)(q22;q22); RUNX1-RUNX1T1	7+3	4 cycles of HiDAC	CR		57.1
PA23	74	F	Initial Diagnosis	AML with mutated NPM1	7+3	1 cycle of HiDAC	Relapse	5.9	
PA24	67	M	Initial Diagnosis	AML with minimal differentiation	7+3	3 cycles of MiDAC	CR		51.9
PA26	72	M	Initial Diagnosis	Acute myelomonocytic leukemia	7+3	4 cycles of HiDAC	Relapse	3.8	
PA29	59	F	Initial Diagnosis	t-AML	7+3	4 cycles of HiDAC	CR		26
PA36	56	M	Initial Diagnosis	AML with mutated NPM1	7+3	3 cycles of HiDAC	CR		23.4
PA38	63	M	Initial Diagnosis	AML with t(8;21)(q22;q22); RUNX1-RUNX1T1	7+3	4 cycles of MiDAC	CR		21.7

Adverse Events Related to Vaccination

Table 2. Adverse Events

Adverse Events	Grade	# of Episodes
Vaccine Site Reaction	1	31
	2	3
Leukopenia	1	5
Urticaria	1	4
Eosinophilia	1	3
Elevated TSH	1	3
Thrombocytopenia	1	3
Pruritis	1	2
	2	1
Increased Monocytes	1	1
Arthralgia	1	1
Myalgia	1	1

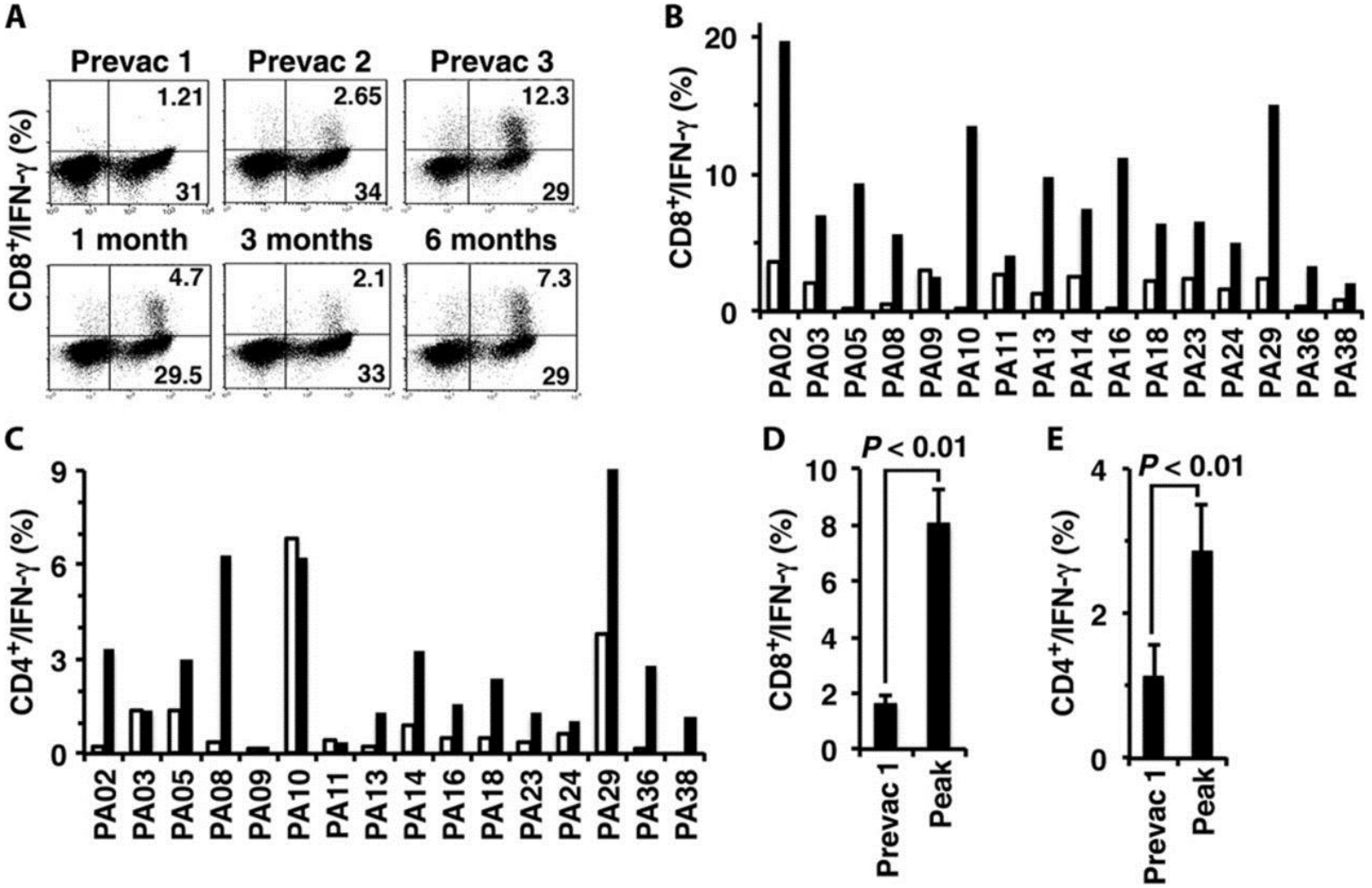
Vaccine Site Reaction



Sci Transl Med 2016;8:368ra171

Science Translational Medicine
AAAS

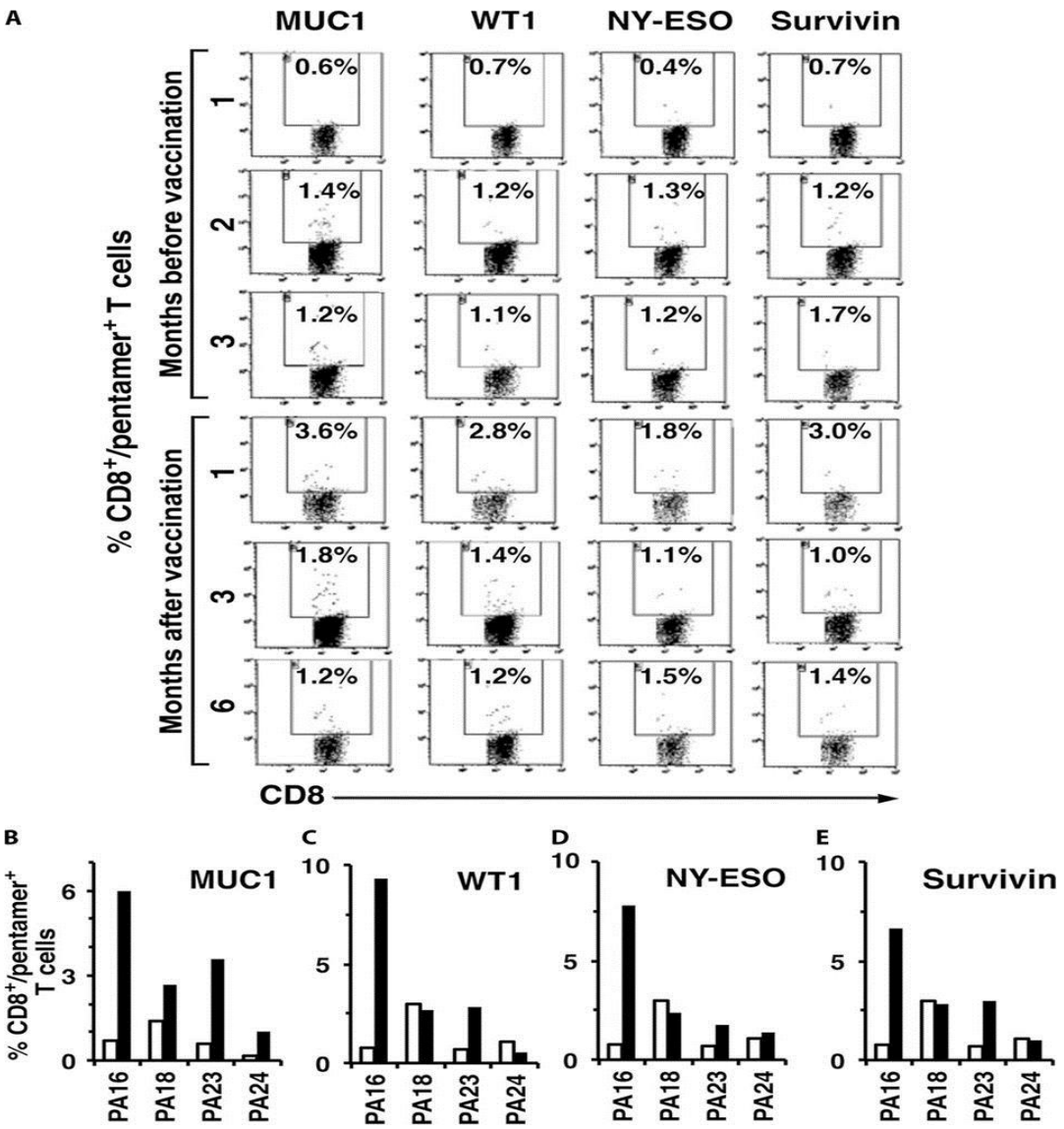
Expansion of leukemia-specific CD4+ and CD8+ T cells after vaccination



Sci Transl Med 2016;8:368ra171

Science Translational Medicine AAAS

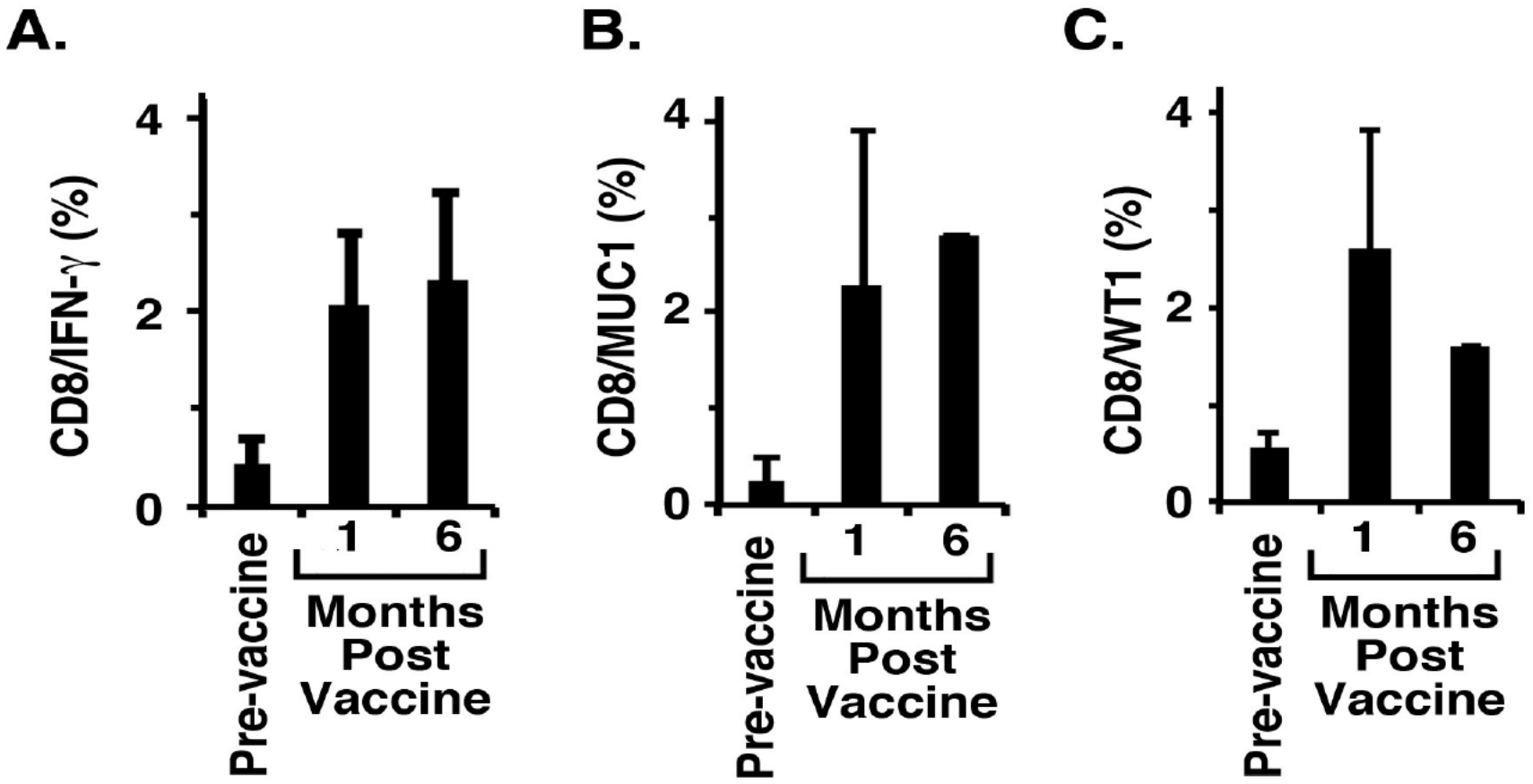
Expansion of antigen specific T cells



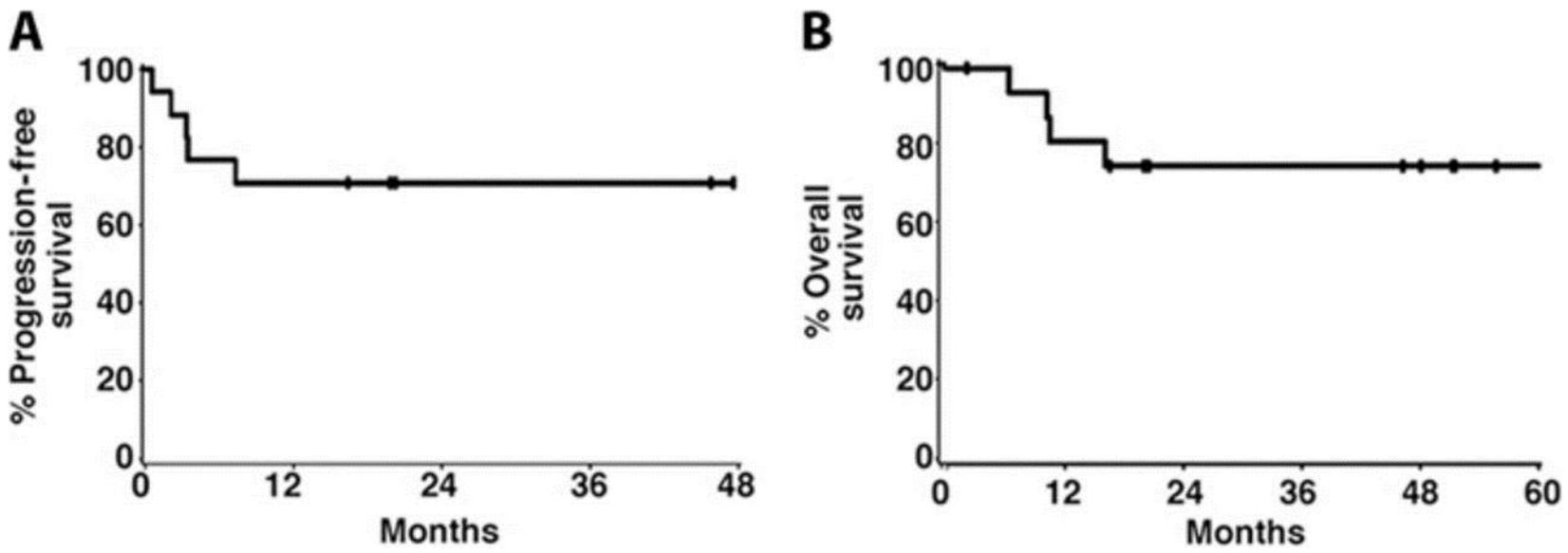
Published by AAAS

Sci Transl Med 2016;8:368ra171

Increased Presence of Leukemia Reactive T cells in the Bone Marrow Following Vaccination



Clinical Outcome



- 12 of 17 patients who received at least one dose of vaccine remain alive and in remission (**71%**; 90% CI, 52 to 89%) at 16.7 to 66.5 months from initiating vaccination
- **Median follow-up: 57 months**

Published by AAAS

Sci Transl Med 2016;8:368ra171

Science Translational Medicine AAAS

Clinical Outcome: Patient 11

04/2010
76 year old lady, presents with AML

Cytogenetics: +8, inv16
Hypomethylating agent +mylotarg
Ara-C 1 gram/m2 x 5 days

05/2010- REMISSION

03/2011- RELAPSE- enrolled on protocol

Cytogenetics: +8, inv 16, newly acquired +21
MEC – **Remission**
Ara-C 1 gram/m2 x 5 days

2 DOSES OF DC/AML fusion cell vaccine → **ONGOING REMISSION**

PRESENTLY
82 years old

Next steps in AML: Randomized Trial

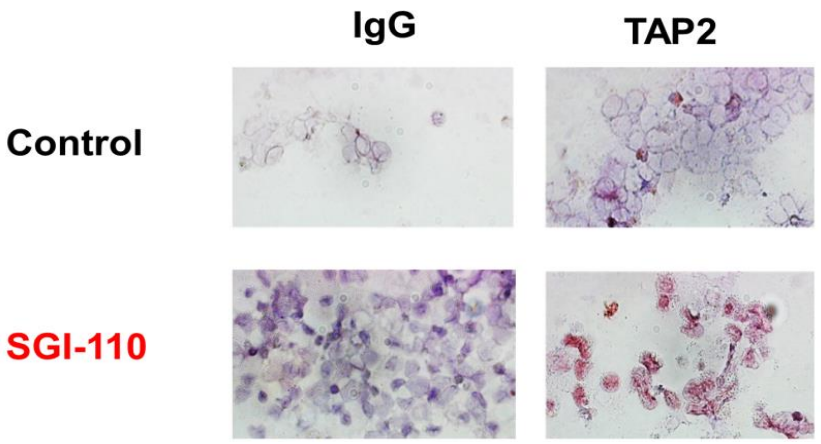
NCT03059485

- Randomized phase II study
- Patients 55 years or older who achieve remission are randomized to either
  - DC/AML fusion vaccine alone
  - DC/AML fusion vaccine in combination with PDL-1 antibody
  - observation

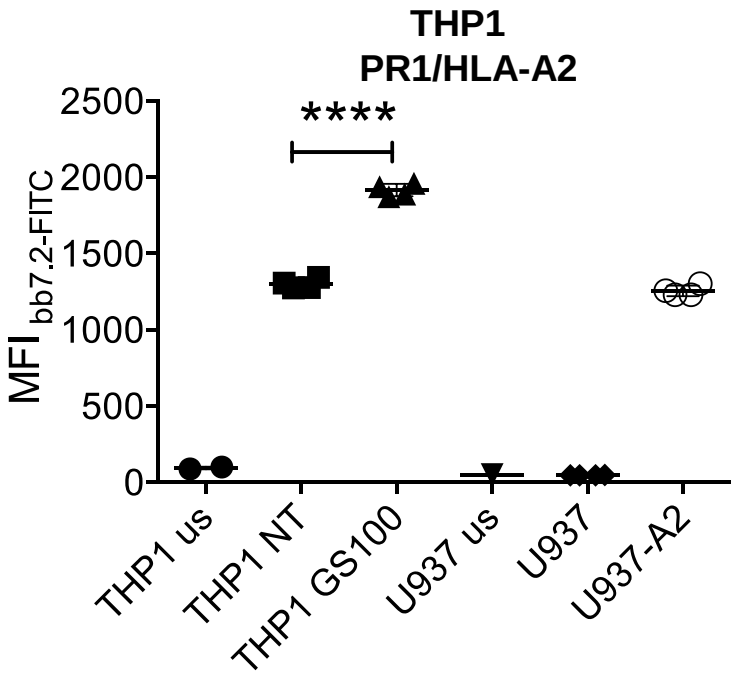
- Primary clinical endpoint: 2-year progression free survival
- Secondary clinical endpoint: overall survival

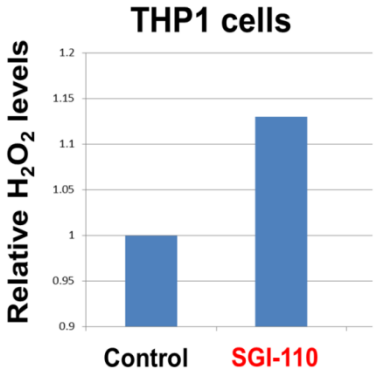
- The study is powered to detect a difference in the expansion of circulating AML specific T cells between each of the three treatment arms.

