Tipping The Immune System Balance In Favor Of Effective Cancer Immunotherapy

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Many Challenges For Developing Cancer Vaccines In The Clinics

- What are the “immune relevant” targets?
- What is the best vaccine approach?
- What are the best immune monitoring methods?
- What approaches will overcome immune tolerance and eradicate cancer?
- What approaches will prevent cancer?

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Immune tolerance mechanisms are the major barriers for developing effective cancer vaccines

- Systemic
  - T regs
  - Ineffective T cell activation
  - Low avidity T cell availability
- Local at the tumor site
  - COX-2 pathways
  - T regs
  - T cell down regulatory signals (new B7 family members)
  - Down-regulatory cytokines
    - IL-10, TGF-beta, VEGF

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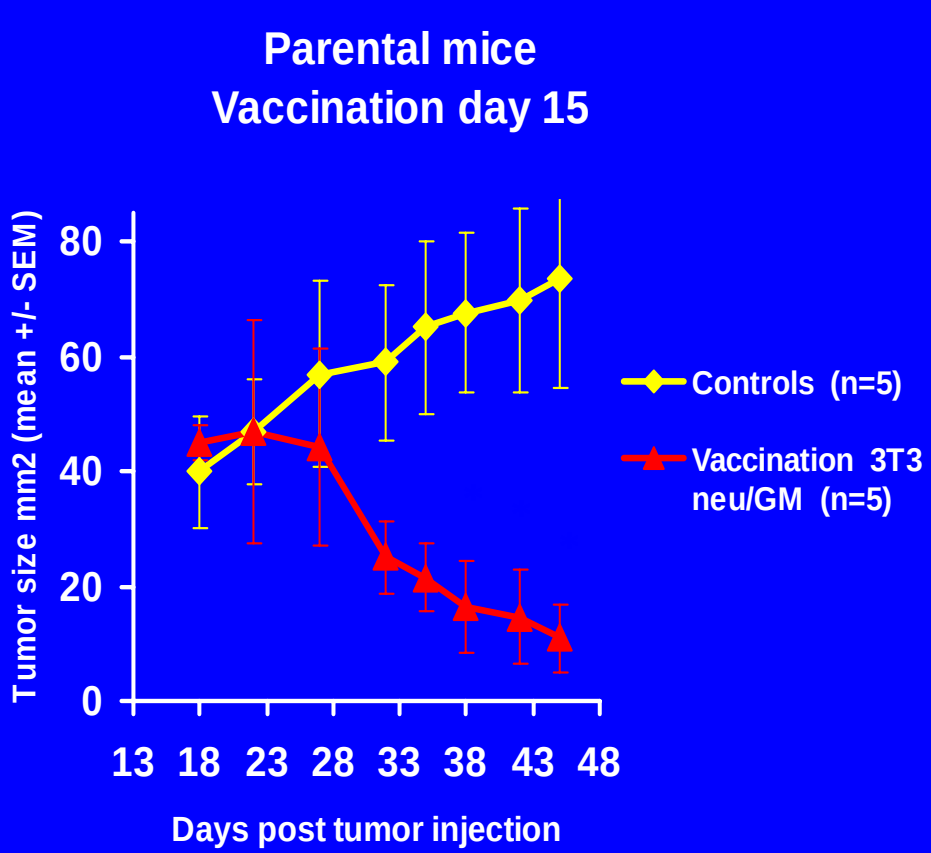
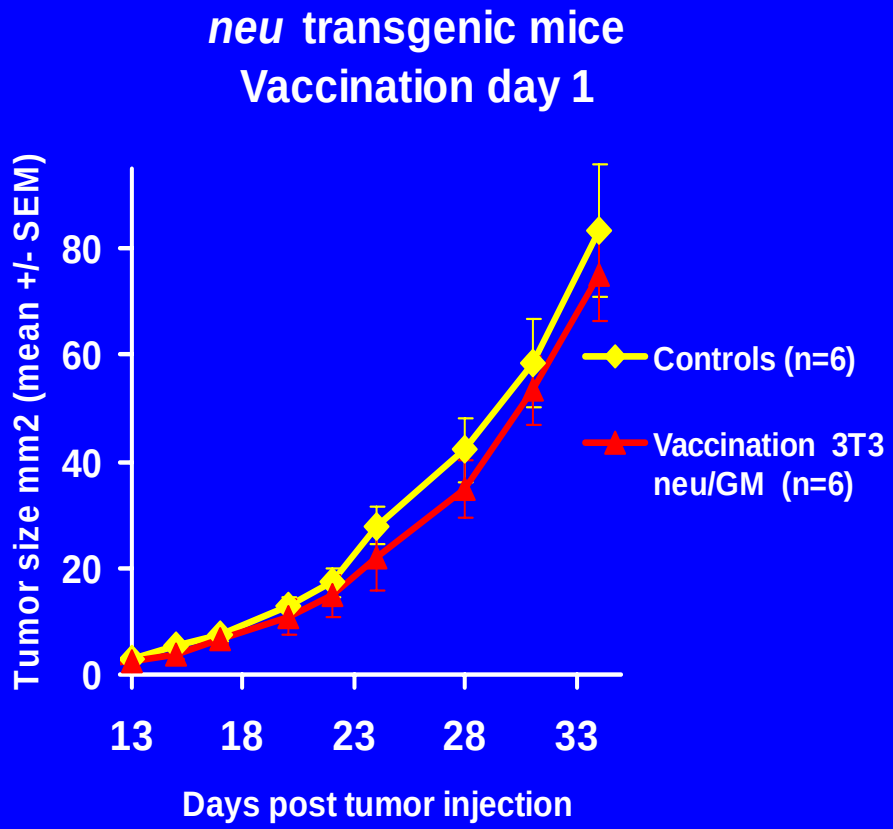
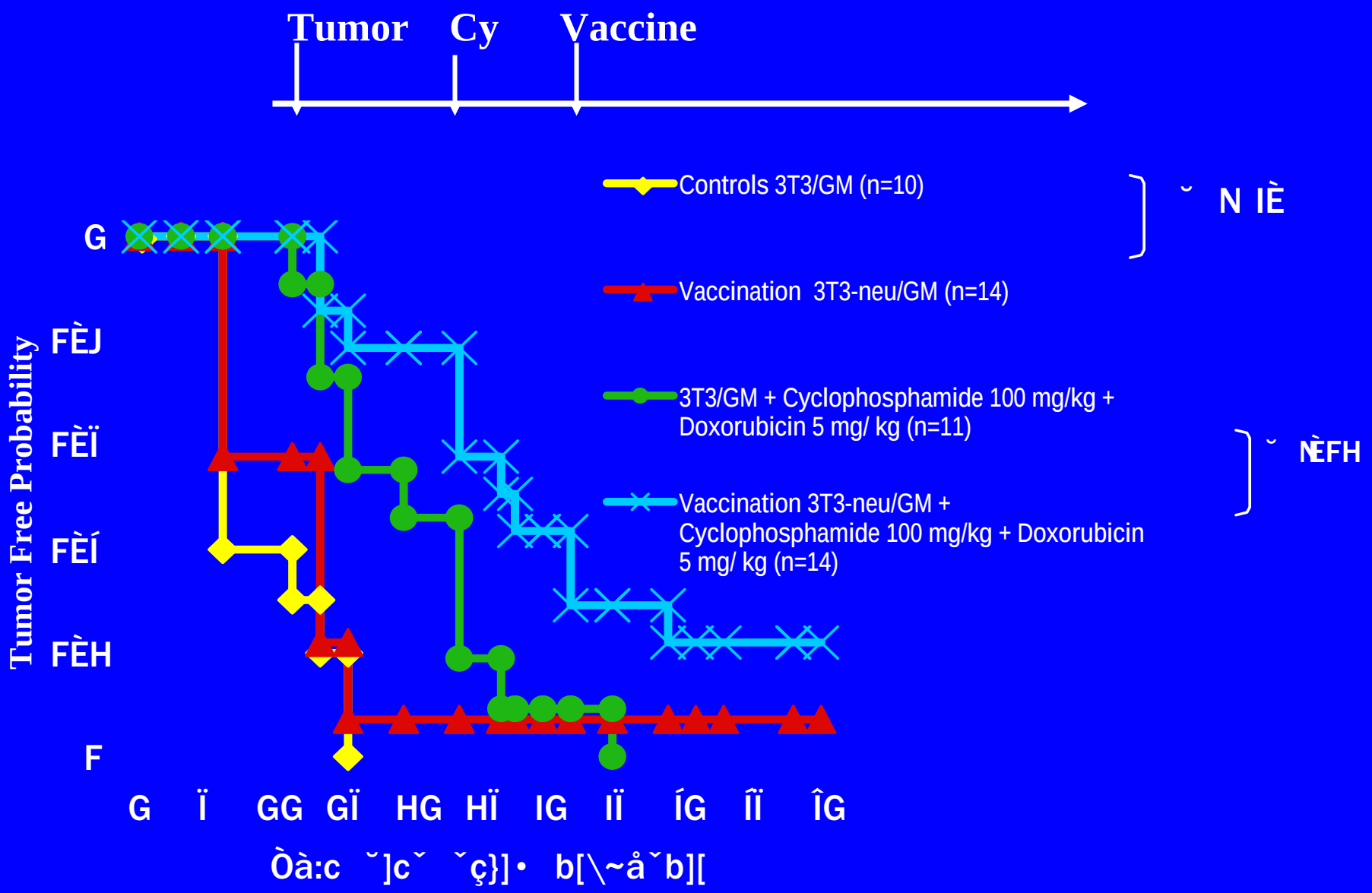
Her2/neu in neu Transgenic Mice Provide a Model of Immune Tolerance

