National Institute of Nursing Research

Radiation-Related Fatigue:
Phenotyping, Pathogenesis, Treatment

CDR Leorey N. Saligan, PhD, RN, CRNP, FAAN
Chief, Symptoms Biology Unit
Division of Intramural Research, NINR

Objectives

At the end of this presentation, we will:

- Define radiation-related fatigue (RRF)
- Describe an approach to phenotype RRF
- Enumerate the methodological approaches utilized in RRF investigations
- Identify recently developed therapeutics for RRF

State of the Nursing Science

- Increasing need to address the aging population and the long-term impact of chronic illnesses
- Addressing the health care needs of a diverse Nation
- Shifting emphasis from treatment to prevention
- Increasing reliance to technology

Purposes of Nursing Research

Develop knowledge to improve quality of life:

- Build scientific foundation for clinical practice
- Prevent disease and disability
- Manage / eliminate symptoms caused by illness
- Enhance end-of-life and palliative care

National Institute of Nursing Research

4 Key Themes Guiding the Implementation of the NINR Strategic Plans

1. Symptom Science: Promoting Personalized Health Strategies
2. Wellness: Promoting Health and Preventing Illness
3. Self-Management: Improving Quality of Life for Individuals with Chronic Illness
4. End-of-Life and Palliative Care: The Science of Compassion

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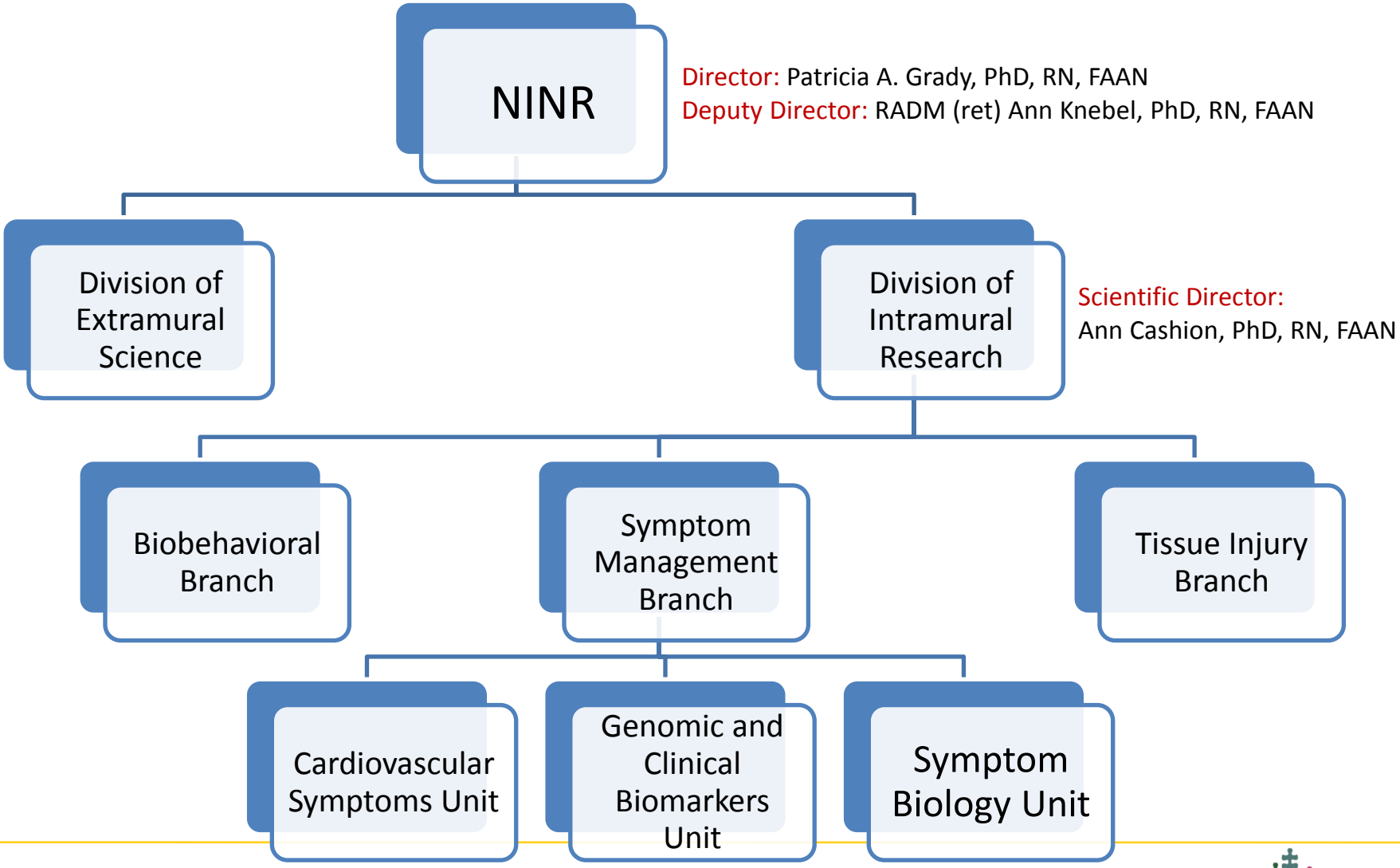


Symptom Management Branch: Research

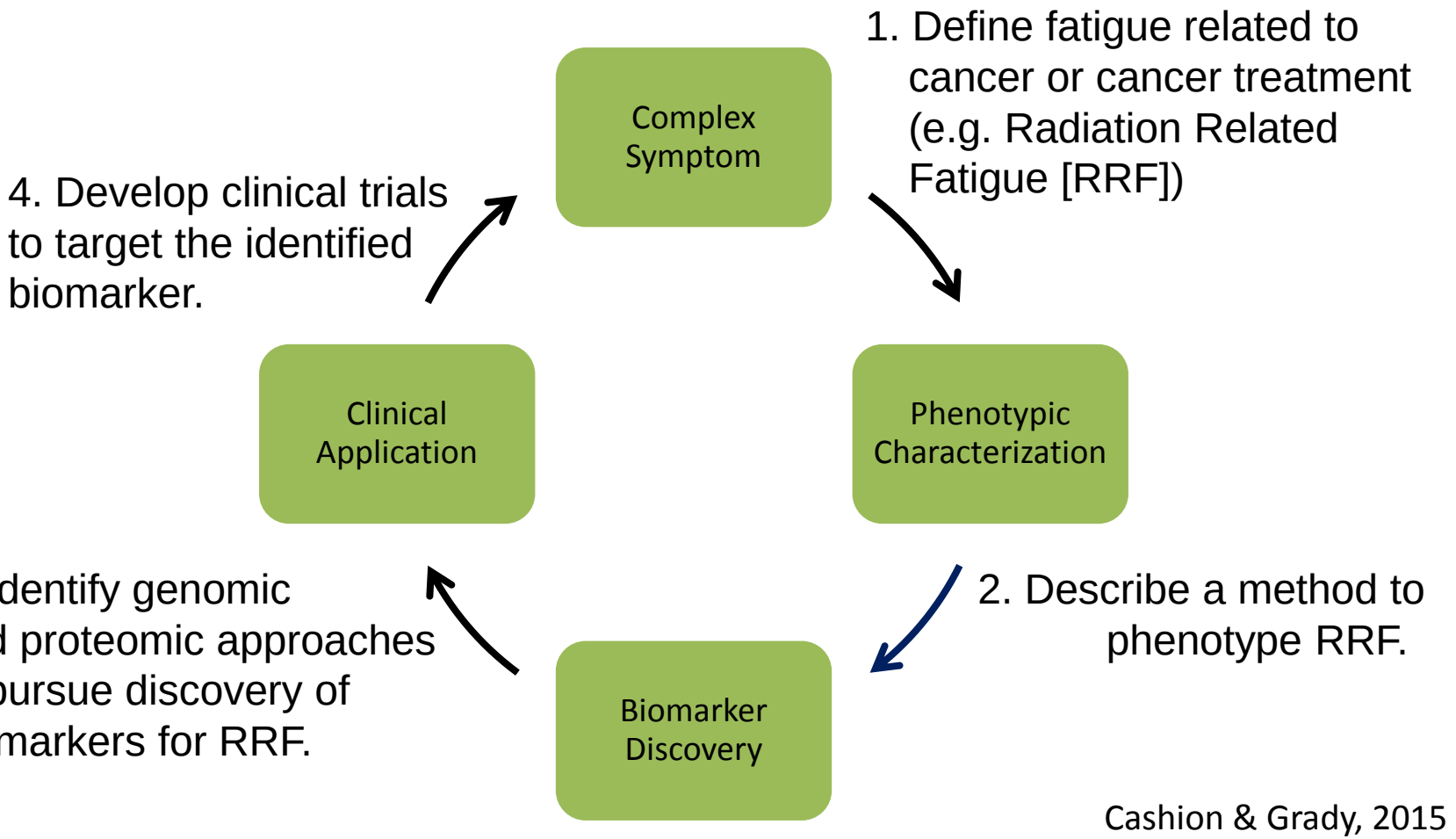
Focus Areas:

- Nature and causes of fatigue in a variety of specific conditions including cancer
- Symptoms associated with fatigue

Leorey Saligan, PhD, RN, CRNP
Chief, Symptom Biology Unit

Purpose: Identify functional pathways for potential therapeutic intervention including lifestyle changes.

NIH Symptom Science Model



Cashion & Grady, 2015

Unmet Needs for Improved Fatigue Management

- Up to 96% of patients with cancer experience fatigue
- No clear case definition of cancer-related fatigue (e.g. RRF) .
- Clinical management of fatigue is compromised because the etiology of CRF remains elusive.
- CRF is associated with negative health outcomes including depression, impaired cognitive function, sleep disturbance, and decreased health-related quality of life (Byar et al., 2006).

Definition and Clinical Guidelines

ICD-10 criteria for CRF

Six (or more) of the following symptoms have been present every day or nearly every day during the same 2-week period in the past month, and at least one of the symptoms is (A1) significant fatigue.

- A1. Significant fatigue, diminished energy, or increased need to rest, disproportionate to any recent change in activity level
- A2. Complaints of generalized weakness or limb heaviness
- A3. Diminished concentration or attention
- A4. Decreased motivation or interest to engage in usual activities
- A5. Insomnia or hypersomnia
- A6. Experience of sleep as unrefreshing or nonrestorative
- A7. Perceived need to struggle to overcome inactivity
- A8. Marked emotional reactivity (eg, sadness, frustration, or irritability) to feeling fatigued
- A9. Difficulty completing daily tasks attributed to feeling fatigued
- A10. Perceived problems with short-term memory
- A11. Postexertional malaise lasting several hours
- B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
- C. There is evidence from the history, physical examination, or laboratory findings that the symptoms are a consequence of cancer or cancer therapy.
- D. The symptoms are not primarily a consequence of comorbid psychiatric disorders such as major depression, somatization disorder, somatoform disorder, or delirium.

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NCCN guideline

Non-pharmacologic

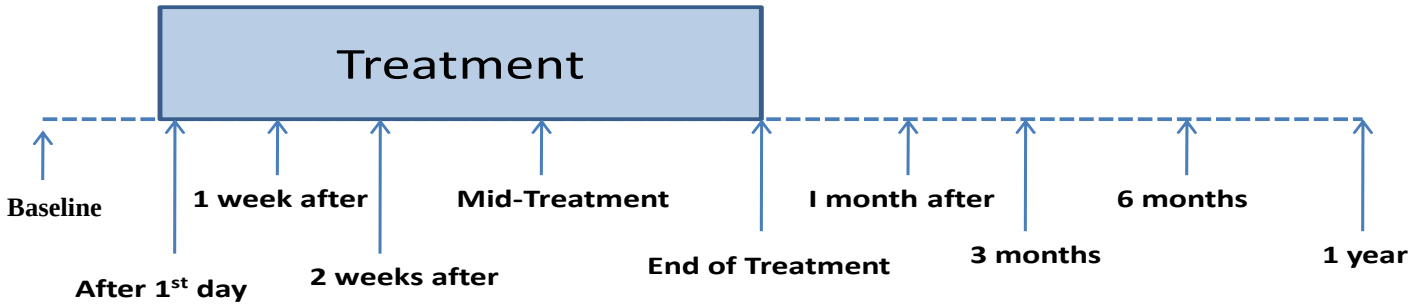
- activity enhancement
- psychosocial interventions
- attention-restoring therapy
- nutrition
- sleep therapy

Pharmacologic

- attention restoring agent

Natural History Study

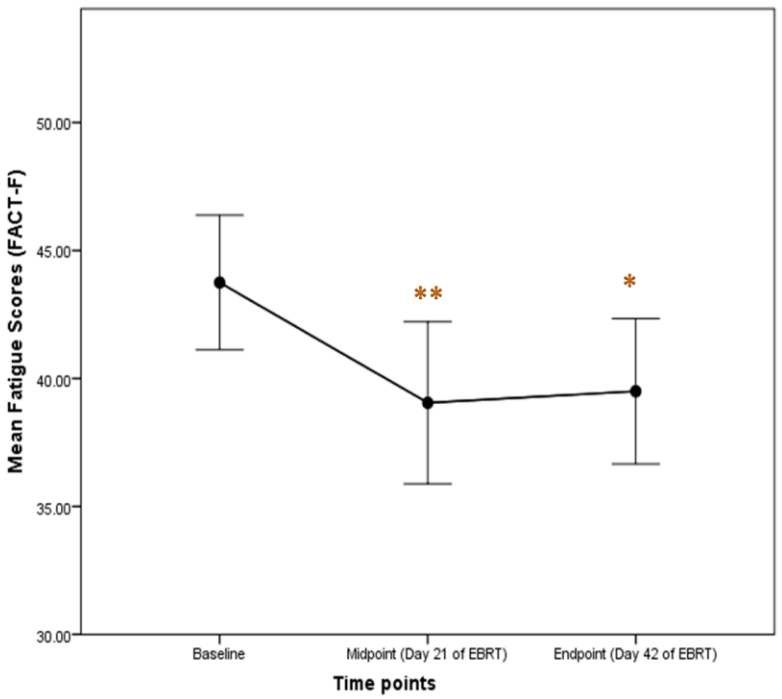
Design: prospective, descriptive, observational study
Methods: questionnaires, computerized cognitive tests, portable hand-grip test, physical activity monitor, blood



Fatigue During Radiation Therapy

Clinical Study (NCT00852111)

