Stress Management Effects on Biological and Molecular Pathways in Women Treated for Breast Cancer

APS/NCI Conference on “Toward Precision Cancer Care: Biobehavioral Contributions to the Exposome”
Chicago IL

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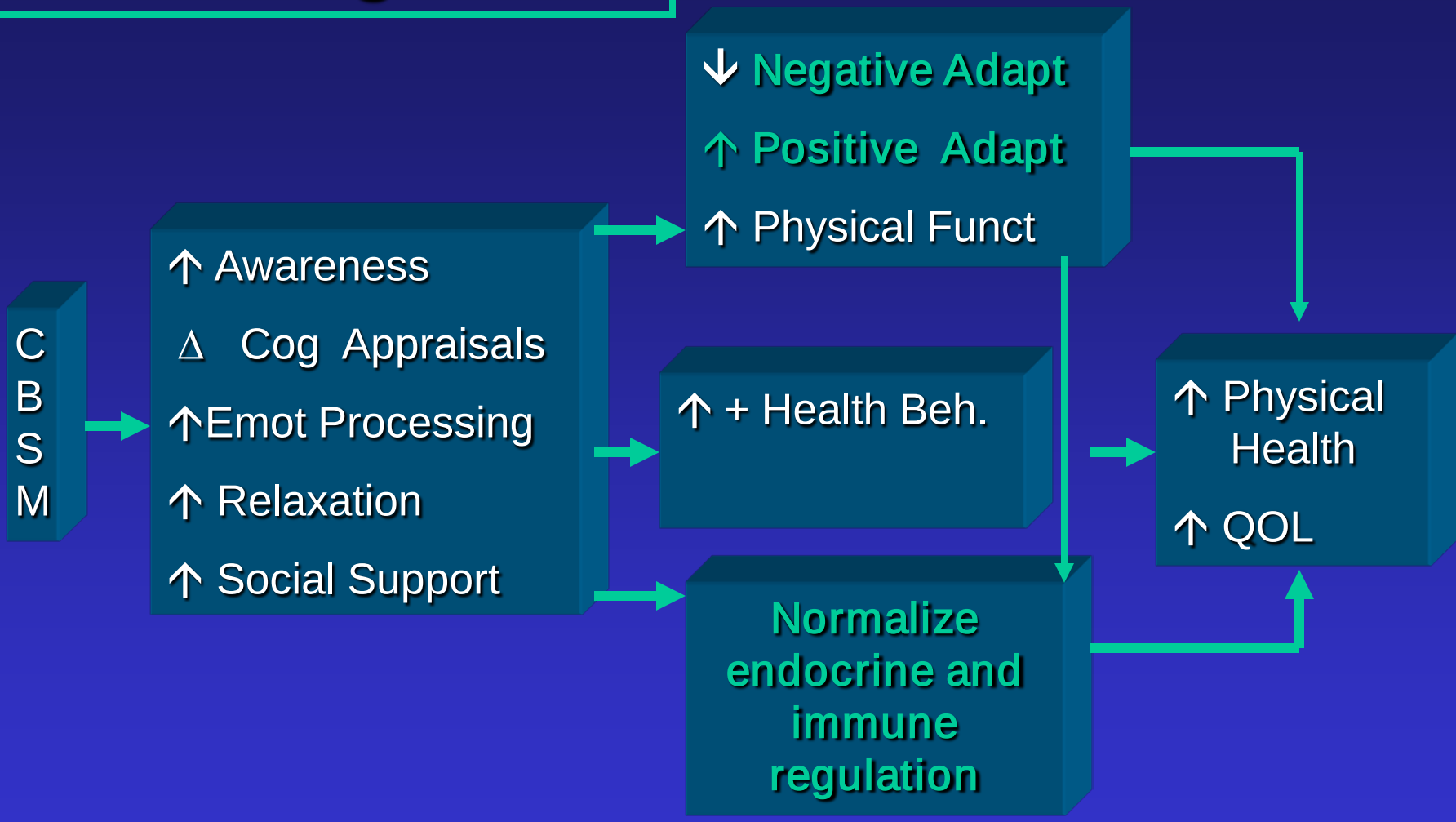
E.g., Stress Management for Women with Breast Cancer

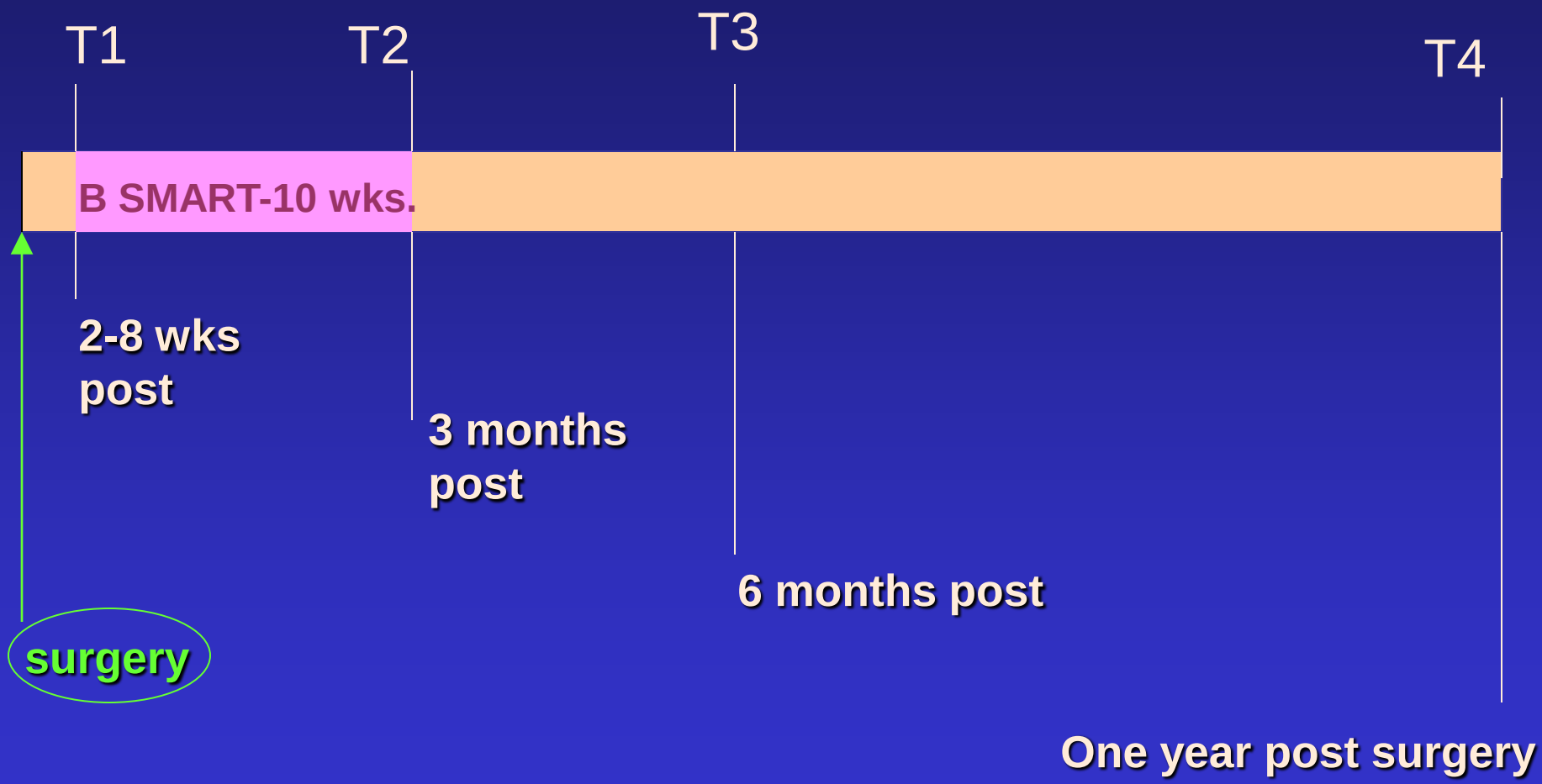
- **Rationale**
  - **Breast Cancer (BCa) is a stressor**
  - **Challenges of surgery and adjuvant tx**
  - **Patient assets can facilitate adjustment**
  - **Cognitive Behavioral Stress Management (CBSM) can fortify these assets in women with BCa**
  - **Improving Psychosocial Adaptation may Affect Physiological Adaptation**

Theoretical Model for CBSM during CA Tx



Antoni (2003). *Stress Management for Women with Breast Cancer.* American Psychological Association.

Assessment Time Points



Topics of CBSM

Week	Relaxation	Stress Management
1	PMR 7	Stress & Awareness
2	PMR 4/D.B.	Stress & Awareness/Stress Appraisals
3	D.B./PMR	*Disease-Specific*, Automatic Thoughts
4	Autogenics	Auto. Thghts, Distortions, Thght Rep.
5	D.B./Visualiz.	Cognitive Restructuring
6	Sunlight Med.	Effective Coping I
7	Color Meditation	Effective Coping II
8	Meditation	Social Support
9	Mindfulness	Anger Management
10	Part. Choice	Assertion Training & Program Review

(Antoni et al., 2003, 2007; Penedo et al., 2008)

Control Condition

- **Std Care Plus Half-day Psychoeducational Seminar**
  - **Groups of 4 – 6 women**
  - **Health Educational on BCa**
  - **Outlined Stress Management Techniques**
  - **Akin to Self-Help Seminar**

CBSM Intervention after Surgery for Breast Cancer:

Psychological adaptation:

- **decreased negative adaptation: Neg Affect, anx, soc disruption, fatigue, sleep disrupt**
- **increased positive adaptation: Pos Affect, benefit finding and optimism**
- **increased perceived relaxation skills, CBT and emotion processing important**

Physiological adaptation????

