overall reaction is energetically very favorable because C-H bonds are stronger than Si-H bonds, whereas Si-F bonds are stronger than C-F bonds. The silylium cation abstracts fluoride from the fluorocarbon, whereas the resulting carbocation abstracts hydride from the triethylsilane and regenerates the catalyst (see the figure, middle panel).

Douvris and Ozerov have used this reagent and catalyst on three different fluorocarbons. The first substrate, $C_6F_5CF_3$, contains both aromatic and aliphatic C-F bonds. The unprecedented result was complete disappearance of the substrate at 25°C after 6 hours and an 86% yield of $C_6F_5CH_3$ (see the figure, bottom panel). The reaction is thus completely selective for the saturated C-F bonds and leaves the aromatic C-F bonds untouched, even though the aromatic bonds are more reactive toward conventional reagents.

In the second substrate, $C_6H_5CH_2CH_2CF_3$, the CF_3 group is located far from the benzene ring, and it was thus possible to exclude any effect of the ring. When the authors dissolved this substrate in benzene and applied the catalyst-reagent mixture, they again observed complete disappearance of the substrate. This time, the product, $C_6H_5CH_2CH_2CH_2C_6H_5$,

resulted from hydrodefluorination and reaction with the solvent.

The final substrate, $CF_3(CH_2)_3C_2H_5$, contains saturated C-F and saturated C-H bonds. It demanded higher temperature, more catalyst, and longer reaction times (50°C and 120 hours), but strikingly, the authors observed complete conversion to linear, branched, and cyclic hexanes in various isomeric forms (see the figure, bottom panel).

Three parameters indicate that all of these reactions are highly effective: Conversion of the starting material exceeds 97%, small amounts of catalyst are needed, and turnover numbers (the number of times the catalyst runs the reaction) are high (14). These results open up the possibility of catalytic conversion of fluorocarbons to hydrocarbon products that could be reused or incinerated without special equipment. In addition to prospects for more satisfactory disposal of fluorocarbons, there are exciting possibilities for applying these principles in synthesis. However, in either case we will need ready access to hexachlorocarborane salts, and the system must be optimized to achieve even higher turnovers. The principle has yet to be extended to perfluoroalkanes—that is, fully

saturated molecules without C-H, such as $F_3CCF_2CF_3$. This remains a major challenge because it is likely that the initial reaction of perfluoroalkanes with Douvris and Ozerov's catalyst is energetically unfavorable.

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14. The catalyst loading, defined as the mole ratio of catalyst per reactive C-F bond in the substrate, is between 0.036% and 0.5%. The turnover number, defined as the number of C-F bonds in the substrate reacted per molecule of catalyst, is between 200 and 2700.

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DEVELOPMENTAL BIOLOGY

Neuron Research Leaps Ahead

Robert H. Brown Jr.

Technologies that reprogram adult dermal cells into motor neurons should advance our understanding of neurodegenerative diseases.

There has been substantial progress in defining the primary molecular defects causing inherited forms of major neurodegenerative diseases such as Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and Parkinson's disease. However, developing therapies for these diseases has been hindered by several experimental limitations, including the absence of in vitro models that accurately reproduce the genetic milieu of the disease and inadequate systems to dissect the roles of diverse cell types in the pathogenesis of these diseases. On page 1218 in this issue, Dimos *et al*. (*1*) demonstrate that new technologies in stem cell biology may overcome these barriers by reprogramming adult fibroblasts into embryonic stem cells that can subsequently yield patient-specific neural cells (neurons and astroglial cells) (*1*). The study focuses on ALS, but the findings are applicable to

diverse neurological diseases.

The Dimos *et al*. study follows a series of pioneering investigations on the production of embryonic stem cells. In 2006, Takahashi and Yamanaka showed that forced expression of four transcription factors (Oct4, Sox2, Kfl4, and Myc) reprogrammed adult mouse fibroblasts into mouse embryonic stem cells, designated induced pluripotent stem cells (*2*). Over the past 18 months, the same strategy, with some modifications, has been used to reprogram human cells to become the equivalent of embryonic stem cells (*3–6*).

Dimos *et al*. obtained fibroblasts from two elderly sisters (in their 80s) with ALS-associated mutations in the gene encoding superoxide dismutase (*SOD1*). One of the sisters had developed the neurodegenerative disorder. Fibroblasts from a skin biopsy of this patient were transduced with retroviruses that expressed the four key transcription factors, thus producing induced pluripotent stem cells (see the figure). Analysis of several parameters (e.g., mor-

phology, cell cycle status, cell surface markers, and gene expression patterns) verified that the derived cells were similar to embryonic stem cells. When propagated in culture, these induced pluripotent stem cells formed embryoid bodies, a hallmark of embryonic stem cells. Using a protocol from Wichterle and colleagues (*7*), Dimos *et al*. triggered the differentiation of motor neurons from embryoid bodies by treatment with sonic hedgehog and retinoic acid, agents that modify transcription and differentiation. Moreover, the *SOD1* mutation of the original donor was present in the patient-derived motor neurons. Within the same cultures, glial cells were also identified.

