Chronic social stressors and breast cancer biology: laboratory insights

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Biological Effectors of Social Determinants of Health in Cancer: Identification and Mitigation
A National Cancer Policy Forum Workshop
Wednesday, March 20th, 2024

Disclosures

I am a co-inventor on methods patent issued to The University of Chicago to identify glucocorticoid receptor signaling pathways in triple-negative breast cancer cells.

Discovery that glucocorticoid receptor (GR) activation has a deleterious role in estrogen receptor-negative breast cancer biology

[CANCER RESEARCH 60, 867–872, February 15, 2000]

Advances in Brief

The Glucocorticoid Receptor Mediates a Survival Signal in Human Mammary Epithelial Cells[1]

Timothy J. Moran, Stacy Gray, Christina A. Mikosz, and Suzanne D. Conzen[2]

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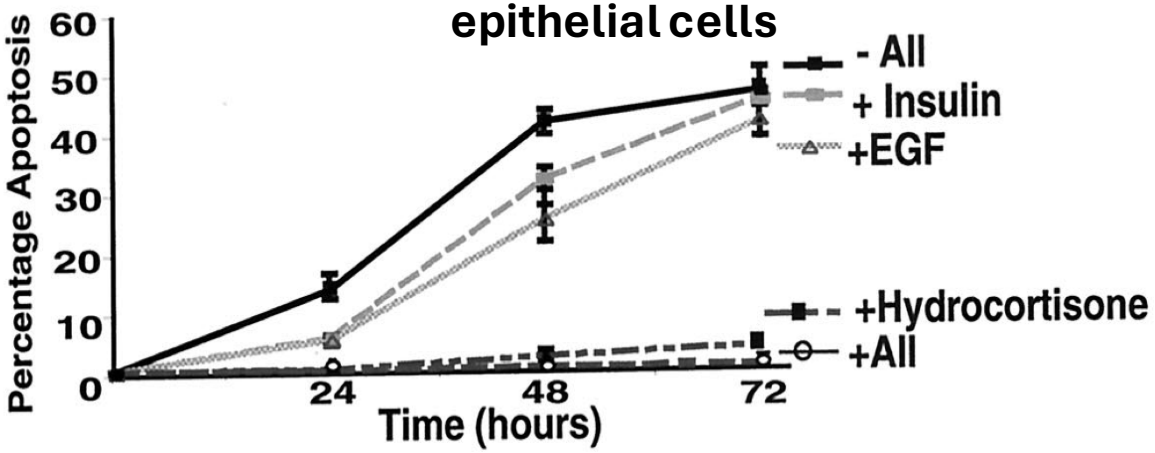
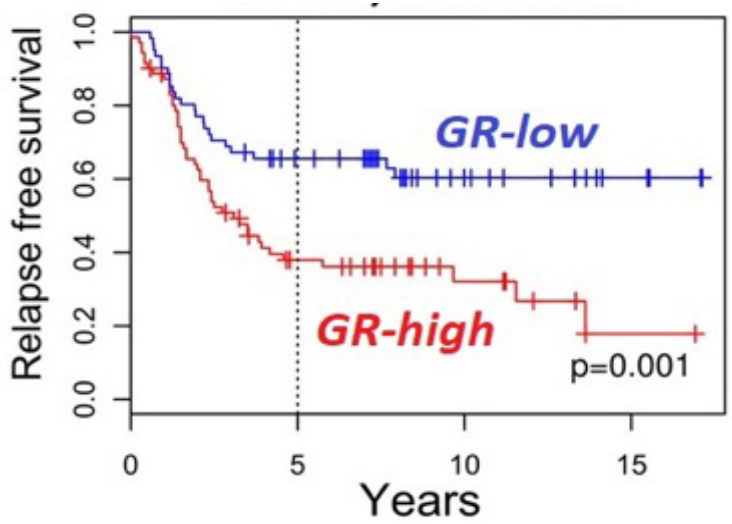
Estrogen receptor-negative breast epithelial cells



