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New Frontiers in Cancer Control Research: Stress Regulation of Tumor Biology

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RFA Concept Presentation
NCI Board of Scientific Advisors
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RFA Purpose

- Understand the biological and clinical relevance of stress mediators and corresponding receptors within the tumor microenvironment
- Delineate the molecular mechanisms and signal transduction pathways of stress-mediated effects on tumor progression and metastasis

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RFA Vision

Support transdisciplinary collaborations of cancer biology and stress biology expertise to:

1. Expand the range of tumor types analyzed for effects of stress biology on cancer progression
    - Maximize the breadth of patient populations that might benefit from stress protective pharmacological interventions
2. Expand the range of tumor biology parameters analyzed for regulation by stress biology
    - Maximize biomarkers of stress effects on tumor biology for use in clinical/translational studies

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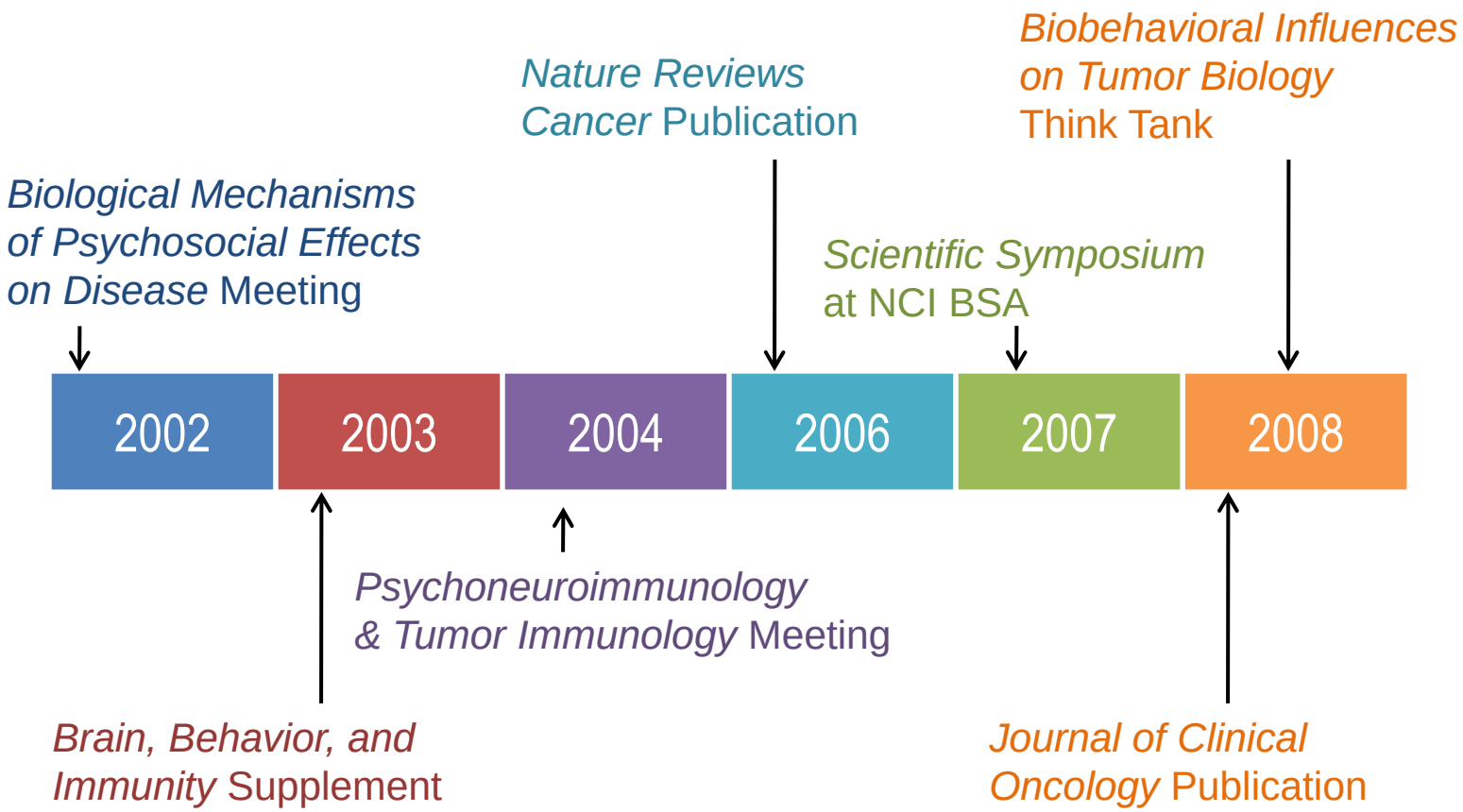

