Baksh *et al*. may open the door to the automated characterization of a wide range of complex molecular interactions that are at present poorly understood. ■

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Stem cells

How to make eggs and sperm

M. Azim Surani

Embryonic stem cells can develop into many specialized cell types in culture dishes. It now seems that they can also generate primordial germ cells, which then go on to form sperm and eggs.

A fertilized egg is potentially immortal: this fusion of egg and sperm gives rise not only to a new individual, but also (theoretically at least) to an endless series of generations. Three groups now suggest that it is possible to generate both of these remarkable cells — known collectively as germ cells — in a culture dish. Geijsen and colleagues[1], writing on page 148 of this issue, and Toyooka *et al.*[2], writing in *Proceedings of the National Academy of Sciences*, describe how they obtained sperm-like cells from mouse embryonic stem cells (ES cells) *in vitro*. Geijsen *et al.* even discovered that injecting their sperm-like cells into natural mouse eggs resulted in early embryonic development. Meanwhile, Hübner *et al.*[3] reported earlier this year in *Science* that they have succeeded in obtaining egg-like cells from mouse ES cells. So it is possible to produce germ cells with at least some attributes of sperm and eggs *in vitro*. These findings raise the possibility of deriving similar germ cells from human ES cells in culture — an idea that raises ethical issues as well as the prospect of unprecedented medical advances.

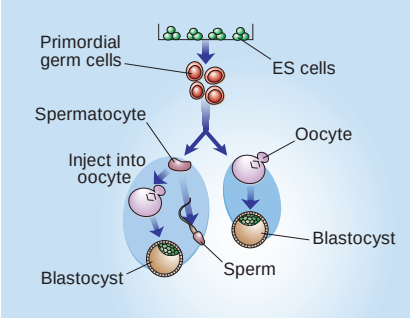

Figure 1 **Germ cells from stem cells. In two of the new papers[1,2], embryonic stem cells (ES cells), cultured as aggregates, formed structures resembling early embryos ('embryoid bodies'); in a third paper[3], the aggregates were permitted to undergo spontaneous differentiation. In all cases, a proportion of the ES cells produced primordial germ cells. Left, Geijsen *et al.*[1] found that some of these cells differentiated into spermatocytes (precursors of sperm) in the embryoid bodies. Moreover, injecting the spermatocytes into unfertilized eggs led to development to the early, blastocyst stage. Toyooka *et al.*[2] found that culturing primordial germ cells with cells from fetal testis also produced sperm. Right, Hübner *et al.*[3] isolated, re-aggregated and cultured primordial germ cells, which formed complex structures within which were found developing eggs. Release of these oocytes from the surrounding cells led to spontaneous activation and development to the blastocyst stage.**

ES cells derived from five-day-old mouse or human embryos ('blastocysts') have the exceptional potential — depending on the culture conditions — to either multiply indefinitely or develop into an array of specialized cells[4]. To try to persuade mouse ES cells to generate eggs and sperm (Fig. 1), Geijsen *et al.*[1] and Toyooka *et al.*[2] allowed aggregates of the cells to differentiate into structures that somewhat resemble early embryos; Hübner *et al.*[3] allowed ES-cell aggregates to undergo random differentiation spontaneously. The result was that, in the embryo-like structures and among the randomly differentiated cells, there were cells resembling primordial germ cells, which the authors detected by the expression of certain marker genes. The authors then isolated some of these primordial germ cells — the precursors of sperm and eggs — and allowed them to proliferate in culture. Curiously, all three groups noticed that the gene-expression pattern of the primordial germ cells showed highly accelerated development. Developmental timers are normally exquisitely regulated, so it will be important to know why the timing went awry in these cases.

