

Understanding how chronic stress modulates immune activity in the tumor microenvironment



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AGS/NIA R13 Bench-to-Bedside Conference Series

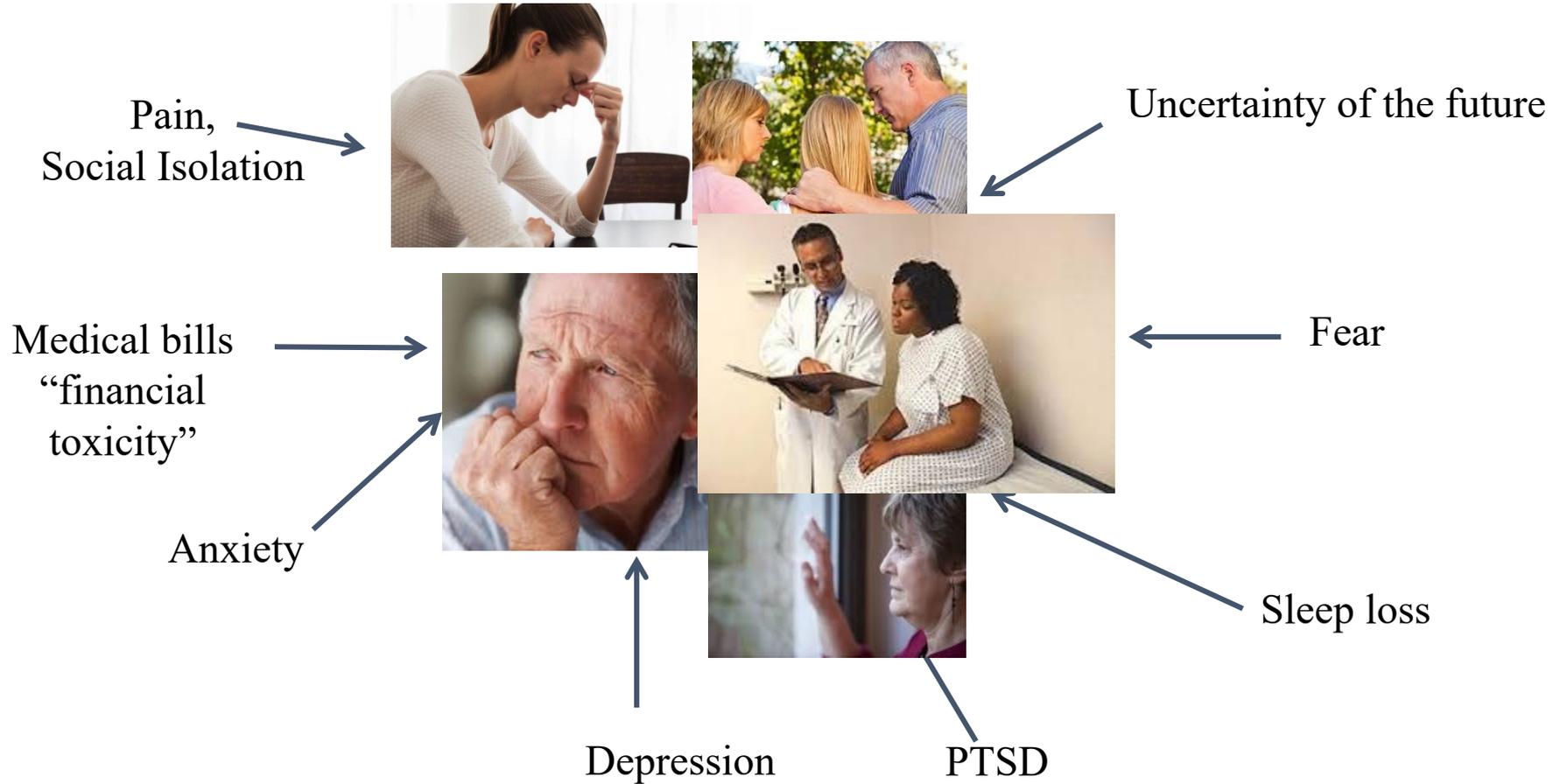
Stress Tests and Biomarkers of Resilience

