Combining Immunotherapy and Targeted Therapy in Melanoma

8:45 am - 9:15 am

Antoni Ribas, M.D., Ph.D.
Professor of Medicine
Professor of Surgery
Professor of Molecular and Medical Pharmacology
Director, Tumor Immunology Program,
Jonsson Comprehensive Cancer Center (JCCC)
University of California Los Angeles (UCLA)

Disclosure Information
Antoni Ribas

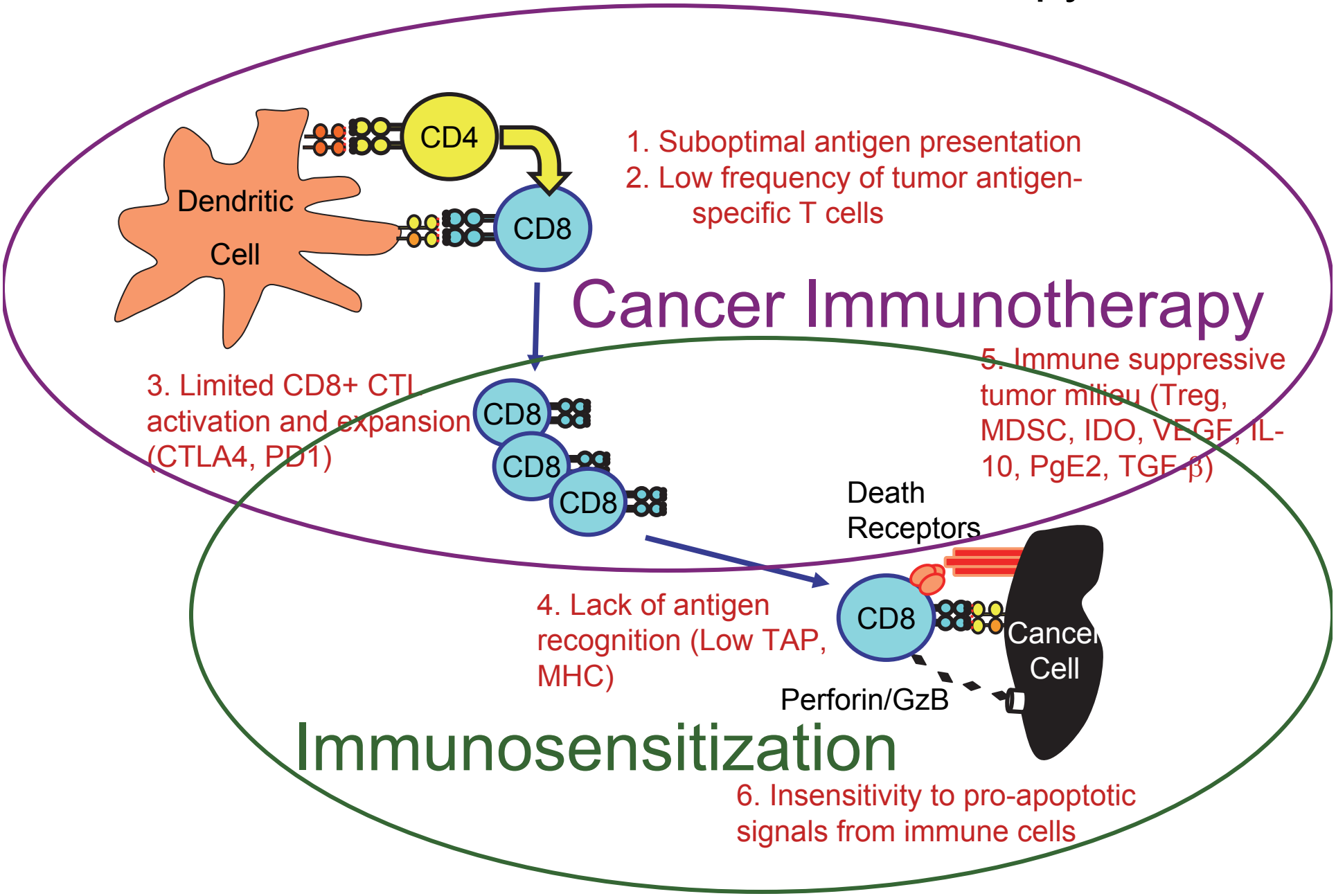
I have the following financial relationships to disclose:

- Consultant for: Kite Pharma
- Speaker's Bureau for: None
- Grant/Research support from: None
- Stockholder in: Kite Pharma
- Honoraria from: Amgen, Celgene, Genentech-Roche, GSK, Millennium, Novartis, Prometheus
- Employee of: None

-and -

- I will discuss the following off label use and/or investigational use in my presentation: vemurafenib

Limitations of Tumor Immunotherapy



Immunosensitization with Targeted Therapies

- Desired features for an immune sensitizing agent:
  - On tumor cells:
    - Target a key oncogenic pathway
    - Inhibit anti-apoptotic molecules
    - Increase pro-apoptotic molecules
    - Increase ligands for immune cells (tumor antigen, MHC, NK activating receptors)
  - On immune system cells:
    - Not kill immune cells
    - No interference on key signaling events in immune system cells (TCR, NK receptor)

Perspective

Targeted Therapies to Improve Tumor Immunotherapy

Jonathan Begley[1,2] and Antoni Ribas[2,3,4]

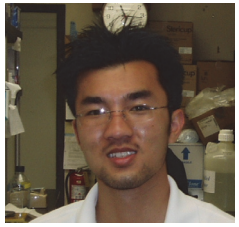
Clin Cancer Res 2008;14(14) July 15, 2008

