Frequency of Strong Antibody Responses Following Combination Immunotherapy Correlates with Increased PSA-Doubling Time in Men with Androgen-independent Prostate Cancer

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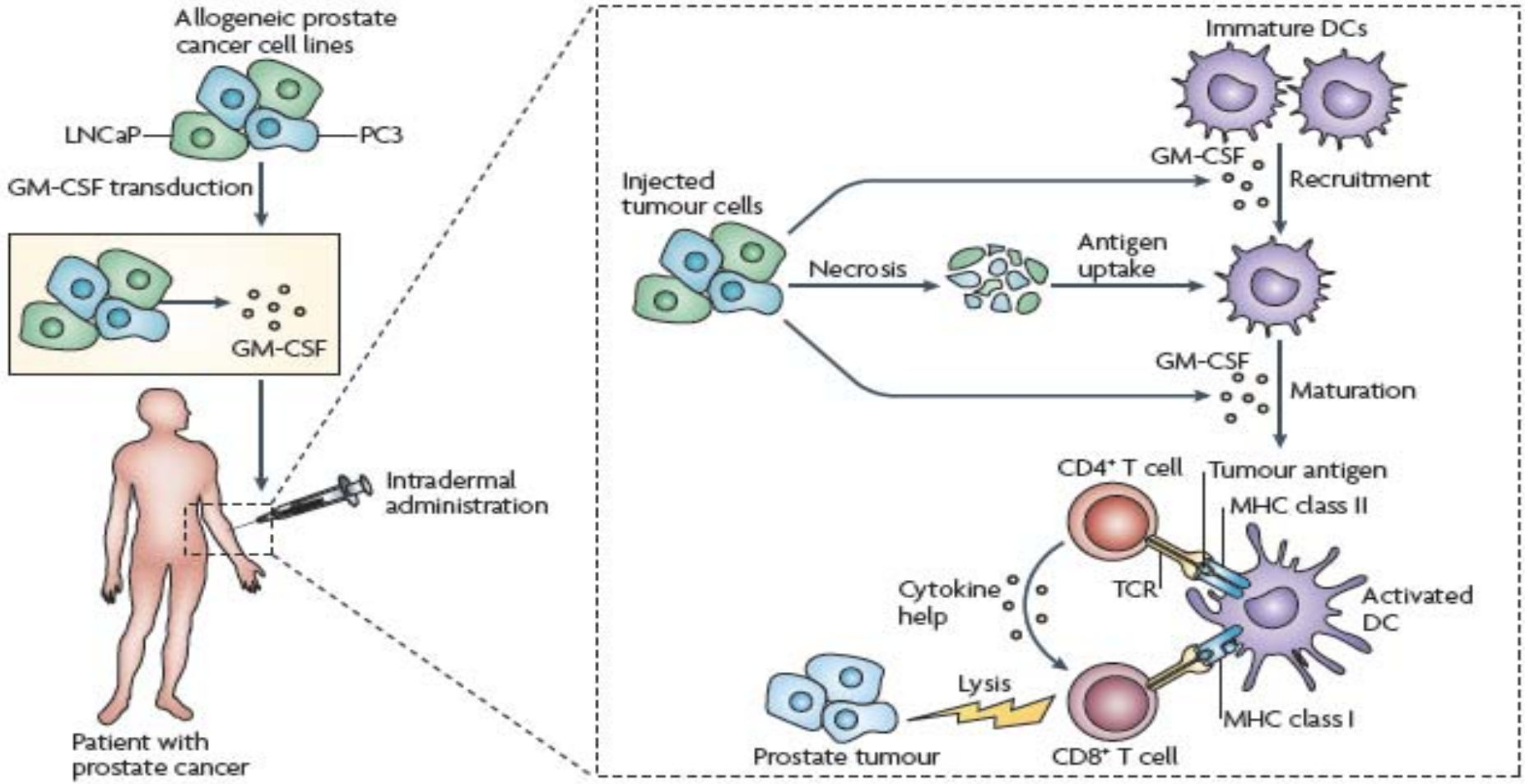
No Relationships to Disclose

Development of an Immune Response to the allogeneic prostate GVAX™ vaccine



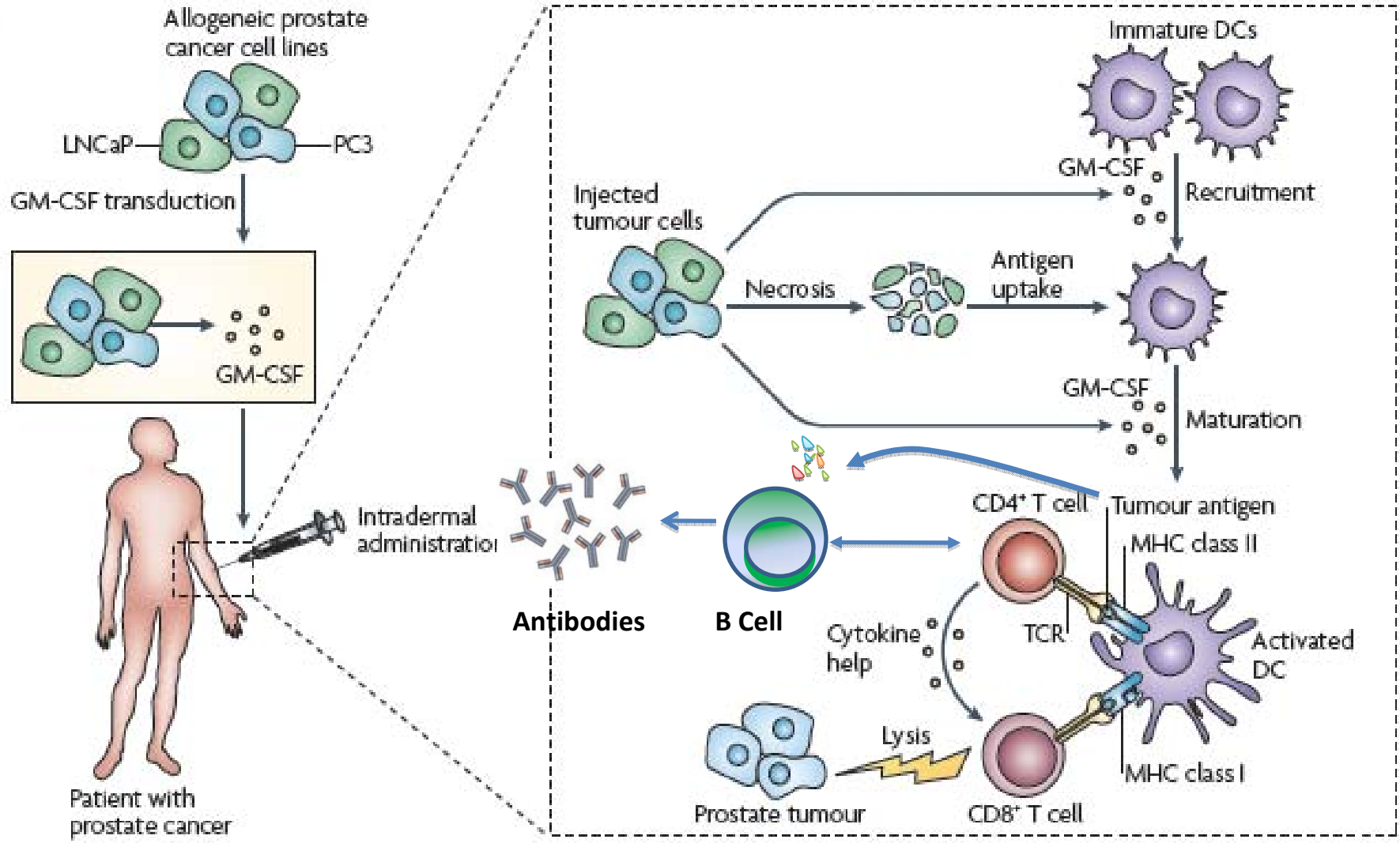
Charles G. Drake. Nat Rev Immunol. 2010 Aug;10(8):580-93.