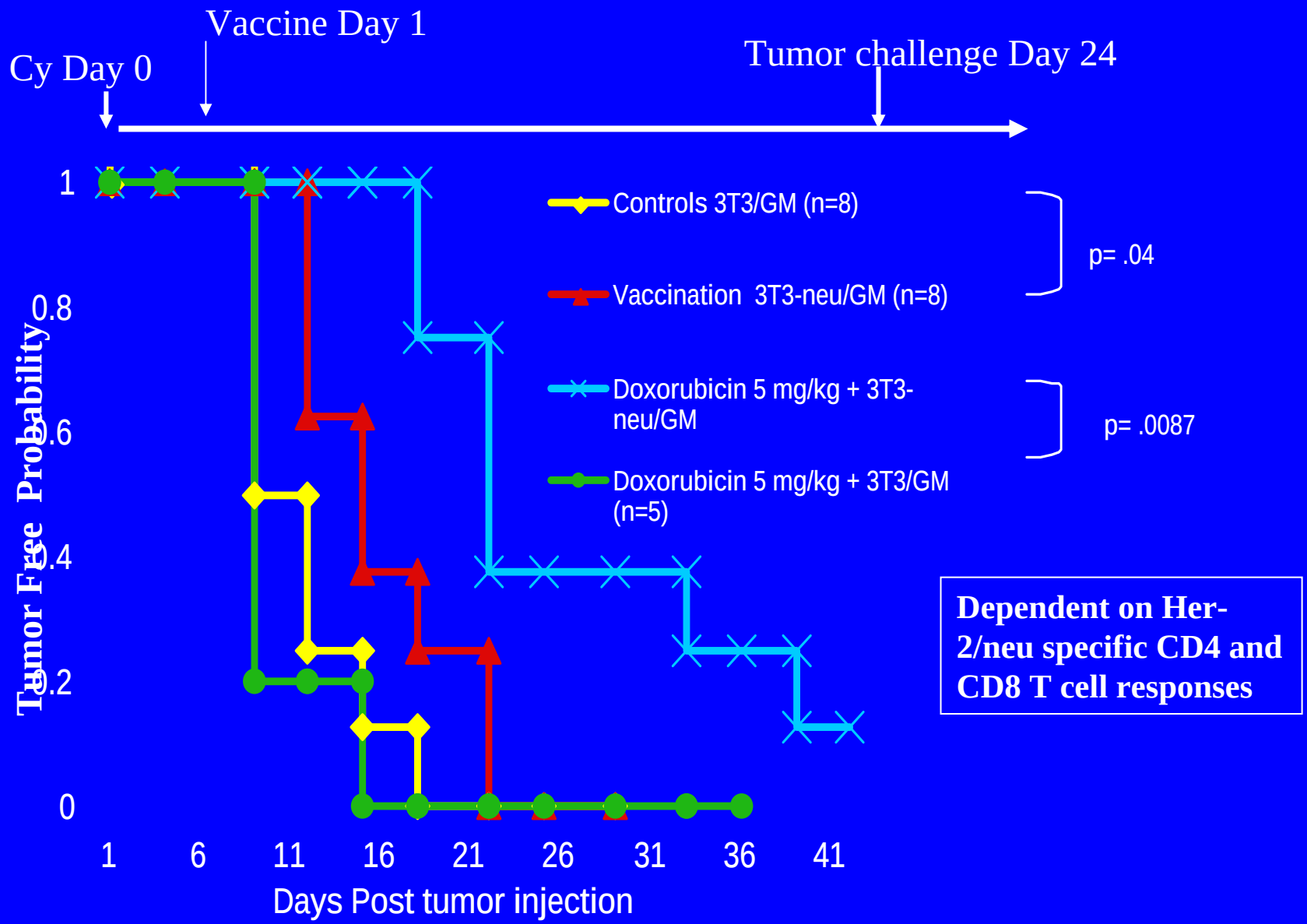




CY Given Prior to Priming Enhances The Anti-Tumor Effect Of The Vaccine



Cy Enhances The Potency Of The Vaccine Through A Mechanism Distinct From Direct Tumor Lysis

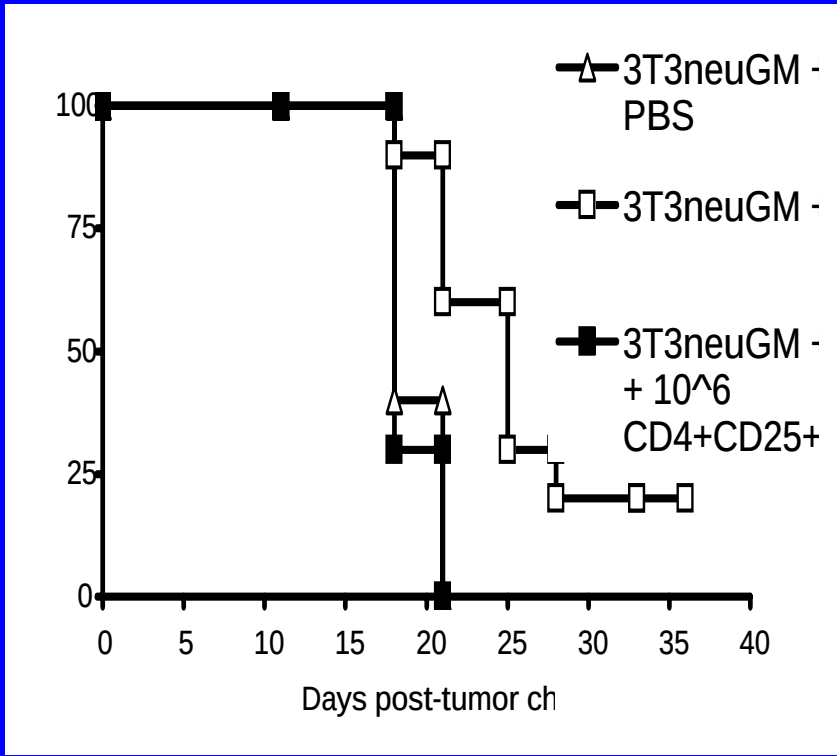


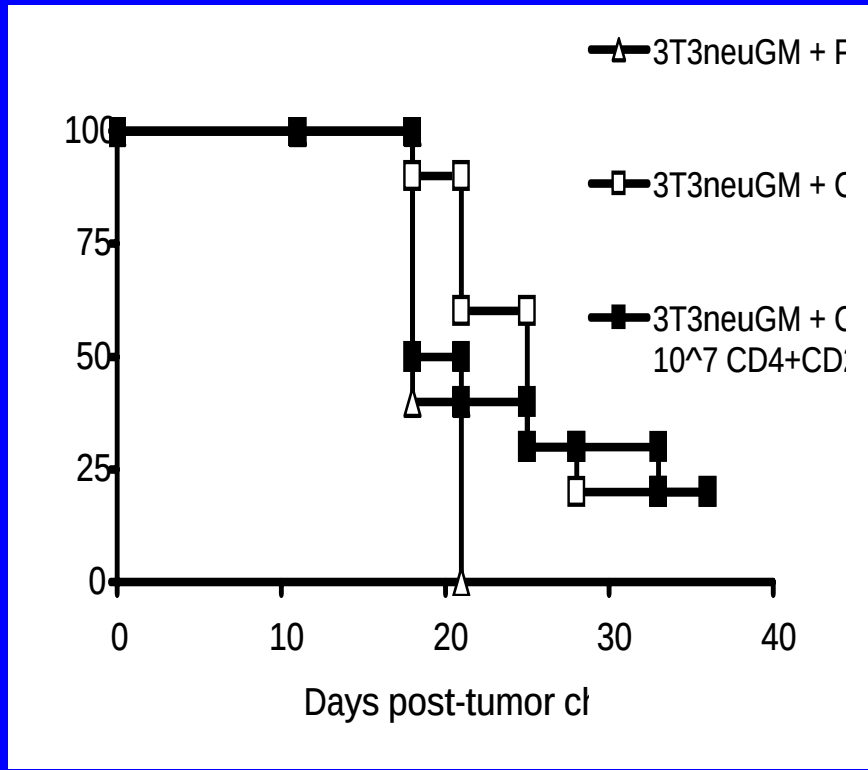
Dependent on Her-2/neu specific CD4 and CD8 T cell responses

Hypothesis:

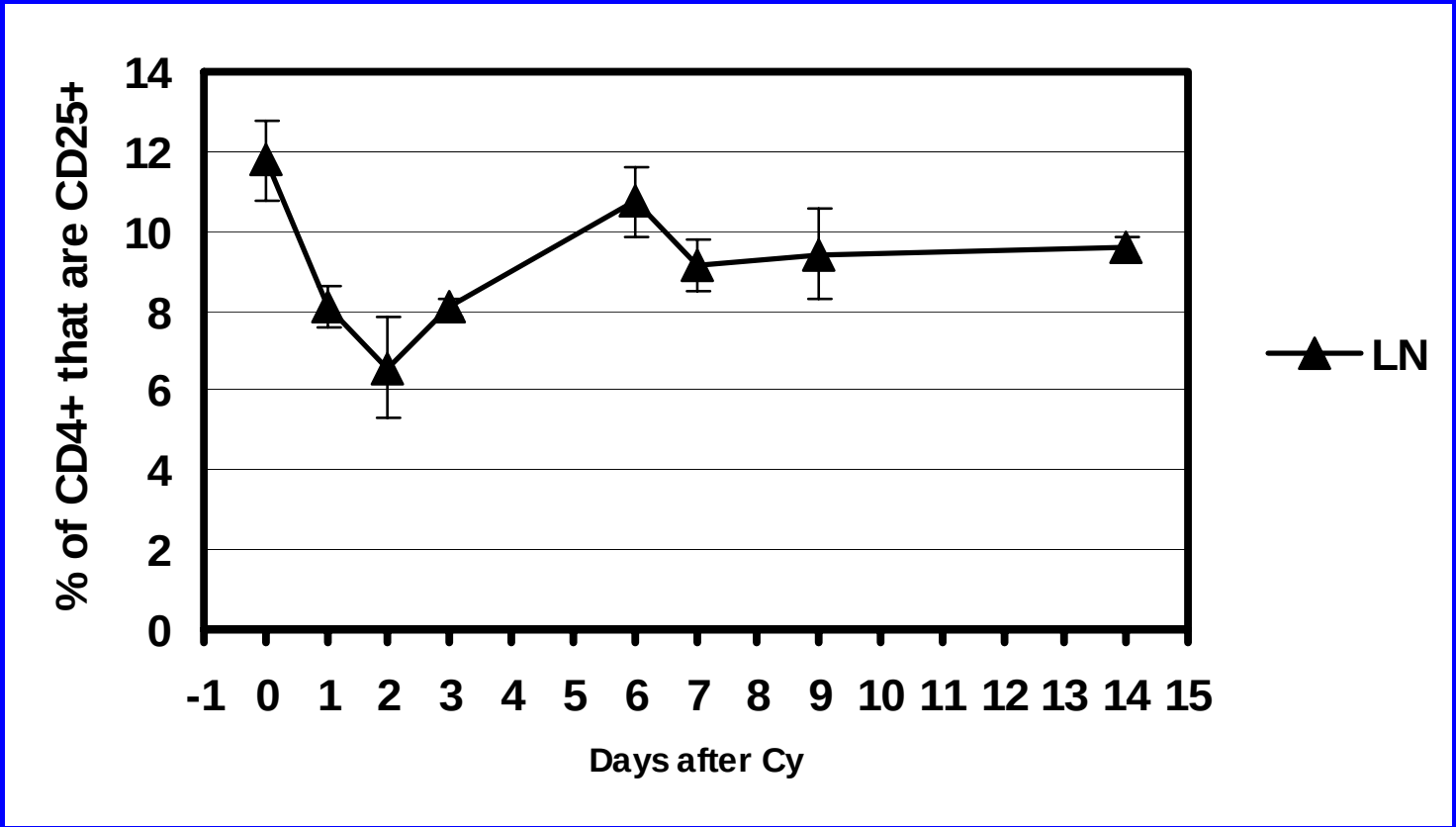
T regulatory cells suppress Cy plus vaccine induced HER-2/neu-specific immunity

