Stress and β-adrenergic signalling in metastatic processes

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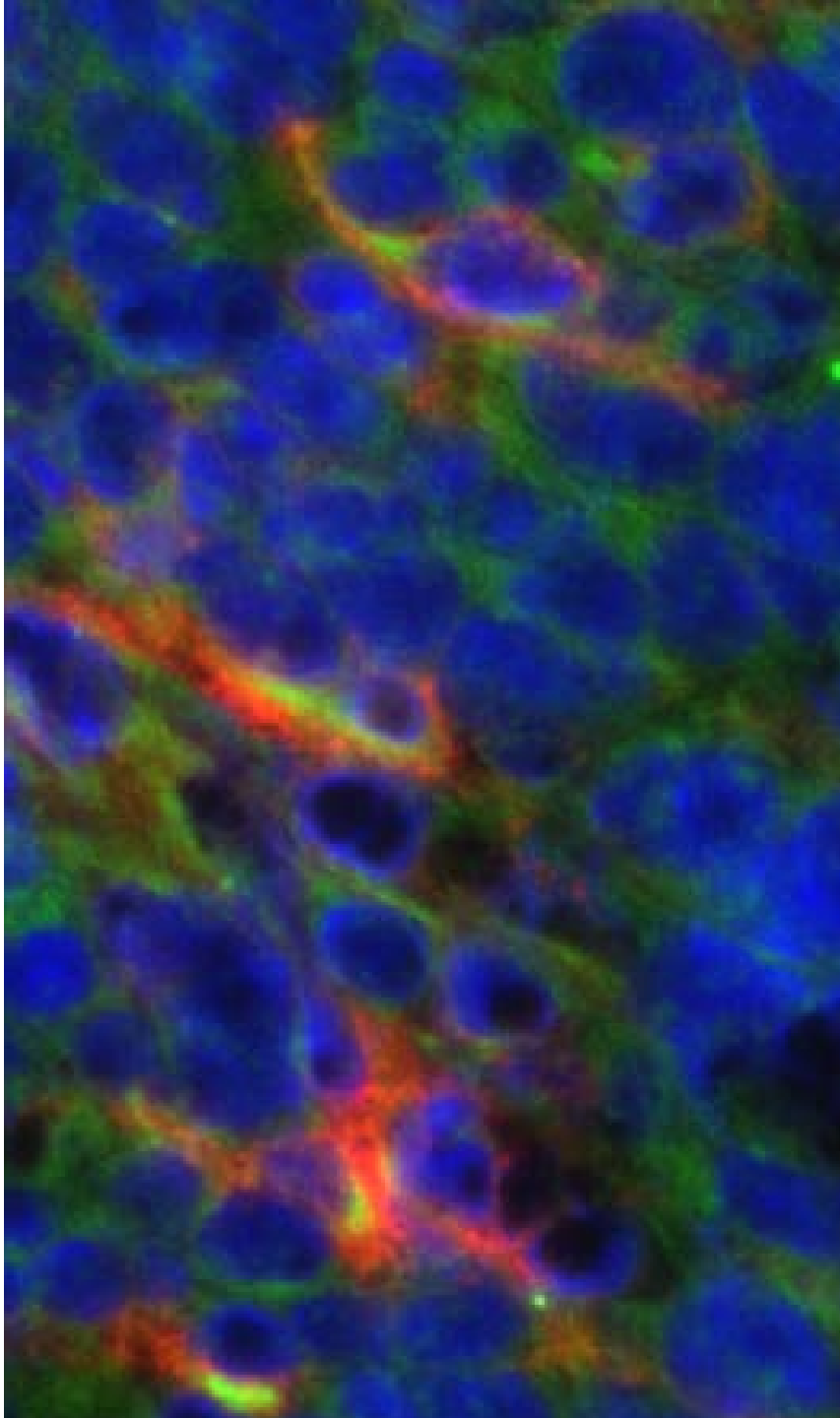


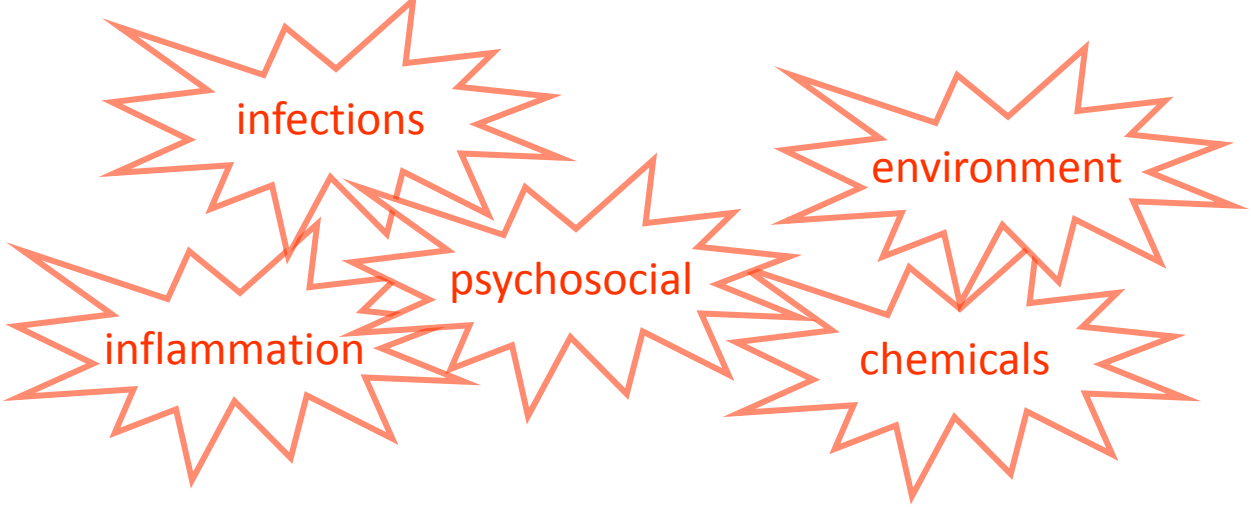
Learning objectives

1. To define the physiological signaling pathways that enhance metastasis.

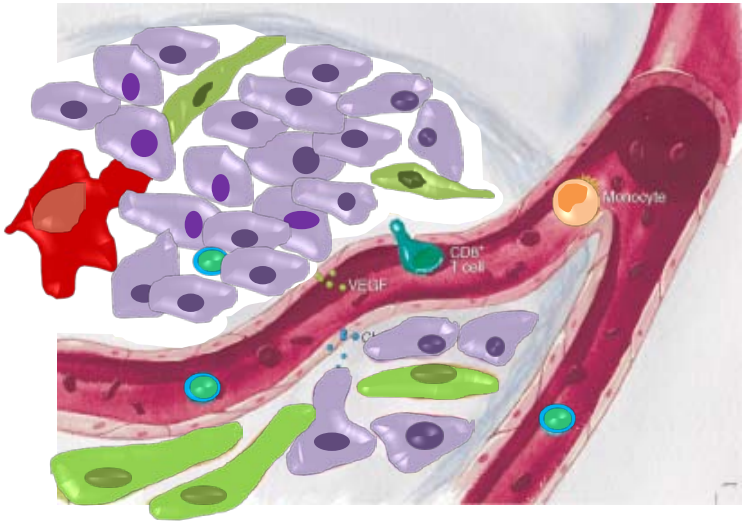
2. To describe how does neural signaling facilitates tumor cell dissemination.

3. To explain how beta-blockers may protect against cancer progression.

Exposure



Tumor microenvironment

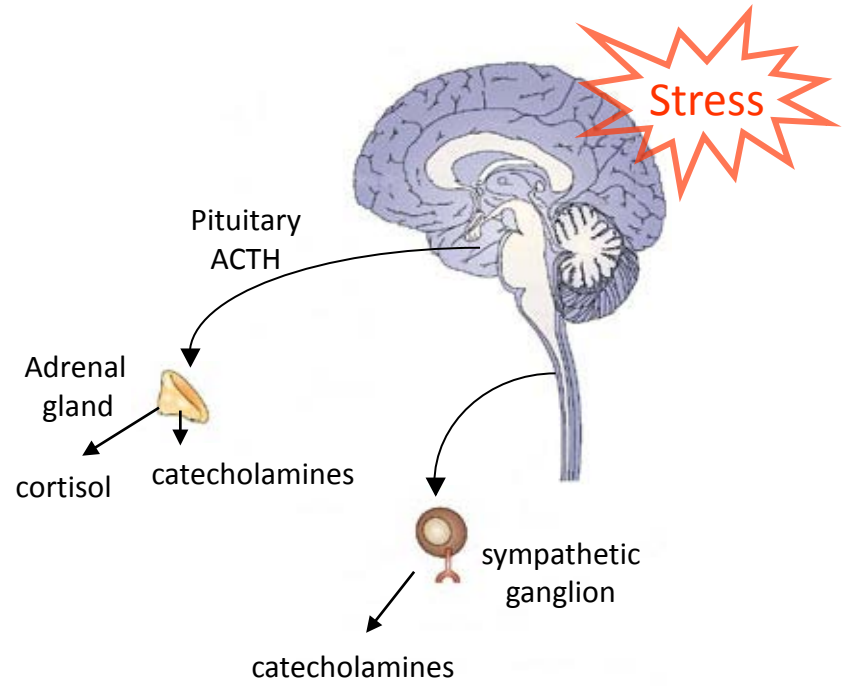


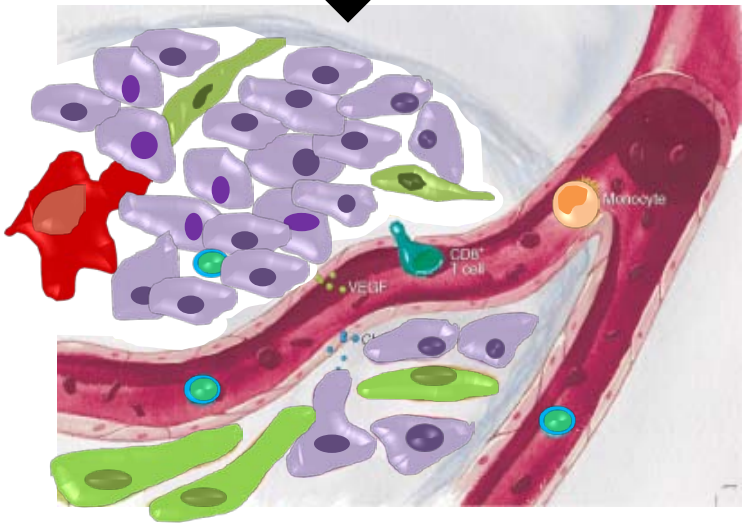
Adapted from Antoni et al., 2006 Nature Cancer Reviews & R&D systems website

