Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format. Questions? Contact Health Research Program staff at 717-783-2548.

1. **Grantee Institution:** University of Pittsburgh- of the Commonwealth System of Higher Education

2. **Reporting Period (start and end date of grant award period):** 1/01/2010 – 12/31/2013

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** Margaret C. McDonald, PhD

4. **Grant Contact Person's Telephone Number:** 412-383-7474

5. **Grant SAP Number:**4100050913

6. **.Project Number and Title of Research Project:** 03 - Establishing New Biobehavioral Paradigms for Translational Research in Cancer Prevention and Control

7. **Start and End Date of Research Project:** 1/01/2010 – 12/31/2011

8. **Name of Principal Investigator for the Research Project:** Dana H. Bovbjerg, PhD

9. **Research Project Expenses**.

   9(A) Please provide the total amount of health research grant funds spent on this project for the entire duration of the grant, including indirect costs and any interest earned that was spent:

   $ 1,425,319

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project	Cost
Bovbjerg, Dana	Principal Investigator	20% (1/2010 – 7/2010); 30% (8/2010-9/2012); 28.6% (10/2012)	$198,218.48
Horn, Charles	Co-Investigator	75% (1/2010-8/2012); 65.7% (9/2012)	$280,150.17
Lotze, Michael	Co-Investigator	20% (1/2010-6/2012); 57.05% (7/2012-4/2013); 28.52% (5/2013)	$169,174.57
Jenkins, Frank	Co-Investigator	25% (1/2010-12/2011); 3.5% (1/2012)	$81,697.76
Land, Stephanie	Biostatistician	5% (8/2010-6/2011)	$6,121.71
Meyers, Kelly	Research Technician	100% (1/2010-9/2011); 90% (10/2011-6/2012)	$94,054.51

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project
Shuda, Yoko	Research Scholar	50%
Episcopo, Britteny	Research Technician	10%
Lim, Audrey	Student	5%
Dye, Matthew	Student	5%
Pak, Diana	Student	5%
Henry, Severine	Student	5%

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
None		

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes_____ No____X_____

If yes, please indicate the source and amount of other funds:

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes_____X____ No_____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert "not funded" in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
Stress-Induced DNA Damage: A Translational Analysis	☒NIH ☐ Other federal (specify:_____) ☐ Nonfederal source (specify:_)	October 2011	$1,885,767	Not funded
Stress, DNA Damage, Carcinogenesis: Preclinical Models & Molecular Mechanisms	☒NIH ☐ Other federal (specify:____) ☐ Nonfederal source (specify:_)	May 2013	$1,924,063	Not funded
Stress and DNA Damage in Humans: Experimental Analysis of Molecular Mechanisms	☒NIH ☐ Other federal (specify:____) ☐ Nonfederal source (specify:_)	November 2013	$2,865,880	Pending
IOS Preliminary Proposal: The Neurophysiological Substrate for Emetic Stimulation and Production of Divergent Behavioral Responses	☐NIH ☒ Other federal (specify:_NSF) ☐ Nonfederal source (specify:_)	January 2014	$2,000,000	Pending
AVON Foundation Letter of Intent: Stress Hormones and DNA Damage in Breast Carcinogenesis:	☐NIH ☐ Other federal (specify:_____) ☒ Nonfederal	January 2014	$297,000	Pending

Molecular models and mechanisms	source (specify: AVON Foundation)			

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes___X_____ No_____

If yes, please describe your plans:

We plan to generate additional preliminary data for a future NIH resubmission.

12. Future of Research Project. What are the future plans for this research project?

Based on the work supported by the CURE funds, we have initiated several new lines of research that we plan to continue in coming years as funding allows. One exciting area of research focuses on the effects of psychological stress on DNA damage that could lead to increased risk of cancer. We have published initial results documenting that stress hormones such as epinephrine can induce DNA damage in a premalignant mouse cell line, and that such damage can result in phenotypic changes consistent with neoplastic transformation as well as increased tumorigenicity *in vivo*. In future research we plan to translate this work into studies with human cell lines *in vitro*, as well as studies of DNA damage associated with psychological stress in humans. A second exciting area of future research will explore the neural mechanisms underlying delayed nausea and vomiting that many patients experience for days after chemotherapy treatment for cancer. During the project period, we were able to perform two critical studies using a unique small animal model for chemotherapy research, the musk shrew, which is a maintained as a breeding colony at the Hillman Cancer Center. First, we delineated the gut-to-brain neural pathways that control emesis in this translational model. Second, we developed computational approaches to study delayed nausea and emesis after chemotherapy in this animal model. These critical results have set the stage for future research to evaluate novel treatment strategies for chemotherapy-induced nausea and vomiting that may substantially reduce this highly aversive experience for tens of thousands of cancer patients.

13. New Investigator Training and Development. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes____X_____ No_____

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male	1			
Female	3			
Unknown				
Total	**4**			

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic	4			
Unknown				
Total	**4**			

	Undergraduate	Masters	Pre-doc	Post-doc
White	2			
Black				
Asian	2			
Other				
Unknown				
Total	**4**			

14. Recruitment of Out-of–State Researchers. Did you bring researchers into Pennsylvania to carry out this research project?

Yes_____ No_____X_____

If yes, please list the name and degree of each researcher and his/her previous affiliation:

15. Impact on Research Capacity and Quality. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes_____ No_____X____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes_____ No____X_____

If yes, please describe the collaborations:

16(B) Did the research project result in commercial development of any research products?

Yes_____ No_____X_____

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes_____ No_____X_____

If yes, please describe involvement with community groups that resulted from the research project:

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant agreement). Summarize the progress made in achieving these goals, objectives and aims for the period that the project was funded (i.e., from project start date through end date). Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

Biomedical research in cancer has long been grounded in a translational perspective, in which basic laboratory findings from tissue culture and animal models provide empirically-guided input to human studies on cancer etiology and treatment. Mind-body research, in contrast, has commonly begun the research enterprise with human correlational or interventional research approaches largely without benefit of directly relevant preclinical findings. The overarching long-term objective of the work proposed is to lead the way in bringing the powerful biomedical approach to bear on mind-body research in cancer. To that end, we proposed to build upon existing preclinical models to develop new paradigms for biobehavioral investigation of mind-body effects on: Aim 1 - the side effects of chemotherapy, using a species (the musk shrew), which unlike rodents, is capable of vomiting and can thus allow investigation of that particularly aversive side effect as well as other well-known aversive consequences of chemotherapy (e.g., anorexia, fatigue); Aim 2 - the development and progression of cancer, using: a) transgenic mice with genetic modulations known to affect susceptibility to mammary cancer (e.g., over expression of erbB-2; and, b) human breast cancer cell lines.

The specific hypotheses to be tested under Aim 1 are: 1) emetic episodes (comprised of retching and abdominal contractions) stimulated by cancer chemotherapy are pathological when compared to "natural" emetic stimuli, e.g., gut toxins; 2) side effects of chemotherapy, including emesis, anorexia, and fatigue, occur as symptom clusters; and, 3) activation of nausea, vomiting, and other symptoms following chemotherapy involves a forebrain contribution, that is responsive to psychological stress.

The specific hypotheses to be tested under Aim 2 are: 1) mammary tumors from chronically stressed transgenic mice (e.g., mouse mammary tumor virus (MMTV)-neu) will show evidence of more vascularization (microvascular density per mm^2) than those from control mice; 2) the tumor microenvironment in chronically stressed mice will show evidence of higher levels of vascular endothelial growth factor (VEGF), matrix metalloproteinase (MMP)-2, and MMP-9 in tumor cells, normal epithelial cells, and/or tumor associated macrophages; 3) the tumor microenvironment in chronically stressed mice will show evidence of higher levels of proinflammatory cytokines (e.g., tumor necrosis factor alpha (TNFα), interleukin (IL)-1β and IL-6) and activation of downstream cell signaling pathways involved in tumorogenesis (e.g., nuclear factor (NF)kB, AKT, mitogen-activated protein kinase (MAPK)); 4) mammary tissue with no evidence of tumor concurrently collected from chronically stressed mice will also show evidence of higher levels of proinflammatory cytokines and activation of downstream cell signaling pathways involved in tumorogenesis; and 5) in a tissue culture model with human breast cancer cell lines, stress-related hormones (e.g., epinephrine, norepinephrine) will trigger cell signaling pathways (e.g., AKT) involved in tumor progression.

