



Targeting tumor antigen delivery to DC in vivo

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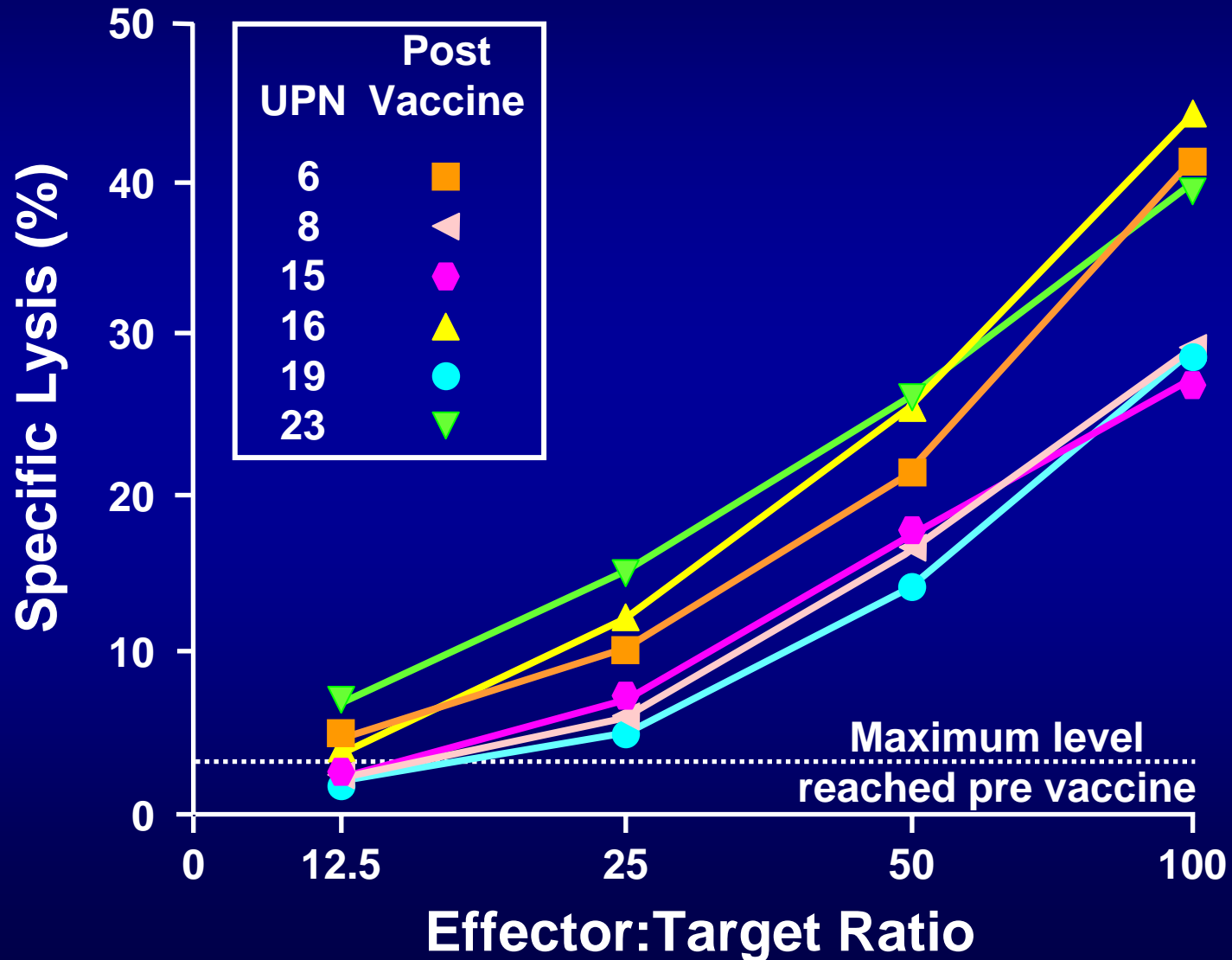
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Are T-cells a “biomarker” for anti-lymphoma clinical responses?

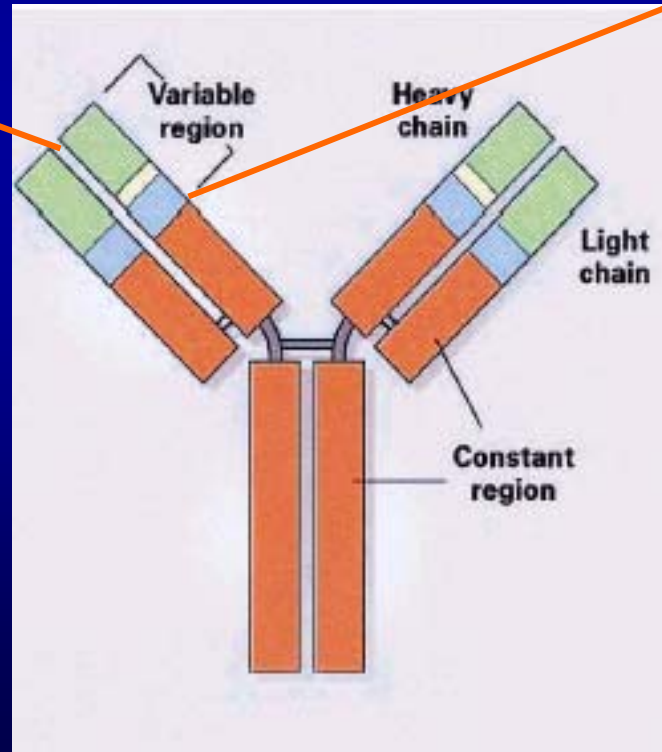
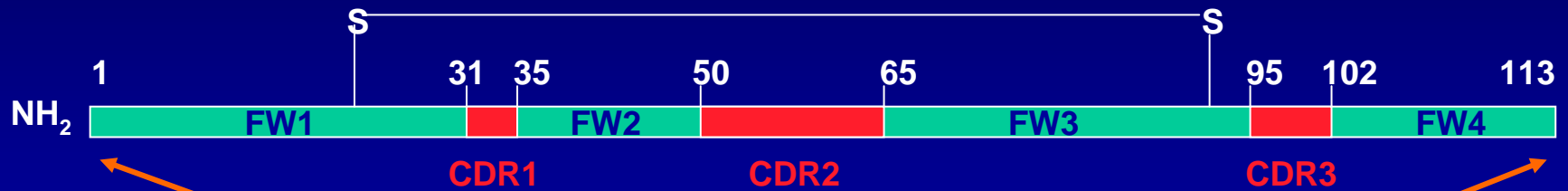
- In 19 of 22 (86%) patients, Id-KLH + GM-CSF vaccination elicited CD8+ T-cells which lysed autologous lymphoma targets *Nature Med.* 1999; 5:1171.
- Most achieved molecular remissions; 3 did so without a detectable antibody response *Nature Med.* 1999; 5:1171.
- In 20 of 23 (87%) vaccinated patients, mantle cell lymphoma-specific T-cells producing type 1 cytokines were detectable by ICS *Nature Med.* 2005; 11:986

