

CANCER WARS

THE METASTASIS STRIKES BACK

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31.05.2008

PLAN OF ATTACK

ငြန်ခဲ့ပေးအဲလျှော့ဝါယာ

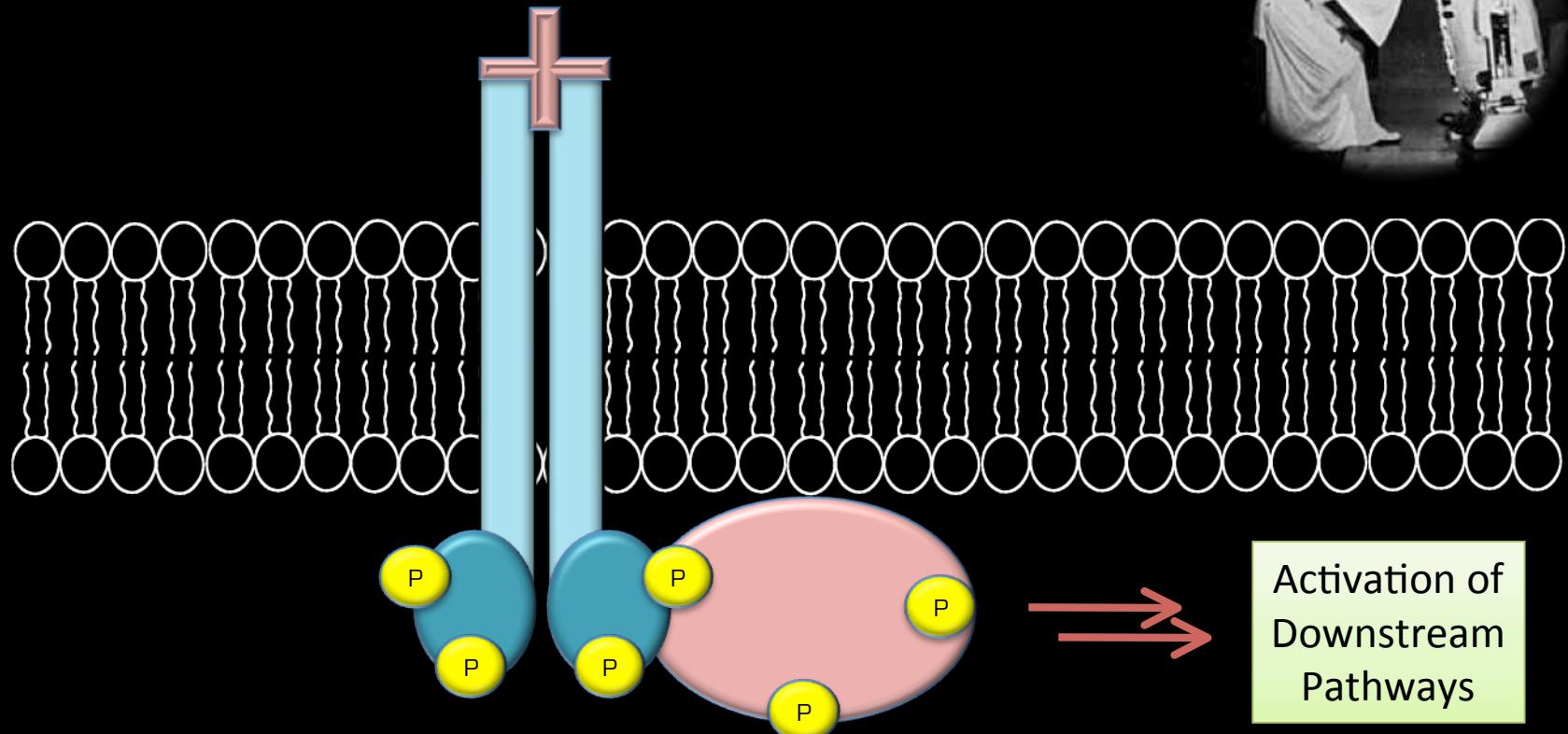


1. "Messages Gone Awry" - Tyrosine Kinases
2. "Loss of Regulation" - The Cell Cycle & p53
3. "Cancer Supply Lines" - Angiogenesis
4. "Radical Changes" - Role of Mitochondria & ROS
1. Summary

TYROSINE KINASES



↓ΥΤΡΟΣΙΝΕ ΚΙΝΑΣΕΣ



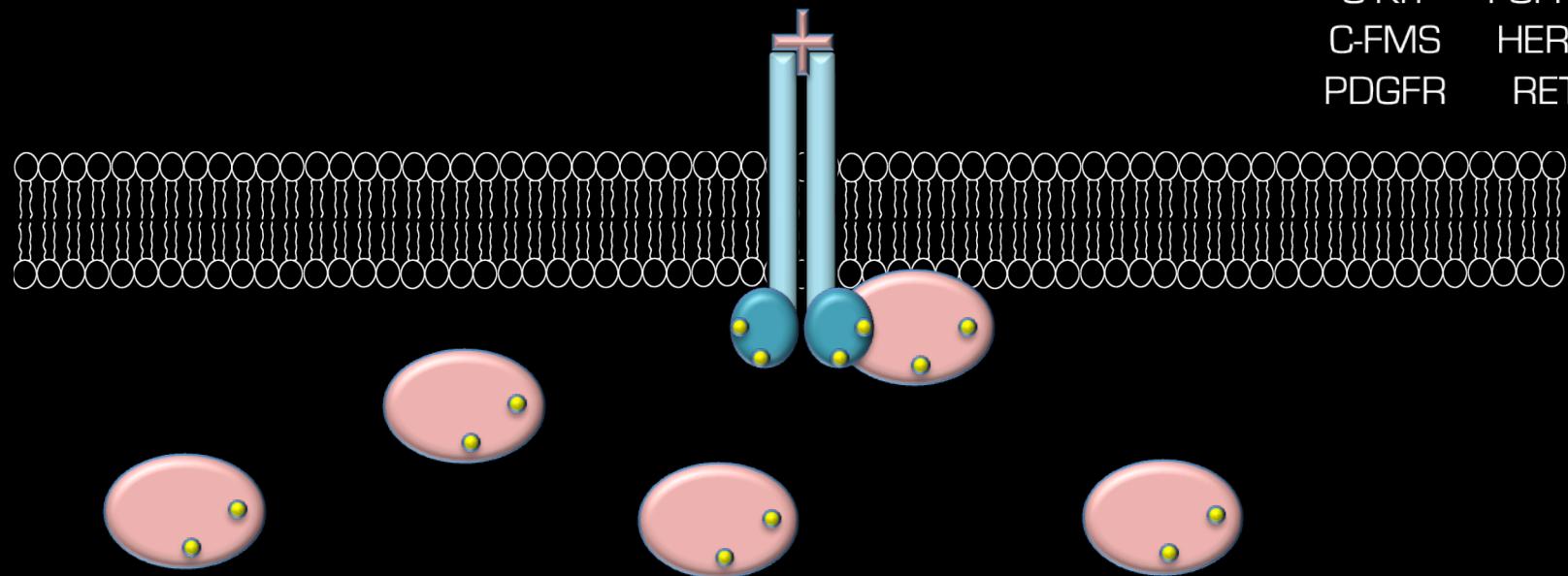
Receptor Tyrosine Kinase

TYROSINE KINASES



↓ΥΤΡΟΣΙΝΕ ΚΙΝΑΣΕΣ

FLT3	EGFR
C-KIT	FGFR3
C-FMS	HER2
PDGFR	RET



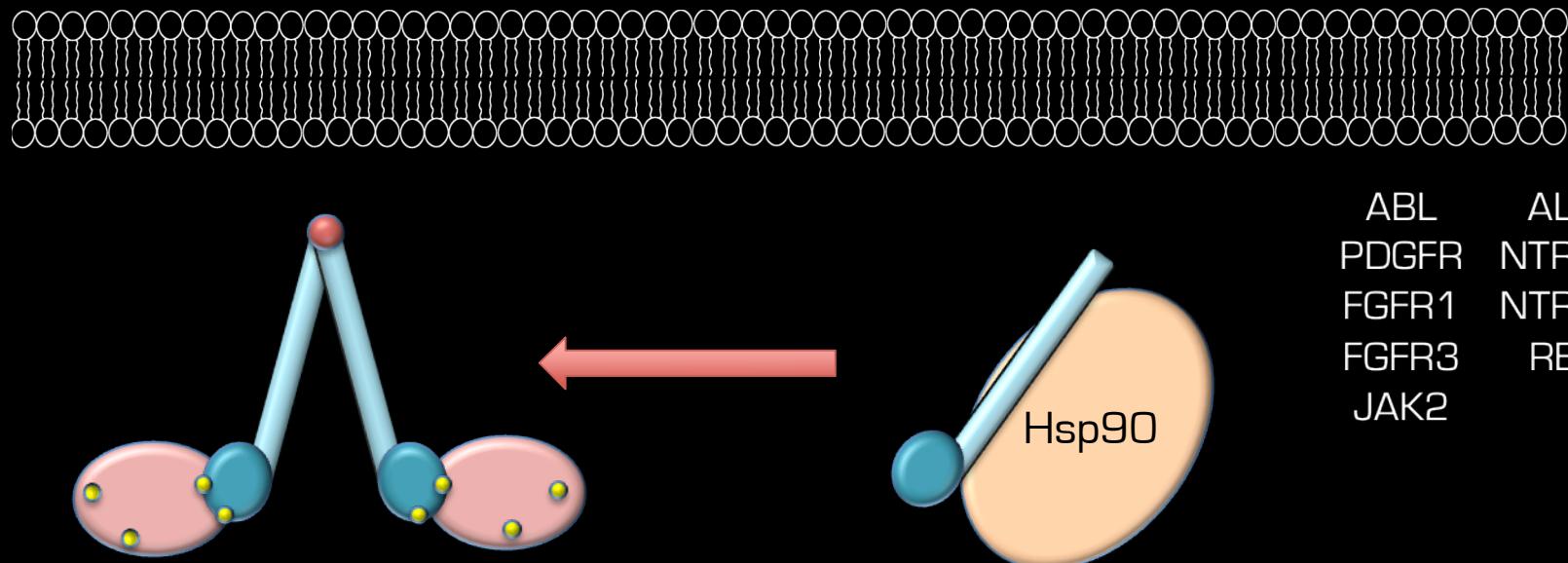
Constitutively Active Receptor Tyrosine Kinase

Krause, D.S.; Van Etten, R.A. *N. Engl. J. Med.* **2005**, 353, 172-187.

