

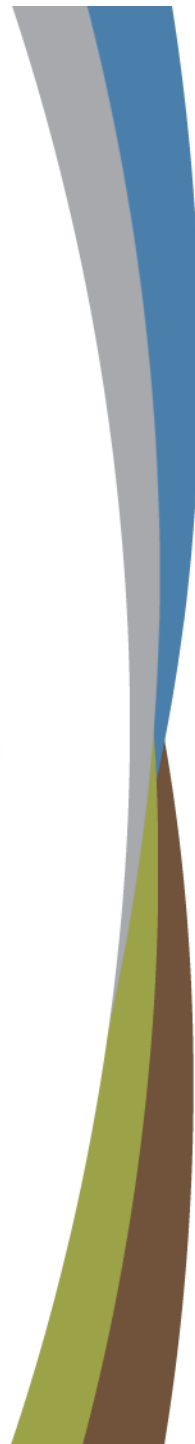
National Cancer Institute

U.S. DEPARTMENT
OF HEALTH AND
HUMAN SERVICES

National Institutes
of Health

Biobehavioral Influences on Cancer Biology

AN EMERGING OPPORTUNITY



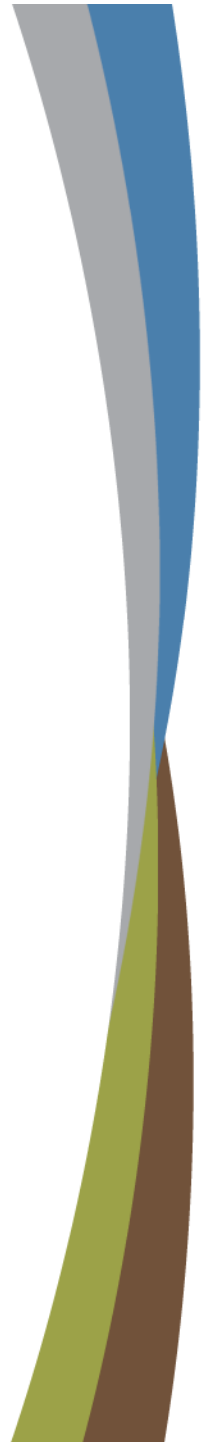
Biobehavioral Influences on Cancer Biology: An Emerging Opportunity

Paige A. McDonald, PhD, MPH
Acting Chief

Basic and Biobehavioral Research Branch
Behavioral Research Program



*Division of
Cancer Control and
Population Sciences*
NATIONAL CANCER INSTITUTE



Acknowledgements

- **Steve Cole, PhD**
- **Suzanne Conzen, MD**
- **Anil Sood, MD**

- **Shamgar Ben-Eliyahu, PhD**
- **Firdaus Dhabhar, PhD**
- **Ronald Glaser, PhD**
- **Susan Lutgendorf, PhD**
- **Eric Yang, PhD**

Symposium Purpose

- **Facilitate knowledge of this emerging area in the NCI behavioral research portfolio**
- **Obtain BSA input on how NCI can best:**
 - **Expand the breadth and depth of this transdisciplinary science**
 - **Catalyze productive high impact collaborations**

Presentation Purpose

- Define biobehavioral risk factors
- Review epidemiology
- Review biobehavioral signaling pathways
- Review biobehavioral influences on cancer biology

Biobehavioral Risk Factors

Distinction from other behavioral sciences

- Focus on neuroendocrine mediation

Distinction from systemic and environmental stress

- Physical activity
- Environmental tobacco smoke
- Alcohol
- Diet/nutrition

Biobehavioral risk factors

- Social isolation / social support
- Depression
- Chronic psychological stress

Epidemiology of Biobehavioral Influences on Cancer

Inconsistent association with cancer incidence

- Nielsen & Gronbaek, 2006
- Dujits et al, 2003

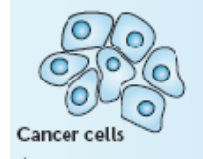
More consistent association with cancer progression and mortality

- Antoni et al, 2006
- Kroenke et al, 2006
- Soler-Vila et al, 2003

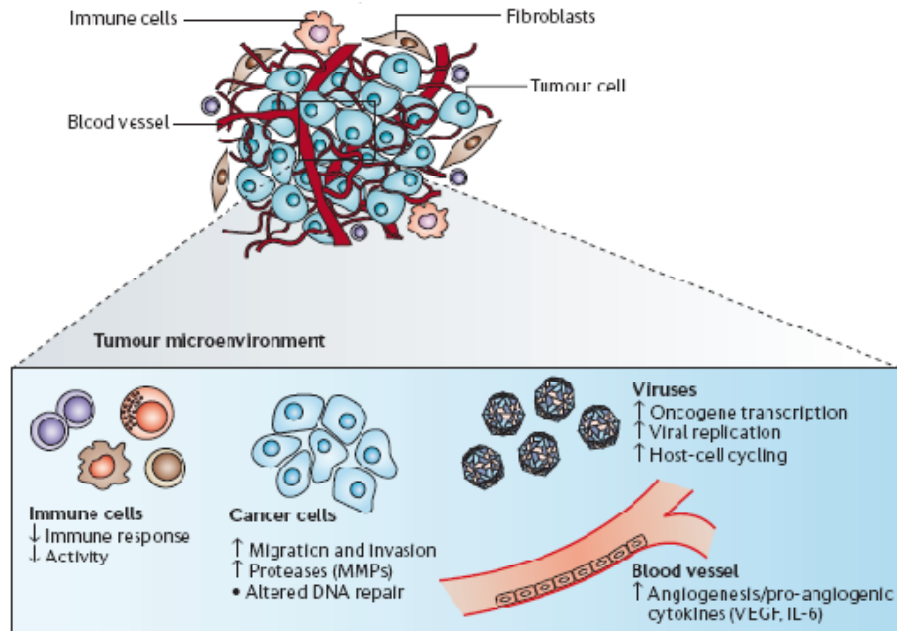
Stress as a Biobehavioral Influence

- **Perception that a threatening or challenging external event (“stressor”) exceeds the organism’s ability to respond**
- **Challenge biological homeostasis**
- **Neuroendocrine and sympathoadrenal stress response systems**

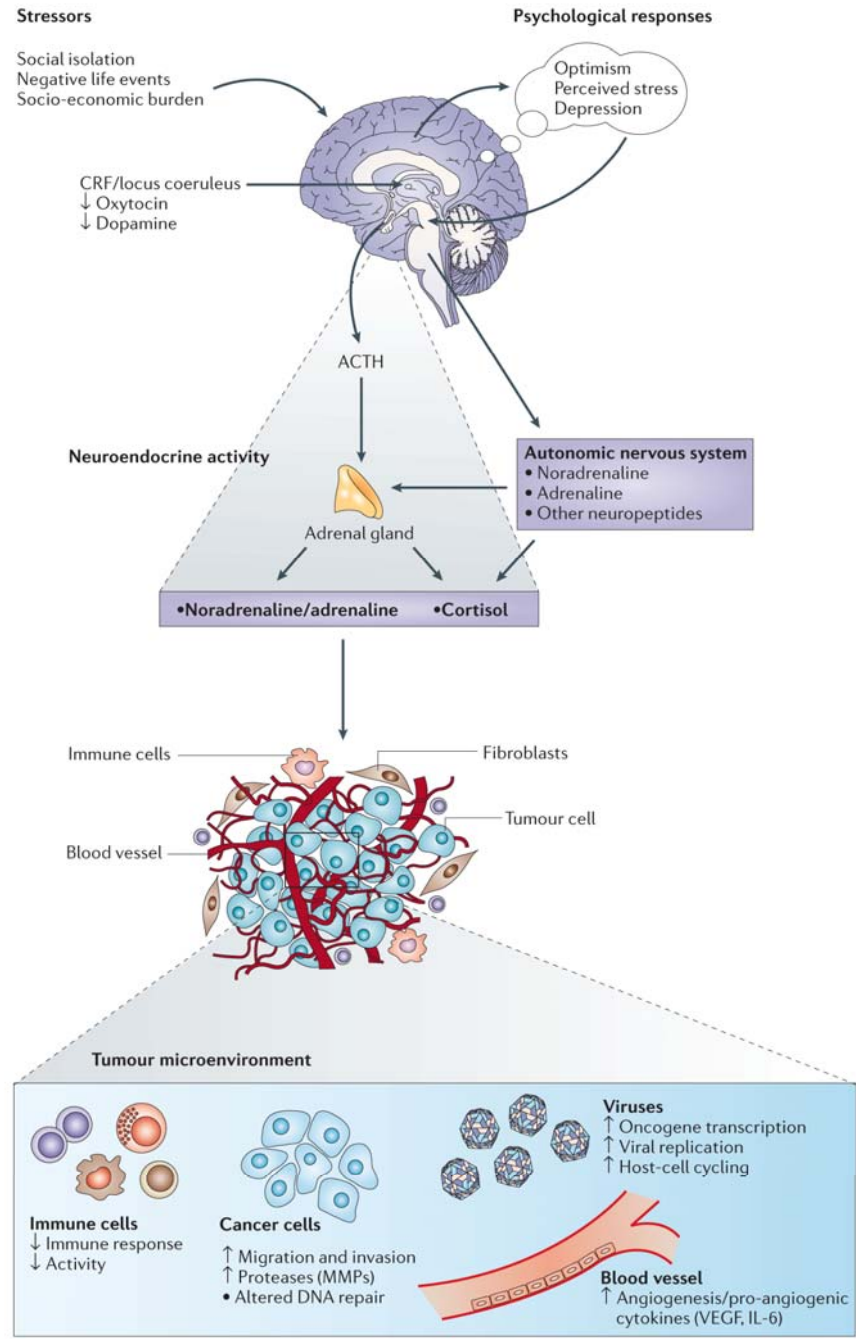
Biobehavioral Signaling Pathways



Biobehavioral Signaling Pathways



Biobehavioral Signaling Pathways



The influence of bio-behavioural factors on tumour biology: pathways and mechanisms

Michael H. Antoni, Susan K. Lutgendorf, Steven W. Cole, Firdaus S. Dhabhar, Sandra E. Sephton, Paige Green McDonald, Michael Stefanek and Anil K. Sood



Biobehavioral Influences on Tumor Biology

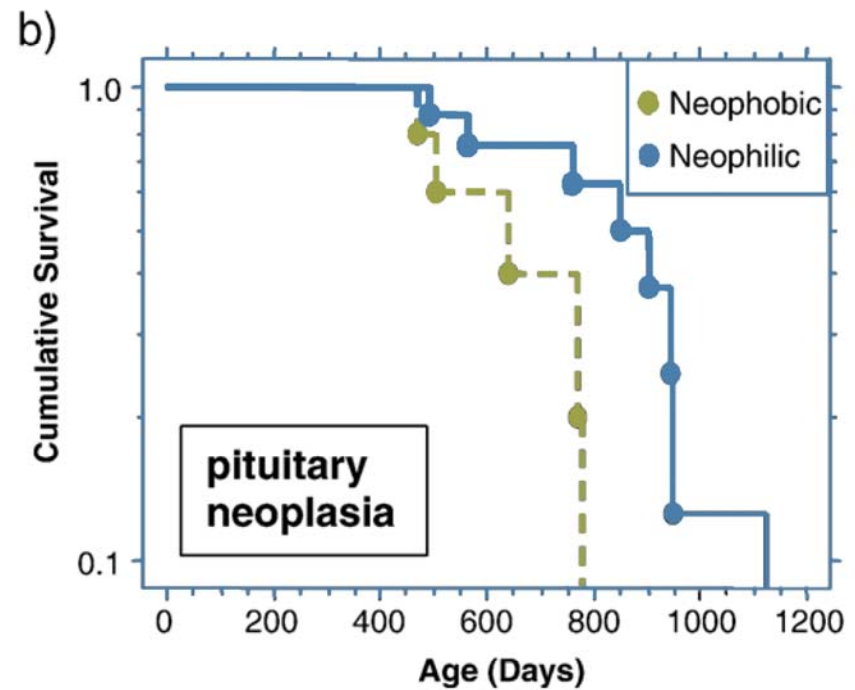
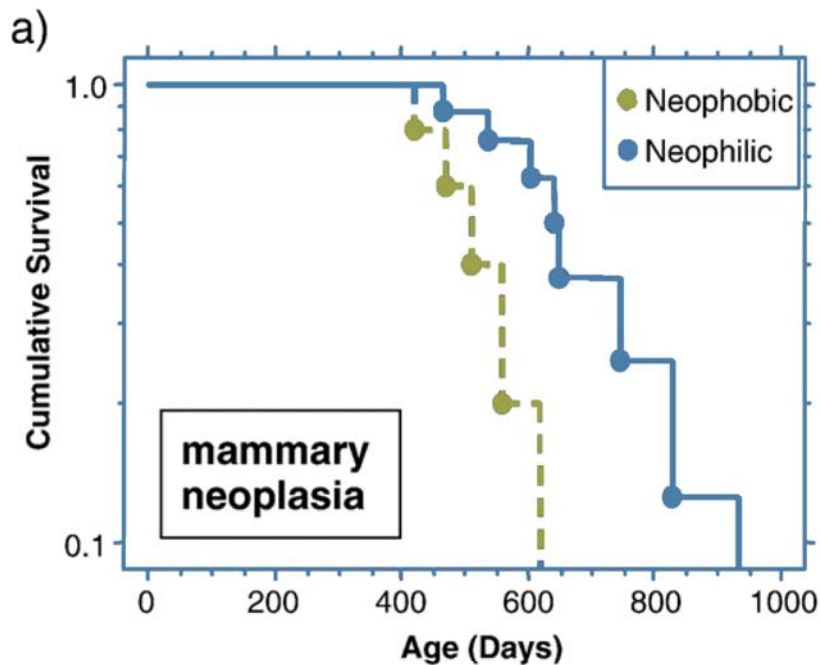
- **Neoplastic cell growth**
- **Tumor gene expression**
- **Viral gene expression**
- **Cell-mediated immunity**
- **Invasion**
- **Tumor growth and progression**

Neoplastic cell growth

Hormones and Behavior 50 (2006) 454-462

Infant temperament predicts life span in female rats that develop spontaneous tumors

Sonia A. Cavigelli^{a,*}, Jason R. Yee^{b,c}, Martha K. McClintock^{b,c,d}



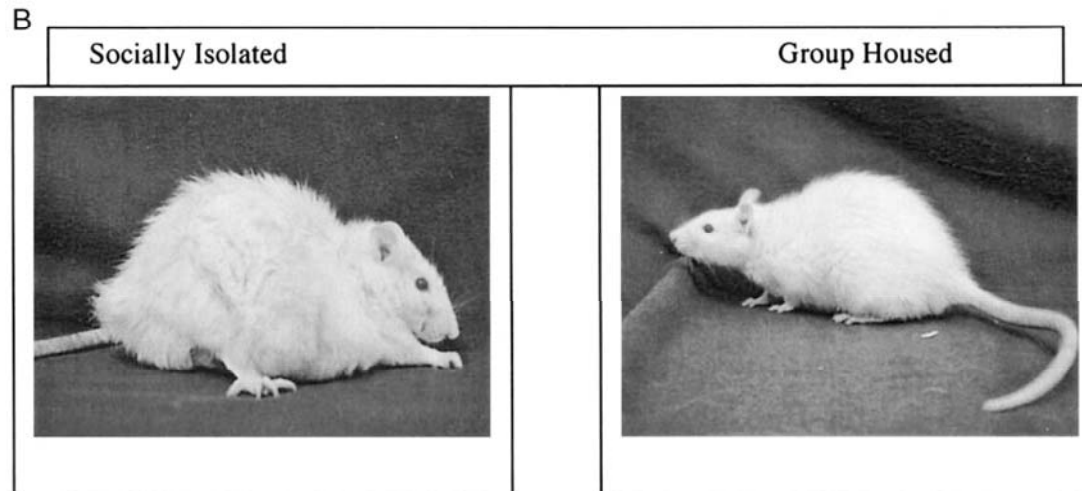
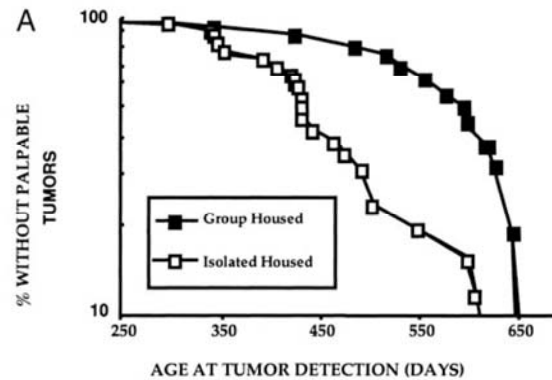
In vivo

Tumor Gene Expression

Journals of Gerontology: SERIES B

Mammary Cancer and Social Interactions: Identifying Multiple Environments That Regulate Gene Expression Throughout the Life Span

Martha K. McClintock,^{1,2} Suzanne D. Conzen,^{1,3} Sarah Gehlert,^{1,4}
Christopher Masi,^{1,3} and Funmi Olopade^{1,3}



Neuroendocrine activation of human tumor viruses

Human tumour virus	Malignancy	Sensitivity*
Human papilloma viruses 16 and 33	Cervical and head/neck cancer	HPA
Hepatitis B virus	Hepatocellular carcinoma	HPA
Hepatitis C virus	Hepatocellular carcinoma	HPA
Epstein–Barr virus	Lymphoma, and nasopharyngeal carcinoma	HPA
Human T-cell lymphotropic viruses 1 and 2	Adult T-cell leukaemia/lymphoma	ANS
Kaposi sarcoma-associated herpesvirus	Kaposi sarcoma, and primary effusion lymphoma	ANS

In vitro

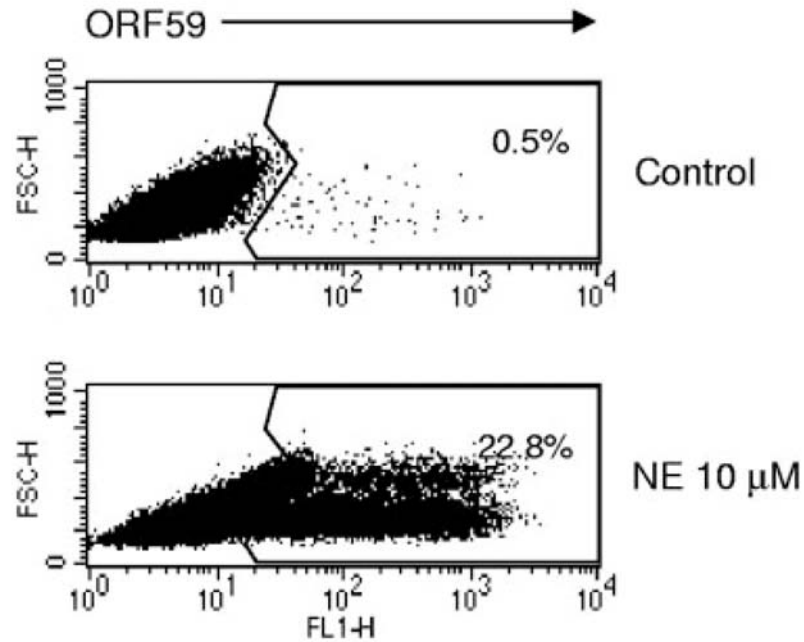
Neuroendocrine activation of KSHV

JOURNAL OF VIROLOGY, Nov. 2005, p. 13538–13547

β -Adrenoreceptors Reactivate Kaposi's Sarcoma-Associated Herpesvirus Lytic Replication via PKA-Dependent Control of Viral RTA

Margaret Chang,¹ Helen J. Brown,² Alicia Collado-Hidalgo,^{3,6} Jesusa M. Arevalo,³
Zoran Galic,³ Tonia L. Symensma,^{2,4} Lena Tanaka,⁴ Hongyu Deng,²
Jerome A. Zack,^{1,3,5} Ren Sun,^{2,5} and Steve W. Cole^{3,5,6*}

Viral replication



In vitro

UV-induced skin cancer in stressed mice

J Am Acad Dermatol
DECEMBER 2004

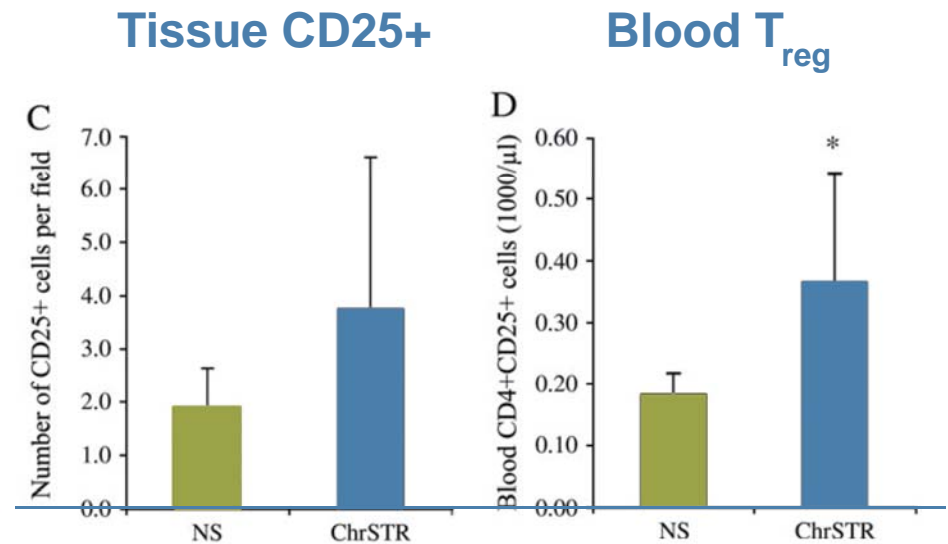
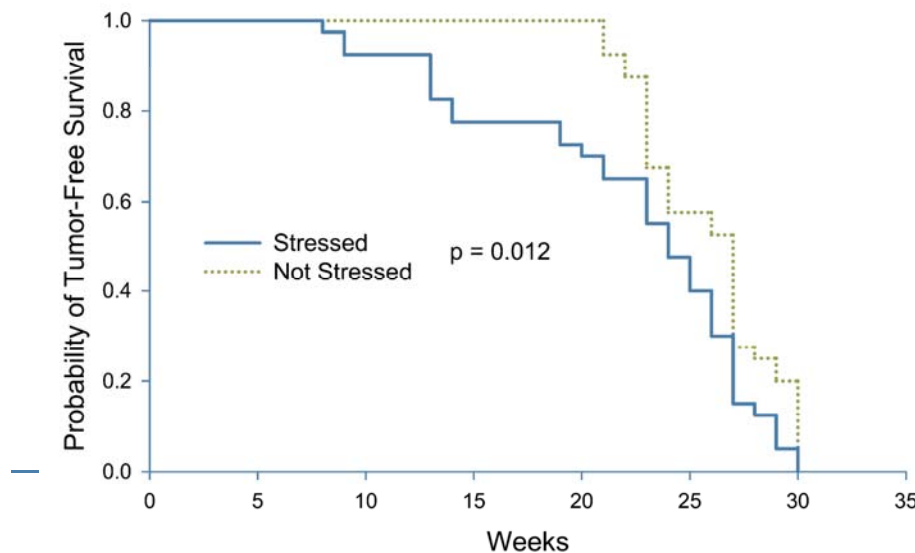
Chronic stress accelerates ultraviolet-induced cutaneous carcinogenesis

Jason Parker, MS,^a Sabra L. Klein, PhD,^b Martha K. McClintock, PhD,^c Warwick L. Morison, MD,^a Xiaobu Ye, MD, PhD,^c Claudio J. Conti, DVM, PhD,^f Norman Peterson, PhD,^d Carlos H. Nousari, MD,^g and Francisco A. Tausk, MD^a

Journal of the National Cancer Institute, Vol. 97, No. 23, December 7, 2005

Chronic Stress and Susceptibility to Skin Cancer

Alison N. Saul, Tatiana M. Oberyzyzn, Christine Daugherty, Donna Kusewitt, Susie Jones, Scott Jewell, William B. Malarkey, Amy Lehman, Stanley Lemeshow, Firdaus S. Dhabhar