Hypomethylating Agent Augments Tumor Antigen Presentation



C.





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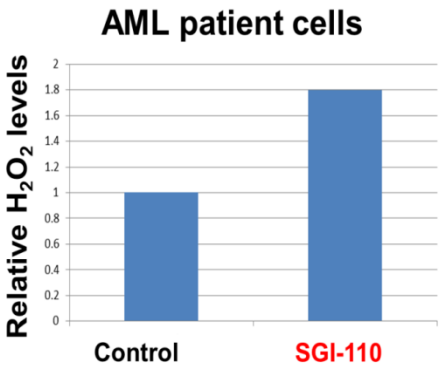
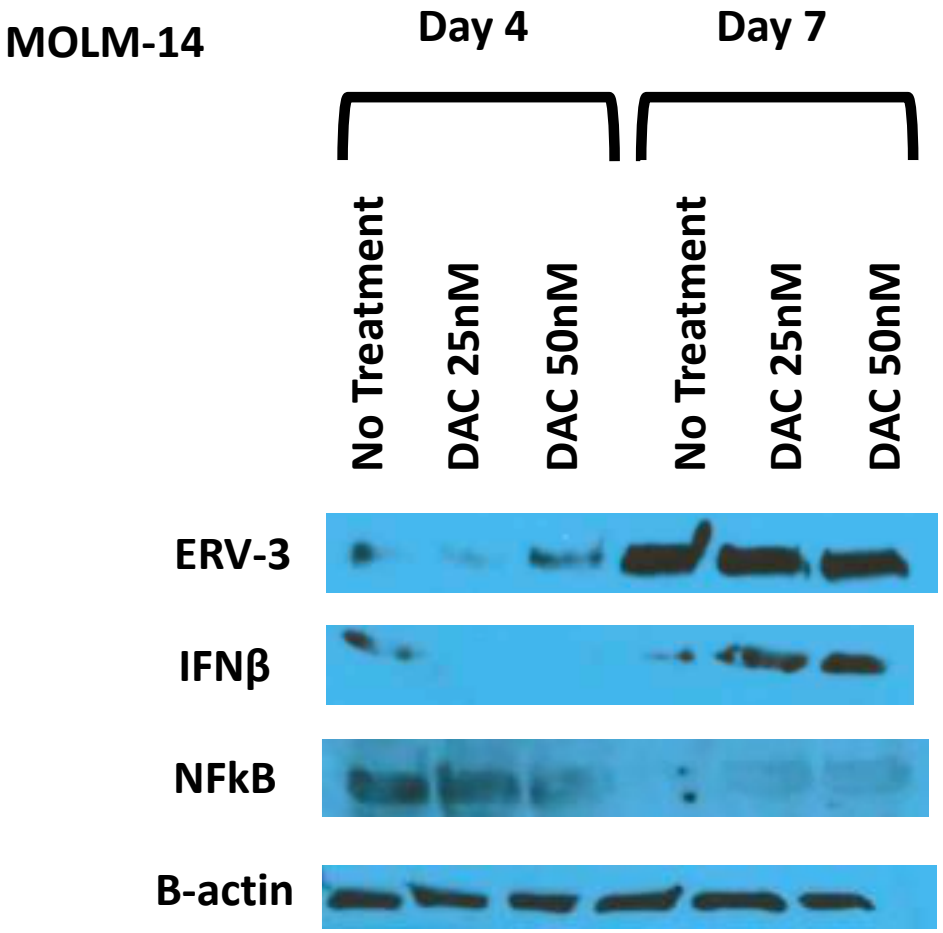
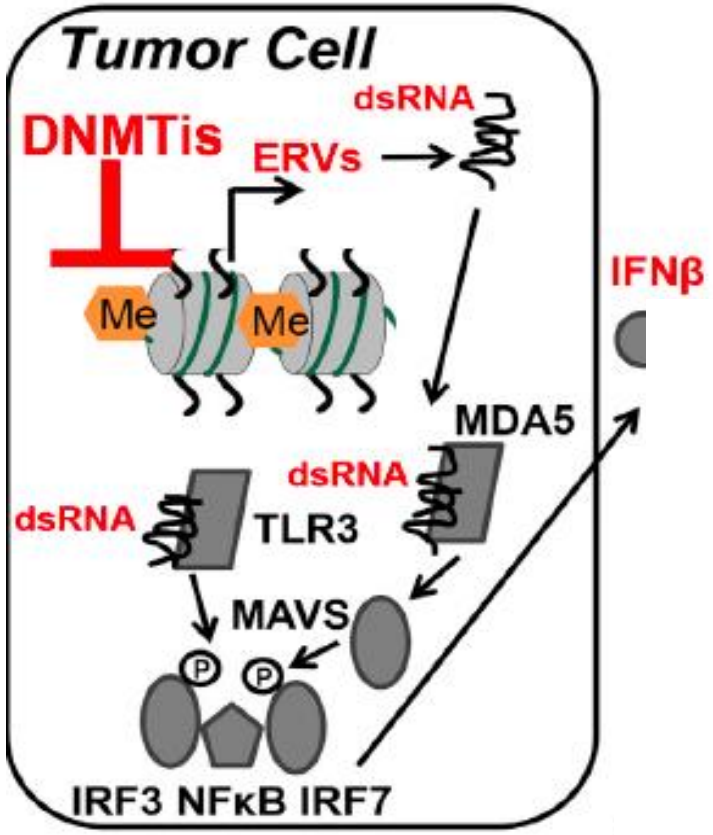
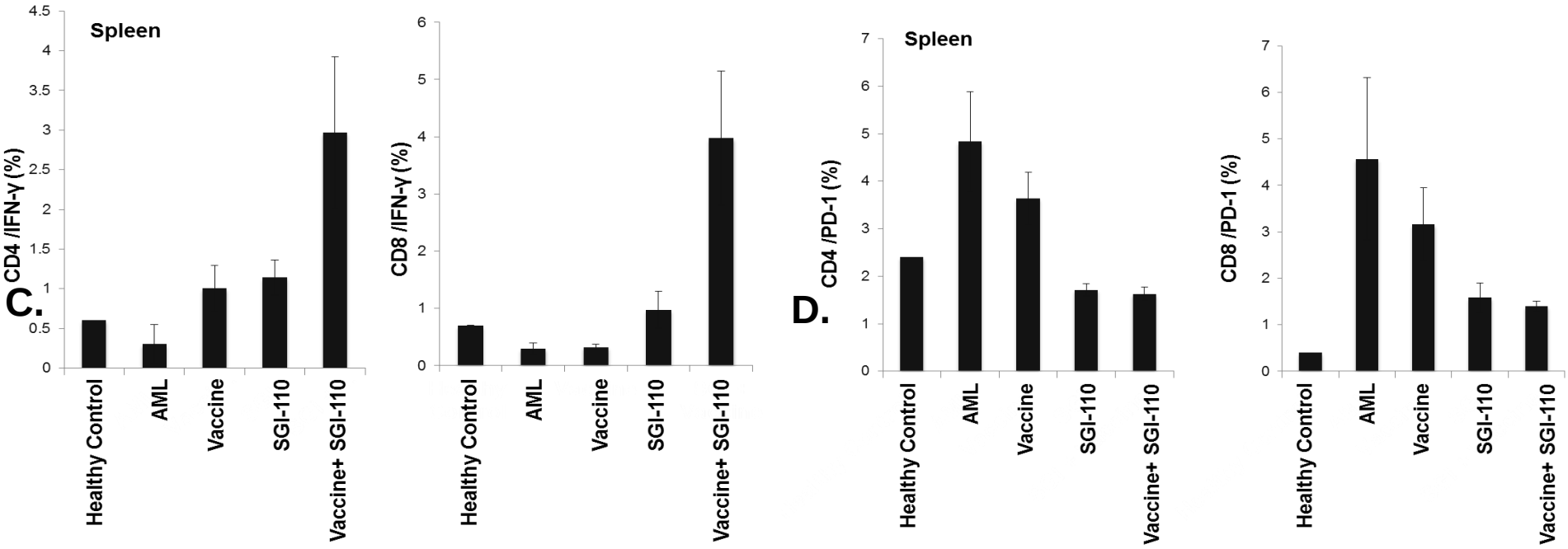


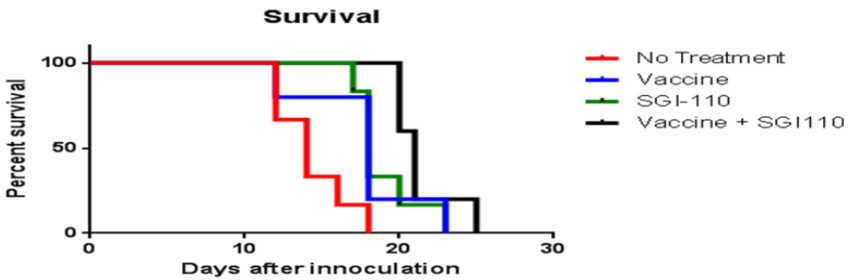


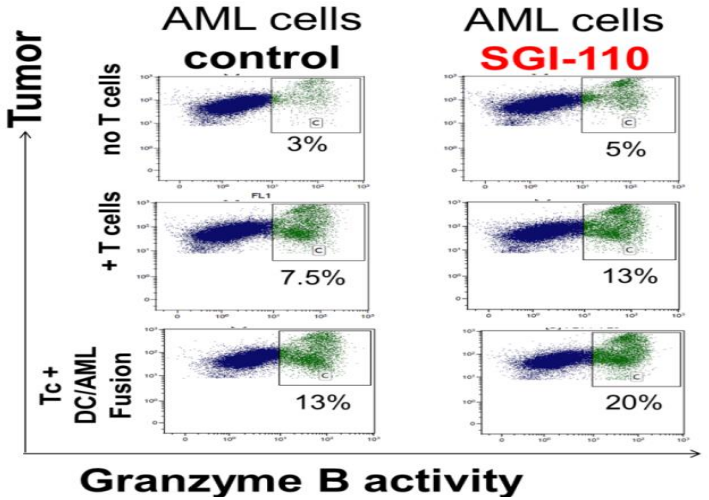


Viral RNA sensing proteins (ie: TLR3 on endosomal membrane and MDA5, PKR, and RIG-I in the cytoplasm) induce IRF3, IRF7, and NF-kB to **translocate** to the nucleus and activate transcription of IFNb1

Vaccination and HMA Therapy for AML: Murine Model







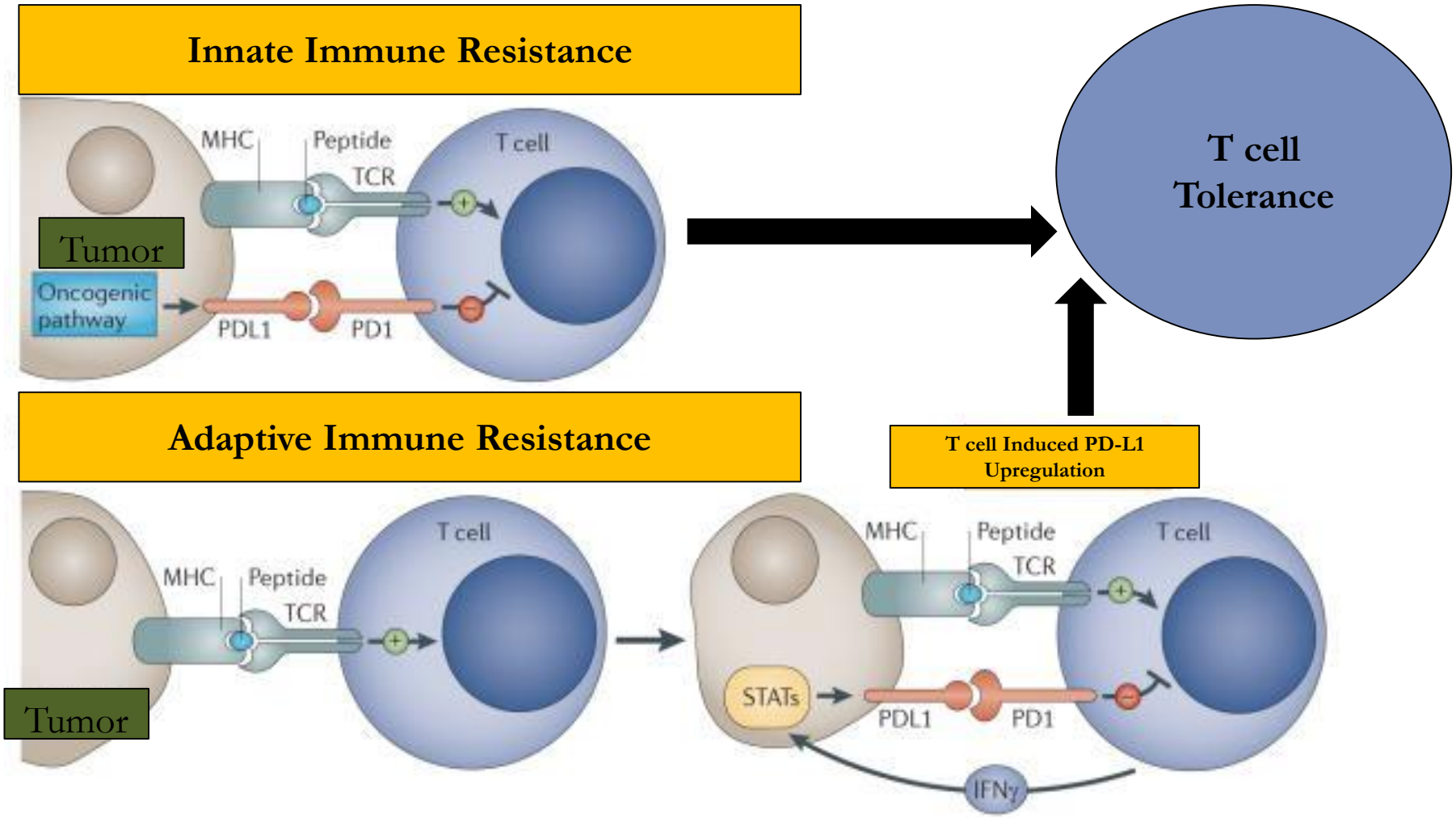
Next steps in AML: Clinical Trial of Vaccination with donor DC/AML fusions in high risk patients

- AML patients with high risk features who undergo allogeneic transplantation in remission will undergo post-transplant vaccination with donor DC/AML fusions alone or in conjunction with HMA

- **Primary clinical endpoint**: to assess vaccine associated toxicity including impact on GVHD.
- **Secondary clinical endpoint**: to examine the effect of vaccination on relapse-free survival
- To assess the **immunologic response** following post-transplant vaccination alone or with HMA

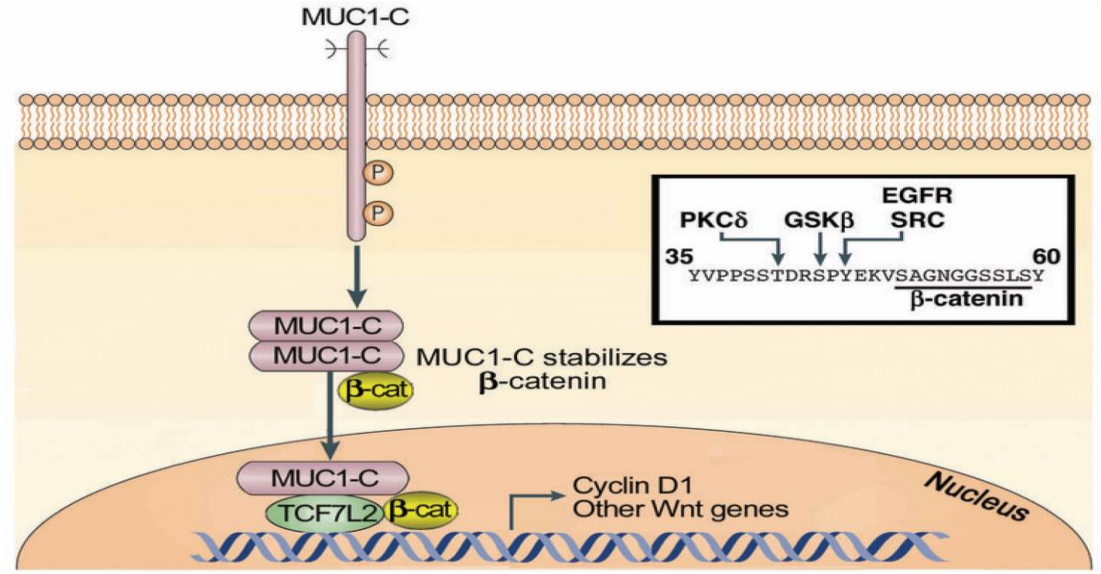
SPORE IN LEUKEMIA, 1 P50 CA 206963-01; PROJECT 4

