Oncogene Inactivation (Addiction) and CD4+ T-cells

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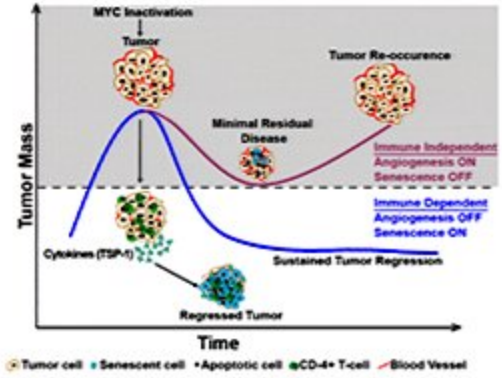
SITC Workshop 2012

Modeling Oncogene Addiction Inside and Out



Oncogene Addiction is both Tumor Intrinsic and Host-Dependent

Mechanisms of Oncogene Addiction and the Immune System

- Restoration of Tumor Intrinsic Fail-Safe Mechanisms:
  - Shut Down of *Self-Renewal* Programs: Role of Cellular Senescence
- Restoration of Host Fail-Safe Mechanisms:
  - Shut Off of Angiogenesis
- Importance of Immune System and Autocrine/Chemokine Signaling

Combining Targeted Therapeutics + Immune Therapy

Oncogene Addiction, Senescence and the Immune System

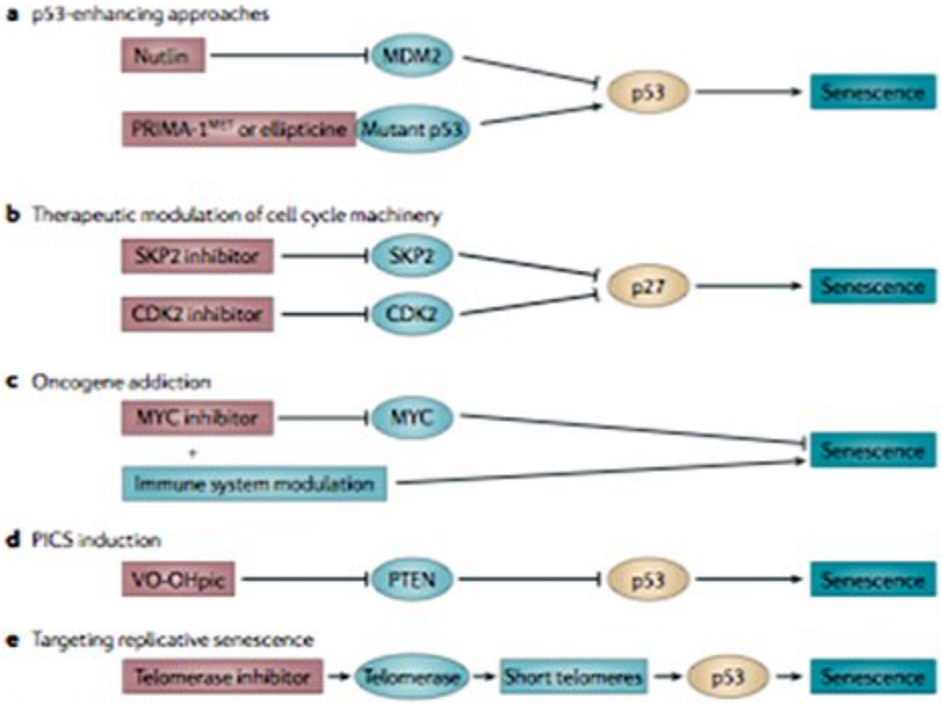
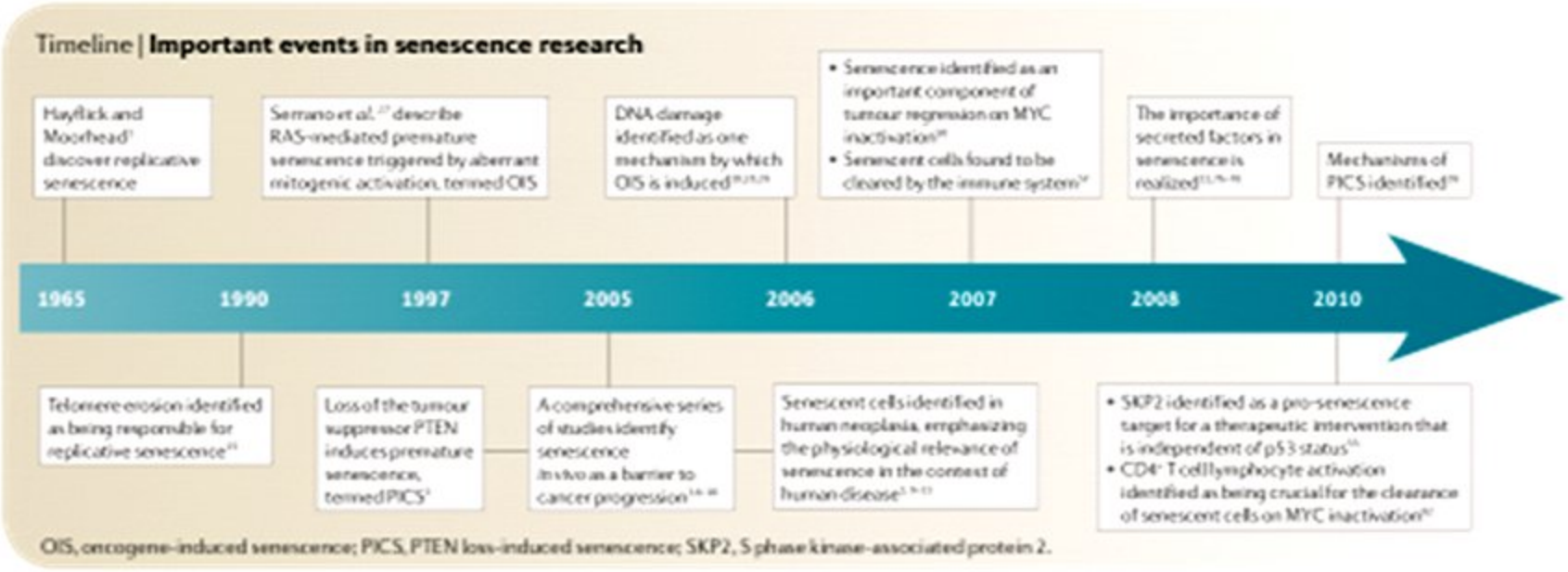


Figure 2 | **Strategies for the therapeutic activation and enhancement of senescence.** Schematic view of the approaches that are readily available for the implementation of pro-senescence therapy in cancer treatment. Inhibitors are shown in red boxes and target proteins in blue ovals. **a** | Enhancement of p53 activity through either inhibition of the interaction between MDM2 and wild-type p53 (for example, a nutlin) or restoration of mutant p53 activity (for example, PRIMA-1^{MET} or ellipticine). **b** | Modulation of cell cycle machinery, for example through either inhibition of S phase kinase-associated protein 2 (SKP2) or cyclin-dependent kinase 2 (CDK2). Both approaches result in increased p27 (also known as KIP1) activity and a consequent senescence response. **c** | Induction of senescence in tumours that are addicted to MYC through the inhibition of the MYC oncogene in combination with an immunomodulatory approach. **d** | Induction of PTEN loss-induced cellular senescence (PICS) through inhibition of PTEN and consequent mTOR-mediated activation of p53. **e** | Induction of replicative senescence through inhibition of telomerase and subsequent telomere shortening.

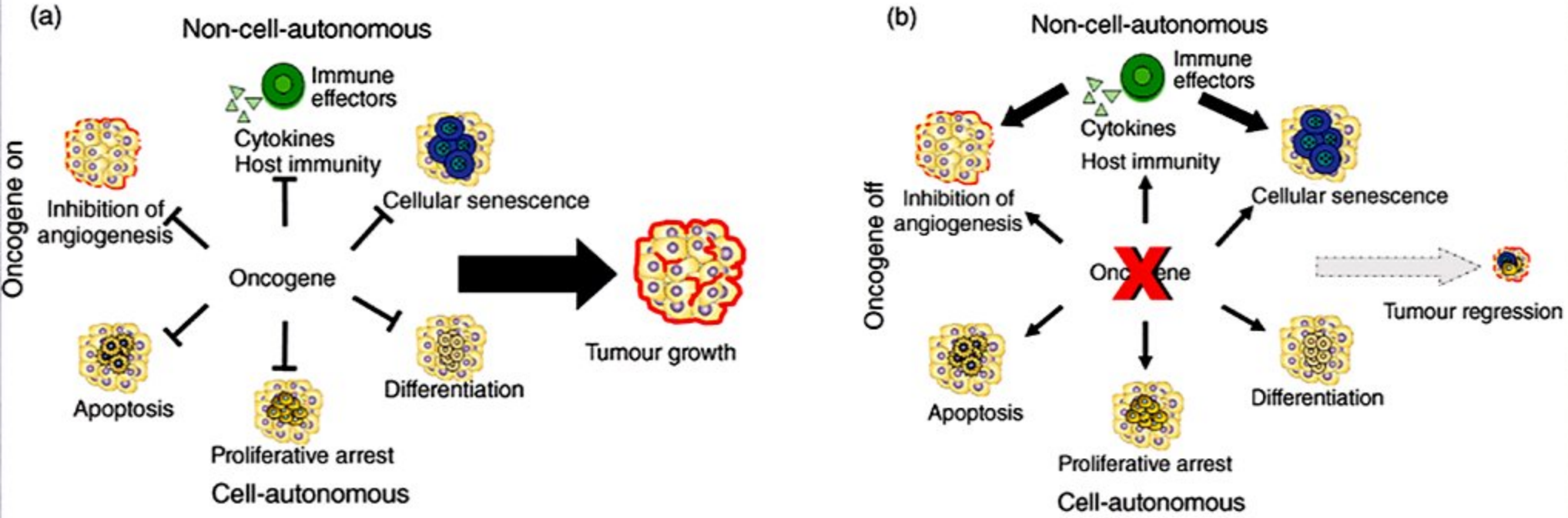
Nardella and Pandolfi, NRC, 2011

Oncogene Addiction, Senescence and the Immune System



Nardella and Pandolfi, NRC, 2011

Hallmarks of Cancer, Oncogene Addiction and the Immune System



Bendapudi, Rakhra et al CEI, 2011

Oncogene Addiction and the Immune System

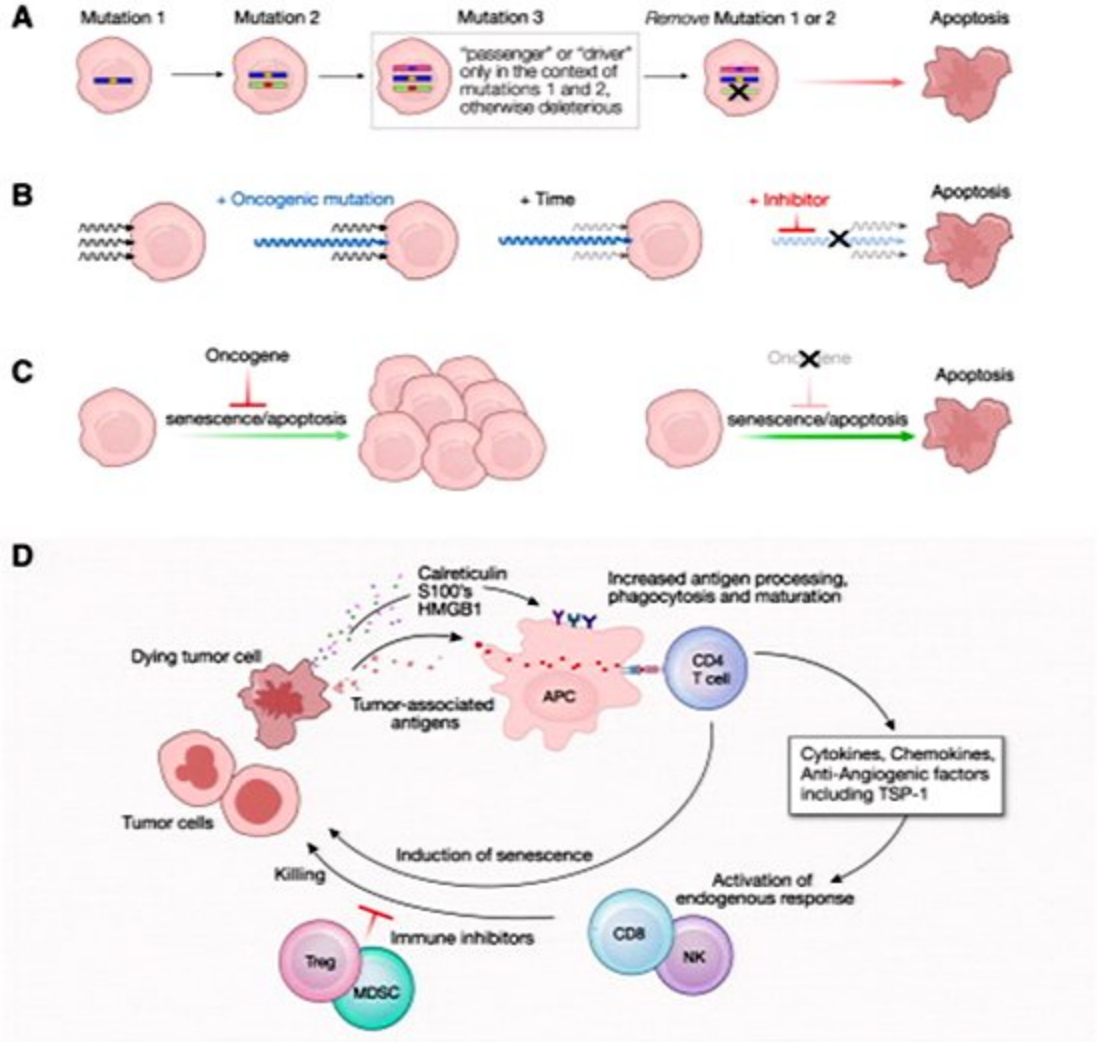
Table 1. Examples of immune system-mediated oncogene addiction. Murine models of *MYC* and *BCR-ABL* inactivation as well as *P53* restoration directly implicate immune involvement in implementing the consequences of oncogene addiction. Below, oncogenes whose tumorigenicity rely heavily on immune evasion and/or pro-tumour inflammation highlight the potentially broad generalizability of the concept of immune system-mediated oncogene addiction.

Oncogene	Tumour type	Involved immune compartment	Immune-mediated mechanism	References
MYC	T cell acute lymphoblastic lymphoma	Adaptive immunity ($CD4^+$ T cells)	Induction of senescence and suppression of angiogenesis	[69]
BCR-ABL	Pro-B cell acute lymphocytic leukaemia	Adaptive immunity ($CD4^+$ T cells)	Induction of senescence and suppression of angiogenesis	[69]
P53	Hepatocellular carcinoma	Innate immunity (neutrophils, macrophages, NK cells)	Tumour clearance	[82]
		Other oncogenic links to tumour immunity		
MYC	B cell lymphoma; pancreatic islet cell tumour	Innate immunity (macrophages; mast cells)	Macrophages induce senescence; mast cells promote angiogenesis	[42,66]
RAS	Cervical cancer; renal cell carcinoma	Innate immunity (neutrophils)	Neutrophils recruited by IL-8, IL-6 secretion	[58,59]
MET	Papillary thyroid carcinoma	?Innate immunity/activation of proinflammatory programme	Innate cells recruitment via proinflammatory cytokines/chemokines	[52,57]
PML	Acute promyelocytic leukaemia; prostate carcinoma	Adaptive immunity ($CD8^+$ T cells)	*PML* influences MHC class I antigen presentation	[53,54]
BRAF	Melanoma	Adaptive immunity (dendritic cells, CTLs)	BRAF inhibition up-regulates antigen presentation and decreases IL-10, IL-6	[55,56]

CTL: cytotoxic T lymphocyte; IL: interleukin; MHC: major histocompatibility complex; NK: natural killer.