TYROSINE KINASES



↓ΥΤΡΟΣΙΝΕ ΚΙΝΑΣΕΣ
Tyrosine Kinases



ABL	ALK
PDGFR	NTRK1
FGFR1	NTRK3
FGFR3	RET
JAK2	

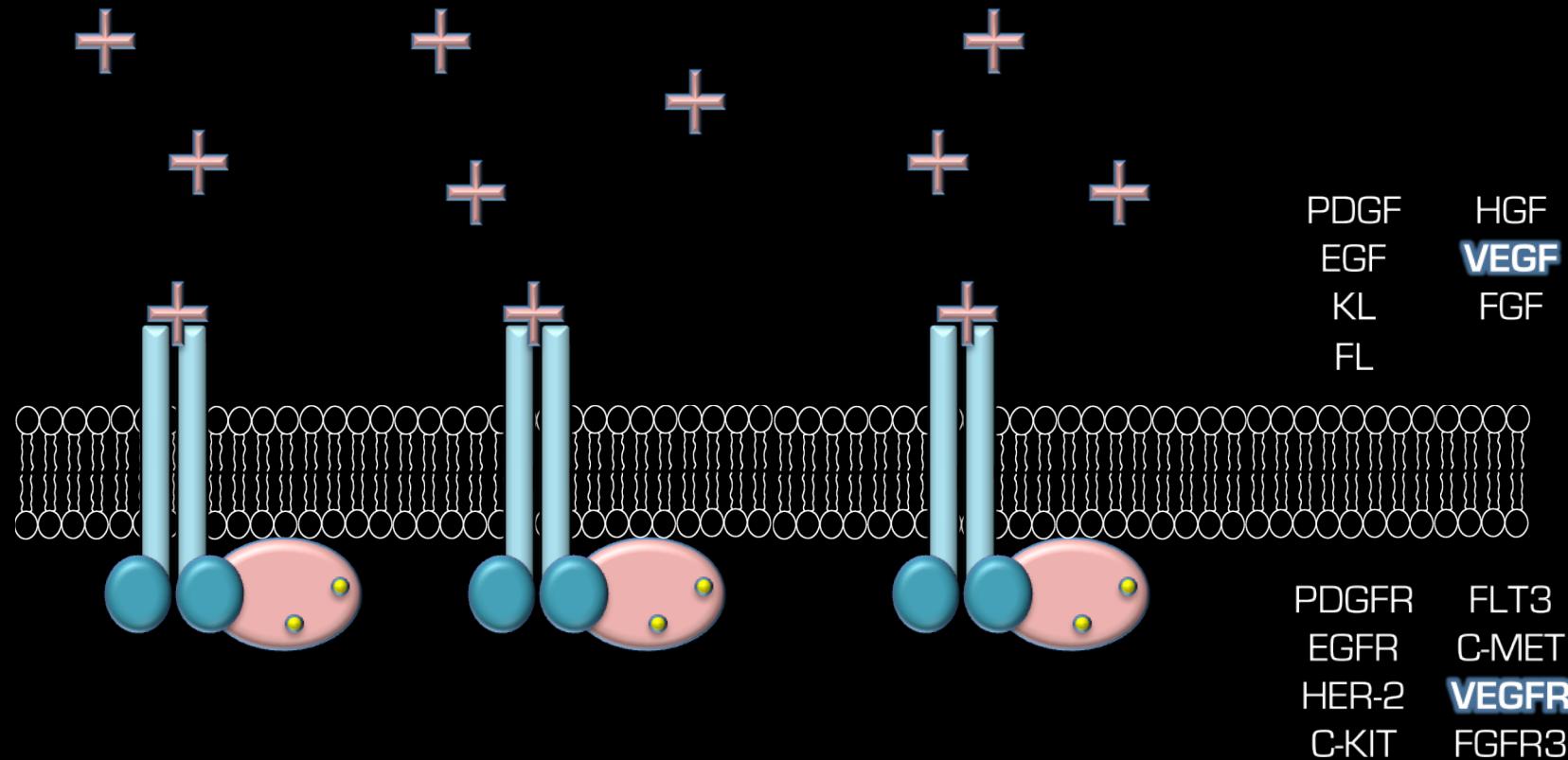
Fusion of Tyrosine Kinases to
Partner Proteins with Oligomerization

Krause, D.S.; Van Etten, R.A. *N. Engl. J. Med.* **2005**, 353, 172-187.

TYROSINE KINASES



↓ΥΤΡΟΣΙΝΕ ΚΙΝΑΣΕΣ



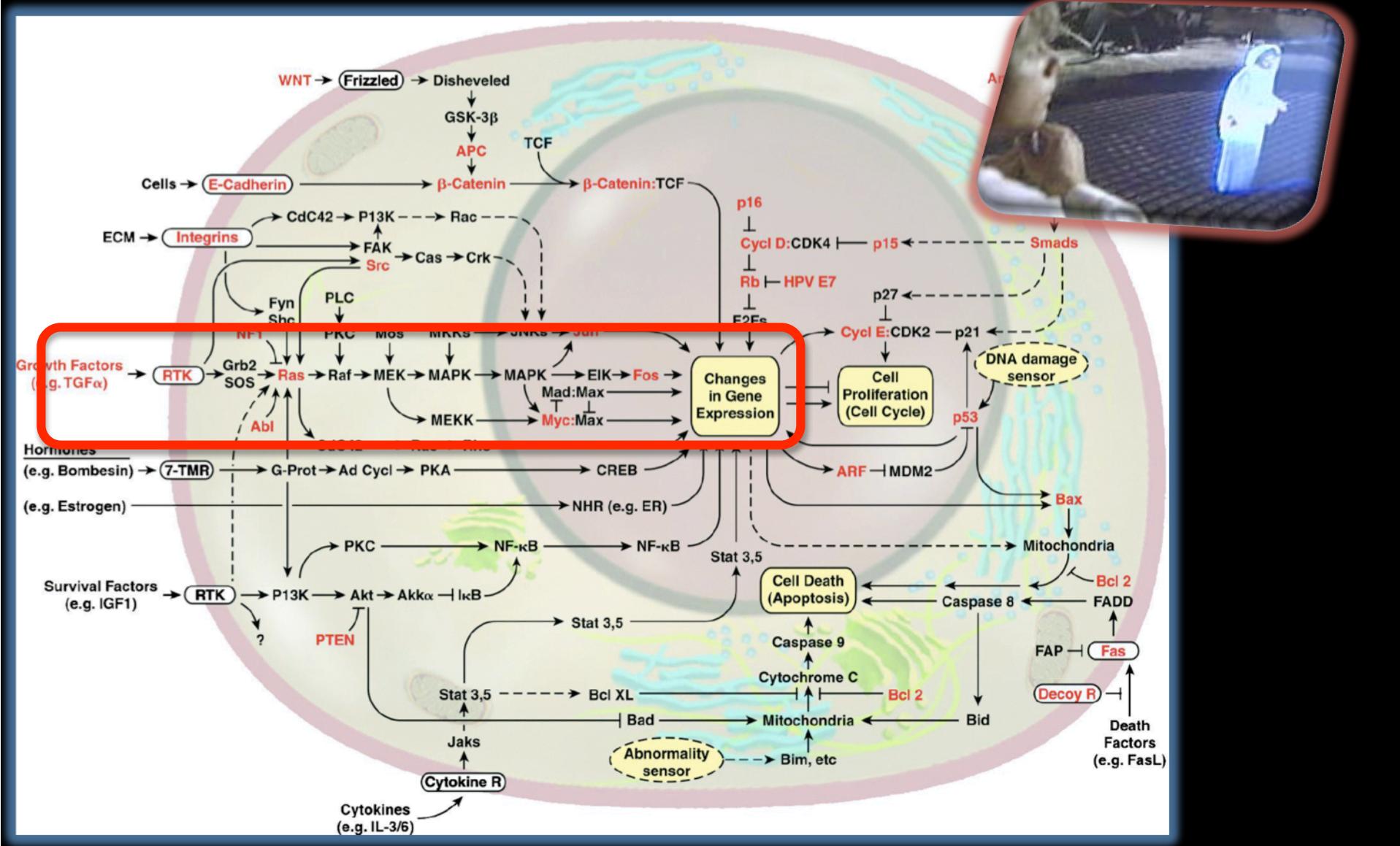
Overexpression of Receptor Tyrosine Kinase or Ligand

Krause, D.S.; Van Etten, R.A. *N. Engl. J. Med.* 2005, 353, 172-187.