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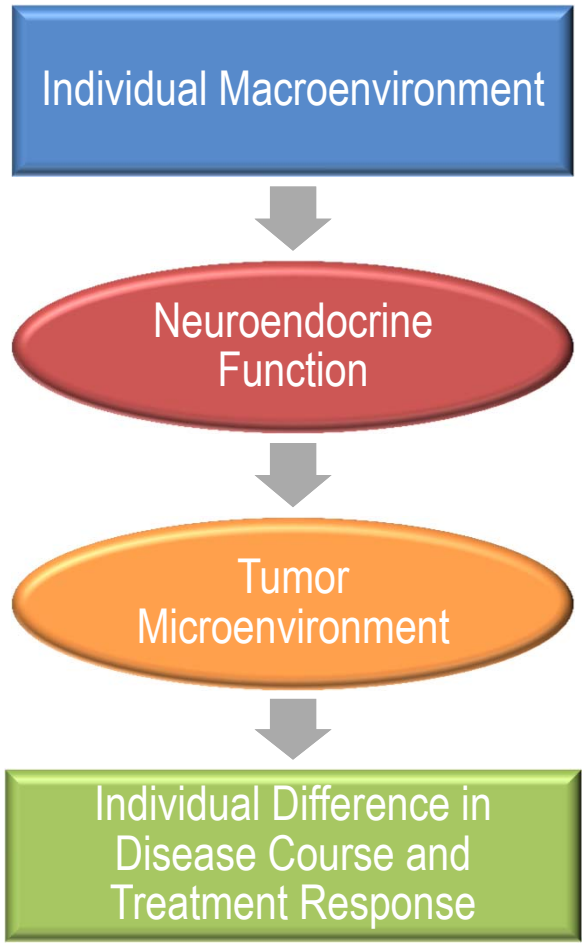
Conceptualization of stress

- Dynamic state of threatened or perceived threatened homeostasis
- Activation of primary stress systems
  - Hypothalamic-pituitary-adrenal axis (HPA)
  - Sympathetic nervous system (SNS)
- Principal stress hormones
  - Catecholamines
  - Glucocorticoids



Adapted from Cole (2008)