The next stage involved transforming the primordial germ cells into sperm or eggs, which is a complex process that, *in vivo*, occurs within specific microenvironments[5,6]. To achieve this *in vitro*, the groups adopted different approaches. Geijsen *et al.* allowed the process to occur spontaneously in the embryo-like structures; Toyooka *et al.* cultured the primordial germ cells with normal fetal gonadal cells. In the work by Hübner *et al.* the primordial germ cells were allowed to form aggregates again. Either sperm-like[1,2] or egg-like[3] cells were produced (possibly depending on the procedure used). At this time, the number of chromosomes must be halved to allow male and female germ cells to make equal genetic contributions at fertilization[7]. This apparently occurred, although additional confirmation would be desirable.

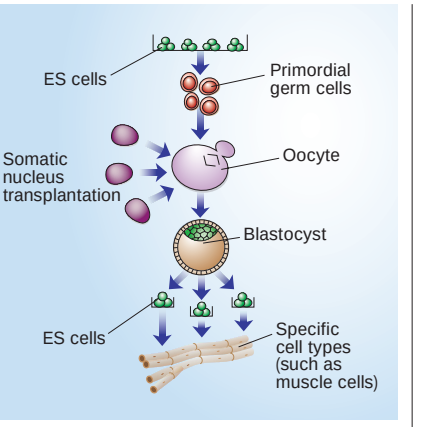

Figure 2 **A possible use for eggs derived from ES cells — nuclear transplantation. As shown in Fig. 1, oocyte-like cells could be made in culture from ES cells, by way of primordial germ cells[3]. After stripping the oocytes of their own genetic material, they could be used as recipients for nuclei from adult (somatic) cells such as skin cells. The somatic nucleus could then be 'reprogrammed' by factors present in the oocyte, which is then allowed to develop to the blastocyst stage. Blastocysts contain epiblast cells, from which new ES cells can be derived. Each type of ES cell will inherit some properties of the adult donating the somatic nucleus, such as a propensity for certain complex diseases. The ES cells could then be used to derive specific cells with which to study the progression of those diseases, and perhaps to generate treatments[10].**

Developing sperm and eggs must also acquire their characteristic identity tags, or 'imprints'[8], which regulate their complementary functions when embryonic development begins after fertilization. However, it is not yet known whether the eggs and sperm now generated[1–3] have the appropriate imprints. This information will be crucial, because sperm and eggs can seem normal even without the appropriate marks — but their functions will be affected after fertilization when development starts[8]. So, although Geijsen and colleagues did obtain blastocysts when they injected their sperm-like cells into unfertilized eggs, we cannot make any predictions about the long-term development of these early embryos. It is also interesting that the eggs generated by Hübner *et al.* developed spontaneously to the blastocyst stage once released from the surrounding cells — even though mature eggs should remain 'arrested' until they are fertilized or

artificially activated. Encouragingly, these blastocysts exhibited an appropriate gene-expression pattern. But their full developmental potential is unknown.

These caveats aside, the three papers[1–3] represent steps towards deriving primordial germ cells and, subsequently, eggs and sperm from ES cells. In the future, it will be important to develop means of controlling ES-cell differentiation into germ cells more tightly: in many respects, current methods rely on spontaneous and stochastic events, which makes it difficult to analyse each of the complex steps leading to the production of sperm and eggs. Systematic studies of germ-cell specification and properties (see, for example, refs 8, 9) will benefit from greater control over these steps *in vitro*.

So, what could be done with the 'synthetic' eggs and sperm? At present we are largely in the realms of 'fantastical thought experiments' — can we, for instance, generate viable embryos from synthetic germ cells? This could find applications in animal breeding, although researchers have yet to make ES cells from most mammalian species. Perhaps it might also prove possible to derive germ cells from human ES cells. If so, it would allow studies of human germ cells, about which very little is known. Use of such cells might also illuminate the causes of infertility and germ-cell tumours. It might even be possible to use synthetic sperm to treat male infertility. And, with improvements, the culture system could be used to examine many complex processes, including the roles of key genes and the mechanisms underlying imprinting and the halving of chromosome numbers.