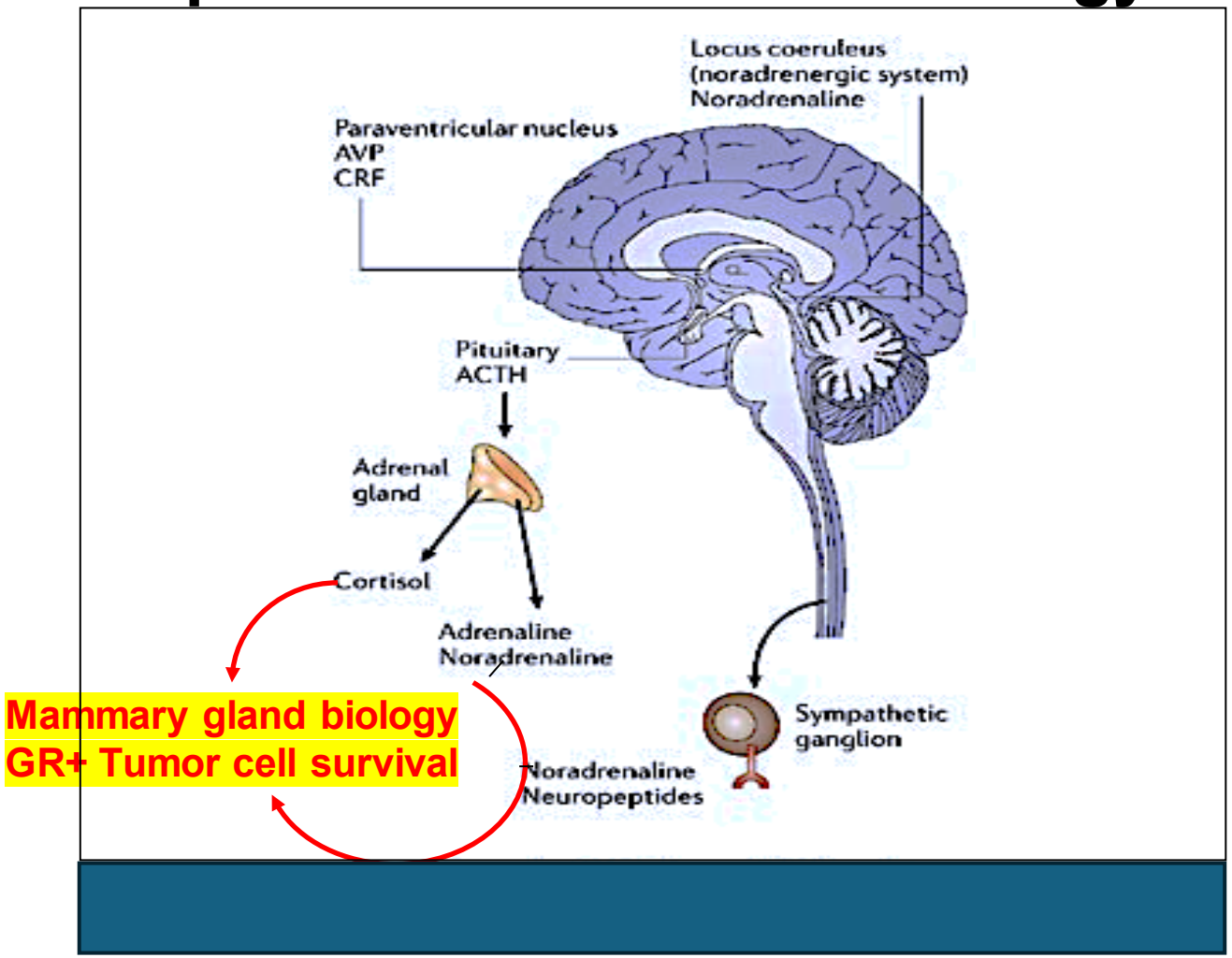
Moran T et al. Cancer Res, 2000

Triple-negative breast cancer patients



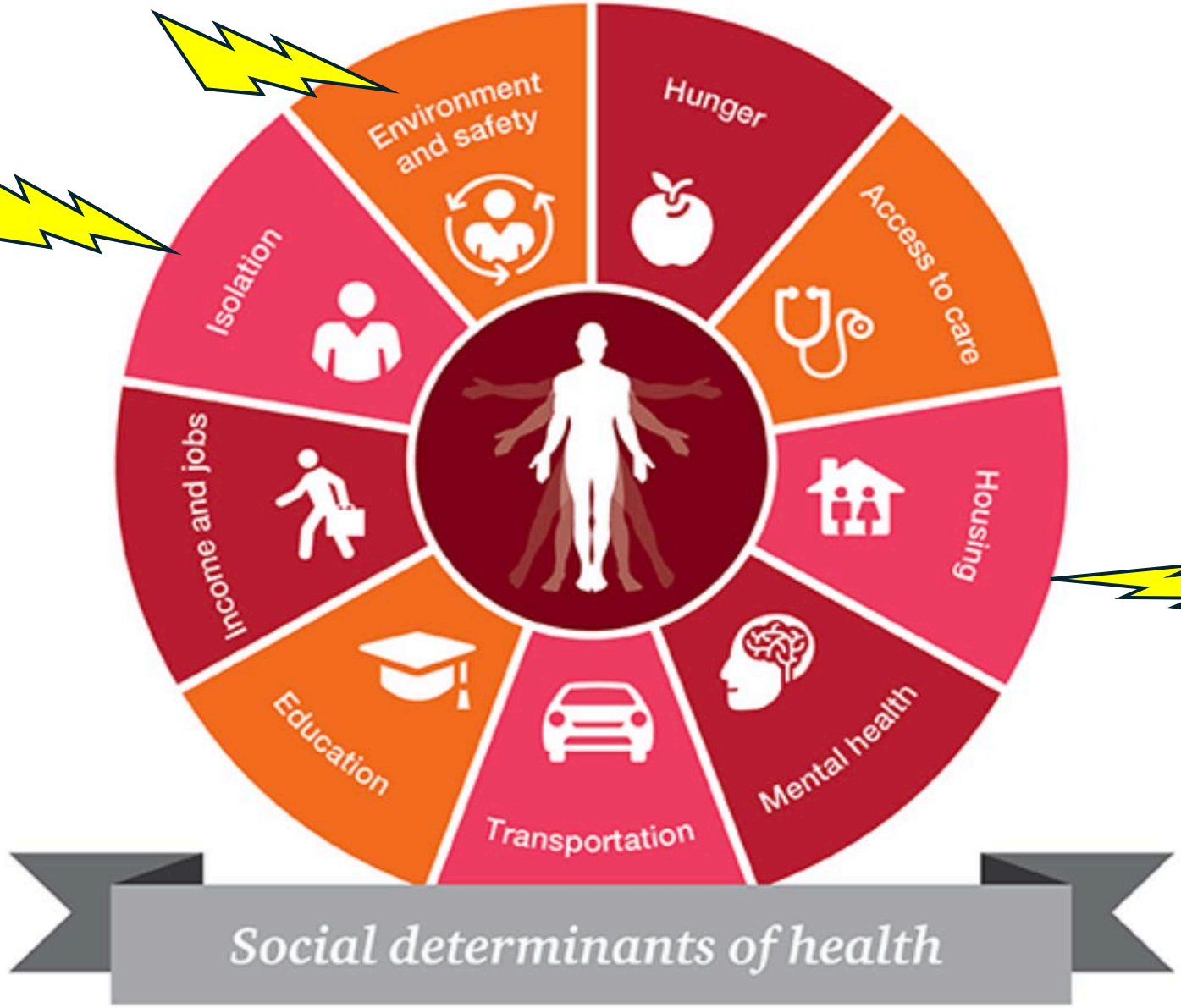
Pan D, et al Cancer Res, 2013

Psychosocial stressors and the ensuing physiological response: role in cancer biology?



Antoni et al. *Nature Reviews Cancer* 6, 2006
Volden PA, Conzen SD. *Brain Behav Immun*. 2013

Background: Chronic stressors, physiological biomarkers-breast cancer biology ?



Lyndee Chin, Retrieved from https://hitconsultant.net/2019/03/18/social-determinants-of-health-sdoh-collection/

Can **physiological** responses to low-level and unremitting chronic stressors be modeled in cancer?

Adaptive Response

Acute process

- **Energy mobilization**
  - -Glucose mobilization
  - -Increased BP
  - -Increased HR
- **Cognitive and sensory shifts**
  - - Aspects of memory improve
  - - Senses sharpen

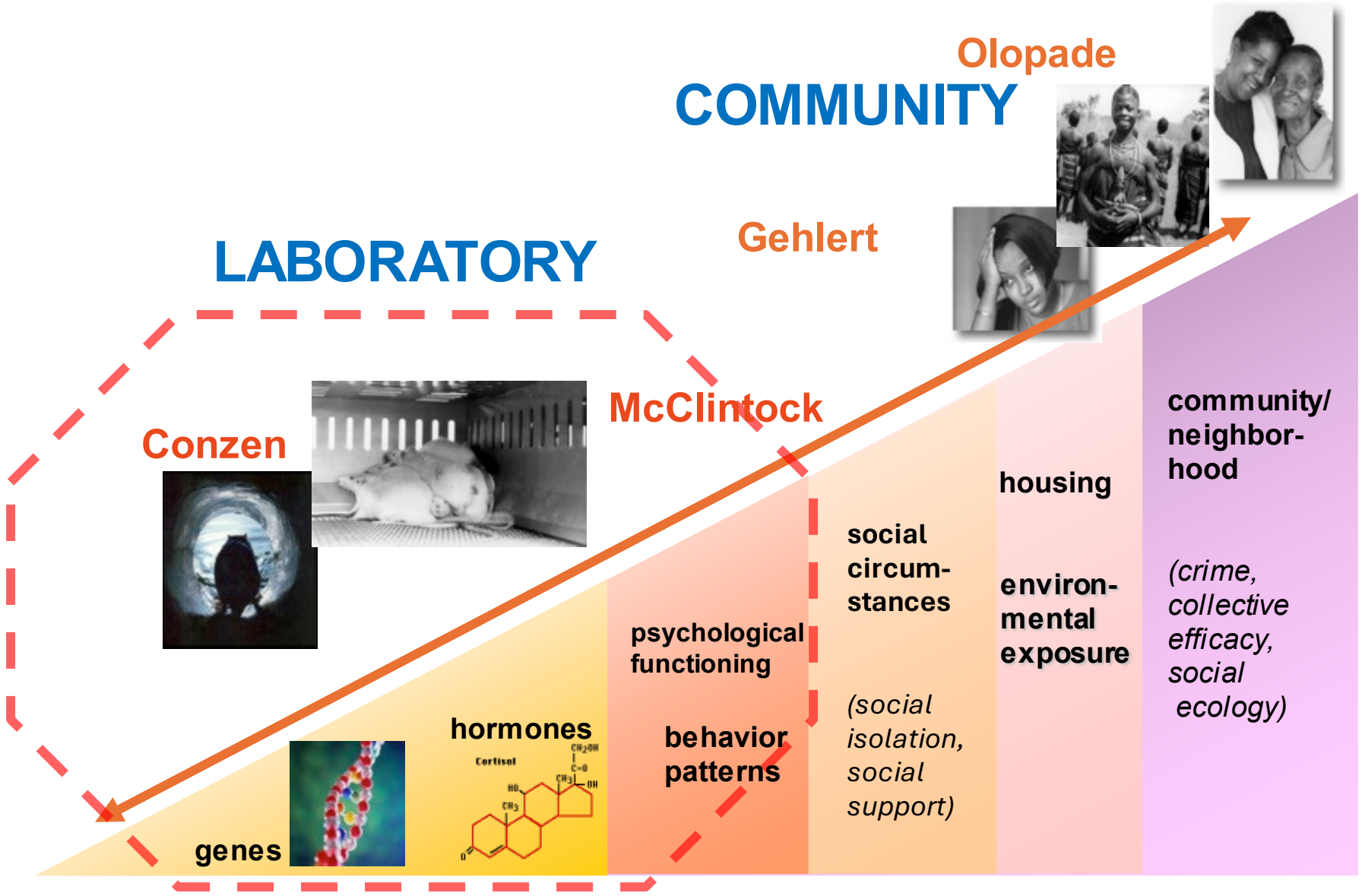
Maladaptive Response

Chronic processes disturbed homeostasis

- - Increased inflammation
- - Hypertension
- - Reproductive abnormalities
- - Immune system
- - Metabolic diseases
- - **? Malignancy**

