Animal Models for Combination Immunotherapy in Cancer

Nils Lonberg, Bristol-Myers Squibb

NCPF Workshop
June 14, 2011

Bristol-Myers Squibb

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- The opportunity for synergy in combination therapy is increased when different agents target distinct pathways/mechanisms
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in vitro assays can detect synergy for combinations directed to cell-intrinsic pathways

Br. J. Cancer (1994), **69**, 299–306

Synergistic interaction between cisplatin and taxol in human ovarian carcinoma cells *in vitro*

A.P. Jekunen, R.D. Christen, D.R. Shalinsky & S.B. Howell

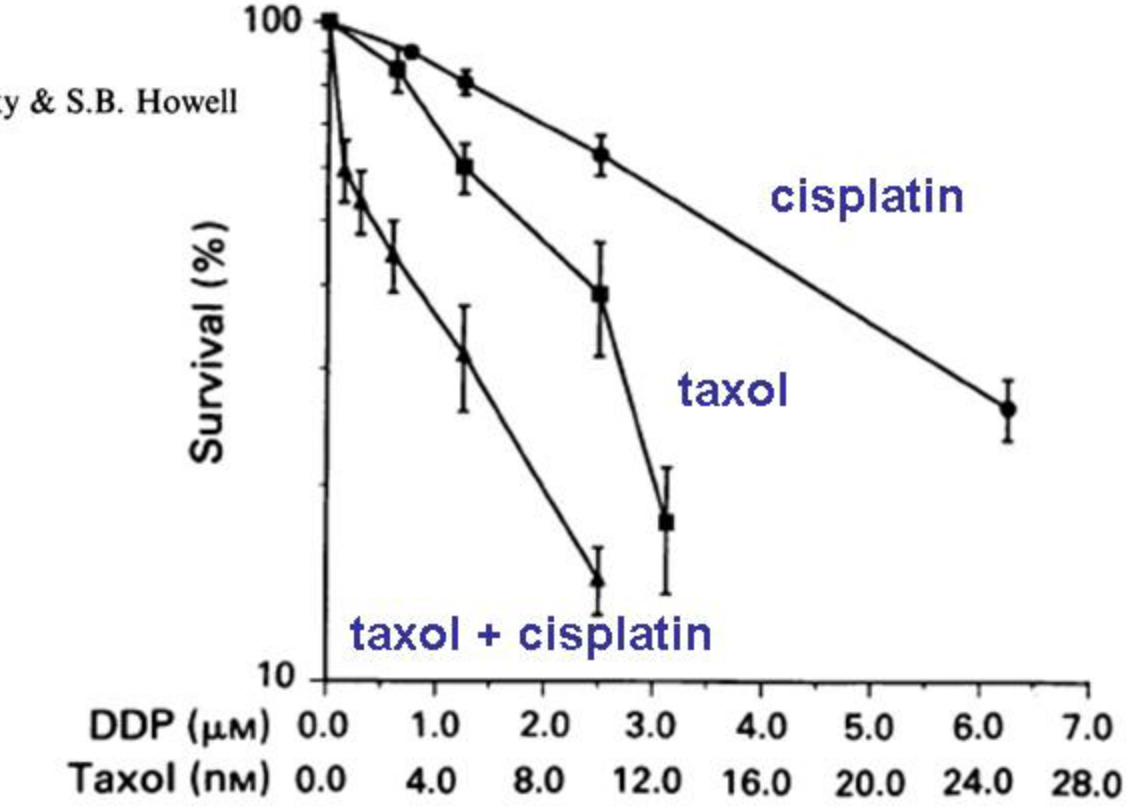
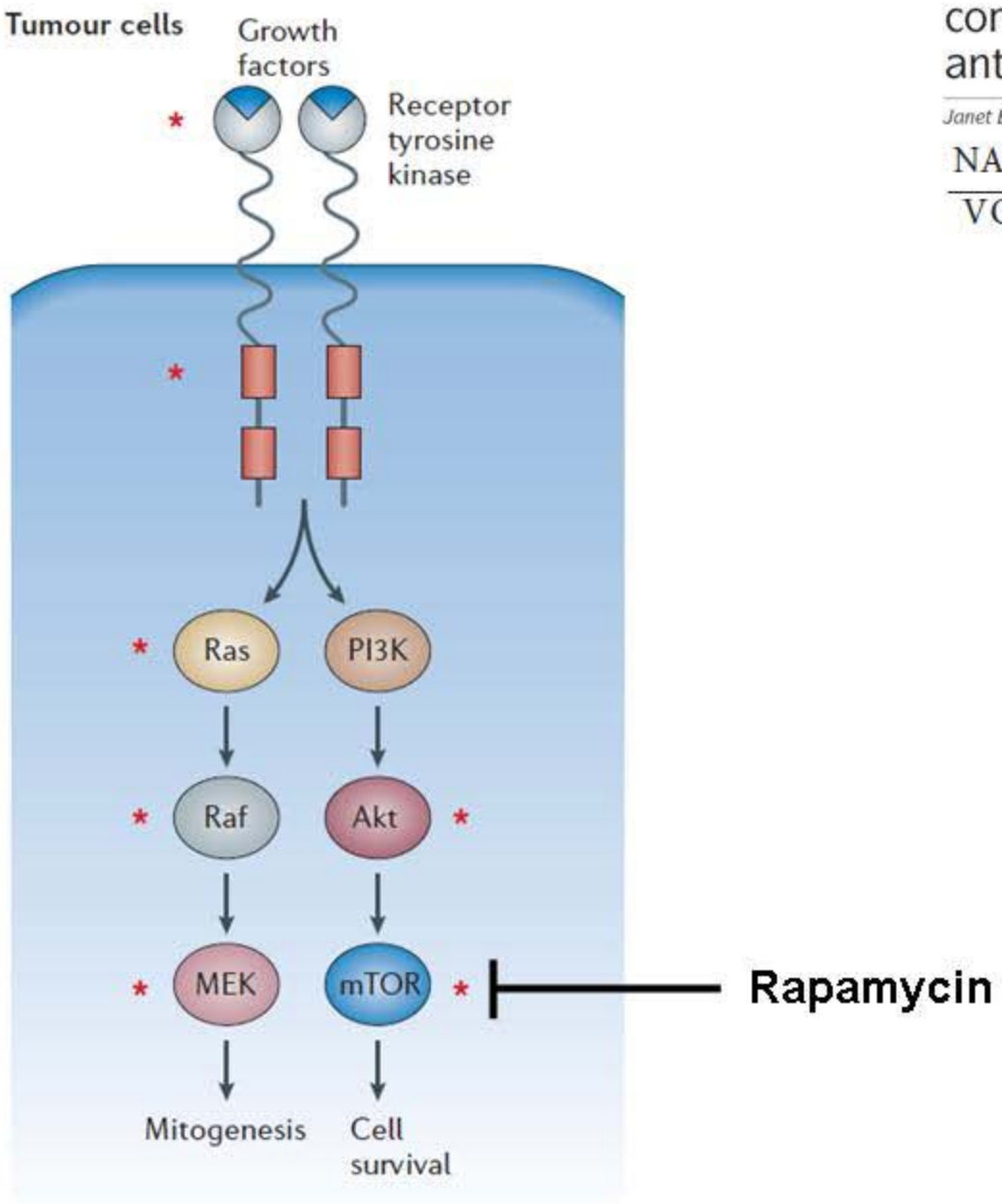


Figure 1 Percentage survival as a function of drug concentration for 2008 cells exposed to DDP for 1 h (circles), taxol for 19 h (squares), and the combination of DDP and taxol, exposed first to taxol for 19 h and then to taxol and DDP for 1 h at a fixed molar ratio of 250:1 (triangles). Each point in all plots represents the mean of three experiments using triplicate cultures (s.e.).

tumor graft mouse models will also detect synergy for combinations directed to cell-intrinsic pathways



Strategies for optimizing combinations of molecularly targeted anticancer agents

Janet E. Dancey and Helen X. Chen

NATURE REVIEWS | DRUG DISCOVERY
VOLUME 5 | AUGUST 2006 | 649

Shivanni Kummar, Helen X. Chen, John Wright, Susan Holbeck, Myrtle Davis Millin, Joseph Tomaszewski, James Zweibel, Jerry Collins and James H. Doroshow

NATURE REVIEWS | DRUG DISCOVERY
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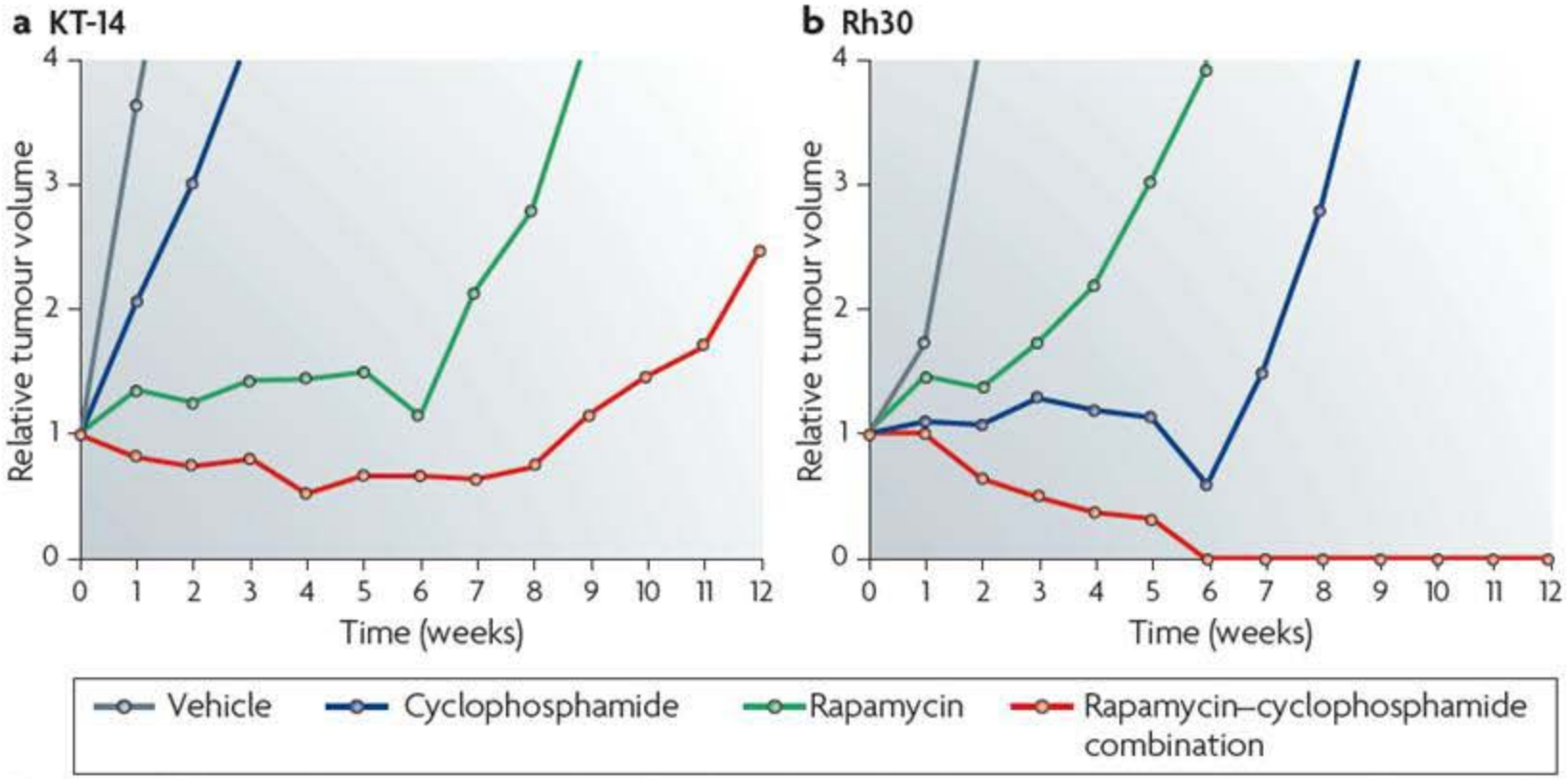


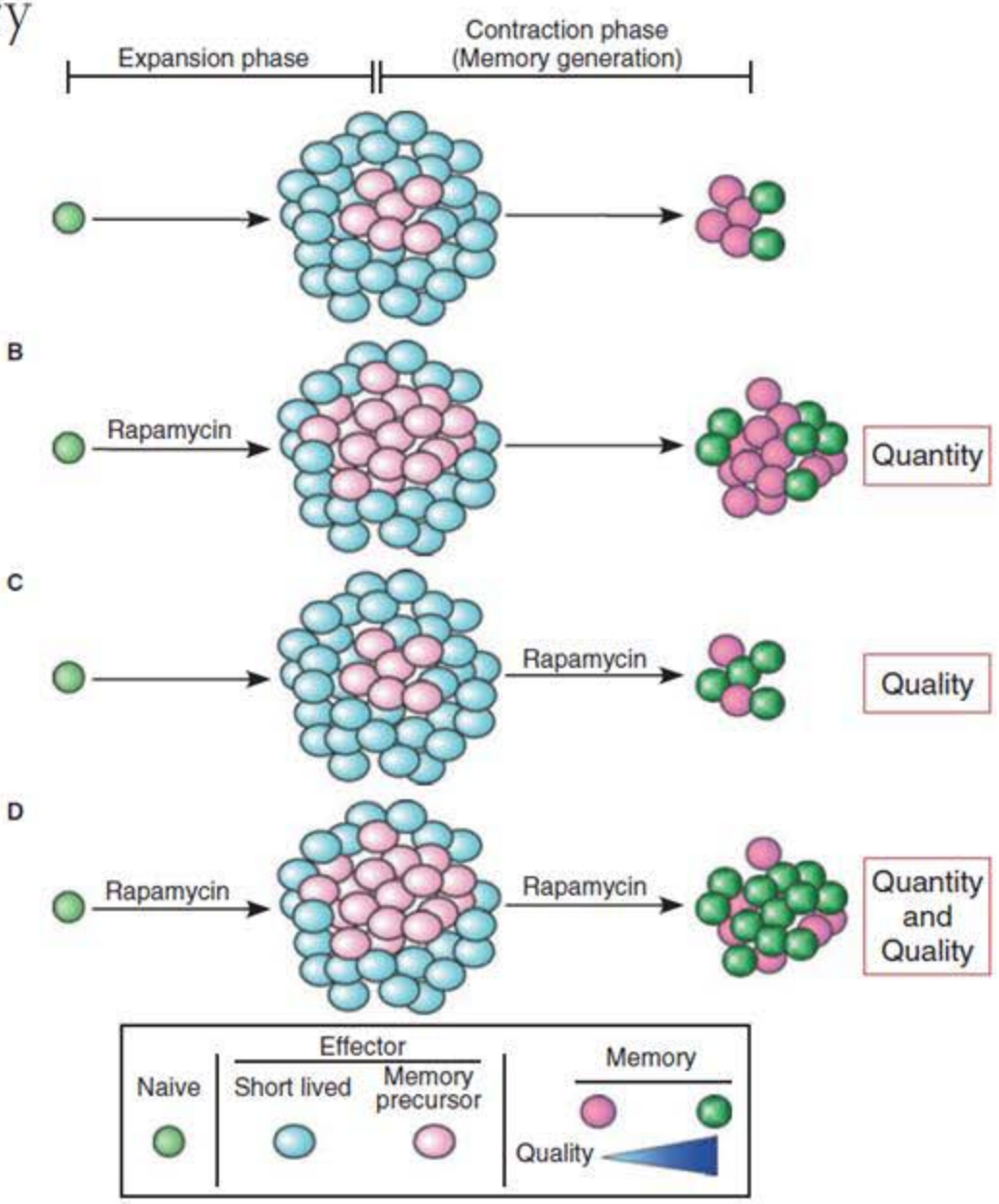
Figure 2 | **Effects of rapamycin and cyclophosphamide alone and in combination.** Studies of a human KT-14 rhabdoid tumour xenograft of the kidney and a human Rh30 rhabdomyosarcoma xenograft in female severe combined immunodeficient mice. Mice were treated with the single agent rapamycin at its maximally tolerated dose (MTD) level of 5 mg per kg daily for 5 consecutive days for 6 weeks or with the single agent cyclophosphamide at its MTD of 150 mg per kg daily for 6 weeks or with the combination of both agents at their MTDs.

tumor graft mouse models will also detect synergy for combinations directed to cell-intrinsic pathways… *but may not fully recapitulate complexity of host tumor interactions affected by agents*