Aim 1: Chemotherapy Side Effects

Study 1: Effect of cisplatin on emesis

Musk shrews (a mouse-sized insectivore) are commonly used to investigate the effects of cancer chemotherapy on vomiting because laboratory rodents lack this response. We have developed a computer algorithm in Matlab (Mathworks; Natick, MA) to automatically track emesis in short- and long-term video files. In our first experiment, we injected 10 male musk shrews with the chemotherapy agent cisplatin using an emetic threshold dose (20 mg/kg, intraperitoneal [ip]) and videotaped their behavior for 2 hours (h). Emesis was scored independently by two observers and these results were compared to those generated from the

computer algorithm. Half of the shrews developed vomiting and the second half served as non-vomiting controls. For computer detection, the body contour in each video frame was normalized to a parameterized shape template, and projected to a feature space maximizing the shape variations in the consecutive frames during retching. These analyses show that musk shrew emetic episodes occur in bouts of ~1 second with retching occurring at a speed of approximately 8 Hz (much faster than reported from an anesthetized preparation (Andrews, Torii et al. 1996)), which indicates that the current approach is a very sensitive method for behavioral detection of emesis (this is the first report of the measurement of individual retches in a free moving musk shrew). The emesis events were detected following three consecutive retches occurring above a detection threshold. This method initially detected 91% of the emetic episodes that were identified by the two observers.

In a more recent study, we injected 4 male musk shrews with 30 mg/kg cisplatin (ip) and video recorded their behaviors for 24 h prior to injection and 72 h post-injection, an approach similar to a published report designed to capture the acute and delayed emetic effects of cisplatin treatment (Sam, Cheng et al. 2003). Figure 1 shows an example of emesis detection from one of these animals. This anaylsis demonstrates the acute and delayed phases of cisplatin-induced emesis that are reported in animal and human studies (Martin 1996, Sam, Cheng et al. 2003, du Sert, Rudd et al. 2009).

The computer algorithm detected fewer emetic events compared to manual scoring; however, we were able to train the algorithm to achieve better detection with more data that was collected in subsequent experiments. Development of this novel technology led to a publication in the *Journal of Neuroscience Methods* (Huang, Meyers et al. 2011).

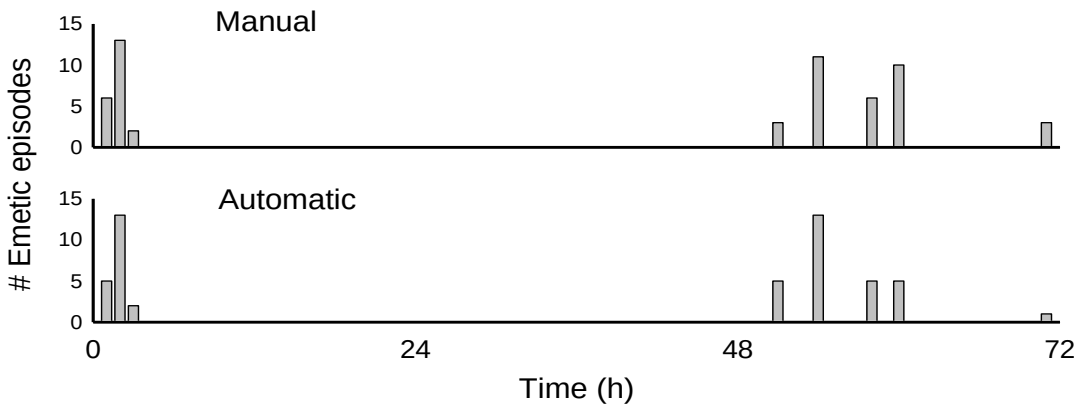


Figure 1. Video analysis of emetic events for 3 days after injection of cisplatin (30 mg/kg, ip). Events were scored manually (above) or automatically using a computer algorithm (below). The acute effects of cisplatin are shown in the first few hours after injection and the delayed effects occur after 48 hours.

We then used this system, along with the statistical method t-pattern (temporal pattern) analysis, to determine patterns of behavior that are temporally associated with emesis. Musk shrews were injected with cisplatin to induce acute (< 24 h) and delayed (> 24 h) emesis. Emesis and other behaviors were manually coded and automatically tracked from video files

(Table 1). In summary, t-pattern analysis revealed that musk shrews show a large number of non-random patterns of behavior associated with emetic episodes, including sniffing, changes in body contraction, and locomotion. There was little evidence that locomotion was inhibited by the occurrence of emesis. However, eating was not significantly associated with emesis-related behavioral patterns. Eating and drinking, and other larger body movements including rearing, grooming, and rotation, were significantly less common in emesis-related behavioral patterns in real versus randomized data (Figure 2). These results provide preliminary evidence for the expression of emesis-related behavioral patterns of sickness, including reduced ingestive behavior, grooming and exploratory behaviors. This work was published: Horn et. al., Front Neurosci. 2011 Jul 14;5:88.

Table 1. Musk shrew behavioral event types

Manually coded

emesis	a sequence of contractions of the abdomen (retching)
eat	putting the head into the food container for ≥ 2 s and visible movement of head and jaw
drink	placing the snout on the sipper tube for ≥ 1 s
sniff	moving the snout with elongation of the body
rear	standing on back legs, against the wall, sometimes jumping

Automatically tracked

Locomotion

dchi, dclo	distance moved, body center, high
	distance moved, body center, low
mc	movement (velocity, begin > 2 cm/s, end < 1.75 cm/s)

Turning

rot,	rotation-clockwise (a turn of 360 degrees),
rotc	rotation-counter clockwise
tanhi,	turn angle of the nose, high
tanlo	turn angle of the nose, low
tachi,	turn angle of the body center, high
taclo	turn angle of the body center, low

Movement in place

con	contracted
norm	normal
long	elongated body contour
immob	Immobile (< 1%)
mob,	mobile (> 1%, < 8%)
mobhi	and highly mobile (> 8%; change in body contour)
dnhi	distance moved, nose, high
dnlo	distance moved, nose, low

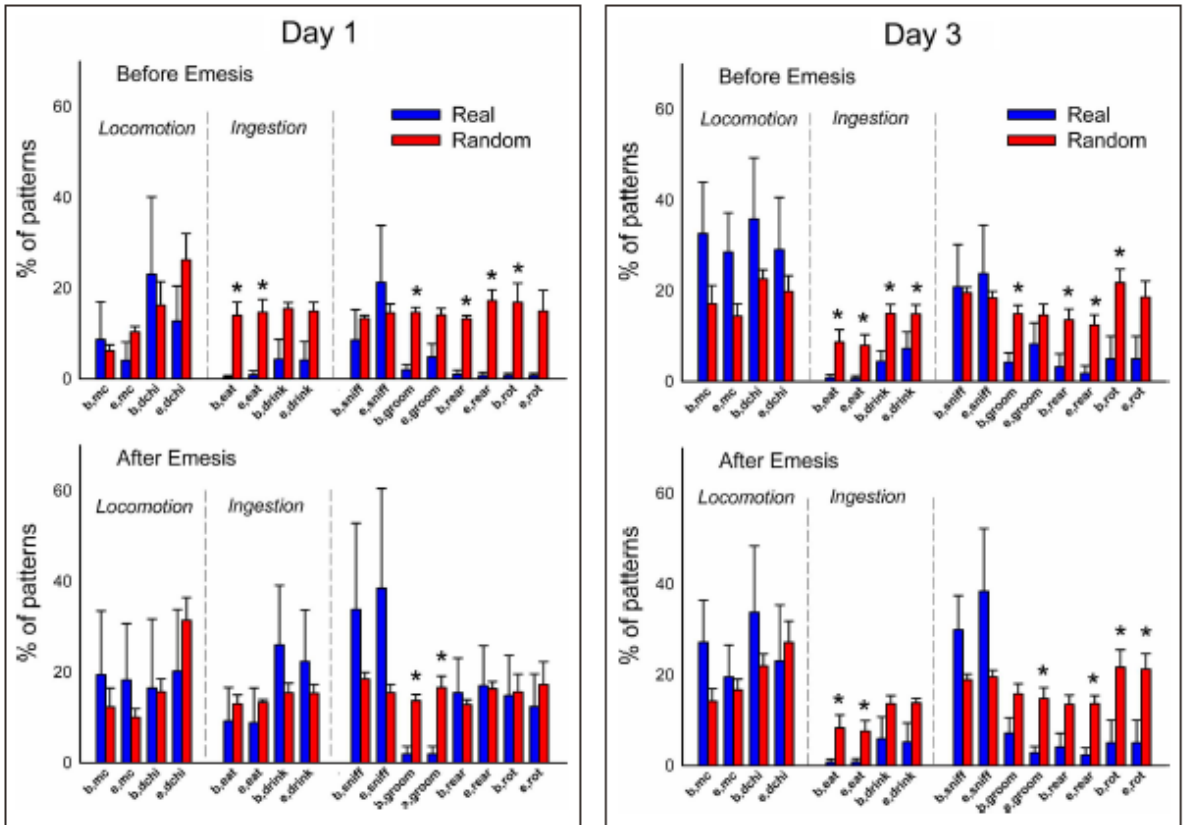


Figure. 2. Comparison of event types in emesis-related t-patterns detected on Days 1 and 3 after injection with cisplatin, 30 mg/kg, ip, n = 6. Results represent the mean ± SEM. * = $p < 0.05$, two-tailed t-test, real vs. random data. See Table 1 for listing of event types. Each event type has a "b" for beginning and "e" for ending, for example, "b,mc" = beginning of movement.

