

Serial Immune Monitoring:

**Essential to Resolve Immune
Dynamics for Improving Clinical
Effectiveness of Immunotherapy**

***SITC Immunotherapy Workshop,
Washington DC, 7 Nov 2013***

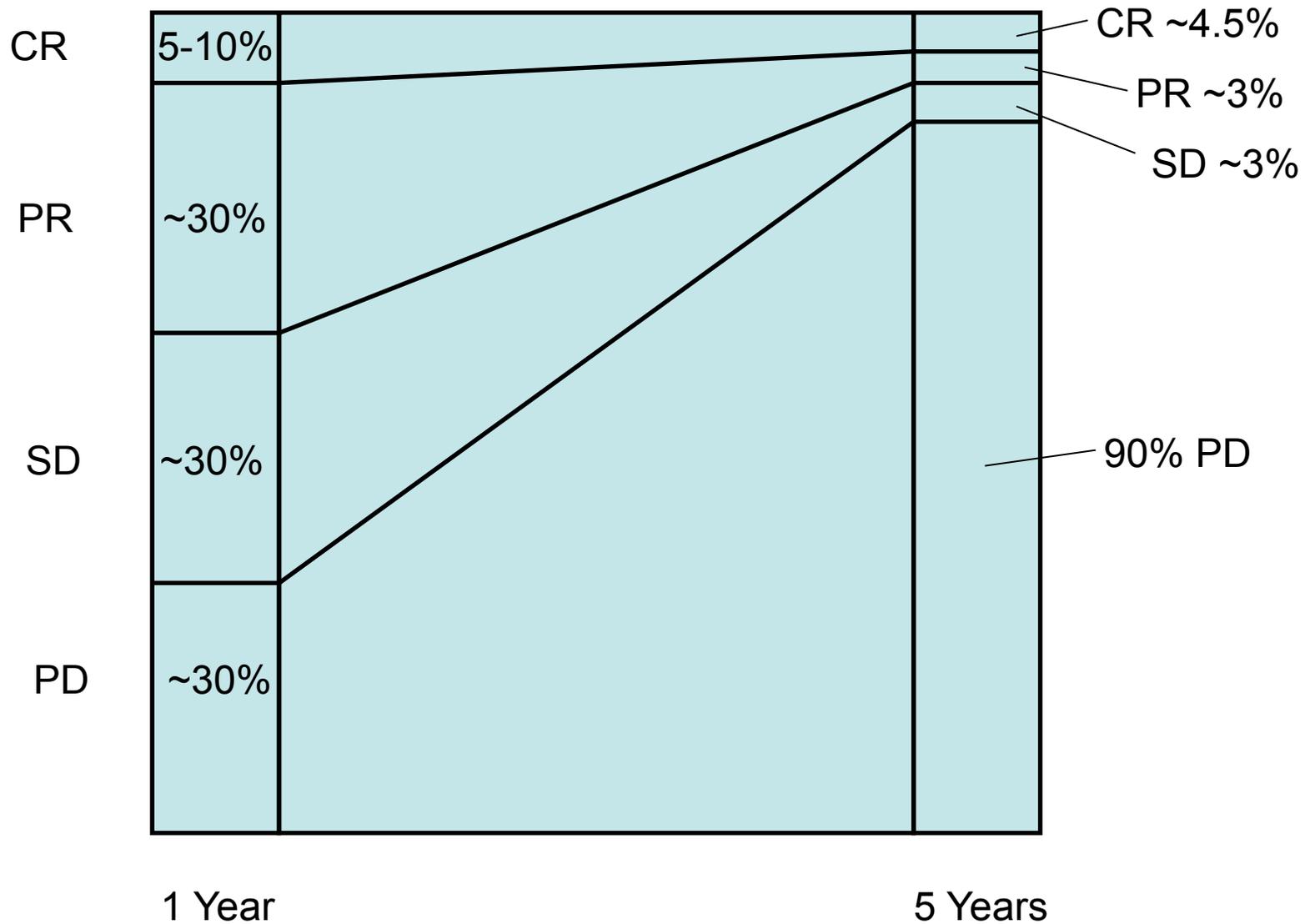
**Brendon J. Coventry BMBS PhD FRACS FACS FRSM
*Dept of Surgery, University of Adelaide,
Royal Adelaide Hospital, Adelaide, South Australia &***

***Martin L Ashdown BAppSc, Dept of Medicine,
University of Melbourne, Melbourne, Australia***

Main Aim

**Monitoring & Targeted Therapy
to
Induce Complete Responses
and
Long-Term Survival
in
Advanced Cancer**

Advanced Cancer Response Rates



Meta Analysis Data Set 160 trials /studies = 9,964 patients

Agent	% CR Rate	Study No.	Authors	No. of Patients /Trials	
IL2	IL2 High Dose Combo M/A	4.40%	14	Coventry, Ashdown 2013	1066 in 14 trials
	IL2 High Dose Mono M/A	6.60%	13	Coventry, Ashdown 2013	2741 in 19 trials
	IL2 Intermediate Dose Comb M/A	2.60%	16	Coventry, Ashdown 2013	400 in 5 trials
	IL2 Intermediate Dose Mono M/A	1.60%	15	Coventry, Ashdown 2013	184 in 2 trials
	IL2 Low Dose Combo M/A	5.20%	18	Coventry, Ashdown 2013	362 in 11 trials
	IL2 Low Dose Mono M/A	4.50%	17	Coventry, Ashdown 2013	286 in 13 trials
	IL-2 Meta Analysis (M/A) 62 Trials	5.60%	12	Coventry, Ashdown 2013	5312 in 62 trials, 1988-2012

Agent	% CR Rate	Study No.	Authors	No. of Patients /Trials	
CTLA4	Ipilimumab+ Nivolumab BMS	6%	29	Wolchok 2013	86
	Ipilimumab	10%	2	Farolfi 2012	36
	Ipilimumab + gp120 esc	6%	5	Prieto2012	85
	Ipilimumab + surgery	7.50%	6	Ku 2010	53
	Ipilimumab +gp120	7%	3	Prieto 2012	56
	Ipilimumab +IL2	17%	4	Prieto2012	36
	Tremelimumab	15.70%	24	Huang 2011	19
	Temelimumab	0%	25	Kirkwood 2010	241
	Tremelimumab	5.10%	27	Ribas 2008	39
	Tremelimumab	2.20%	28	Comacho 2009	89
	Tremelimumab + INFa2b	11.40%	23	Tahinni AA 2012	35
	Tremelimumab MART-1 DC	12.50%	26	Ribas 2009	16

Agent	% CR Rate	Study No.	Authors	No. of Patients /Trials	
ChemoRx	Meta Analysis, cytotoxic agents	7%	21	Coventry, Ashdown 2013	2756 in 68 trials, 2000-2008
	Temozolomide Meta Analysis	7.12%	22	Yatomi Clarke 2013	541 in 9 trials 2010-2013

Agent	% CR Rate	Study No.	Authors	No. of Patients /Trials	
Braf	Dabrafenib (Break II)	7%	11	Ascierto 2013	75
	Dabrafenib /Mek150/1	6%	8	Flaherty 2012	54
	Dabrafenib Mono	4%	9	Flaherty 2012	54
	Dabrafenib/Mek 150/2	9%	7	Flaherty 2012	54
	Vemurafenib	6.25%	1	Ravnan 2012	32
	Vemurafenib	6%	10	Sosman 2012	132

Agent	% CR Rate	Study No.	Authors	No. of Patients /Trials	
PD-1/L	PD-1 Mab (mono) BMS	3.30%	30	Wolchok, 2013	30
	PD-1 Mab Merck	9.70%	20	Hamid O, 2013	103
	PD-1L Mab Genentech	7%	19	Gordon, AACR 2013	30

Av 6.6% CR rate

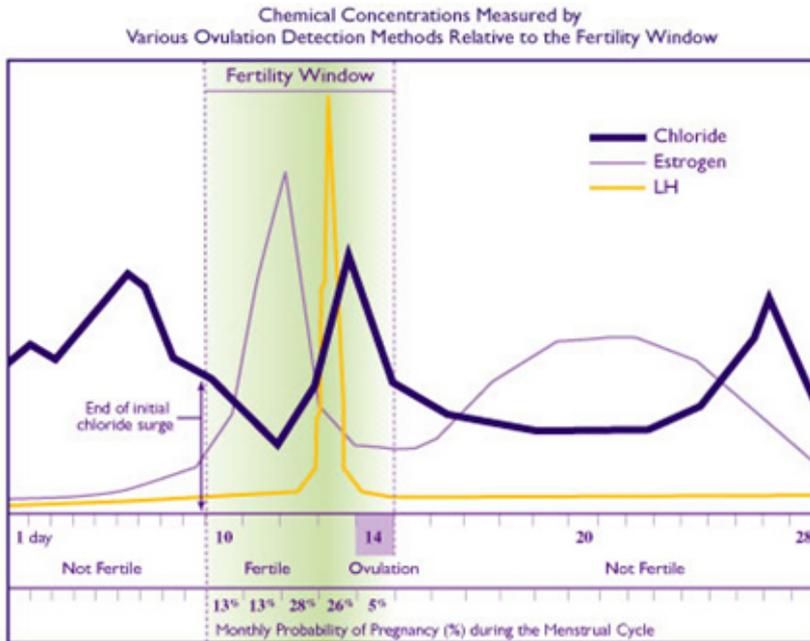
QUOTES

"You won't know how to vaccinate until you know how to immunize.

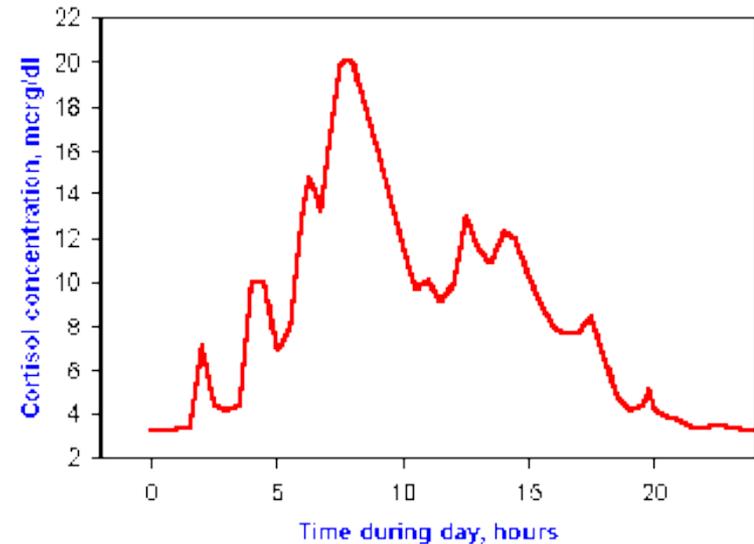
And you won't know how to immunize until you know how to monitor."

- Lloyd J. Old, M.D. Director, Cancer Vaccine Collaborative, CRI, NYC....2003

Examples of repeating Bio-rhythms



The ~ 28 day Menstrual Cycle



The 24Hr Cortisol Cycle

* Well documented and understood due to close serial daily data

CANCER PATIENT MONITORING WITH THERAPIES

Animal expts - inadequate monitoring

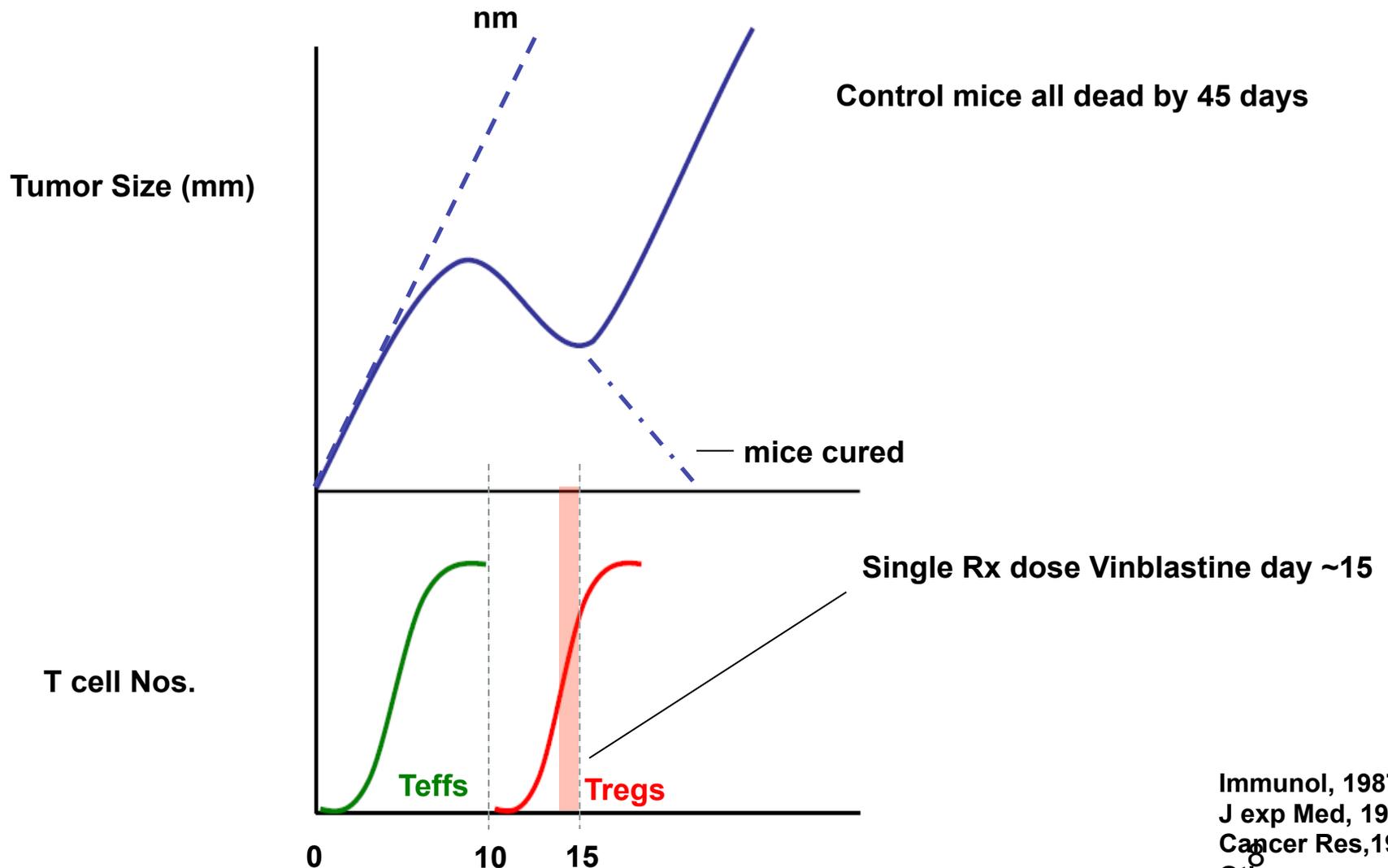
Human expts - inadequate monitoring

Successful Essential Close Serial Monitoring

- *Fertility*
- *Diabetes*
- *Cortisol*
- *Antibiotics*
- *Cardiac*

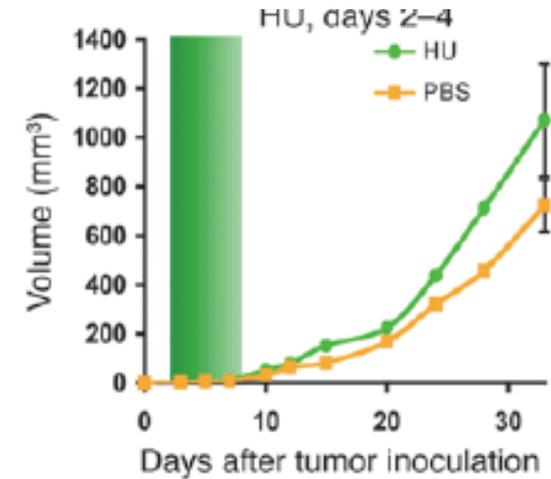
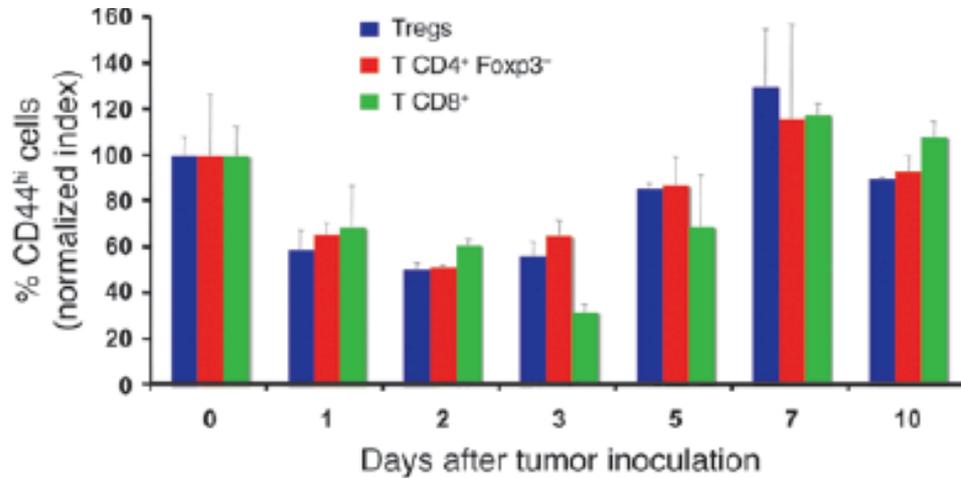
Robert J North - T Cell Mediated Murine Tumor Regression

Trudeau Inst. NY.