DOWNSTREAM EVENTS



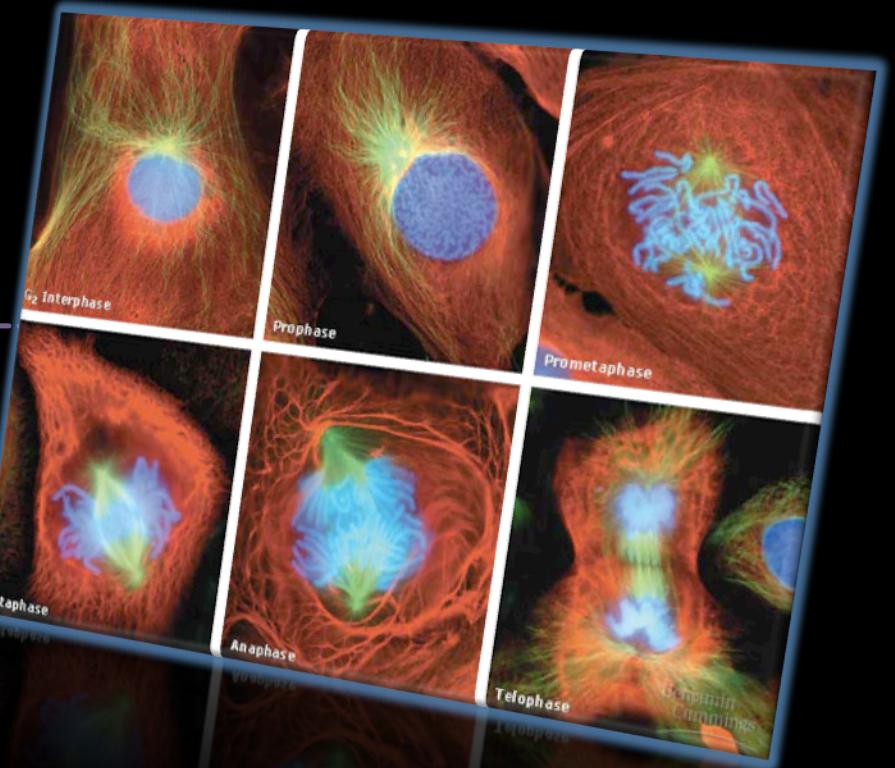
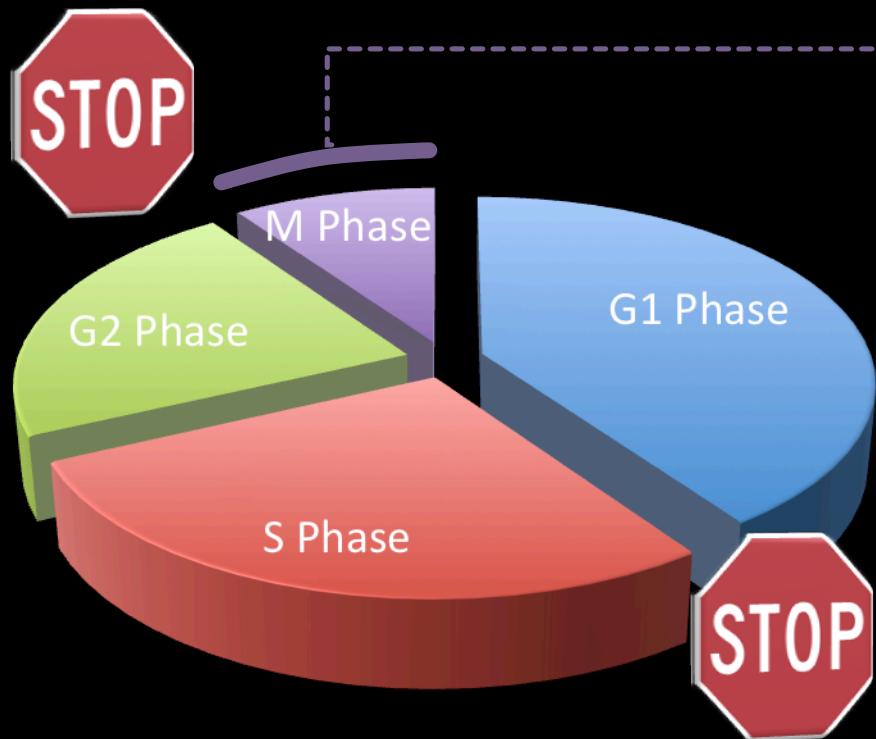
ଫୋନ୍‌ଟାଇପ୍‌ର ବିଭିନ୍ନ କମ୍ପ୍ୟୁଟର୍‌ଟାଇପ୍‌ରେ ଲାଗୁ ହେବାର ପାଇଁ





THE CELL CYCLE

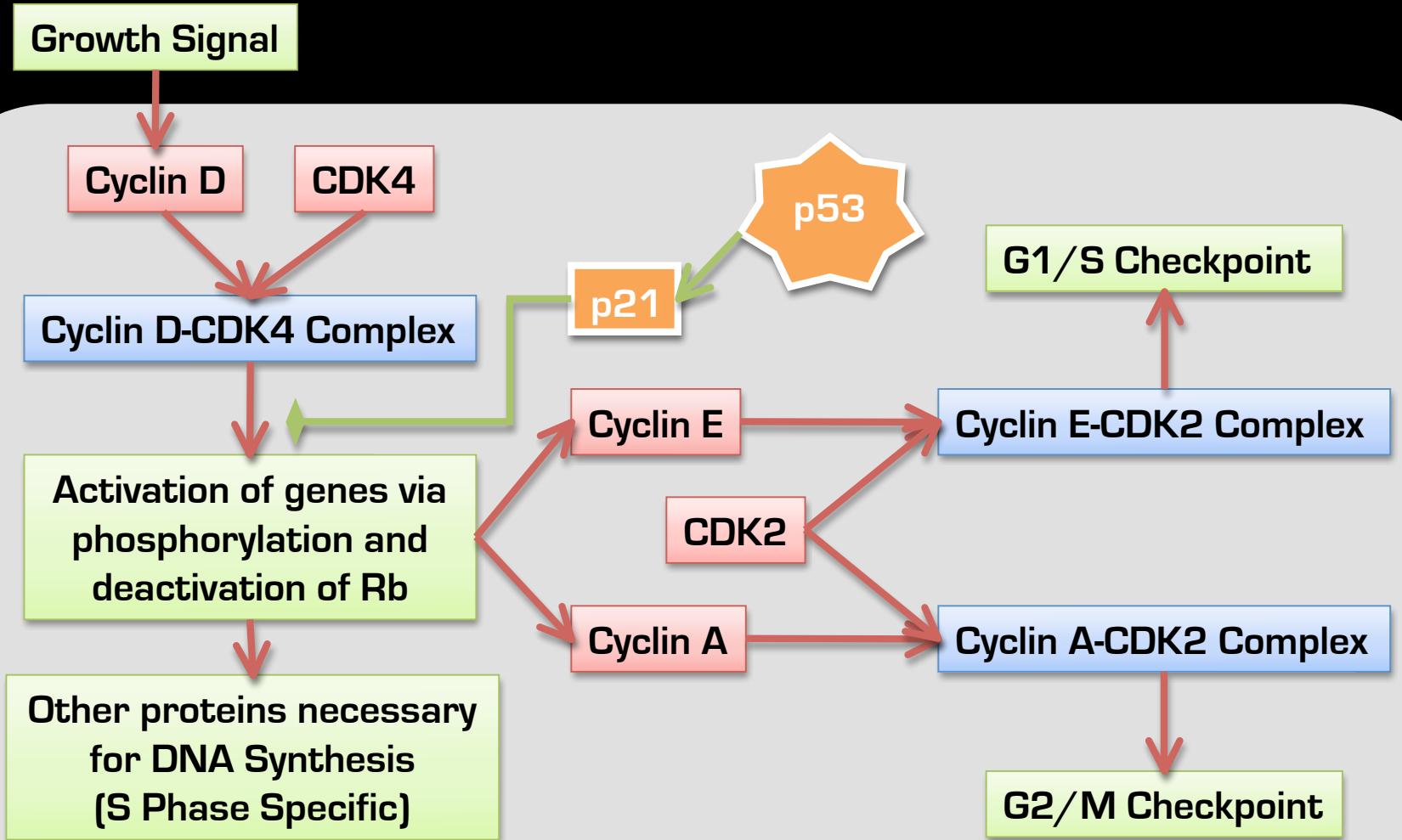
↓≡VI ↳VN VIVVN



CELL CYCLE REGULATION



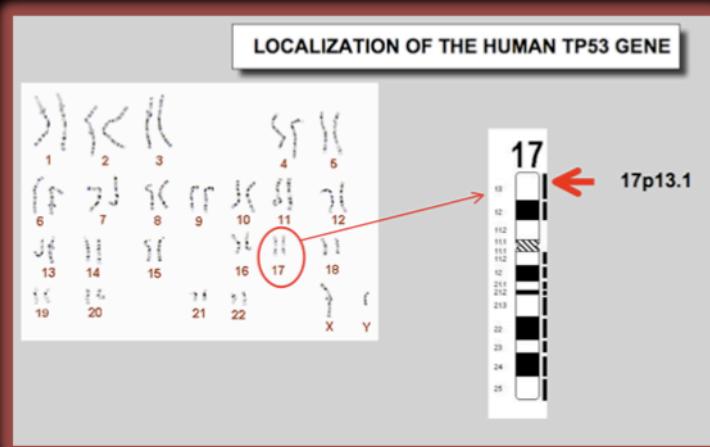
1. INTRODUCTION
2. CELL CYCLE REGULATORS
3. CYCLIN-CDK COMPLEXES
4. CHECKPOINTS
5. CONCLUDING REMARKS



MUTATIONS IN P53



◀◀◀◀◀ 1 ▶▶▶▶▶



Uncontrolled Cell Division

Li-Fraumeni Syndrome

Classical Tumors:

Breast Cancer
Osteosarcoma
Soft Tissue Sarcoma
Adrenocortical Carcinoma
Leukemia
Astrocytoma
Meningioma

Other Associated Tumors:

Gastric Cancer
Pharyngeal Cancer
Choroid Plexus Carcinoma
Pancreatic Cancer
Melanoma
Germ Cell Tumors
Wilm's Tumor
Colorectal Cancer
Ovarian Cancer
Thyroid Cancer
Endometrial Cancer
Prostate Cancer
Cervical Cancer

