

The use of biological countermeasures to reduce cancer risks from exposures to space radiation

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There is mounting evidence that exposure to space radiation (even with shielding) is likely to increase health risks associated with long-term space exploration. For example, current NASA permissive exposure limits for fatal cancer risk would not presently permit safe Mars missions. NASA programs must follow the ALARA (As Low As Reasonably Achievable) principles to ensure astronauts do not approach dose limits. Clearly more new research is needed to model these risks but it is prudent to now initiate investigations into biological countermeasures that may help reduce these risks and thus permit more safe days for astronauts in space. While shielding may help in preventing increases in damage due to solar particle events, the penetrating nature of the GCR (Galactic Cosmic Radiation) is believed to cause complex DNA damage leading to increases in cancer even with shielding. It will be impractical to test a large number of biological countermeasures in sufficient numbers of biological models to demonstrate efficacy using track-segment approaches with multiple HZE (high-Z high energy) nuclei types and energies. Thus NASA will need to develop at the NSRL (NASA Space Radiation Laboratory) a small number of design reference fields for both GCR and SPE (Solar Particle Event) to support future space countermeasure research. While there is a lot of interest in radiation countermeasure research, a contrarian view is that biological countermeasures may not only prevent radiation initiated cells from dying by apoptosis, but also permit such initiated cells to now proliferate and to actually increase the incidence of fatal cancer. Thus it is critical to initiate new research in this area to determine if countermeasures may or may not be helpful.

The requirements for developing a new biological countermeasure would be the same as those required by the FDA to approve any new biological: proven mechanism of action, demonstration of efficacy or activity in at least one animal model, sufficient benefit to be worthwhile for a specific scenario (e.g. protection from space radiation damage), similarity of action between species tested and man, and safety in an otherwise healthy population. For long-term missions to space a small light weight oral available biological would also be desirable that affected many different cancer types as well as being of benefit for multiple indications (e.g. CNS, cardiovascular, and cancer risks).

There are already a number of candidate agents to protect, at least partially, against acute damage and one of these is amifostine, a drug already approved as a radiation protector. The problem with amifostine is that it is quite toxic and must be injected due to the fact that it is broken down in the gastrointestinal (GI) tract. So for avoiding an acute mission failure scenario, amifostine would certainly be one agent available. There are also tissue specific countermeasures. For example, a bacterial protein, flagellin, injected prior to irradiation protects mice from doses of gamma irradiation that would produce mortality due to GI tract acute radiation syndrome. This compound also is injected and would only protect the GI tract. Finally, there has been quite a bit of research on antioxidants and dietary supplements, and some of these may be useful for reducing radiation-associated acute damage since they in general would not require FDA approval. It is uncertain if the dietary supplements would be

effective countermeasures against late effects such as solid tumors but new research conducted at the NSRL would certainly help to gain this knowledge.

There is mounting evidence that cancer is related to inflammatory processes and a group of novel compounds are being developed known as anti-inflammatory modulators (or AIMS). One such compound is bardoxylone methyl (also called BARD, CDDO-Me or RTA-402). BARD is a synthetic derivative of a class of plants compounds known as triterpenoids and much is known about their mode of action. While a bit oversimplified, BARD causes a transcription factor sequestered in the cell cytoplasm (Nrf-2) to translocate into the nucleus and to bind to gene promoters containing antioxidant response elements (AREs) which then turn on phase II enzymes such as SOD and HO-1. BARD is oral available, works in the nanomolar range, is well tolerated and with an excellent safety profile in humans. For example, BARD is currently in Phase IIB clinical trials for renal insufficiency in patients with type II diabetes.

The interest in BARD as a radiation countermeasure is based on data showing that it protects against radiation-induced mucositis in a hamster cheek pouch assay as well as protecting against radiation-induced proctitis in a nude rat study. Finally, BARD protects against radiation-induced intestinal damage in zebrafish development. Our recent studies show that BARD is both an effective countermeasure of both gamma-irradiation and space-associated radiation with dose modifying factors in the 1.7 to 2.0 range for gamma-IR. More recently, we have evidence that if BARD is provided within 30 minutes after gamma-irradiation there is radiation mitigation activity. In experiments conducted at the NSRL human colonic epithelial cells were irradiated 0.25 Gy ^{16}O day 1 (250 MeV, LET 25) \rightarrow 0.25 Gy ^{28}Si day 2 (350 MeV, LET 70) \rightarrow and 0.25 Gy ^{56}Fe day 5 (600 MeV, LET 250). Prior to each ion exposure (16 hrs) the cells were treated with 50nM BARD. After the final treatment with ^{56}Fe , the cells were not further treated with BARD, and then passaged in cell culture for 12 weeks. The control and BARD irradiated cells (as well as the unirradiated control cells) were placed in soft agar to determine anchorage-independent growth and there is clear evidence of protection from anchorage-independent cell growth (unpublished results). In another series of experiments the same type of cells were irradiated with 2 Gy of protons (1GeV) followed 24 hours later with 0.5 Gy of ^{56}Fe (1 GeV). We included control irradiated (- BARD) and sham control (+ and - BARD) and single ion exposures. Irradiated and sham treated cells were cultured for 9 weeks to allow potentially transformed cells to populate the culture. We then seeded the colonic epithelial cells into soft agar to determine anchorage-independent growth as a measure of tumorigenesis. The results demonstrated not only a 50% reduction in colony formation in the colonic epithelial cultured in BARD for 18 hours prior to irradiation, but those colonies that did form were significantly smaller (*Radiation Research*, in press 2010). While these are encouraging initial results, we now need to demonstrate the protective effect in animal models of cancer to determine if BARD works in vivo against the type of radiation present in space.

In summary, the hope is that ongoing research into cancer risks from space radiation are not as bad as we may believe right now based on modeling terrestrial-based radiation exposure epidemiological data as well as experiments conducted at the NSRL during the past 5-8 years. If this is true then biological countermeasures may not be needed. However, should the current risk estimate hold up to new research, then countermeasure research will take the front and center for making the future of long-term space missions safer.