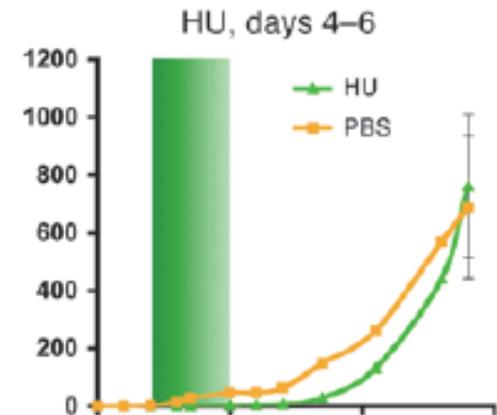
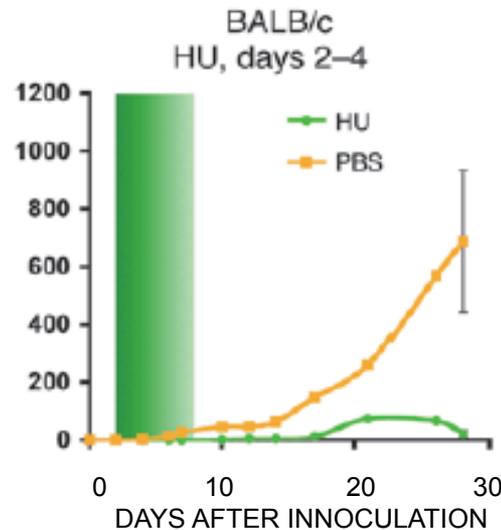
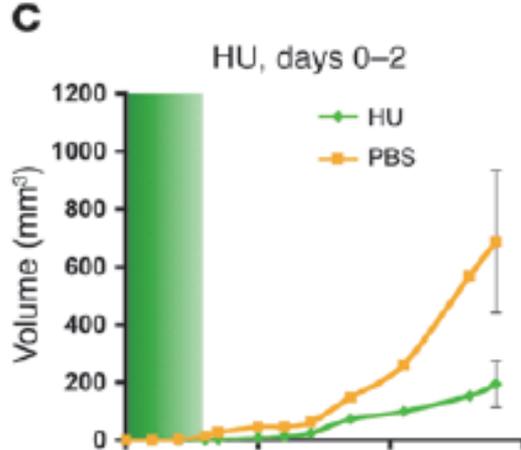


Immunol, 1987.
J exp Med, 1988.
Cancer Res, 1989.
Others.

Critical Timing Effect

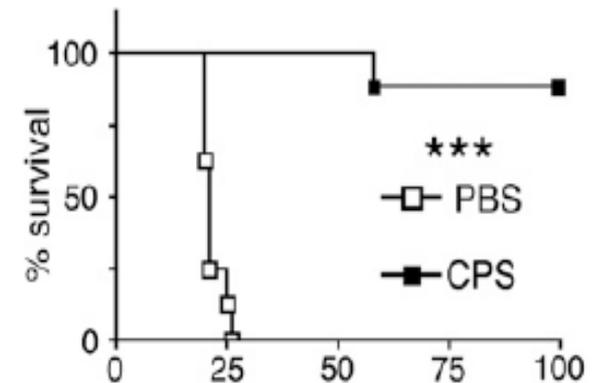
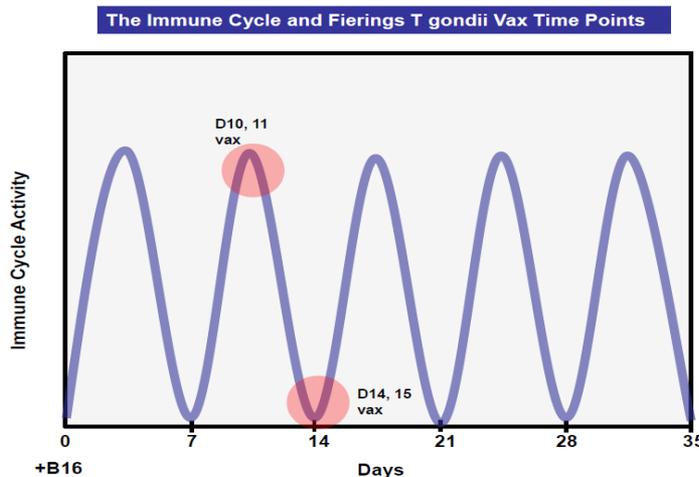
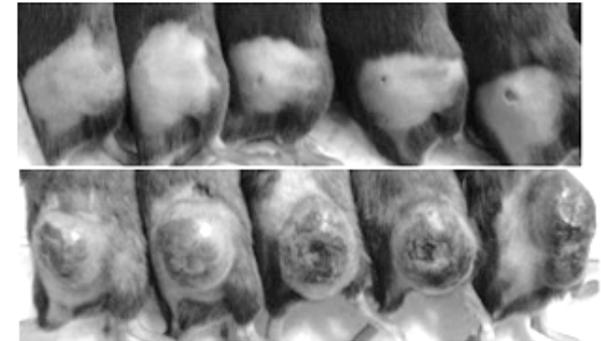
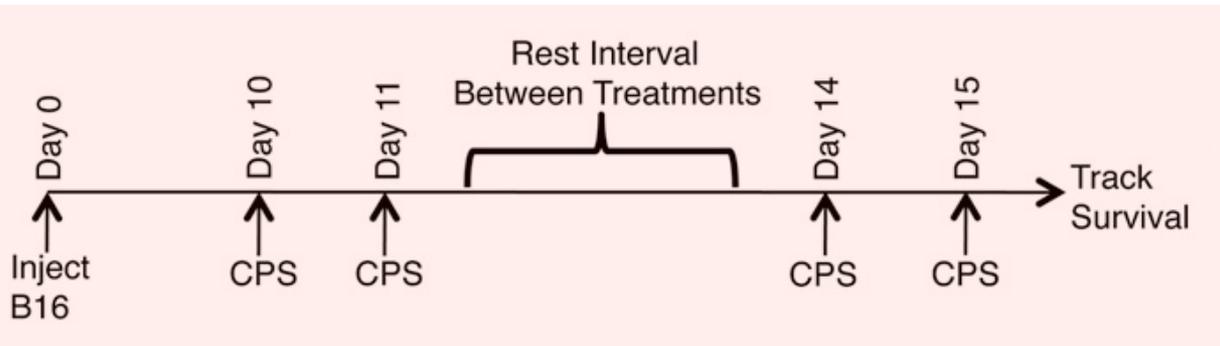


C

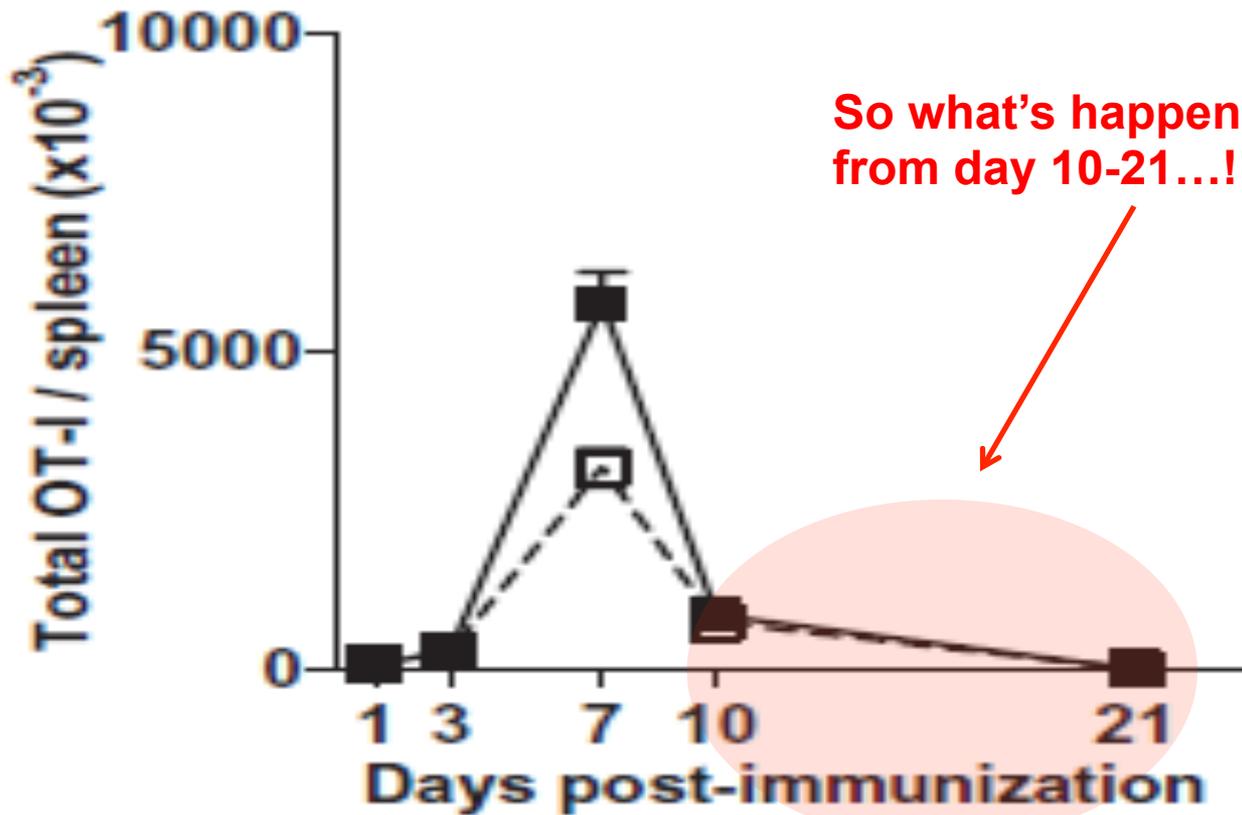


Immune-Mediated Regression of Established B16F10 Melanoma by Intratumoral Injection of Attenuated *Toxoplasma gondii* Protects against Rechallenge

Baird & Fiering *The Journal of Immunology*, 2013, 190: 469–478.

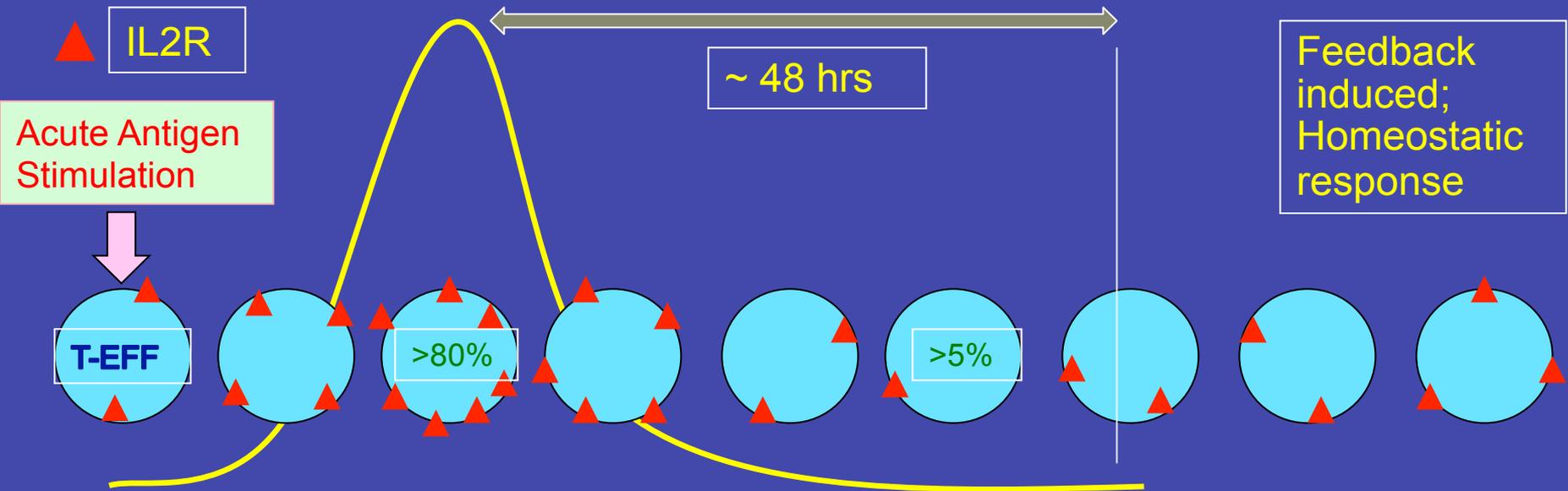


“Monotherapy cps (Tg) treatment of B16F10 also stands out from many other immunotherapy approaches by relying on manipulation of the endogenous immune response in vivo.”



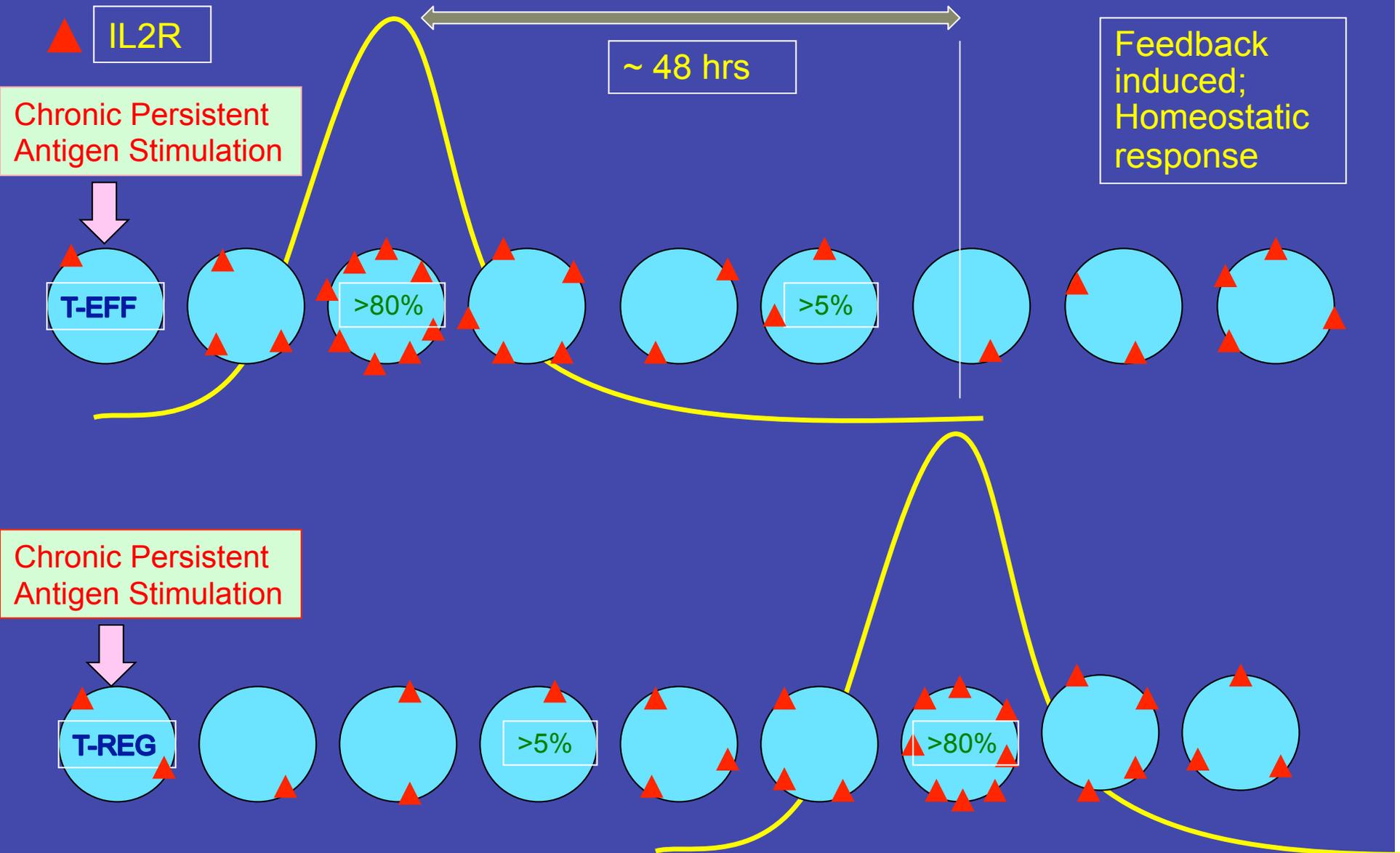
[McNally Proc Natl Acad Sci U S A. 2011 May 3;108\(18\):7529-34.](#)

IL-2 RECEPTOR EXPRESSION ON T-CELLS



Coventry BJ, Ashdown ML. **The 20th anniversary of interleukin-2 therapy: bimodal role explaining longstanding random induction of complete clinical responses.** Cancer Management Res. 2012;4:215-21.

