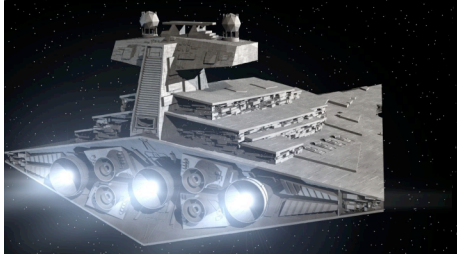
Cancer Wars

The Metastasis Strikes Back



Amir H. Faraji

31.05.2008

Plan of Attack

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

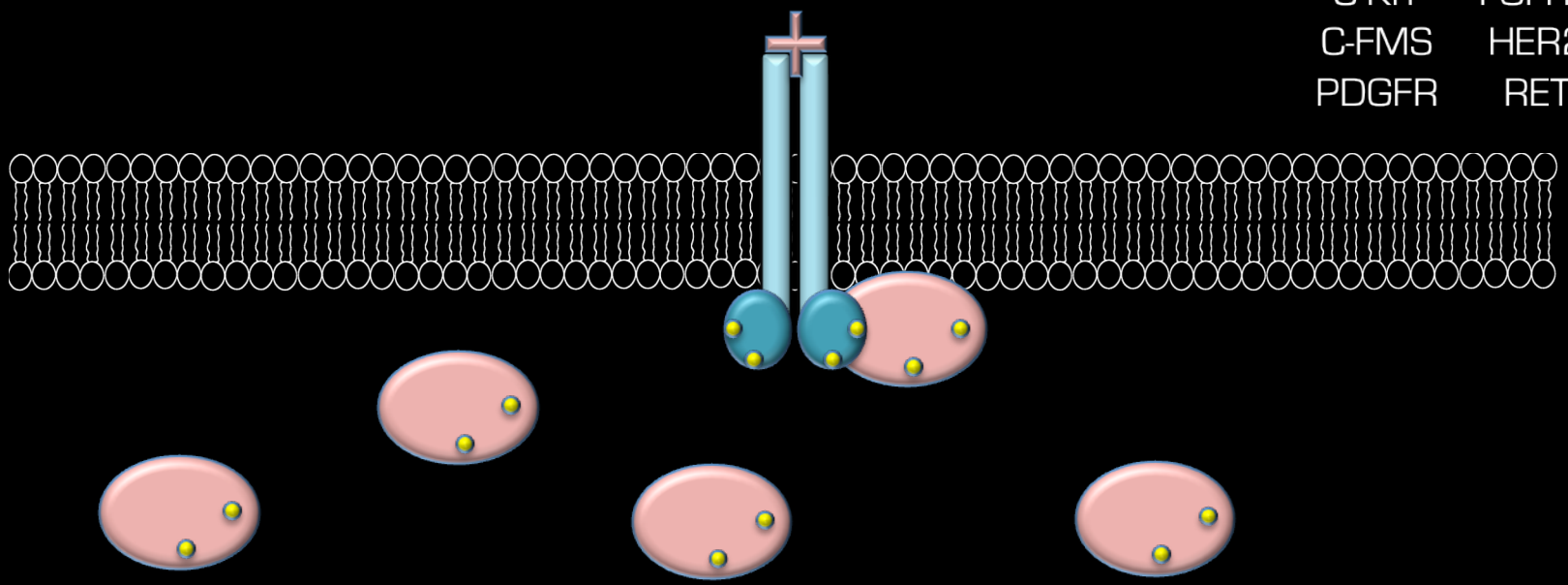
1. Summary

Tyrosine Kinases

Receptor Tyrosine Kinase

Tyrosine Kinases

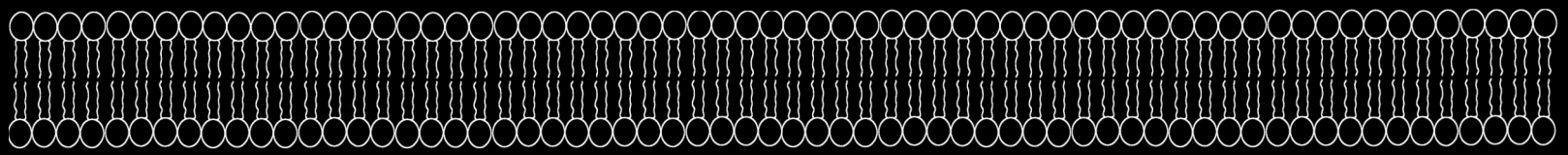
FLT3
C-KIT
C-FMS
PDGFR
EGFR
FGFR3
HER2
RET

