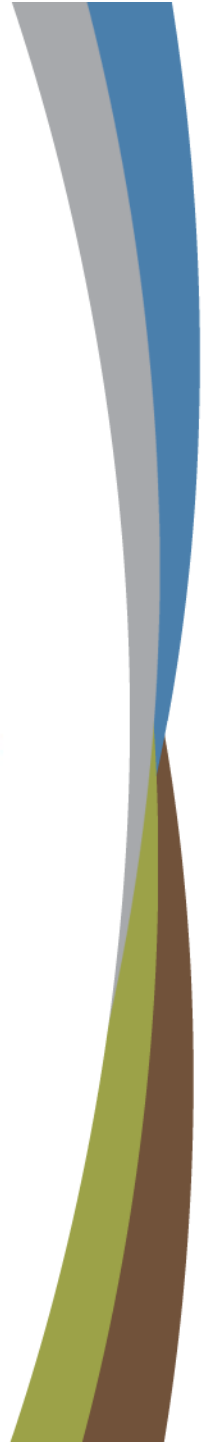


National Cancer Institute

U.S. DEPARTMENT
OF HEALTH AND
HUMAN SERVICES
National Institutes
of Health

Biobehavioral Influences on Cancer Biology

AN EMERGING OPPORTUNITY



Social Environment and Tumor Biology: The Role of Glucocorticoid-mediated Tumor Cell Survival