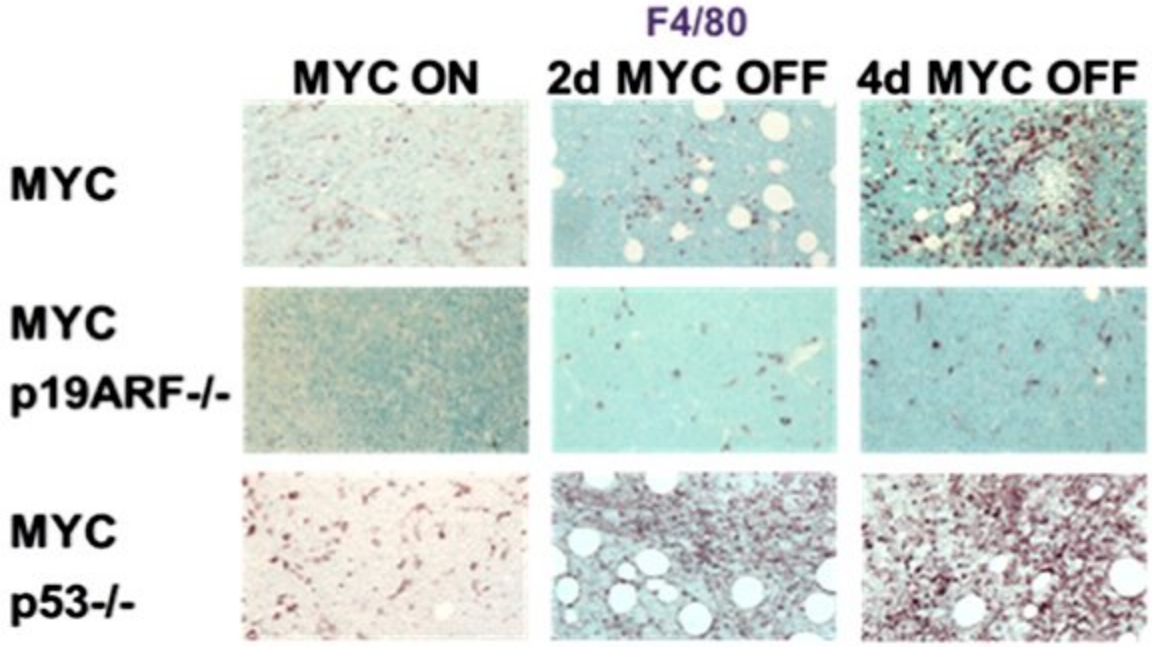
Bendapudi, Rakhra et al CEI, 2011

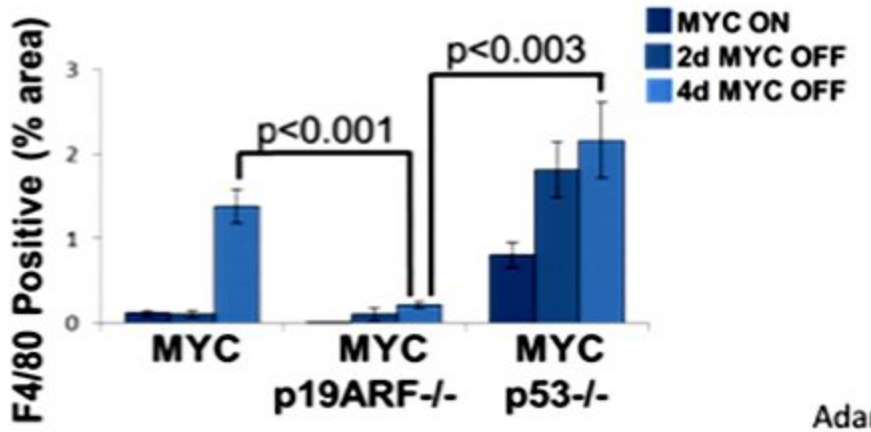
Oncogene Addiction and Immune Therapy



Restifo, Cancer Cell, 2010

p19ARF but not p53 Null Tumors Exhibit a Marked Reduction in Macrophage Infiltration





Adam, Yetil *et al.*, unpublished

Pathway Analysis of Gene Expression Identifies Innate Immunity Pathways

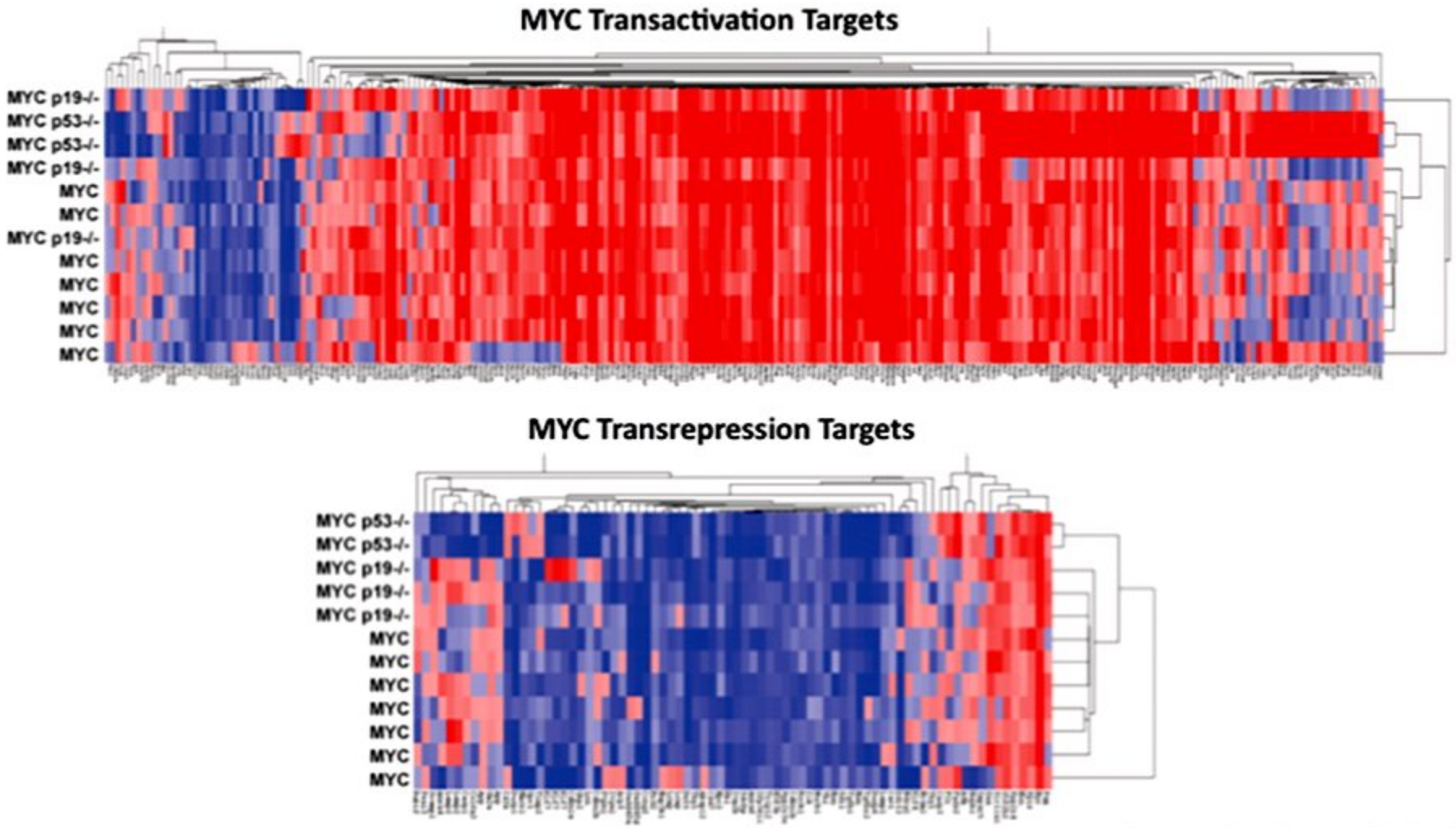
Significant Genes
MYC ON/MYC OFF
Fold Change ≥ 2.0
$p \leq 0.05$

	MYC	MYC p53-/-	MYC p19-/-
Senescence/Cell Aging Pathways	1	1	0
Macrophage Activation/Infiltration Pathways	4	5	0
Innate Immune Cell Activation/Infiltration Pathways	4	6	0
Platelet Related Pathways	4	7	3

Pathway Analysis Cut-off - $p \leq 0.05$

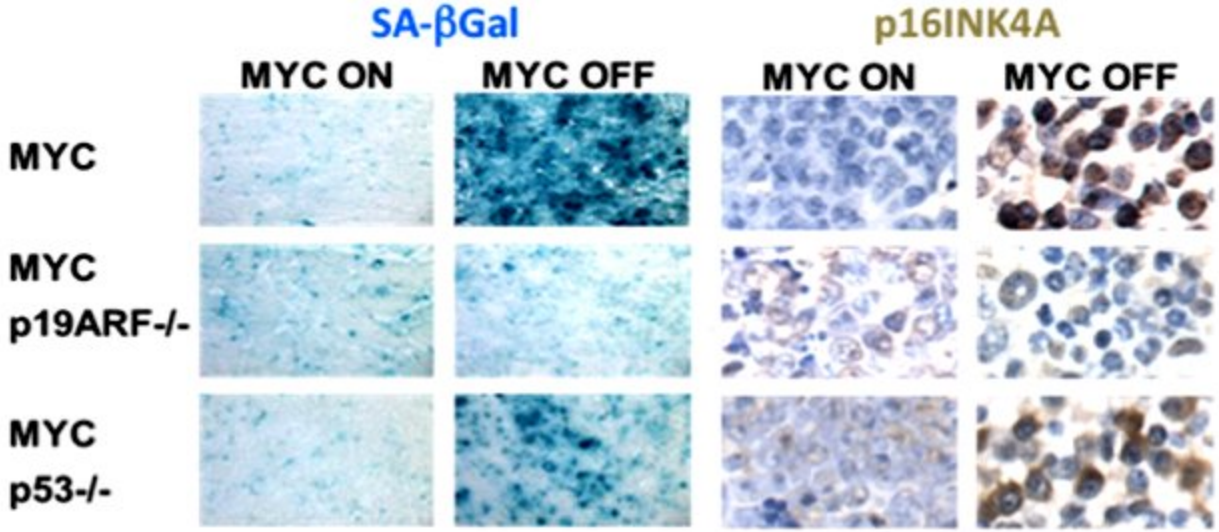
Adam, Yetil *et al.*, unpublished

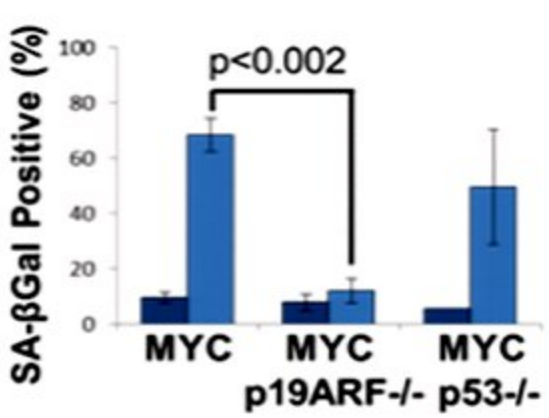
Loss of p19ARF Has no Global Effect on MYC Transcription

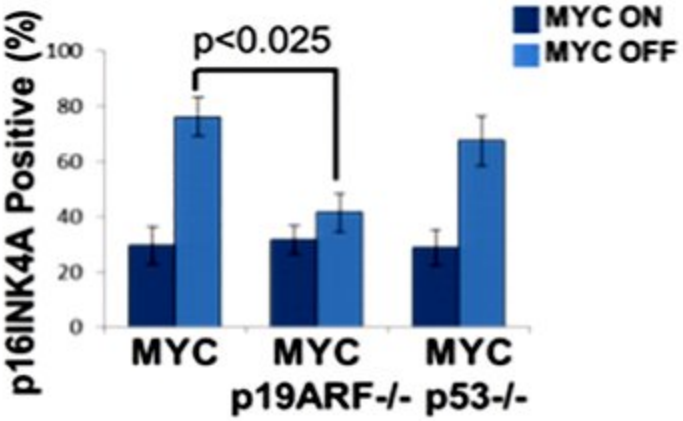


Adam, Yetil *et al.*, unpublished

Loss p19ARF but not p53 Impedes Senescence upon MYC Inactivation

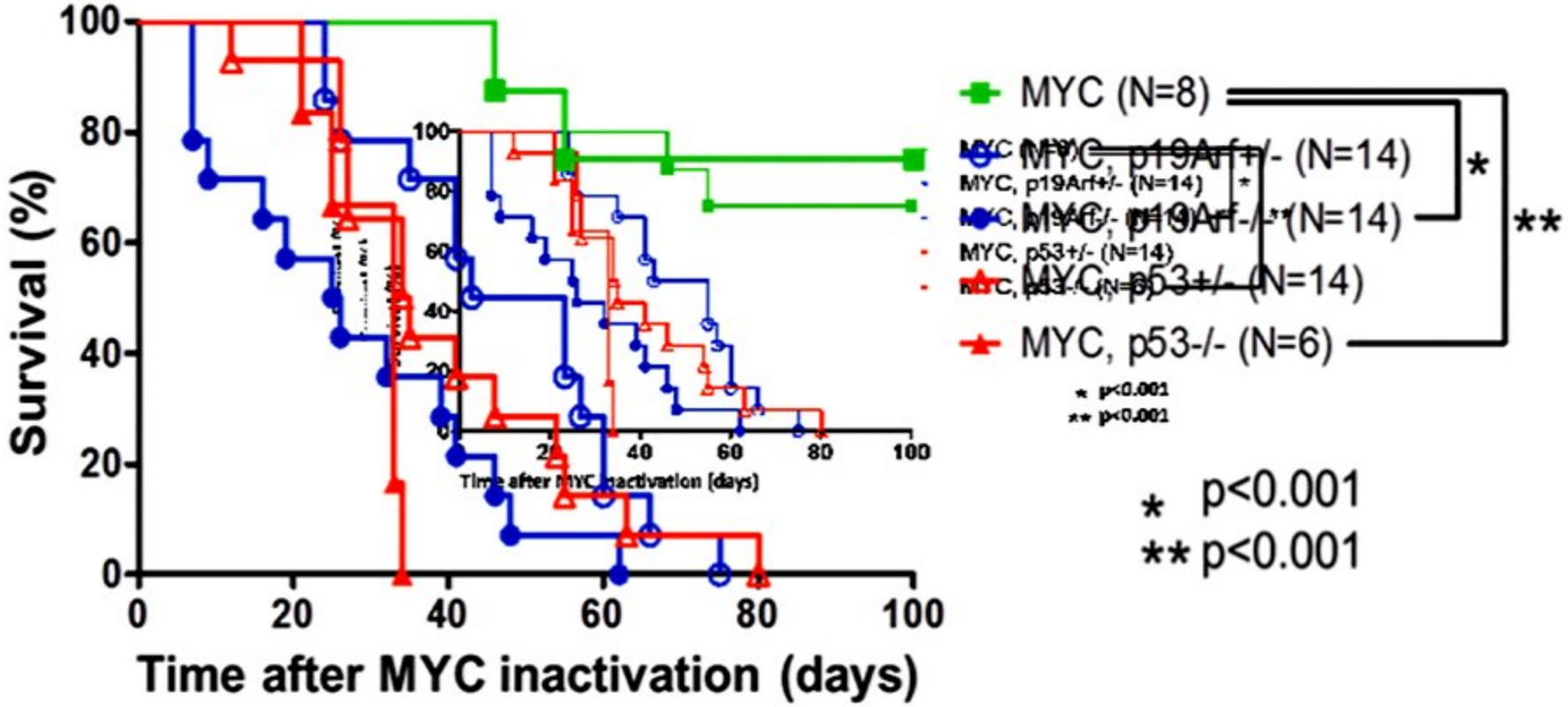






Adam, Yetil *et al.*, unpublished

Loss of p19ARF or p53 Prevents MYC Inactivation from Inducing Sustained Regression

