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Stress Regulation of Tumor Biology

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Concept Presentation
NCI Board of Scientific Advisors
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Introduction

- Concept presentation at November 2008 BSA Regular Meeting
- New subcommittee assigned to review concept
- Call to strengthen presentation of clinical data and highlight translational relevancy

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Annotated bibliography

- Stress exposure and clinical outcomes
  - Chida et al. (2008)
  - Kronke et al. (2006)
  - Andersen et al. (2008)
- Stress exposure and tumor biology in clinical samples
  - Costanzo et al. (2005)
  - Lutgendorf et al. (2008)
  - Lutgendorf et al. (2009)
- Neuroendocrine modulation of tumor biology: pre-clinical models
  - Antoni et al. (2006)
  - Armaiz-Pena et al. (2009)

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Stress effects on cancer survival and mortality

1. In 330 studies, stress-related psychosocial factors were associated with poorer cancer survival ($P<0.001$)

2. Largest survival effects documented for:

• Hepatobiliary cancer	1.88 (1.07-3.30)
• Head and neck cancer	1.58 (1.22-2.03)
• Lymphoid or hematopoietic cancer	1.32 (1.11-1.56)
• Lung cancer	1.17 (1.03-1.34)
• Breast cancer	1.13 (1.05-1.21)

3. In 53 studies, stress-related psychosocial factors were associated with higher cancer mortality ($P<0.001$)

Chida et al. (2008) *Nature Clinical Practice Oncology*

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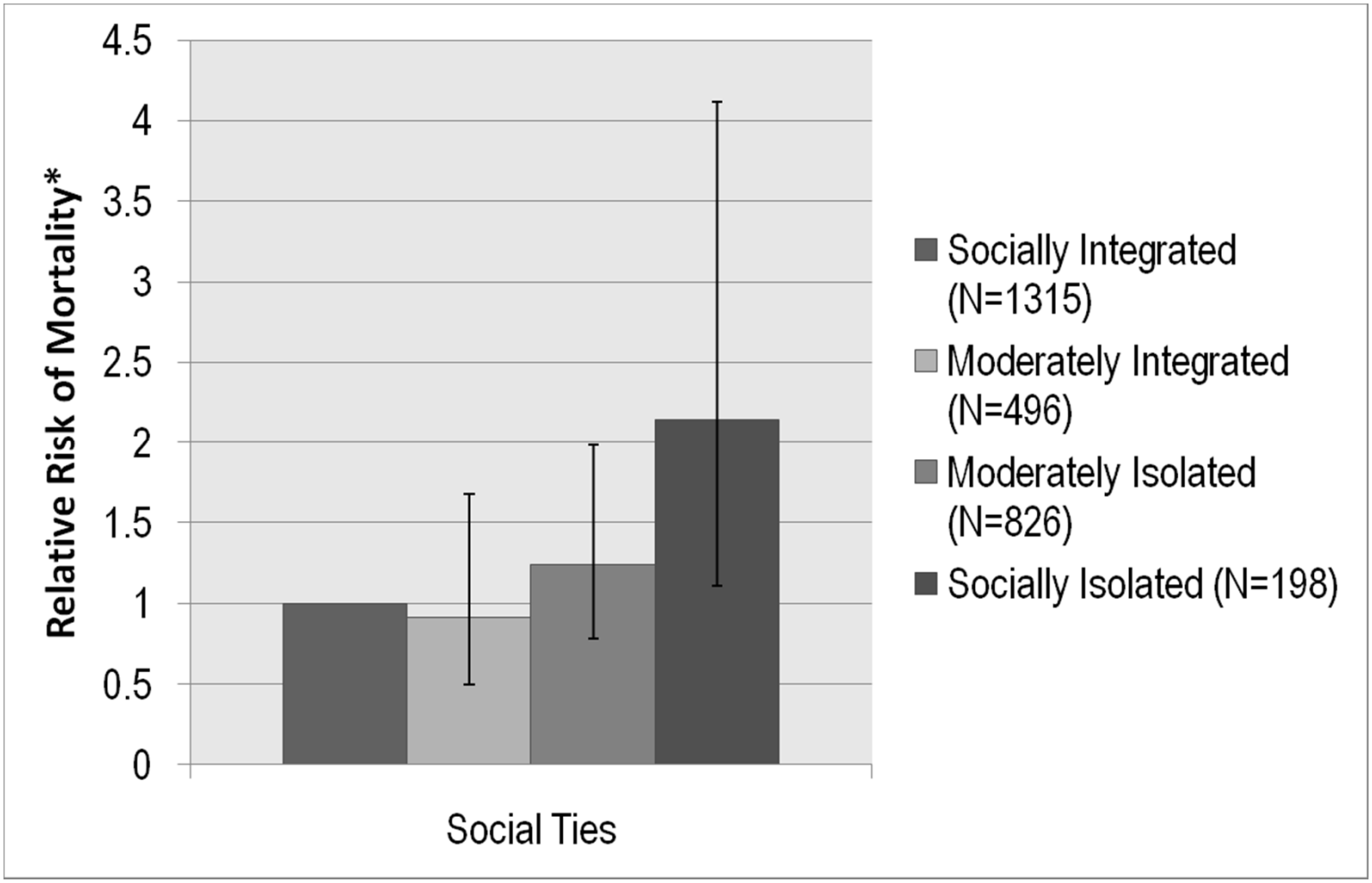
Breast cancer mortality risk: Nurses' Health Study



