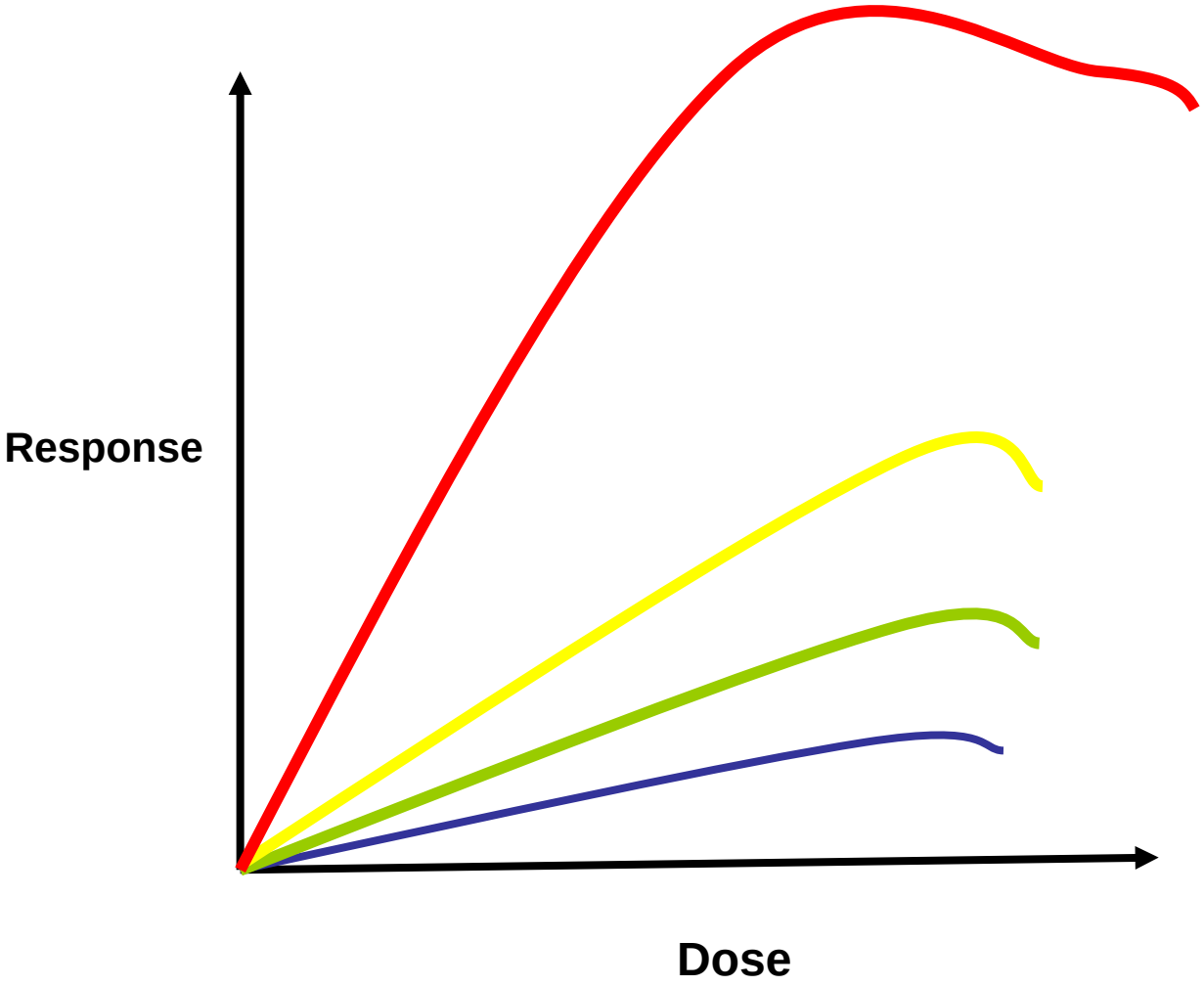
Combination opportunities in immunotherapy with **immunostimulatory mAb.**

SYNERGY

***syn-ergos*, *συνεργός*, meaning 'working together'.**

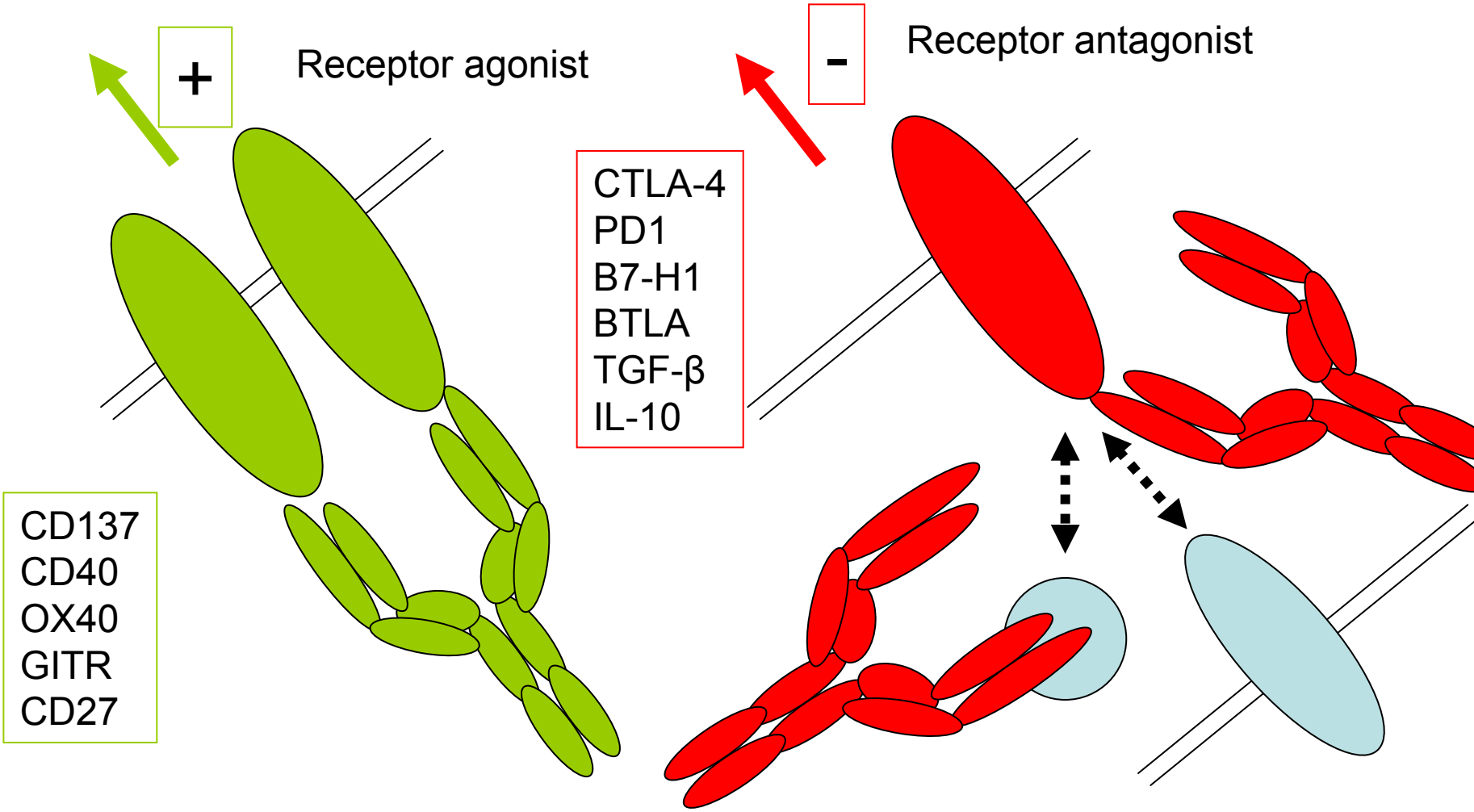
SYNERGY

TWO AGENTS ACTING TOGETHER
SUCH THAT THE WHOLE IS GREATER THAN THE SUM OF THE PARTS



1. Different **mechanism of action.**
2. **Cooperative** effect

What is an immunostiulatory monoclonal antibody?



