BUILDING SUCCESSFUL BIOTECHS
MIT TECHNOLOGY BREAKFAST

Christoph Westphal MD PhD, Chair and CEO, NASDAQ: VSTM

Verastem, Inc. Confidential

Success in Biotech

People

Idea

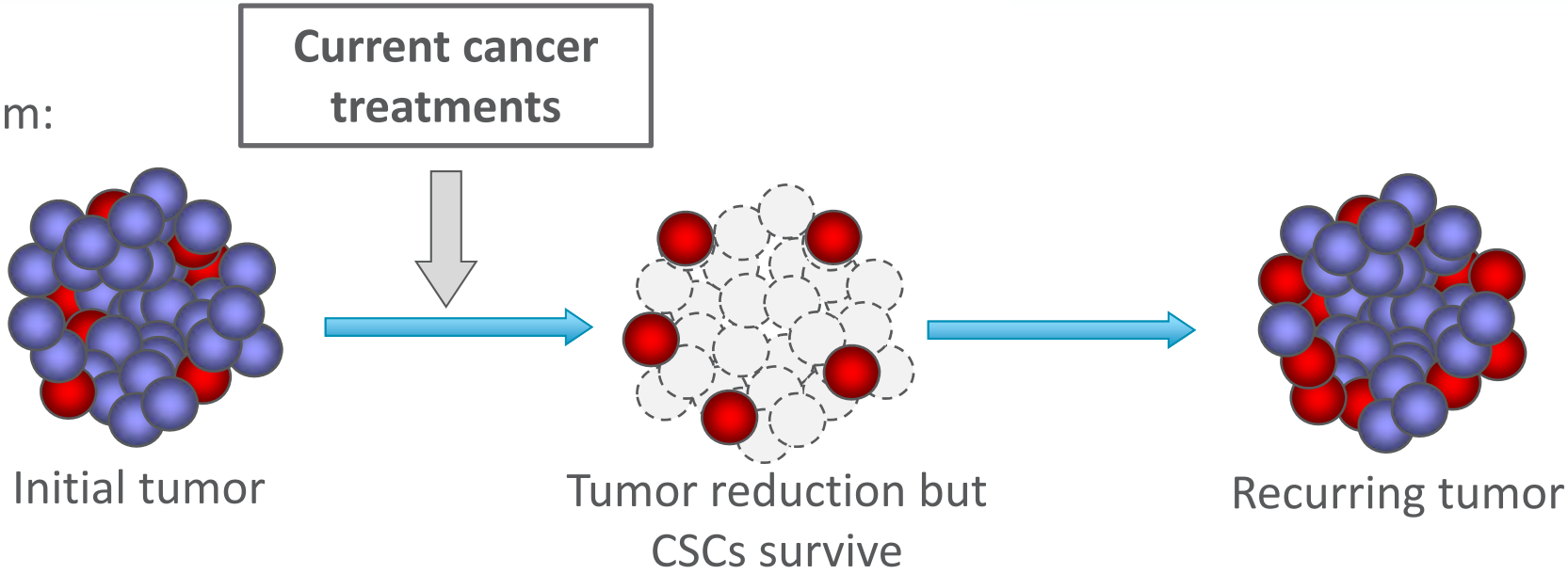
Financing

SIRT
ALNY
MNTA
VSTM

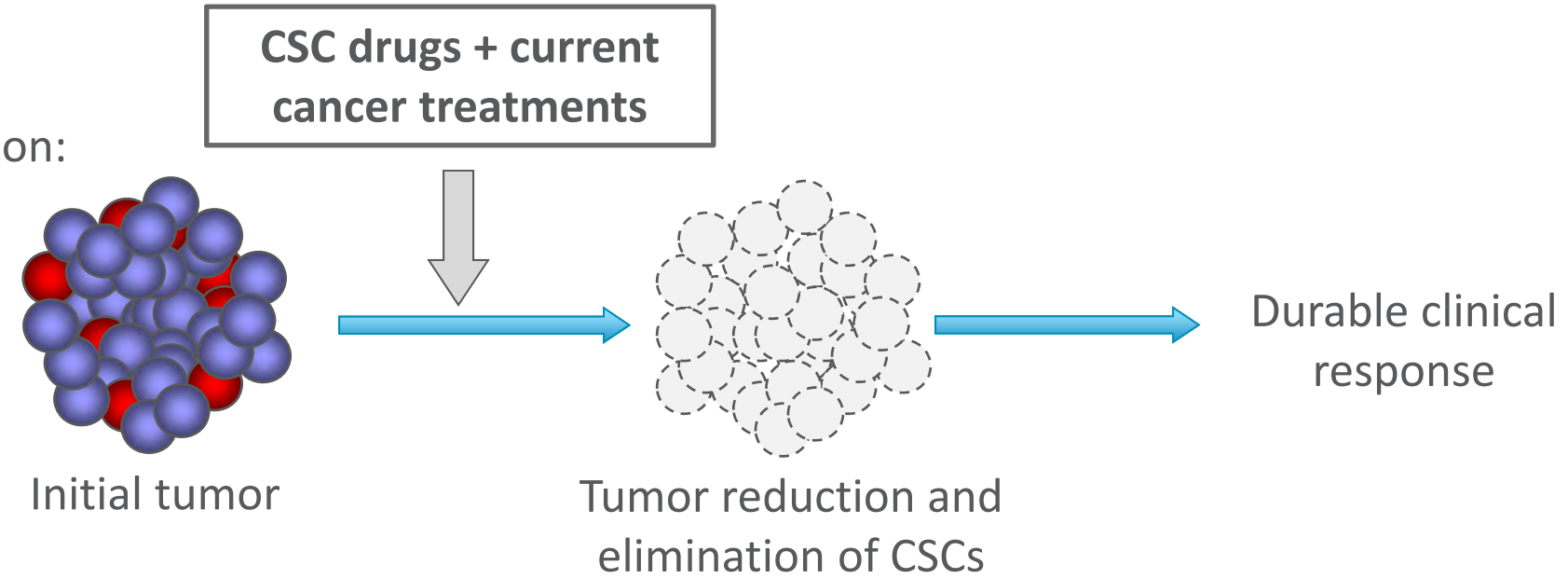
Sirtris – The Idea: Sirtuins Control Aging

VSTM IDEA: Targeting Cancer Stem Cells for a Durable Response

Problem:



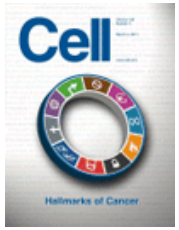
Solution:



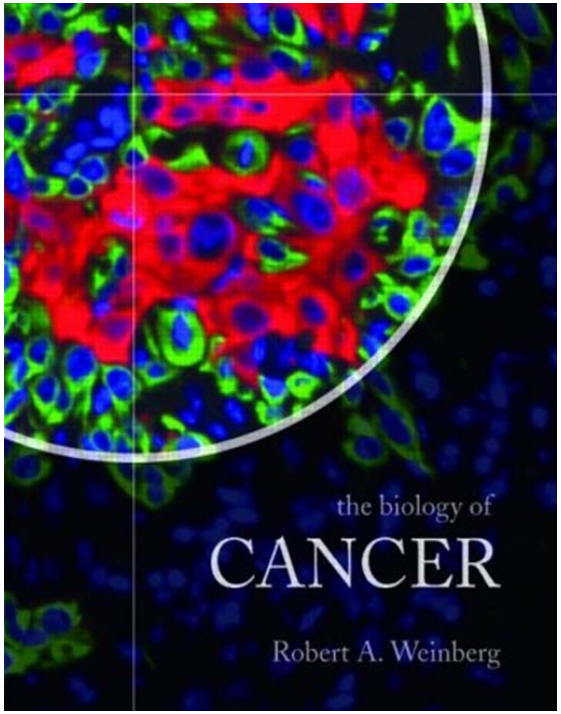
THE IDEA: Verastem is at the Forefront of Cancer Stem Cell Biology

Identification of Selective Inhibitors of Cancer Stem Cells by High-Throughput Screening
Gupta, Weinberg, Lander, et al. 2009

The Epithelial-Mesenchymal Transition Generates Cells With Properties of Stem Cells
Mani, Weinberg, et al. 2008



Hallmarks of Cancer: The Next Generation
Hanahan, Weinberg. 2011



The New York Times

THE WALL STREET JOURNAL.

Other companies involved in cancer stem cell drug development

Eisai

gsk GlaxoSmithKline

DAINIPPON SUMITOMO PHARMA

OncoMed PHARMACEUTICALS

BAYER

astellas Leading Light for Life

Boehringer Ingelheim

Stemline

Success in Biotech – THE PEOPLE

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Acceleron
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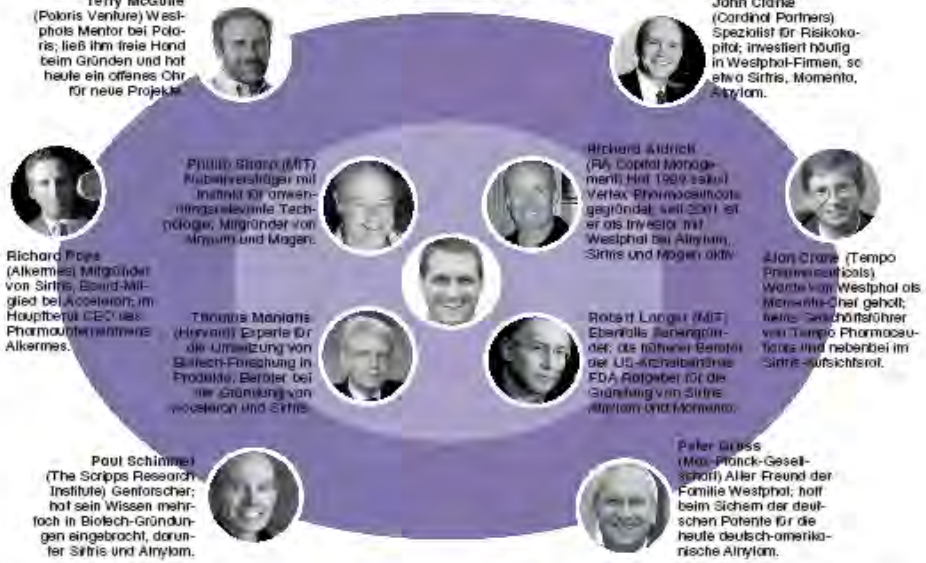
Verastem, Sirtris, etc – THE PEOPLE: Boston Biotech

Westphals Netzwerk



ren entscheidende Fortschritte gemacht. Seit den dreißiger Jahren ist bekannt, dass Mäuse bei bester Gesundheit länger leben, wenn die Kalorienzufuhr auf ein Mindestmaß beschränkt wird. Erst seit etwa zehn Jahren sind die Forscher dabei zu entschlüsseln, warum diese sogenannte Kalorienrestriktion funktioniert: Offenbar aktiviert sie bestimmte Proteine, die das Erbgut besonders gut verpacken können, die Sirtuine.

David Sinclair, Professor an der Harvard University, machte sich auf die Suche nach Substanzen, die die Aktivität der Sirtuin-Proteine steigern können, vor allem von Sirtuin 1 (Sirt-1), einer der sieben Sirtuin-Varianten des Menschen. Er stieß auf Resveratrol, einen Stoff, der auch im Rotwein vorkommt. Allein durch Gabe einer kräftigen Dosis Resveratrol erhöhte sich die Lebenserwartung von Hefezellen um 70 Prozent – und in ähnlichem Ausmaß auch die von Fliegen, Würmern, Fischen und Mäusen. Diese Arbeit elektrisierte Westphal. Dann veröffentlichte Sinclair Ergebnisse, nach denen Resveratrol in der Lage war, übergewichtigen, zuckerkranken Mäusen die gleiche Lebenserwartung zu verschaffen wie normal gefütterten Nagern. Westphal sah sofort das Potenzial einer Pille gegen die epidemieartig zunehmenden Diabeteserkrankungen weltweit – mit der Option, auch das Leben selbst zu verlängern.

An diesem Punkt setzt der Sirtris-Chef ein ernstes Gesicht auf: „Unser Ziel ist nicht, das Leben zu verlängern. Das Ziel ist, ein neues, sicheres Medikament gegen Altersdiabetes zu entwickeln." Denn auch wenn er einen solchen Effekt nicht ausschließen will, würde wohl nicht einmal ein Christoph Westphal genug Geld zusammenbekommen, um die elend langwierige klinische Studie zu finanzieren, die eine lebensverlängernde Wirkung beweisen könnte. Beim Nachsinnen darüber verfällt er ins Englische: Antibiotika hätten die Lebenserwartung um zwei bis drei Jahre verlängert, Hygienemaßnahmen wie Händewaschen und die Kanalisation der Abwässer um mindestens fünf bis zehn Jahre, Krebsmedikamente schätzungsweise um ein bis zwei Jahre. Das Aktivieren von Sirtuinen hat in allen getesteten Tiermodellen die Lebenserwartung um dreißig bis siebzig Prozent erhöht. „That can change the world", sagt Westphal, „als ich das zum ersten Mal gelesen habe, dachte ich sofort, das könnte wichtiger sein als Google."

PÜNKTLICH UND MIT OFFENER TÜR

Während das Sirtris-Medikament den Alterungsprozess hemmen soll, tut CEO Westphal alles dafür, dass sein Unternehmen so schnell wie möglich heranreift. Mitunter vielleicht sogar etwas zu schnell, meint Co-Vorstand Bohlin, der selbst schon ein Unternehmen von der Größe Sirtris' zum eigenständigen Pharmaunternehmen mit 1600 Mitarbeitern aufgebaut hat: „Christoph ist schnell, aber manchmal ist es besser, über eine Entscheidung etwas länger nachzudenken."

Irgendwelche typisch deutschen Charakterzüge? Michelle Dipp fällt dazu nur die notorische Pünktlichkeit ihres Chefs ein. Hierarchie-Denken hingegen sei ihm völlig fremd, seine Bürotür immer offen. Denn Distanz zum Management kann gerade bei jungen Biotechfirmen tödlich sein, sagt Westphal, und seine Rolle als Santa Claus erscheint in einem ganz anderen Licht: „Nur so sagen mir die Leute auch wirklich, was Sache ist, wenn ein ernstes Problem auftritt oder ein Fehler gemacht wurde." Die „beer hour", bei der jeden Freitagnach-

AP PHOTOS

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Founding Team

Whitehead Institute

Broad Institute

sirtris Pharmaceuticals

Momenta

Alnylam Pharmaceuticals

CoNCERT Pharmaceuticals Inc.

OvaScience Improving Fertility Through Science

Acceleron Pharma

Longwood Fund

Cardinal Partners

Bessemer Venture Partners

MPM Capital

Scientific Advisory Board

Robert Weinberg, Ph.D.
Whitehead Institute/MIT
Co-founder & Chairman of SAB

Peter Elliott, Ph.D.
Former SVP/Head – R & D, SIRT (now GSK)
Millennium (co-developed Velcade®)

Eric Lander, Ph.D.
Broad Institute/MIT/HMS
Pioneer of Human Genome Project

Richard Sackler, M.D.
Chairman – Purdue Pharma

Joseph (Yossi) Schlessinger, Ph.D.
Yale Medical School
Cofounder: Sugen (Pfizer), Plexxikon (Daiichi-Sankyo)

Phil Sharp, Ph.D.
MIT – 1993 Nobel Prize in Medicine
Cofounder: Biogen, Alnylam; Sirtris SAB

Roger Tung, Ph.D.
President & CEO/Cofounder – Concert
Vertex (co-invented Lexiva® and Agenerase®)

Chris Walsh, Ph.D.
Harvard Medical School
Cofounder: Genzyme, Vicuron; Sirtris SAB

Translational Research

José Baselga, M.D., Ph.D.
Physician in Chief
Memorial Sloan-Kettering

Max Wicha, M.D.
Director – University of Michigan
Comprehensive Cancer Center

Daniel Haber, M.D., Ph.D.
Director – MGH Cancer Center
Harvard Medical School/HHMI

George Daley, M.D., Ph.D.
Director – Stem Cell Program
Harvard Medical School/HHMI

Eric Winer, M.D.
Director – Breast Oncology Center
Dana Farber Cancer Institute/HMS

Verastem Team

Executive Management

Christoph Westphal, M.D., Ph.D.
Chairman/CEO, Cofounder
Cofounder/CEO: MNTA, ALNY, SIRT (now GSK)
Cofounder: Alnara (now Lilly), OvaScience

Robert Forrester
President/COO
CEO/CFO, CombinatoRx (now ZLCS)
SVP, COLY (now Pfizer)

Joanna Horobin, M.B., Ch.B.
Chief Medical Officer
President, Syndax Pharmaceuticals
VP, Oncology, Rhone-Poulenc Rorer (now Sanofi)

Jonathan Pachter, Ph.D.
VP, Head of Research
Head of Cancer Biology, OSI (now Astellas)
Schering-Plough (now Merck)

Daniel Paterson
VP, Head of Corporate Development and Diagnostics
CEO: The DNA Repair Co. (now On-Q-ity)
PharMetrics (now IMS), Axion

Board of Directors

Henri Termeer
Lead Director
Former CEO/Chair Genzyme

Richard Aldrich
Longwood Fund

John K. Clarke
Cardinal Partners

Michael Kauffman, M.D., Ph.D.
CEO Karyopharm, former CMO Onyx

Alison Lawton
Former Genzyme (now Sanofi)

Louise Phanstiel
BOD: Cedars Sinai, MYGN

Success in Biotech – THE FINANCING

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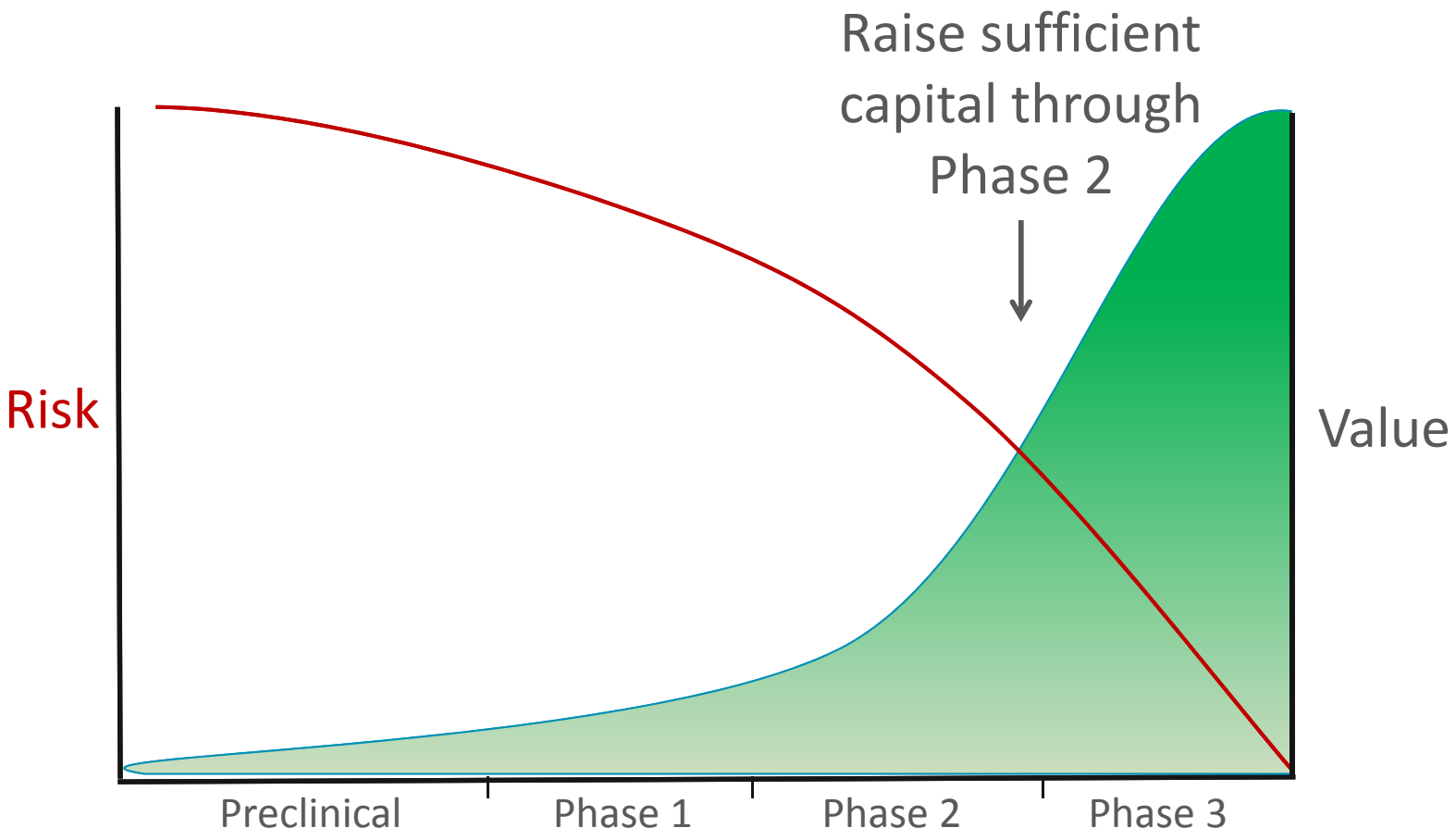
Financing Plan for Risk Mitigation



Finance appropriately to buy the time to do the right science, the right clinical trials…the right way

Verastem

Finance appropriately to buy the time to do the right science and the right clinical trials to evaluate your hypothesis

Investors	Series A	Series B	Series C
Longwood Fund	✓	✓	✓
Bessemer Venture Partners	✓	✓	✓
Cardinal Healthcare Partners	✓	✓	✓
MPM Capital	✓	✓	✓
Astellas Venture Fund		✓	✓
Advanced Technology Ventures		✓	✓
Eastern Capital			✓
H & Q Life Sciences / Healthcare			✓
Peter Lynch			✓

- $131.7 million raised
- Cash balance 9/30/12: $97.4 million [1]
- 22 Full-time employees [2]