$CD4^+CD25^+$, FoxP3+ but not $CD4^+CD25^-$, $FoxP3^-$ T cells suppress CY+ vaccine induced anti-tumor immunity





Cyclophosphamide treatment transiently suppresses peripheral Tregs

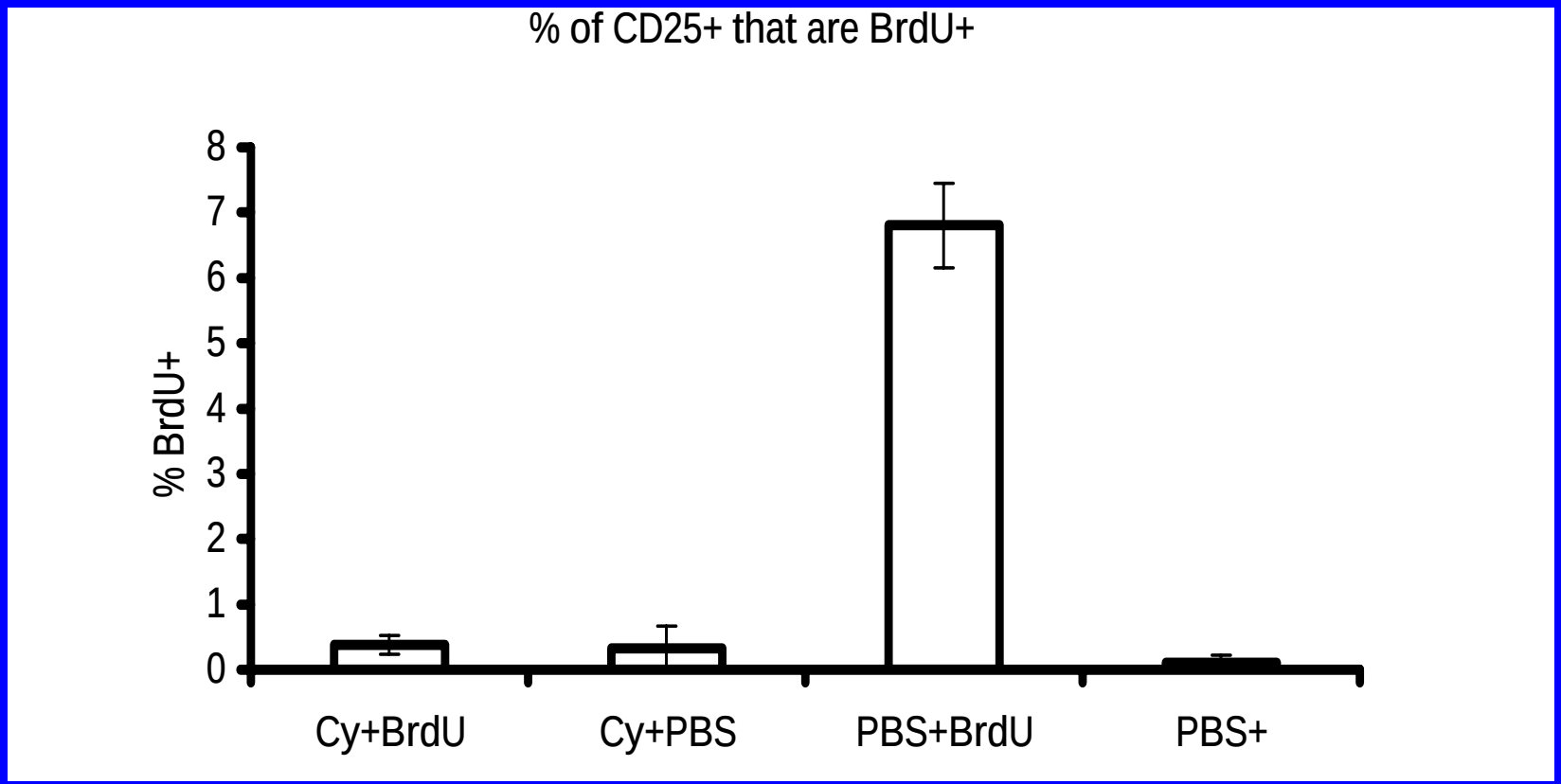


Cy selectively deletes cycling T cells in tumor bearing mice

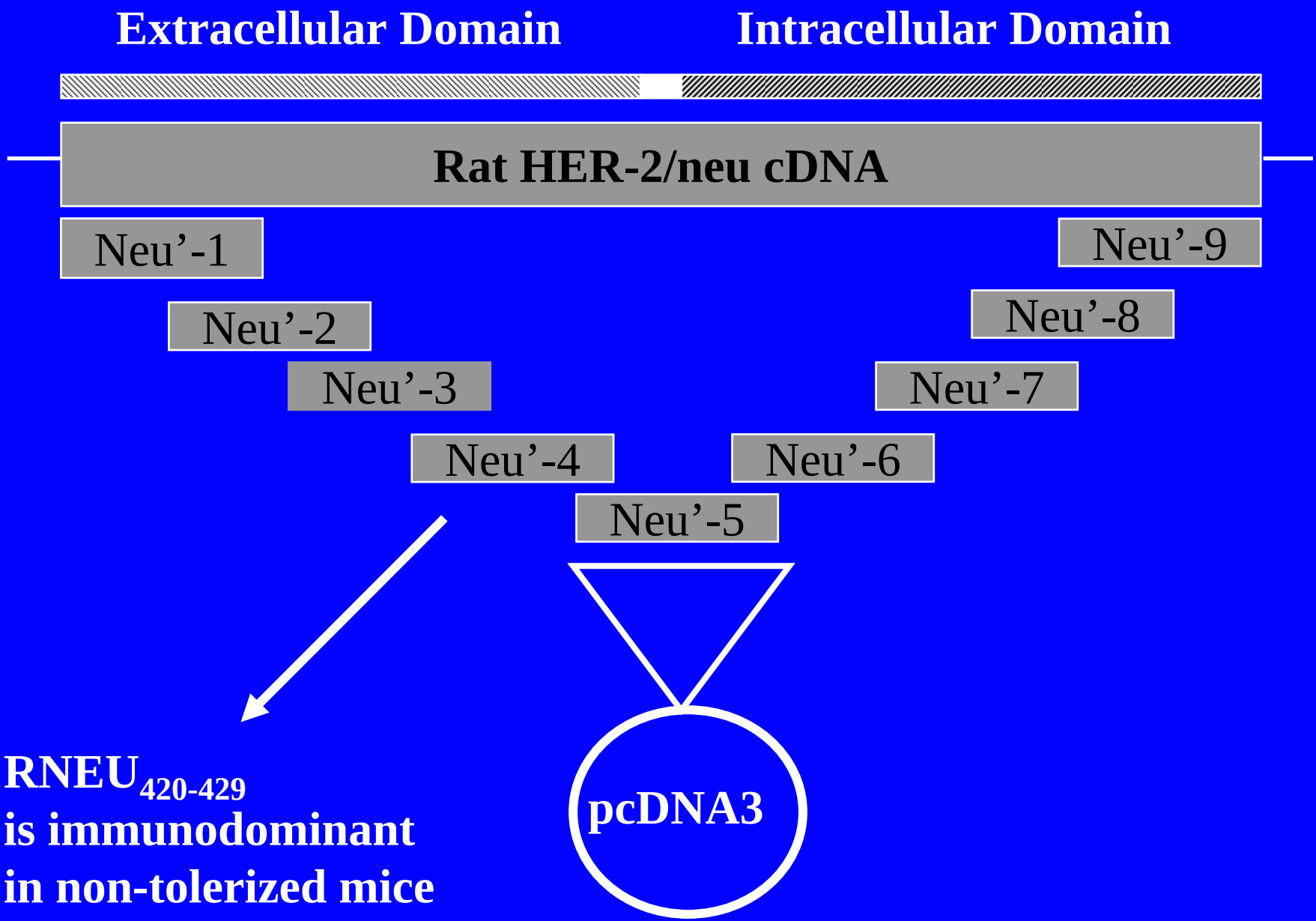
Cy on Day 1

BdrU on Day 2

Analyze splenic T cells for CD4CD25- and CD4CD25+ T cells



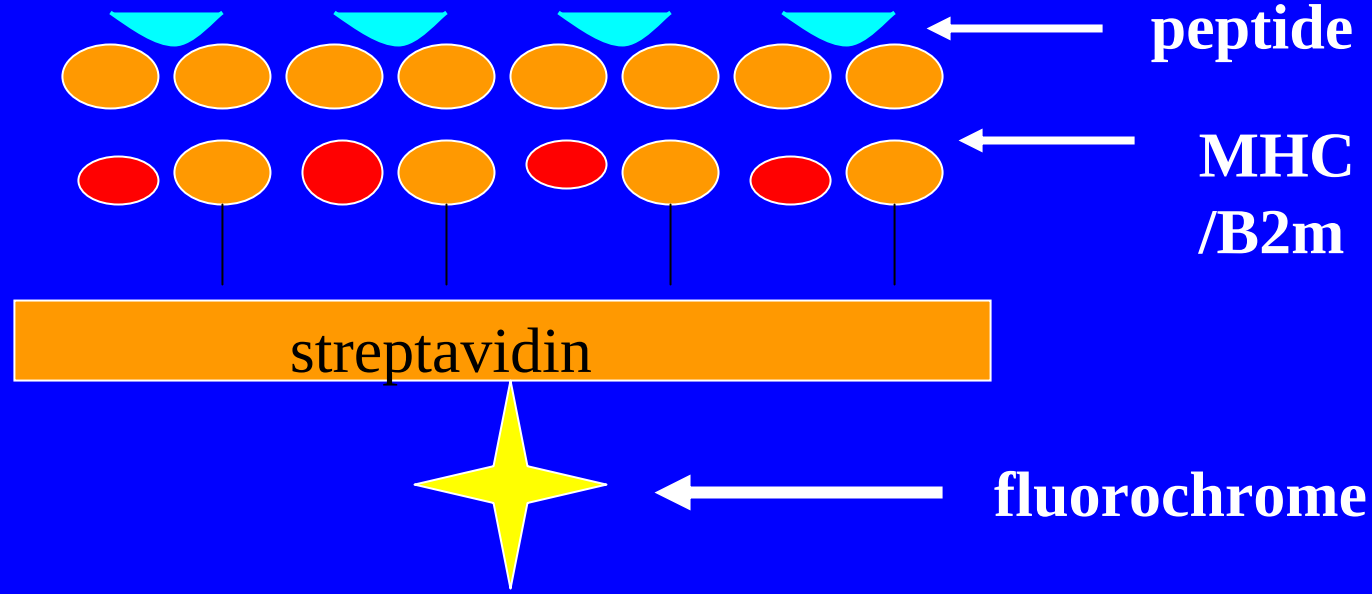
Dissecting the mechanisms of immune tolerance to HER-2/neu requires knowledge of HER-2/neu derived T cell epitopes



