ducts of two recipient monkeys. Two morula-stage embryos were transferred laparoscopically to a third monkey. A normal singleton gestation resulted from the transfer of the morulas, ending in the birth last year of a healthy female weighing 500 g (Fig. 2).

To our knowledge, this is the first successful fertilization and pregnancy to follow egg collection from fresh transplanted ovarian tissue in a primate. Although the kidney supported endocrine function in the transplanted tissue, the arm and abdomen transplantation sites provided easier access for retrieving oocytes.

The procedure described here has the potential to rescue fertility in cancer survivors. However, before widespread clinical application is feasible, it will be necessary to test whether cryopreserved ovarian tissue can be transplanted to the oocyte donor, as well as whether it can sustain ovarian steroid-hormone support during her pregnancy[8].

D. M. Lee, R. R. Yeoman, D. E. Battaglia, R. L. Stouffer, M. B. Zelinski-Wooten, J. W. Fanton, D. P. Wolf

Oregon Health & Science University, Department of Obstetrics and Gynecology, Pediatrics, Physiology and Pharmacology, Oregon National Primate Research Center, Division of Reproductive Sciences, Portland, Oregon 97201, USA

e-mail: leedavi@ohsu.edu

1. Parrott, D. M. *J. Reprod. Fertil.* **1**, 230–241 (1960).
2. Gosden, R. G., Baird, D. T., Wade, J. C. & Webb, R. *Hum. Reprod.* **9**, 597–603 (1994).
3. Schnorr, J. *et al. Hum. Reprod.* **17**, 612–619 (2002).
4. Le Porrier, M., von Theobold, P., Roffe, J. L. & Muller, G. *Cancer* **60,** 2201–2204 (1987).
5. Oktay, K. *et al. J. Am. Med. Assoc.* **286**, 1490–1493 (2001).
6. Duffy, D. M. & Stouffer, R. L. *Hum. Reprod.* **17**, 2825–2831 (2002).
7. Ouhibi, N., Zelinski-Wooten, M. B., Thomson, J. A. & Wolf, D. P. in *Contemporary Endocrinology: Assisted Fertilization and Nuclear Transfer in Mammals* (eds Wolf, D. P. & Zelinski-Wooten, M. B.) 253–284 (Humana, Totowa, New Jersey, 2001).
8. Lutjen, P. *et al. Nature* **307**, 174–175 (1984).

Competing financial interests: declared none.

Supplementary information accompanies the communication on *Nature*'s website.

Tissue engineering

Creation of long-lasting blood vessels

The construction of stable blood vessels is a fundamental challenge for tissue engineering in regenerative medicine. Although certain genes can be introduced into vascular cells to enhance their survival and proliferation, these manipulations may be oncogenic. We show here that a network of long-lasting blood vessels can be formed in mice by co-implantation of vascular endothelial cells and mesenchymal precursor cells, by-passing the need for risky genetic manipulations. These networks are stable and functional for one year *in vivo*.

To create stable vessels, we first seeded human umbilical-vein endothelial cells (HUVECs) and 10T1/2 mesenchymal precursor cells in a three-dimensional fibronectin–type I collagen gel (for methods, see supplementary information). The 10T1/2 cells differentiate into mural cells through heterotypic interaction with endothelial cells[1–3].

To permit continuous observation of the engineered vascular networks *in vivo*, we implanted the three-dimensional constructs into mice bearing transparent 'windows'[4].The gene for enhanced green fluorescent protein (EGFP) was introduced in order to track the implanted HUVECs[5].

Initially, the HUVECs formed long, interconnected tubes with many branches that showed no evidence of perfusion (Fig. 1a). Subsequently, they connected to the mouse's circulatory system and became perfused (Fig. 1b; for movie, see supplementary information). This led to a rapid increase in the number of perfused vessels in the first two weeks, followed by stabilization (Fig. 1c), whereas the number of non-perfused vessels gradually decreased and eventually disappeared. By contrast, constructs prepared from HUVECs alone showed minimal perfusion and had generally disappeared after 60 days (Fig. 1c), even though early morphological changes were similar in the two types of construct.

