Understanding the Biology of Metastasis
Opportunities for New Therapy

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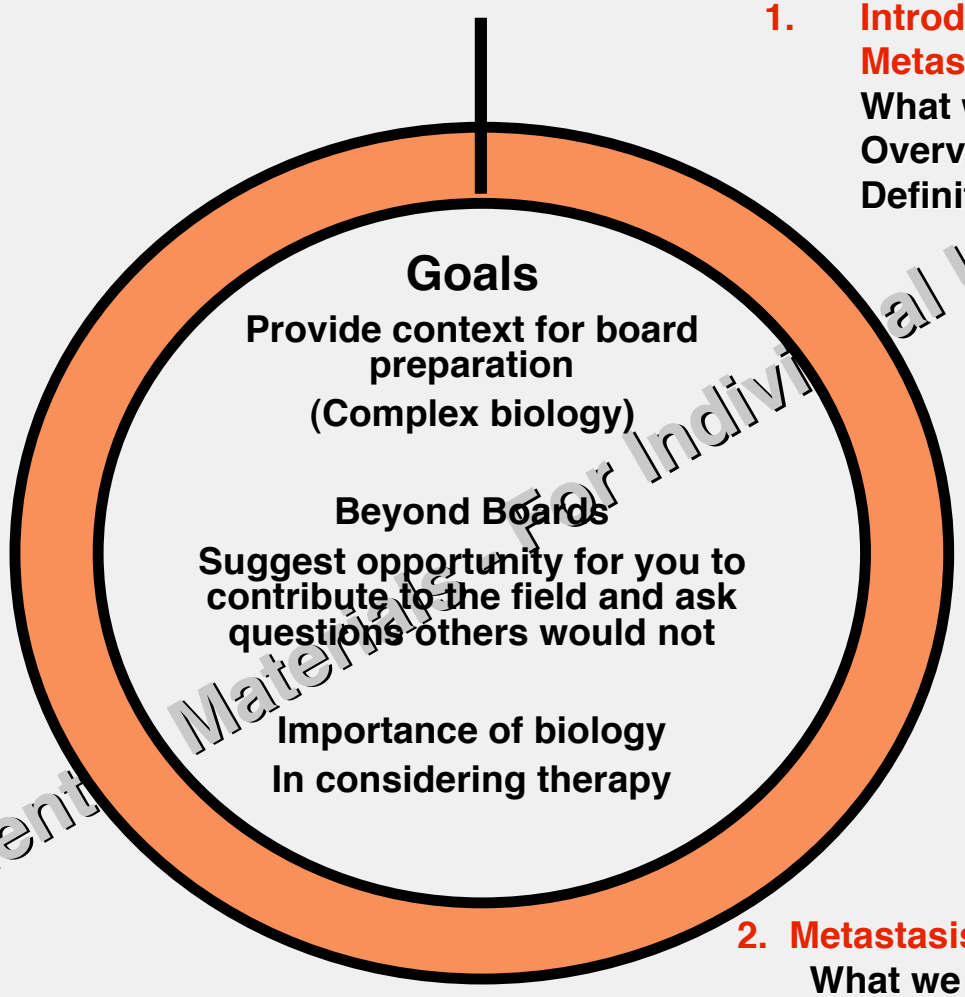
VCS 2009 "Craig Clifford" Resident R

Overview: Literature review, data, conjecture

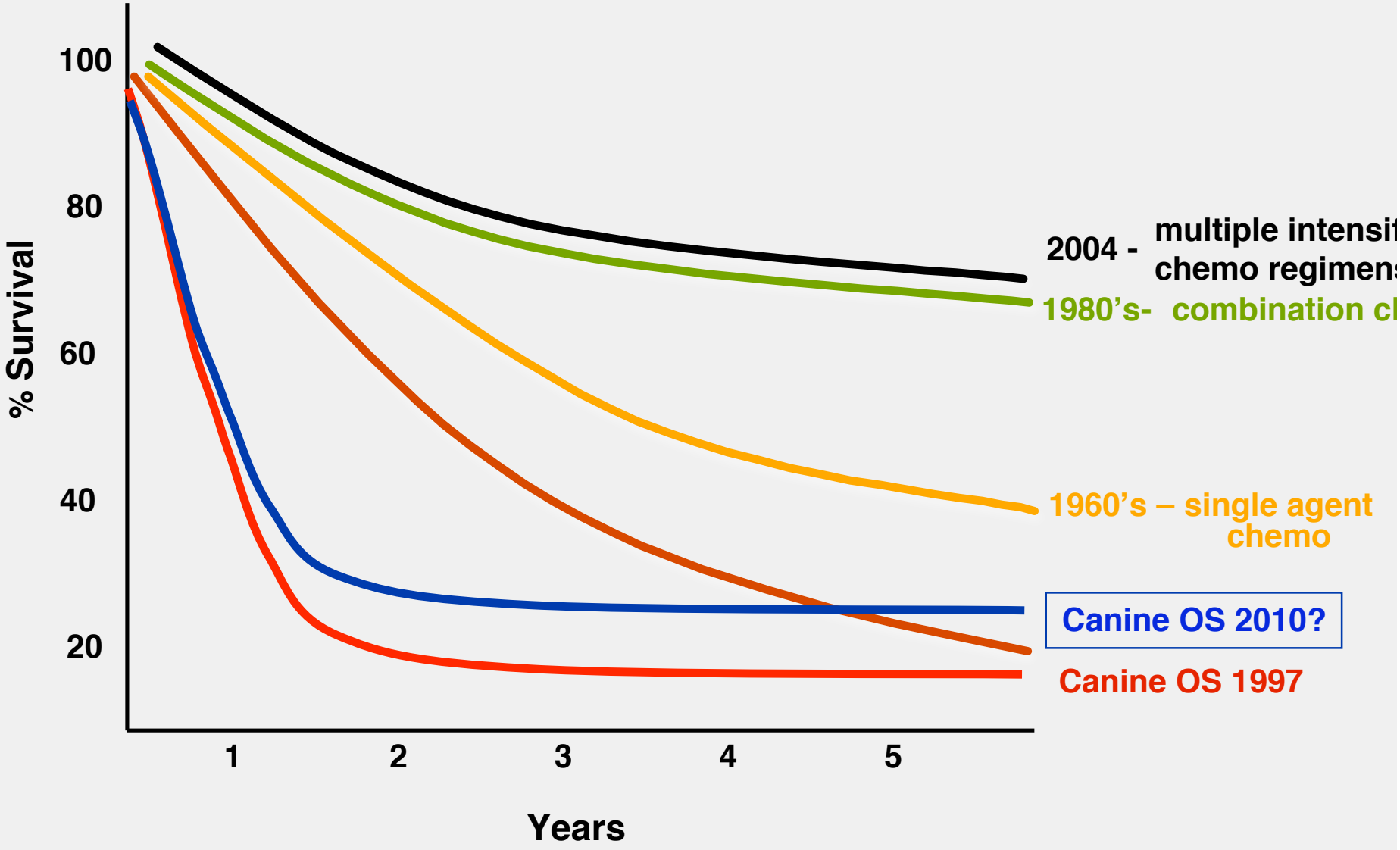
1. **Introduction: The Problem o**
   Metastasis
   - What we think we know and a
   - Overview of the metastatic ca
   - Definition of metastasis



3. Steps in the Metastatic Cascade
- Connecting Biology with Therapy
- Ezrin - my favorite protein

2. **Metastasis Concepts and Contro**
   - What we don't know and don't a
   - Emergence of the metastatic ph
   - Inefficiencies in Metastasis
   - Dormancy of metastasis
   - Resistance to therapy

SURVIVAL OF PATIENTS WITH LOCALIZED OSTEOSARCOMA



Comparative Approach Towards Improving our Understandi of Osteosarcoma Metastasis

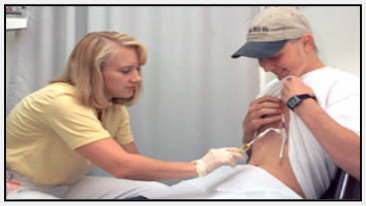
Rodent Models

Genetically Engineered Mouse Models

Xenografts

Canine Model

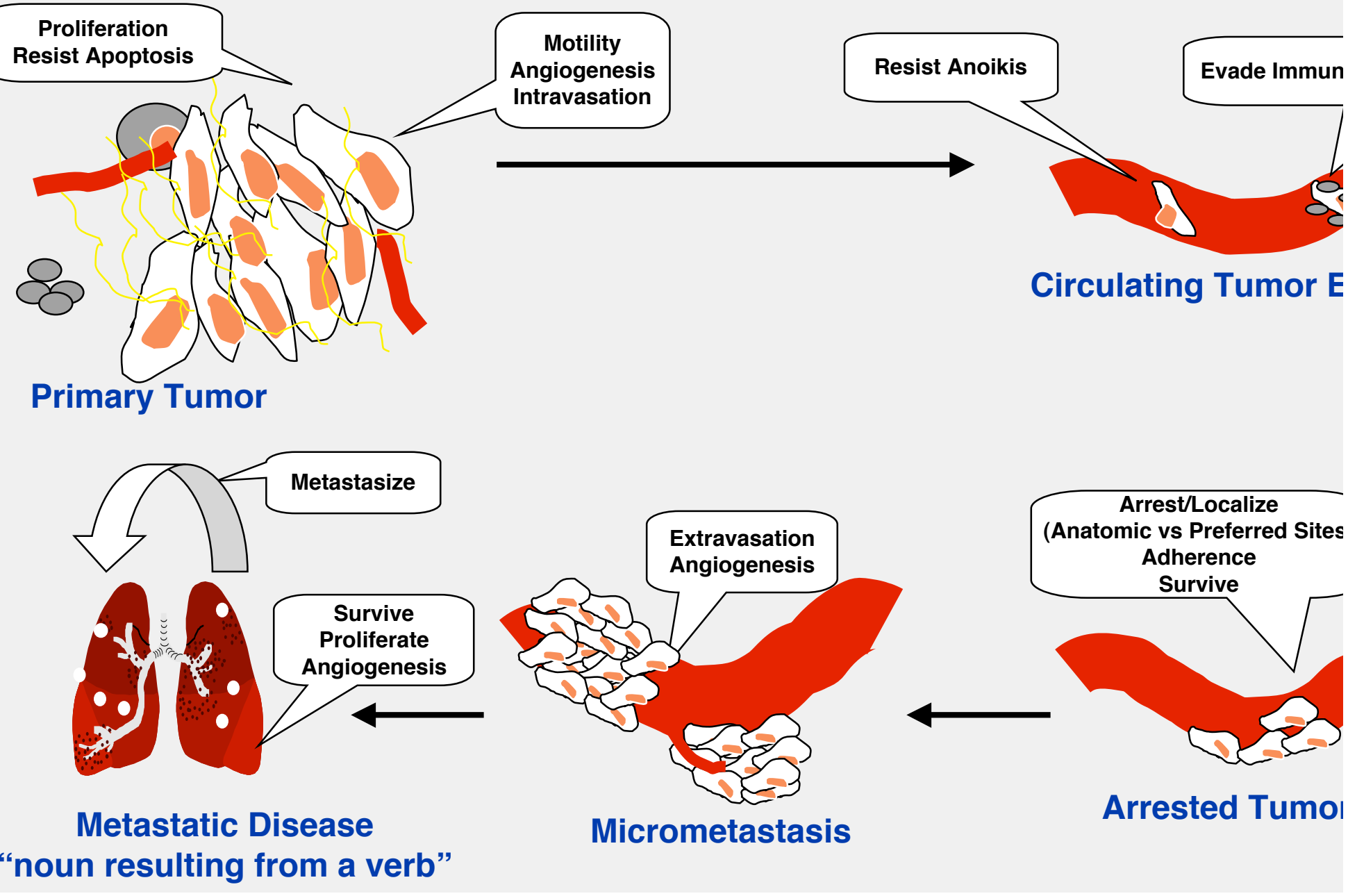
CCR ·
Compara
Oncolo
Progra



Pediatric Osteosarcoma Model

Improved Understanding of Biology and Improved Treatment Outcomes

Metastasis Biology: The Dogma



What makes metastatic cells unique?

Phenotype	**Normal cell(s)**
Invasion	Leukocytes, neurons, stem cell
Intermittent adhesion	Leukocytes, stem cells
Resistance to anoikis	Circulating leukocytes, stem ce
Modulation of 2º site	L'cytes, stem cells
Proliferation at 2º site	Macrophages, stem cells
Persistent proliferation at 2º site	Stem cells

… all properties must co-exist within the same cell

Metastasis (2008)

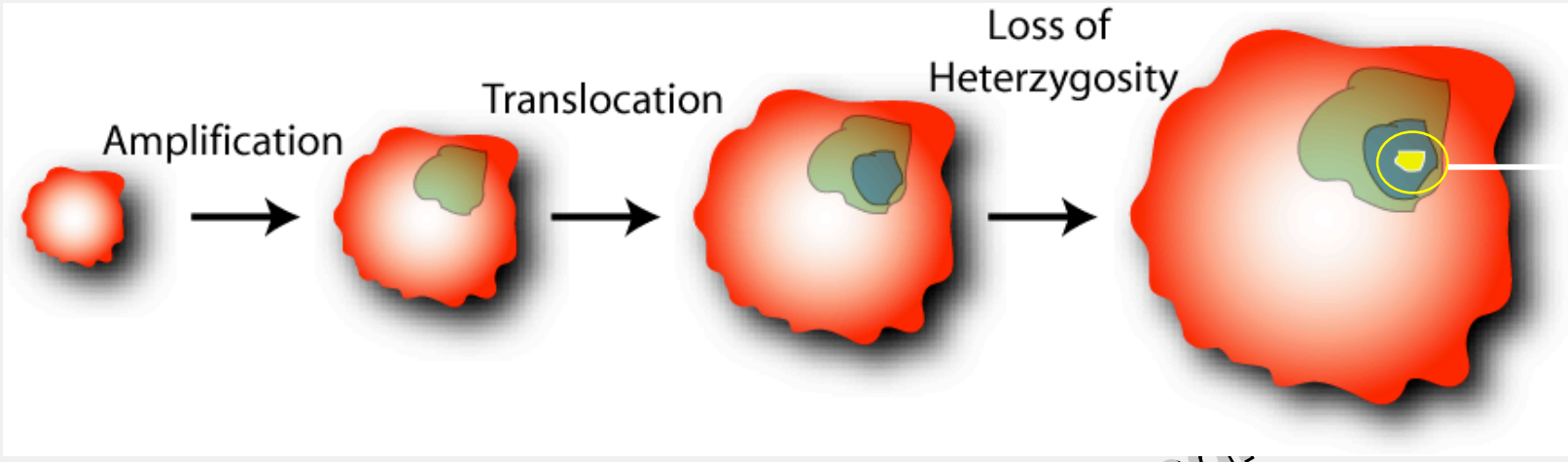
- Dissemination of neoplastic cells to discontinuous nearby or distant secondary (or higher order) sites where they proliferate to form an extravascular macroscopic mass

  - **Implicit requirement – primary tumor**
  - *Not* **direct extension of primary tumor**
  - *Not* **dependent upon** *route*
  - *Not* **defined by** *site* **of secondary lesion**
  - *Not* **yet defining macroscopic, but more than single cell**
  - **Extravasation** *not* **required before proliferation**

D. Welch, Personal communication 20

When does the Metastatic Phenotype Emerge?

Metastatic Progression Model



Clinical Significance of Progression Model:

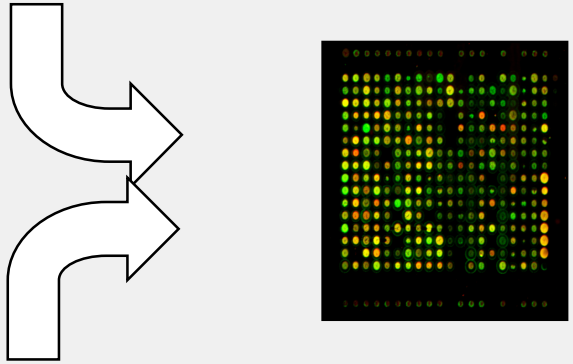
- A minority of cancer cells in a primary tumor are able to metastasize
- Early detection of a primary tumor should be associated with more favorable outcome
- Effective and definitive treatment of early and small tumors will reduce risk of metastatic phenotype acquisition
- Suggests lack of value in primary tumor response predicting response at metastatic sites

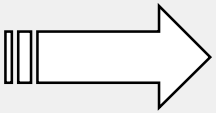
A molecular signature of metastasis in primary solid tumors

Nature Genetics volume 33 pg 1-6, 2003.

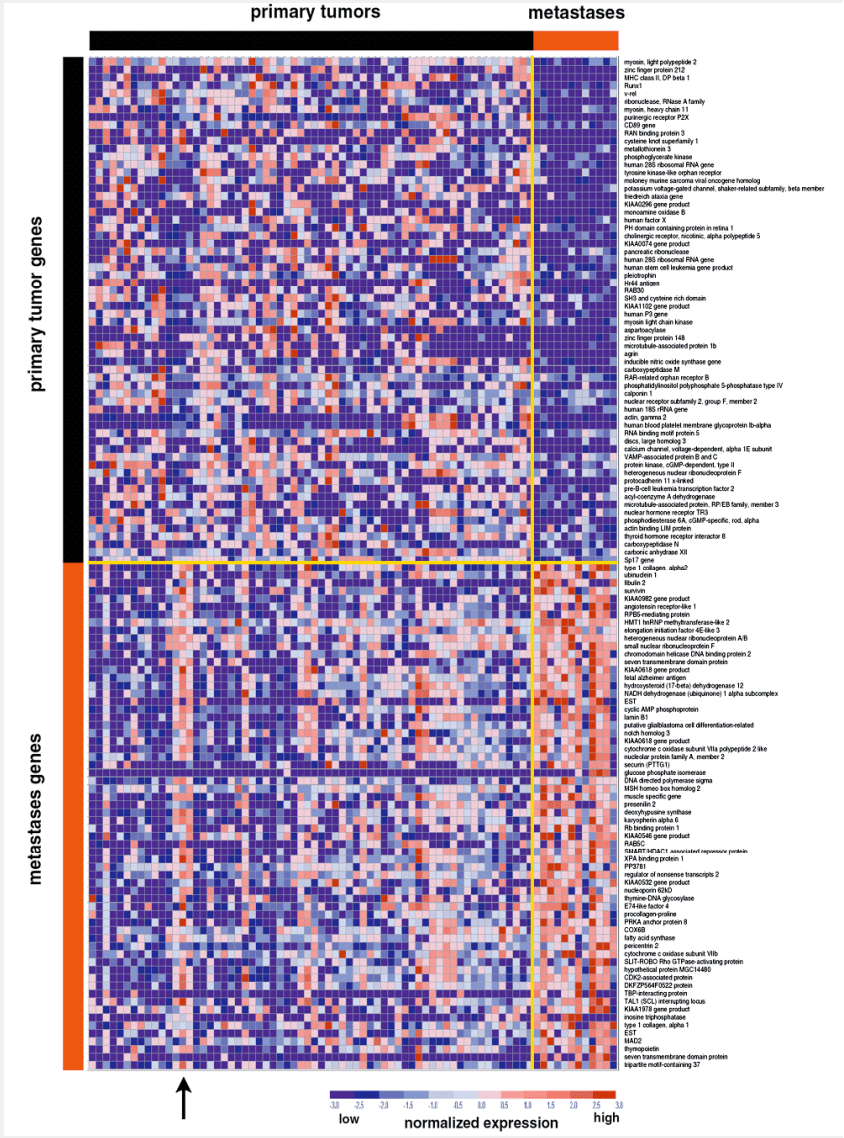
Sridhar Ramaswamy, Ken N. Ross, Eric S. Lander & Todd R. Golub

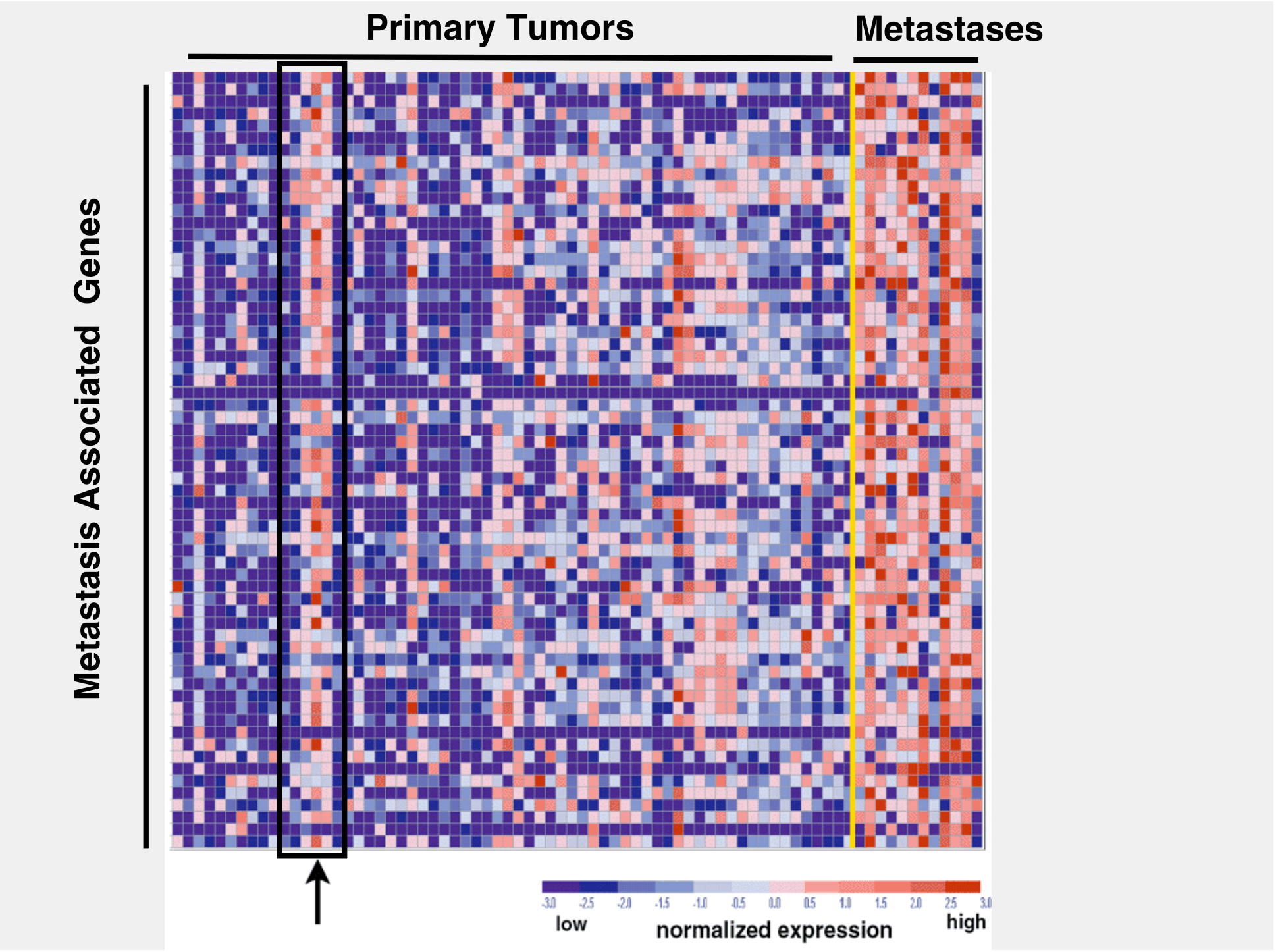
64 Primary Carcinomas





12 Metastatic Carcinomas

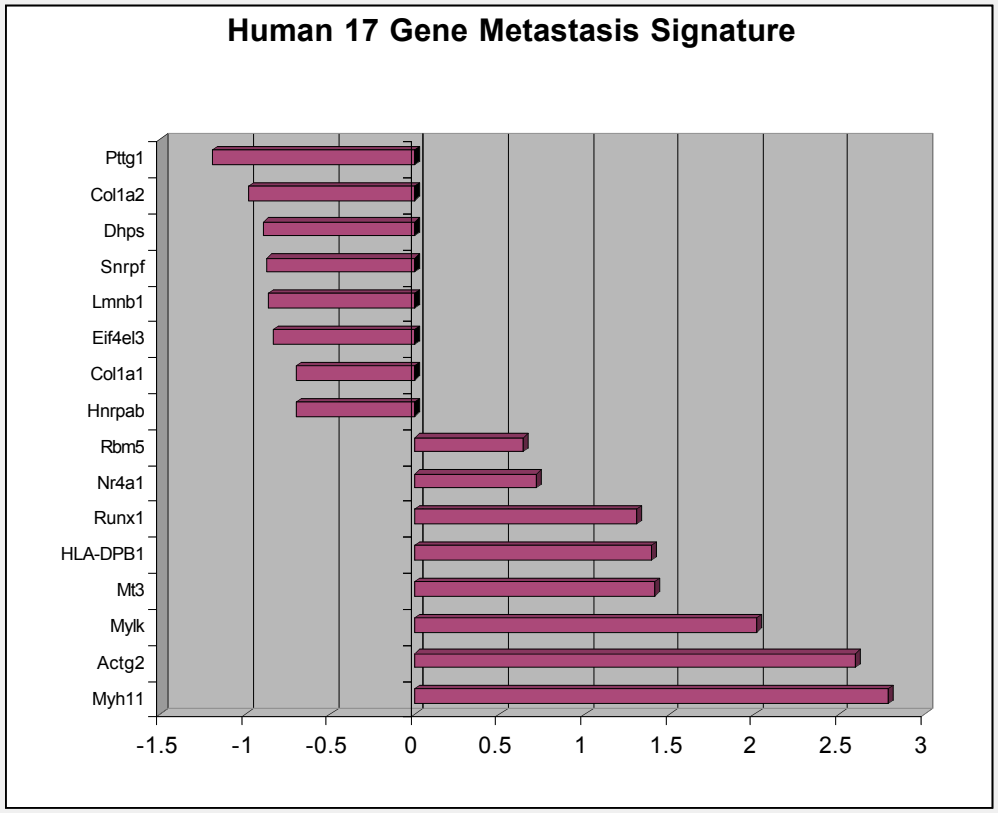


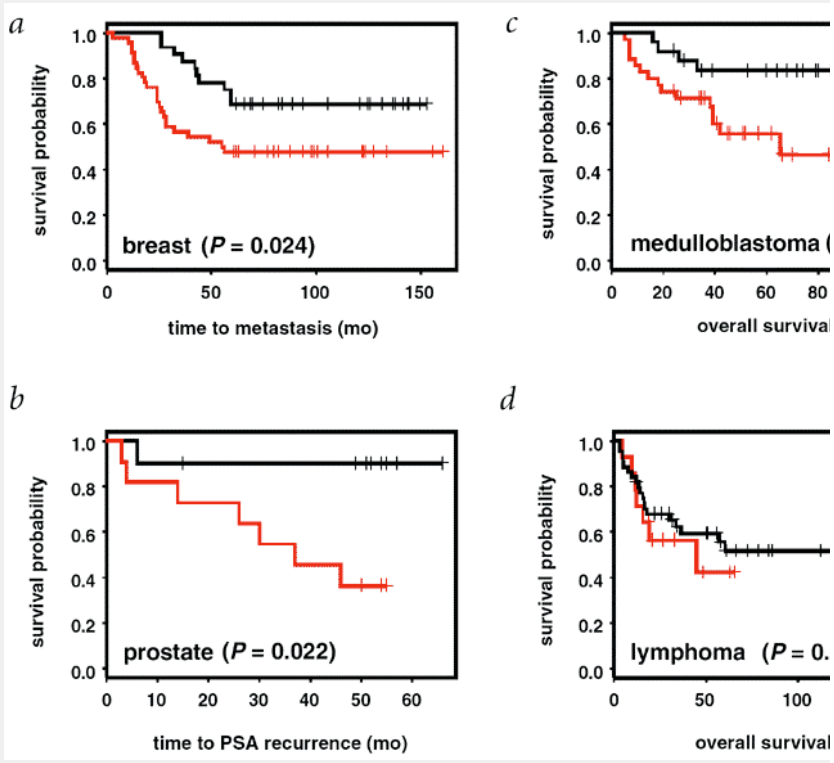

Primary Tumors
Metastases
Metastasis Associated Genes
-3.0 -2.5 -2.0 -1.5 -1.0 -0.5 0.0 0.5 1.0 1.5 2.0 2.5 3.0
low
normalized expression
high

A molecular signature of metastasis in primary solid tumors

Nature Genetics volume 33 pg 1-6, 2003.