QUESTION:

- **How to monitor the development of a T cell response following immunotherapy with a “Complex” vaccine?**

  - Do not have access to autologous tumor cell lines

B cells also respond to vaccination.



Modified from
Charles G. Drake. Nat Rev Immunol. 2010 Aug;10(8):580-93.
Christopher C Goodnow et al, Nature Immunology. Aug ; 10(11): 681-688

Hypothesis:

Identification of a new or increased IgG antibody response following immunotherapy will provide a surrogate for generation of an anti-tumor T cell response.

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Rationale supported by:

Reports in both human and murine systems

- Valmori D. et.al., PNAS U S A. 2007 May 22;104(21):8947-52.
- Willimsky G. et.al., J Exp Med. 2008 Jul 7;205(7):1687-700.

Integrated NY-ESO-1 antibody and CD8$^+$ T-cell responses correlate with clinical benefit in advanced melanoma patients treated with ipilimumab

Jianda Yuan[a], Matthew Adamow[a], Brian A. Ginsberg[a], Teresa S. Rasalan[a], Erika Ritter[b], Humilidad F. Gallardo[a], Yinyan Xu[a], Evelina Pogoriler[c], Stephanie L. Terzulli[a,c], Deborah Kuk[d], Katherine S. Panageas[d], Gerd Ritter[b], Mario Sznol[e], Ruth Halaban[e], Achim A. Jungbluth[b], James P. Allison[a,c,f], Lloyd J. Old[b,c,1], Jedd D. Wolchok[a,b,c,e,1,2], and Sacha Gnjatic[b,1,2]

[a]Ludwig Center for Cancer Immunotherapy, Immunology Program, Sloan–Kettering Institute, New York, NY 10065; [b]Ludwig Institute for Cancer Research, New York Branch, New York, NY 10065; [c]Department of Medicine, [f]Howard Hughes Medical Institute, and [d]Department of Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY 10065; and [e]Department of Medicine, Yale University, New Haven, CT 06520

Contributed by Lloyd J. Old, July 5, 2011 (sent for review June 10, 2011)

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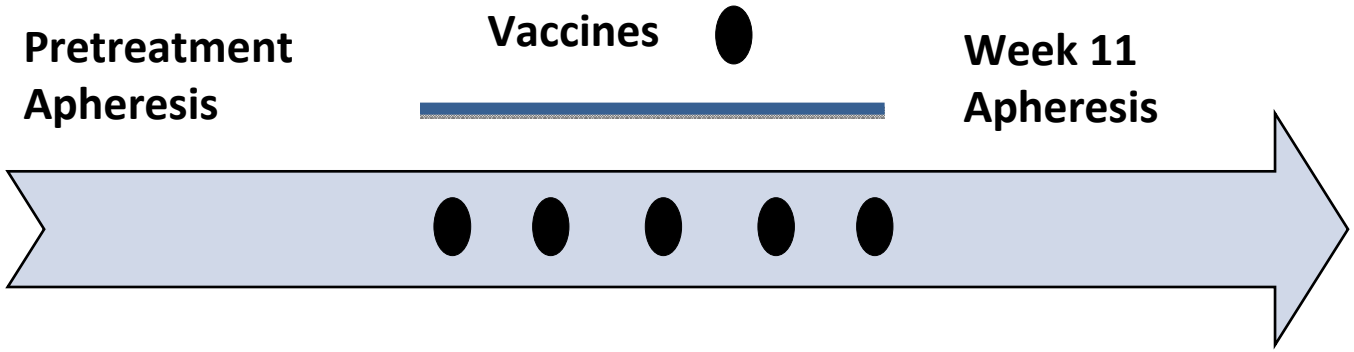
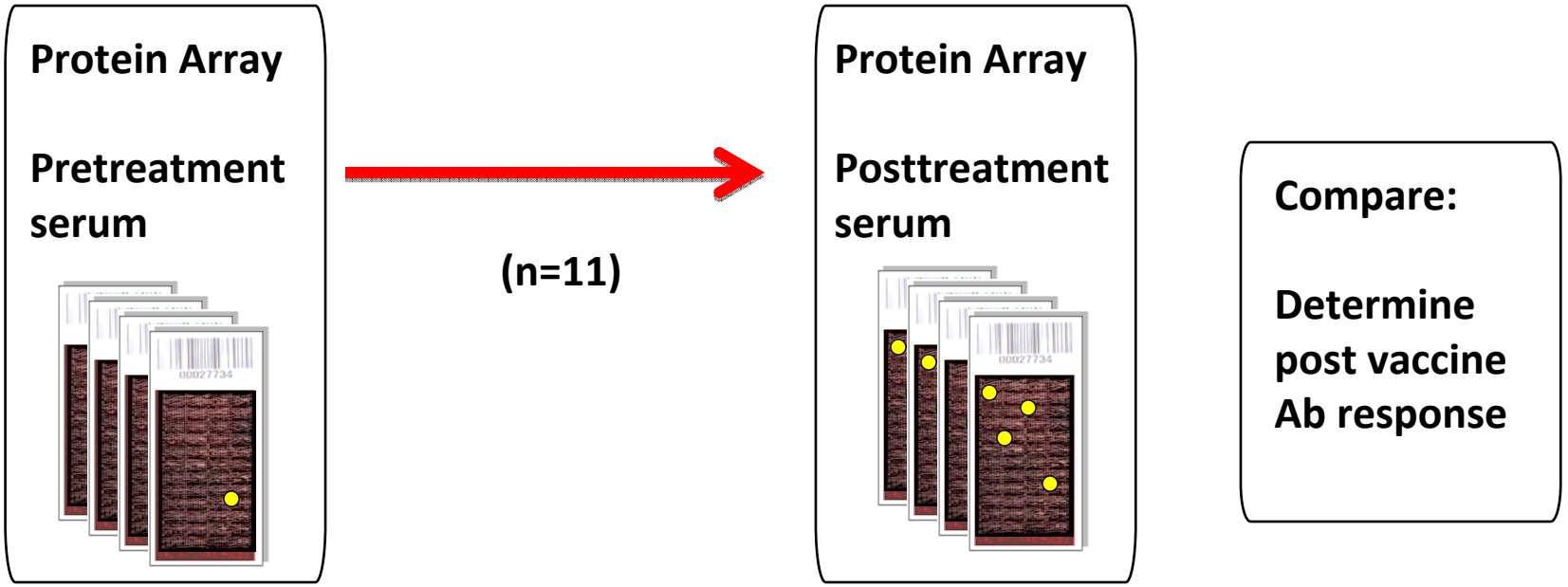
- **Patients who respond to immunotherapy may have a coordinated immune response (T and B cells).**
- **Identification of the target of the B cell response may provide the target for the T cell response.**