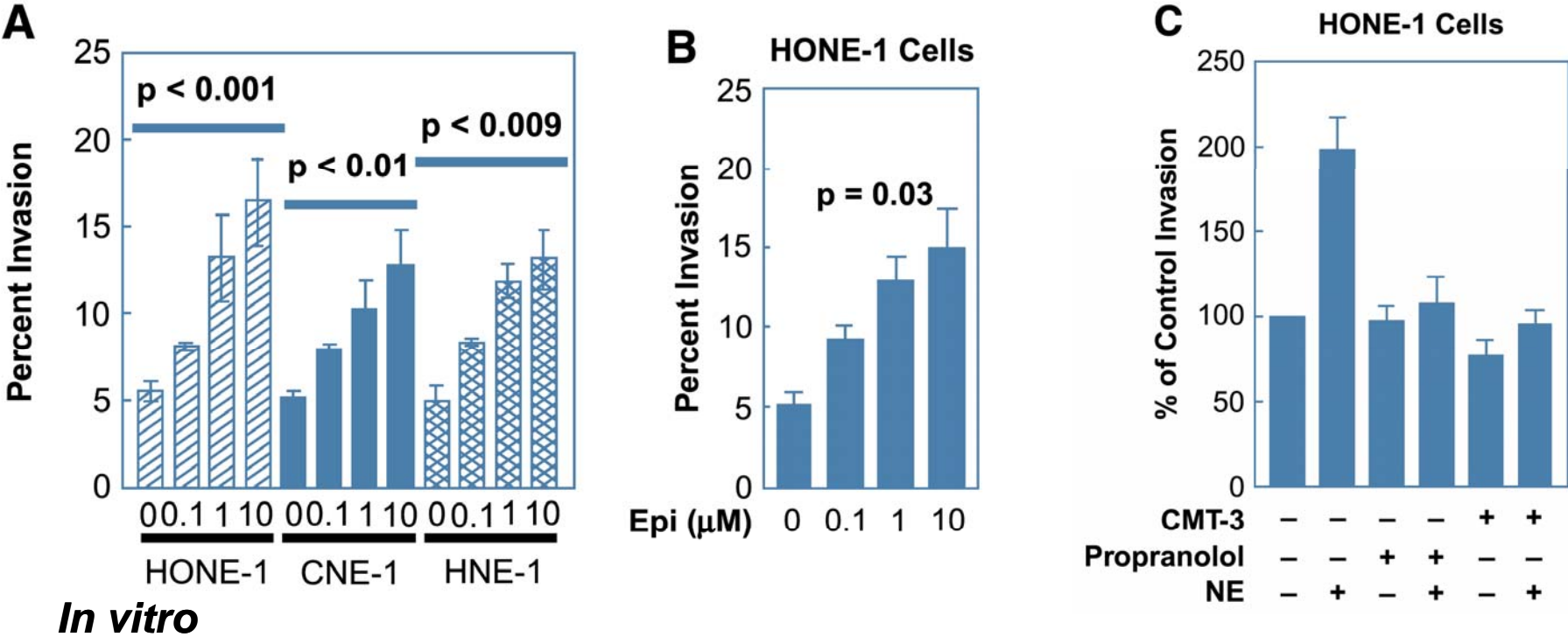
In vivo

Nasopharyngeal carcinoma cell invasion

Cancer Res 2006; 66: (21). November 1, 2006

Norepinephrine Up-regulates the Expression of Vascular Endothelial Growth Factor, Matrix Metalloproteinase (MMP)-2, and MMP-9 in Nasopharyngeal Carcinoma Tumor Cells

Eric V. Yang,^{1,2} Anil K. Sood,⁹ Min Chen,² Yang Li,⁹ Tim D. Eubank,^{4,6} Clay B. Marsh,^{3,4,6} Scott Jewell,^{3,5} Nicholas A. Flavahan,⁴ Carl Morrison,^{3,5} Peir-En Yeh,² Stanley Lemeshow,^{2,7,8} and Ronald Glaser^{1,2,3,6}

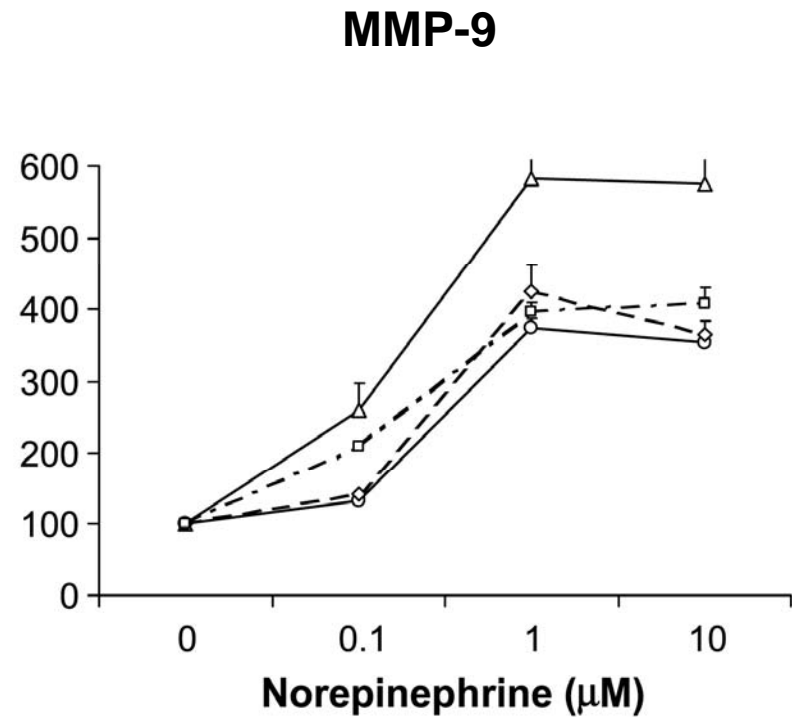
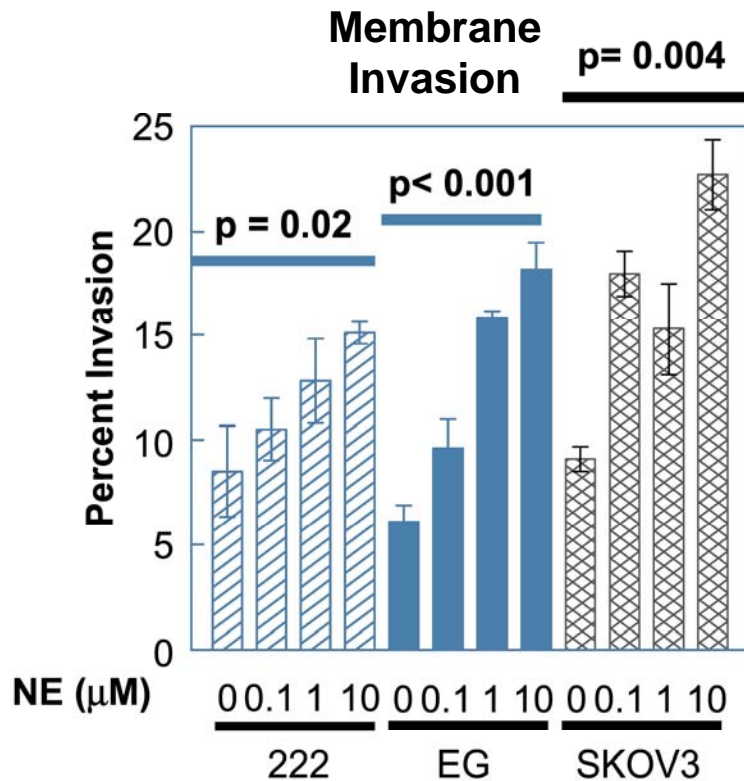


Human ovarian cancer cell invasion

Clin Cancer Res 2006;12(2) January 15, 2006

Stress Hormone – Mediated Invasion of Ovarian Cancer Cells

Anil K. Sood,^{1,2} Robert Bhatt,³ Aparna A. Kamat,¹ Charles N. Landen,¹ Liz Han,¹ Premal H. Thaker,¹ Yang Li,¹ David M. Gershenson,¹ Susan Lutgendorf,⁴ and Steven W. Cole⁵



In vitro

Cytokine levels in human ovarian cancer

CANCER July 15, 2005 / Volume 104 / Number 2

Psychosocial Factors and Interleukin-6 among Women with Advanced Ovarian Cancer

Erin S. Costanzo, M.A.¹
Susan K. Lutgendorf, Ph.D.^{1,2}
Anil K. Sood, M.D.³
Barrie Anderson, M.D.²
Joel Sorosky, M.D.⁴
David M. Lubaroff, Ph.D.⁵

CANCER August 15, 2002 / Volume 95 / Number 4

Vascular Endothelial Growth Factor and Social Support in Patients with Ovarian Carcinoma

Susan K. Lutgendorf, Ph.D.¹
Erica L. Johnsen, M.A.¹
Brian Cooper, M.D.²
Barrie Anderson, M.D.²
Joel I. Sorosky, M.D.²
Richard E. Buller, M.D., Ph.D.²
Anil K. Sood, M.D.²

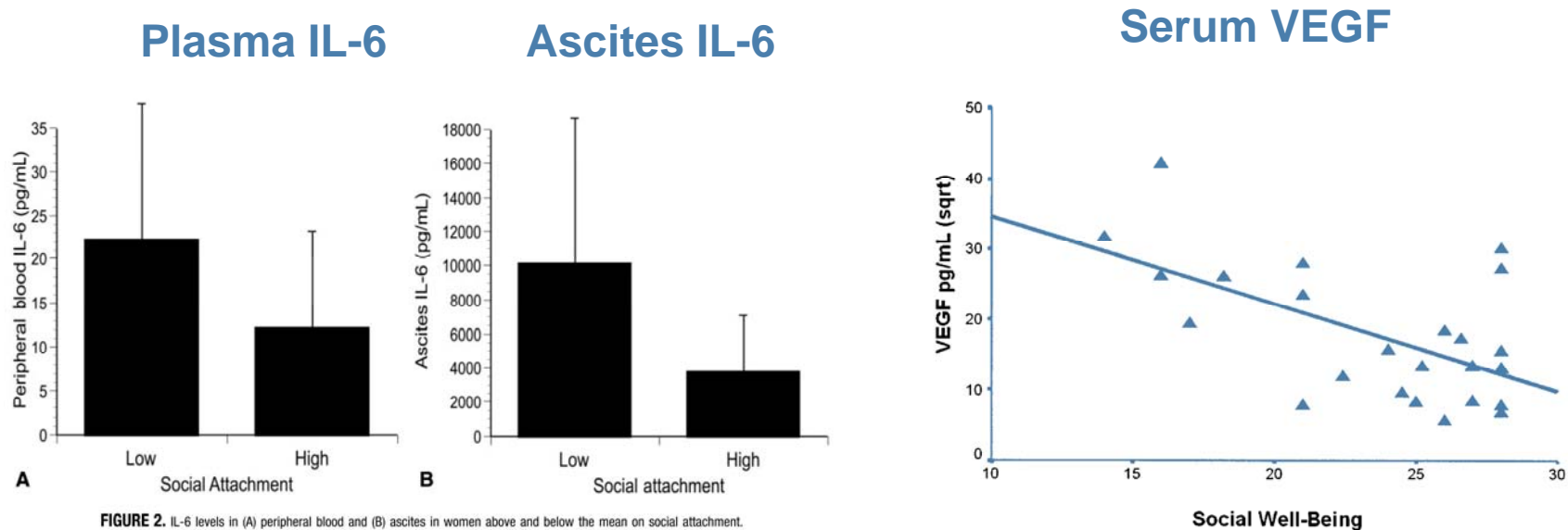
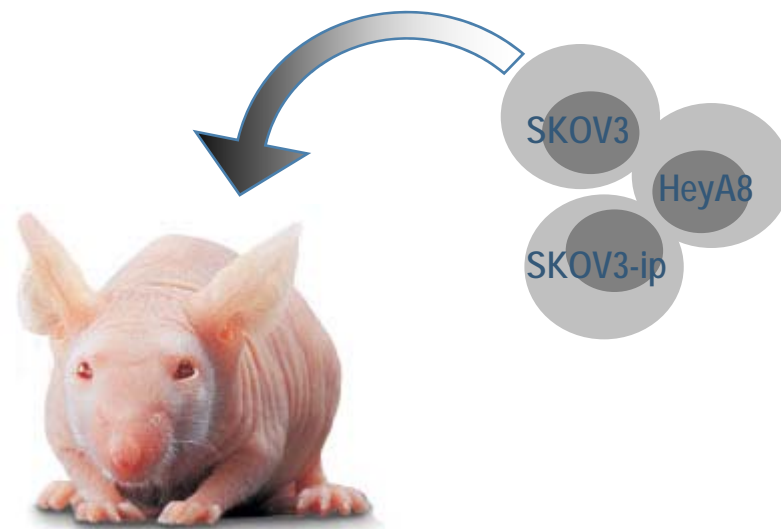


FIGURE 2. IL-6 levels in (A) peripheral blood and (B) ascites in women above and below the mean on social attachment.

In vivo

Human ovarian tumor cells in stressed mice



nature
medicine

VOLUME 12 | NUMBER 8 | AUGUST 2006

Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma

Premal H Thaker^{1,10}, Liz Y Han^{1,10}, Aparna A Kamat^{1,10}, Jesusa M Arevalo², Rie Takahashi², Chunhua Lu¹, Nicholas B Jennings¹, Guillermo Armaiz-Pena¹, James A Bankson³, Murali Ravoori⁴, William M Merritt¹, Yvonne G Lin¹, Lingegowda S Mangala¹, Tae Jin Kim¹, Robert L Coleman¹, Charles N Landen¹, Yang Li¹, Edward Felix⁵, Angela M Sanguino⁶, Robert A Newman⁵, Mary Lloyd⁷, David M Gershenson¹, Vikas Kundra^{4,8}, Gabriel Lopez-Berestein⁶, Susan K Lutgendorf⁹, Steven W Cole² & Anil K Sood^{1,7}

In vivo

Overarching Themes*

- **Stress biology can influence tumor biology**
 - 1.5 – 3-fold effects observed
- **Mechanisms are being elucidated**
 - Neuroendocrine regulation of:
 - Neoplastic cell growth
 - Tumor gene expression
 - Viral gene expression
 - Cell-mediated immunity
 - Invasion
 - Tumor growth and progression
- **Opportunity to test adjuvant interventions**

* See also: *Biobehavioral Influences on Cancer Biology: An Emerging Opportunity* (2007)

Agenda

- **15 minute presentation**
- **Five minute question and answer**
- **Discussion**

Effects of Chronic Stress on Cancer Growth and Progression

Anil K. Sood, MD, Professor
Professor
Departments of Gynecologic Oncology and
Cancer Biology
Director, Ovarian Cancer Research

THE UNIVERSITY OF TEXAS
MDANDERSON
CANCER CENTER

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



Gene-Social Environment Interactions in Cancer A Bioinformatic Approach

Steven W. Cole, PhD

Associate Professor

Department of Medicine

Division of Hematology-Oncology

UCLA School of Medicine

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- **Facilitate knowledge of this emerging area in the NCI behavioral research portfolio**
- **Obtain BSA input on how NCI can best:**
 - **Expand the breadth and depth of this transdisciplinary science**
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Biobehavioral Influences on Cancer Biology

AN EMERGING OPPORTUNITY

Effects of Chronic Stress on Cancer Growth and Progression

March 5, 2007

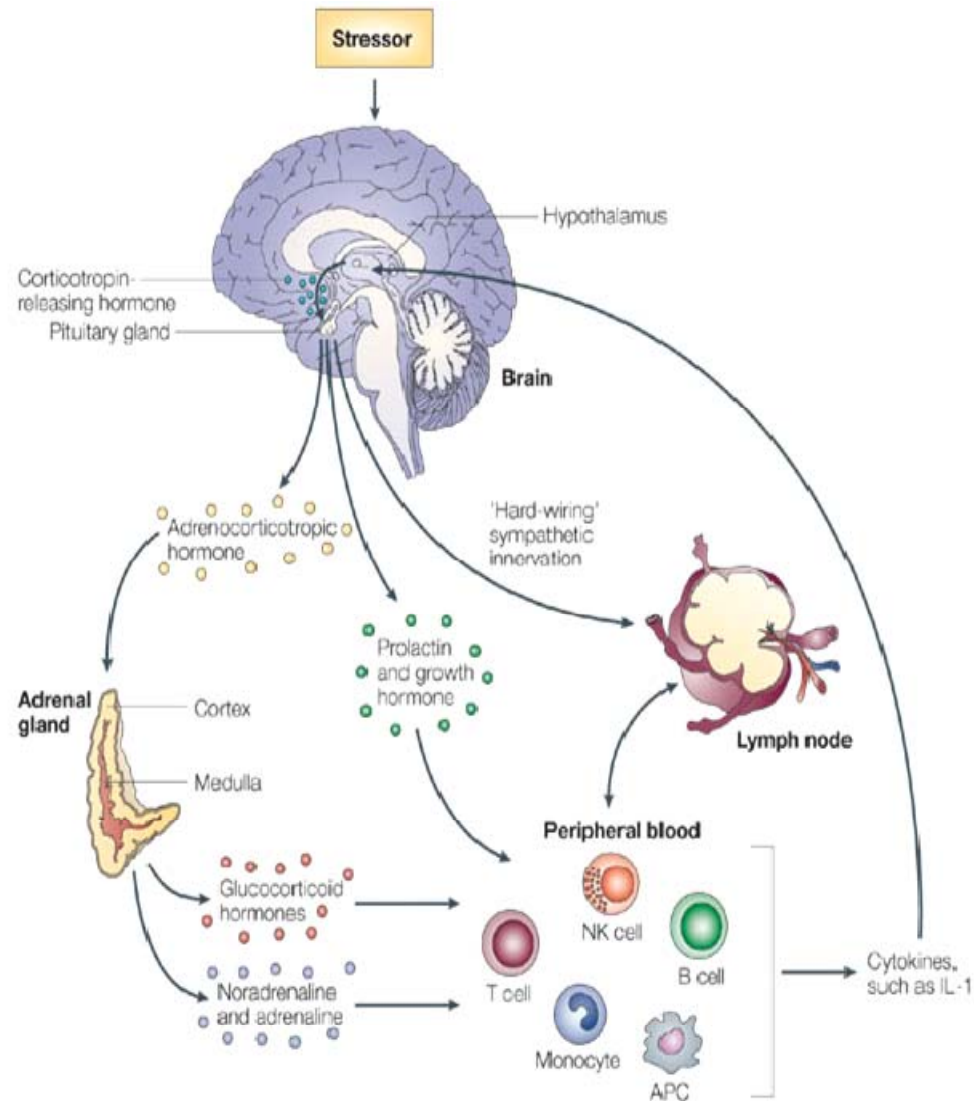
**Anil K. Sood, M.D., Professor
Director, Ovarian Cancer Research
Departments of Gynecologic Oncology
and Cancer Biology**

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER

OVERVIEW

- ❖ **Response to stress**
- ❖ **Mechanisms of effects on tumor microenvironment**

The Stress Response



Glaser and Kiecolt-Glaser, *Nat Rev Immunol*, 2005

Effects of Chronic Stress

❖ Immune System:

decrease cell mediated immunity
(i.e., natural killer cells, lymphocytes)

decrease humoral response
(i.e., antibodies)

Glaser and Kiecolt-Glaser, *Nat Rev Immunol*, 2005

❖ Cancer Biology:

- modulate apoptosis
- increase matrix metalloproteinases
- increase in VEGF

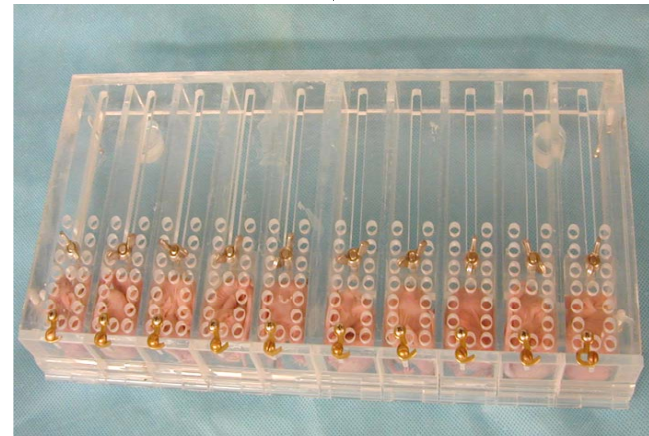
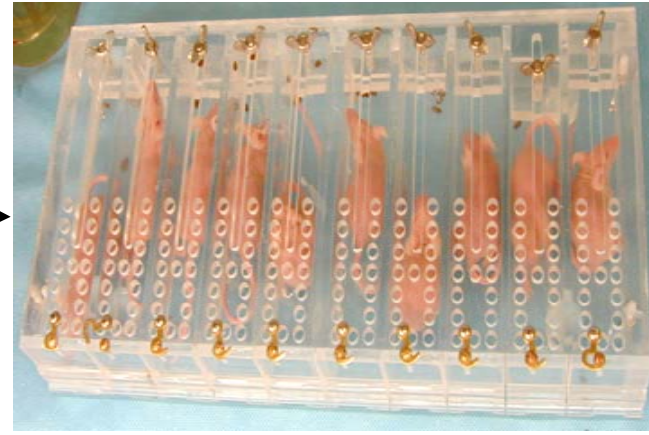
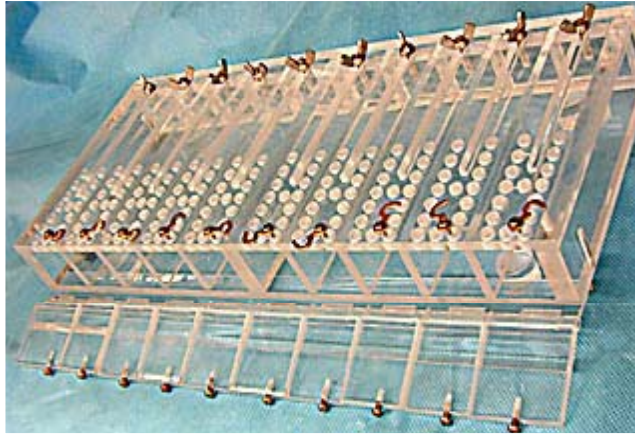
Lutgendorf, Sood et al., *Cancer*, 2002

Lutgendorf, Sood et al., *Clin Cancer Res*, 2003

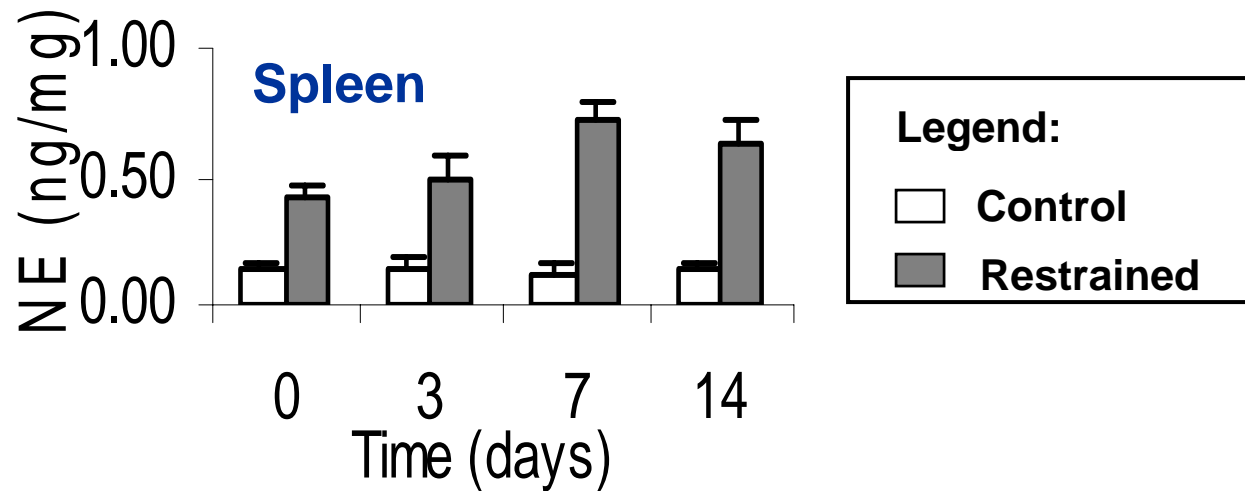
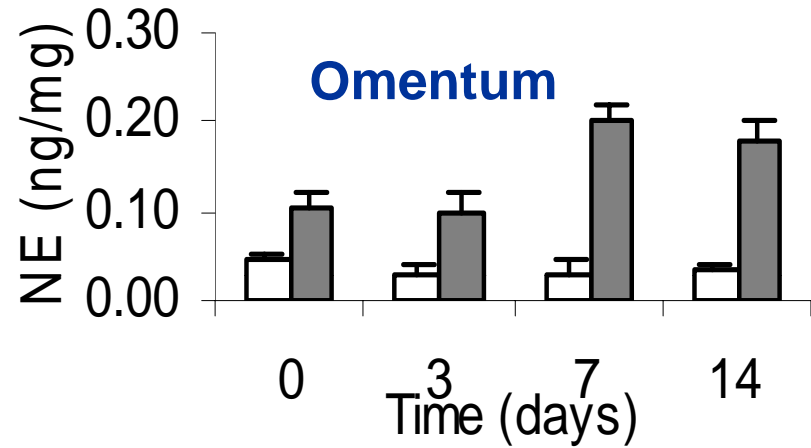
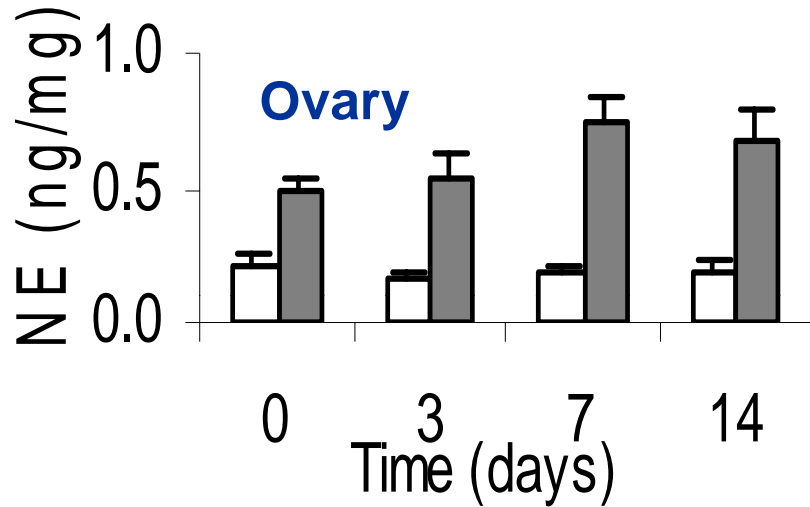
Antoni...Sood, *Nat Rev Cancer*, 2006