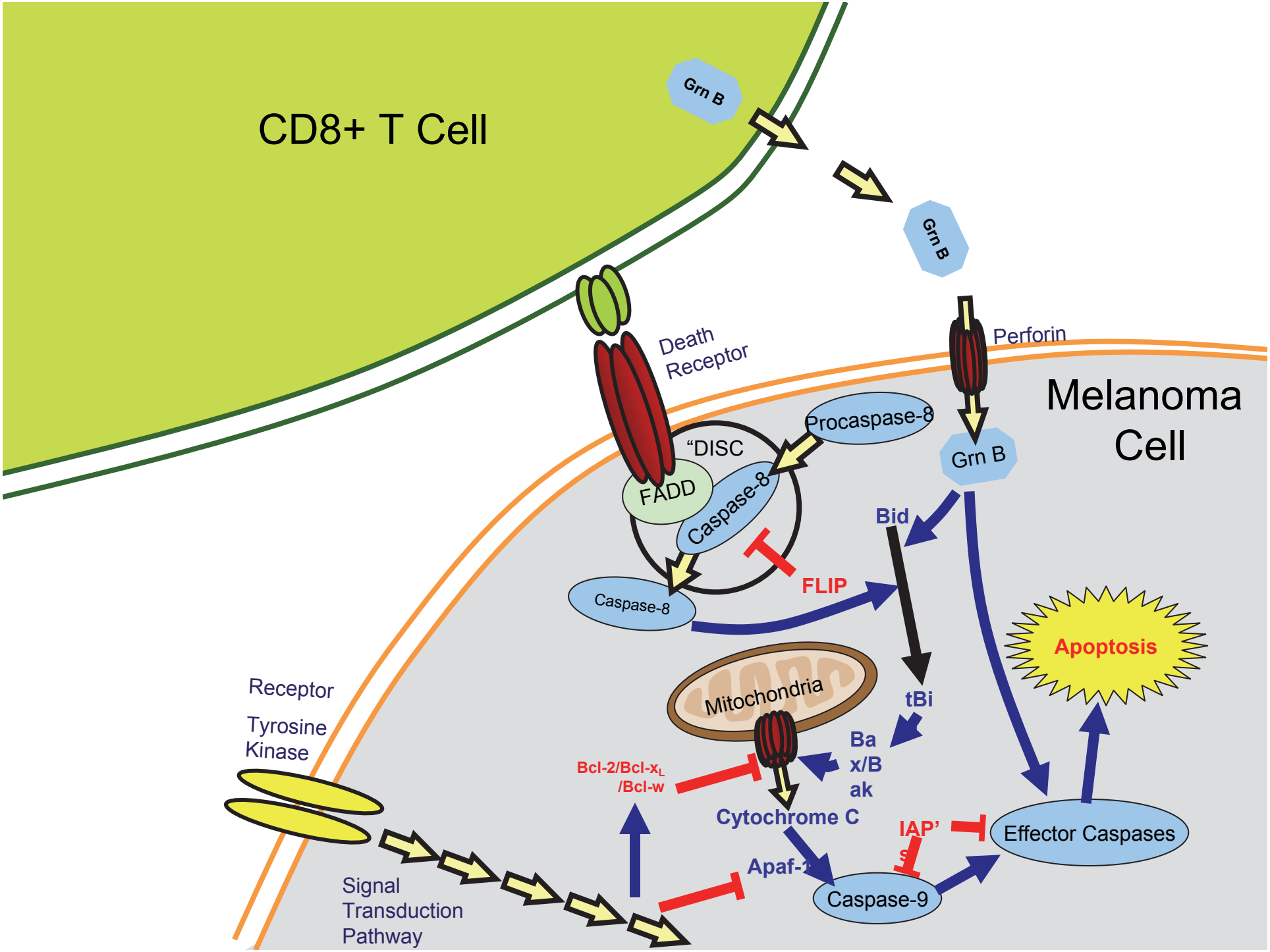
Testing of the Concept of Immunosensitization in Animal Models

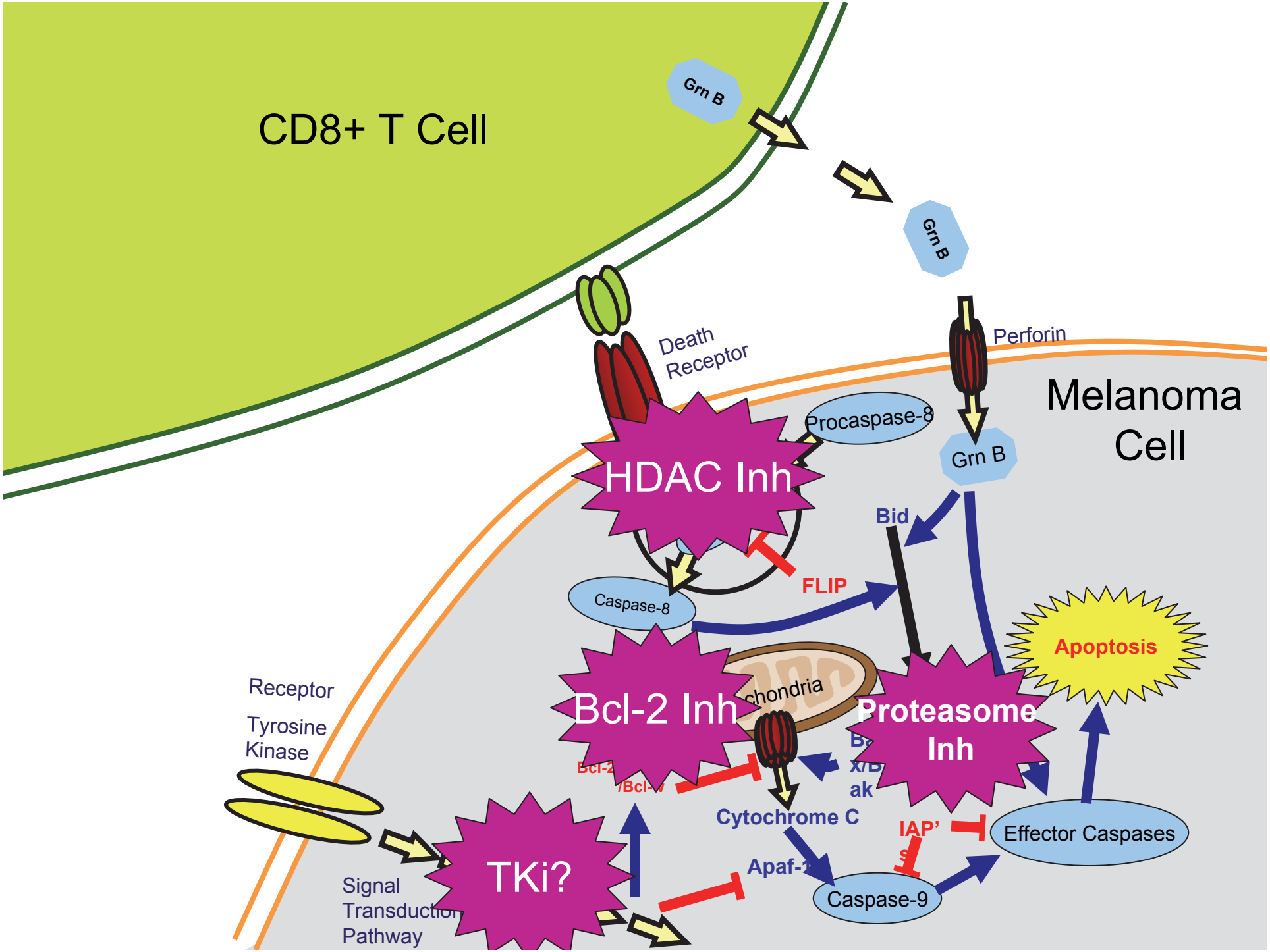
- Bortezomib (proteasome inhibitor) to sensitize to NK cells
  - Schumacher *et al*. JI 2005