Hyatt Regency, Bethesda MD

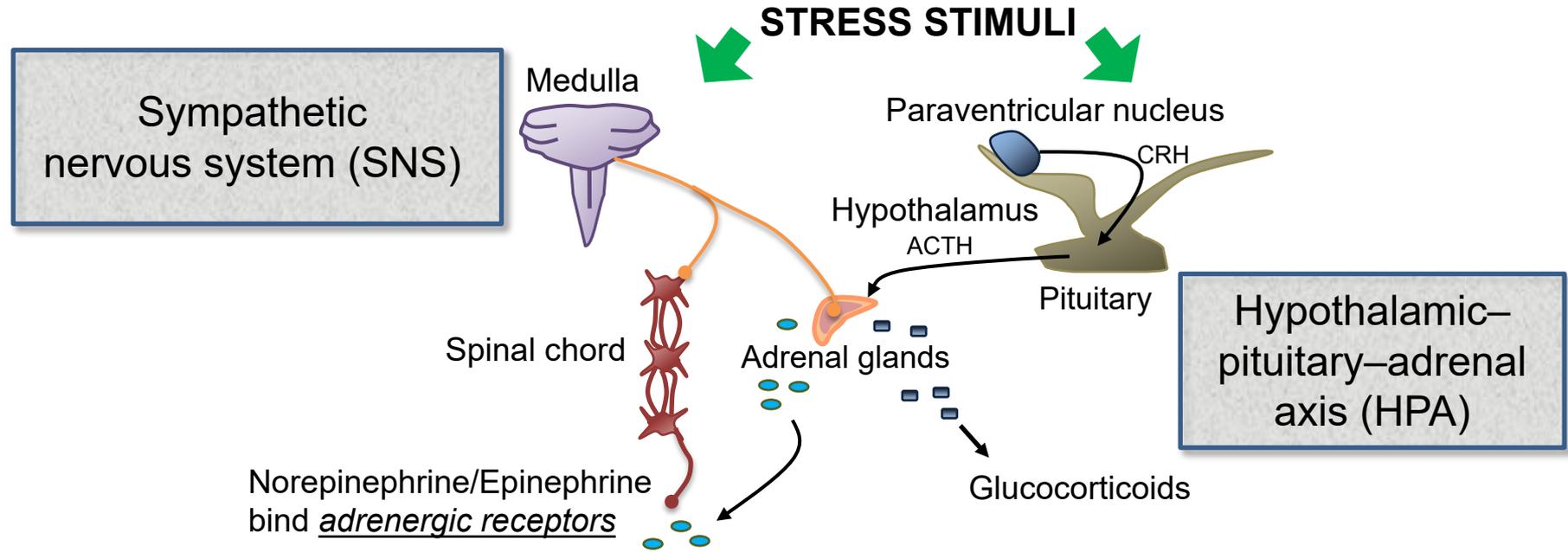
March 4-5, 2024

No Disclosures

Increased chronic stress in cancer patients

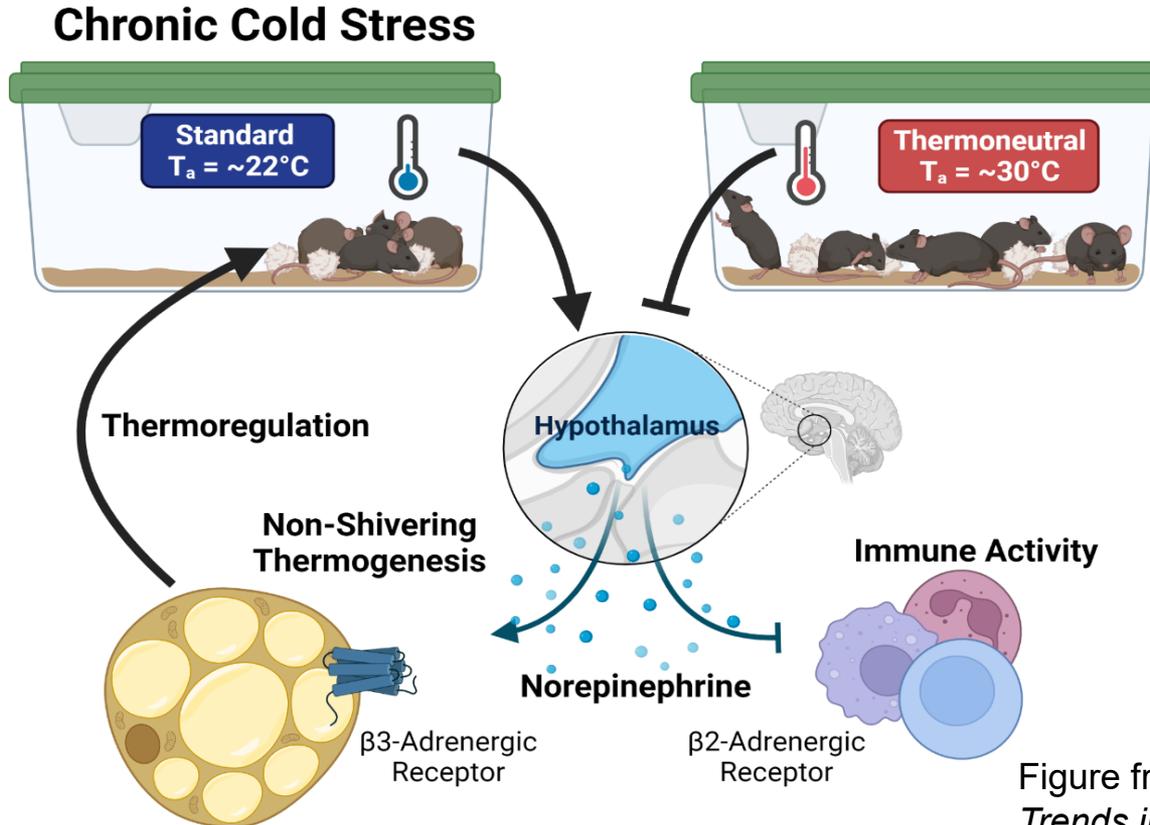


Systemic stress response is regulated by two major pathways



FIGHT or FLIGHT RESPONSE and psychological forms of stress (anxiety, fear, depression) **including thermal stress** (hot or cold)

Housing temperature: A useful model system to study the impact of chronic adrenergic stress on immuno-oncology