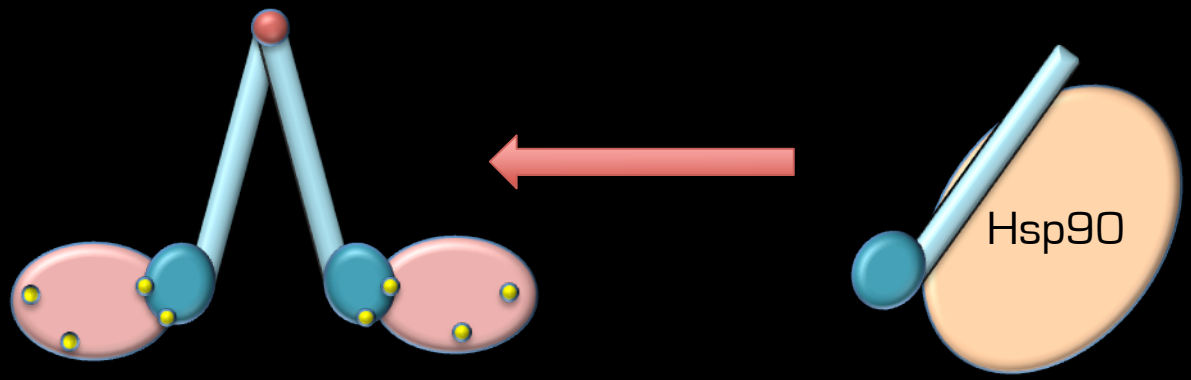


Constitutively Active Receptor Tyrosine Kinase

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

Tyrosine Kinases



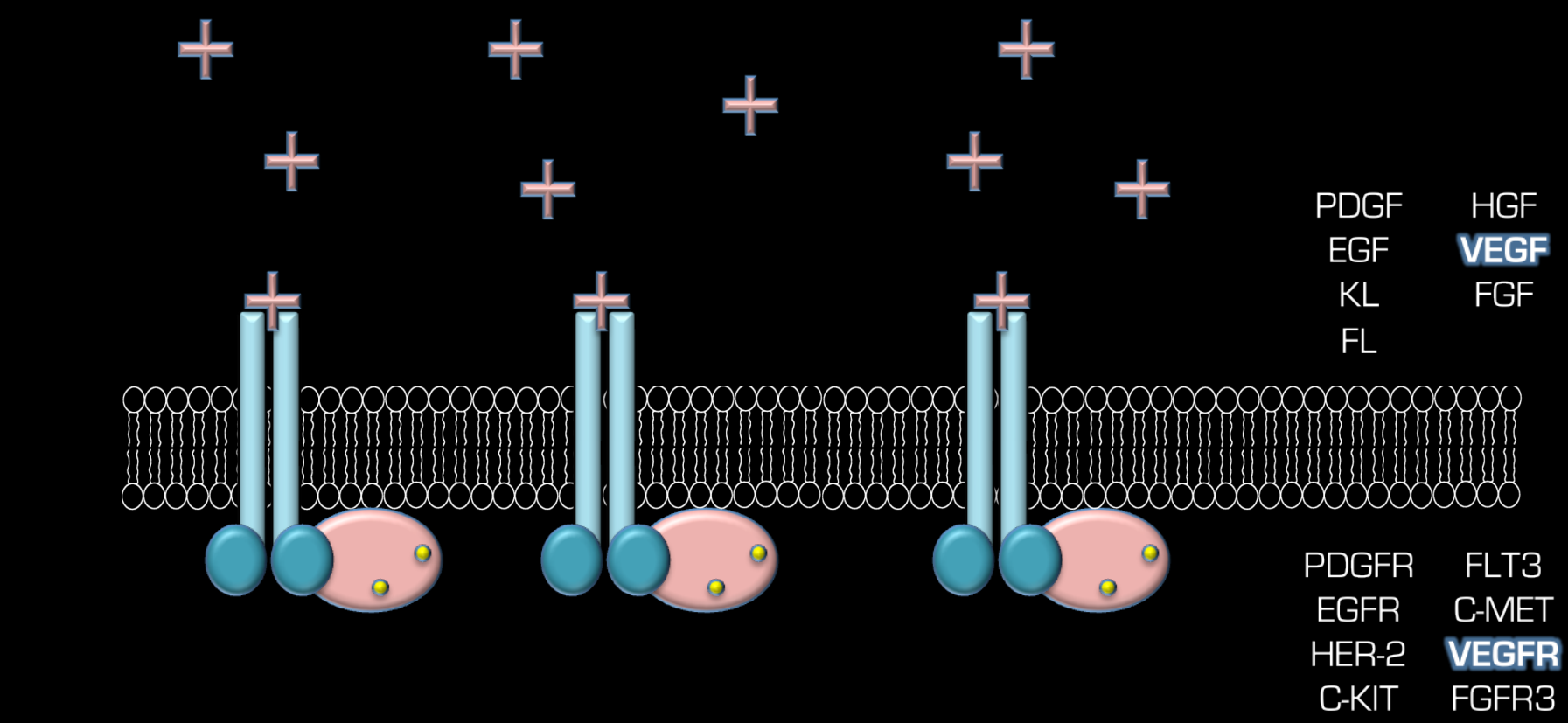


ABL
PDGFR
FGFR1
FGFR3
JAK2
ALK
NTRK1
NTRK3
RET

Fusion of Tyrosine Kinases to Partner Proteins with Oligomerization

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

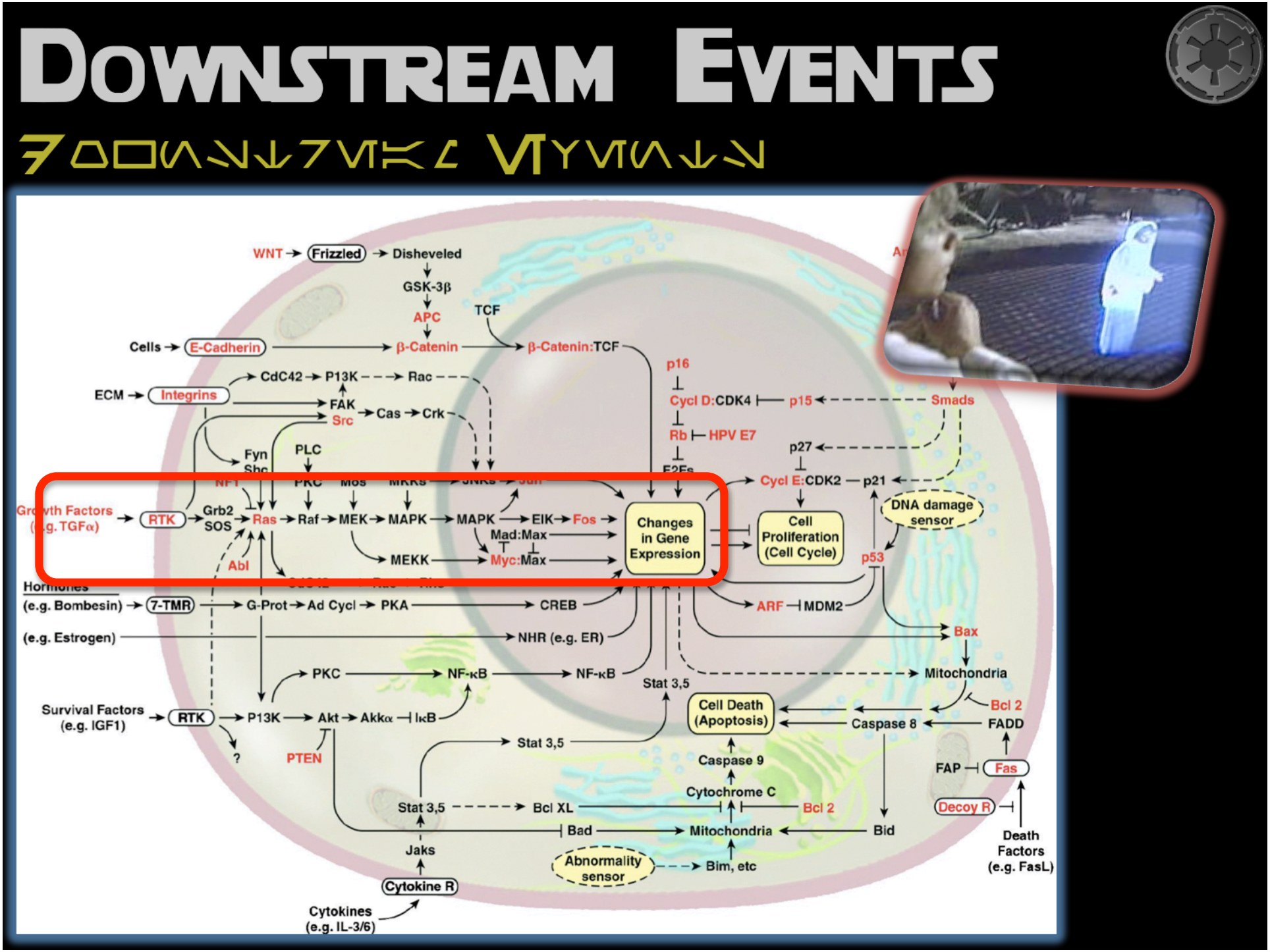
Tyrosine Kinases



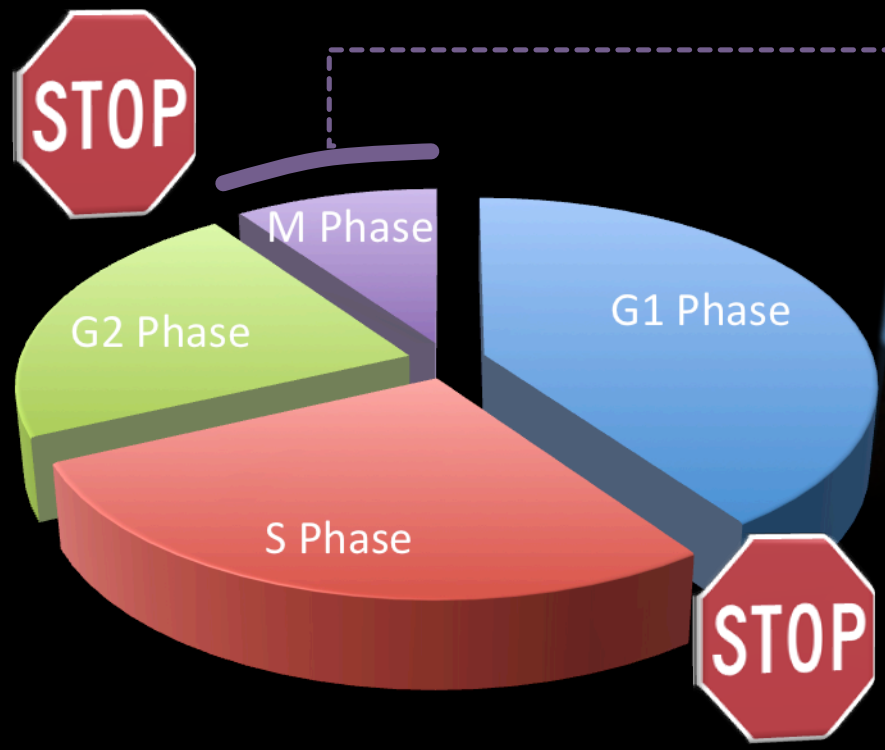
Overexpression of Receptor Tyrosine Kinase or Ligand