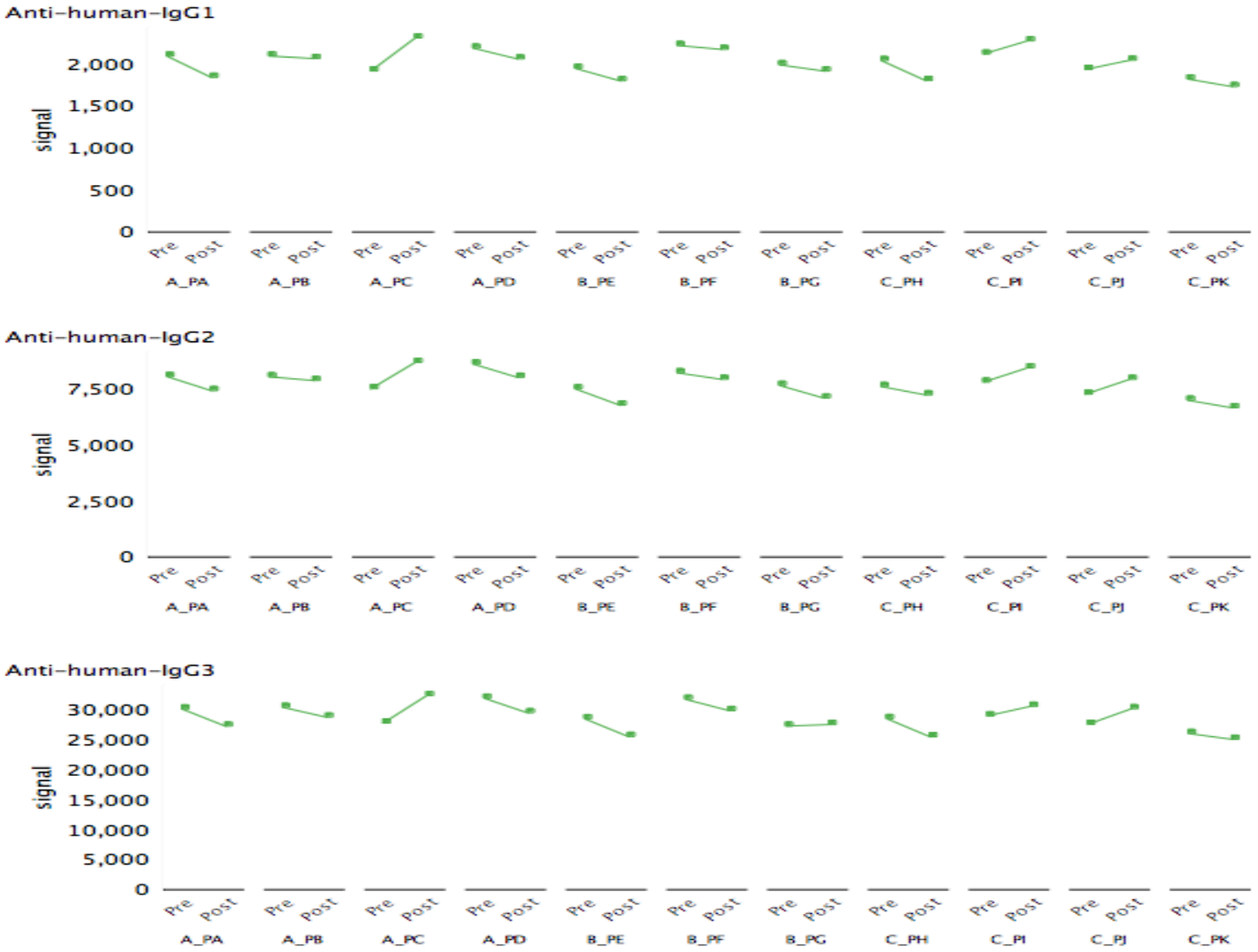
Immunological Monitoring Strategy:

Protein Arrays to Identify the targets of Antibody Response

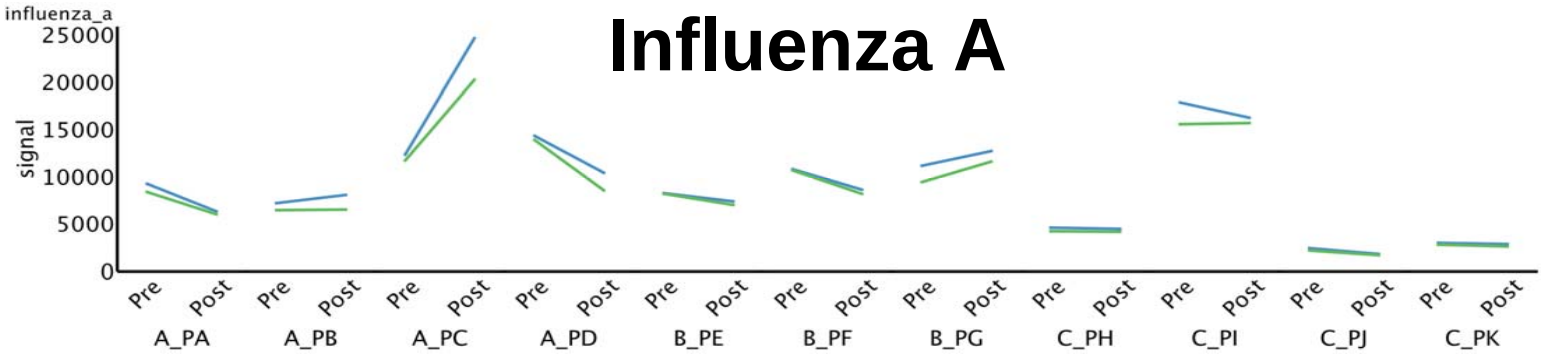




Comparison of IgG levels in (1, 2, 3) Pre and Post Treatment Serum



Identification of Antibody Responses to Specific Antigens



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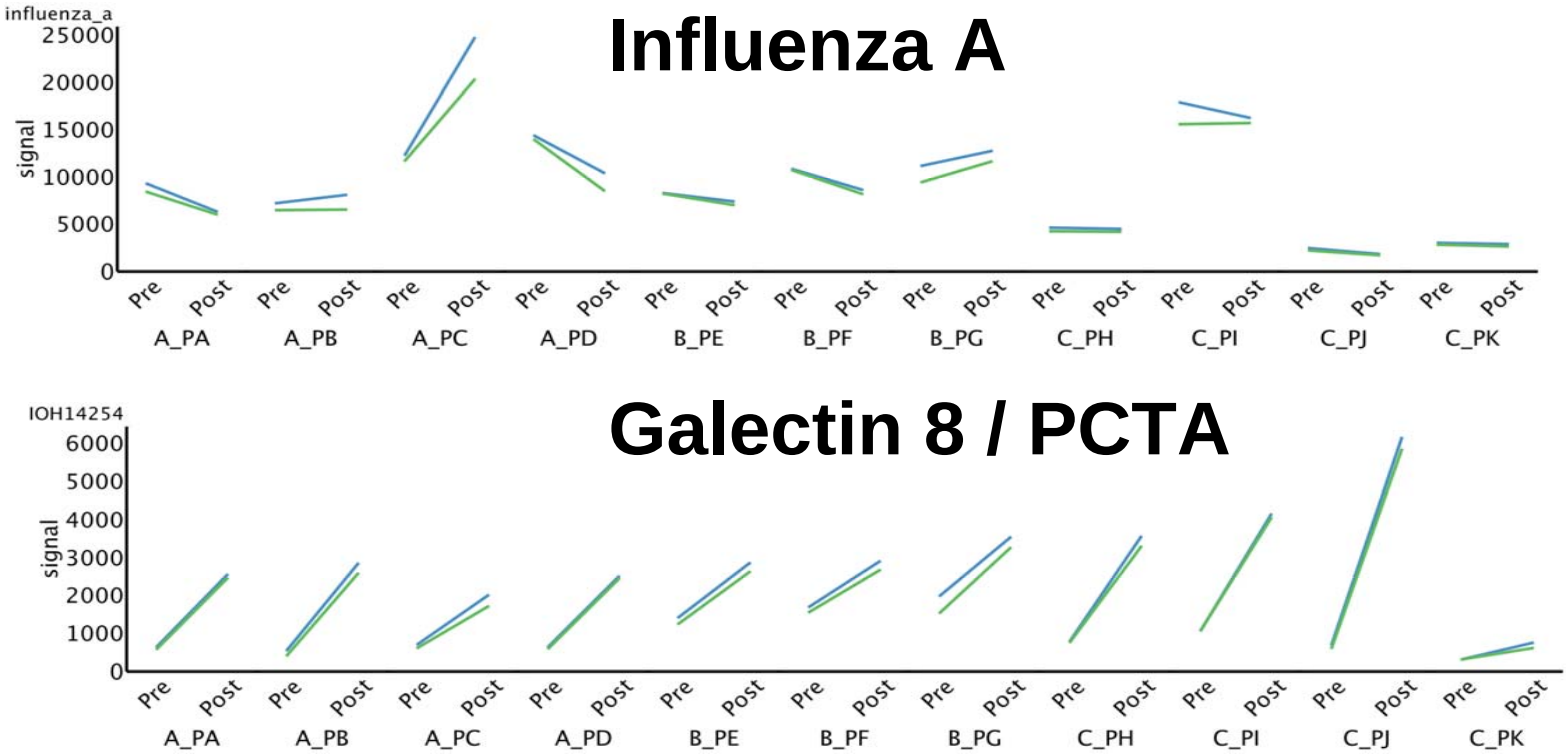

