

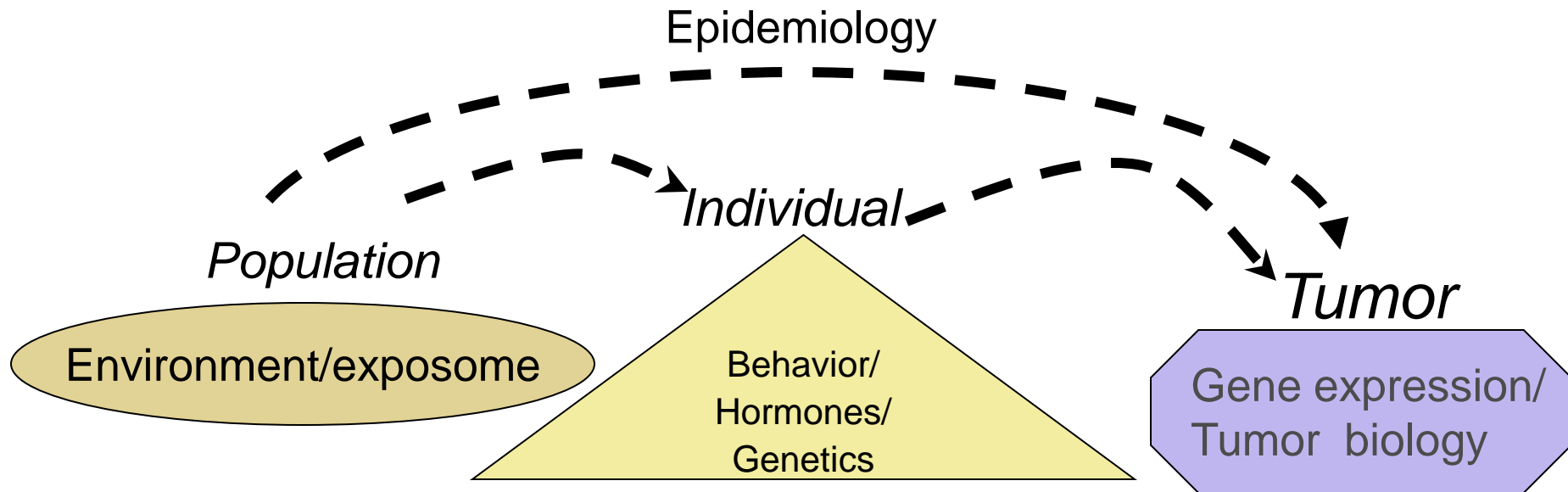


Toward Precision Cancer Care: Informed by Biobehavioral Contributions to the Exposome

Closing Discussion
APS Special Conference
October 26th, 2012

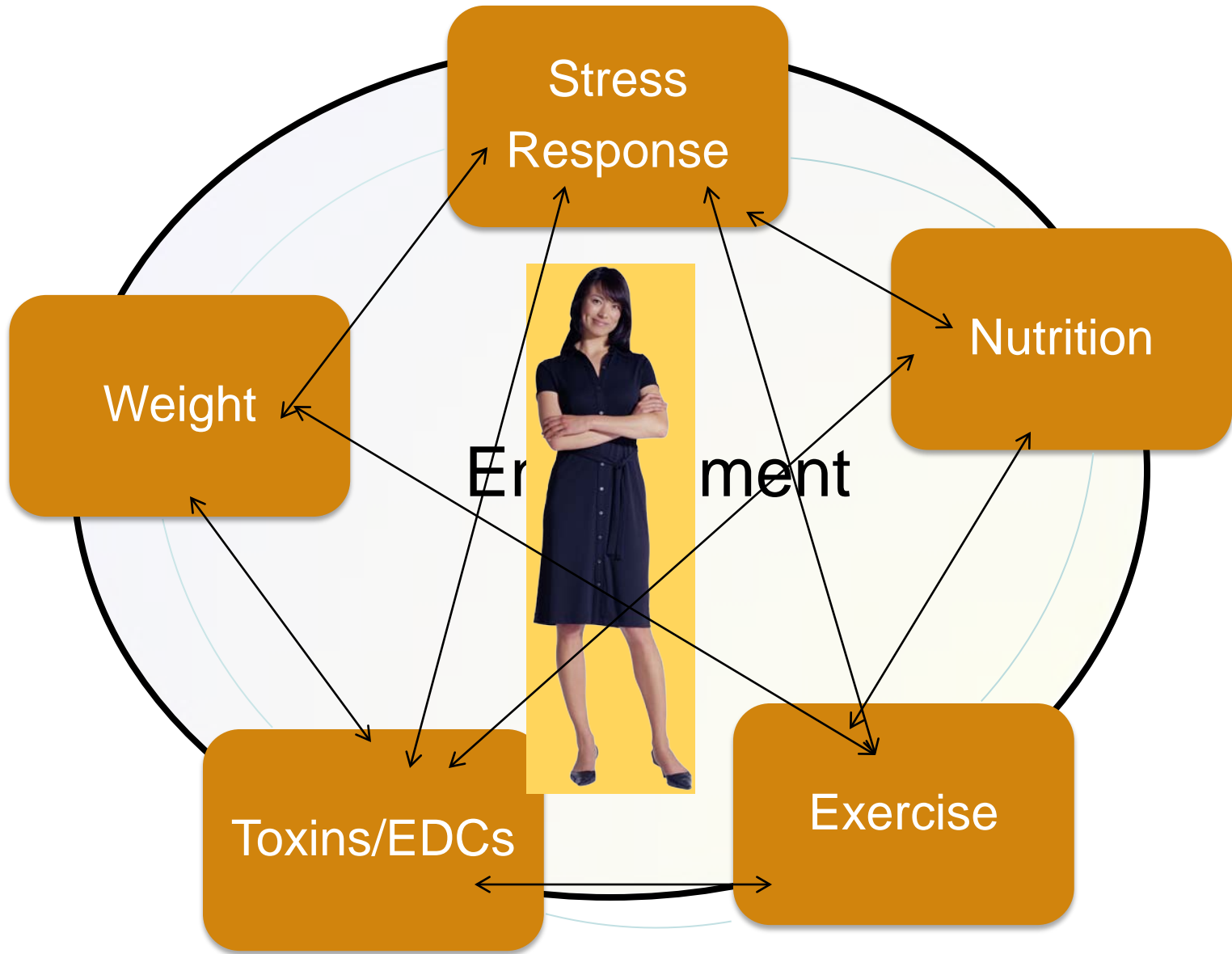
Suzanne D. Conzen, MD
Department of Medicine-Medical Oncology
Ben May Department of Cancer Biology
The Institute of Mind and Biology
The University of Chicago

Question: By what biological mechanisms do environmental exposures alter downstream tumor biology?



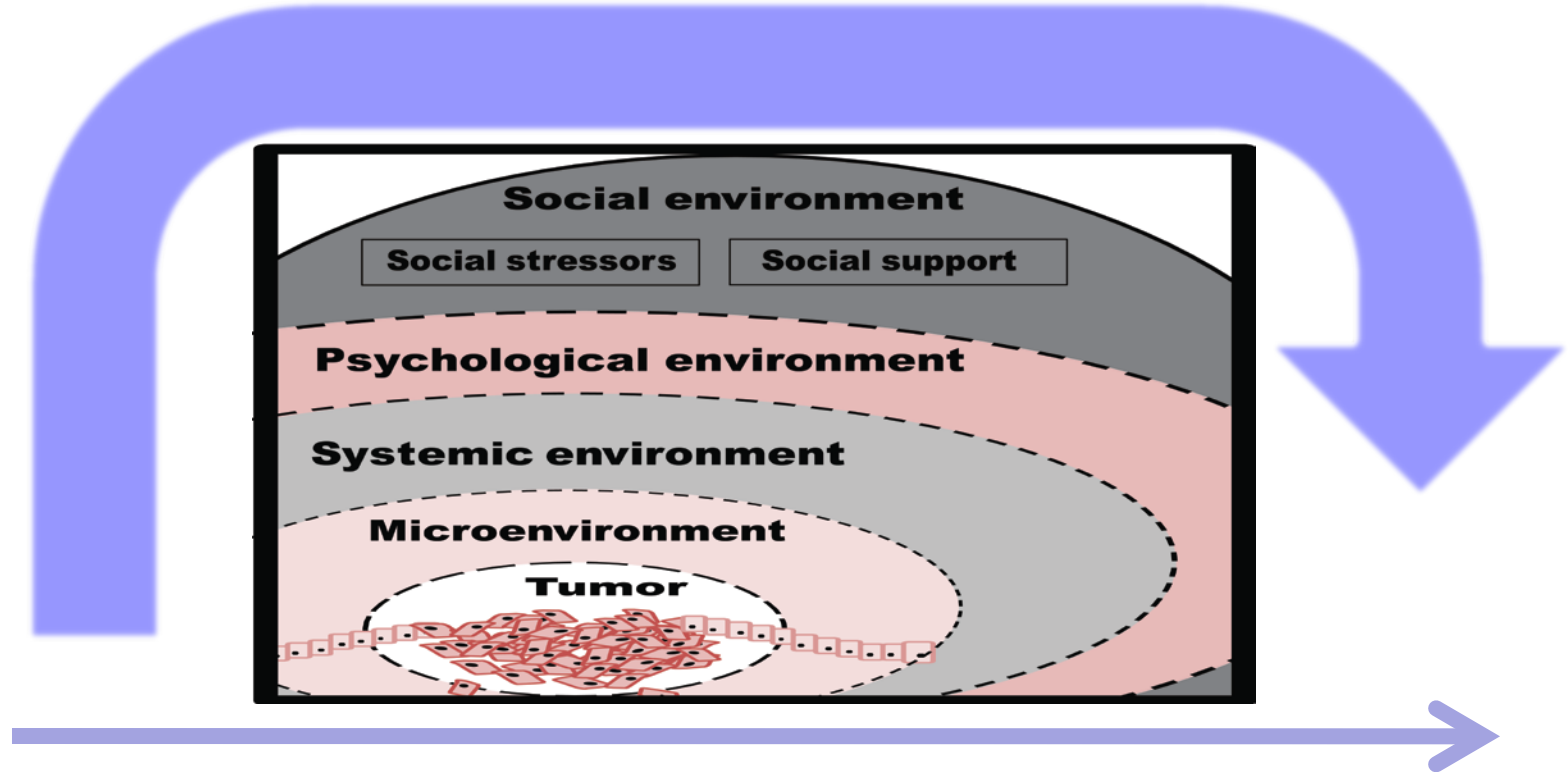
Understanding **molecular mechanisms of tumor biology** are crucial for effectively designing and evaluating interventions.

The environment interacts with itself and the individual



Precision Care of the Cancer Patient

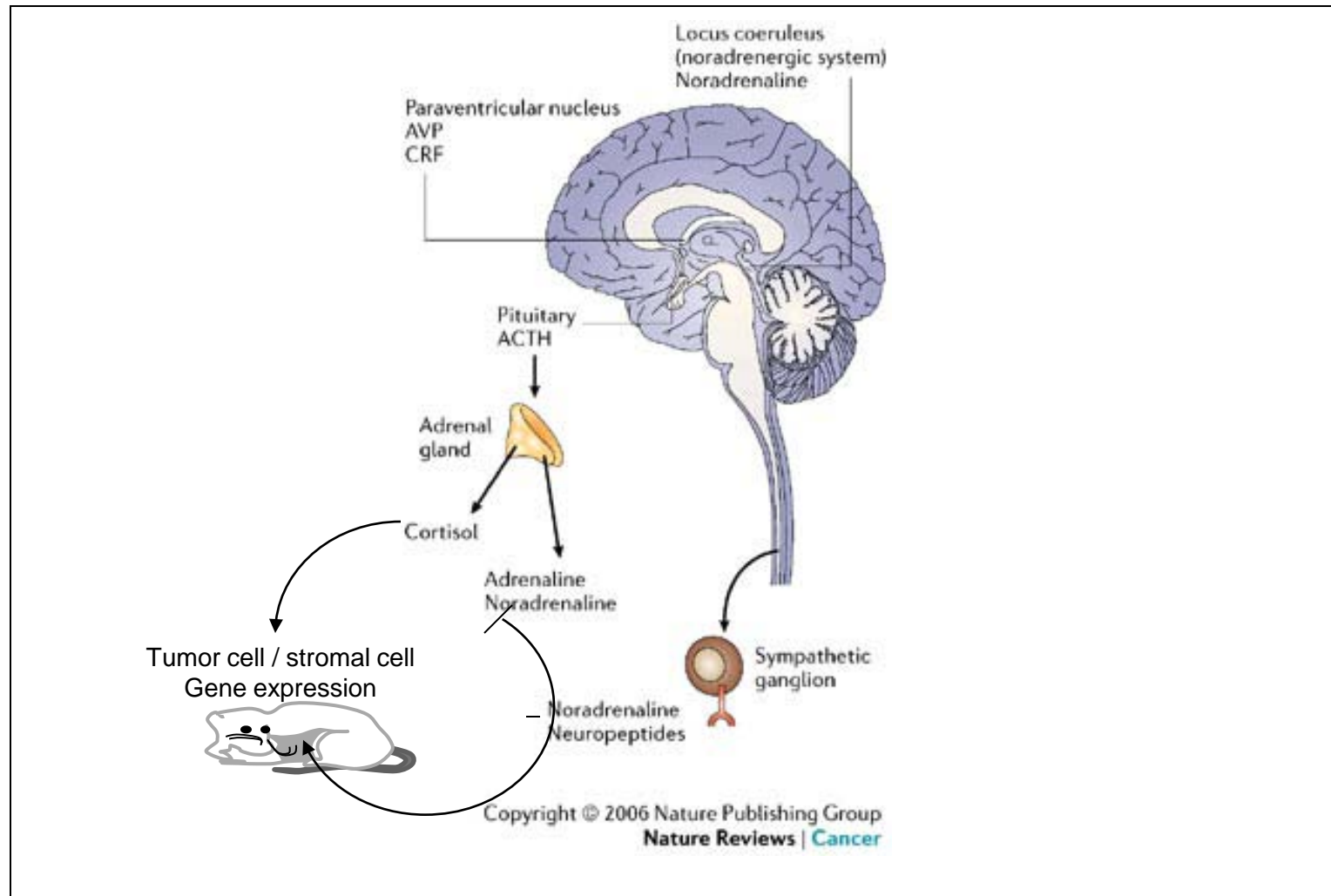
Spatial components of the cancer patient-
environment, individual context, and subtype of tumor biology