Sridhar Ramaswamy, Ken N. Ross, Eric S. Lander & Todd R. Golub

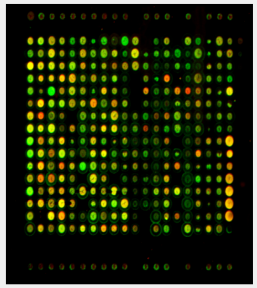




Data suggests that metastasis phenotype is identifiable in the primary tumor

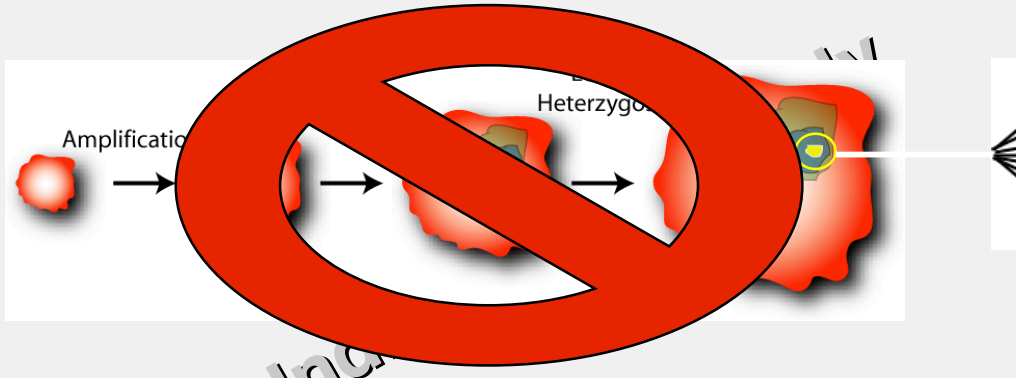
Alternate Model of Metastatic Progression

64 Primary Carcinomas

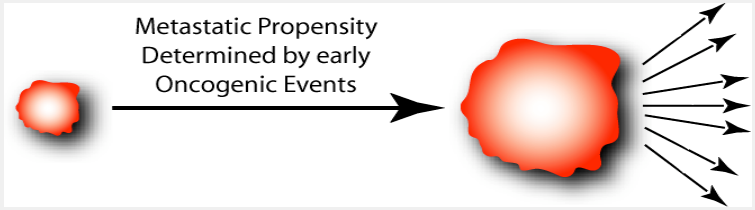


12 Metastatic Carcinomas

Progression Model

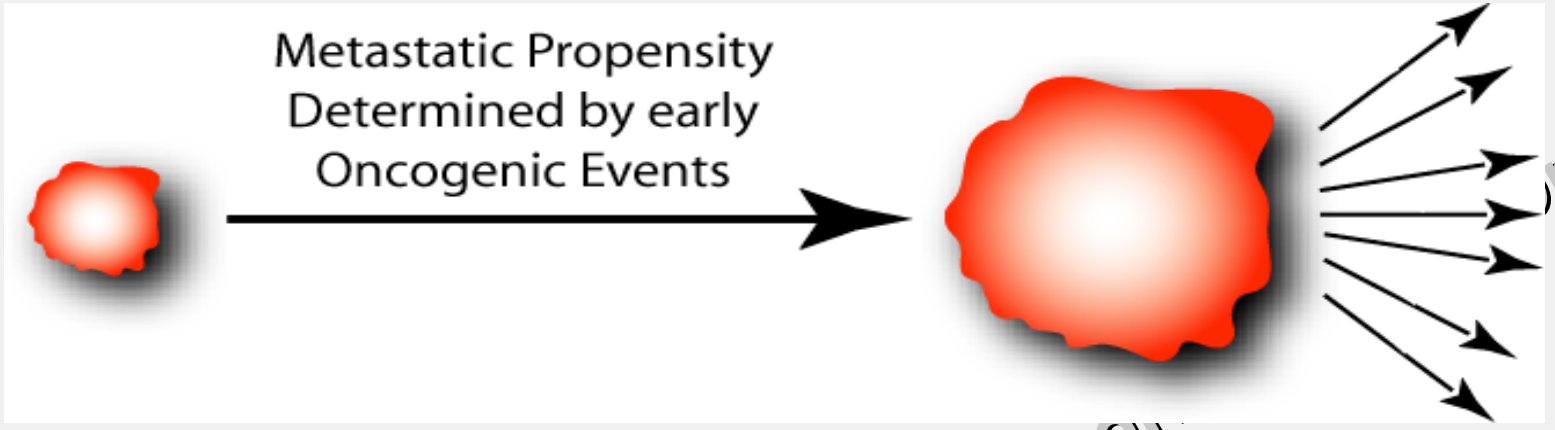


Early Oncogenic Combination Model



Features of metastatic cancers are present in the majority of cells in the primary tumor

Early Oncogenic Combination Model



Metastatic phenotype NOT strongly associated with tumor size/time

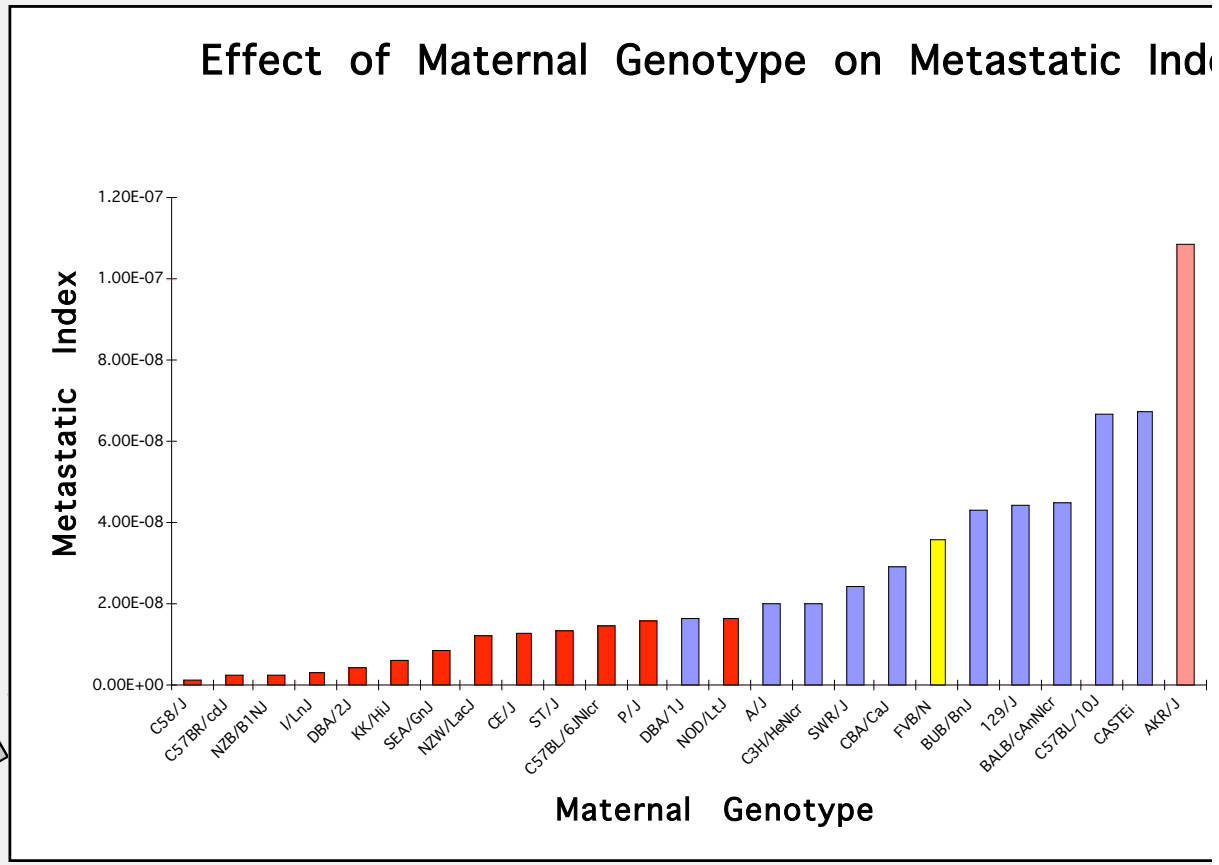
Clinical Significance of Progression Model:

- Metastatic behavior is defined by initial oncogenic events
- Explains cancers of multiple primary sites (hemangiosarcoma)
- Explains metastasis with unknown primary tumor
- Suggests that for some cancers effective and definitive treatment of early and small tumors **NOT** reduce risk of metastatic phenotype acquisition
- Supports the use of neoadjuvant therapy to guide adjuvant therapy

The host genetic background is a major determinant of metastatic outco

Experiment in transgenic mice driven by the same initiating oncogenic event.

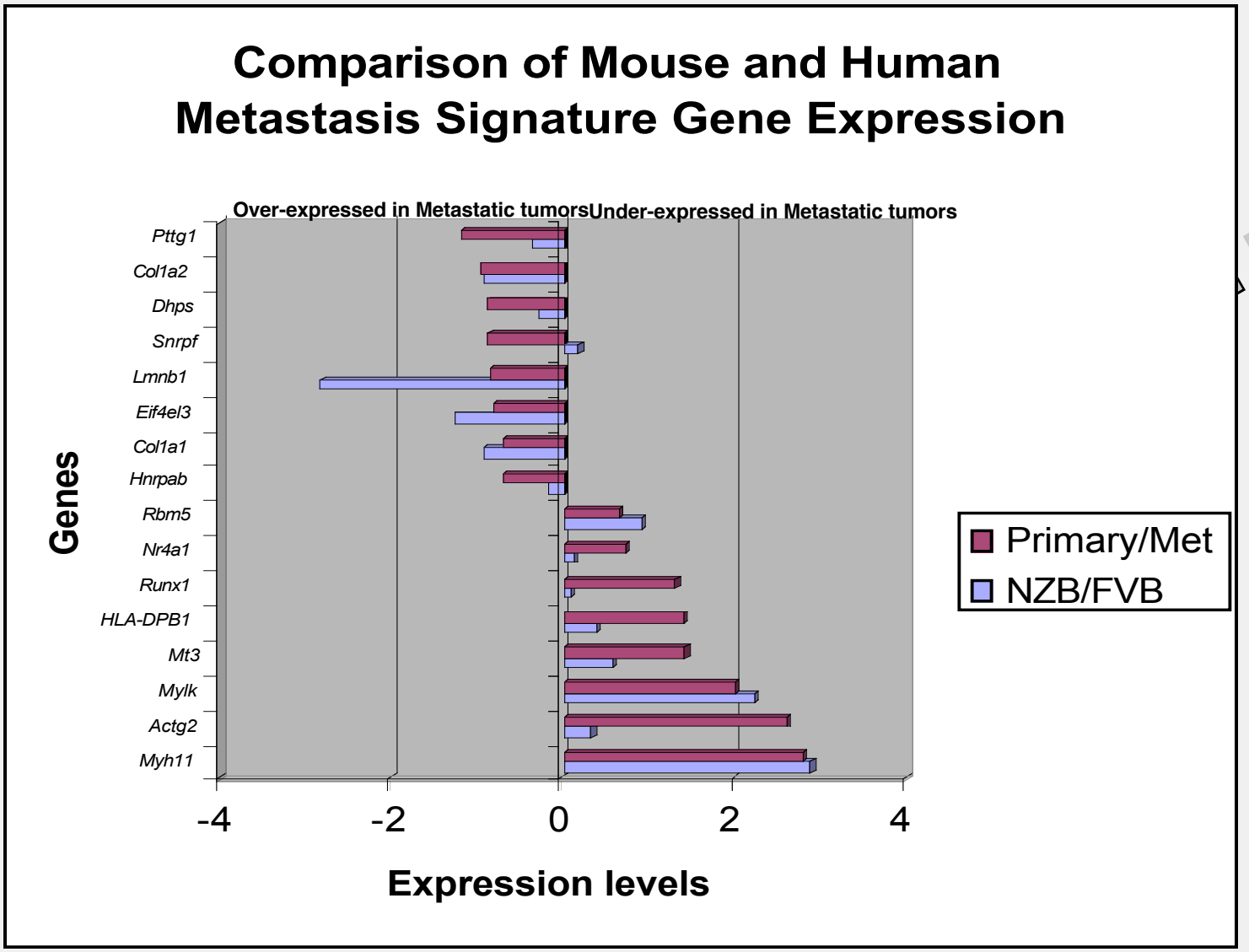
Examined if differences in genetic background would influence metastatic behavior.



Data suggests that genetic background is a majo determinant of metastatic propensity

Hunter et al Nature Genetics 20

Genetic background is a major determinant of metastatic outc



Genes that predict metastatic phenoty found in the prima tumor, are frequen host related genes

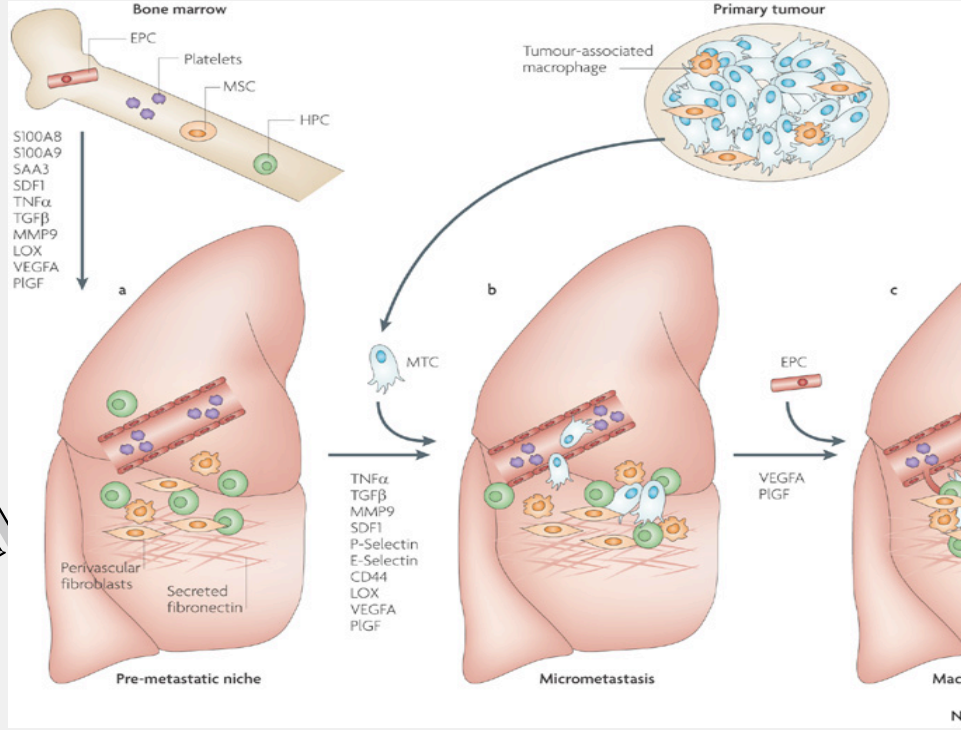
Individuals (breed may have unique metastatic behav that is independe primary tumor bio A genetic predisposition for "pro-metastatic" s

Genetic background is an important determinant of metastatic potential
Nature Genetics 2003, volume 34 no. 1 pp 23 - 24
Kent Hunter1, Danny R. Welch2 & Edison T. Liu3

The premetastatic niche

The primary tumor creates a microenvironment conducive to metastatic progression.

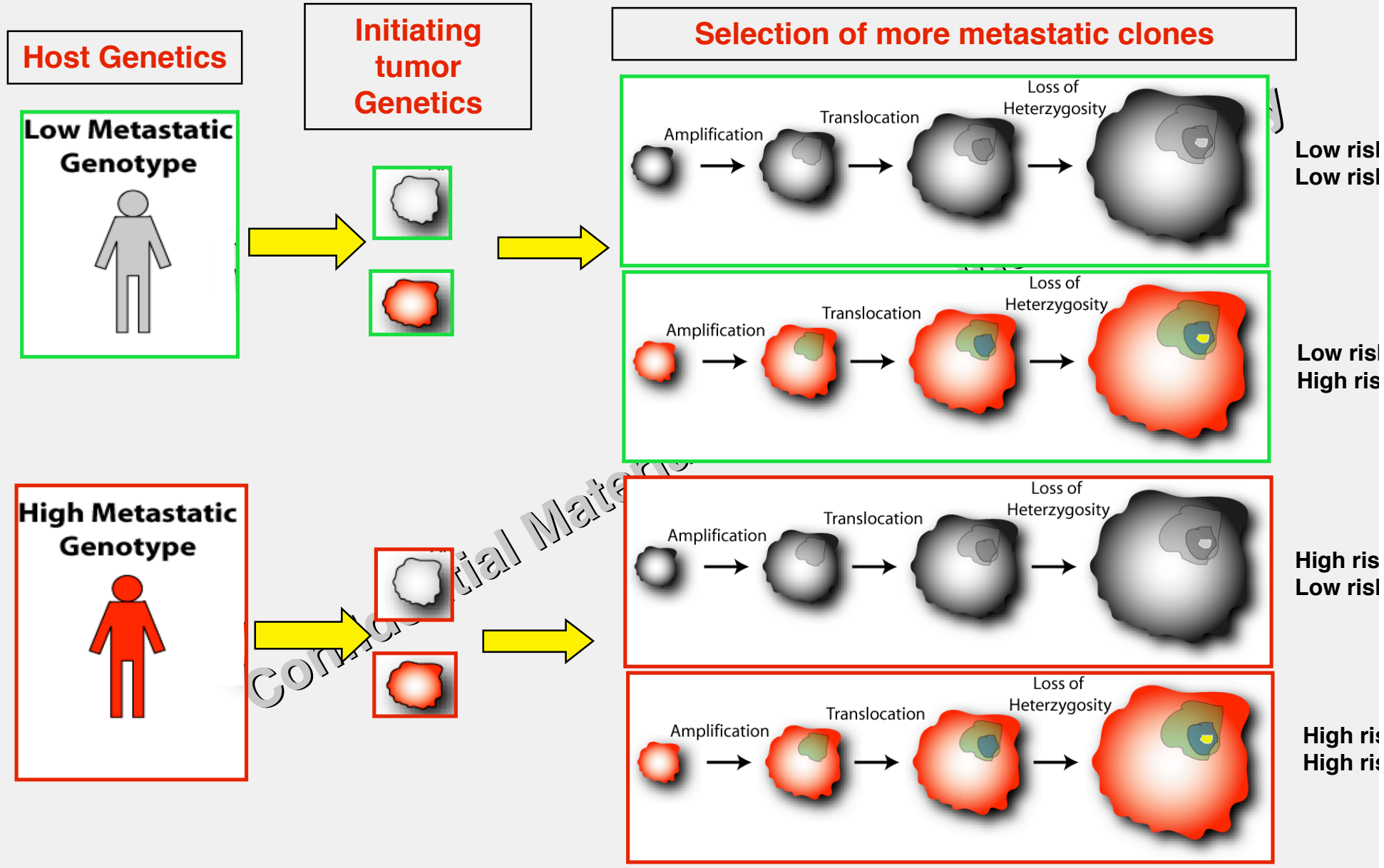
Bone marrow derived cells arrive at distant metastatic sites in advance of the metastatic cells themselves.



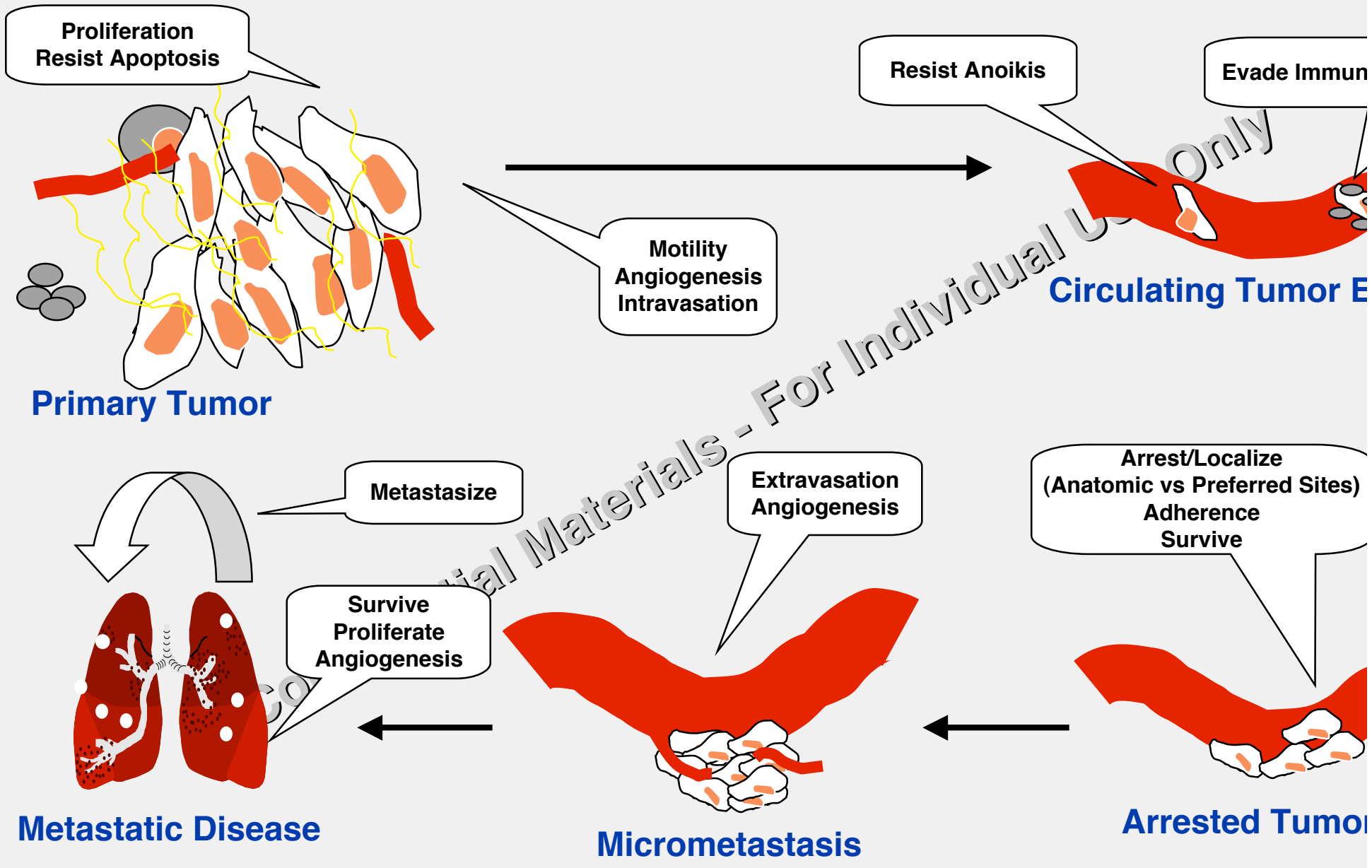
Cells of the premetastatic niche may be treatment targets

Bone marrow derived cells: VEGF-R; TSP-I responsive

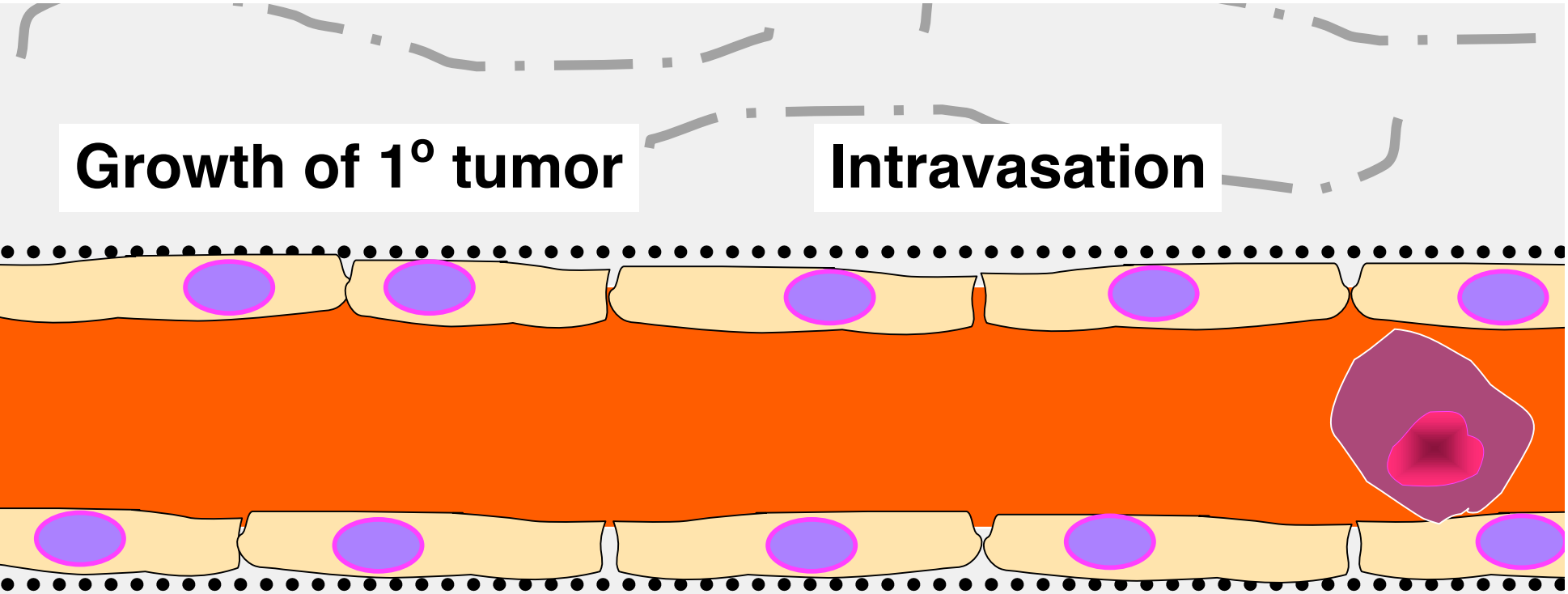
Comprehensive Model of Metastatic Progression

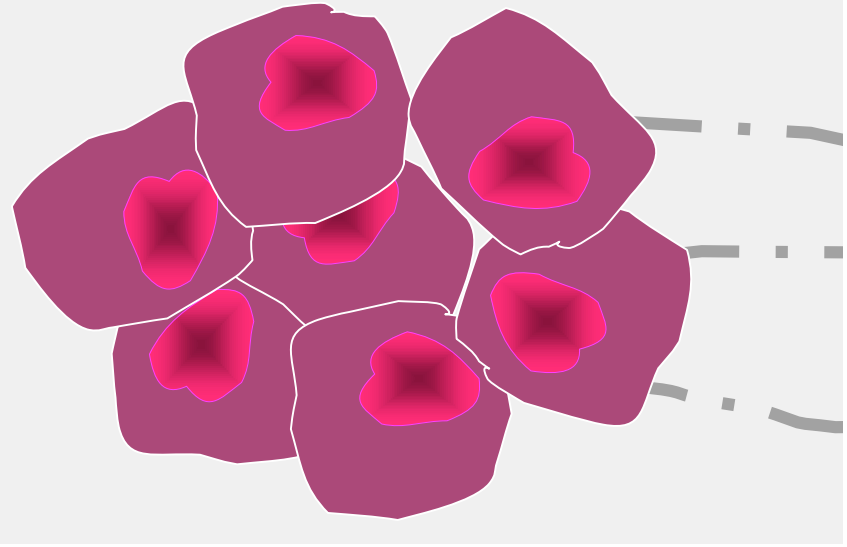


Metastasis Biology: an inefficient but deadly process



Hematogenous Metastasis





Entry to circulation is not a high hurdle for metastati

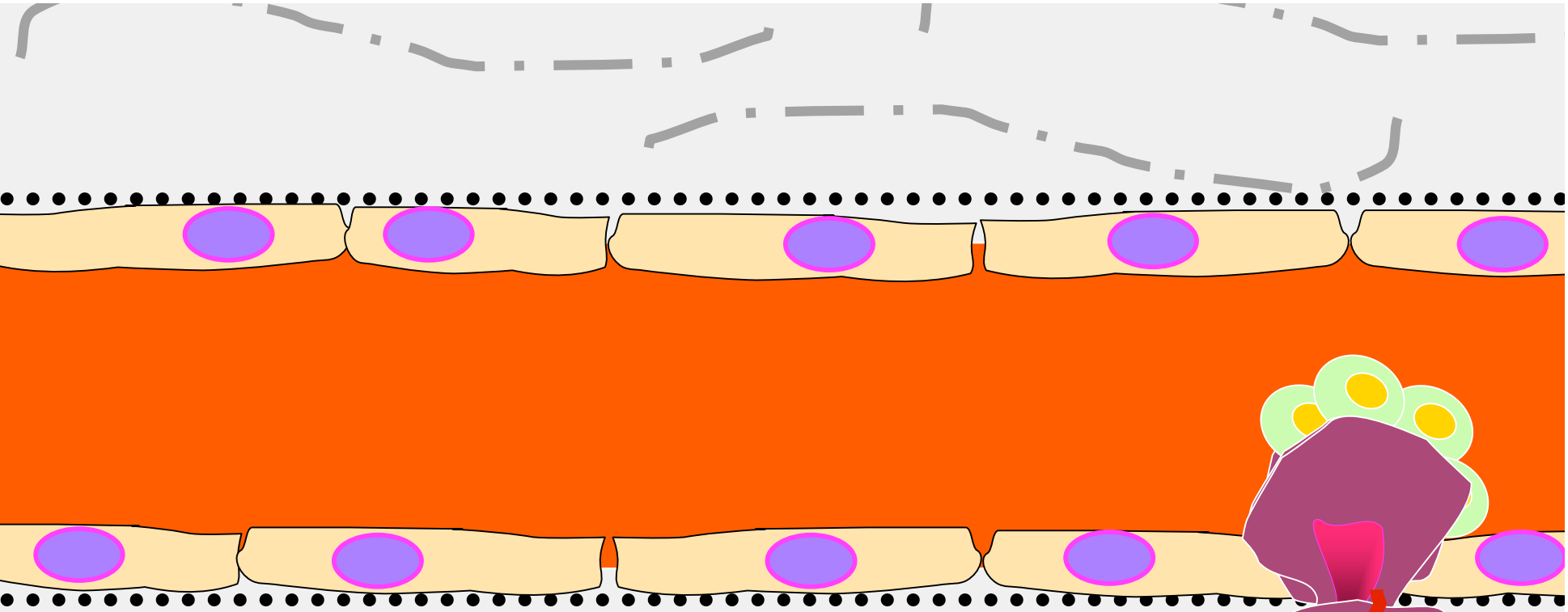
1 - 4 x 10^6 cells/day/gm tumor
Butler & Gullino (1975) *Cancer Res*

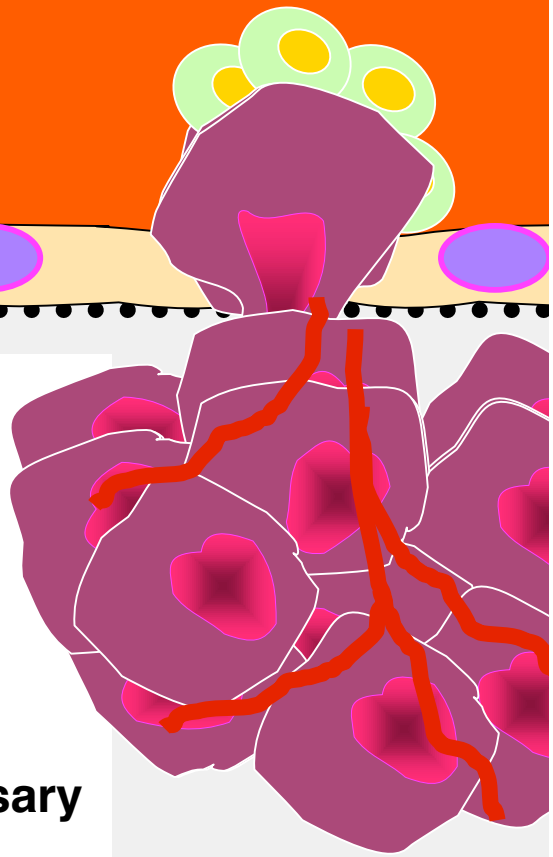
Porto-venous shunt studies

Predictive value of circulating tumor cells

<0.01%of ciruculating cells successfully metastasize
Fidler (1973) *Nature*

Hematogenous Metastasis





Extravasation and survival at distant sites is a high hurdle. Many cells that enter the circulation do not successfully adhere or extravasate.

Most cells that extravasate will not form successful metastases.