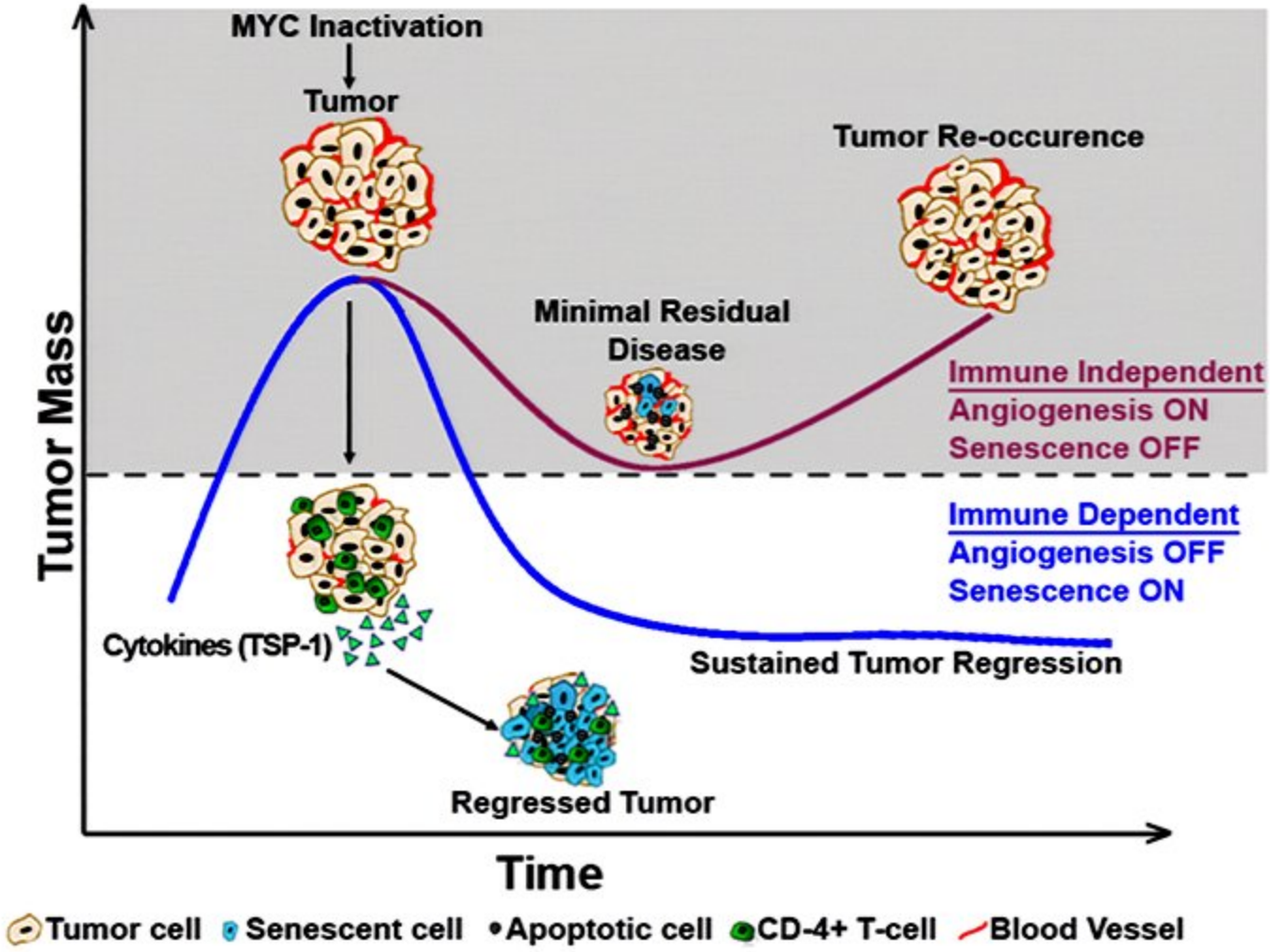


MYC and a p19ARF Senescence Switch

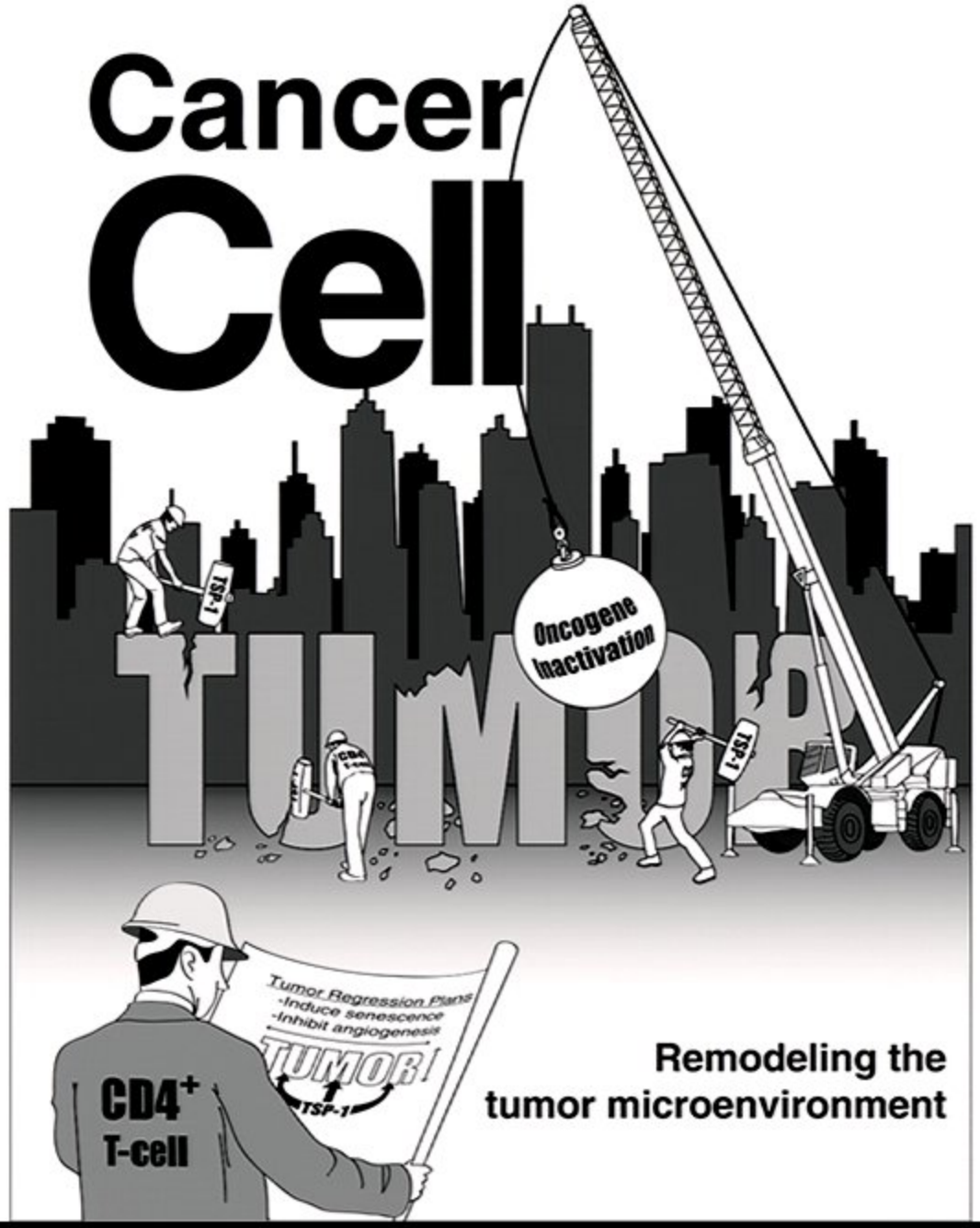
Alper Yetil PhD

Stacey Adam, PhD

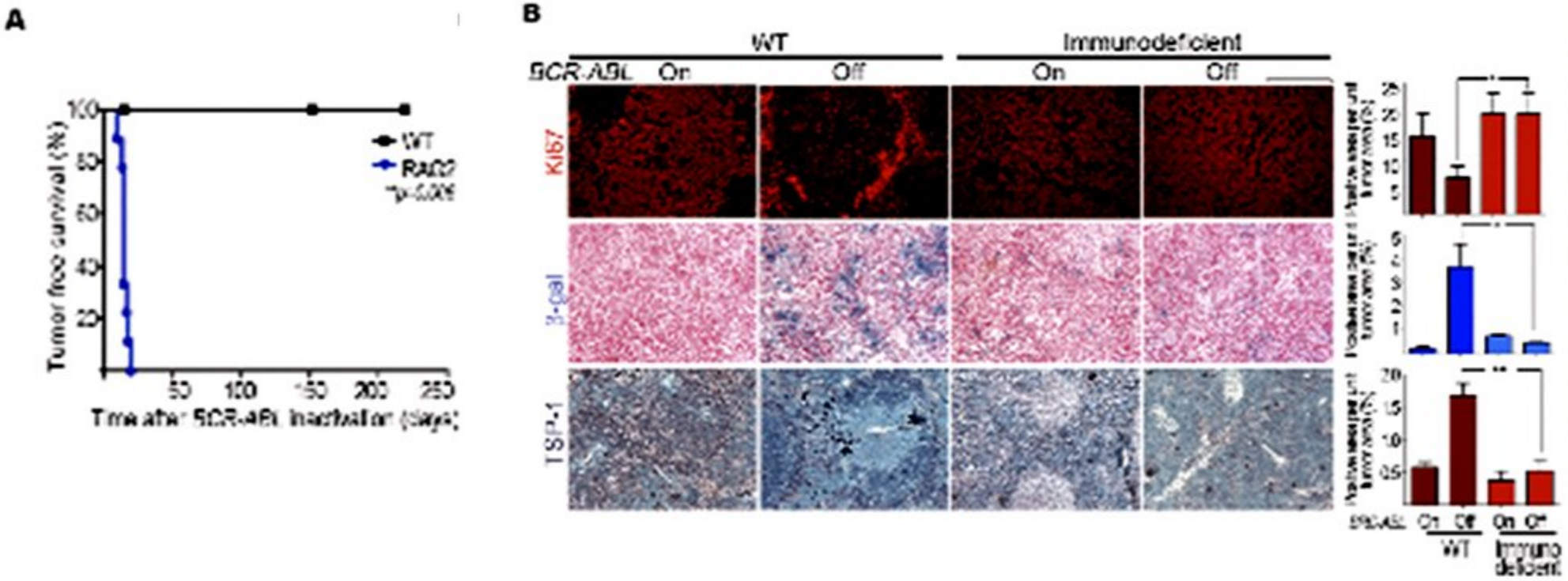
Role of Immune Effectors in Oncogene Addiction



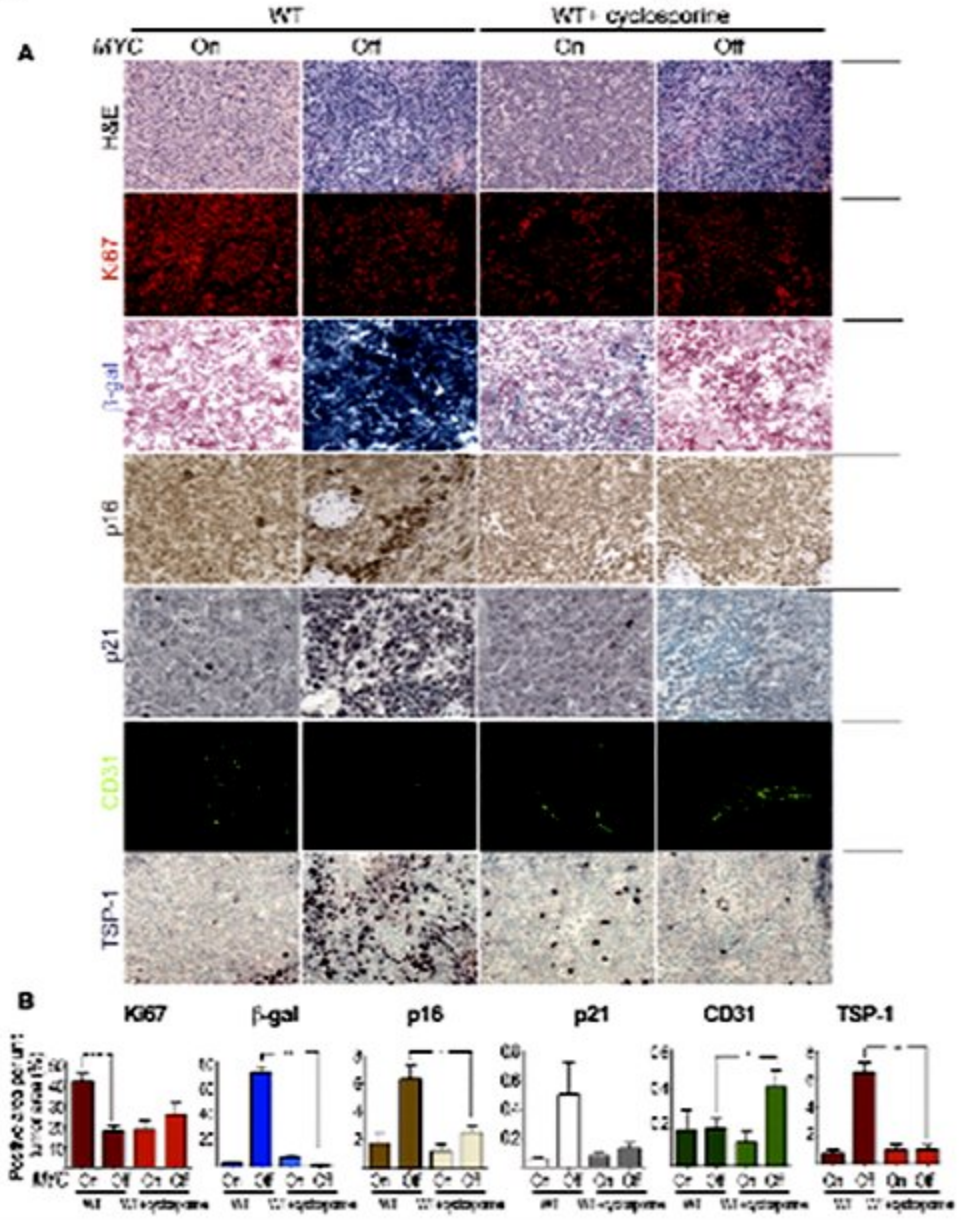
Rakhra et al, Cancer Cell, 2010


Cancer
Cell
TSP-1
Oncogene
Inactivation
TUMOR
TSP-1
Tumor Regression Plans
-Induce senescence
-Inhibit angiogenesis
TUMOR
TSP-1
CD4+
T-cell
Remodeling the
tumor microenvironment

BCR-ABL Inactivation Elicits Oncogene Addiction only in an Immune Intact Host

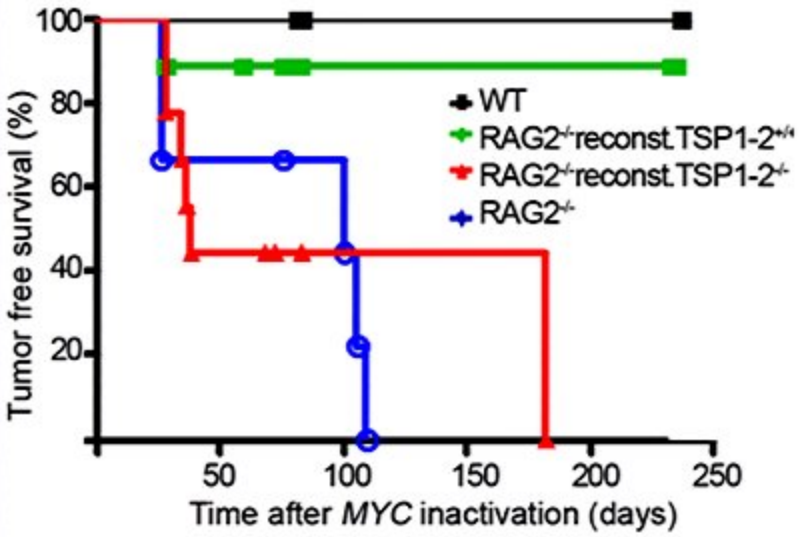


Cyclosporine Blocks Oncogene Addiction

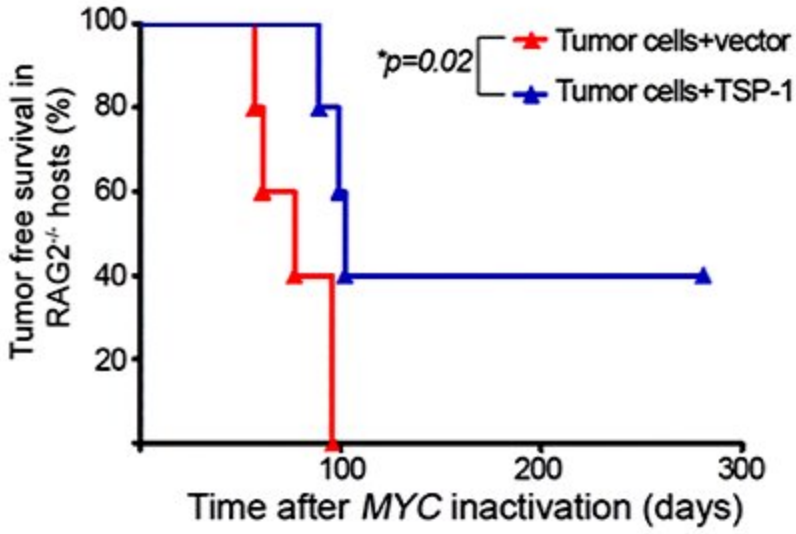


Thrombospondins are Required to Elicit Oncogene Addiction upon MYC Inactivation

Lymphocytes must express TSPs

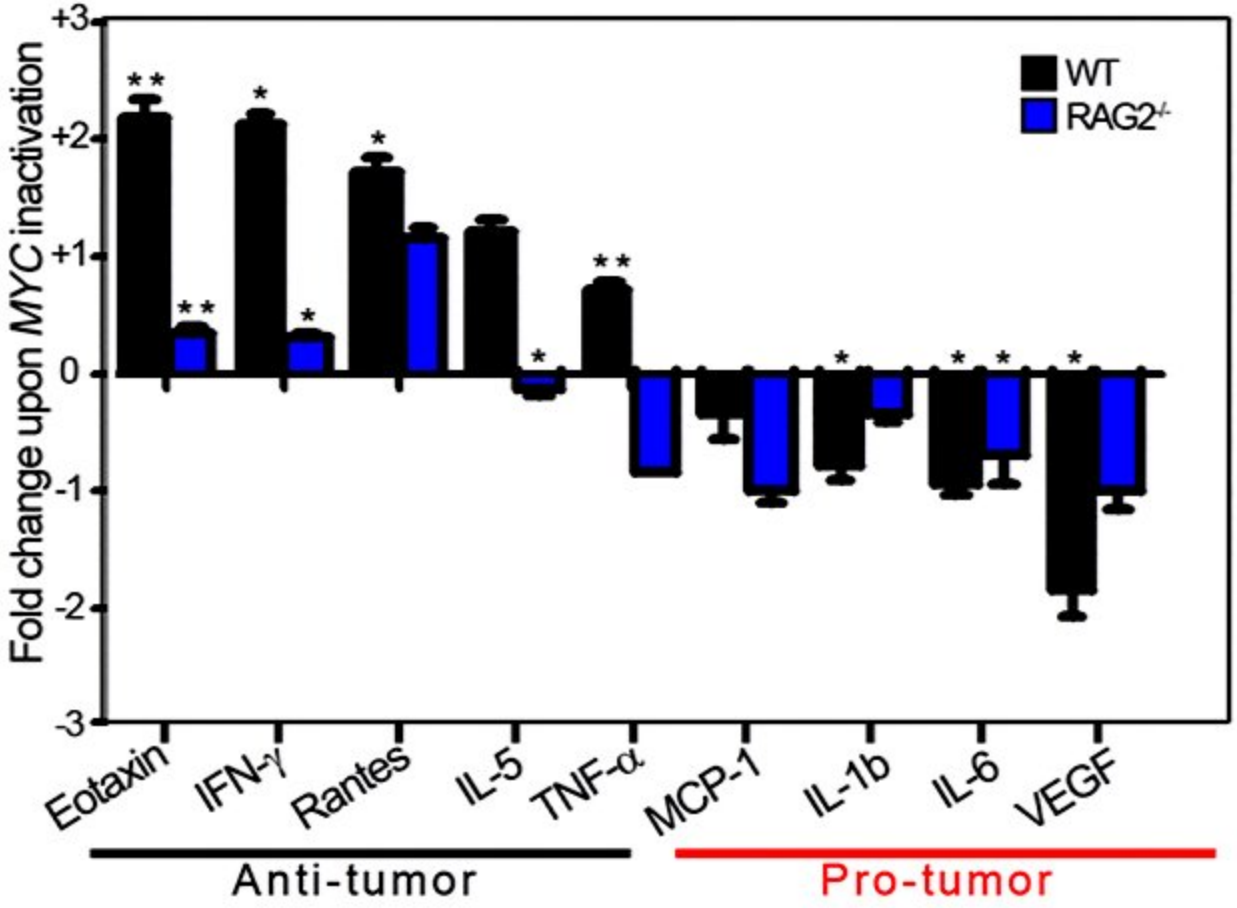


Tumor expression of TSP-1 Bypasses Immune Defect



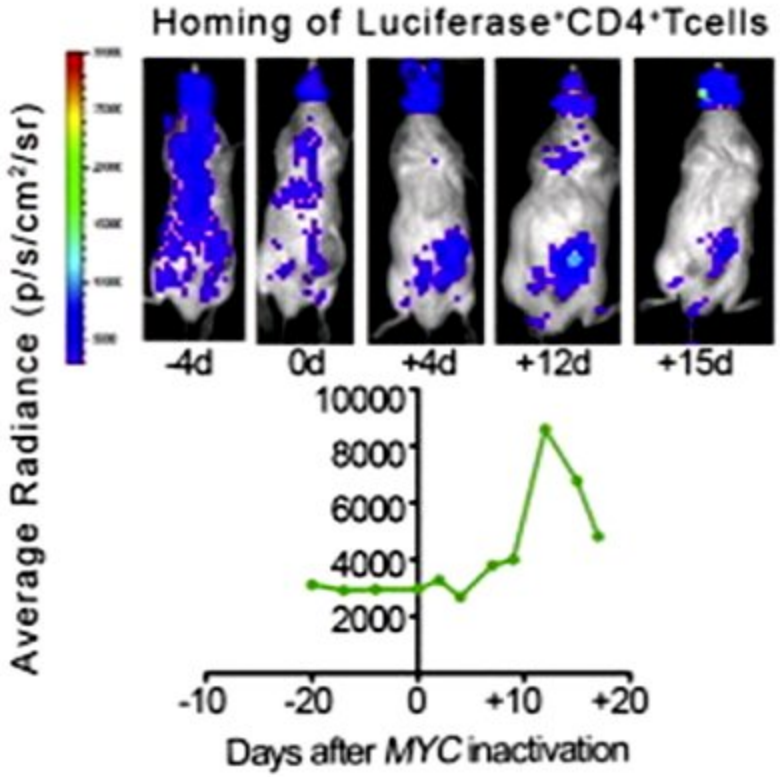
Rakhra et al, Cancer Cell, 2010

Immune System is Required for "Chemokine Switch" that Contributes to Tumor Regression upon Oncogene Inactivation

