

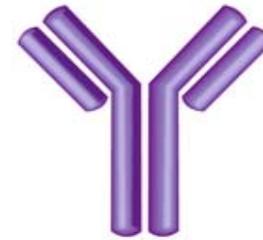
Antibody-Targeted Vaccines

Tibor Keler, PhD

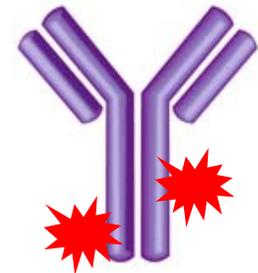


Monoclonal Antibodies as Therapeutics

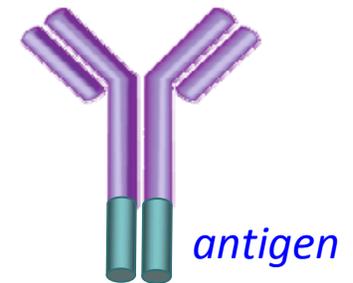
- Unconjugated mAbs: Passive vaccines
 - Target the cancer or pathogen or pathogenic molecule



- Conjugated mAbs: Toxin/radionuclide conjugates
 - Target the cancer

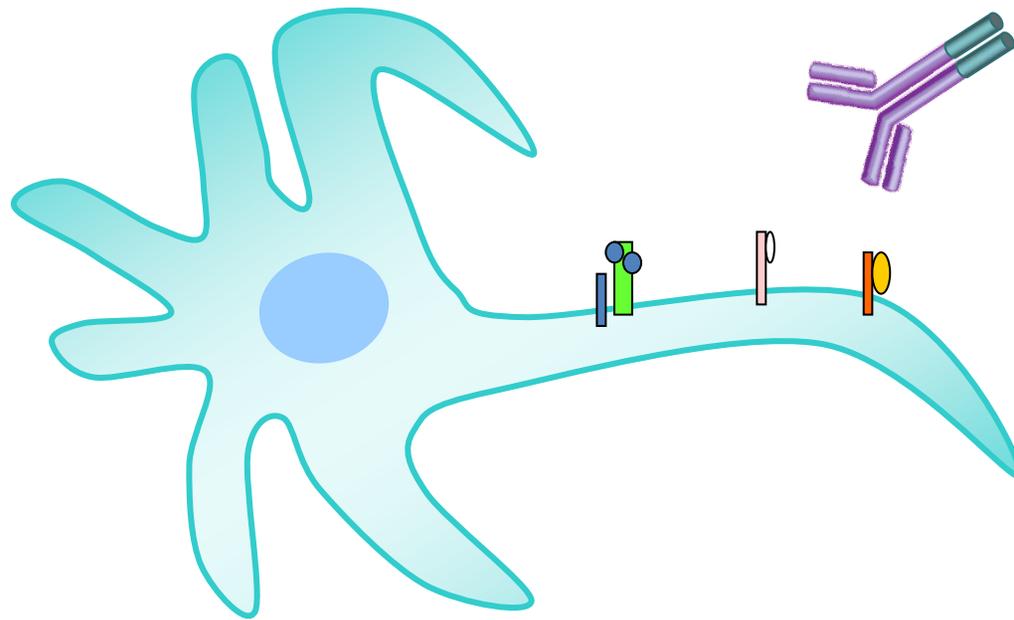


- Antibody-targeted vaccines: Antigen conjugates
 - Target the immune system to respond to cancer or pathogen



In vivo antigen Delivery

Targeting to endocytic receptors on DCs and other APCs



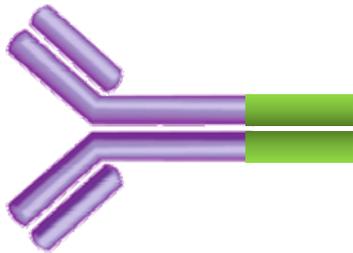
Antibody Specificity:

Fc receptors
C-type lectins
Complement receptors
MHC

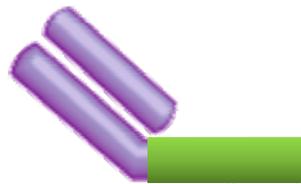
- Enhance efficacy of protein vaccines
- Improved cross-presentation to CD8+ T cells
- Broad response to multiple epitopes