We now have a system in place that permits the simultaneous acquisition of behavioral data from 4 individually housed musk shrews (Figure 3A). Using this system, it is feasible to collect concurrent longitudinal data on up to 4 singly housed animals each week. The digital cameras have 40 gigabytes of internal storage, which is sufficient for 24 h of continuous recording before data are offloaded at the time that animals are weighed each day. Following storage of video, these files are played back and scored visually using commercial software (Observer XT; Noldus Information Technology, The Netherlands). Figure 3B shows acute and delayed emesis after a single injection of cisplatin (30 mg/kg; ip; n = 6). It is known that animals show a behavioral profile of sickness, associated with reduced feeding and movement, and possibly these general measures are signs that the animal is experiencing nausea. Following injection with cisplatin, emesis and other behaviors were coded and tracked from video files using computer software (Ethovision XT and Observer XT) for up to 72 h after injection. As seen previously, t-pattern analysis (Theme 6.0; Noldus) revealed patterns of behavior associated with emesis, including sniffing, changes in body contraction, and locomotion. Again, there was little evidence that overall locomotion was inhibited by the occurrence of emesis. However, eating, drinking, and other larger body movements, including rearing, grooming, and body rotation, were significantly

less common in emesis-related behavioral patterns in experimental compared to control groups (Figure 4). Food intake, water intake, and body weights were also significantly reduced by chemotherapy (Figure 5).

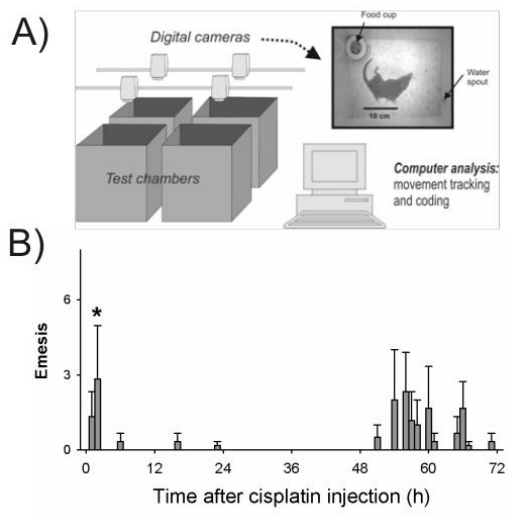


Figure 3. Experimental chambers and cisplatin-induced emesis in shrews. A) Animals tested in sets of 4. Image shows one shrew in a chamber with food and water available. Digital videos are scored offline using software (Observer; Noldus). B) Hourly occurrence emesis after cisplatin injection (30 mg/kg, ip). * $p < 0.05$ vs. time before injection.

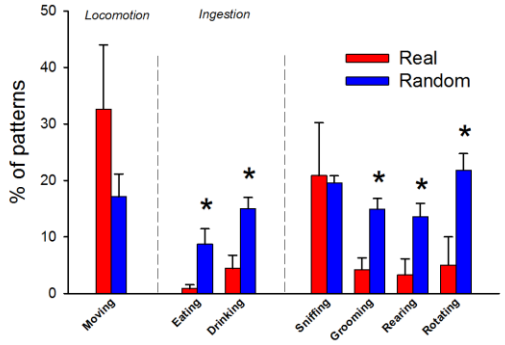


Figure 4: Behavioral patterns occuring before cisplatin-induced emesis. Comparison of behaviors in emesis-related t-patterns from real versus randomized control data. * $p < 0.5$, real vs. random.

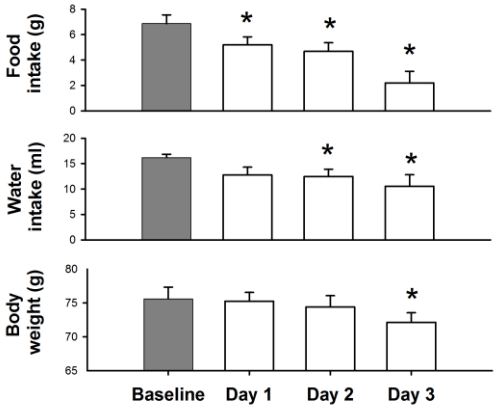


Figure 5. Daily changes in food intake, water intake, and body weight for 3 days after injection of cisplatin (30 mg/kg, ip; n = 6). * $p < 0.05$ versus baseline.

Study 2: Effects of restraint stress on open field activity

Anxiety and distress appear to potentiate nausea and vomiting induced by chemotherapy treatment in cancer patients. In order to test the interaction between stress and emesis in the musk shrew, we assessed the behavioral responses to restraint stress in an open field test. We predicted that, like rodents, musk shrews with prior restraint would spend less time in the center region of an open field. Musk shrews were restrained in a small aerated cylinder (0, 20, 60, or 120 minutes [min]; n = 8 in each condition) and were then released in the middle of an open field (60 x 60 x 60 centimeters [cm]) where their behavior was video recorded for 10 min. Movement detection and analysis were conducted using computer software (Noldus). A center region was specified as 36% of the total central area of the open field and the following measures were determined automatically: locomotion, time and frequency (in center, immobile, mobile, highly mobile), and velocity. Mobility (a change in body contour) limits were set as ≤ 2% change = immobile, > 2% and < 15% = mobile, > 15% = highly mobile. Mobility is a measure of movement that can potentially occur in one location, e.g., turning or elongation. There were no significant effects of restraint on velocity and total movement (or high mobility). However, animals restrained for 120 min compared to animals without prior restraint spent less time in the center region during the last 5 min of the test period and were also more mobile (Figure 6). Manual scoring indicated that these mobility events correspond to rearing on the side of the chamber. This study suggests that musk shrews, like rodents, respond to restraint stress by decreasing the time spent in the center of the open field, and indicates that restraint stress produces a behavioral profile in musk shrews that might be used in studies to determine how stress responses interact with other behavioral effects of chemotherapy, including vomiting and reduced food intake.

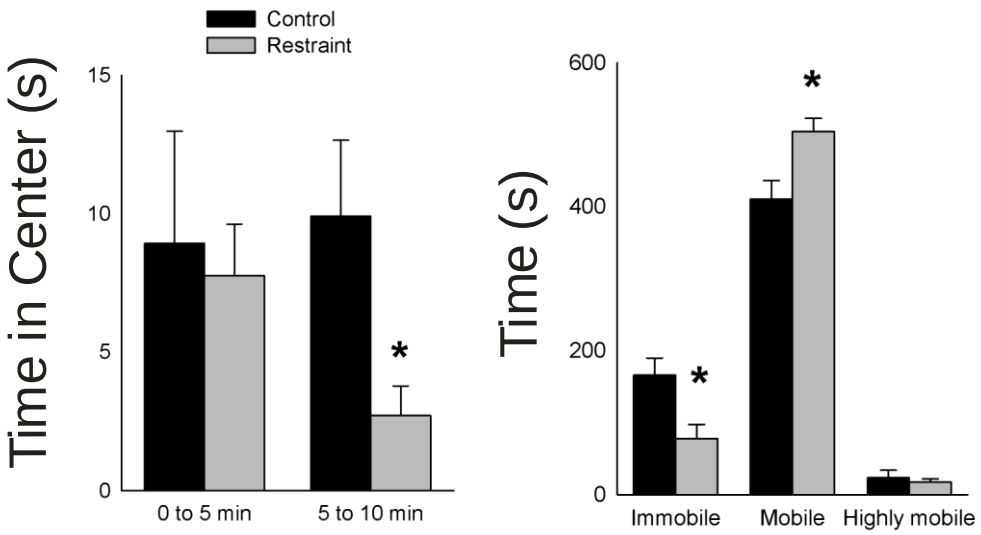


Figure 6: Effects of 120 min of restraint versus no restraint control. *Left:* time in center. *Right:* time as immobile, mobile or highly mobile. * $p < 0.05$, t-test, 2-tailed.