- ABT-737 (Bcl-2 inhibitor) to sensitize to T cells
  - Begley *et al*. CII 2008

- LAQ824 (HDAC inhibitor) to sensitize to T cells
  - Vo *et al*. CR 2009




CD8+ T Cell
Grn B
Grn B
Death Receptor
Perforin
Melanoma Cell
Procaspase-8
"DISC
FADD
Caspase-8
Grn B
Bid
FLIP
Caspase-8
Apoptosis
Mitochondria
tBi
Receptor
Tyrosine Kinase
Ba x/B ak
Bcl-2/Bcl-x$_L$ /Bcl-w
Cytochrome C
IAP'
Effector Caspases
Apaf-
Caspase-9
Signal Transduction Pathway

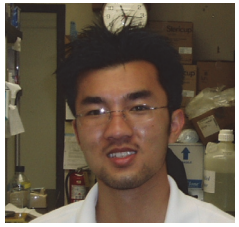

CD8+ T Cell
Grn B
Grn B
Death Receptor
Perforin
Melanoma Cell
Procaspase-8
HDAC Inh
Grn B
Bid
FLIP
Caspase-8
Apoptosis
Receptor
Tyrosine Kinase
Bcl-2 Inh
chondria
Proteasome Inh
Cytochrome C
IAP'
Effector Caspases
TKi?
Apaf-
Caspase-9
Signal Transduction Pathway

Testing of the Concept of Immunosensitization in Animal Models

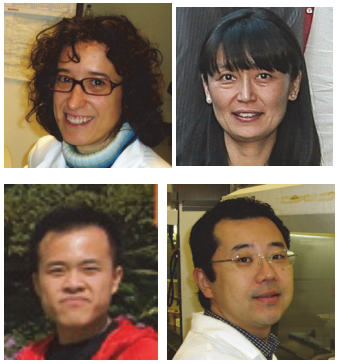
- Bortezomib (proteasome inhibitor) to sensitize to NK cells
  - Schumacher *et al*. JI 2005

- ABT-737 (Bcl-2 inhibitor) to sensitize to T cells
  - Begley *et al*. CII 2008

- LAQ824 (HDAC inhibitor) to sensitize to T cells
  - Vo *et al*. CR 2009



- PLX4032 (BRAF inhibitor) to sensitize to T cells
  - Comin-Anduix *et al*. CCR 2010
  - Koya *et al*. CR 2012



Pre-clinical evidence supporting the feasibility of combinations of BRAFi + immunotherapy

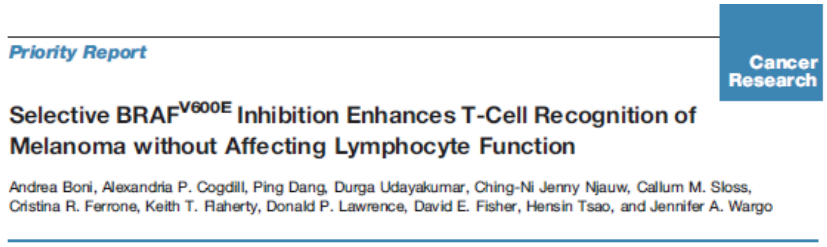
The BRAF–MAPK signaling pathway is essential for cancer-immune evasion in human melanoma cells

JEM

Hidetoshi Sumimoto, Fumie Imabayashi, Tomoko Iwata, and Yutaka Kawakami

J Exp Med 2006 June 26; 203 (7): 1651-6.

Oncogenic BRAF-induced production of immune suppressive factors (IL-6, IL-10, VEGF) is inhibited with a MEK inhibitor



Priority Report

Cancer Research

Selective BRAF^{V600E} Inhibition Enhances T-Cell Recognition of Melanoma without Affecting Lymphocyte Function

Andrea Boni, Alexandria P. Cogdill, Ping Dang, Durga Udayakumar, Ching-Ni Jenny Njauw, Callum M. Sloss, Cristina R. Ferrone, Keith T. Flaherty, Donald P. Lawrence, David E. Fisher, Hensin Tsao, and Jennifer A. Wargo

Cancer Res 2010 Jul 1; 70 (13): 5213-9.

Vemurafenib increases melanosomal antigen expression and T cell recognition

Cancer Therapy: Preclinical

Clinical Cancer Research

The Oncogenic BRAF Kinase Inhibitor PLX4032/RG7204 Does Not Affect the Viability or Function of Human Lymphocytes across a Wide Range of Concentrations

Begoña Comin-Anduix[1,2], Thinle Chodon[3], Hooman Sazegar[3], Douglas Matsunaga[3], Stephen Mock[3], Jason Jalil[3], Helena Escuin-Ordinas[3], Bartosz Chmielowski[3], Richard C Koya[1], and Antoni Ribas[1,2,3]

Clin Cancer Res 2010 Dec 15; 16 (24): 6040-8.