Suzanne D. Conzen, MD

Associate Professor

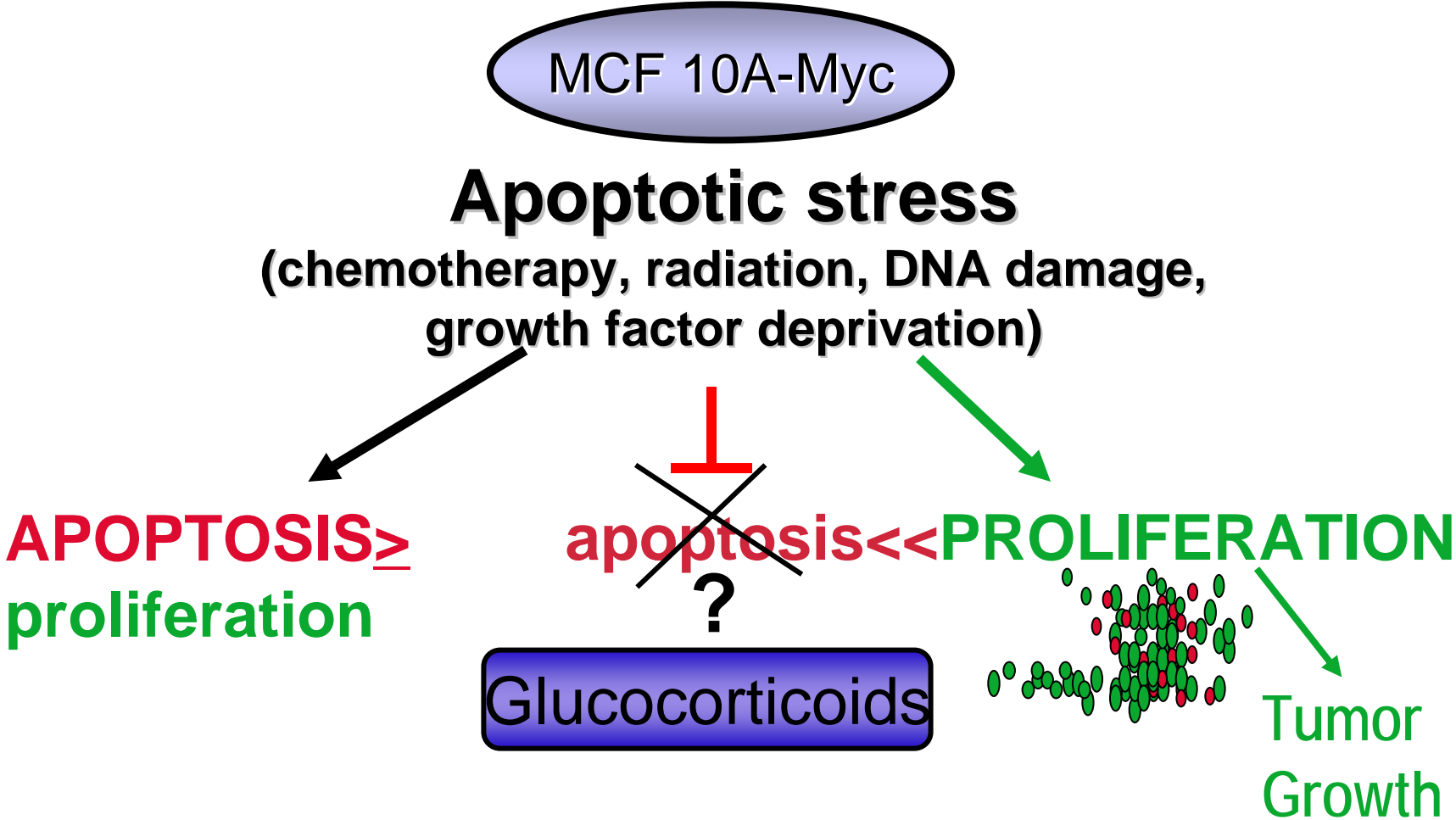
Department of Medicine and

The Ben May Institute of Cancer Research

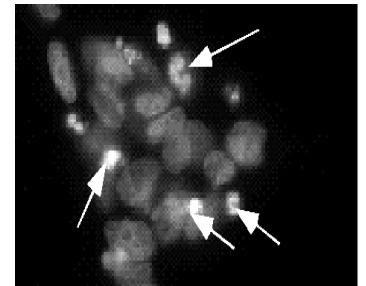
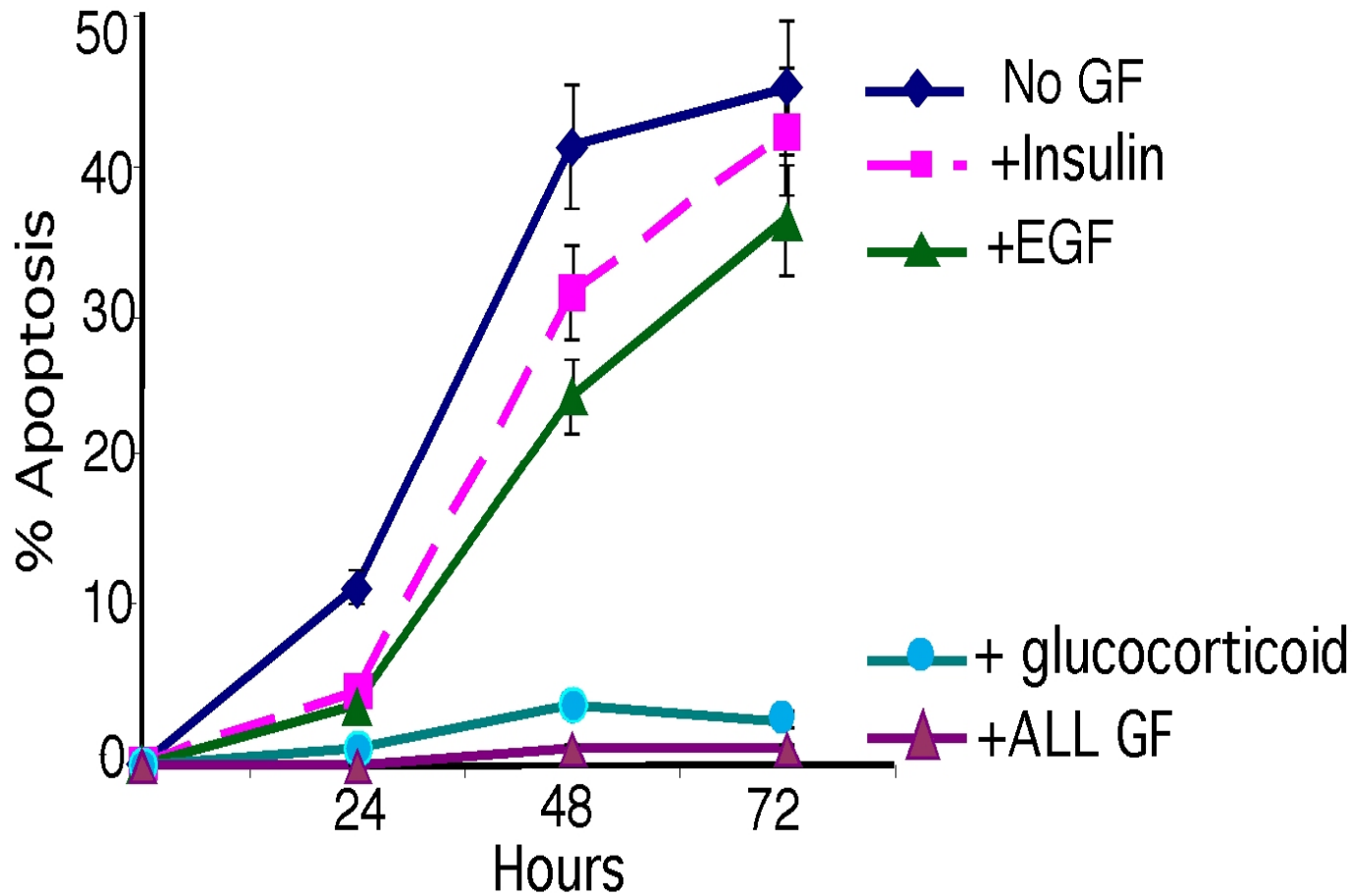
The University of Chicago



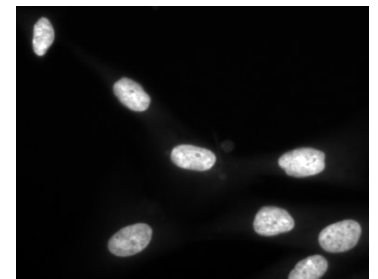
Identification of novel anti-apoptotic signals



Glucocorticoids (GCs) provide a potent anti-apoptotic signal to MCF10A-Myc cells



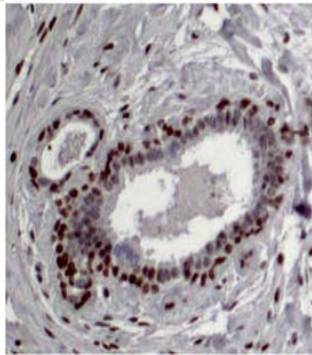
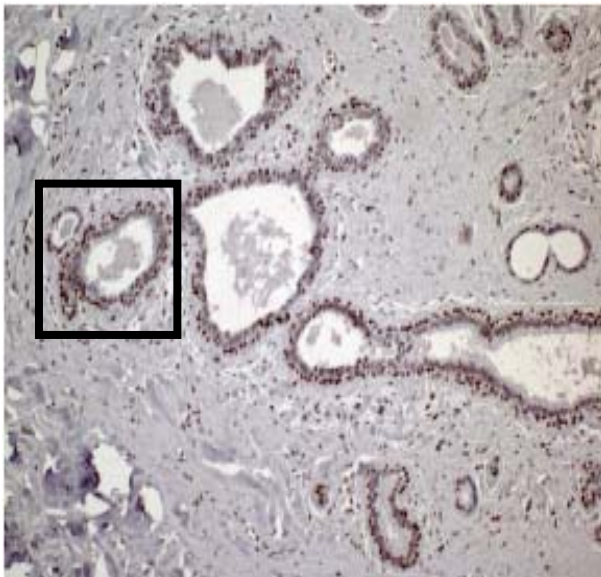
-GCs



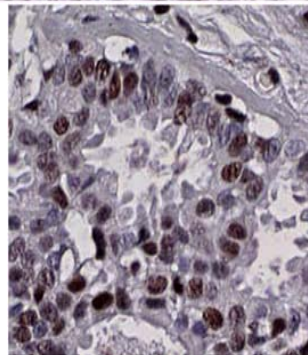
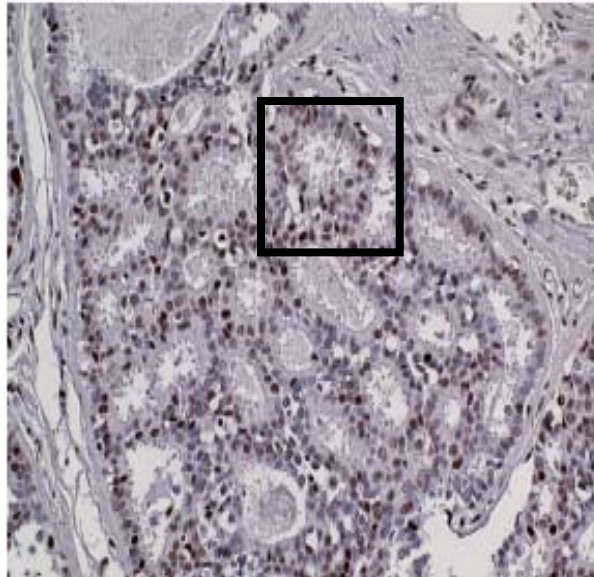
+GCs

Primary human breast epithelium and cancers express glucocorticoid receptors

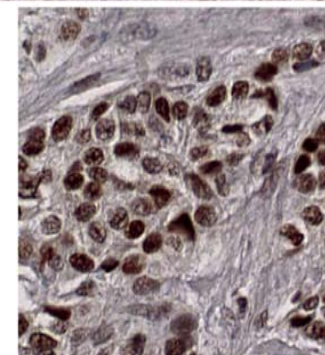
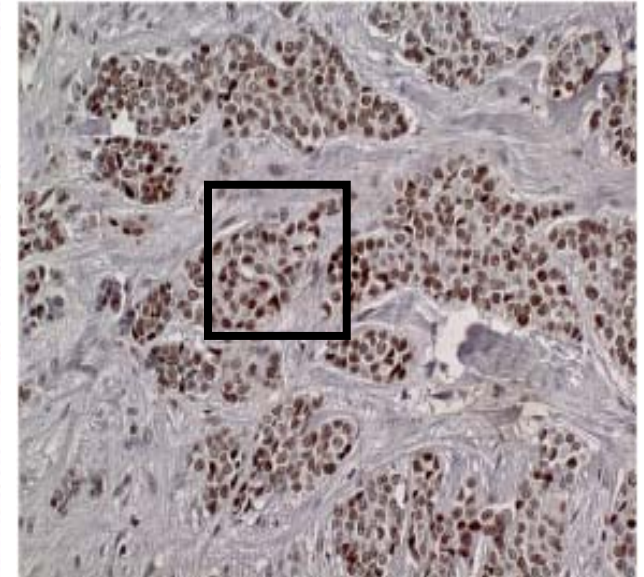
Normal