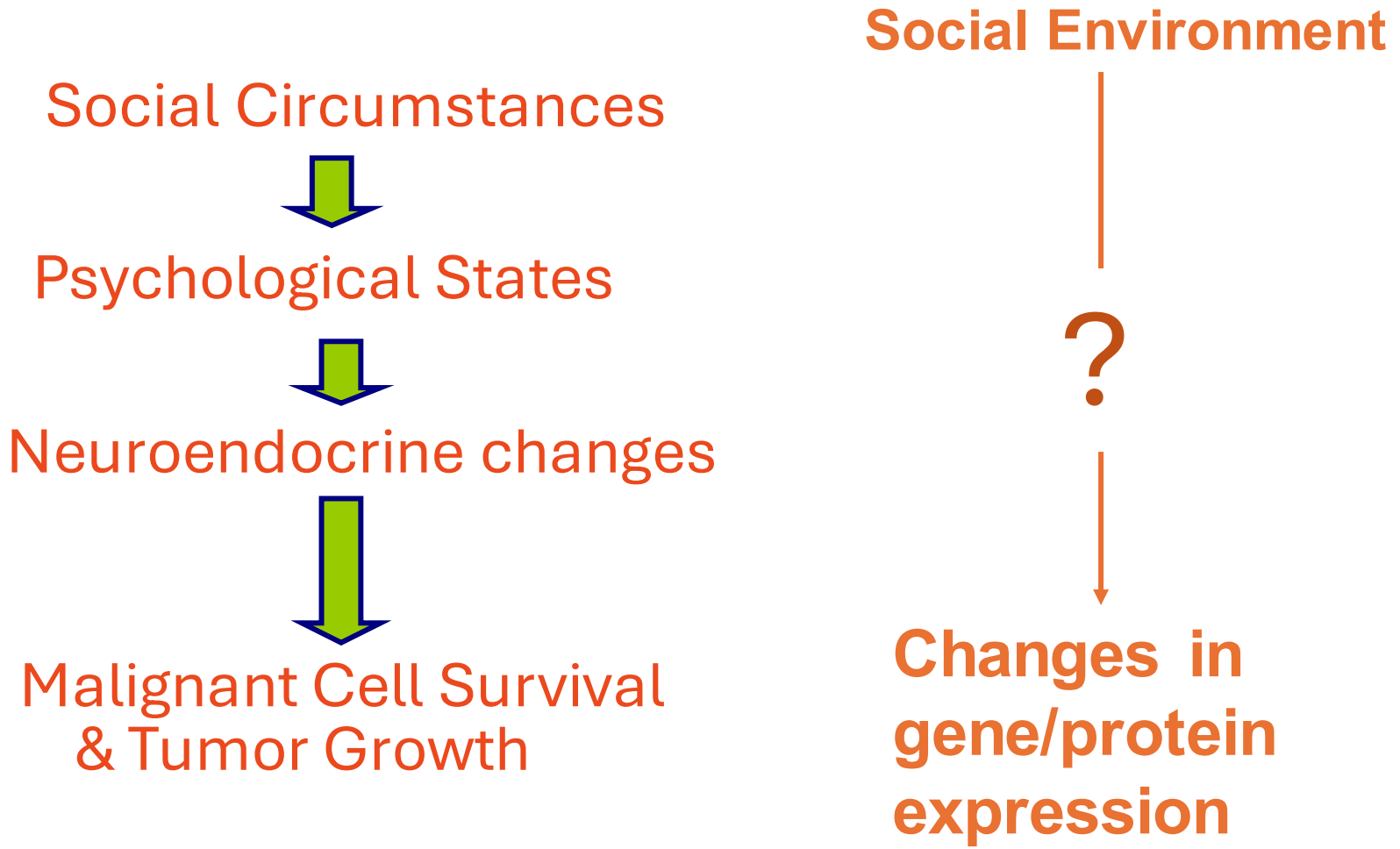
Selye H. The Physiology and Pathology of Exposure to Stress, A treatise based on the concepts of the General-Adaptation-Syndrome and the Diseases of Adaptation. Montreal, Canada: ACTA, Inc. Medical Publishers 1950.

UChicago CIHDR: Social Stressors and Cancer

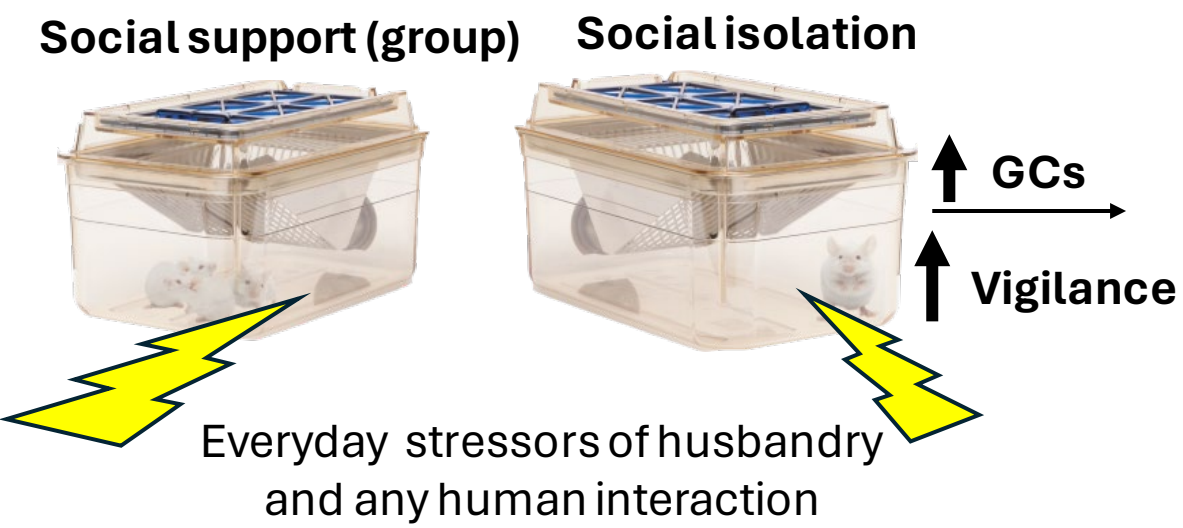


P50-ES012382- McClintock MK et al *J Gerontol B Psychol Sci Soc Sci*, 2005..

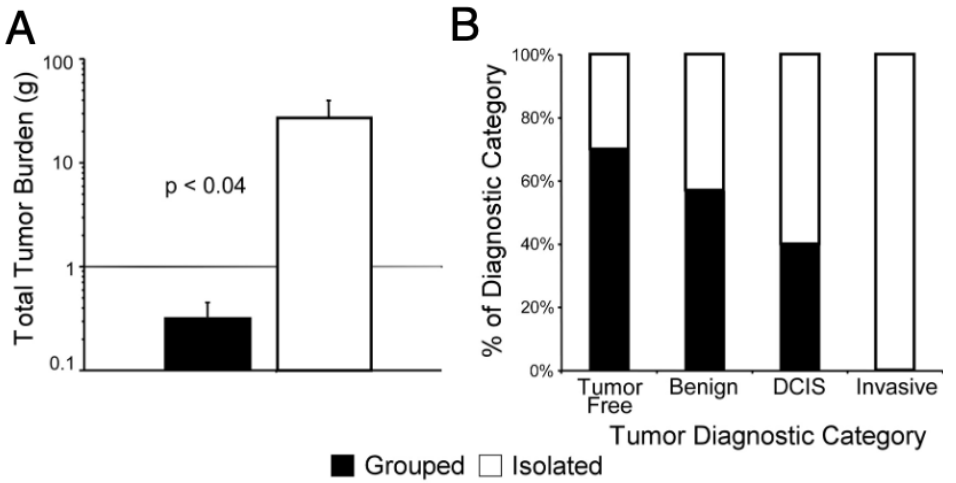
CIHDR Multi-level Model for Studying Health Disparities in Breast Cancer



Can social stress responses be studied along with mechanistic studies of breast cancer biology?