* Multivariate-adjusted for 18 epidemiological and clinical factors, including age, stage, treatment.

Kroenke et al. (2006) *Journal of Clinical Oncology*

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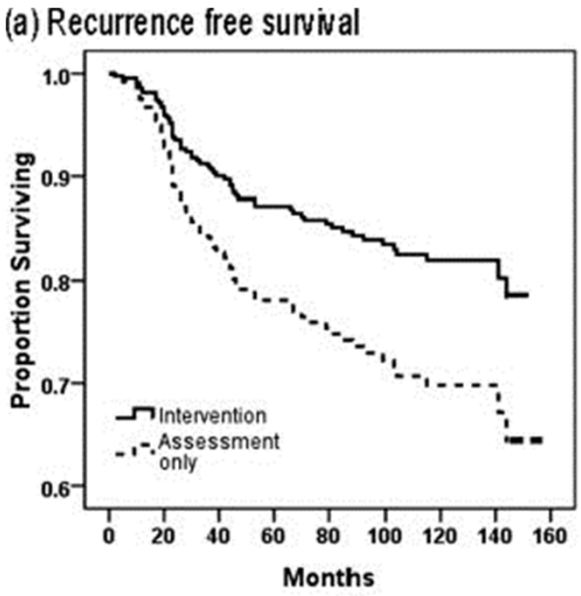
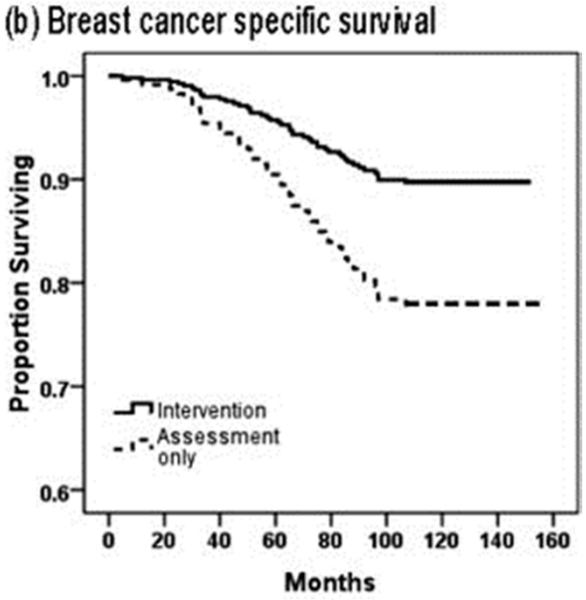
Survival effects of a stress targeted intervention



HR of 0.55; P=0.034



HR of 0.44, P=0.016

- Stage IIA – IIIB breast carcinoma patients (N=227)
- Group intervention of 26 sessions over 12 months
- 11 years median follow-up (range, 7-13 years)

Andersen et al. (2008) *Cancer*

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Summary

1. Substantial body of clinical research documents an association between stress and cancer survival and cancer mortality

2. As an example, data from the Nurses' Health Study show a two-fold increased risk of breast cancer mortality in socially isolated patients compared with socially integrated patients

3. Randomized trial shows that a stress-targeted intervention can improve long term prognosis following breast cancer treatment

- Major need to identify biological mechanisms that account for these effects

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Additional background slides

