Psychoneuroimmunological Mechanisms of Psychosocial Effects on Hematopoietic Stem Cell Transplant Outcomes

Jennifer M. Knight, MD, MS, FACLP
Associate Professor, Depts of Psychiatry, Medicine, and Microbiology & Immunology
Divisions of CL Psychiatry and Hematology/Oncology
Medical Director, Psycho-Oncology Program
Medical College of Wisconsin

Academy of Consultation Liaison Psychiatry Webinar
September 11, 2019

CLP 2019

Disclosure: Jennifer Knight, MD

Dr. Knight has received research support for her work in psychoneuroimmunology from the National Marrow Donor Program, the American Cancer Society, the AHW Research and Education Program, the NCI Network on Biobehavioral Pathways in Cancer/Leidos Biomed, the Laura Gralton Philanthropic Fund, the Center for International Blood and Marrow Transplant Research, and a CTSI KL2 Mentored Career Development Award. With respect to the following presentation, there has been no relevant (direct or indirect) financial relationship between Dr. Knight (and/or spouse/partner) and any for-profit company which could be considered a conflict of interest.

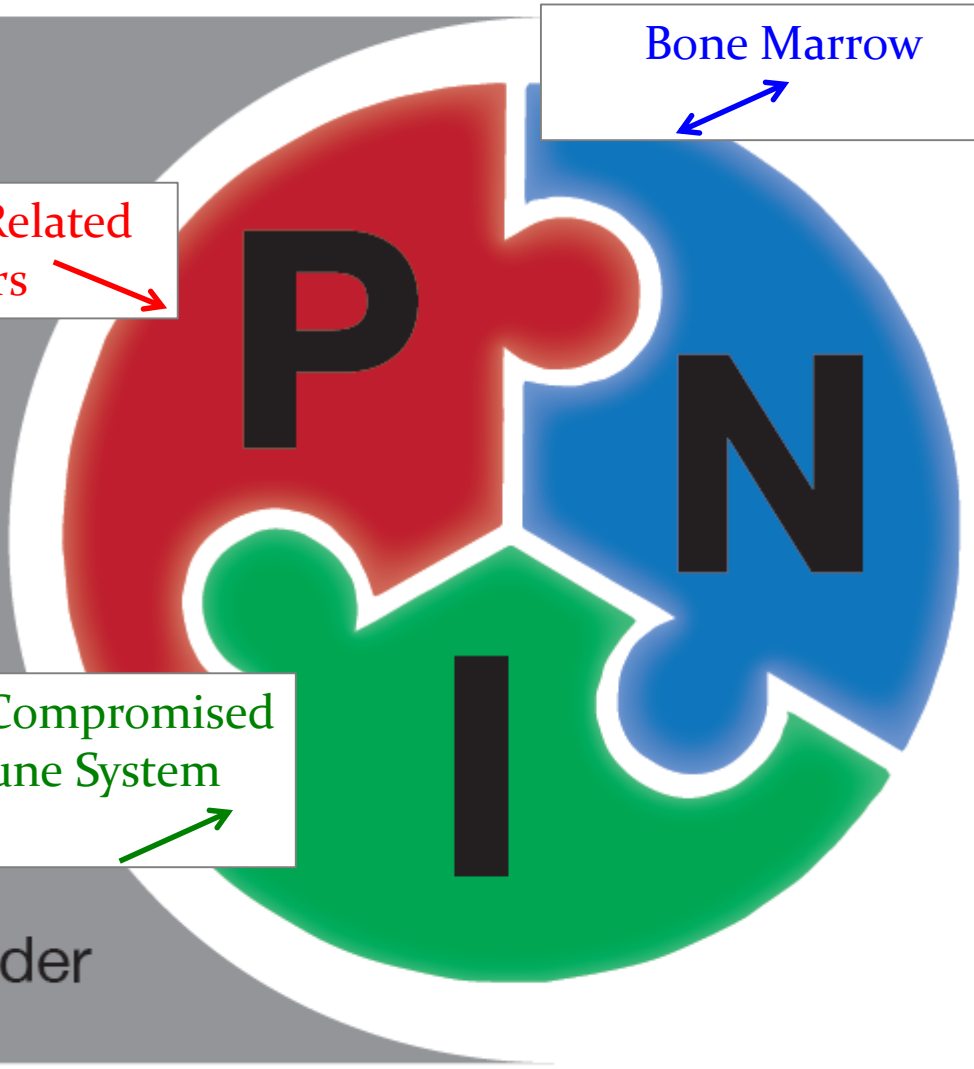
Increased stress leads to cancer progression

HCT patients of lower socioeconomic status have an 18-20% increased risk of death after transplant

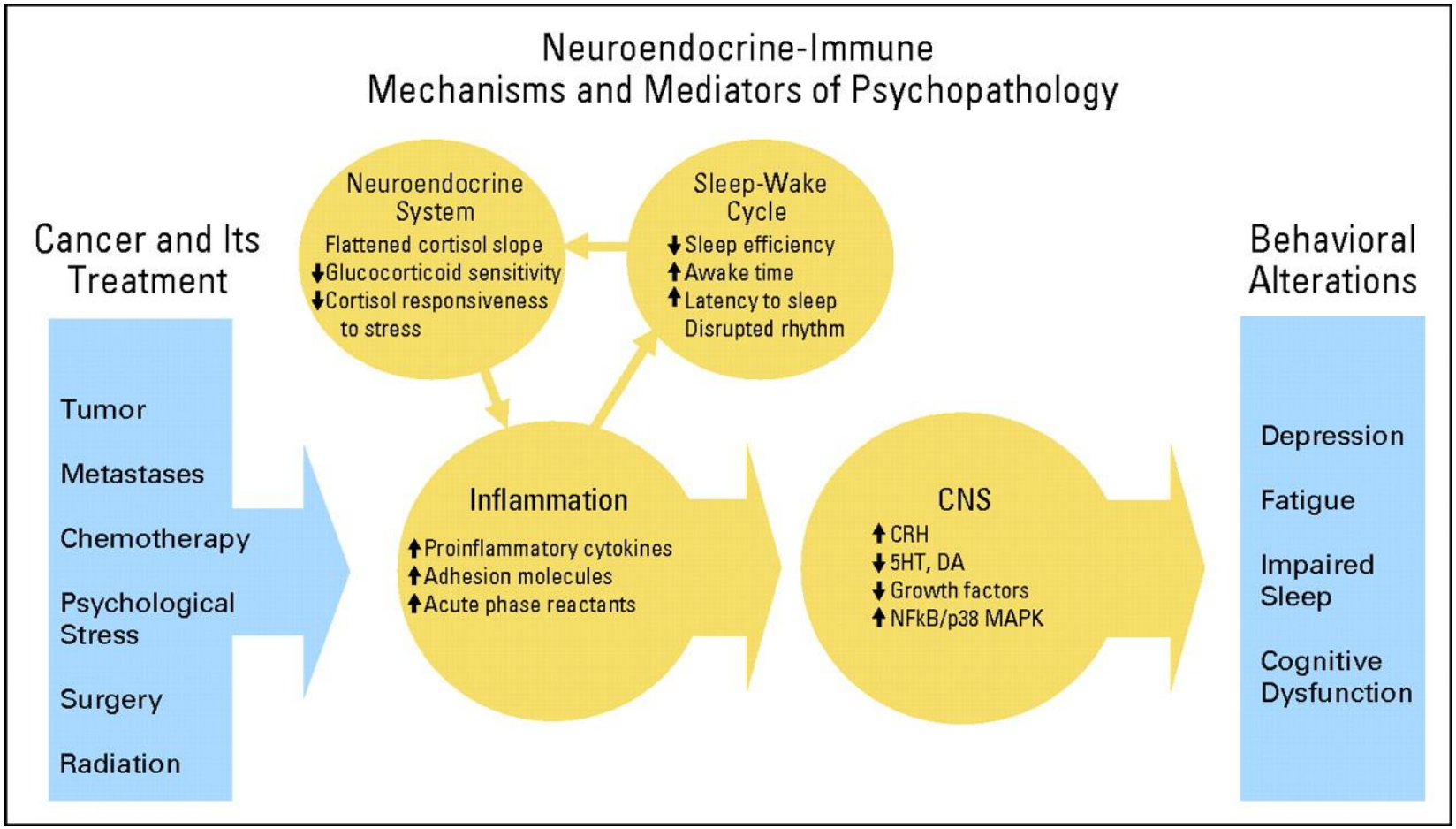
PSYCHONEUROIMMUNOLOGY

Psychoneuroimmunology is a convergence of disciplines — namely, the behav sciences, the neu endocrinology, and immunology — intended to achieve a more complete understanding of the way the interaction among these systems serve homeos ends and influence hea disease.