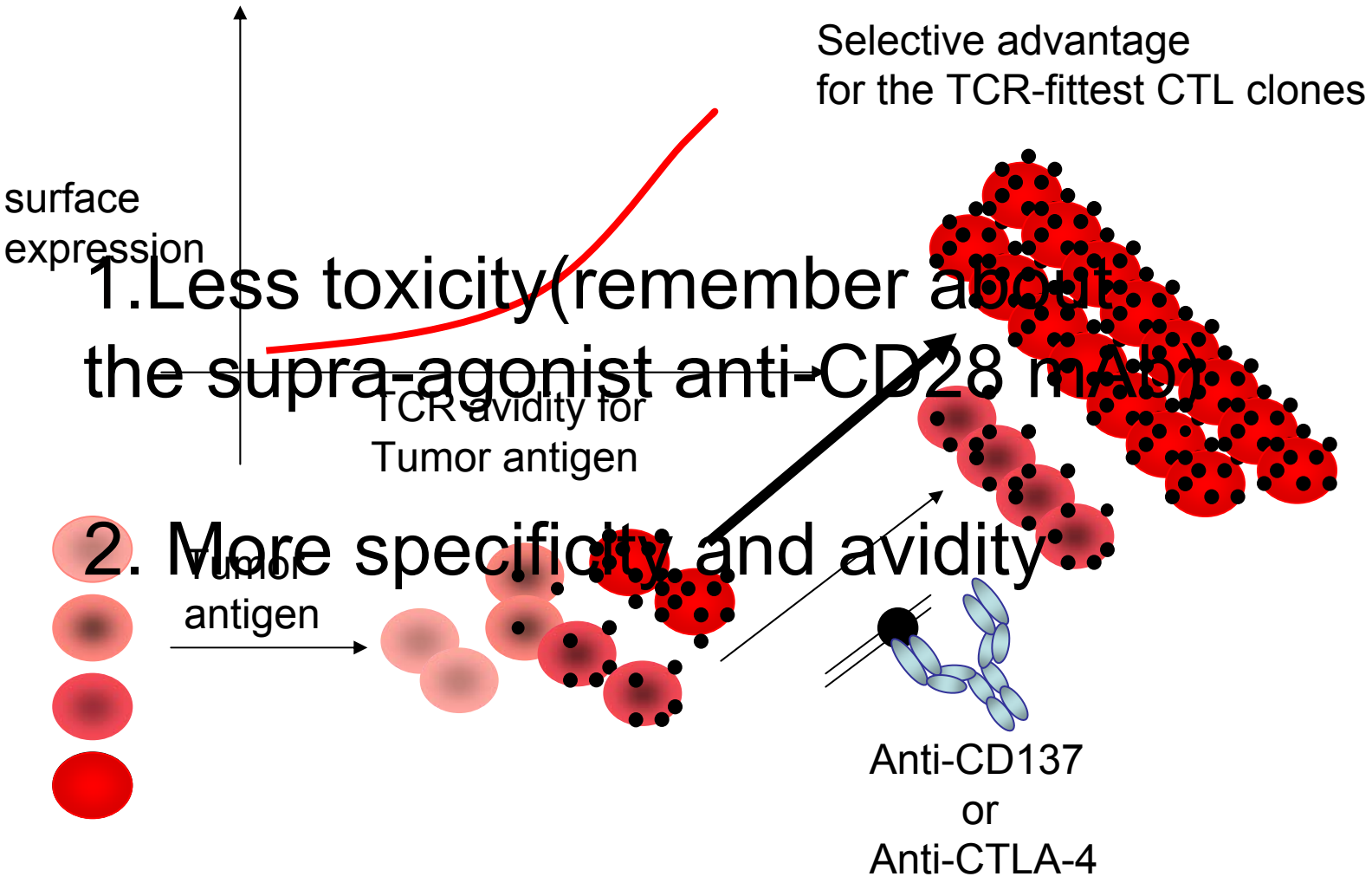
Archivum Immunologiae et Therapiae Experimentalis, 2002, 50, 13–18
PL ISSN 0004-069X

Effective Tumor Immunotherapy: Start the Engine, Release the Brakes, Step on the Gas Pedal, ... and Get Ready to Face Autoimmunity

Iñigo Tirapu, Guillermo Mazzolini, Mercedes Rodriguez-Calvillo, Ainhoa Arina, Belen Palencia, Izaskun Gabari and Ignacio Melero*

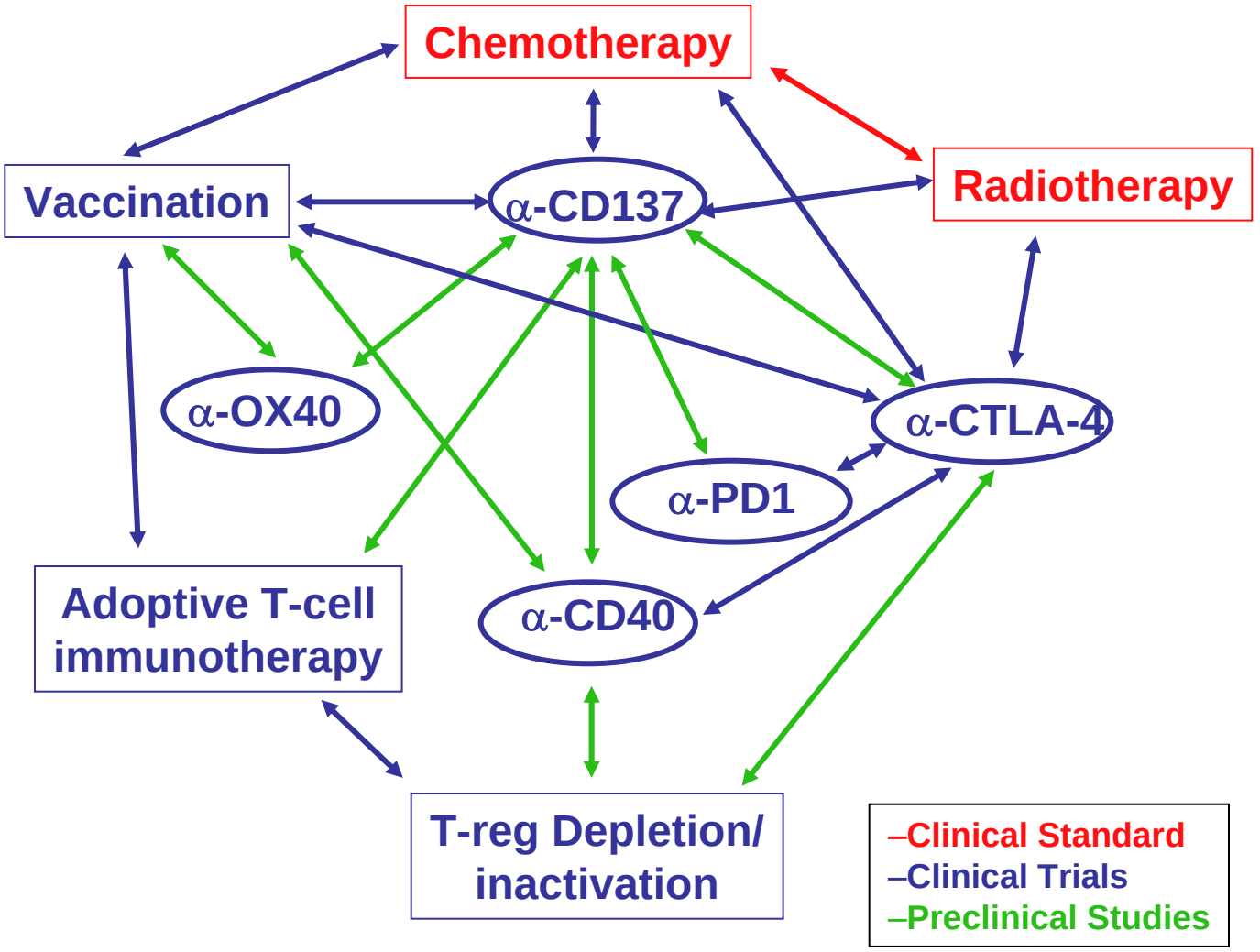
The master switch if you please?