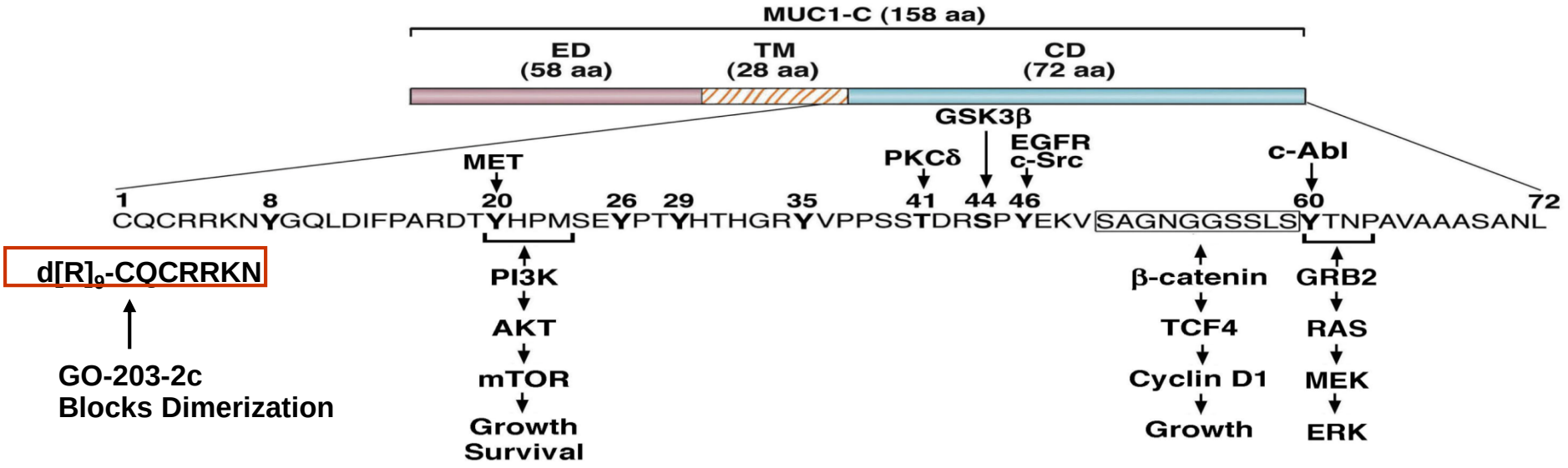
PD-L1/PD-1 Axis and Immune Tolerance



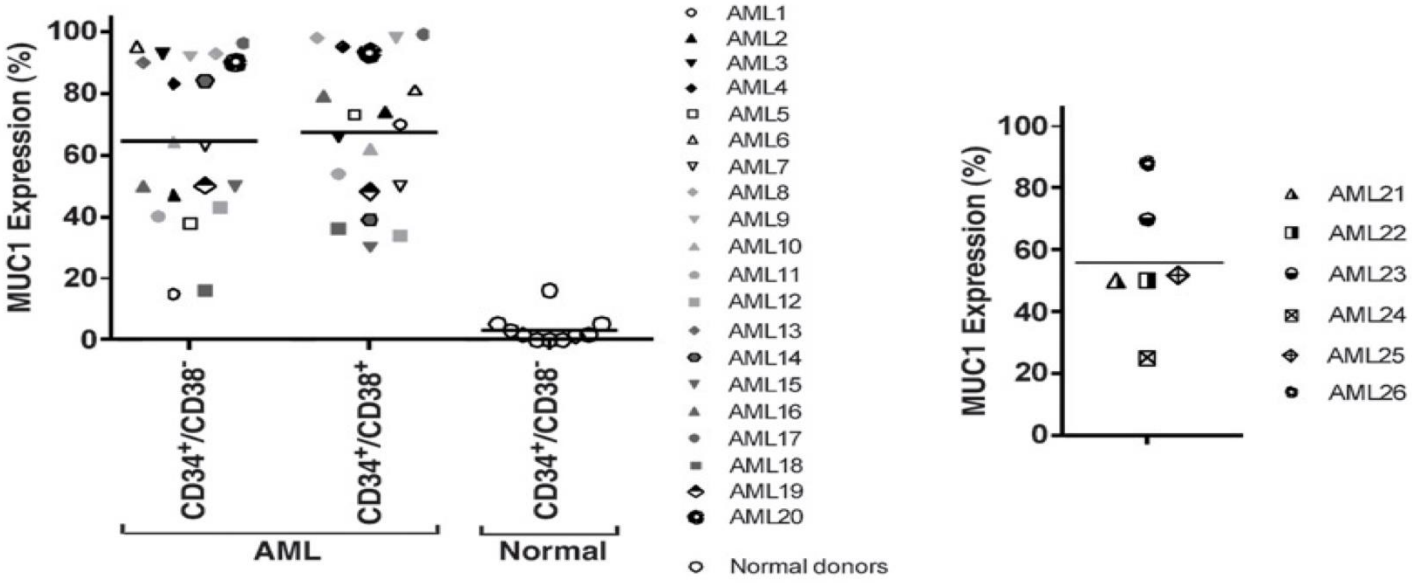
Pardoll. Nat Rev Cancer. 2012 Apr; 12(4): 252–264.

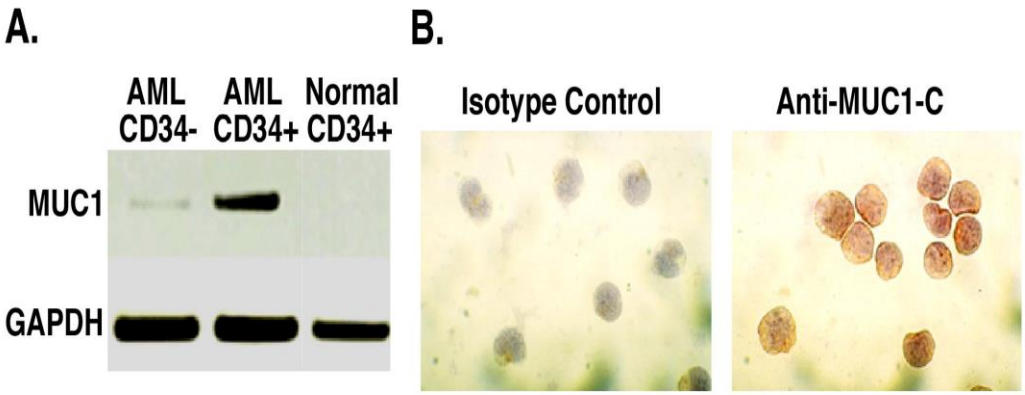
The MUC1 Oncogene and the Tumor Microenvironment

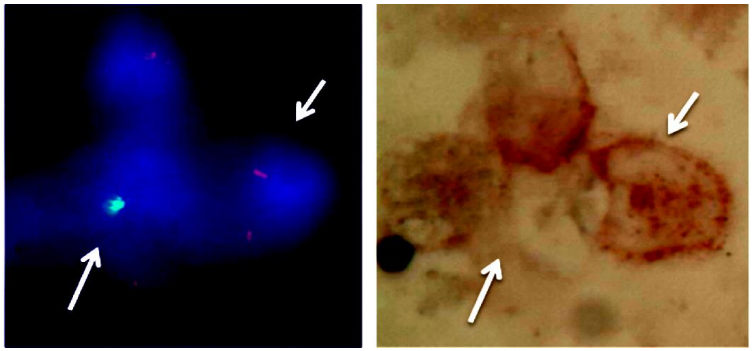




MUC1 is expressed by AML stem cells but not normal HSCs







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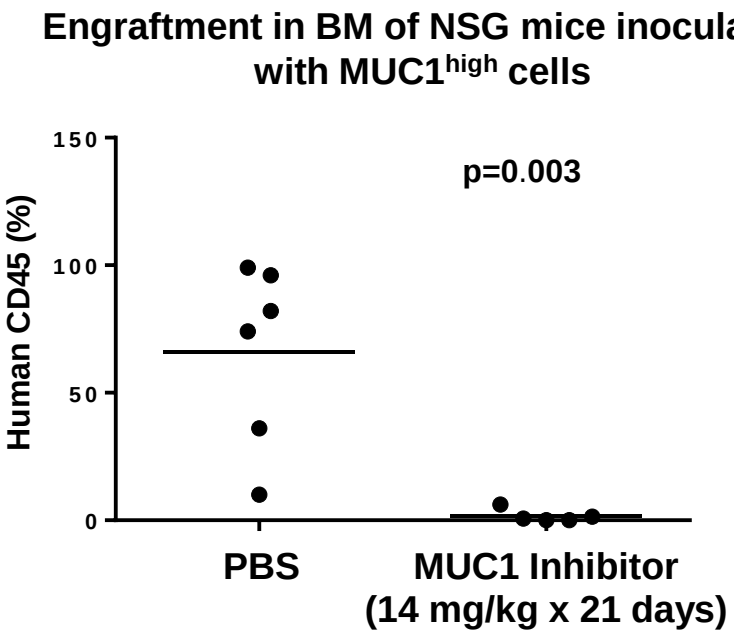
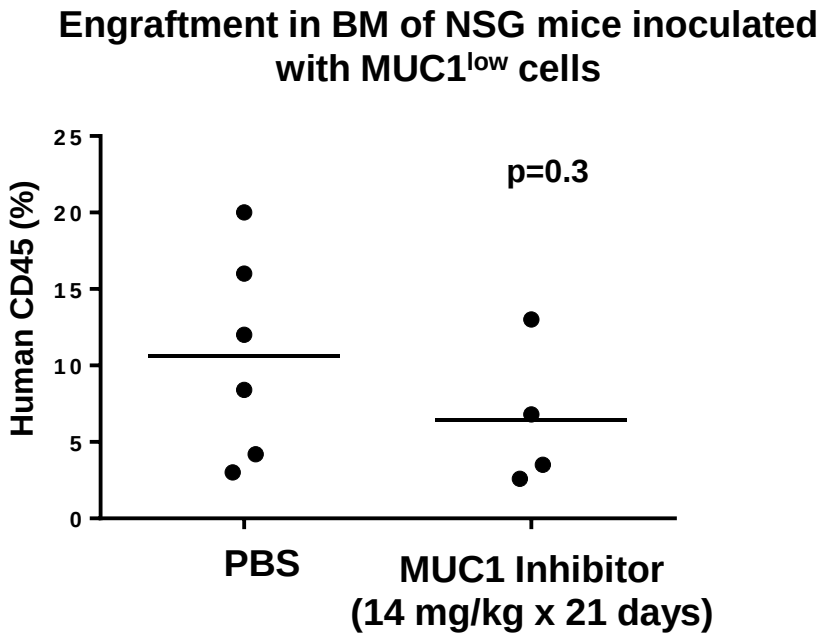
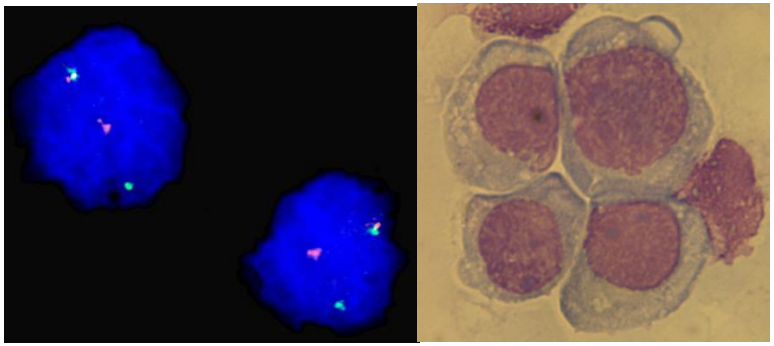
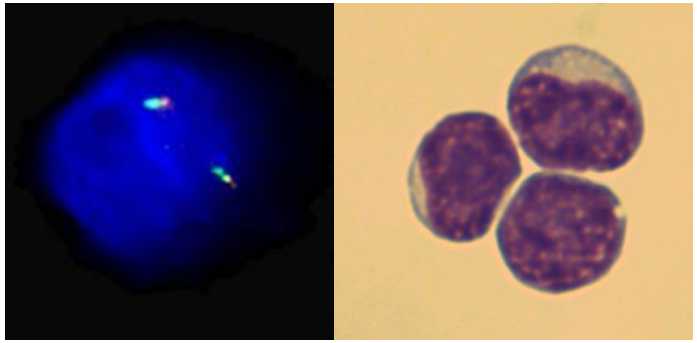
MUC1 Inhibition Eradicates Disease in Previously Engrafted AML









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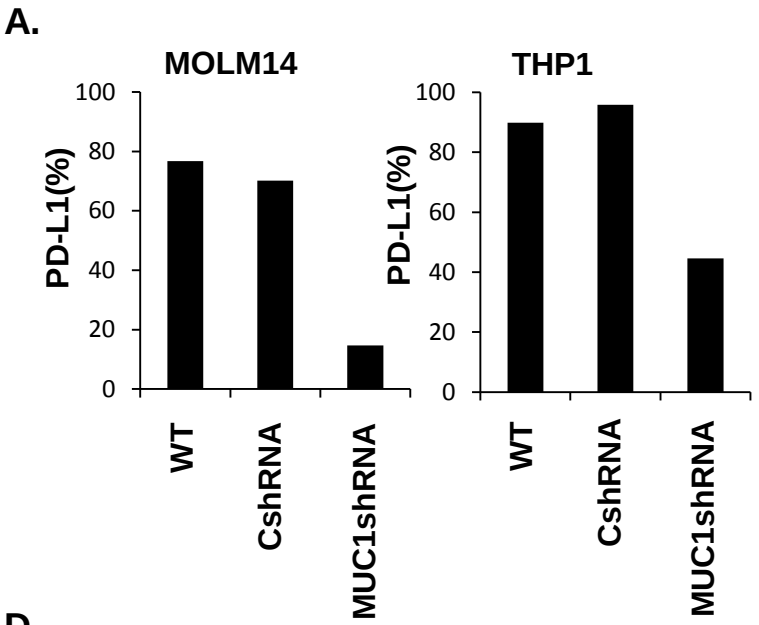
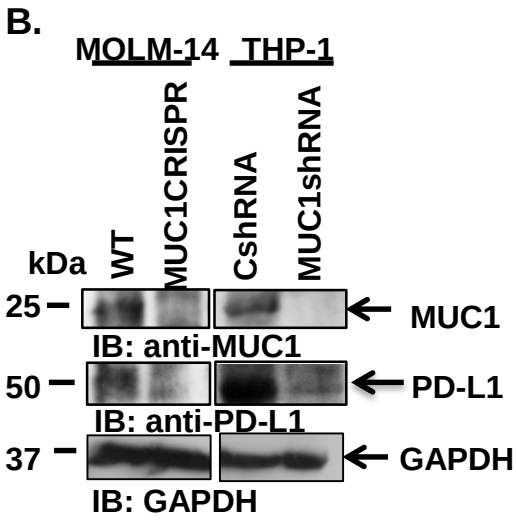
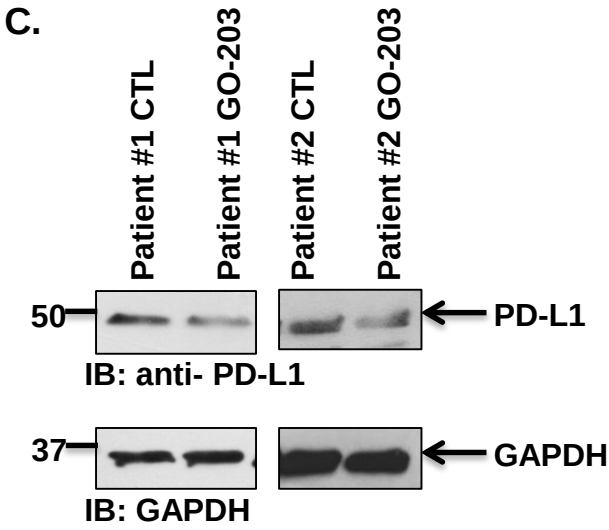
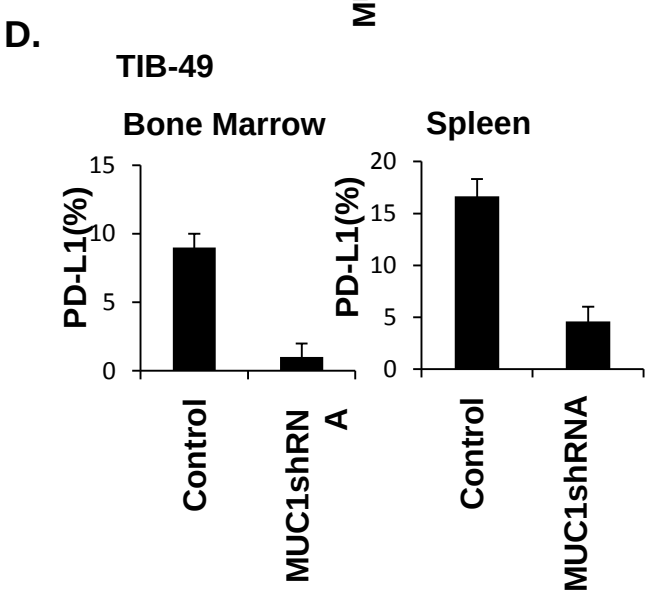
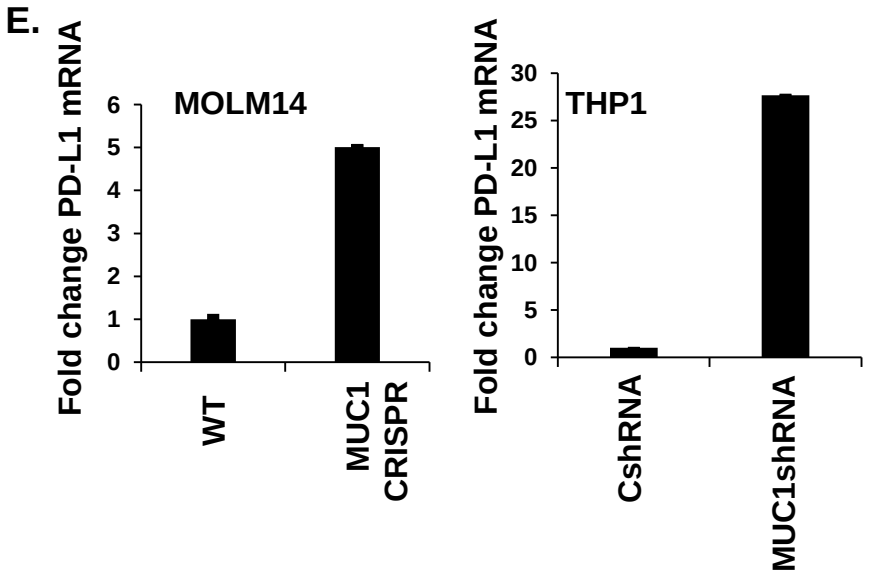
MUC1 Regulates PD-L1 Expression in AML