Exposure

Whole body physiology

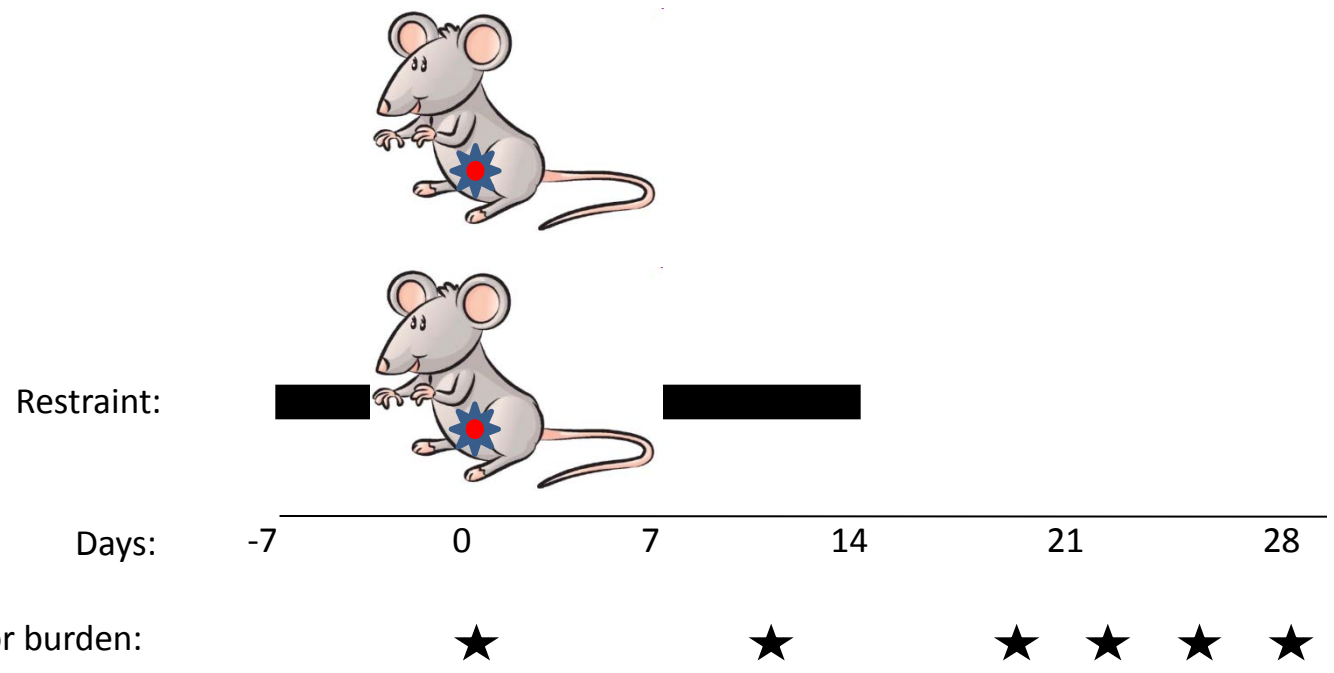
Tumor microenvironment





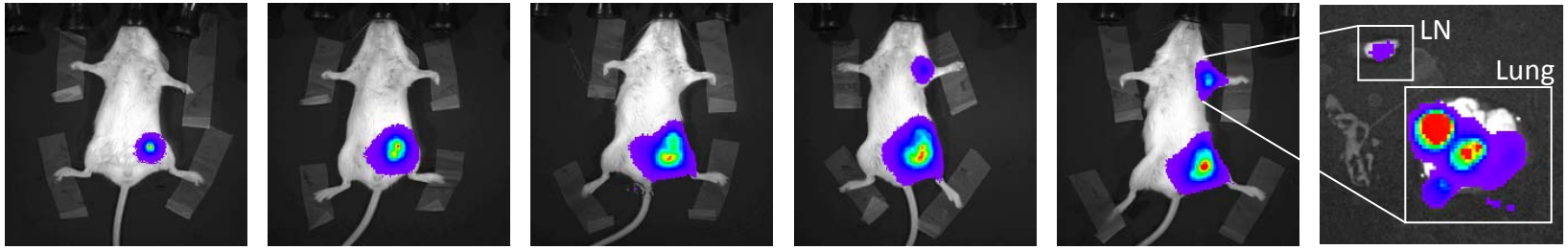
Adapted from Antoni et al., 2006 Nature Cancer Reviews & R&D systems website

What is the impact of physiological SNS signaling on breast cancer?



66cl4 mouse mammary adenocarcinoma
MDA-MB-231HM TNBC
4th left mammary fat pad

In vivo bioluminescence imaging of cancer progression



Day 1

1 x 10^5 cells

Day 12

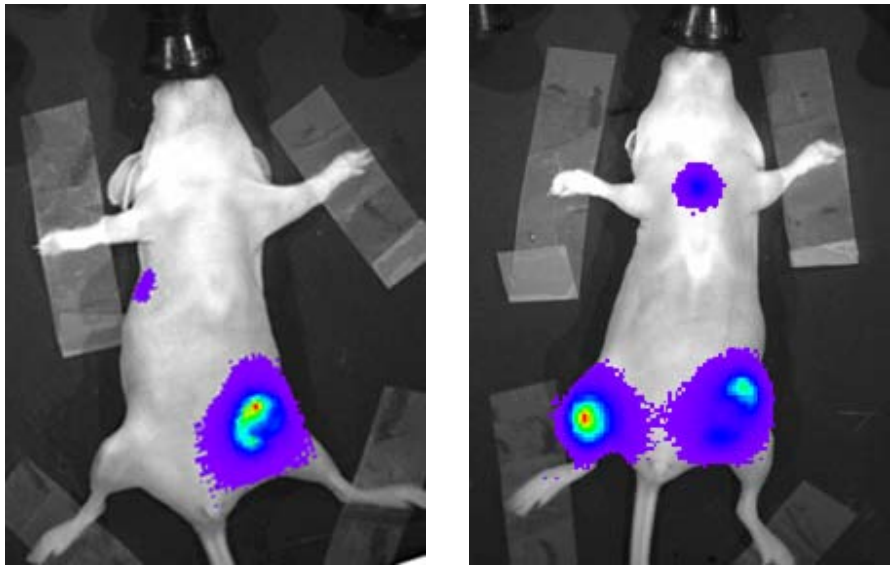
Day 20

Day 24

Day 28

Ex vivo

Chronic stress impacts breast cancer progression

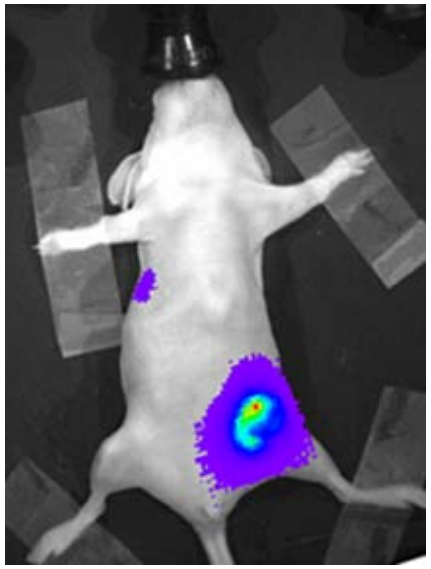


Control

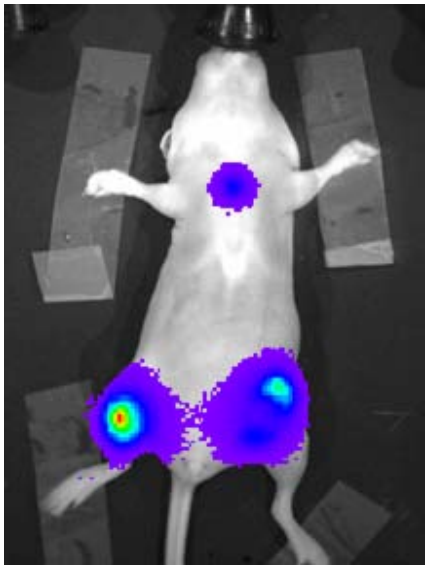
Stress

Sloan et al. (2010) Cancer Research

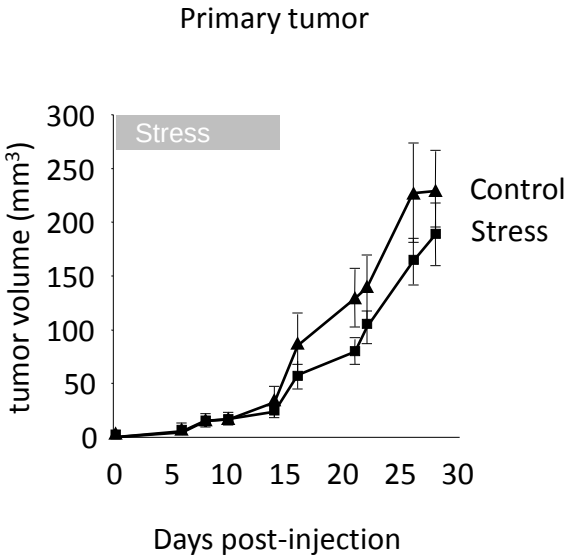
Chronic stress impacts breast cancer progression



