Testimony of

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I am Dr. Micheline Mathews-Roth. I am an associate professor of medicine at the Harvard Medical School, and a Physician at the Brigham and Women's Hospital: both institutions are in Boston, Massachusetts. I want to make it clear, however, that I am not speaking as a representative of either of these institutions, but as an individual physician and medical researcher. I do clinical and basic research on a rare genetic disease called erythropoietic protoporphyria (EPP). I developed what is the FDA-approved treatment for EPP (Annals N.Y. Acad. Science 1993; 691:127-138), and additionally, my collaborators and I have demonstrated that the mouse model of EPP can be cured by gene therapy of the bone marrow stem cells of these EPP mice (Nature Medicine 1999; 5:768-773).

The point of my testimony is to educate you by giving you the scientific information you need to know to understand exactly what is involved in therapeutic cloning, or as it is also called, research cloning, somatic cell nuclear transfer, or nuclear transplantation. The purpose of therapeutic cloning is to obtain embryonic stem cells to be developed into cells or tissues or organs to be used to treat a serious disease, such as Alzheimer's disease or diabetes or Parkinson's disease, that a particular patient has. Cloning is done by taking an oocyte (egg cell) from a female donor, and removing its nucleus. Then, a somatic cell (a body cell, not an egg or sperm cell) is obtained from the patient to be treated, and its nucleus is removed and is placed into that oocyte. The oocyte with its new nucleus, which has all 46 chromosomes, is the first cell, called a zygote, of the cloned individual. This zygote is then stimulated to start its growth and development. The cloned zygote's development is the same as that of a zygote produced by the union of egg and sperm by either sexual reproduction or by in-vitro fertilization (IVF) (see the "Information on Human Development" section and comparison table in the appendix of my written testimony, as well as the figure from the National Academy of Sciences publication on human cloning attached to the end of my testimony's text).

An important fact of embryology that is crucial for you to know is that each member of the human species indeed starts his or her existence as one cell, the zygote: and that this fact applies whether the zygote was formed by the union of egg and sperm in the mother's body or in a petri dish in the process of IVF, or by the processes of reproductive or therapeutic cloning. Again, look in the "Information on Human Development " section of the handout for the scientific references for this fact. So, it is scientifically incorrect to say that a human life begins in the mother's womb - by the time the growing embryo arrives at the mother's womb to implant in it, including a cloned blastocyst, it is already 5 to 6 days old! Again, check the "Information on Human Development" and "Timetable of Human Development" sections and the National Academy of Sciences figure of the handout for the scientific data on this.

There is an additional important scientific fact which must be remembered about embryonic stem cells, whether they are obtained from excess embryos produced by IVF or whether they are

obtained from embryos made by therapeutic cloning: the only way to obtain these cells at the present time is to destroy - that is, to kill - a growing young human of 5 to 7 days of life, the age at which its "inner cell mass", the group of embryonic stem cells that the growing young human contains, can be removed. To put it bluntly, in therapeutic cloning, a human being is made to start its life for the sole purpose of killing it when it gets to be 5 to 7 days old to obtain its useful parts, that is, its embryonic stem cells.

I want to point out that there is an error in scientific terminology in the S-303 bill: there is no such thing as an "unfertilized blastocyst". You must realize that the somatic cell nucleus introduced into the enucleated oocyte in the process of cloning was formed by fertilization - when the sperm from the father of the nuclear donor fertilized the oocyte of the mother of the nuclear donor. That nucleus, as mentioned above, has its full component of 46 chromosomes, as does the nucleus of every cell which will form when the cloned zygote starts to divide. If an oocyte is truly unfertilized, its nucleus will have only 23 chromosomes, and cannot divide - 46 chromosomes are necessary for normal cell division to occur. It should be obvious from this that a cloned baby or cloned cells for therapeutic cloning will indeed have two genetic parents - the mother and father of the nucleus donor. The clone is essentially the identical twin of the nuclear donor! There is a process called parthenogenesis, where either an oocyte or a sperm cell is stimulated to divide without being fertilized, but according to embryology textbooks, in the human species, only a few cell divisions would occur, because too many genetic defects would be present to allow full development: both a maternal and a paternal set of genes are needed for normal development in the human.

It should be obvious from the scientific data I have presented here, that producing embryonic stem cells from a blastocyst obtained from either therapeutic cloning or from excess IVF embryos results in the death of a very young human being, a "new genetically distinct human organism" (O'Rahilly and Muller). What we have to ask ourselves is: do we as a society really want to allow the bringing into existence of many young humans for the sole purpose of killing them to obtain their useful parts, even for the laudable purpose of alleviating the suffering of other members of our species? This is what sanctioning therapeutic cloning really means. And, it seems to me that doing this is a form of blatant discrimination - against very young humans - a vicious form of ageism, declaring that certain human beings are not worth protecting from deliberate killing..