***In Vivo* Effects of Chronic Stress**

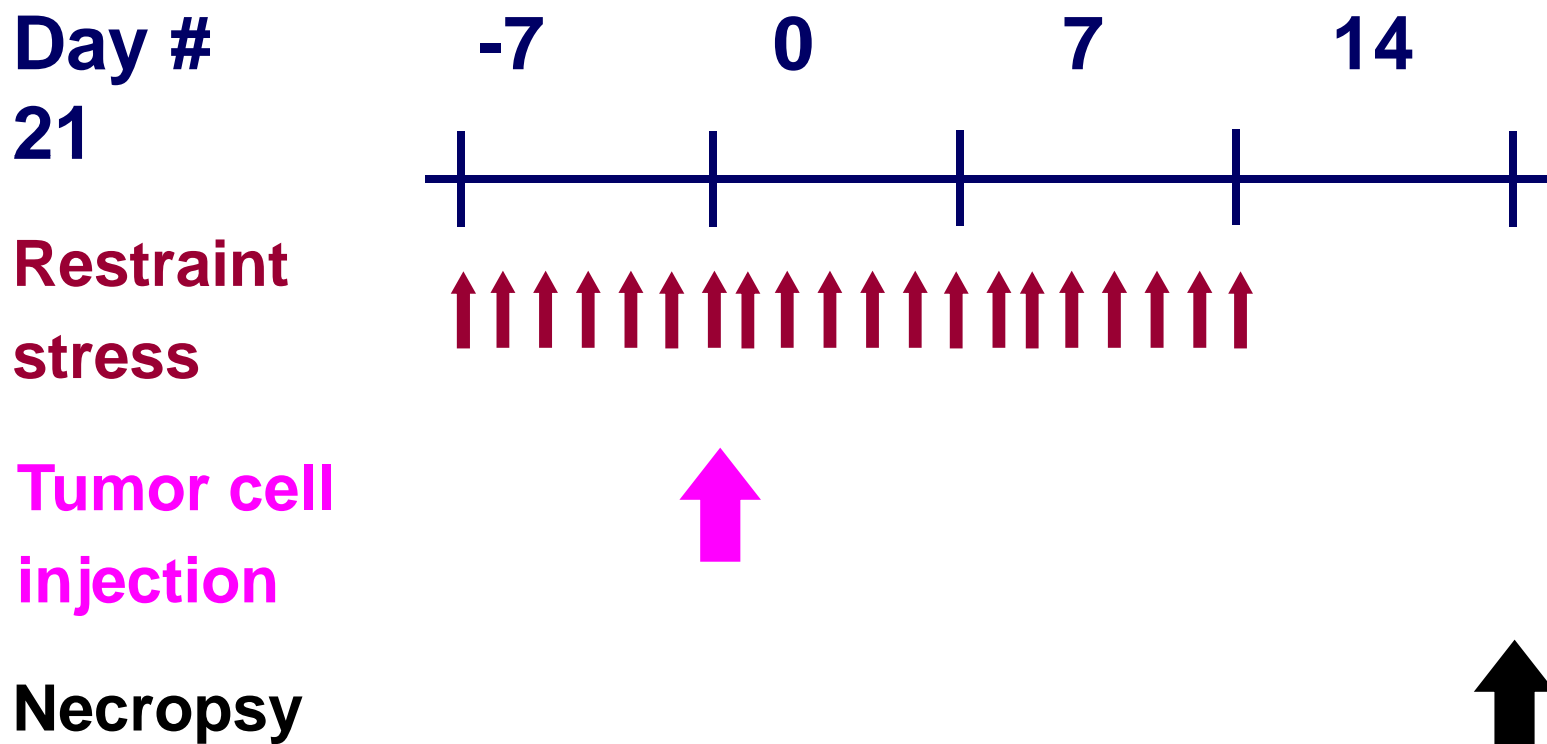
Development of a Model



Norepinephrine Levels

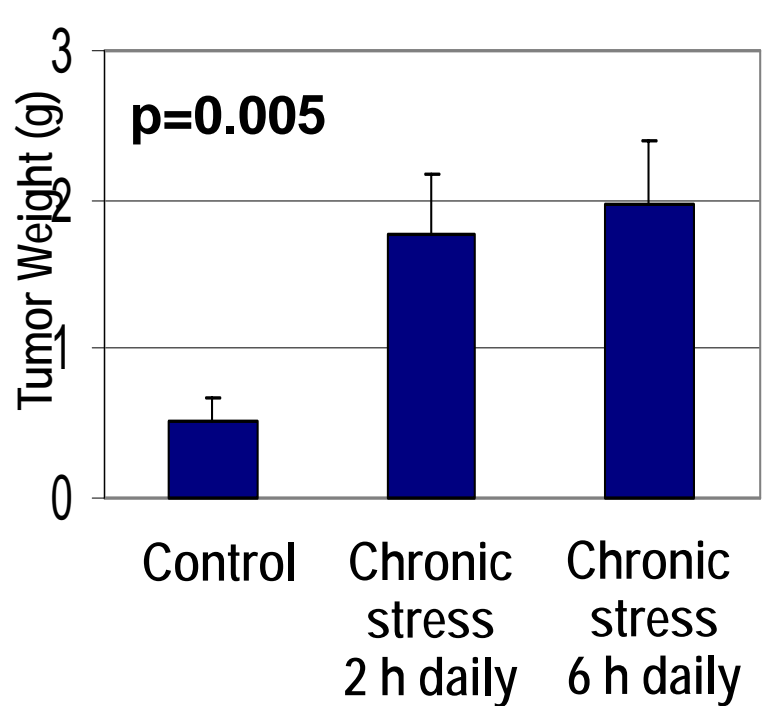


Schema of Chronic Stress Model

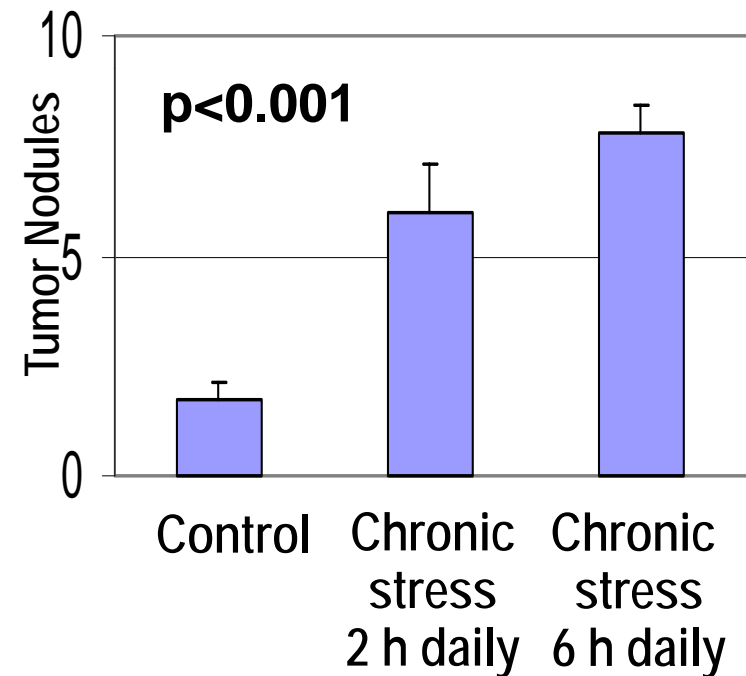


Effect of chronic stress on orthotopic HeyA8 ovarian cancer

Mean Tumor Weight



Mean Tumor Nodules



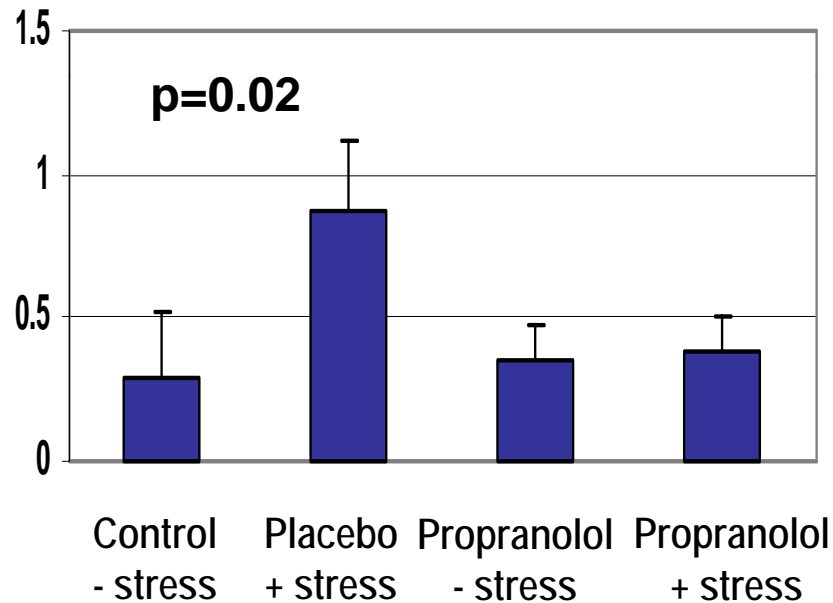
Effect of chronic stress on orthotopic ovarian cancer

- ❖ Controls had disease confined to the peritoneal cavity
- ❖ 50% of stressed animals had parenchymal liver, splenic, or pleural metastasis

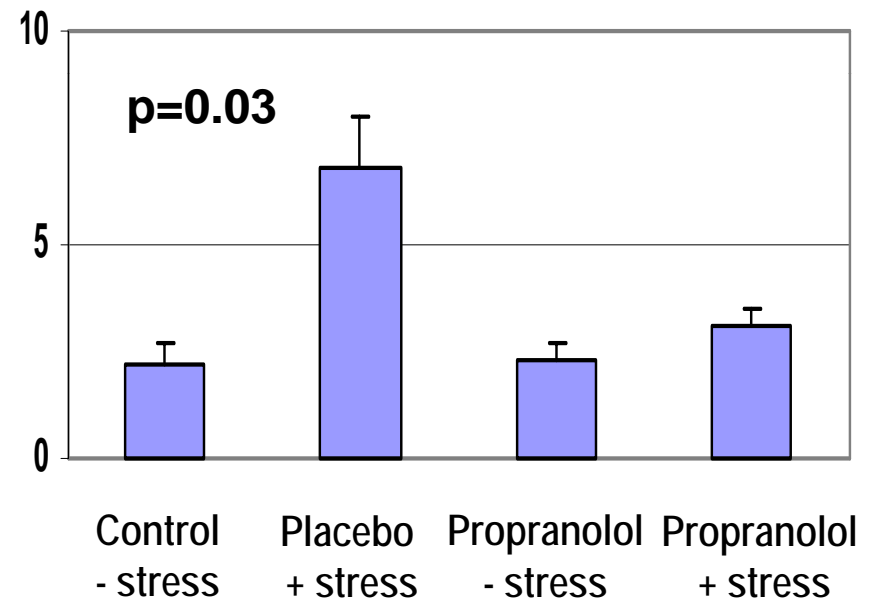


Effect of chronic stress \pm β -blockade on orthotopic HeyA8 ovarian cancer

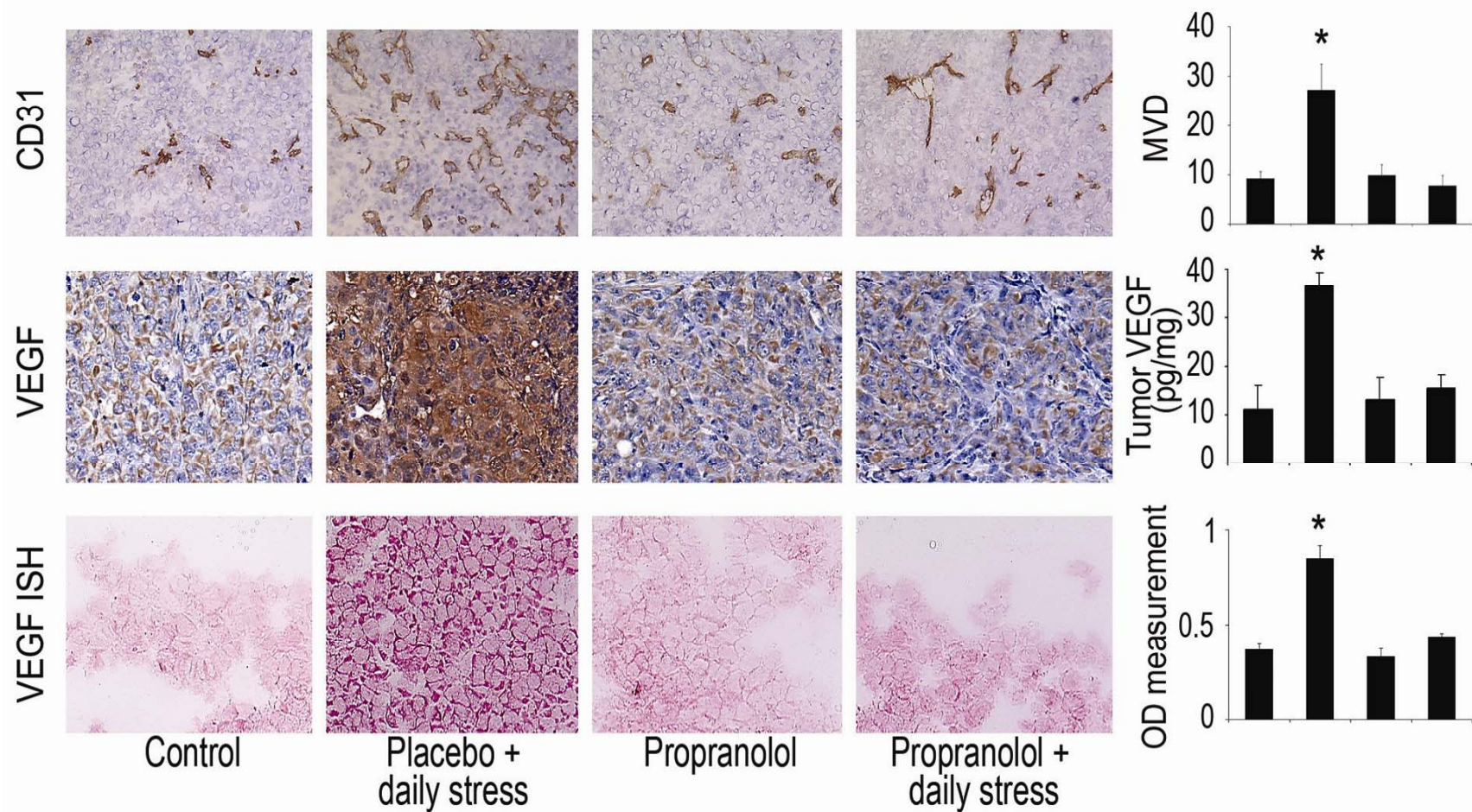
Mean Tumor Weight



Mean Tumor Nodules

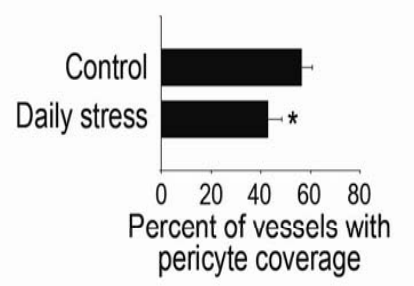
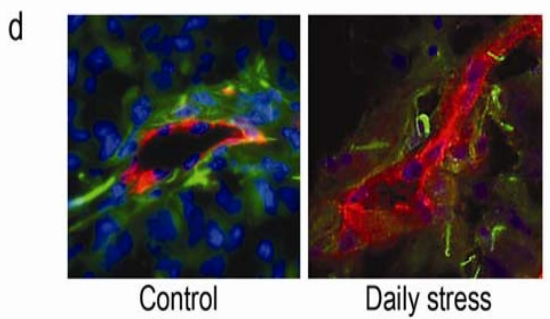
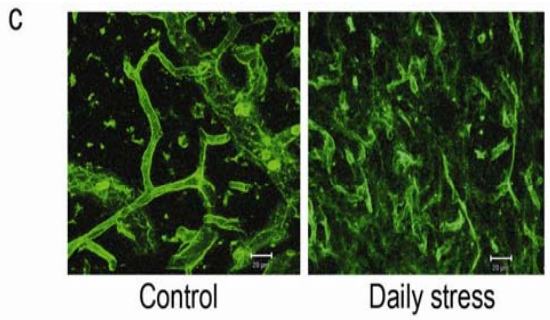
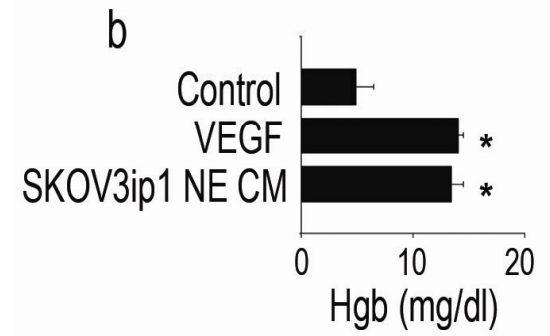
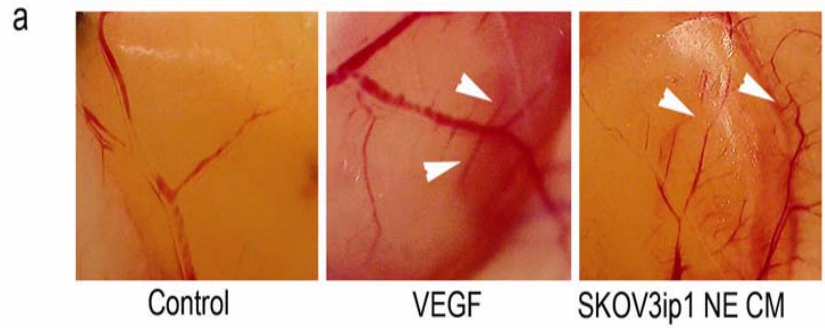


Effect of chronic stress \pm β -blockade on angiogenesis in ovarian carcinoma



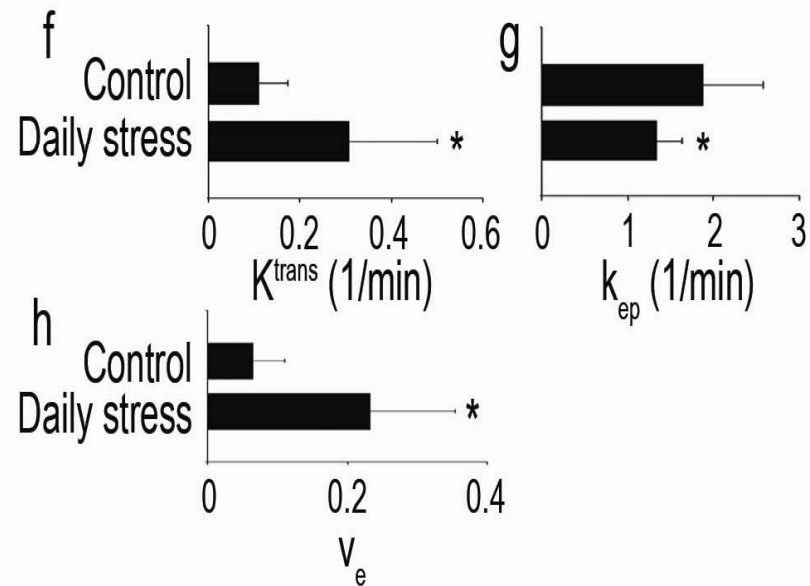
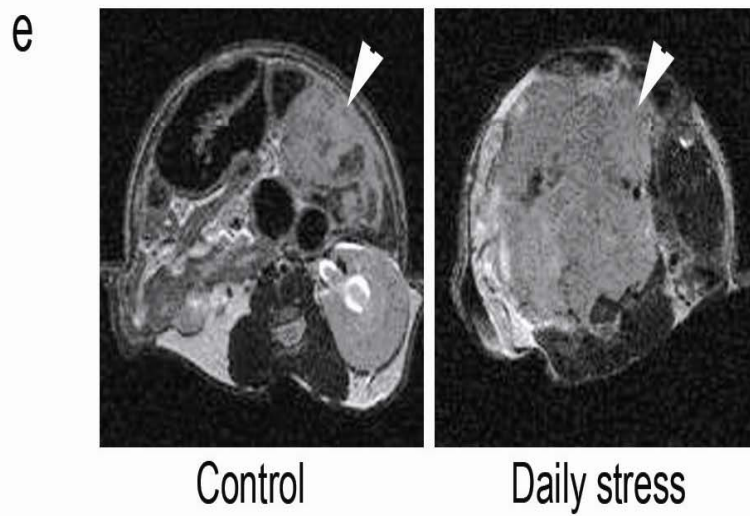
Thaker...Sood, *Nature Med*, 2006

Effect of chronic stress on angiogenesis

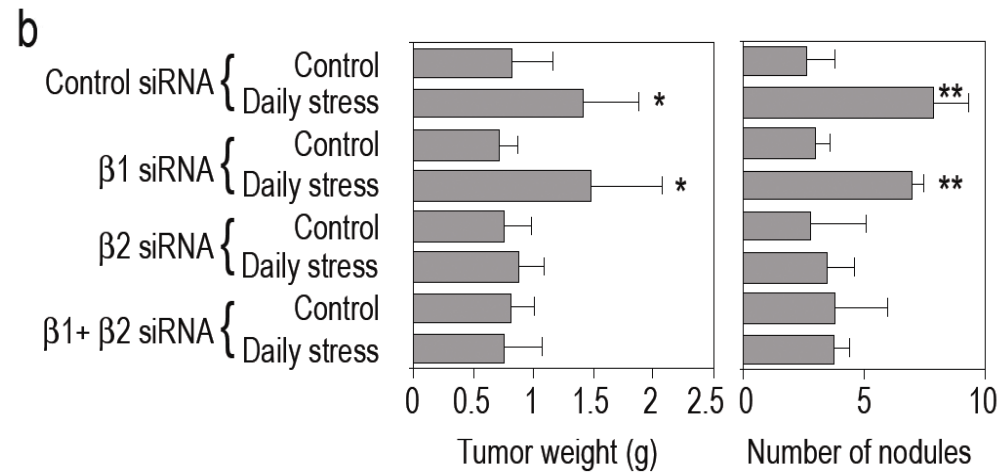
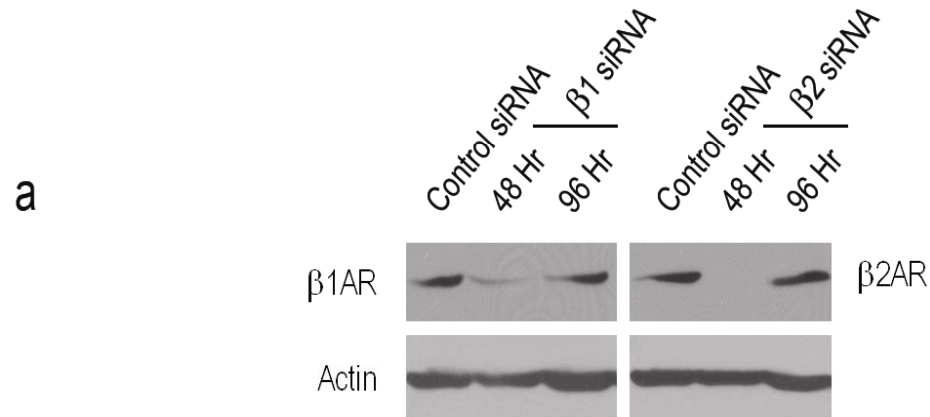