— Robert Ader

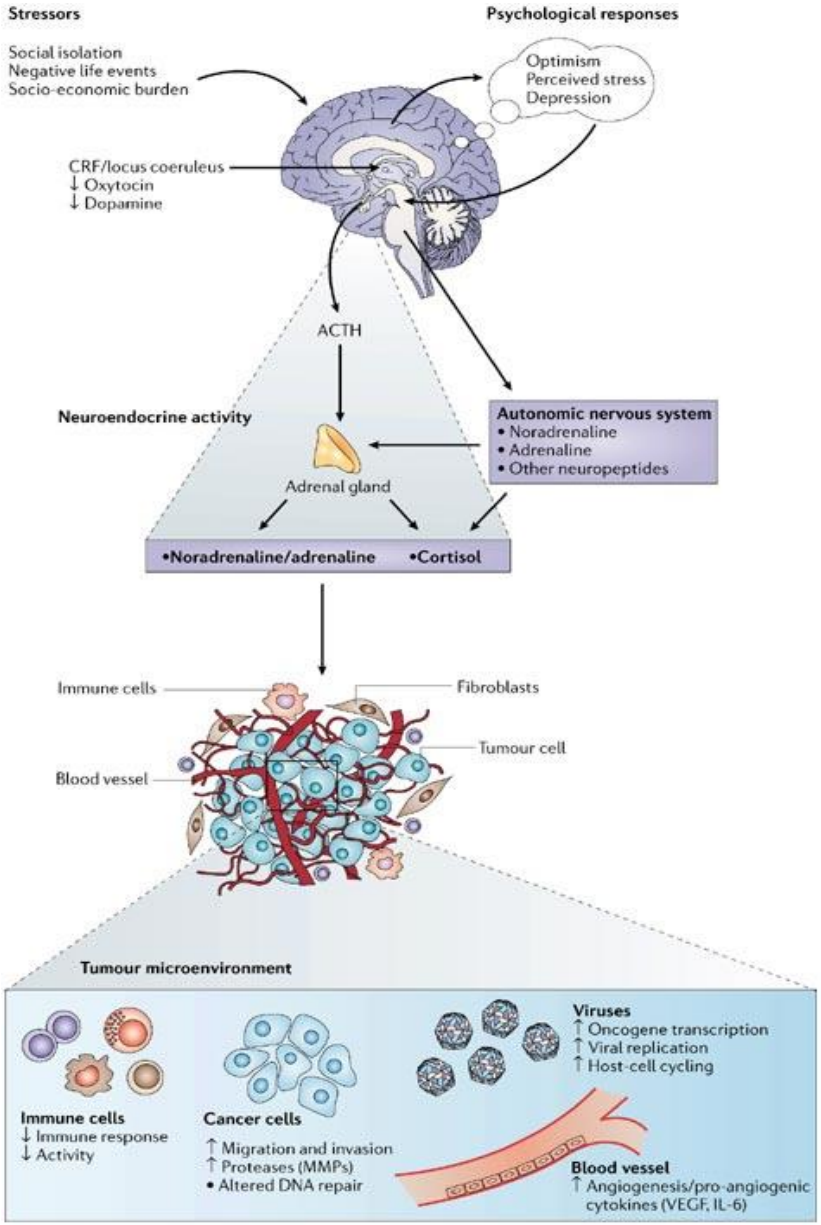


Cancer → Brain



Miller A H et al. JCO 2008;26:971-982

JOURNAL OF CLINICAL ONCOLOGY

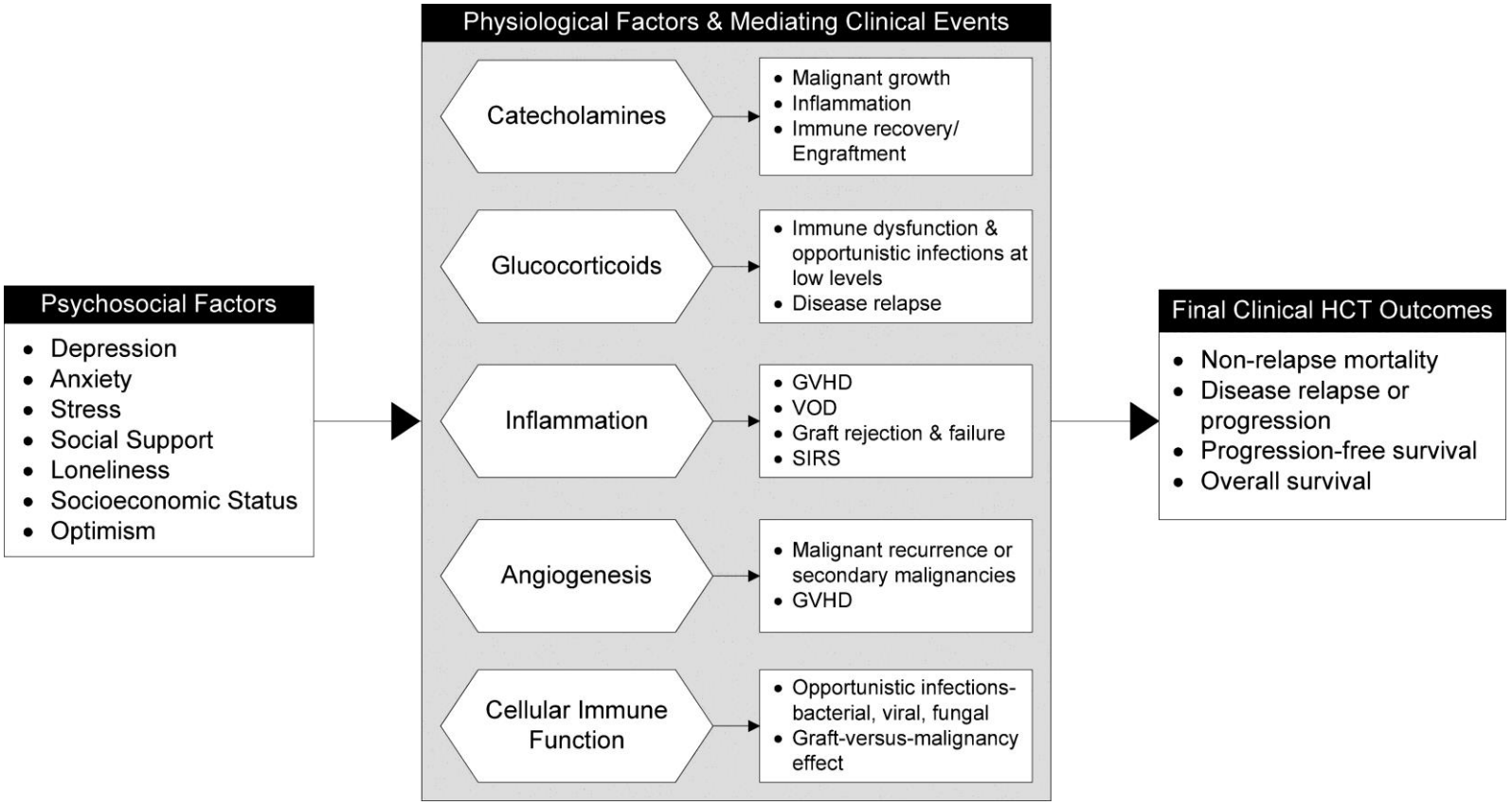


Brain → Cancer

nature REVIEWS CANCER

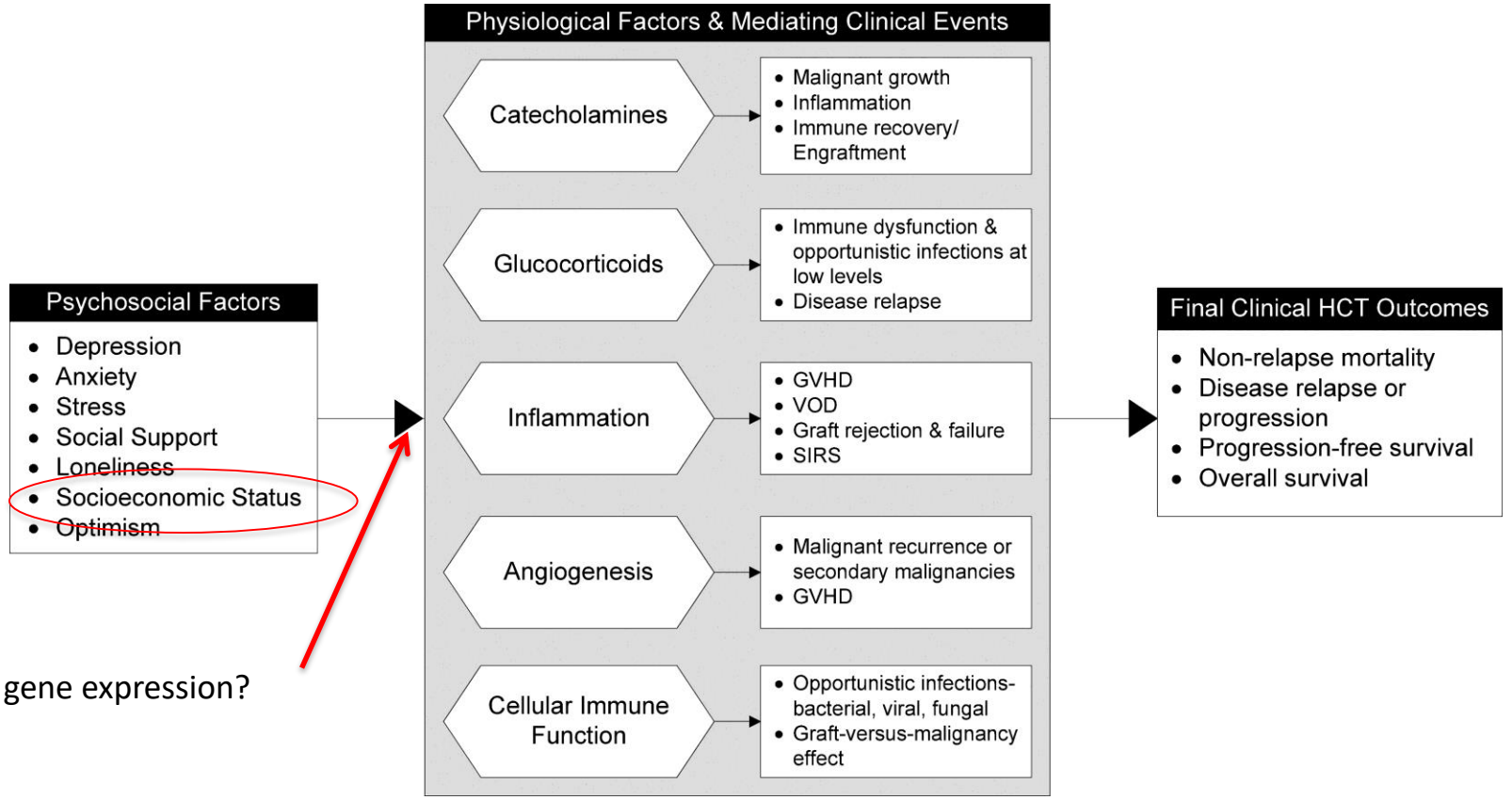
Antoni *et al. Nature Reviews Cancer* **6**, 240–248 (March 2006) | doi:10.1038/nrc1820

Biobehavioral Model of HCT



Knight JM et al. 2013, Psychoneuroendocrinology

SES and Gene Expression in HCT

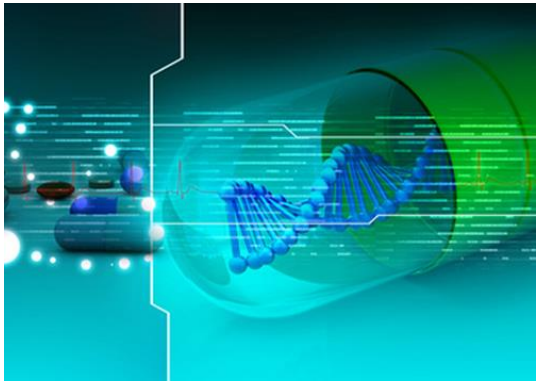


Altered gene expression?

Knight JM et al. 2013, Psychoneuroendocrinology

