October 14, 2013

Gail Dapolito and Bryan Emery
Cellular, Tissue and Gene Therapies Advisory Committee
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Via email: gail.dapolito@fda.hhs.gov, Bryan.Emery@fda.hhs.gov

Dear Ms. Dapolito and Mr. Emery:

We are writing in connection with the public meeting of the FDA Cellular, Tissue and Gene Therapies Advisory Committee scheduled for October 22-23, 2013 to discuss “oocyte modification in assisted reproduction for the prevention of transmission of mitochondrial disease or treatment of infertility.” We understand that this meeting will consider the advisability of allowing researchers working on mitochondrial replacement techniques (MRTs) to proceed with clinical trials of these techniques.

We strongly believe that these techniques should not be allowed to move to clinical trials.

MRTs pose overarching safety, efficacy, social and ethical problems. Scientific understanding of the complex interaction between nuclear and mitochondrial DNA, and the role of epigenetics on an individual’s phenotypic traits, is still at an early stage. MRT involves “constructing” an oocyte using the nucleus of one woman’s egg and the mitochondria from another woman’s egg – an evolutionarily unprecedented and biologically extreme technique that is more akin to cloning (somatic cell nuclear transfer) than to conventional in vitro fertilization. Noted scientists have argued that it is unlikely that such an invasive procedure will not cause unforeseen damage. Importantly, these risks would not be limited to the first generation of children undergoing the proposed modifications; all future generations would be at risk as well.

In addition, there are specific safety concerns about the state of the research under review. Researchers at Oregon Health and Science University (OHSU), using the variant MRT technique called maternal spindle transfer (MST), argue that it is safe enough to proceed with clinical trials on the basis of their work with macaque monkeys and human embryos. However, the three years over which the experiment with macaque monkeys has been conducted is too short a time to generate conclusive data, since mitochondrial diseases often develop late in life and since genetic alterations will be passed to subsequent generations. Additionally, more than half of the human MST zygotes had abnormalities that were not observed in the monkeys, leading the
researchers to conclude that human oocytes are more sensitive to spindle manipulations than monkey oocytes. Normal development of the macaques may not translate to normal development of humans.

It is critically important to note that those bearing the burden of the risks posed by MRT — the future children — are obviously unable to consent to the procedures. Attempting to produce children via MRT would amount to unethical experimentation on human beings on an unprecedented scale. In our view, this is a safety concern of such magnitude that it constitutes a dispositive ethical barrier.

Further, the clinical utility of these techniques is limited. While about one in 5,000-10,000 people suffer from mitochondrial diseases, only about 15% of mitochondrial disease is caused solely by mitochondrial DNA mutations; the rest is associated with nuclear DNA variants and how they interact with mitochondria. The notion that there are many women with mitochondrial diseases who could use these techniques to produce a genetically related child is unfounded; in fact the number who would be candidates is quite small. Furthermore, a safer alternative already exists. Because women can produce eggs with varying degrees of mitochondrial mutations, preimplantation genetic diagnosis (PGD) is proving to be effective for screening embryos resulting from in vitro fertilization, and implanting ones with a low risk.

Finally, MRT raises critically important social, ethical and policy challenges. MRT is a form of "germline" or heritable modification: it would change the genetic makeup not just of every cell in a child resulting from its use, but in future generations as well. Permitting such germline modifications would mean crossing a bright technical and policy line that has been observed internationally for the past three decades, since the prospect of gene therapy was first presented. Although proposed initial applications are for purposes of preventing disease conditions, it could be prohibitively difficult to prevent subsequent applications intended to modify and enhance cosmetic, behavioral, cognitive and other phenotypic traits.

We appreciate the distinction between replacing mitochondria (and the DNA they contain), on the one hand, and attempting to control traits associated with nuclear DNA, on the other. But it is clear that allowing any sort of manipulation of the genes of future children and future generations could open the door to additional germline interventions. Many commentators who have carefully examined these issues recognize that we must put responsible policies in place now to prevent a new era of high-tech eugenics.

More than 40 countries world-wide, including those with the most highly developed biomedical sectors, have adopted policies prohibiting human germline genetic modification. Furthermore, biomedical researchers in countries that have not yet adopted formal public policies on germline modification have observed this prohibition. This emerging global policy consensus has been supported by the major international biomedical and bioethical organizations and councils. We believe that it would be unconscionable for the United States to unilaterally contravene this global consensus regarding human germline genetic modification.

Considering and weighing the benefits of these techniques to a small number of parents who want a genetically related child, against the significant risks to that child and the profoundly disturbing implications for the future of the human community, we believe that the case for maintaining the current proscriptions on human germline genetic modification is clear. We
therefore strongly urge the FDA not to allow the techniques under consideration to move to clinical trial.

Sincerely,

Marcy Darnovsky, PhD
Executive Director