Antoni et al (2001) *Health Psychology*, *20*, 20-32;
Cruess, Antoni et al (2000) *Psychosomatic Medicine*, *61*, 94.
McGregor et al., (2004*) J. Psychosom Res, 56, 1 – 8;*
Antoni et al. (2006) Amer J. Psychiatry

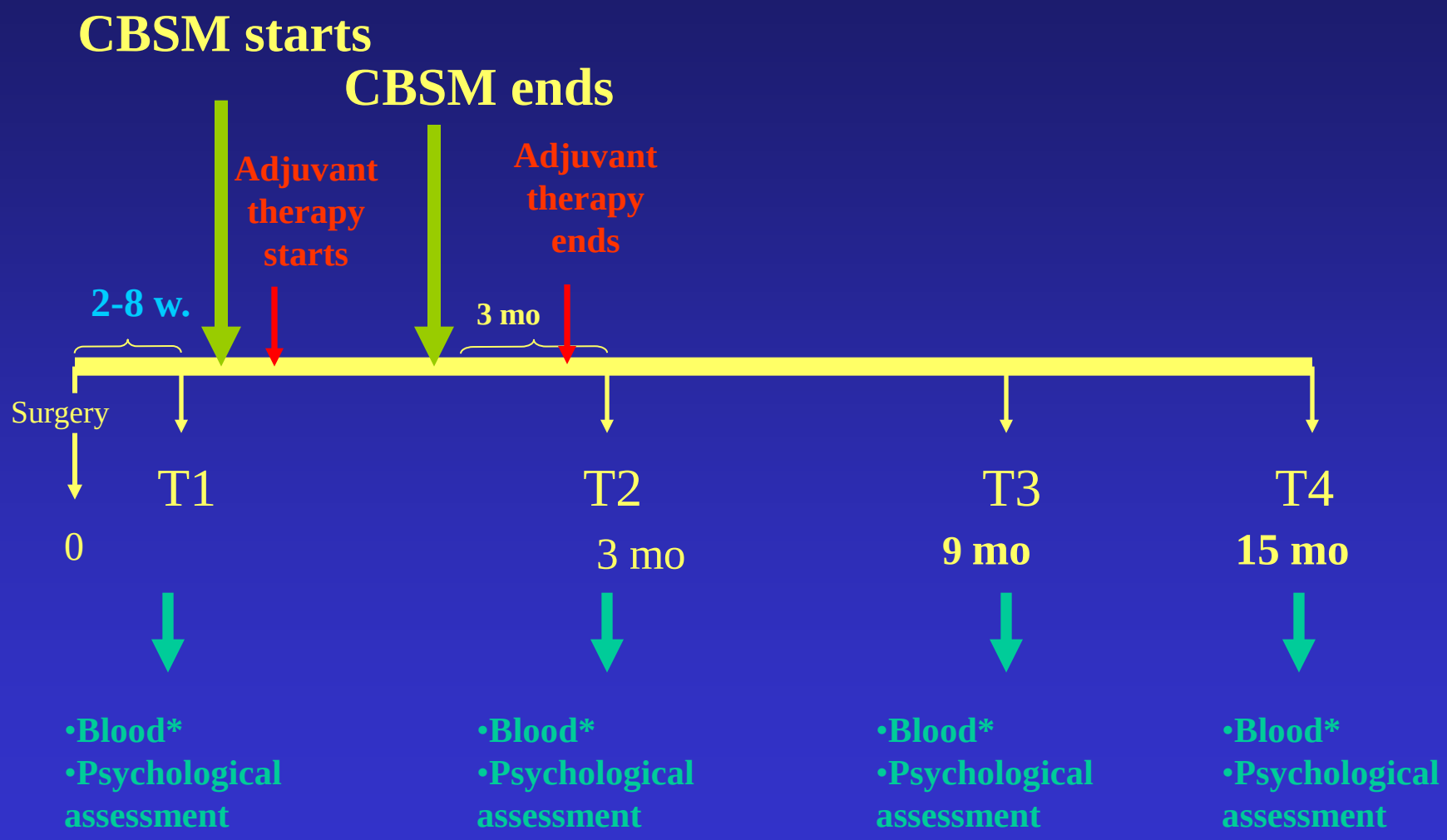
Elements of CBSM and Putative Effects on Physiology

- **Relaxation**
  - PMR, Imagery, Mindfulness, Breathing
  - Decreases tension and anxiety and SNS/HPA activation
  - SNS-immune communications:
    - NE is ligand for immune cells β-adrenoreceptors → down-reg of cellular immunity
    - CRH→cortisol increase via HPA axis→cortisol ligand for GR→down-reg immune

- **Cognitive Restructuring and Coping Effectiveness Training**
  - Raise awareness of stress cues
  - Change negative/inaccurate stressor appraisals
  - Increase pos reframing and acceptance coping
  - Decreases depression and anxiety → SNS and HPA effects

- **Interpersonal Skills Training/Supportive Group**
  - Assertiveness and anger mgmt to attract /maintain social support
  - Group format models seeking and receiving support
  - Social support buffers similar stress-related neuroimmune processes

Detailed Design: Blood Draws



CBSM Intervention after Surgery for Breast Cancer:

Psychological adaptation:

- **decreased negative adaptation: NA, anx, soc disruption, fatigue, sleep disrupt**
- **increased positive adaptation: PA, benefit finding and optimism**
- **increased perceived relaxation skills, CBT and emotion processing important**

Physiological adaptation:

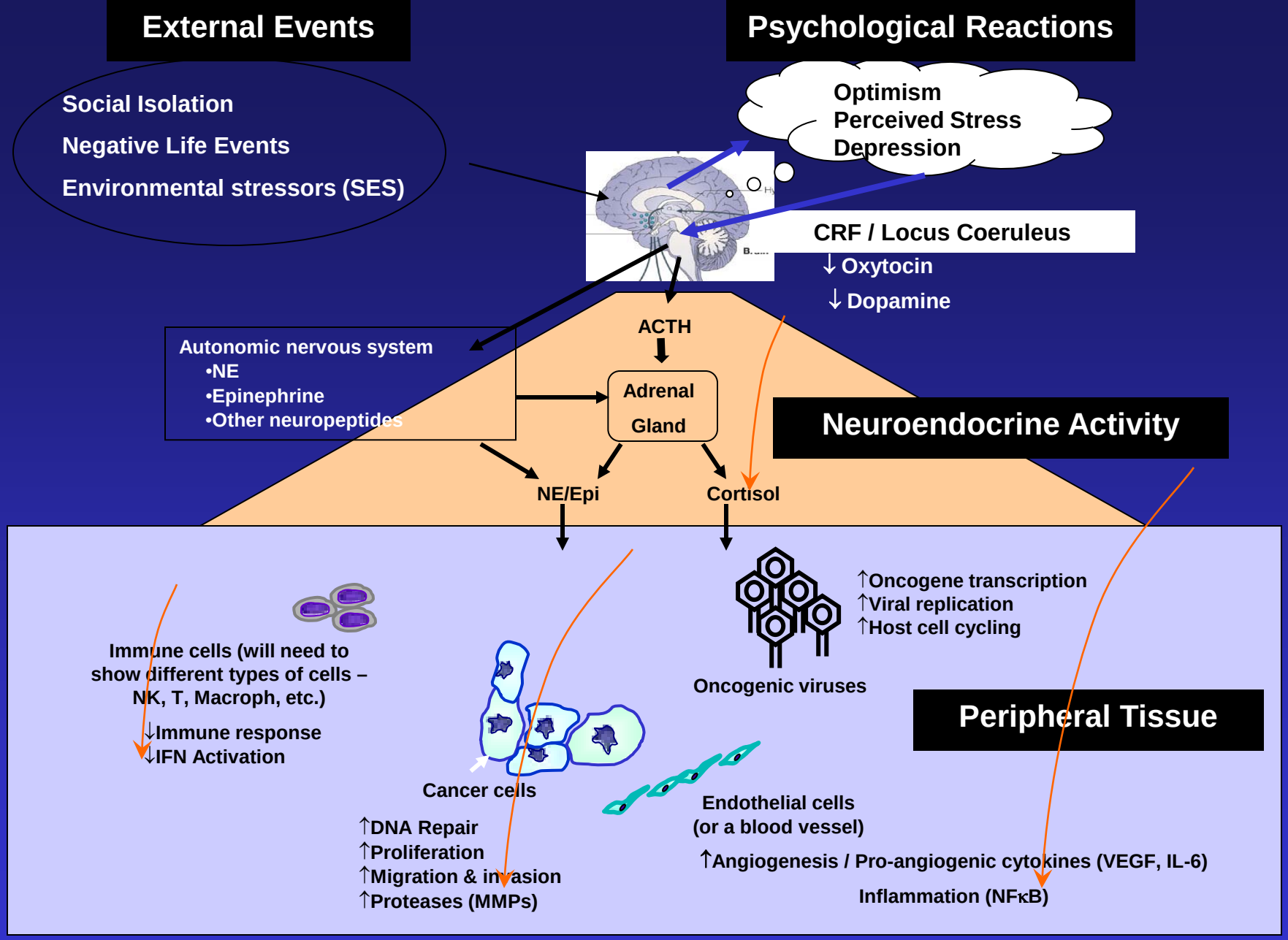
- **decreases in PM cortisol levels**
- **increased LPR to anti-CD3 challenge**
- **increased γ-IFN and IL-2 and Th1/Th2 ratio production during LPR**

Pattern of effects suggest better adaptation after adjuvant therapy in CBSM pts vs controls

Antoni et al (2001) *Health Psychology, 20,* 20-32;
Cruess, Antoni et al (2000) *Psychosomatic Medicine, 61,* 94.
McGregor et al., (2004*) J. Psychosom Res, 56, 1 – 8;*
Antoni et al. *(2006) Amer J. Psychiatry*
Antoni et al., *(2006) JCCP;* Phillips et al. (2008*) Psychosom Med;*
Antoni et al. (2009) *Brain Beh Imm*

Health Relevance of CBSM effects in breast cancer?

