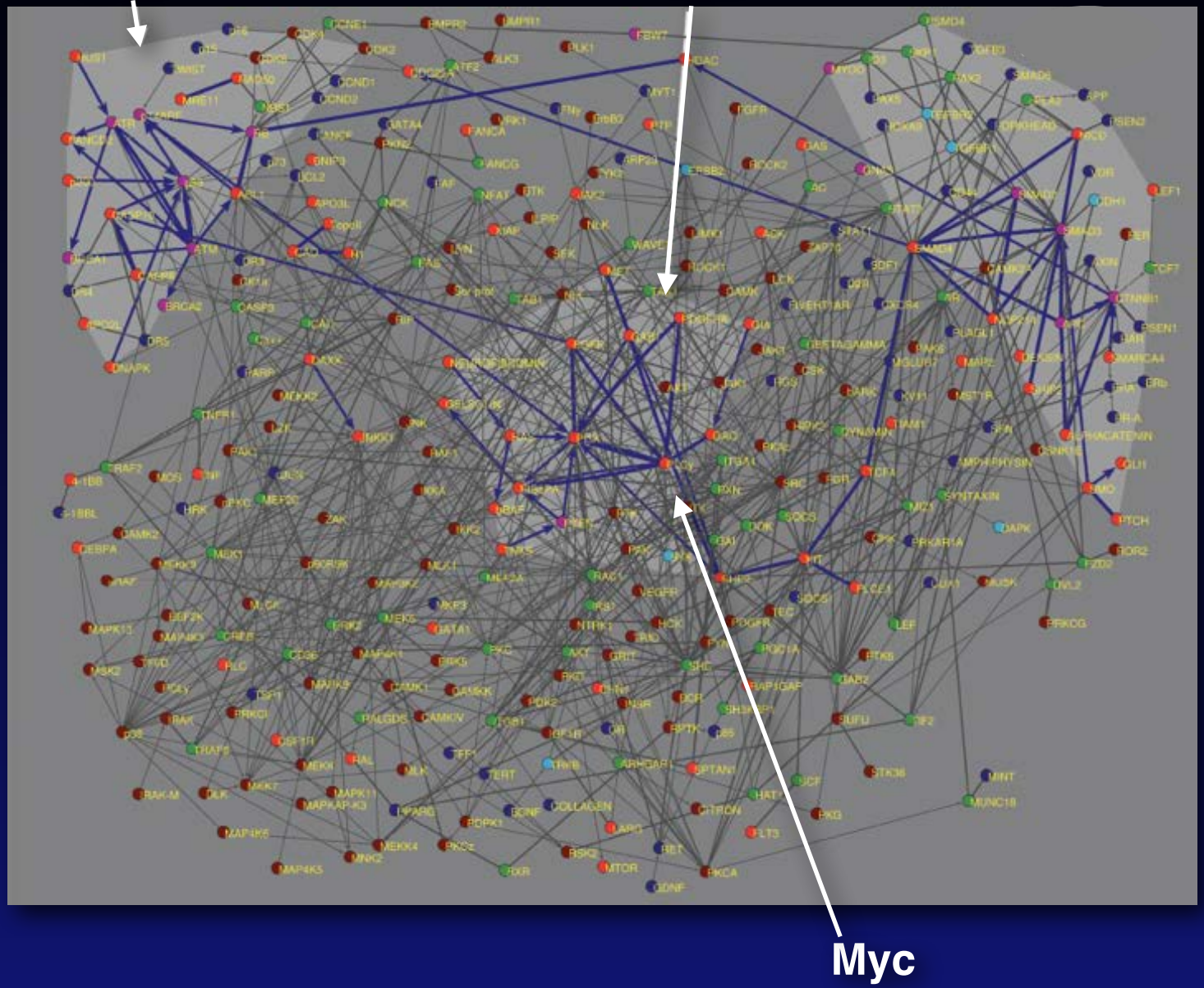
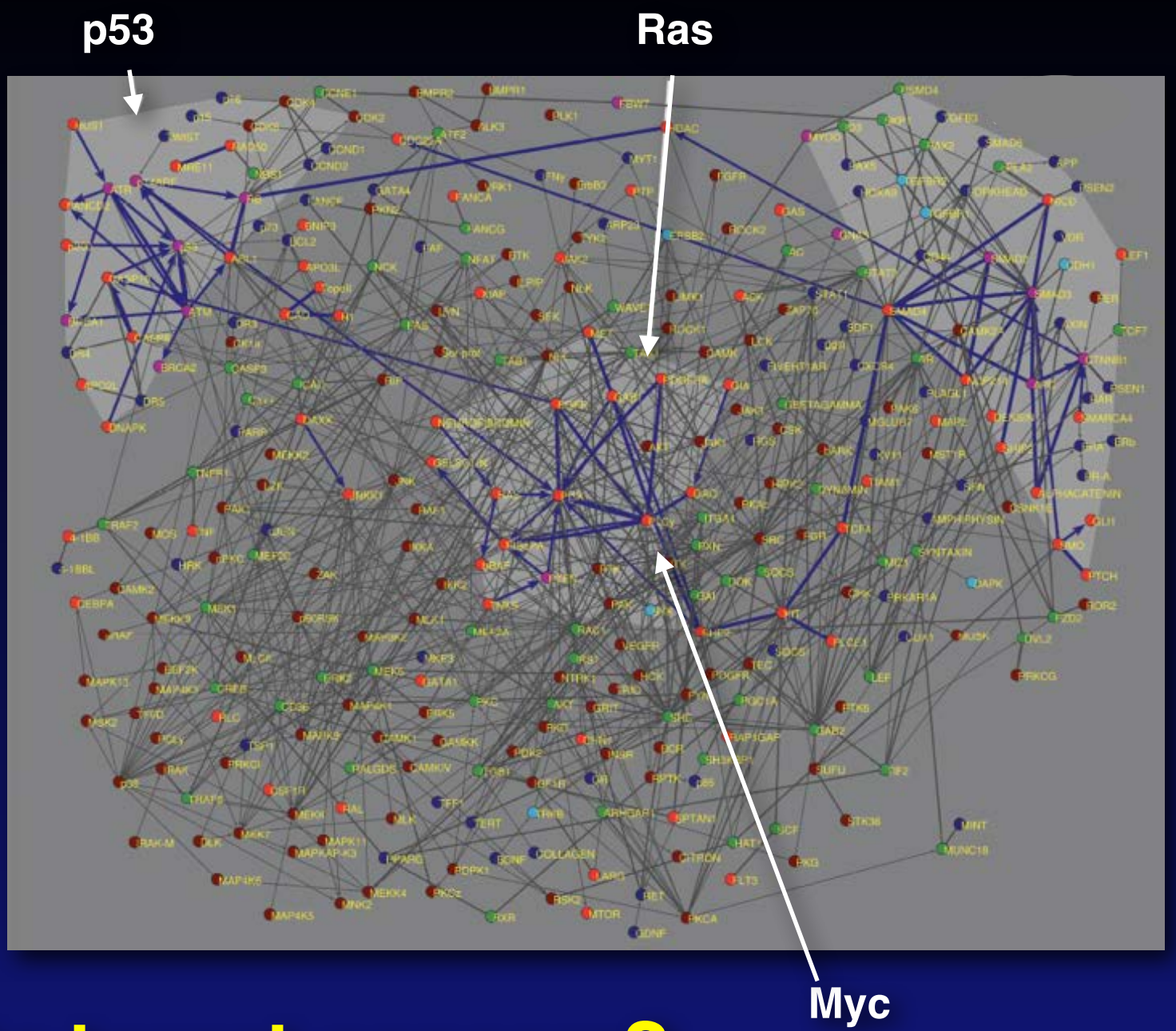
Questions and challenges in cancer biology

Gerard I. Evan
Dept. Biochemistry
University of Cambridge

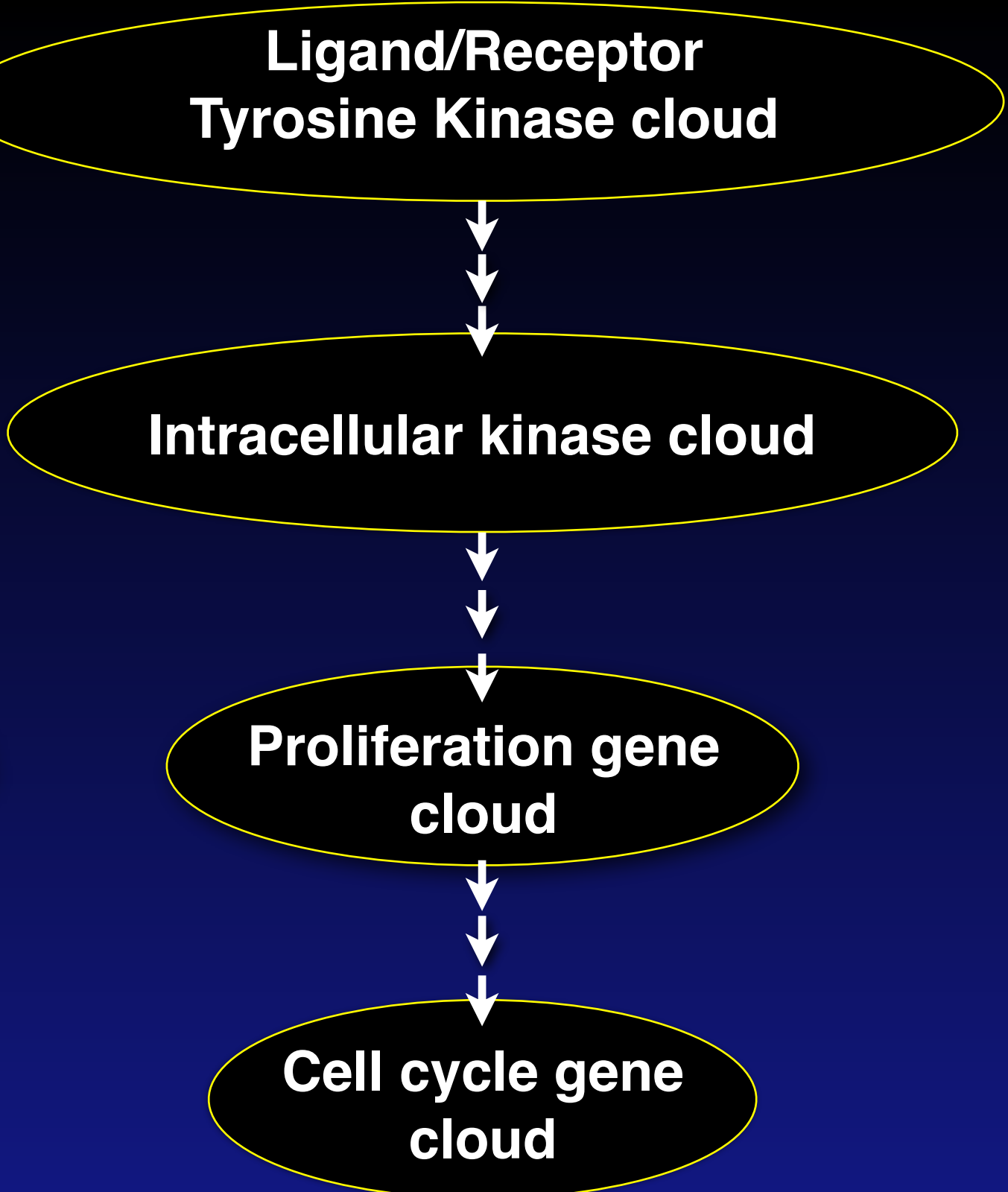

p53
Ras
Myc



Where to target cancers?

Where to target cancers?

The problem of robustness



Where to target cancers?

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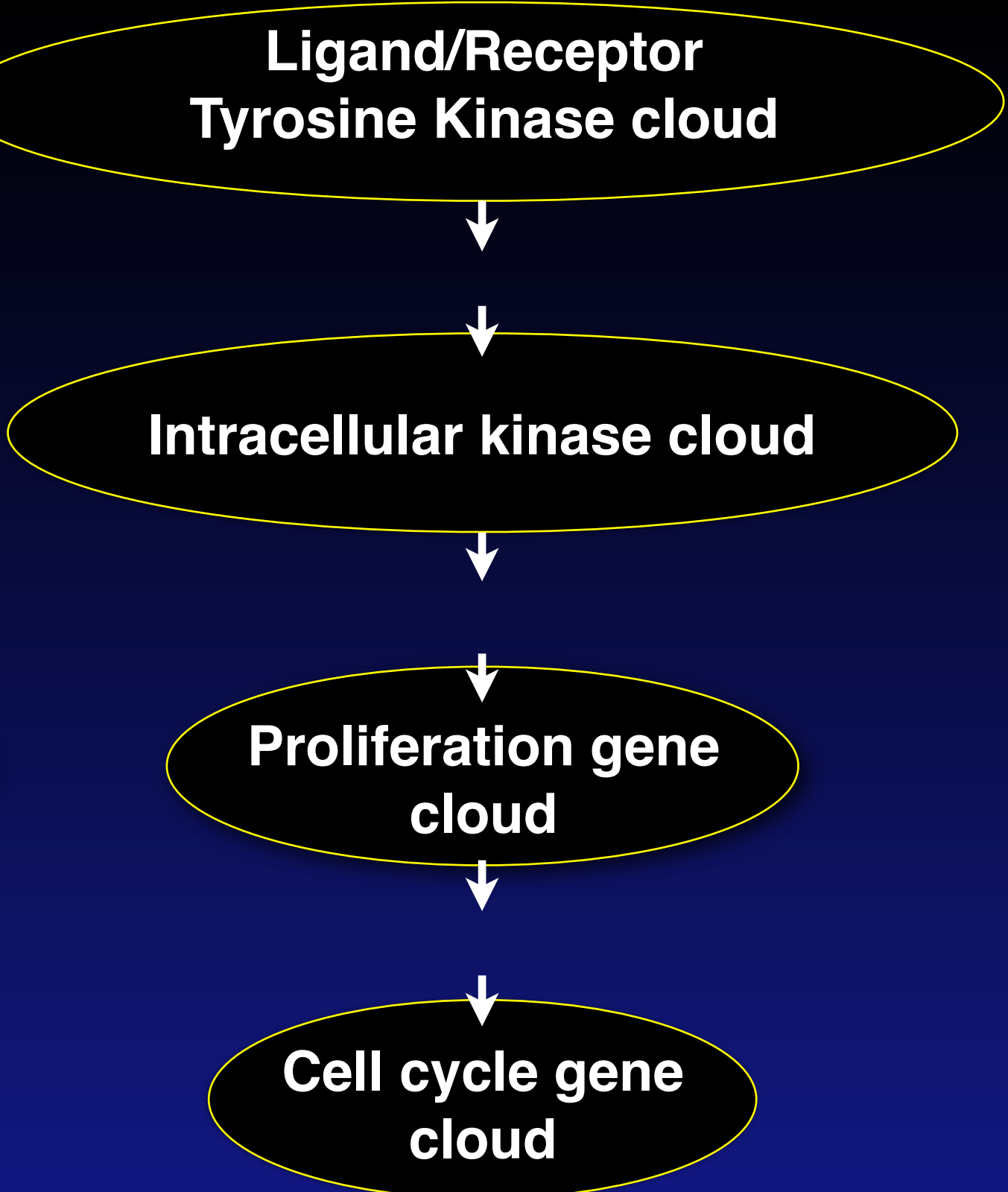


Tools for dissecting biological systems

Tools for dissecting biological systems

Biochemistry & Molecular Biology

Tools for dissecting biological systems

Biochemistry & Molecular Biology

- Reductionist analysis of components

Tools for dissecting biological systems

Biochemistry & Molecular Biology

- Reductionist analysis of components
- Limited analysis of interactions

Tools for dissecting biological systems

Biochemistry & Molecular Biology

- Reductionist analysis of components
- Limited analysis of interactions
- Very limited analysis of interaction dynamics

Tools for dissecting biological systems

Biochemistry & Molecular Biology

Tools for dissecting biological systems

Biochemistry & Molecular Biology

Genetics

Tools for dissecting biological systems

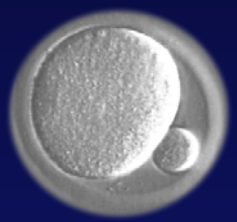
Biochemistry & Molecular Biology

Genetics

Algebraic approach to structure and function

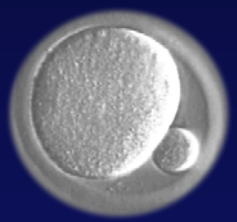
Robustness confounds classical genetics

Mutation



Robustness confounds classical genetics

Mutation

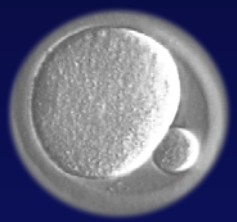


Embryonic lethality

"Essential gene"

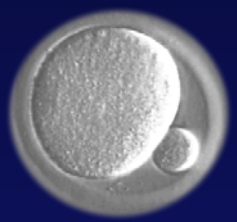
Robustness confounds classical genetics

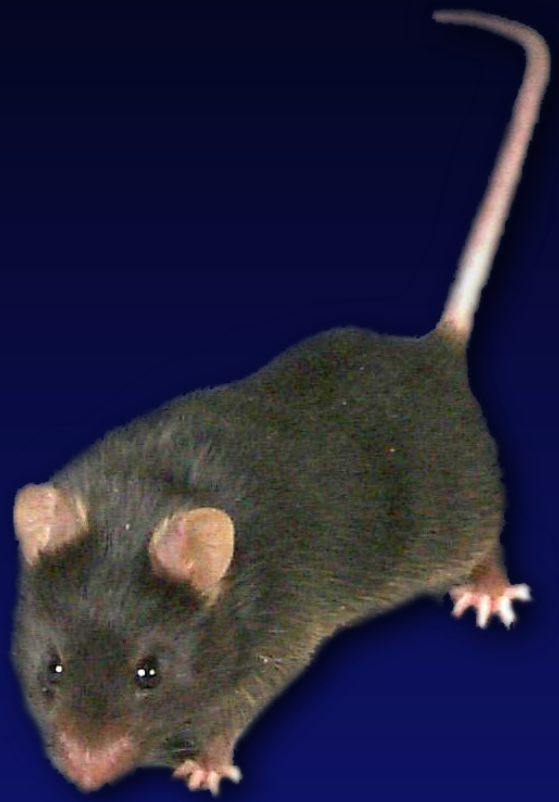
Mutation



Robustness confounds classical genetics

Mutation



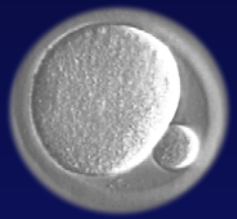


"Redundant" gene"

Compensated adult phenotype

Robustness confounds classical genetics

Mutation



"Redundant" gene"

Partially compensated adult phenotype

Teleology also confounds classical genetics

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Genes, proteins, biological processes have *no* purpose or goal,

Teleology also confounds classical genetics

Genes, proteins, biological processes have *no* purpose or goal,

just contextual function

Tools for dissecting biological systems

Biochemistry & Molecular Biology

Genetics

Tools for dissecting biological systems

Biochemistry & Molecular Biology

Genetics

in silico modeling of systems

Tools for dissecting biological systems

in silico modeling of systems

Tools for dissecting biological systems

in silico modeling of systems

Complexity

Tools for dissecting biological systems

in silico modeling of systems

Complexity

Localization

Tools for dissecting biological systems

in silico modeling of systems

Complexity

Localization

Evolved, not designed, function

Tools for dissecting biological systems

in silico modeling of systems

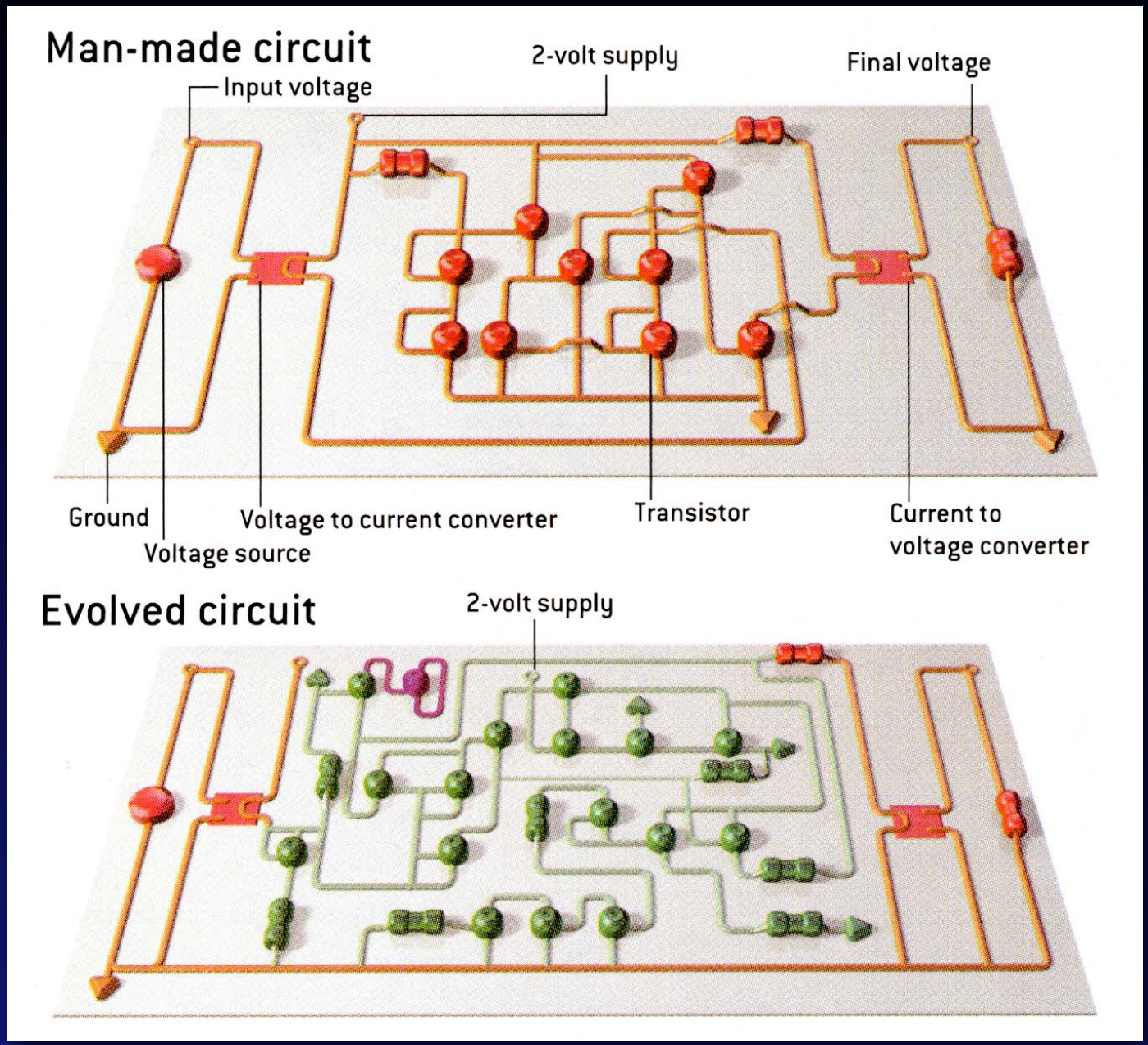
Complexity

Localization

Evolved, not designed, function

Computability?

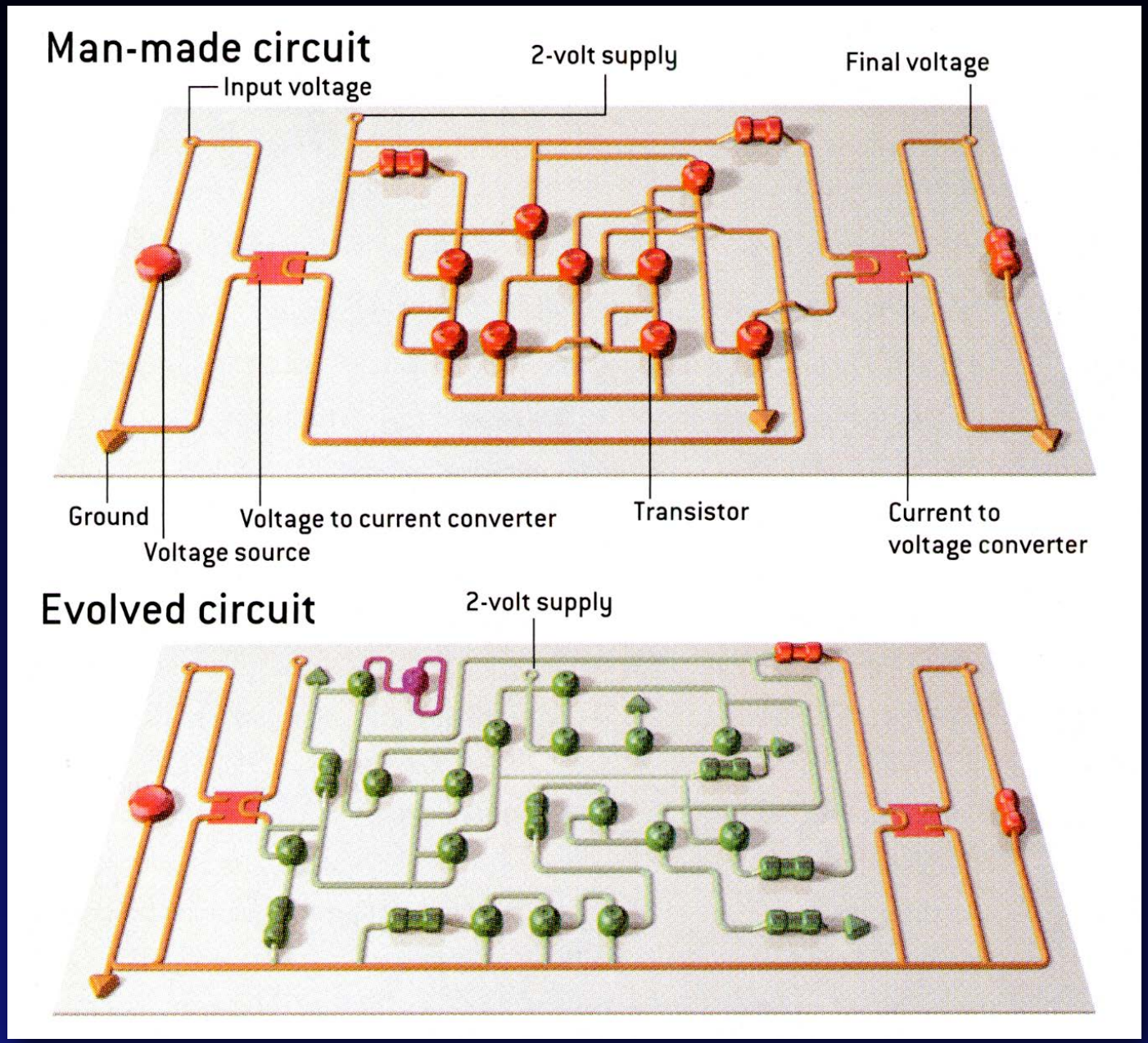
Designed and evolved cubic signal generators



Koza, Keane & Streeter

Scientific American February 2003

Designed and evolved cubic signal generators

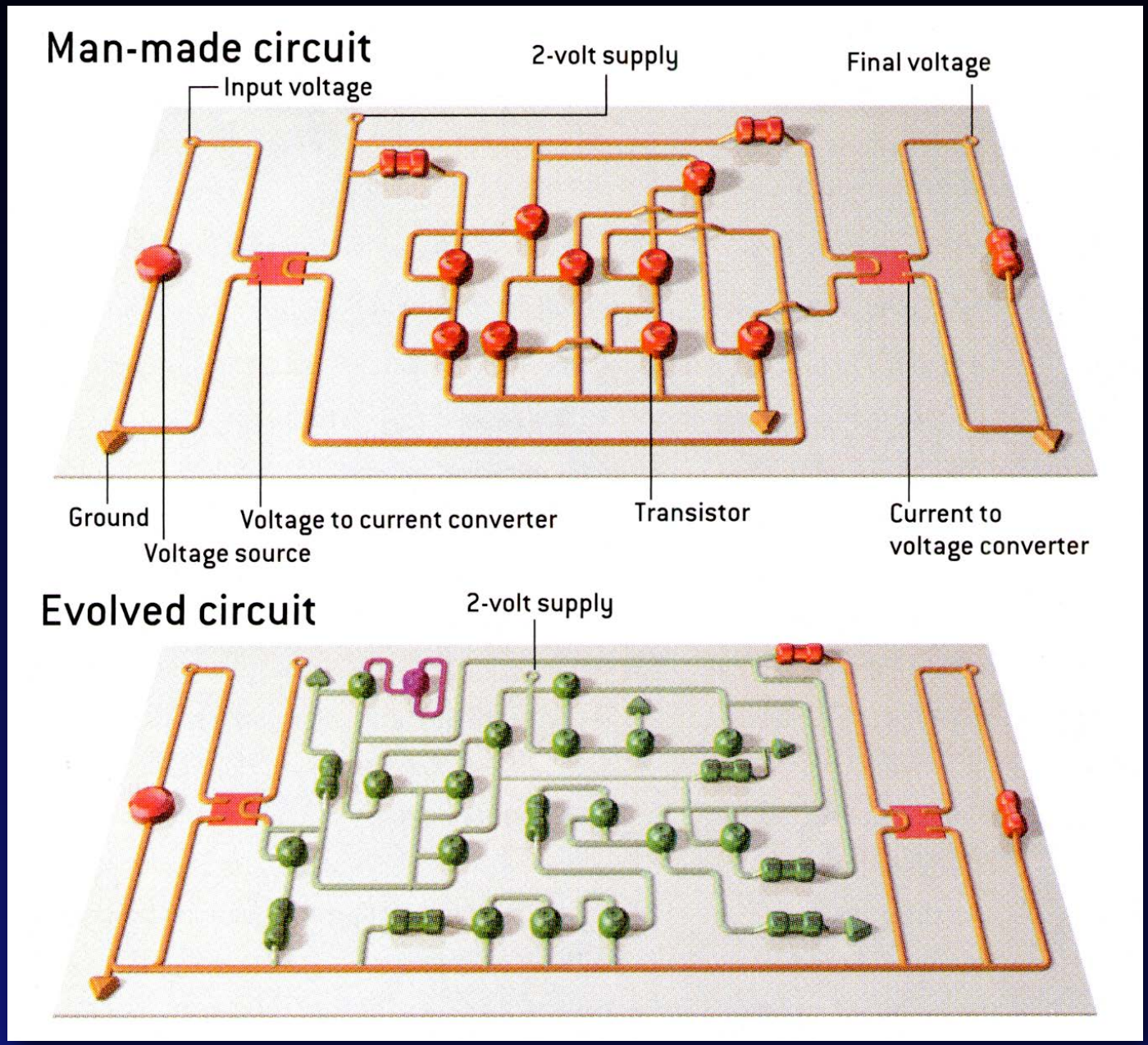


- More efficient

Koza, Keane & Streeter

Scientific American February 2003

Designed and evolved cubic signal generators

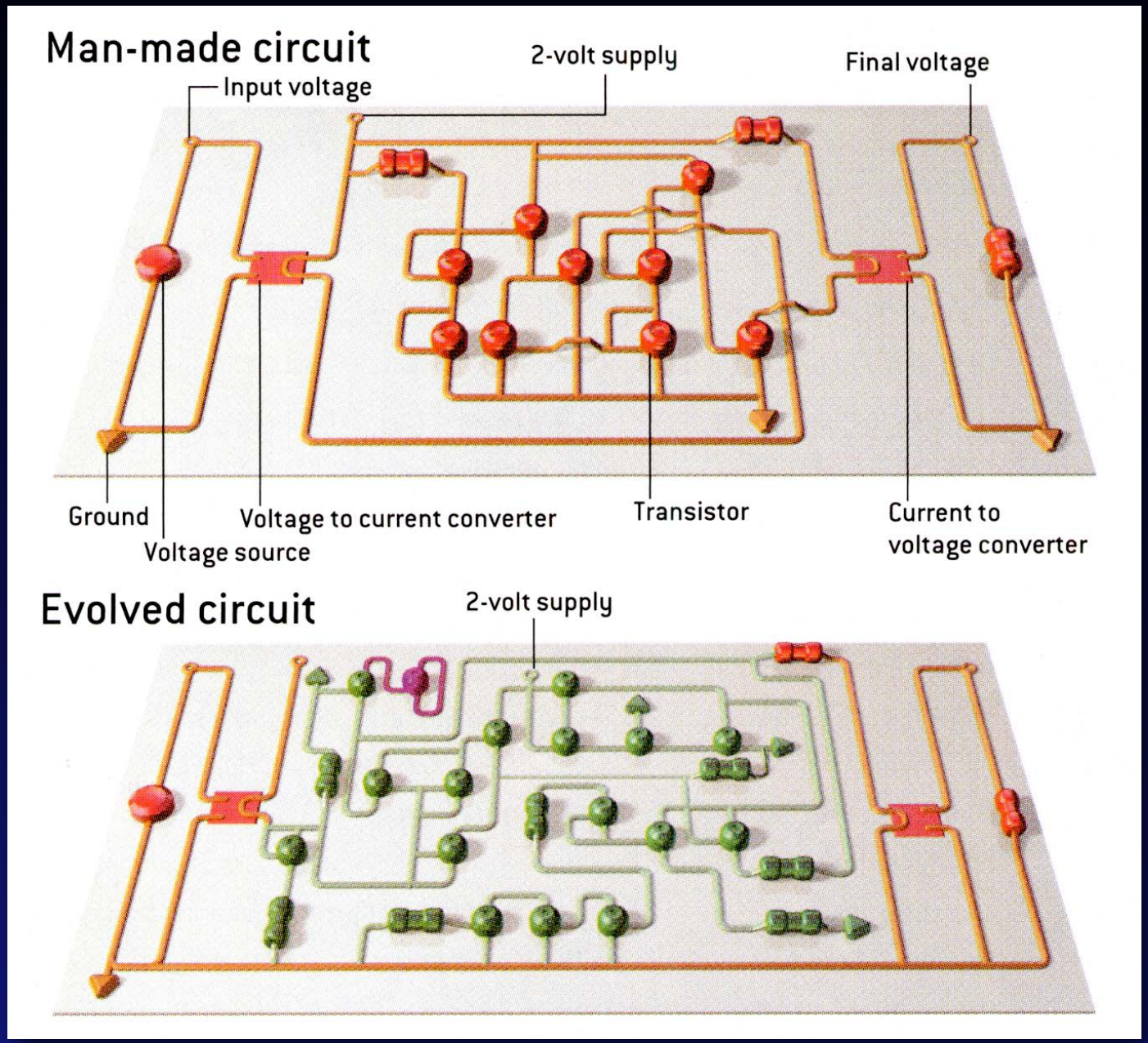


- More efficient
- More complex (irreducibly?)