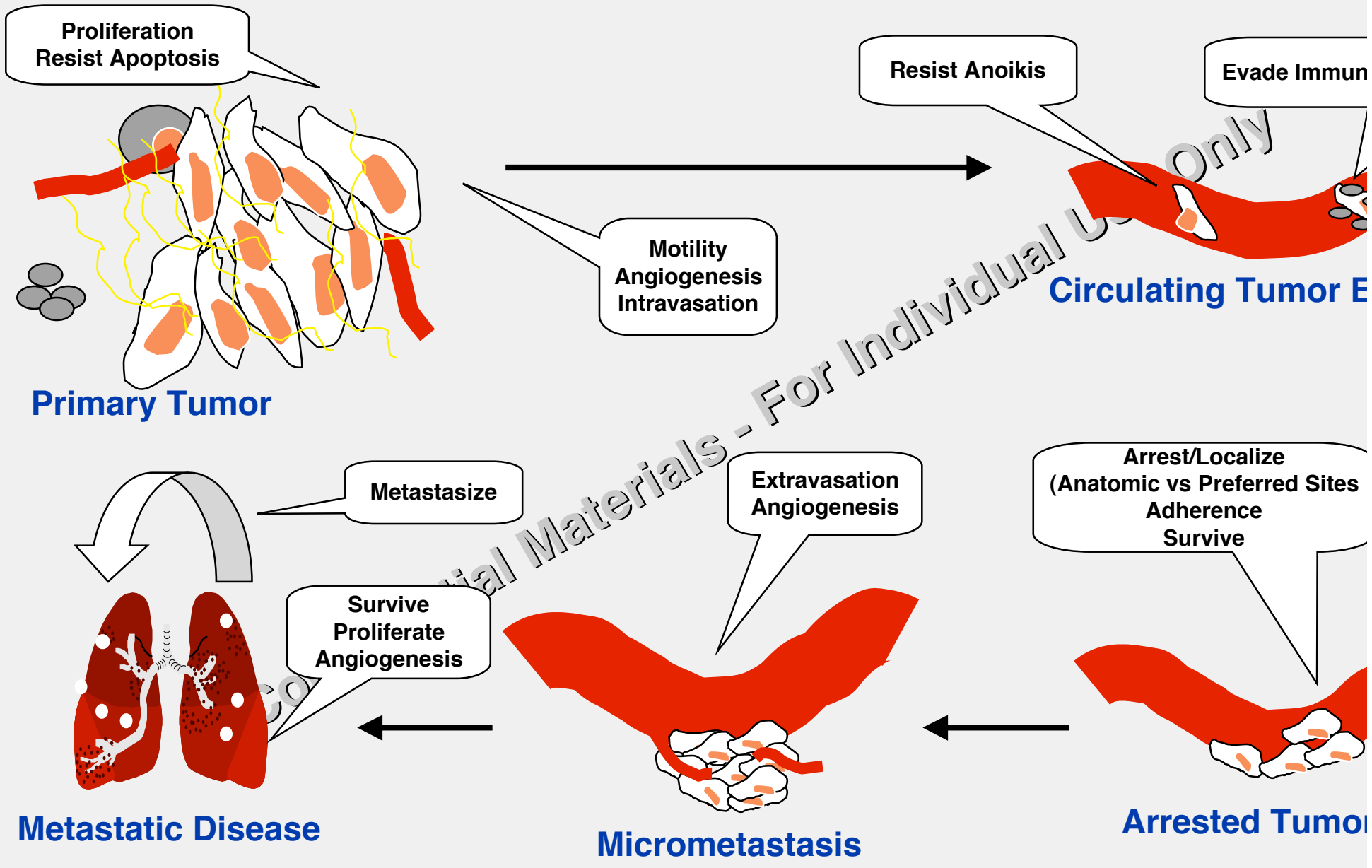
The ability of cells to modulate new environments is necessary for metastatic cells

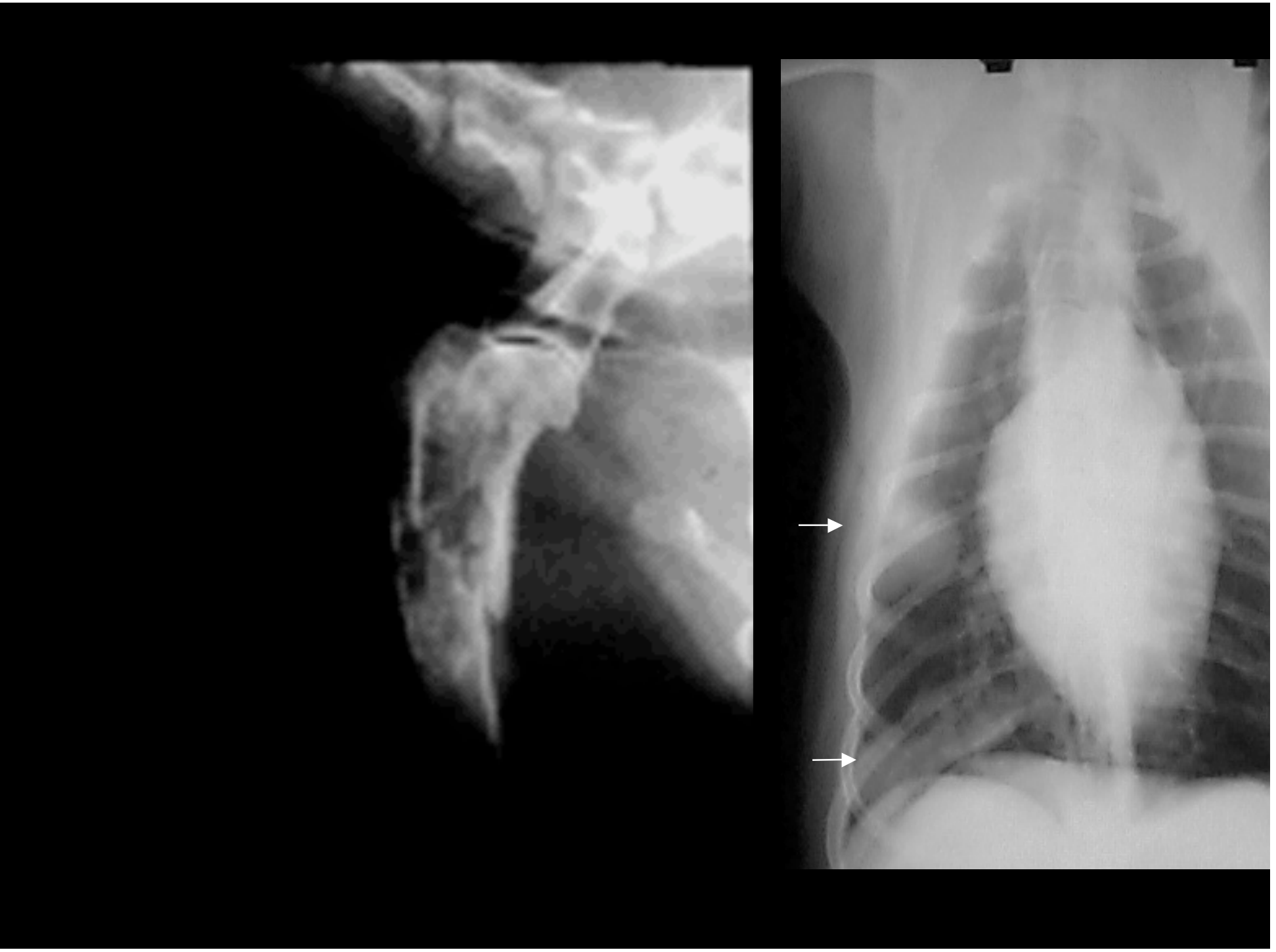
Metastasis Biology: Letting inefficiency work in your favor

Metastsatic Process	Efficiency	Best target for treatment
Intravasation	Inefficient	Possible
Survival in circulation	Efficient	Not Likely?
Arrest at distant site	Efficient	Not Likely?
Survival at distant site	Inefficient	Yes
Initiation of growth	Inefficient	Yes
Persistence of Growth	Inefficient	Yes

From: Chambers et al Breast Cancer Res 20

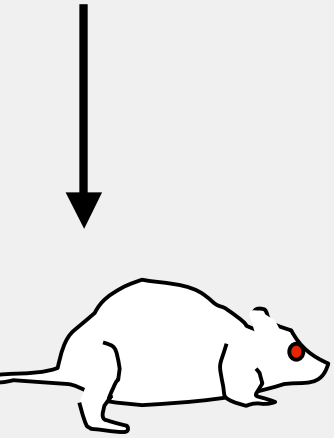
Metastasis Biology: Metastatic Dormancy



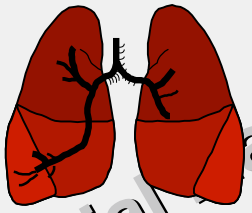


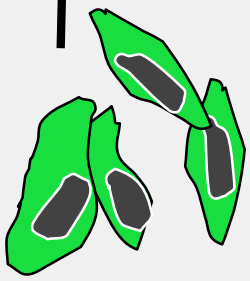
Investigations into Dormant Cells?

Red Vessels:
Texas-Red
Dextran

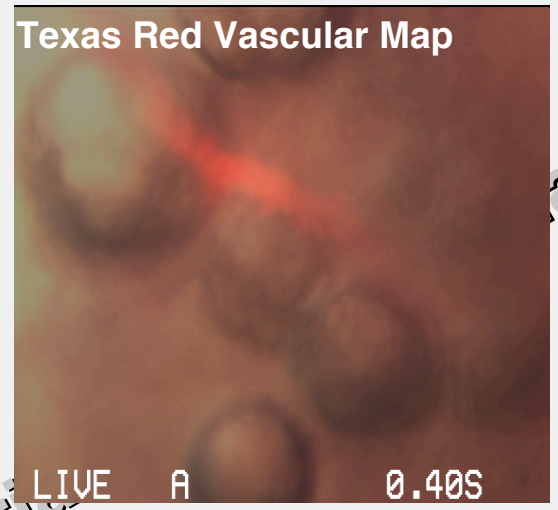


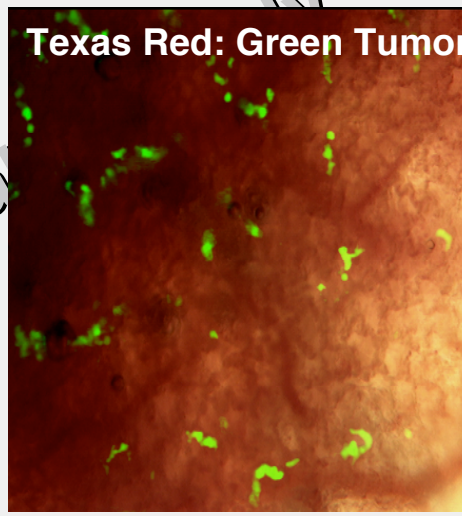
Imaging

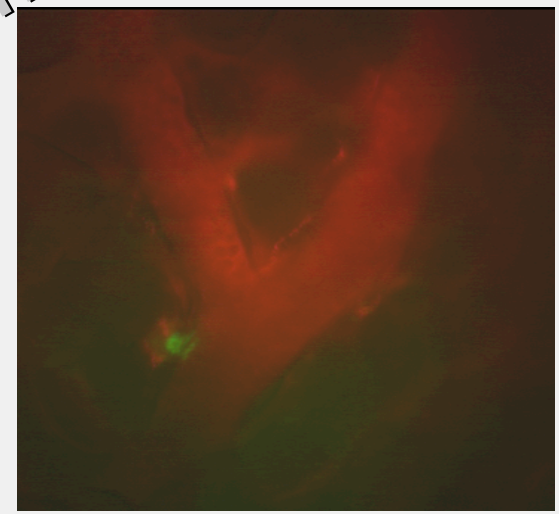


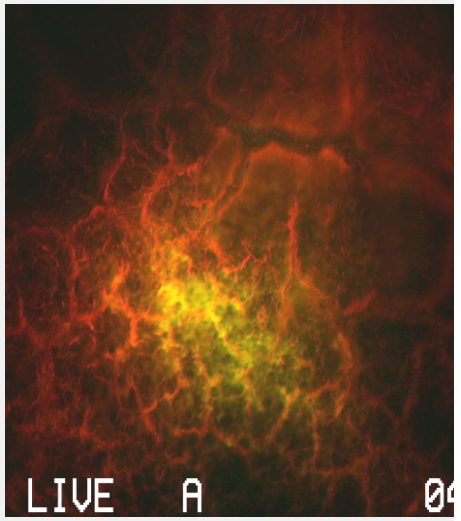


Green Tumor:
CMFDA Label

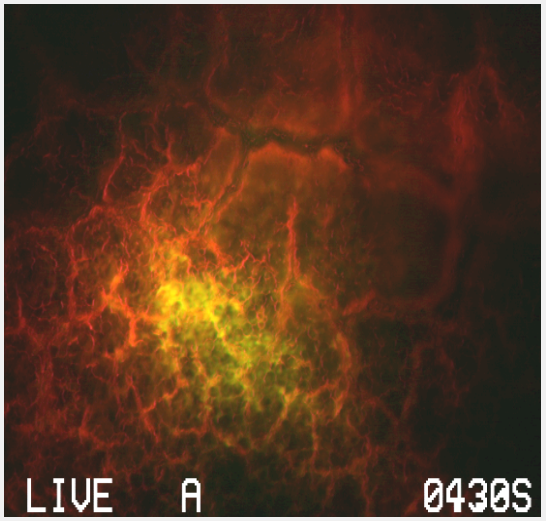






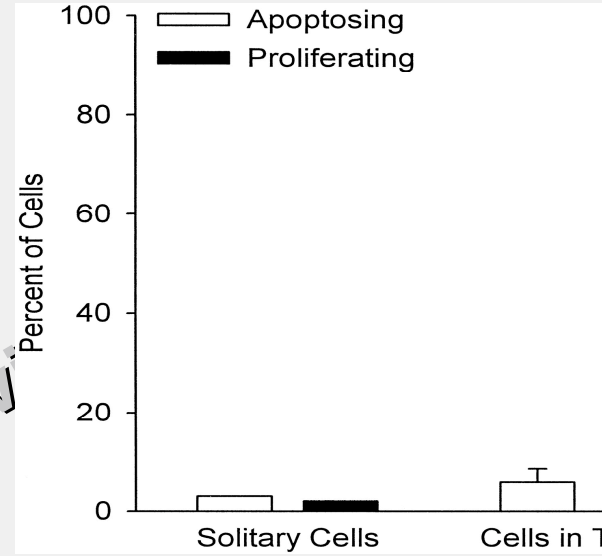


What are dormant cells?

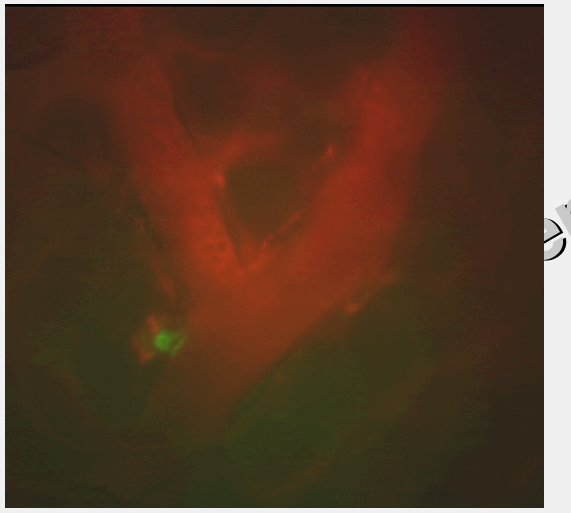


Micrometastases - Balanced division and apoptosis

- Pre or post angiogenic
- May be micrometastases
- Potentially affected by cytotoxic therapy
- Potentially affected by antiangiogenic therapy



Luzzi et al, *Am J Pathology* 1988, 153: 8



Khanna et al, *Nature Med* 2004

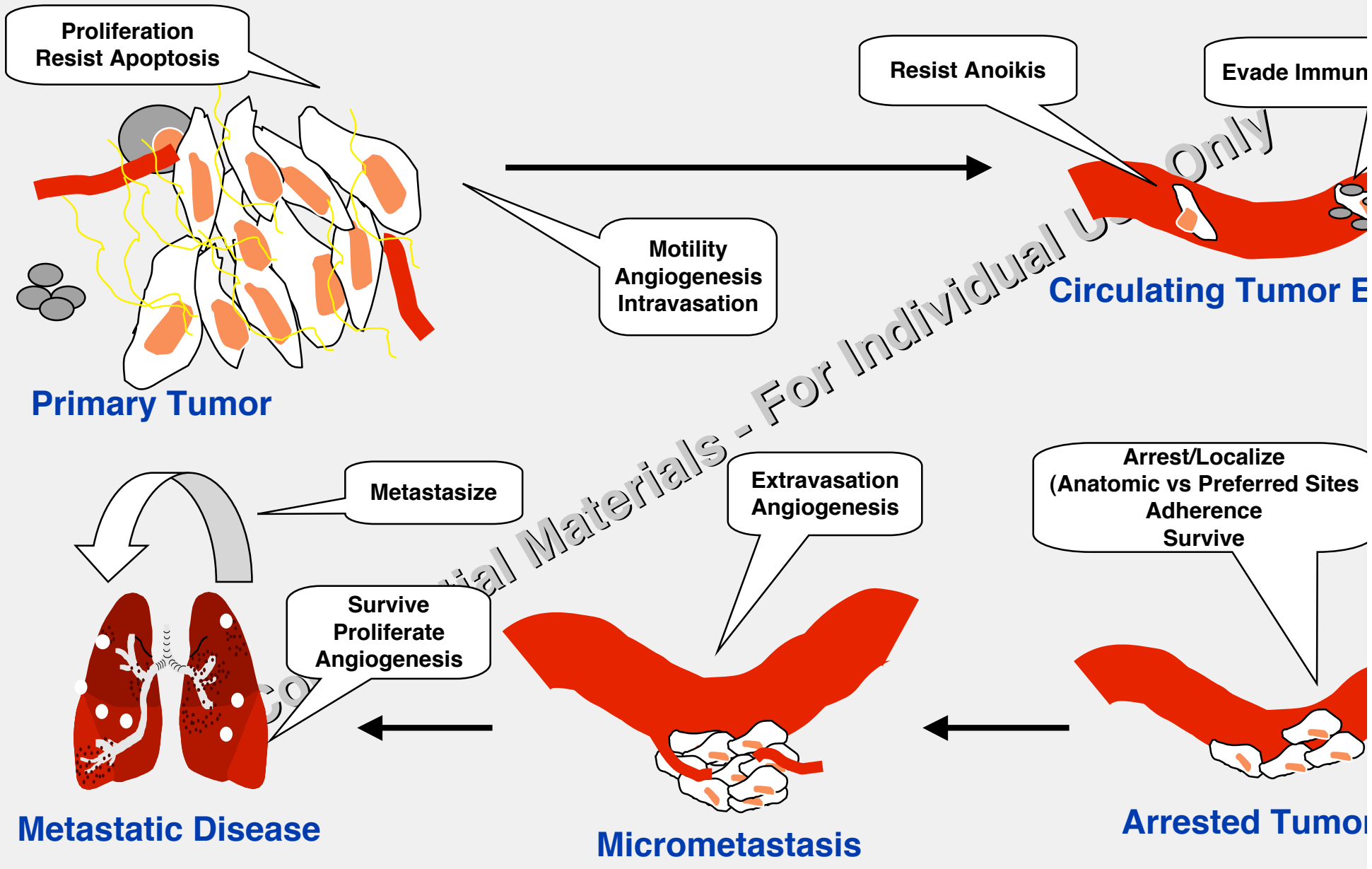
Quiescent dormant Cells - No division or apoptosis

- Pre angiogenic
- NOT micrometastases
- NOT affected by cytotoxic therapy
- NOT affected by antiangiogenic therapy
- Require novel therapies

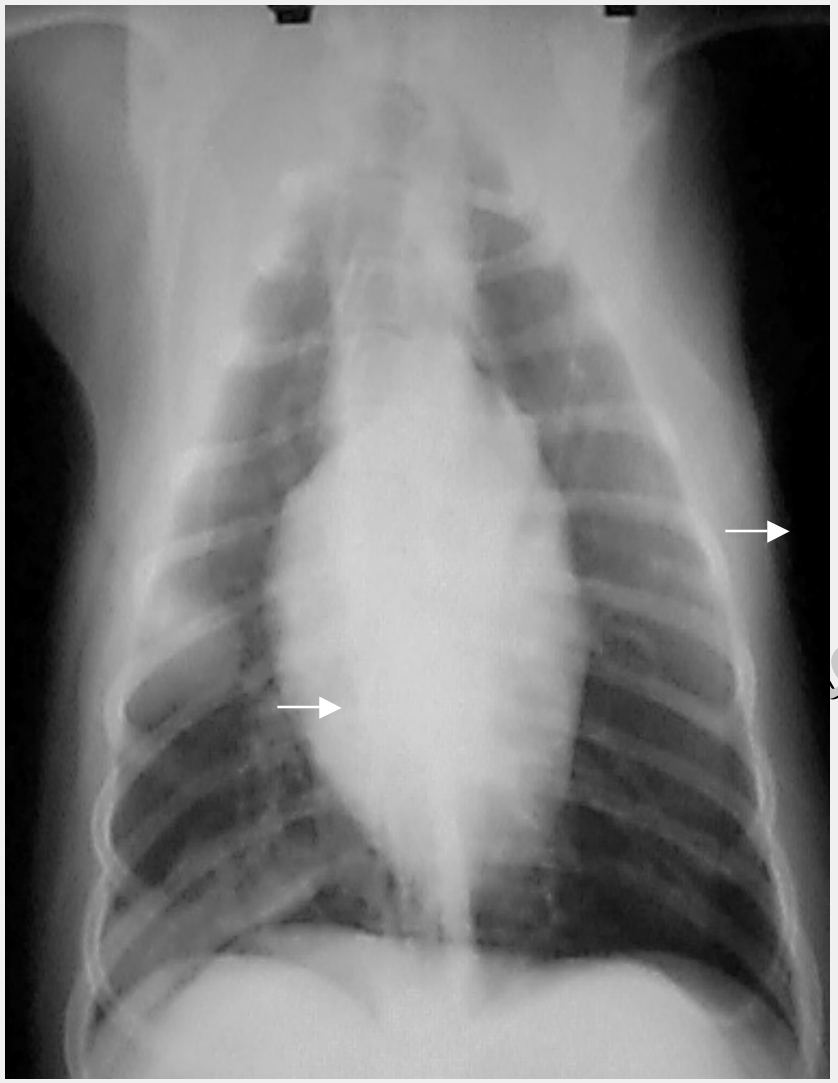
Dormancy in Osteosarcoma

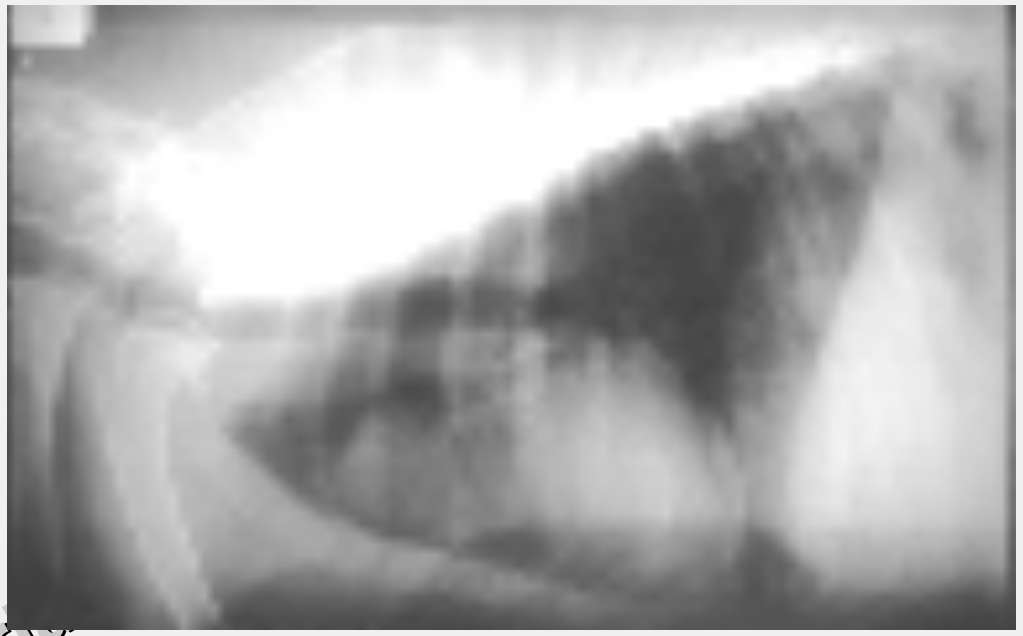
- **Primary tumor control alone - 4 months**
- **Primary tumor control + Chemotherapy - 9-16 months**
  - **Supports presence of chemotherapy sensitive microscopic cells**
    - **Likely post-angiogenic**
    - **Likely in balanced proliferation:apoptosis or favoring proliferation**
    - **Suggested terminology = Micrometastases**
- **Primary Tumor control + chemotherapy (Late recurrence)**
  - **Late plateau in survival curve - Less than 20% are cured**
  - **Supports presence of chemotherapy RESISTANT microscopic cells**
    - **Pre-angiogenic**
    - **No division or apoptosis**
    - **Suggested Terminology = Dormant metastatic cells**

Metastasis Biology: Chemoresistance of established metastases



Chemoresistance of Gross Pulmonary Metastases

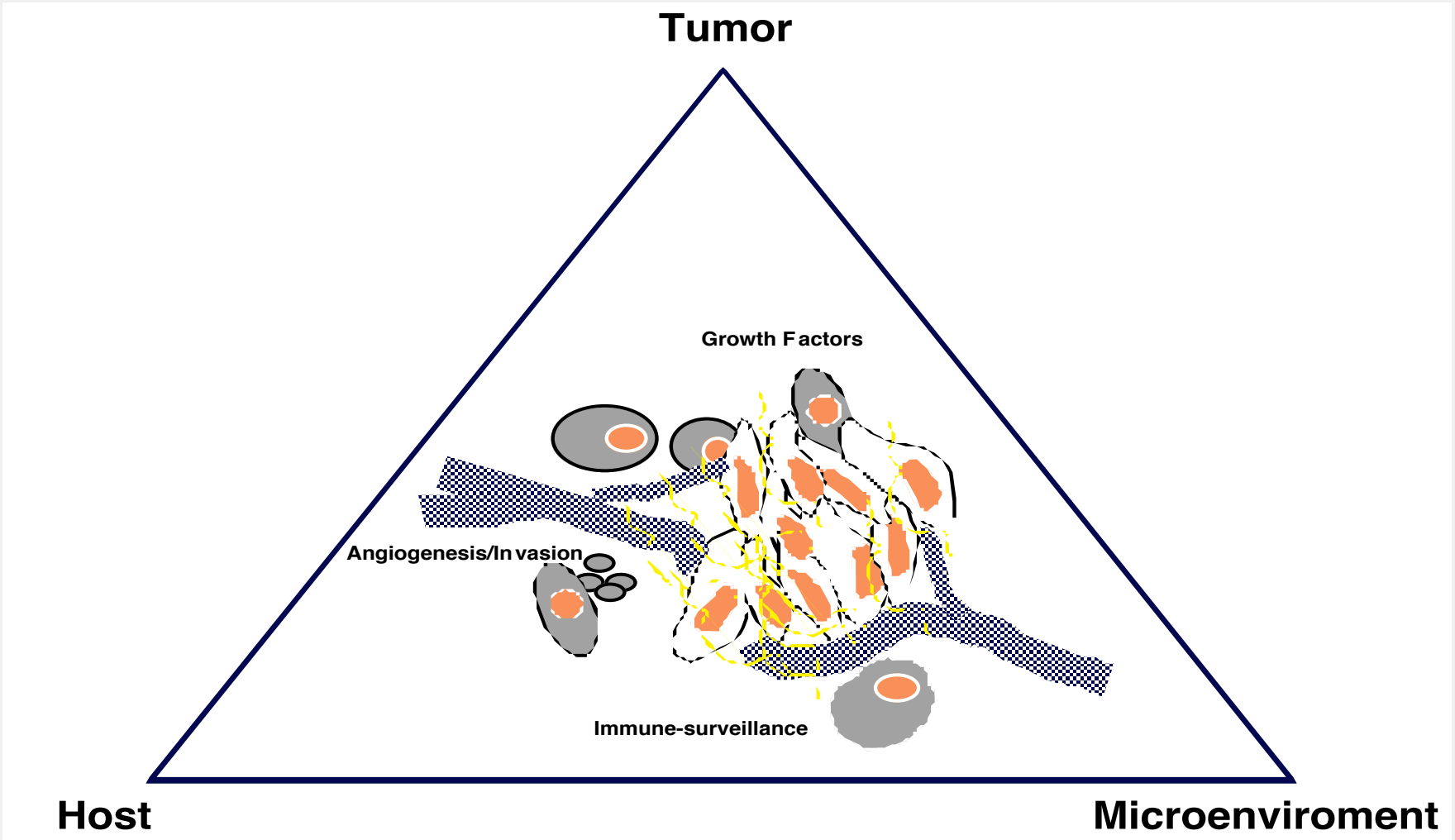




Osteosarcoma Pulmonary Metastases
Study of 42 dogs
-Single agent chemotherapy
-one objective response
-response duration of 21 days

-anecdotal experience suggest better outcomes with multiagent therapy

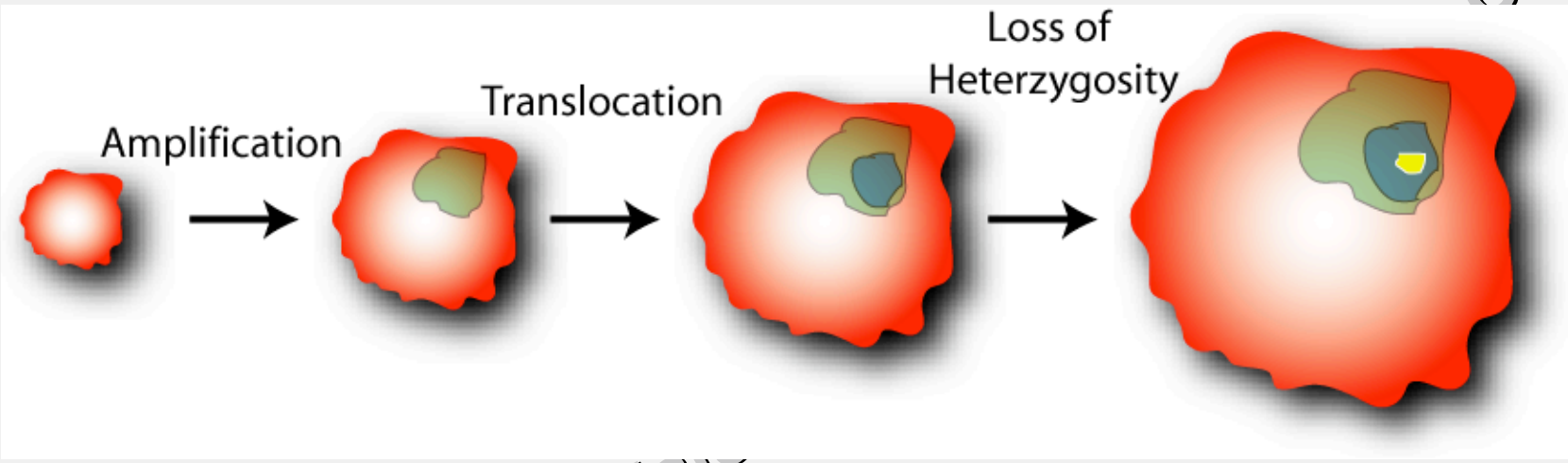
Host - Tumor - Microenvironment Define Metastasis Biology



- tumor growth and metastasis are influenced by host, microenvironment and tumor determinants.

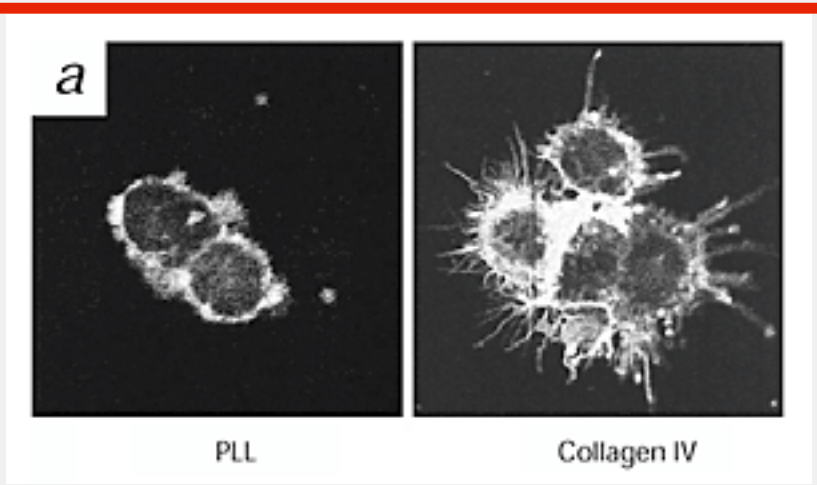
Why are Gross Metastases Resistant?

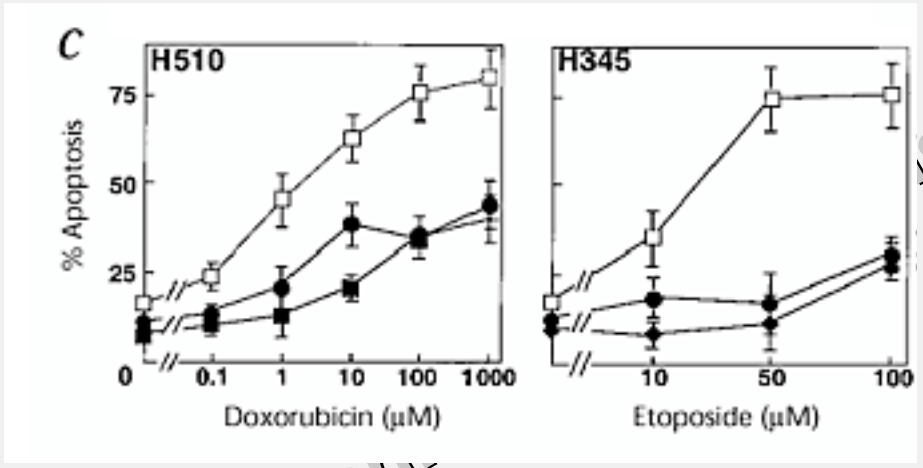
Metastatic Clones are the decathaletes…therefore they are expected to be more resistant than the primary tumor



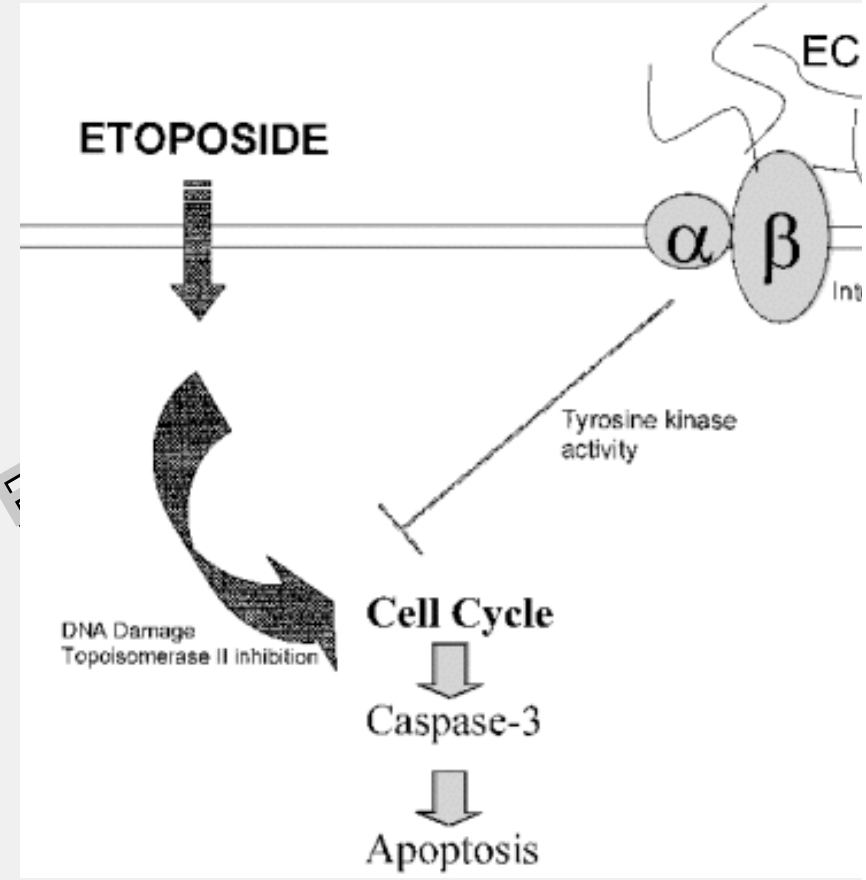
Why then is adjvuant therapy for micrometastatic disease active; Whereas gross metastases is not as active?