REASONS TO PLAY WITH INDUCIBLE TARGETS



1. Less toxicity (remember about the supra-agonist anti-CD28 mAb)

2. More specificity and avidity…



Melero I. *et al* Nat rev cancer (2007)

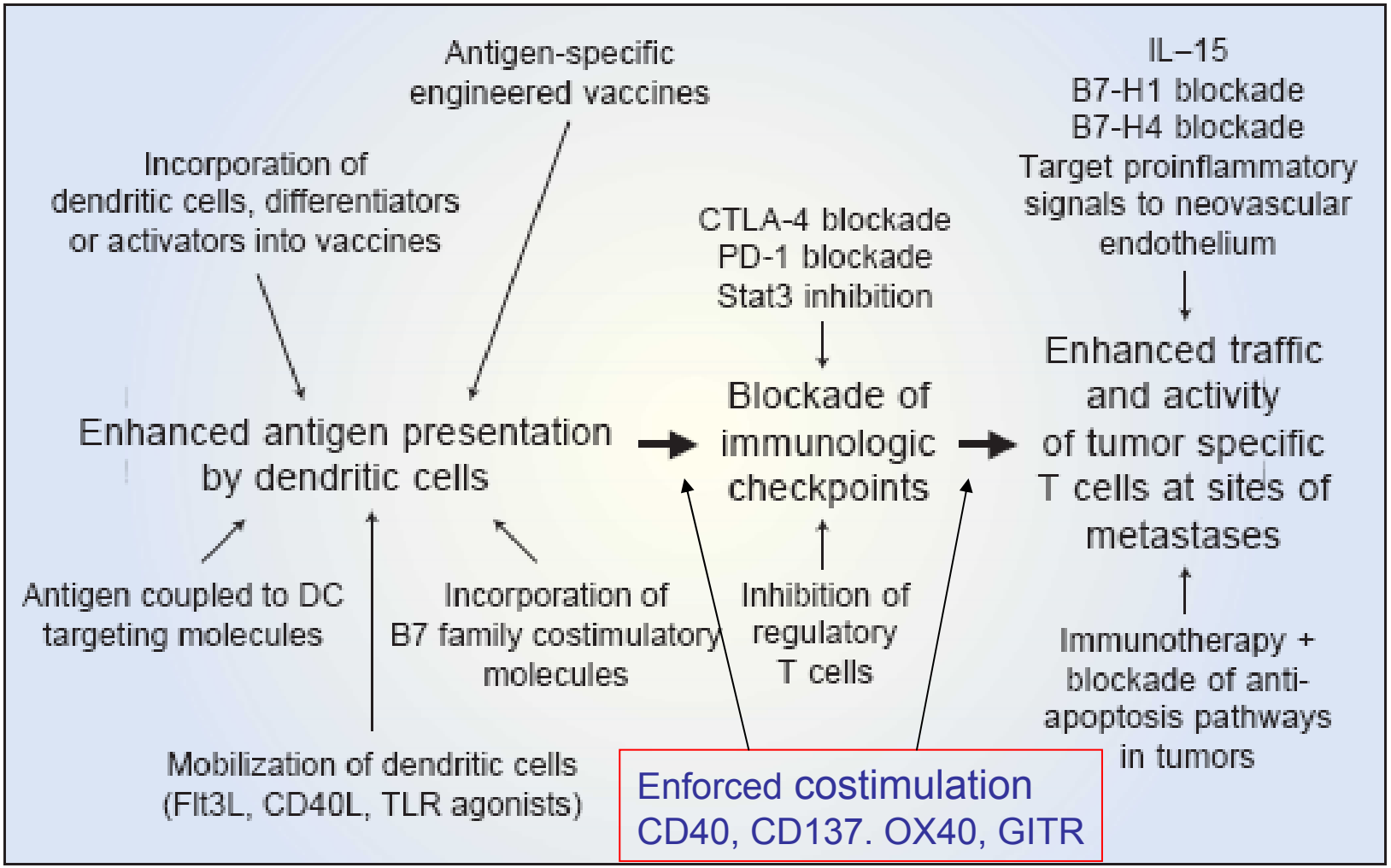


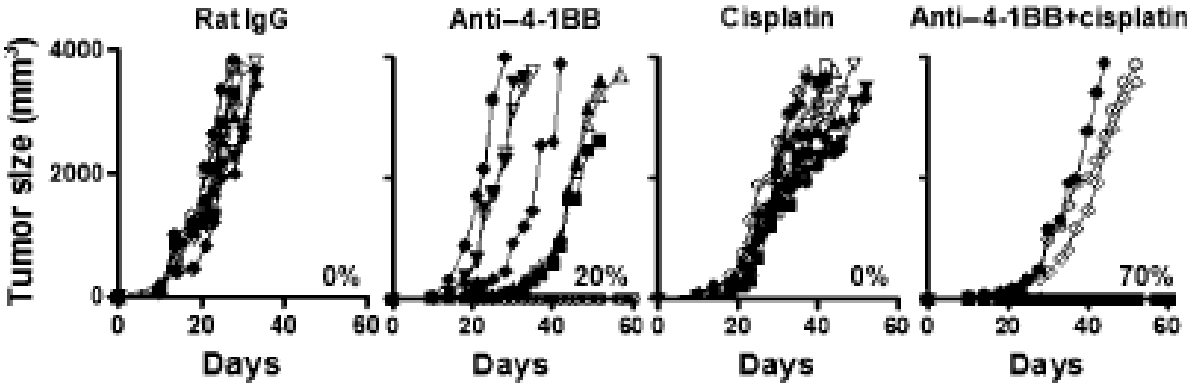
Figure 1 Multiple points of intervention to engender successful cancer immunotherapy. Successful strategies will involve the integration of multiple elements that activate dendritic cell presentation of antigens to most effectively initiate immune responses, block immunologic checkpoints to amplify these responses and, finally, enhance the traffic and activity of T cells against metastatic tumors. The specific examples of molecular pathways shown for each step do not represent a comprehensive list. DC, dendritic cell; TLR, toll-like receptor.

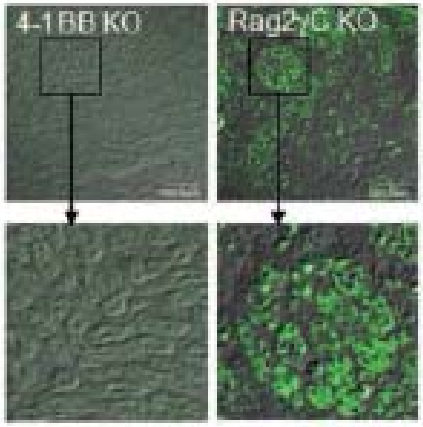
COMBINATION WITH STANDARD TREATMENTS (chemotherapy)

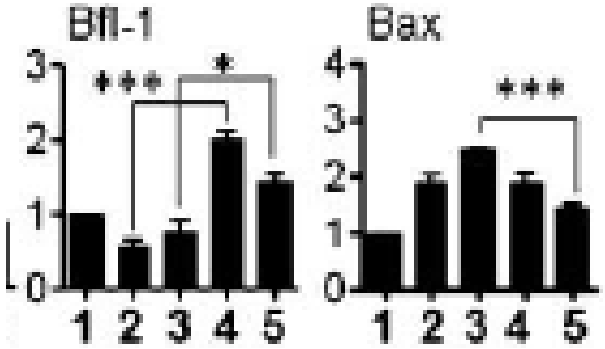
- Will happen anyway
- Maybe not the most efficacious combinations
- Interesting points of synergy:
  - Immnogenic cell death
  - Lymphopenia
  - Nice surprises

Combination Therapy with Cisplatin and Anti–4-1BB: Synergistic Anticancer Effects and Amelioration of Cisplatin-Induced Nephrotoxicity

Young H. Kim,[1] Beom K. Choi,[1] Kwang H. Kim,[1] Sang W. Kang,[2] and Byoung S. Kwon[1,3]