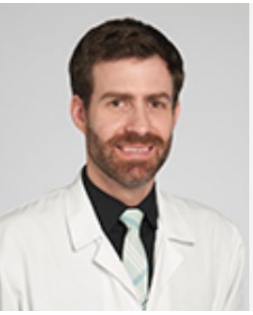
Earlier and more aggressive breast cancers



Modeling social stressors in rodents
(Model #1: Transgenic mice develop GR+ triple-negative breast cancer)

GROUPED HOUSING
SOCIAL SUPPORT

SOCIAL ISOLATION
ISOLATION



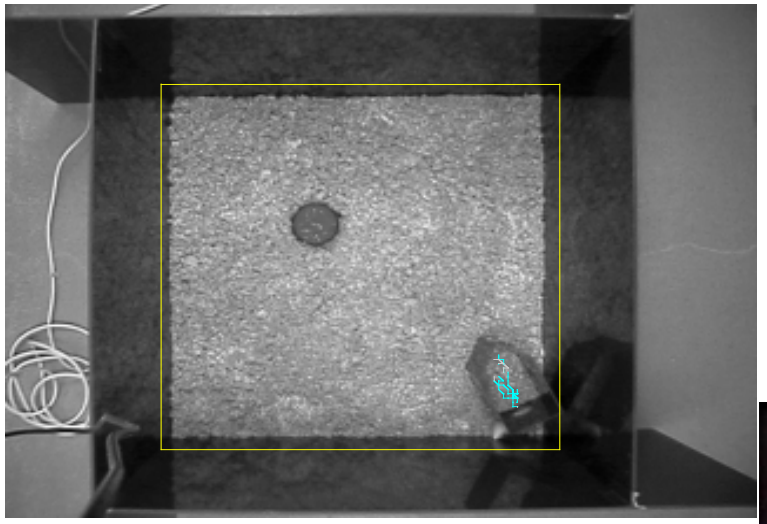
Brad Williams

<u>Hypotheses:</u>

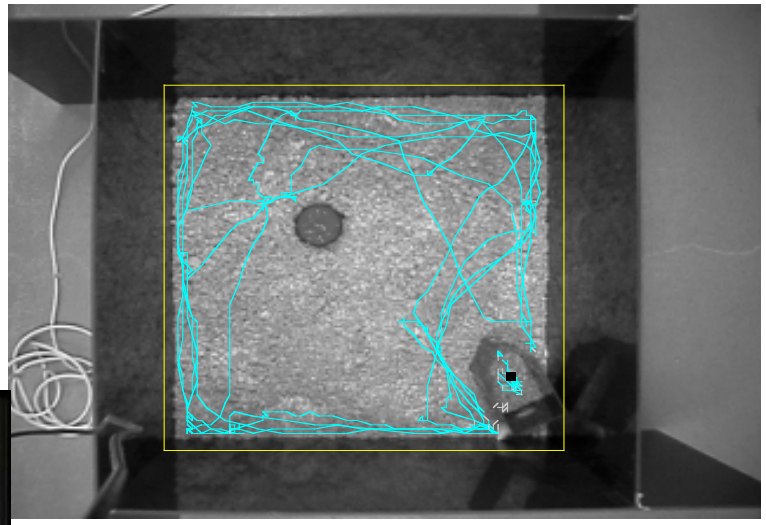
Chronic social isolation will result in:

- an acquired vigilant behavioral phenotype
- increased corticosterone response to acute stressors
- increased mammary tumor growth (? inhibit apoptosis)

Behavior: “Vigilance” in a potentially threatening environment can be measured



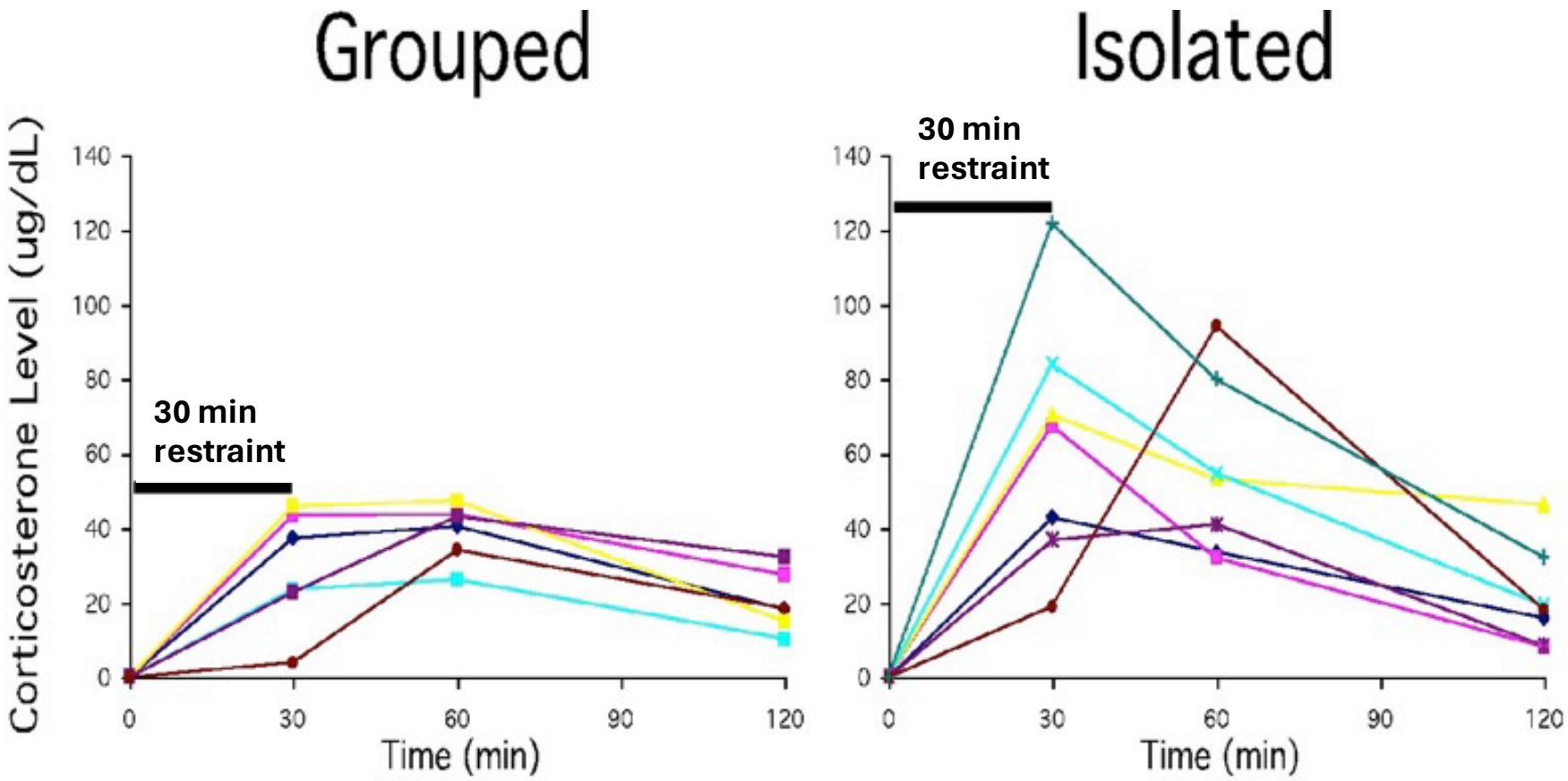
Socially Isolated
Vigilant



Group Housed
Exploratory

Williams JB et al *Can Prev Res* 2009

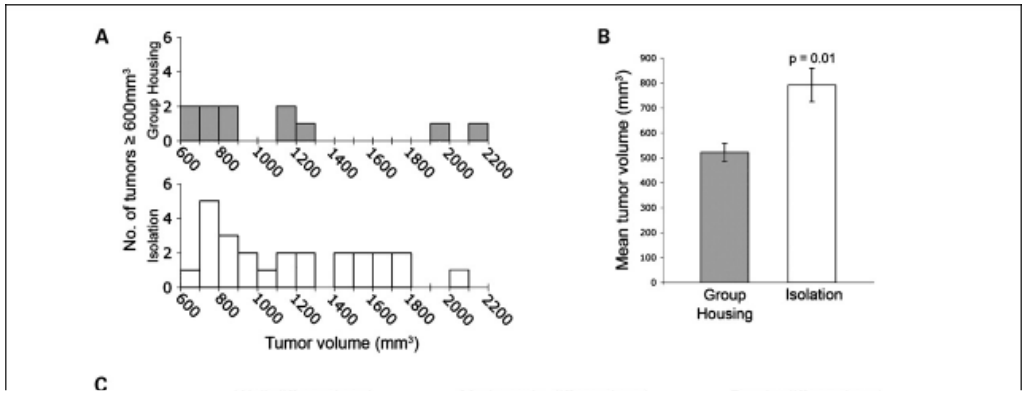
Endocrine response: Effect of social isolation (chronic) on corticosterone levels following mild restraint (acute)



