

# Precision Medicine

Precise Landing for a Cancer Moonshot

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May 15 2016  
Adelaide Australia



Kurna People  
Ninna Marni

The Royal Australasian  
College of Physicians

# Disclosure

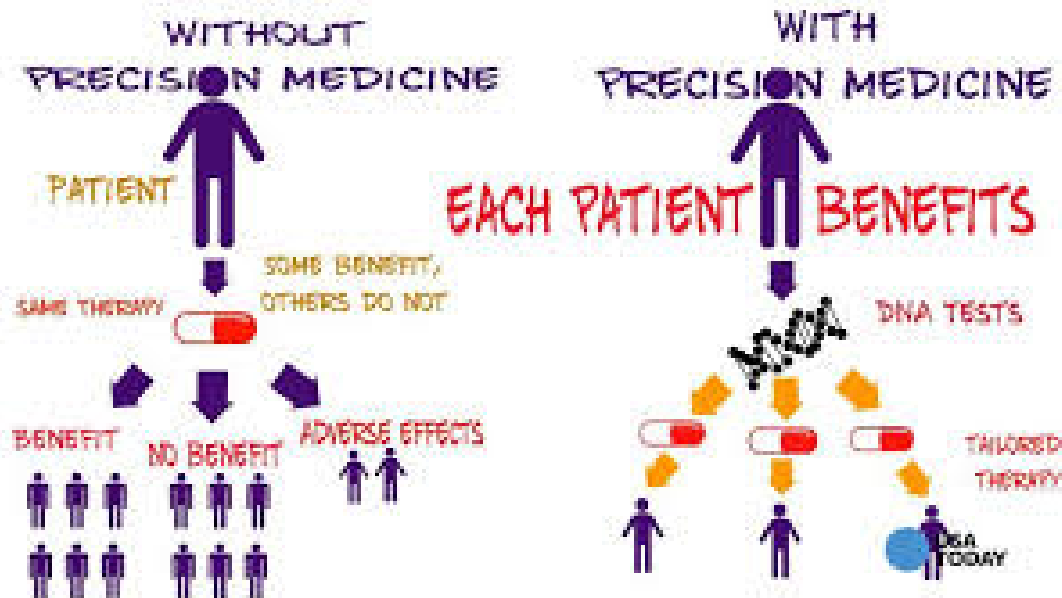
- Supported from NIH (R01CA70896, R01CA75503, R01CA107382, R01CA8607 P30CA56036)
- Supported from Breast Cancer Research Foundation
- Supported from Marian Falk Foundation
- Supported from State of Pennsylvania Department of Health
- Founder and CSO of AAA Phoenix and ProstaGene
- External Advisor to 7 NCI cancer centers

# Precise Medicine

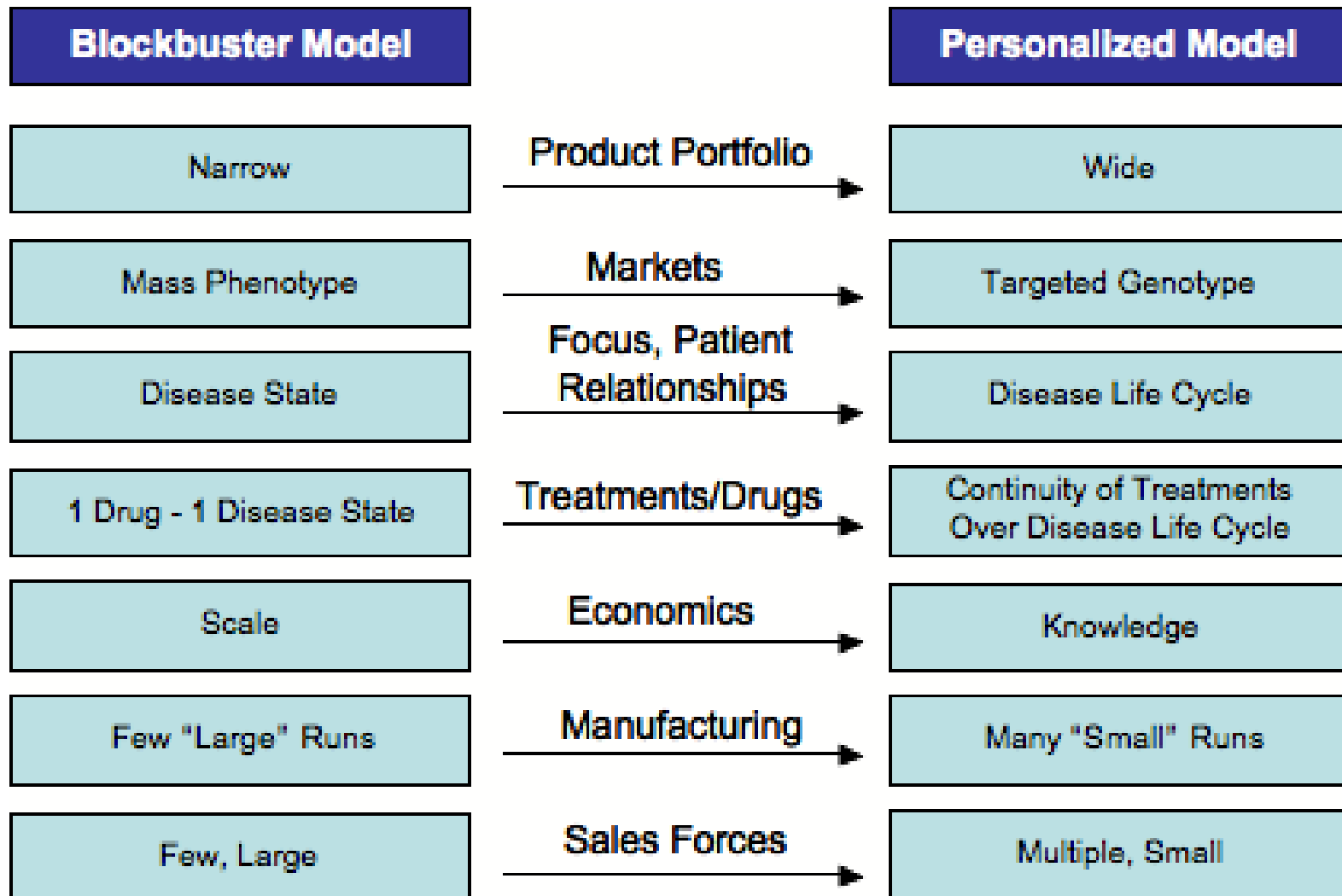
- Definition
- Resourcing
- Ethics
- FDA Approved Drug - Retasking

# Precision Medicine

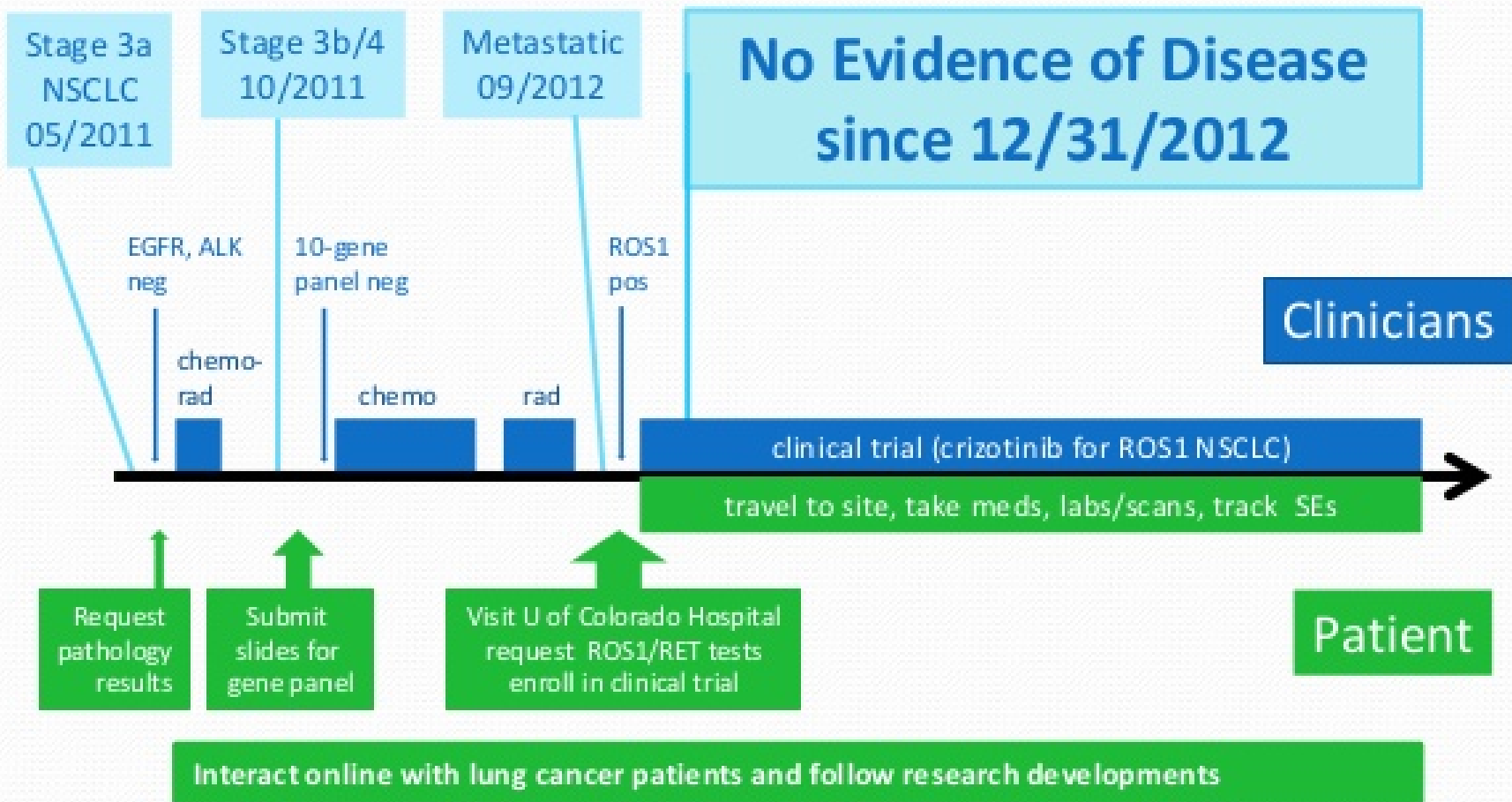
- Medical Model
- Customizes Healthcare
- Decision practice and products
- Tailored to the individual patient



# Precise Medicine- evolution of medical culture












# I'm Alive Thanks to Precision Medicine ... and Other Patients



## CANCER THERAPY TYPE

## EXAMPLES

	Chemotherapy	5-Fluorouracil Carboplatin
	Hormone therapy	Abiraterone acetate Fulvestrant
	Epigenetic modifiers	Azacitidine Decitabine
	Immune stimulators & Checkpoint inhibitors	Aldesleukin Pembrolizumab
	Angiogenesis inhibitors	Bevacizumab Regorafenib
	Vaccines	Sipuleucel-T DCVax-L
	Adoptive immunotherapy	Anti-CD19 CAR-T cell therapy CART-Meso
	Therapeutic antibodies	Cetuximab TDM-1
	Cell signaling inhibitors	Ibrutinib Imatinib Ceritinib

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Within each category, some therapeutics are more precise than others

**AACR** American Association  
for Cancer Research

©2015 American Association for Cancer Research

# Precision Medicine



- 2015 Precision Medicine Initiative
- Public trust
- Accountability
- Data sharing, quality integrity





# Moon Shot Initiative



- 2016 moon shot initiative
- \$1B initiative
- Discovery
- Delivery

And the goal of this initiative — this “Moonshot” — is to seize this moment. To accelerate our efforts to progress towards a cure, and to unleash new discoveries and breakthroughs for other deadly diseases.

-Vice President Joe Biden, January 13, 2016

- Cancer Vaccine
- Early cancer detection
- Immunotherapy/combination
- Genomic profiling- microenvironment
- Pediatric Cancer
- FDA- virtual center of excellence

# Ethics of Precision Medicine

## Barriers to Precision Medical Care

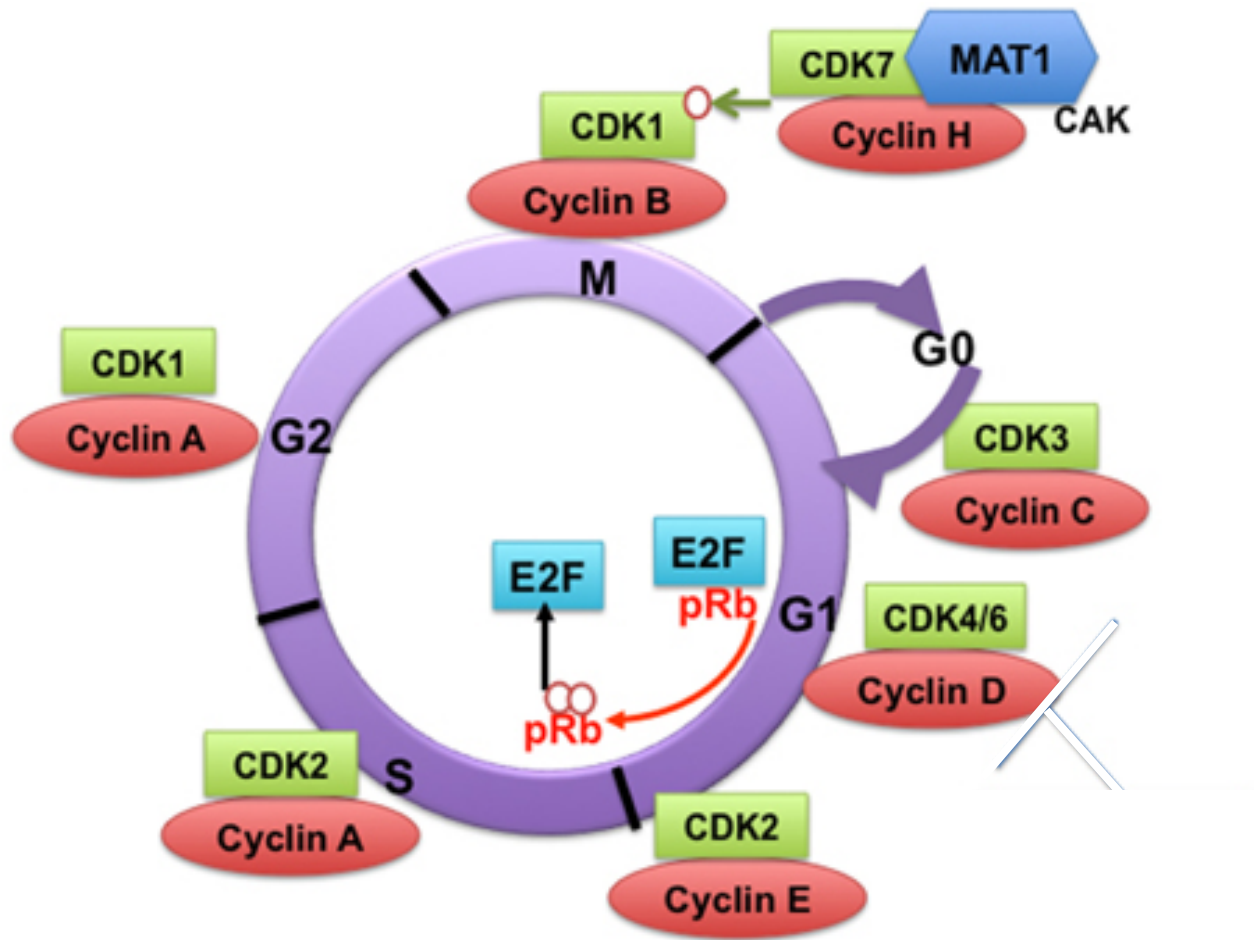
- Financial barriers
  - Reimbursement,
- Discrimination
  - Medical insurers, employers
- Legal barriers to innovation and development
  - Patent protection -Federal court- (Myriad ruling), Patent,
- Incumbent inertia
  - Current dogma, financial incentive to status quo.