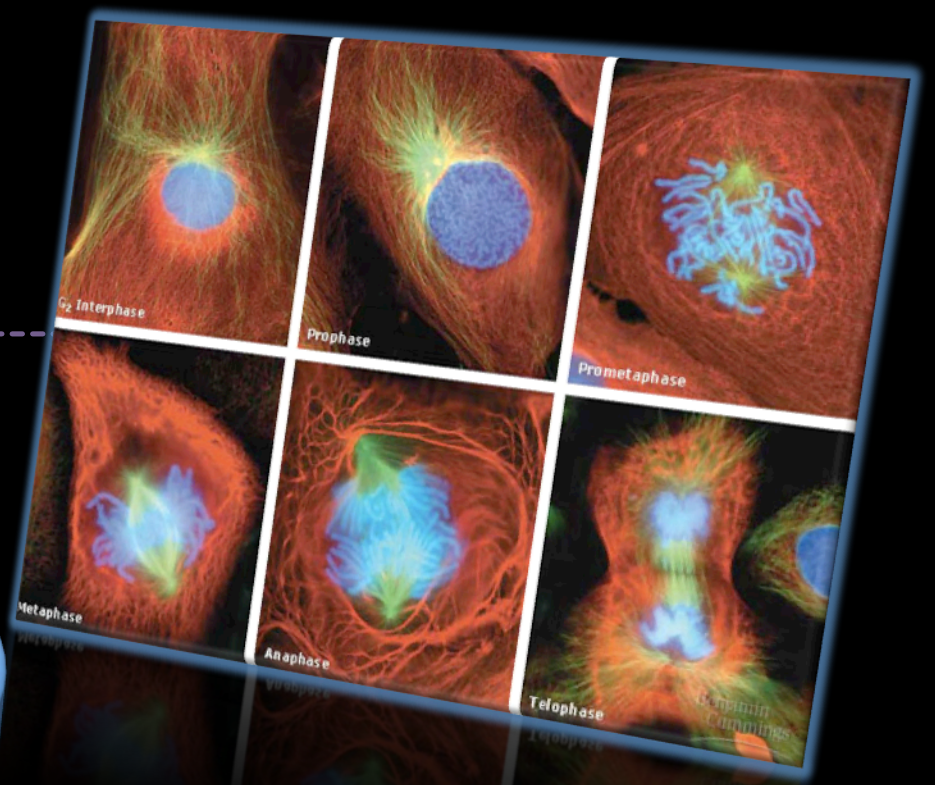
Krause, D.S.; Van Etten, R.A. *N. Engl. J. Med.* **2005**, 353, 172-187.

Downstream Events

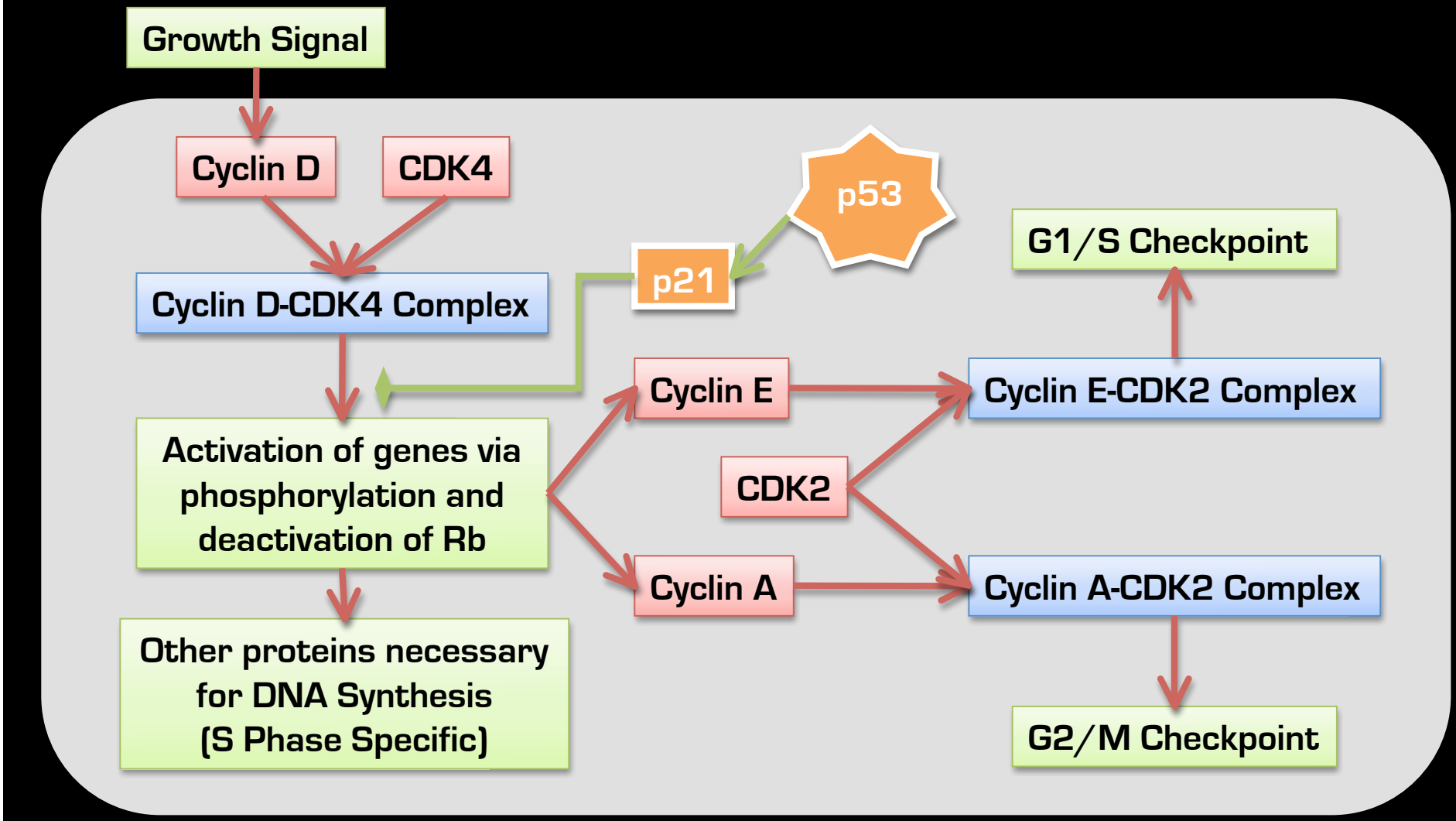


The Cell Cycle

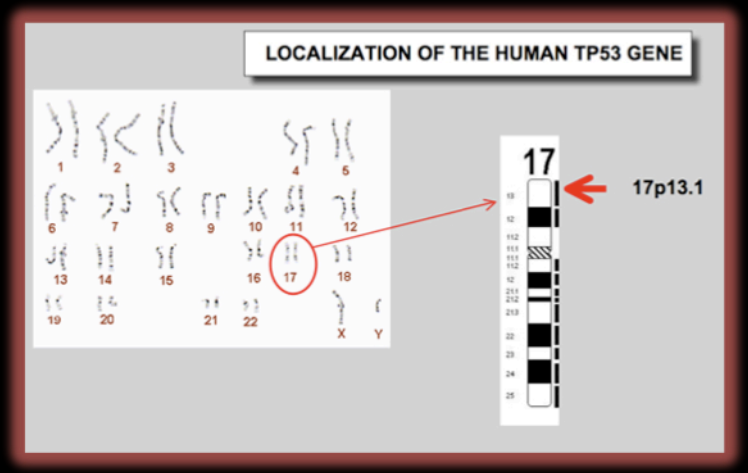




Cell Cycle Regulation



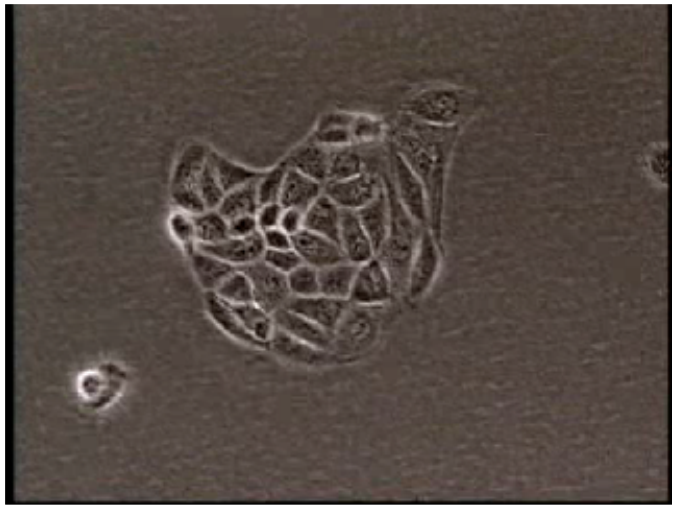
Mutations in p53



Li-Fraumeni Syndrome

Classical Tumors:
- Breast Cancer
- Osteosarcoma
- Soft Tissue Sarcoma
- Adrenocortical Carcinoma
- Leukemia
- Astrocytoma
- Meningioma