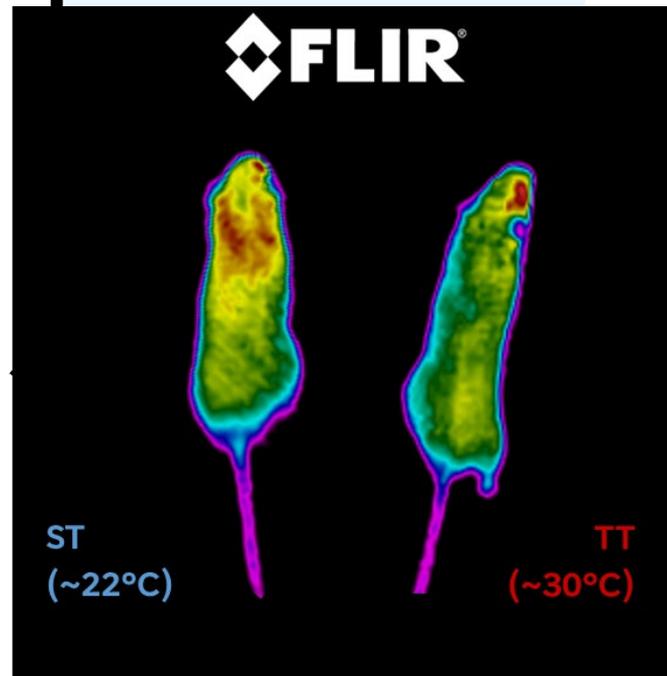
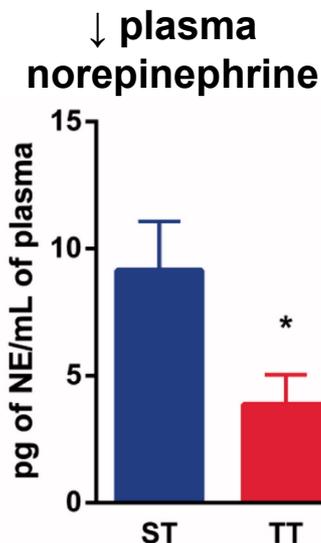
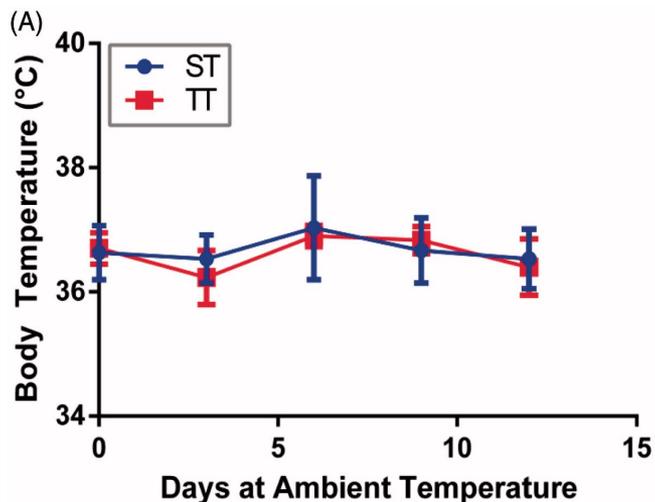


- Kokolus et al., PNAS 2013
- Eng et al., Nat Comm 2015
- Bucsek et al., Can Res 2017
- Mohammadpour et al., JCI 2019
- Chen et al., Nat Comm 2020
- Qiao et al., Can Imm Res 2021
- Mohammadpour et al., Cell Reports 2021

Figure from MacDonald/Choi et al./Repasky
Trends in Molec. Med. 2023

Standard housing temperatures induce chronic β -adrenergic stress

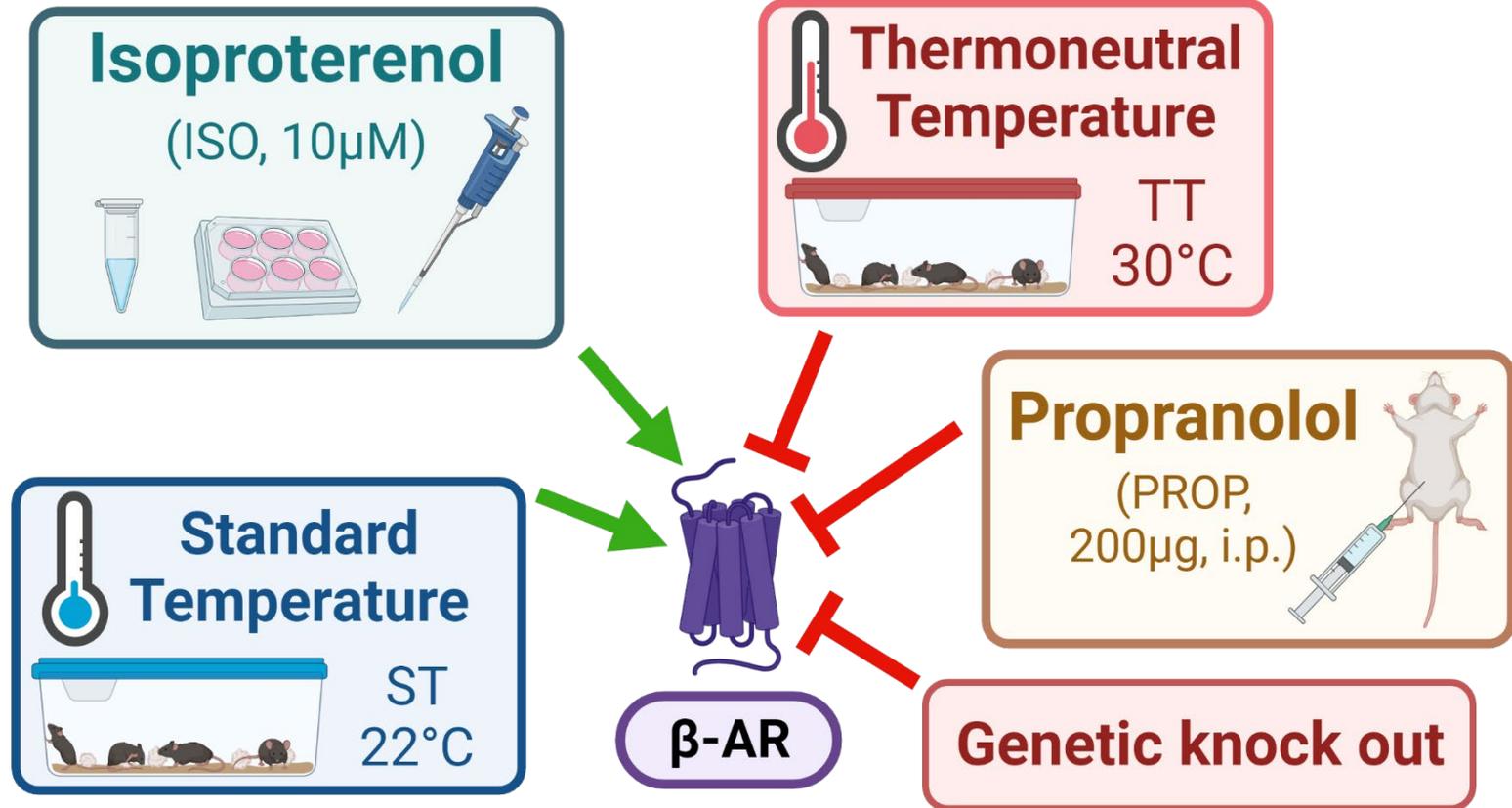
Thermoneutral housing (30°C) decreases circulating norepinephrine but does not change core body temperature!