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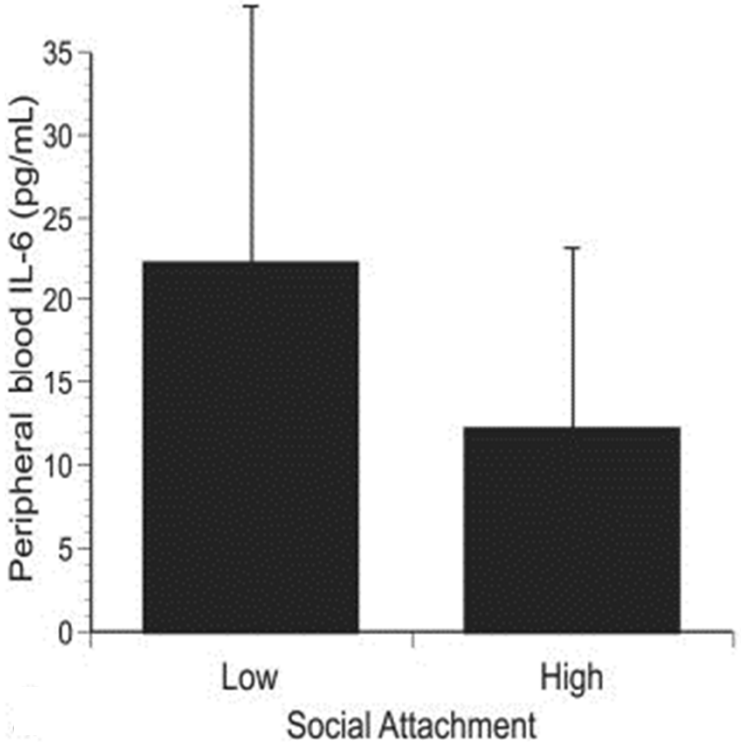
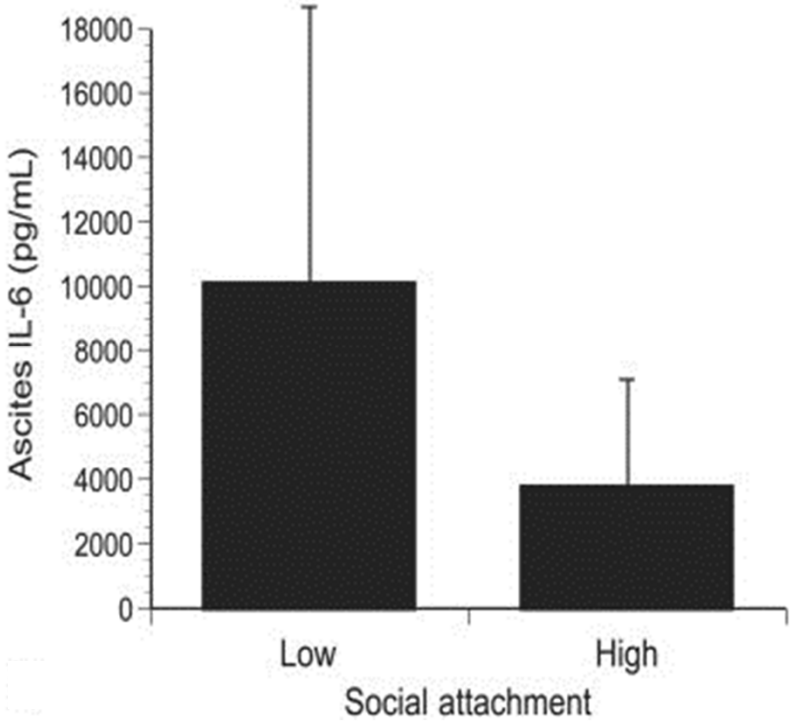
Low social ties associated with IL-6 in ovarian carcinoma