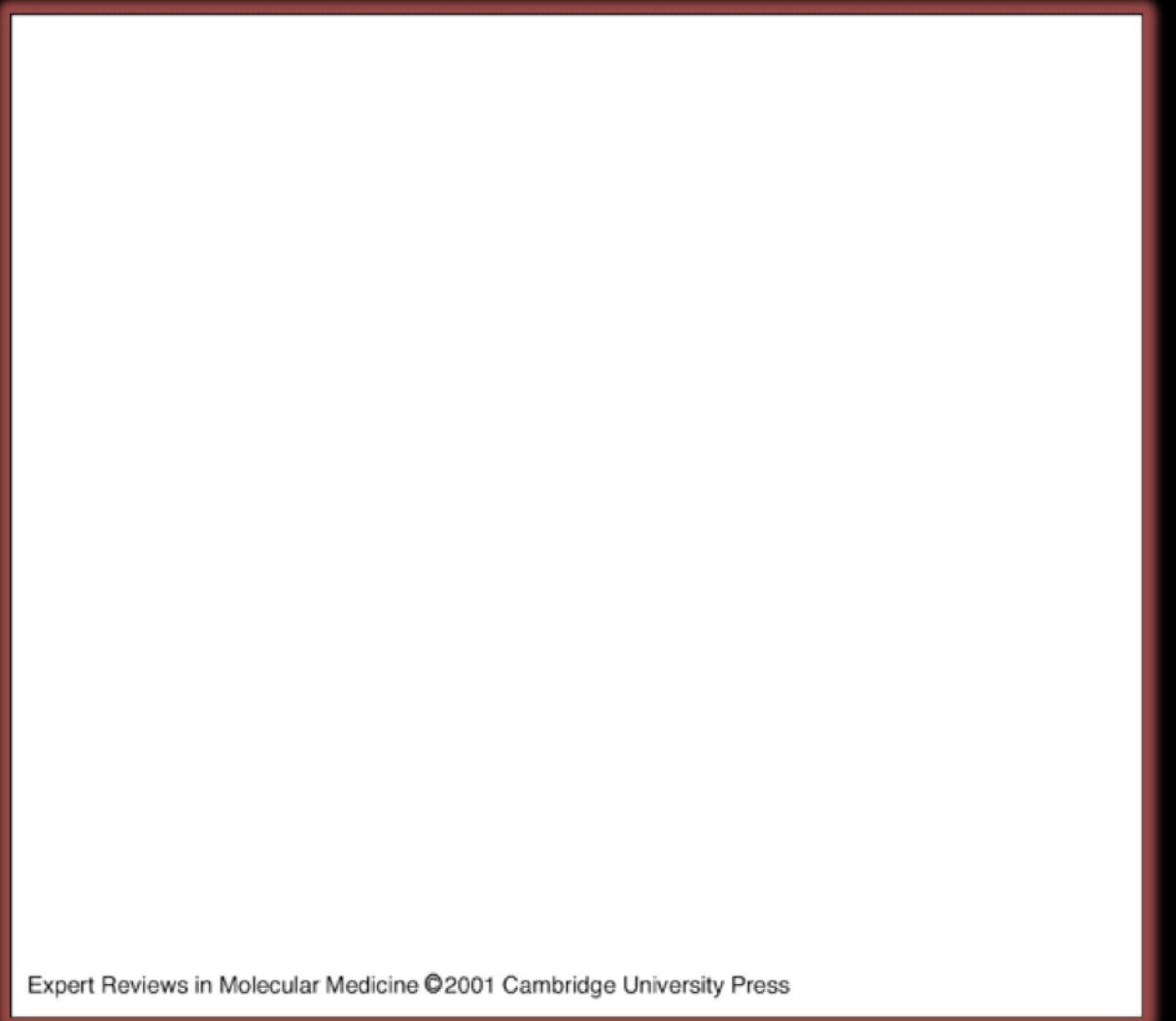
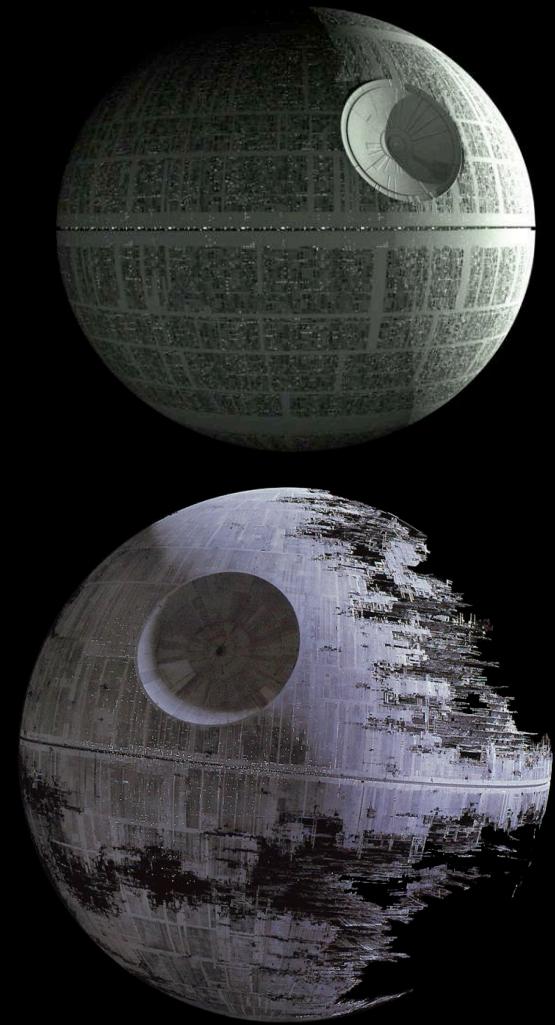


Li, F.P.; Fraumeni, Jr. J.F.; *Ann. Intern. Med.* **1969**, 71, 747-52.

Two-Hit Theory



↙□△-Ξ1↙ ↓ΞΜΔΖΥ



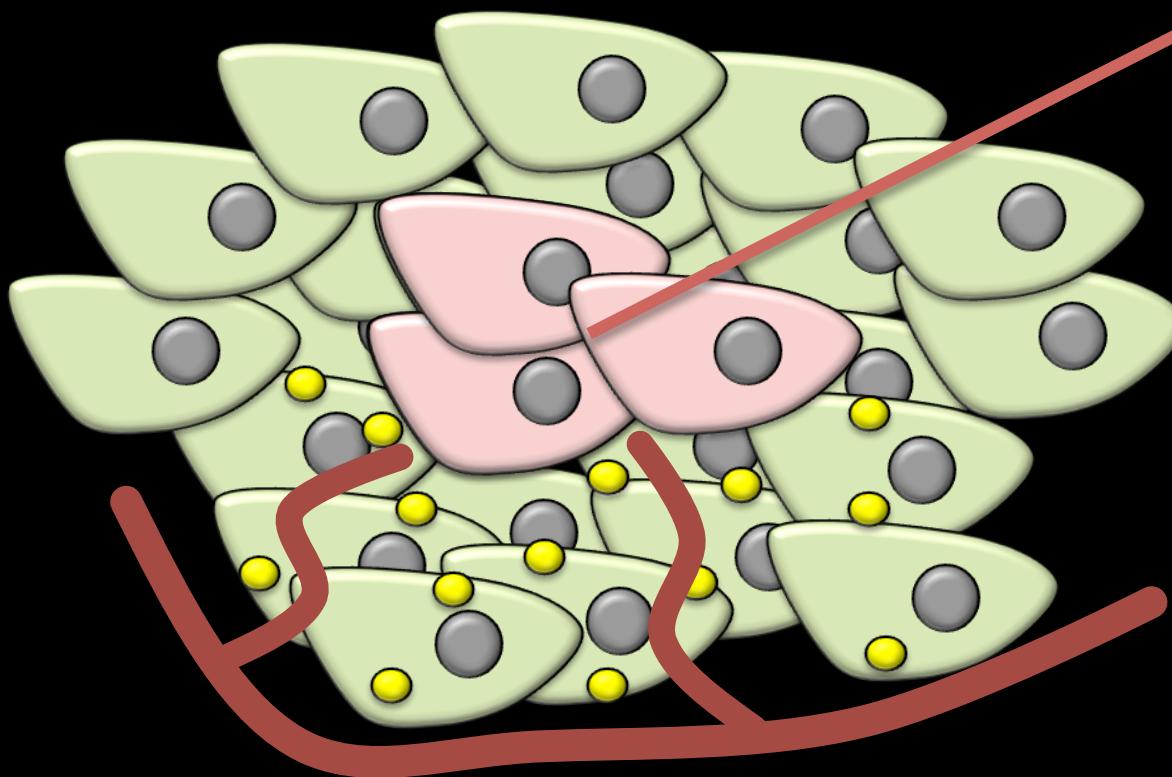
Expert Reviews in Molecular Medicine ©2001 Cambridge University Press

Nordling, C. *Br. J. Cancer* **1953**, 7, 68-72.
Knudson, A. *Proc. Natl. Acad. Sci. USA* **1971**, 68, 820-823.

