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Geoffrey Lomax Dr.PH.
Senior Officer for Medical & Ethical Standards
California Institute for Regenerative Medicine
210 King Street
San Francisco, CA 94107

Re: Research uses of embryos from paid IVF Donors

Dear Dr. Lomax:

A subcommittee of the Stanford SCRO has met to discuss CIRM policy on the use of embryos for research from paid IVF Donors. CIRM regulations prohibit payments to donors of gametes, embryos and somatic cells for funded research.[1] The prohibition extends to hESC lines derived in other jurisdictions. We support this regulation as protection against instances of direct payment by researchers to egg, sperm and embryo donors. The practical consequence of this rule, however, is that it extends to transactions outside the research context. This limits the number of high quality embryos that might be used to address important scientific questions. In our view, the IVF arrangement should not be captured by the regulation.

About one in eight couples undergoing fertilization treatment paid for gametes from others.[2] IVF clinics generally produce a greater number of embryos than is required for immediate transfer for reproductive purposes. This common practice provides the recipient couple with a high probability of having a child, and reflects the fact that: 1) In many cases, the only live birth comes from the last embryo in the cohort of frozen embryos, and 2) it is difficult to predict the success of in vitro fertilization. Importantly, although many embryos are cryopreserved, often the couples may not be at an age where they can have multiple children. Therefore, they may wish to donate these embryos to research than discarding or donating them to others.

[1] Specifically, 17 CCR §100080(e)(2): All covered stem cell lines used in CIRM-funded research must be "acceptably derived." To be" acceptably derived," the stem cell line must have been derived under the following [condition]: Donors of gametes, embryos somatic cells or human tissue did not receive valuable consideration; § 100080 (e)(3): A person may not knowingly, for valuable consideration, purchase or sell gametes, embryos somatic cells or human tissue for research purposes; § 100095 (b)(3): The donation of oocytes for research is done without valuable consideration either directly or indirectly; §100095 (b)(5): If the procurement of oocytes involves use of materials donated for reproductive use by another woman and with valuable consideration in excess of reimbursement for permissible expenses for the oocyte donor, then oocytes may not be used for CIRM-funded research.

[2] As noted in the 2/27/08 MES discussion memo, about 12 per cent of stored IVF embryos use gametes from paid donors.

In the context of IVF, women who supply gametes for these procedures are paid for their time, effort, discomfort, loss of privacy, and to help the couple build a family. This fiduciary agreement is entirely separate from the recipient couple's decision to donate extra embryos for research. For existing embryos made with paid-for gametes, we understand that due to CIRM's current rules, it will be necessary to contact the persons originally supplying the gametes, and that this consent may be difficult to obtain. In the future, it is possible to develop approaches to request consent from suppliers of gametes using existing protocols designed for the donation of other IVF embryos.

In light of the above, there are compelling reasons to modify the CIRM regulations.

I) Scientific need

Using genetic and cell culture studies, high quality embryos made from donated gametes can be compared to IVF patients' embryos to uncover fundamental problems of infertility, developmental disorders, and other questions facing stem cell research.

- Limitations on the number and type of embryos used have hampered efforts to examine fundamental properties of human embryo development, including gene activation, imprinting, genome-wide demethylation and methylation, histone modification, chromosome segregation and X chromosome inactivation/reactivation.[3]
- IVF is routinely used to assist infertile men and women in achieving parenthood. But many aspects of the treatment have not been optimized, such as the conditions for optimal human embryo culture.[4]
- Traditionally, grading of embryos for optimal transplantation is based on simple morphological observations such as the presence of uniformly sized, mononucleate blastomeres and assessment of cellular fragmentation. Yet, evidence suggests that these criteria are not enough.[5] Comparative studies will help to address adverse events such as multiple pregnancies, embryo loss, miscarriage, and low and very low birth weight.
- Comparative studies may determine whether hESC lines are more efficiently derived using embryos from donors with no history of infertility than those obtained from IVF clinics. This may reduce the absolute number of embryos used in future experiments.
- Lines made from these embryos may have experimental advantages, such as consistency in culture or stability of karyotype.
- In the future, cells derived from such lines may have therapeutic advantages, such as increased ability to home, engraft, repair, and renew tissue.

[3] Gicquel, C., Gaston, V., Mandelbaum, J., Siffroi, J., Flahault, A. and Bouc, Y.L. (2003) In vitro fertilization may increase the risk of Beckwith-Wiedemann syndrome related to the abnormal imprinting of the KCN10T gene. Am. J. Hum. Genet., 72, 1338–1341.
[4] Milki, A.A., Hinckley, M.D., Gebhardt, J., Dasig, D., Westphal, L.M. and Behr, B. (2002) Accuracy of day 3 criteria for selecting the best embryos. Fertil. Steril., 77, 1191–1195.
[5] Lan, K., Huang, F., Lin, Y., Kung, F.T., Hsieh, C.H., Huang, H.W., Tan, P.H. and Chang, S.Y. (2003) The predictive value of using a combined Z-score and day 3 embryo morphology score in the assessment of embryo survival on day 5. Hum. Reprod., 18, 1299–1306.

II) Regulatory inconsistency

CIRM regulations are more restrictive than national guidelines and at least three other states, and are inconsistent with California state law.

- In November 2006, Connecticut's Attorney General interpreted the direct or indirect payment ban in that state's stem cell research law in a way that fulfills the legislative intent of promoting research. He reviewed the question whether "eggs or sperm which have been solicited and paid for, for use in *in vitro* fertilization, [are] prohibited for use in stem cell research if they were unused in the *in vitro* procedure." He determined the materials can be used for research: "the payment for unfertilized eggs and sperm or fertilized embryos for the purpose of implantation and *in vitro* fertilization is not prohibited and does not preclude subsequent donation, without payment, of such products for stem cell research at a later time."[6]
- Missouri, in its constitutional provision supporting stem cell research, defined "valuable consideration" to exclude "consideration paid to a donor of human eggs or sperm by a fertilization clinic or sperm bank, as well as any other consideration expressly allowed by federal law."[7]
- New York is developing ethical standards for its new stem cell funding program. Its grantee contract conditions seem to permit the use of gametes or embryos if originally created from a paid reproductive gamete donor. It references the ISSCR Guidelines, which state that there should be no reimbursement or payment for the actual donation to research. It further states that if payment history is not available, "ESCROs need not ensure that payment history complies with either NAS or ISSCR guidelines."[8]
- Written by an international panel of experts, ISSCR guidelines permit use of materials where an agency paid a woman to provide eggs for fertility care.
- The NAS guidelines restrict payment to reimbursement of a donor's expenses. They are silent, however, on whether compensation for materials for a non-research purpose may be used. There is no prohibition in the guidelines on such use.
- There is inconsistency with pre-existing California law (Health and Safety Code § 125315), which equally applies to CIRM-funded research.[9] This section states that IVF patients "shall be presented with the option of storing any unused embryos, donating them to another individual, discarding the embryos, or donating the remaining embryos for research." IVF patients must be presented with these options, including the donation-to-research option. There is no exception indicating that patients who use a gamete donor have fewer options, including no research option. The statute separately says that a

[6] Formal Opinion 2006-025, Nov. 13, 2006, available at http://www.ct.gov/ag/cwp/view.asp?A=1770&Q=328050#_ftn3.
[7] Missouri Stem Cell Research and Cures Initiative, Art. III, Sec. 38(d)(6)(17), available at http://www.sos mo.gov/elections/2006petitions/ppStemCell.asp.
[8] NY State Department of Health and the Empire State Stem Cell Board: 2008 RFA, Appendix A-2 Contract Policy Statements and Conditions, Sec. E(3), available at http://www health.state.ny.us/funding/rfa/0802071100/0802071100.pdf
[9] Proposition 71 [§ 125290.35(a)] authorizes CIRM to develop its own medical and ethical standards notwithstanding other current or future law relating to research in this field "except Section 125315."

person cannot buy or sell embryonic tissue "for research purposes," but a payment for fertility reasons is legal and is not a payment for research purposes. [10] [11]

In summary, it is our view that both those who wish to donate embryos and CIRM-funded researchers would be best served by a policy that allowed donation of embryos made from paid gamete donors. Such donation is ethically permitted and is consistent with existing and emerging national and state regulation.

Sincerely yours,

Theo Palmer on behalf of Stanford University SCRO
Stem Cell Research Oversight Panel Chair

[10] Health and Safety Code § 125320.
[11] Furthermore, since the State has developed parallel guidelines, the restrictions on materials created from egg donors extend to both CIRM and non-CIRM stem cell research. Thus, directing patients to non-CIRM stem cell research is not an option.