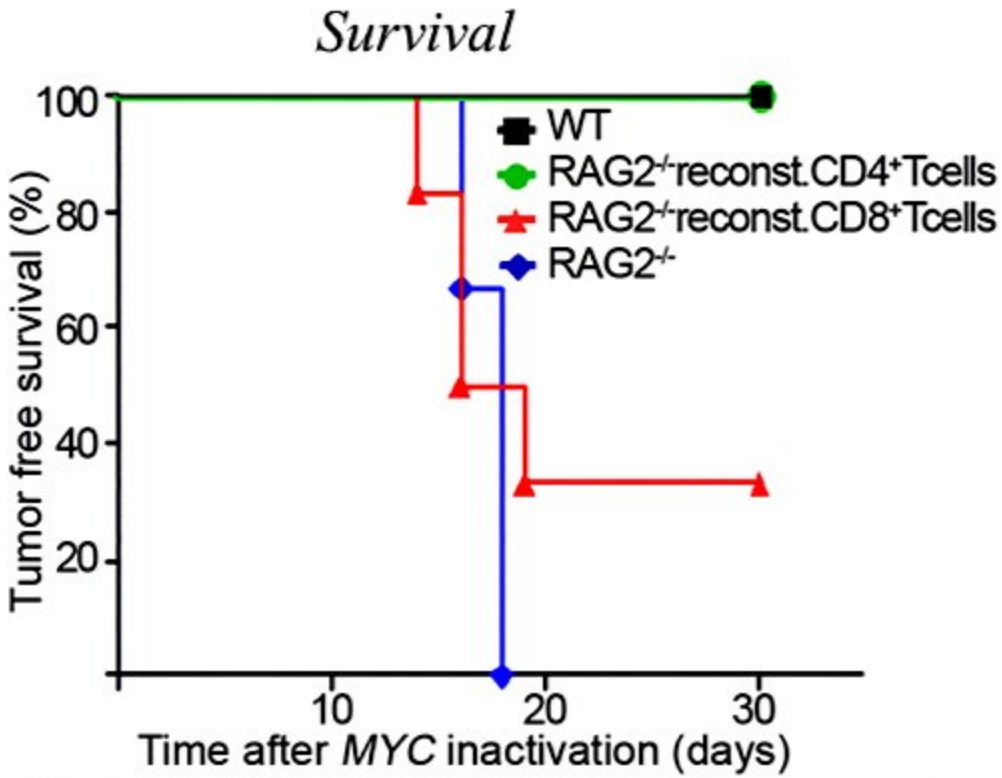


Rakhra et al, Cancer Cell, 2010

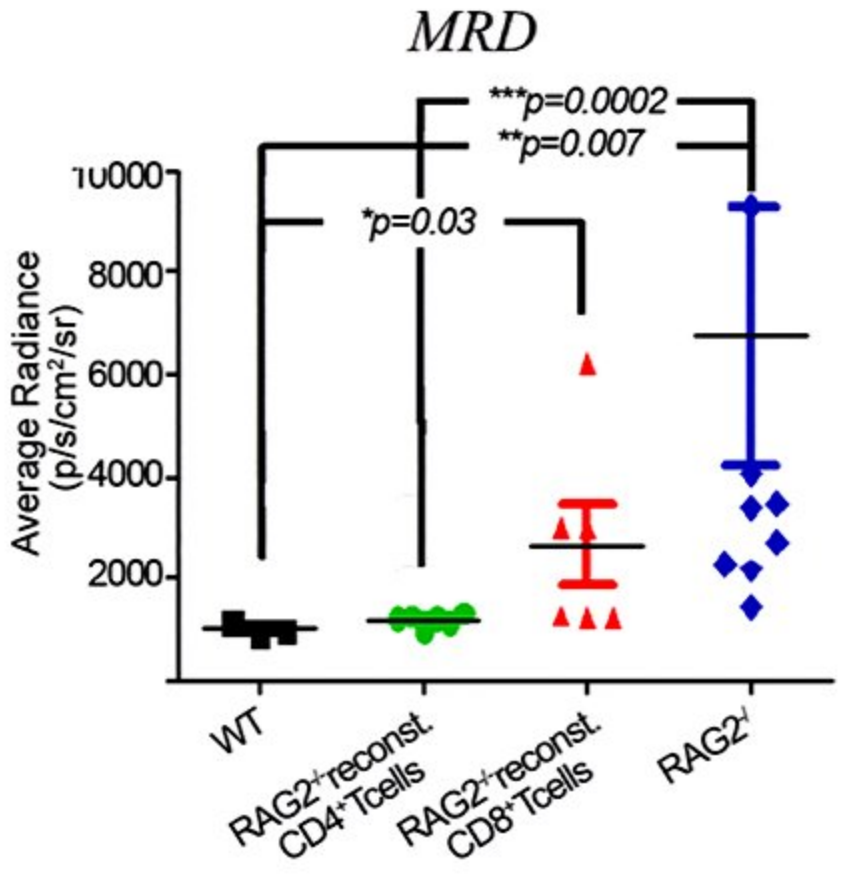
Immune Effectors Home to Tumor Site upon MYC Inactivation



Reconstitution of CD4+ T-cells Alone Restores Tumor Regression upon MYC Inactivation

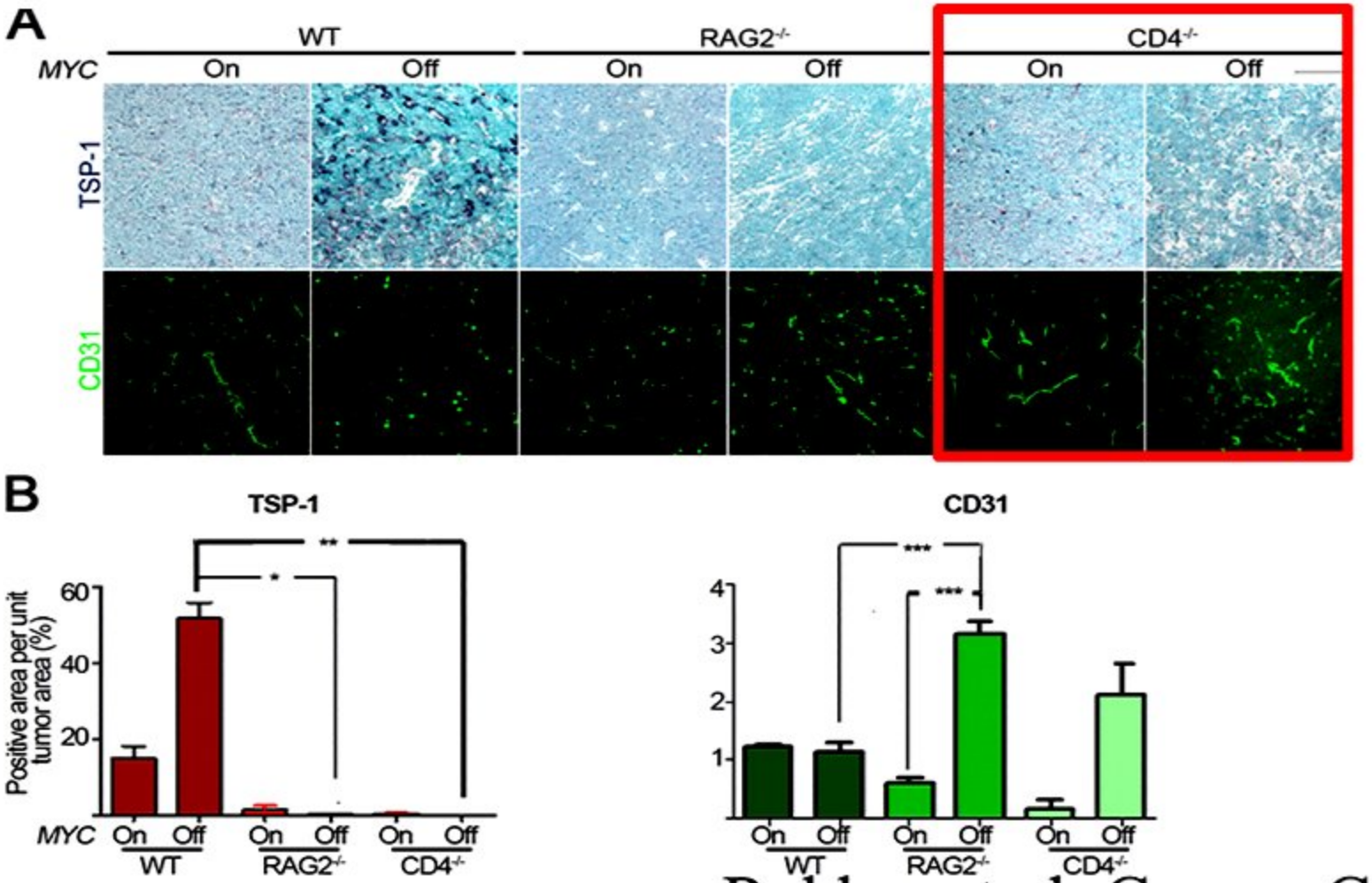


	RAG2$^{-/-}$	RAG2$^{-/-}$CD8$^{-/-}$	WT
RAG2$^{-/-}$CD4$^{-/-}$	***p=0.007*	**p=0.03*	*ns*



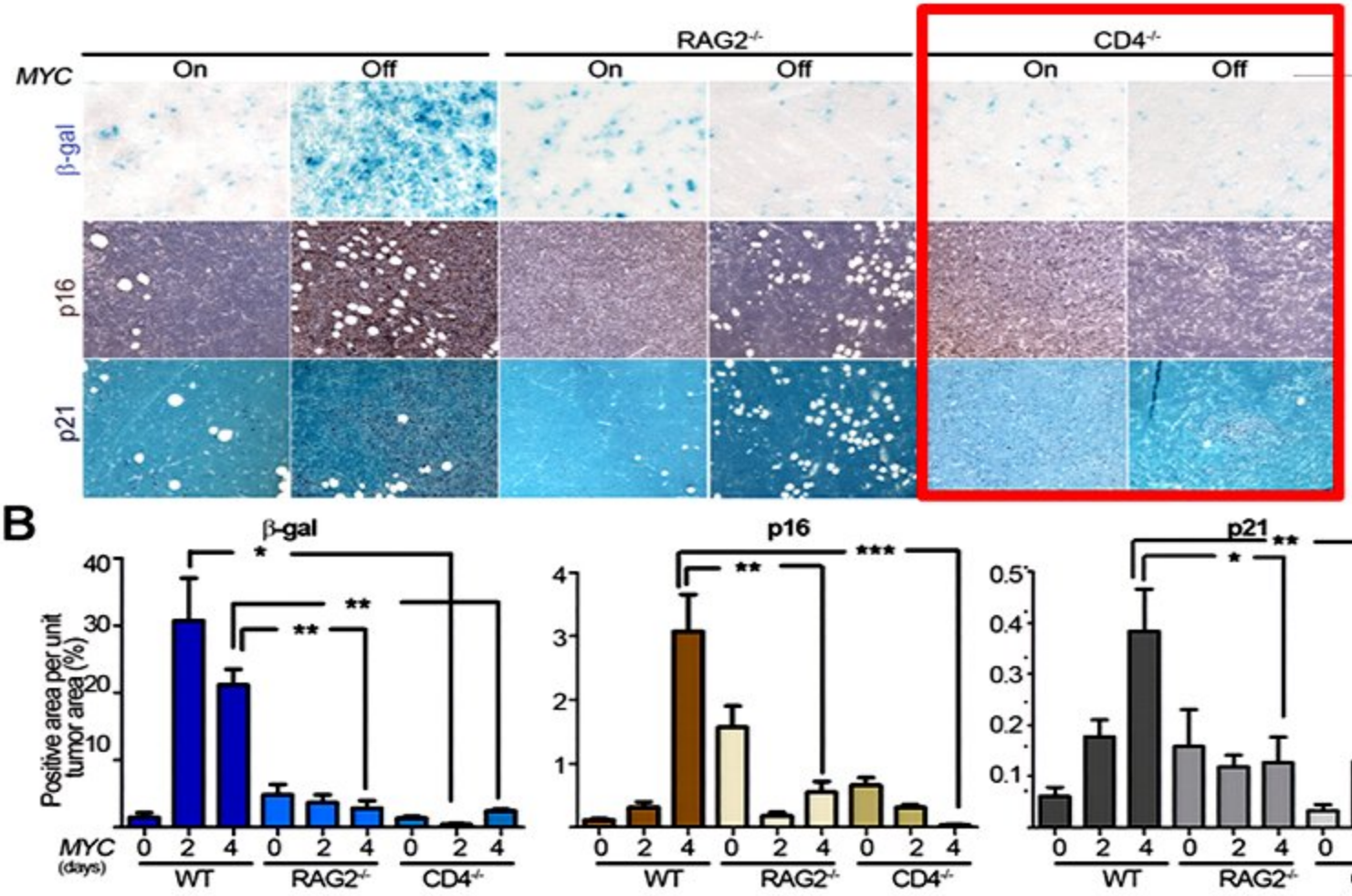
Rakhra et al, Cancer Cell, 2010

Immune System (CD4+ T-cells) is Required for the Induction of TSP-1 and the Suppression of Angiogenesis



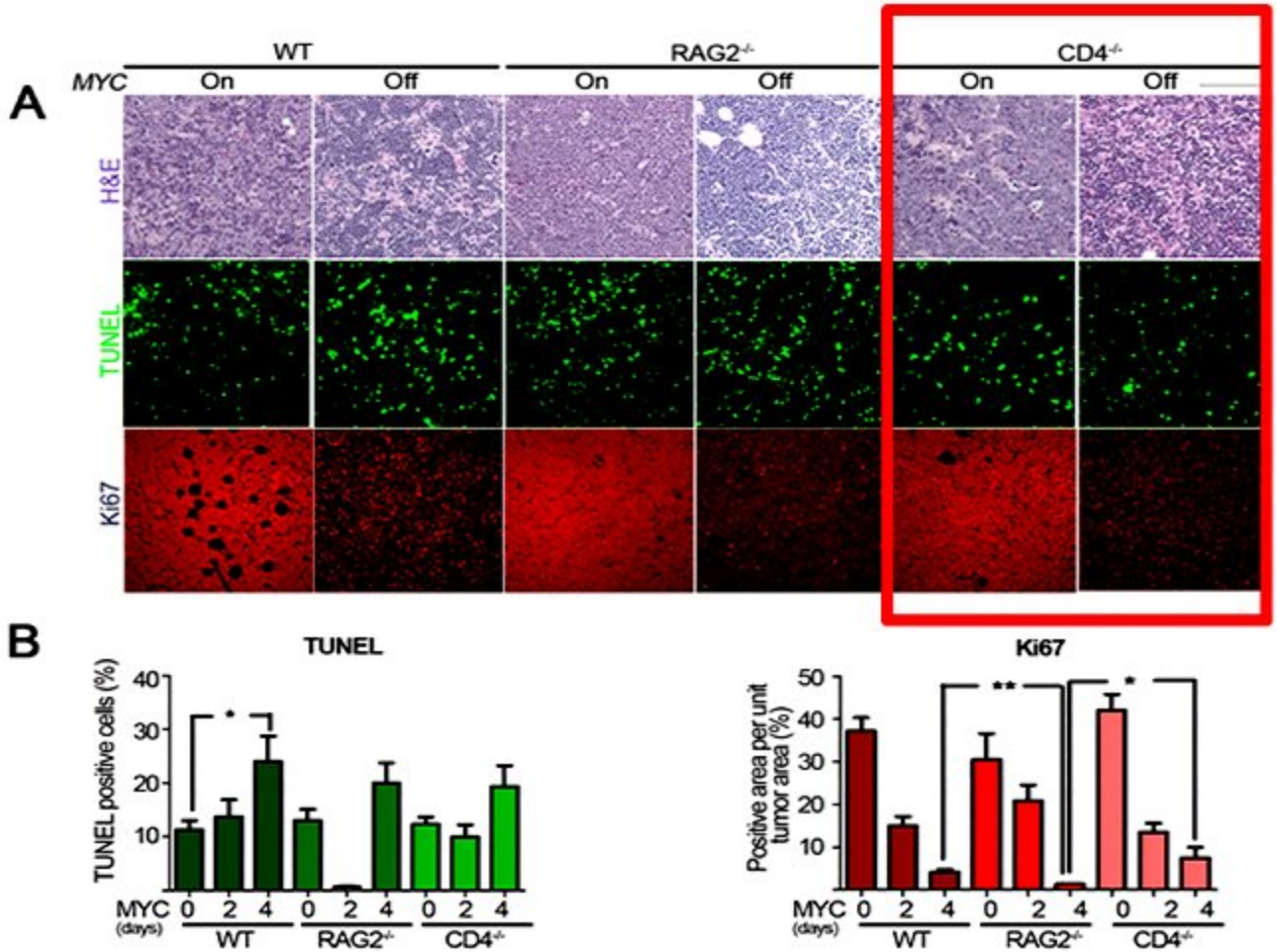
Rakhra et al, Cancer Cell, 2010

Immune System (CD4+ T-cells) is Required for Cellular Senescence upon MYC Inactivation



Rakhra et al, Cancer Cell, 2010

Immune System is Not Required for Proliferative Arrest or Apoptosis upon MYC Inactivation