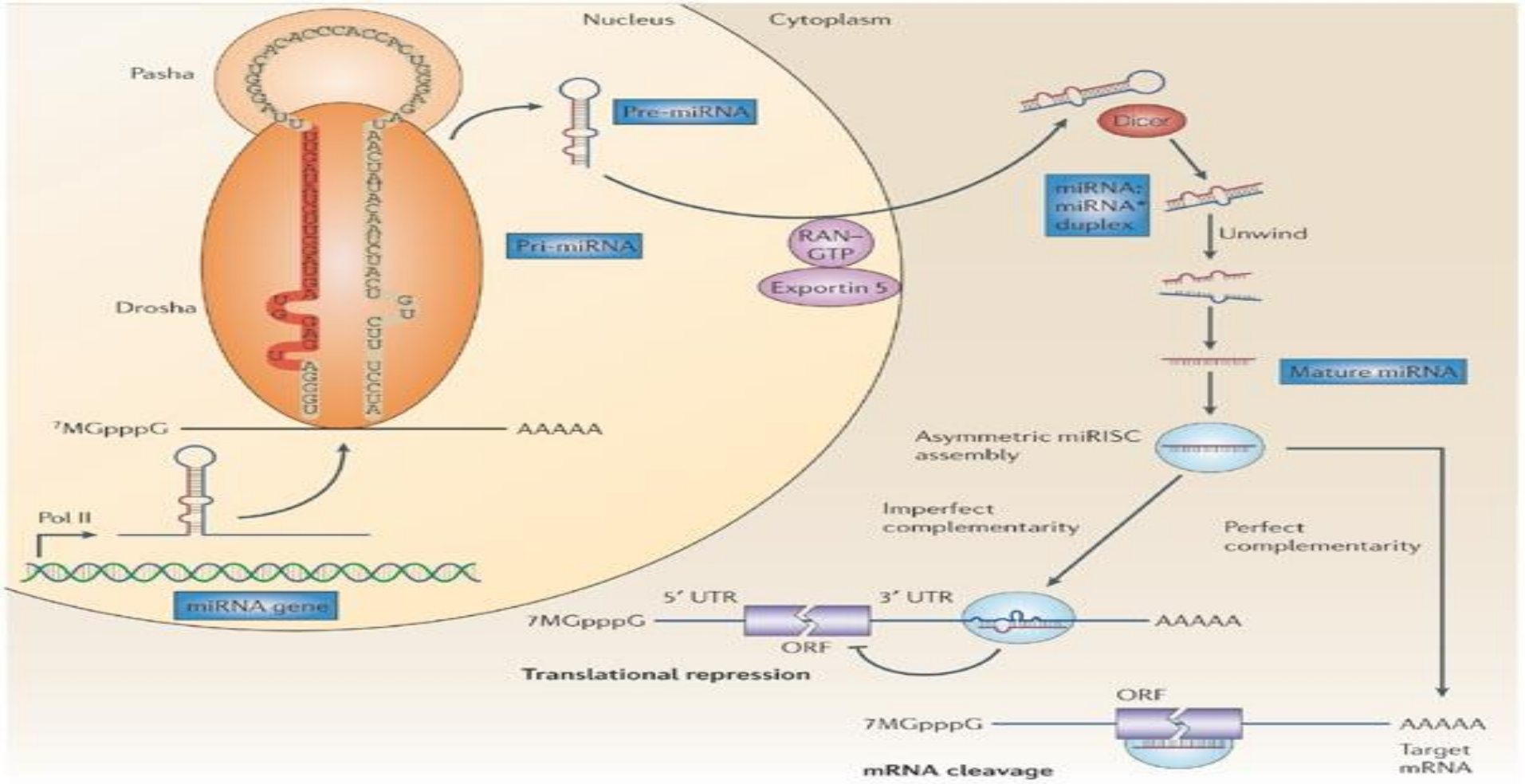




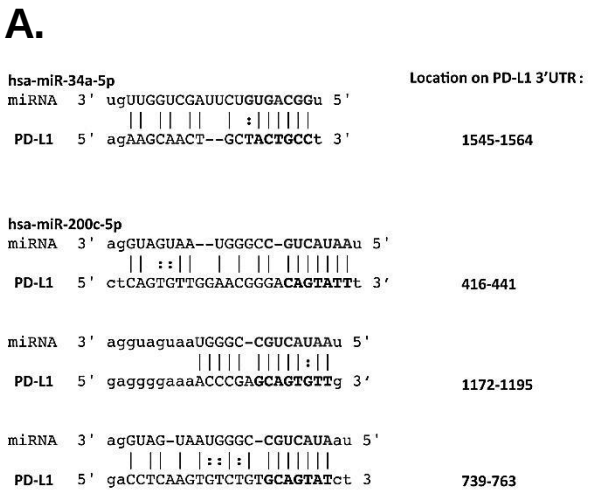


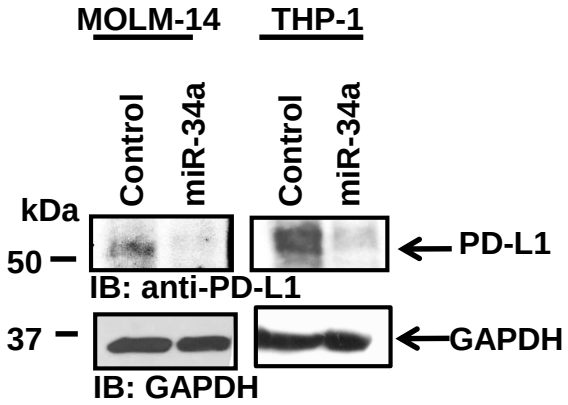


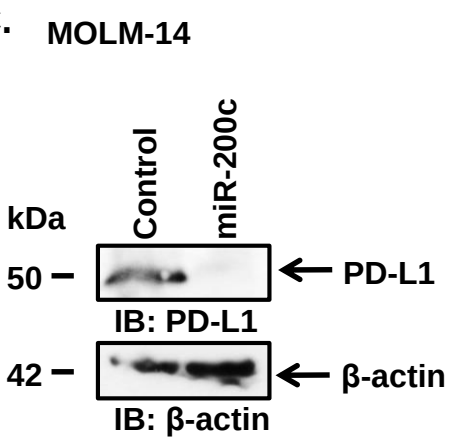
Noncoding RNAs a Critical Regulator of Protein Transcription

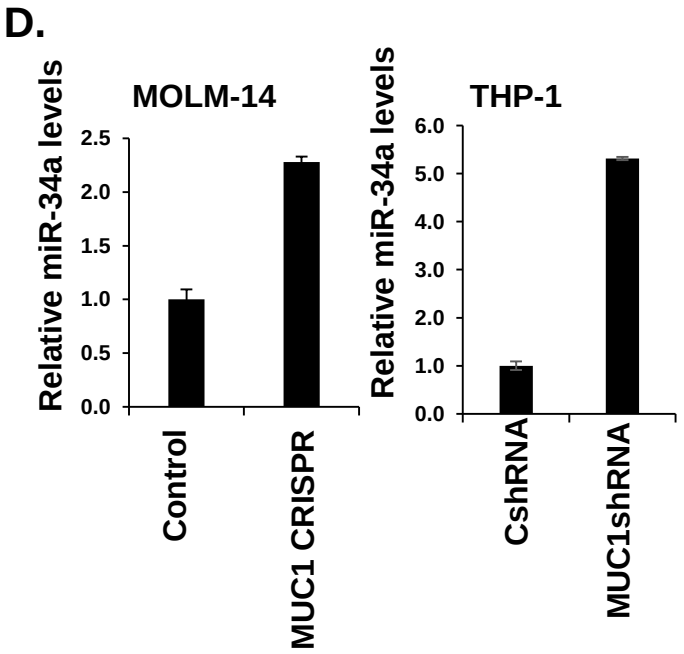


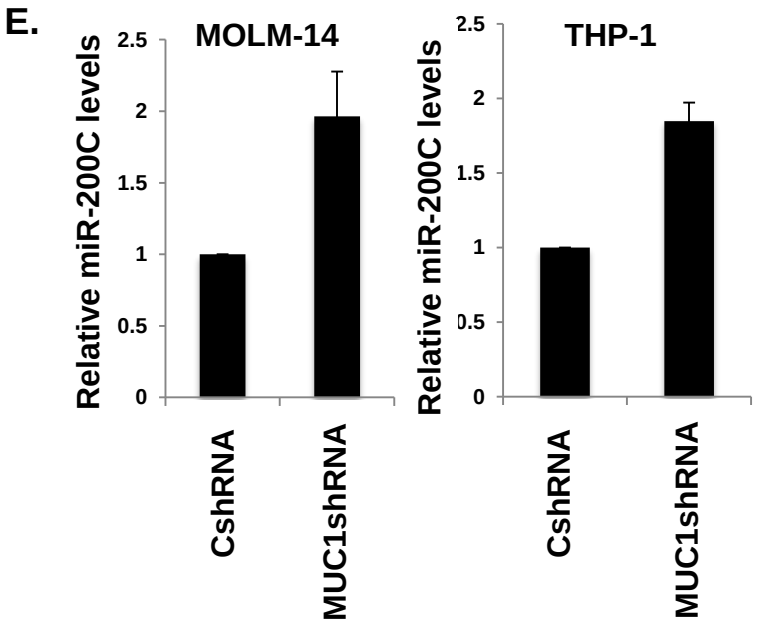
MUC1 regulates PD-L1 in AML via miR200c and miR34a



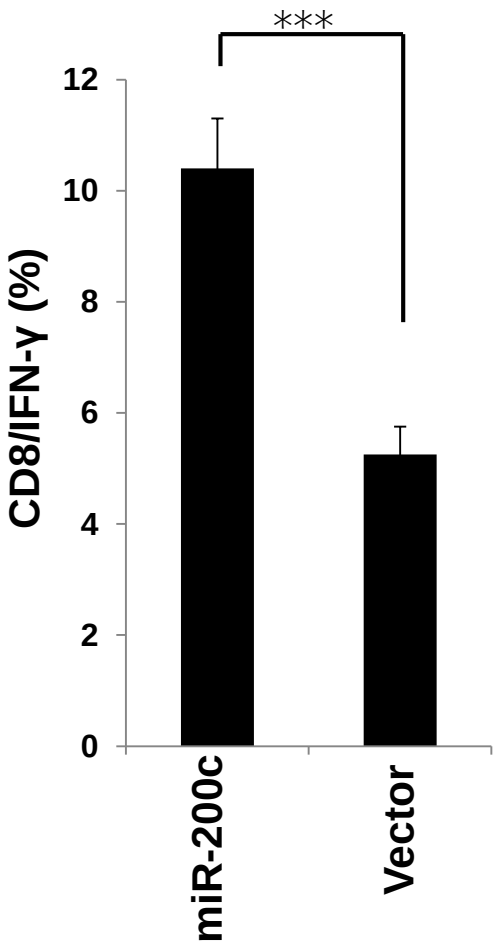


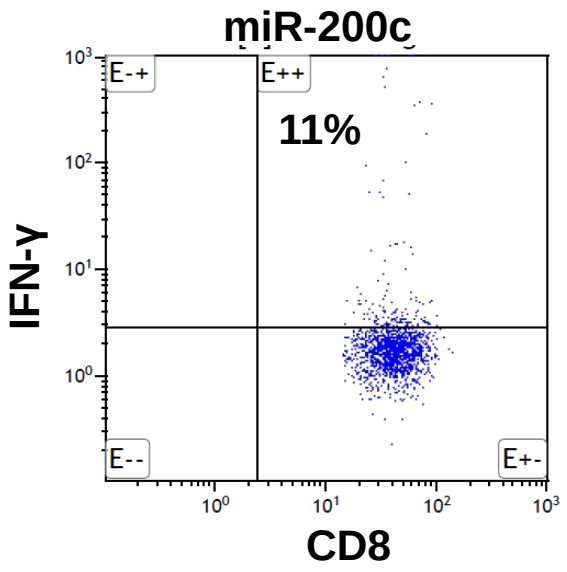


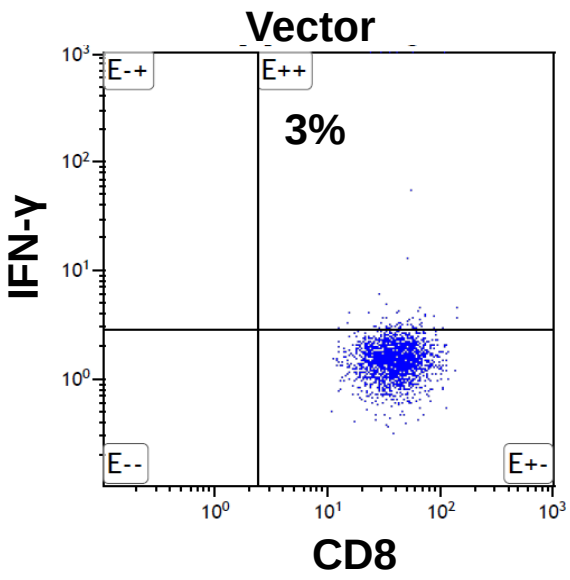




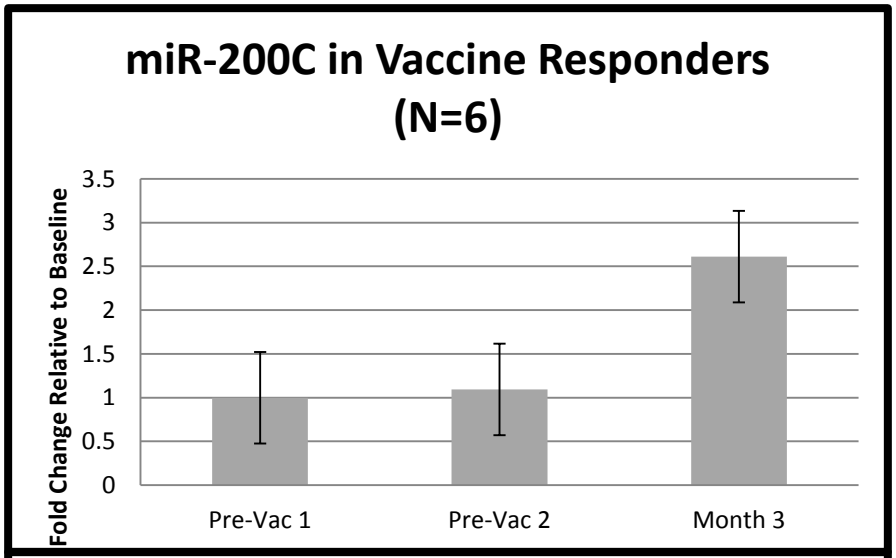
Upregulation of miR200c Results in Increased Tumor Specific Immunity