Lysis of Autologous Tumor Targets

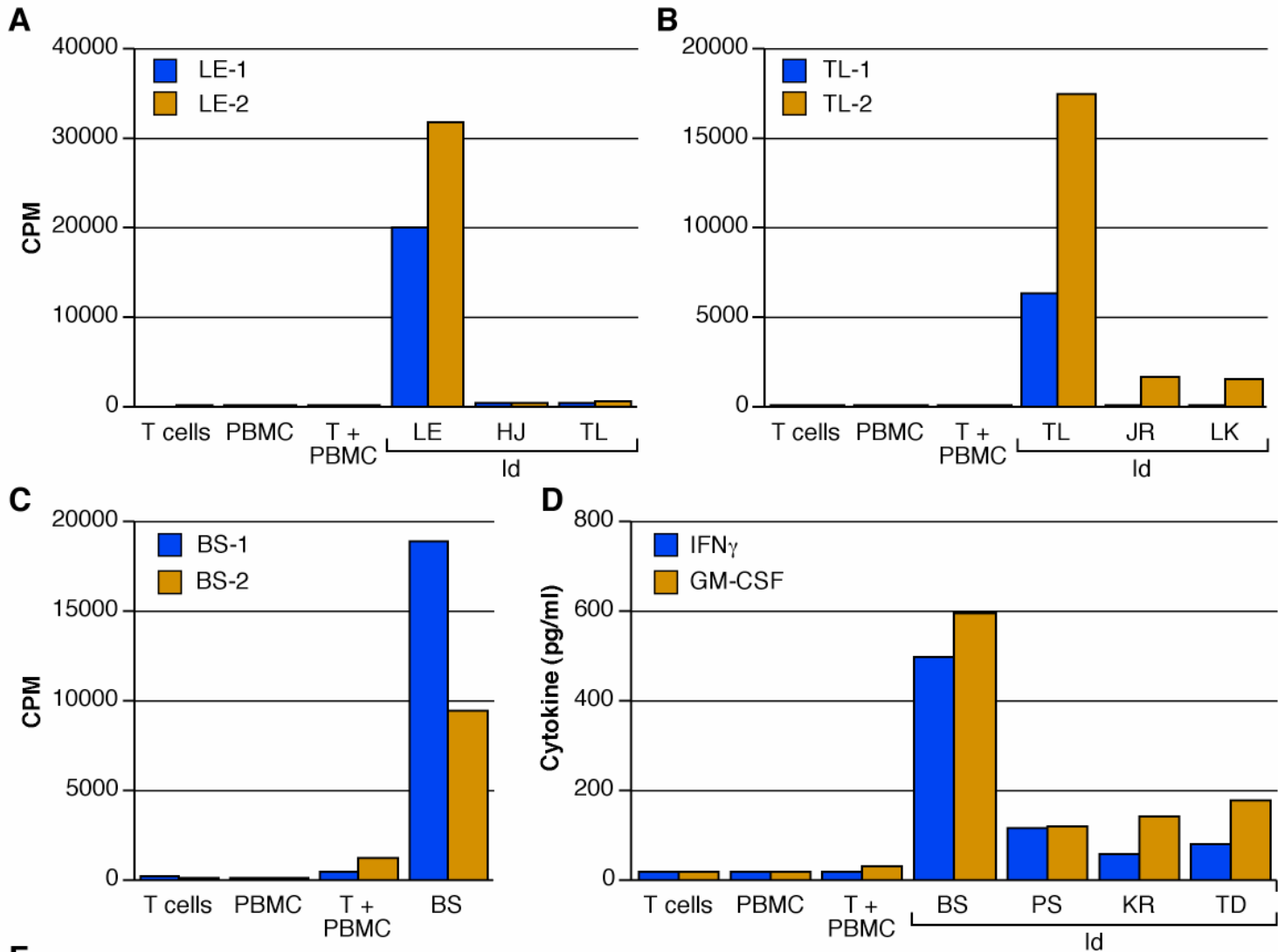


Idiotype

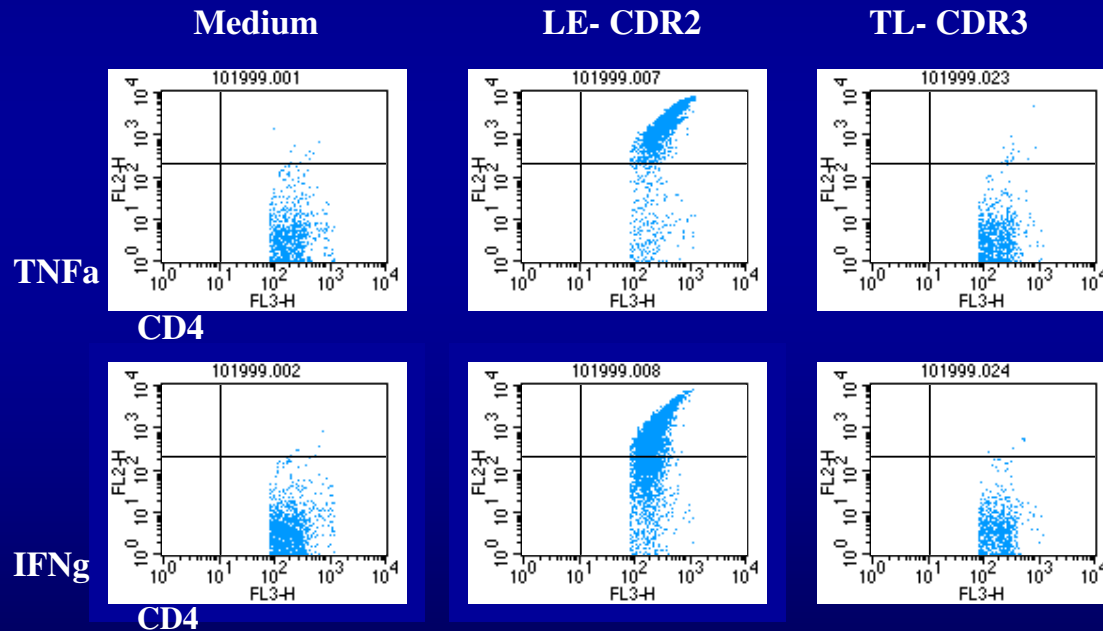
Variable Region - Heavy Chain



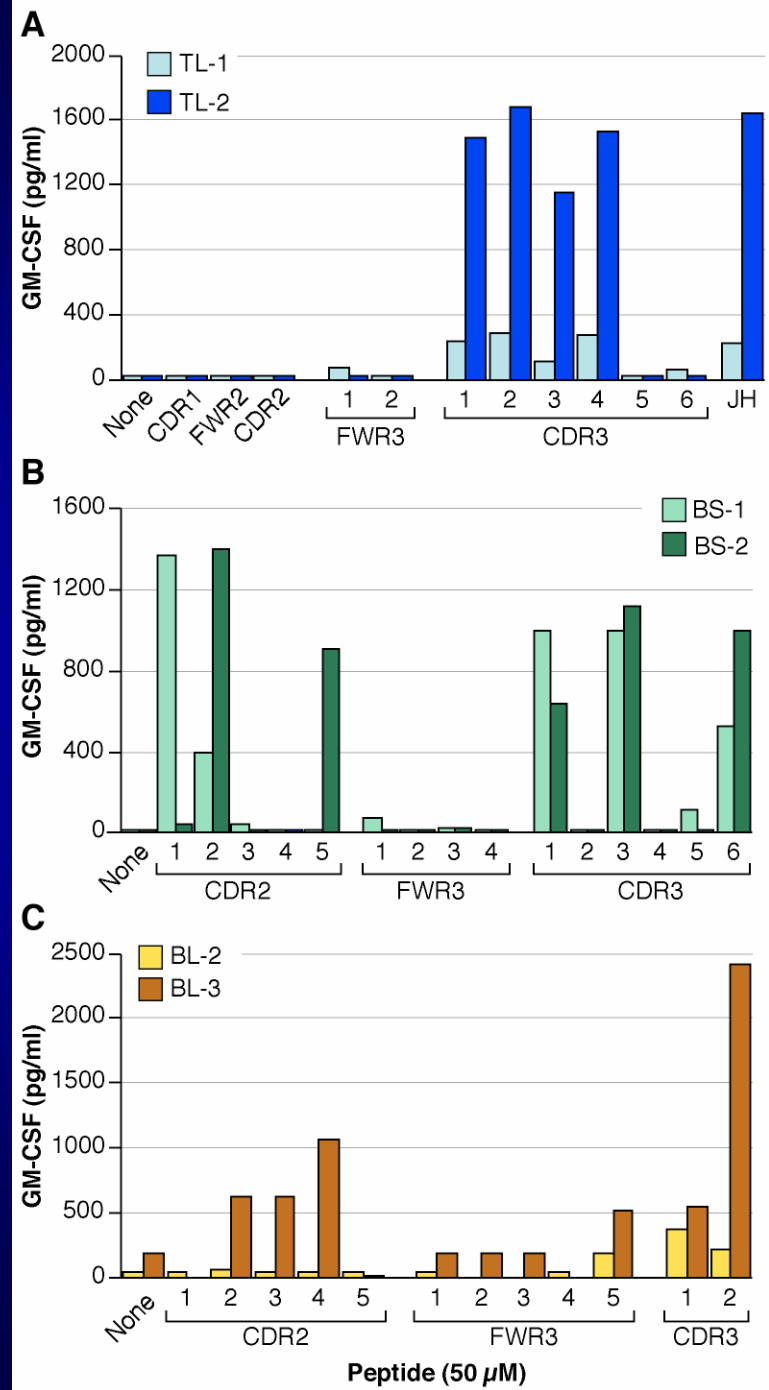