Additionally, we have to remember that there is no guarantee that we will be able to master the process of directing embryonic stem cells from either cloned embryos or IVF embryos into developing into the kinds of differentiated cells or tissues we need for therapy without causing harm to the recipient of these cells or tissues: we are years away from achieving the goal of safe and effective embryonic stem cell therapy. The theoretical advantage of using cells and tissues derived from cloned embryonic stem cells is that there should be no immunological rejection of cells or tissues formed from them when these are transplanted into the nucleus donor to treat his or her disease, but this may not be completely true. Although by using the patient's own cells to produce the clone, one eliminates the problem of frank immunological rejection, immunological problems are not totally eliminated because of the presence of foreign mitochondria in the replacement tissue (i.e. the mitochondria of the enucleated oocyte, which will give rise to all the mitochondria in the cloned replacement cells or tissue). This can lead to some degree of

immunological problems in the patient receiving the transplanted cloned cells or tissue, perhaps such as inducing autoimmune problems. Additionally, since many mutations occur in the early embryo in the first few days of life, a cloned embryo would not be exempt from developing these mutations, which would be transmitted to the inner mass cells (i.e. the embryonic stem cells). In normal intrauterine development, the majority of these defective blastocysts would be eliminated because they can't develop to implantation and beyond, but when development is stopped at 5 to 7 days, these early mutations are not eliminated. There is the possibility that these mutations may cause problems in the differentiated cells developed from the defective clone's embryonic stem cells. Also, reprogramming and imprinting errors developed in the early embryo would probably remain in the stem cells developed from that embryo, and may lead to future problems, perhaps malignancies, in the cells and tissues developed from them. And also the problem of teratoma (tumor) formation still exists. The bottom line is that much more research must be done in animal models (mouse and especially primate) to demonstrate the safety of transplanted cloned tissue, let alone its efficacy, before any human studies are even contemplated.

Now for some ethical considerations. Physicians are not supposed to kill human beings of any age. Trying to justify the killing of what we know are very young (5 to 7-day old) human beings, even for the very laudable purpose of trying to cure disease, is ethically unacceptable: a good end (successfully treating disease) never justifies using evil means (killing a young human to get its cells) to obtain the good end. Additionally, one cannot justify such deliberate killing of young humans by invoking the known fact that about 40% to 45% of zygotes never implant anyway.

In addition, researchers who develop new drugs or therapies are obliged to give sufficient and accurate information about these drugs or therapies to the patients who will receive them, so that the patients may give truly informed consent to receiving these therapies. This applies especially to pioneering treatments like cell and gene therapy (regenerative medicine). For patients receiving IVF embryo-derived or therapeutic cloning-derived stem cells, to give truly informed consent, these patients will need to be clearly informed that a very young human (and in the case of therapeutic cloning, their very young identical twin) will need to be killed to obtain the stem cells to be used in their treatment, even though these stem cells will be differentiated into specific cells, tissues or organs. If these facts are not made completely clear to the patients receiving either source of embryonic stem cell-derived cells, tissues or organs, then the researchers will have failed in their obligation to the patients to provide enough information for the patients to give truly informed consent. It is possible that some patients would not undergo the procedure if they know that killing a young human is involved, and once they find this out, they may be upset enough to consider bringing legal action against the researchers. Thus, it is to everyone's advantage that the complete truth about the derivation of stem cells - that is, the well-established scientific facts about the beginning of a life, and its necessary destruction to get stem cells - be given to potential patients, so that each can make a truly informed choice about whether they wish to receive cells or tissues which were obtained at the cost of another human's life. Regenerative medicine is certainly the wave of the future, but the scientific and medical establishment, as well as the government, has the obligation to allow only those therapeutic investigations to proceed which will not result in the deliberate killing of any human being of any age during the process of developing the therapeutic modalities, and which will not further jeopardize the health of the recipient of the generated cells, tissues or organs.

So are we denying treatment to our patients if we deny them the use of embryonic stem cells? Absolutely not - because there is good evidence that there are certain kinds of adult stem cells which are proving to be very versatile in being able to be transformed into the different kinds of tissues which are needed to treat serious diseases. Already there are many examples in the medical literature: in fact Dr. Weldon prepared a list of such papers. In one very exciting example, Dr. Catherine Verfaillie has discovered cells which are found in the bone marrow which she calls multipotent adult progenitor cells (MAPCs) which can be made to differentiate into cells of all three embryonic layers - endoderm, mesoderm and ectoderm. She finds these in human marrow, as well as in mouse marrow. She finds that they do not form teratomas, tumors which are commonly formed by embryonic stem cells, and suggests that since the MAPCs can divide extensively without loss of their potential to diferentiate into different tissues, they may be an ideal cell source for therapy of inherited or degenerative diseases (Nature 2002; 418:41-49; see also pages 1 and 25 of that issue). Another exciting recent study is that of Dr. Eliezer Huberman, who has found a cell from peripheral blood which is also expandable and can be differentiated into endothelial cells, nerve cells and liver cells (Proceedings of the National Academy of Sciences 2003;100:2426-2431). Neither of these cell types seem to undergo fusion with mature cells, which makes them very exciting for potential therapeutic use.

In summary, do we as a country really want to sanction the deliberate production of tiny bona-fide members of our human species for the only purpose of killing them to obtain their useful parts, in spite of the fact that using adult stem cells is also effective? Even if embryonic stem cell therapies were shown to work better than using adult stem cells, which I think is doubtful in view of the work by Verfaillie, Huberman and other scientists, it would not remove the fact that we are using an evil means, the killing of very young members of our species, to attain the good aim of curing disease. You, our ligislative leaders, had better think long and hard about this - do you really want to allow this atrocity to happen?