Koza, Keane & Streeter

Scientific American February 2003

Designed and evolved cubic signal generators



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Koza, Keane & Streeter

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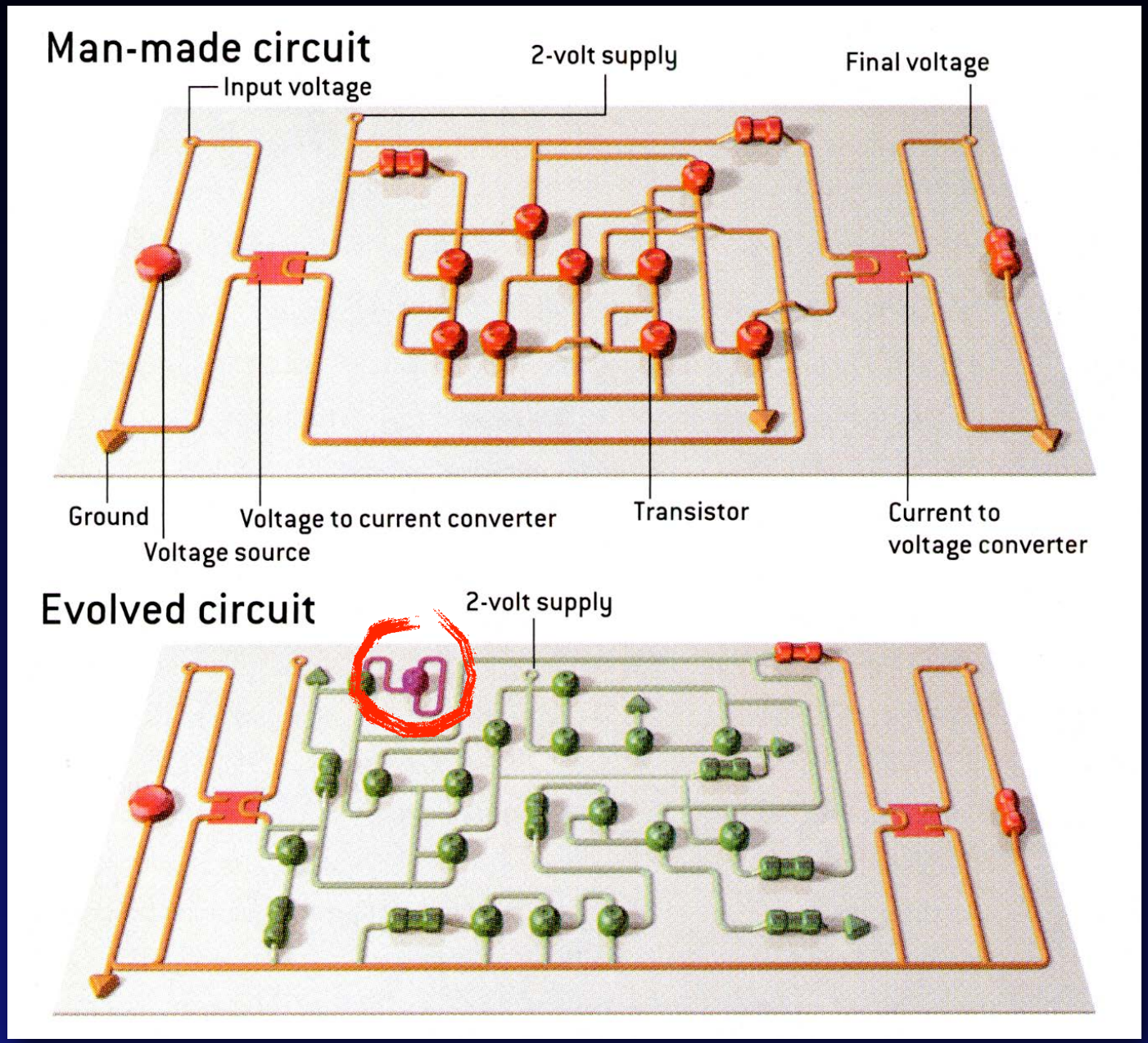
Designed and evolved cubic signal generators



- More efficient
- More complex (irreducibly?)
- More complicated
- Redundant parts

Koza, Keane & Streeter

Scientific American February 2003

The problems with rationally targeting cancers

The problems with rationally targeting cancers

- Cancer cells and tissues are very similar to their regenerating normal counterparts

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- Cancer cells adapt to pharmacological perturbation and evolve under pharmacological selection

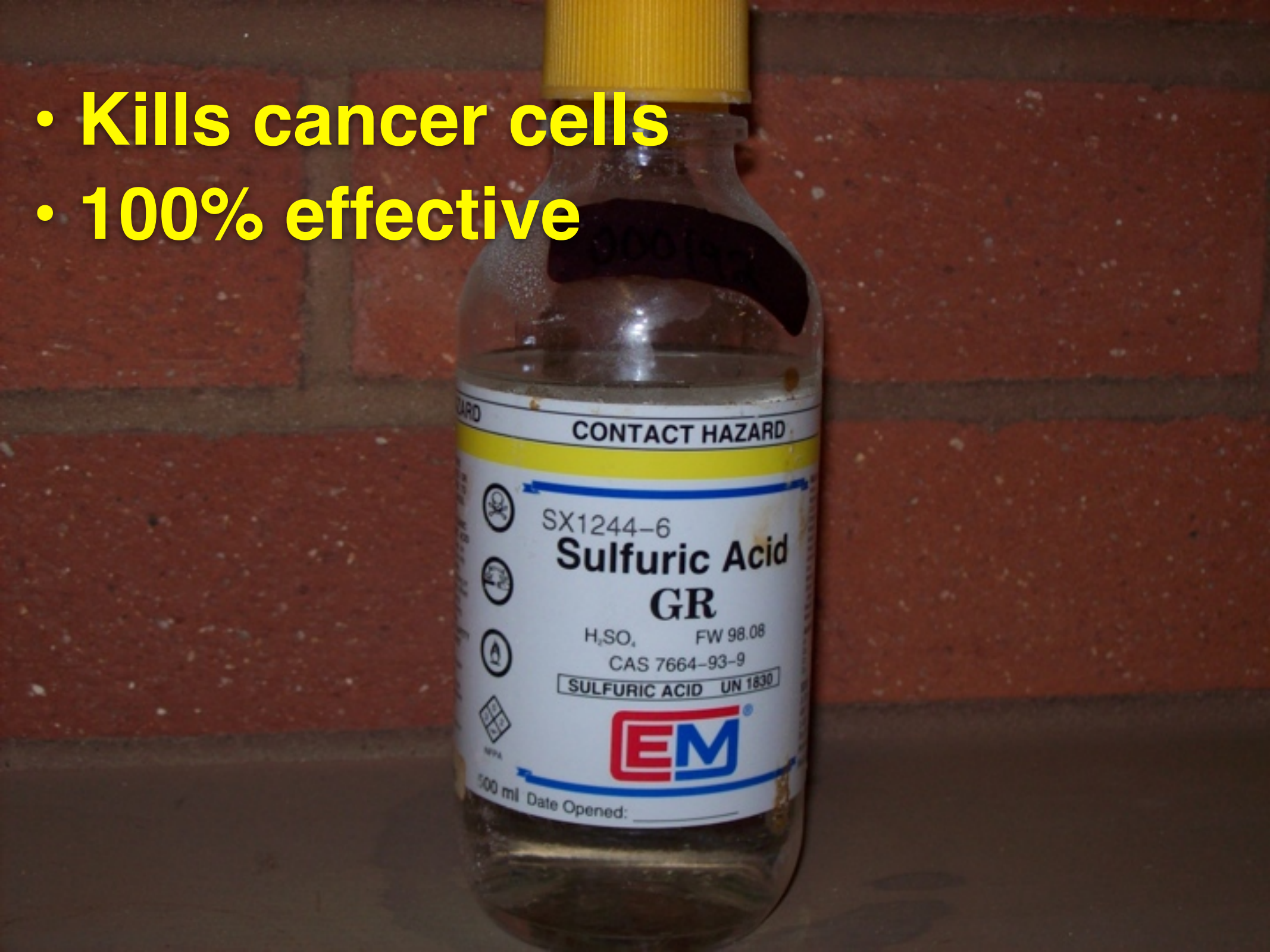
The problems with rationally targeting cancers

- Cancer cells and tissues are very similar to their regenerating normal counterparts
- Even our best targeted drugs fail to correct the actual oncogenic dysfunction (which is signal *misregulation*)
- We don't know why any of our cancer therapies *kill* cancer cells
- Cancer cells adapt to pharmacological perturbation and evolve under pharmacological selection


CONTACT HAZARD
SX1244-6
Sulfuric Acid
GR
H_2SO_4 FW 98.08
CAS 7664-93-9
SULFURIC ACID UN 1830
EM
500 ml Date Opened:

- **Kills cancer cells**

- Kills cancer cells
- 100% effective




• Kills cancer cells
• 100% effective
• No resistance ever emerges
CONTACT HAZARD
SX1244-6
Sulfuric Acid
GR
H_2SO_4 FW 98.08
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The “ideal” cancer drug target

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- *Target is common to many/most/all cancers*

"Impersonalized Medicine"

p53

p53

- Transcription factor activated by DNA damage and other stresses

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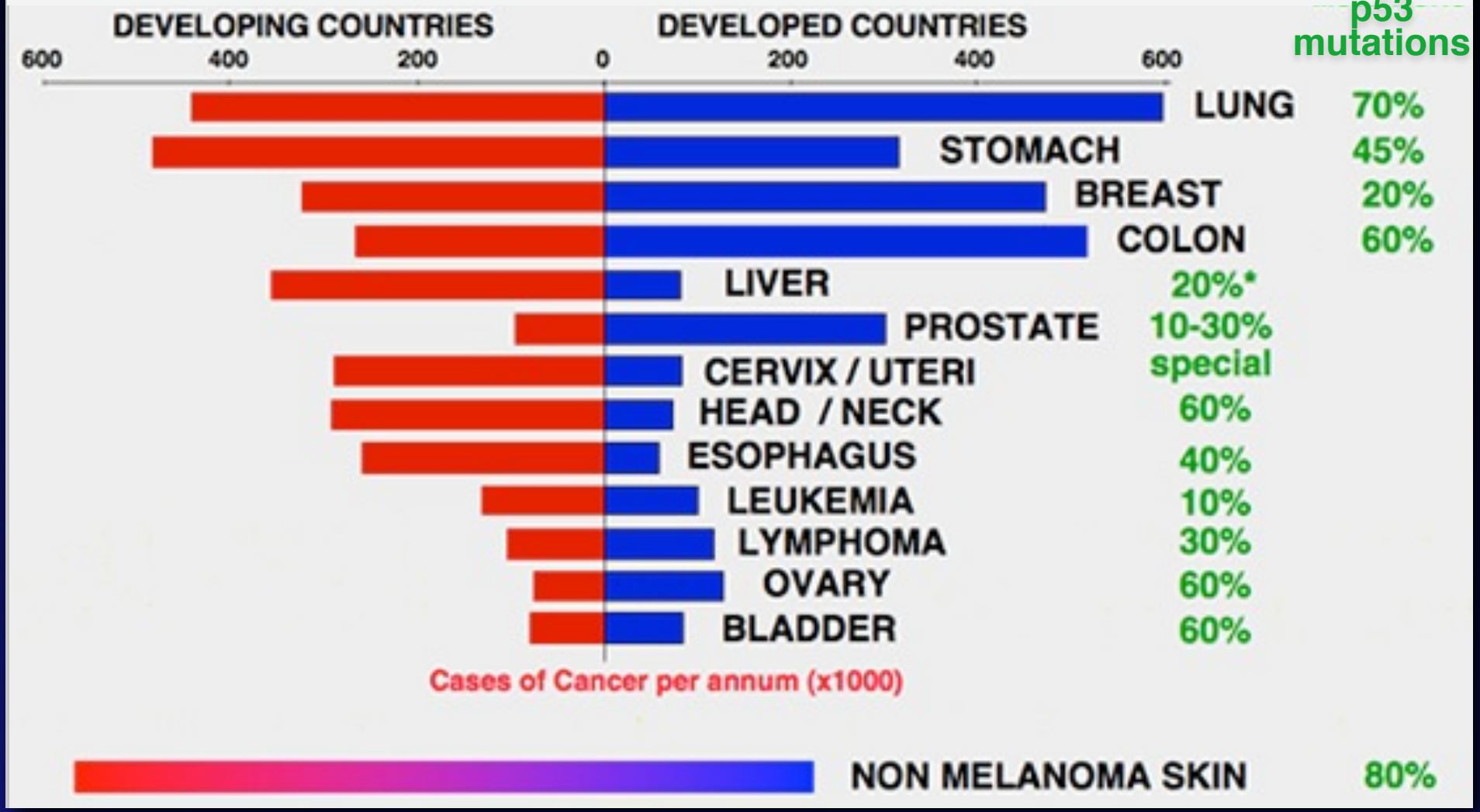
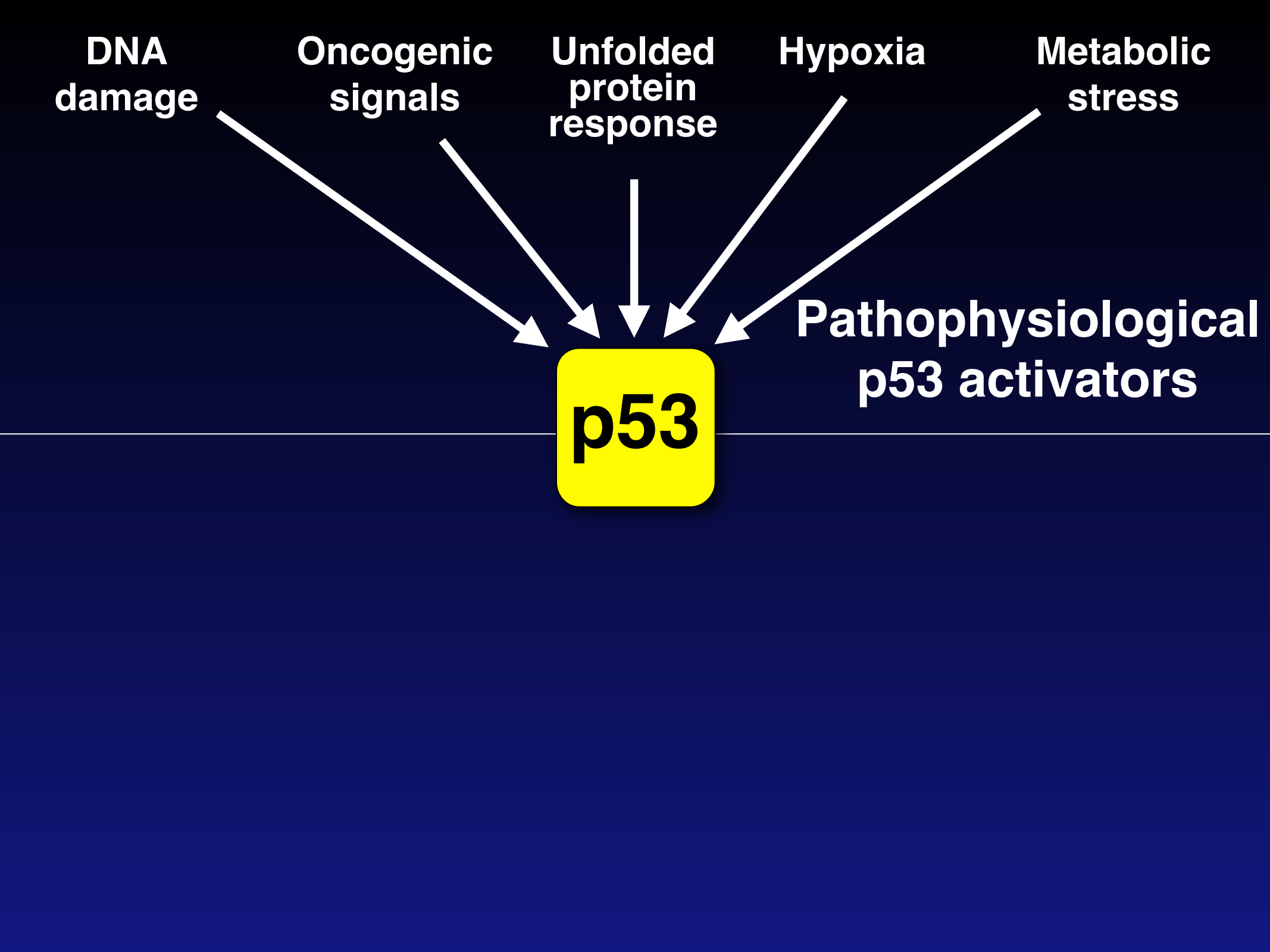
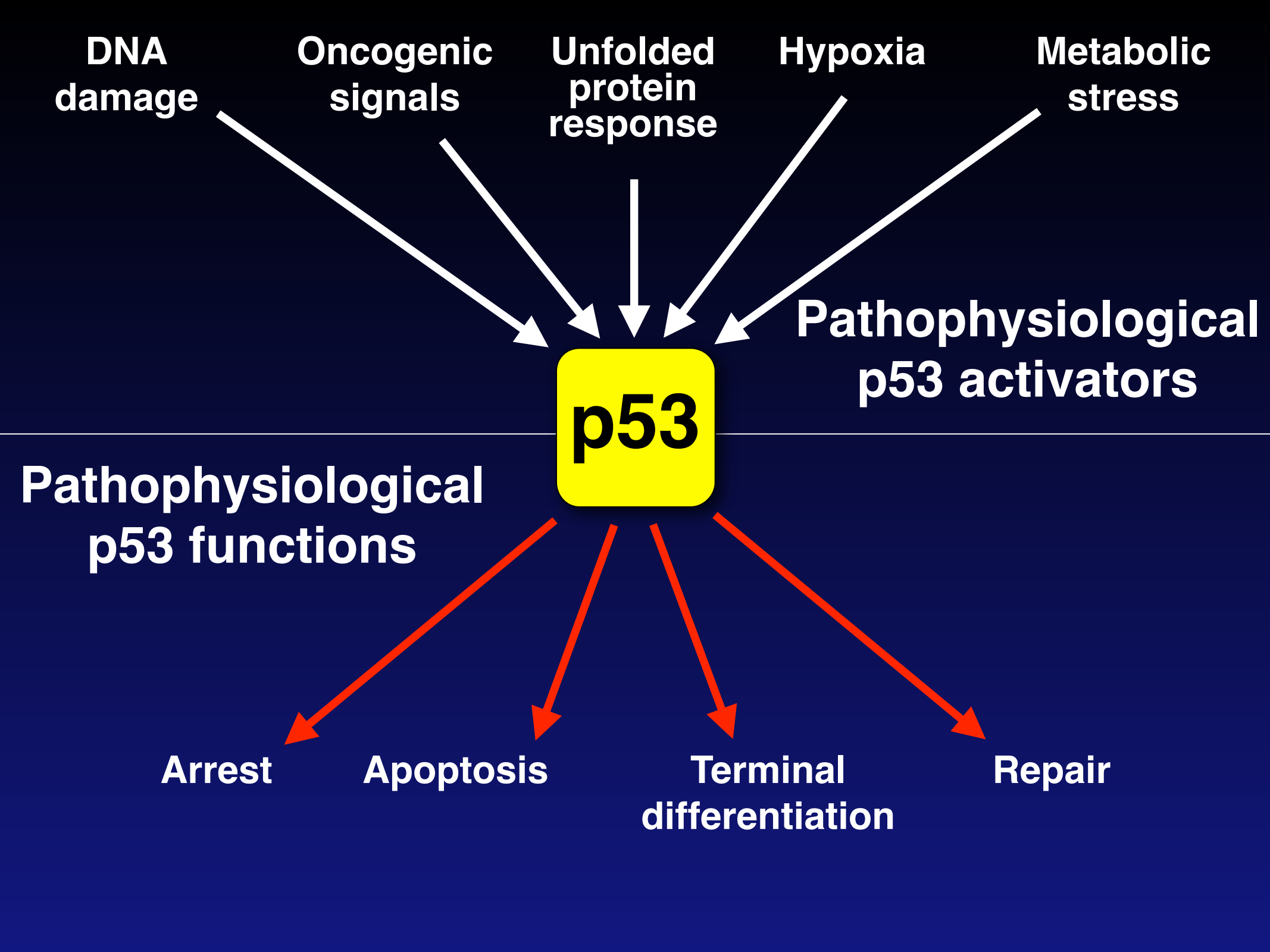
- Transcription factor activated by DNA damage and other stresses
- Once activated, p53 triggers cytostatic and/or apoptotic effectors
- Either p53 or components of its attendant pathways are functionally inactivated in >85% of human cancers
- So there is something about p53 that tumor cells could not, or cannot, tolerate

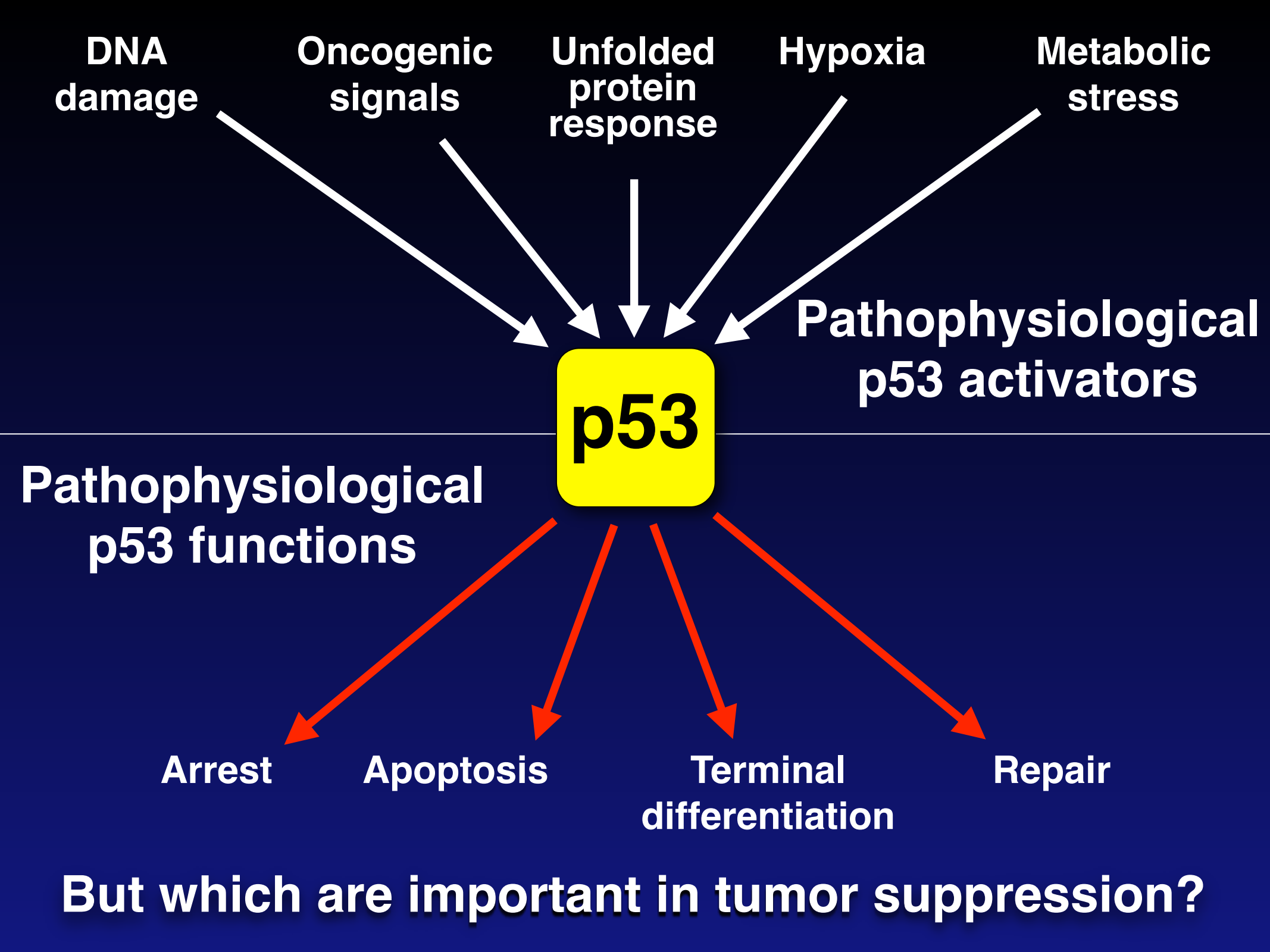
Worldwide distribution of cancers and p53 mutations



p53


DNA damage
Oncogenic signals
Unfolded protein response
Hypoxia
Metabolic stress
p53
Pathophysiological p53 activators


DNA damage
Oncogenic signals
Unfolded protein response
Hypoxia
Metabolic stress
Pathophysiological p53 activators
p53
Pathophysiological p53 functions
Arrest
Apoptosis
Terminal differentiation
Repair


DNA damage
Oncogenic signals
Unfolded protein response
Hypoxia
Metabolic stress
Pathophysiological p53 activators
p53
Pathophysiological p53 functions
Arrest
Apoptosis
Terminal differentiation
Repair
But which are important in tumor suppression?

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1. Antiproliferative and pro-apoptotic effects of three fungal exocellular β-glucans in MCF-7 breast cancer cells is mediated by oxidative stress, AMP-activated protein kinase (AMPK) and the Forkhead transcription factor, FOXO3a.
   Queiroz EA, Fortes ZB, da Cunha MA, Barbosa AM, Khaper N, Dekker RF.
   Int J Biochem Cell Biol. 2015 Aug 5. pii: S1357-2725(15)00204-6. doi: 10.1016/j.biocel.2015.08.003. [Epub ahead of print]
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   Noel N, Couteau J, Maillet G, Gobet F, D'Aloisio F, Minier C, Pfister C.
   Anticancer Res. 2015 Sep;35(9):4915-21.
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4. Loss of **p53** enhances the function of the endoplasmic reticulum through activation of the IRE1α/XBP1 pathway.
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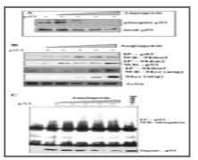
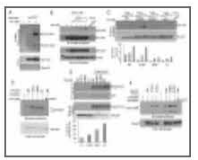
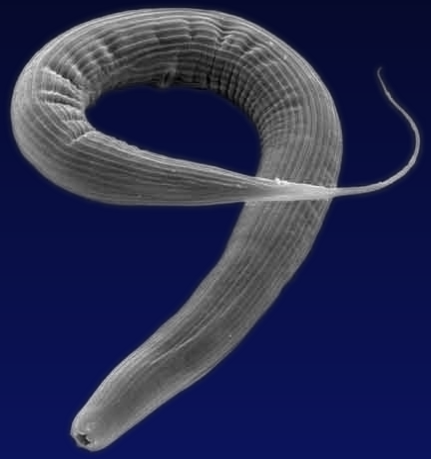



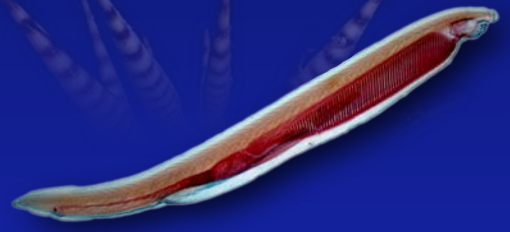
p53-mediated tumor suppression

p53-mediated tumor suppression

How, why, when and where?

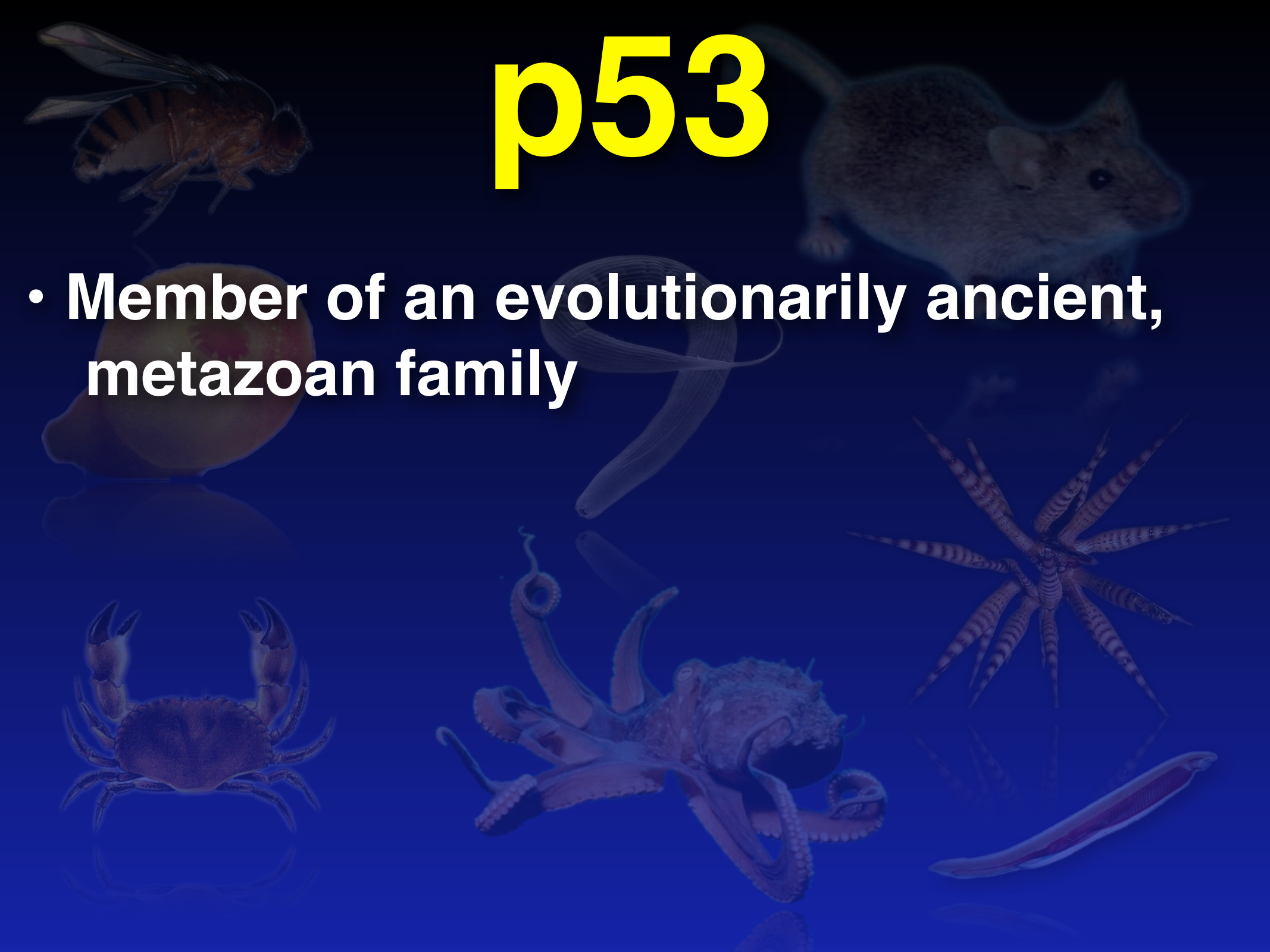
p53





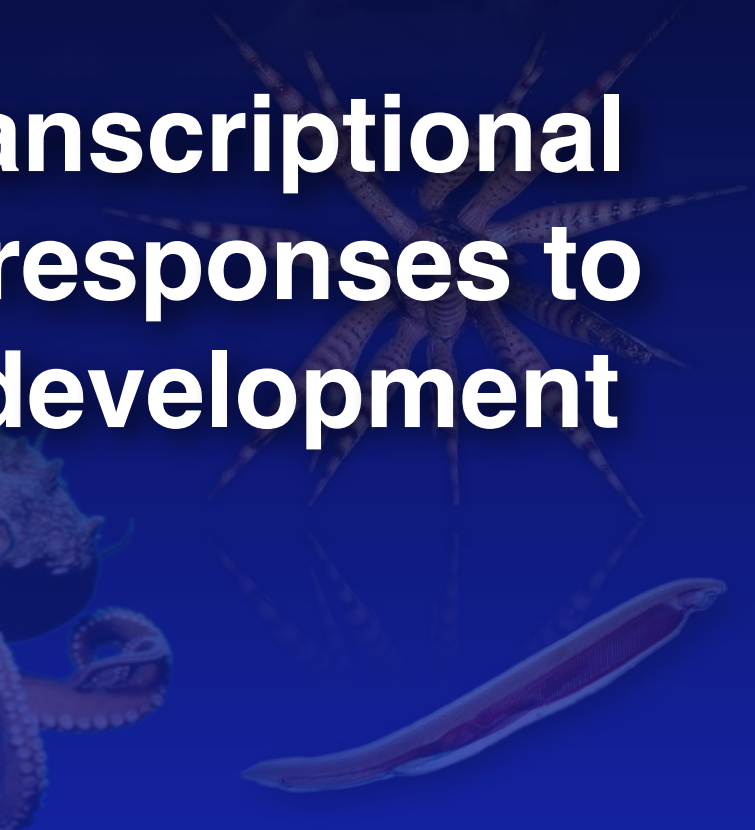
p53

- Member of an evolutionarily ancient, metazoan family



p53



- Member of an evolutionarily ancient, metazoan family
- Evolved originally as transcriptional coordinator of cellular responses to stress/damage during development

p53

- Member of an evolutionarily ancient, metazoan family
- Evolved originally as transcriptional coordinator of cellular responses to stress/damage during development
- Tumor suppression is a “recent” evolutionary retrofit

p53 - an ancient multifunctional effector

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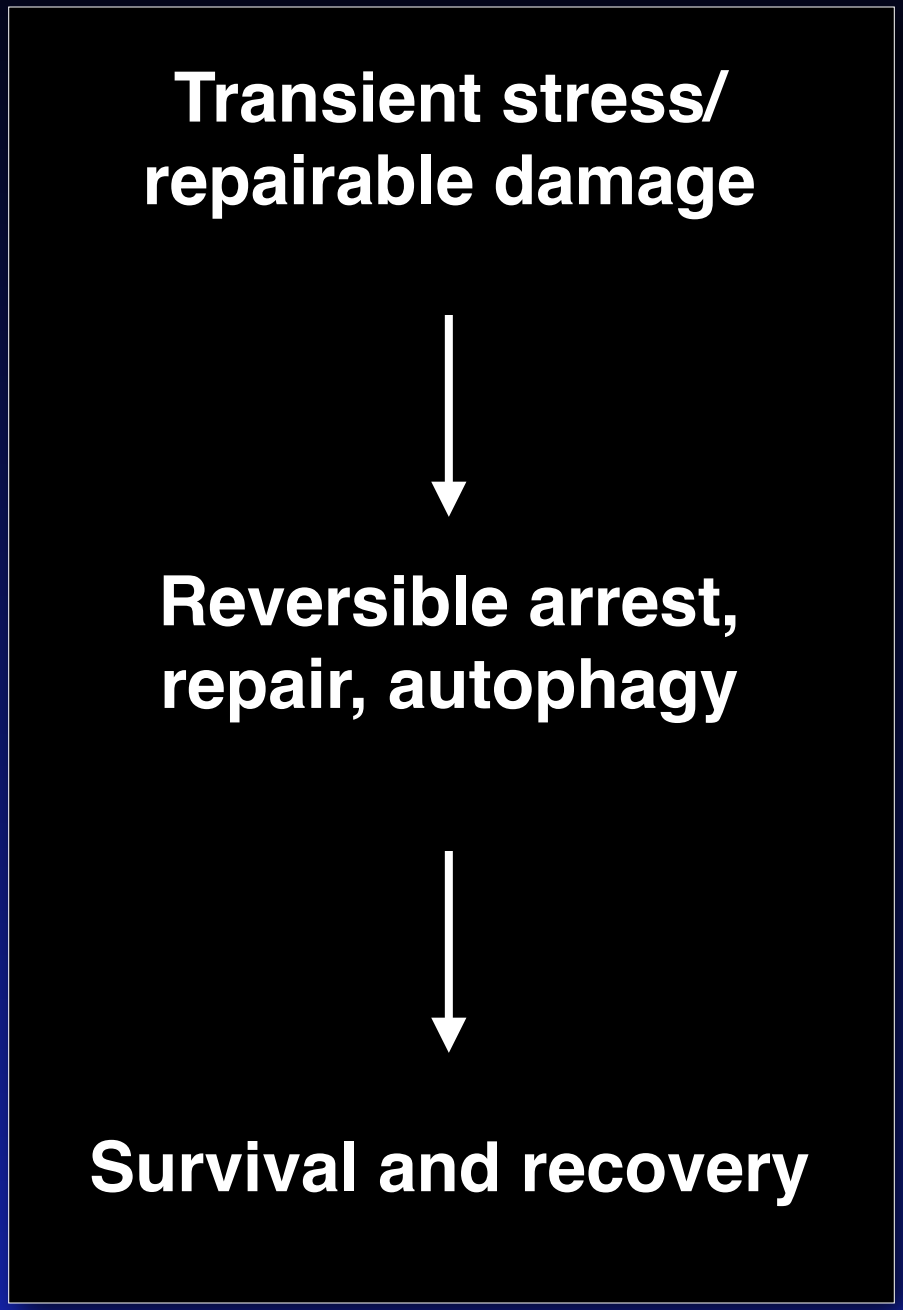


p53 - an ancient multifunctional effector

Transient stress/ repairable damage

↓

Reversible arrest, repair, autophagy

↓

Survival and recovery

Persistent signals (oncogenic, irreparable damage)