T-cell lines specifically recognize autologous Id protein



LE-I.1 T cells Produce Th1 Cytokines in Response to Specific CDR2 Peptide



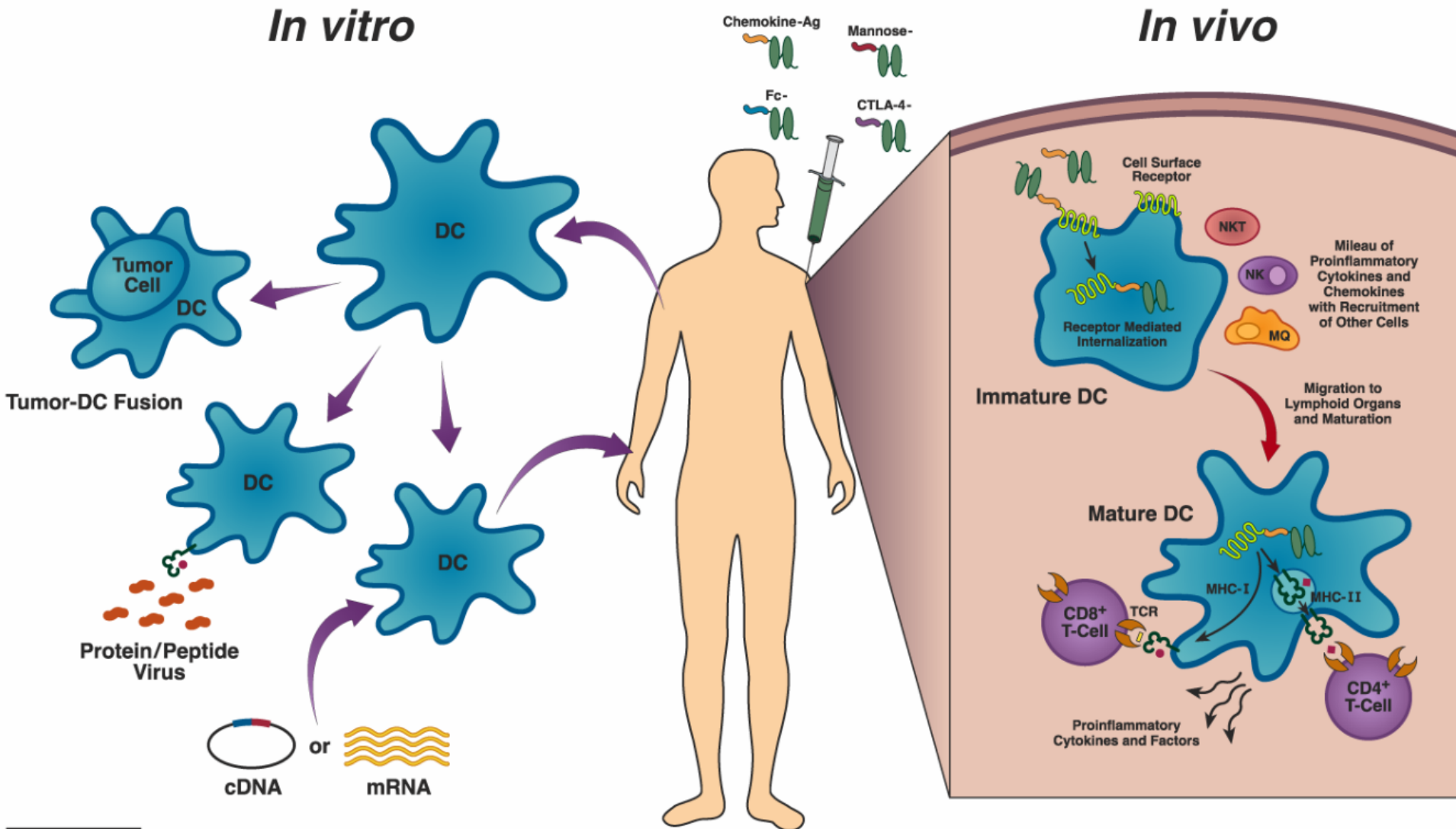
Immunodominant
T-cell epitopes
localize to CDR,
not FWR,
regions of V_H