# Precision Medicine- Cancer Targets

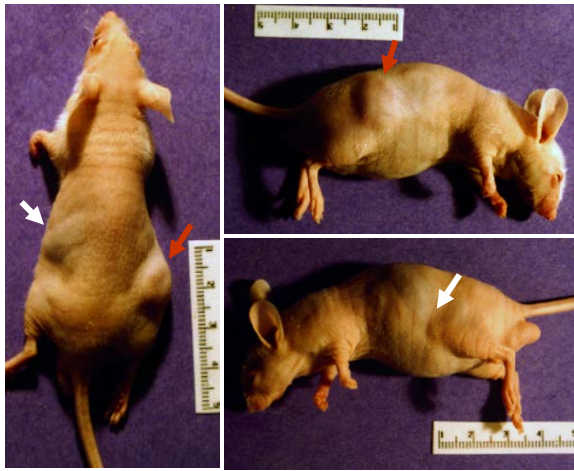
1. Cell-cycle and cyclin D1 kinase
2. Nuclear receptor acetylation
3. CCR5

# 1. Cyclin D1 kinase inhibitors



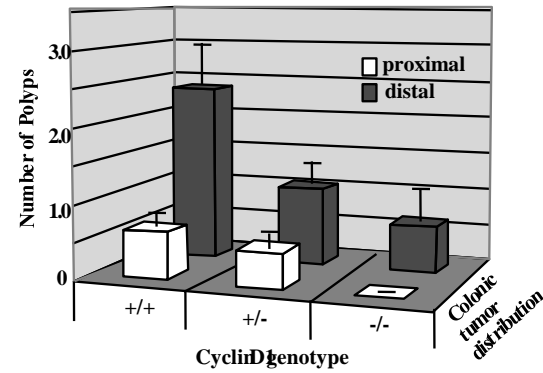
# 1. Cyclin D1 kinase inhibitors

**Cyclin D1 gene  
Anti-sense reduces tumor formation**



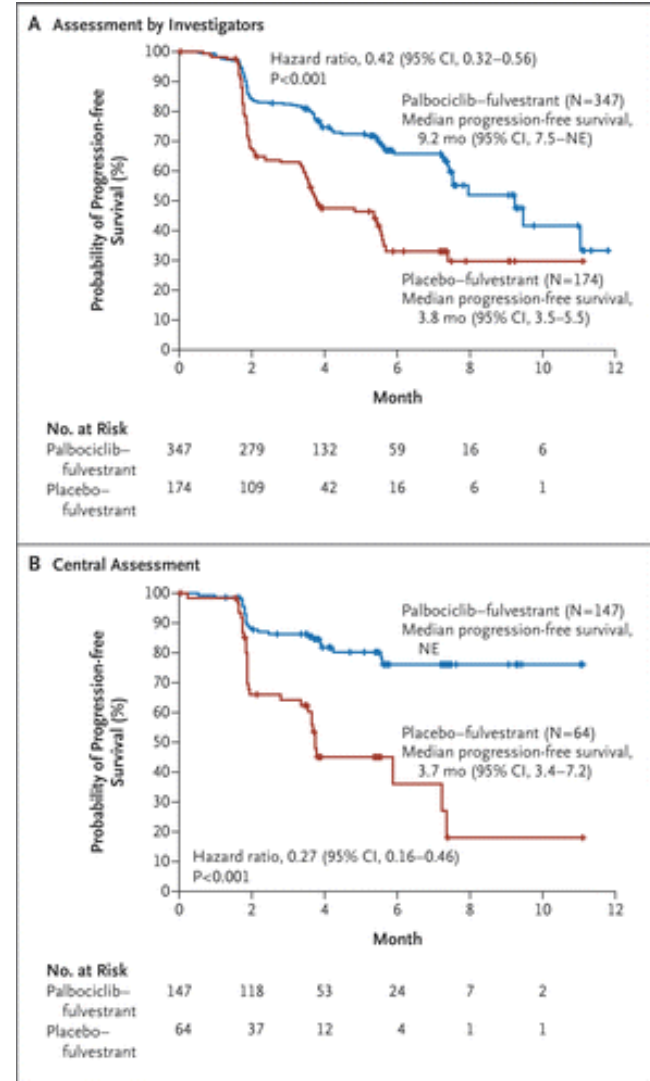
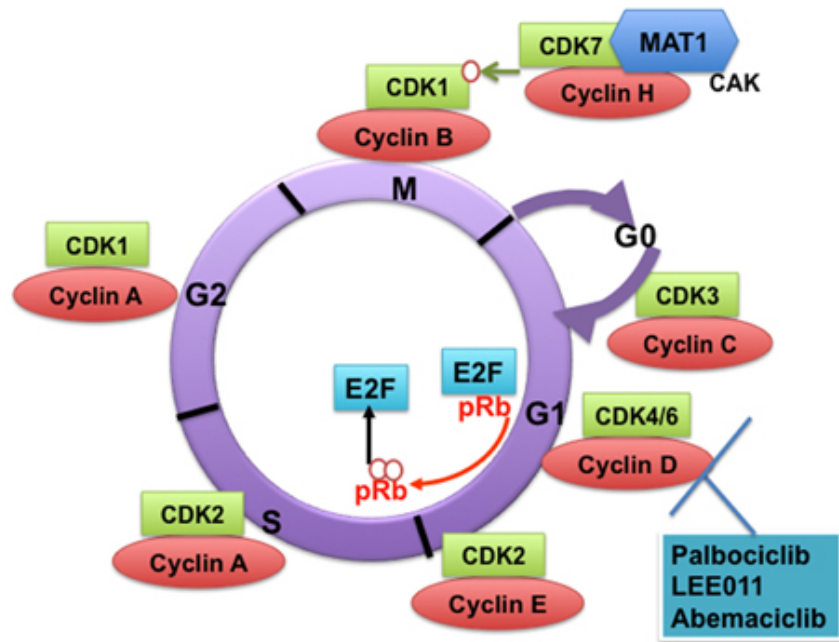
Lee, R, Pestell, R, (MCB) 2001

**Cyclin D1 gene  
deletion reduces tumor formation**



Hult, J, Pestell, R, (MCB) 2003

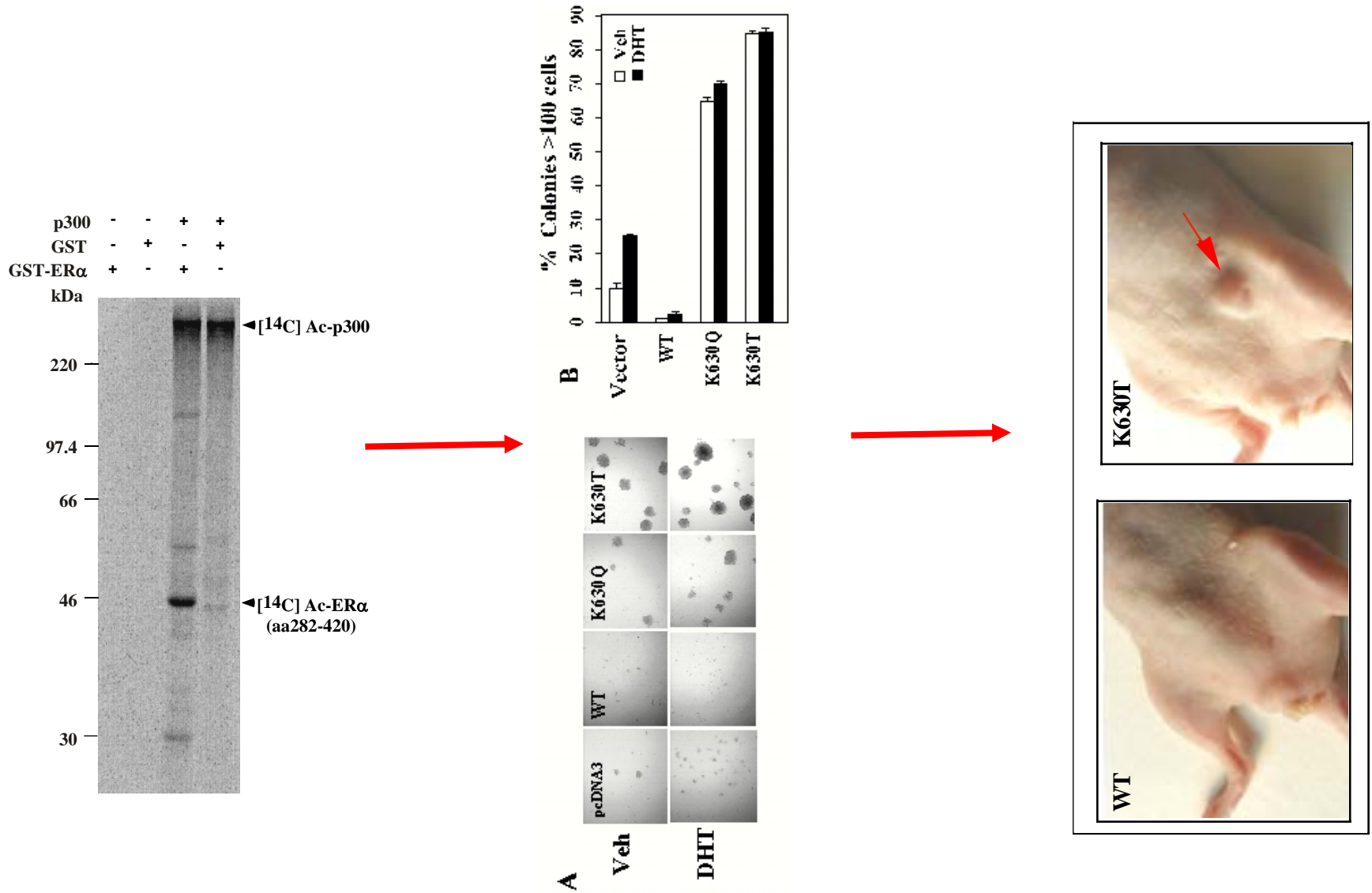
# 1. Cyclin D1 kinase inhibitors



# Precision Medicine- Cancer Targets

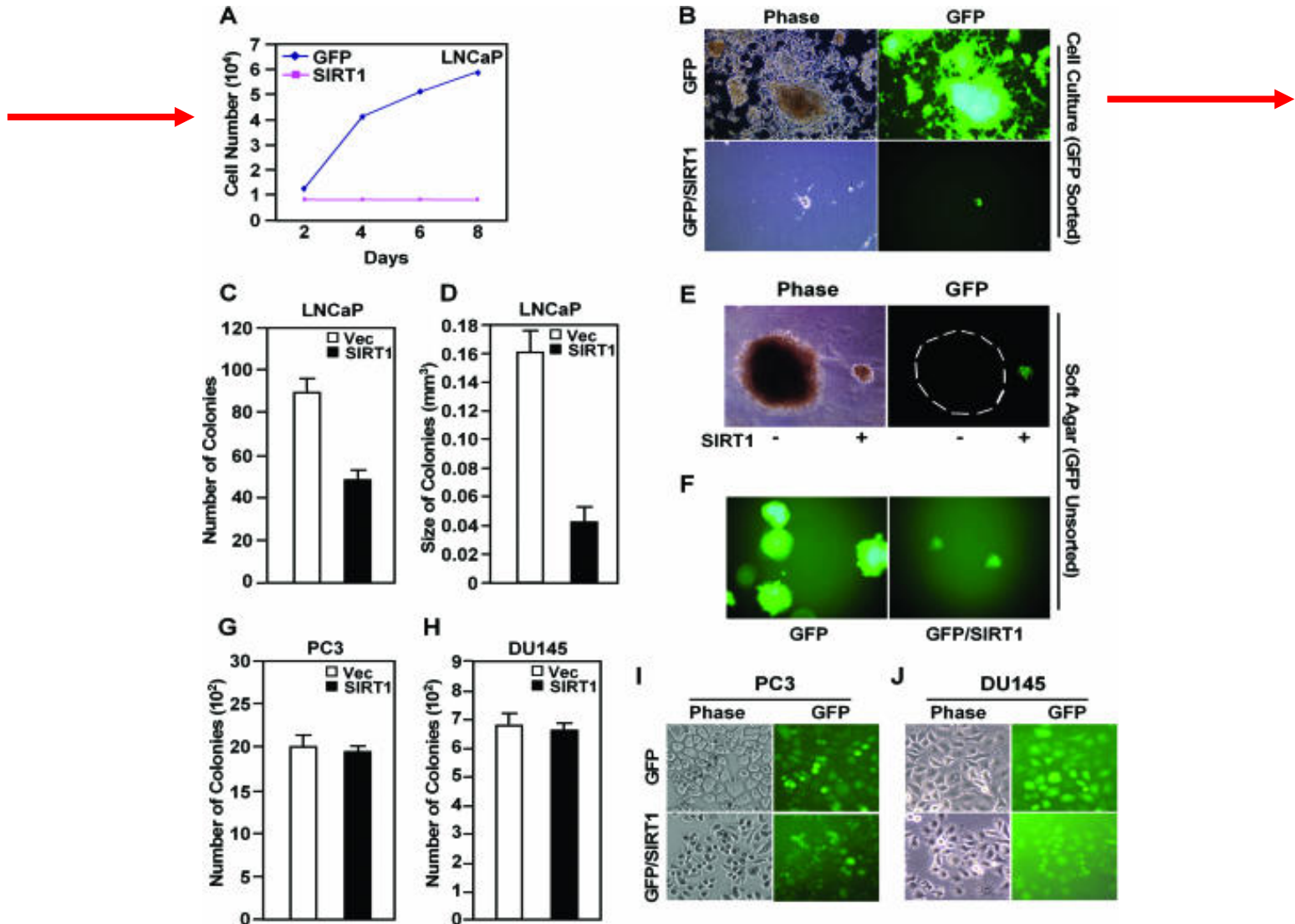
1. Cell-cycle and cyclin D1 kinase
2. Nuclear receptor acetylation
3. CCR5

