Special Notice 13-SN-0024
Special Program Announcement for 2013 Office of Naval Research
Research Opportunity:
Host/ Gut Microbiota Response to Stressors: Informing Resiliency

I. INTRODUCTION

This announcement describes a research thrust, entitled "**Host/ Gut Microbiota Response to Stressors: Informing Resiliency"** to be launched under the ONRBAA13-001, Long Range Broad Agency Announcement for Navy and Marine Corps Science and Technology which can be found at http://www.onr.navy.mil/Contracts-Grants/Funding-Opportunities/Broad-Agency-Announcements.aspx. If the ONRBAA13-001 should be superseded by the upcoming FY14 ONR Long Range BAA (ONRBAA14-001), then subsequent submissions, evaluations and awards shall be made under the new Long Range BAA. The research opportunity described in this announcement specifically falls under numbered paragraphs 2a & 2n of the Warfighter Performance/ Warfighter Protection and Applications sub-section. The submission of proposals, their evaluation and the placement of research grants will be carried out as described in that Broad Agency Announcement.

The purpose of this announcement is to focus attention of the scientific community on (1) the area to be studied, and (2) the planned timetable for the submission of white papers and proposals.

II. TOPIC DESCRIPTION

The proposed topic will explore host-intestinal microbial interactions in response to specific stressors, with a long-term goal of enhancing warfighter resilience. Stressors such as those experienced during training or deployment can potentially lead to serious physical or psychological impacts. Identification of new strategies to increase warfighter resilience to stress can lead to reductions in infection and traumatic injuries, enhanced performance, and extended mission (i.e., diving) duration or profiles. The program will pursue the study of effects of various naval relevant stressors on the interactions between gut microbiota and the host (or host cells). It is expected that gaining such knowledge will inform novel, future strategies to increase resilience of our warfighters to these insults via manipulation of the gut microbial community.

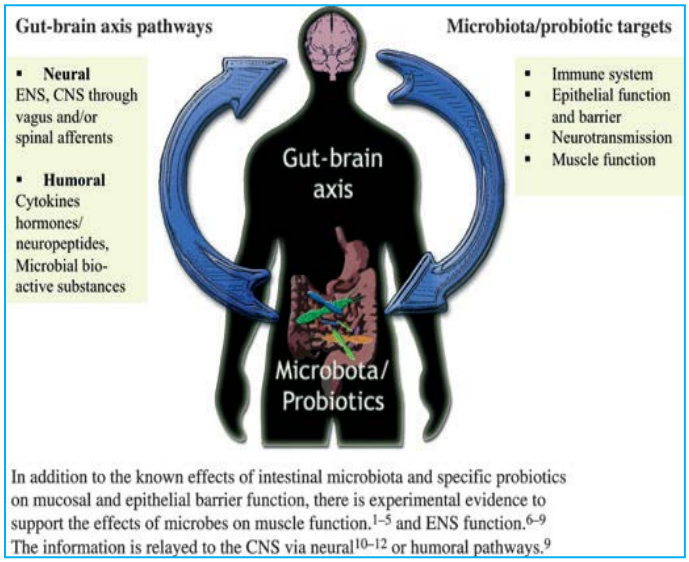
Background:

Humans are colonized by thousands of microbial species that live in and on our bodies. The number of microbial cells outnumbers human cells 10-to-1, and even more importantly, the human-associated microbial genome has 150 times more genes than our human genome[1]. The commensal bacteria, fungi and viruses that comprise the human microbiome, or 'microbial organ' as it is known, have been shown to have

tremendous influence on development of the brain, central and enteric nervous systems[2]; human mucosal immune system and protection against pathogens[3], perception of pain; extraction of nutrients from food; distribution of fat; as well as playing a direct role in several diseases[4]. It is thus critically important to enhance our understanding of this 'microbial organ' with a focus on its role in response to external stressors that can affect human resilience.