The role of mTOR in memory $CD8^+$ T-cell differentiation

Koichi Araki
Ben Youngblood
Rafi Ahmed

Immunological Reviews 2010
Vol. 235: 234–243



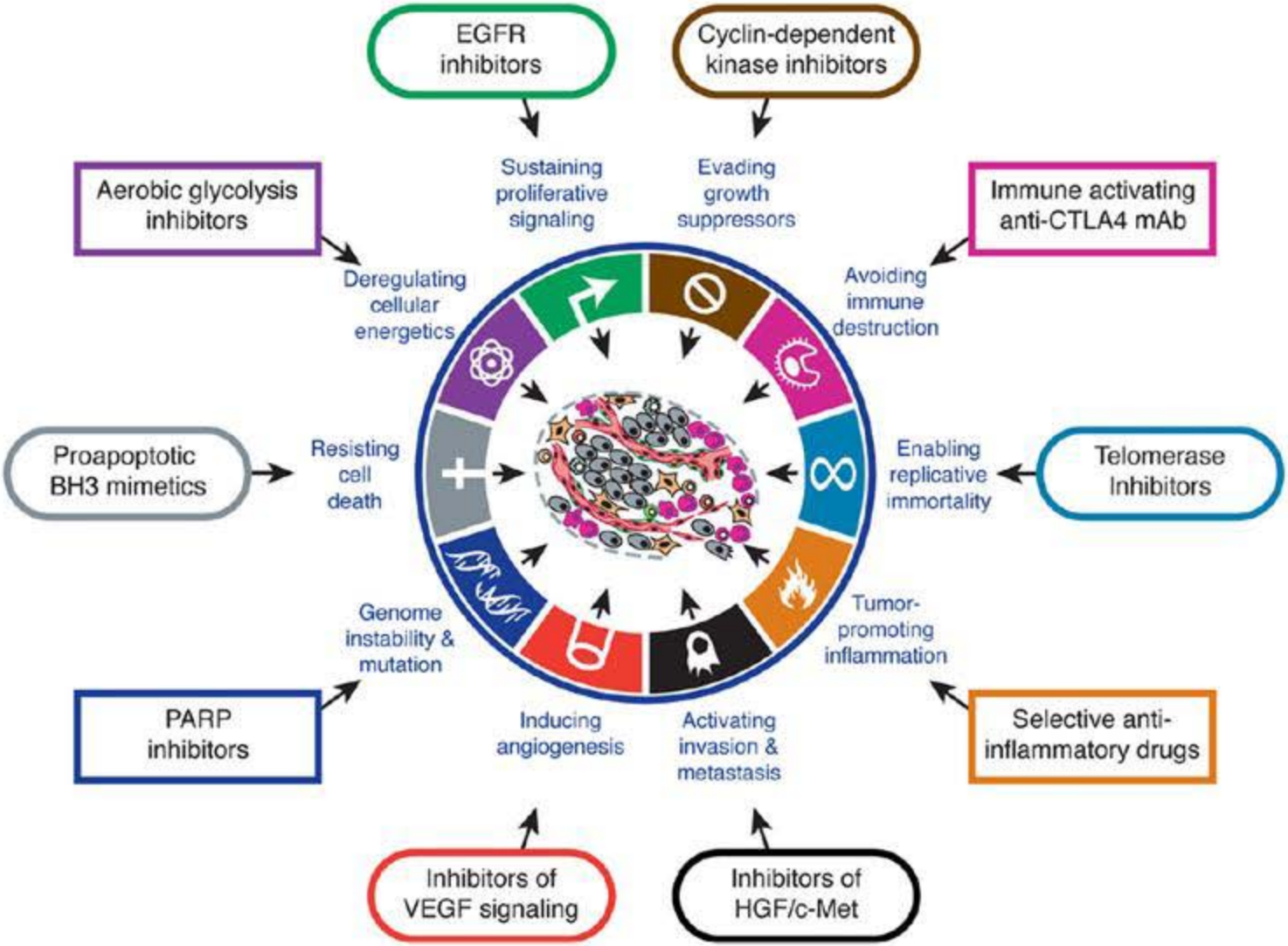
Rapamycin improves the quantity and quality of memory $CD8^+$ T cells.

Cell

Leading Edge
Review

Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]

Hallmarks of Cancer: The Next Generation



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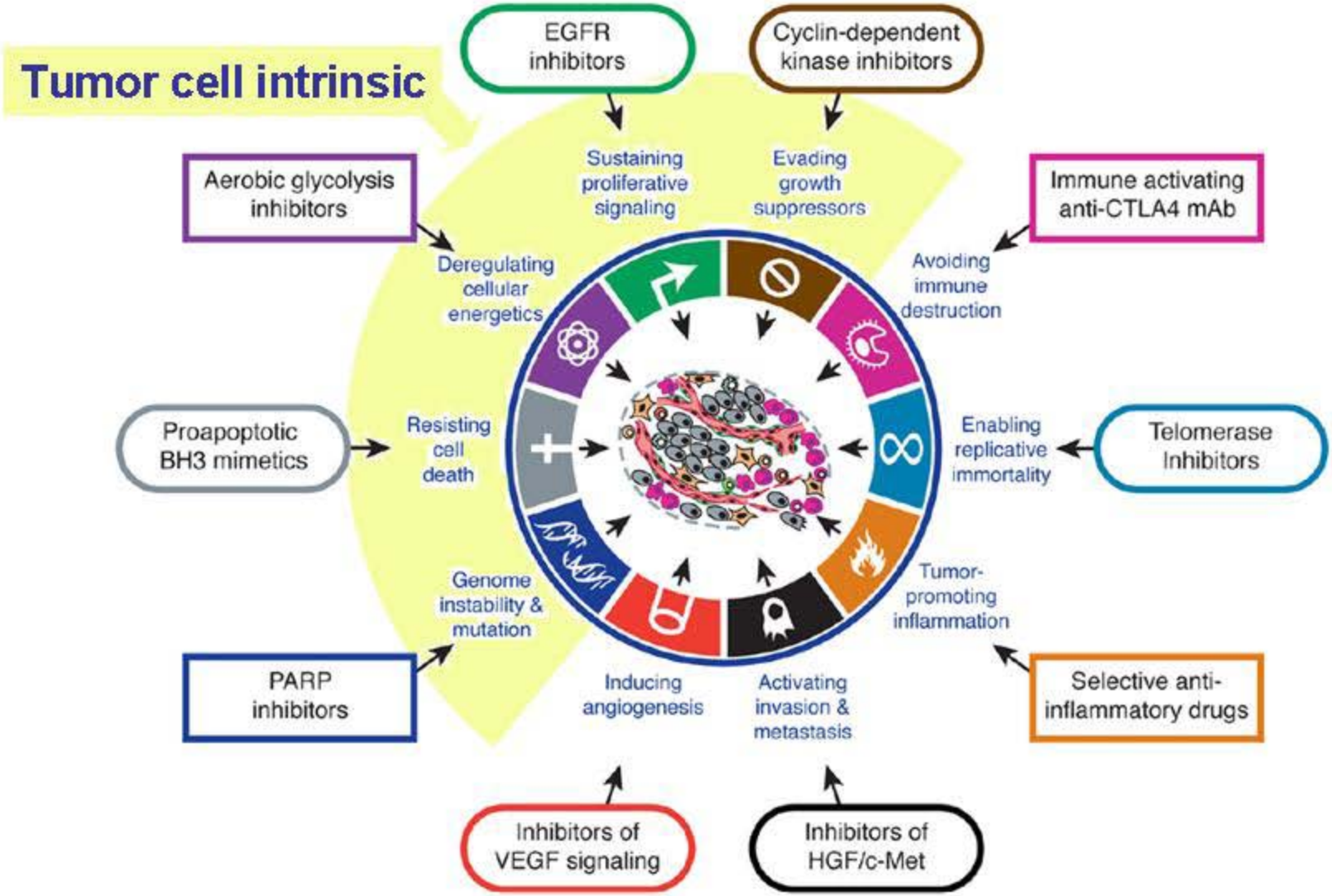

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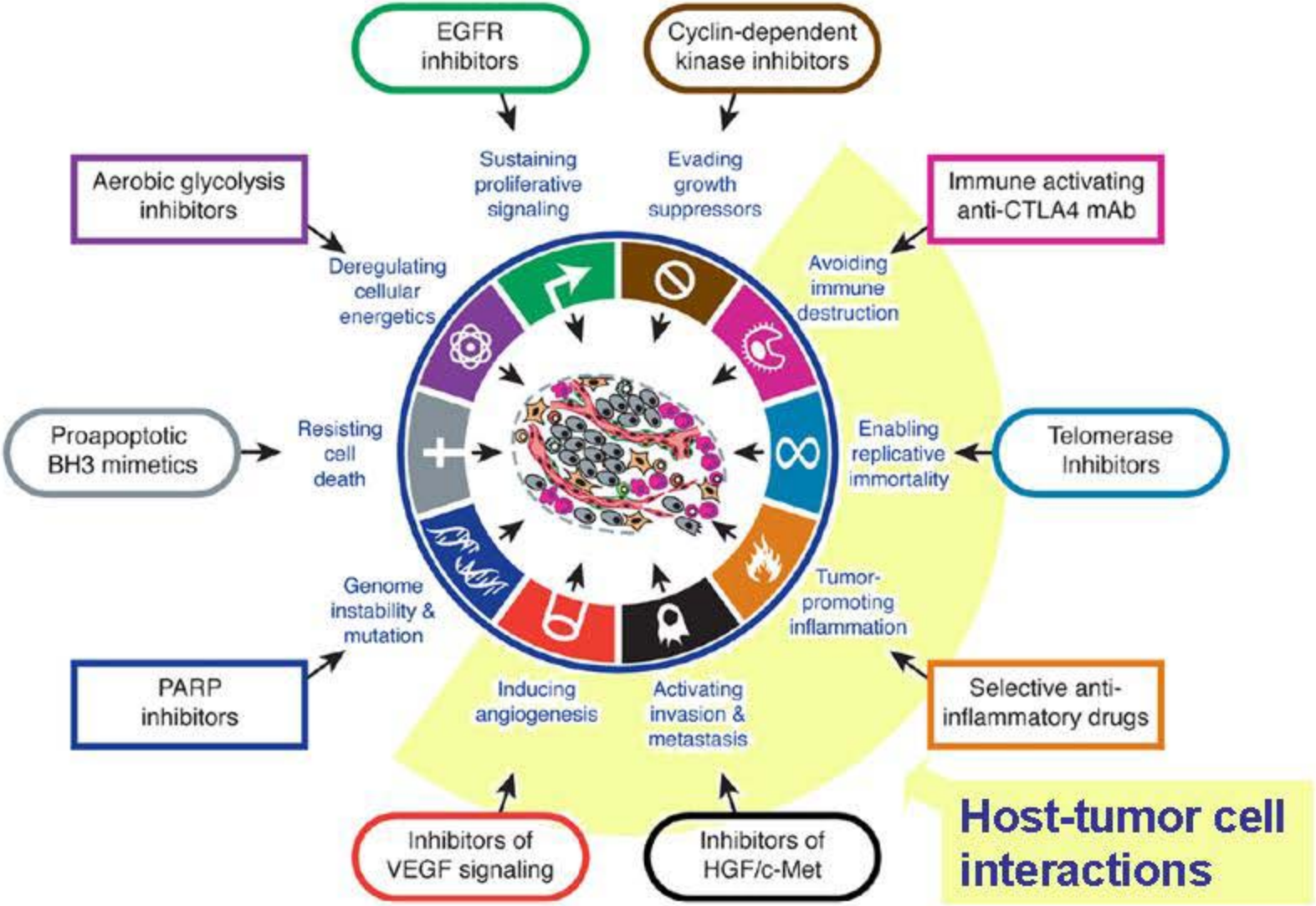
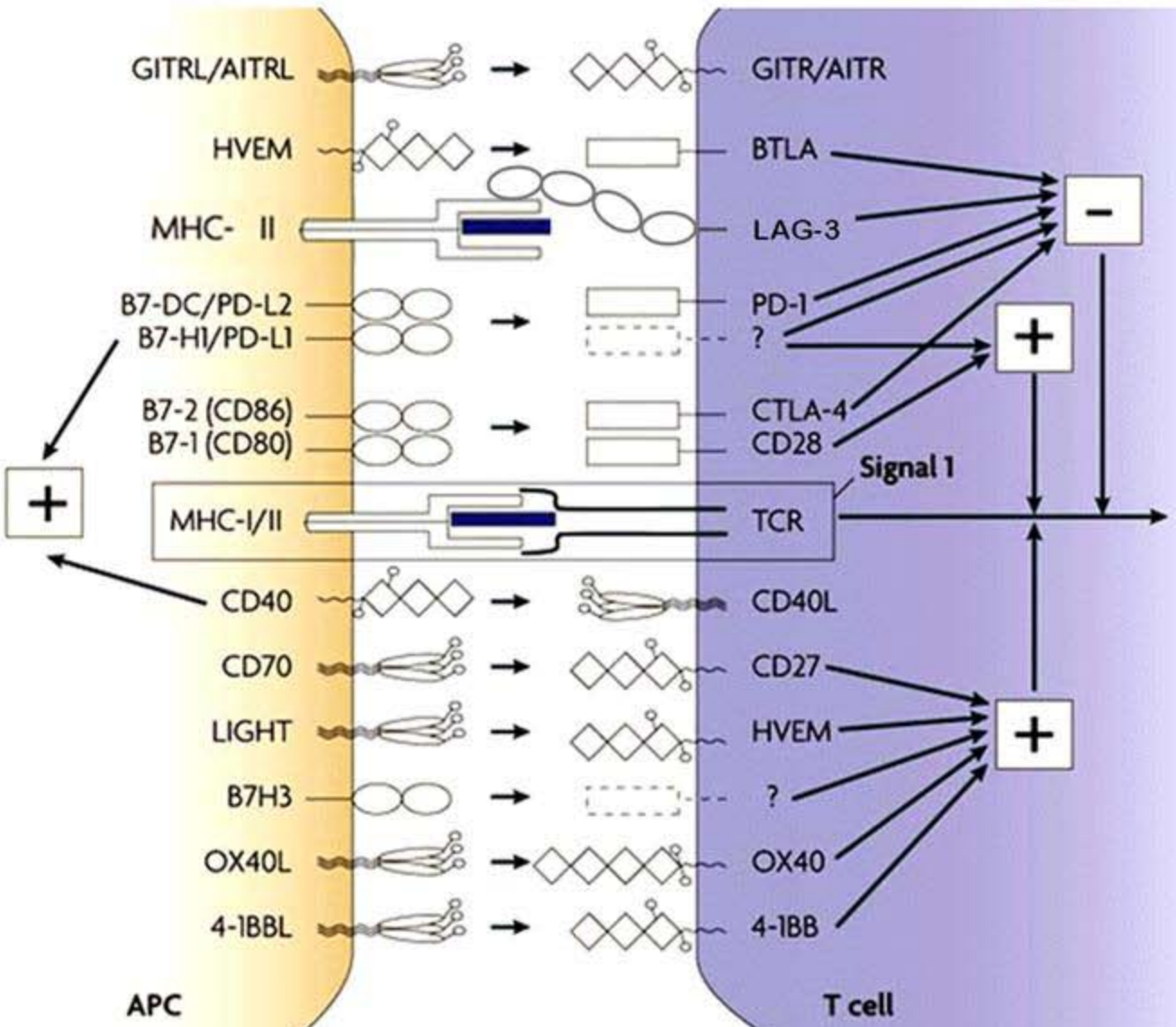


Checkpoint pathways in T cell activation



Melero et al. (2007) Nature Rev. Cancer 7: 95

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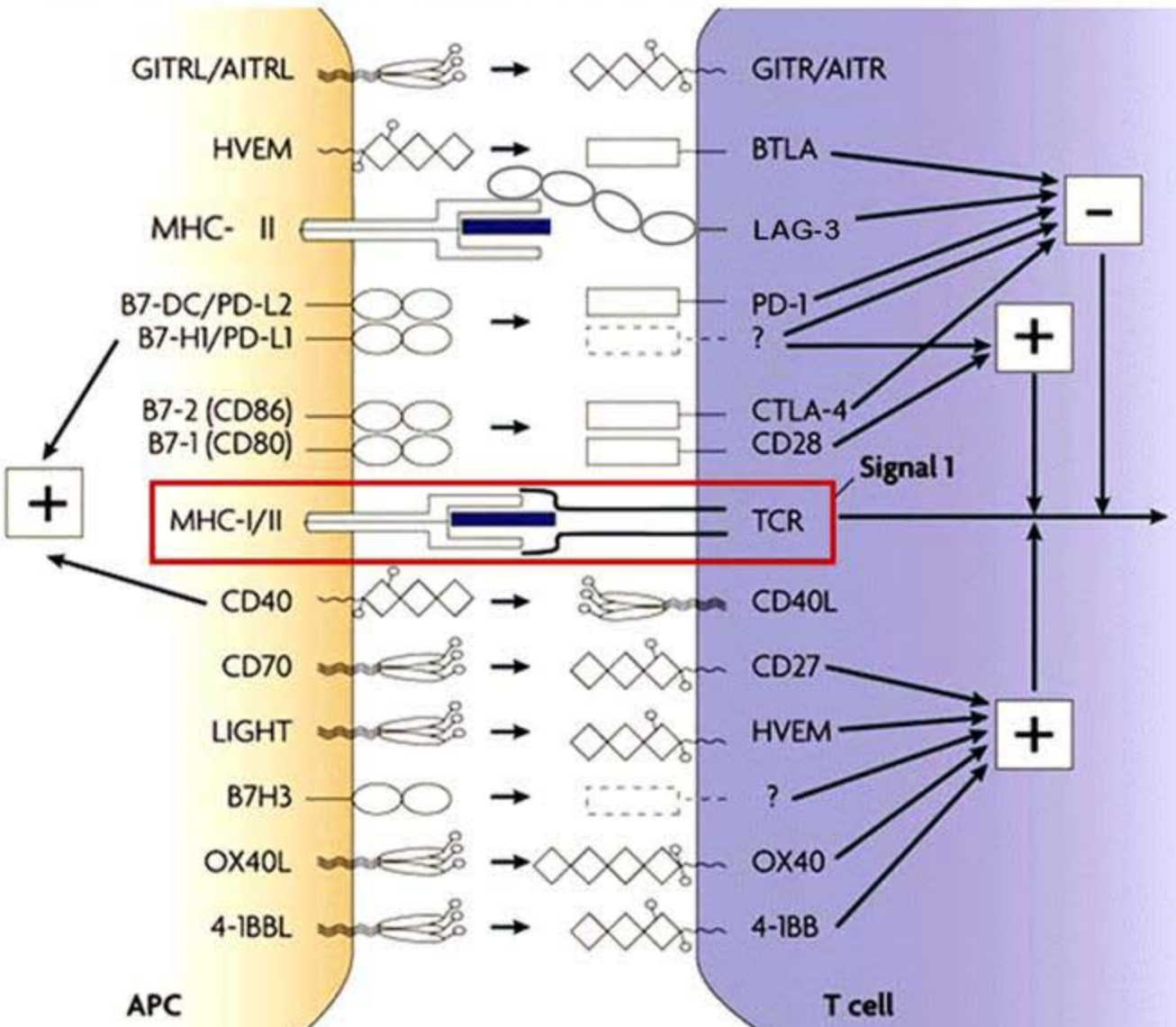

