

Society for Immunotherapy of Cancer (SITC)

Rationale for Combining Immunotherapy with Chemotherapy or Targeted Therapy

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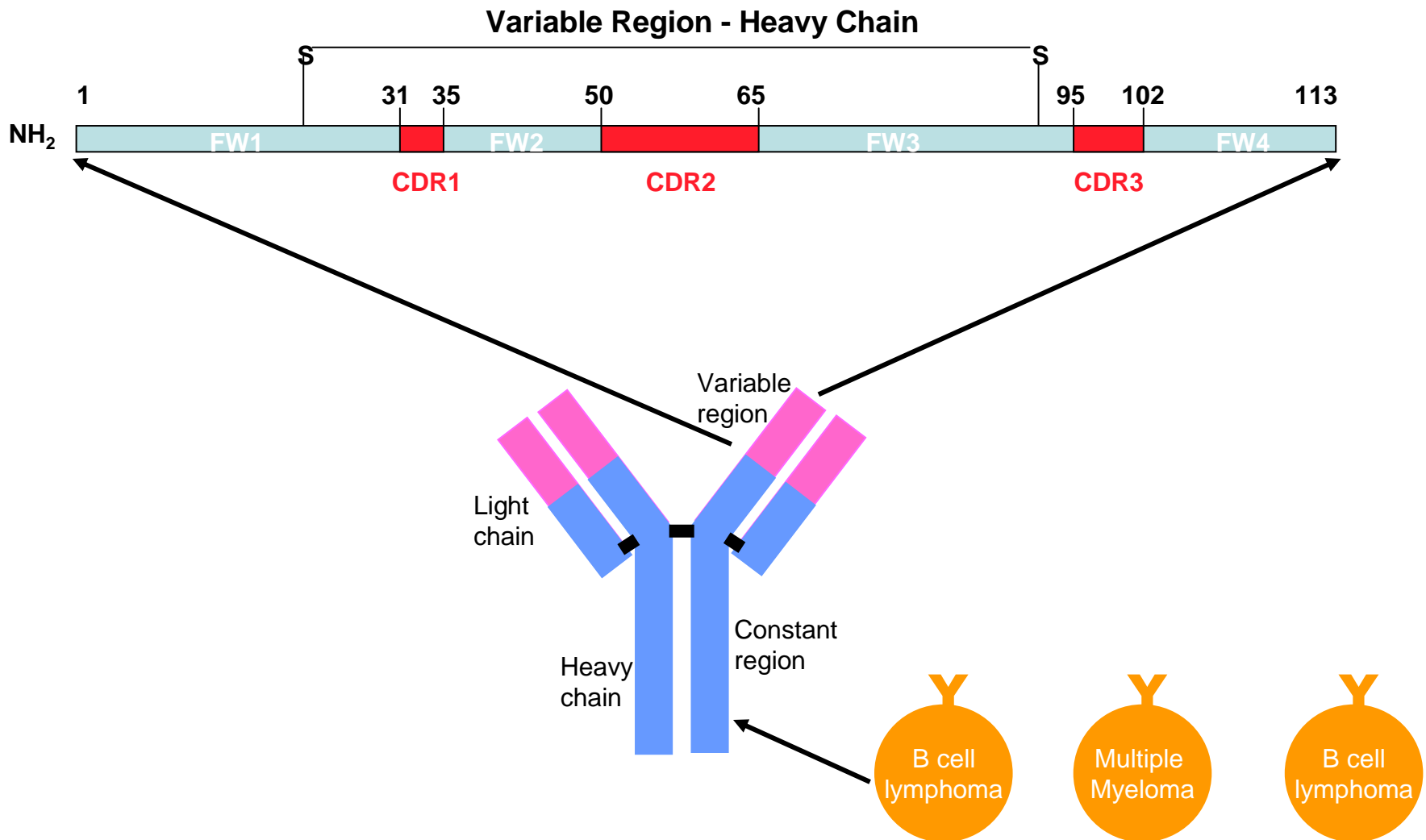
Lerner Research Institute

Cleveland Clinic

Why Immunotherapy for Cancers

- Current therapeutics unable to cure cancers
- Vaccines are the best defense against infectious diseases
- Powerful and yet specific immune system:
 - Able to reject mismatched organs
 - Immunological memory
 - Polyclonal immune responses
 - Target different antigens

Idiotypic: Unique Amino Acid Sequences in CDRs



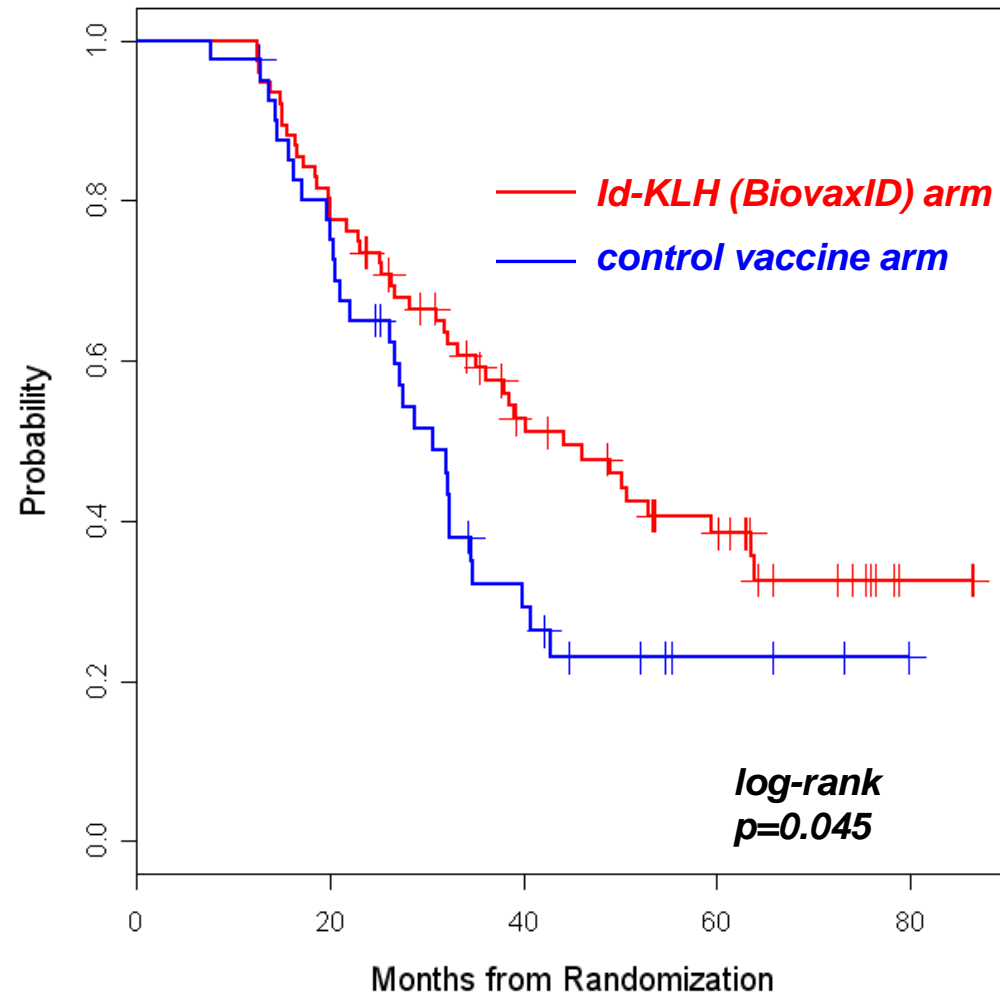
Preclinical Studies of Id Vaccines

- Active immunization with idiotypic was first demonstrated to induce resistance to tumor challenge in the early 1970's – *Lynch et al. Proc Natl Acad Sci, 1972.*
- Optimal immunization required conjugation to a strongly immunogenic carrier protein, such as keyhole-limpet hemocyanin (KLH) – *Kaminski et.al. J Immunol, 1987.*
- Use of GM-CSF as an adjuvant to the Id-KLH vaccine facilitated the induction of tumor-specific CD8+ T cell responses. – *Kwak et.al. PNAS, 1996.*
- Dendritic cells present Id fragments and induce type-1 T cell immunity – *Yi et.al. Br J Haematol, 1998.*