Peripheral blood



Ascites



Costanzo et al. (2005) *Cancer*

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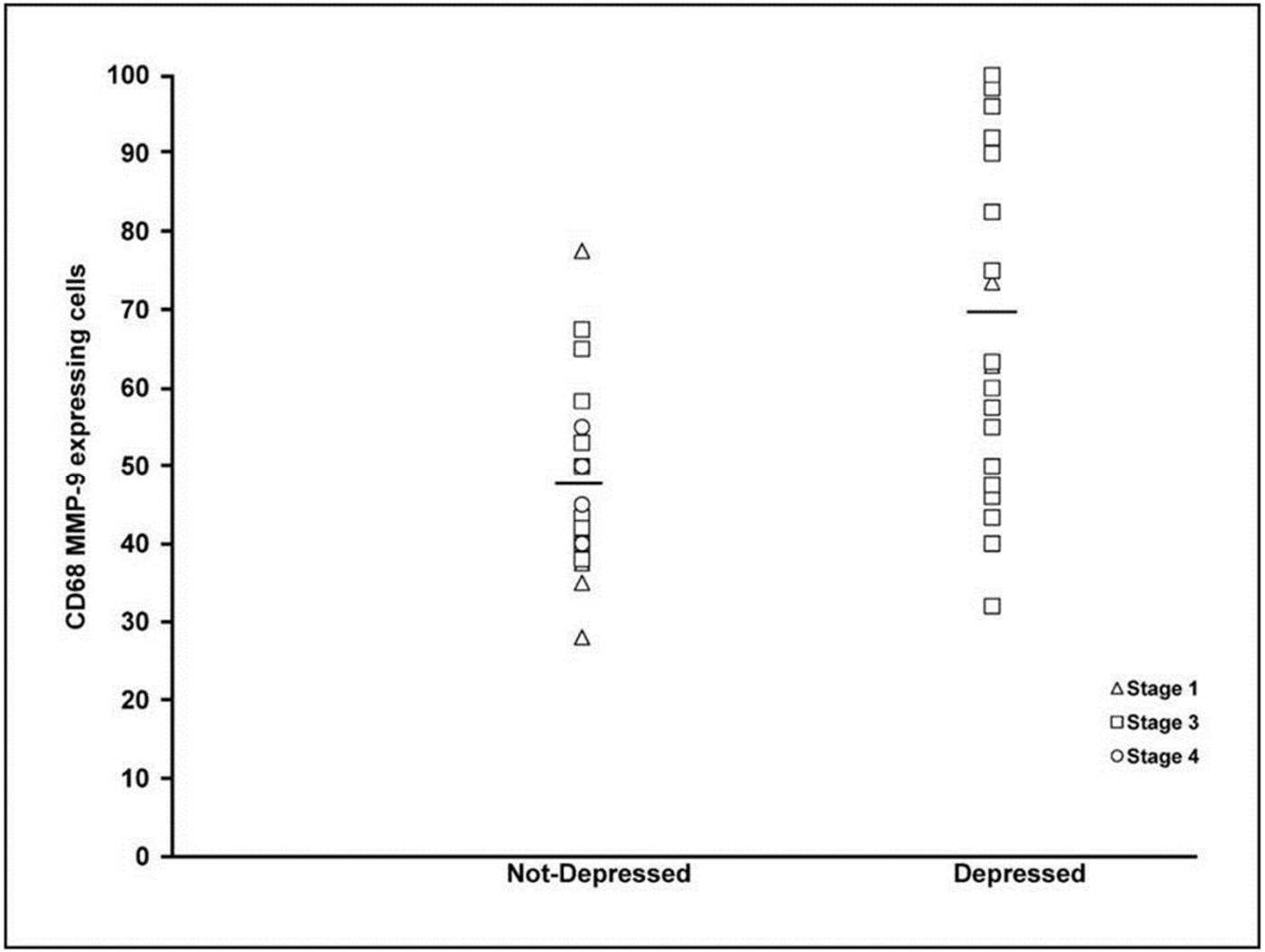
Depression and tumor-associated macrophage (CD68+ cells) expression of MMP*-9