# 2. Nuclear Receptor Acetylation Governs tumor growth





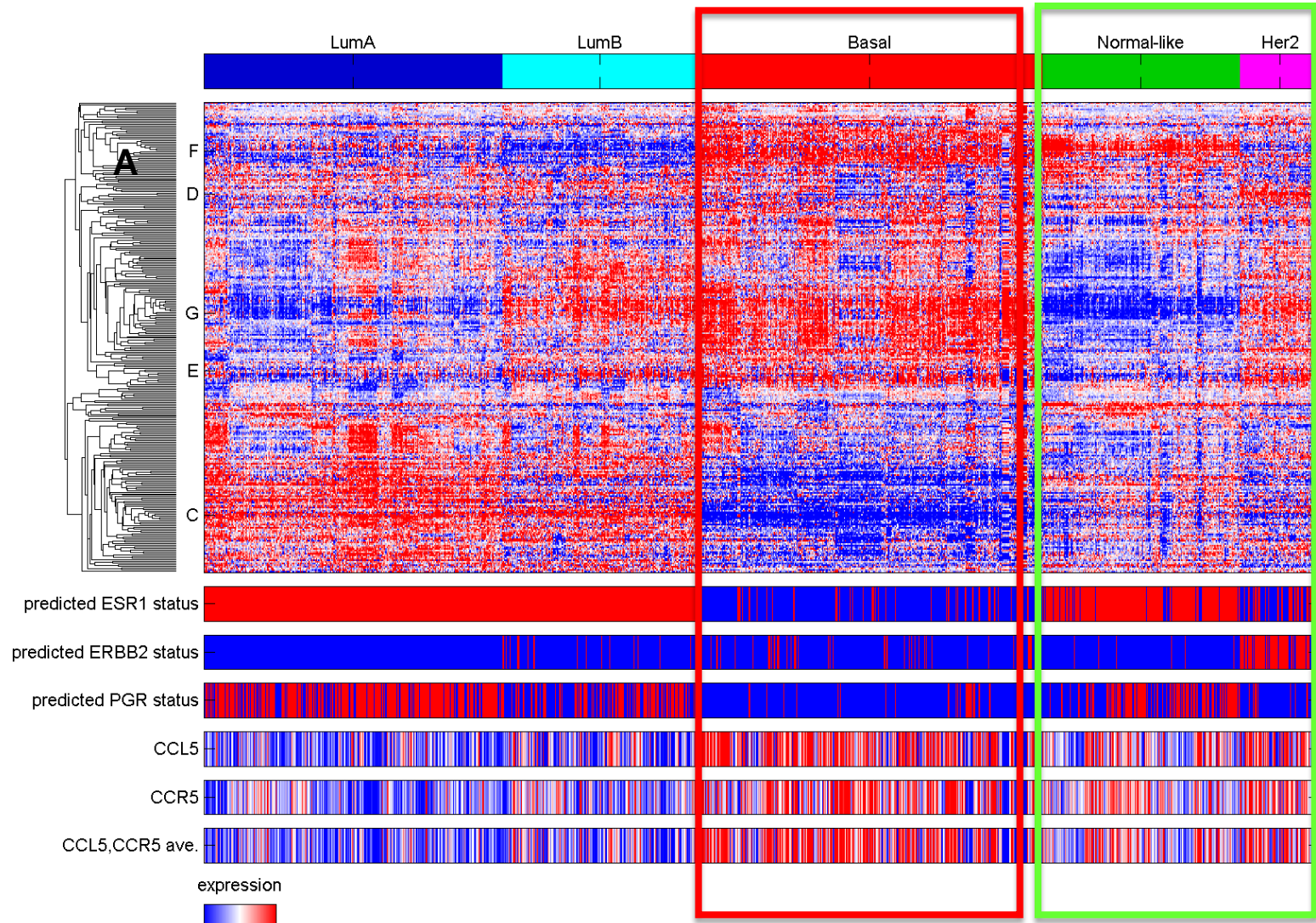
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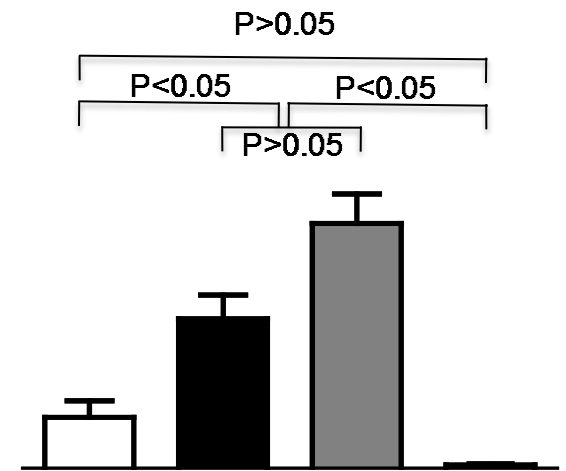
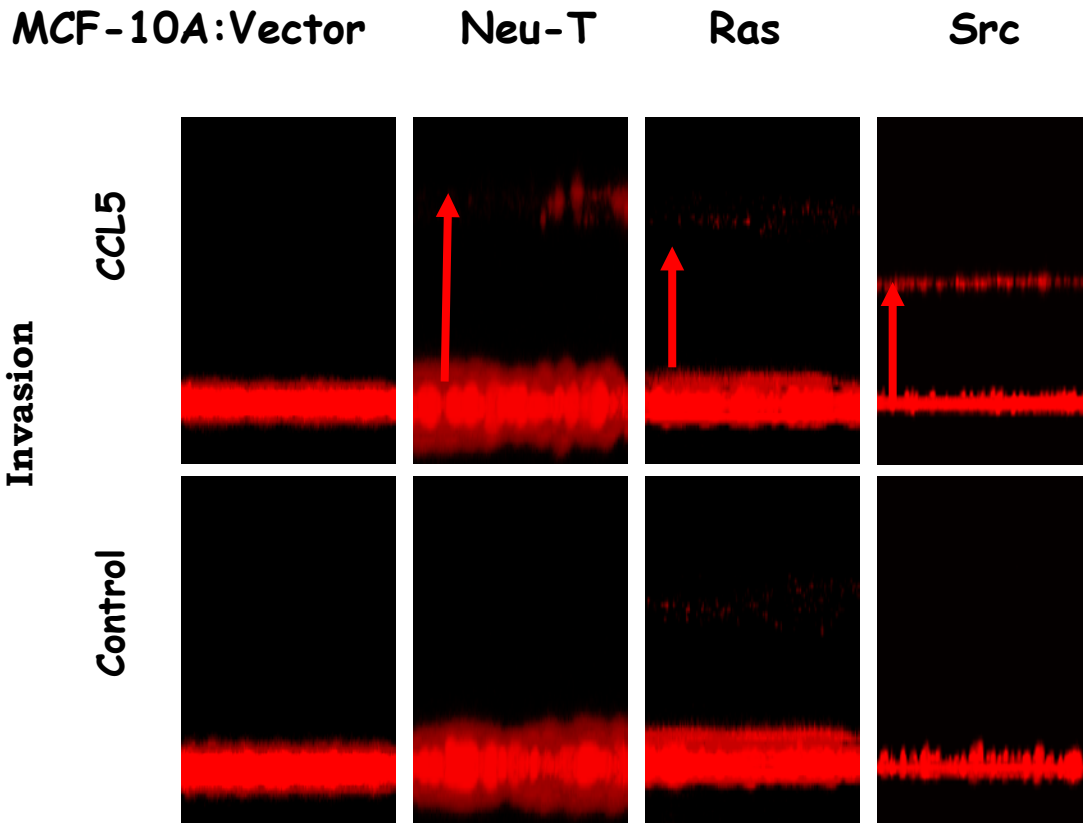
# Precision Medicine- Cancer Targets

1. Cell-cycle and cyclin D1 kinase
2. Nuclear receptor acetylation
3. **CCR5 – HIV co-receptor**

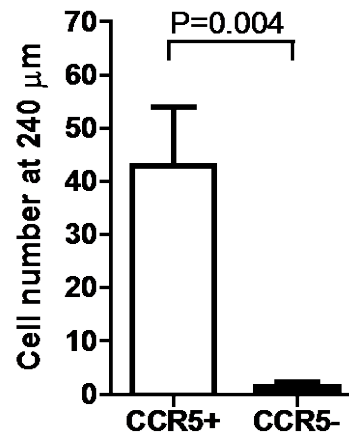
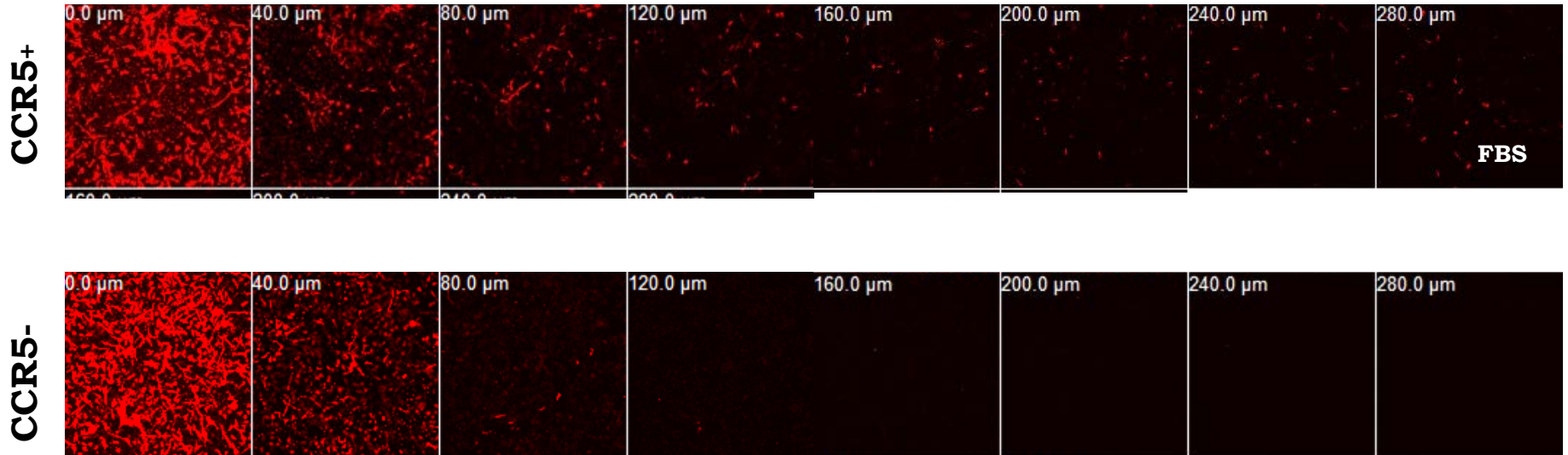
# 3. CCR5 Receptor is expressed in Breast Cancer



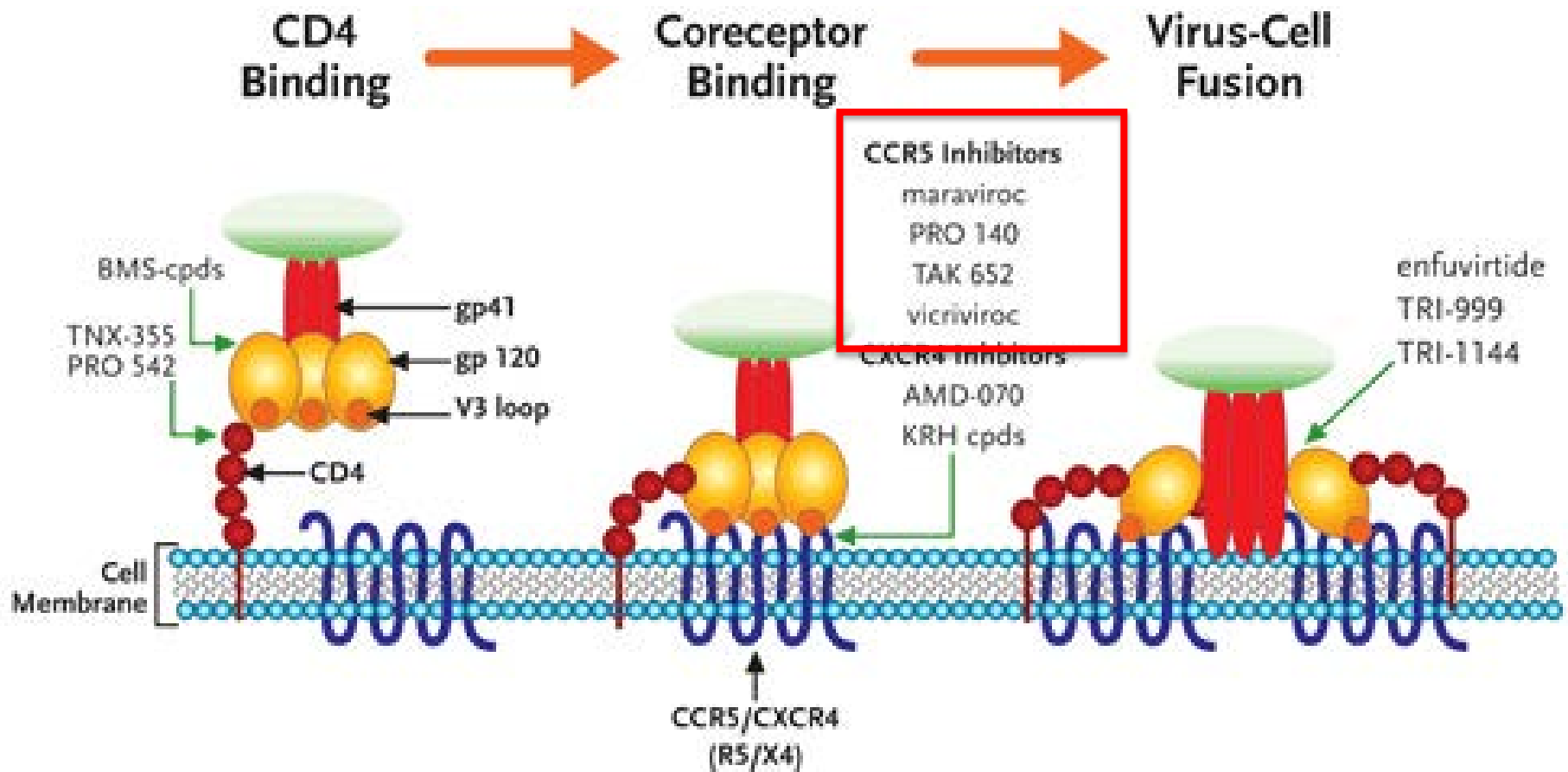
# Breast oncogene induction of CCR5 Receptor Signaling and Invasion