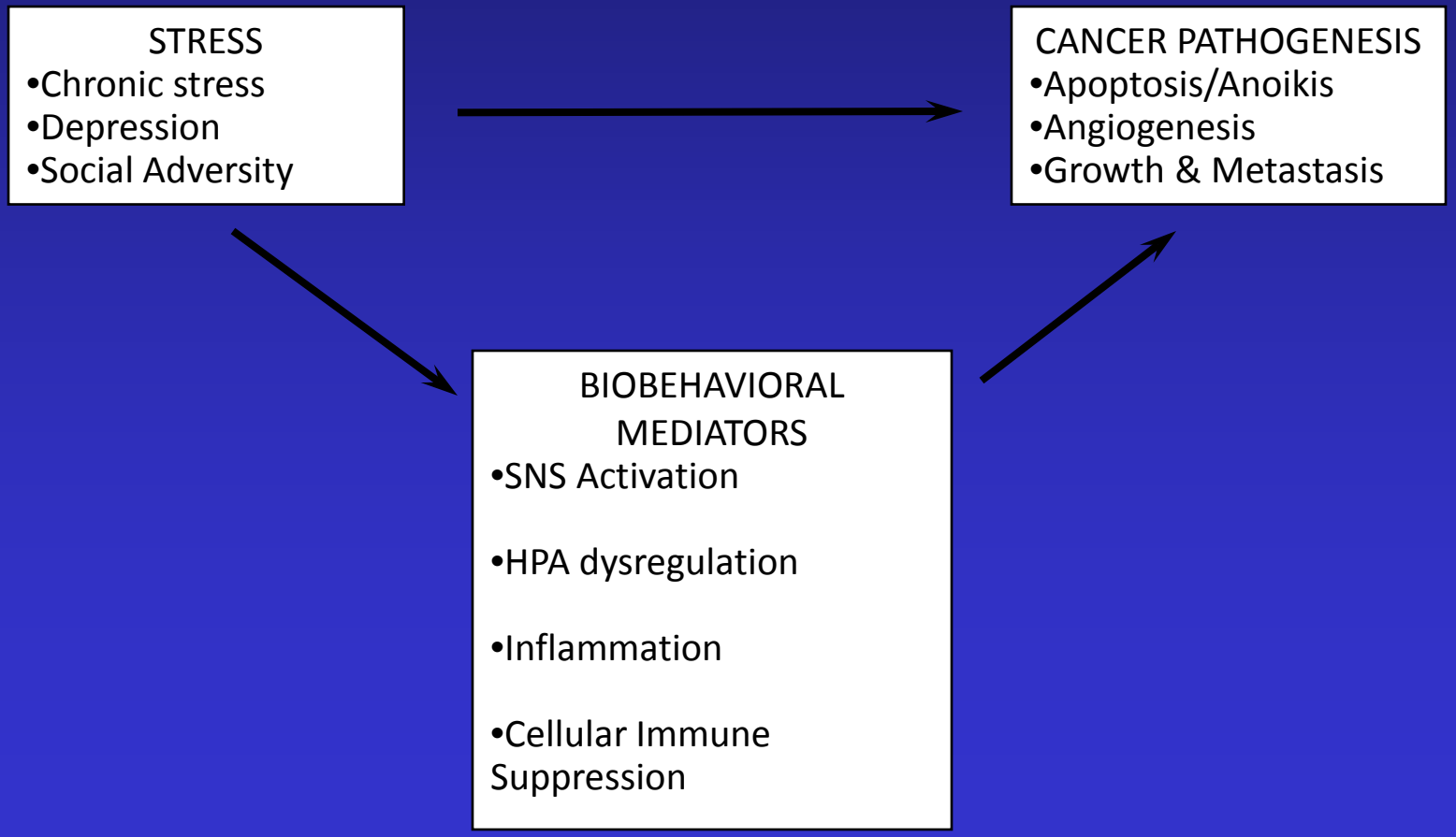
- Can we develop more health relevant biobehavioral empirical basis?
- Which pathways need to be explored?



Antoni, Lutgendorf, Cole, Sephton, Dhabar, McDonald, Stefanek & Sood (2006). *Nature Reviews Cancer, 6,* 240-248.

Plausible Biobehavioral Pathways Associated with Stress and Cancer Pathogenesis

(Miller & Cole, 2009 *Ann Rev Psychol*.)

