The HUMAN BREAST L#4
and
NEOPLASTIC PROGRESSION

Robert D. Cardiff, MD, PhD.

Welcome Trust Delta Project

January 12, 2022

WHAT IS NEOPLASTIC PROGRESSION

- **Historical Background:** Empirical evidence has always suggested a neoplastic progression from relatively benign to invasive to metastatic disease.

  1. What initiates neoplasia? (INITIATION)

  2. How does it progress? (PROMOTION)

  3. How does it spread? (METASTASIS)

A Review in Time: The History of Breast Cancer

1960s: Jensen discovers ER receptors and develops ligand binding assays

1978:Bill Mcguire identifies the role of ER and PR markers in BC treatment

1970s: Doxorubicin & Cyclophosphamide approved in the metastatic and adjuvant settings

1977: Swedish trials to investigate screening begin

1947: Haagensen declares DCIS is cancer but LCIS is not

1951: First cancer treatment with Cobalt-60 radiation took place

CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION

CEBP Focus

The Evolution of Our Understanding of the Biology of Cancer Is the Key to Avoiding Overdiagnosis and Overtreatment

Kelly Hewitt, Jennifer Son, Alexa Glencer, Alexander D. Borowsky, Matthew R. Cooperberg, and Laura J. Esserman

DOI: 10.1158/1055-9965.EPI-20-0110 Published December 2020 Check for updates

linear accelerator used for radiation treatment

1990s: Ontario Group HF 1998: START A & B Trials 1998: IORT Trials begin

equivalent for OS, mastectomy rates for hormone + Stage 1 cancers

partial breast radiation found to be equally effective as whole breast radiation

studies show larger doses of radiation for short period is as effective as smaller doses for a long period

that hyper-fractionated, lower doses of radiation are better with regards to long term side effects

1890–1970 | **1970–1985** | **1985–2005** | **2005–2015**

1882: Halstead radical mastectomy preformed

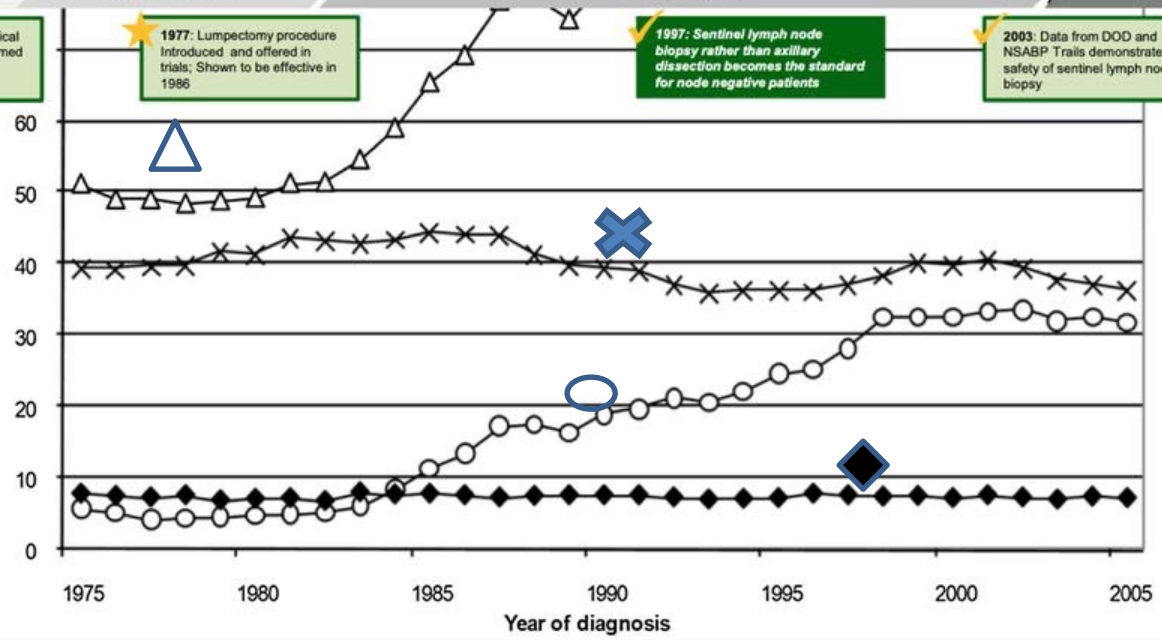
1977: Lumpectomy procedure Introduced and offered in trials; Shown to be effective in 1986

1997: Sentinel lymph node biopsy rather than axillary dissection becomes the standard for node negative patients

2003: Data from DOD and NSABP Trails demonstrate safety of sentinel lymph node biopsy

2009 : Sentinel lymph node biopsy considered safe for node positive patients

2014: Total skin sparing mastectomy shown to be safe follow-up data



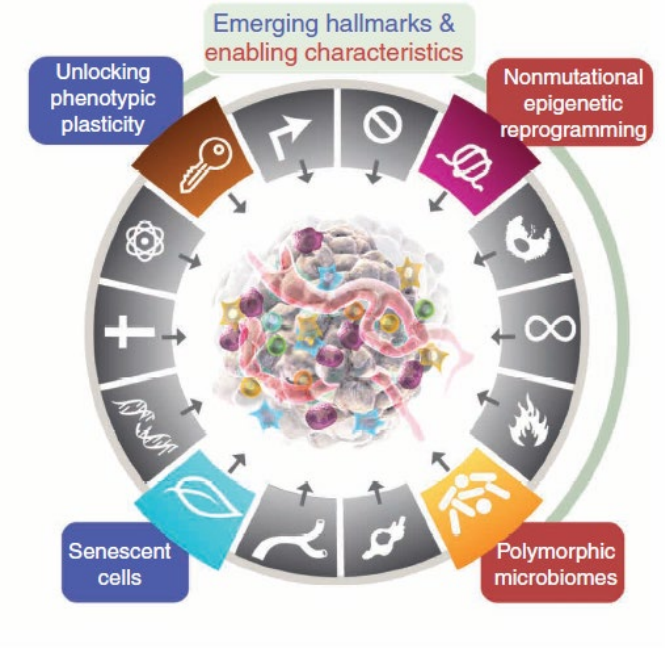
KEY

Darkened boxes highlight events that shifted th focus to less invasive treatments for low risk tumors

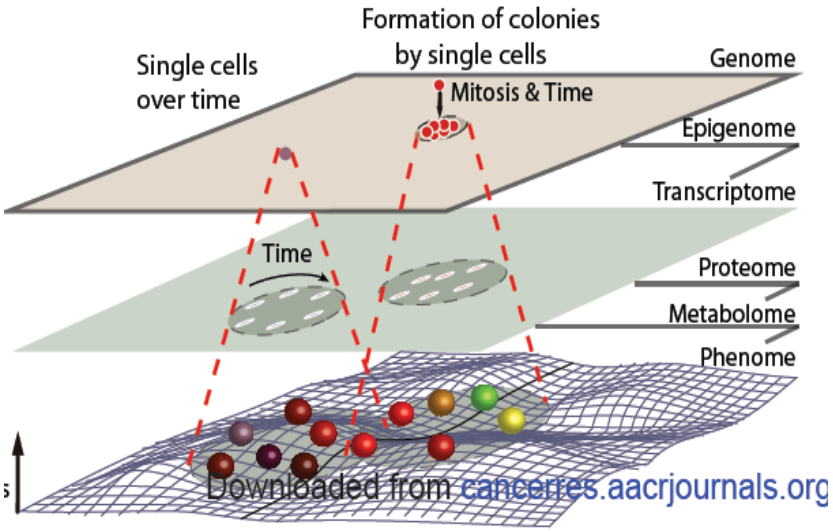
- Surgical advances
- Radiation oncology advances
- Medical oncology advances
- Prevention advances
- Hormone therapy advances
- Screening advances
- Molecular biology advances
- DCIS and low risk studies/
- Reclassifications initial discovery/trial initiated
- Confirmation of effectiveness/ safety

Localized rate
Regional rate
In situ rate
Distant rate

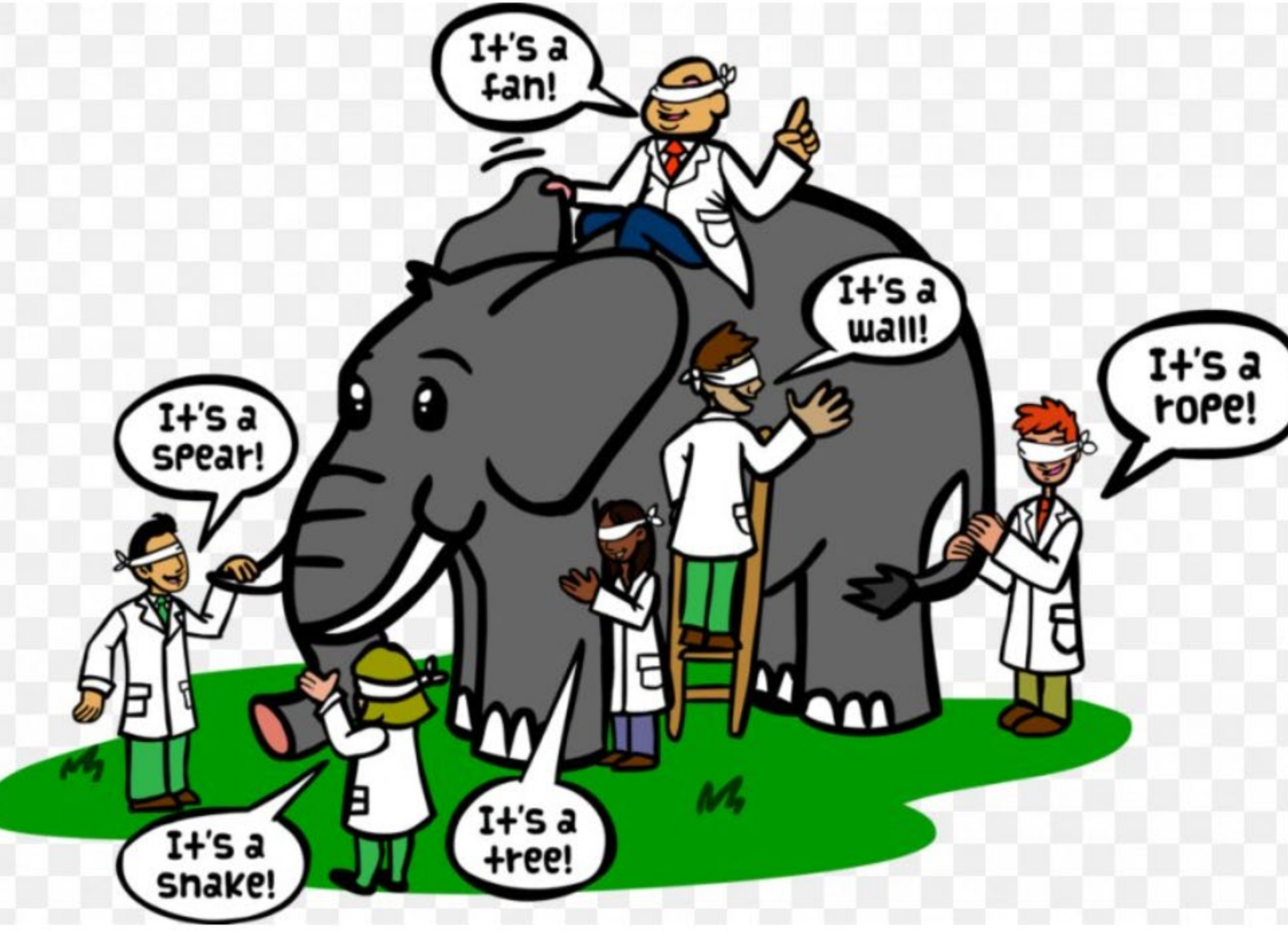
NEOPLASTIC PROGRESSION



Epigenetic Reprogramming



Evolutionary Selection:
eG-P Cone


It's a fan!
It's a wall!
It's a rope!
It's a spear!
It's a snake!
It's a tree!

OPEN ACCESS

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Predicting Relapse in Patients With Triple Negative Breast Cancer (TNBC) Using a Deep-Learning Approach

*Guangyuan Yu[1,2†], Xuefei Li[2†‡], Ting-Fang He[3], Tina Gruosso[4,5], Dongmei Zuo[4], Margarita Souleimanova[4], Valentina Muñoz Ramos[4], Atilla Omeroglu[6], Sarkis Meterissian[5,7], **Marie-Christine Guiot**[6,8], Li Yang[1], Yuan Yuan[9], Morag Park[4,5,10*], Peter P. Lee[3*] and Herbert Levine[11,12*]*

[1] Department of Physics and Astronomy, Rice University, Houston, TX, United States, [2] Center for Theoretical Biological

Tumor-section images of 29 patients in an independent cohort were used to test the predictive power of our algorithm. In the test cohort, 6 (out of 29) patients who belong to the poor outcome group were all correctly identified by our algorithm; for the 23 (out of 29) patients who belong to the good-outcome group, 17 were correctly predicted with some evidence that improvement is possible if other measures**, such as the grade of tumors, are factored in.** Our approach **does not involve arbitrarily defined metrics** and can be applied to other types of cancer in which the **abundance/location of CD8C T lymphocytes/other types of cells is an indicator of prognosis**.

Front Physiol. 2020; 11: 511071.Published online 2020 Sep 23. doi: 10.3389/fphys.2020.511071
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RESEARCH ARTICLE

Sox11 regulates mammary tumour-initiating and metastatic capacity in *Brca1*-deficient mouse mammary tumour cells

Siu Man Tsang, Hyojin Kim, Erik Oliemuller, Richard Newman, Naa-Anyima Boateng, Naomi Guppy and Beatrice A. Howard*

ABSTRACT

Little is known about the role of Sox11 in the regulation of mammary progenitor cells. Sox11 is expressed by mammary bud epithelial cells during embryonic mammary gland development and is not detected in mammary epithelial cells after birth. As Sox11 is an oncofetal gene, we investigated the effects of reducing Sox11 levels in embryonic mammary progenitor cells and found that Sox11 regulates

(Zvelebil et al., 2013). We have recently shown that SOX11 confers features of multipotency, impairs differentiation processes and alters tropism of ER− breast cancer cells to metastatic sites (Oliemuller et al., 2020). Although a number of studies have shown that Sox11 is expressed in mammary stem cells during embryonic mouse mammary development, it is not known whether it has any functional role in regulating normal embryonic mammary progenitor cells (Chung et al., 2019; Makarem et al., 2013;

Contents lists available at ScienceDirect

Seminars in Cancer Biology

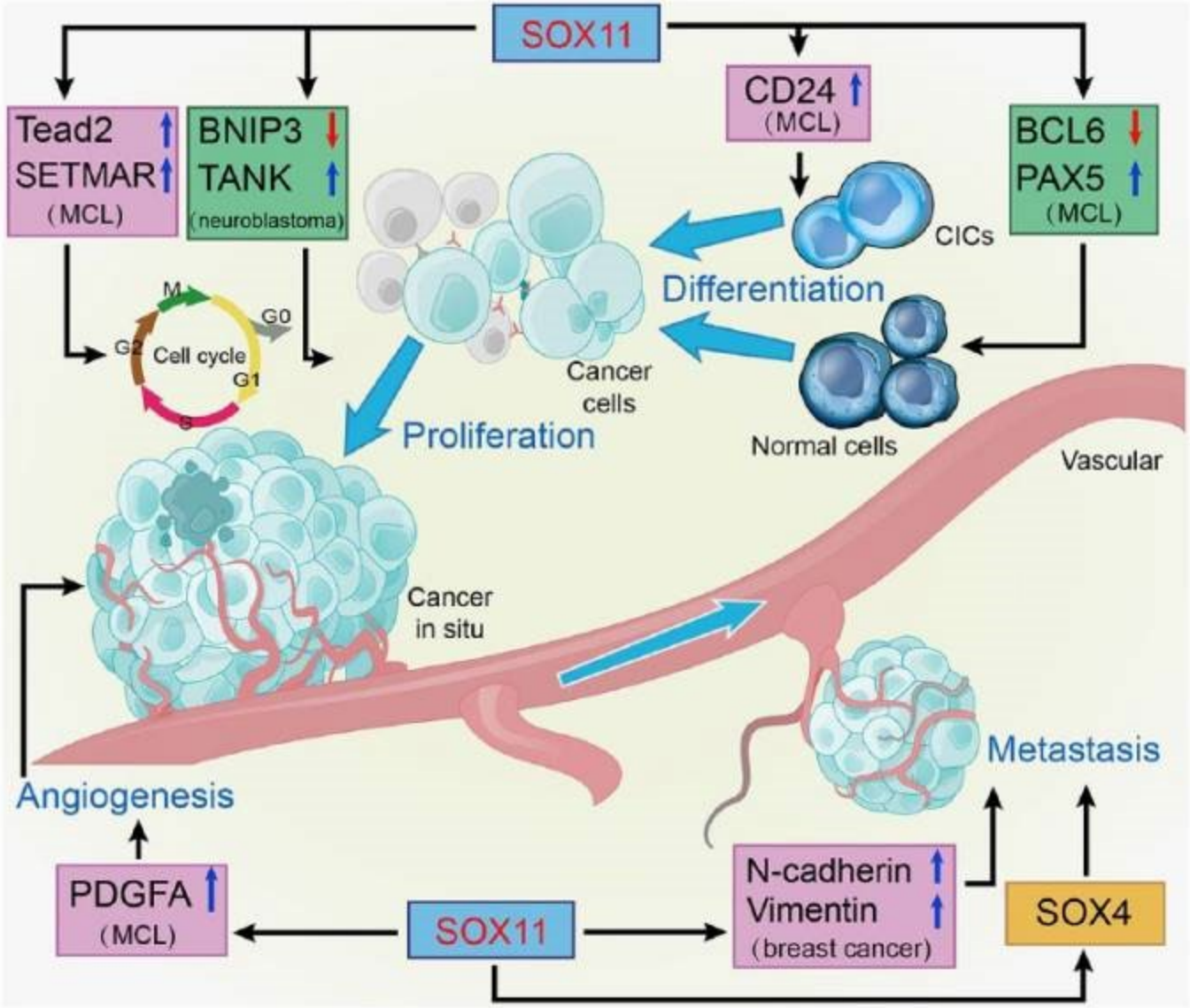
journal homepage: www.elsevier.com/locate/semcancer

Review

Regulatory roles for SOX11 in development, stem cells and cancer

Siu Man Tsang, Erik Oliemuller, Beatrice A. Howard*

The Breast Cancer Now Toby Robins Research Centre, Division of Breast Cancer Research, The Institute of Cancer Research, London, UK


SOX11
Tead2
SETMAR
(MCL)
BNIP3
TANK
(neuroblastoma)
CD24
(MCL)
BCL6
PAX5
(MCL)
CICs
Differentiation
M
G0
G2
Cell cycle
G1
S
Cancer
cells
Proliferation
Normal cells
Vascular
Cancer
in situ
Metastasis
Angiogenesis
PDGFA
(MCL)
SOX11
N-cadherin
Vimentin
(breast cancer)
SOX4

LETTER

doi:10.1038/nature14665

Reactivation of multipotency by oncogenic PIK3CA induces breast tumour heterogeneity

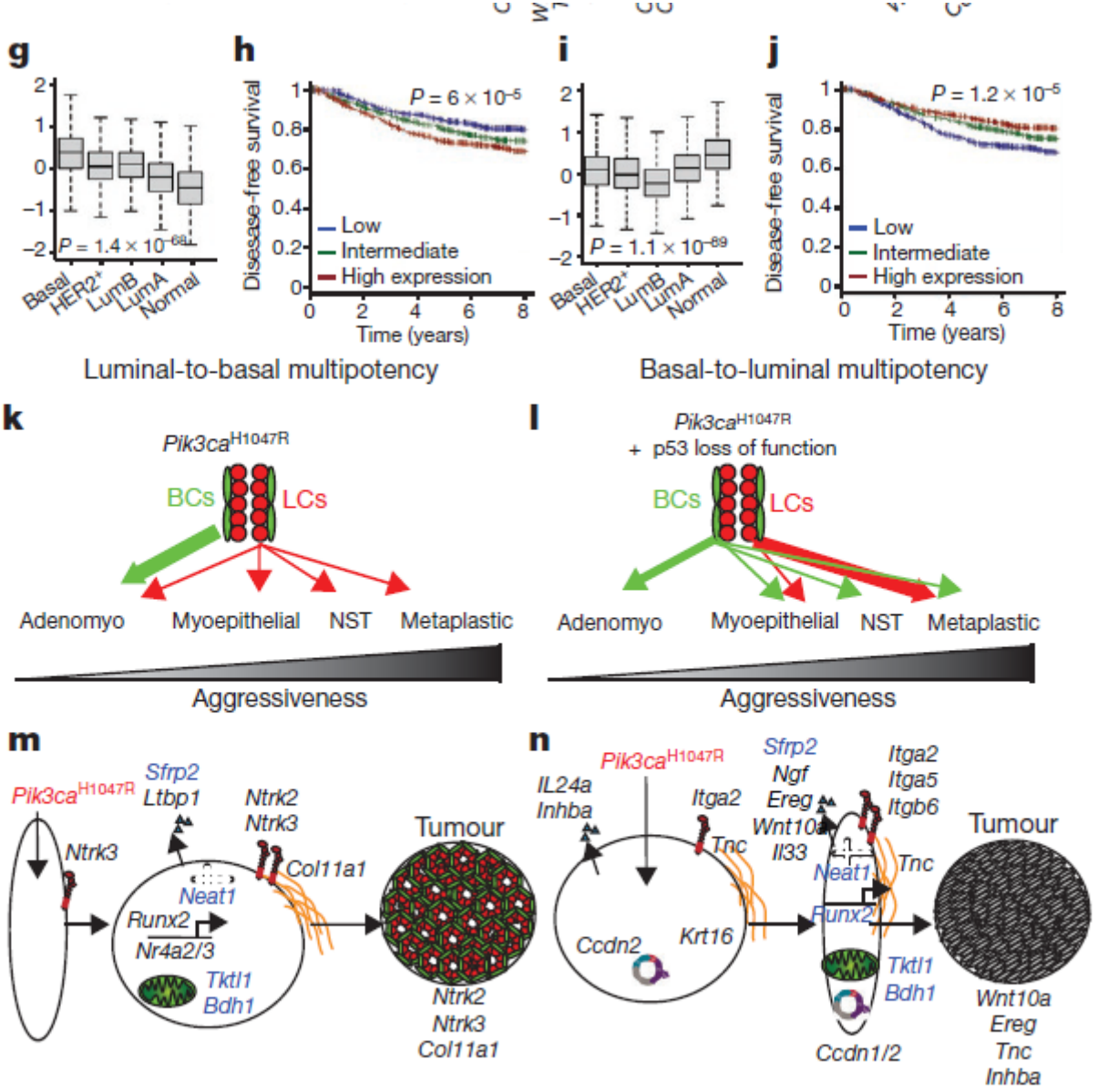
Alexandra Van Keymeulen[1]*, May Yin Lee[1]*, Marielle Ousset[1], Sylvain Brohée[2], Sandrine Rorive[3,4], Rajshekhar R. Giraddi[1], Aline Wuidart[1], Gaëlle Bouvencourt[1], Christine Dubois[1], Isabelle Salmon[3,4], Christos Sotiriou[2], Wayne A. Phillips[5,6] & Cédric Blanpain[1,7]

Breast cancer is the most frequent cancer in women and consists of heterogeneous types of tumours that are classified into different histological and molecular subtypes[1,2]. *PIK3CA* and *P53* (also known as *TP53*) are the two most frequently mutated genes and are associated with different types of human breast cancers[3]. The cellular origin and the mechanisms leading to *PIK3CA*-induced tumour heterogeneity remain unknown. Here we used a genetic approach in mice to define the cellular origin of *Pik3ca*-derived tumours and the impact of mutations in this gene on tumour heterogeneity. Surprisingly, oncogenic *Pik3ca*^{H1047R} mutant expression at physiological levels[4] in basal cells using keratin (K)5-CreER^{T2} mice induced the formation of luminal oestrogen receptor (ER)-positive/progesterone receptor (PR)-positive tumours, while its expression in luminal cells using K8-CReER^{T2} mice gave rise to luminal ER^{+}PR^{+} tumours or basal-like ER^{-}PR^{-} tumours. Concomitant deletion of *p53* and expression of *Pik3ca*^{H1047R} accelerated tumour development and induced more aggressive mammary tumours. Interestingly, expression of *Pik3ca*^{H1047R} in unipotent basal cells gave rise to luminal-like cells, while its expression in unipotent luminal cells gave rise to basal-like

upon expression of the *Pik3ca*^{H1047R} mutant in the mammary gland is currently unknown.

To determine whether breast tumour heterogeneity is determined by the cancer cell of origin, we developed a genetic strategy allowing the expression of the oncogenic *Pik3ca* mutant at physiological levels using Cre-inducible *Pik3ca*^{H1047R} knock-in mice[4], specifically in basal cells (BCs) using K5-CreER^{T2} or in luminal cells (LCs) using K8-CreER^{T2} mice[14] and followed their fate and tumorigenic potential over time. Tamoxifen (TAM) was administered at a dose that does not impair long-term mammary gland development and homeostasis, and resulted in the specific labelling of about 20% of BCs (Extended Data Fig. 1) in 4–5-week-old K5-CreER^{T2}/*Pik3ca*^{H1047R} mice (Fig. 1a). While it has been suggested that the mammary gland contains bipotent basal stem cells[15,16], our data using K5-CreER^{T2} knock-in or K14-rtTA/TetO-Cre mice, despite the labelling of 20–50% of BCs, showed no contribution of BCs to the luminal lineage (Extended Data Fig. 1). Further lineage-tracing studies that label all BCs or all LCs will be required to determine whether the discrepancy between the different

a c K5-CreER^{T2}/YFP e


g
h
i
j
P = 1.4 × 10−68
Basal
HER2+
LumB
LumA
Normal
Disease-free survival
P = 6 × 10−5
Low
Intermediate
High expression
Time (years)
P = 1.1 × 10−89
P = 1.2 × 10−5
Luminal-to-basal multipotency
Basal-to-luminal multipotency
k
l
Pik3caH1047R
BCs
LCs
Adenomyo
Myoepithelial
NST
Metaplastic
Aggressiveness
Pik3caH1047R
+ p53 loss of function
m
n
Sfrp2
Ltbp1
Ntrk2
Ntrk3
Ntrk3
Col11a1
Neat1
Runx2
Nr4a2/3
Tktl1
Bdh1
Tumour
Ntrk2
Ntrk3
Col11a1
IL24a
Inhba
Itga2
Tnc
Ccdn2
Krt16
Sfrp2
Ngf
Ereg
Wnt10a
Il33
Itga2
Itga5
Itgb6
Tnc
Neat1
Runx2
Tktl1
Bdh1
Ccdn1/2
Tumour
Wnt10a
Ereg
Tnc
Inhba

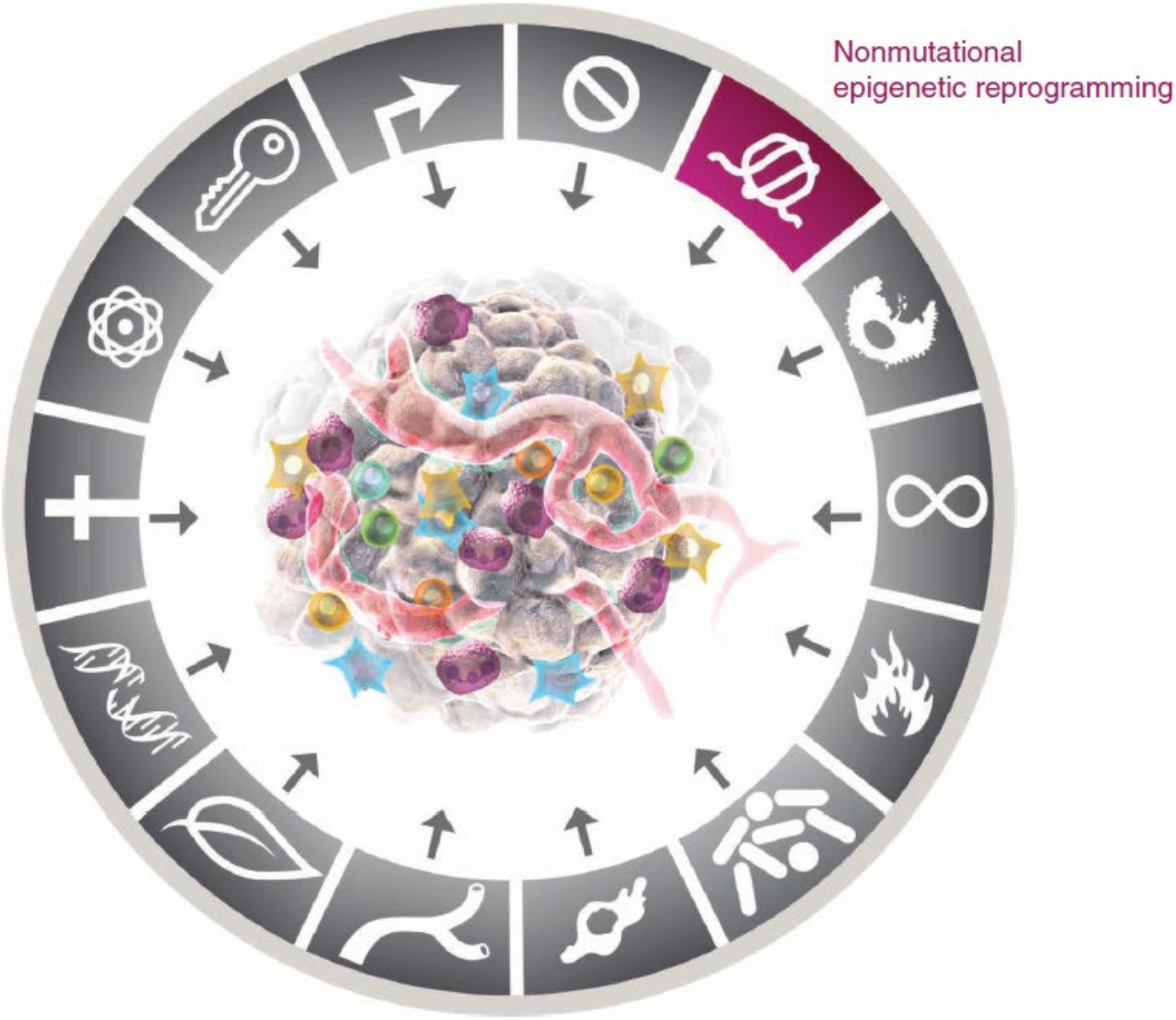


Figure 3. Nonmutational epigenetic reprogramming. Much as during embryogenesis and tissue differentiation and homeostasis, growing evidence makes the case that instrumental gene-regulatory circuits and networks in tumors can be governed by a plethora of corrupted and co-opted mechanisms that are independent from genome instability and gene mutation.