Chronic stress affects transcriptional activity

- "Conserved Transcriptional Response to Adversity" (CTRA) gene expression profile
  - Circulating immune cells (PBMCs) demonstrate a systematic shift in basal gene expression profiles during extended periods of stress, threat, or uncertainty[1-2]
  - 53 genes: high inflammation (19 genes), low interferon response (Type I, 31 genes), low antibody synthesis (3 genes)
  - Regulated by β-adrenergic system



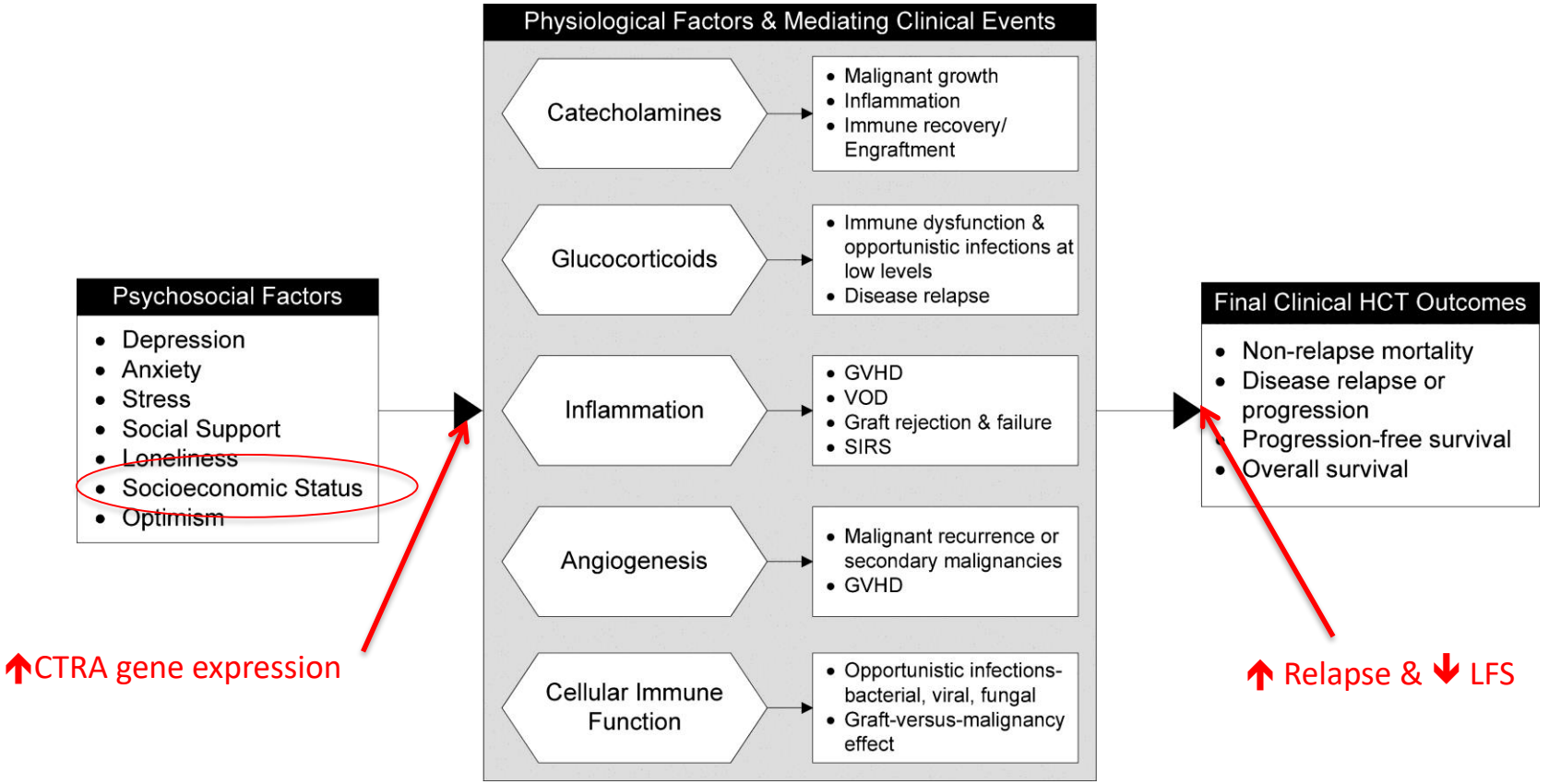
[1]Cole SW 2007, Genome Biology
[2]Powell ND et al. 2013, PNAS

