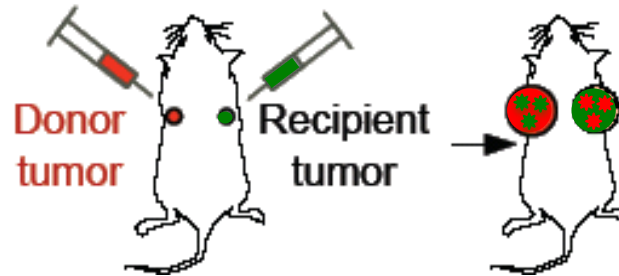


# Regardless of the Normal Cell of Origin it is the Functional State of the Cancer Cell That Matters

**Larry Norton, MD**

Memorial Sloan Kettering  
Cancer Center

May, 2015

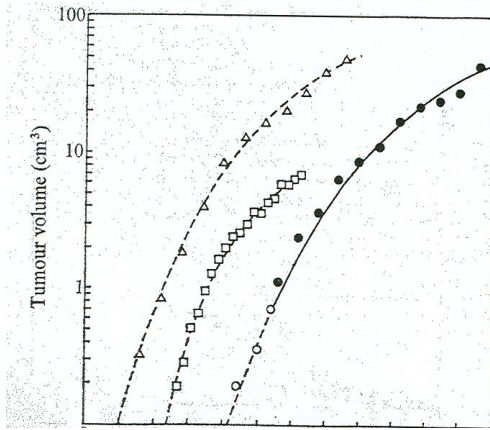


- Cancer Stem Cells
- Epithelial-Mesenchymal Transition
- Circulating Cancer Cells

**= Cancer Cell Mobility**

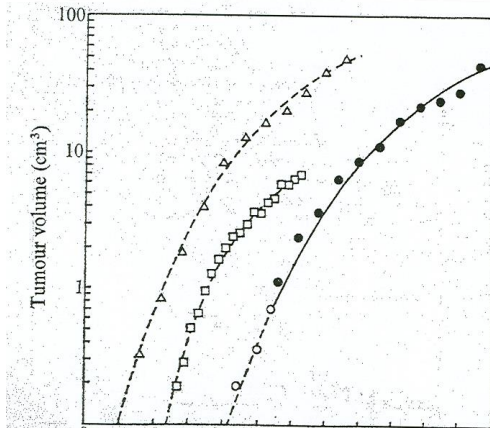


# This presentation focuses on four aspects of the topic

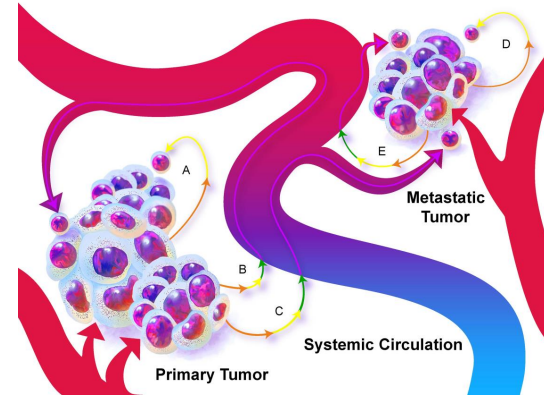


How do cancers grow?

# This presentation focuses on four aspects of the topic

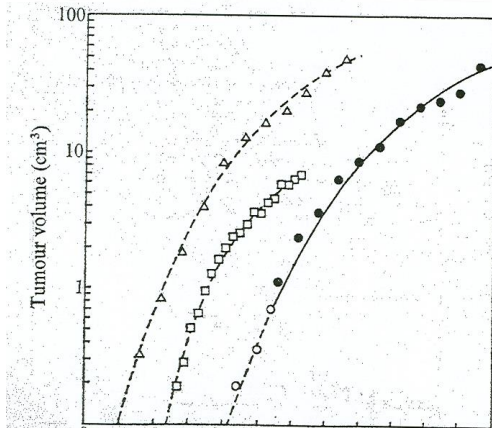


**How do cancers grow?**

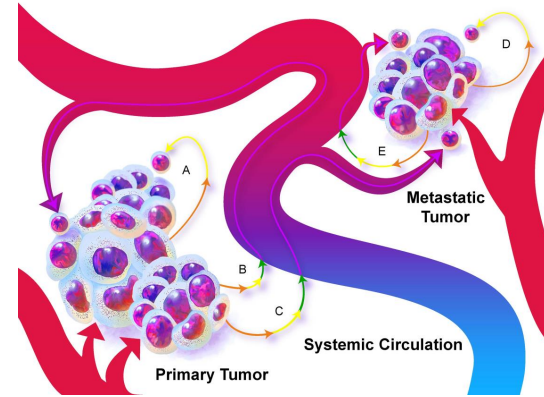


**Why do they grow that way?**

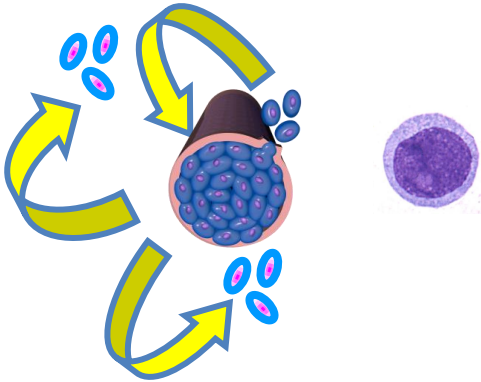
# This presentation focuses on four aspects of the topic



**How do cancers grow?**



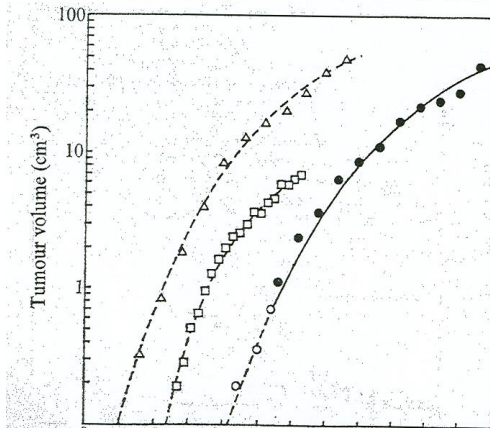
**Why do they grow that way?**



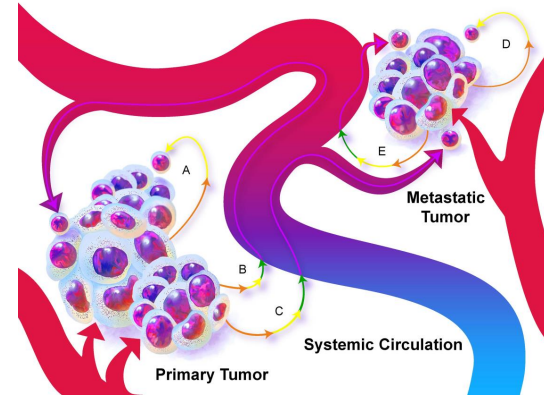
**What does it all mean?**



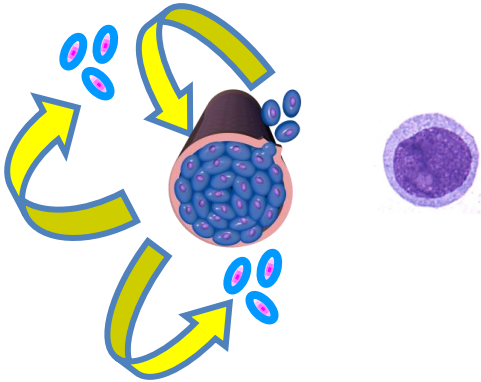
# This presentation focuses on four aspects of the topic



**How do cancers grow?**



**Why do they grow that way?**



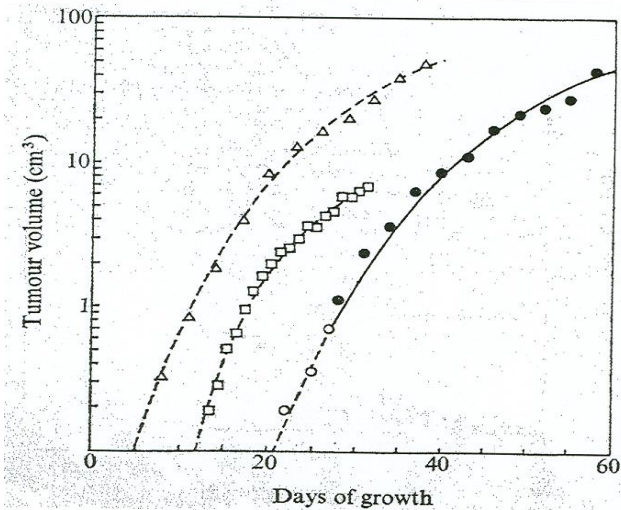
**What does it all mean?**



**What can we do about it?**



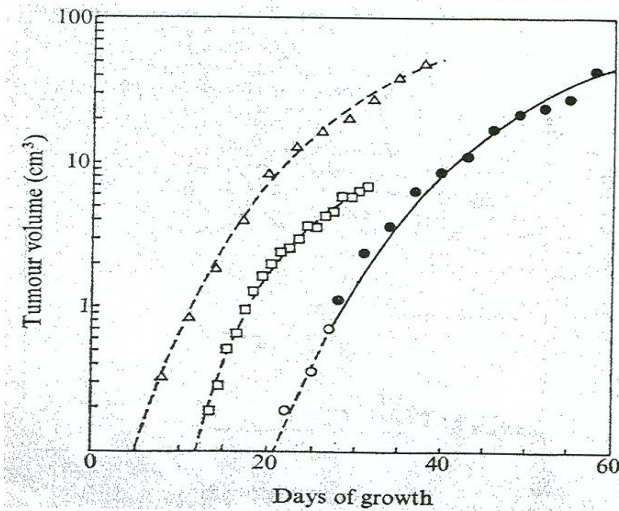
# Gompertzian growth is not an hypothesis, it is an observation



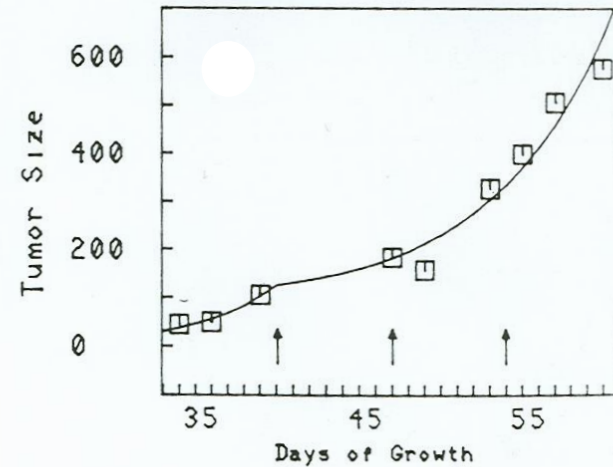
**Norton L *et al.*, Nature 1976**



# Gompertzian growth allows for improved cell killing by increasing the *density* of therapy



Norton L *et al.*, Nature 1976



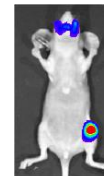
Norton L *et al.*, Ca Treatment Rep 1977

# Tumor growth and cancer cell metastases are linked

MDA MB 231

Parental

— SPARC  
— IL13RA2  
= MMP1  
— ERG  
— COX2  
  
= CXCL1  
= MMP2  
  
— ID1  
  
= RARRES3  
= EFEMP1  
= MANT2  
— LY6E

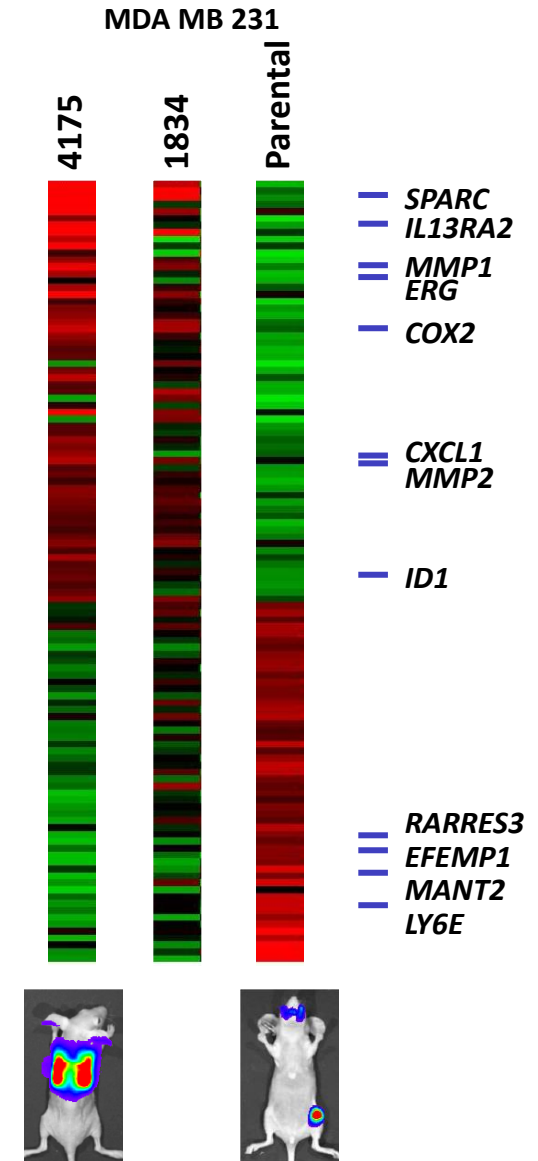


Minn *et al.*, Nature, 2005





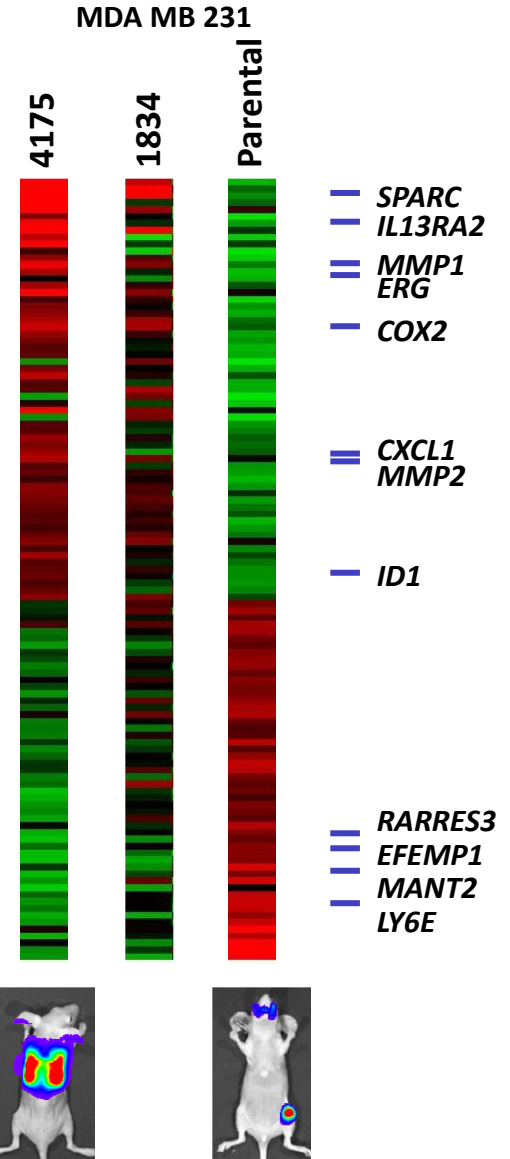
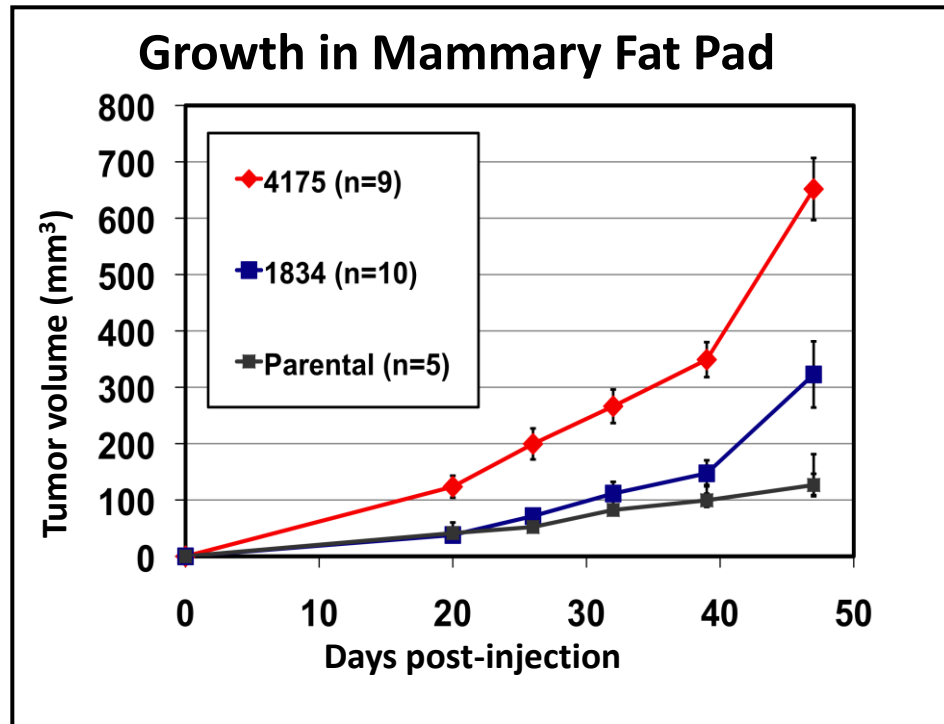
# Tumor growth and cancer cell metastases are linked



Minn *et al.*, Nature, 2005



# Tumor growth and cancer cell metastases are linked



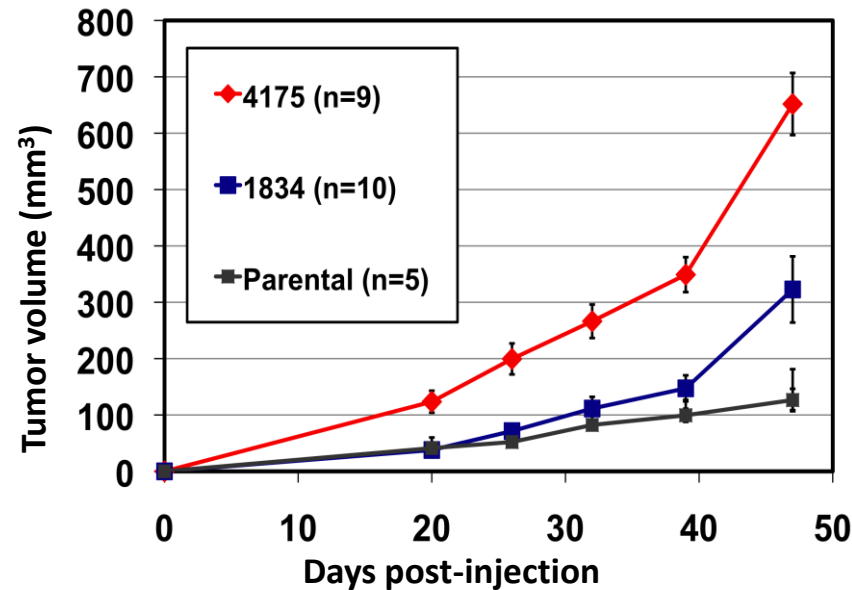
Minn *et al.*, Nature, 2005



# Tumor growth and cancer cell metastases are linked

## S-Phase Fraction (Ki67) Not Different

### Growth in Mammary Fat Pad



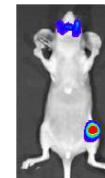
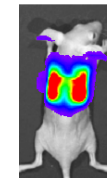
MDA MB 231

4175

1834

Parental

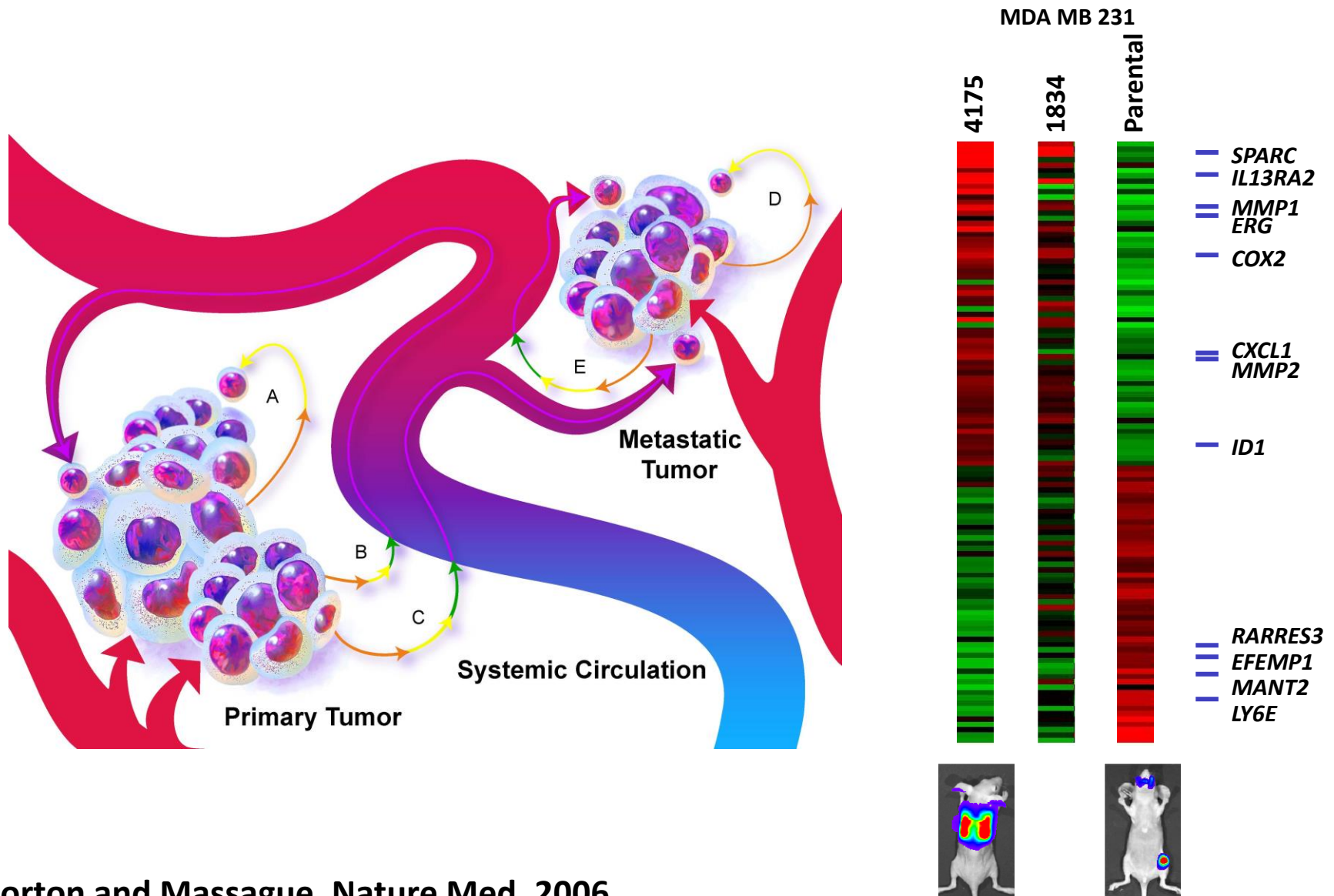
SPARC  
IL13RA2  
MMP1  
ERG  
COX2  
  
CXCL1  
MMP2  
  
ID1  
  
RARRES3  
EFEMP1  
MANT2  
LY6E



Minn *et al.*, Nature, 2005



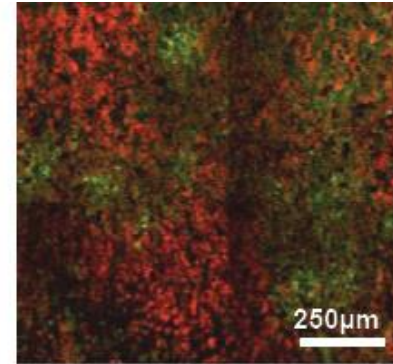
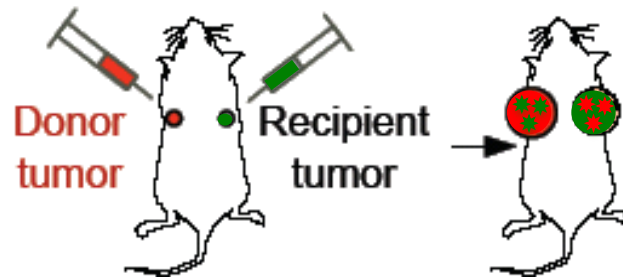
# Tumor growth and cancer cell metastases are linked



Norton and Massague, Nature Med, 2006



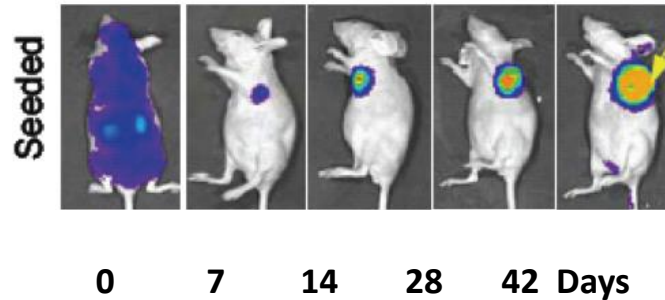
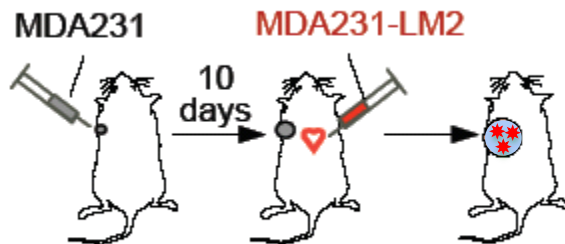
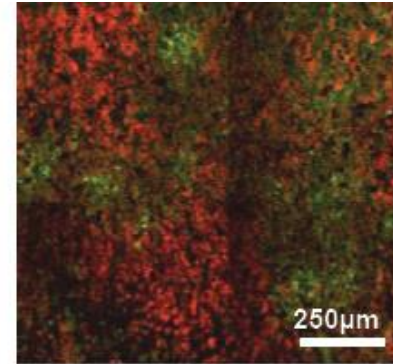
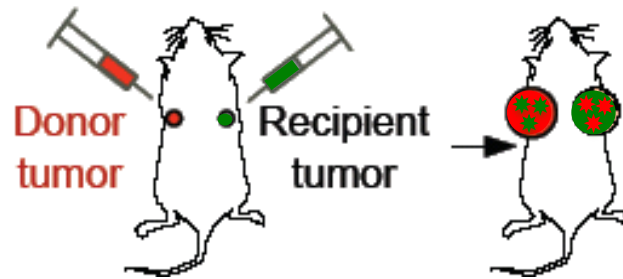
# Tumor growth and cancer cell metastases are linked



Kim *et al.*, Cell, 2009

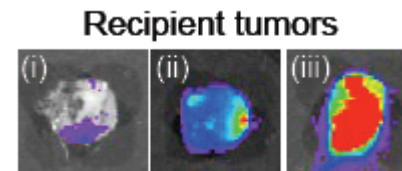
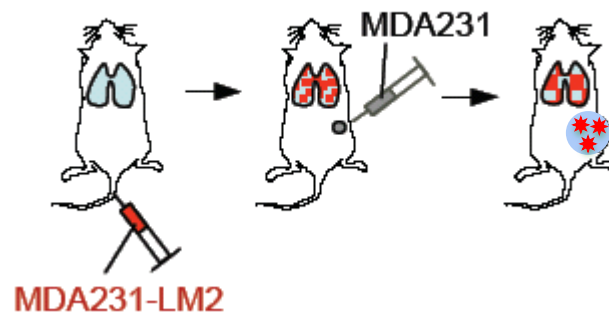
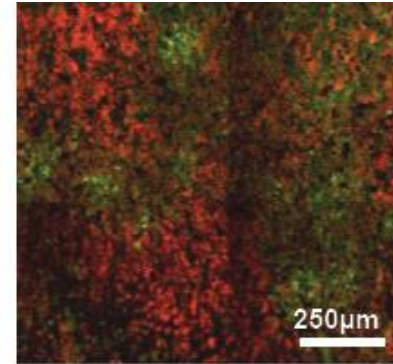
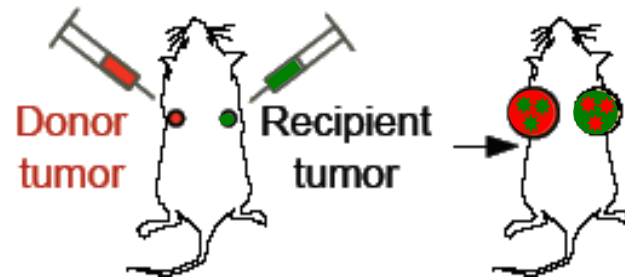


# Tumor growth and cancer cell metastases are linked



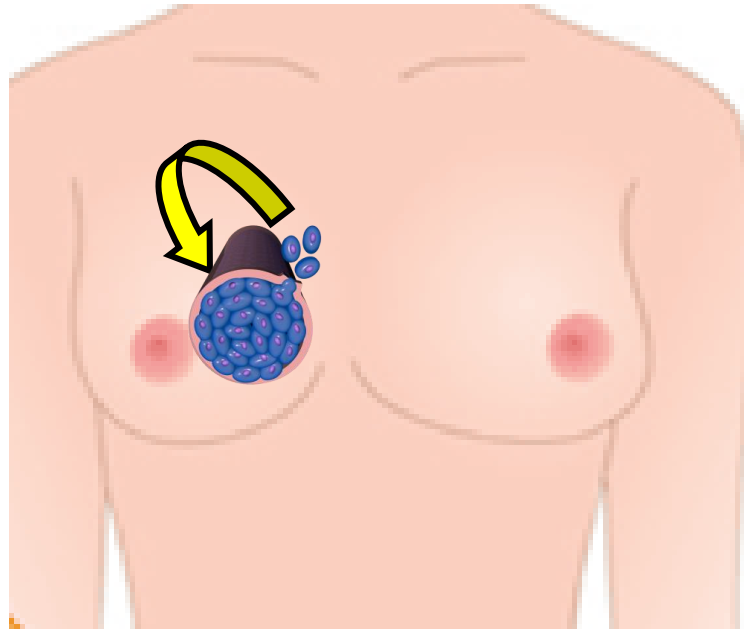
Tumor Seeding but No Lung Seeding!

# Tumor growth and cancer cell metastases are linked



# Cancer is a dynamic process

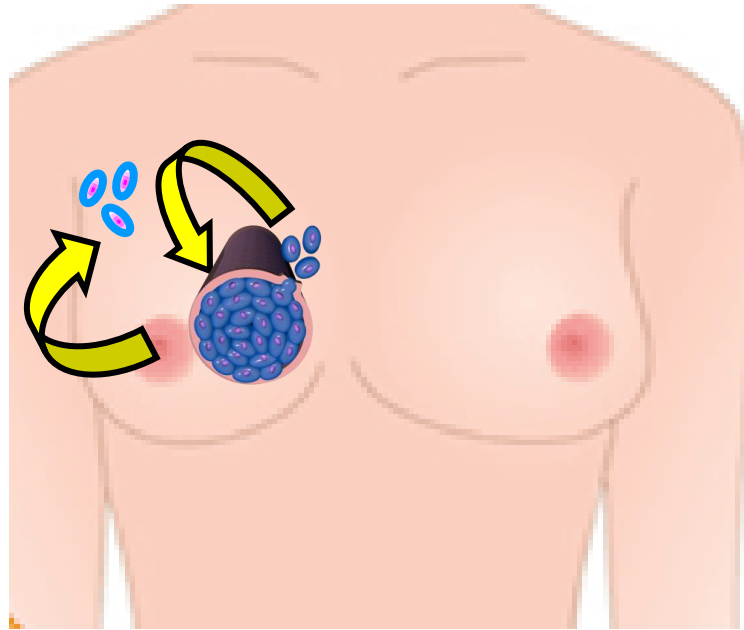
## Stage 1





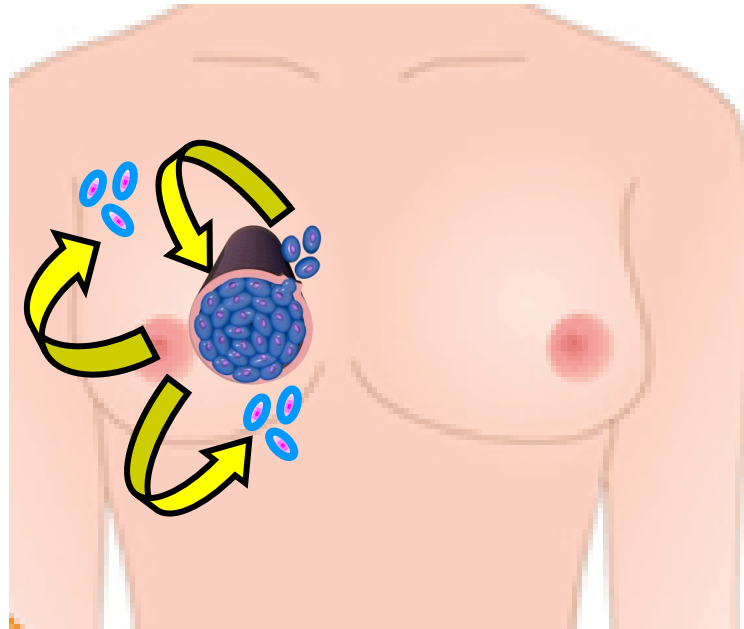
# Cancer is a dynamic process

## Stage 2



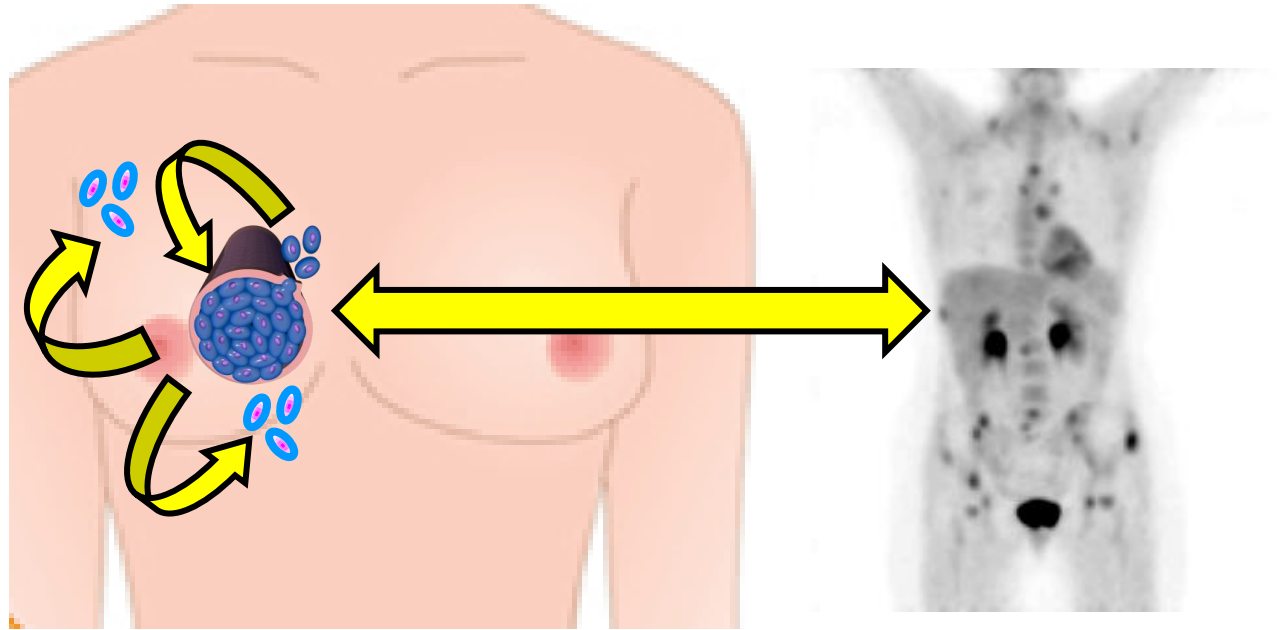
# Cancer is a dynamic process

## Stage 3



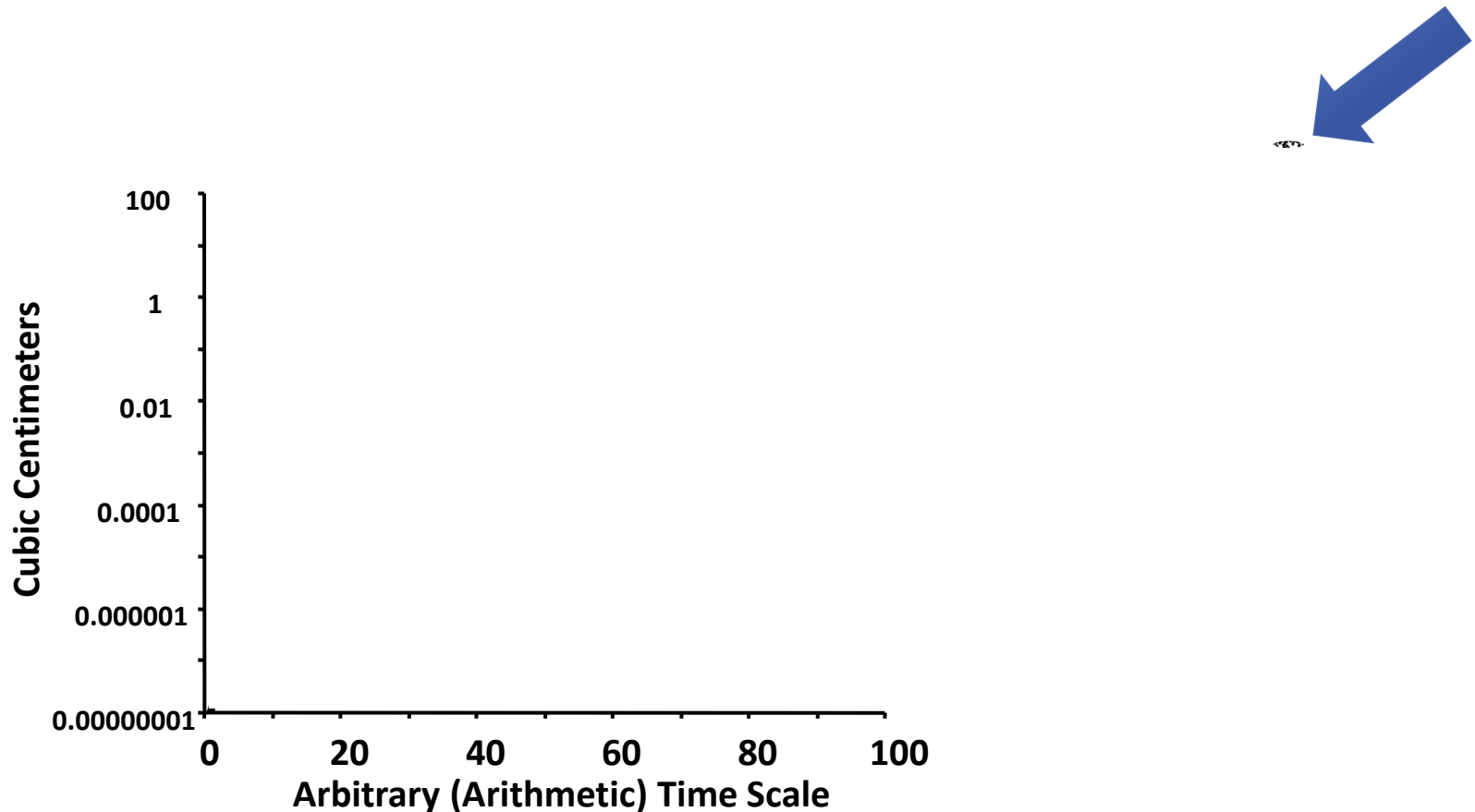
# Cancer is a dynamic process

## Stage 4

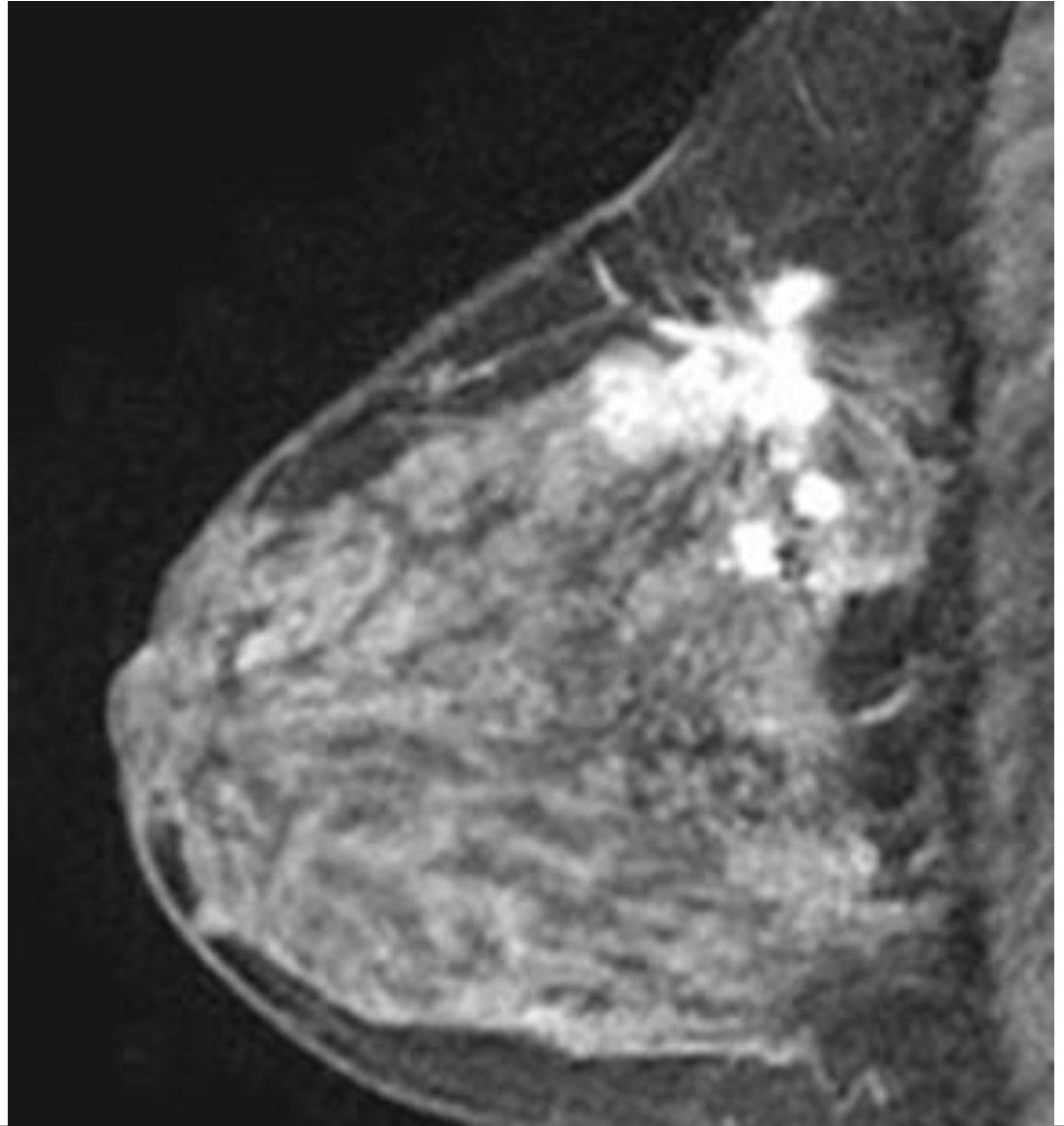


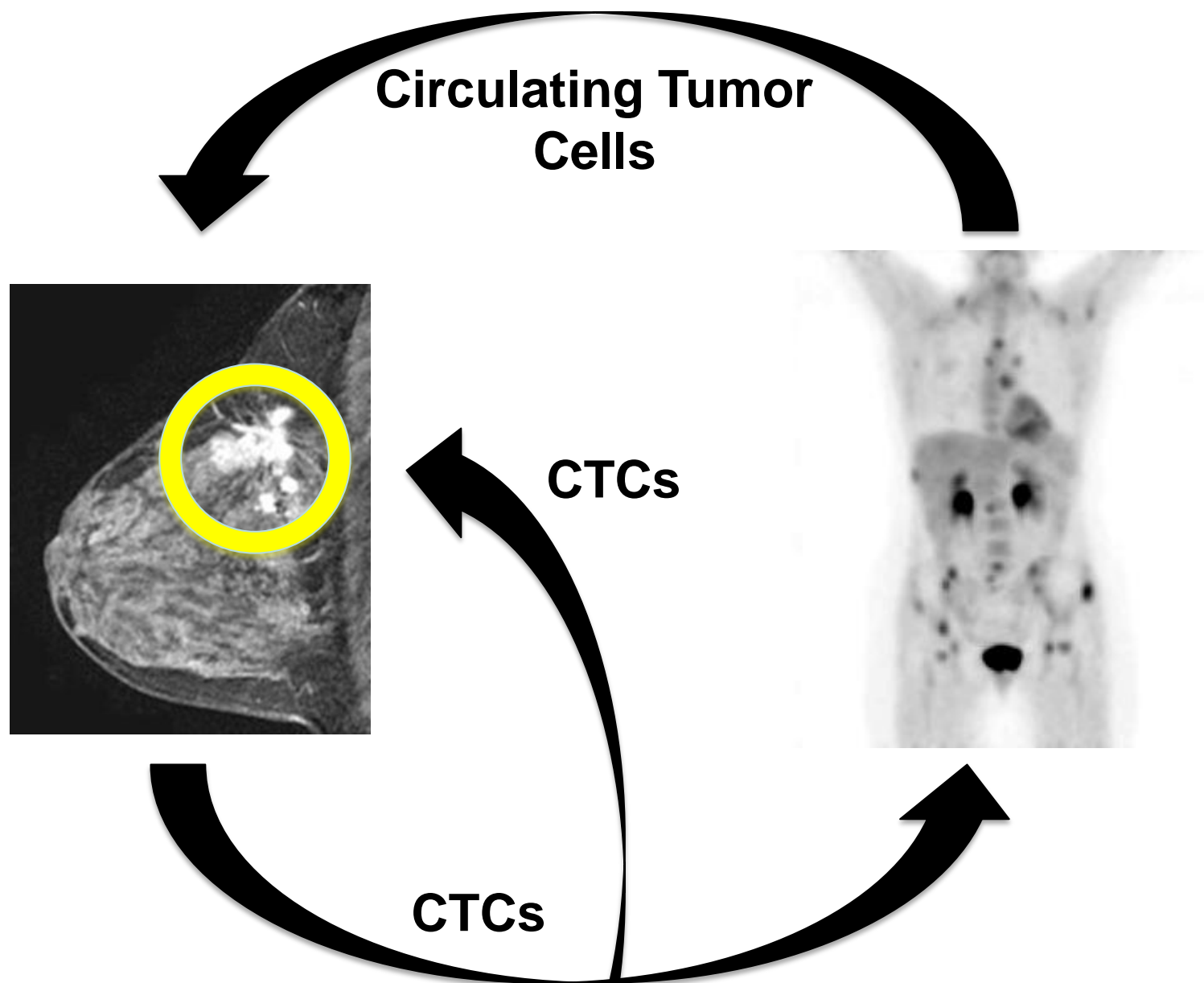
# Seeding explains the Gompertzian pattern of growth

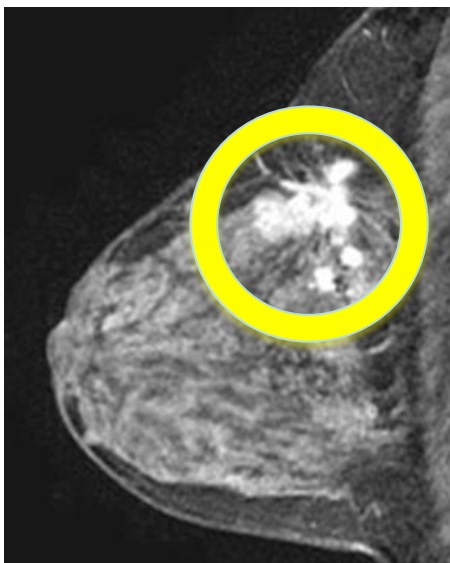
As objects get larger their surface to volume ratio decreases



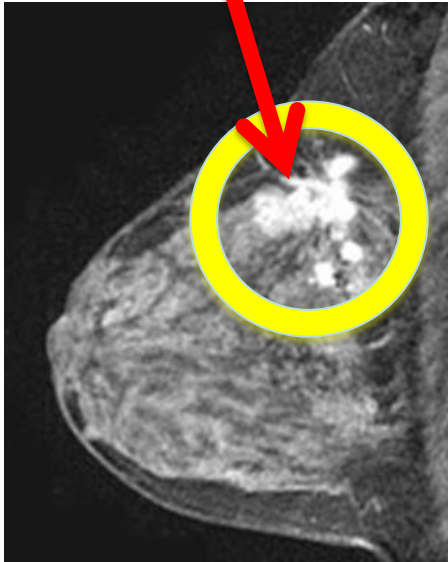
# Gompertzian growth explains cancer anatomy







## Local Therapy



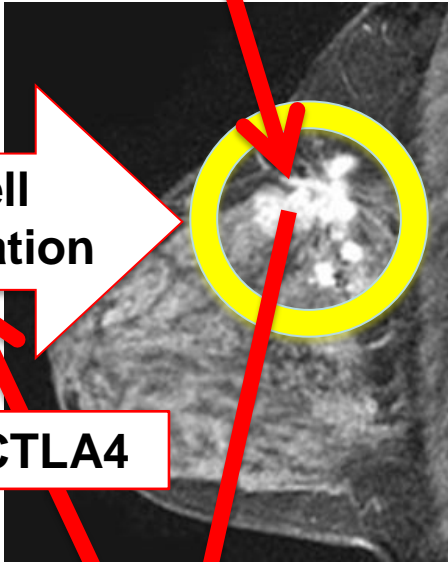


**Local Therapy**

**T-Cell  
Stimulation**

**Anti-CTLA4**

**Release of  
Antigens**



**Local Therapy**

**Circulating Tumor Cells**

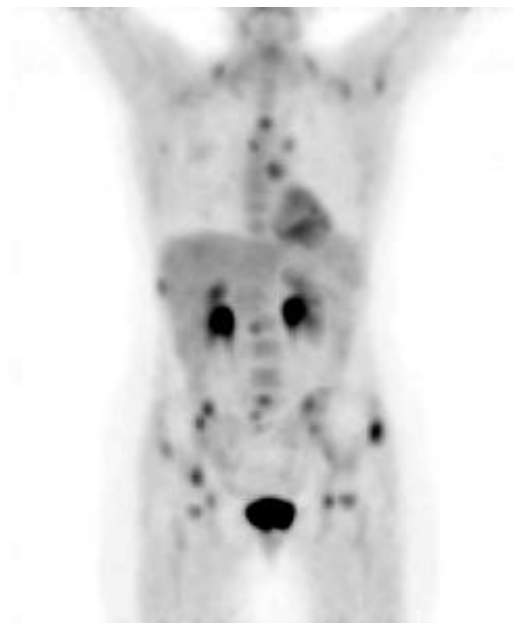
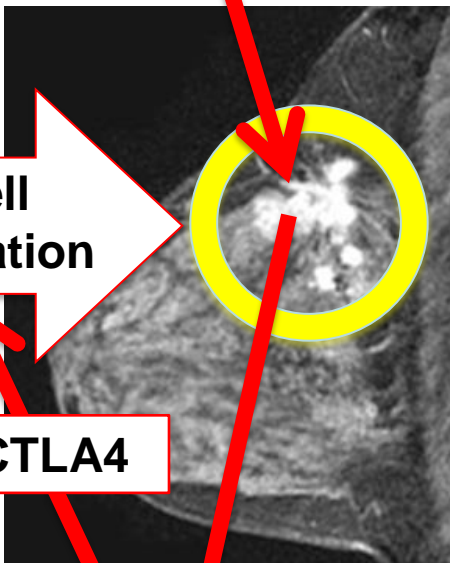
**T-Cell Stimulation**

**Anti-CTLA4**

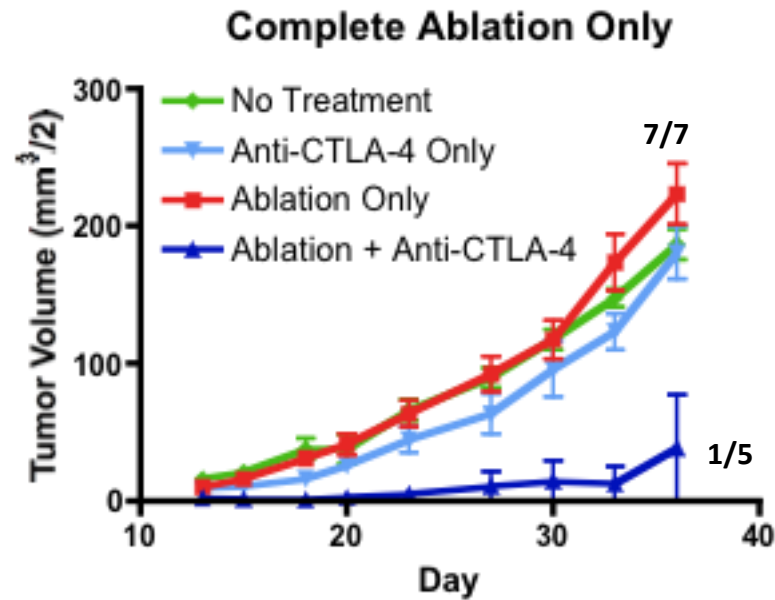
**Release of Antigen**

**CTCs**

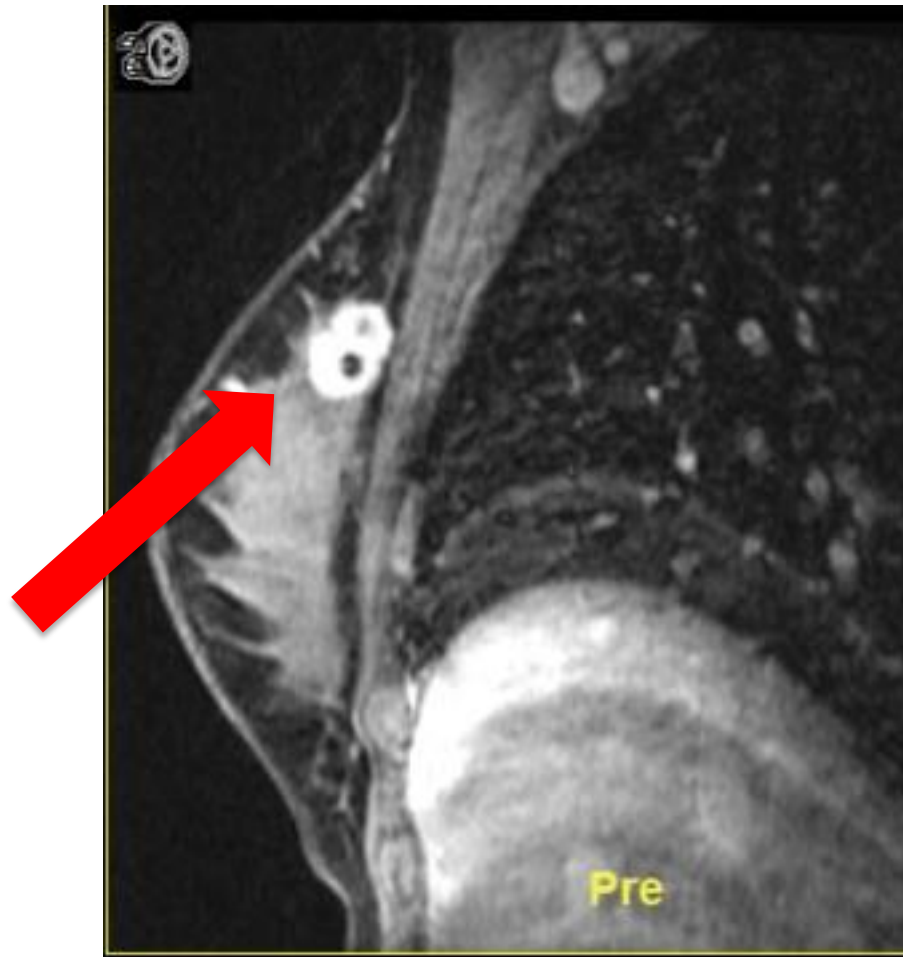
**CTCs**



# TRAMP C2 Cryoablation +/- Anti-CTLA-4



# Pilot Study in Primary Breast Cancer



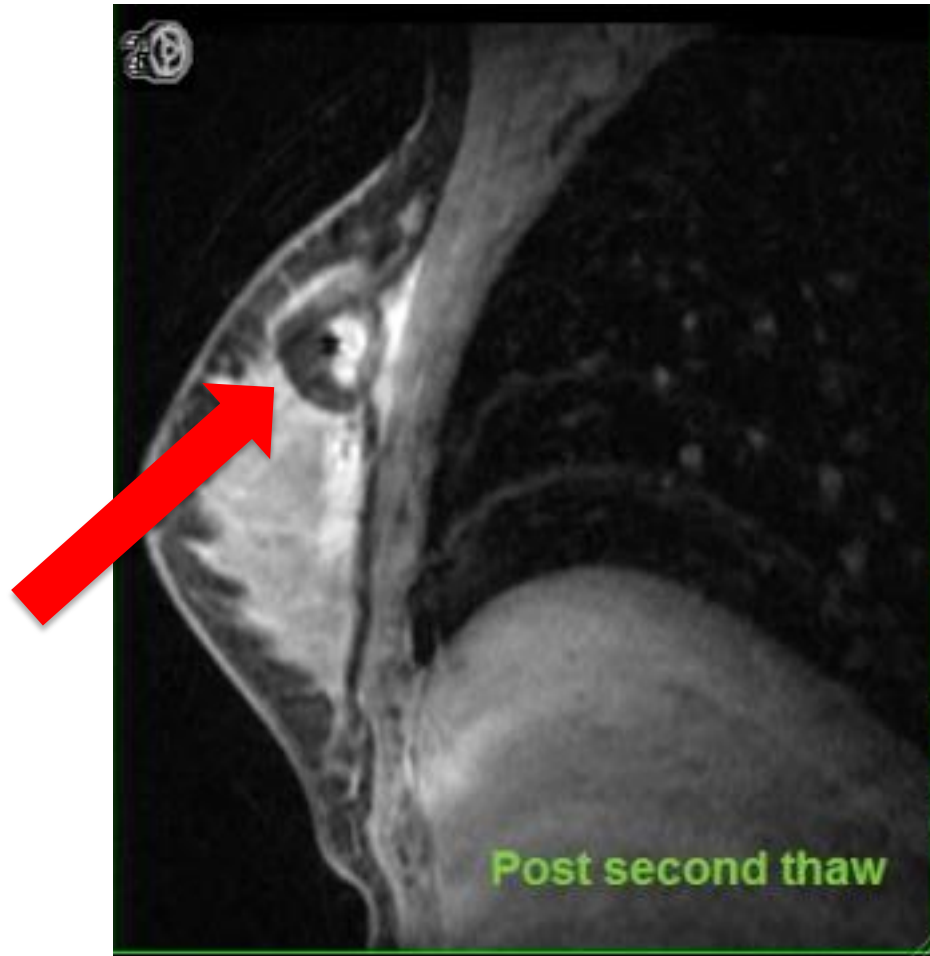
McArthur H, Diab A, Solomon S, Norton L *et al.*, 2013

# Pilot Study in Primary Breast Cancer



McArthur H, Diab A, Solomon S, Norton L *et al.*, 2013

# Pilot Study in Primary Breast Cancer



McArthur H, Diab A, Solomon S, Norton L *et al.*, 2013

**Local Therapy:  
Cryoablation?  
Radiation?**

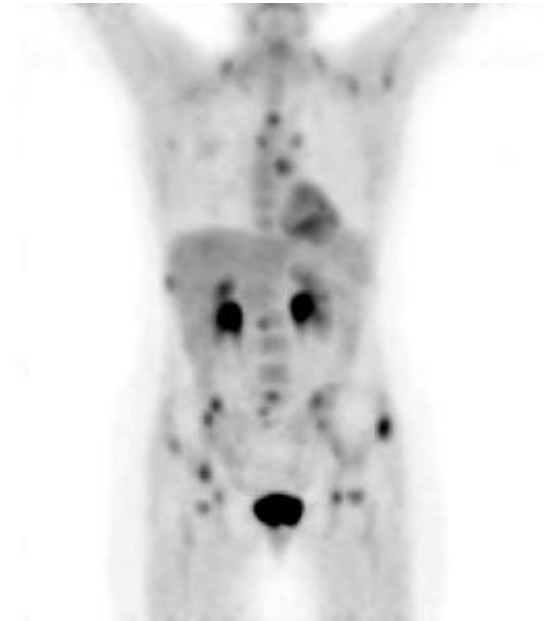
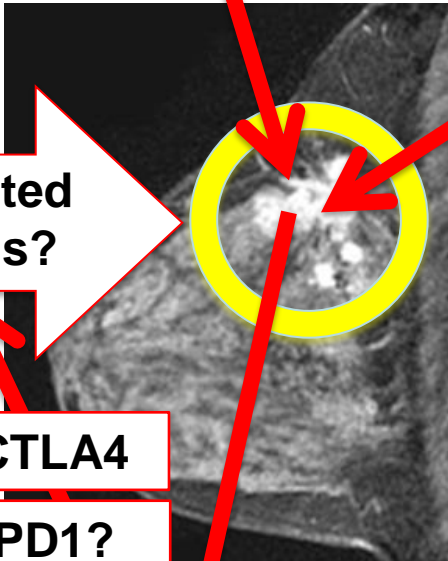
**Transgenes:  
IL12?**

**Educated  
T-Cells?**

**Anti-CTLA4**

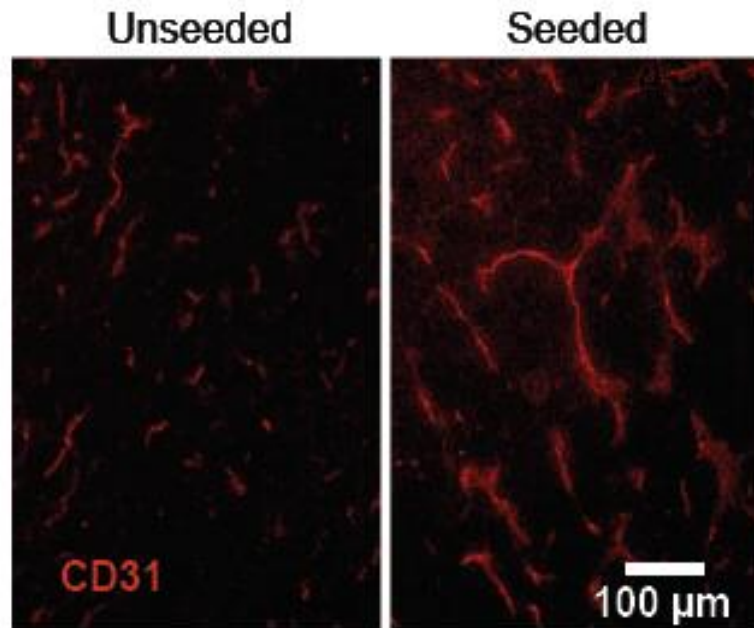
**Anti-PD1?**

**Release of  
Antigens**



# Breast cancer seeds create their own microenvironment by recruitment

## Angiogenesis



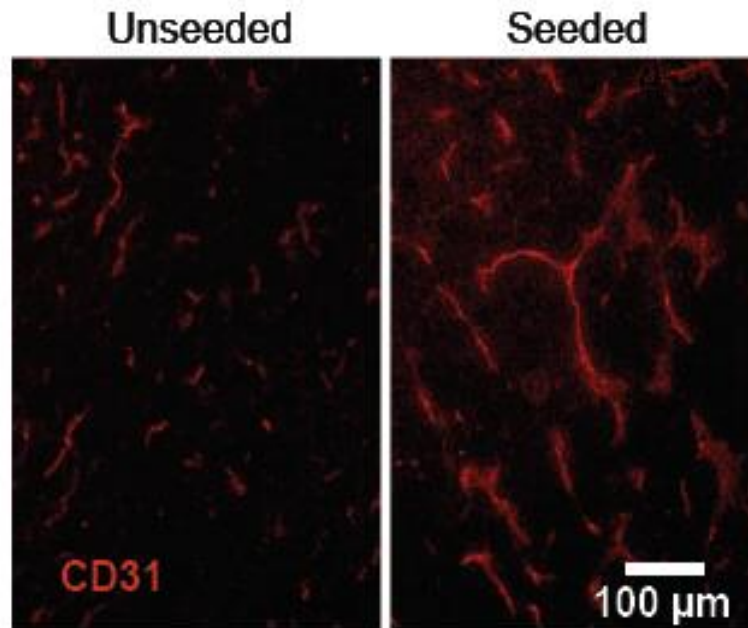
Kim MY *et al.*, Cell, 2009



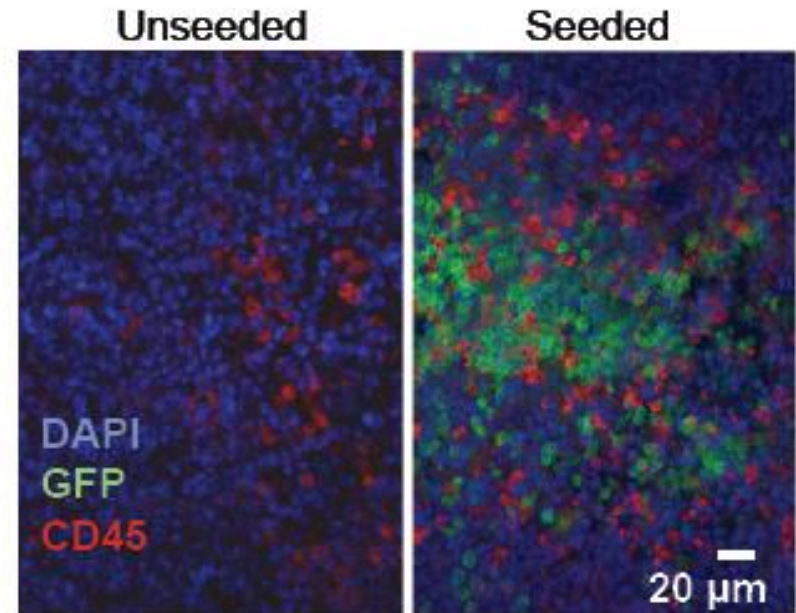


# Breast cancer seeds create their own microenvironment by recruitment

Angiogenesis



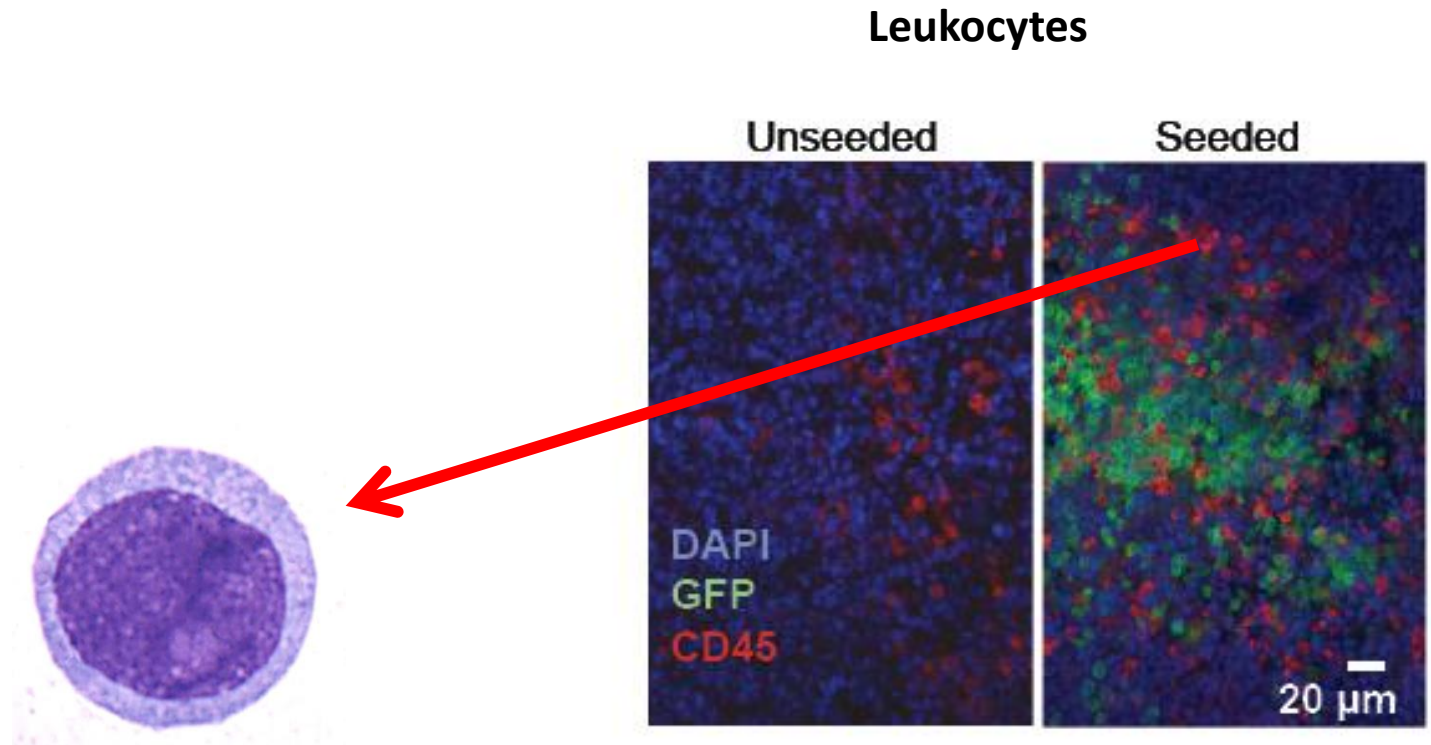
Leukocytes



Kim MY *et al.*, Cell, 2009



# Are tumor infiltrating leukocytes genetically normal?



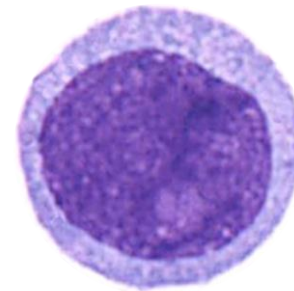
Comen E *et al.* SABCS 2014. Abstract # 896



# Oncogenic mutations found in the infiltrating leukocytes in 2/3 of 15 cases of primary human breast cancer

Sample	Gene	Mutation	Frequency
1	<i>EP300</i>	p.G1777C	0.06
2	<i>DNMT3A</i>	p.Y533C	0.185
	<i>TP53</i>	p.R248L	0.086
3	<i>EZH2</i>	p.A483S	0.46
	<i>IDH2</i>	p.W164L	0.13
	<i>DNMT3A</i>	p.T260N	0.1
	<i>TP53</i>	p.M169I	0.029
4	<i>BCOR</i>	p.P1156L	0.49
	<i>EPHA7</i>	p.G592S	0.14
	<i>WT1</i>	p.T278I	0.11
	<i>TET2</i>	p.Q1702*	0.06
	<i>PNRC1</i>	p.R97Q	0.048
	<i>EGFR</i>	p.A871E	0.042
5	<i>ALK</i>	p.R1209Q	0.21
	<i>ETV6</i>	p.P25S	0.038
6	<i>IDH2</i>	p.K205R	0.245
	<i>NOTCH2</i>	p.P1101T	0.18
	<i>NF1</i>	p.Q2434H	0.099
	<i>SMARCA4</i>	p.D694E	0.087
12	<i>BCOR</i>	p.P1613L	0.483
13	<i>TET2</i>	p.E1874K	0.17
15	<i>TP53</i>	p.R283P	0.065

**Somatic  
Mutations in  
Known Cancer  
Genes**

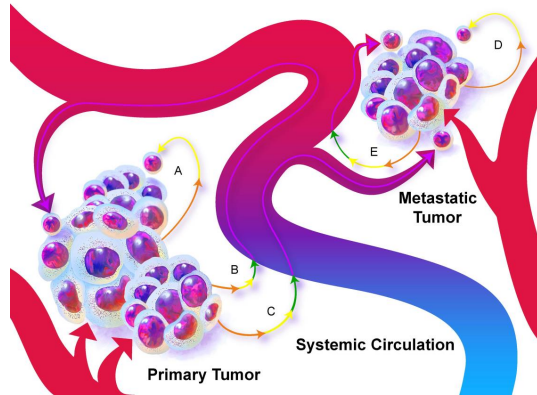


Comen E *et al.* SABCS 2014. Abstract # 896

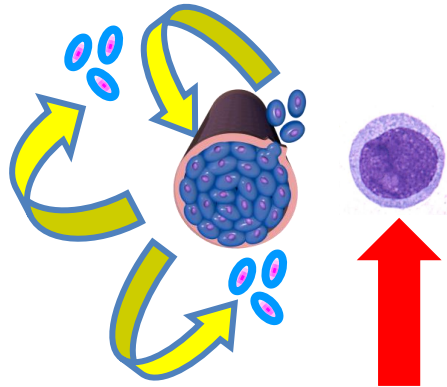


# The functional state of cancer is cellular mobility

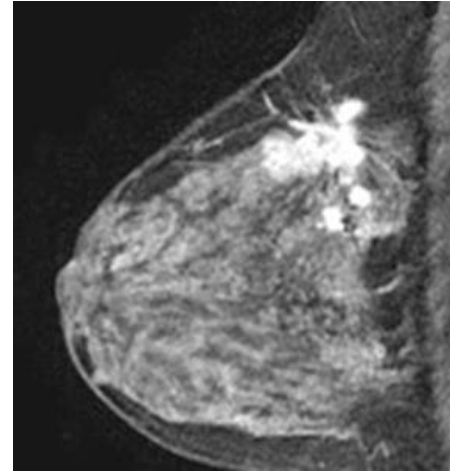
**Growth is a  
Consequence  
of Mobility**



**Stroma May Be  
a Therapeutic  
Target**



**Explains  
Gompertzian  
Growth and  
Cancer  
Anatomy**



**Novel  
Interventions  
are Under  
Development**

