The ideal method to prevent detrimental changes to the musculoskeletal system during spaceflight would be to recapitulate the normal mechanical loading environment found on earth. However, that has proven to be difficult to accomplish. Therefore, alternative methods need to be considered. We propose that pharmacological methods be used to prevent catastrophic bone loss in individuals in which exercise provides insufficient protection during spaceflight. Disuse results in uncoupled bone remodeling; bone resorption is increased and bone formation is decreased. The optimal pharmacological intervention would be to normalize bone turnover. We are not aware of any individual agent capable of accomplishing this goal. We, therefore, have investigated the possibility of using combinations of pharmacological agents in a ground-based rat model for spaceflight. In these studies, we have investigated the actions of parathyroid hormone and Selective Estrogen Receptor Agonists, alone and in combination on bone mass and turnover in hindlimb unloaded rats. As in astronauts, hindlimb unloading results in cancellous bone loss in hindlimb unloaded adult male and female rats. Also, the bone loss is due to increased bone resorption and decreased bone formation. As a consequence, trabecular number and thickness decrease. We have shown that parathyroid hormone (PTH), a potent bone anabolic agent being investigated for treatment of postmenopausal osteoporosis, prevents the inhibitory effects of hindlimb unloading on bone formation and reduction in trabecular thickness. The SERM, Raloxifene, on the other hand, an anti-resorptive agent, reduces the decrease in trabecular number which follows hindlimb unloading. Combination therapy, with PTH and raloxifene, was more effective than either agent alone in preventing the skeletal changes.

Although these studies were directed at developing a method to prevent bone loss during spaceflight, the results are highly relevant to human disease. In the course of these studies, we identified PDGF-A as a putative causative factor for parathyroid hormone bone disease and established that antagonism of PDGF-A signaling can greatly reduce hypercalcemia, focal bone resorption, and osteitis fibrosa in an animal model for hyperparathyroidism. If confirmed in humans, drugs that target PDGF-A signaling could be used to treat patients with renal osteodystrophy as well as individuals with primary and other forms of secondary hyperparathyroidism. We have also shown that “bone specific” and “kidney specific” genes are expressed in white blood cells and respond in an analogous manner to PTH as in bone and kidney. These findings suggest that white blood cells can be used as a surrogate tissue to monitor positive as well as adverse responses to systemic factors in organs which cannot be directly evaluated without use of excessively invasive procedures.

In summary, our results support the concept that a pharmacological approach can be used to reduce the detrimental effects of skeletal unloading on bone mass, architecture and turnover and that it may be possible to monitor changes in bone metabolism during spaceflight by assaying gene expression in white blood cells.