# CCR5 Receptor Expression Promotes Breast Cancer Cell invasion

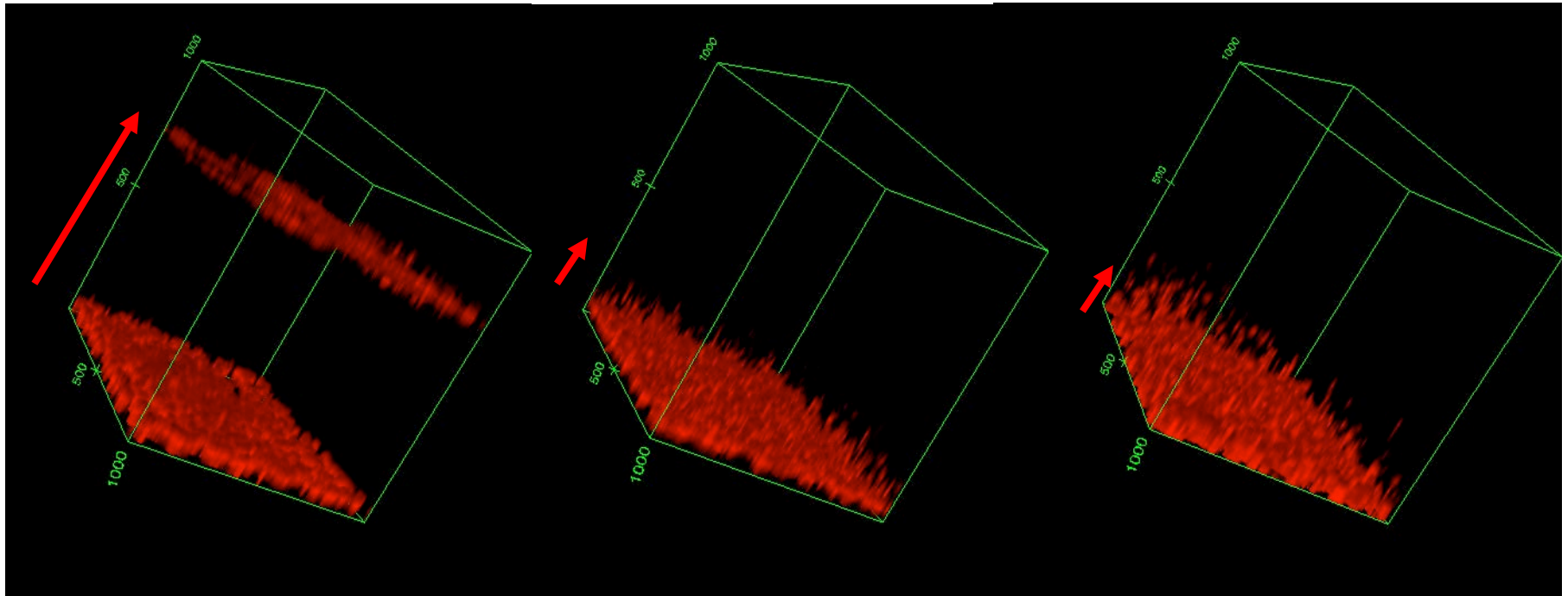


# The HIV CCR5 Receptor Signaling and Function





# CCR5 Receptor Inhibition blocks Breast Cancer invasion

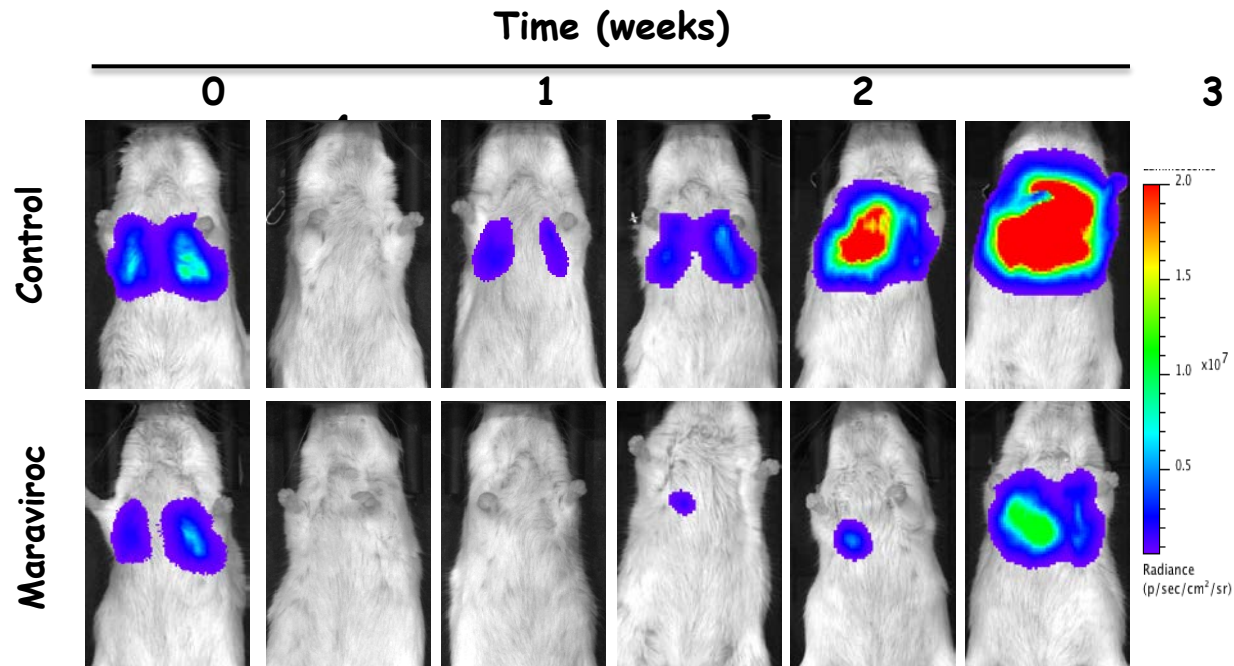


Control

Maraviroc 100 nM

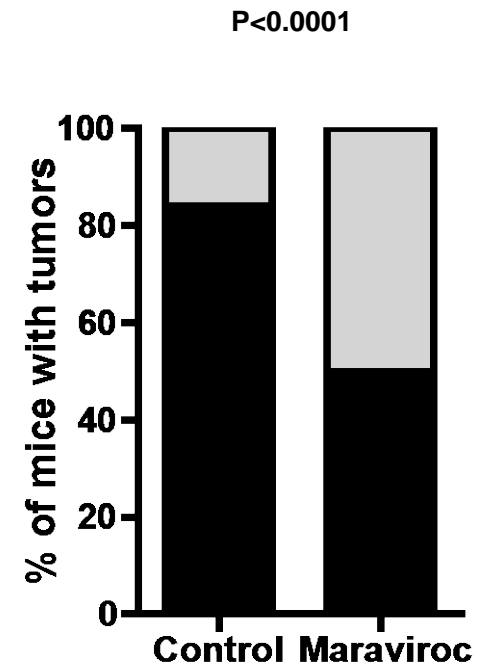
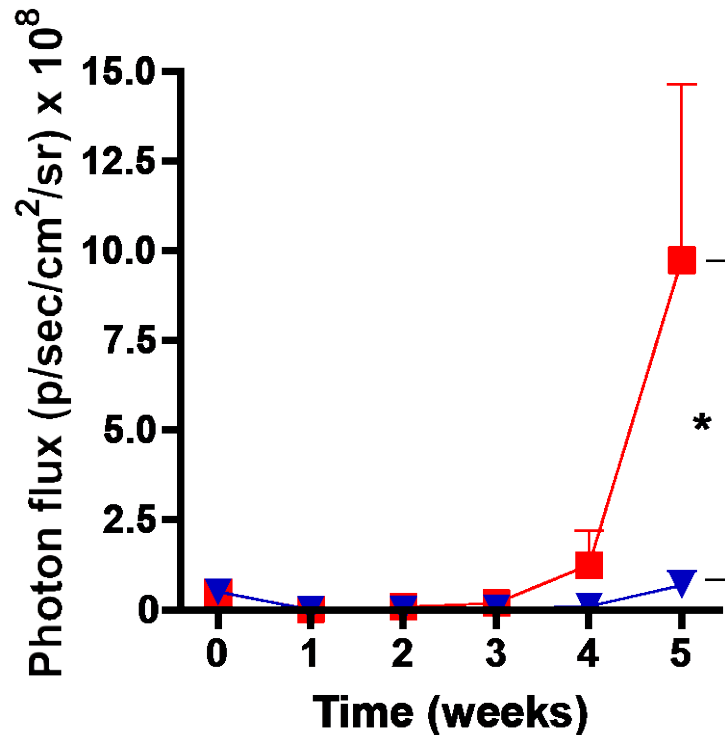
Vicriviroc 100 nM<sup>B</sup>

# CCR5 Receptor Inhibition blocks Breast Cancer Metastases lung metastasis in vivo

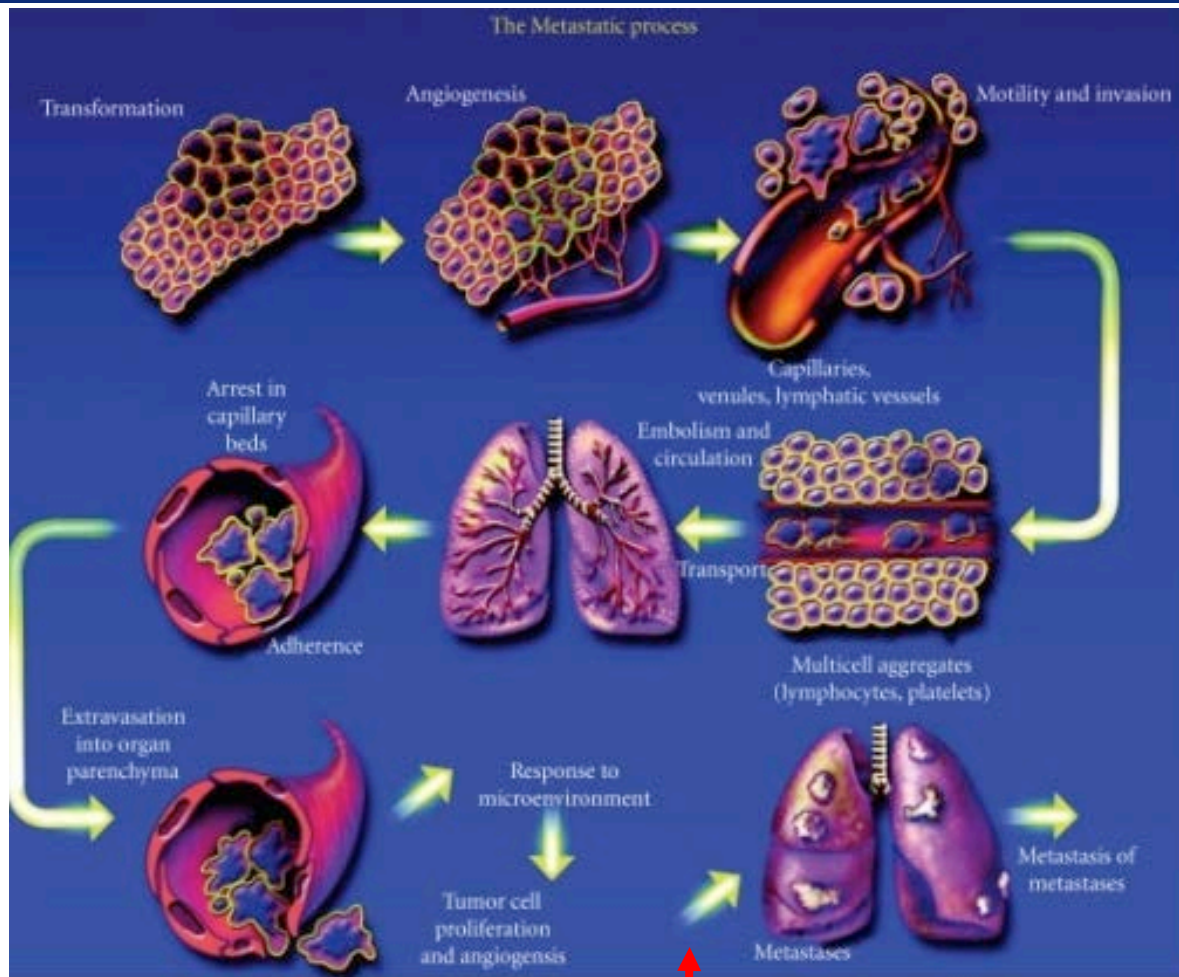




# CCR5 Receptor Inhibition blocks Breast Cancer Metastases in vivo

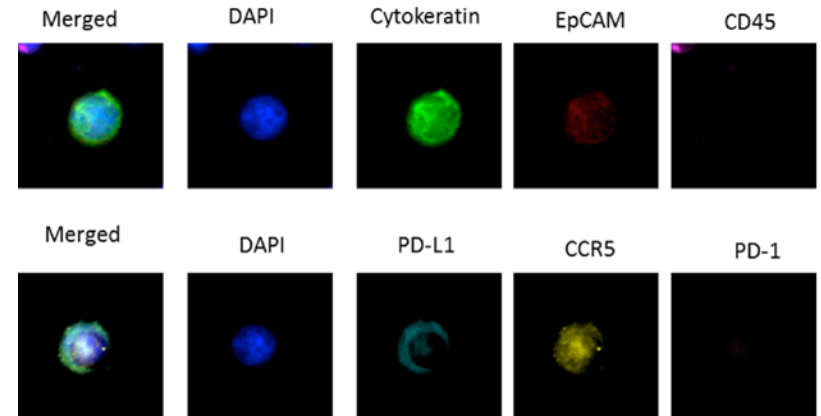
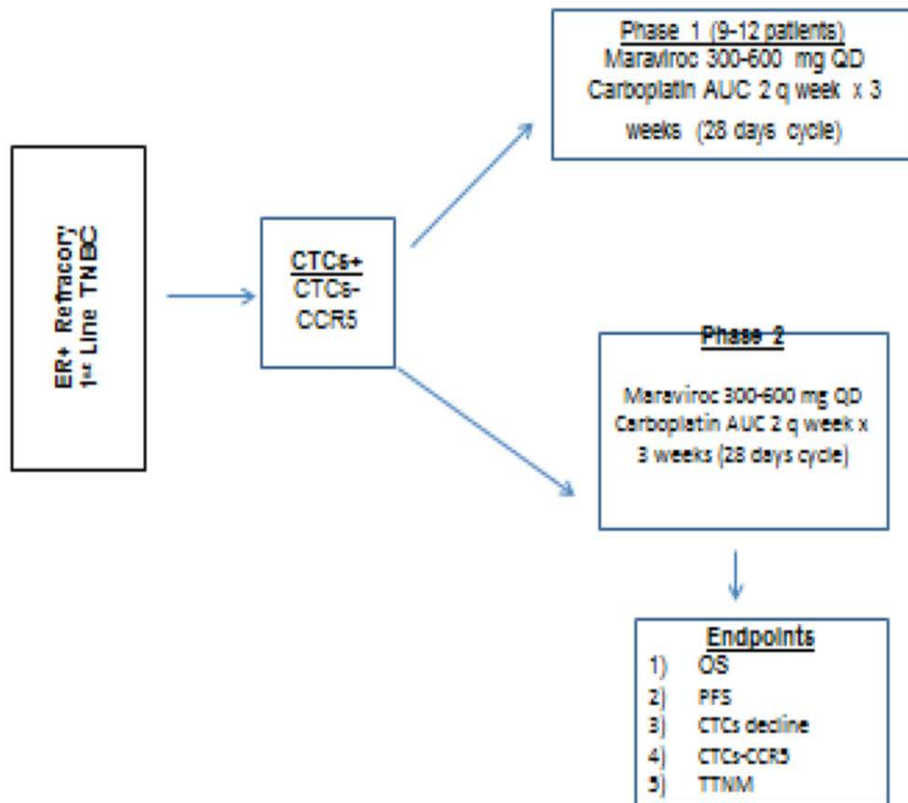


# CCR5 Receptor Inhibition blocks homing step of Metastases in vivo



# Clinical Trial Breast Cancer

## Study Diagram



# CCR5 function in Breast cancer

- CCR5 signaling induced in human basal breast cancer
- Oncogenes induce CCR5 signaling
- CCR5 overexpressed in basal breast epithelial cells
- CCR5 induces invasion and metastasis
- CCR5 inhibition blocks basal breast cancer metastasis in pre-clinical models
- FDA approved safety- expedited Phase I/II clinical trial (in progress)

# Prostate Cancer

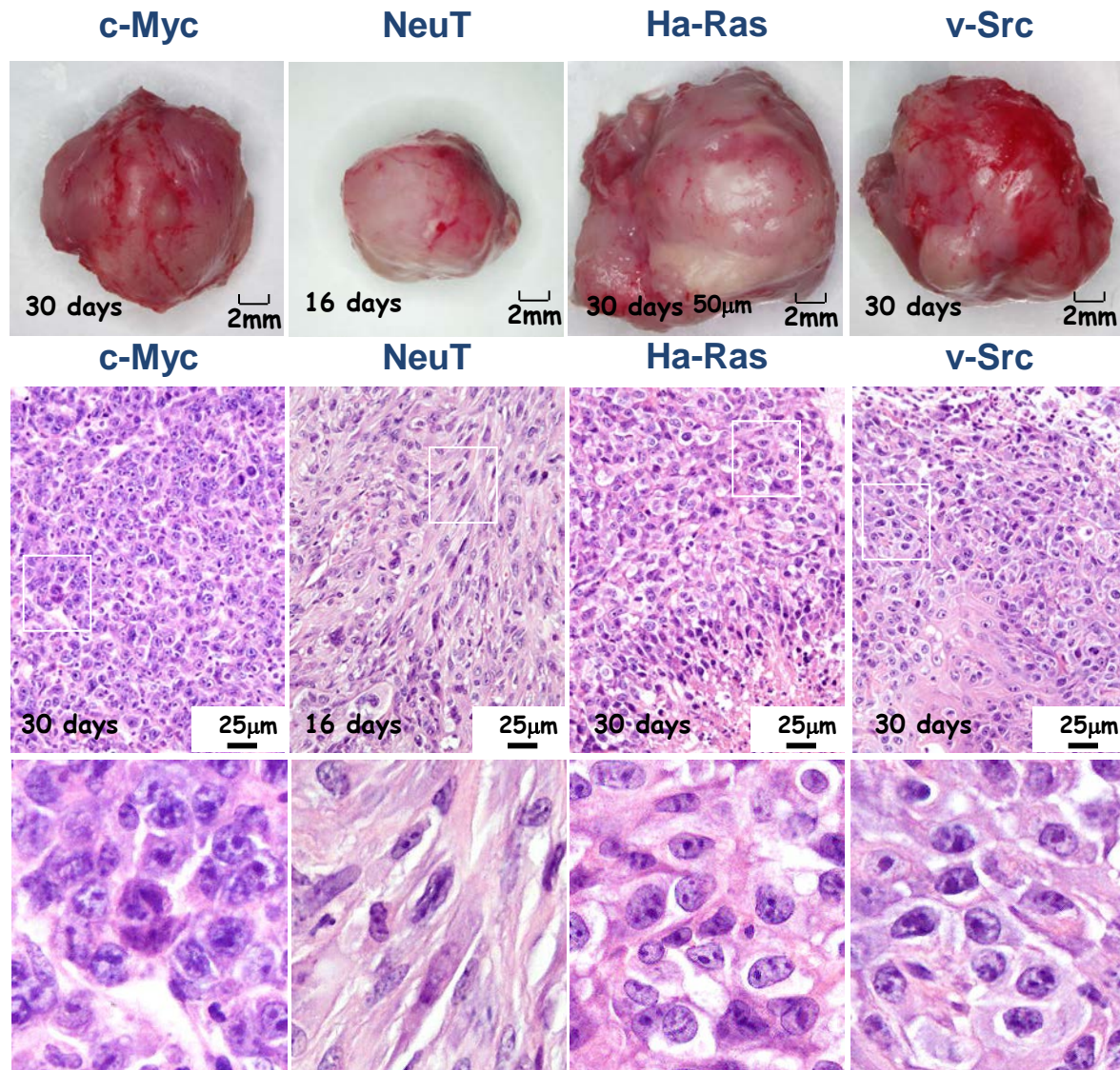
- Most common cancer in American men (ACS 2012)(1/6 men)
- 241,740 men will acquire this year
- 28,170 deaths/per year
- 2.5 M current survivors- no reliable predictors of survivors
- Increasing incidence globally
- Death from metastasis (bone, brain)
- No reliable pre-clinical testing metastasis models

# Development of immune-competent metastatic prostate cancer model

- Immune system participates in human prostate cancer
- Immune competent systems (transgenics)- unreliable metastasis
- Transgenic of Probasin-c-Myc- reflect human disease
- Pre-clinical need for therapy testing in immune-competent animals