Slope of the rise: p=.022
Absolute increase: p=.032

Williams JB et al *Can Prev Res* 2009

Chronic isolation is also associated with increased GR+ triple-negative breast cancer model



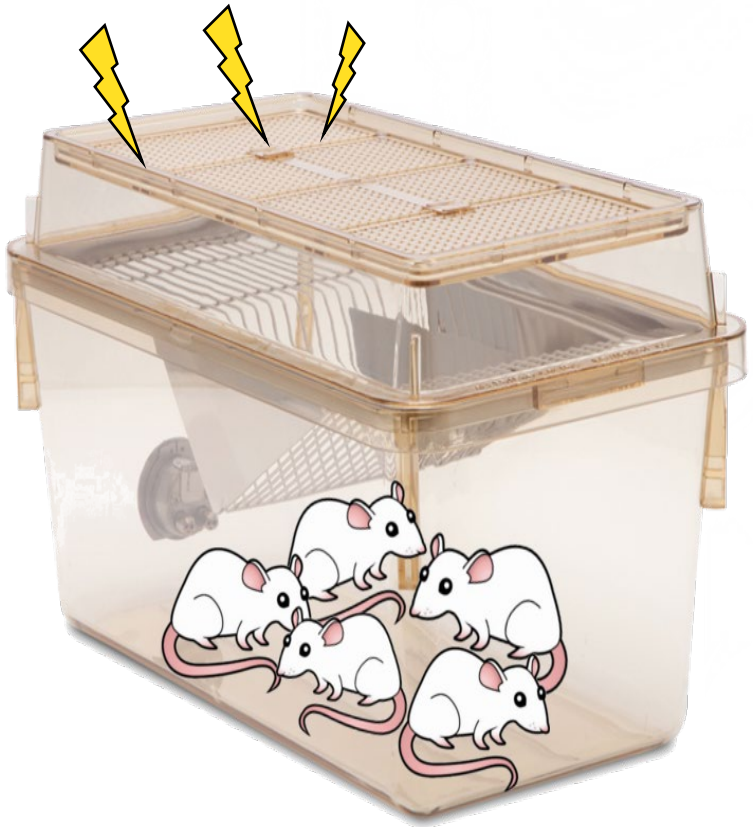
Williams JB et al. *Can Prev Res* 2009

Isolates- metabolic phenotype

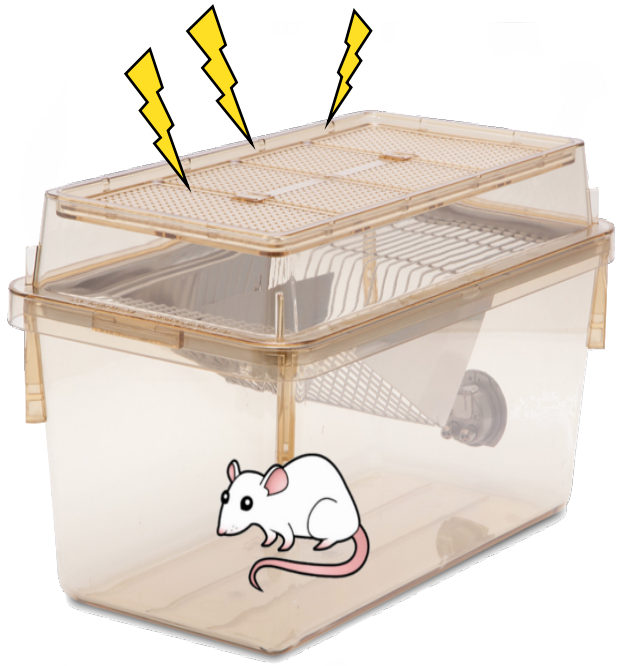
Volden PA et al.. *Cancer Prev Res*. 2013

Volden PA et al. *Cancer Prev Res* 2016

Model #2: Female Sprague-Dawley Rat (spontaneous tumors)