Temporal components-

- 1) Lifespan of the individual and timing of the exposure
- 2) Tumor progression/response (tumor evolution)

Environmental stressors and physiological responses to stressors



Adapted from Antoni *et al.* *Nature Reviews Cancer* 6, 240–248
(March 2006)

Mediators of the stress response

- **B-adrenergic system/SNS**

- mediates gene expression changes – immune cells, hypertension and vascular disease

- **Glucocorticoid signaling**

- mediates responses through cognate receptors

- associated with weight gain and metabolic disturbances like insulin resistance

Biobehavioral response mechanisms

Direct endocrine mechanisms:

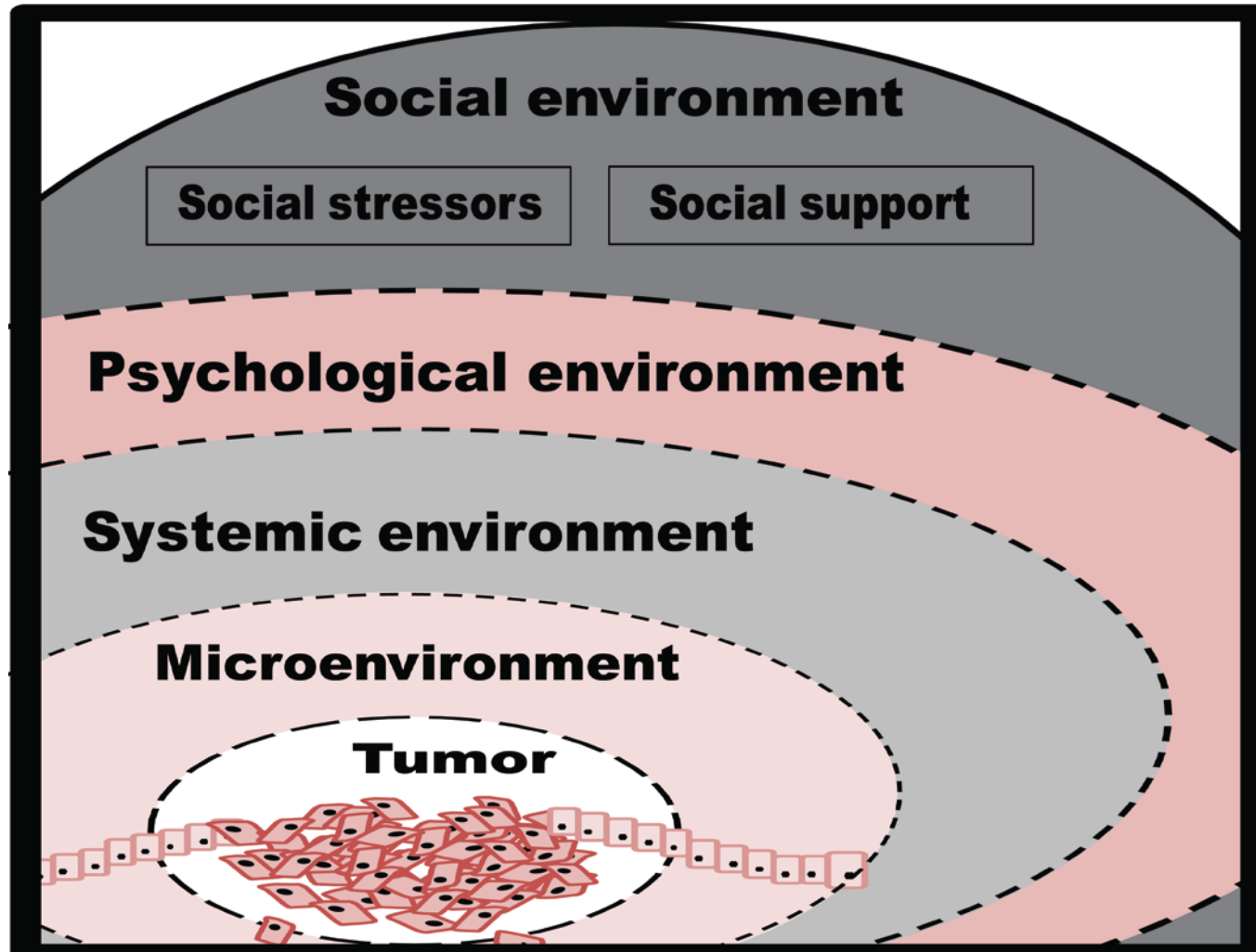
--SNS/adrenergic signals can affect lymphocyte function, macrophage differentiation and tumor cell growth.

--Glucocorticoids can affect lymphocytes, epithelial cell survival and the microenvironment.

Indirect mech. due to the stress response:

Altered eating, sleeping, inanition and other behaviors affecting energy balance.

Chicago Center for Interdisciplinary Health Disparities model for studying social environment and stress response in breast cancer



Mutually Informative, Multi-Level and Multi-Modal Approach

Projects 1 & 4

Projects 2 & 3

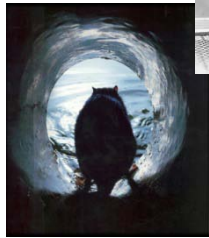
Gehlert

Olopade

McClintock

Conzen

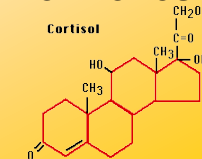
community/
neighborhood



genes



hormones



psychological
functioning

behavior
patterns

social
circum-
stances

(social
isolation,
social
support)

housing

environ-
mental
exposure

(crime,
collective
efficacy,
social
ecology)

Background: Epidemiology of social stress and breast cancer biology

Elevated Biomarkers of Inflammation Are Associated With Reduced Survival Among Breast Cancer Patients

Brandon L. Pierce, Rachel Ballard-Barbash, Leslie Bernstein, Richard N. Baumgartner, Marian L. Neuhaus, Mark H. Wener, Kathy B. Baumgartner, Frank D. Gilliland, Bess E. Sorensen, Anne McTiernan, and Cornelia M. Ulrich

Biomarkers sensitive to social stress were predictive of breast cancer recurrence in a large, multiethnic cohort

Report

Racial and ethnic disparities in breast cancer rates by age: NAACCR Breast Cancer Project

Sue A. Joslyn¹, Mary L. Foote², Kiumarss Nasser³, Steven S. Coughlin⁴, and Holly L. Howe⁵
¹University of Northern Iowa, Cedar Falls, IA; ²Wisconsin Department of Health and Family Services, Madison, WI; ³Public Health Institute, Tri-Counties Regional Cancer Registry, Santa Barbara, CA; ⁴Centers for Disease Control and Prevention, Atlanta, GA; ⁵North American Association of Central Cancer Registries, Springfield, IL, USA

African-American women report more stressful life events, higher perceived stress, and lower social support than Caucasian women

Racial Discrimination and Breast Cancer Incidence in US Black Women

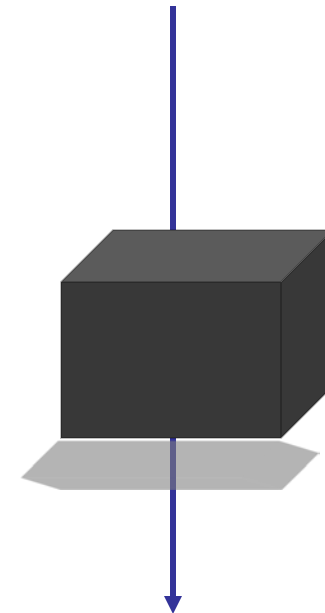
The Black Women's Health Study

Teletia R. Taylor^{1,2}, Carla D. Williams¹, Kephher H. Makambi¹, Charles Mouton³, Jules P. Harrell², Yvette Cozier⁴, Julie R. Palmer⁴, Lynn Rosenberg⁴, and Lucile L. Adams-Campbell¹

A retrospective analysis of the Women's Health Study documented a positive correlation between the experience of racial bias and risk for breast cancer in this population

Model for Health Disparities in Breast Cancer

Social Environment



**Changes in
gene/protein
expression**

Social Circumstances



Psychological States



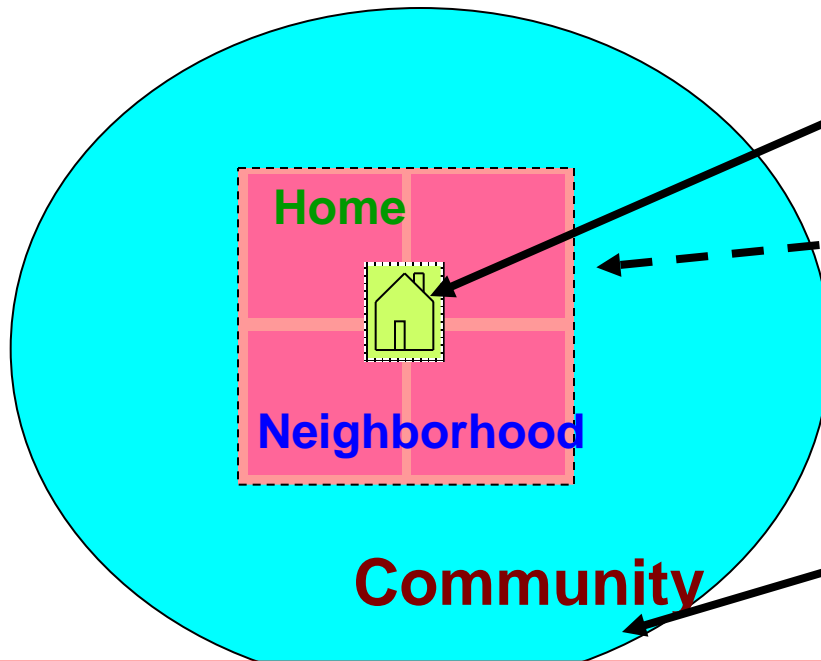
Neuroendocrine changes



Modulation of
established
malignant cell survival
& tumor growth

Multi-level sources of psychosocial, hormonal and built environment data from newly diagnosed women

Gehlert directs two-day visits every 6 months for 1.5 years (10 visits/woman with >18 hours of face-to-face contact).



Home: (interview in home) psychosocial functioning, social network, health behaviors, perceived discrimination, life events, daily (4x) salivary cortisol.

Neighborhood: (four block radius around home; Built Environment Team) opportunities for social interaction (vacant lots, traffic in neighborhood, vacant buildings).

Community: (geocoded data) violent crime, collective efficacy, dilapidation of housing, SES, trust, health indicators.

Conzen/McClintock develop rodent models to study social isolation and breast cancer biology

Olopade collects and analyzes breast tumors from same women

In home interviews: demographics, histories and validated scales

DAY ONE

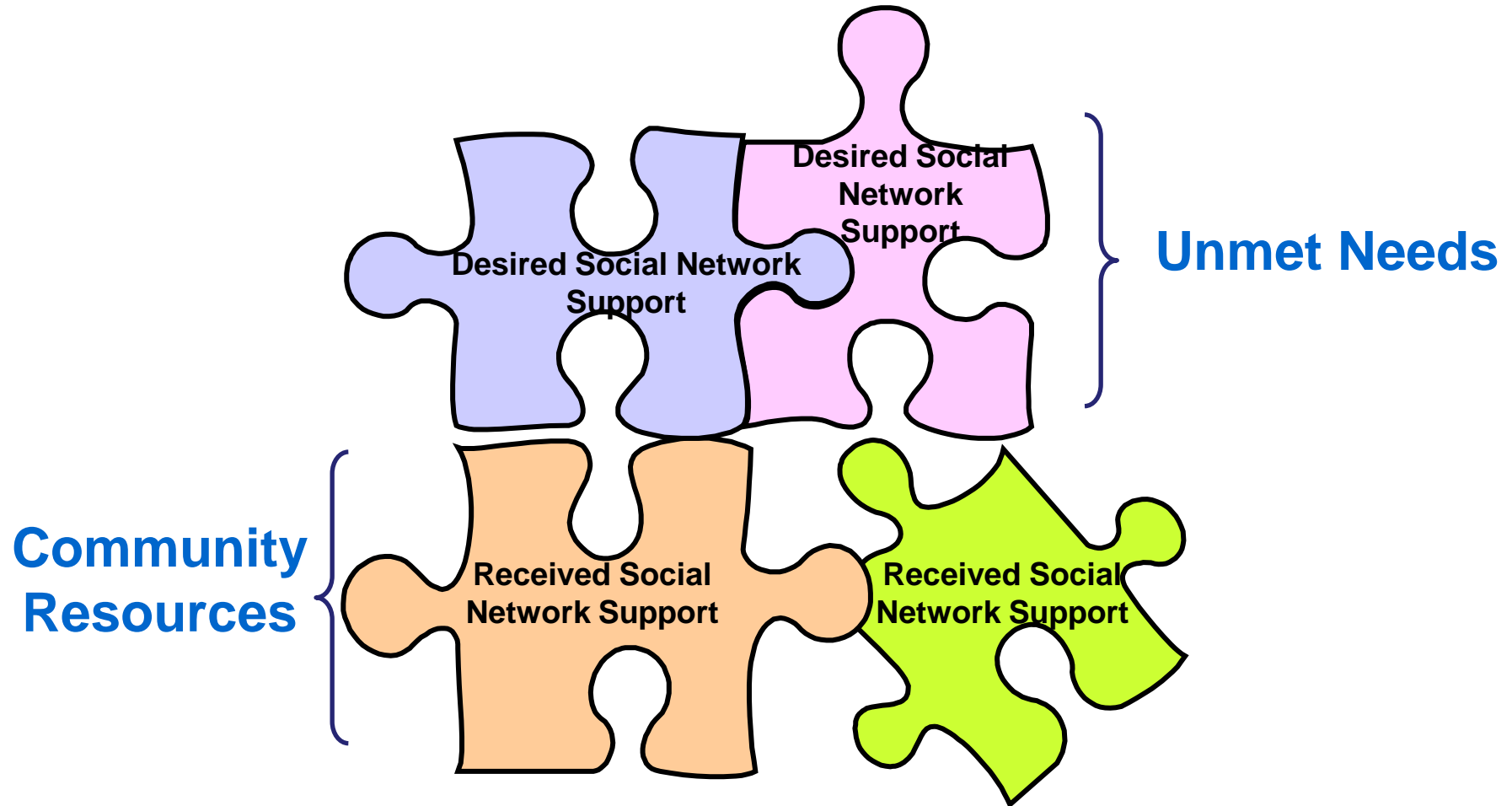
Demographics
Typical Day Record
Social Relationships and Health - Health Behavior Questionnaire
Pittsburgh Sleep Quality Index (PSQI)
Social Relationships and Health - Exercise Short Form for Health (SF-12v2)
Collective Efficacy Scale (Sampson)
Religion and Spirituality Scale
Coping Style (COPE Y3 – 8-item version)
Perceived Stress Scale (PSS)