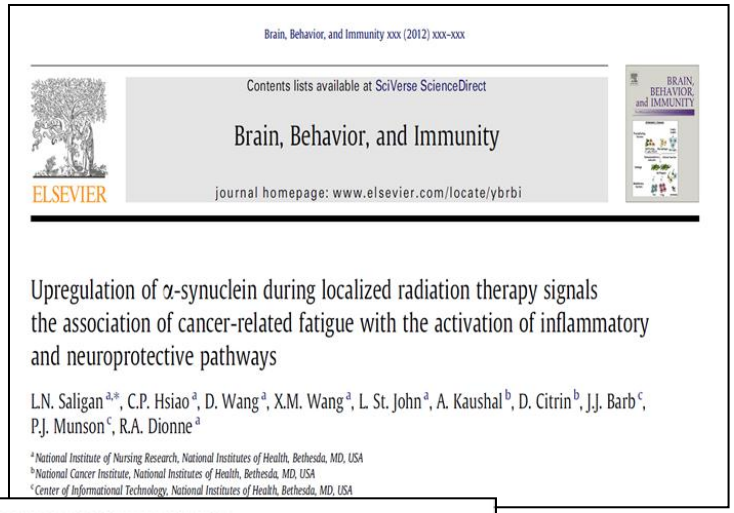
N=45



*p<.05, **p<.001

Low scores = High fatigue

- Inflammation (e.g. *IFI27*)
- Neuroprotection (e.g. *SNCA*)



Brain, Behavior, and Immunity xxx (2012) xxx-xxx

Contents lists available at SciVerse ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

ELSEVIER

Upregulation of α-synuclein during localized radiation therapy signals the association of cancer-related fatigue with the activation of inflammatory and neuroprotective pathways

L.N. Saligan[a,*], C.P. Hsiao[a], D. Wang[a], X.M. Wang[a], L. St. John[a], A. Kaushal[b], D. Citrin[b], J.J. Barb[c], P.J. Munson[c], R.A. Dionne[a]

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Int. J. Mol. Sci. **2013**, *14*, 16943-16957; doi:10.3390/ijms140816943

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International Journal of Molecular Sciences

ISSN 1422-0067

www.mdpi.com/journal/ijms

Article

The Association of *IFI27* Expression and Fatigue Intensification during Localized Radiation Therapy: Implication of a Para-Inflammatory Bystander Response

Chao-Pin Hsiao [1,2,*], Maria Araneta [2], Xiao Min Wang [2] and Leorey N. Saligan [2,*]

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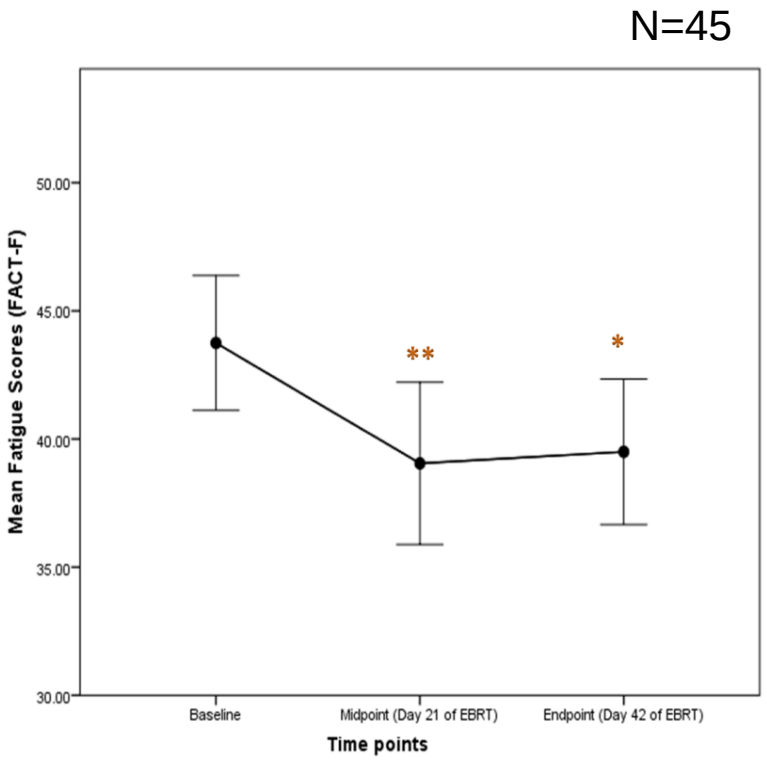
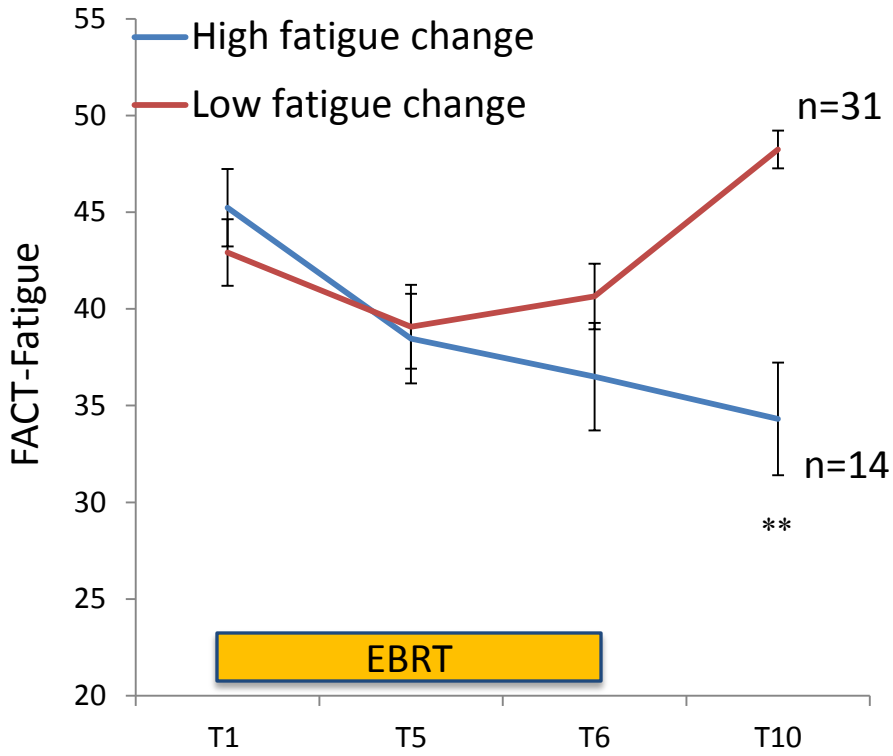
[2] National Institute of Nursing Research, National Institutes of Health, 9000 Rockville Pike, Building 10, Room 2-1339, Bethesda, MD 20892, USA; E-Mails: maria.araneta@nih.gov (M.A.), xmwang@mail.nih.gov (X.M.W.)

Fatigue During Radiation Therapy

Clinical Study (NCT00852111)





**$p<.001$

Low scores = High fatigue

Review of CRF Science

Support Care Cancer (2015) 23:2461–2478
DOI 10.1007/s00520-015-2763-0

REVIEW ARTICLE

The biology of cancer-related fatigue: a review of the literature

Leorey N. Saligan[1] · Karin Olson[2] · Kristin Filler[1] · David Larkin[3] · Fiona Cramp[4] · Yennu Sriram[5] · Carmen P. Escalante[5] · Auro del Giglio[6] · Kord M. Kober[7] · Jayesh Kamath[8] · Oxana Palesh[9] · Karen Mustian[10] · Multinational Association of Supportive Care in Cancer Fatigue Study Group–Biomarker Working Group

Received: 19 November 2014 / Accepted: 30 April 2015 / Published online: 15 May 2015