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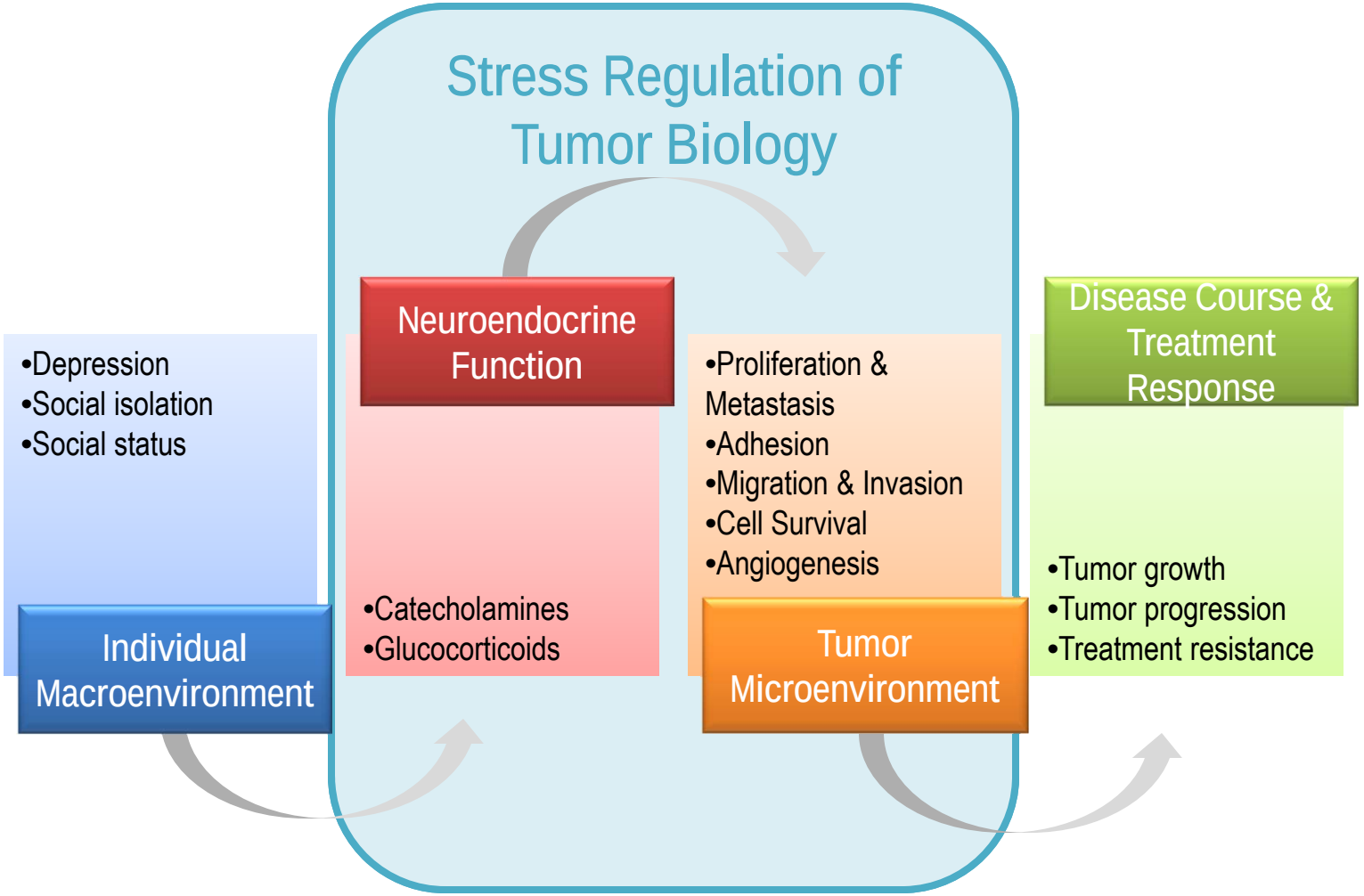
Scientific scope of RFA



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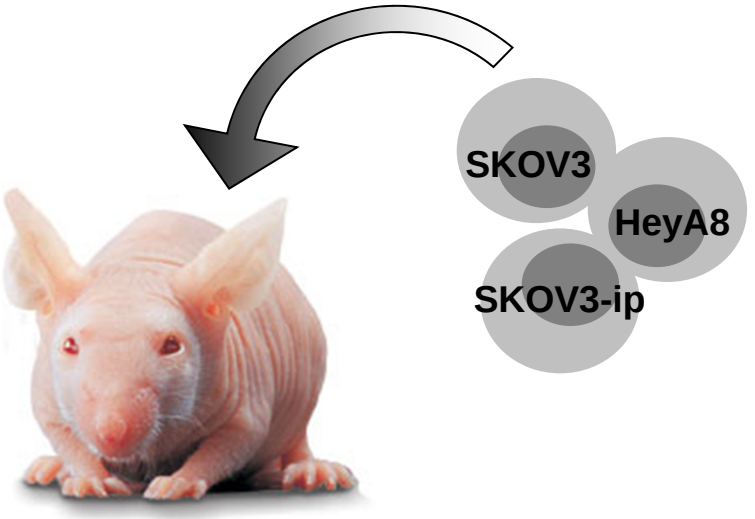
Exposure to chronic stress promotes tumor growth and angiogenesis