Chemoresistance of Gross Metastases





Sethi et al, Nat Med. 1999 Jun;5(6):662-8.



Rintoul et al, Clin Sci. 2002 Apr;102(4):417-2

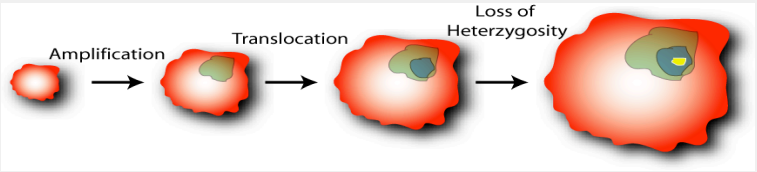
Tumor-microenvironment interactions provide a basis t
understand the resistance of metastasis to conventional th

Temporal Chemoresistance of Metastases…

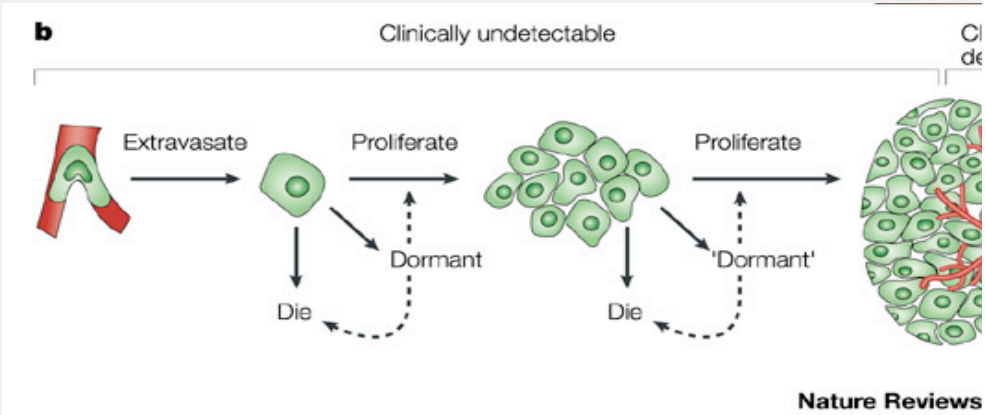
Primary tumor

Chemosensitive

Progressive acquisition of resistant phenotype



Chemoresistant



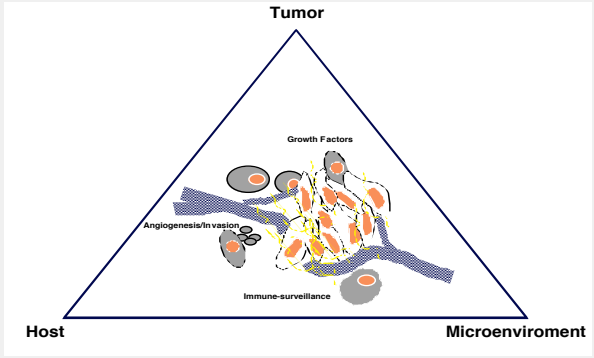
Dormant Metastasis

Chemoresistant

Micrometastasis

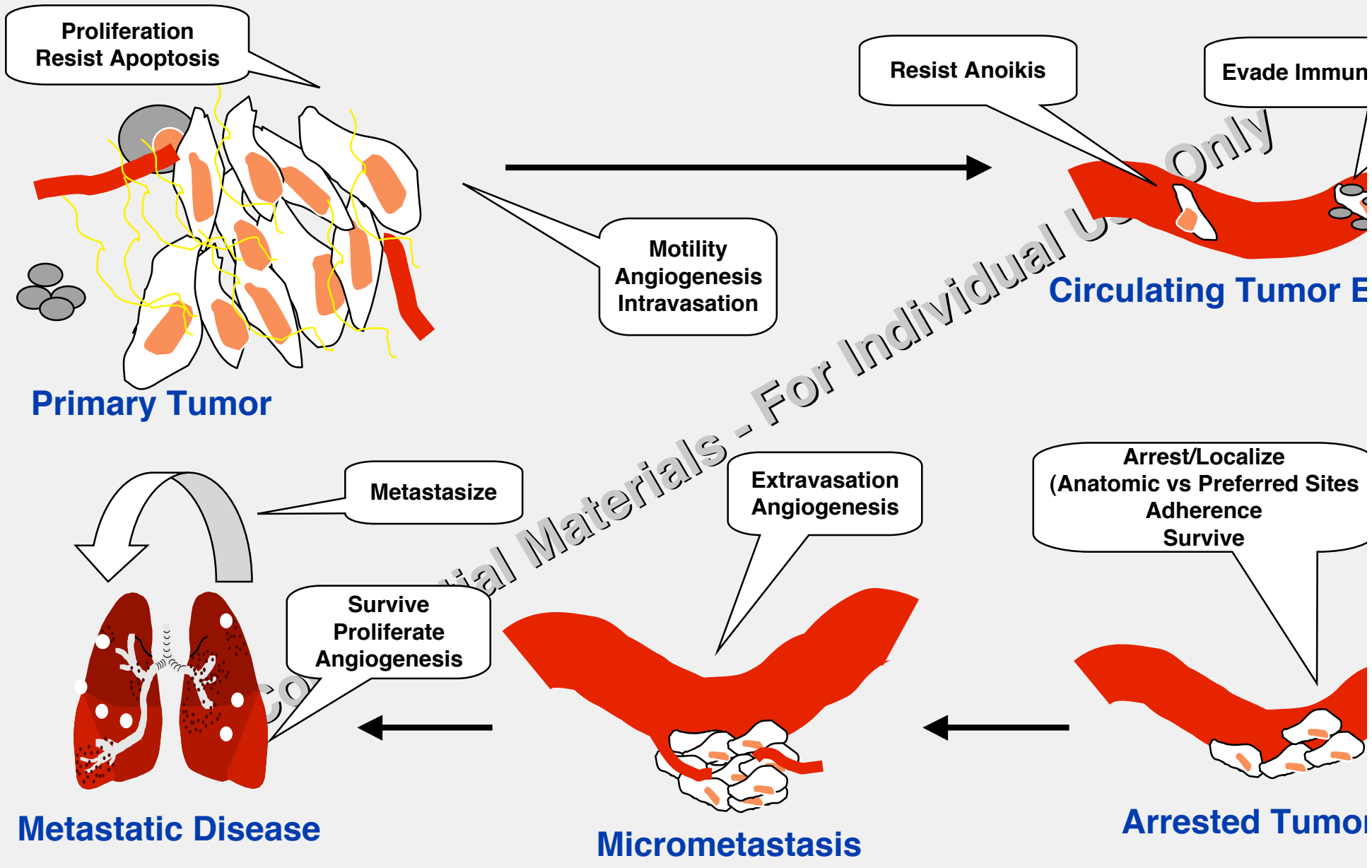
Chemosensitive

Established Metastasis

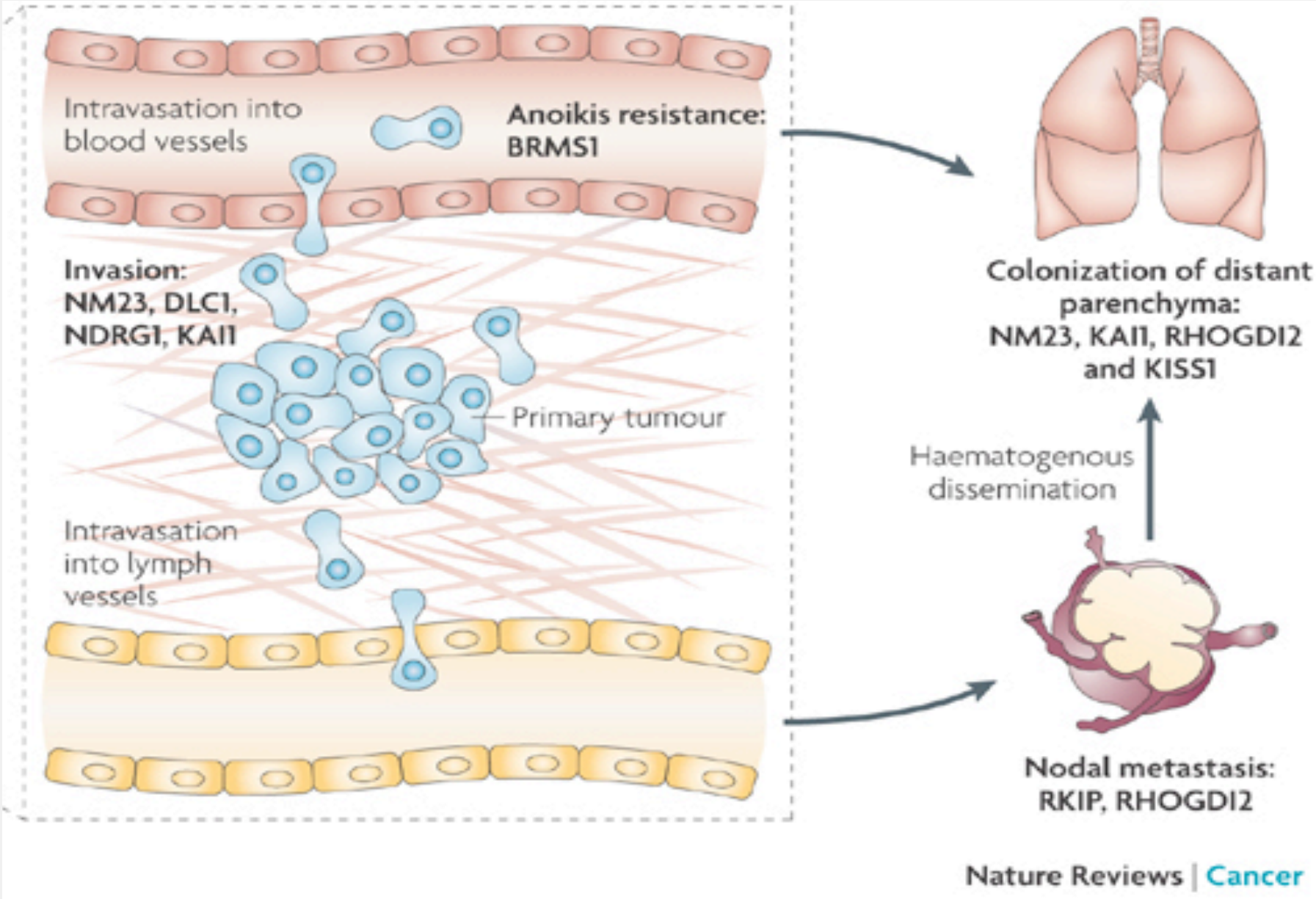


Chemore

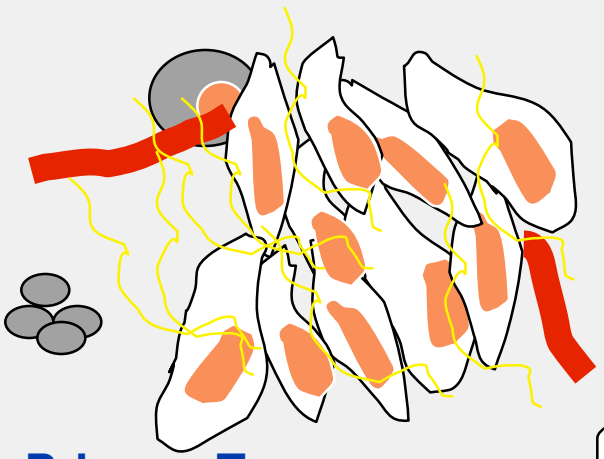
Metastasis Biology: Metastasis-Associated Genes and Pathways



Metastasis Suppressors



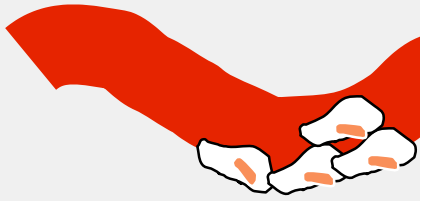
Metastasis Biology: Metastasis-Associated Genes and Pathways



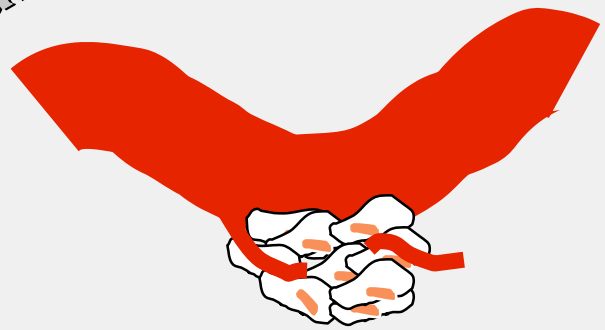
Primary Tumor

Epithelial Mesenchymal Transition
Motility/Invasion

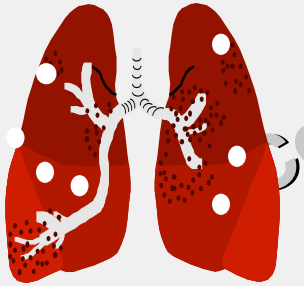
Circulating Tumor E



Arrested Tumor

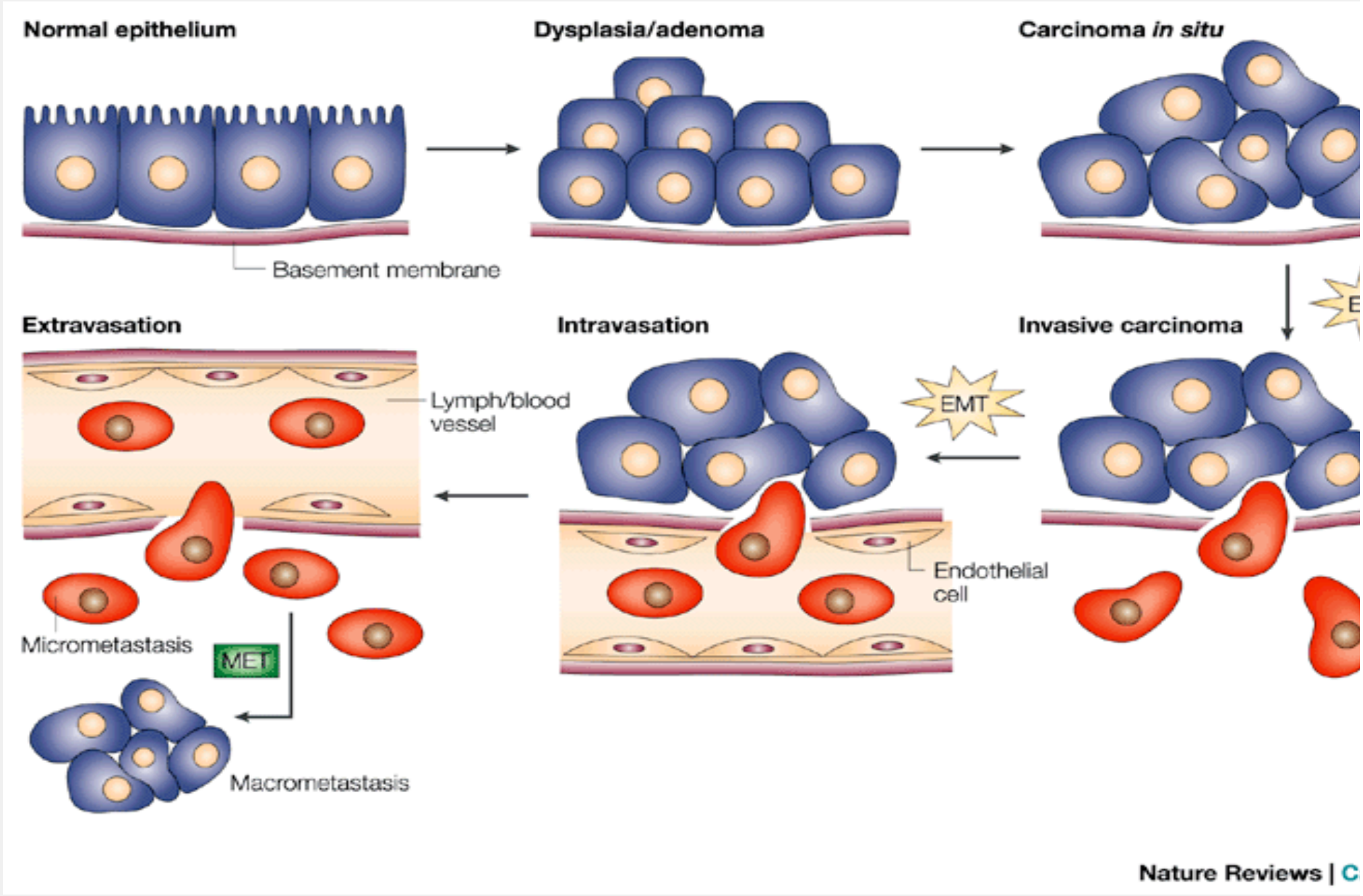


Micrometastasis

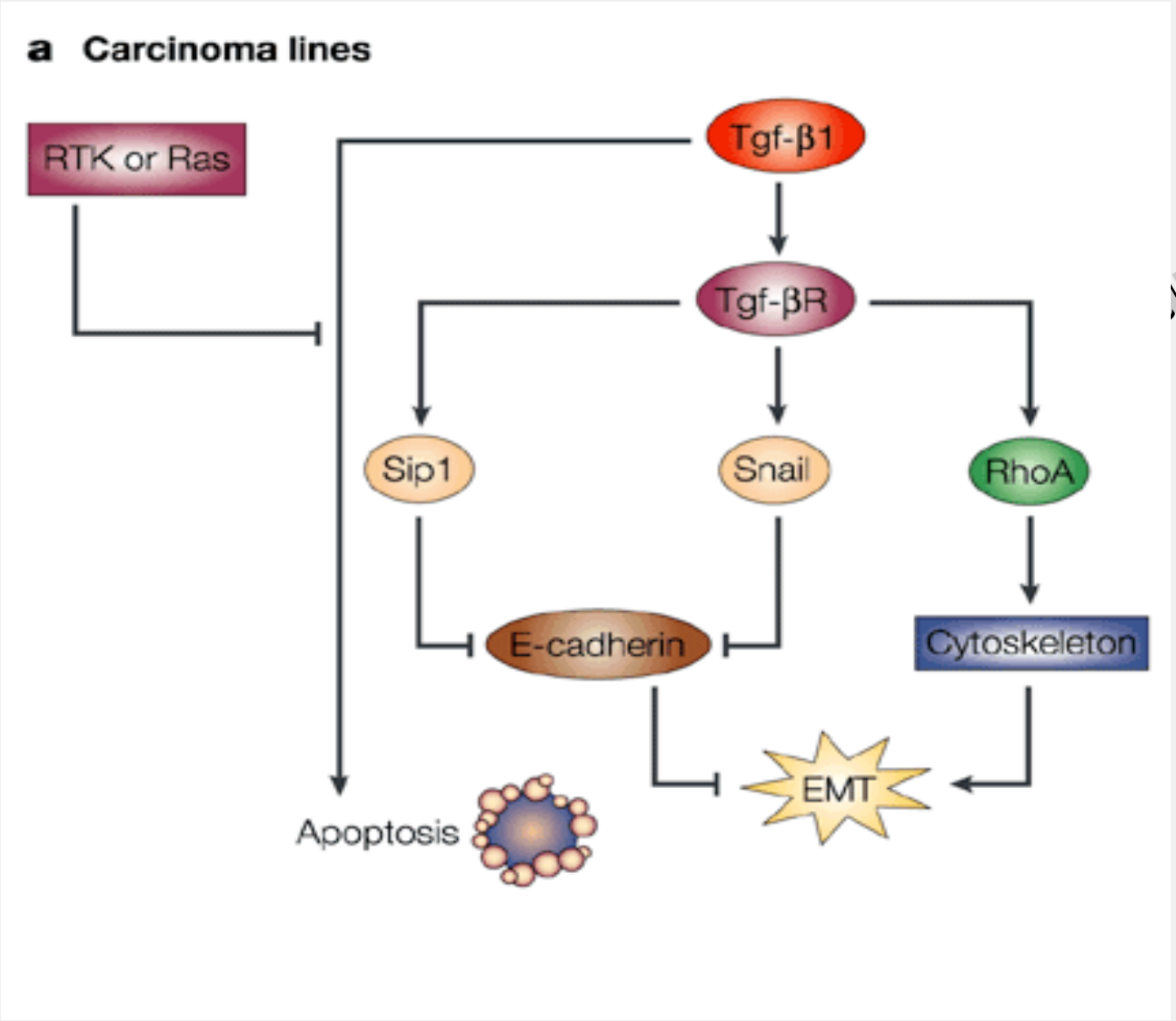


Metastatic Disease

Epithelial to Mesenchymal and then Mesenchymal to Epithelial Transitions



Regulation of EMT involves loss of cell-cell interaction and cytoskeleton mobiliza



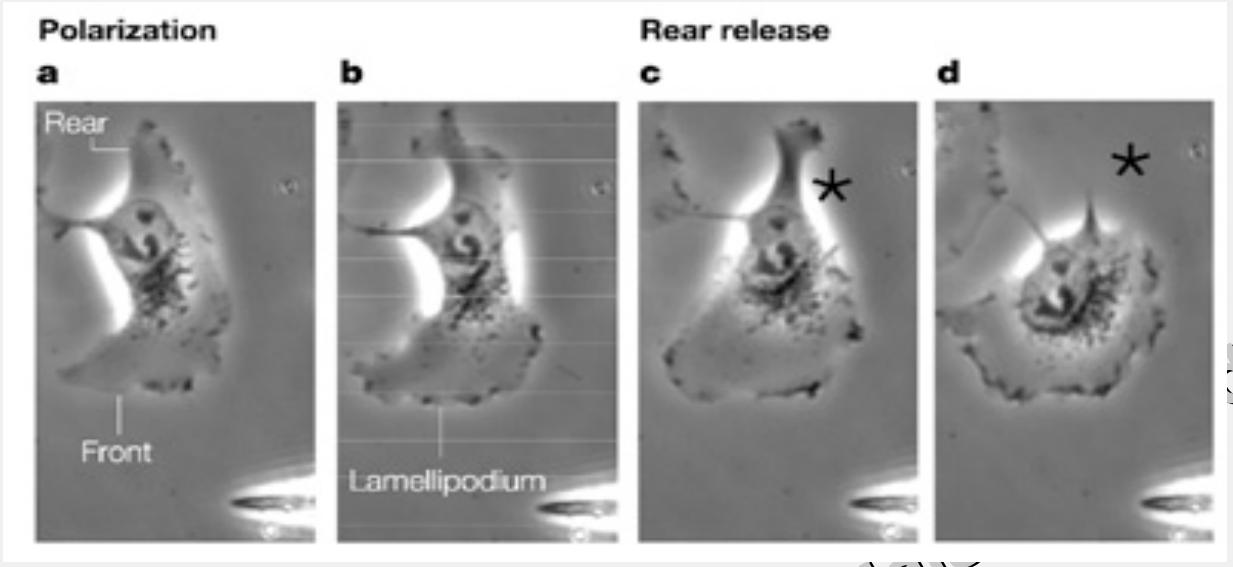
Step 1:
Signal activation

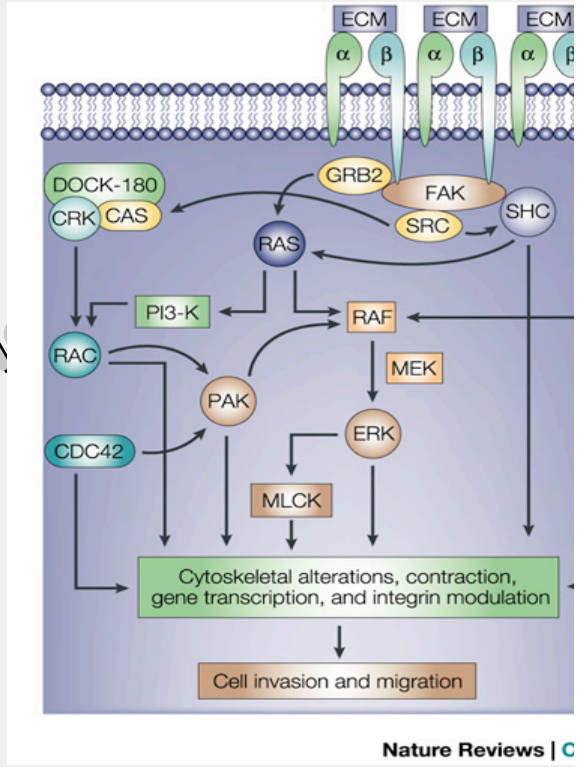
Step 2:
Disruption of cell-cell contacts

Step 3:
Cytoskeleton mobiliza

Step 4:
Re-establish cell cont

The invasive and motile phenotype





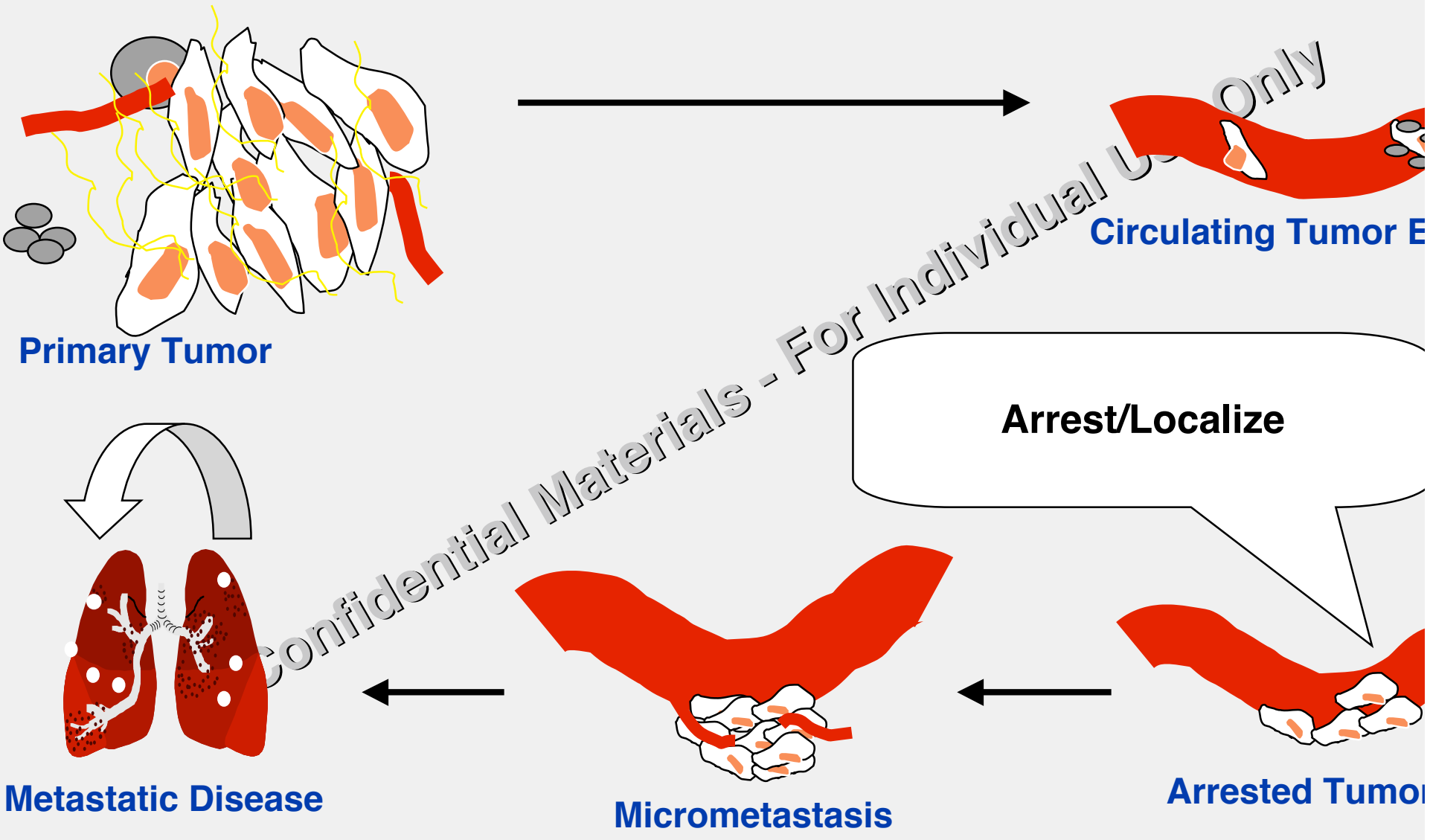
Signalling pathways linked to motile and invasive phenotype:

- Integrins
- RAS/RAC
- PI3 Kinase
- MEK

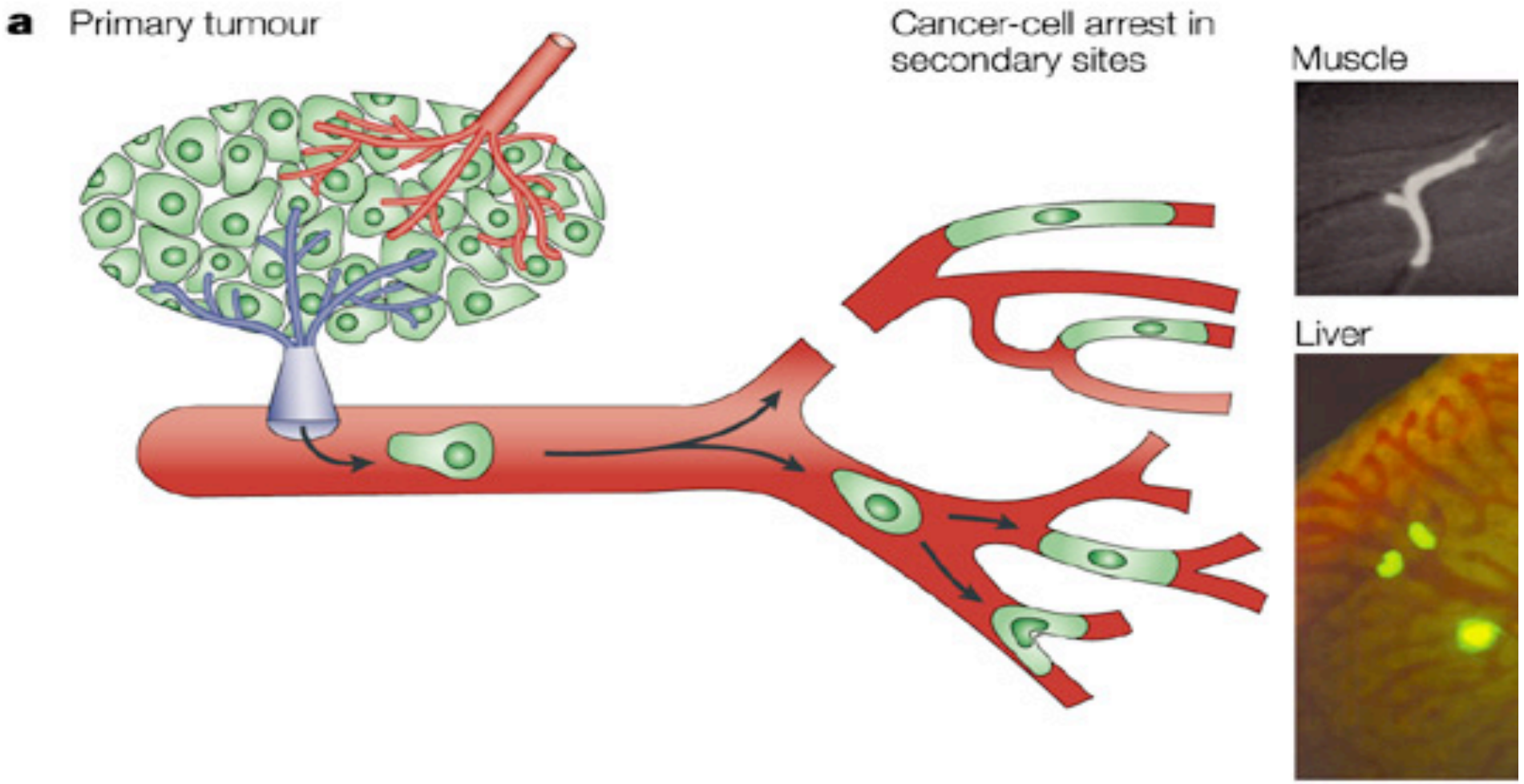
Effectors of motile and invasi phenotype:

- Focal adhesion kinase
- Ezrin
- Paxillin
- MLCK
- Matrix metalloproteins

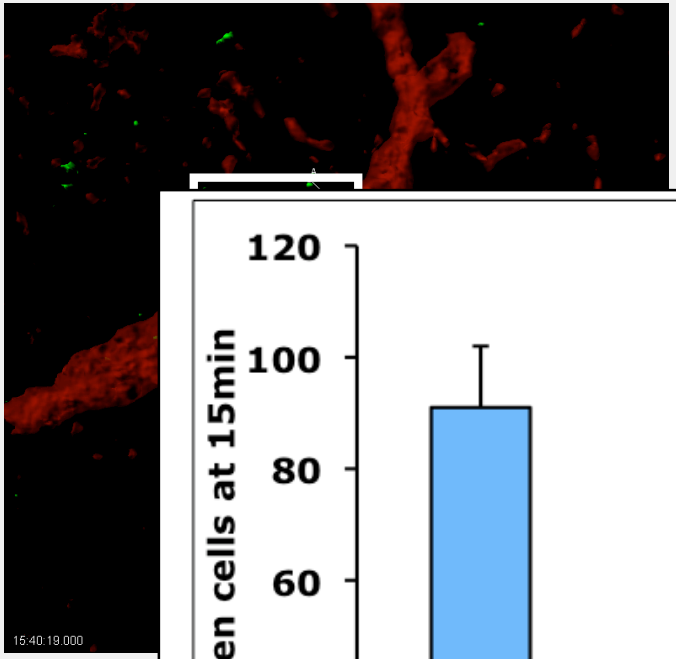
Metastasis Biology: Metastasis-Associated Genes and Pathways

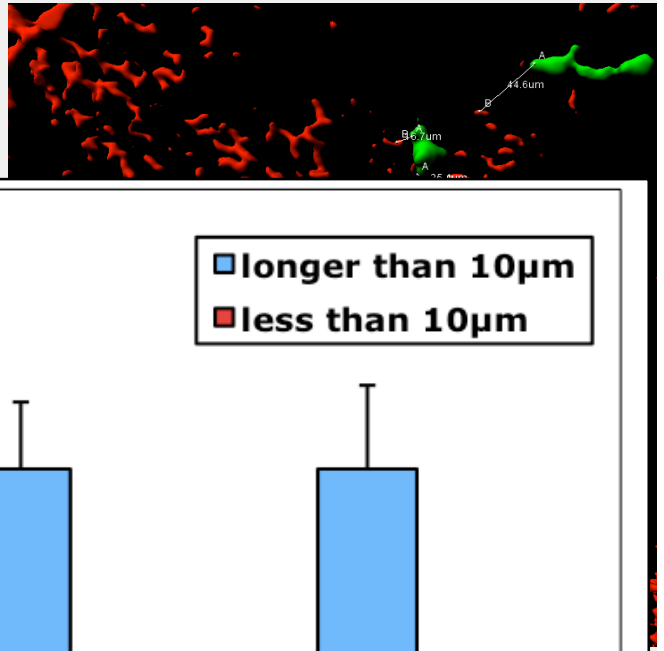


Arrest at secondary sites results from vascular trapping

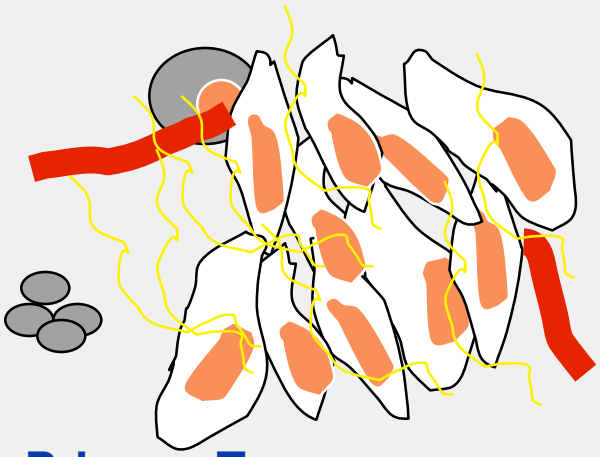


Rapid transendoethelial migration occurs early in both metastatic and non-metastatic cells





Metastasis Biology: Metastasis-Associated Genes and Pathways



Primary Tumor

Circulating Tumor E

Adherence
Survive

Arrested Tumor

Micrometastasis

Metastatic Disease

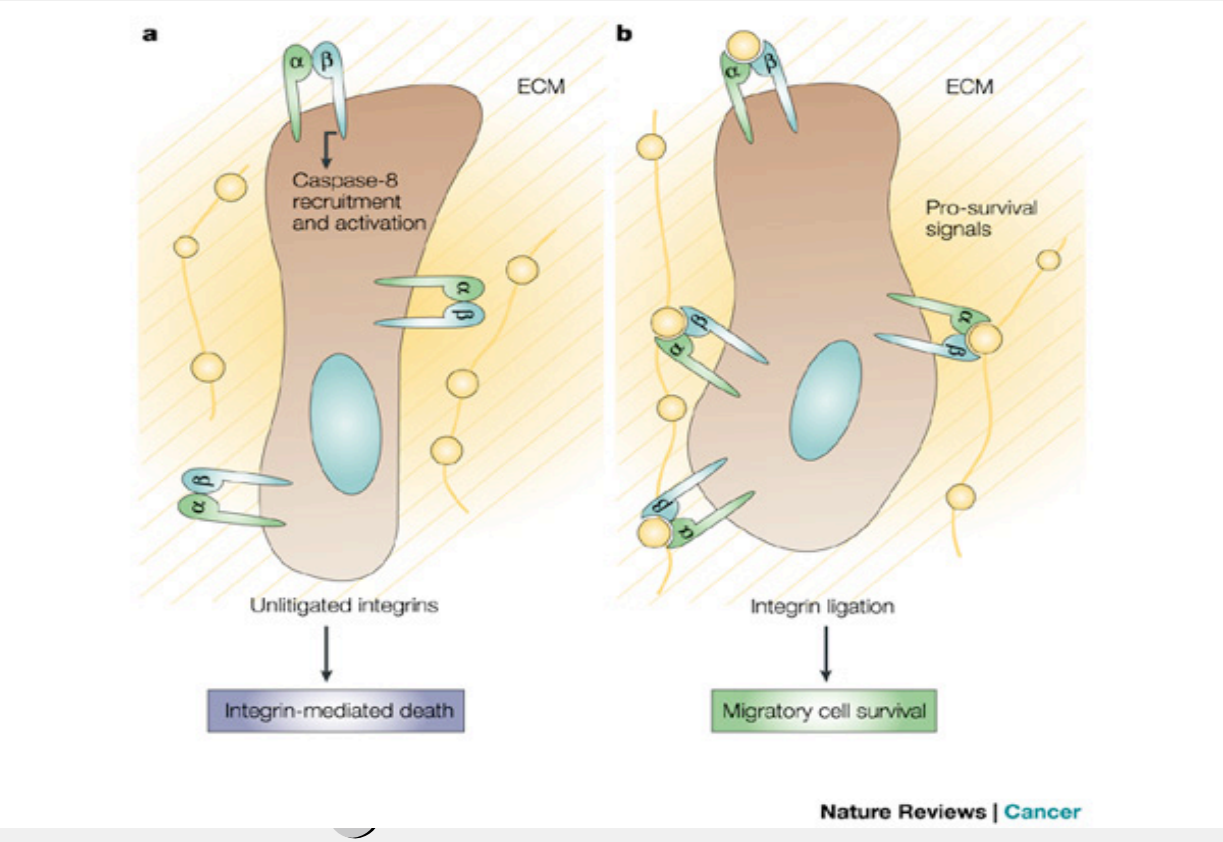
Paget's seed and soil

A model for describing organ specific metastasis

Hypothesis for determinants of metastatic success

A mechanism to explain the seed and soil hypothesis

Non permissive soil **Permissive soil**



Non Permissive Soil

- Each integrin heterodimer binds distinct sets of extracellular mat (ECM) molecules, and ECM composition is tissue-type spec
- Integrin binding to extracellular ligands prevents apoptosis.
- Neoplastic cells must overcome ability of the extracellular matrix to induce 'integrin-mediated dea

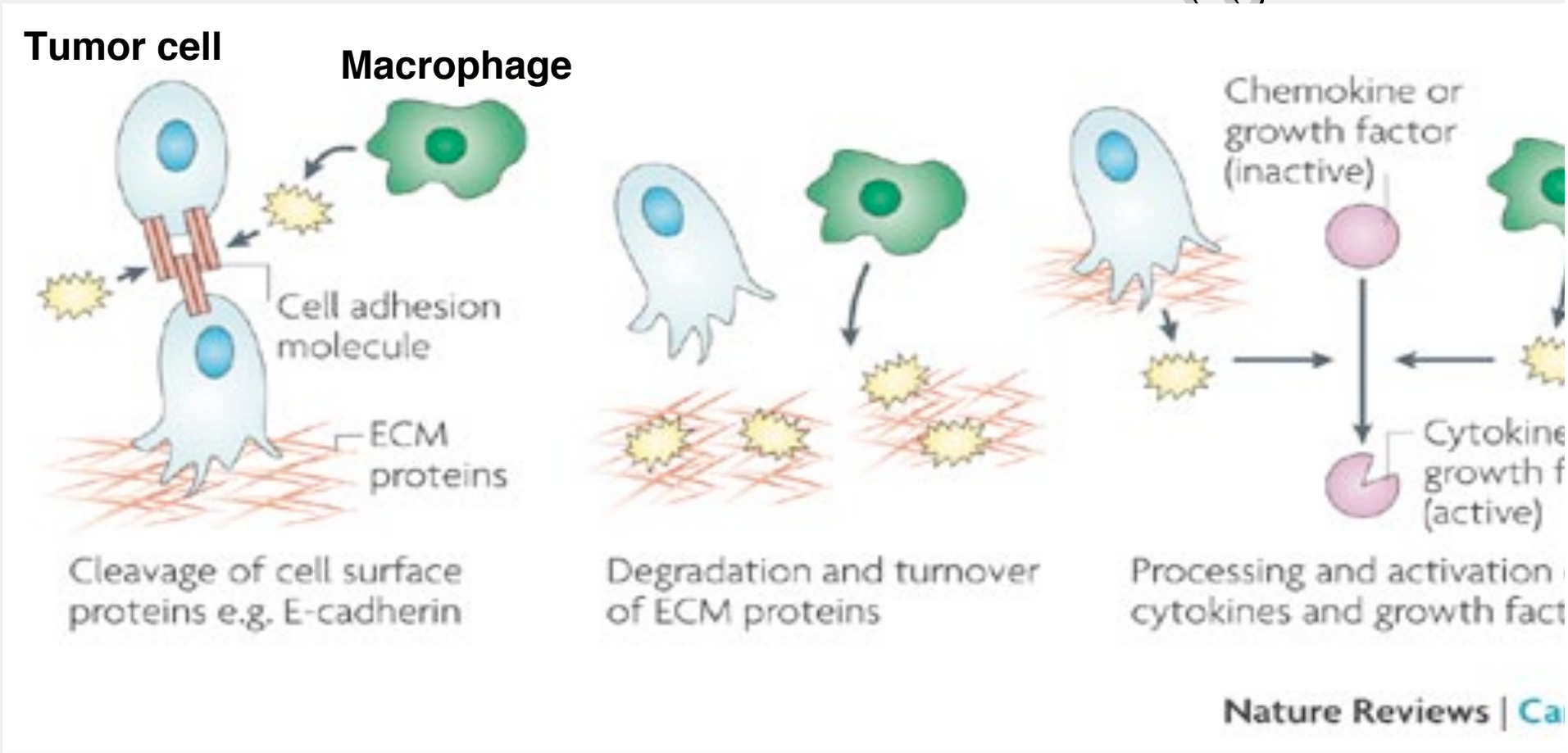
Permissive Soil

- If the ECM contains the appropr ligands, the integrin is properly thereby inducing pro-survival si

ECM composition governs cell survival as a function of the integrins t are expressed on the surface of a cell that is occupying new territor

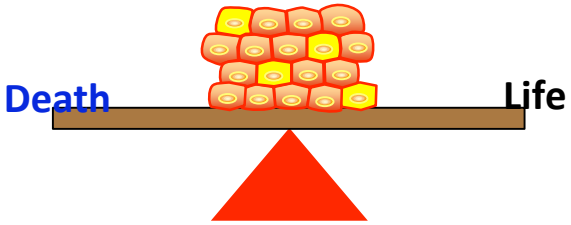
The role of the macrophage in metastasis progression

Macrophage Phenotypes:
GM-CSF: immunomodulatory
CSF-1 (IL-10): cancer promoting

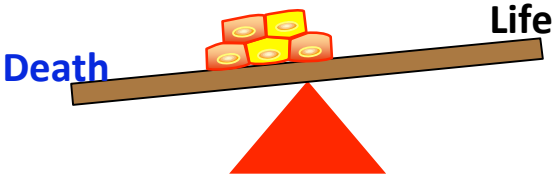


Stress

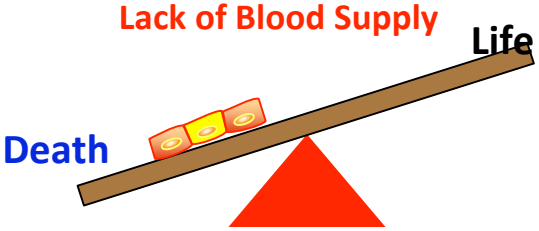
Nutrition, Reactive Species, Inflammation



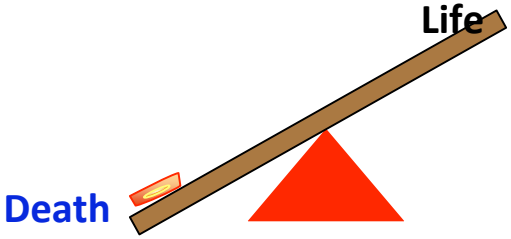
Anoikis, Immune Cells,
Circulatory Turbulence



Foreign Microenvironment,
Lack of Blood Supply

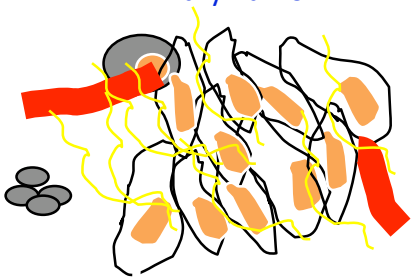


Hypoxia, pH stress, Apoptosis

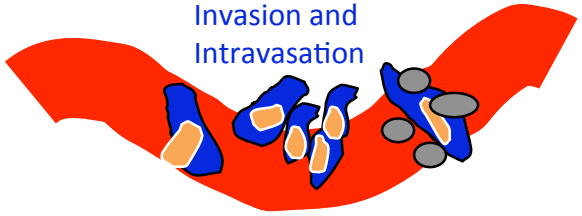


Stage

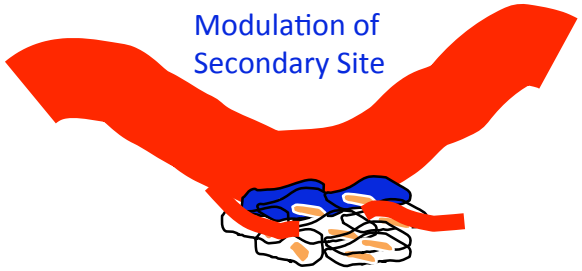
Primary Tumor



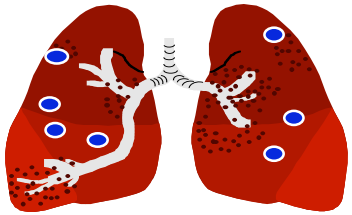
Invasion and
Intravasation



Modulation of
Secondary Site

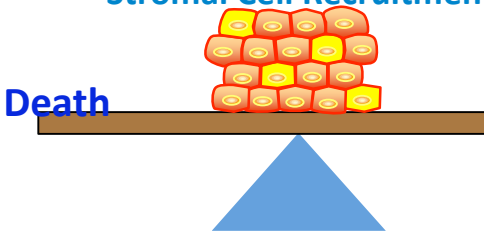


Metastatic Disease

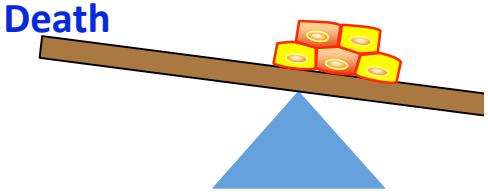


Coping Mechanism

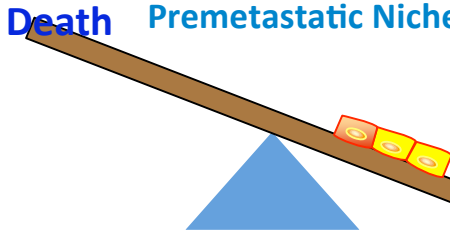
Angiogenesis, GF Productio
Stromal Cell Recruitment



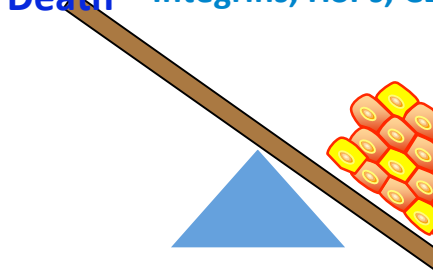
MMPs, Immune Suppress



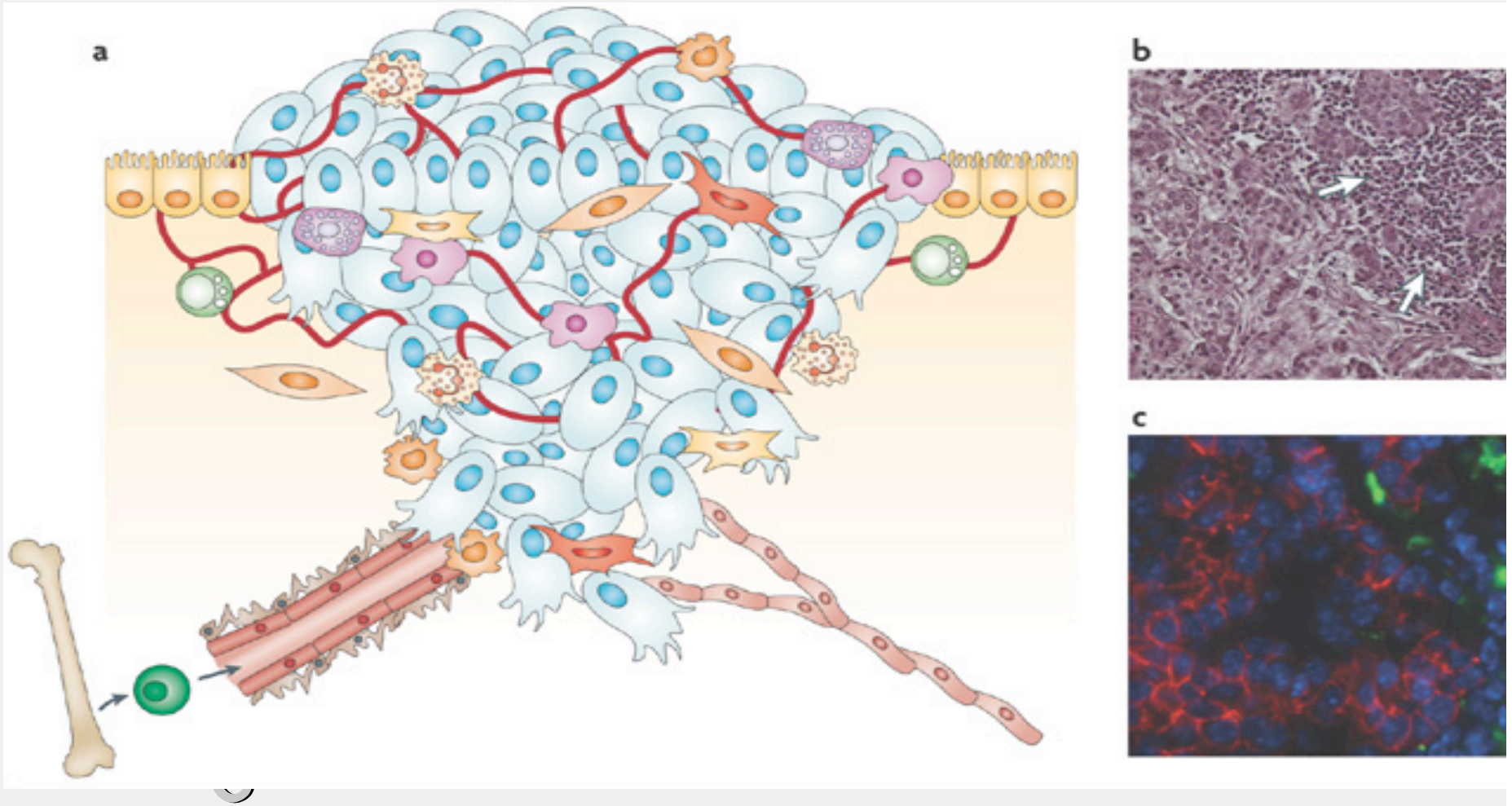
Chemokines, Angiogen
Premetastatic Niche



Signaling Networks Acti
Integrins, HSPs, Cl



Tumor - microenvironment interaction defines metastatic phenotype



Targeting metastatic stress

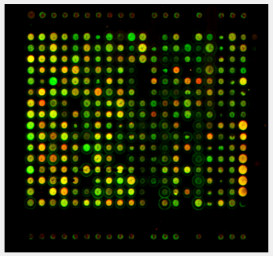
- **Coordinate efficient generation of new proteins (and other biomolecules).**
  - **Enabled translation initiation**
  - **Protect valuable proteins (HSP)**
    - **Example Ezrin - mTOR**
    - **Therapeutic opportunity - Rapamycin**
- **Coordinate efficient disposal of proteins (and other biomolecules).**
  - **Active proteosomal and degredation paths**
  - **Manage stress of chronic "unfolded protein response" (UPR)**
    - **Therapeutic opportunity - Proteosome inhibitors**
- **Efficiently manage energy use and maintain cellular energy**
    - **Example glucose and lipid homeostasis**
    - **Therapeutic opportunity - Metformin**
- **Actively engage the microenvironment**
    - **Example Endothelin axis in osteosarcoma**
    - **Therapeutic opportunity - Endothelin inhibitors**

Metastasis Biology: The Dogma that is in dispute

Metastsatic Process	Efficiency	Best target for treatment
Intravasation	Inefficient	Possible
Survival in circulation	Efficient	Not Likely?
Arrest at distant site	Efficient	Not Likely?
Survival at distant site	Inefficient	Yes
Initiation of growth	Inefficient	Yes
Persistence of Growth	Inefficient	Yes

From: Chambers et al Breast Cancer Res 20

Ezrin Is Associated With the Metastatic Phenotype in a Murine Osteosarcoma Mode



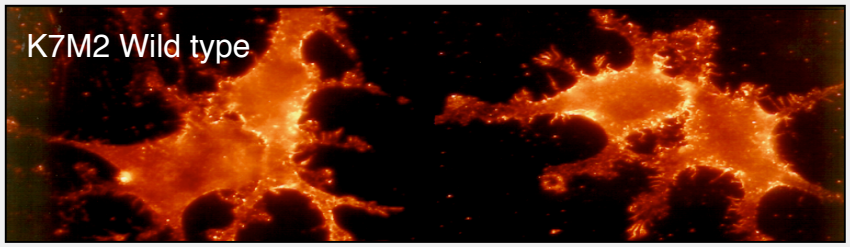
Highly Metastatic K7M2 Primary Tumor

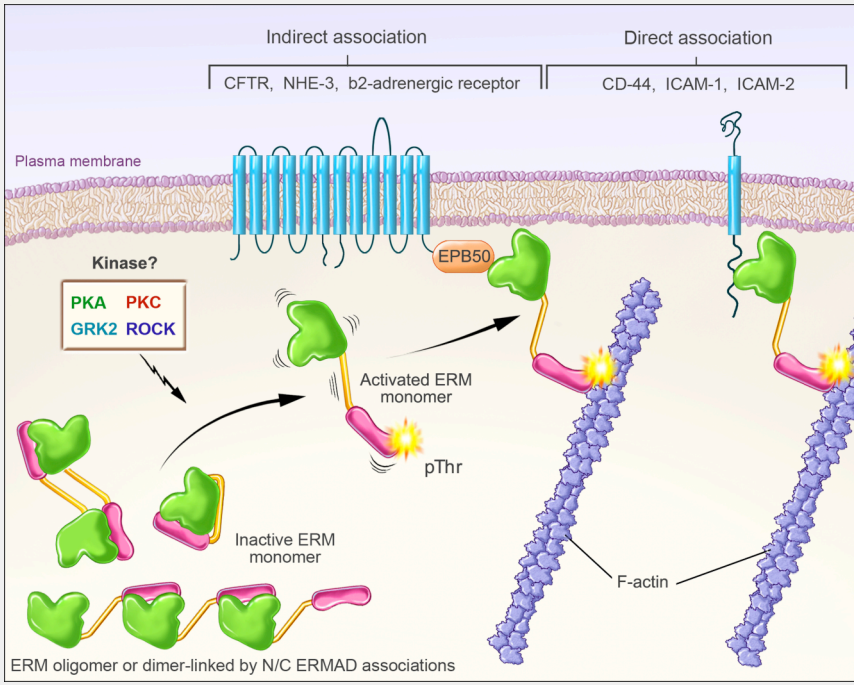
VS

Less Metastatic K12 Primary Tumor

Khanna et al Clin and Exp Metas

EZRIN (Vil2)

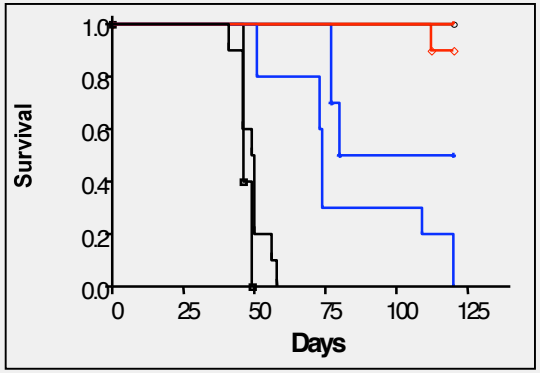




***Khanna et al Cancer Research*, 2002**

Ezrin Is Consistently Associated With Metastatic Progression in Osteosarcoma - Across Sp

Rodent Models

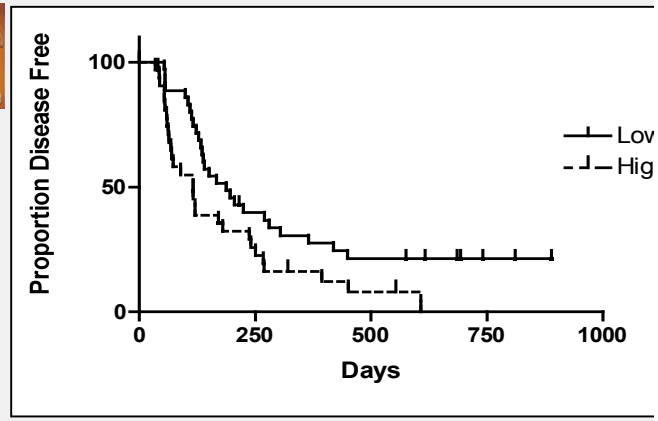


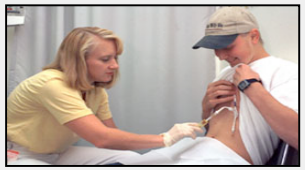
Low Ezrin

Intermed Ezrin

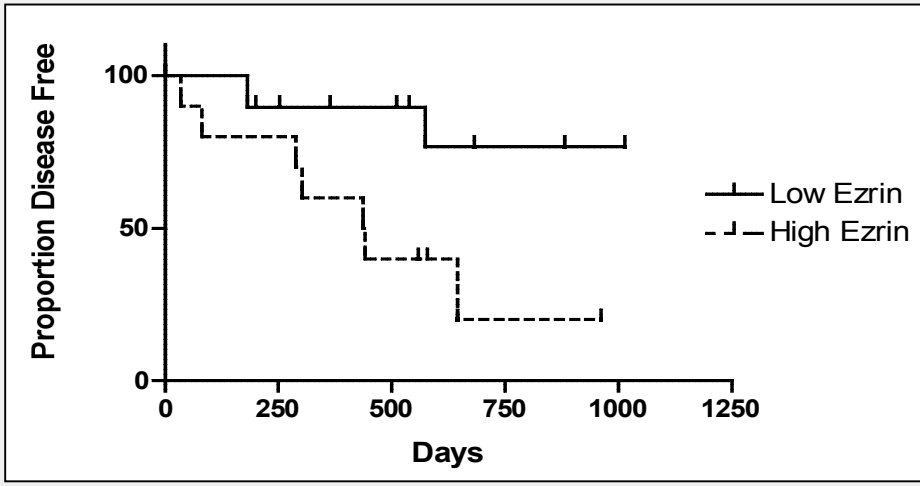
High Ezrin

Canine Model





Pediatric Osteosarcoma Patients



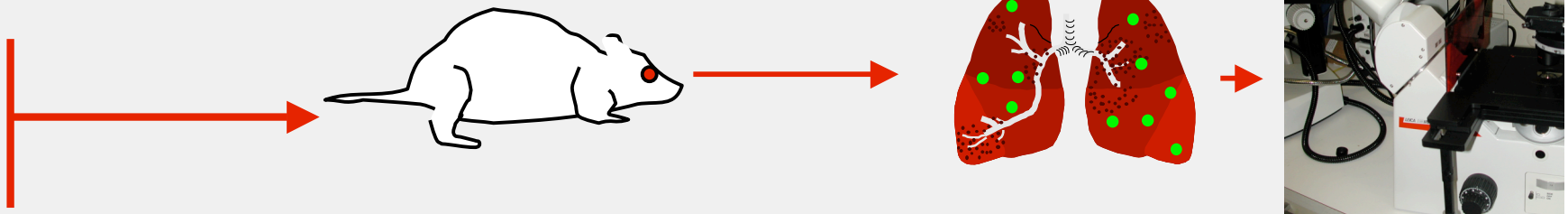
Khanna et al Nature Mec

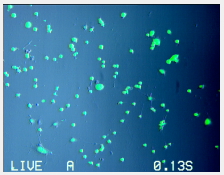
Ezrin and Cancer/Metastasis

- **Osteosarcoma (Nature Medicine, 2004a)**
  - **Necessary for metastasis in murine and canine osteosarcoma models**
  - **Associated with early metastatic failure in children**
- **Rhabdomyosarcoma (Nature Medicine, 2004b)**
  - **Necessary and sufficient for metastasis**
- **Ewings sarcoma (Clin Exp Metastasis, 2006)**
  - **Contributes to xenograft primary tumor growth and metastasis**
- **Other cancers (Clin Exp Metastasis, 2007)**
  - **Expressed in most human cancers**
  - **Aberrant expression in mesenchymal versus epithelial cancers**
- ***Literature***
  - ***Expression associated with disease free interval in melanoma, soft tissue sarcoma breast cancer***
  - ***Advanced histological grade cancers of the endometrial, prostate, and brain***
  - ***Protective role of Ezrin in cancers of the ovary and gastric mucosa***