Personalized Medicine and Imaging

Clinical Cancer Research

Low Socioeconomic Status, Adverse Gene Expression Profiles, and Clinical Outcomes in Hematopoietic Stem Cell Transplant Recipients

Jennifer M. Knight[1], J. Douglas Rizzo[2], Brent R. Logan[2], Tao Wang[2], Jesusa M.G. Arevalo[3], Jeffrey Ma[3], and Steve W. Cole[3]



Knight JM et al. 2016, Clinical Cancer Research

Knight JM et al. 2013, Psychoneuroendocrinology

CCR Translations

Clinical Cancer Research

Is It Better to Be Rich or Relaxed? Sociobiology Meets Bone Marrow Transplant

Lucie M. Turcotte and Michael R. Verneris

Low socioeconomic status in hematopoietic cell transplant recipients is associated with increased treatment-related mortality and relapse, resulting in reduced survival. No biologic mechanism has been identified for these associations. The stress-related gene expression profile, termed the "conserved transcriptional response to adversity," may be a predictor of these negative outcomes. *Clin Cancer Res; 22(1); 1–3. ©2015 AACR.*

See related article by Knight et al., p. 69

Invited Commentary, CCR 2016:

"…these data might get to the core of an untapped area in cancer therapeutics: understanding how to manage chronic stress to positively influence outcomes."

Turcotte LM & Verneris MR 2016, Clinical Cancer Research

CCR Translations

Clinical Cancer Research

Is It Better to Be Rich or Relaxed? Sociobiology Meets Bone Marrow Transplant

Lucie M. Turcotte and Michael R. Verneris

Low socioeconomic status in hematopoietic cell transplant recipients is associated with increased treatment-related mortality and relapse, resulting in reduced survival. No biologic mechanism has been identified for these associations. The stress-related gene expression profile, termed the "conserved transcriptional response to adversity," may be a predictor of these negative outcomes. *Clin Cancer Res; 22(1); 1–3. ©2015 AACR.*

See related article by Knight et al., p. 69

Invited Commentary, CCR 2016:

"potentially using the CTRA profile as a stress biomarker, which could, in turn, be incorporated into pre-HCT disease risk stratification…"

Turcotte LM & Verneris MR 2016, Clinical Cancer Research

CCR Translations

Clinical Cancer Research

Is It Better to Be Rich or Relaxed? Sociobiology Meets Bone Marrow Transplant

Lucie M. Turcotte and Michael R. Verneris

Low socioeconomic status in hematopoietic cell transplant recipients is associated with increased treatment-related mortality and relapse, resulting in reduced survival. No biologic mechanism has been identified for these associations. The stress-related gene expression profile, termed the "conserved transcriptional response to adversity," may be a predictor of these negative outcomes. *Clin Cancer Res; 22(1); 1–3. ©2015 AACR.*

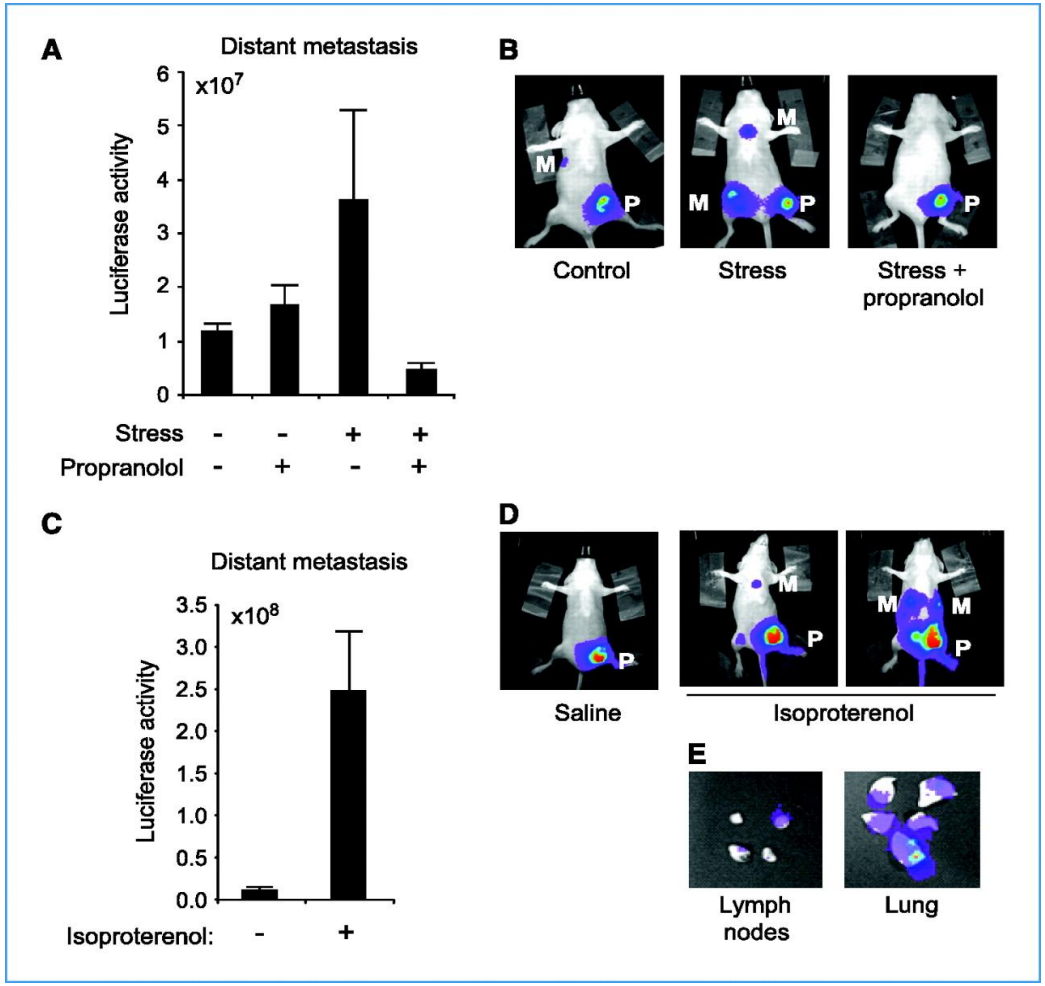
See related article by Knight et al., p. 69

Invited Commentary, CCR 2016:

"The authors further posit that the use of β-adrenergic antagonists (β-blockers)…may be of potential benefit in individuals with altered gene transcription patterns and that CTRA expression could be monitored over time to assess treatment response."