Support Care Cancer
DOI 10.1007/s00520-015-2965-5

COMMENTARY

Defining cancer-related fatigue for biomarker discovery

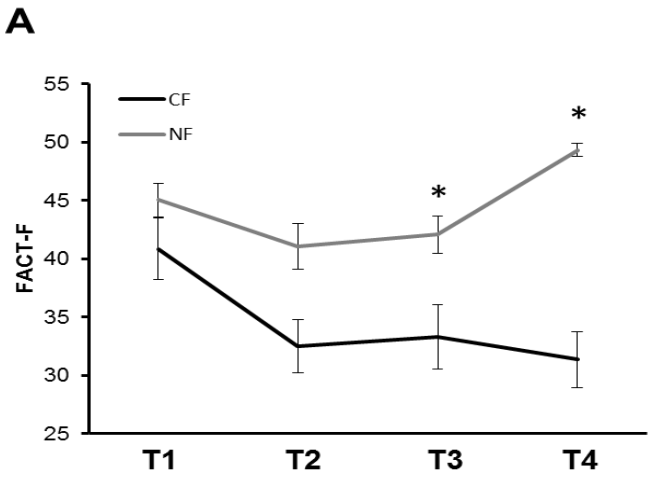
Kristin Filler[1] · Leorey N. Saligan[1]

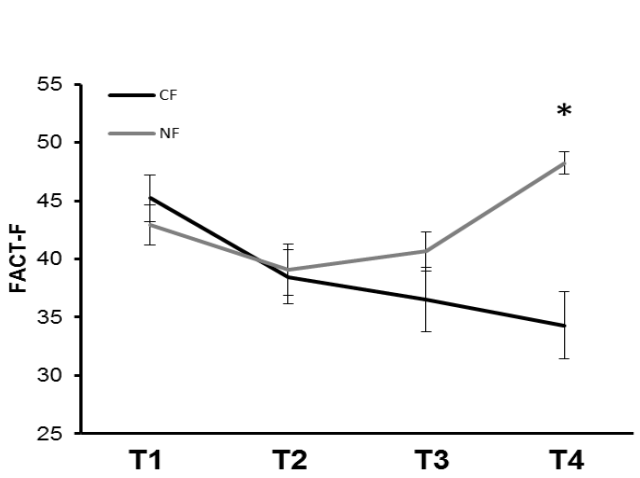
Received: 22 July 2015 / Accepted: 21 September 2015

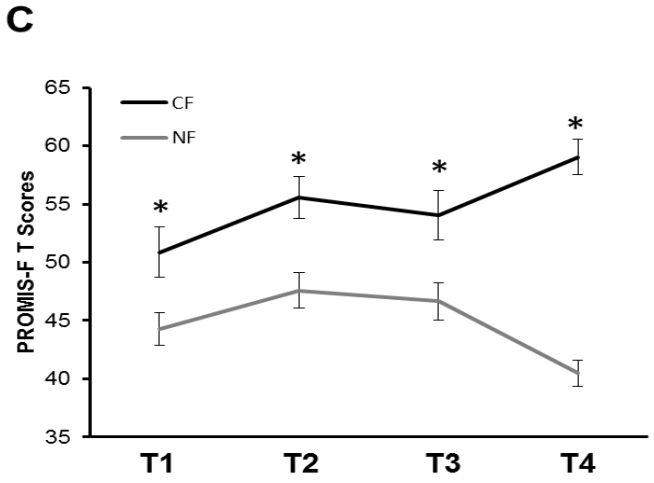
47 articles reviewed:

- CRF was measured using 23 different questionnaires
- Even when the same questionnaire was used, different scoring rubrics were applied to phenotype CRF

RRF Phenotyping Approaches



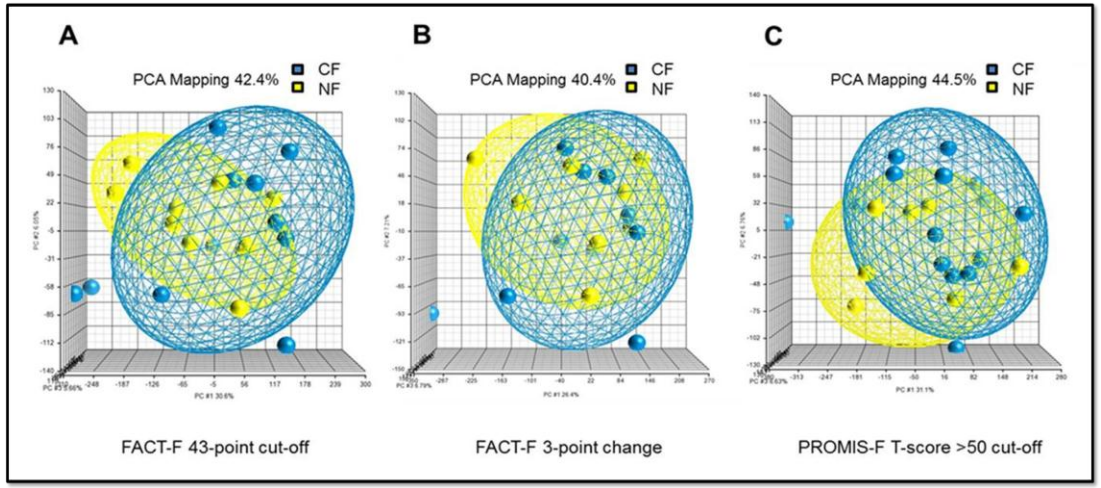




RRF Phenoytping Approaches:

A. FACT-F 43-point cutoff
   - captures fatigue experience best correlated with differences in gene expression
B. FACT-F 3-point change
   - can isolate chronic fatigue
C. PROMIS-F 50 T-score cutoff
   - most sensitive to subtle changes in fatigue.

Issues with RRF Phenotyping



	Approach 1 FACT-F 43-point cut-off			Approach 2 FACT-F 3-point change			Approach 3 PROMIS-F T-score >50		
	Gene ID	**FC**	**P value**	**Gene ID**	**FC**	**P value**	**Gene ID**	**FC**	**P value**
Top up-regulated genes	*PI3*	1.92	1.64E-4	*LEF1*	1.67	1.01E-5	*MARCKSL1*	1.40	1.30E-6
	IL18RAP	1.83	2.25E-4	*CLTB*	1.48	1.37E-6	*FBLN5*	1.40	1.15E-5
	FAM84B	1.68	2.40E-4	*LEF1-AS1*	1.45	2.68E-6	*IGLV1-44*	1.38	2.01E-5
	IGLL3P	1.68	5.58E-5	*FBLN5*	1.45	1.77E-5	*SLC35F2*	1.26	2.03E-5
	ACTB	1.63	1.66E-4	*FDFT1*	1.41	3.14E-5	*ACTR1A*	1.25	1.91E-5
Top down-regulated genes	*NUDT6*	-1.40	3.04E-5	*CENPN*	-1.31	1.74E-5	*VEPH1*	-1.29	2.38E-6
	ZC2HC1C	-1.37	7.48E-5	*GALNT2*	-1.30	8.52E-6	*SLC22A9*	-1.28	1.33E-5
	RRAD	-1.34	4.32E-6	*SIM1*	-1.30	7.58E-6	*QSOX1*	-1.26	6.64E-6
	CDC25C	-1.32	3.48E-5	*YPEL2*	-1.28	1.51E-6	*UBE2Z*	-1.22	4.40E-6
	OLIG2	-1.32	6.91E-5	*MTBP*	-1.27	1.58E-8	*GOLGA3*	-1.19	1.23E-5

Principal component analyses showing differences in transcriptome profiles of the RRF phenotype using 3 different fatigue phenotyping approaches.

GO enrichment analyses

Approach 1: 244 genes
- biological adhesion (46%)

Approach 2: 40 genes
- biogenesis (22%)

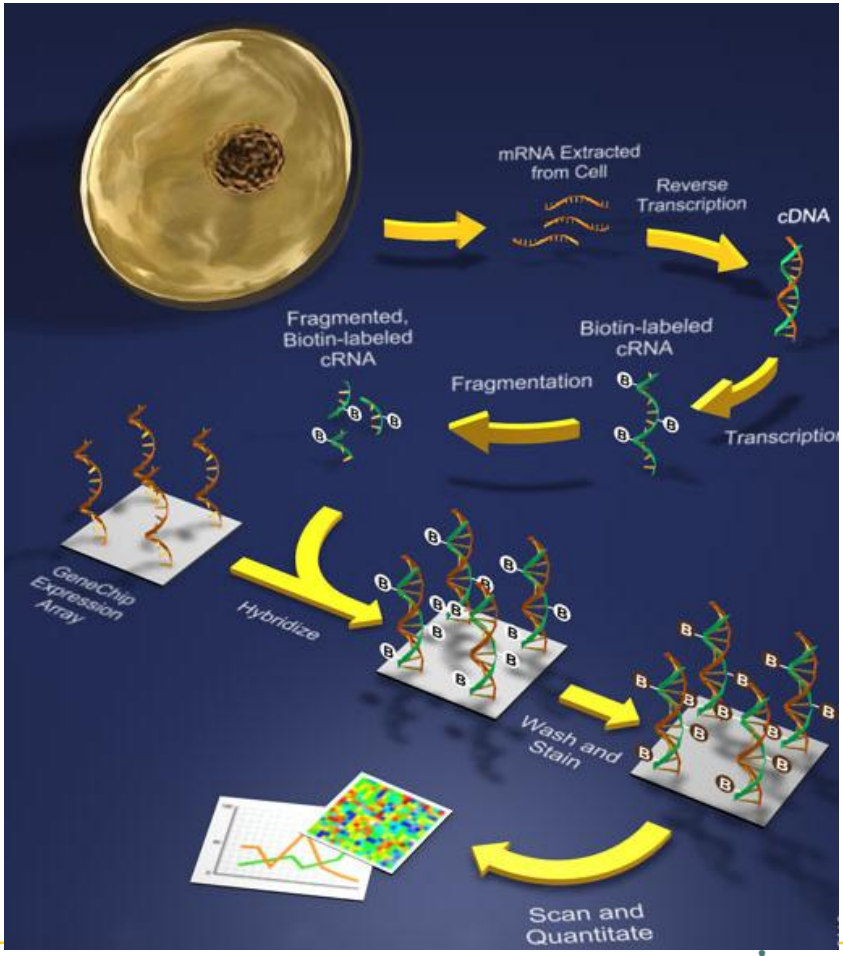
Approach 3: 21 genes
- circadian rhythm (17%)

Genomics

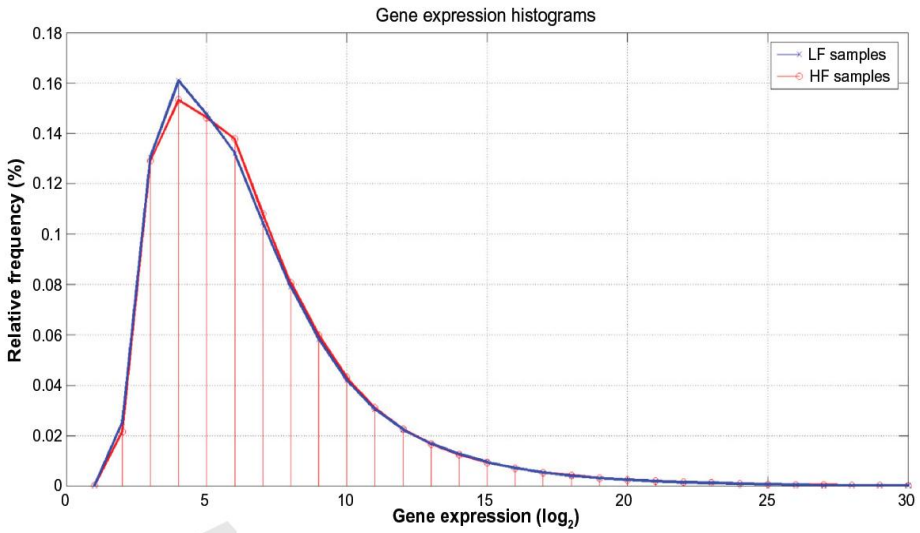
Whole blood collected using Paxgene tube

Extracted RNA

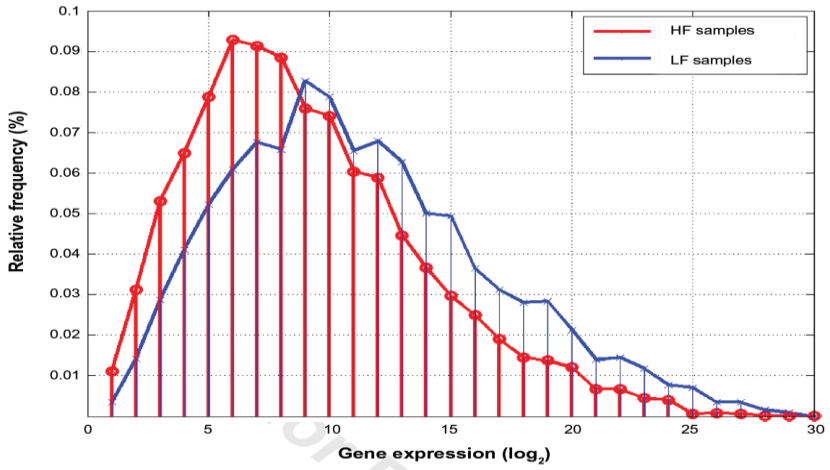
Microarray



Microarray



Gene expression + Fisher's ratio



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Cancer Informatics

Supervised Classification by Filter Methods and Recursive Feature Elimination Predicts Risk of Radiotherapy-Related Fatigue in Patients with Prostate Cancer

Leorey N. Saligan[1], Juan Luis Fernández-Martínez[2], Enrique J. deAndrés-Galiana[2] and Stephen Sonis[3]

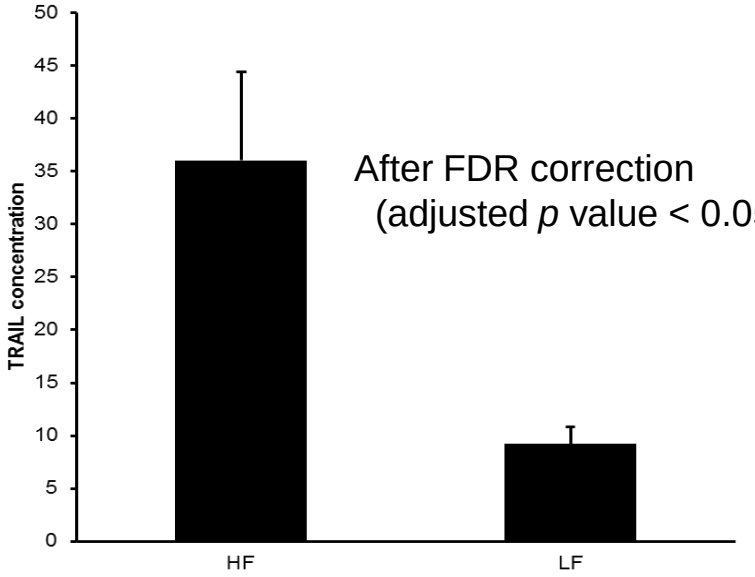
[1]National Institute of Nursing Research, National Institutes of Health, Bethesda, Maryland, USA. [2]Universidad de Oviedo, Spain. [3]Biomodels, LLC, Watertown, MA, USA.

Symbol	Name
GRM8	Metabotropic glutamate receptor
GRM5	
GRIK2	Ionotropic glutamate receptor
GRIK3	
ARG2	NMDA receptor

Proteomics

Methods: 2-DIGE, LC-MS, WB, ELISA

- TRAIL (TNF-related apoptosis-inducing ligand)
- Neurometabolites (Apo-E)
- BDNF



After FDR correction
(adjusted *p* value < 0.05)

Vol. ■ No. ■ ■ 2013 Journal of Pain and Symptom Management 1

Original Article

Proteomic Serum Profile of Fatigued Men Receiving Localized External Beam Radiation Therapy for Non-Metastatic Prostate Cancer

Nada Lukkahatai, PhD, RN, Sajni Patel, MS, Marjan Gucek, PhD, Chao-Pin Hsiao, PhD, RN, and Leorey N. Saligan, PhD, RN, CRNP
National Institute of Nursing Research (N.L., C.-P.H., L.N.S.); and National Heart, Lung and Blood Institute (S.P., M.G.), National Institutes of Health, Bethesda, Maryland, USA

The World Journal of Biological Psychiatry, 2015; Early Online: 1–7

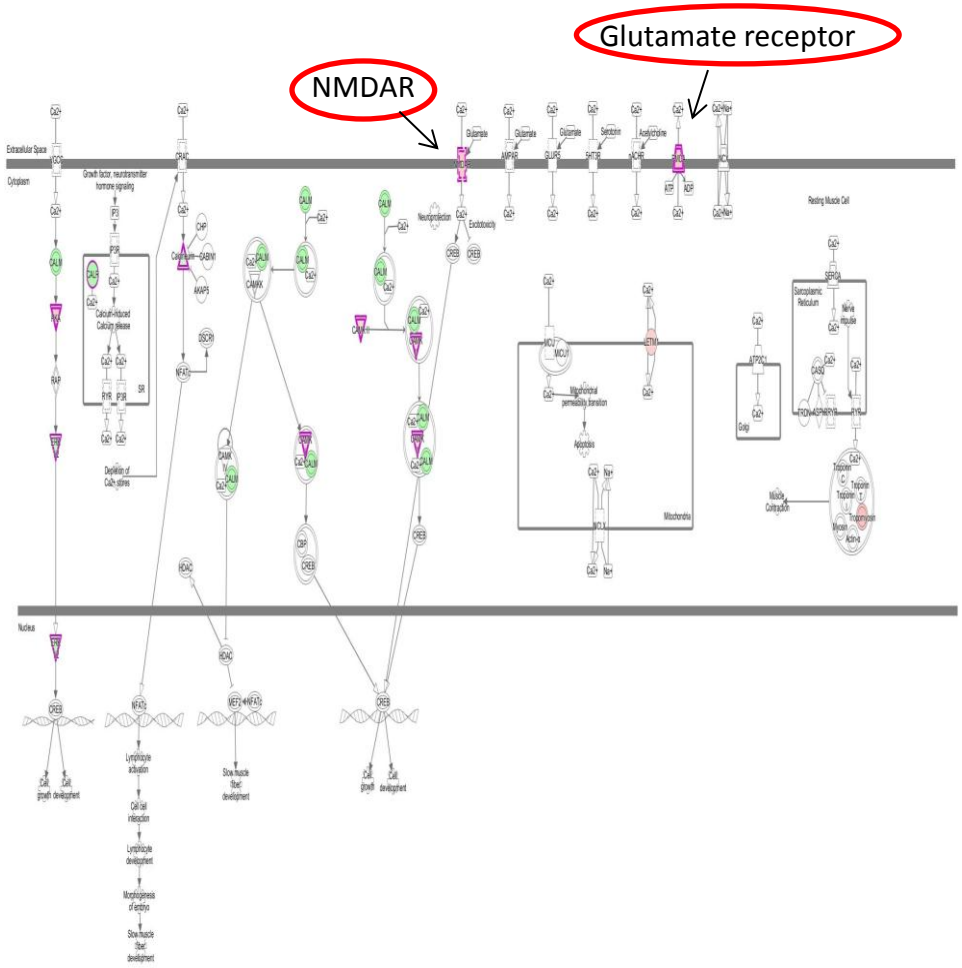
ORIGINAL INVESTIGATION

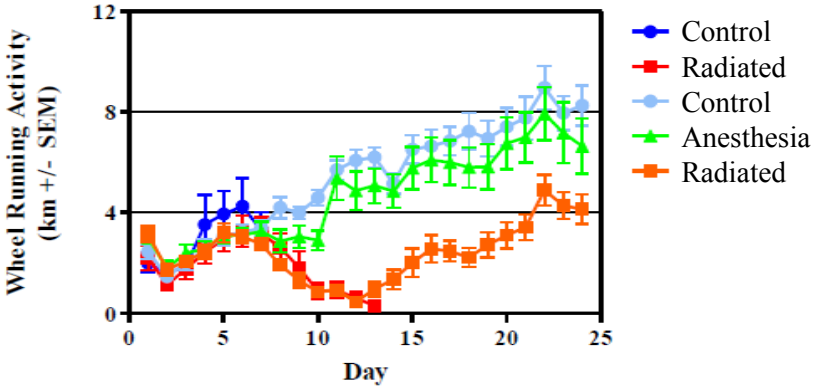
Lower brain-derived neurotrophic factor levels associated with worsening fatigue in prostate cancer patients during repeated stress from radiation therapy

L.N. SALIGAN[1], N. LUKKAHATAI[1,2], G. HOLDER[1], B. WALITT[1] & R. MACHADO-VIEIRA[3]

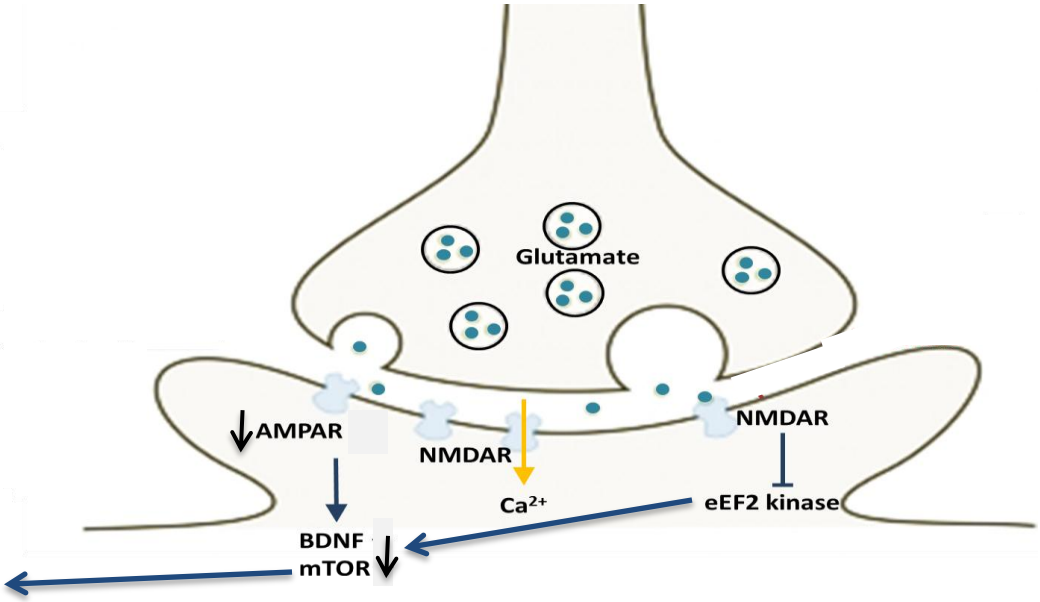
[1]National Institute of Nursing Research, National Institutes of Health, Bethesda, MD, USA, [2]University of Nevada, Las Vegas, School of Nursing, Las Vegas, NV, USA, and [3]National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA

Radiation-Induced Fatigue Mouse Model





Etiology of RRF



↓ synaptogenesis

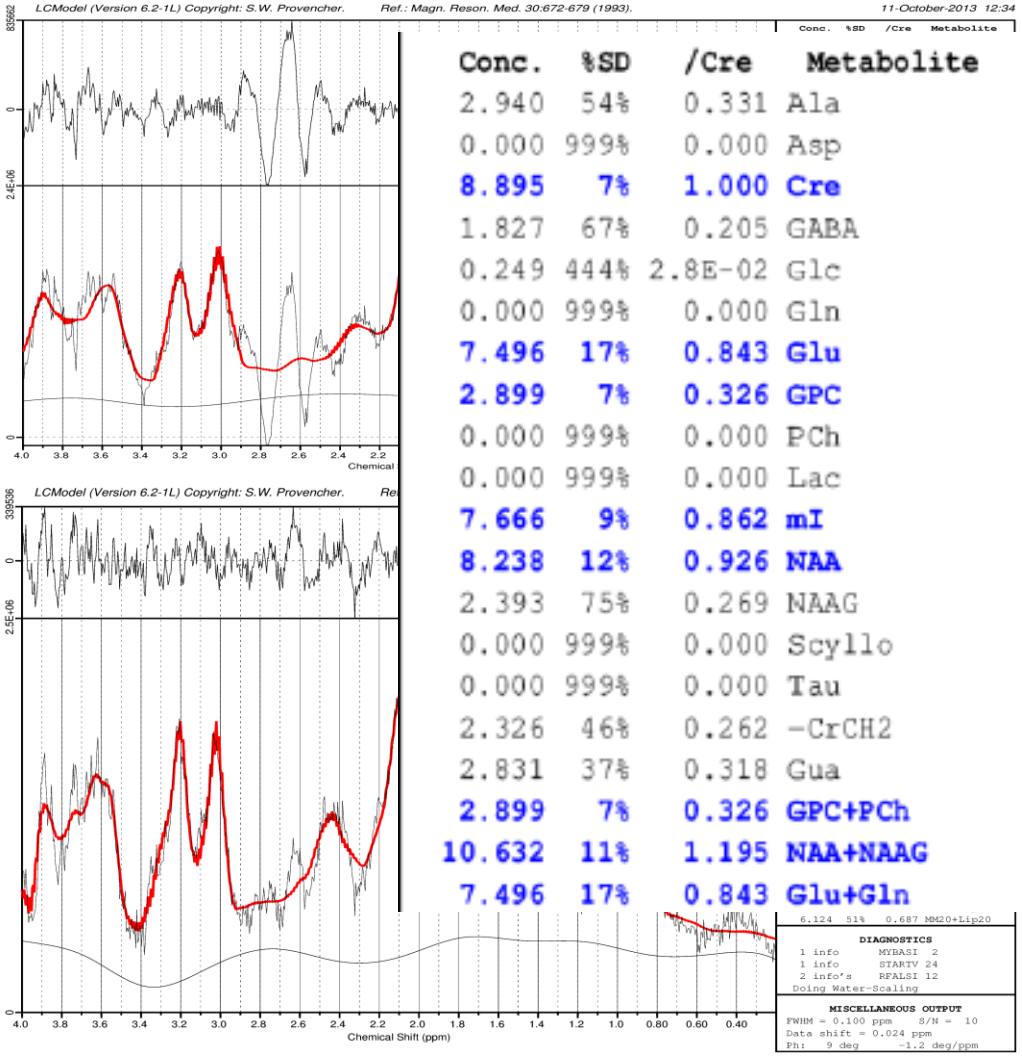
↓ firing of 5-HT neurons or ↓ response to serotonin

↑Fatigue

References:
1. Stan et al., 2014
2. Homayoun and Moghaddam, 2007
3. Meeusen et al., 2006
4. Papuc et al., 2010
5. Weyman et al., 2014

Neuroimaging

- **Purpose**: Quantify central levels of glutamate during RRF.
- **Hypothesis**: RRF is associated with decreasing glutamate signals.
- **Method**: MRS (3.0 Tesla)



Experimental Therapeutics

Hypothesis: Improving fatigability will reduce overall fatigue.

Objectives:
1. To determine if improving fatigability will reduce RRF.
2. To measure expression and association of BDNF with levels of RRF.

Collaborator: NIH Clinical Center Rehab Medicine

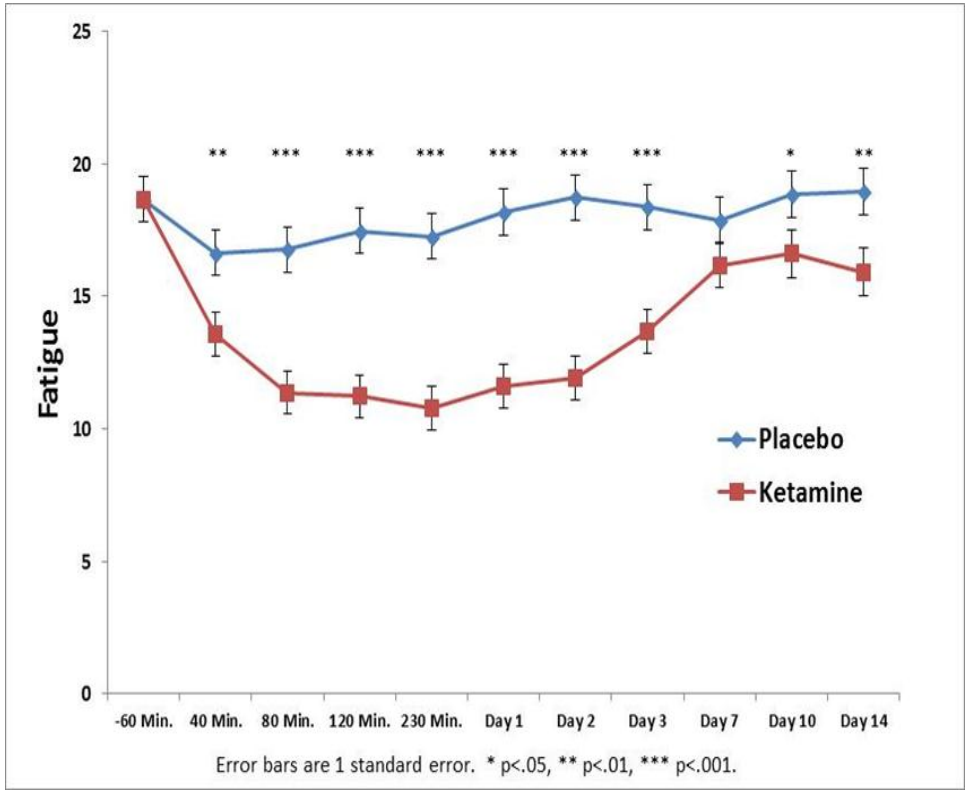
Exercise Intervention
(amendment to NCT00852111)

1. **Continuous training**
   – target heart rate: 60-70% more than resting

2. **High impact intensity training**
   – target heart rate: >90% more than resting

Effect of Ketamine on Fatigue

04-M-0222 (N=39)



Bonferroni post hoc tests indicated significantly lower fatigue scores from 40 minutes following ketamine infusion through day 2 ($p<.05$).