[1] *Cash balance includes investments at 9/30/12*

[2] *Full-time employee count is as of 9/30/2012*

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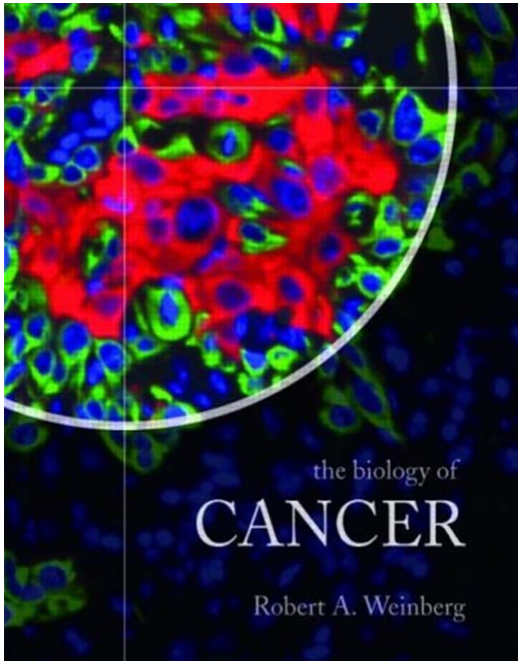
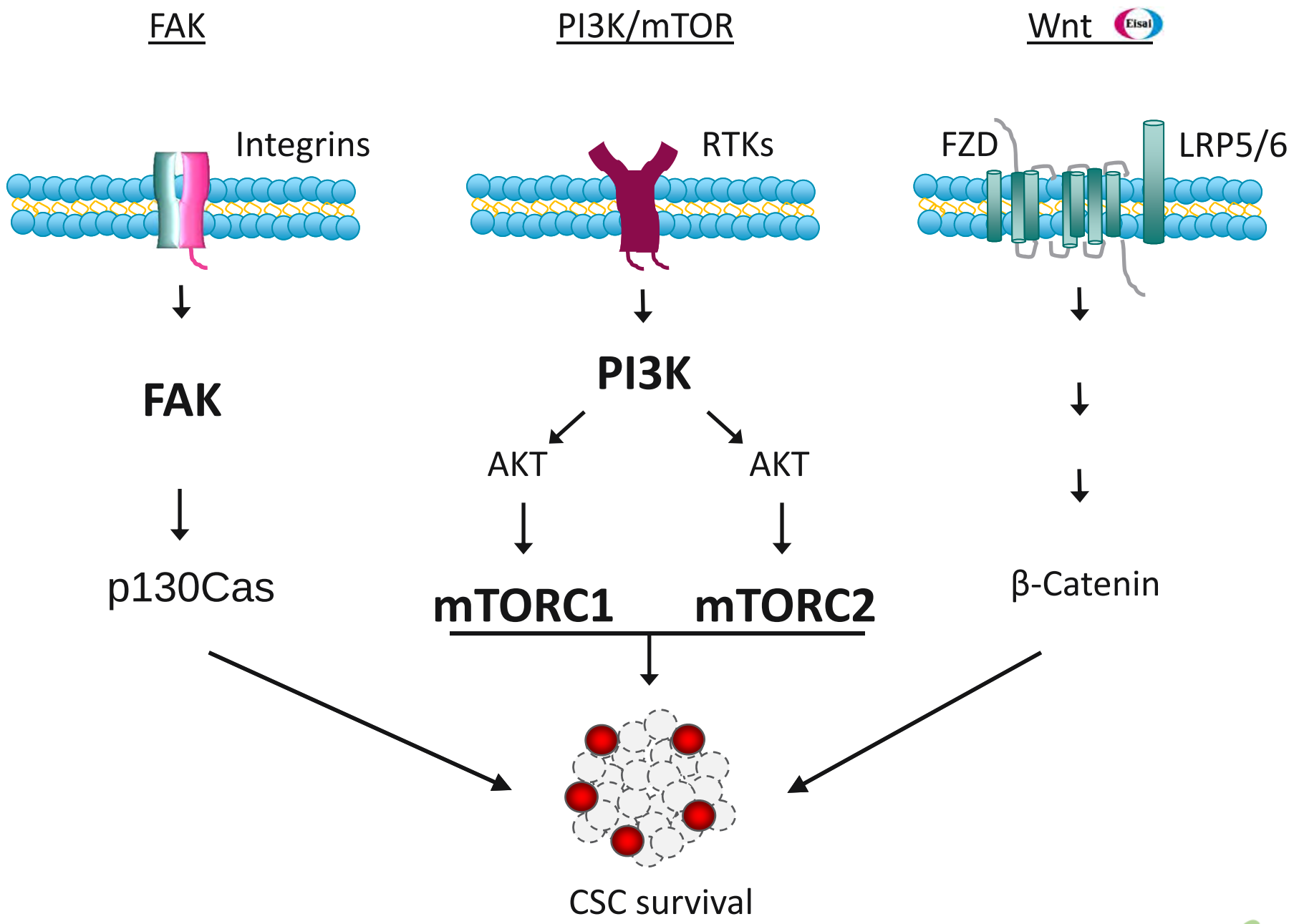
Verastem: Key Highlights

- Drugs targeting cancer stem cells for a durable clinical response
- Three product candidates:
  - Focal Adhesion Kinase (FAK)
    - VS-6063
    - VS-4718
  - PI3K/mTOR
    - VS-5584

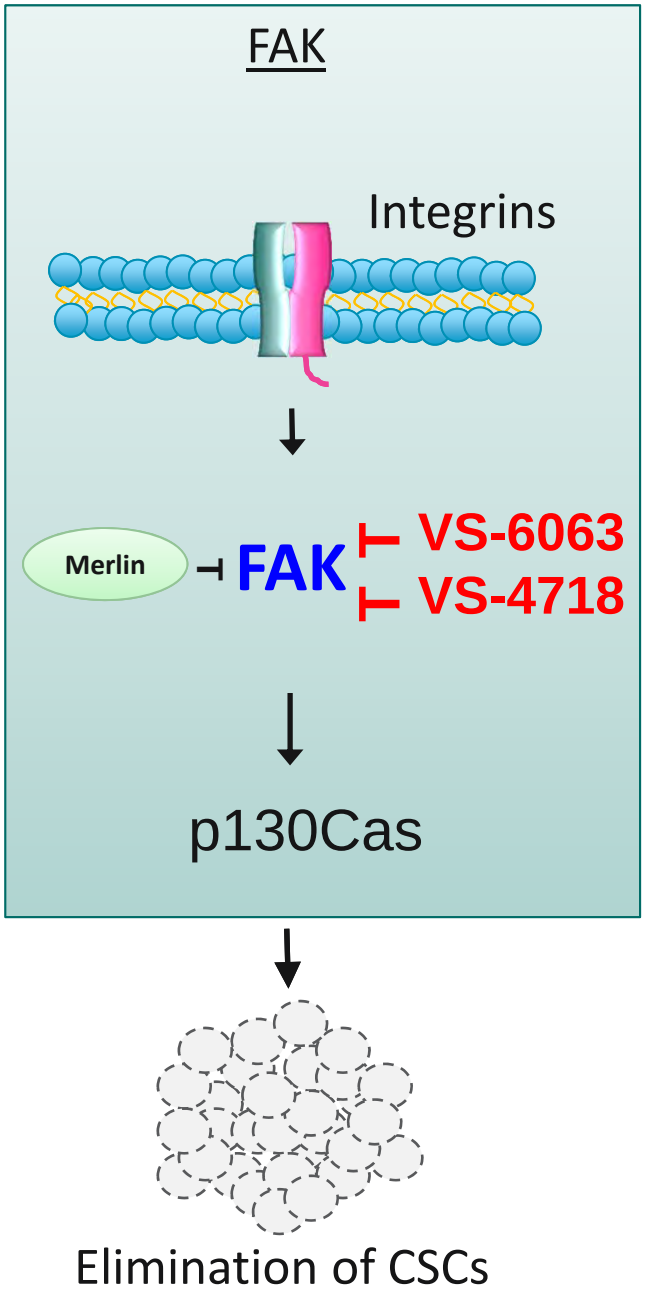


- Potentially pivotal study of VS-6063 planned for mid-2013
- Strong balance sheet and team to execute development plan

Verastem is Targeting 3 Critical Cancer Stem Cell Pathways

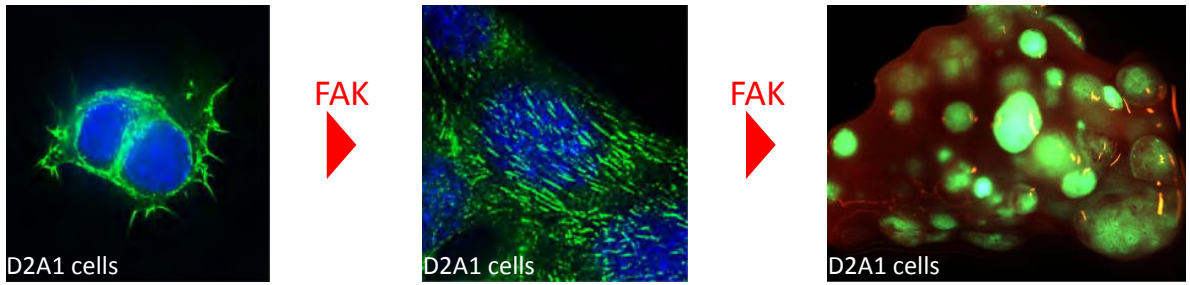


FAK is Critical for Cancer Stem Cells



- FAK drives tumor-initiating capability
- FAK is a critical pathway for cancer stem cells
- FAK is a key regulator in disease progression

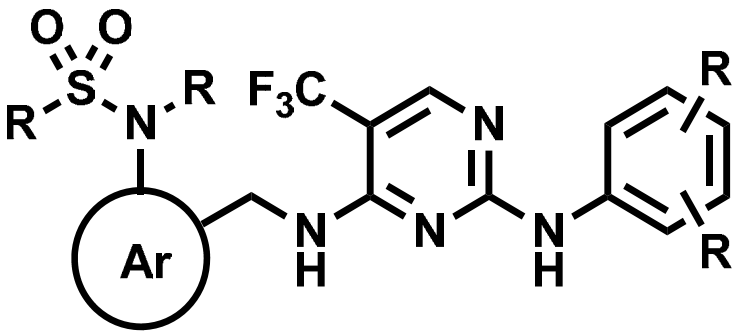
Weinberg et. al.; Cancer Discovery 2012 Aug;2(8):706-21



Cell mobility **Proliferation** **Tumor initiation**

VS-6063 – Lead FAK Inhibitor

- Good safety profile and initial signs of activity in Phase 1
- Oral administration dosed twice daily (BID)
- Potentially pivotal study in mesothelioma planned to initiate midyear 2013
- Phase 1/2 in combination with paclitaxel in ovarian cancer

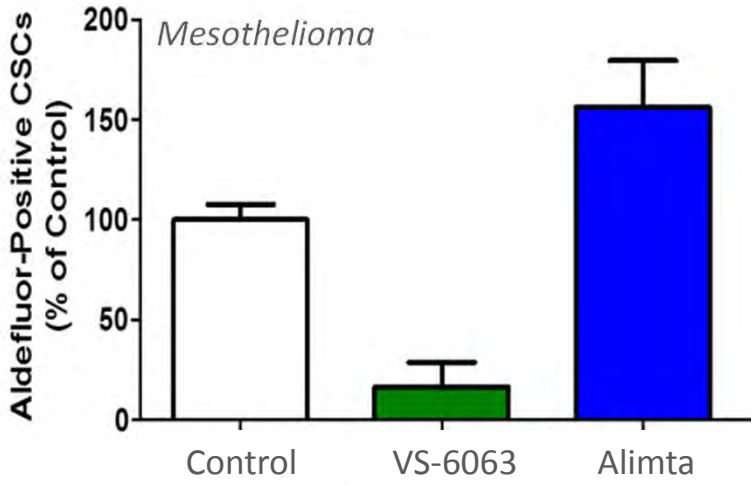


FAK Enzymatic IC_{50} = 24 nM
FAK Cellular EC_{50} = 28 nM

Composition of matter though 2029

Mesothelioma

- Highly aggressive and lethal disease where chemotherapy is not curative (12 month median survival)
  - ~12,000 cases WW (2,500-3,000 in US) increasing incidence in AUS, JP, UK, EU
- Alimta + cisplatin is only approved drug treatment for mesothelioma
- VS-6063 targets and kills CSCs in contrast to Alimta



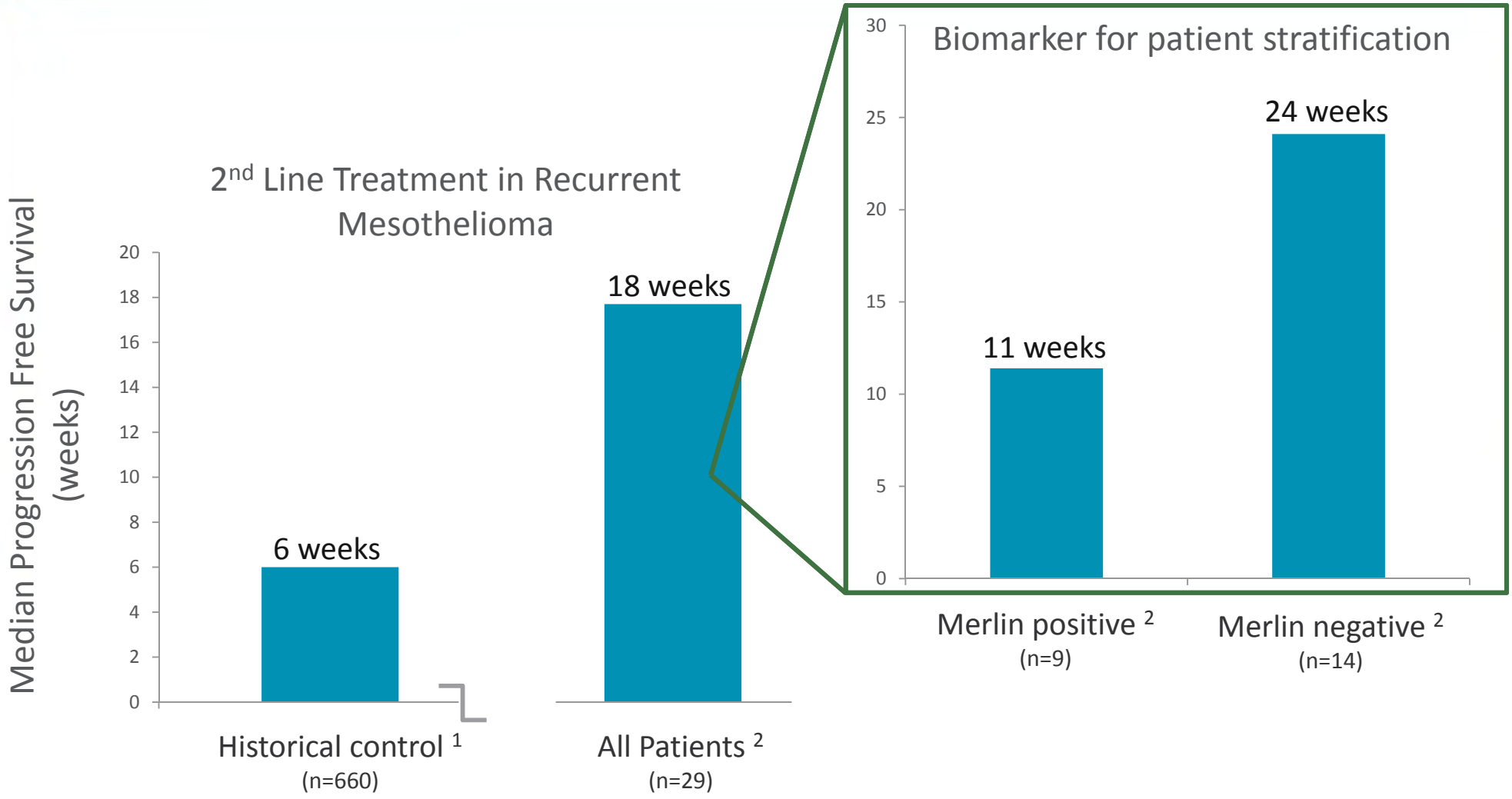
Initial clinical proof of concept for FAK inhibitors by GSK:

Increase in PFS to 18 weeks

Typical Treatment of Advanced Mesothelioma

1st line	Treatment holiday	2nd line
4-6 cycles Alimta + cisplatin		Chemo
Duration: ~4mo	PFS: 4mo	PFS: 6wks

GSK Clinical Data: Initial Proof of Concept for FAK Inhibitors in Mesothelioma



[1] *Historical data from Vorinostat Phase 3 (Krug et al; ESMO 2011)*

[2] *Phase 1 trial of GSK2256098 presented at EORTC-NCI-AACR Molecular Therapeutics meeting (Nov. 6-9, 2012)*

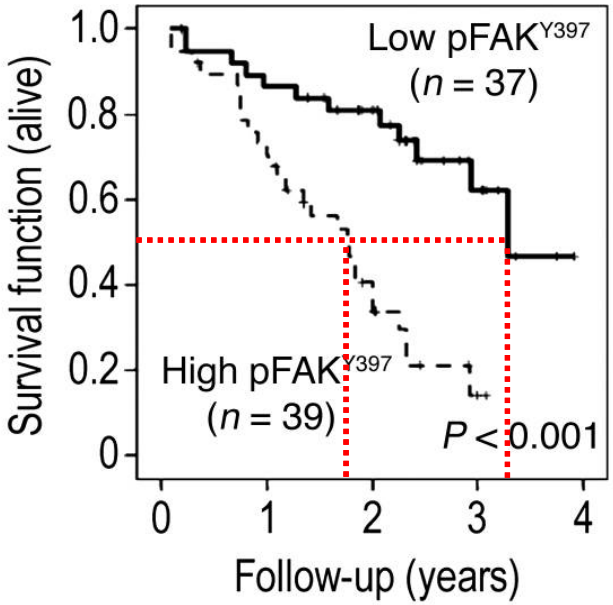
Potentially Pivotal Study in Malignant Pleural Mesothelioma (MPM)

- Patient Population:
  - Controlled disease post-first line therapy with Alimta + cisplatin
- Study Design:
  - Randomized, double blind, placebo controlled study
  - Stratification based on Merlin status (LabCorp) with an adaptive enrichment design
  - Endpoints of Progression Free Survival and Overall Survival
- Anticipated Initiation: mid-2013
- Potentially pivotal study that may allow for approval

Typical Treatment of Advanced Mesothelioma

Ovarian Cancer – Driven by Cancer Stem Cells

- 225,000 cases WW and 22,000 in the US
  - 15,000 deaths per year in US
- 85% of ovarian cancers are diagnosed late-stage and demonstrate a rapid development of resistance to chemotherapy
- Platinum based therapy is initially active but not curative
  - Increases the proportion of cancer stem cells
  - No standard of care for platinum refractory disease
- Activity of VS-6063 observed in ovarian cancer during Phase 1



Mean survival (high/low) 1.7 vs 3.2yrs

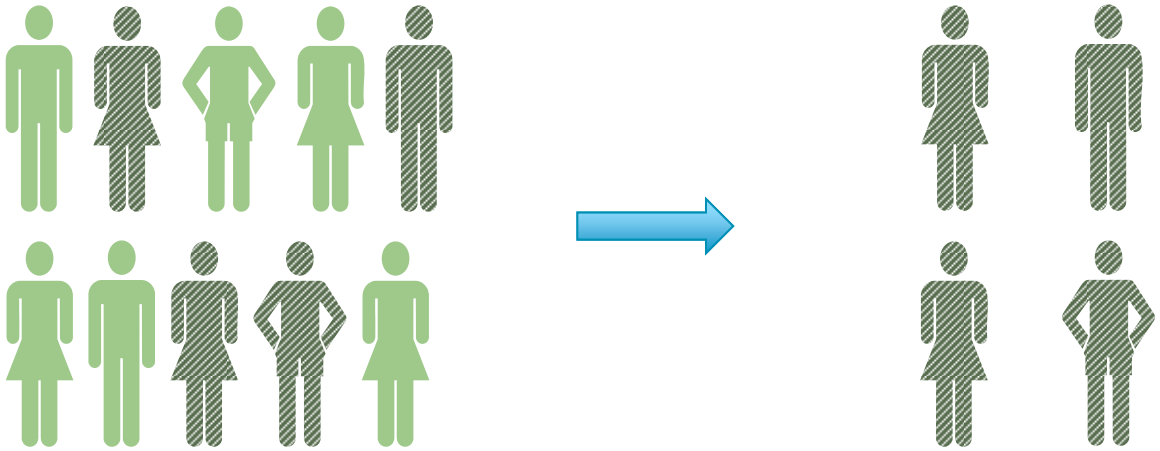
Sood et al. J. Clin Invest. April 2010

Phase 1/2 Ovarian Program: VS-6063 in Combo with Paclitaxel

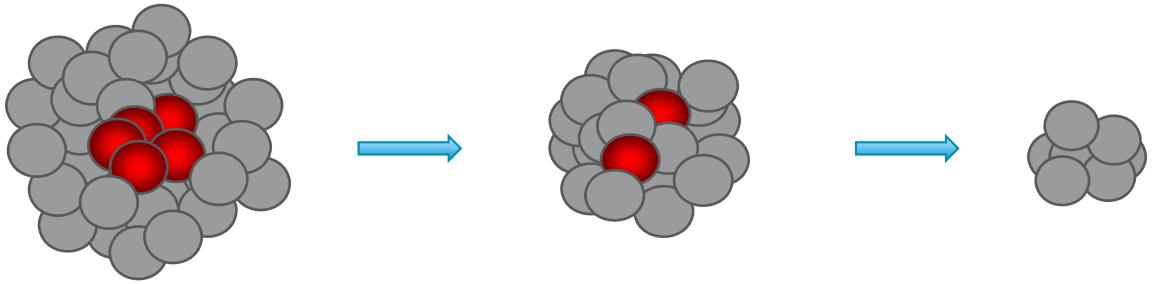
- Patient Population:
  - Recurrent, advanced ovarian cancer patients
  - Progressed on prior treatment with platinum-based therapy
- Study Design:
  - Dose escalation of VS-6063+paclitaxel in all-comers
  - Expansion cohort with platinum resistant disease receiving VS-6063+paclitaxel
  - Endpoints: Efficacy, safety, tolerability, PK, PD and biomarkers
- Number of Patients: ~20-30
- Status: Recruiting
- Combination with paclitaxel paves the way to other indications