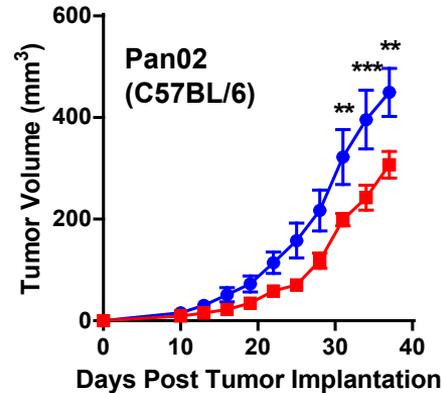
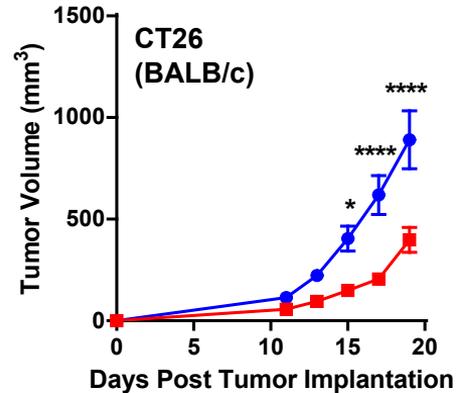
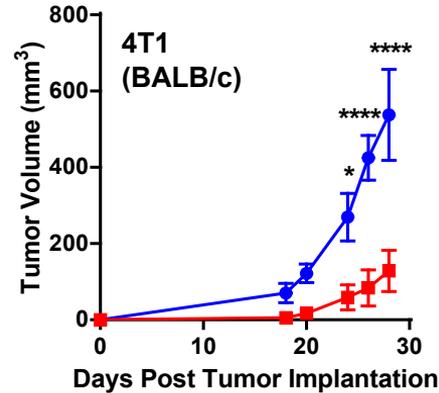
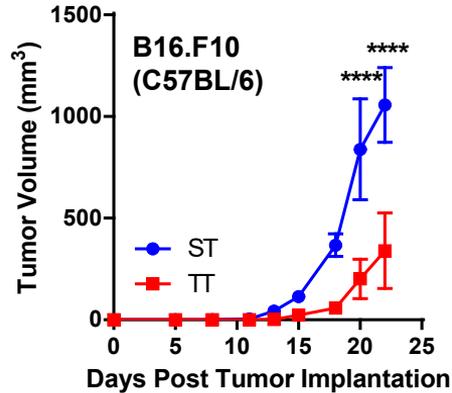
Eng, *Int J Hypertherm*, 2014.

National Research Council (US) Committee for the Update of the Guide for the Care and Use of Laboratory Animals, 2011, National Academies Press; James et al., *Temperature*, 2022

We use several ways to manipulate β -AR signaling in mice



Tumor growth is slower in mice housed at 30 °C

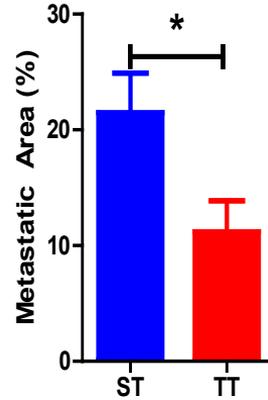
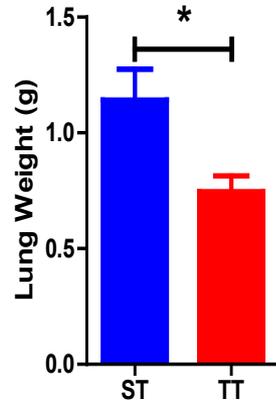