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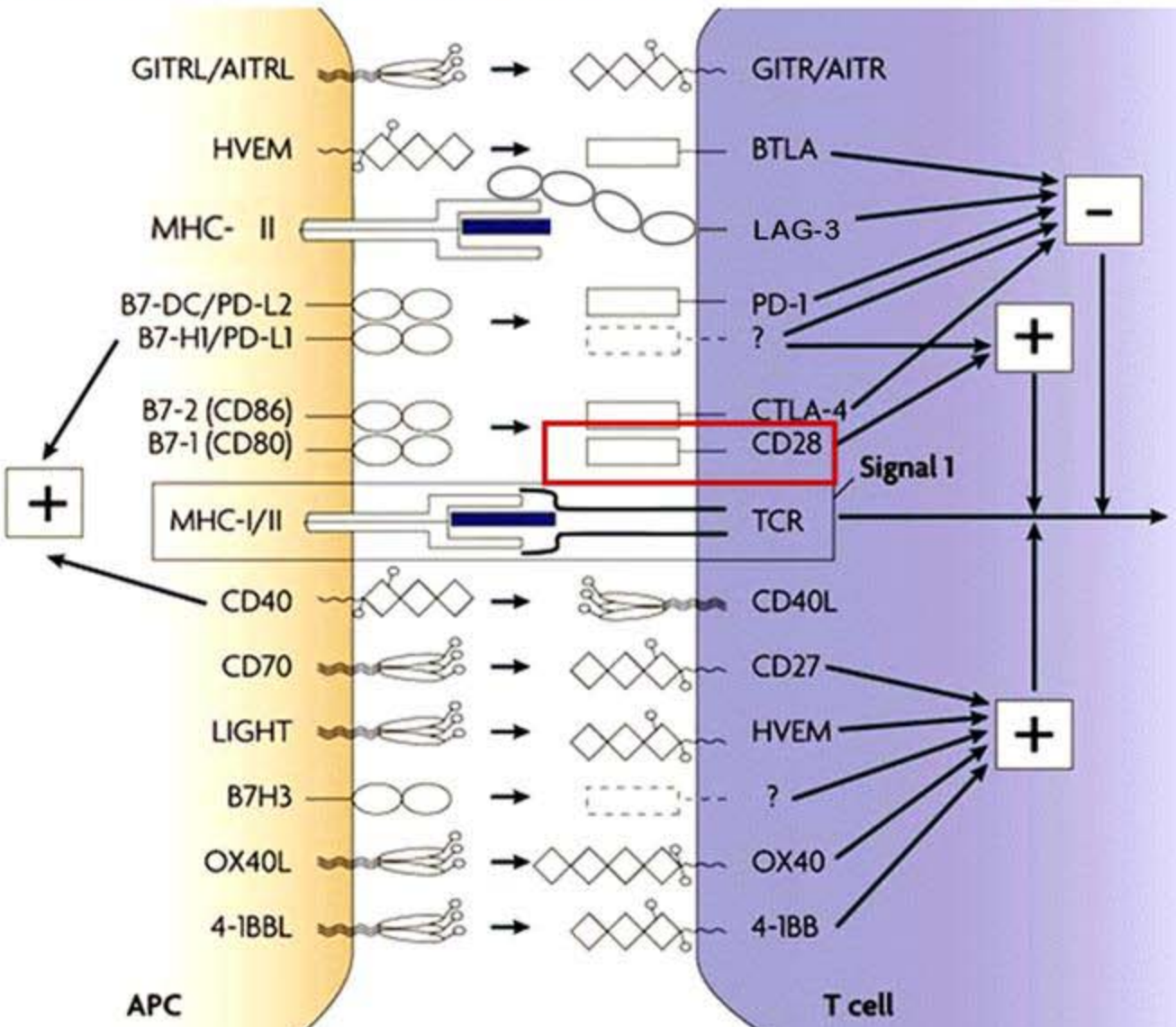

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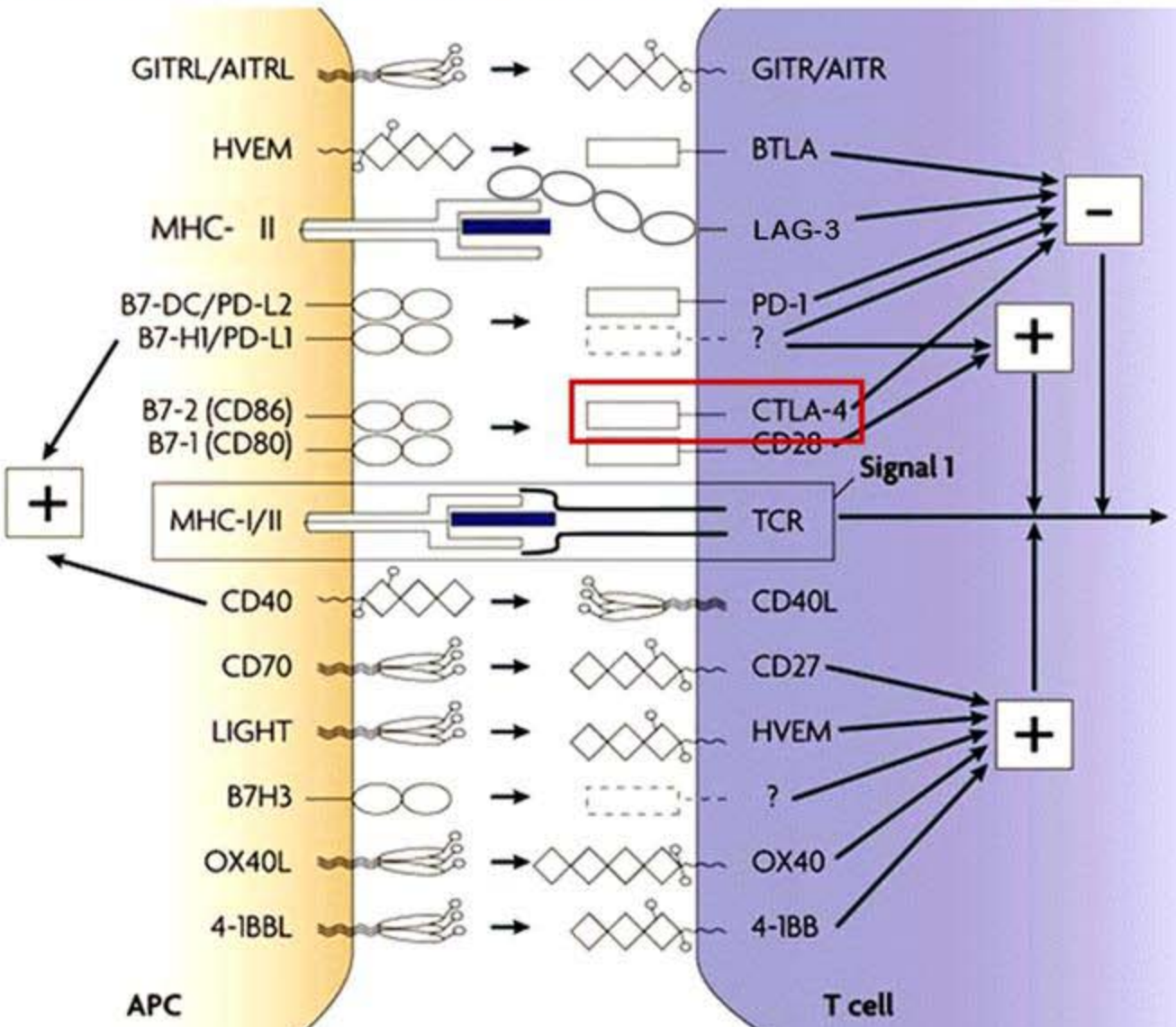

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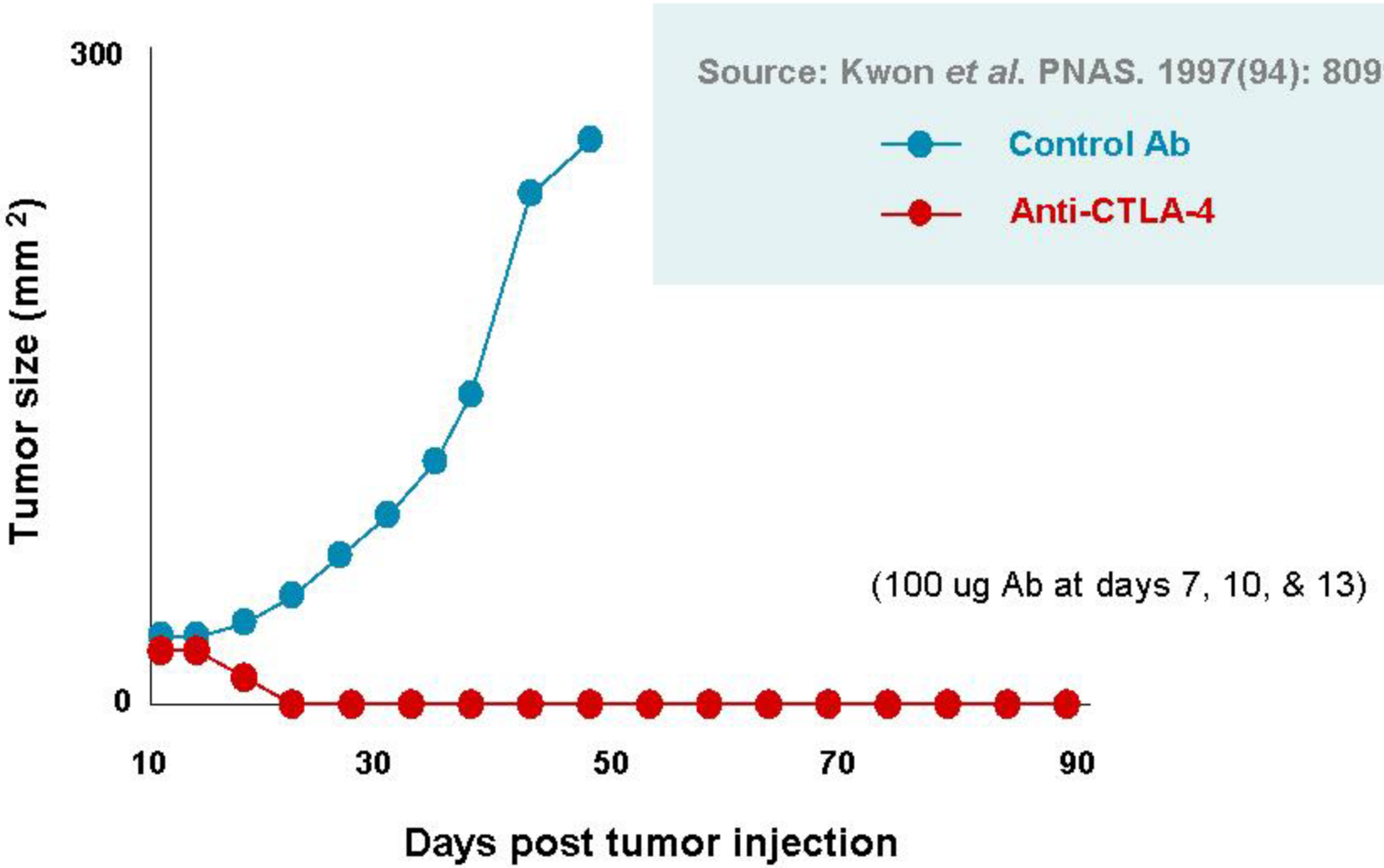
αMurine CTLA-4 mAb in mouse prostate cancer model



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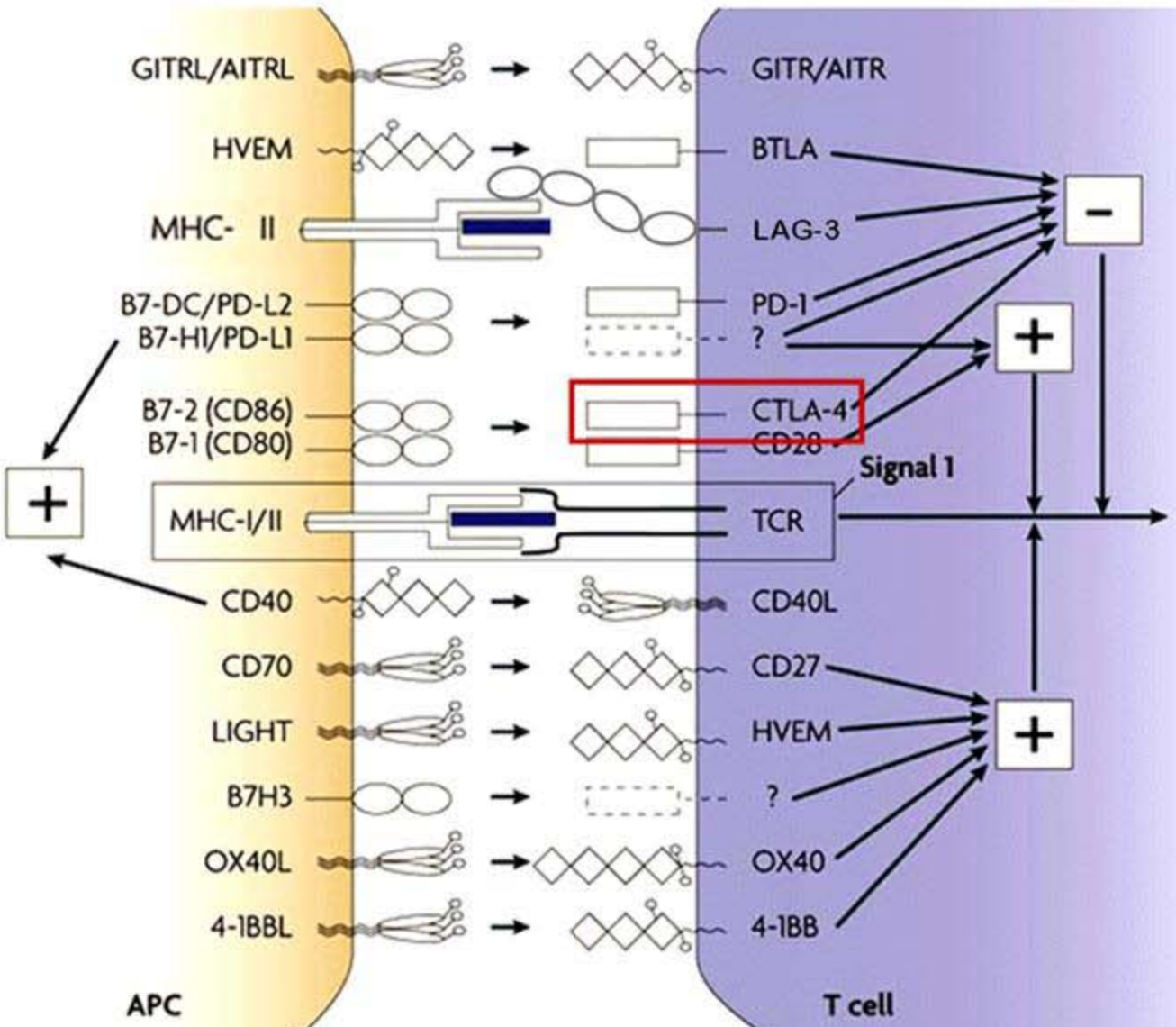