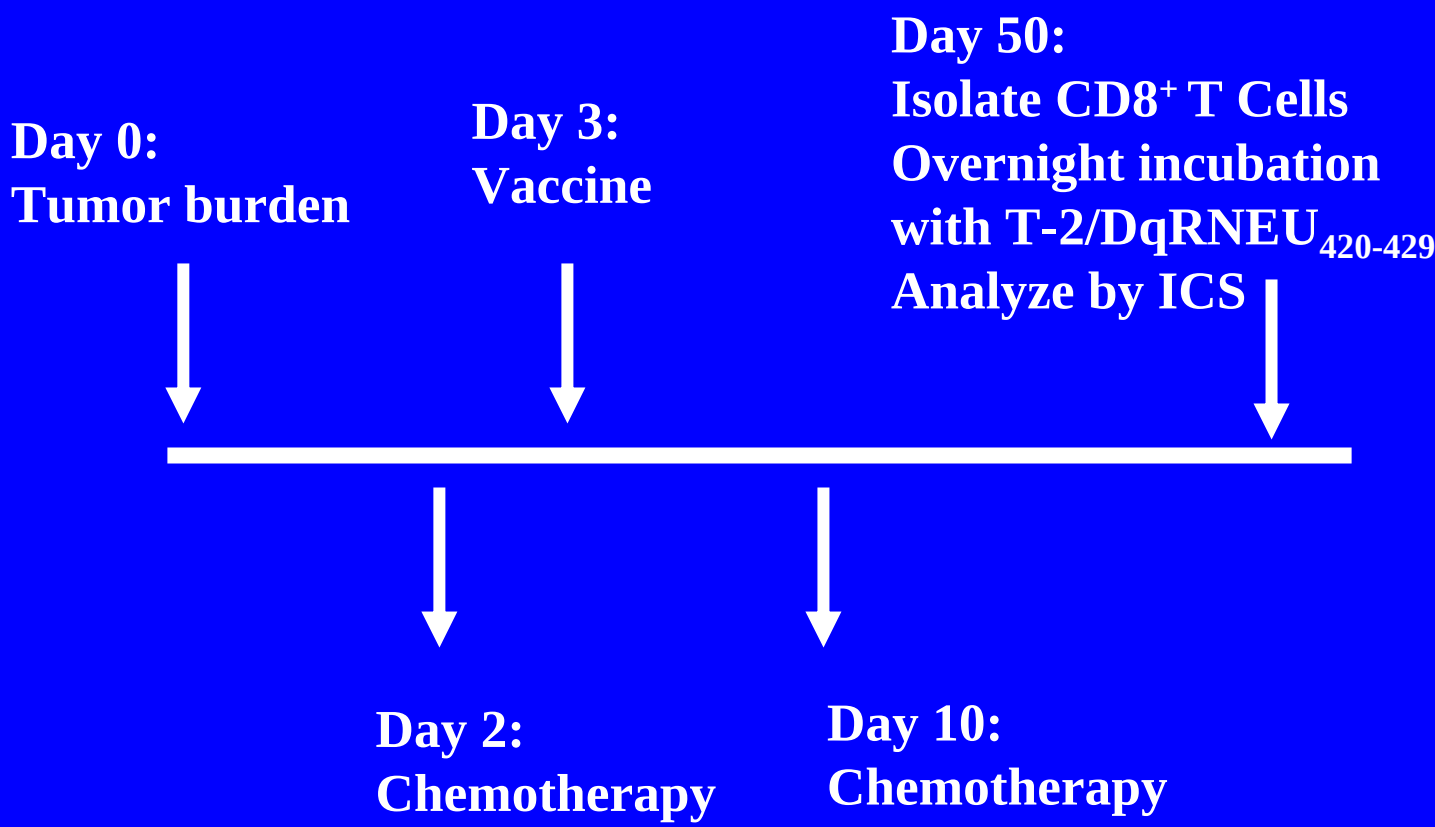
$RNEU_{420-429}$ is immunodominant in non-tolerized mice

Ercolini et al, Journal of Immunology (2003); 170:4273-80.