DCIS

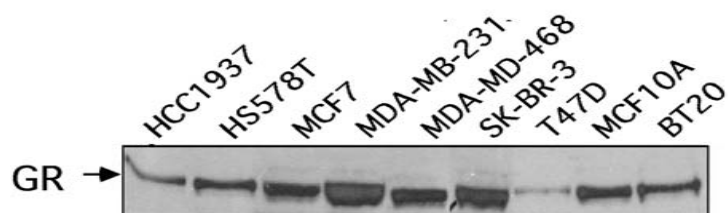


Invasive



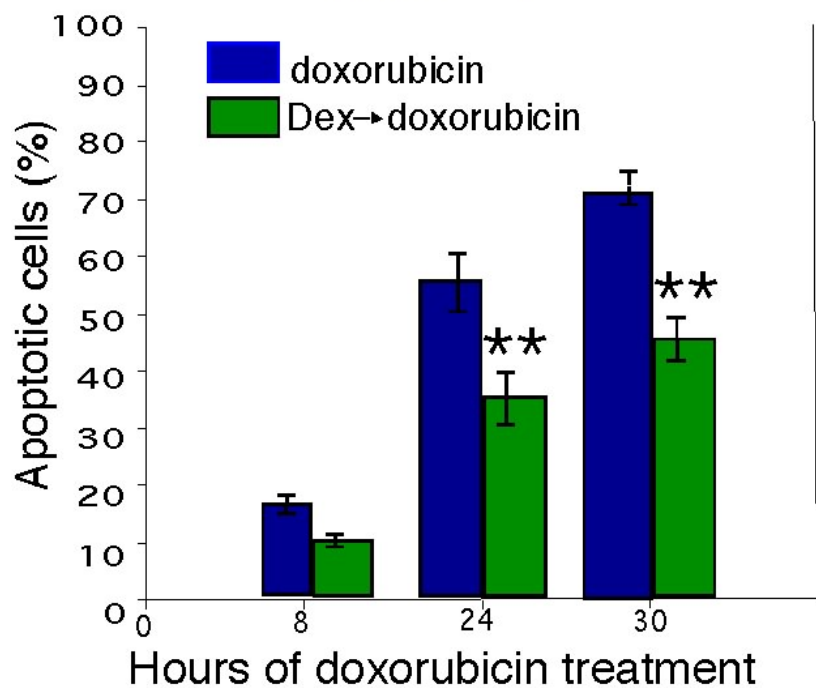
Williams, Delgado and Conzen, In prep.

GCs inhibit chemotherapy-induced apoptosis

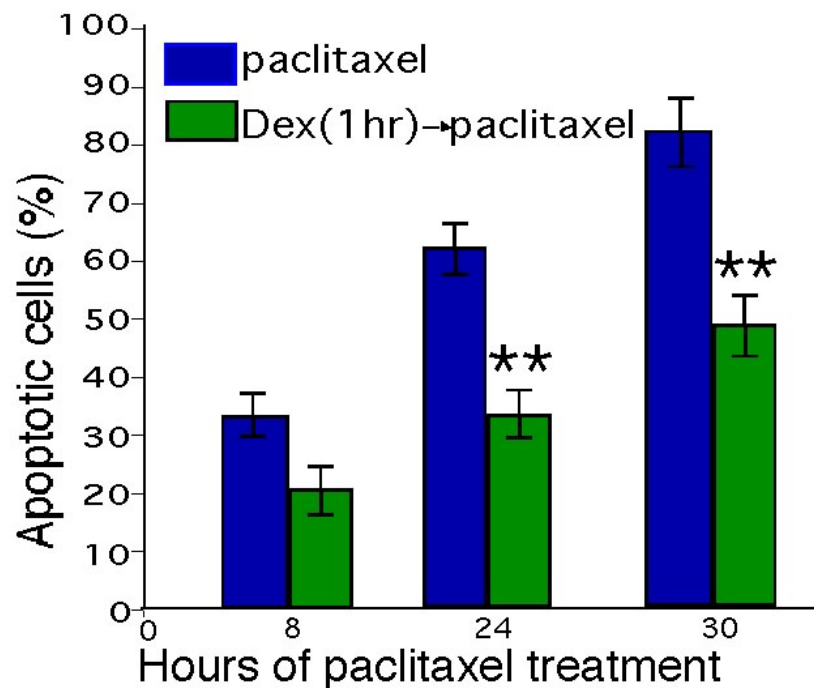


Western analysis

MCF-7



MDA-MB-231

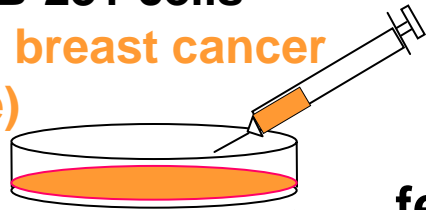


Mikosz et al., *JBC*, 2002

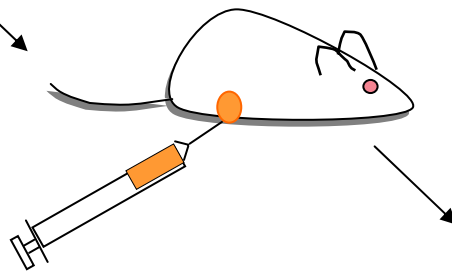
Wu et al., *Cancer Research* 2004

Does GR activation inhibit tumor response to chemotherapy *in vivo*???

MDA-MB-231 cells
(human breast cancer
cell line)