Antibody-Targeted Vaccines

Recombinant fusion proteins

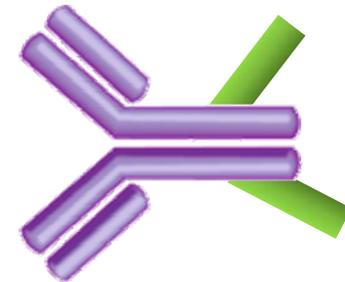


IgG-antigen

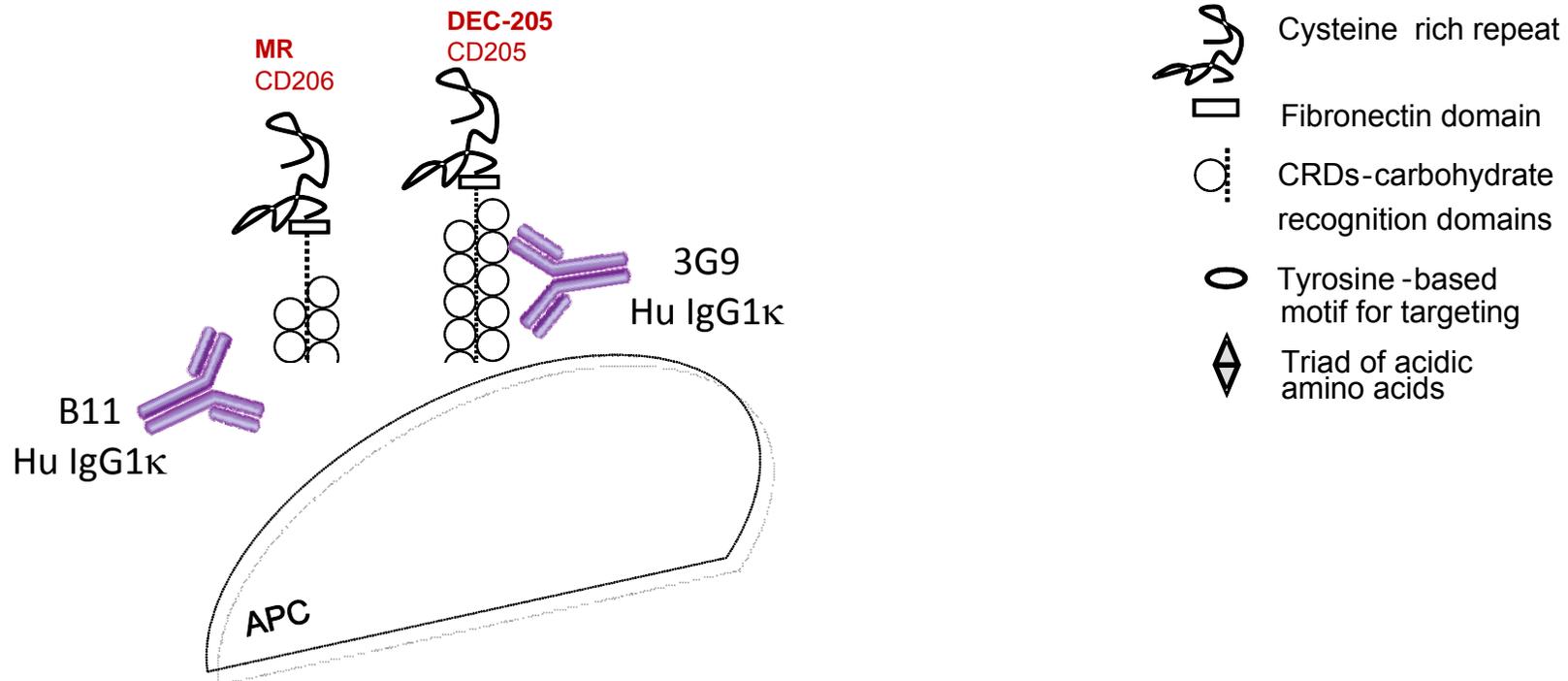


Fab-antigen

Chemical conjugation



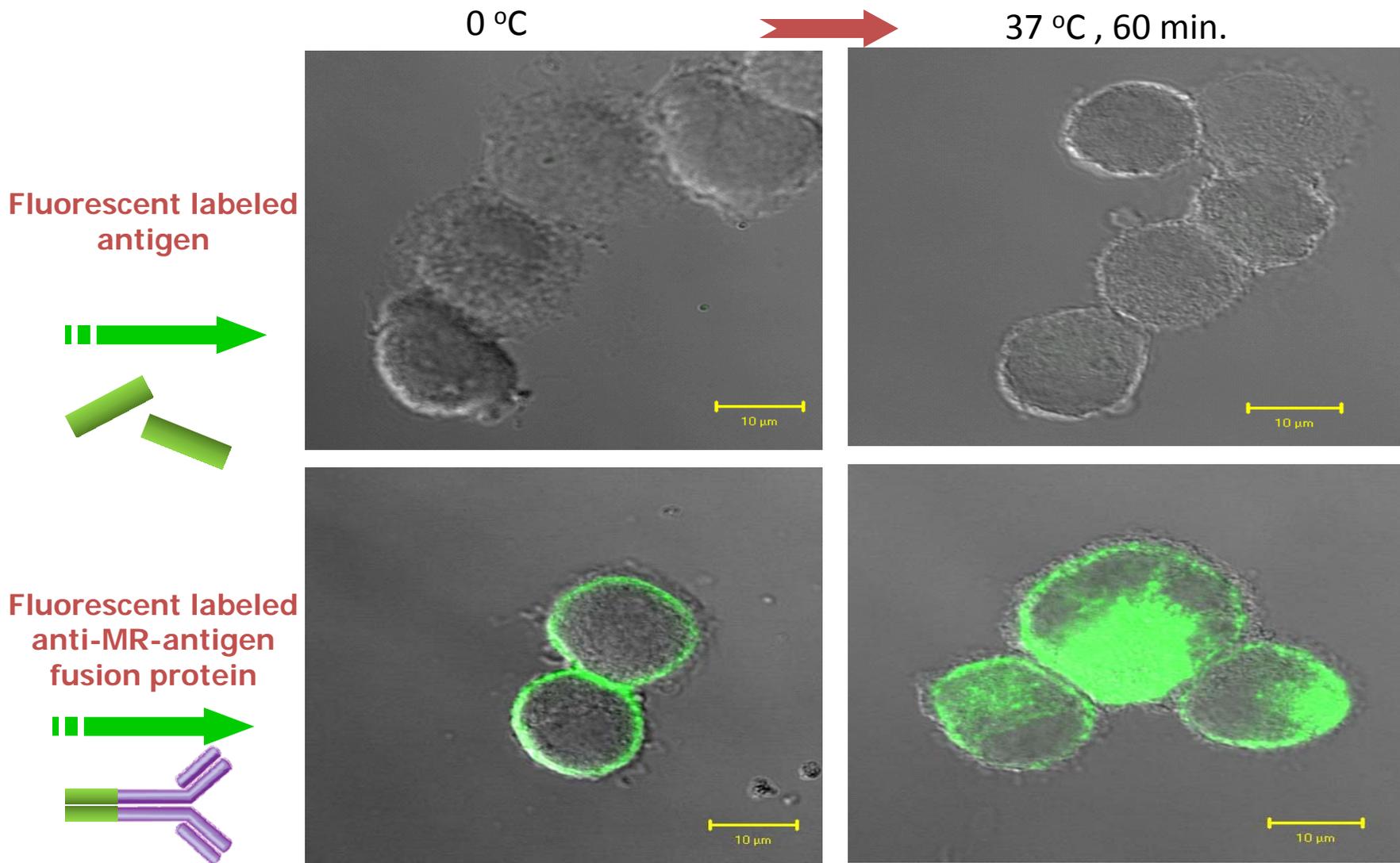
Targeting C-Type Lectin Receptors



Antibody	Specificity	APC Binding in human tissues	Affinity KD (M)
B11	Mannose receptor	Dermal DCs, Interstitial DCs, macrophages in most tissues	$\sim 7 \times 10^{-10}$
3G9	DEC-205	DCs in lymph nodes, tissue DCs	$\sim 2 \times 10^{-10}$

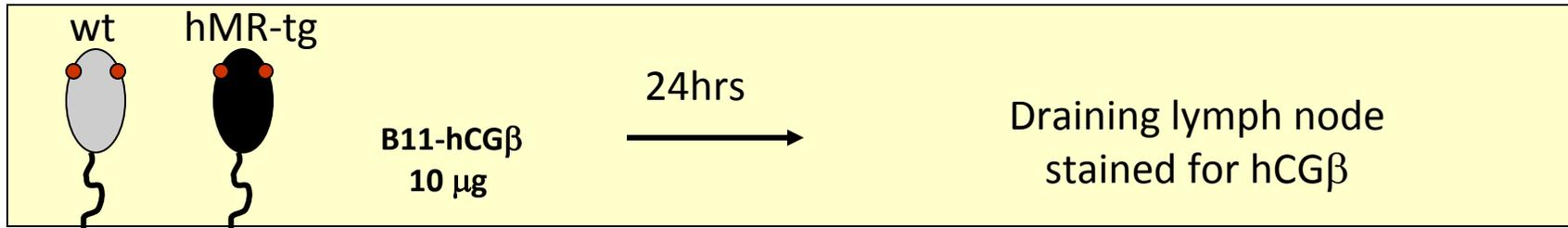
APC targeting

Vaccine Uptake by human DCs *in vitro*

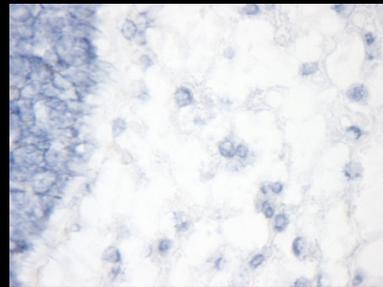
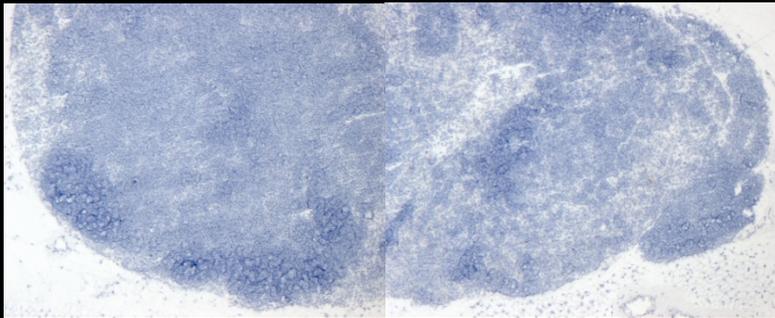