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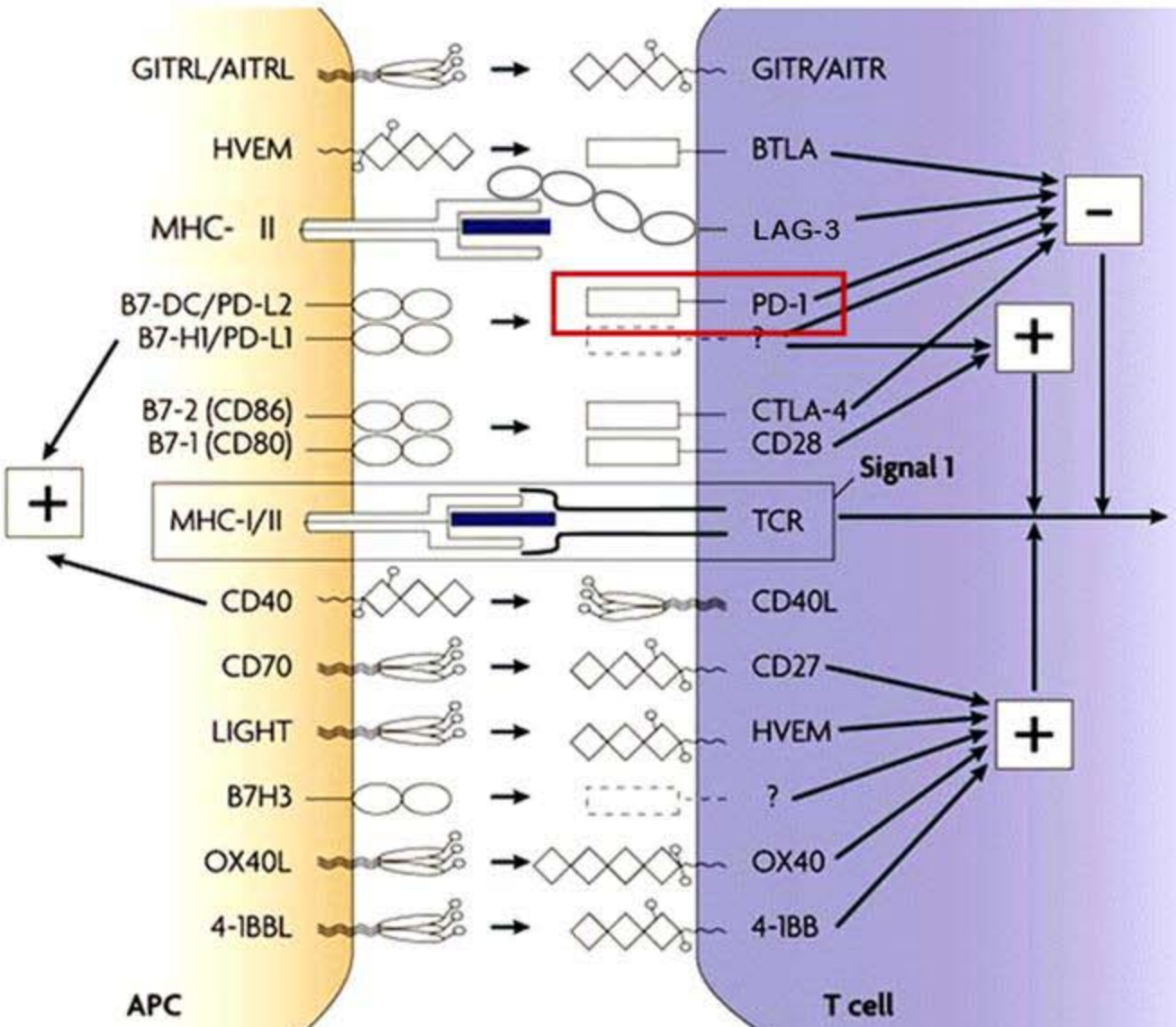

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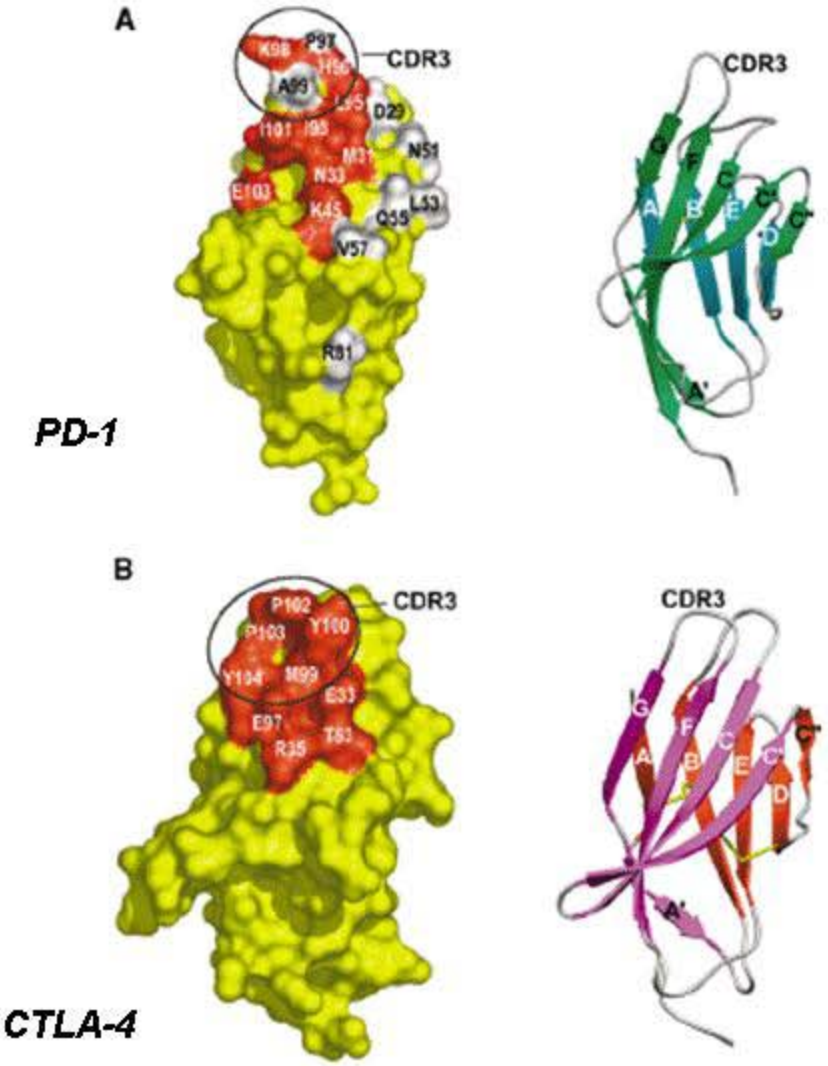
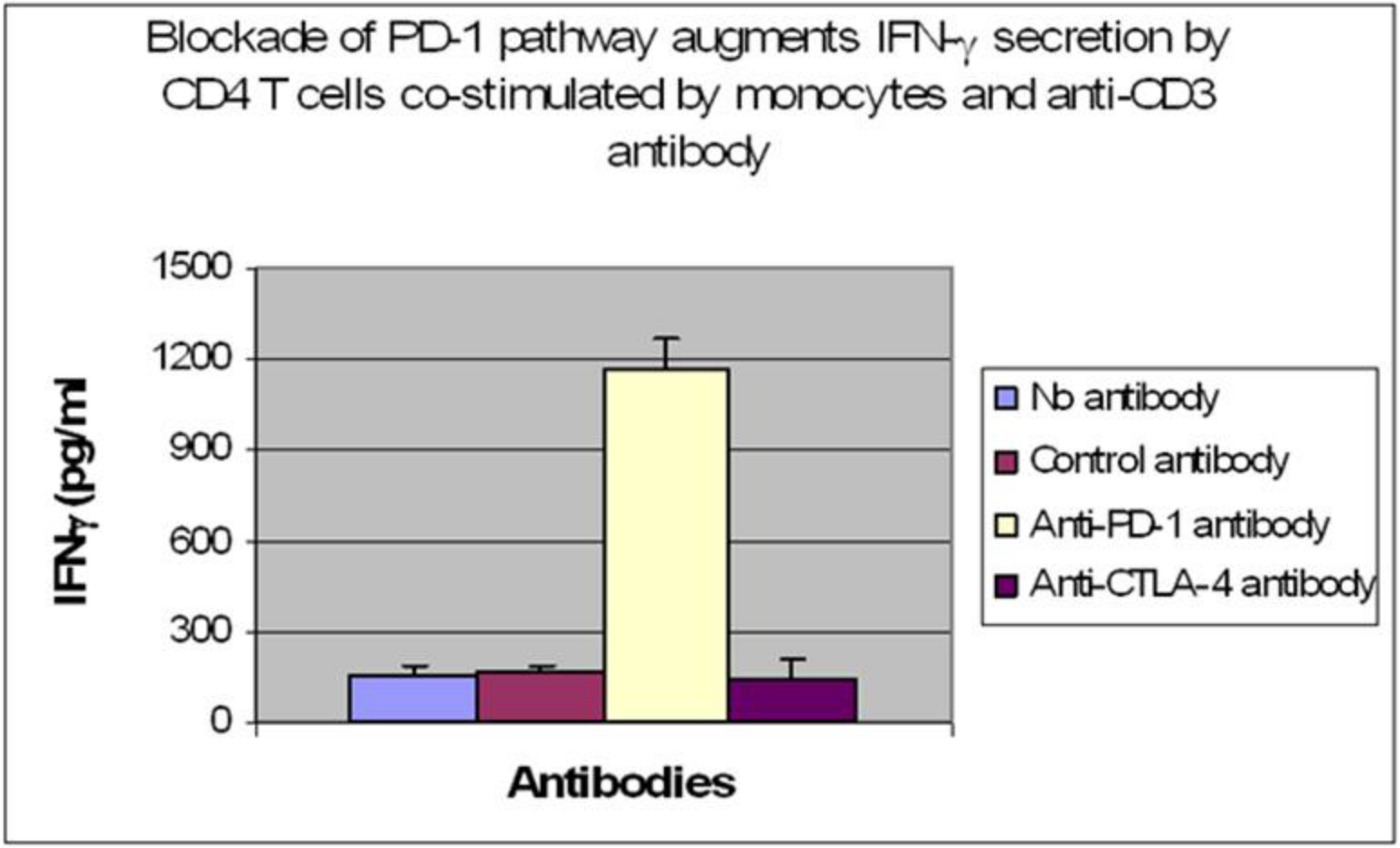
PD-1 is structural homolog of CTLA-4



Source: Zhang, X., et al. Immunity 20:337 (2004)

αPD-1 Antibody Promotes T Cell Activation and γ-IFN Secretion



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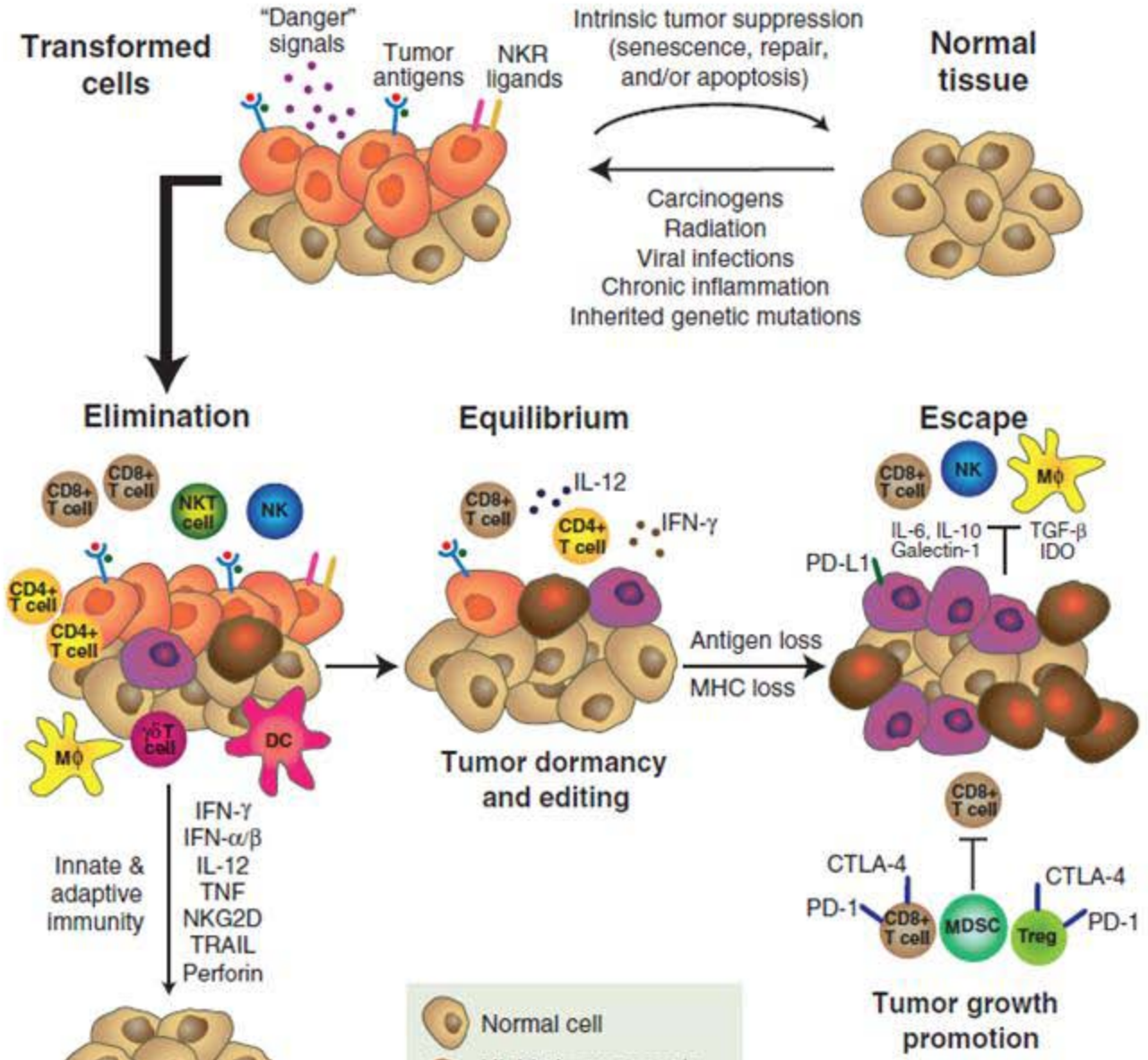

Cancer Immunoediting: Integrating Immunity's Roles in Cancer Suppression and Promotion
Robert D. Schreiber, *et al.*
Science **331**, 1565 (2011);
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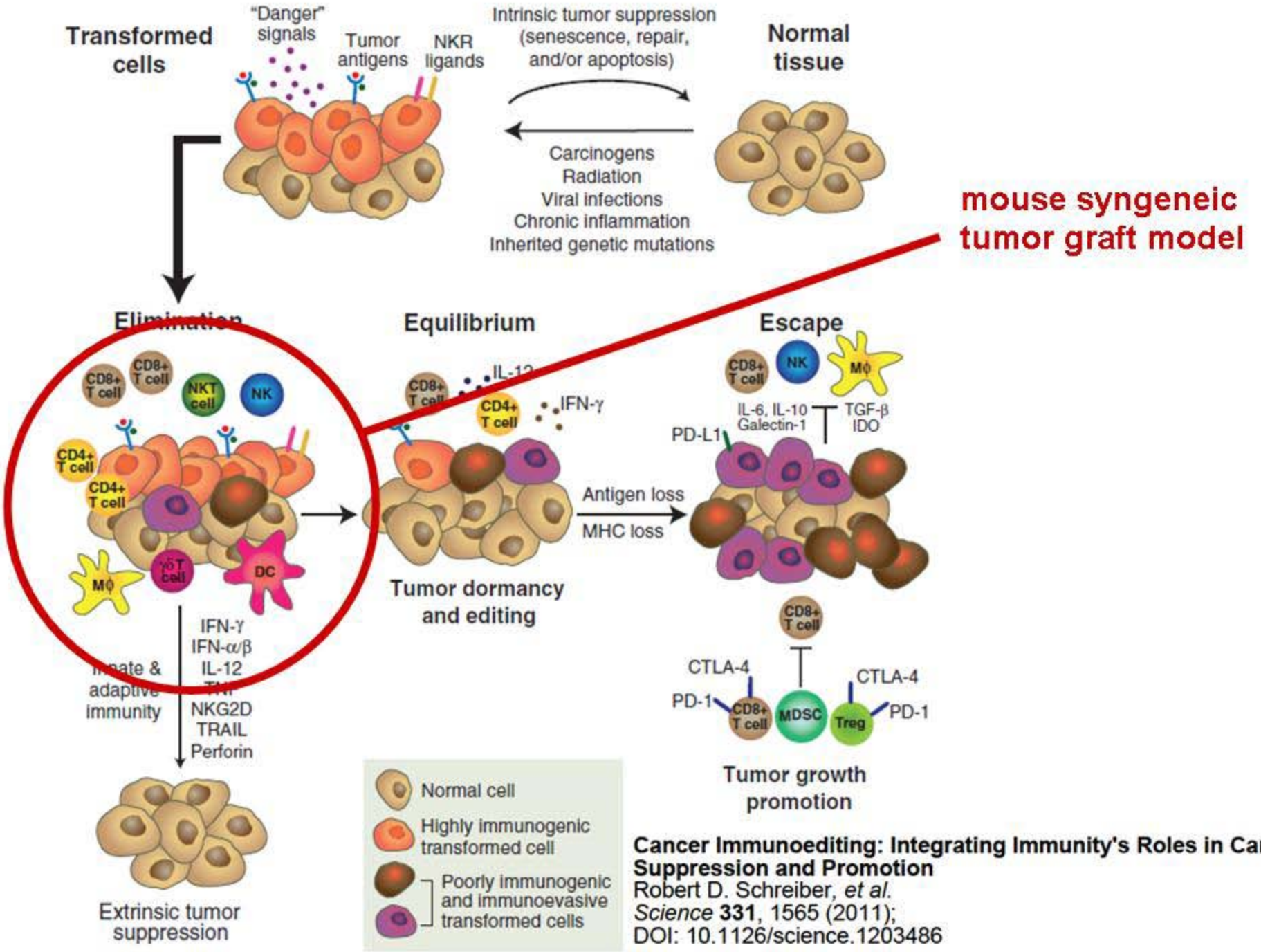

