A Way Around the Cloning Objection Against ANT? A Brief Response to the Joint Statement on the Production of Pluripotent Stem Cells by Oocyte Assisted Reprogramming

• **Adrian J. Walker** •

"OAR, like all the other methods of ANT, is not the creation of stem cells without the creation of an embryo, but the cloning of a modified embryo. OAR, in a word, is cloning with a twist."

Oocyte Assisted Reprogramming (OAR) is the name of a variant of the Altered Nuclear Transfer (ANT) proposal that has recently been advanced under the aegis of a number of respected, mostly "pro-life" scholars in a short Joint Statement describing and endorsing the new procedure.[1] The endorsers present OAR as an improvement on the hitherto existing proposed methods of ANT, which aim to produce an entity that "undergoes or mimics embryonic development"—and

[1]Hadley Arkes et al., "Production of Pluripotent Stem Cells by Oocyte Assisted Reprogramming. Joint Statement." A text of the Joint Statement can be found at http://www.eppc.org/publications/pubID.2374/pub_detail.asp. All citations in what follows are from the Joint Statement.

Communio 32 (Spring 2005). © 2005 by *Communio: International Catholic Review*

so cannot entirely quiet the suspicion that we are dealing with the cloning of defective embryos after all. OAR, by contrast, seeks to obviate any suspicion of cloning by "*immediately* produc[ing]" "a pluripotent cell that could be cultured to establish a pluripotent stem cell line." OAR, in other words, would forestall the cloning objection against ANT by directly producing a cell that itself is already a pluripotent stem cell and was never anything else, certainly not anything that could be confused with an embryo. OAR, like a savvy entrepreneur, seeks to make ANT airtight against the charge that it is cloning with a twist by springing right from investment (the donor cell genome) to profit (pluripotent stem cell) while cutting out the developmental middle man altogether.

The OAR proposal hangs on the claim that "the nature of each cell depends on its epigenetic state, i.e., which subset of the approximately thirty thousand human genes is switched on or off and, if on, at what level." Thus the fact that ANT brings into being a cell having a complete human genome is not yet sufficient to define that cell as a totipotent human zygote. The additional, decisive factor is still missing. That factor is the "epigenetic 'reprogramming'" performed by the oocyte cytoplasm. Left to itself, as it would be in cloning, "the oocyte cytoplasm is sufficient to reprogram the somatic nucleus to a totipotent state." The point of OAR, accordingly, would be precisely *not* to leave the enucleated egg to itself, but to steer its epigenetic reprogramming activity to the immediate production of a pluripotent stem cell without ever "passing go"—without ever creating a one-celled embryo—in the process. How would OAR do this?

The basic strategy of OAR unfolds in two steps:

(1) Step One: the scientist identifies the "key transcription factors" whose expression "positively defines and distinguishes mere pluripotent cells from embryos." He pins down, in other words, one or more genes that have to be turned on for the cell to do what a pluripotent embryonic stem cell typically does—"for establishing and maintaining the pluripotent behavior of ES cells." One possible candidate, among several, for this job is the gene Nanog, which recent research has shown to be a "positive factor instructing cells to be pluripotent, i.e., to behave like an ES cell."

(2) Step Two: the scientist pre-sets the enucleated egg cell to re-program the donor cell nucleus genome in the desired direction. How? By getting Nanog (and/or similar factors) to express at sufficiently high levels in the donor cell and/or introducing the

mRNA for Nanog (and/or the similar factors) into the enucleated egg cell—and all this *prior* to the actual nuclear transfer. Thanks to Step Two, then, the scientist—relying on the primacy of epigenetics in determining cell identity—would "ensure that the epigenetic state of the resulting single cell would immediately be different from that of an embryo and like that of a pluripotent stem cell: the somatic-cell nucleus would be formed into a pluripotent stem-cell nucleus and *never* pass through an embryonic stage."

The Joint Statement endorsing OAR as the favored method of ANT contains an oblique retraction of the strategy that its architects first laid before the public in December 2004.[2] This strategy, as the Joint Statement describes it, would "achieve its objective . . . by a gene deletion that precludes embryonic organization in the cell produced." The problem with this strategy, however, is that it entails the fallacious inference that the failure of the ANT entity's hitherto embryo-like physical organization at point B means that it was never an embryo at point A either. That scientists plan the entity's organizational breakdown at point B before it even came into being does nothing to improve this bad logic. All this fact need really mean is that at point A there was an embryo, but that it was destined through biochemical engineering to die an untimely death at point B. The original ANT strategy seems more to produce embryos with timed genetic defects than no embryos at all.

OAR seems to offer a remedy to this conceptual *impedimentum dirimens* to the acceptability of the original ANT strategy insofar as it uses the "power of epigenetic reprogramming in combination with controlled alterations in gene expression" to skip over the embryonic middle man, or anything that might look too suspiciously like him. The question we need to ask, then, is this: does OAR really bypass or remedy the conceptual flaw in the original ANT strategy—or does it not rather just repeat it in a subtler way?

When one cuts through the complex jargon in which the Joint Statement swathes the OAR proposal, it boils down to this: instead of *inhibiting* the timely expression of, say, Cdx2 so as to keep the new cell from continuing to develop normally beyond a certain point, as in the original proposal, let us *encourage* the premature

---

[2]See William B. Hurlbut, "Altered Nuclear Transfer as a Morally Acceptable Means for the Procurement of Human Embryonic Stem Cells," paper presented to the President's Council on Bioethics, 3 December 2004.

expression of, say, Nanog to give this new cell "the distinctive molecular characteristics and developmental behavior of a pluripotent cell." But whether the method is negative or positive, and whether the effect is early or late, in both cases we are dealing with an engineered defect that prevents what is in fact a one-celled embryo from expressing itself normally as such. OAR is just the old ANT in a new package, which consists in making a totipotent zygote act like a pluripotent stem cell (to some unspecified extent—certainly not totally and in every respect). Such is my thesis. In order to state briefly why I think it is true, I would like to apply to the question at hand the argument that I lay out at greater length in the companion to the present article, "The Primacy of the Organism. A Reply to Nicanor Austriaco," which the reader may consult at his leisure in this number of *Communio*.

Father Austriaco, like the endorsers of the Joint Statement (of whom he is also one), seeks to undermine the charge that ANT is cloning by citing the supposed fact that epigenetics determines cellular identity.[3] In response, I try to show that epigenetics, being logically and ontologically posterior to the substantial actuality of the human organism, can determine the phenotypical manifestation of the one-celled embryo, but not its (ontological) identity as such. Given this primacy of the embryonic organism in the normal case, however, it follows that we are not entitled to claim non-embryonic status for what ANT brings into being simply because we have pre-engineered it out of the "epigenetic state" we associate with the phenotype "zygote." Such a claim could be legitimate only if we could show, on grounds other than what ANT does to its product's epigenetic state, that the procedure hasn't actually brought a new human being into existence. The chances of doing so are slim. Here is why.

The Joint Statement says that the egg cell reprograms the epigenetics of the donor cell nucleus genome. This is misleading. If any such epigentic reprogramming occurs, it can occur only *once the egg cell and the donor cell nucleus have actually fused*. In other words: the fusion comes first, and the epigenetic reprogramming comes only afterwards. This is true no matter how small the interval of time is

---

[3]The only difference between Father Austriaco's argument and the Joint Statement is that Father Austriaco does not explicitly mention the possibility of directly creating a pluripotent cell in place of the totipotent zygote.

that elapses between the genesis of the new entity and its pluripotent stem-cell-like manifestation. Even if, theoretically, the interval were reduced to zero, the fusion of the egg cell and the donor cell nucleus would come logically and ontologically first. OAR can therefore never be the actual immediate creation of a pluripotent stem cell, but always only the modification of the phenotype/developmental path of a—logically and ontologically—already existing human organism. OAR may be able to reduce the time lapse between the genesis of the totipotent zygote and its confinement within its pluripotent straitjacket to what seems to be zero. But it cannot transform the fusion of the enucleated egg cell and the donor cell nucleus into anything other or less than a mimicked conception, a mimicked conception resulting in a human organism that is already in existence before anyone can pronounce that it was never there.

OAR is parasitic on nature's way of procreating new human beings. The Joint Statement, like all the other accounts of ANT of which I am aware, pays scant attention to this parasitism. It speaks confidently of control over nature, not of dependence on it. The fact of the matter, however, is that OAR is always more dependent on nature than it is in control of nature. Why? We cannot pull pluripotent stem cells out of thin air, or even, for that matter, assemble them from pre-existing parts. All we can really do is modify the developmental process that leads to them—which means that, so long as we want human pluripotent stem cells, we have to have the human organisms that undergo the development. Since OAR is not a proposal, say, to regress adult stem cells to a pluripotent state without recourse to nuclear transfer, it must be the case that OAR would get the organisms it needs by actually bringing them into being itself. Whether proponents acknowledge it or not, then, OAR is conceptually parasitic on mimicked conception. Which leads me back to my thesis: OAR is not the creation of a pluripotent stem cell from scratch, but the phenotypical/developmental modification of an existing human organism brought about by mimicked conception. OAR, like all the other methods of ANT, is not the creation of stem cells without the creation of an embryo, but the cloning of a modified embryo. OAR, in a word, is cloning with a twist.