Confocal microscopy images of human DCs

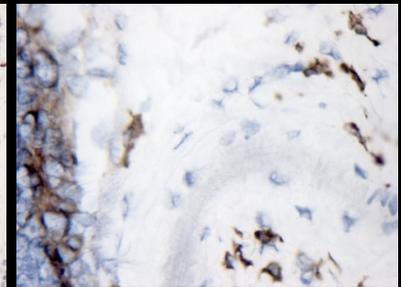
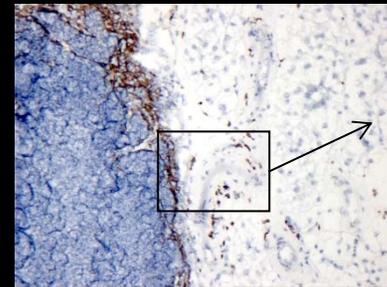
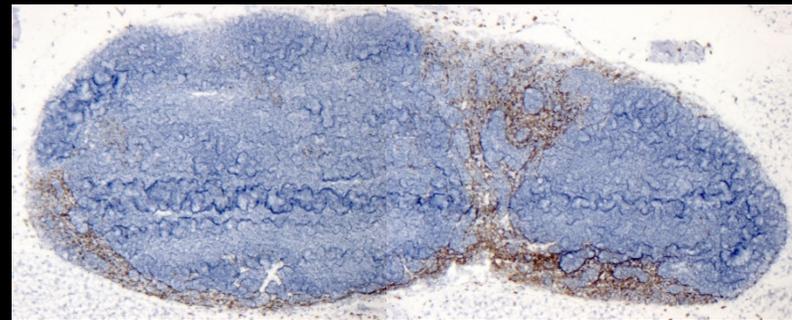
Targeted delivery to APCs *in vivo*