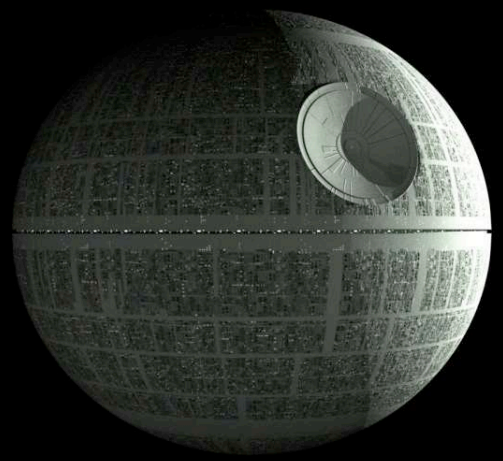
Other Associated Tumors:
- Gastric Cancer
- Pharyngeal Cancer
- Choroid Plexus Carcinoma
- Pancreatic Cancer
- Melanoma
- Germ Cell Tumors
- Wilm's Tumor
- Colorectal Cancer
- Ovarian Cancer
- Thyroid Cancer
- Endometrial Cancer
- Prostate Cancer
- Cervical Cancer

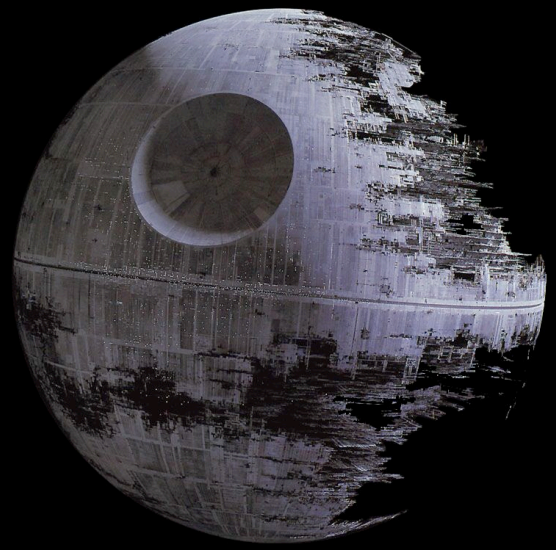


Uncontrolled Cell Division

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

Two-Hit Theory





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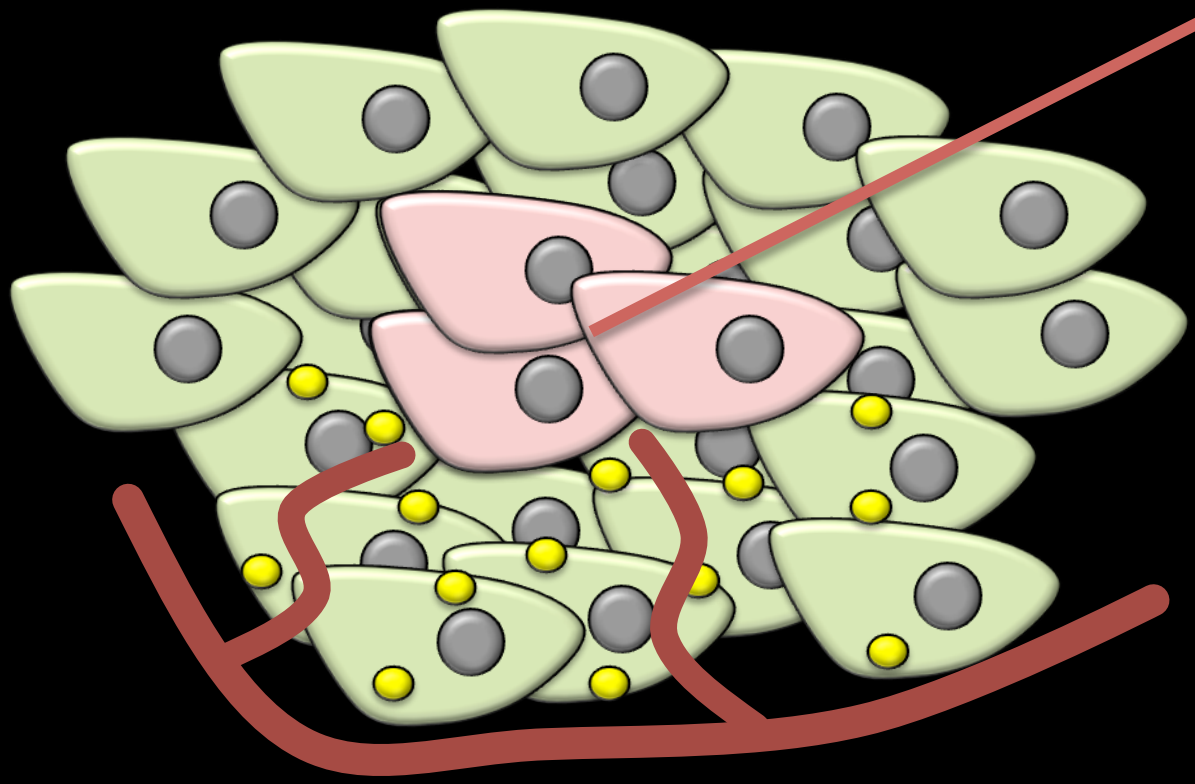
Nordling, C. *Br. J. Cancer* **1953**, 7, 68-72.
Knudson, A. *Proc. Natl. Acad. Sci. USA* **1971**, 68, 820-823.

Angiogenesis



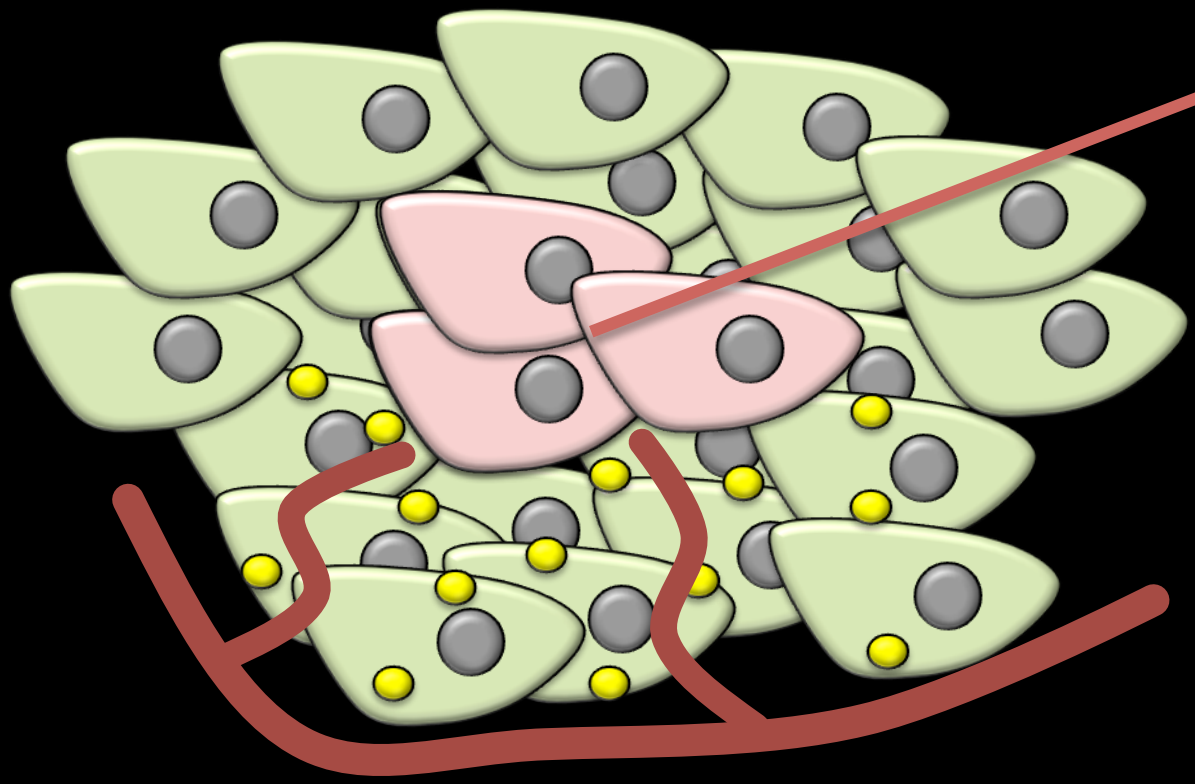
Growing tumor isolates interior cells from blood supply