Rakhra et al, Cancer Cell, 2010

Mechanisms of Tumor Regression upon MYC Inactivation

Tumor: MYC On

MYC Inactivation

Apoptosis

Cellular arrest or Senescence

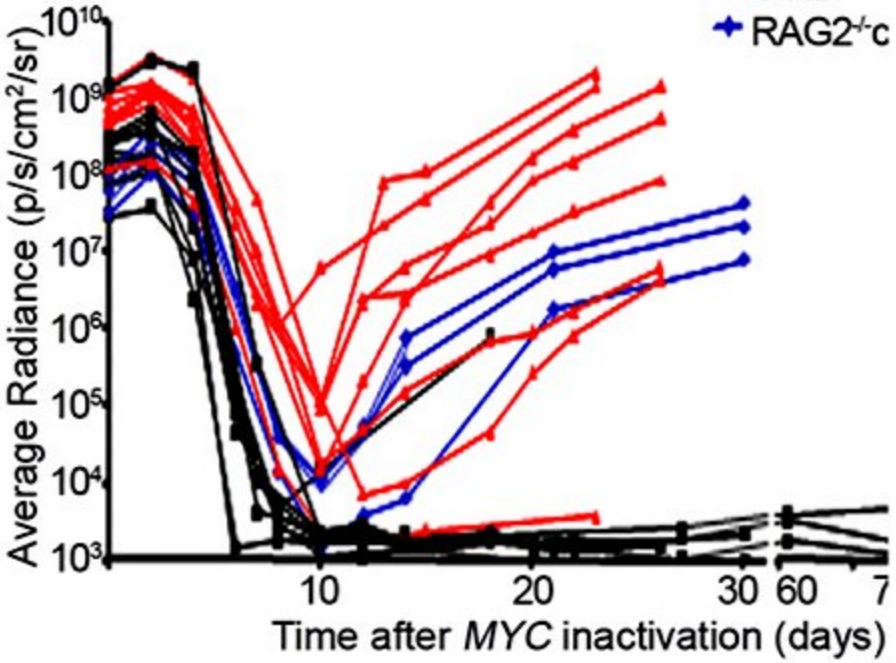
Differentiation

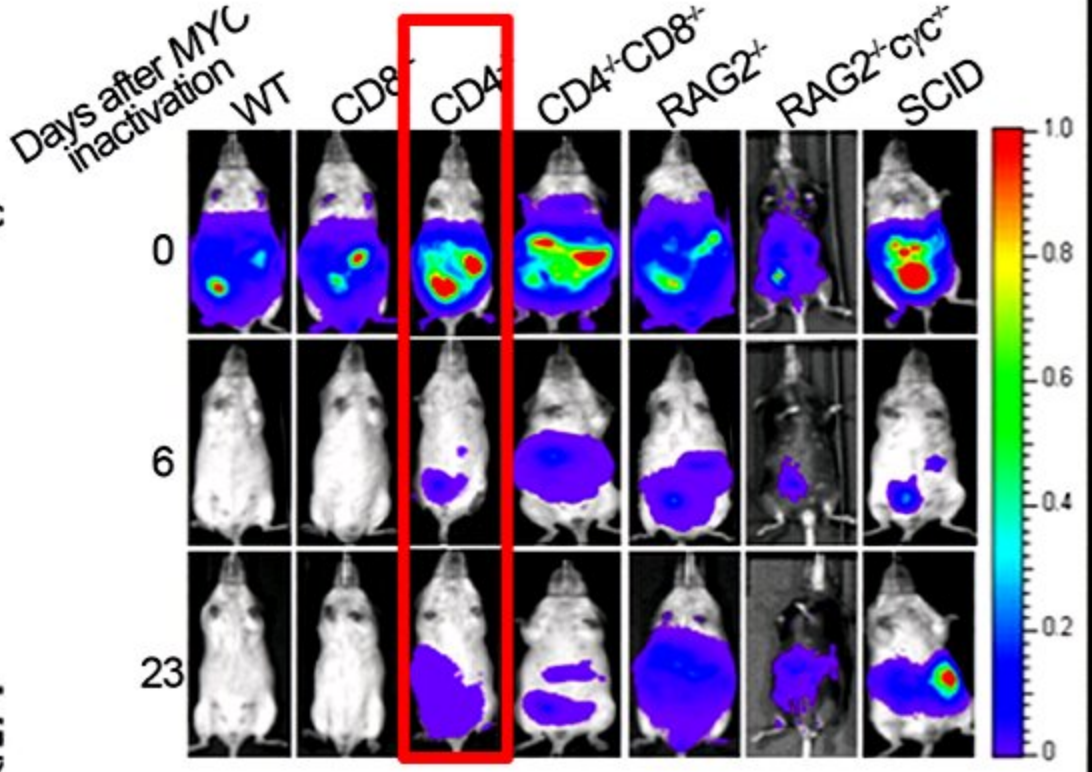
Inhibition of angiogenesis

Jain et al, Science, 2002
Shachaf et al, Nature, 2004
Giuriato et al, PNAS, 2006
Wu et al, PNAS, 2007
Van Riggelen, Genes and Develop, 2010

Adapted from Felsher D.W (2003)

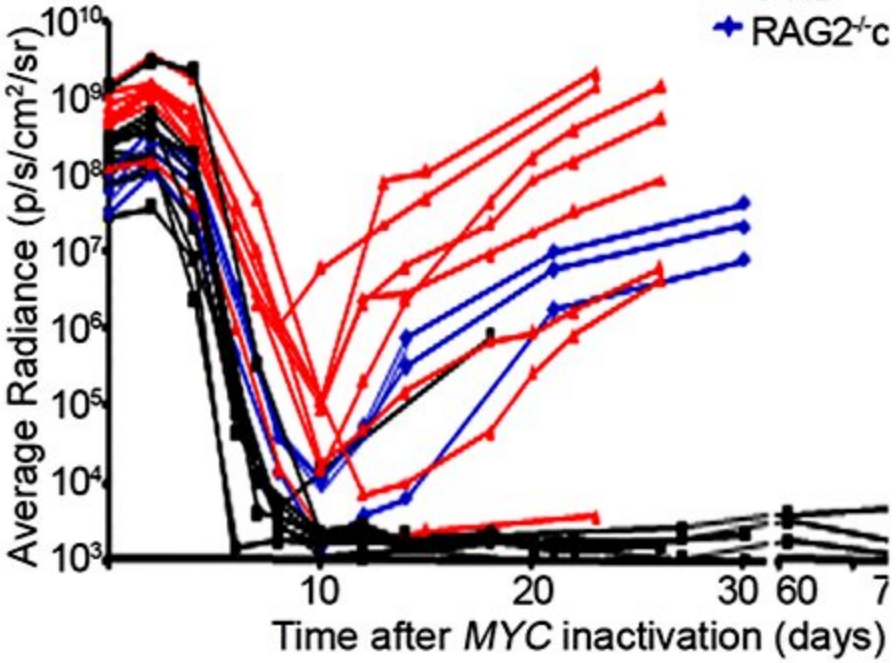
Immune System is Essential for Sustained Tumor Regression upon MYC Inactivation

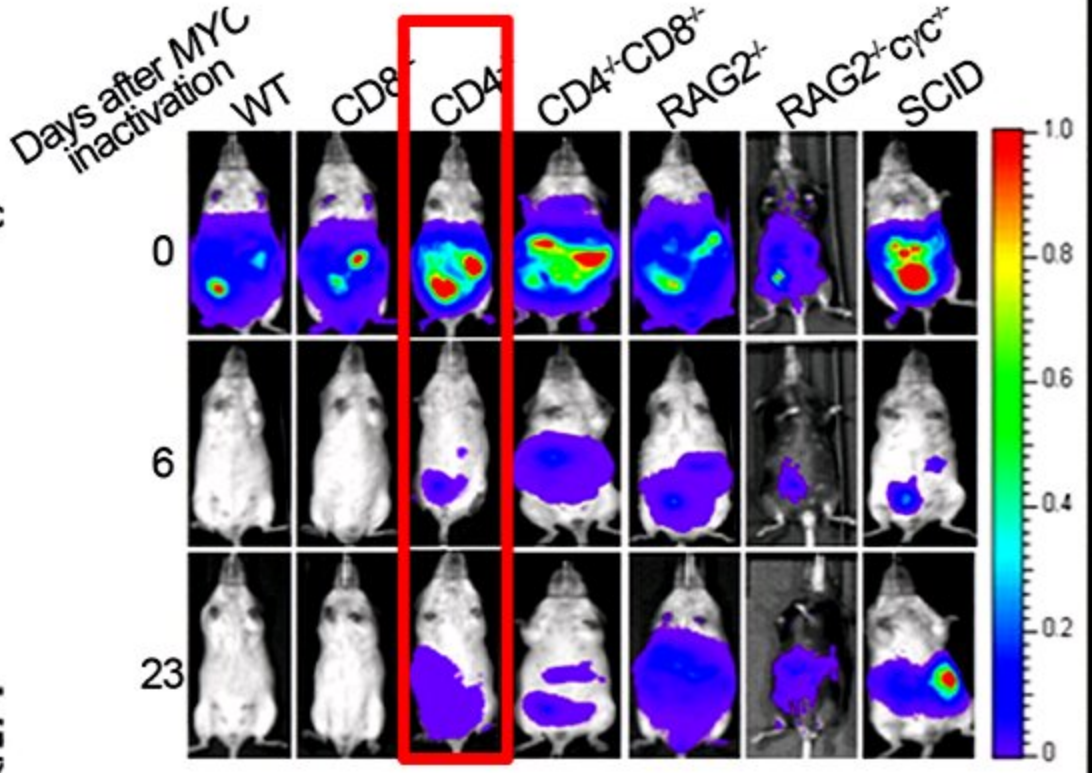




Rakhra et al, Cancer Cell, 2010

Immune System is Essential for Sustained Tumor Regression upon MYC Inactivation





Rakhra et al, Cancer Cell, 2010

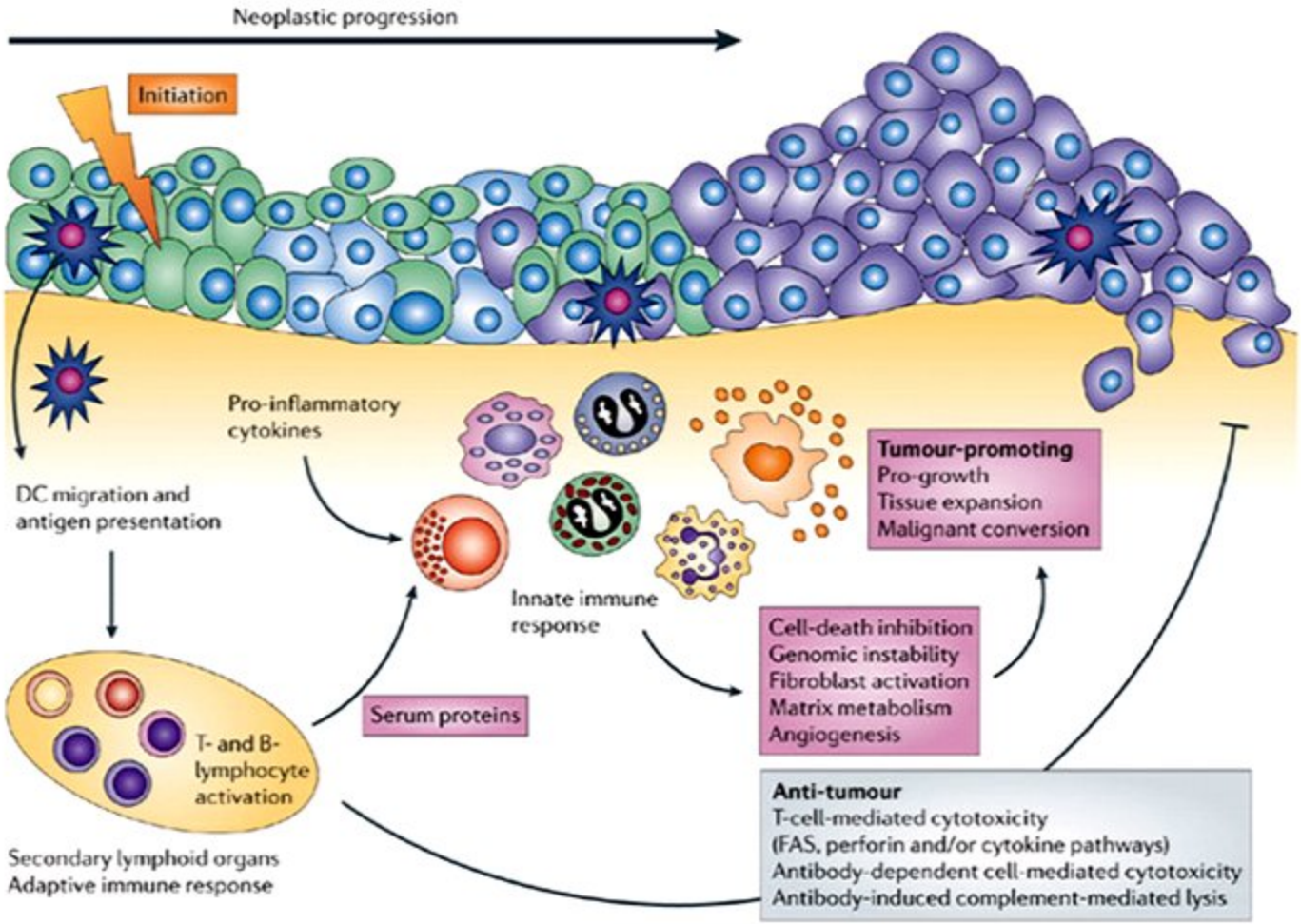
Immune System, Senescence, Angiogenesis and Oncogene Addiction

Kavya Rakhra

Pavan Bachireddy, MD

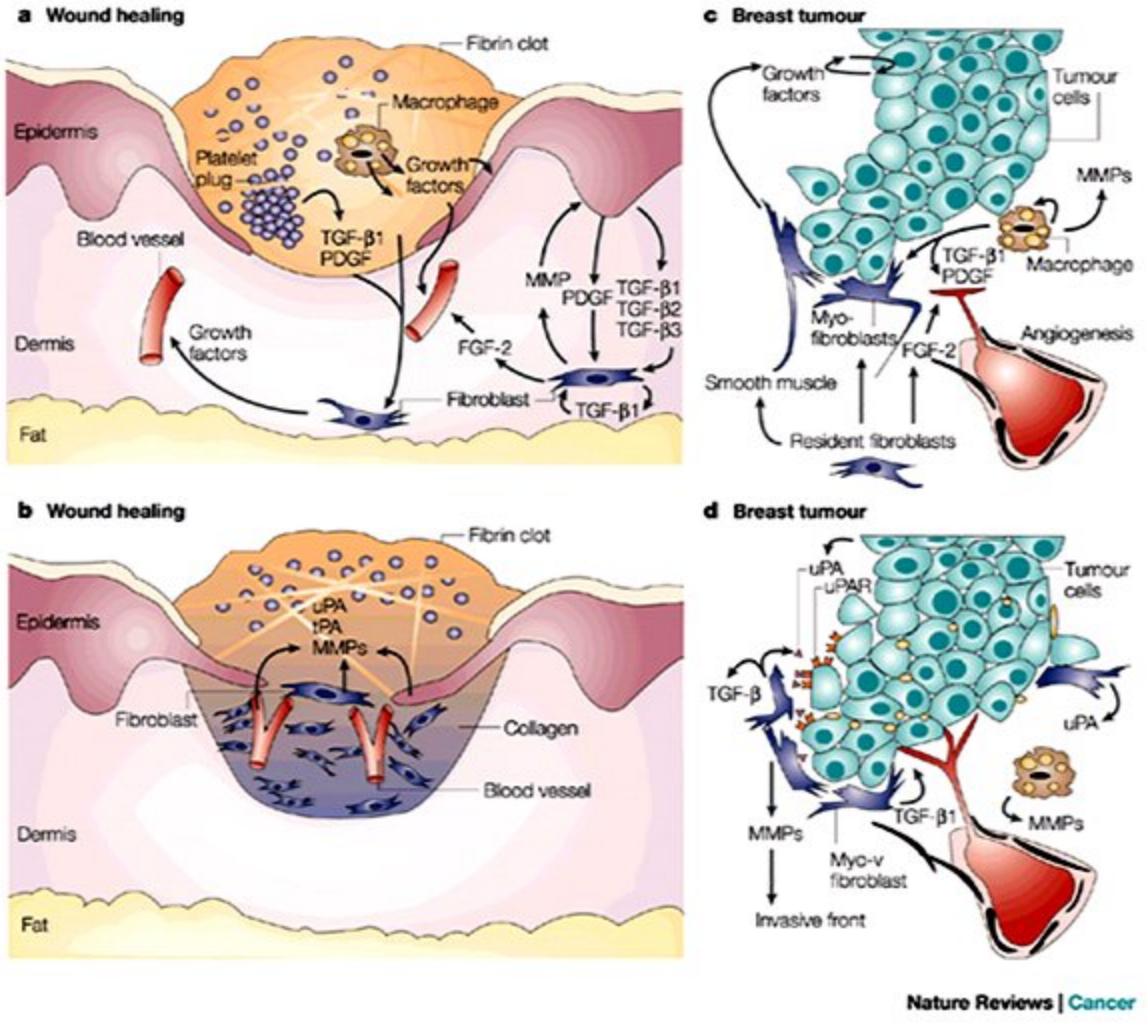
Tahera Zabuawaia, PhD

Immune System and Tumorigenesis



Coussens 2006

Tumorigenesis and Microenvironment



Bissell 2001

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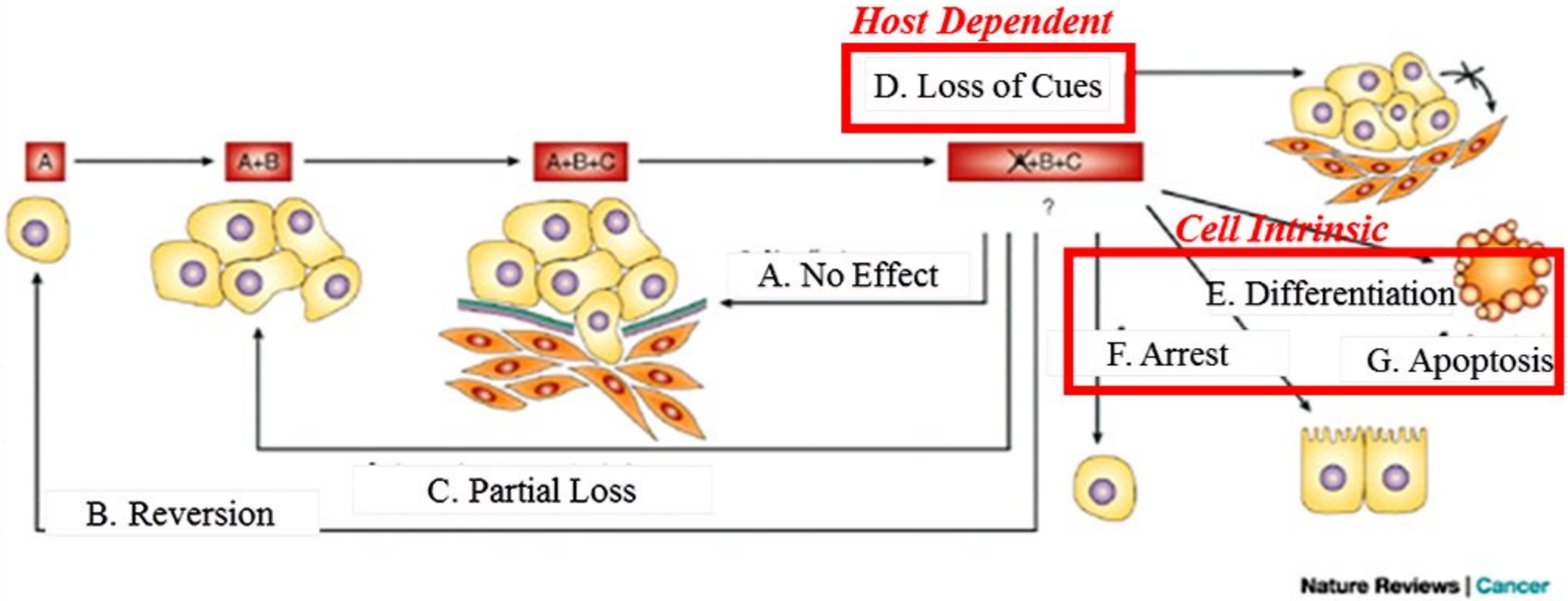
Giuriato et al, PNAS, 2006
Wu et al, PNAS, 2007
Van Riggelen, Genes and Develop, 2010

