France, India, Japan, Russia, and the United States. According to Article IX of that treaty: "Parties shall pursue studies of outer space, including the Moon and other celestial bodies, and conduct exploration of them as to avoid the harmful contamination of extraterrestrial bodies and also adverse changes in the environment of Earth resulting from the introduction of extraterrestrial matter and when necessary, adopt appropriate measures for this purpose."

"The LIFE experiment poses a far greater risk of the 'harmful contamination' proscribed by Article IX of the Outer Space Treaty than any other prior mission to the Mars system," says Darlene Cypser, a Colorado-based attorney who specializes in this branch of international law. "In addition, we do not know for a fact that microorganisms transported from Mars to Phobos by asteroid impacts are incapable of surviving there, whether active or in some form of stasis and, thus, the Outer Space Treaty requires that a sample returned from Phobos be treated with all the same precautions as a sample from Mars."

"The Russians have informed us that they will meet planetary protection international guidelines as set forth by COSPAR [Committee on Space Research] on the Phobos-Grunt mission," Friedman says.

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Metal Balance Helps Explain Survival of Microbial "Superhero"

"If there's a superhero microbe, it's *Deinococcus radiodurans*," says Michael J. Daly from the Uniformed Services University of the Health Sciences in Bethesda, Md. For this bacterial extremophile to withstand massive doses of radiation and other physical insults, he adds, "what really counts is not just Mn^{2+} accumulation, but the balance between Mn^{2+} and Fe^{2+} as well as the ability of manganese to form free-radical-devouring chemical complexes." He reports in the March issue of *Nature Reviews Microbiology* (7:237–245) that this and other microbial species with high manganese-to-iron ratios are extremely resistant to γ-radiation-induced protein oxidation, while those with low manganese-to-iron ratios are hypersensitive.

D. radiodurans is "endlessly fascinating but very stubborn and malodorous," Daly continues noting that "it's also virtually impervious to desiccation and easily survives massive exposures to ionizing radiation, both X-rays and γ-rays, ultraviolet light, and chemical oxidizing agents." In 2007, Daly showed that the hardiness of *D. radiodurans* comes from protecting its proteins with accumulated manganese (Mn^{2+}) ions, thus sparing a sufficient number of enzymes critical for repairing its genome (*Microbe*, July 2007, p. 327; http://www.asm.org/microbe/index.asp?bid=51529).

Now, Daly and his collaborators report that *D. radiodurans* and other similarly gifted microbes depend on particular metal ions as part of their protein-sparing apparatus. Notably, *D. radiodurans*, which has very efficient systems for Mn^{2+} uptake, typically accumulates 100 times more manganese than do radiation-sensitive bacteria. "Unlike ferrous ions (Fe^{2+}), Mn^{2+} ions are innocuous in aerobic environments with virtually no negative redox consequences," he says. "Fe^{2+} but not Mn^{2+} catalyzes the Fenton reaction, one of the most powerful oxidizing reactions known." Further, extreme radiation and desiccation resistances depend on formation of superoxide-scavenging Mn^{2+}-phosphate complexes and accumulation of hydroxyl radical-consuming small organic molecules.

"X-ray fluorescence microspectroscopy has just shown that manganese is dispersed throughout *D. radiodurans*, but much of its iron is partitioned between dividing cells, which helps explain how global enzyme protection is accomplished," Daly says. "Because the hydrogen peroxide (H_2O_2) generated during irradiation diffuses widely, manganese and iron portioning serves to minimize the Fenton reaction." In contrast, iron-rich and manganese-poor bacteria suffer a torrent of reactive oxygen species (ROS) during irradiation, which inactivates many enzymes. "Unless an irradiated cell can protect its enzymes from oxidation, even the most minor DNA damage will kill it," he notes.

Knowing that diploid yeast cells can recover from exposure to γ-radiation, Daly is developing "*Deinococcus*-inspired" radioprotectants—combining Mn^{2+} with ligands such as phosphate and other small molecules. "The right mix, when delivered into human cells, could spontaneously form intracellular complexes that scavenge superoxide and related ROS," he says. Potential applications include "making radiation therapy more tolerable for cancer patients, protecting astronauts from radiation during long-duration space travel, cleaning up the 'slumgullion' of radioactive waste left over from the Cold War, and developing ways to slow down the aging process. I'm excited that in the last few years, this research has moved from the realm of science fiction to plausible reality."

Daly's results are being closely monitored by other scientists, including cell biologist Colin Dingwall at Kings College London. Dingwall has shown that BACE1, or beta-secretase, a principal component of senile plaques, is linked to copper in the brains of patients with Alzheimer's disease. "Substituting Mn^{2+} for Cu^{+} to prevent redox chemistry is an interesting idea and, if it works, small molecules such as peptides might be used as delivery agents," he says.

"Daly's convincing demonstration that simple manganese complexes protect proteins from oxidative damage in vivo makes me wonder if manganese is acting similarly in more complex organisms," says biochemist Joan S. Valentine from the University of California Los Angeles, adding that "perhaps the antioxidant effects of manganese supplementation that we've been attributing to increases in manganese superoxide dismutase enzymes might really be due to simple manganese complexes."

Commenting on how *D. radiodurans* evolved its manganese-based resistance to high-dose radiation, Rodney L. Levine from the National Institutes of Health in Bethesda, Md., says "it's unlikely that it evolved to survive high-dose radiation as such, it's more likely an example of cross-resistance, probably acquired as a consequence of its ability to survive desiccation; organisms which evolve or induce a resistance to one stress are more often than not resistant to multiple other stresses." But, he adds, "as Daly points out, we live in a DNA-centric world which holds that cells die because of genome injury, and this is not entirely correct. *Deinococcus* DNA is as diced and sliced by irradiation as that of *E. coli*, but *Deinococcus* survives when *Escherichia* dies. Daly's experimental data show why this happens; it's all about the proteins."

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