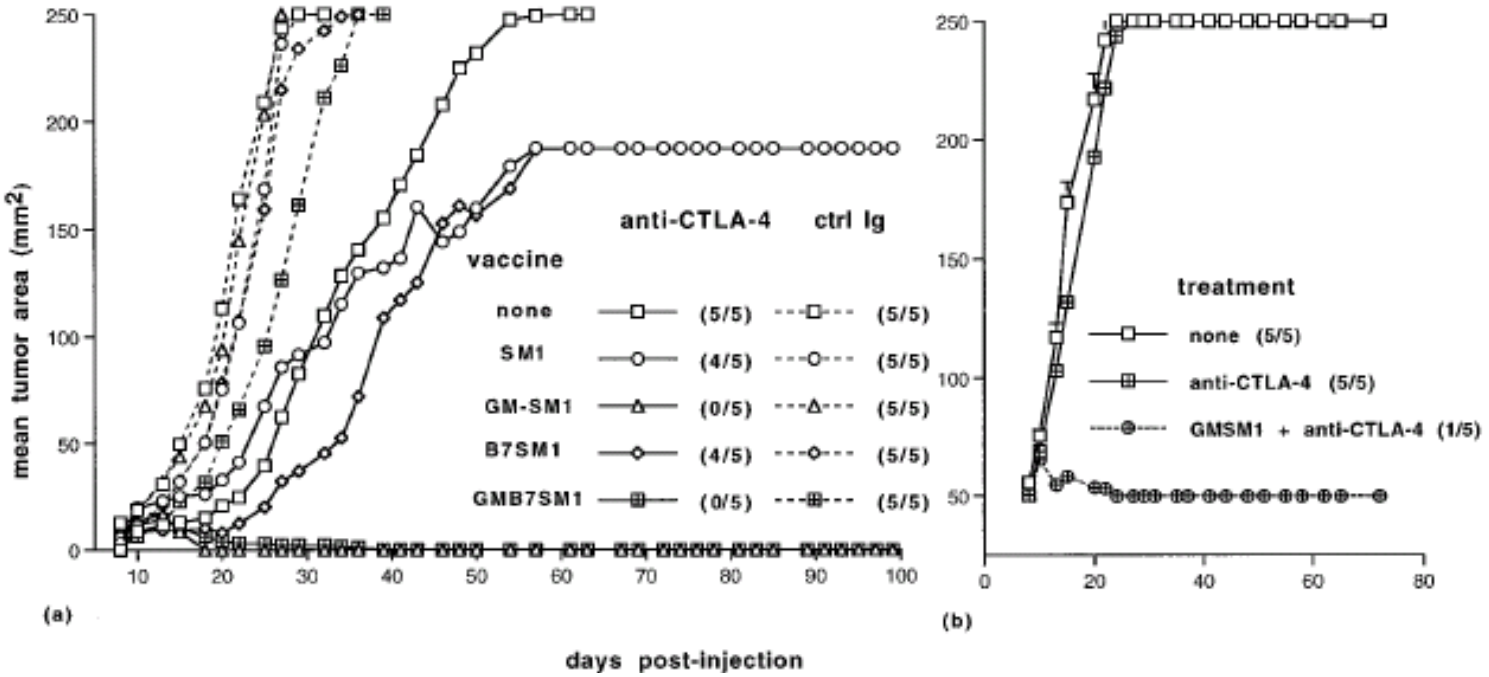




Combinations with VACCINES

CTLA-4 blockade synergizes with tumor-derived granulocyte–macrophage colony-stimulating factor for treatment of an experimental mammary carcinoma

ARTHUR A. HURWITZ*, TINA F.-Y. YU, DANA R. LEACH, AND JAMES P. ALLISON



Provision of antigen and CD137 signaling breaks immunological ignorance, promoting regression of poorly immunogenic tumors

Ryan A. Wilcox,[1] Dallas B. Flies,[1] Gefeng Zhu,[1] Aaron J. Johnson,[1] Koji Tamada,[1] Andrei I. Chapoval,[1] Scott E. Strome,[2] Larry R. Pease,[1] and Lieping Chen[1,3]

Table 1
Treatment of mice bearing established C3 tumors

Treatment[A]				
Ab	Peptide	Tumor-free/total (%)	Mean tumor diameter (mm)[B]	*P* value[C]
2A	E7 (aa 49–57)	16/38 (42%)	7.6 ± 2.4	–
Rat IgG	E7 (aa 49–57)	0/11 (0%)	10.5 ± 3.0	0.017
2A	Vp2 (aa 121–130)	2/23 (9%)	11.4 ± 4.0	0.004
Rat IgG	Vp2 (aa 121–130)	0/8 (0%)	11.5 ± 3.5	0.005

[A]Mice were injected with 1×10^6 C3 cells. Two weeks later, mice were immunized with the indicated peptide, as previously described. On the day of immunization and again 3 days later, mice were given 100 μg of either mAb 2A or a control rat IgG intraperitoneally. Tumor size was assessed weekly. Data shown were pooled from several experiments. [B]Twenty-one days after treatment, the mean tumor diameter was calculated for those tumors that had failed to completely regress. [C]The unpaired Student *t* test was used to calculate *P* values, comparing the mean tumor diameter of the treatment group that received both the E7 peptide and mAb 2A with that of the control group.

Immunologic and clinical effects of antibody blockade of cytotoxic T lymphocyte-associated antigen 4 in previously vaccinated cancer patients

F. Stephen Hodi[a,b], Marcus Butler[a], Darryl A. Oble[c], Michael V. Seiden[d,e], Frank G. Haluska[f], Andrea Kruse[a], Suzanne MacRae[a], Marybeth Nelson[a], Christine Canning[a], Israel Lowy[g], Alan Korman[g], David Lautz[h], Sara Russell[h], Michael T. Jaklitsch[h], Nikhil Ramaiya[i], Teresa C. Chen[j], Donna Neuberg[k], James P. Allison[b,j], Martin C. Mihm[c], and Glenn Dranoff[a]

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 19, 2010 VOL. 363 NO. 8

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.

Combinations with vaccines

CCR Translations

Palettes of Vaccines and Immunostimulatory Monoclonal Antibodies for Combination

□□*Commentary on Li et al., p. 1623*

Ignacio Melero,[1,2] Ivan Martinez-Forero,[1] Juan Dubrot,[1] Natalia Suarez,[2] Asis Palazón,[1] and Lieping Chen[3]

- Especially important in the minimal residual disease setting.

….What about turning one/some of the existing tumor lessions into a vaccine?

1. Chemotherapy-induced immunogenic cell death.

2. Intratumoral injections of TLR agonists or cytokines
While causing some tissue destruction:
CpG, Poly I:C, Imiquimod, IL-12, IFNα, GM-CSF…

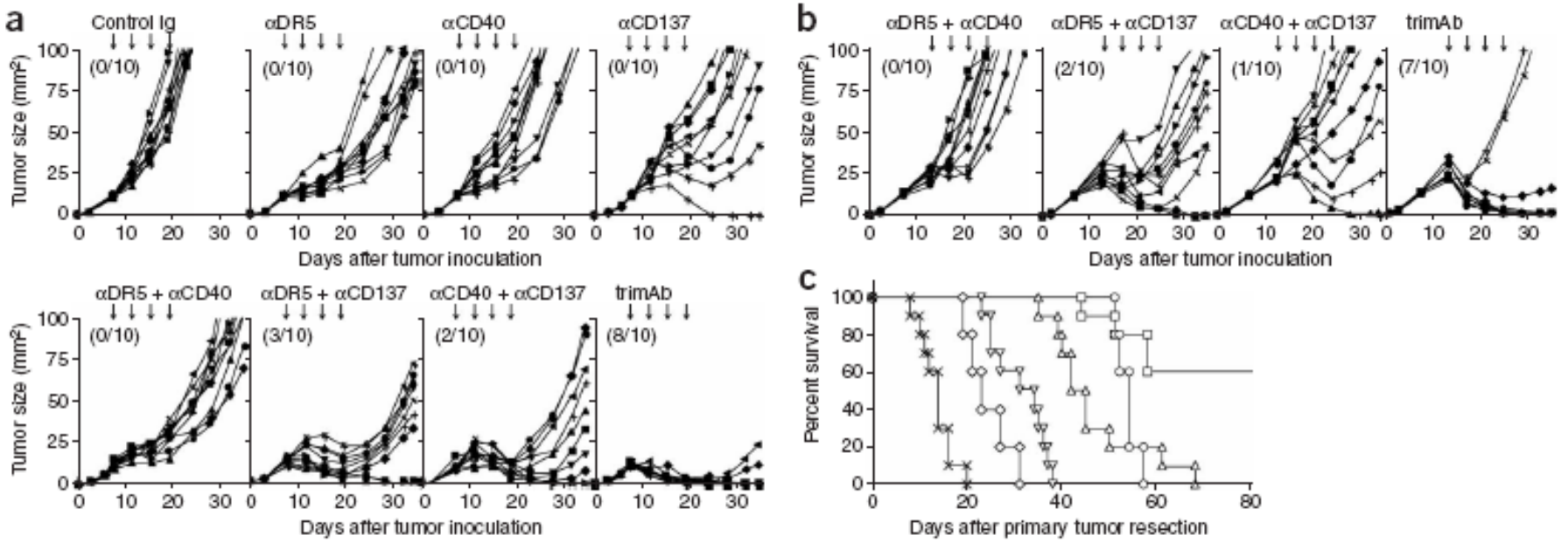
Follow research by Lawrence Zitvogel, Ron Levy…

