

National Cancer Institute

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

---

# Biobehavioral Influences on Cancer Biology

AN EMERGING OPPORTUNITY



# Effects of Chronic Stress on Cancer Growth and Progression

Anil K. Sood, MD, Professor  
Professor

Departments of Gynecologic Oncology and  
Cancer Biology

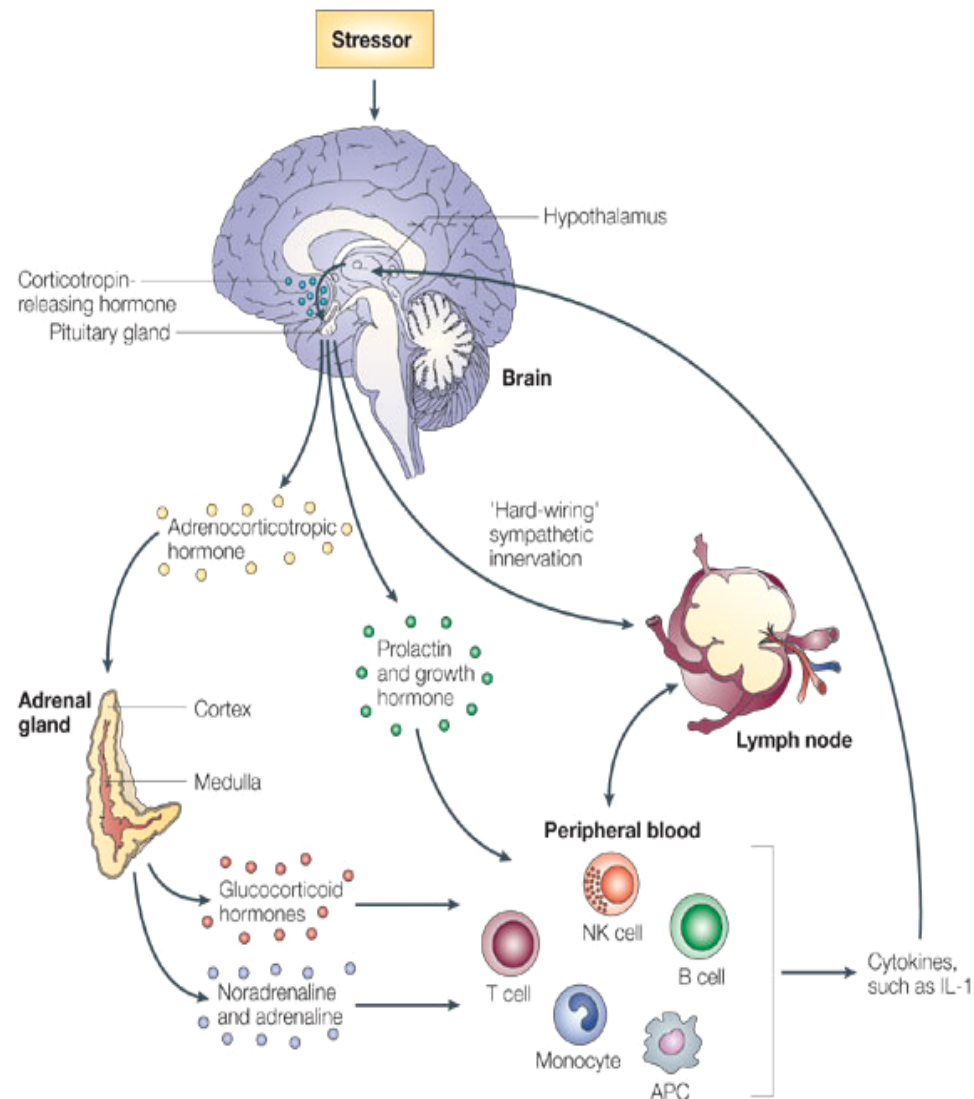
Director, Ovarian Cancer Research

THE UNIVERSITY OF TEXAS  
MDANDERSON  
CANCER CENTER

# 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

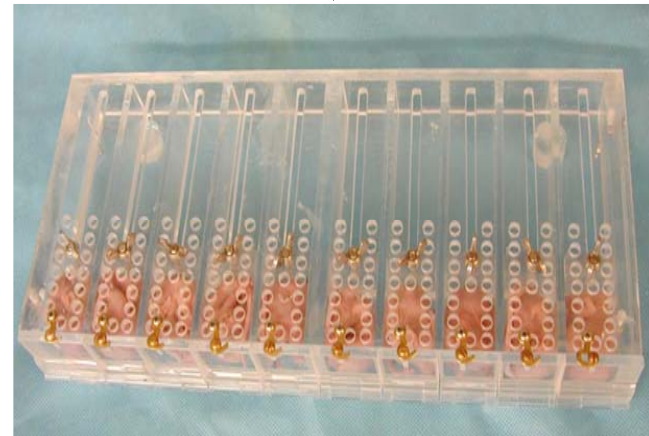
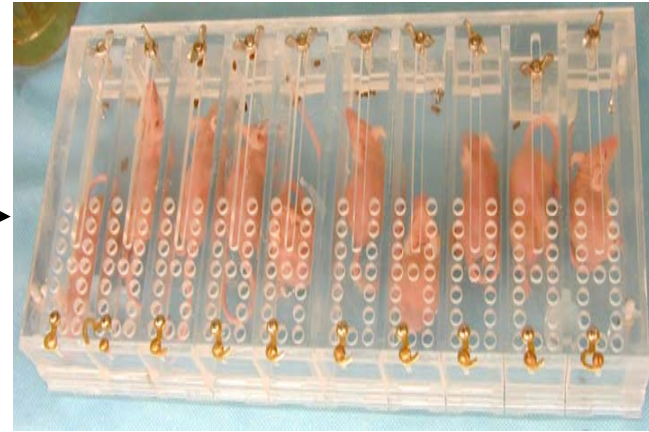
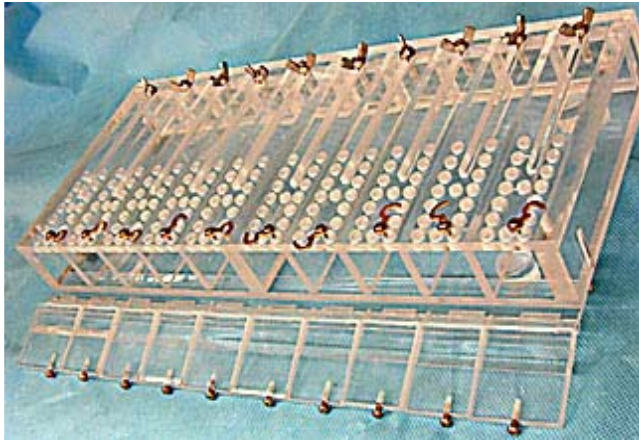
Lutgendorf, Sood et al., *Cancer*, 2002