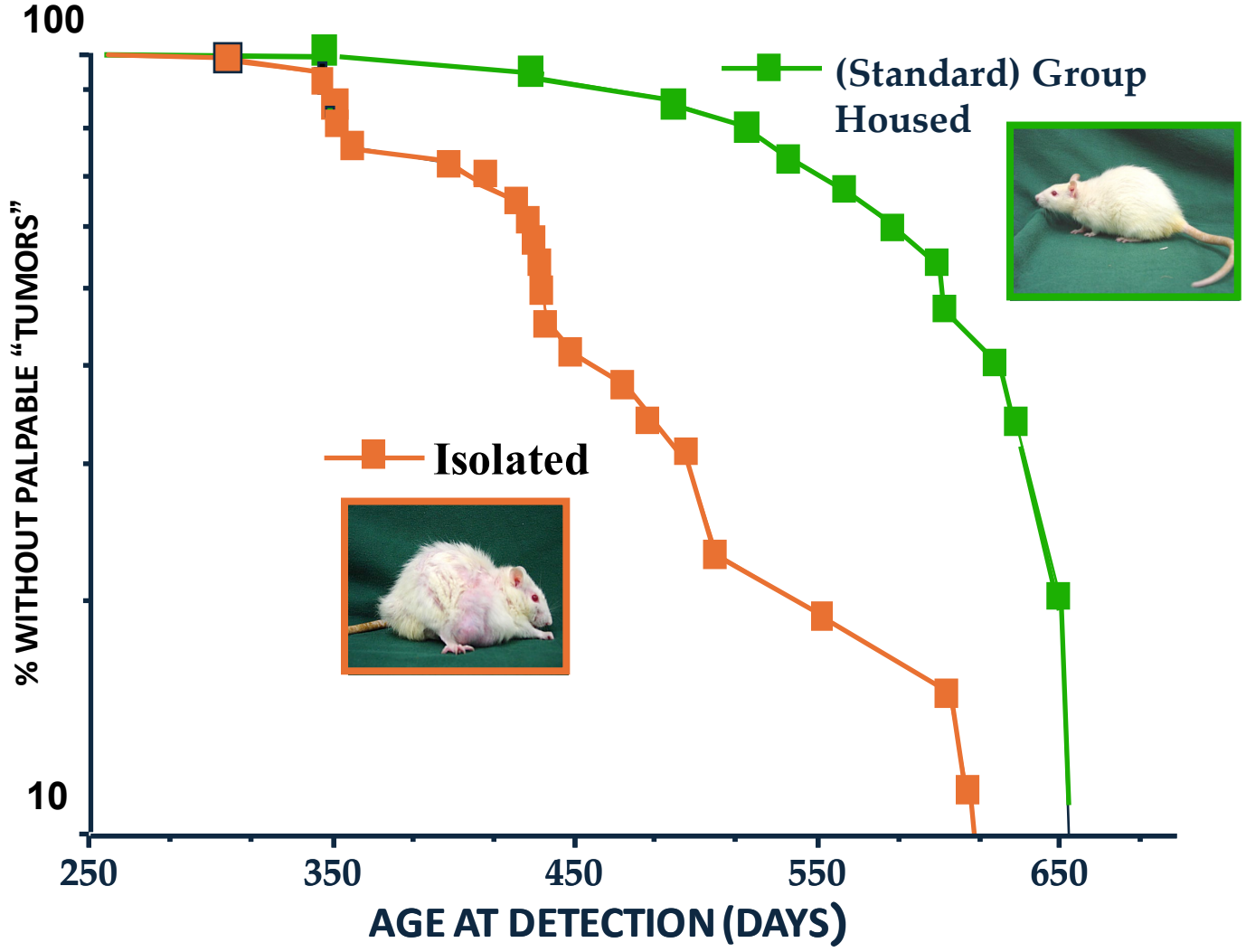
GROUPED HOUSING
SOCIAL SUPPORT



SOCIAL ISOLATION
ISOLATION

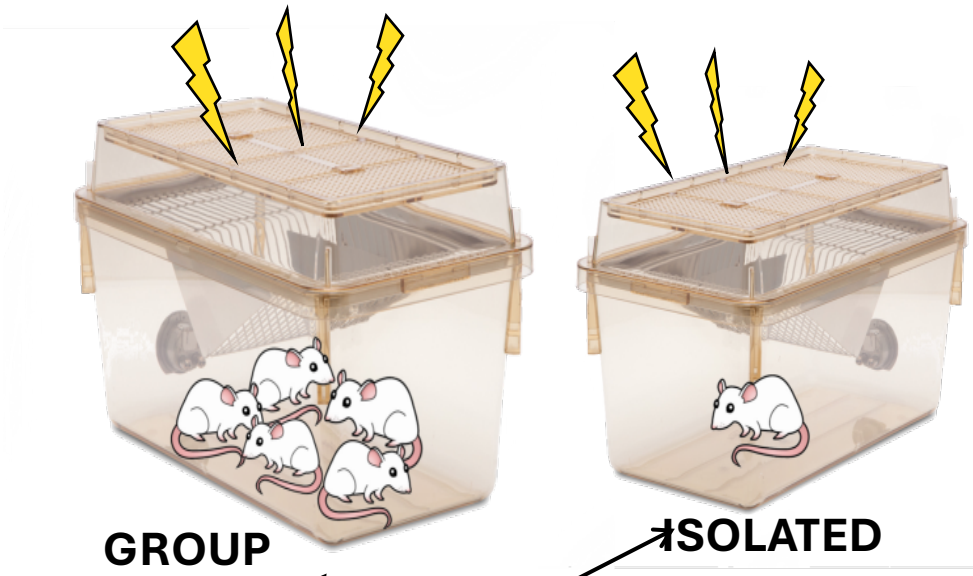
Hermes et al, PNAS (2009)

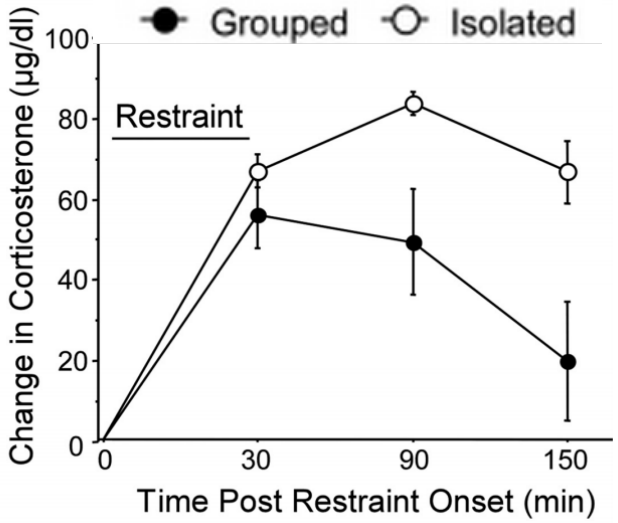
Social Isolation is associated with earlier onset rat breast cancer

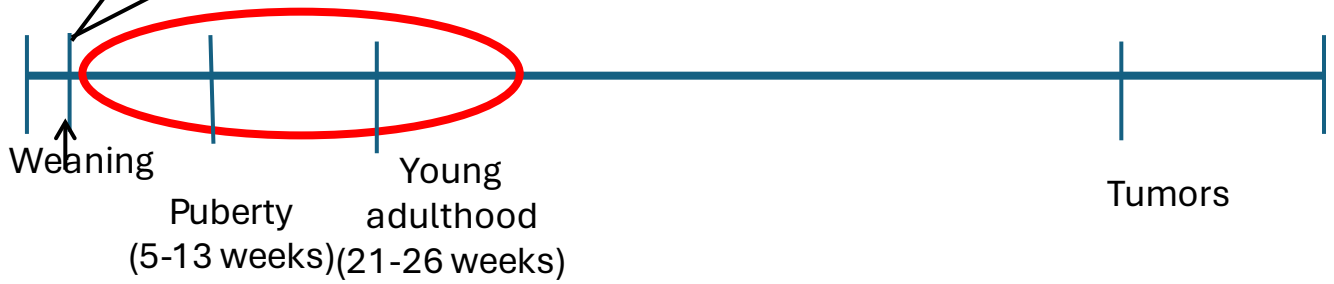


Hermes et al, PNAS (2009)

Social isolation in the rat model – When is MG development "sensitive" to isolation ?

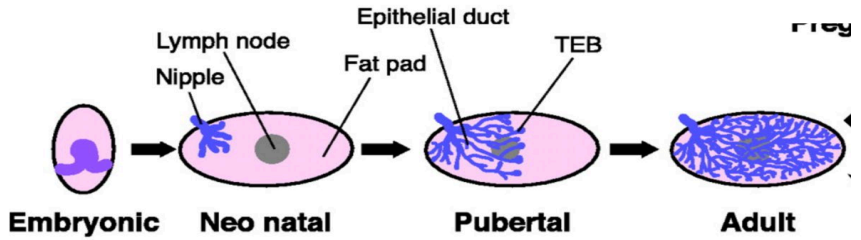






Hermes et al, PNAS (2009)

