The final challenge will be to transplant these delicate cells into animal models of disease, and prove they can integrate and repair damaged tissues. This alone is an enormous feat given the immune rejection problems, particularly following grafts into tissues outside the CNS.

Perhaps the best example highlighted by Paul *et al.* where stem cells could first be used is PD. Of particular interest is a recent paper, which has been published since the review was completed, where neurons derived from mouse ES cells were shown to mature into dopamine neurons and restore function following transplantation into a rat model of PD [2]. This is encouraging, but a large number of animals also developed teratoma-like tumors and had to be excluded from the study. This elegantly reveals both the excitement and necessary caution that needs to be exerted before taking ES cells to the clinic.

Adult stem cells are of course ethically acceptable, and there is an impressive clinical history already available for haematopoietic stem cells being used to treat a wide range of diseases [3]. The excitement over new plasticity of adult stem cells is warranted, given the range of new papers suggesting such events might occur. However, this is tempered by the rarity of such events and in nearly all cases (particularly with regard to neural replacement) there is little evidence that the cells are functional. This has prompted several cautionary commentaries [4,5]. Furthermore, despite more than 30 years of research, blood stem cells cannot be easily expanded to large numbers in the tissue culture dish, a feature shared by most other adult stem cells.

One missing type of stem cell from the review by Paul *et al.* is the fetal stem cell. This is an interesting type of stem cell, and falls between the two extremes of ES cells (totally non committed cells that need entire programming to become differentiated tissue) and adult stem cells (highly committed and perhaps require some de-programming). Fetal stem cells can be isolated from a range of developing organs but a particularly interesting example is the human neural stem cell, which can be derived from the late embryonic or early fetal brain between six and 20 weeks. These cells are less likely to form tumors, and are already committed to a neural lineage – two useful attributes that are still difficult to achieve from ES cells [6]. However, it is also possible that the developmental power present within ES cells will ultimately be required to generate the range of different neuronal phenotypes required for different diseases. In particular, large dopamine neurons that are lost in PD are difficult to generate from expanded populations of fetal derived neural stem cells, but can be produced from ES cells, as mentioned previously.

Clearly, future studies need to focus on comparisons between these various types of stem cells. Hype *and* hope will permeate the field during these early stages. The onus is on authors, journal editors and the media to be responsible. The data should be presented in a way that, while not distracting from the excitement of this field, does not raise false hopes.

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Clive Svendsen
Professor, Anatomy and Neurology
Stem Cell Research Program
The Waisman Center
University of Wisconsin-Madison
1500 Highland Avenue
Madison, WI 53705, USA
tel: +1 608 265 8668
fax: +1 608 265 4103
URL: http://www.waisman.wisc.edu/scrp/index.htmlx

Osteoprotegerin and bone loss associated with spaceflight ▼

In a recently published article [1], Grimaud *et al.* gave an excellent overview of significant advances in the understanding of bone biology since the discovery of osteoprotegerin (OPG) approximately five years ago [2]. The roles that OPG, RANK (receptor activator of nuclear factor κB) and RANK ligand (RANKL) play in the differentiation, activation and eventual death of osteoclasts is one of the most fundamental discoveries related to the maintenance of bone health in recent decades.

In addition to describing the interacting mechanisms of these three cytokines, Grimaud *et al.* describe initial research activities in the development of OPG as a potential drug. Preclinical studies have indicated that OPG could effectively treat both osteoporosis and the bone loss associated with metastatic bone cancer. It is our understanding that Amgen (Thousand Oaks, CA, USA) is proceeding with FDA clinical trials for these two indications.

As investigators who work with the National Aeronautics and Space Administration (NASA) to promote a commercial interest and exploitation of the spaceflight environment to help discover, develop and test new drugs, we would suggest that OPG might also be an appropriate treatment for the bone loss that is caused by extended

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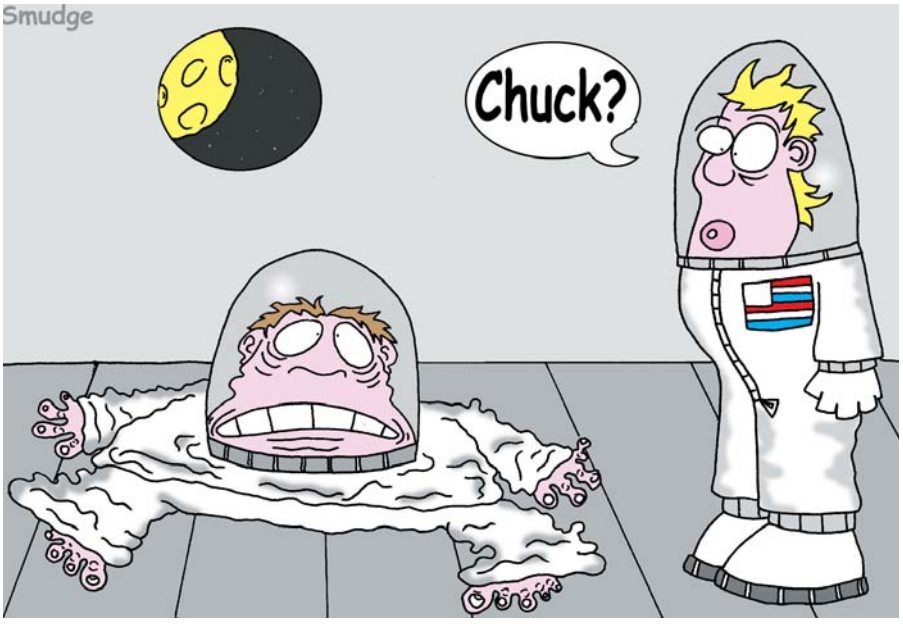
exposure to microgravity (spaceflight). This bone loss occurs at a much greater rate than either Type I (postmenopausal) or Type II (senile) osteoporosis. At approximately 0.5–2.0% reduction in mass per month [3], an astronaut can lose as much bone mass in one year of spaceflight as a woman can lose in five to seven years after menopause. Additionally, recovery of bone might not be complete after an astronaut returns to Earth [4].

None of the existing therapies for terrestrial osteoporosis is appropriate for use in astronauts while in space. Estrogen and selective estrogen receptor modulators (SERMs) are not indicated for males or premenopausal females. Currently approved bisphosphonates require oral administration that can lead to esophagitis and gastrointestinal ulcerations, which might be exacerbated by weightlessness. Parathyroid hormone therapy requires daily subcutaneous injections, a frequency unlikely to be tolerated in microgravity. Possible future treatment with intravenous administration of bisphosphonates is an option being examined by the National Space Biomedical Research Institute (NSBRI; Houston, TX, USA) in human disuse models (traumatic spinal cord injury).

However, OPG could also be a viable and desirable treatment for bone loss caused by weightlessness, and should be evaluated along with bisphosphonates for the following reasons:



- Administration would be by subcutaneous injection once every few weeks or months.
- OPG is a naturally occurring protein that does not become incorporated into the skeletal system.
- The mechanism of action has been thoroughly characterized.

Although FDA approval of OPG is probably several years away, it could eventually be an excellent therapy for one of the more serious problems associated with long-term spaceflight.

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Ted A. Bateman
Director of Biomedical Research
Stefanie Countryman
Director of Business Development
BioServe Space Technologies
University of Colorado
Boulder
CO 80309-0429
USA