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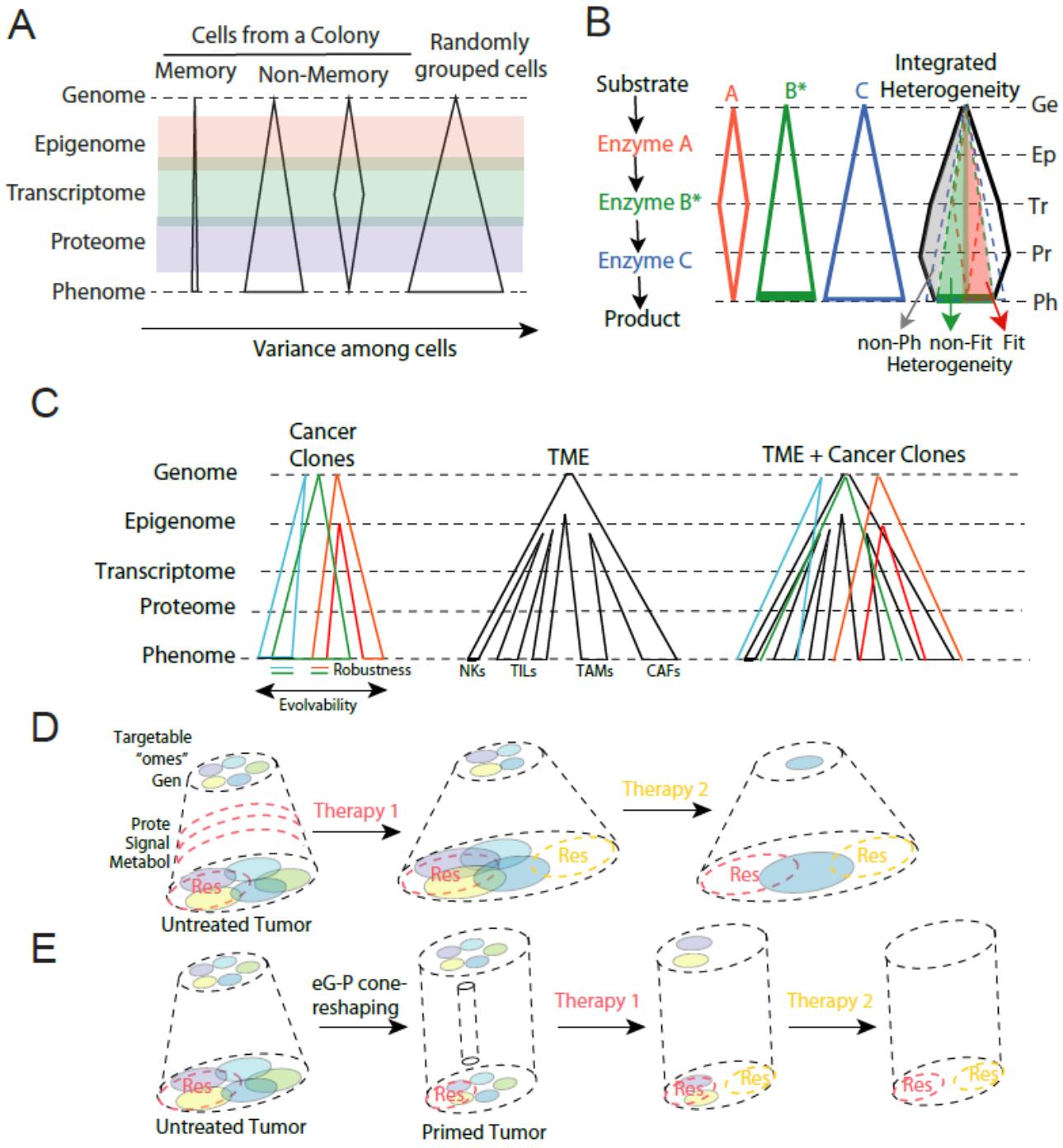
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

The Origins of Phenotypic Heterogeneity in Cancer

Guido Lenz[1,2*], Giovana R. Onzi[3], Luana S. Lenz[1,2],
Julieti H. Buss[1,2], Jephesson A. dos Santos[1,2] and Karine R. Begnini[1,2]

Abstract

Heterogeneity is a pervasive feature of cancer, and understanding the sources and regulatory mechanisms underlying heterogeneity could provide key insights to help improve the diagnosis and treatment of cancer. In this review, we discuss the origin of heterogeneity in the phenotype of individual cancer cells. Genotype-phenotype (G-P) maps are widely used in evolutionary biology to represent the complex interactions of genes and the environment that lead to phenotypes that impact fitness. Here, we present the rationale of an extended G-P (eG-P) map with a cone structure in cancer. The eG-P cone is formed by cells that are similar at the genome layer but gradually increase variability in the epigenome, transcriptome, proteome, metabolome and signalome layers to produce large variability at the phenome layer. Experimental evidence from single-cell -omics analyses supporting the cancer eG-P cone concept is presented, and the impact of epimutations and the interaction of cancer and tumor microenvironmental eG-P cones are integrated with the current understanding of cancer biology. The eG-P cone concept


A
Cells from a Colony
Memory
Non-Memory
Randomly grouped cells
Genome
Epigenome
Transcriptome
Proteome
Phenome
Variance among cells
B
Substrate
Enzyme A
Enzyme B*
Enzyme C
Product
A
B*
C
Integrated Heterogeneity
Ge
Ep
Tr
Pr
Ph
non-Ph
non-Fit
Fit
Heterogeneity
C
Cancer Clones
TME
TME + Cancer Clones
Genome
Epigenome
Transcriptome
Proteome
Phenome
Robustness
Evolvability
NKs
TILs
TAMs
CAFs
D
Targetable "omes"
Gen
Prote
Signal
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Therapy 1
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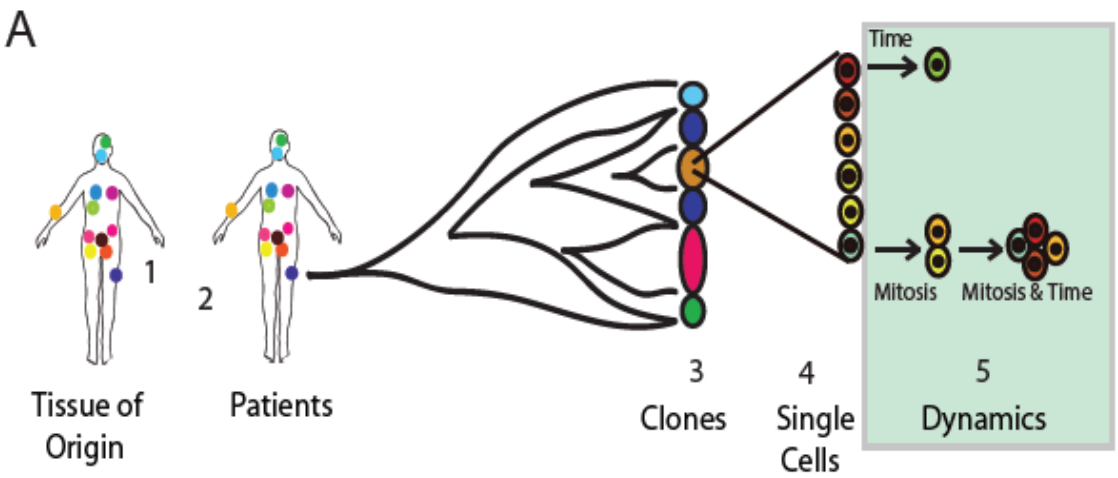
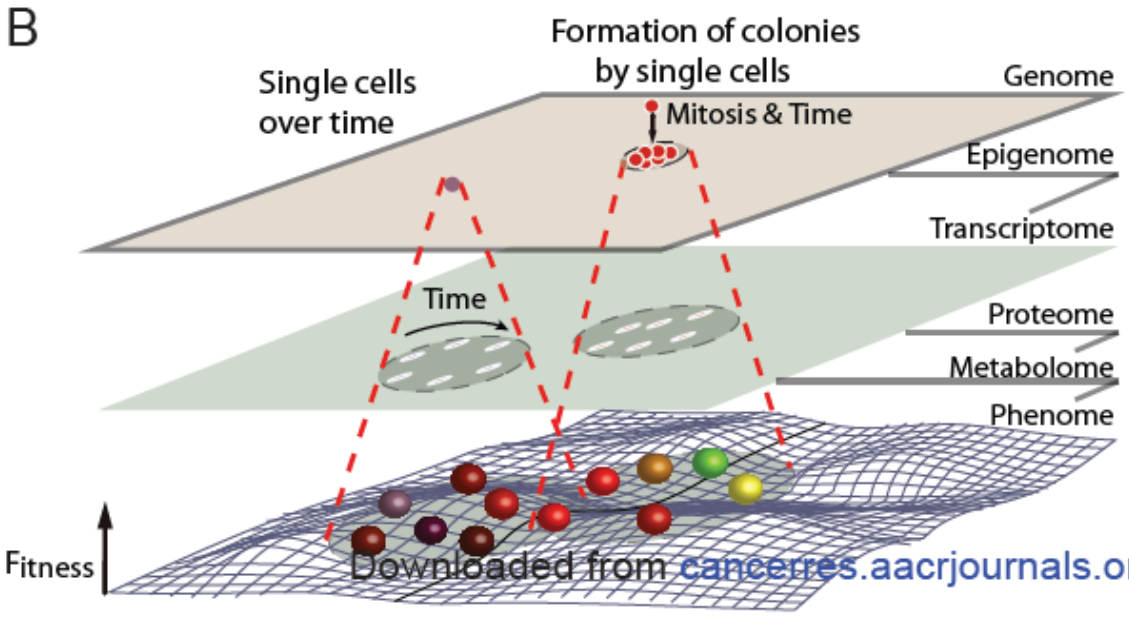
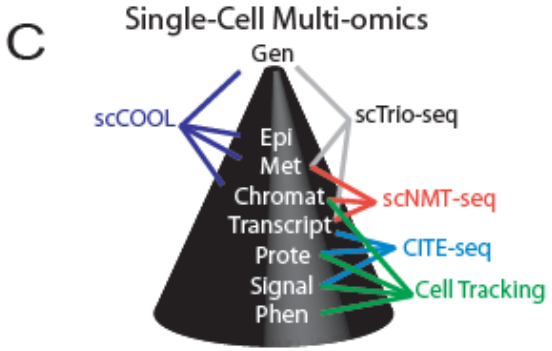
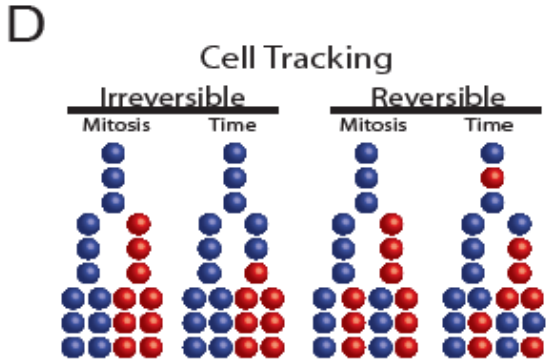
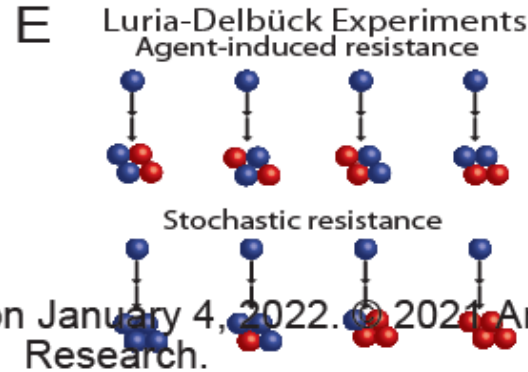
Untreated Tumor
E
eG-P cone-reshaping
Therapy 1
Therapy 2
Untreated Tumor
Primed Tumor











ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 29: 895–902, 2018
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Published online 22 January 2018

ORIGINAL ARTICLE

Unravelling triple-negative breast cancer molecular heterogeneity using an integrative multiomic analysis

Y. Bareche[1†], D. Venet[1†], M. Ignatiadis[2], P. Aftimos[2], M. Piccart[2], F. Rothe[1‡] & C. Sotiriou[1,2*,‡]

[1]J.-C. Heuson Breast Cancer Translational Research Laboratory; [2]Department of Medical Oncology, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium

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†Both authors contributed equally as co-first authors.

‡Both authors contributed equally as co-last authors.

Background: Recent efforts of genome-wide gene expression profiling analyses have improved our understanding of the biological complexity and diversity of triple-negative breast cancers (TNBCs) reporting, at least six different molecular subtypes of TNBC namely Basal-like 1 (BL1), basal-like 2 (BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL) and luminal androgen receptor (LAR). However, little is known regarding the potential driving molecular events within each subtype

Annals of Oncology

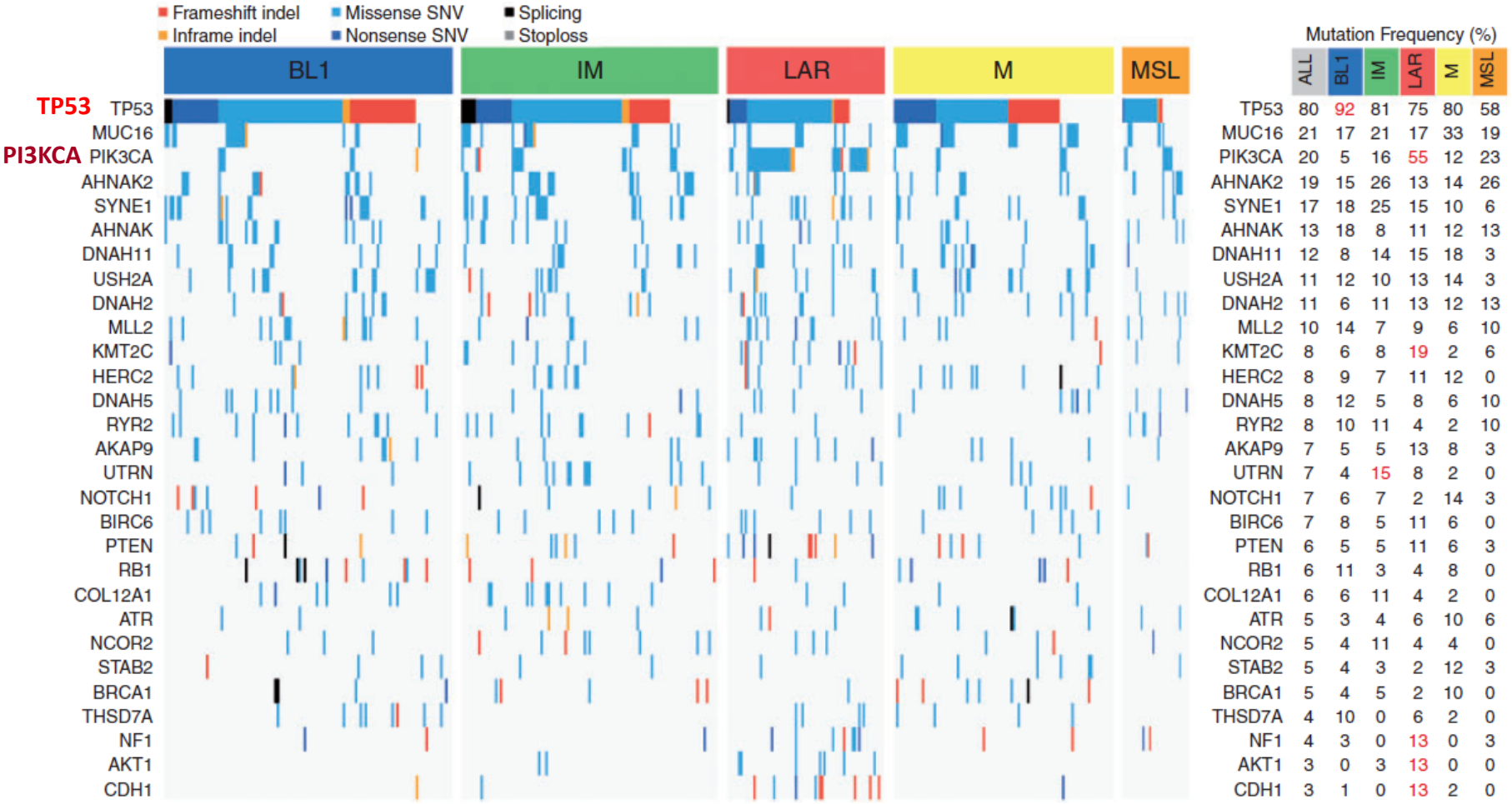


Figure 1. Mutational landscape of TNBC molecular subtypes. Frequencies of mutations across each TNBC molecular subtype according to the different types of mutations. Only genes mutated at a frequency >10% in at least one subtype are displayed. Significant differences (FDR < 0.05) are shown in red (right panel).

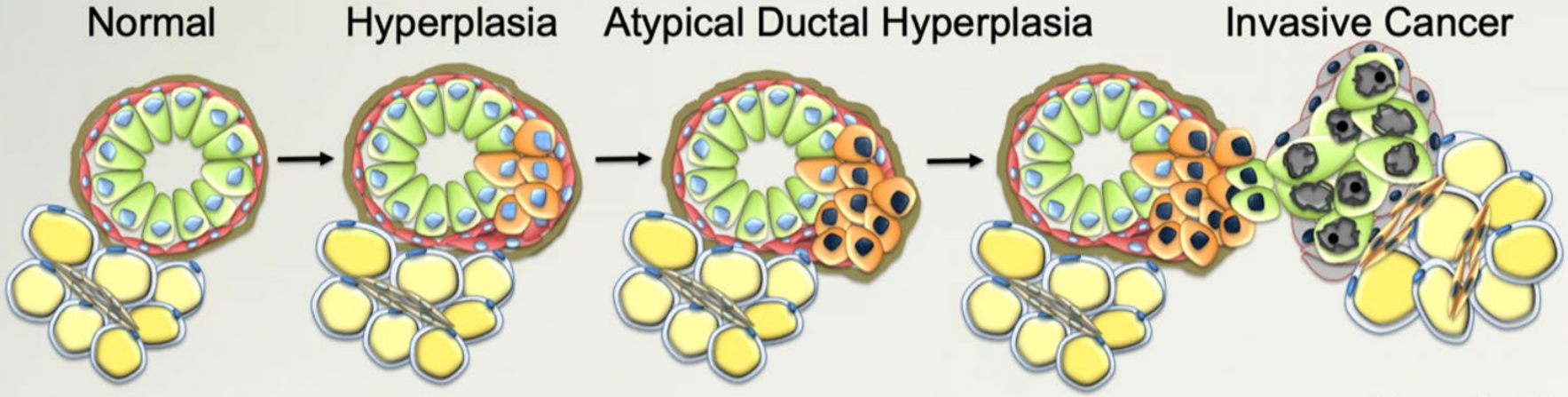
TNBC namely Basal-like 1 (**BL1**), basal-like 2 (BL2), immunomodulatory (IM), mesenchymal (**M**), mesenchymal stem-like (MSL) and luminal androgen receptor (**LAR**)

Systems Approach for Early Detection of Aggressive Breast Cancer Biology: A working model

Sundus Shalabi[1#], David Frankhouser[1#], Jerneja Tomsic[1#], Christopher Sistrunk[1#], JesuchristopherJoseph[1#], Daniel Schmolze[1], Robert Cardiff[1,2], Jožefa McKiernan[1], Stanley Hooker[1], Rick Kitles[1], Jinhui Wang[1], Kristina Tourville[3], Jackelyn Alva-Ornelas[1], Meagan Razo[1], Angela Sanchez[1], Nancy Sanchez, Christine Thai[1], Tanya Chavez[1], Alan Nuñez[1], Vanessa Myriam Robles[1], Cristal Resto[1], Angela Wong[1], Veronica Jones[1], Lisa Yee[1], Lily Lai[1], David Ann[1], Dan Crichton[4], Gustavo Miranda Carboni[5], Eric Dietze[1], Terry Hyslop[3], Ruth O'Regan[6], Tijana Talisman[1], Lucio Miele[7], Ernest Martinez[8], Mark LaBarge[1*], Ashish Mahabal[9*], Victoria Seewaldt[1*]

[1]City of Hope Comprehensive Cancer Center, Duarte, California; [2]Center for Comparative Medicine, University of California, Davis, Davis

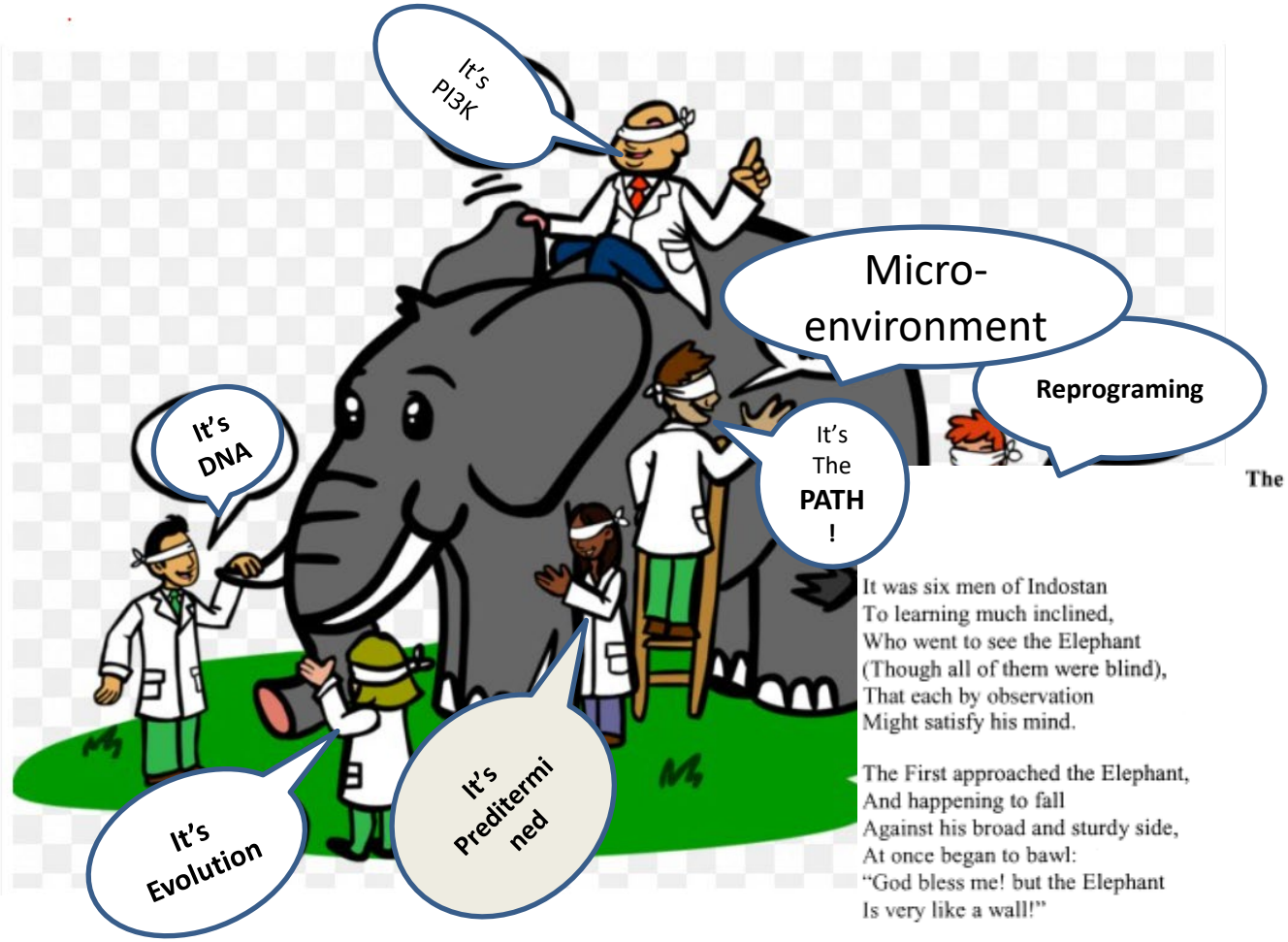
A. Proposed Progression Model



Candidate Hypotheses

- **Epigenetic Reprogramming**

- **Evolutionary Adaptation (Predeterminism)**



The Blind Men and the Elephant
John Godfrey Saxe
(1816-1887)

It was six men of Indostan
To learning much inclined,
Who went to see the Elephant
(Though all of them were blind),
That each by observation
Might satisfy his mind.

The First approached the Elephant,
And happening to fall
Against his broad and sturdy side,
At once began to bawl:
"God bless me! but the Elephant
Is very like a wall!"

The Second, feeling of the tusk,
Cried, "Ho! what have we here
So very round and smooth and sharp?
To me 'tis mighty clear
This wonder of an Elephant
Is very like a spear!"

The Third approached the animal,
And happening to take
The squirming trunk within his hands,
Thus boldly up and spake:
"I see," quoth he, "the Elephant
Is very like a snake!"

The Fourth reached out an eager hand,
And felt about the knee.
"What most this wondrous beast is like
Is mighty plain," quoth he;
"'Tis clear enough the Elephant
Is very like a tree!"

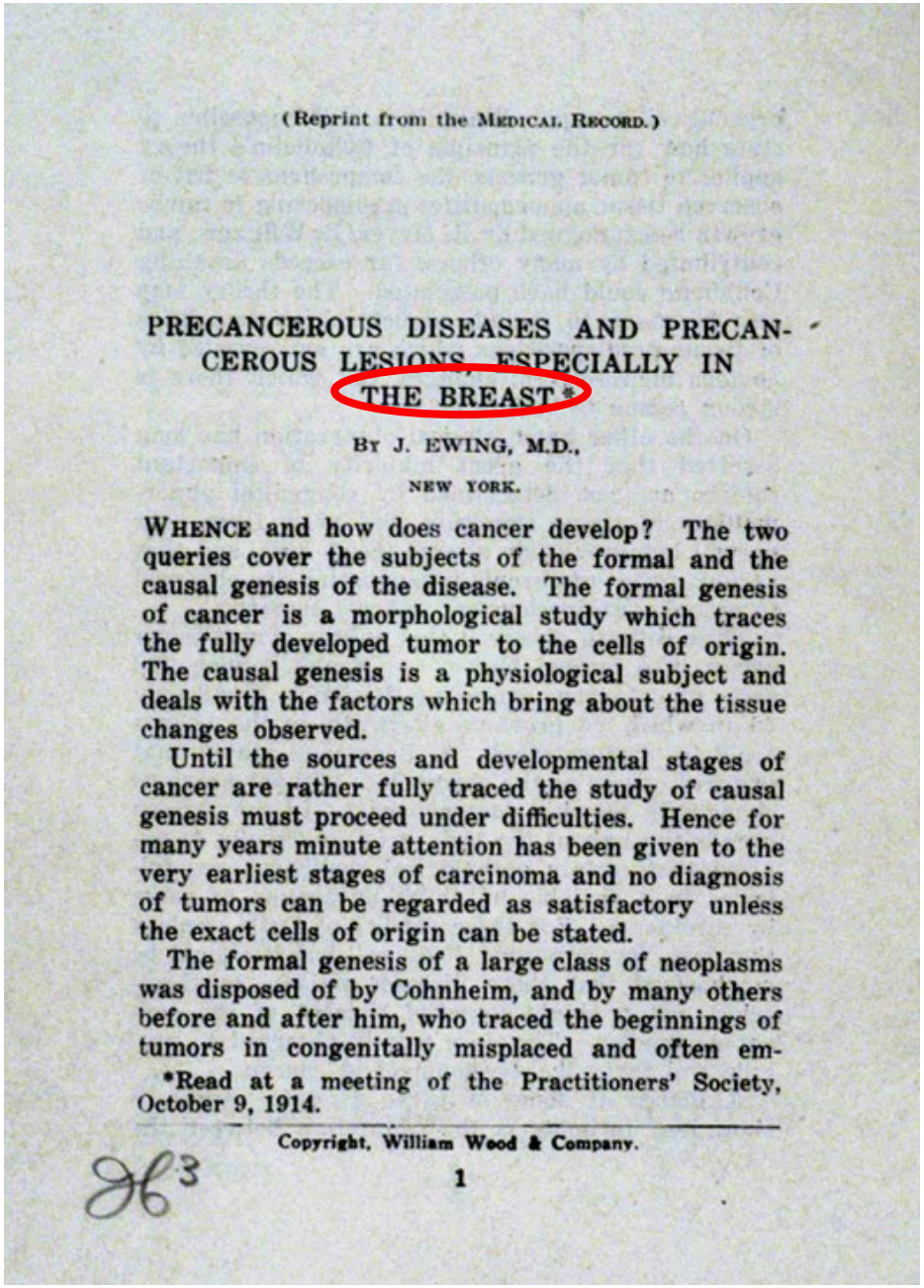
The Fifth, who chanced to touch the ear,
Said: "E'en the blindest man
Can tell what this resembles most;
Deny the fact who can
This marvel of an Elephant
Is very like a fan!"