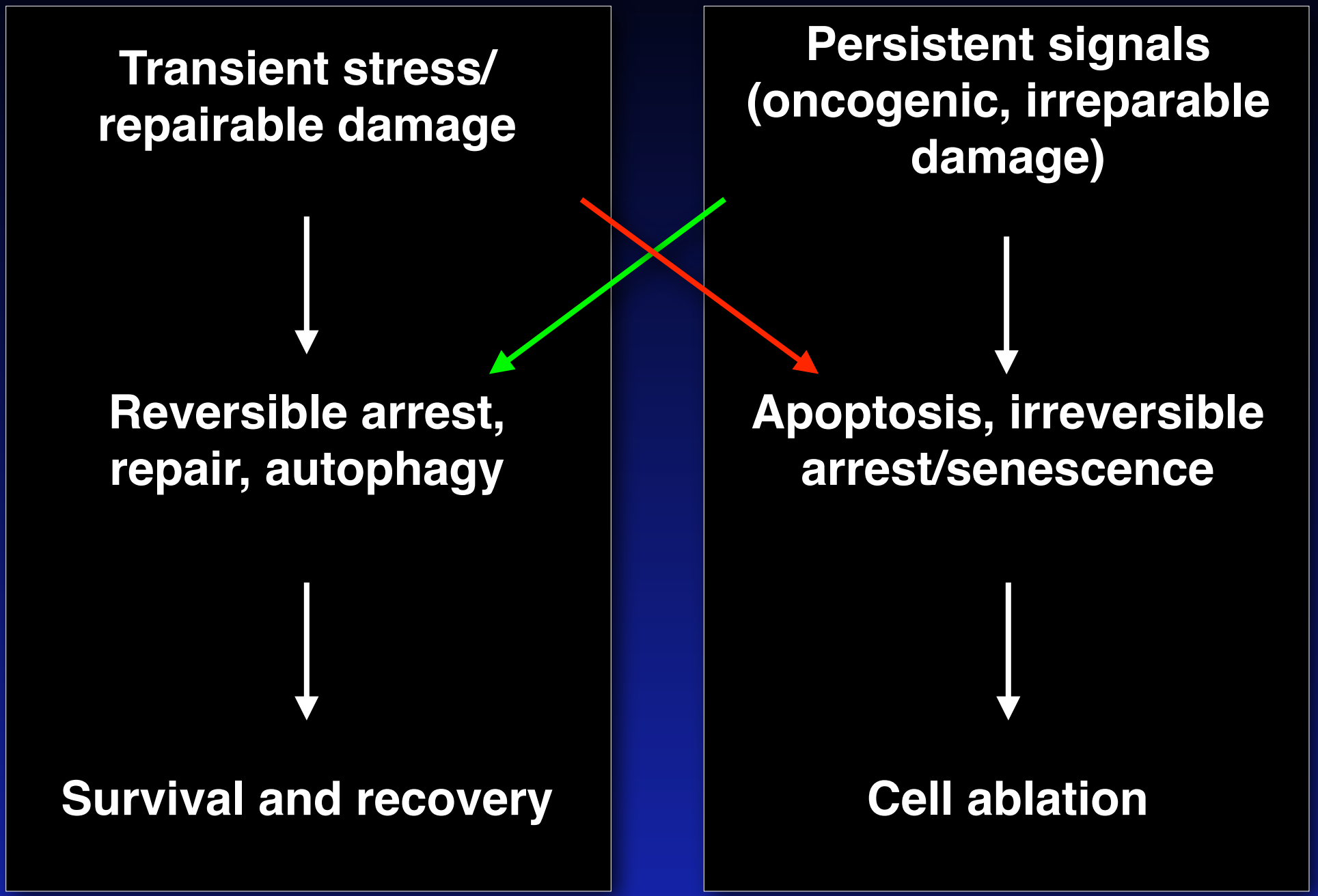
↓

Apoptosis, irreversible arrest/senescence

↓

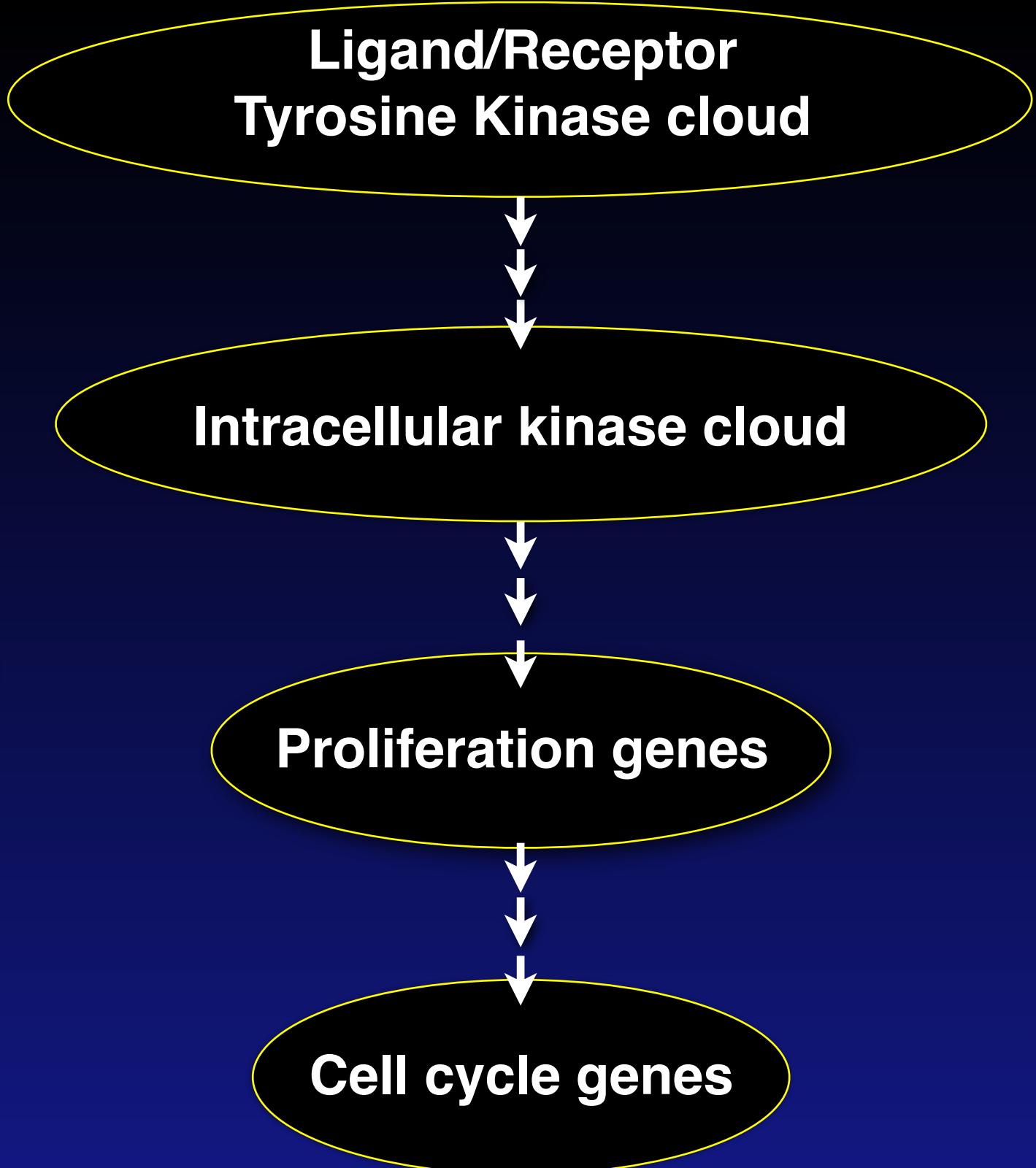
Cell ablation

p53 - an ancient multifunctional effector

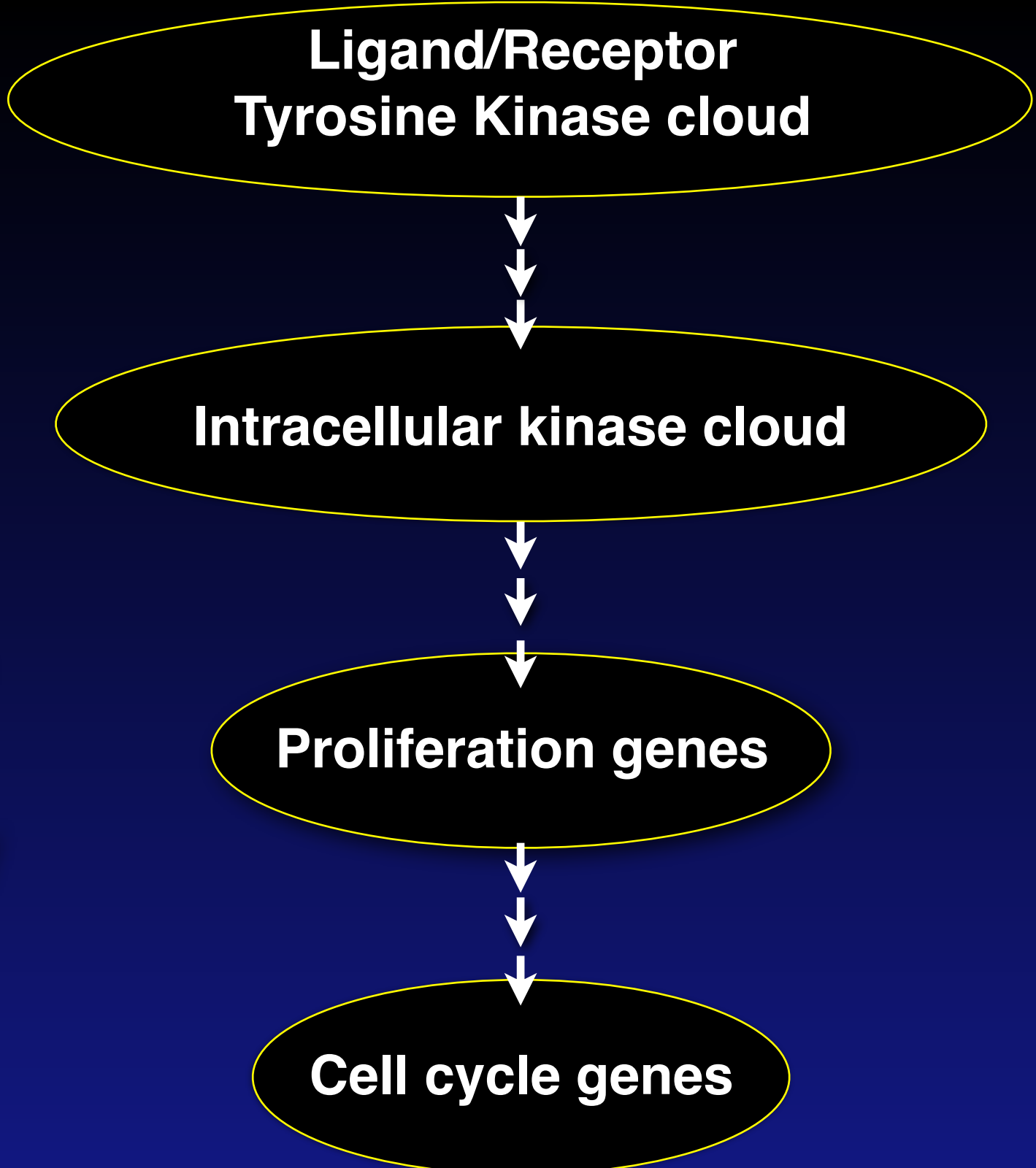


Where to target cancers?

Robustness



Where to target cancers?



Robustness

vs

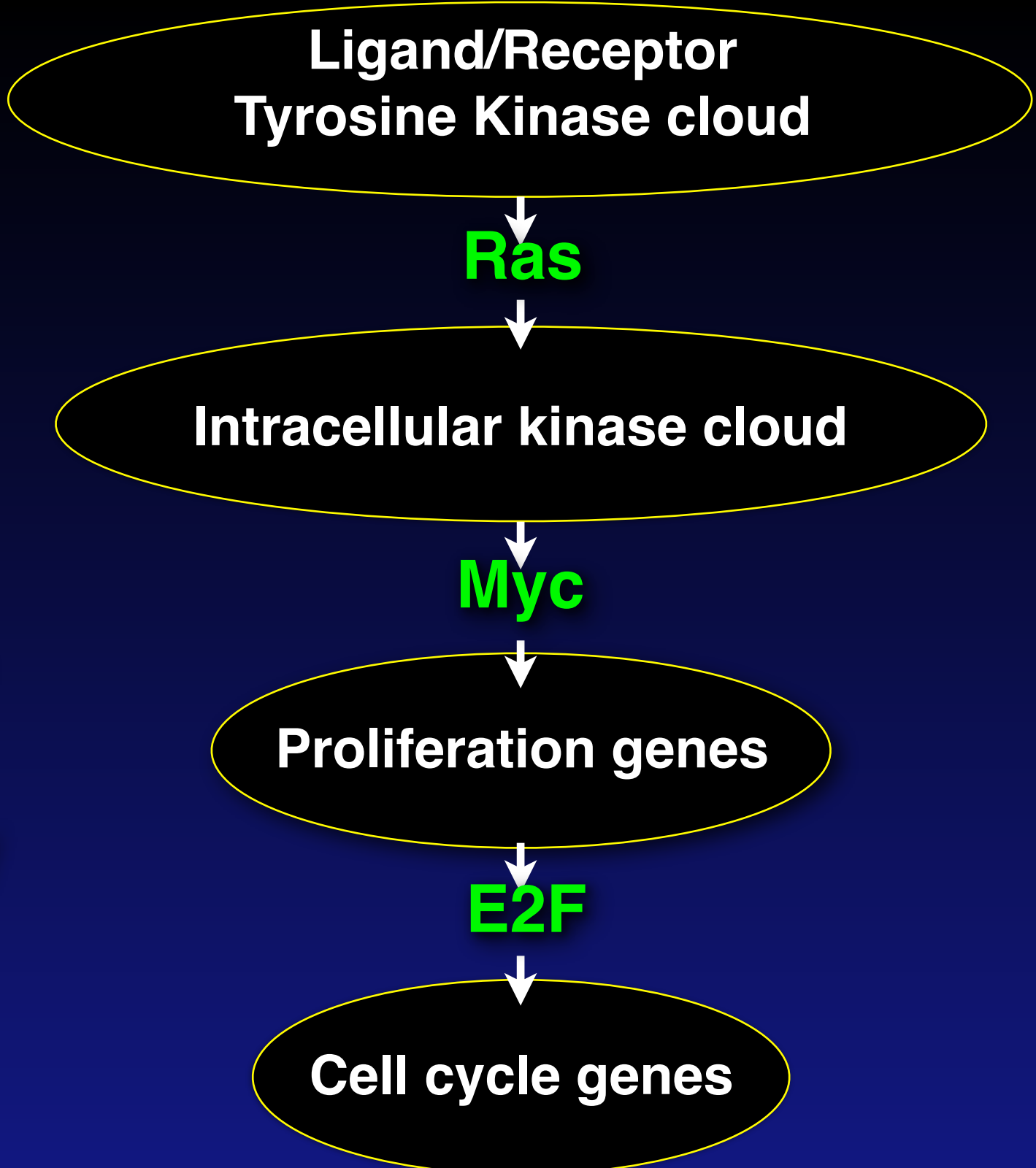
Switchability

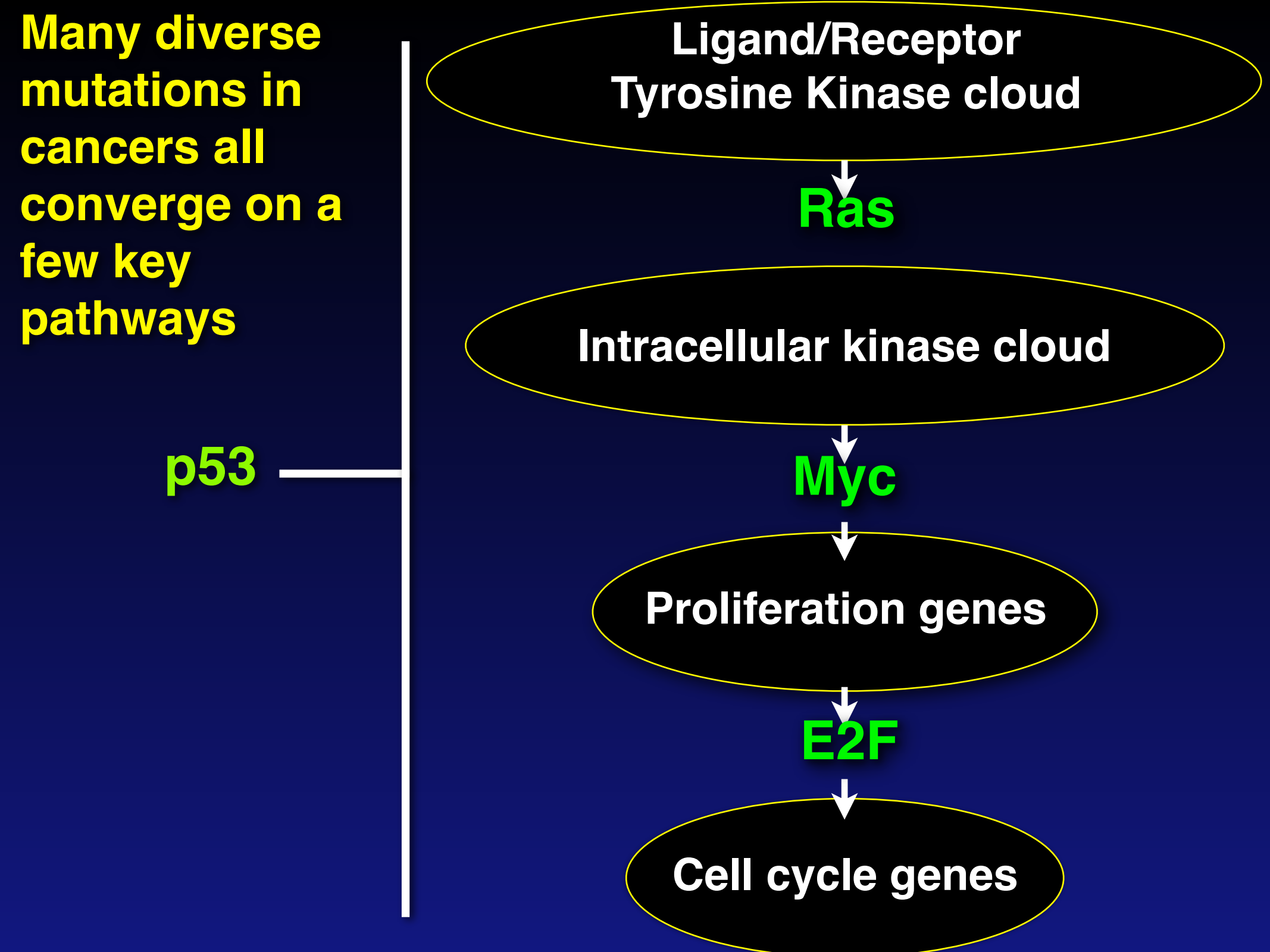
Where to target cancers?

Robustness

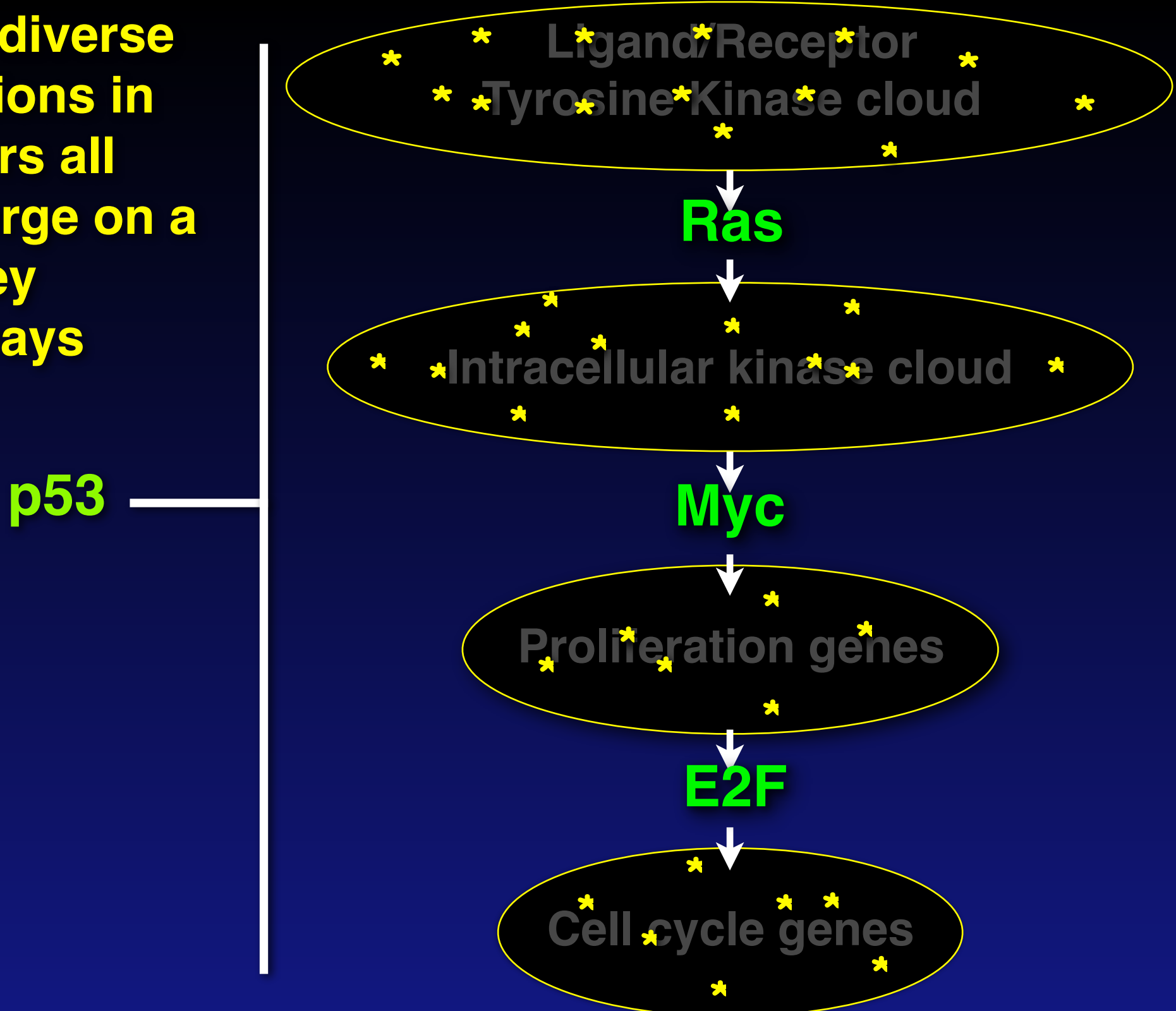
vs

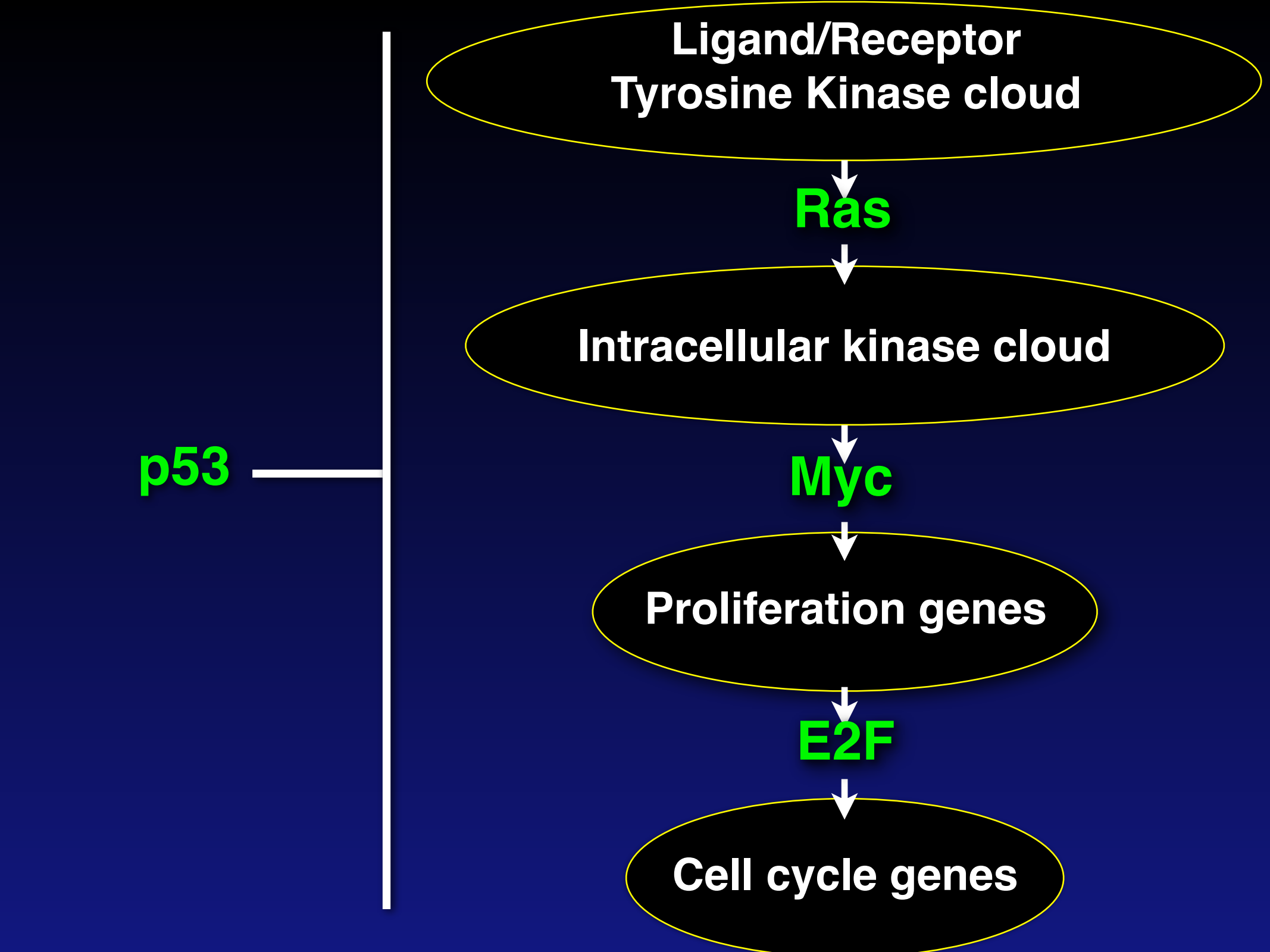
Switchability




Many diverse mutations in cancers all converge on a few key pathways
p53
Ligand/Receptor Tyrosine Kinase cloud
Ras
Intracellular kinase cloud
Myc
Proliferation genes
E2F
Cell cycle genes

Many diverse mutations in cancers all converge on a few key pathways




Ligand/Receptor
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Myc
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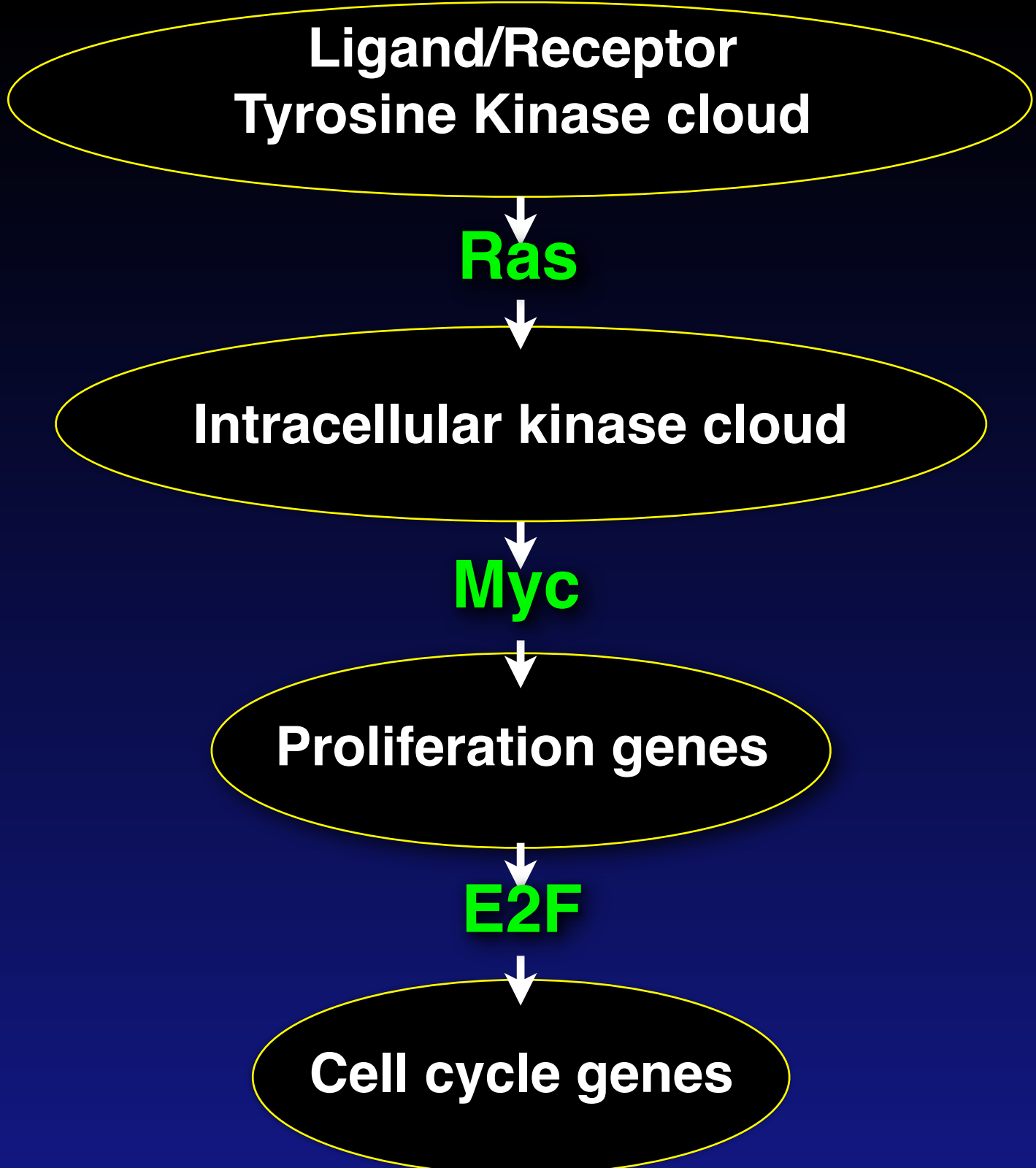
Cell cycle genes

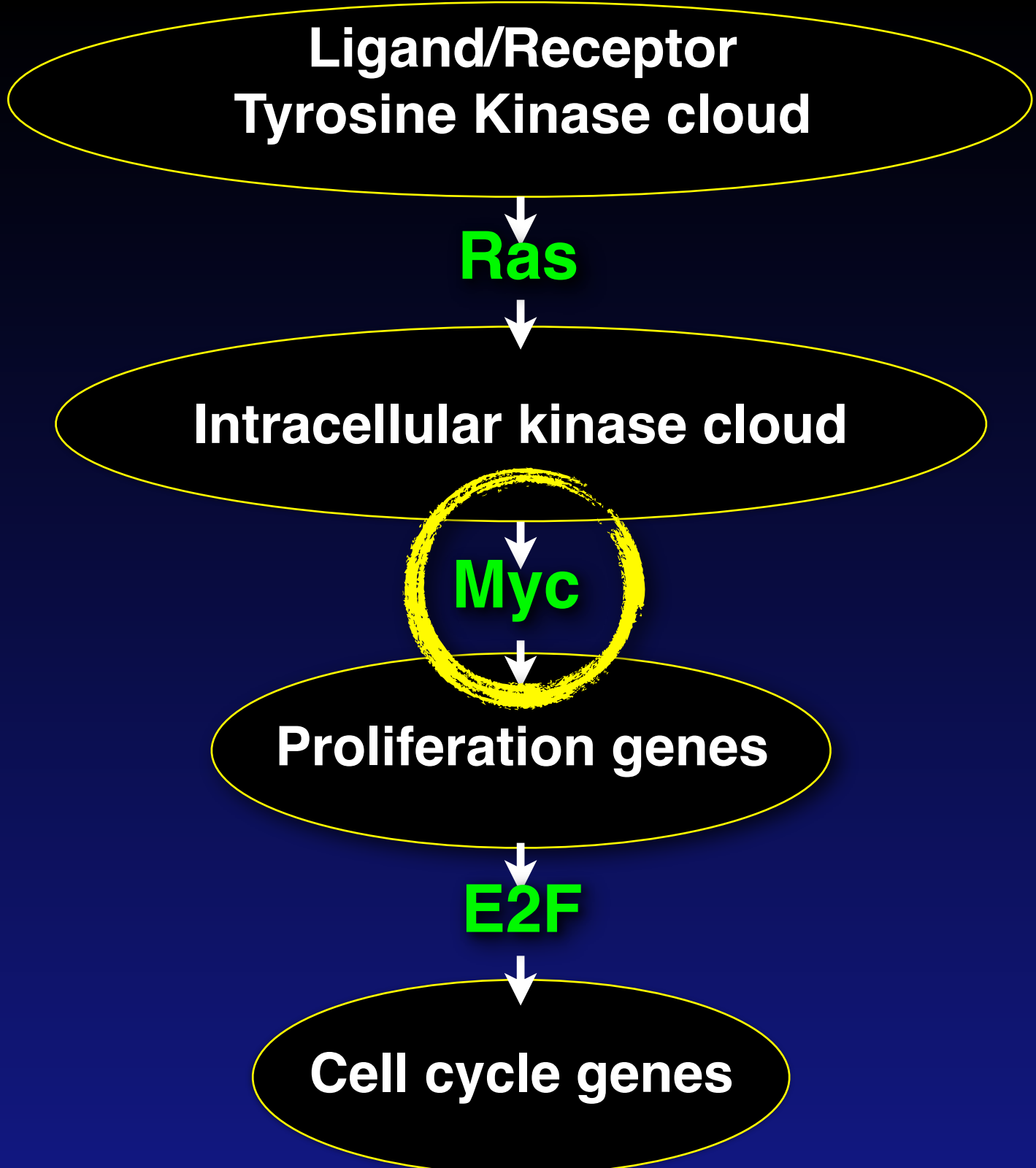
How can we model inhibition of the common cancer pathways?

