GREEK ORTHODOX ARCHDIOCESE OF AMERICA

Fearfully and Wonderfully Made: The Science

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The National Council of Churches position statement on biotechnologies, entitled Fearfully and Wonderfully Made, has a companion document called A Study Document on Human Biotechnologies. The Study Document is helpful in covering the basic descriptions of the technologies discussed in the recommendation statement, but my goal for this presentation is to go into more depth describing the technologies that are in use and under development. I will review in vitro fertilization, reproductive genetic testing, stem cell research, therapeutic cloning of human embryos, and genetic modification.

In *vitro* Fertilization

In vitro fertilization or IVF is a process by which germ cells (sperm and eggs) are removed from a male and female and put together in a dish. When the sperm fertilizes an egg, it begins to divide. After 3-5 days of development, some of the embryos are transferred back to the woman's uterus in the hopes of starting a pregnancy. Excess embryos may be frozen for future attempts at beginning a pregnancy. Excess embryos can also be donated to other infertile couples, donated for research purposes, or allowed to die.

Reproductive Genetic Testing

Genetic testing detects alterations in DNA or chromosomes. The results of genetic tests can be used to diagnose genetic disease, predict risks of disease, and identify carriers of genetic disease. Reproductive genetic testing can take place at five different stages of the reproductive process.

1. Carrier testing

Adults thinking about having children can undergo carrier screening if they are concerned that they may be at risk to have a child with a genetic disease. Carrier screening determines whether an individual could pass a copy of a disease gene to his/her child. Carrier testing is offered for numerous childhood diseases including, β Thalassemia (Mediterranean anemia), Cystic Fibrosis, and Sickle

Cell Disease. Couples who learn they are at risk of passing a genetic disease on to their children can choose to a) do nothing differently, b) adopt or choose not have children, c) conceive using donor egg or sperm, d) use preimplantation genetic diagnosis (described below), or e) use prenatal diagnosis and then make a decision about whether or not to abort an affected fetus.

2. Sperm sorting

In an ideal world, we would be able to prevent many genetic diseases by testing sperm and eggs before the point of conception, but genetic testing of reproductive cells requires killing the cell. The only current technology available that uses genetics to pick out certain reproductive cells prior to conception is sperm sorting for sex selection. Special dyes are introduced that cause the sperm to glow. The sperm with an X chromosome (which will result in a girl baby) glow brighter than the sperm with a Y chromosome (which will result in a boy baby). A device is used to sort the X and Y sperm to enhance the changes of creating a child of a specific sex. The sperm is then introduced into the uterus through artificial insemination or can be used to fertilize eggs that have been harvested from a woman using in vitro fertilization techniques.

3. Preimplantation genetic diagnosis

Preimplantation genetic diagnosis (PGD) is a genetic test of a single cell that has been removed from a 3 day old embryo. Embryos are created through an IVF process. A single cell from the embryo is carefully removed and tested. Embryos with specific genetic characteristics (or the absence of a gene for a genetic disease) are selected to transfer into a woman's uterus. PGD is typically used to avoid known risks for genetic diseases like Cystic Fibrosis, but it may also be used to select embryos that do not have a chromosome abnormality like Down Syndrome. Some women undergoing IVF for infertility are now being offered PGD to enhance their changes of getting pregnant and to avoid chromosome abnormalities. PGD can also be used to determine the sex of the embryos so that only those embryos of the desired sex are transferred to the woman's uterus. Finally, PGD has been used to ensure that the embryos that are transferred to the woman's uterus are a genetic match for an existing sibling. Children with some deadly diseases can benefit from blood transfusions from the umbilical cord of their siblings, but only if the sibling is a genetic match.

4. Prenatal testing

Prenatal genetic testing of a developing fetus during pregnancy can identify genetic alterations that may cause diseases. One prenatal genetic testing technique, amniocentesis, has been available for more than 20 years. A needle is inserted into the pregnant woman's uterus and amniotic fluid is extracted. Fetal cells found floating in the fluid are isolated and tested. Amniocentesis is done at 15-16 weeks gestation. A newer procedure is called chorionic villus sampling or CVS. A needle is used to take a small tissue sample from the placenta. This

placental tissue is examined for evidence of chromosomal abnormalities or genes that cause disease. CVS can be done at 11-12 weeks gestation. Prenatal testing is routinely offered to women over the age of 35, and is available to younger women who request it or who have a family history of genetic disease. Reasons to do prenatal testing include, a) pregnancy management, b) prenatal therapy, c) early post-natal therapy, d) emotional preparation, and e) pregnancy termination.