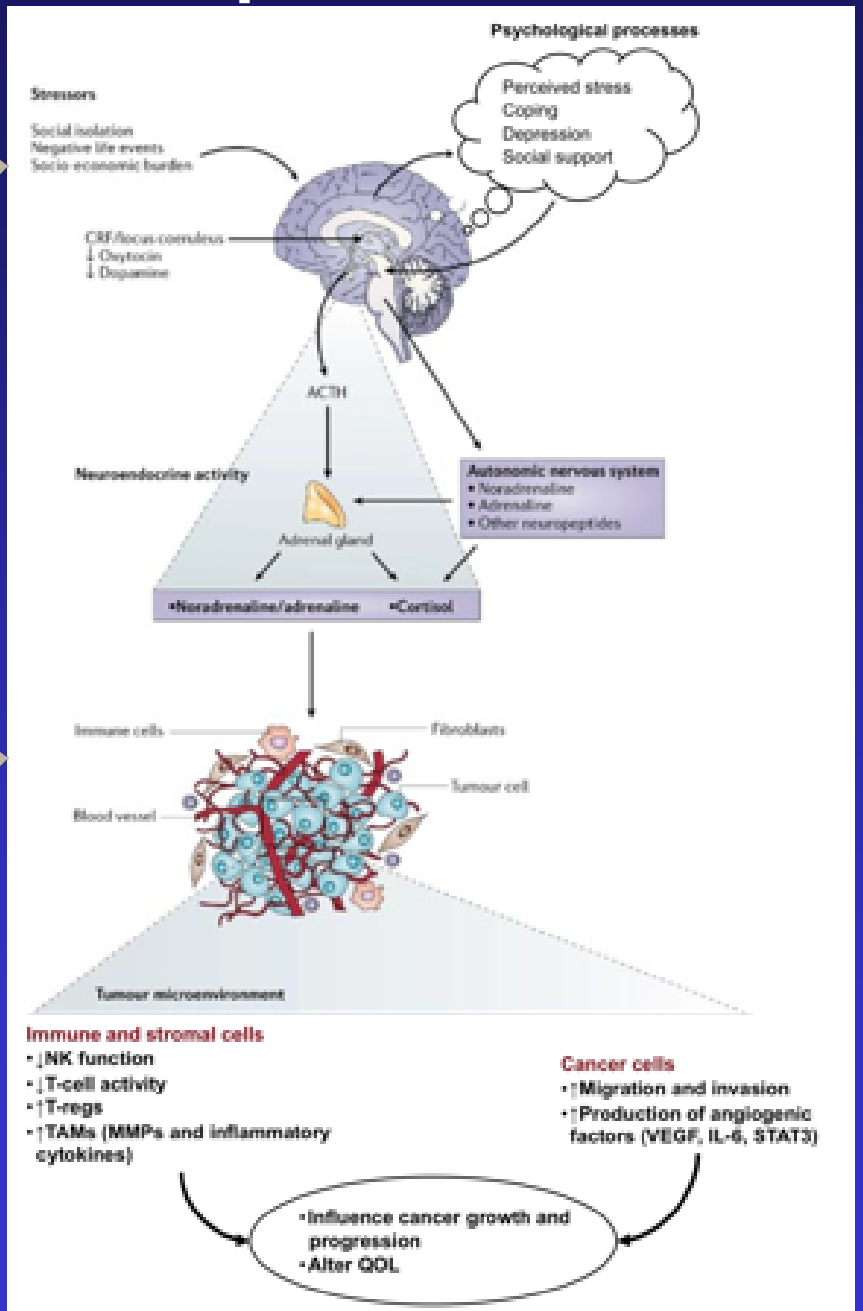


Model's Health Implications

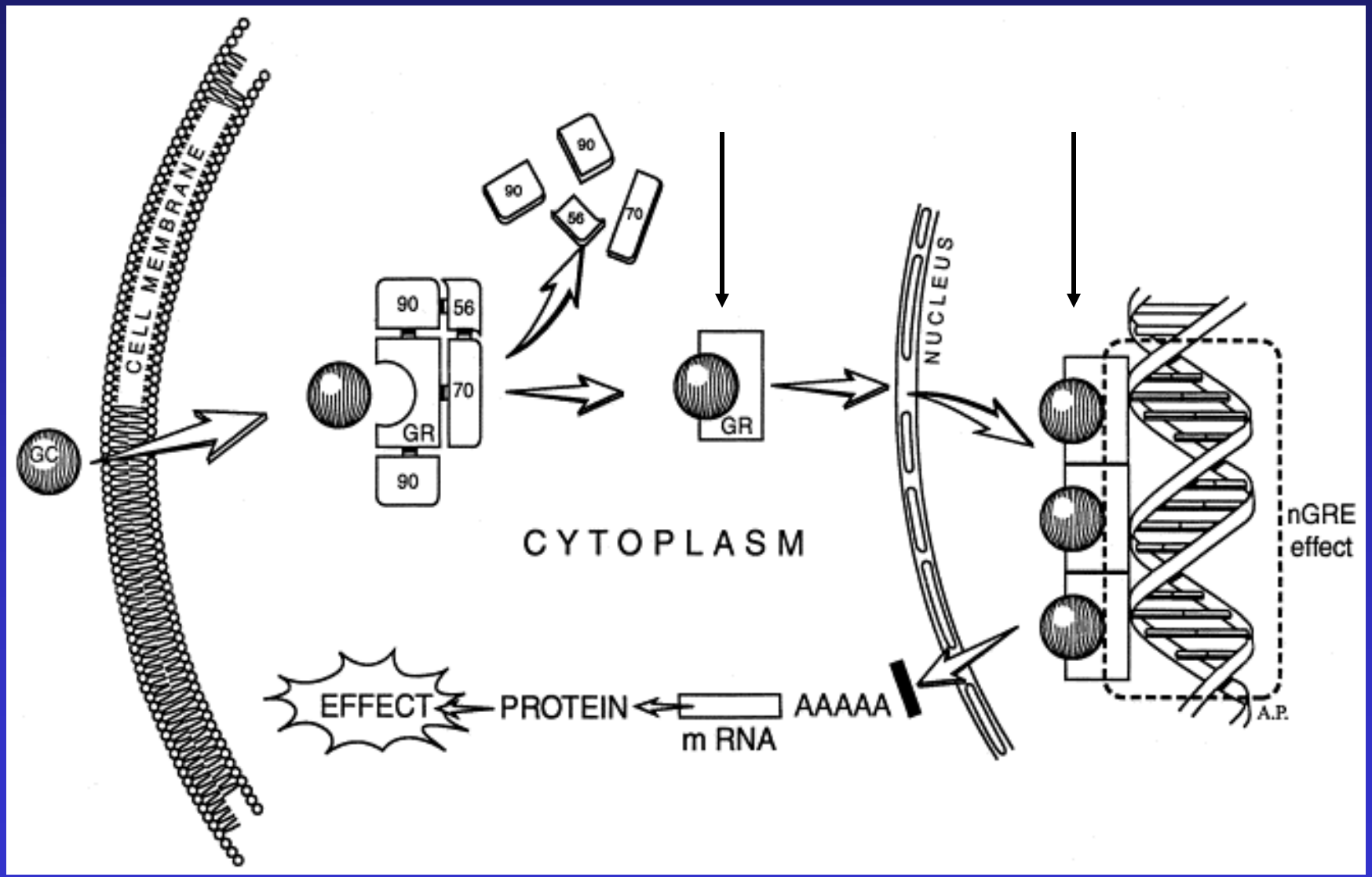
- Individual Differences in Intra-Personal Processes (chronic stress perceptions, negative affect) may contribute to poorer stress adaptation during the cancer experience

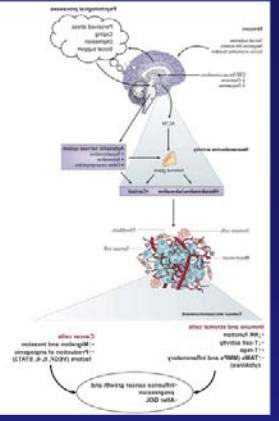
- These adaptations may be transduced by neuroendocrines into transcriptional (gene expression) changes in disease tissue (e.g., tumor) and circulating immune cells

- One pathway of interest: stress-associated Inflammation



Stress-related Neuroendocrines can modulate cell-signaling and inflammatory protein synthesis. Chronic Stress may alter GR sensitivity (Miller & Cohen, 2002)

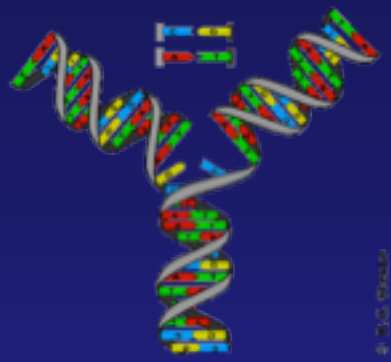




Model's Implications in Breast Cancer

- Individual Differences in Psy Factors may contribute to stress adaptation during the cancer experience
- Adaptation may accompany neuroendocrine changes
- Neuroendocrine changes → transcriptional changes in circulating immune cells that could interact with tumor (stromal cells) to promote disease progression

- **Implication**: If so, can we facilitate adaptation early in the disease process via psychosocial intervention to influence circulating immune cells and ultimately clinical disease course?



Genomic Study

- **Aim 1:** Determine whether individual differences in psychological adaptation relate to differences in leukocyte gene expression among women early in their treatment for primary (non-metastatic) breast cancer.

- **Aim 2:** Test whether a psychosocial intervention (CBSM) designed to facilitate adaptation is associated with changes in leukocyte gene expression over time

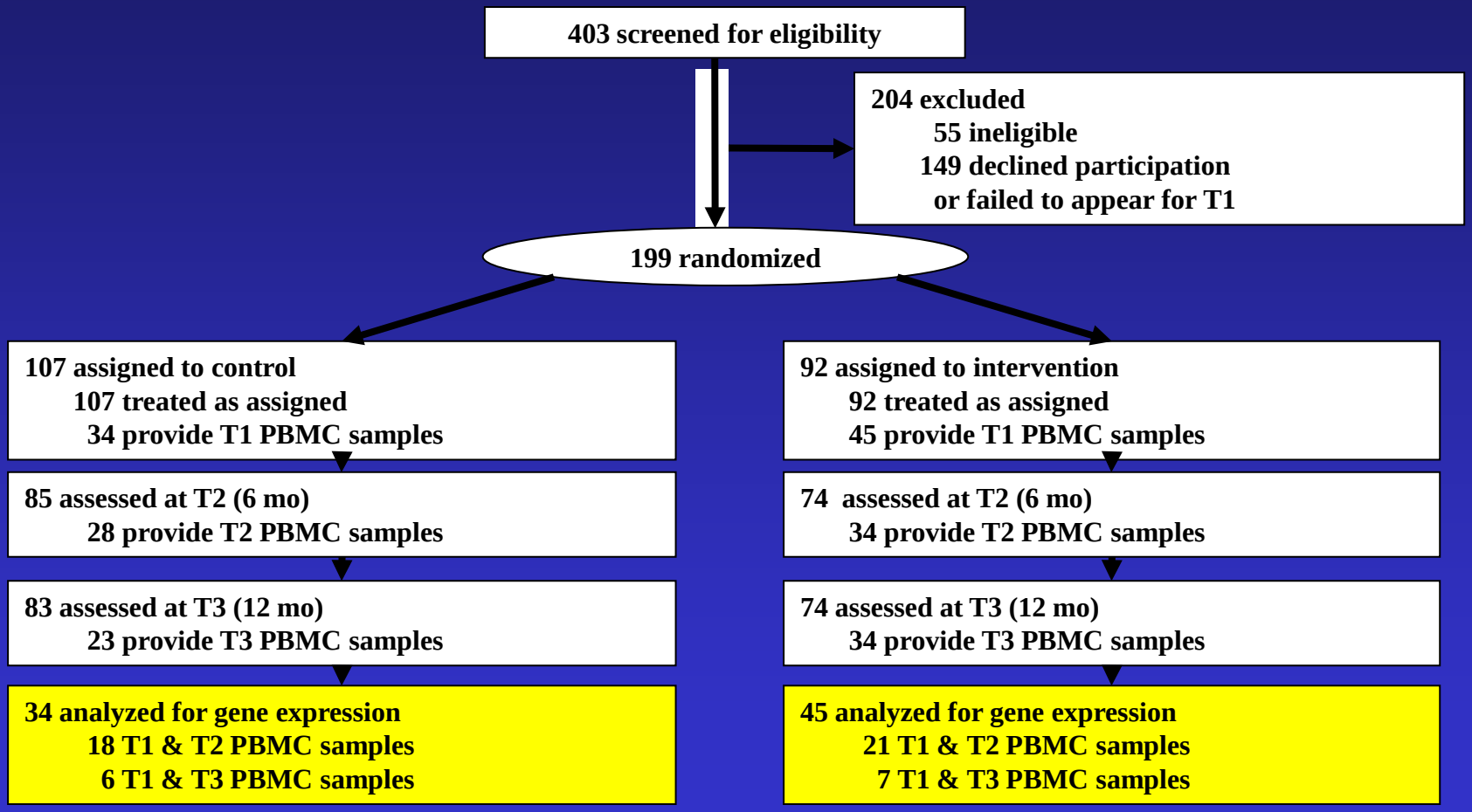
Hypotheses

- **Hyp 1: Greater Levels of Adaptation (Positive: Negative** affective state = ABS composite score) **will relate to a better leukocyte transcriptional profile**
  - **Less Pro-Inflammatory Signaling** (cytokines, chemokines, Cox2/PG, oxidat stress)
  - **Less Pro-Metastatic Signaling** (enzymes for tissue invasion, remodeling and epithelial-mesenchymal transition)
- **Hyp 2: CBSM will facilitate adaptation and improve leukocyte transcriptional profile**
  - Increased Positive Affect
  - Decreased Negative Affect
  - Increased Affect Balance (Positive – Negative Afect)
  - Less Pro-Inflammatory Signaling
  - Less Pro-Metastatic Signaling
  - Greater Glucocorticoid Receptor Sensitivity