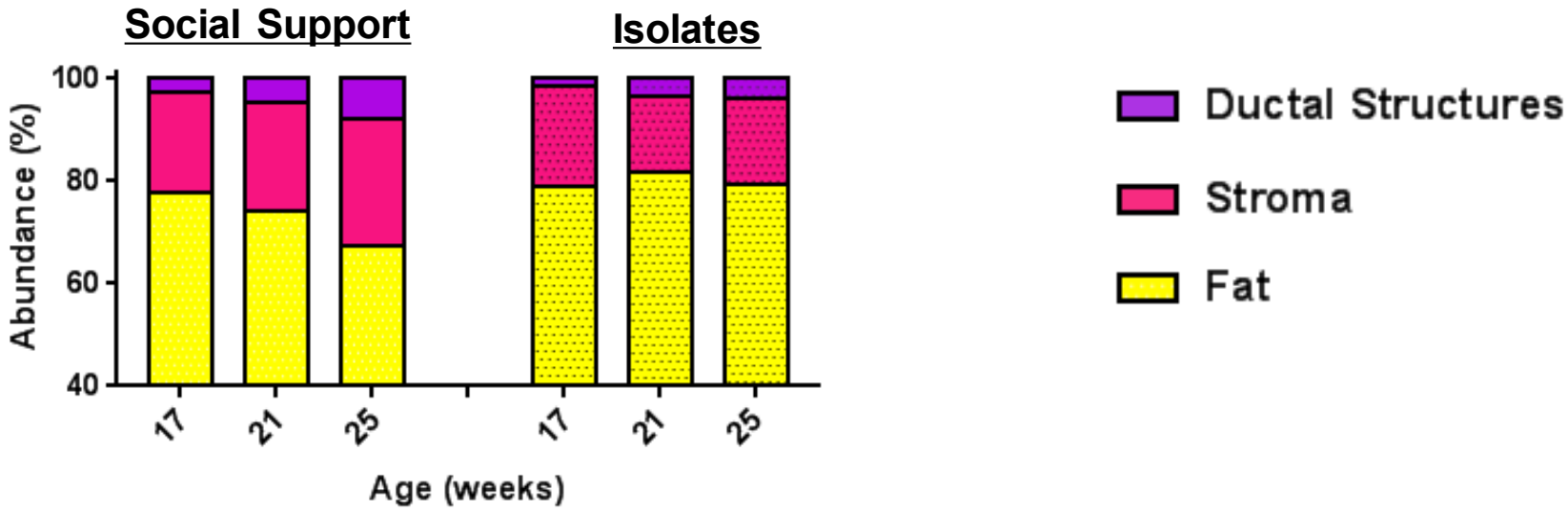
Rat Experimental Schema

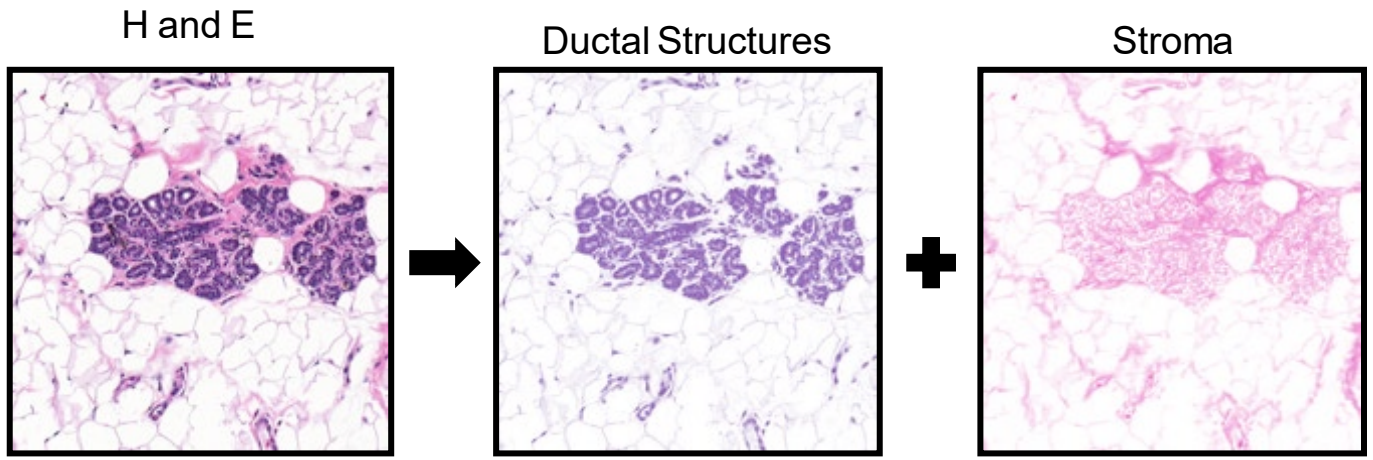


Reproductive Lifespan Events: **Mammary, Adrenal, and Ovarian**		**Weaning** Prepubertal Temperament	**Early and Late Puberty** TEBs ➡ TDs and Abs HPO matured	**Early Adulthood** - Ducts differentiate - Duct tree lengthens and expands - GC stress reactivity with recovery after everyday stressors - MaSC population drops
Age (weeks)		**3-4**	**5-12**	**13-22**
Conditions:	**Social Environment:**	**Grouped(grey)**	**Weaning ➡ Socially Isolated(white)**	**Early Adulthood**
A **GROUPED**	**G ➡ G**			
B ISOLATION	**SI ➡ SI**			

Johnson MB et al. *J Mammary Gland Biol Neoplasia*. 2018

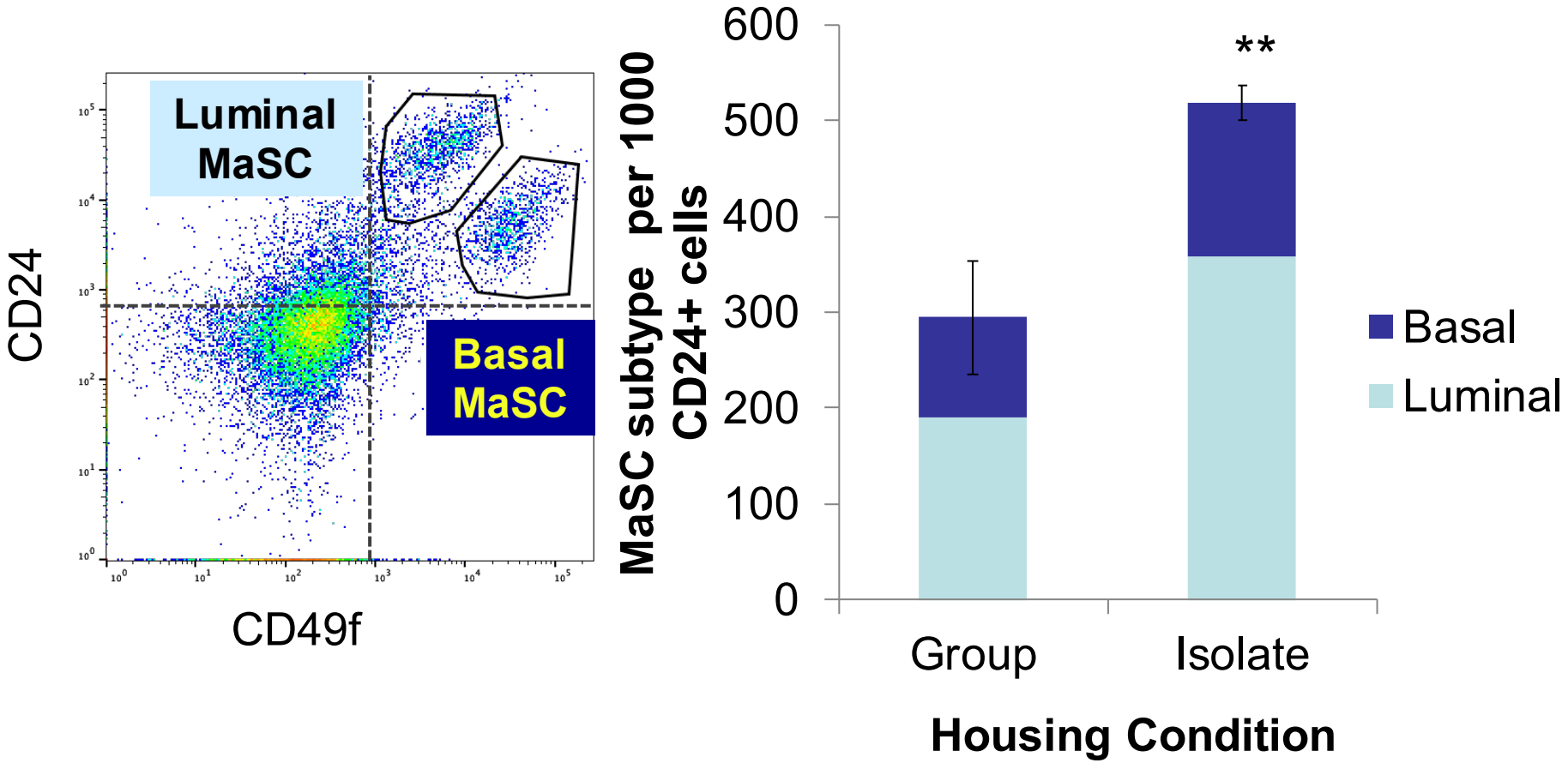
Early Adulthood (17w- 25 w): Social isolation is associated with significantly impaired ductal structure development





Marianna Johnson, PhD

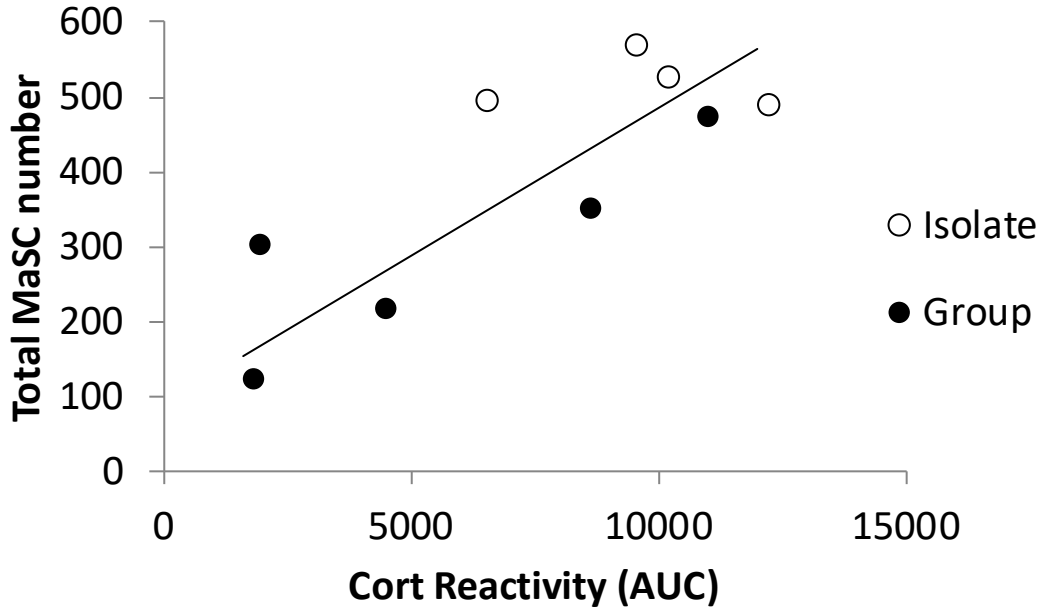
Early Adulthood (17 weeks): Social isolation-induced stress response is associated with an increase in the mammary stem cell population