CARDIA IV Perceived Discrimination Scale
UCLA Loneliness Scale
Center for Epidemiologic Studies-Depression Scale (CES-D)
Social Relationships and Health (LEQ2)
The Health and Retirement Study (HRS)
Module 6: Loneliness, Stress, and Social Support/Social Burden (LSSSB)
Events in Puberty Questionnaire
Medical History – Past 5 years
Income/Financial/Insured Status Information

DAY TWO

The Women' s Quality of Life Scale
Social Network Scale (Youm)
Home Safety Questionnaire
Neighbors Survey
Safety of Neighborhood Questionnaire
Need to Belong Scale

Conclusion: Mismatch of support needed & support received



African American women with newly diagnosed breast cancer report antecedent loneliness

▪ Loneliness

*CIHDR Sample 5.1

(Cook County 4.2)

Dislocation

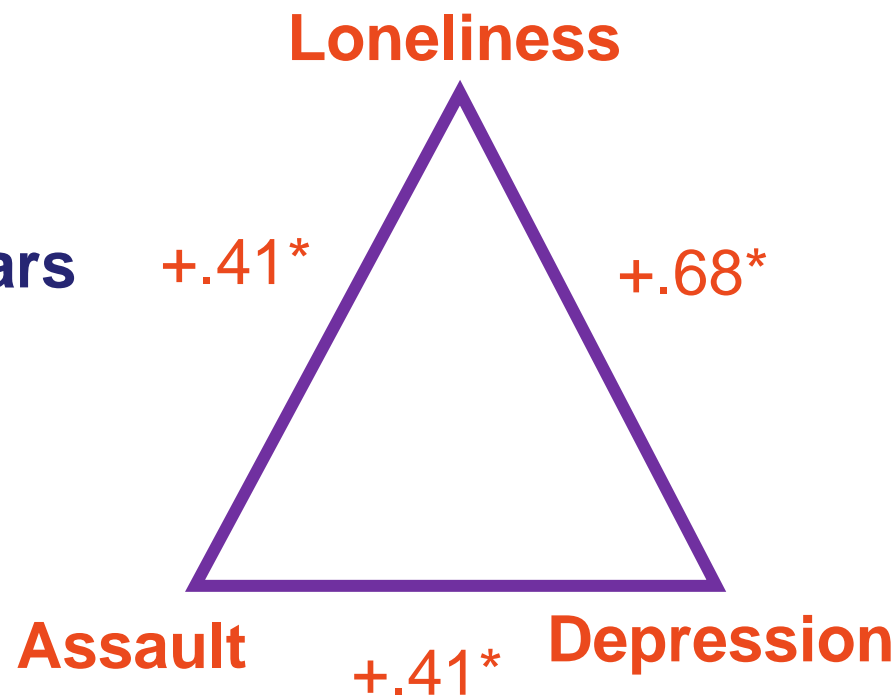
68% moved in past 10 years

▪ Sexual Assault

31% suffered an assault

▪ Depression

32% clinically depressed



*p=0.001

Mutually Informative, Multi-Level and Multi-Modal Approach

Projects 1 & 4

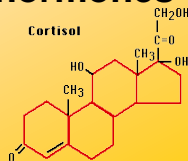


Conzen



McClintock

hormones



genes



behavior patterns

psychological functioning

social circumstances
(social isolation, social support)

housing

environmental exposure

community/neighborhood
(crime, collective efficacy, social ecology)

Projects 2 & 3

Gehlert



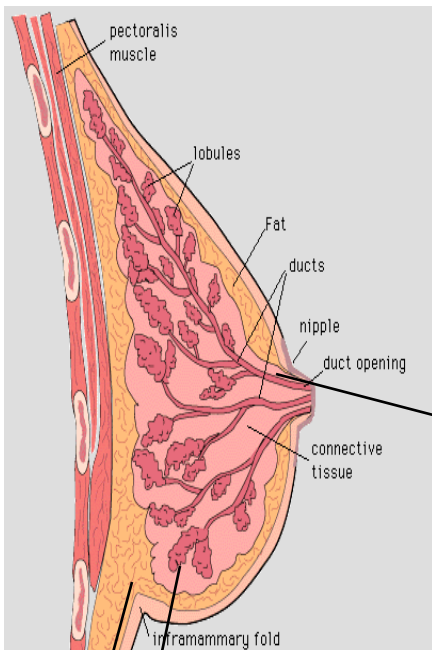
Olopade



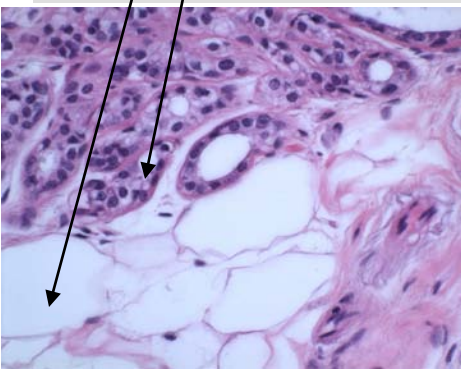
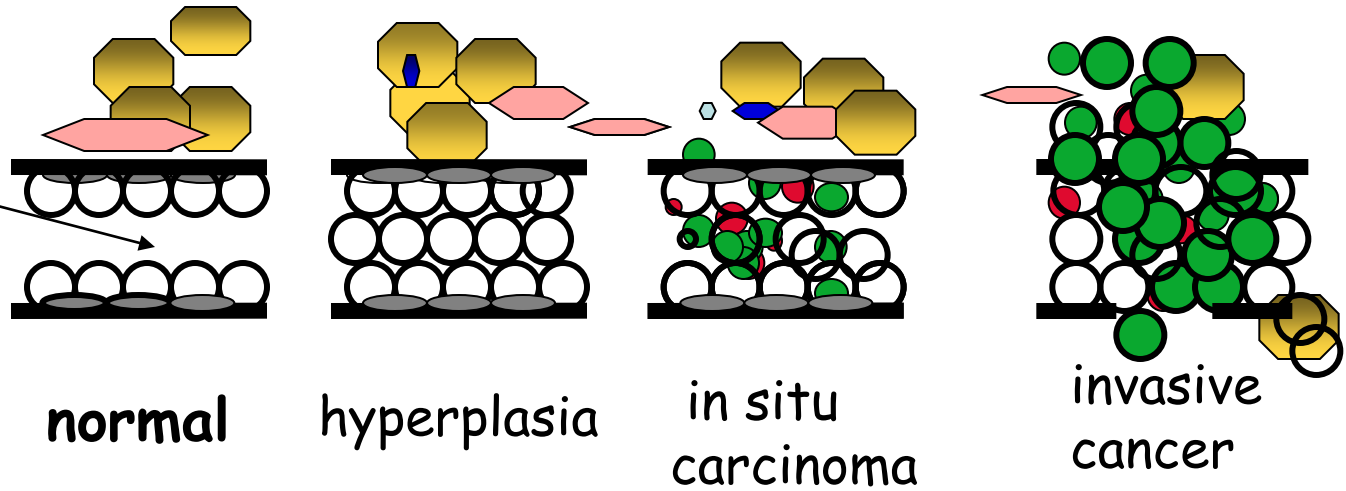
The molecular basis of breast cancer progression

+++ Myc, Cyclin D1, HER2, ?

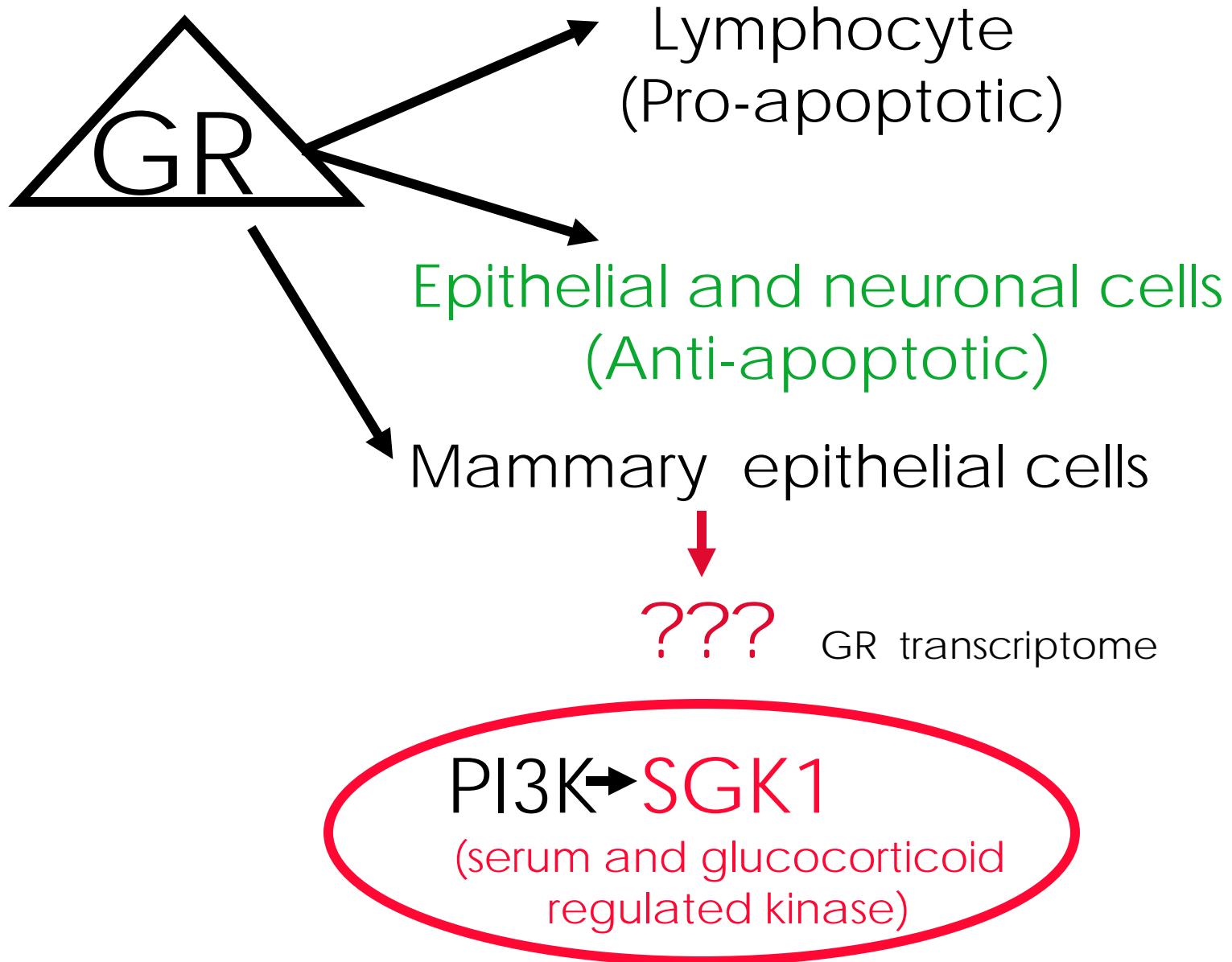
--- BRCA1/2, p53, pRb



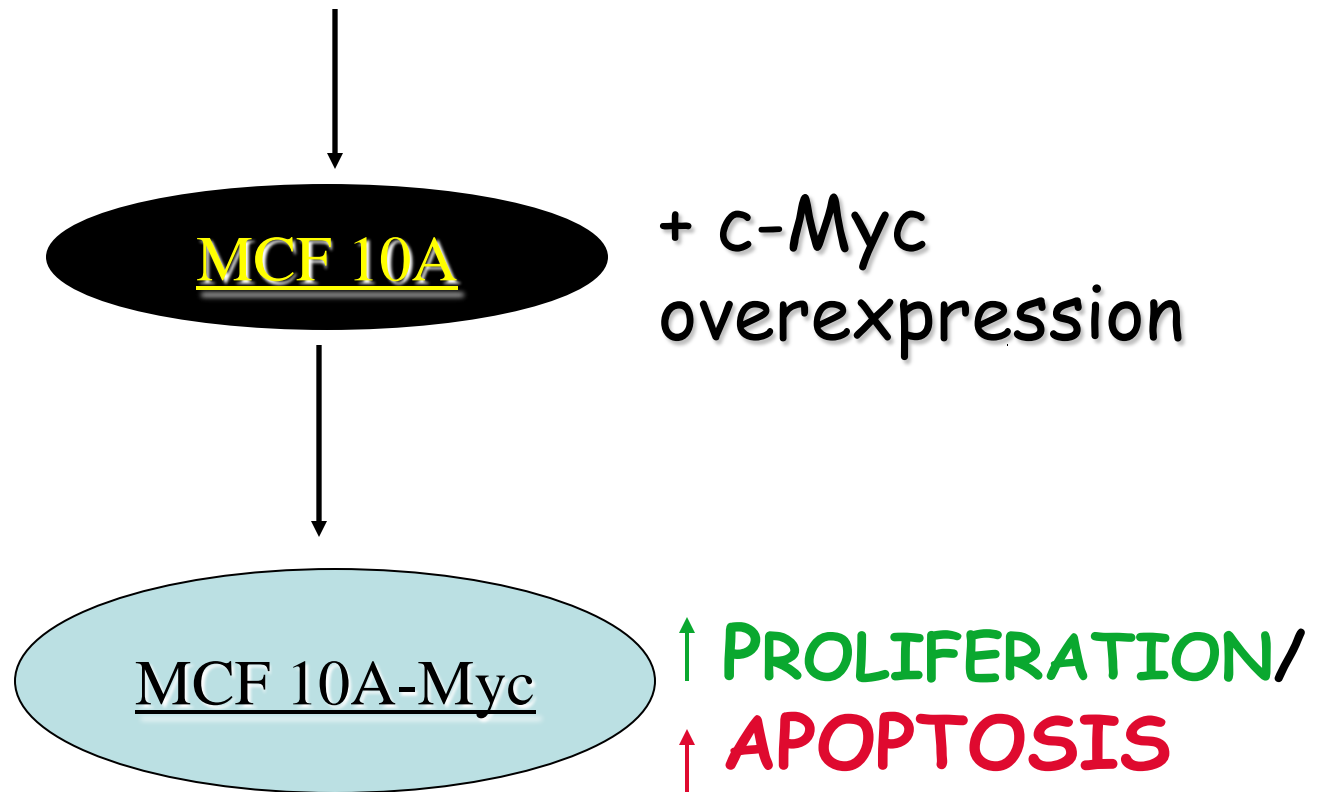
This image was produced by the National Library of Medicine in cooperation with the National Cancer Institute



