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HJR 588: Medical, Ethical, & Scientific Issues Relating to Stem Cell Research Conducted in the Commonwealth

September 21, 2005

HIGHLIGHTS

- **Joint subcommittee presentations focused on the stem cell research activities in Virginia, particularly at the Commonwealth's three medical schools.**
- **Dr. Ogle of the University of Virginia Health System discussed the strengths and weaknesses of both adult and embryonic stem cells.**

The September meeting of the Joint Subcommittee Studying Medical, Ethical, and Scientific Issues Relating to Stem Cell Research Conducted in the Commonwealth focused on stem cell research activities in Virginia, particularly at the state's three medical schools.

UNIVERSITY OF VIRGINIA HEALTH SYSTEM PRESENTATION

The first speaker was Dr. Roy C. Ogle, a Professor of Neurosurgery, Cell Biology and Plastic Surgery, and the Director of the Center for Human Stem Cell Translational Research at the University of Virginia School of Medicine. Dr. Ogle's research interests include investigations of bone repair, including cranial bone repair with adipose-derived stem cells and regeneration of calvarial (dome of the cranium) defects with adipose-derived stem cells and multipotent stem cells from dura mater (the membrane covering the brain and spinal cord). Dr. Ogle's presentation covered stem cell research, as well as the use of cell-based therapies.

Characteristics of Stem Cells

Dr. Ogle began his presentation by explaining that stem cells can divide and differentiate into at least one other cell type. After clarifying the common terminology of embryonic stem cells, fetal stem cells, and adult stem cells, he stressed that better terminology would be pluripotent stem cells and multipotent stem cells. Stem cell research, he emphasized, holds promise for drug development and an improved understanding of gene control.

Dr. Ogle noted that each type of stem cell has strengths and weaknesses and embryonic and adult stem cell research are complementary. The strengths of embryonic stem cells are that they are pluripotent—capable of differentiating into any cell type and have infinite replication capacity. The weakness of the hES stem cell lines, which are currently approved for federal funding, is that differentiation is difficult to control. These stem cell lines also have the potential for tumor formation, cover only limited immunotypes, and are contaminated with bovine and murine proteins/ pathogens.

The strengths of adult multipotent stem cells are abundance, more uniform differentiation, restricted differentiation potential, and the potential for use in autologous therapies that use the patient's own tissue. The weaknesses of adult stem cells are limited replication potential and plasticity—the ability to build tissue. Adult stem cells are readily available in adipose tissue, because fat is plentiful and easy to collect. The resident stem cells are more abundant in adipose tissue than in bone marrow, which are more difficult and painful to harvest.

Sources of Stem Cells and Stem Cell Therapies

Some adult stem cell sources are blood, bone marrow, adipose tissue, and dura mater. Blood and blood components that are separated by a technique called apheresis contain at least four types of stem cells. Multipotent stem cells are important in bone marrow transplants, because they migrate to the recipient's bone marrow and differentiate to produce all types of blood cells, fat, cartilage, bone, muscle, adipose tissues, nerve cells, and glia—the supporting tissue of the brain and spinal cord.

Umbilical cord blood has some advantages over bone marrow and other blood. For example, cord blood is almost pure stem cells, and because it is young it lacks cell markers; it reproduces into mature, functioning blood cells faster and more effectively than in bone marrow stem cells taken from a donor. Also, because the T-cells at this young stage are not yet completely functional, there is less risk of severe graft-versus-host disease.

On the other hand, because of the presence of mature, fully functioning immune cells that exist in pancreatic islet cells transplanted to treat Type I diabetes, the risk of graft-versus-host disease is high. The treatment offers a cure, but it requires lifelong treatment with immunosuppressants.

Reconstructive surgery also uses adipose, muscle, blood vessels, and bone to mold new tissues, with the lasting results attributable to the stem cells in the transplanted tissue. Multilineage cells from human adipose, tissue have been shown to differentiate *in vitro* to become cells that may form fat, cartilage, muscle, and bone under the proper environmental conditions.

Cell-based therapies that depend primarily on stem cells include blood and blood product transfusions and infusions, bone marrow transplants, pancreatic islet transplantation, organ transplantation, reconstruction with autologous tissues, and fertility and contraception treatments. Bone marrow stem cells are used to replace diseased bone marrow in leukemias, aplastic anemia, and sickle cell anemia. These stem cells can also be used to rescue damaged bone marrow after radiation or chemotherapy in lymphomas, neuroblastomas, and breast cancers.

