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
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)
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*
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
Survival effects of a stress targeted intervention

- 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)

HR of 0.55; P=0.034  HR of 0.44, P=0.016

Andersen et al. (2008) Cancer
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.
Additional background slides
Low social ties associated with IL-6 in ovarian carcinoma

Costanzo et al. (2005) Cancer
Depression and tumor-associated macrophage (CD68+ cells) expression of MMP*-9

* Matrix metalloproteinase

Lutgendorf et al. (2008) Clinical Cancer Research
Tumor gene expression in ovarian carcinomas

High Risk: 220 up-regulated, 46 down-regulated

Low Risk

Lutgendorf et al. (2009) *Brain, Behavior, and Immunity*
Beta-blockade inhibits experimental stress effects on ovarian cancer growth

Thaker et al. (2006) Nature Medicine
Experimental stress effects on angiogenesis

Neuroendocrine modulation of the tumor microenvironment

Stressors
- Social isolation
- Negative life events
- Socio-economic burden

Psychological responses
- Optimism
- Perceived stress
- Depression

CRF/locus coeruleus
↓ Oxytocin
↓ Dopamine

ACTH

Neuroendocrine activity

Adrenal gland
- Noradrenaline/adrenaline
- Cortisol

Autonomic nervous system
- Noradrenaline
- Adrenaline
- Other neuropeptides

Antoni et al. (2006) Nature Reviews Cancer
Neuroendocrine modulation of the tumor microenvironment

↑ Immune response
↑ Activity

↑ Oncogene transcription
↑ Viral replication
↑ Host-cell cycling

Catecholamines
Cortisol
Cytokines

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

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

Antoni et al. (2006) Nature Reviews Cancer
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
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
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

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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
American Association for Cancer Research

- Biology, Behavior, and the Physical Environment: Exploring Interactions to Address Health Disparities
- Cancer Susceptibility: Environment-Gene Interaction
- Translational Models of Bio-behavioral Stress
- 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