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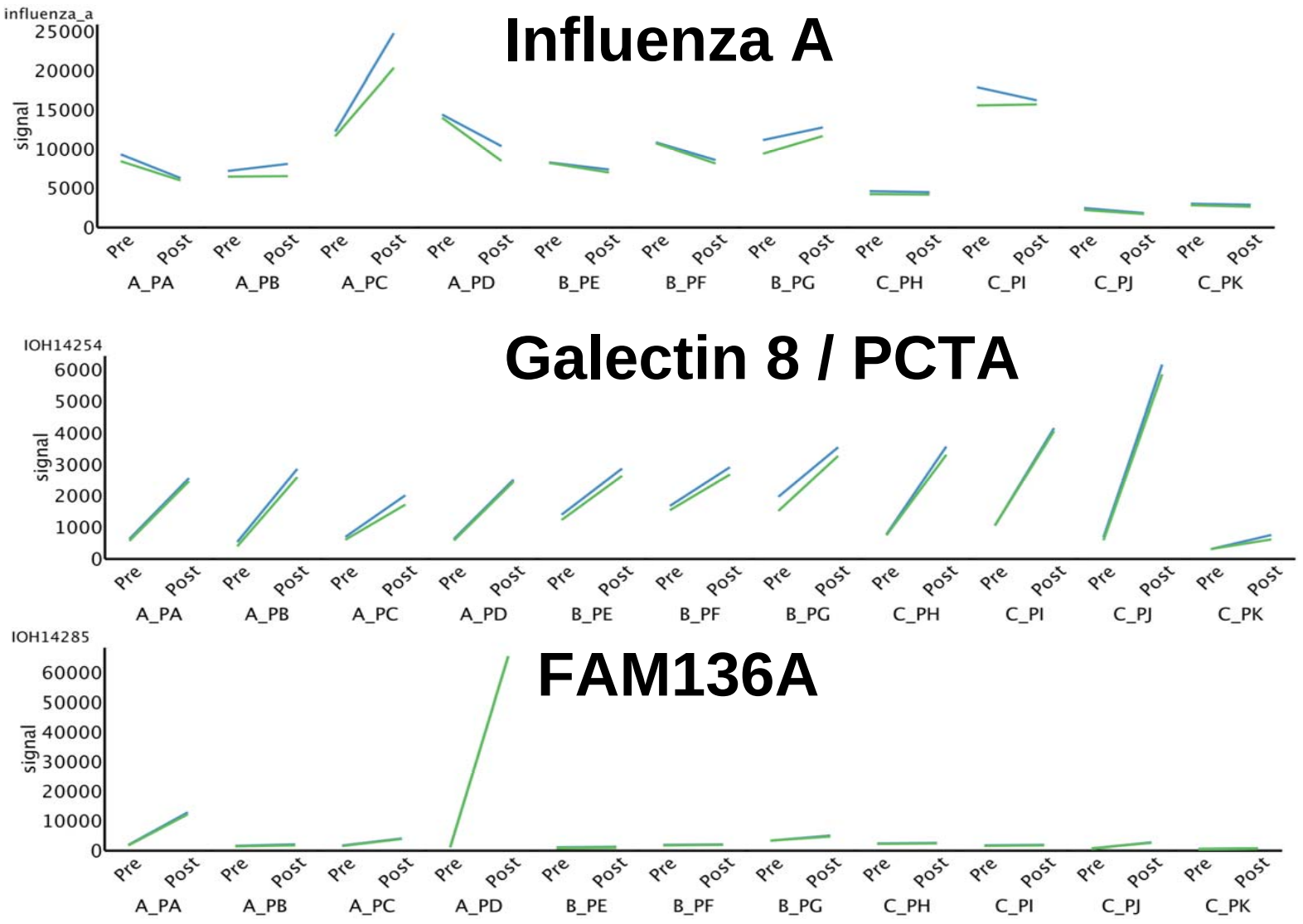

Question:

Did the patient's tumor cells express the genes identified by the antibodies?

Problem:

How to evaluate tumor gene expression when no biopsies available and patients have expired?

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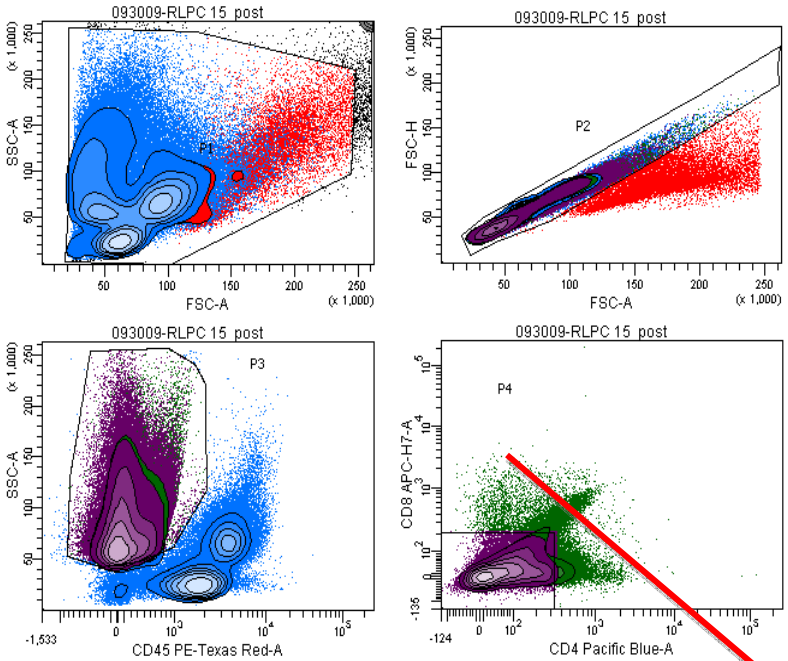
Circulating Tumor Cells (CTC)

Schema for sorting CTCs and T cells from cryopreserved PBMC (aphereses)



CD8$^+$ T cells (CD45$^+$, CD8$^+$, EpCAM$^-$)

CTC (CD45$^-$, CD8$^-$, CD4$^-$, EpCAM$^+$)