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

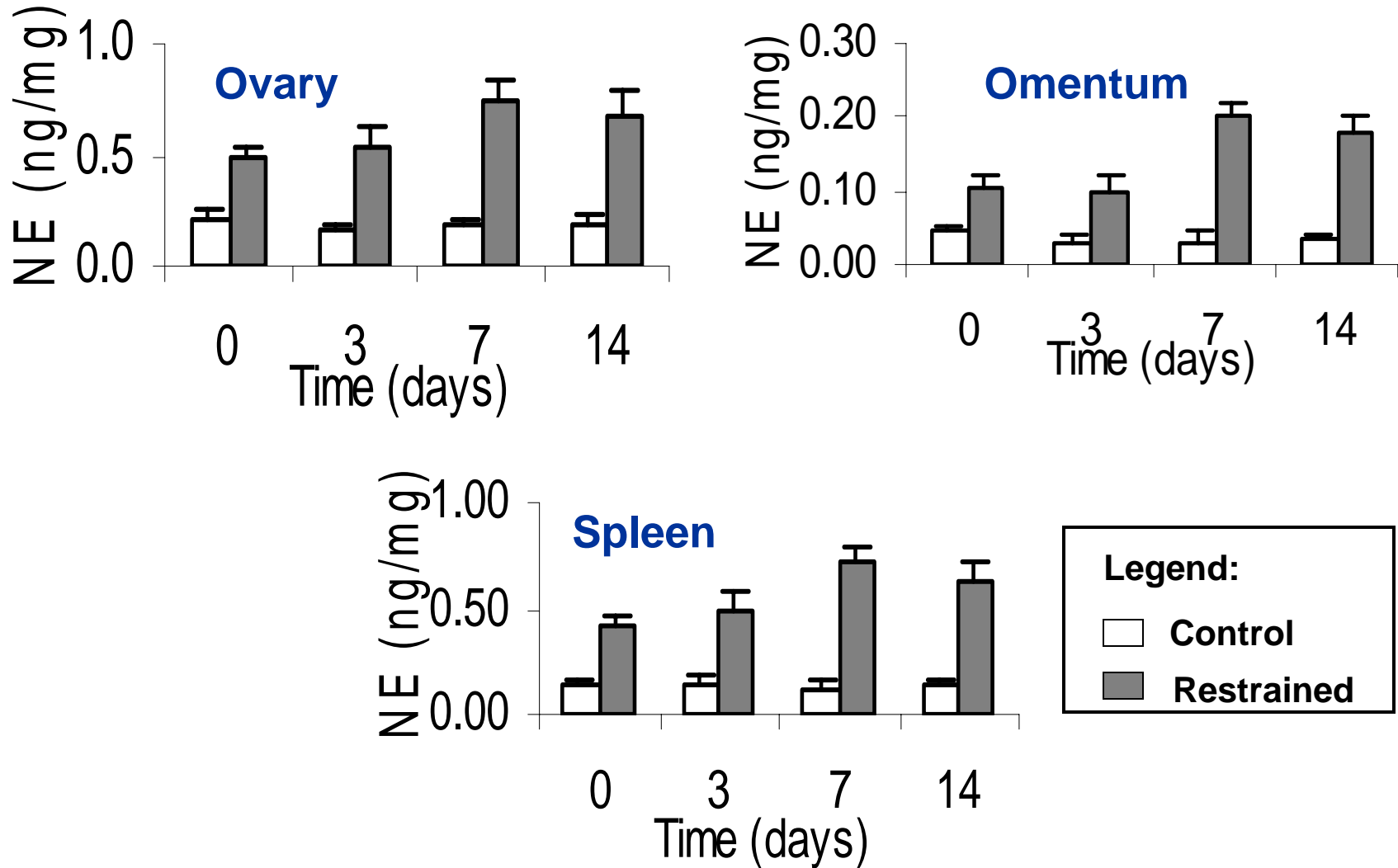
Antoni...Sood, *Nat Rev Cancer*, 2006

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

# Development of a Model

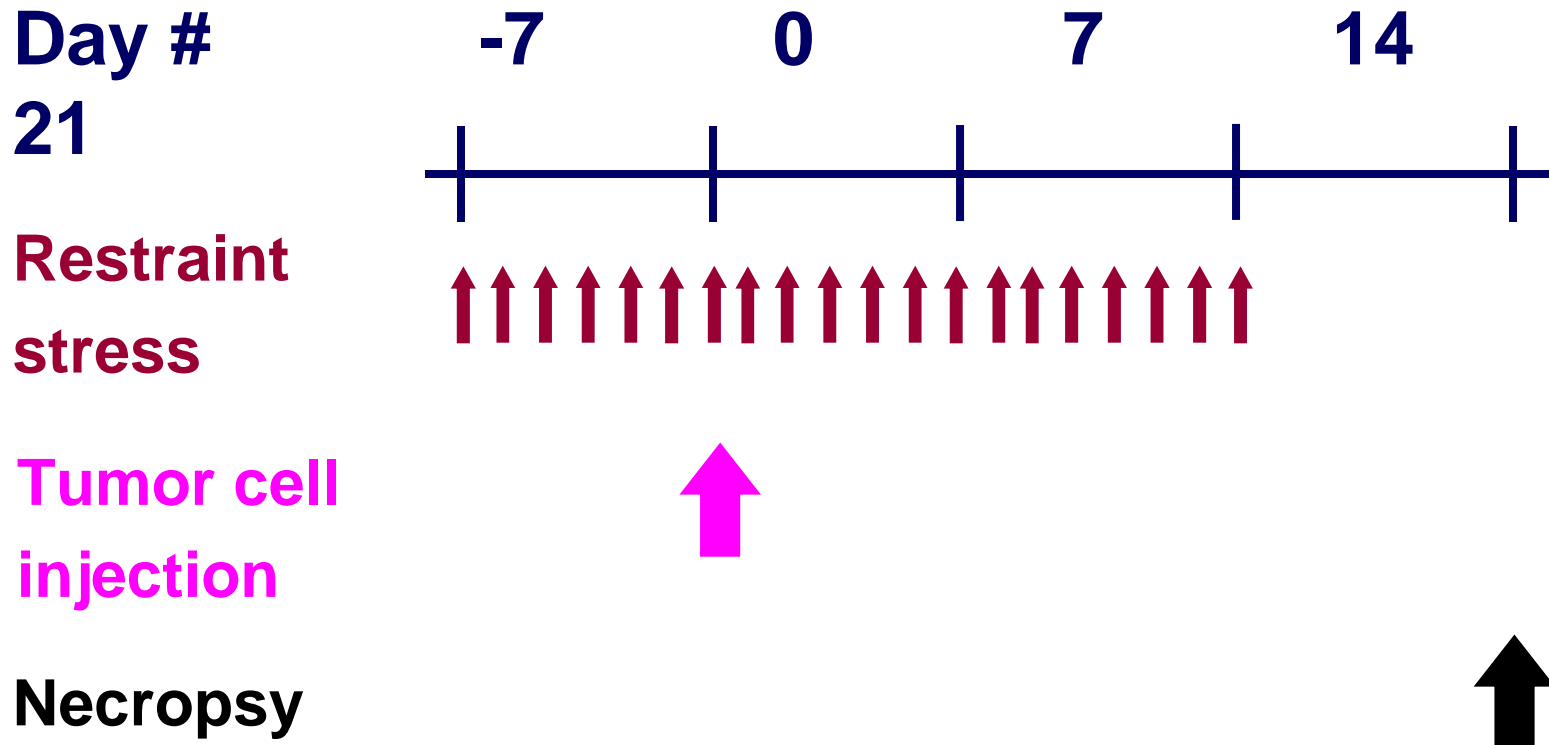


# Norepinephrine Levels



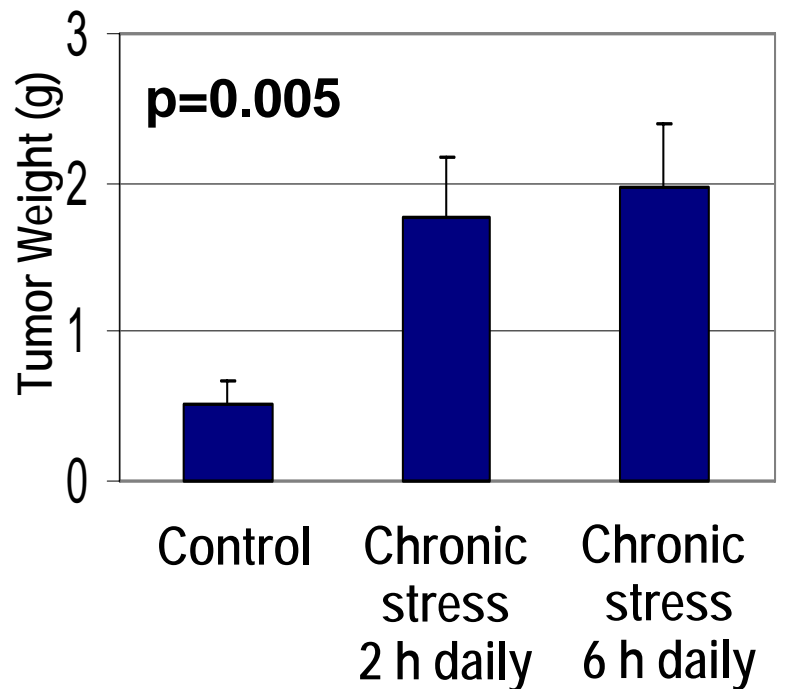


# Schema of Chronic Stress Model

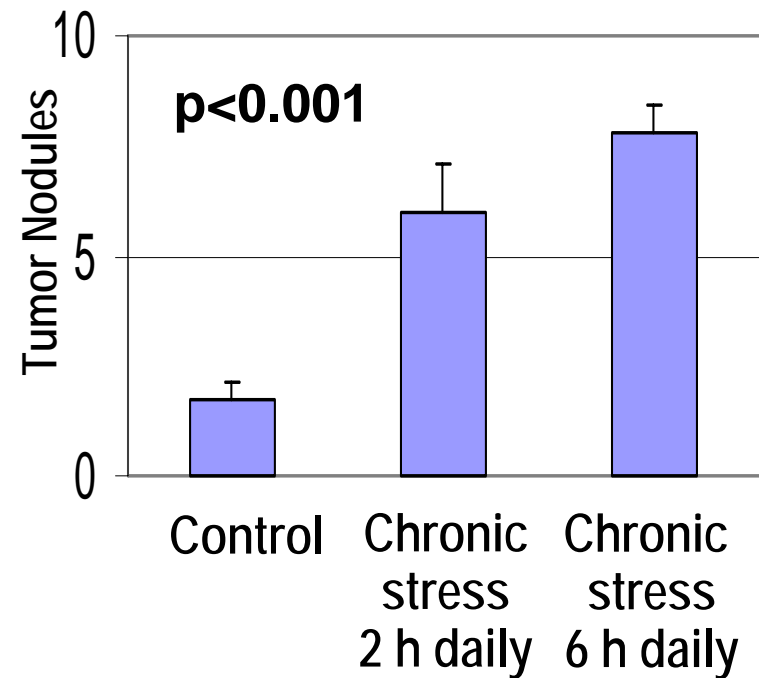