Adapted from Felsher D.W (2003)

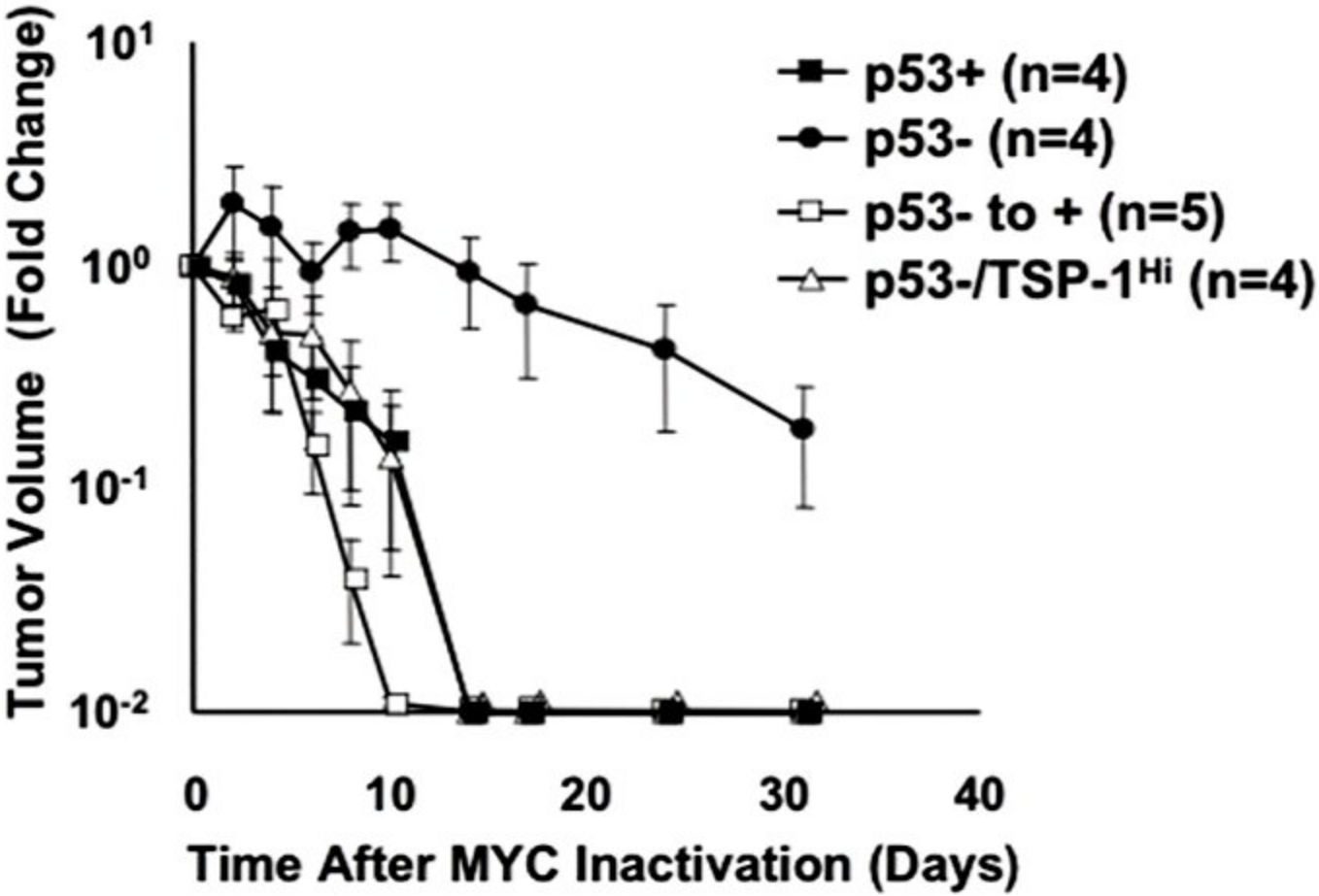
Mechanisms of Oncogene Addiction



Reversing tumorigenesis through restoration of both:
cell intrinsic fail-safe mechanisms and a normal microenvironment

Felsher, Nature Reviews Cancer, 2003

Restoration of Either p53 or TSP-1 is Sufficient for Tumor Regression Upon MYC Inactivation

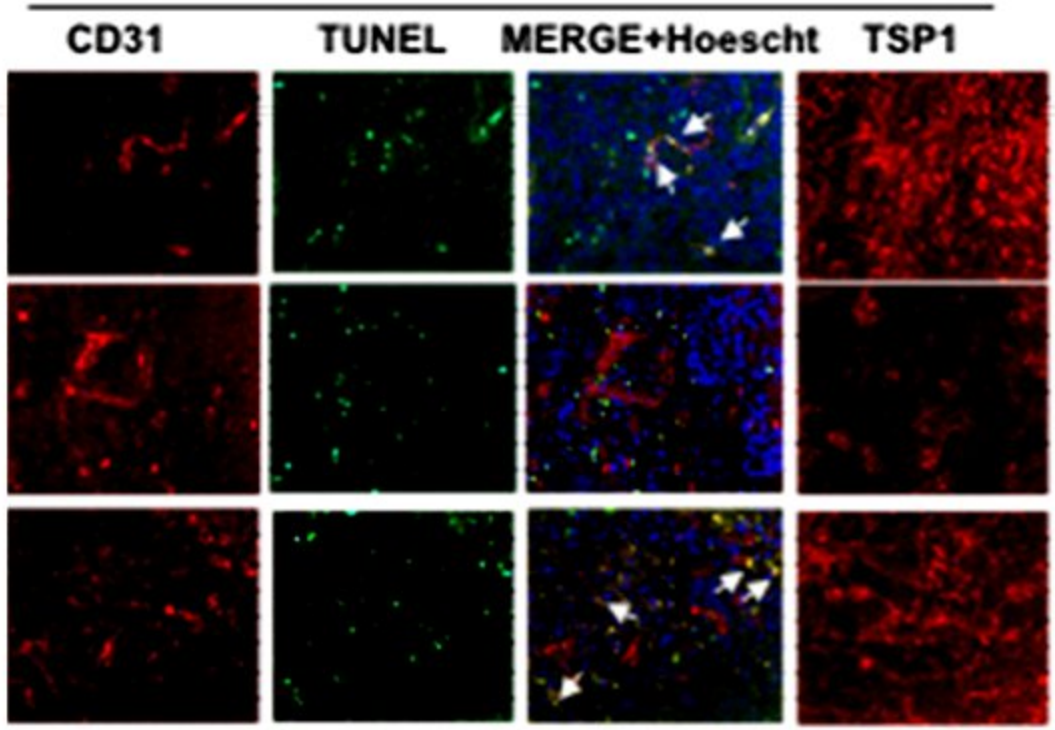


Giuriato et al, PNAS, 2007

Oncogene Addiction and the Angiogenic Switch

MYC-regulated p53-dependent TSP-1 Switch

MYC OFF



Giuriato, Ryeom, Fan, Bachireddy et al, PNAS, 2007

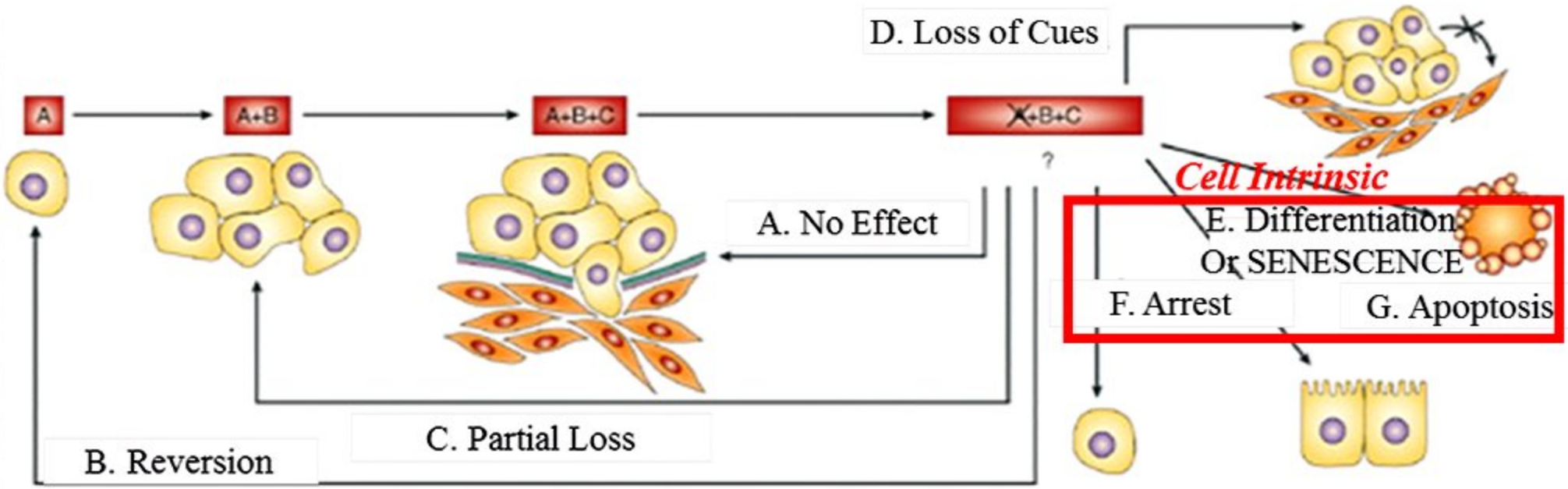
MYC, Oncogene Addiction and Angiogenesis

Sylvie Giuriato, PhD

Sandra Ryeom, PhD

Alice Fan, MD

Oncogene Addiction and Senescence

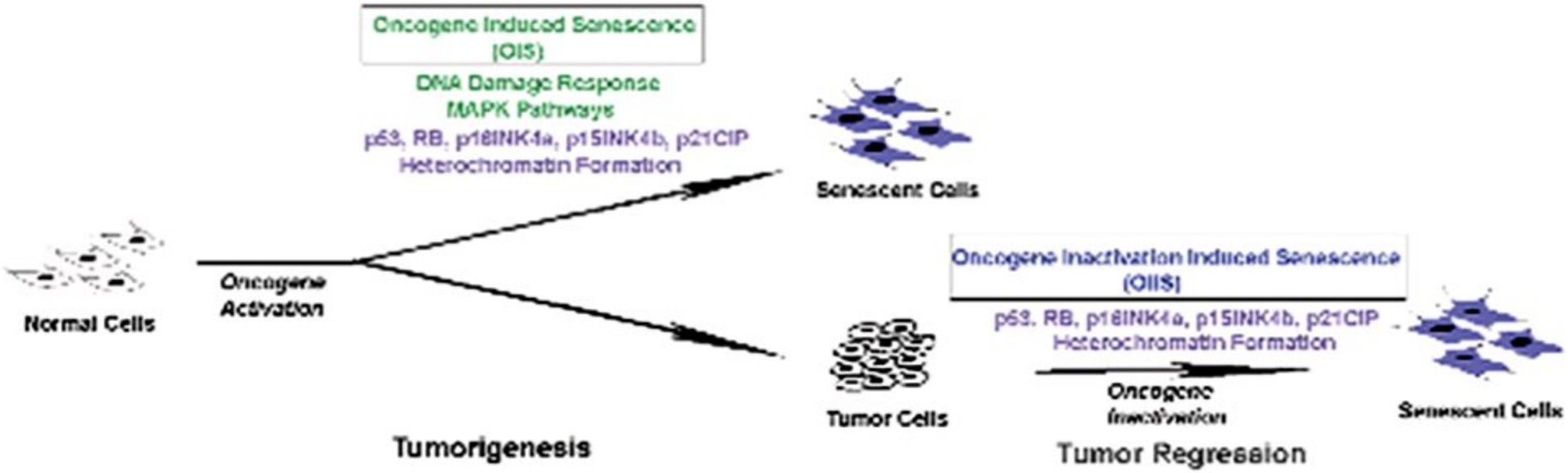


Nature Reviews | Cancer

Oncogene inactivation restores normal cellular programs that prevent tumorigenesis by resulting in the permanent loss of self-renewal

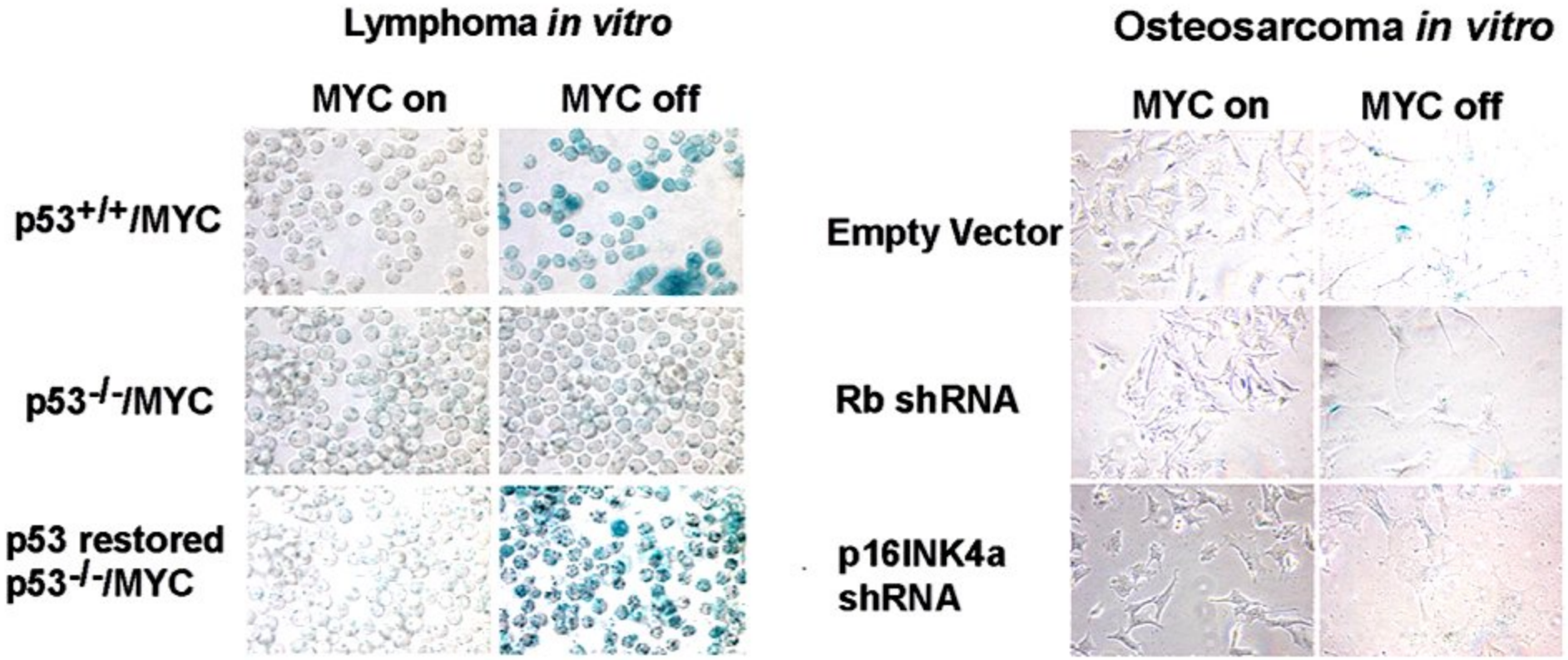
Felsher, Nature Reviews Cancer, 2003

Senescence a Barrier to Tumorigenesis and Mechanism of Oncogene Addiction



Wu et al PNAS *2007*

Loss of p53, RB or p16 Impedes MYC Inactivation from Inducing Cellular Senescence

