GENE REGULATION IN PLURIPOTENT HUMAN STEM CELLS. James E. Trosko and C.C. Chang, Dept. Pediatrics and Human Development, 246 Natl. Food Safety and Toxicology Center, MSU.

"Reproductive" and "therapeutic" cloning of human stem cells has caught the attention of the public's eyes and ears (1, 2). The cloning of "toti-potent" stem cells for the expressed use of producing a human being ("reproductive" cloning) is not the objective of this proposal. Rather, with the theoretical possibility that tissue and organ replacement might be the result of cloning "pluri-potent" stem cells and understanding how the genes in "pluri-potent" stem cells are regulated to differentiate into the appropriate cells of the tissue/organ to be replaced, basic research on the fundamental regulation of genes expressed in both the pluri-potent stem cells and their differentiated daughter cells needs to be done. Aside from the academic interest in understanding the mechanisms of gene regulation in human stem cells, the rationale for applying this basic information for "tissue engineering" is because of the increasing frequency of various chronic diseases (Parkinson's; Type 1 diabetes; osteoporosis; liver diseases) due to the "aging" of the population and accidents (burn victims; spinal cord injuries, etc.), replacement of diseased or damaged tissue might restore normal function. In addition to the use of pluri-potent stem cells for basic research on gene regulation and tissue replacement, they will be useful cells for the study of human cancers since cancer cells are derived from pluri-potent stem cells. Since it is not possible to expose human beings to carcinogens, and exposure to these carcinogens to either rodents or non-target human cells *in vitro* are not good models for human carcinogenesis, the use of human pluri-potent stem cells, *in vitro*, might be the closest investigators will ever come to a mechanistic understanding of human carcinogenesis. In addition, "gene" therapy for the correction of genetic deficiencies will only be possible if the corrected gene is engineered into a pluri-potent stem cell. Finally, a very practical use of pluri-potent stem cells will be for screening potential nutrients, therapeutic, chemopreventive and pharmacological agents that will aid the differentiation of human stem cells or for the detection of the toxicities of chemical products that might interfere with the gene regulation in the stem cells.

These stem cells studies can be applied to several on-going inter-disciplinary projects (production of a semi-synthetic bone; calibration of DNA micro-array technology; production of insulin-producing human beta cells; *in vitro* screening assay to detect toxicity of environmental engineered remediated chemicals; etc.)

1. D. Thompson, "The biological mother lode", *Time*, Nov. 16, 1998, pp. 96-97.
2. R.A. Pedersen, "Embryonic stem cells for medicine", *Scientific American*, April, 1999, pp. 69-73.