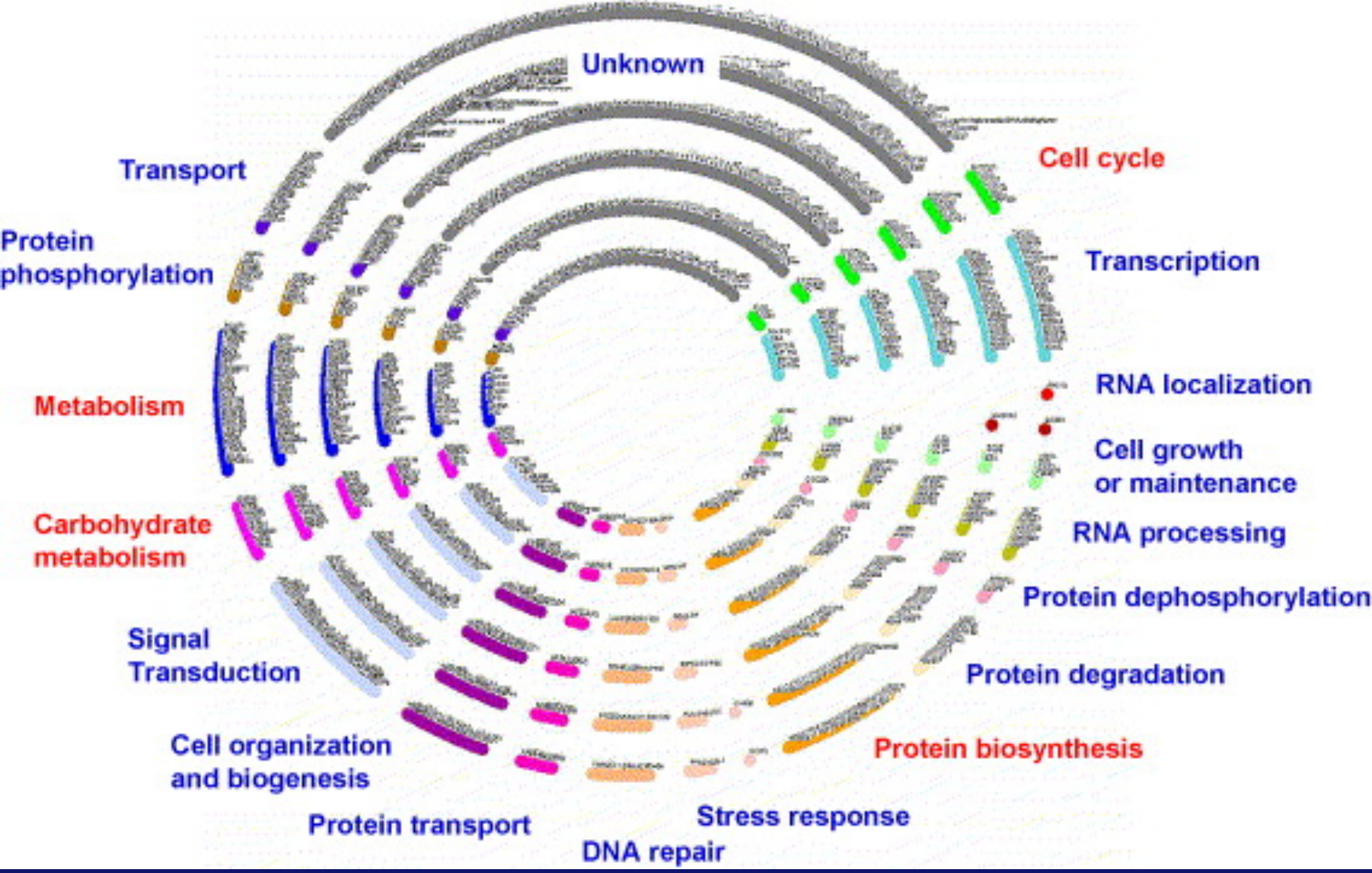
p53

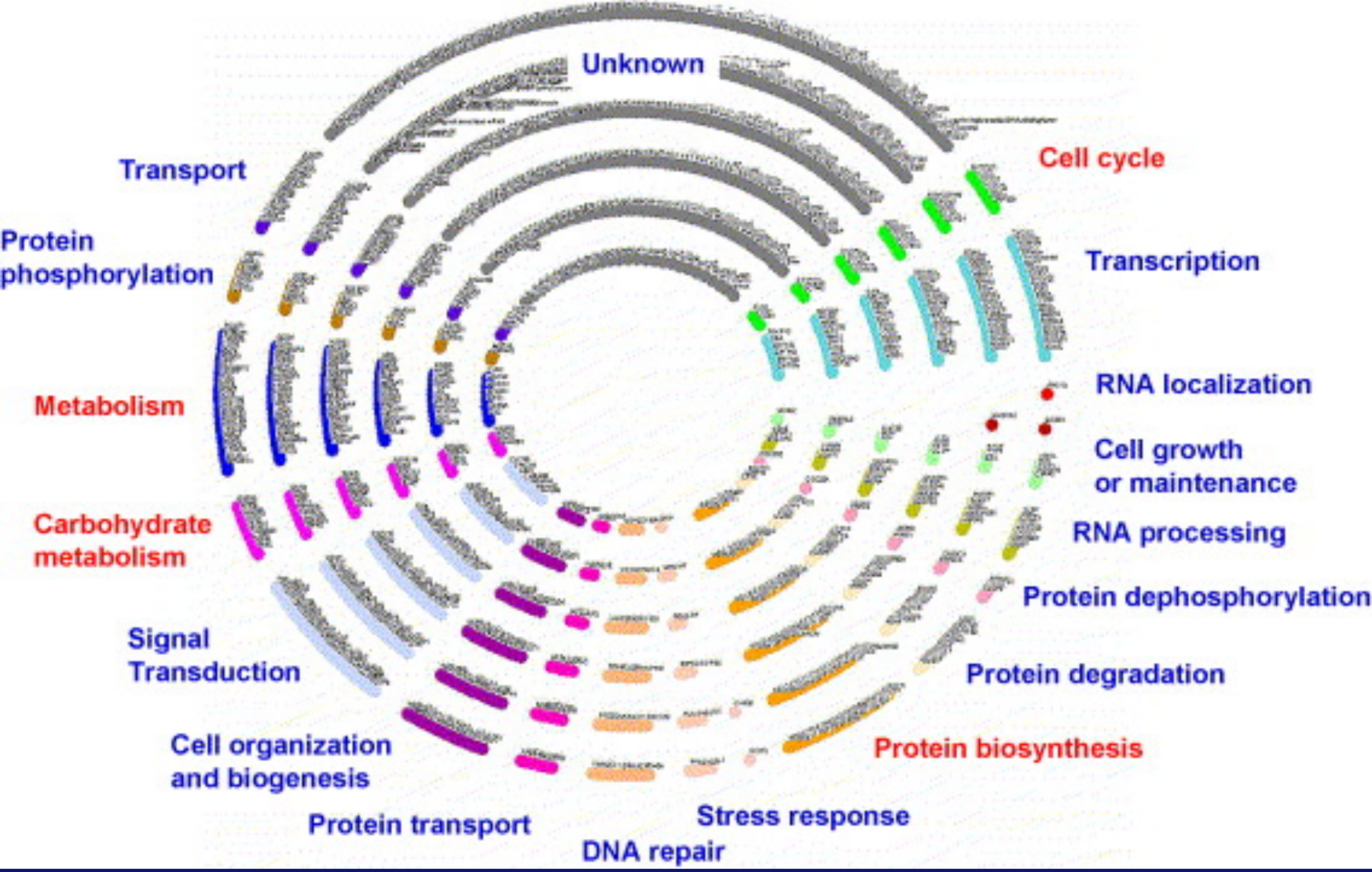


How can we model inhibition of the common cancer pathways?

p53

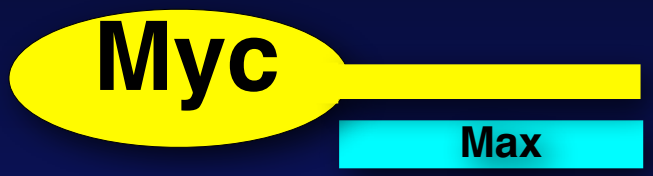



Unknown
Transport
Cell cycle
Protein phosphorylation
Transcription
Metabolism
RNA localization
Cell growth or maintenance
Carbohydrate metabolism
RNA processing
Protein dephosphorylation
Signal Transduction
Protein degradation
Cell organization and biogenesis
Protein biosynthesis
Protein transport
Stress response
DNA repair



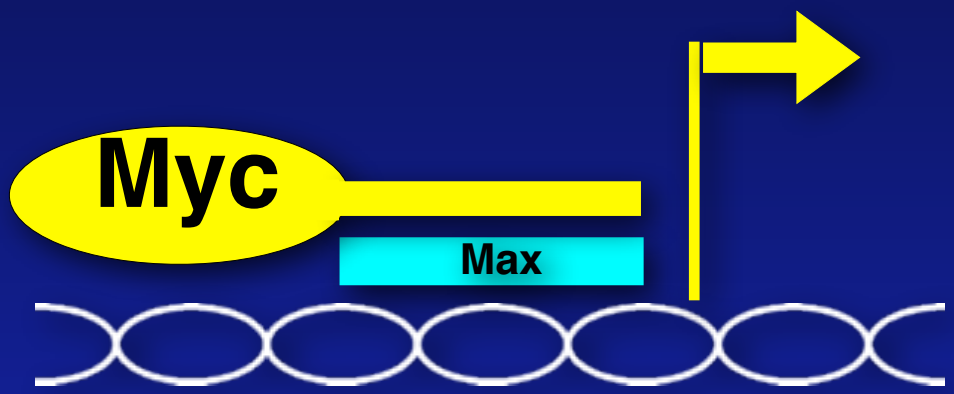
What was the question?

Inhibiting endogenous Myc in normal and tumour tissues *in vivo*



Sergio Nasi
Laura Soucek

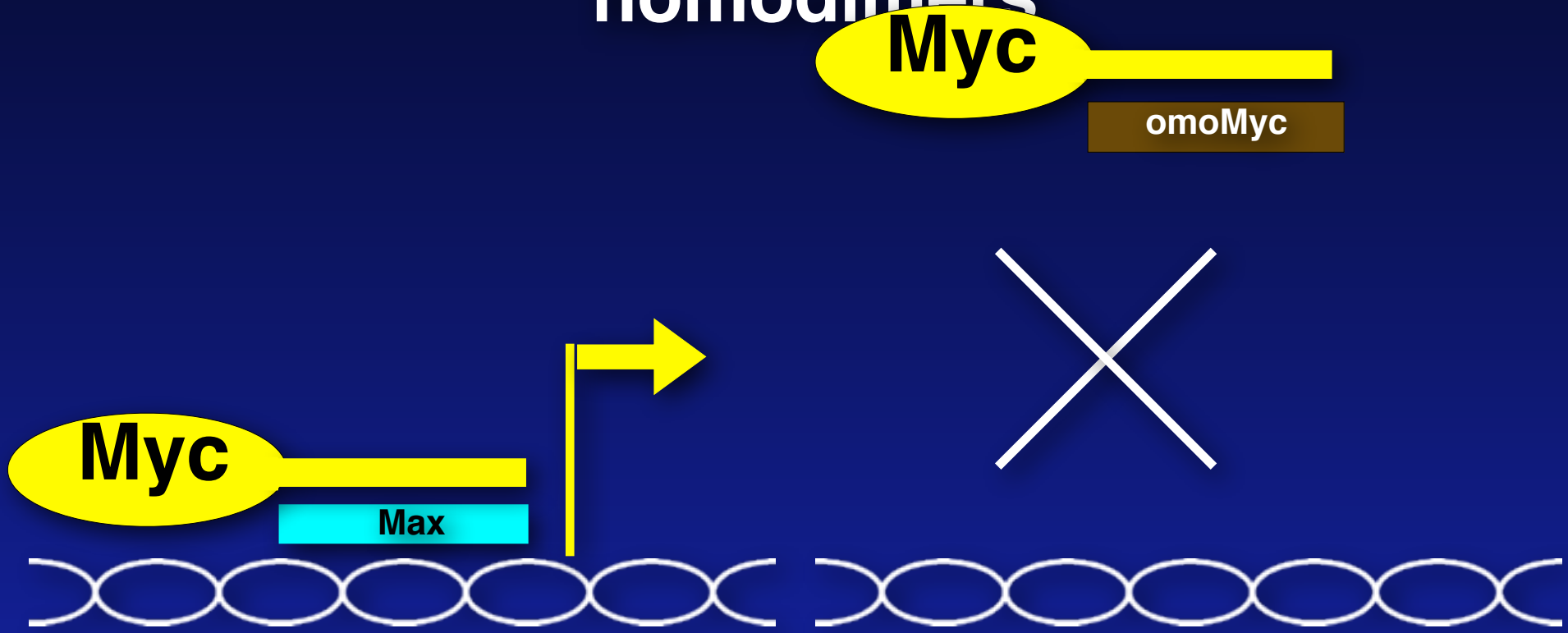
Inhibiting endogenous Myc in normal and tumour tissues *in vivo*



Sergio Nasi
Laura Soucek

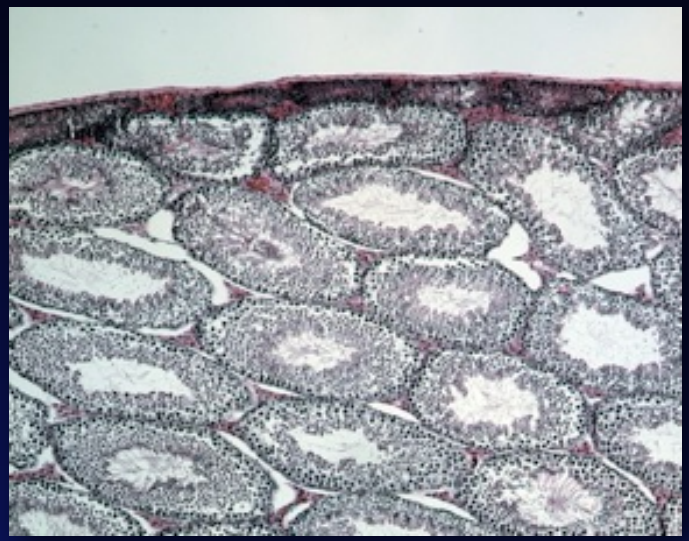
Inhibiting endogenous Myc in normal and tumour tissues *in vivo*

OmoMyc: a dominant negative HLH-leucine zipper that competitively inhibits Myc:Max homodimers

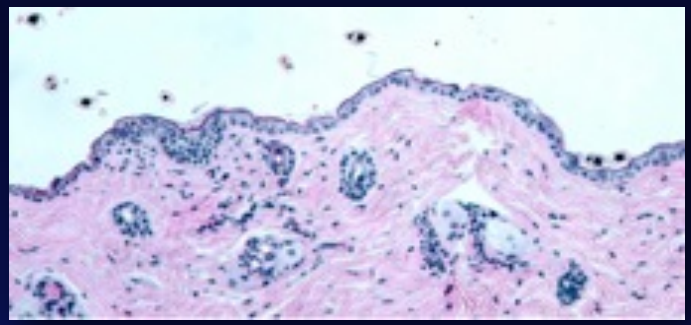


Sergio Nasi
Laura Soucek

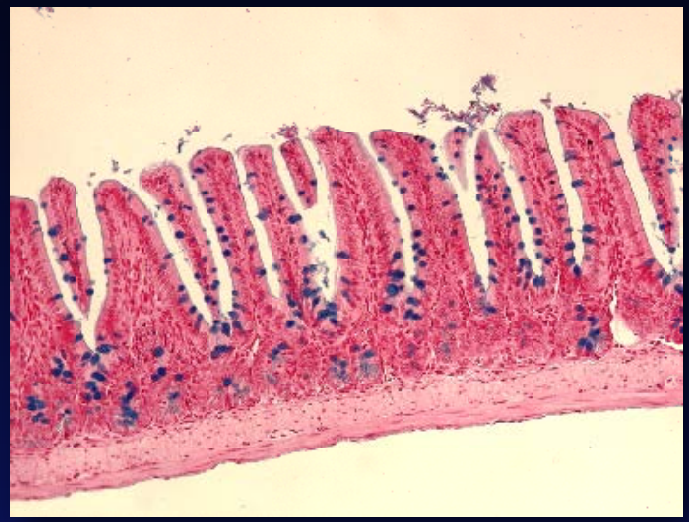
Systemic Myc inhibition suppresses proliferation in normal tissues



testis

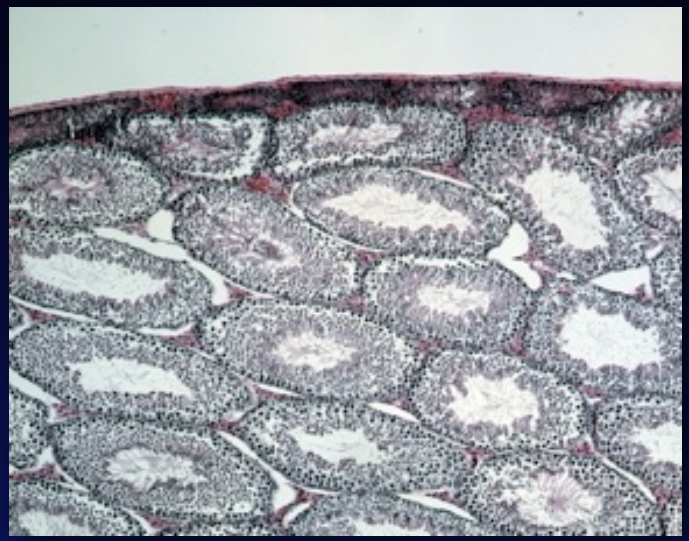


Skin

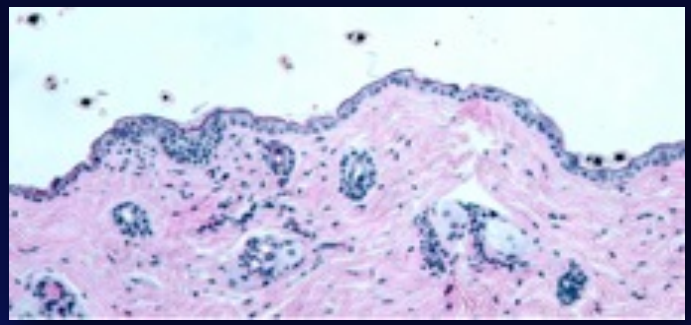


intestine

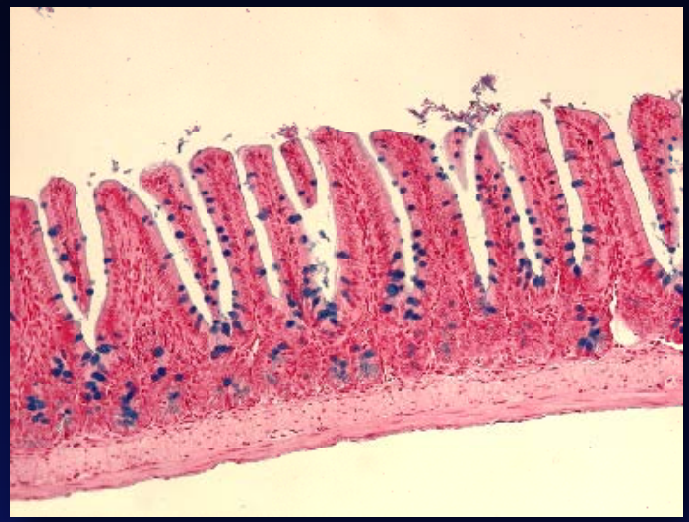
Systemic Myc inhibition suppresses proliferation in normal tissues



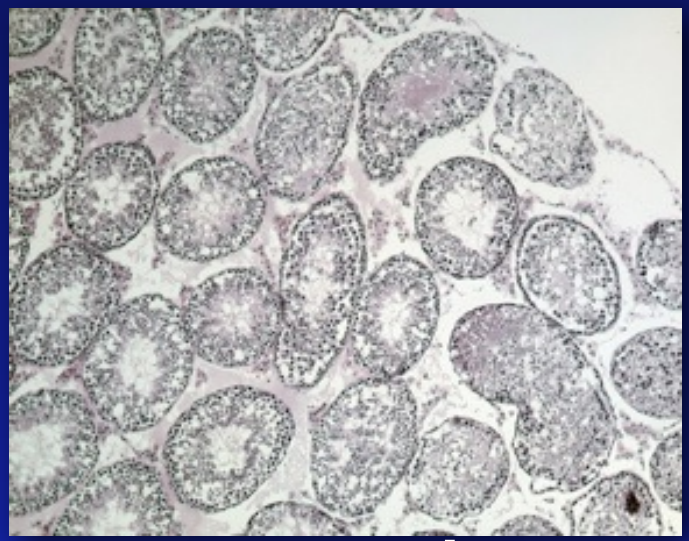
testis



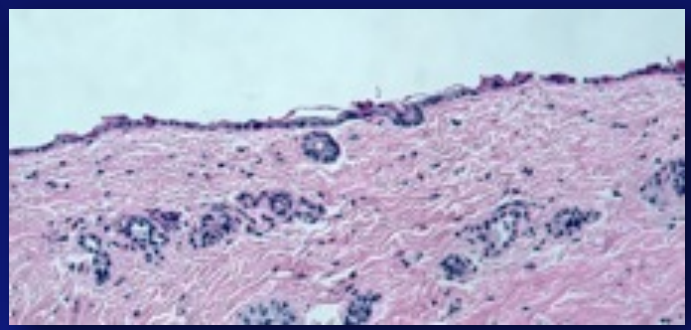
Skin



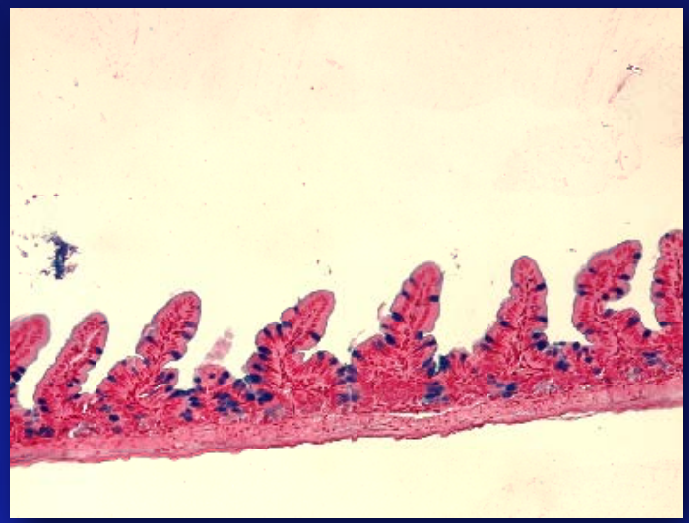
intestine



aspermia



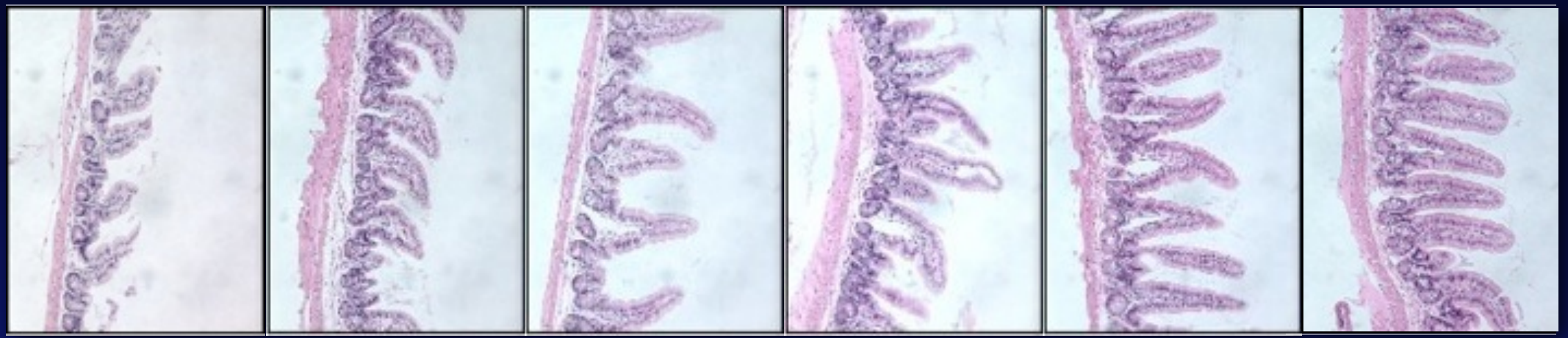
epidermal thinning
arrested hair growth



villus attrition

Restoration of Myc triggers rapid and complete GI recovery

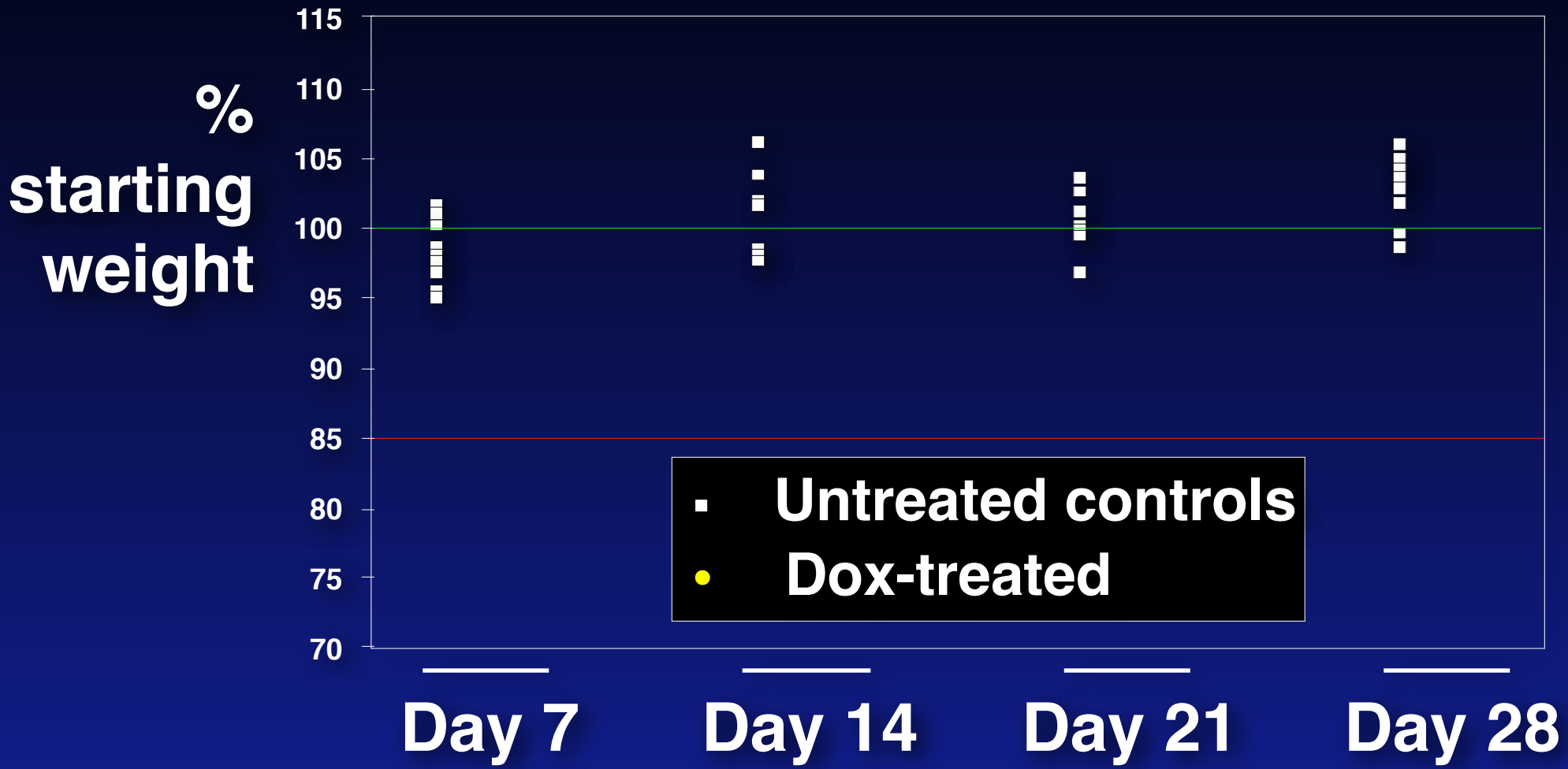
Restoration of Myc triggers rapid and complete GI recovery