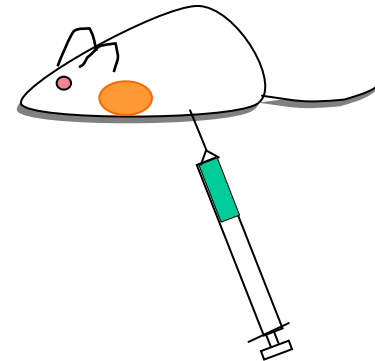


5-6 week old
female SCID mouse

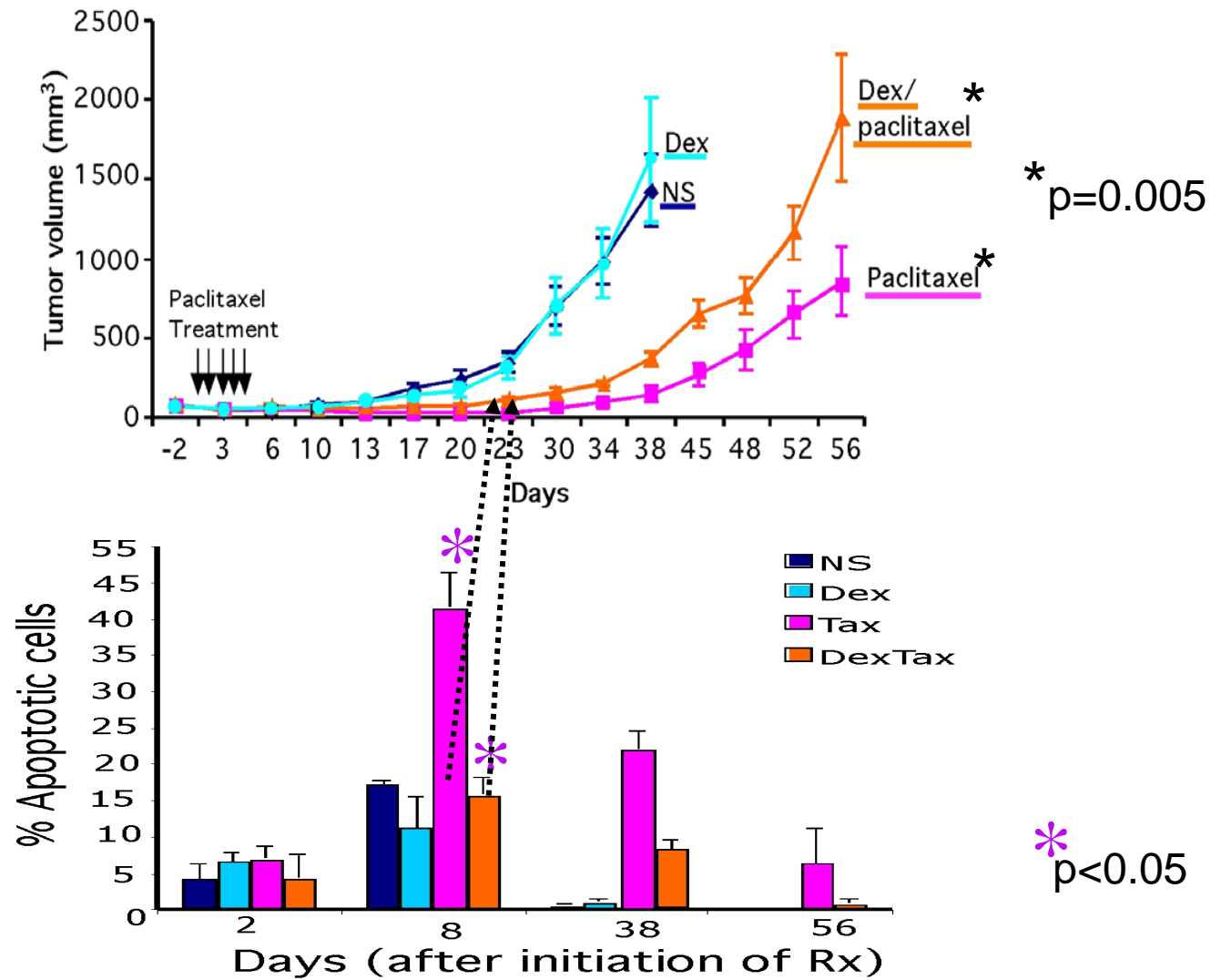


MDA-MB-231 injected
into mammary fat pad

Paclitaxel +/-Dex Days 1-5

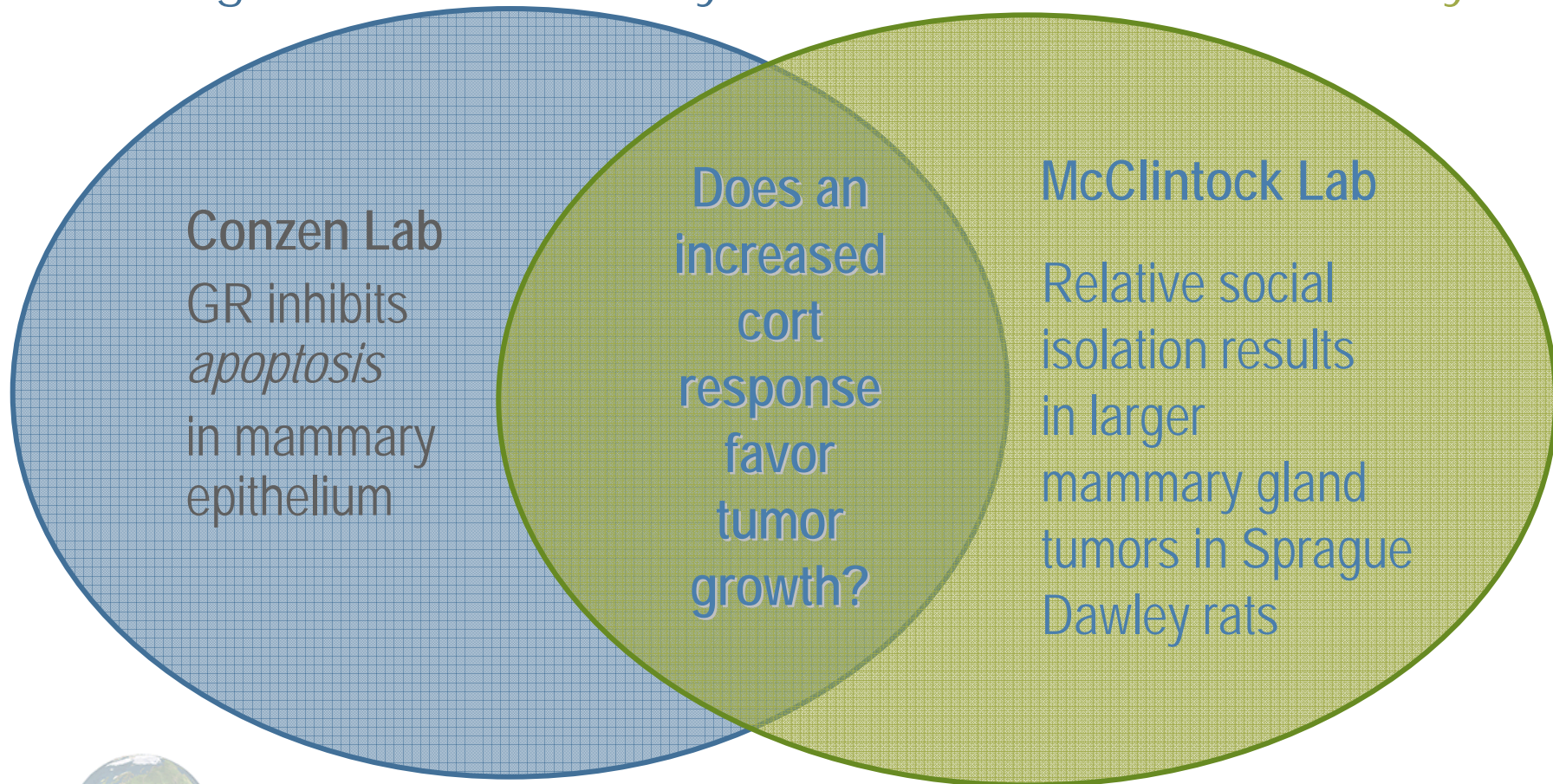


MB-MDA-231 xenografts: Glucocorticoids decrease paclitaxel-induced apoptosis



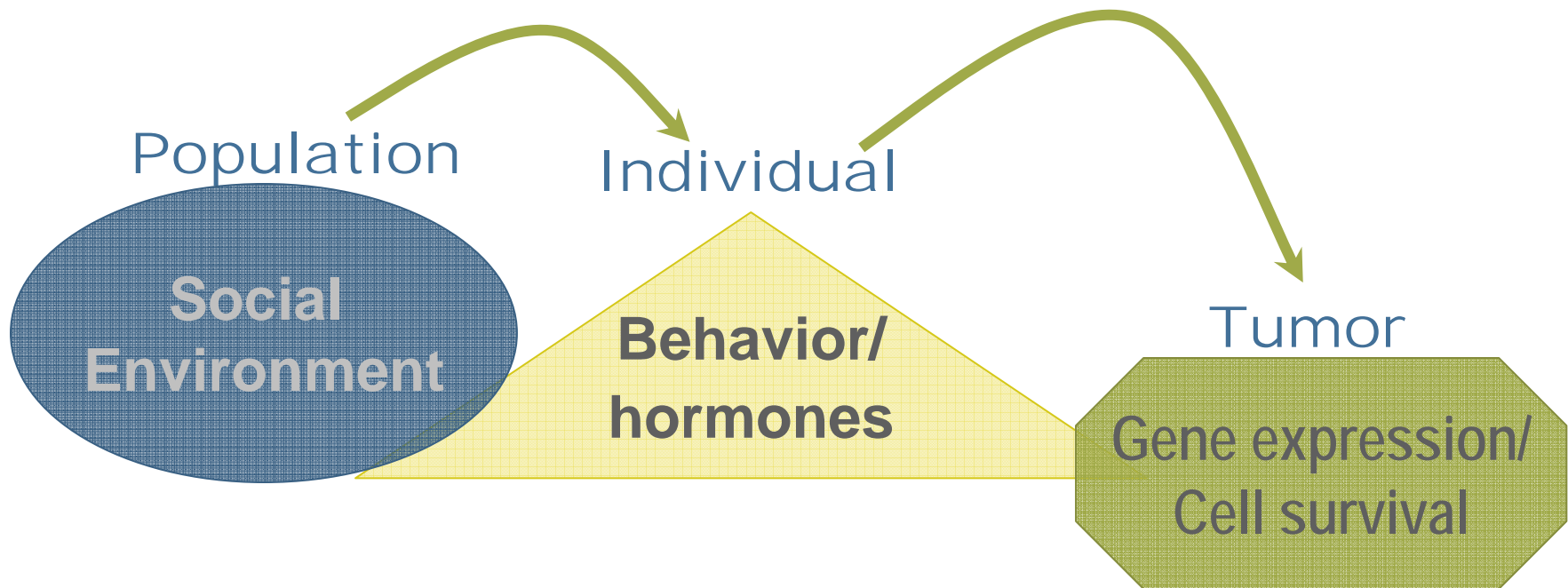
What is the basis of our transdisciplinary work with behavioral/social scientists?

The glucocorticoid story — The social isolation story



Can social environment affect tumor growth?

← Cross-disciplinary research →



What model can be used to test this framework?

C3(1) SV40 Tag transgenic mice*