17 weeks of age, n = 9

t-test; *P* =0.01

Individual rat corticosterone reactivity positively correlates with 17 week MaSC numbers



Correlation Coefficient: 0.82
**p-value: 0.005

Johnson M, ms in preparation

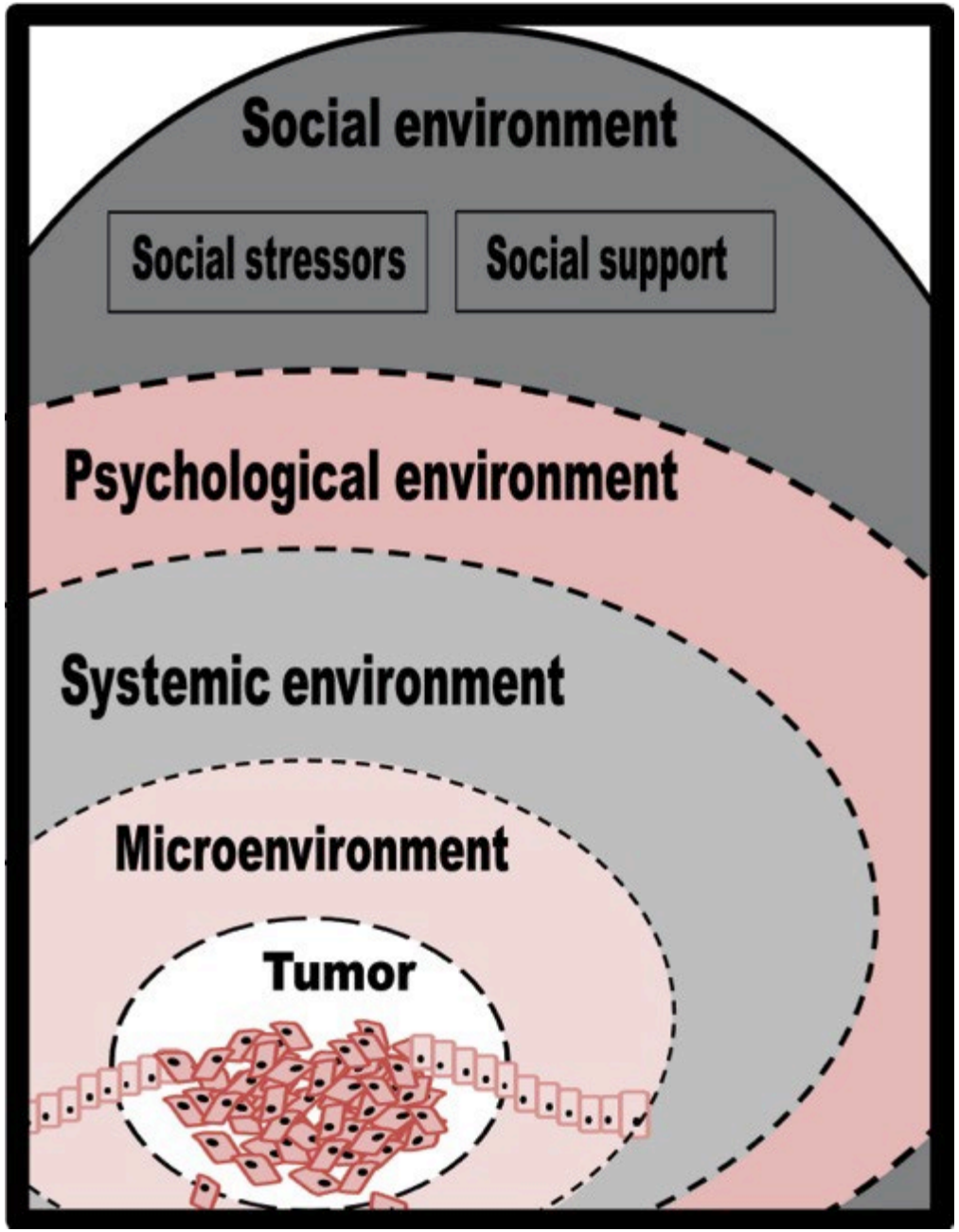
Intervention- Can social support in early adulthood reverse the mammary gland defect and decrease MaSCs and breast cancer risk?

Reproductive Lifespan Events: **Mammary, Adrenal, and Ovarian**		**Weaning** Prepubertal Temperament	**Early and Late Puberty** TEBs ➡ TDs and Abs HPO matured	**Early Adulthood** - Ducts differentiate - Duct tree lengthens and expands - GC stress reactivity with recovery after everyday stressors - MaSC population drops
Age (weeks)		**3-4**	**5-12**	**13-22**
Conditions:	**Social Environment:**	**Grouped(grey)**	**Weaning** ➡ **Socially Isolated(white)**	**Early Adulthood**
A	**G ➡ G**			
B	**SI ➡ SI**			
C	**SI ➡ G**			**Intervention** re-grouping

Briana Banks, PhD Student

Conclusions

- Social isolation, a SDOH, **can be modeled to study cancer.**
- The ***physiological stress response*** to social isolation includes increased stress hormone accompanied by behavioral vigilance.
- Following chronic stress, mammary gland tumors occur **earlier and are more aggressive.**
- **Late puberty/early adulthood** appears to be a **sensitive period** for blunted MG development =?related to BC risk .
- Experiments are ongoing to determine if stress-associated changes and MG cancer risk can be mitigated by **reintroducing social support.**



Acknowledgements

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Gretchen Hermes
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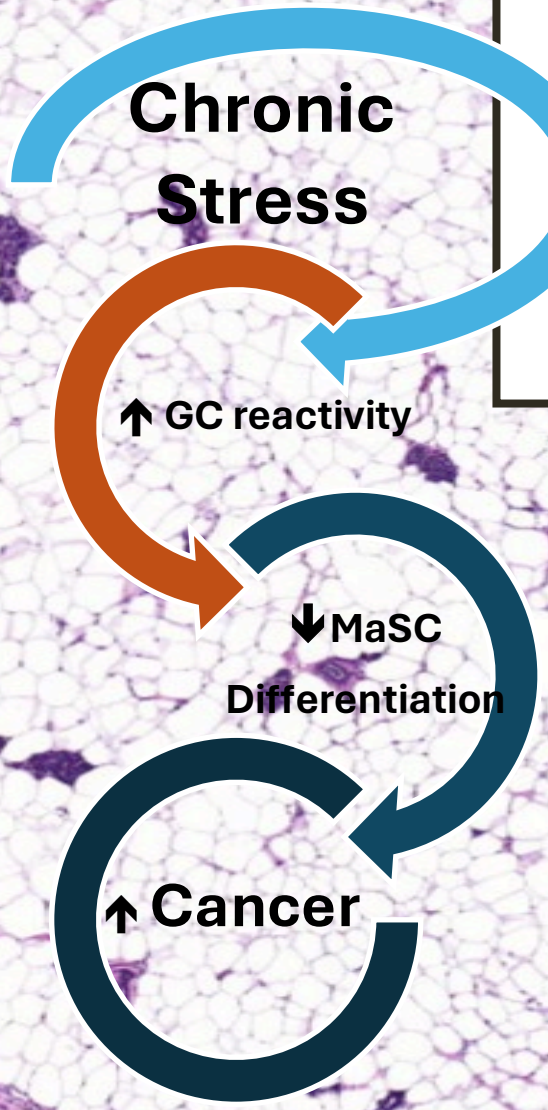
Briana Banks

Community Participants



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