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ANT-OAR fails on all counts

There are serious scientific and ethical flaws in the recent ANT-OAR approach to harvesting embryonic stem cells

By W. Malcolm Byrnes and José Granados

The altered nuclear transfer-oocyte assisted reprogramming (ANT-OAR) proposal has serious scientific and philosophical flaws, and it is not a morally acceptable means of obtaining embryonic stem cells.

OAR's origin in ANT

A statement supporting ANT-OAR—or simply OAR—was adopted by a group of 35 mainly Christian scientists, bioethicists and moral theologians in spring of 2005 as a way around an ethical problem associated with the original ANT proposal.

The original ANT procedure was proposed by Dr. William Hurlbut, a physician and a consulting professor in the Program in Neuroscience at Stanford University. ANT involves disabling the gene for CDX2, a developmentally-important *transcription factor*, or protein that regulates the expression of genes in the nucleus. The ANT-derived *CDX2*-deficient embryo that is created develops essentially normally until the blastocyst stage, which forms four to six days after the nuclear transfer event that initiates its existence.

At this stage, however, the blastocyst becomes profoundly disorganized in its outer layer. But the blastocyst's inner cell mass, which

contains embryonic stem cells, remains intact. These stem cells can be removed and used for medical research.

What was the reasoning used to support ANT in its original formulation? First, its proponents rightly pointed out that a respect for life recognizes the human status of the embryo from the moment of fertilization onward. With fertilization, a new entity appears that is directed by an intrinsic teleological process toward the formation of an adult person. This process of formation is a continuum: No single moment can be found in which a substantial change occurs, a change that allows us to speak of a human being only after this moment, and not before.

But, ANT proponents argue, since the final product of the process will not be a human being but only a disorganized clump of cells, the entire teleological process is different. From this, they conclude that the entity is not human.

There is, however, an important objection to this reasoning. Before the blastocyst stage, the ANT entity must go through developmental stages that are indistinguishable from those of a normal embryo. Could we not say, then, that we have created a defective embryo that is from the outset prevented from developing fully?

Moreover, what would happen if a different genetic modification were introduced, one that allowed the entity to develop for, say, a little more time before its development became chaotic and disorganized? When would this “little more time” become “too much time” for the procedure to be ethically acceptable?

The problem here is that one ends up trying to determine the exact "enough" point, whether temporal or structural, beyond which the entity would have a degree of organization that characterizes it as human. But this goes precisely against the main assumption of the position that respects human life from its beginning, that the process of development is a continuum. It is therefore impossible to find such a point.

Scientific problems with ANT-OAR

OAR was put forth in an attempt to overcome the ethical problem associated with the time delay inherent in ANT. This would be achieved by engineering an entity that would be defective *from the very beginning*. As with ANT, OAR would involve the transfer of a genetically altered somatic cell nucleus into an egg from which the nucleus has been removed.

However, OAR would be different in the sense that it would involve the immediate overexpression of the transcription factor NANOG from both the newly-introduced nuclear DNA and from RNA injected into the egg before transfer. Studies in mice show that expression of NANOG normally occurs in the morula and blastocyst stages—but not earlier—where it acts to maintain pluripotency or "stemness" and prevent differentiation into different cell types.

The result of the OAR procedure, say supporters, would be a cell that, once created, moves backward from the differentiated state of a somatic cell to a multipotent state and finally to a pluripotent state. It never reaches the totipotent state of an embryo because the presence of NANOG and reprogramming factors in the oocyte cytoplasm prevent it from doing so. Thus,

the cell that is created would be a pluripotent stem cell and never be an embryo at all. Or so the thinking goes.

But this thinking is scientifically incorrect. It is naïve to assume that overexpression of NANOG in a cloned one-celled embryo would reprogram it to the pluripotent state. Why would one *a priori* think that NANOG overexpression would have *exactly* the desired result—creation of a pluripotent stem cell? There is no evidence that it would.

Indeed, the opposite seems to be true. As more and more is being learned about pre-implantation mouse embryos, the particular role of NANOG in development is becoming clearer. Collectively, what these studies are showing is that NANOG functions within a certain *developmental context*. Scientific intuition tells us that expression of NANOG outside of this context in the newly cloned embryo will not lead to a stem cell, but will lead to either an entity that is so grossly defective that it dies early on or, due to the robust reprogramming ability of the oocyte cytoplasm, an embryo that is unaffected by the presence of NANOG and therefore develops essentially normally.

Ethical problems

But let us put aside our scientific concerns with OAR for the moment, and assume that OAR actually *could* work to produce stem cells. The question then becomes whether OAR overcomes the ethical problem raised by the time delay inherent in ANT, whether the procedure avoids the creation of an embryo or simply makes a defective one.

At first glance, this seems to be the case, because the OAR-derived entity appears to share no developmental stage in common with a normal

human being. Ostensibly, the genetic and biochemical modifications that are introduced prevent the formation of an embryo even at its earliest stage (that of a totipotent cell). According to this argument, the OAR-derived entity, from the very beginning, would never share any stage of development with a normal embryo.

An ethical problem associated with OAR comes into view, however, when we compare OAR with cloning, or somatic cell nuclear transfer (SCNT). When do we start to have a human being in SCNT? SCNT differs from normal fertilization because there is a period of nuclear reprogramming—unique to cloning—that occurs after the somatic cell nucleus has been introduced into the oocyte lacking a nucleus.

Now, if we use the teleological argument of the position that respects life, then the introduction of the nucleus is the *initial event* from which we have a unified teleological process. This means, in turn, that the reprogramming process that occurs during SCNT is part of the process of development of a human being, albeit a cloned one. Thus, the OAR entity *does* share the initial stages of its formation (the first steps of the process of reprogramming) with another entity (the SCNT product) that has to be considered human.

From a philosophical standpoint, then, what we have with OAR is the creation of an entity that starts off just like any cloned embryo. From this starting point, it undergoes at least the initial stage of a reprogramming process that is part and parcel of cloning.

If we assume that NANOG can successfully change the cloned cell into a pluripotent cell, then this process must take some time. During this time the OAR-derived entity is as human as a cloned embryo. Furthermore, even if

NANOG succeeds in diverting the developmental trajectory of the newly cloned entity toward formation of a pluripotent stem cell, the *subject* upon which NANOG acts will be an embryo that is trying to put itself through the paces of normal human development.

What all this means is that OAR is equivalent to ANT. In both ANT and OAR we have altered or introduced a factor that has its transforming effect some time later in the development of the entity. The only difference is the amount of time that has elapsed: It is shorter in the case of NANOG, which (hypothetically) changes the endpoint of an early reprogramming process, as opposed to CDX2, whose absence is felt later at the blastocyst stage. The ethical objection that applies to ANT also applies to OAR.

Back to square one

From these arguments, we can draw at least two conclusions about OAR. First, it is unlikely to work from a scientific point of view. But second, even if it could work, it would be unethical because the entity created would share in its initial stages of development those of a cloned human embryo, which is a human being.

W. Malcolm Byrnes is assistant professor of biochemistry and molecular biology at the Howard University College of Medicine in Washington, D.C. José Granados is assistant professor of theology at the John Paul II Institute for Studies on Marriage and Family at The Catholic University of America in Washington, D.C.