Human T cells exposed to vemurafenib are fully functional

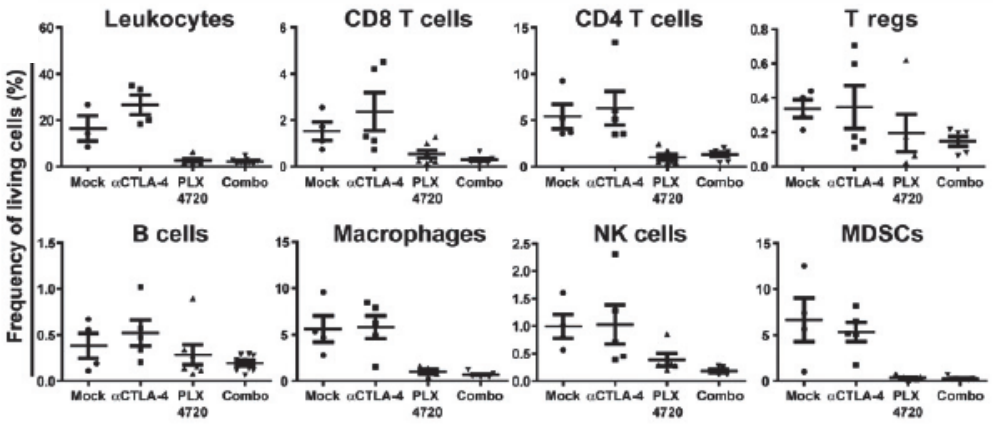
Pre-clinical evidence against the feasibility of combinations of BRAFi + immunotherapy

RESEARCH PAPER

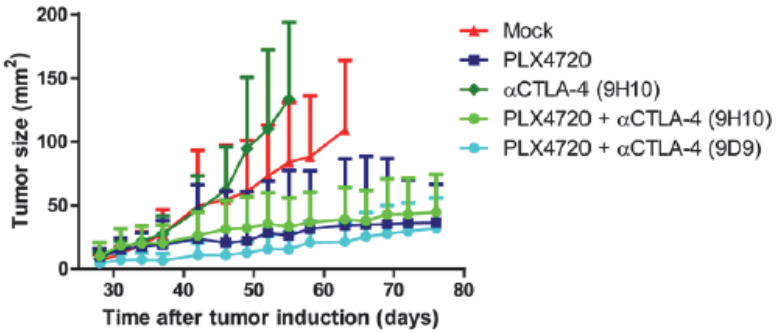
Oncolmmunology 1:6, 1-9; September, 2012; © 2012 Landes Bioscience

Selective BRAF inhibition decreases tumor-resident lymphocyte frequencies in a mouse model of human melanoma

Anna I. Hooijkaas,[1,†] Jules Gadiot,[1,†] Michelle Morrow,[2] Ross Stewart,[2] Ton N. Schumacher[1] and Christian U. Blank[1,3,*]



PLX4720 treatment leads to a decreased frequency of immune cells in BRAFV600E/PTEN-/- melanomas and this cannot be restored by CTLA-4 blockade



Addition of anti-CTLA-4 mAb treatment to PLX4720 treatment does not further improve tumor growth control

Clinical evidence supporting the feasibility of combinations of BRAFi + immunotherapy

Cancer Therapy: Clinical
See commentary by Bajor and Vonderheide, p. 1192

Clinical Cancer Research

Selective BRAF Inhibitors Induce Marked T-cell Infiltration into Human Metastatic Melanoma

James S. Wilmott[1,2], Georgina V. Long[1,2,6,7,8], Julie R. Howle[1,2,8], Lauren E. Haydu[1,2], Raghwa N. Sharma[2,4,8], John F. Thompson[1,2,3], Richard F. Kefford[1,2,6,7,8], Peter Hersey[1,2,5], and Richard A. Scolyer[1,2,3]

Clin Cancer Res 2012 March 1; 18 (5).

CD8+ T cell infiltration in regressing melanoma lesions after BRAFi therapy

Cancer Therapy: Clinical

Clinical Cancer Research

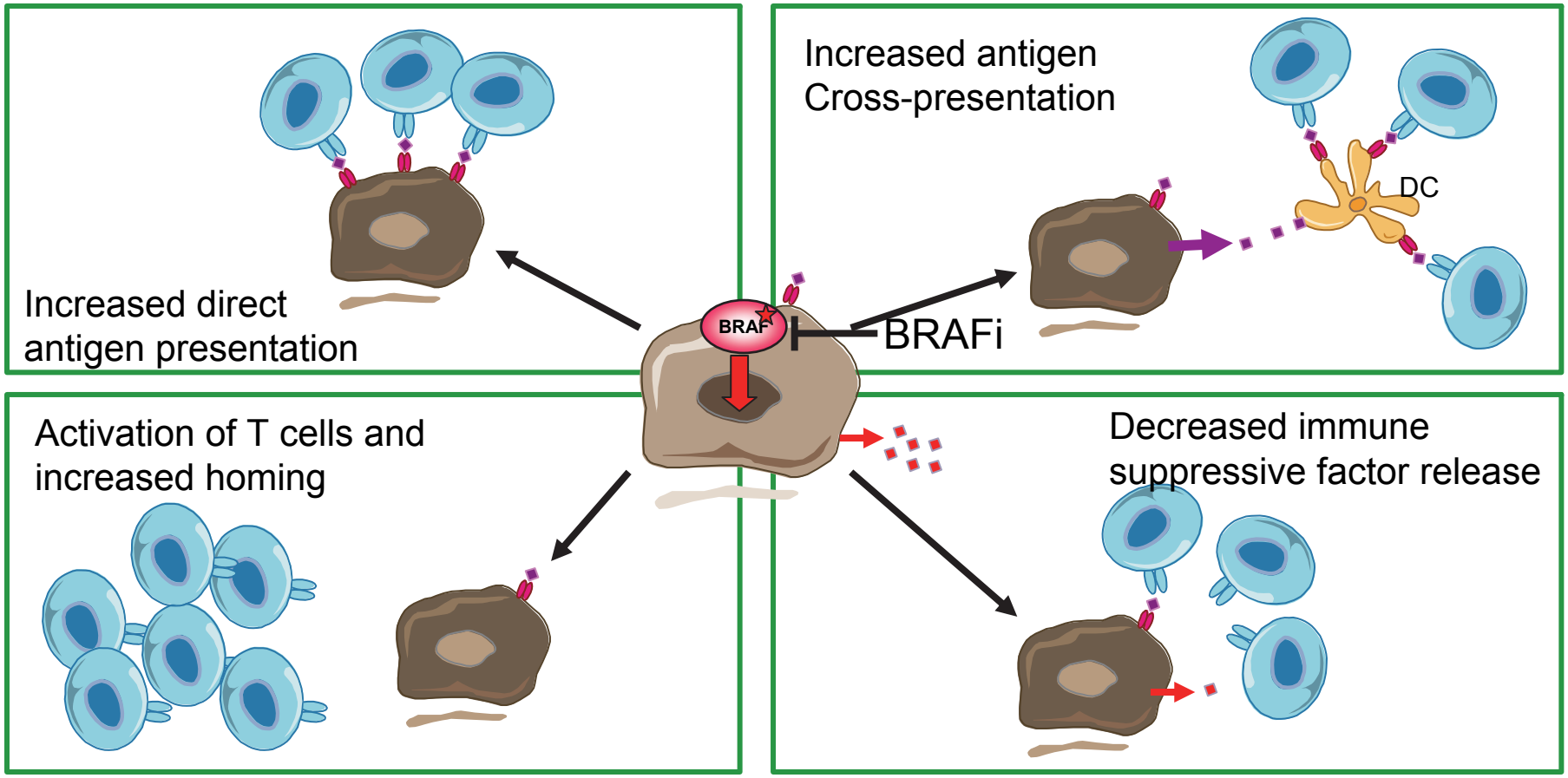
BRAF(V600) Inhibitor GSK2118436 Targeted Inhibition of Mutant BRAF in Cancer Patients Does Not Impair Overall Immune Competency