Phase III Id-KLH+GM-CSF Vaccine Trials in FL

Sponsor	Induction therapy	Randomize	Vaccination	DFS/PFS/TTP
NCI/Biovest	PACE	→ CR/CRu	 Id-KLH+GM-CSF or KLH+GM-CSF	Significant
Genitope	CVP	→ CR/CRu PR	 Id-KLH+GM-CSF or KLH+GM-CSF	Not significant
Favrille	Rituximab	→ CR/CRu PR/SD	 Id-KLH+GM-CSF or Placebo+GM-CSF	Not significant

NCI/Biovest Phase III trial: DFS from Randomization



N = 117

Id-KLH (BiovaxID) N = 76

Control vaccine N = 41

Median Follow-up

56.6 mo (range 12.6 – 89.3)

Median DFS

Id-KLH (BiovaxID) = 44.2 mo

Control vaccine = 30.6 mo

Schuster et al. J Clin Oncol 2011

Vaccination with Id Proteins in MM

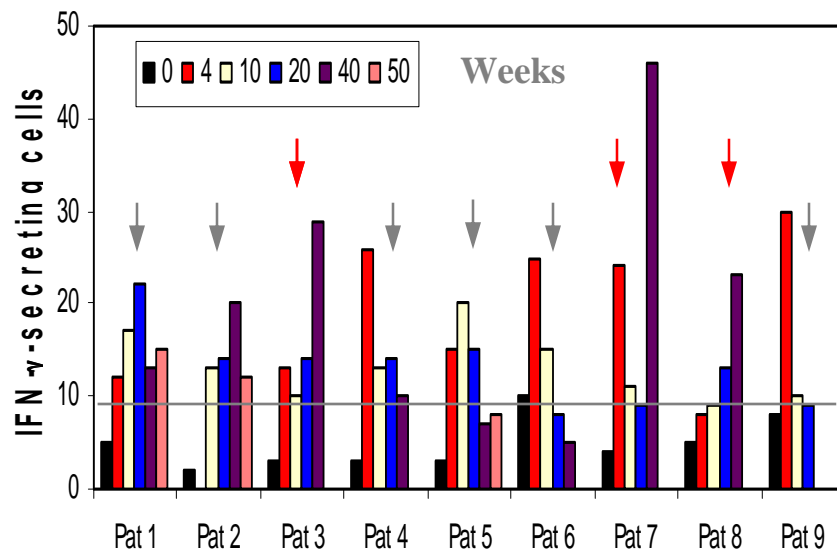
- Bergenbrant, Yi *et al*, 1996
 - Id/Alu vaccines in 5 (4 untreated, 1 after HDT); IFN- γ in 3, all SD
- Österborg, Yi *et al*, 1998
 - Id-Alu/GM-CSF in 5 (2 untreated, 3 after HDT); IFN- γ in 5; 4 SD and 1 partial remission (65% reduction)
- Massaia *et al*, 1999
 - Id-KLH/GM-CSF in 12 (CR after HDT); DTH in 8/10 and T-cell proliferation in 2; no favorable clinical outcome
- Mellstedt *et al*, 2003
 - Id/IL-12+GM-CSF in 6 (stage I MM); T cells in 3, tumor reduction in 4 (one with complete molecular remission)

Intranodal Id-DC vaccination

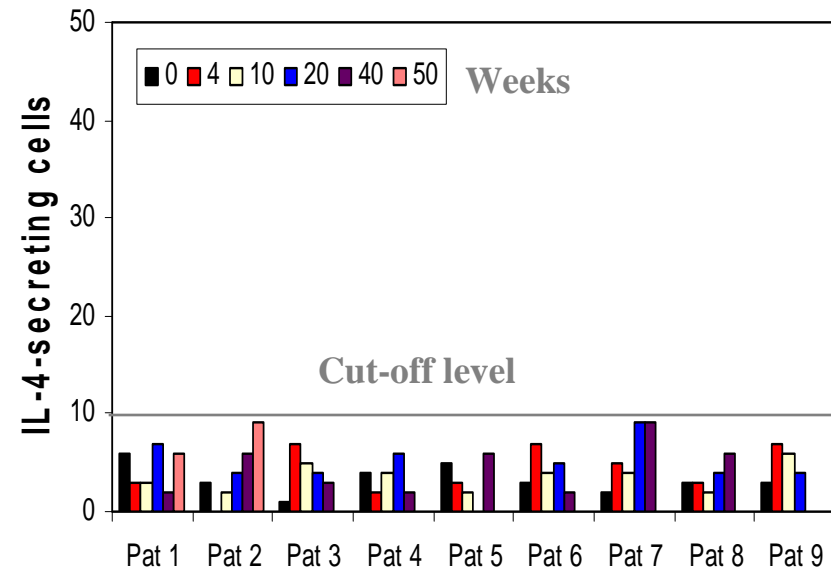
- To date 10 (7 IgG and 3 IgA) indolent or smoldering MM enrolled
- CD4 count > 600/ μ l
- Each received, per injection, 14.6×10^6 (range 1.2-35.6 $\times 10^6$), Id- and KLH-pulsed, CD40L(Immunex)-matured DCs
- ELISPOT assays, proliferation and DTH

