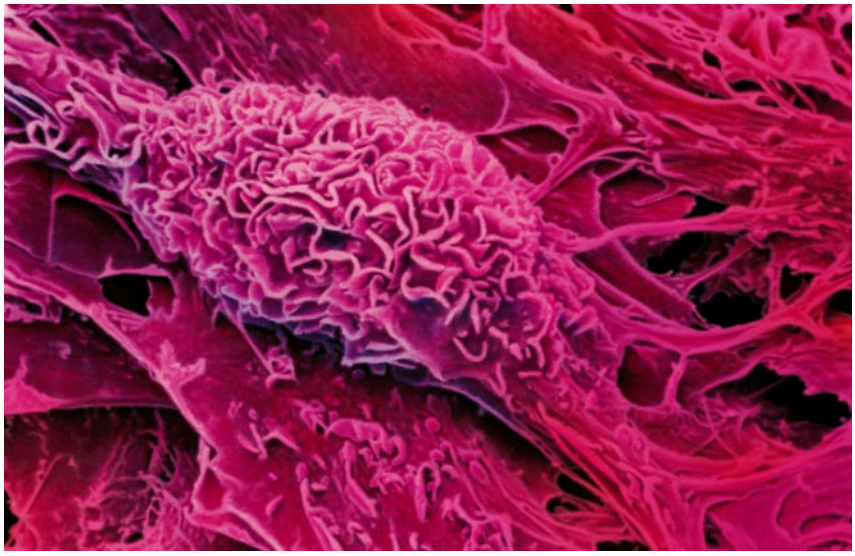
Stem-cell competition

Stuart H. Orkin and Sean J. Morrison

The debate continues over the relative merits of using embryonic and adult stem cells for research — and perhaps, one day, to treat patients. Two new papers look at the abilities of these remarkable cells.



YORGOS NIKAS/SPL

Figure 1 **Embryonic stem cell — primetime exposure.**

Last August tiny cells in Petri dishes captivated primetime television audiences. In a carefully worded address, US President George Bush discussed the medical potential, risks and ethics of studying human embryonic stem (ES) cells. For proponents, these cells represent our greatest hope for treating devastating disorders such as Parkinson's disease, diabetes and spinal-cord injuries. But for those who are adamantly opposed to the use of cells derived from human embryos, stem cells from adults have been advocated as an ethically palatable and experimentally reasonable alternative.

Two papers in this issue rekindle the debate. On page 50, Kim and colleagues[1] describe how they generated a specific class of neurons from cultured mouse ES cells and used the neurons to reverse symptoms of Parkinson's disease in rats. In other words, ES cells can generate specialized cell types that are therapeutically effective in animals. Meanwhile, Jiang and colleagues[2] (page 41) have derived remarkably versatile cells from the bone marrow of adult mice, rats and humans. These two studies further the promise of stem cells even while they stoke the debate about whether such cells should be obtained from embryos or adults.

Stem cells, essential building blocks of multicellular organisms, have two defining properties — they can produce more stem cells and they can generate specialized cell types such as nerve, blood or liver cells. Stem cells come in different varieties, relating to when and where they are produced during development, and how versatile they are. Pluripotent stem cells give rise to all cell types. The best characterized are ES cells (Fig. 1), which are derived from very early mouse or human embryos. These cells proliferate indefinitely in culture, while retaining the potential to differentiate into virtually any cell type when coaxed. So, in principle, ES cells might be able to generate large quantities of any desired cell for transplantation into patients.

Stem cells collected from tissues of adults or older embryos are typically more restricted in their developmental potential and ability to proliferate. For example, blood-forming (haematopoietic) stem cells make all types of blood cells *in vivo*, but proliferate little in culture and have been thought not to make cells of other tissues. Recent studies have raised the possibility that some adult stem cells can give rise to cells outside their tissue of origin; however, these results are controversial[3] and have often proved difficult to reproduce[4]. Nonetheless, those opposed to using human ES cells tout the possibility of pluripotent adult stem cells as a way of realizing medical gain without ethical pain. Although researchers generate ES cells from pre-implantation embryos in culture, and several countries have sanctioned deriving human ES-cell lines from 'surplus' embryos created through *in vitro* fertilization, some remain uncomfortable with the destruction of human embryos, even those destined never to be implanted in a uterus.