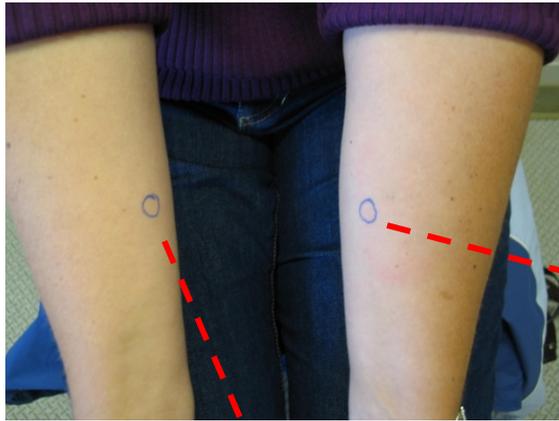
WT



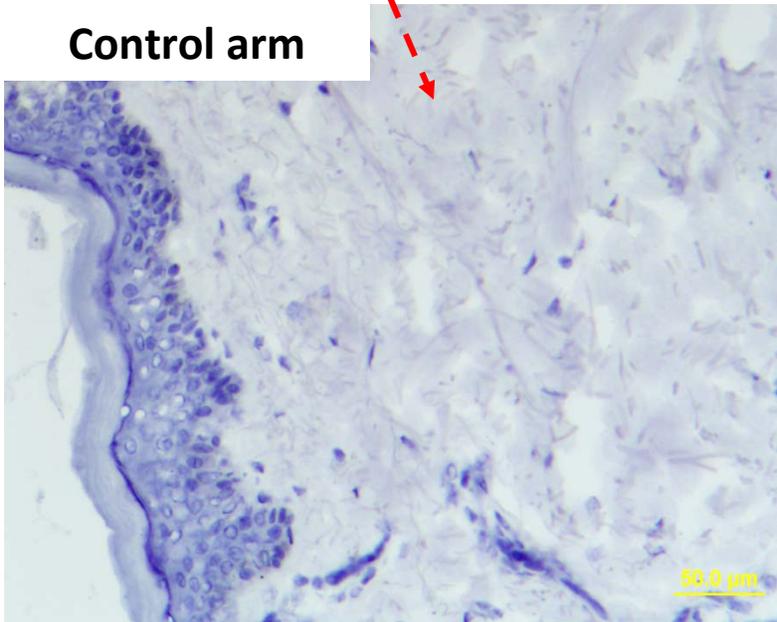
hMR-TG



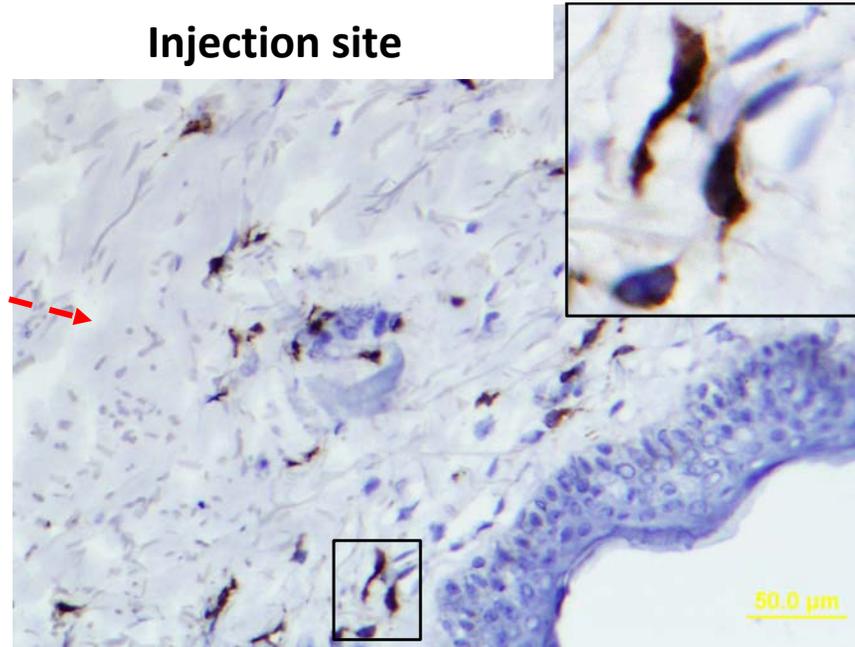
Vaccine Uptake – *in vivo*



Control arm



Injection site

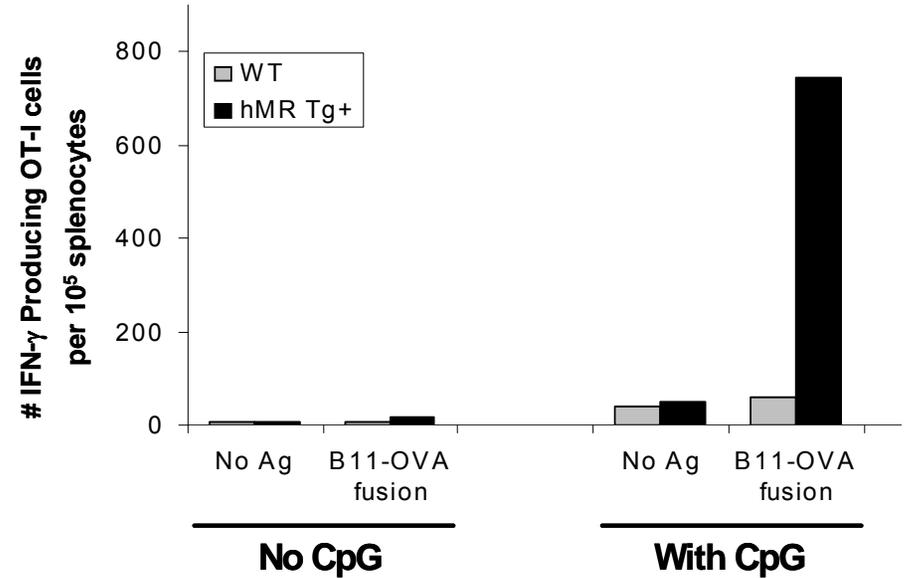
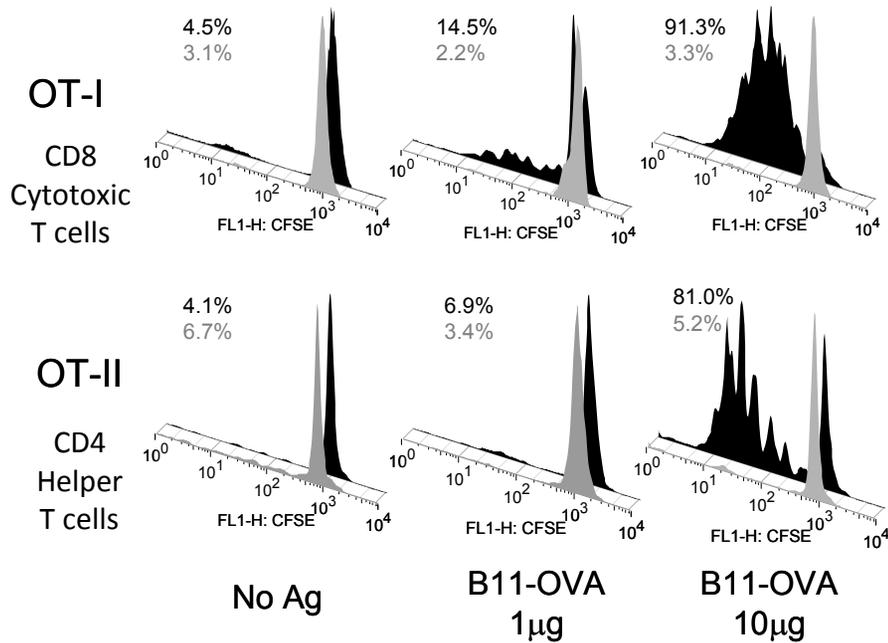
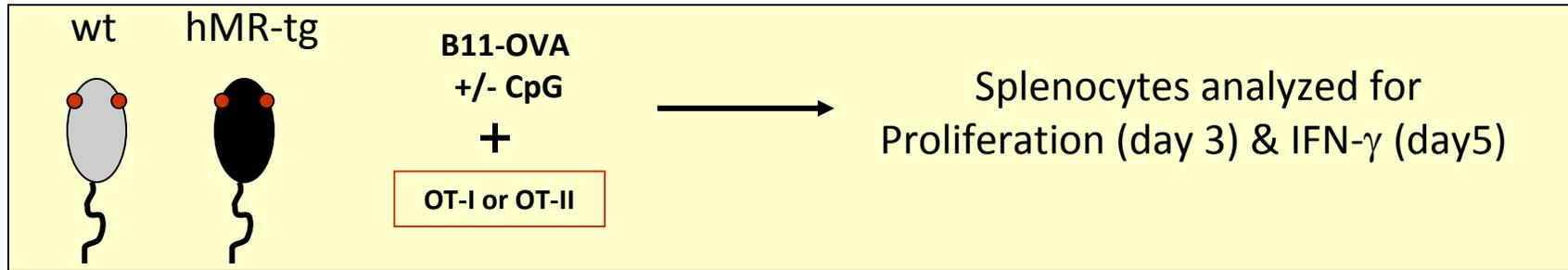