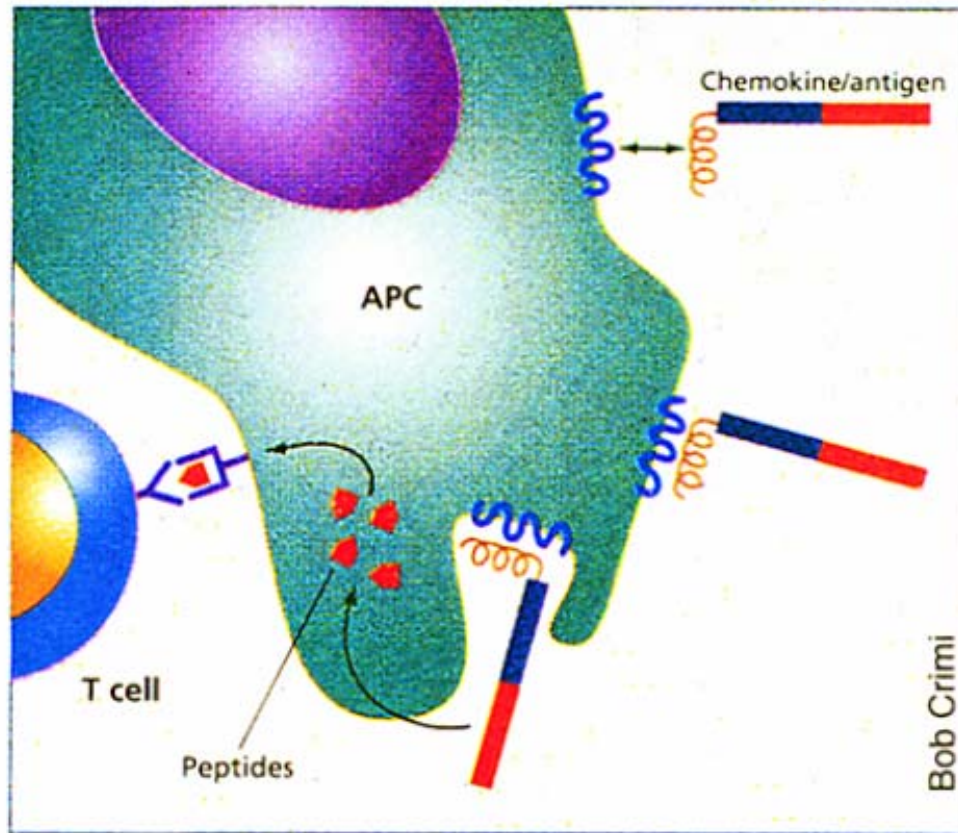


T Cell Epitopes in Lymphoma Ig V_H Regions

Patient	Synthetic Peptide	Position	Response
TL	ATTTGGGLNFGLDVW	CDR3	YES
	FLQMNSLRV	FWR3	NO
	VPKGGLVWV	FWR2	NO
BL	GDDWSGYFK	CDR3	YES
	YVDSVKGRF	CDR2	YES
	SQSGSDTSY	CDR2	NO
	LRVEDTAIY	FWR3	NO
	GSDTSYVDS	CDR2	NO
BS	ANTIQEGSQKNYVDS	CDR2	YES
	RHNDDTSVTFDYWGQ	CDR3	YES
	LQMSSLRVEDTALYY	FWR3	NO
	RFTISRDNNAKNIVFL	FWR3	NO

Harnessing DC for Tumor Vaccine Therapy





Reproduced with permission from Kipps. *Nature Biotech.* 1999;17:226 (editorial).

38C-13 lymphoma-derived:

sFv38



protein

IP10sFv38



protein

IP10sFv38(INV)



protein

IP10dsFv38



protein

IP10TsFv38



protein

MCP3sFv38



protein

MCP3sFv38(INV)



protein

PreS2sFv38



protein

DomAsFv38



protein

psFv38(INV)



Naked DNA

pMCP3sFV38(INV)



Naked DNA

pPreS2sFv38(INV)



Naked DNA

A20 lymphoma-derived:

IP10sFv20



protein

MCP3sFv20



protein

psFv20A



Naked DNA

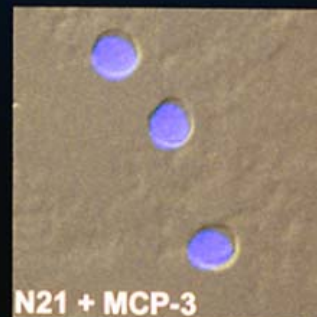
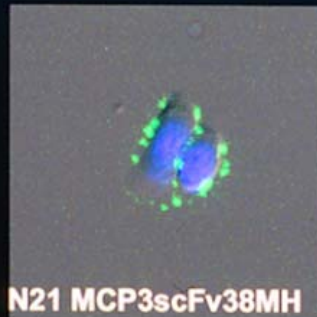
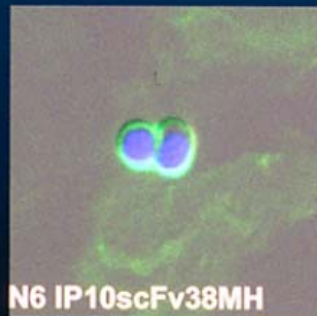
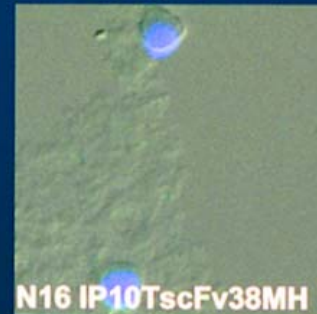
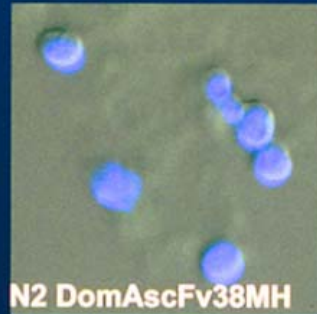
pMCP3sFv20



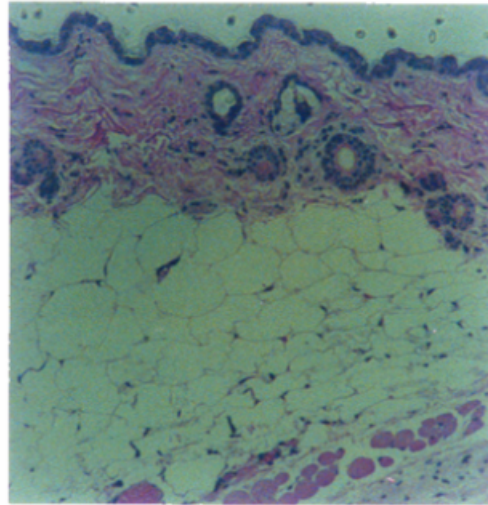
Naked DNA

Vaccine delivery

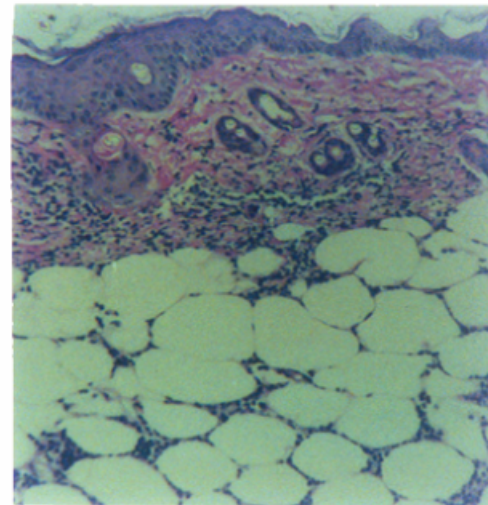
IP-10 and MCP-3–fused scFv bind specifically to murine chemokine receptors



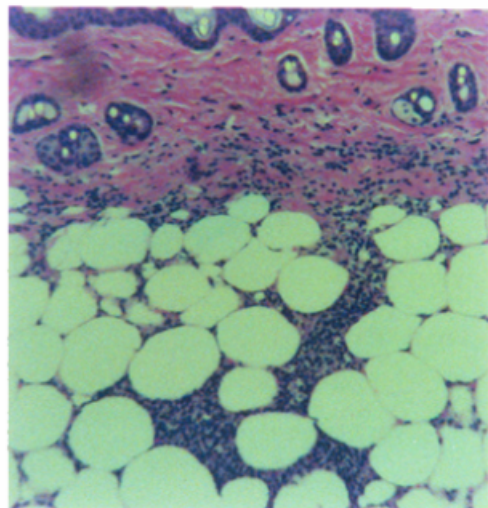
In vivo Chemotaxis by scFV Fusion
Proteins (72h, Injected 10 μ g s.c.)