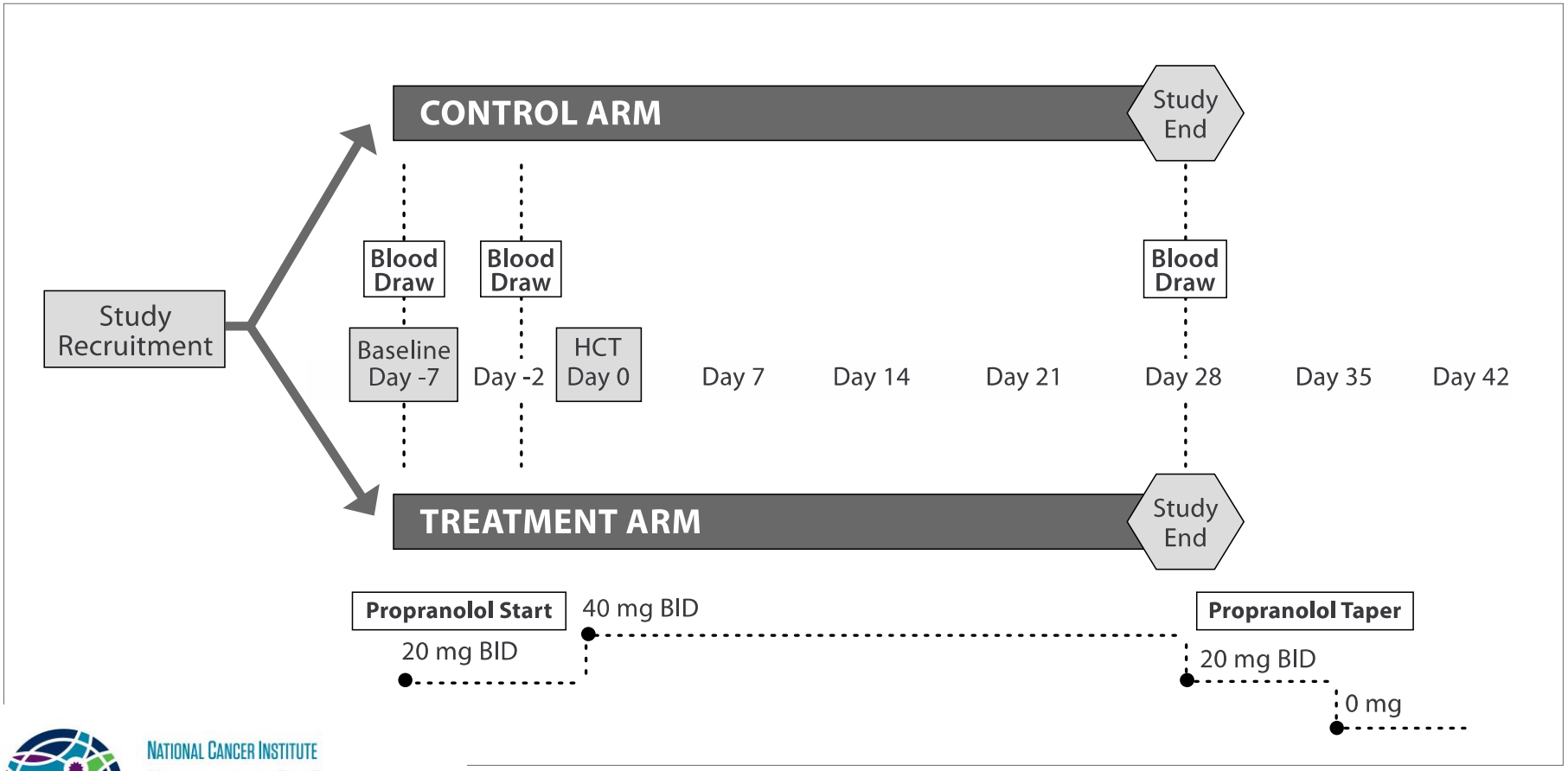
Turcotte LM & Verneris MR 2016, Clinical Cancer Research

β-blockers stop metastatic spread of stress-induced cancer progression in mice



Sloan E K et al. Cancer Res 2010;70:7042-7052

Pilot study using propranolol to decrease gene expression of stress-mediated β-adrenergic pathways in HCT recipients



National Cancer Institute
Network on BioBehavioral Pathways in Cancer

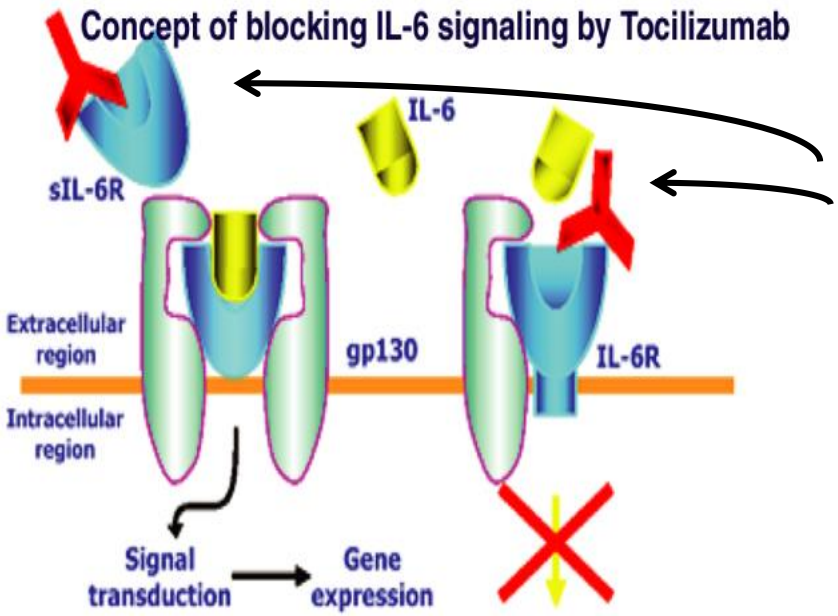
Propranolol Conclusions

- Propranolol administration during HCT is feasible
- Peri-transplant administration of propranolol decreases genome-wide transcriptional pathways involved in β-adrenergic signaling
- Propranolol has clinically meaningful impact on early post-HCT outcomes
- Ongoing follow-up and future replication studies are required to assess impacts on clinical outcomes

HCT Treatments and CNS Functioning

" PHASE II OPEN LABEL OF TACROLIMUS/METHOTREXATE AND TOCILIZUMAB FOR THE PREVENTION OF ACUTE GRAFT VERSUS HOST DISEASE AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION" (Drobyski, PI)

Humanized anti-IL-6 receptor antibody that blocks IL-6 signaling and has been FDA-approved for the treatment of severe active rheumatoid arthritis



Blocks both membrane and soluble forms of the IL-6R

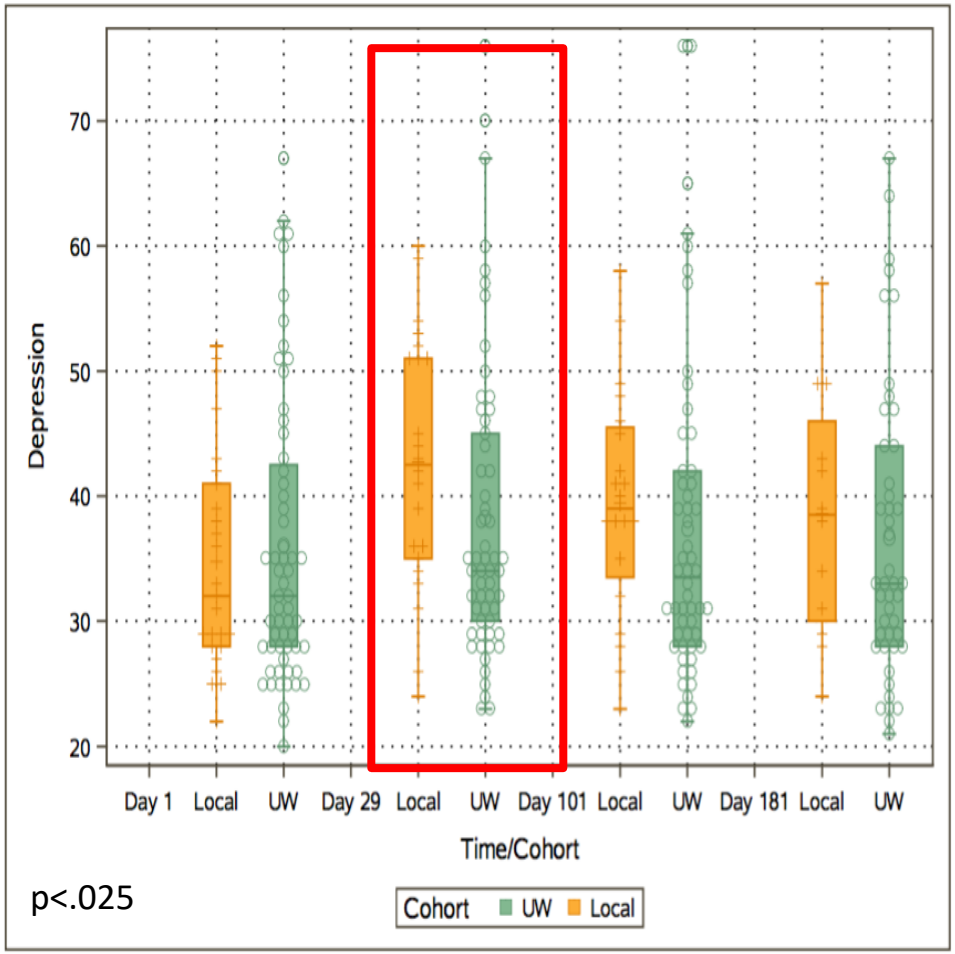
TOCILIZUMAB FOR THE PREVENTION OF DEPRESSION, COGNITIVE CHANGES, ADVERSE GENE EXPRESSION, AND LOSS OF RAP1 PRENYLATION AMONG ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION RECIPIENTS