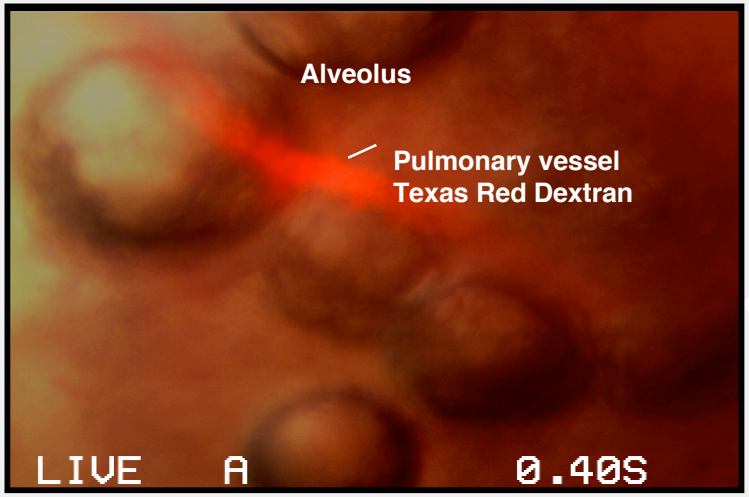
Illuminating the Black-Box of the Metastatic Cascade: Single metastatic cell Imagi

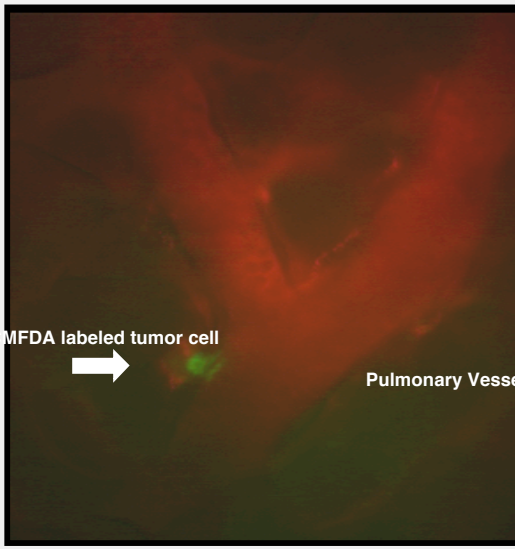
Texas-red Dextran
70000 MW, 10mg/ml
(.2 mls)

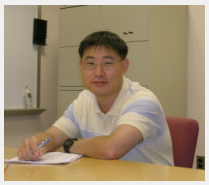




K7M2 OSA cells grown and labeled in-vitro (CMFDA cell tracker label)

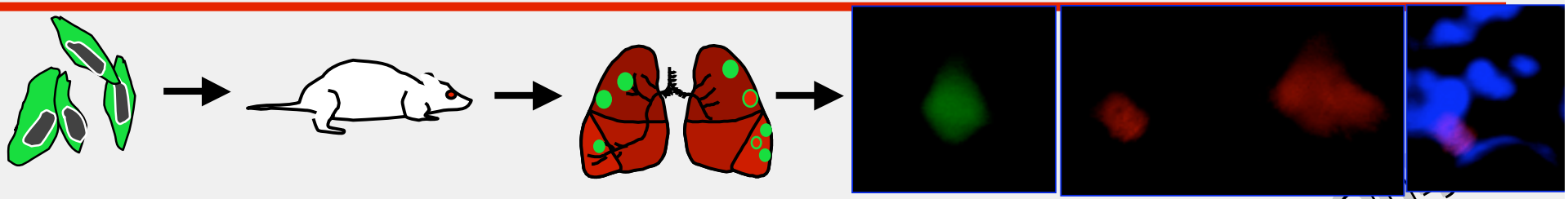




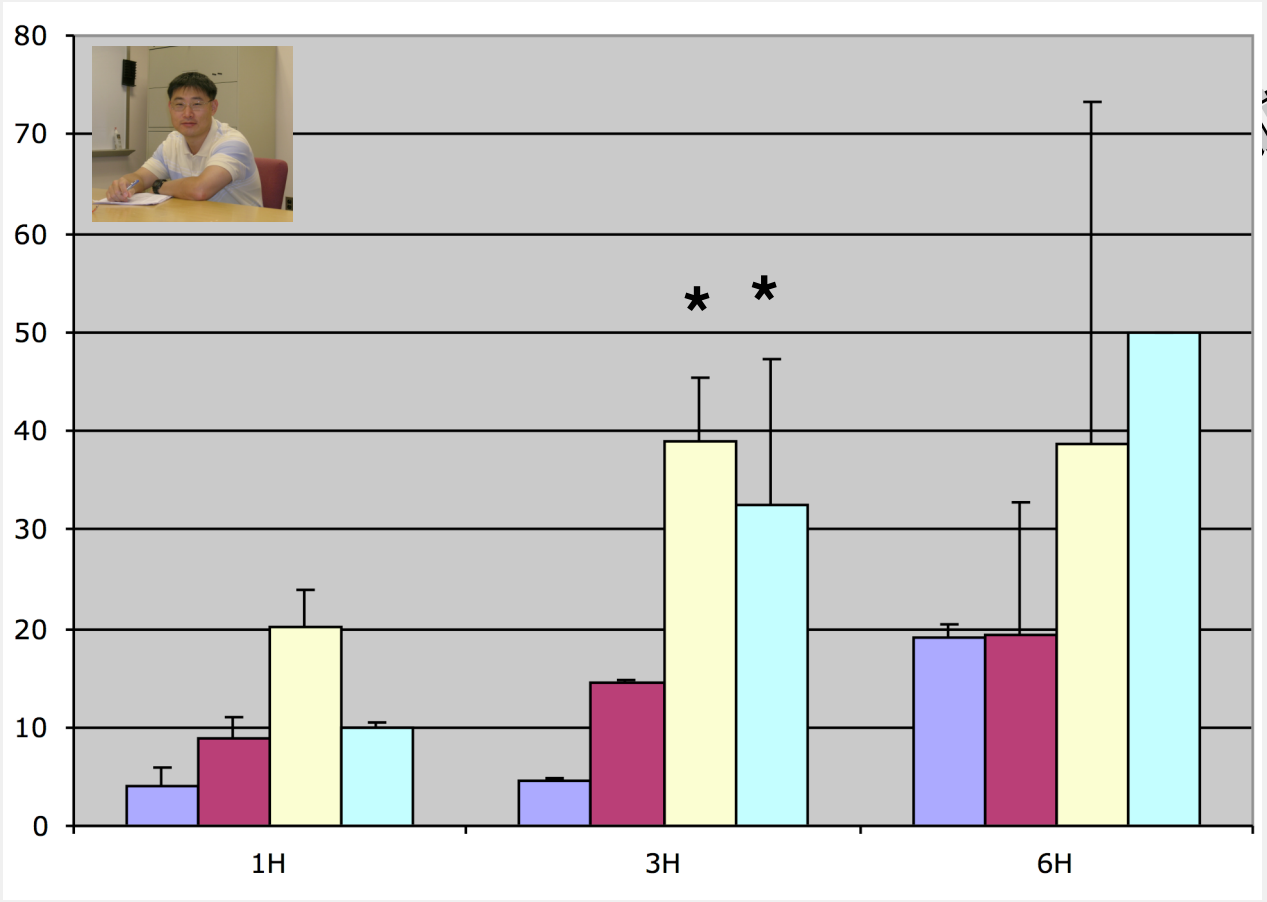


Sung Hyeok Hong
Arnulfo Mendoza
Noma Olumo

Ezrin Protects Cell from Apoptotic Death Early After Arrival in the Lung



Double positive events:
CMFDA -Tumor cell
TUNEL - Apoptotic cell



K7M2 - High Ezrin WT

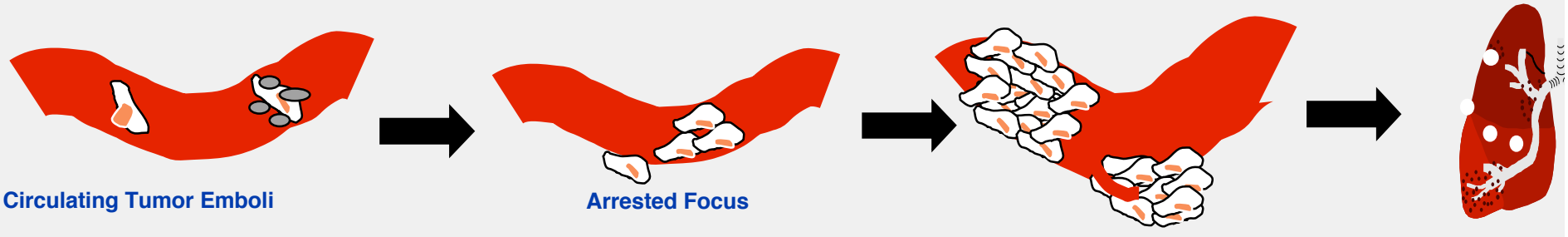
K7M2 Neo - High Ezrin

K7M2 1.46AS - Low Ez

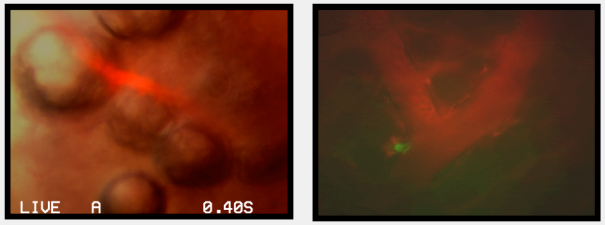
K7M2 1.52AS - Low Ez

TUNEL positive/total tumor c
* p<0.001, Fischer's exact t-

Hypothesis: Ezrin Contributes to Early Metastatic Survival



Ezrin



Adherence (no ezrin effect) -
-vitro (not shown)

Transendothelial migration (no ezrin effect) -
-in vivo/ex vivo

Protection against apoptosis (Marked effect) ✓
-in vivo/ex vivo

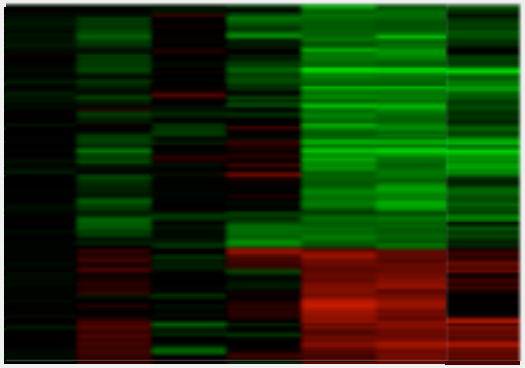
- ***Ezrin provides cancer cells with ability to endure the stress of metastasis.***

Question: How Does Ezrin Contribute to Metastatic Phenotype?

Approach: Define the ezrin transcriptome.

cDNA microarray subtraction of high and low isogenic osteosarcoma clones

High Ezrin Low Ezrin

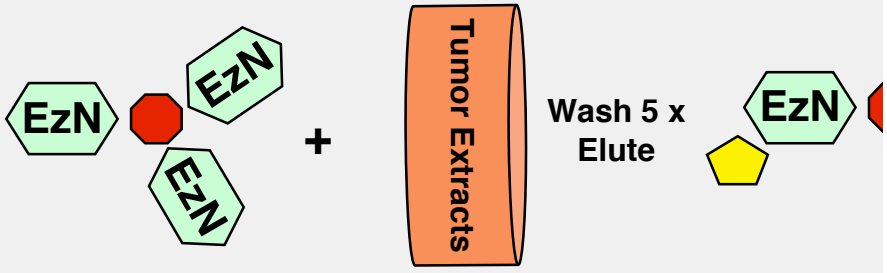


EASE (Expression Analysis Systemic Explorer) ontological analysis of ezrin transcriptional phenotype

- Translation
- Translation initiation

Approach: Define ezrin protein bindi partners (interactome).

Affinity chromatography proteomic assessment of ezrin binding proteins



Couple ezrin-N to beads

Incubate extracts with beads

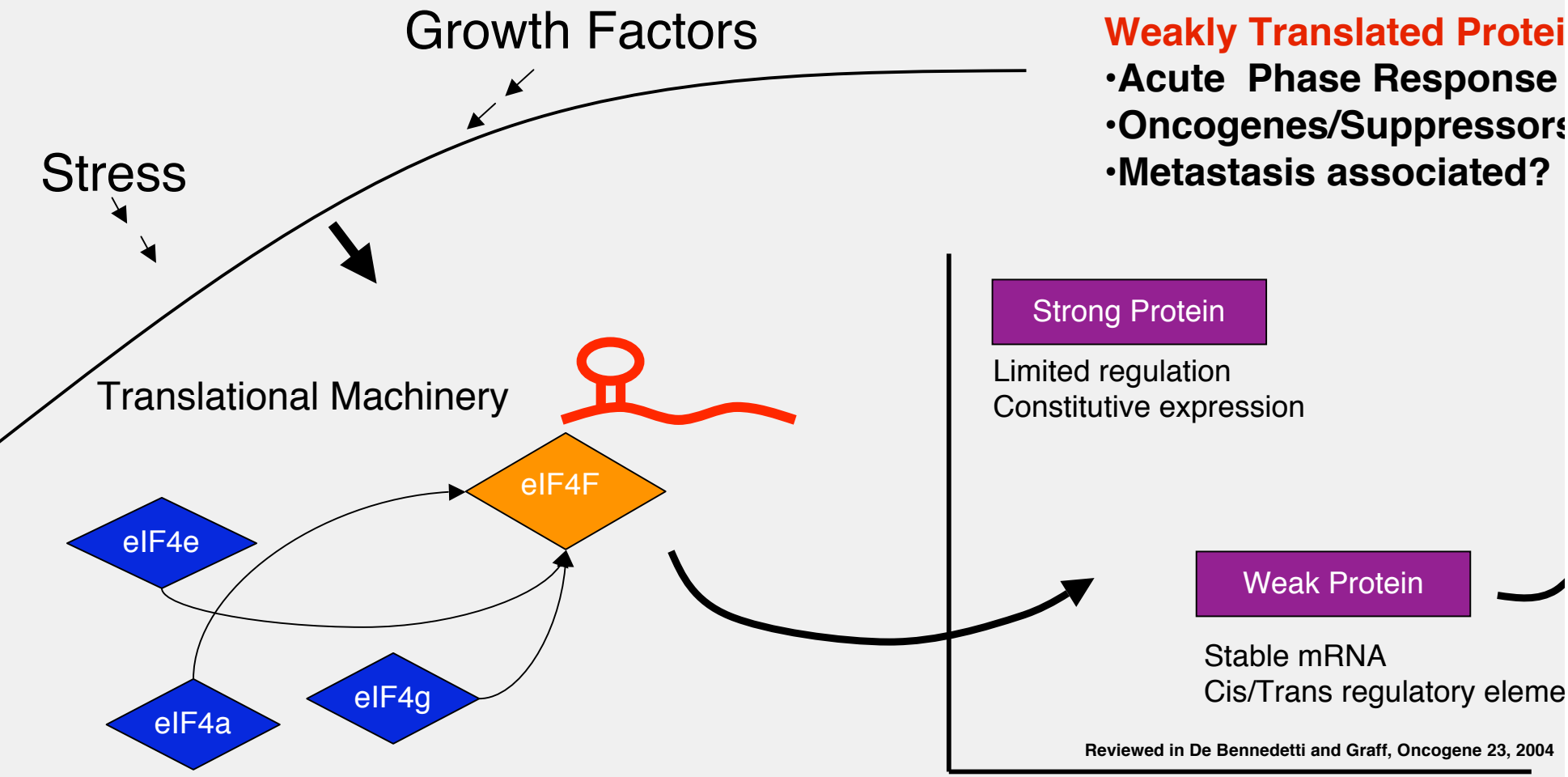
Identify proteins

Functions of 11 of 77 ezrin binding prot linked to translation and translation init

Jessica Cassavaugh

Hypothesis: Ezrin contributes to metastasis through modulation of translation and translation initiation.

Hierarchy of Weakly and Strongly Translated Proteins



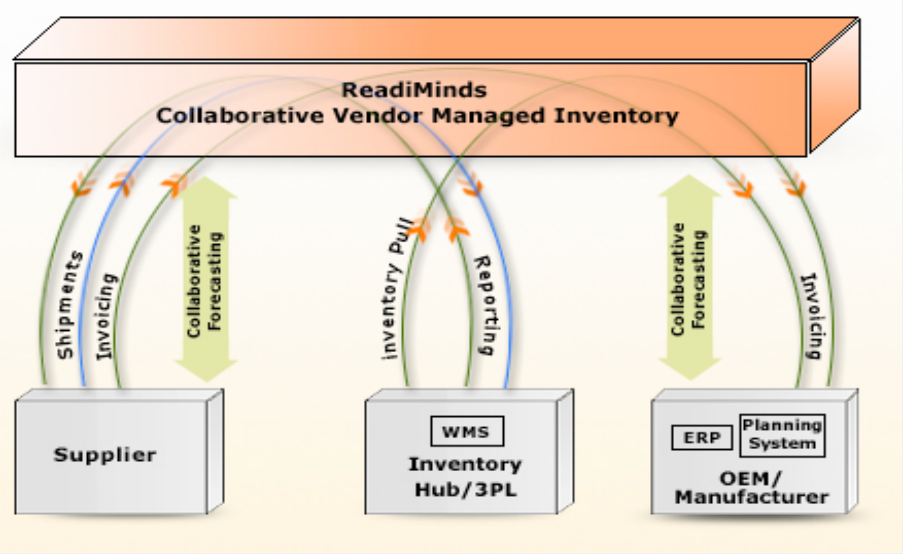
Hypothesis: *Efficient translation (initiation) may be a critical determinant of the ezri metastatic phenotype.*

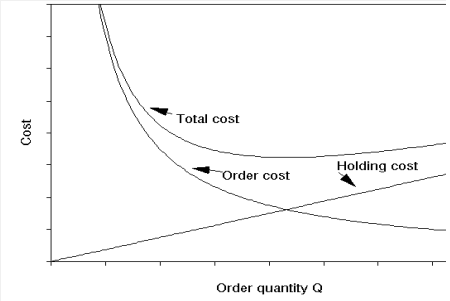
Extension: *Efficient translation (initiation) may be a defining feature of the metastatic phenotype?*

Enabled Translation in Metastasis:
Just In Time (JIT) Inventory in Business

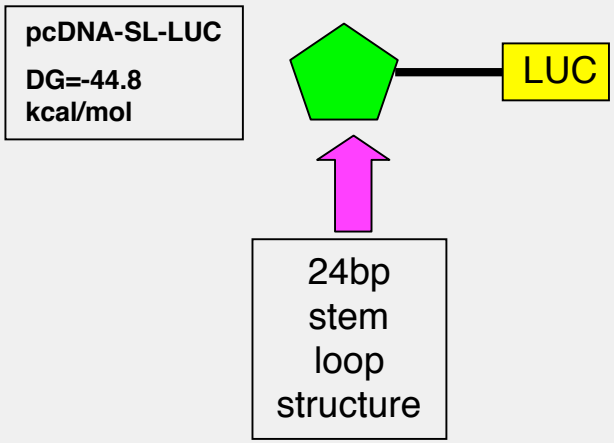
An inventory strategy implemented to improve the return on investment of a business by reducing in-process inventory and its associated costs.

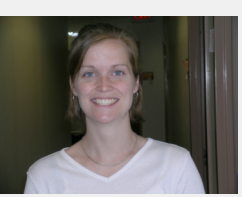
Developed by Taiichi Ohno's: derived from his observances of an American supermarket of the 195

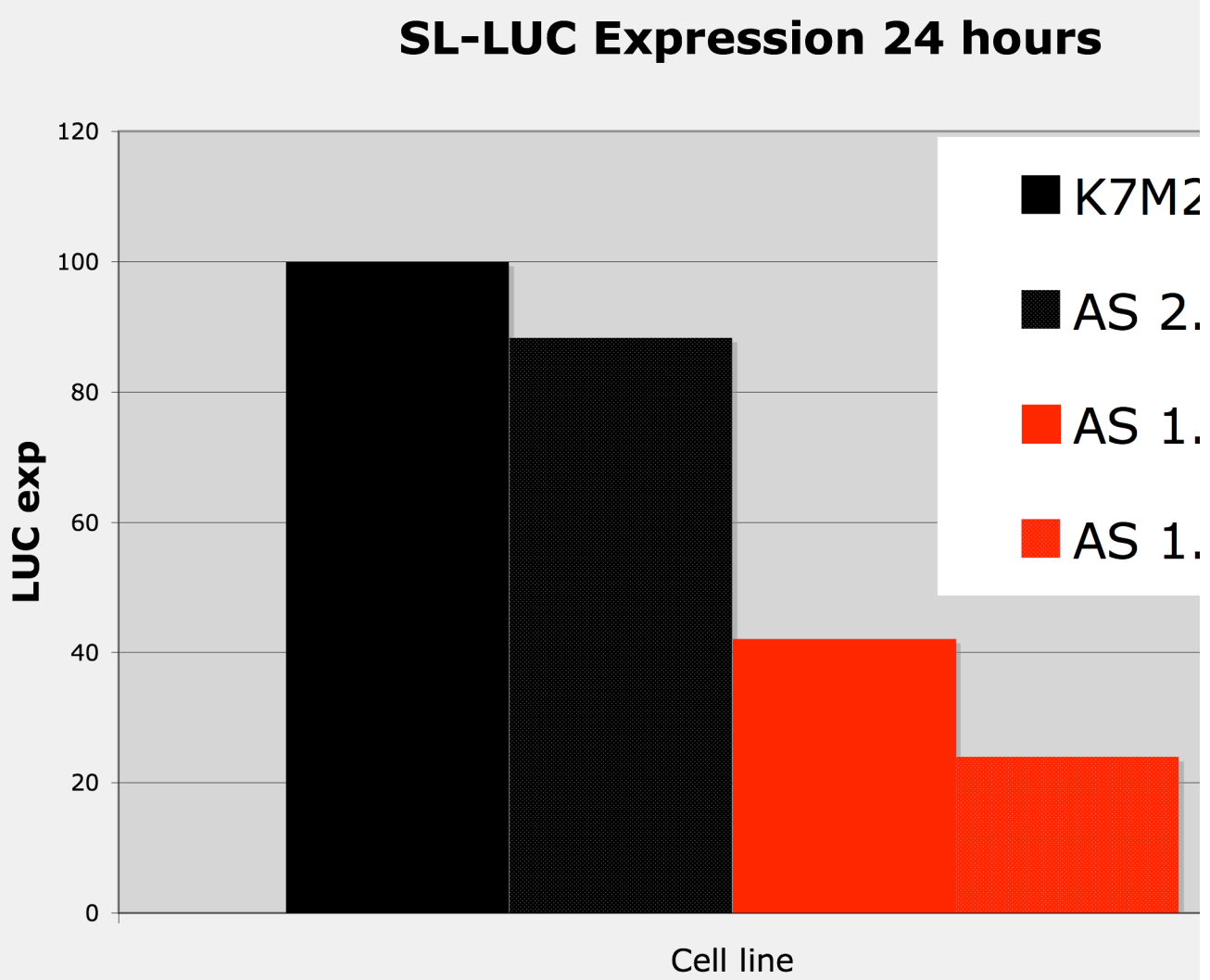




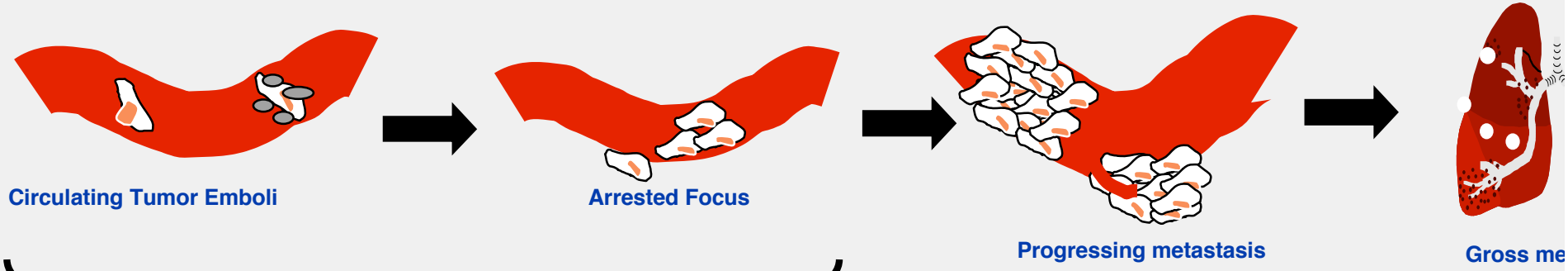
Ezrin Suppression Reduces the Expression of a Comp 5'UTR Protein in K7M2 Osteosarcoma Cells



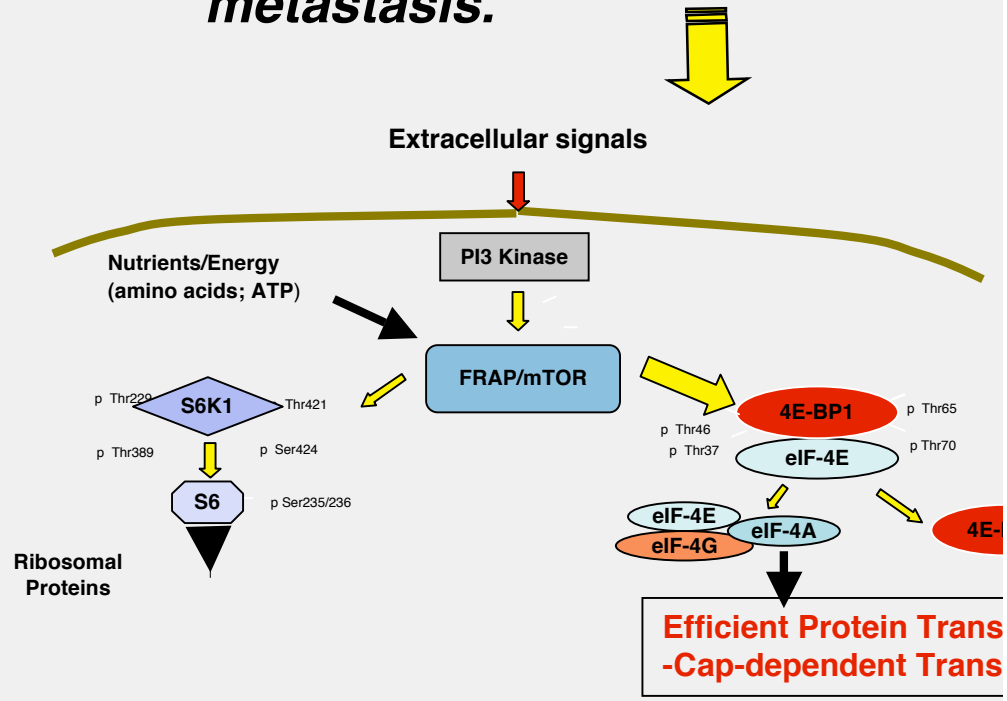




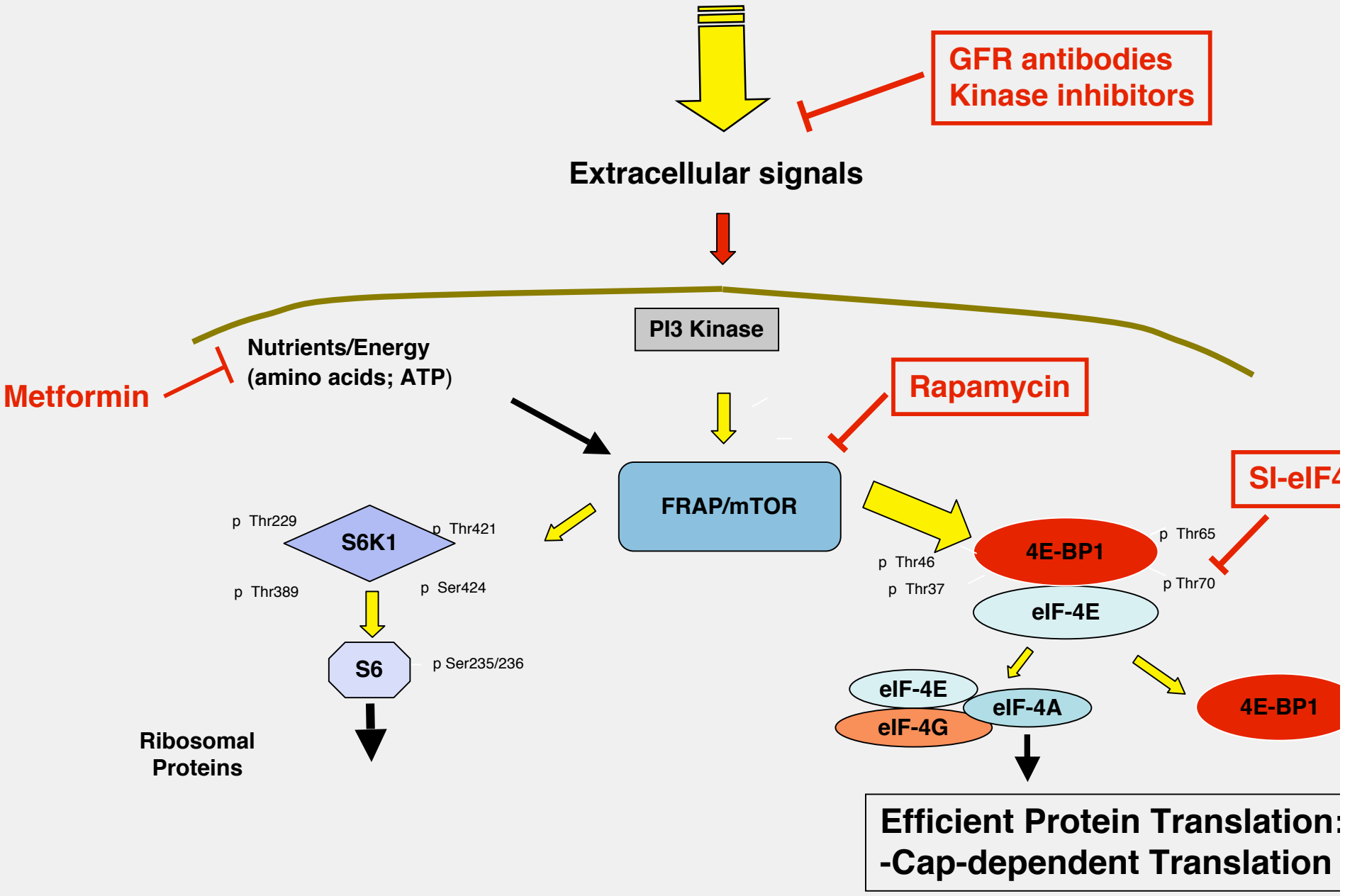
Understanding the role of Ezrin in Cancer Metastasis through a Comparative Approach



Ezrin provides cancer cells with ability to endure the stress of metastasis.