David S. Hong[1], Luis Vence[2], Gerald Falchook[1], Laszlo G. Radvanyi[2], Chengwen Liu[2], Vicki Goodman[3], Jeffery J. Legos[3], Sam Blackman[3], Antonio Scarmadio[1], Razelle Kurzrock[1], Gregory Lizee[2], and Patrick Hwu[2]

Clin Cancer Res 2012 April 15; 18 (8): 2326-35.

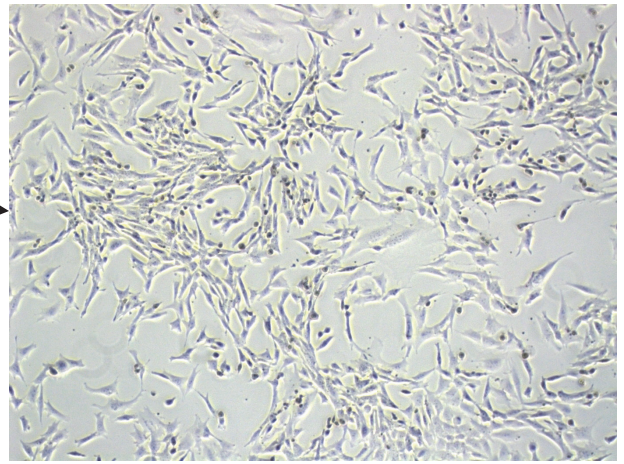
T cells from patients treated with dabrafenib are fully functional

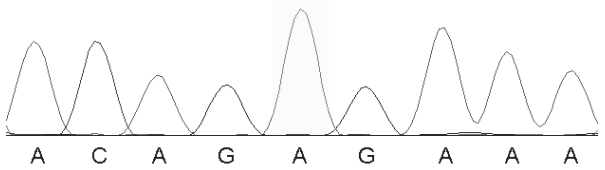
How can BRAF targeted therapy increase the activity of tumor immunotherapy?



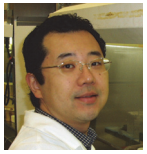
SM1: A $BRAF^{V600E}$-driven Melanoma Syngeneic to Immunocompetent Mice

Goel, Haluska *et al*. Melanocytic nevus-like hyperplasia and melanoma in transgenic BRAFV600E mice. Oncogene. 2009; 28 (23): 2289-98.





$BRAF^{V600E}$ mutation

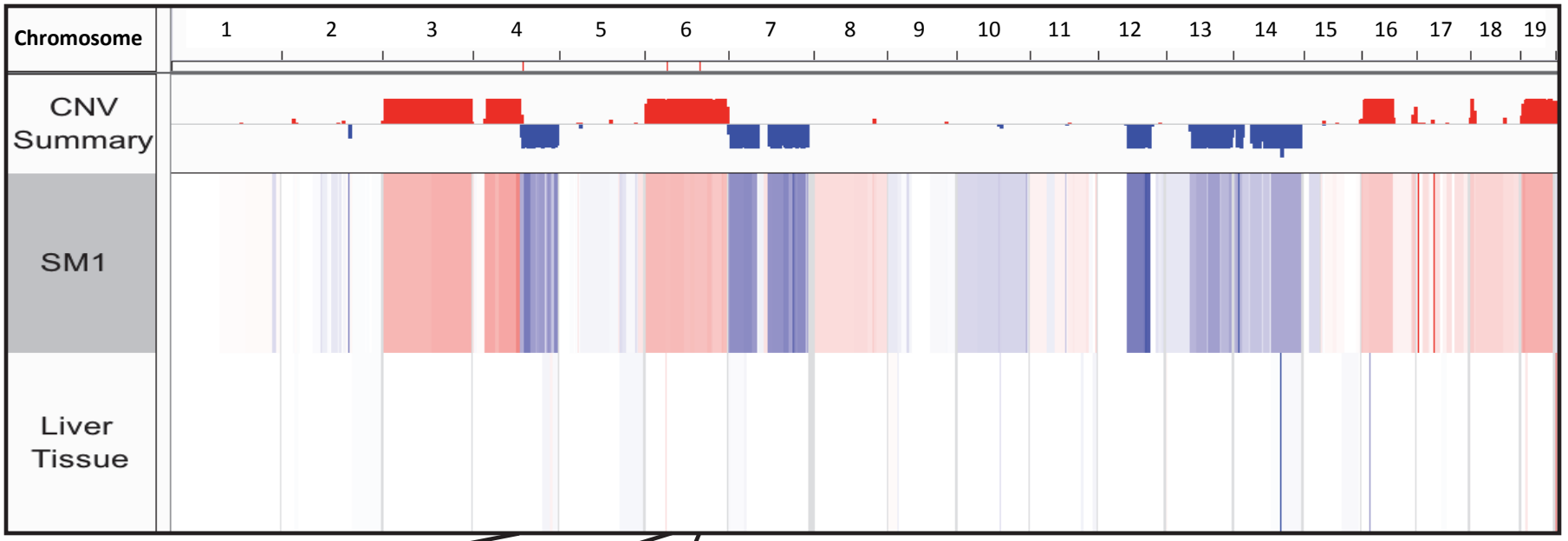


Richard Koya, MD, PhD

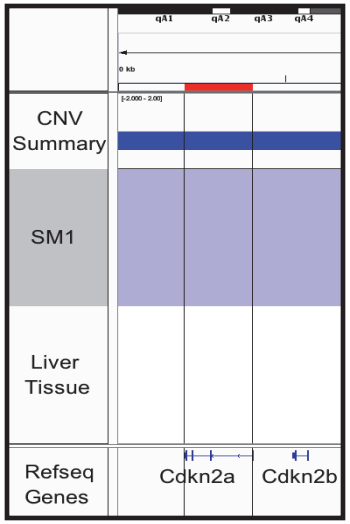
Stephen Mok

Koya *et al*. Cancer Res 2012

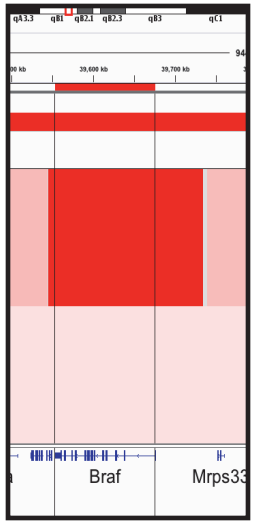
Gene copy number variations (CNV) in SM1 is similar to human melanomas