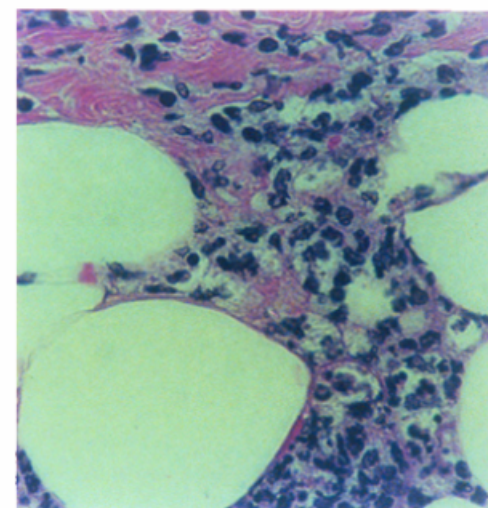
PreS2-scFV38
(x100)



MCP3-scFV
(x100)

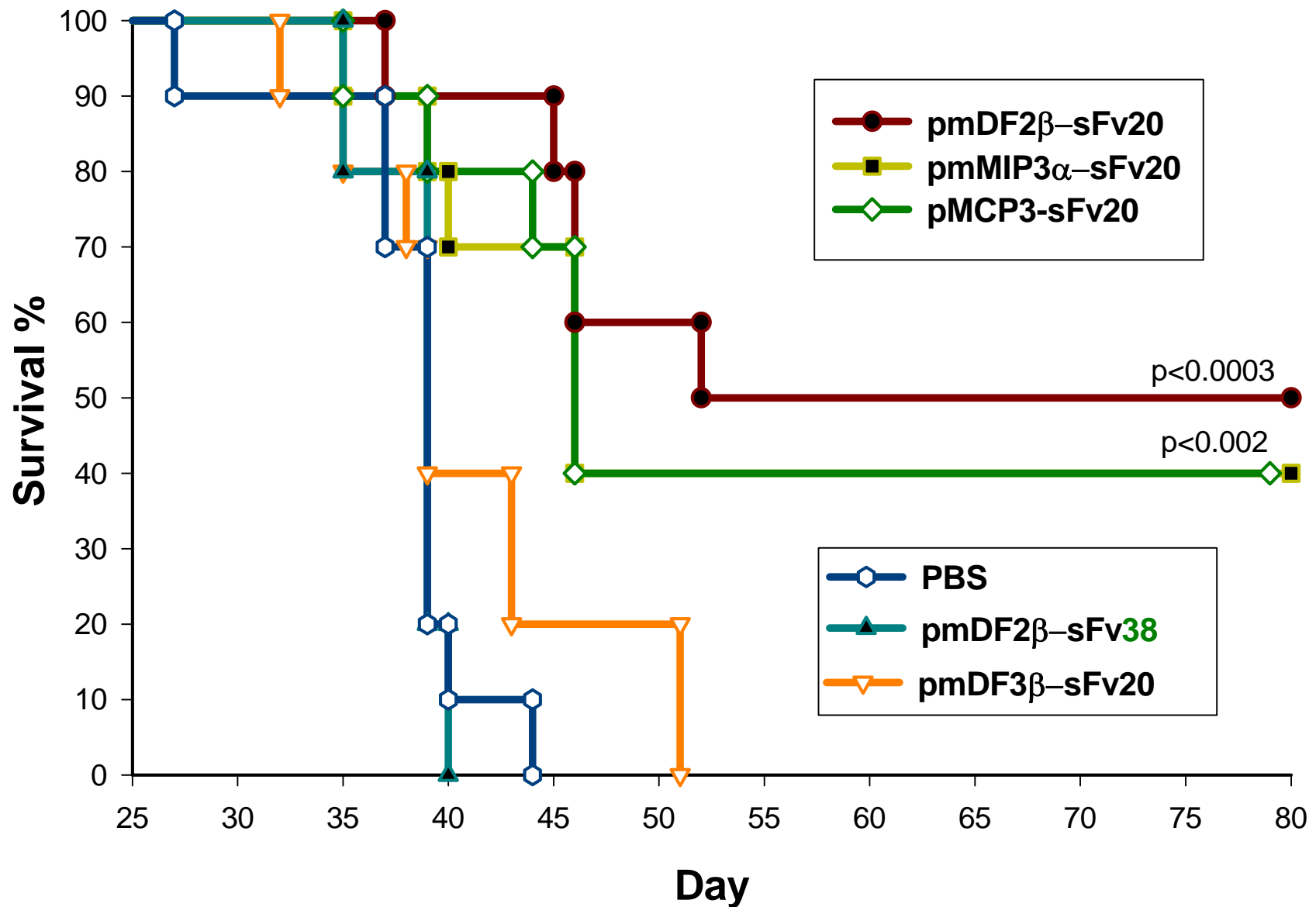


IP10-scFV38

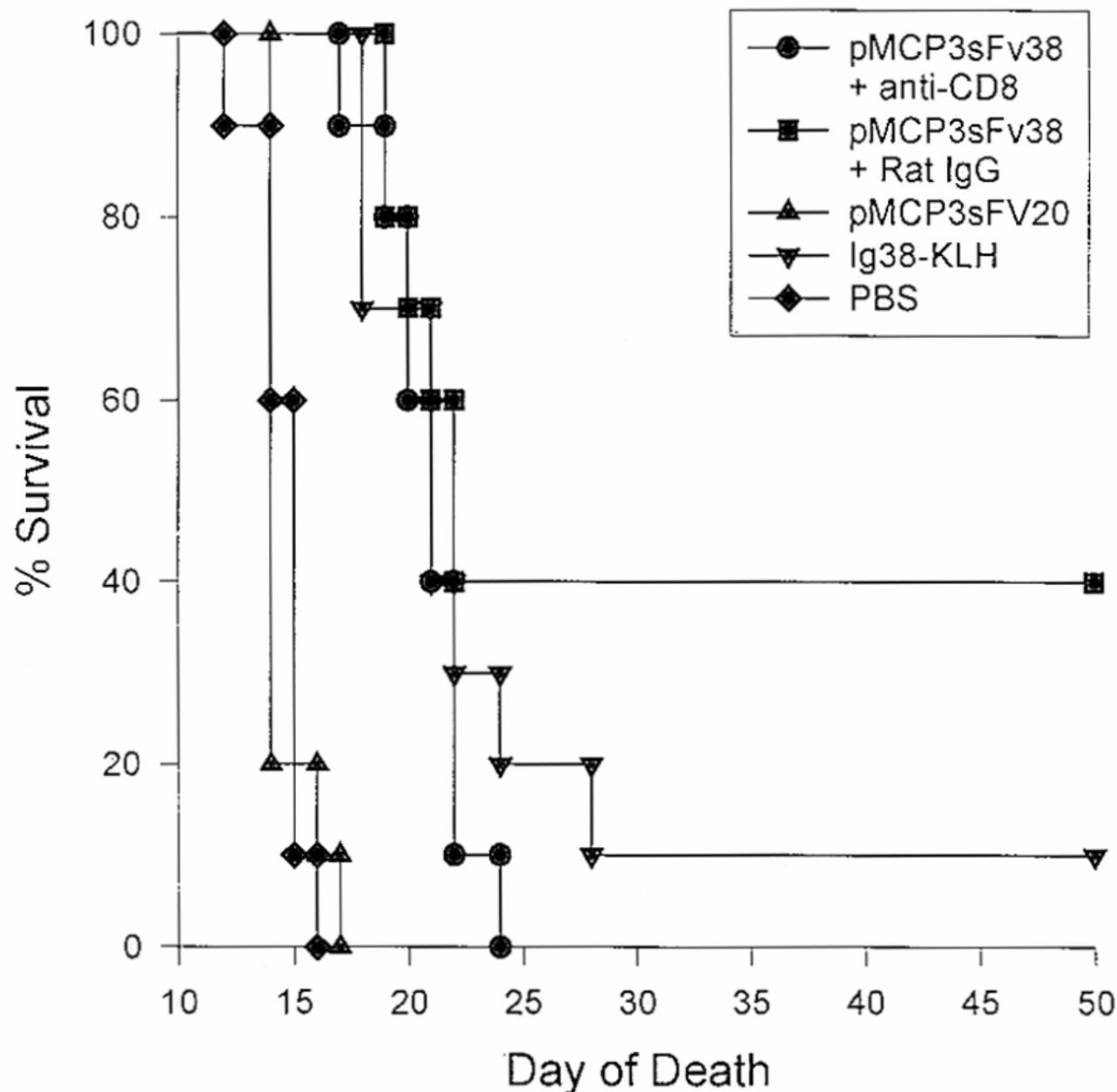


IP10-scFV38
(x400)

Injection of plasmid DNA encoding iDC chemo-attractant fusions elicit therapeutic antitumor immunity

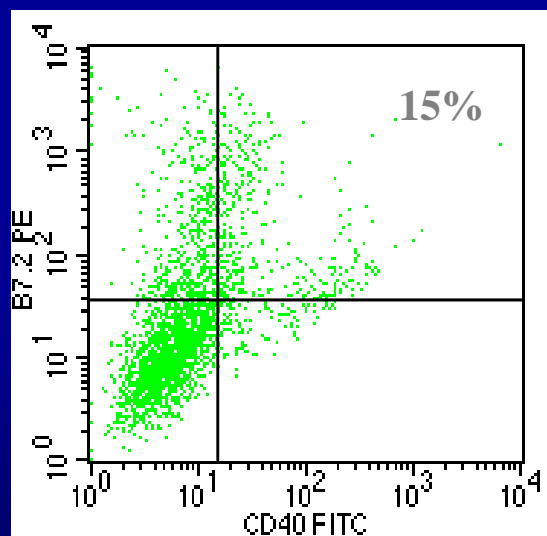


Protective immunity induced by naked DNA MCP3-sFv38 vaccine requires effector CD8⁺ T cells.