Effects of contextual fear conditioning on musk shrews
In order to develop a psychological stress paradigm that closely mimics the experience of cancer patients who undergo chemotherapy, we used several approaches to produce and behaviorally test stress responses in shrews. These experiments included restraint stress and electrical shock-induced contextual conditioning. One example from this series of experiments that used contextual fear conditioning is described here. Twenty shrews were randomly assigned into two groups (n's = 10): control (no shock) and shock. The experiment was conducted from 9:30-11:30 each day. On each of three consecutive training days, the animals were put into a contextual chamber for a total of 8 min (Figure 7A). Three minutes after the shrews were placed into the chamber, the shock group received a total of 5 shocks (0.7mA, 3 s duration, 1 min inter-shock interval). The shrews were returned to the home cage 1 min after the last shock (Figure 7B). On the test day (24 h after the last training session), each of the shrews was placed into the contextual chamber for a total of 10 min without shocks. Behavior during training and testing was recorded using a video camera positioned above the chamber (Sony, DCR-SR300). Re-exposure to the test chambers in which the animals had received brief foot shocks produced an increased frequency of immobility (similar to the conditioned freezing response reported for rats and mice in studies of contextual fear conditioning) (Figure 7C). These results provide the first evidence that musk shrews show similar behavioral fear responses to those that have been extensively documented in mice and rats.

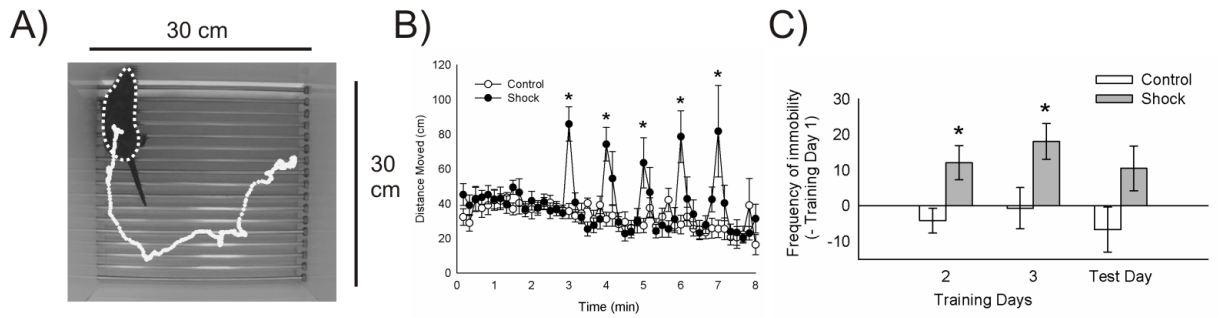


Figure 7: Contextual fear conditioning in shrews. A) Chamber and metal grid used for foot shock and example of computer software tracking of movement (white line) (Ethovision; Noldus). B) Effects of foot shock (0.7 mA, 3 s) on locomotion (cm) (time bins = 10 s), C) Frequency of immobility on training days 2 and 3 and the test day (minus training day 1), * = $p < 0.05$, compared to control.

Unconditioned effects of electrical current on movement. Four shrews were tested individually in a behavioral chamber (Med Associates Inc.; mouse module) followed by a step-wise increase in electrical current (increments of 0.1 mA every 30 s) applied to floor grid for 3 s (AM Systems pulse stimulator). Behavior was recorded using a high-resolution digital video recorder (Sony, DCR-SR300) positioned above the test arena. Movement detection and analysis were conducted offline using automated software (EthoVision XT 7; Noldus). Shrews consistently vocalized

with multiple squeaks and locomoted at levels of 0.6 to 0.7 mA (Figure 8). This level of electrical current is similar to the intensity used in studies of contextual conditioning in mice.

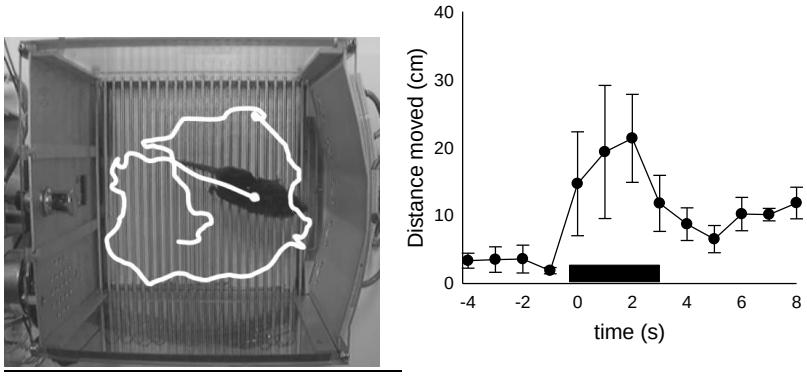


Figure 8: *Left*: Chamber (18 x 22 cm) with a musk shrew. White line indicates the path of the animal tracked by computer software. *Right*: Effect of 0.6 mA on movement. Black bar = duration of shock.

Effects of pairing electrical shock and context on movement. To confirm that electrical shock (0.7 mA, 3 s) can be an unconditioned stimulus for contextual learning in shrews, we used a protocol similar to those previously used in rodent studies. Fourteen naïve shrews were randomly assigned to two groups (n's = 7): no shock controls and 3 shocks (3 s duration, 60 s inter-shock interval). Shocks began 3 min after an animal was placed in the contextual chamber and shrews were returned to the home cage 60 s after the last shock. No shock controls experienced the same amount of time in the contextual chambers. One day after training, animals were exposed to the chamber (15 min) without shock and behavior was recorded using a video camera and analyzed with computer software. Measures included locomotion and immobility. Immobility, a measure of freezing behavior, was set at a limit of ≤ 2% change in body contour based on manual observation of freezing. Musk shrews with even just one session pairing the chamber with electrical shock showed less movement and more immobility (freezing) when re-exposed to the chamber compared to no shock control animals (Figure 9). Electrical shock paired with a context produced effects in musk shrews that are similar to those seen in rodents, including that shocked animals moved less when re-exposed to the chamber. These preliminary data confirm that musk shrews can be trained to show conditioned responses to a context.

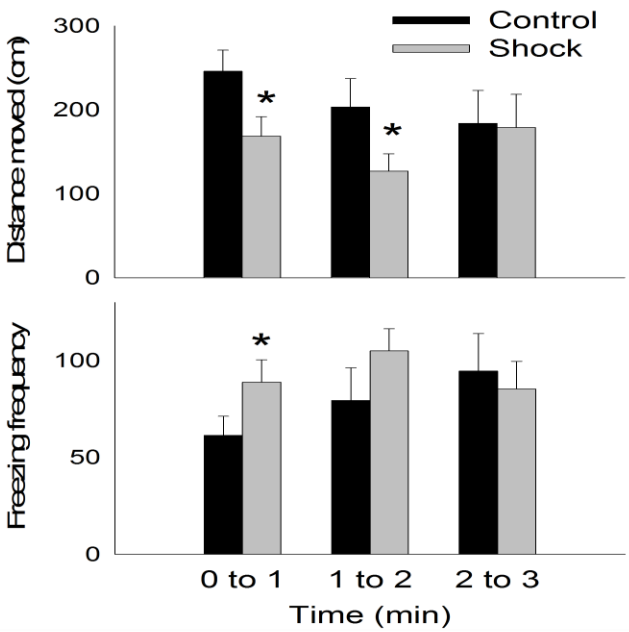


Figure 9: Top: Distance moved (cm). Bottom: Freezing (immobility) frequency (≤ 2% change in body contour from previous video frame, analyzed at 12 frames per second). * = p< 0.05.

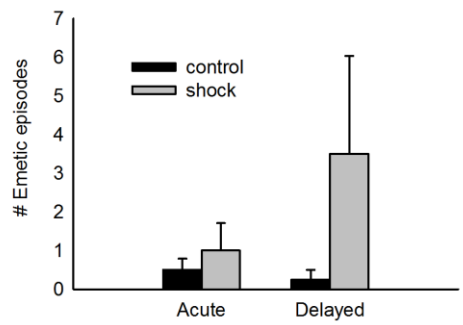


Figure 10: Effects of foot shock on acute (0 to 4 h) and delayed (48 to 62 h) cisplatin-induced emesis (n = 4, each group.

Study 3: Effect of restraint stress on cisplatin-induced emesis, feeding, drinking and activity

In our initial test, we used unconditioned foot shock (0.7 mA, 5 trials) followed by injection of cisplatin (ip) to induce emesis. A low dose of 20 mg/kg cisplatin was used in this experiment to produce low levels of acute and delayed emesis. These preliminary data with just 4 animals in each group show a trend (although not statistically significant) for foot shock immediately prior to chemotherapy administration to increase delayed emesis (Figure 10). The effects of stress on delayed, but not acute emesis are consistent with data in the clinical literature linking pretreatment levels of emotional distress specifically to patients' experience of delayed nausea and vomiting and not to acute responses.

Study 4: Transneuronal tracing of pathways from the intestine and stomach
Sensory pathways from gut to brain that are responsible for stimulating vomiting and perceiving nausea are not completely understood. A variety of gastric stimuli produce emesis in musk shrews, including distension and chemical irritation. The aim of this study was to define the sensory component of the gut-brain axis of the shrew using transneuronal viral tracing.