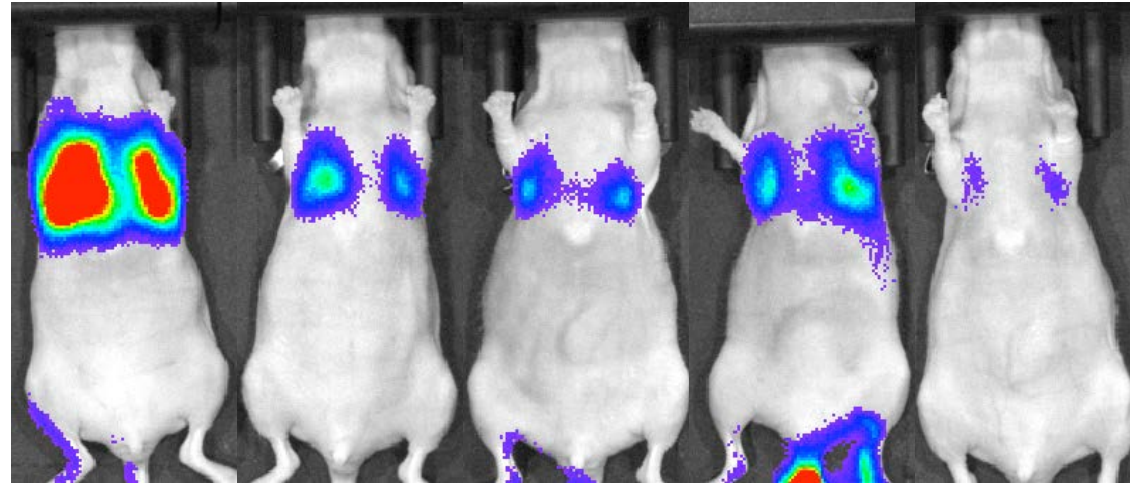


# Lung Metastases of Prostate Cancer lines



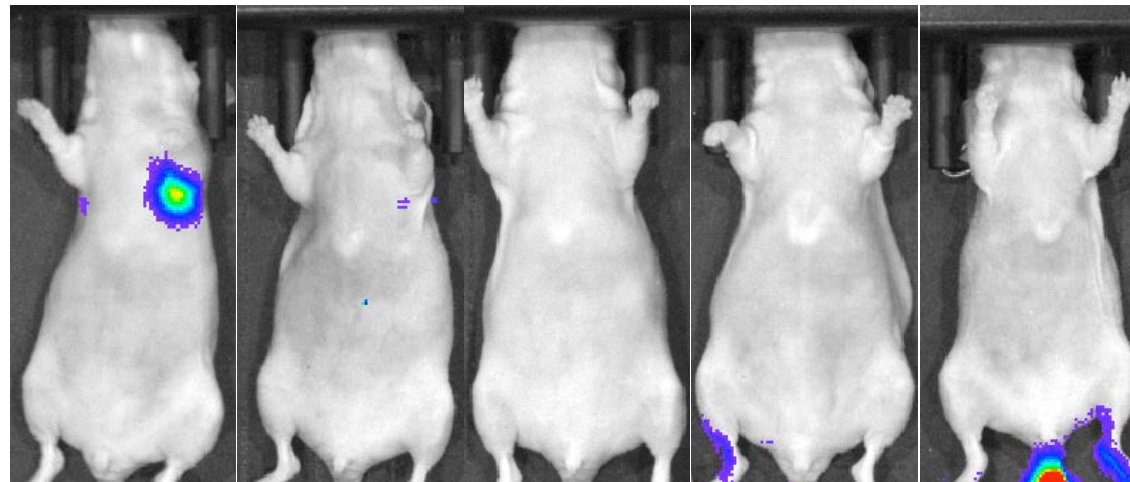
# Vicriviroc blocks lung metastasis

Control

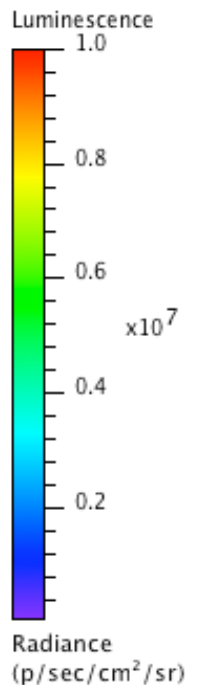


- Vicriviroc blocks lung metastasis

Vicriviroc

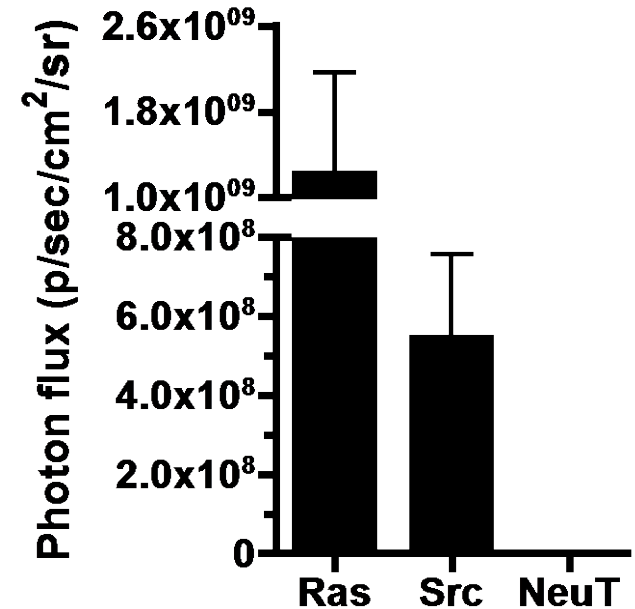
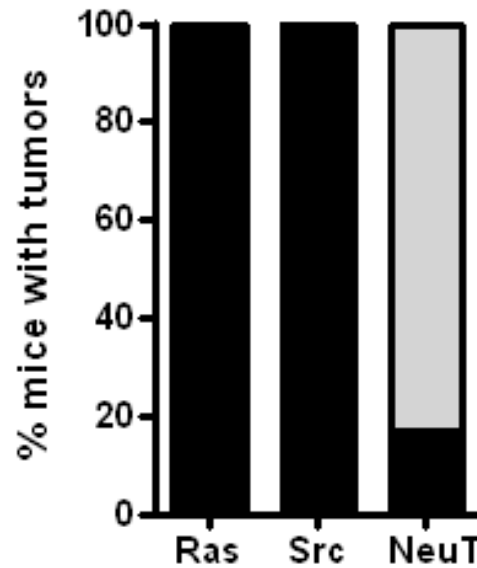
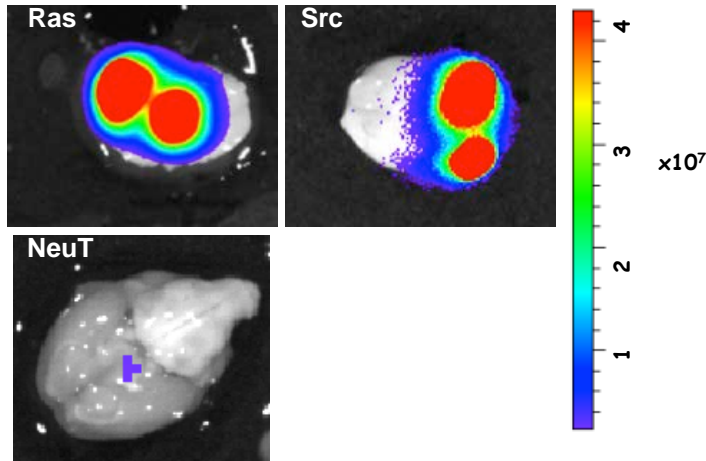


- Preclinical testing demonstrates efficacy

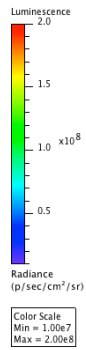




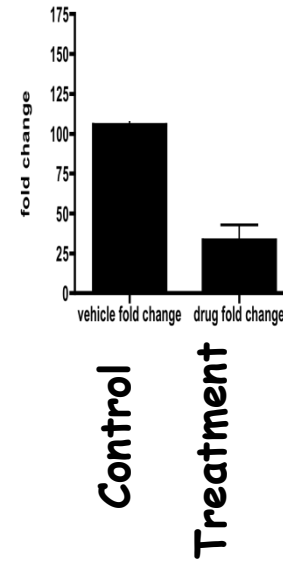
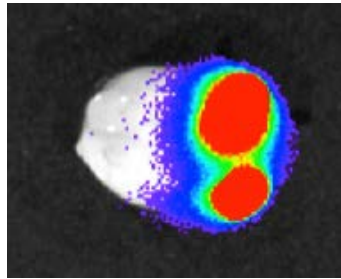
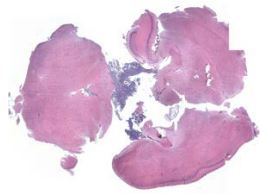
# Isogenic Prostate Cancer Lines Reliably Metastasize to Brain in Immune-competent Mice



# Maraviroc blocks brain metastasis



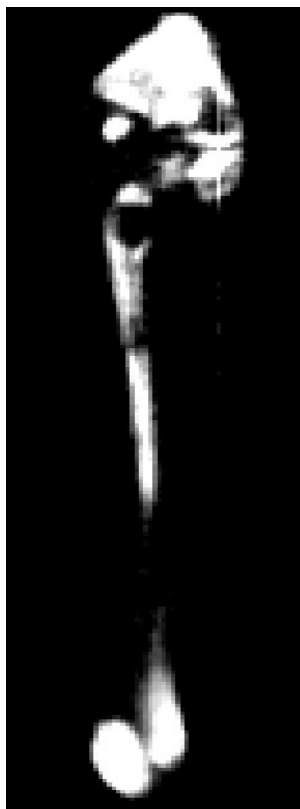
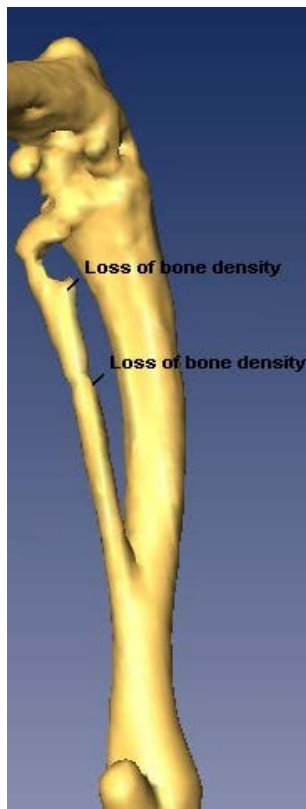
Brain



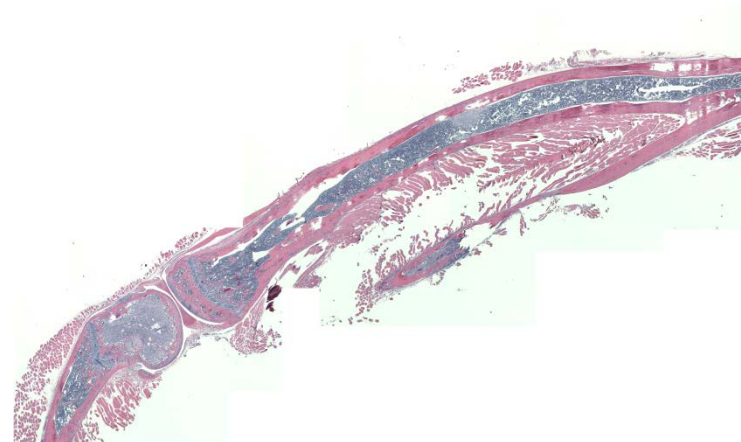
# Isogenic Prostate Cancer Lines Reliably Metastasize to Bone in Immune-competent Mice