DC Vaccines Induce Th1-Type Response

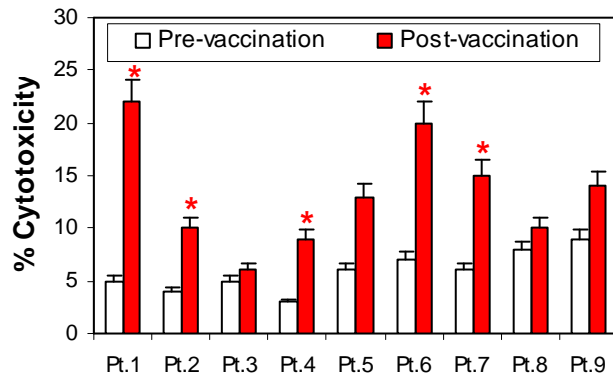
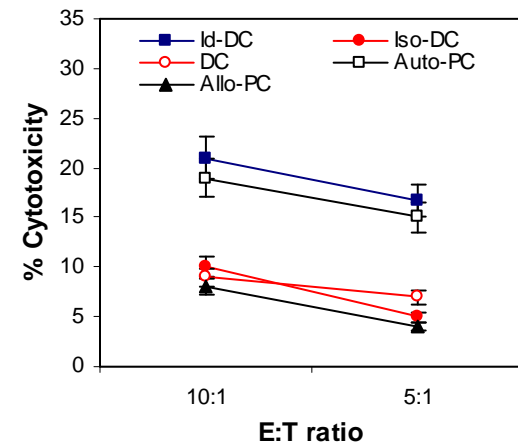
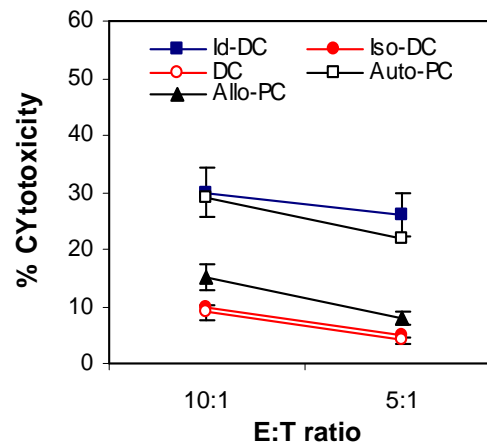
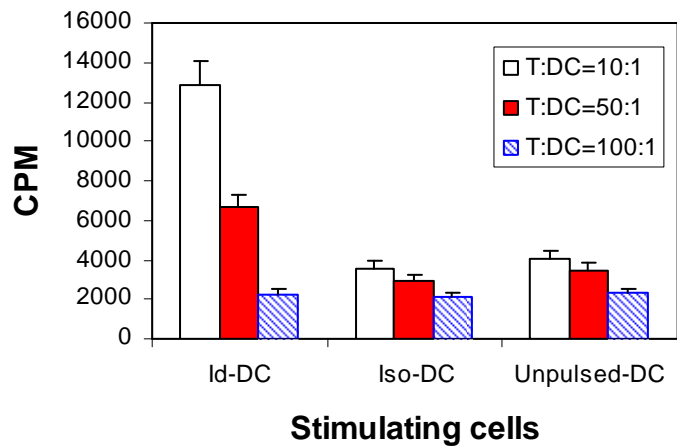
IFN- γ Response



