Linking physiological pathways to translational strategies

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Where we’re at:

1. Mounting pre-clinical evidence
   - Stress biology can causally impact tumor biology & cancer progression
   - Most consistent effects: early progression/metastasis
     Possible “initiation” exceptions: Inflammatory and viral-mediated initiation
   - Neural-immune activation (macrophage) more prominent than neuro-immune suppression (cellular immune response)

2. Entrenched clinical/translational skepticism
   - Critics: we believe you - stress is bad for cancer.
     Little credible evidence that stress-targeted interventions meaningfully impact clinical cancer progression.
     (Also: Stress is everywhere, I can’t measure it, blah blah blah)

3. Needed: a strong clinical success story
   - Neural/endocrine-targeted intervention (e.g., β-blockers)
   - Social/behaviorally-targeted intervention (e.g., Andersen, Antoni)
Translational rationale:

1. Stress biology is a “big” problem:
   - Pleiotropic effects of neural / endocrine systems
   - Multiple progression mechanisms (EMT/invasion, angio, survival, evasion)
   - Multiple cell types (tumor, myeloid, T cell)
   - Multiple genes (10s – 100s)

2. Stress biology is a highly leveraged opportunity:
   - One intervention can impact multiple biological processes

3. The challenge:
   - How to harness that promise & maximally reduce (ca-relevant) stress biology

   1. Choose the right battle (pt & disease context)
   2. Credible theory of action (basic science rationale, rational metrics)
   3. Plausible intervention strategy (empirically tested, “bias-compliant”)
   4. Clinical feasibility (easy, cheap, consistent/reliable)
Tumor “macroenvironment” model

Social environment

CNS function

Peripheral neurobiology

Cell signal transduction

Transcription factors

Gene expression

Tumor progression

Disease progression
Tumor “macroenvironment” model

Targeting questions:
1. Which intervention(s)?
2. Which outcomes?
3. Which mediators?
4. Which disease?
5. Which person?

1° tumor (CRP, PBMC?)
Imaging (CTC? DNA?)
OS, PFS / recurrence
Increment to 5 year cancer-specific survival (%)

Socio-Economic Status (SES)
- Median income per year:
  - $9,000-$19,000
  - $20,000-$39,000
  - $40,000-$59,000
  - $60,000-$82,000

Primary Relationship Status (PRS)
- Single
- Married
- Separated
- Divorced
- Widowed
Figure 2

PRS increment to 5 year cancer-specific survival (%)

-5 0 5 10 15 20 25 30

Carcinoma
Sarcoma
Nervous
Hematologic
Other
Tumor “macroenvironment” model

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Tumor “macroenvironment” model

Social environment

CNS function

SNS activity
- β-adrenergic signaling
  - CREB, GATA AP-1, etc.
  - Myeloid, EMT, Angio

HPA-axis activity
- GR signaling
  - GR translocation
  - Survival, Ctx Resist

Tumor progression

Disease progression
Translational horizon 2013:

1. Phase II biomarker data:
   - “Small” randomized trials with biomarker outcomes
   - Tumor biomarkers (imaging, window biopsy protein/gene, CTC)
   - Gateway to well-powered clinical outcome studies

2. Externally “plausible” interventions
   - Strong pharmacologic candidate: Propranolol
   - Biomarker-validated behavioral interventions? (don’t forget physical activ)
   - “Combination therapy” (e.g., Ben-Eliyahu)
   - Be straightforward about feasibility / cost / scaling potential.

3. Personalization
   - Stress targeting?
   - Tumor genomic “sensitivity/resistance” to biobehavioral interventions
CREB

β

2 adrenergic

receptor

Norepinephrine

Adenylyl
cyclase

PKA

ATP            cAMP

Sp1

Transcription of
disease-related genes
Selection for β-AR pathway gene alterations in ovarian cancer
Selection for β-AR pathway gene alterations in ovarian cancer
Selection for $\beta$-AR pathway gene alterations in ovarian cancer

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13 / 14: $p = .00006$
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