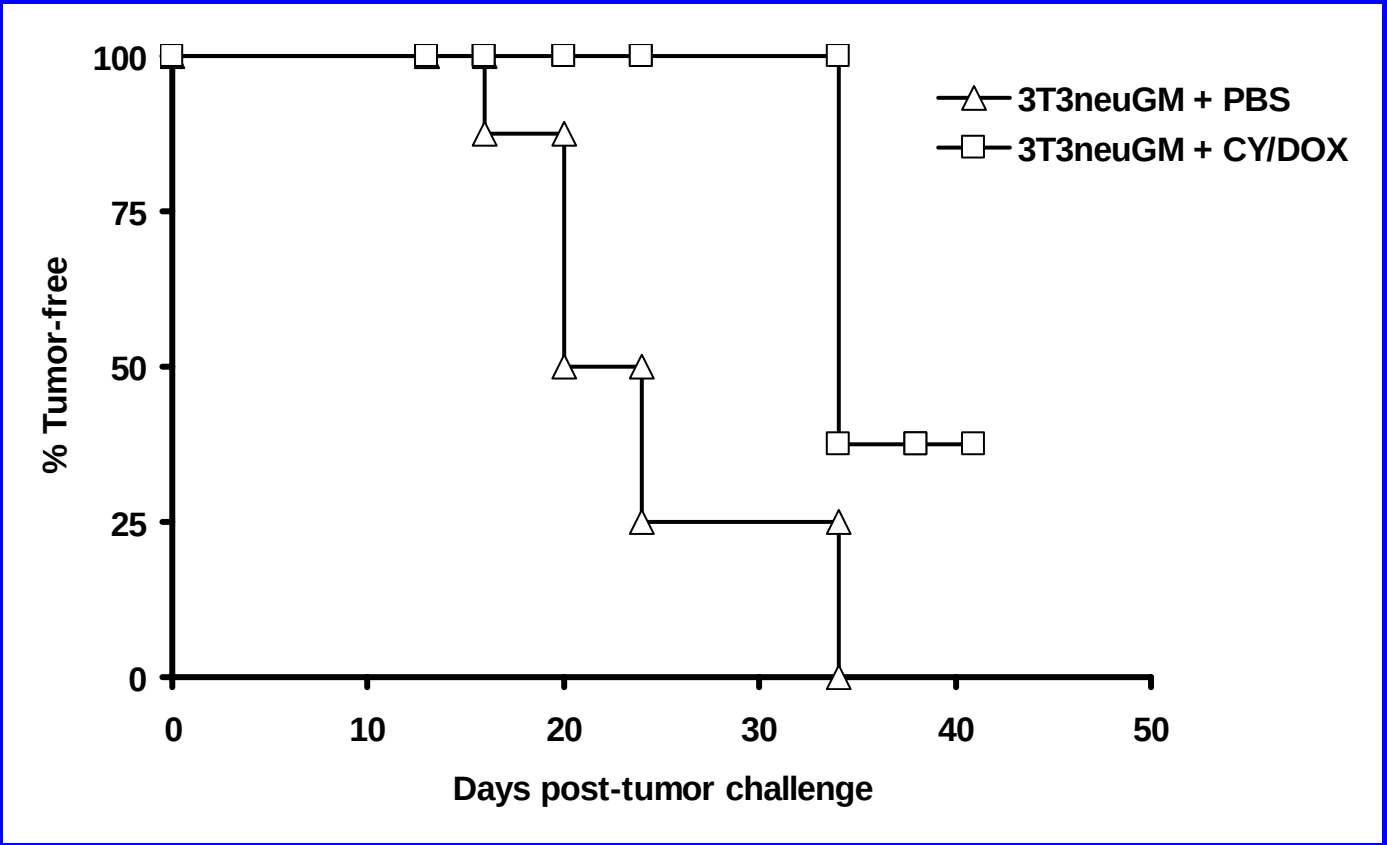
H-2D^{q} MHC/RNEU$_{420-429}$ Tetramer

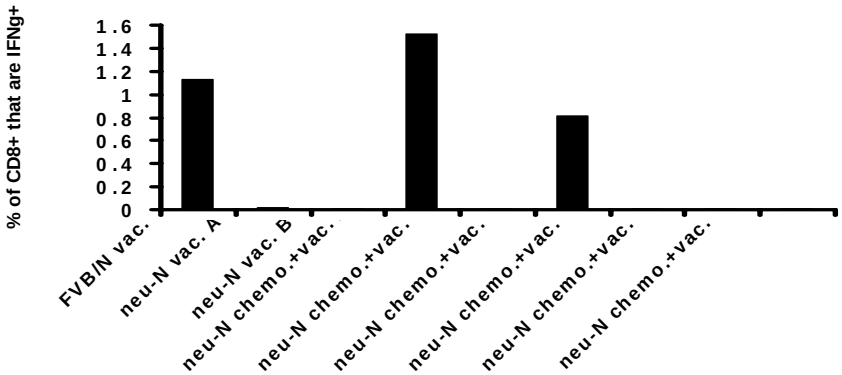


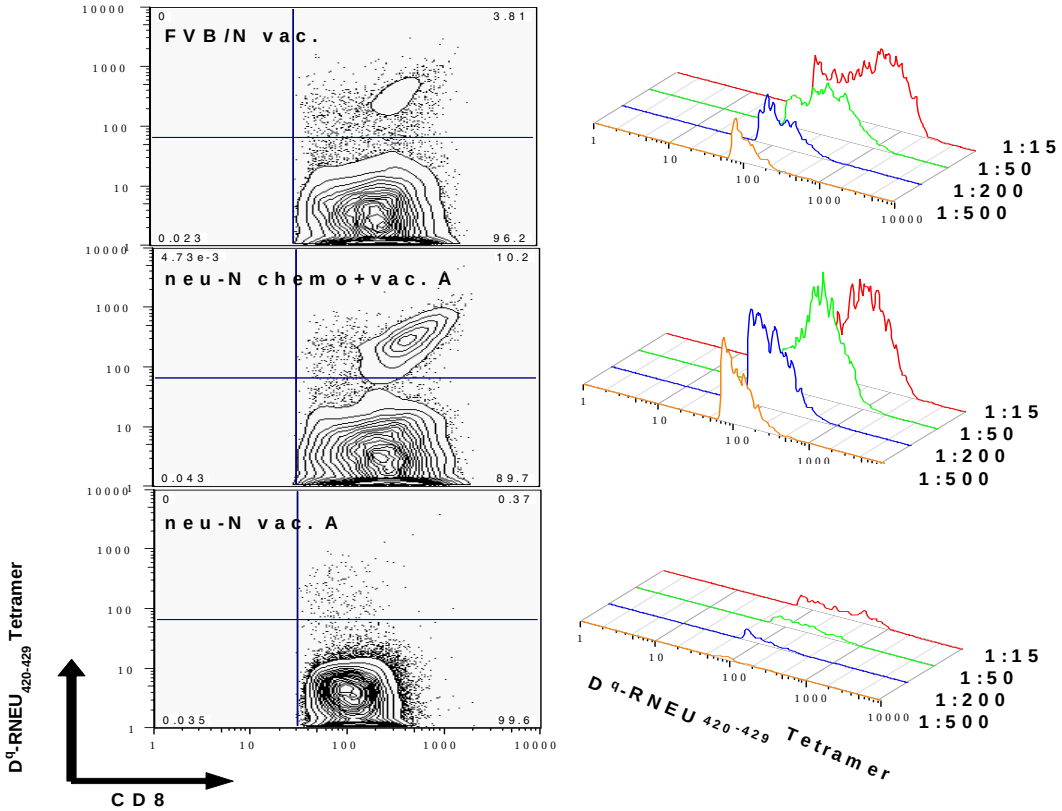
Can $RNEU_{420-429}$ T cells be isolated directly from vaccinated mice that are cured of their tumor?



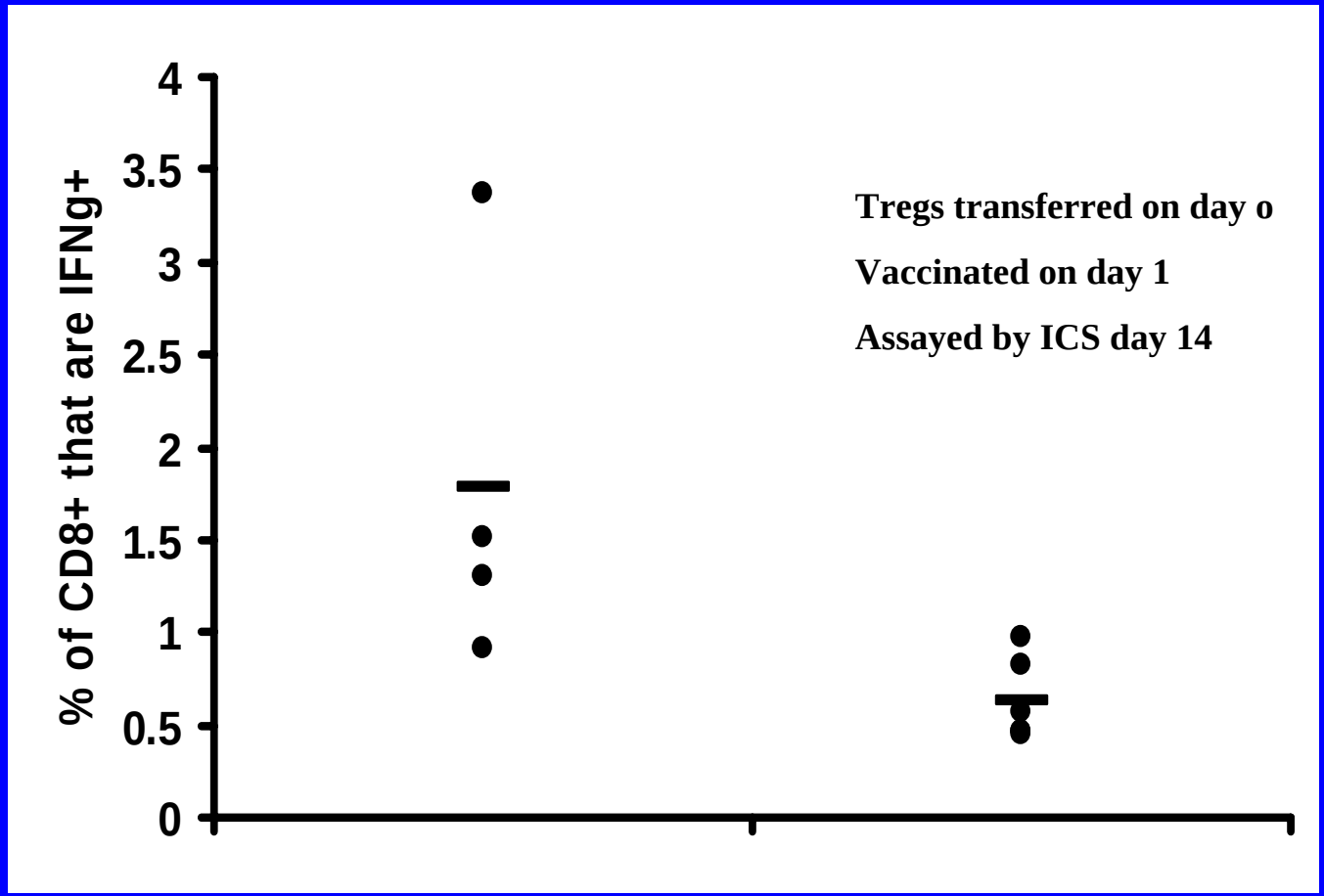
$RNEU_{420-429}$-specific T cells can be isolated from mice treated with Cy + vaccine



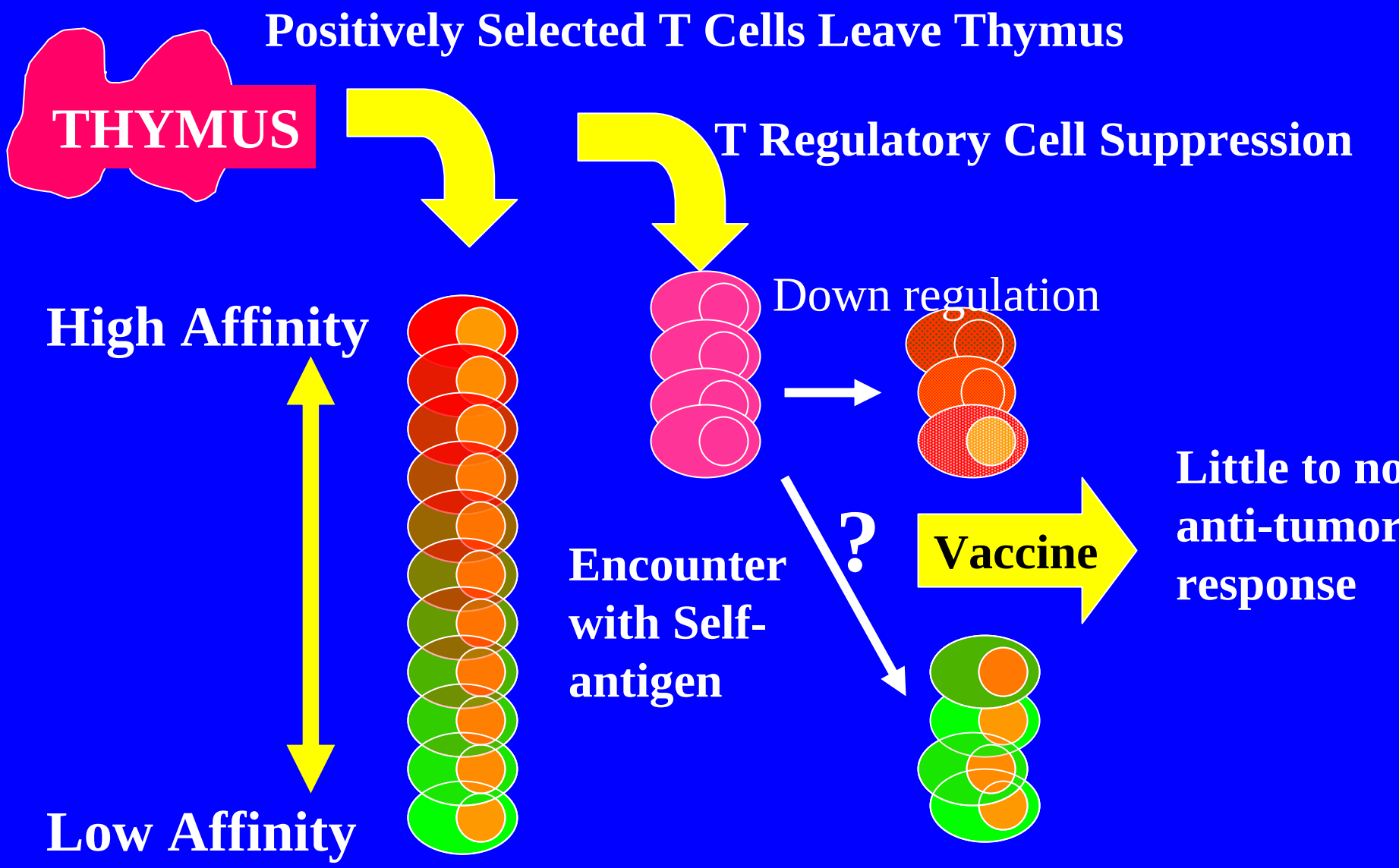

% of CD8+ that are IFNg+
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
FVB/N vac.
neu-N vac. A
neu-N vac. B
neu-N chemo.+vac.
neu-N chemo.+vac.
neu-N chemo.+vac.
neu-N chemo.+vac.
neu-N chemo.+vac.
neu-N chemo.+vac.
neu-N chemo.+vac.


