

PHYSIOLOGY  
OR MEDICINEMature cells can be  
rejuvenated

The recipients of the Nobel Prize in Physiology or Medicine are John B. Gurdon and Shinya Yamanaka, whose research — spanning more than four decades — showed that differentiated adult cells can be reprogrammed to become immature cells capable of developing into all the cell types of an organism (see figure).

FROM SCIENCE FICTION TO SCIENCE FACT  
by Janet Rossant

Even though the cloned animals John Gurdon produced were only tadpoles, the publication of his experiments<sup>1</sup> caused a media stir: the production of armies of identical cloned humans seemed to be moving from science fiction towards science fact.

But it took decades before cloning was achieved in mammals. Ian Wilmut and colleagues' 1997 creation of Dolly<sup>2</sup> — a sheep generated by transfer of an adult cell nucleus into an oocyte — opened up practical applications for cloning. This technology has been key to the generation of genetically modified pigs, sheep and cows, and cloned animals have been used to make pharmaceutical products in milk, to generate rejection-resistant pigs

for organ transplantation into humans, and as preclinical models of human disease. But it has also caused controversy: the spectre of human cloning still looms large in the public eye, despite the absence of any evidence that nuclear transfer from adult human cells could ever be effective or safe.

Nonetheless, a specialized form of nuclear transfer, in which the nucleus from an egg containing faulty mitochondria in its cytoplasm is transferred to the healthy cytoplasm of another egg<sup>3</sup>, has the potential to treat mitochondrial disease and is being developed for use in humans. From frogs to sheep to humans, the impact of Gurdon's experiments continues to challenge nature and to break boundaries.

A CELLULAR VERSION OF A PATIENT  
by Christine Mummery

Yamanaka and his co-author<sup>4</sup> showed that induced pluripotent stem (iPS) cells, which can form any kind of differentiated cell, can be derived from anyone. These cells are genetically identical to the person from whom they are obtained. So, once the technical hurdles are overcome, differentiated cells derived from iPS cells could be transplanted back into a patient without being rejected, to replace cells that have been damaged or lost through disease or trauma.

These cells are also fantastic disease models. In other words, the iPS cells can essentially become 'the patient'. They may carry the same disease-causing mutations present in a patient, or have genetic variants associated with predisposition (or resistance) to a disease. Once the iPS cells differentiate to form the cell types associated with the illness, the effects of these genetic variants may reveal the underlying causes of its symptoms. Moreover, researchers

might discover how a disease develops and look for ways to slow this down or even reverse it. Looking ahead, such insights might reveal windows of opportunity for treating the condition before symptoms appear.

Generating patient-specific cells from iPS cells is an exciting development for the pharmaceutical industry too. Reagents that restore gene or protein expression to normal levels in its derived cells may form the basis of therapies for disorders for which there is no treatment. Similarly, these cell models should help to identify drug targets or reveal side effects of medications. Moreover, they could recapitulate human diseases for which there are no good animal models, such as heart failure and some forms of muscular dystrophy.

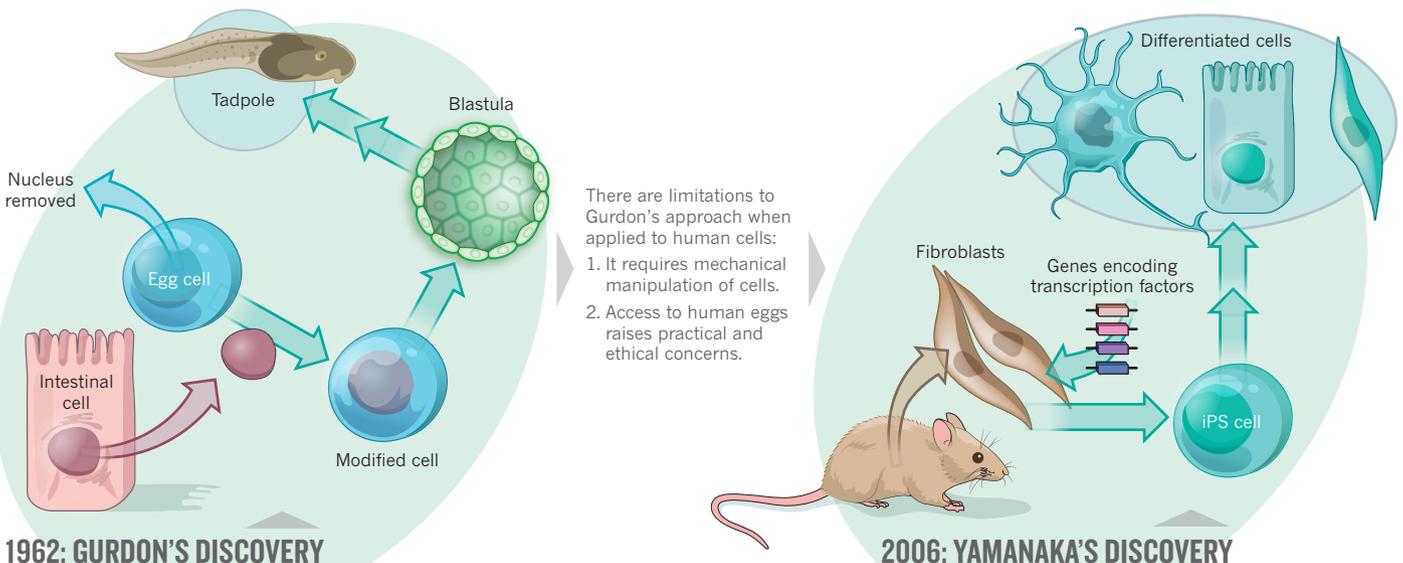
Because iPS cells can be derived from individuals of any ethnic background, they may eventually reveal why some conditions affect certain races more than others, why some drugs are preferentially toxic to some people and why patients may not respond to certain treatments. The potential of iPS cells is almost limitless, and there are exhilarating times ahead. ■

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4. Takahashi, K. & Yamanaka, S. *Cell* **126**, 663–676 (2006).



## 1962: GURDON'S DISCOVERY

When the nucleus of a differentiated intestinal cell is transferred into a nucleus-free egg, the resulting modified cell can go through normal embryonic development to form a blastula, which can generate a tadpole.

## 2006: YAMANAKA'S DISCOVERY

Introduction of genes encoding just four transcription factors into an intact, differentiated fibroblast can reprogram it into an induced pluripotent stem (iPS) cell that can differentiate into various cell types of the body.