The Promise of Personalized Medicine: Cancer Stem Cell Diagnostics

Select patients based on their individual tumor composition



Monitor response to therapy

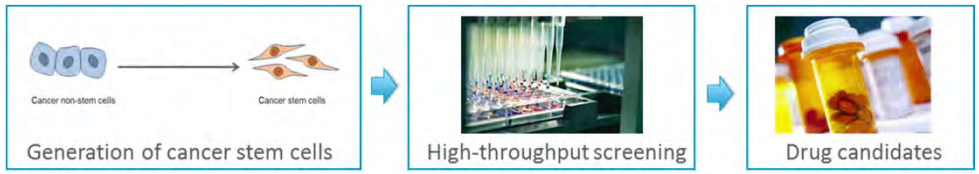


Key Intellectual Property

CSC biology and biomarkers

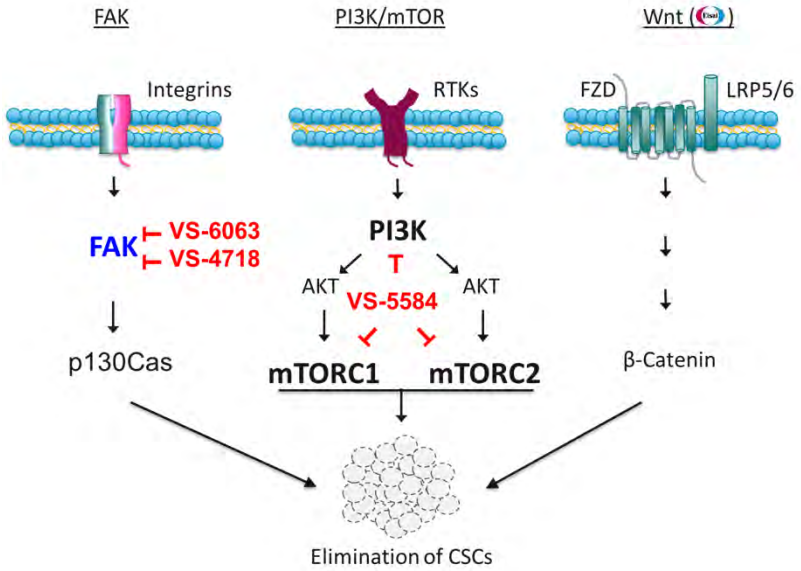
- ✓ *Progenitor Cells and Uses Thereof (Expiration 2026)* [1]
- ✓ *Methods of Diagnosing, Preventing and Treating Cancer Metastasis. (Expiration 2025)* [2]
- ✓ *Compositions and Methods for Modulating EMT and Uses Thereof (Expiration 2031)* [1]

High-throughput screening of CSCs



- ✓ *A Method for the Discovery of Agents Targeting and Exhibiting Specific Toxicity for Cancer Stem Cells. (Expiration 2029)* [1]

Inhibitors of CSC survival



- ✓ *Inhibitors of Focal Adhesion Kinase*
  - *VS-6063* [2]
    - ✓ *Expiration 2029*
  - *VS-4718* [1]
    - ✓ *Expiration 2028-2031*
- ✓ *Inhibitors of PI3K/mTOR*
  - *VS-5584* [1]
    - ✓ *Expiration 2029*

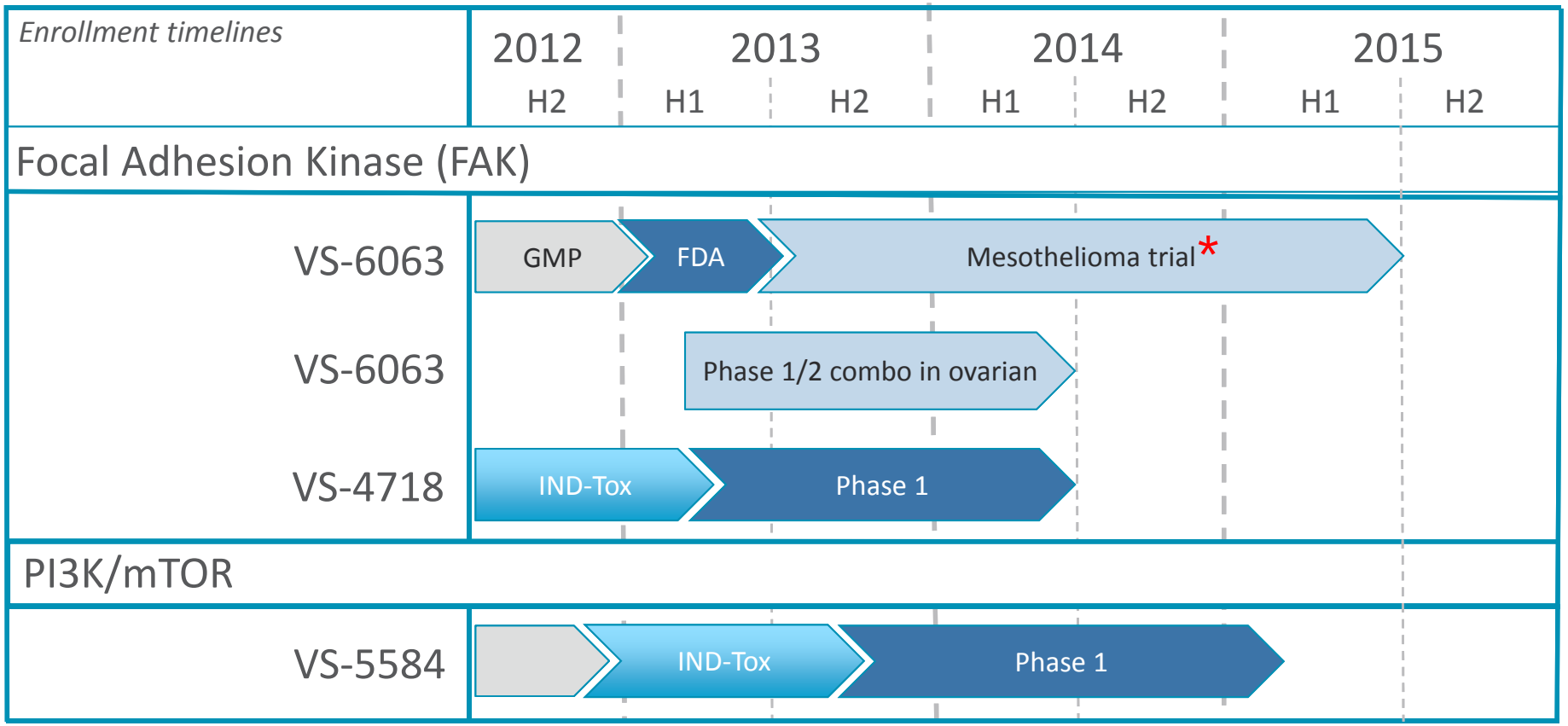
[1] *Pending patent application* [2] *U.S. patent issued*

Sufficient Capital to Execute on Proposed Development Plan

$131.7 million raised

Cash balance 9/30/12
$97.4 million

22 Full-time employees



*Potential regulatory filing for approval following this study

Estimates based on proposed clinical plans. Alternatives are being considered

Fidelity INVESTMENTS
QVT Financial LP
BLACKROCK
Putnam INVESTMENTS
FRANKLIN TEMPLETON INVESTMENTS
Emerald FINANCIAL ADVISORS
JENNISON ASSOCIATES

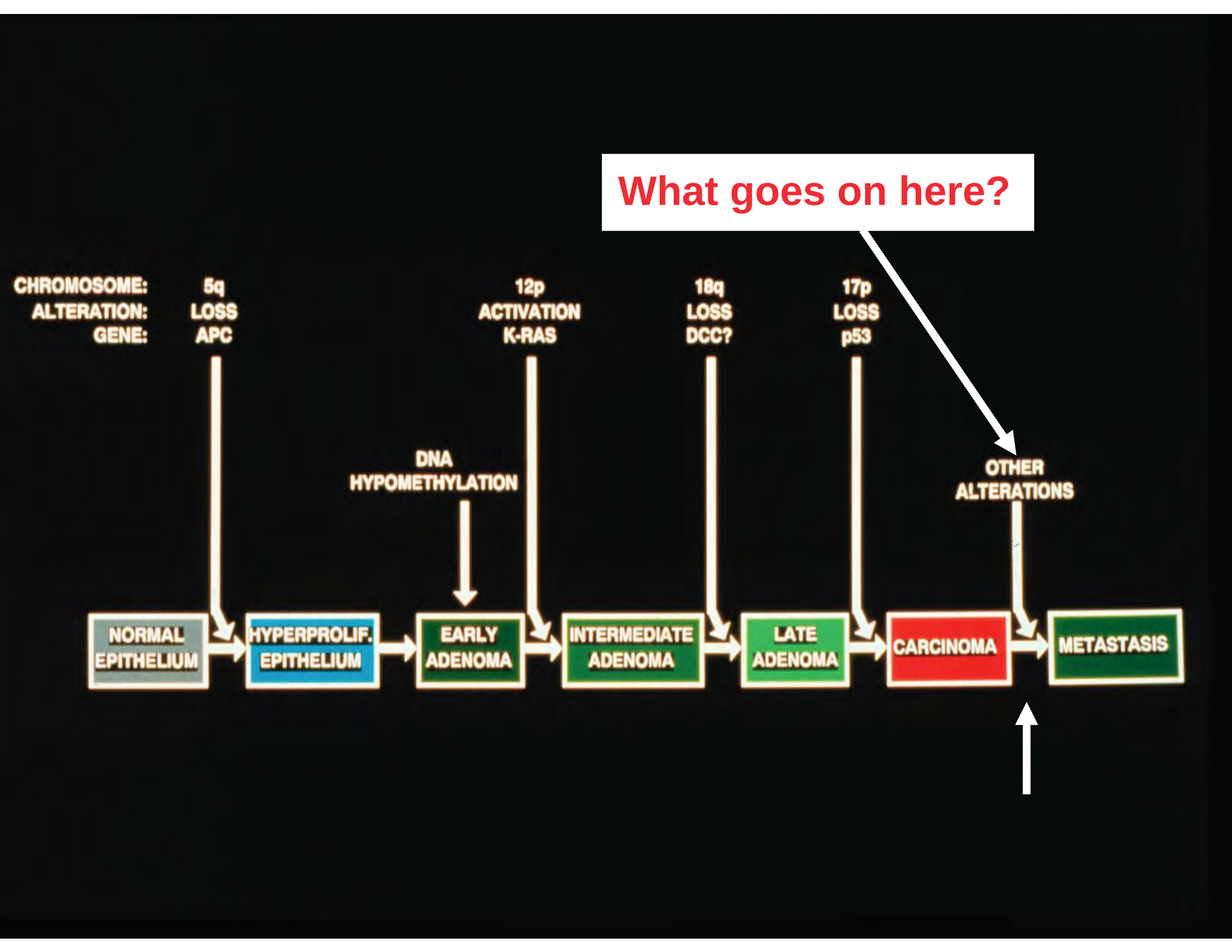
Holders as of 9/30/12

Building Biotech Companies

Key Learnings:

1. All about idea, people, financing
2. The money buys you time to do the right things (for the science, and for our patients)
3. Need amazing science and compelling vision to have a chance at success
4. Importantly, you need to FOCUS to get something amazing done

Verastem Team


What goes on here?
CHROMOSOME:
ALTERATION:
GENE:
5q
LOSS
APC
12p
ACTIVATION
K-RAS
18q
LOSS
DCC?
17p
LOSS
p53
DNA
HYPOMETHYLATION
OTHER
ALTERATIONS
NORMAL EPITHELIUM
HYPERPROLIF. EPITHELIUM
EARLY ADENOMA
INTERMEDIATE ADENOMA
LATE ADENOMA
CARCINOMA
METASTASIS

Cell-of-Origin Determines Tumor Morphology and **Behavior**

(Standard medium) (Special medium)

	HMLER	BPLER
Ductal differentiation	No	Yes
Invasion	Minimal	Yes
Stromal recruitment	Minimal	Yes
Metastasis	No	Yes
Tumorigenicity	10^6 cells needed to seed tumor	$<10^2$ cells needed to seed tumor

Tan Ince

Cell -of -Origin Determines Tumor Morphology and **Behavior**

	HMLER (Standard medium)	BPLER (Special medium)
Ductal differentiation	No	Yes
Invasion	Minimal	Yes
Stromal recruitment	Minimal	Yes
Metastasis	No	Yes
Tumorigenicity	10^6 cells needed to seed tumor	$<10^2$ cells needed to seed tumor

Differing concentrations of tumor-initiating cells (correlated) with differing metastatic propensities

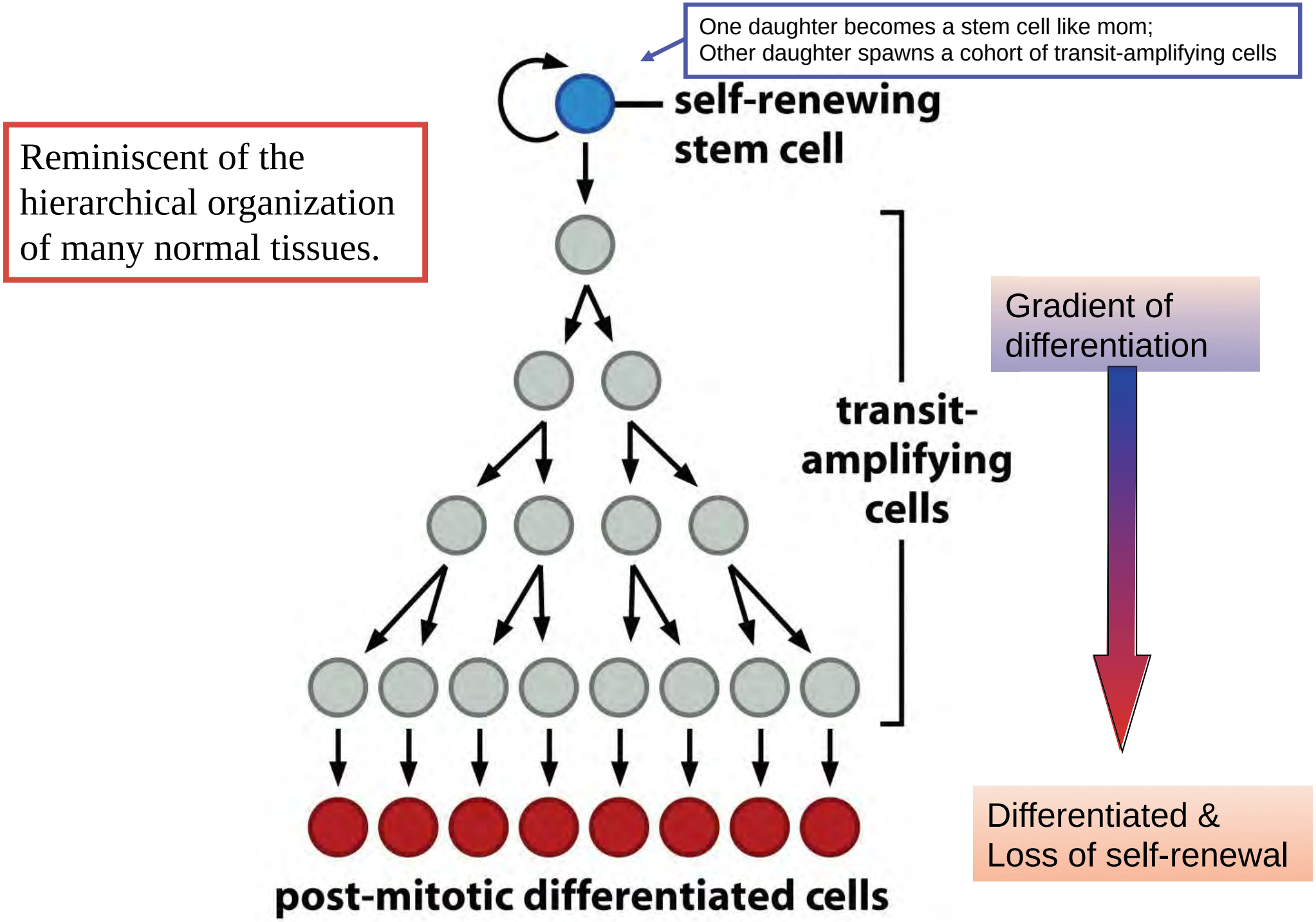
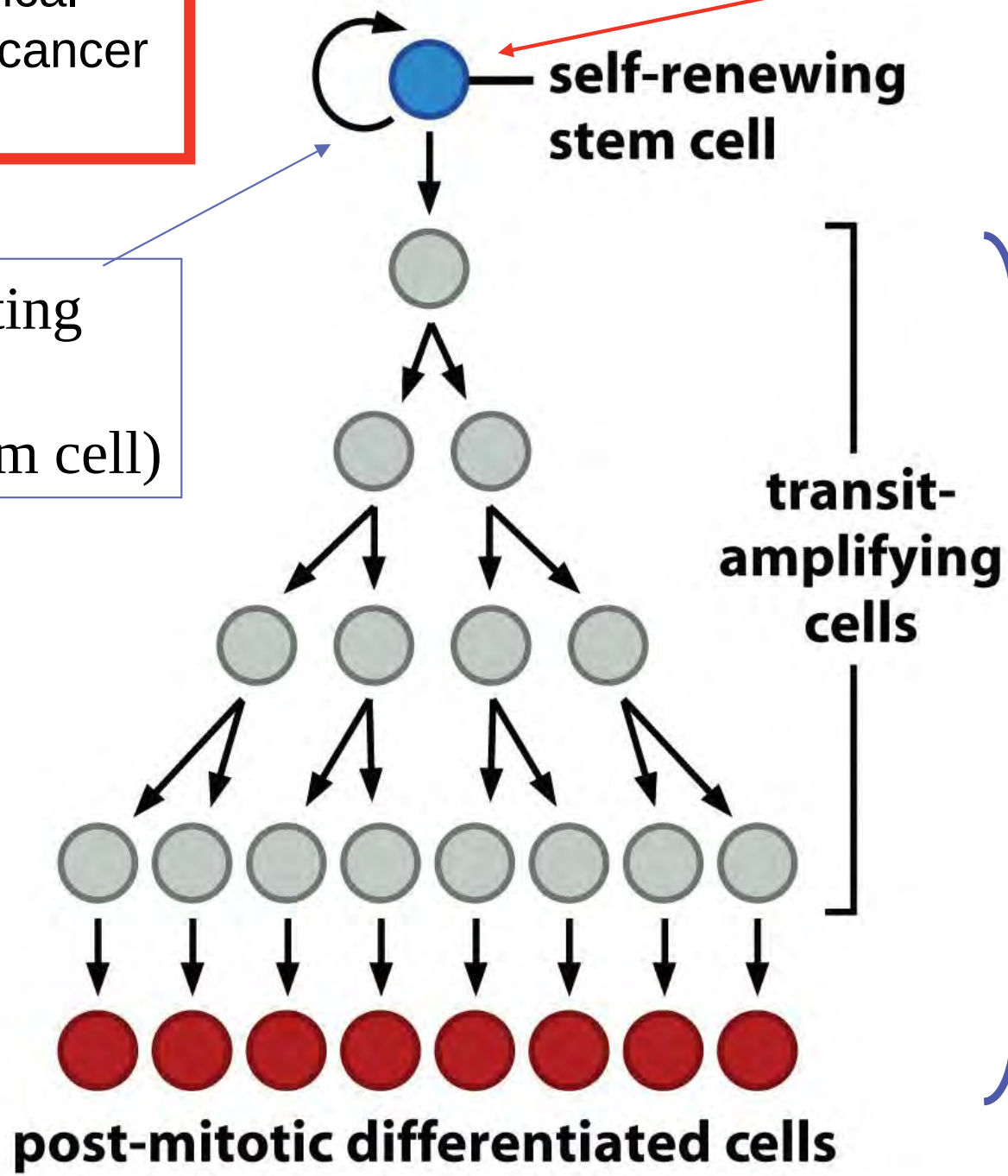


Figure 11.16b *The Biology of Cancer* (© Garland Science 2007)