* Matrix metalloproteinase

Lutgendorf et al. (2008) *Clinical Cancer Research*

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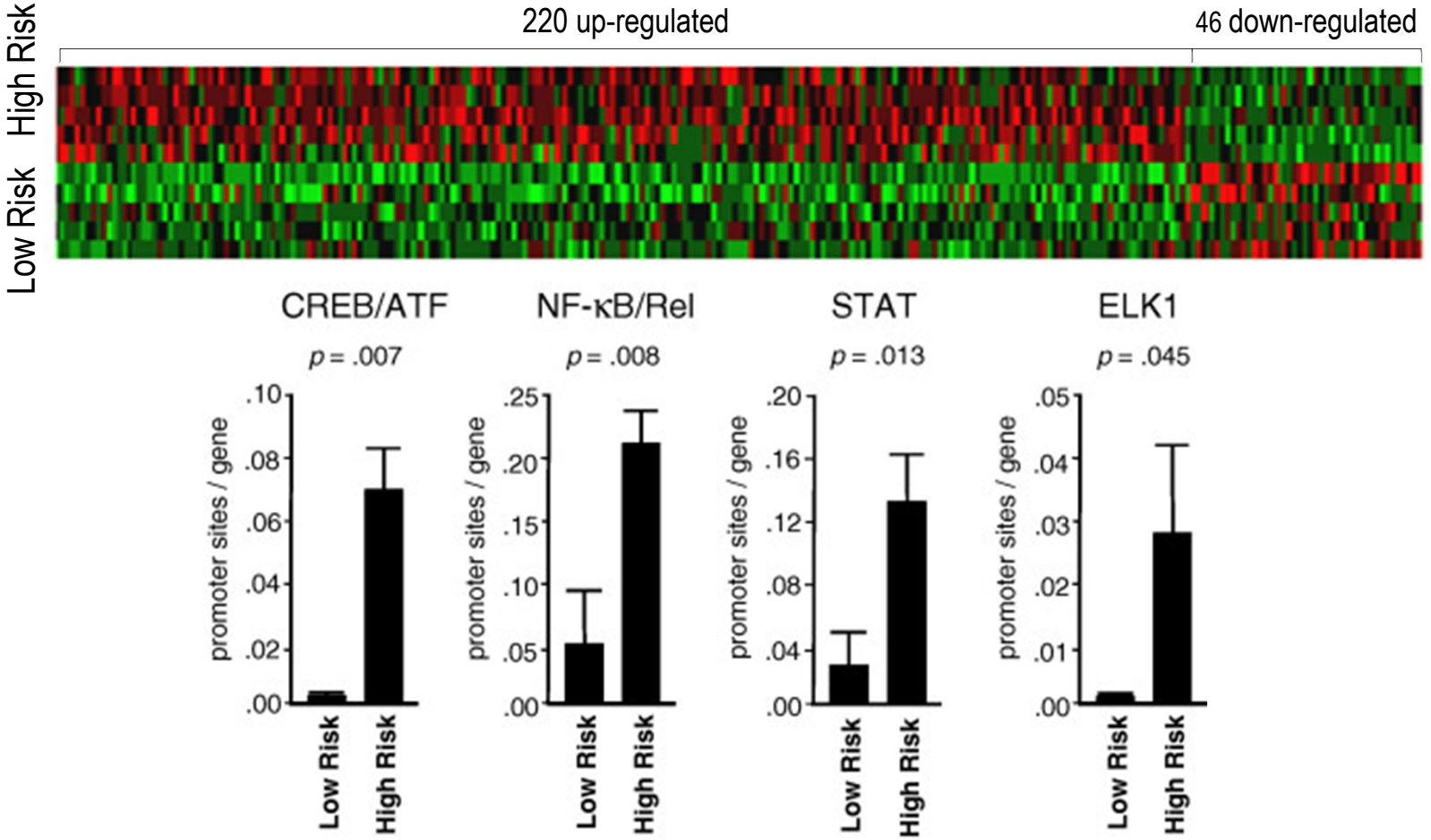
Tumor gene expression in ovarian carcinomas



Lutgendorf et al. (2009) *Brain, Behavior, and Immunity*

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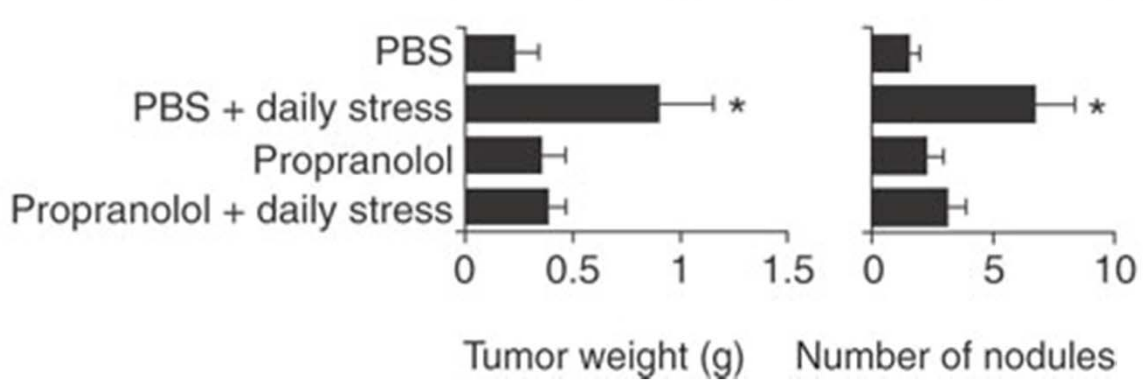
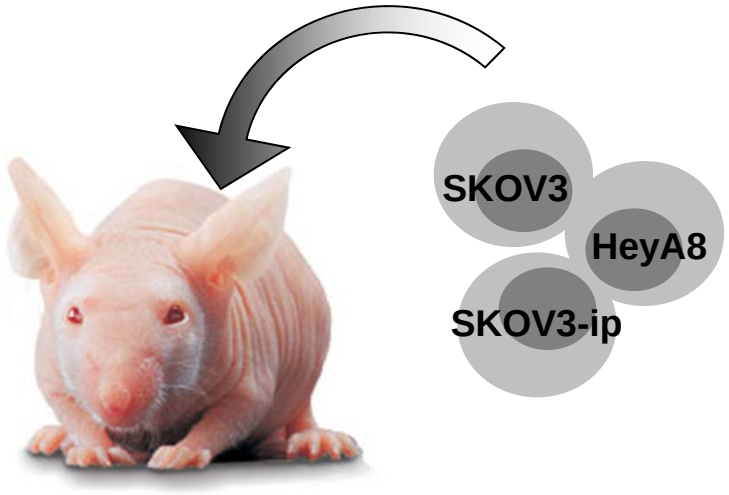
Beta-blockade inhibits experimental stress effects on ovarian cancer growth