⇧ HIF-1α, HIF-2α

⇧ VEGF

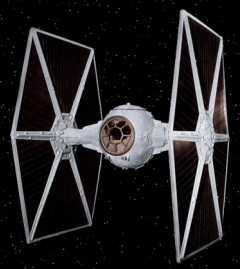
⇧ Angiogenesis

Metastasis

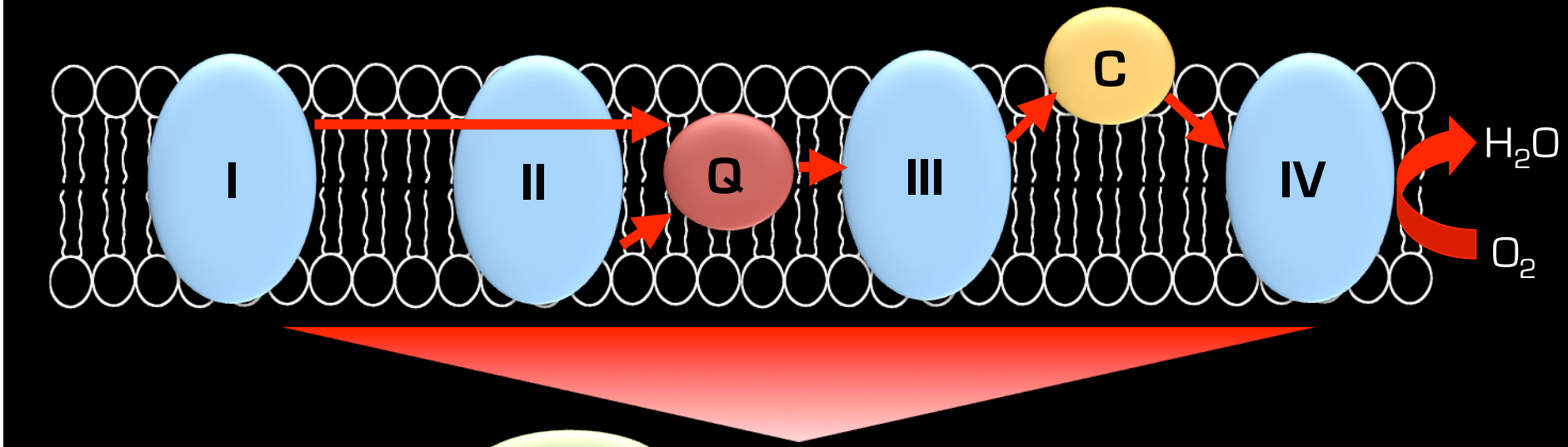


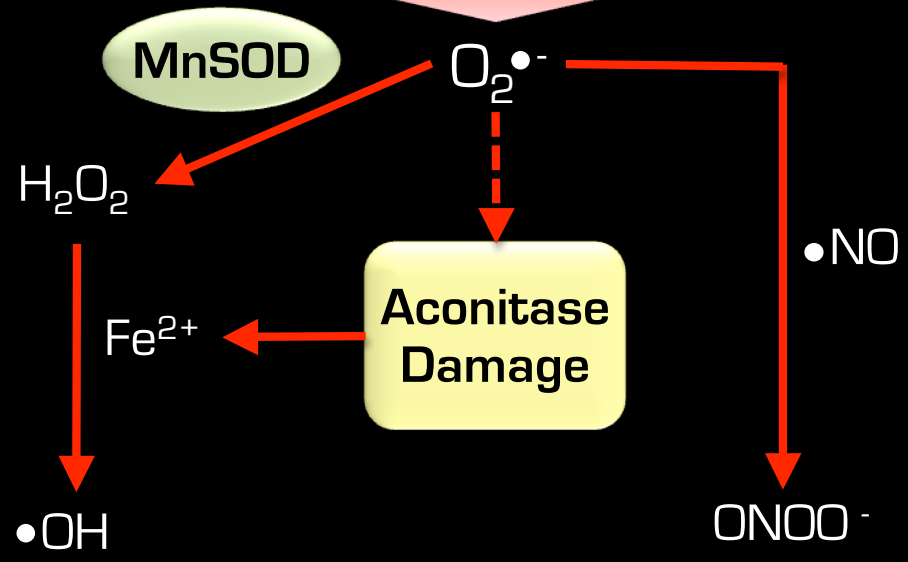
Hypoxic Cells Have Three Options:

1. Apoptosis
2. Neoangiogenesis
3. Metastasis



MitoConnection



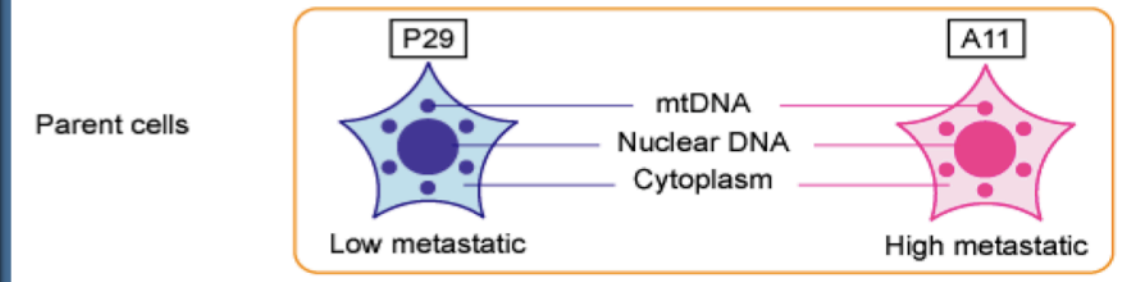


mtDNA Cybrids

Lewis Lung Carcinoma Cell Lines

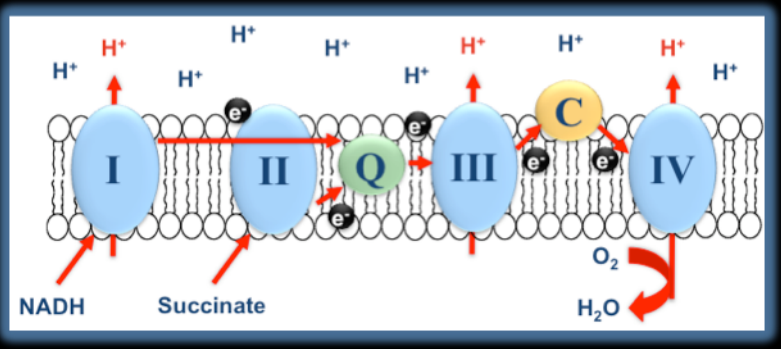
P29: Low Metastatic Potential

A11: High Metastatic Potential

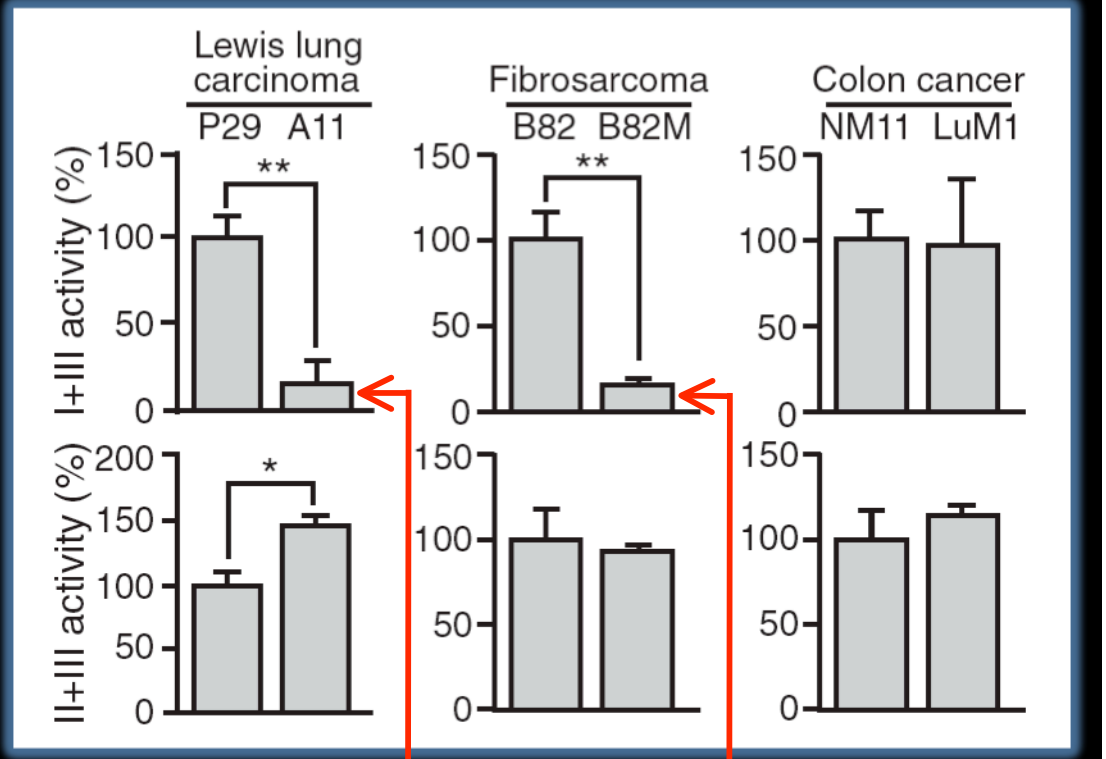


Ishikawa, K. *et al. Science* **2008**, 320, 661-664.

ETC Defects



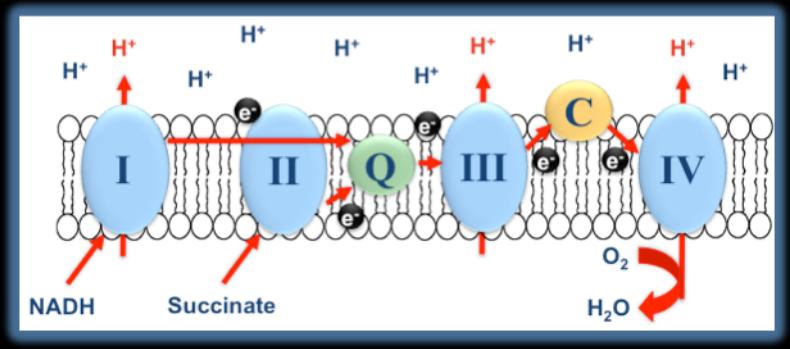
	Lewis Lung Carcinoma	Fibro-sarcoma	Colon Cancer
Low Metastatic Potential	**P29**	**B82**	**NM11**
High Metastatic Potential	**A11**	**B82M**	**LuM1**