Thaker...Sood, *Nature Med*, 2006

Effect of chronic stress on angiogenesis

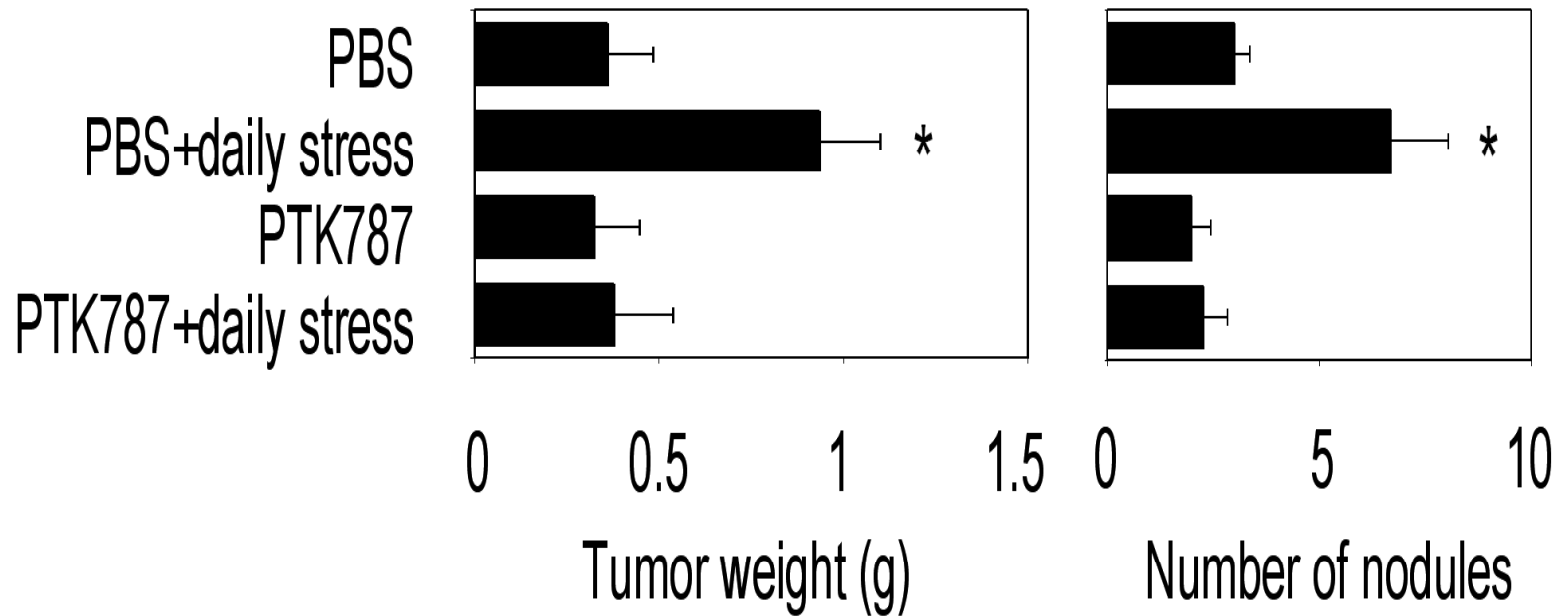


Effect of β -receptor silencing



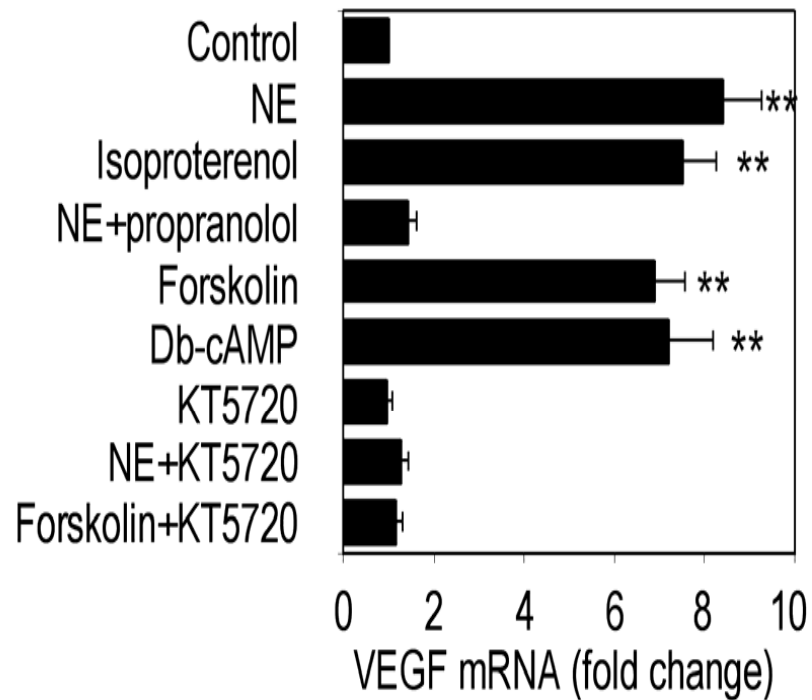
* $p < 0.01$
** $p < 0.001$

Effect of VEGF-R inhibition

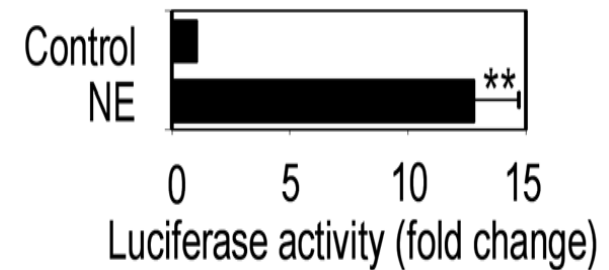


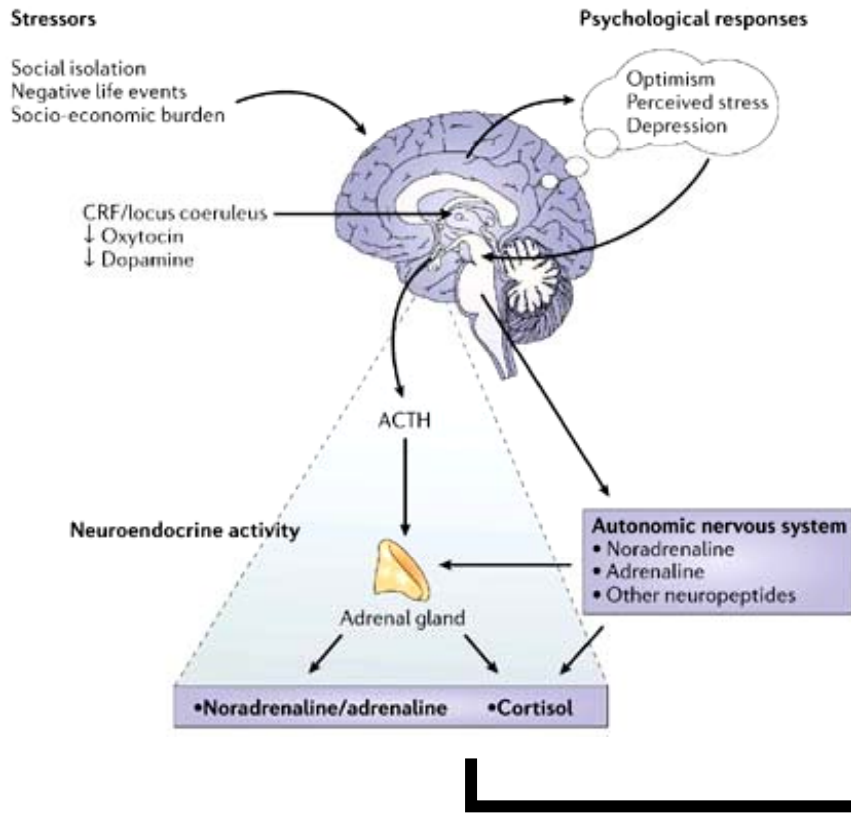
Mechanisms of VEGF Activation

a

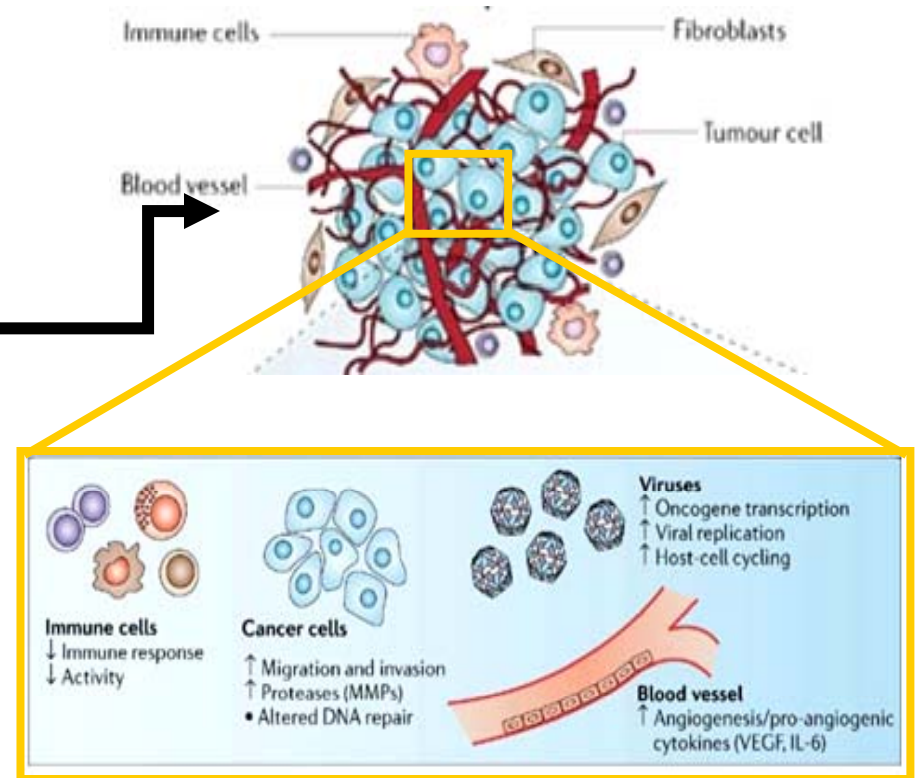


b





Effects of stress on tumor microenvironment



Antoni, Lutgendorf, Cole, Dhabhar, Sепhton, McDonald, Stefanek, Sood
Nature Reviews Cancer, 2006

Conclusions

- ❖ **Chronic stress not only accelerates ovarian cancer growth, but also causes a more invasive pattern of spread in this model.**
- ❖ **These effects are mediated by beta-receptors that establish a favorable microenvironment for tumor growth.**

Future Directions

- ❖ **Examine the microenvironment in human tumors in the context of behavioral factors**
- ❖ **Mechanisms (immune and non-immune) by which biobehavioral factors affect tumor growth**
- ❖ **Develop intervention strategies – behavioral and/or pharmacological**



Collaborators

- ❖ **Susan Lutgendorf**
- ❖ **Steve Cole**
- ❖ **Robert Newman**
- ❖ **Gabriel Lopez-Berestein**

Support

- ❖ **NCI (CA110793-01)**
- ❖ **NCI (CA109298-01)**
- ❖ **Ovarian Cancer**
- ❖ **SPORE**

Biobehavioral Influences on Cancer Biology

AN EMERGING OPPORTUNITY

Social environment and tumor biology: The role of glucocorticoid-mediated tumor cell survival

Suzanne Conzen, MD

Associate Professor

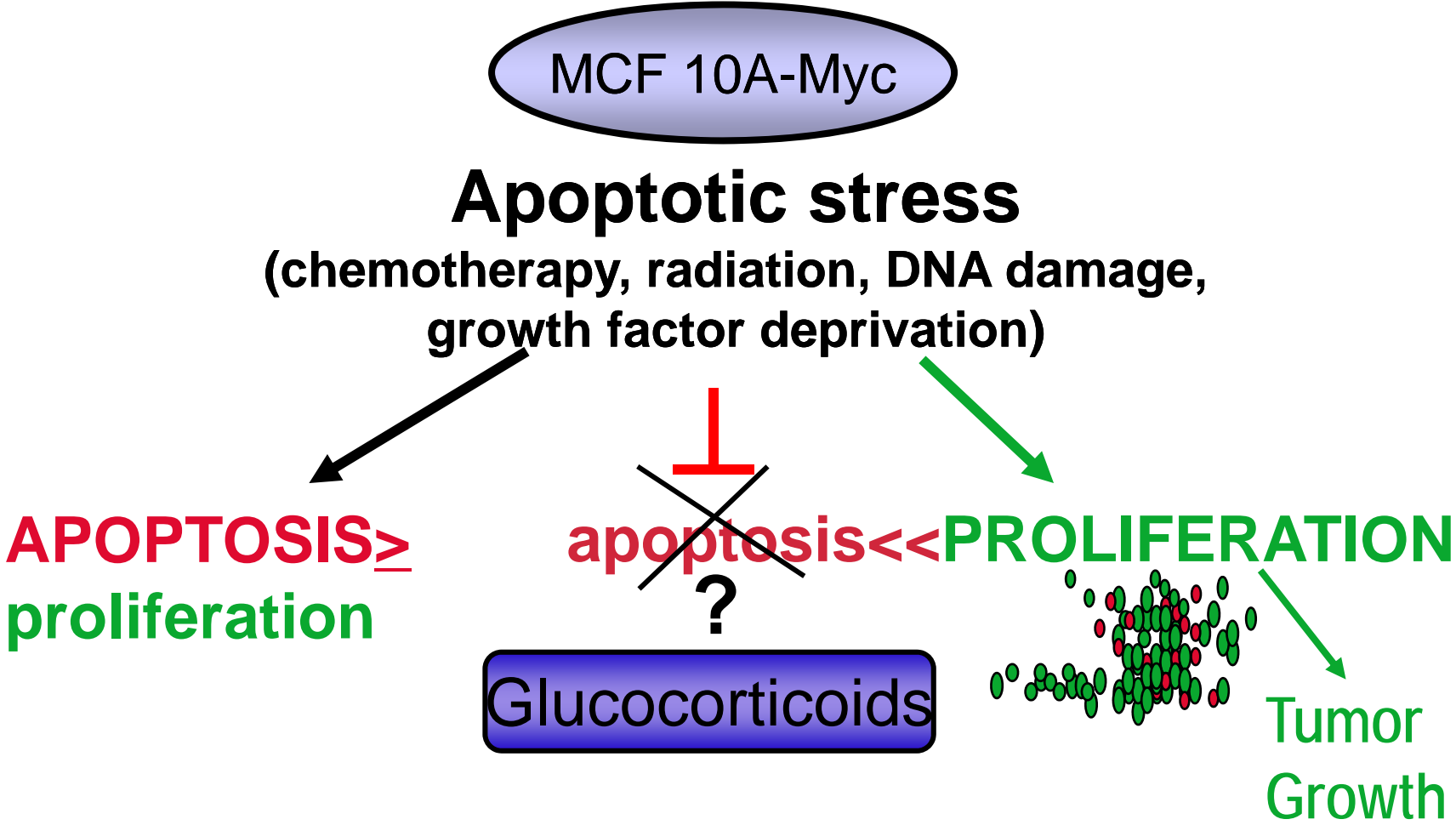
Department of Medicine and

The Ben May Department of Cancer Research

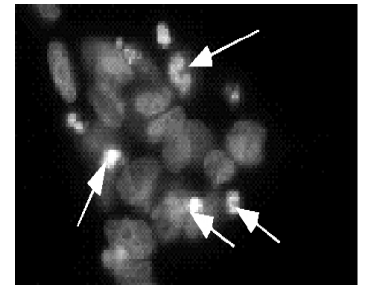
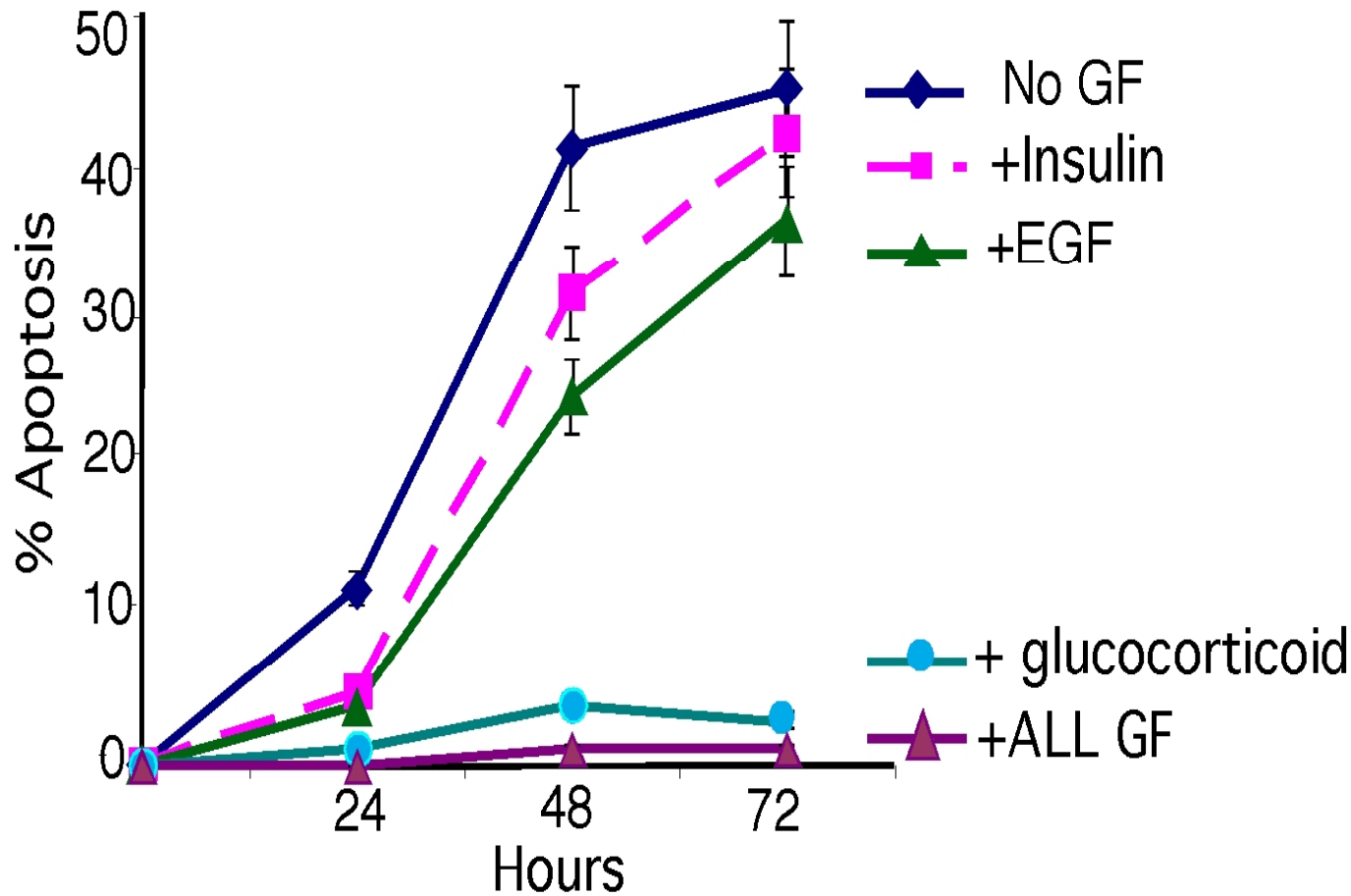
The University of Chicago



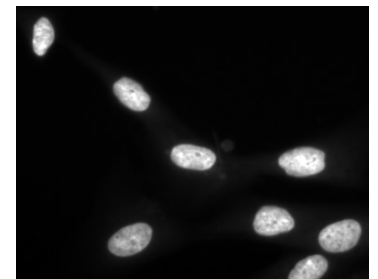
Identification of novel anti-apoptotic signals



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



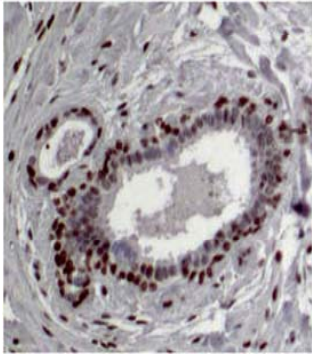
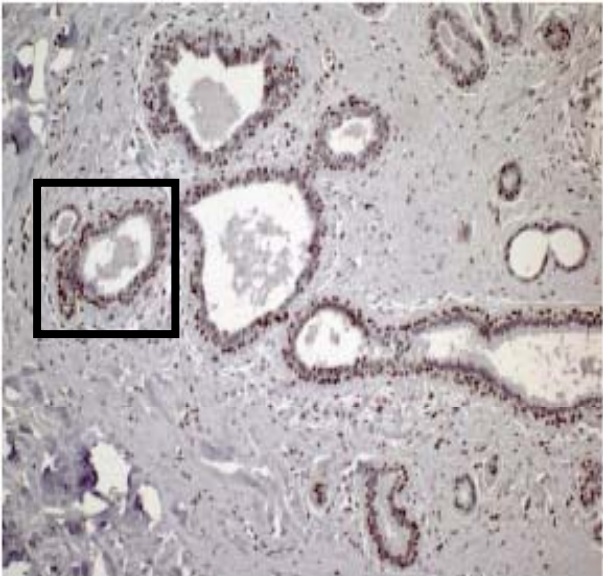
-GCs



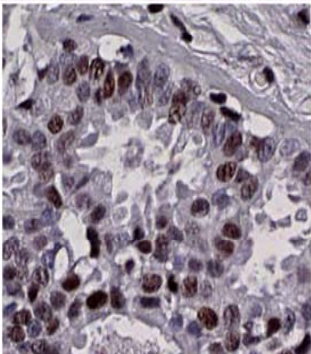
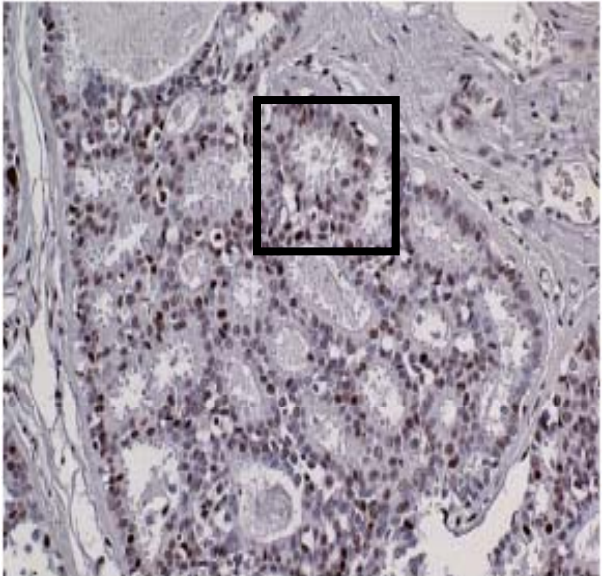
+GCs

Primary human breast epithelium and cancers express glucocorticoid receptors

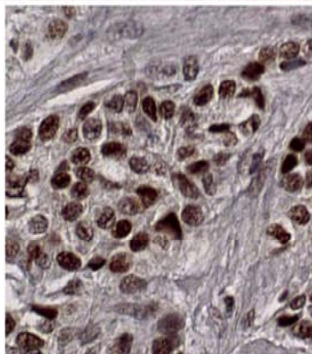
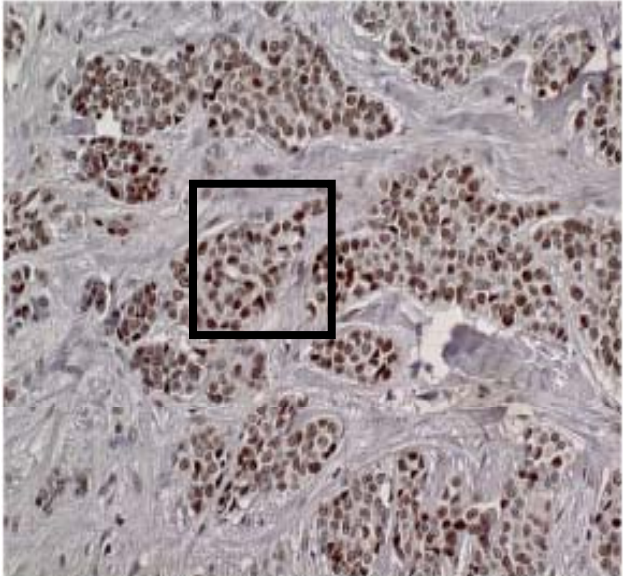
Normal



DCIS

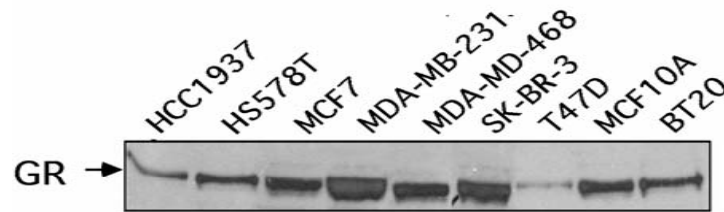


Invasive



Williams, Delgado and Conzen, In prep.