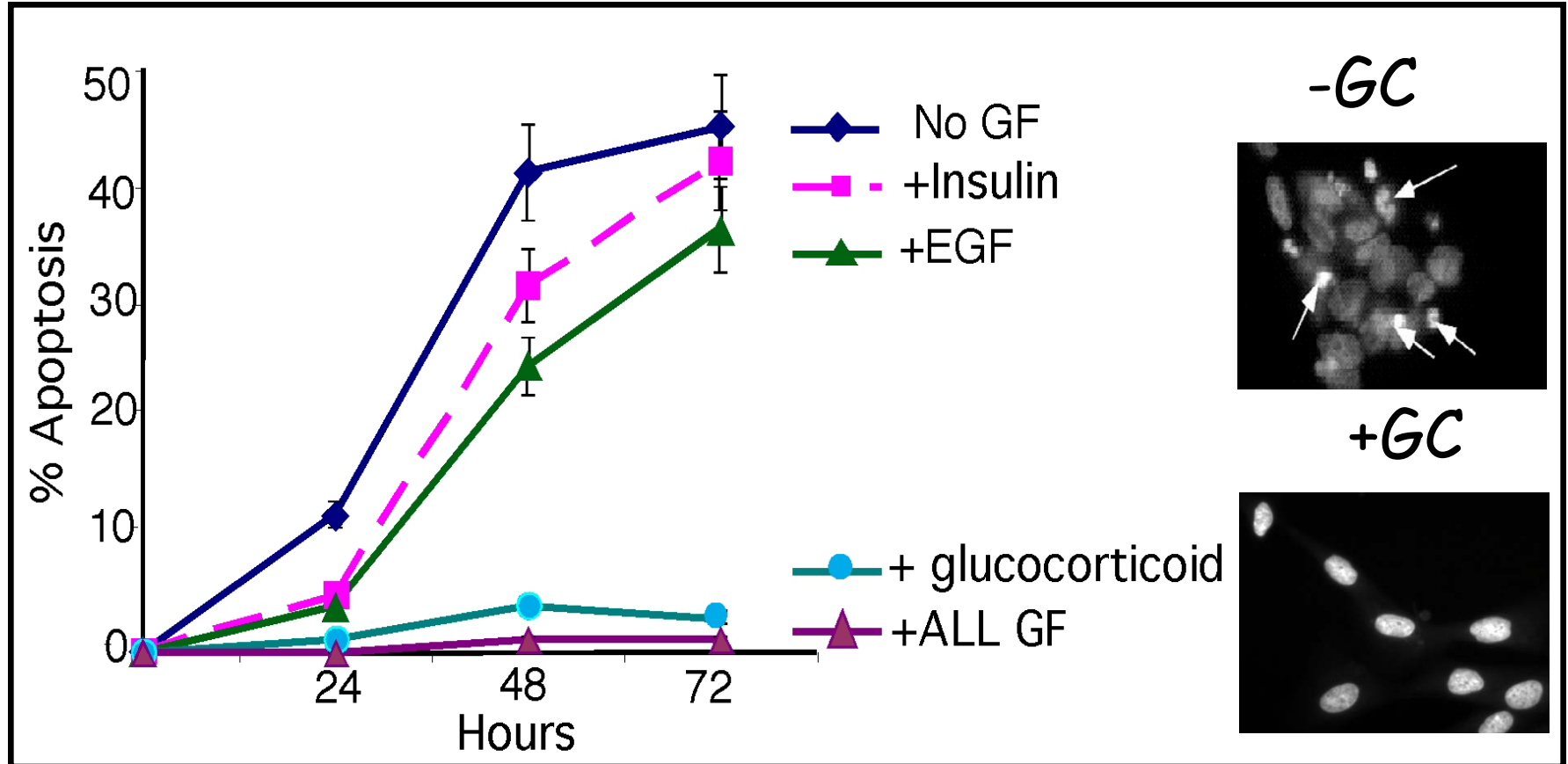
Circa 1999: Most cellular functional studies of the GR were largely limited to lymphocytes and neuronal cells



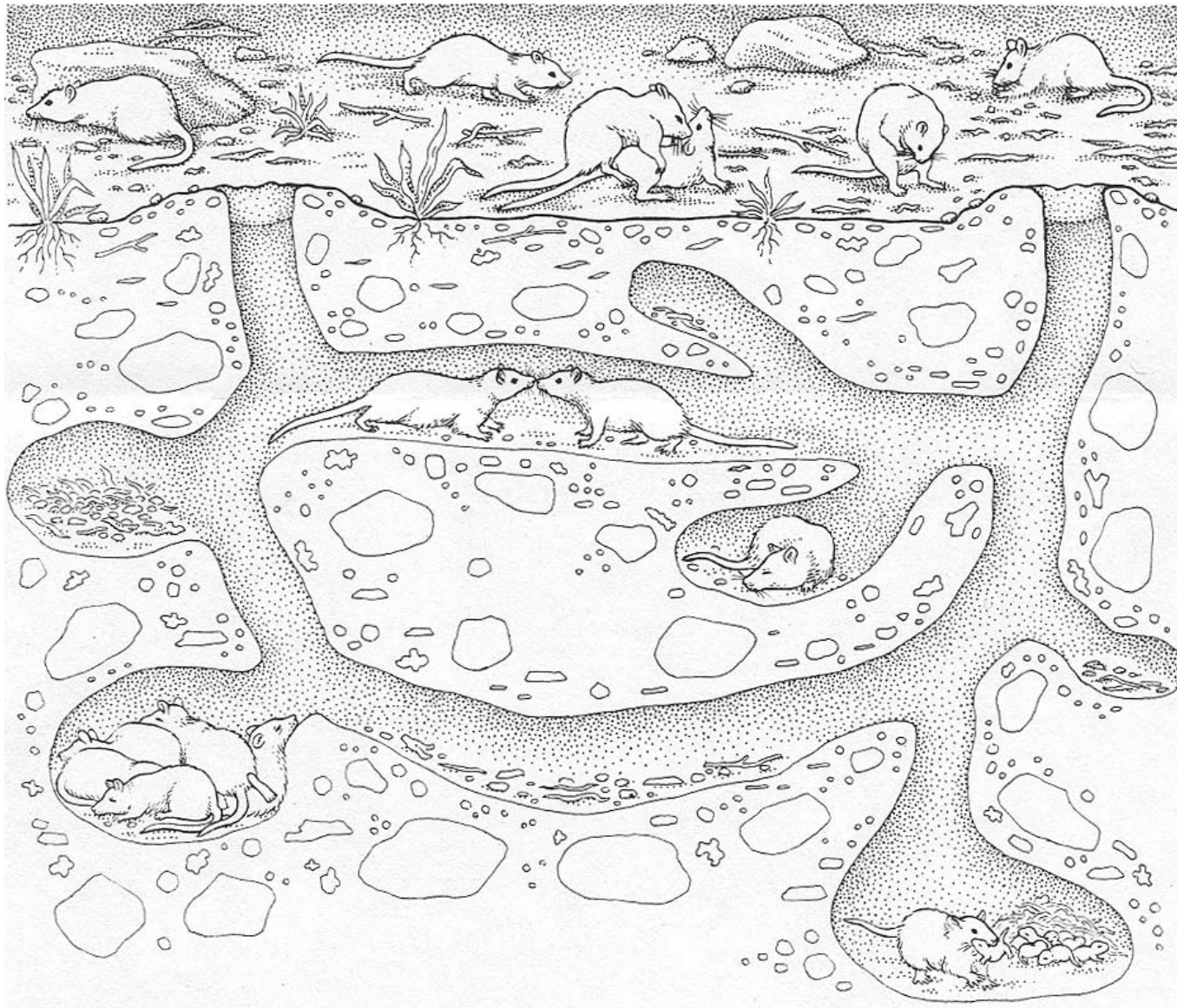
Immortalized MEC cell line (MCF10A)
(ER/PR/Her2 negative, i.e. “Triple Negative”)



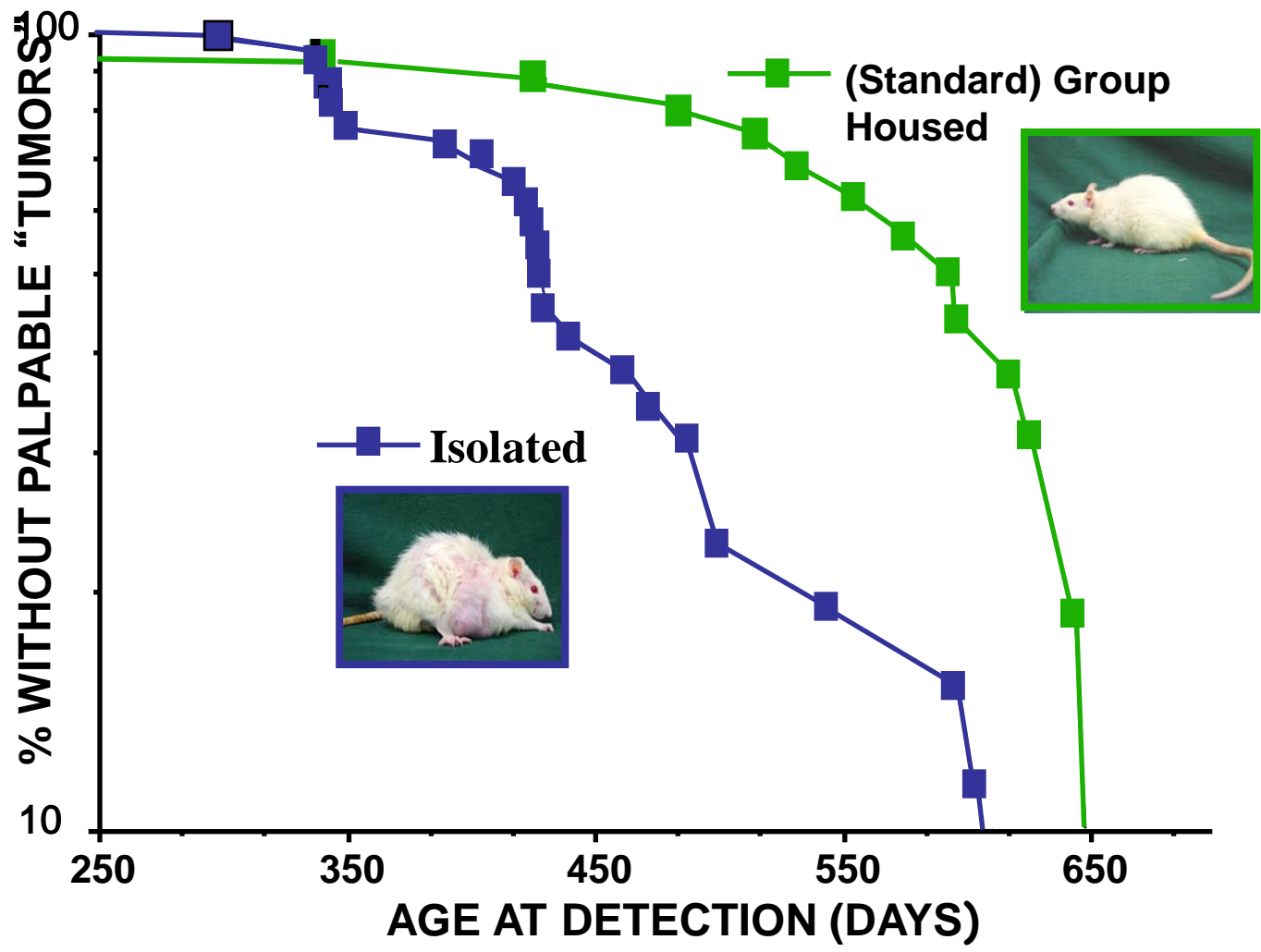
Glucocorticoids (GCs) provide a potent anti-apoptotic signal to MCF 10A-Myc cells