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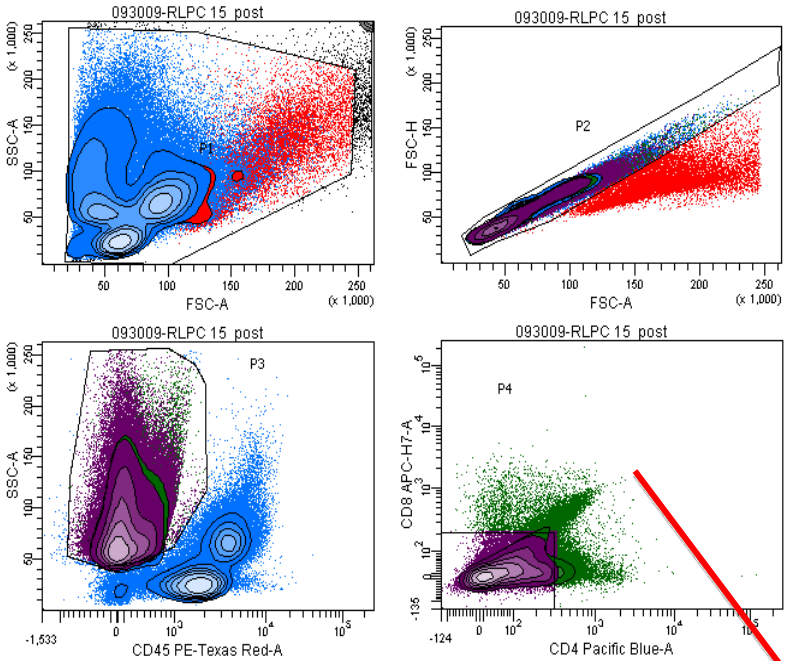
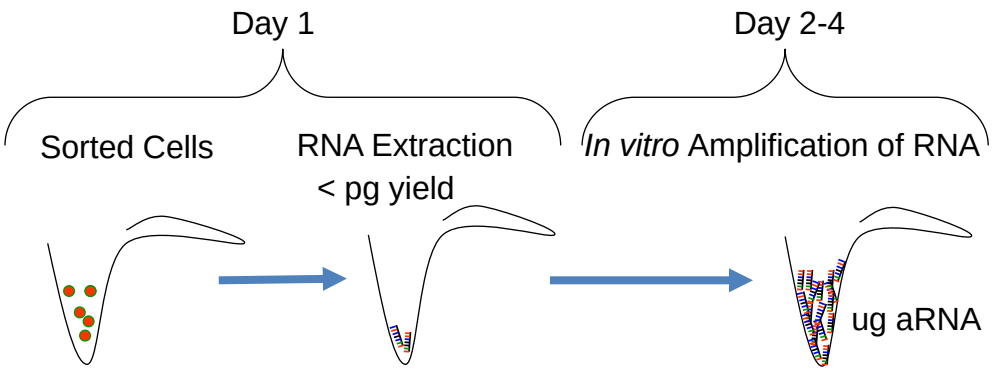


CD8

CTC

Schematic of Sorting and Linear Amplification



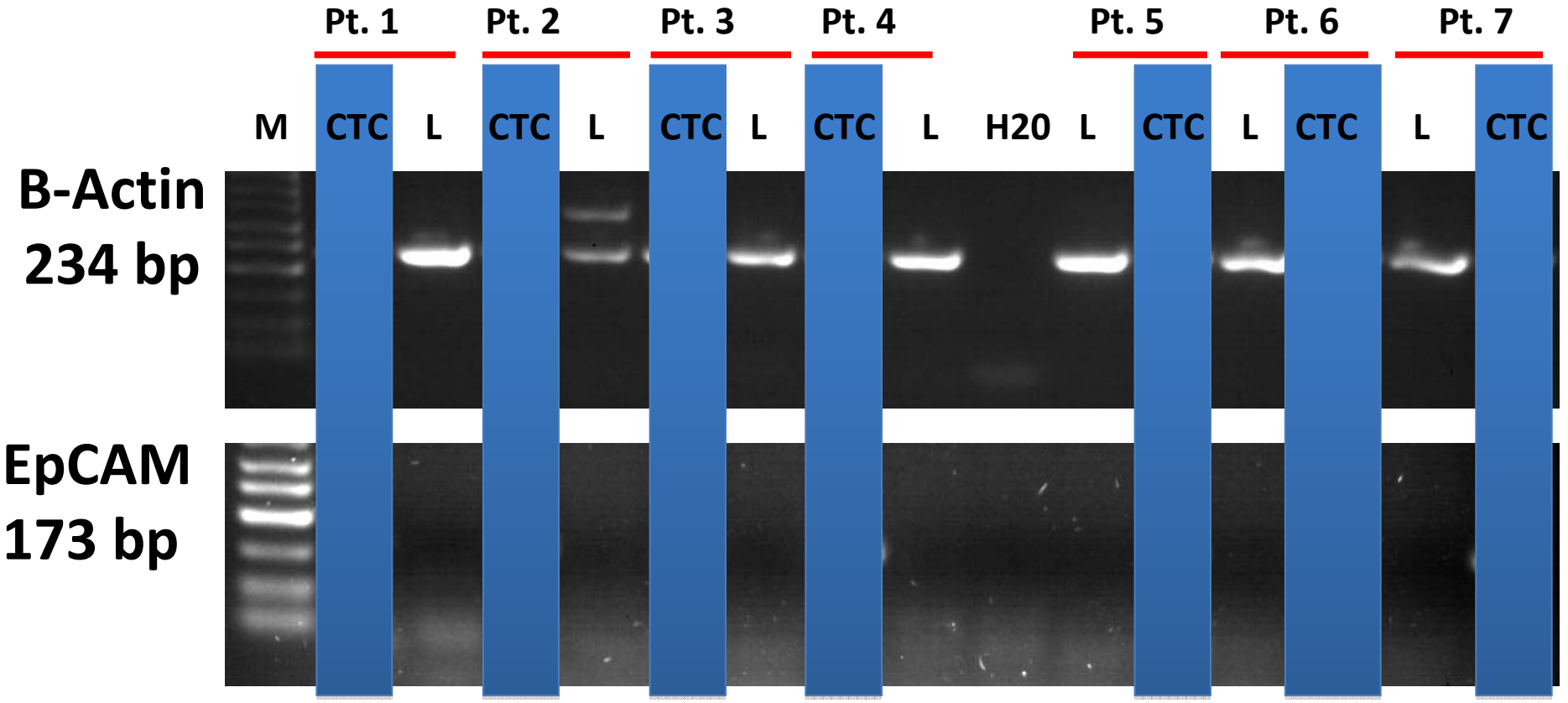
Evaluate

1) **EpCAM**
2) **Antibody targets**
3) **Gene expression**

Analysis of aRNA from sorted CTC and T cells

Sorted CTC express EpCAM

T cells do not express EpCAM



Analysis of aRNA from sorted CTC and T cells

Sorted CTC express PCTA (4/4) and FAM136A (3/4)

Patient	PCTA	FAM 136 A
1	+	+
2	+	+
3	+	+
4	+	-

Gene expression profiling - Affymetrix Human Gene 1.0 ST microarrays.