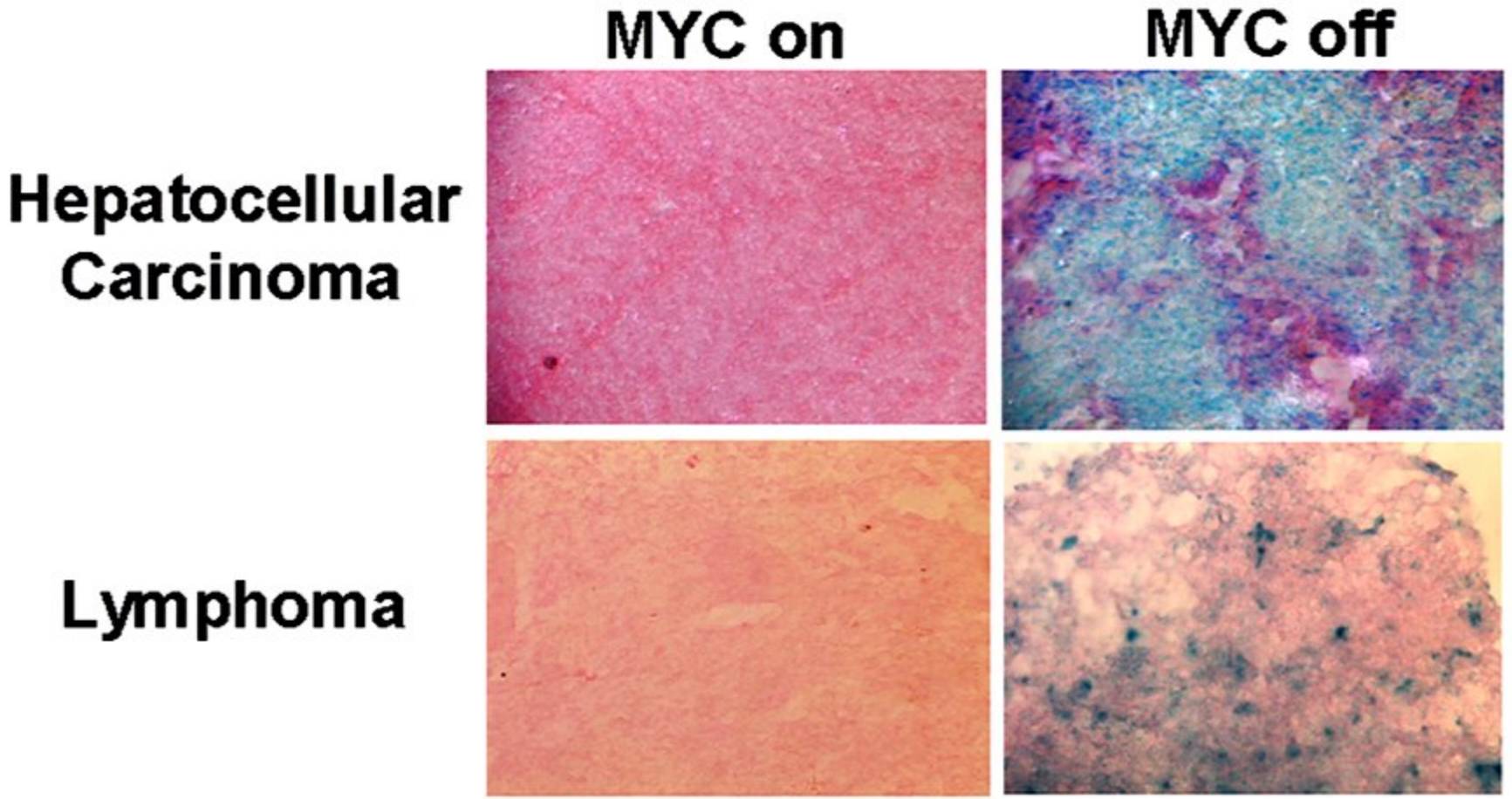


Wu et al PNAS *2007*

Oncogene Addiction and Senescence

MYC-regulation of self-renewal

beta-galactosidase staining



Wu et al PNAS *2007*

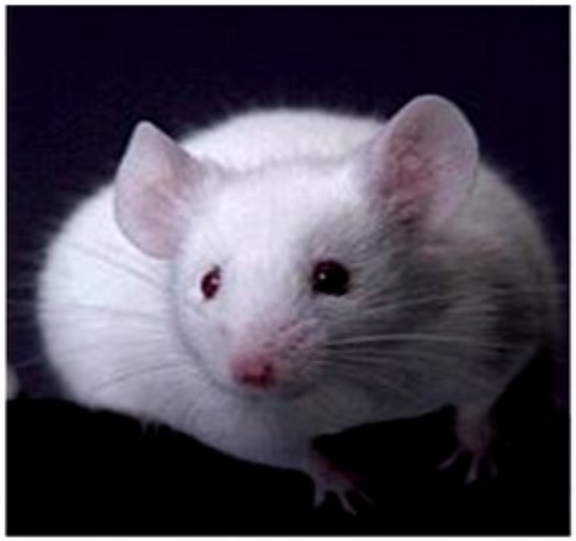
Cellular Senescence and Oncogene Addiction

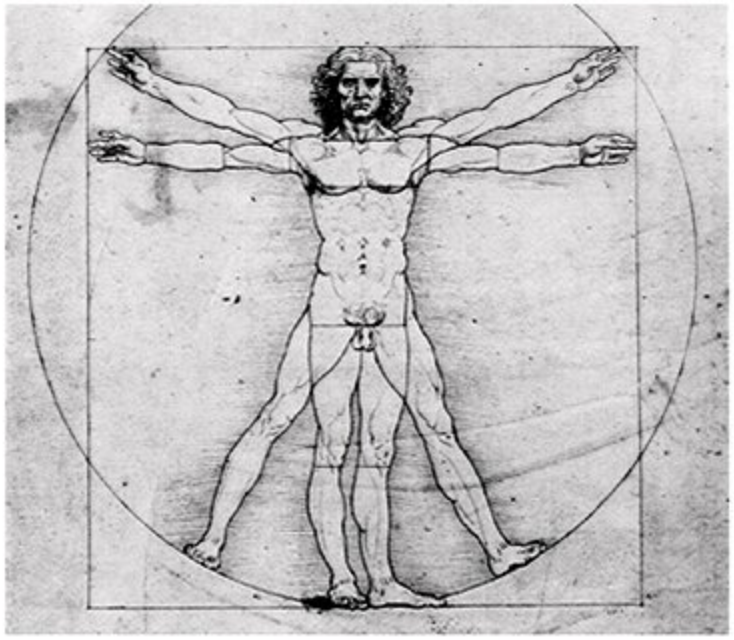
Natalie Wu

Alper Yetil

Jan van Riggelen

From Mouse to Man

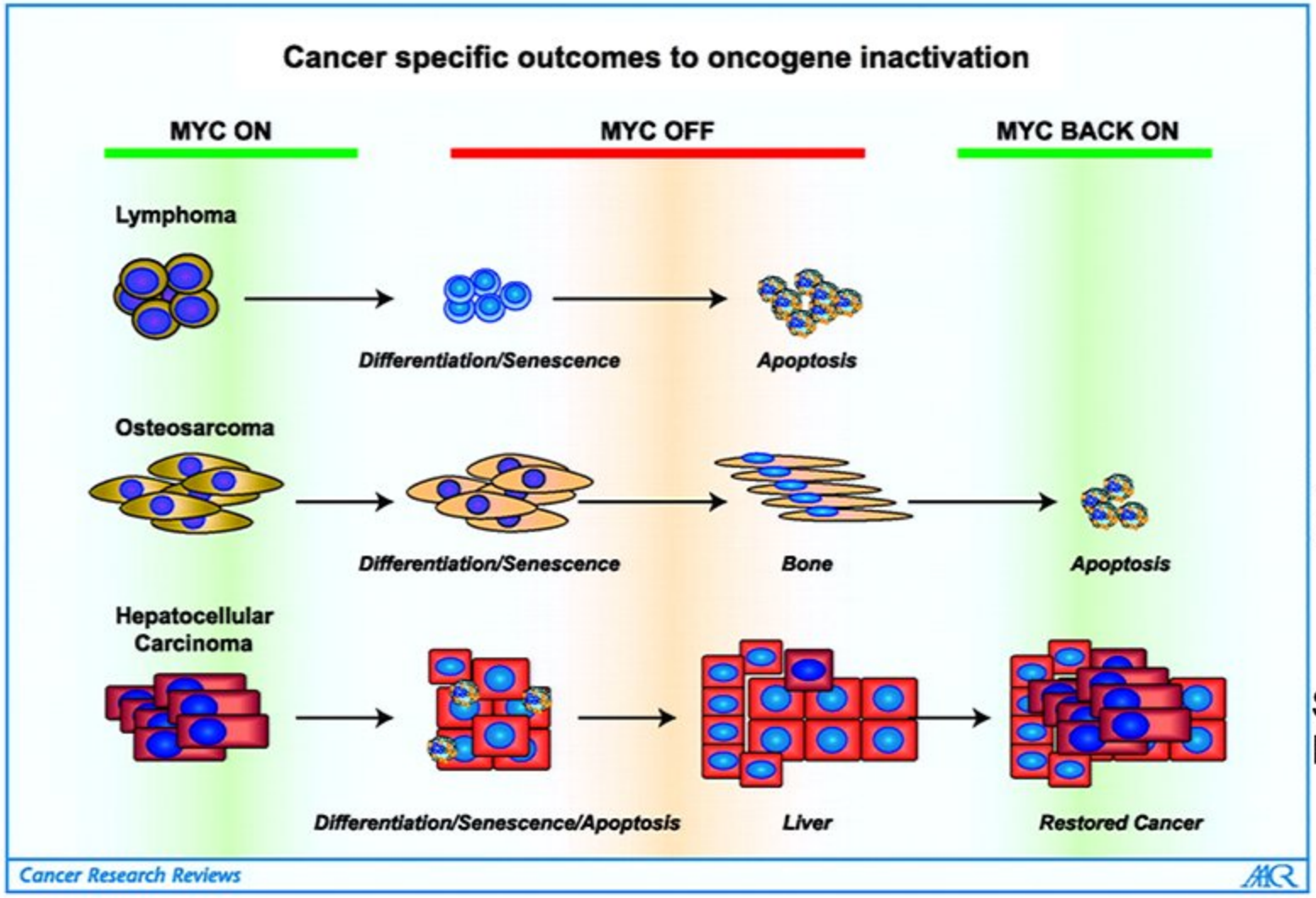




Part II. Mechanism

Oncogene Addiction:

MYC inactivation Induces Differentiation (Senescence)



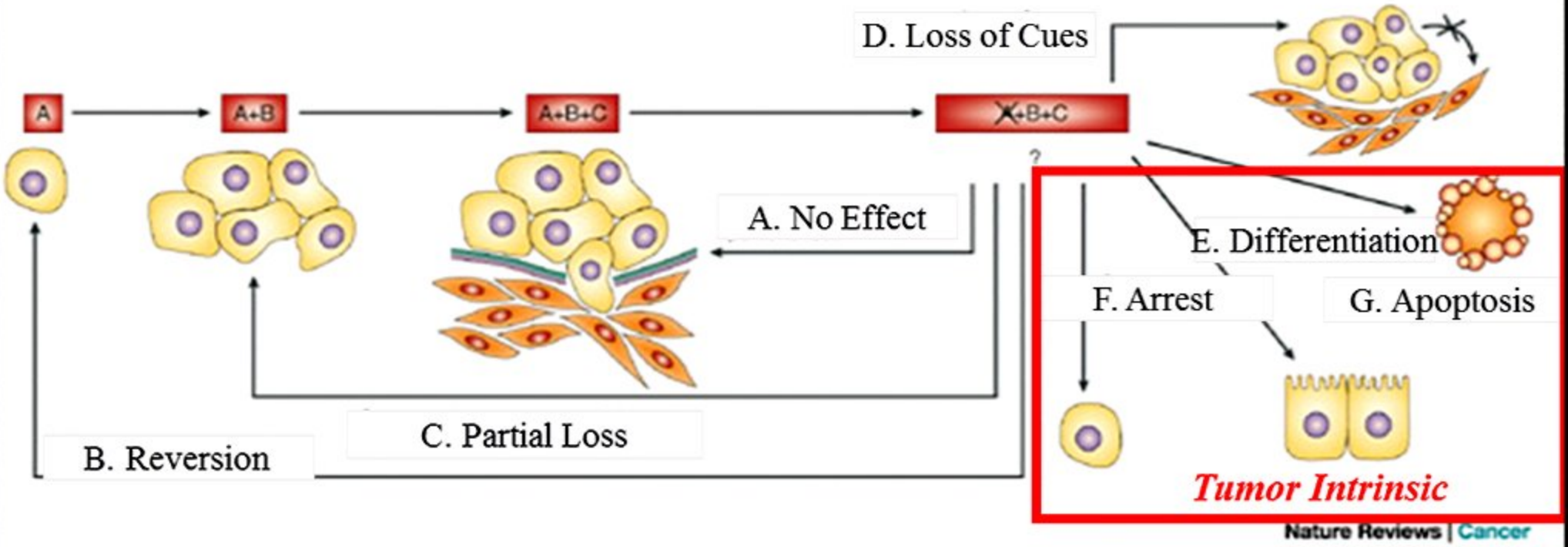
Felsher et.al. Molecular Cell (1999)

Jain et.al. Science (2002)

Shachaf et.al Nature (2004)

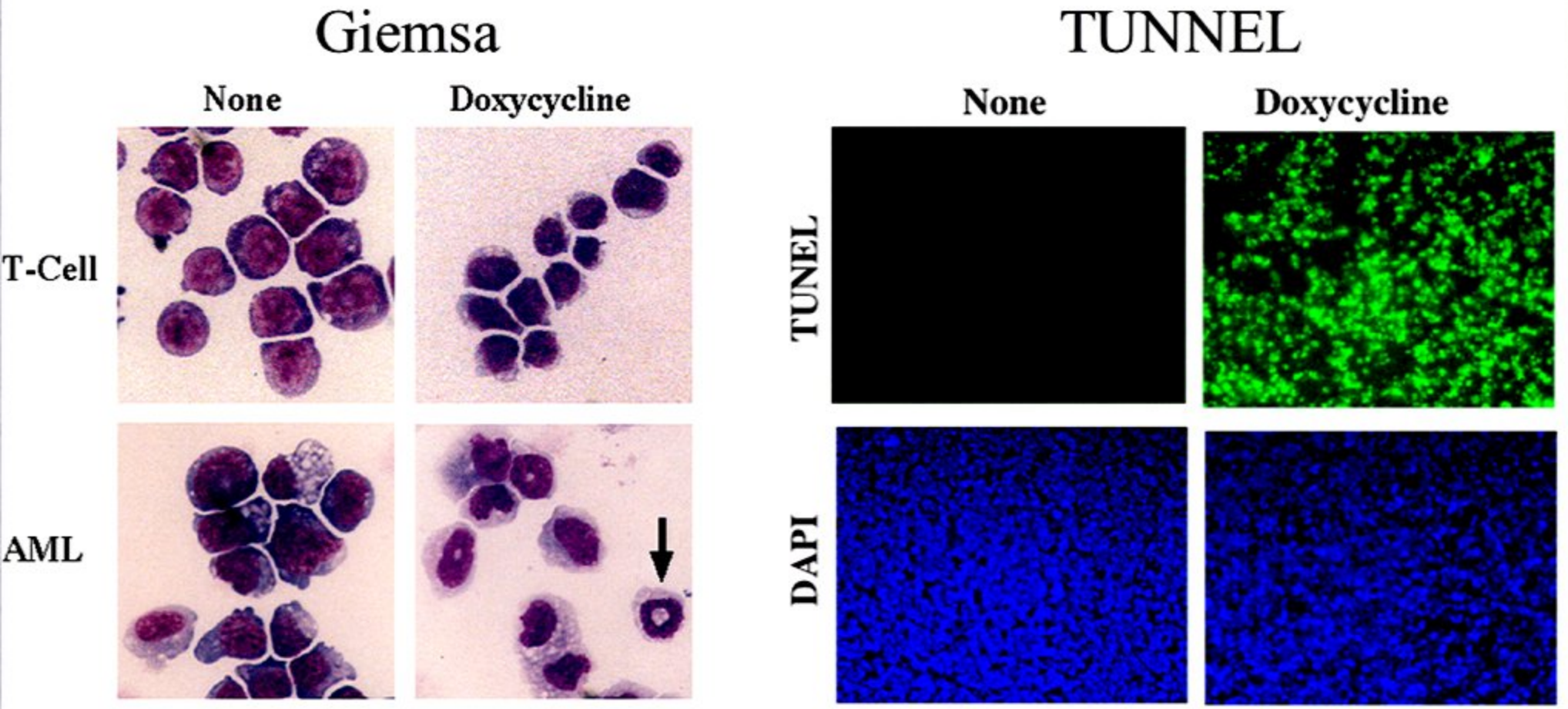
Felsher, D. W. Cancer Res 2008;68:3081-3086