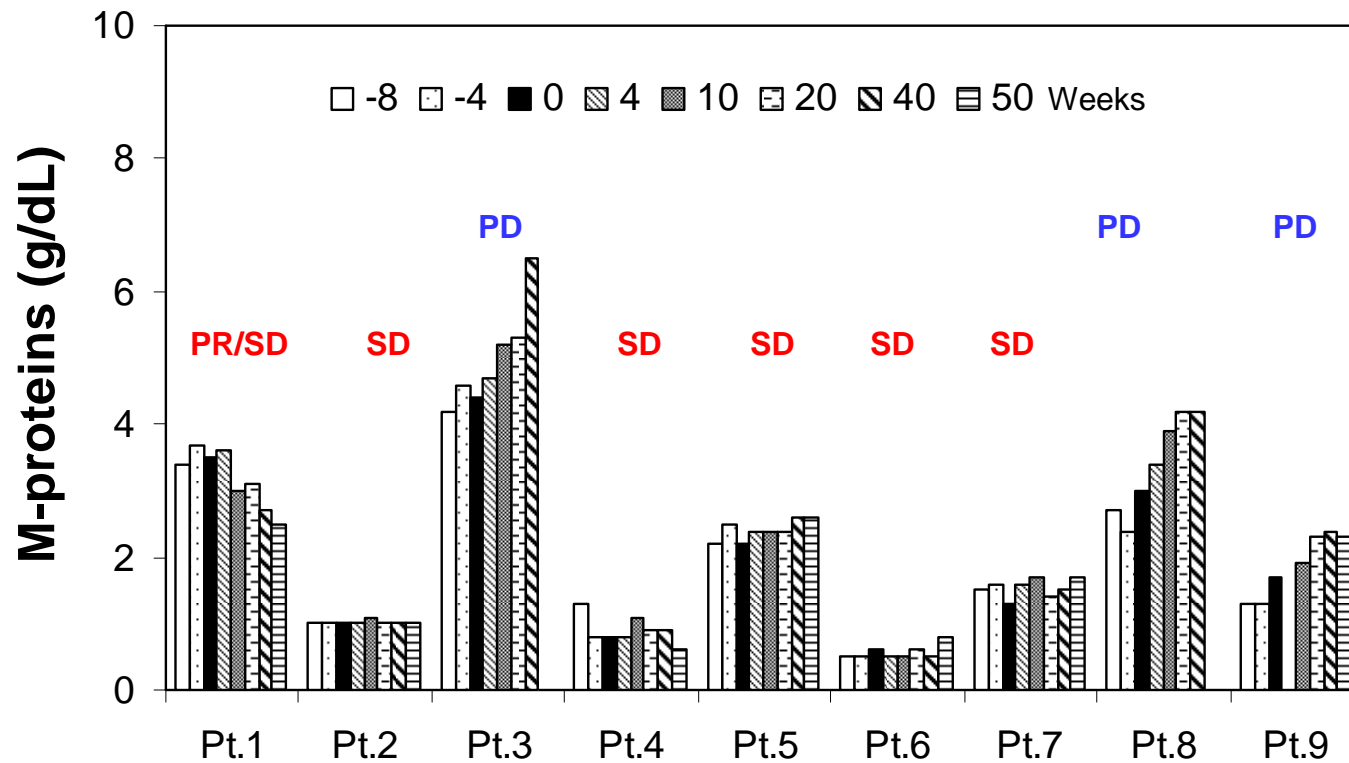
IL-4 Response



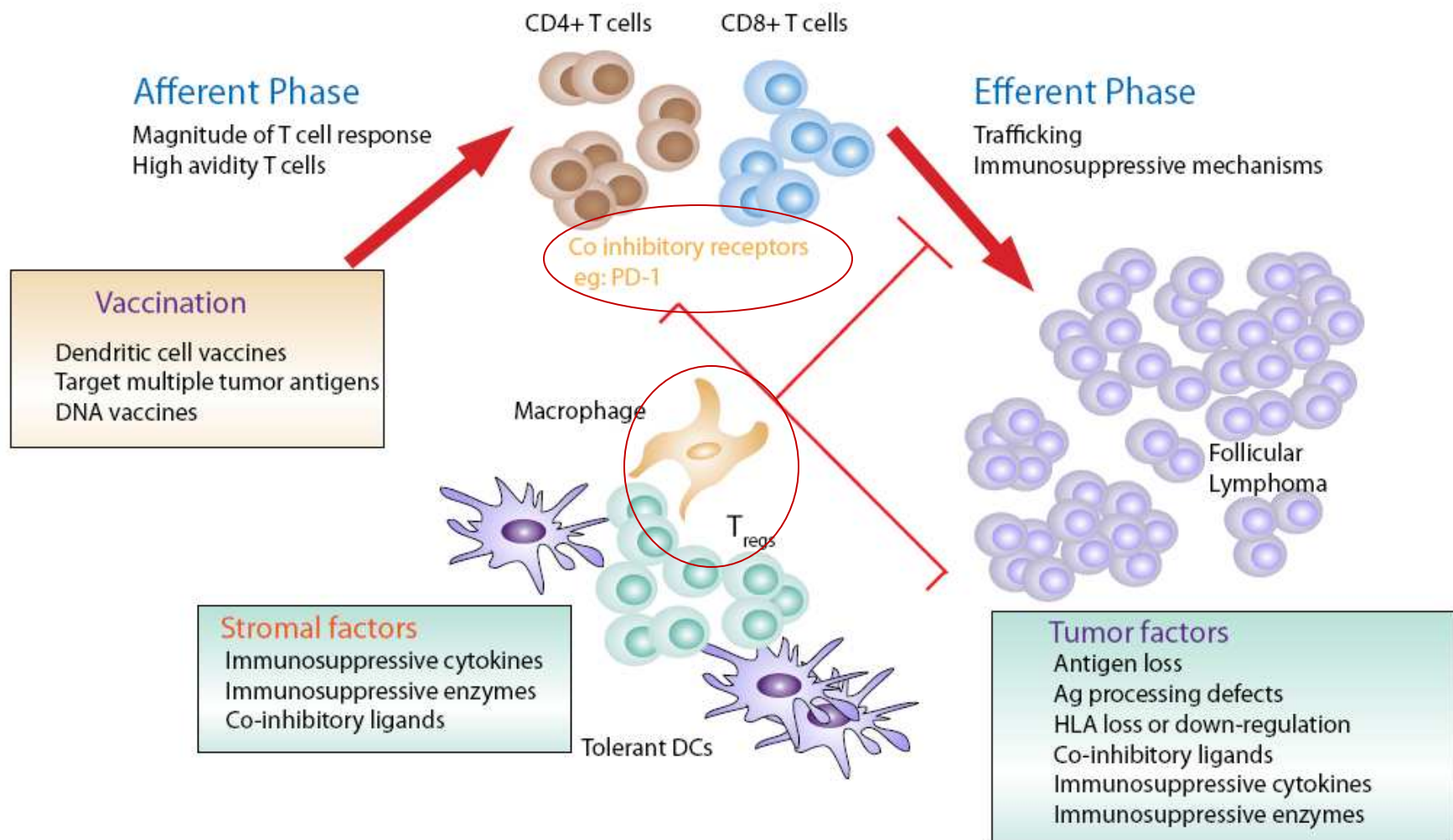
Id-Specific CTLs Detected 4 Weeks After Vaccination



Vaccination Induces PR or SD in Most Patients



Potential Reasons for Low Clinical Responses with Vaccine Therapy



Approach

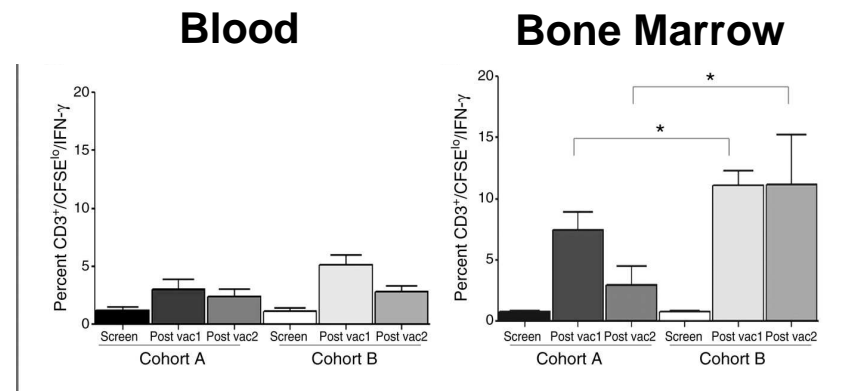
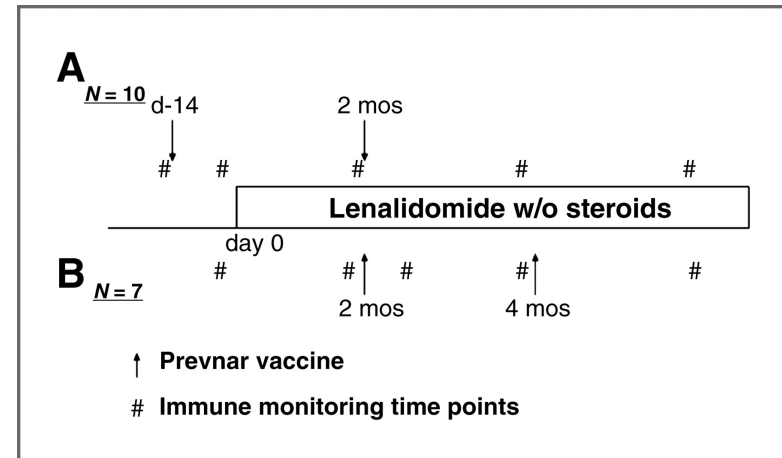
Combinational therapy of
vaccines and chemotherapy to
break immune suppression