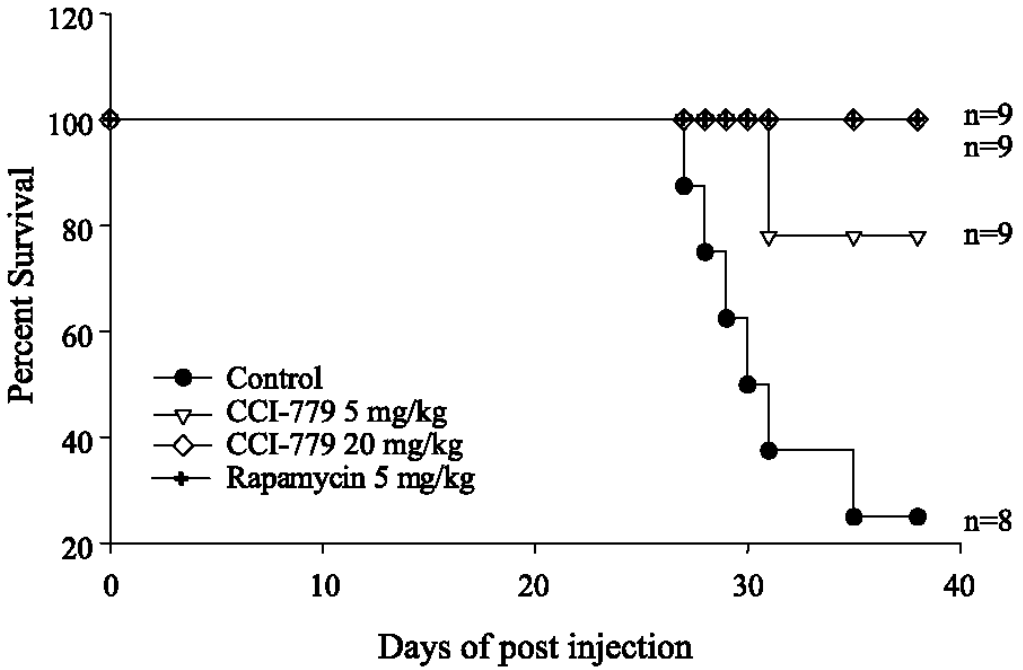


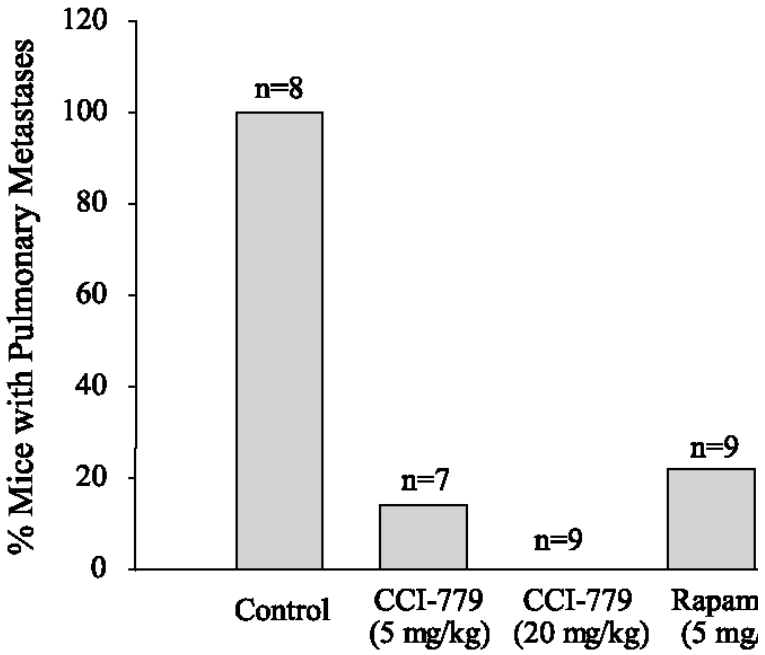
Targeting Translation and Energy Use in Metastases



mTOR Inhibition Results in Suppression of Metastas

Murine Osteosarcoma Model

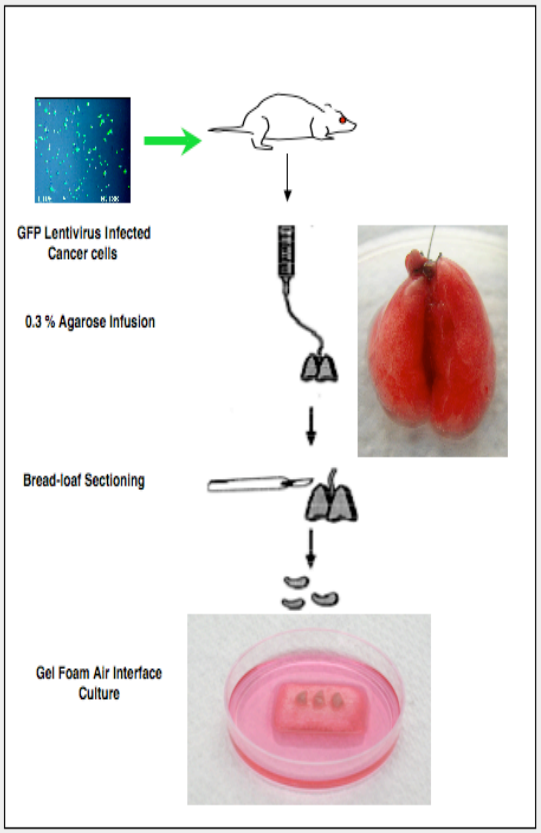


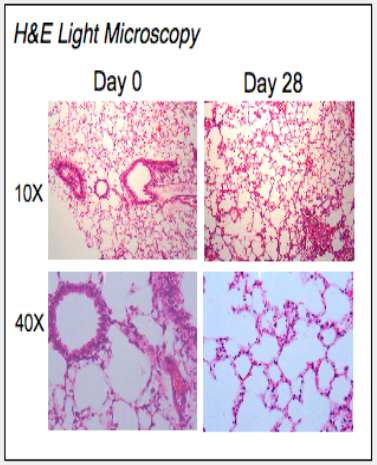


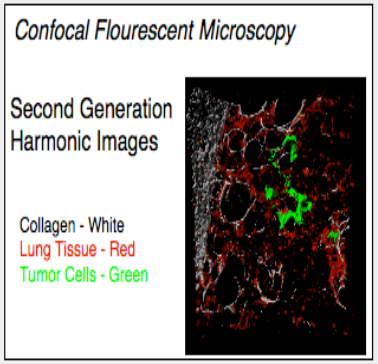
Wan et al, Cancer Researc

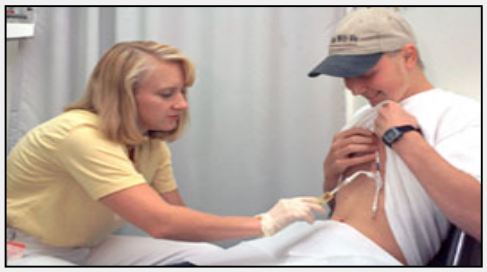
Opportunities to Optimize the Drug Development Path for Cancer Metasta

Metastasis is a noun:
Novel Models

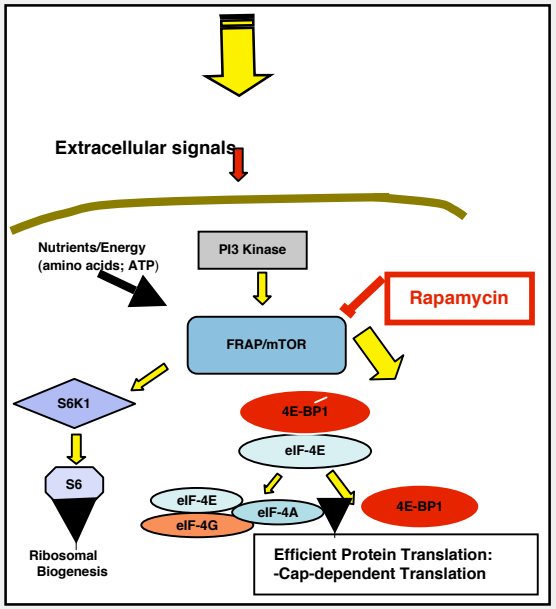


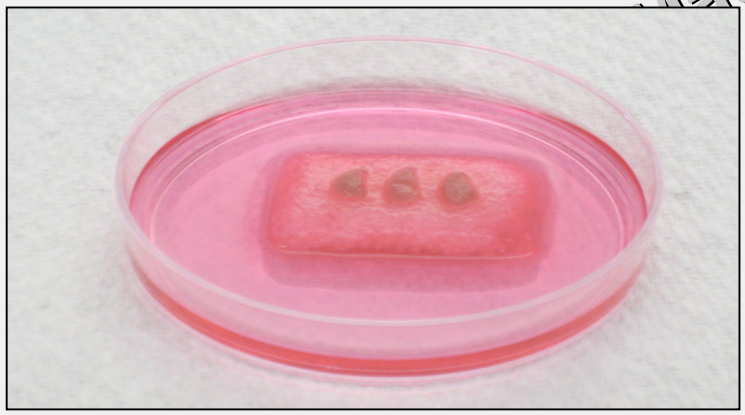


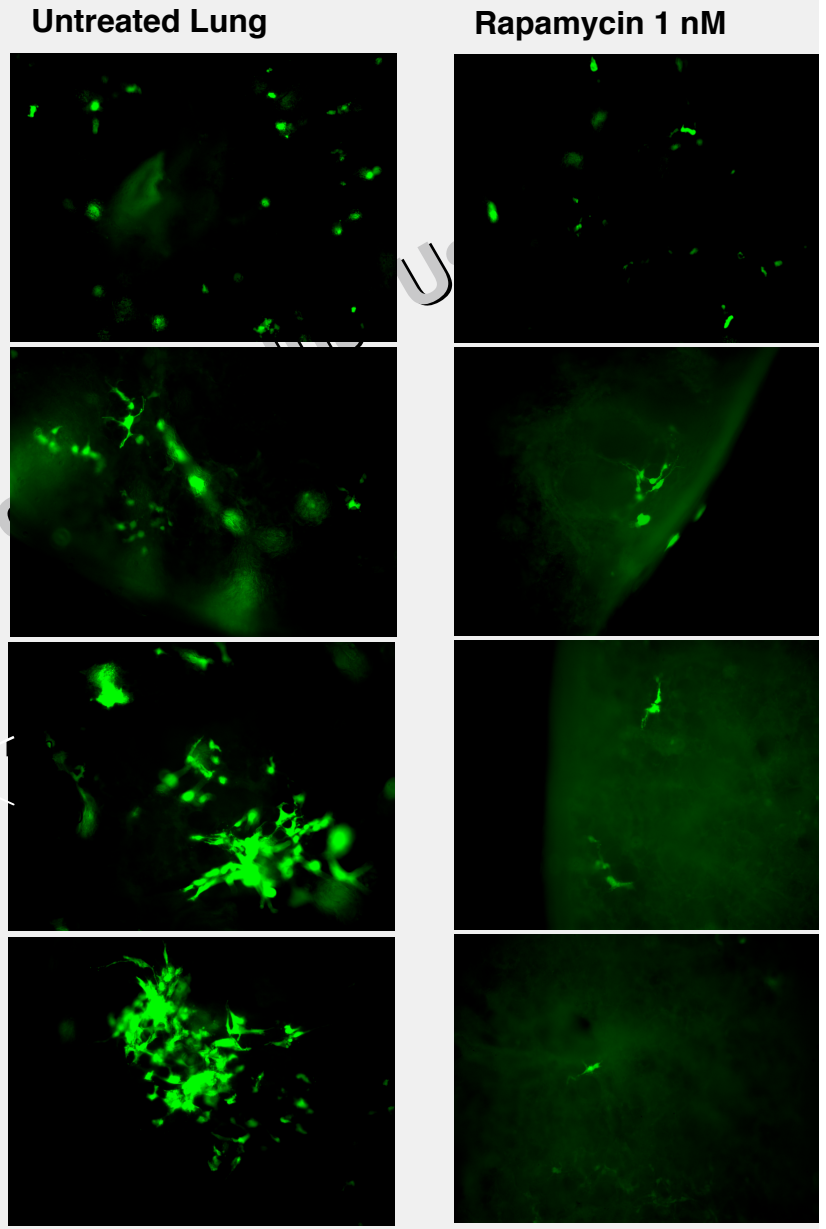




Rapamycin is Active Against the Metastatic Phenotype of Cancer

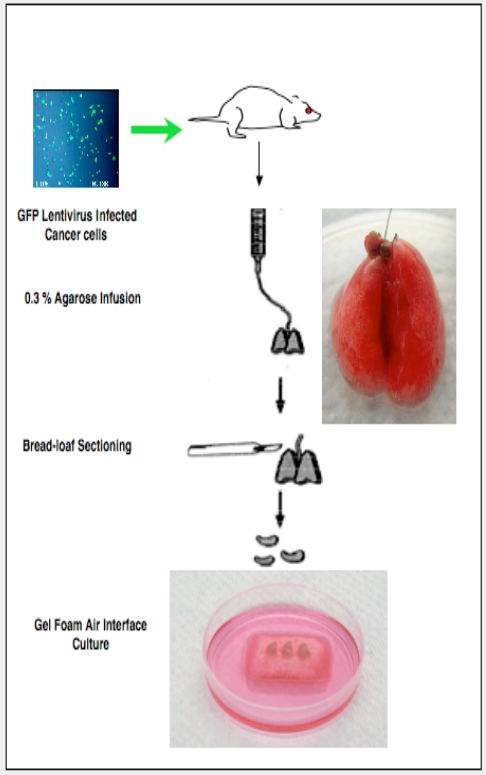


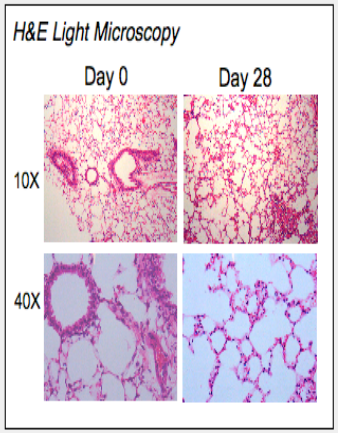


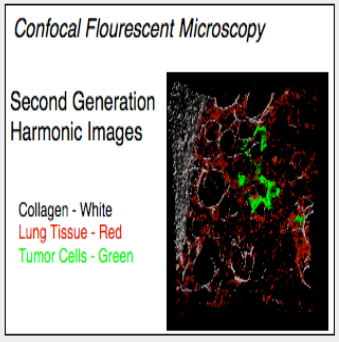


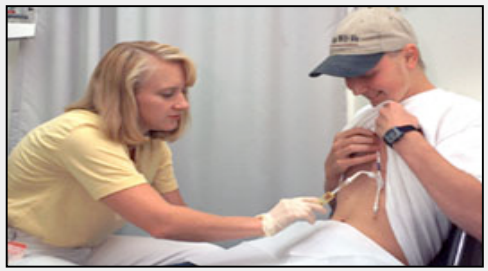
Opportunities to Optimize the Drug Development Path for Cancer Metasta

Metastasis is a noun:
Novel Models

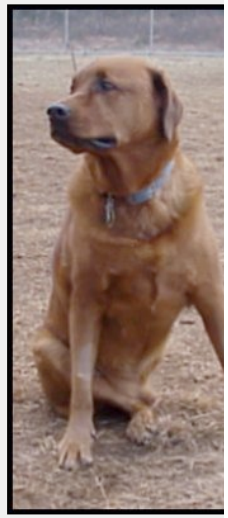








Integrated As



Innovative Trial Designs

Rapalogs: Integrated Comparative Approach

Non-Human Primate
Beagle Dog

Small Animal
Preclinical

Early Phase Human
Clinical Trials

Phase II Human
Clinical Trials

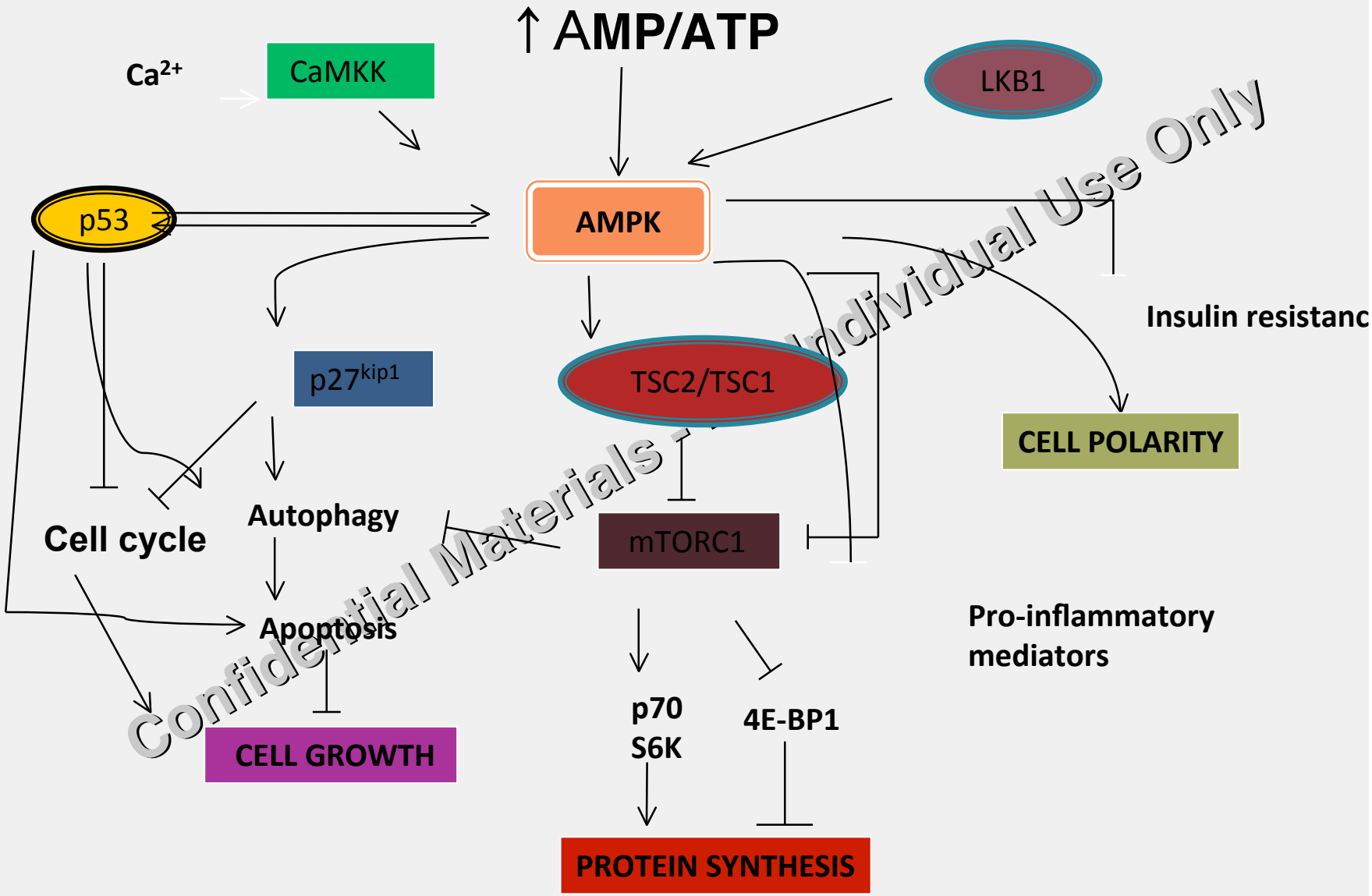
Phase II
Clinica

New Cancer

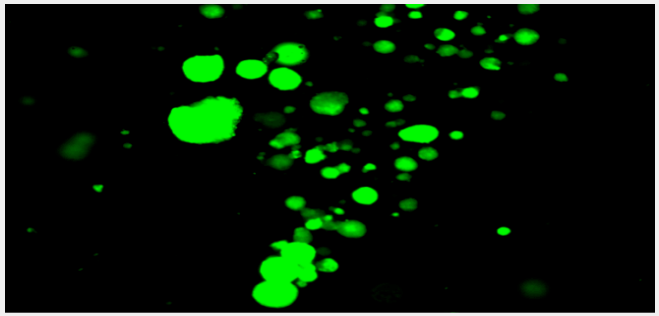
Tumor-Bearing
Dog Studies

Regimen/Schedule
Biomarkers
Responding histologies
Combination therapies
Adjvuant therapy

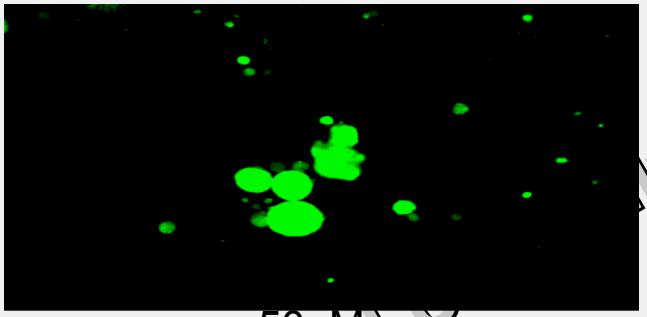
Regulation of Cellular Energy - Warburg Revisted



Metformin inhibits osteosarcoma colony formation in vitro



Control



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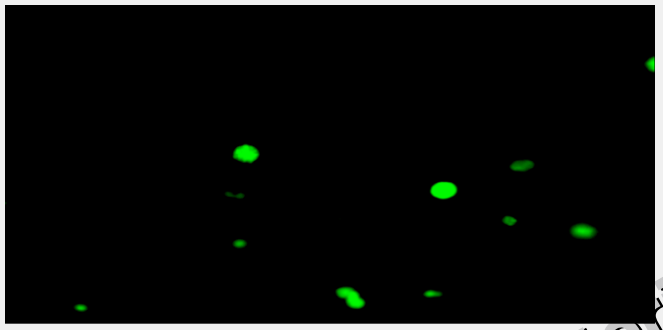

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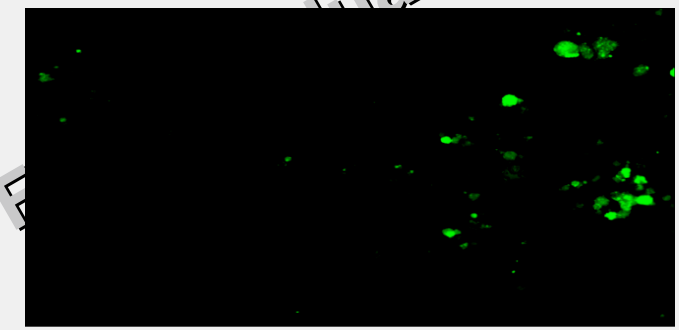
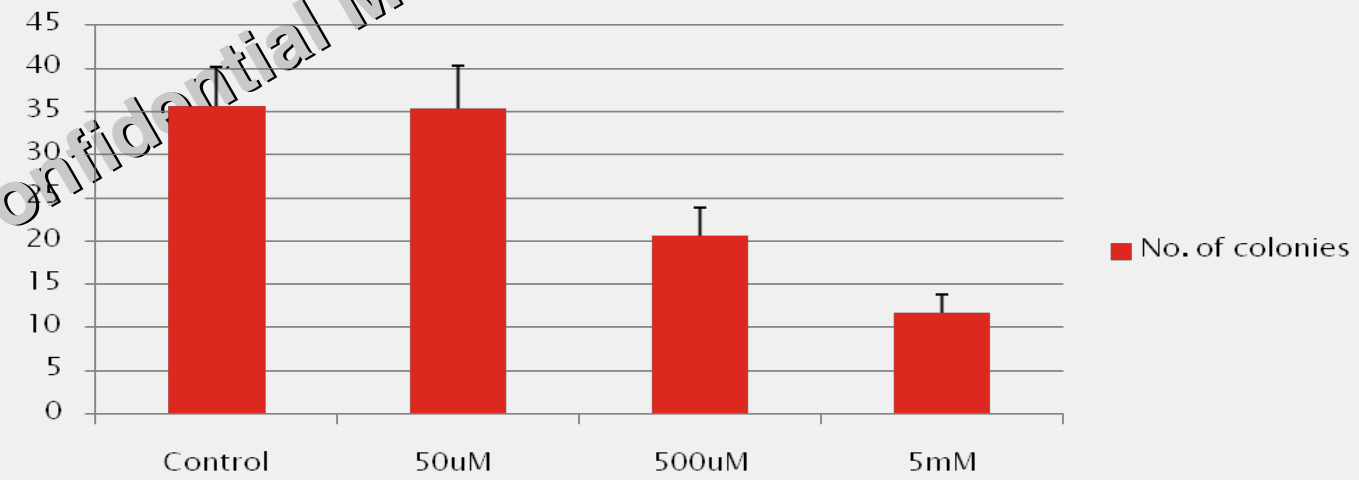
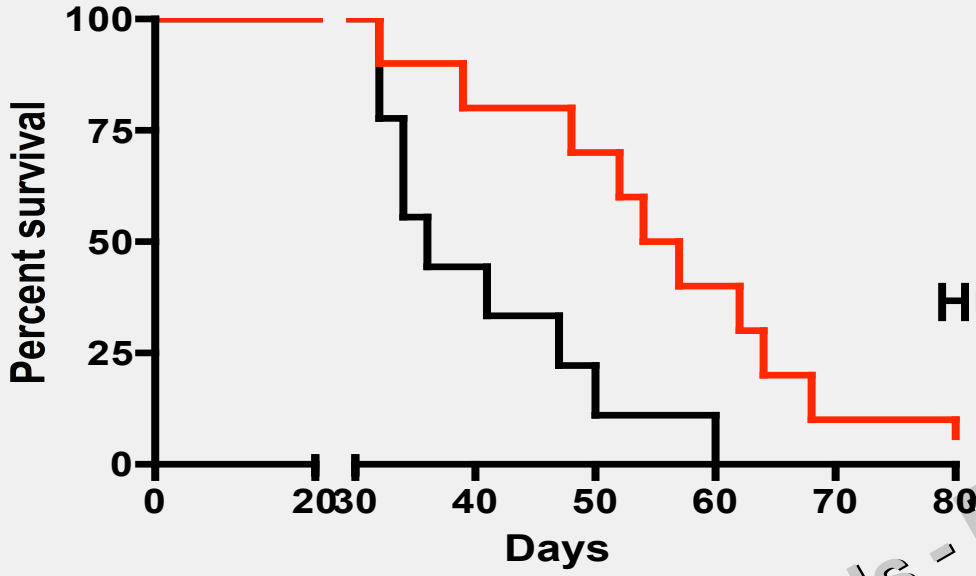


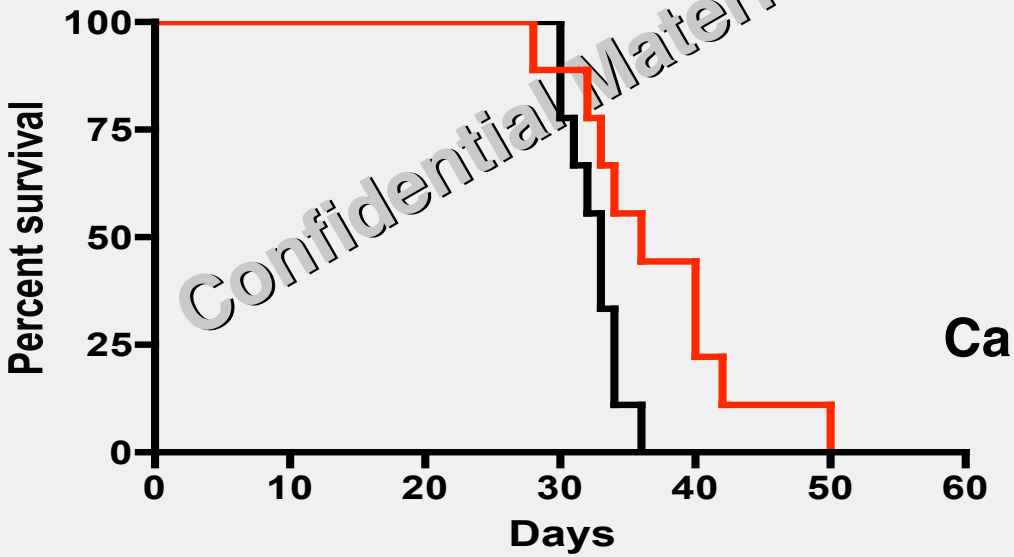
5mM



Metformin inhibits metastatic progression of osteosarcoma



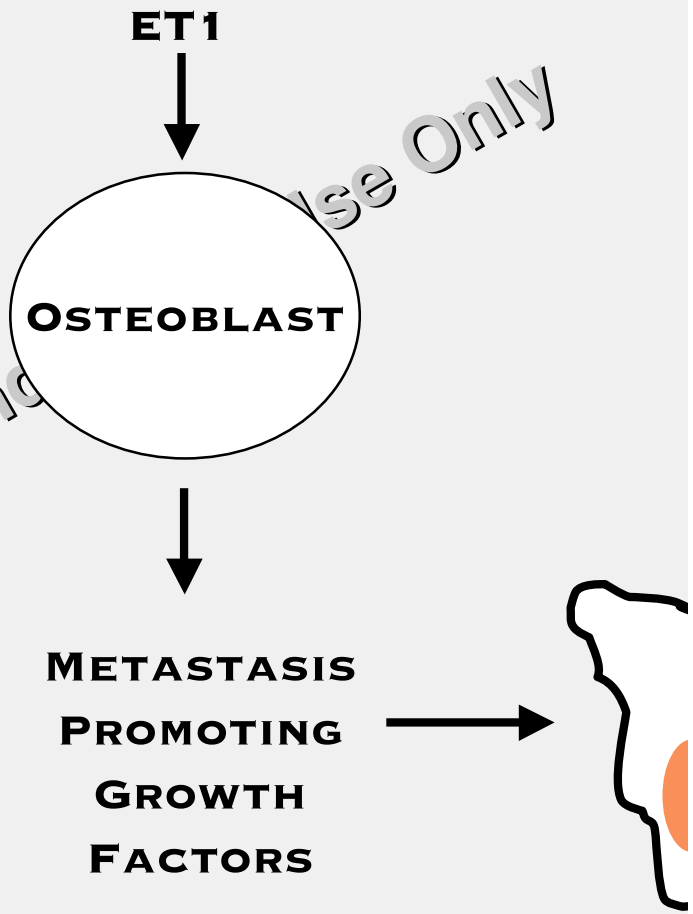
Human Osteosarcoma



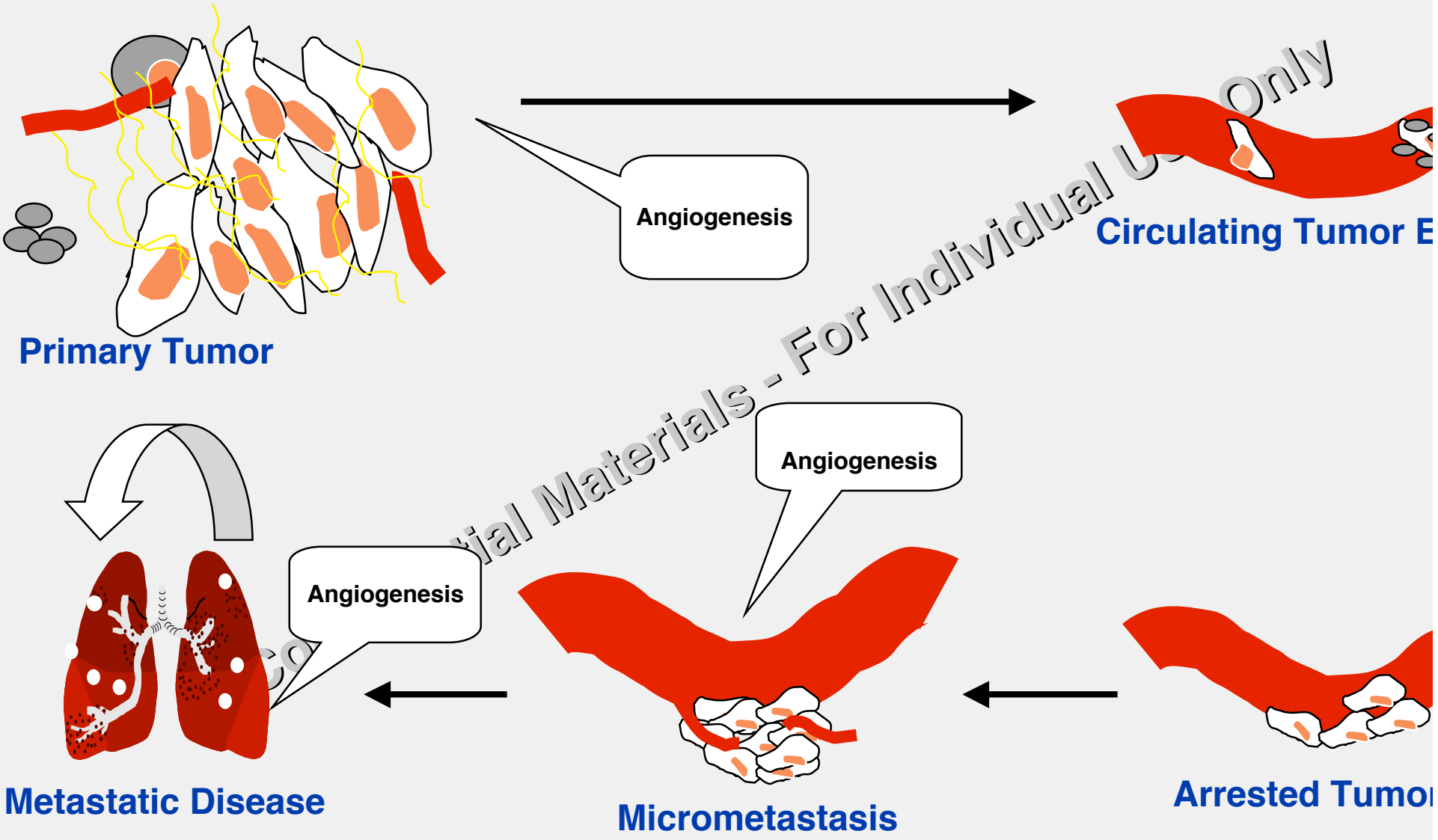
Canine Osteosarcoma

Targeting host-tumor interactions?