Kokolus et al/ Repasky
PNAS, 2013

N = 5 - 6; * p < 0.05, ** p < 0.01, *** p < 0.001, **** p < 0.0001

Mice Housed at TT Develop Fewer Metastatic Tumors

4T1 mouse model
Triple Negative BreCa

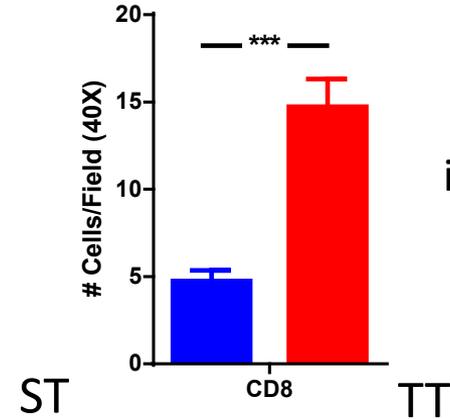
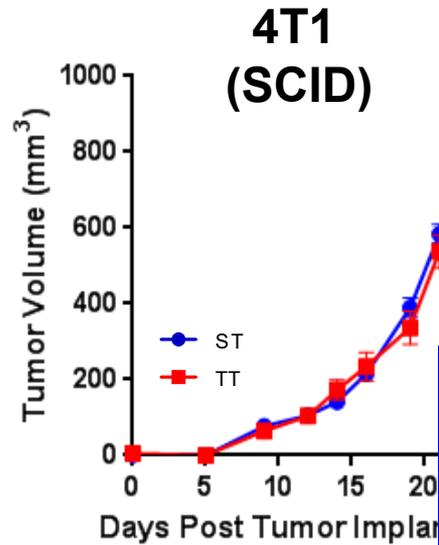
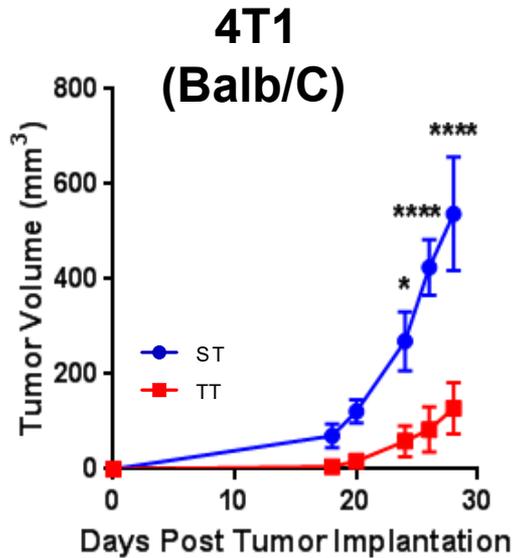


Standard Temperature

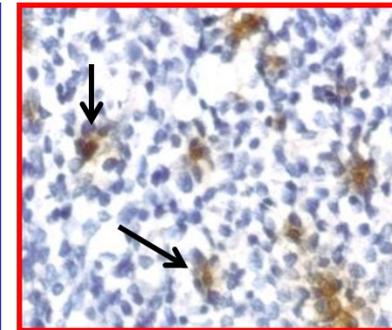
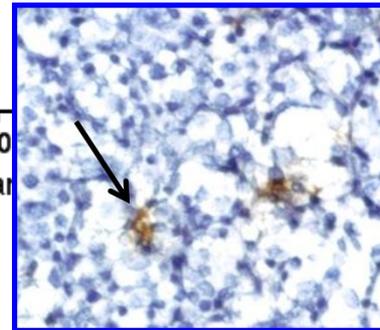
Thermoneutral Temperature



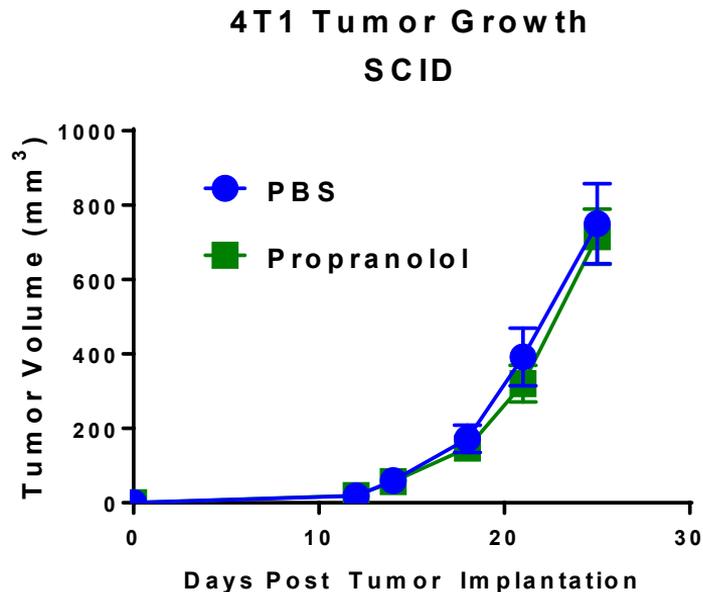
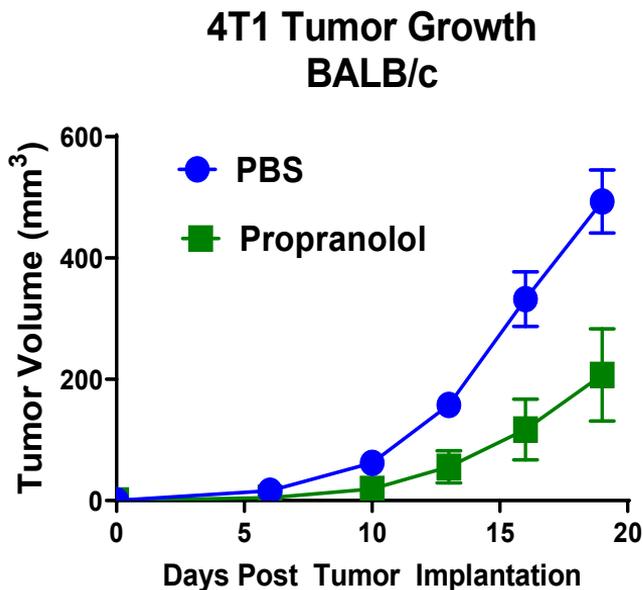
Relief from cold stress slows tumor growth rate: *This effect is lost in SCID mice.*