Control



Stress



Sloan et al. (2010) Cancer Research

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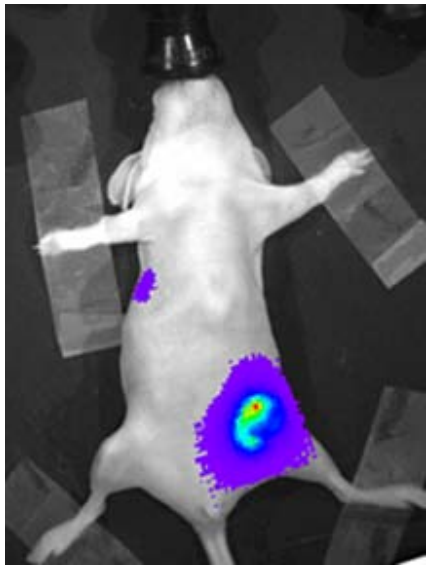

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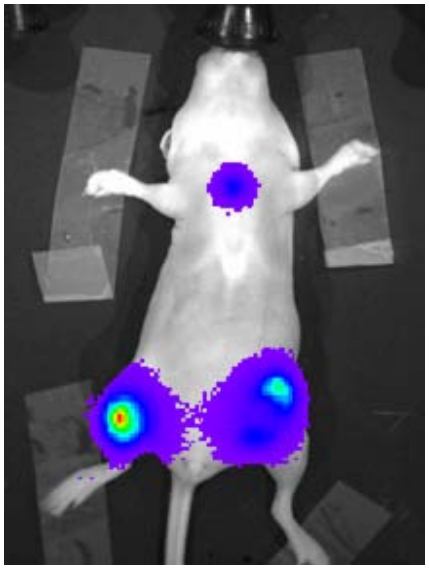
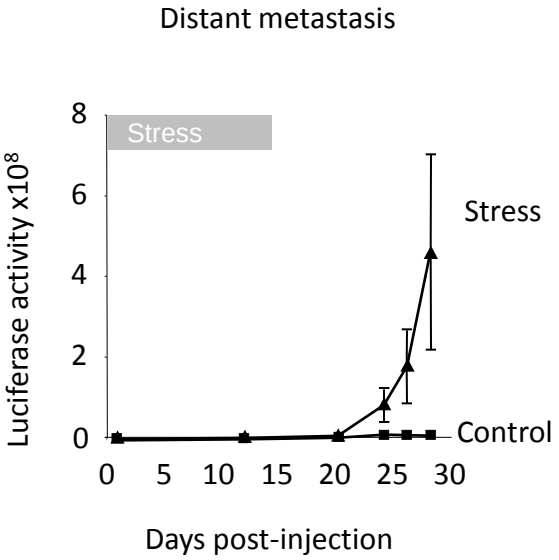
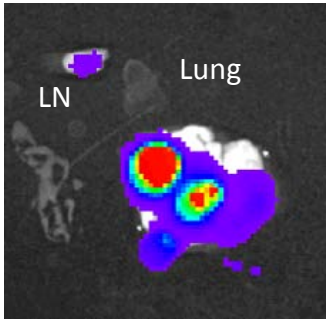


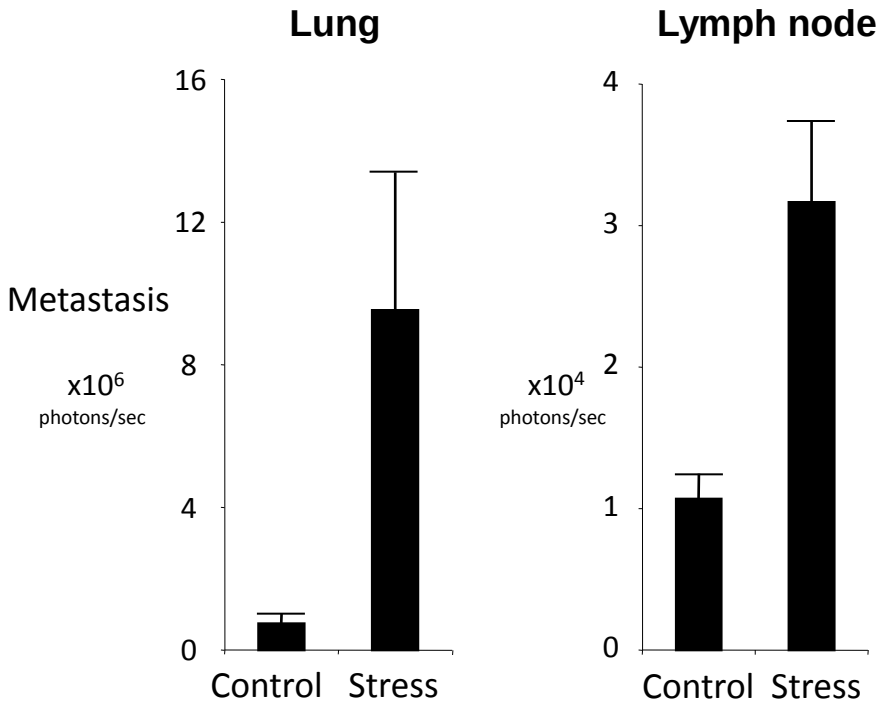
Stress



Sloan et al. (2010) Cancer Research

Ex vivo imaging
28 days after inoculation





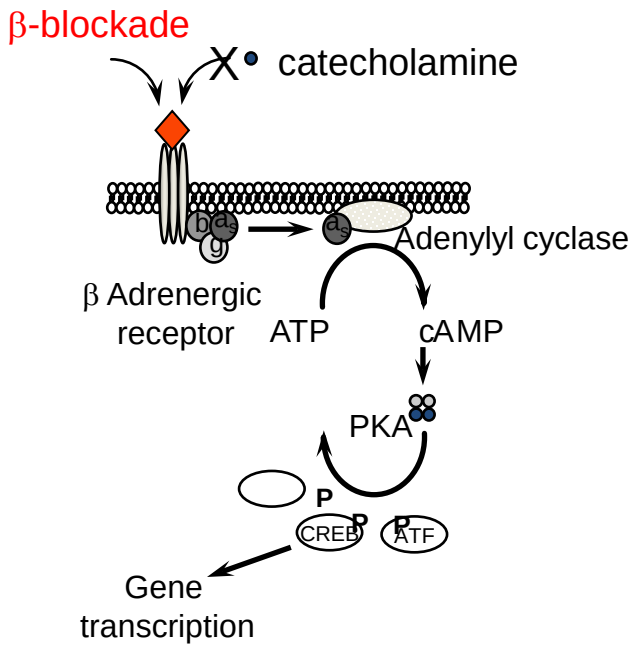
- Exposome impacts TME

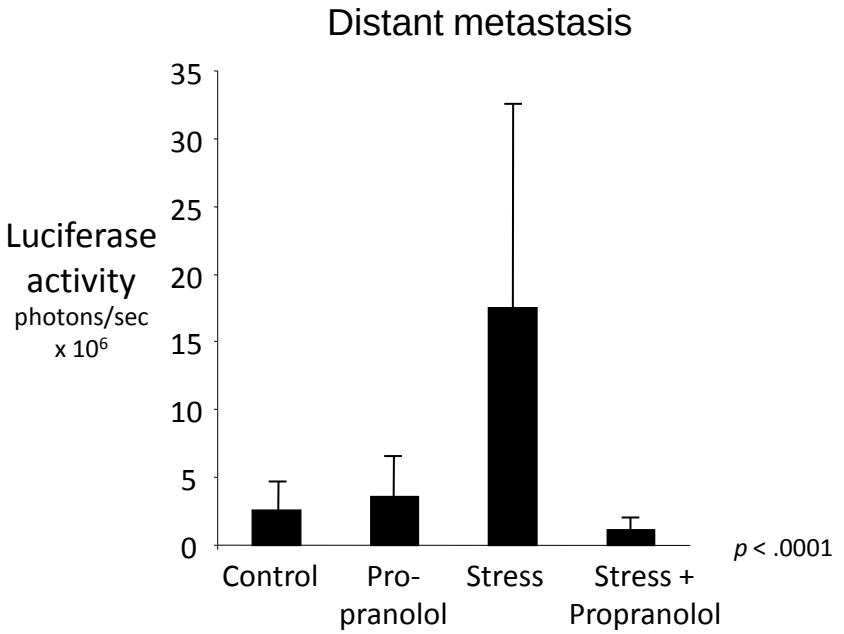
Which physiological signaling pathways enhance metastasis?

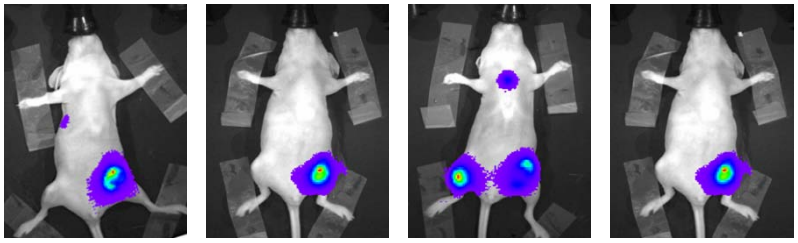
How does SNS signaling facilitate tumor cell escape?

Does SNS neural signaling impact other tumor types?