Preliminary results: Gene expression of isolated CTCs was more similar to prostate cancer cell lines (LNCaP and PC3) than to T cells

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Suggests that strategy for isolating CTC is working

Phase I/II study of allogeneic prostate GVAX™ in advanced prostate cancer patients. DAMD 17-03-1-0097

- No Objective Clinical Responses
- Three of 10 evaluable men had a 3 fold or greater increase in PSA doubling time - **“Responders”**
- Seven men had stable or decreased PSA-DT - **“Non Responders”**

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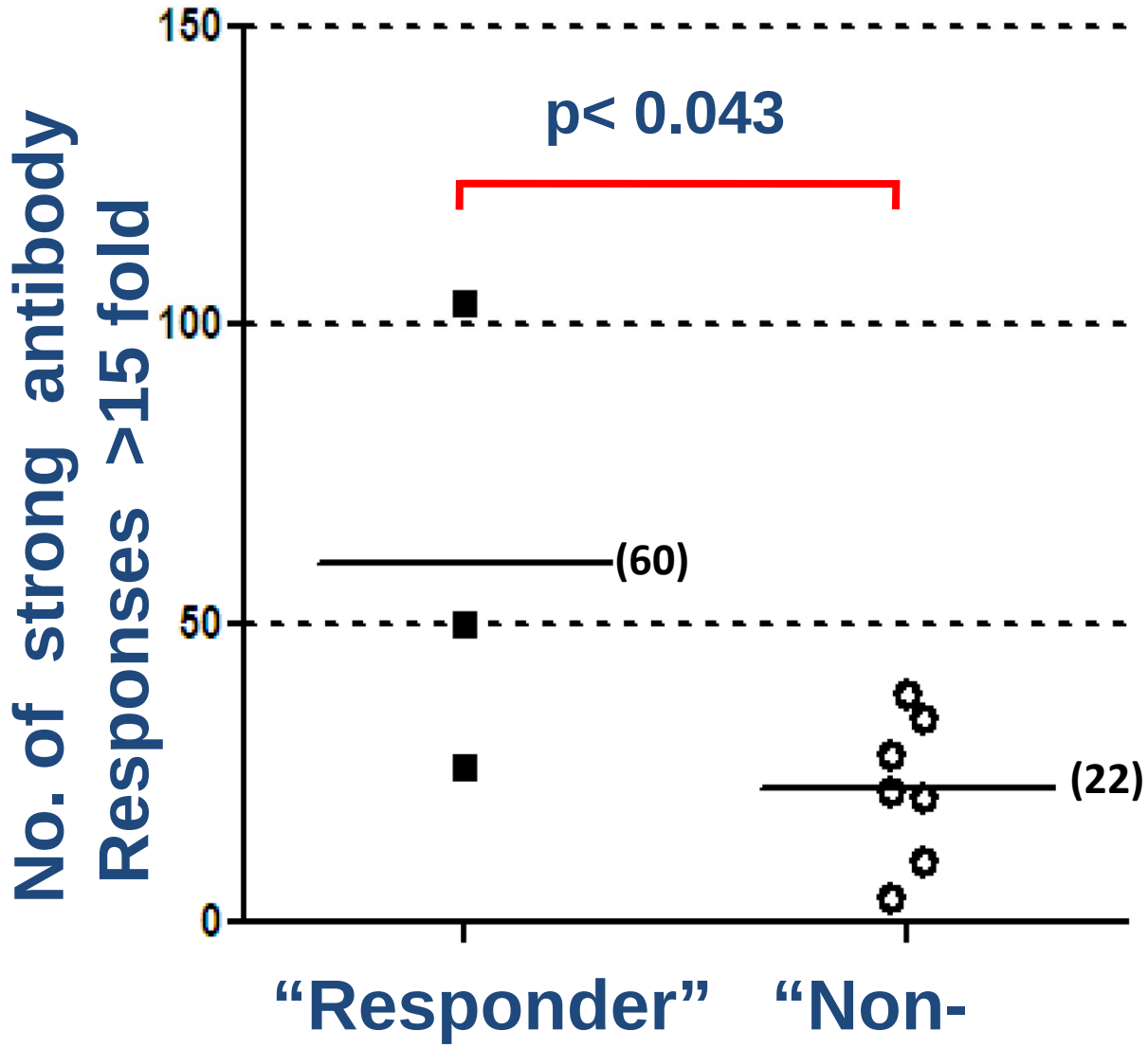
Hypothesis:

“Responder” patients would develop strong antibody responses against multiple antigens

Significant (p<0.043) correlation between strong vaccine-induced antibody responses (>15 fold) and increase in PSA-DT (3 fold)