Similar hierarchical organization of cancer cells in a tumor

This cell is qualified to **seed a new tumor**

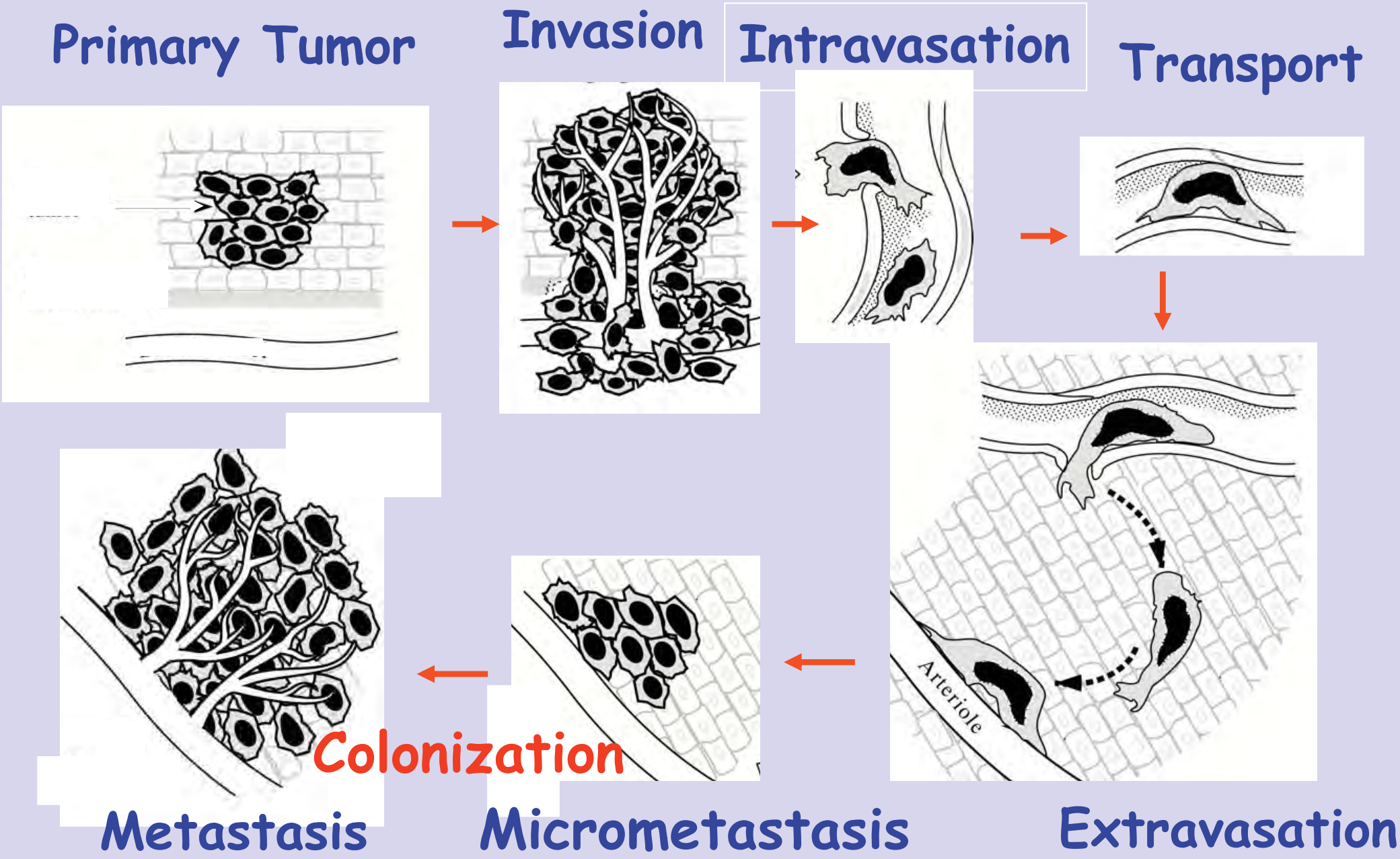
Tumor-initiating cell
(= cancer stem cell)



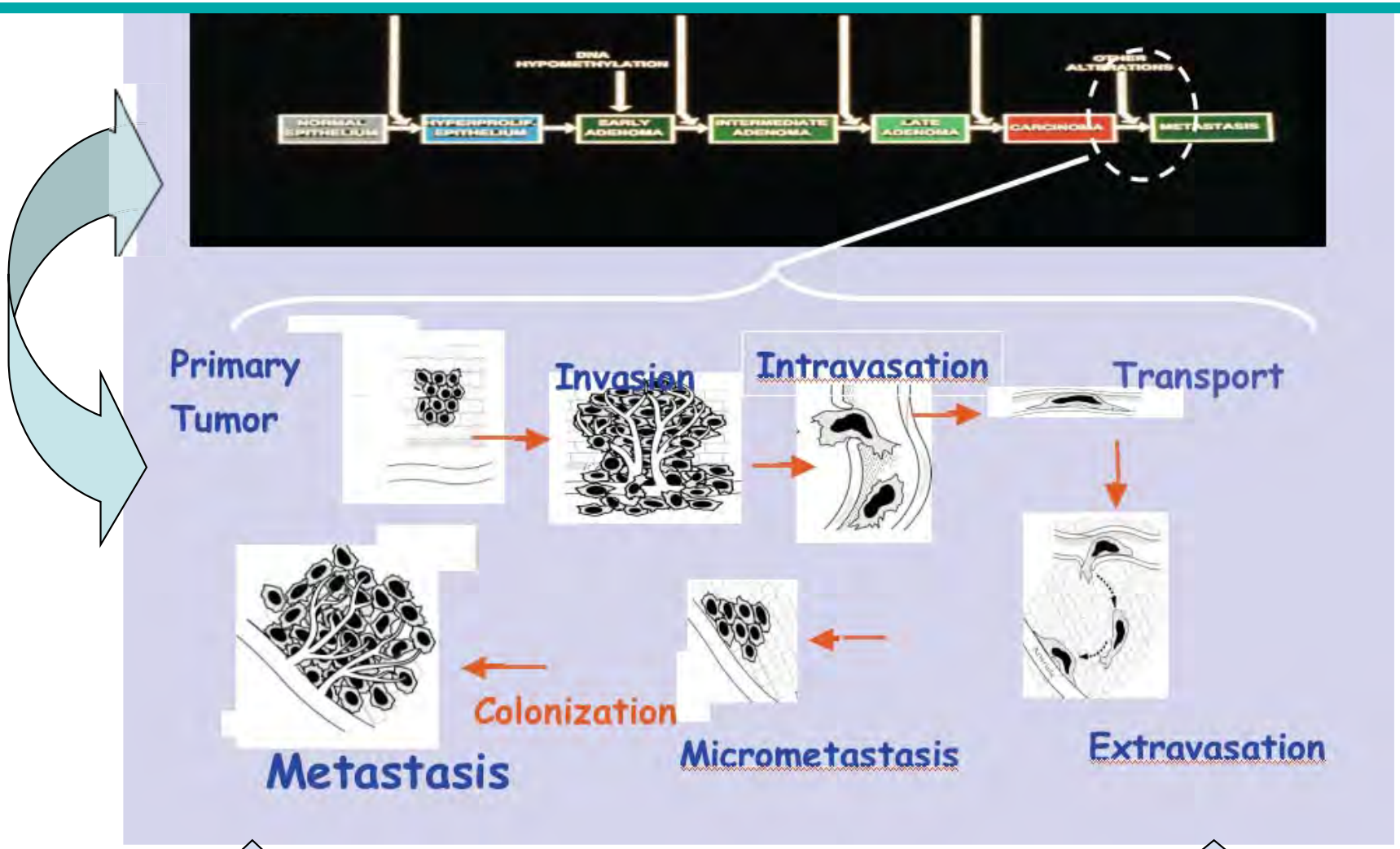
These cells **cannot seed a new tumor (because they lack self-renewal capability)**

Figure 11.16b *The Biology of Cancer* (© Garland Science 2007)

How do cancer cells actually metastasize?
The invasion-metastasis cascade:

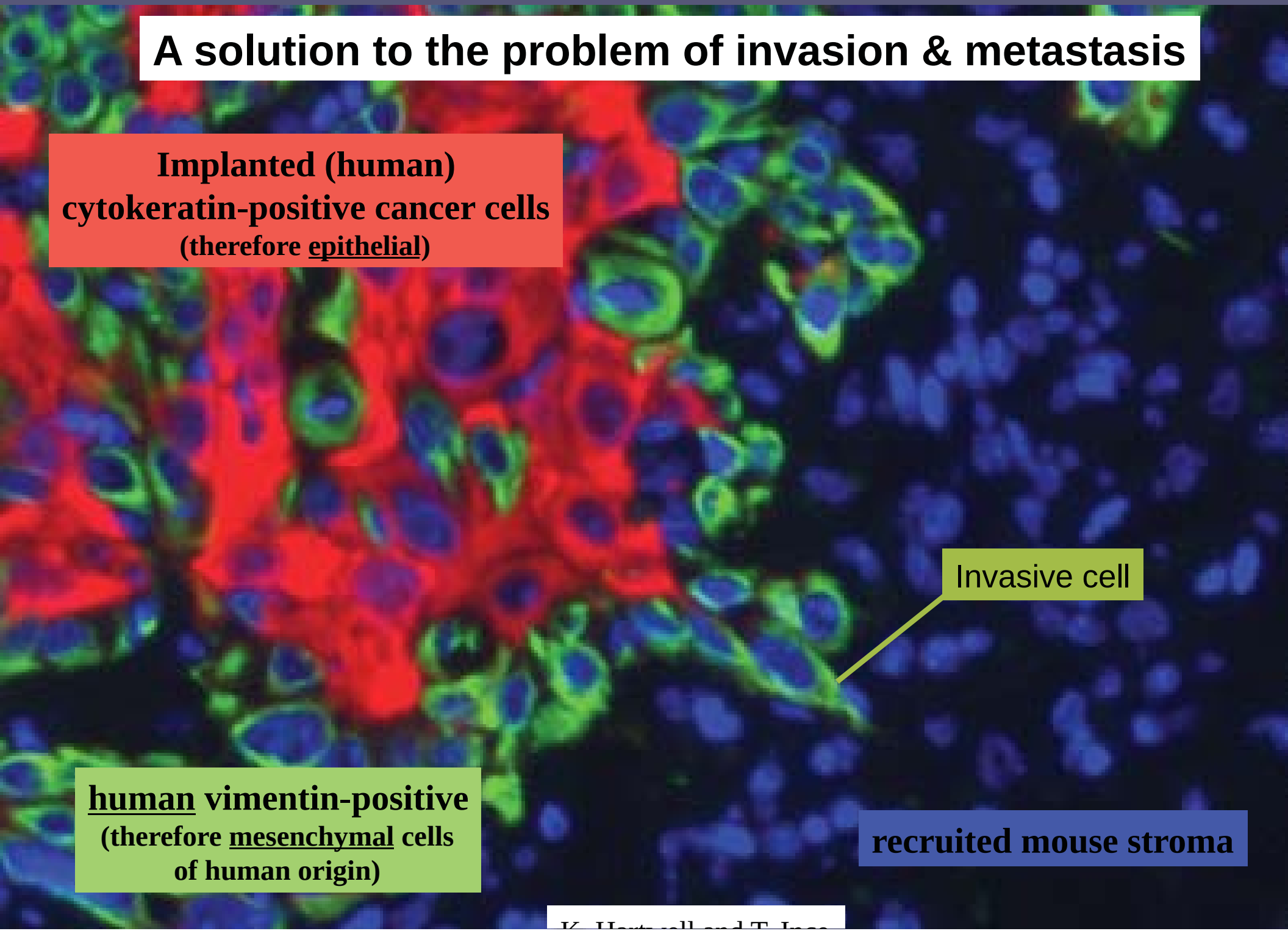


How do cancer cells cobble together the diverse traits that are required in concert to negotiate the successive steps of the invasion-metastasis cascade??

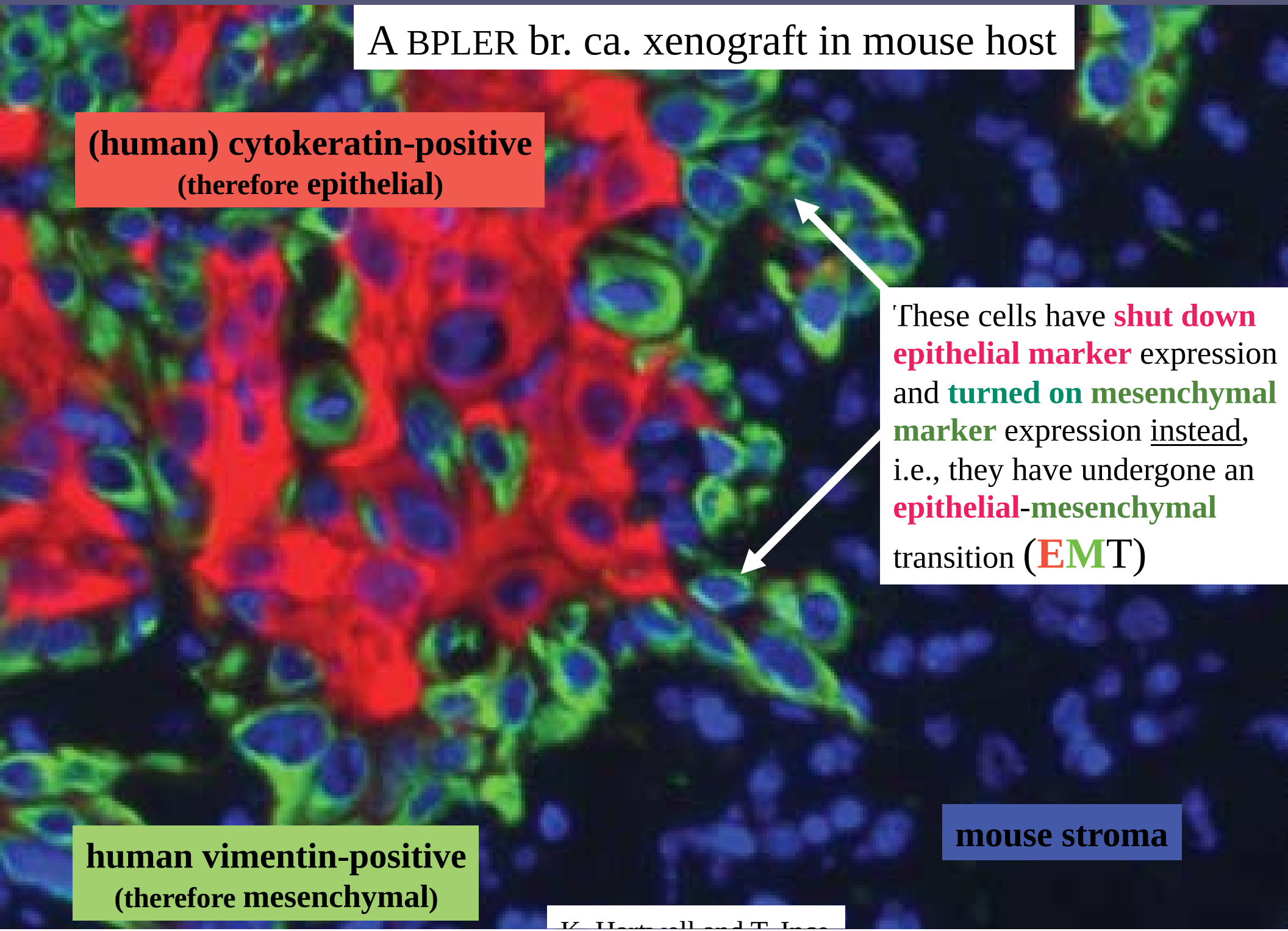


invasion-metastasis cascade

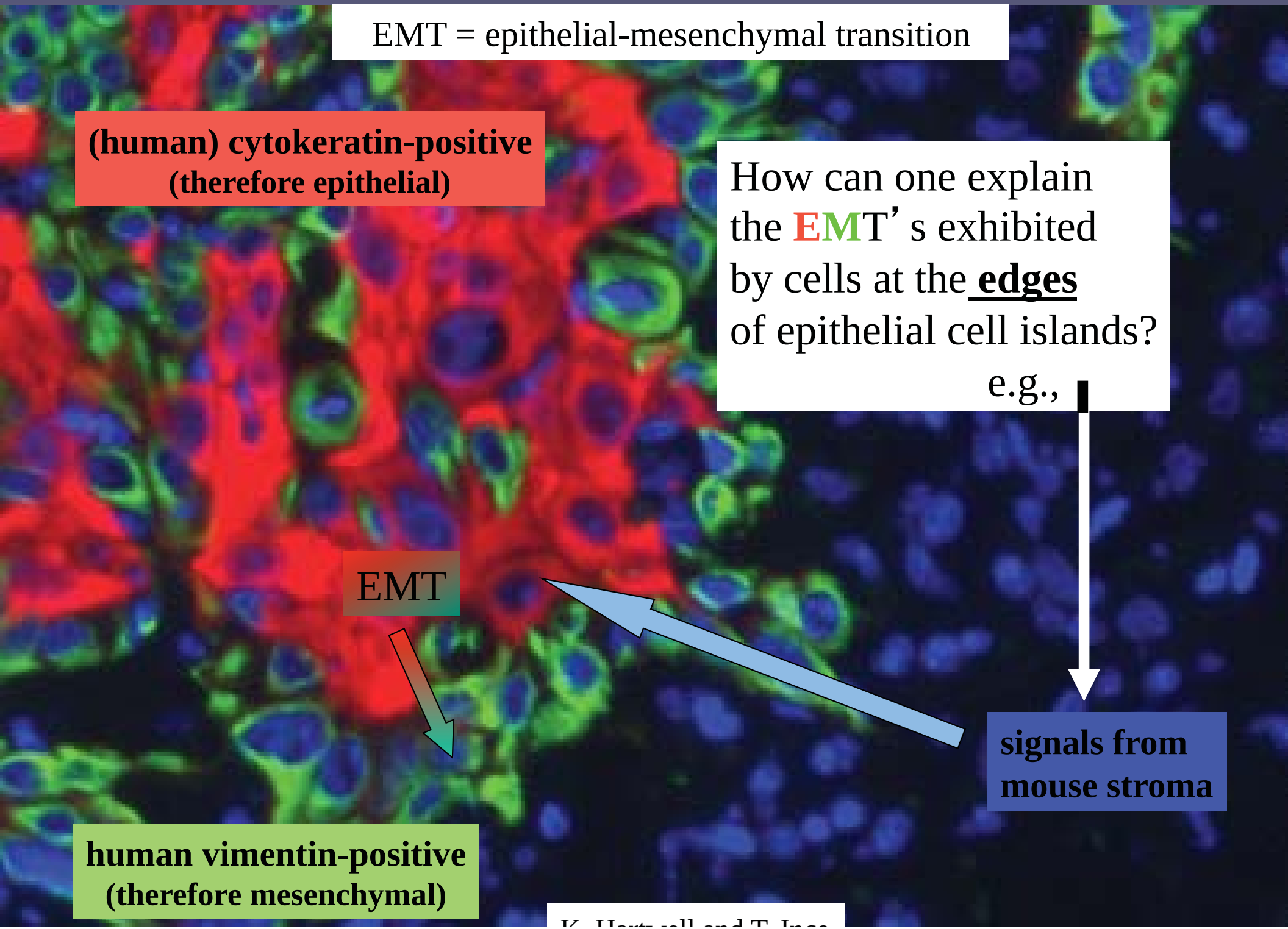
A solution to the problem of invasion & metastasis



A BPLER br. ca. xenograft in mouse host



K. Hartwell and T. Ince


EMT = epithelial-mesenchymal transition
(human) cytokeratin-positive
(therefore epithelial)
How can one explain the EMT's exhibited by cells at the edges of epithelial cell islands?
e.g.,
EMT
signals from mouse stroma
human vimentin-positive
(therefore mesenchymal)

These cells have undergone an EMT

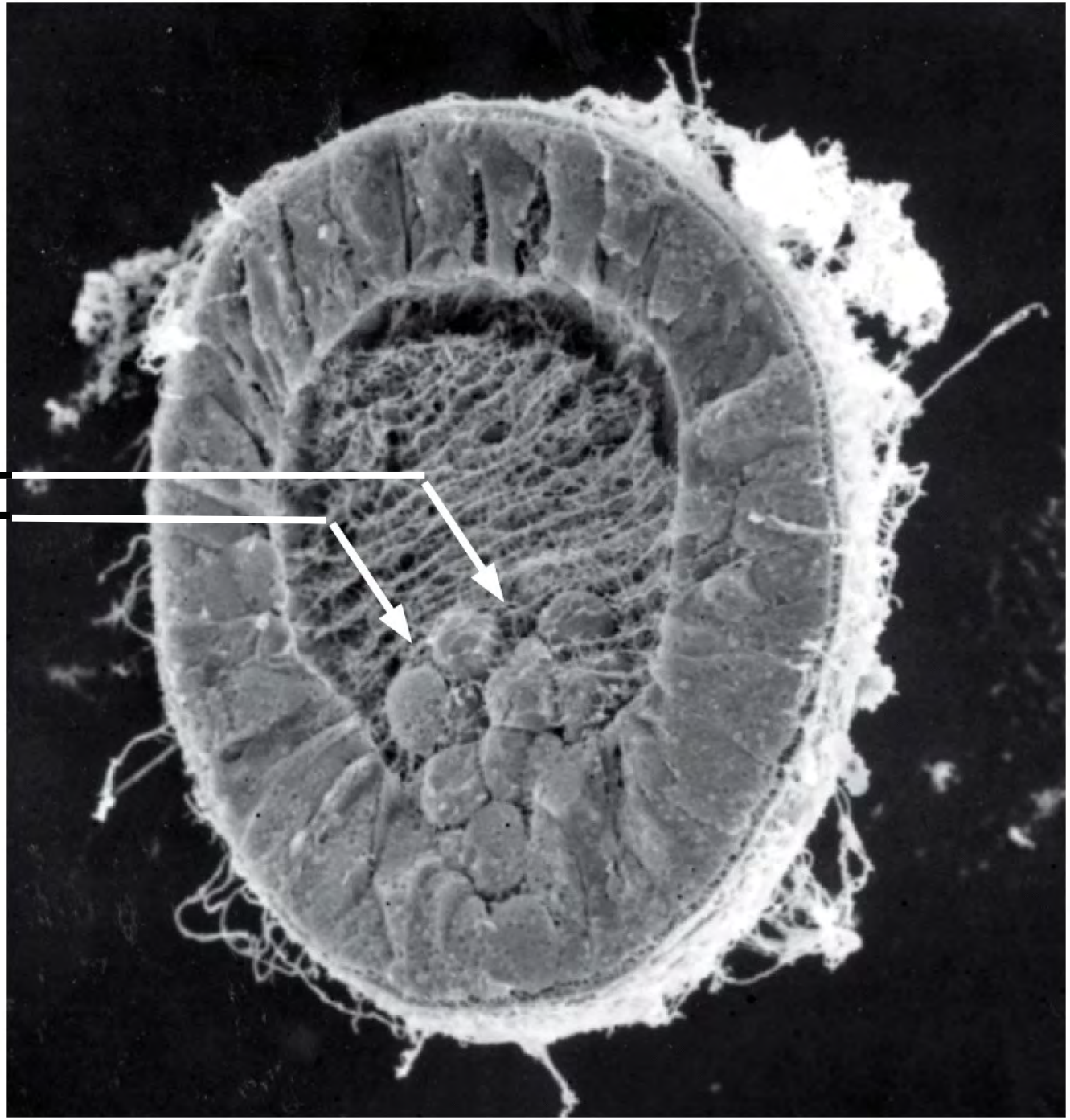
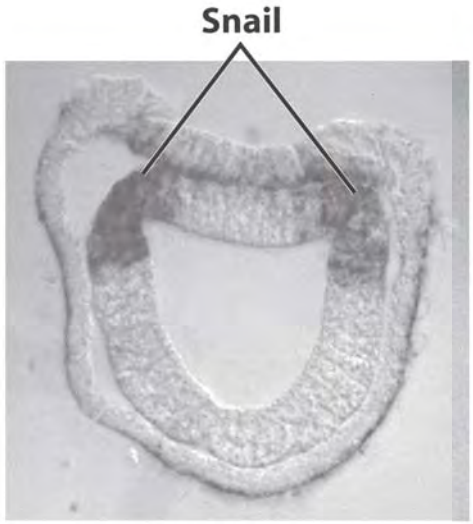
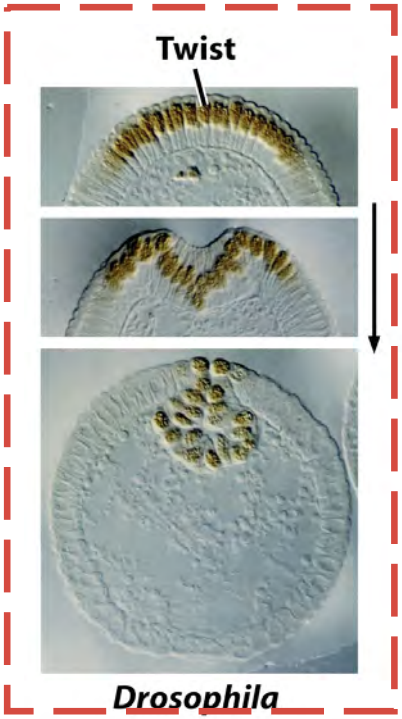