- Well-defined genetic predisposition **for mammary gland cancer**
- **C3(1)** promoter **targets Tag to MG** but is not activated by the GR
- Blocking apoptosis increases the growth of **Tag MG tumors (e.g., Tag x *BAX*^{-/-})**
- However, **behavioral studies** in SV40 Tag mice have not been performed.

*

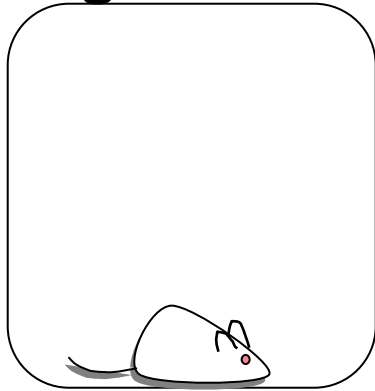


MMHCC
the Mouse Models
of Human Cancers Consortium



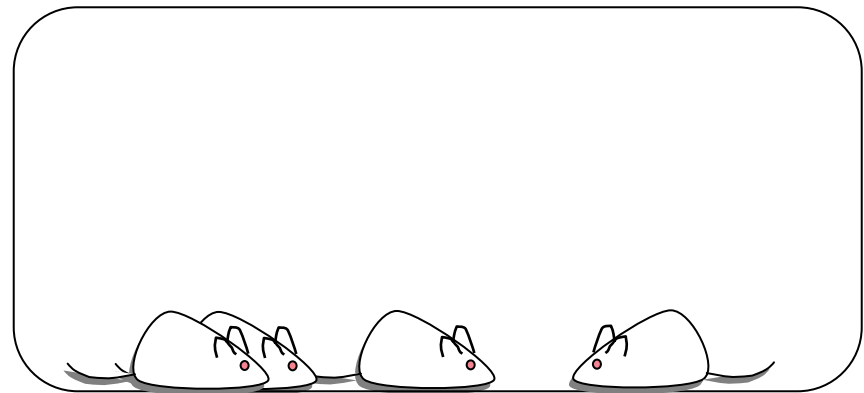
A Model of Social Isolation – SV40 Tag Mice

Single-housed



versus

Group-housed

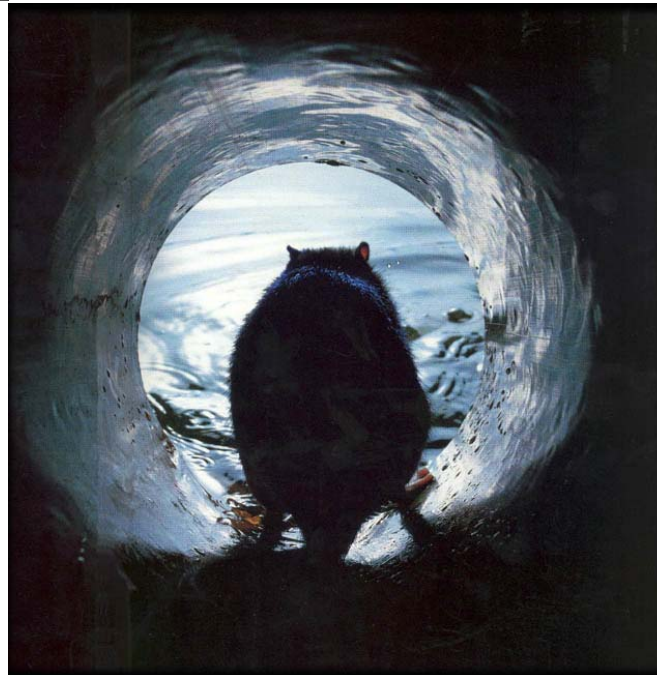
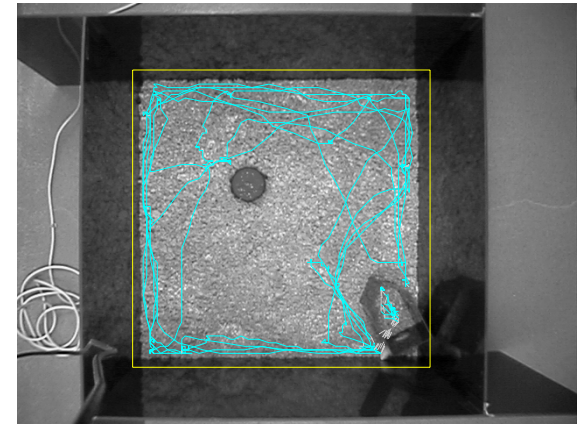
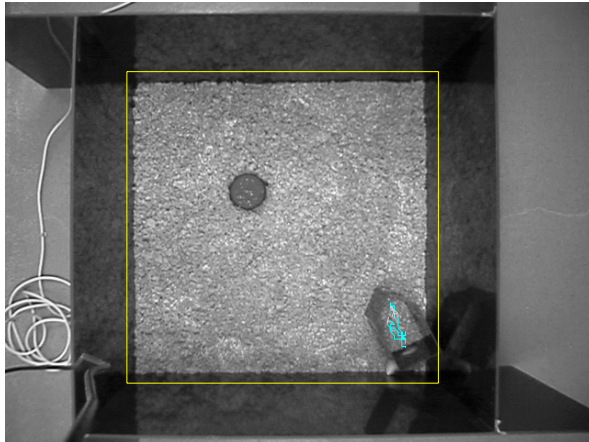