COMBINATIONS AMONG IMMUNOSTIMULATORY MAB

nature medicine

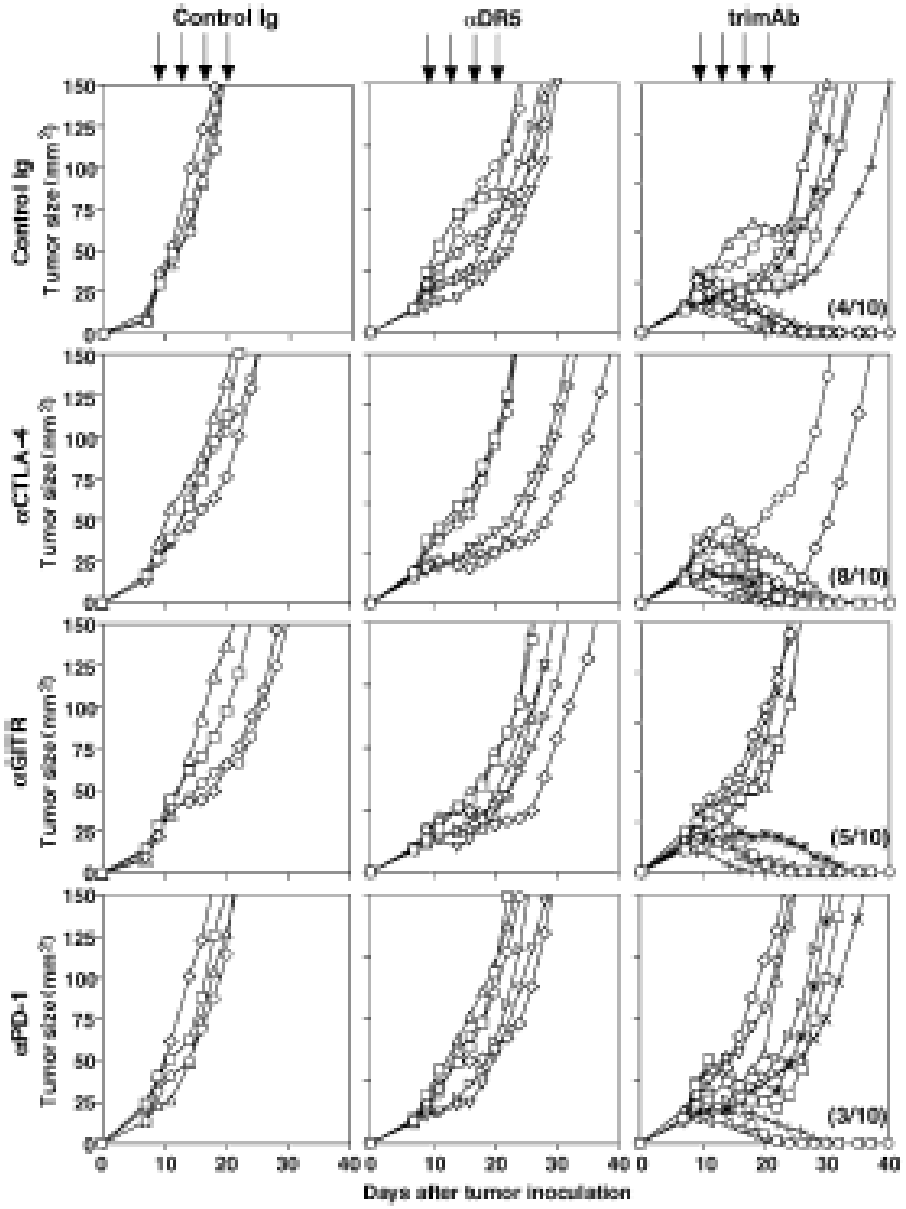
Eradication of established tumors in mice by a combination antibody-based therapy

Tomoyasu Uno[1,2], Kazuyoshi Takeda[1,3], Yuko Kojima[4], Hirohisa Yoshizawa[5], Hisaya Akiba[1], Robert S Mittler[6], Fumitake Gejyo[2], Ko Okumura[1], Hideo Yagita[1] & Mark J Smyth[3]



Trail-like induced tumor cell apoptosis+ DC maturation+ Tcell costimulation

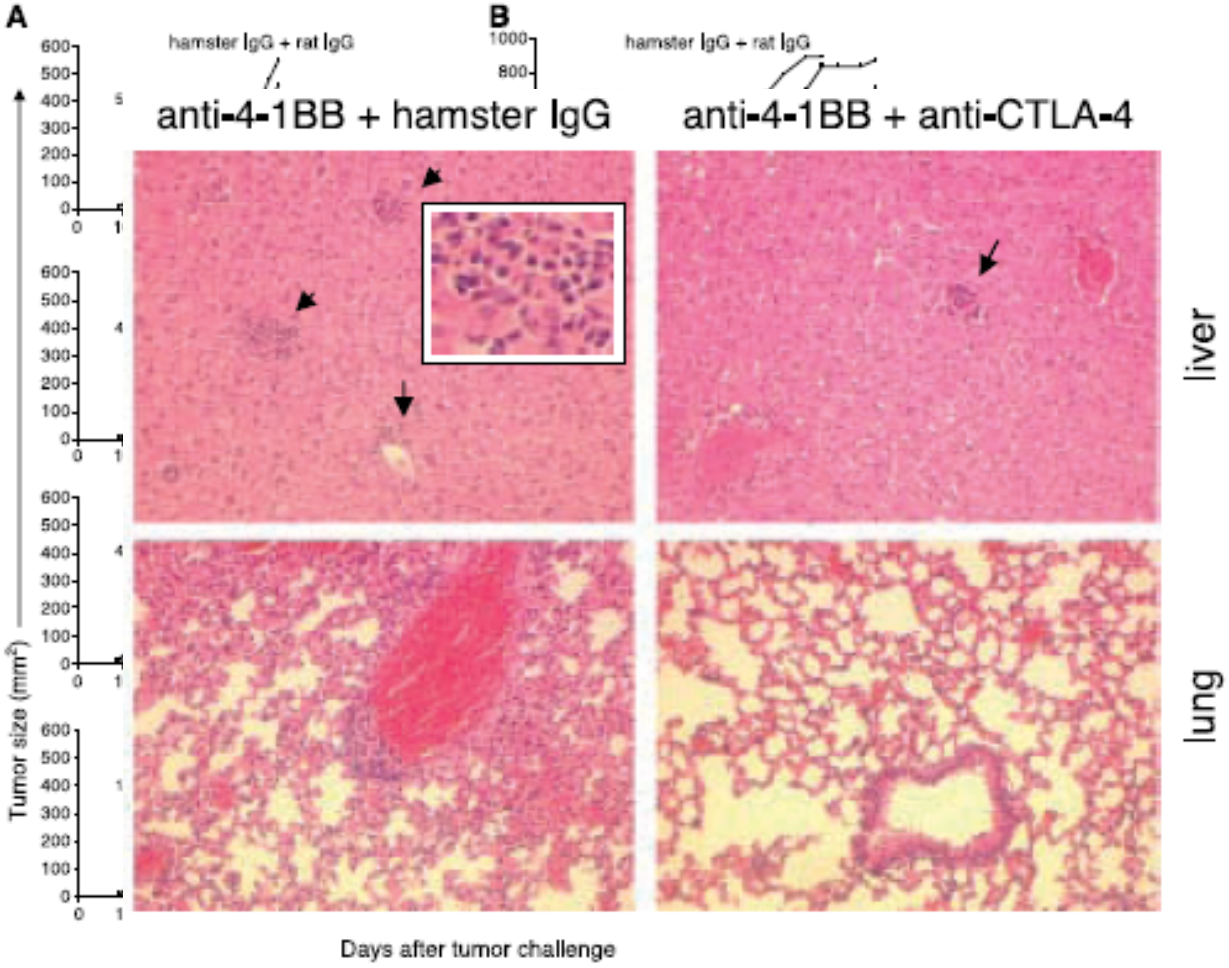
Furthermore…



	rejection rate
trimAb + Control Ig	4/10 2/5 2/5 3/6 : 11/26
trimAb + αCTLA-4	8/10 4/5 3/5 4/6 : 19/26 *
trimAb + αGITR	5/10 2/5 2/5 2/5 : 11/25
trimAb + αPD-1	3/10 2/5 2/5 3/6 : 10/26