SNS neurotransmitters signal through β-adrenergic receptors

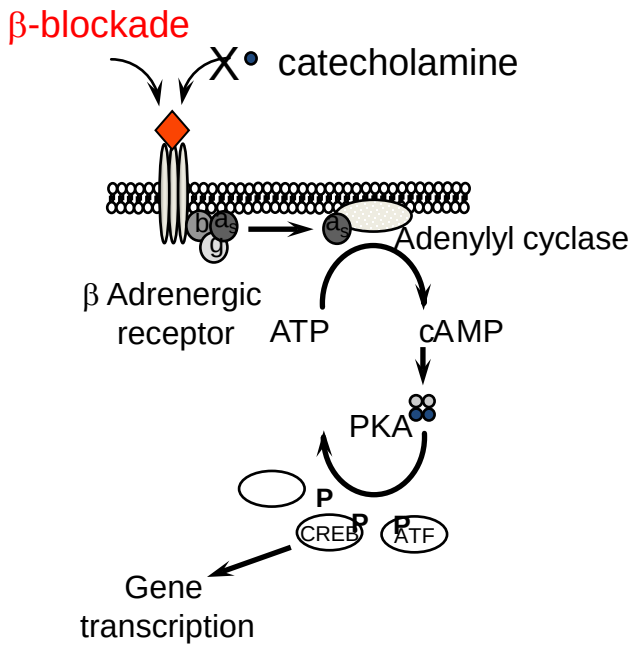


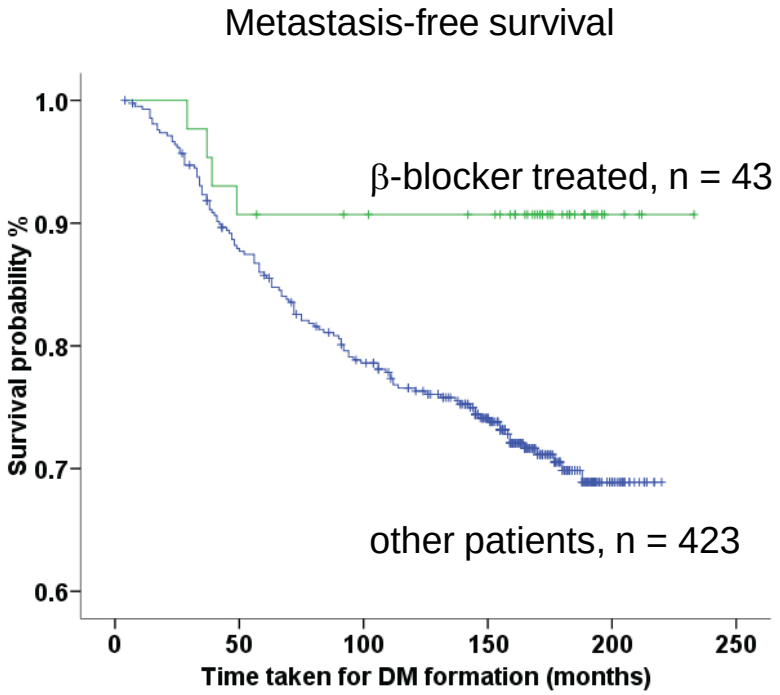




Sloan et al. (2010) Cancer Research

SNS neurotransmitters signal through β-adrenergic receptors





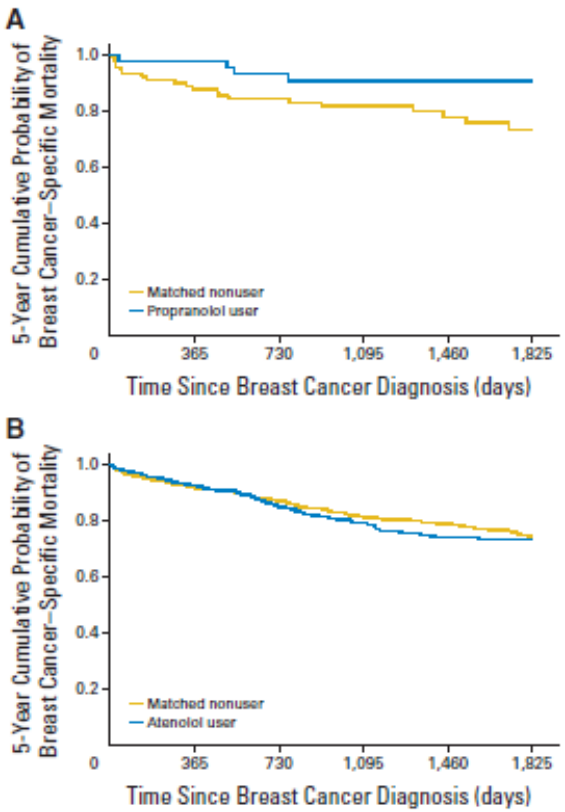
Powe et al., Oncotarget 2010.

Which beta-blocker to use?