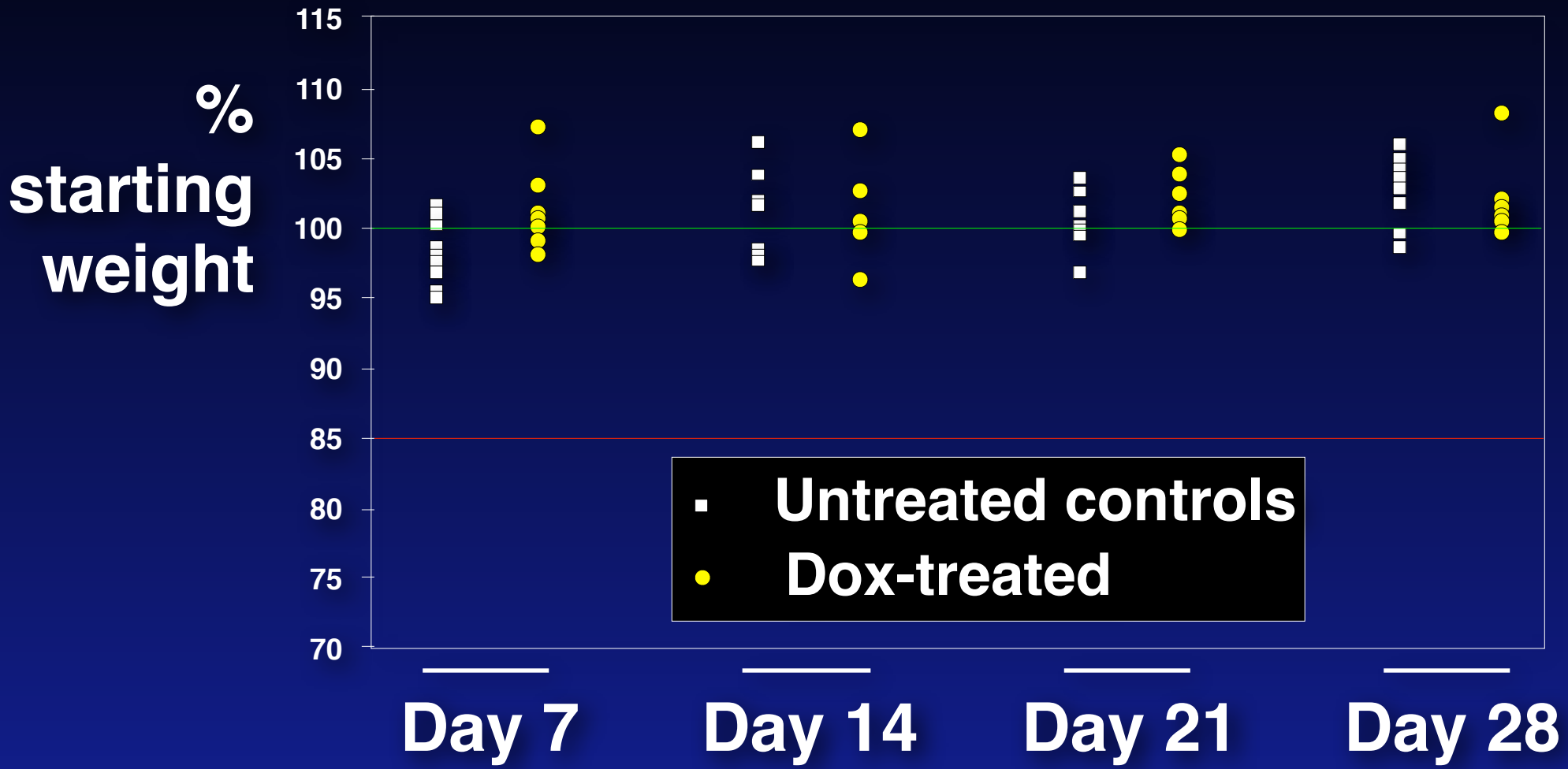
0 1 d 2 d 3 d 4 d 5 d

Days after Omomyc switch off

Impact of competitive systemic Myc inhibition on body weight



Impact of competitive systemic Myc inhibition on body weight

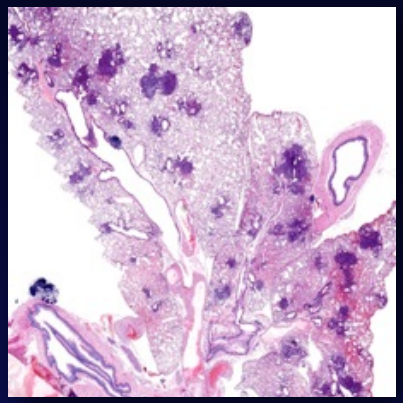


Impact of competitive systemic Myc inhibition on body weight

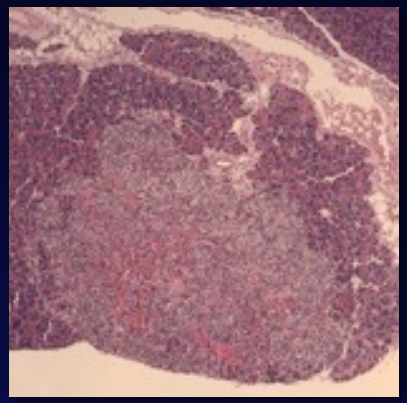
Mice remain healthy and “seem” happy

Systemic Myc inhibition triggers regression of multiple tumor types

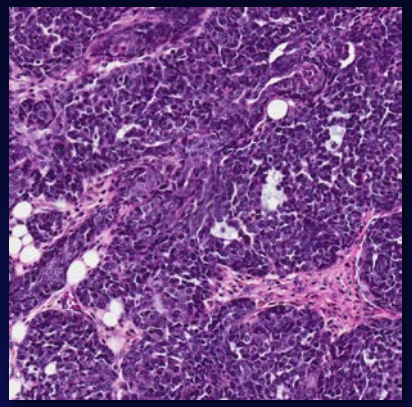
KRas^{G12D} Lung Tumors



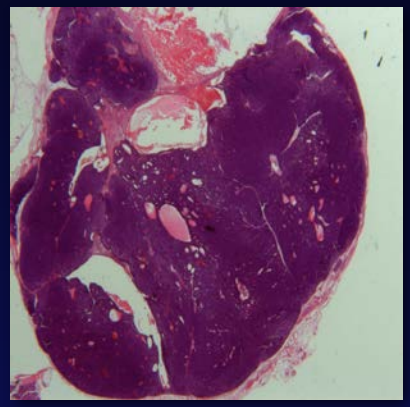
SV40 LT/ST Lung Tumors



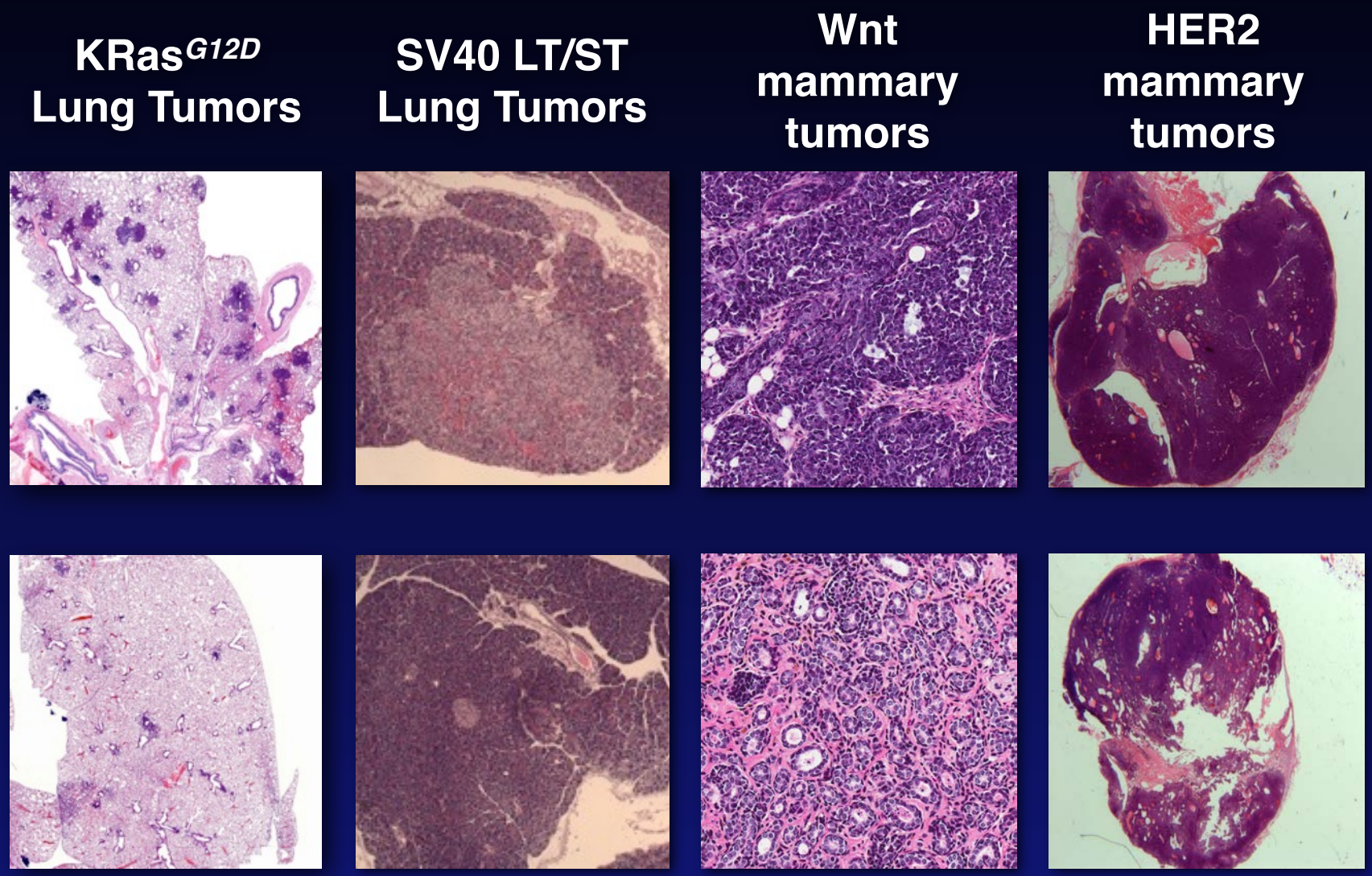
Wnt mammary tumors



HER2 mammary tumors



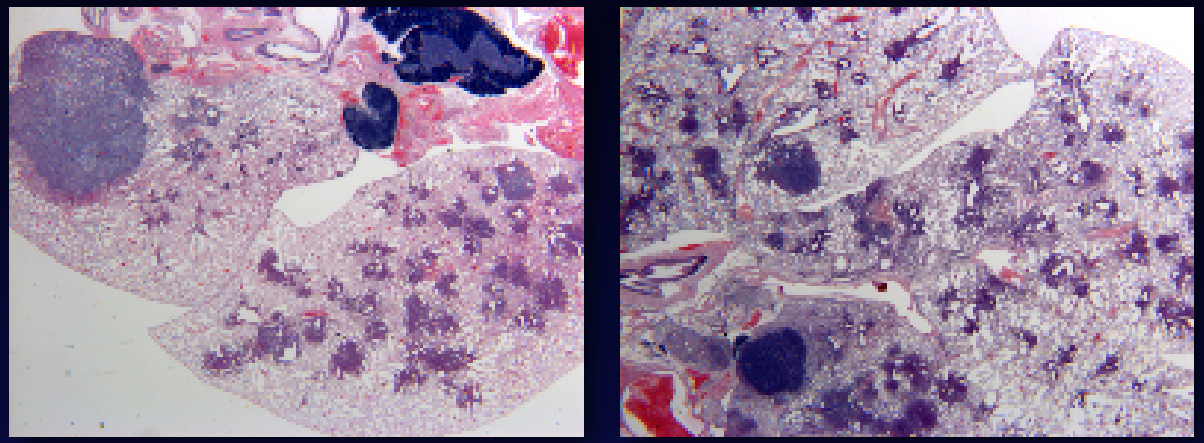
Systemic Myc inhibition triggers regression of multiple tumor types



Myc inhibited by systemic induction of OmoMyc (DN Myc)

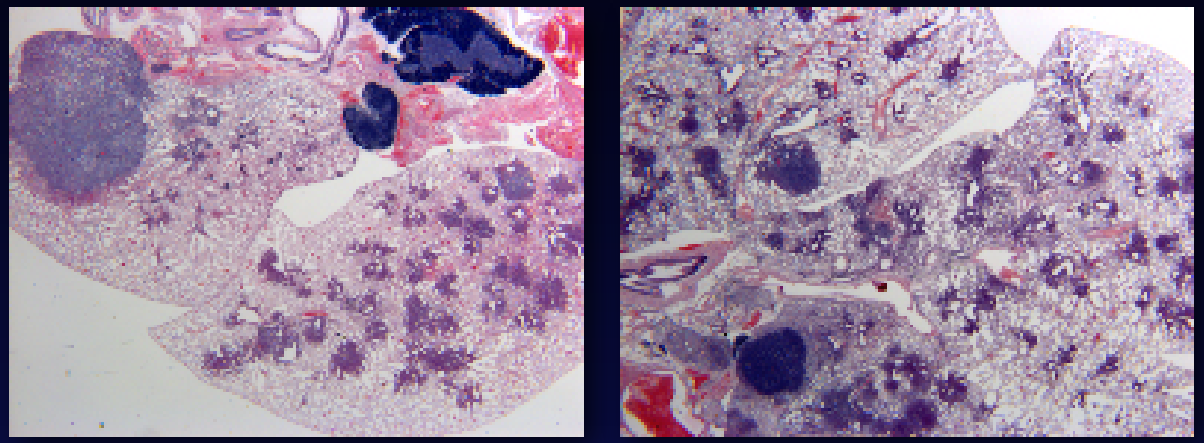
Tumors recur at reduced multiplicity following Omomyc cessation

16 weeks
KRas ^{G12D}
activity

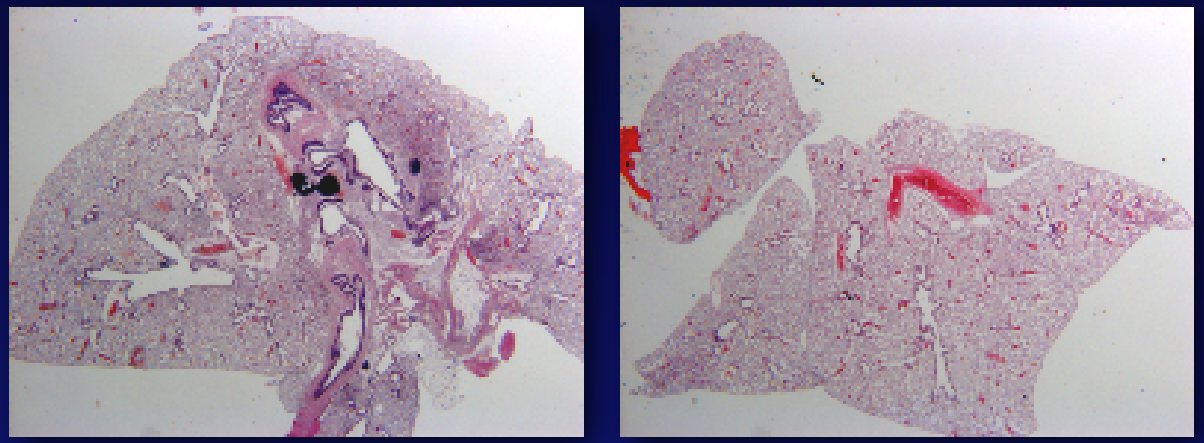


Tumors recur at reduced multiplicity following Omomyc cessation

16 weeks KRas ^{G12D} activity

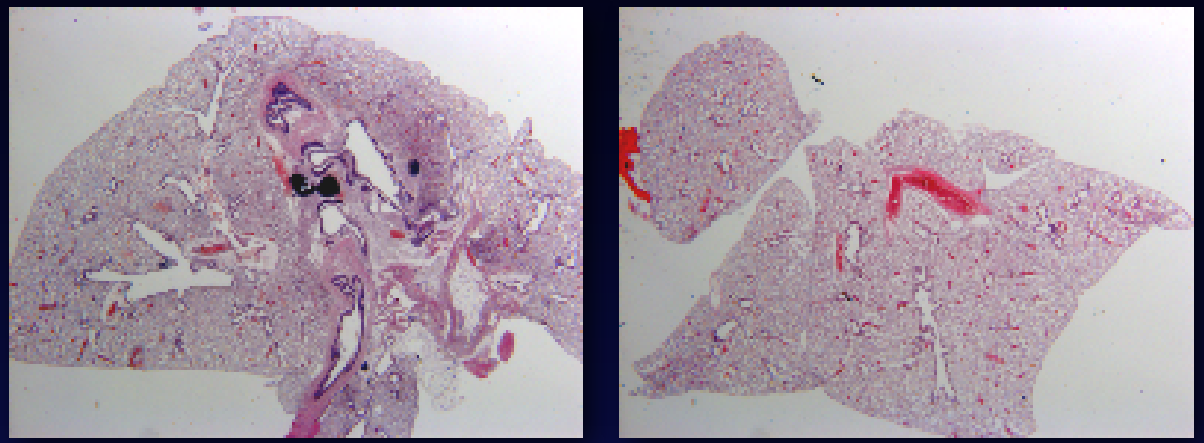


+ 4 weeks Myc inhibition

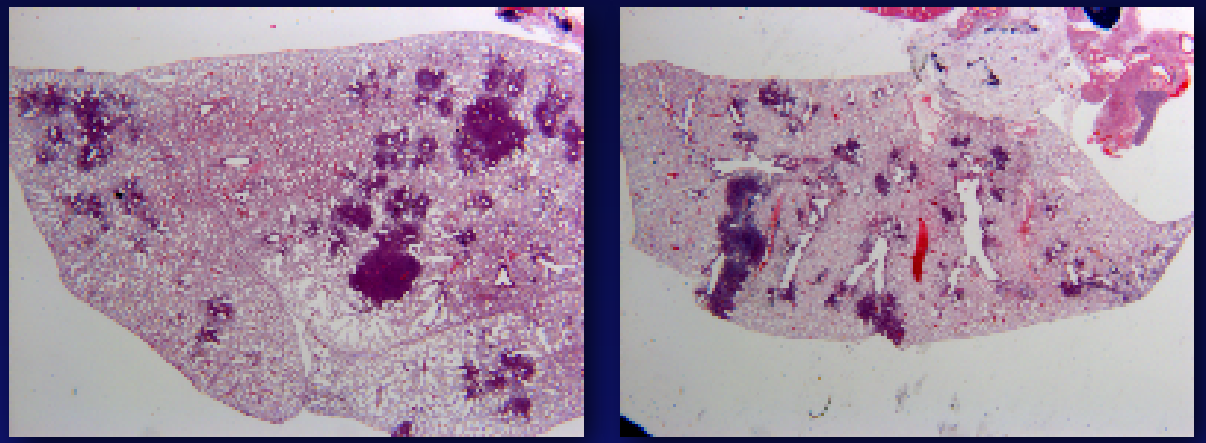


Tumors recur at reduced multiplicity following Omomyc cessation

+ 4 weeks Myc inhibition



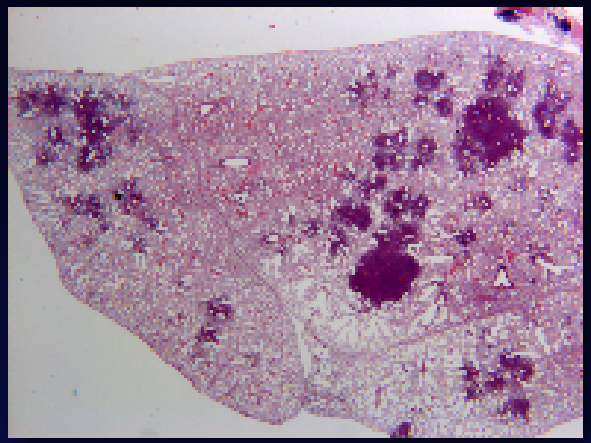
Recurrence at 8 weeks

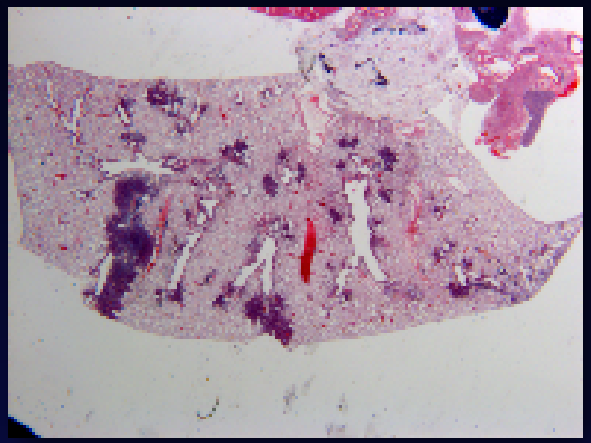


37% mean reduction in tumor multiplicity

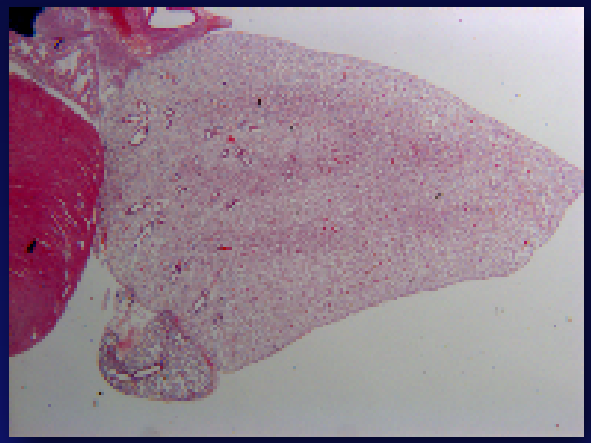
And remain completely susceptible to repeated Myc inhibition

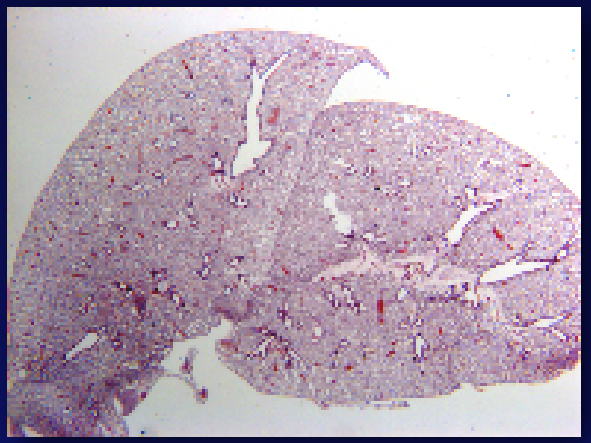
Recurrence at 8 weeks



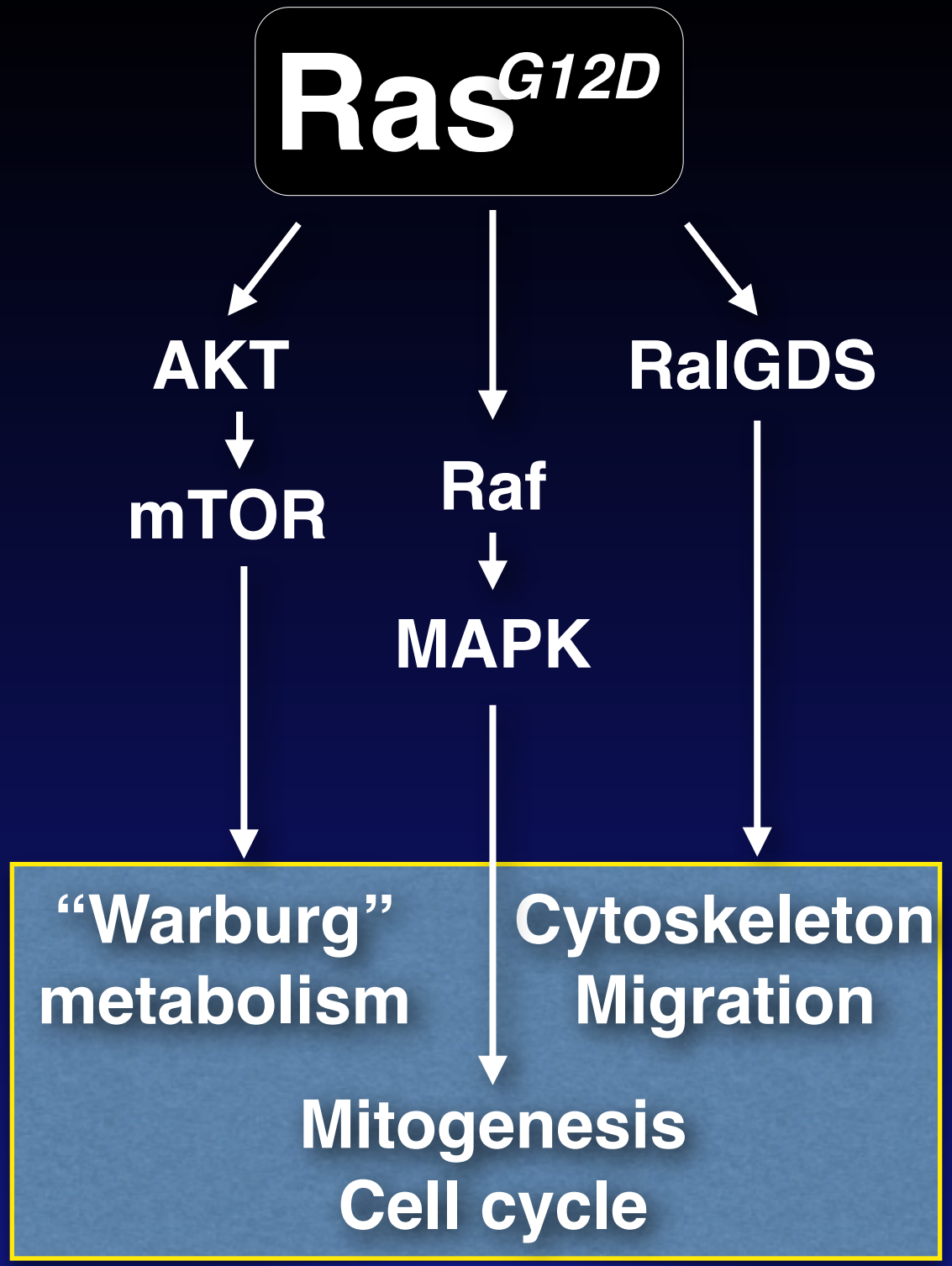


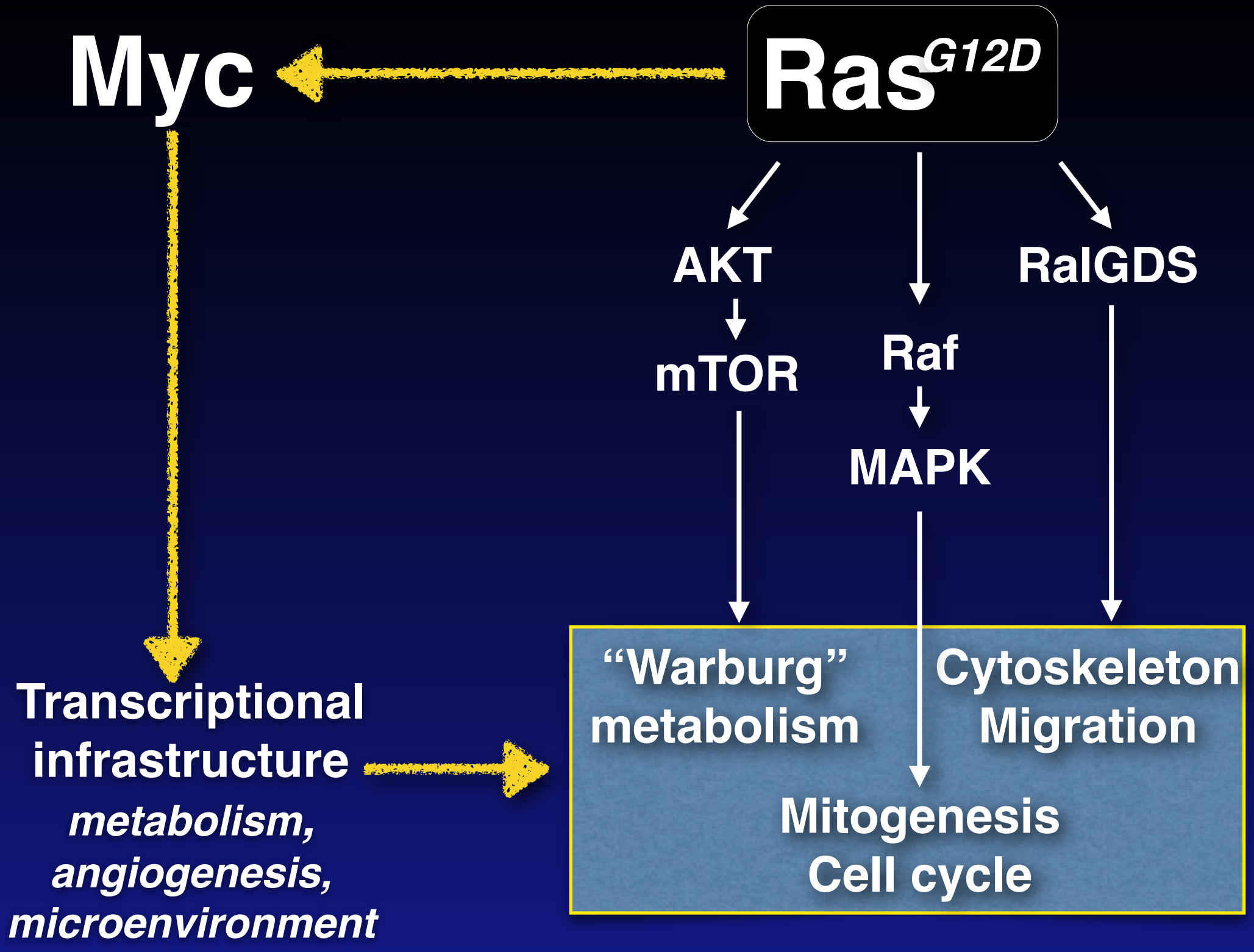
2nd round Myc inhibition (1 wk)

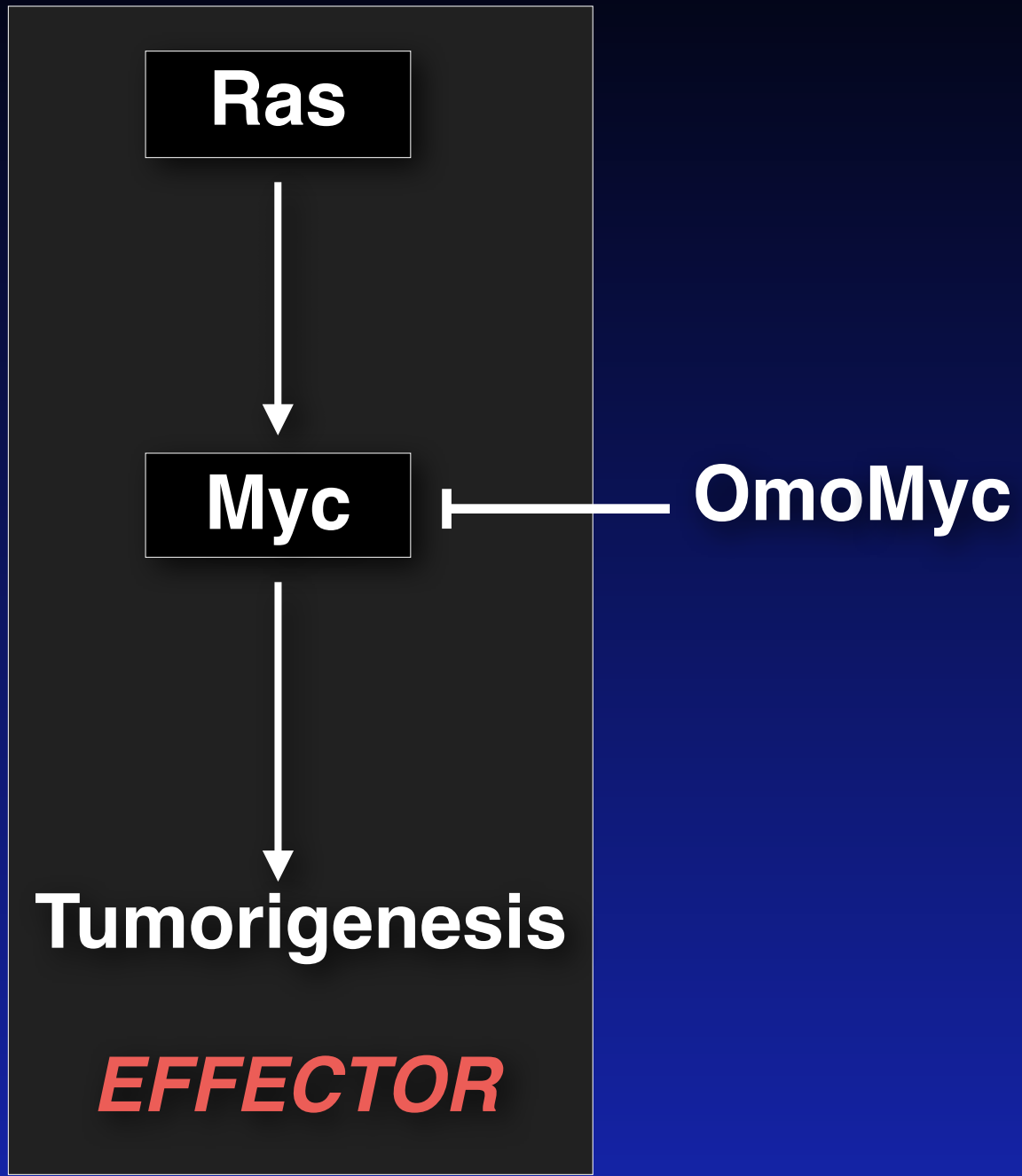




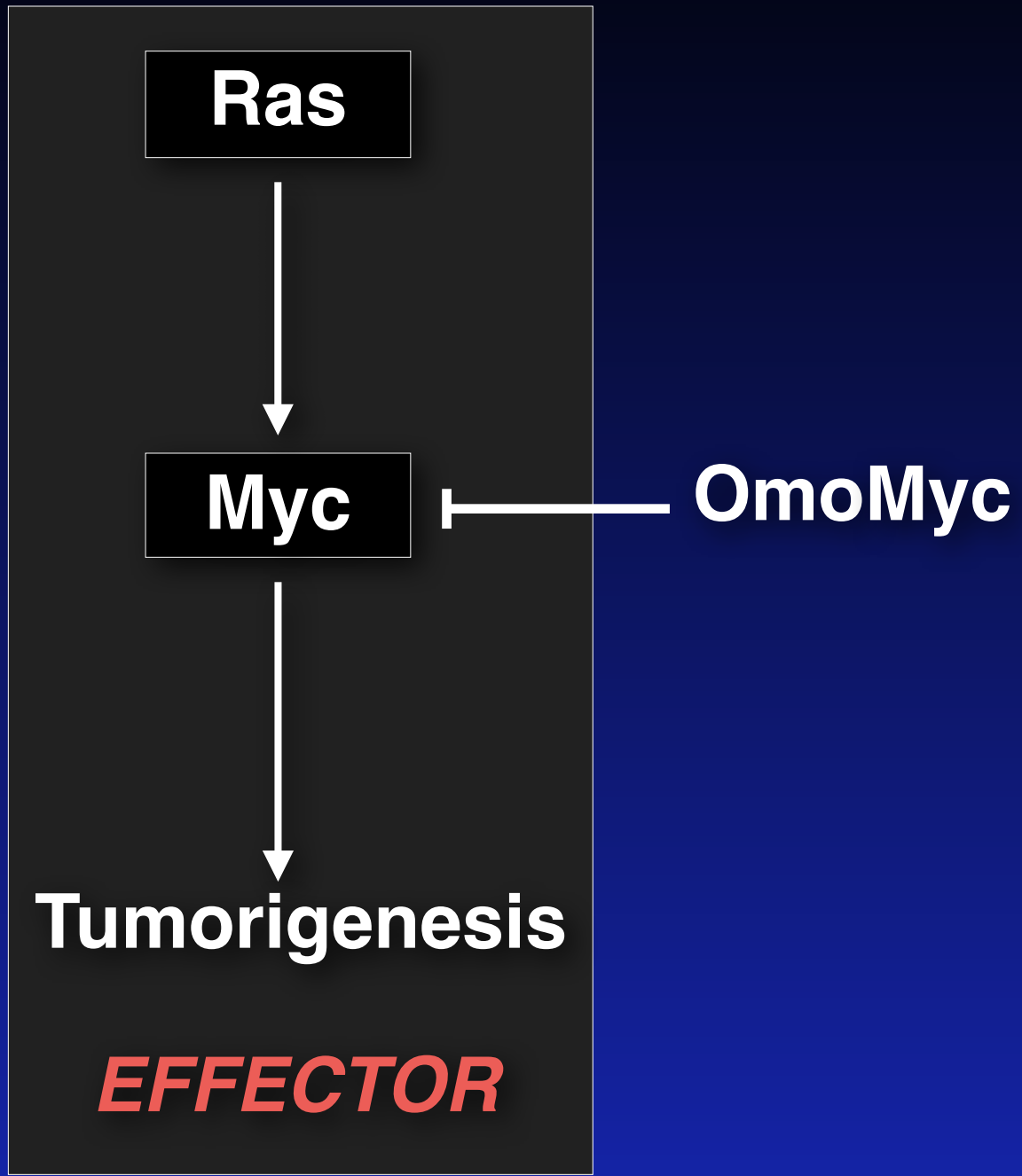

Ras G12D


Ras G12D
AKT
mTOR
Raf
MAPK
RalGDS
"Warburg" metabolism
Cytoskeleton Migration
Mitogenesis Cell cycle