**Skin punch-biopsies taken from
injection site and opposite arm-
48 hrs post injection of
1mg B11-hCG β , i.d.**

IHC - rabbit anti-hCG β

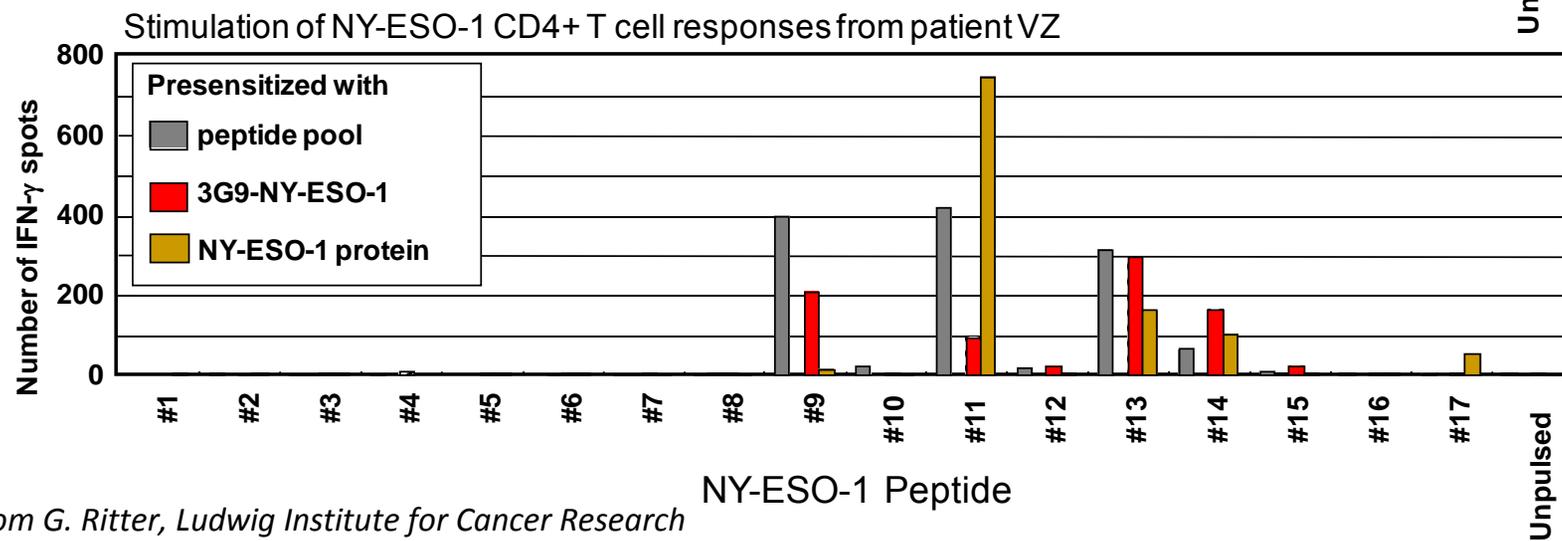
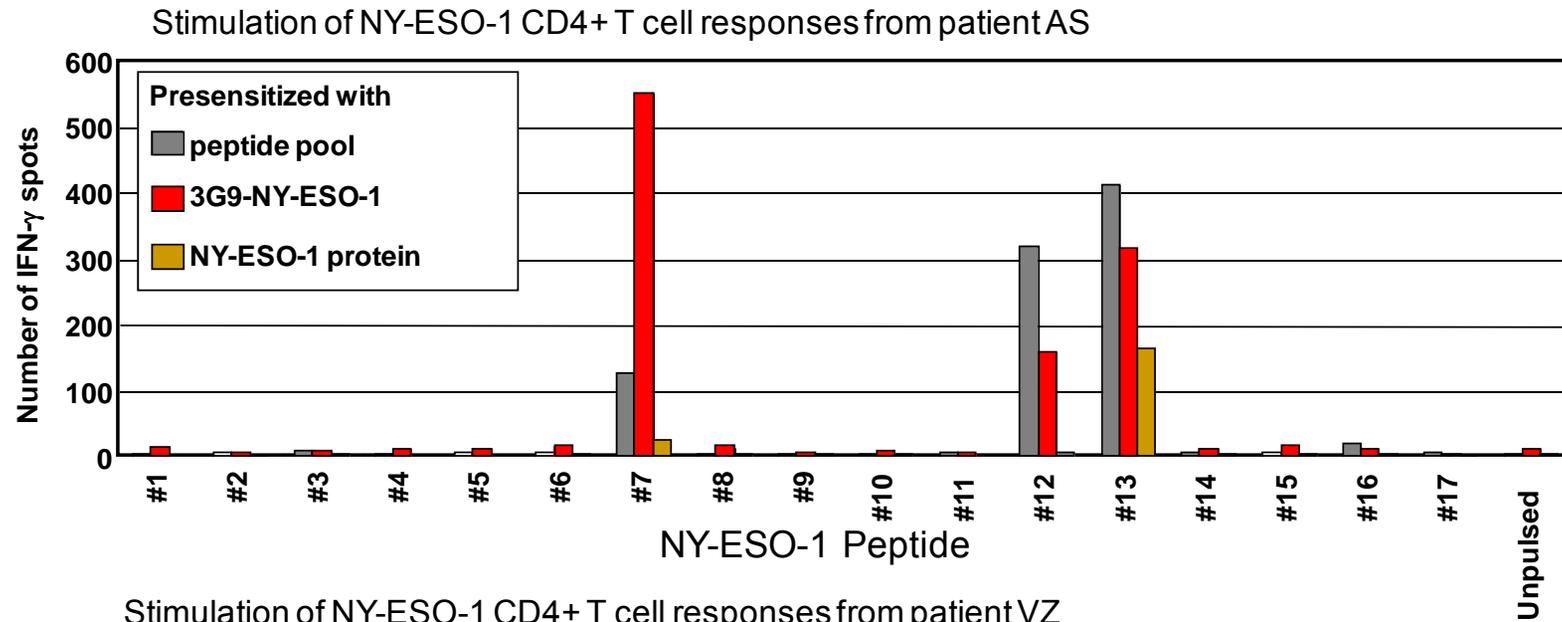
Cross-Presentation

Cross-presentation of MR-targeted antigen



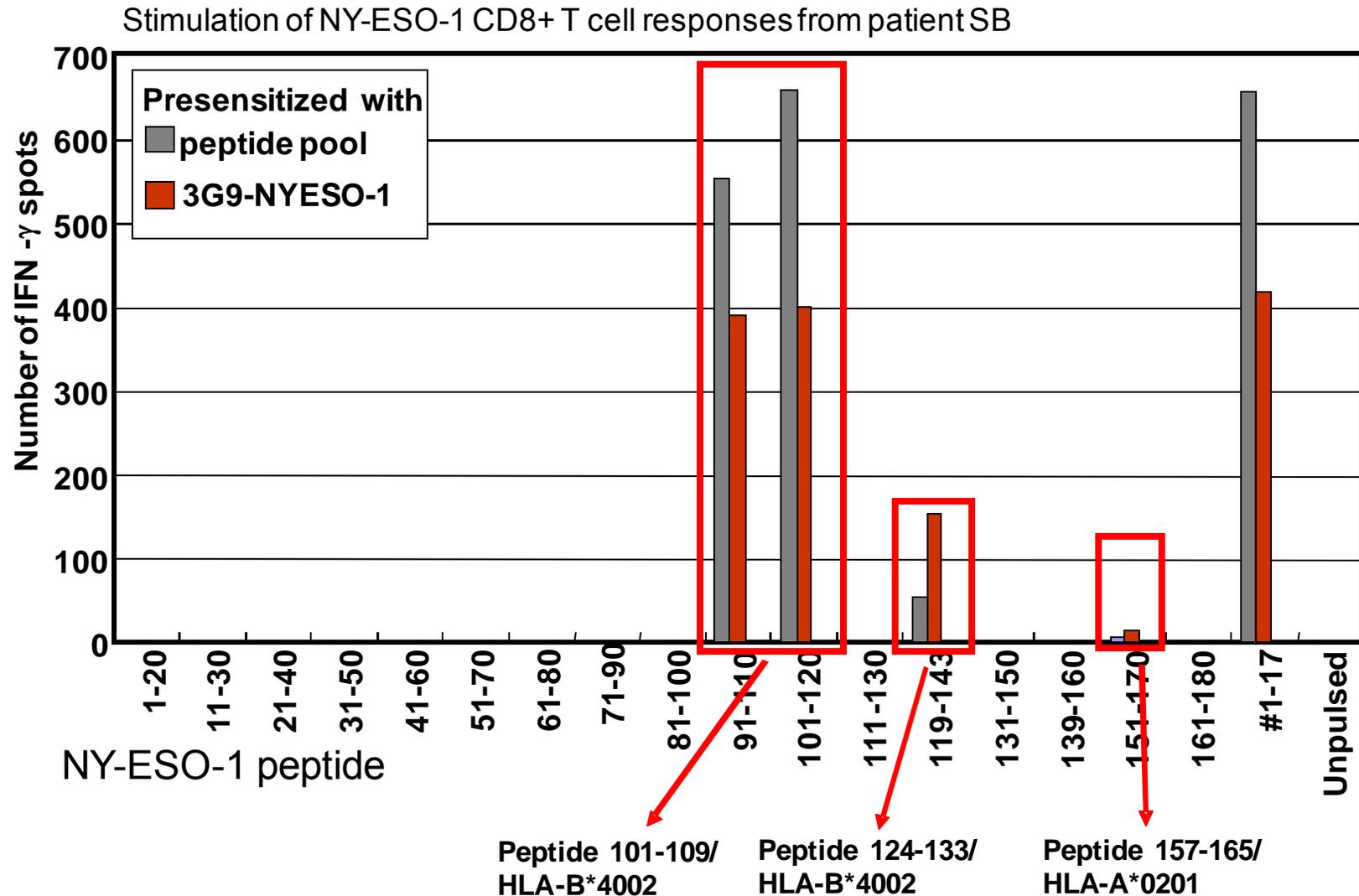
Breadth of T cell response

Presentation of multiple NY-ESO-1 MHC II epitopes with α -DEC-205-NY-ESO-1



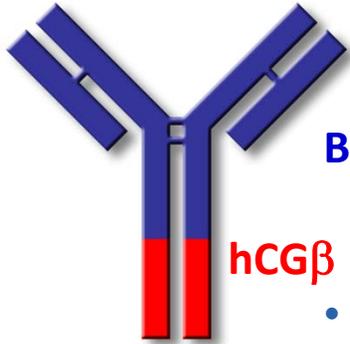
Data from G. Ritter, Ludwig Institute for Cancer Research