Beyond these ethical issues, there are technical obstacles to the use of ES cells. First, these cells can be obtained only from very early embryos and, although several human ES-cell lines have been made, they will not be immunologically compatible with most patients who require cell transplants. So researchers will need either to derive many more ES-cell lines or to customize ES cells on a patient-by-patient basis by 'therapeutic cloning'. Second, undifferentiated ES cells form teratomas — benign tumours containing a mixture of tissue types — after being transplanted. Thus ES cells must be reliably differentiated into the appropriate cell type in culture before transplantation.

Moreover, until now it had not been proved that specialized cells derived from cultured ES cells can actually function within tissues after transplantation[5,6]. For example, mouse ES cells produce insulin-secreting cells in culture, but such cells have not been shown to reverse high blood sugar levels in mice with symptoms of diabetes[6]. It is perhaps not surprising that cells generated *in vitro* might not be equivalent to those arising *in vivo*, given the extensive cellular interactions and 'education' that take place during development. But Kim *et al.*[1] have now overcome this problem in their work on rats with symptoms of human Parkinson's disease.

Parkinson's disease is caused by the death of neurons, found in the striatal region of the brain, that produce the neurotransmitter dopamine and are involved in controlling movements. The symptoms of Parkinson's disease have been successfully treated in animals by transplanting dopamine-producing neurons into the striatum to replace lost neurons. In humans, however, results have been mixed[7]. A central problem has been the scarcity of suitable neurons. These neurons would be abundant if they could be produced from cultured ES cells, but this has proved inefficient and it has been uncertain whether the resulting neurons would be effective.

Enter Kim *et al.*[1]. To enhance the yield of dopamine-producing neurons, the authors expressed the Nurr1 protein — which is needed to generate these neurons *in vivo* — in cultured ES cells. The resulting neurons survived

100 YEARS AGO

Mr. Marconi's Results in Day and Night Wireless Telegraphy. **I can assure Prof. Joly that his explanation will not do. The observed effect, which if confirmed is very interesting, seems to me to be due to the conductivity, and consequent partial opacity, of air, under the influence of ultra-violet solar radiation. No doubt electrons must be given off from matter (dust as well as other matter) in the solar beams; and the presence of these will convert the atmosphere into a feeble conductor. Conducting power in the sea-water surface assists and guides the waves, retaining them in two dimensions after the same fashion as a telegraph wire retains them in one; but conductivity in the dielectric itself will tend to dissipate and enfeeble the waves, by a process of reflection resulting in some amount of distortion.** **O. Lodge**

From *Nature* 3 July 1902.

50 YEARS AGO

During the past three years, experiments have been conducted with subjects who have been given the task of solving mental-test items of a particular type. Suppose P_C be the probability that a particular subject will continue to work at a particular problem for some time t before giving it up, and let P_E be the probability that if a solution is recorded within this time it will be the correct one. If the universe of discourse is now restricted to correctly solved items, the probability (P_S) that a particular correct solution will be returned within a period of t sec. after the moment the problem is presented will be a function both of the dynamics of the problem-solving process as such and also of P_C.... Let P_S be defined as the probability which would obtain if $P_C = 1$ for $t = \infty$. No comprehensive statement can be made about a person's ability to solve a problem which does not involve at least these three probabilities, that is, any attempt to measure 'intelligence' by mental-test methods should involve assessments of P_C, P_E and P_S.... D is the difficulty of the problem being considered, defined in the conventional but arbitrary fashion $D = [100 - R]$, and R is the percentage of an adult British population (unselected) who achieve success with the item.

From *Nature* 5 July 1952.

Property	ES cells	MAPCs
Origin	Embryo	Adult bone marrow
Growth potential	Indefinite	Indefinite
Differentiate into most cell types?	Yes	Yes
Require growth factor LIF?	Yes	Yes (for mouse MAPCs)
Stability of chromosome integrity	Reasonably stable	High
Expression of marker protein Oct-4	High	Very low
Contribute to germ cells?	Yes	Not known
Produce blood cells on transplantation?	No	Yes
Display dosage compensation?	No	Not known
Efficiency of gene modification	High	Not known
Possibility of autotransplantation?	No	Yes