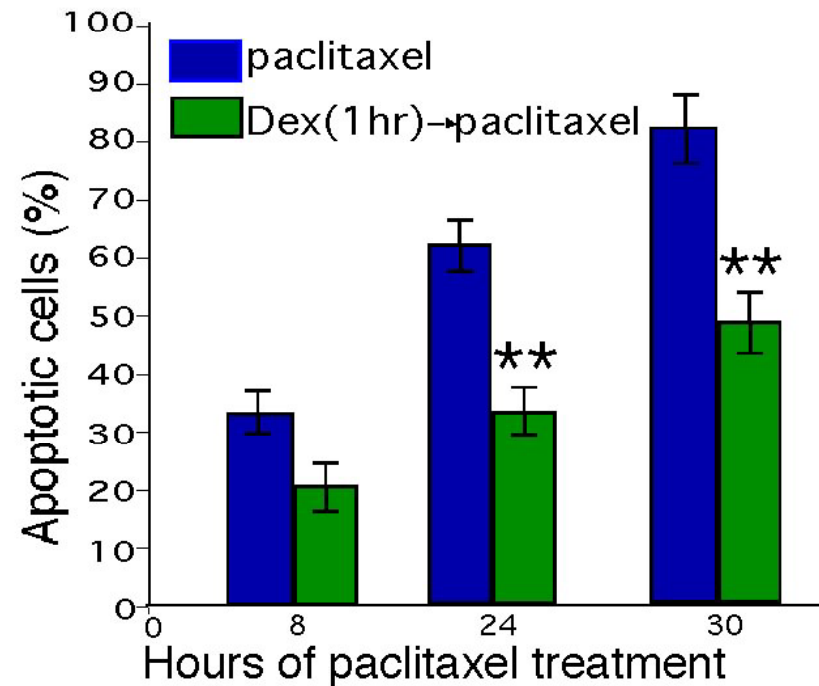
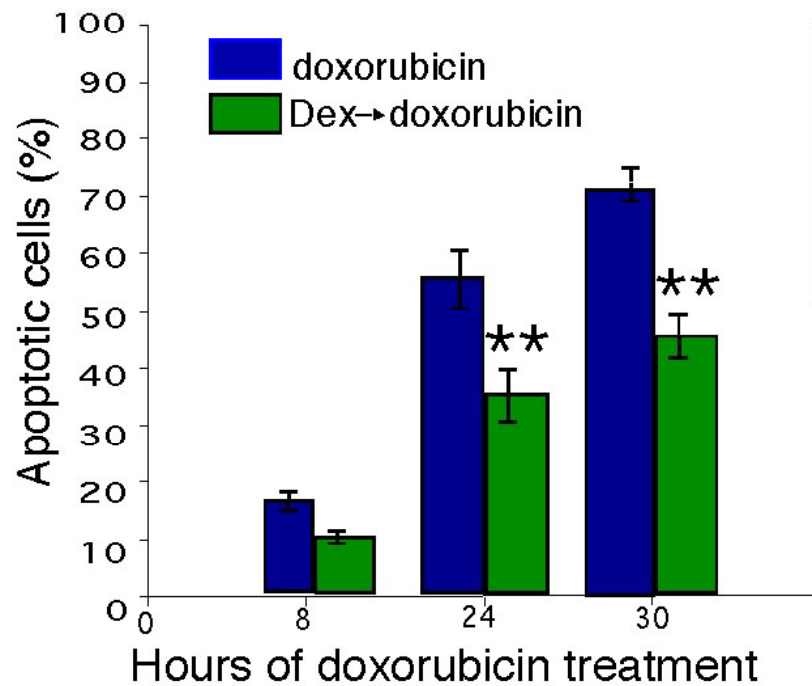
GCs inhibit chemotherapy-induced apoptosis



MCF-7

Western analysis

MDA-MB-231

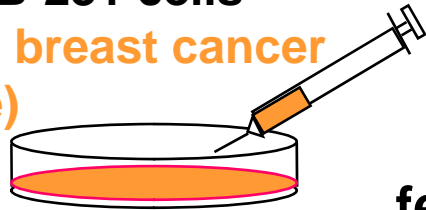


Mikosz et al., *JBC*, 2002

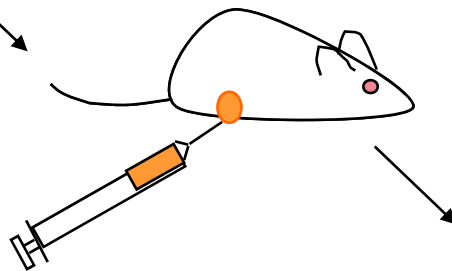
Wu et al., *Cancer Research* 2004

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

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

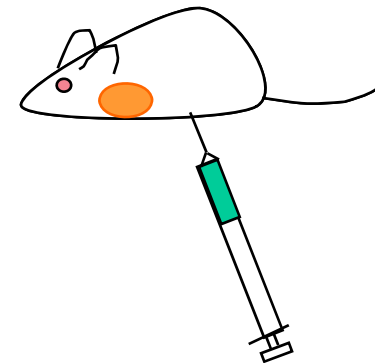


5-6 week old
female SCID mouse

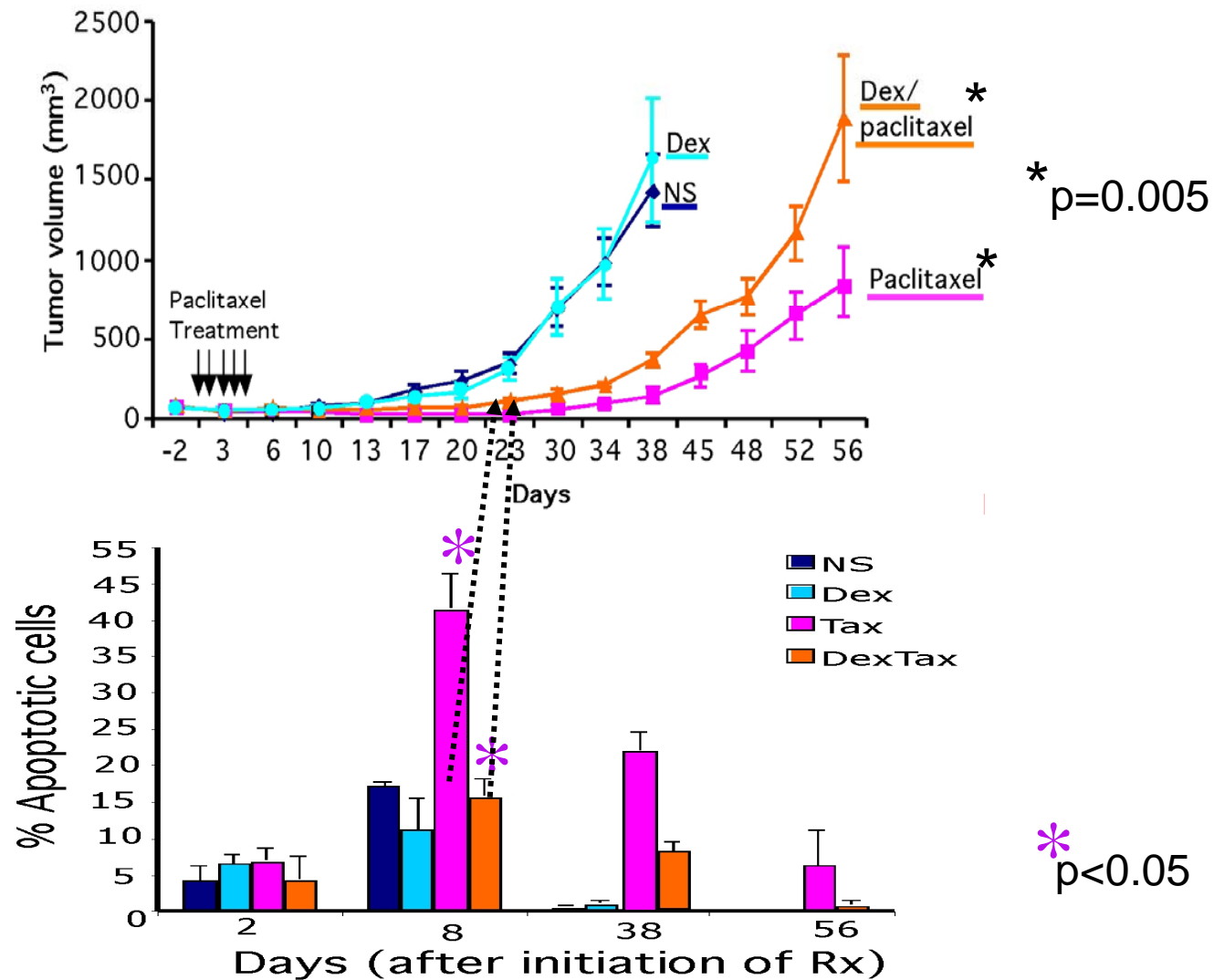


MDA-MB-231 injected
into mammary fat pad

Paclitaxel +/-Dex Days 1-5

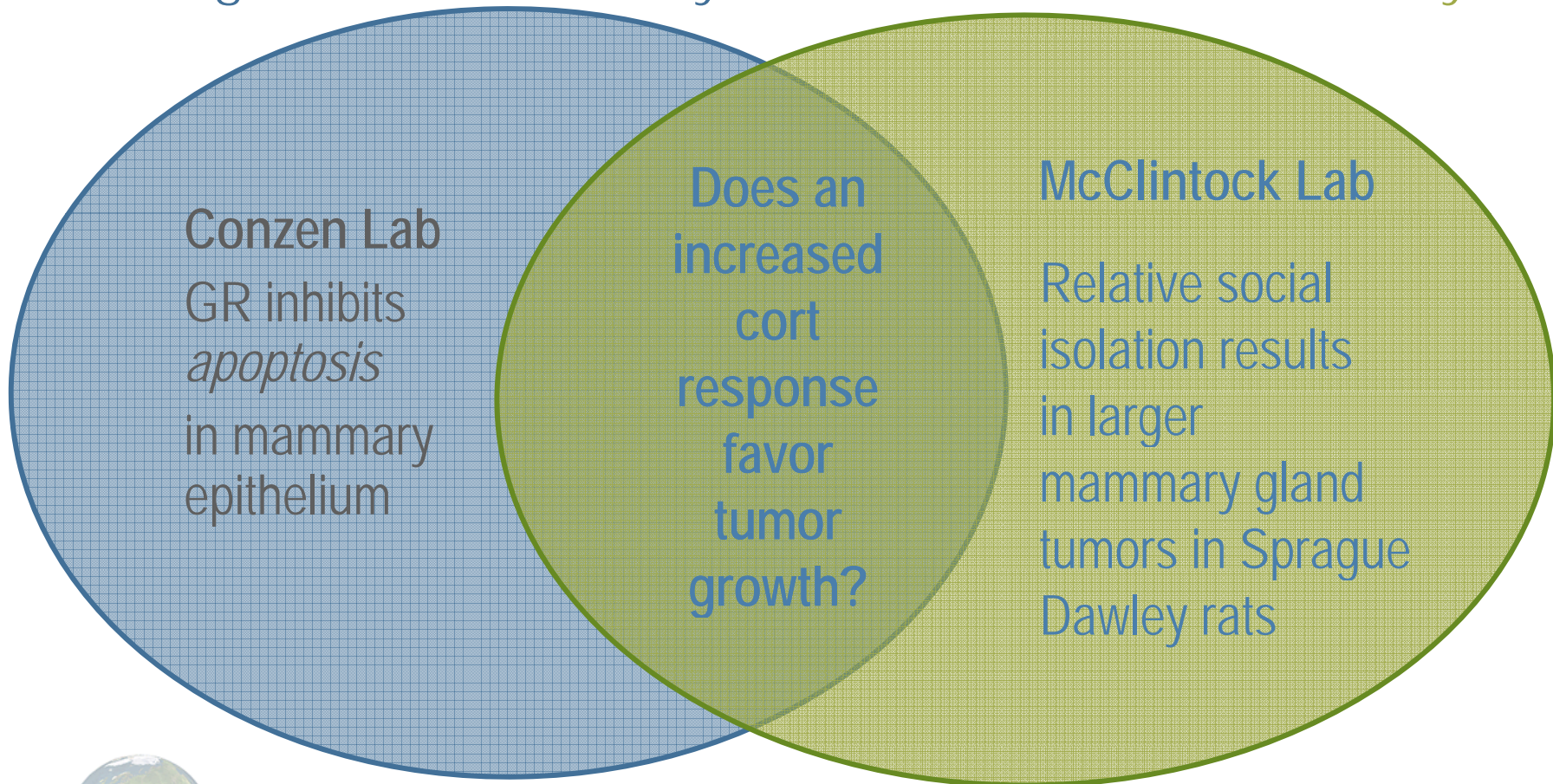


MB-MDA-231 xenografts: Glucocorticoids decrease paclitaxel-induced apoptosis



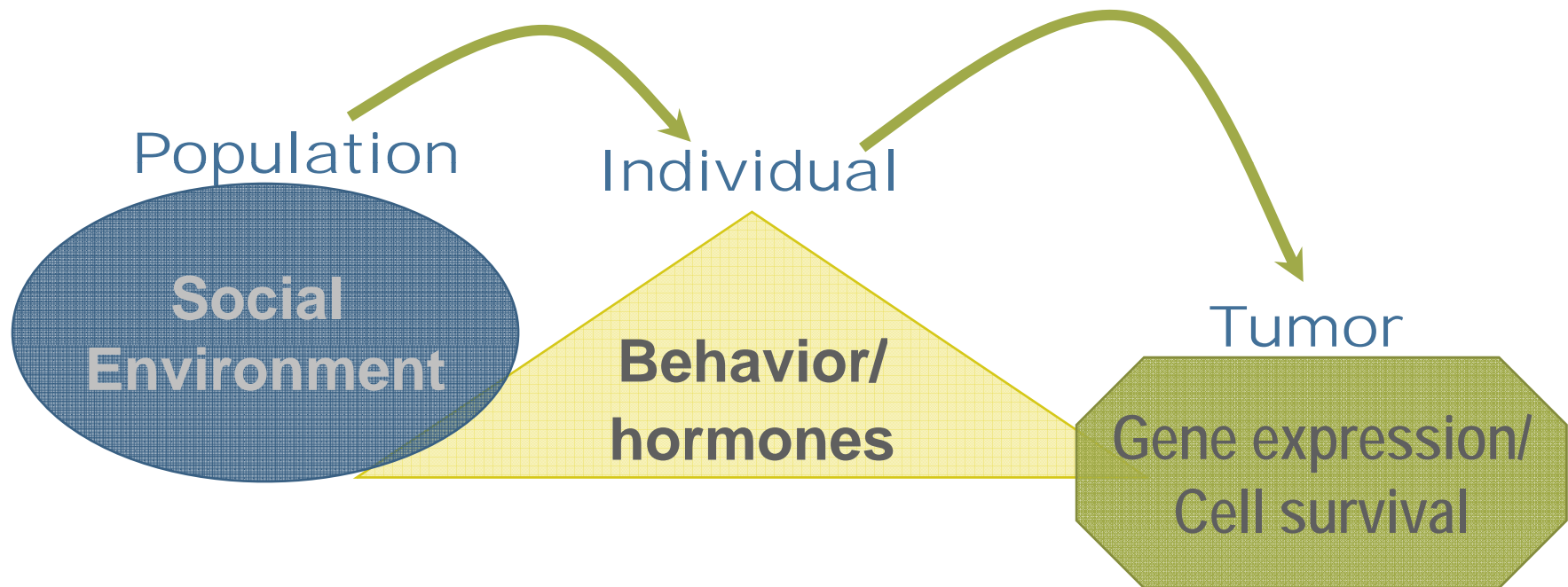
What is the basis of our transdisciplinary work with behavioral/social scientists?

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.

*

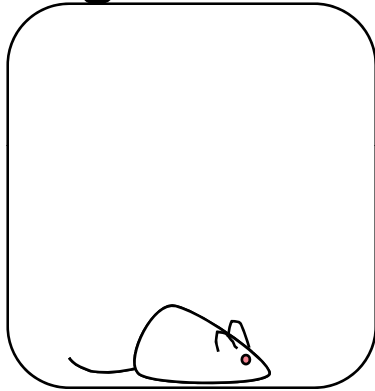


MMHCC
the Mouse Models
of Human Cancers Consortium



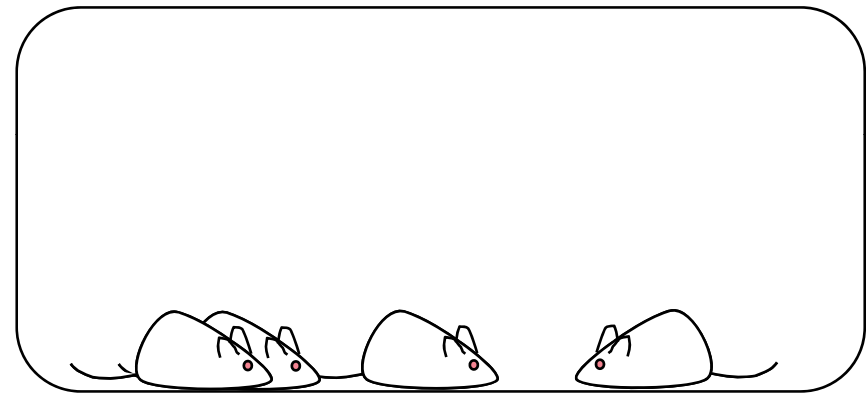
A Model of Social Isolation – SV40 Tag Mice

Single-housed



versus

Group-housed

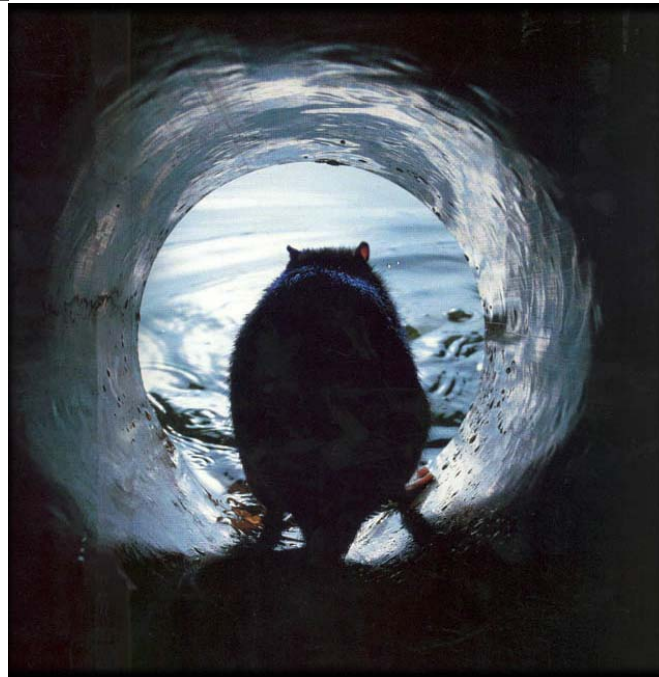
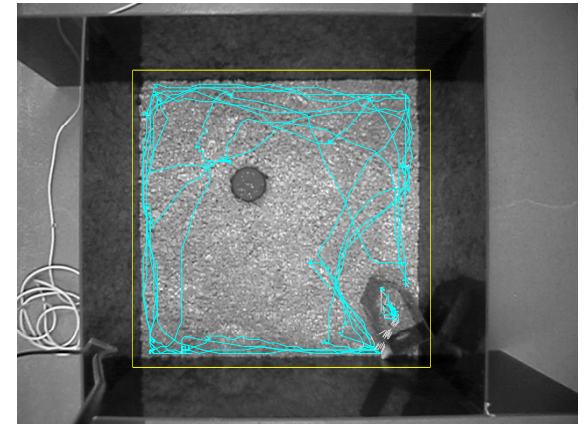
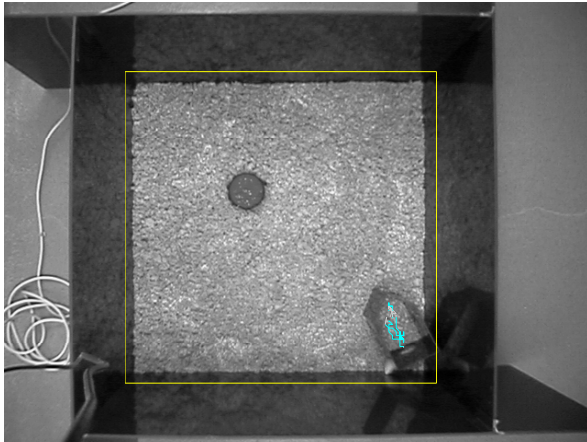


Hypothesis:

Chronic social isolation will result in

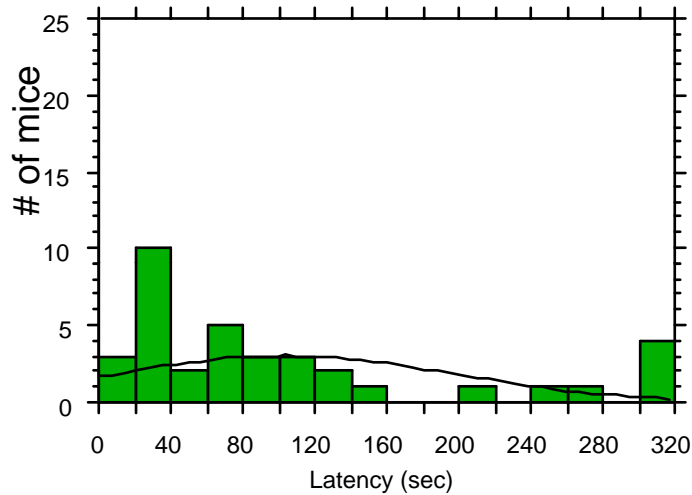
- an acquired vigilant behavioral phenotype
- increased corticosterone response to acute stressors
- increased mammary tumor growth (? inhibit apoptosis)

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



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

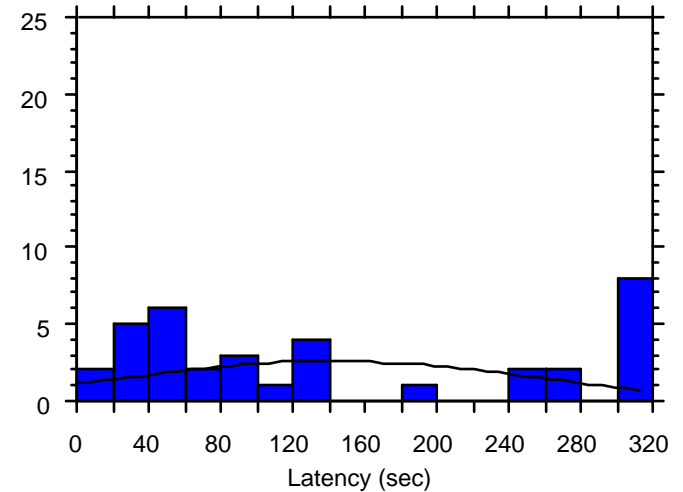
Grouped (n=36)



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

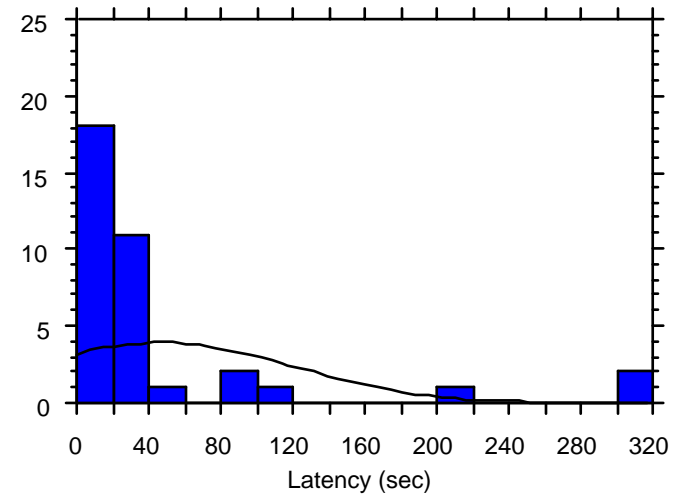
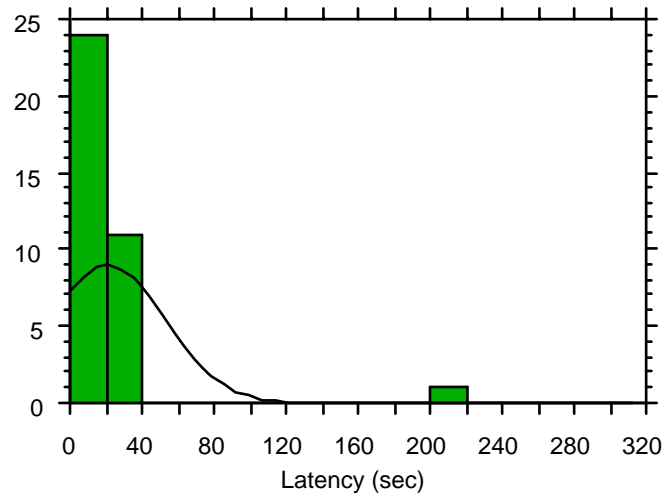
($p = 0.20$)