Lenalidomide and IMiDs

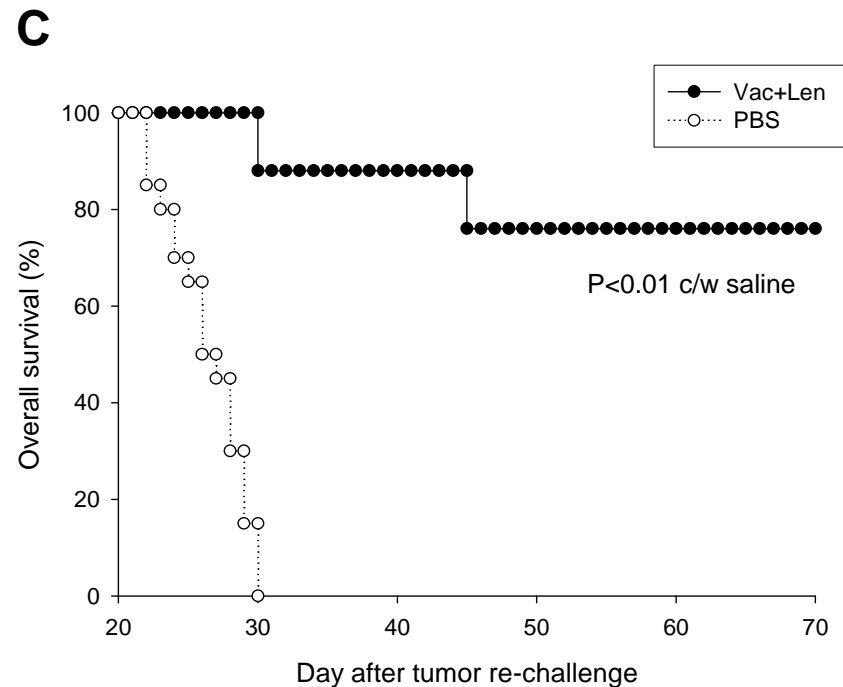
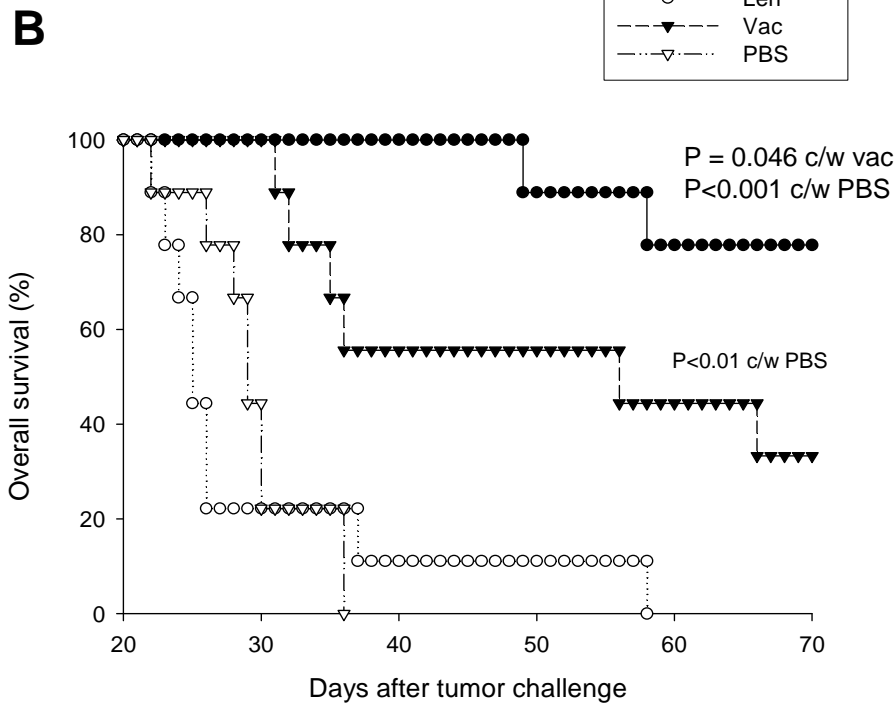
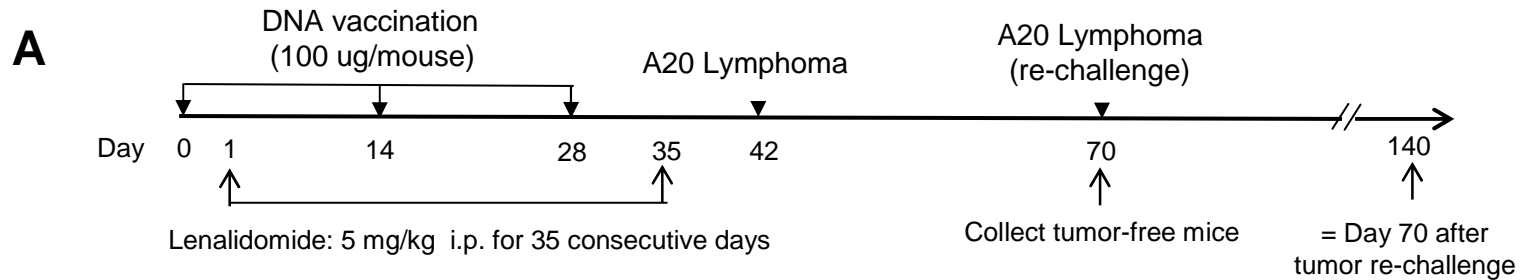
- Novel drugs for treatment of myeloma and B-cell lymphomas
- Inhibiting angiogenesis and TNF- α
- Immunomodulatory
 - Activating NK cells and increasing NK numbers
 - Enhancing T cell proliferation and cytokine production
 - Polarizing T-cell immunity toward Th1 responses
 - Repairing T-cell immunologic synapse dysfunction

Lenalidomide Enhances Vaccine Responses in Myeloma

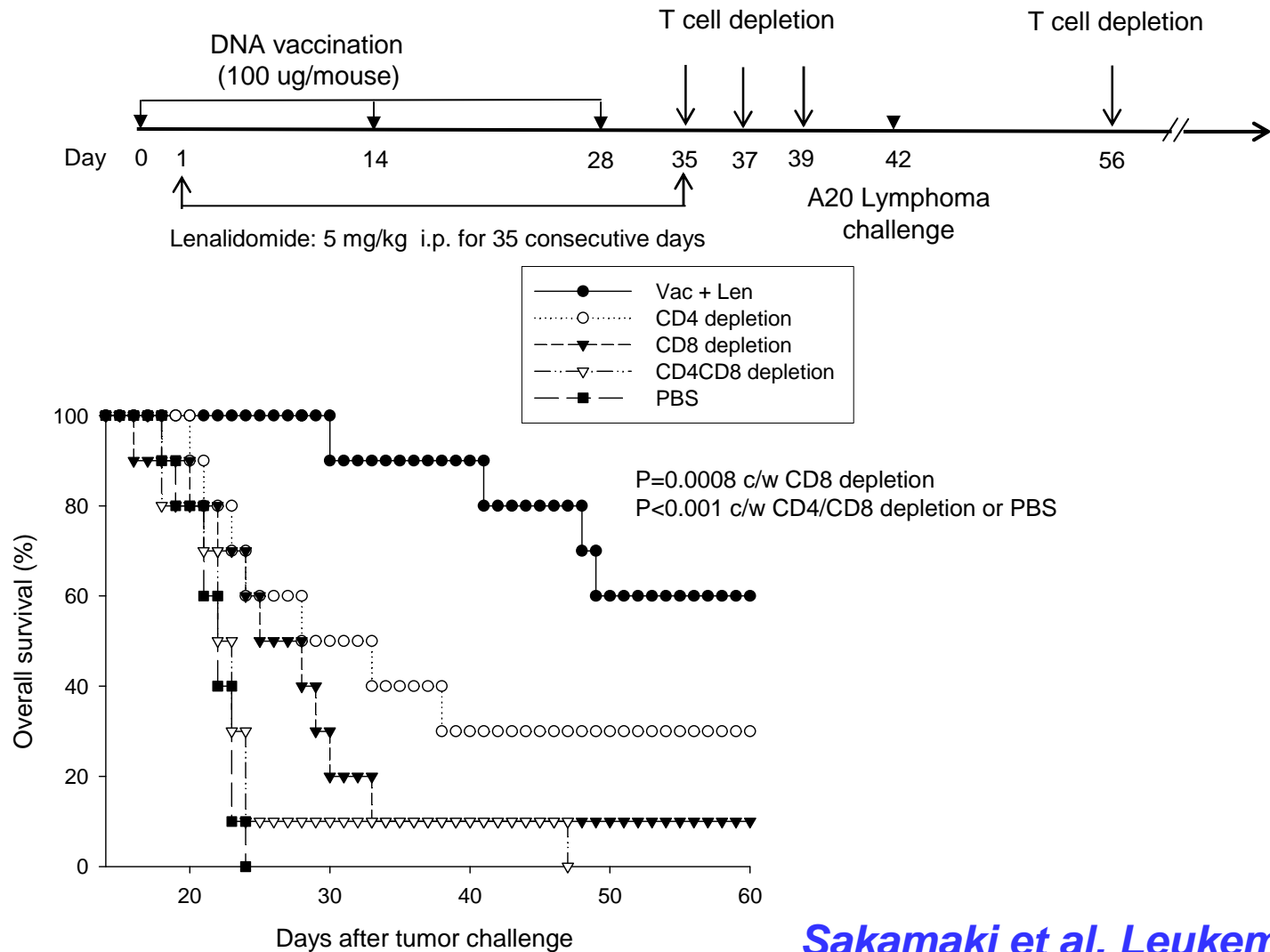
- Myeloma patients receiving lenalidomide randomized to A or B
- Vaccine: pneumococcal 7-valent conjugate vaccine (PCV)
- PCV-specific humoral and cellular responses greater in Cohort B than Cohort A