Modeling chronic stressor exposure in rodent models

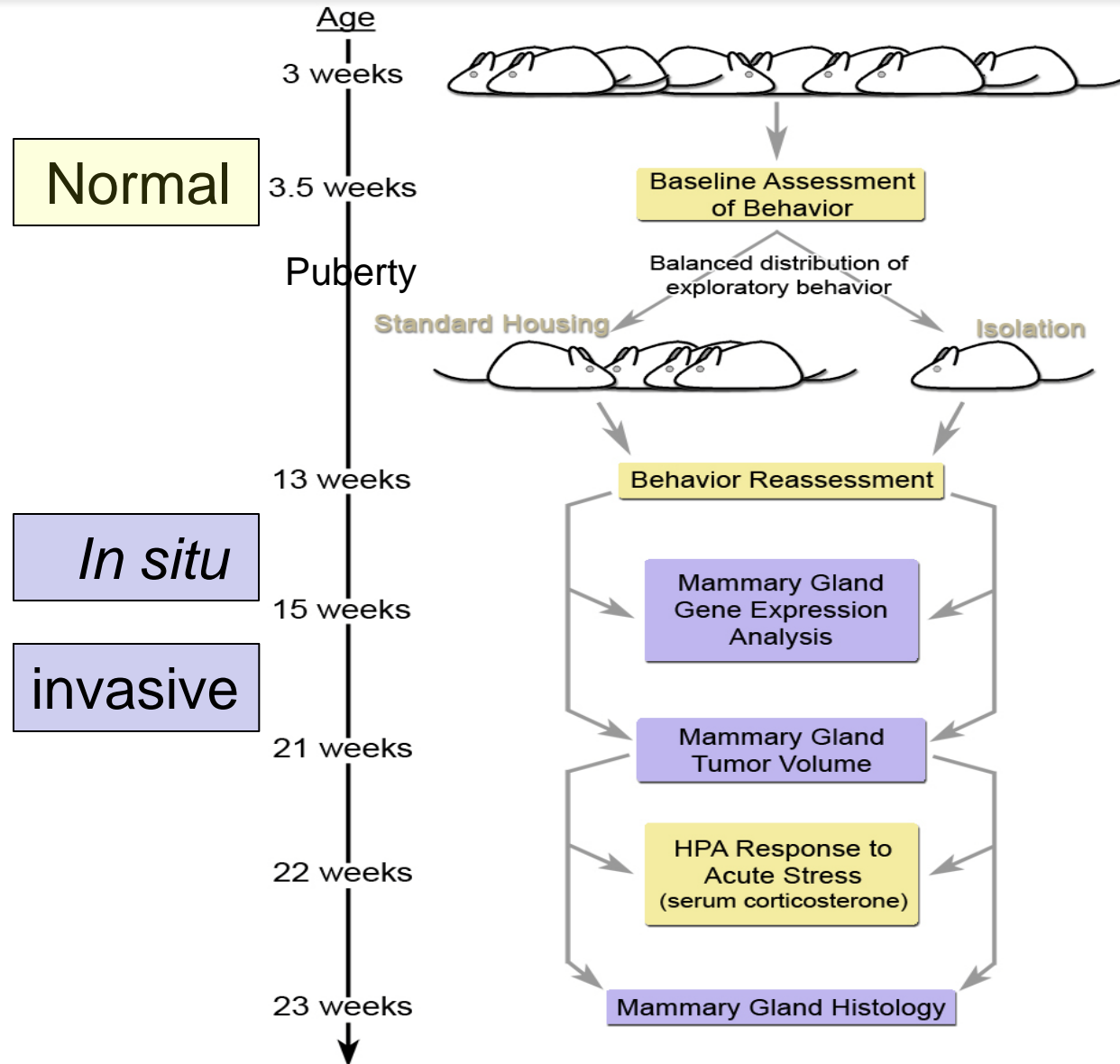


Socially-isolated female rats develop spontaneous mammary gland tumors earlier than grouped



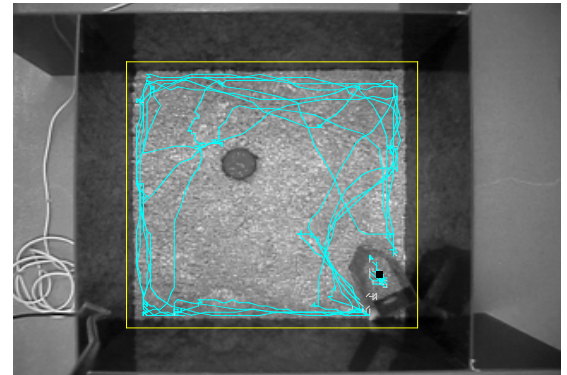
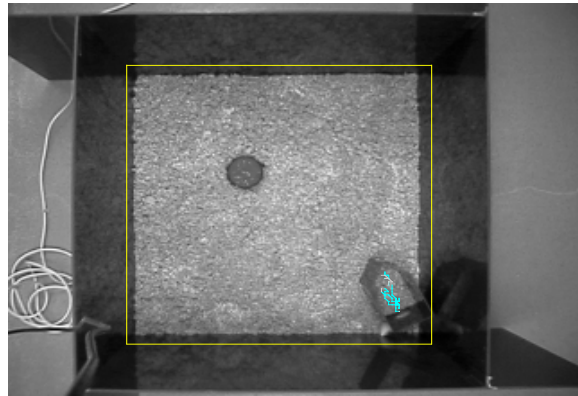
(Hermes et al, PNAS, 2009)

Background: Social isolation as a chronic stressor in transgenic mice

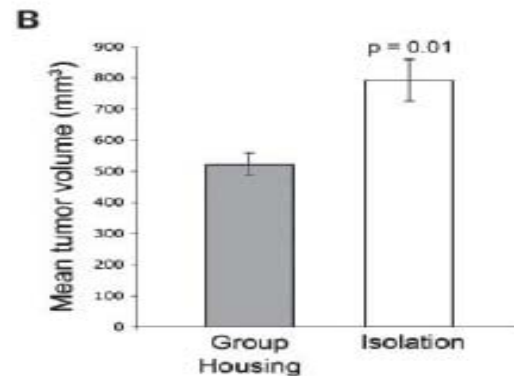
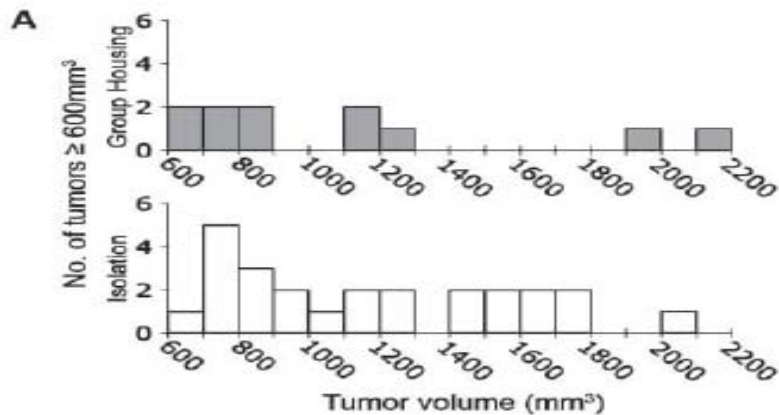




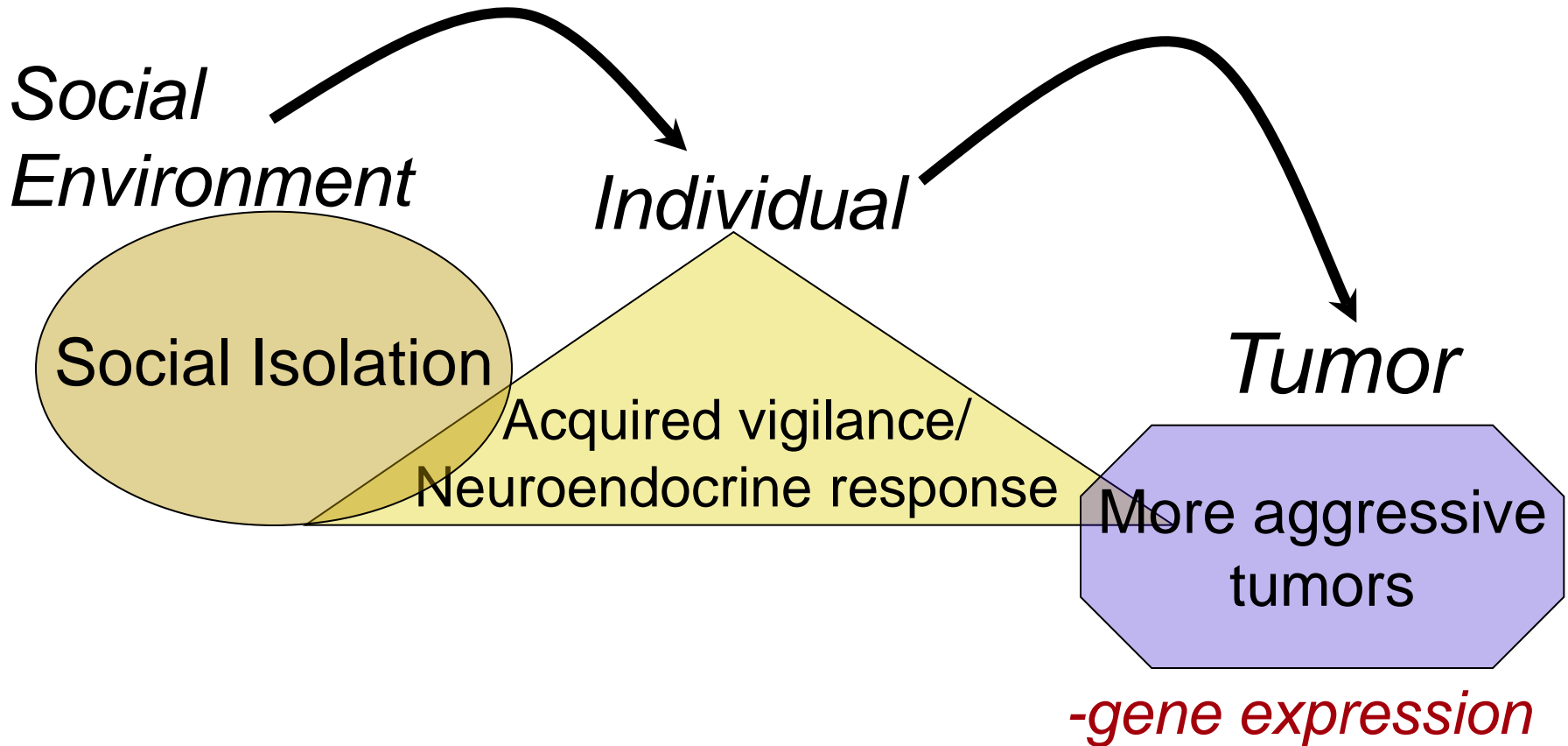
Behavior: "Vigilance" in a potentially threatening environment can be measured



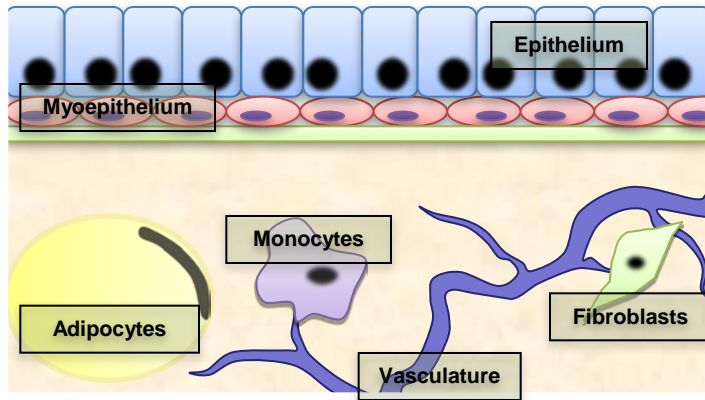
Chronic isolation is associated with increased tumor growth in the SV40 model



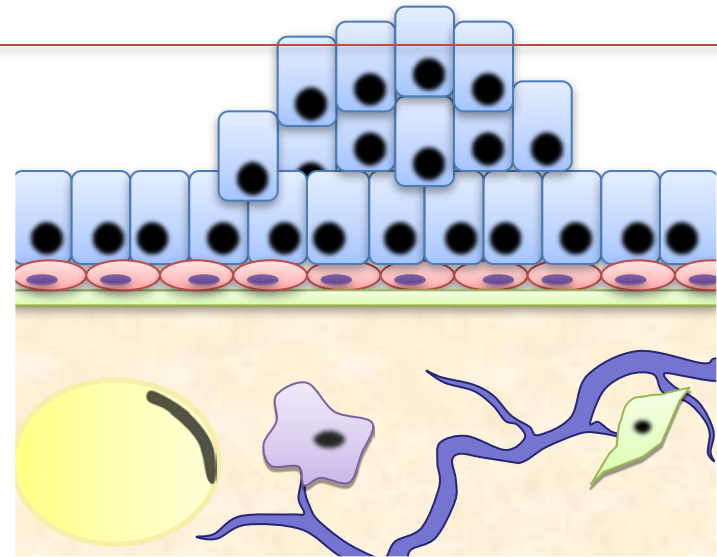
How does social environment affect tumor growth?