Figure 2 **Comparison of embryonic stem (ES) cells, and the multipotent adult progenitor cells (MAPCs) described by Jiang *et al.*[2]. ES cells (and mouse MAPCs) need LIF for growth; other cultured cells do not, so this seems to be a unique feature of pluripotent stem cells. The expression of Oct-4 in ES cells correlates with their versatility; if MAPCs are similar to ES cells one might expect comparable expression of Oct-4. Germ cells are eggs or sperm. Dosage compensation inactivates one X chromosome in females, so that males (which have one X and one Y chromosome) and females (XX) express X-chromosome genes to the same degree. Autotransplantation refers to the possibility of taking stem cells from patients, deriving the required specialized cells, and transplanting them back in the patients.**

after being transplanted into rats with symptoms of Parkinson's disease, and showed appropriate electrophysiological properties. More impressively, the rats started to recover normal movements. Others have transplanted partly differentiated ES cells to ameliorate Parkinson's symptoms in rats, but observed tumours in some of the animals[8]. By demonstrating efficacy while avoiding tumour formation, Kim *et al.* have achieved a proof of principle, although ES cells that have been genetically modified in this way might not be desirable for use in people.

To sidestep the disadvantages of ES cells, it would be ideal to identify a pluripotent adult stem cell that proliferates indefinitely in culture. This is just what Jiang *et al.*[2] seem to have done. Prior work[9] indicated that there is a population of stem cells in bone marrow, known as mesenchymal stem cells, that can form muscle, cartilage, bone and fat. Taking a similar approach, Jiang *et al.* started with non-haematopoietic bone marrow cells, cultured them, and isolated a population that they called multipotent adult progenitor cells (MAPCs).

In culture, single mouse MAPCs proliferated indefinitely and differentiated into many specialized cell types. Upon injection into mouse blastocyst-stage embryos, individual MAPCs contributed widely to developing tissues. And when injected intravenously into adult mice they gave rise to several blood and epithelial cell types. These stunning findings cannot readily be explained by incorrect identification of the progeny of the transplanted stem cells. But it remains possible that the MAPCs might have fused with blastocyst cells[10,11], explaining their versatility in that experiment.

Are MAPCs the adult equivalent of ES cells? More data are needed, yet so far it seems that there are both similarities and important differences between these cells (Fig. 2). What, then, are MAPCs? They might be very rare pluripotent stem cells that persist from the embryo into adult life. To prove this it would be necessary to identify these cells prospectively *in vivo* (rather than retrospectively *in vitro*) by the marker proteins they express, and to purify them without an intervening culture step.

Alternatively, MAPCs might not actually exist *in vivo*. The extended period of culture might have triggered certain bone marrow cells to regress to a more primitive state, just as primordial germ cells — from which eggs and sperm are produced — can be reprogrammed in culture to acquire properties like those of ES cells[12,13]. (In fact, ES cells do not exist as such in embryos; they arise after being cultured.) If so, we have much to learn about how cells can be reprogrammed in culture.

MAPCs might prove useful in treating diseases irrespective of their origin. But, until they have been identified *in vivo*, it's premature to speculate that they might have a natural role in repairing injured tissues. Moreover, although MAPCs can generate many specialized cell types, it remains to be seen whether those cells function normally and could be used to treat animals, as Kim *et al.*[1] used ES-cell-derived neurons. Such experiments will now be a priority, given the possibility of isolating MAPCs from the bone marrow of any patient, and transplanting the progeny of these cells back to the patient without risk of rejection.

The potential benefits of treating diseases by using specialized cells generated *in vitro* are enormous. But much further work is needed. Possible risks include the tendency of ES cells to form teratomas, and the unknown hazards of using cells — whether ES cells or MAPCs — that have been cultured

for long periods. And, although MAPCs seem to have normal chromosomes, it is important to establish that the pathways governing cell proliferation are unperturbed. Otherwise, short-term gains might fall prey to long-term complications.

The work of Kim *et al.*[1] and Jiang *et al.*[2] will not resolve the debate over embryonic versus adult stem cells. Rather, it underscores the need for research in this area to continue unfettered by political concerns. Only then will the public have a chance to get what it deserves: novel, validated and safe treatments for intractable diseases. ■