Defects in NADH Dehydrogenase

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

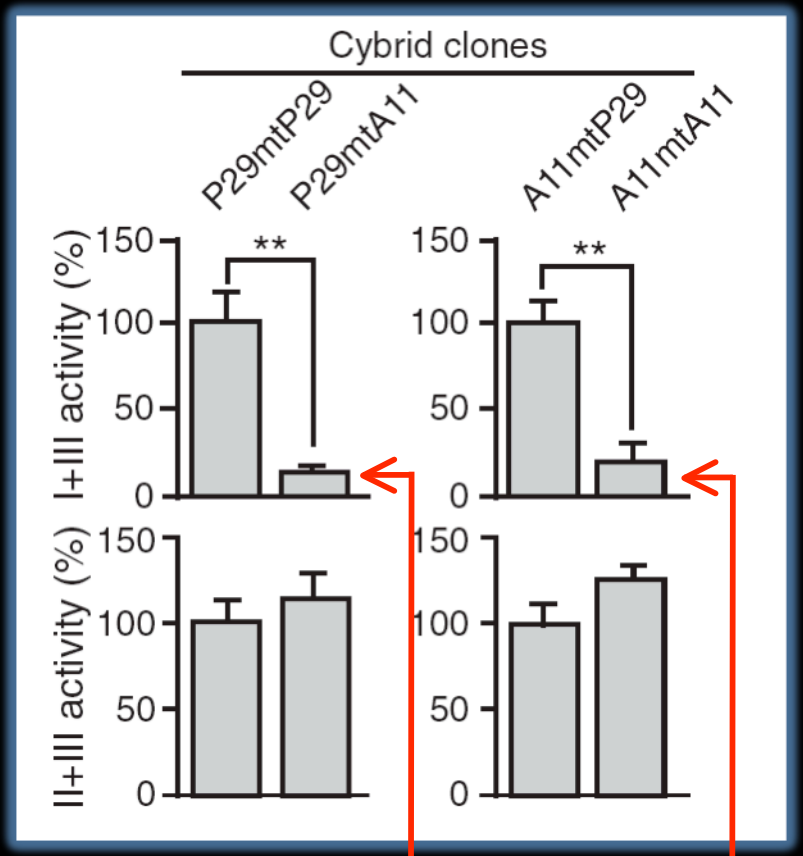
ETC Defects



Lewis Lung Carcinoma Cell Lines

P29: Low Metastatic Potential & Normal ETC Function

A11: High Metastatic Potential & Decreased ETC Function



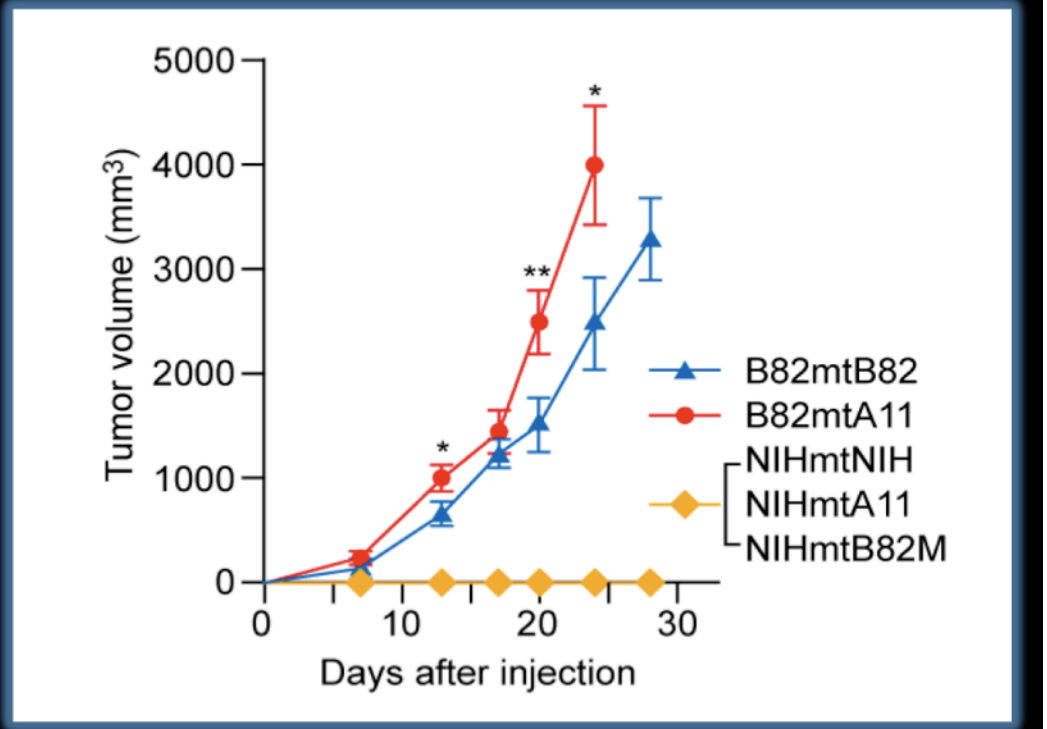
Defects in NADH Dehydrogenase

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

Tumor Growth

Conclusion 1

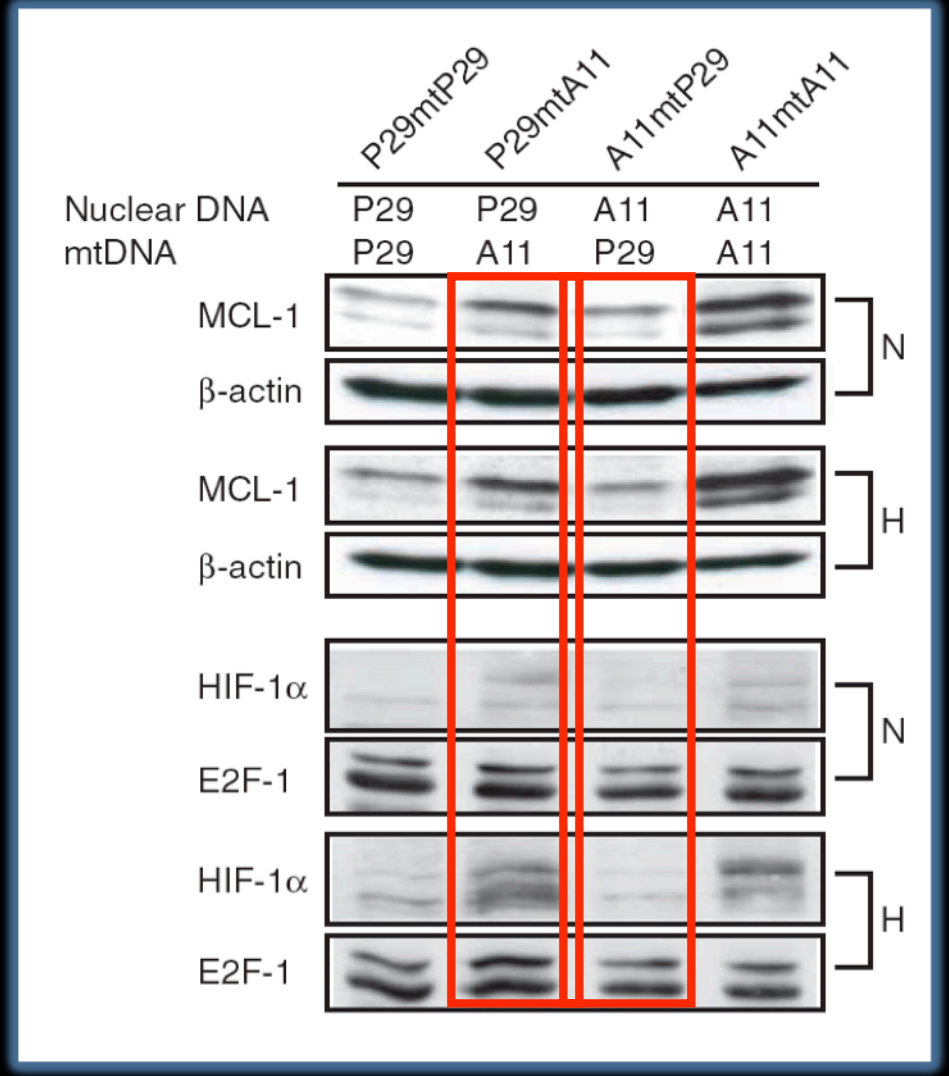
ETC mutation accelerates growth of transformed cell lines, but does not control the development of tumorigenicity and metastasis in nontransformed cells.



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**

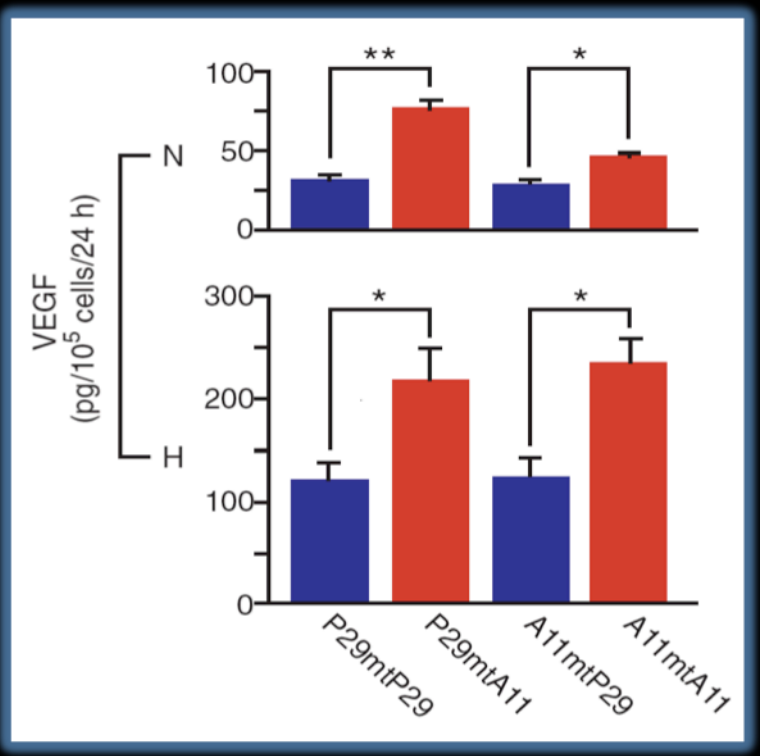
Ishikawa, K. *et al. Science* **2008**, 320, 661-664.

Mutation Cotransfer



Conclusion 2

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

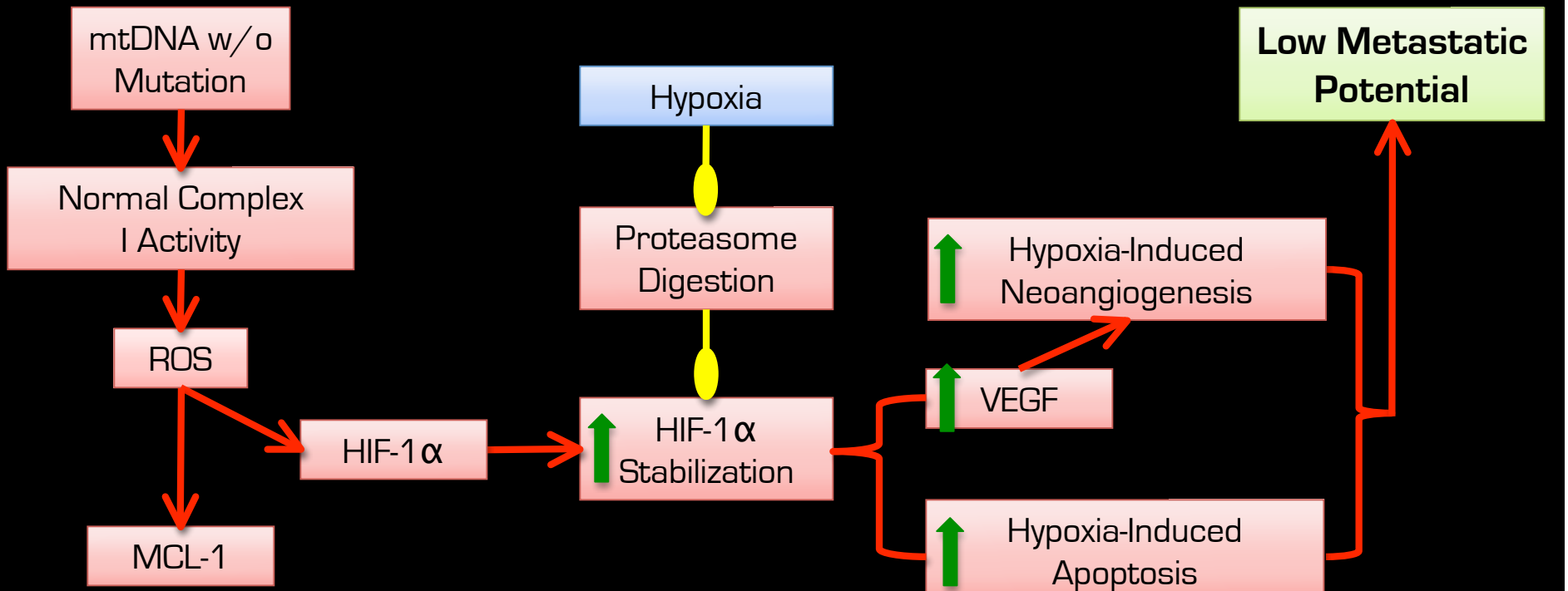


Ishikawa, K. *et al. Science* **2008**, 320, 661-664.