Research on the human microbiome has attracted significant interest and investment by the NIH[5,6] and an international Human Microbiome Consortium[7]. These programs, however, are highly focused on (1) characterizing the baseline "normal" host microbiota at various life stages and geographic locations[8, 10], (2) linking certain organisms to specific diseases or unhealthy states (e.g., Crohn's disease, obesity, urogenital infections, gastric ulcers)[1,8] and (3) identifying probiotic strains to support immune health and gastro-intestinal (GI) tract health[10]. In September 2010, ONR 341 organized a workshop on gut microbiology which concluded that research on effects of naval-relevant external stressors on host resilience was not a focus of currently funded programs and that study of the molecular mechanisms of these stressors could clearly benefit through consideration of the role of GM. **Of particular interest is the study of behavioral stressors (e.g., fear, anxiety, social crowding) and physical stressors (e.g., extreme environmental shifts, fatigue, disrupted circadian rhythms).**

The interplay between a host and its GM is complex and fascinating. In the gut, the host epithelium forms a tight barrier between the lumen of the digestive tract, and the bloodstream. It prevents invasion by pathogenic bacteria while allowing two-way flow of nutrients, proteins, chemical signals, and gases produced or consumed by GM and/or host epithelial cells. The immune system is tasked with recognition of pathogens as well as inflammatory response, and is closely connected to the gut epithelium where it can respond to cytokines and other immunomodulatory signals received from both the epithelial cells and the GM. During periods of physical and emotional stress, the epithelial cell barrier can fail due to inflammation, allowing bacteria to penetrate into the blood or lymphoid tissue, thus interrupting the delicate balance between host and microbes[1, 3].



Recently, increasing evidence for a role of GM as a signaling component in the "gut-brain-axis" (GBA) has emerged. "The GBA is a bi-directional communication system comprised of neural pathways, such as the enteric nervous system, vagus, sympathetic and spinal nerves, and humoral pathways, which include cytokines, hormones, and neuropeptides as signaling molecules"[3]. Neural, endocrine and immunological mechanisms underlie gut–brain interactions. At the molecular level, host production of compounds like noradrenaline and epinephrine are thought to influence the GM by mediating bacterial adherence and diversity. Conversely, the GM can produce many neuroactive substances such as serotonin, melatonin, gamma aminobutyric acid (GABA), catecholamines, histamine and acetylcholine, as well as gases (CO, H_2S, NO), shown to be involved in neurotransmission in the peripheral and CNS. Other GM products such as putrescine, spermidine, spermine and cadaverine, have all been shown to be involved in the central nervous system responses to stress. A specific role for GM in behavioral stress-induced immunomodulation (e.g., disrupted GM composition[8], enhanced macrophage activity and susceptibility to infection[9], increased cytokine production[10]), in emotional behavior[5,11], in anxiety[12] , memory and cognitive function[3] and neurotransmitter receptor expression[13] has been documented, primarily in mice. These data are intriguing and support a definite role for the GM in the gut-brain-axis[, 7], and overall homeostasis, as illustrated the figure on the preceding page (from Ref 7).

Objective:

The Office of Naval Research (ONR) is interested in receiving proposals on research directed at understanding the effects of certain behavioral and physical stressors on the host/gut microbiota, with an emphasis on deducing the role the gut microbiota (GM) may play in mediating physiological, psychological and possibly cognitive effects of such exposures. As stated above, there is tantalizing evidence that the GM plays a pivotal role as the interface between the neurological, immunological, and metabolic well-being of the host. For this topic, we do not anticipate funding any human studies.

Specific objectives of this Special Notice topic are:

(1) To characterize the psychological, physiological and cognitive responses of the host and GM (behavior, organism, tissue and molecular levels) following exposure to various behavioral and physical stressors, such as: abnormal circadian cycles or living conditions (such as those found on a submarine), extreme/rapid environmental shifts (e.g., altitudinal, temperature, elevated ambient noise), fatigue, anticipatory anxiety or fear.

(2) To ascertain if specific gut microbial community members, metabolites or functions play a role in the observed host response to the stressor(s) listed above. Comparison with data obtained for different hosts may be informative in

deducing microbial functions on host response. Specific attention will be focused on 'gut-brain-axis' routes of signaling.