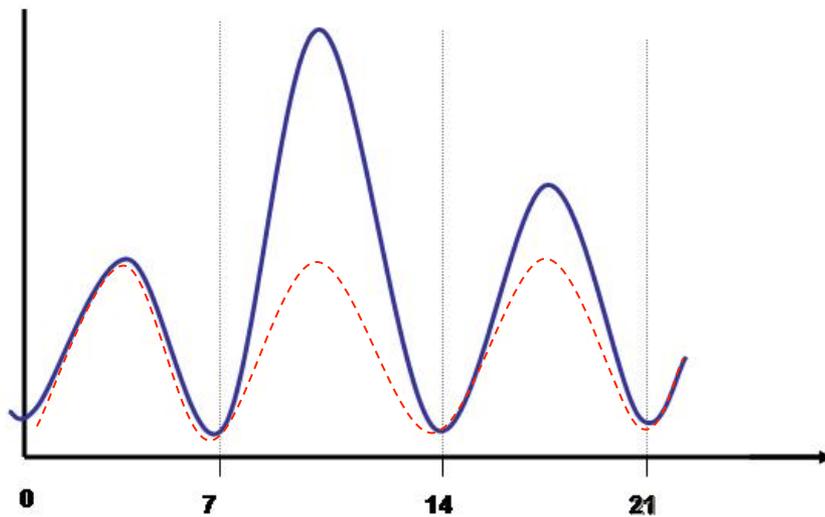
IL-2 RECEPTOR EXPRESSION ON T-CELLS



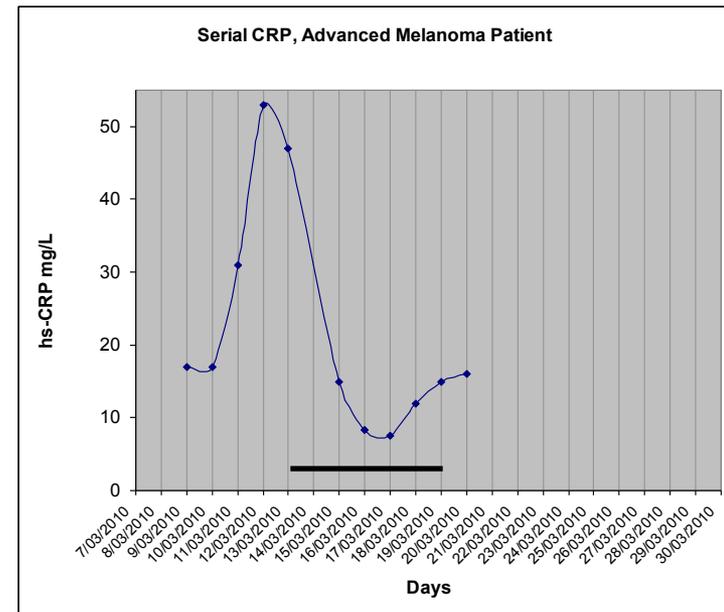
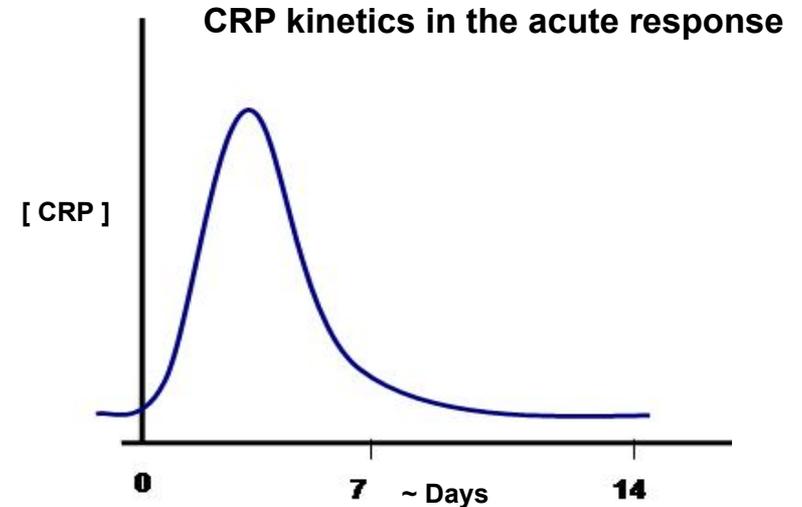
C- Reactive Protein (CRP) – a surrogate biomarker of immune kinetics

CRP

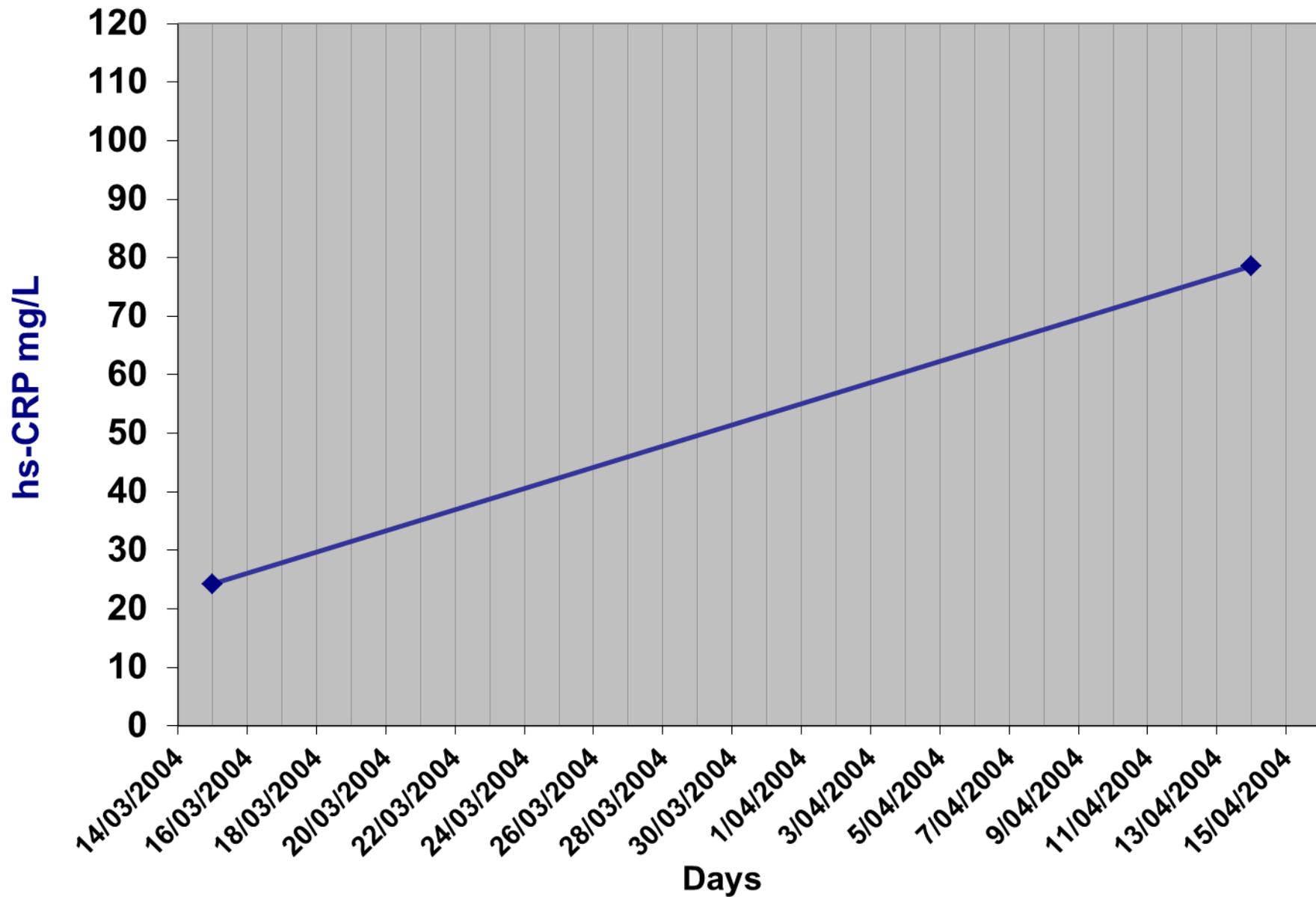
- Pentraxin
- Opsonin
- Functional analogue of Ig
- Binds cellular debris
- Binds Fcγ IIR on DCs
- Initiates the adaptive IR
- Rises/ Falls with IR initiation/ termination
- Elevated in cancer patients



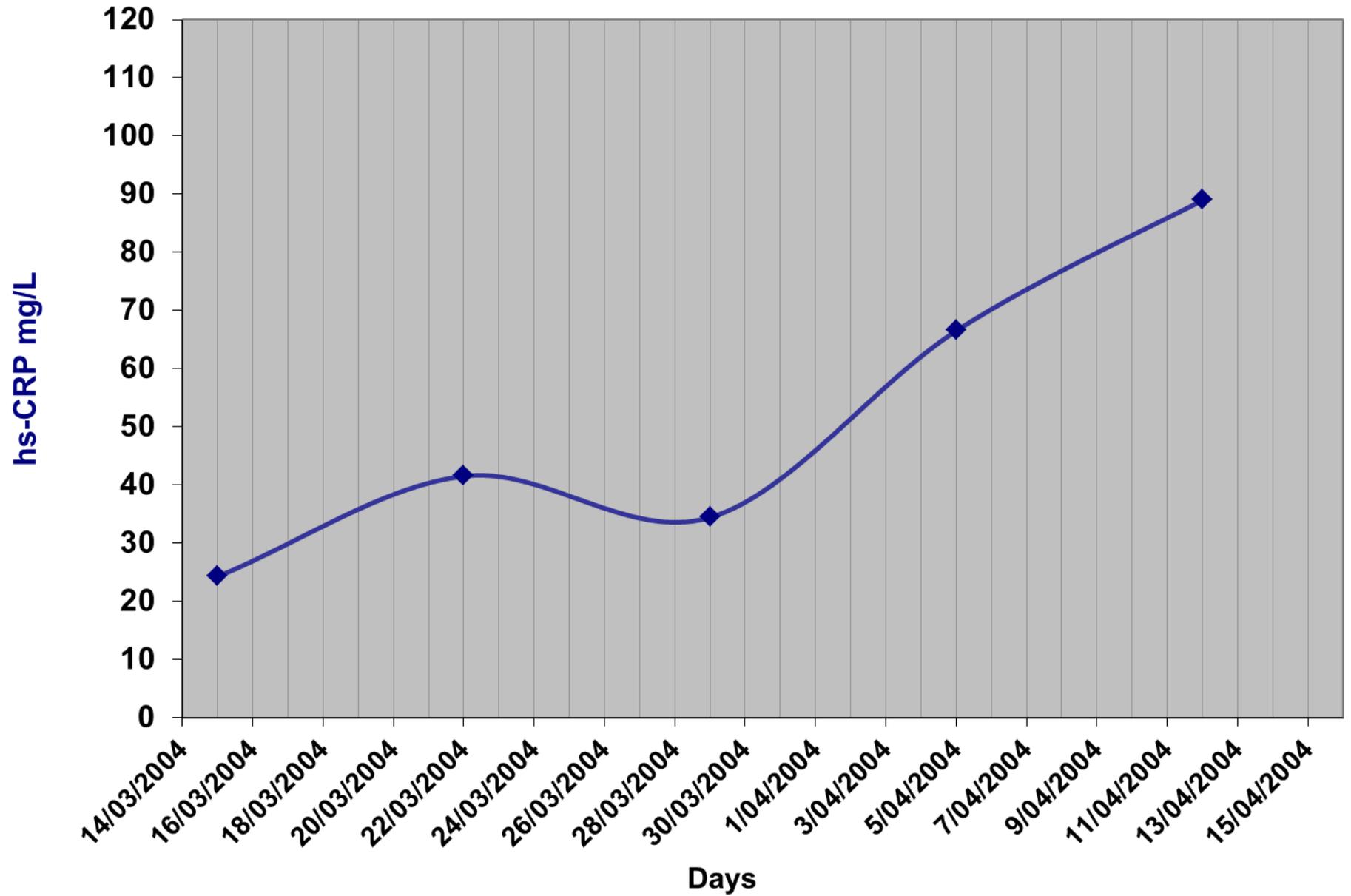
CRP kinetics in the late stage cancer patient



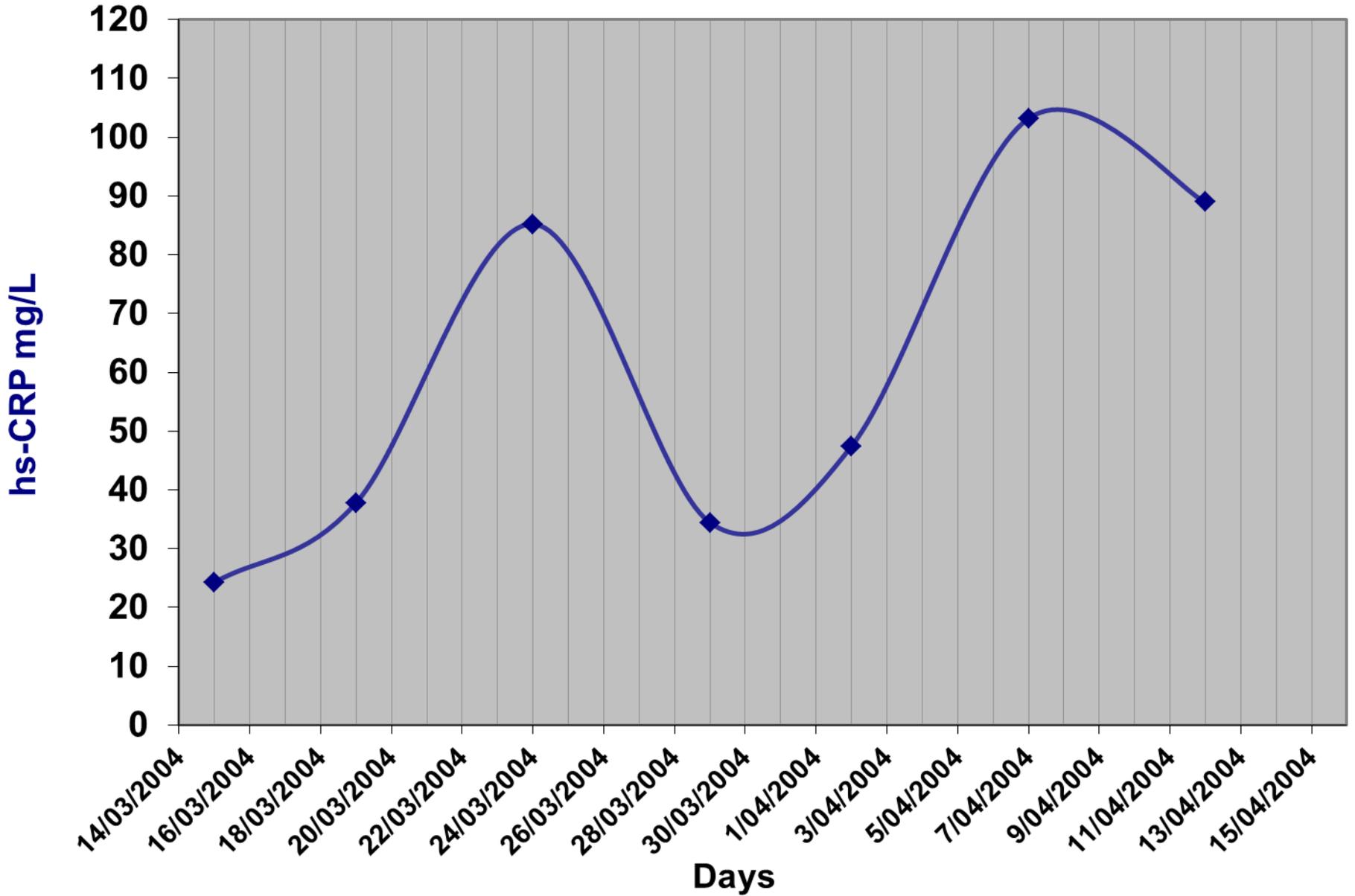
Serial hs-CRP over 4weeks, Stage IV Melanoma