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Planetary science

An older face for Mars

Sean C. Solomon

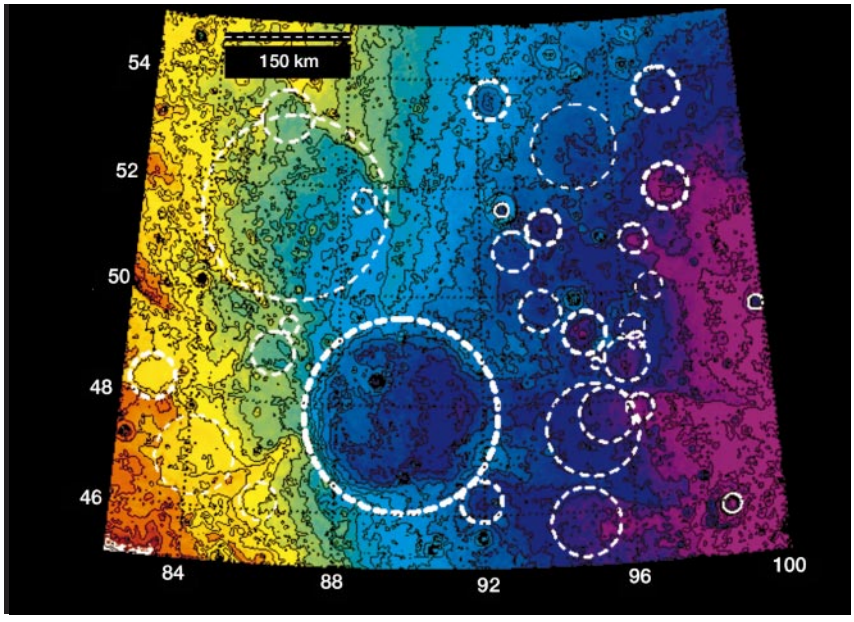
Mars has a north–south divide in the age of its surface, as judged by the density of impact craters. Altimetry data, which by inference provide a subsurface view of the planet, reveal that the divide is only skin deep.

A surprising finding from the exploration of Mars by orbiting spacecraft in the 1970s was that the southern and northern hemispheres have very different surfaces. The density of impact craters seen in images taken by Mariner 9 and Viking Orbiter indicated that the surface of the topographically high southern hemisphere is old enough to have preserved the effects of the early, heavy impact bombardment of the inner Solar System (known from lunar studies to have occurred before about 3.7 billion years ago). The surface of the northern hemisphere, in contrast, was revealed to be generally lower in elevation, to consist of smooth plains, and to contain a far lower density of impact features — implying a surface age hundreds of millions to billions of years younger.

A new view of this striking hemispherical contrast, the Martian 'crustal dichotomy', has come from an analysis of observations collected by the Mars Global Surveyor spacecraft, which has been in Martian orbit since 1997. From subtle signatures in topography measured by the Mars Orbiter Laser Altimeter Experiment[1], Frey and others[2] have identified a large population of nearly buried impact structures in both hemispheres that were not evident in the spacecraft images. More importantly, the areal density of these features, together with those previously mapped, indicates that the northern hemisphere has a buried surface that is essentially as old as the surface of the southern uplands.

Frey and colleagues[2] took the following approach in their search for buried impact features. From regional altimetric maps, in which different colours were assigned to narrow intervals of elevation from a global gridded data set, the group catalogued all roughly circular, localized depressions. They identified such depressions as candidate impact features if concentric segments of contours collectively totalled at least 180° of arc, and if the preserved relief exceeded 50 m — a figure much larger than the altimetry accuracy[1] of about a metre. Many of the features so catalogued had been identified as impact craters from orbiter images. As shown in Fig. 1, however, many others had not. In particular, Frey *et al.* counted 644 potential impact features greater than 50 km in diameter in the northern lowlands, many more than the 90 such features discernible from Viking Orbiter images. A strong argument that most, if not all, of the newly identified features are largely buried impact craters is that their areal density as a function of their diameter has the same form as the distribution for known impact structures. The southern highlands also contain buried impact craters newly recognized by this method, but they do not increase the total population of impact structures by as large a factor as in the north.

Frey and colleagues' main conclusion is that the geologically younger units constituting the uppermost crust of the northern hemisphere are a relatively thin veneer of material that incompletely masks an underlying ancient surface. There were a few previous clues that this was so. Careful photogeological mapping led to the suggestion[3] that underlying the deposits in the Utopia



H. V. FREY AND J. H. ROARK

Figure 1 **Partly buried impact craters, identified by Frey *et al.*[2], in the northern lowlands of Mars. The part of the planet shown is near the Utopia region. Elevation is colour-coded, with purple grading through blue and green to yellow, orange and red as height increases (orthographic projection, 50-m contour interval). Craters greater than 15 km in diameter visible in the earlier Viking Orbiter images are circled by solid lines. The many more craters discernible only from their topographic signatures are shown by thick dashed lines; thinner dashed lines denote less confident identifications.**