We labelled 10T1/2 cells with EGFP for *in vivo* microscopy to confirm that they had been incorporated into the vessel wall (Fig. 1d). Cells derived from 10T1/2 cells invested along the perfused vessels. Immunohistochemistry revealed that human cells positive for CD31 (an endothelial cell marker) lined the lumen of the engineered vessels and that these vessels were fortified by 10T1/2-derived cells that expressed the mural-cell marker smooth-muscle α-actin (results not shown).

The 10T1/2 cells that were not associated with new blood vessels did not express appreciable amounts of mural-cell marker. Some mural cells of the engineered vessels derived from the host. However, the engineered vessels in the HUVEC-alone construct rarely survived. Delays in mural-cell recruitment from the underlying host tissue resulted in the regression of most of the vessels engineered from HUVECs alone. In the co-implantation constructs, however,

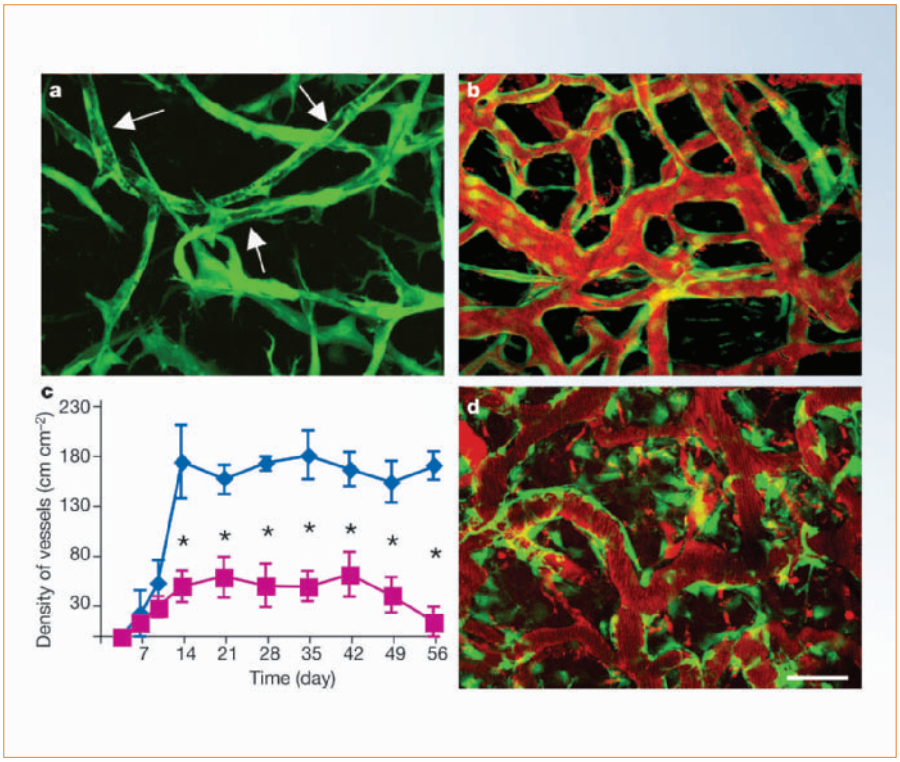

Figure 1 Morphological and functional analysis of engineered blood vessels. Human umbilical-vein endothelial cells (HUVECs) and 10T1/2 mesenchymal precursor cells, or HUVECs alone, were seeded in three-dimensional constructs and then implanted in mice. **a, b,** Three-dimensional, intravital, multiphoton laser-scanning microscopy[4] images of engineered vessels (green, HUVECs expressing enhanced green fluorescent protein (EGFP); red, functional blood vessels contrast-enhanced with Rho–dextran). **a,** Four days after implantation of a HUVEC + 10T1/2 construct. Large vacuoles in the tubes (arrows) resemble the lumen of a capillary vessel but are not perfused (as indicated by the absence of red). **b,** Four months after implantation of a HUVEC + 10T1/2 construct: engineered vessels are still stable and functional. **c,** Temporal changes in functional density of engineered vessels (total length of perfused vessel structure per unit area); $n = 4$; mean ± s.e.m. is shown; asterisks indicate significance ($P < 0.05$) between the two groups (Mann–Whitney *U*-test). Top curve, HUVEC + 10T1/2 construct; lower curve, HUVEC-alone construct. **d,** Three-dimensional image of engineered vessels, 4 weeks after implantation of a HUVEC + EGFP-expressing 10T1/2 construct (green, 10T1/2 deprived cells; red, functional blood vessels). Scale bar, 50 μm. Further details are available from the authors.