Figure 14.13a *The Biology of Cancer* (© Garland Science 2007)

A group of pleiotropically acting **master regulators** that choreograph EMT at various stages of embryogenesis



amphioxus



Drosophila

Xenopus laevis

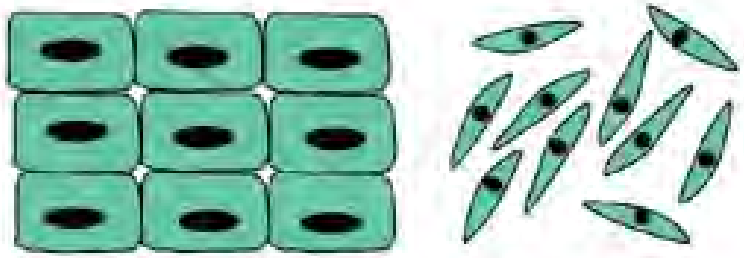
Xenopus

amphioxus

mouse

The epithelial-mesenchymal transition EMT is a complex, multi-faceted program involving multiple changes in cell properties.

epithelial → mesenchymal

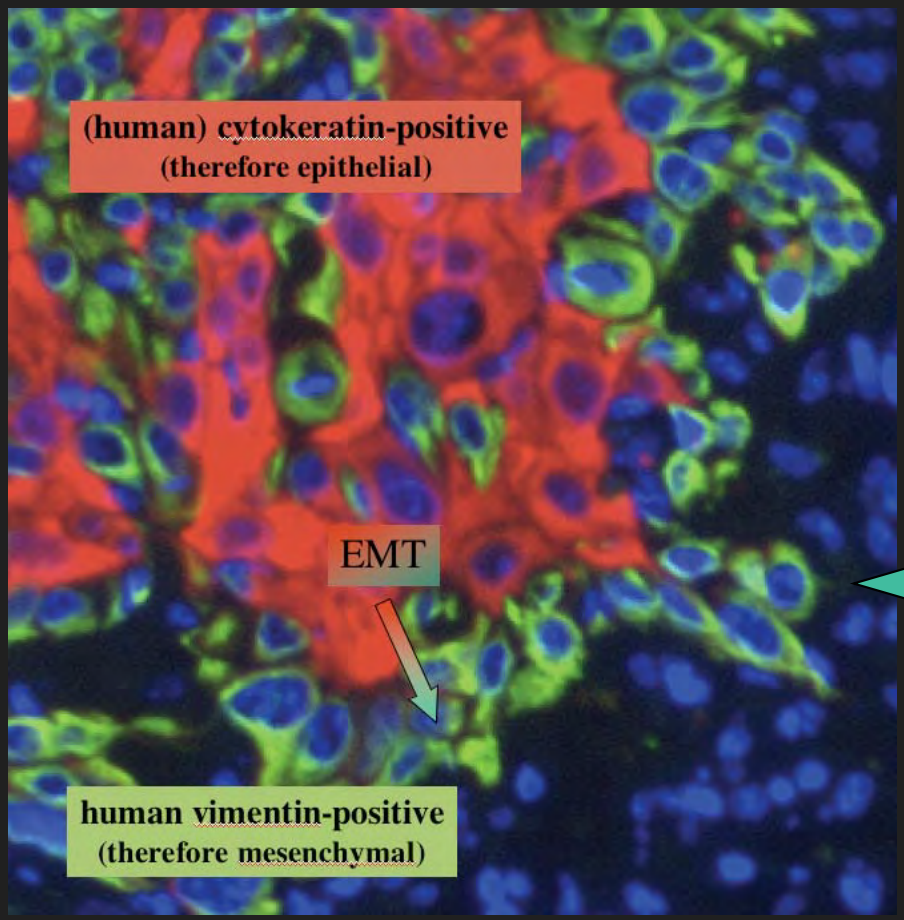


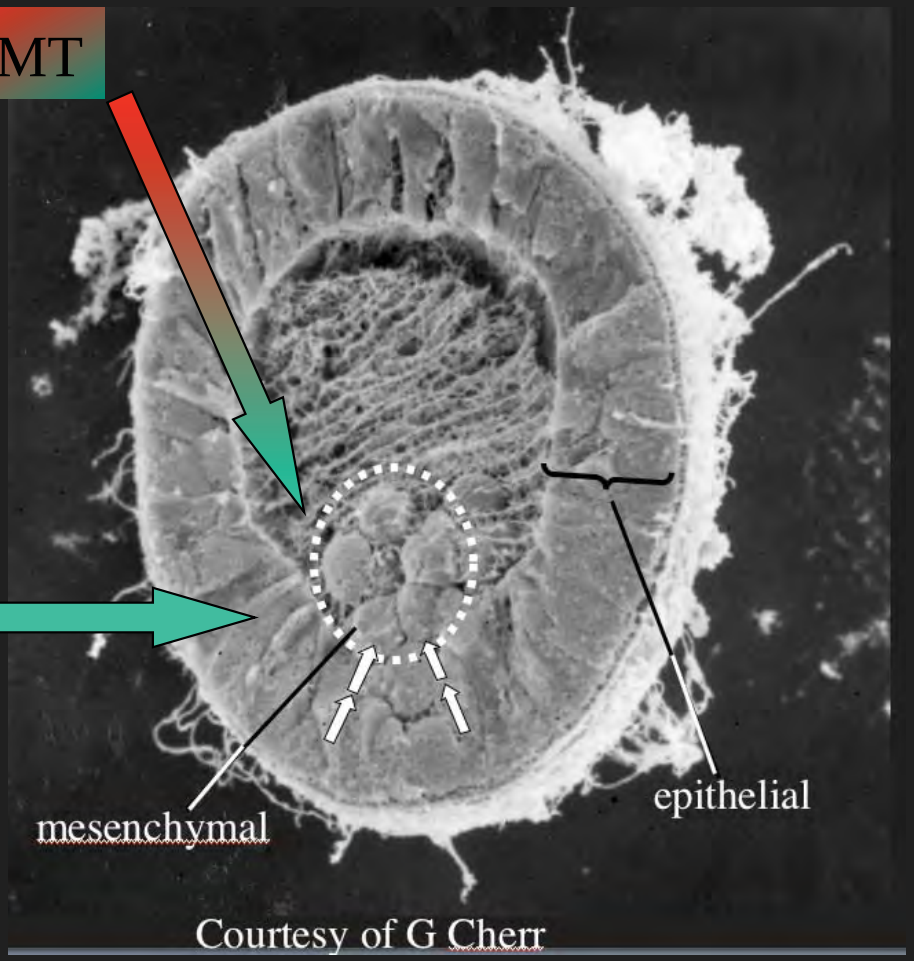
Cobblestone	Elongated
Non-motile	Motile
Non-invasive	Invasive
Polarised	Non-polarised
Epithelial markers	Mesenchymal markers
• E-cadherin	• N-cadherin
• Desmoplakin	• Vimentin
• Keratin	• Fibronectin

epithelial → mesenchymal

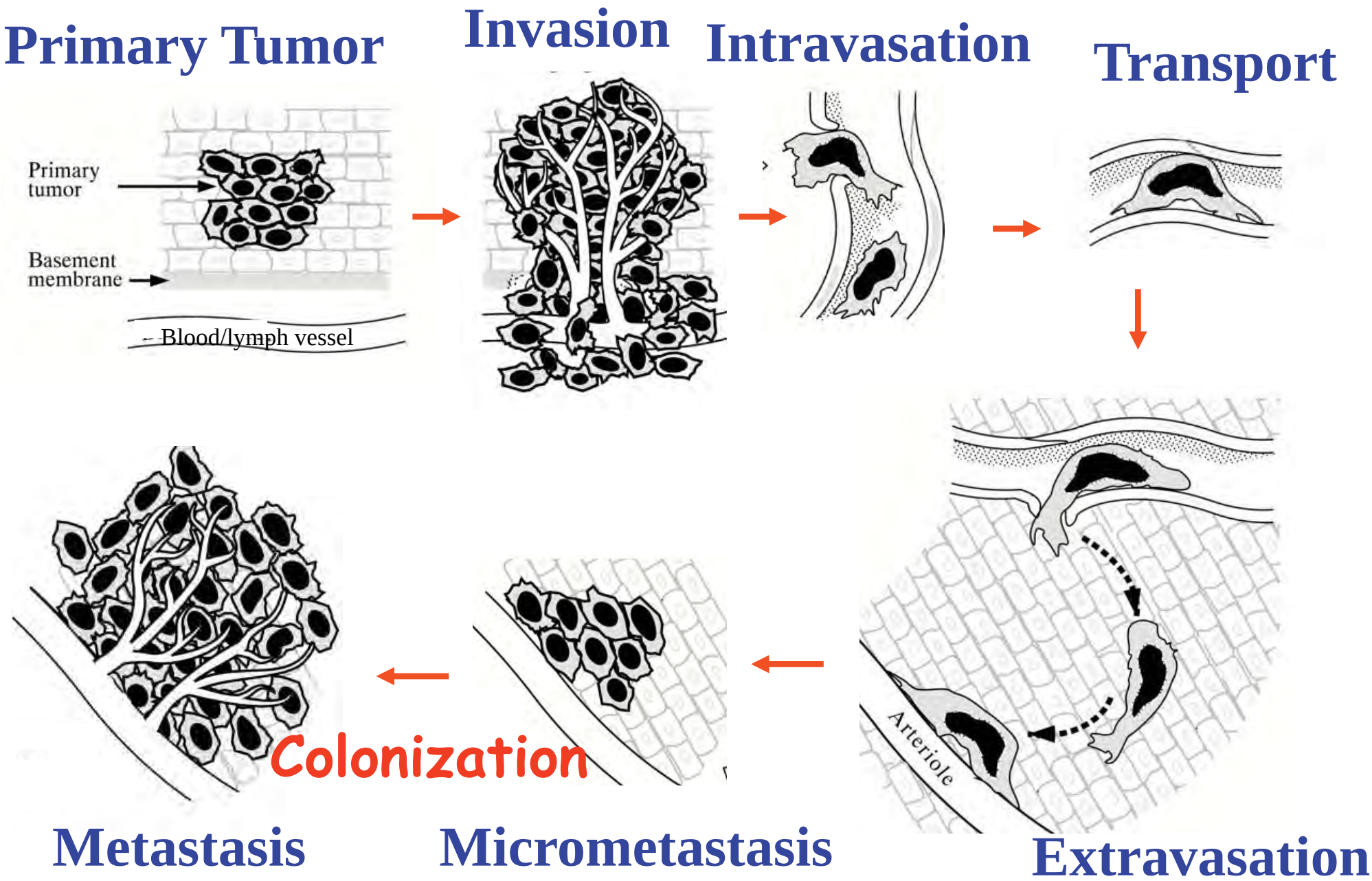
EMT

Model: Cancer cells appropriate early embryogenic programs in order to acquire traits of high-grade malignancy

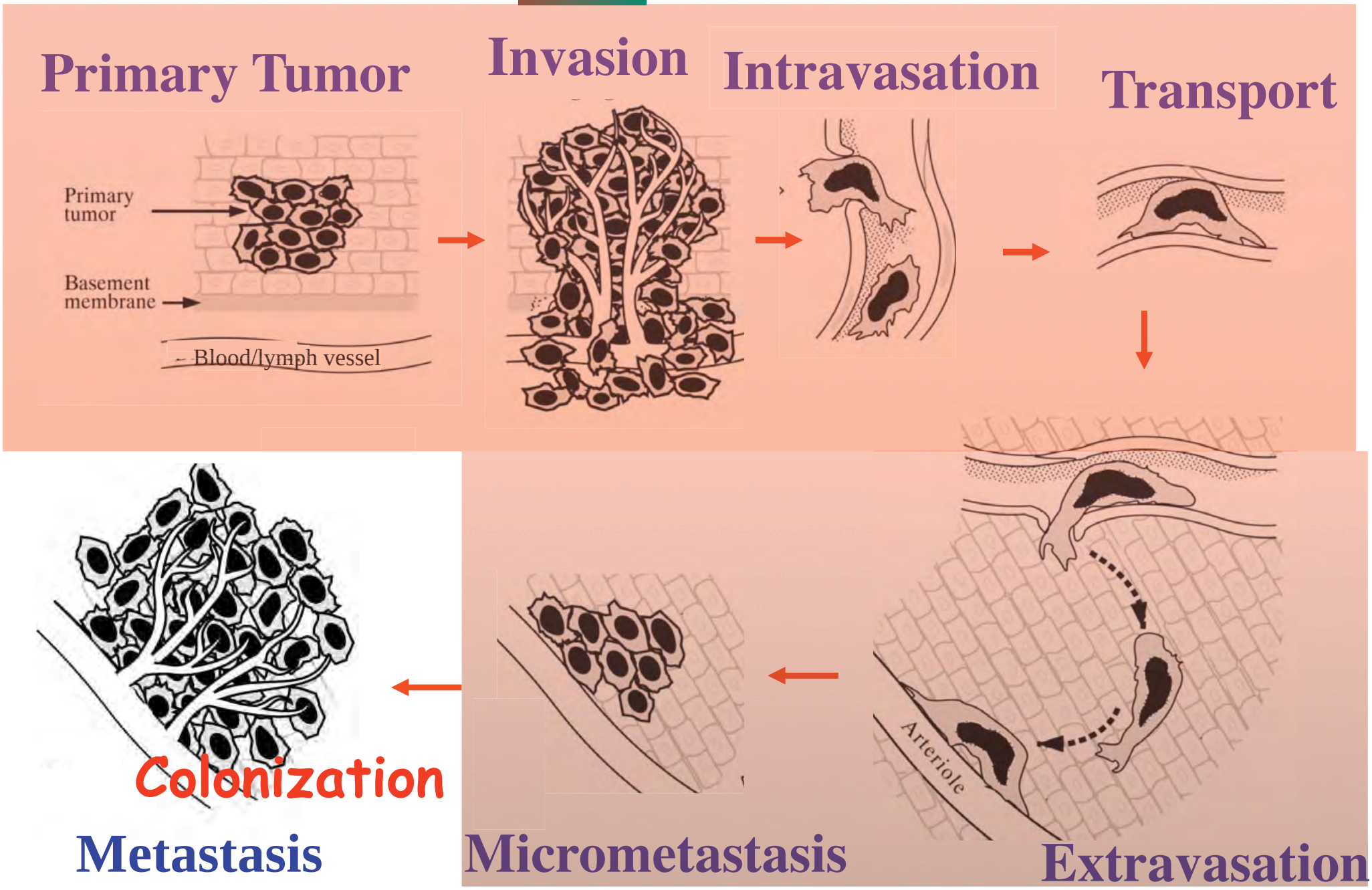




How many steps of the invasion-metastasis cascade can the EMT Twist program enable?

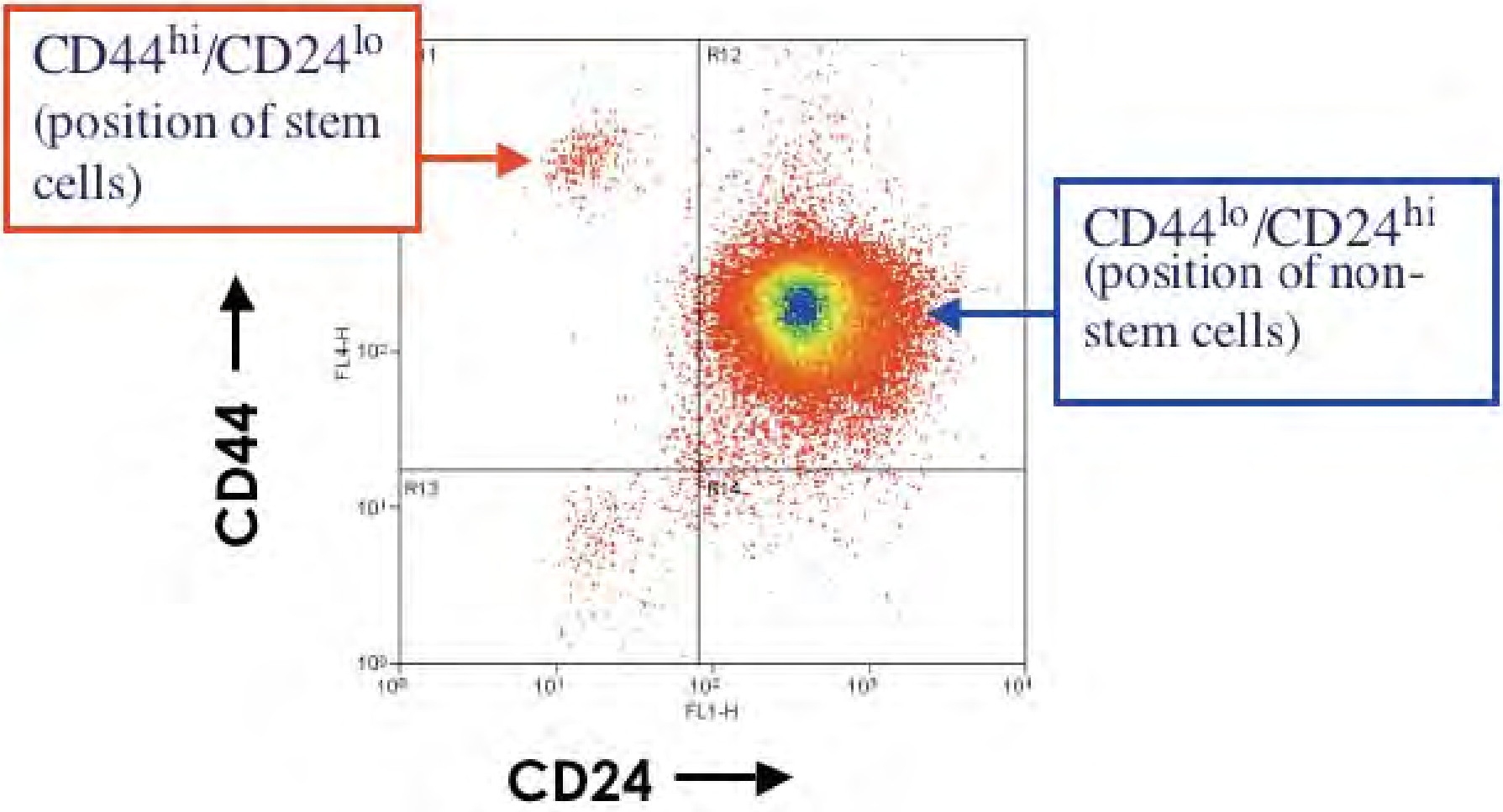


How many steps of the invasion-metastasis cascade can the EMT program enable?



What connection, if any, is there between the EMT on one side and stem cells (including CSCs) on the other?