Study Sample and Measures

- Sample: 79 Women undergoing surgery for non-metastatic BCa in prior 2 – 10 wks and not yet started adjuvant therapy
- Psychological Adaptation
  - Positive Affect/Negative Affect Balance (Affect Balance Scale, ABS, Derogatis, 1975)
- Other Psy Factors
  - Sources of Social Support Scale (Carver)
  - Perceived stress management skill efficacy (MOCS, Carver)
  - Personal growth (benefit finding scale: BFS, Tomich & Helgesen)
  - Sleep quality (PSQI, Buyse et al)
- Transcriptional Indicators
  - miRNA expression: pro-inflam cytokines, chemokines and tumor promoting transcripts
  - Gene Library convergence: pro-inflammatory and wound healing pathways
  - Bioinformatically inferred upstream transcripts: NFκB, GATA, STAT, GR
- Criteria for differential expression
  - 50% up- or down-regulation (< 5% false discovery rate)
  - Traditional *p*-value
- Controls
  - Sociodemographic (age, race, SES)
  - Biomedical (disease stage, ER/PR/HER1Neu, surgery type, days since surg, meds)

CONSORT DIAGRAM



	Control (n=34)	CBSM (n=45)	*p*
Age (years)*	49.2 ± 7.8	50.1 ± 7.5	0.594
Income ($1,000)*	80.3 ± 65.4	72.8 ± 31.4	0.536
Ethnicity (%)			0.503
Non-hispanic white	67.7	79.1	
Hispanic	23.5	14.0	
African American	8.8	7.0	
Stage (%)			0.449
0	8.8	16.3	
I	55.9	39.5	
II	29.4	32.6	
III	5.9	11.6	
Lymph nodes+*	0.4 ± 0.2	1.5 ± 3.4	0.062
ER+ (%)	91.3	77.8	0.194
PR+ (%)	82.4	66.7	0.275
Surgery type (%)			0.109
Lumpectomy	32.4	54.6	
Mastectomy	47.1	36.4	
Bilat. mastectomy	20.6	9.1	
Days post-surgery (at study baseline)*	41.6 ± 22.6	38.6 ± 21.6	0.561
Chemotherapy			
Ever (%)	38.2	46.7	0.454
Within 3 weeks of 6-month follow-up (%)	20.8	10.8	0.281
Within 3 weeks of 12-month follow-up (%)	0.0	0.0	0.999
Radiation therapy			
Ever (%)	26.5	44.4	0.101
Within 3 weeks of 6-month follow-up (%)	20.8	2.8	0.020
Within 3 weeks of 12-month follow-up (%)	0.0	0.0	0.999
Endocrine therapy (%)	34.4	37.1	0.813
Affects Balance Scale (at baseline)*	31.2 ± 16.3	24.3 ± 22.2	0.147
Affects Balance Scale (linear trend / follow-up yr)*	+1.0 ± 3.6	+17.5 ± 4.1	0.004

Genomic Studies: Microarray Analysis Pre-Post

- PBMCs analyzed with **Illumina Human HT-12 v3 Expression BeadChips**
- Expression of 27,455 human genes derived from low-level fluorescence intensity values & quantile normalized w/ Illumina Genome Studio software
- **Genes > 50% difference** in average expression in **CBSM** vs **control** identified as differentially expressed (False Discovery Rate ≤ 5%)
- Functional characteristics-GOstat Gene Ontology, GeneCards, EntrezGene
- Activity of specific transcription control pathways* assessed by TELiS bioinformatic analysis of transcription factor-binding motif (TFBM) distributions in the promoters of differentially expressed genes:

  IFN response, NF-κB, STAT1, GCS Receptor (GR)
- *Transcript Origin Analysis* was employed to identify the specific leukocyte subsets predominately mediating CBSM effects on the overall PBMC pool transcriptome.

*transcripts identified as differentially expressed by microarray analysis were re-verified using quantitative RT-PCR with TaqMan gene expression assays (Applied Biosystems Inc), a one-step enzyme system (Quantitect RT-PCR; Qiagen), and manufacturer's specified thermal cycling protocol on a iCycler real-time PCR instrument (BioRad Inc.). Data were analyzed by standard threshold cycle analysis after normalization to parallel-assayed *ACTB* mRNA concentrations

Study Analyses

- **Genomic-Affect Association**: Relationships between baseline affective state (ABS composite score) and expression of each analyzed transcript were assessed by multiple regression
  - controlling for age, race (white vs. non-), and tumor stage, estrogen receptor (ER)-, and progesterone receptor (PR) status. Genes showing > 50% differential expression per 1 SD of ABS composite scores identified as differentially expressed

- **Effects of CBSM** on expression of each analyzed transcript were assessed in a 2 (Group: CBSM vs. Control) x 3 (Time: baseline, 6-, and 12-month follow-up) mixed model factorial design
  - controlling for individual differences in age, race, tumor stage, ER status, PR status, treatment with chemotherapy, and treatment with radiation.
  - All analyses were conducted on an intent-to-treat basis with parameters estimated in the context of mixed effect linear models including all cases

Affect and Gene Expression

- 201 named human genes showed > 50% difference in expression across the range of ABS composite scores at study entry (2 – 8 wks post-surgery).
- 177 genes were up-regulated in association with ABS ratio reflecting more negative affect, including:
  - genes encoding pro-inflammatory cytokines (*IL1A*, *IL1B*, *IL6*, *TNF*)
  - the prostaglandin-synthesis enzyme COX2 (*PTGS2*)
  - the oxidative stress response (*SOD2*)
  - inflammatory chemokines and related receptors (*CCL3*, *CCL3L1*, *CCL4L2*, *CCL7*, *CCL20*, *CXCL9*, *CXCL10*, *CXCR6*, *CXCR7*)
  - transcripts involved in tissue remodeling and epithelial-mesenchymal transition (*LMNA*, *MMP9*).
- Bioinformatic Analysis

  GOstat Gene Ontology Analyses (p's < .0001) for pro-inflammatory and wound-healing signaling

  Upstream Signaling Implicated: NFkB

  Inferred Cell Populations: Myeloid

Comparing Mood X Leukocyte Gene Expression Associations in Different Cancer Populations

Antoni et al. (2012) *Biol. Psychiatry*

Breast Cancer (*N = 79)*

Negative Affect associated w/ 50% diff in exp of 201 genes:

- **Pro-Inflammatory Signaling**:
  - **Cytokines** [IL1A,IL1B,TNF,IL6,IL1RN]
  - **Chemokines** [CCL2, CCL3, CCL3L1, CCL4L2, CCL7, CCL20, CACL9, CXCL10, CXCR6, CXCR7]
  - **Oxidative Stress** [SOD2]
  - **COX 2** [COX2/PTGS2]
- **Pro-Metastatic Signaling** (PBMCs)**:**
  - MMP9
- **Gene Ontology Analyses:**
  - Transcripts converging on pro-inflammatory signaling (*p* < .0001)
- **Inferred* Upstream Signaling**
  - NFκB
- **Implicated* PBMC Population**
  - Myeloid

* Based on TeLiS Bioinformatic Program

Cohen et al. (2012) *PLoS One*

Metastatic RCC (*N = 30)*

Depression associated w/ 50% diff in exp of 177 genes:

- **Pro-Inflammatory Signaling:**
  - **Cytokines** [IL1A,IL1B,TNF,IL6,IL1RN]
  - **Chemokines** [CCL2, CCL3, CCL3L1, CCL4L2, CCL7, CCL8, CCL20, CCR7, CXCL1, CXCL16]
  - **Oxidative Stress** [SOD2]
  - **COX 2** [COX2/PTGS2]
- **Pro-Metastatic Signaling (**tumor**)**
  - MMP9, MMP2
- **Gene Ontology Analyses**:
  - Transcripts converging on pro-inflammatory signaling (*p* < .0001)
- **Inferred* Upstream Signaling**
  - NFκB
- **Implicated* PBMC Population**
  - Myeloid (greater TAMs in depressed)

Study Analyses

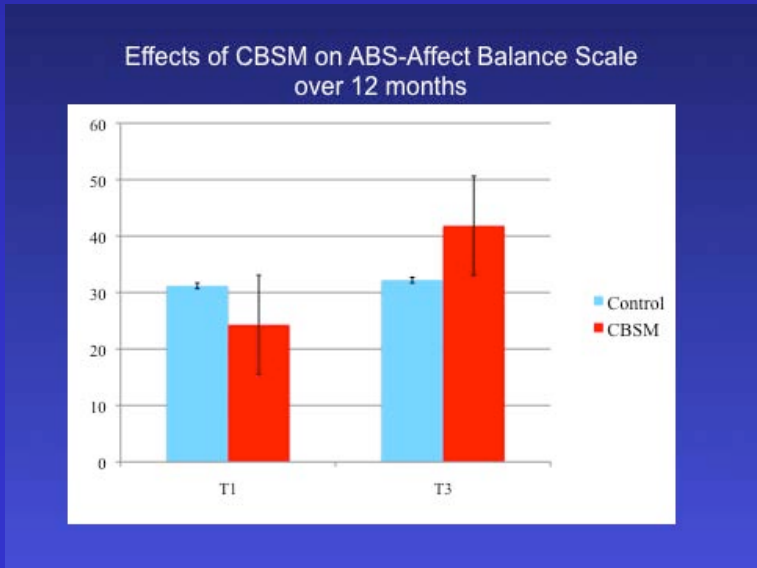
- **Genomic-Affect Association**: Relationships between baseline affective state (ABS composite score) and expression of each analyzed transcript were assessed by regression
  - controlling for age, race (white vs. non-), and tumor stage, estrogen receptor (ER)-, and progesterone receptor (PR) status. Genes showing > 50% differential expression across per 1 SD of ABS composite scores were identified as differentially expressed

- **Effects of CBSM** on expression of each analyzed transcript were assessed in a 2 (Group: CBSM vs. Control) x 3 (Time: baseline, 6-, and 12-month follow-up) factorial design
  - controlling for individual differences in age, race, tumor stage, ER status, PR status, treatment with chemotherapy, and treatment with radiation.
  - All analyses were conducted on an intent-to-treat basis with parameters estimated in the context of mixed effect linear models including all cases

Did CBSM Facilitate Psy Adaptation?