Perhaps more importantly, however, a limitless supply of human eggs derived from existing ES-cell lines could have a radical impact on medicine. These synthetic eggs need not be perfect because, stripped of their own genetic material, they could be used as recipients for nuclei or genetic material from adult cells such as skin cells. If such reconstituted eggs can 'reprogramme' the adult nucleus and develop to the blastocyst stage, researchers could derive new ES cells from them (Fig. 2). These cells in turn could be prompted to produce specific cell types for transplantation, to treat specific human conditions. Progress in this area is currently hampered by the scarcity of human eggs, the use of which also involves legitimate ethical considerations.

Human eggs derived in culture could also have an even more exciting use. By following the same procedure, it might be possible to use these eggs to generate ES cells that produce diseased tissues — the adult nuclei for the process being taken from patients with complex diseases such as diabetes. As noted at a meeting earlier this year, such ES cells would provide an unlimited resource, allowing approaches to the study of disease that are currently impossible[10]. This might, in turn, lead to new treatments.

And simply being able to study human germ cells in culture might allow more thorough investigations into the origin and properties of these remarkable cells. This could give us a grip on our destiny in more ways than we can imagine. ■

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Ecology

Clouded futures

J. Alan Pounds and Robert Puschendorf

Global warming is altering the distribution and abundance of plant and animal species. Application of a basic law of ecology predicts that many will vanish if temperatures continue to rise.

Evidence that climate change is affecting life on Earth continues to mount[1,2]. But how great is the threat to biodiversity? On page 145 of this issue, Thomas *et al.*[3] show that global warming, projected to the year 2050, could sharply increase extinction probabilities for a sample of 1,103 species representing terrestrial regions from Mexico to Australia. If temperatures follow middle-of-the-road projections, the study suggests, about one-quarter of these species may disappear — a loss that would exceed that expected from habitat destruction.

Thomas *et al.* assume that each species can persist only under a particular set of climatic conditions. This 'climate envelope', assessed by modelling current geographical distribution in relation to climatic gradients, serves to predict future distribution. As warming alters these gradients, many species are shifting towards the poles or to higher elevations, their ranges often contracting as the area of

100 YEARS AGO

Some experiments have recently been made to test whether the radio-activity of radium is influenced by the continuous bombardment to which it is subjected by its own radiations. In an article in this Journal on radium (April 30, 1903) Prof. J. J. Thomson suggested that the radio-activity of radium may possibly depend upon its degree of concentration, and that a given quantity of radium, diffused through a mass of pitchblende, may be less than when concentrated in a small mass. In order to test this point, measurements of the radio-activity of radium bromide were made when in the solid state and when diffused throughout the mass of a solution more than a thousand times the volume occupied by the radium compound… This experiment shows that, over the range investigated, the radio-activity of radium is not influenced by its own intense radiations. E. Rutherford

From *Nature* 7 January 1904.

50 YEARS AGO

During September 21–25, 1953, a conference was held by invitation of Prof. Linus Pauling at the California Institute of Technology in Pasadena, to discuss progress in the X-ray studies of the structure of proteins (and to a lesser extent of nucleic acids). The last conference of this kind was that arranged by the Royal Society and held in London during May 1952; it had been the first to include a full-scale discussion of the new polypeptide chain configurations proposed by Pauling and Corey, especially the α-helix… The most general and fundamental concept underlying the discussions was that helical arrangements are at the basis of many important biological structures, either at the atomic level as a type of configuration for long-chain molecules, or at the molecular level as a way in which larger units of structure may naturally aggregate. Although a helical model had been proposed for the polypeptide chain by H. S. Taylor as early as 1941, … it cannot be said that the helix as a structural principle had entered into the fundamentals of our thinking up to the time of the Royal Society conference: indeed on that occasion there was strong disagreement as to the existence of helical chains. The Pasadena conference revealed that the helix has now come into its own with a vengeance; finding helices is a game played by nearly everyone in the field. J. C. Kendrew

From *Nature* 9 January 1954.