Tumor Intrinsic Mechanisms of Oncogene Addiction



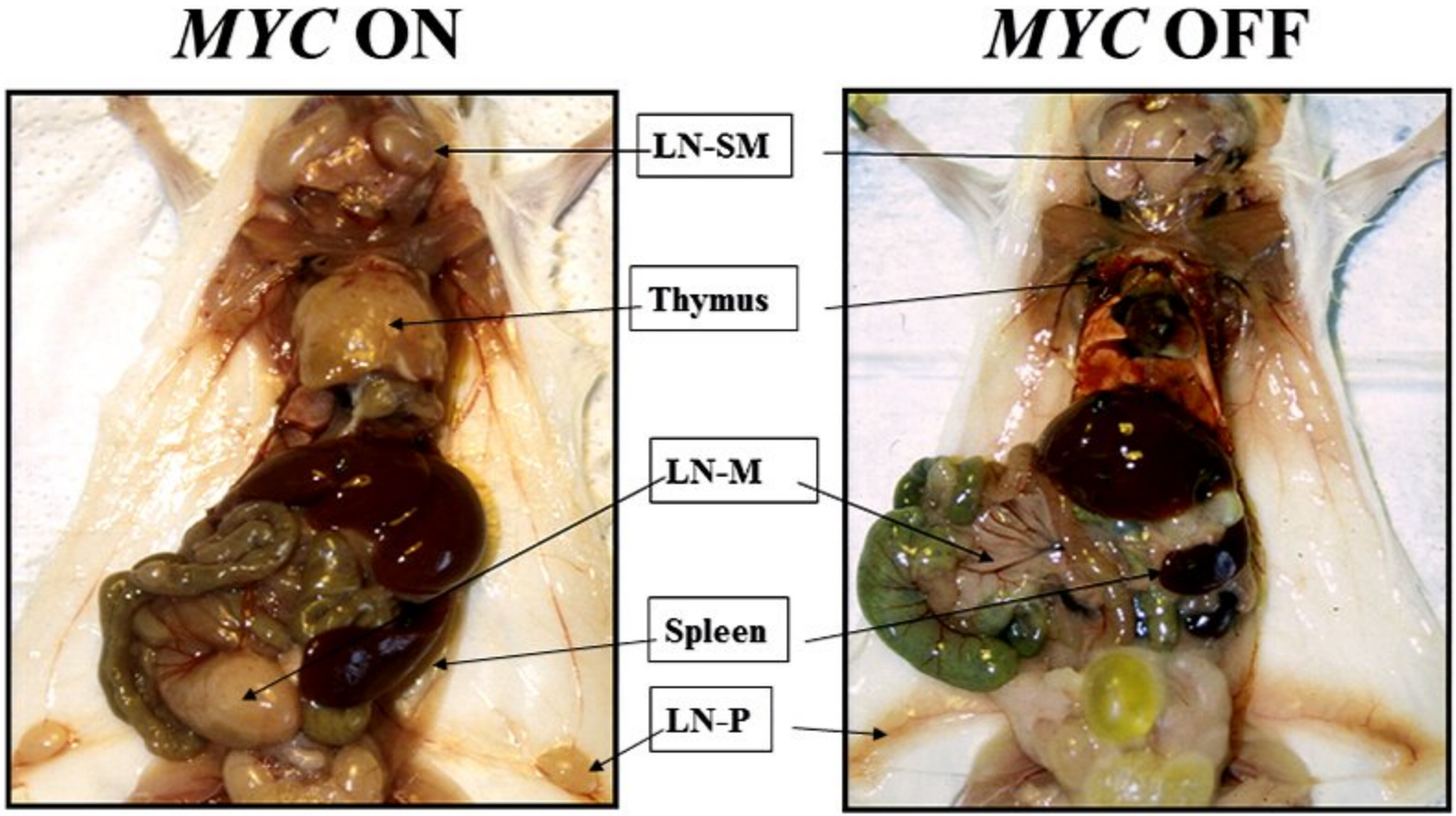
Felsher, Nature Reviews Cancer, 2003

MYC Inactivation in Lymphoma Results in Arrest, Differentiation and Apoptosis



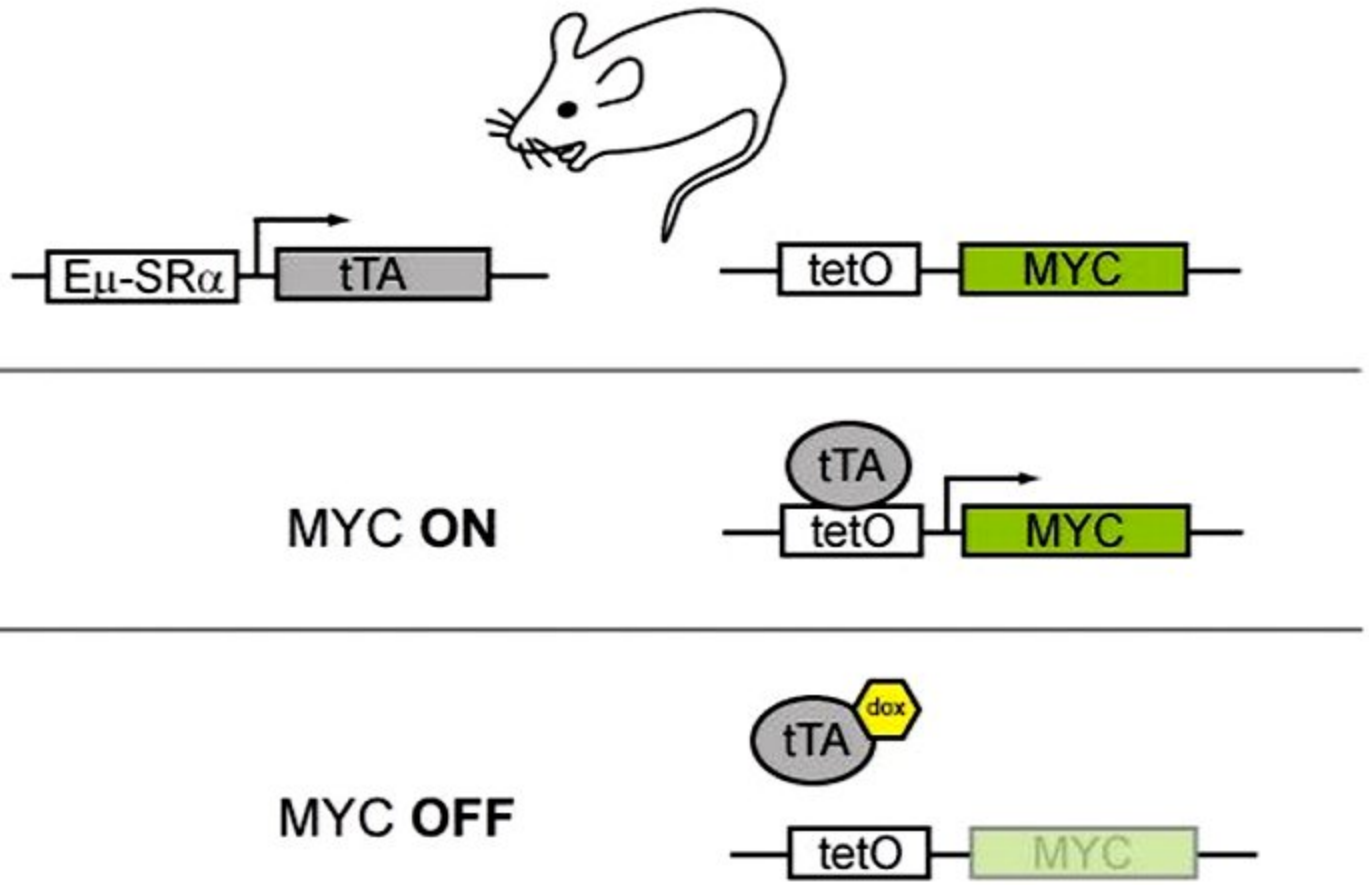
Felsher and Bishop, Molecular Cell,

MYC Induced Lymphomagenesis is Reversible

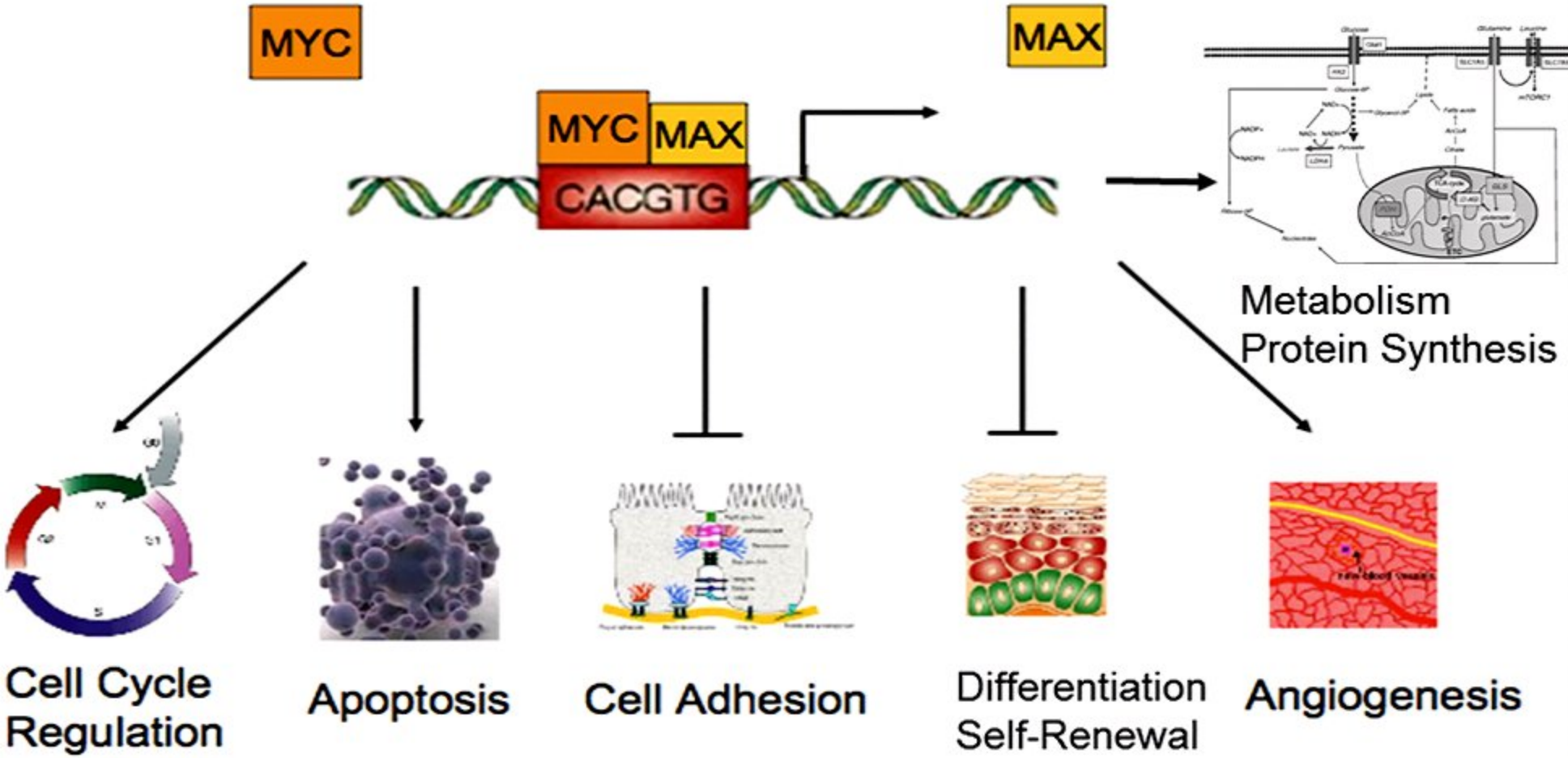


Felsher and Bishop, Molecular Cell,

Conditional Transgenic Mouse Models of Cancer



Cellular functions of MYC

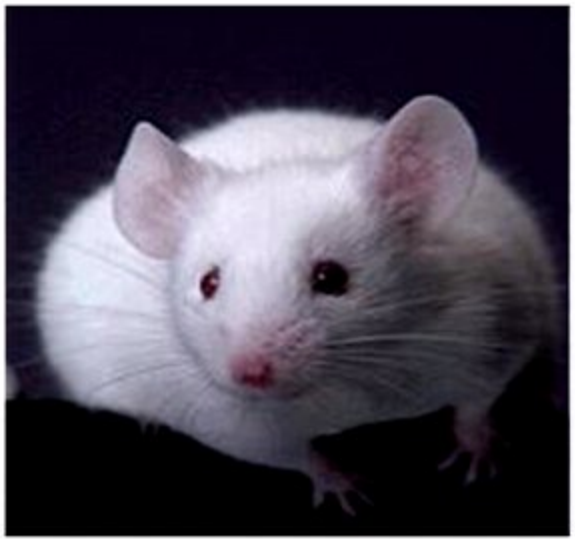


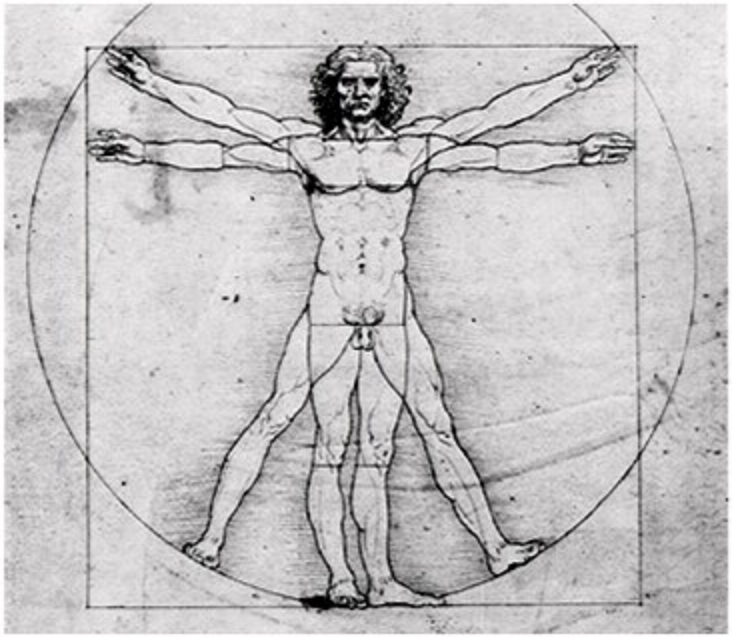
Adapted from Boxer and Dang, 2001; Perengeris et. al., 2002

Rules of Oncogene Addiction

- Oncogene inactivation reverses tumorigenesis.
  [Molecular Cell, 1999]
- Brief oncogene inactivation can induce tumor regression.
  [Science, 2002]
- Cellular, developmental and genetic context influence the consequences of oncogene inactivation.
  [Nature, 2004; PLoS Biology 2004]
- Senescence and Angiogenesis and oncogene addiction
  [PNAS 2007; PNAS 2007, PLoS Genetics 2012]
- Nanoscale proteomic analysis of clinical specimens.
  [Nature Medicine, 2009]
- Autocrine Programs and the Immune System
  [Genes and Development, 2010; Cancer Cell 2010]
- Modeling Oncogene Addiction
  [Science Translational Medicine, 2011]

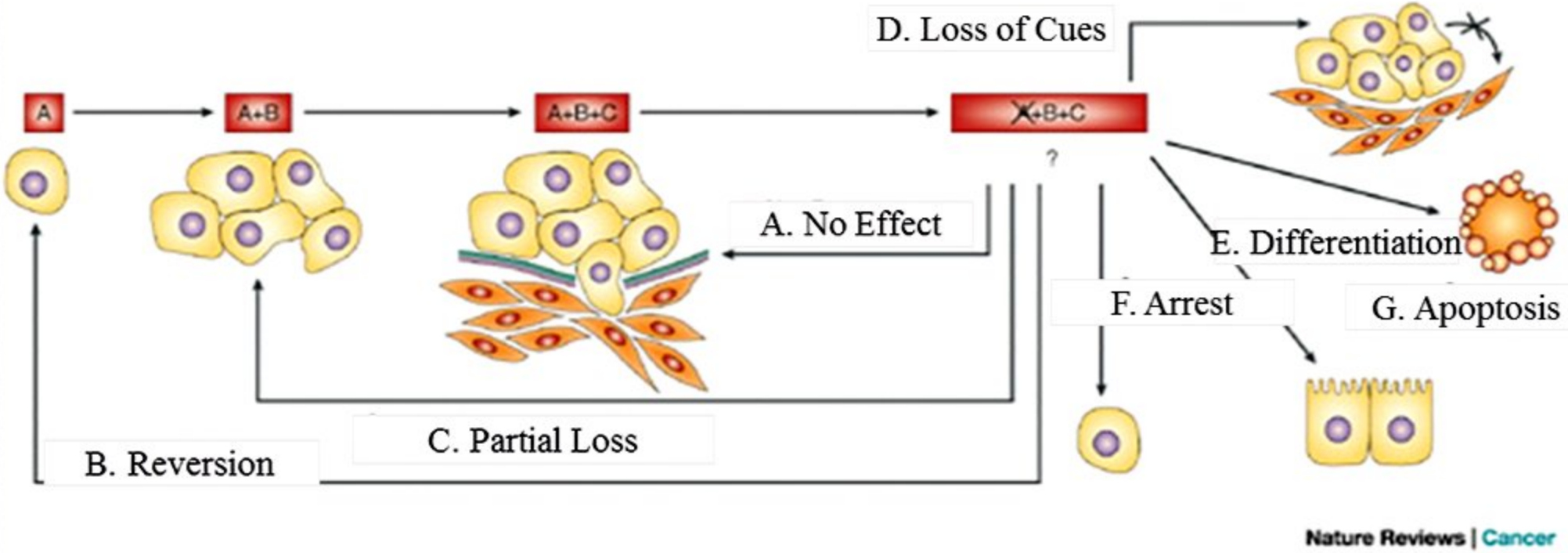
From Mouse to Man





Why do "targeted therapies" work?

Oncogene Addiction: *the Achilles Heel of Cancer*



Felsher and Bishop 1999
Chin and Depinho 1999
Huetner and Tenen 2000
D'Cruz and Chodosh 2001
Fisher and Varmus 2001

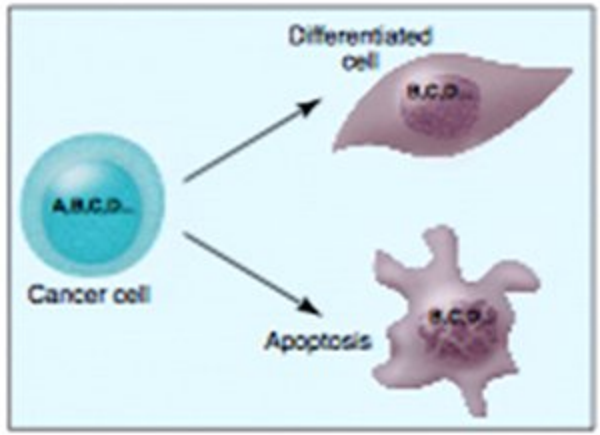
Felsher, Nature Reviews Cancer, 2003

Oncogene Addiction: *the Achilles Heel of Cancer*

Bernard Weinstein, MD

PERSPECTIVES: CANCER

Addiction to Oncogenes—the Achilles Heal of Cancer



A one-step remedy. Cancer cells acquire abnormalities in multiple oncogenes and tumor suppressor genes (A, B, C, and D). Inactivation of a single critical oncogene (A) can induce cancer cells to differentiate into cells with a normal phenotype or to undergo apoptosis. This dependence on (addiction to) A for maintaining the cancer phenotype provides an Achilles heel for tumors that can be exploited in cancer therapy.

Science, 2002