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Response to the Commentary from Bevelacqua et.al.

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We are pleased that our article entitled “New concerns for neurocognitive function during deep space exposures to chronic, low dose rate, neutron radiation” has stimulated interesting discussions and different perspectives on what may or may not be relevant to estimating the risks of CNS dysfunction following exposure to the space radiation environment. Here we provide our response to the commentary from Bevelacqua *et.al.*

Bevelacqua *et al.* stated that there were a few major shortcomings with our approach and we would like to clarify our stance regarding those statements. The first and perhaps most disconcerting statement was their assertion that we have “ignored…that

in a realistic space environment, cells will be exposed to multiple low LET protons before being traversed by intermediate and high-LET HZE particles." The authors of Acharya et al. have conducted research at heavy ion particle accelerators around the world for more than a decade, the implication that we might be unaware of the complexities of the radiation fields in space is misguided (Parihar et al., 2015; Parihar et al., 2016; Lee et al., 2017; Parihar et al., 2018).

During long term missions into deep space astronauts will be exposed to a complex radiation field that includes high LET components from high energy, heavy ions (HZE particles) at low dose rates of about 0.5 mGy/d for long durations. About twenty percent of the dose is delivered with LET greater than 10 keV/μm.

Particle accelerators are capable of simulating components of the GCR spectrum. The main impediment to performing accelerator-+based experiments, that are designed to simulate exposures to high LET radiations during extended missions in space, is that it's not reasonable to irradiate large numbers of rodents continuously over many months at meaningful and relevant doses and dose rates. Fast neutrons from nuclear fission create charged particle nuclei in tissues that have an LET ranging from 10 keV/μm to 200 keV/μm. We were careful not to imply that the radiation environment in the ^{252}Cf facility is an exact replica of conditions within a spacecraft or habitat in deep space. However, the charged particles generated by neutrons are produced uniformly in small animals with a dose averaged LET that is similar to many of the HZE components of the GCR and about a factor of two higher than space radiation fields resulting from

58 penetrating particles and nuclear fragmentation downstream of shielding.

59

60 We disagree with the statement that precision measurements of dose rates and
61 radiation quality for the mixed fields within this facility, "... is significantly easier than
62 determining the dose from a spectrum of protons and HZE particles of much greater
63 energy." Complex dosimetry was required for a large facility capable of exposing 900
64 mice and 60 rats simultaneously. The radiation field at the exposure location consists of
65 direct neutrons from the source as well as albedo neutrons from the walls and
66 floor. There is also a component of direct photons emitted from the source and
67 scattered photons from the surrounding shielding. Tissue equivalent proportional
68 counters (TEPC) were used to measure neutrons. A miniature GM counter and CaF_2
69 TLDs were used to measure photons. Data from the TEPCs provide direct estimates of
70 the dose rate from neutrons around the room as well as patterns of energy deposition in
71 volumes of tissue similar to the size of a mammalian cell (i.e., lineal energy). These data
72 encompass all the direct and complex environmental modifications to the radiation
73 exposures. Eighty percent of the total dose is from nuclear recoil particles produced by
74 neutron interactions in tissue and twenty percent from incident photons. Further details
75 regarding the radiation dosimetry of this facility have been published (Borak et al., 2019).

76

77 The authors correctly point out that the animals in the ^{252}Cf facility are not subjected to
78 "multiple low LET protons before being traversed by intermediate and high LET
79 particles". They imply that this sequential process of exposure can lead to the induction
80 of adaptive responses in space. However, it must be noted that, in our ^{252}Cf facility

81 animals are exposed continuously to low LET photons with intermittent production high
82 LET nuclear recoils.
83
84 The assertion that this study should have taken into account the possibility of adaptive
85 responses seems misguided. Adaptive responses have never been convincingly
86 demonstrated *in vivo* and are considered by many radiobiologists to be artifacts of *in*
87 *vitro* cell culture (Sowa et al., 2010; Sowa et al., 2011). To that end, none of the
88 references provided in the commentary documented conclusive evidence regarding the
89 adaptive response *in vivo*, much less in the CNS. Further, the idea that functional CNS
90 endpoints such as cognition, behavior and electrophysiology would resemble what has
91 been found using *in vitro* cultures of various cancer cell lines is incongruous. Precisely
92 how *in vitro* studies using transformed cancer cells can shed any light on the
93 functionality of an intact brain is unclear. No agency responsible for radiation protection
94 has incorporated adaptive response into risk assessment models because this effect is
95 not adequately supported in animals or humans.
96
97 We are confused with the authors criticism of this work based on the premise that, "…,
98 absorbed dose does not correspond to a biological detriment". The suggestion of
99 Bevelacqua et al, to introduce ICRP stochastic quality factors or radiation weighting
100 factors is meaningless for neurocognitive function. These dose modifying factors are
101 based on carcinogenesis in humans with most information derived from acute
102 exposures. The objectives of investigations at the ^{252}Cf facility are to establish dose,
103 dose rate and radiation quality effects on biological endpoints that are beyond the reach

of other available experimental protocols. It could be argued that these results will provide valuable information for creating the next generation of dose modifying factors for radiation risk analysis.

One of the primary driving forces for establishing the neutron facility at CSU was to investigate dose rate effects, since there is a large and reproducible body of literature demonstrating that lowering the dose rate (cGy/hr) provides for the temporal overlap of DNA repair during dose delivery. The end result is that nearly all the adverse effects of ionizing radiation exposure are ameliorated at low dose rate simply due to effective DNA repair. It stands to reason then that at space relevant dose rates similar reductions in adverse effects would be observed, which was not the case in the study by Acharya et. al. It is also important to keep in mind that a critical difference between Acharya et al. and the references cited by Bevelacqua and colleagues is that we did not investigate putative carcinogenic endpoints in cultured cells. Dose rate effects can be expected to play a relatively minor role in a largely post-mitotic organ such as the brain, especially when considering the multifaceted functions that characterize the CNS. At the low doses and dose rates used in Acharya et al., radiation effects are not likely the result of cell kill, but rather an accumulation of damage to networks of cells that adversely impact neurotransmission.

Regardless of the mechanism, findings from Acharya et al. demonstrated significant impairments in the brain under the stated irradiation conditions, with no evidence for attenuation by adaptive and/or DNA repair processes over the protracted exposure time.

Despite our disagreements with the commentary proffered, we hope these discussions can help NASA and other agencies properly evaluate the CNS risks associated with exposure to the deep space radiation environment (Limoli, 2017).

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