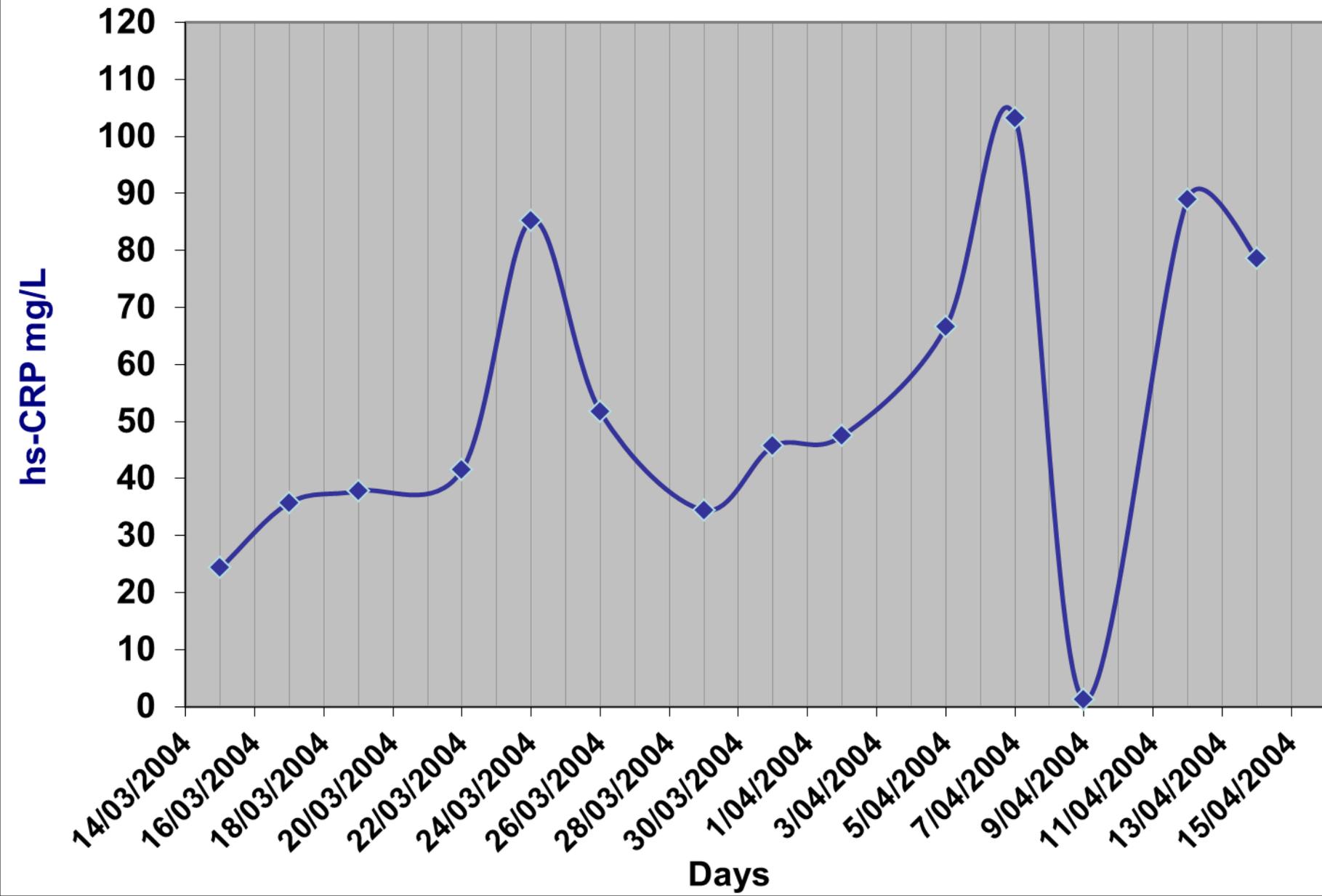
Serial hs-CRP over 4weeks, Stage IV Melanoma



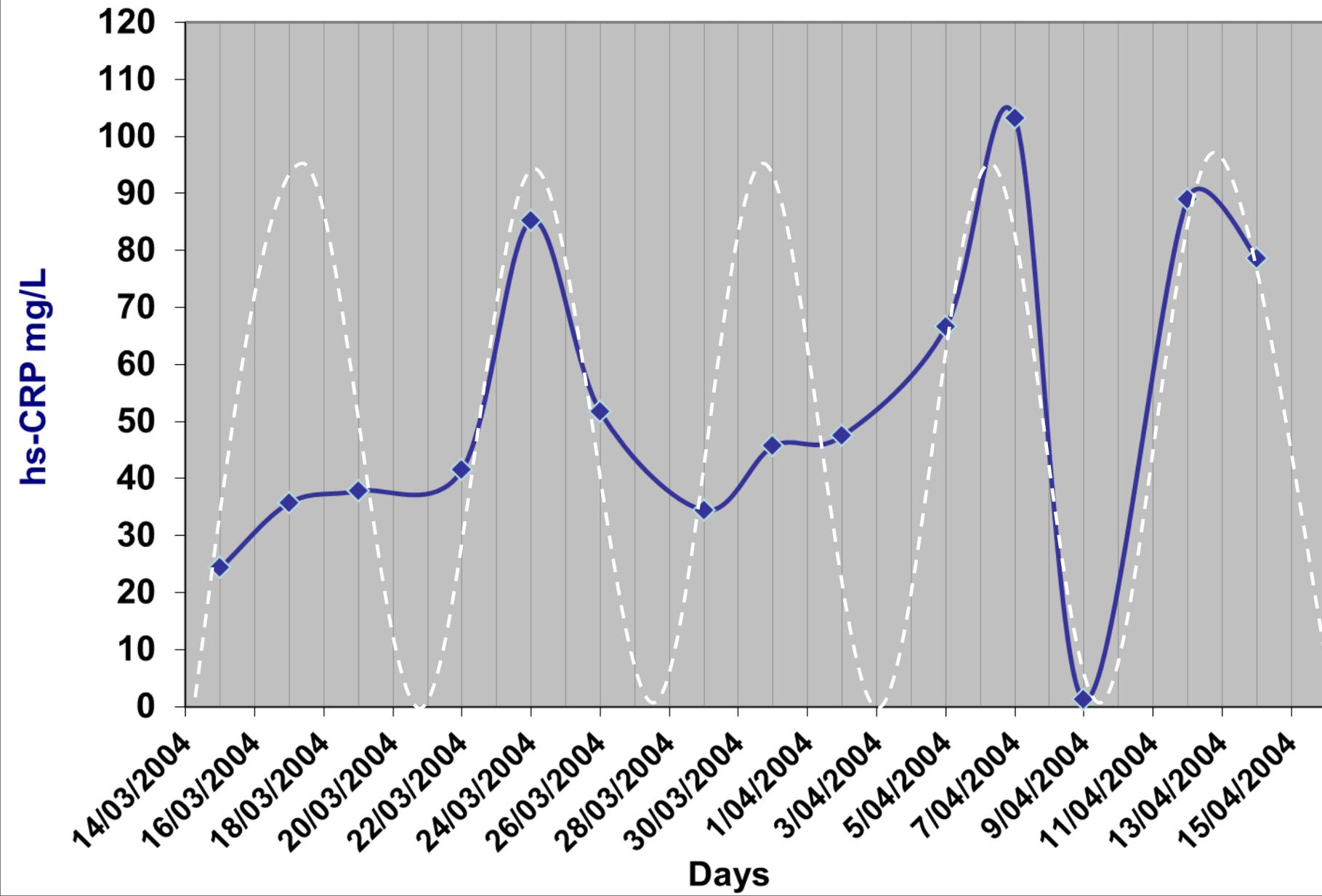
Serial hs-CRP over 4weeks, Stage IV Melanoma



Serial hs-CRP over 4weeks, Stage IV Melanoma



Serial hs-CRP over 4weeks, Stage IV Melanoma



Vaccine Therapy for Malignant Melanoma Metastases

Vaccinia Melanoma Cell Lysate (VMCL) – Peter Hersey, NU

- No toxicity, tested in over 400 patients previously Vax
- Simple protocol, I/D Vax fortnightly



August 2005



December 2005

VMCL VACCINE STUDY

- DATA ANALYSIS TO END DEC 2010, All Evaluable Patients

RESPONSE RATES (N = 54 patients)

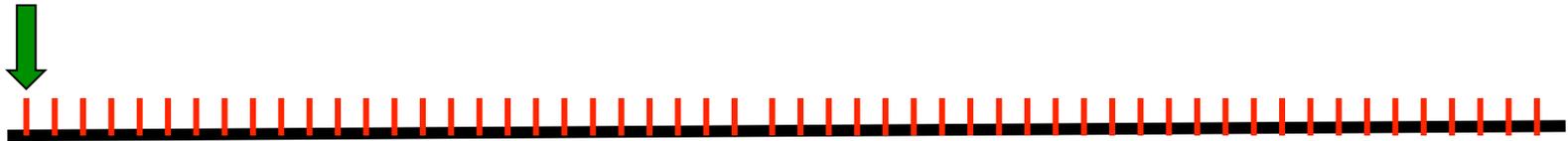
- **CR** **9 patients (16.7%)**
- **SD** **25 patients (46.3%)**
- **PR** **8 patients (14.8%)**
- **Progressive Disease** **12 patients (22.2%)**

Does timing WRT immunological cycles/oscillations affect efficacy??

VMCL VACCINE STUDY

Vaccine events

Repetitive vaccinations 

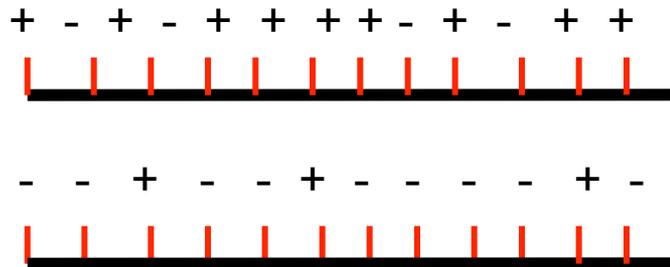


***Continued Repetitive Vaccination Events
– Persistent Immune Stimulation***

VMCL VACCINE STUDY

Vaccine events

Repetitive vaccinations →



CLINICAL EFFECT

+ Responsiveness

- Tolerance

***Continued Repetitive Vaccination Events
– Persistent Immune Modulation***

Major Dilemma in Control of the Immune System

How are either **Tolerance** and **Responsiveness** controlled and determined *in-vivo*?

How is the **CRITICAL BALANCE** orchestrated ?

How is 'Immunological Homeostasis' achieved?

Implications for Cancer Immuno-Chemotherapy?

Multiple Vaccinations: Friend or Foe

Sarah E. Church, Shawn M. Jensen, Chris Twitty, Keith Bahjat, Hong-Ming Hu, Walter J. Urba, and Bernard A. Fox

Robert W. Franz Cancer Research Center, Earle A. Chiles Research Institute, Providence Cancer Center, Providence Portland Medical Center, Portland, Oregon

Departments of Molecular Microbiology and Immunology, Oregon Health and Science University, Portland, Oregon
Cancer Research and Biotherapy Center, The Nanjing Second Hospital, Nanjing, Jiangsu. China

Cancer J. 2011 ; 17(5): 379–396.

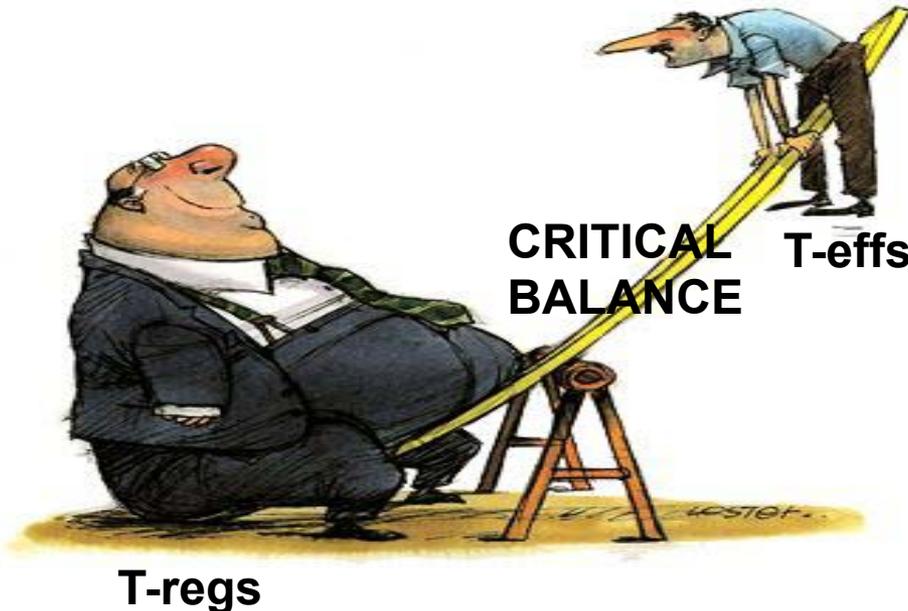
Homeostatic Regulated Immune Kinetics in Cancer

- How to Break Tolerance.

Drivers

Ag*
IL-2*
IL-4
IL-10*
IL-12*
IL17*
IL-21*
TGFb1
CTLA4*
GITR*
VLA4*
CD134*
PD-1*
INF γ *

Tolerance



Responsiveness

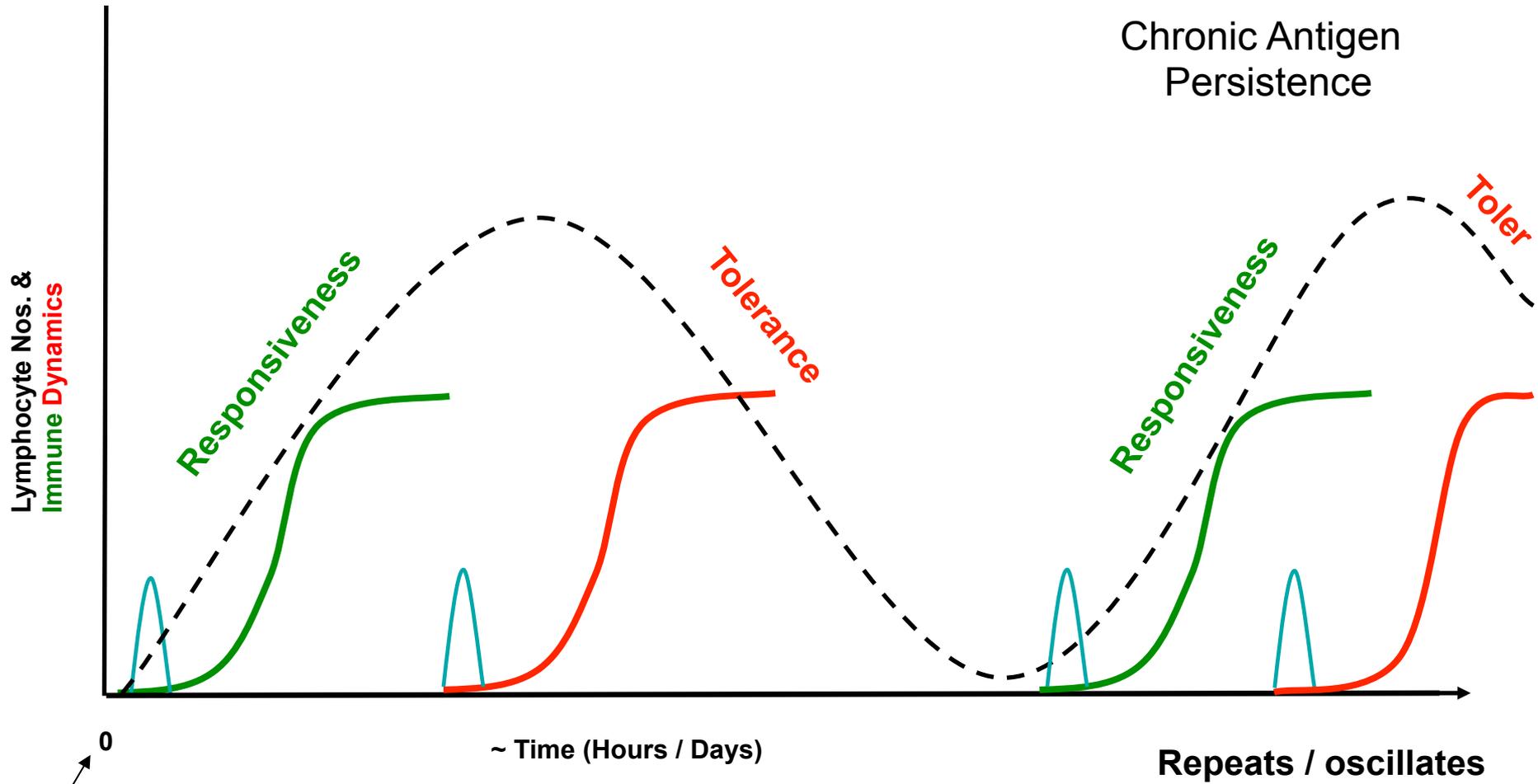
Drivers

Ag*
IL-2*
IL-10*
IL-12*
IL17*
IL-21*
CTLA4*
GITR*
VLA4*
CD134*
PD-1*
INF γ *

"Nature exists in a delicate balance, the immune system being no exception."