Presentation of multiple NY-ESO-1 MHC I epitopes with α -DEC-205-NY-ESO-1



Translation to clinical studies

Clinical Vaccine Candidates

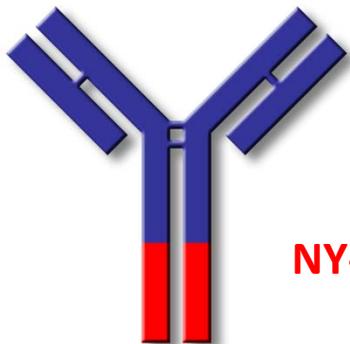


B11

CDX-1307

hCGβ - β -chain of human chorionic gonadotropin

- expressed by various epithelial and germ cell tumors
- expression correlates with poor outcome
- implicated in protection of tumors from apoptosis
- human CTLs efficiently recognize and kill cancer cell lines expressing hCG β



3G9

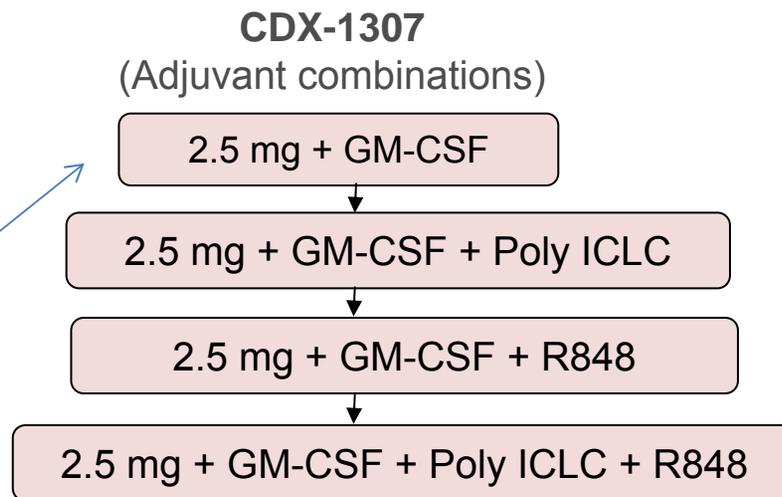
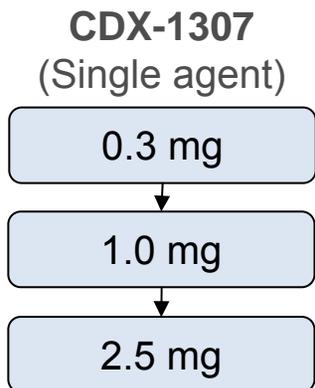
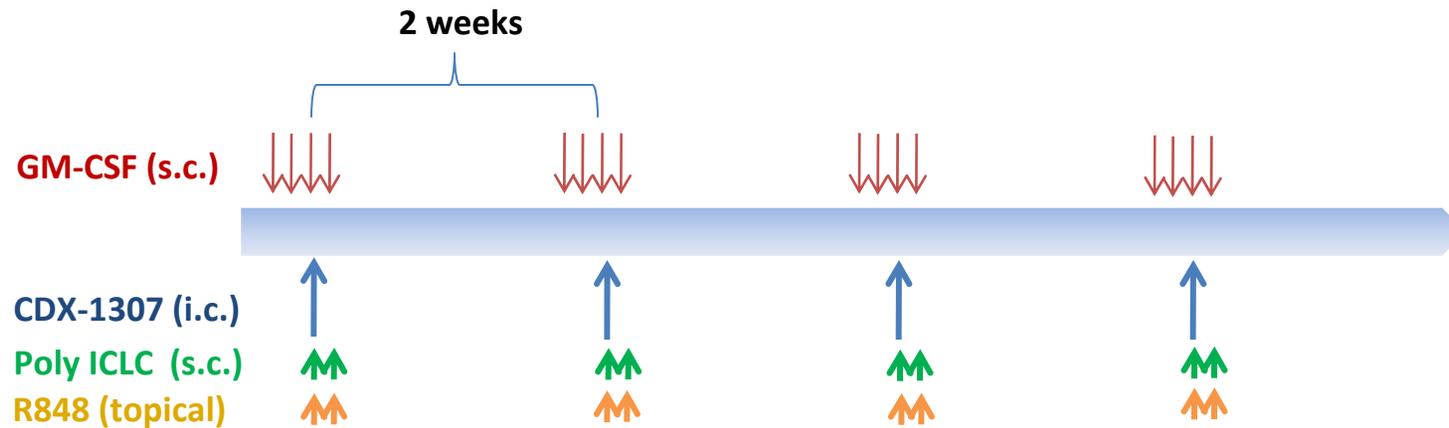
CDX-1401

NY-ESO-1 – Cancer-testis antigen

- expressed by sarcomas, melanoma and other tumors
- immunogenicity in humans well documented
- Adoptive transfer of NY-ESO-1 specific T cells can lead to significant clinical regressions