Breast cancer-specific mortality

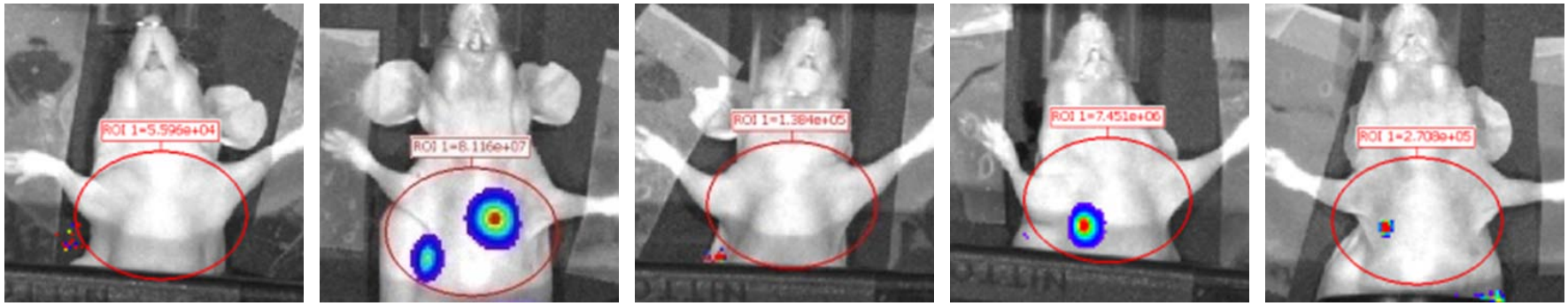
Propranolol

Atenolol



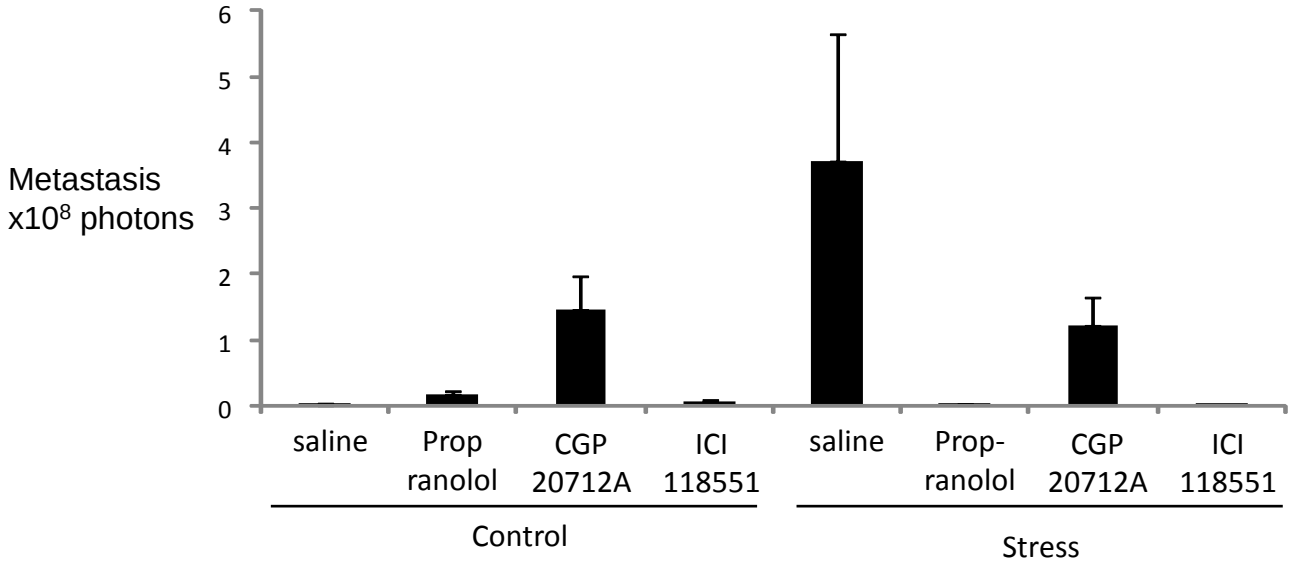
Barron, JCO, 2011 Jul 1;29(19):2635-44

Distant metastasis



Control | Saline | Non-selective β-antagonist | β1-antagonist | β2-antagonist

Stress



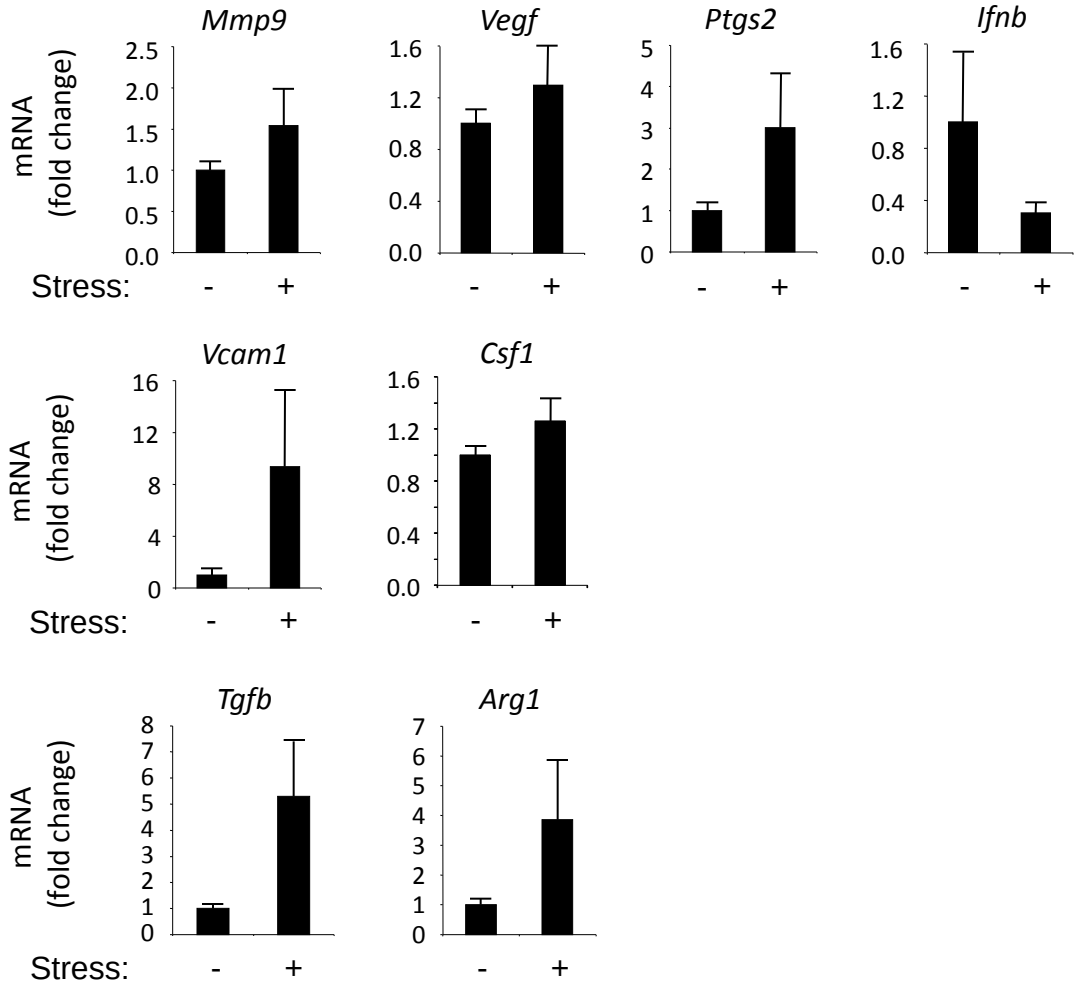
Ming Chai

Stress modulates primary tumor gene expression

Metastasis

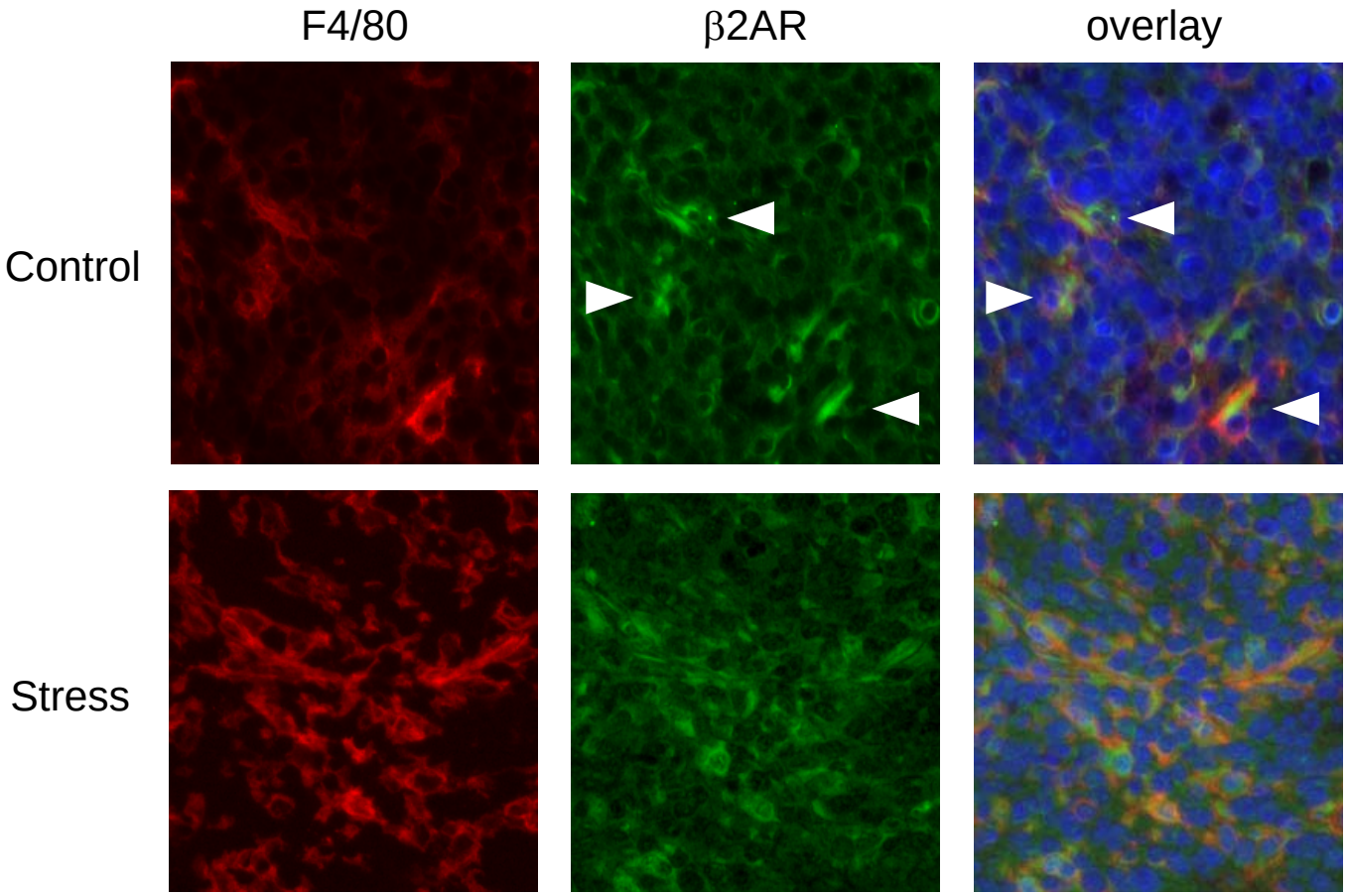
Macrophage recruitment

M2 polarization



Sloan et al. (2010) Cancer Research

β-AR regulation of tumor-associated macrophages



Sloan et al. (2010) Cancer Research

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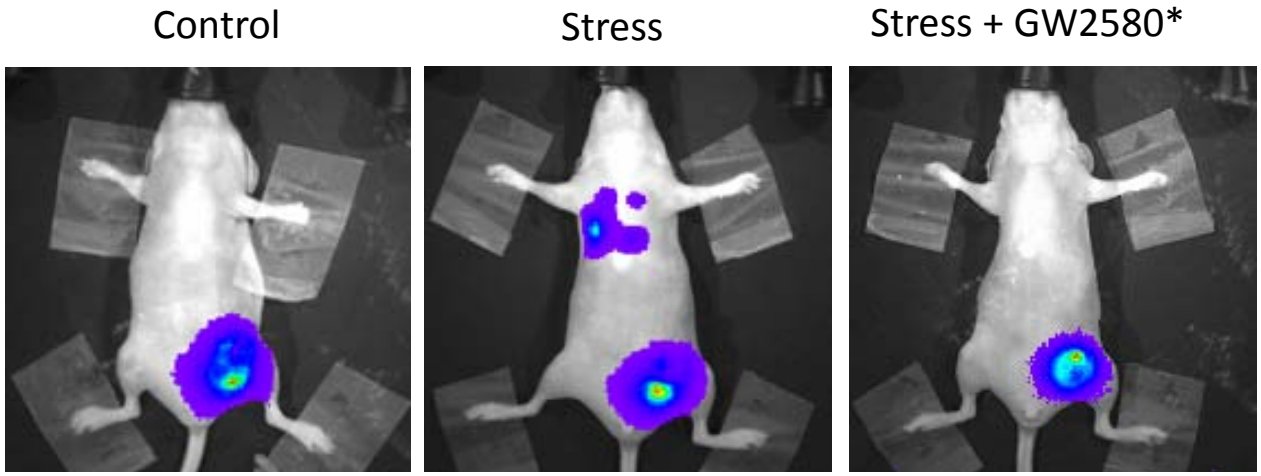
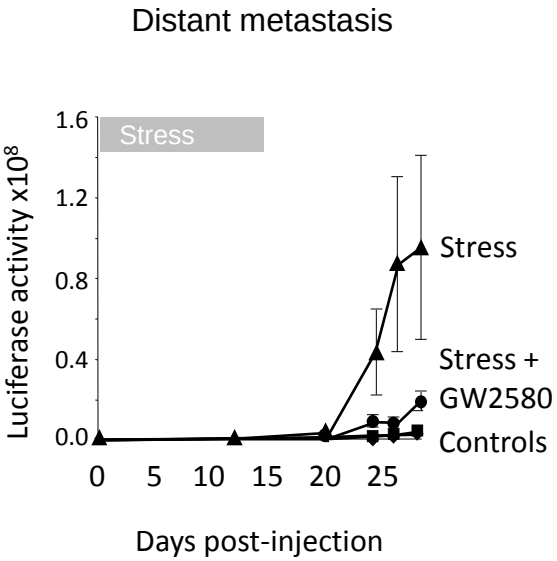


*_CSF1R_/M-CSF receptor antagonist

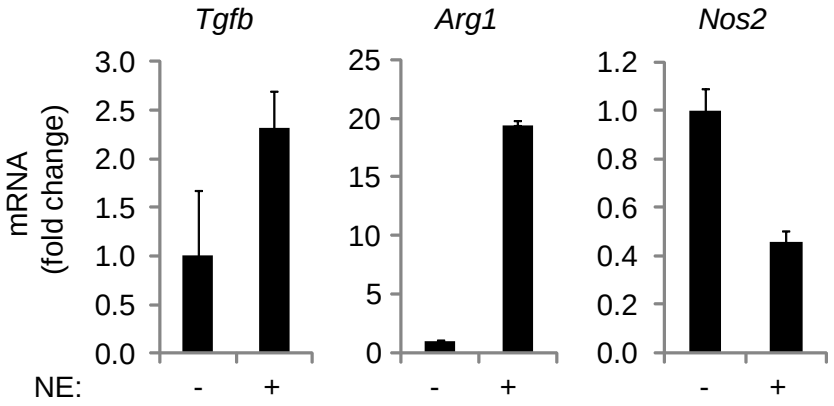


Sloan et al. (2010) Cancer Research

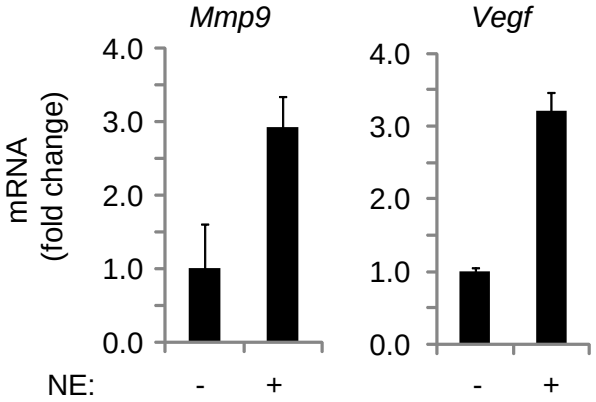
Neural signaling makes macrophages pro-metastatic

- BMDM

M2 polarization



Metastasis



Matthew Pimentel

Which physiological signaling pathways enhance metastasis?