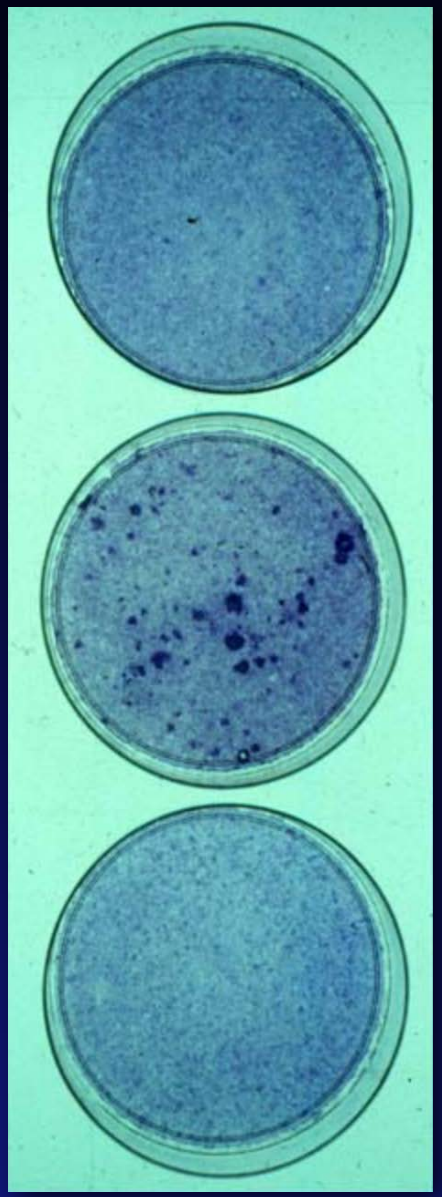

Myc
Ras G12D
AKT
mTOR
Raf
MAPK
RalGDS
Transcriptional infrastructure
metabolism, angiogenesis, microenvironment
"Warburg" metabolism
Cytoskeleton Migration
Mitogenesis Cell cycle


Ras
Myc
OmoMyc
Tumorigenesis
EFFECTOR

Myc is a Ras downstream effector



1982: Myc and Ras cooperate to transform fibroblasts in culture



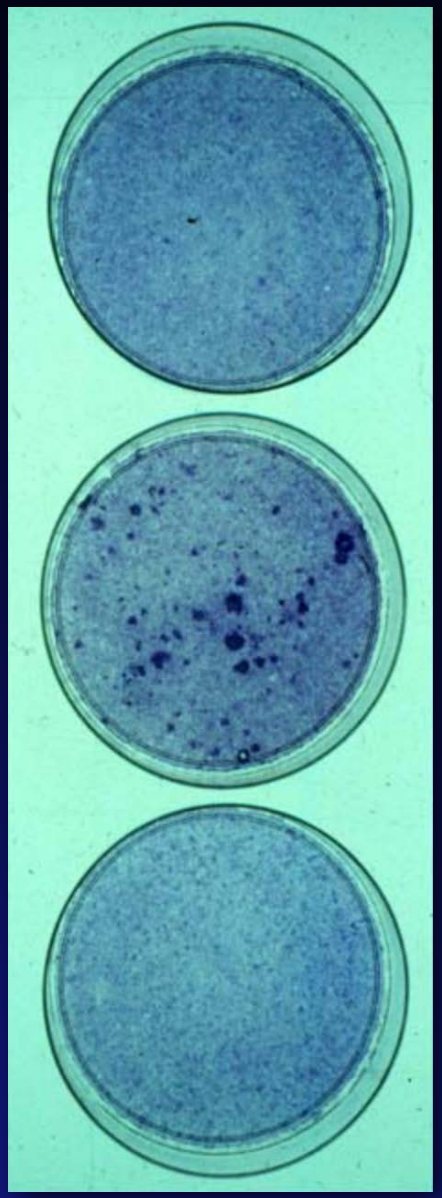
Land, Parada & Weinberg

HRas^{V12}

HRas^{V12} + Myc

Myc

1982: Myc and Ras cooperate to transform fibroblasts in culture



Land, Parada & Weinberg

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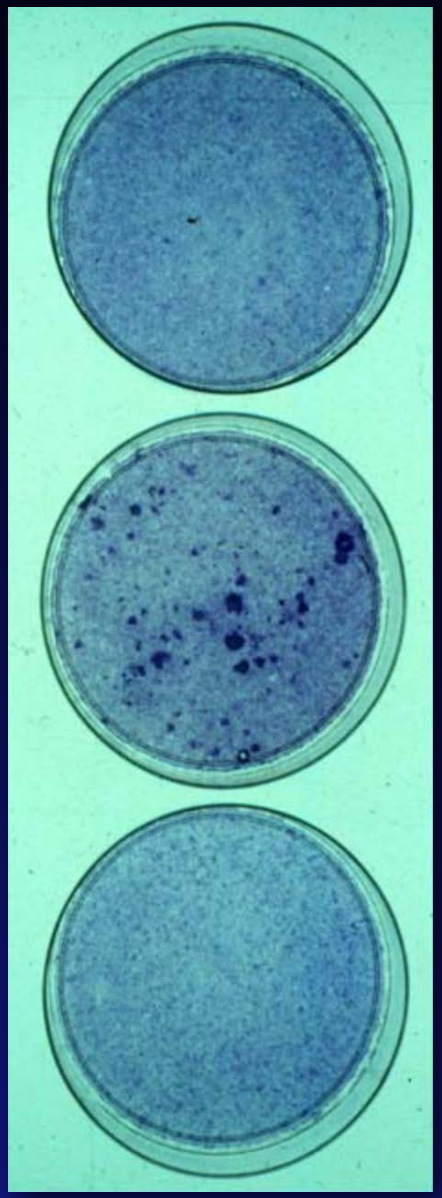


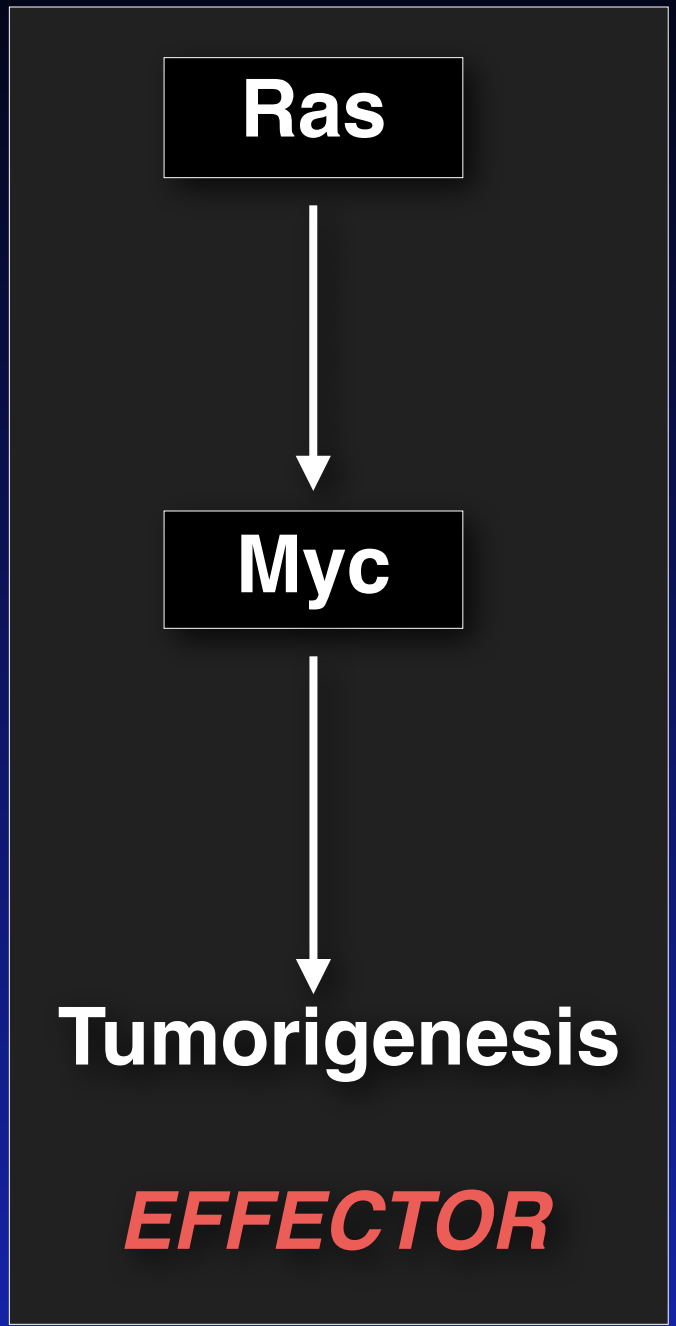
Land, Parada & Weinberg

HRas^{V12}

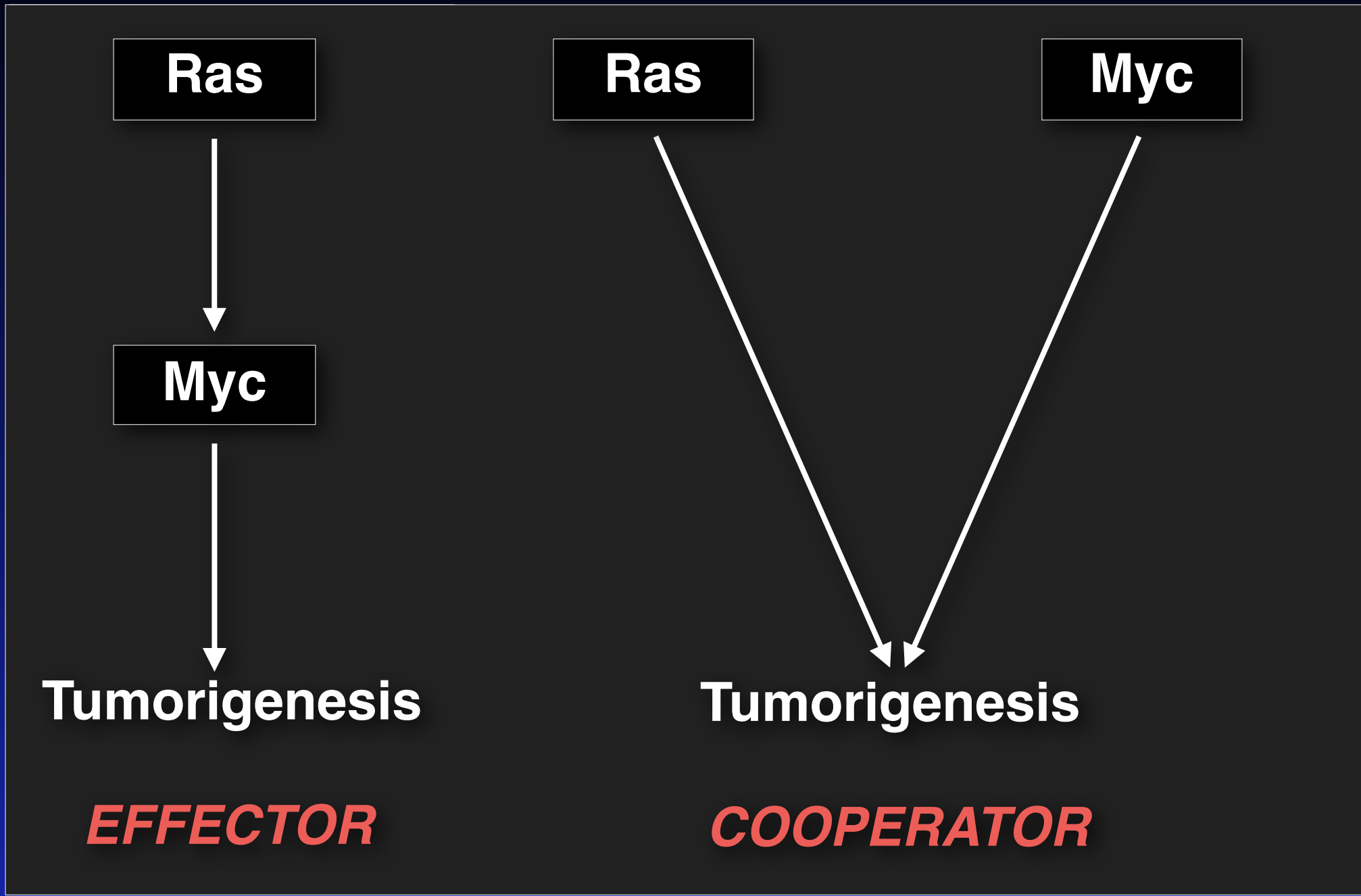
HRas^{V12} + Myc

Myc

What does Myc do for Ras and Ras do for Myc?


Ras
Myc
Tumorigenesis
EFFECTOR

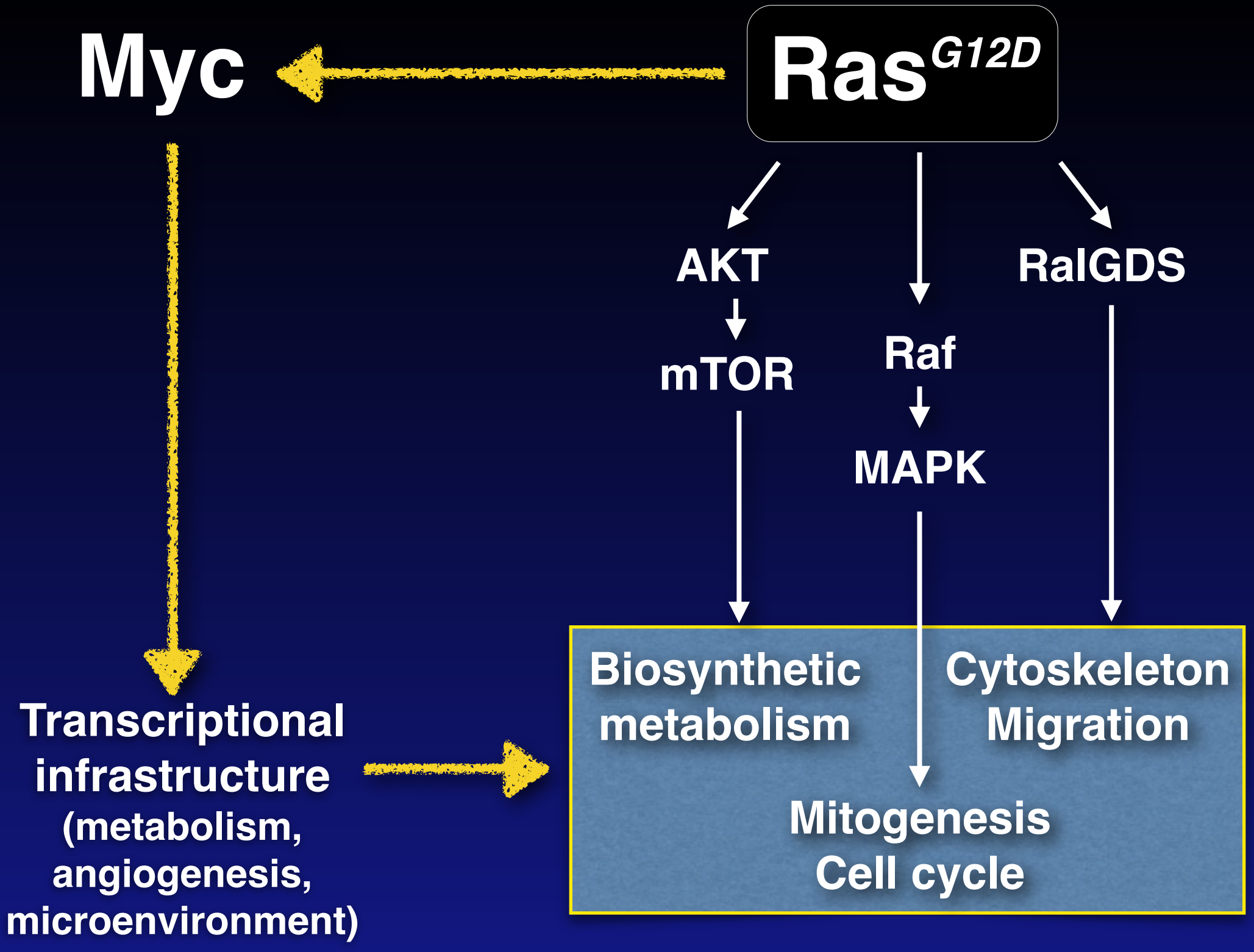
Is Myc a Ras effector or cooperator?

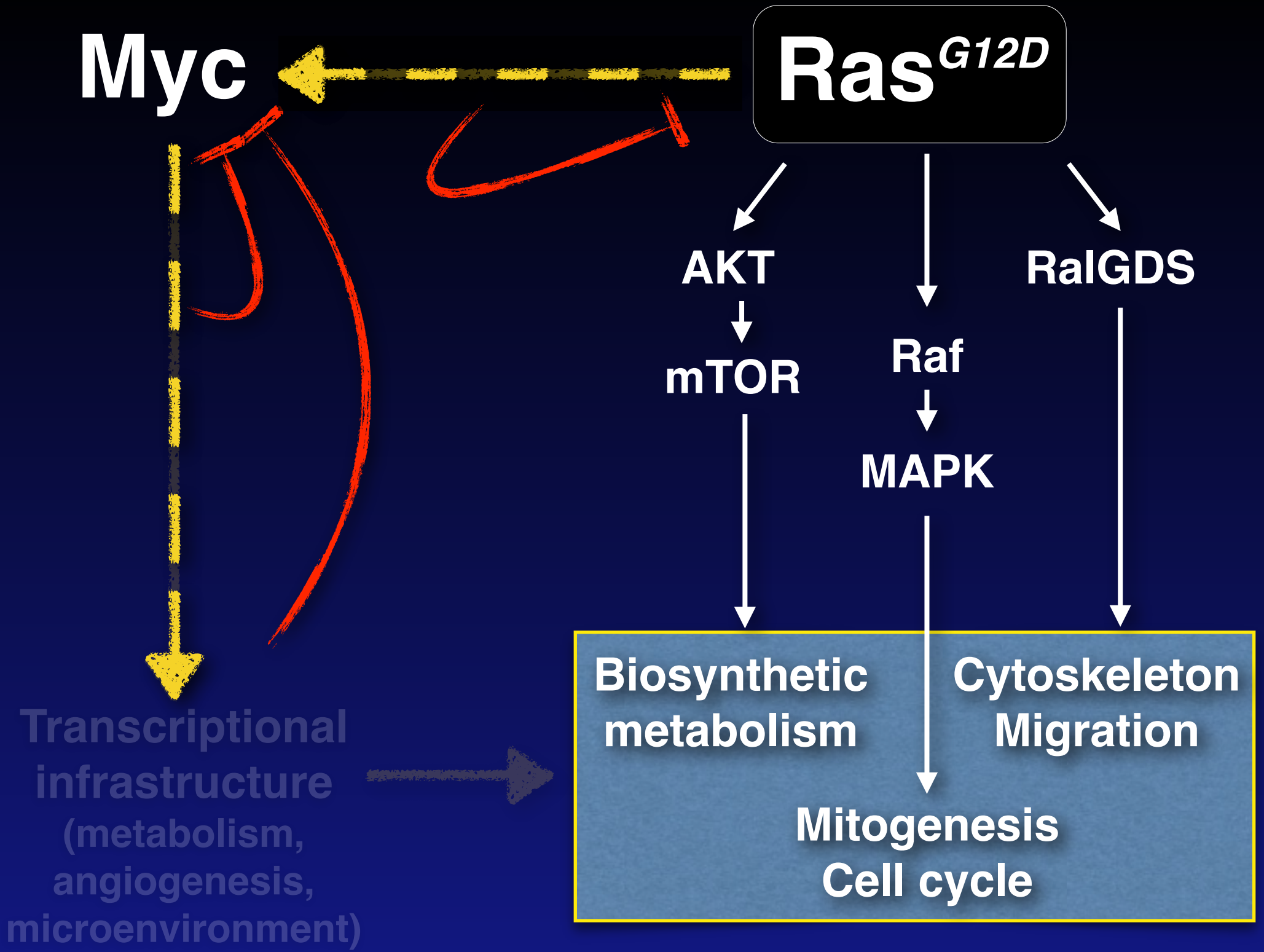


If Ras can drive Myc, why does Ras need Myc for oncogene *cooperation*?

If Ras can drive Myc, why does Ras need Myc for oncogene *cooperation*?

Oncogenic Myc is deregulated and often over-expressed


Myc
Ras^{G12D}
AKT
mTOR
Raf
MAPK
RalGDS
Transcriptional infrastructure
(metabolism, angiogenesis, microenvironment)
Biosynthetic metabolism
Cytoskeleton Migration
Mitogenesis Cell cycle


Myc
Ras G12D
AKT
mTOR
Raf
MAPK
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Biosynthetic metabolism
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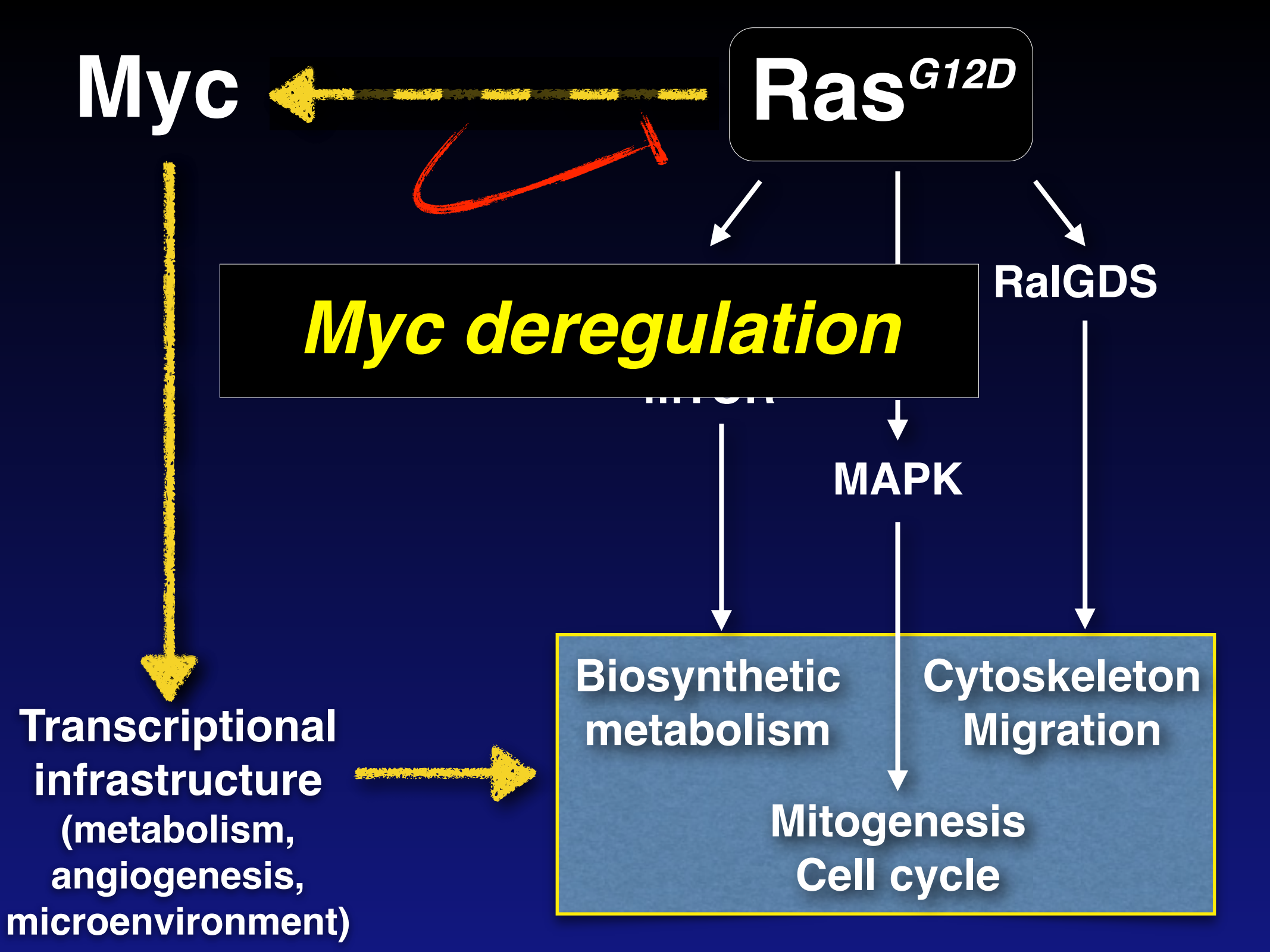
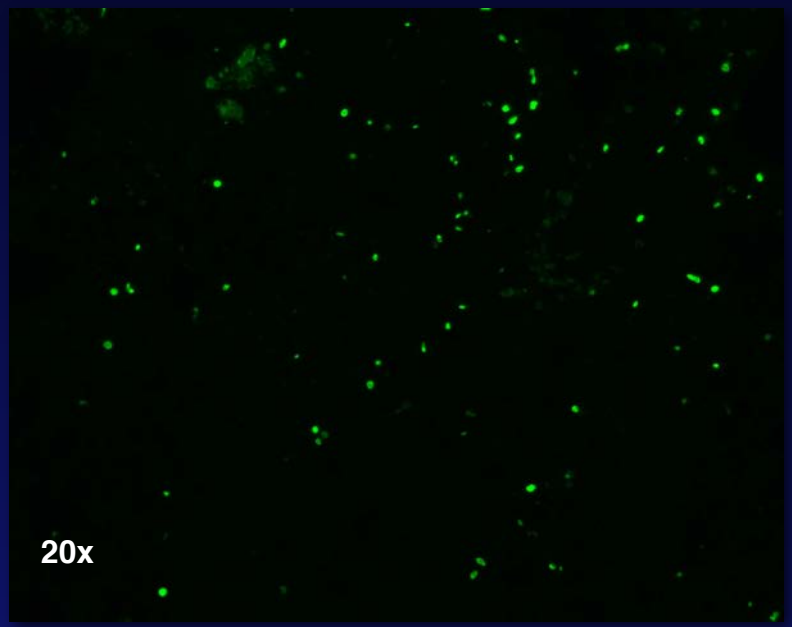
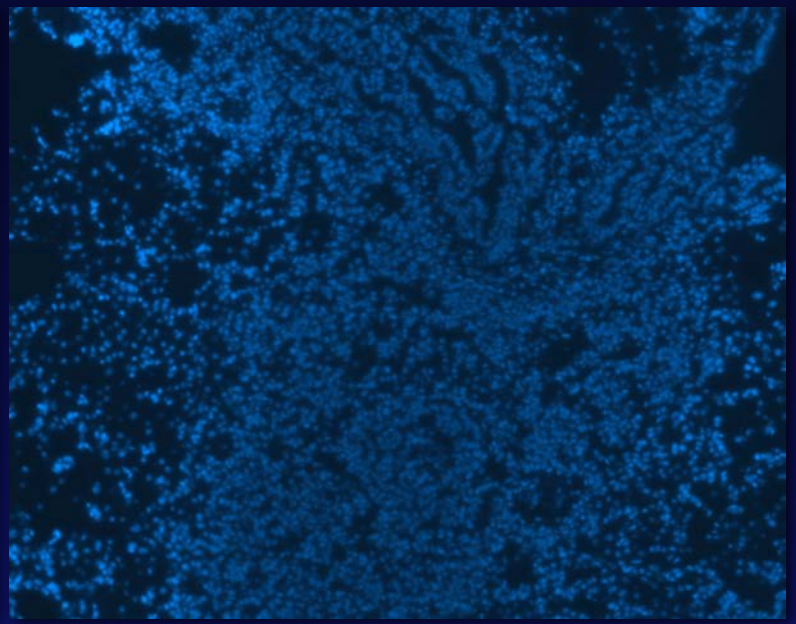
Mitogenesis Cell cycle
Transcriptional infrastructure
(metabolism, angiogenesis, microenvironment)


Myc
Ras^{G12D}
Myc deregulation
RalGDS
MAPK
Transcriptional infrastructure (metabolism, angiogenesis, microenvironment)
Biosynthetic metabolism
Cytoskeleton Migration
Mitogenesis Cell cycle