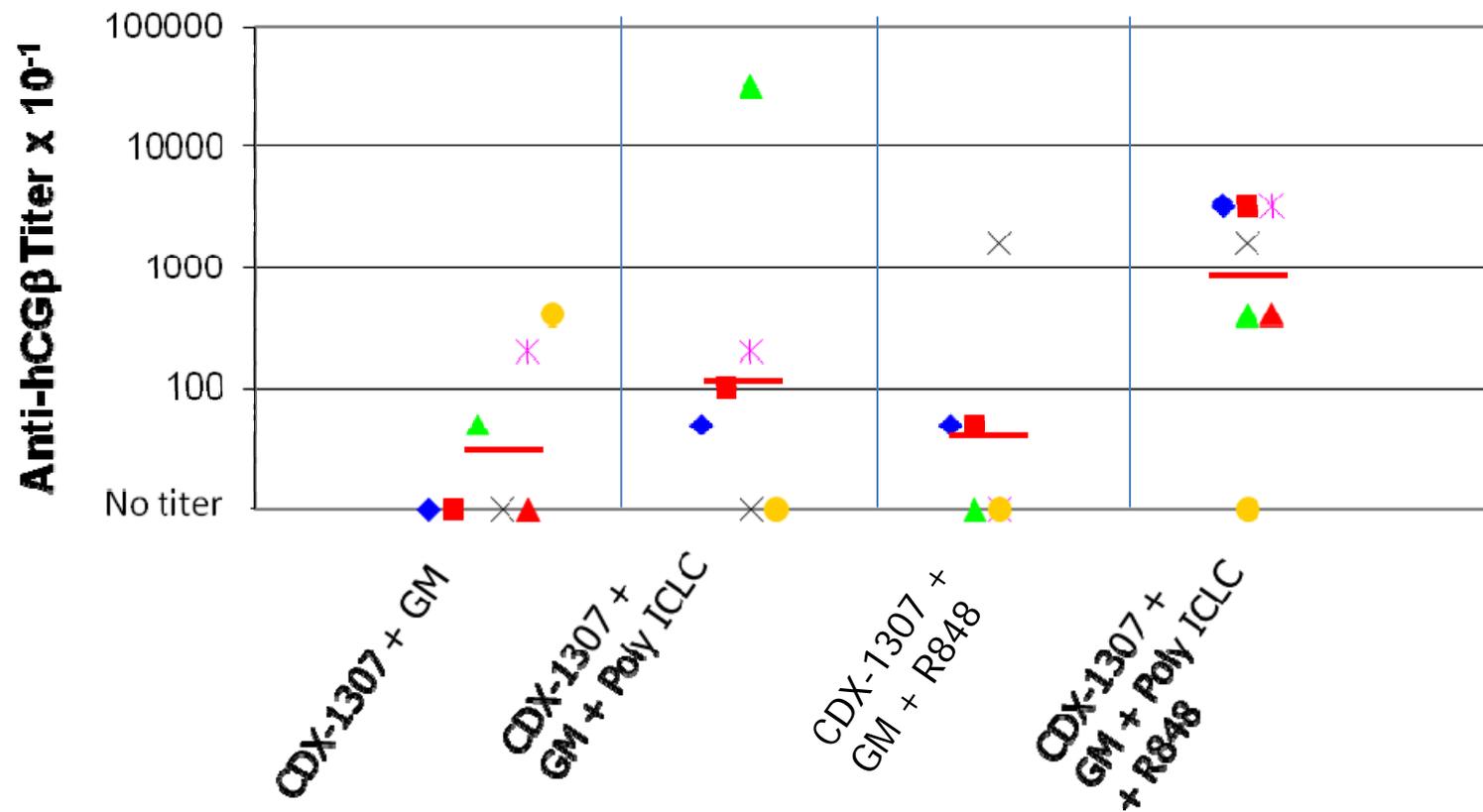
CDX-1307 (α -MR-hCG β) - Clinical Trial Design

Phase 1 Study – Advanced breast, colorectal, and pancreatic cancers



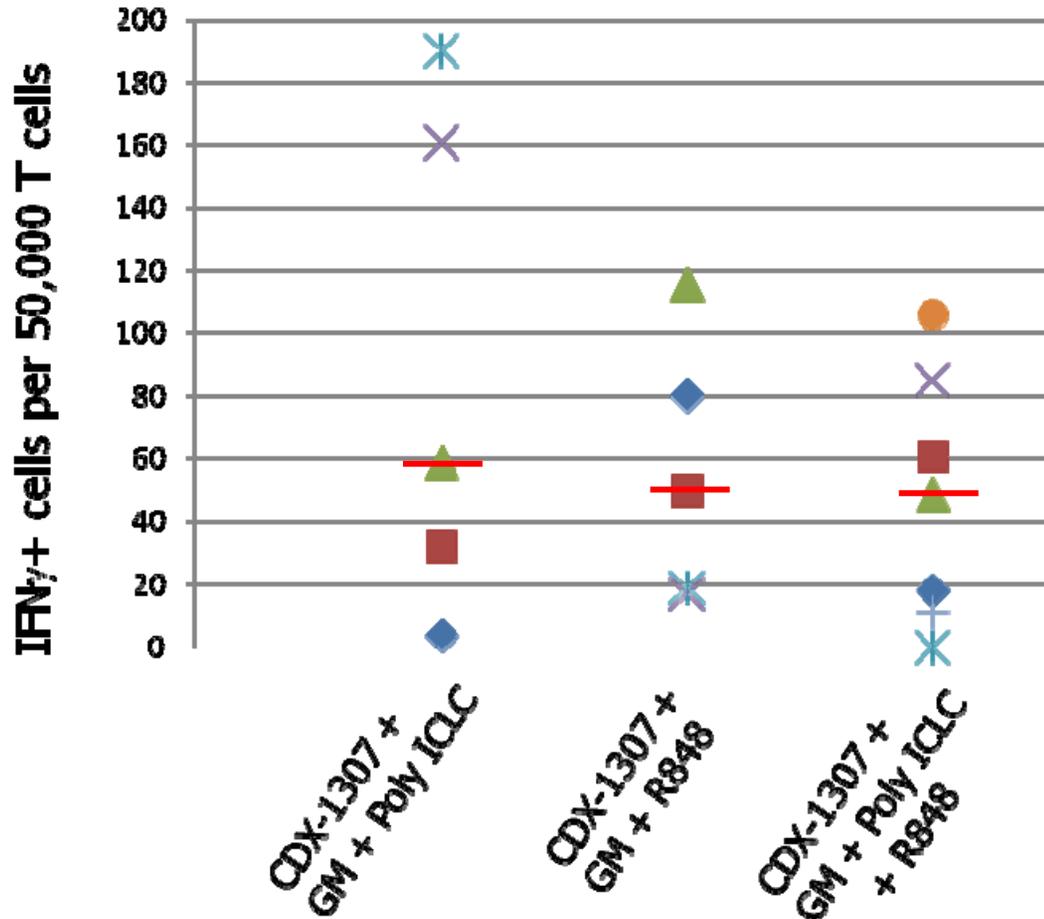
- 6 patients per cohort
- Safety assessment after 3 patients in each cohort
- No dose limiting toxicities