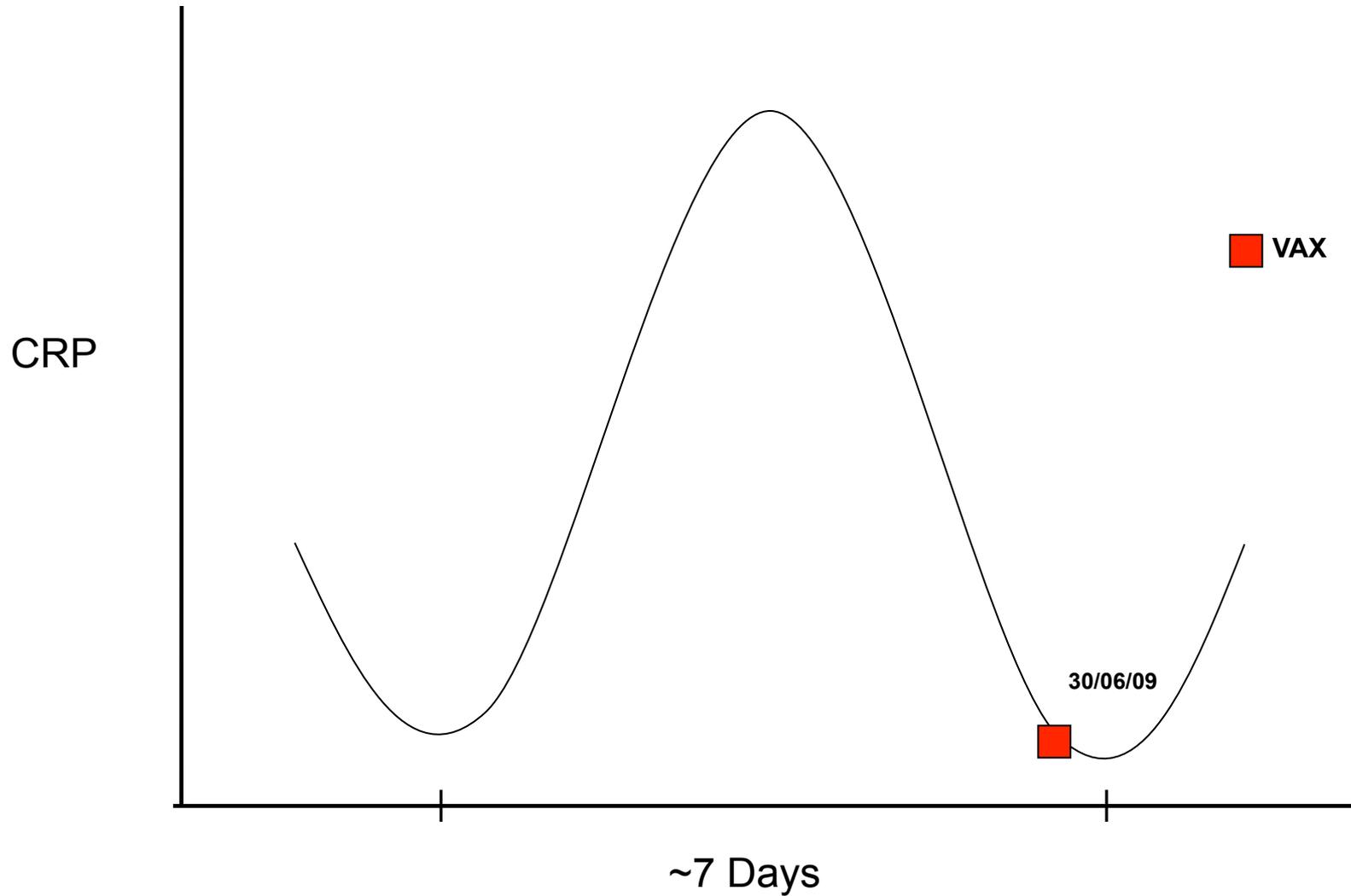
Many Drivers for Responsiveness same as for Tolerance

The Functional Unit of the Adaptive Immune Response

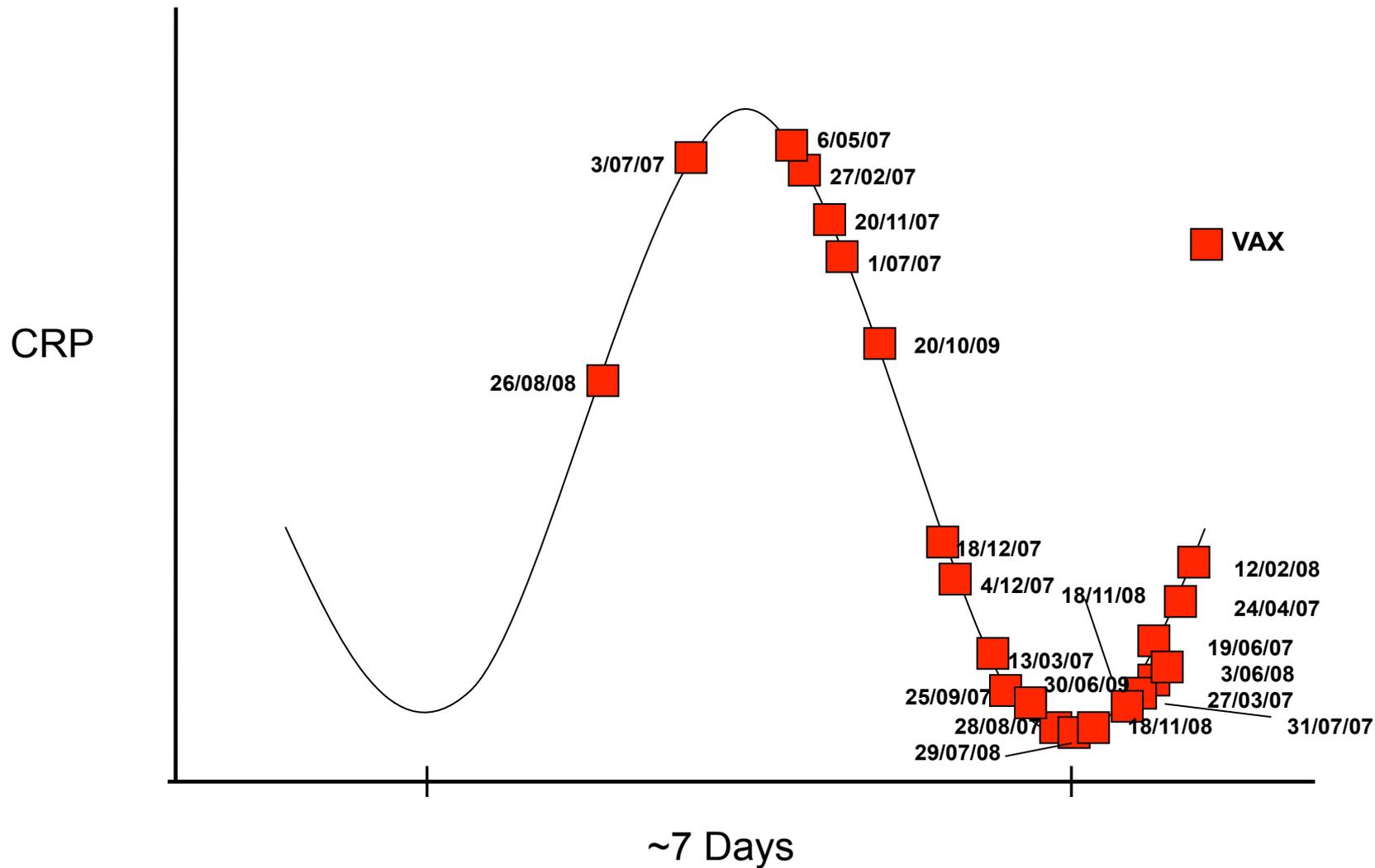


Stimulus – chronic antigen

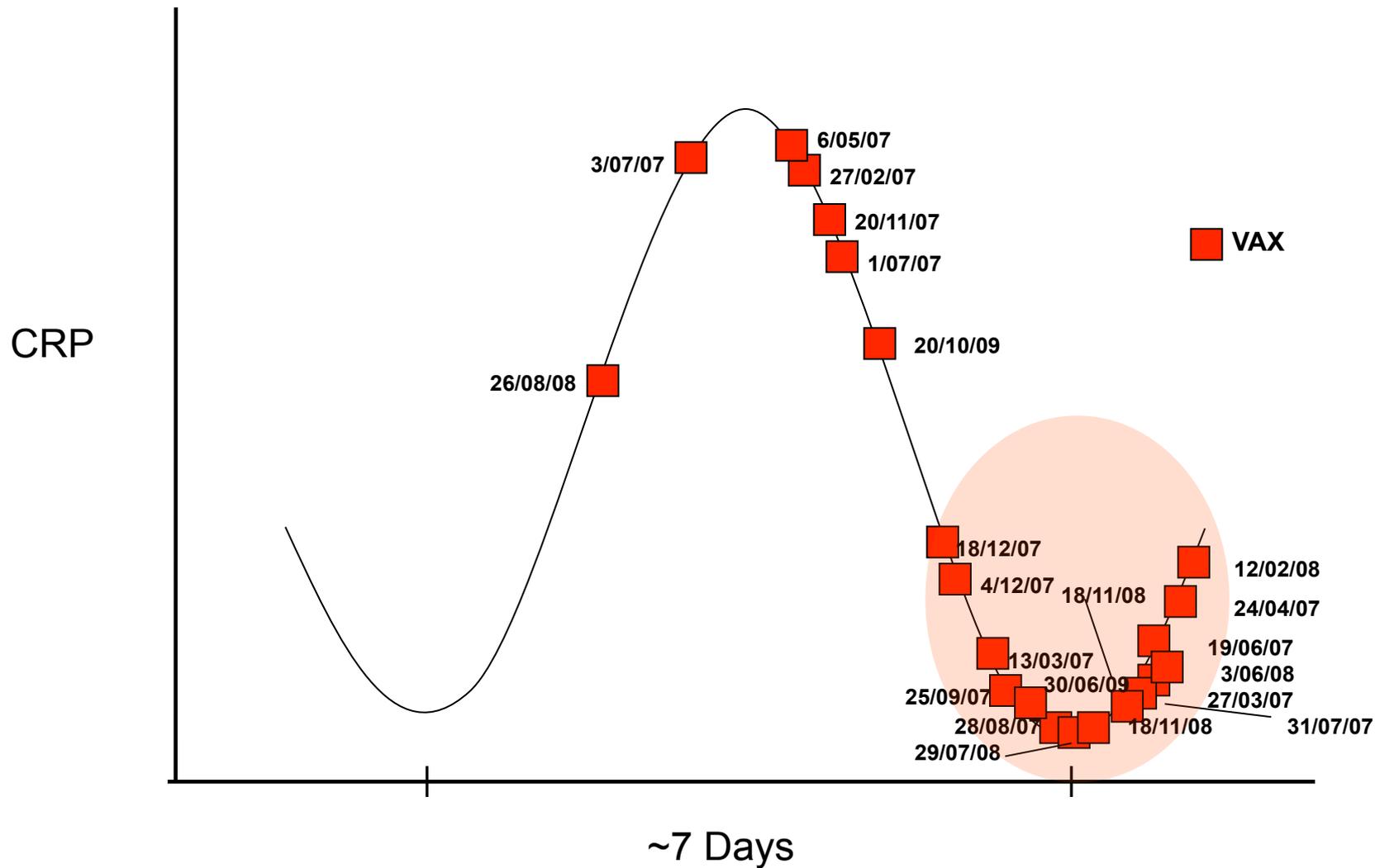
Patient CG Vax treatment date & relative position on CRP cycle 2007-2009



Patient CG Vax treatment date & relative position on CRP cycle 2007-2009



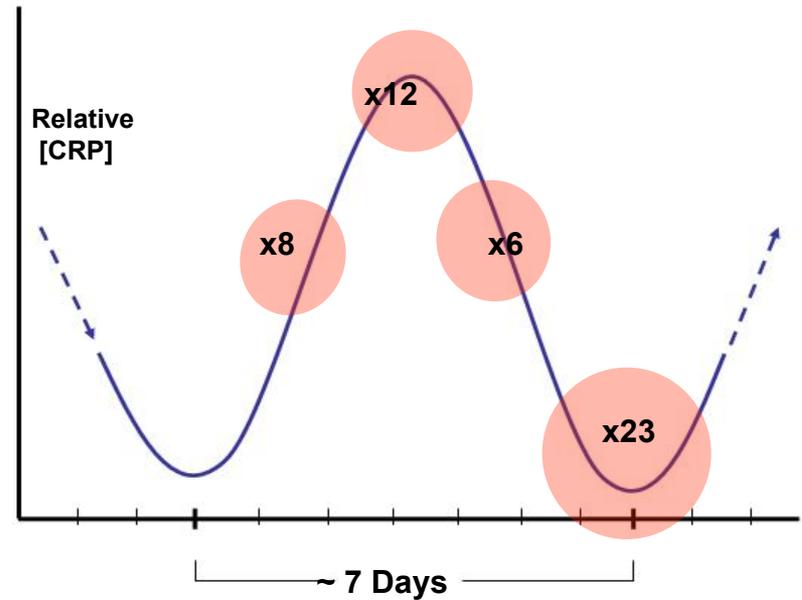
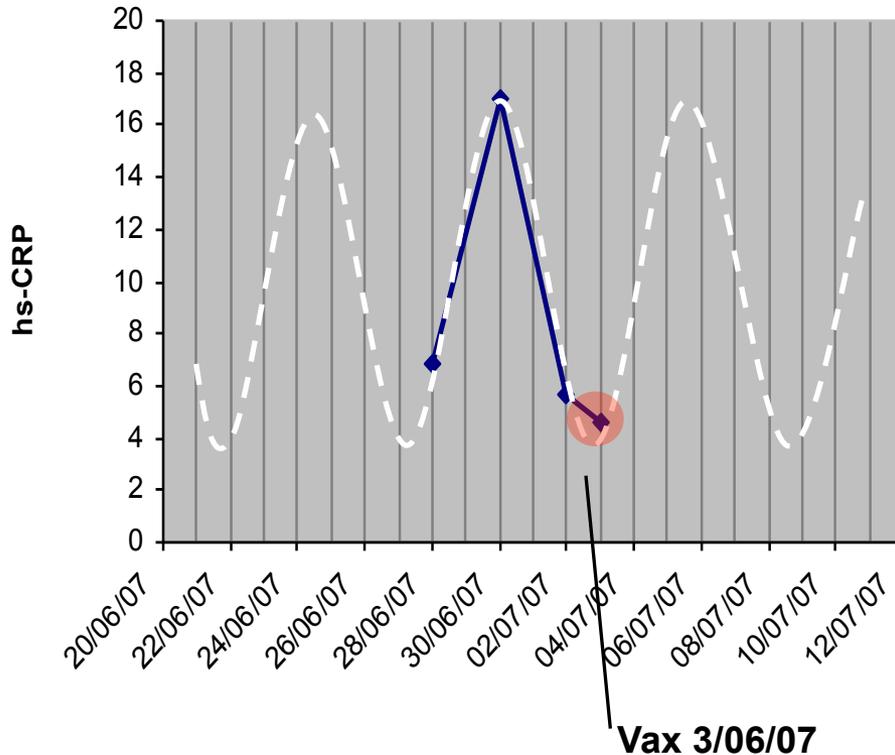
Patient CG Vax treatment date & relative position on CRP cycle 2007-2009



Vaccinia Melanoma Cell Lysate (VMCL) vaccine therapy for advanced melanoma

49 Vaccinations from 3/6/07 – 30/7/09 .

Timing Vaccine administration WRT CRP Cycle

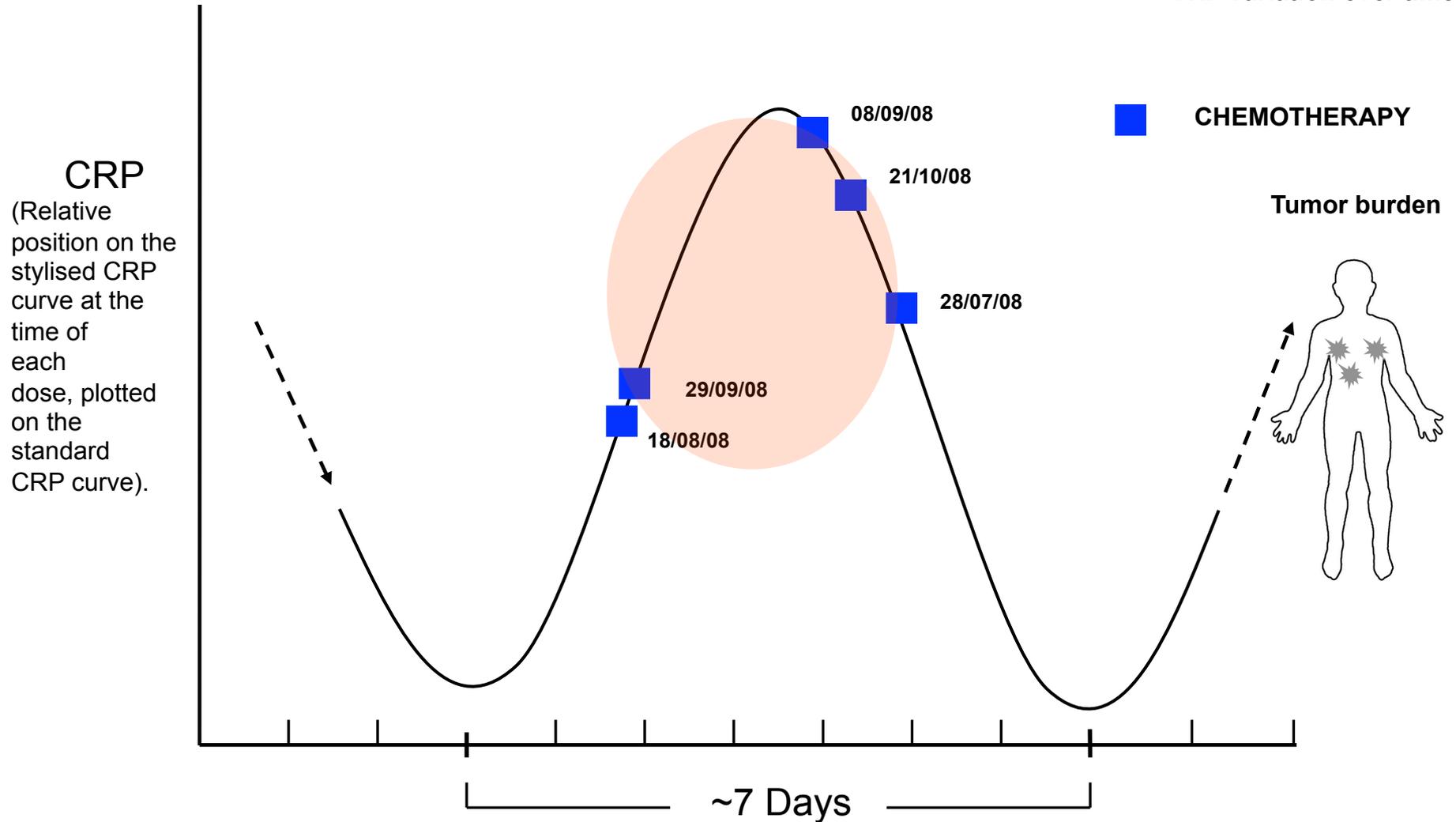


Serial monitoring hs-CRP the week before and the day of vaccination. Note how the cycle kinetics can be approximately resolved with a week of serial data.