ANGIOGENESIS



AKA D1D D7V1A V1A1N



Growing tumor isolates interior cells from blood supply

↑ HIF-1 α , HIF-2 α

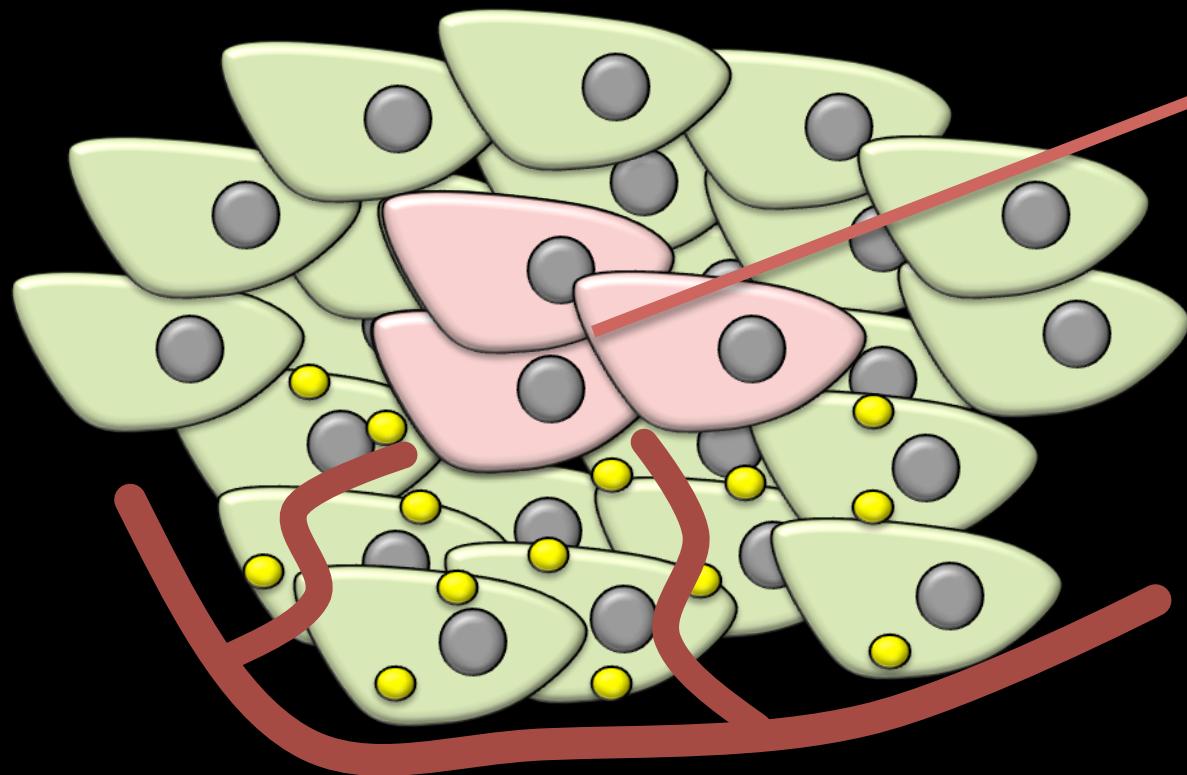
↑ VEGF

↑ Angiogenesis



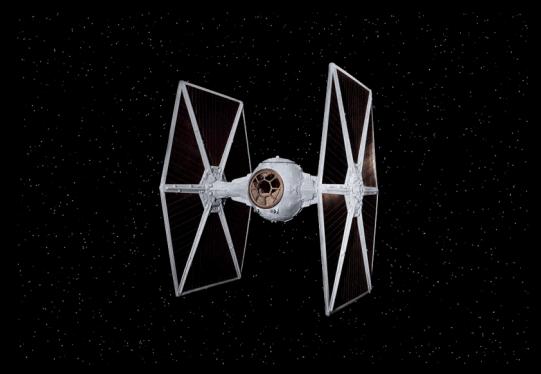
METASTASIS

CV_↓KVV_↓KVV1V



Hypoxic Cells Have
Three Options:

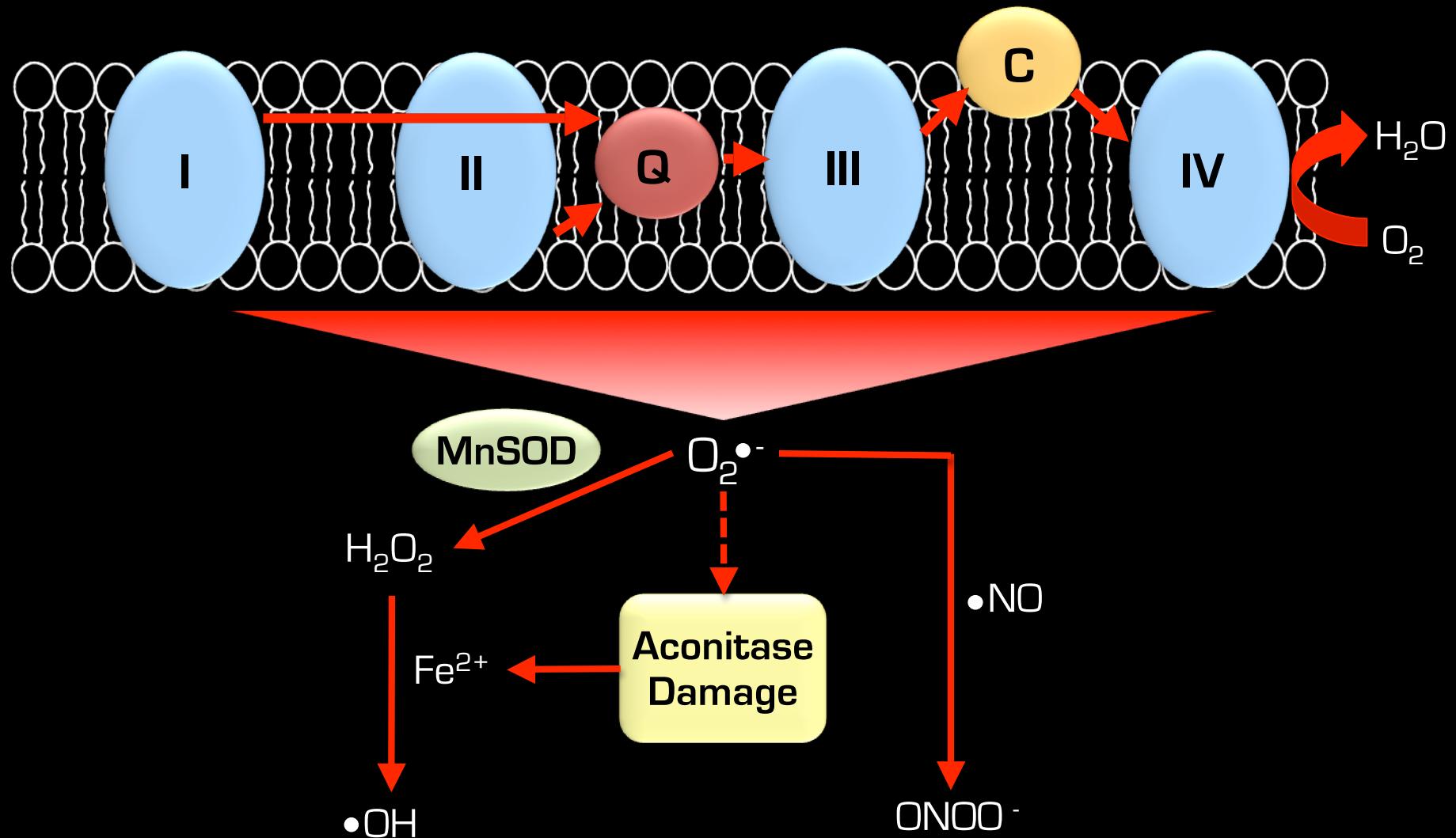
1. Apoptosis
2. Neoangiogenesis
3. Metastasis