University of Virginia Stem Cell Related Activities

At the University of Virginia, embryonic stem cell research using mice is centered on kidney development, smooth muscle differentiation, and bone regeneration. Human embryonic stem cell research at UVA involves the study of smooth muscle differentiation and bone regeneration and uses only NIH approved cell lines. In 2004, 48 adult and 1 pediatric transplants were performed at the University. Over the past 12 months, 8 pediatric bone marrow, cord blood, and peripheral blood transplants were performed.

Tissue engineering procedures involving knee joints, nerves, and the cranial bones have been developed and are being advanced. Dr. Ogle showed slides of the regeneration of the skull of a 7-year-old child who had received treatment with autologous bone, adipose stem cells, and fibrin glue. He also showed slides of the reconstruction of facial atrophy of a 17-year-old German child. The remarkable results in both of these children are attributed to stem cell therapies. Pancreatic islet cell transplantation is performed on individuals having Type I diabetes.

Adult or multipotent stem cells are used as model systems in research laboratories at the University of Virginia in studies of myeloid leukemia, diabetes, breast cancer, blood vessel formation, heart function, renal failure, and fracture healing.

Benefits to Virginians from Stem Cell Research and Therapy

Dr. Ogle concluded his presentation by reviewing the potential benefits of stem cell research and therapy:

- Improved quality of health care.
- Reduction in the cost of health care and long-term care.
- Increased productivity.
- Economic development through biotechnology.

HIGHLIGHTS

- **Using only NIH approved cell lines, University of Virginia embryonic stem cell research is centered on smooth muscle differentiation and bone regeneration.**
- **Adult stem cells are used in research laboratories at the University of Virginia in studies of myeloid leukemia, diabetes, breast cancer, blood vessel formation, heart function, renal failure, and fracture healing.**

JOINT SUBCOMMITTEE STUDYING MEDICAL, ETHICAL, AND SCIENTIFIC ISSUES RELATING TO STEM CELL RESEARCH IN THE COMMONWEALTH

HIGHLIGHTS

- **Some alternatives to stem cell therapies are isolation of stem cells from extraembryonic fetal tissues, activation of endogenous stem cells, and reprogramming of adult cells to be like the embryonic cell.**
- **The goal of VCU's regenerative medicine initiative is to advance organ and cell transplantation, to develop biomaterials and devices and drugs and biologicals, as well as advance research and the clinical application of stem cells.**
- **Over 200 bone marrow transplants are performed each year at VCU, and the bone marrow transplant center is a recognized National Marrow Donor Program.**

He also listed the characteristics of a national immunotype library that would establish, characterize, and distribute embryonic stem cells. A national immunotype library would be created by a pending federal bill, HR 810.

VIRGINIA COMMONWEALTH UNIVERSITY SCHOOL OF MEDICINE PRESENTATION

Dr. Jerome F. Strauss, Dean of the Virginia Commonwealth University School of Medicine and Executive Vice President for Medical Affairs of the VCU Health System, came to VCU from the University of Pennsylvania Medical Center where he also serves as Director of the National Cooperative Center in Infertility Research. Dr. Strauss's research interests include regulation of steroid hormone biosynthesis, the genetics of polycystic ovary syndrome; trophoblast differentiation and placental endocrine function, biology of fetal membranes; molecular control of sperm motility; and embryonic stem cell differentiation. Dr. Strauss's presentation focused on the role of regenerative medicine at Virginia Commonwealth University.

Virginia Commonwealth University's strategic blueprint enables research in genetics, bioinformatics, the neurosciences, microbiology and immunology, cellular and molecular biology, and structural biology. VCU's mission is based on research goals relating to maternal and child health, behavioral medicine, pathogens and the environment, aging and metabolism, cancer, cardiopulmonary disease, and especially, regenerative medicine. The rationale for emphasizing regenerative medicine is to reduce unmet needs and health care costs and increase accessibility to quality health care. Dr. Strauss explained that the aging of Virginia's population and the concomitant burden of chronic disease, the expense of more invasive therapies, and the complex health issues created by trauma, war, natural disasters, and bioterrorism render regenerative medicine an attractive alternative.

Dr. Strauss elaborated on the appeal of embryonic stem cells, explaining that they are immortal, can be cloned, are undifferentiated, and have great developmental potential. He also discussed challenges to the development of embryonic stem cell therapeutics:

- Definitive proof of embryonic stem cell capabilities has not yet been discovered.
- Purity remains a problem in the approved cell lines because of contamination with bovine and murine cells.
- Limited number of available immunotypes.
- Apparent genetic instability and risk of cancer.
- Difficulties in production, as well as and the ethical issues.
- Ongoing controversy concerning whether embryonic or adult stem cells are more efficient.
- Alternative proposals for generating pluripotent cells.
- Appropriate development of preclinical models.
- Whether intellectual property is in the public or private domain.

Dr. Strauss mentioned several alternatives to stem cell therapeutics, such as isolation of stem cells from extraembryonic fetal tissues, activation of endogenous stem cells, chemical or genetic initiation of nuclear reprogramming of adult cells to be like theembryonic cell, and various biomaterials and devices.

Regenerative Medicine at Virginia Commonwealth University

Regenerative Medicine at VCU involves interaction between the transplant center, level I trauma center, burn center, and Reanimation Engineering Shock Center (VCURES). The goal of the regenerative medicine initiative is to advance organ and cell transplantation and clinical application and research in stem cells. Development of biomaterials and devices, as well as drugs and biologicals is also key. In addition VCURES, a multidisciplinary collaboration among clinicians, basic scientists, and engineers, is working on microvascular response to hemorrhagic shock, acute decompression illness, and blood substitute

development, which is particularly relevant to stem cell research.

Virginia Commonwealth University's Stem Cell Related Activities

At this time, VCU's stem cell related activities are focused on adult stem cells, alternative strategies, the interface between engineering and biology, and activation of endogenous stem cells. Over 200 bone marrow transplants are performed each year. The bone marrow transplant center at VCU is a recognized National Marrow Donor Program that performs both pediatric and adult transplants and bone marrow harvests. The organ transplant program includes liver, pancreas, kidney, pancreas-kidney transplants (for Type I diabetics with end stage renal disease), islet cell transplantation, heart, lung, and heart-lung transplants. VCU's Institute for Structural Biology and Drug Discovery and the Institute for Oral and Craniofacial Molecular Biology, among others, are housed at the Virginia BioTechnology Research Park.

EASTERN VIRGINIA MEDICAL SCHOOL

Dr. William J. Wasilenko is the Associate Dean for Research and Adjunct Associate Professor in the Department of Microbiology and Molecular Cell Biology at Eastern Virginia Medical School (EVMS). Dr. Wasilenko directs the EVMS Biomedical Sciences Ph.D. Program and is administrative director of the EVMS Biotechnology Workforce Training Program. Dr. Wasilenko's research interests include tumor and cell biology, signal transduction, and medical modeling and simulation.

Dr. Wasilenko began his presentation by noting that EVMA was founded in 1973 and is a much smaller institution than either the University of Virginia or Virginia Commonwealth University. EVMS, however, is highly regarded as a cutting edge institution in reproductive technology, and the medical school's Jones Institute is well known throughout the world for its infertility program.

Previous Stem Cell Research

In 2001, researchers at EVMS derived three embryonic stem cell lines from human blastocysts created through in vitro fertilization using donor gametes. Dr. Wasilenko clarified that no human embryonic stem cell research is being conducted at this time, and that the researchers who conducted and published the 2001 study are no longer at the medical school.

Current EVMS Stem Cell Related Activities

Currently, EVMS has stem cell related activities in regenerative medicine in diabetes. The Research Institute of the Strelitz Diabetes Institutes at EVMS has conducted pioneering research with the pancreatic islet neogenesis associated protein, commonly referred to as INGAP. In 1997, the Institutes announced the discovery of the INGAP gene, as part of ongoing research relating to genes and protein products that may cause pancreatic islet cells to regenerate and produce insulin. Subsequent work has been focused on the purifying and engineering of the gene. Phase II Clinical Trials are in progress on the results of some of the Institute's work. Other stem cell related activities relate to the treatment of various cancers, infectious diseases, and reproductive and infertility disorders. EVMS also collects cord blood, if the parents so wish.

WORK PLAN & NEXT MEETING

The Joint Subcommittee discussed plans for its final meeting, which will be held on November 15, 2005, and will include an additional presentation on Virginia stem cell activities, a public hearing, and a work session for determining findings. Pictures from the September meeting and materials and audio-streaming from the previous meeting may

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The Hon. R. G. Marshall, *Chairman*

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HIGHLIGHTS

- **Eastern Virginia Medical School is highly regarded as a cutting edge institution in reproductive technology, and the medical school's Jones Institute is well known throughout the world for its infertility program.**
- **The Research Institute of the Strelitz Diabetes Institutes at EVMS has conducted pioneering research with the pancreatic islet neogenesis associated protein, commonly referred to as INGAP.**