More tumor infiltrating CD8+ T cells seen at TT

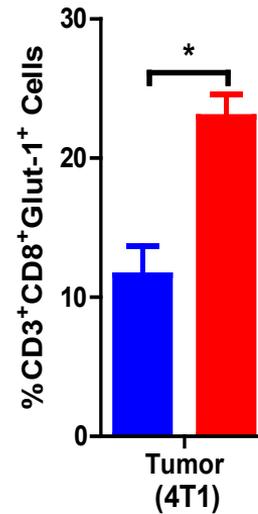
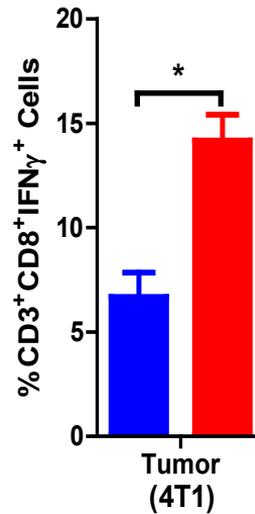
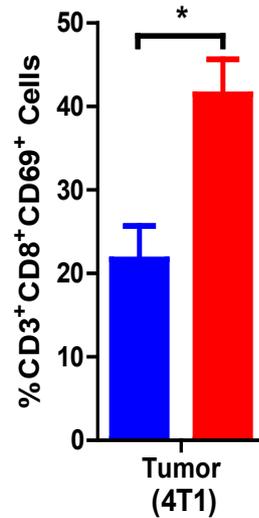
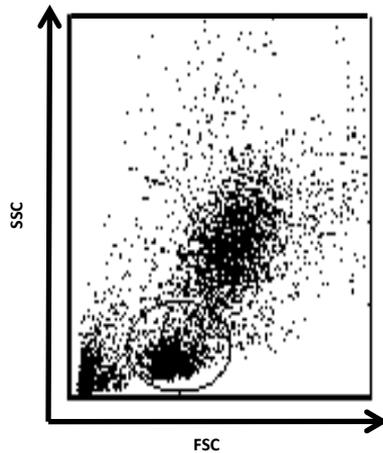


Adrenergic signaling blockade improves tumor growth control at ST: depends on adaptive immune system



Propranolol: pan- β -AR antagonist

T-cells isolated from tumors of mice housed at TT have a more “activated” phenotype

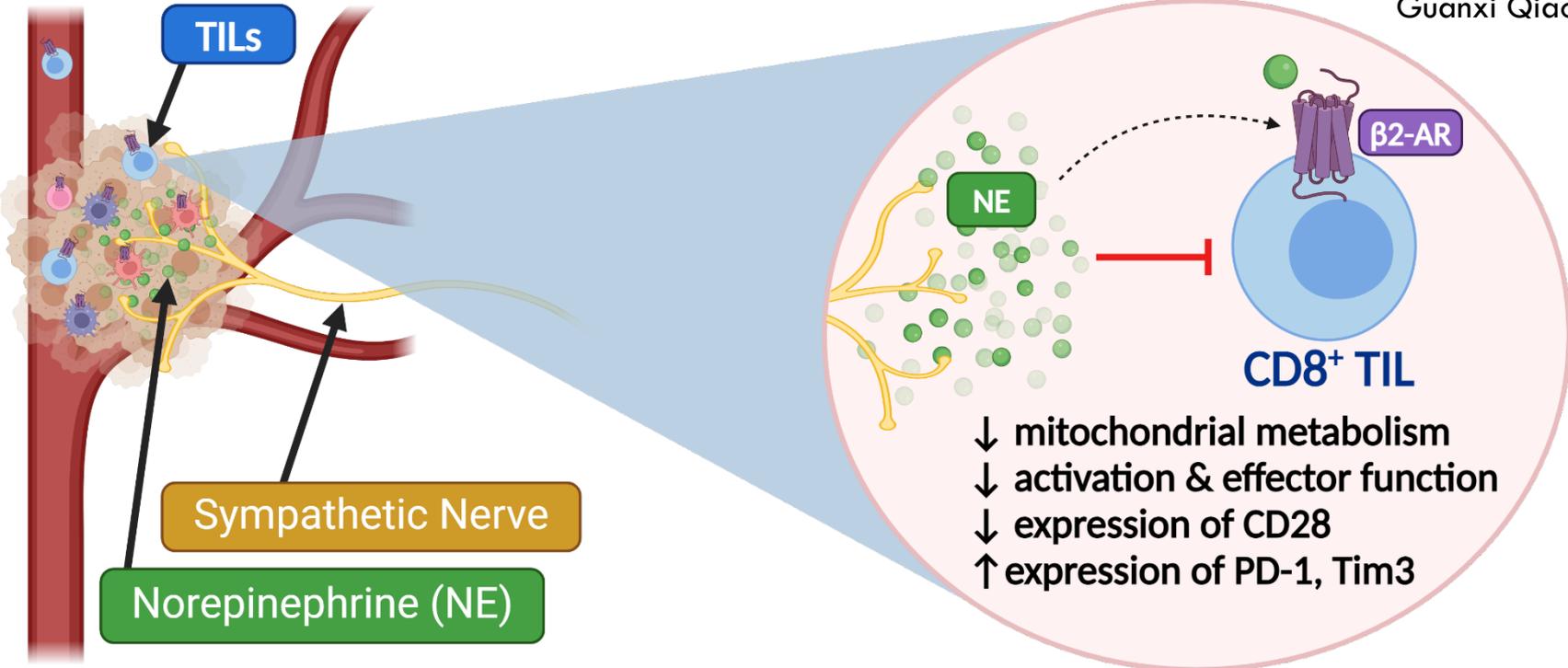


N=5/group *p<0.05

β -AR stress signaling drives CD8⁺ T cell exhaustion in the tumor microenvironment