MITO CONNECTION



L1↓ΔI↓ΔII↓ΔIII↓ΔIV



MTDNA CYBRIDS

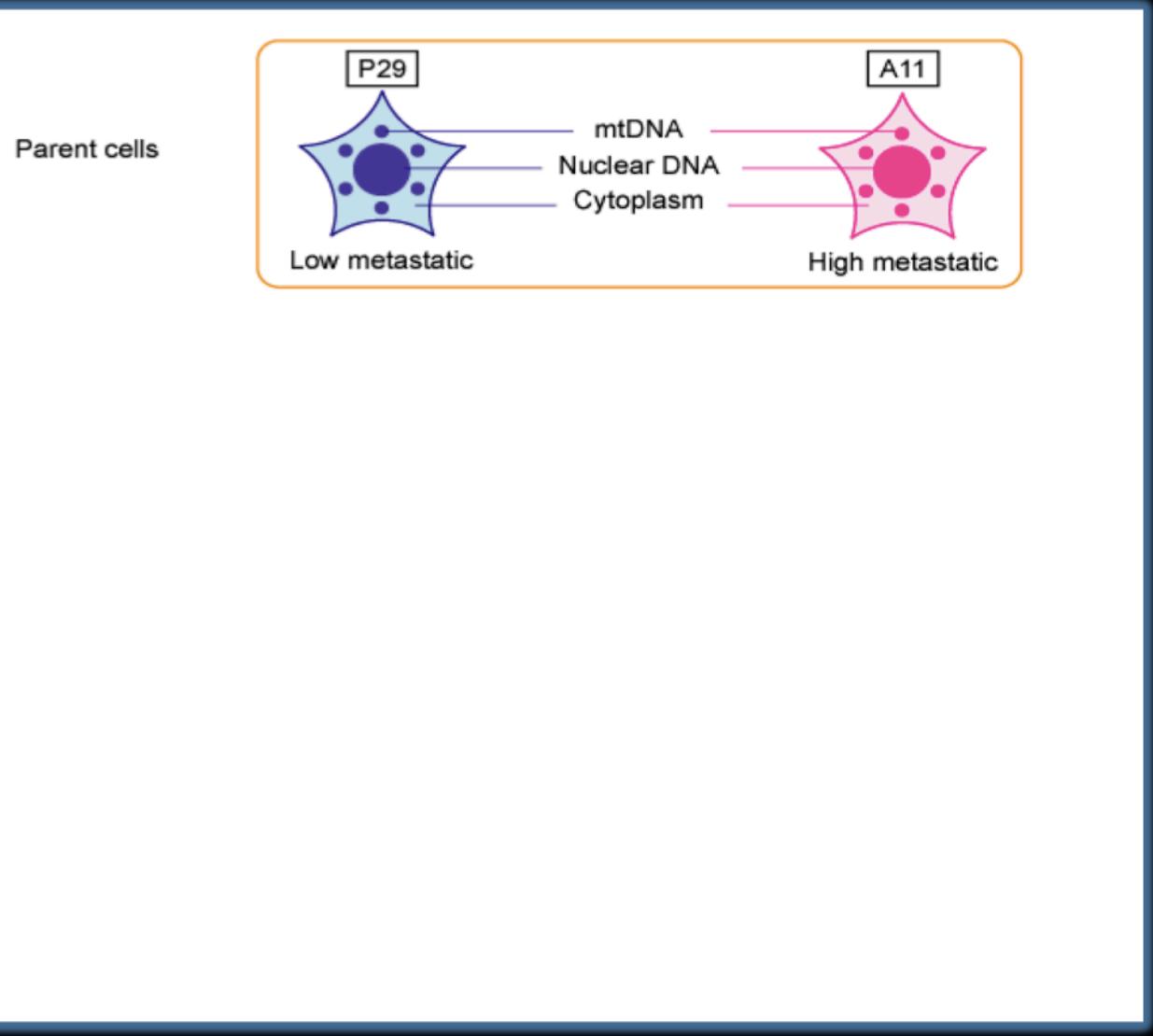


レーベル
リバティ

Lewis Lung
Carcinoma Cell Lines

P29: Low Metastatic
Potential

A11: High Metastatic
Potential

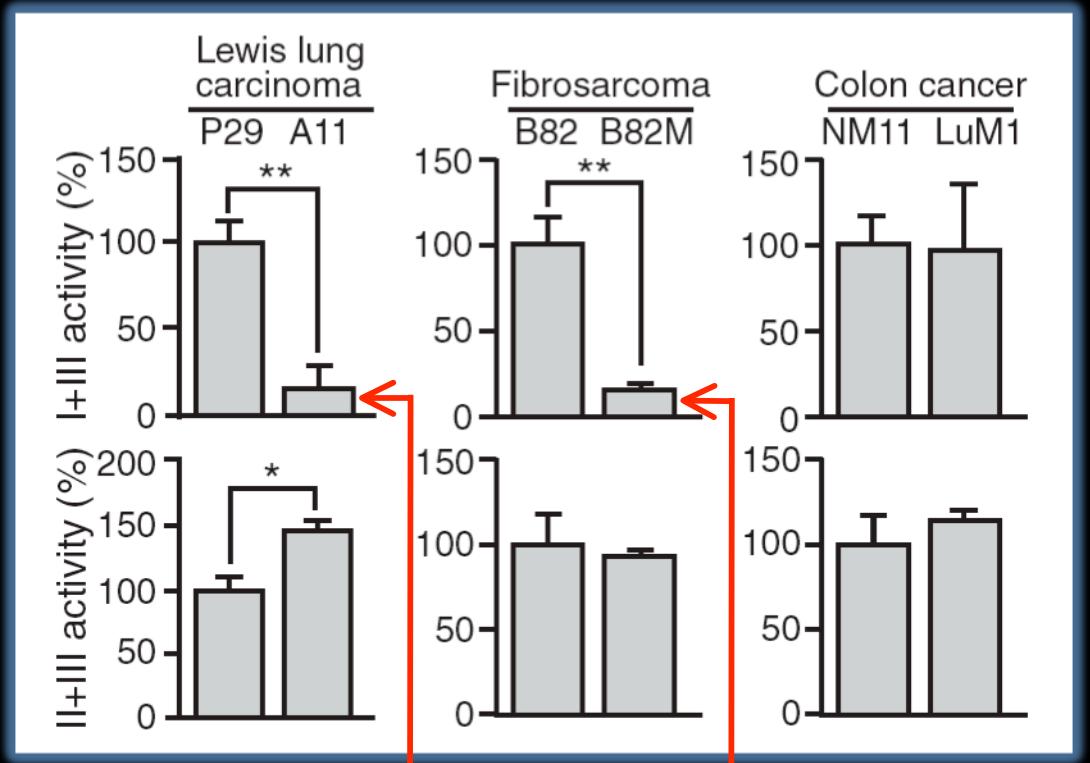
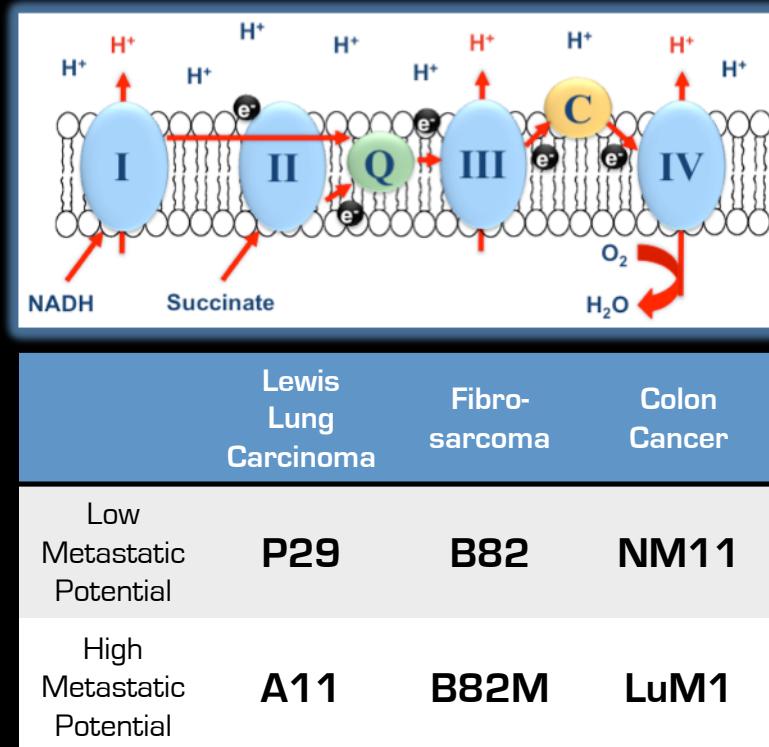


Ishikawa, K. et al. *Science* 2008, 320, 661-664.

ETC DEFECTS



VI ↓ II → VI + VII ↓ V



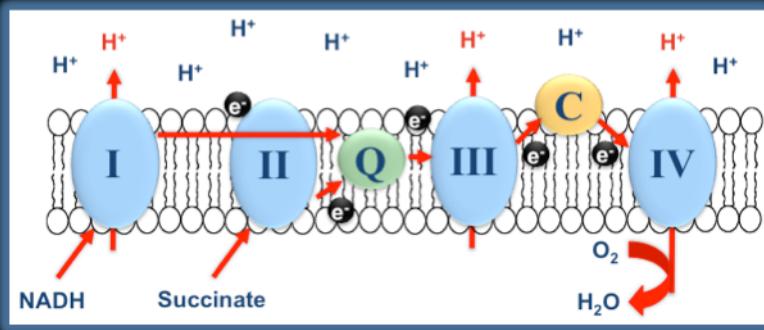
Defects in NADH Dehydrogenase

Ishikawa, K. et al. *Science* 2008, 320, 661-664.

ETC DEFECTS



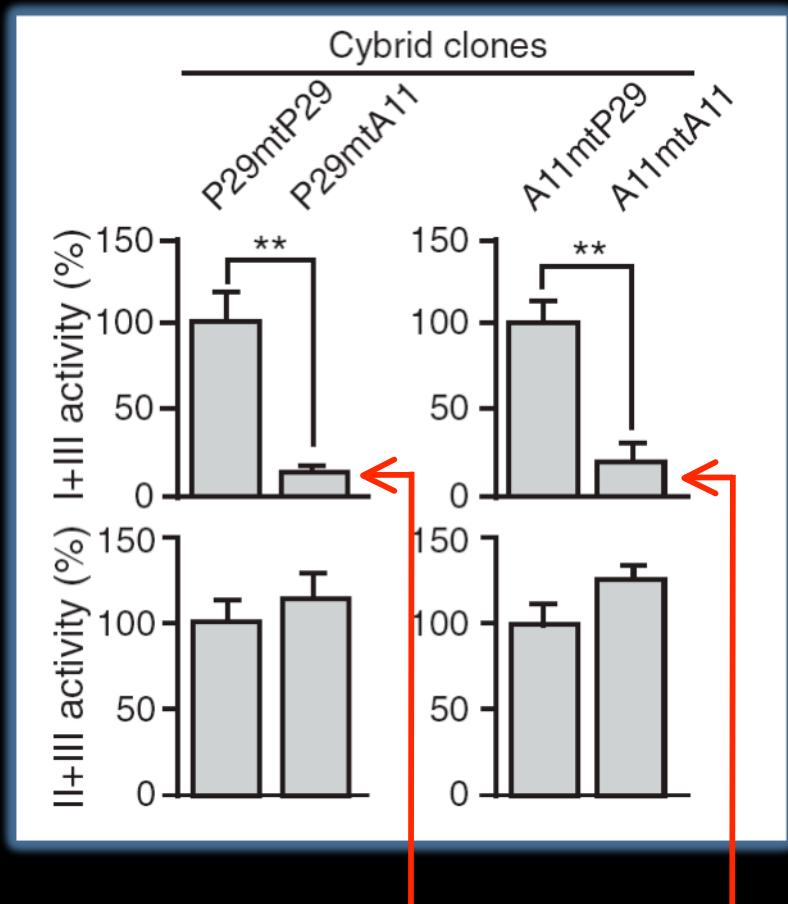
VI ↓ I II → VI + V I II ↓ IV



Lewis Lung Carcinoma Cell Lines

P29: Low Metastatic Potential & Normal ETC Function

A11: High Metastatic Potential & Decreased ETC Function



Defects in NADH Dehydrogenase

Ishikawa, K. et al. *Science* 2008, 320, 661-664.