PIs: William Drobyski, MD, Marcelo Pasquini, MD, MS, Jennifer Knight, MD, MS

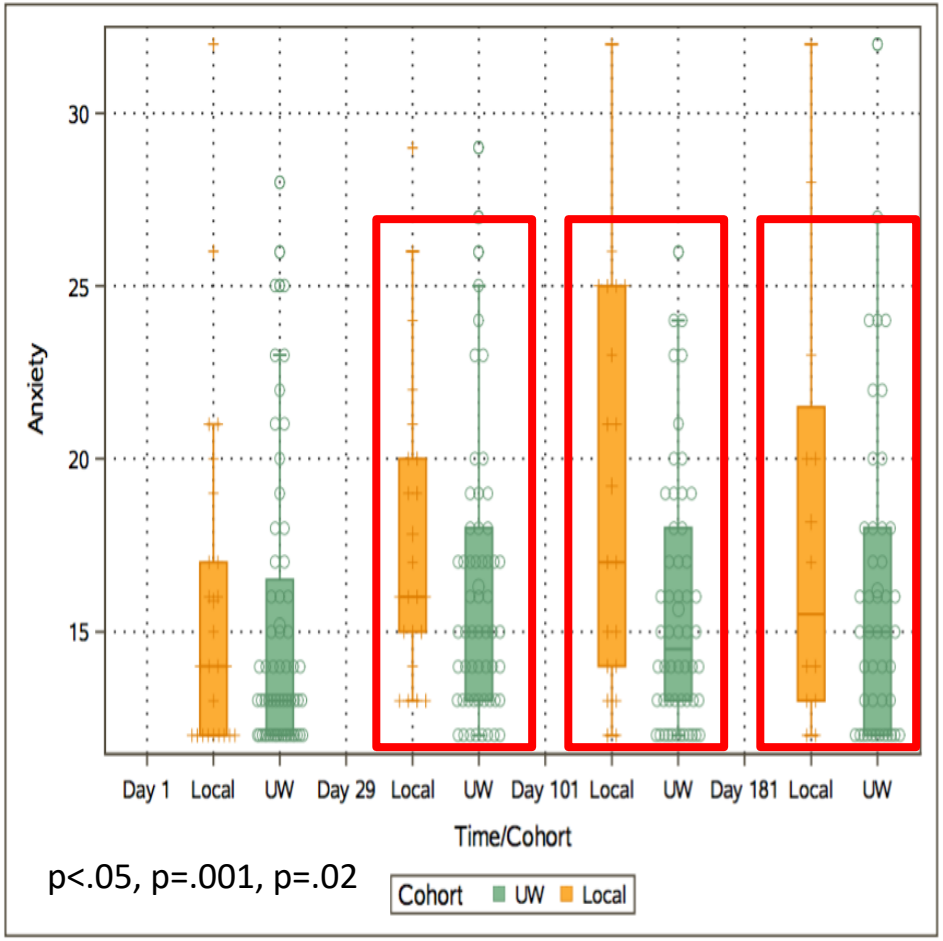
Central Hypothesis:

Patients receiving tocilizumab will have improved depression, anxiety, fatigue, sleep, and pain as compared to patients not receiving tocilizumab.

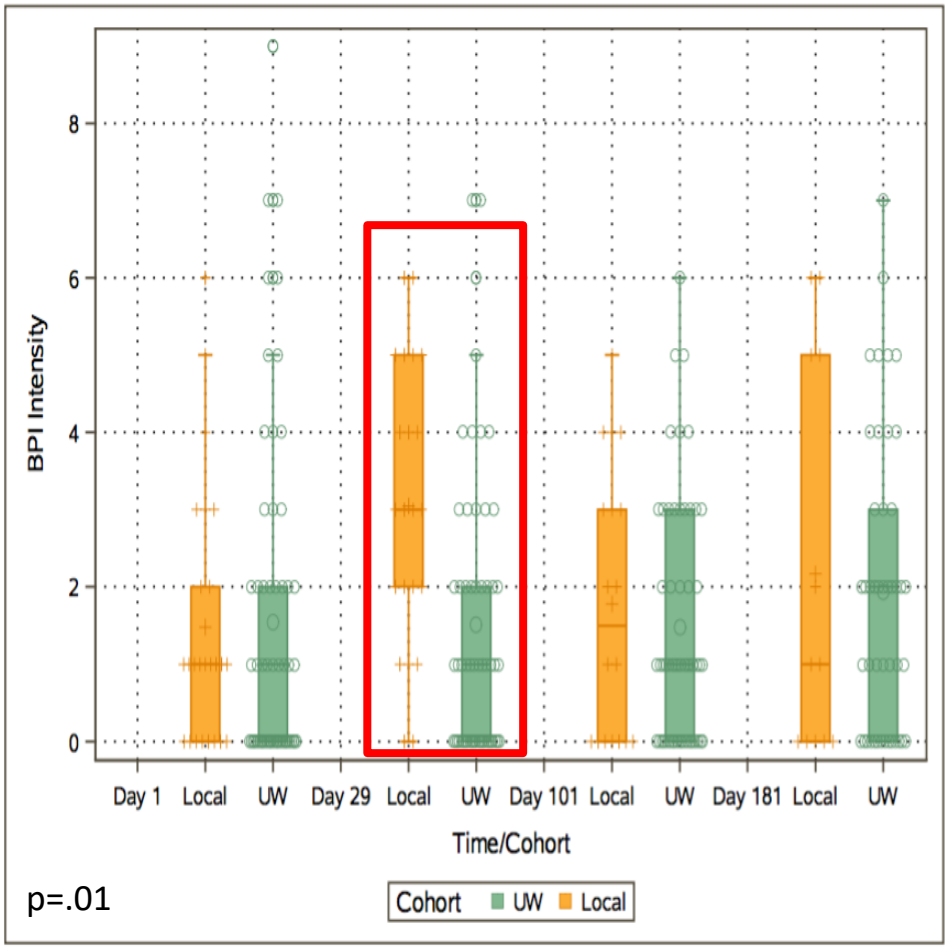
HCT patients exposed to tocilizumab have higher depression scores at Day +29