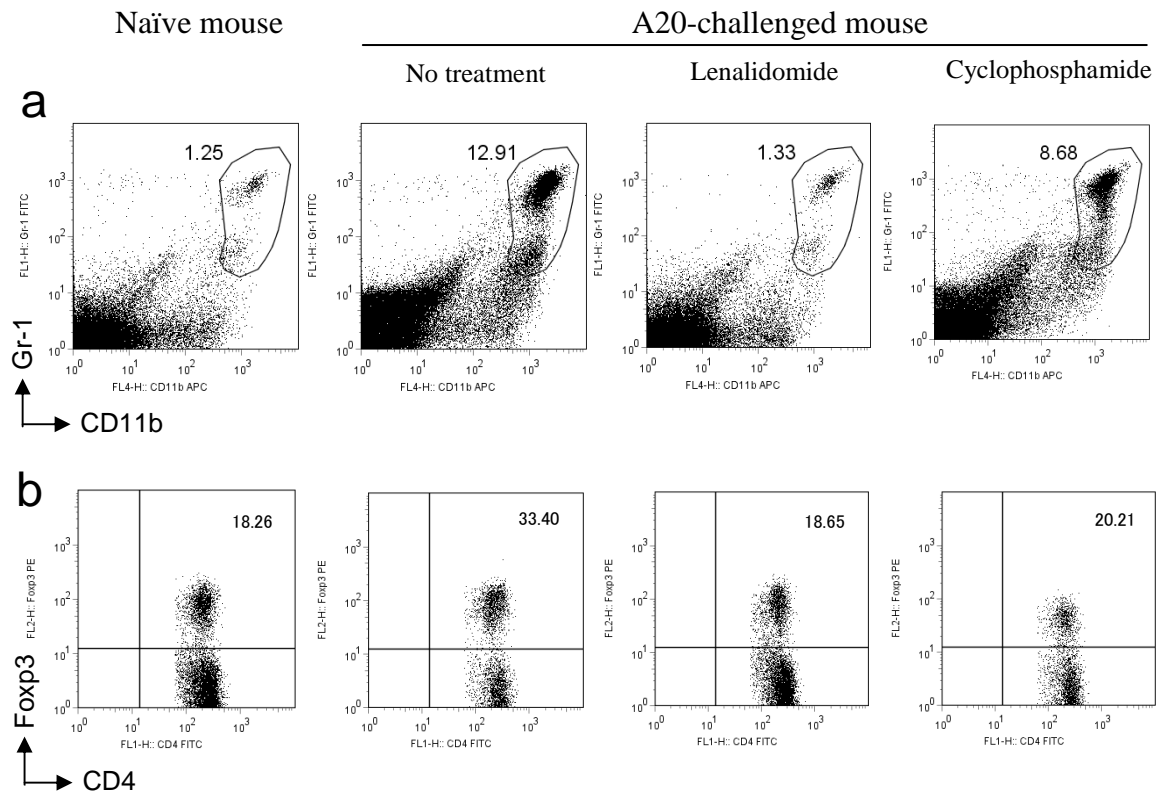
Lenalidomide Enhances Vaccine Responses in Lymphoma



Lenalidomide Enhances Vaccine Responses in Lymphoma



Lenalidomide Enhances Vaccine Responses in Lymphoma

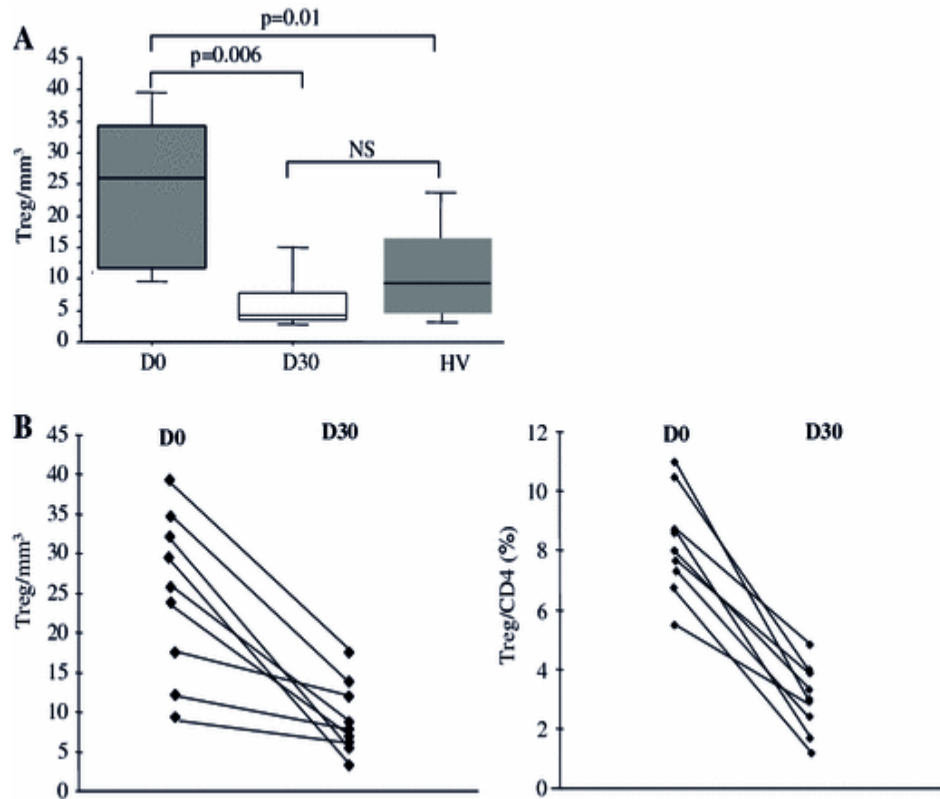


Cyclophosphamide

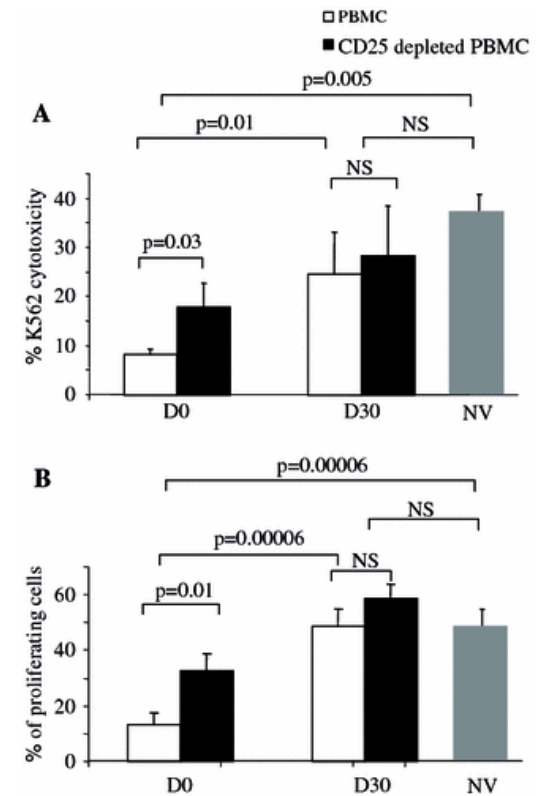
- An alkylating agent to treat cancers
- Immunosuppression
- Immunopotentialiation
 - Selective inhibition of Treg
 - T-cell activation by regulating type-1 interferons
 - Action of NK cells and their activity