Background: Mammary tumorigenesis- the microenvironment

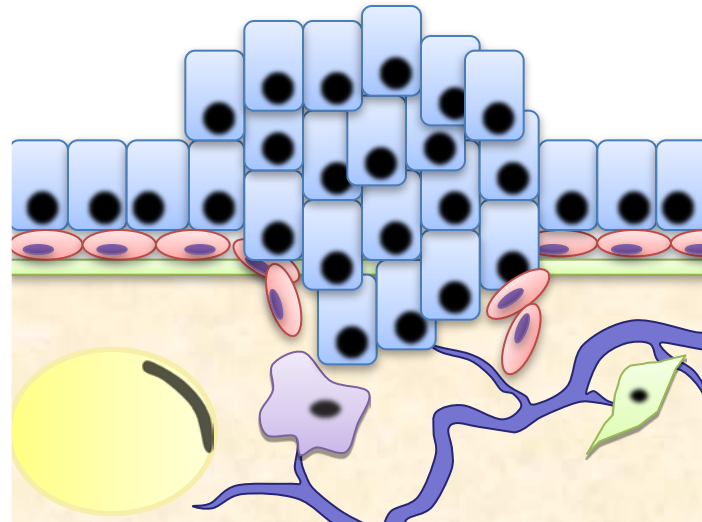


NORMAL MAMMARY GLAND

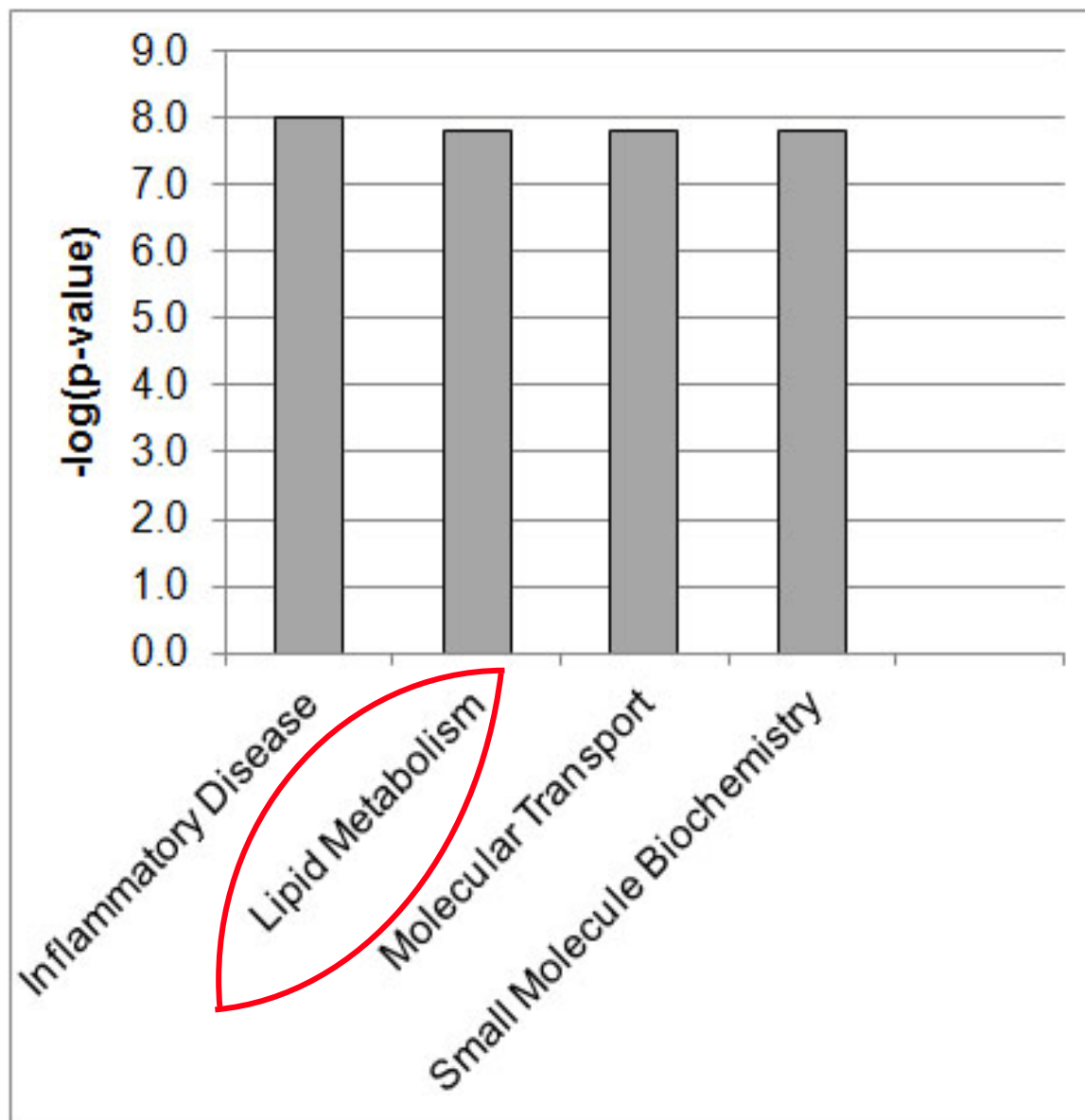


Carcinoma in Situ (CIS)=15 weeks

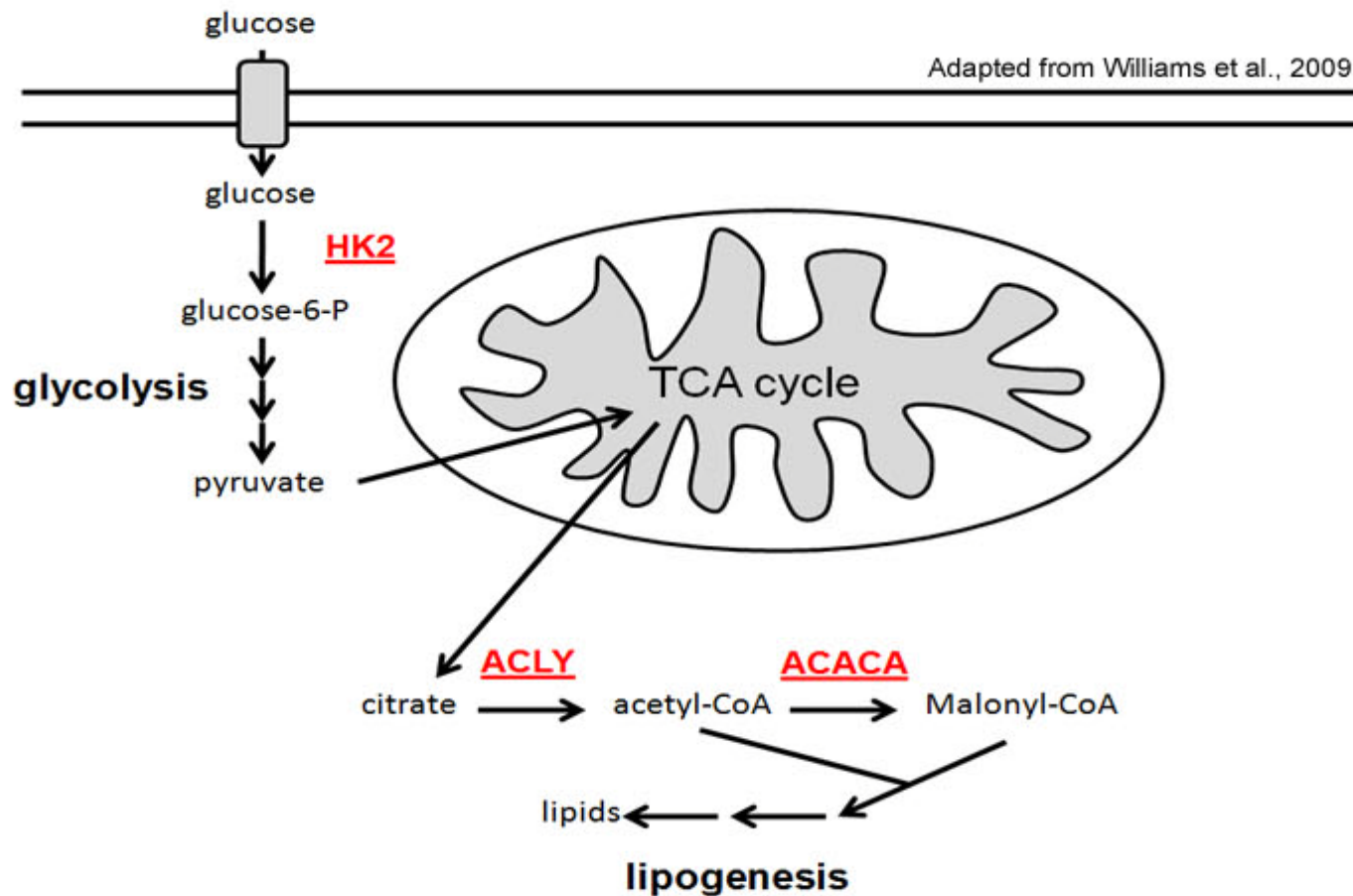
INVASION/Tumor Formation (20 weeks)



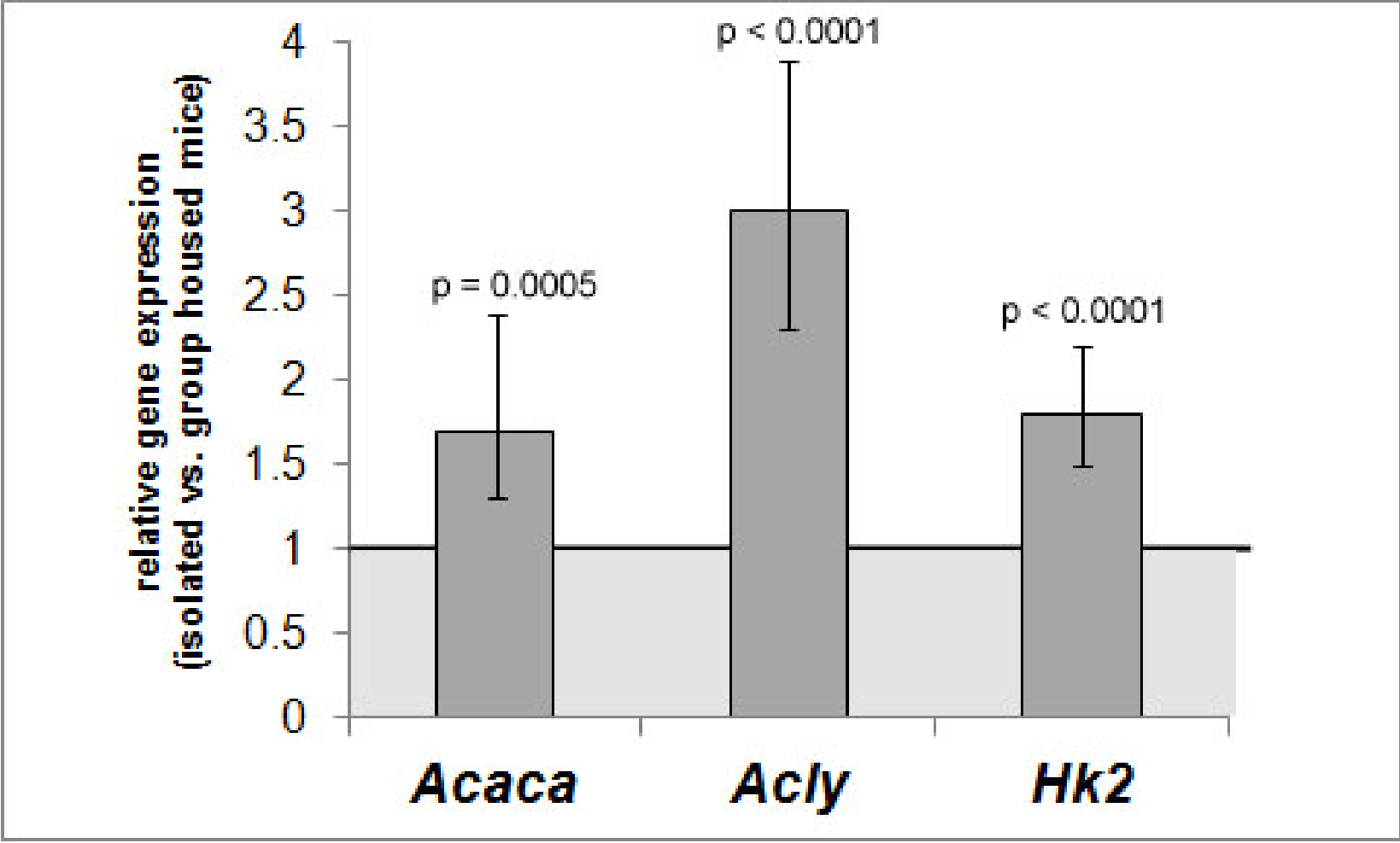
Differentially expressed genes reveal lipid metabolism-related pathway is seen at 15 weeks



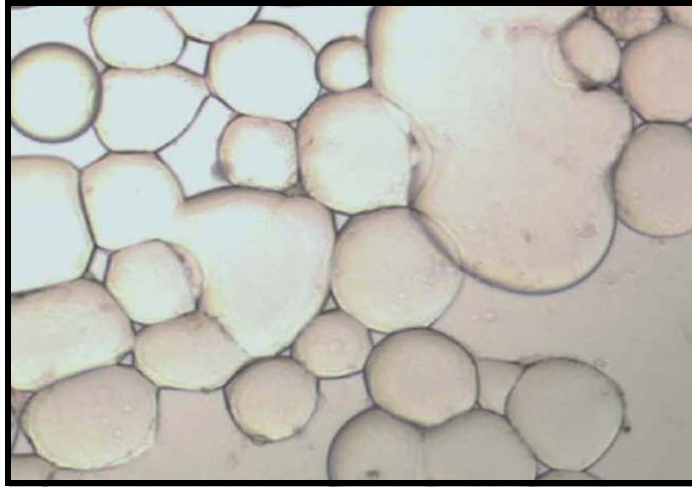
In isolated MGs at 15w, there is a relative upregulation of genes encoding **KEY** enzymes in glucose uptake and lipogenesis