5. Newborn genetic screening

Genetic testing of newborn babies can identify some genetic diseases or conditions. Typically state public health programs decide which tests should be offered in order to facilitate early diagnosis and treatment.

Stem Cell Research

There are three classes of stem cells: totipotent, pluripotent, and multipotent. A fertilized egg is considered totipotent, meaning that its potential is total; it gives rise to all the different types of cells in the body plus the tissues needed to gestate the fetus, such as the placenta. Pluripotent stem cells can give rise to any type of cell in the body except those needed to develop a fetus. Stem cells that can give rise to only a small number of different cell types are generally called multipotent.

Stem cells are found in different parts of the body and have the remarkable potential to develop into many different cell types in the body. Serving as a sort of repair system for the body, they can theoretically divide without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential to either remain a stem cell or become another type of cell with a more specialized function such as a muscle cell, a red blood cell, or a brain cell.

Adult stem cells typically generate the cell types of the tissue in which they reside. A blood-forming adult stem cell in the bone marrow, for example, normally produces many types of blood cells such as red blood cells, white blood cells and platelets. Until recently, it had been thought that a blood-forming cell in the bone marrow would not give rise to the cells of a very different tissue, such as nerve cells in the brain. However, a number of experiments over the last several years have raised the possibility that stem cells from one tissue may be able to give rise to cell types of a completely different tissue, a phenomenon known as plasticity. Examples of such plasticity include blood cells becoming neurons, liver cells that can be made to produce insulin, and bone marrow stem cells that can develop into heart muscle. Therefore, exploring the possibility of using adult stem cells for cell-based therapies has become a very active area of investigation by researchers.

Human embryonic stem cells are derived from 4-5 day old embryos. At this point in development, the embryo looks like a hollow microscopic ball of cells called a blastocyst. The blastocyst includes three structures: the trophoblast, which is

the layer of cells that surrounds the blastocyst; the blastocoel (labeled with a “C” on the slide), which is the hollow cavity inside the blastocyst; and the inner cell mass (labeled “ICM” on the slide), which is a group of approximately 30 cells at one end of the blastocoel. This inner cell mass is what will eventually grow into the fetus. The trophoblast will grow into the placenta.

Human embryonic stem cells are isolated by transferring the inner cell mass into a plastic laboratory culture dish that contains a nutrient broth known as culture medium. The cells divide and spread over the surface of the dish. The inner surface of the culture dish is typically coated with mouse embryonic skin cells that have been treated so they will not divide. This coating layer of cells is called a feeder layer. The reason for having the mouse cells in the bottom of the culture dish is to give the inner cell mass cells a sticky surface upon which they can attach. Also, the feeder cells release nutrients into the culture medium. Recently, scientists have begun to devise ways of growing embryonic stem cells without the mouse feeder cells. This is a significant scientific advancement because of the risk that viruses or other macromolecules in the mouse cells may be transmitted to the human cells. All of the 22 embryonic stem cell lines available for research using federal funding are contaminated with mouse feeder cells.

After six months or more, the original 30 cells of the inner cell mass yield millions of embryonic stem cells. Embryonic stem cells are pluripotent – capable of growing into any type of cell in the human body. Embryonic stem cells that have grown in cell culture for six or more months without differentiating, are pluripotent, and appear genetically normal are referred to as an embryonic stem cell line. Once cell lines are established, batches of them can be frozen and shipped to other laboratories for further culture and experimentation.

Human embryonic and adult stem cells each have advantages and disadvantages regarding potential use for cell-based regenerative therapies. Of course, adult and embryonic stem cells differ in the number and type of differentiated cells types they can become. Embryonic stem cells can become all cell types of the body because they are pluripotent. Adult stem cells are generally limited to differentiating into different cell types of their tissue of origin.

Large numbers of embryonic stem cells can be relatively easily grown in culture, while adult stem cells are rare in mature tissues and methods for expanding their numbers in cell culture have not yet been worked out. This is an important distinction, as large numbers of cells are needed for stem-cell replacement therapies.

A potential advantage of using stem cells from an adult is that the patient's own cells could be expanded in culture and then reintroduced into the patient. The use of the patient's own adult stem cells would mean that the cells would not be rejected by the person’s immune system. This represents a significant advantage as immune rejection is a difficult problem that can only be circumvented with immunosuppressive drugs.