Cyclophosphamide in Cancer Patients

Depleting Treg



Activating T and NK cells



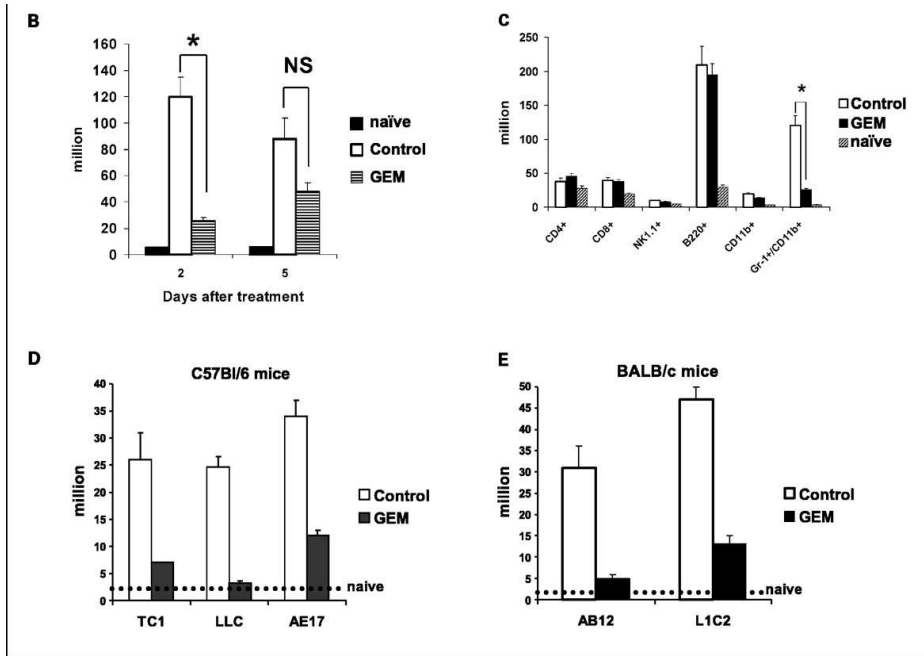
Ghiringhelli F et al. Cancer Immunol Immunother 2007; 56:641-648

Gemcitabine

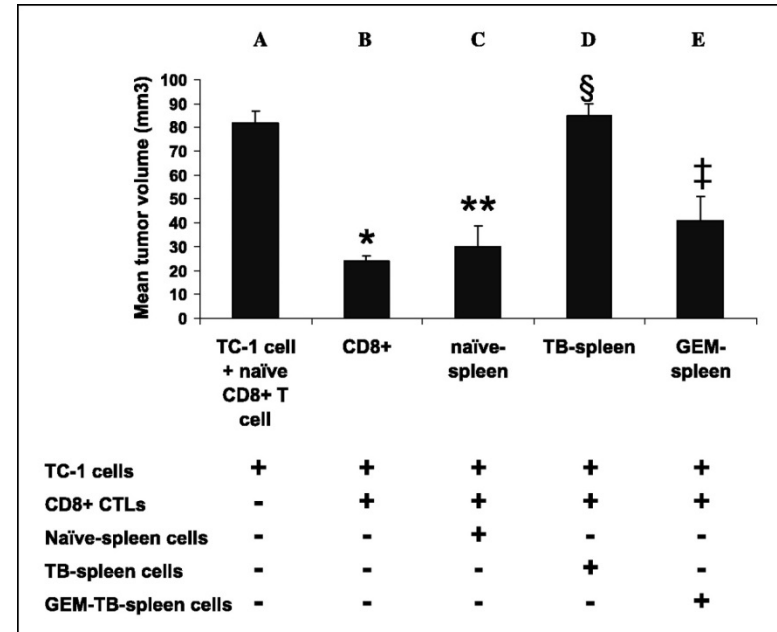
- An anti-metabolite analogue of nucleoside
- Induction of cancer apoptosis by dysfunctional DNA synthesis
- Immunopotentialiation
 - Selectively eliminating MDSCs
 - Promoting T-cell immunity
 - Inhibiting B-cell proliferation