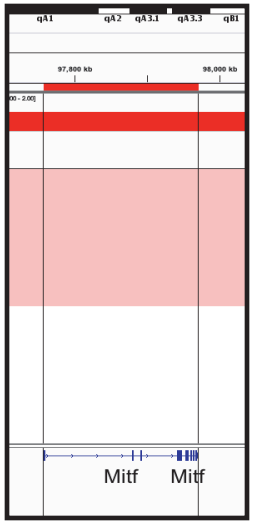
Cdkn2a



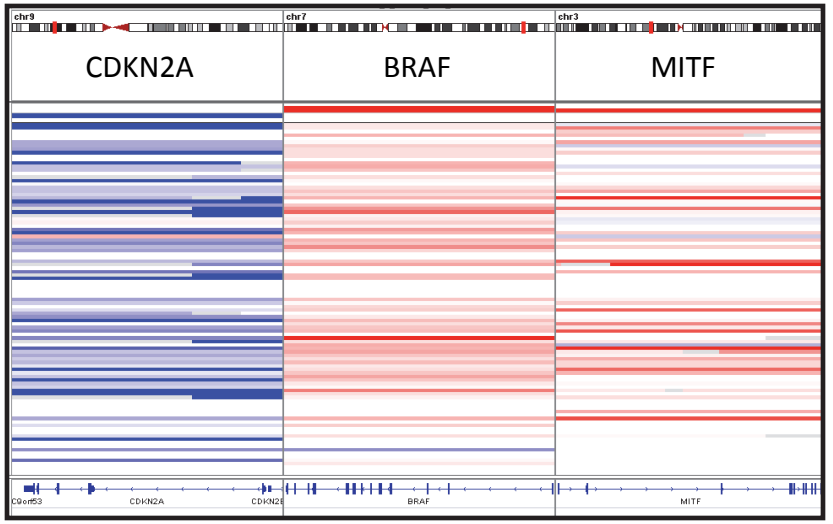
Braf



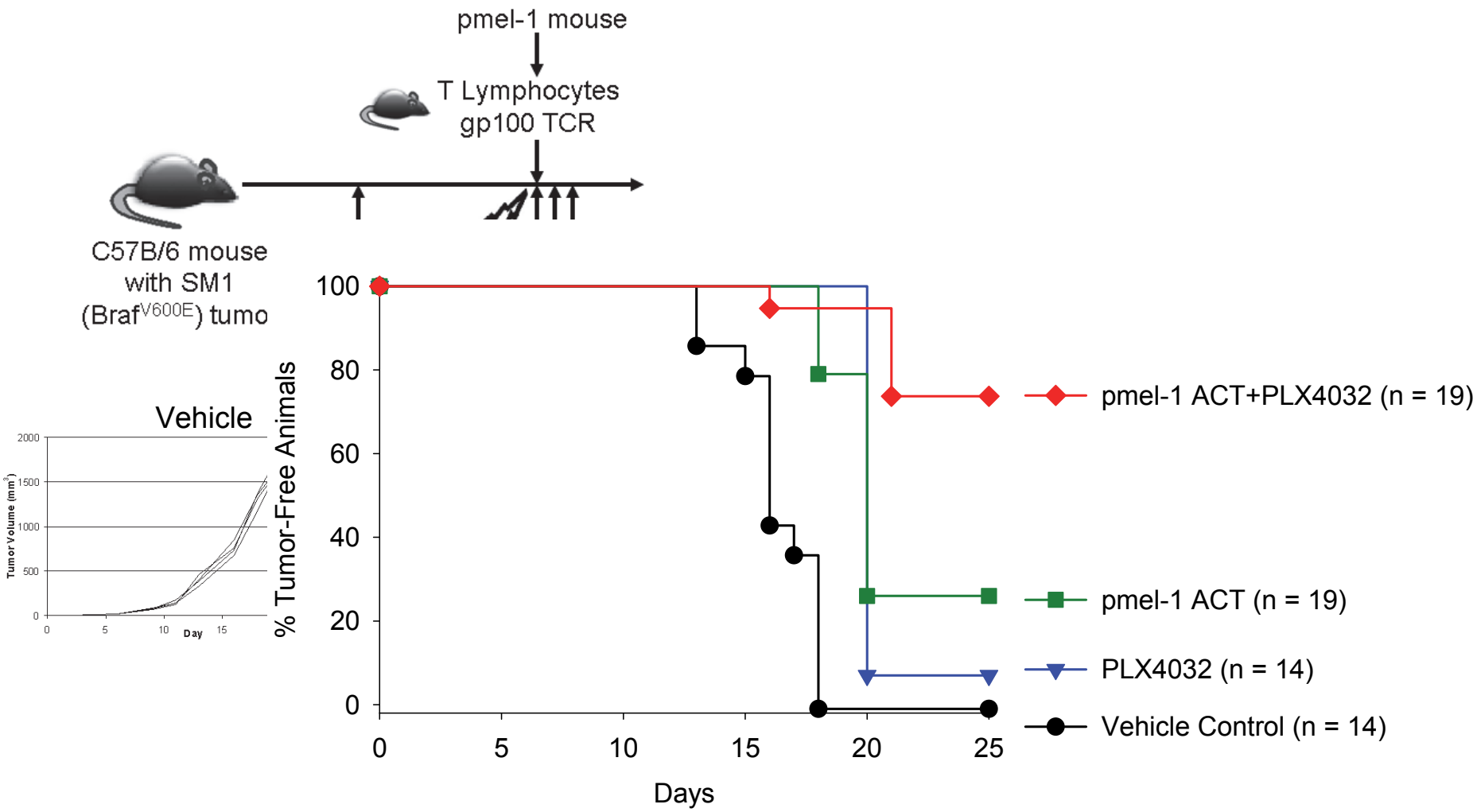
Mitf