(3) Support the development of novel tools for real-time analysis of microbes, the surfaces they adhere to, and microbial products in the GI tract to more closely map microbial heterogeneity and identify specific links to their function.

III. WHITE PAPER SUBMISSION

A white paper is required to be submitted prior to a full proposal. Each white paper will be evaluated by the Government to determine whether the technology advancement proposed appears to be of particular value to the Department of the Navy. Initial Government evaluations and feedback will be issued via e-mail notification from the Technical Point of Contact. The initial white paper appraisal is intended to give entities a sense of whether their concepts are likely to be funded.

Detailed Full Proposal (Technical and Cost volumes) will be subsequently encouraged from those Offerors whose proposed technologies have been identified through the above referenced e-mail as being of "particular value" to the Government. However, any such encouragement does not assure a subsequent award. Full Proposals may also be submitted by any offeror whose white paper was not identified as being of particular value to the Government or any offeror who did not submit a white paper.

For white papers that propose efforts that are considered of particular value to the Navy but either exceed available budgets or contain certain tasks or applications that are not desired by the Navy, ONR may suggest a full proposal with reduced effort to fit within expected available budgets or an effort that refocuses the tasks or application of the technology to maximize the benefit to the Navy.

White papers should not exceed 4 single-sided pages, exclusive of cover page and resume of principal investigator, and should be in 12-point Times New Roman font with margins not less than one inch. White papers shall be in Adobe PDF format (preferred) or in Microsoft Word format compatible with MS Office 2007.

The cover page should be labeled "White Paper for ONR 2014 Research Opportunity: "**Host/ Gut Microbiota Response to Stressors: Informing Resiliency"** and include the following information: title of the proposed effort, technical point of contact, telephone number, fax numbers, and e-mail address.

The 4-page body of the white paper should include the following information:

(1) Principal Investigator;
(2) Relevance of the proposed effort to the research areas described in Section II;
(3) Technical objective of the proposed effort;
(4) Technical approach that will be pursued to meet the objective;

(5) A summary of recent relevant technical breakthroughs; and
(6) A funding plan showing requested funding per fiscal year.

A resume of the principal investigator, not to exceed 1 page, should also be included after the 4-page body of the white paper.

To ensure full, timely consideration for funding, white papers should be submitted **no later than 10 September 2013**. White papers received after that date will be considered as time and availability of funding permit.

The planned date for completing the review of white papers is **03 October 2013**.

V. FULL PROPOSAL SUBMISSION AND AWARD INFORMATION

Full proposals should be submitted under **ONRBAA13-001** by **21 November 2013**. Full Proposals received after that date will be considered as time and availability of funding permit.

ONR anticipates only **grants** will be issued for this effort. All full proposals must be submitted through www.grants.gov. The following information must be completed as follows in the SF 424 to ensure that the application is directed to the correct individual for review: Block 4a, Federal Identifier: Enter N00014; Block 4b, Agency Routing Number, Enter the three (3) digit Program Office Code 342 and the Program Officer's name, last name first, in brackets ("Chrisey, Linda A."). All attachments to the application should also include this identifier to ensure the proposal and its attachments are received by the appropriate Program Office.

ONR plans to fund a mixture of individual and team awards with a value of $125,000-$400,000 per year, using research funds.

The period of performance for projects may be upto 4 years.

Although ONR expects the above described program plan to be executed, ONR reserves the right to make changes.

Funding decisions should be made by **26 December 2013**. Selected projects will have an estimated award date in **May 2014**.