The Sixth no sooner had begun
About the beast to grope,
Than, seizing on the swinging tail
That fell within his scope,
"I see," quoth he, "the Elephant
Is very like a rope!"

And so these men of Indostan
Disputed loud and long,
Each in his own opinion
Exceeding stiff and strong,
Though each was partly in the right,
And all were in the wrong!

Our Clinical History:
The limits of inferential Logic

WORD "PRECANCER": FIRST USED AND DESCRIBED IN 1913



(Reprint from the MEDICAL RECORD.)

PRECANCEROUS DISEASES AND PRECANCEROUS LESIONS, ESPECIALLY IN THE BREAST*

BY J. EWING, M.D.,

NEW YORK.

WHENCE and how does cancer develop? The two queries cover the subjects of the formal and the causal genesis of the disease. The formal genesis of cancer is a morphological study which traces the fully developed tumor to the cells of origin. The causal genesis is a physiological subject and deals with the factors which bring about the tissue changes observed.

Until the sources and developmental stages of cancer are rather fully traced the study of causal genesis must proceed under difficulties. Hence for many years minute attention has been given to the very earliest stages of carcinoma and no diagnosis of tumors can be regarded as satisfactory unless the exact cells of origin can be stated.

The formal genesis of a large class of neoplasms was disposed of by Cohnheim, and by many others before and after him, who traced the beginnings of tumors in congenitally misplaced and often em-

*Read at a meeting of the Practitioners' Society, October 9, 1914.

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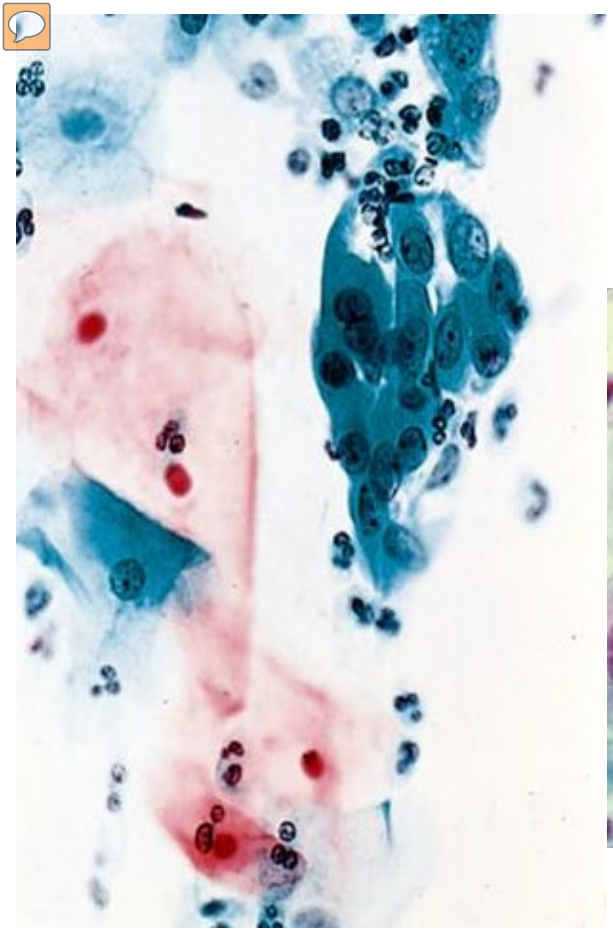
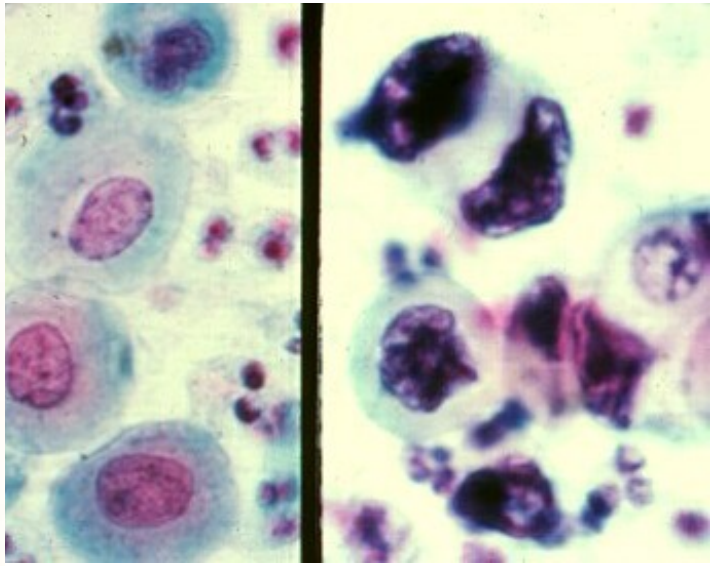
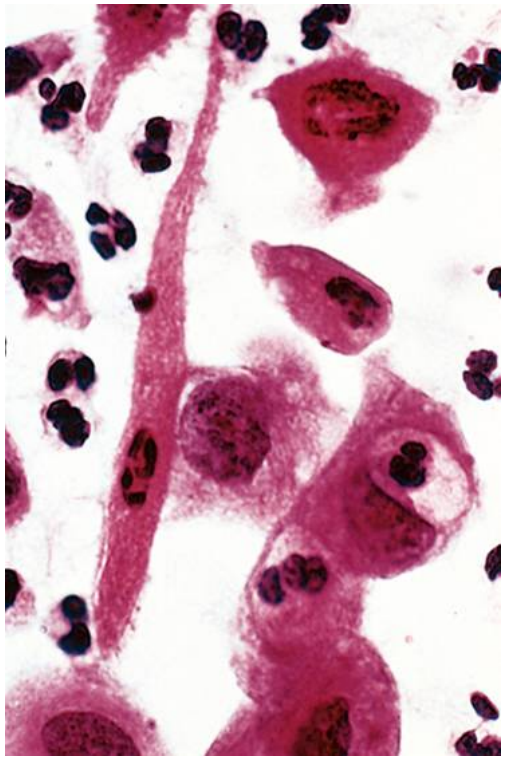


Normal Human Cervical Cells



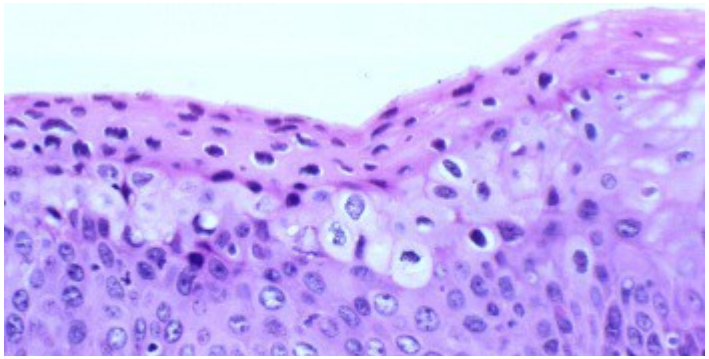


Malignant Human Cervical Cells

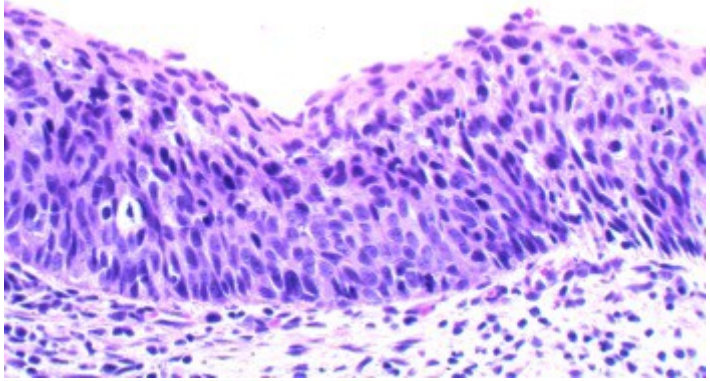
73%
REDUCTION

Papanicolaou, G. New Cancer Diagnosis. Proceedings Third Race Betterment Congress, 1928. p. 528.

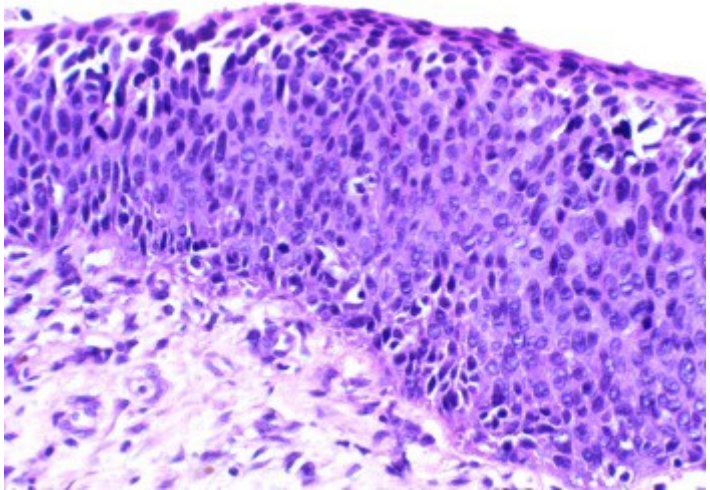
Cervical Precancer Progression



CIN I



CIN II



CIN III

George Papanicolaou

CANCER (Invasion)

G.N. Papnicolaou, H.F. Traut
The diagnostic value of vaginal smears in carcinoma of the uterus
Am. J. Obstet. Gynecol., 42 (1941), pp. 193-224

American Cancer Society Guidelines for the Early Detection of Cancer

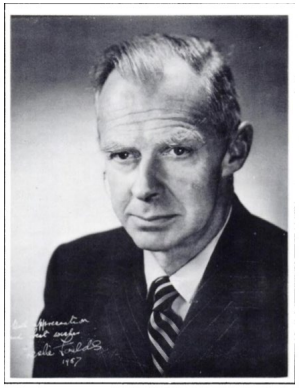
Screening tests are used to find cancer *before* a person has any symptoms. Here are the American Cancer Society's recommendations to help guide you when you talk to your doctor about screening for certain cancers.

Health care facilities are providing cancer screening during the COVID-19 pandemic with many safety precautions in place. The American Cancer Society Get Screened campaign encourages people to start or restart their recommended cancer screenings. Regular screenings can help find and treat pre-cancers and cancers early, before they have a chance to spread. Visit Get Screened to learn about screening tests and what you can do

NEOPLASTIC DEVELOPMENT

LESLIE FOULDS

London



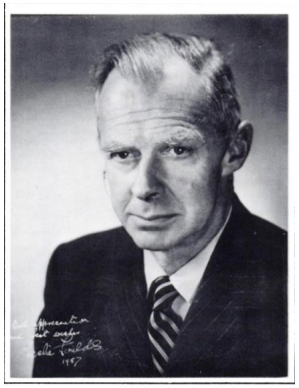
Leslie Foulds
1902–1974

VOLUME 2

1975
ACADEMIC PRESS
London New York San Francisco
A Subsidiary of Harcourt Brace Jovanovich

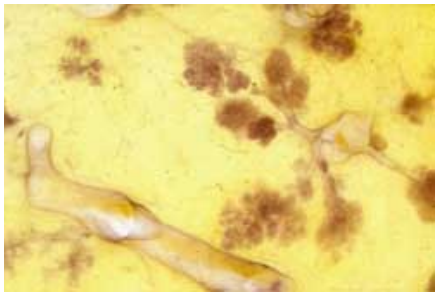
L.L. Foulds' Six Principals:

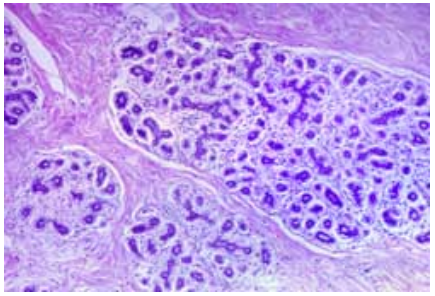
PROGRESSION
1954


Leslie Foulds
1902–1974

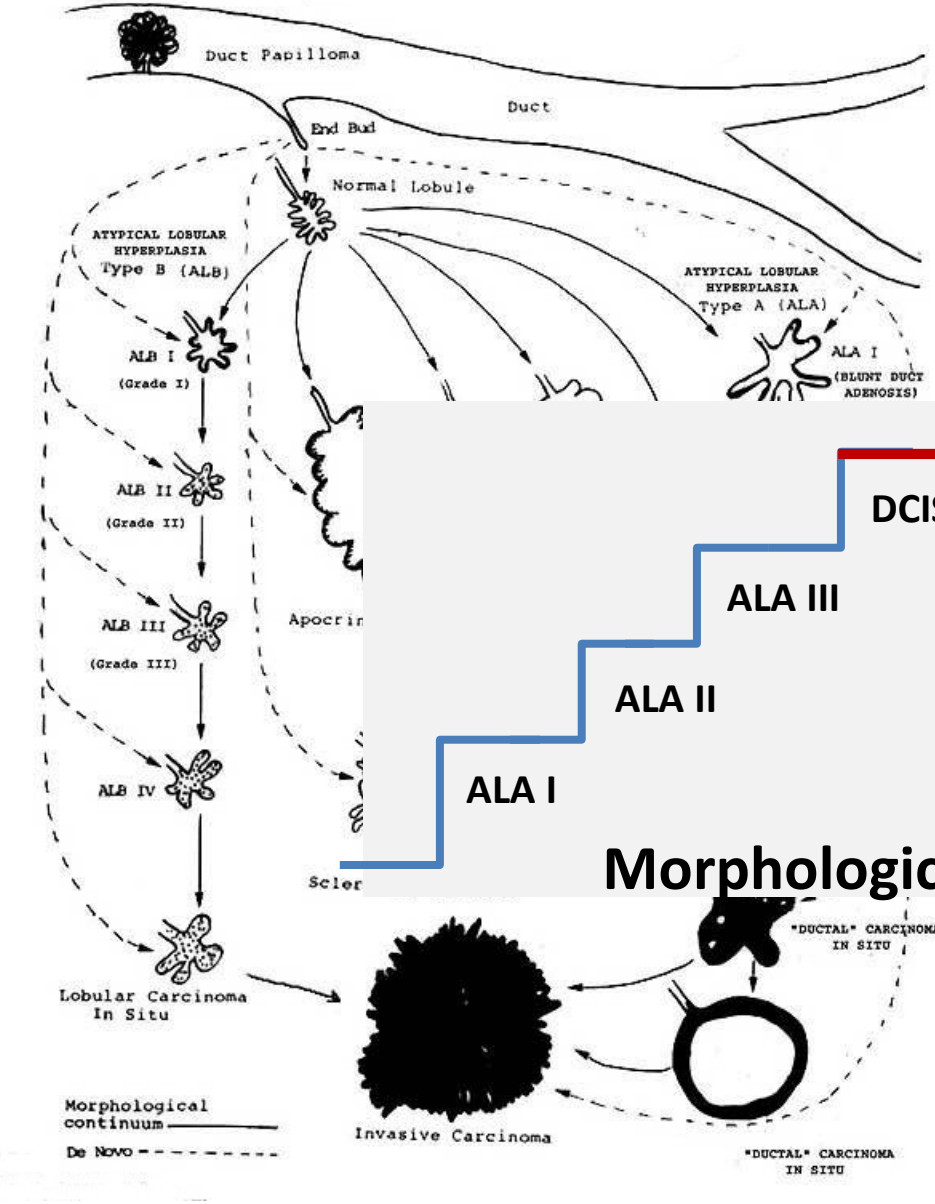
1. Independent Progression of tumors
2. Independent Progression of characters
3. Progression is Independent of growth
4. Progression is *continuous* or *discontinuous* by gradual change or by steps.
5. Progression flows one of alternate paths of development
    a) Different paths leading to different end-points
    b) Different paths leading to similar end –points
6. Progression does not always reach an end-point within the life-span of the host

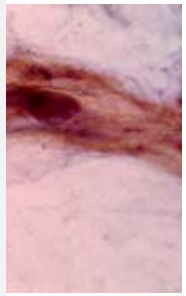
PROGRESSION OF THE NORMAL TDLU TO CARCINOMA AS DEPICTED IN 1973

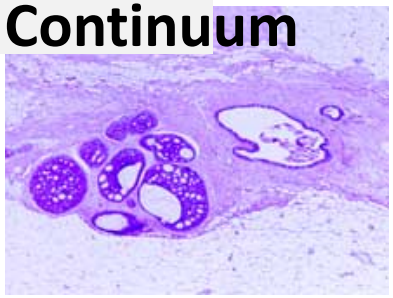




NORMAL TDLU







DCIS

Wellings, S.R and Jensen, H. M. On the Origin and Progression of Ductal Carcinoma in the Human Breast . JNCI, 1973, Vol 50, pp 1111 -1118.
Foulds, L. *Neoplastic Development* 1975. Academic Press, London

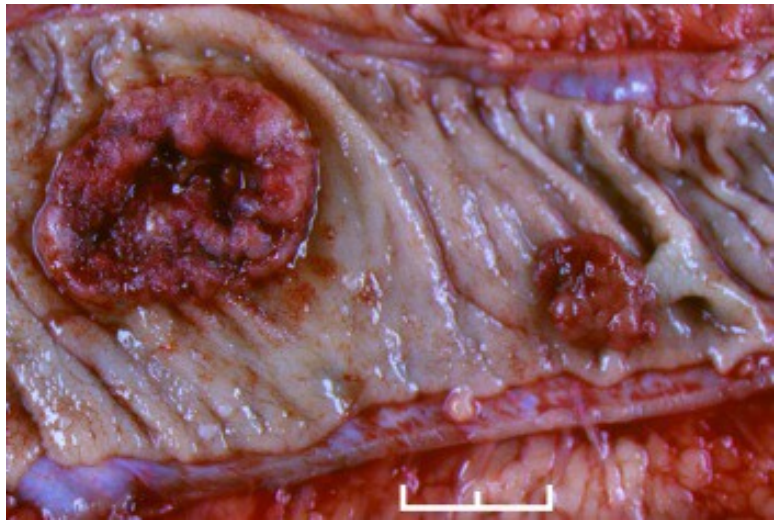
Stepwise Molecular Progression:

Transformation

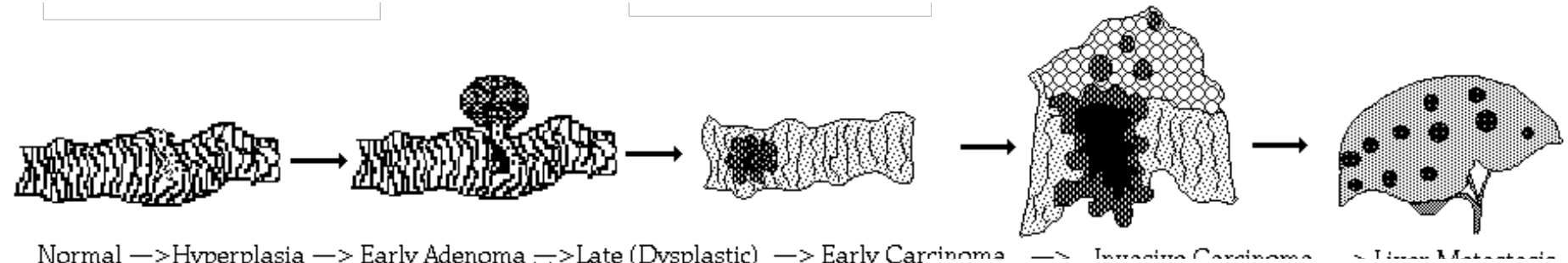
Growth

Invasion

Metastasis



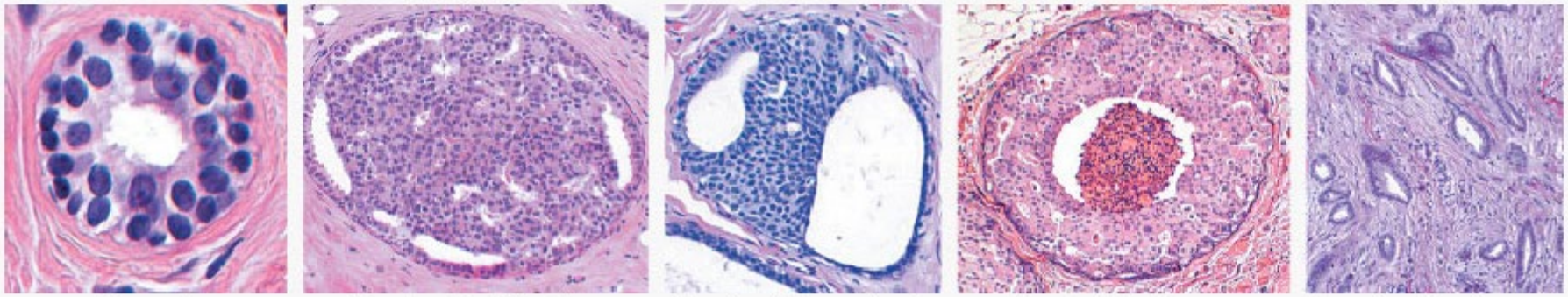
- "Multi-hit" hypothesis



"Vogelgram"

Possible example of a sequence of mutations in the pathogenesis of colon carcinoma. Order is not important, but accumulation of mutations is the key.

Fearon, ER and Vogelstein, B: Cell. 1990, 61:759-767



Accumulation of genetic and epigenetic changes

Abnormal response to growth factors (e.g., estrogen receptor)

Abnormal oncogene expression (e.g., *HER2/neu*)

Tissue invasion (gain of function by malignant cells vs. loss of function of normal cells)

Loss of tumor-suppressor function (e.g., p53)

Stromal changes (e.g., angiogenesis)

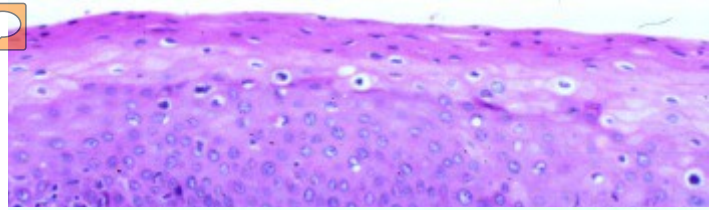
Failure to respond to normal signals for apoptosis

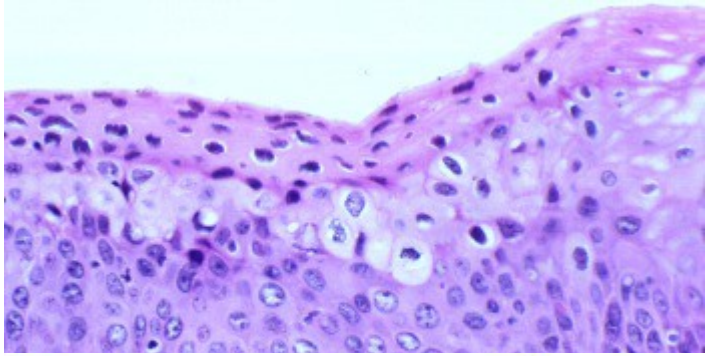
Genetic instability (e.g., loss of heterozygosity)

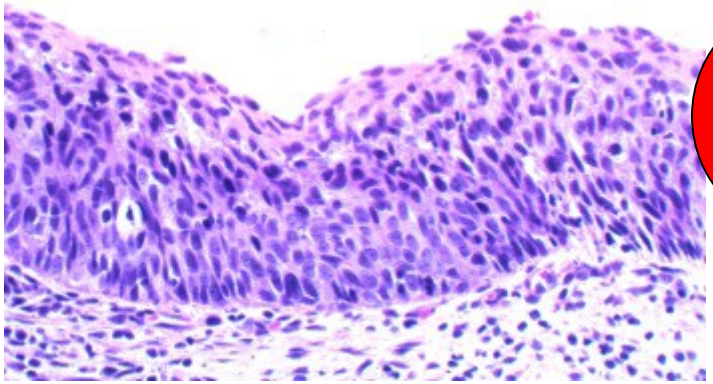
Clinical phenotype of tumor determined

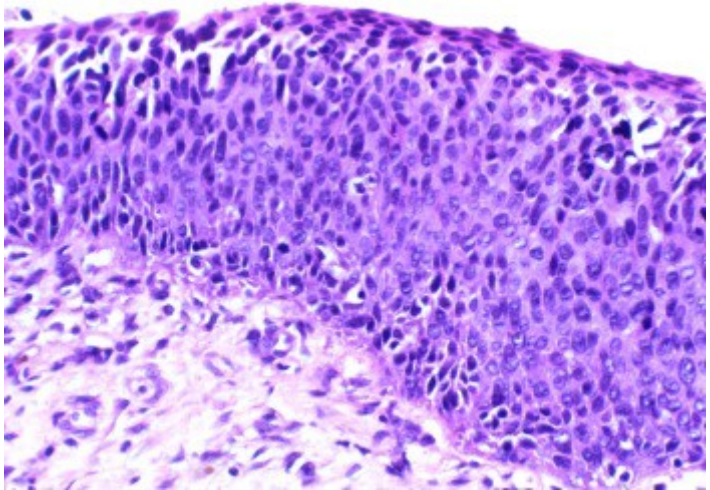
Early Detection Based on Cellular Phenotype Reinforced by Molecular Type

HOWEVER







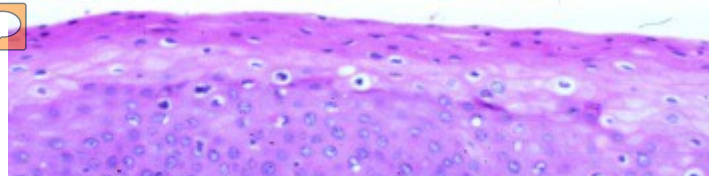


Cervical Precancer Progression

CIN I ← Low Risk HPV Type Infection

CIN II ← High Risk HPV Type Infection

CIN III → CANCER (Invasion)



Cervical Precancer

The Nobel Prize in Physiology or Medicine 2008

Harald zur Hausen
Françoise Barré-Sinoussi
Luc Montagnier

Share this

Harald zur Hausen
Facts

© The Nobel Foundation.
Photo: U. Montan

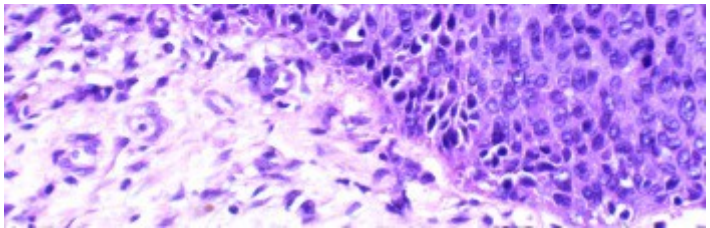
Harald zur Hausen
The Nobel Prize in Physiology or Medicine 2008

Born: 11 March 1936, Gelsenkirchen, Germany

Affiliation at the time of the award: German Cancer Research Center, Heidelberg, Germany

Prize motivation: "for his discovery of human papilloma viruses causing cervical cancer."

Prize share: 1/2



CIN III → **CANCER (Invasion)** Papanicolaou 1929

Journal Title : **Surgery, gynecology & obstetrics**

Volume : 92
Issue : 4
Month/Year : Apr 1951
Pages : 443-52

Article Author: MACDONALD, I

Article Title : Biological predeterminism in human cancer

BIOLOGICAL PREDETI NCER

IAN MACDONALD,

"EARLY diagnosis" and "prompt determinative ment" are stock phrases whic possibility of omize current efforts towar ual neoplasm. clinical control of cancer, as e h representing ed both in medical literature and in pro l history of a da for the laity. The idea that thera rs pursued an efficiency in the control of cancer is r ented by the conditioned upon treatment early in th eriod of local ical history of the disease is so firm by distinctive trenched that the degree of neoplastic stic evidence occupation, as well as the probability , then applica- tastatic spread, is generally regarded as would produce in direct ratio to the elapsed time sin retically, too, recognizable onset of the process. According radical treatment at a time during the interval

Special Article

THE THEORY OF BIOLOGIC PREDETERMINISM: ITS QUESTIONABLE USEFULNESS AND VALIDITY AS A MEDICAL TOOL

LOUIS J. NOTKIN, M.D., C.M., F.A.C.G.,
Montreal

THE PHRASE "biologic predeterminism" has been recurring in the medical literature and at medical meetings with increasing frequency. Ian MacDonald first employed the phrase some years ago as "a synoptic expression for a biologic balance between host and neoplasm", established before the neoplastic process becomes clinically detectable.[1-3] Evidence provided in this publication "supported an obvious corollary: the outcome of

The term "biologic predeterminism" would appear to be an unfortunate one because its influence is not susceptible to measurement; it connotes an almost fatalistic approach and does not appear to have any value in furthering the interests of the patient with carcinoma of the stomach. It does convey a sense of frustration, hopelessness and mysticism, and unless clarified to the point of lucidity and usefulness should be dropped.