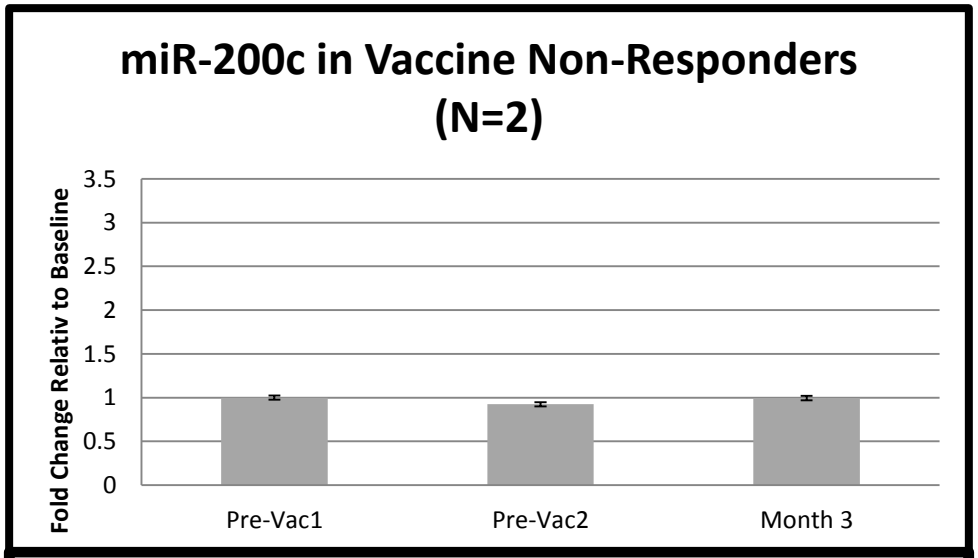


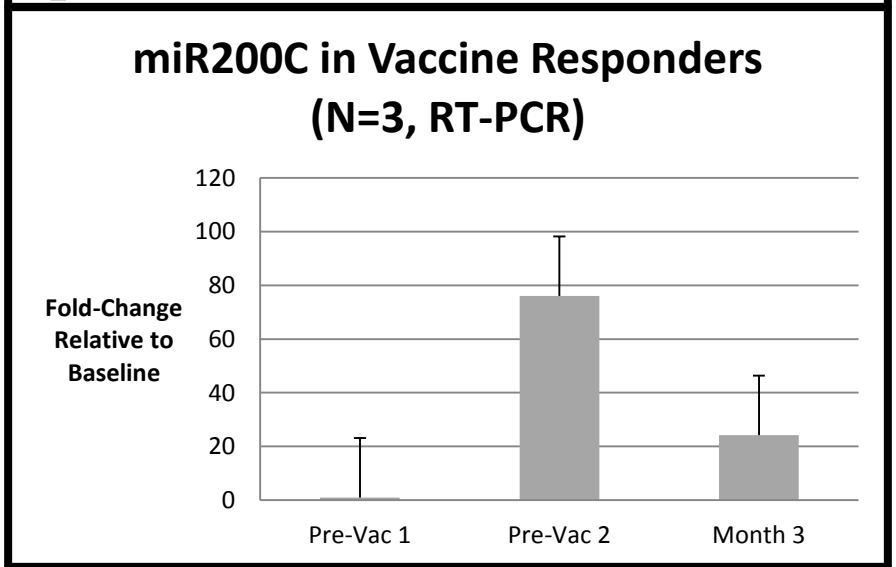


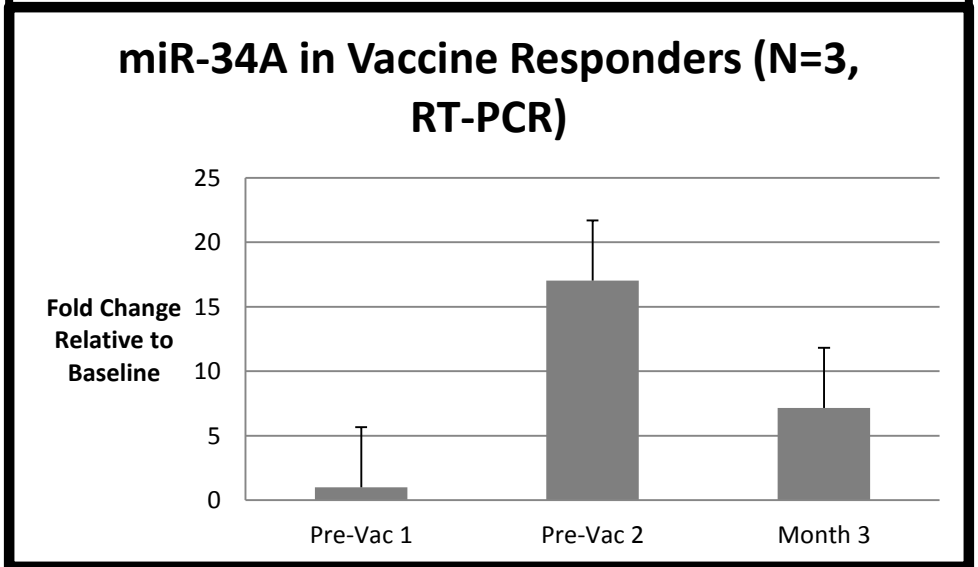


miR200c and miR34a as Biomarkers of Response

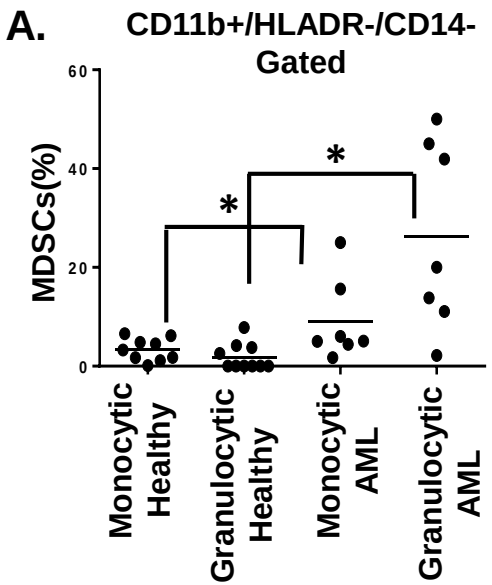


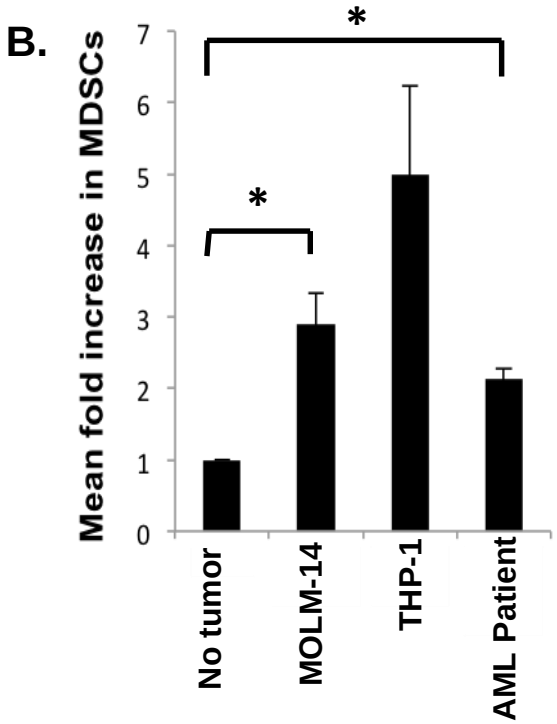


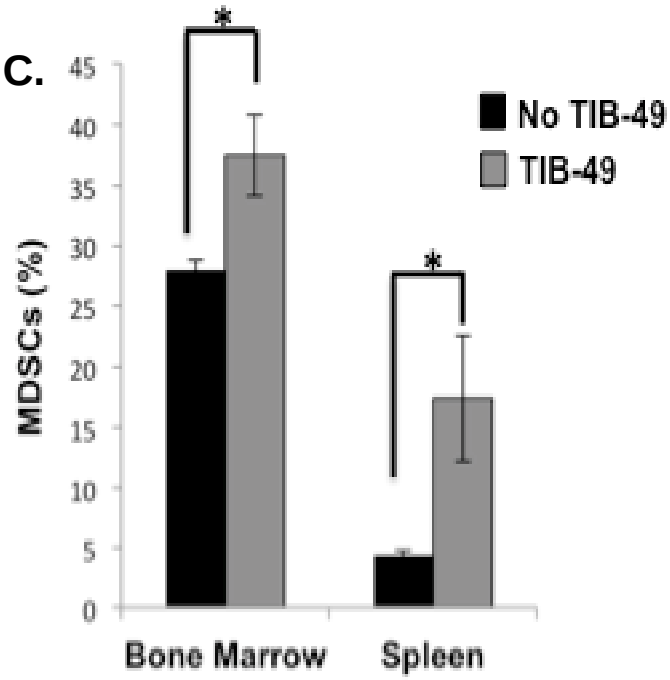




AML mediates MDSC Expansion in the Tumor Bed



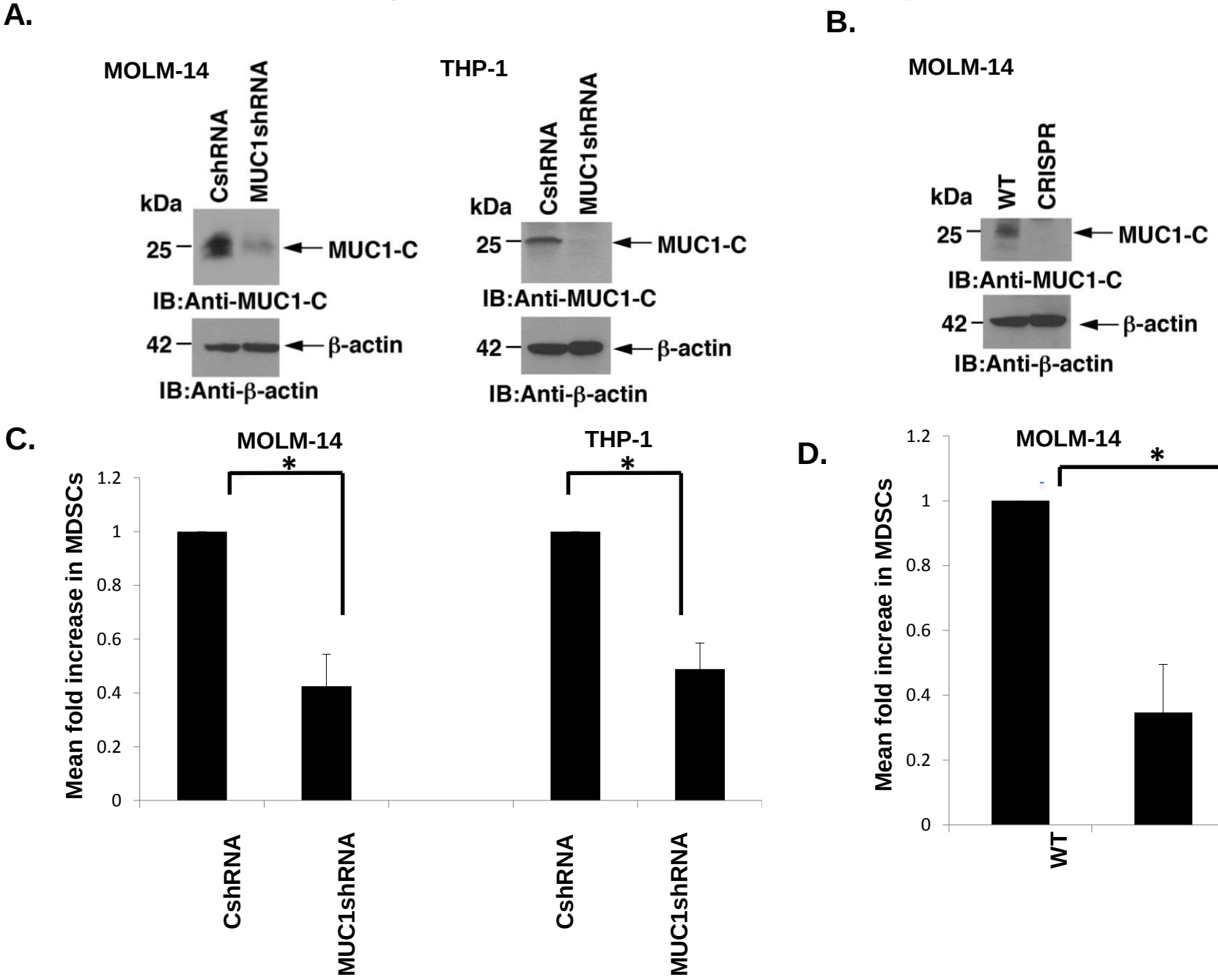




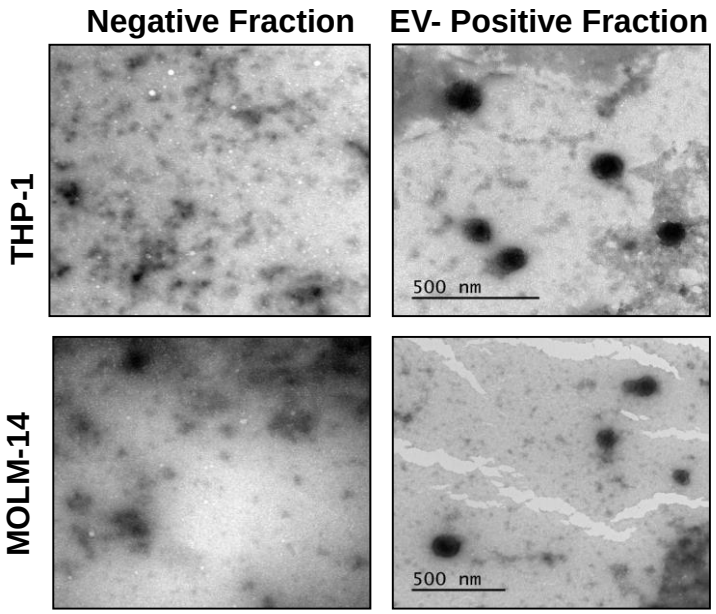
D.

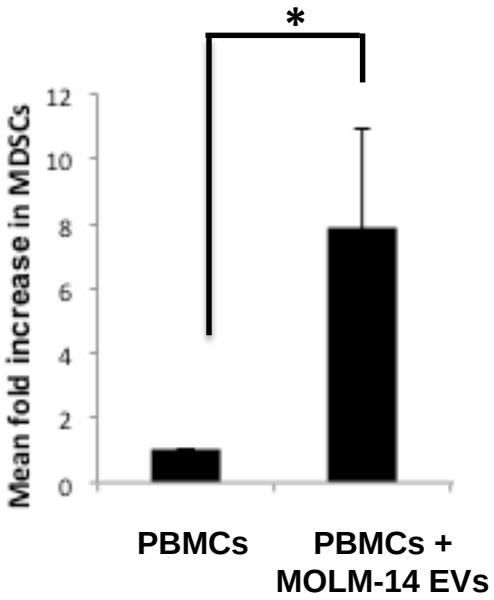
F.

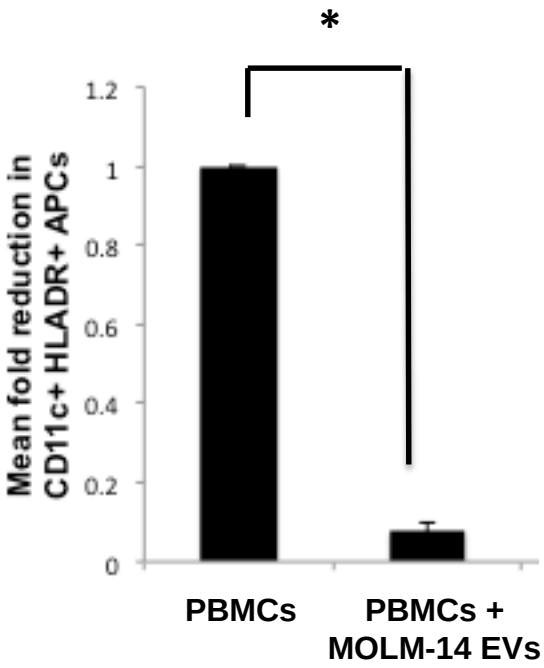
MUC1 silencing leads to a decreased expansion of MDSCs



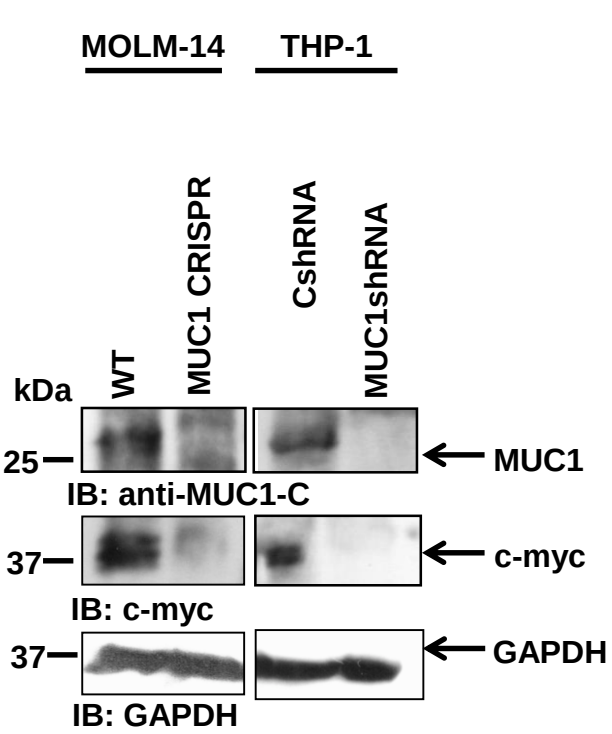
AML EVs mediate MDSC Expansion in the Tumor Bed

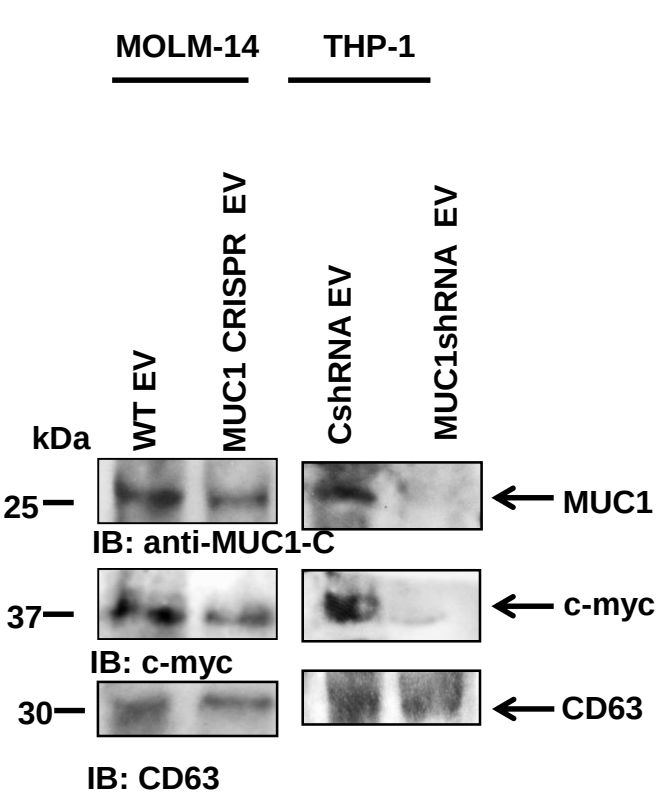


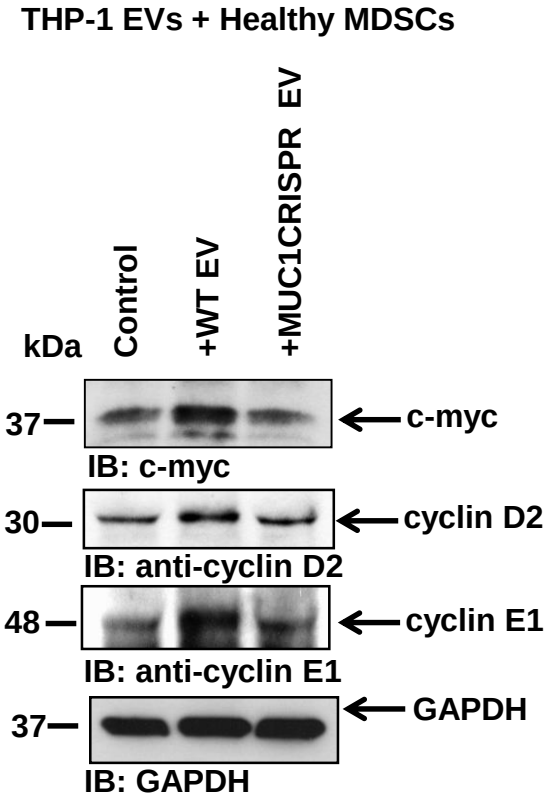




MUC1 promotes c-myc Expression in AML cells and EVs

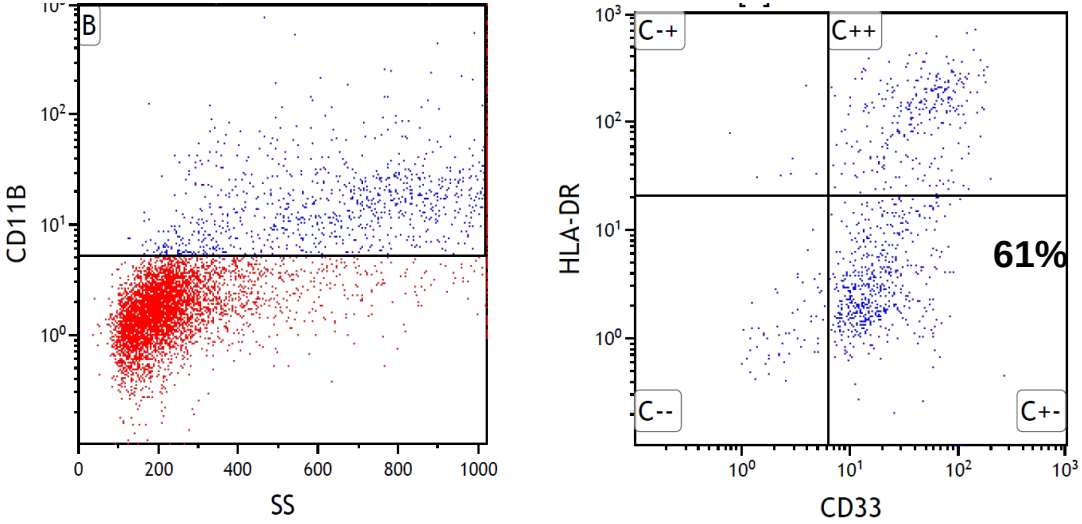




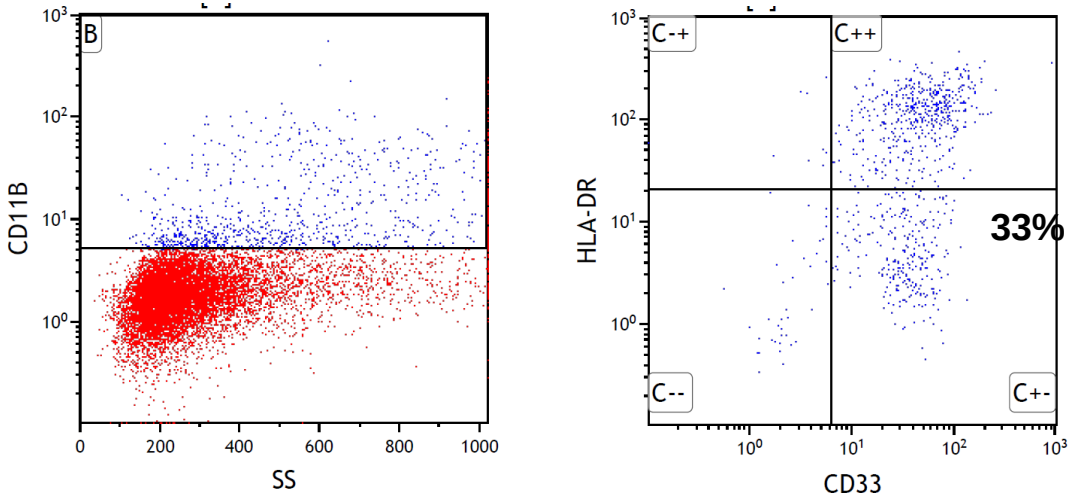


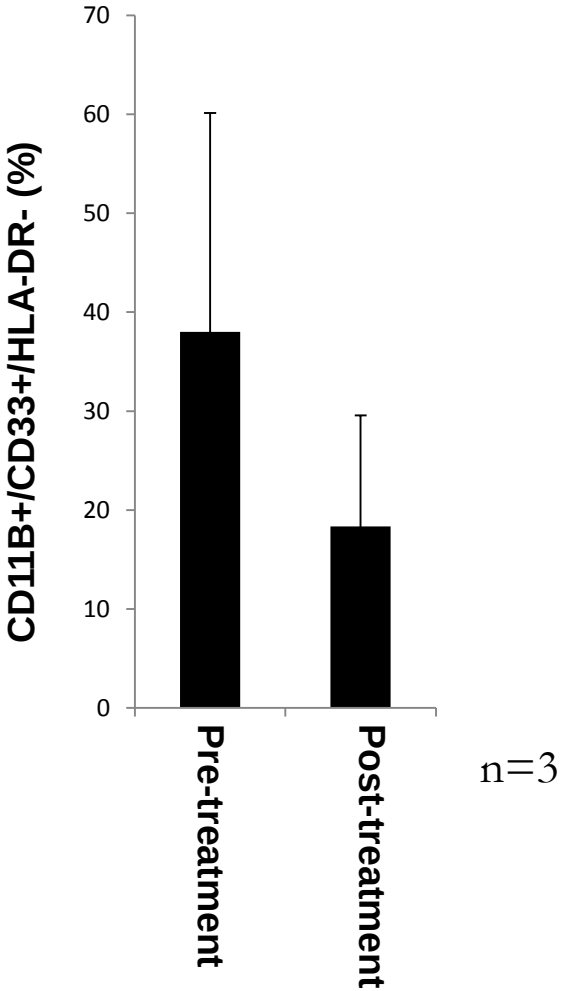
Decrease in Myeloid Derived Suppressor Cells Following Treatment

Pre-treatment

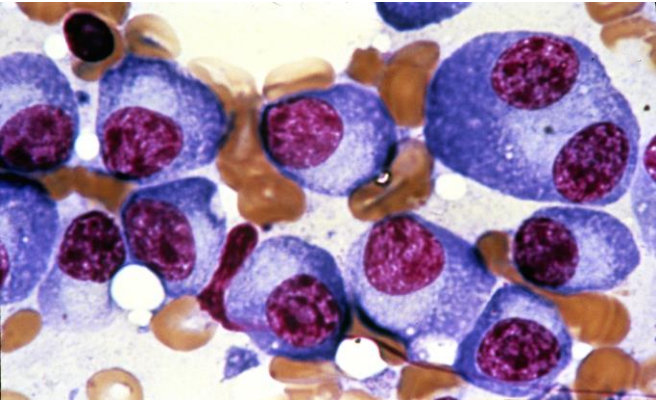


Post-treatment





n=3



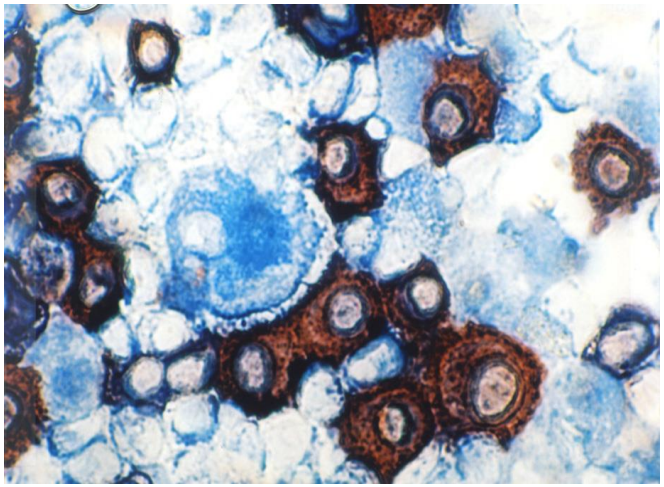
Pursuing Vaccine Therapy in Multiple Myeloma

- Biological therapy and transplant results in high levels of cytoreduction, achievement of MRD- in a subset of patients, and improved long term outcomes
- Patients ultimately experience disease progression
- Can a tumor vaccine effectively target residual disease?