Immortalized human MECs



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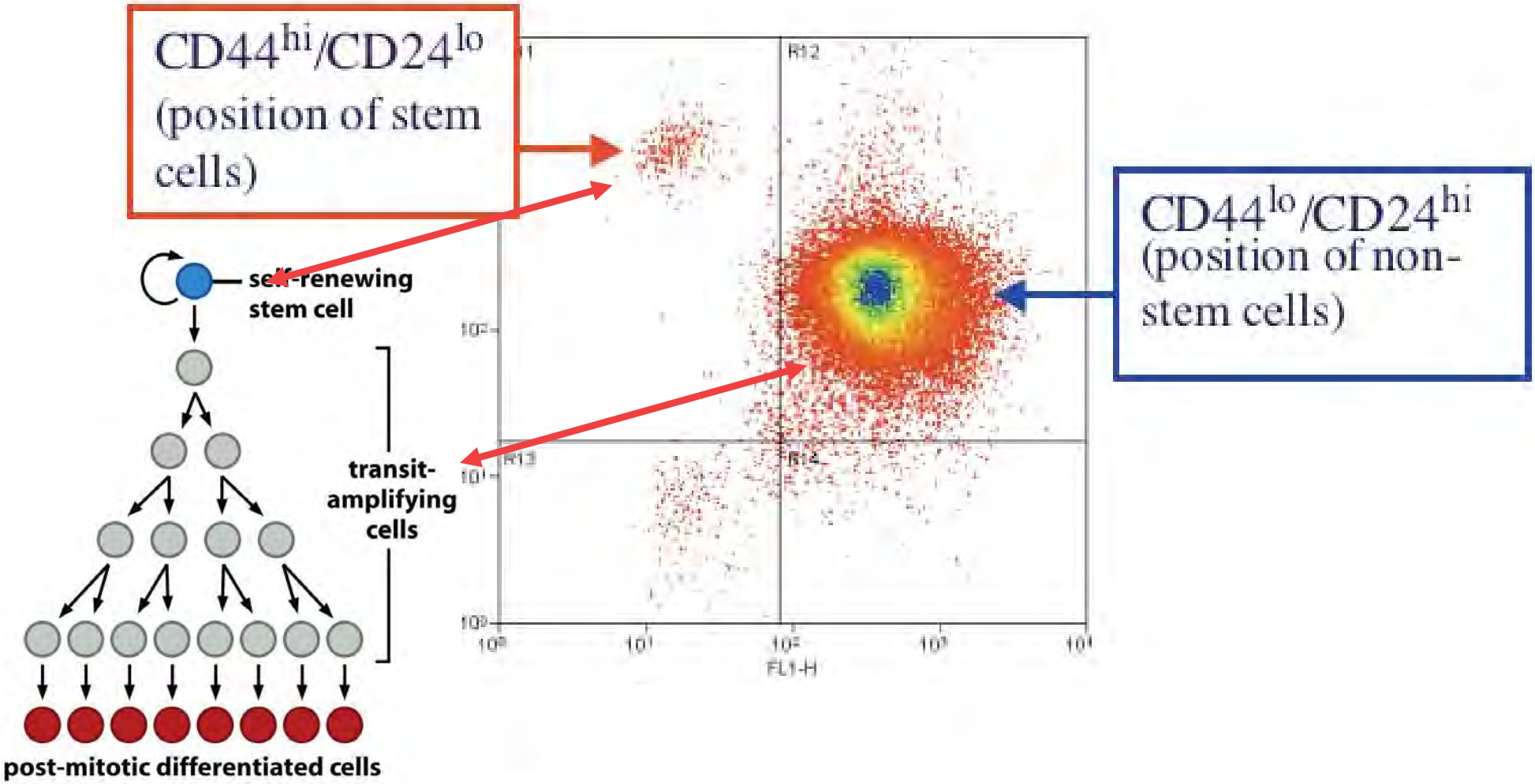
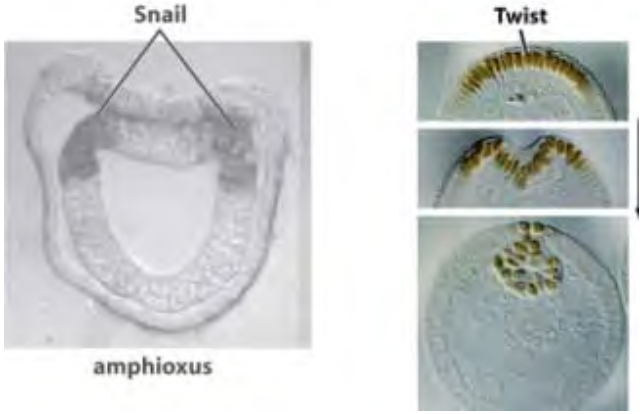
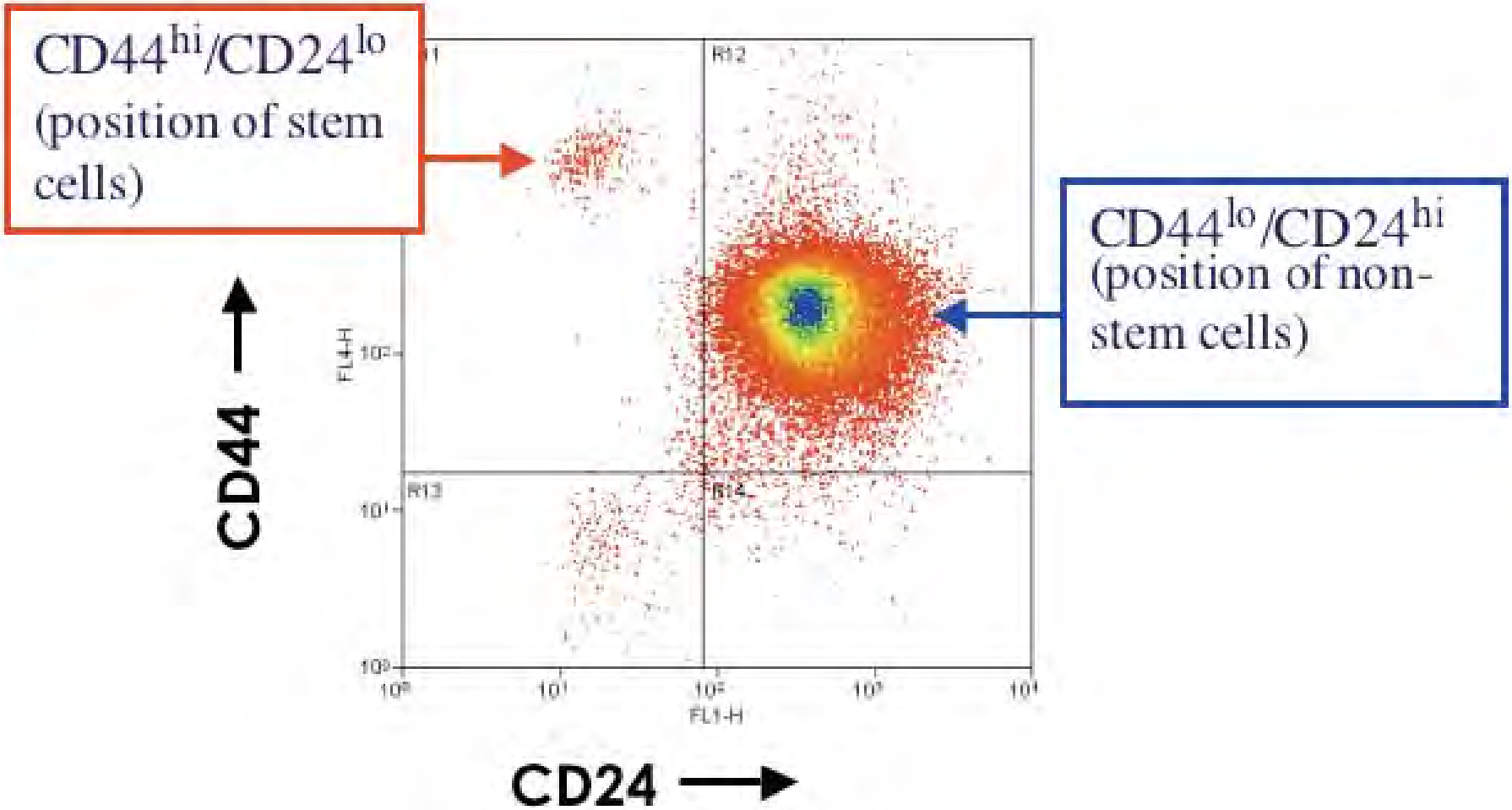
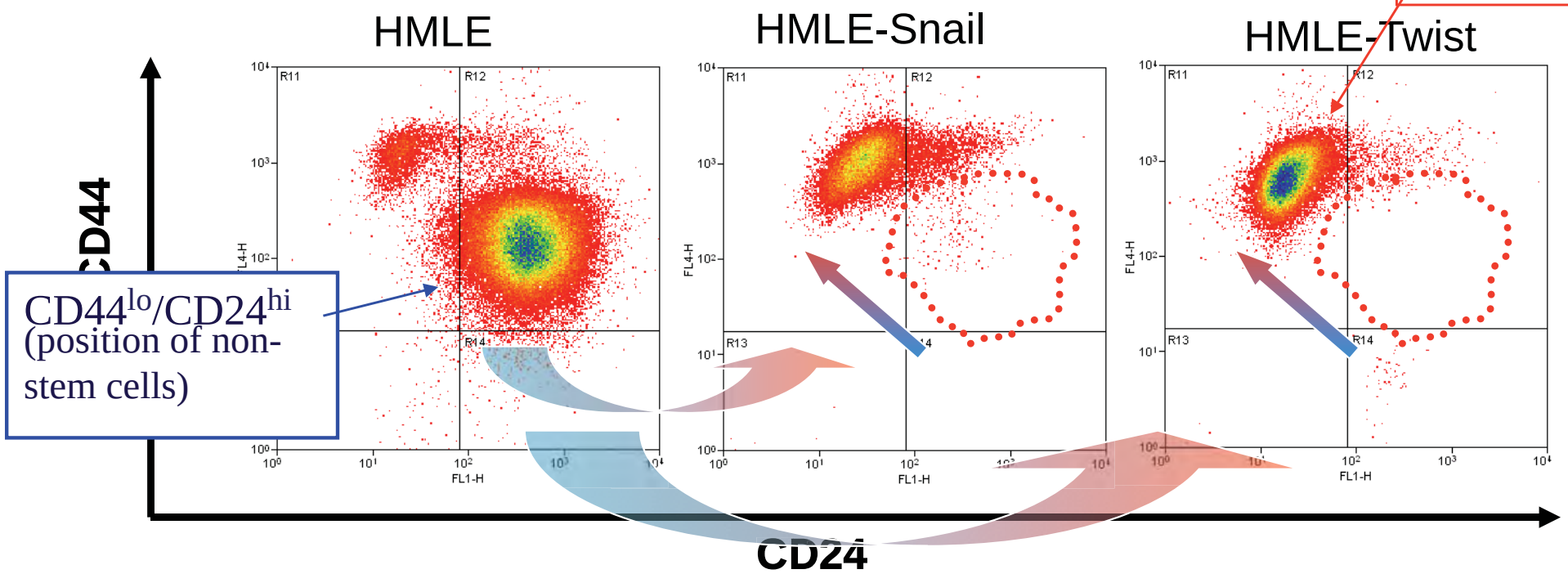



Snail
amphioxus
Twist

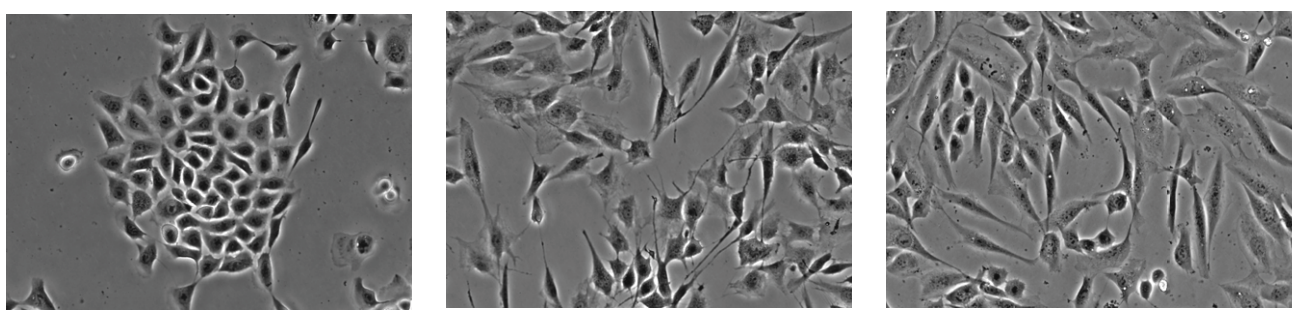

CD44hi/CD24lo
(position of stem cells)
CD44lo/CD24hi
(position of non-stem cells)
CD44
CD24
R12
R13
R14
FL4-H
FL1-H

Induction of EMT by Snail and Twist EMT-inducing TFs also generates CD44^{hi} CD24^{lo} cells

CD44^{hi}/CD24^{lo} (position of stem cells)



Vector **Snail** **Twist**

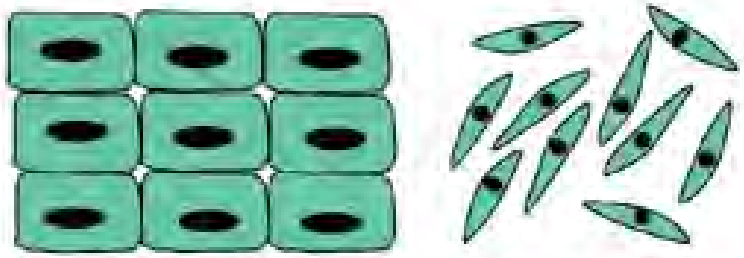


epithelial → mesenchymal

S.A.Mani & W. Guo

The epithelial-mesenchymal transition (EMT) is a complex, multi-faceted program involving multiple changes in cell properties.

epithelial → mesenchymal



Cobblestone	Elongated
Non-motile	Motile
Non-invasive	Invasive
Polarised	Non-polarised
Epithelial markers	Mesenchymal markers
• E-cadherin	• N-cadherin
• Desmoplakin	• Vimentin
• Keratin	• Fibronectin

non-stem cell stem cell

epithelial → mesenchymal

EMT

EMT and cancer progression

1. Normal cells induced to undergo an EMT acquire stem-cell properties.

a. $CD44^{hi}CD24^{lo}$ antigenic phenotype

b. Ability to form mammospheres indefinitely

2. Same outcome with cancer cells

3. Epithelial cells in culture that are naturally $CD44^{hi}CD24^{lo}$ show mesenchymal morphology; same is true of cells from reduction mammoplasty

4. Transient exposure to Snail or Twist causes descendants of exposed cells to form mammospheres indefinitely (as gauged by serial passage).

Hence, induction of an EMT allows cancer cells

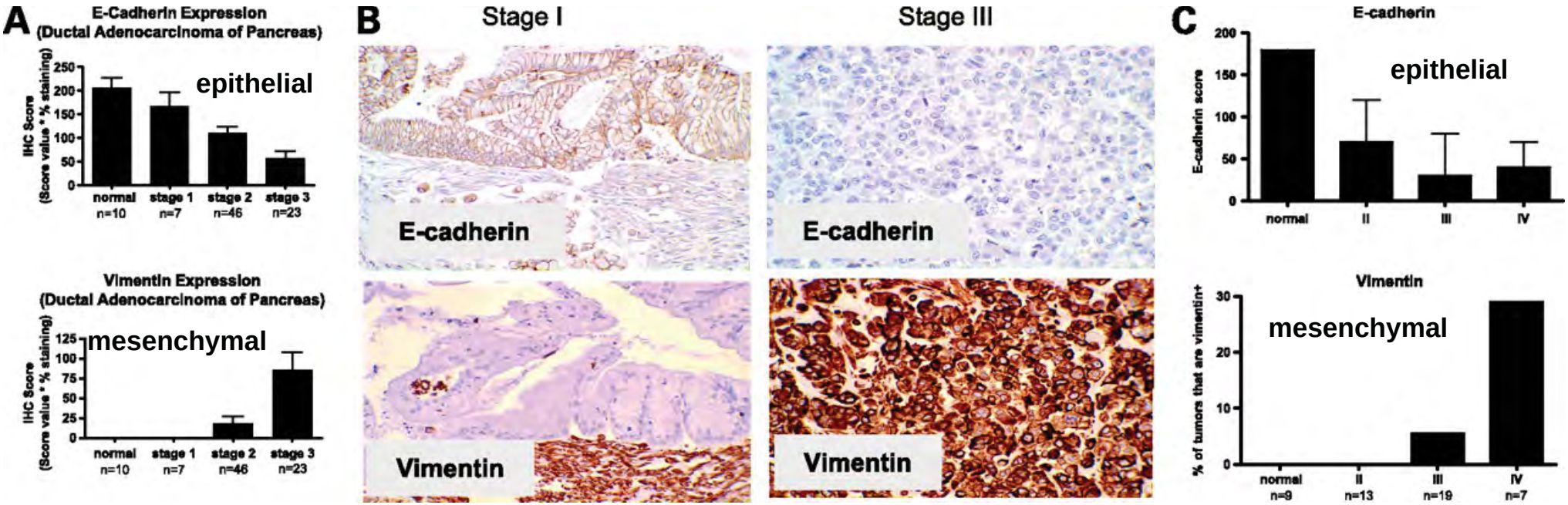
a. To disseminate

b. To become self-renewing

This means that the EMT program holds at least two dangers for the cancer patient.

More aggressive carcinomas are often more mesenchymal i.e., contain cancer cells that have undergone an EMT

pancreatic **E** **M** **colorectal**



Buck, E. et al. Mol Cancer Ther 2007;6:532-541

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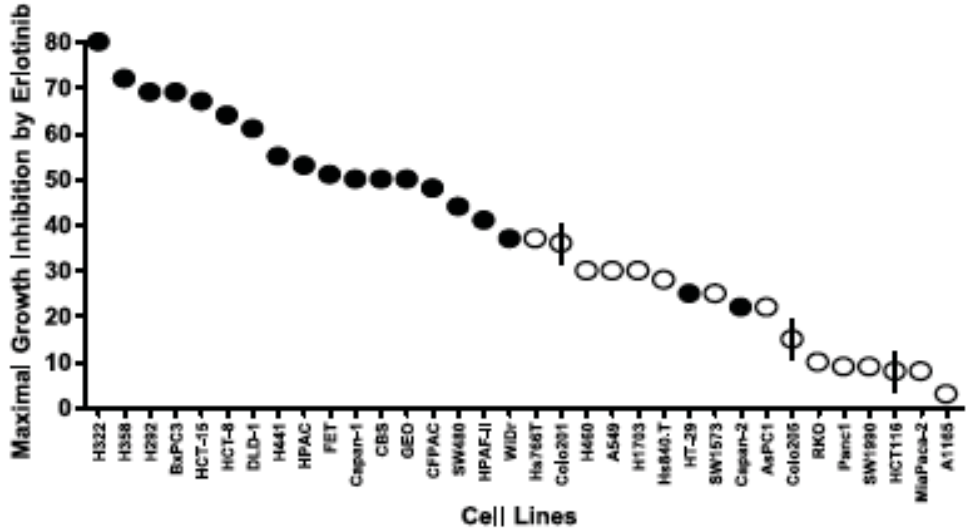
EMT & drug killing

Human (pancreatic, NSCLC, CRC)