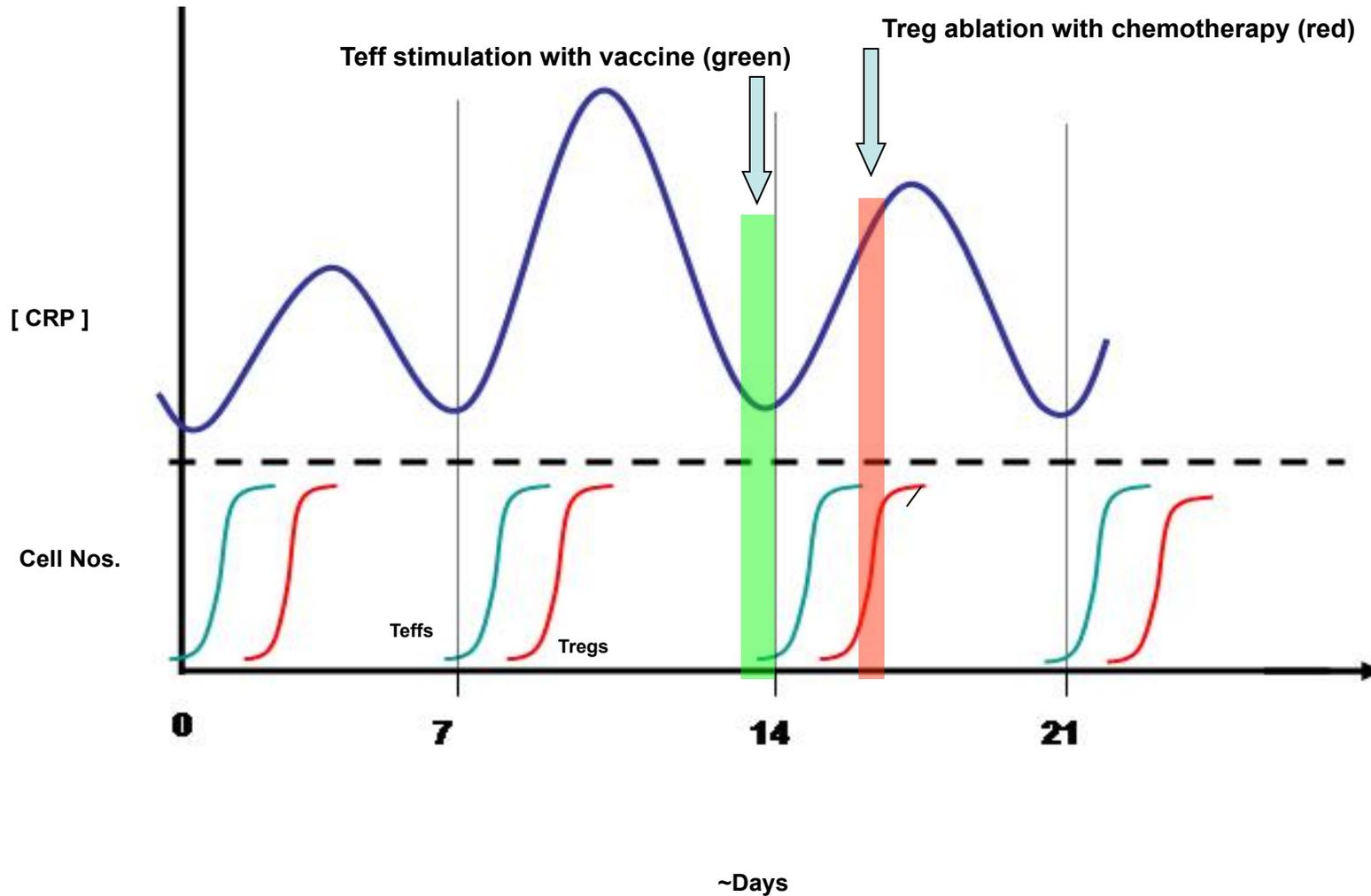
Number of vaccinations and their approximately position on the CRP cycle, either near a peak or a trough, etc. Patient #JM