DC/MM Fusion Vaccination in Conjunction with Autologous Transplantation

- Transplant cytoreduction minimizes immunosuppressive effect of MM
- Transplant mediated lymphodepletion transiently breaks tolerance due to T-reg suppression
- Targeting of post-transplant MRD and more durable response
- Capacity to respond to DC vaccination early post-transplant (Chung et al Canc Immunol Res 2015)

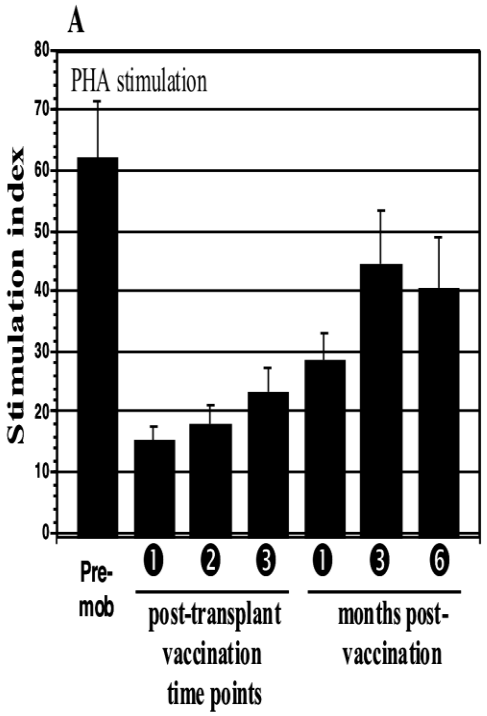
DC/MM Fusion Vaccination in Conjunction with Autologous Transplantation

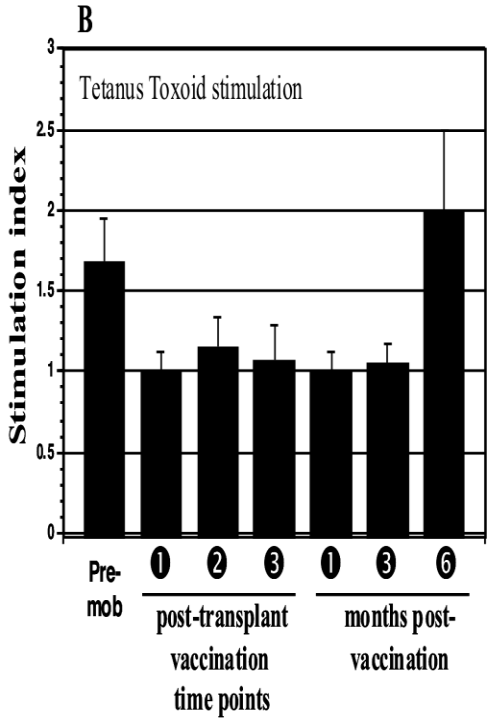


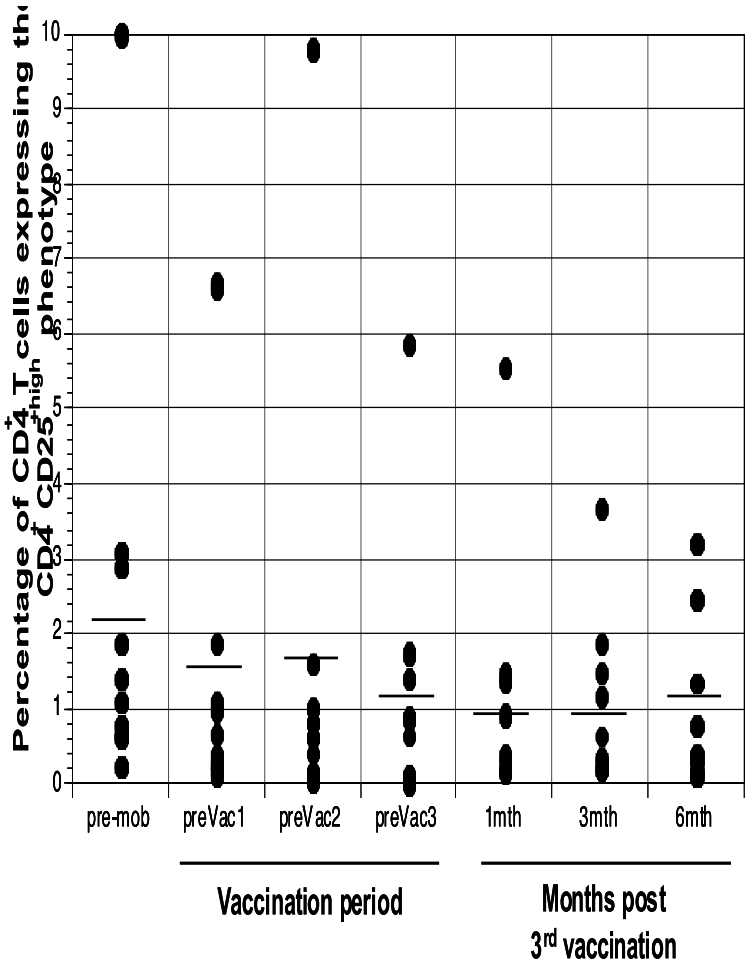
- **Number Enrolled**: 45
  - 80% Male, 20% Female
- **Number Received Vaccine**: 35
- **Median Age at Enrollment**: 58
- **Median Bone Marrow Involvement at Enrollment**: 55% plasma cells
- **Median Time from Transplant to Post-Transplant Vaccine**: 48 days

Rosenblatt et al CCR 2013

Impact of Transplantation on Cell Mediated Immunity and Tregs

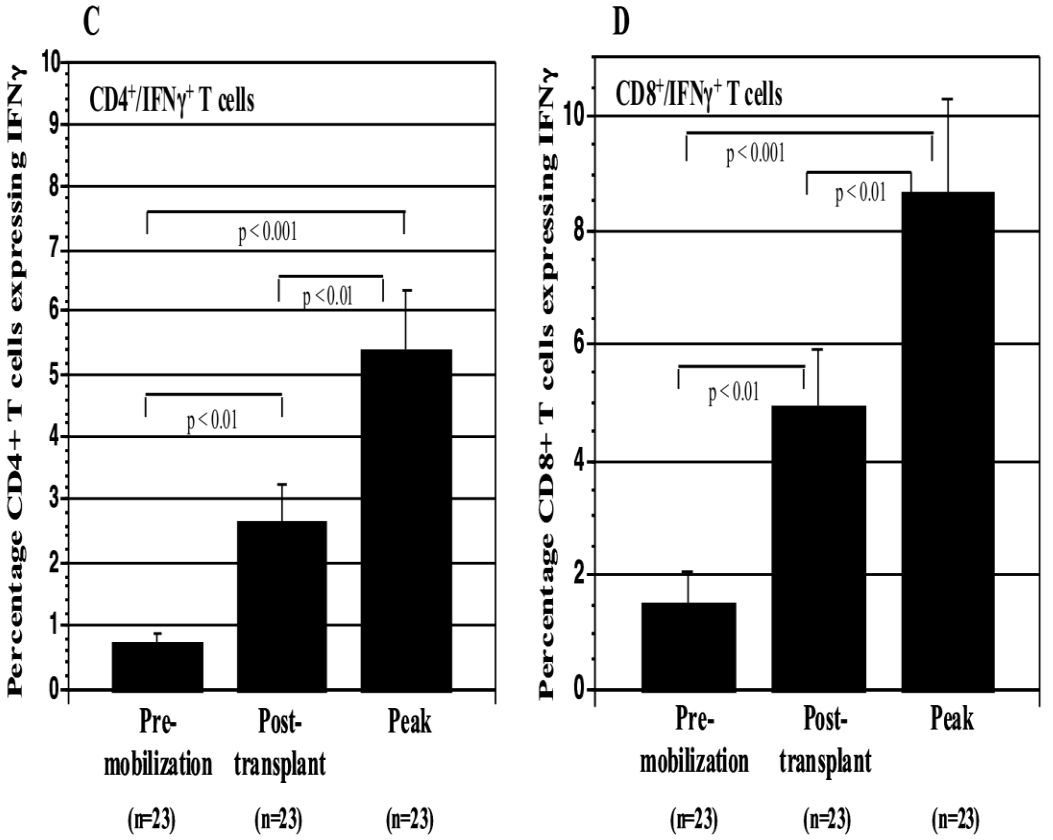


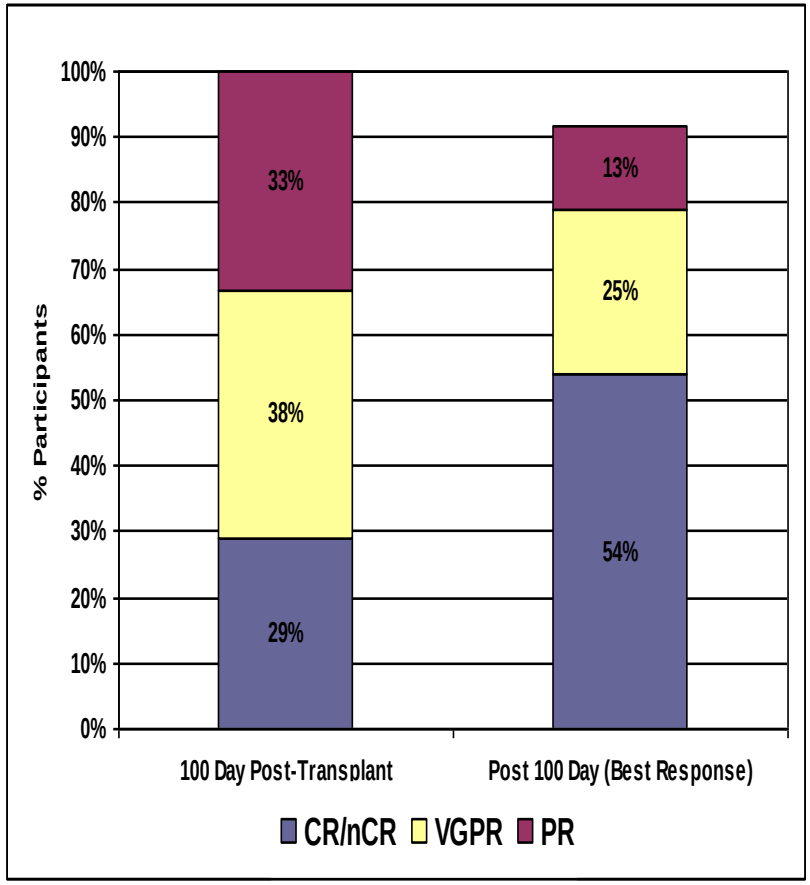




Rosenblatt et al CCR 2013

Vaccination Induced Expansion of MM reactive T cells and Targeting of MRD





Rosenblatt et al CCR 2013

BMT CTN Protocol 1401

Phase II Multicenter Trial of Single Autologous Hematopoietic Cell Transplant Followed by Lenalidomide Maintenance for Multiple Myeloma with or without Vaccination with Dendritic Cell (DC)/Myeloma Fusions

(MY T VAX)

David Avigan, Nina Shah, David Chung

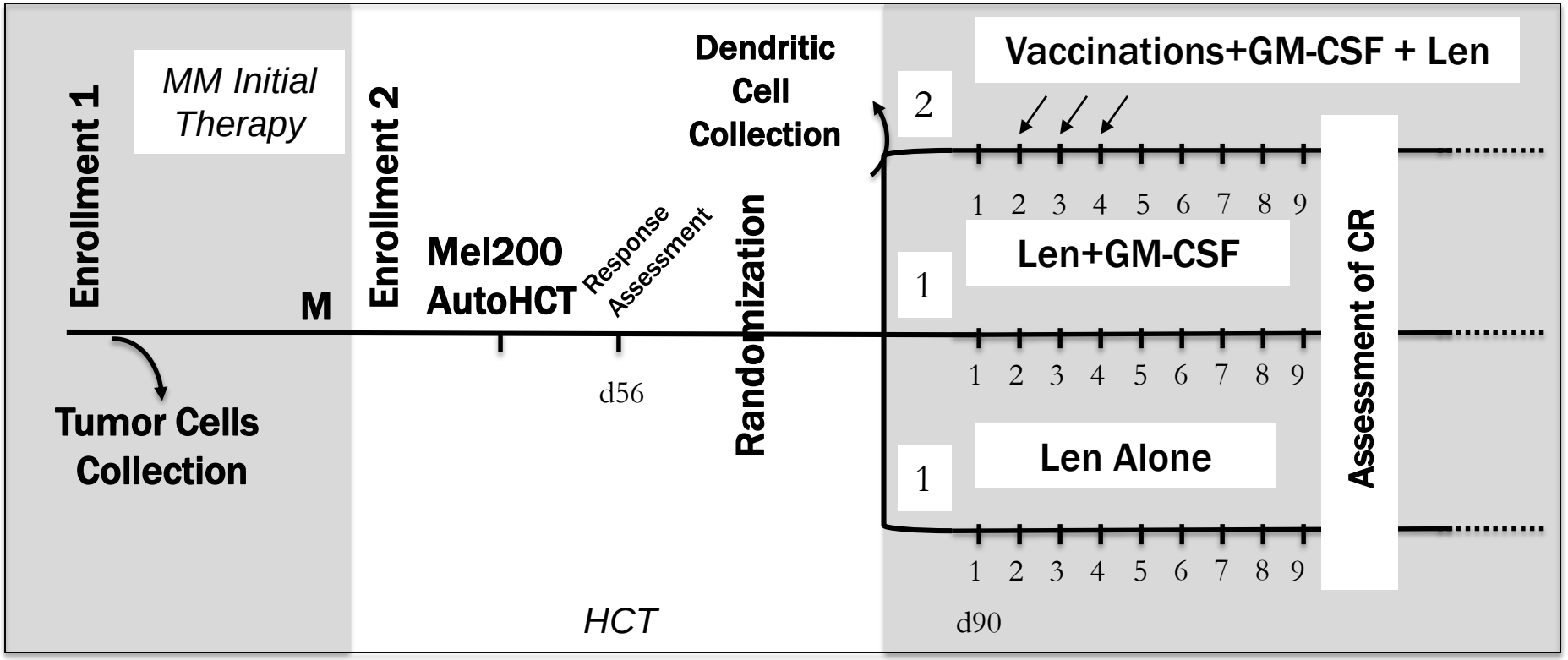
Marcelo Pasquini

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

CTN Protocol 1401

- Academic led multicenter trial for cellular therapy in cooperative groups setting
- Site specific production of DC/tumor fusions
- Central review of vaccine characterization and verification of release criteria
- Integrated scientific assessment of cellular and humoral immune response as team science by centers of excellence

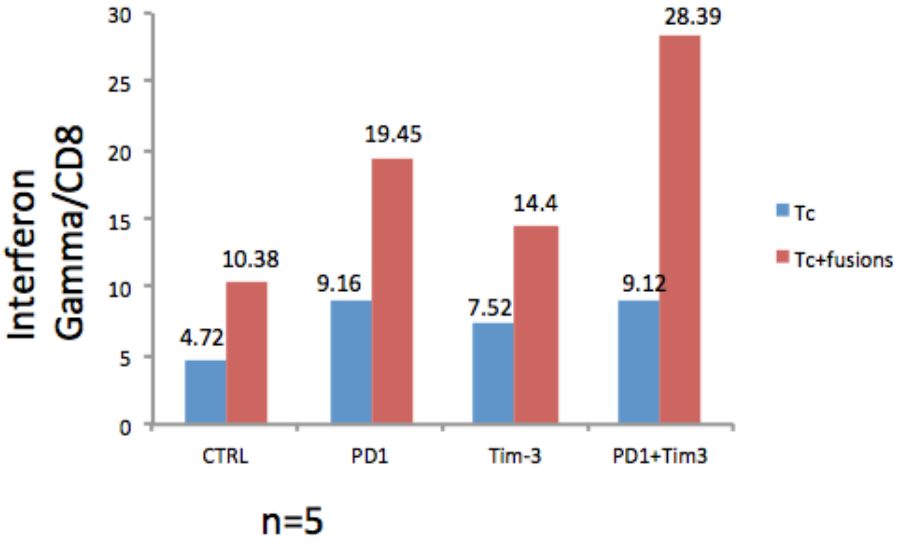
Study Schema

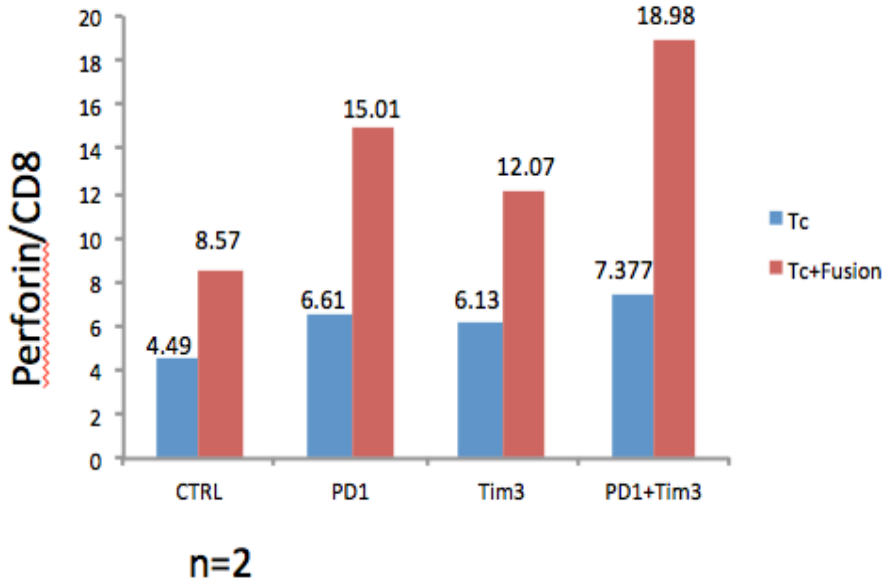


- Accrual targets 188 patients to be enrolled with a target of 132 patients to be randomized
- Assuming about 30% of patients are unable to proceed with post-transplant immunotherapy.
  - Arm A: Maintenance lenalidomide + vaccine + GM-CSF (n=66)
  - Arm B: Maintenance lenalidomode + GM CSF (n=33)
  - Arm C: Maintenance lenalidomide alone (n=33)