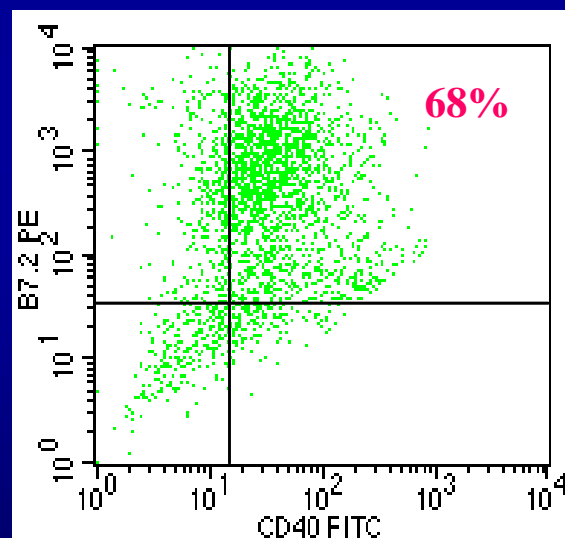


Murine defensin induces maturation of bone marrow-derived immature DC

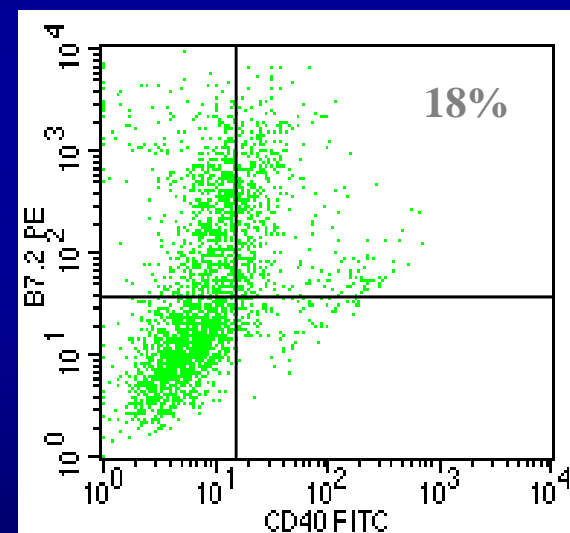
medium alone



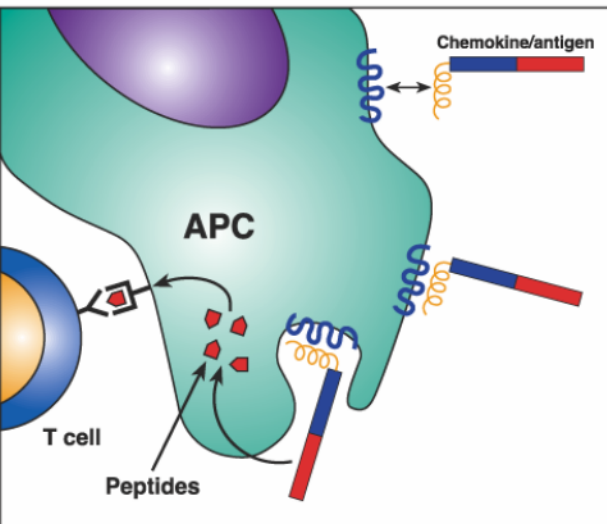
mDefensin2 β



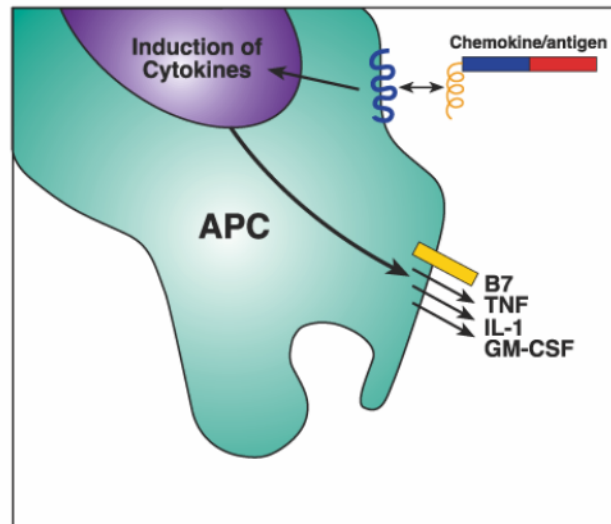
mproDefensin2 β



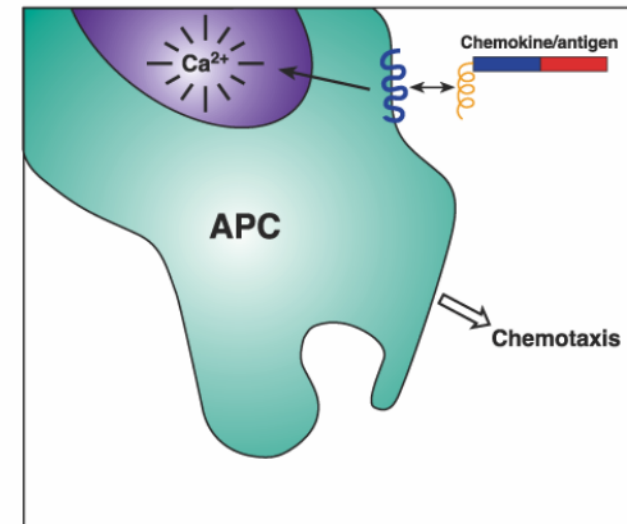
Possible Modes of Action of Chemokine-Ag Fusions In Vivo



APC Receptor Targeting



APC Maturation/Activation



**Chemotaxis of APC
and Other Cells**

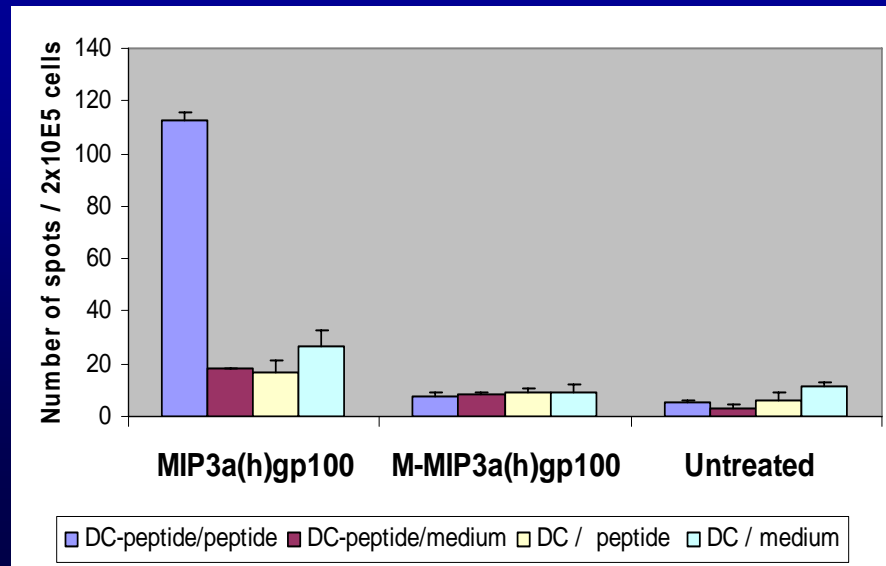
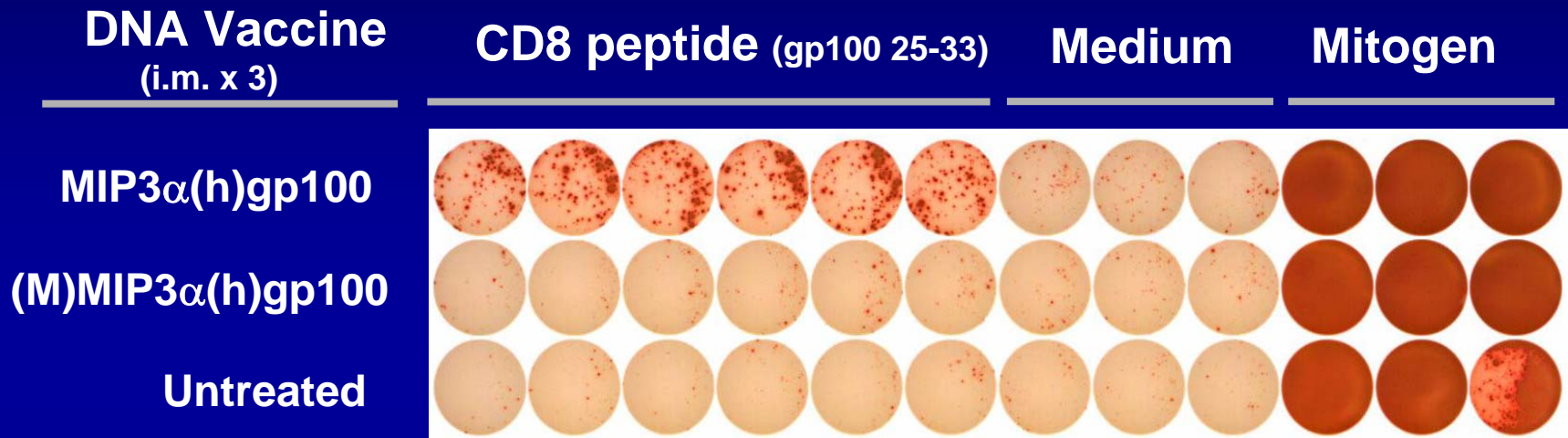
Summary of Published Results: Second-Generation Genetic Vaccines

- Genetic fusion of weak tumor antigens to chemokines or related chemoattractant peptides (eg, defensins) converts them into potent vaccines
- CD8+ effector T-cell immunity is required
- Defensins induce DC maturation through TLR-4, providing a link between innate and adaptive immunity
- Mixing separate plasmids encoding antigen and chemokine failed to elicit immunity