FVB/N vac.
0
3.81
0.023
96.2
neu-N chemo+vac. A
4.73e-3
10.2
0.043
89.7
neu-N vac. A
0
0.37
0.035
99.6
10000
1000
100
10
1
1
10
100
1000
10000
D q-RNEU 420-429 Tetramer
CD 8
1:15
1:50
1:200
1:500
1:15
1:50
1:200
1:500
1:15
1:50
1:200
1:500
D q-RNEU 420-429 Tetramer

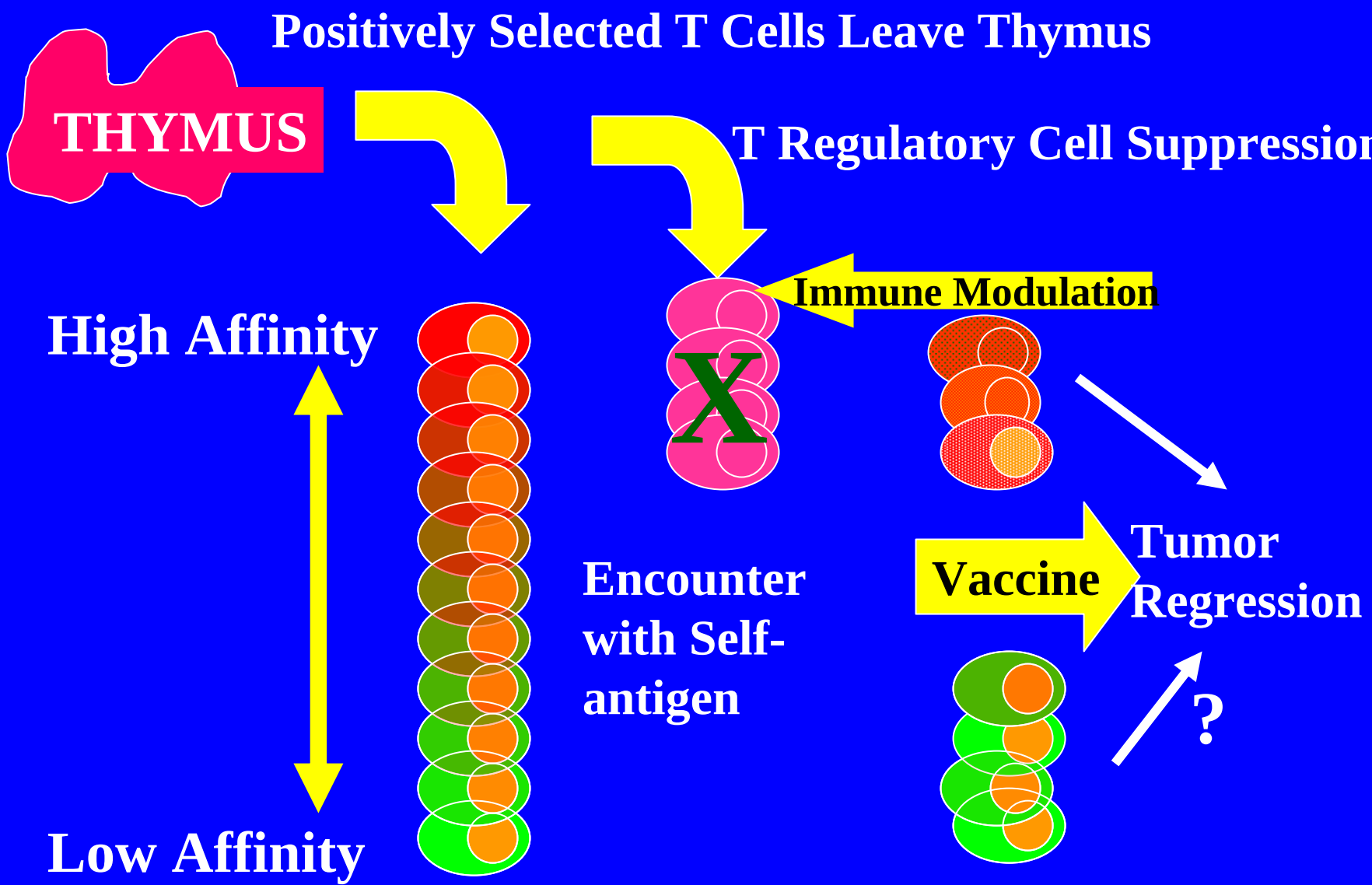
Adoptively Transferred Tregs from Tolerized Mice Suppress $RNEU_{420-429}$-Specific T Cells in Vaccinated Non-Tolerized Mice



Current working model of CD8^{+} peripheral tolerance in *neu* mice



Current Working Model of CD8$^+$ Peripheral Tolerance



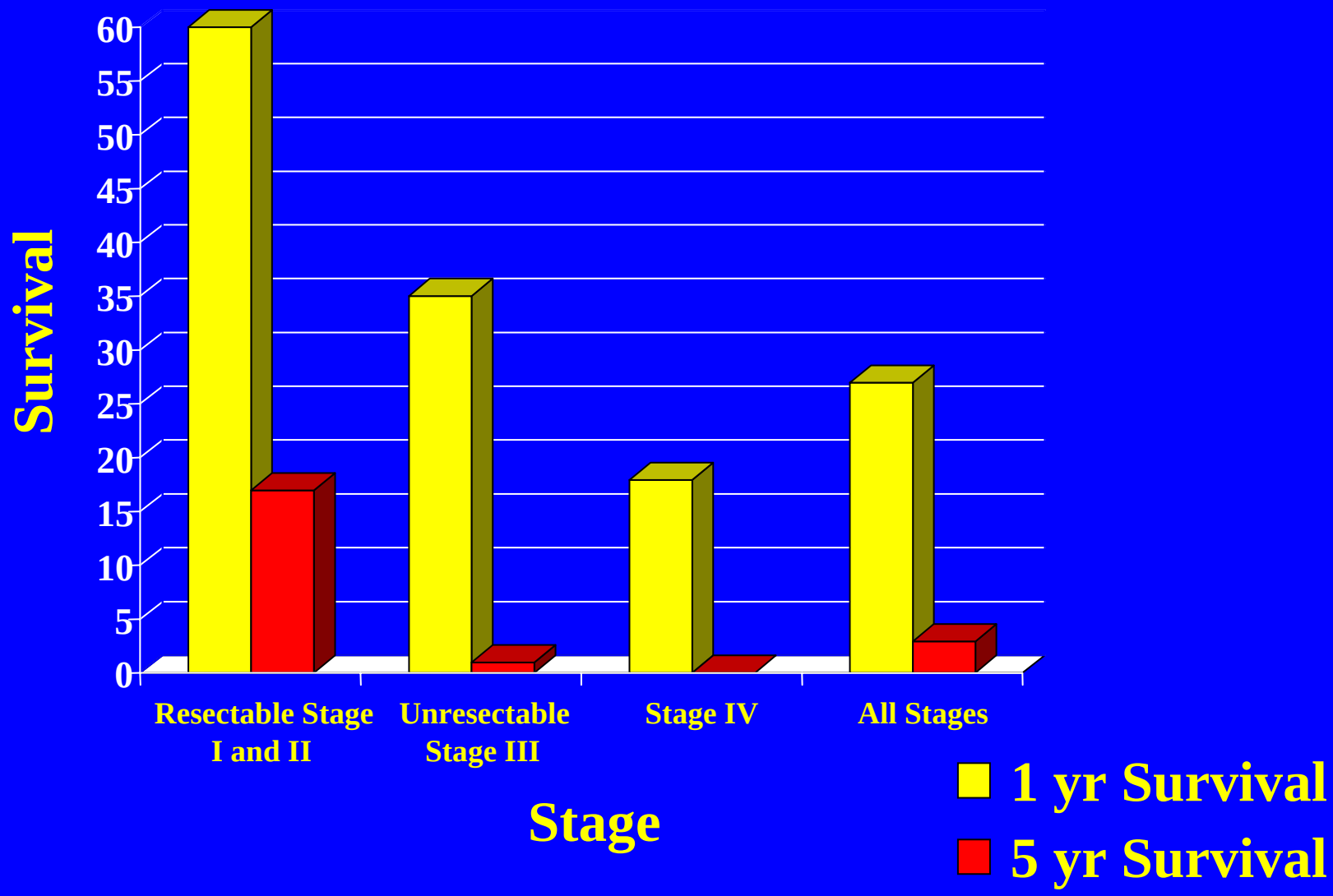
Summary of Mouse Data

- **High avidity $RNEU_{420-429}$ T cells are suppressed rather than deleted in *neu* mice**

- **Inhibition of Tregs allows for the recruitment of high avidity T cells specific for the immuno-dominant epitope $RNEU_{420-429}$ to the immune response**

Ercolini et al., J Exp Med, 2005

Pancreas Cancer by Stage



Pancreatic Cancer Therapy

Stage 1, 2, or 3 (Locoregional)