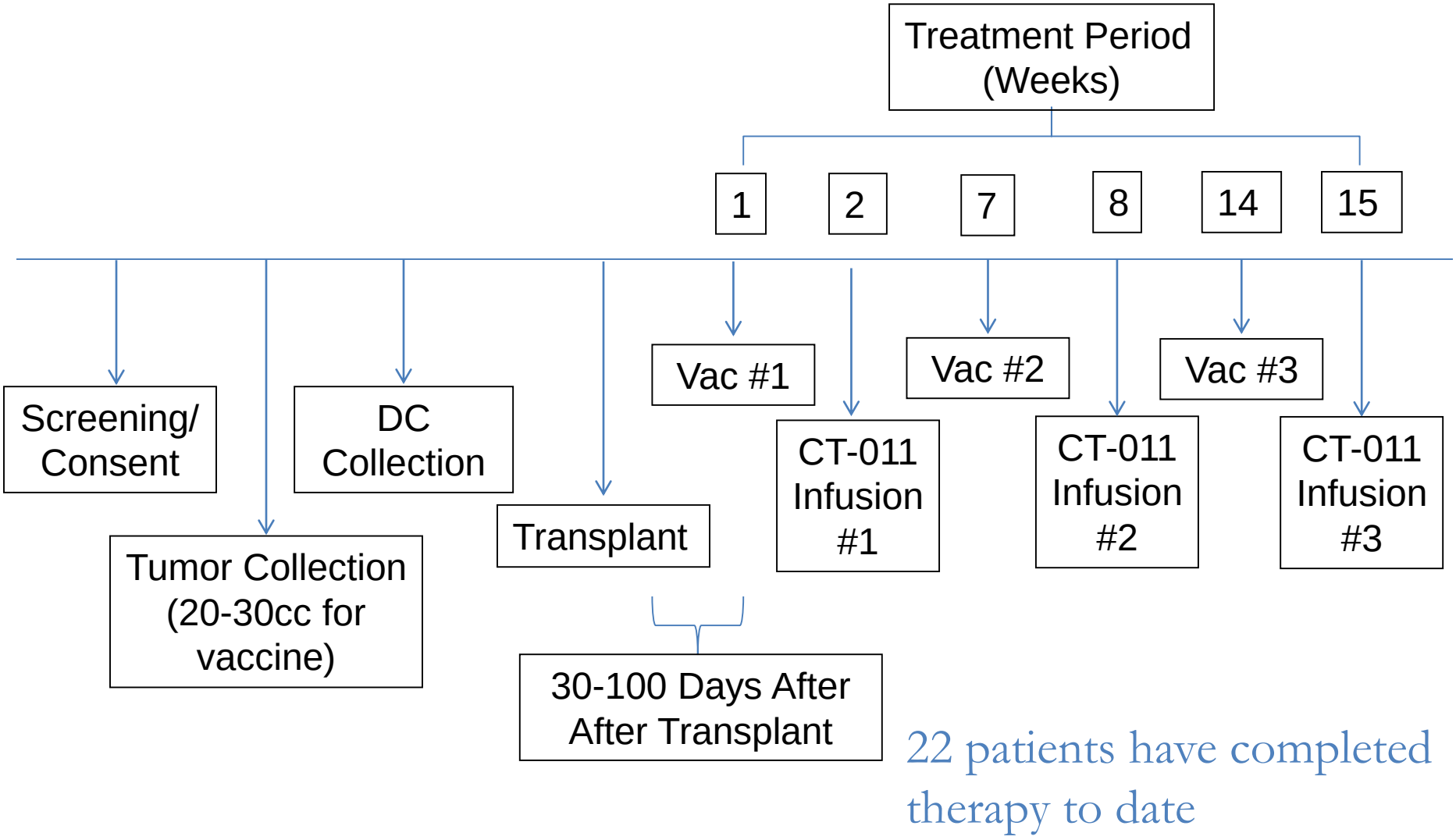
- Patients will be stratified according to disease status at time of randomization between
- CR and sCR and VGPR/PR/Stable disease.

Combination Checkpoint Blockade Enhances Immune Response to DC/MM fusions in vitro



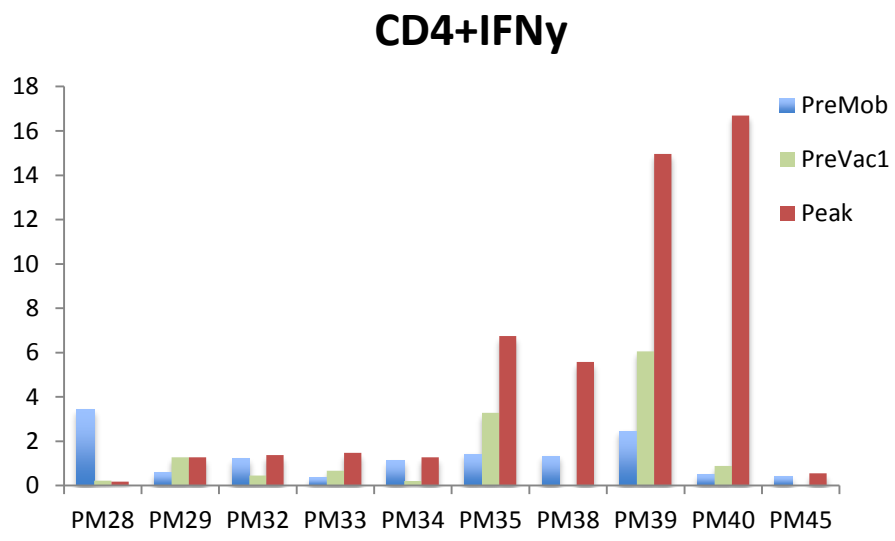


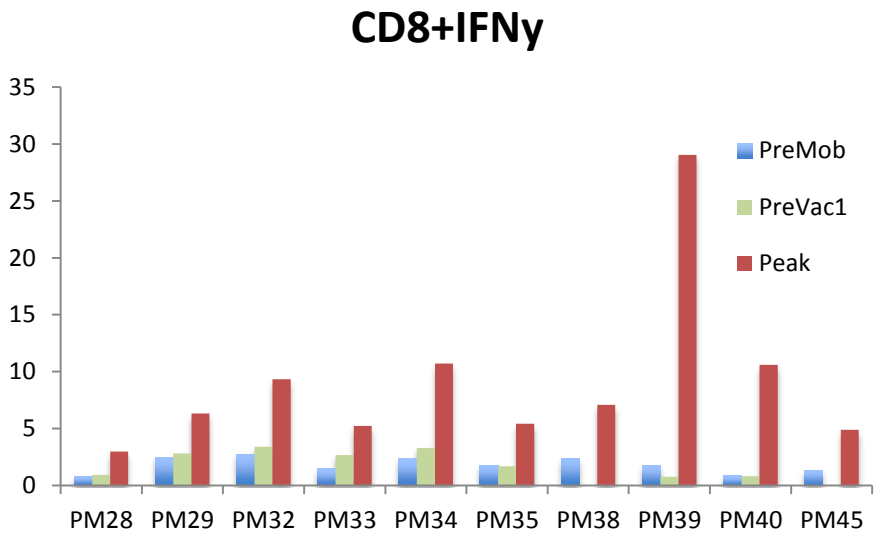
Pidilizumab + DC/MM Fusions Post-transplant

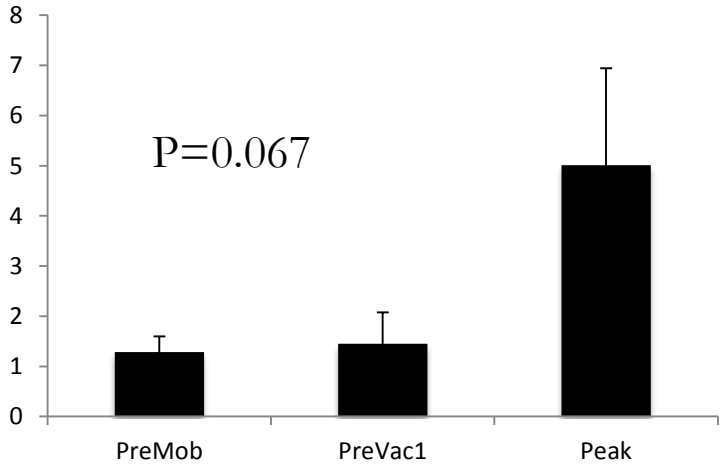


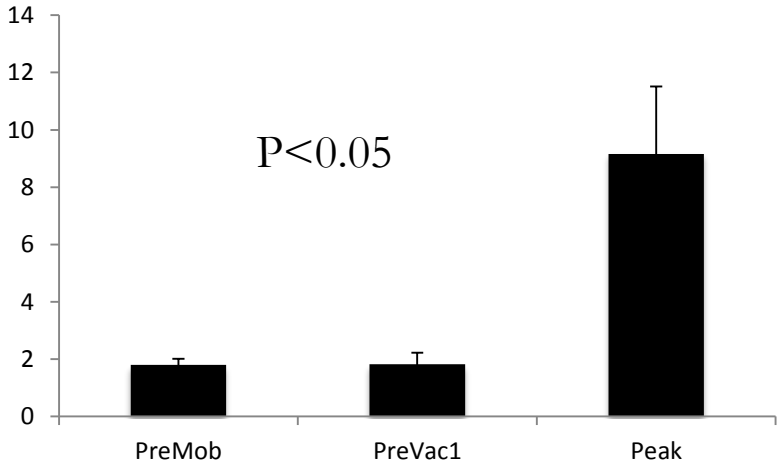
22 patients have completed therapy to date

Immune Response to Vaccine

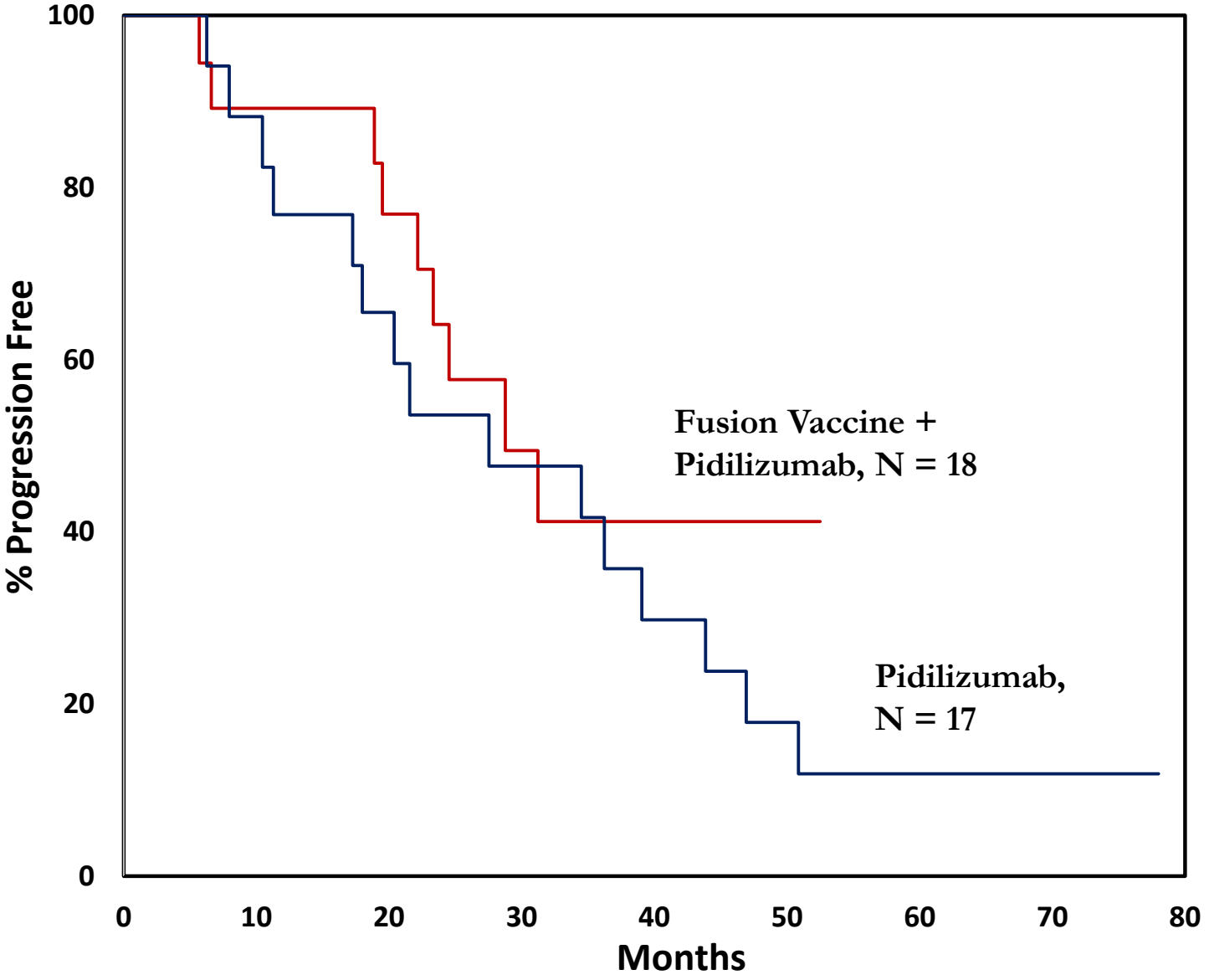








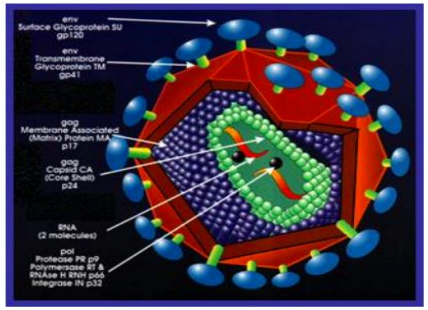
Progression Free Survival: Is There a Plateau?

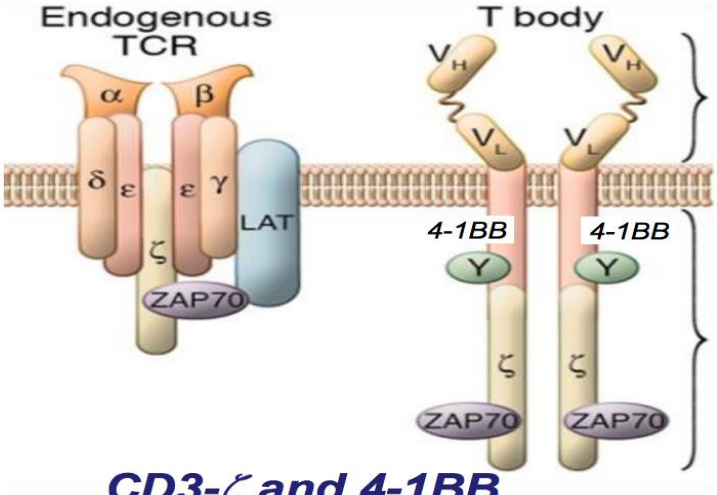


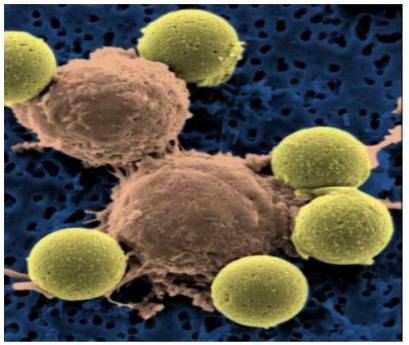
Where are we heading?

2nd Generation CAR for B Cell Malignancy:

Autologous T Cells Transduced w/ Anti-CD19 Receptor Spliced to CD3 zeta and 4-1BB Signaling Domains







Lentiviral vector to deliver construct

CD3-ζ and 4-1BB signaling domains augments proliferation and survival

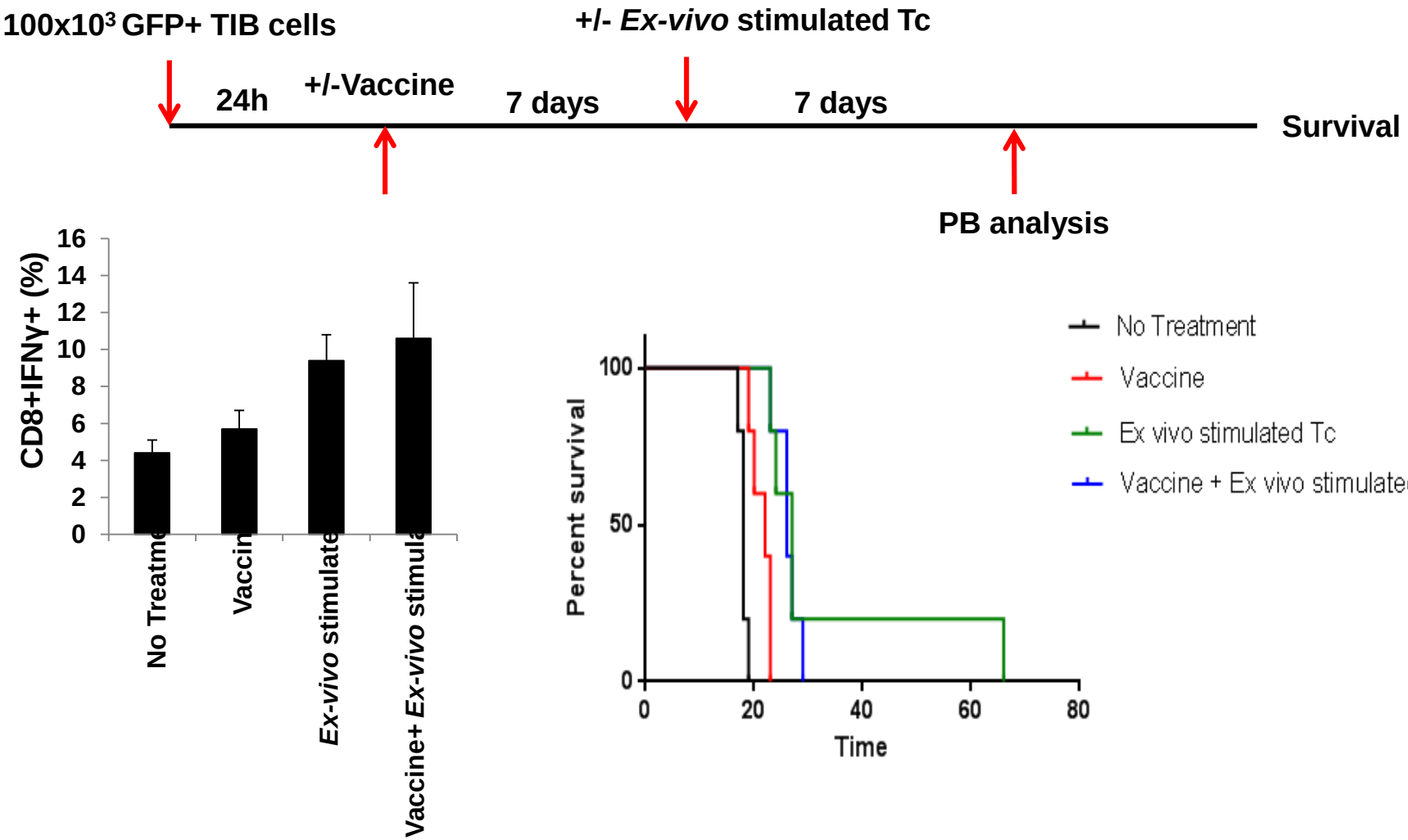
Anti-CD3/anti-CD28 mab coated bead stimulation (artificial DC)