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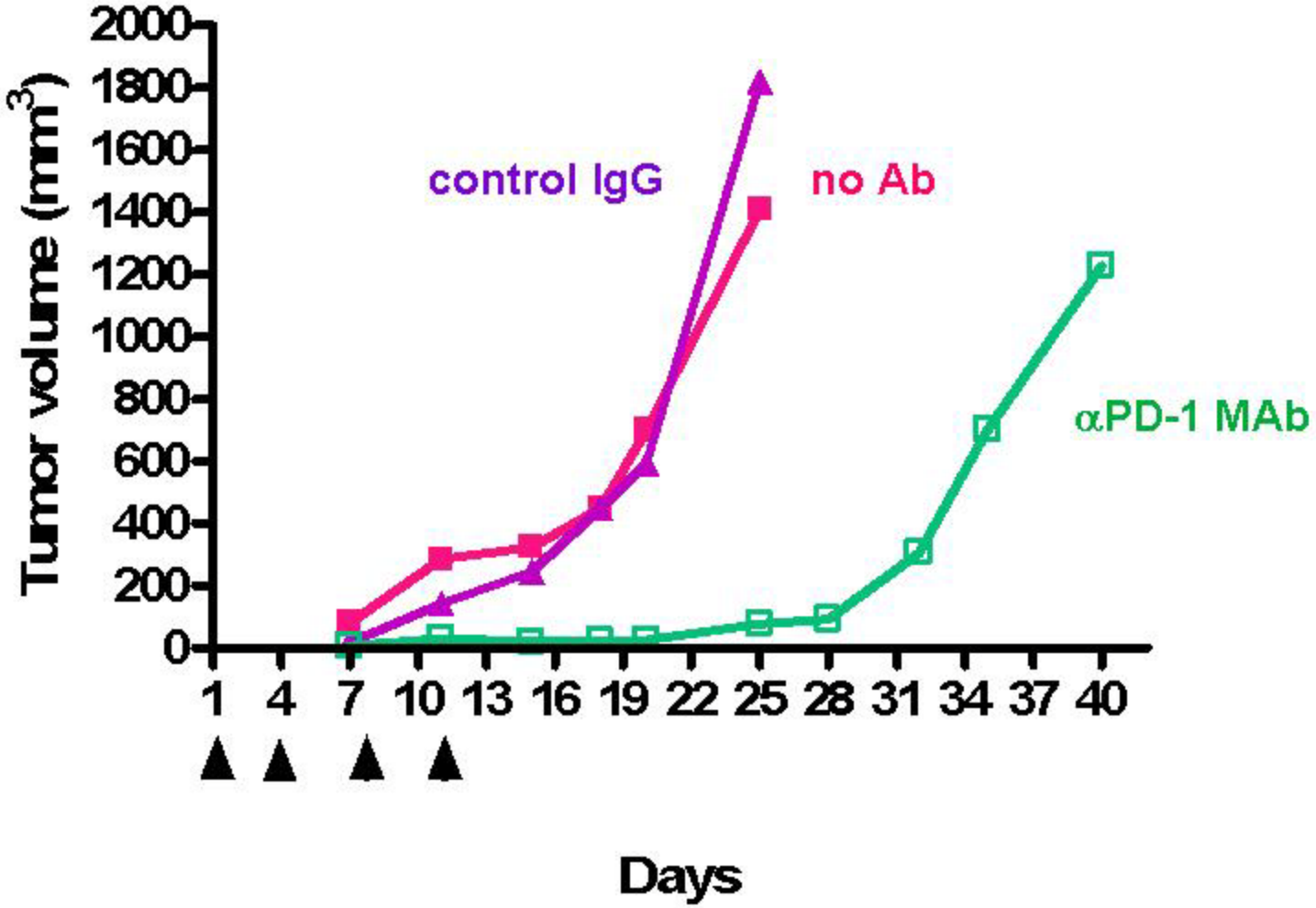
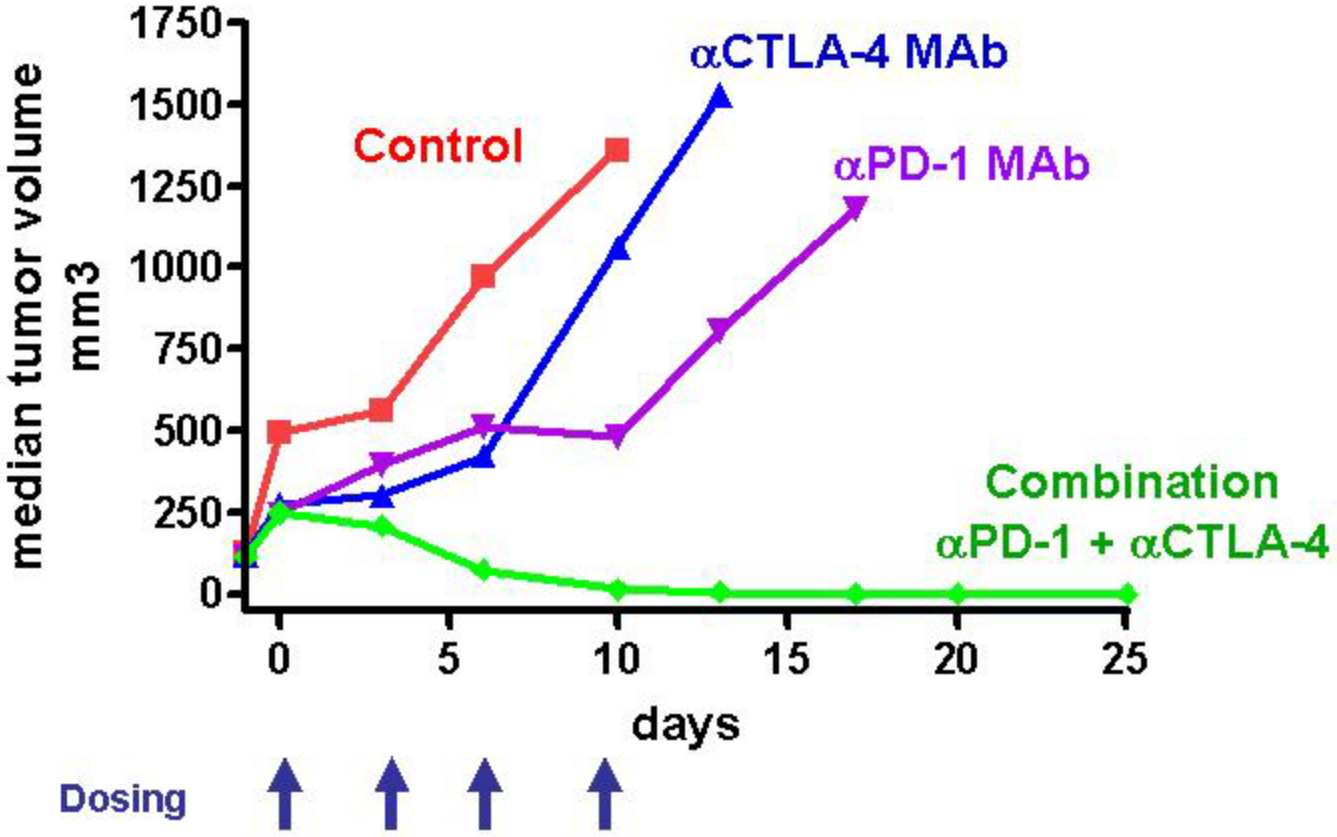
αPD-1 antibody suppresses tumor growth in mouse MC38 colon cancer model

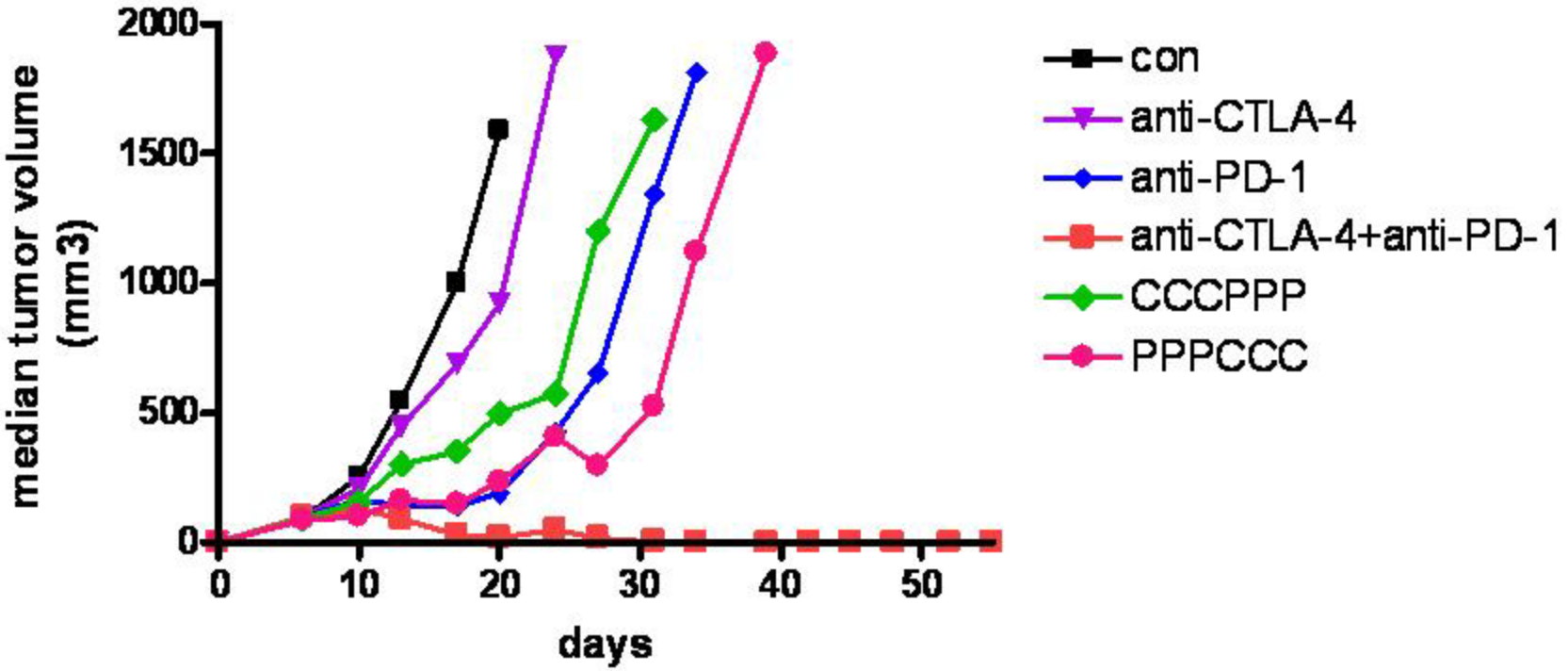


Synergistic activity with αPD-1 and αCTLA-4 antibodies

Combination of non-efficacious doses of αPD1 and αCTLA-4 antibodies is efficacious in mouse MC38 colon cancer model



Concurrent administration of CTLA-4/PD-1 blockade is more efficacious than the sequential administration in MC38 tumor model



Mice were randomized on Day 7 after the tumor implantation. Anti-CTLA-4 (9D9) and anti-PD-1 (4H2) antibodies were given together at 10mg/kg each, or individually with a control rat IgG on Day 7, 10 and 13. CCCPPP and PPPCCC were given as six single doses of either 9D9 or 4H2 antibody at 10mg/kg on Day 7, 10, 12, 14, 17, and 19.

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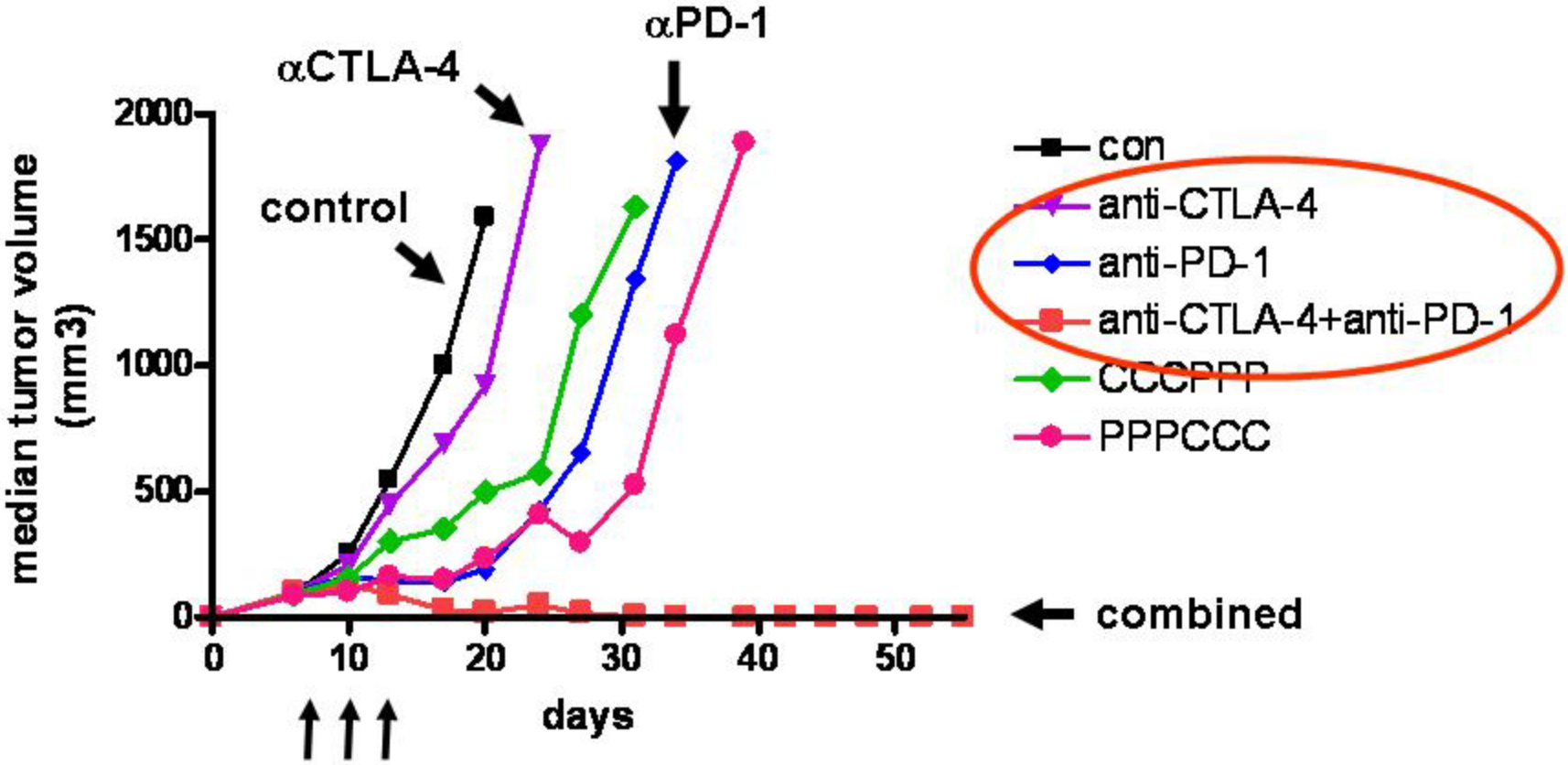