- Surgery
- Adjuvant chemoradiation
- 70-80% recurrence at 1 yr

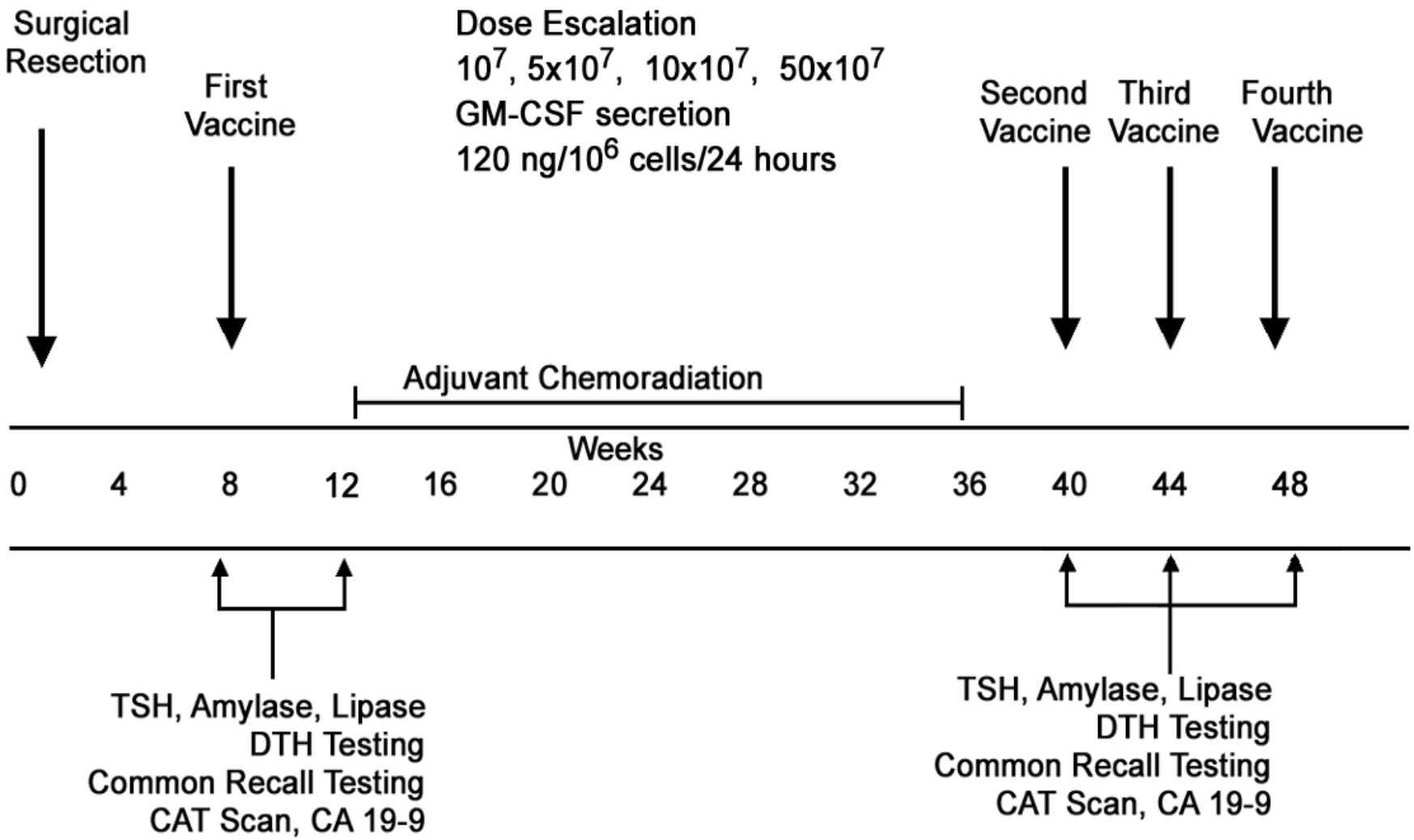
Stage 4 (Metastatic)

- Gemzar +/- other
- Experimental therapy
- Palliation

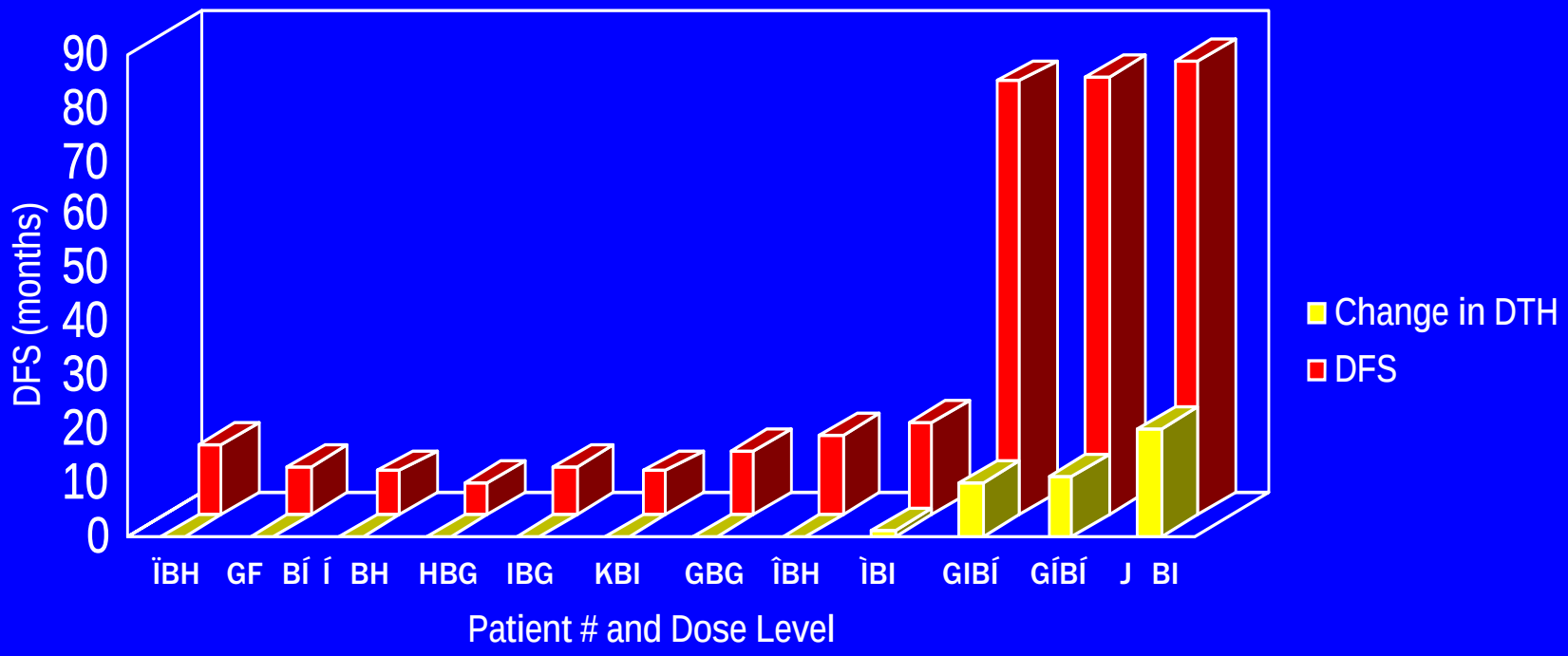
Pancreas Cancer Team at Hopkins

- Surgery
  - John Cameron
  - Charles Yeo
  - Steven Leach
  - Kurt Campbell
- Pathology
  - Ralph Hruban
  - Scott Kern
  - Christine Iacobuzio Donahue
  - Anirban Maitra
- Gastroenterology
  - Marcia Canto
  - Sanjay Jaganneth
  - Michael Goggins
- Vaccine Team
  - Elizabeth Jaffee, **Dan Laheru**, Barb Biedrzycki, Beth Onners, Irena Tartakovksy, Shirley Siguoros, Sara Solt, Guanlan Huang
- Radiology
  - Elliott Fishman
  - Rich Wahl
- Genetics
  - Connie Griffin
  - Jennifer Axilbund
  - Alison Klein/Miriam Tillery
- Medical Oncology
  - Ross Donehower
  - Elizabeth Jaffee
  - Manuel Hidalgo
  - Dan Laheru
  - Wells Messersmith
- Radiation Oncology
  - Deborah Frassica
  - Fariba Asrari

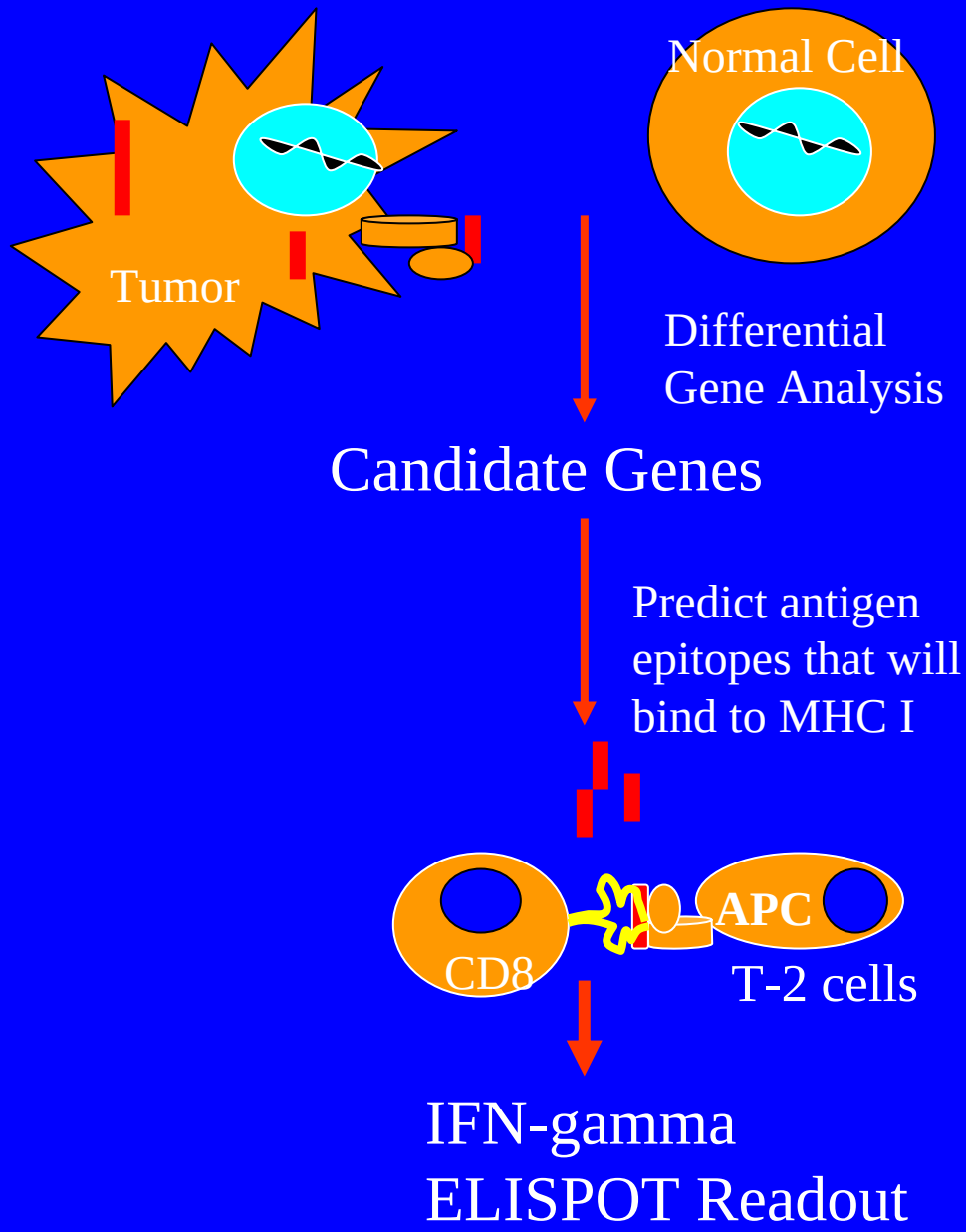
Design of Protocol J9617: A Phase I Study of an Allogeneic GM-CSF Vaccine