the abundance of mural-precursor cells allowed efficient recruitment and investment of mural cells to the engineered vessels, thereby enhancing their stability.

The vascular permeability of the engineered vessels is higher than that of normal, quiescent vessels, but is in the lower range of permeability values induced by various angiogenic molecules (see supplementary information). As in normal microcirculation, arteriolar and venular sides of the engineered vessels are readily identified by the pattern of blood flow. Local administration of a vasoconstrictor, endothelin-1, prompted constriction of the engineered arterial vessels. The few surviving arterioles in the HUVEC-alone constructs were significantly less contractile than those in the combined constructs (see supplementary information). These results indicate that the vessels that formed in the co-implantation construct have a better functionality.

Engineered blood vessels have often been found to be immature and unstable[6]. Genes that enhance the survival and/or proliferation of vascular cells — endothelial cells and mural cells — can be introduced to extend the lifespan of the engineered vessels[5,7,8], but these may prove to be oncogenic. We have created long-lasting blood vessels without such genetic manipulation.

In addition to realizing a crucial step in tissue engineering, our system provides a platform for testing the *in vivo* functions of factors that control angiogenesis, vasculogenesis and vessel maturation. The likely existence of endothelial and of smooth-muscle progenitor cells in adults[9,10] indicates that these cells might serve as a source of autologous cells for engineering blood vessels by using the approach described here.

Naoto Koike, Dai Fukumura, Oliver Gralla, Patrick Au, Jeffrey S. Schechner*, Rakesh K. Jain

Edwin L. Steele Laboratory, Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts 02114, USA
e-mail:jain@steele.mgh.harvard.edu
**Department of Dermatology, Yale University School of Medicine, New Haven, Connecticut 06520-8059, USA*

1. Orlidge, A. & D'Amore, P. A. *J. Cell Biol.* **105,** 1455–1462 (1987).
2. Hirschi, K. K., Rohovsky, S. A. & D'Amore, P. A. *J. Cell Biol.* **141,** 805–814 (1998).
3. Darland, D. C. & D'Amore, P. A. *Angiogenesis* **4,** 11–20 (2001).
4. Jain, R. K., Munn, L. L. & Fukumura, D. *Nature Rev. Cancer* **2,** 266–276 (2002).
5. Schechner, J. S. *et al. Proc. Natl Acad. Sci. USA* **97,** 9191–9196 (2000).
6. Jain, R. K. *Nature Med.* **9,** 685–693 (2003).
7. Yang, J. *et al. Nature Biotechnol.* **19,** 219–224 (2001).
8. McKee, J. A. *et al. EMBO Rep.* **4,** 633–638 (2003).
9. Yamashita, J. *et al. Nature* **408,** 92–96 (2000).
10. Simper, D., Stalboerger, P. G., Panetta, C. J., Wang, S. & Caplice, N. M. *Circulation* **106,** 1199–1204 (2002).

Competing financial interests: declared none.
Supplementary information accompanies the communication on *Nature*'s website.

COMMUNICATIONS ARISING

Animal behaviour

Inequity aversion in capuchins?

Brosnan and de Waal[1] have shown that capuchin monkeys are more likely to reject a cucumber slice after seeing that another capuchin has received a more attractive grape. In interpreting this finding, the authors make a link to work in humans on 'inequity aversion' and suggest that capuchins, like humans, may reject rewards because they are averse to unequal pay-offs. Here I argue that this interpretation suffers from three problems: the results contradict the predictions of the inequity-aversion model that Bosnan and de Waal cite[2]; experimental results indicate that humans do not behave like capuchins in similar circumstances; and the available evidence does not suggest that inequity aversion is cross-culturally universal[3–5].

I consider these points in turn. Brosnan and de Waal link their findings to work showing that a wide range of experimental behaviour in humans can be understood by introducing a preference for equity into the standard self-interested utility function. The effect of introducing this non-selfish preference is to cause individuals — under certain circumstances — to give up some of their pay-off in order to decrease the gains of other individuals.

Applying the Fehr–Schmidt inequity-aversion model[2] cited by Brosnan and de Waal to the capuchin experimental situation predicts that capuchins should always eat the cucumber. It does not predict that inequity-averse individuals will reject the food reward, which is what the monkeys did. Rejecting the cucumber increases, not decreases, inequality. Moreover, the grape-receiving capuchins sometimes reached through the cage and stole their partner's discarded cucumber, exacerbating the inequality.

Consistent with inequity aversion in humans, the results from experimental variations of the ultimatum game suggest that humans would not reject a reward unless that rejection reduced the take of the individual who received more. In the ultimatum game, two players are allotted a sum of money to divide. The first player — the 'proposer' — must offer a portion of the sum to the second player — the 'responder' — who must then decide whether to 'accept' or 'reject' the offer. If the responder accepts, he gets the amount of the offer and the proposer receives the remainder. If he rejects, both players get zero. The game is played once, and players never learn their partner's identity. Inequity aversion can explain the willingness of responders to reject low offers (in contrast, pure self-interest predicts that responders will never reject any non-zero offer). Once some responders are willing to reject low offers, self-interest guarantees that proposers will raise their offers.

Two kinds of variation from the standard ultimatum game suggest that humans, unlike capuchins, would not reject in Brosnan and de Waal's experimental context. Two versions of a reduced-form ultimatum game have been compared[6]: the first was a standard game, except that proposers had only two choices, an equitable allocation or a highly inequitable one; and the second (the 'impunity game') was identical, except that if the responder rejected his offer, the proposer's pay-off remained unchanged (but the responder received zero). In the first version, players were willing to reject inequitable allocations, whereas in the second version (which parallels the capuchin situation), subjects never rejected.

Similar evidence comes from multilateral ultimatum games in which one proposer faces multiple responders (see U. Fischbacher, C. M. Fong & E. Fehr, www.iew.unizh.ch/wp/iewwp133.pdf). In this set-up, as long as one of the responders accepts the offer, the proposer gets his pay-off. As before, the responder's ability to affect the proposer's pay-off by rejecting is mitigated by the other responders who might accept. As predicted by inequity aversion, responders decrease their willingness to reject, and proposers drop their offers accordingly. Therefore, although both of these experimental patterns are consistent with inequity aversion, both also seem to be at odds with Brosnan and de Waal's capuchin findings: that is, they show that humans will not reject unless this affects the other's pay-off.

Brosnan and de Waal also suggest that inequity aversion is probably a human universal, and they cite work that uses the ultimatum game in 15 small-scale societies[3–5]. If responder behaviour (willingness to reject low offers) is taken as the most direct measure of inequity aversion, then our results do not support the universal claim. Although five societies do show evidence consistent with inequity aversion, three others show evidence of trivially little or no inequity aversion. The remainder have so few low offers that no substantial claims can be made.

Joseph Henrich

Department of Anthropology, Emory University, Atlanta, Georgia 30322, USA
e-mail: jhenric@emory.edu

1. Brosnan, S. & de Waal, F. B. M. *Nature* **425,** 297–299 (2003).
2. Fehr, E. & Schmidt, K. M. *Q. J. Econ.* **114,** 817–868 (1999).
3. Henrich, J. *et al.* (eds) *Foundations of Human Sociality: Economic Experiments and Ethnographic Evidence from 15 Small-Scale Societies* (Oxford University Press, New York, in the press).
4. Henrich, J. *Am. Econ. Rev.* **90,** 973–980 (2000).
5. Henrich, J. *et al. Am. Econ. Rev.* **91,** 73–78 (2001).
6. Bolton, G. E. & Zwick, R. *Games Econ. Behav.* **10,** 95–121 (1995).