# Effect of chronic stress on orthotopic HeyA8 ovarian cancer

## Mean Tumor Weight



## Mean Tumor Nodules



# Effect of chronic stress on orthotopic ovarian cancer

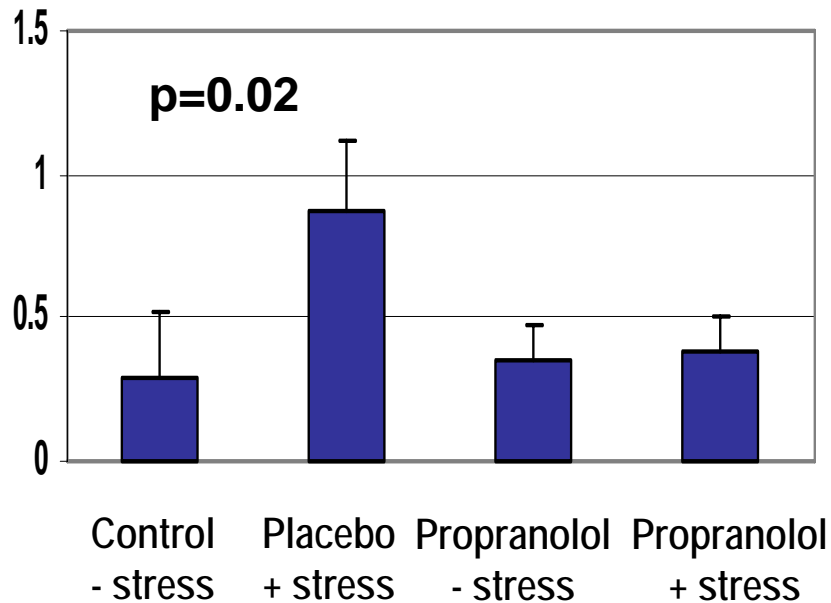
- ❖ Controls had disease confined to the peritoneal cavity
- ❖ 50% of stressed animals had parenchymal liver, splenic, or pleural metastasis