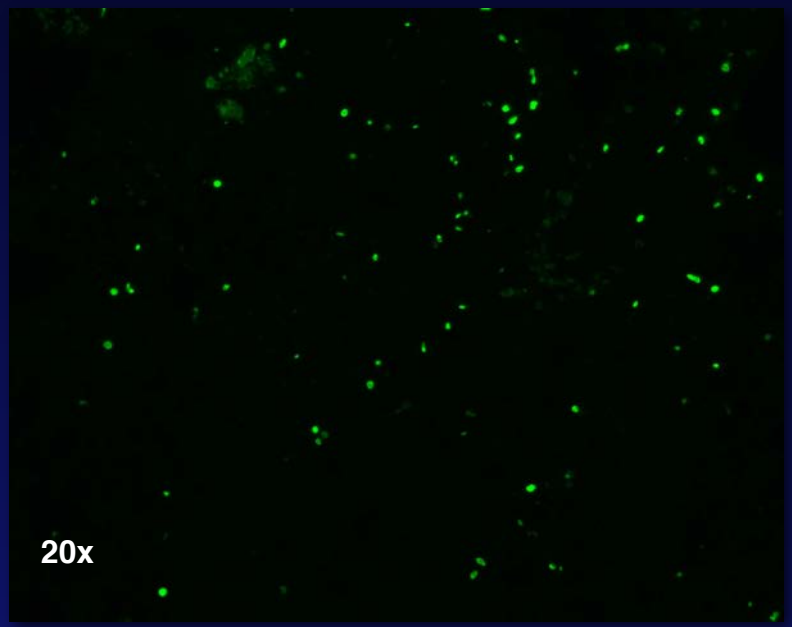




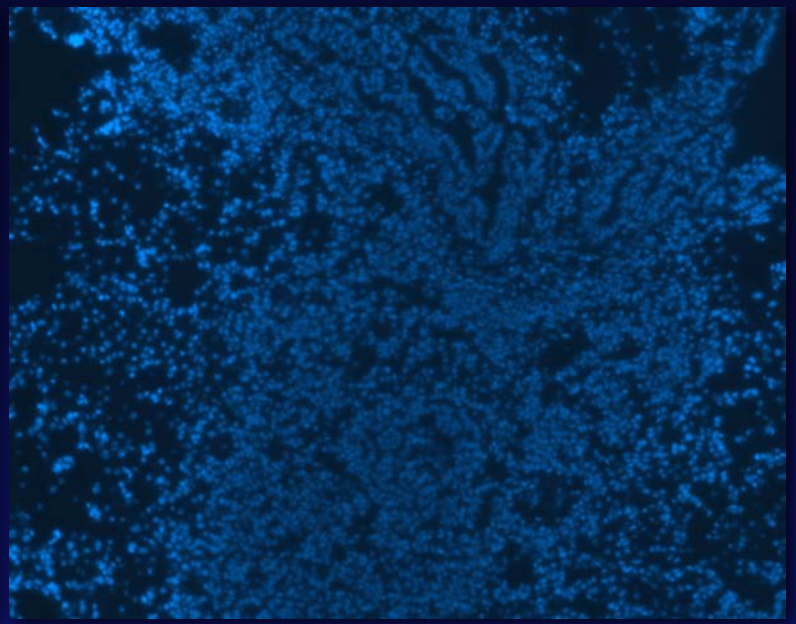
BrdU **Hoechst**

KRas^{G12D}-driven lung tumours

KRas^{G12D}-driven lung tumours have a very low proliferative index



BrdU

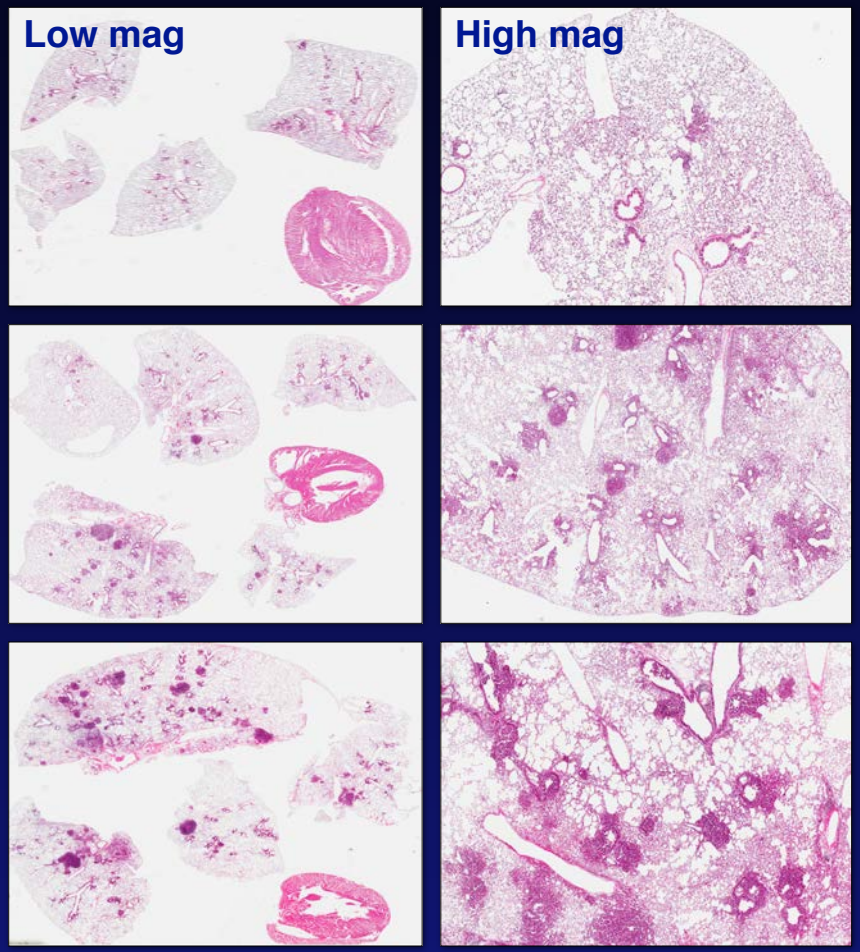


Hoechst

KRas^{G12D}-driven lung tumours

Myc deregulation exacerbates K-Ras^{G12D}-driven lung tumorigenesis

K-Ras^{G12D} alone



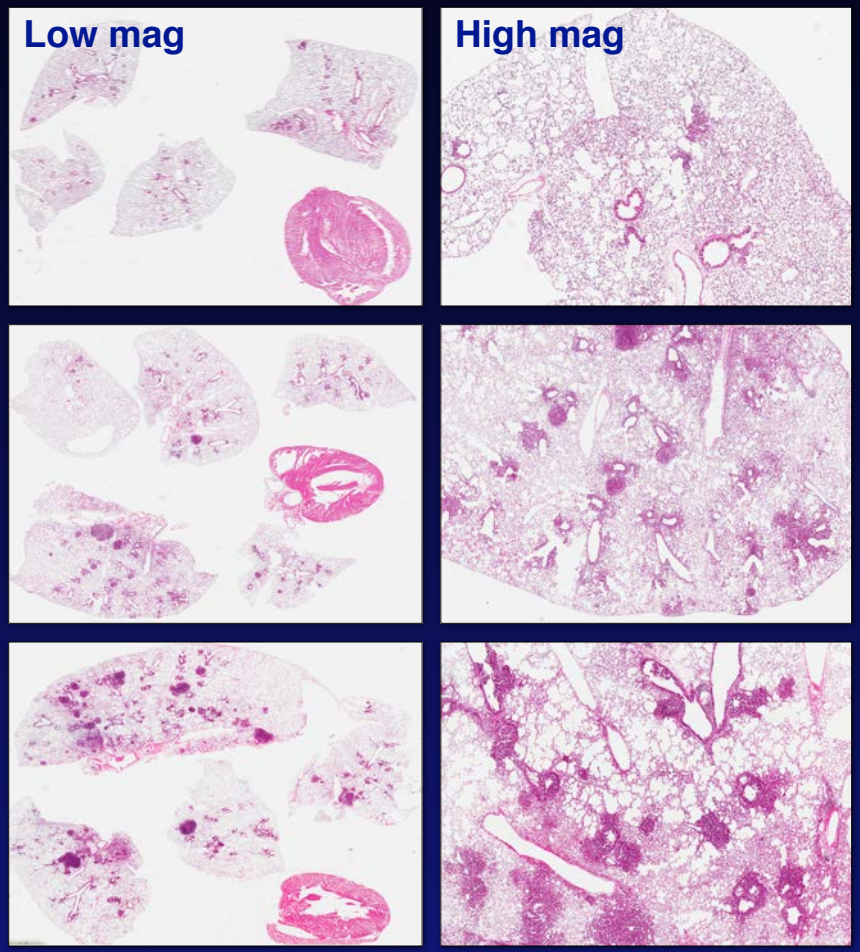
n > 10

H&E staining

Roderick Kortlever

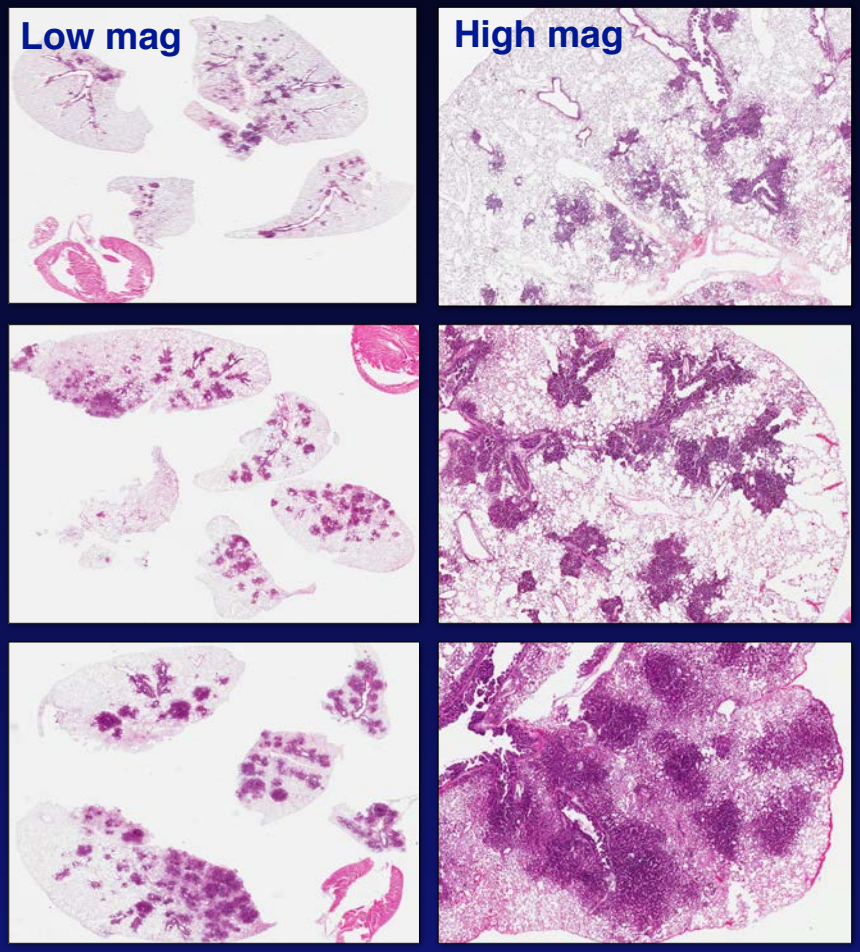
Myc deregulation exacerbates K-Ras^{G12D}- driven lung tumorigenesis

K-Ras^{G12D} alone



n > 10

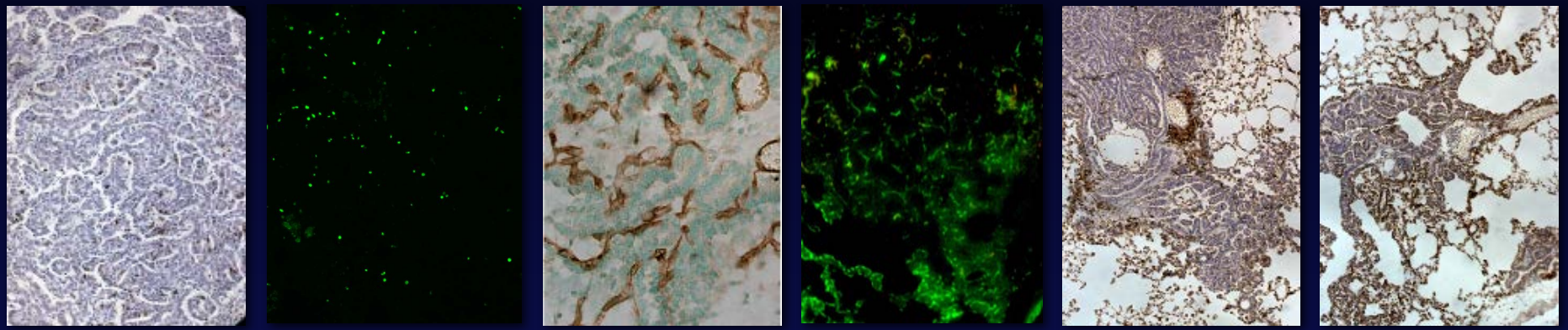
K-Ras^{G12D} + Myc



n > 10

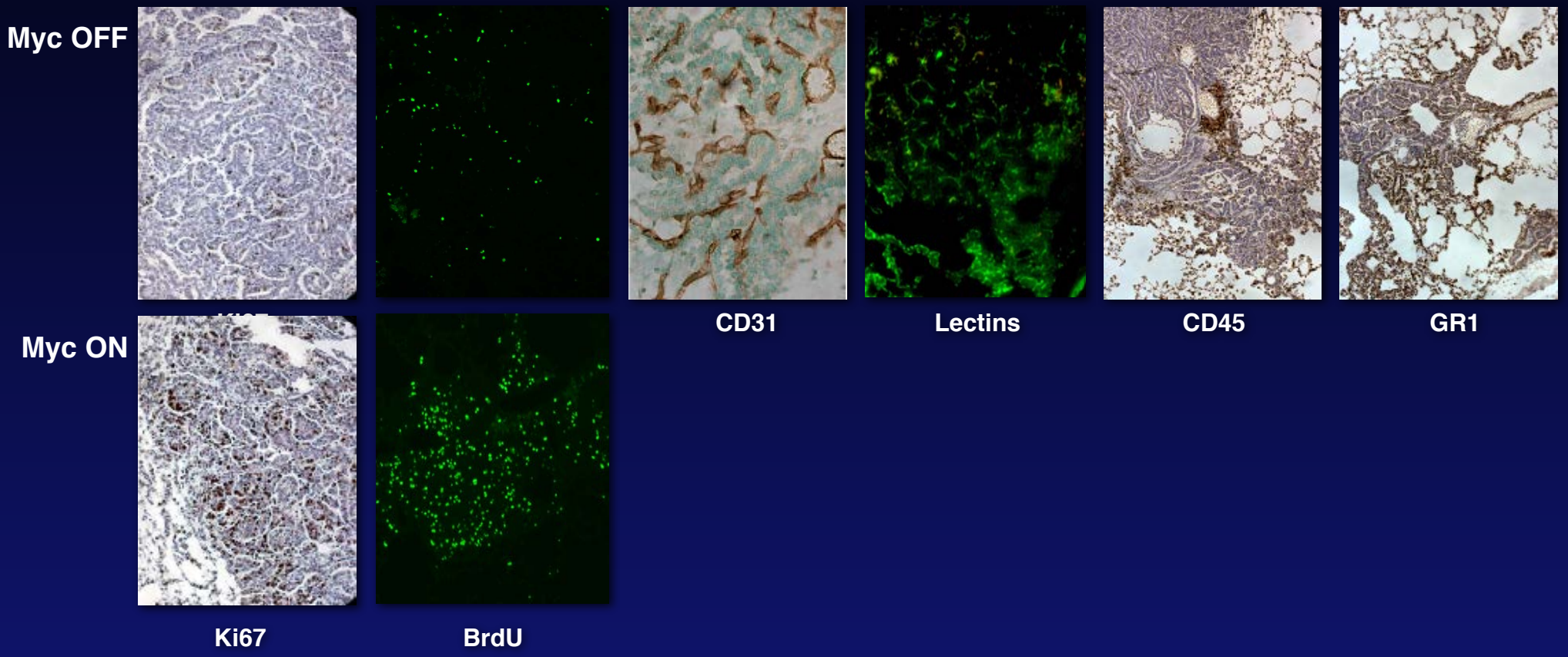
H&E staining

Roderick Kortlever



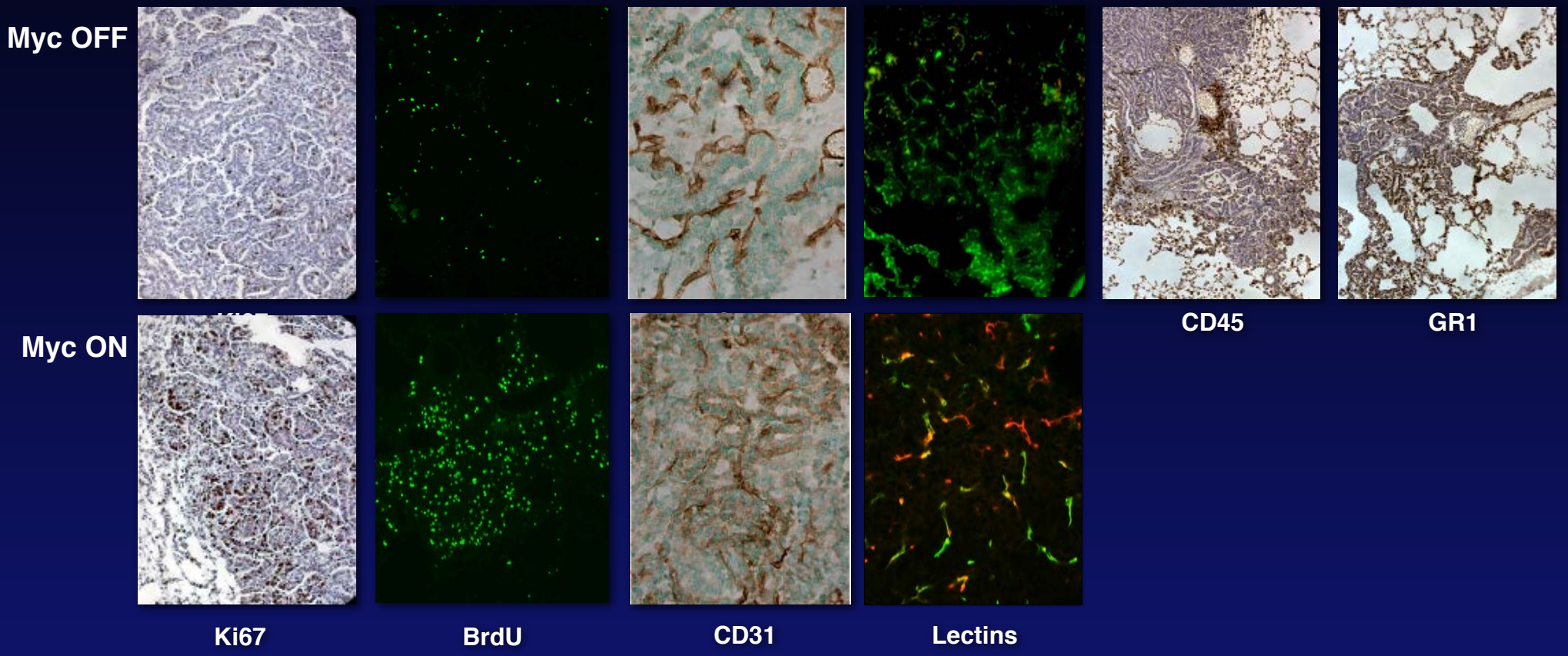
Roderik Kortlever

Acute activation of MycER^{TAM} elicits rapid increase in KRas^{G12D} tumor proliferation,



Roderik Kortlever

Acute activation of MycER^{TAM} elicits rapid increase in KRas^{G12D} tumor proliferation, angiogenesis

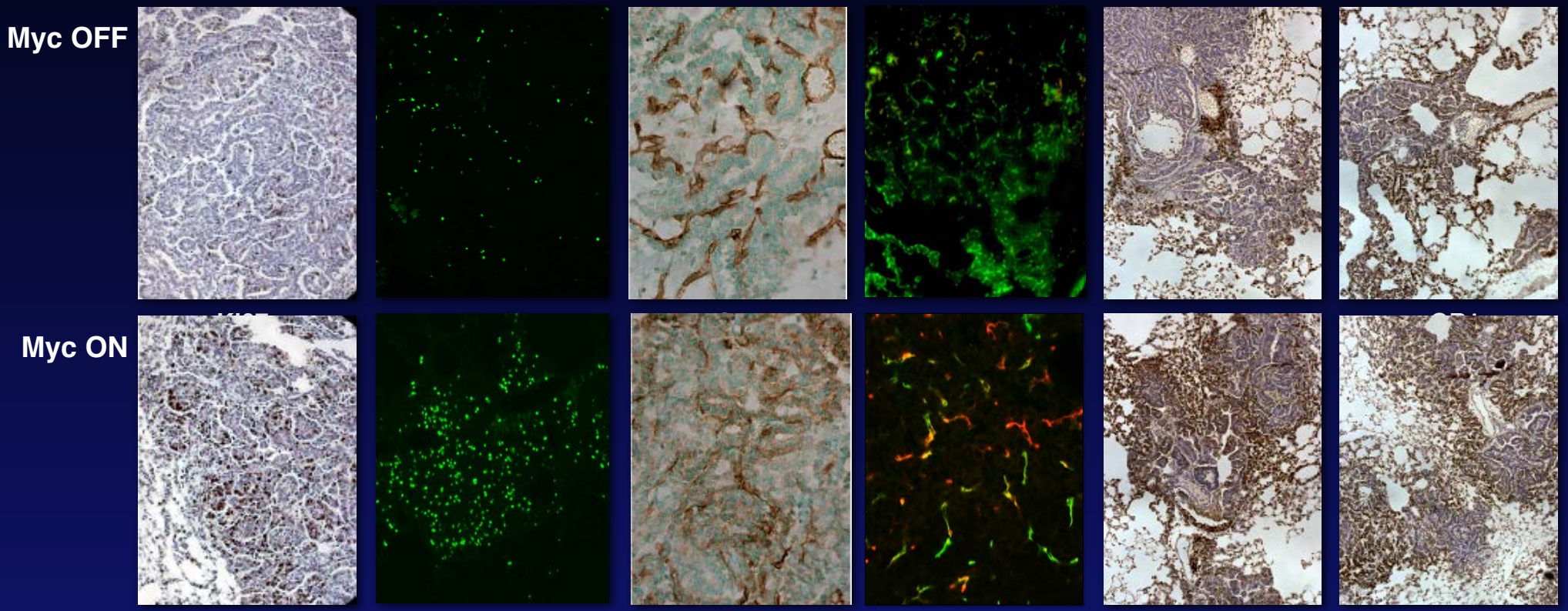


FITC-Lycopersicon esculentum lectin

Rhodamine-Ricinus communis agglutinin (vascular permeability)

Roderik Kortlever

Acute activation of MycER^{TAM} elicits rapid increase in KRas^{G12D} tumor proliferation, angiogenesis and inflammocyte infiltration



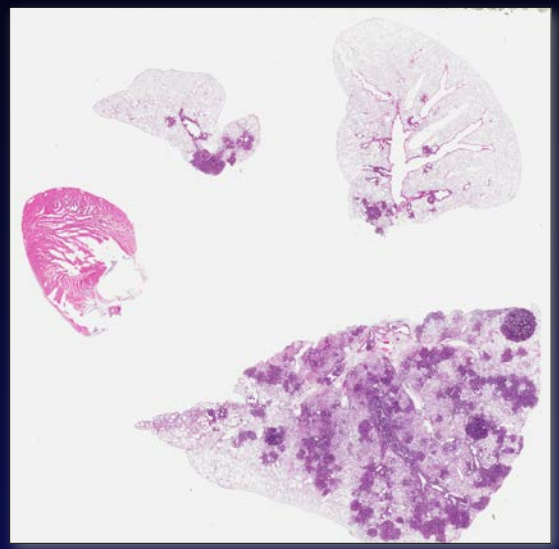
FITC-Lycopersicon esculentum lectin

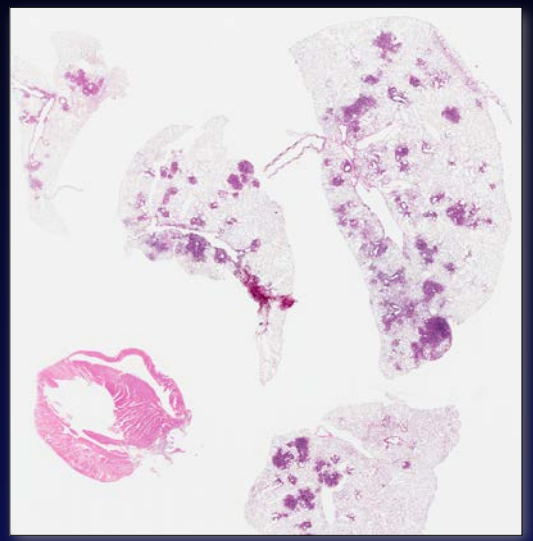
Rhodamine-Ricinus communis agglutinin
(vascular permeability)

Roderik Kortlever

KRas^{G12D}-driven lung tumours acquire dependency upon deregulated Myc

KRas^{G12D} ON for 6 weeks
Then Myc ON as well for 6 weeks





KRas^{G12D}-driven lung tumours acquire dependency upon deregulated Myc

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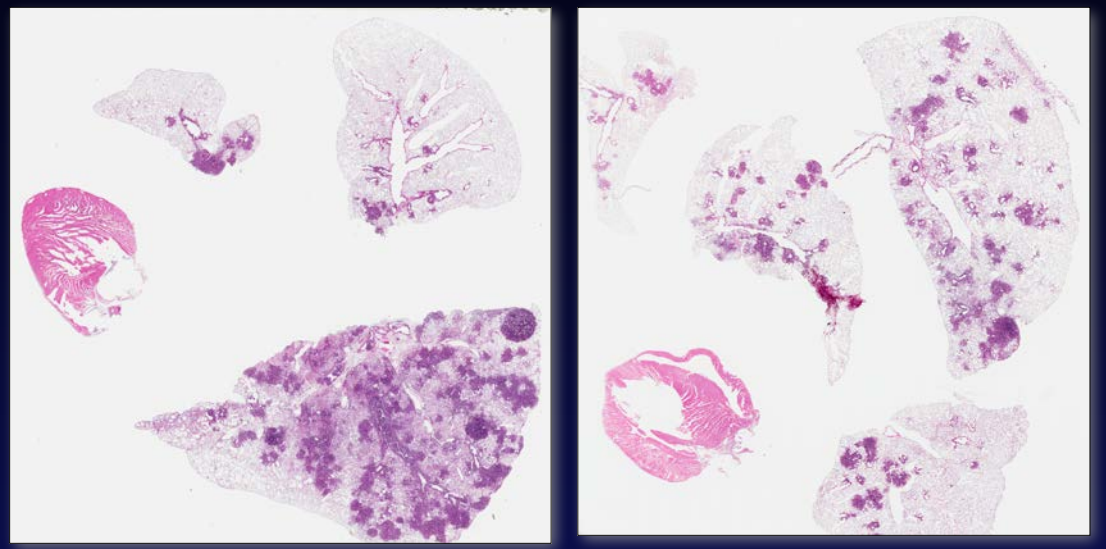
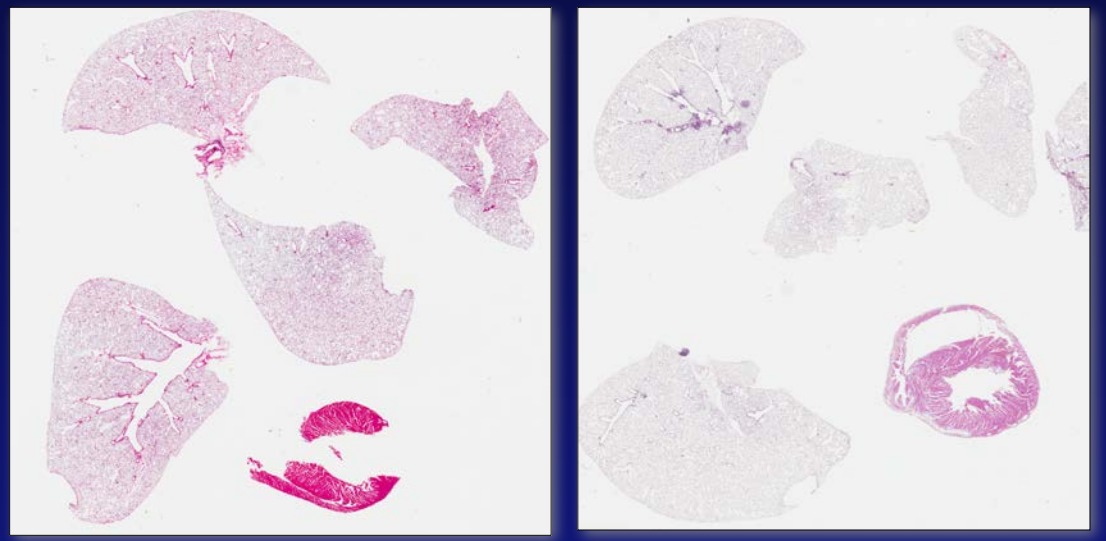
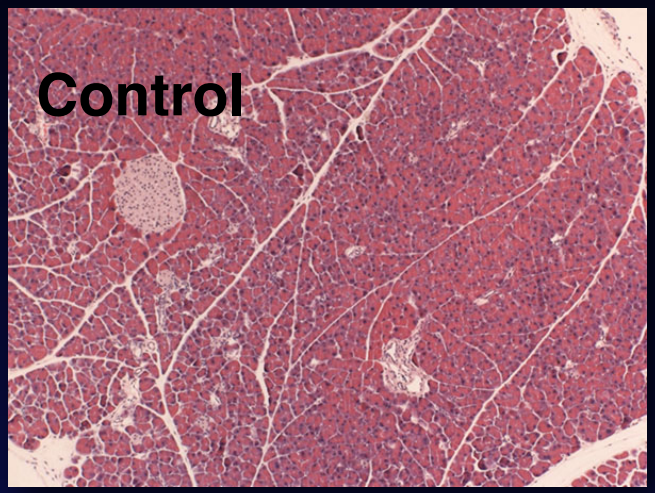


KRas^{G12D} ON for 6 weeks
Then Myc ON as well for 6 weeks
Then Myc OFF for 4 weeks



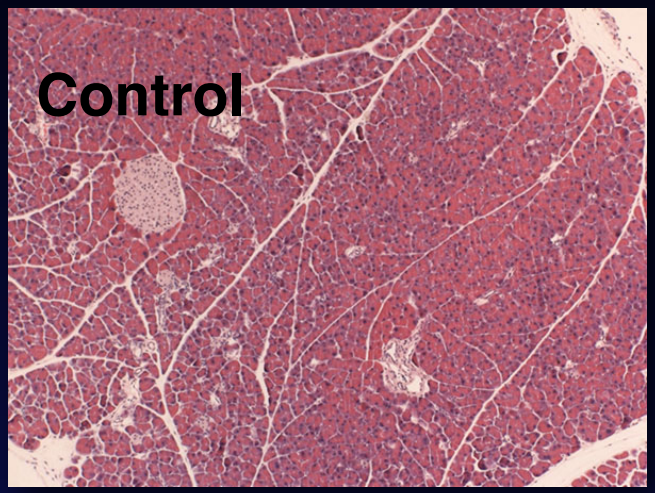
Differential impact of KRas and Myc in pancreatic epithelium

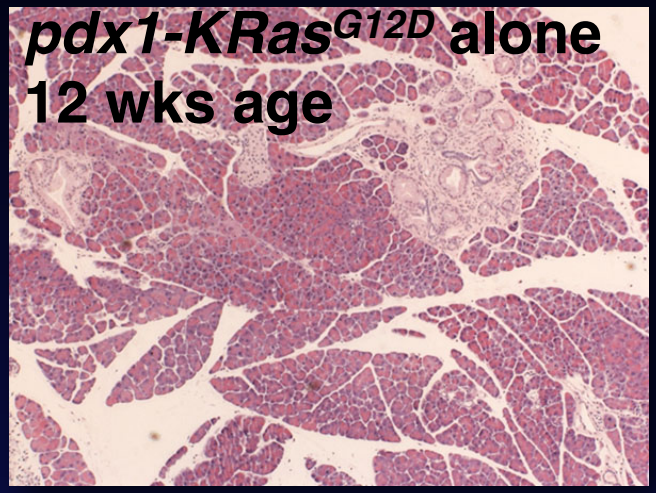


Nicole Sodir

pdx1-Cre; LSL-KRas^{G12D}; R26-LSL-MycER^{TAM}

Differential impact of KRas and Myc in pancreatic epithelium

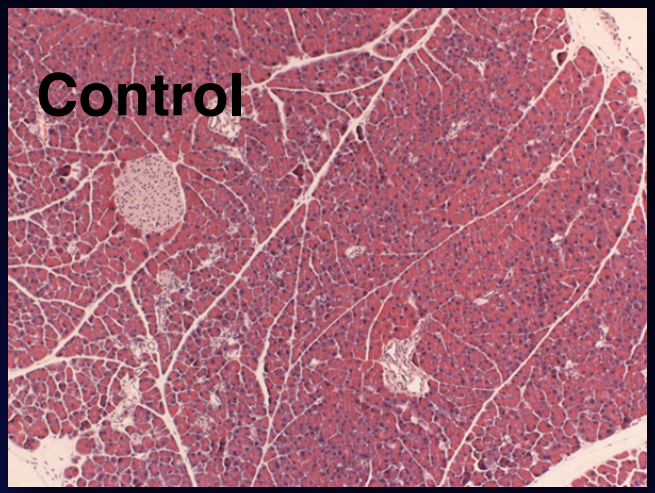


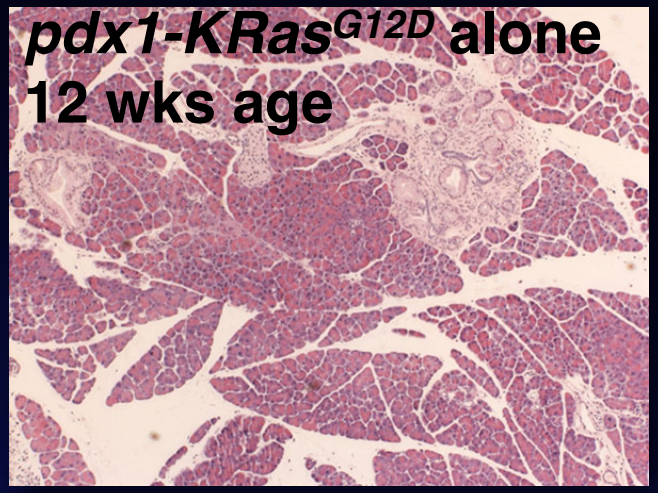


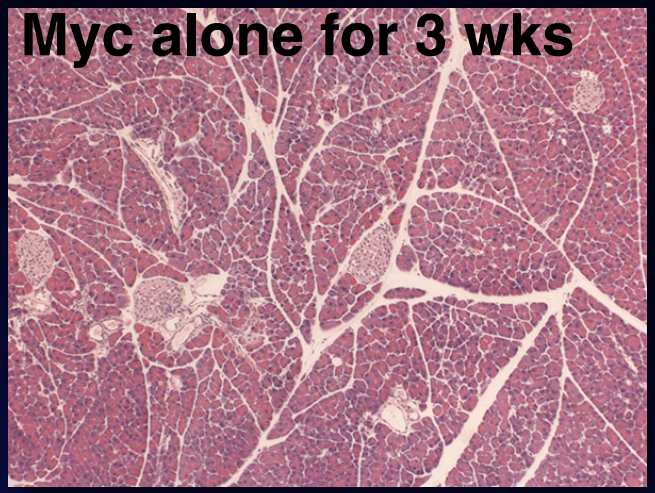
Nicole Sodir

pdx1-Cre; LSL-KRas^{G12D}*; R26-LSL-MycER*^{TAM}

Differential impact of KRas and Myc in pancreatic epithelium



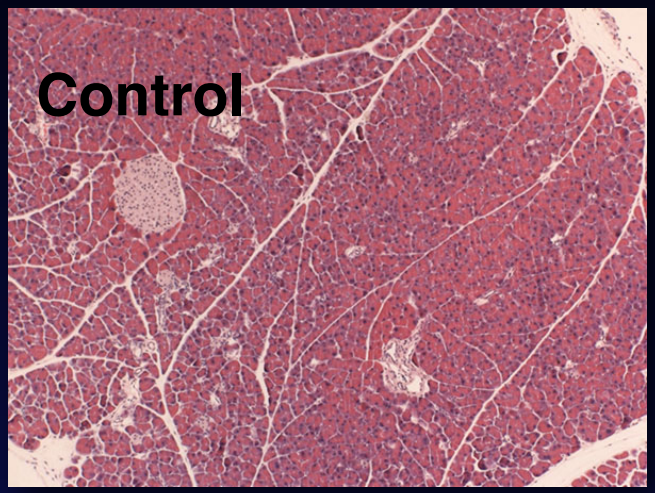


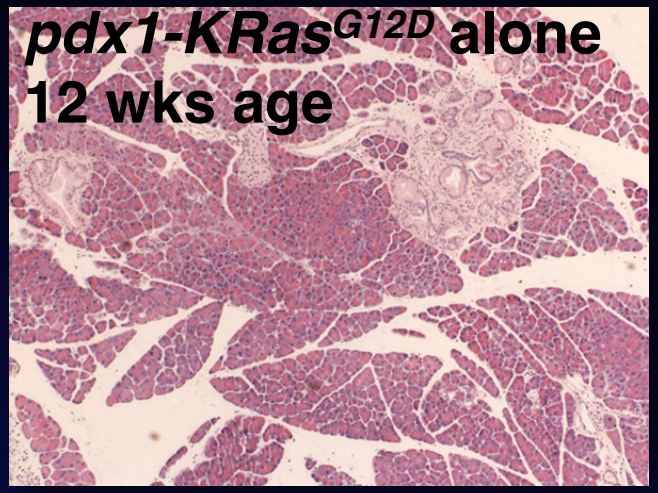


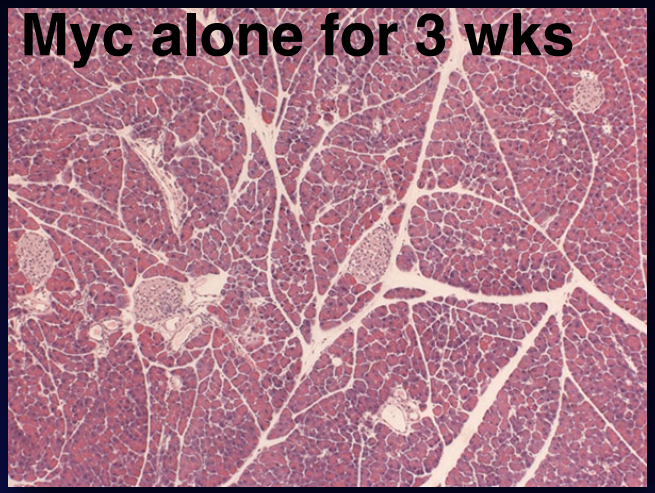
Nicole Sodir

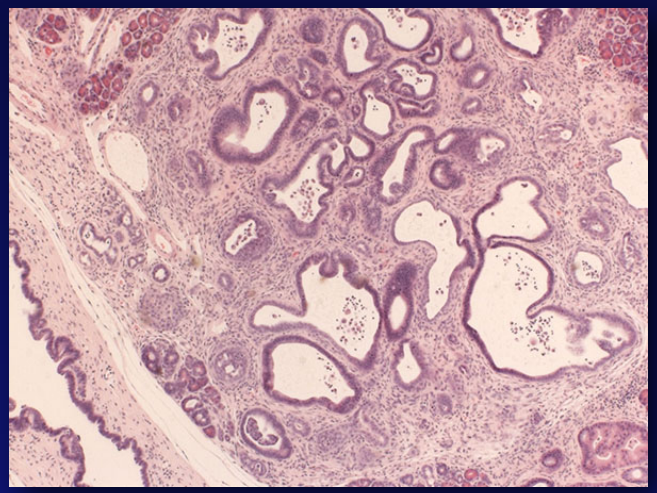
pdx1-Cre; LSL-KRas^{G12D}*; R26-LSL-MycER*^{TAM}