- ABS Affect Balance Score (Group x Time effect, $p = .0042$), with:

- CBSM-treated group showing: (linear time trend over 12 months)
  - increased positive affect: +6.8 ± 2.36, $p = .0055$
  - decreased negative affect: -8.22 ± 2.08, $p = .0003$
  - Increased composite affect balance scores: +17.54 ± 4.12, $p < .0001$
- Control group showed
  - negligible change over time on each dimension:
  - positive affect: -0.16 ± 1.94, $p = .936$
  - negative affect: -4.64 ± 3.94, $p = .245$
  - overall affect balance: 1.00 ± 3.62, $p = .784$.



No Between-Group Differences

- Surgery
- Adjuvant type (chemo, radiation)
- Time since surgery
- Endocrine therapy
- Demographics

2 X 3 Mixed Model Effects of CBSM on Negative Mood-Related Genomic Expression (N = 45 CBSM, 34 controls)

- 62 transcripts showed significantly greater down-regulation in CBSM-treated patients relative to controls (> 50% differential chg), including genes encoding:
  - **pro-inflammatory cytokines** (*IL1A*, *IL1B*, *IL6*)
  - **inflammatory chemokines and their receptors** (*CCL2*, *CCL3*, *CCL3L1*, *CCL3L3*, *CCL4L1*, *CCL4L2*, *CCL7*, *CXCL1*, *CXCL2*, *CXCR7*)
  - **prostaglandin-synthesis enzyme** COX2 (*PTGS2*)
  - **pro-metastatic**: mediators of tissue remodeling and epithelial-mesenchymal transition (*G0S2*, *LMNA*, *MMP9*, *OSM*).

  GOstat Gene Ontology analyses (***p*'s < .0001**)

- 29 genes showed significantly greater up-regulation in CBSM-treated patients vs. controls, including genes involved in:
  - **Type I interferon response** (*IFIT1*, *IFIT2*, *IFIT3*, *IFI44, IFI44L, ISG15, MX2*, *OAS2*, *OAS3*),
  - **Type II interferon signaling** (*IFN-γ*), and interferon signal transduction (*STAT1*, *STAT2*).

  GOstat Gene Ontology analyses (***p*'s < .0001**)

Antoni, Lutgendorf, Blomberg et al…..Cole (2012) *Biological Psychiatry*

2 X 3 Mixed Model Effects of CBSM on Negative Mood-Related Genomic Expression

(Highlighted changes in those genes associated with baseline Negative Affect)

- 62 transcripts showed significantly greater down-regulation in CBSM-treated patients relative to controls (> 50% differential chg), including genes encoding:
  - **pro-inflammatory cytokines** (*IL1A*, *IL1B*, *IL6*)
  - the prostaglandin-synthesis enzyme COX2 (*PTGS2*)
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  - mediators of tissue remodeling and epithelial-mesenchymal transition (*G0S2*, *LMNA*, *MMP9*, *OSM*).

  GOstat Gene Ontology analyses (***p*'s < .0001**)*

Thirty-one (50%) of the total 62 CBSM-downregulated transcripts also appeared on the list of genes upregulated in association with negative affect at baseline (greater than the <1% overlap expected by chance; binomial $p < .0001$).

*pro-inflammatory transcriptional activation effects hold in ancillary analyses that controlled for additional treatment-related variables: chemotherapy or radiation (within 3 weeks before each study visit), primary surgery type (lumpectomy, mastectomy, or bilateral mastectomy), and use of pain medications, anxiolytics, or antidepressants (downregulation of pro-inflammatory genes, GO:0006954; GO:0009611; both p < .0001;

Antoni, Lutgendorf, Blomberg et al…..Cole (2012) *Biological Psychiatry*

Fold Difference in Average Gene Expression Change at 6 – 12 mo f/u in CBSM vs Ctrls (N = 79)

estimated by mixed effect repeated measures ANCOVA controlling for age, ethnicity, tumor grade, disease stage, tumor ER and PR status, use of radiation therapy and chemotherapy

Upregulated	
Gene Symbol	Ratio (CBSM/Control)
IFIT1	2.08
IFIT3	2.04
ISG15	1.93
SAMD9L	1.93
RSAD2	1.86
IFIT2	1.81
TNFSF10	1.76
IFI44	1.74
XAF1	1.71
OAS3	1.71
IFI44L	1.68
HERC5	1.66
LOC100008589	1.63
OAS2	1.62
LAG3	1.62
SNORA12	1.60
STAT2	1.58
C19orf66	1.56
PTGR2	1.56
IL32	1.56
GVIN1	1.55
IFNG	1.54
NCF1	1.54
RN7SK	1.52
MX2	1.52
MIR155HG	1.52
PARP12	1.51
STAT1	1.51
TRIM22	1.50

Downregulated	
Gene Symbol	Ratio (CBSM/Control)
SC5DL	0.66
GPR183	0.66
ABCG1	0.66
MIR302C	0.66
SPSB1	0.66
C13orf15	0.66
EMP1	0.66
KIAA1009	0.66
TNFRSF21	0.65
C3AR1	0.65
AGPAT9	0.65
GNA15	0.65
GJB2	0.64
MXD1	0.64
SLC43A2	0.64
C15orf48	0.63
TMEM158	0.63
NLRP3	0.63
MMP9	0.63
RGS1	0.63
ADORA2B	0.63
DHRS9	0.62
LOC651524	0.62
LMNA	0.61
GPR132	0.61
CXCR7	0.61
ALAS2	0.61
ASPH	0.61
LYPD3	0.61
IL6	0.59
CCL2	0.58
SLC16A6	0.58
THBD	0.58
CD300LB	0.58
CTSL1	0.57
AVPI1	0.57
ZNF331	0.57
CYP1B1	0.56
GPR84	0.56
IER3	0.55
OSM	0.55
C5AR1	0.55
HLA-A29.1	0.54
PHLDA1	0.54
CCL3L3	0.52
CCL4L2	0.52
PLAUR	0.52
G0S2	0.52
CCL7	0.51
CCL3L1	0.48
CCL3	0.48
THBS1	0.47
LOC728835	0.47
CXCL2	0.46
PTGS2	0.46
CXCL1	0.45
CCL4L1	0.41
SERPINB2	0.40
IL1A	0.40
IL1B	0.35
OLR1	0.34
CCL20	0.31

Genes differentially expressed at 12-month follow-up

Gene Symbol	Ratio (CBSM/Control)
Upregulated	
HLA-DRB5	6.56
HSPA1B	5.04
HLA-DRB1	3.62
RPPH1	2.85
HSPA1A	2.80
HBG2	2.76
ISG15	2.69
CXCL10	2.64
HBG1	2.60
LOC100132564	2.46
RGS18	2.46
SAMD9L	2.32
HSPA6	2.25
LCN2	2.24
TNFSF10	2.24
GNG11	2.24
C7orf68	2.23
LOC100008589	2.22
STAT1	2.22
RSAD2	2.18
IFIT1	2.17
IFI44L	2.15
IFNG	2.14
IFIT3	2.11
LOC85389	2.10
SDPR	2.09
HBA1	2.09
LOC650557	2.09
AHSA2	2.06
SNORD46	2.06
EPSTI1	2.01
PFKFB4	2.00

TNFRSF21	0.50
ASPH	0.50
PRDM8	0.49
LOC641768	0.49
S1PR1	0.49
LOC645979	0.49
SLC16A6	0.48
SPSB1	0.48
LOC441377	0.48
LOC100133329	0.48
ITGAV	0.47
ABCA1	0.47
LOC642567	0.46
FAM108C1	0.46
MN1	0.46
IL1A	0.46
GPR132	0.45
ABCG1	0.44
LOC401717	0.44
IL1R1	0.44
PMEPA1	0.43
LOC400652	0.43
NEU4	0.43
ZNF331	0.43
THBS1	0.42
SLC7A5	0.42
CCL7	0.41
EMP1	0.41
ELL2	0.40
RPS26P10	0.40
ADORA2B	0.40
AUTS2	0.39
AGPAT9	0.39
SERPINB2	0.39
LOC731682	0.38
OLR1	0.37
C19orf59	0.36
LOC644936	0.31
CYP1B1	0.26

Antoni, Lutgendorf, Blomberg et al…..Cole (2012)

