These tests are designed to access the change in the response of mice to the effects of ionizing radiation and bacterial infection. Radiation causes complex, adverse changes in many tissues. The drugs to be tested are intended to alleviate these adverse effects of radiation and infections. Many pathogenic bacteria cause common responses and disease process in animals, which cannot be mimicked readily by substitutes.

Protocol 6- 68 Mice

Analgesics adversely affect undamaged hematopoietic cells and interfere with NADPH oxidase, an important phagocytic enzyme.

Opiod analgesics are known to cause immunomodulation.

Non–narcotic analgesics are anti-inflammatory and would interfere with the inflammatory responses of the normal tissue to *Shigella* and irradiation.

Protocol 7- 206 Mice

Analgesics will not be used because of their adverse effects on undamaged immune system cells, which would interfere with the end results of this study.

Protocol 8- 322 Mice

The Pro-Neuron compounds have already been tested in cell culture and final testing must be performed in intact animals.

Pro-Neuron has evidence that the pain relievers that would be expected to exert any analgesic effect in mice might also affect the activity of the compound in such a way as to confuse the experimental results of bone marrow transplantation and irradiation. The studies which uncovered this evidence were performed at Pro-Neuron and are proprietary in nature. Therefore, pain relievers will not be given, as this would ultimately result in a waste of animals and effort.

Protocol 9- 299 Mice

Analgesic compounds cause adverse effects on undamaged hematopoietic cells and interferes with NADPH oxidase, a key polymorphonuclear leukocyte involved in the ability of these cells to phagocytize and kill bacteria.

Opioid analgesics are immunomodulatory.

Protocol 10- 3978 Mice

Opioid analgesics are immunomodulatory non-narcotic analgesics with anti-inflammatory efficacy. These would interfere with the inflammatory responses of the hemopoietic tissues to infections and, therefore, cause adverse effects on undamaged hematopoietic cells. As a result, opioid analgesics would interfere with NADPH oxidase, a key polymorphonuclear leukocyte enzyme that is involved in the ability of these polymorphonuclear leukocyte cells to phagocytize and kill bacteria.

Protocol 11- 372 Mice; 44 Guinea pigs

The doses of ionizing radiation to be used are sub-lethal and will not cause pain or distress, however we can presume that infection will cause discomfort. In vaccination and therapeutic experiments we can presume that the majority of the vaccinated and a portion of the drug-treated animals will be protected and pain-free. However we will be testing efficacy following the unknown effects of radiation on immunity thus we will assume that all animals that receive radiation and bacterial challenge will be in the un-alleviated pain or distress category.

Protocol 12-401 Mice

All animals will receive a local anesthetic for pellet placement, however the drug delivery system being tested in this protocol involves subcutaneous release requiring the biological interactions at the tissue

level which would not be achievable in non-animal models. The implanted drugs may have a pain/distress alleviating action. Other drugs with known pharmacokinetic actions will masks the efficacy of these drugs and render the study invalid; so they should not be used.