Thaker et al. (2006) *Nature Medicine*

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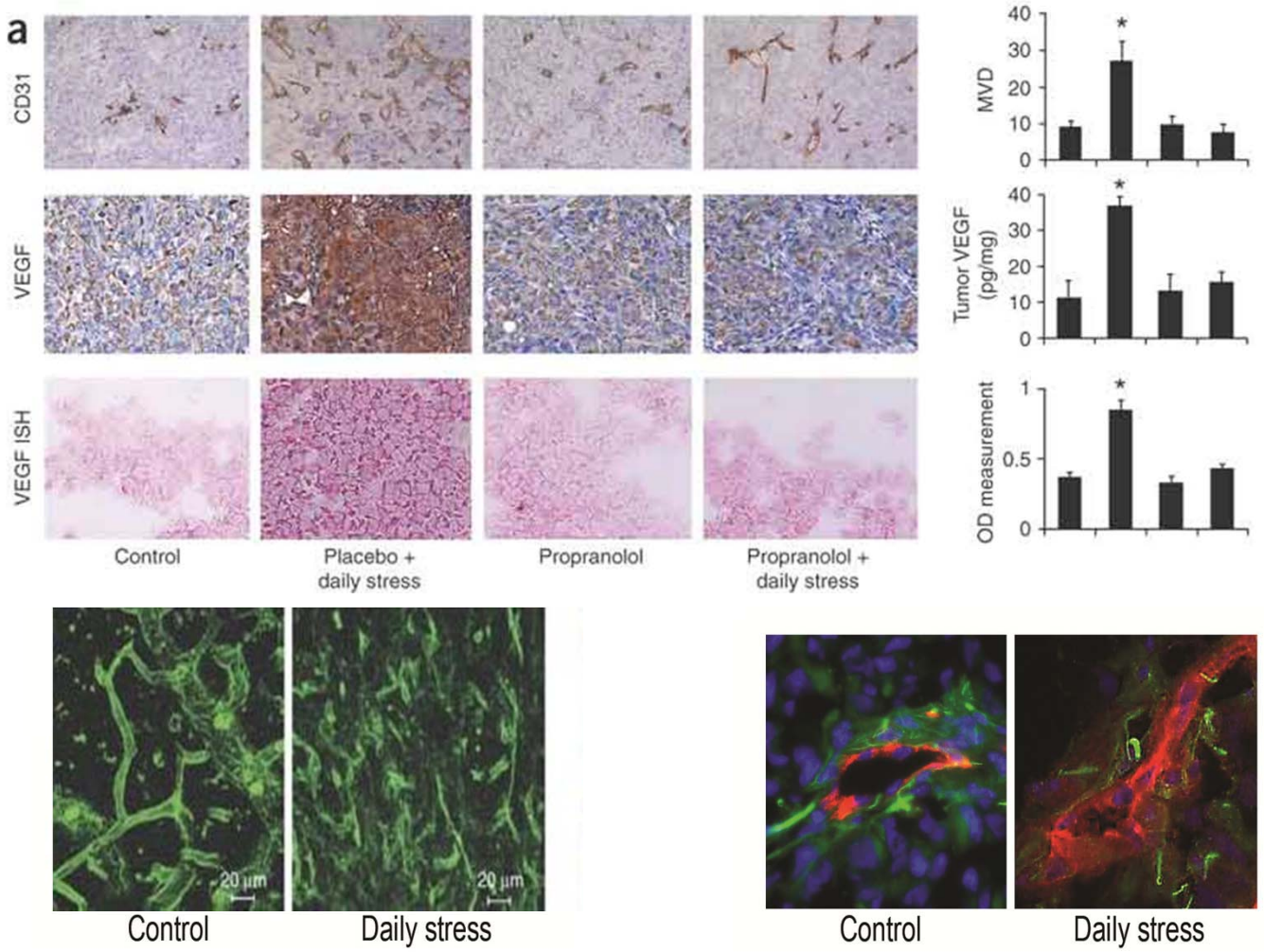
Experimental stress effects on angiogenesis