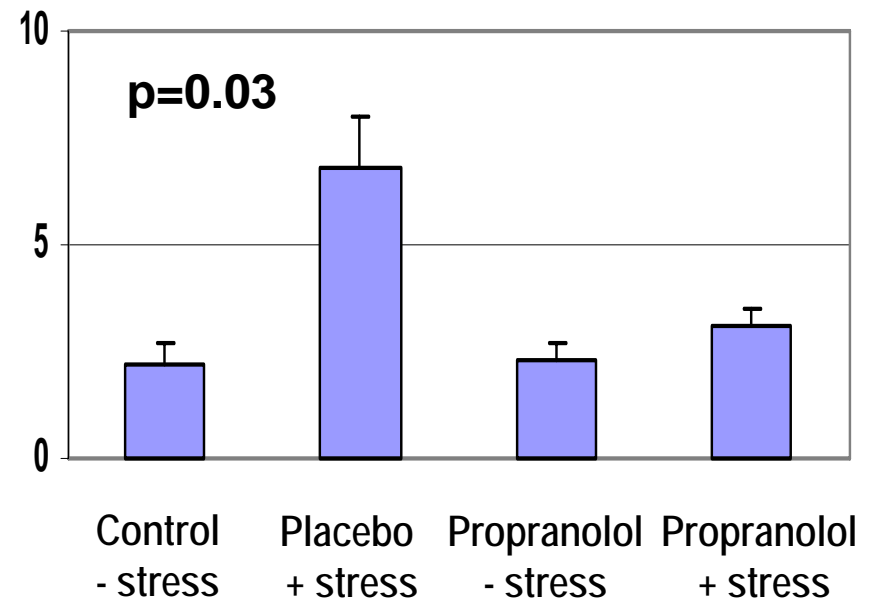
Thaker...Sood, *Nature Med*, 2006

# Effect of chronic stress $\pm$ $\beta$ -blockade on orthotopic HeyA8 ovarian cancer

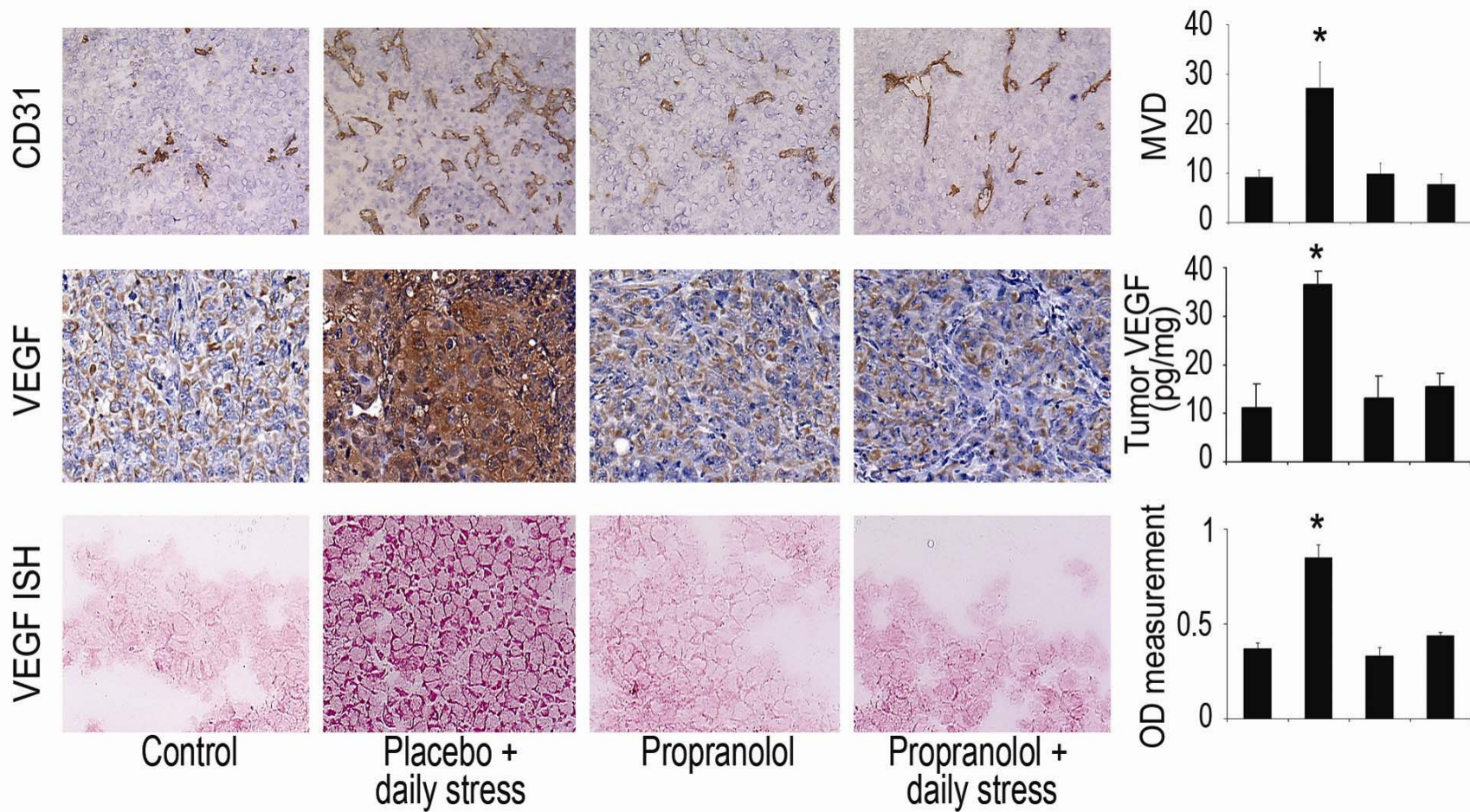