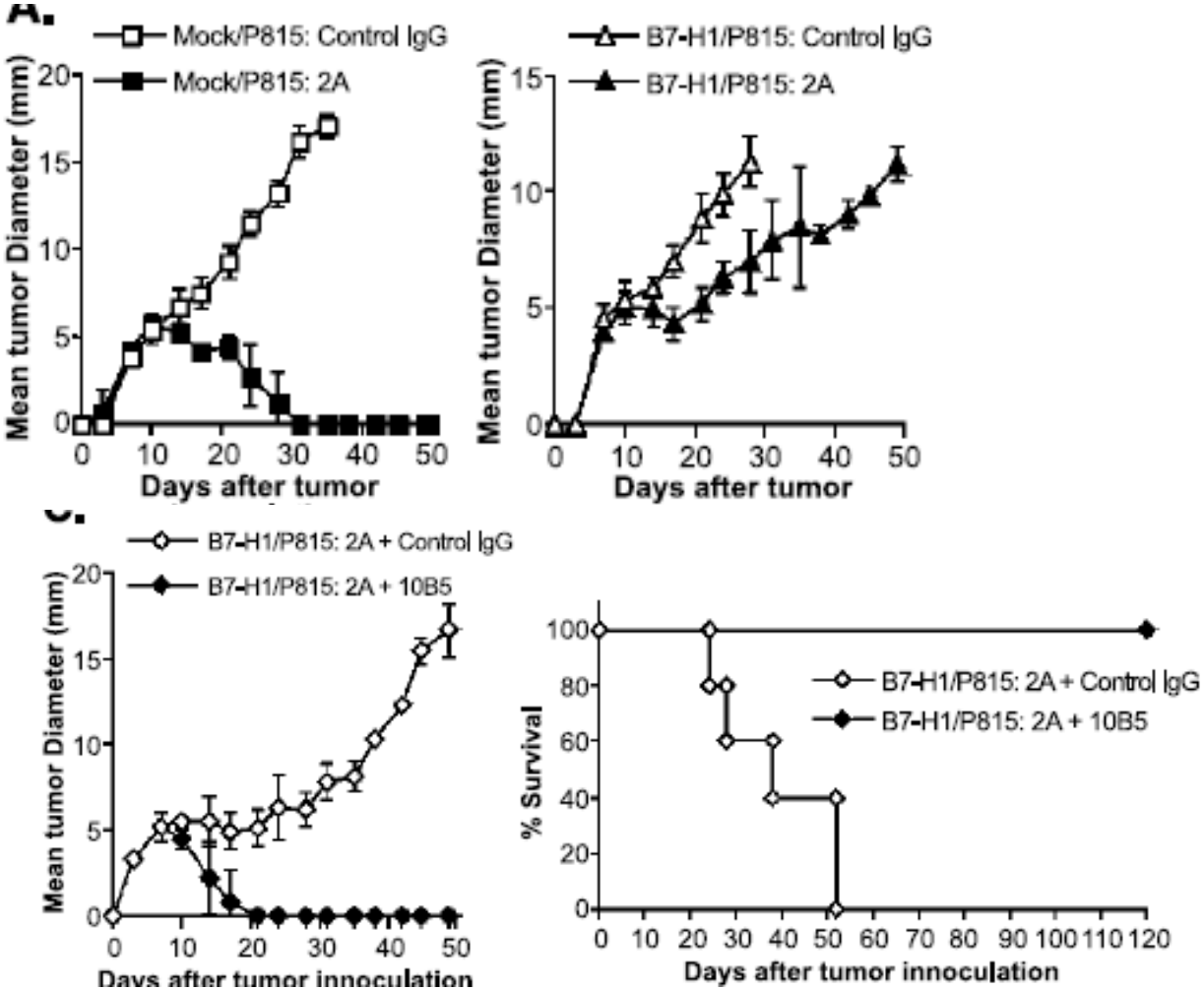
Combination Therapy with Anti–CTL Antigen-4 and Anti-4-1BB Antibodies Enhances Cancer Immunity and Reduces Autoimmunity

Ergun Kocak,[1,2] Kenneth Lute,[1] Xing Chang,[1] Kenneth F. May, Jr.,[1] Katie R. Exten,[1] Huiming Zhang,[1] Shahab F. Abdessalam,[2] Amy M. Lehman,[3] David Jarjoura,[3] Pan Zheng,[1] and Yang Liu[1]



Blockade of B7-H1 and PD-1 by Monoclonal Antibodies Potentiates Cancer Therapeutic Immunity

Fumiya Hirano,[1] Katsumi Kaneko,[1] Hideto Tamura,[1] Haidong Dong,[1] Shengdian Wang,[1,2] Masao Ichikawa,[1,2] Cecilia Rietz,[1,2] Dallas B. Flies,[1,2] Julie S. Lau,[1] Gefeng Zhu,[1,2] Koji Tamada,[1,2] and Lieping Chen[1,2]



European Journal of
Immunology

Optimising anti-tumour CD8 T-cell responses using combinations of immunomodulatory antibodies

Juliet C. Gray[1], Ruth R. French[1], Sonya James[1], Aymen Al-Shamkhani[1], Peter W. Johnson[2] and Martin J. Glennie[1]

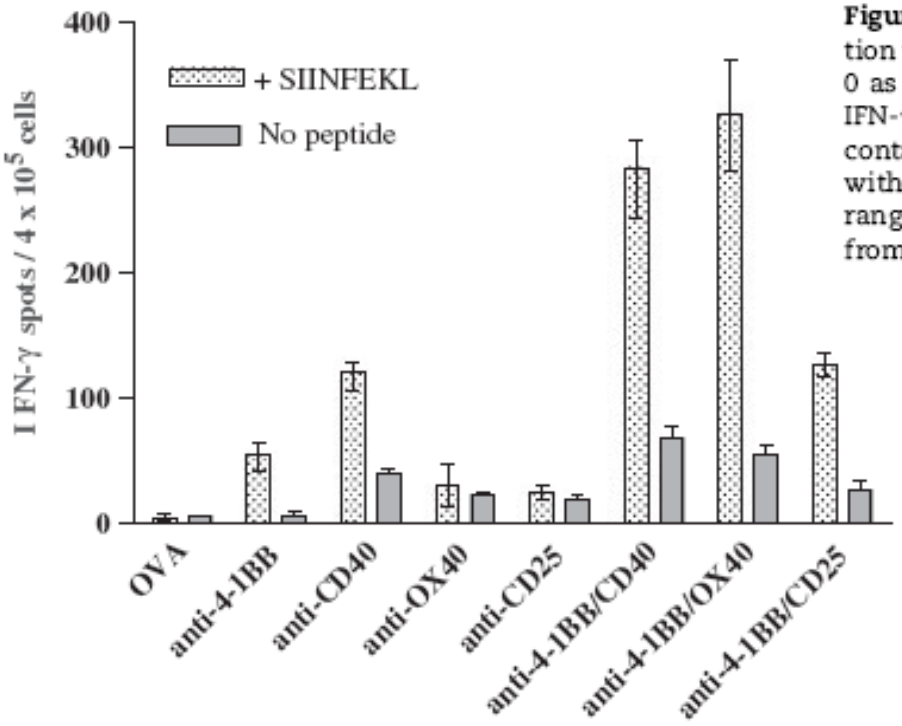


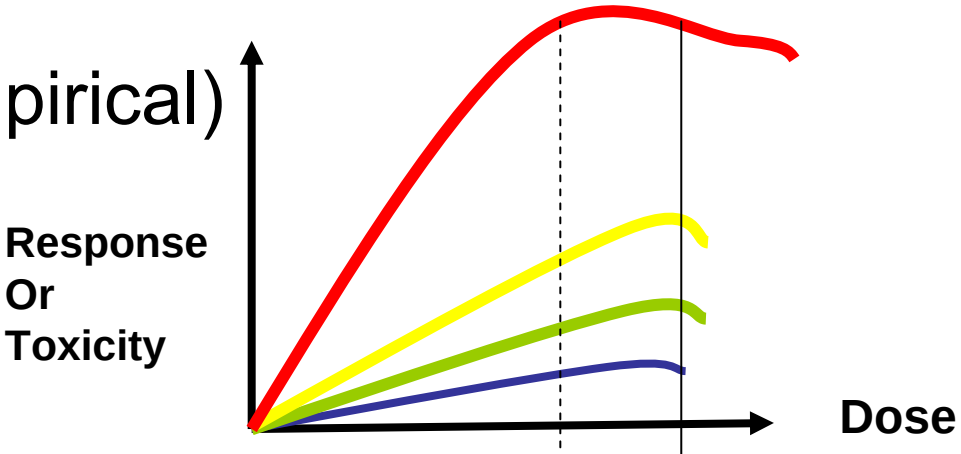
Figure 5. Endogenous SIINFEKL-specific T-cell responses to immunisation with OVA and mAb. Mice received OT-I cells, mAb and OVA on day 0 as in Fig. 1. Splenocytes were harvested on day 7 and assessed for IFN-γ secretion by ELISPOT. For each mouse, triplicate wells, each containing 4×10^5 splenocytes, were incubated for 24 h with and without 0.1 μM SIINFEKL peptide. The histogram shows the mean and range of the number of IFN-γ spots per 4×10^5 splenocytes. Data are from one of two experiments, each with 2 mice per group.

COMBINATIONS AMONG IMMUNOSTIMULATORY MABS

- Non-overlapping mechanism of action.
- Non-overlapping mechanism of toxicity.
- Driven by immune correlates and biomarkers.

PRE-POST TUMOR BIOPSIES.