- Use of mouse host-human tumor hybrid model
- First experimental evidence that behavioral stressors can enhance pathogenesis of ovarian carcinoma *in vivo*
- Neuroendocrine stress response affects the growth and activity of malignant tissue through hormone receptors expressed by tumor cells



nature medicine

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

Thaker et al., (2006)

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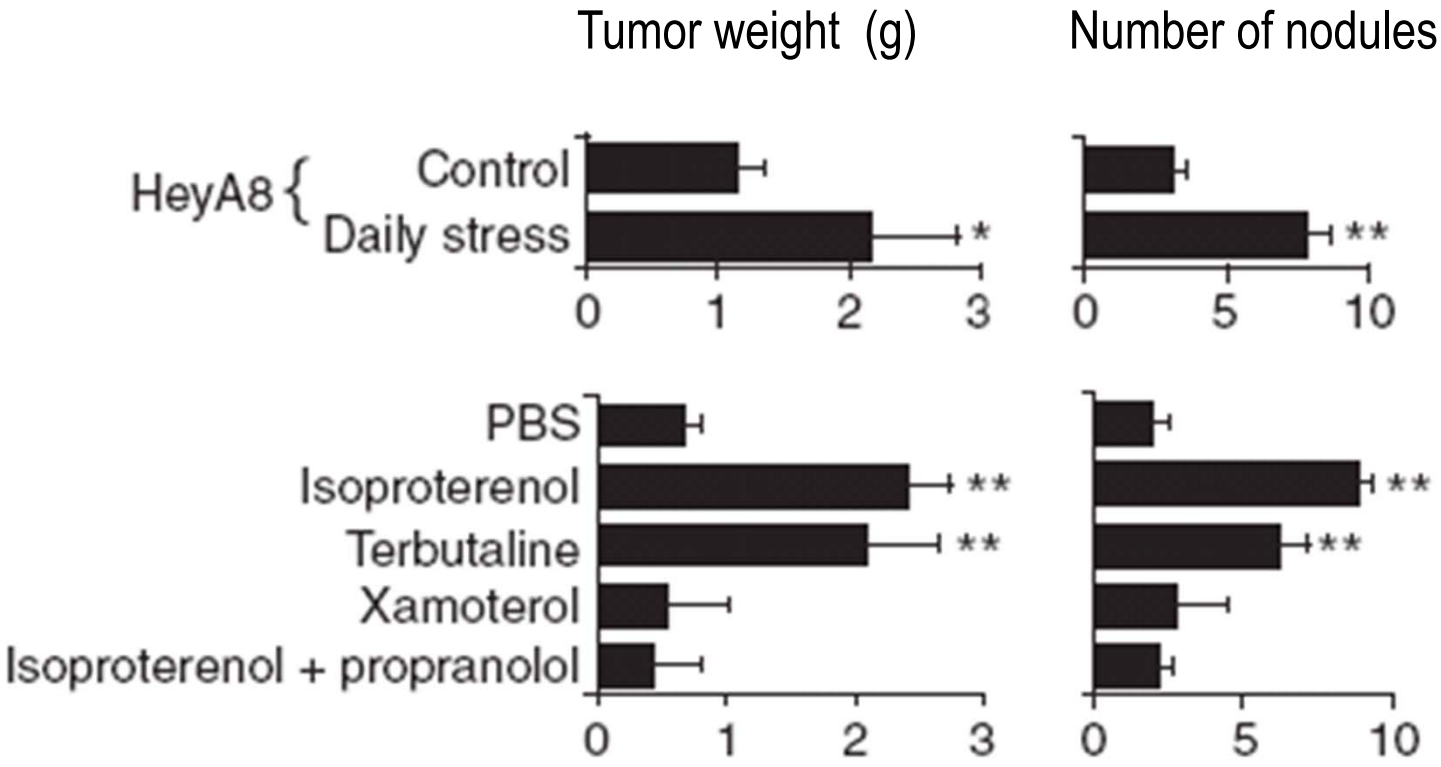
Exposure to chronic stress: Ovarian carcinoma growth *in vivo*