## Mean Tumor Weight



## Mean Tumor Nodules

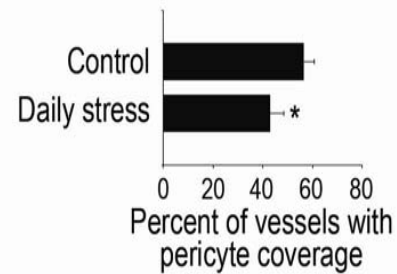
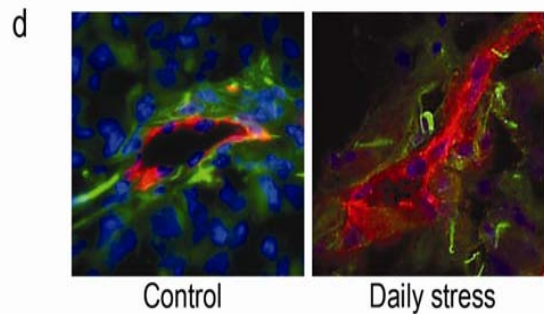
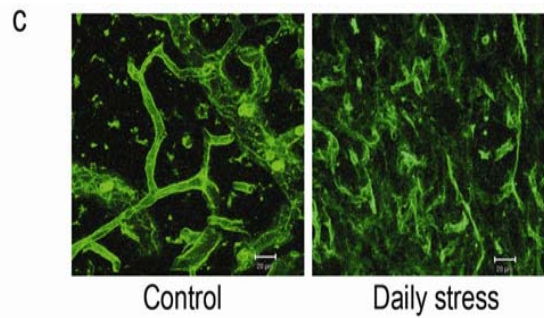
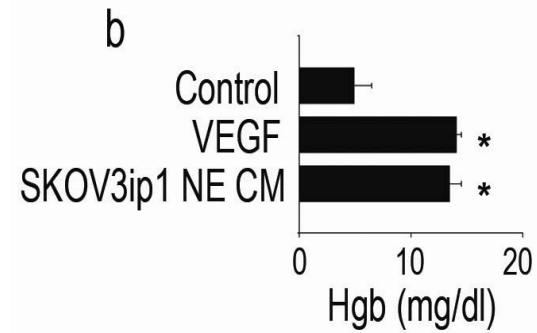
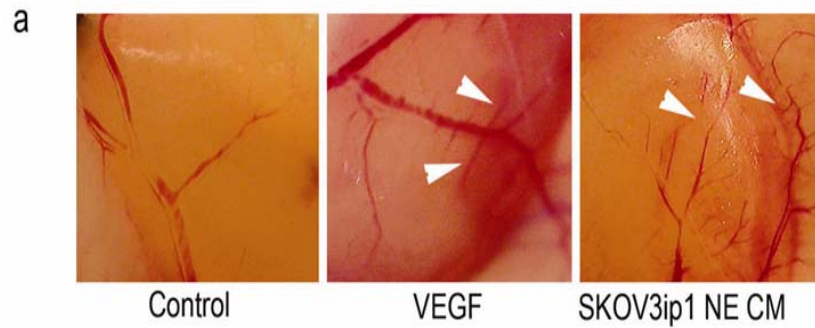