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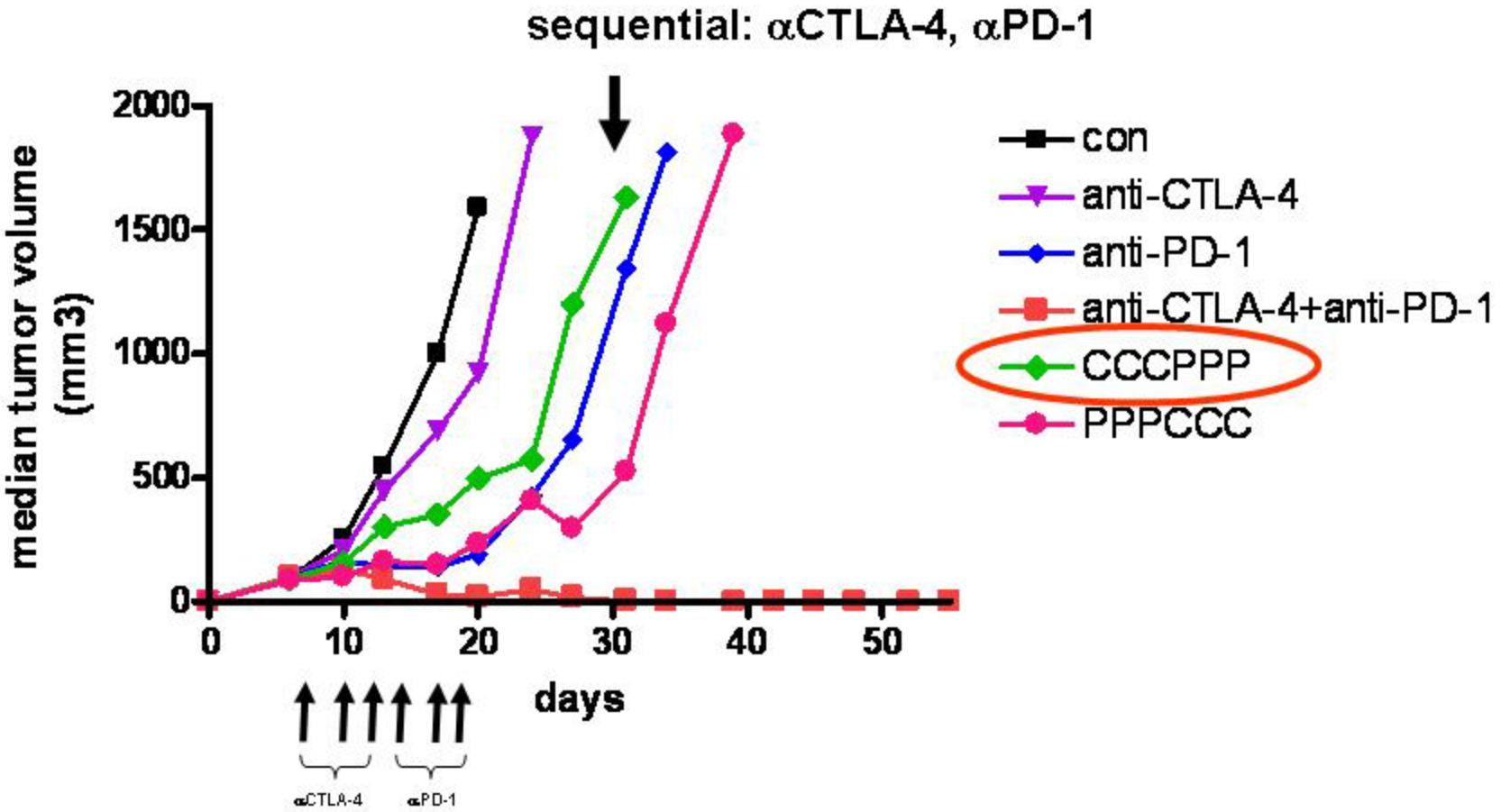

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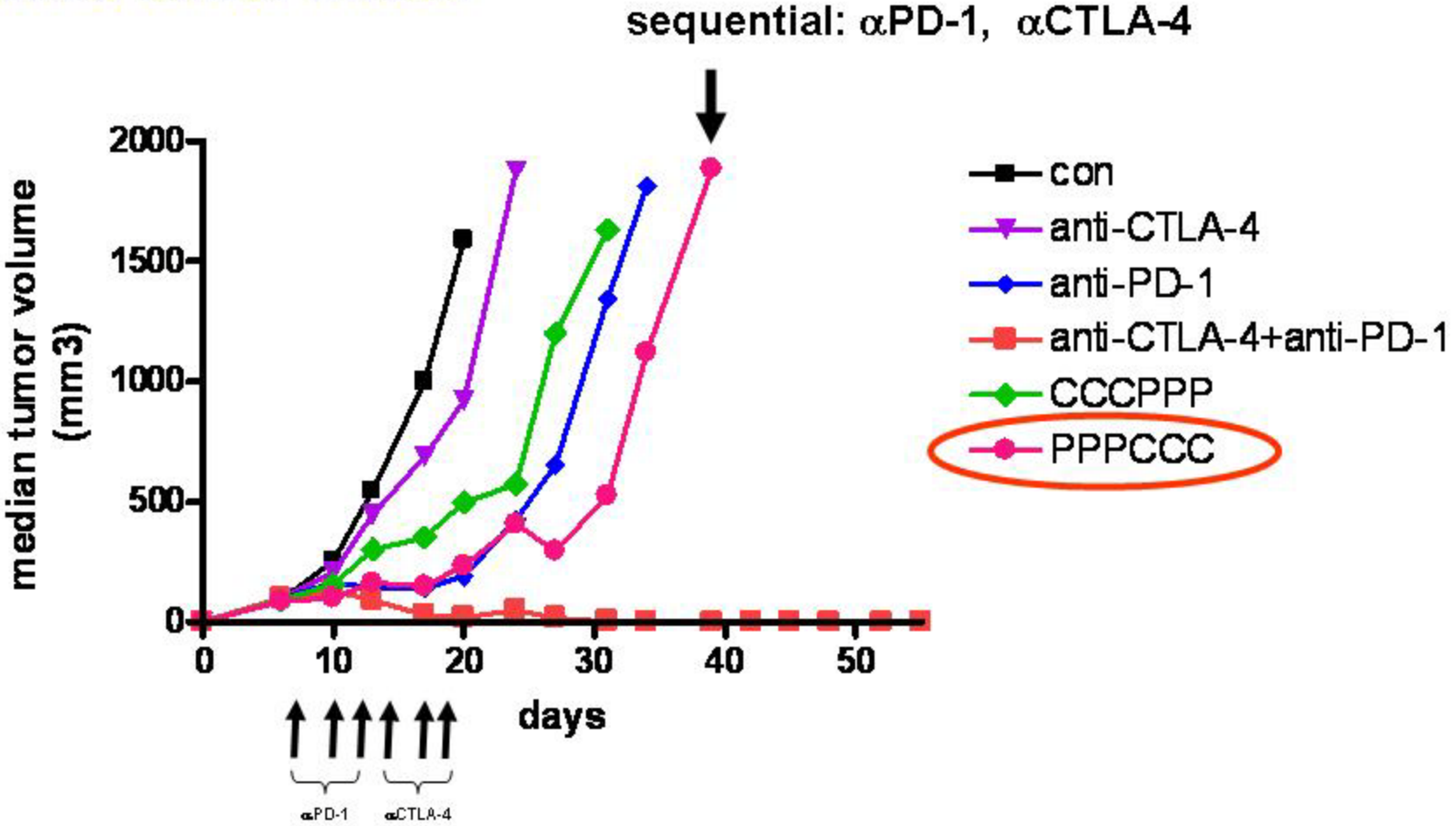

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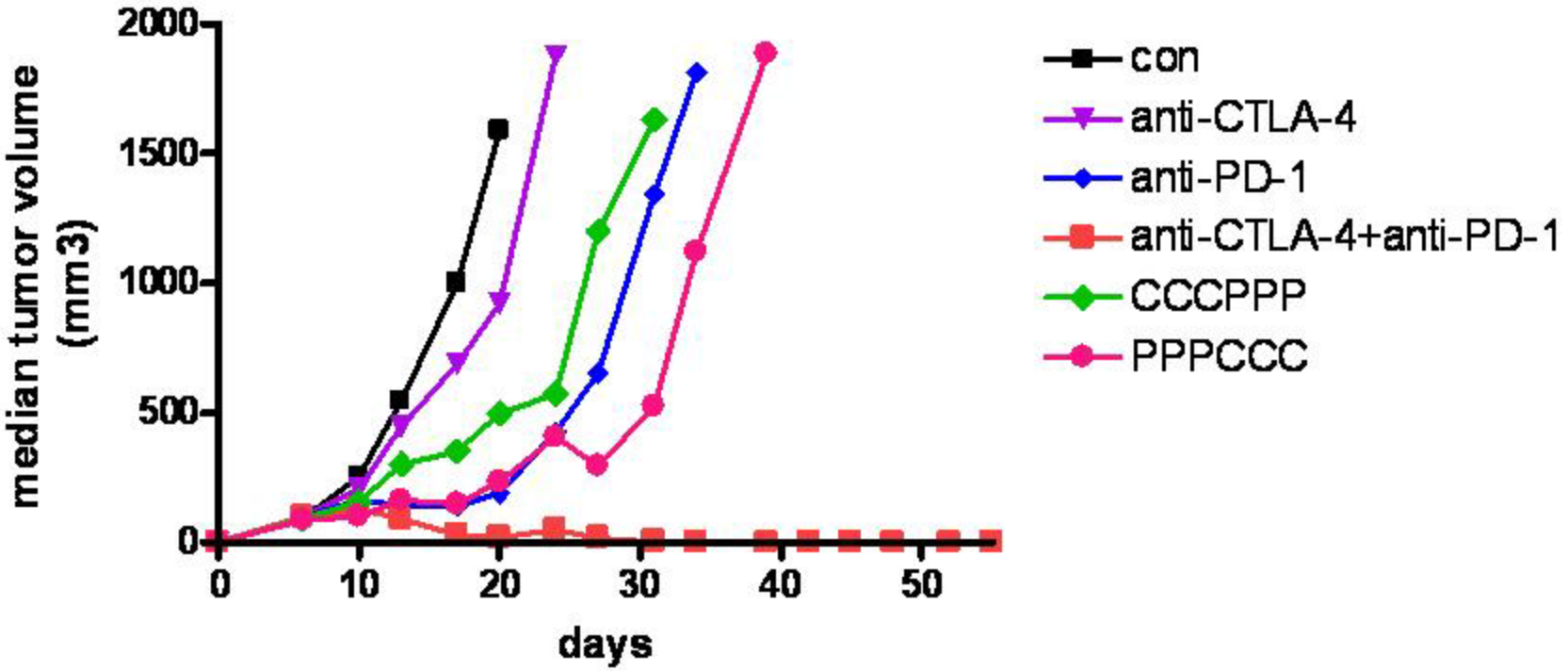

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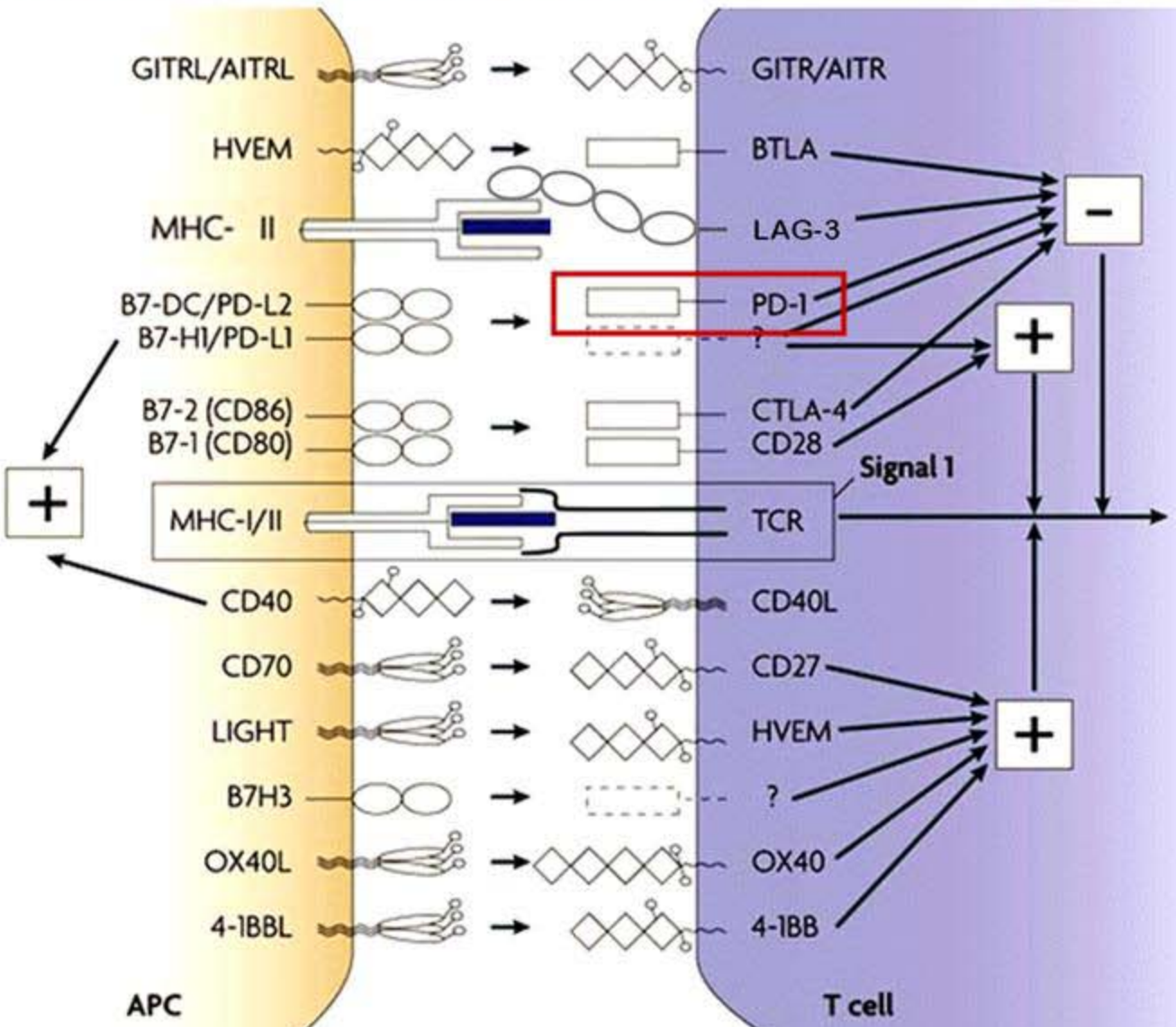

Melero et al. (2007) Nature Rev. Cancer 7: 95

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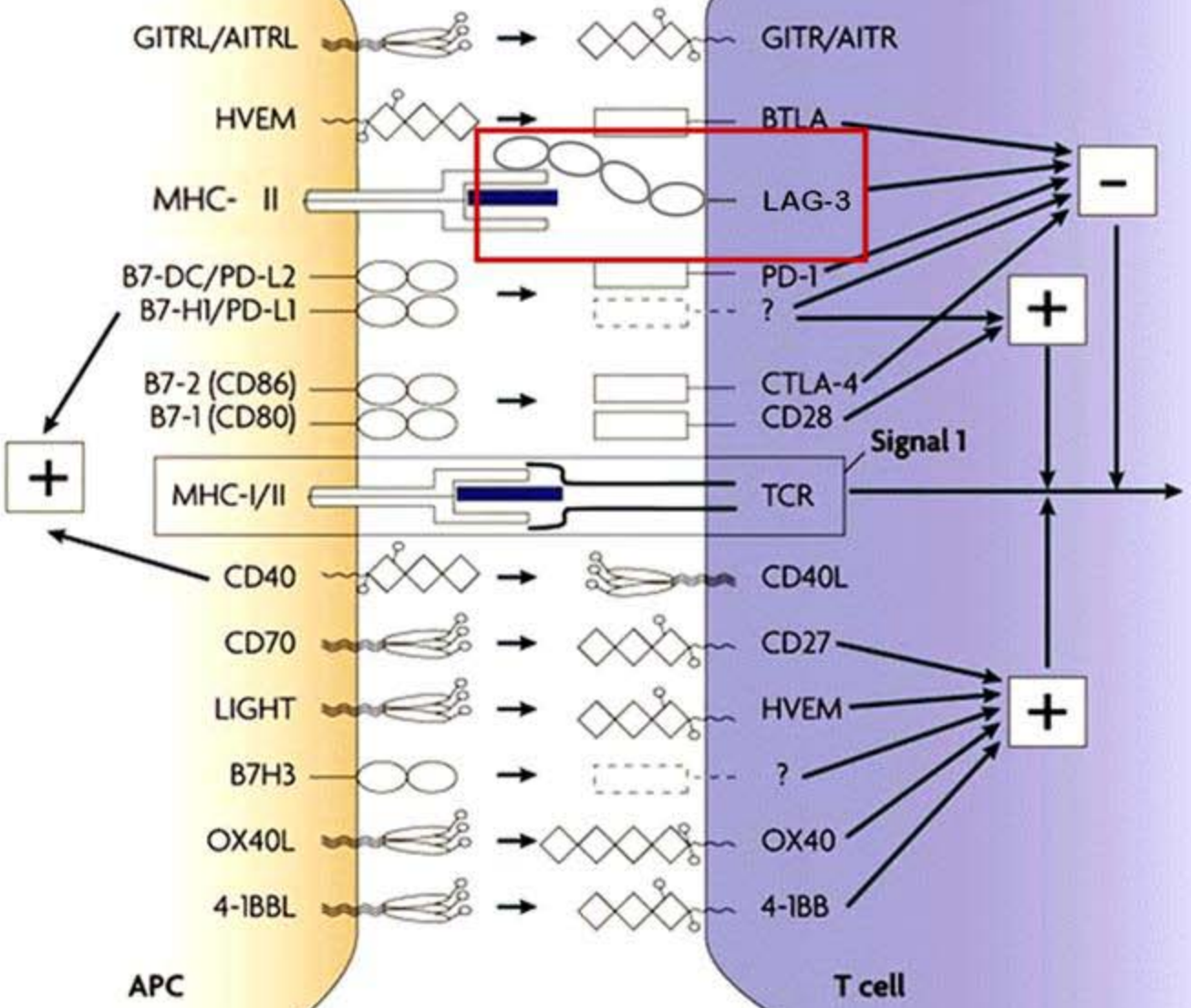