X-ray SURFACE RENDERED

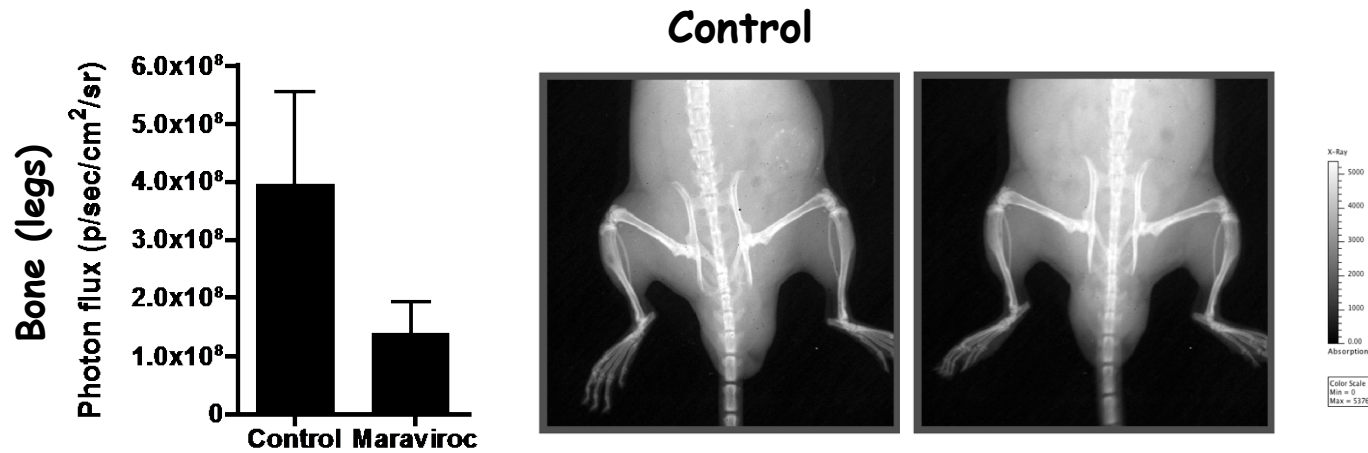
CT



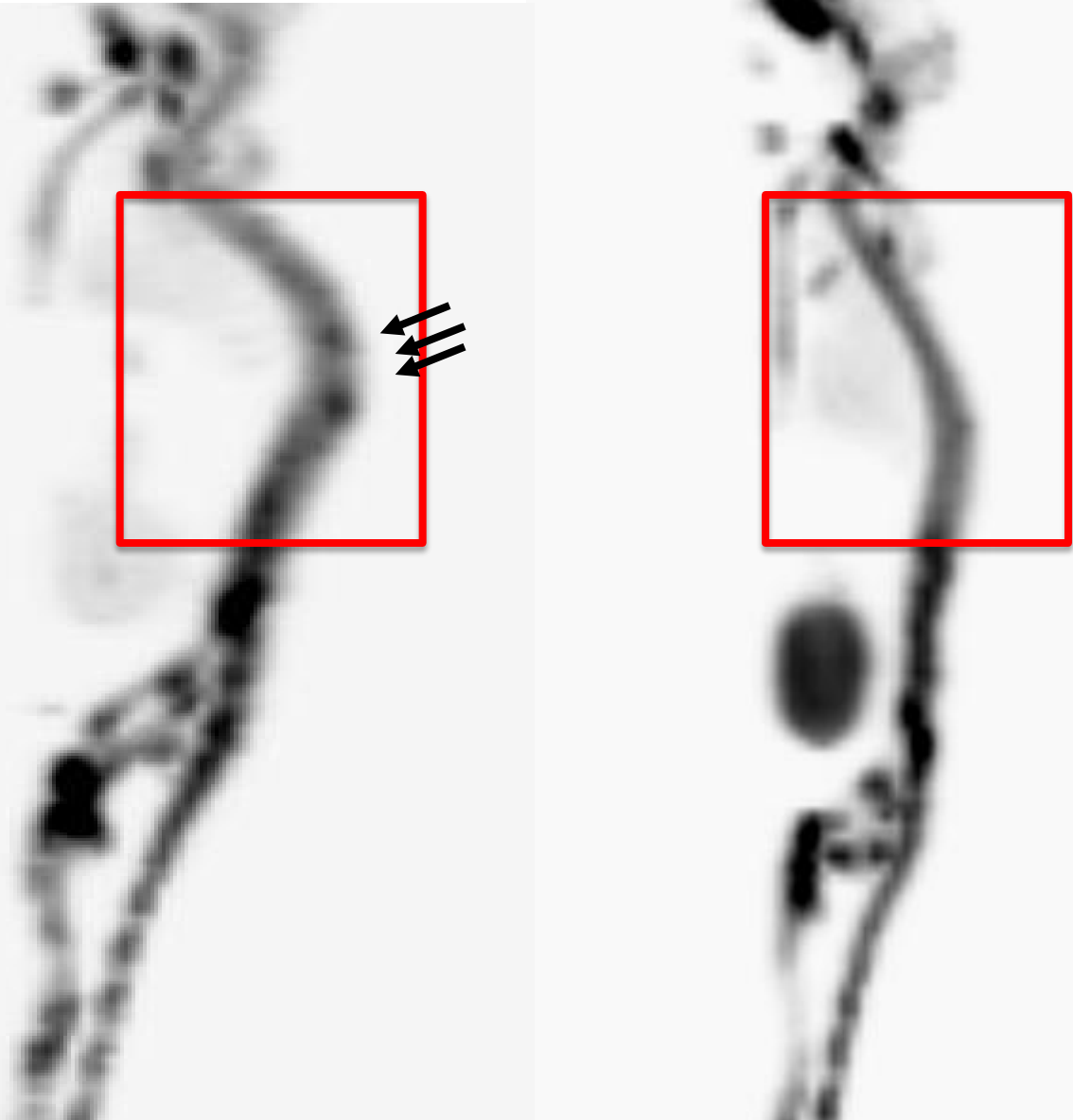
H&E



# CCR5 Receptor inhibition reduces bone metastasis in vivo



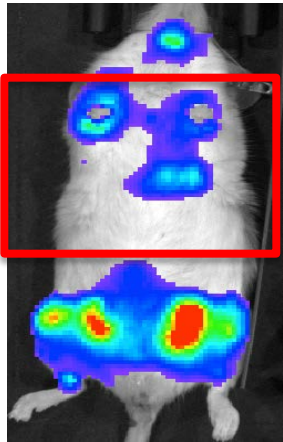
# Maraviroc blocks bone metastasis



# Maraviroc blocks bone metastasis

Control

A



B



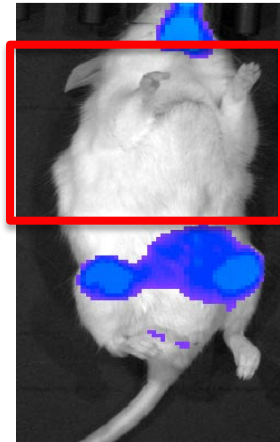
C



D

Maraviroc

F



G



H



I

# CCR5 in Prostate Cancer

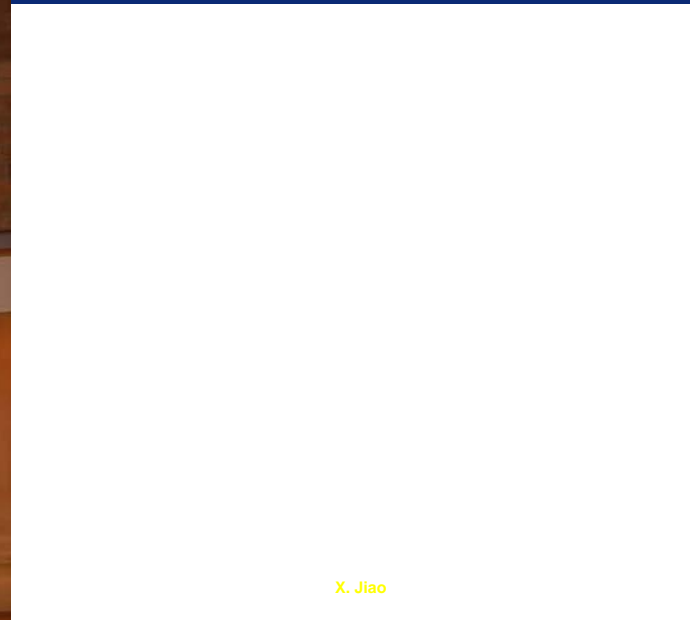
- CCR5 signaling activated in vivo in immune competent animals
- Reliable metastasis of isogenic prostate cancer lines
- CCR5 inhibitors reduce metastasis in immune-competent mice in vivo (total body, lung, bone and bone)
- FDA approved safety- expedited Phase I/II clinical trial

# CCR5 in Human Cancer

- Expressed in broad array of human cancers (breast, prostate, lung, brain, lymphoma)
- Expressed in significant proportion of patients with cancer (>50% of BCa, PCa)
- Expressed on CTC (surrogate for clinical trial/management)
- Enhances DNA damage of chemotherapy- in tumor
- CCR5 inhibitors reduce metastasis in immune-competent mice in vivo (total body, lung, bone and bone).
- FDA repurposing



# Acknowledgements



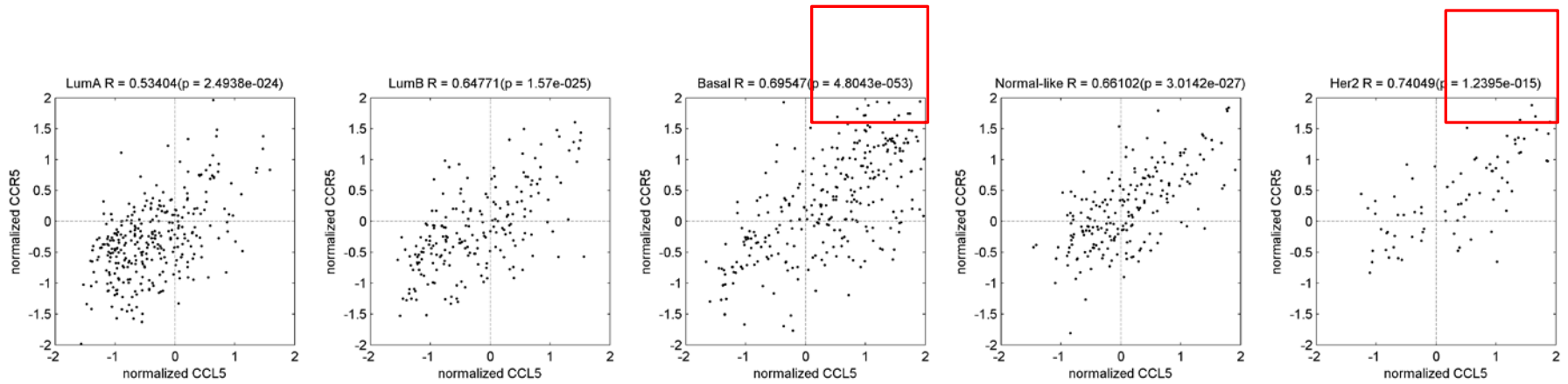
X. Jiao



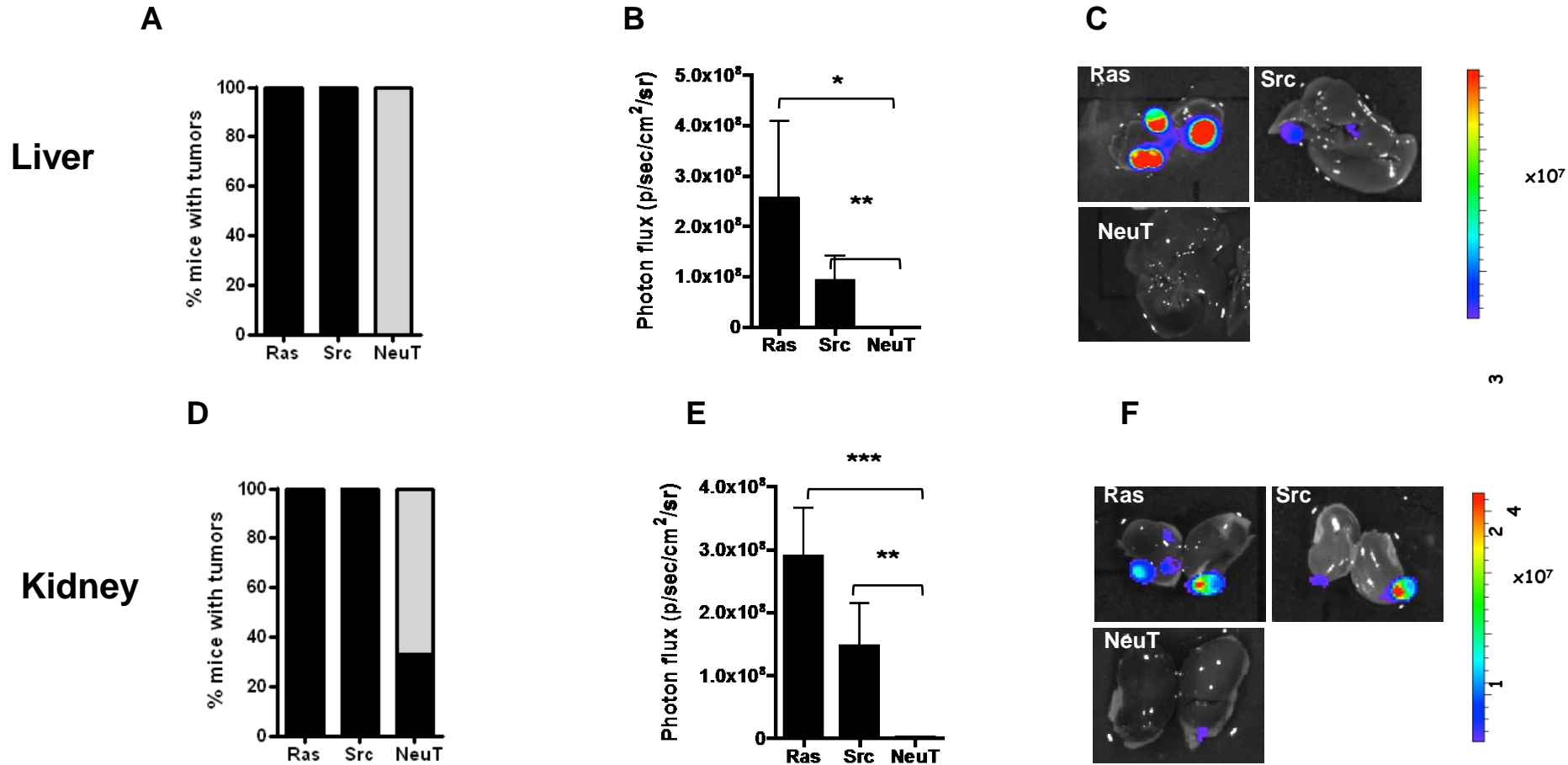
**Spend more time with your family and friends, eat your favorite foods, visit the places you love.**



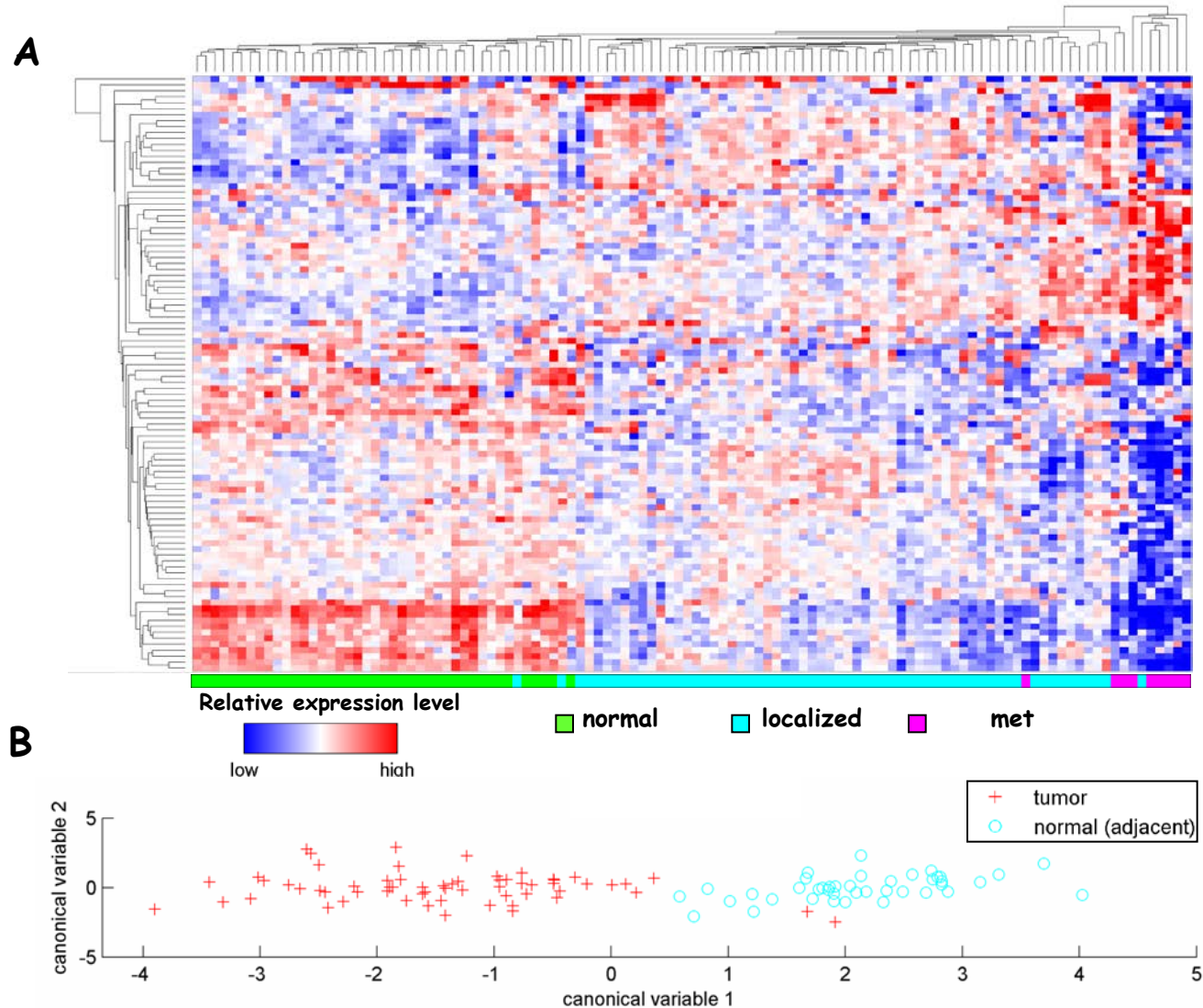
# CCR5 Receptor In Breast and Prostate Cancer Metastases



# Isogenic Prostate Cancer Lines Reliably Metastasize to Liver in Immune-competent Mice

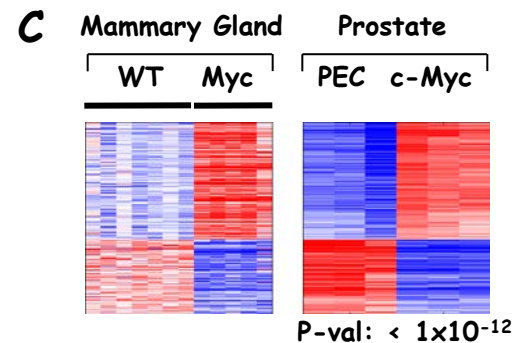
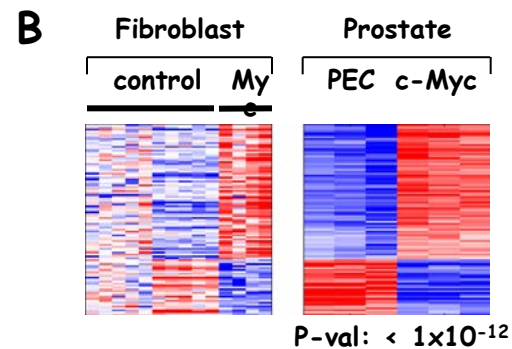
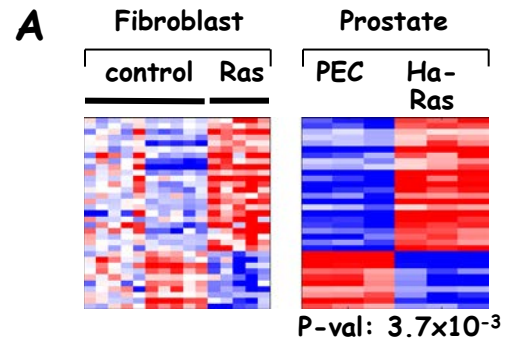