Isolated (n=36)



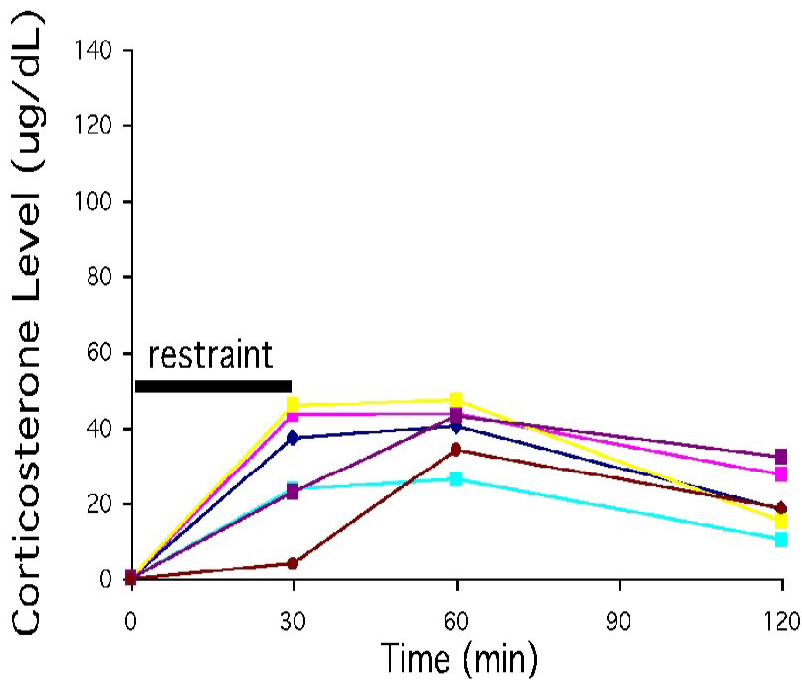
~ 13 weeks old
10 weeks of
differential
housing

($p = 0.018$)

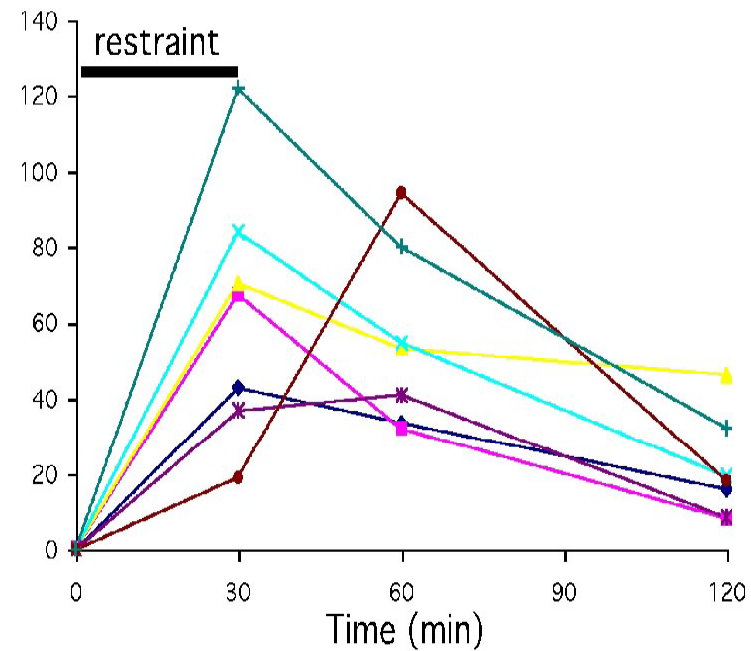


Endocrine response: Effect of social isolation on corticosterone levels following a mild stressor

Grouped



Isolated



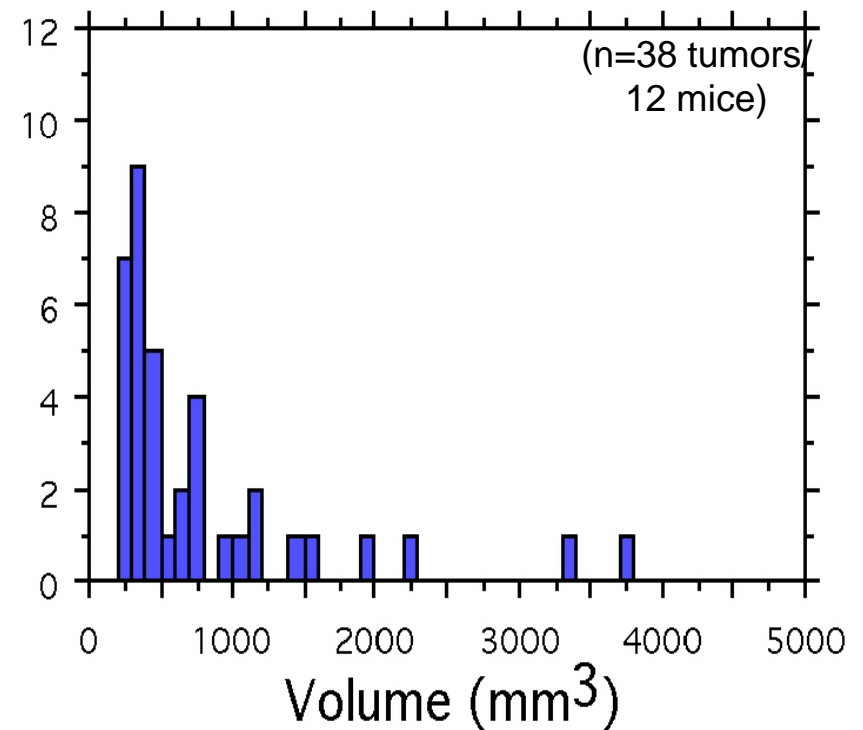
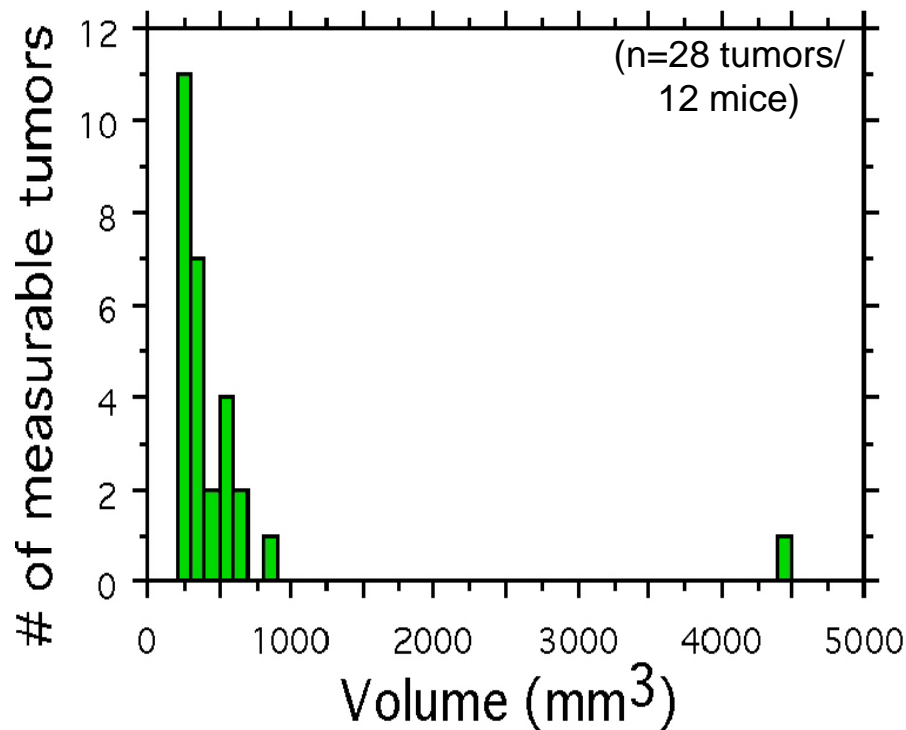
Slope of the rise: $p=.022$
Absolute increase: $p=.032$

Tumor growth: Effect of social isolation on mammary tumor size

(22 weeks)

Grouped (n=15)

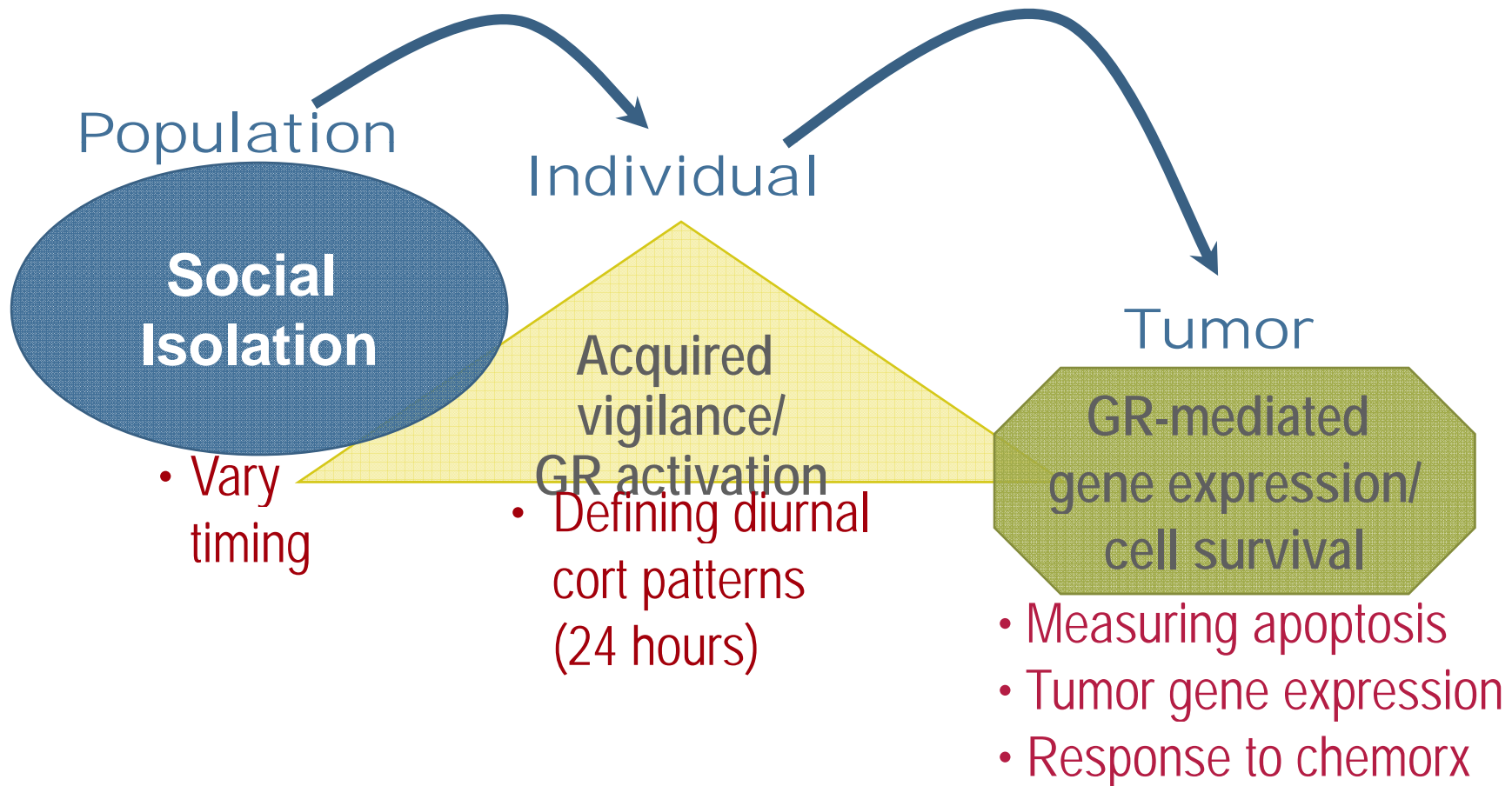
Isolated (n=15)



mixed effects ANOVA $p = .024$

How does social environment affect tumor growth?

Future Plans



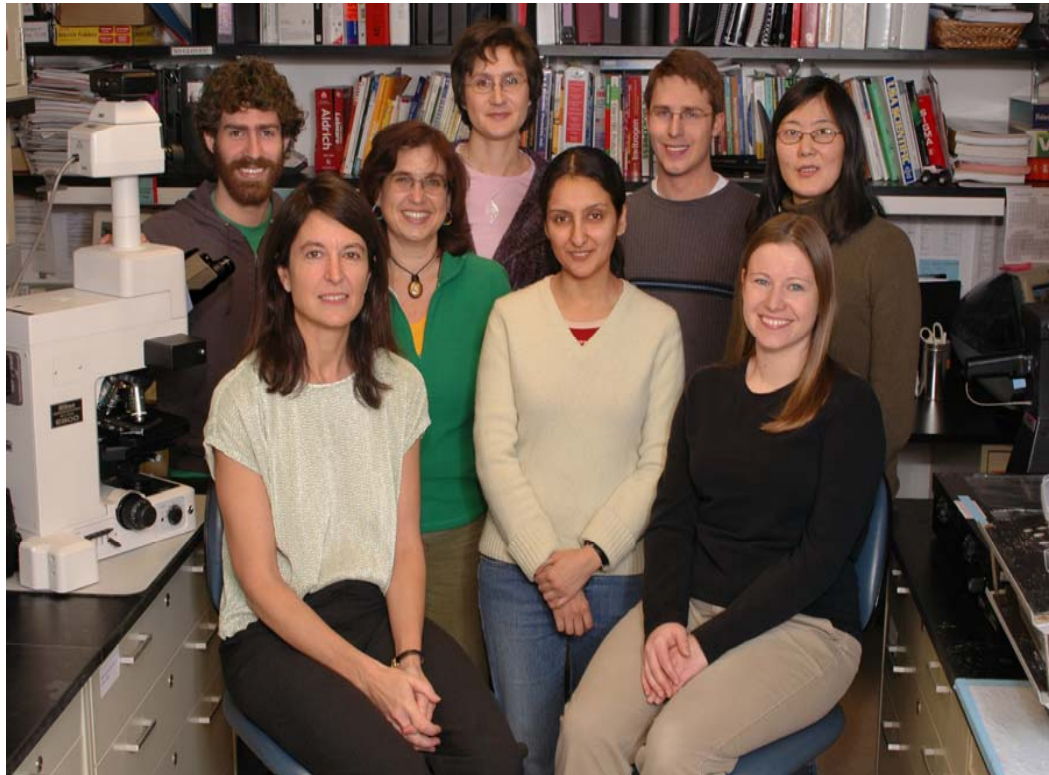
Translational Implications

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

Biobehavioral Influences on Cancer Biology

AN EMERGING OPPORTUNITY

Gene-Social Environment Interactions in Cancer

A bioinformatic approach

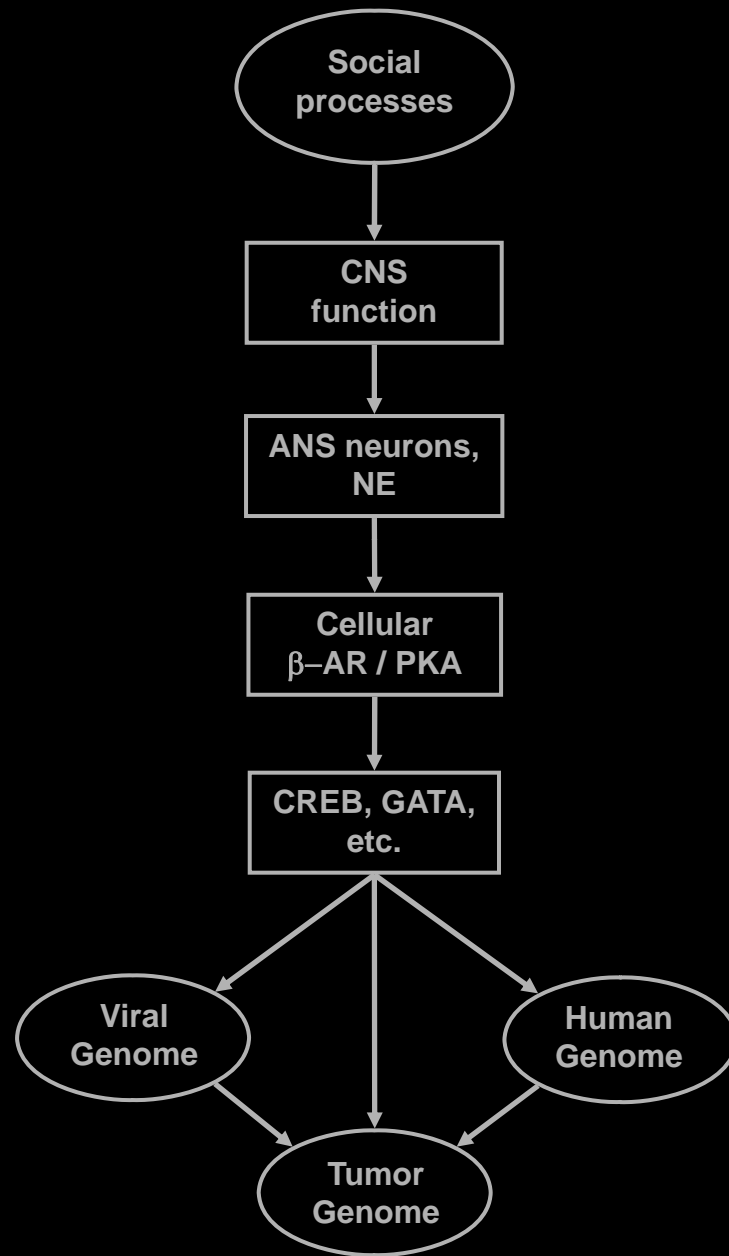
Steve W. Cole, Ph.D.

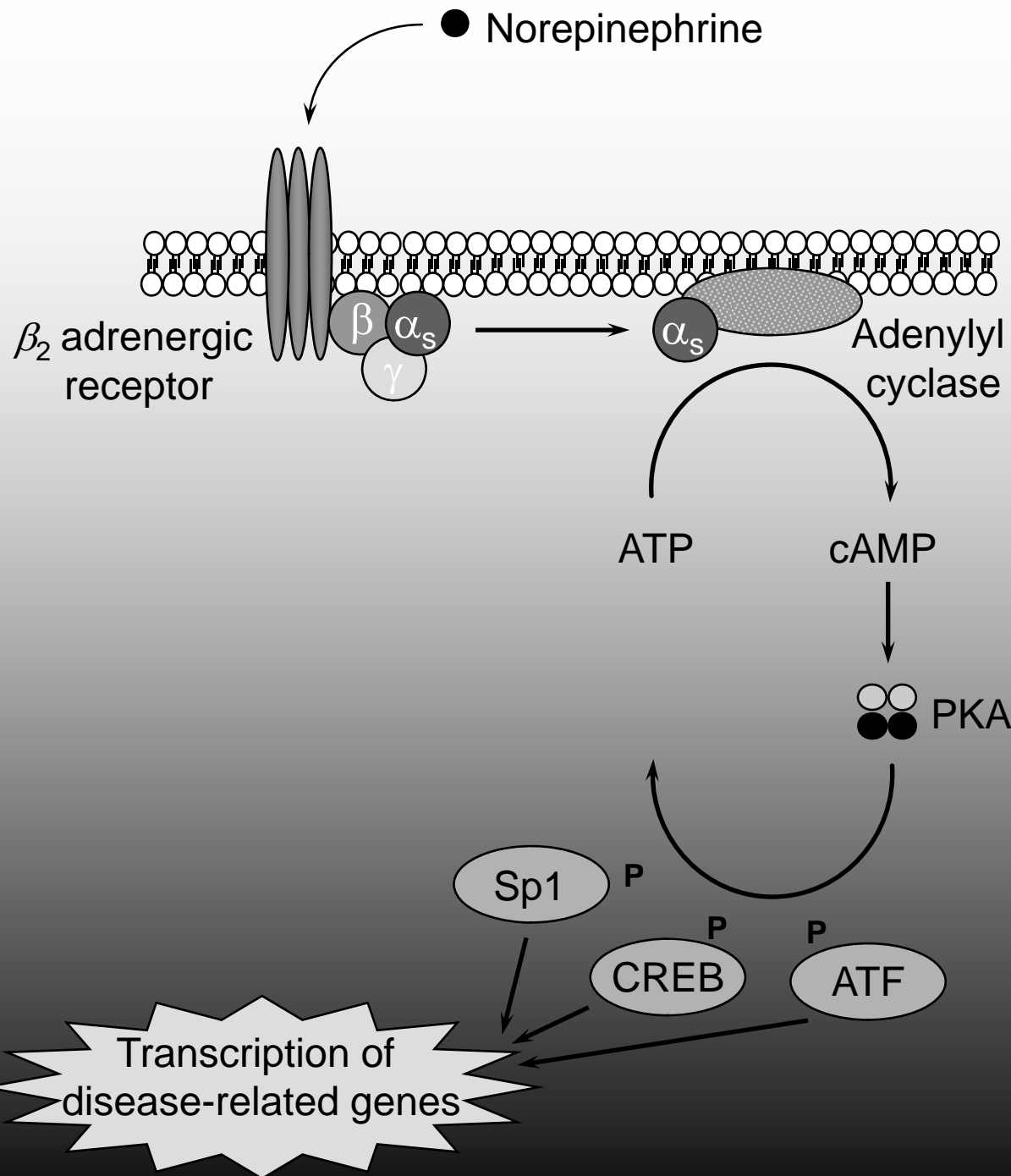
UCLA School of Medicine

Division of Hematology-Oncology

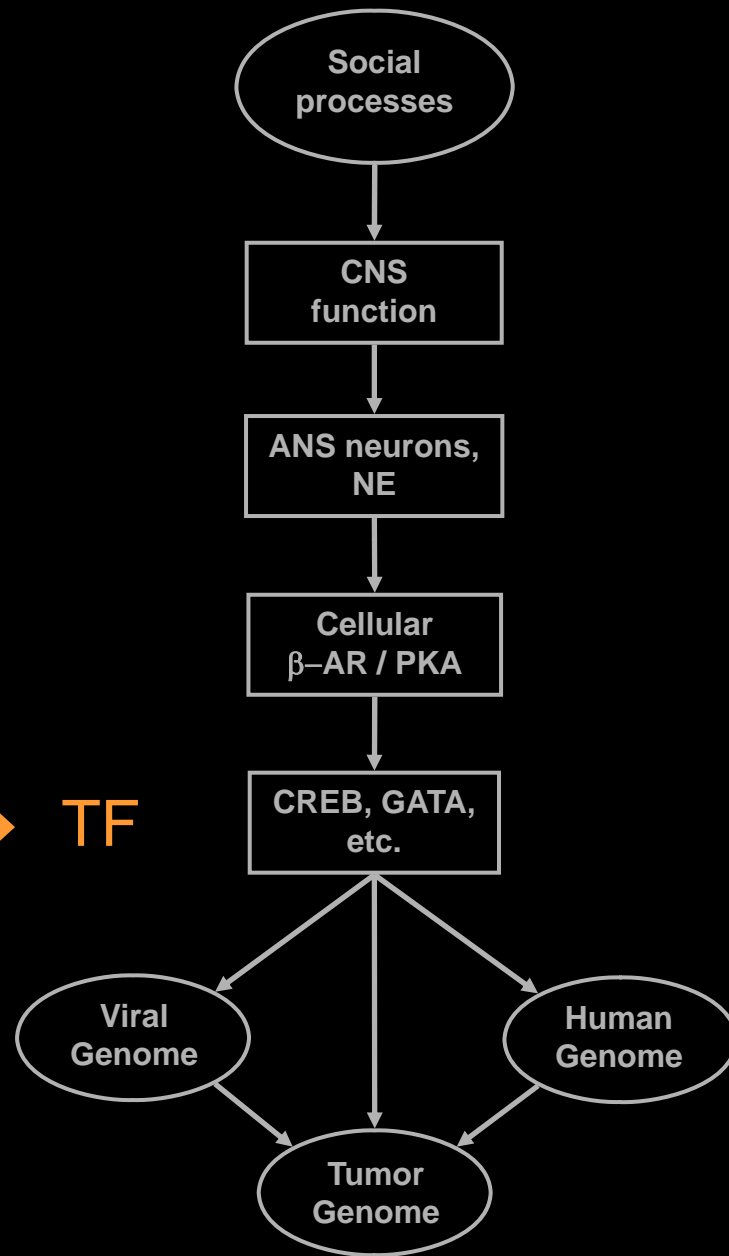
Biobehavioral regulation of gene expression in cancer

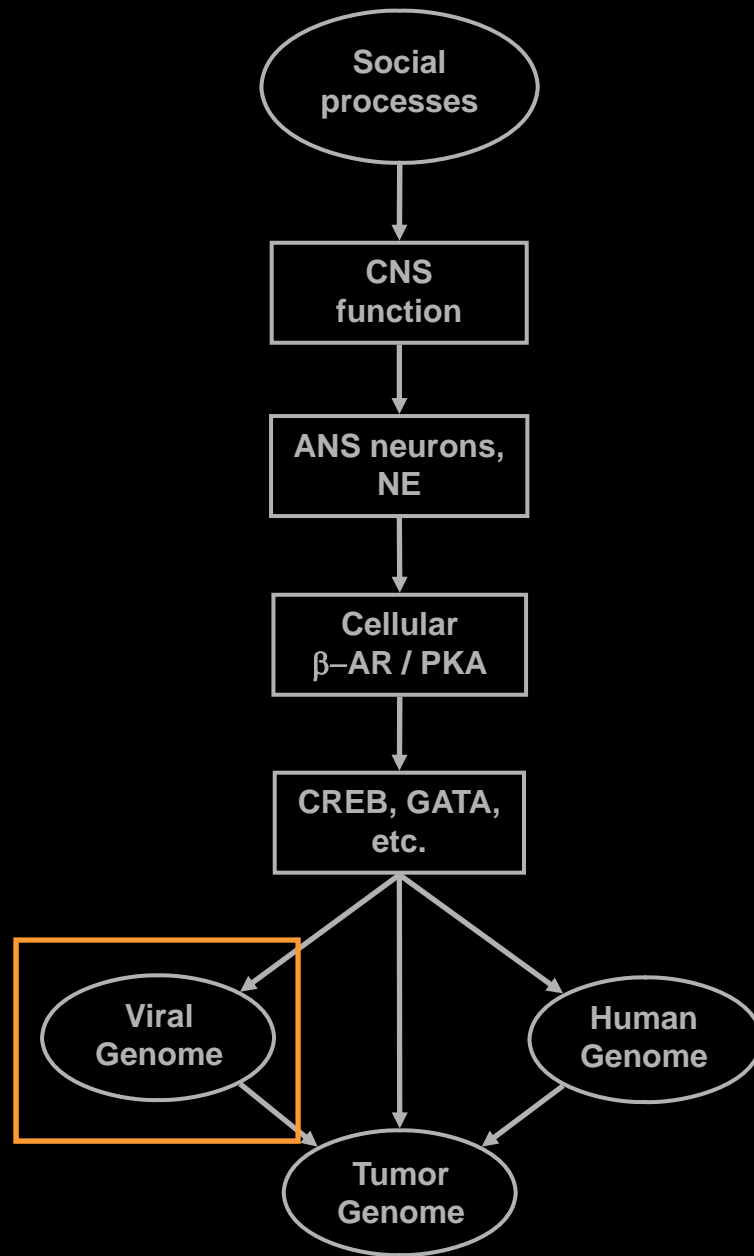
1. How do social factors regulate gene expression?
2. Are these “social signal transduction” pathways active in clinical cancer?
3. Do they shape the evolution of the tumor genome?
4. What are the prospects for protective intervention?