The H129 strain of herpes simplex virus-1 was previously used in rats to define ascending gut-brain sensory circuits. In the present study, H129 was microinjected into the ventral stomach wall in shrews and rats in order to compare results between species (Figure 11). Five days later, brain and spinal cord tissues were collected. In both shrews and rats, immunohistochemistry revealed transported virus within key circuit nodes of ascending visceral sensory pathways, including the spinal cord dorsal horn, nucleus of the solitary tract, parabrachial nucleus, reticular formation, and hypothalamus.

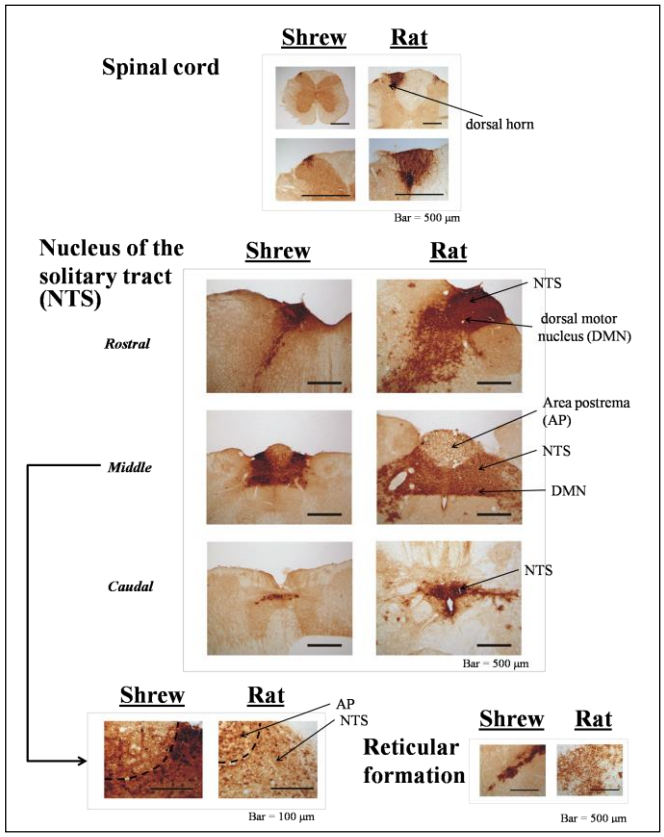


Figure 11. Comparison of H129 staining in the hindbrain of the musk shrew versus the rat. H129 was injected into the ventral surface of the stomach 5 days before tissue collection.

Subsequent experiments showed transport of H129 from the gut to the hindbrain, but limited transport to the forebrain (Figure 12).

Since the conclusion of the funding period, these studies have been extended and published (Horn et al., Am J Physiol Regul Integr Comp Physiol. 2014 Jan 15; a pdf accompanies this report), supporting that brainstem anatomical circuits are activated by GI signaling in the musk shrew.

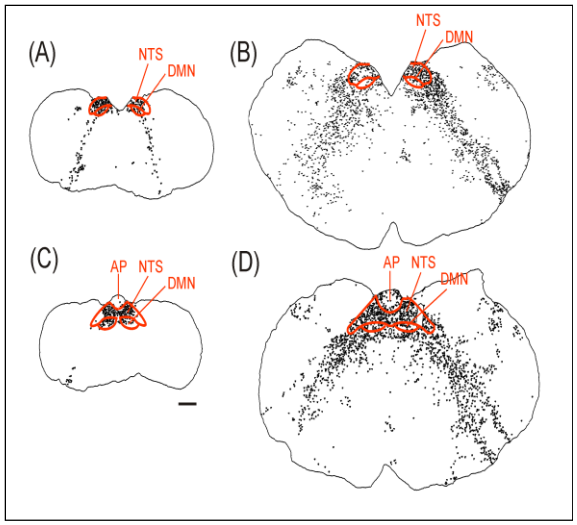


Figure 12. Transneuronal tracing of ascending gut-brain axis sensory pathways in musk shrew (A and C) and rat (B and D). NTS = nucleus of the solitary tract; DMN = dorsal motor nucleus; AP = area postrema.

Aim 2: Cancer Development and Progression

Study 1: To investigate possible stress-induced differences in angiogenic processes in mouse mammary tissue collected from glands with and without tumor

During the first phase of this study, we conducted systematic literature reviews to update proposed methodologies in the context of emerging findings from other laboratories, and based on that review process, developed panels of specific antibodies selected from different commercial suppliers that can be used together for quantification of immunofluorescent labeling of the biological markers proposed for concurrent assessment in this study using Quantum-dot (Q-dot) technology.

We also received training on the use of the dedicated imaging equipment and computer software that is necessary to collect, transfer, store, and analyze the data. The Nuance system detects and removes autofluorescence from paraffin section preparations and detects and quantifies the amount of emission from up to eight different chromagens in a single section, even when the stains are bound to the same cell. Preliminary studies were conducted to determine optimal dilutions and staining conditions for the Q-dot approach used in this project (Figures 14 and 15). These control images demonstrate reliable staining of one of the proposed panels of antibodies using spleen as a convenient tissue in which monocytes are expected to be present.

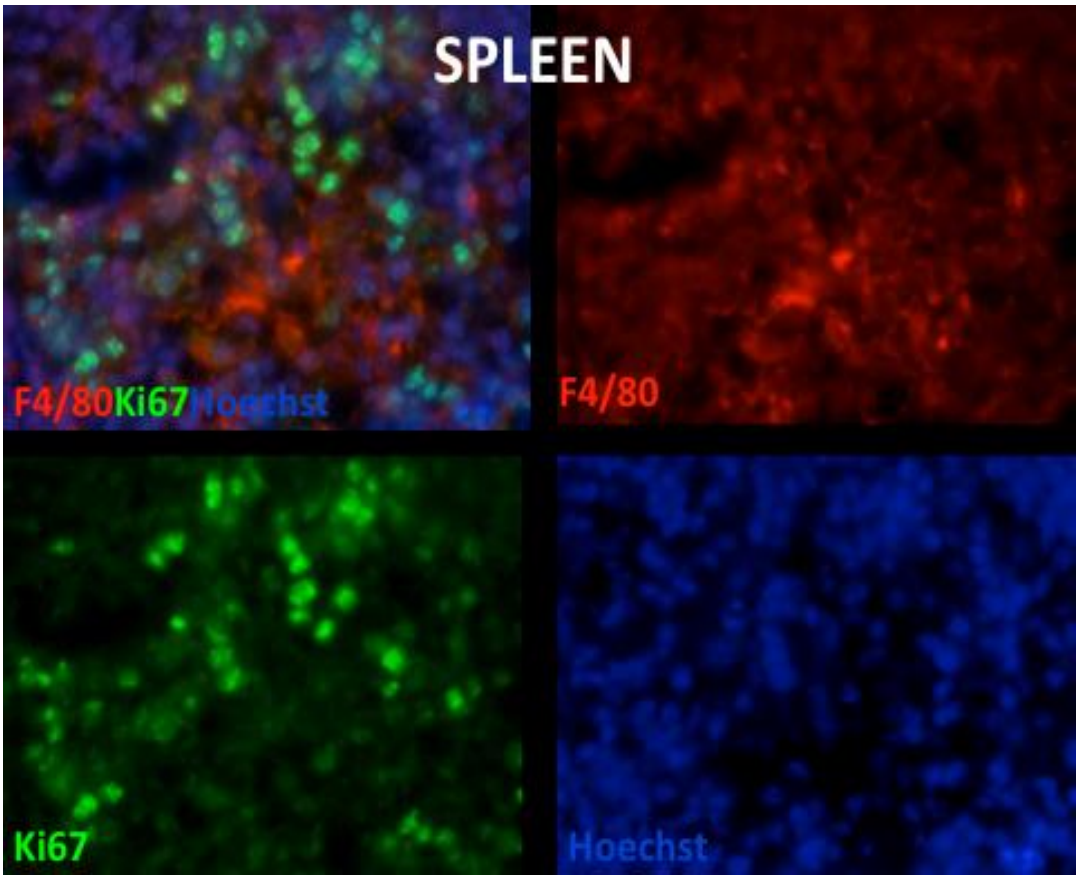


Figure 14. Q-dot immunofluorescence of control spleen of MMTV-neu mice.