Embryonic stem cells from a donor introduced into a patient could cause transplant rejection. However, whether the recipient would reject donor embryonic stem cells has not been determined in human experiments. One of the properties that make embryonic stem cells advantageous, may also be a disadvantage. Embryonic stem cells live a long time; as a result, they have created cancerous tumors in animals.

There are numerous potential sources of embryonic stem cells. There are embryos leftover from IVF procedures that otherwise might be destroyed. There are IVF embryos that have stopped dividing and no longer have the potential to become a living human being even though the individual cells within the embryo are still alive. There is the possibility that stem cells could be harvested from embryos that are intended to be transferred to a woman's uterus, similar to a PGD biopsy (but this would be of no value to the human embryo, and would likely be unethical). There is the possibility that scientists could find a way to "cripple" reproductive cells before fertilization so that the resulting "embryo" did not have the potential to grow into a living human being. Human eggs have also been manipulated in the lab to start dividing without fertilization – a process called parthenogenesis. Parthenodes, the group of cells produced from parthenogenesis, do not have the ability to grow beyond a certain stage of development. Embryonic stem cells can be derived through cloning (discussed below). Finally, there is limited evidence that scientists may be able to manipulate adult stem cells to change them from being multipotent to being pluripotent. Many of these alternatives to obtain pluripotent stem cells are discussed in a report of the President's Council on Bioethics called Alternative Sources of Human Pluripotent Stem Cells. <www.bioethics.gov>

Cloning

Cloning techniques can be used to create genetic duplicates of an animal or to create embryonic stem cells for research purposes. Cloning an organism, such as an animal, creates an animal with the exact same nuclear genome as the first. The process by which clones and embryonic stem cells are made is called somatic cell nuclear transfer (SCNT).

For human SCNT, eggs are obtained from a woman who has been treated with hormones that cause her to generate and ovulate many eggs at one time. The eggs are collected, and the center of the egg that contains the nucleus or DNA is removed. Next, a somatic (body) cell collected from an adult donor is fused with the hollow egg. The nucleus of the somatic cell with its DNA becomes the nucleus and DNA of the egg. The egg containing the new genome is activated and coaxed to start dividing. After five to seven days in culture, the embryo (a clone of the somatic cell donor) develops to the blastocyst stage.

Reproductive cloning results when this cloned blastocyst is transferred into a uterus. If the transferred blastocyst implants to establish a pregnancy, the resulting baby is a clone of the somatic cell donor. There have been no credible

reports of any cloned human babies. Many animals, including mice, sheep, cats, and dogs have been cloned; however, hundreds of cloned embryos were needed to find the one that was truly totipotent and capable of growing into the organism. In addition, these cloned animals have experienced a host of medical problems.

Research cloning results when cells from the inner cell mass of the cloned blastocyst are removed and cultured in a dish to form a new embryonic stem cell line. These embryonic stem cells are pluripotent, meaning they have the ability to become all the different cell types normally found in an adult. A report that a Korean scientist and his colleagues had successfully produced embryonic stem cell lines from cloned human embryos in 2004 has been discredited. As of Spring 2007, there are no reports of the successful creating of embryonic stem cell lines from cloned human embryos, though research in the U.S. and abroad continues.

Genetic Modification

Genetic modification, sometimes referred to as gene therapy, changes the genetic content – the DNA sequence – of a cell, many cells, or a whole organism. Genetic modification is possible in bacteria, plants, and animals. There are two "types" of human genetic modification: somatic and germline.

Somatic gene therapy involves introducing a gene or gene segment into specific tissues or organs in patients to treat or cure an existing condition. Gene therapy has been successful only once in clinical trials, in treating X-chromosome linked severe combined immunodeficiency syndrome (X-SCID). However, some of the children who underwent this gene therapy developed leukemia as a result of the therapy. Somatic gene therapy alters the genetic make-up of some of the cells or tissues of the person treated, but can not be passed to future generations because the altered gene does not exist in the person's eggs or sperm (reproductive cells).

Human germline genetic modification (HGGM) involves introducing into a person’s germline or reproductive cells (the eggs or sperm) a gene or gene segment. Genetic modification of germline cells is meant to permanently alter the genetic make-up of future generations. In HGGM, the transferred gene is meant to replace and correct or overcome deleterious effects of an existing non-functioning or malfunctioning gene. Alternatively, one could add a new gene or genes to introduce a new and previously non- existent gene function. In addition to adding or replacing whole genes, HGGM could alter gene segments to enhance or abolish the function of an existing gene. No attempts of HGGM have been reported.