Guanxi Qiao, PhD

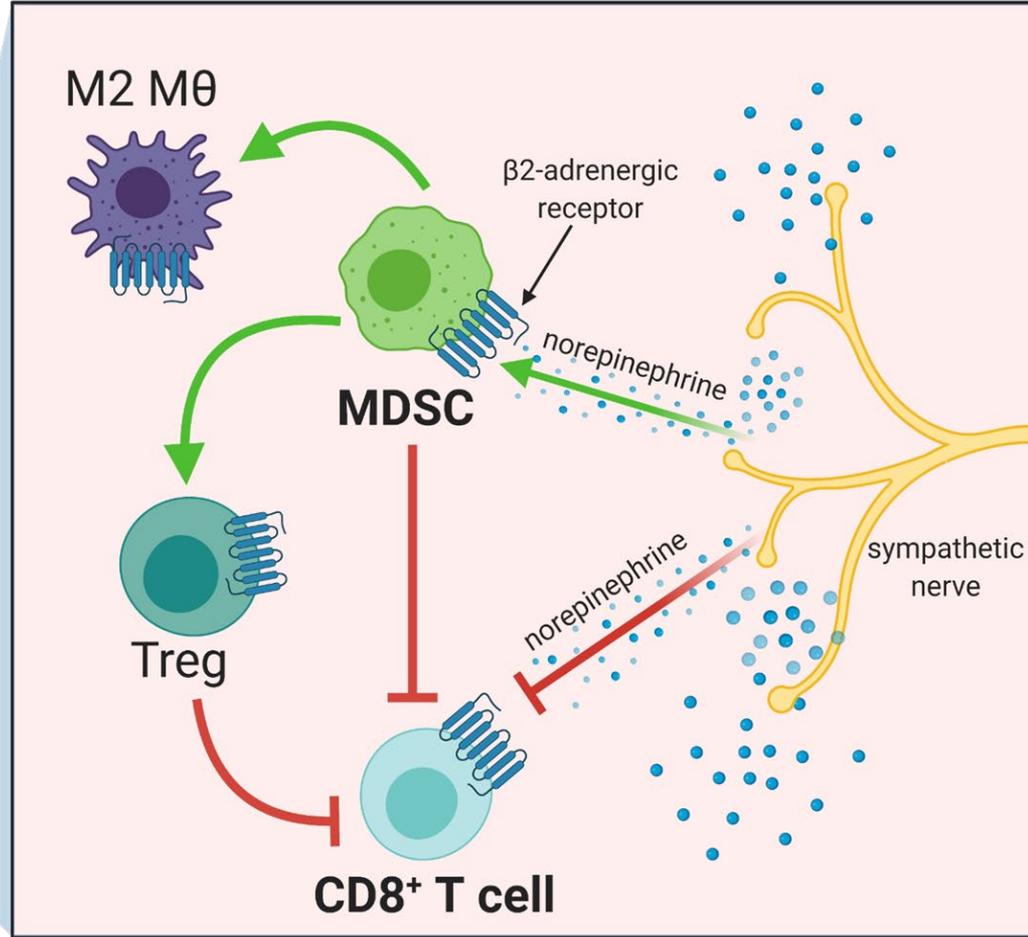
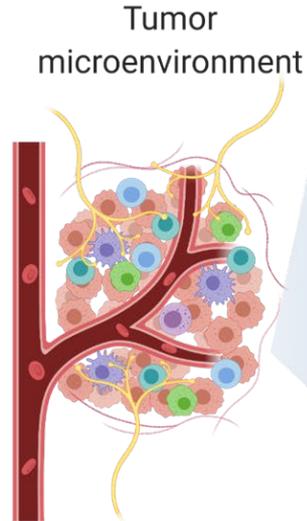


Qiao et al., *Cancer Immunol Res*, 2021
Qiao et al., *Cancer Immunol Immunother* 2019

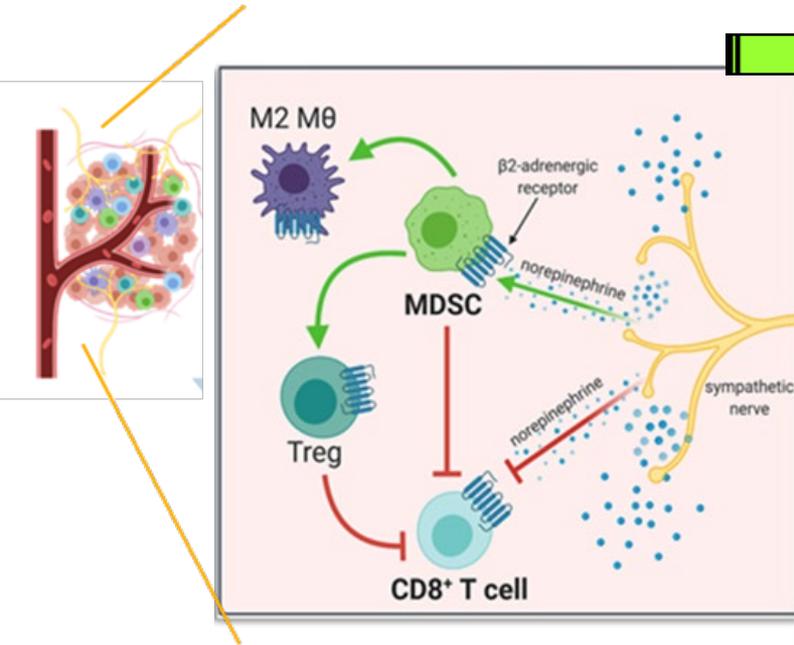
Inhibition of T cell function by adrenergic signaling is combined with enhanced MDSC survival and function



Hemn Mohammadpour, PhD



Ongoing clinical translation using propranolol in combination with immuno- and/or radio-chemotherapies



Clinical Translation

New Trials

Melanoma:

Phase I Trial Gandhi (TII) PI **Clin Can Res 2020**
Multi-center Phase II Shipra Gandhi, PI

M Myeloma:

Phase I/II Trial, Hillengass (PI)

Esophagus:

Phase Ib/II Singh, PI;

Esophagus:

Phase II Mukherjee, PI

Breast Cancer:

CPI refractory population: Pilot to Phase II (Gandhi, PI)
seeking collaborators and funding.