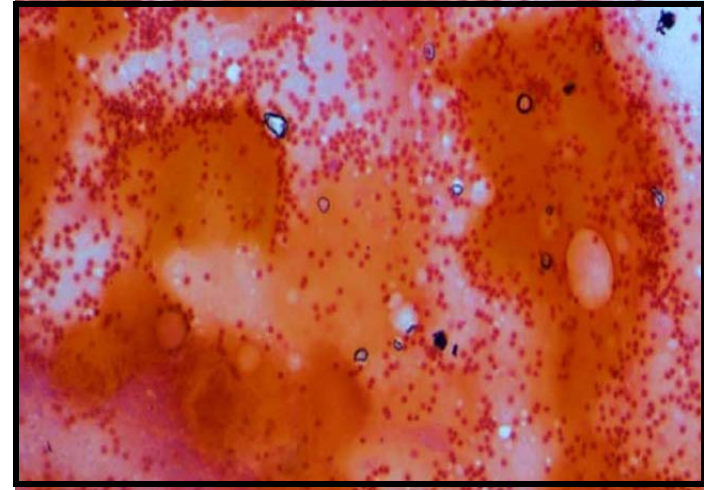
Increased MG gene expression of **key** metabolic genes



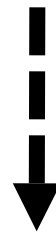
Mince mammary gland, collagenase digest, centrifuge



Isolate
adipocyte RNA



Isolate
epithelial, stromal cell RNA

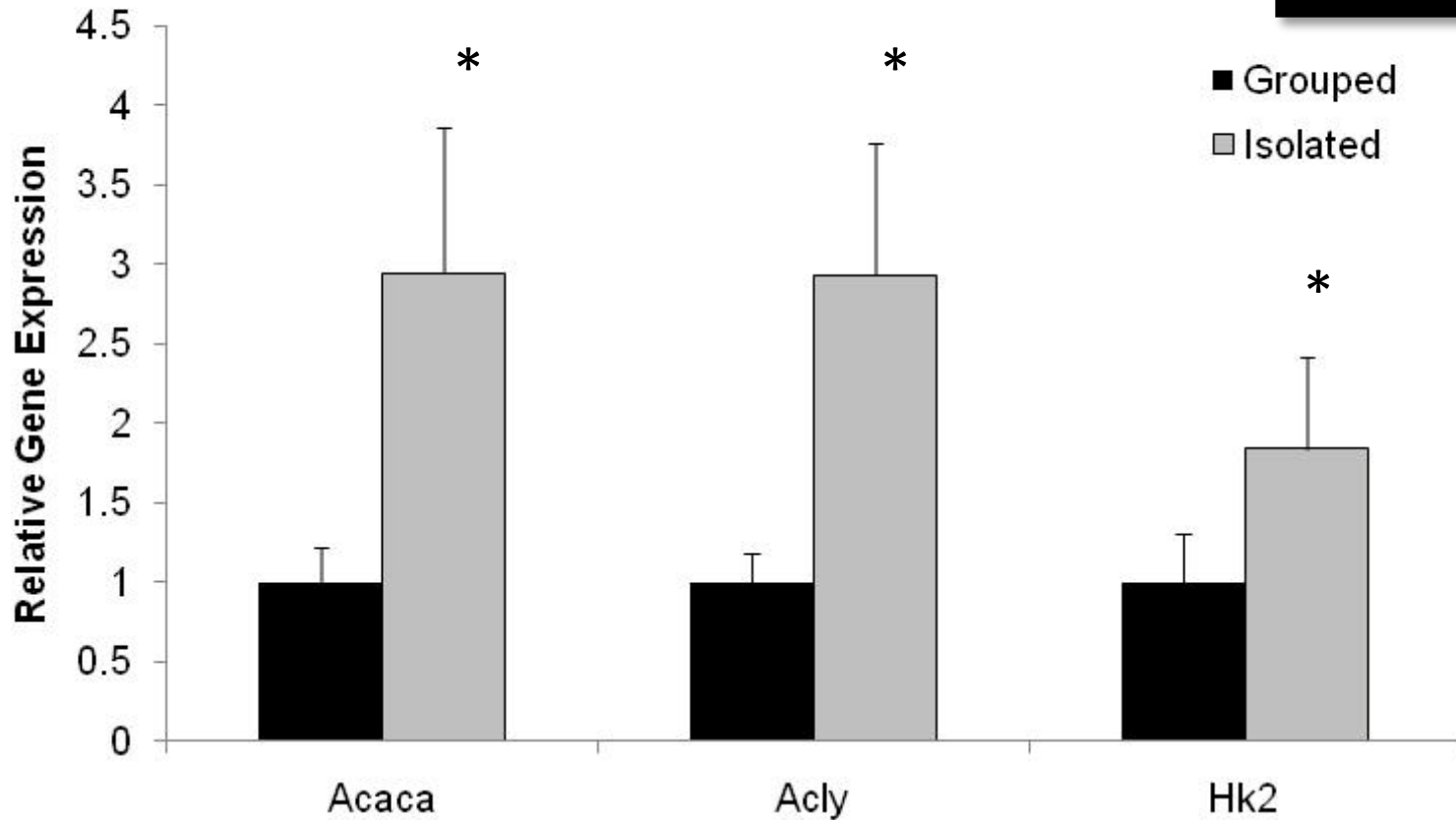


Gene Expression

Metabolic gene expression in mammary adipocytes

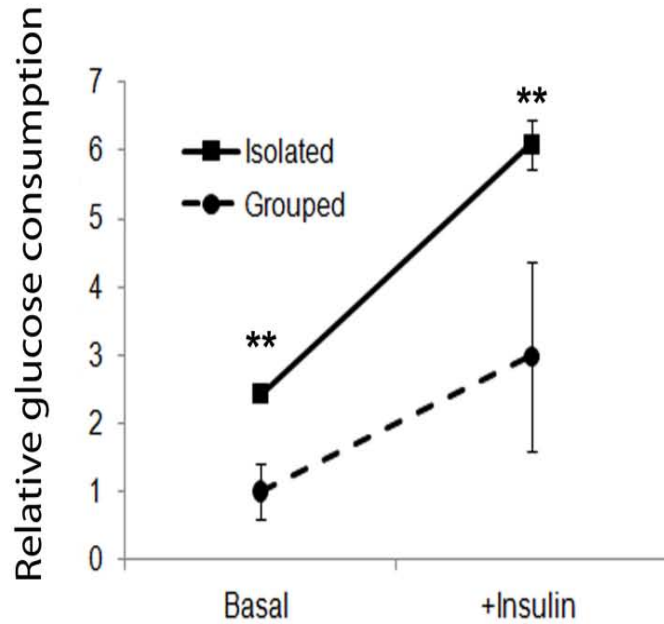


Isolated Adipocyte Gene Expression:
Grouped Vs. Isolated



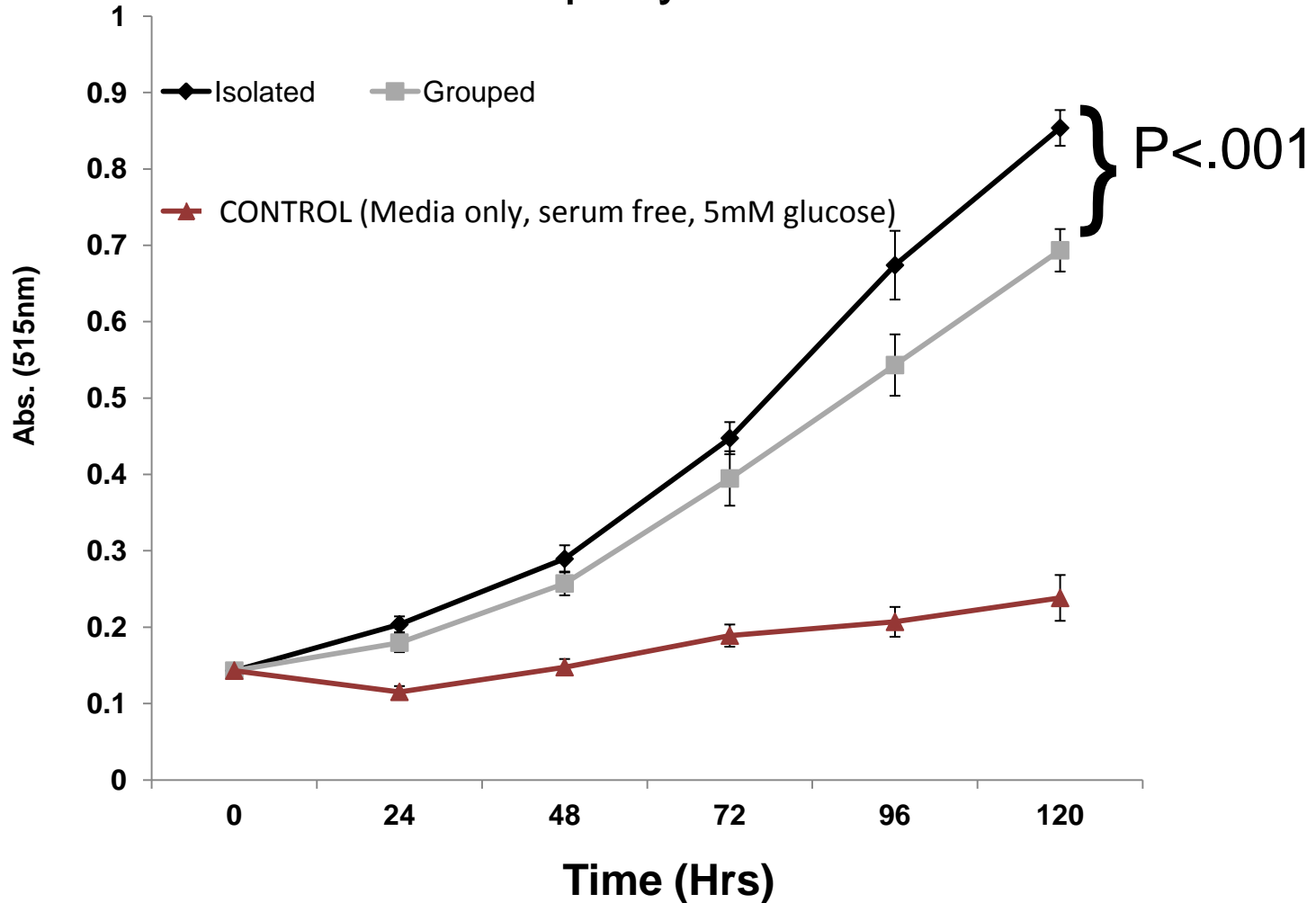
Increased A) glucose consumption and B) lipogenesis in adipocytes from isolated mice mammary glands

A

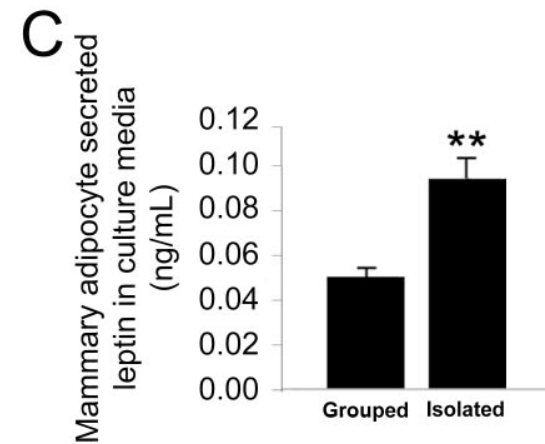
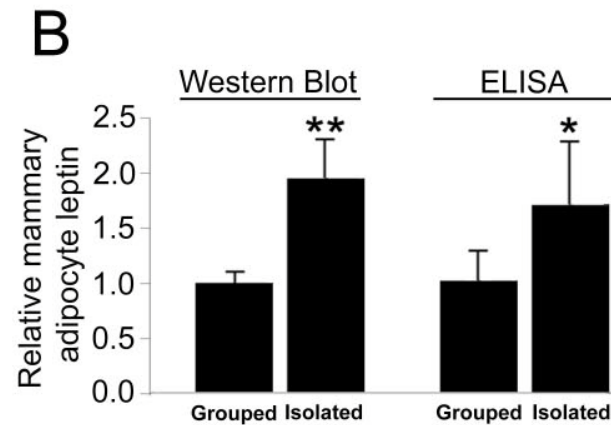
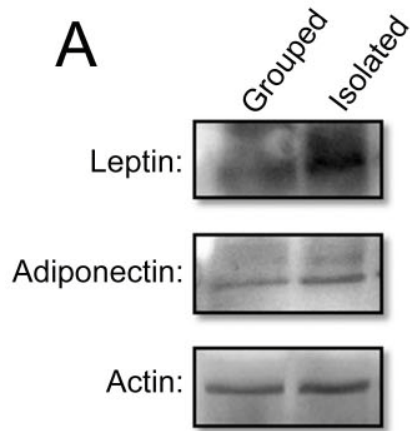


Mammary gland epithelial cell line proliferation is increased with conditioned media from social isolates