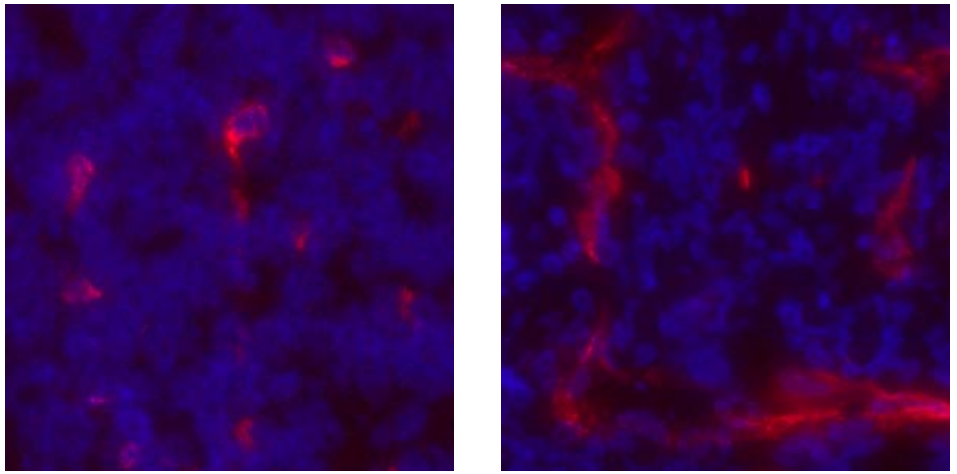
Neural pathways - βAR signaling

Tumor side – M2 myeloid recruitment

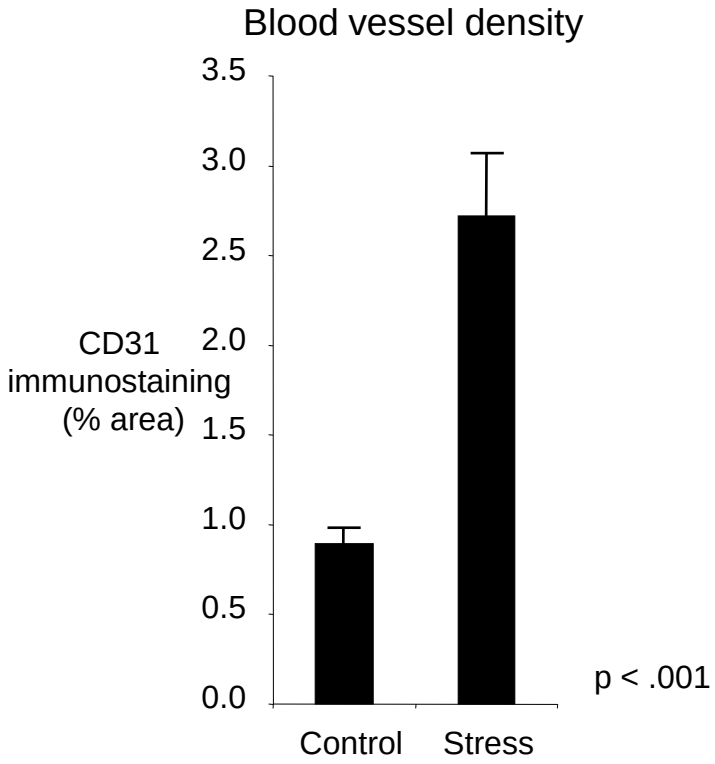
How does SNS signaling facilitate tumor cell escape?