Thaker et al., (2006) *Nature Medicine*

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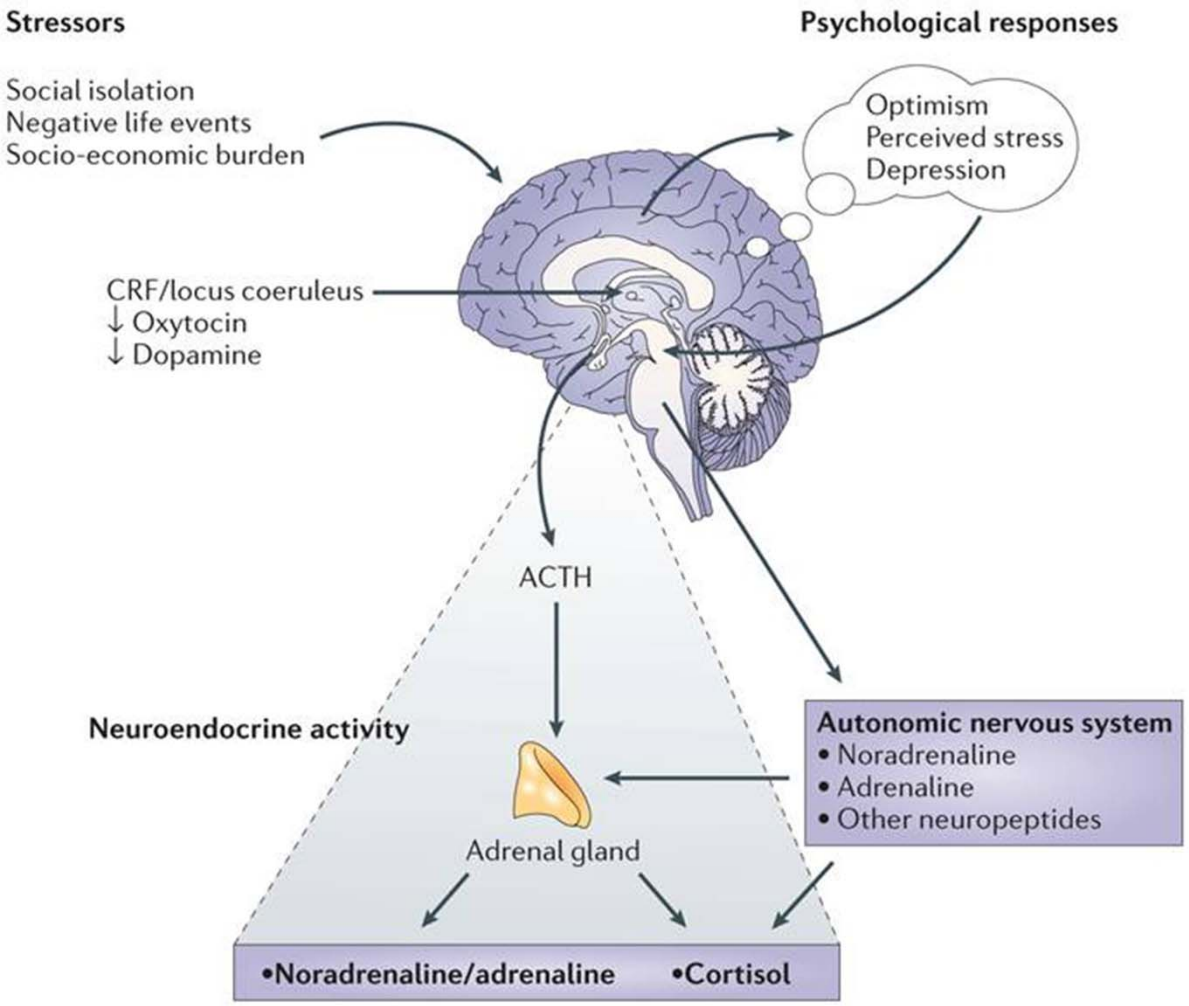
Neuroendocrine modulation of the tumor microenvironment