Correlation of Post-Vaccination DTH with Disease-Free Survival



Functional Genomic Approach



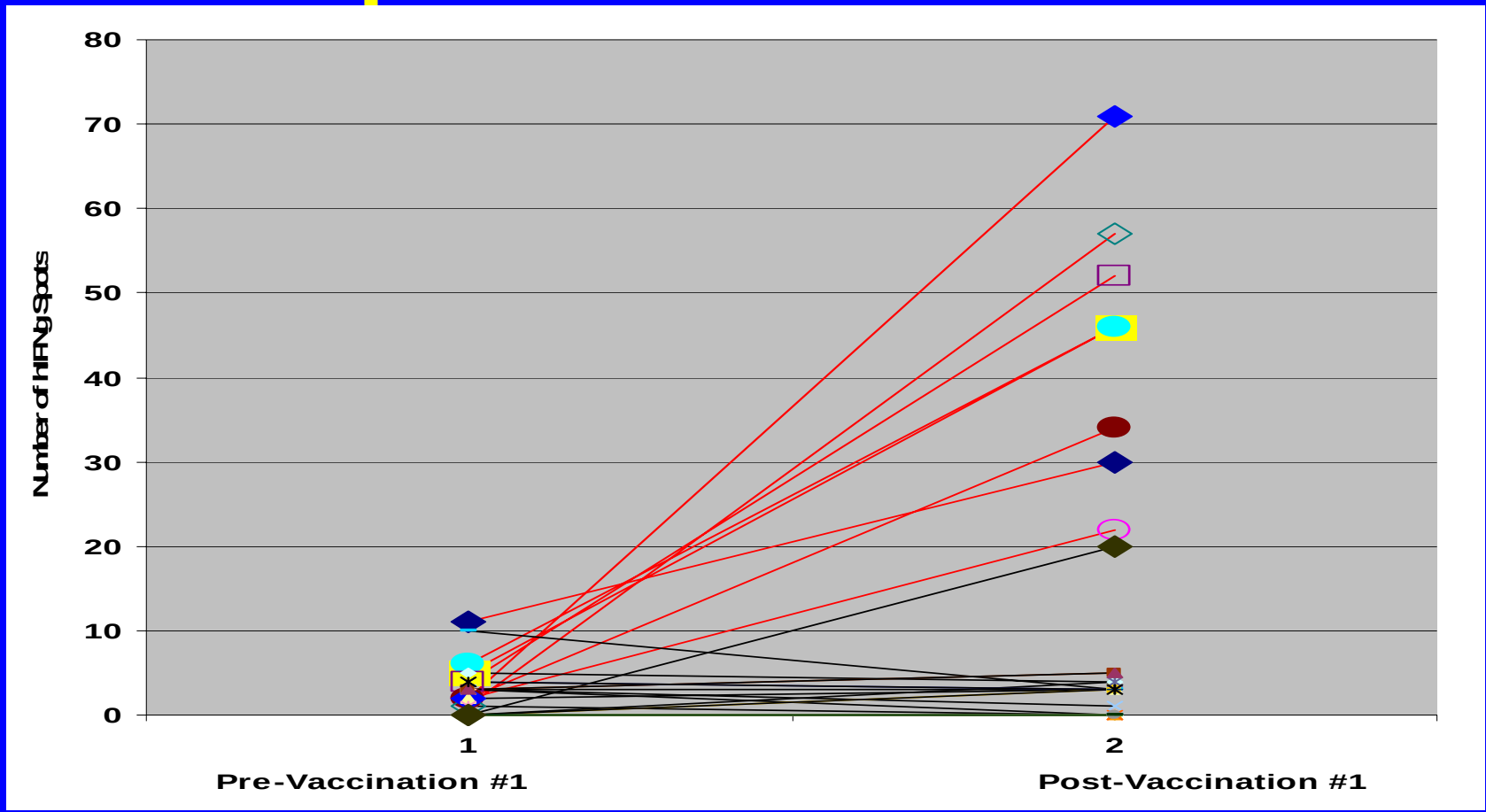
Experimental Methods

- Three day ELISPOT procedure

- **Day 1**: Coat plate with primary Ab
- **Day 2**: Pulse T2 cells with peptide and add freshly thawed and enriched $CD8^+$ T cells
- **Day 3**: Add secondary Ab and develop plate

- Developed plates are read using KS ELISPOT

Summary of Mesothelin Responses for 14 Patients



Peptide Symbol Legend

■=MesothelinA2$_{(20\text{-}29)}$ ❍=MesothelinA2$_{(530–539)}$ ♦=HIVGAGA □=MesothelinA3$_{(83\text{-}92)}$ ●=MesothelinA3$_{(225\text{-}234)}$ Δ=HIVNEFA3$_{(9}$ ◊=MesothelinA24$_{(435\text{-}444)}$ ♦=MesothelinA24$_{(475\text{-}484)}$ ♈=TyrosinaseA24$_{(206\text{-}214)}$

Pre-clinical data driving the next clinical trials

Design of a Phase II study of an Allogeneic GM-CSF Secreting Tumor Vaccine (GVAX) Alone or in Sequence with Cyclophosphamide for Metastatic Pancreatic Cancer

Laheru, et al and Cell Genesys

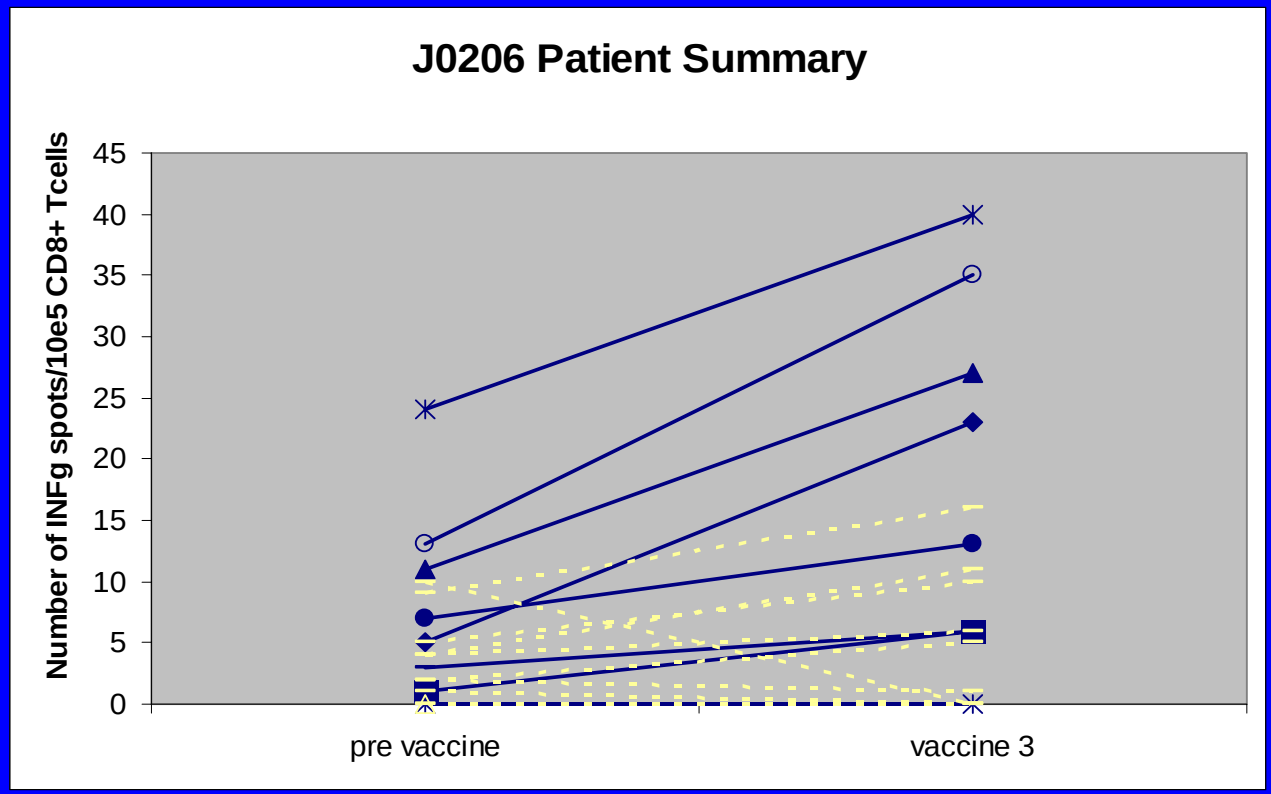
Cohort A treatment: $50x10^7$ vaccine cells alone (30 patients)

Cohort B treatment: 250 mg/m^2 Cy given 1 day prior to vaccination with $50x10^7$ vaccine cells (20 patients)

SUMMARY

Cohort	Toxicity Grade 1/2 Local	Serum GM-CSF Levels	Stable Dz During Therapy (18 weeks)
Vaccine Only (30 Pts)	Tolerated well in Pts with ≥2 prior therapies	Peaked at 48 hours	16%
Cy (250 mg/m2) + Vaccine (20 Pts)	Tolerated well in Pts with ≥2 prior therapies	Peaked at 48 hours	40%

Mesothelin specific T cells observed in predominantly Cy + vaccine treated patients



Solid line=Cy+vaccine

Dashed line=vaccine only

Improved Survival Associated with Mesothelin-Specific T Cell Responses Following Vaccination

Patient	HLA-A locus	# vaccinations	Mesothelin Specific T cells/10e5 CD8 T cells				Survival (mo)
			Pre		Vaccine 3	Vaccine 6	Follow-up	
4.006	A2	2	10		NA	NA	NA	1.47
4.012	A2	1	0		NA	NA	NA	1.47
4.018	A2	2 (+ Cy)	5		33	NA	NA	3.23
4.023	A2	3 (+ Cy)	153		108	NA	NA	6.53
4.024	A2	4 (+ Cy)	24		40	NA	NA	7.73
4.026	A3	6 (+ Cy)	0		0	21	7	25+
4.028	A3	3 (+ Cy)	7		13	19	NA	8.13
4.033	A2	6 (+Cy)	0		0	10	10	13.07

Future Directions

- Assess T cell avidity differences in patients treated with Cy+vaccine versus vaccine alone
- Test combinations of vaccine with inhibitors of additional checkpoints
  - Systemic targets
  - Tumor micro-environment targets
- Test combinatorial immune based approaches at earlier stages of disease

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NCI RAID Program

Cell Genesys

Conflict of Interest Statement

Under a licensing agreement between Cell Genesys and the Johns Hopkins University, the University is entitled to milestone payments and royalty on sales of the vaccine product described in this presentation. The terms of this arrangement are being managed by the Johns Hopkins University in accordance with its conflict of interest policies.