Genomic Studies: Microarray Analysis Pre-Post

- PBMCs analyzed with **Illumina Human HT-12 v3 Expression BeadChips**

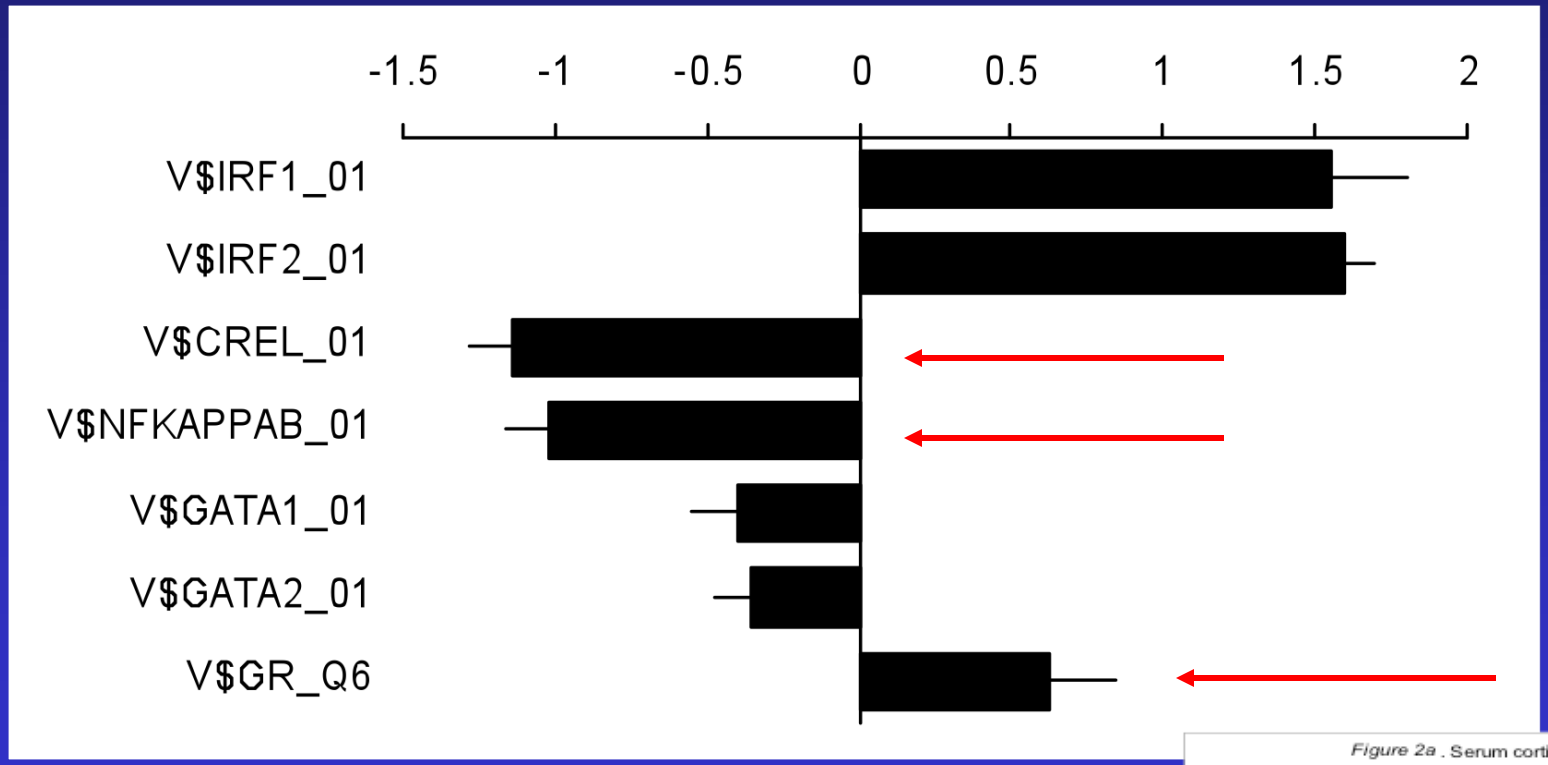
- Expression of 27,455 human genes derived from low-level fluorescence intensity values & quantile normalized w/ Illumina Genome Studio software
- **Genes > 50% difference** in average expression in **CBSM** vs **control** identified as differentially expressed (False Discovery Rate ≤ 5%)
- Functional characteristics-GOstat Gene Ontology, GeneCards, EntrezGene

- Activity of specific transcription control pathways* assessed by TELiS bioinformatic analysis of transcription factor-binding motif (TFBM) distributions in the promoters of differentially expressed genes:

  CREB/ATF, IFN response, NF-kB, STAT1, GC Receptor

*transcripts identified as differentially expressed by microarray analysis were re-verified using quantitative RT-PCR with TaqMan gene expression assays (Applied Biosystems Inc), a one-step enzyme system (Quantitect RT-PCR; Qiagen), and manufacturer's specified thermal cycling protocol on a iCycler real-time PCR instrument (BioRad Inc.). Data were analyzed by standard threshold cycle analysis after normalization to parallel-assayed *ACTB* mRNA concentrations

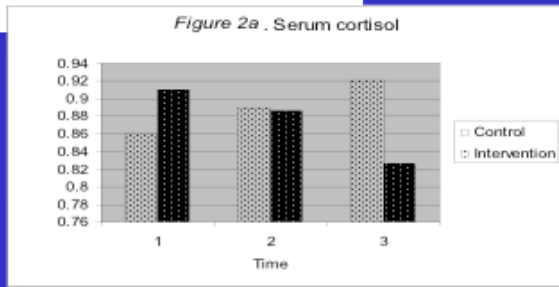
Fold Difference in TFBM Expression over 6 – 12mo (log CBSM vs Control)