- Business reasons weigh a lot but should follow good scientific reasons
- Dose optimization
- (and let us be very empirical)



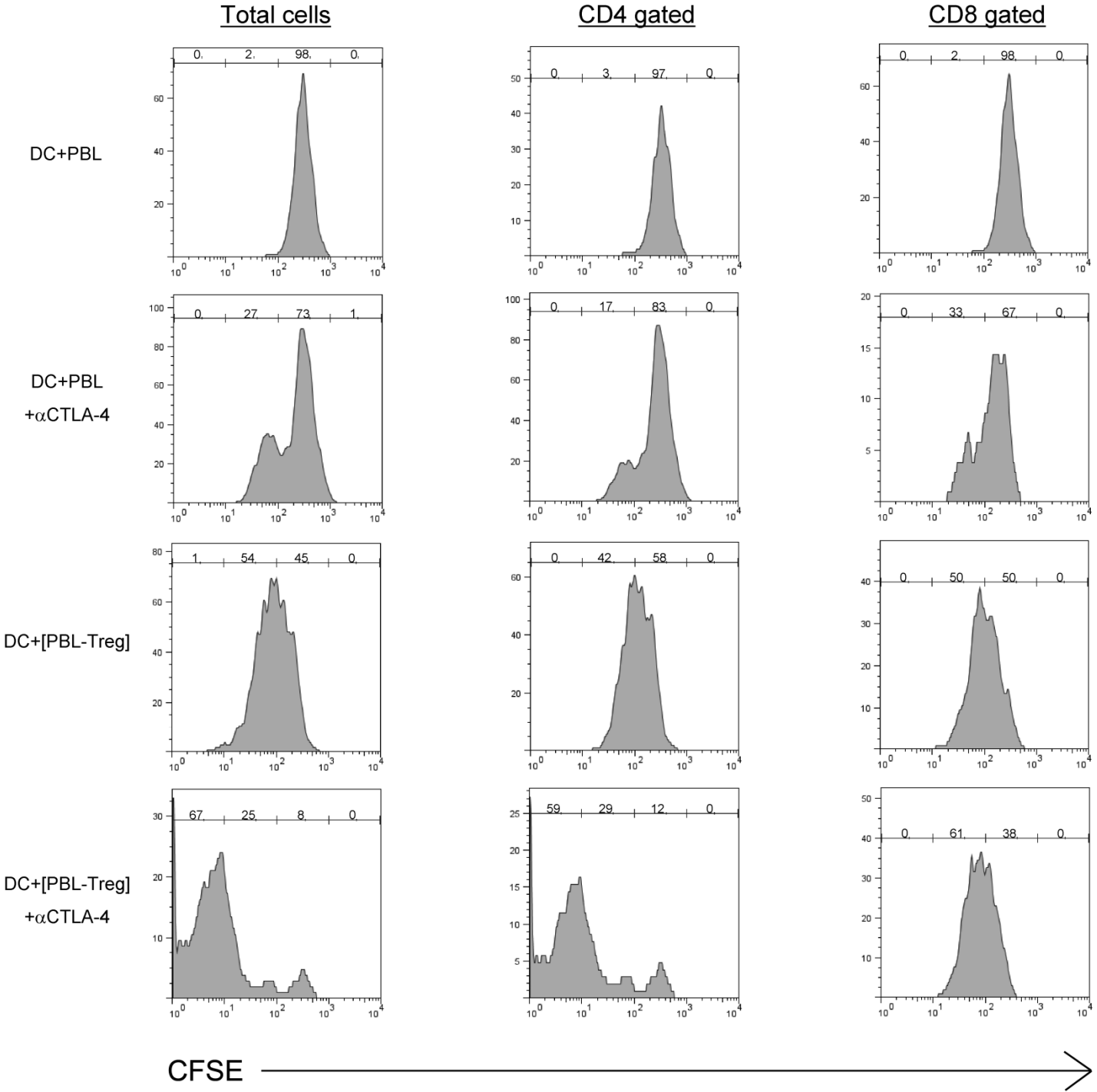
Do something on Treg and MDSC

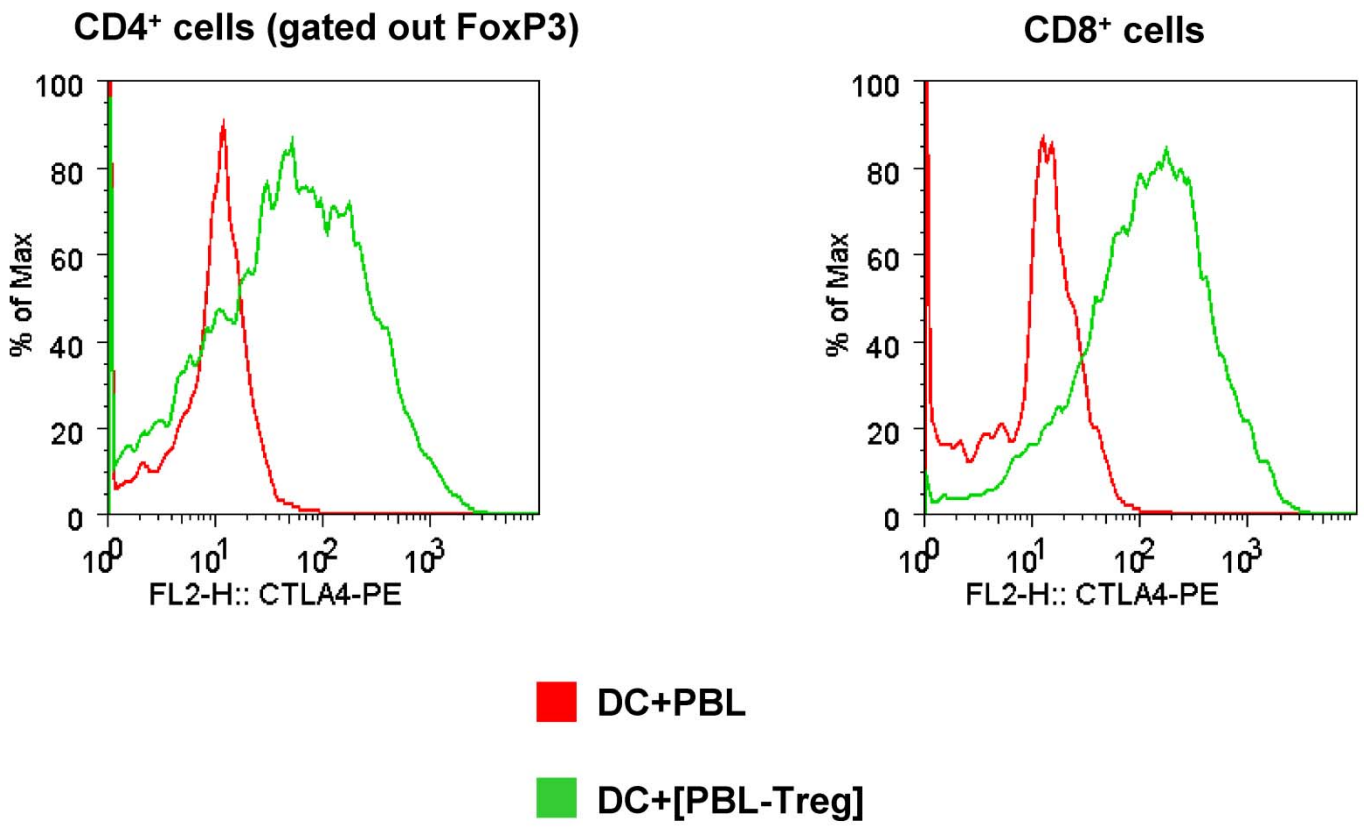
Synergism of Cytotoxic T Lymphocyte–associated Antigen 4 Blockade and Depletion of CD25$^+$ Regulatory T Cells in Antitumor Therapy Reveals Alternative Pathways for Suppression of Autoreactive Cytotoxic T Lymphocyte Responses

Roger P.M. Sutmuller,[1] Leonie M. van Duivenvoorde,[1]
Andrea van Elsas,[1] Ton N.M. Schumacher,[2] Manon E. Wildenberg,[1]
James P. Allison,[3] Rene E.M. Toes,[1] Rienk Offringa,[1]
and Cornelis J.M. Melief[1]