Thaker et al., (2006)

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Stress effects on ovarian carcinoma growth *in vivo*

- Experimental results demonstrate that chronic exposure to stress and to social isolation result in enhanced tumor growth

- Two molecular mechanisms identified:
  1. Stress regulation:
     Catecholamine signaling via beta-adrenergic receptors
  2. Tumor biology:
     Up-regulated angiogenesis

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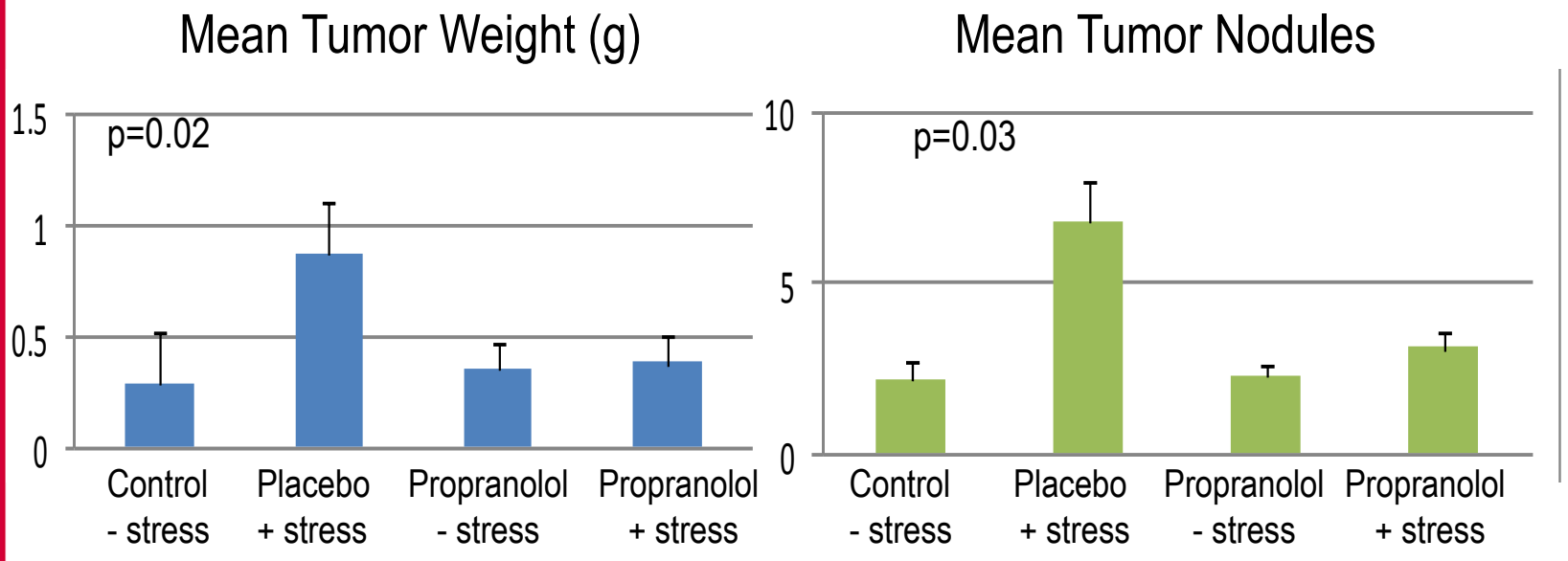
Propranolol counteracts the effects of chronic stress