# Effect of chronic stress $\pm$ $\beta$ -blockade on angiogenesis in ovarian carcinoma



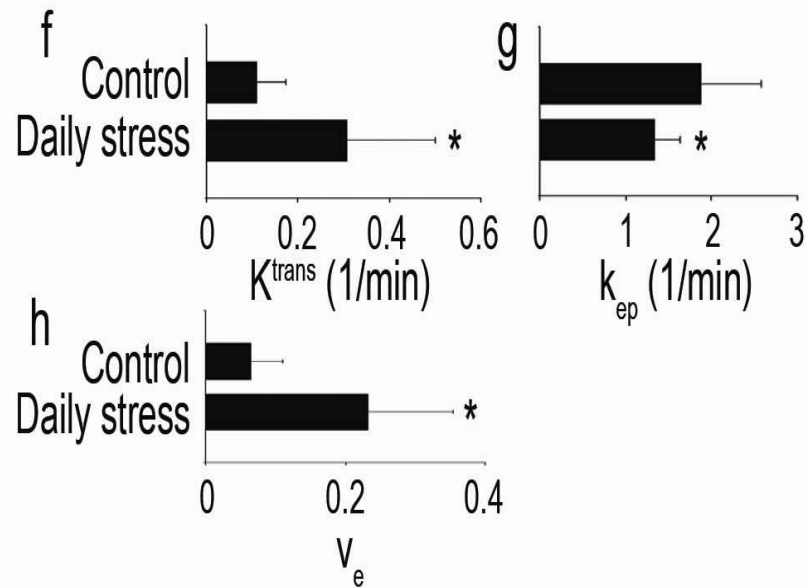
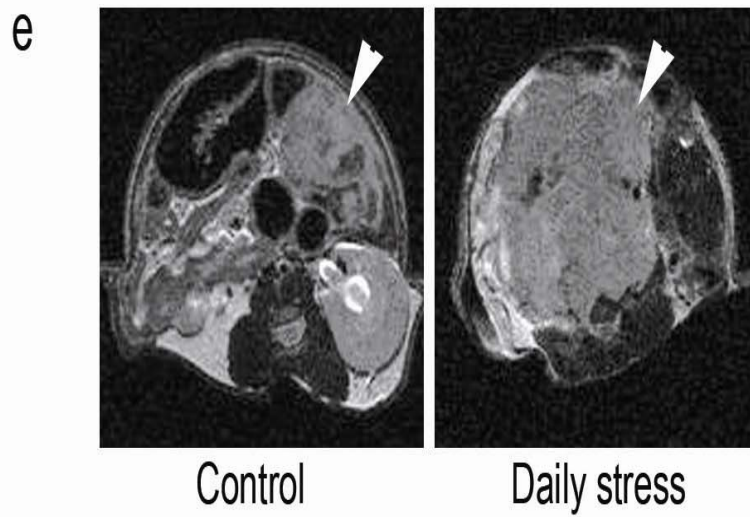
Thaker...Sood, *Nature Med*, 2006

# Effect of chronic stress on angiogenesis

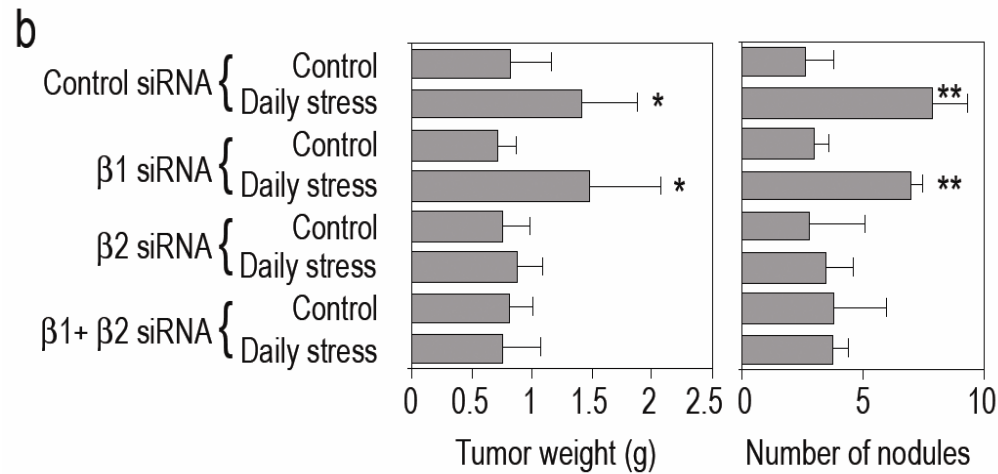
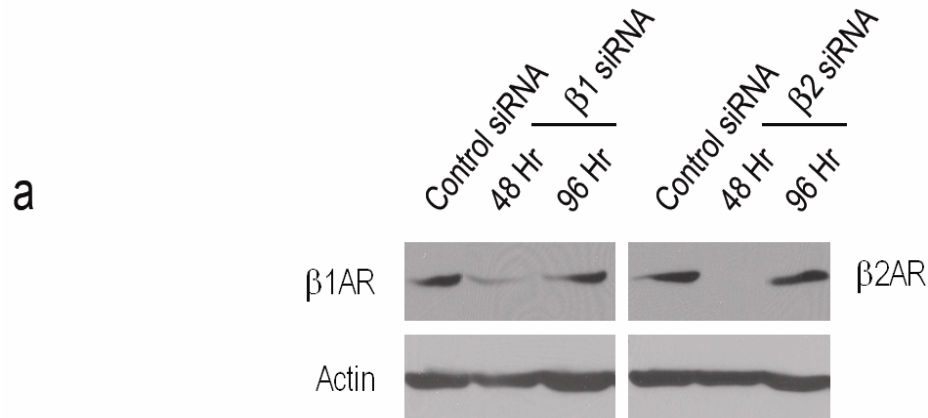


