Synthetic Torpor as a Strategy for Survivability of Long Duration Human Exploration Missions: *The Need for Fundamental Investigations in Rodents*

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Unacceptable Risk of Long-Duration Space Flight

For the very longest exploration missions to Mars and beyond, the risk of deleterious health effects will probably never be acceptable unless something new comes along to help NASA deal with these problems. The most glaring issue is space radiation. Given the slow pace of development of radiation countermeasures and the difficulty of validating these countermeasures in clinically-relevant settings that are meaningful to NASA, it seems unlikely that risk reduction will be possible any time soon (NCRP 2014). Although there is uncertainty in our current estimates of risk, the probability of cancer developing in an astronaut returning to earth from Mars is clearly too high. Even with refinement of radiation risk estimates (Cucinotta, To, and Cacao 2017; Walsh et al. 2019), it is unlikely that the lengthy trip to Mars and back--considering galactic cosmic radiation, secondary particle radiation and solar particle event radiation--will allow the mission to be accomplished with less than a 3% chance of an astronaut developing a fatal neoplastic process (Cucinotta et al. 2013). Added to the risk of cancer is the risk of radiation-induced impairment of the central nervous system, which is difficult to model experimentally and therefore difficult to quantify (Pariset et al. 2020). For a human mission to Mars round trip, which may be two to three years in duration (Drake 2009), it may not be possible to adequately ensure the health of astronauts, given the shielding resources and other tools we expect to have available (Montesinos et al. 2021). Cancer, degenerative diseases and mental health may all be important considerations.

Although space radiation seems to attract the most attention as the most serious risk of long duration space travel, we should not forget that reduced gravity and weightlessness, resulting in muscle wasting and bone demineralization, can have serious deleterious effects on human health, too. On the very longest duration missions to deep space destinations, muscle wasting and bone demineralization may not be fully reversible.

Metabolic Stasis or "Hibernation"—A Novel Concept for Protecting Astronauts on Long-duration Space Missions that has been Around for a Long Time

For human spaceflight missions to Mars and beyond, it may be desirable (or, frankly, necessary) for crew members to be placed in a state of "hibernation" in order to minimize the health consequences of space radiation exposure, microgravity and other features of the spaceflight environment. This strategy represents a radical departure from the generally accepted notion of keeping astronauts awake and "at full metabolic rate" for the duration of the mission. While the term "hibernation" generally applies to the dormant state that some animals naturally enter as a "winter-overing" strategy, a similar state of *induced* "hibernation" may be possible in

humans and may serve as an important strategy for opening the door to much more ambitious deep space missions with improved survivability than would otherwise be possible.

The concept of deliberately placing crew members in some sort of condition of hibernation (commonly referred to as "Synthetic Torpor") as a way of better enduring the rigors of space travel is not new, with the first discussions of the concept taking place in the 1960s (Cockett and Beehler 1962; Hock 1960). While protection of the health of astronauts is one benefit, other benefits of Synthetic Torpor include a reduction in food required to sustain the crew members and a reduction in the consumables needed for life support systems. A reduction in mass requirement for transit to a deep space destination means that more resources can be made available to astronauts once they reach their destination. This shift in mass allocation can have a profound impact on mission scope and architecture. In one recent study (Bradford et al. 2018) funded by NASA's NIAC program, a concept of rotating 14-day periods of Synthetic Torpor ("induced hypothermia") for a 4-person crew was proposed (Bradford et al. 2018), with three crew members in stasis at any one time and a fourth crew member fully awake. The concept was based on the fact that up to 14 days of induced hypothermia has been used successfully in humans to help treat traumatic brain injury (Jiang, Yu, and Zhu 2000). This NIAC study demonstrated that the proposed model would result in a 25% reduction in launch costs, with economies across all mission systems contributing to the cost reduction.

Evidence for a Radioprotective Effect of Natural Hibernation or Synthetic Torpor

Hibernation or natural torpor is a fascinating physiological process in which metabolic rate, core body temperature and behavioral activity are reduced to save energy during harsh seasonal conditions. The radioprotective effect of torpor was first studied in ground squirrels--animals that exhibit hibernation naturally. Using gamma irradiation, a dose-reduction factor of 1.4 was observed in winter-hibernating squirrels compared to active squirrels (Musacchia and Barr 1968).

To test the hypothesis that a torpor-like state in a non-hibernator is radio-protective, studies were carried out in zebrafish using melatonin treatment and reduced temperature to induce torpor. Experimental animals were irradiated to a total of 32.68 cGy on day #2 and day #8 after inducing torpor. Genomic analyses indicated that low dose radiation caused DNA damage and oxidative stress triggering a stress response, including steroidal signaling and changes to metabolism, and, cell cycle arrest. Torpor attenuated the stress response through an increase in pro-survival signals, reduced oxidative stress via the oxygen effect and detection and removal of misfolded proteins. This proof-of-concept model provides compelling initial evidence for utilizing an induced torpor-like state as a potential countermeasure for radiation exposure.