CARs directed against CD19 have been tested in CLL and ALL

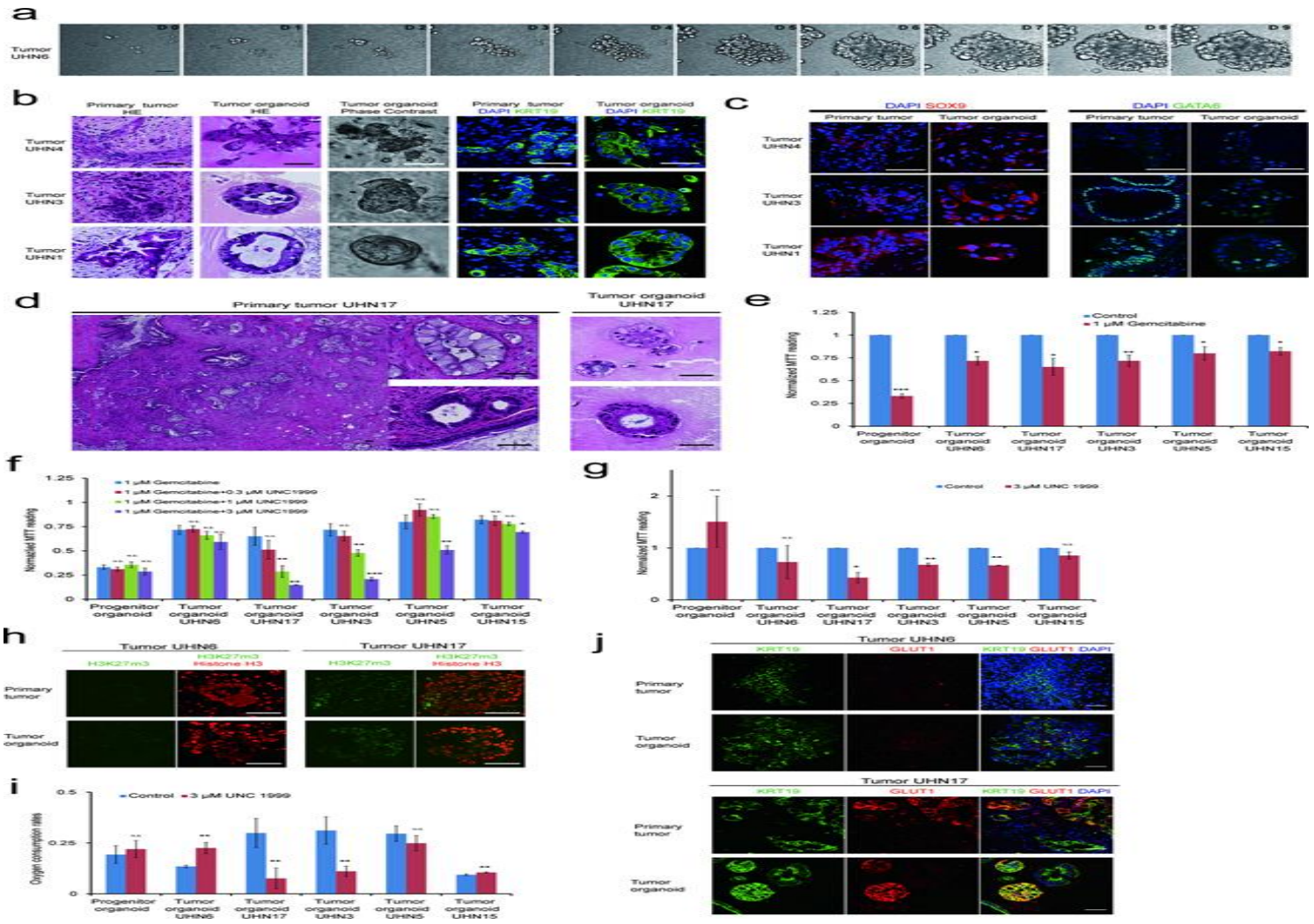
Toxicity due to unregulated expansion of activated T cells

Resistance due to lack of persistence and escape by antigen negative variants

Vaccination in Conjunction with Activated Effector Cells

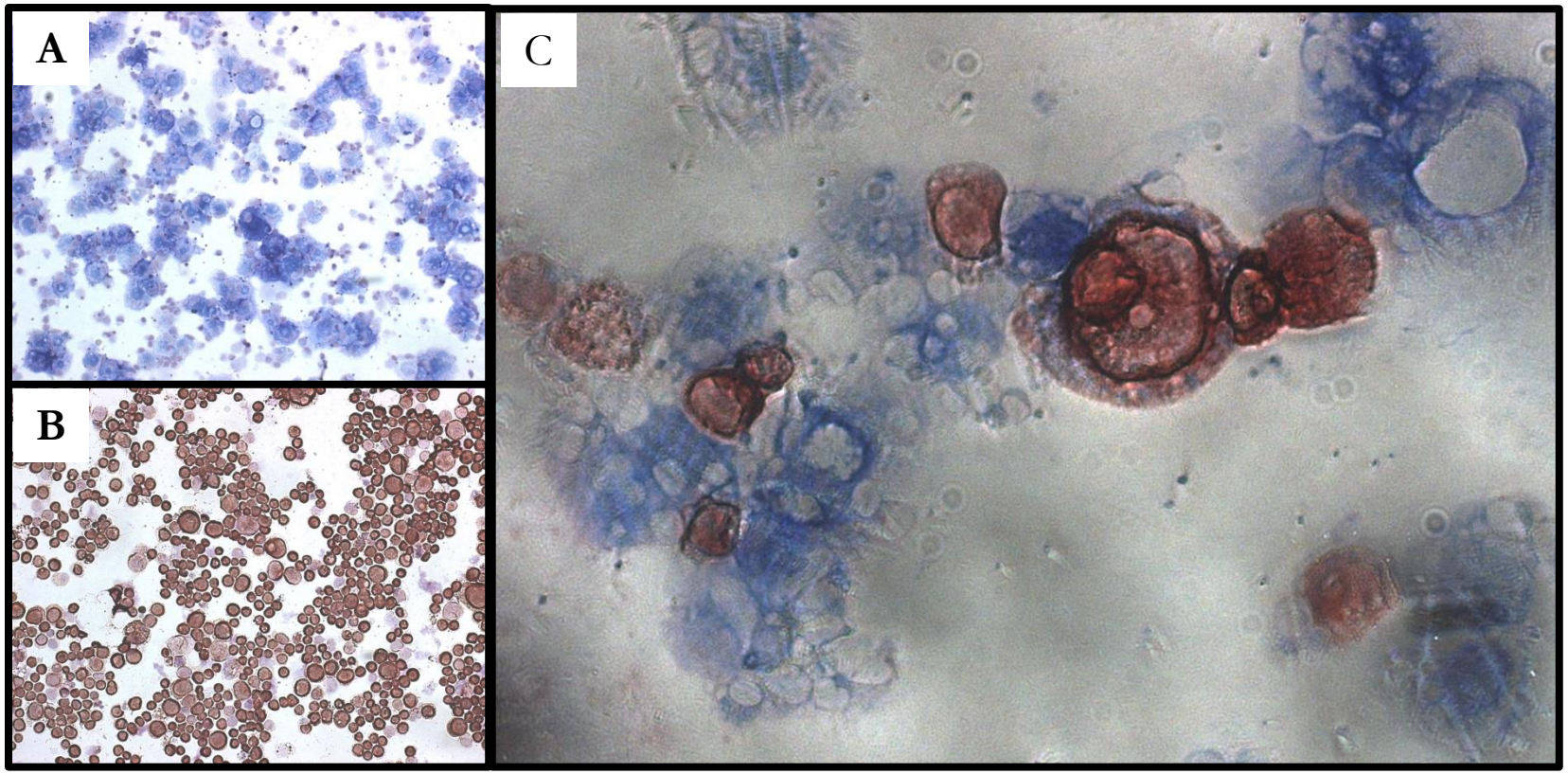


Organoids for Pancreatic Cancer
A Platform for Tumor Ex Vivo Expansion



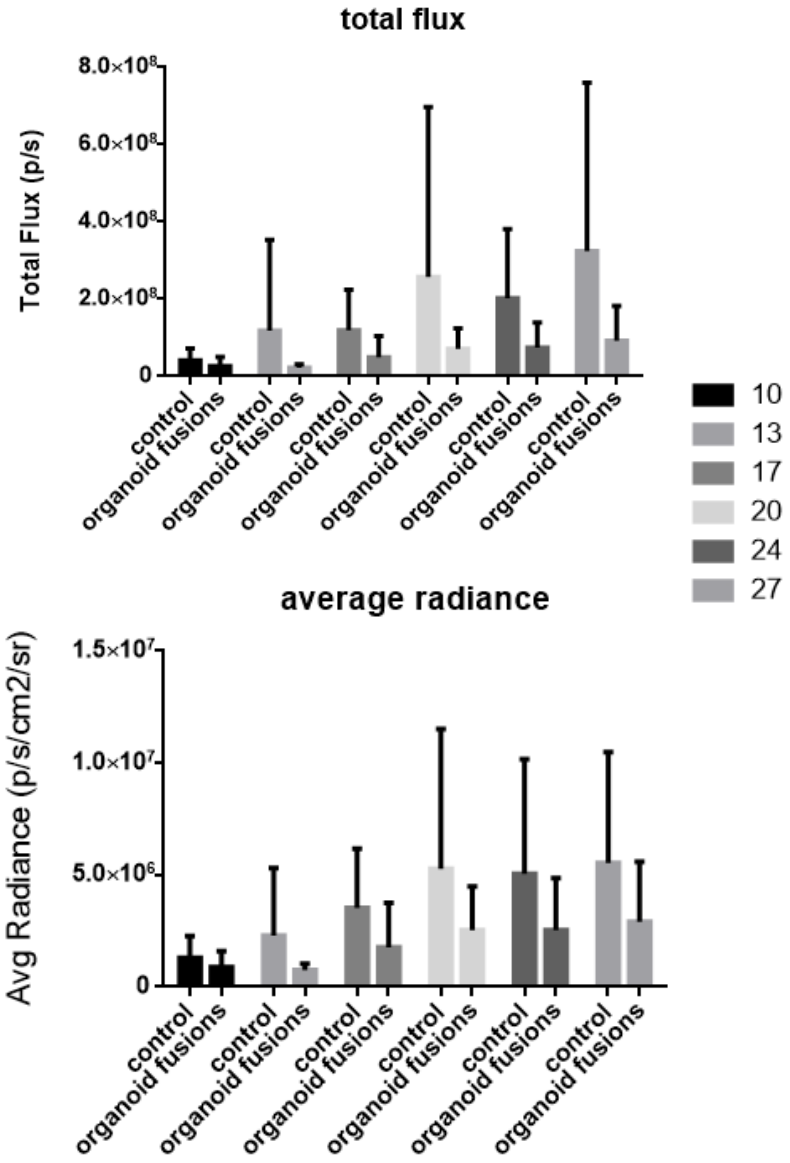
Huang et al Nat Medicine 2015

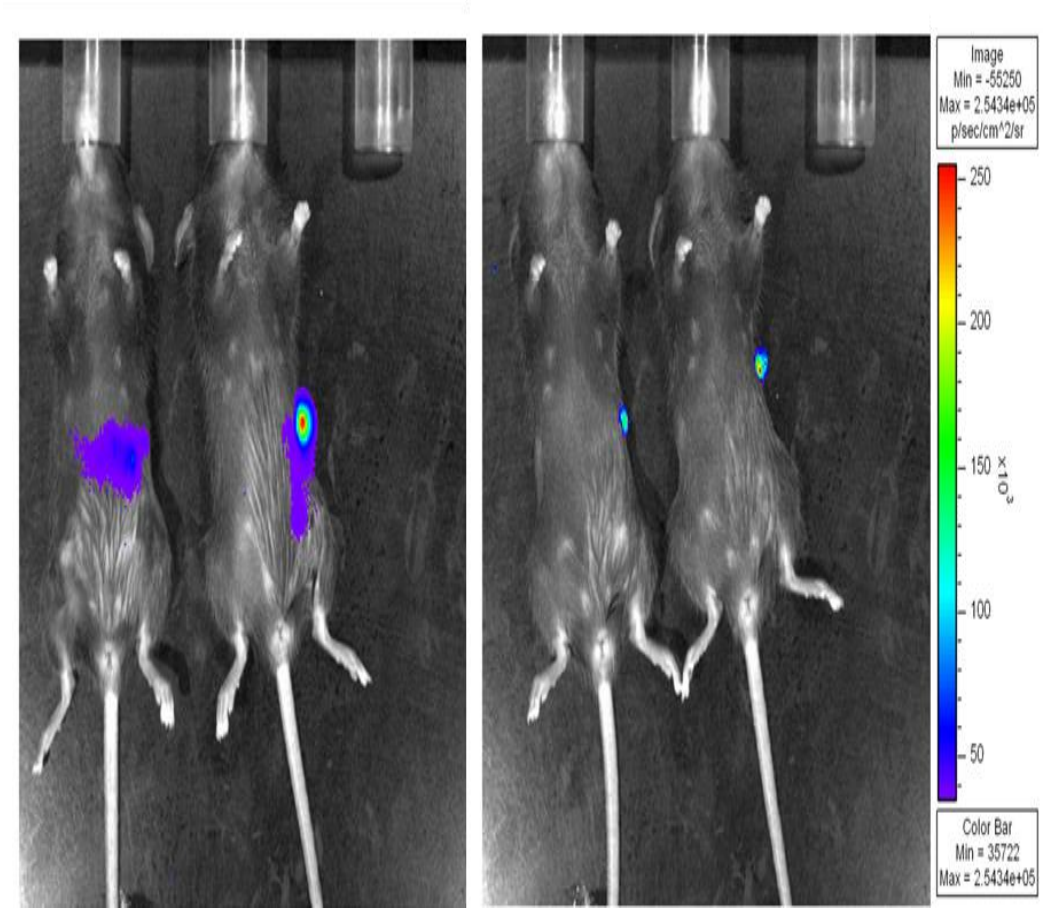
Fusions of human cells derived from organoids to murine derived dendritic cells



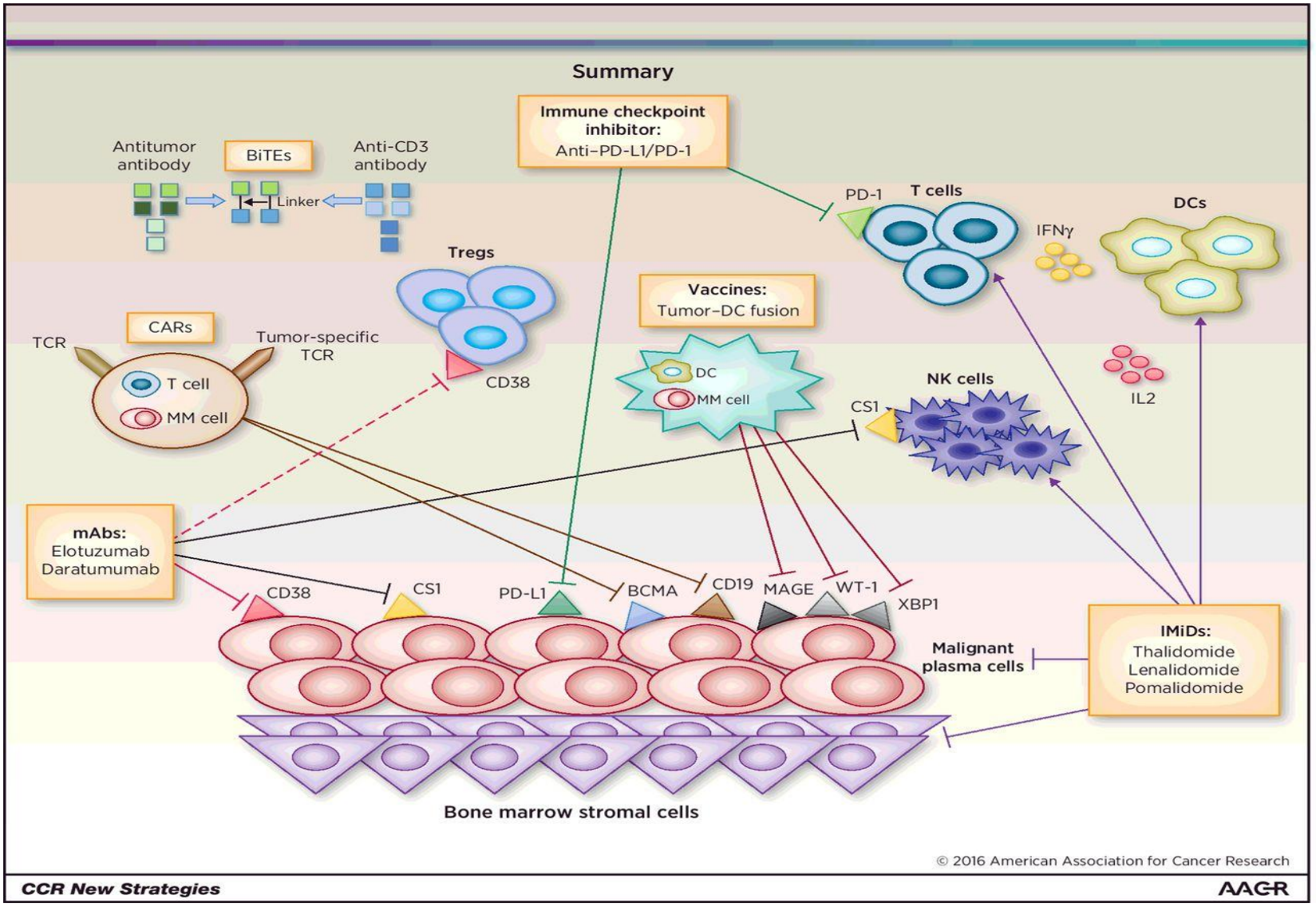
(A) Murine DCs stained for CD86. (B) 363 cell line following dissolving of the organoid to obtain a single cell suspension. The cells are stained for MS-a CK19. (C) Fusions of DCs and 363 cells can be seen by co-localization of the two stains.

Decreased luciferase signal in mice treated with vaccine





Pursuing Combination Immune Based Therapy



Clinical Cancer Research
AACR American Association for Cancer Research

Paola Neri et al. Clin Cancer Res 2016;22:5959-5965

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DOD Gateway for Cancer Research