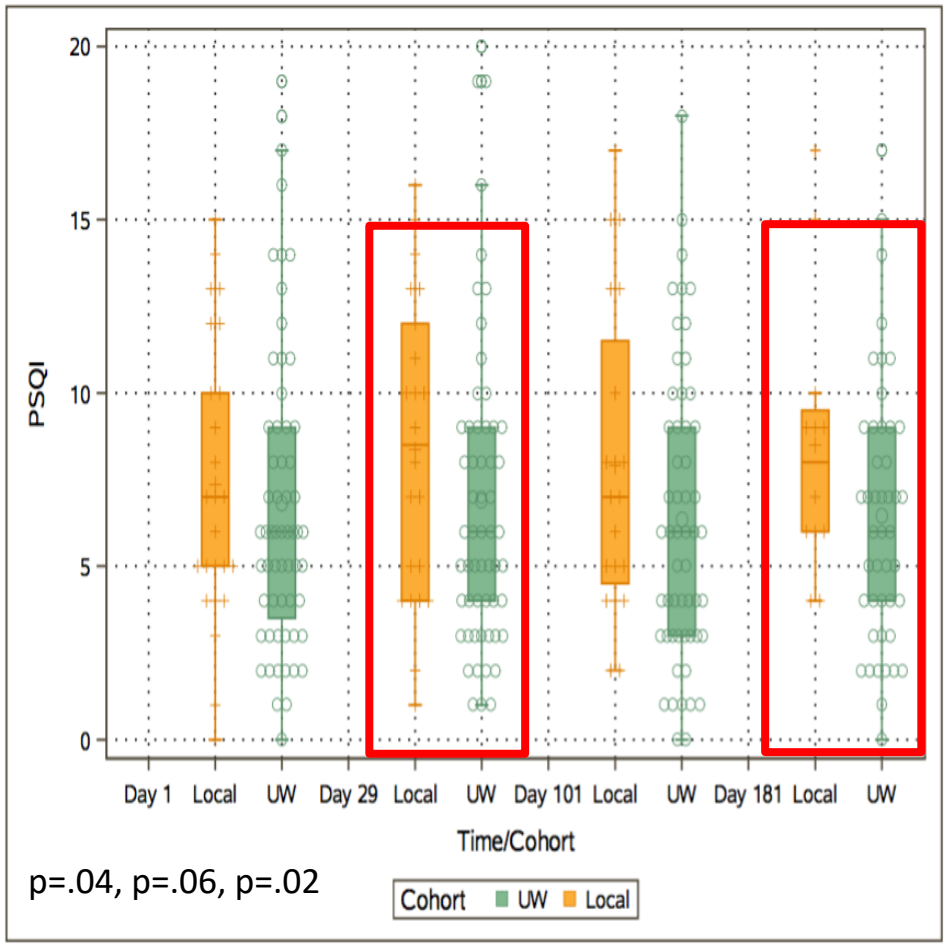
Patients receiving tocilizumab exhibited greater anxiety at all 3 time points following HCT



HCT patients receiving tocilizumab experienced greater pain intensity at Day +29

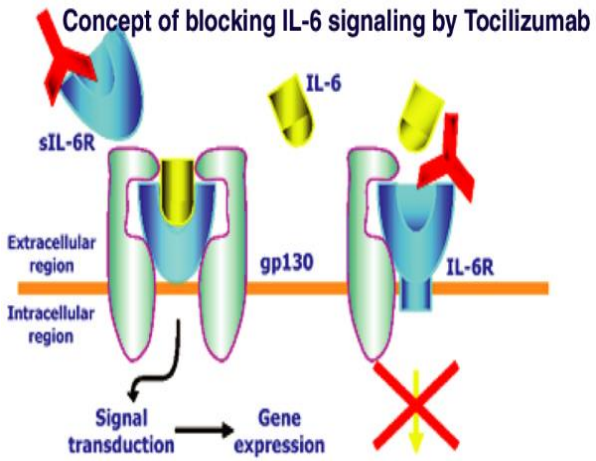


Patients receiving tocilizumab experienced worse sleep at all time points following HCT



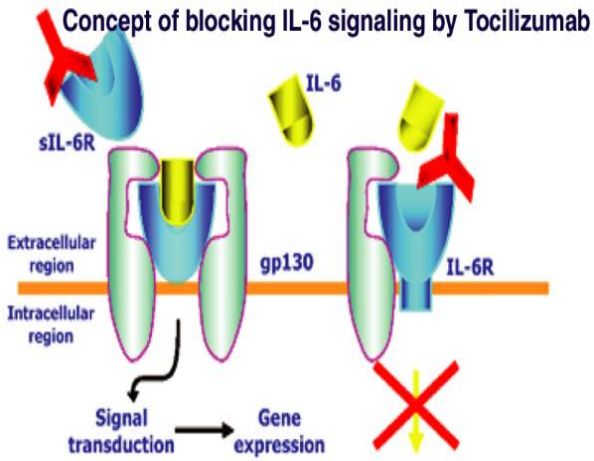
Tocilizumab Conclusions

1. <u>Biological psychiatry</u>: informs etiology of inflammation and mood disorders/cognitive function