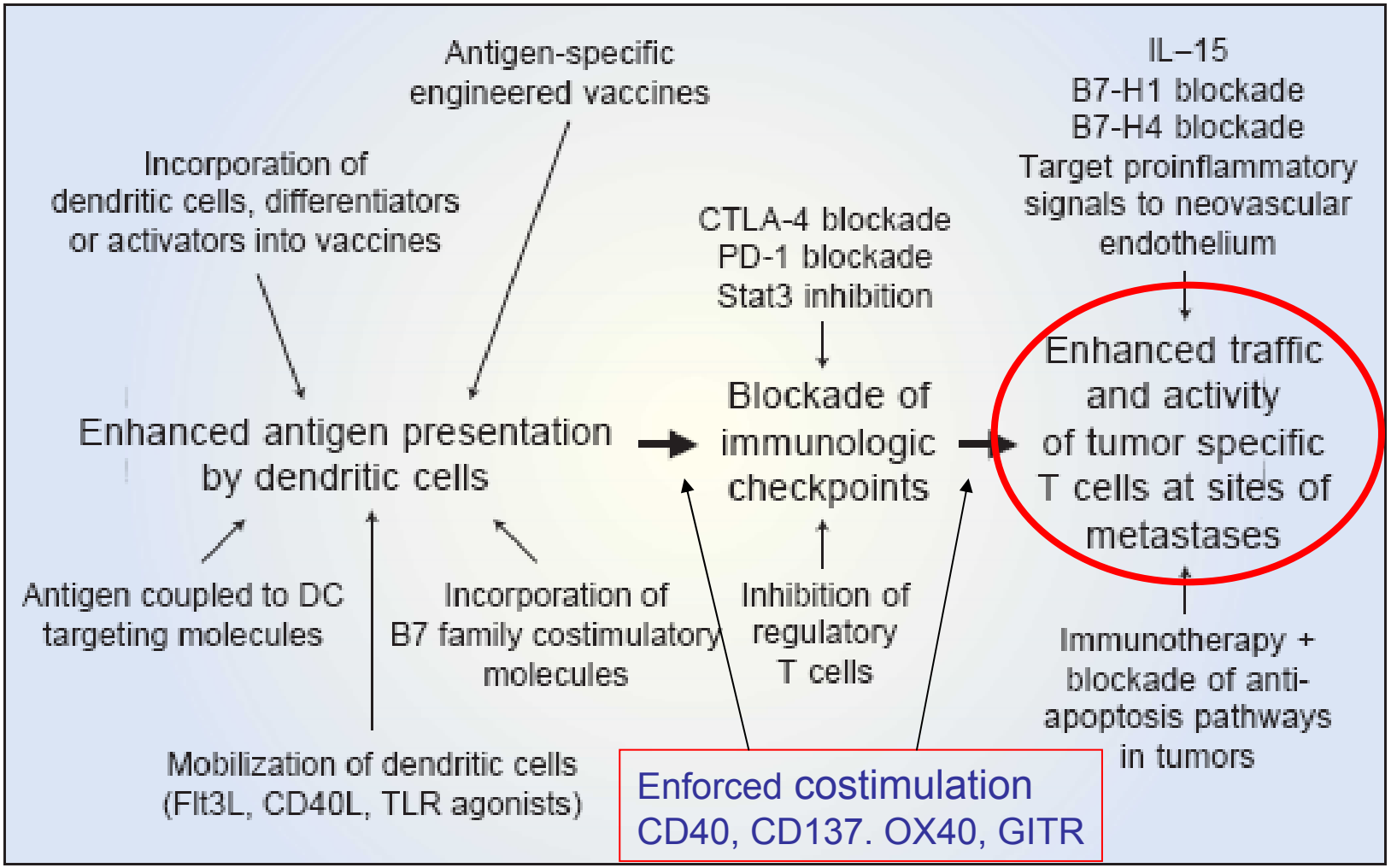
Anti-CTLA-4 is not a good anti-Treg treatment.

- CTLA-4 is brightly expressed on Treg cells
- Selective genetic defficiency of CTLA-4 in FOXP-3 cells leads to autoimmunity
- Paradoxically, selective CTLA-4 blockade on Treg with mAb has a modest effect.
- Patients under ipilimumab or tremelimumab treatment have largely normal Treg numbers and function.


Total cells
CD4 gated
CD8 gated
DC+PBL
DC+PBL
+αCTLA-4
DC+[PBL-Treg]
DC+[PBL-Treg]
+αCTLA-4
0. 2. 98. 0.
0. 3. 97. 0.
0. 2. 98. 0.
0. 27. 73. 1.
0. 17. 83. 0.
0. 33. 67. 0.
1. 54. 45. 0.
0. 42. 58. 0.
0. 50. 50. 0.
67. 25. 8. 0.
59. 29. 12. 0.
0. 61. 38. 0.
CFSE


CD4+ cells (gated out FoxP3)
CD8+ cells
% of Max
100
80
60
40
20
0
10^0
10^1
10^2
10^3
FL2-H:: CTLA4-PE
DC+PBL
DC+[PBL-Treg]

We have neglected lymphocyte traffic to tumors



Clinical development of combination strategies in immunotherapy: are we ready for more than one investigational product in an early clinical trial?

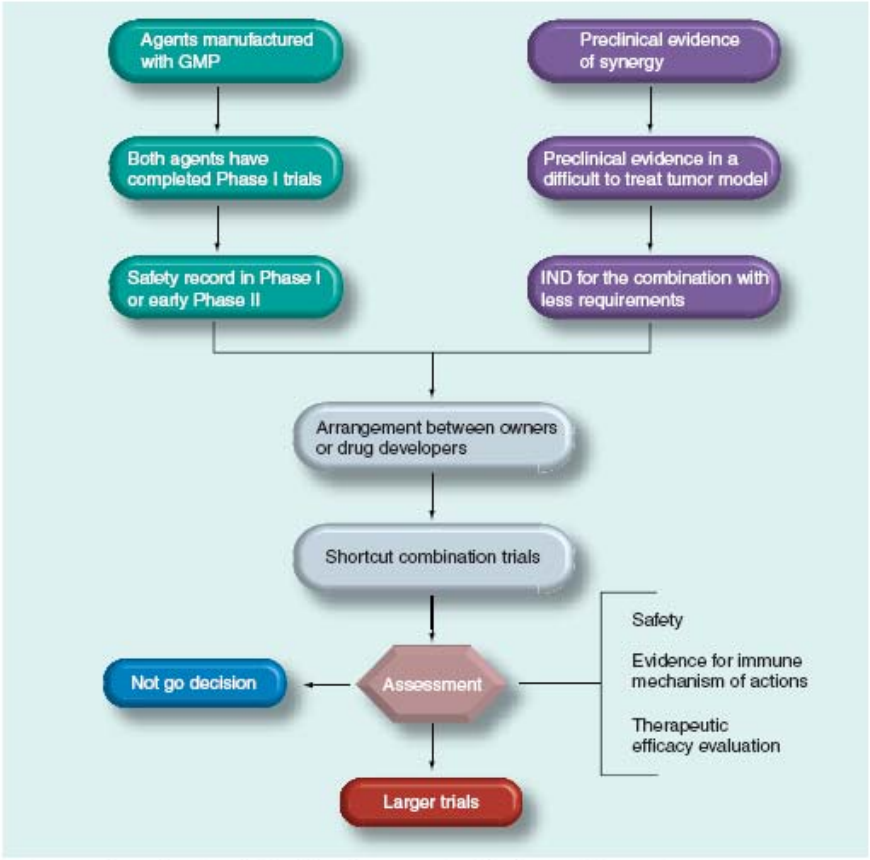


Figure 1. Flow chart for clinical development of trials that combine various immunotherapeutics agents testing for synergy.
IND: Investigational new drug.

Jose L Perez-Gracia[1],
Pedro Berraondo[1],
Ivan Martinez-Forero[1],
Carlos Alfaro[1],
Natalia Suarez[1],
Alfonso Gurpide[1],
Bruno Sangro[1],
Sandra Hervas-Stubbs[1],
Carmen Ochoa[1],
Jose A Melero[1] &
Ignacio Melero[1†]

Immunotherapy (2009)

'Shortcut' combination clinical trials in immunotherapy: early assessment of safety, mechanism of action & clinical response for combination immunotherapies

Dr.Melero can you predict the future a little bit?

Standard treatment

And

Local intervention to enhance immunogenicity in some tumor lesions

Or

A vaccine in minimal residual disease status

Do something to Treg

Disclaimer:

1) Almost all I have to predict the future with are mice.
2) I am glad to inform you that mice are similar, but not identical to humans.

+

Check point blockade:

-CTLA-4
-PD1
-B7-H1

+

Enforce costimulation:

-CD137
-OX40
-GITR
-CD40

The sequence of these treatments?:
-concomitant
-Sequential

……to be empirically learnt

Sancho, my friend: is it a Quixotean task to COMBINE THESE IMMUNOTHERAPIES?

My lord, some used to say so, but it must be done.
Let me talk to friends in
Pharma industry, Regulatory agencies,
and funding agencies at ISBTC and
let us see what happens…

José L Pérez Gracia
Bruno Sangro
Jorge Quiroga
Alfonso Gúrpide
Javier Rodriguez
Jesús García-Foncillas
Maurizio Bendandi
Alberto Benito
Ivan Peñuelas

Carlos Alfaro
Natalia Suarez
Lorena Erro
Sarai Solano
Izaskun Gabari

Sandra Hervas
Juan Dubrot
Asis Palazon
Oihana Murillo
Arantza Azpilikueta
Uxua Mancheño
Eneko Elizalde
Elena Ciordia

Digna-Biotech
Bristol Myers Squibb
Pfizer
Roche

Lieping Chen