hi E-cadherin

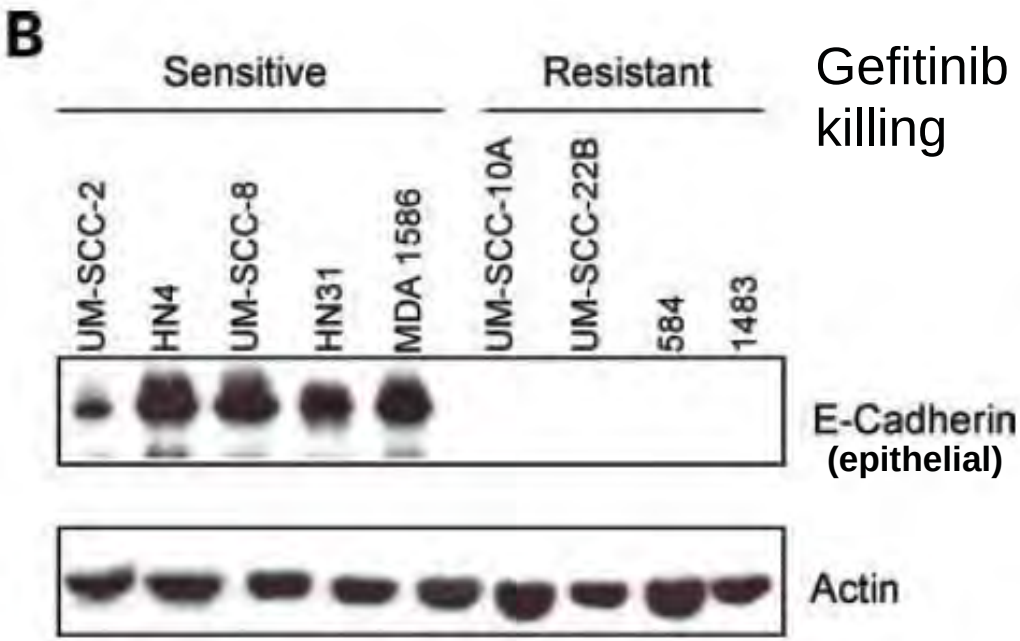
low E-cadherin

erlotinib killing



E. Buck et al. 2007, *Mol. Cancer Therap.*

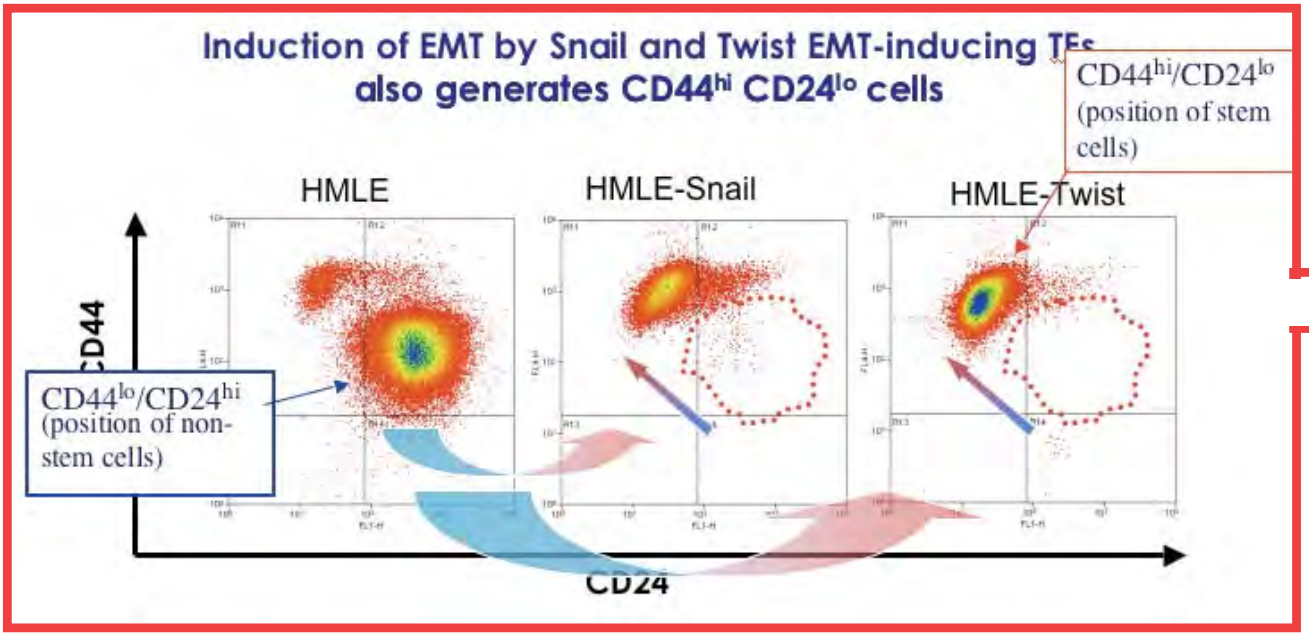
Human HNSCC



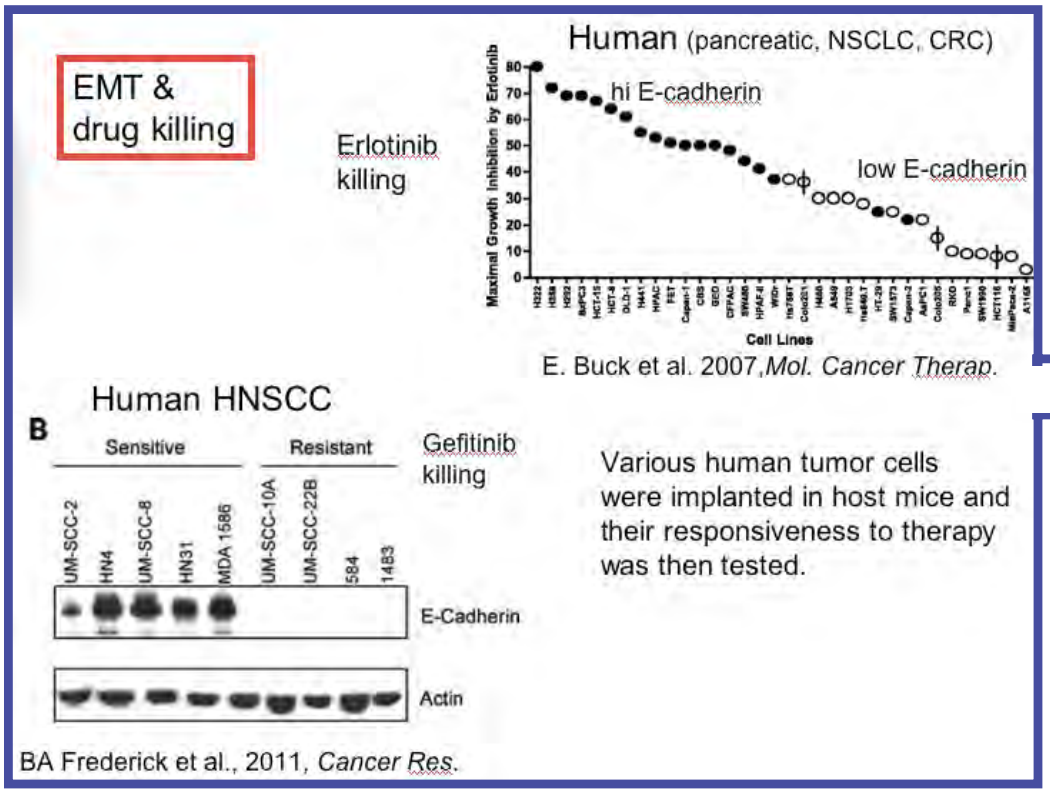
Gefitinib killing

Various human tumor cells were implanted in host mice and their responsiveness to therapy was then tested.

BA Frederick et al., 2011, *Cancer Res*.



EMT→ SCs
& EMT→ mesenchymal cells
∴ SCs≈mesenchymal cells

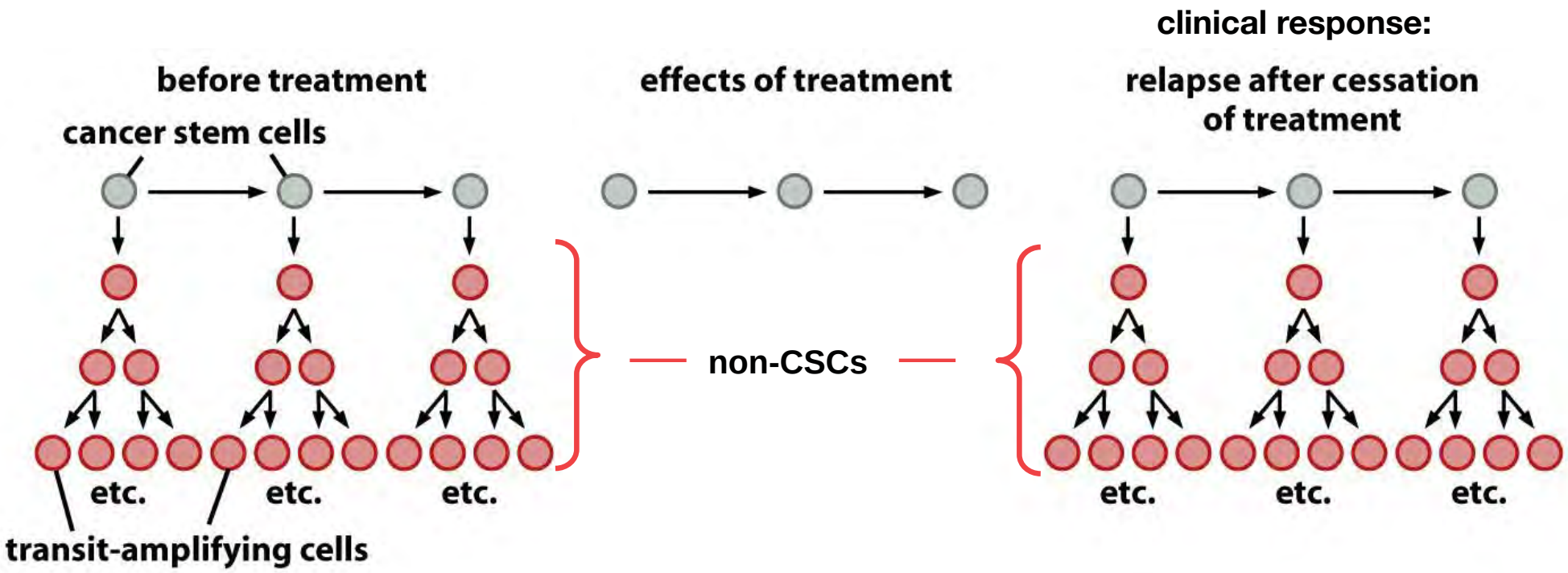


Therapy kills epithelial cells
(preferentially)
Epithelial cells ≠ SCs

∴ Therapy kills non-SCs

Most currently used chemotherapeutics kill non-CSCs preferentially.

Putative effects of eliminating the non-CSCs therapeutically

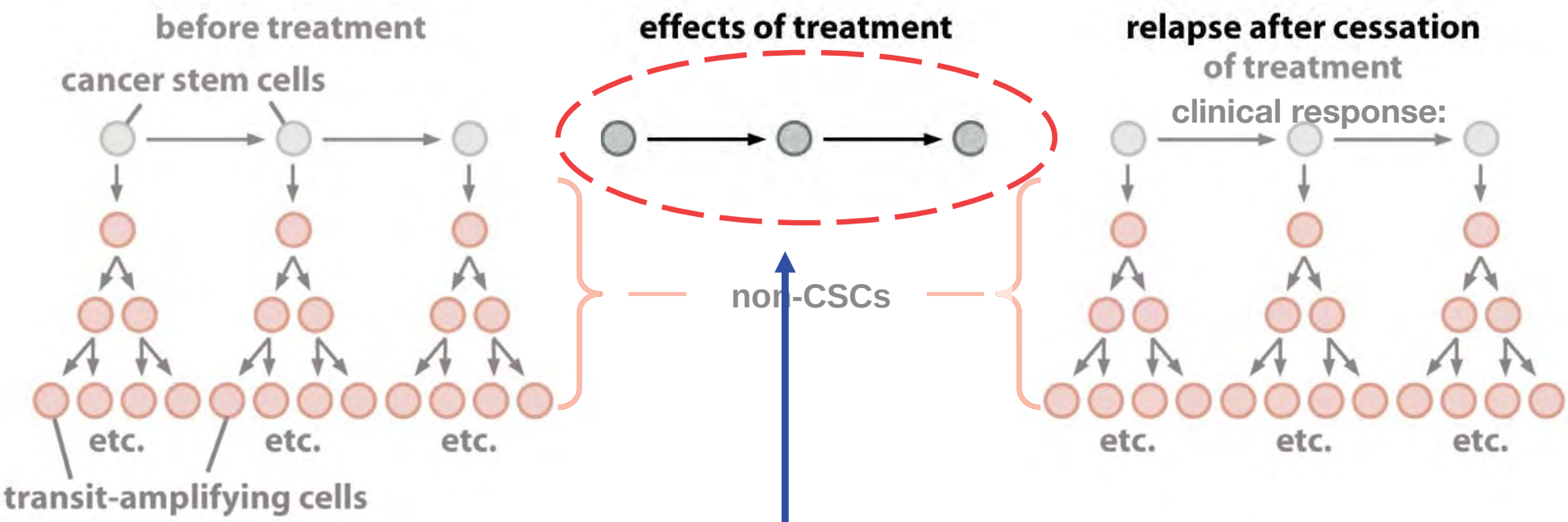


CSC = cancer stem cell

Figure 16.30 *The Biology of Cancer* (© Garland Science 2007)

Most currently used chemotherapeutics kill non-CSCs preferentially.

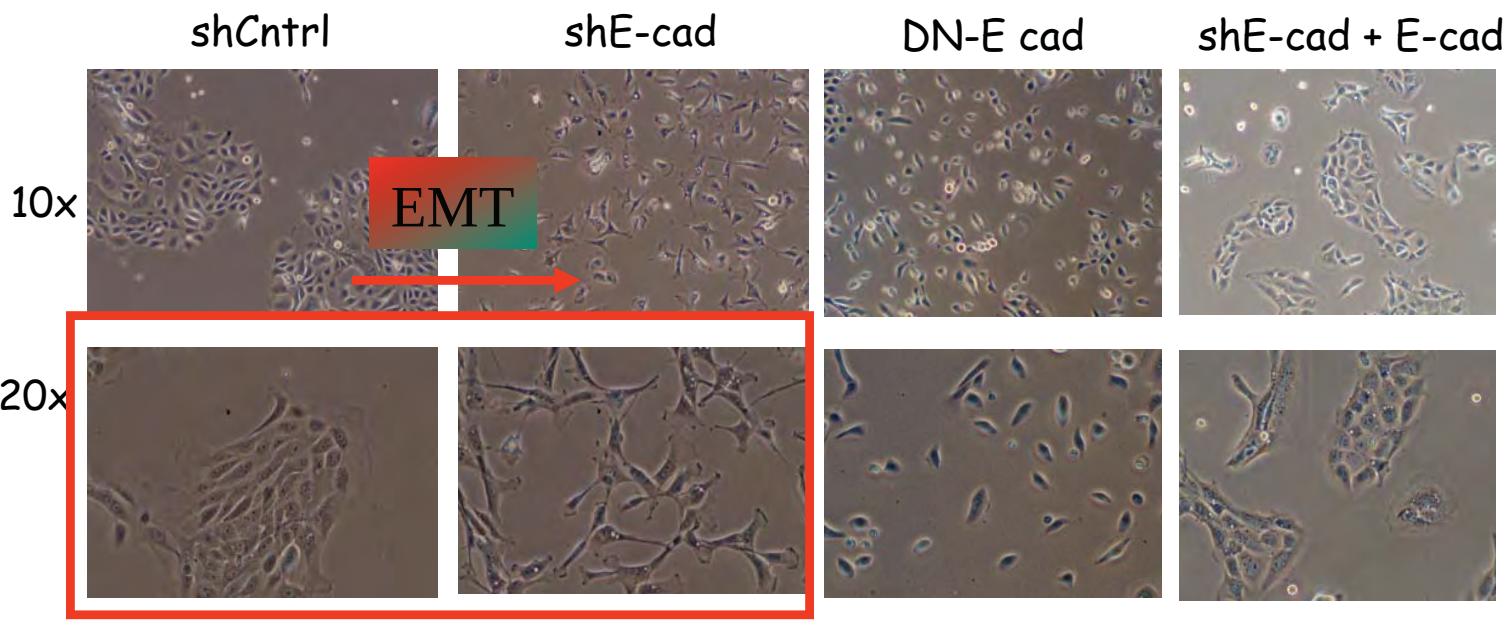
CSC = cancer stem cell

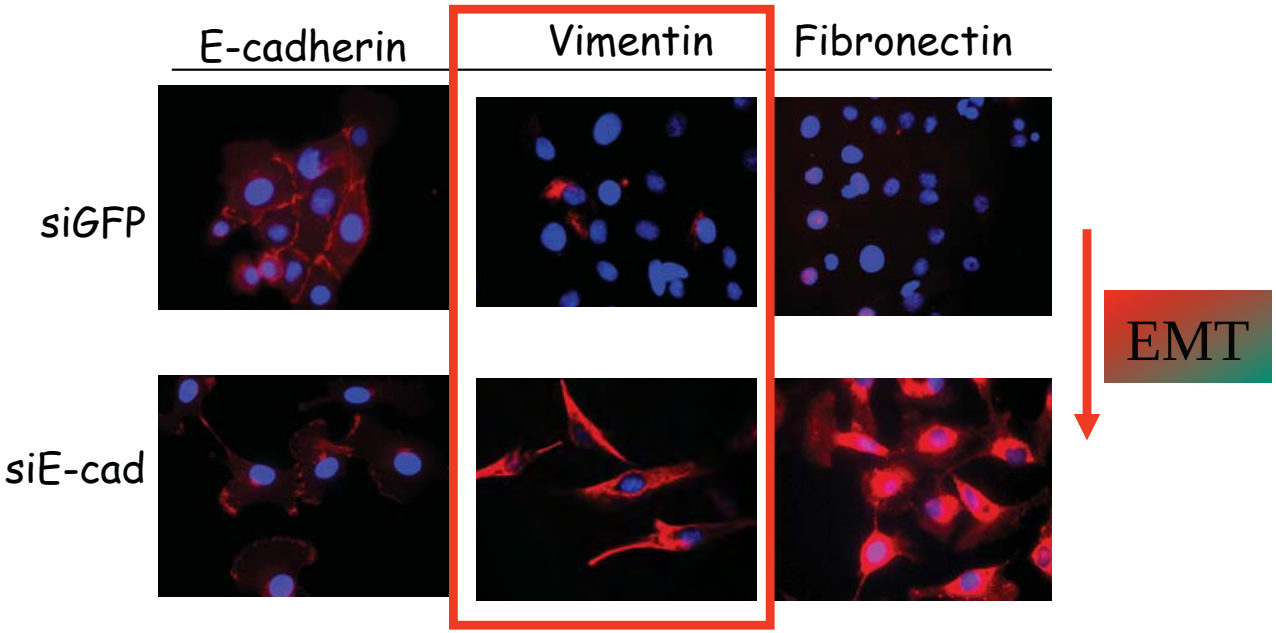


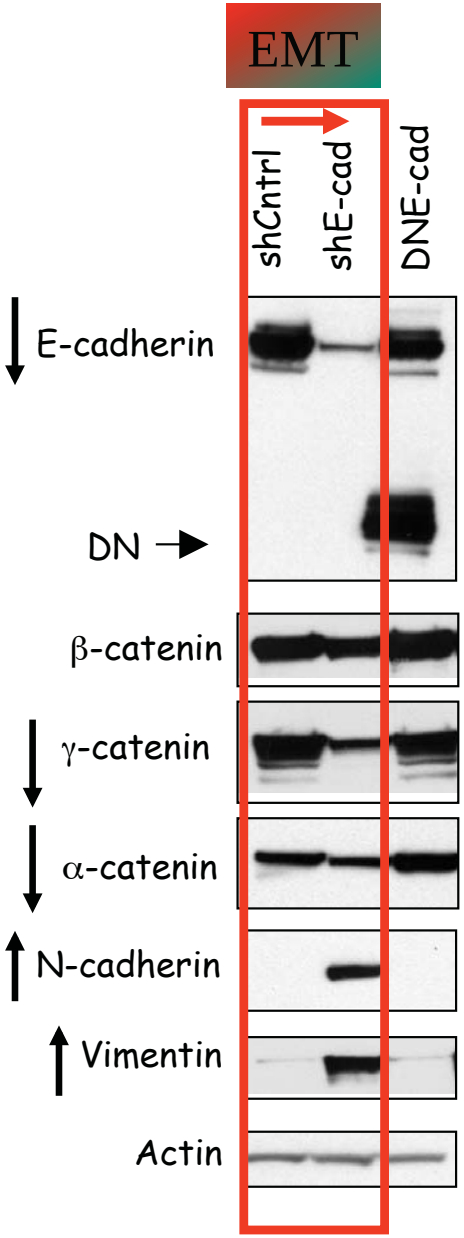
Can we develop agents that preferentially kill the CSCs?

Figure 16.30 *The Biology of Cancer* (© Garland Science 2007)

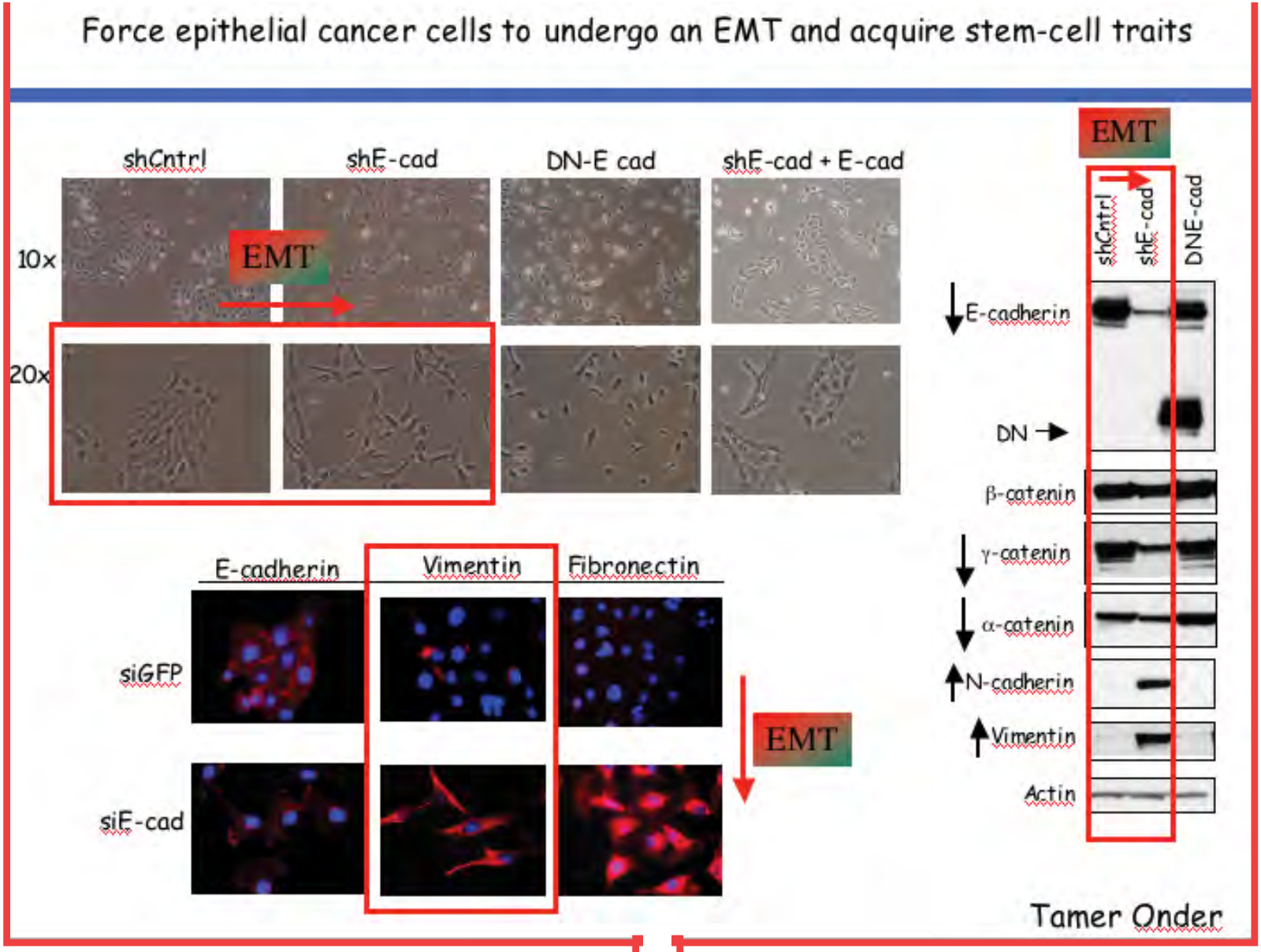
Force epithelial cancer cells to undergo an EMT and acquire stem-cell traits