The effect size of the ketamine-placebo difference was greatest at day 2 ($d=0.59$)

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Development of a clinician-administered National Institutes of Health-Brief Fatigue Inventory: A measure of fatigue in the context of depressive disorders

Leorey N. Saligan [b, *], David A. Luckenbaugh [a], Elizabeth E. Slonena [a], Rodrigo Machado-Vieira [a], Carlos A. Zarate Jr. [a]

[a] Experimental Therapeutics & Pathophysiology Branch, Intramural Research Program, National Institute of Mental Health, Bethesda, MD, USA
[b] National Institute of Nursing Research, National Institutes of Health, Bethesda, MD, USA

Experimental Therapeutics

Title: Effect of Ketamine on Fatigue following Cancer Therapy NCT02317341

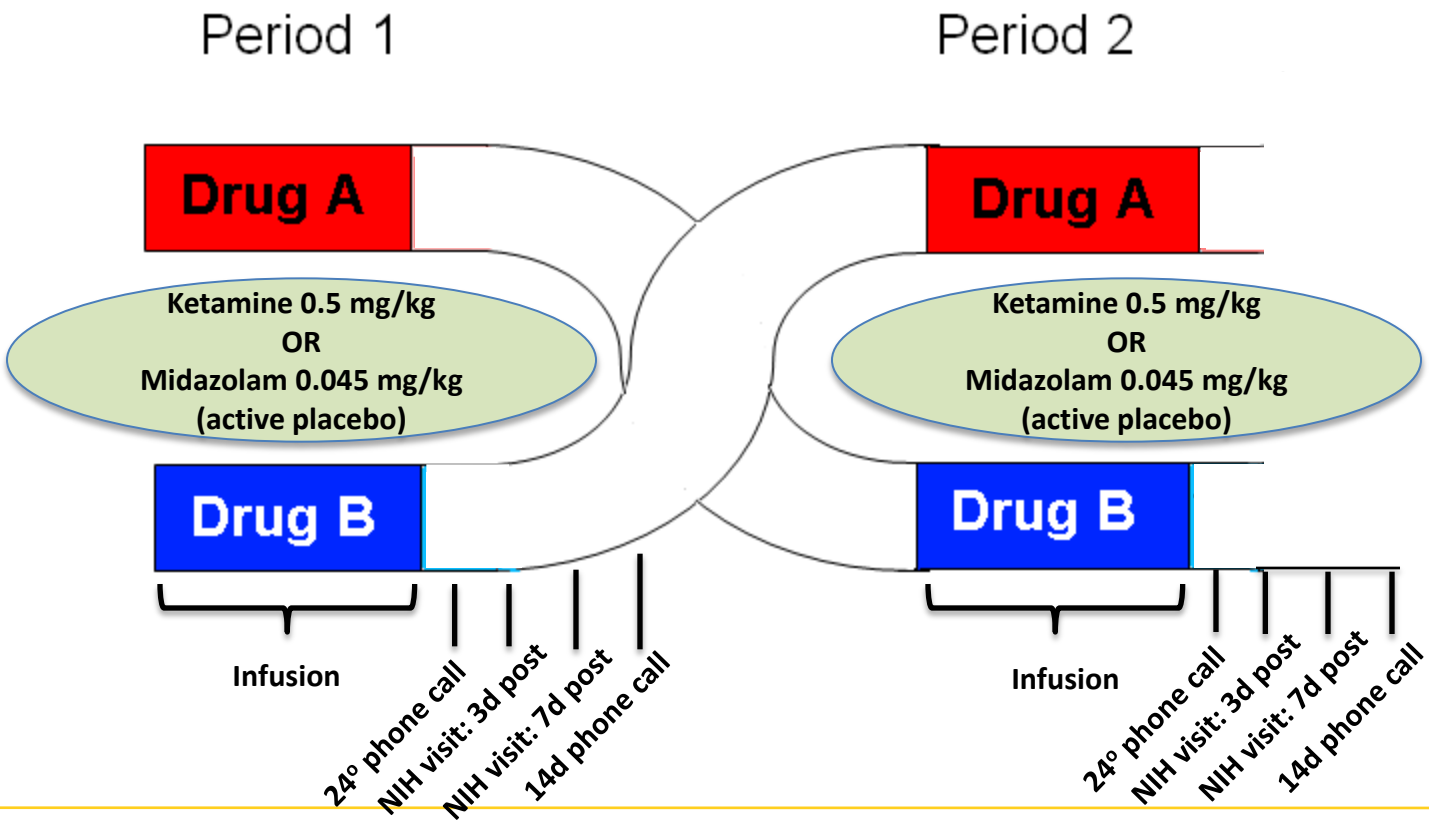
Objectives:

1. To determine the *immediate effect* of a single, IV dose of ketamine in reducing clinically-significant fatigue in individuals who completed radiation therapy for cancer.

2. To investigate the effect of ketamine on BDNF levels, markers of inflammation and mitochondrial function, as well as on cognitive function and skeletal muscle strength.

Sample and Study Design

Sample: 40 subjects who completed radiation therapy for cancer
Design: double-blind, active placebo-controlled, cross-over study

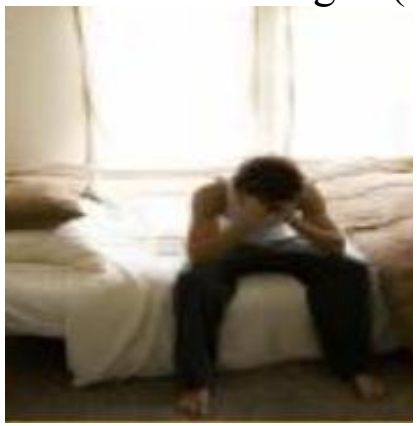


Ongoing Research Activities

- Clinical trials: optimizing extramural collaborations
  - Univ. of Maryland, Univ. of Florida, Georgetown, VCU
- Lab activities:
  1. RNA sequence
  - post-transcriptional modifications, mutations
  - cellular pathway alterations during radiation
  2. central versus peripheral
  - protein levels in blood versus CSF
- Animal:
  - knock-out mouse models
  - treatments that increases BDNF

Summary

Cancer-Related Fatigue (CRF)



Review: Gap in Literature

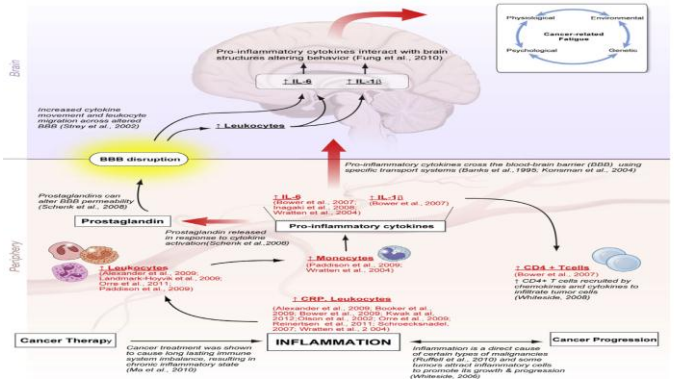
Saligan & Kim, 2012

Brain, Behavior, Immunity

Clinical Observation

Laboratory Investigation

Molecular Markers of CRF



Reduce CRF

↑ Health-related Quality of Life

Acknowledgement

SBU Staff

Research fellow: Rebekah Feng, PhD
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Research nurse: Michelle Millwood, BSN, RN
Post-bac fellow: Alexandra Espina, BS
Technical IRTA: Michael Renner, BS

Post-doc graduates: Nada Lukkahatai, PhD, RN
Chao-Pin Hsiao, PhD, RN

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