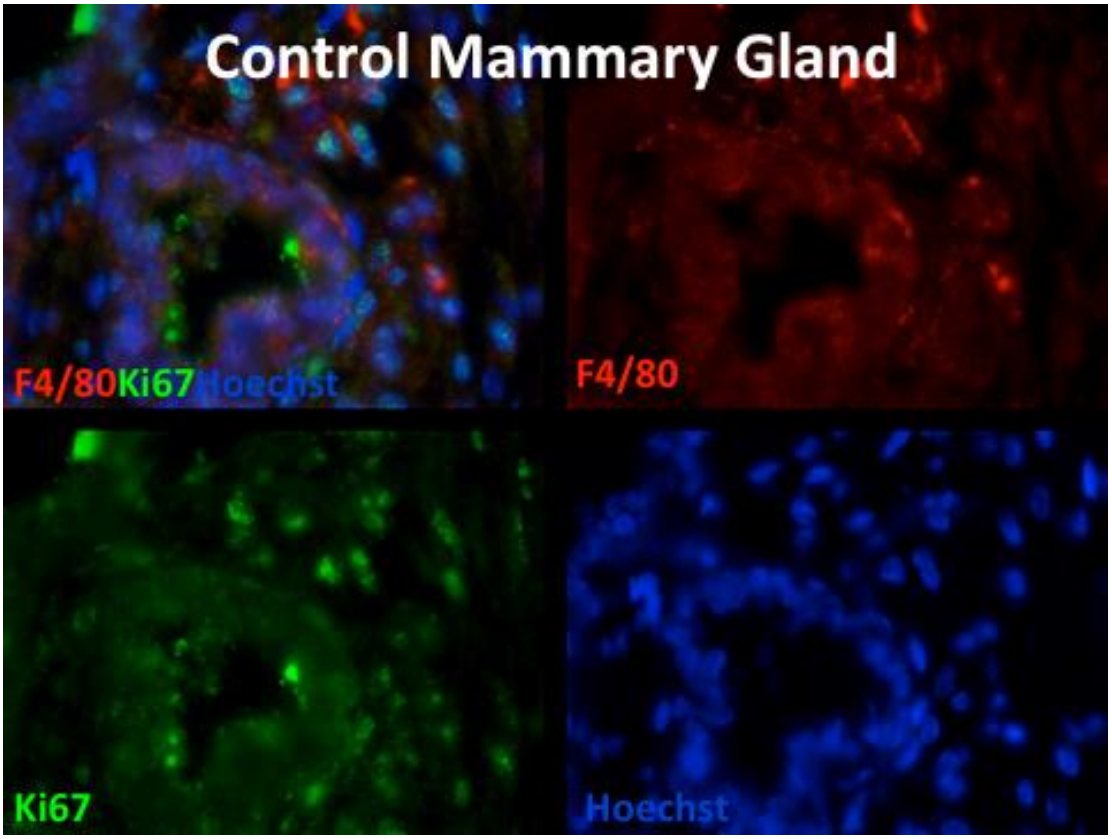


Figure 15. Q-dot immunofluorescence of control mammary tissue of MMTV-neu mice.

During the next phase of the funded research, we focused on determining differences in angiogenesis in mammary tissue sections obtained for our initial study of environmental stress effects in MMTV-neu mice. Paraffinized tissue blocks were produced containing the left and right mammary gland from each mouse, regardless of whether a tumor was present or absent. This design resulted in two mammary tissue blocks from each mouse (one from the left gland and one from the right gland) with some blocks containing tumor and some being tumor free. One section from each tissue block was stained with hematoxylin and eosin and re-evaluated by a board-certified veterinary pathologist in order to classify each section as to whether it contained tumor, hyperplasia or was histologically normal.

To determine the level of angiogenesis in the tissue sections, microvessel density (MVD) was determined on each tissue section. Briefly, each tissue section was stained with an antibody directed against CD31, an endothelial cell marker. Each slide was scanned using the Aperio ScanScope XT. This process results in an image of the entire slide, which can be viewed using Aperio ImageScope Software. The software allows the user to zoom in on any area

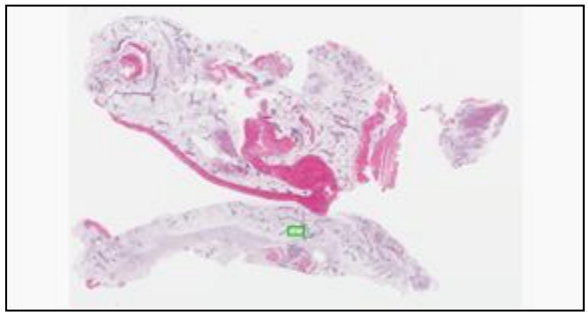


Figure 16. Monocytes are evident in mammary tissue from the MMTV-neu mice.

of the slide (to a maximum of 20X), take pictures, and annotate. Figure 16 shows an example of a single scanned slide (an hematoxylin and eosin staining of a mammary tissue). In this figure, the green rectangle denotes the area shown in Figure 17, which represents a 20X image of this area. The capability of scanning whole slides and using the Aperio software to view, annotate and take images allows us to more easily analyze our immunohistochemistry. Figure 18 shows an example of immunohistochemistry of the mammary sections using the CD31 antibody for MVD analyses. As seen in Figure 18, the antibody directed against CD31 clearly identifies the blood vessels (indicated by solid lines) while the mammary ducts (which are lined with epithelial, not endothelial, cells) are not stained (indicated by dashed lines). We have completed all of the CD31 staining and have determined the average microvessel density (MVD) for each tissue. Two separate readers who were blinded to the identity of the tissue sections separately performed the counting required to quantify MVD. Analyses of mean MVD between tumors from control mice (81.08) and tumors from stressed mice (75.79; social stress + restraint stress) failed to demonstrate a significant difference (p=0.407; Student's T-test).

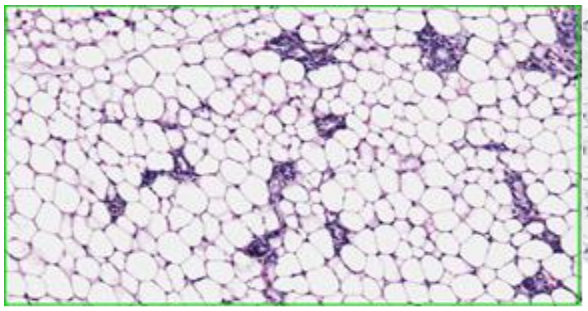


Figure 17

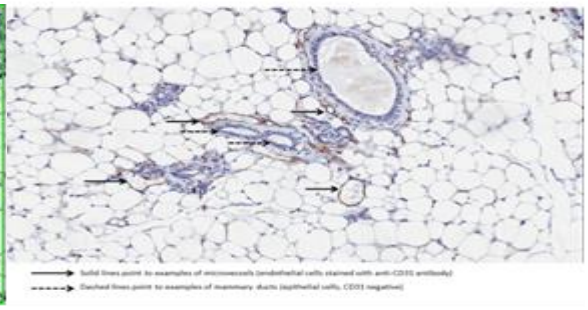


Figure 18

Study 2: To explore possible differences between stressed and control mice in expression of proinflammatory cytokines and signaling pathways involved in tumorigenesis in mouse mammary tissue collected from glands with and without evidence of tumor.
It is hypothesized that, at the molecular level, the physiological response to chronic stress will result in detectable increases in expression of phosphorylated AKT, nuclear factor (NF)κB, and mitogen-activated protein kinase (MAPK).

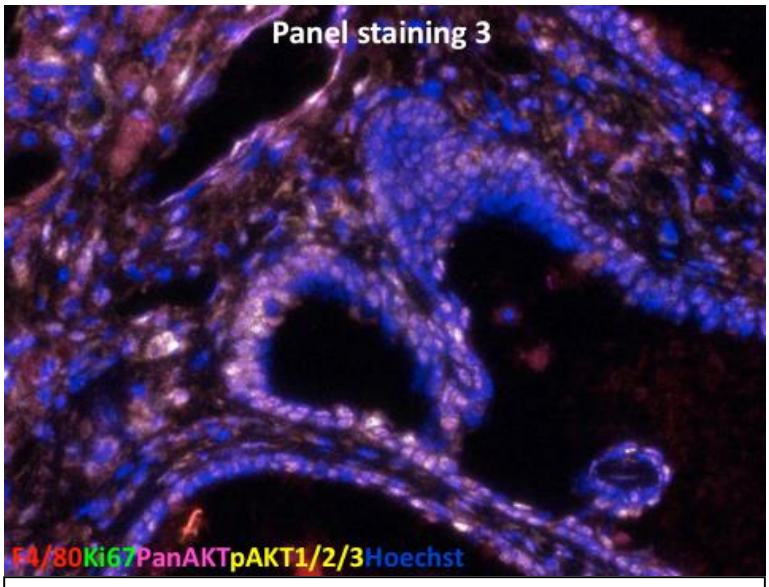
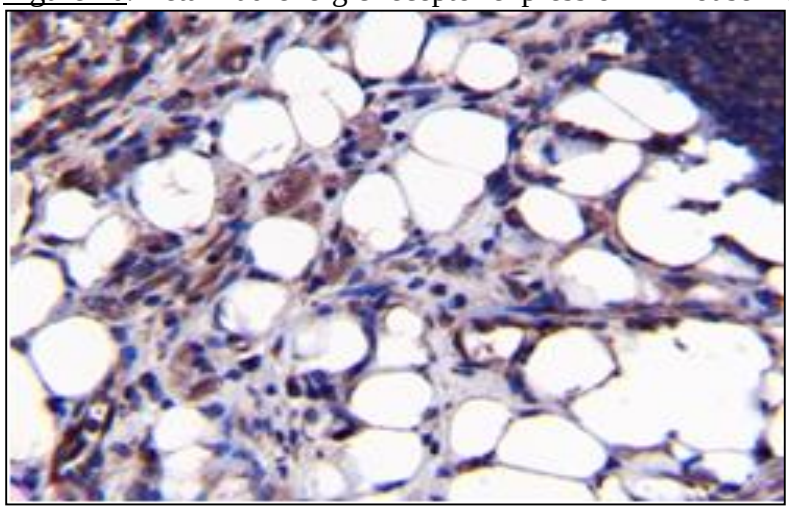


Figure 19. Representative staining of mammary tissue from MMTV-neu mice.