# Oncogene Signature Distinguishes Normal vs. Tumor



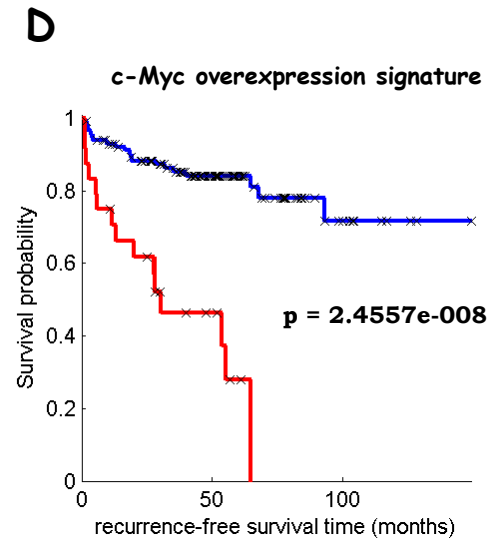


# Prostate Cancer Isogenic Lines-conserved oncogene signature



Relative expression level

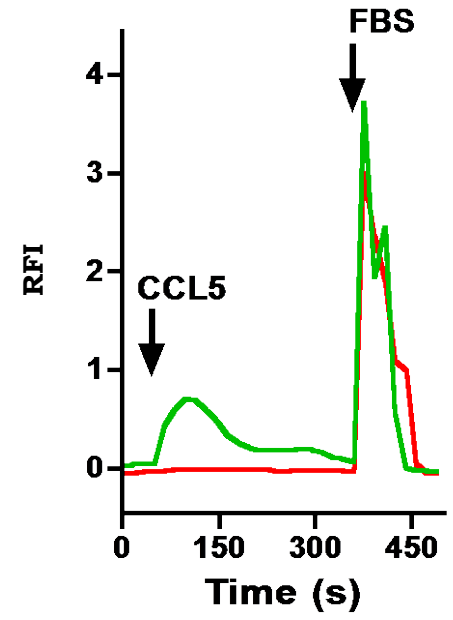
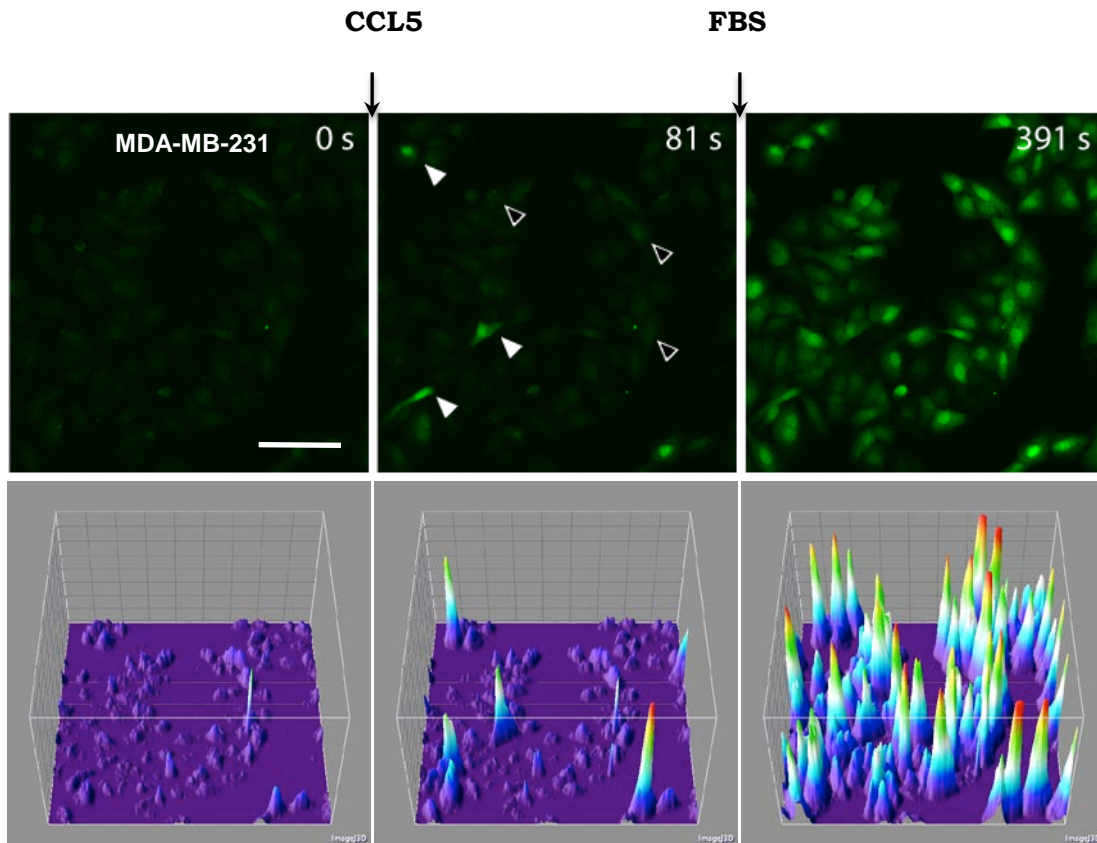
low high



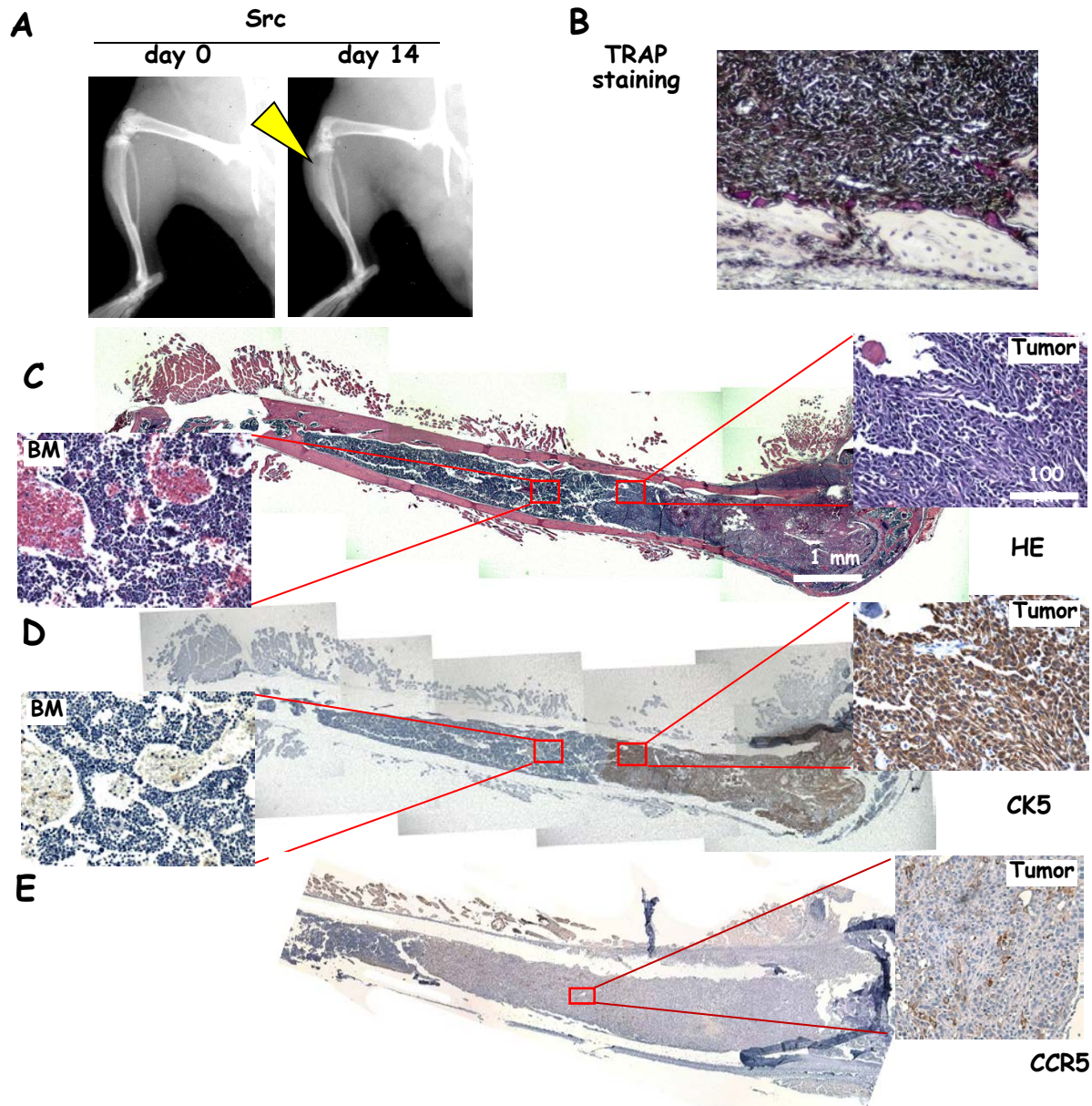
— Low Expression ( $< 75$ th percentile,  $n = 115$ )

— High Expression ( $> 75$ th percentile,  $n = 39$ )

# 3. CCR5 Receptor Signals In Breast Cancer



# Isogenic Prostate Cancer Lines Reliably Metastasize to Bone in Immune-competent Mice

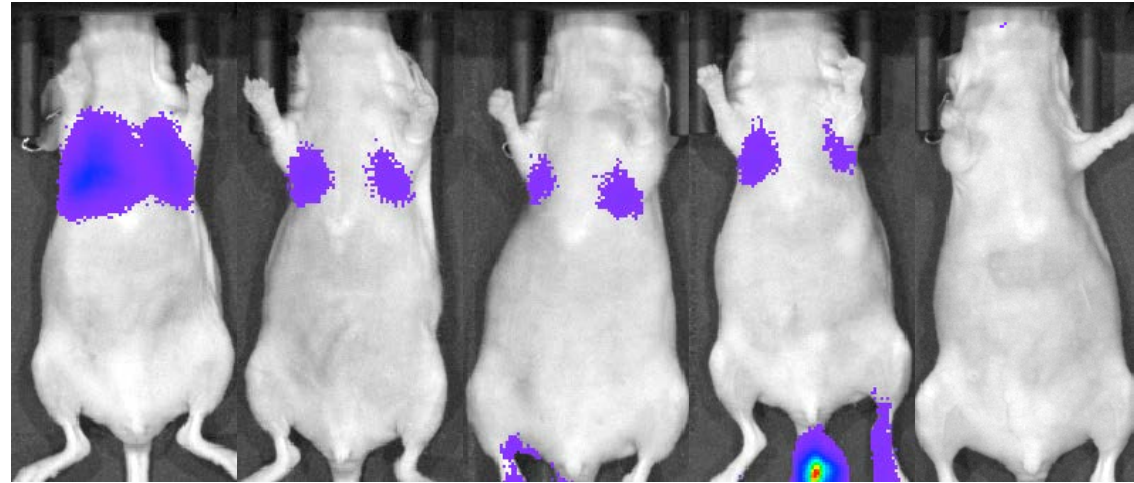




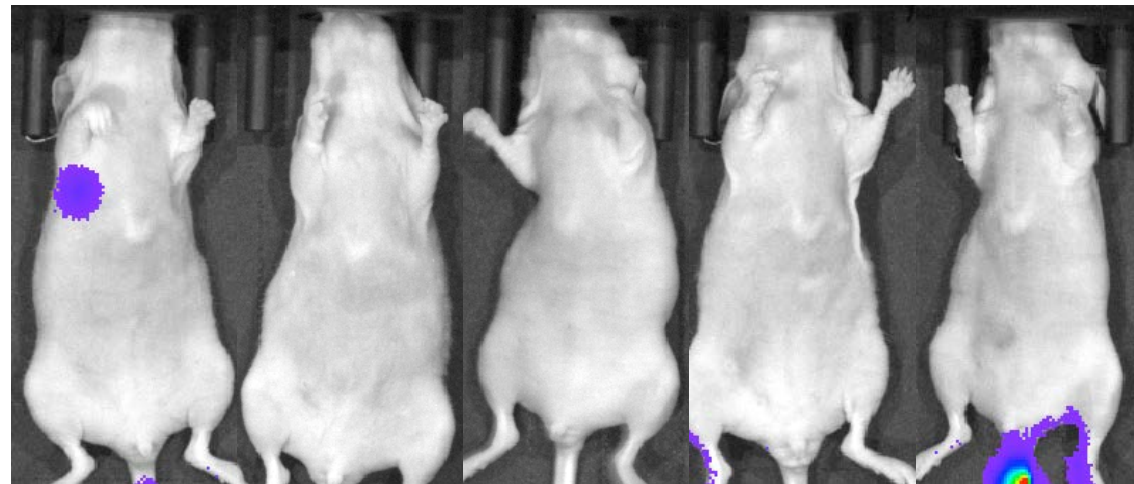
# Vicriviroc blocks lung metastasis 2 weeks

- Vicriviroc blocks lung metastasis
- Preclinical testing demonstrates efficacy

Control



Vicriviroc



Luminescence

1.0

0.8

0.6

0.4

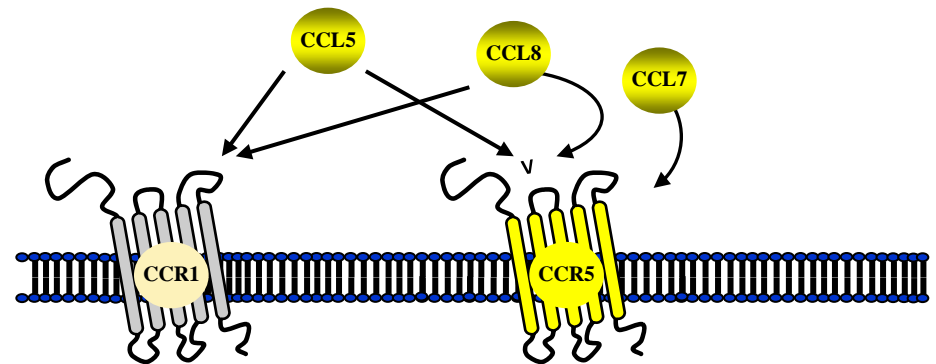
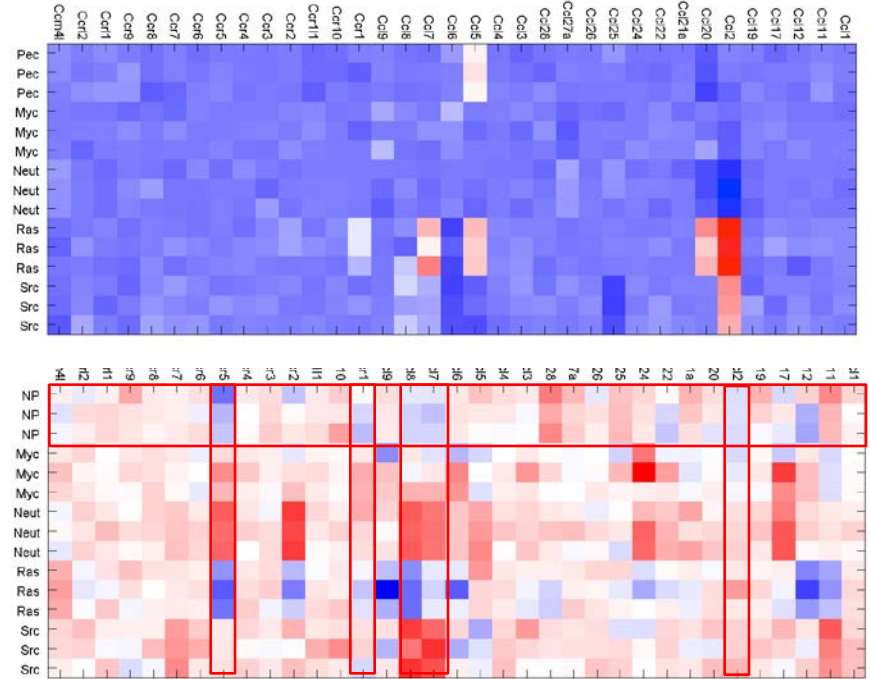
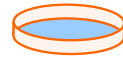
0.2

Radiance

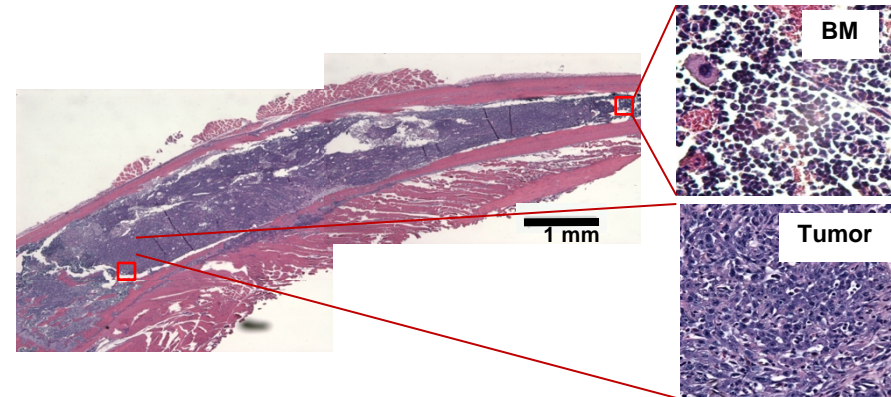
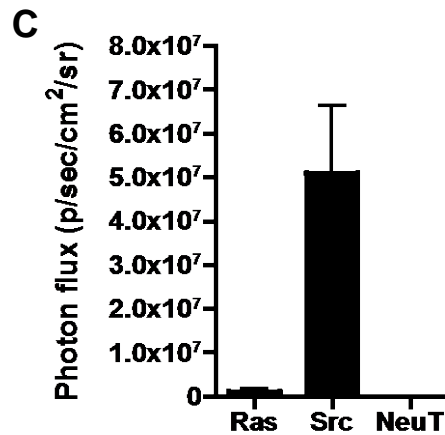
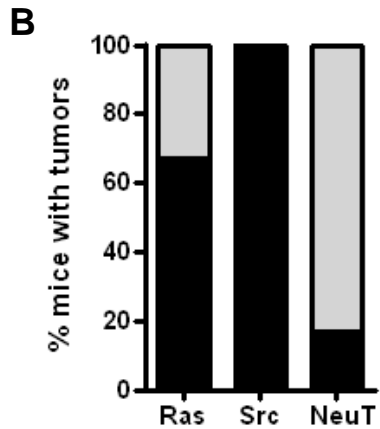
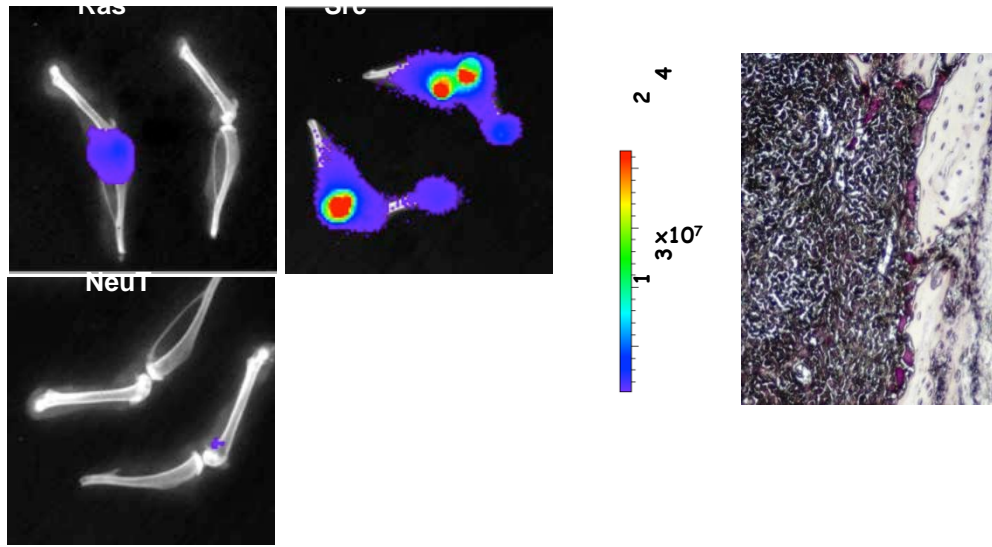
(p/sec/cm<sup>2</sup>/sr)