Summary of hCG- β -specific humoral responses



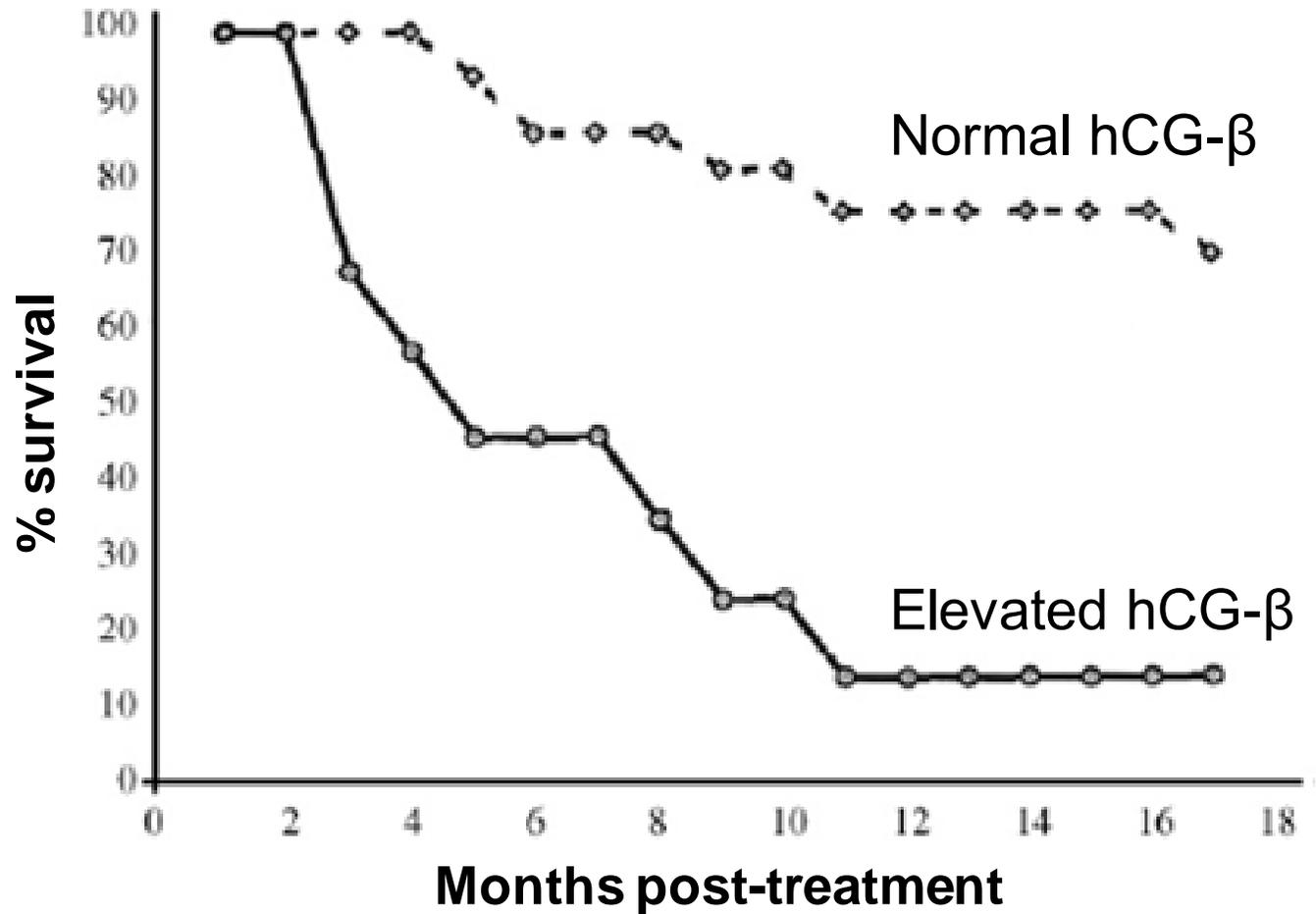
Humoral responses to purified hCG β were measured by ELISA. The values reported represents the maximum titer (reciprocal dilution) for each patient that received at least 3 doses of vaccine.

Induction of hCG- β -specific T cell responses



Cellular responses were measured by IFN- γ ELISpot assay using T cells (CD4 and CD8) isolated from patient PBMCs after a 7-day in vitro stimulation with hCG β -derived peptide pool. Values represent the highest hCG β -specific T cell response (with control peptide subtracted) for patients treated in combination with TLR agonists. Significant T cell responses were not observed in cohorts without TLR agonist.

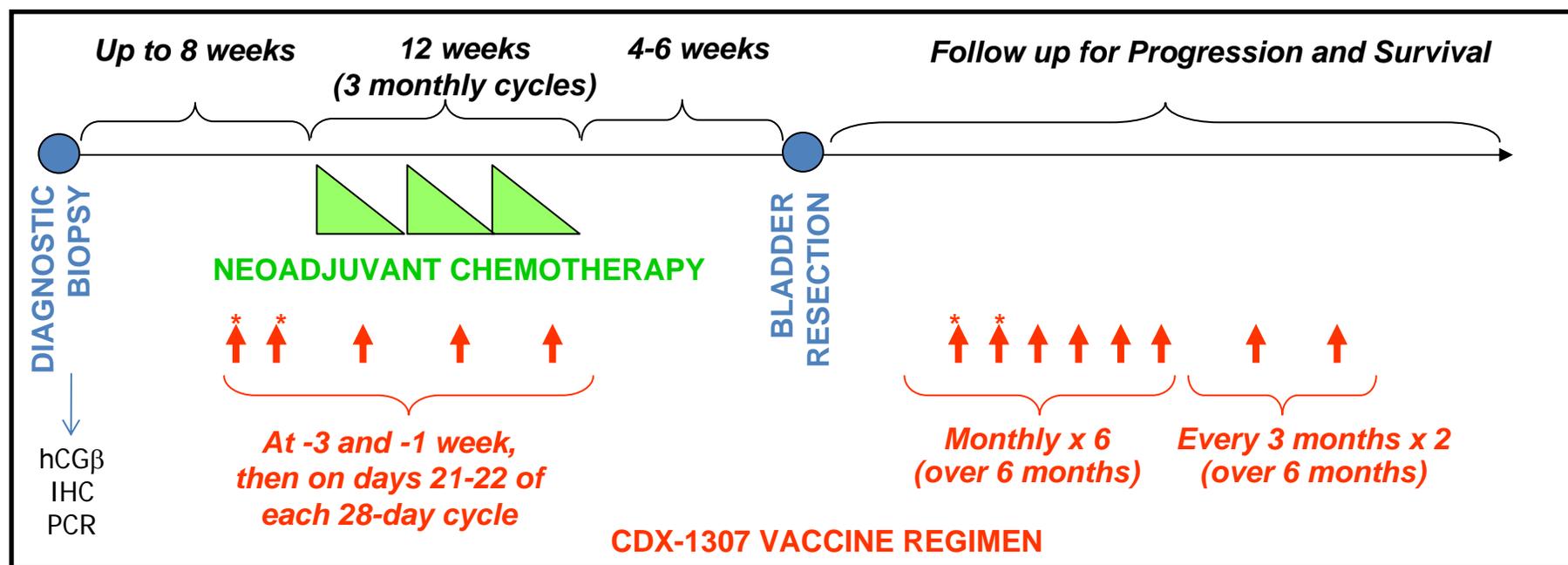
Elevated hCG- β Levels Correlate with Reduced Survival in Patients with Invasive (T2-T4) Bladder Cancer



PHASE 2 TRIAL IN BLADDER CANCER:

The “N-ABLE” Trial *Neoadjuvant and Adjuvant Bladder Cancer Trial*

Randomized (1:1), controlled trial (n=60) in hCG- β expressing, muscle-invasive bladder cancer



- Neoadjuvant setting allows for pathologic assessment of tumor response to therapy (necrosis, immune infiltration, persistence of hCG- β expression).
- Outcome measures: PFS (primary), OS, safety, immune response (during neoadjuvant chemo and adjuvant vaccine), tumor response (radiographic and pathologic)
- Initial data anticipated late 2011 - 2012

Conclusions

- Delivery of protein antigens to endocytic receptors on APCs results in:
 - Robust humoral/cellular immunity
 - Requires concomitant administration of adjuvants
- Antibody-targeted vaccines provide a practical approach to vaccines:
 - Based on well established antibody technology
 - Off-the -shelf and not HLA specific
 - Can be used for multiple antigens
- Early clinical data demonstrate feasibility, safety, and immunogenicity

Acknowledgements

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