Hypothesis:

Chronic social isolation will result in

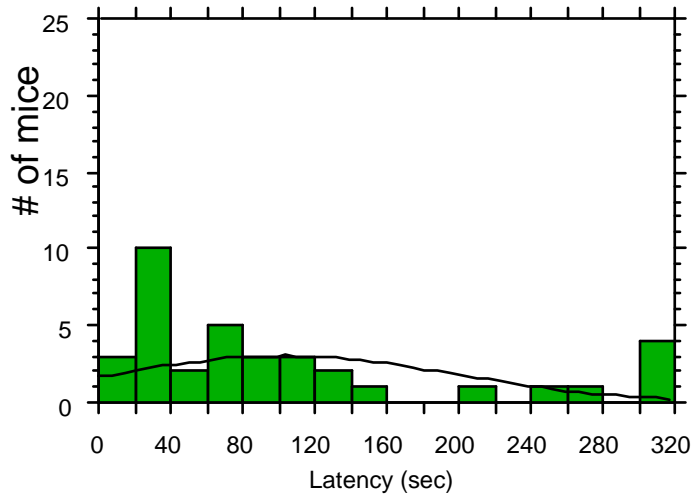
- an acquired vigilant behavioral phenotype
- increased corticosterone response to acute stressors
- increased mammary tumor growth (? inhibit apoptosis)

Behavior: "Vigilance" in a potentially threatening environment can be measured



Behavior: Effect of social isolation on vigilance in SV40 Tag mice

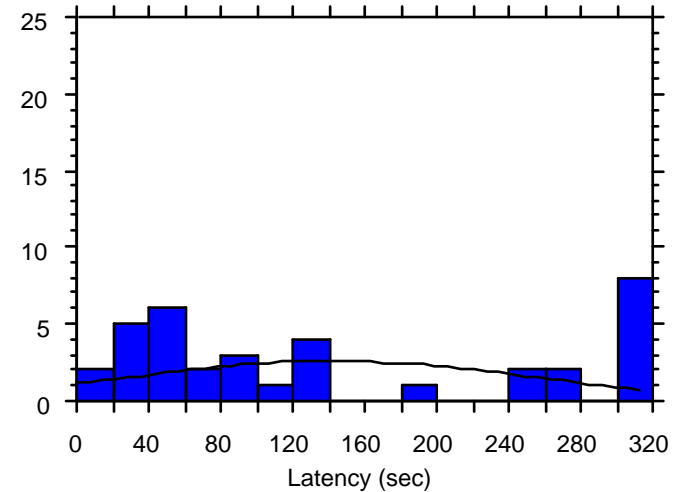
Grouped (n=36)



~3.5 weeks old
*Prior to placement
in isolated or group-
housed conditions*

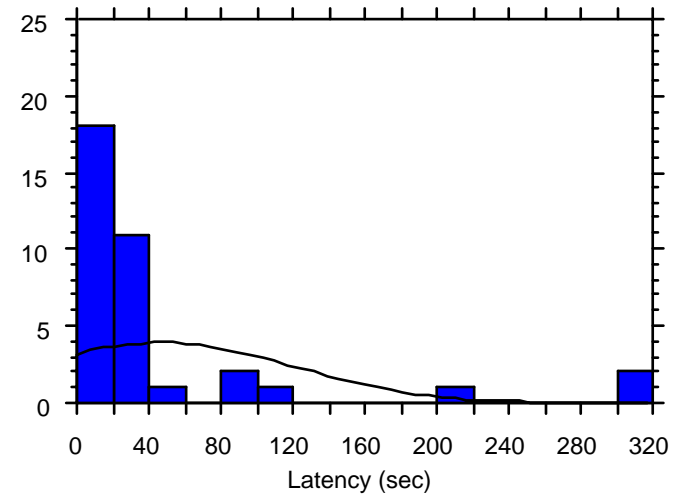
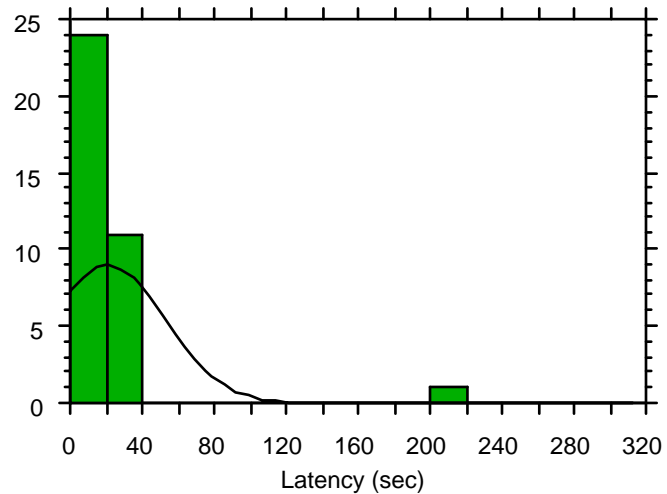
($p = 0.20$)

Isolated (n=36)



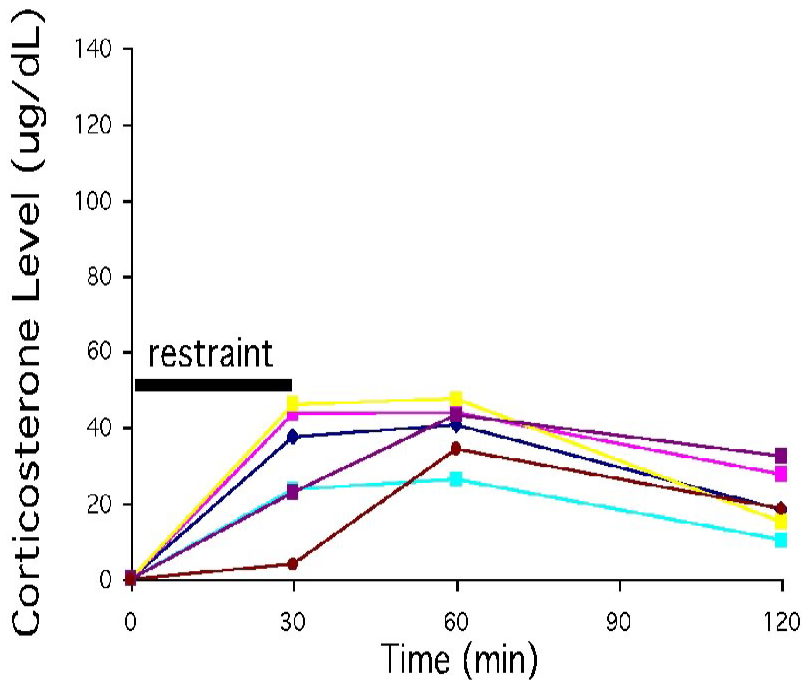
~ 13 weeks old
10 weeks of
differential
housing