Antoni et al. (2006) *Nature Reviews Cancer*

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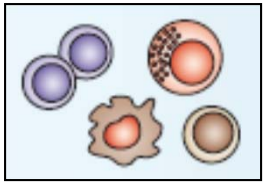
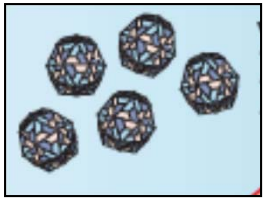
Neuroendocrine modulation of the tumor microenvironment

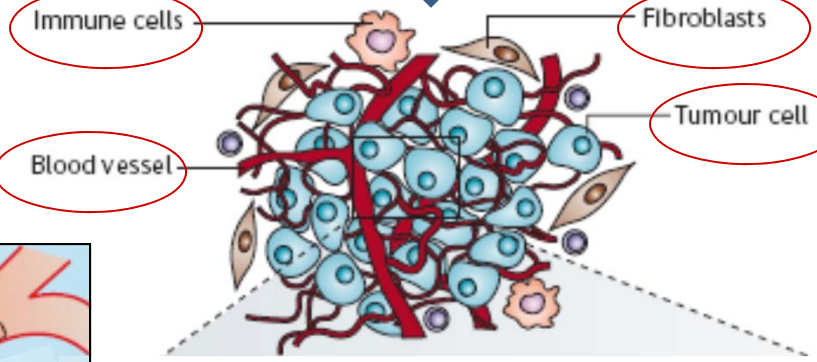
↑ Immune response
↑ Activity



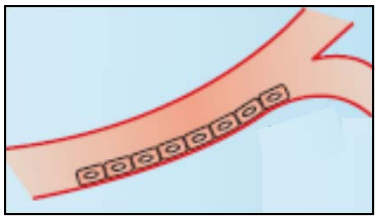
Catecholamines
Cortisol
Cytokines

↑ Oncogene transcription
↑ Viral replication
↑ Host-cell cycling

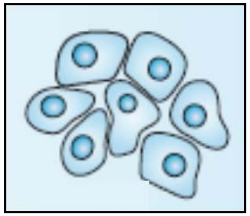




Tumor Microenvironment



↑ Angiogensis/pro-angiogenic cytokines (VEGF, IL-6, STAT3)



↑ Migration and invasion
↑ Proteases (MMPs)
* Altered DNA repair

Antoni et al. (2006) *Nature Reviews Cancer*

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RFA Purpose

Immediate goal:

- Establish new collaborations of basic cancer biologists, stress biologists, and translational scientists to clarify the range and mechanisms of stress effects on tumor growth, progression, and metastasis

Long-term goals:

- Maximize the breadth of patient populations that could benefit from stress protective pharmacological interventions

- Maximize biomarkers of stress effects on tumor biology for use in clinical/translational studies

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Justification for use of RFA mechanism

- Incentive needed to encourage new transdisciplinary teams and scientific investment
- Critical mass of funded research needed to maximize network environment and leverage relevant expertise
- Targeted funding needed to accelerate progress

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Scope of the RFA

- Support of 8 -10 awards
- R21 and R01 mechanisms solicited
  - R01 applications:
    - Encouraged to use multiple PI designation
    - Required to use human/clinical samples
    - Inclusion of comparative studies with other model organisms

Year 1	Year 2	Year 3	Year 4	Total
R21/R01	R21/R01	R01	R01	
$4.5M	$4.5M	$2.8M	$2.8M	$14.6M

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Evaluation of the RFA

Did the initiative promote the discovery of:

1. Tumor types most subject to regulation by stress biology
2. Mechanisms involved in direct effects of stress mediators on tumor biology
3. Relevant biomarkers of stress in tumor tissue or serum
4. Molecular and therapeutic targets

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American Association for Cancer Research

- Biology, Behavior, and the Physical Environment: Exploring Interactions to Address Health Disparities
  - Second AACR Conference on the Science of Cancer Health Disparities (2009)
- Cancer Susceptibility: Environment-Gene Interaction
  - 99th AACR Annual Meeting (2008)
- Translational Models of Bio-behavioral Stress
  - First AACR International Conference on the Science of Cancer Health Disparities (2007)
- Immune System as a Target for Prevention
  - Sixth AACR International Conference on Frontiers in Cancer Prevention Research (2007)
- Genes Associated with Tumor Progression and Resistance
  - 98th AACR Annual Meeting (2007)
- Biobehavioral Mechanisms and Cancer Progression
  - Fifth AACR International Conference on Frontiers in Cancer Prevention Research (2006)