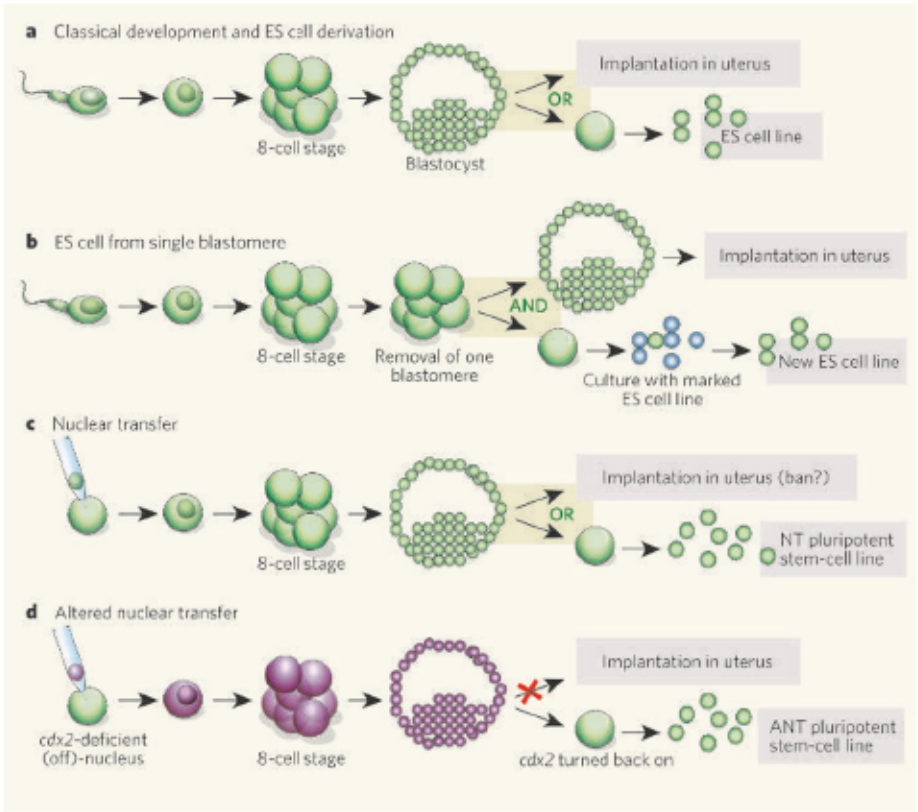

Figure 1 | Producing pluripotent stem-cell lines. a, The classical derivation of embryonic stem (ES) cells destroys the embryo from which they are derived. **b**, Lanza and colleagues[1] have used a modified method that does not compromise the embryo, but is not donor-specific. **c**, Donor-specific pluripotent stem cells can be made using nuclear transfer (NT) techniques. **d**, An altered nuclear transfer (ANT) method developed by Meissner and Jaenisch[2] blocks expression of the *cdx2* gene until the blastocyst stage, making it unable to implant.

pluripotent genes. Embryoid blastocysts have an inner cell mass like normal blastocysts, and these cells can become pluripotent stem cells. Such NT stem cells can, like ES cells, self-renew or differentiate to become most types of mature body cell. Technological advances[4] have improved NT in humans to the point that a single egg donor can produce enough eggs in one round of donation to ensure a patient-specific NT pluripotent stem-cell line.

Very rarely, animal embryoid blastocysts have reprogrammed enough genes to be able to implant in the uterus and complete all the developmental stages to birth. But in all species tested, more than 99% of embryoid blastocysts fail, many at later stages of pregnancy where the failure can injure or kill the mother bearing it. This has led a panel of the US National Academies to call for a legally enforceable ban on human 'reproductive cloning'[5]. Nonetheless, because human NT stem cells come from embryoid blastocysts, their derivation has raised objections on political, ethical and religious grounds. A possible solution to the controversy, proposed by many who want the medical science to progress, might be to invent a process that produces an entity that cannot implant in the uterus — termed alternative nuclear transfer (ANT) by William Hurlbut, a member of President Bush's Council on Bioethics[6].

Meissner and Jaenisch[2] (page 212) have now developed a method to accomplish ANT. Their technique builds on previous work by Strumpf *et al.*[7], who studied a gene called *cdx2* and its role in establishing the mouse trophectoderm and, later, the intestinal tract. Their results suggested that if this gene was suppressed in the nucleus of the donor cell during the NT process, it might allow the generation of NT entities that could not implant.

Meissner and Jaenisch demonstrate that this is indeed the case, using a clever method to control *cdx2* expression at various stages. They introduced into the donor cell a gene encoding an RNA that inhibits *cdx2* expression, and this gene was transmitted with the donor nucleus to the egg and continued to be active during the NT. Once they had derived the ANT pluripotent stem-cell line from the resulting embryoid blastocysts, they clipped out the inhibitor gene to enable the resulting ANT stem cells to produce mature intestinal epithelia given the right cues (Fig. 1d). These ANT pluripotent stem-cell lines can form many other mature cells, just as the classical ES and NT cell lines do.

It is highly speculative whether either blastomere-derived ES cell lines[1] or ANT pluripotent stem-cell lines[2] can also be derived from human cell sources. Nonetheless, there have already been hearings in the US Congress at

50 YEARS AGO

"Physiological control of population growth" — As Dr. Gregory Pincus, of the Worcester Foundation for Experimental Biology, pointed out, there is no doubt that progesterone can inhibit ovulation in rabbits and apparently, also, in rats. According to his own studies, the indications are that progesterone, when taken by mouth, will also inhibit ovulation in women, as determined by various indirect indices. This view was not, however, shared by Dr. Massomi Ishikawa ... nor by Dr. A. Stone ... [as was clear from all the physiological papers] the practical goal of these urgently needed researches — the discovery of a 'pill' which can be taken by mouth, and the only physiological effect of which would be that of inhibiting the development of the fertilized ovum, or of suppressing ovulation or gametogenesis at will — is so remote from realization that at this stage no one can say how, when or even whether success will ever be achieved. **Sir Solly Zuckerman**

From *Nature* 14 January 1956.

100 YEARS AGO

"The training of the body and mind" — In the afternoon Sir Lauder Brunton took the chair, and discussed education in connection with the threefold character of man. At first, he said, moral training was provided, and churches and cathedrals were built long before the people could read or write; then mental culture was considered, and became very general; and, lastly, it was being recognised that the condition of the body had considerable effect upon the morals and the mind, so that a physical training was also considered necessary. He gave some interesting instances to show how character and habits had been entirely altered by accidents to the brain, and said that while Newton was physically weak, Young, who was his superior, even in mental capacity, was a circus rider, and could perform almost any bodily feat.

From *Nature* 11 January 1906.

50 & 100 YEARS AGO