($p = 0.018$)

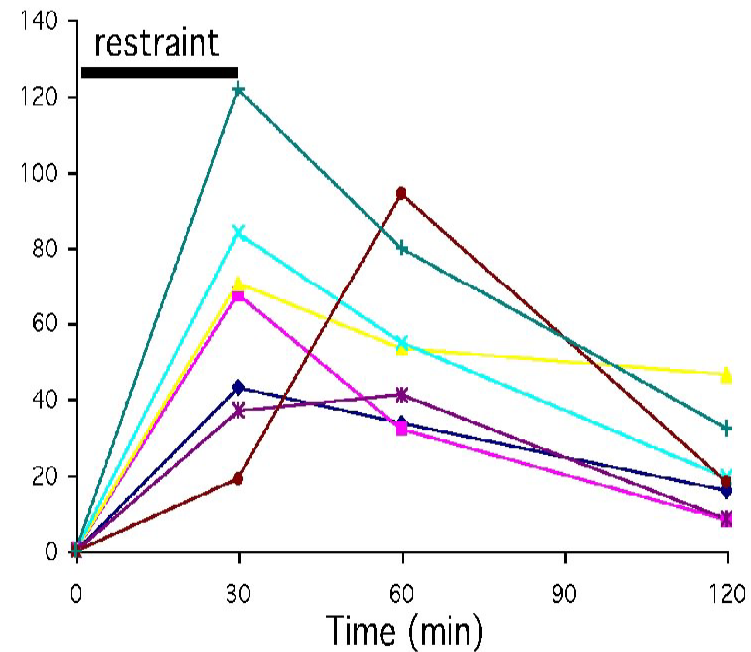


Endocrine response: Effect of social isolation on corticosterone levels following a mild stressor

Grouped



Isolated



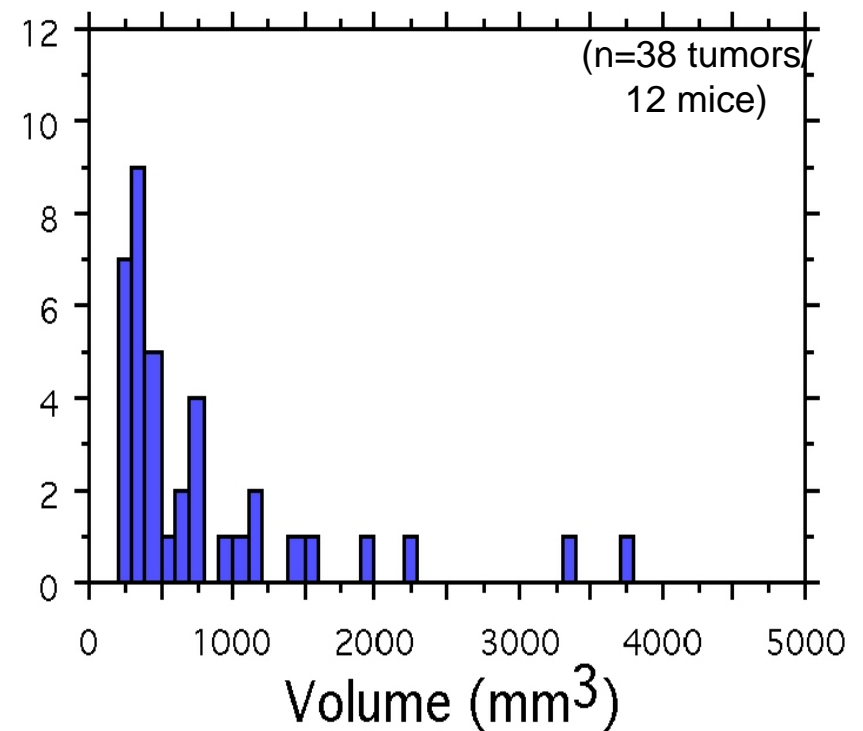
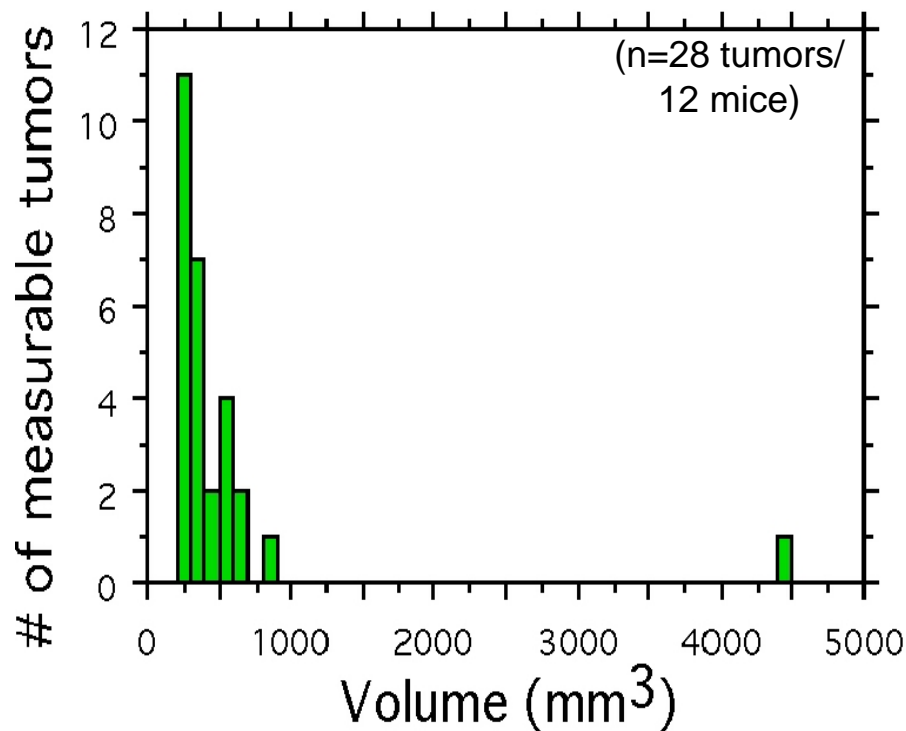
Slope of the rise: $p=.022$
Absolute increase: $p=.032$

Tumor growth: Effect of social isolation on mammary tumor size

(22 weeks)

Grouped (n=15)