CNV comparing SM1 with 108 human melanomas

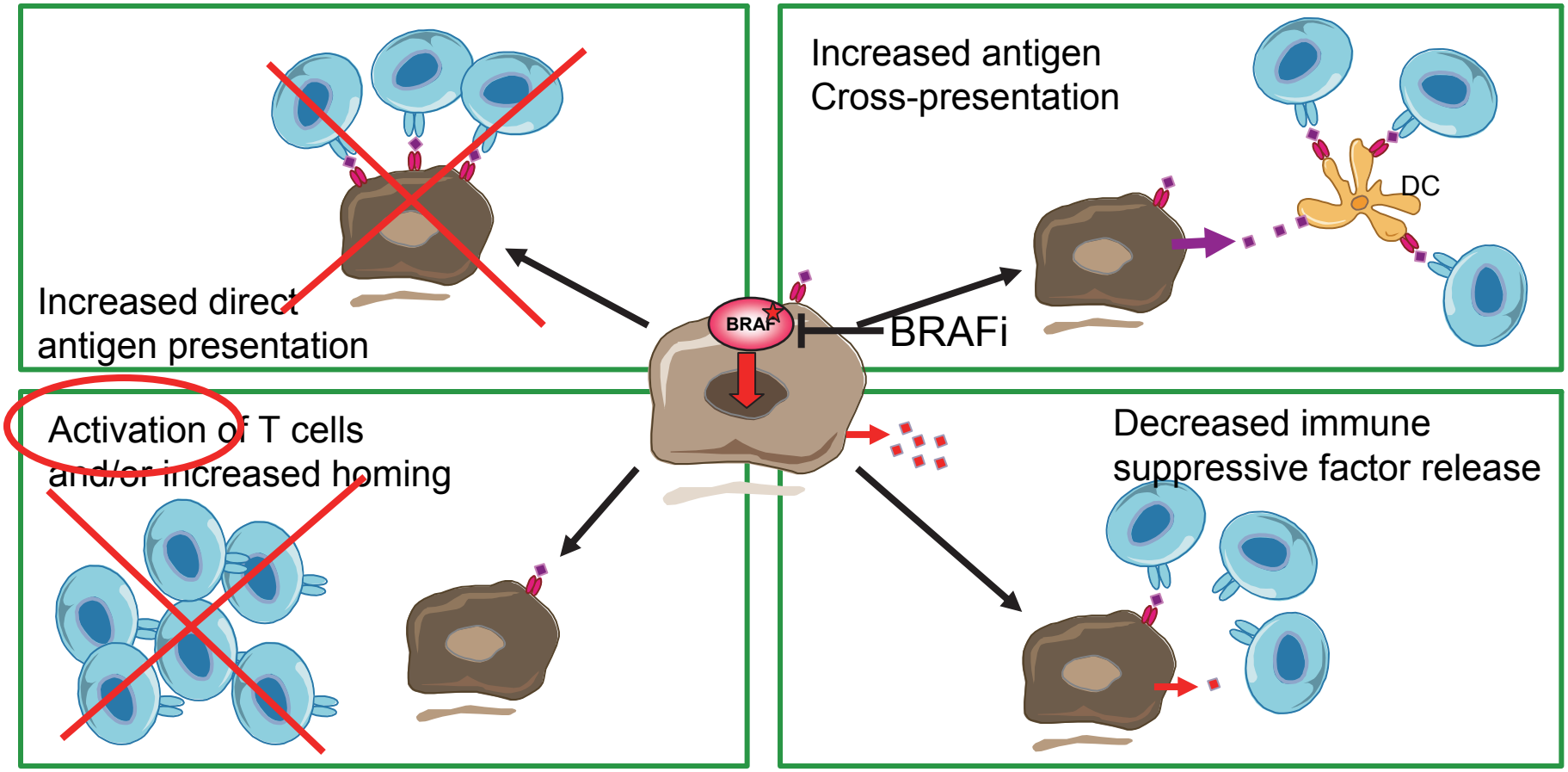


pmel-1 ACT immunotherapy+BRAF targeted therapy against SM1 (murine melanoma driven by *BRAF^{V600E}*)