Interferon Imm Act

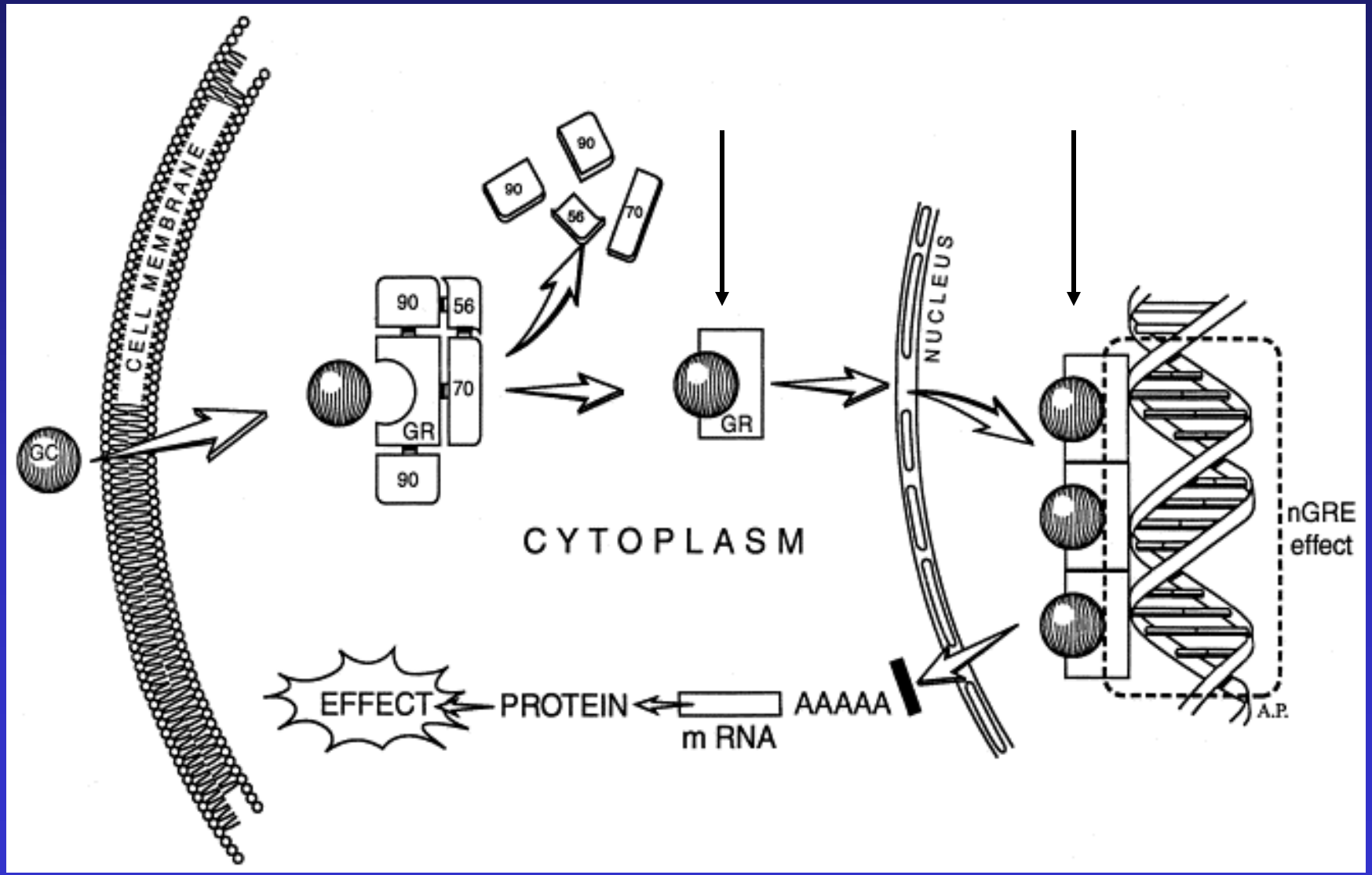
NFkB Inflammation

GCS Sens



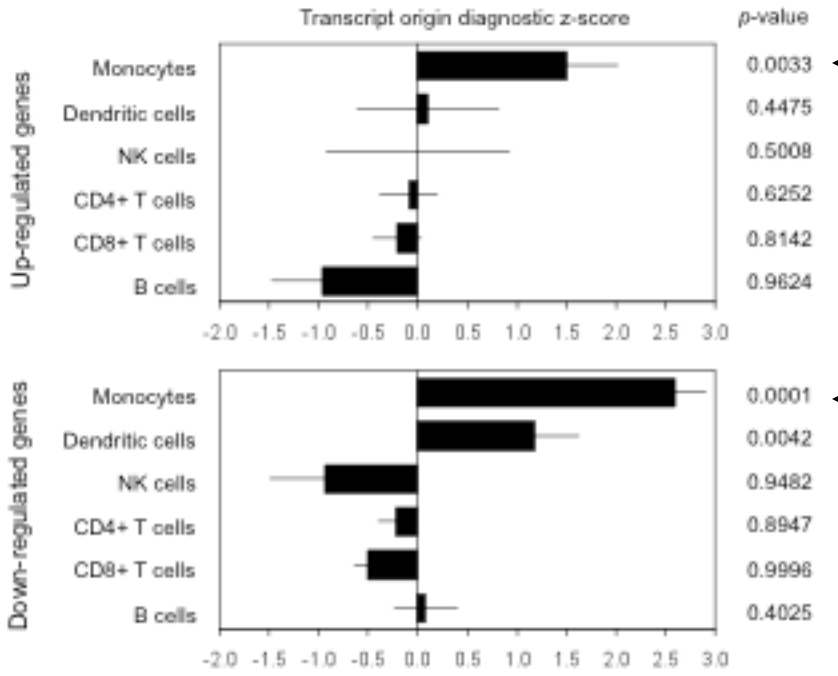
Antoni, Lutgendorf, Blomberg et al…..Cole, *Biological Psychiatry* (2012)

Did CBSM work via GR sensitivity changes? In which cells?



Cells Involved in Up-Regulation and Down-Regulated Genes?

Figure 2



Transcript Origin Analysis was employed to identify the specific leukocyte subsets predominately mediating CBSM effects on the overall PBMC pool transcriptome.

Antoni, Lutgendorf, Blomberg et al…..Cole (2012) *Biological Psychiatry*

Table 1. Valence and magnitude of cognitive behavioral stress management (CBSM) intervention effects on genomic indicators representing different biological pathways relevant to carcinogenesis over a 6 – 12 month period in women with breast cancer

Biological Pathway[1]	Genomic Indicator	Cell Type Origin[2]	Valence	Magnitude (CBSM: control fold diff)
Inflammation				
Pro-inflammatory cytokine	IL1A, IL1B, IL6	Mo, pDC	down-regulation	0.35 – 0.59
Pro-inflammatory chemokines and their receptors	CCL2, CCL3, CCL3L1 CCL3L3, CCL4L1, CCL4L2, CCL7, CXCL1, CXCL2, CXCR7	Mo, pDC	down-regulation	0.41 - 0.61
Prostaglandin-synthesis enzyme	PTGS2 (a COX2 marker)	Mo, pDC	down-regulation	0.46
Metastasis Promotion				
Tissue remodeling/epithelial-mesenchymal transition	G0S2, LMNA, MMP9, OSM	Mo, pDC	down-regulation	0.55 – 0.63
Cellular Immunity				
Type I interferon response	IFIT1, IFIT2, IFIT3, IFIT44, IFIT44L, ISG15, MX2, OAS2, OAS3	Mo	up-regulation	1.68 – 2.08
Type II interferon signaling	IFNG	Mo	up-regulation	1.54
Interferon signal transduction	STAT1, STAT2	Mo	up-regulation	1.51 – 1.58

[1]Inferred from TeLis bioinformatics program (Cole, 2009) [2]Inferred from Transcript Origin Analysis (Cole et al., 2011)
Mo: Monocyte pDC: plasmacytoid dendritic cell

Antoni, Lutgendorf, Blomberg et al…..Cole (2012) *Biological Psychiatry;*
Antoni (in press)*. Brain, Behavior & Immun*

Examining Leukocyte Transcription Changes after CBSM in BCa provides information:

- **Can CBSM modulate gene expression in PBMCs for**:
  - Inflammation? (NFkB, STAT→ cytokine/chemokine/PGs)
  - HPA regulation? (GR sensitivity changes with adaptation?)
  - Disease progression promoters? MMP-9, LMNA, G0S2
  - Anti-viral immunity? Type 1 IFN signaling
  - Myeloid cells (monocytes and DCs) likely mediators

- **$$$ Questions: Are these changes in expression tied to:**
  - QOL and symptom management?
  - Faster recovery from surgery or adjuvant therapy?
  - Ability to tolerate larger dosage of adjuvant tx?
  - Success of cancer treatments vs resistance?
  - Clinical disease outcomes (recurrence, mortality)?

Health Effects of Psy Interventions in Breast Cancer research over Past 3 Decades???

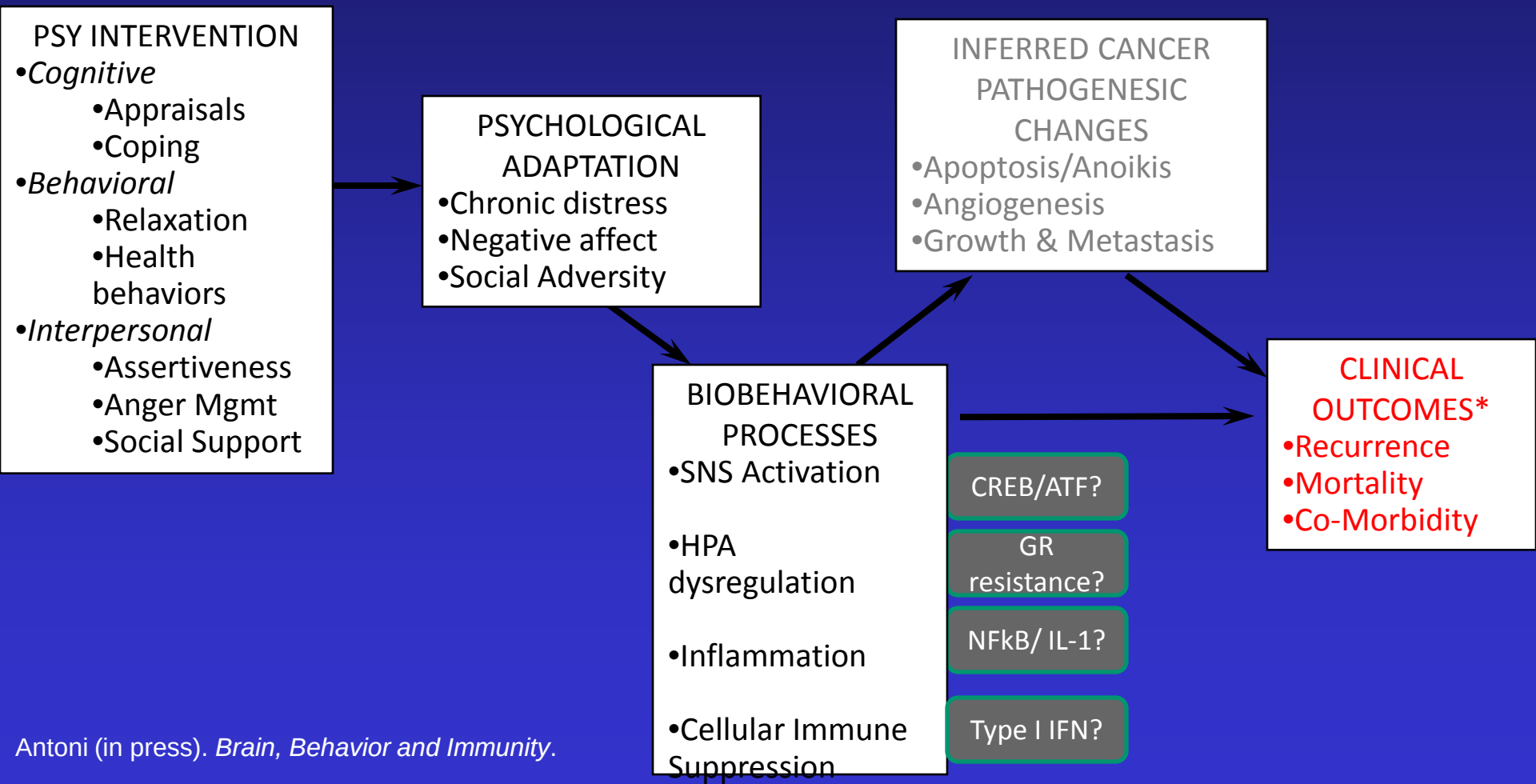
- **Psy Intervention Effects on Survival and Disease Recurrence-evidence is mixed:**

  (+) Spiegel et al., 1989----------→Andersen et al., 2008

  (-) Kissane et al., 2005----------→Spiegel et al., 2007

- **Biobehavioral Processes to explain?**
  - **Andersen work hints at inflammation**
  - **Need Study that measures biobehavioral processes AND clinical outcomes**

Model for Psychosocial Intervention Effects on Psychological Adaptation, Biobehavioral Processes and Cancer Pathogenesis and Clinical Outcomes



Antoni (in press). *Brain, Behavior and Immunity*.

**being funded in NCI Network study of 8 – 13 yr f/u*

Gaps Remaining

- Integrating Changes in Psychological and Physiological Adaptation with Clinical Outcomes
- Identifying Intervention Moderators?
- Best Timing for Delivering CBSM in the context of care?
- Briefer Forms Effective?
- What are essential ingredients?
- Alternative Methods Effective for Delivering to Underserved Populations?

Other Ongoing Work In CBSM

- Can CBSM be delivered effectively (and potently):
  - In abbreviated components?
  - In the community?
  - In different languages?
  - Over the telephone→videophone→Web

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