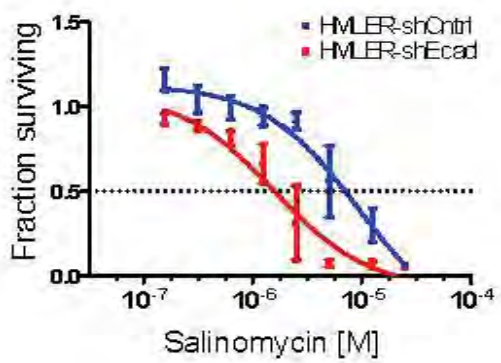
Tamer Onder

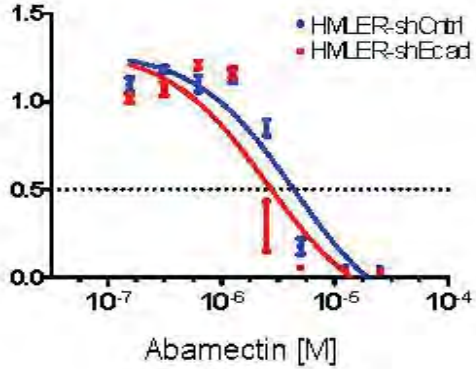


Use the EMT to generate essentially unlimited numbers of CSCs

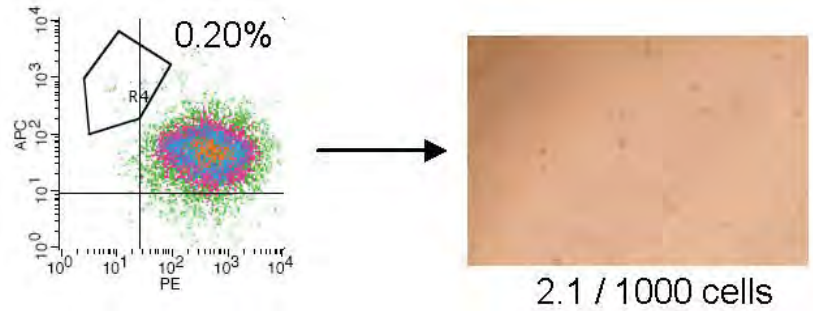
HTS: Screen 16000 compounds
Salinomycin selectively kills cancer stem cells

CSC-targeted agents

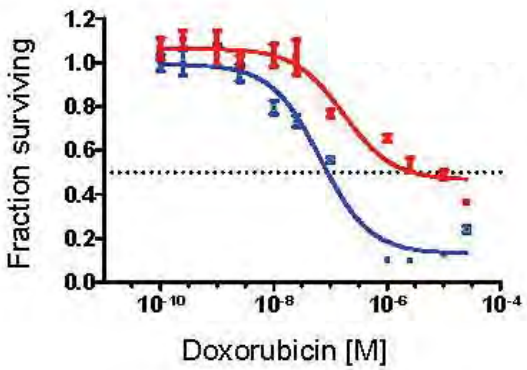


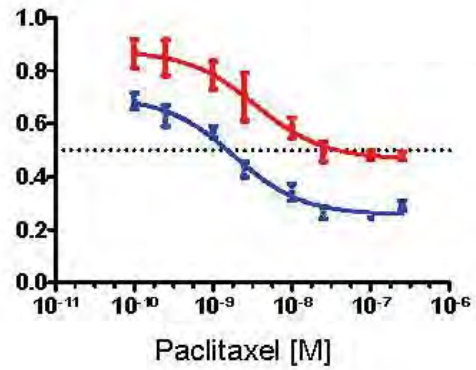


Salinomycin (1uM)

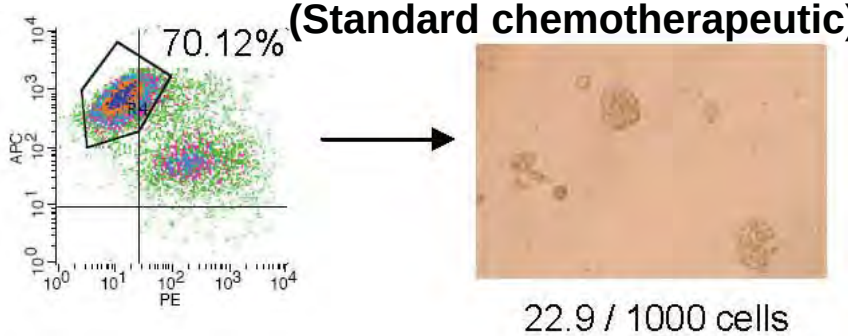


Conventional chemotherapeutics





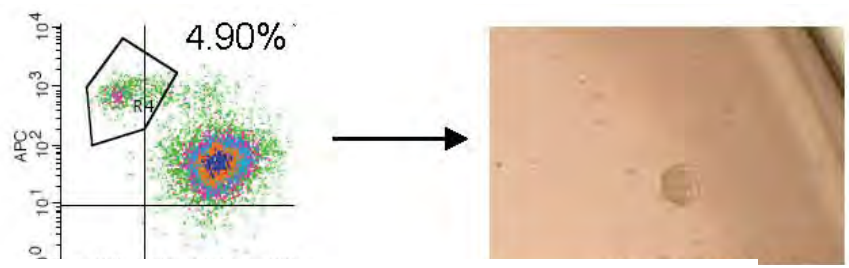
Paclitaxel (2.5nM)
(Standard chemotherapeutic)



CSCs

Non-CSCs

Vehicle control

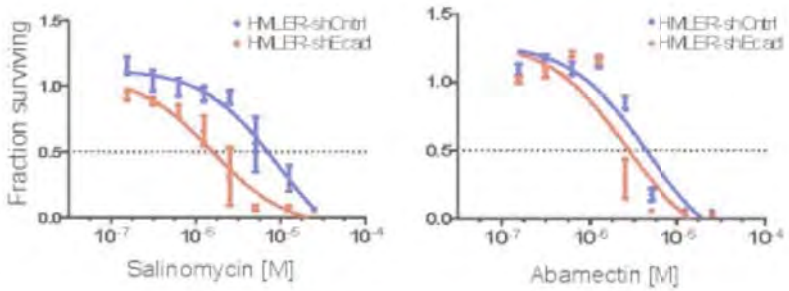


P. Gupta (Lander) & T. Onder

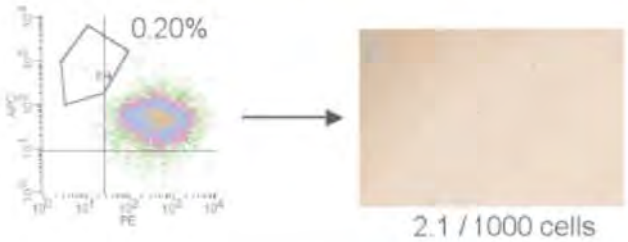
But is this the answer to cancer??

HTS: Screen 15000 compounds
Salinomycin selectively kills cancer stem cells

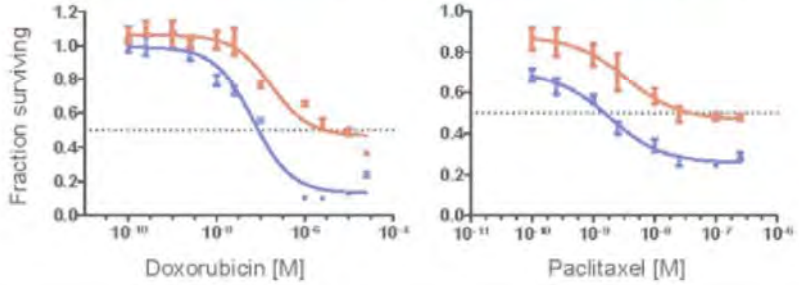
CSC-targeted agents



Salinomycin (1uM)



Conventional chemotherapeutics



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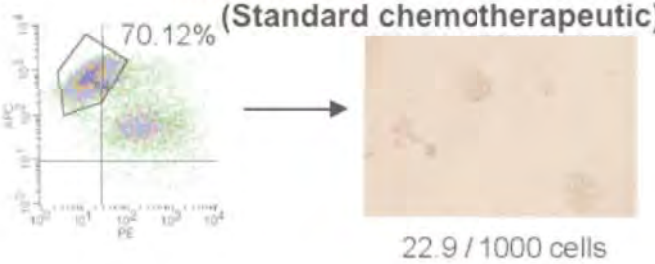
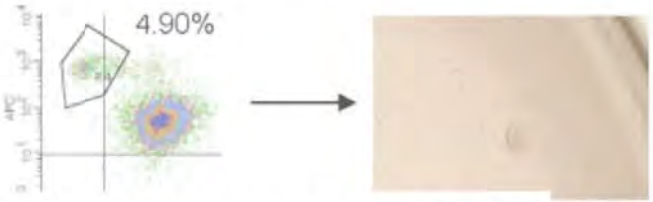


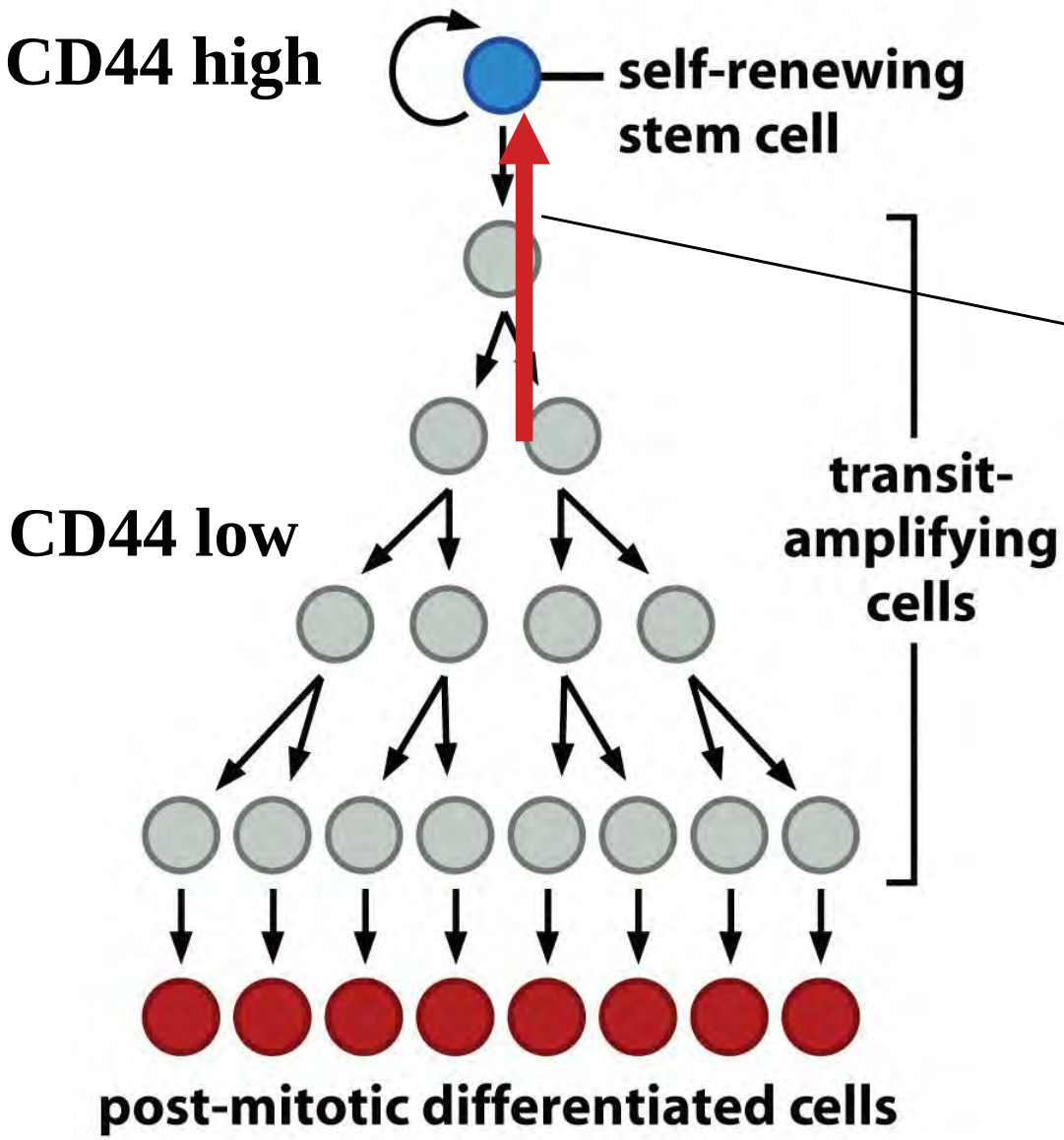
CSCs

Non-CSCs

Vehicle control



P. Gupta (Lander) & T. Onder

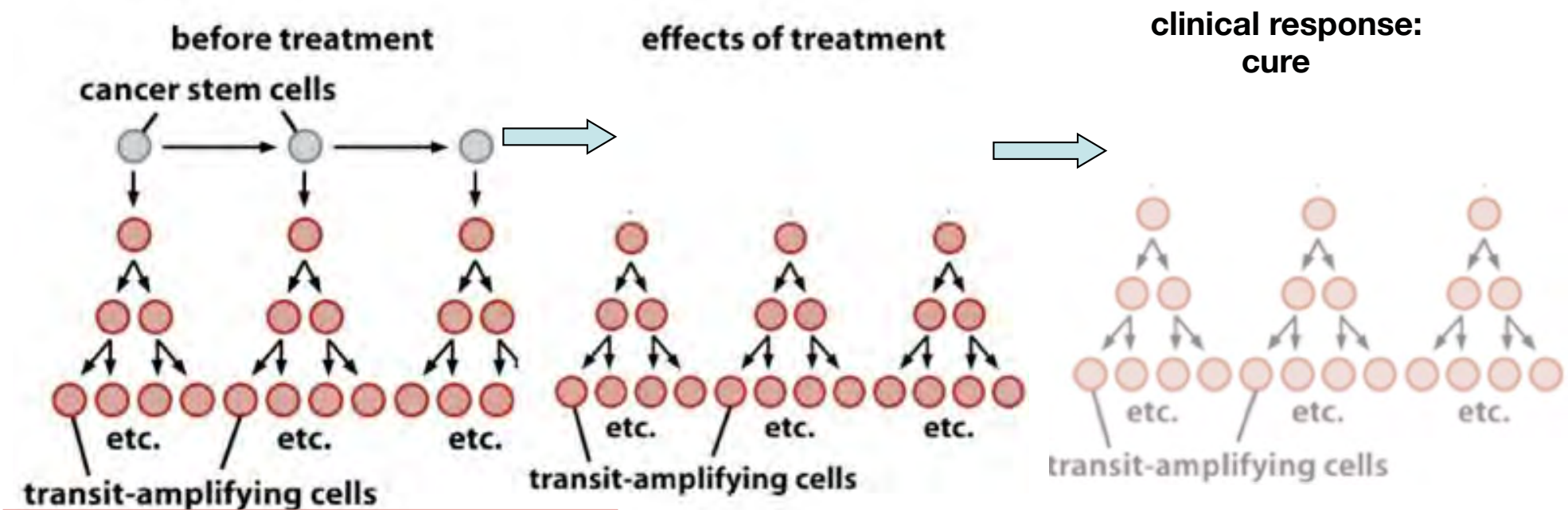


2. The CD44^{low} fraction gives rise to CD44^{high} cells

May need to add new arrow!!

This suggests that populations of more differentiated epithelial cells can spontaneously de-differentiate into stem-cell-like cells.

This is the desired response to an anti-CSC treatment:



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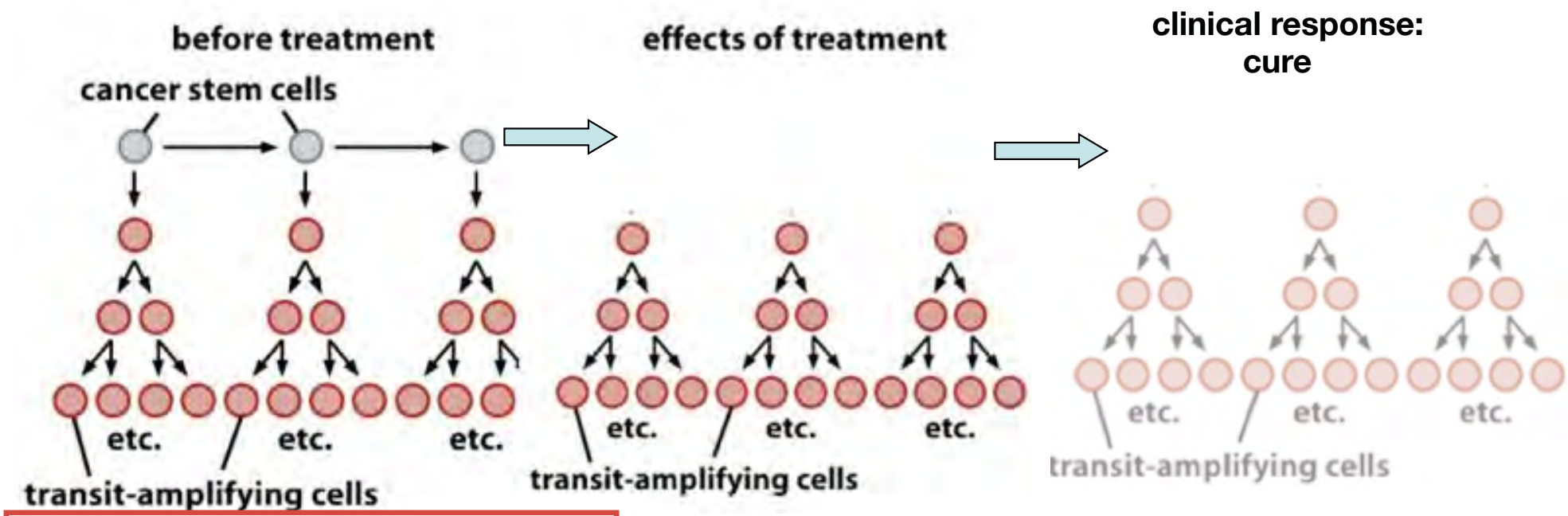
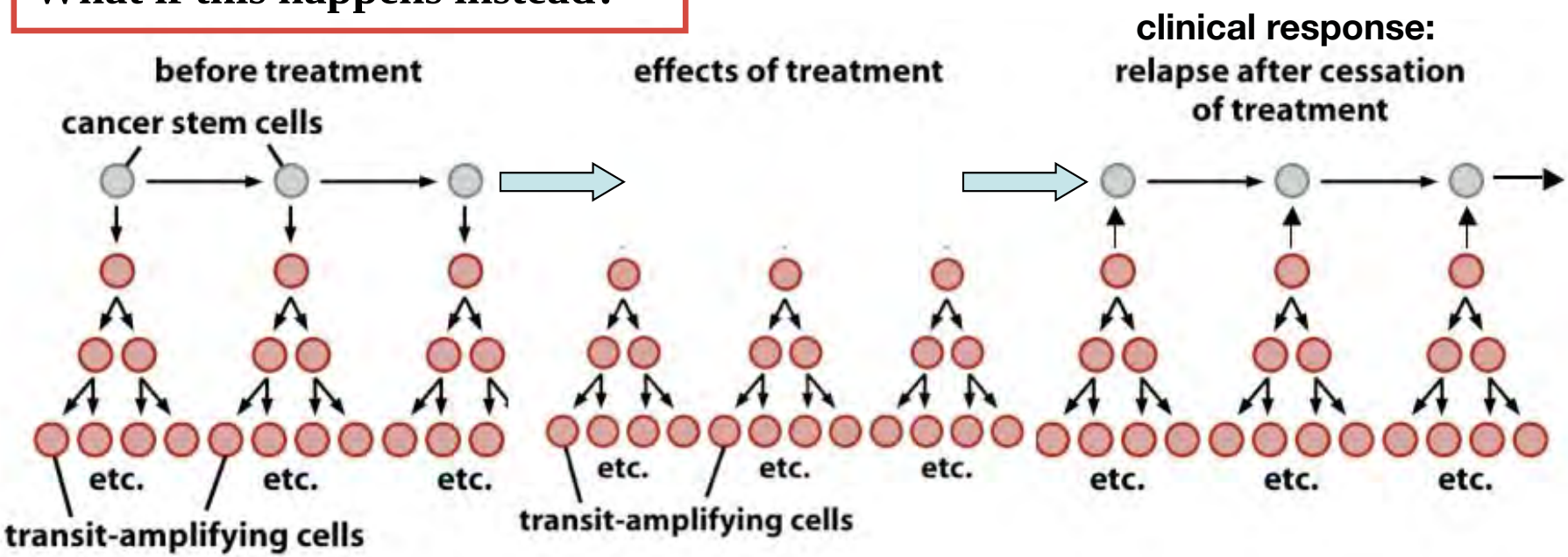
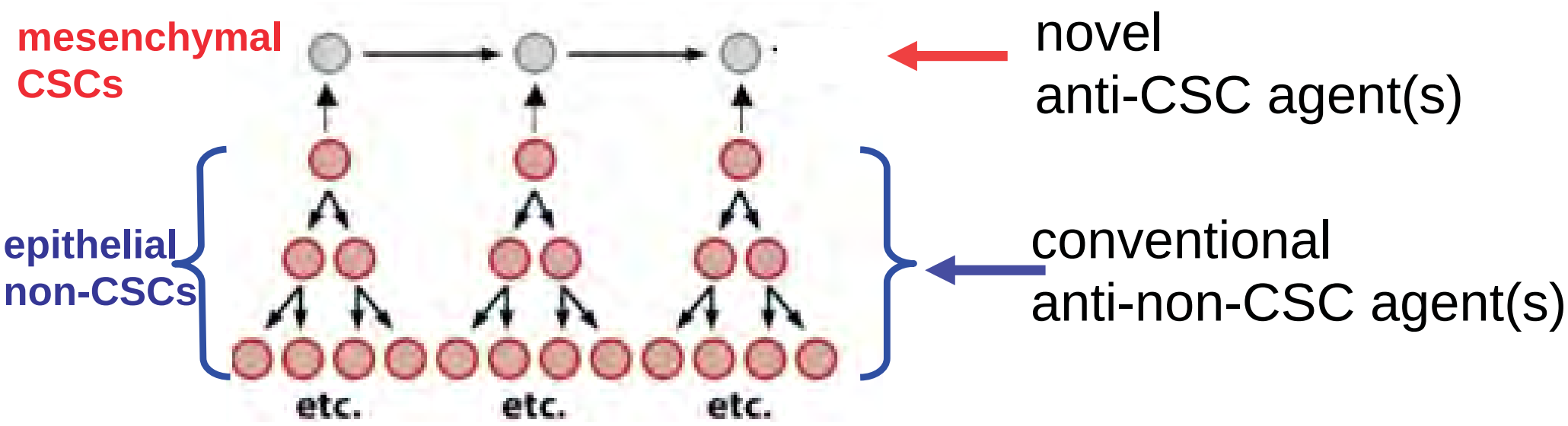


What if this happens instead?



Our conclusion:
Durable clinical responses in solid tumors will require targeting <u>both</u> populations of cells: