

JOINT STATEMENT ON THE OOCYTE ASSISTED REPROGRAMMING (OAR) PROPOSAL: A RESPONSE TO CRITICISMS

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“Nothing other than a cell with
the required epigenetic primordia is capable
of receiving a human substantial form.”

Since publishing a joint statement signed by 35 ethicists and scientists, there has been some criticism of the position.¹ As signatories of this statement we would like to respond to some of these criticisms. First, however, for those who may not have read the original statement or the critiques, we will briefly summarize them.

Our original statement outlined a proposal for using a form of Altered Nuclear Transfer (ANT), in other words OAR, which we believe would allow the production of pluripotent stem cells without creating and destroying embryos. We must emphasize that this proposal is for initial research using only non-human animal cells. We stated that further research with human cells would only be allowed to proceed if it can be established beyond a reasonable doubt that no embryo is formed. Our initial analysis seemed to indicate that this was a distinct possibility.

¹“Production of Pluripotent Stem Cells by Oocyte Assisted Reprogramming,” *Origins* 35, no. 8 (7 July 2005): 126–128.

To put it briefly, OAR is based upon our position that the nature of a cell is defined by its epigenetic state, in other words, which subset of the approximately 30,000 human genes are turned on or off and if turned on, at what level. The protein called “Nanog” is present in pluripotent embryonic stem cells, is not present in the oocyte (ovum) or zygote (single cell embryo), but is present in the inner cell mass (ICM) of the blastocyst (approximately a week-old embryo). Thus, this OAR proposal will evaluate whether it is possible to reprogram a somatic nucleus inserted into an enucleated oocyte, to immediately produce pluripotent stem cells by turning on the relevant gene in chromosome 7, and, thereby, bypassing the formation of an embryo.

There have been several criticisms leveled against this proposal. The first was published by *Communio* editor, David Schindler.² A second critique was proffered by neurologists William Burke, M.D. and Patrick Pullicino, M.D. together with ethicist Fr. Edward Richard published in the web-based magazine *Women for Faith and Family*, on 15 August 2005 and entitled, “Is Oocyte Assisted Reprogramming (OAR) a Moral Procedure to Retrieve Embryonic Stem Cells?”³ A third is by Catholic journalist Vivian W. Dudro, published in the online magazine *Ignatius Insight*.⁴ Dudro’s article is essentially a popularization of the first two critiques. There is some overlap among these articles, especially the third with the first two. Here we have space only to briefly summarize some of the most salient criticisms.

The first four come from Schindler (however, the first argument is also put forth by the other two articles). The first argument is the assertion that we are being, albeit unwittingly,

²David L. Schindler, “A Response to the Joint Statement, ‘Production of Pluripotent Stem Cells by Oocyte Assisted Reprogramming,’” *Communio* 32, no. 2 (Summer 2005): 369–380.

³William Burke, Patrick Pullicino, and Edward Richard, “Moral Dilemmas in Stem Cell Research: Is Oocyte Assisted Reprogramming (OAR) a Moral Procedure to Retrieve Embryonic Stem Cells?” *Voices* 20, no. 2 (15 August 2005) available at <http://www.wf-f.org/05-2-OAR-StemCells.html>; accessed 26 October 2005.

⁴Vivian W. Dudro, “Cells and Souls: Is OAR an Acceptable Cloning Technique for Pro-Lifers?” *Ignatius Insight* online magazine (23 August 2005), available at http://www.ignatiusinsight.com/features2005/vdudro_oarcells_aug05.asp; accessed 25 October 2005.

mechanistic in presuming that the epigenetic state defines the being, or ontology, of a cell. The contention is that the status of the entity created by the insertion of the reprogrammed somatic nucleus into the oocyte may very well be a deformed embryo rather than simply a pluripotent stem cell. In other words, the ontological status of this entity, which comes about by a process which mimics conception, cannot be determined by the empirical evidence which would result from any experimentation. This procedure would then be no different from other ANT proposals which simply limit the ability of the embryo to develop. A second argument prescind from the first but focuses on the fact that OAR presupposes that we can exhaust the knowledge of the beginnings of human life through scientific inquiry and thus by using this knowledge OAR supposes that it can control life's origins. However, the mystery of the human person cannot be exhausted in this manner. We do not and cannot exhaustively know or control the beginning of human life, thus OAR is fundamentally unjustifiable. The third issue is formulated primarily in a question that should be answered. One big difference between adult stem cells and embryonic stem cells for stem cell research is that the former have reached their finality naturally while the latter is an attempt to artificially force the cells into a particular finality *in vitro*. The question is whether the complete failure of progress in workable treatments with embryonic stem cells suggest a fundamental but unobservable difference between them that is perhaps unreachable through empirical means. Schindler stresses that this is not an appeal to ignorance but rather an admonition to caution. Finally, he asks whether the apparent tacit capitulation to the use of the oocyte as a tool for production and harvesting of parts is consistent with the Church's theology of the body because the oocyte is bound so intimately to the body and its reproductive organs. Given these issues which have not seemingly been addressed, Schindler asks if we have not been too hasty in publicly advocating this proposal by appearing to short-circuit the discussion.

The second article, in addition to its agreement with Schindler's first issue, adds four mostly technical (biological) issues associated with OAR. The first suggests that OAR underestimates the reprogramming power of the oocyte and thereby finds that it is doubtful that simply controlling the Nanog transcription factor will prevent it from reprogramming the donor cell to totipotency. The second, which is a biological analog to Schindler's first issue, is that

OAR assumes that the presence of Nanog indicates the overcoming of totipotency. This critique claims that what Nanog does is to prevent the zygote from differentiating past a certain stage of development so that OAR does no more than produce a crippled embryo incapable of developing into a healthy infant. The third criticism is that the term pluripotent is ambiguously applied and not universally employed by scientists. In fact, they say that distinguishing pluripotency from totipotency is making a distinction without an essential difference, making it an unworkable criterion for determining whether or not the entity formed by OAR is a zygote. Finally, they present the issue of statistical uncertainty and the current limits in determining the presence or absence of the protein, Nanog. Current detection limits together with the limited statistical uncertainty of ascertaining the non-presence of Nanog does not approach the moral certainty required for OAR, assuming that the other issues can even be resolved. Again, the final article simply popularizes these issues and so we will not review it here.

While perhaps this went unstated in our original statement, we are happy to see this discussion take place. Our statement was intended to be read not as the final word but as a preliminary proposition in this necessary discussion. These authors have contributed important concerns to the wider discussion which needs to take place prior to the proposed research moving beyond the non-human stage. To this end, the statement has begun to accomplish one of its intended purposes.

That said, there are perhaps some initial responses that can be made to the specific issues that Dr. Schindler raised in the first critique, and Drs. Burke and Pullicino and Fr. Richard raised in the second. Turning first to Schindler's concerns, we completely agree that, in general, the way that many scientists view the world is essentially mechanistic and often detached from moral concerns. Schindler is correct in cautioning about the implications of capitulating to the use of the oocyte as a means of production, which is his fourth concern. There certainly is much more that needs to be discussed in this wider view of the problem and Schindler's comments are an excellent first step in that direction. However, it was the intention of our statement to focus on a particular concern. Namely, our statement was addressing the issue of whether or not a zygote is formed in this procedure. This then

brackets the discussion of the wider problem brought up in the fourth issue of his response.⁵

It seems to us that to answer Schindler's first two issues, there is one fundamental question to be answered. Does the lack of epigenetic primordia for internally directed growth of a human being convincingly indicate the non-existence of a human being? The second issue raised by the Burke-Pullicino-Richard article seems to weigh in Schindler's favor. They state that biologically the result of OAR is really a defective zygote. The questions that must be asked are what constitutes a human being at the level of a zygote, and can the external manifestation at such an early stage determine with sufficient confidence that the entity produced by OAR is not a human being?

First, let us turn to the issue of certainty. Of course, Schindler is right when he suggests that one cannot prove that a human soul is or is not present. In the Congregation for the Doctrine of the Faith (CDF) document on procured abortion, footnote 19, the Magisterium agrees that it is outside the competence of science to prove the existence of a soul. Further, in this footnote the Magisterium does not take a position on when the soul enters the body but asserts that destruction of an embryo is still destroying human life.⁶

⁵This bracketing of a larger problem and focusing on a concrete moral situation is a standard method in moral theology. A magisterial example of this can be found in a 9 June 2005 letter from the Pontifical Academy for Life on the liceity of vaccinating children with vaccines prepared using cell lines derived from aborted fetuses (see "On Vaccines Made From Cells of Aborted Fetuses," *Zenit* [26 July 2005] available at <http://www.zenit.org/english/visualizza.phtml?sid=74741>; accessed 26 October 2005). In the letter, the Pontifical Academy forwarded their commission's study of the issue which was approved by the Congregation for the Doctrine of Faith. The analysis looked at the entire chain of production from the initial research and its direct involvement with abortion, to the subsequent production, marketing and distribution, use by doctors and use by parents. It evaluated each specific act for formal and material cooperation, passive and active cooperation, and the remoteness and proximity of participation in the evil. While condemning the wider problem and exhorting those involved, even parents, to demand moral alternatives, it did find that in some circumstances the principle of double effect would apply because of the remote, material cooperation and the gravity of the consequences to the child and to society of not vaccinating children.

⁶Sacred Congregation for the Doctrine of the Faith, *Declaration on Procured Abortion*, AAS 66 (1974), 736–738. *Donum vitae*, published 1987, reaffirms that the Magisterium still has not taken a position on when the human soul first becomes present (*Donum vitae*, I,1, AAS 80 [1988], 70–102).

It goes on to say that even if the presence of the soul cannot be determined with certainty, it suffices that the presence of the soul be probable.⁷ *Evangelium vitae*, more than two decades later, asserts much the same thing: “Furthermore, what is at stake is so important that, from the standpoint of moral obligation, the mere probability that a human person is involved would suffice to justify an absolutely clear prohibition of any intervention aimed at killing a human embryo.”⁸ The first point that both of these documents make is that it is clear that the zygote is human life. That is not the case with the product of OAR, otherwise there would be no debate. The second point these documents make is that the “probability,” in the sense of credibility, further justifies any contrary assumptions about the non-presence of human life. This term “probability” seems to have application to our concern. We will come back to this momentarily.

Schindler argues that we cannot rely on empirical observation alone but must go beyond the empirical to the metaphysical.⁹ We completely agree. The Magisterium also, while not relying totally on scientific data, does take it into account for these types of determinations. The context of *Evangelium vitae* 60 suggests that the Magisterium considers it credible that a soul is present based upon the scientific evidence and the philosophical understanding that the soul is the substantial form of the human person. As we said, there is no certainty that the product of OAR is a zygote. Thus we are left with some uncertainty. What is the threshold of confidence we should be considering? Do we have to rule out any possibility that the cell is a nascent human being, albeit one sufficiently deformed that there is only one thing he or she can do and that is to produce pluripotent cells? Absolute certainty is not possible.

To illustrate this point, let us offer what we think is a parallel case. It is true that a pregnant woman should not consume alcohol

⁷In Latin *probabilis* (cf. *Declaratio de abortu procurato*, 18 November 1974, *AAS* 66 [1974], 738) which carries the sense of credible. Probable in the sense of “likely” would be better rendered *verisimilis*.

⁸*Evangelium vitae* 60, *AAS* 87 (1995), 469. Here again, the Latin *probabilitas* is rendered in English as probability.

⁹Schindler, “A Response,” 375: “To insist on a cognitional act that goes beyond the empirical to the metaphysical is not at all to suggest that one can or should stop looking at the physical. On the contrary, it is to look at the physical more comprehensively.”

because of the dangers to her baby that this consumption would pose. If the moral standard is absolute certainty then any sexually active woman who has not had a hysterectomy could never consume alcohol with moral liceity. This is so because she could never have *absolute* certainty that she was not in the early stages of pregnancy. Even postmenopausal women have the possibility of becoming pregnant. Scripture provides two examples with Sarah in the Old Testament and Elizabeth in the New Testament. Understandably then, the Church does not require absolute certainty which would oblige the faithful to an unattainable standard. Therefore, based upon the magisterial use of “probability” for moral certainty, it must be “credible” that the cell produced by OAR is a human being. This credibility should be based on an interpretation of empirical data which uses the philosophical model of the human person which the Church employs, i.e., that the soul is the substantial form of the human person.¹⁰

This leads directly to the questions, what is a human being and can this be discerned at the level of a zygote?¹¹ Schindler rightly asserts that being precedes act. He is correct in suggesting that the lack of human action, in this case zygotic activity, does not necessarily prove the non-existence of a zygote. In fact, Burke-Pullicino-Richard have asserted that the product of OAR is a “crippled embryo incapable of fully developing into a human infant.”¹² Certainly, one should consider the possibility. Now none of our critics would argue with the assertion that the somatic nucleus itself is not a human being. It does not on its own have the potency to become a human person. Thus, a somatic nucleus need not be treated with the same dignity as a human person. What is it that

¹⁰Cf., e.g., DS 902 (481) stated at the *Council of Vienne*, 1311–1312.

¹¹Our method of argument will essentially proceed along the lines of the following syllogism: major premise: any living entity, to be a human being, must contain the epigenetic primordia necessary for internally directed growth toward a mature human being in order to receive a human soul and thus be a human being; minor premise: the product of ANT/OAR does not have the required epigenetic primordia for this internally directed growth toward a mature human being; conclusion: therefore, the product of ANT/OAR can never receive a human soul and is not a human being. Our major premise leaves open the question as to whether a human soul is infused at the same instant as a being that contains this human epigenetic primordia comes to be, but we believe it does.

¹²Burke, Pullicino, Richard, “Moral Dilemmas.”

enables the nucleus to become a human being? Does the simple insertion of any diploid nucleus taken from a human cell into the environment of an enucleated oocyte, *per se*, become a human being? Does this mechanical transfer of the nucleus itself bestow new being upon the entity? There are compelling reasons to think not.

There are various defects arising from fertilization which cannot be considered human beings. For example, hydatidiform moles are masses of growing tissue that are genetically distinct from the mother and arise when the maternal nucleus is lost and only two paternal nuclei remain.¹³ This cell from the start does not have the epigenetic primordia necessary to become a human person. In fact, only when these epigenetic primordia are present do we find that a human being develops. From the external evidence then, it appears that the human being comes into existence when the enucleated oocyte reprograms the nucleus into a totipotent zygote. This reprogramming provides it with all of the epigenetic primordia necessary for inward development into a mature human being. But we need not reduce this to a purely empirical observation. There is a philosophical rationale for this interpretation.

This reasoning can be seen in asking the question, what would be the difference between a defective embryo and a pluripotent stem cell produced from the transfer of a somatic nucleus into an enucleated oocyte? Because the soul is the form of the human body and the body expresses the soul, it is reasonable to assume that nothing other than a cell with the required epigenetic primordia is capable of receiving a human substantial form, i.e., a soul. It does not seem to us probable (i.e., credible) to assume that the mere change of environment, without any change to the nucleus's genetic transcription, suffices for the new entity—i.e., the enucleated oocyte containing the altered somatic nucleus—to be considered a human person. Nor does it seem reasonable that the new cell that looks and acts like a pluripotent stem cell and has only the capacity for producing more of the same with no further differentiation could receive a human substantial form or be considered a human being. We believe that Schindler and the others set the bar of confidence higher than does the Magisterium. The philosophical reasoning and

¹³Cf. Germain Grisez, *Living a Christian Life*, vol. 2 (Quincy, Ill.: Franciscan Press, 1993), 495, fn. 68.

scientific evidence do not provide “probable” or “credible” reasons to believe that the product of OAR is a human being.

In considering the criticisms of Burke-Pullicino-Richard, it would seem that their first concern, that we are underestimating the reprogramming power of an oocyte and so OAR will not work, is exactly the purpose of the proposal. If they are correct, we will only know by implementing the research program on non-human cells. The remaining three issues are excellent questions which should be resolved through dialogue aided by the empirical results of our proposal. Recall our statement that “if, but only if, such research establishes beyond a reasonable doubt that oocyte-assisted reprogramming can reliably be used to produce pluripotent stem cells without creating embryos, would we support research on human cells.”¹⁴ These concerns will not be answered without assistance from the empirical data.

We certainly do not consider this the last word on these issues. We are encouraged by the discussion but we do not think that anything yet presented by the critics obviates the liceity of our proposal or yet rules out the advisability of proceeding with the research with non-human cells. □

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¹⁴Joint Statement, “Production of Pluripotent Stem Cells,” 127.