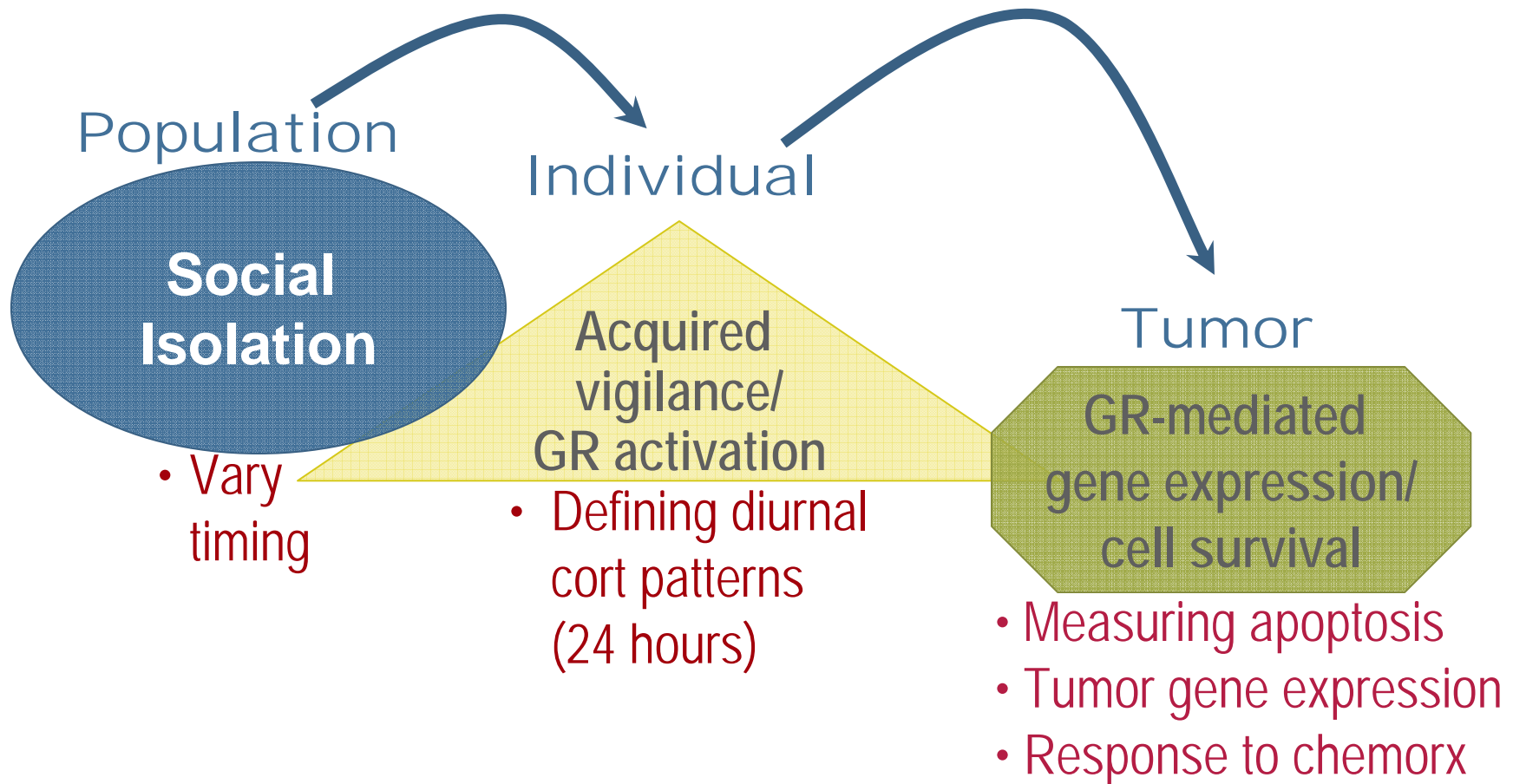
Isolated (n=15)



mixed effects ANOVA $p = .024$

How does social environment affect tumor growth?

Future Plans



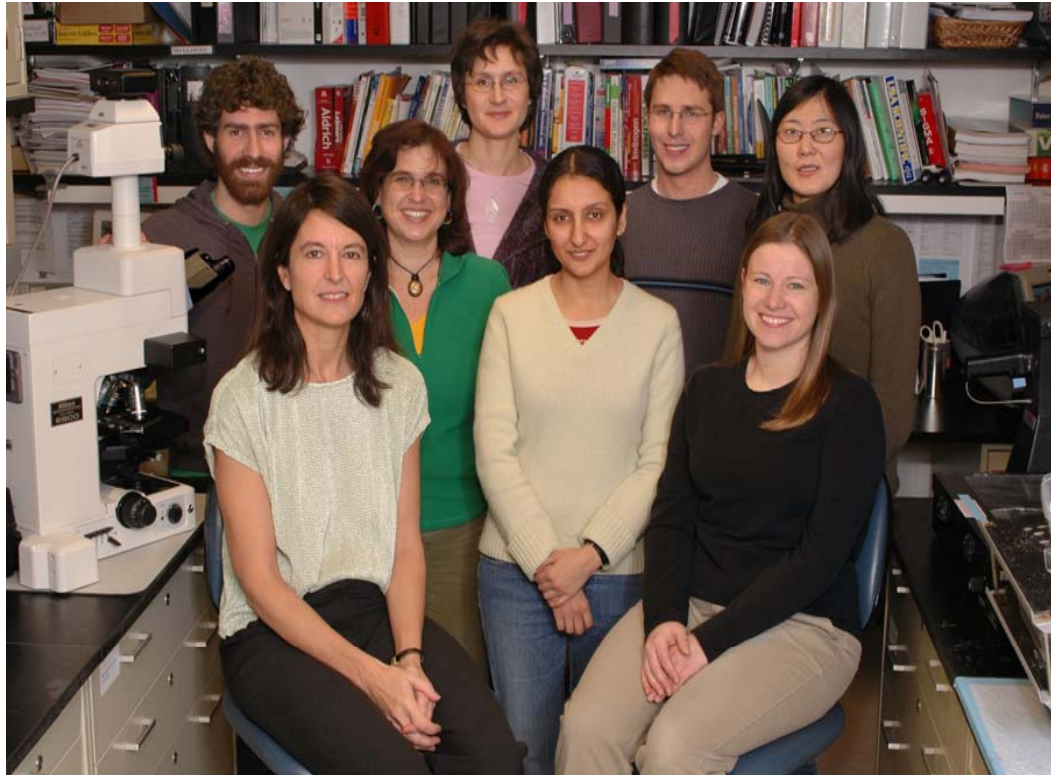
Translational Implications

Observations

- Understanding of GR mechanisms in progression and resistance to therapy
- Blocking GR targets can increase tumor cell sensitivity to chemotherapy/ radiotherapy *in vitro*
- Implication of possible adverse effect of glucocorticoid administration on chemorx responsiveness
- Cortisol responses to stress differ depending upon social environment and support systems

Translational Implications

- ➔ Examine GR in breast cancer subtypes to assess GR as a predictive or prognostic marker
- ➔ Test selective inhibitors of GR and of its downstream effectors in preclinical models and Phase 0/1 clinical trials
- ➔ Prospective clinical trial with and without glucocorticoid premedication
- ➔ Collaborate with social scientists to examine cortisol and GR expression in studies on social isolation and cancer



Acknowledgments:

R01 CA89208-06 "Glucocorticoid-Mediated Signaling in Breast Cancer"
P50 ES012382-04 Center for Interdisciplinary Health Disparities Research -
Project 4 "Social Isolation and Mammary Cancer"
P30 CA01459-32 The University of Chicago Cancer Center Support Grant