Adapted from Thaker et al., (2006)

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Stress effects on ovarian carcinoma growth *in vivo*

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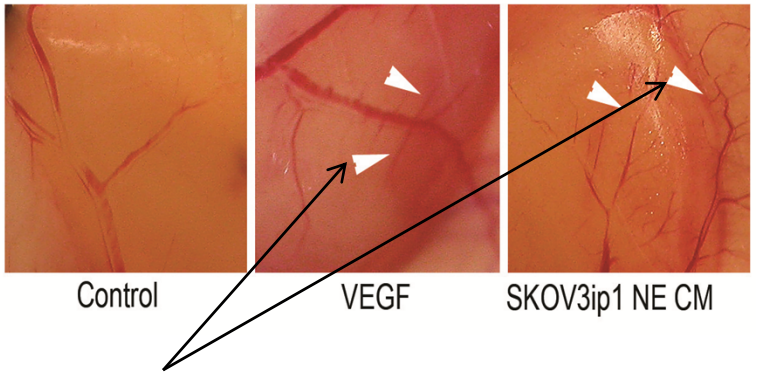
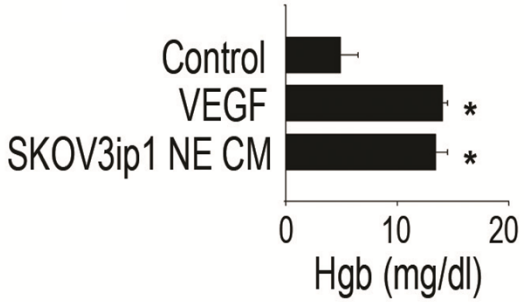
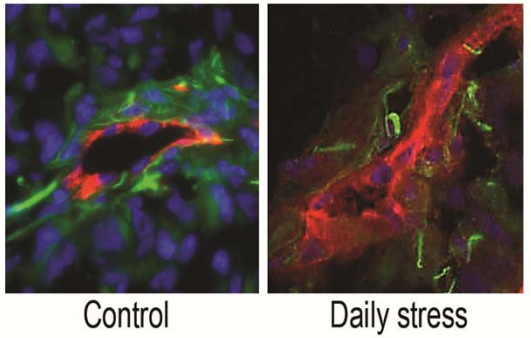
Effects of chronic stress on angiogenesis



Newly Formed
Blood Vessels
in Matrigel

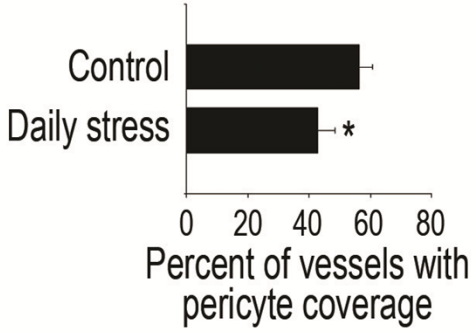




Pericytes

Nuclei

Endothelial
Cells



Thaker et al., (2006)