Patient #EG Chemotherapy treatment date & relative position on CRP cycle

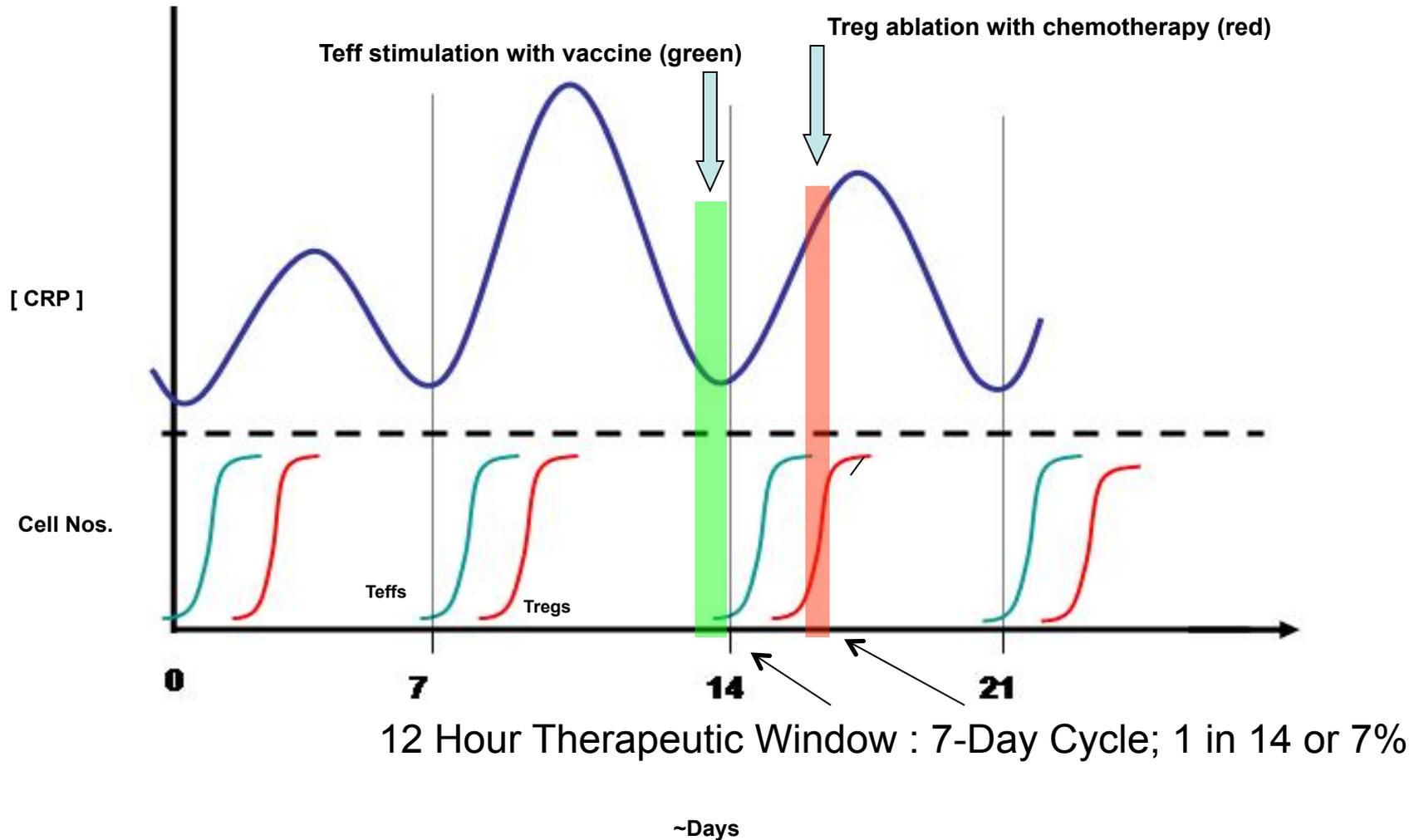
CRP variation over time



C- Reactive Protein (CRP) – a potential surrogate biomarker of immune kinetics

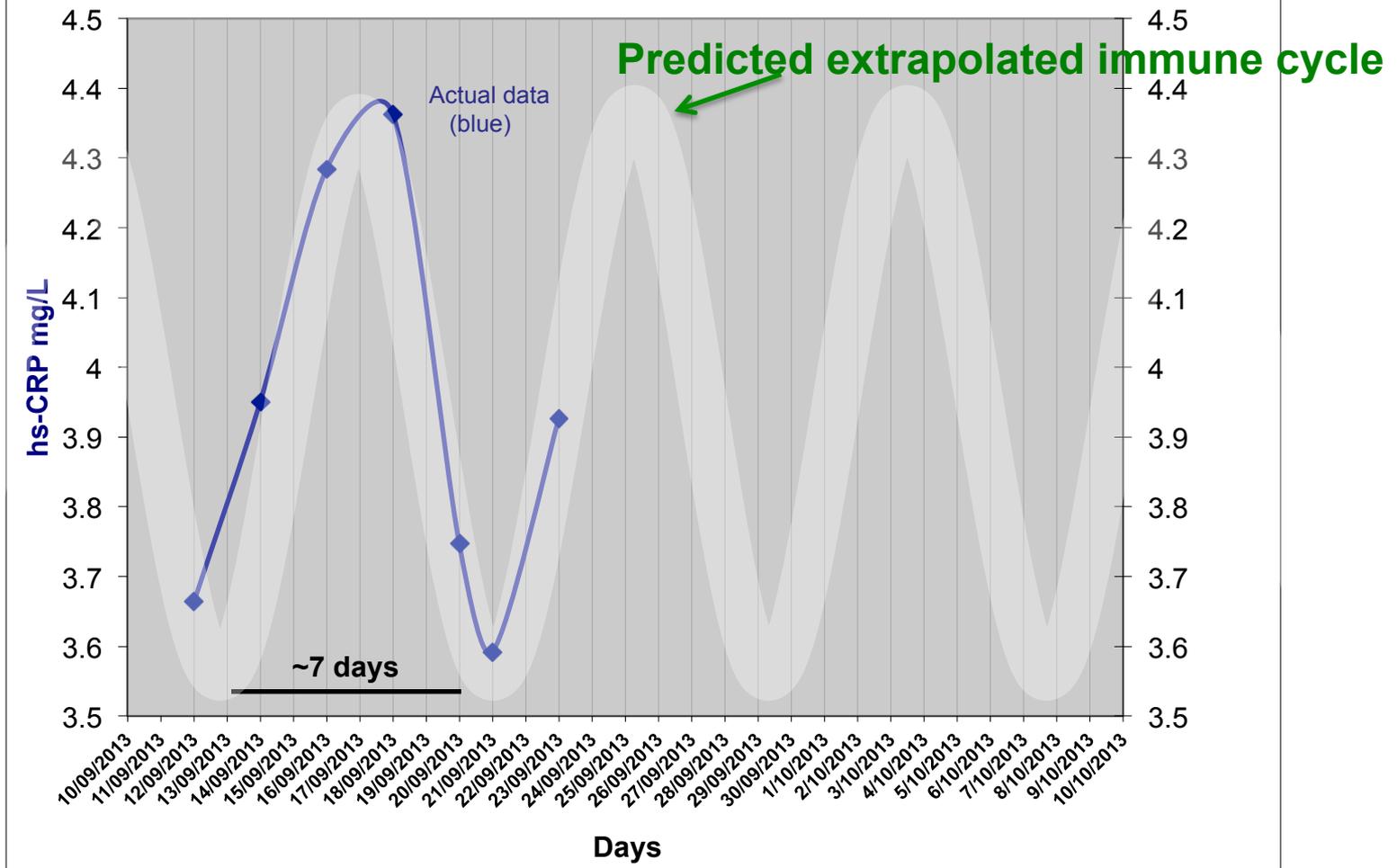


C- Reactive Protein (CRP) – a potential surrogate biomarker of immune kinetics

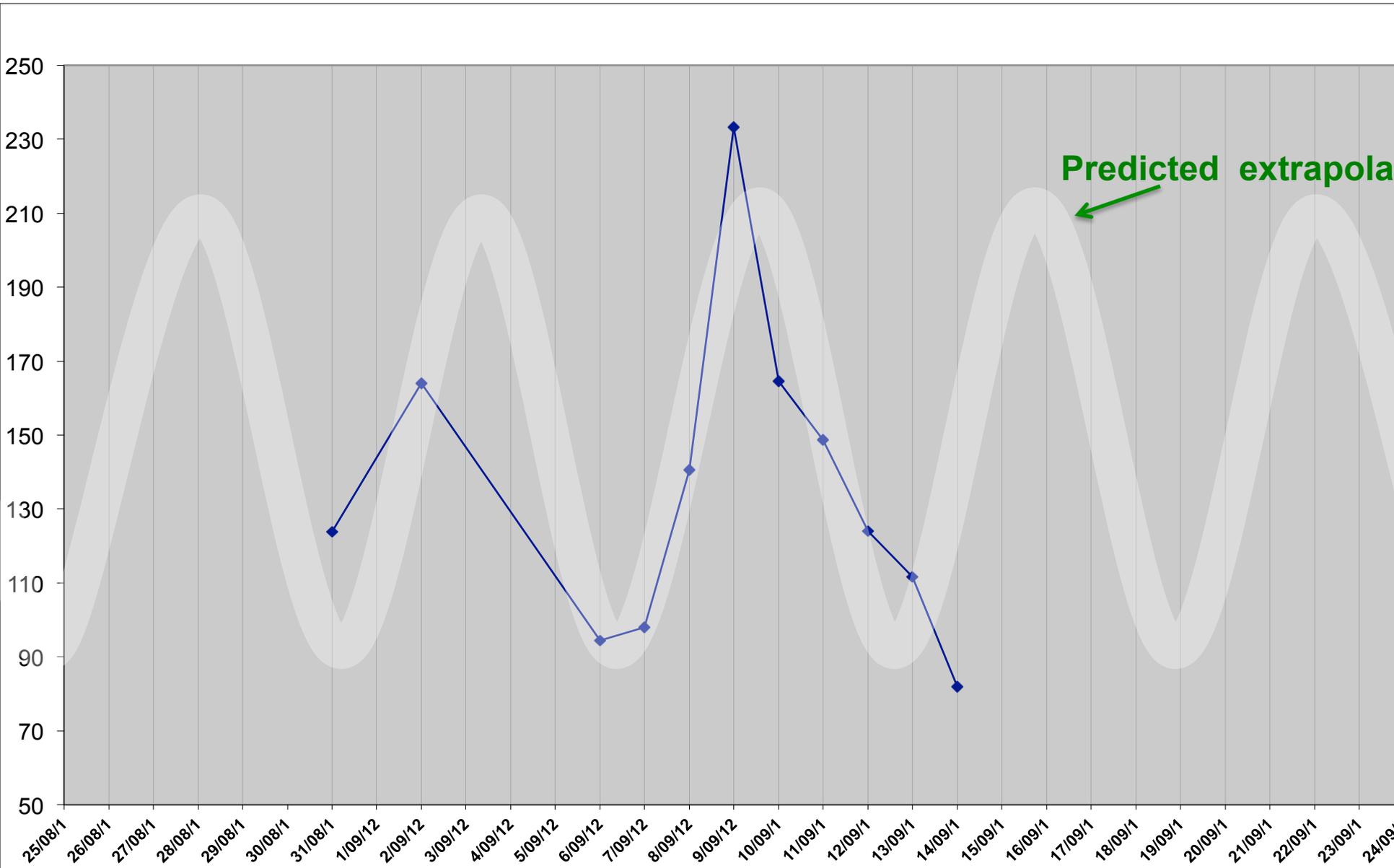


Melanoma

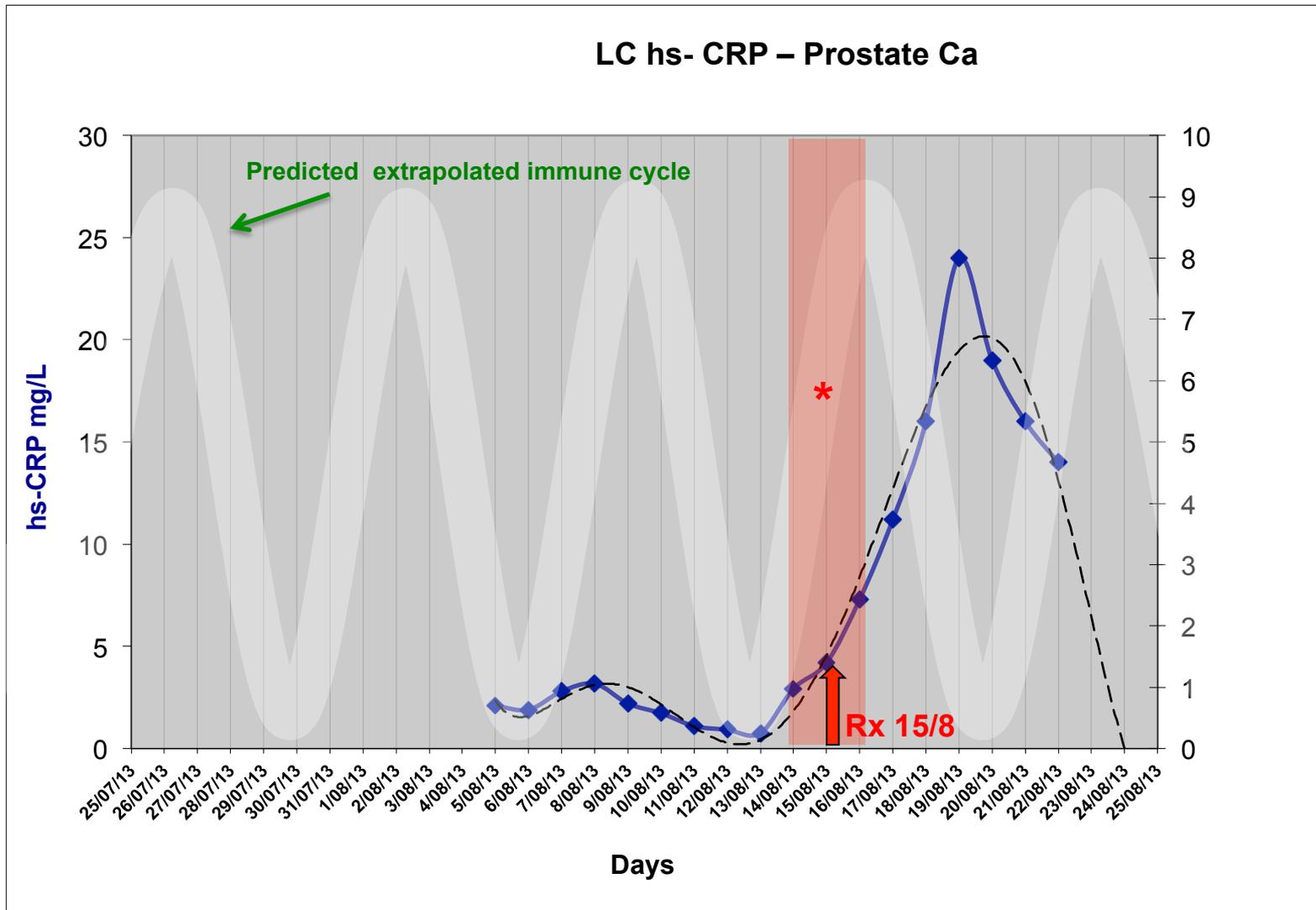
Patient : S S (Colorado USA) Melanoma, hs- CRP



Lung Ca



Advanced Prostate Ca



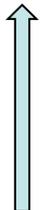
DN CRP CYCLE SERIES - THERAPY



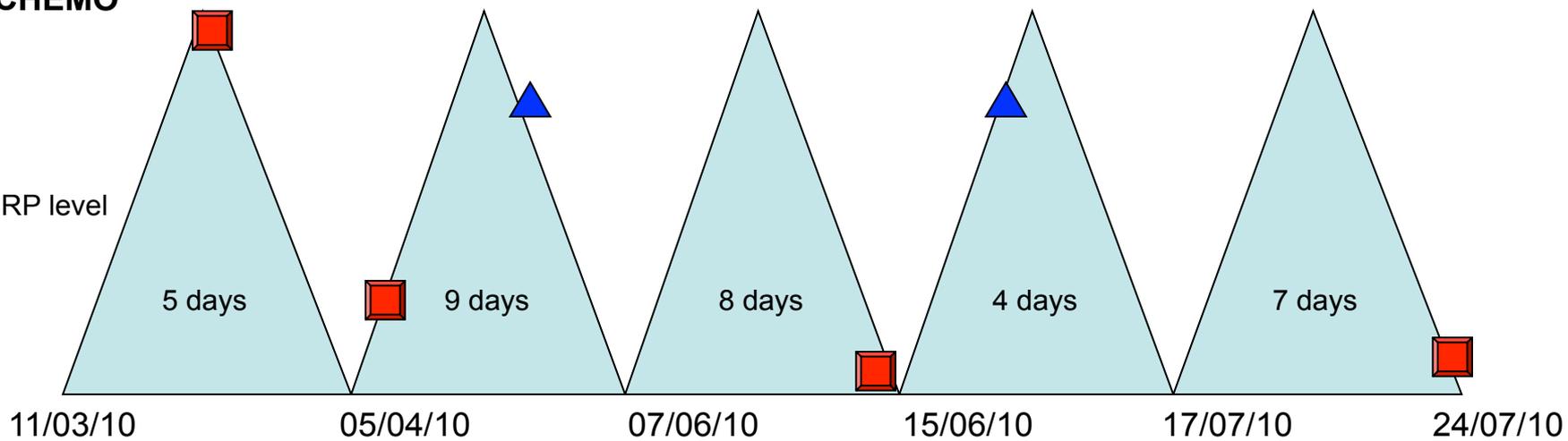
VAX



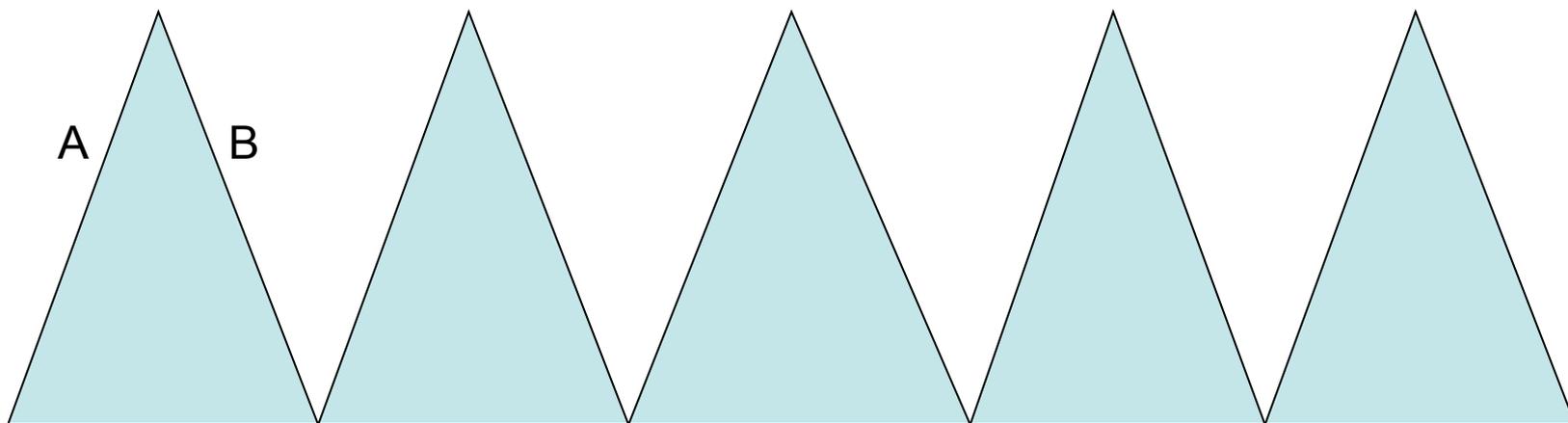
CHEMO



CRP level



 Complete Response



C

CRP identifies homeostatic immune oscillations in cancer patients: a potential treatment targeting tool? Coventry BJ, Ashdown ML, Quinn MA, Markovic SN, Yatomi-Clarke SL, Robinson AP *J Transl Med* 2009.;7: 102. Review.

A Matter of Time. Ashdown ML Coventry BJ *Australasian Science* 2010 May: 18-20.

Immuno-Chemotherapy Using Repeated Vaccine Treatment Can Produce Successful Clinical Responses in Advanced Metastatic Melanoma. Coventry BJ, Hersey P, Halligan A-M, Michele A *Journal of Cancer Therapy*, 2010, 1: 205-213.

IMMUNE THERAPIES FOR CANCER: BIMODALITY - THE BLIND SPOT TO CLINICAL EFFICACY – LOST IN TRANSLATION Coventry, B; Ashdown, M; Markovic, S *SITC Journal of Immunotherapy* 2011, Oct: 717.

The dynamic human immune response to cancer: it might just be rocket science. Holtan et al. *Immunotherapy* (2011) 3(9), 1021–1024

Fluctuation of Systemic Immunity in Melanoma and Implications for Timing of Therapy. Leontovich A, Dronca R, Suman VJ, Ashdown ML, Nevala WK, Thompson MA, Robinson A, Kottschade LA, Kaur JS, McWilliams RR, Ivanov LV, Croghan GA, Markovic SN *Frontiers in Bioscience* E4, 958-975, January 1, 2012 [in Press]

Coventry BJ, Ashdown ML. **Complete clinical responses to cancer therapy caused by multiple divergent approaches: a repeating theme lost in translation.** Cancer Management Res. 2012;4:137-149.

Coventry BJ, Ashdown ML. **The 20th anniversary of interleukin-2 therapy: bimodal role explaining longstanding random induction of complete clinical responses.** Cancer Management Res. 2012;4:215-21.

Cancer Mortality Data

- ***Successful Cancer Therapy remains an international unsolved problem.***

New Trial Commencing

**'TIMED' vs 'UNTIMED' Vaccine +/-
Oral Chemotherapy**

Candidate Molecules for Serial Monitoring

- **CRP**
- **SAA**
- **IL-2R soluble**
- **IL-2 cytokine**
- **γ IFN**

The Complete Response Probability Equation

$$0.07_{(P_{CR})} \approx \frac{W_{Rx}}{\lambda_{IC}}$$

λ_{IC} = Immune Cycle Periodicity (~7 days)

W_{Rx} = Width of Therapeutic Window (~12hrs or 0.5 day)

$P_{(CR)}$ = Probability of a CR (0.5/7; 1:14 or 0.07, or 7%)

Conclusion

- **MONITORING**
- **IMMUNE SYNCHRONISATION OF THERAPY**
- **2 POSTERS**

CONCLUSIONS

- **Antigen Recognition does not appear to be the problem**
- **Repeated Persistent Vaccinations / Cell Damage**
 - **Re-Directs the In-vivo Immune Response**
- **Immune Oscillation from Chronic Stimulation**
 - **offers repeated therapeutic opportunity**
- **Missing the ‘window’ for immune re-direction**
 - **can be corrected by repeated dosing**
- **Cure is likely to reside in the TIMING of dosing**

CONCLUSIONS

Close SERIAL MONITORING IS ESSENTIAL

to

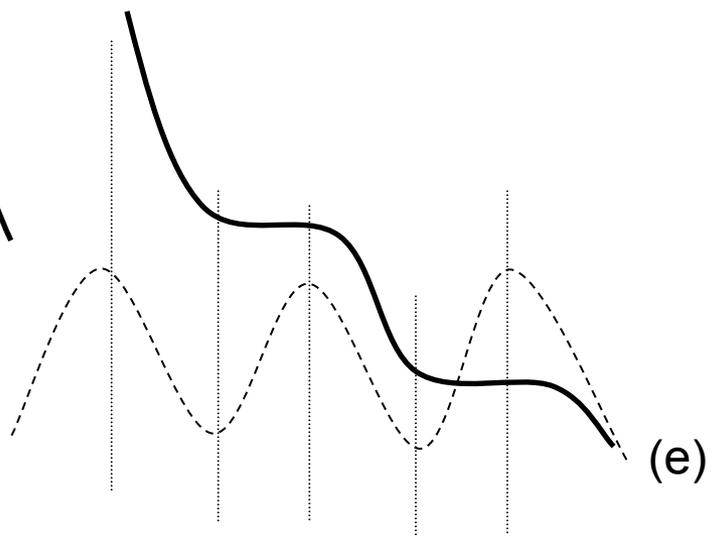
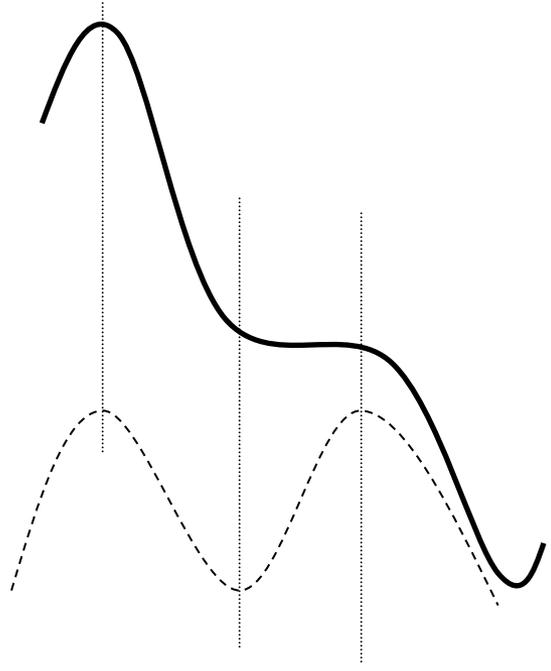
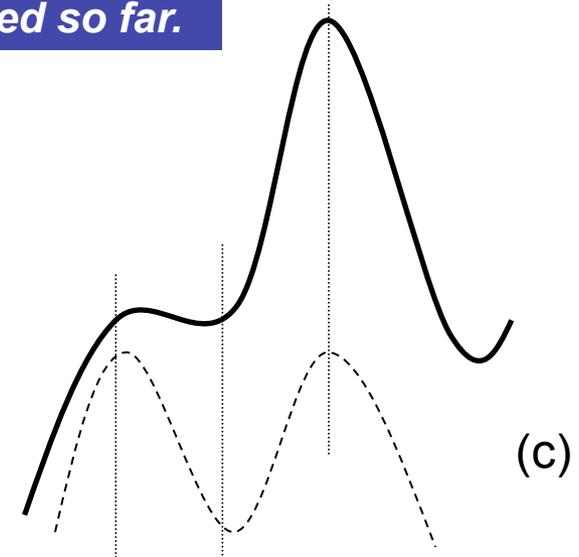
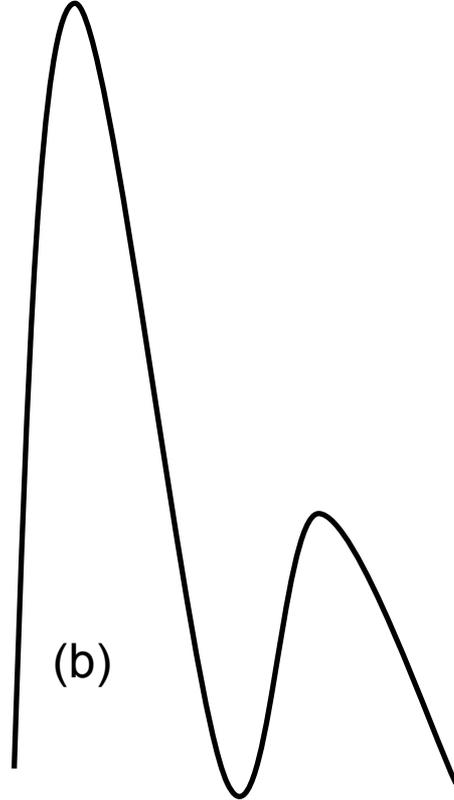
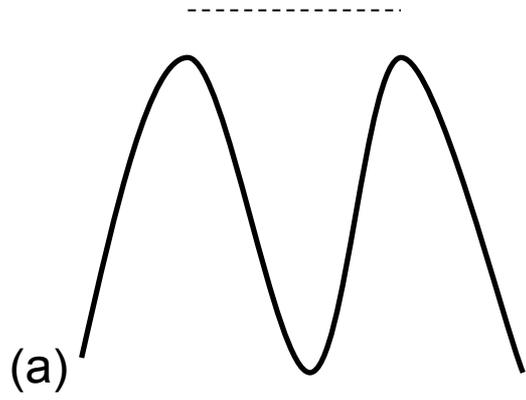
determine when to vaccinate or treat

with immuno-modulatory agents

ADDITIONAL SLIDES

Serial CRP waveforms.....experienced so far.

Wavelength ~7 days



"....why hasn't Coley's approach been forged into a widely available therapy with a predictable benefit for cancer patients....."

The best reason,...