Canine and Human Sarcoma: Phase II, with Cornell Univ Veterinary Hospital (in development)

ICI- Bucsek et al., Cancer Res. 2017

Radiation- Chen et al., Nat. Comm, 2019

Chemotherapies- Eng et al., Nature Comm. 2015

SUMMARY: Chronic stress negatively influences cancer treatment outcomes through:

❖ Suppression of anti-tumor immune activity

These data may contribute to our understanding of how chronic stress leads to more aggressive cancers in patients and to the identification of novel biomarkers in patients in need of greater stress-reducing interventions.

Question? How does chronic stress affect anti-tumor immune function in older individuals compared to those who are younger?

Whatever we accomplish is due to the combined effort.” Walt Disney

Repasky Lab

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Sarbjit Mukherjee, MD
Phil McCarthy, MD

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McDonald, and Mohammadpour F 30,
and 32 NRSA pre- and postdoctoral
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Independence Award (2021-2026):**

RPCCC Comparative Oncology

Shared Resource

Sandra Sexton VDM
Mike Moser, PhD (IACUC)

John Loftus, PhD Cornell Vet College
Edith Lord, Scott Gerber URMC

David Farrar, PhD, UT SouthwesternMC

Todd Schell , PhD; Penn State Hershey
Joe Drabick MD; Penn State Hershey
Andrew Lane PhD and Teresa Fan, PhD
Univ. of Kentucky

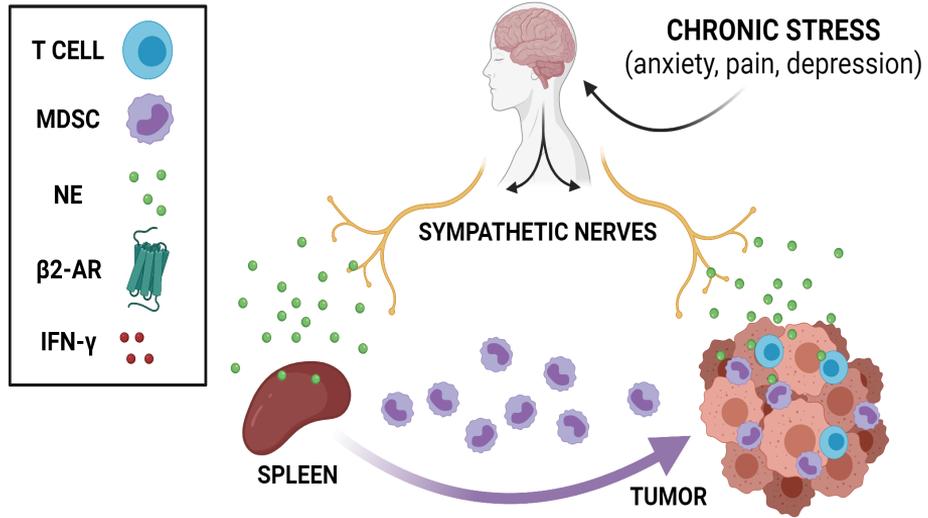
Breast Cancer Coalition of Rochester, The
NYS Peter T. Rowley Breast Cancer Research
Grant, The Harry J. Lloyd Charitable Trust,
The Roswell Park Alliance Foundation; Herd
of Hope Foundation.

β 2 adrenergic receptor-mediated signaling regulates the immunosuppressive potential of myeloid-derived suppressor cells

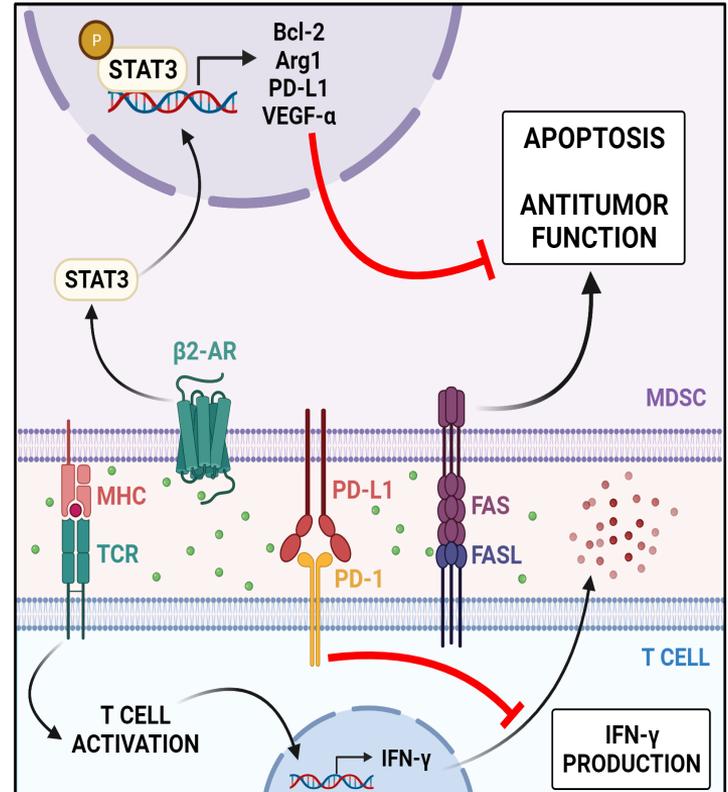
The Journal of Clinical Investigation

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β 2-AR signaling promotes MDSC survival & protumorigenic function



β 2-AR signaling increases immunosuppression by MDSCs