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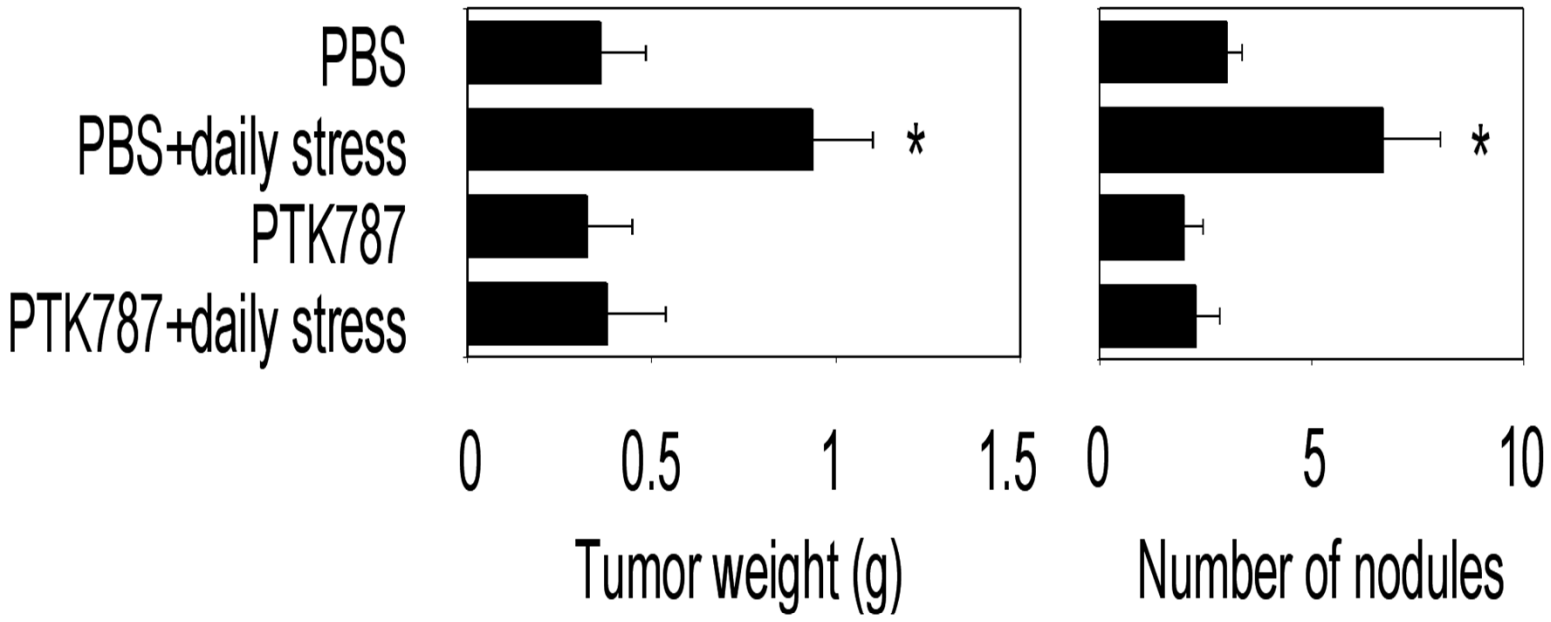
Effect of VEGF-R inhibition on HeyA8-injected mice



Thaker et al., (2006)

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Implications and limitations

- Implication: β-blockade might help slow tumor progression in human ovarian cancer
- Limitation:
  - Relevance to other cancer types
  - Role of other tumor biology mechanisms
    - Invasive capacity
    - Oncogene activity
    - Cell survival and adhesion
    - Inflammation
    - Chemotherapeutic resistance

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Justification for the RFA

- Facilitate clinical translation by defining breadth and mechanisms of neuroendocrine effects on tumor biology
- Collaborative transdisciplinary research teams required
  - Cancer biology
  - Neuroendocrinology
- A special emphasis panel is essential
  - The concept will require special criteria for review and diverse expertise to evaluate the merit of the applications

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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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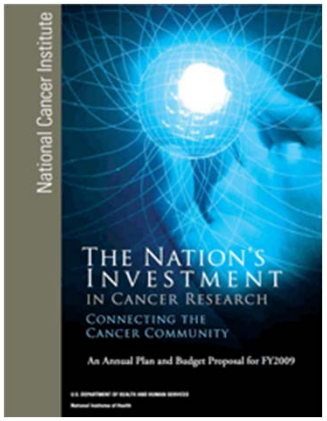
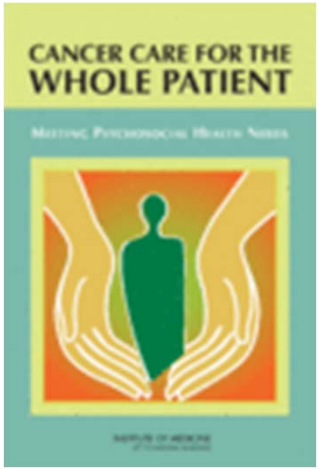
Timeliness of RFA