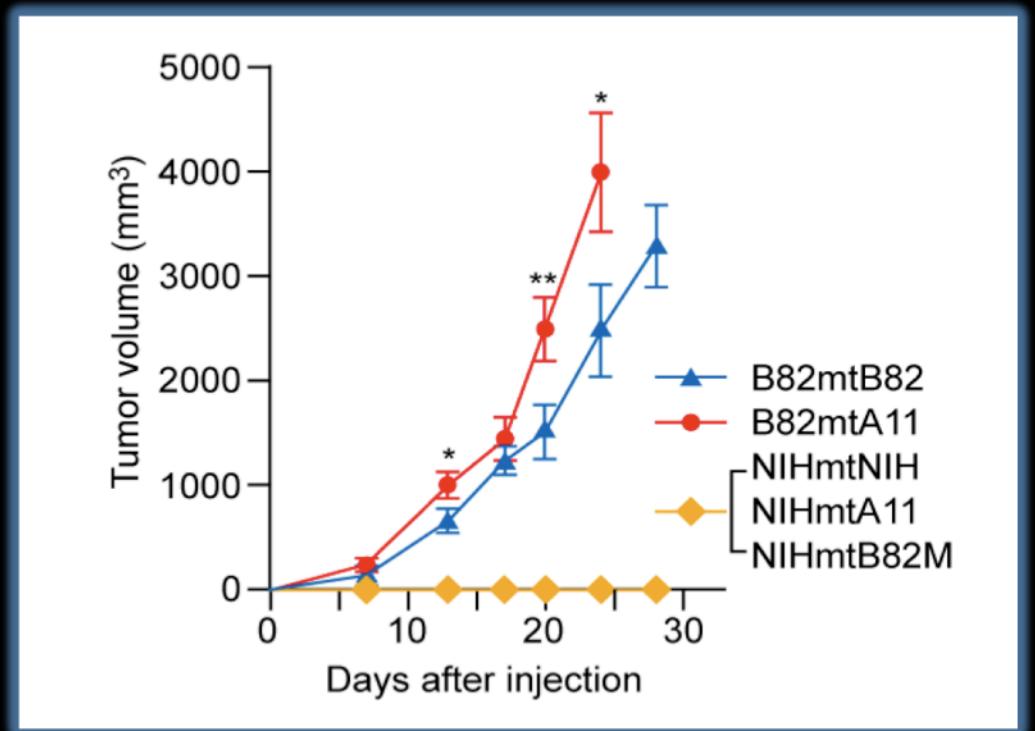
TUMOR GROWTH



↓LCD7 □77D□↓☰

Conclusion 1

ETC mutation accelerates growth of transformed cell lines, but does not control the development of tumorigenicity and metastasis in nontransformed cells.



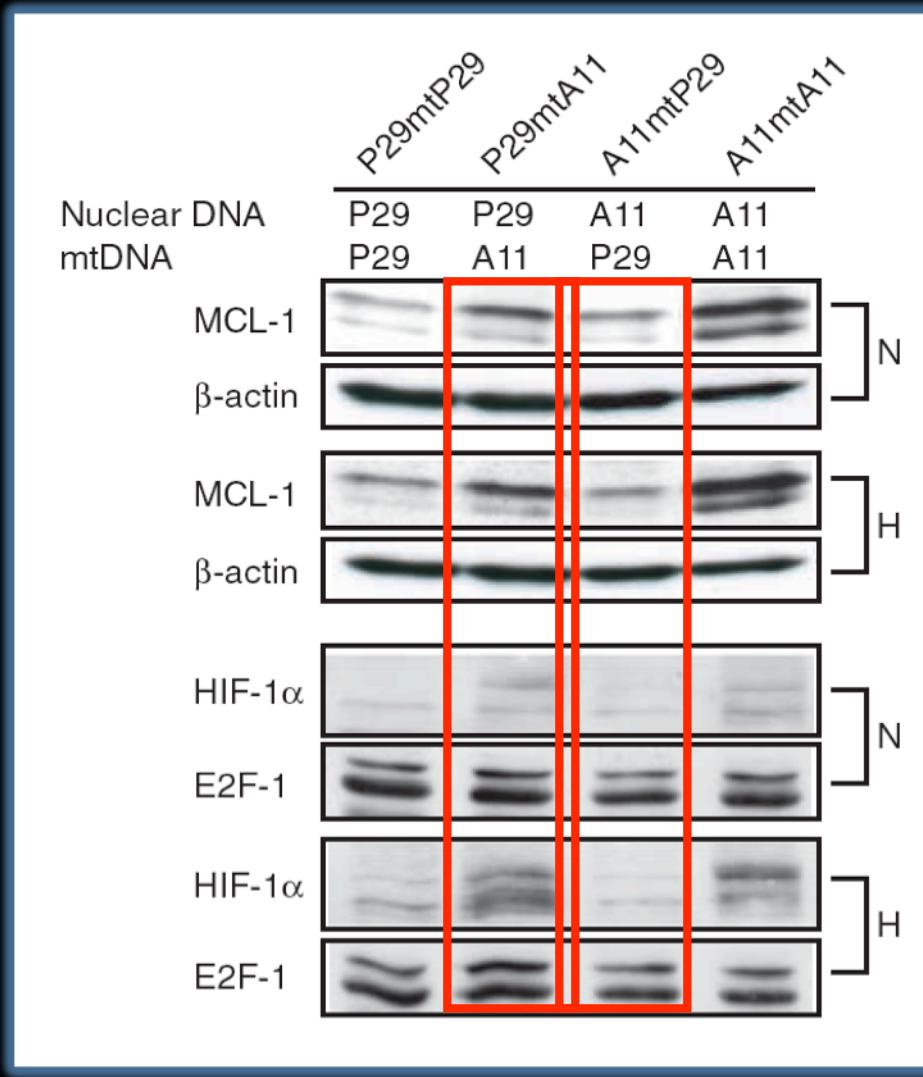
B82mtB82	Low Metastatic Fibrosarcoma	
B82mtA11	Cybrid w/ High Metastatic LLC	Accelerated Growth
NIHmtNIH	Nontransformed NIH3T3 Cells	No Growth
NIHmtA11	Cybrid w/ High Metastatic LLC	No Growth
NIHmtB82M	Cybrid w/ High Metastatic Fibrosarcoma	No Growth

Ishikawa, K. et al. *Science* 2008, 320, 661-664.

MUTATION COTRANSFER

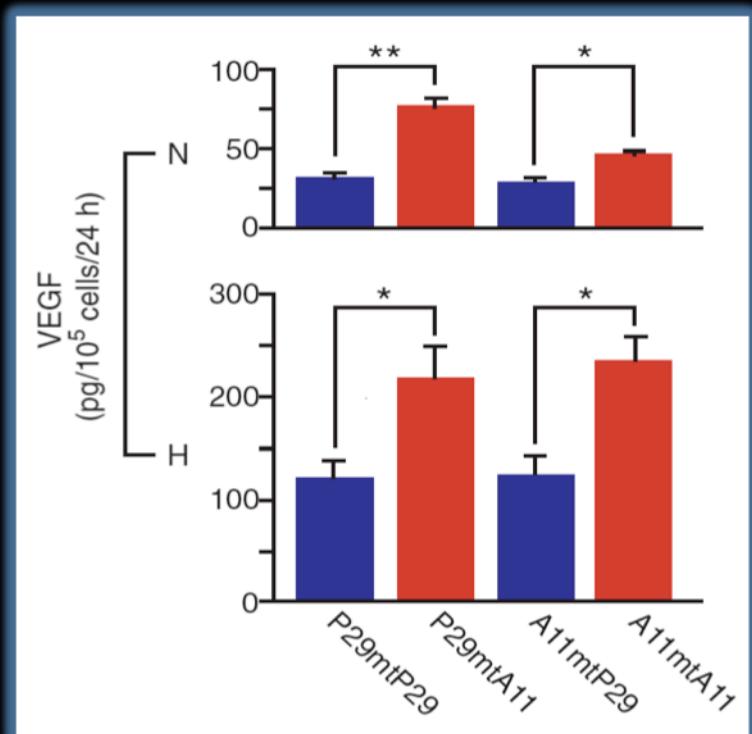


ETC mutation co-transfer and its biological effects



Conclusion 2

ETC mutation is co-transferred with an up-regulation of MCL-1, HIF-1 α , and VEGF.



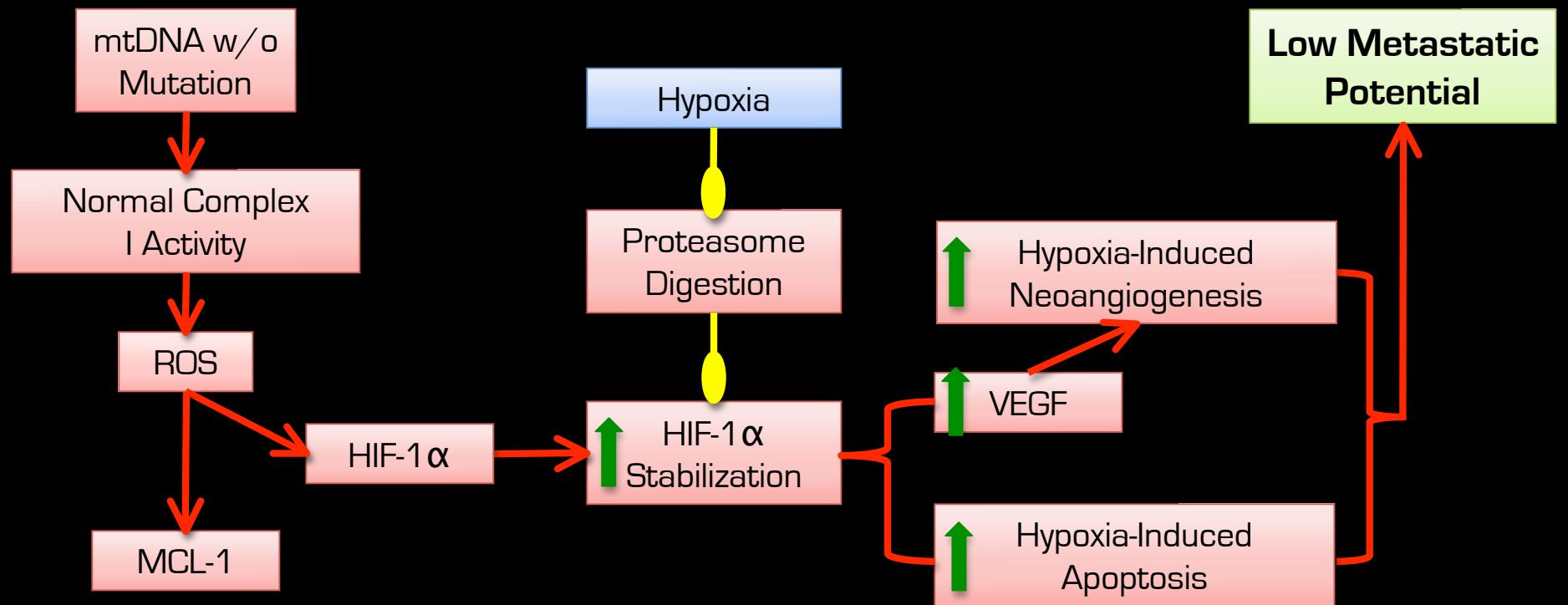
Ishikawa, K. et al. *Science* 2008, 320, 661-664.