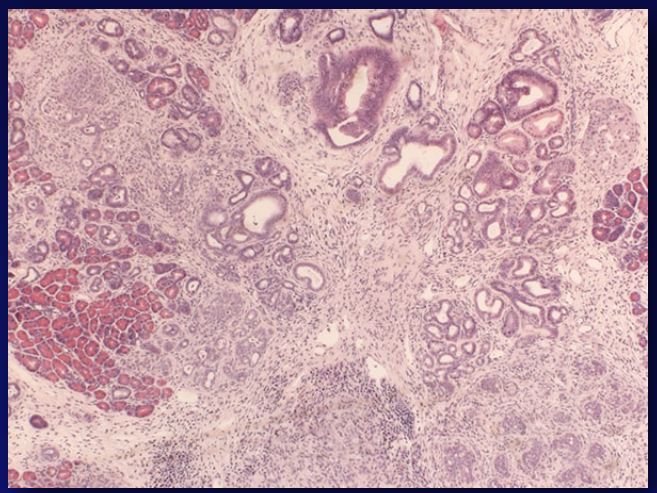
Activation of MycER^{TAM} in KRas^{G12D}-driven PanIN triggers the signature PDAC desmoplastic reaction











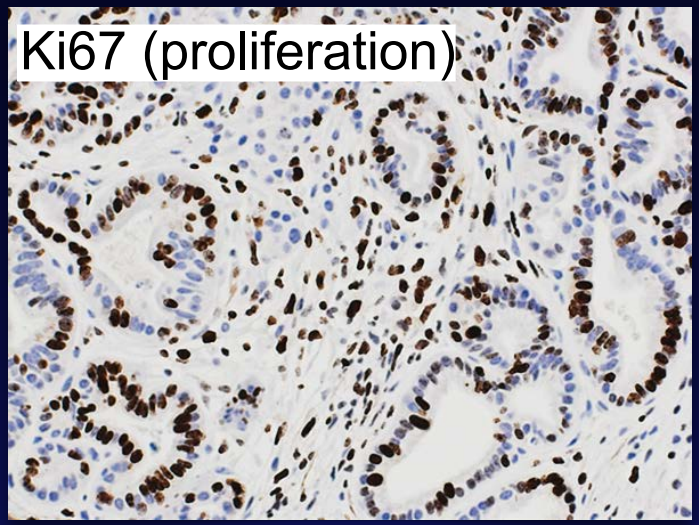
***pdx1-KRas*^{G12D}**
+ Myc 3 wks

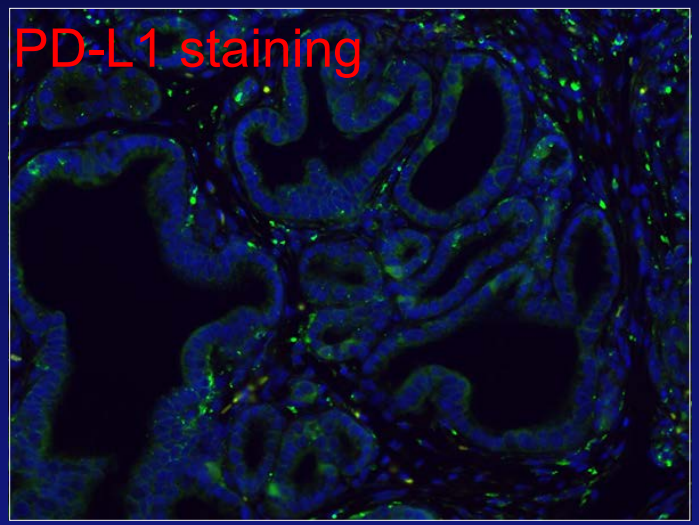
Nicole Sodir

pdx1-Cre; LSL-KRas^{G12D}; R26-LSL-MycER^{TAM}

Myc de-activation triggers rapid growth arrest and loss of immune evasion

Kras
Myc ON 2 wk

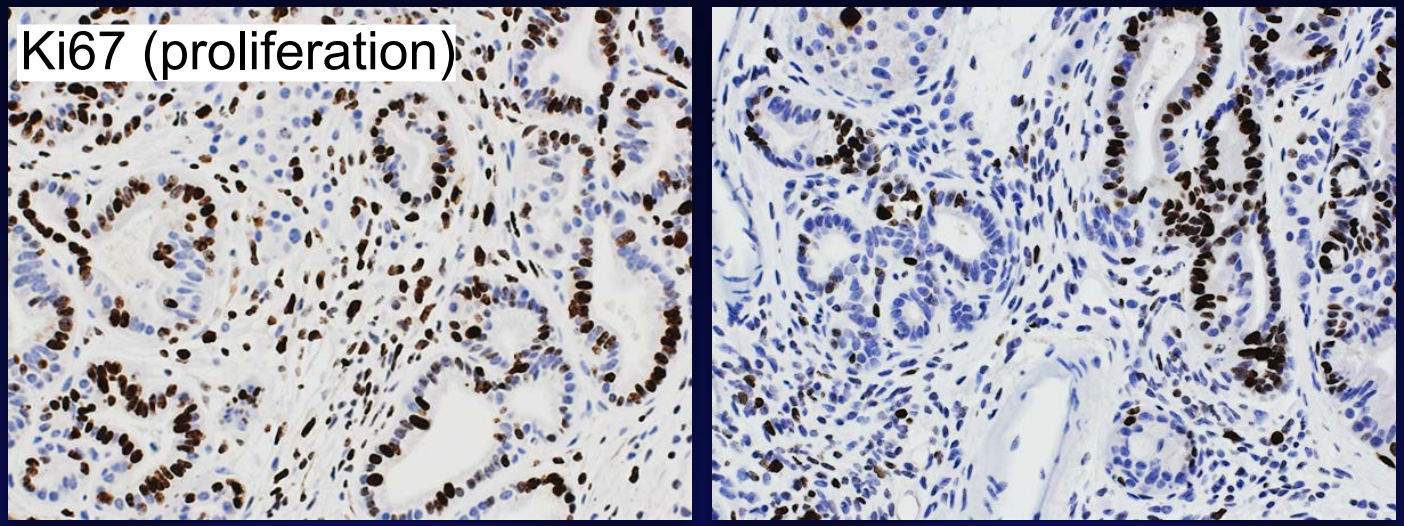


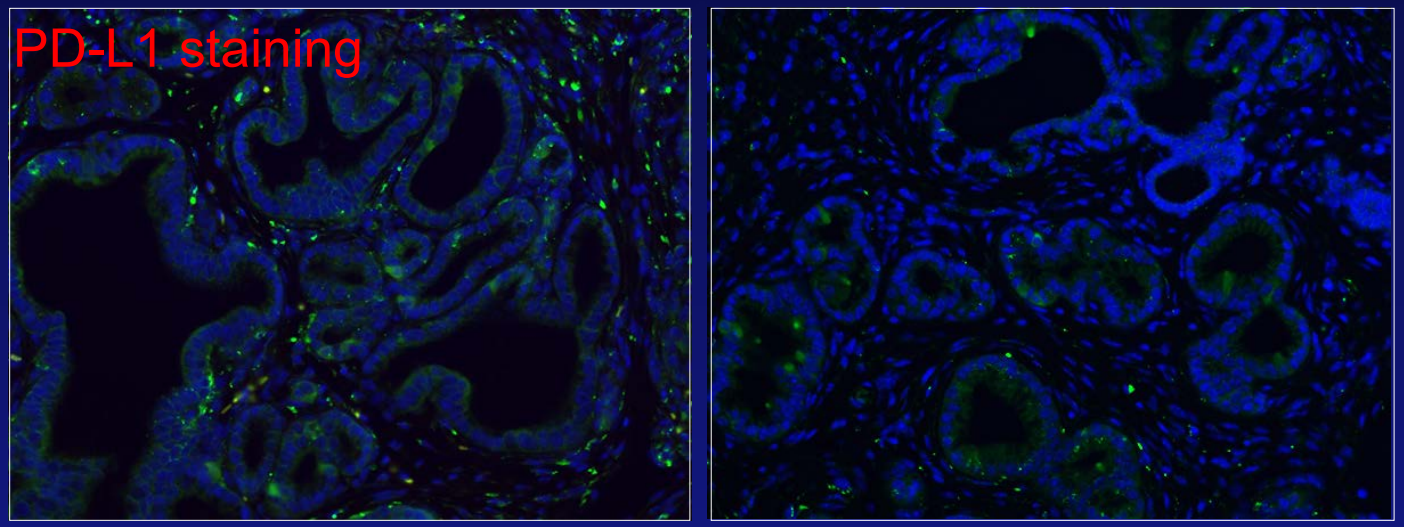


Myc de-activation triggers rapid growth arrest and loss of immune evasion

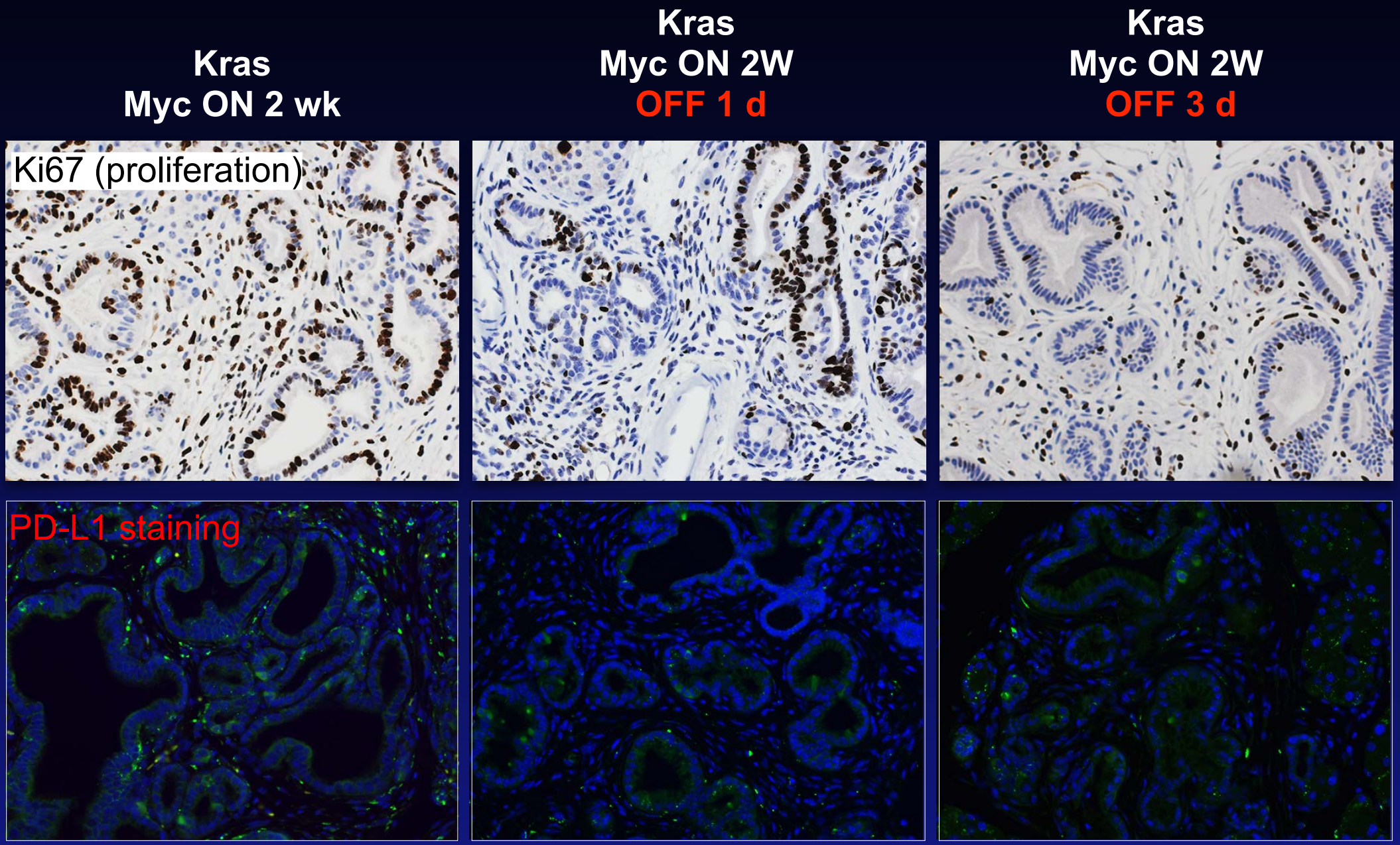
Kras
Myc ON 2 wk

Kras
Myc ON 2W
OFF 1 d

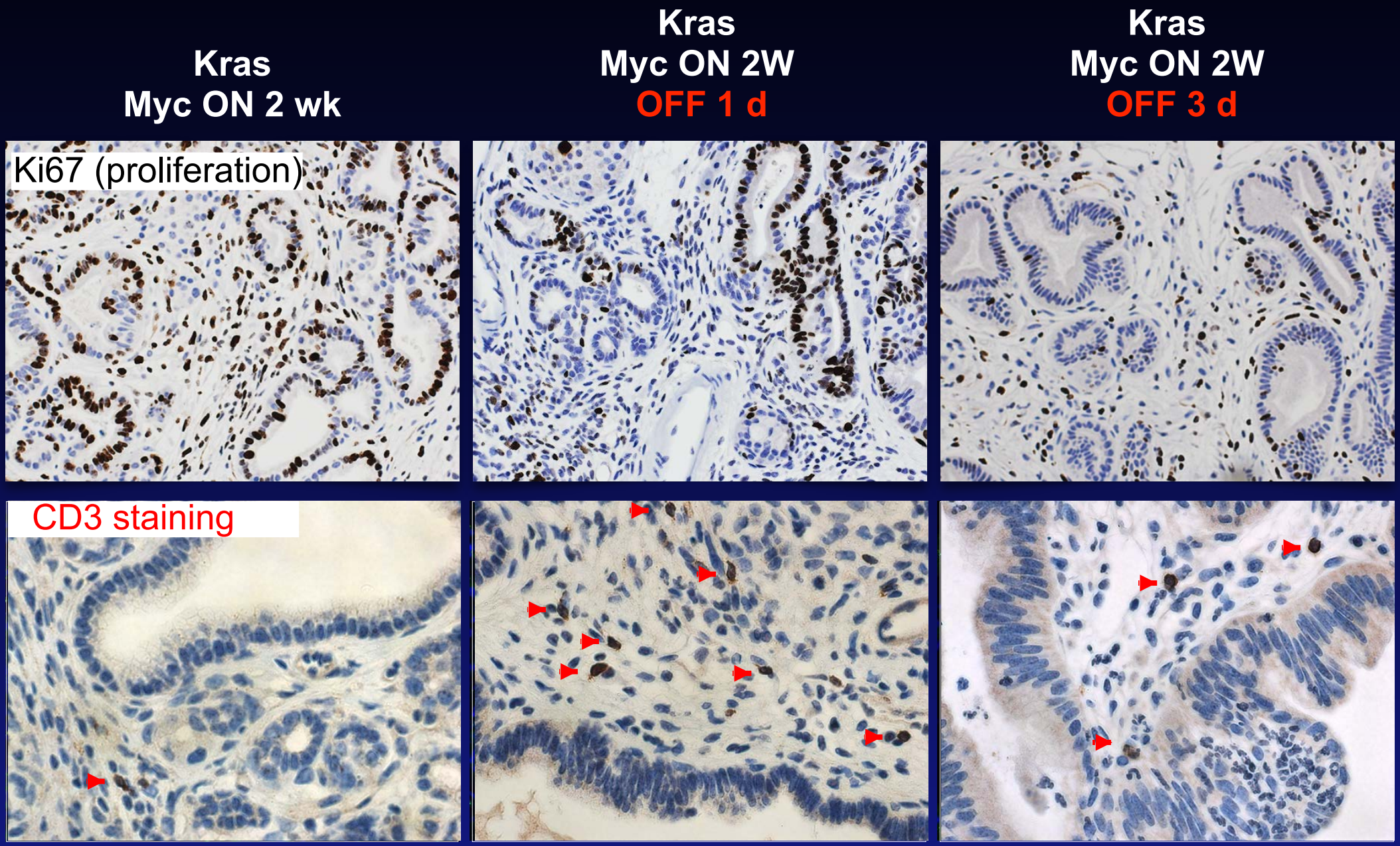




Myc de-activation triggers rapid growth arrest and loss of immune evasion



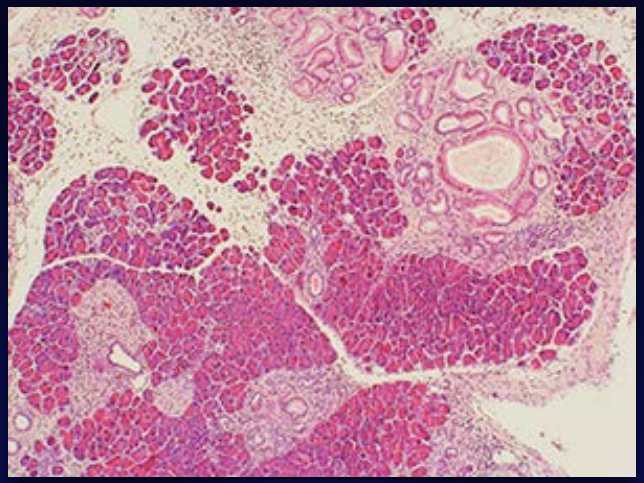
Myc de-activation triggers rapid growth arrest and loss of immune evasion



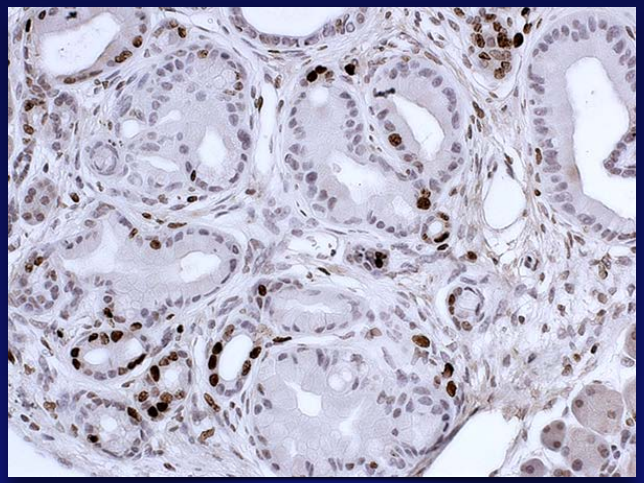
Sustained Myc de-activation induces PDAC regression

Pdx1-cre; LSL-kras$^{G12D/+}$
Myc OFF

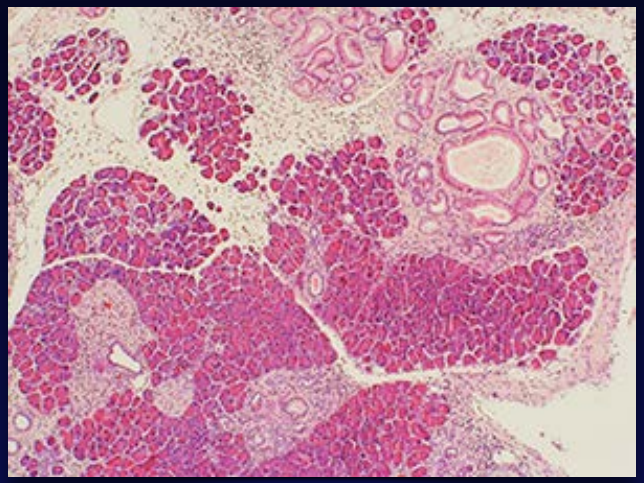
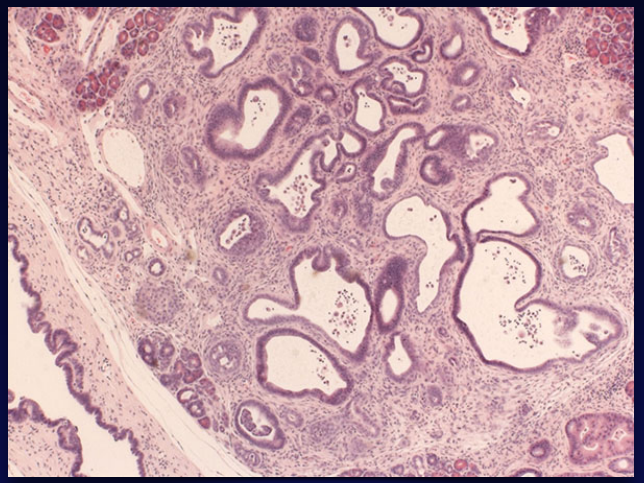
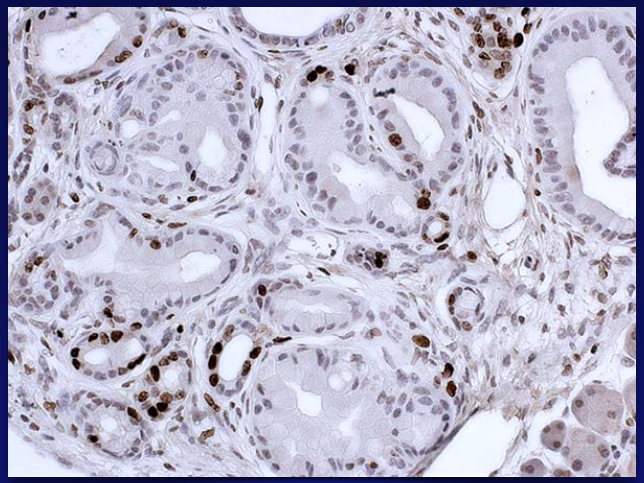
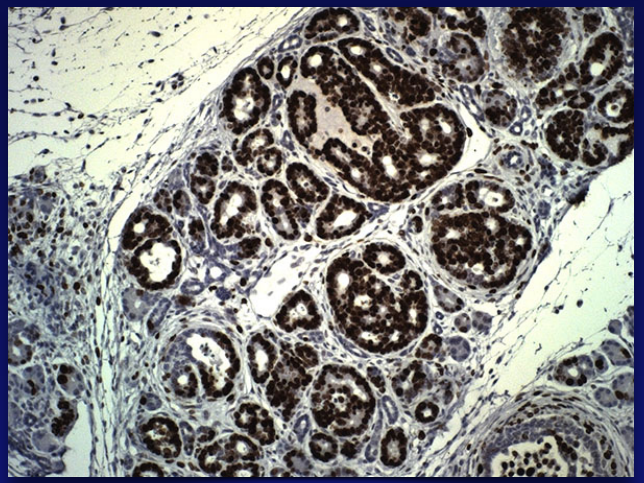
H&E



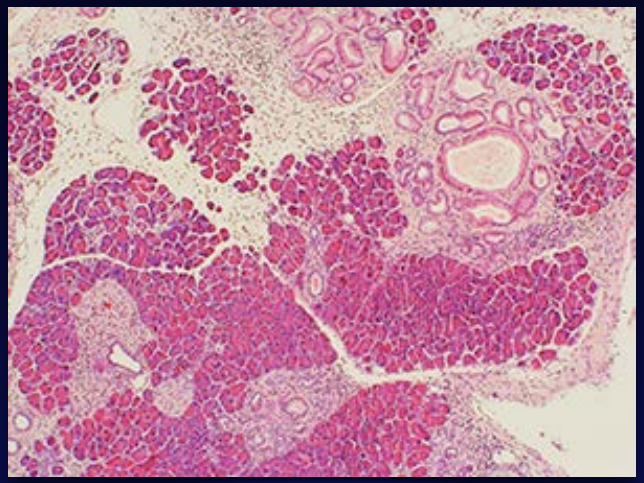
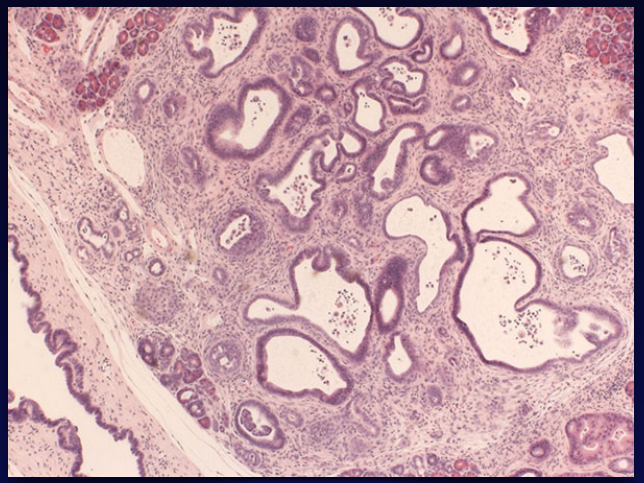
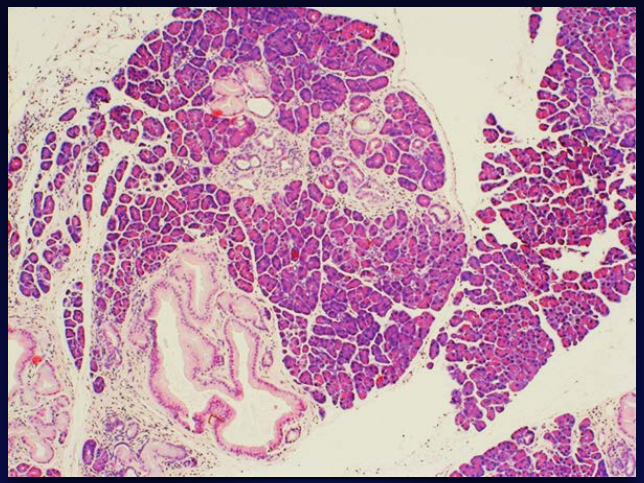
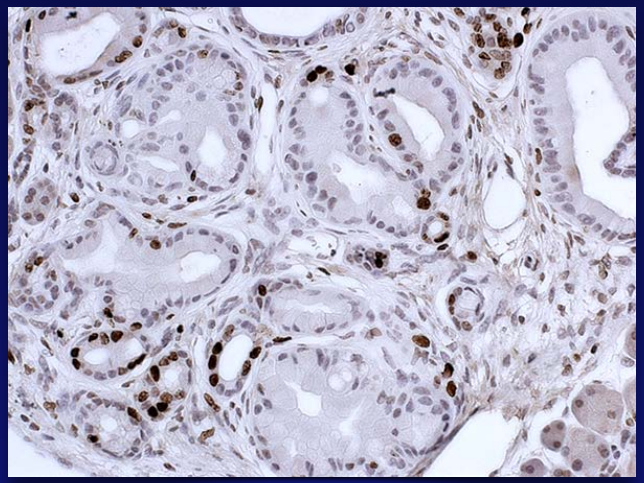
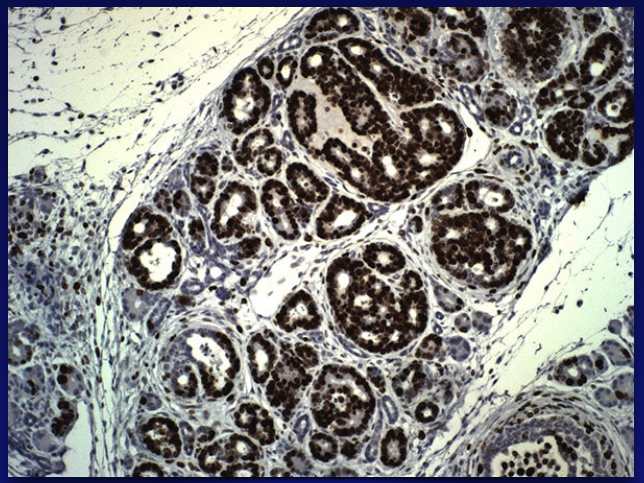
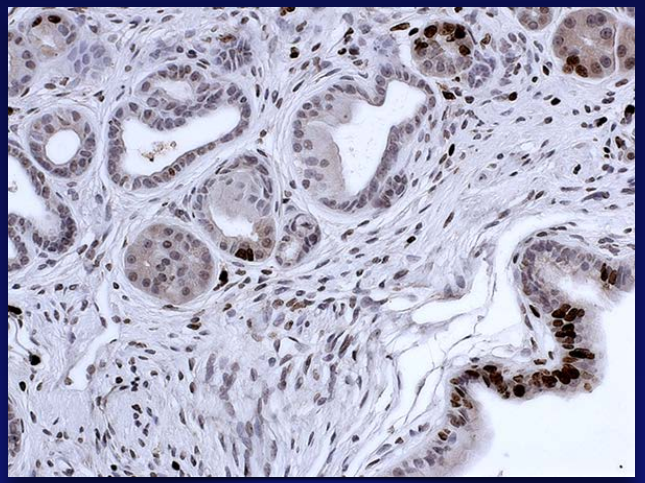
KI67



Sustained Myc de-activation induces PDAC regression

	Pdx1-cre; LSL-kras$^{G12D/+}$ Myc OFF	*Pdx1-cre; LSL-kras$^{G12D/+}$* Myc ON (3 wk)
H&E		
KI67		

Sustained Myc de-activation induces PDAC regression

	Pdx1-cre; LSL-kras$^{G12D/+}$ Myc OFF	*Pdx1-cre; LSL-kras$^{G12D/+}$* Myc ON (3 wk)	*Pdx1-cre; LSL-kras$^{G12D/+}$* Myc ON (3 W); Myc OFF (3W)
H&E			
KI67			

Myc-driven regenerative programmes - pancreas *vs* lung

Pancreas	Lung
Highly proliferative PanIN⟶PDAC	Highly proliferative Adenoma⟶Adenocarcinoma
Avascular, highly desmoplastic	Highly angiogenic, little desmoplasia
normoxia⟶hypoxia	hypoxia⟶normoxia
Influx of macrophages and neutrophils	Influx of PD-L1+ macrophages
Clearance of CD3+ T cells (PD-L1 on tumor cells)	Clearance of CD3+ T cells (PD-L1 on incoming MΦ)
Maintenance is Myc-dependent	Maintenance is Myc-dependent