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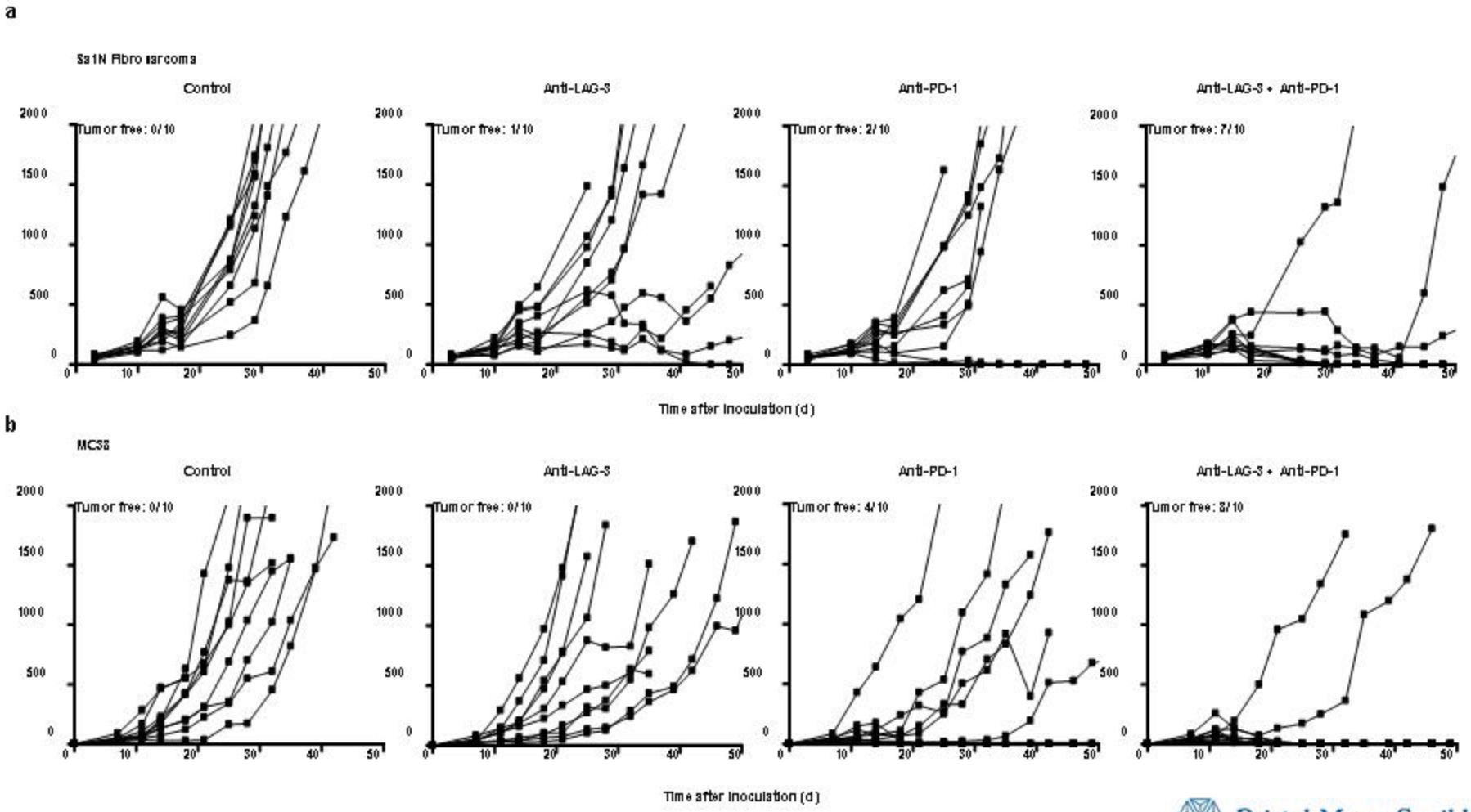
The inhibitory molecules LAG-3 and PD-1 synergistically regulate T cell function and prevent anti-tumor immunity

Seng-Ryong Woo, Monica V. Goldberg, Jaishree Bankoti, Mark Selby, Christopher J. Nirschl, Matthew L. Bettini, Peter Vogel, Joseph F. Grosso, George Netto, Matthew P. Smeltzer, Alcides Chaux, Creg J. Workman, Drew M. Pardoll, Alan J. Korman, Charles G. Drake, and Dario A.A. Vignali



Bristol-Myers Squibb

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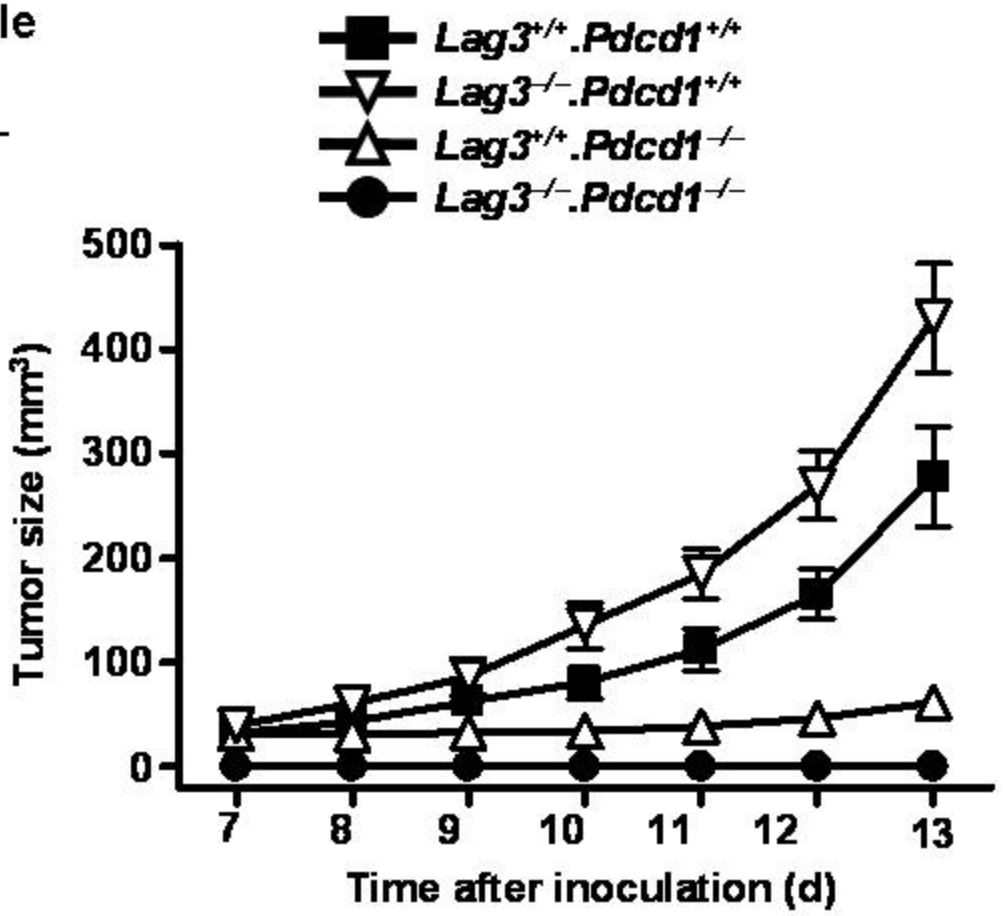
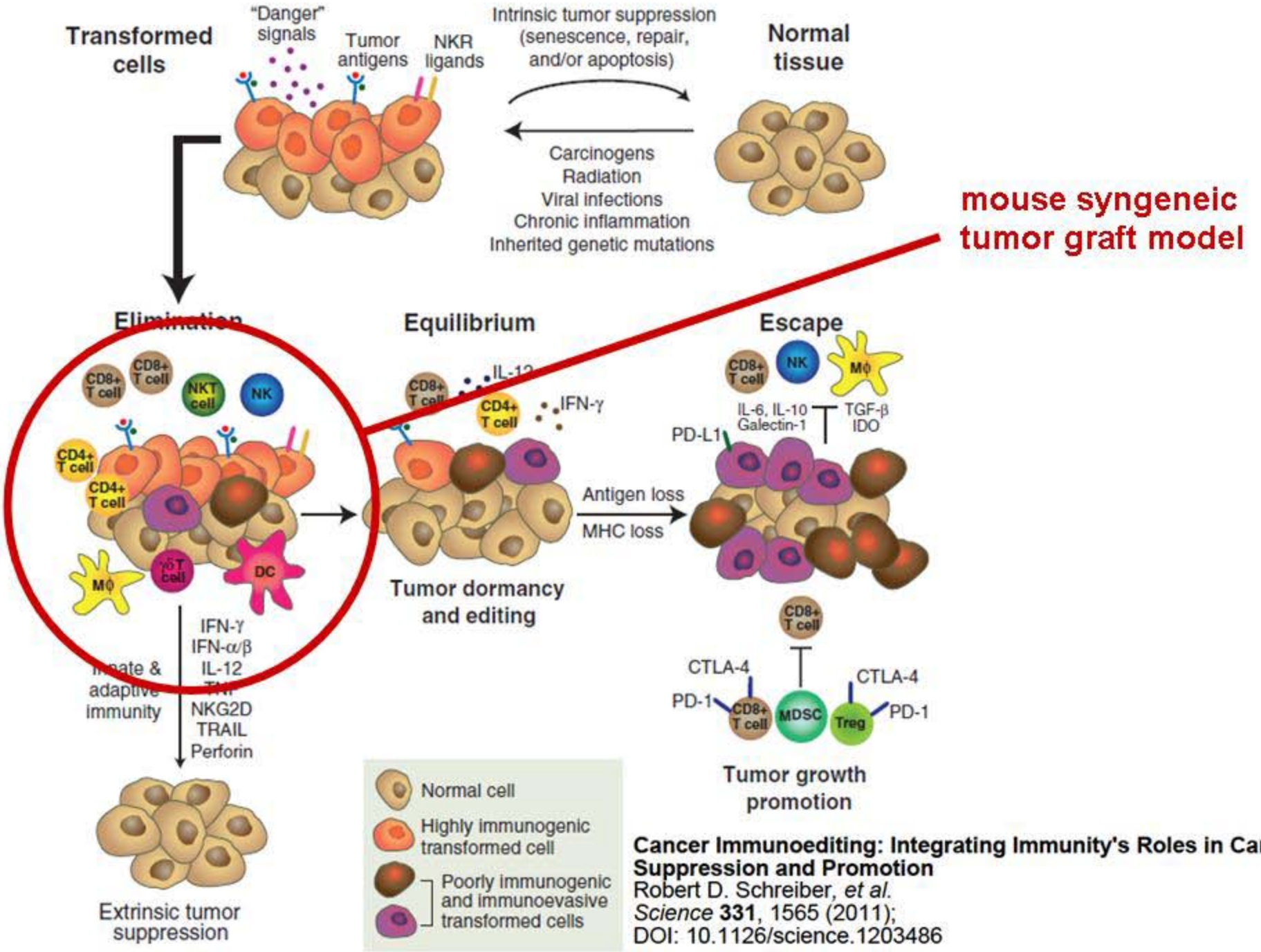
Syngeneic tumor model in single and double knockout mice. B16 melanoma fails to grow in *Lag3–/–Pdcd1–/–* mice.



B16 tumor volume was determined over time post-inoculation in WT, *Lag3–/–*, *Pdcd1–/–* and *Lag3–/–Pdcd1–/–* mice



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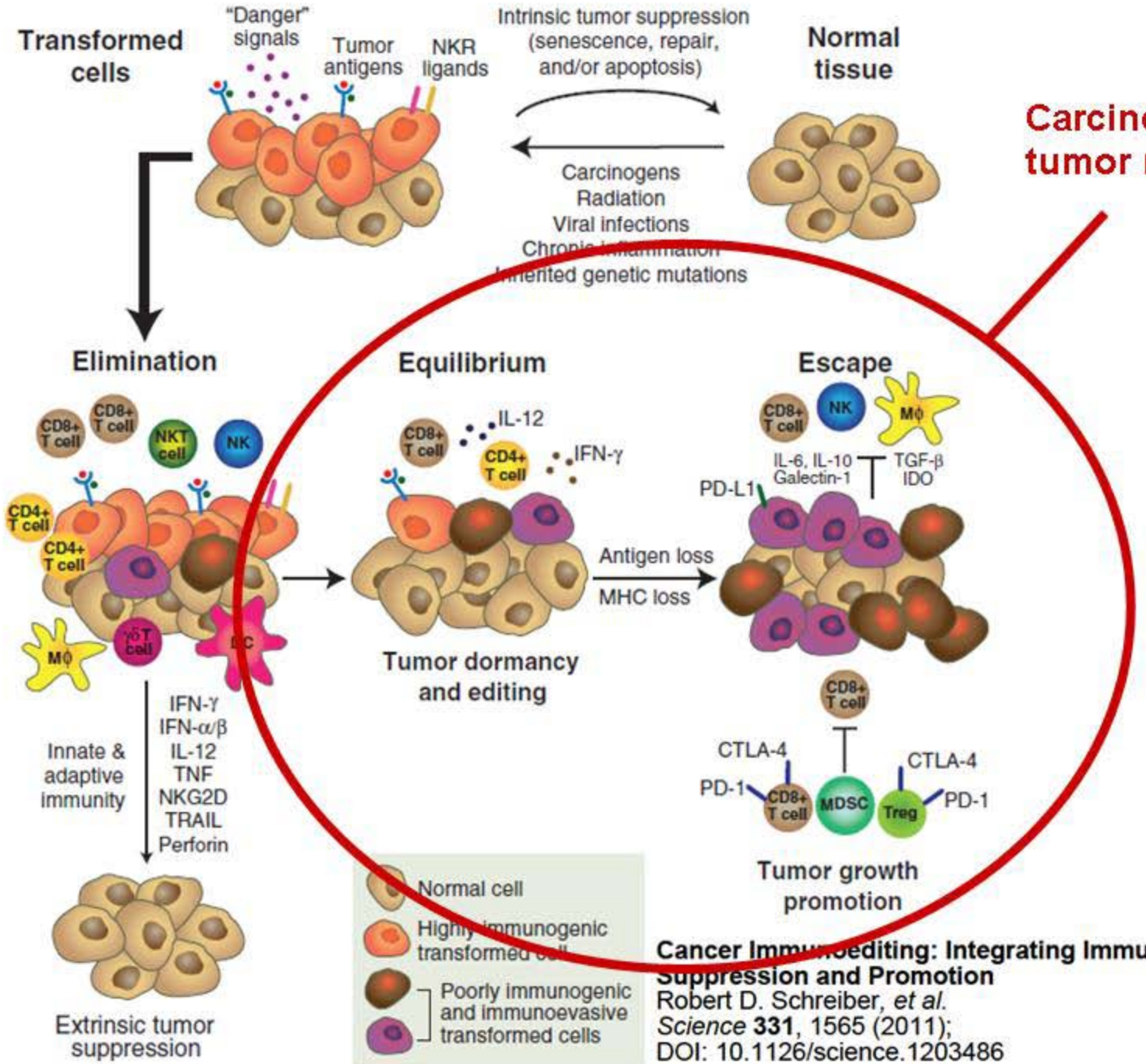