3 replicate experiments, $p < 0.0001$ by log rank test

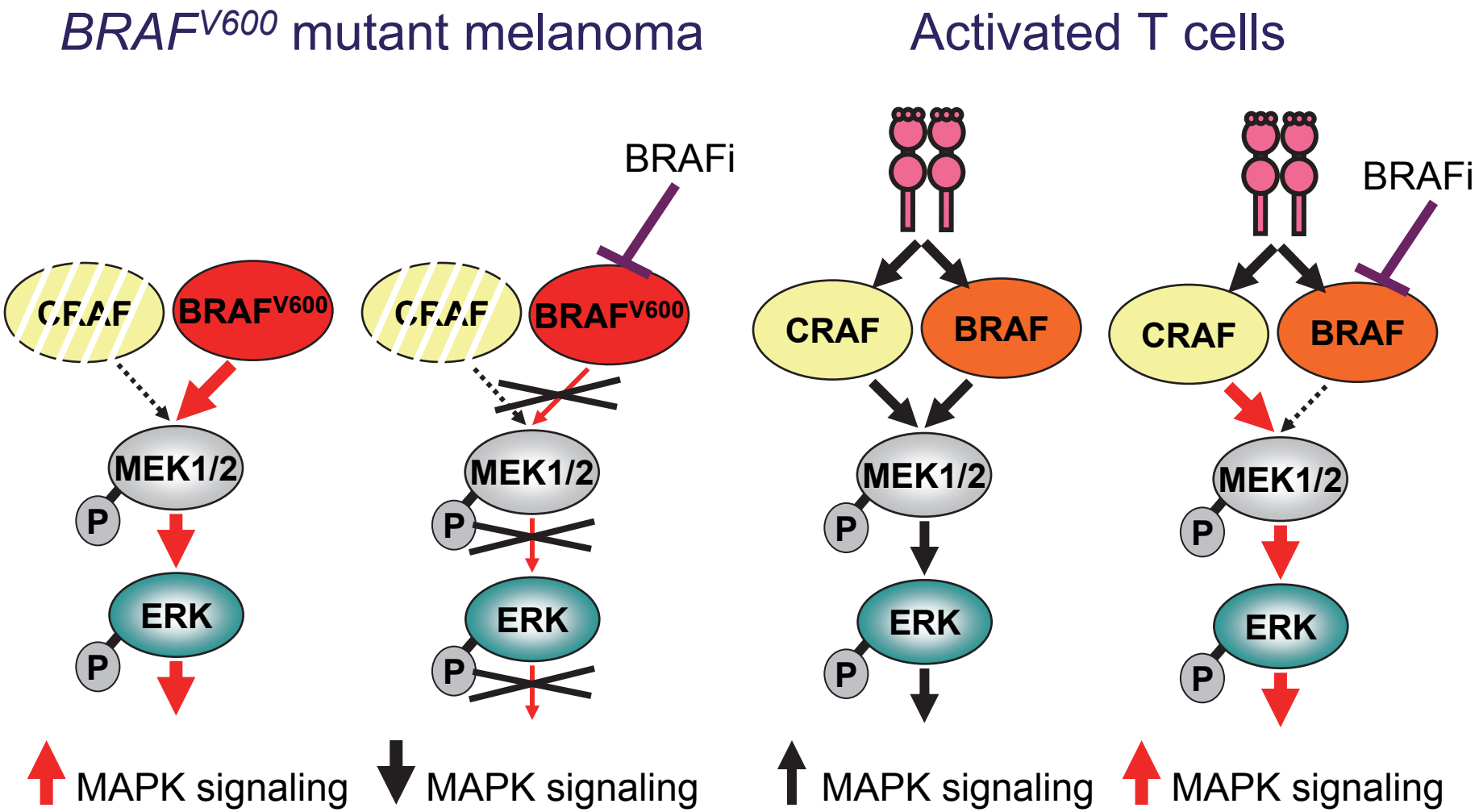
How can BRAF targeted therapy increase the activity of tumor immunotherapy?



Koya *et al*. CR 2012:

- No change in gp100 or MHC expression by SM1 exposed to vemurafenib
- No change in adoptively transferred T cell distribution by BLI
- No increase in intratumoral infiltrates by adoptively transferred T cells

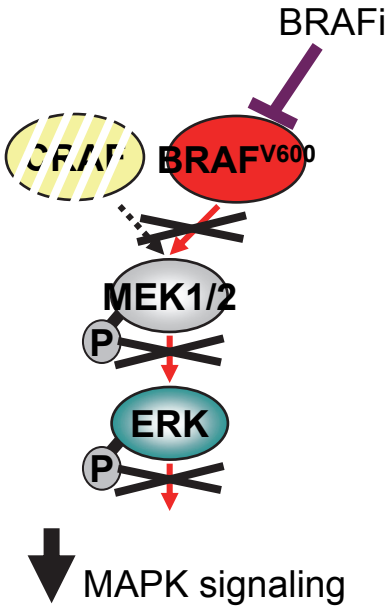
Differential effects of BRAF inhibition in *BRAF*^{V600} mutant melanoma and activated T cells

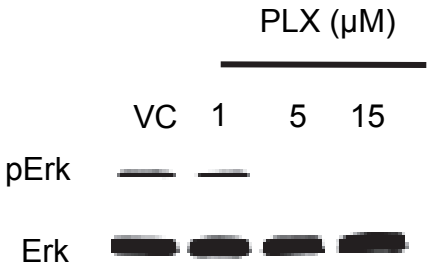


Modeled from Hatzivassiliou *et al*. Nature 2010, Heidorn *et al*. Cell 2010, Poulikakos *et al*. Nature 2010

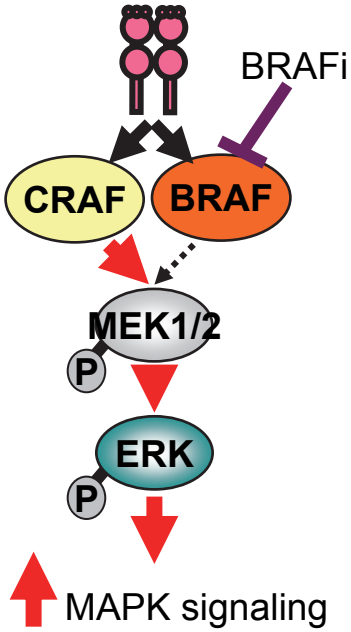
Paradoxical activation of pERK with exposure of lymphocytes to vemurafenib

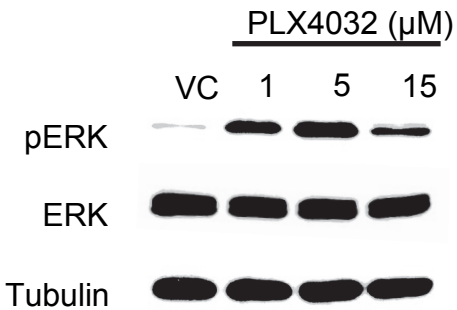
SM1





pmel-1





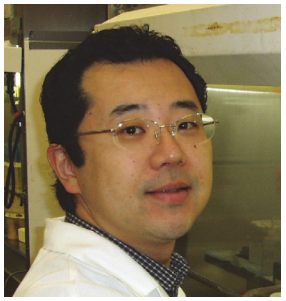
Koya *et al*. Cancer Res 2012

Conclusions

- Novel targeted therapies may synergize with immunotherapy:
  - Improve antigen presentation
  - Sensitize cancer cells to apoptotic death
  - Inhibit suppressive factors in the tumor
  - Improve lymphocyte function

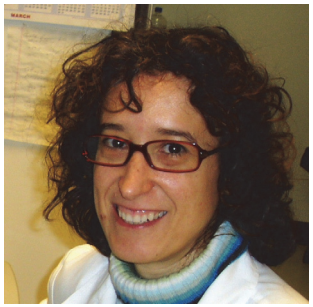
- In a mouse model, increased benefit of a BRAF inhibitor with ACT immunotherapy is mediated by:
  - Increased immune cell functionality (paradoxical MAPK activation)
  - Modulation of the tumor microenvironment?

Acknowledgements



Richard Koya, MD, PhD

Stephen Mok



Begonya Comin-Anduix, PhD

Thinle Chodon, MD, PhD

Tom Graeber, PhD
Ashley Cass
Aspram Minasyan
Nick Graham, PhD