Thaker...Sood, *Nature Med*, 2006

# Effect of chronic stress on angiogenesis



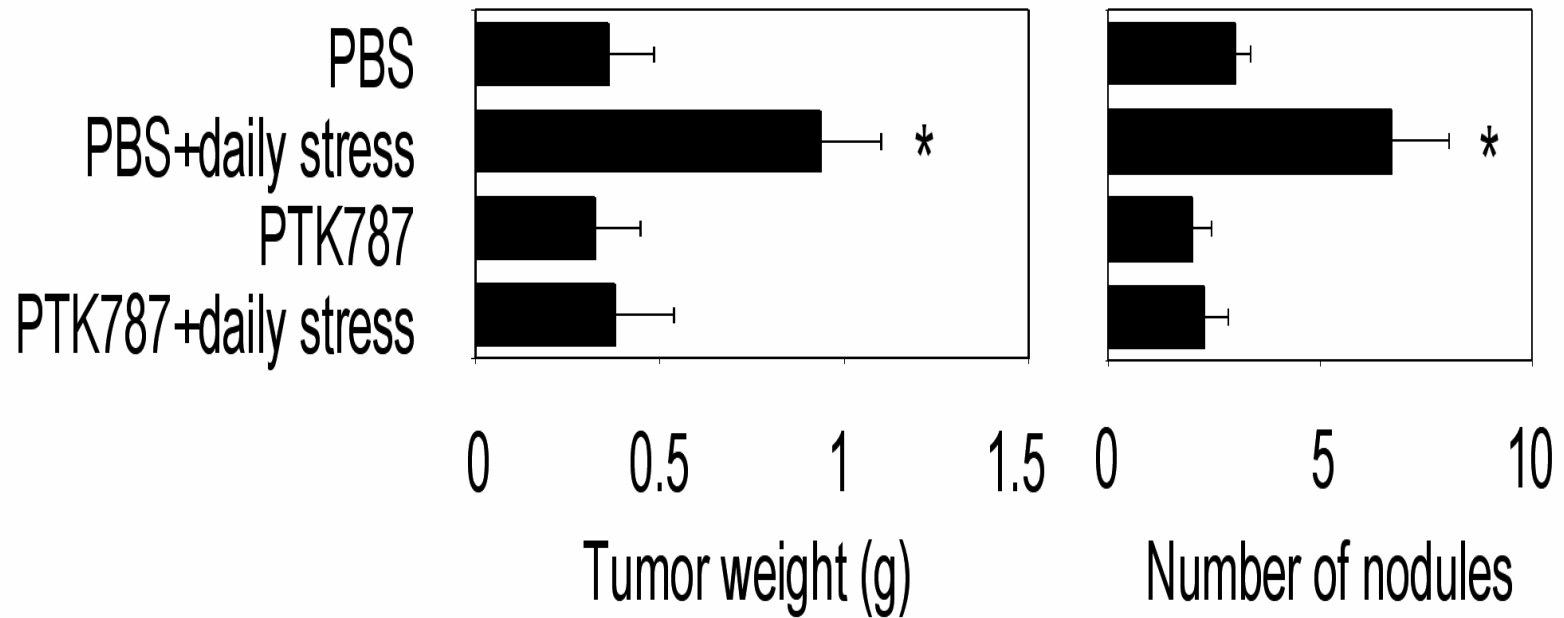
# Effect of $\beta$ -receptor silencing



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

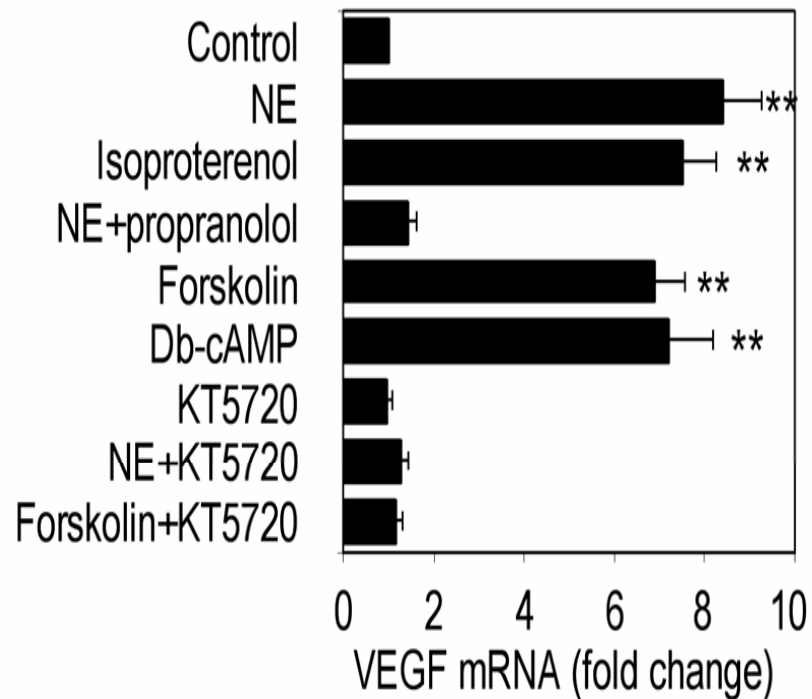