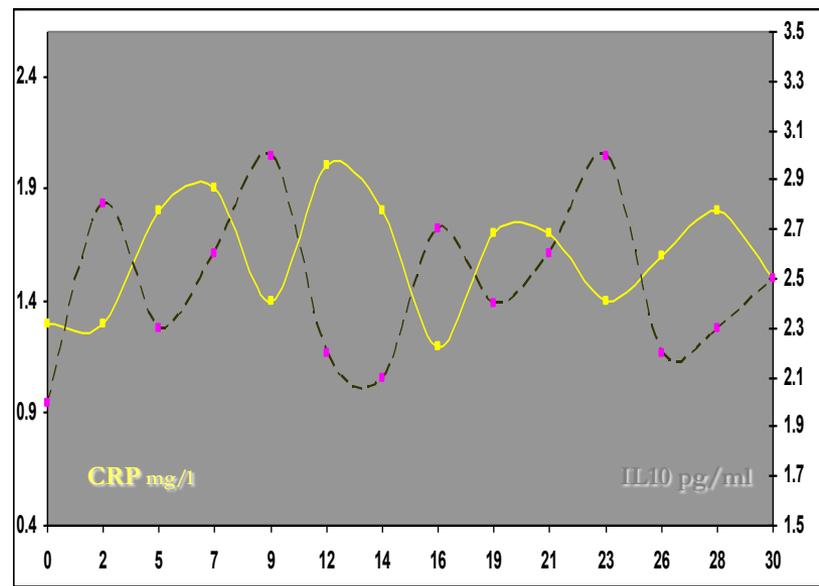
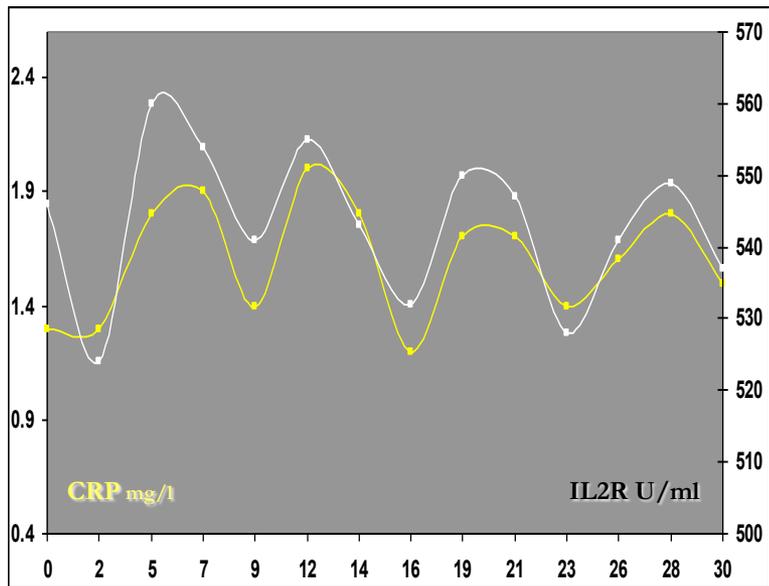
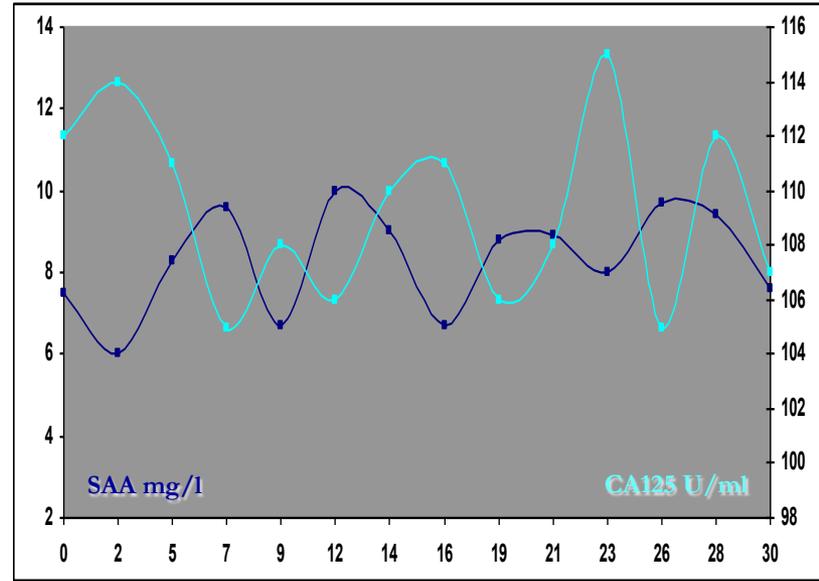
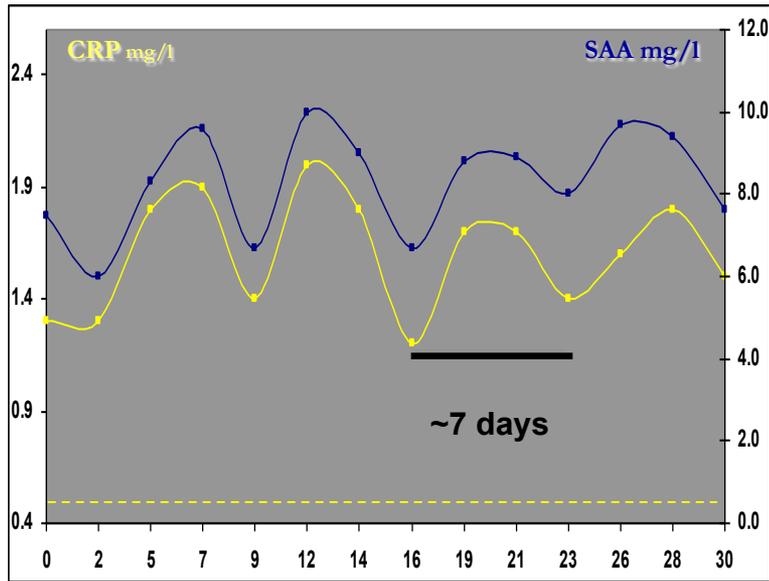
...**science had to catch up** with the Coley phenomenon and that the cellular and molecular language of inflammation and immunity had to be understood before the forces that Coley unleashed could be predictably translated into tumor cell destruction."

- Lloyd J. Old..1993 immunology symposium re Coley:
Commotion in the Blood – Steven S. Hall 1996

The Value of Health and Longevity

Murphy & Topel, Uni Chicago. Journal of Political Economy Vol 114, No.5: 2006

“... a permanent 1 percent reduction in mortality from cancer has a present value to current and future generations of Americans of nearly \$500 billion, whereas a cure (if one is feasible) would be worth about \$50 trillion.



Patient FO. Serial acute phase marker, cytokine & cancer marker fluctuations in a late stage asymptomatic ovarian cancer patient (as marked) over a 4 week period indicating a periodicity of ~7 days (Quinn MA & Ashdown ML).

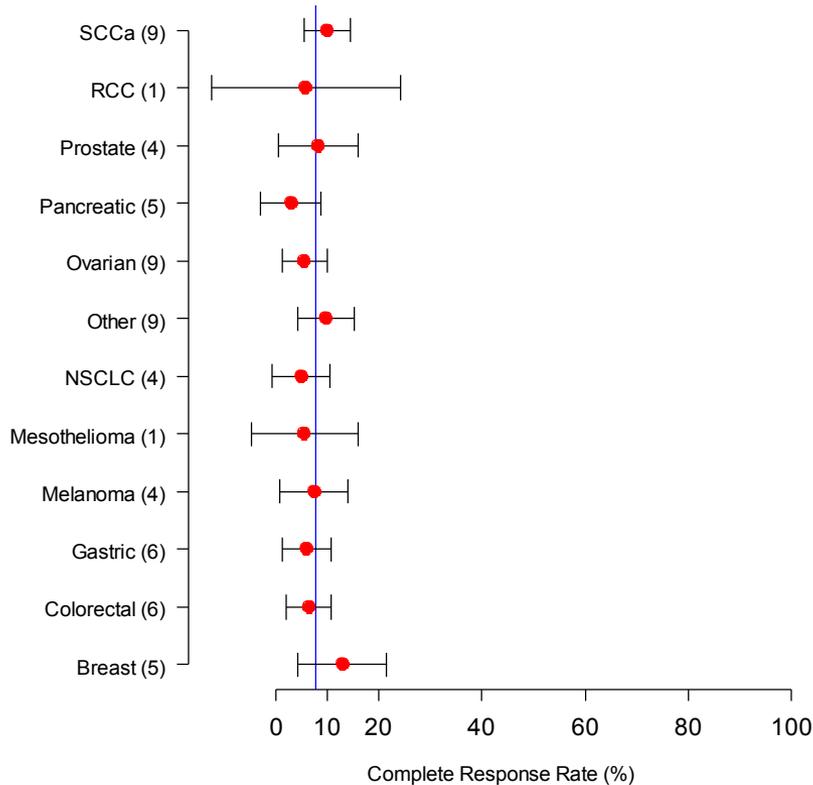
Complete Response Rates – various modalities

Agent	Indication	Reported CR Rate (average)
Coley Toxins (c 1903)	Sarcomas / Carcinomas	~ 10%
Std Cytotoxic agents Large Clin Trial MetaAnalysis	Various Solid Cancers	~ 7%
IL2 (1988 – 2010)	Advanced Melanoma/ RC (OvCa)	~7% (10%)
Ontak (2003- 2010)	Advanced Melanoma/CTCL	~ 5-10%
DC Vaccine (QIMR)	Advanced Melanoma	~ 10%
Provenge (Dendreon)	Prostate	~ 0.3%
CSL/ Ludwig (NYESO-1)	Melanoma	~ 0%
Median CR rate		7%

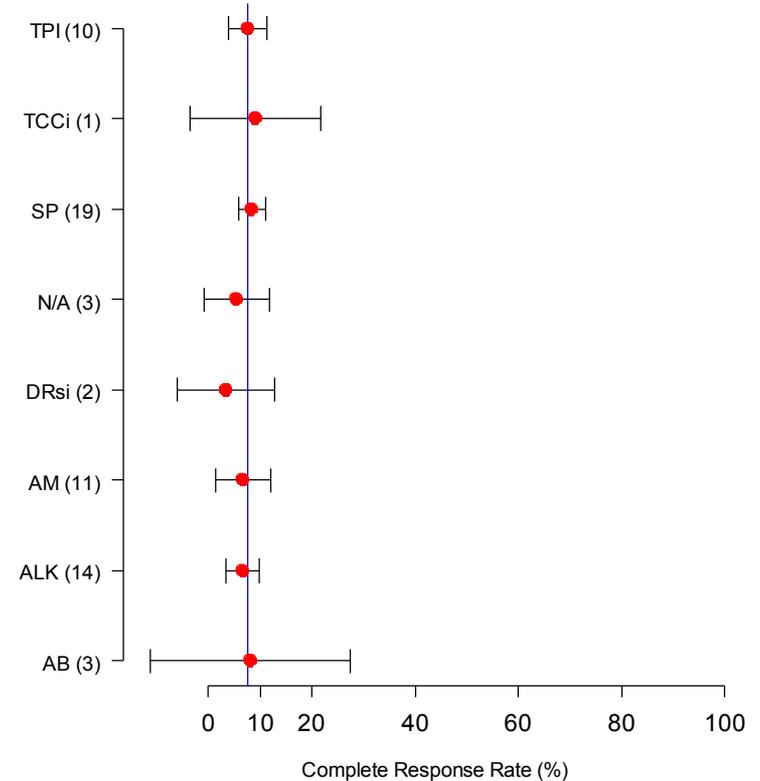
CR by Cancer Type

CR by Drug Type

(a)

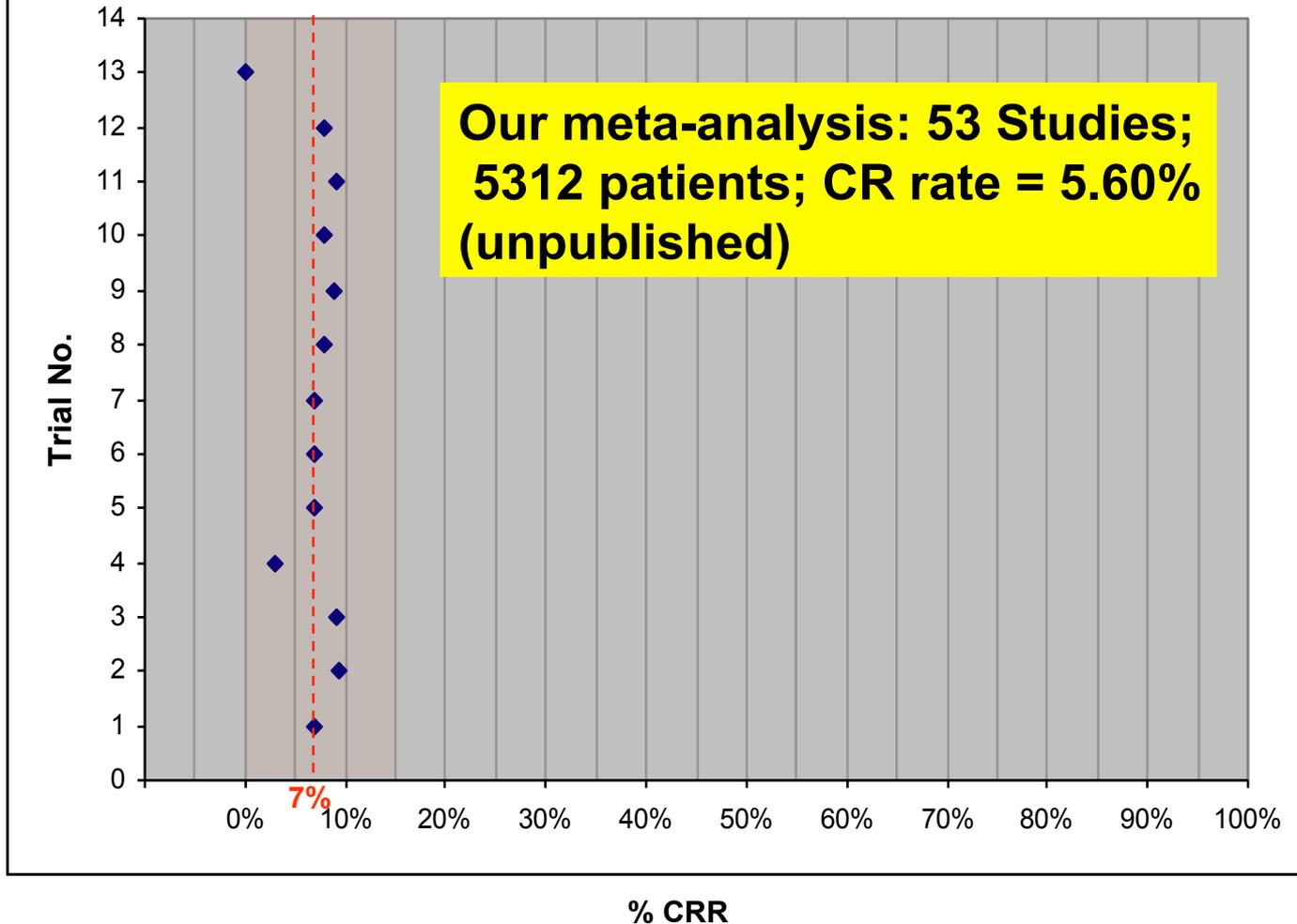


(b)



When considered by cancer type and by drug type there was no evidence that any particular cancer or drug was higher or lower than 7% CR [n = 68 Chemotherapy Trials 2000-2007]. 52

IL2 Rx Trials Complete Response Rates, MM &RCC*



Grivas P & Redman B et al.
Current Clinical Pharmacology, 2011, 6, 151-163

**NB. 2015 patients in 13 trials
Av CR Rate = 6.7%**

Complete Response Rates – various modalities

Agent	Indication	Reported CR Rate (average)
B-Raf Inhibitor Roche	Melanoma	6%
B-Raf Inhibitor GSK	Melanoma	4%
B-Raf Inhibitor GSK/ Mek	Melanoma	6%/ 9%
CTLA-4 Mabs	Advanced Melanoma	~ 0.2%/ 1.5%
PD-1/ PD-L1	Melanoma	1%/ 6%
CTLA4/ PD-1	Melanoma	9.6%
Median CR rate		6 %

Complete Response Rates – various modalities

Agent	Indication	Reported CR Rate (average)
VCML Vaccine	Advanced Melanoma	~18% (n=37); 18(n=54)
CTLA-4 / IL-2	Advanced Melanoma	17%
Median CR rate		17.5 %

The Price We Pay for Progress: A Meta-Analysis of Harms of Newly Approved Anticancer Drugs

Saroj Niraula, Bostjan Seruga, Alberto Ocana, Tiffany Shao, Robyn Goldstein, Ian F. Tannock, and Eitan Amir

38 RCT Studies of 38 targeted agents 2000-2010
for therapy of advanced solid malignancies

Agent Toxicity-related death increased - OR 1.40

Treatment discontinuation greater - OR 1.33

Grade III/IV Toxicity increased - OR 1.52

Conclusion: ‘Off target’ effects of ‘targeted’ agents overall appear more severe and extensive than many ‘non-targeted’ agents.

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Cancer Patients