Postulated Pathway

Conclusion

P29mtP29 & A11mtP29 Cybrids – Low Metastatic Potential

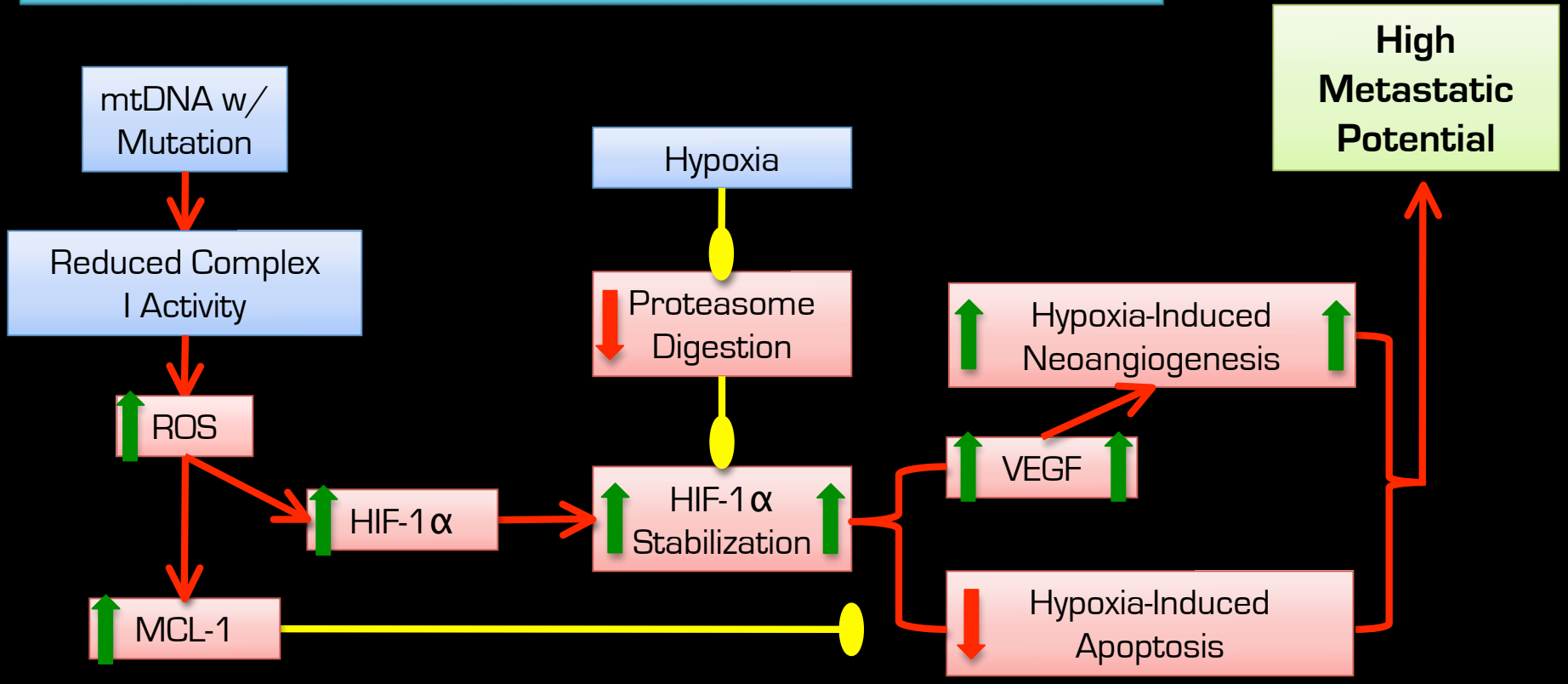


Ishikawa, K. *et al. Science* **2008**, 320, 661-664.

Postulated Pathway

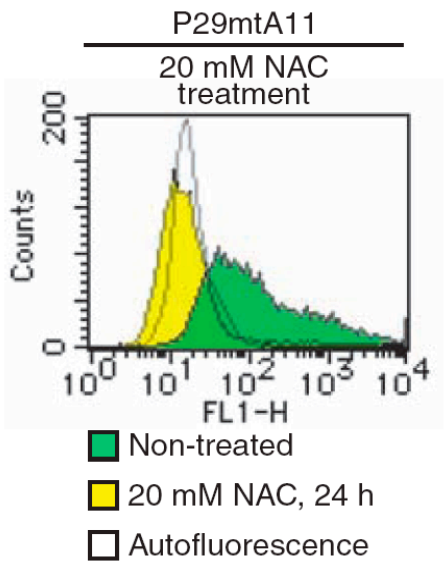
Conclusion

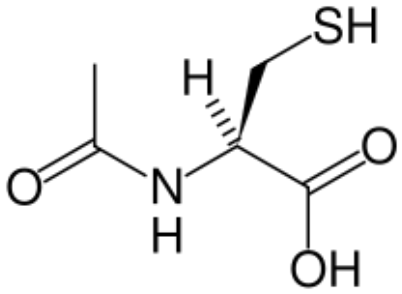
P29mtA11 & A11mtA11 Cybrids – High Metastatic Potential



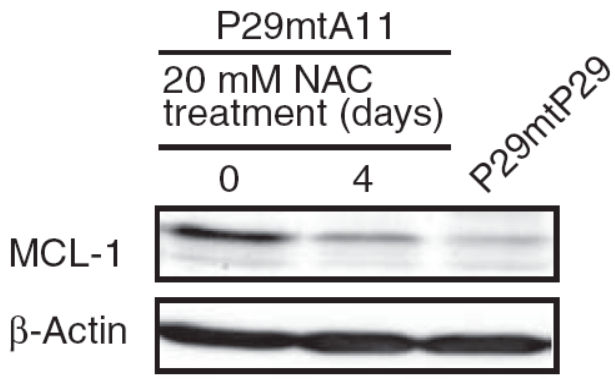
Ishikawa, K. *et al. Science* **2008**, 320, 661-664.

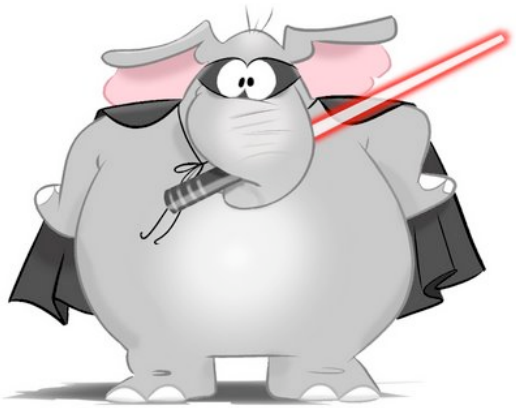
ROS Scavengers

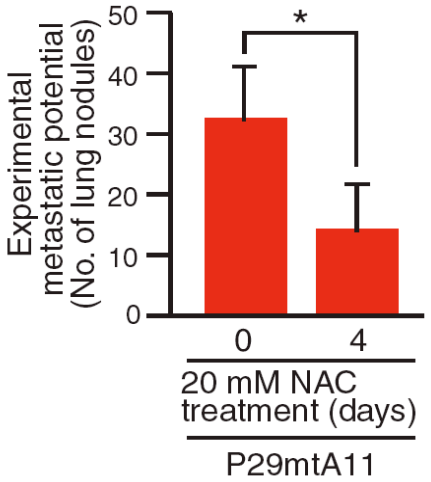


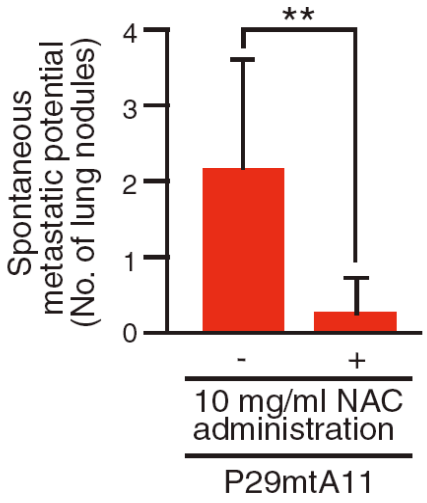


N-Acetylcysteine (NAC)









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

Summary

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-1α, 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