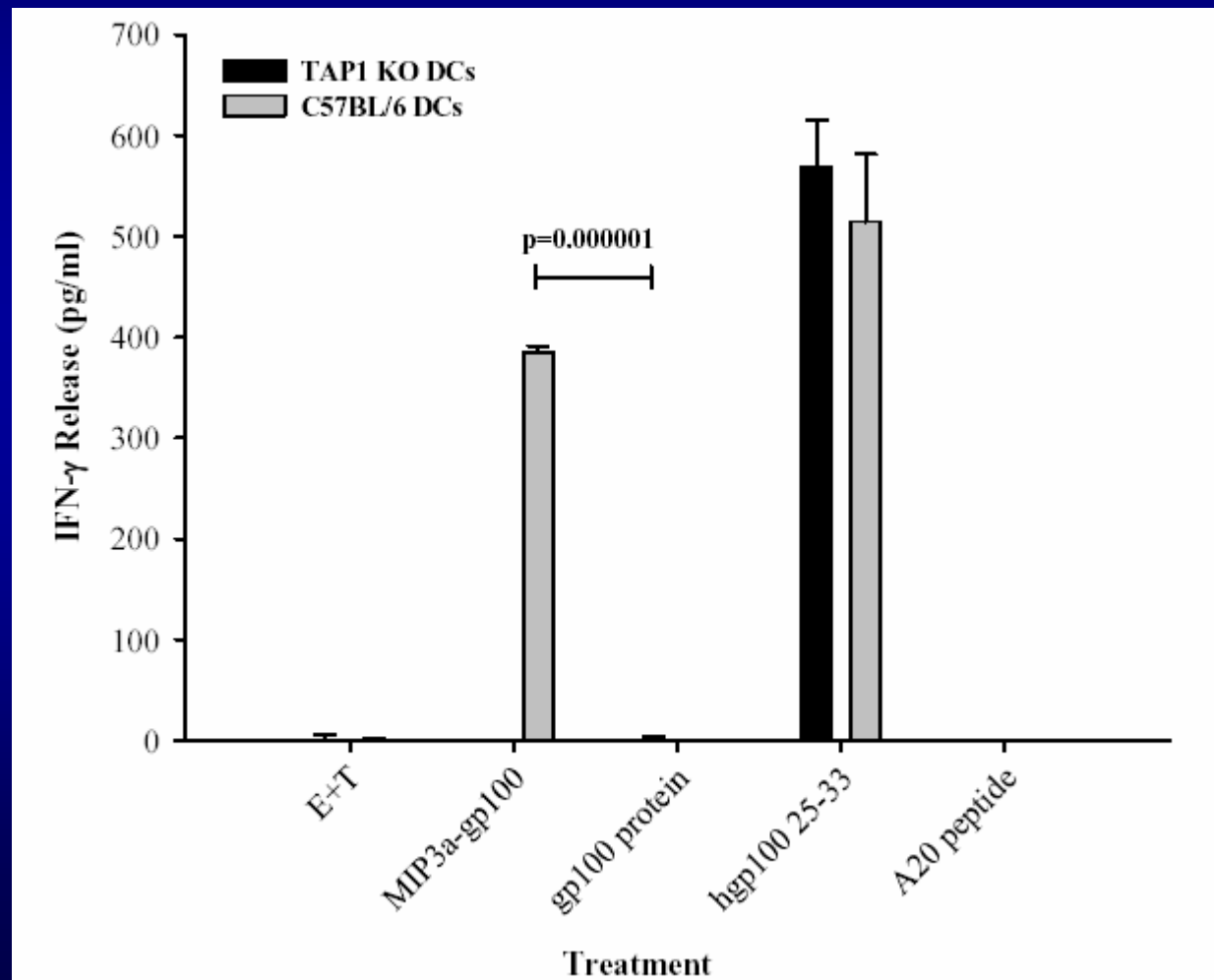
Future Plans

- Determine the mechanism(s) of action of sFv-chemokine fusion DNA vaccines (vivo and vitro)
- Test selected additional chemokine receptor ligands for fusion to sFv antigen
- Design a pilot clinical trial of sFv-chemokine fusion DNA vaccination

Priming in vivo to melanoma Ag gp100 is facilitated by chemokine fusion



Cross-presentation of chemokine – gp100 fusions



Schiavo et al.
Blood 2006

Translational Development of Vaccines for Lymphoma and Myeloma

LAB

2nd Generation Vaccines

- Id-Chemokine Fusions
- HIV DNA Vaccines

T-Cell Adjuvants

- GM-CSF

Characterization of Id T-cell epitopes

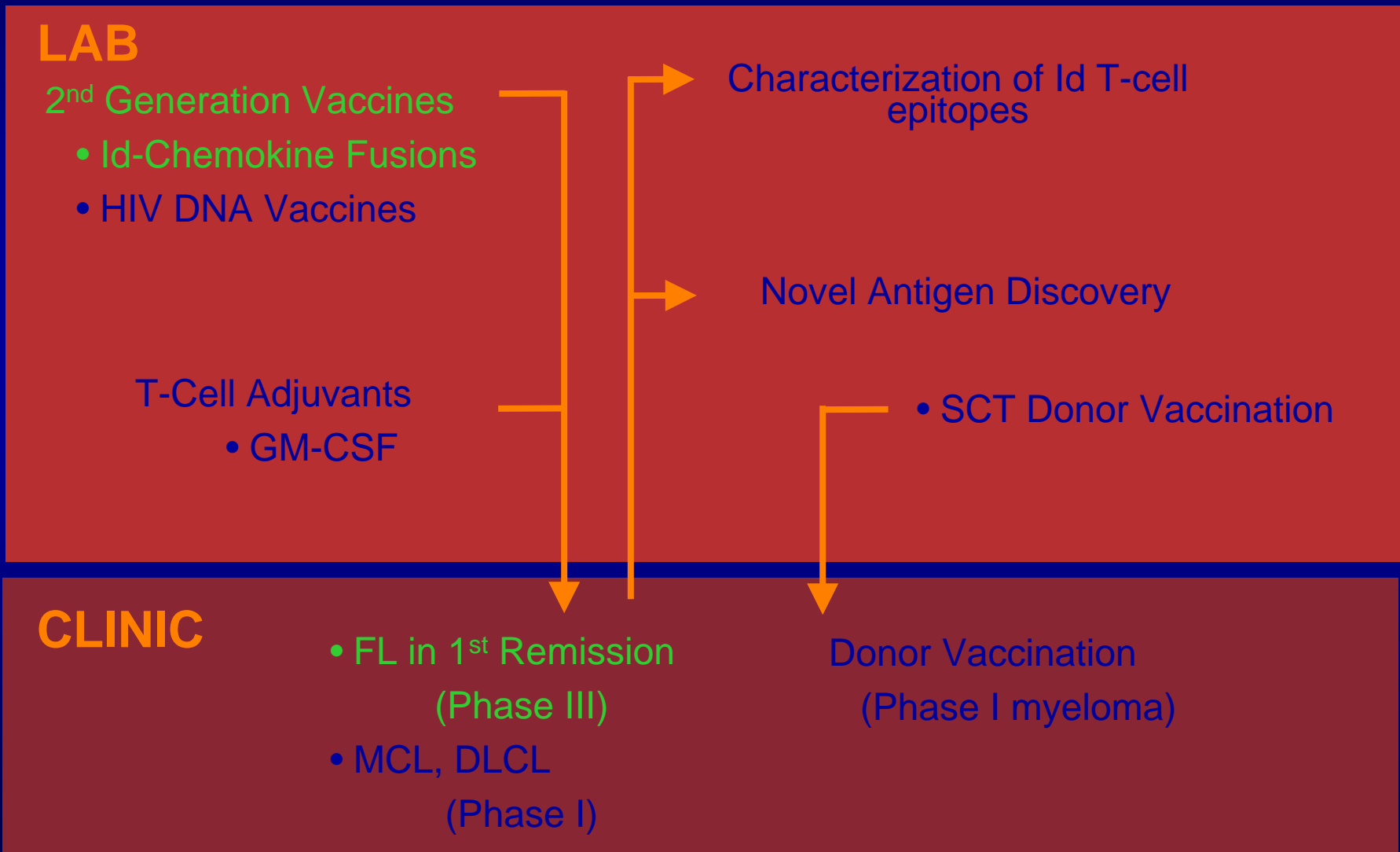
Novel Antigen Discovery

- SCT Donor Vaccination

CLINIC

- FL in 1st Remission
(Phase III)
- MCL, DLCL
(Phase I)

Donor Vaccination
(Phase I myeloma)



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NCI research contractor
Industry

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**“Plans fail for lack of counsel, but with
many advisors they succeed”**

Proverbs 15:22

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Edison Liu, MD

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