Initial optimization results are shown in Figure 19. This control image demonstrates reliable staining of one of the proposed panels of antibodies in mammary tissue from the MMTV-neu mice.

We spent considerable effort in optimizing our staining with the different antibodies, and have focused on identification of cells that express the beta-2 adrenergic receptor (a receptor for the stress hormones epinephrine and norepinephrine). As shown in Figure 20, we have documented expression of beta-2 adrenergic receptor in our mouse mammary tissue.

Figure 20. Beta-2 adrenergic receptor expression in mouse mammary tissue.



In presenting our initial findings on the effect of stress on tumor development at a national meeting, it was brought to our attention that the MMTV promoter used to drive the Neu gene in this transgenic mouse strain has been demonstrated *in vitro* to be induced by glucocorticoids. That data raises the possibility that the differences in tumor formation seen in stressed animals (in our initial findings) could be due to a stress hormone-induced promoter effect rather than effects on individual signaling pathways involved in Her-2 tumor formation. Given this potential alternative explanation for stress effects in the tumor model, we decided further research on these tumors was unwarranted.

Study 3: To test the hypothesis that stress-related proinflammatory cytokines and hormones will have significant molecular level effects on breast cancer cell lines in a tissue culture model.
We conducted a systematic review of the literature to determine current knowledge of stress responsive elements (e.g., beta adrenergic receptors) on widely available human breast cancer cell lines with well characterized genotypes and phenotypes that permit molecular analyses of treatment effects on the hypothesized pathways. It is hypothesized that stimulation of the beta-adrenergic receptor will have significant effects on breast cancer cell lines at the molecular level, including increased AKT phosphorylation and NFκB, MAPK, and signal transducer and activator of transcription 3 (STAT-3) activation. We were encouraged that functional adrenergic receptors have been documented on several well-established breast cancer cell lines in a paper that also provided evidence of an association with heightened human epidermal growth factor receptor 2 (HER2) expression in breast tissue samples obtained from breast cancer patients.

We obtained 5 breast cancer cell lines (MCF10A, MCF7, MDA-MB-231, MDA-MB-468 and SKBR3). We decided to focus our efforts on the MCF10A cell line as this cell line has been widely accepted as a normal human breast epithelial cell line that can be used for research on tumorigenesis. Our reasoning for the choice of this cell line over the others was based on our primary interest in the effects of stress hormones on cancer development. In initial experiments

with this cell line, we determined that the stress hormones epinephrine and norepinephrine did not affect the growth kinetics of MCF10A cells.

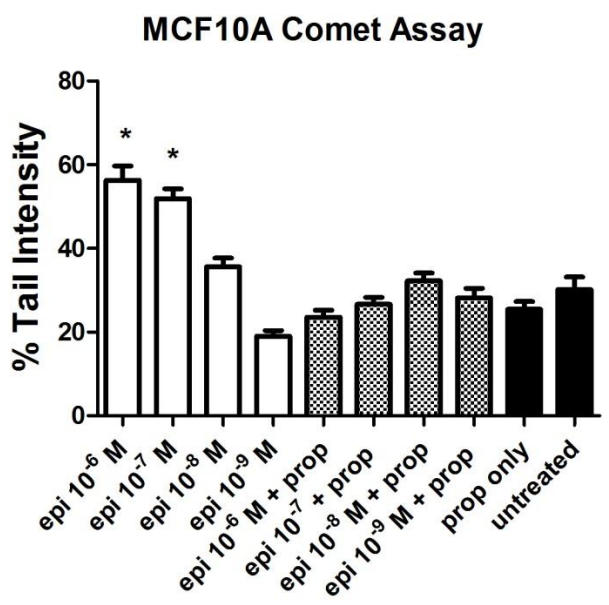


Figure 21: DNA damage induced by beta-adrenergic stimulation

Previous studies in our laboratory demonstrated that treatment of NIH 3T3 cells with the stress hormones epinephrine and norepinephrine causes significant single stranded DNA damage that results in increased transformed phenotype and tumorigenicity (Flint et al, 2007, 2012). This DNA damage is a result of beta-adrenergic stimulation, as it can be blocked with propranolol. To determine if these stress hormone effects are also seen with MCF10A cells, we treated them for 24 hr with epinephrine and determined the amount of DNA damage (as measured by the alkaline comet assay). As seen in Figure 21, there was a dose-response to epinephrine treatment resulting in significant DNA damage in cells treated with 1 or 0.1 micromolar epinephrine (as compared to untreated cells). This damage (like that seen in NIH 3T3 cells) was due to beta-adrenergic stimulation since propranolol effectively blocked the DNA damaging effects of epinephrine. As the funding period of this project ended in 2011, we have sought funding from other sources to pursue this new exciting line of research. Based on our previous and initial results (under this award), we have developed a molecular model for stress hormone-induced DNA damage. This model and a review of the literature is described in a review article that we recently authored, and which is currently in press (Effects on DNA Damage and/or Repair Processes as Biological Mechanisms Linking Psychological Stress to Cancer Risk. FJ Jenkins, B Van Houten, DH Bovbjerg, *Journal of Applied Biobehavioral Research*, 2014). We have also recently submitted two NIH R01 grants to explore this proposed molecular model in both tissue culture and animal models, as well as in human studies. One was reviewed in January and not scored, but we plan to resubmit it this summer. The other is still pending review.

Literature Cited

Andrews, P., et al. (1996). "The pharmacology of the emetic response to upper gastrointestinal tract stimulation in Suncus murinus." Eur.J.Pharmacol. 307(3): 305-313.

du Sert, N. P., et al. (2009). "The delayed phase of cisplatin-induced emesis is mediated by the area postrema and not the abdominal visceral innervation in the ferret." Neurosci Lett.

Horn, C. C., et al. (2011). Behavioral patterns associated with chemotherapy-induced emesis: A potential signature for nausea in musk shrews. Society for Neuroscience Annual Meeting. Washington, DC.

Horn, C. C., et al. (2011). Transneuronal viral tracing of sensory pathways from the stomach to the brain in the musk shrew, a small animal model for vomiting research. Experimental Biology Annual Meeting Washington, DC.

Huang, D., et al. (2011). "Computerized detection and analysis of cancer chemotherapy-induced emesis in a small animal model, musk shrew." Journal of Neuroscience Methods 197(2): 249-258.

Martin, M. (1996). "The severity and pattern of emesis following different cytotoxic agents." Oncology 53 Suppl 1: 26-31.

Sam, T. S., et al. (2003). "Action of 5-HT3 receptor antagonists and dexamethasone to modify cisplatin-induced emesis in Suncus murinus (house musk shrew)." Eur J Pharmacol 472(1-2): 135-145.

"The Utility of the Nuance™ Imaging system to visualize multiple markers on individual cells with bright-field and fluorescent immunohistochemistry for biobehavioral and other cancer research studies" in Proceedings of the 23rd Annual UPCI Retreat (Pittsburgh, PA).

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
___X__No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
___X__No

If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

_____Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

_____Number of subjects originally targeted to be included in the study
_____Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
_____Males
_____Females
_____Unknown

Ethnicity:
_____Latinos or Hispanics
_____Not Latinos or Hispanics
_____Unknown

Race:
_____American Indian or Alaska Native
_____Asian
_____Blacks or African American
_____Native Hawaiian or Other Pacific Islander
_____White
_____Other, specify:_____
_____Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____Yes
__X___ No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?