# Effect of VEGF-R inhibition

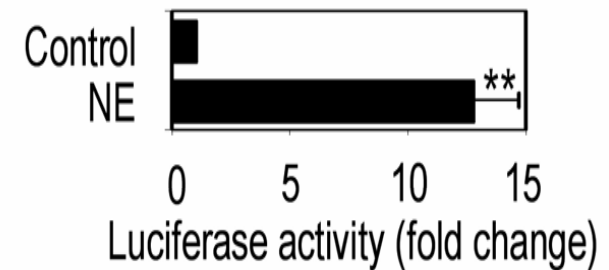


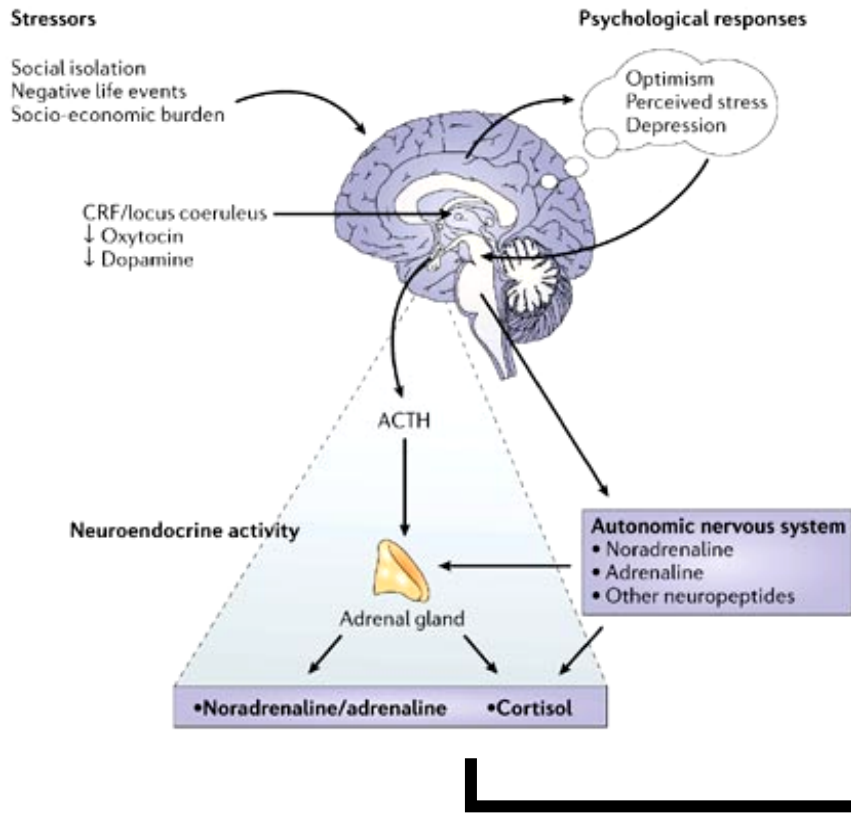
# Mechanisms of VEGF Activation

**a**

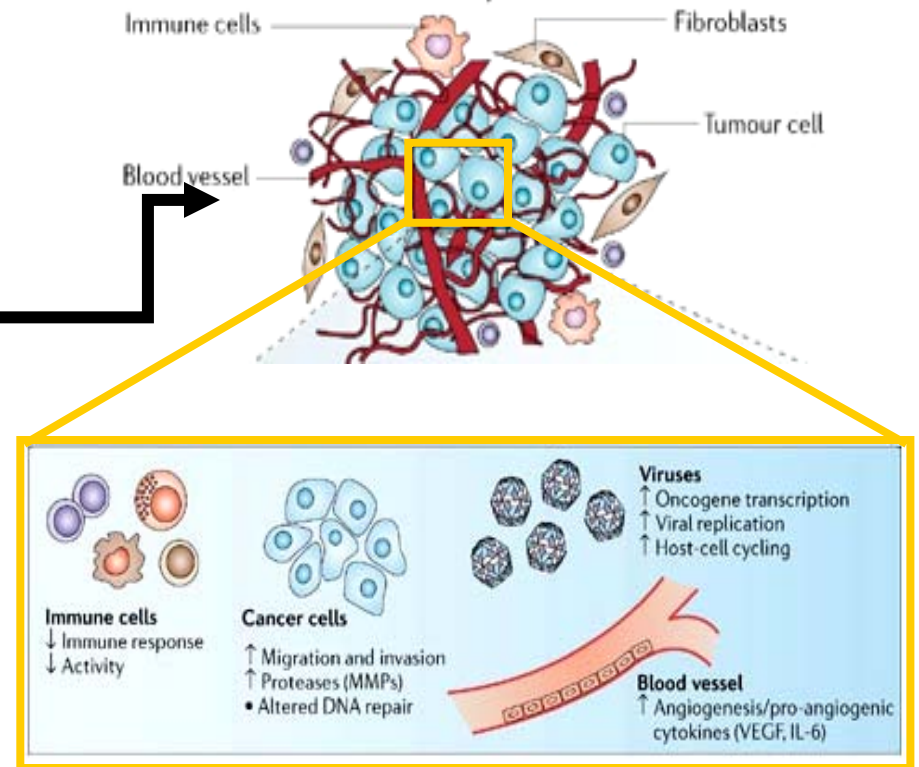


**b**





# 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**