Stress impacts pathways of tumor cell dissemination

CD31



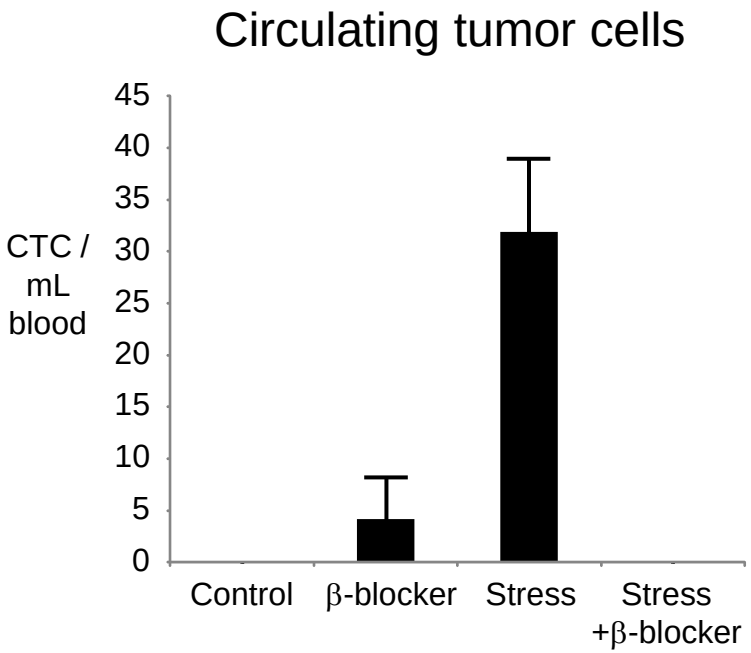
Control Stress

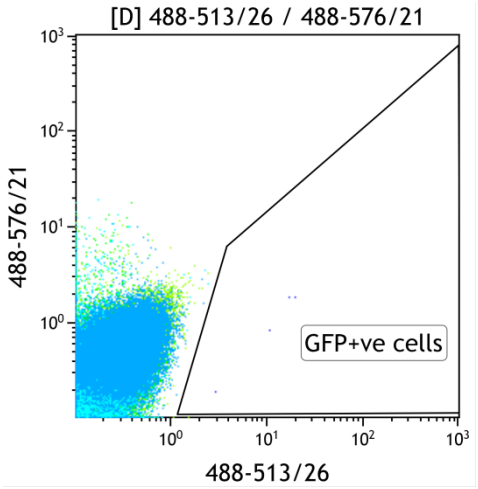


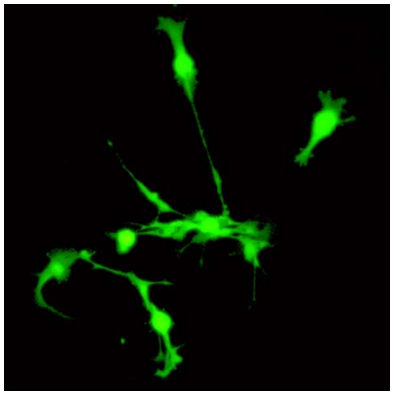
- Dependent on macrophage recruitment

Sloan et al. (2010) Cancer Research

Stress impacts pathways of tumor cell dissemination





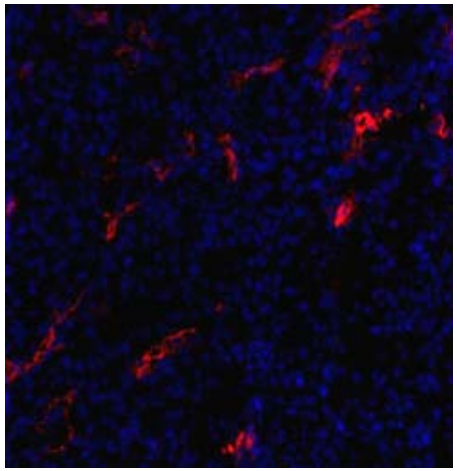


cultured CTC

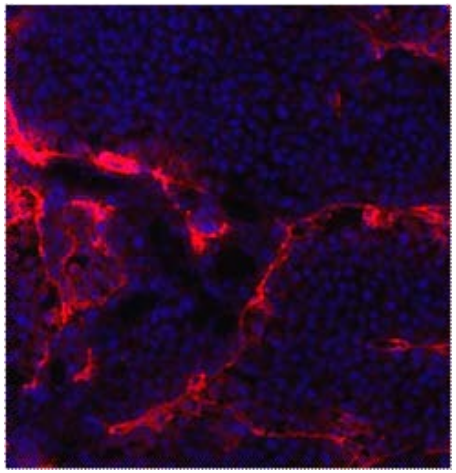
Ming Chai, Ben Finnin

Stress impacts pathways of tumor cell dissemination

Lyve-1

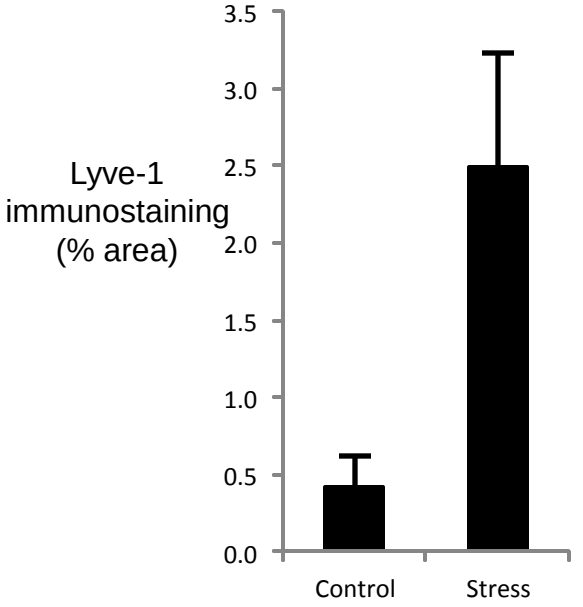


Control



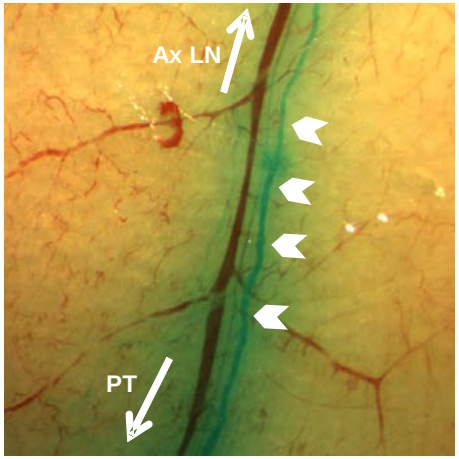
Stress

Lymphatic vessel density

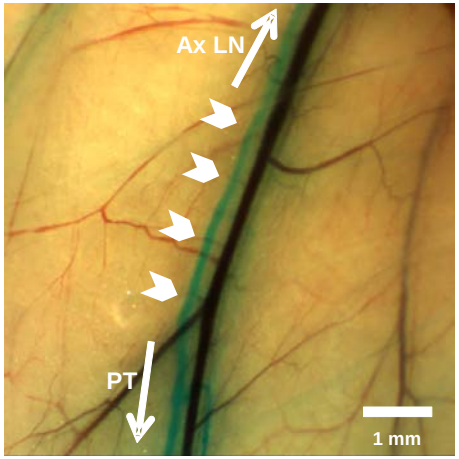


Caroline Le

Stress impacts pathways of tumor cell dissemination

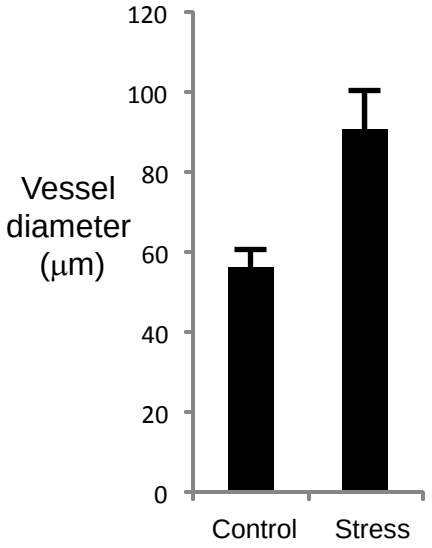


Control



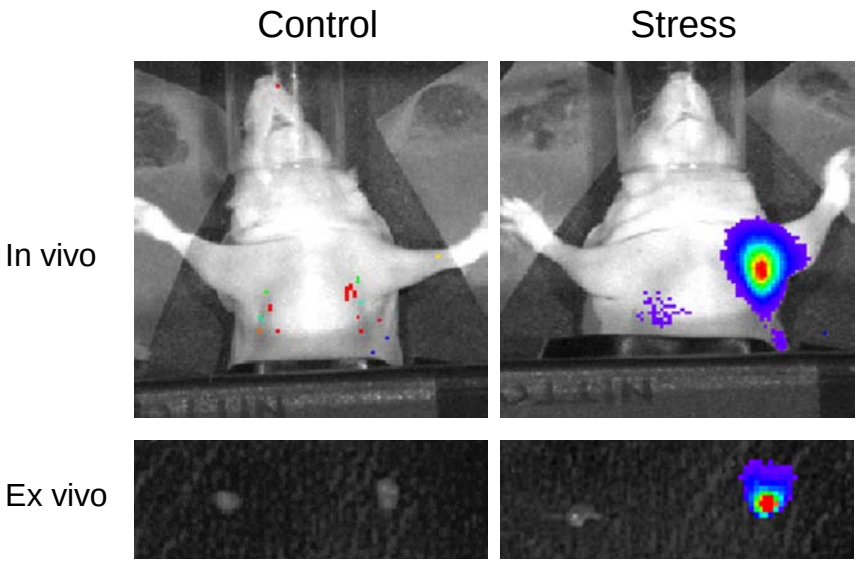
Stress

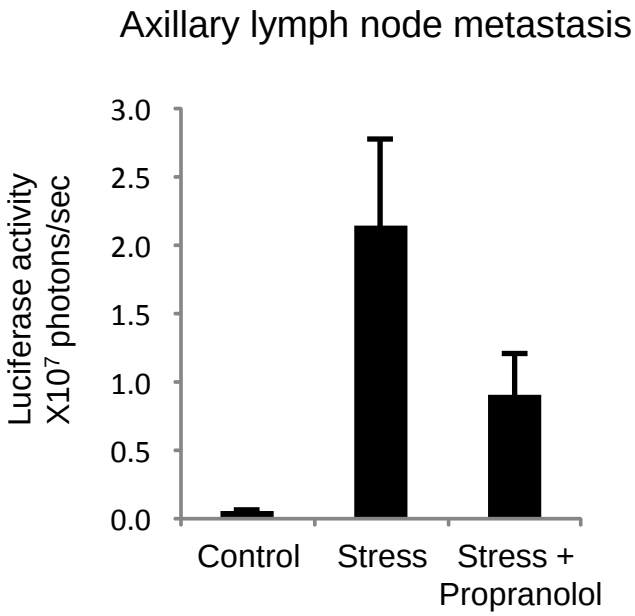
Lymphatic collectors



Caroline Le

Stress impacts pathways of tumor cell dissemination





Caroline Le

Which physiological signaling pathways enhance metastasis?

Neural pathways - βAR signaling

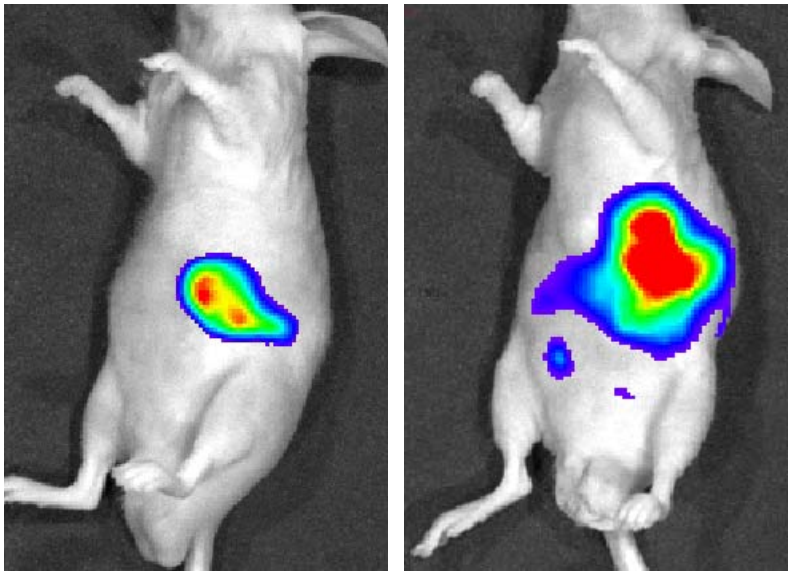
Tumor side – M2 myeloid recruitment

How does SNS signaling facilitate tumor cell escape?

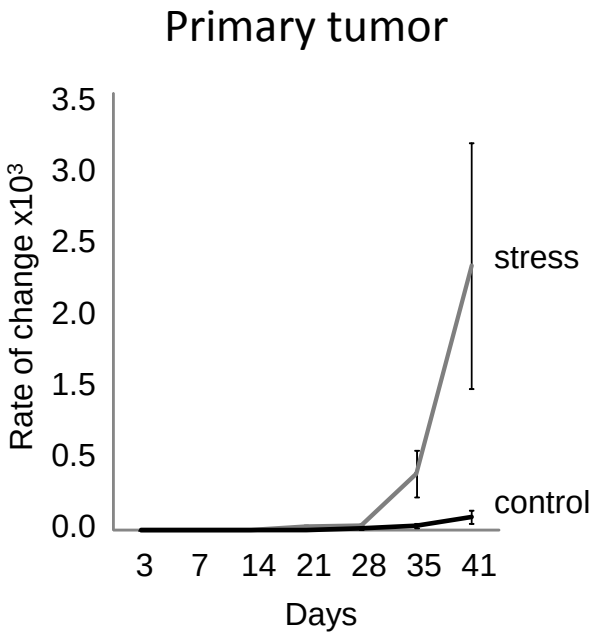
Angiogenesis & lymphangiogenesis

Does SNS neural signaling impact other tumor types?