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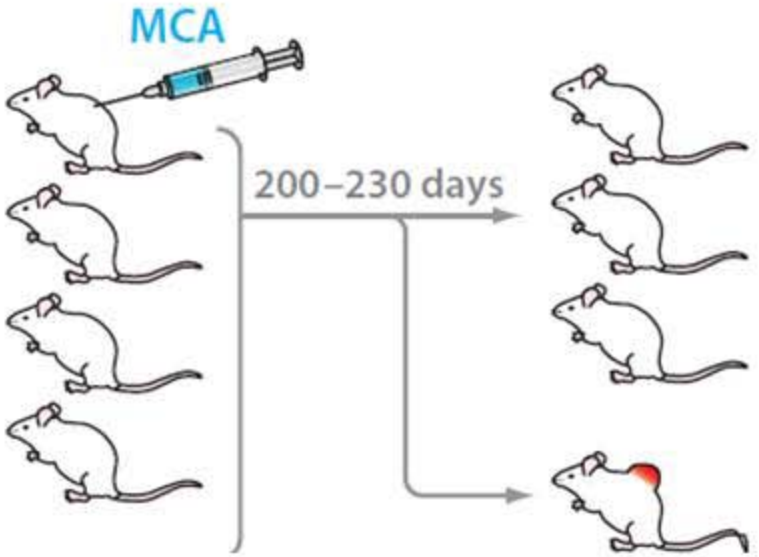
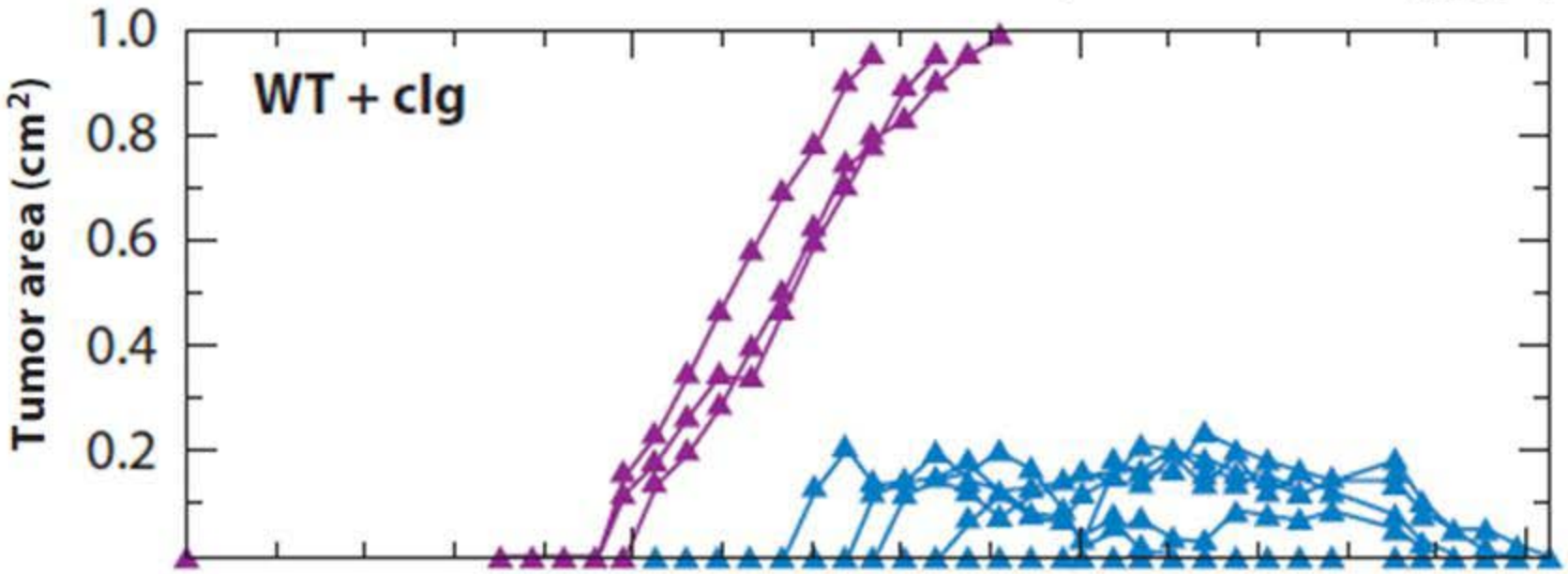
Carcinogen induced mouse models may better recapitulate host-tumor immune interactions

Natural Innate and Adaptive Immunity to Cancer

Matthew D. Vesely,[1] Michael H. Kershaw,[2,3,4] Robert D. Schreiber,[1] and Mark J. Smyth[2,3]

Annu. Rev. Immunol. 2011. 29:235–71





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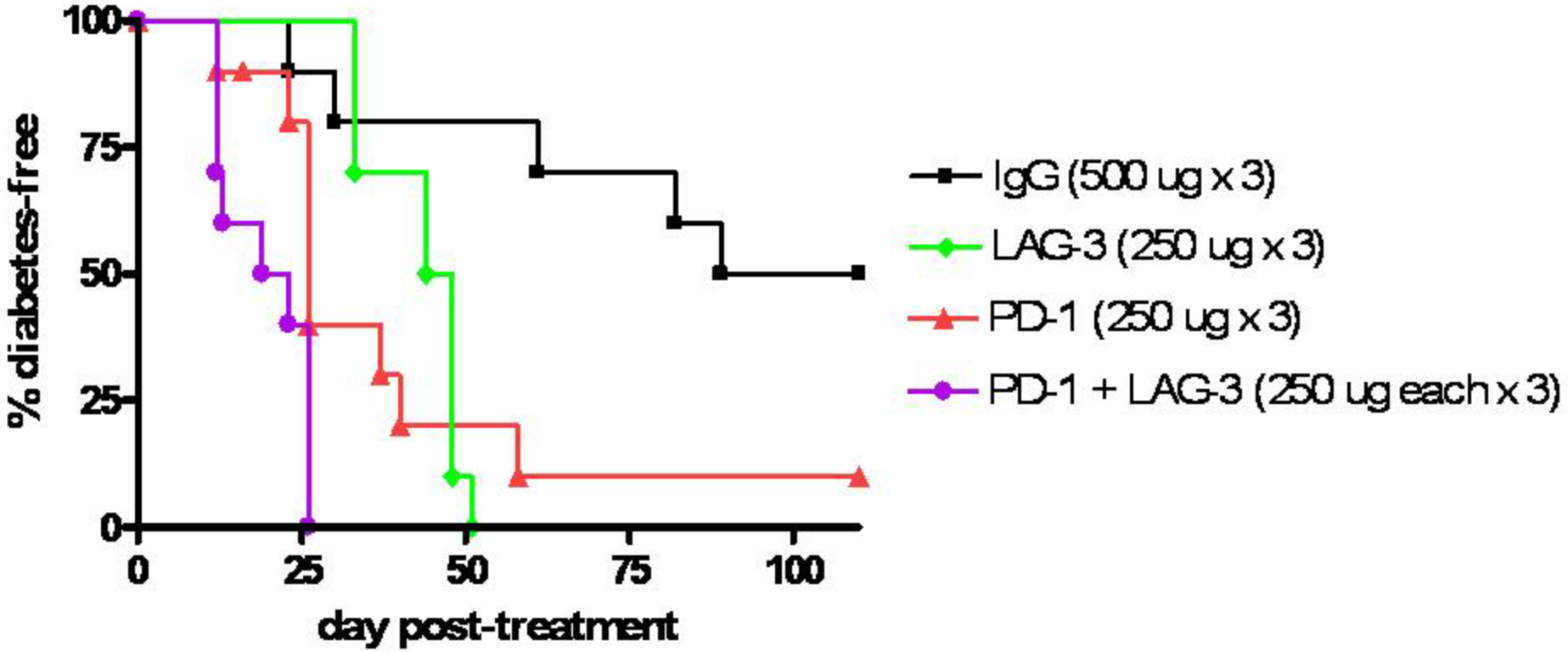
NOD autoimmune model as surrogate for immunotherapy activity



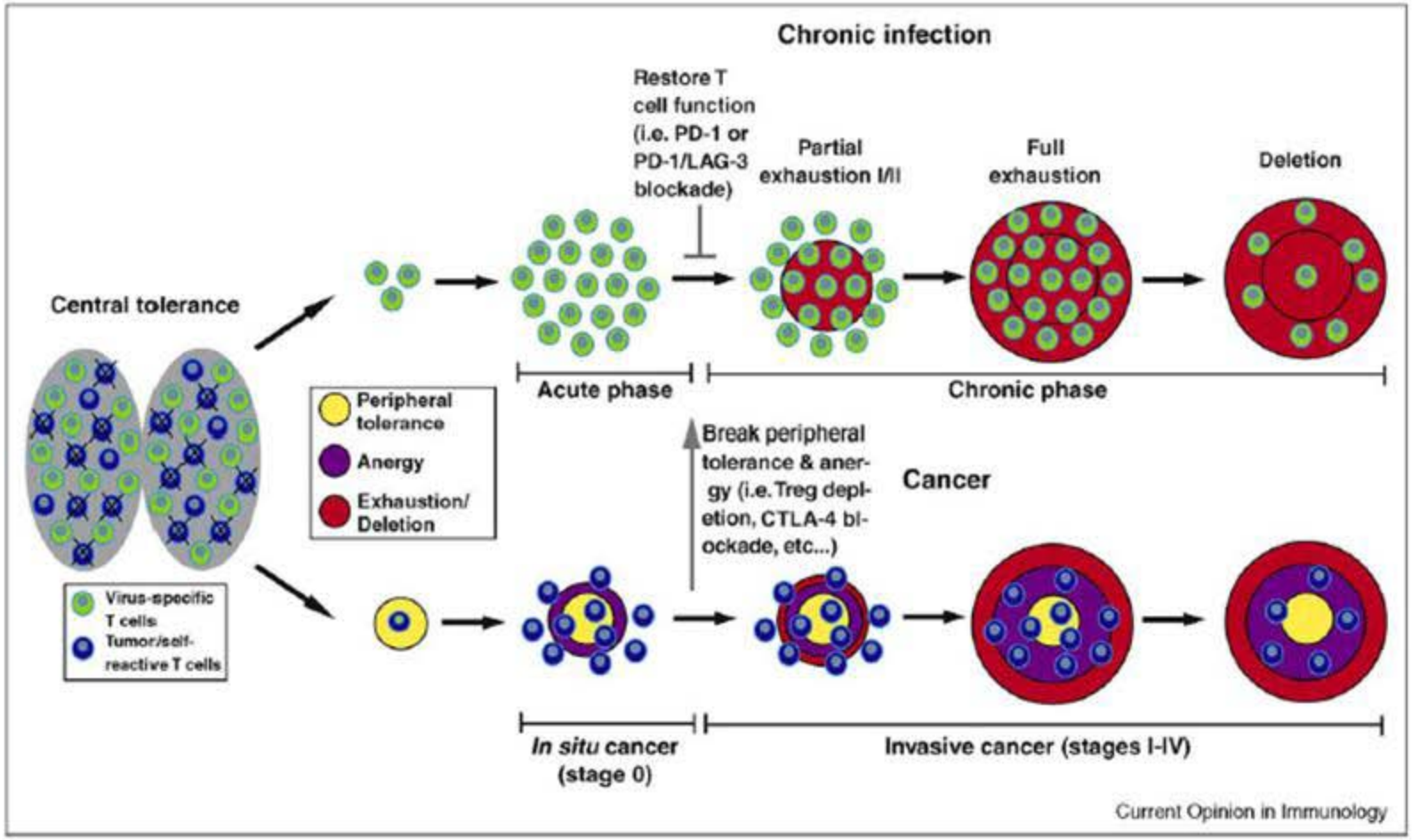
Dosing d1,3,5@ 250 ug/dose

Anti-LAG-3 mAb accelerates diabetes in the NOD model and potentiates anti-PD-1

Features of responding T cells in cancer and chronic infection

Peter S Kim and Rafi Ahmed

Current Opinion in Immunology 2010, **22**:223–230



Comparison of T cell dynamics between chronic infection and cancer. In chronic infection, antigen load primarily drives T cells to hierarchical exhaustion and ultimately deletion. In cancer, tumor/self-reactive T cells are initially kept in check by central and peripheral tolerance. Anergy is believed to occur immediately in tumor pathogenesis perhaps as early as in *in situ* cancer, whereas exhaustion/deletion most probably affects T cell function in more invasive cancer stages. One of the main purposes of tumor immunotherapy is to break immune tolerance and anergy. Treg depletion and CTLA-4 blockade can unleash tumor-reactive T cells for a potent antitumor response, but exhaustion/deletion may ultimately limit the treatment efficacy. Therefore, the therapeutic strategies used in chronic infection to rescue T cells from exhaustion, such as PD-1 or PD-1 plus LAG-3 blockade, also should be considered in tumor immunotherapy.

Coregulation of CD8+ T cell exhaustion by multiple inhibitory receptors during chronic viral infection

Shawn D Blackburn[1], Haina Shin[1], W Nicholas Haining[2,3], Tao Zou[1], Creg J Workman[6], Antonio Polley[1], Michael R Betts[5], Gordon J Freeman[4], Dario A A Vignali[6] & E John Wherry[1]

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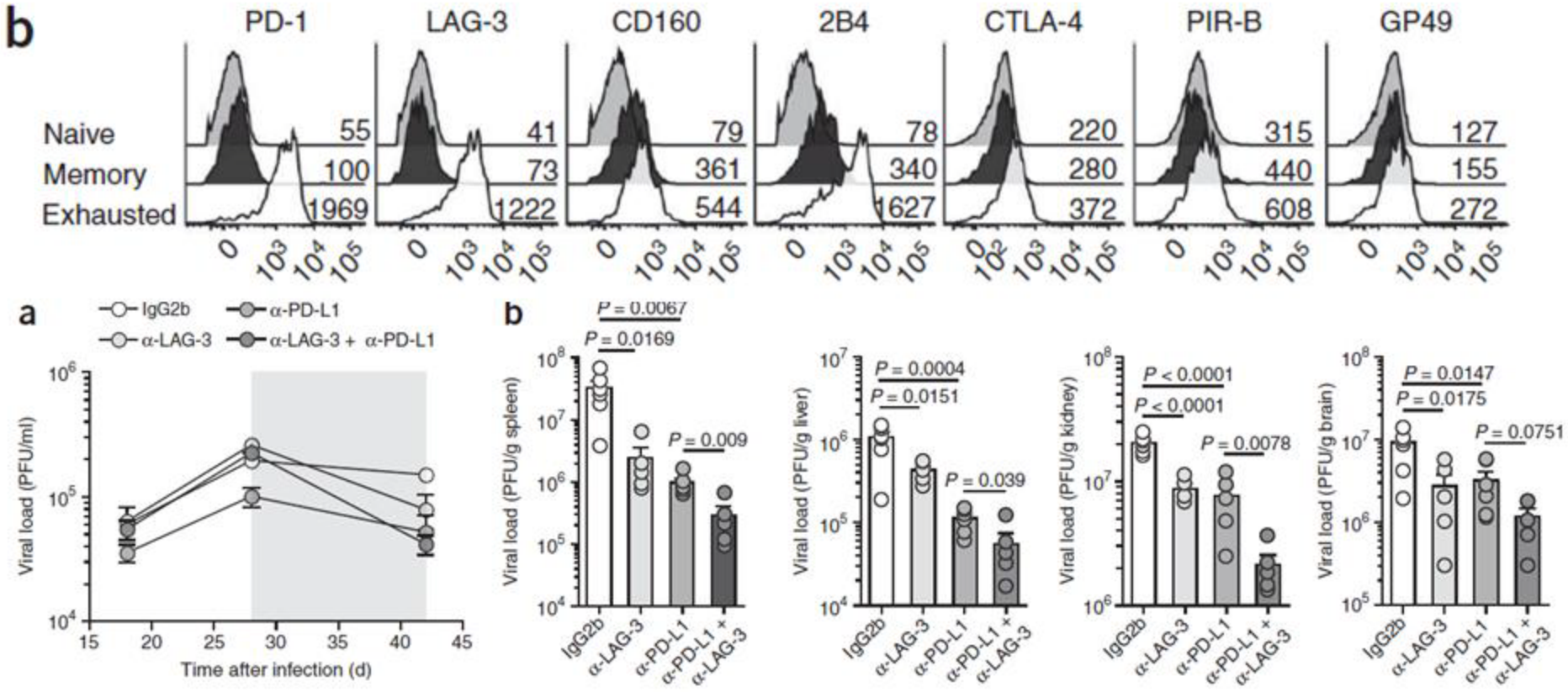

Figure 7 Greater viral control after dual blockade of PD-L1 and LAG-3. (**a**) Longitudinal analysis of viral load in serum of mice depleted of CD4+ T cells and infected with clone 13 and treated with isotype-matched control antibody (IgG2b), anti-LAG-3, anti-PD-1, or anti-LAG-3 and anti-PD-1. (**b**) Viral load in spleen, liver, kidney and brain of mice infected and treated as described in **a**. Each symbol in bars indicates an individual mouse. Data are representative of three independent experiments with five to seven mice per group in each experiment (error bars, s.d.).

- Animal models have been useful predictors of clinical activity in cancer immunotherapy
- The opportunity for synergy in combination therapy is increased when different agents target distinct pathways/mechanisms
- An animal model will not be useful for testing a combination of agents unless that model recapitulates the cancer pathways targeted by all the tested agents
- Individual animal models may comprise only a subset of the pathways exploited by human tumor cells
- Non-cancer disease models may provide surrogate efficacy endpoints for testing combination immunotherapy agents prior to human testing in oncology

Animal Models for Combination Immunotherapy in Cancer

Nils Lonberg, Bristol-Myers Squibb

NCPF Workshop
June 14, 2011

Bristol-Myers Squibb