The concept that a longer history means a more favourable prognosis in a specific cancerous lesion appears to be a very confusing, though partially true, statement of fact. It is not at all illogical to believe that patients in whom carcinoma of the stomach is diagnosed, and who have a long history, may survive longer. What appears to be illogical is the implied assumption that it is therefore not harmful, and even beneficial, to delay operation. Such an assumption can be tragically harmful if, for instance, it should be finally demonstrated that the Alice-in-Wonderland concept of *The Later The Earlier* may have a very simple explanation,

belief that, should this concept become widely known and accepted, the already deeply rooted pessimism prevalent among general practitioners regarding the value of the surgical approach in cancer of the stomach will be reinforced. This is hardly desirable.

TWO FACTOR MODEL

Journal List › J Exp Med › v.80(2); 1944 Aug 1 › PMC2135455

JEM Journal of Experimental Medicine
Rockefeller University Press

This article at JEM.org | Editors | Contact | Instructions for Authors

J Exp Med. 1944 Aug 1; 80(2): 101–126.
doi: 10.1084/jem.80.2.101

PMCID: PMC2135455
PMID: 19871401

THE INITIATING AND PROMOTING ELEMENTS IN TUMOR PRODUCTION

AN ANALYSIS OF THE EFFECTS OF TAR, BENZPYRENE, AND METHYLCHOLANTHRENE ON RABBIT SKIN

William F. Friedewald and Peyton Rous

TWO FACTOR MODEL

Journal List › Br J Cancer › v.1(4); 1947 Dec › PMC2007538

Br J Cancer. 1947 Dec; 1(4): 379–382.
doi: 10.1038/bjc.1947.35
PMCID: PMC2007538
PMID: 18906315

The Role of Croton Oil Applications, Associated with a Single Painting of a Carcinogen, in Tumour Induction of the Mouse's Skin

I. Berenblum and P. Shubik

Three Models for Progression of Heterogeneous Breast Tumors

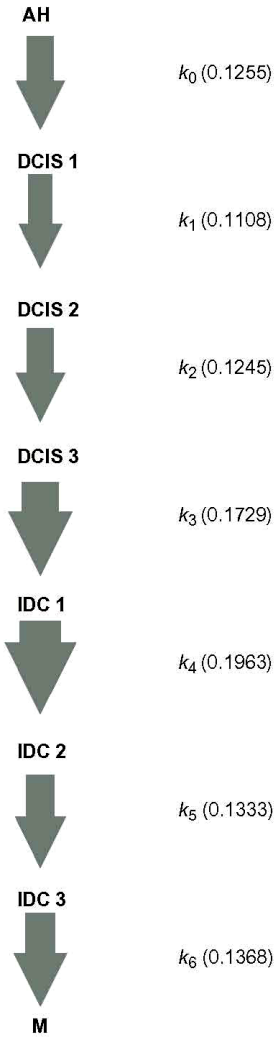


Fig. 1. Linear pathway. The rate constants shown are the average of the best fit to the Van Nuys and Holland observations, normalized to one. The thickness of each arrow is proportional to the rate constant. Atypical hyperplasia (AH), ductal carcinoma in situ (DCIS), invasive ductal carcinoma (IDC), and metastasis (M). Grades of DCIS and IDC are indicated by 1, 2, and 3.

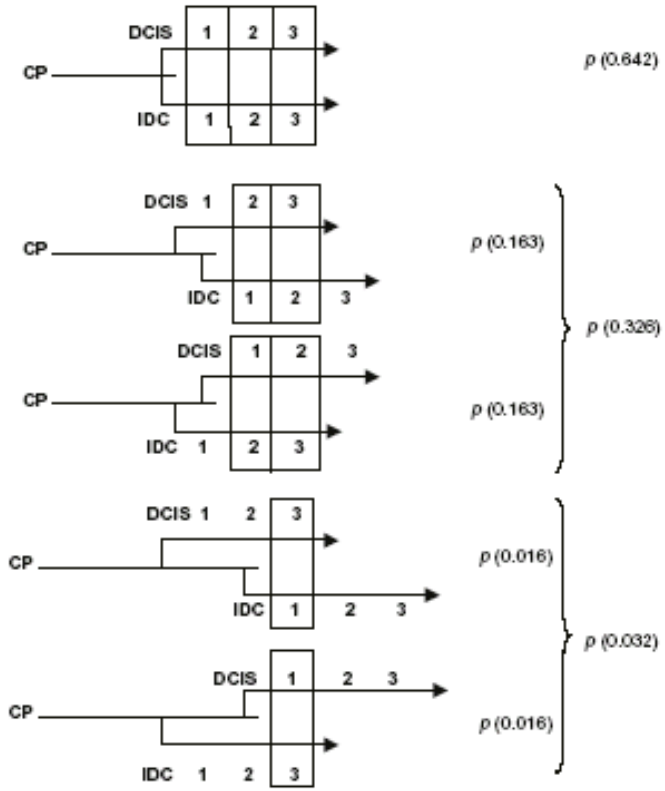


Fig. 4. Parallel pathway. DCIS and IDC diverge from a common progenitor (CP) and progress at about the same rate through grades 1, 2, and 3. Divergence may occur at the same time or at different times in different groups of patients. The proportion (p) of patients in each group is indicated. Grades that co-occur are shown above and below each other in the same box. This pathway is best at simulating the clinically observed co-occurrence frequencies.

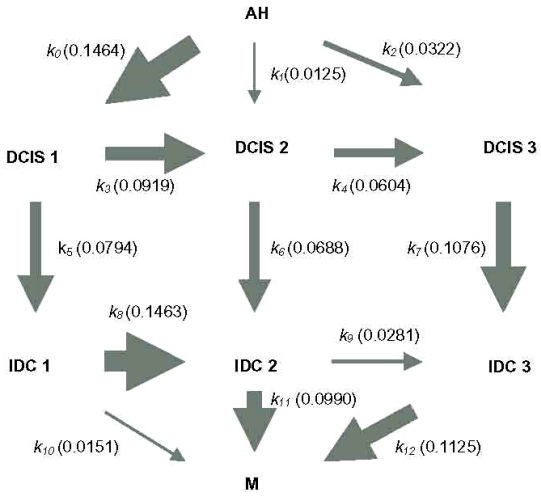


Fig. 3. Branched pathway. The rate constants shown are the average of the best fit to the Van Nuys and Holland observations, normalized to one. The thickness of each arrow is proportional to the rate constant. Atypical hyperplasia (AH), ductal carcinoma in situ (DCIS), invasive ductal carcinoma (IDC), and metastasis (M). Grades of DCIS and IDC are indicated by 1, 2, and 3.

Linear Model

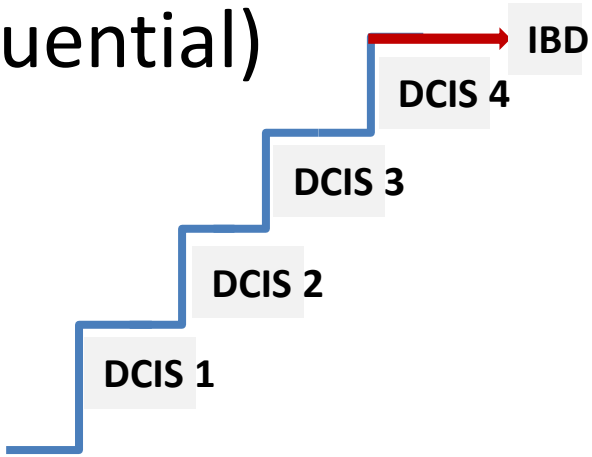
Parallel Model

Branched Model

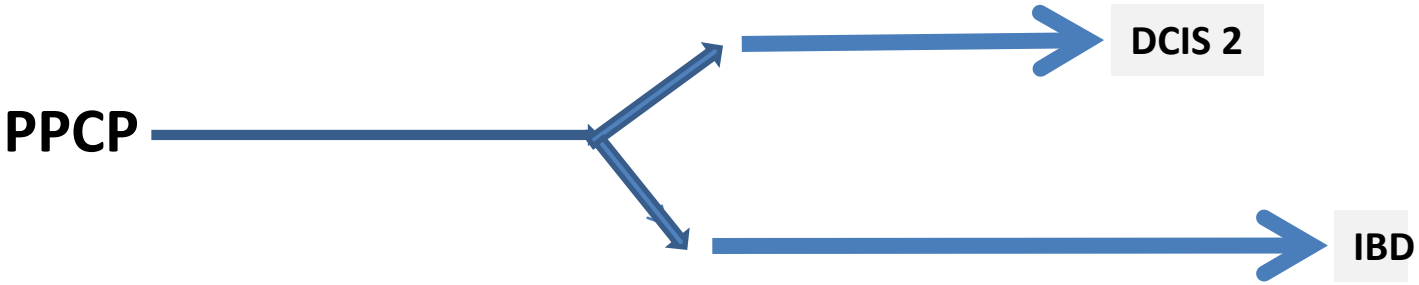
Sontag, L and Axelrod, DE (2005) Jour Theoretical Biol 232:179-189

TWO MODELS

1. MULTISTEP LINEAR PROGRESSION (Sequential)



2. PRE-PROGRAMMED CANCER PROGENITOR



Sontag and Axelrod

VIEWPOINT

Overdiagnosis and Overtreatment in Cancer
An Opportunity for Improvement

Laura J. Esserman, MD, MBA
University of California, San Francisco.

Ian M. Thompson Jr, MD
University of Texas Health Science Center at San Antonio.

Brian Reid, MD, PhD
Fred Hutchinson Cancer Research Center, Seattle, Washington.

Over the past 30 years, awareness and screening have led to an emphasis on early diagnosis of cancer. Although the goals of these efforts were to reduce the rate of late-stage disease and decrease cancer mortality, secular trends and clinical trials suggest that these goals have not been met; national data demonstrate significant increases in early-stage disease, without a proportional decline in later-stage disease. What has emerged has been an appreciation of the complexity of the pathologic condition called cancer. The word "cancer" often invokes the specter of an inexorably lethal process; however, cancers are heterogeneous and can follow multiple paths, not all of which progress to metastases and death, and include indolent disease that causes no harm during the patient's lifetime. Better biology alone can explain better outcomes. Although this complexity complicates the goal of early diagnosis, its recognition provides an opportunity to adapt cancer screening with a focus on identifying and treating those conditions most likely associated with morbidity and mortality.

Changes in cancer incidence and mortality[1] reveal 3 patterns that emerged after inception of screening (**Table**). Screening for breast cancer and prostate cancer appears to detect more cancers that are potentially clinically insignificant.[4] Lung cancer may follow this pattern if high-risk screening is adopted.[5] Barrett esophagus and ductal carcinoma of the breast are examples for which the detection and removal of lesions considered precancerous have not led to lower incidence of invasive cancer. In contrast, colon and cervical cancer are generally leads to overtreatment. This Viewpoint summarizes the recommendations from a working group formed to develop a strategy to improve the current approach to cancer screening and prevention.

Periodic screening programs have the potential to identify a reservoir of indolent tumors.[4] However, cancer is still perceived as a diagnosis with lethal consequences if left untreated.

An ideal screening intervention focuses on detection of disease that will ultimately cause harm, that is more likely to be cured if detected early, and for which curative treatments are more effective in early-stage disease. Going forward, the ability to design better screening programs will depend on the ability to better characterize the biology of the disease detected and to use disease dynamics (behavior over time) and molecular diagnostics that determine whether cancer will be aggressive or indolent to avoid overtreatment. Understanding the biology of individual cancers is necessary to optimize early detection programs and tailor treatments accordingly. The following recommendations were made to the National Cancer Institute for consideration and dissemination.

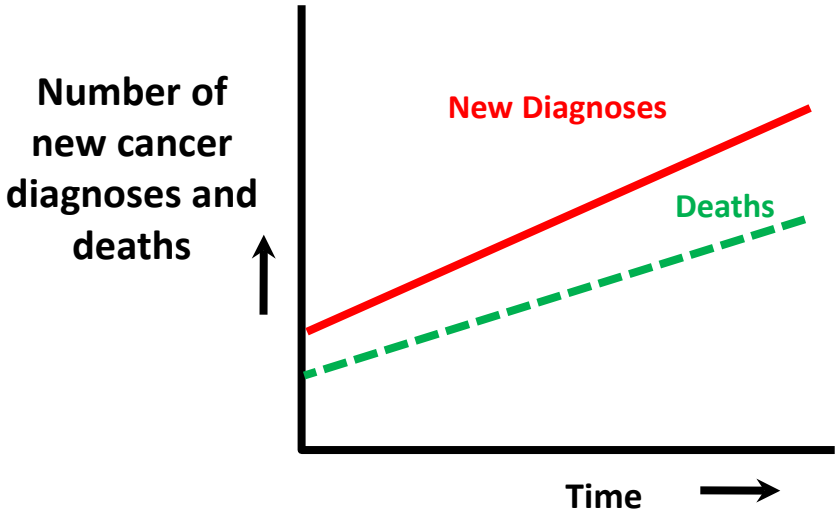
Physicians, patients, and the general public must recognize that overdiagnosis is common and occurs more frequently with cancer screening. Overdiagnosis, or identification of indolent cancer, is common in breast, lung, prostate, and thyroid cancer. Whenever screening is used, the fraction of tumors in this category increases. By acknowledging this consequence of screening, ap-

OVERDIAGNOSIS

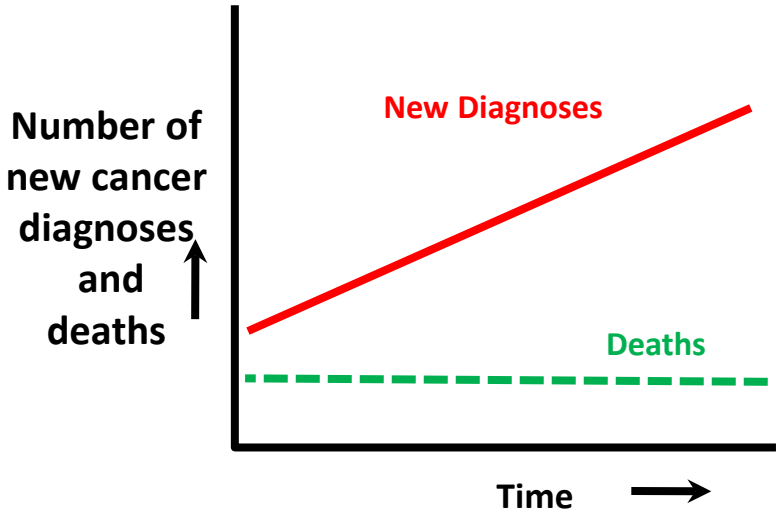
DEFINITION: A SETTING IN WHICH DIAGNOSES INCREASE (OFTEN MARKEDLY) IN A POPULATION THAT HAS A STABLE OR DECLINING RATE OF DEATH FROM THAT DISEASE.

Welch, HG and Black, WC. JNCI 102:605-613 (2010). From a presentation by Barry Kramer, NCI

Patterns of Rapid Increase in Cancer Incidence: True Increase vs. Overdiagnosis



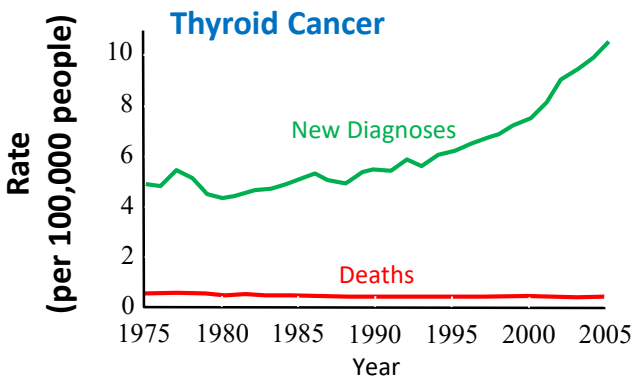
Suggests a true increase in the amount of cancer

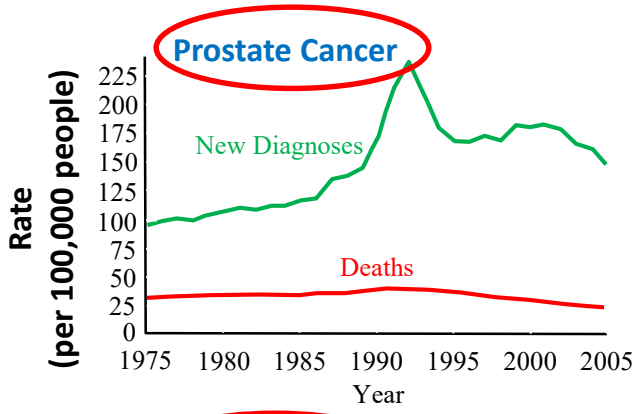


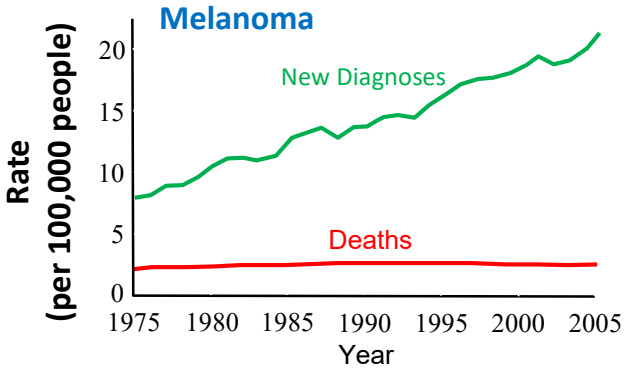
Suggests overdiagnosis of cancer

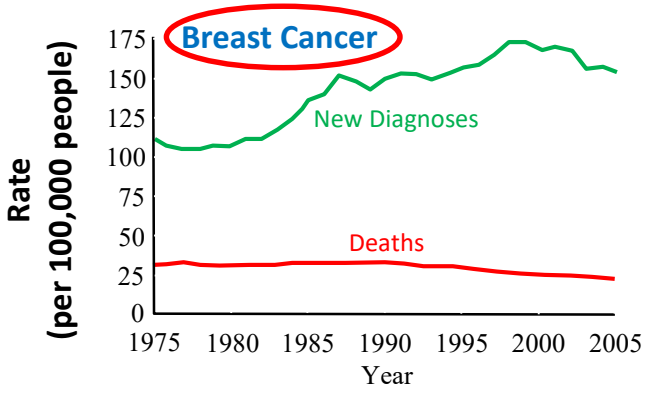
Welch, HG and Black, WC. JNCI 102:605-613 (2010).
From a presentation by Barry Kramer, NCI

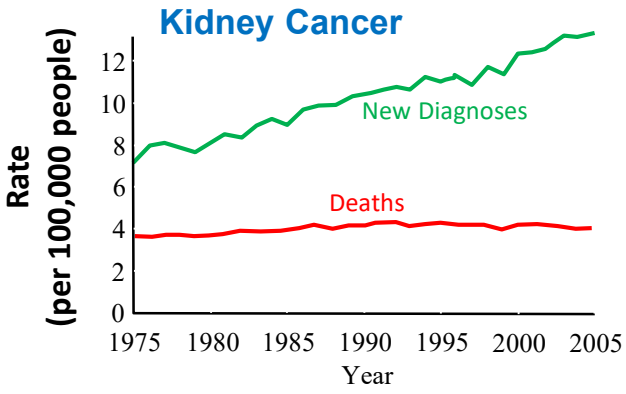
Incidence and Mortality of Five Cancers:
(Surveillance, Epidemiology, and End Results: SEER)





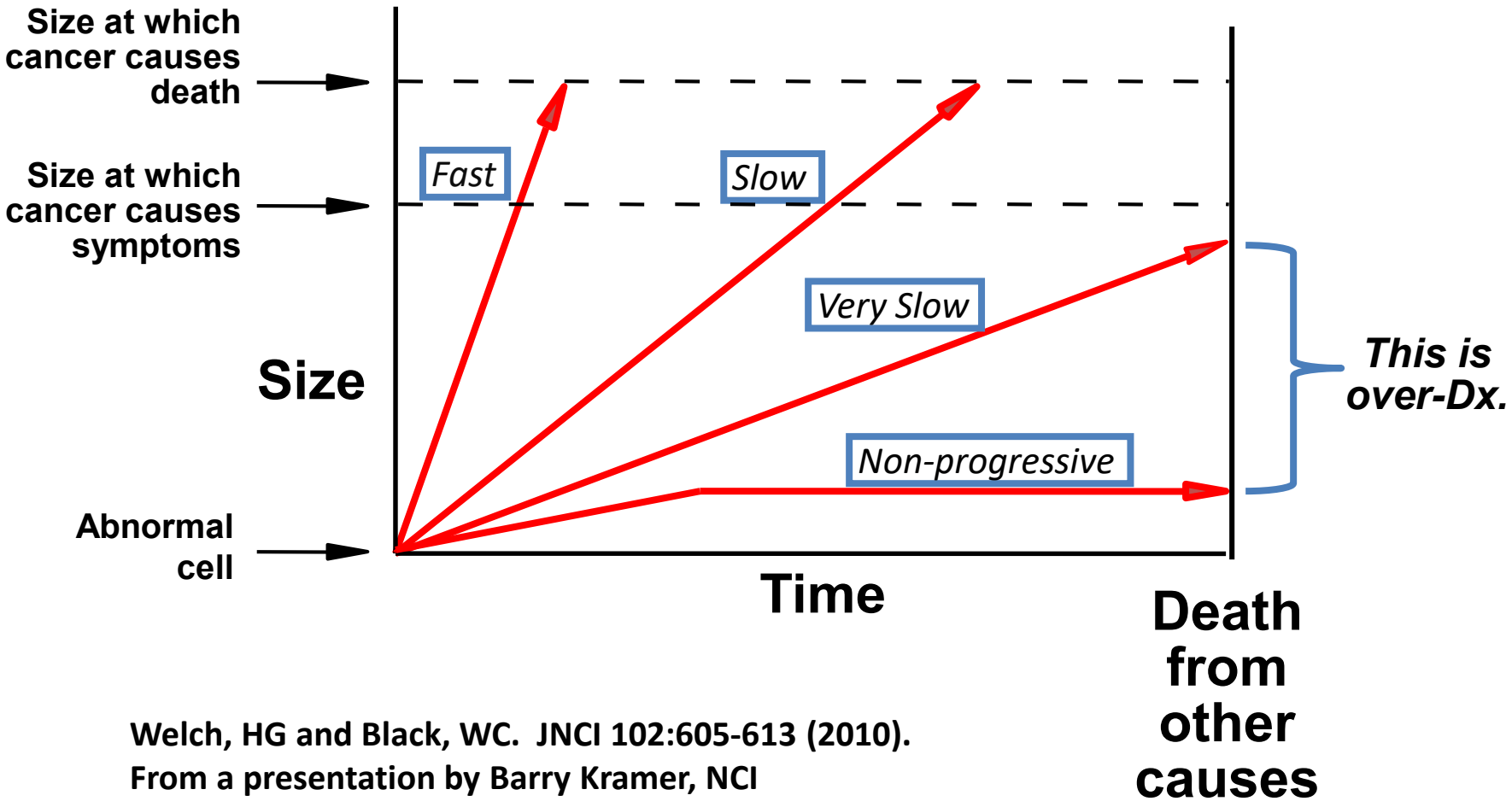






Welch, HG and Black, WC. JNCI 102:605-613 (2010).
From a presentation by Barry Kramer, NCI

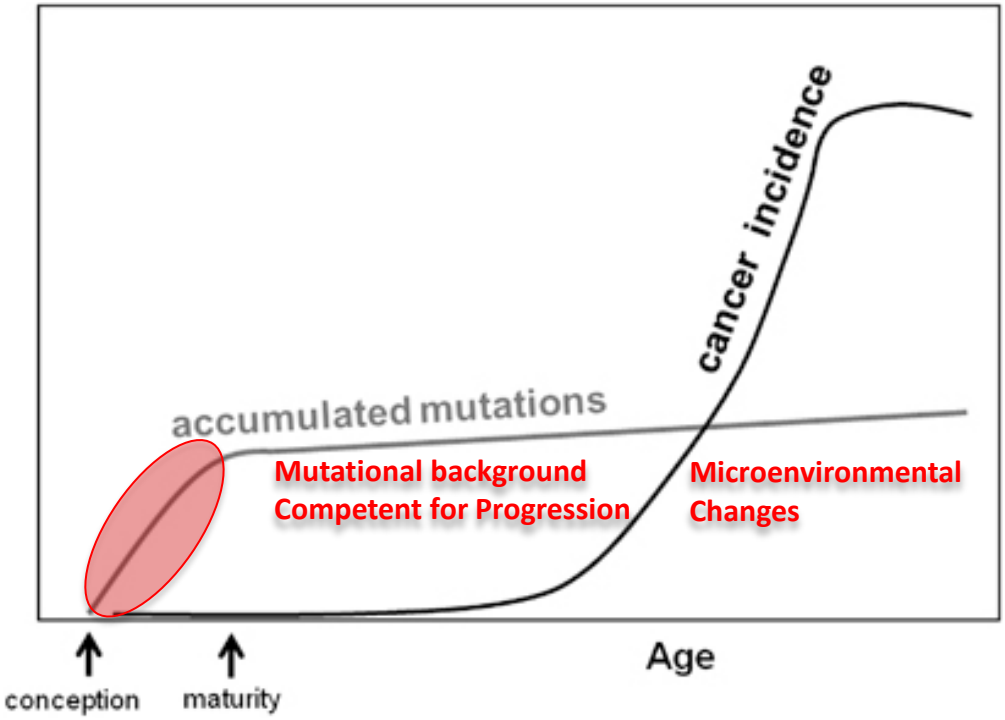
The Heterogeneity of Cancer Progression



Welch, HG and Black, WC. JNCI 102:605-613 (2010).
From a presentation by Barry Kramer, NCI

Challenging the axiom: does the occurrence of oncogenic mutations truly limit cancer development with age?

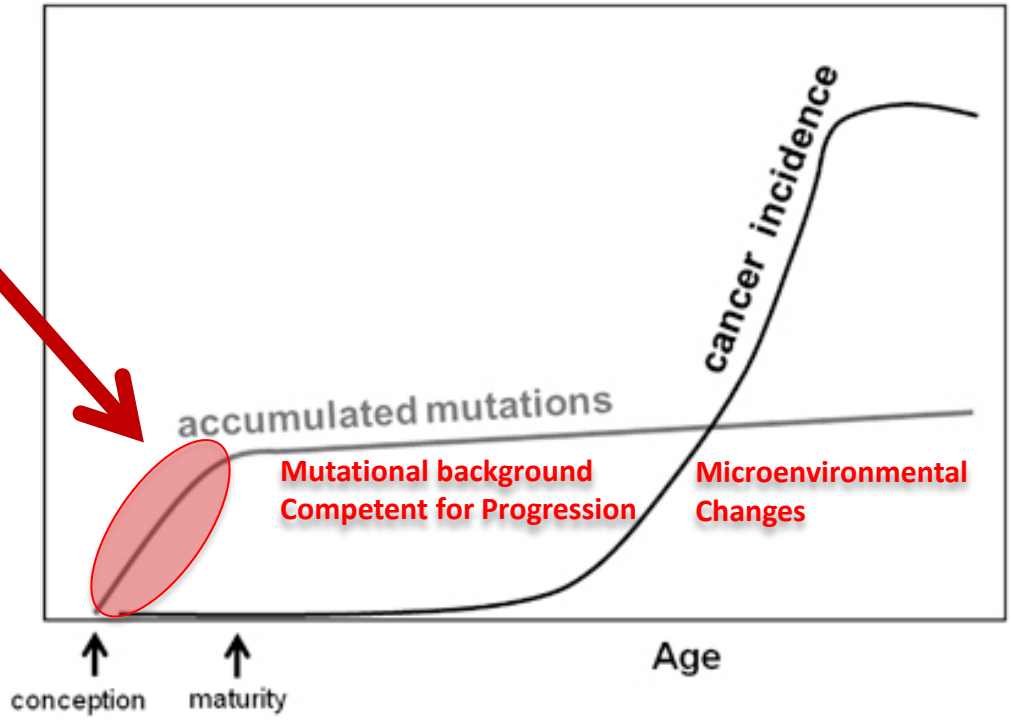
J. DeGregori (Oncogene (advance online publication, 2 July 2012; doi:10.1038/onc.2012.281)



ADAPTIVE ONCOGENESIS

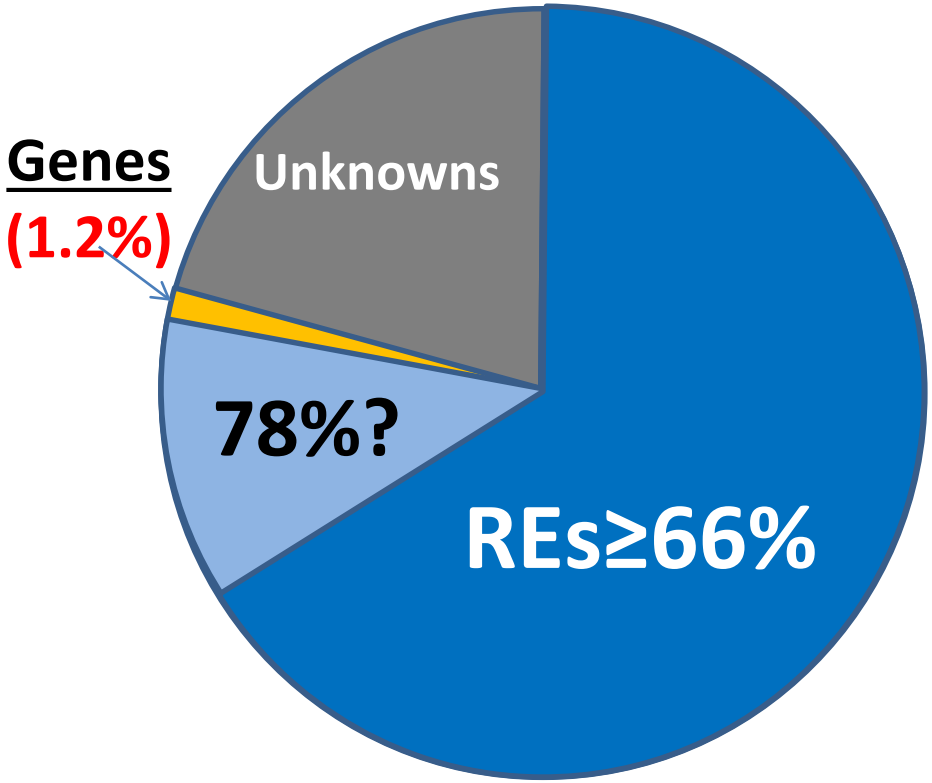
The Window of Susceptibility
Mammary Cancer
Russo, Medina

Virus
Chemical
Radiation
Pregnancy
Transgenesis



ADAPTIVE ONCOGENESIS

Genes vs. Non-gene elements
The New Frontier



The Human Genome Information System

<TREome: at least 45% of non-gene elements>

Data adapted from Koning et al., *PLoS ONE* 7(12):e1002384, 2011

PubMed.gov

non coding rna and tnb

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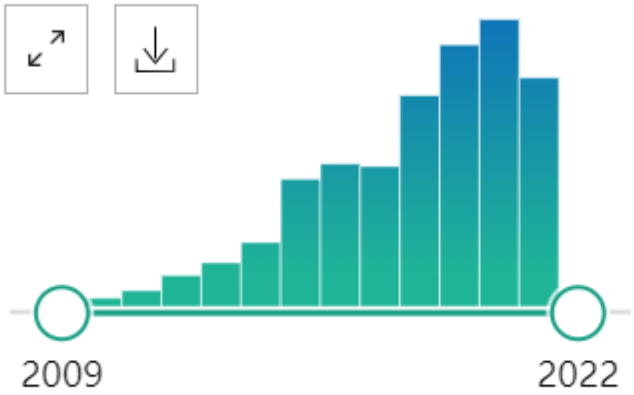
MY NCBI FILTERS

549 results

RESULTS BY YEAR



1 article found by citati

Long non-coding R
Expression analysis

Wang L, et al. J Cell Phys

Filters applied: Free full text

TEXT AVAILABILITY

Circular **RNA**:

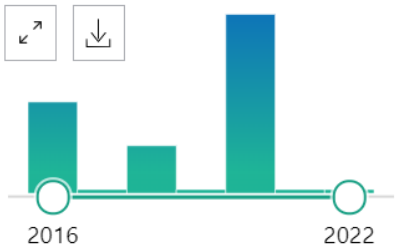
Save | Email | Send to | Sorted by: Publication date | Display options

MY NCBI FILTERS

7 results

Page 1 of 1

RESULTS BY YEAR



TEXT AVAILABILITY

- [ ] Abstract
- [x] Free full text

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Showing results for *repetitive element dna and tnbc*

Your search for *repetitive elements dna and tnbc* retrieved no results

1

Opportunities for Antigen Discovery in Metastatic Breast Cancer.

Sood AK, Nemeth M, Wang J, Wu Y, Gandhi S.

Cite

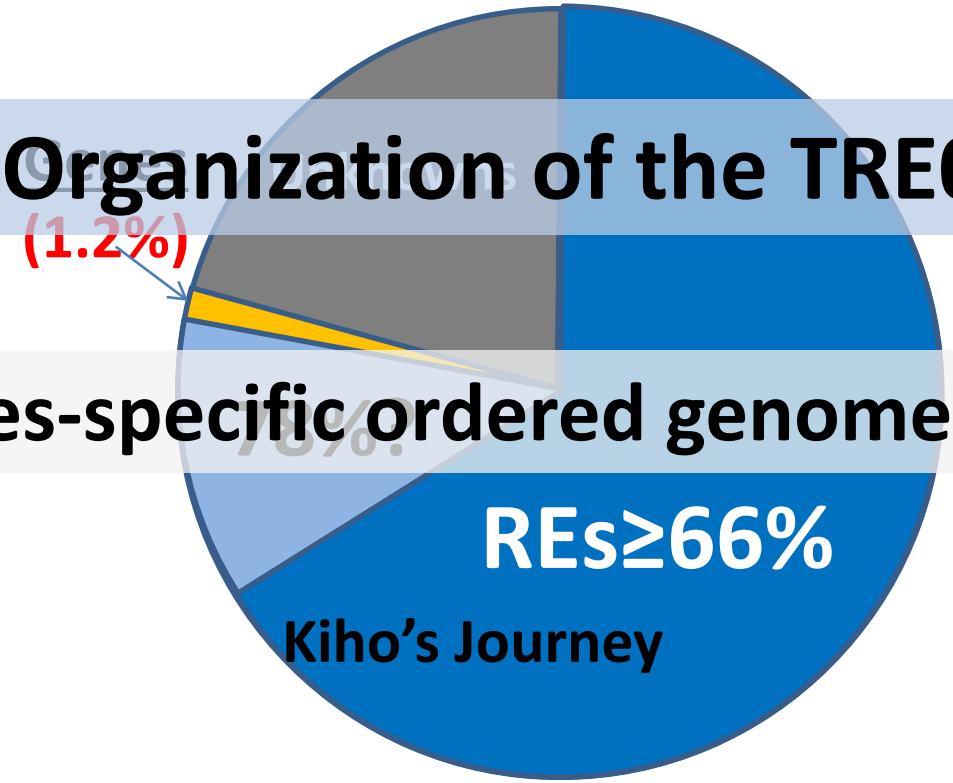
Front Immunol. 2020 Oct 30;11:570049. doi: 10.3389/fimmu.2020.570049. eCollection 2020.

PMID: 33193348 **Free PMC article.**

Share

Immune checkpoint inhibitor-based immunotherapy (ICI) of breast cancer is currently efficacious in a fraction of triple negative breast cancers (**TNBC**) as these cancers generally carry high tumor mutation burden (TMB) and show increased tumor infiltration by CD8(+) T cells. ...

The Organization of the TRE0ME



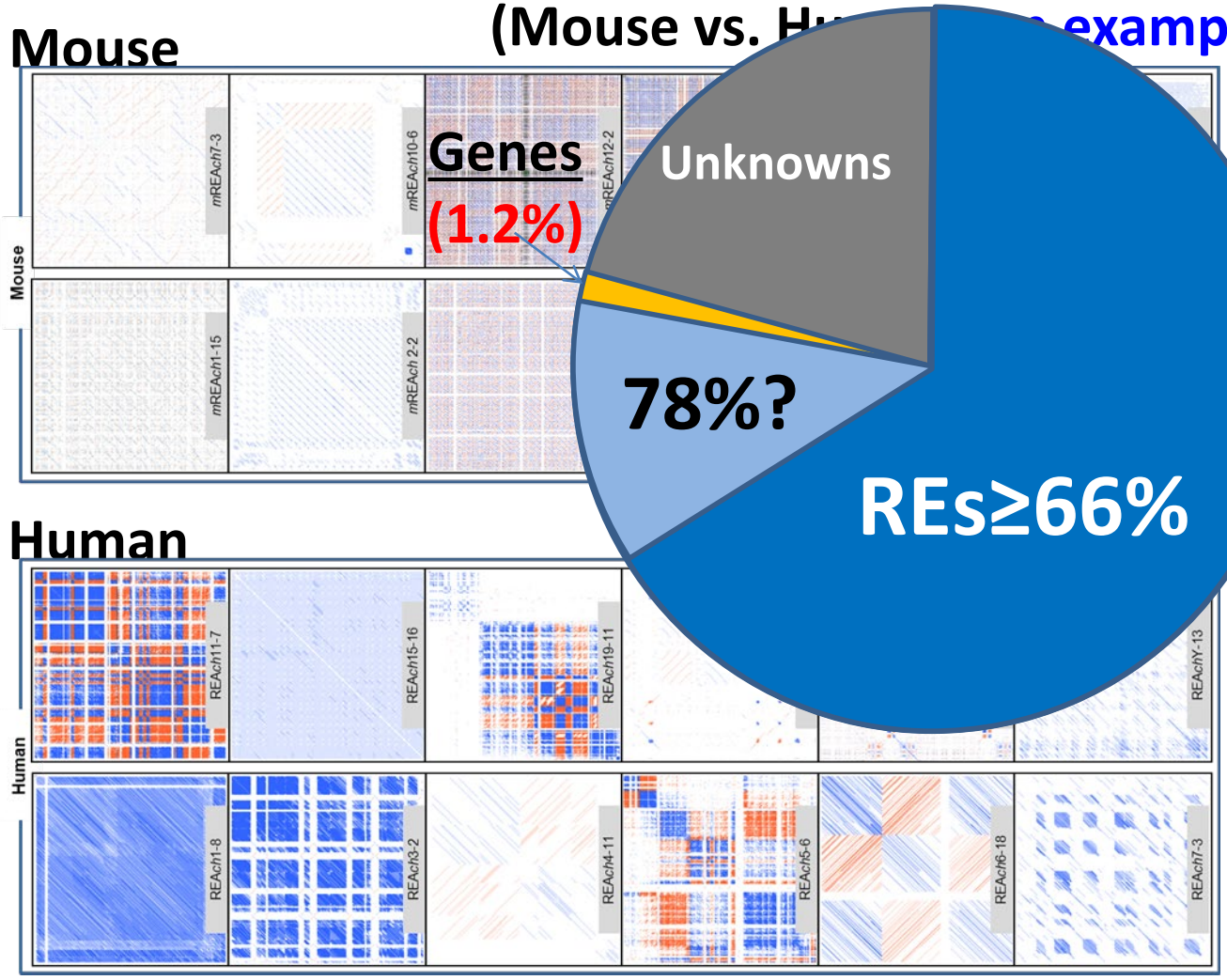
Species-specific ordered genome units

Species-specific genomic RE array maps:
ORGANIZED AND SPECIES SPECIFIC

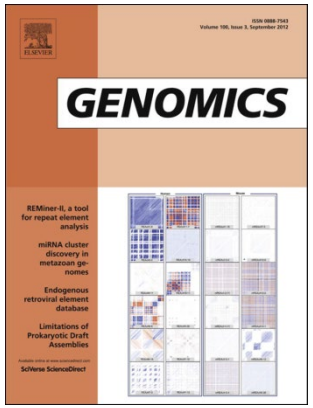
(Mouse vs. Hu[illegible] example)

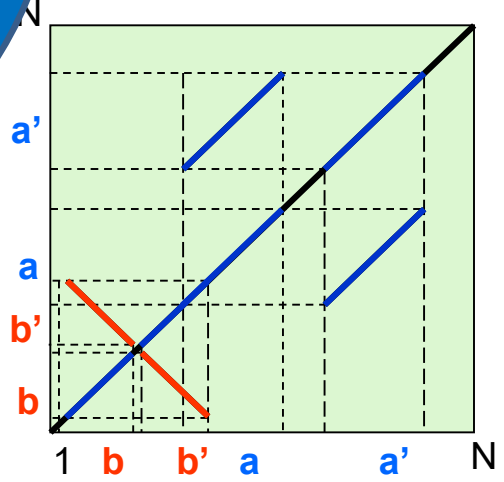
Mouse

Human



Cover Image of ***GENOMICS***
(September, 2012)

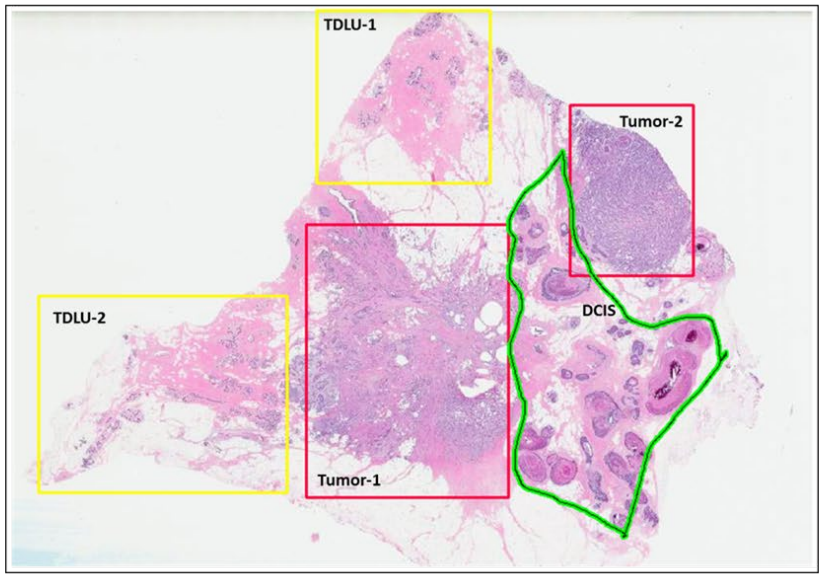


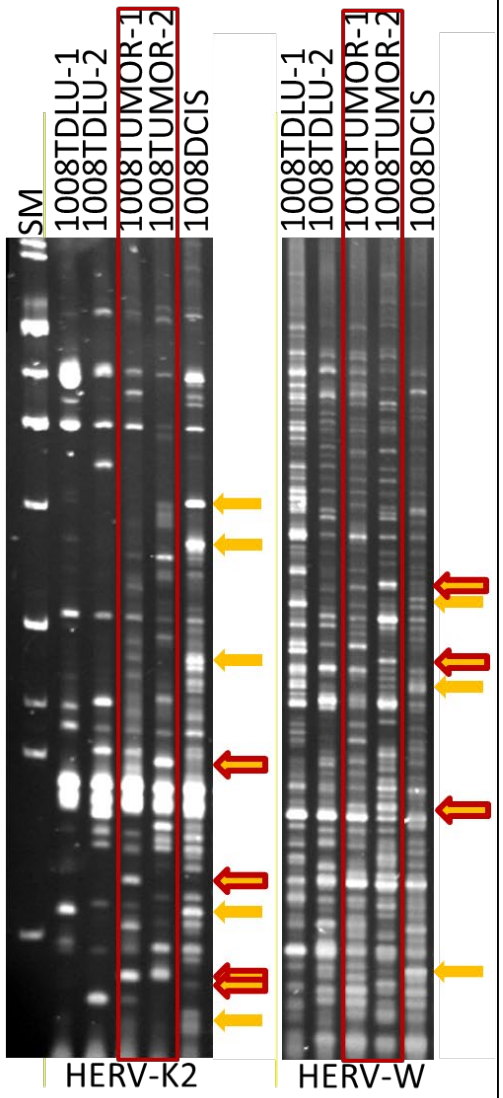


Identification of a HERV-related sequence (from a breast biopsy) **absent in the NIH's reference human genome**

Variable HERV landscape of a breast cancer patient

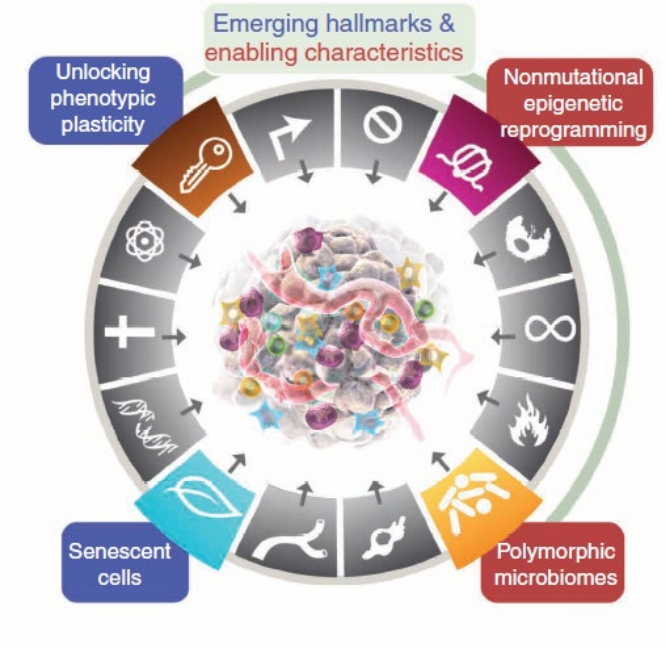
(TDLU-normal vs. Tumor vs. DCIS [ductal carcinoma in situ])



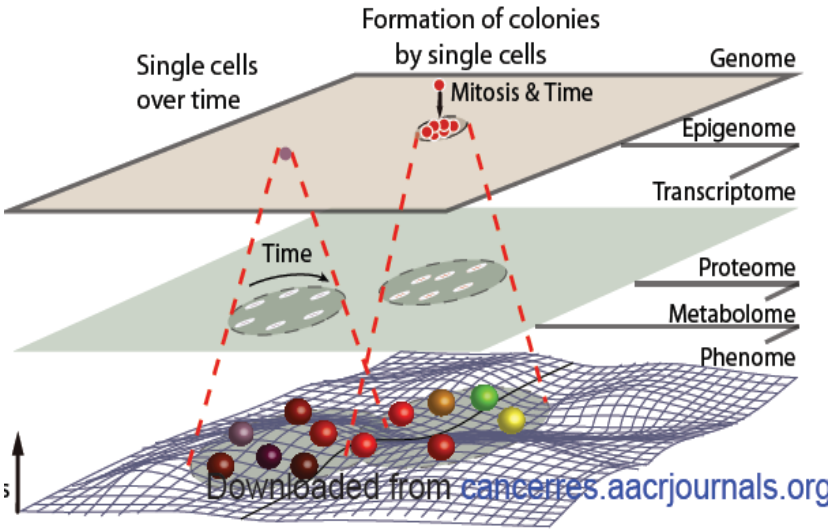


HERV (human endogenous retrovirus); TDLU (terminal ductal lobular unit)

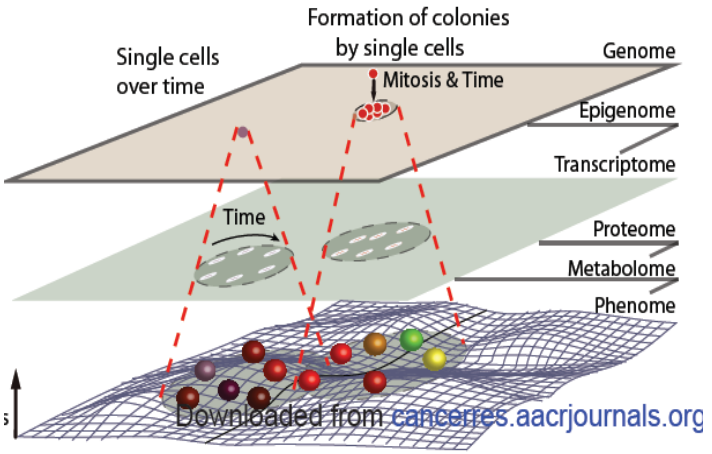
NEOPLASTIC PROGRESSION



Epigenetic Reprogramming



Evolutionary Selection:
eG-P Cone



THE END

Thank You

THE GENOMIC ERA

THE ELEGANT SIR GEM

Progression Agenda

- Invasion
- Metaplasia
- Clonal expansion
- Genetic Background
- Microenvironment
  - Inflammation
  - Immune responses
  - Landing platforms
  - Microbiome

Models of Neoplastic Progression

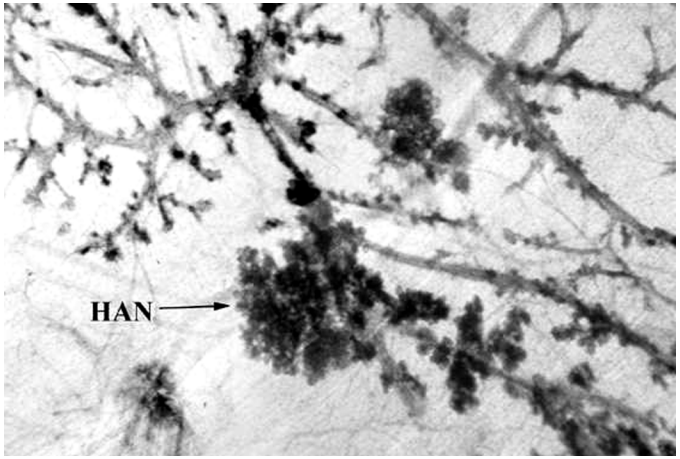
- **Human**: observation, demographics, epidemiology and statistical analysis of heterogeneous populations ***(Guilt-by-association)***.
  - Experimental: tissue culture and xenografts.

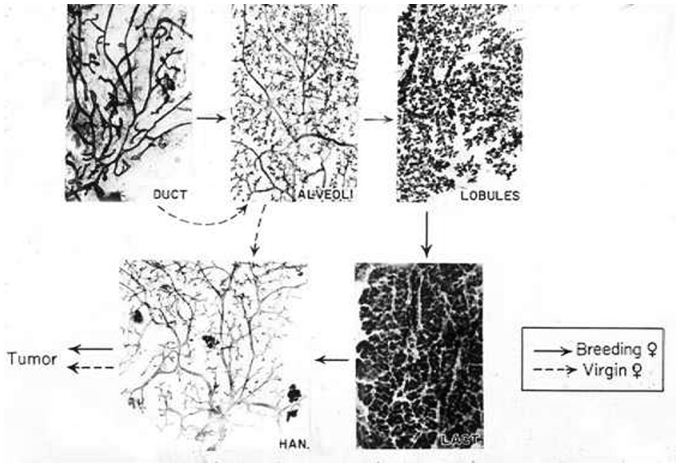
- **Mouse**: observation, demographics, genetic engineering, and statistical analysis of homogeneous populations.
  - Experimental: Test by transplantation into syngeneic host and orthotopic sites. (***Test-by-transplantation***).

Jensen, CO. Cent. f. Bakt. 1903,34:28,122

The ***Biology*** of Preneoplasia

Dr. K.B. DeOme
CRGL, UCBerkeley





Two Step Transformation:

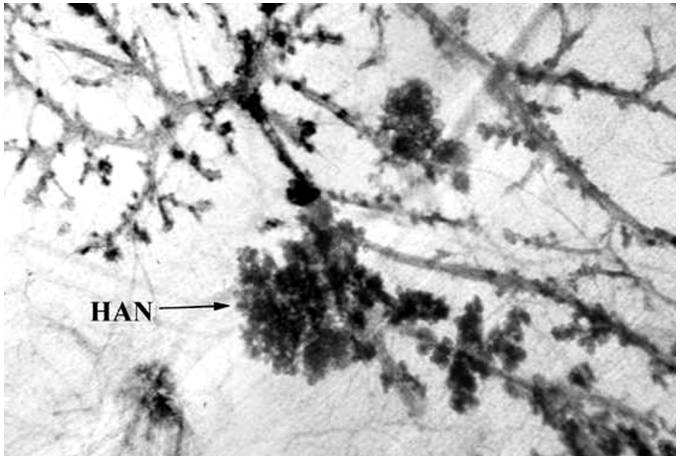
Nodulogenesis Tumorigenesis

Normal → HAN → Tumor

(Described in 1958)

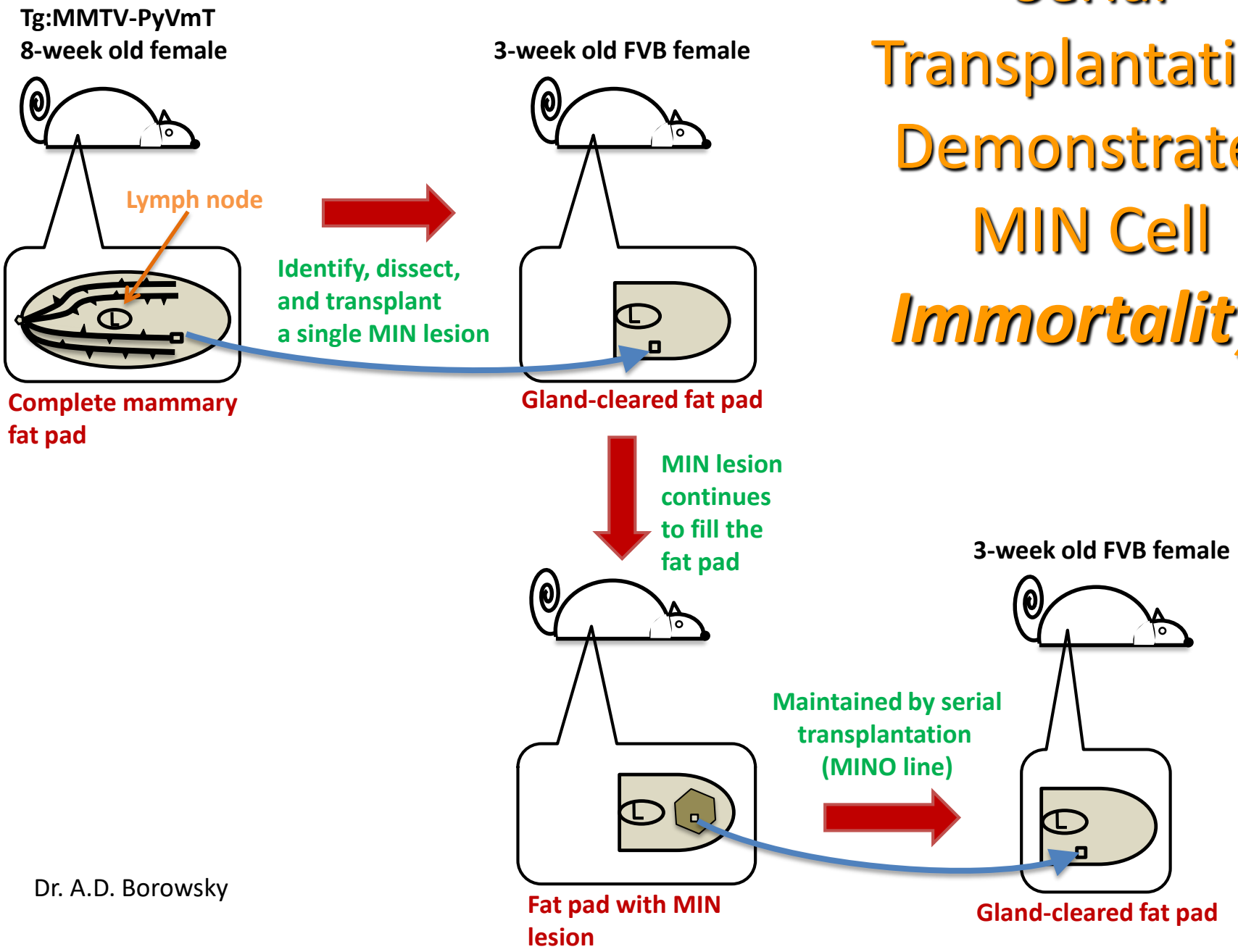
Studying the ***Biology*** of Preneoplasia

Dr. K.B. DeOme
Developed "Test-by-transplantation"



1. **Identification**
2. **Isolation**
3. **Transplantation**
4. **Observation**
5. **Repetition**

Serial Transplantation Demonstrates MIN Cell *Immortality*:



Dr. A.D. Borowsky

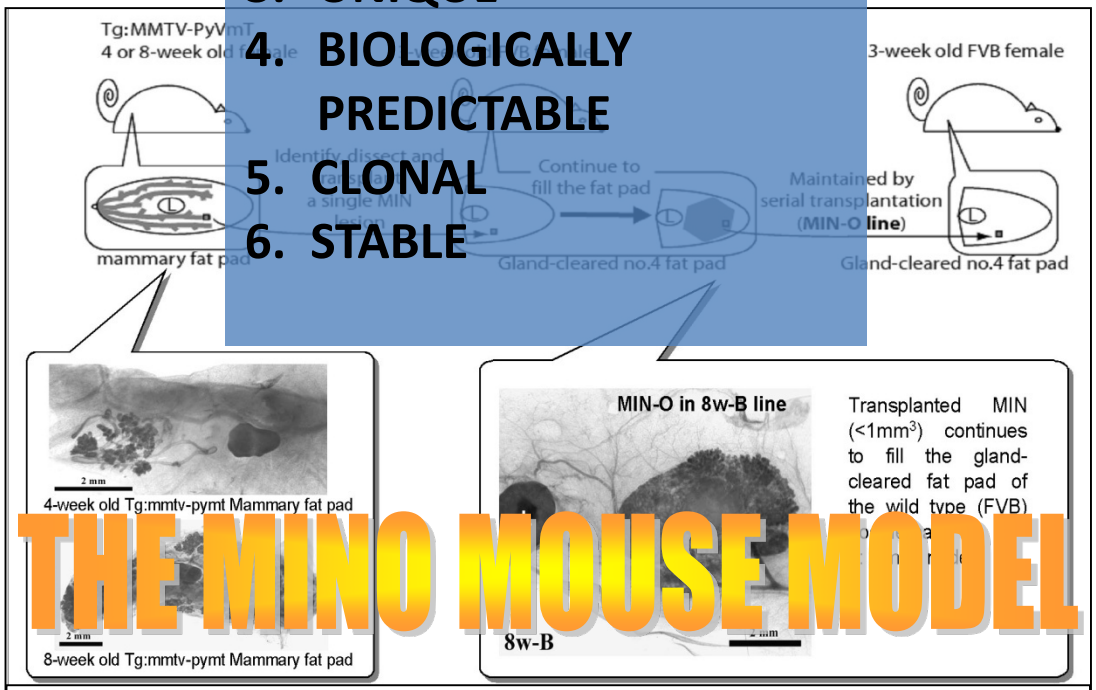
Serial Transplantation Confirms Progression of Precancer to Cancer

Tissue	Subcutaneous	Cleared Fat Pad	Serially Transplantable?
Normal	No growth	Normal Mammary Structures	5-6X
Hyperplastic	No growth	Non-invasive hyperplastic outgrowth	Indefinitely
Hyperplastic/ Premalignant (MIN)	No growth	Non-invasive hyperplastic outgrowth/ Tumors develop within	Indefinitely
Malignant	Growth (Tumor)	Tumor	Indefinitely

CANCER BIOLOGY IN ANIMALS: GENETICALLY ENGINEERED MICE

PRECANCER Essential Facts:

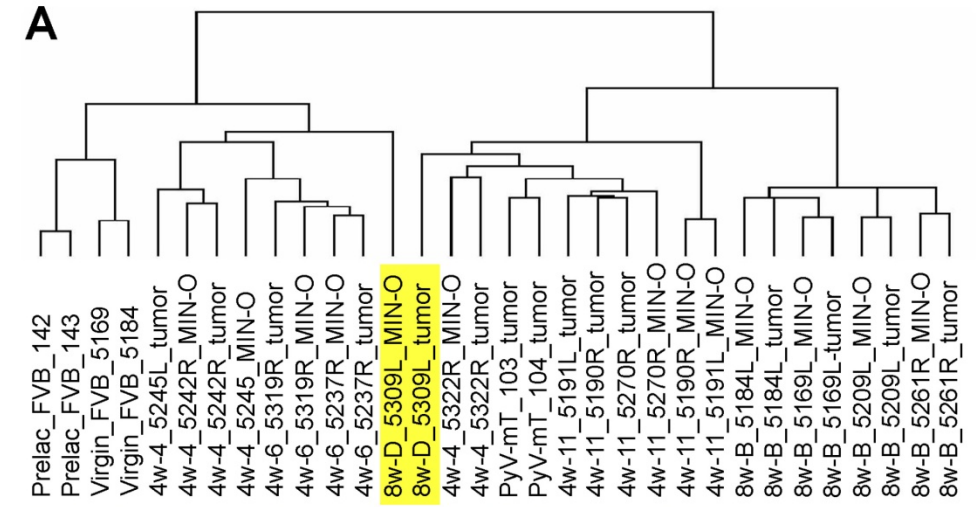
1. SITE RESTRICTED
2. IMMORTAL
3. UNIQUE
4. BIOLOGICALLY PREDICTABLE
5. CLONAL
6. STABLE

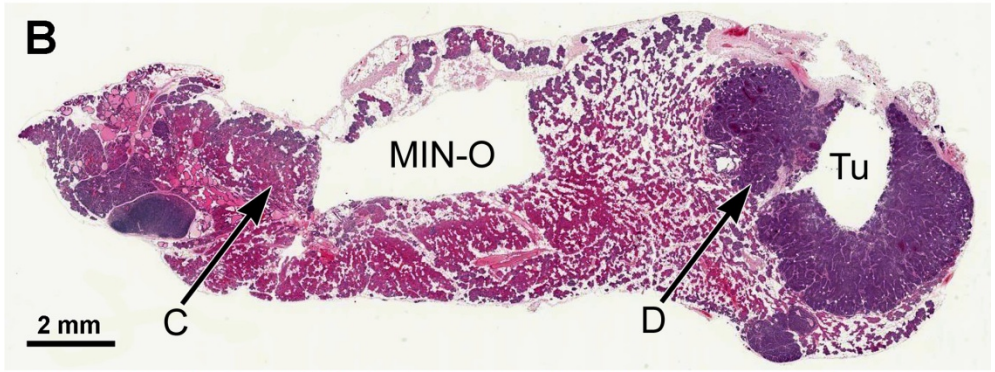


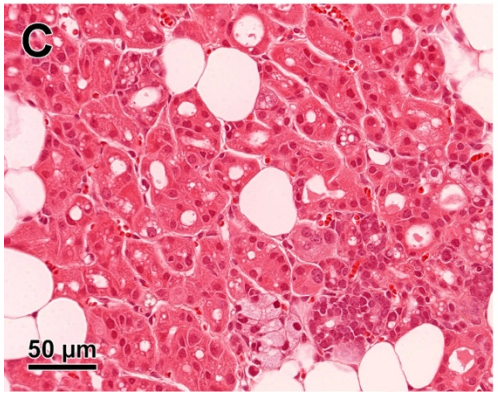
THE MINO MOUSE MODEL

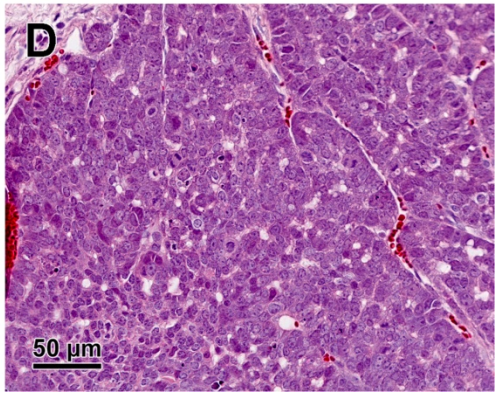
Figure 1. Diagram of MIN-O derivation and maintainance. Tissues derived from Tg(*Py-mT*) mice are maintained by serial transplantation into the gland cleared fat pad. Representative morphology shown.

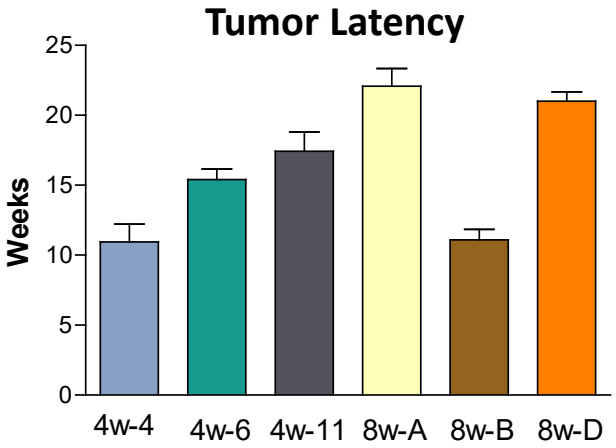
EXPRESSION MICROARRAY



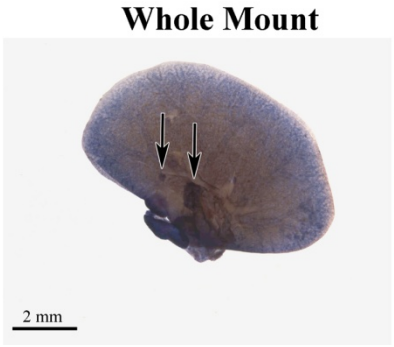


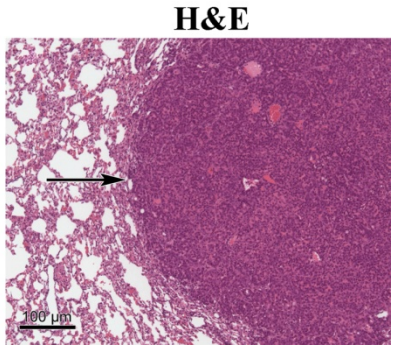






Hierarchical clustering of expression and latency suggests the MINOs encode the outcome.

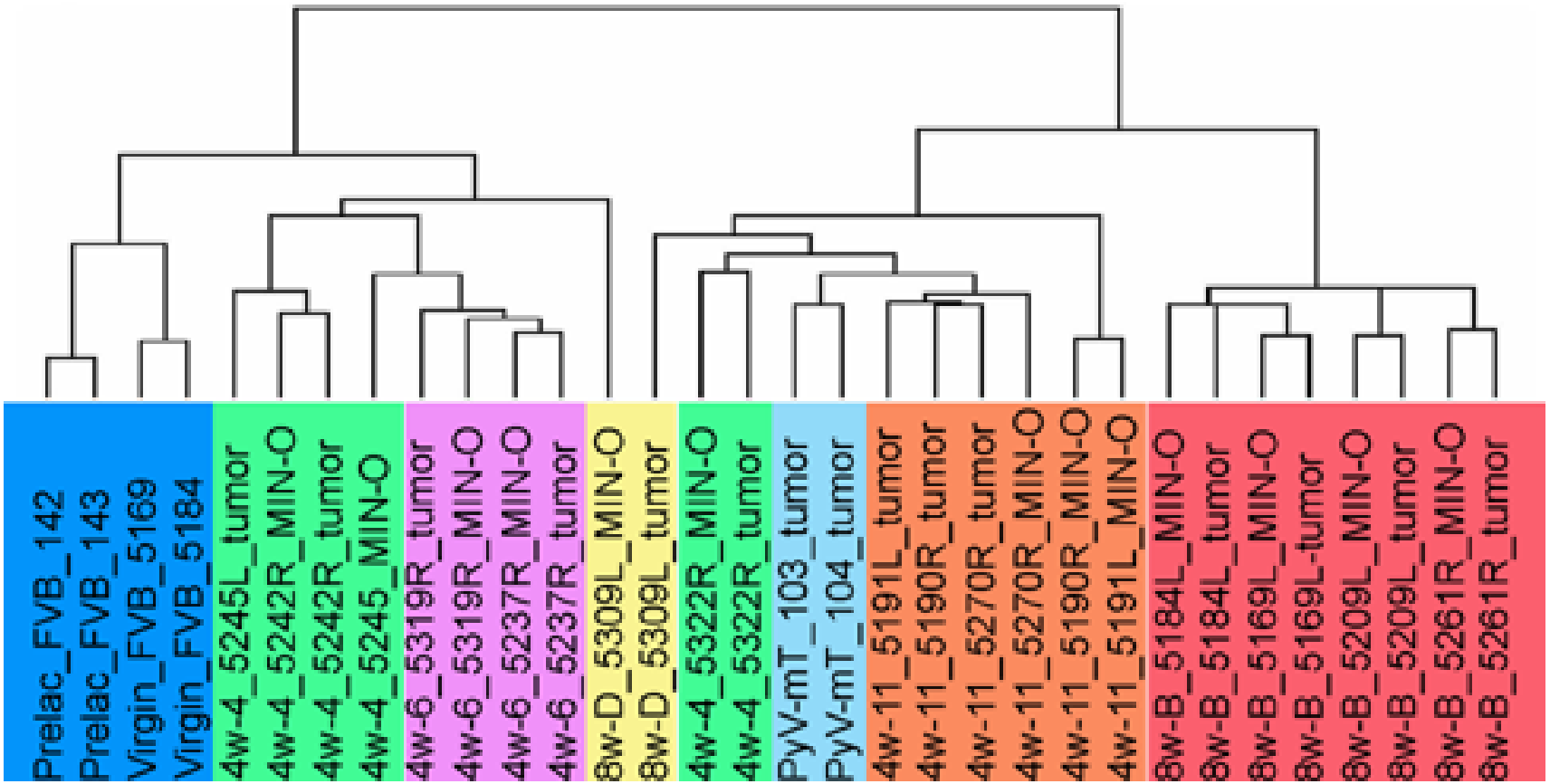




Metastases in lungs of mice with tumors from MINO lines 8w-A, 8w-D, 8w-11

Maglione *et al,* Mol. Ca Ther PMID: 15299077 2003

Expression Profile Cluster Analysis: *Order* in *Heterogeneity*



MIN-O/TUMOR PAIRS

Research

Mamma

stem ce

Patrizia Dar

and Alexan

[1]Center for Com

California 9561

[2]UCSF Departm

Correspondin

Received: Se

Breast Cancer R

Access

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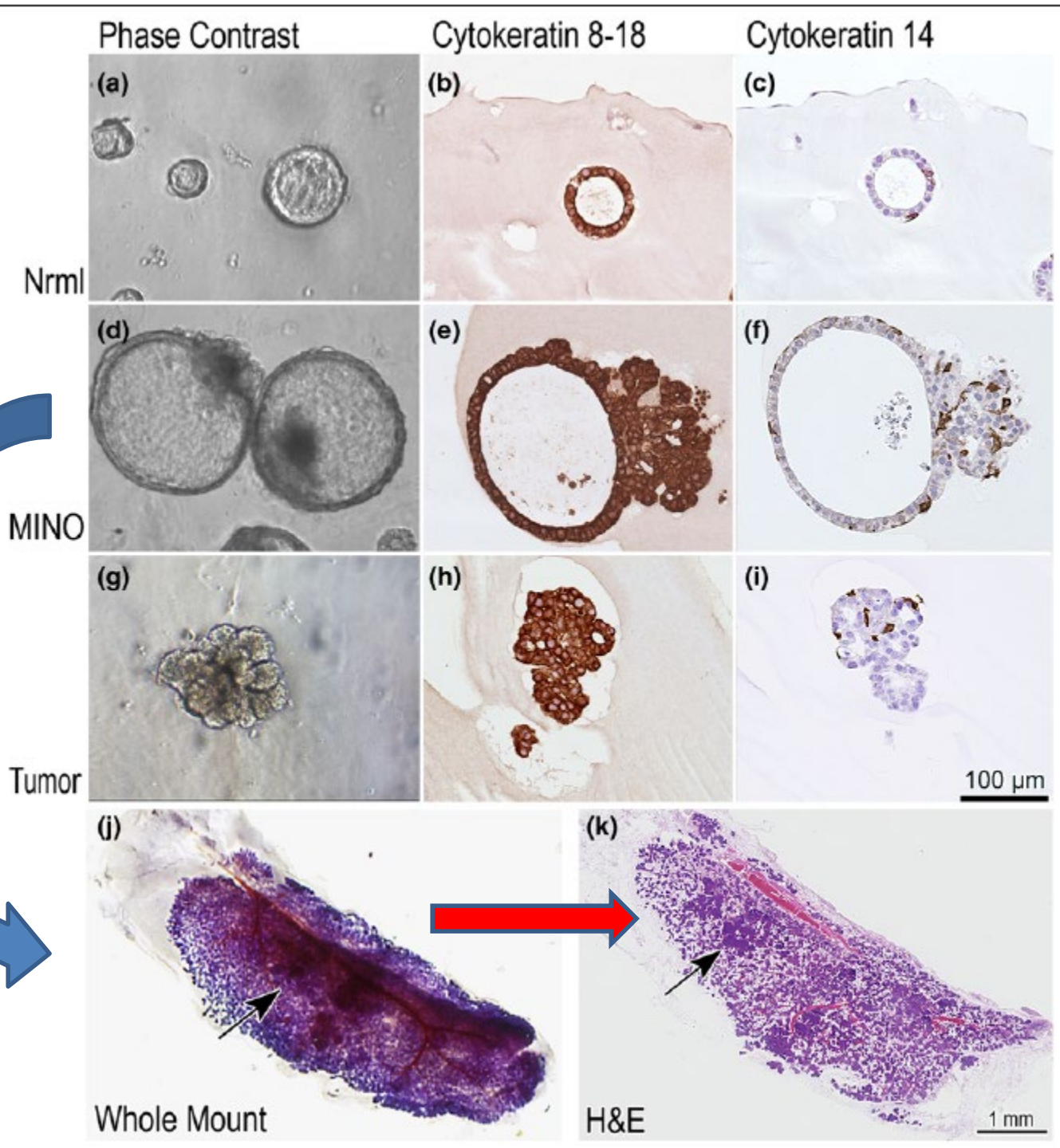
D Cardiff[1]

Drive, Davis,

A

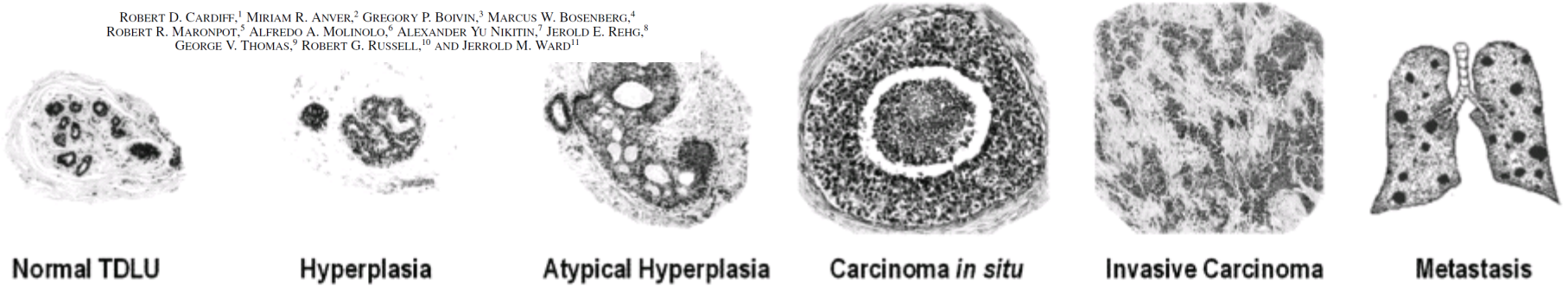
: 3 Jun 2008

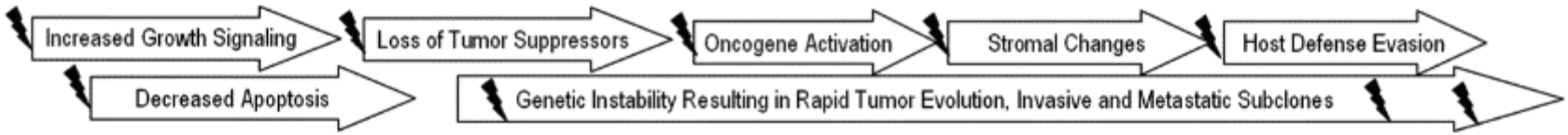


ISSN: 0192-6233 print / 1533-1601 online
DOI: 10.1080/01926230600930129

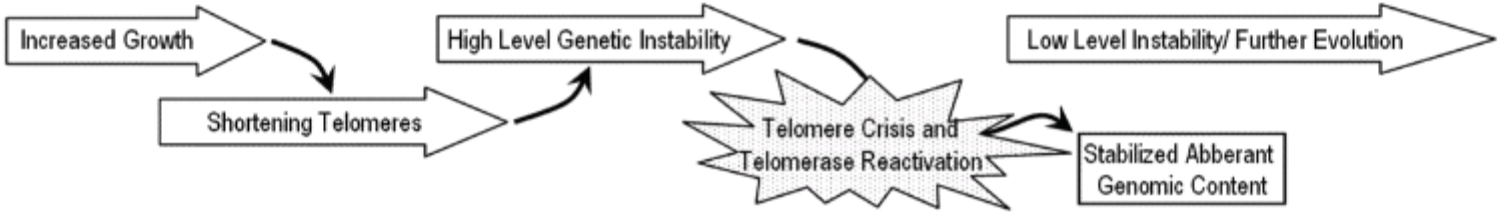
Precancer in Mice: Animal Models Used to Understand, Prevent, and Treat Human Precancers

Robert D. Cardiff,[1] Miriam R. Anver,[2] Gregory P. Boivin,[3] Marcus W. Bosenberg,[4] Robert R. Maronpot,[5] Alfredo A. Molinolo,[6] Alexander Yu Nikitin,[7] Jerold E. Rehg,[8] George V. Thomas,[9] Robert G. Russell,[10] and Jerrold M. Ward[11]





A. Step-wise Sequential Acquisition Model



B. Telomere "Crisis" Model

C. Imprinted Stem Cell Model

Progression Agenda

- Invasion
- Metaplasia
- Clonal expansion
- Genetic Background
- Microenvironment
  - Inflammation
  - Immune responses
  - Landing platforms
  - Microbiome

THE GENOMIC ERA

(I am also an Experimentalist)

THE ELEGANT SIR GEM

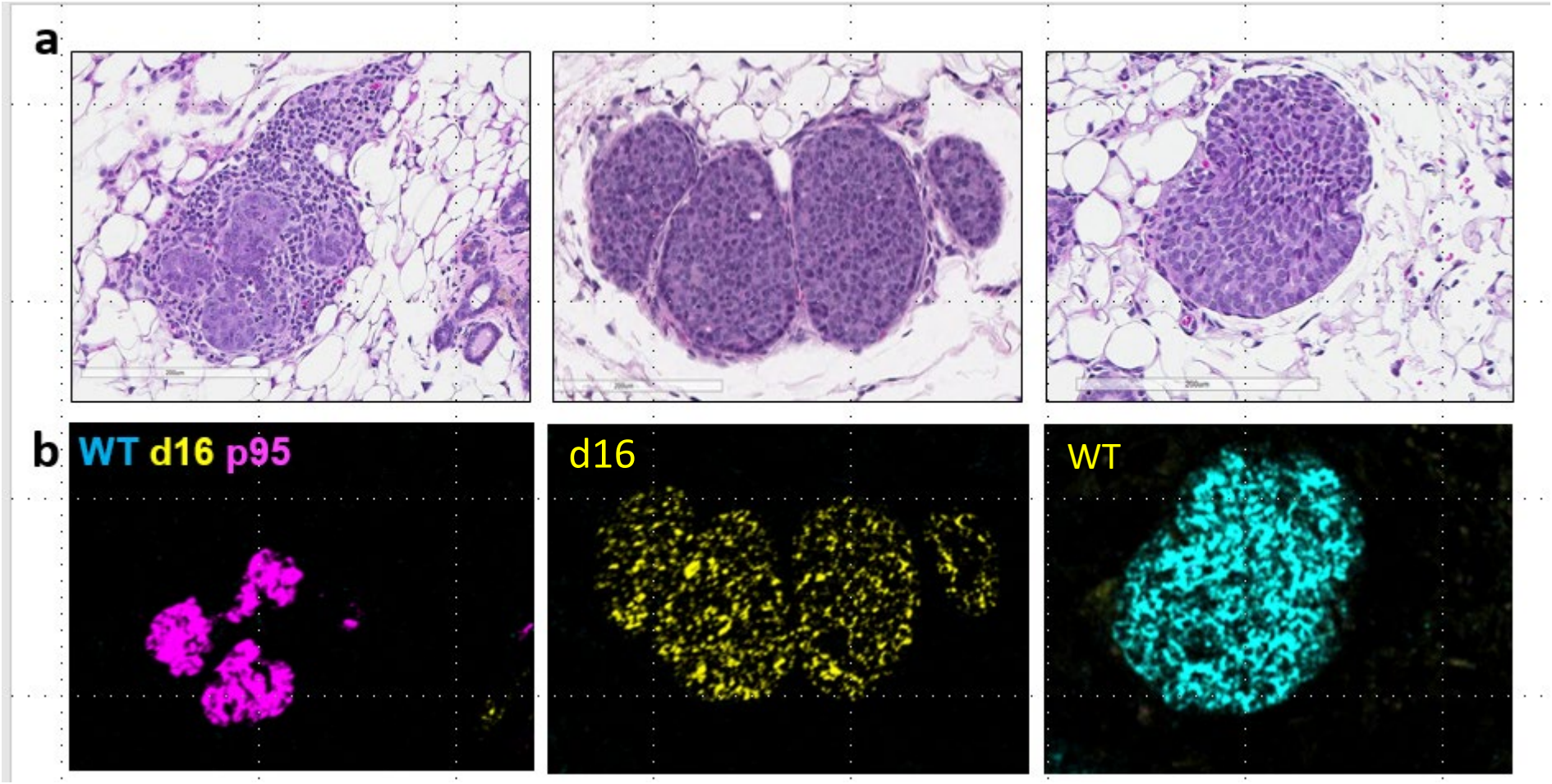
Models of Neoplastic Progression

- **Human**: observation, demographics, epidemiology, AI, and statistical analysis of heterogeneous populations ***(Guilt-by-association)***.
  - Experimental: tissue culture and xenografts.

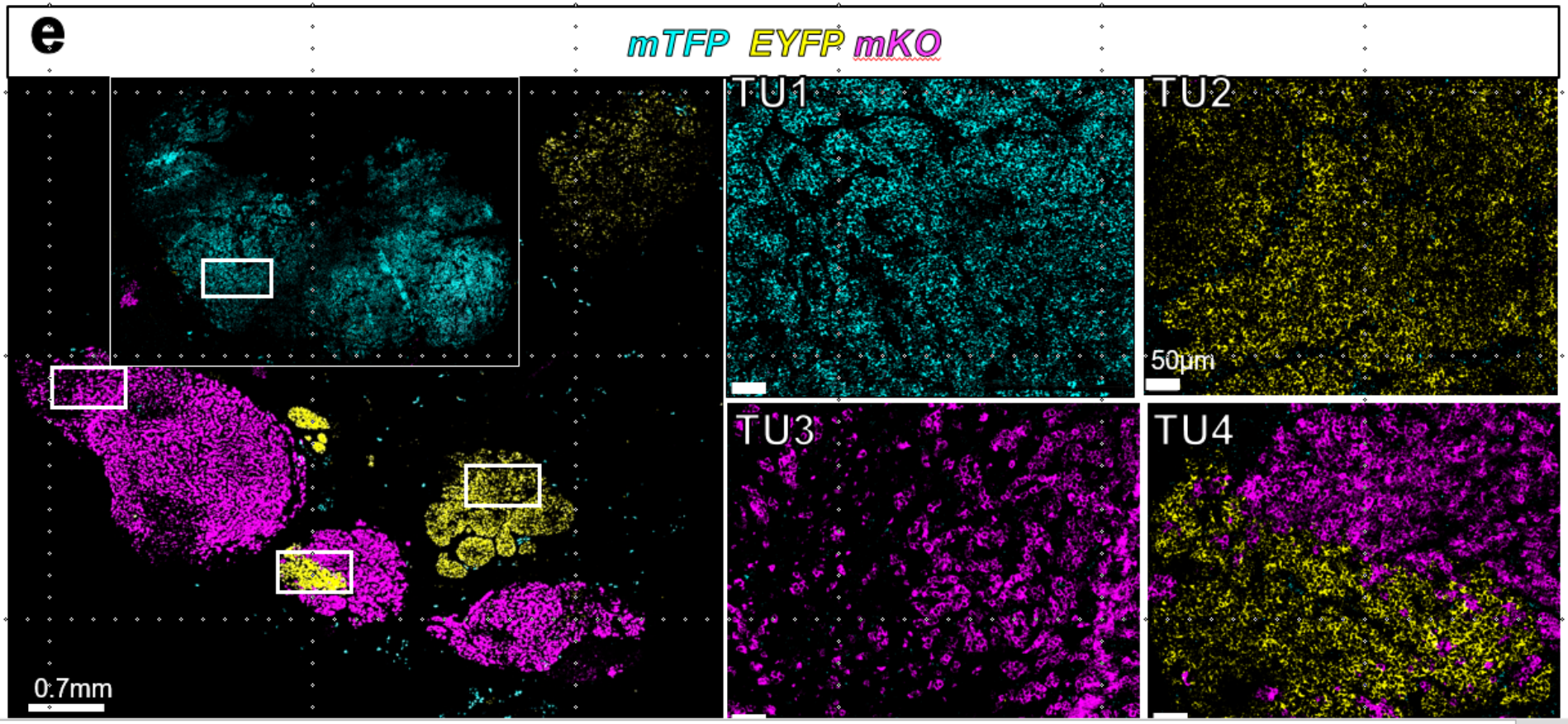
- **Mouse**: observation, demographics, genetic engineering, and statistical analysis of homogeneous populations.
  - Experimental: Test by transplantation into syngeneic host and orthotopic sites. (***Test-by-transplantation***).

Jensen, CO. Cent. f. Bakt. 1903,34:28,122

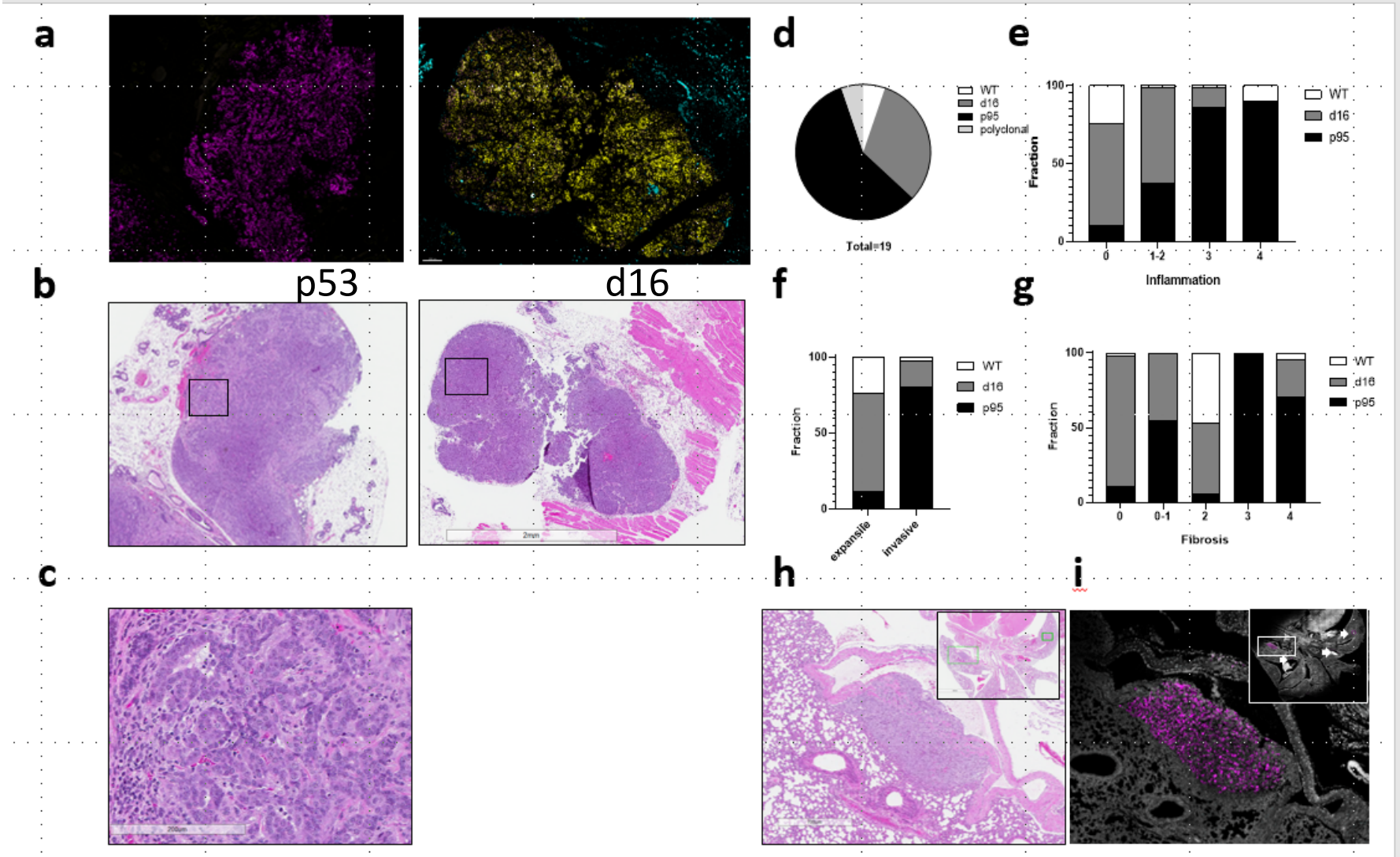
HER-2 CRAINBOW
ONE MOUSE-THREE **MIN** GENOTYPES

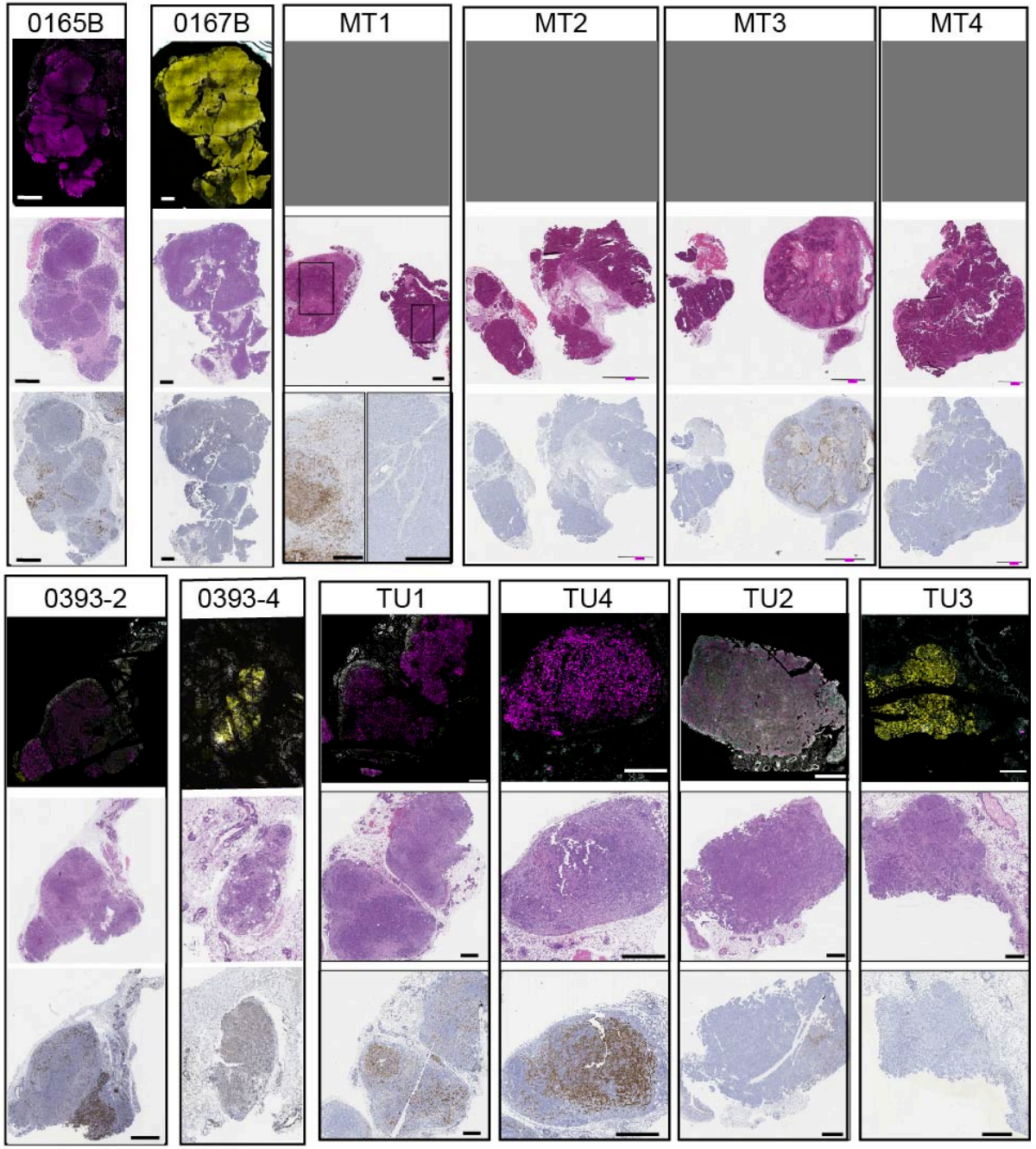


HER-2 CRAINBOW
ONE MOUSE-THREE **TUMOR** GENOTYPES



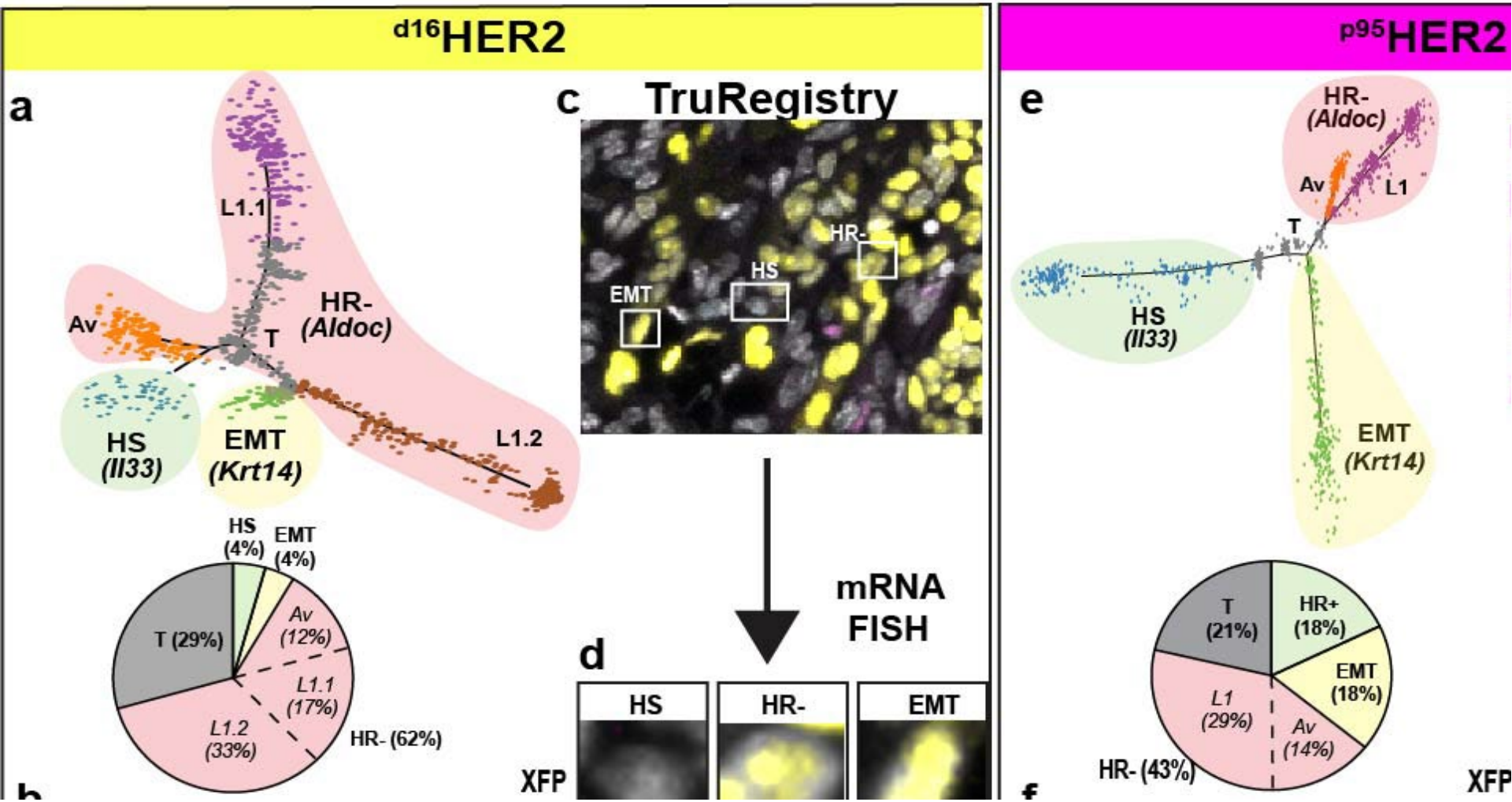
HER-2 CRAINBOW
ONE MOUSE-ONE METASTATIC **TUMOR** PHENOTYPE



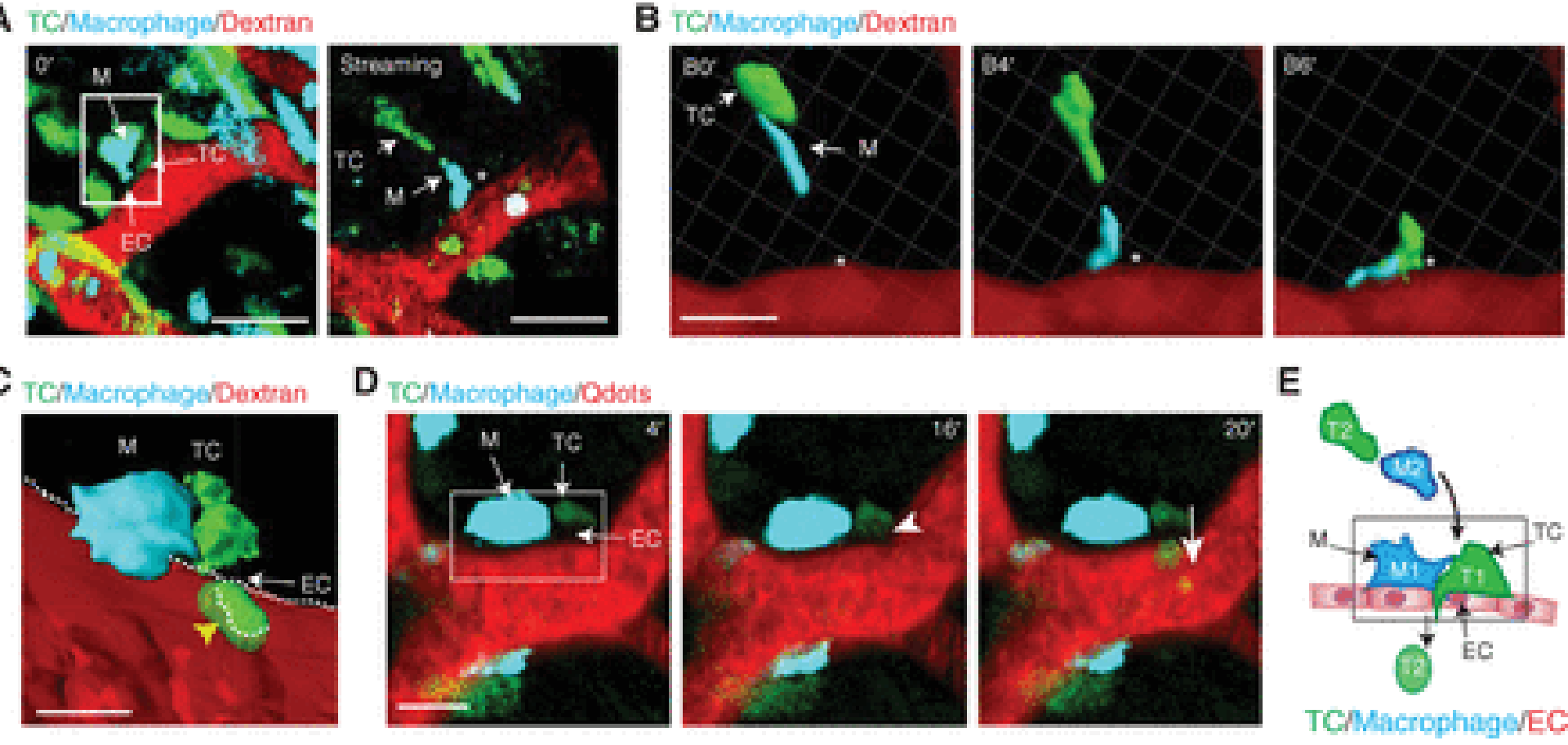


Extended Data 4. MaXFISH coregistry of sequenced tumors. A portion of tumors used for scRNAseq were MaXFISH coregistered (top) with H&E (middle) and IHC for

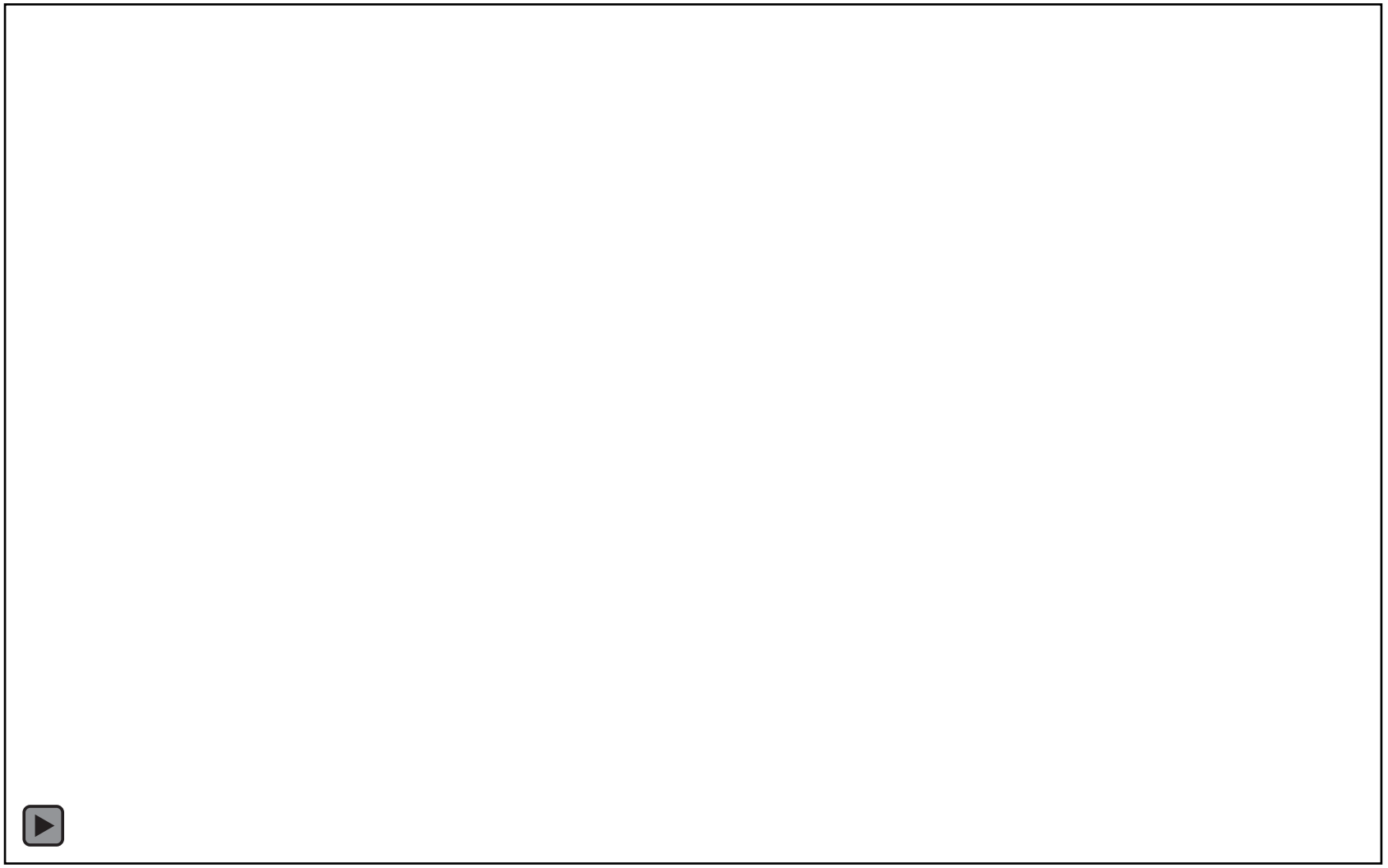
Figure 6


d16HER2
a
L1.1
HR-
(Aldoc)
Av
T
HS
(Il33)
EMT
(Krt14)
L1.2
HS (4%)
EMT (4%)
Av (12%)
T (29%)
L1.1 (17%)
L1.2 (33%)
HR- (62%)
b
c TruRegistry
HR-
HS
EMT
mRNA FISH
d
HS
HR-
EMT
XFP
p95HER2
e
HR- (Aldoc)
Av
L1
T
HS (Il33)
EMT (Krt14)
T (21%)
HR+ (18%)
EMT (18%)
L1 (29%)
Av (14%)
HR- (43%)
f
XFP

Macrophages escort tumor cells to blood vessels Condeelis(In Vitro)



Three dimensionally reconstructing HER2+ cancer progression- 16 weeks old with HER2+ MIN



Magenta= p95 Her2 nuclei Green=KRT 14 cytoplasm

Neoplastic “Progression”

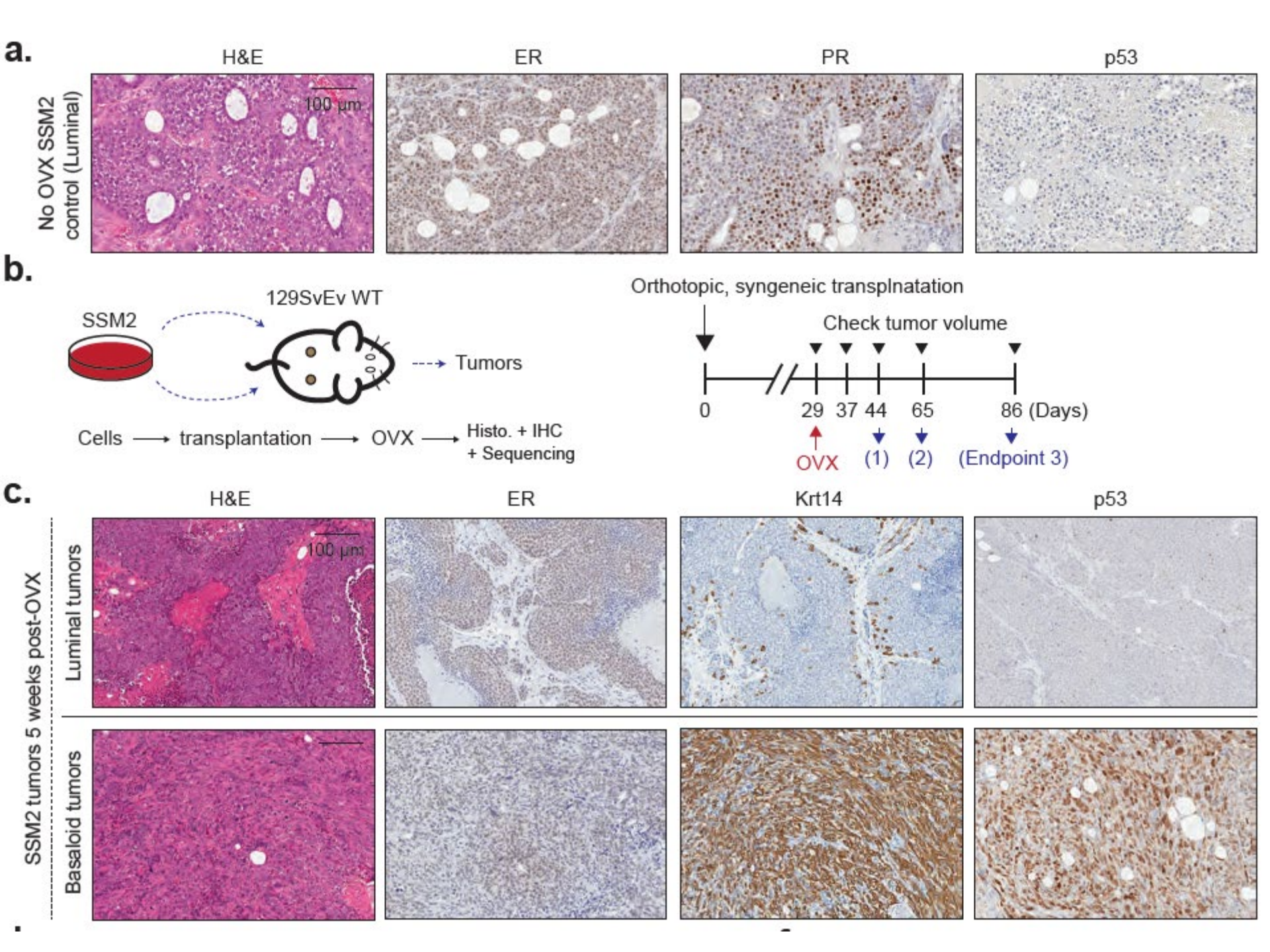
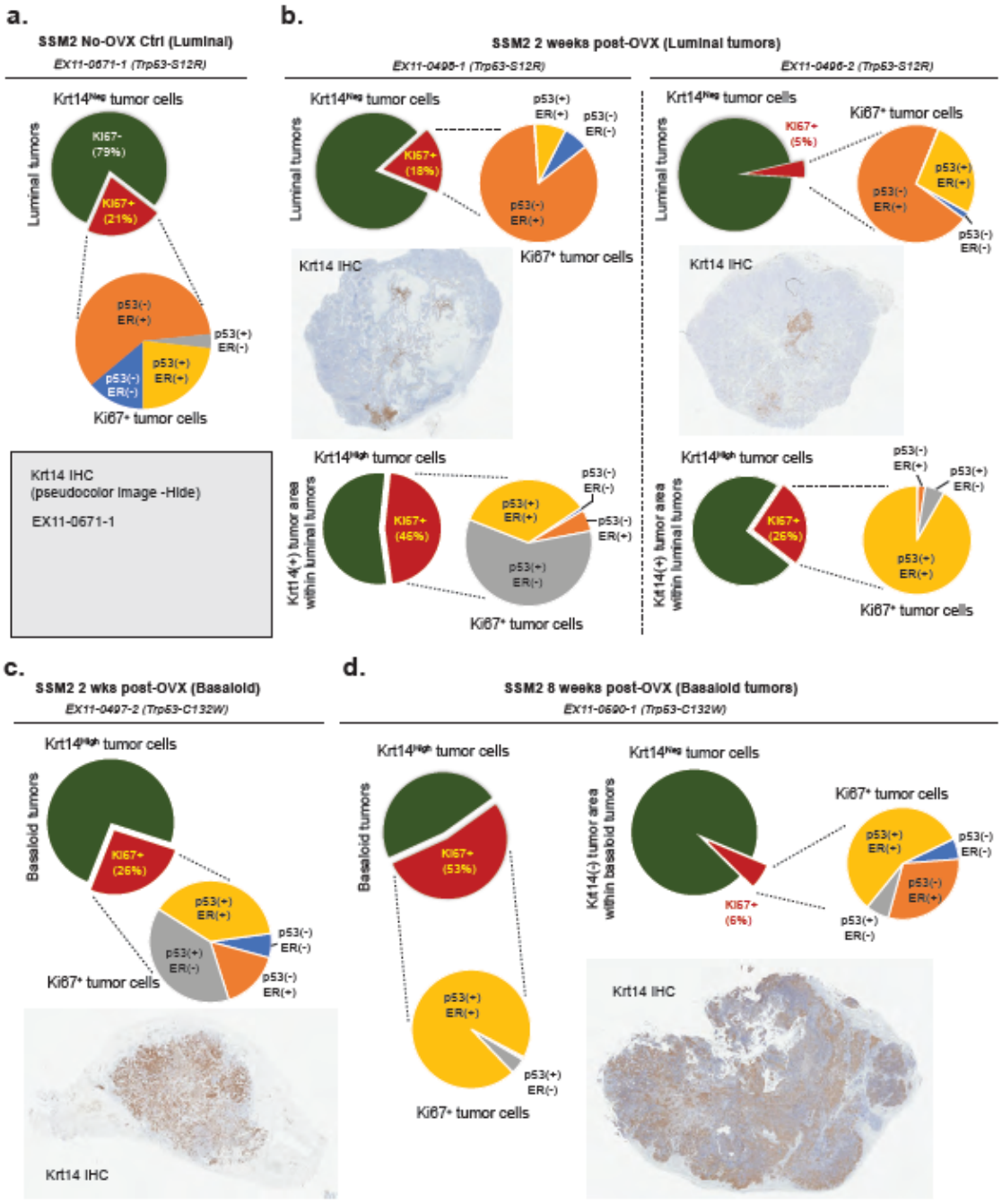

a.
H&E
ER
PR
p53
No OVX SSM2 control (Luminal)
100 µm
b.
SSM2
129SvEv WT
Tumors
Cells
transplantation
OVX
Histo. + IHC + Sequencing
Orthotopic, syngeneic transplnatation
Check tumor volume
0
29
37
44
65
86 (Days)
OVX
(1)
(2)
(Endpoint 3)
c.
H&E
ER
Krt14
p53
SSM2 tumors 5 weeks post-OVX
Luminal tumors
Basaloid tumors
100 µm

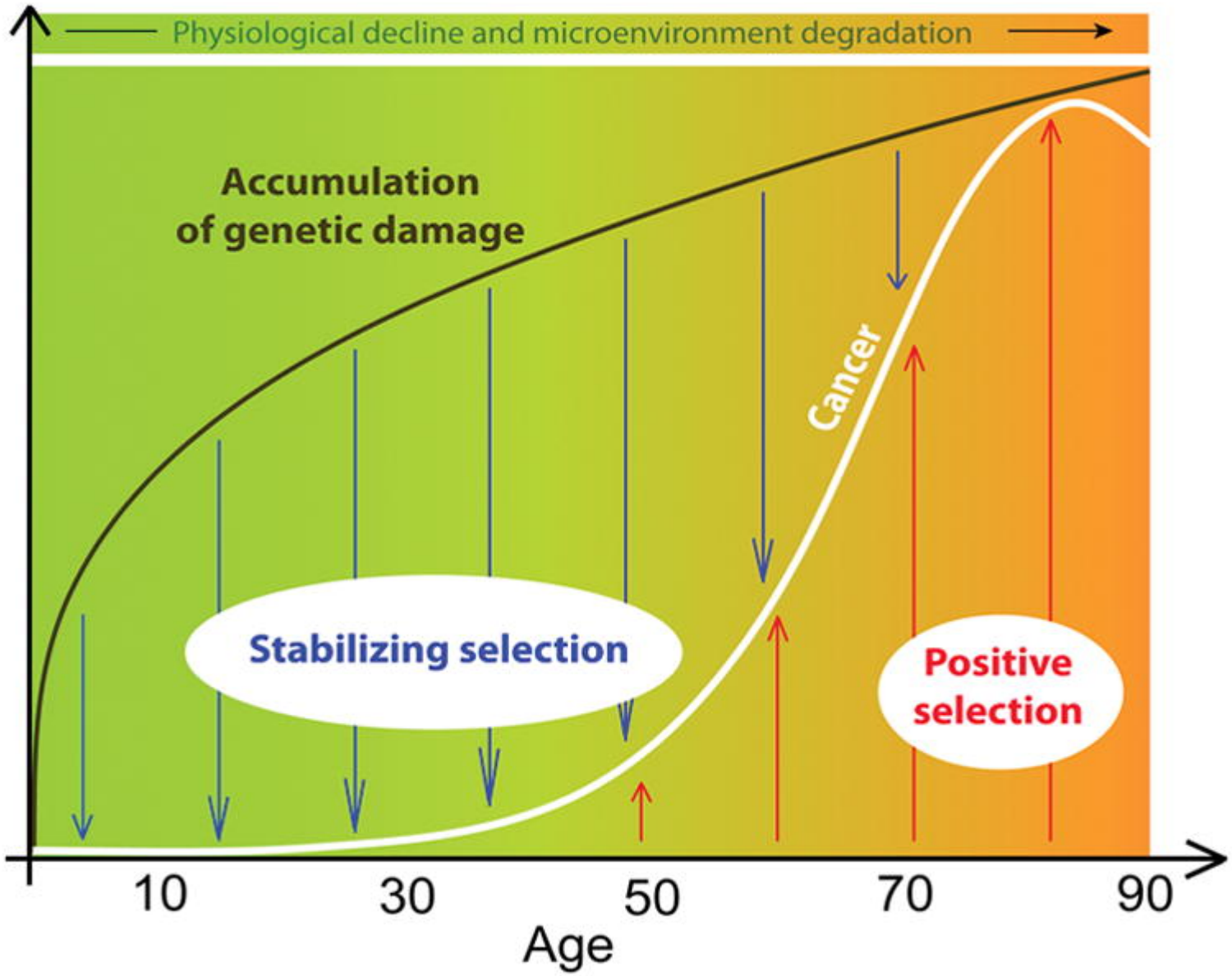
Figure 4.


a.
SSM2 No-OVX Ctrl (Luminal)
EX11-0671-1 (Trp53-S12R)
Krt14Neg tumor cells
Luminal tumors
Ki67- (79%)
Ki67+ (21%)
p53(-) ER(+)
p53(+) ER(-)
p53(+) ER(+)
p53(-) ER(-)
Ki67+ tumor cells
Krt14 IHC (pseudocolor Image -Hide)
EX11-0671-1
b.
SSM2 2 weeks post-OVX (Luminal tumors)
EX11-0495-1 (Trp53-S12R)
EX11-0496-2 (Trp53-S12R)
Krt14Neg tumor cells
Luminal tumors
Ki67+ (18%)
p53(+) ER(+)
p53(-) ER(-)
p53(-) ER(+)
Ki67+ tumor cells
Krt14 IHC
Ki67+ (5%)
Ki67+ tumor cells
Krt14High tumor cells
Krt14(+) tumor area within luminal tumors
Ki67+ (46%)
Ki67+ tumor cells
Ki67+ (26%)
c.
SSM2 2 wks post-OVX (Basaloid)
EX11-0497-2 (Trp53-C132W)
Krt14High tumor cells
Basaloid tumors
Ki67+ (26%)
Ki67+ tumor cells
Krt14 IHC
d.
SSM2 8 weeks post-OVX (Basaloid tumors)
EX11-0690-1 (Trp53-C132W)
Krt14High tumor cells
Basaloid tumors
Ki67+ (53%)
Ki67+ tumor cells
Krt14Neg tumor cells
Krt14(-) tumor area within basaloid tumors
Ki67+ (6%)
Ki67+ tumor cells
Krt14 IHC

Supplementary Table 1. Summary of *Trp53* mutations in STAT1-null primary and transplanted tumors, and transplanted SSM2^{UCD} tumors before and after ovariectomy.

Sample ID (EX No.)	Detail	Whole exome sequencing			Sanger sequencing	
		Missense variants	Exons	SIFT score#	Missense variants	Exons
12-0420-1	Stat1^{KO} primary tumor (Low-p53 tumor)	No SNVs found	N/A	N/A	No SNVs found	N/A
14-0340-2 14-0341-2 14-0342-2	Primary low-p53 OVX transplantations	•	•	•	No SNVs found	N/A
12-0416-5	Stat1^{KO} primary tumor (High-p53 tumor)	*Trp53-P187R* *Trp53-H190P* *Trp53-A273G*	6/11 6/11 8/11	0.02 0.00 0.01	*Trp53-P187R*	6/11
14-0340-1 14-0341-1 14-0342-1	Primary high-p53 OVX transplantations	•	•	•	*Trp53-P187R*	6/11
Sample ID (EX No.)	**Detail**	**Whole exome sequencing**			**Sanger sequencing**	
		Missense variants	**Exons**	**SIFT score#**	**Missense variants**	**Exons**
11-0671-1-B	SSM2 Control tumor	*Trp53-S12R*	2/11	0.07	*Trp53-S12R*	2/11
11-0495-1 11-0497-1	2-weeks post-OVX (Luminal SSM2)	*Trp53-S12R*	2/11	0.07	*Trp53-S12R*	2/11
11-0498-1 11-0496-2		•	•	•	*Trp53-S12R*	2/11
11-0530-1 11-0529-1	5-weeks post-OVX (Luminal SSM2)	*Trp53-S12R*	2/11	0.07	*Trp53-S12R*	2/11
11-0497-2	2-weeks post-OVX (Basaloid SSM2)	*Trp53-C132W*	5/11	0.00	*Trp53-C132W*	5/11
11-0495-2		•	•	•	*Trp53-C132W*	5/11
11-0530-2 11-0529-2	5-weeks post-OVX (Basaloid SSM2)	*Trp53-C132W*	5/11	0.00	*Trp53-C132W*	5/11
11-0590-1	8-weeks post-OVX (Basaloid SSM2)	•	•	•	*Trp53-C132W*	5/11

#SIFT score: > 0.05, tolerated; 0.00-0.02 (< 0.05), deleterious
' • ', no data available



•. 2017 Nov 15;77(22):6065-6068.
doi: 10.1158/0008-5472.CAN-17-1207. Epub 2017 Jul 28.

Connecting Cancer to Its Causes Requires Incorporation of Effects on Tissue Microenvironments

James DeGregori[1]

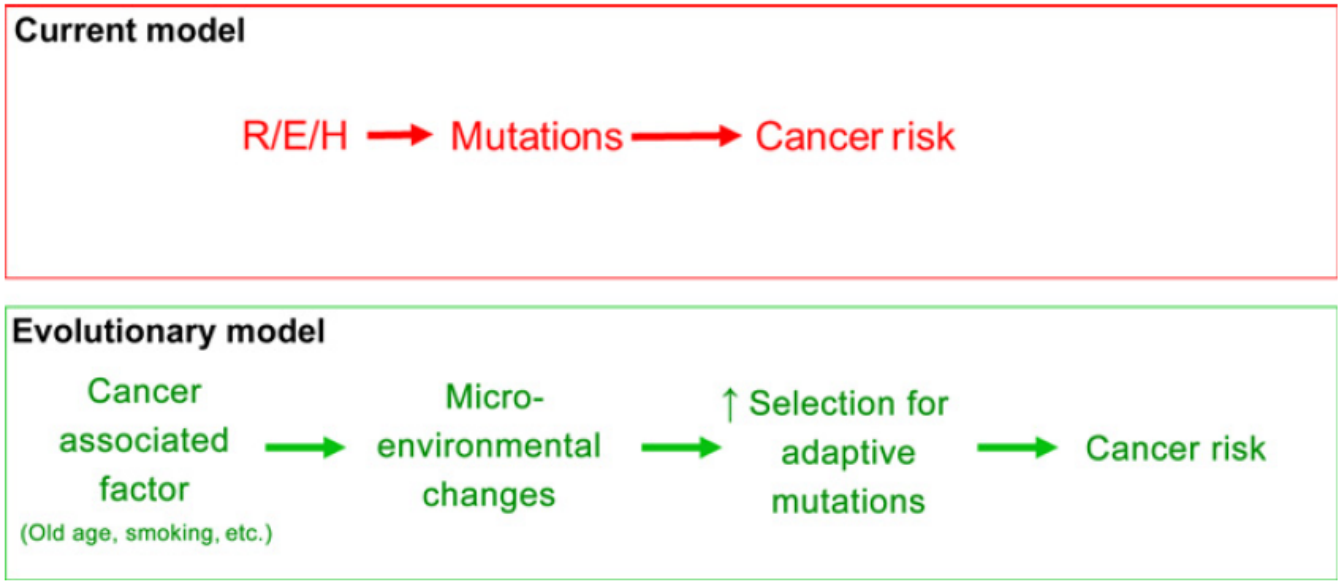
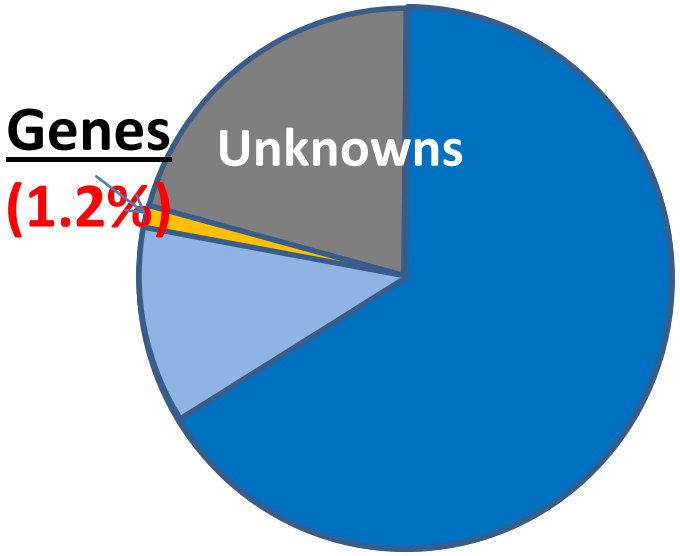


Figure 1.

Models connecting cancer to its causative contexts. Top, according to the current paradigm that forms the foundation for the Tomasetti and colleagues model, the primary role of R, E, and H in determining cancer risk is through increasing mutational burden in tissue stem cells. Bottom, an alternative model posits that the major impact for contexts like old age and environmental exposures on cancer risk is through alterations in tissue microenvironments that promote selection for adaptive mutations that contribute to cancer development. Adaptive mutations could emanate from R, E, and/or H, and increases in mutational burden from R, E, and/or H should increase cancer risk. However, the impact of cancer-associated factors on selection will have a much greater deterministic role.

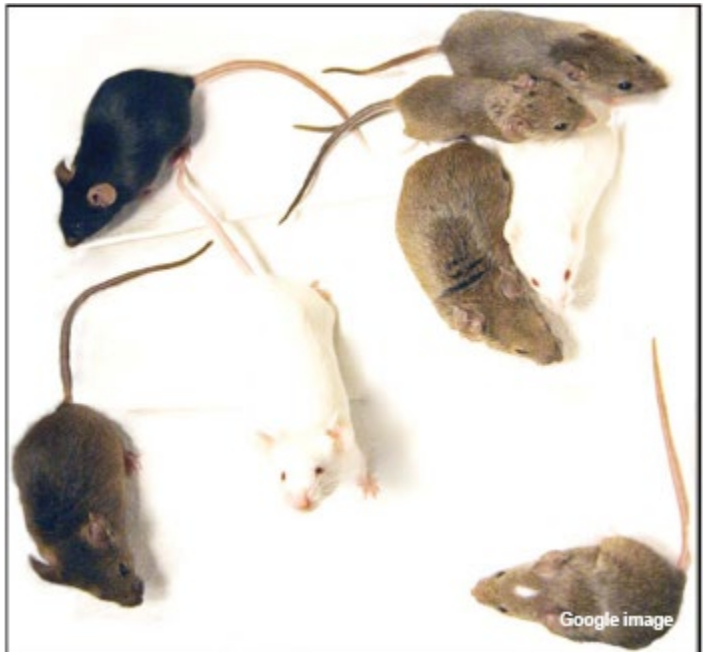
Genes, Genomes
and
Phenotypes



Gene sequences of humans and mice

→ **Reported to be ~80% homologous**

VS



Kiho's Journey

~80% similarity in phenotype ?

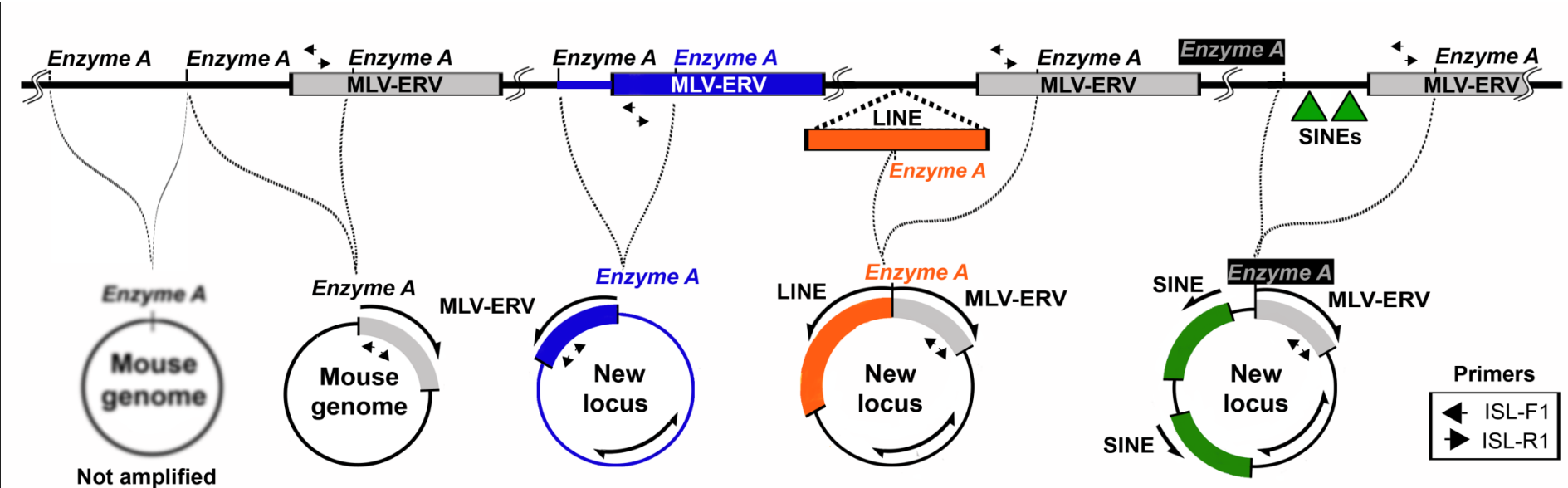

Google image

REPETITIVE ELEMENT SPECIFIC

1. LINE

2. SINE

3. ERV



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mirna and breast cancer

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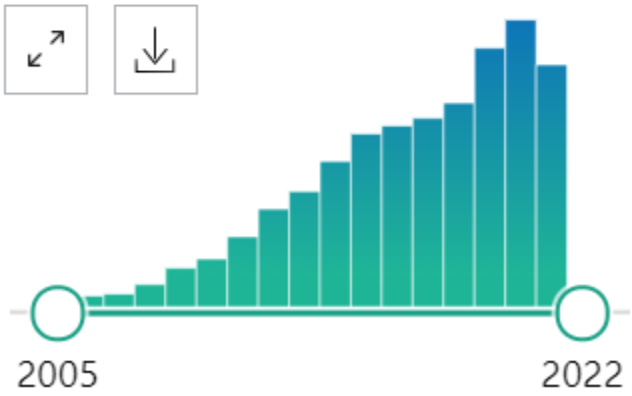

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Circulating microRNA-1(for **breast cancer**.

Liu H, Bian QZ, Zhang W, Cui H

Oncol Lett. 2022 Jan;23(1):38. d

PMID: 34966454 **Free PMC**

Breast cancer (BC) is the most

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non coding rna and breast cancer

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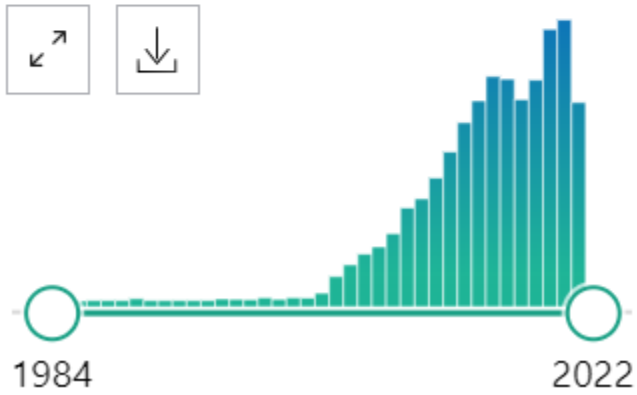

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Did you mean ***non coding iran and breast cancer*** (

1 Cite Share

Long **non-coding RNA** GAS6-AS1 enh
by functioning as a competing endoge
enhance SOX9 expression.

Wu XP, Xu ZQ, Xie WM, Lai YL, He K, Jiang Y, Xu Z

Exp Ther Med. 2022 Jan;23(1):109. doi: 10.3892/et

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non coding rna and tnb

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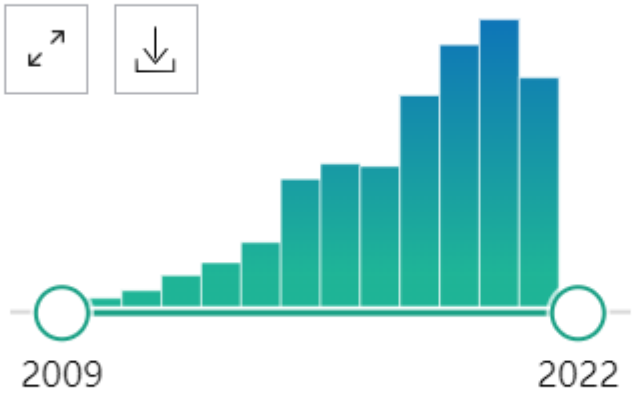
RESULTS BY YEAR



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Long non-coding R
Expression analysis

Wang L, et al. J Cell Phys

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Circular **RNA**:

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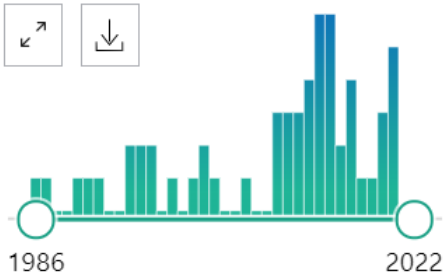

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Cite

Share

DNA methylation level in blood and relations to **breast cancer**, risk factors and environmental exposure in Greenlandic Inuit women.

Wielsøe M, Tarantini L, Bollati V, Long M, Bonefeld-Jørgensen EC.

Basic Clin Pharmacol Toxicol. 2020 Oct;127(4):338-350. doi: 10.1111/bcpt.13424. Epub 2020 May 18.

PMID: 32352194 **Free PMC article.**

This case-control study evaluated blood methylation level of two **repetitive elements** and selected **breast cancer**-related genes in relation to **breast cancer** risk, and the associations with serum level of persistent organic pollutants (POPs) ...

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7 results

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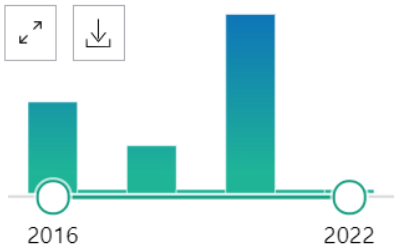

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- [x] Free full text

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Your search for *repetitive elements dna and tnbc* retrieved no results

1

Opportunities for Antigen Discovery in Metastatic Breast Cancer.

Sood AK, Nemeth M, Wang J, Wu Y, Gandhi S.

Cite

Front Immunol. 2020 Oct 30;11:570049. doi: 10.3389/fimmu.2020.570049. eCollection 2020.

PMID: 33193348 **Free PMC article.**

Share

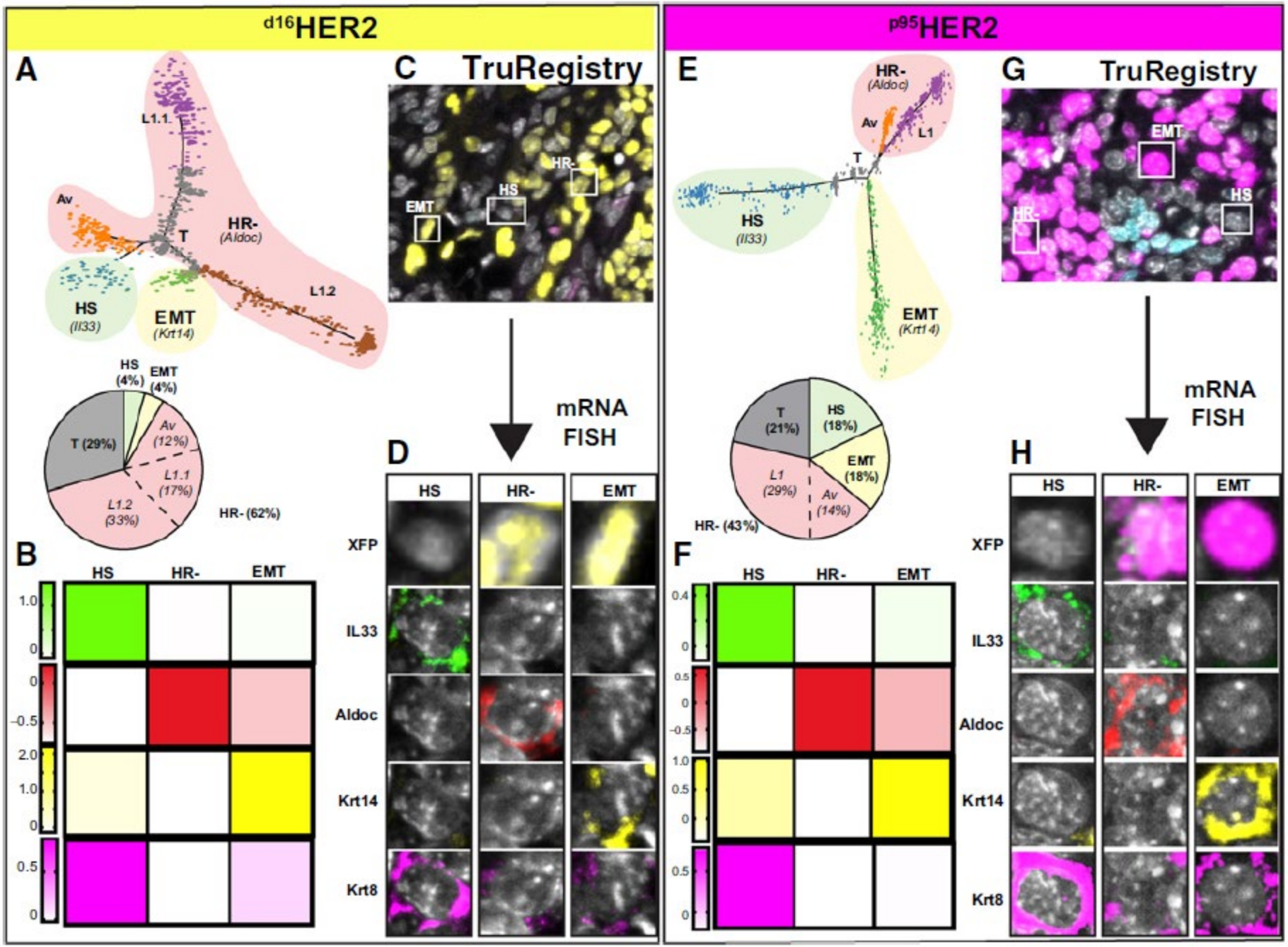
Immune checkpoint inhibitor-based immunotherapy (ICI) of breast cancer is currently efficacious in a fraction of triple negative breast cancers (**TNBC**) as these cancers generally carry high tumor mutation burden (TMB) and show increased tumor infiltration by CD8(+) T cells. ...

THE END
It has been a pleasure
THANK YOU

Mutations in Noncoding *Cis*-Regulatory Elements Reveal Cancer Driver Cistromes in Luminal Breast Cancer

Samah El Ghamrasni[1], Rene Quevedo[1,2], James Hawley[1,2], Parisa Mazrooei[1,2,3], Youstina Hanna[1], Iulia Cirlan[1], Helen Zhu[1,2,4,5], Jeff P. Bruce[1], Leslie E. Oldfield[1], S.Y. Cindy Yang[1,2], Paul Guilhamon[6,7], Jüri Reimand[2,5,8], Dave W. Cescon[1], Susan J. Done[1,2,9], Mathieu Lupien[1,2,5], and Trevor J. Pugh[1,2,5]

ABSTRACT


d16HER2
p95HER2
A
L1.1
Av
T
HR-
(Aldoc)
L1.2
HS
(Il33)
EMT
(Krt14)
HS (4%)
EMT (4%)
T (29%)
Av (12%)
L1.1 (17%)
L1.2 (33%)
HR- (62%)
B
HS
HR-
EMT
C TruRegistry
EMT
HS
HR-
mRNA FISH
D
HS
HR-
EMT
XFP
IL33
Aldoc
Krt14
Krt8
E
HR-
(Aldoc)
Av
L1
T
HS
(Il33)
EMT
(Krt14)
T (21%)
HS (18%)
EMT (18%)
L1 (29%)
Av (14%)
HR- (43%)
F
HS
HR-
EMT
G TruRegistry
EMT
HS
HR-
mRNA FISH
H
HS
HR-
EMT
XFP
IL33
Aldoc
Krt14
Krt8

Using GEM to Understand Precancer

Can structure, function and therapy merge?

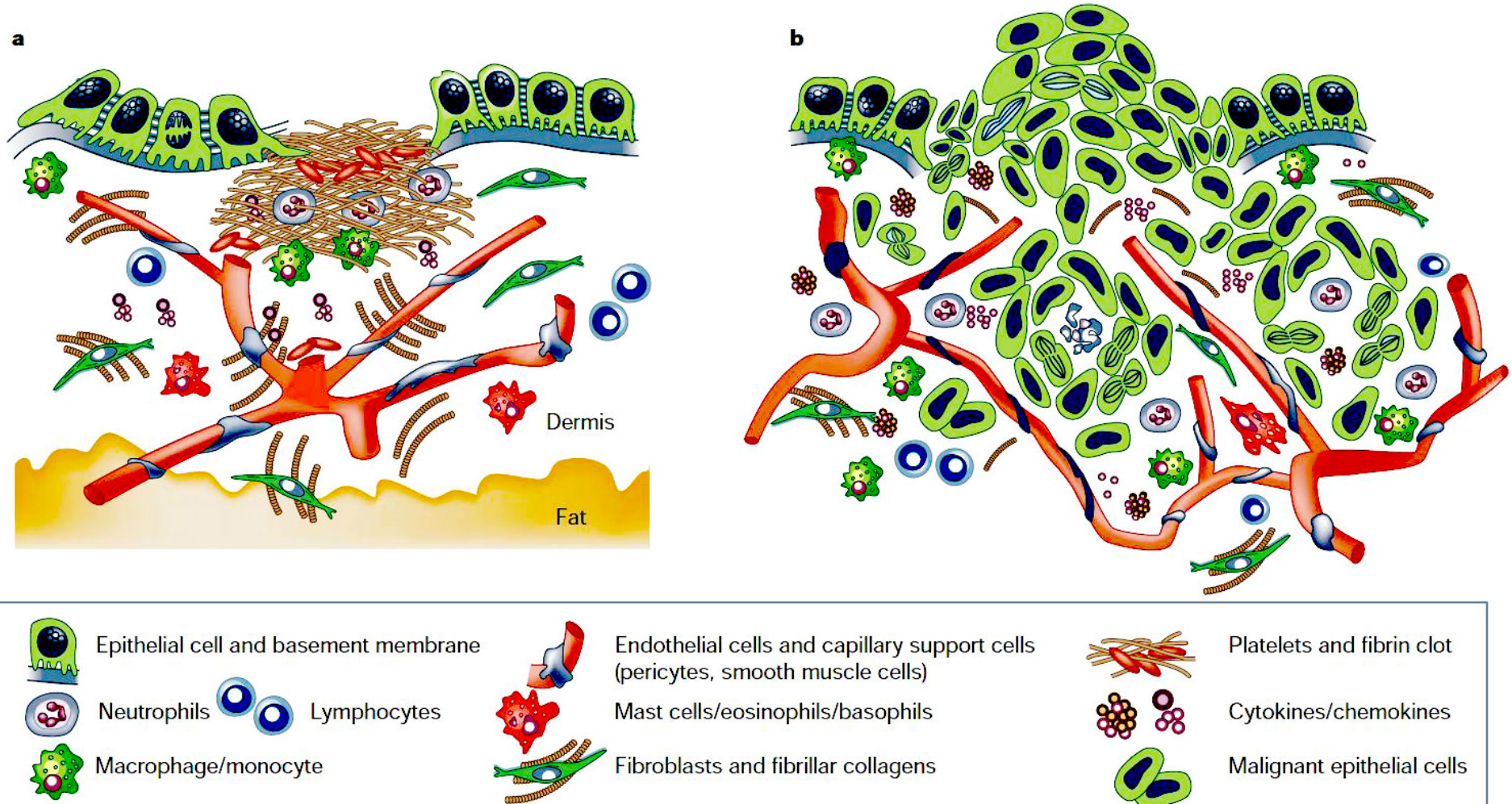
Invasive and Metastatic Disease

- Microinvasion
- Invasive vs expansile growth
- Non invasive metastasis (tumor emboli)
- Metastasis

Similarities Between Wound Healing and Tumor Growth

Wound Healing

Tumor Growth



Coussens, LM and Werb, Z (2002) Nature 420:860-867

A VERY OLD DEBATE: A Brief History

- The History of Precancer
  - Waldheyer and origin of cancer: Direct continuity. 1867
  - Ewing
  - Apolant/Haaland
  - Papanicalou
- Experimental Pathology
  - Rous: Initiation and Progression
  - Foulds: Neoplastic Development
    - DeOme and two hit hypothesis: Sequential Acquisition of Traits.
  - Mutation and Multistep-Sequential Acquisition
    - Bovari-
    - Peto: Five hits, Armitage and Doll
    - DCIS :
      - Wellings and sequential acquisition
      - Page and DCIS
      - Polyak and DCIS
    - Vogelstien and sequential acquisition
  - GEM
    - Stepwise Progression hypothesis: Pandolfi
- The Natural History of Cancer in Breast
    - DCIS
    - Biological Predeterminism
    - Window of Susceptibility
    - Russo, Medina, DeGregori
    - Sontag and Axelrod
- Structure and Biology of Precancer: Sequential Acquisition VS Predetermination
  - HAN, HPO Medina
  - MINO Model
  - Adaptive Oncogenesis Model