$\times 10^7$

# Prostate Cancer CCR5 Receptor Signaling activated in vivo

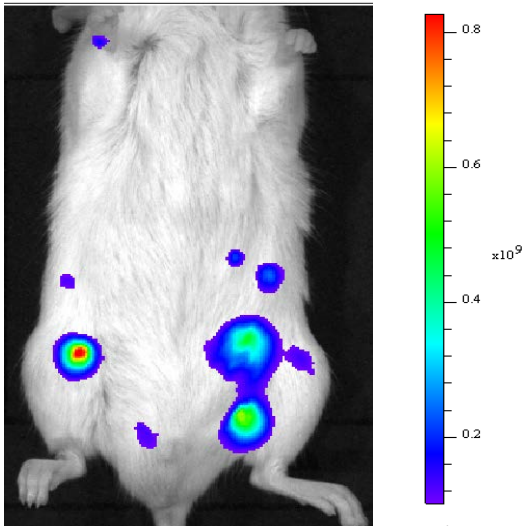


# Isogenic Prostate Cancer Lines Reliably Metastasize to Bone in Immune-competent Mice

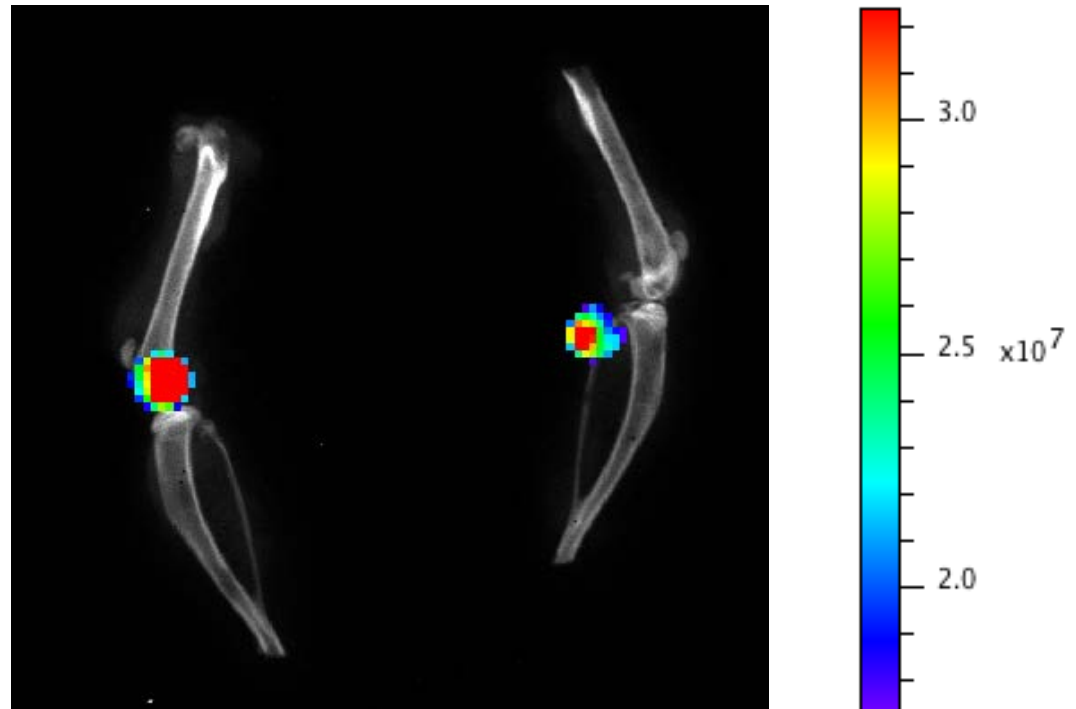


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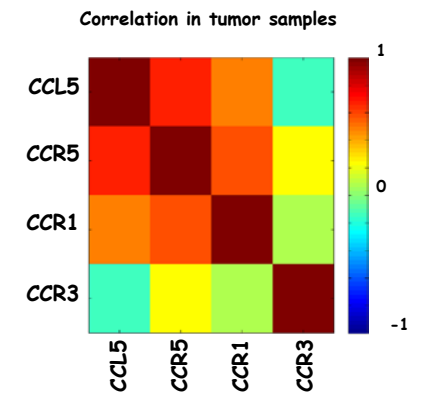
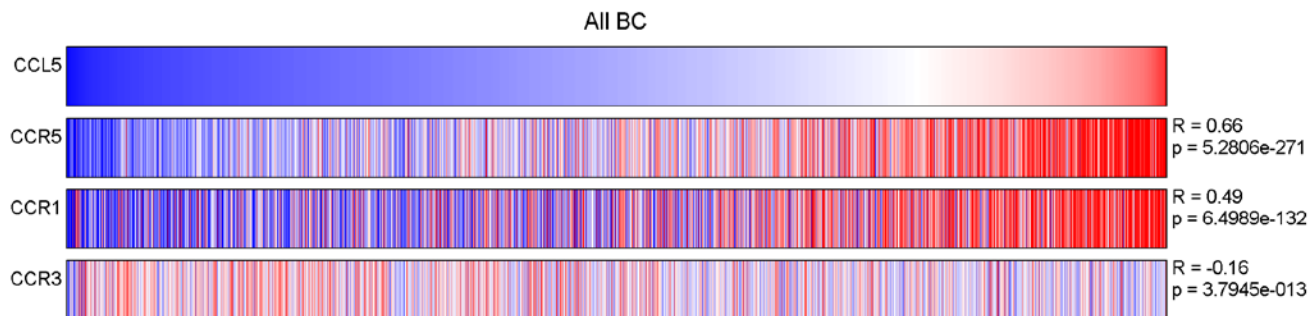
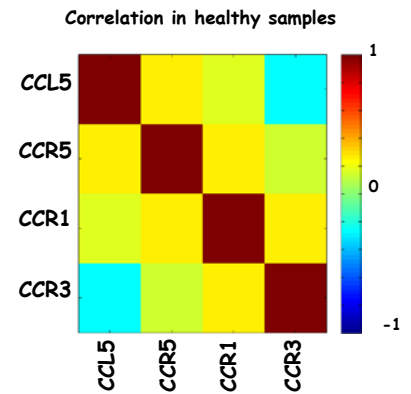
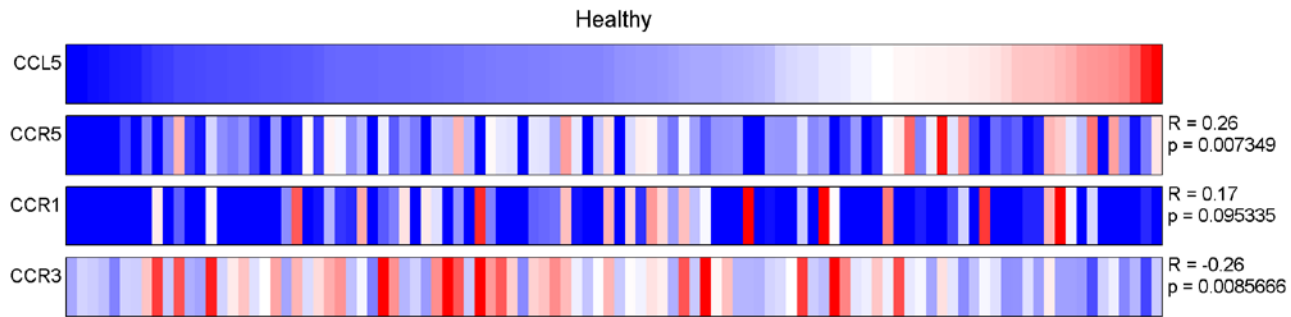
*In vivo* BLI



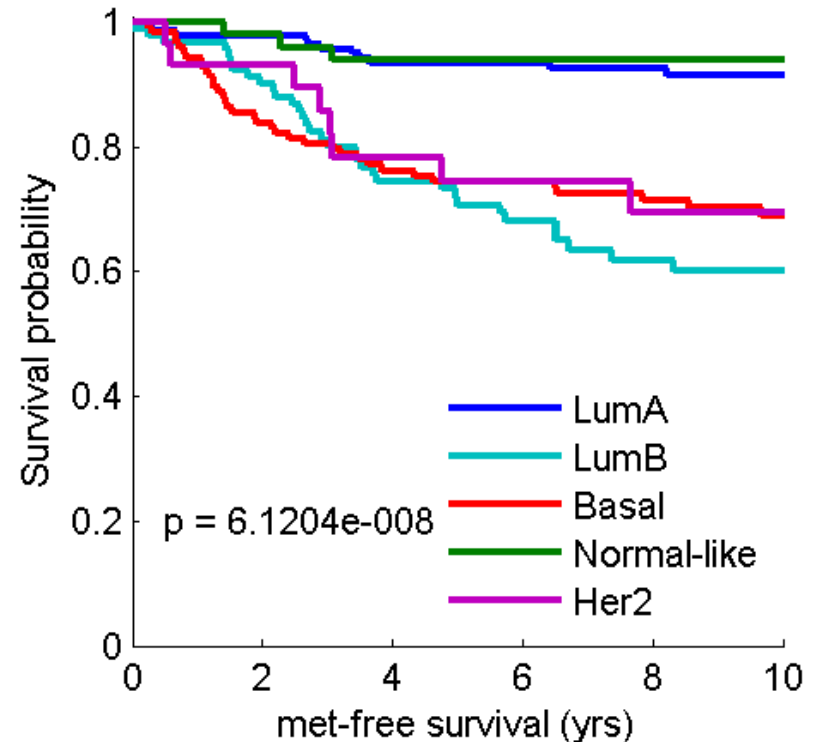
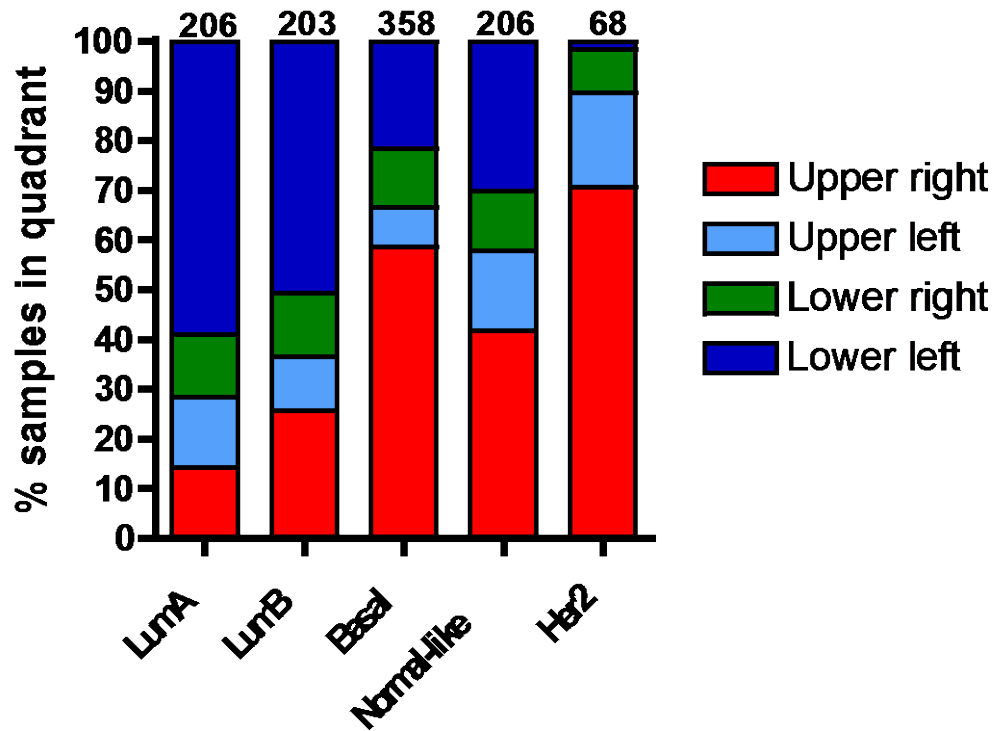
*Ex vivo* BLI



# CCR5 Signaling induction In Breast Cancer



# CCR5 Receptor and Breast Cancer Outcome

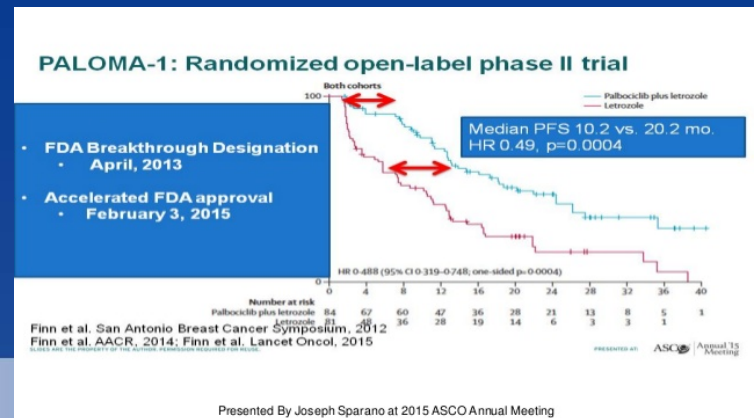
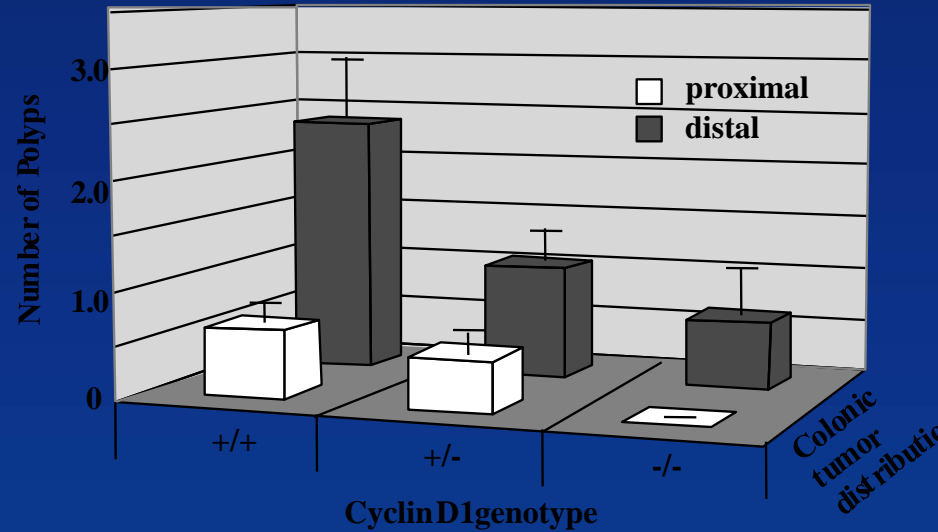




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Lee, R, et al, (MCB) 2001



# Maraviroc blocks brain metastasis