Gemcitabine in Tumor-Bearing Mice

Depleting MDSCs



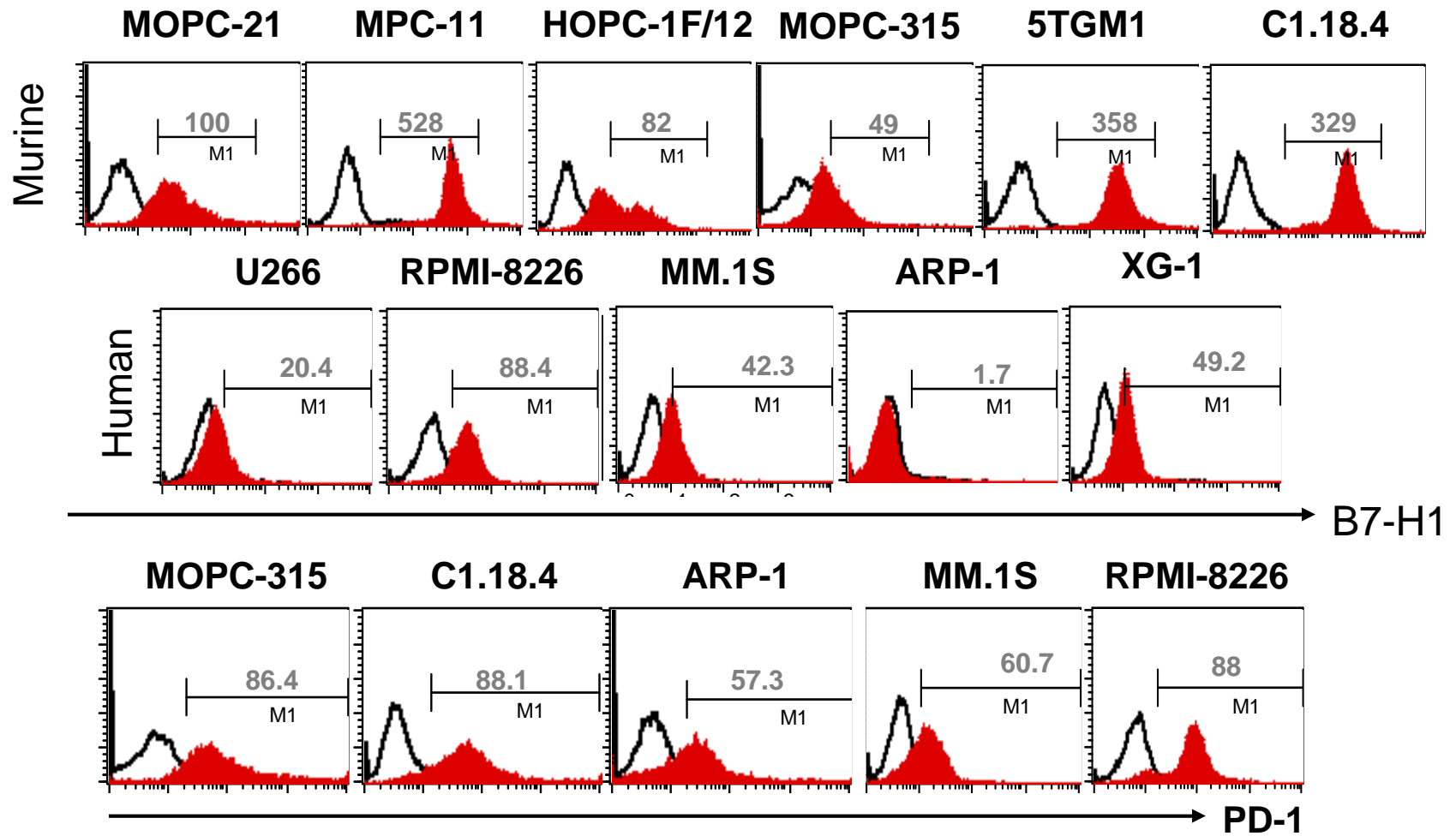
Reducing immunosuppression



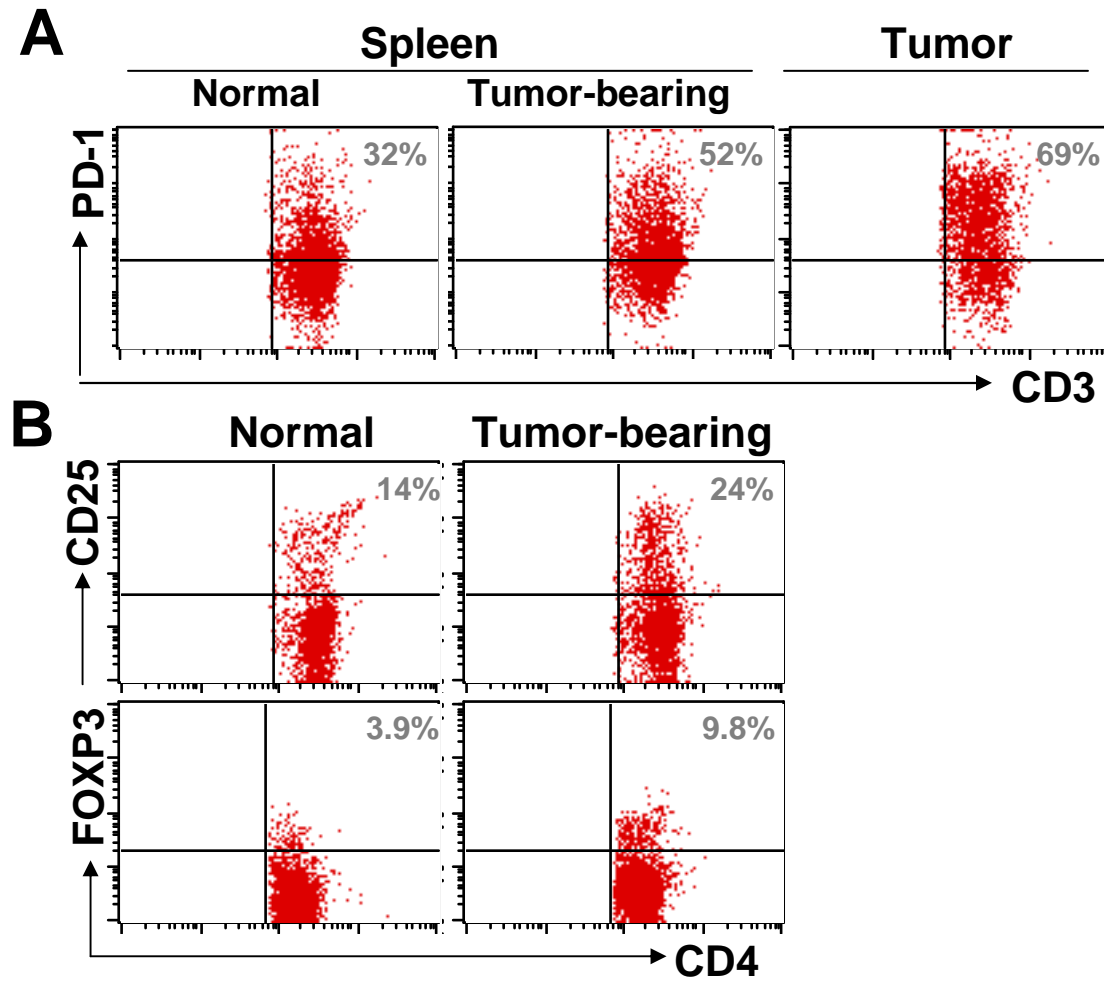
Approach

Combinational therapy of
vaccines and novel agents to
break immune suppression

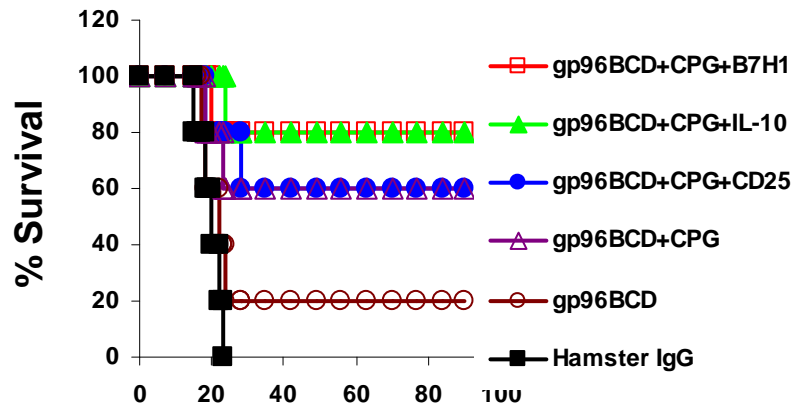
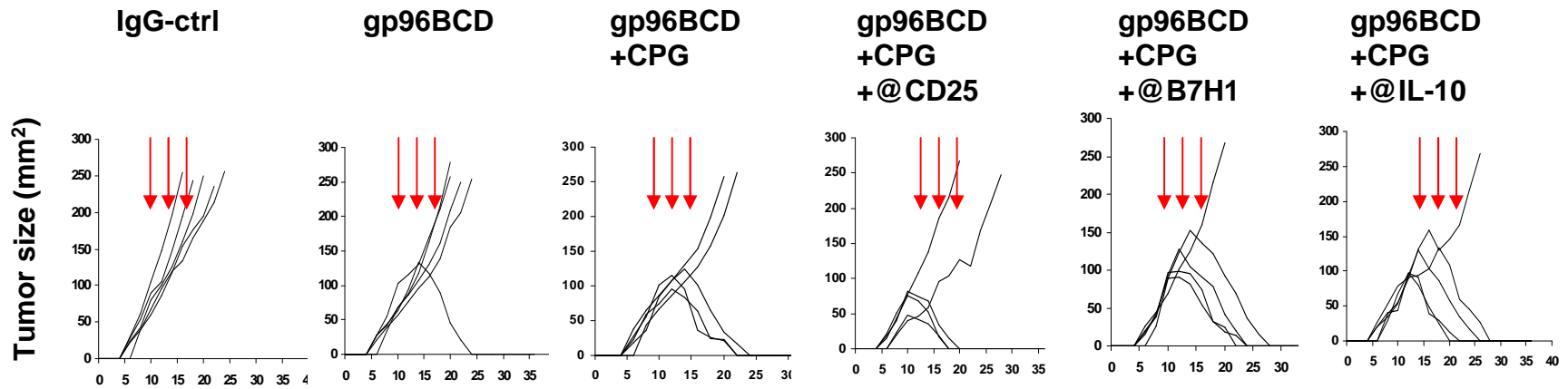
Myeloma Cells Express B7-H1 and PD-1



PD-1⁺ T cells and Treg Are Increased in Tumor-Bearing Mice



Blocking B7-H1 or Neutralizing IL-10 Enhance Vaccine Effects



Combination Immunotherapy