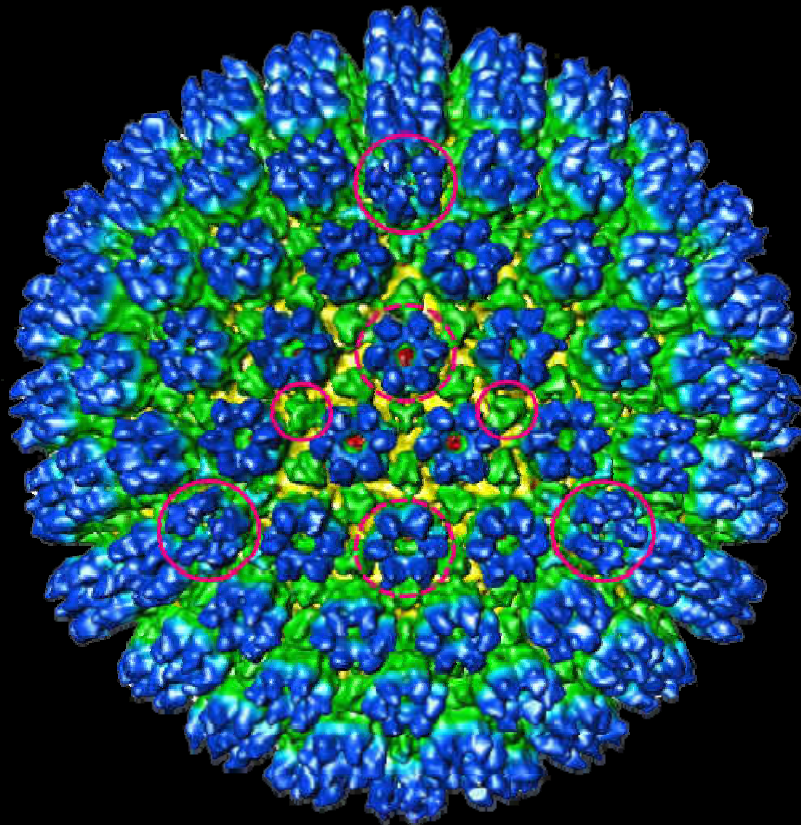


psychology → TF

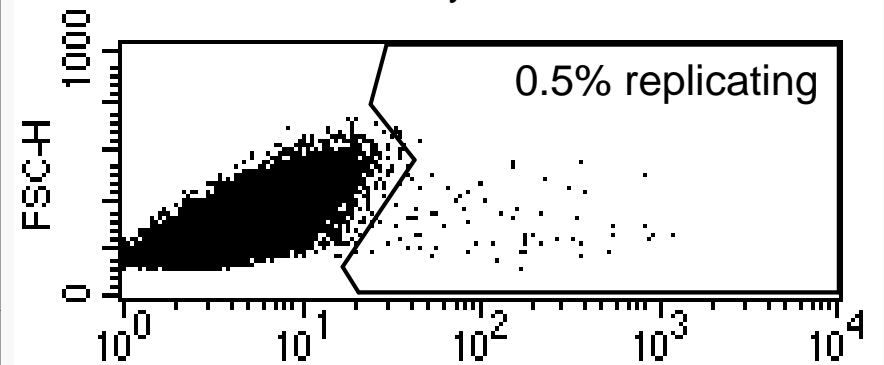




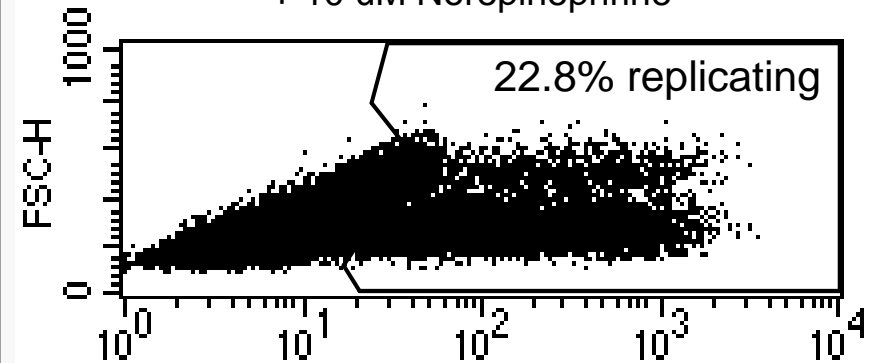
KSHV / HHV-8

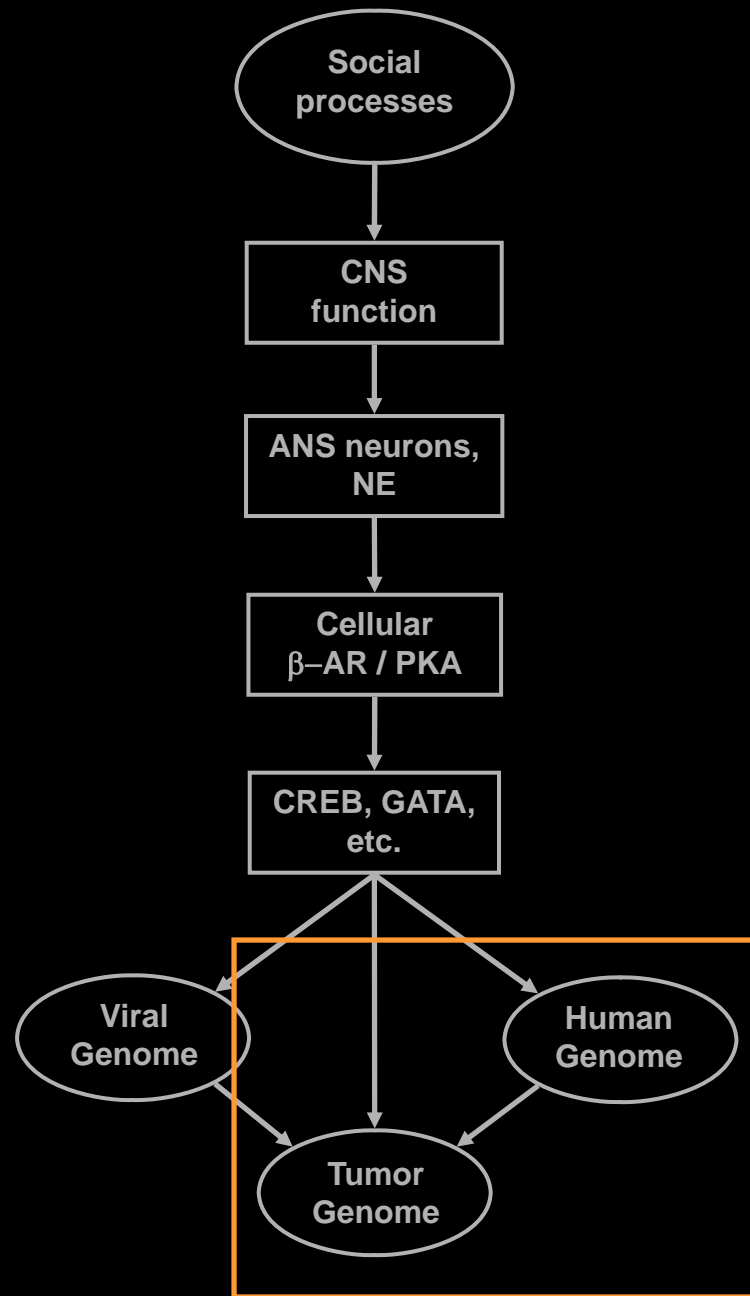


BC3 cells latently infected with KSHV



+ 10 uM Norepinephrine





Biobehavioral regulation of gene expression in cancer

1. How do social factors regulate gene expression?
2. Are these “social signal transduction” pathways active in clinical cancer?
3. Do they shape the evolution of the tumor genome?
4. What are the prospects for protective intervention?

Answer: Neuroendocrine activation of cellular signal-transduction pathways.

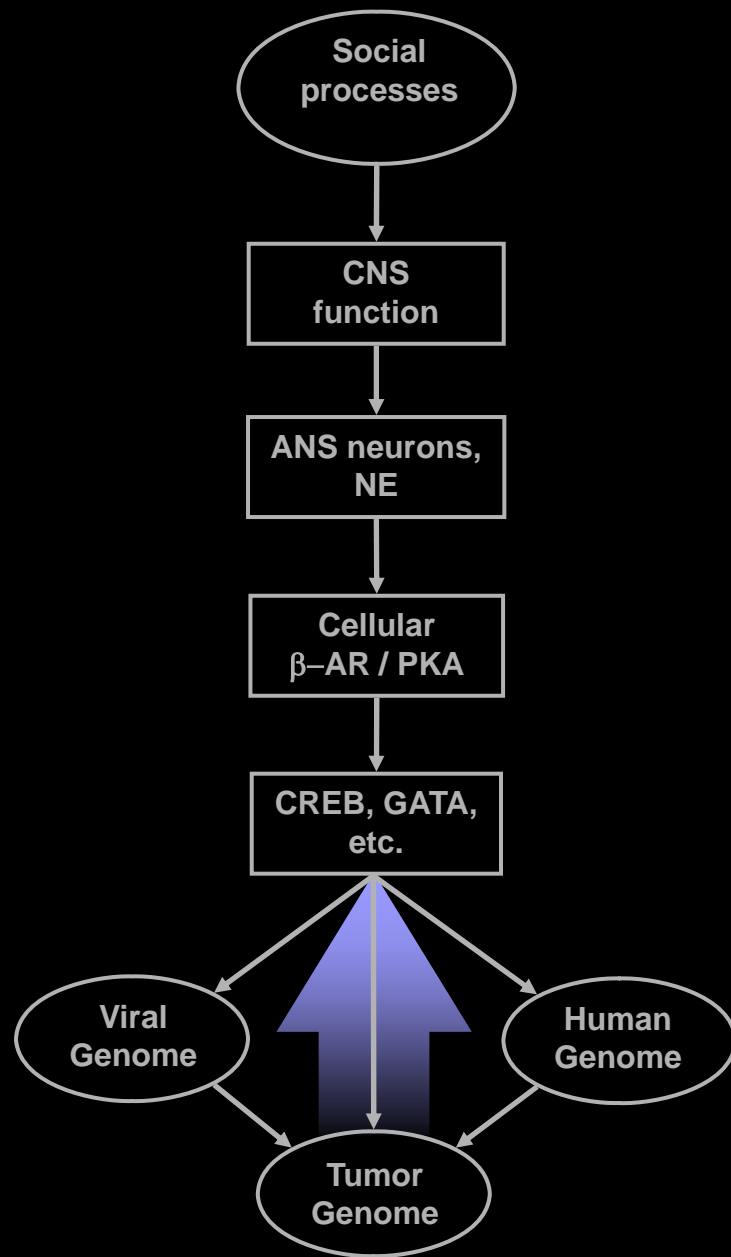
Biobehavioral regulation of gene expression in cancer

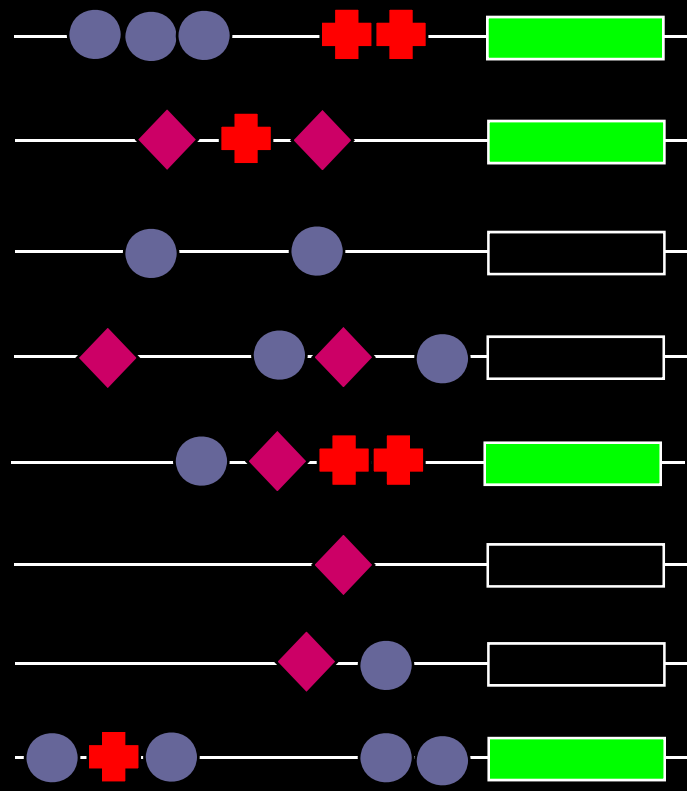
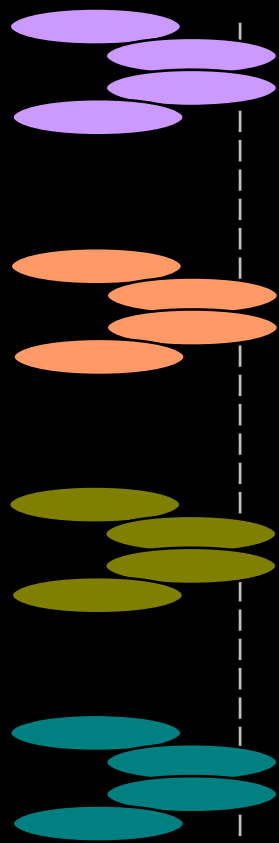
1. How do social factors regulate gene expression?




2. Are these “social signal transduction” pathways active in clinical cancer?

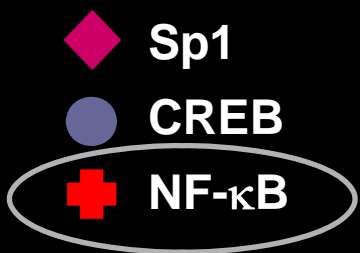
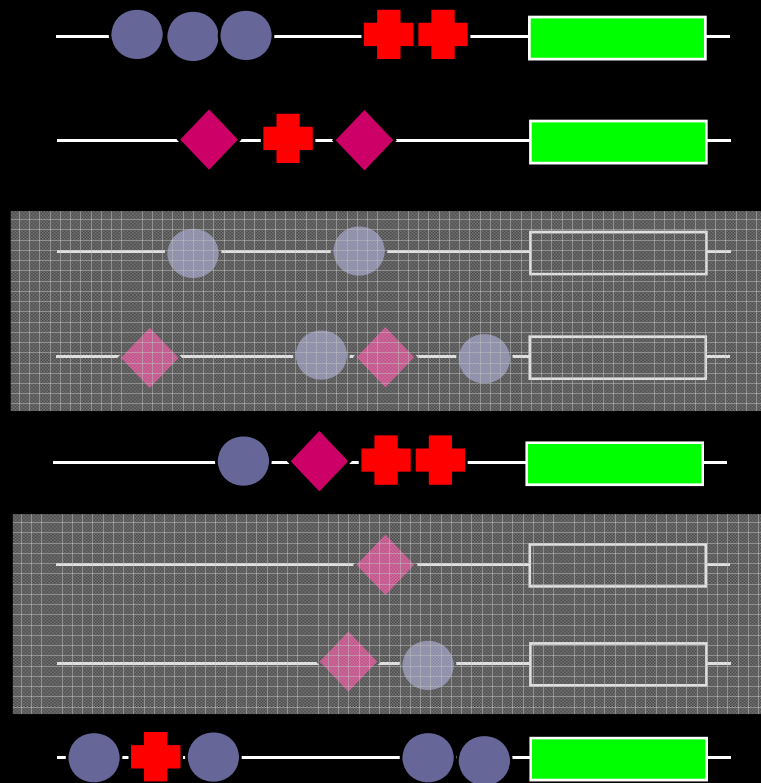
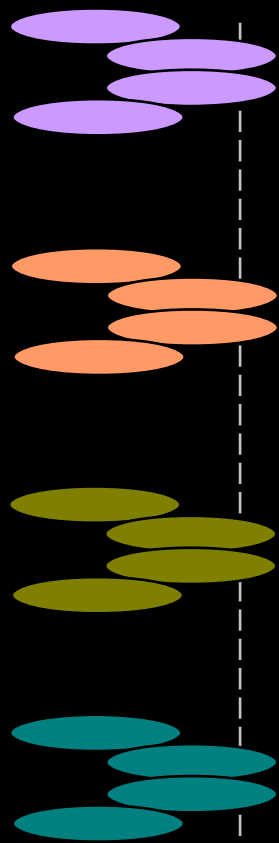
3. Do they shape the evolution of the tumor genome?

4. What are the prospects for protective intervention?





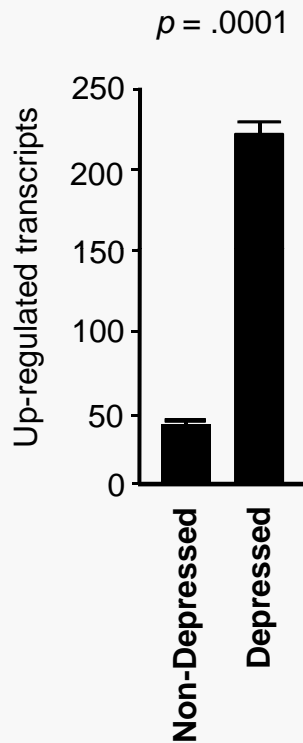
 Sp1
 CREB
 NF- κ B



Depression and ovarian carcinoma: functional genomics

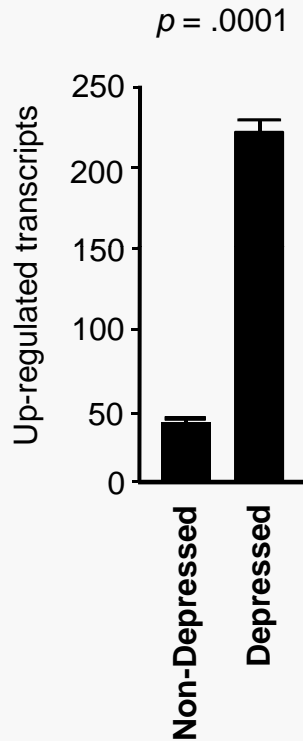
- 10 primary ovarian epithelial carcinomas
 - 5 pt. with high social support and low depression
 - 5 pt. with low social support and high depression
 - matched on Grade, Stage, and histological subtype
- Global gene expression profiling
 - Affymetrix U133A high-density oligonucleotide arrays
 - simultaneous hybridization in UCLA / Jonsson Cancer Center DNA Microarray Core
 - low-level expression analysis by Robust Multi-array Averaging (RMA)
- Bioinformatics
 1. Identify differentially expressed genes (> 2-fold)
 2. Identify upstream transcription control pathways (www.telis.ucla.edu)

Depression and ovarian carcinoma: functional genomics



PPFIBP1	PLAT	FLJ10970	DCN	HLA-B	SPARC
CST4	ATF3	EGFL6	DUSP1	WFDC2	NALP1
SQLE	CTGF	FXYD1	CSPG2	TM4SF1	PAPOLA
EPS8L1	COL11A1	GAS1	FMOD	DUSP5	SMARCD3
STX18	SGNE1	LR8	SNX7	LTA4H	PSMD8
NDRG1	FOS	PNOC	HLA-DPA1	PLOD2	HLA-DQA1
CST1	CPVL	SERPING1	CYR61	PAPOLA	PITPNC1
SMARCA4	ATP6V1B1	HLA-DRB1	HLA-DQB1	INHBA	FGFR3
EPB41L4B	CXCL12	HLA-DRA	SCPEP1	KIAA0657	SPARC
UQCRH	LYPDC1	C4A /// C4B	ARL1	XCL1 / XCL2	PLA2G7
DST	HBA2	HBB	COL5A2	ECHDC3	SLC7A11
DPEP3	KLK11	OLFML3	KCTD14	GUCY1B3	CSPG2
TEKT2	UBD	HBA1	PRSS2	TRBC1	LSM4
TACC2	COL11A1	JUN	WNT5B	GLT8D2	HLA-B
NQO2	CP	PHYH	PRELP	ZFP36	PLEKHB1
SFN	C4A /// C4B	HLA-DRB1	SELENBP1	CALD1	GJA1
EFHC2	FOSB	HBA1	DUSP6	IGHM	NOL7
TBX2	LUM	CSPG2	GMPR	TMEM14B	CDH11
ALCAM	LCRISP2	KIAA0657	FN1	CTSB	CST3
SOX11	HLA-DRA	PFN2	PFKP	FXYD5	RPA3
SRP68	ARL7	D4S234E	CCL2	IMP-3	KLF10
MUC16	JUNB	SGCE	IGKC	PRSS21	TRBC1
NR2E3	CPE	HRASLS3	DUSP6	IGFBP2	EGR3
TBL1X	CGI-116	DUSP6	ANKRD6	CHPT1	RGC32
HIST1H1C	LOC440871	KNS2	PTGDS	TU3A	THY1
UNG2	LOC492304	GPC4	TIMP3	PLXNC1	GALC
VGLL1	DKFZp564I1922	ARL7	BTG1	SH3BP5	INHBB
SLC6A8	FXYD3	CECR1	DHRS8	FBLN5	POLD2
HOXA9	SEPP1	BBOX1	MYL9	NUP37	HLA-DPA1
EPS8L1	POSTN	RARRES2	FN1	SPOCK	LOC388650
KRT23	TM4SF1	TM4SF1	AKR1C3	HLA-B	PTGDS
OVGP1	HLA-DQA1	VCAM1	CSPG2	HLA-DMA	FBXO17
B7-H4	HBB	ID1	CXCL11	CYR61	JUND
ASRGL1	EGR1	TU3A	POU2AF1	DCN	CKLFSF6
ENDOG	HBA1	ICAM2	BEXL1	HLA-DRB1	NRIP1
HSPA1A	BTG2	RPL5	PYCARD	FLJ10159	PLOD2
KIAA1641	NRCAM	KIAA0217	PIGV	COL5A1	IER3
HOXB6	SERPINE1	IGHD	MSRB2	C11orf9	LAMP2
VAV3	HBA2	TRIB1	CXCL9	THBS2	PGA3
SLC3A1	IGKC	ZDHHC4	ABAT	GATA6	LOC51315
PROM1	IGLC2	PHLDA1	CACNA2D2	HCA112	
AMY2A			COL3A1	MFAP2	