VI. SIGNIFICANT DATES AND TIMES

Event	Date	Time
Recommended White Paper Submission Date*	10 September 2013	3:00 PM EST

Notification of White Paper Valuation*	03 October 2013	3:00 PM EST
Recommended Full Proposal Submission	21 November 2013	3:00 PM EST
Notification of Selection: Full Proposals *	26 December 2013	3:00 PM EST
Awards *	May 2014	None

Note: * These are approximate dates**.**

VII. POINTS OF CONTACT

In addition to the points of contact listed in ONRBAA13-001, the specific points of contact for this announcement are listed below:

Technical Points of Contact:
Linda A. Chrisey, Ph. D.,
Program Officer for Naval Biosciences
EMAIL: linda.chrisey@navy.mil>

Business Point of Contact:
Ganesh Krish
ONR Contracts
EMAIL: Ganesh.Krish@navy.mil

VIII. ADDRESS FOR THE SUBMISSION OF WHITE PAPERS AND FULL PROPOSALS FOR GRANTS

White papers should be submitted electronically to the program technical points of contact, Linda A. Chrisey, Ph.D., linda-chrisey@navy.mil. Files exceeding 10MB in size should not be emailed, but instead transitted via a file transfer service, for example AMRDEC Safesite, https://safe.amrde.army.mil, or mailed on DCROM or DVD.

The DVD or CD-ROM of the Full Proposal including all supporting documentation should be sent to the Office of Naval Research at the following address:

Point of Contact
Office of Naval Research Attn: Linda A. Chrisey, Ph. D. ONR Department Code 341 875 North Randolph Street Arlington, VA 22203-1995

IX. SUBMISSION OF QUESTIONS

Any questions regarding this announcement must be provided to the Technical Points of Contact and/or the Business Point of Contact listed above. All questions shall be submitted in writing by electronic mail.

Answers to questions submitted in response to this Special Notice will be addressed in the form of an Amendment and will be posted to the following web pages:

- Grants.gov Webpage – http://www.grants.gov/
- ONR Special Notice Webpage - http://www.onr.navy.mil/Contracts-Grants/Funding-Opportunities/Special-Notices.aspx

Questions regarding **White Papers or Full Proposals** should be submitted NLT two weeks before the dates recommended for receipt of White Papers and/or Full Proposals. Questions after this date may not be answered.

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[1] Zhu, B.; Wang, X., and Li, L. (2010), "Human gut microbiome: the second genome of the human body", Protein Cell, 1:718-725.
[2] Heijitz, R.D. et al., (2011), "Normal gut microbiota modulates brain development and behavior", Proc. Natl. Acad. Sci. 108: 3047-3052.
[3] Lee, Y. K., and Mazmanian, S.K. (2010), "Has the Microbiota Played a Critical Role in the Evolution of the Adaptive Immune System?", Science, 330: 1768-1773.
[4] Collins, S.M. and Bercik, P. (2009), "The relationship between intestinal microbiota and the central nervous system in normal gastrointestinal function and disease", Gastroenterology, 136: 2003-2014.
[5] https://commonfund.nih.gov/hmp/
[6] The NIH Human Microbiome Program ends after FY12.
[7] http://www.human-microbiome.org/
[8] Bailey, M.Y., Dowd, S.E., et al (2011); "Exposure to a social stressor alters the structure of the intestinal microbiota: Implications for stressor-induced immunomodulation", Brain, Behavior and Immunity **25:** 397-407
[9] Bailey, M.T. (2012) "The contributing role of the intestinal microbiota in stressor-induced increased in susceptibility to enteric infection and systemic immunomodulation", Hormones and Behavior, doi:10.1016/j.yhbeh.2012.02.006
[10] Allen, R.G.; Lafuse, W.P. et al., (2011); "The intestinal microbiota are necessary for stressor-induced enhancement of splenic macrophase microbiocidal activity", Brain, Behavior and Immunity, **26**: 371-382
[11] Bienenstock, J., and Collins, S. (2010), "99th Dahlem Conference on Infection, Inflammation and Chronic Inflammatory Disorders: Psycho-neuroimmunology and the intestinal microbiota: clinical observations and basic mechanisms", Clinical and Experimental Immunology", **160**: 85-91
[12] Neufeld, K.M., Kang, N., Bienenstock, J., and Foster, J.A. (2010), "Reduced anxiety-like behavior and central neurochemical change in germ-free mice", Neurogastroenterology and Motility, **23:** 255-264
[13] Bravo, J.A., Forsythe, P., et al., (2011), "Ingetsion of *Lactobacillus* strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve", PNAS **108:** 16050-16055