POSTULATED PATHWAY



Downstream
Upstream

P29mtP29 & A11mtP29 Cybrids – Low Metastatic Potential



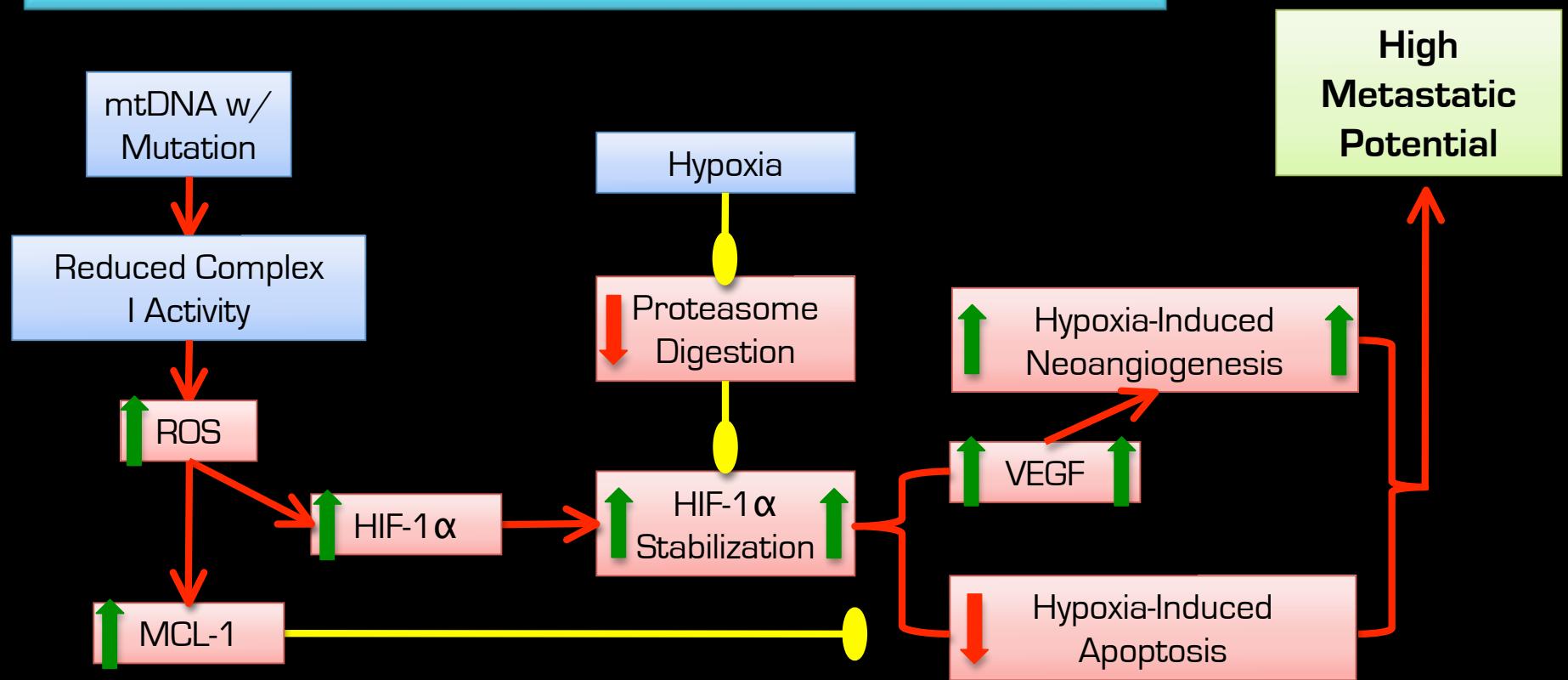
Ishikawa, K. et al. *Science* 2008, 320, 661-664.

POSTULATED PATHWAY



Downstream
Upstream

P29mtA11 & A11mtA11 Cybrids – High Metastatic Potential

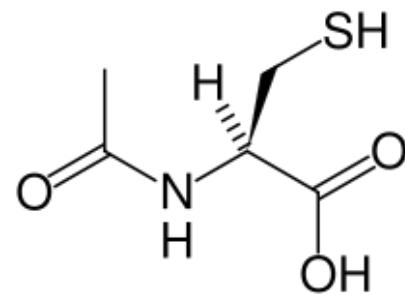
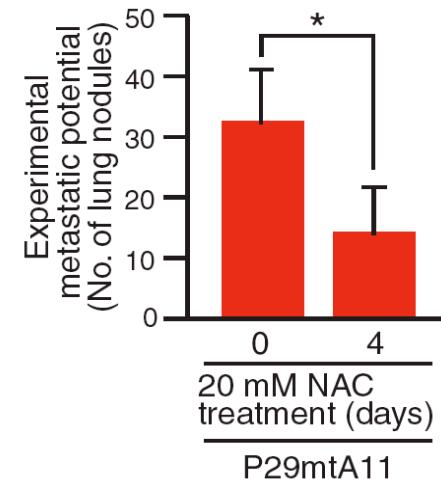
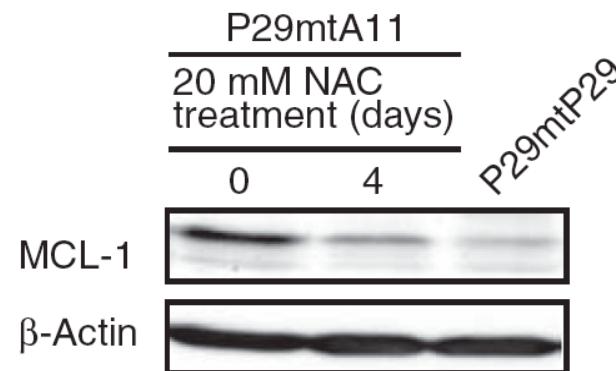
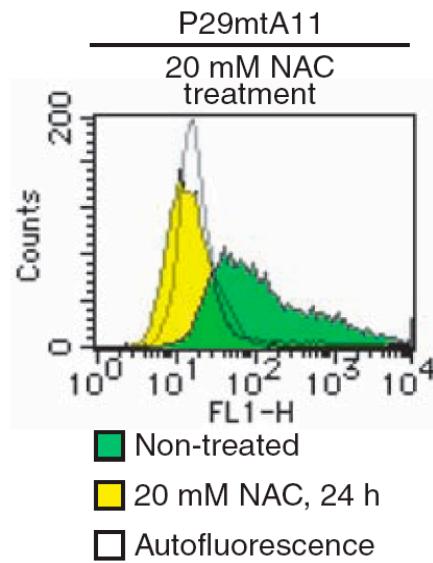


Ishikawa, K. et al. *Science* 2008, 320, 661-664.

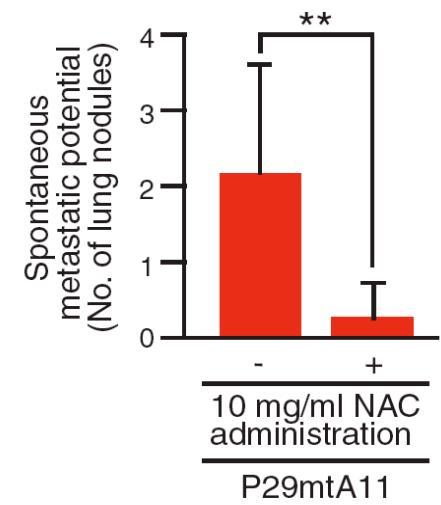
ROS SCAVENGERS



7ΩΝ ΝΙΚΥΜΑ ΙΖΜΙΖΝ



N-Acetylcysteine (NAC)



Ishikawa, K. et al. *Science* 2008, 320, 661-664.

<http://marionvandewiel.blogspot.com/2008/04/i-recently-joined-new-forum-toonweekly.html>

SUMMARY

LOCK7V



1. Tyrosine kinases are a target for cancer therapies, as they provide the “first hit” allowing transformation to a cancer phenotype; they are dysregulated in a variety of cancers.
2. Mutations in p53 provide the “second hit” allowing transformation to a cancer phenotype; uncontrolled cell cycling leads to tumor growth.
3. As a tumor grows, interior cells are isolated from blood vessels, nutrients, and oxygen; hypoxia is a prognostic factor for metastasis.
4. Metastasis is regulated by ROS-mediated reversible up-regulation of nuclear genes, such as MCL-1, HIF-1 α , and VEGF, especially under hypoxic conditions.
5. ROS Scavengers may be therapeutically effective in suppressing metastasis – i.e.: mitochondrial-targeted hemigramicidin?

CANCER WARS

THE METASTASIS STRIKES BACK



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