_____Yes

_____ No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, and an abbreviated title of the publication. For example, if you submit two publications for Smith (PI for Project 01), one publication for Zhang (PI for Project 03), and one publication for Bates (PI for Project 04), the filenames would be:

Project 01 – Smith – Three cases of isolated
Project 01 – Smith – Investigation of NEB1 deletions
Project 03 – Zhang – Molecular profiling of aromatase
Project 04 – Bates – Neonatal intensive care

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. Delineation of vagal emetic pathways: Intragastric copper sulfate-induced emesis and viral tract tracing in musk shrews	Charles C. Horn Kelly Meyers Audrey Lim Matthew Dye Diana Pak Linda Rinaman, Bill J. Yates	Am J Physiol Regul Integr Comp Physiol. 2014 Jan 15.	November 2013	☐Submitted ☐Accepted X Published
2. The Medical Implications of Gastrointestinal Vagal	Charles C. Horn	Curr Pharm Des. 2013 Jul 26.	May 2012	☐Submitted ☐Accepted X Published

Afferent Pathways in Nausea and Vomiting				
3. Behavioral patterns associated with chemotherapy-induced emesis: a potential signature for nausea in musk shrews	Charles C. Horn Severine Henry Kelly Meyers Magnus Magnusson	Front Neurosci. 2011 Jul 14;5:88.	May 2011	☐Submitted ☐Accepted X Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes____X_____ No_____

If yes, please describe your plans:

We are preparing a manuscript describing the effect of psychological stress on Her2 tumor development in the transgenic mouse model with a discussion of alternative mechanisms and the challenges of finding appropriate models for the study of stress effects on tumor development.

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project. Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment. Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance

of work under this health research grant? Yes_____ No___X_____

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____
If yes, indicate number of patent, title and date issued:
Patent number:
Title of patent:
Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No____

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes___ No____

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____ No_____X_____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages.

BIOGRAPHICAL SKETCH

NAME Bovbjerg, Dana Howard	POSITION TITLE Visiting Professor Leader, UPCI Biobehavioral Medicine in Oncology Program (BMOP)
eRA COMMONS USER NAME DR_DANA_H_BOVBJERG	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR	FIELD OF STUDY
University of Iowa, Iowa City, IA	B.S.	1977	Psychology
Univ. Rochester School of Med., Rochester, NY	Ph.D.	1983	Neuroscience
Cornell University Medical College, NY, NY	Postdoc.	1983-84	Immunology/Geriatrics

A. Positions and Employment

1984 – 1989 Instructor, Asst Prof, Dept Med Cornell University, Medical College, NY, NY
1989 – 1996 Asst Prof, Dept of Neuroscience and Neurol, Cornell Univ Med College, NY, NY
1989 – 1996 Asst Member, Psychiatry Service, Memorial Sloan-Kettering Cancer Ctr, NY, NY
1996 – 1998 Asst Member, Dept Psychiatry, Memorial Sloan-Kettering Cancer Ctr, NY, NY
1998 – 2008 Assistant, Associate, and Full Professor (Tenured), Cancer Prevention and Control, Department of Oncological Sciences, Mount Sinai School of Medicine, New York, NY
1998 – 2008 Director, Biobehavioral Medicine Program, Derald H. Ruttenberg Cancer Center, Mount Sinai School of Medicine, New York, NY
2008 - Adjunct Prof, Dept Oncological Sciences, Mount Sinai School Med, NY, NY
2008 - Visiting Professor, Department of Psychiatry, School of Medicine; Department of Behavioral and Community Health Sciences, Graduate School of Public Health; Department of Psychology, School of Arts and Sciences; University of Pittsburgh, Pittsburgh, PA
2008 - Leader, UPCI Biobehavioral Medicine in Oncology Program, Pittsburgh, PA

B. Selected peer-reviewed publications

1. Vin-Raviv N, Hillyer GC, Hershman DL, Galea S, Leoce N, **Bovbjerg DH**, Kushi LH, Kroenke C, Lamerato L, Ambrosone CB, Valdimarsdottir H, Jandork L, Mandelblatt JS, Tsai WY, Neugut AI. Racial disparities in posttraumatic stress after diagnosis of localized breast Cancer: The BQUAL study. J Natl. Cancer Inst. 2013 Apr 17;105(8):563-72. PMID: 23434900. PMCID: PMC3627645.
2. Nolen BM, Orlichenko LS, Marrangoni A, Velikokhatnaya L, Prosser D, Grizzle WE, Ho K, Jenkins FJ, **Bovbjerg DH**, Lokshin AE. An extensive targeted proteomic analysis of disease related protein biomarkers in urine from healthy donors. PLoS ONE 8(5): e63368. PMID: 23723977. PMCID: PMC3665773.
3. Belfer I, Schreiber KL , Shaffer JR, Shnol H, Blaney K, Morando A, Englert D, Greco C, Brufsky A, Ahrendt G, Kehlet H, Edwards RR, **Bovbjerg DH**. Persistent post-mastectomy pain in breast cancer survivors: analysis of clinical, demographic and psychosocial factors. J Pain 2013.Oct;14(10):1185-1195. PMID: 23890847. "PMCID: PMC Journal – In Press"
4. Gong Z, Ambrosone CB, McCann S, Zirpoli G, Chandran U, Hong C-C, **Bovbjerg DH**, Jandorf L, Ciupak G, Pawlish K, Lu Q, Hwang H, Khoury T, Wiam B, Bandera E. Associations if dietary folate, vitamin B6, B12 and methionine intake with risk of breast cancer among African American

and European American women. Int J Cancer 2013. Aug 30. doi:10.1002/ijc.28466. PMID: 23996837. "PMCID: PMC Journal – In Press"
5. Gong Z, Quan L, Yao S, Zirpoli G, Bandera EV, Roberts M, Coignet JG, Cabasag C, Sucheston L, Hwang H, Ciupak G, Davis W, Pawlish K, Jandorf L, **Bovbjerg** DH, Ambrosone CB, Hong CC. Innate immunity pathways and breast cancer risk in African American and European-American women in the Women's Circle of Health Study (WCHS). PLoS ONE. 2013 Aug;21;8(8):e72619. PMID: 23991131. PMCID: PMC3749137.
6. Quan L, Gong Z, Yao S, Bandera EV, Zirpoli G, Hwang H, Roberts M, Ciupak G, Davis W, Sucheston L, Pawlish K, **Bovbjerg DH**, Jandorf L, Cabasag C, Coignet JG, Ambrosone CB, Hong C-C. Cytokine and cytokine receptor genes of adaptive immune response are differentially associated with breast cancer risk in American women of African and European Ancestry. Int J Cancer 2013. Aug 28. PMID: 23996684. "PMCID: PMC Journal – In Press"
7. Yao S, Graham K, Shen J, Sucheston LE, Singh P, Zirpoli G, Roberts M, Ciupak G, Davis W, Hwang H, Khoury T, **Bovbjerg DH**, Jandorf L, Pawlish KS, Bandera EV, Liu S, Ambrosone CB, Zhao H. Genetic variants in microRNAs and breast cancer risk in African American and European American women. Breast Cancer Res Treat. 2013 Oct;141(3):447-59. PMID: 24062209.
8. Ambrosone CB, Zirpoli G, Ruszczyk M, Shankar I, Roberts M, Ciupak G, Hwang H, Khoury T, Jandorf L, **Bovbjerg DH**, Pawlish K, Bandera E. Parity and breastfeeding among African-American women: Differential effects on breast cancer risk by estrogen receptor status in the Women's Circle of Health Study. Cancer Cause Control. 2013 Nov 19. PMID: 24249438

Ongoing Research Support

NCI CA047904 Davidson (PI), Bovbjerg (Co-I) 09/10/97 - 07/31/15
Cancer Center Support Grant
This Comprehensive Cancer Center grant supports the work of the Biobehavioral Medicine in Oncology Program, as well as 11 other research programs, in an effort to improve understanding of how cancer develops; to characterize new lifesaving approaches for cancer prevention, detection, diagnosis, and treatment; and to educate future generations of scientists and clinicians.

NCI CA131148 Keefe (PI), Bovbjerg (Site-PI) 01/01/09 – 12/31/14
Pain, Distress and Mammography Use in Breast Cancer Patients
This longitudinal study assesses pain at the time of mammography and examines its impact on sustained mammography use in women treated for breast cancer.

ACS MSRG-10-079-01-CPPB Linkov (PI), Bovbjerg (Mentor) 01/01/10 – 12/31/14
Bariatric Surgery: Implications for Endometrial Cancer Risk
This career development award supports educational opportunities for Dr. Faina Linkov, mentored by Dr. Bovbjerg, and a training study of overweight women exploring the relationships between weight loss surgery, weight loss, physical activity levels, psychological factors and a selected set of biomarkers associated with the risk of endometrial cancer.

NCI CA165146 Zuley (PI), Bovbjerg (Co-I) 09/18/12 - 08/31/14
Painless Mammography
This project uses a combination of full field digital mammography (FFDM) and tomosynthesis in conjunction with new compression paddles to investigate the possibility of performing high quality screening for early detection of breast cancer while reducing breast compression to a point where pain due to breast compression is no longer an issue for patients.