In a recent study in rats (Tinganelli et al. 2019), which do not normally hibernate, the effect of Synthetic Torpor (induced by injection of the GABA-A agonist, muscimol, into the nucleus Raphe Pallidus of the brain stem) on radiation-induced tissue damage was studied. Animals were irradiated with 3 Gy X-rays and organs were collected 4 h after exposure. Histological

analysis of liver and testicle showed substantially reduced radiation toxicity in animals irradiated while in Synthetic Torpor compared to control animals. In the liver, the expression of ataxia telangiectasia mutated (ATM) was significantly downregulated in the group of animals in Synthetic Torpor. In the testicle, genes involved in the DNA damage signaling were downregulated during Synthetic Torpor as well. These data show for the first time that Synthetic Torpor is a radioprotector in non-hibernating mammals, similar to natural torpor in hibernating mammals. These exciting results pave the way toward the development of space radiation studies in rodents induced into torpor, with a long-term view toward protection of humans on deep space missions.

The Need for Space Biology Studies of Synthetic Torpor

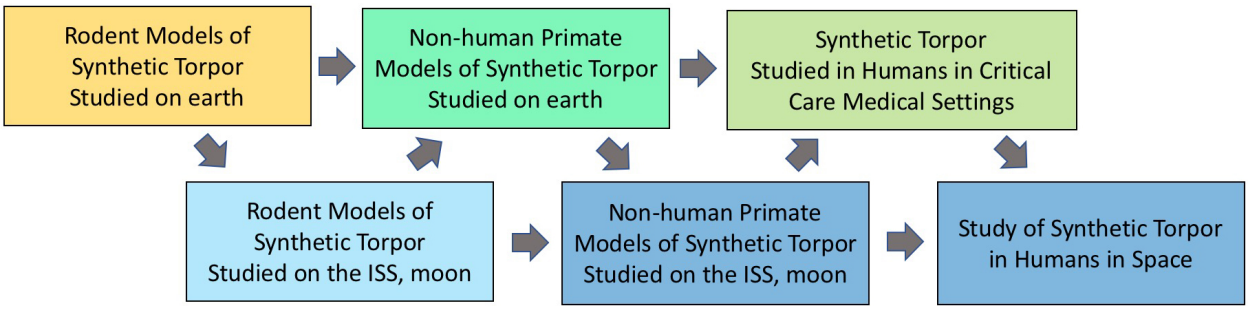

Fig. 1. Advancement of Synthetic Torpor Technology from Animal Models to Humans in Space.
Space Biology will play a critical role in the development of Synthetic Torpor as a technology for enabling deep space human exploration missions. Critical steps will involve study of rodent models on earth, the transition of rodent models from earth to space (ISS, moon and deep space), transition to non-human primate models, and, eventually, transition to studies in humans. Study of Synthetic Torpor in humans will likely first take place in critical care medicine patients, before the technology is tested on space travelers.

A variety of methods of initiating Synthetic Torpor should be considered in order to decide which methods should be developed for NASA Applications. Fundamental mechanistic understanding of the wide range of techniques for modulating metabolic activity is needed. For these basic investigations, rodents are the natural choice, but non-human primates should be considered as well. Recent studies in mice (Hrvatin et al. 2020; Takahashi et al. 2020), for example, have demonstrated that activation of a specific neurological pathway can induce profoundly reduced metabolic activity that mimics the state of torpor that mice are known to enter ("daily torpor"). This is an especially attractive animal model system of biostasis that would be ideal for ground-based studies. Other methods of inducing Synthetic Torpor are available as well. Study of neurally-induced torpor using Space Biology resources at NASA and outside of NASA would help to advance the technology of Synthetic Torpor to benefit NASA. As a top priority, effort should be directed at the experimental demonstration of the radioprotective effect of Synthetic Torpor, using the NASA Space Radiation Lab at Brookhaven National Laboratory as a source of simulated space radiation. Additional endpoints could include comprehensive omics studies to better understand the biochemical and metabolic aspects of neurally-induced biostasis. Experiments on the ISS would be the first step toward

demonstrating the feasibility of this Synthetic Torpor system in an authentic space environment. Eventually, rodents could be transported into deep space, in order to more authentically replicate the conditions that crew members one day will face. An initiative to develop Synthetic Torpor technology for NASA applications coud involve NASA, academic partners, and other space agencies such as the European Space Agency (ESA) and the Japan Aerospace Exploration Agency (JAXA). It is noteworthy that ESA already has a research group (an ESA "Topical Team") specifically focused on hibernation research for space exploration (Seedhouse and Shayler 2020).

Summary

Unless a breakthrough in radiation countermeasures appears soon, long-duration human explorations to Mars and even more distant destinations will likely require the development of Synthetic Torpor technology to protect the health of crew members. Inducing a "hibernation-like state" in crew members would substantially reduce the risk of radiation-induced cancer, radiation-induced central nervous system effects and other degenerative processes that pose a threat to astronauts. This is a paradigm shift that will benefit NASA, other space agencies and, eventually, the commercial space industry, too. Initial effort to develop Synthetic Torpor for NASA applications falls squarely within the realm of Space Biology (Griko and Regan 2018), with both rodent studies and non-human primate studies needed to advance the technology readiness level (TRL) and prepare for studies in humans. With access to the moon in the next few years as a new venue for Space Biology studies outside of Low Earth Orbit, now is the time to begin assessing the most promising mechanisms for inducing torpor in rodents and developing a roster of investigations that will help to establish feasibility of Synthetic Torpor. Many of the ground-based resources for conducting the necessary studies are already in place and the core knowledge is mature enough to support space-based investigations. Space Biology has a critical role to play in the development of this important enabling technology for deep space human exploration.

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