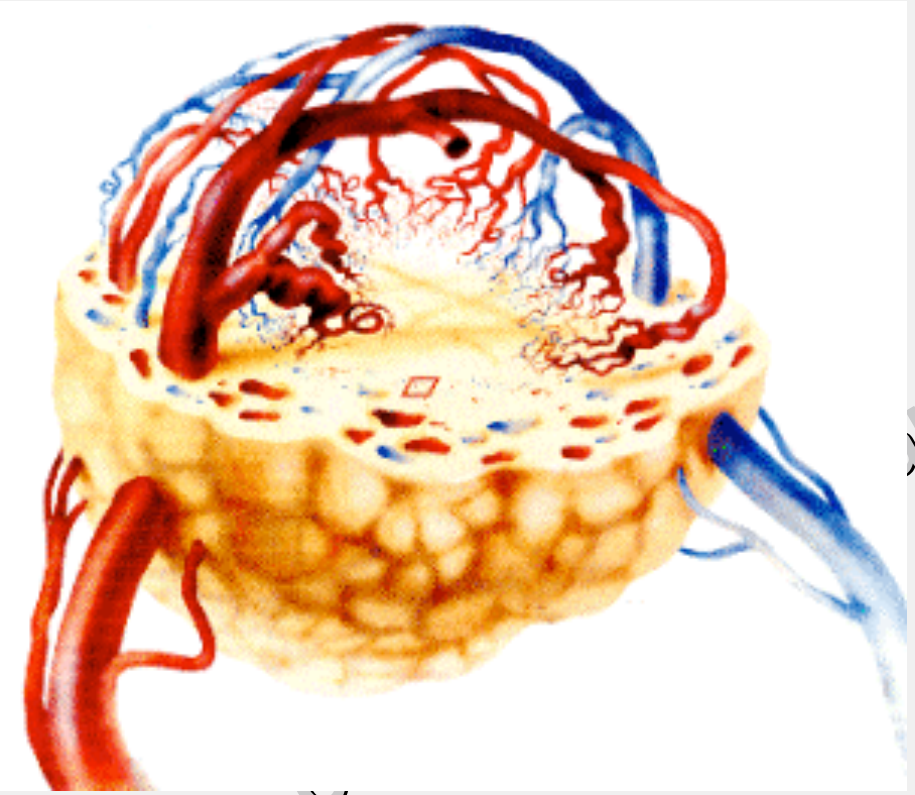
- **Endothelin axis** consists of a family of ligands (ET-1, ET-2, and ET-3) and receptors (ET-A and ET-B)
- Activation of ET-A by the circulating ligand, ET-1, results in osteoblast activation and the resultant production of bone derived growth factors

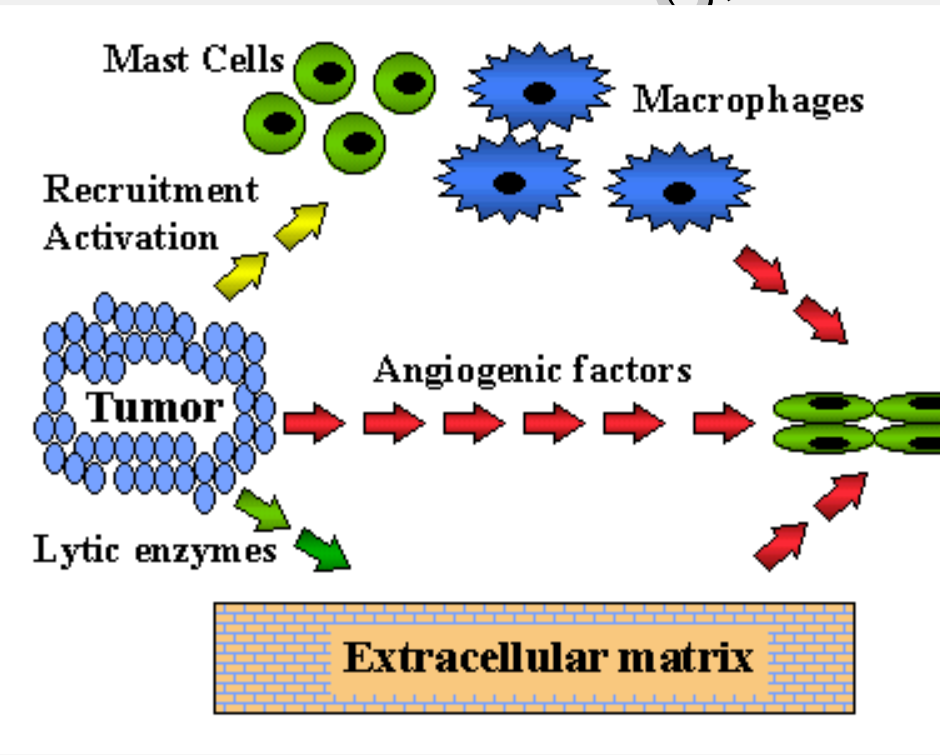


Metastasis Biology: Metastasis associated genes and pathways



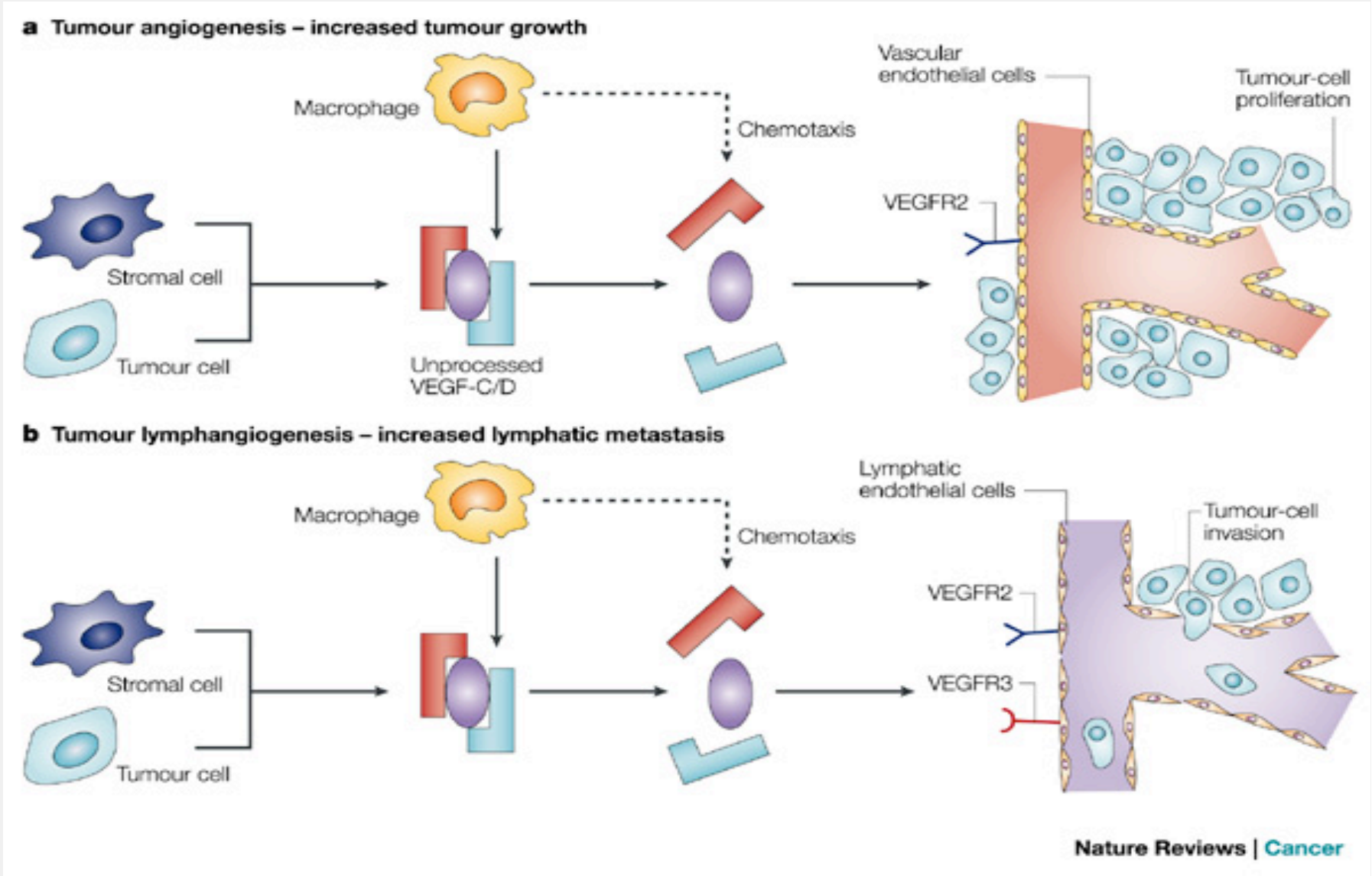
Angiogenesis



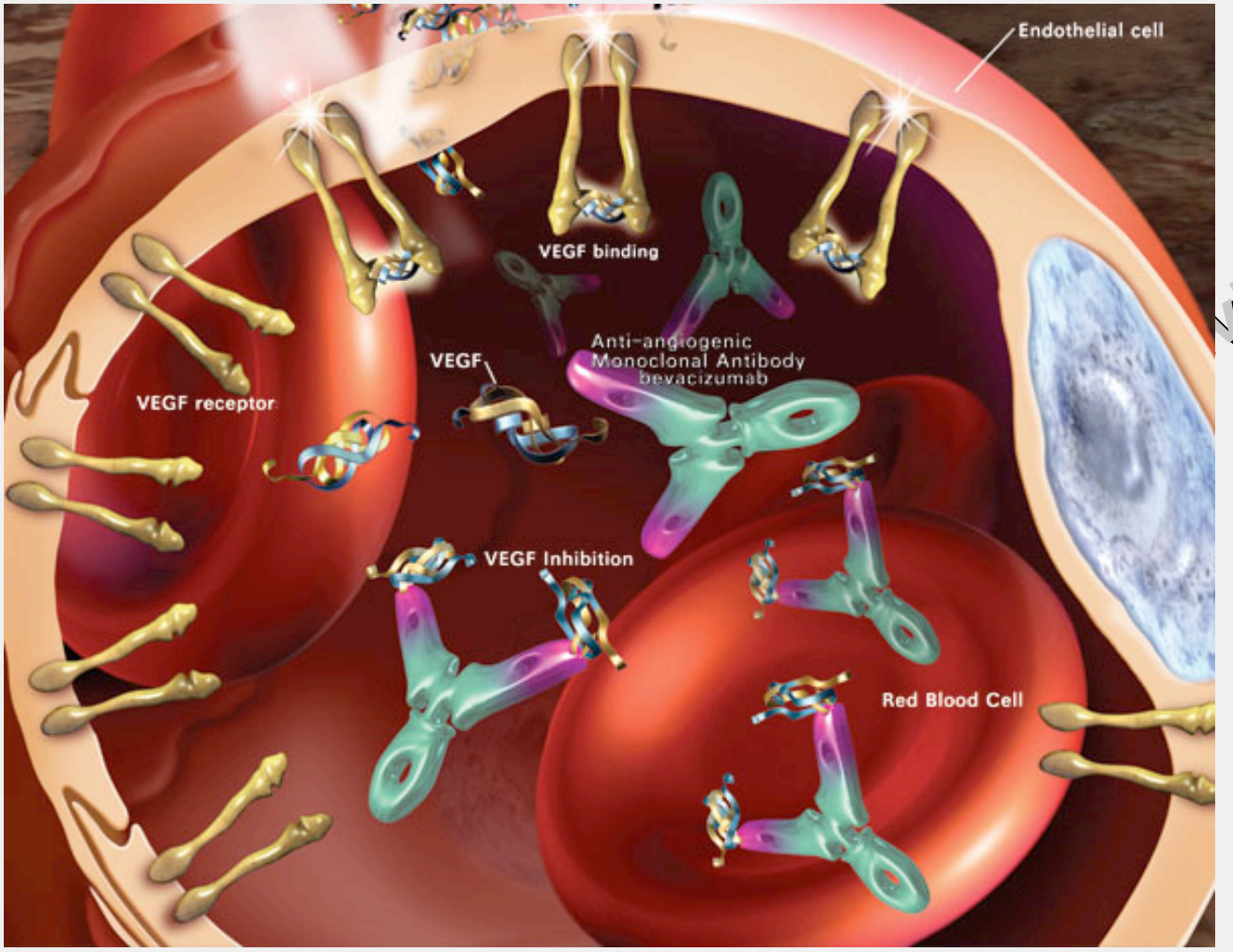


ANGIOGENESIS: DEFINING FEATURE OF MALIGNANT CELL

Angiogenesis and lymphangiogenesis



Angiogenesis Inhibitors

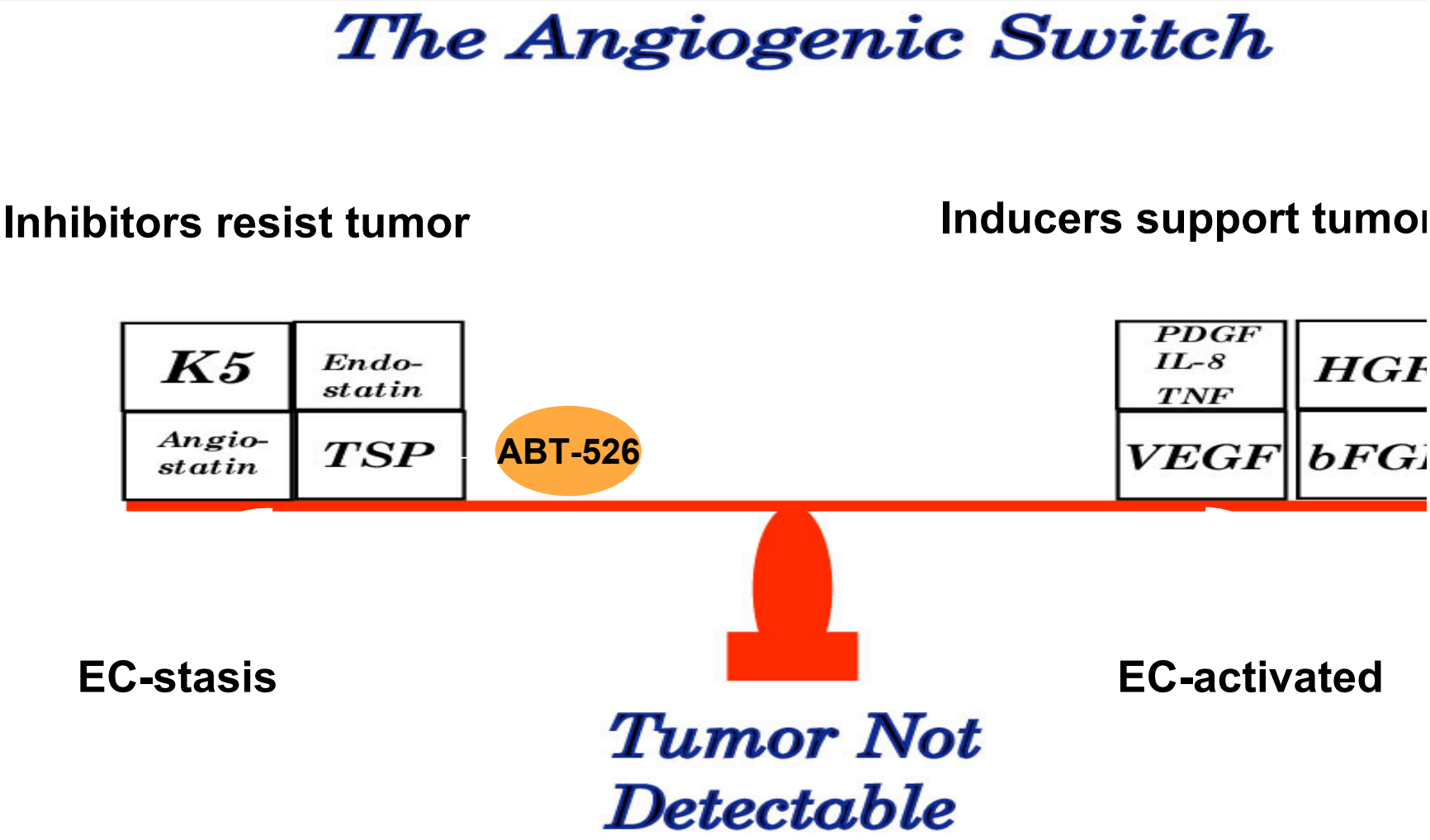


Targets:

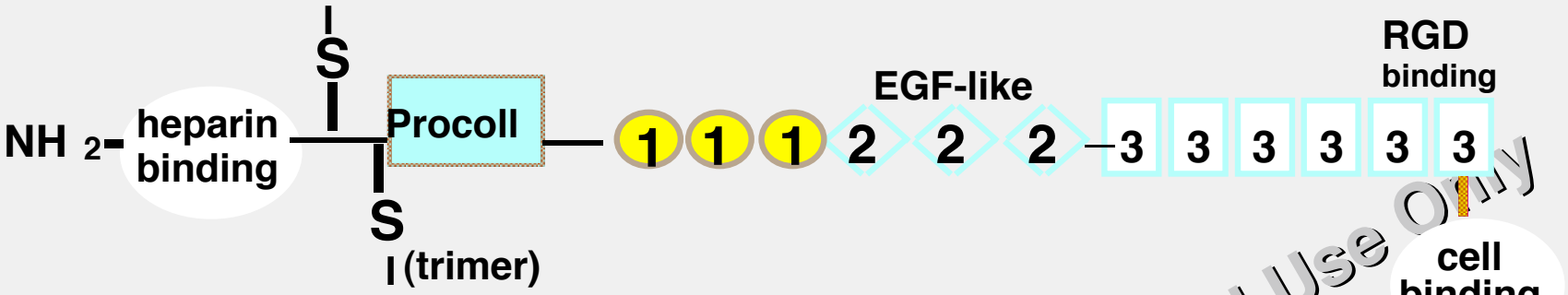
- **Endothelial growth fac and receptors**
  - **Antibodies**
  - **Small molecules**
- **Natural inhibitors of angiogenesis**
- **Host tumor interactior**

http://www.biooncology.com/bioonc/anatct.jsp

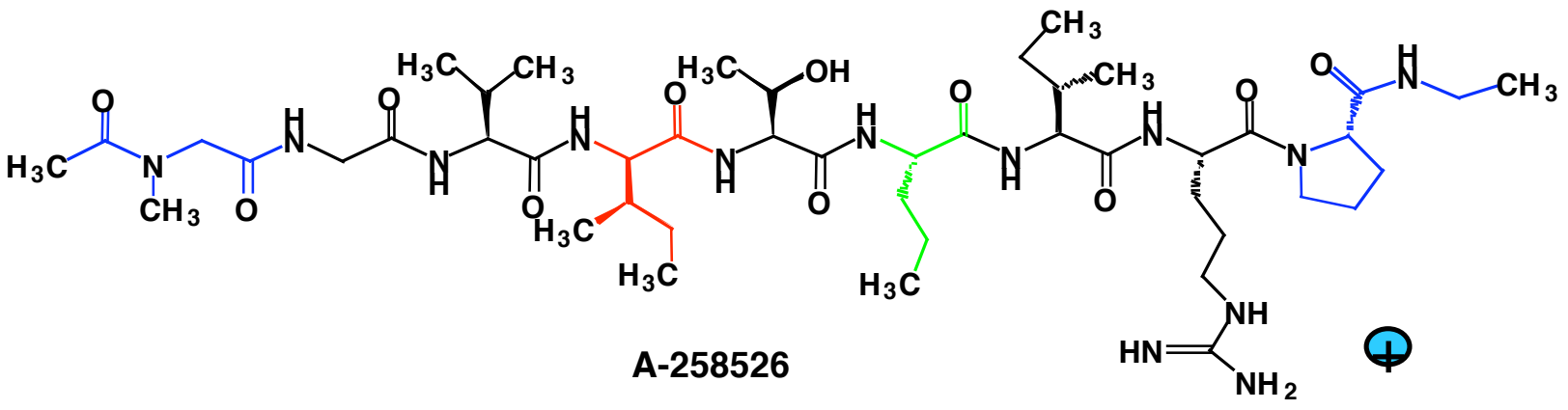
The Angiogenic Switch



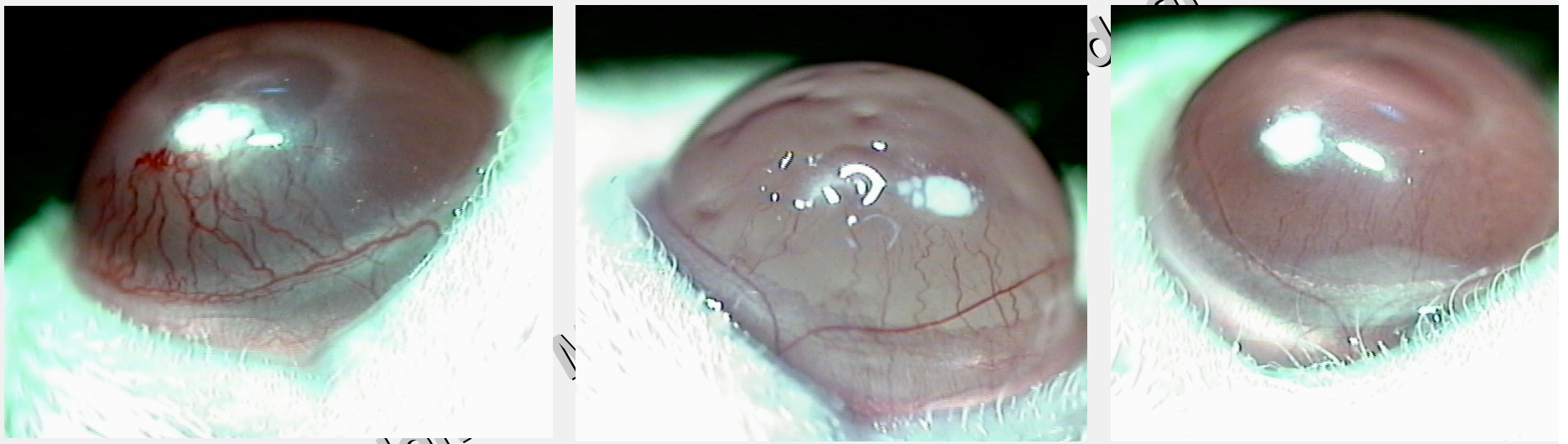
Thrombospondin-I



- Large multi-domain protein with multiple receptors
- Anti-angiogenic domain is 2nd Type-1 Repeat
  - Drs. Noel Bouck, Olga Volpert, Jack Henkin
- Series of related TSP-I peptides



TSP-I Inhibits Mouse Corneal Neovascularization



Thrombospondin-I Peptides in pet dogs with measurable malignant cancers

Design: Open label single agent

Eligibility:
Histologically confirmed
Measurable
No concurrent cancer therapy
Washout of 21 days

Endpoints:
Toxicity
Pharmacokinetics (limited)
Tumor Response
Significant disease stabilization
Objective response

Results

- **Accrual:**
  - **197 Cases**
  - **145 on therapy for 30 days (evaluable)**
- **Well tolerated**
  - **No arthritis**
  - **No keratitis**
  - **No delays in wound healing**

Rusk et al, Clinical Cancer Resear

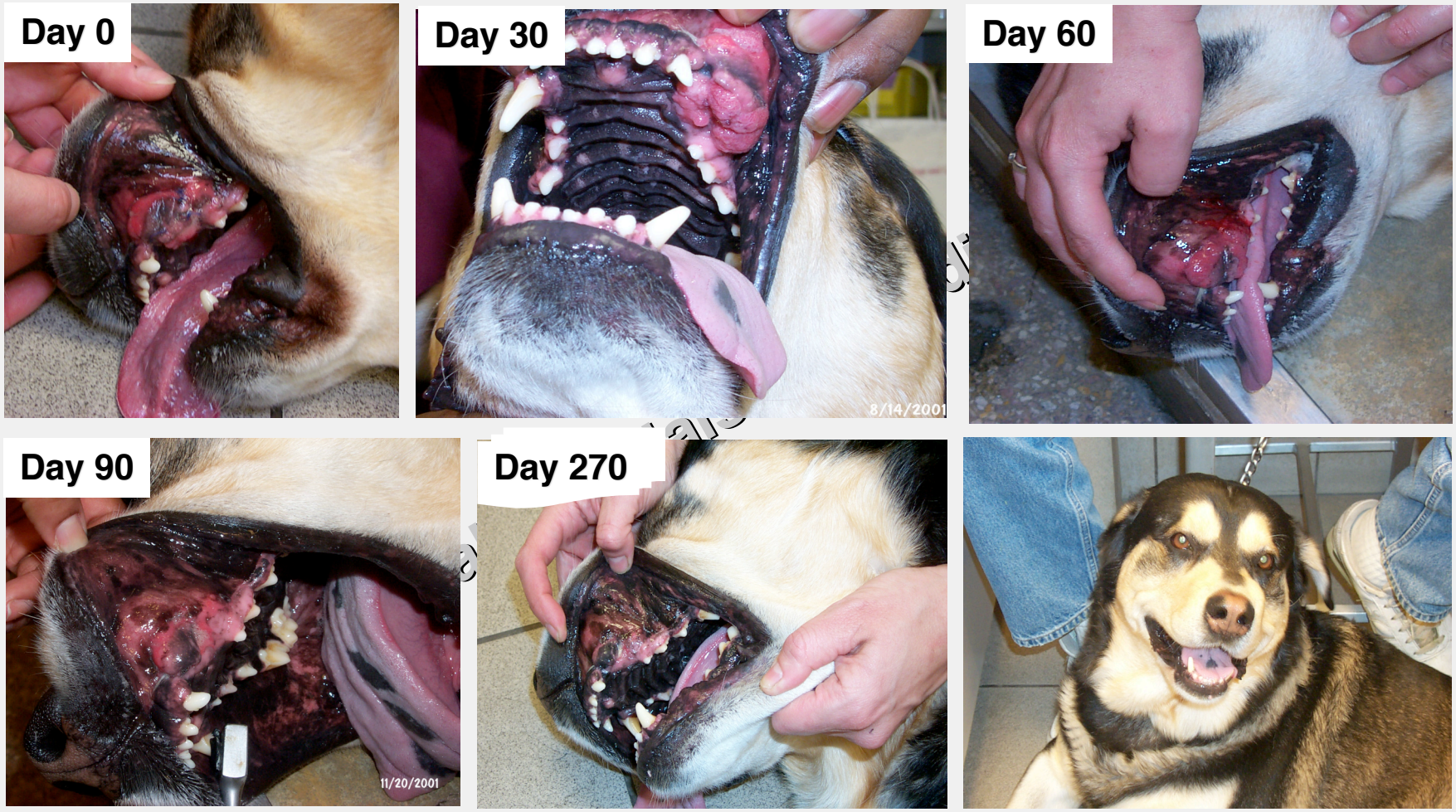
Thrombospondin-I Peptides in pet dogs with measurable malignant cancers

Results

- Stable disease seen in 18/145 evaluable cases = 13%
- Objective responses “measurable lesions”: 17/145 evaluable cases = 12%
  - Head and Neck Carcinoma
  - Mammary Carcinoma
  - NH lymphoma
  - cutaneous lymphoma
  - Sarcoma
    - Hemangiosarcoma
    - Soft tissue Sarcoma
    - Synovial Sarcoma

Rusk et al, Clinical Cancer Resear

TSP-I-p: Maxillary squamous cell carcinoma (T3N0M0): Agent TSP-I



Rusk et al, Clinical Cancer Resear

B. Objective response - Lingual/Atrial hemangiosarcoma

Targeted Therapies with Potential Activity in Metastas

Masivet

- **Kinase spectrum: c-KIT, FAK, PDGFR**

Beyond mast cells:

- **FAK inhibition may be valuable in metastases**
- **PDGFR inhibition targets angiogenesis and tumor microenvironment**

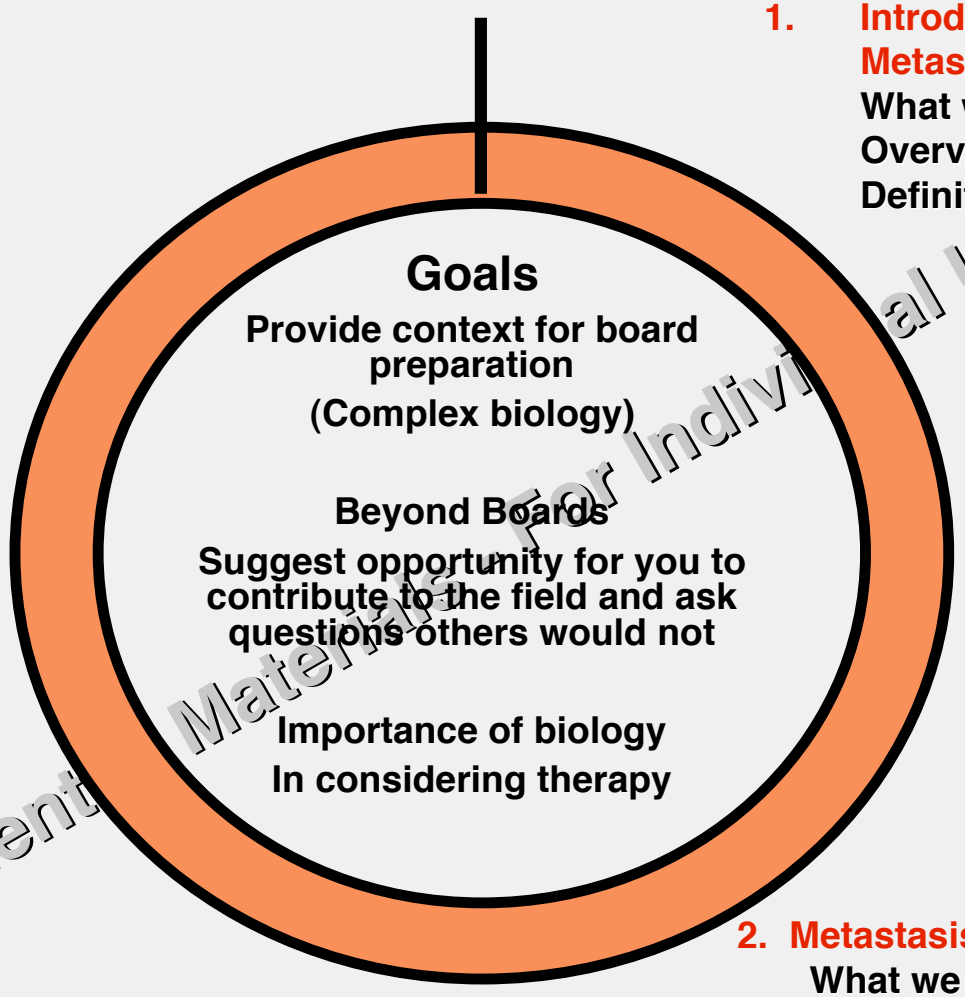
- **Kinase spectrum: c-KIT, VEGFR, PDGFR, F**

Beyond mast cells:

- **VEGFR inhibition linked to classical angiogenesis**
- **VEGFR inhibition may target premetastatic niche**
- **PDGFR inhibition may target angiogenesis and tun microenvironment**
- **FGFR inhibition likely of value in selected cancers mutations in receptor**

Overview

1. **Introduction: The Problem o**
   Metastasis
   - What we think we know and a
   - Overview of the metastatic ca
   - Definition of metastasis



3. **Steps in the Metastatic Cascade**
   - Connecting Biology with Therapy
   - Ezrin - my favorite protein

2. **Metastasis Concepts and Contro**
   - What we don't know and don't a
   - Emergence of the metastatic ph
   - Inefficiencies in Metastasis
   - Dormancy of metastasis
   - Resistance to therapy

Acknowledgments

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Choh Yeung
Jessica Cassavaugh
Lauren Buquo
Gaurav Khanna HHMI 2004
Ben Bruce HHMI 2005
Lauren Shapiro HHMI 2006
Kirk Campbell HHMI 2007
Ali Khan HHMI 2008
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