- Importance of individual differences
  - The Nation's Investment in Cancer Research, NCI 2008
- Recognition that stressors created or exacerbated by cancer can exert direct effects on biological processes that regulate tumor progression
  - Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs, IOM 2007
- Opportunity to leverage resources and knowledge
  - The Genes, Environment and Health Initiative (GEI)





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RFA Concept:
Stress regulation of tumor biology

- Promising pre-clinical research in ovarian cancer

- Aim: Facilitate clinical translation
  - Define breadth of tumor types affected
  - Define range of tumor biology mechanisms involved

- Mechanism: Collaborative transdisciplinary research teams
  - Cancer biology
  - Neuroendocrinology

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Clinical opportunities

- Test prognostic value of b-receptor expression and polymorphisms
- Determine effects of chronic stress and catecholamine levels and its effects on the tumor microenvironment
- Identify novel biomarkers that can identify those cancer types and biobehavioral risk profiles that are most likely to be affected by the stress response
- Determine the effects of pharmacological and or/ behavioral interventions on biomarker modulation, progression free survival and eventually overall survival

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Historical perspective: Stress and cancer

- Clinical observations
- Epidemiological associations inconsistent
  - More consistent associations for disease progression than for disease incidence
- Early experimental and clinical studies
  - Virally induced tumors in experimental animal models
  - Role of immune response

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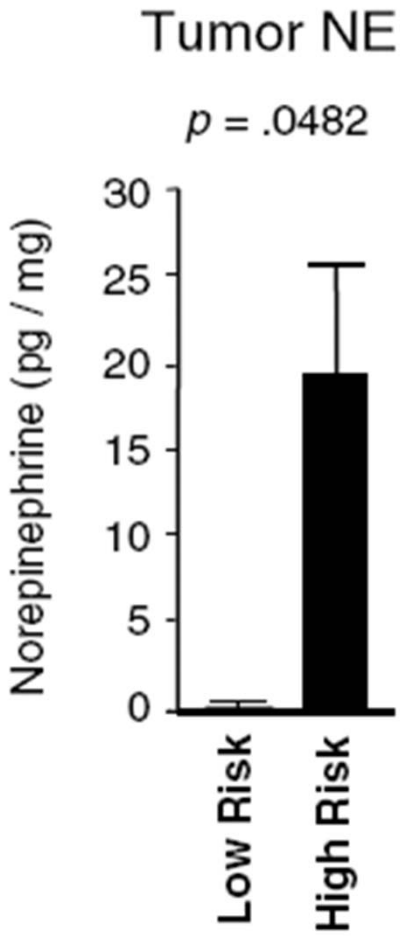
Contemporary perspective: Stress and cancer

- Emerging focus on:
  - Biochemical mediators of stress, rather than the subjective experience of stress
  - Assessing relationships within the tumor and its microenvironment, rather than the periphery
- Substantial support in experimental animal models
  - Recent observations in rigorous experimental designs:
    - Validated animal models and stressor paradigms with translational relevance



Lutgendorf et al., (2008)

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Key Recommendations

- Determine mechanisms, pathways, and critical targets
- Consider important methodological considerations
  - Tumor type, accessibility, microenvironment, disease course
- Engage diverse expertise, encourage transdisciplinary collaboration and cultivate a research network environment

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Potential Research Topics

- Determine which tumor types and tumor genomes are sensitive to the physiologic stress response (PSR)
- Determine which endocrine and neurobiological molecules mediate effects of stressors on tumor biology
- Characterize specific aspects of tumor biology that are affected by the PSR
- Understand the biological influence of the PSR on the cancer continuum and during the perioperative period, treatment, and progression free survival
- Identify molecular pathways by which behavioral or pharmacological interventions can protect against the deleterious effects of the PSR on tumor biology