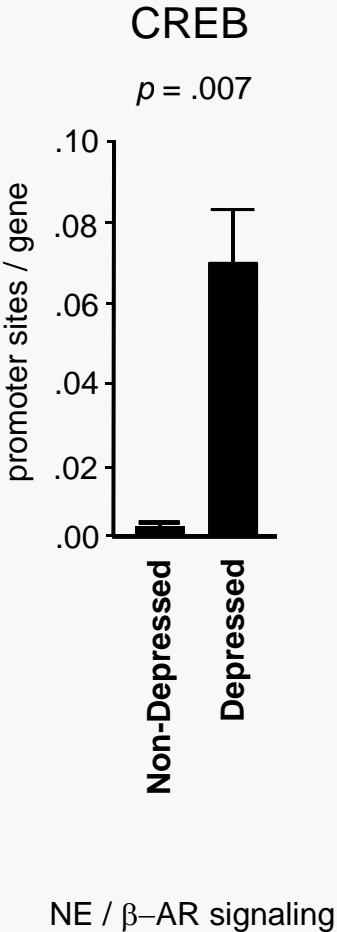
Depression and ovarian carcinoma: functional genomics



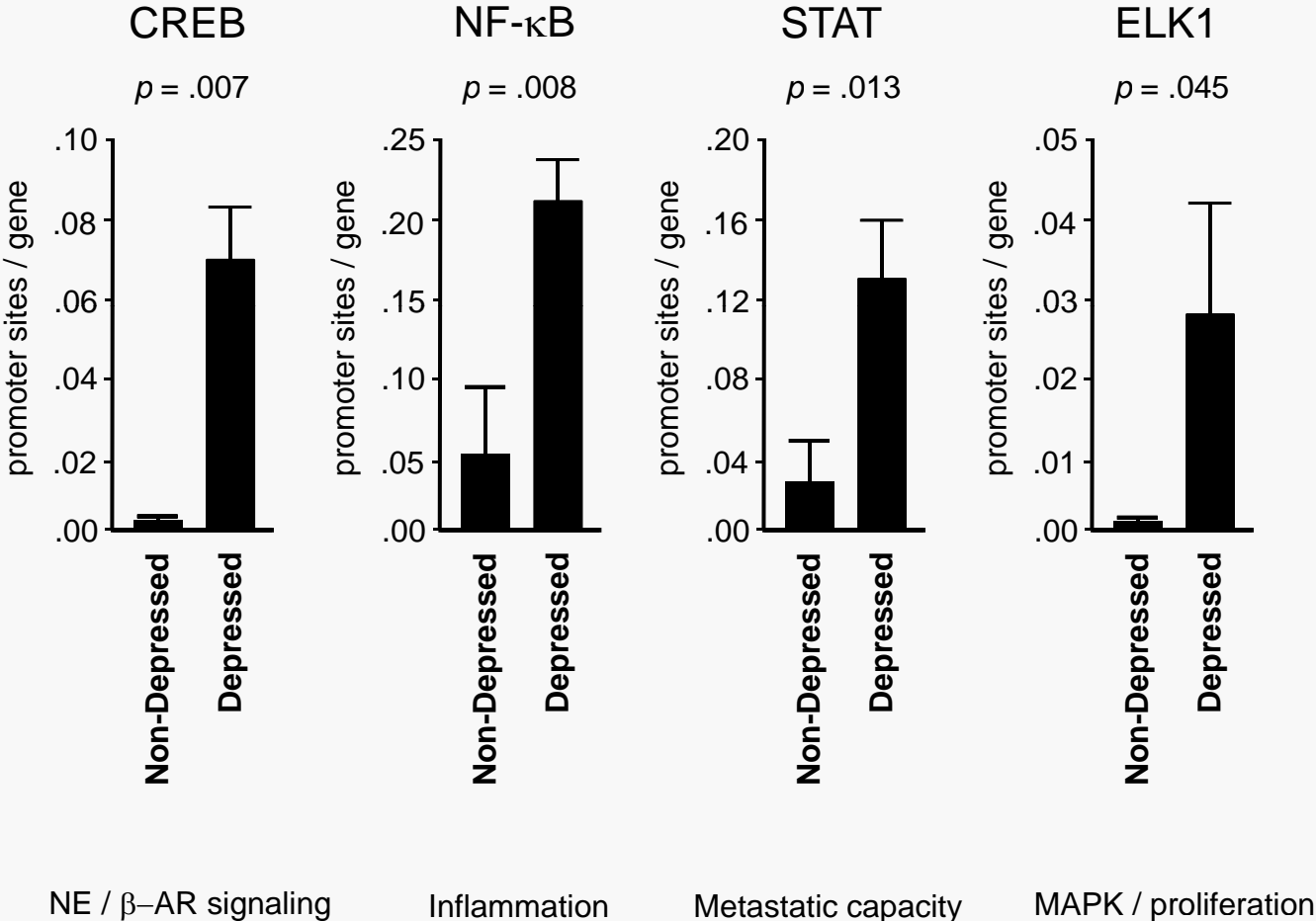
Transcription factors

PPFIBP1	PLAT	FLJ10970	DCN	HLA-B	SPARC
CST4	ATF3	EGFL6	DUSP1	WFDC2	NALP1
SQLE	CTGF	FXD1	CSPG2	TM4SF1	PAPOLA
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STX18	SGNE1	LR8	SNX7	LTA4H	PSMD8
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EPB41L4B	CXCL12	HLA-DRA	SCPEP1	KIAA0657	SPARC
UQCRH	LYPDC1	C4A /// C4B	ARL1	XCL1 / XCL2	PLA2G7
DST	HBA2	HBB	COL5A2	ECHDC3	SLC7A11
DPEP3	KLK11	OLFML3	KCTD14	GUCY1B3	CSPG2
TEKT2	UBD	HBA1	PRSS2	TRBC1	LSM4
TACC2	COL11A1	JUN	WNT5B	GLT8D2	HLA-B
NQO2	CP	PHYH	PRELP	ZFP36	PLEKHB1
SFN	C4A /// C4B	HLA-DRB1	SELENBP1	CALD1	GJA1
EFHC2	FOSB	HBA1	DUSP6	IGHM	NOL7
TBX2	LUM	CSPG2	GMPR	TMEM14B	CDH11
ALCAM	LCRISP2	KIAA0657	FN1	CTSB	CST3
SOX11	HLA-DRA	PFN2	PFKP	FXD5	RPA3
SRP68	ARL7	D4S234E	CCL2	IMP-3	KLF10
MUC16	JUNB	SGCE	IGKC	PRSS21	TRBC1
NR2E3	CPE	HRASLS3	DUSP6	IGFBP2	EGR3
TBL1X	CGI-116	DUSP6	ANKRD6	CHPT1	RGC32
HIST1H1C	LOC440871	KNS2	PTGDS	TU3A	THY1
UNG2	LOC492304	GPC4	TIMP3	PLXNC1	GALC
VGLL1	DKFZp56411922	ARL7	BTG1	SH3BP5	INHBB
SLC6A8	FXD3	CECR1	DHRS8	FBLN5	POLD2
HOXA9	SEPP1	BBOX1	MYL9	NUP37	HLA-DPA1
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KRT23	TM4SF1	TM4SF1	AKR1C3	HLA-B	PTGDS
OVGP1	HLA-DQA1	VCAM1	CSPG2	HLA-DMA	FBXO17
B7-H4	HBB	ID1	CXCL11	CYR61	JUND
ASRGL1	EGR1	TU3A	POU2AF1	DCN	CKLFSF6
ENDOG	HBA1	ICAM2	BEXL1	HLA-DRB1	NRIP1
HSPA1A	BTG2	RPL5	PYGARD	FLJ10159	PLOD2
KIAA1641	NRCAM	KIAA0217	PIGV	COL5A1	IER3
HOXB6	SERPINE1	IGHD	MSRB2	C11orf9	LAMP2
VAV3	HBA2	TRIB1	CXCL9	THBS2	PGA3
SLC3A1	IGKC	ZDHHC4	ABAT	GATA6	LOC51315
PROM1	IGLC2	PHLDA1	CACNA2D2	HCA112	
AMY2A			COL3A1	MFAP2	

Depression and ovarian carcinoma: functional genomics



Depression and ovarian carcinoma: functional genomics



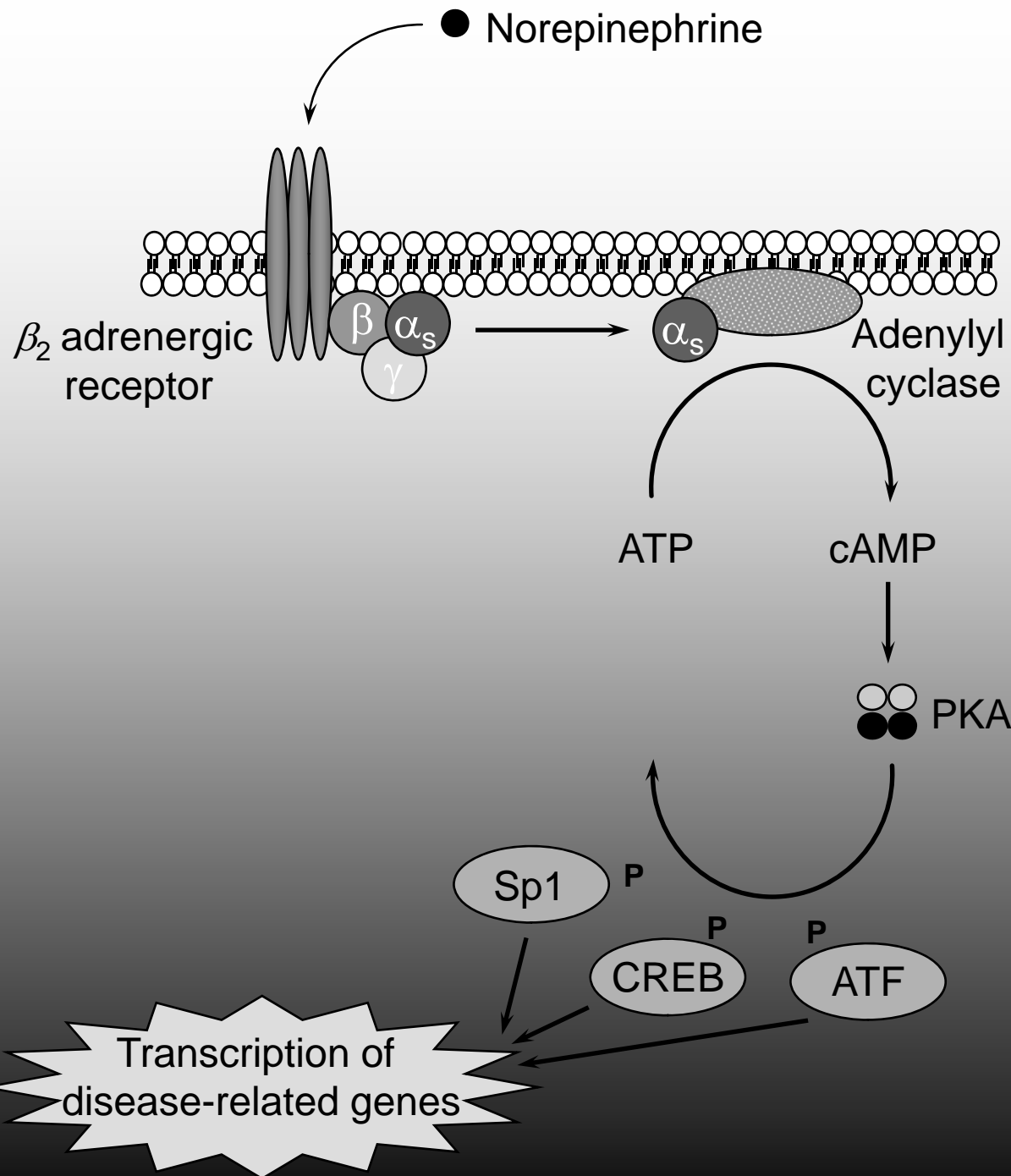
Biobehavioral regulation of gene expression in cancer

1. How do social factors regulate gene expression?
2. Are these “social signal transduction” pathways active in clinical cancer?
3. Do they shape the evolution of the tumor genome?
4. What are the prospects for protective intervention?

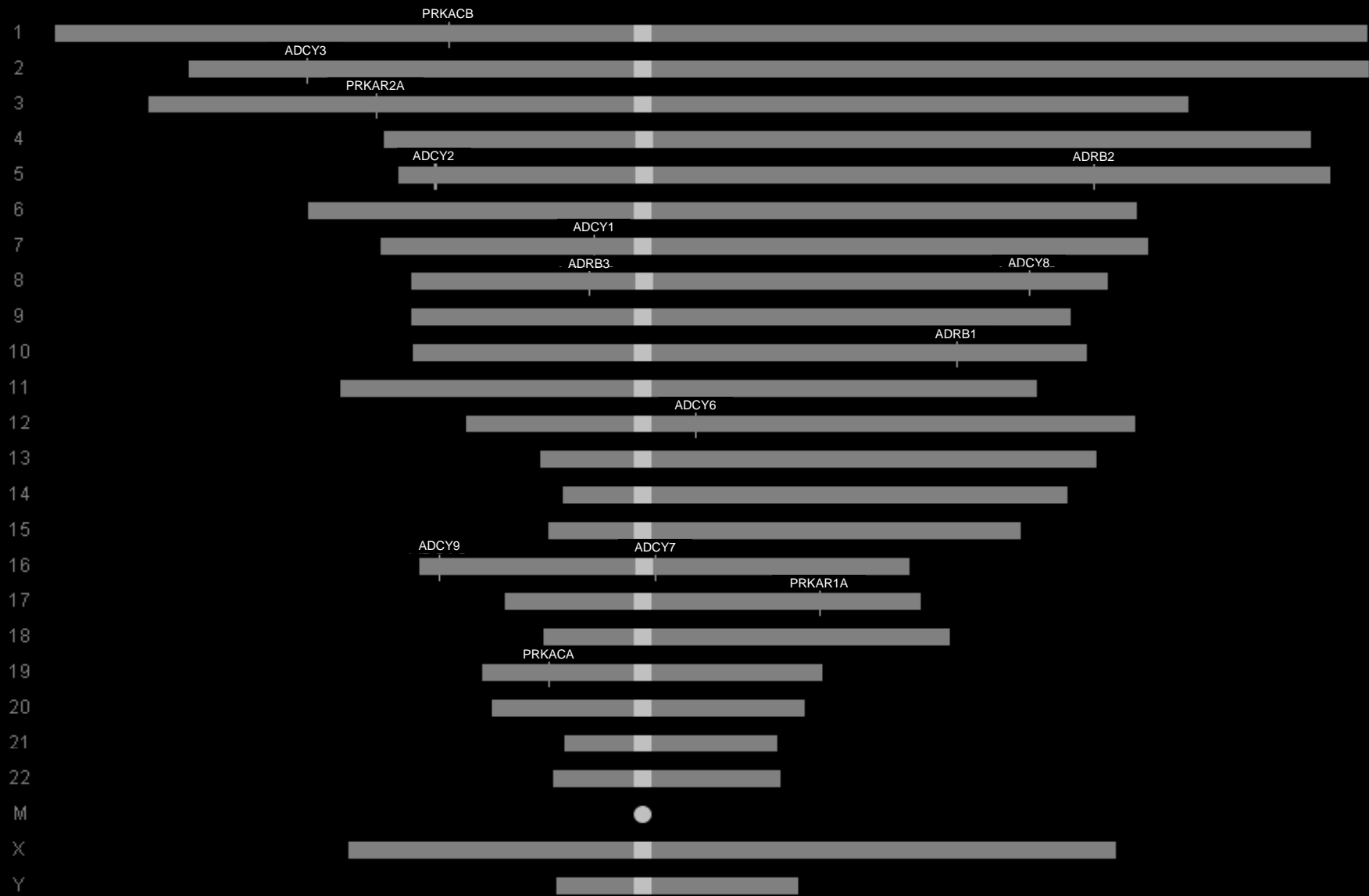
Answer: Risk-related activation of the cAMP / PKA / CREB pathway in primary ovarian tumors

Biobehavioral regulation of gene expression in cancer

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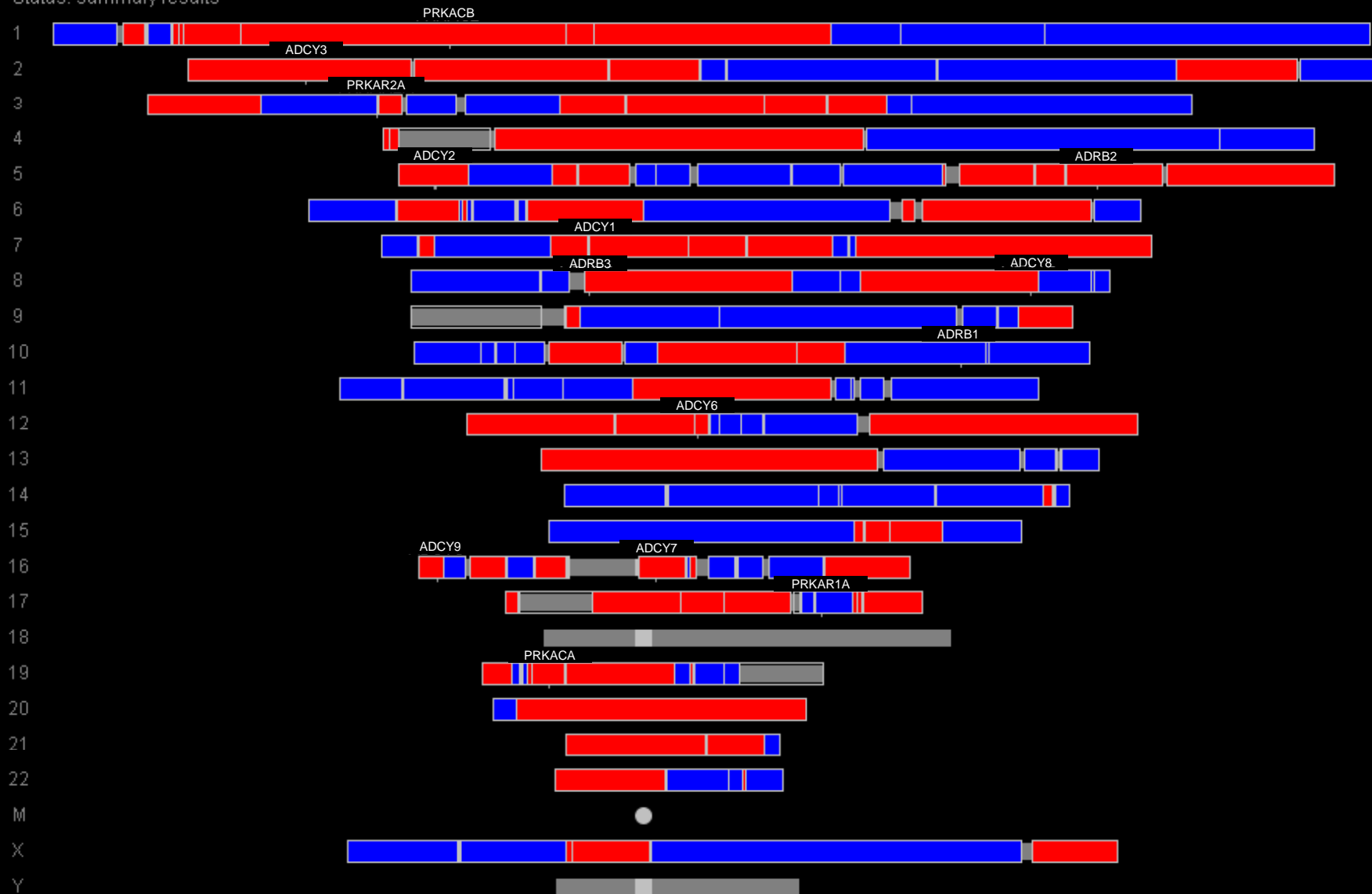


β -AR pathway genes: ovarian carcinoma



β -AR pathway genes: ovarian carcinoma

Status: summary results



β -AR pathway genes: ovarian carcinoma

Gene	Functional relationship	Regional alteration	Consistency
<i>ADRB1</i>	+	-	-
<i>ADRB2</i>	+	+	+
<i>ADRB3</i>	+	+	+
<i>ADCY1</i>	+	+	+
<i>ADCY2</i>	+	+	+
<i>ADCY3</i>	+	+	+
<i>ADCY6</i>	+	+	+
<i>ADCY7</i>	+	+	+
<i>ADCY8</i>	+	+	+
<i>ADCY9</i>	+	+	+
<i>PRKACA</i>	+	+	+
<i>PRKACB</i>	+	+	+
<i>PRKAR1A</i>	-	-	+
<i>PRKAR2A</i>	-	-	+

◀ 13 / 14: Haplotype $p = .00006$

Biobehavioral regulation of gene expression in cancer

1. How do social factors regulate gene expression?
2. Are these “social signal transduction” pathways active in clinical cancer?
3. Do they shape the evolution of the tumor genome?
4. What are the prospects for protective intervention?

Answer: Evidence of selection for β -AR / PKA genes in ovarian cancer

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Basic science: Pathway identification

- rational targeting of interventions (agent selection, personal risk profiling)
- genomic biomarkers for intervention impact

Translational opportunity: β -AR pathway

- β -blockade (safe, cheap, effective?)
- molecular manipulation (*ADRB2*, *ADCY*, transcription factors, stay upstream for leverage)

Support

NCI 1R01-CA116778

NCI 1R01-CA110793

NCI 1R01-CA109298

NIDCR 1R01-DE015970

NIDCR 1R03-DE016569

NIAID 1R01-AI52737

MacArthur Foundation

James Pendelton Trust

HopeLab Foundation



Biobehavioral Influences on Cancer Biology

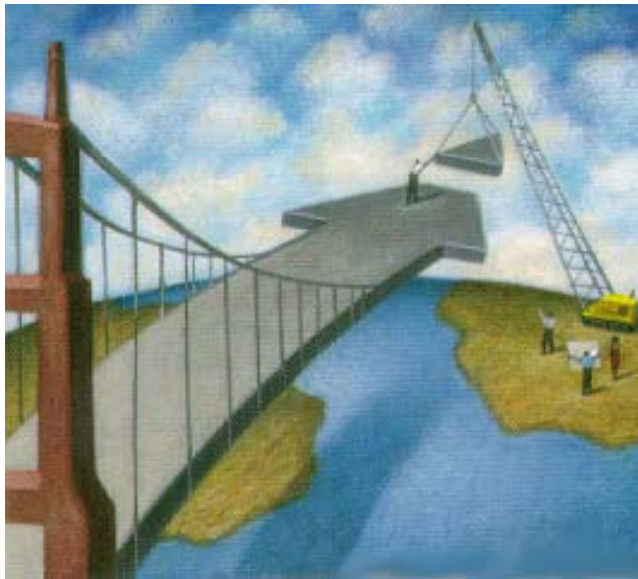
AN EMERGING OPPORTUNITY

Overarching Themes*

- **Stress biology can influence tumor biology**
 - 1.5 – 3-fold effects observed
- **Mechanisms are being elucidated**
 - Neuroendocrine regulation of:
 - Neoplastic cell growth
 - Tumor gene expression
 - Viral gene expression
 - Cell-mediated immunity
 - Invasion
 - Tumor growth and progression
- **Opportunity to test adjuvant interventions**

* See also: *Biobehavioral Influences on Cancer Biology: An Emerging Opportunity* (2007)

Future Directions



- Breadth of effects
- Biological mechanisms
- Clinical impact

Opportunities



- **Basic science**
- Quantitative experimental models
- Pharmacologic and molecular tools
- In vivo models of human tumor biology
- **Translational science**
- Pilot trials for neuroendocrine modifiers
- Biomarkers for biobehavioral influences
- **Transdisciplinary science**

Symposium Purpose

- **Facilitate knowledge of this emerging area in the NCI behavioral research portfolio**
- **Obtain BSA input on how NCI can best:**
 - **Expand the breadth and depth of this transdisciplinary science**
 - **Catalyze productive high impact collaborations**

Biobehavioral Influences on Cancer Biology

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