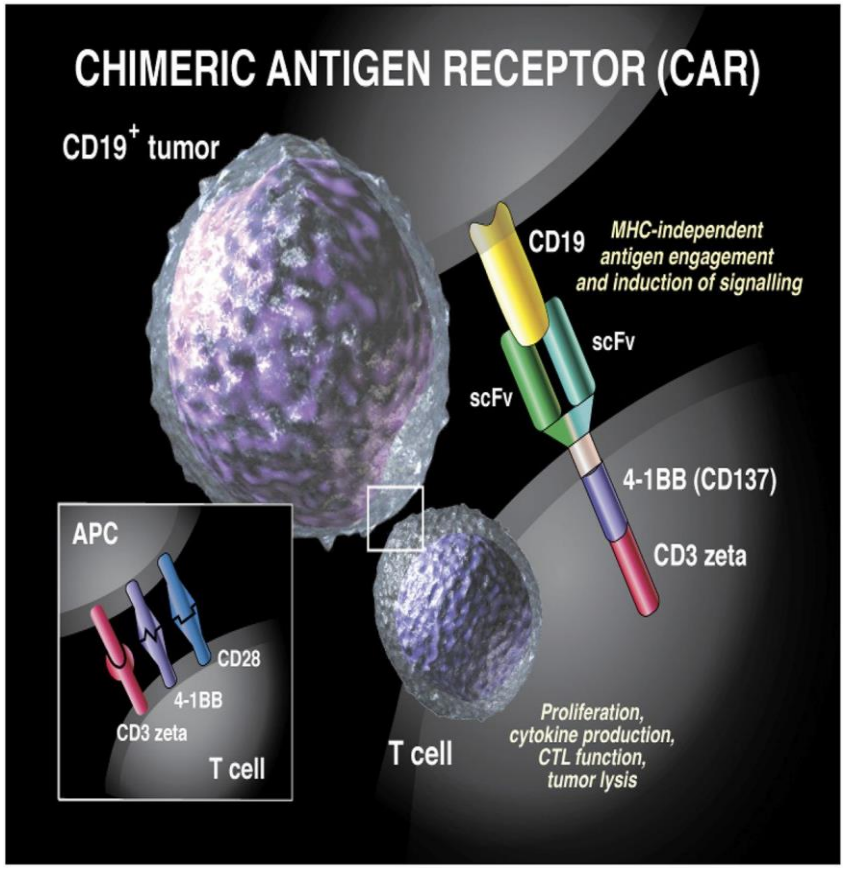


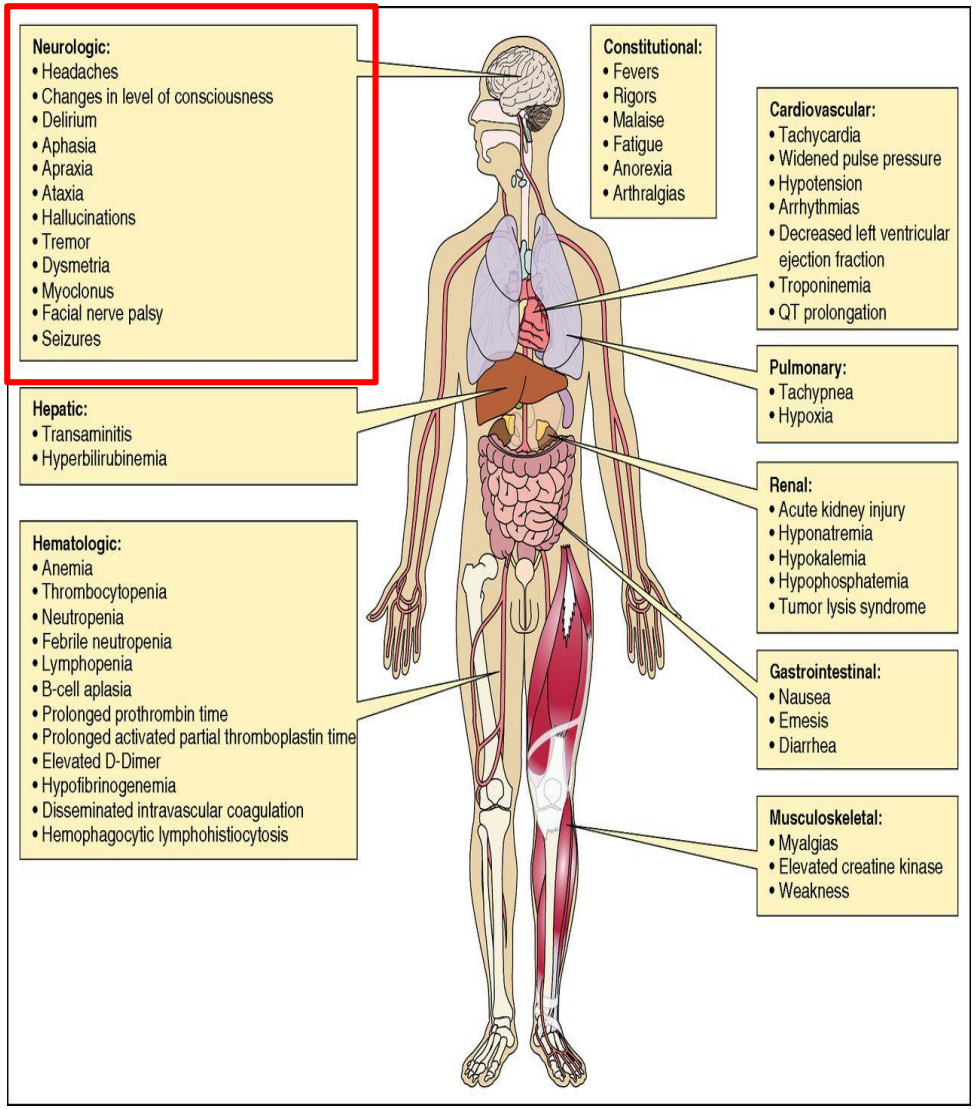
Tocilizumab Conclusions

1. Biological psychiatry: informs etiology of inflammation and mood disorders/cognitive function
2. Cancer: informs side effect profile of FDA approved drug for treatment of cytokine release syndrome - tocilizumab (August 2017)



Chimeric Antigen Receptor (CAR) T Cell Therapy

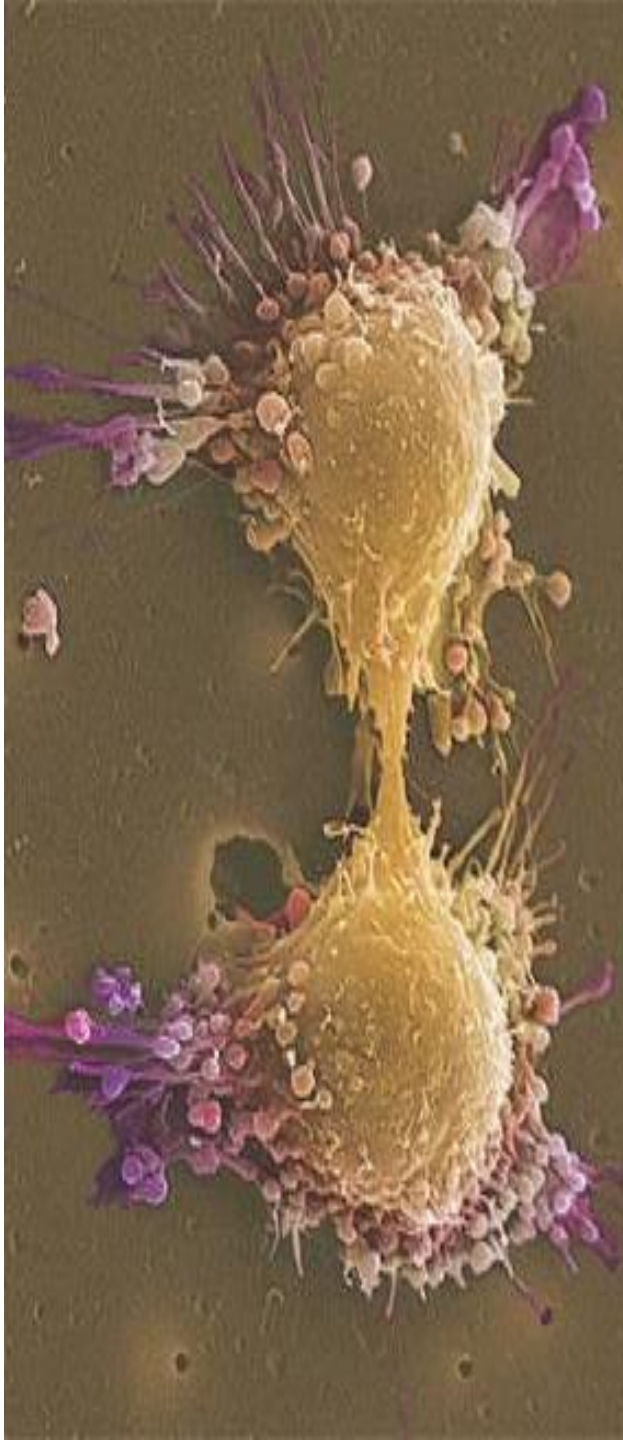




Major side effect of this therapy is Cytokine Release Syndrome which can cause life threatening neurotoxicity which does not respond to IL-6-directed therapies.

CONCLUSIONS

- HCT is a relevant and understudied population for PNI and translational biobehavioral oncology research
- Stress impacts HCT biology and outcomes
- Candidate interventions
- HCT treatments impact CNS function
- Additional work is needed to identify the most pertinent pathways mediating this relationship and subsequent effective interventions



Acknowledgements

Mentors/Mentees/Collaborators:

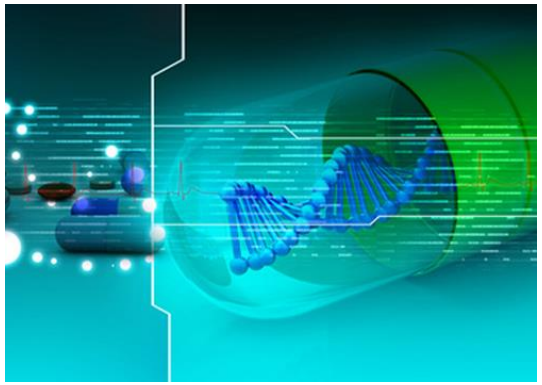
Chris Coe, PhD (UW-Madison)
Steve W. Cole, PhD (UCLA)
Erin Costanzo, PhD (UW-Madison)
Anita D'Souza, MD, MS
William Drobyski, MD
Karen Giles, MD, MS
Parameswaran Hari, MD, MS
Cece Hillard, PhD
Mary Horowitz, MD, MS
Stephanie Kerswill, BS
Brent Logan, PhD
Ann Nattinger, MD, MPH
Marcelo Pasquini, MD, MS
J. Douglas Rizzo, MD, MS
Suraj Singh, MD
Melinda Stolley, PhD
Aniko Szabo, PhD
Tao Wang, PhD
Carol Williams, PhD
Ziyan Yin, MS

Funding Support:

- CTSI KL2 Mentored Career Development Award
- National Marrow Donor Program
- American Cancer Society MCW IRG
- AHW Research and Education Program
- NCI Network on Biobehavioral Pathways in Cancer/Leidos Biomed
- MCW Department of Psychiatry
- MCW Neuroscience Research Center
- Laura Gralton Philanthropic Fund
- CIBMTR

Clinical Research Coordinators:

Kimberly Harris
Neil Smith
Luke Richard
Stephanie Kerswill
Sharon Yim
Kaylee Meisinger
Jeanie Esselmann



QUESTIONS, COMMENTS?