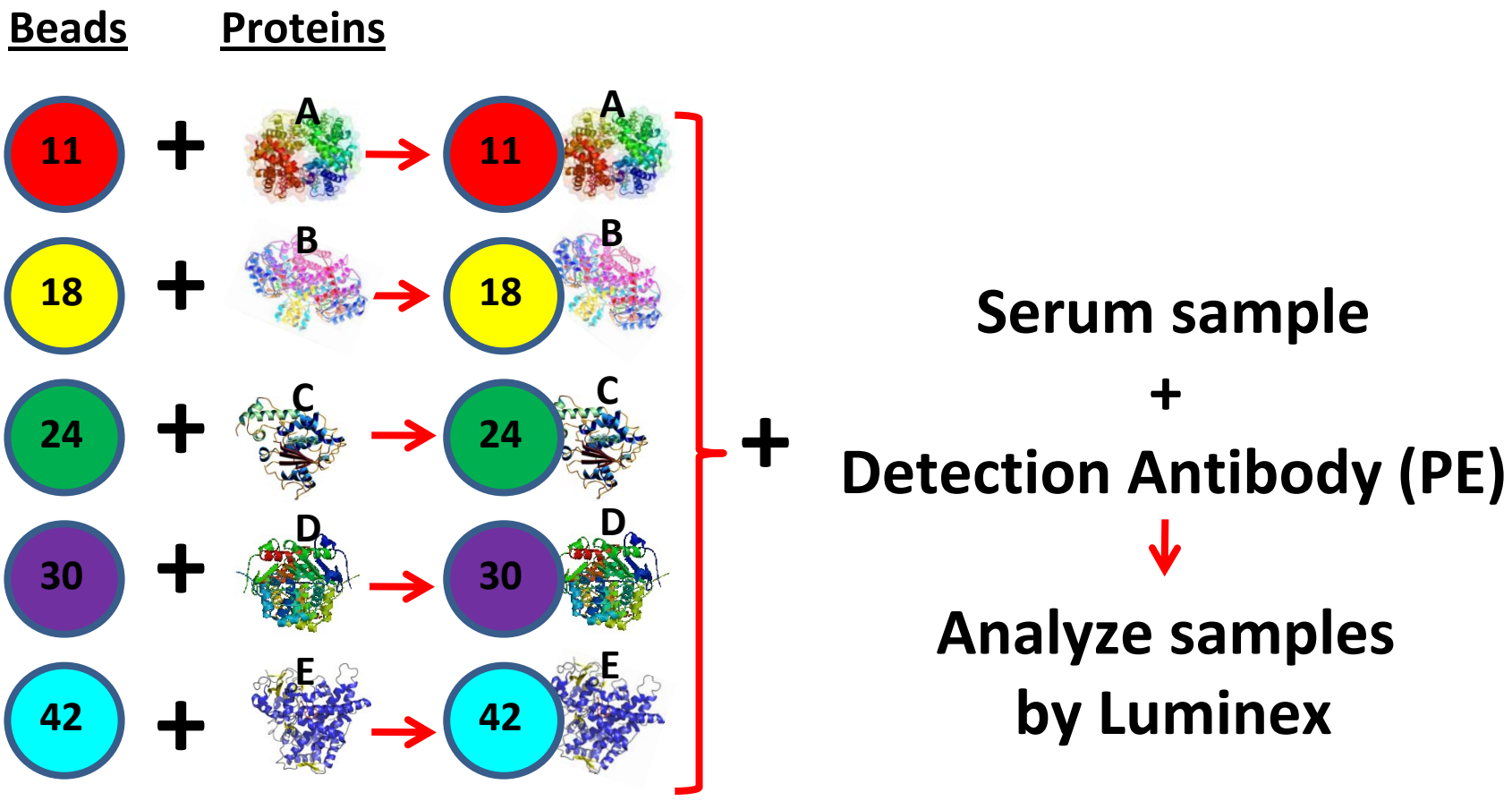


Protein arrays are capable of detecting increased antibody responses but are expensive

Option:

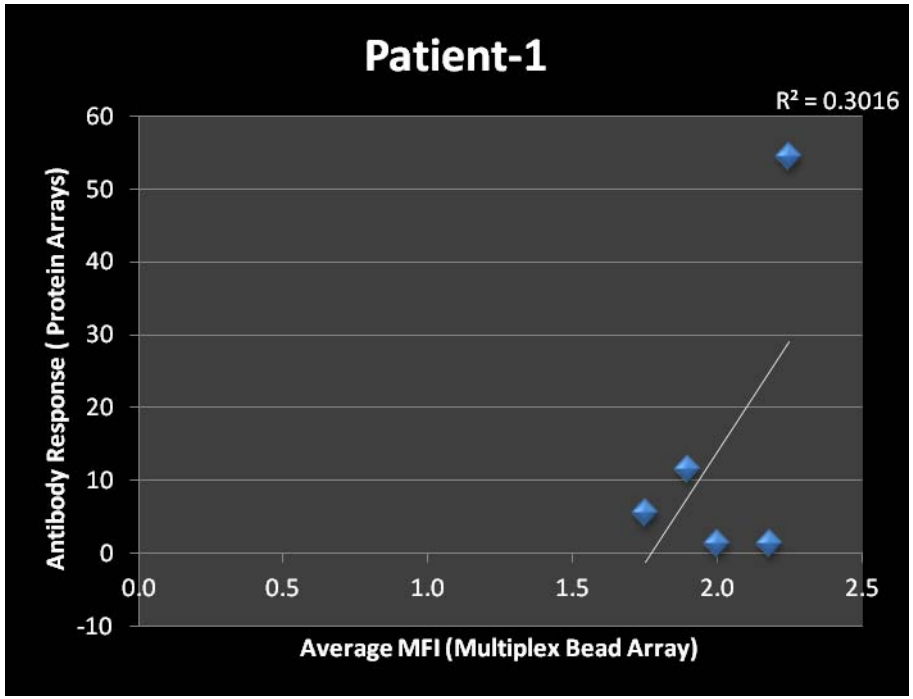
Create multiplex beads with a panel of antigens that were identified as common from our protein array studies. Use these as a High Throughput Screen (HTS).

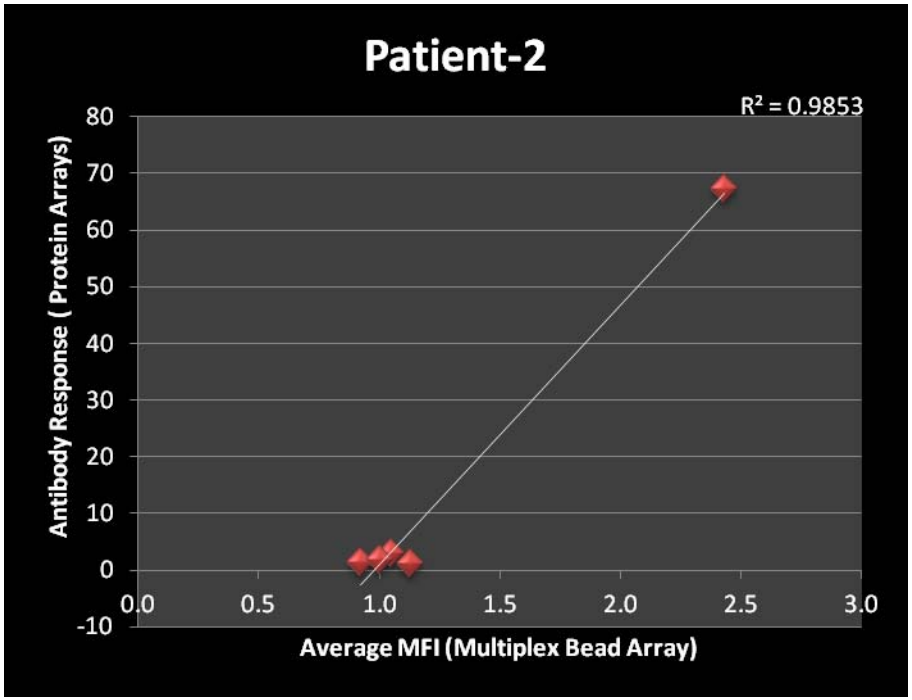
Schema for Multiplex Bead Array



Beads coupled with individual proteins

Preliminary Multiplex Assay results for 5 protein beads.





Summary:

1.Protein arrays can be used to identify antibody responses following immunotherapy

2.CTC can be isolated from cryopreserved aphereses products using FACS and used to identify whether targets of the antibody are expressed by a patient's tumor cells (CTC)

3.An increased number of strong antibody responses correlated with "Response" to Therapy /increase in PSA-DT

4.Current efforts are directed at characterizing the T cell response against targets of the antibody response and developing a HTS method to asses antibody responses to common protein targets identified by protein arrays

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Thank You