M27 cell line (*carcinoma in situ*) proliferation in adipocyte media



Leptin expression and secretion is increased in mammary fat from isolated mice

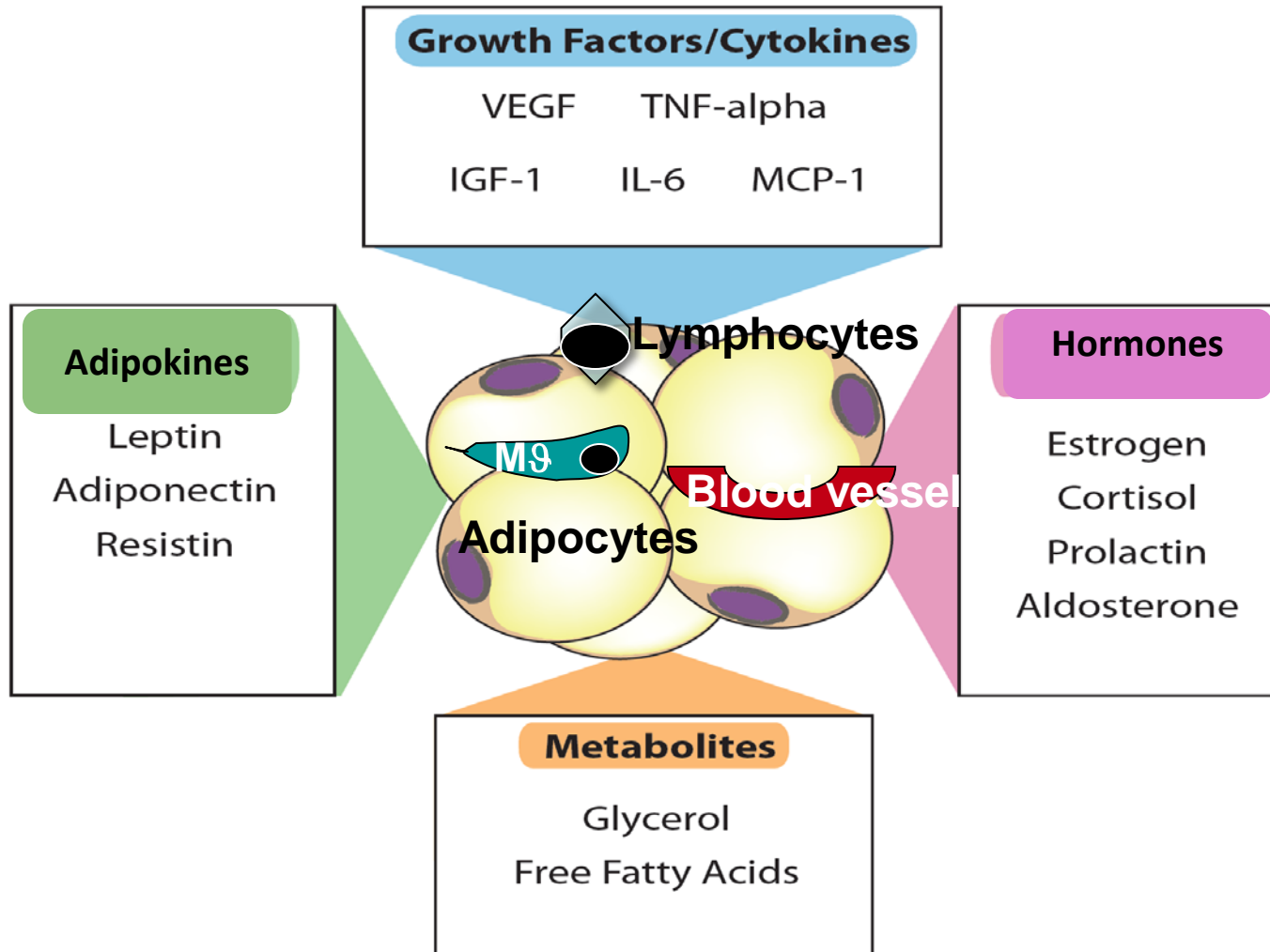


Serum “biomarkers” do not necessarily reflect the mammary gland changes

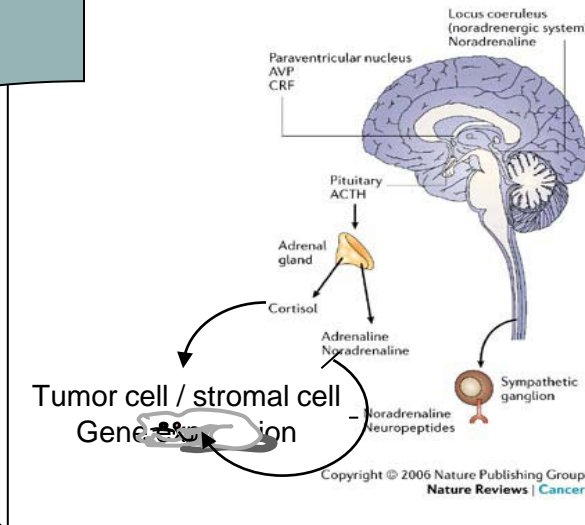
	Grouped	Isolated	p-value
Blood Glucose (mg/dL)	113.4 \pm 27.9	113.1 \pm 11.6	0.98
Serum Insulin (pg/mL)	361.5 \pm 222.8	385.5 \pm 215.6	0.84
NEFA (mEq/L)	0.93 \pm 0.20	0.79 \pm 0.18	0.24
Serum Leptin (ng/mL)	2.03 \pm 1.20	2.74 \pm 0.91	0.18
Weight gain: 8-10wks (g/wk)	0.60 \pm 0.18	0.27 \pm 0.13	0.16
Food consumption: 8-10wks (kcal/wk)	65.3 \pm 3.7	74.2 \pm 1.8	<0.05
Weight gain: 11-17wks (g/wk)	0.27 \pm 0.15	0.42 \pm 0.10	0.34
Food consumption: 11-17wks (kcal/wk)	73.3 \pm 2.2	88.0 \pm 1.4	<0.01

Energy consumption is increased

Adipose tissue secretes **many** substances (pre-adipocytes, macrophages, lymphocytes, blood vessels)



Stress response



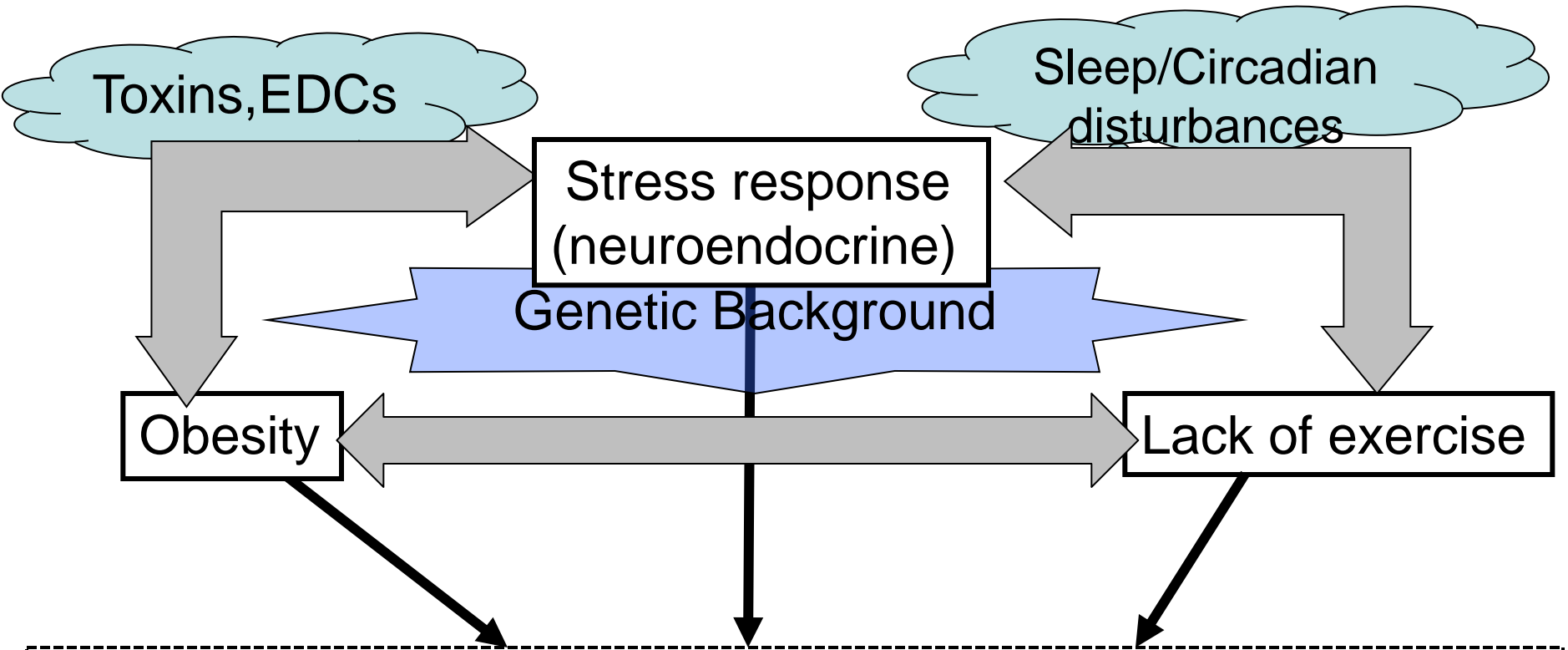
Energy intake

Lack of physical exercise

- Systemic endocrine/catecholamine disruption
- High insulin levels, increased/decreased estrogen

Increased tumor growth and ? initiation

Altered cancer biology: 1) initiation vs. 2) progression



- Timing of exposure & dvptal changes (e.g. early puberty)
- Systemic* endocrine/catecholamine disruption (e.g. high insulin levels, increased estrogens, cortisol)
- Local* effects on tumorigenesis via microenvironment
- Systemic* and local effects on immunity and inflammation

Shared mechanisms of energy balance disruption cancer risk/recurrence

Systemic: Insulin resistance, increased circulating insulin, increased PI3K activation in epithelial tumors

Local: increased adipose tissue and increased adipose tissue activity, altered secretion of local growth factors, such as leptin.

Back to the precision cancer care

Do these local and systemic physiological changes alter:

- 1) Tumor initiation (initial risk/premalignant)
- 2) Tumor recurrence (early stage cancers)
- 3) Tumor progression of metastatic cancer

By the same mechanisms in different stages?

Different stages of tumorigenesis require different analyses

Tumor initiation

- Normal-cancer mechanism
- Individual genetics important
- Prevention of primary is goal

Early stage cancer

- tumor type is known
- Interventions are likely tumor subtype dependent
- Reduce the risk of recurrence

Metastatic cancer

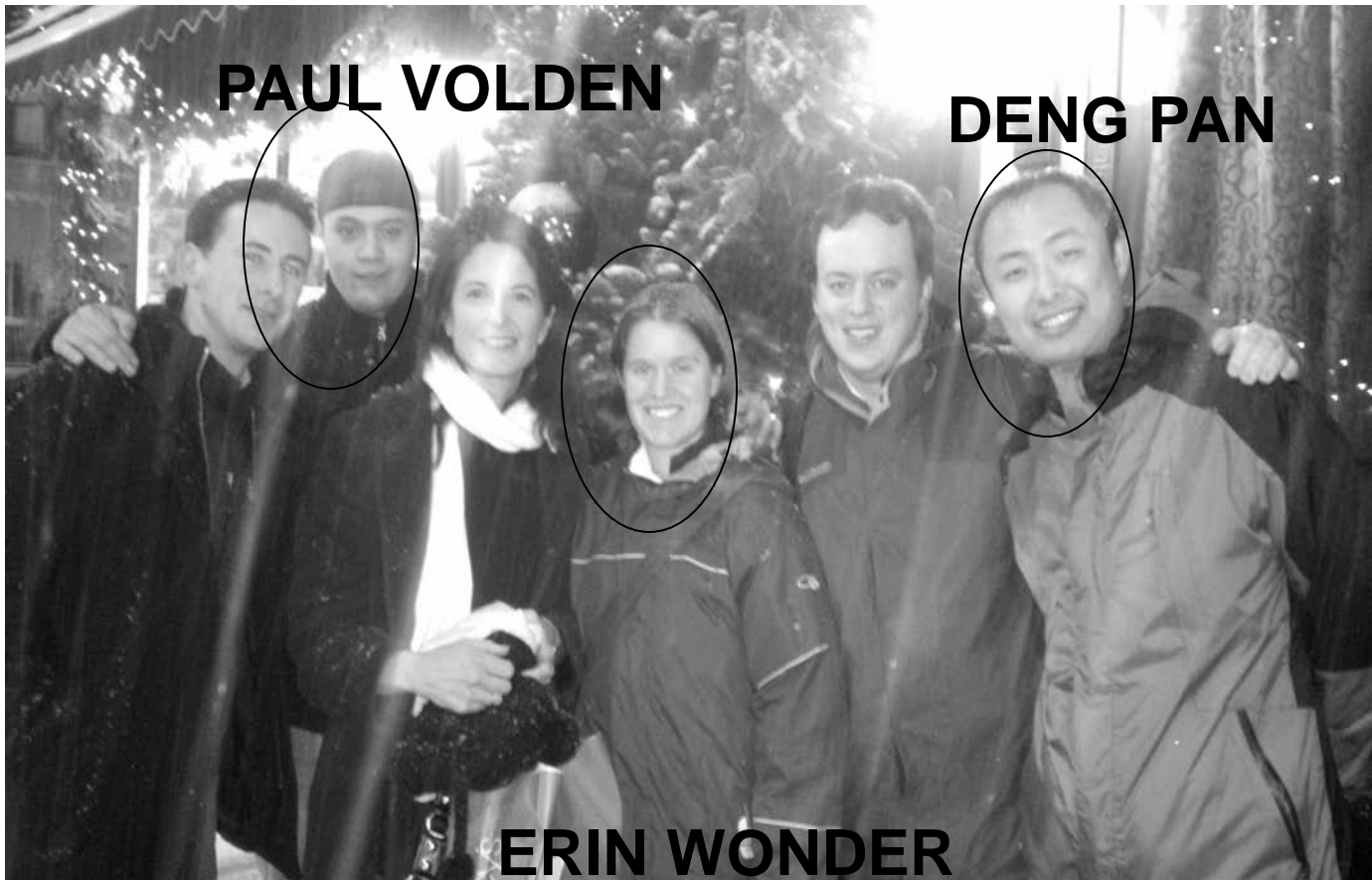
- Tumor cells are dispersed
- Treatment is ongoing
- QOL versus lifespan

How do we provide *precision* cancer care?

1. ? Focus on cancer survivors: Survivors of early-stage cancer appear to be perhaps the “best” group of patients to target strategies to reduce risk of measurable *recurrence*. (Would require cooperative groups to achieve adequate numbers)
2. Consider the tumor subtype: For example with breast cancer, the risks in ER+ and ER- breast cancer are not be the same.

Toward Precision Cancer Care

- *Understand* the mechanisms downstream of the stress response, and elements that modify the stress response
 - » Diet
 - » Exercise
- *Understand/Identify* these molecular mechanisms in the context of tumor growth.
- *Identify* individuals/tumors at highest risk.
- *Design* interventions that target the (behavioral) mechanisms upstream of modulating tumor growth.



PAUL VOLDEN

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NCI, AVON, Komen and the DOD