Despite its differences from other forms of ANT, then, OAR is burdened with the same conceptual flaw as they. For OAR, like all the other forms of ANT, is parasitic upon conception, even as it simultaneously claims that the manipulation of factors (in this case epigenetic factors) that are logically and ontologically posterior to

conception ensures that no conception has in fact taken place. The plausibility of this shell game rests entirely on denying this logical and ontological priority, hence, on some kind of reduction of the substantial ontology of organism to its developmental process, of the whole to the parts—in a word, on some kind of mechanism. I freely grant, of course, that OAR might succeed in producing something that looks enough like a pluripotent stem cell to satisfy proponents of the procedure that it "works." What I am arguing is that their satisfaction would nevertheless depend, not on the empirical evidence *per se*, but rather on the tacit reductionism/mechanism (expressed, for example, in the claim that epigenetics has primacy in determining cellular identity) that undergirds the proposal of ANT/OAR and that guides their perception and description of the empirical evidence.

Defenders of ANT still owe us a non-mechanistic, non-reductionistic account of how it is that empirical research could by itself "establi[sh] beyond a reasonable doubt that oocyte assisted reprogramming can reliably be used to produce pluripotent stem cells." Moreover, given the logical and ontological priority of organismic identity over epigenetics, they cannot base such an account on the claim that epigenetics is the primary determinant of cellular identity—without question-begging, that is. Of course, it is just this question-begging that both lends OAR its plausibility and causes its proponents to miss the extent to which the procedure is parasitic on mimicked conception, and so on the production of a new human organism.[4]

The problem with OAR, then, is the problem with ANT in general: it parasitizes conception, while using bad metaphysics (the reduction of ontology to development, whole to parts), backed up by question-begging, to deny that such a conception has taken place. This problem affects not only the previous versions of ANT, not only OAR, but all conceivable versions of ANT—so long, that is,

---

[4]The Joint Statement observes that the mere presence of a human genome in a cell does not automatically bestow on it the status of a complete human organism. This is true, but it is no rebuttal of my argument, the point of which is not simply that new ANT-produced cell has a complete human genome, but that this genome got there by means of an event resembling conception. Proponents of OAR/ANT must explain how what looks for all the world like a mimicked conception either is not one or in any case does not count against the intuition that the *conceptus* is really a human embryo. And they cannot base such an explanation on the supposed primacy of epigenetics in determining cellular identity—at least not without question-begging.

as they rely on nuclear transfer and use it as a step towards getting human pluripotent stem cells. I repeat: we cannot assemble pluripotent stem cells or pull them out of thin air, we can only get them from organisms. And since we are not talking about already existing adult organisms—as we would be if it were a question of, say, regressing adult stem cells to a pluripotent stage without using anything at all like nuclear transfer—then we must be talking about the creation of new embryonic ones. OAR, like every other conceivable form of ANT, cannot get around this adamantine fact. It can only appear to do so—with the help of bad metaphysics and faulty logic.

I must confess that I find the tenacity with which proponents of ANT pursue the goal of "pluripotent stem cells without embryos" troubling. I understand, of course, that they are motivated by a laudable desire to replace current methods of embryonic stem cell research with a morally acceptable alternative. Nevertheless, their willingness to invade, and to attempt to refashion, the beginnings of human life seems an odd way to go about saving it. Despite their praiseworthy wish to forestall the creation and destruction of human embryos for research purposes, proponents of ANT end up conceding much too much to the mentality that underlies and legitimates that practice in the first place. After all, if ANT's defenders really had the power over nature's way of procreating that they—under the cover of bad metaphysics and faulty logic—claim to have, would this not strip procreation, and the human life that flows from it, of any intrinsic dignity that could not be bestowed and removed by the fiat of the scientist? If we consider that embryonic stem cell research is much less scientifically promising than adult stem cell research, and that the larger scientific community is likely to react to OAR/ANT with dismissive scorn, as it has in fact already begun to do, then one has to wonder if proponents of OAR/ANT have not sold their birthright for a mess of pottage. True, many, if not most, of the scholars who have endorsed the Joint Statement proposing OAR are publicly identified with the Catholic Church's Magisterium on the whole range of contemporary issues affecting marriage, sex, and procreation. I have nothing but praise for the work that they have hitherto done in these areas. Precisely for this reason, however, their support of ANT/OAR threatens to weaken the integrity of the Church's witness to the value of the embodied human person vis-à-vis the "culture of death." □

Adrian J. Walker *is an associate editor of* Communio.