Stress accelerates pancreatic cancer progression



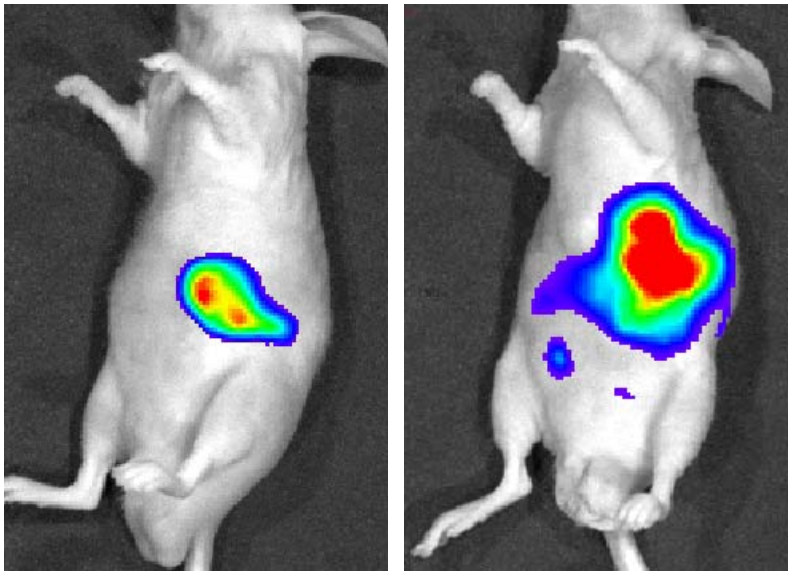
Control Stress



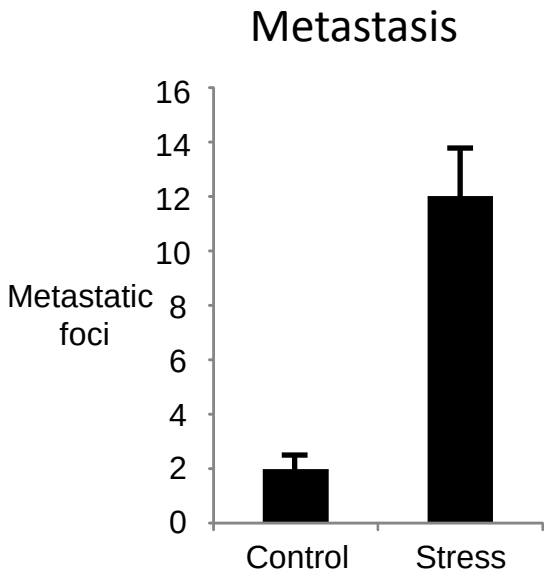
6 weeks, Panc-1

Corina Kim-Fuchs

Stress impacts pancreatic cancer



Control Stress

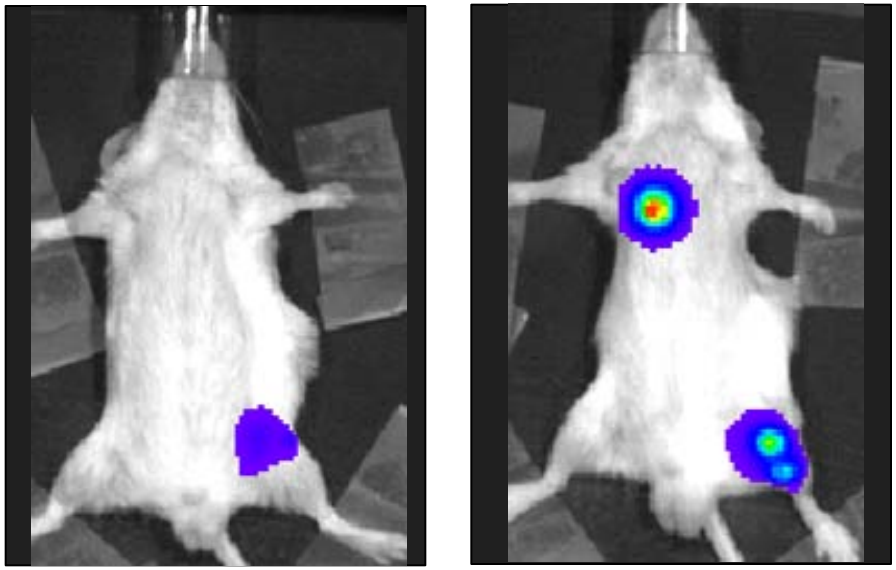


6 weeks, Panc-1

Corina Kim-Fuchs

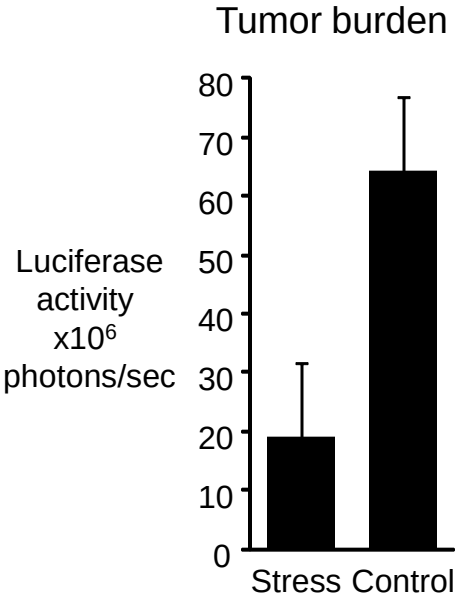
SNS accelerates hematopoietic malignancy

Don Lamkin



Control

Stress

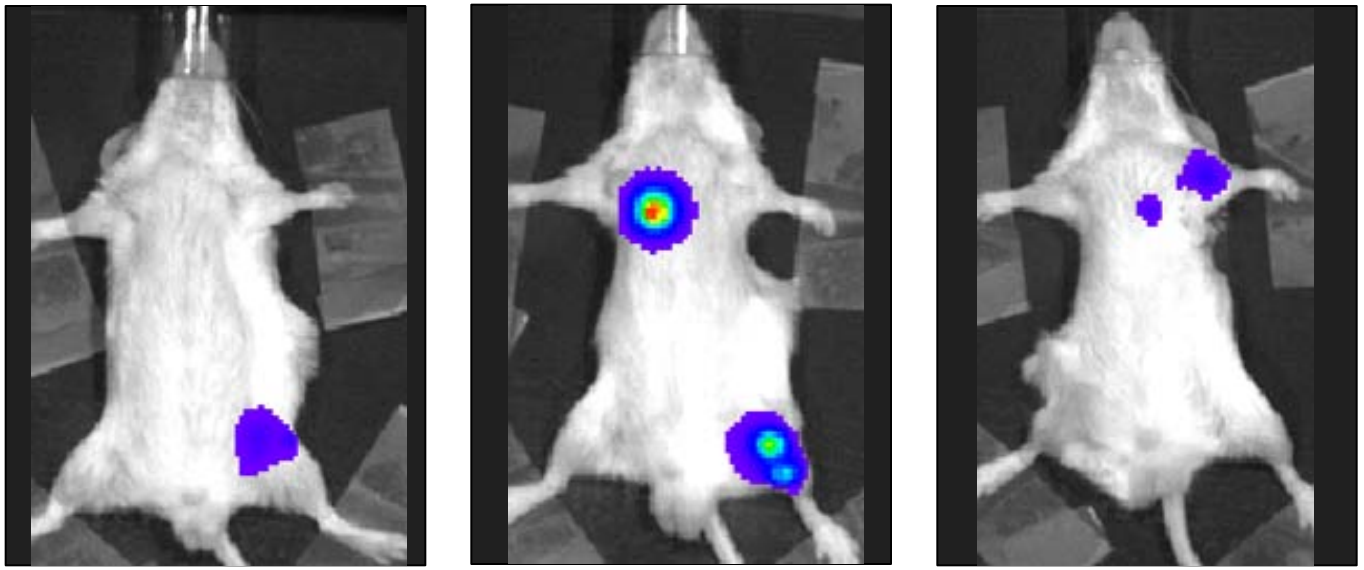


14 day Nalm-6 pre-B ALL

Lamkin et al., Brain, Behav, Imm 2012

SNS accelerates hematopoietic malignancy

Don Lamkin



Control | Stress | Stress + Propranolol

14 day Nalm-6 pre-B ALL
Lamkin et al., Brain, Behav, Imm 2012

Lamkin et al., Brain, Behav, Imm 2012

Which physiological signaling pathways enhance metastasis?

Neural pathways - βAR signaling

Tumor side – M2 myeloid recruitment

How does SNS signaling facilitate tumor cell escape?

Angiogenesis & lymphangiogenesis

Does SNS neural signaling impact other tumor types?

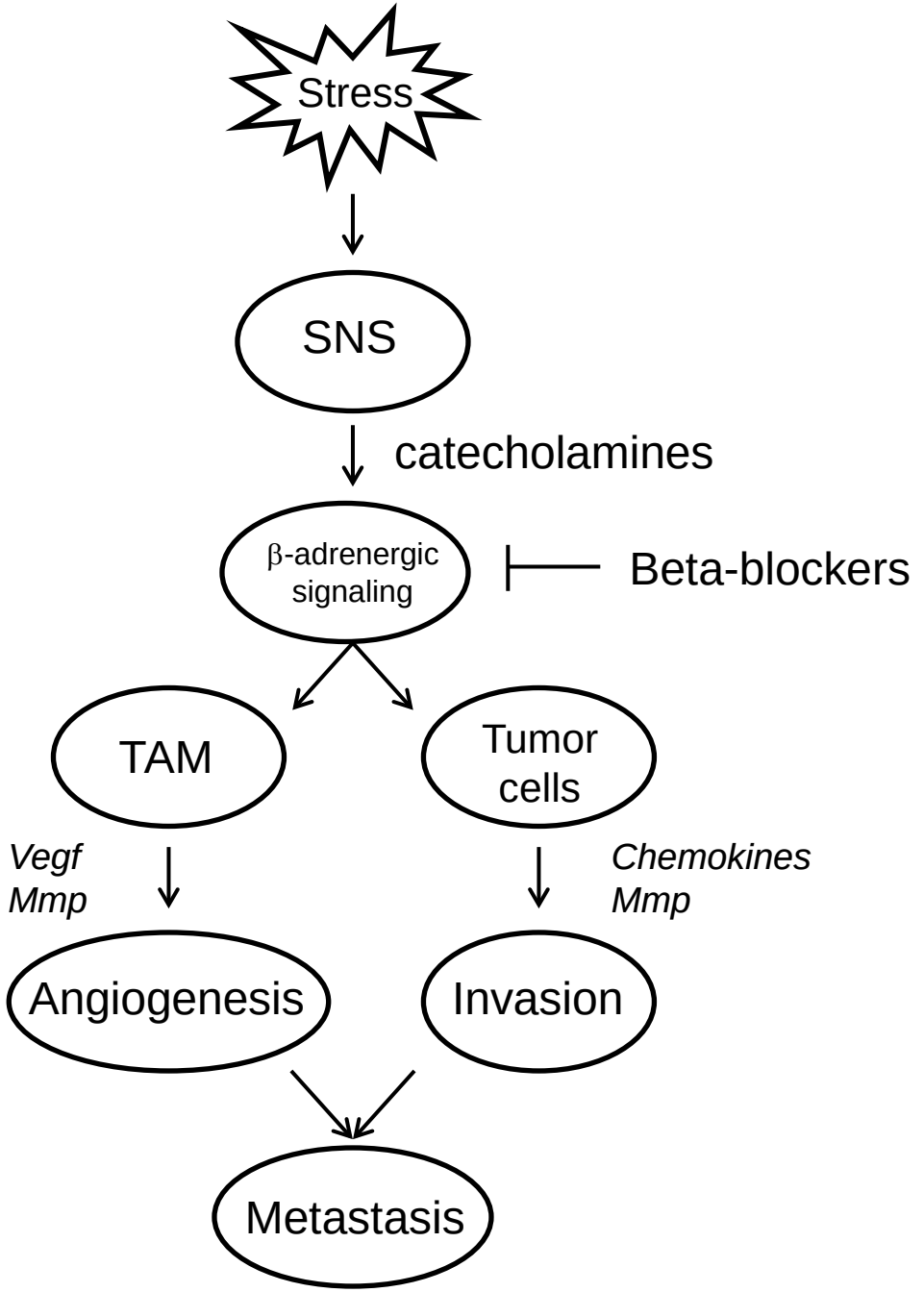
Other solid tumors

Hematopoietic malignancies

Exposure

Physiology

Tumor microenvironment



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Patricia Ganz, MD

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Andreas Möller, PhD
Steven Stacker, PhD

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Ming Chai
Corina Kim, MD
Matthew Pimentel
Ben Finnin