Dimos *et al*. not only demonstrate that human neural cells—in particular, disease-related neural cells—can be generated from induced pluripotent stem cells, but also that the method can be successfully applied to fibroblasts derived from elderly patients, a key issue for age-dependent disorders (like most of the neurodegenerative diseases).
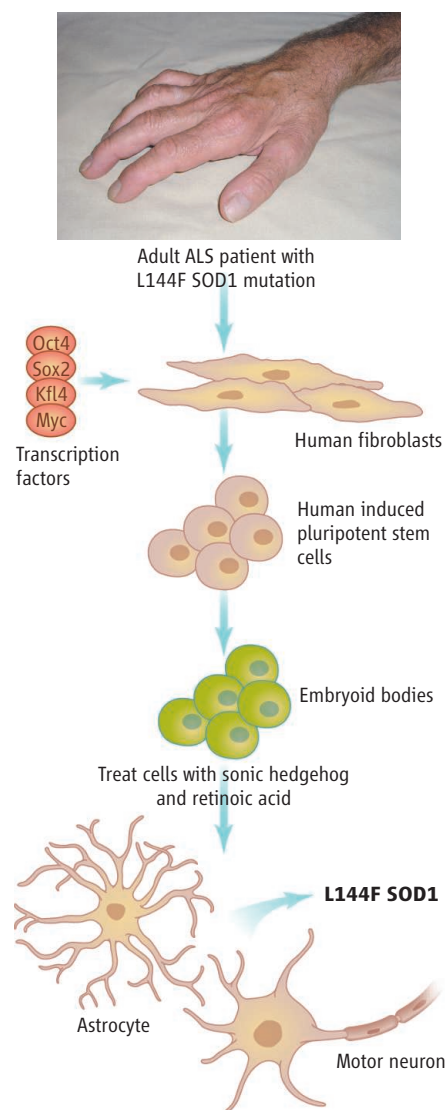
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Moreover, the study shows the feasibility of producing large numbers of induced pluripotent stem cells from a small skin biopsy.

One anticipates that this approach will be immediately useful in the analysis of motor neuron diseases. It should soon be possible to investigate disease-related characteristics of each type of patient-derived cells. In ALS, studies of rodents that are genetically engineered to express extremely high amounts of mutant SOD1 protein document multiple types of neuronal pathology, including perturbations of mitochondrial function, excessive excitation, and altered transport of molecules through axons (8, 9). In the same rodent models, data suggest that transport of glutamate into astroglia is defective (8, 9). It should now be possible to reexamine these phenomena by using neurons and glia that express physiological amounts of the mutant SOD1 protein, and establish a hierarchy of importance of the multiple findings from rodent models. It should also be possible to reanalyze the non–cell autonomous aspects of this disease. A study by Di Giorgio et al. recently showed that astroctyes from the transgenic amyotrophic lateral sclerosis animals secrete substances in vitro that adversely affect motor neurons (10); it should now be possible to determine whether this finding is reproducible in nontransgenic cells.

Our current understanding of the molecular basis for the neurodegenerative diseases is predicated largely on studies of gene defects transmitted as Mendelian traits. Still unknown is the degree to which the overall genetic makeup of patients with sporadic neurodegenerative diseases alters disease susceptibility or characteristics. A plausible hypothesis is that combinations of gene variants in sporadic ALS may increase sensitivity to harmful environmental influences. The use of genome analyses to address this challenging problem has thus far produced inconsistent results, although the field of complex genetics of sporadic neurodegeneration is still in its infancy (11, 12). The use of induced pluripotent stem cells should make it possible to study human embryonic motor neurons from sporadic patients in vitro, permitting analysis both of factors in the patients' genetic makeup that enhance disease susceptibility and of external factors that promote disease in the context of a patient-specific genotype.

The ability to generate induced pluripotent stem cells also has implications for developing therapies to treat neurological diseases. To the extent that disease phenotypes can be defined in vitro, these are now amenable to high-throughput approaches to drug screening, because large amounts of the implicated

Skin cells generate human neural cells. Fibroblasts from a patient's skin biopsy are transduced with four transcription factors to form pluripotential cells and then embryoid bodies which, after exposure to sonic hedgehog and retinoic acid, generate both motor neurons and astrocytes.

cell types can be generated from human fibroblasts. The availability of large numbers of neural cells that accurately reproduce the genotype of patients may also facilitate strategies of cell transplantation therapy. It has been proposed, for example, that transplantation of neural precursor cells into the spinal cord of patients with amyotrophic lateral sclerosis may be beneficial as a platform for delivering neurotrophic factors that promote neuron differentiation and growth (13).

For many years, a holy grail in neurodegenerative disorders has been the repopulation of the affected neural tissue with new neurons. In the most optimistic view, the Dimos et al. study can be cautiously viewed as a step

in that direction. It raises the prospect of using induced pluripotent stem cell technology to generate new motor neurons ex vivo that are genetically identical to those of a given patient and potentially useful for transplantation without rejection by the patient's immune system. Noteworthy is the observation that dopaminergic neurons derived by induced pluripotent stem cell technology can confer functional improvement when transplanted into a rat model of Parkinson's disease (14). Yet another option arising from this technology is the possibility that transcription factors could be delivered directly to the spinal cord to reprogram endogenous cells to generate new motor neurons.

Several cautionary questions arise. Given that the studies to date have relied on retroviruses to transduce the cells targeted for reprogramming, does the induced pluripotent stem cell method entail a risk for tumorigenesis? It is hoped that alternative induction methods (transient delivery of the transcription proteins or the use of small molecules mimicking the proteins) will address this issue. Will the embryonic neurons generated via induced pluripotent stem cells in vitro differentiate into mature motor neurons capable of extending axonal processes to allow functional innervation of muscle? If the biology of the disease in vivo is recapitulated in the induced pluripotent stem cell–derived neurons in vitro, will this prohibit effective use of patient-derived cells as donors in novel transplantation strategies? These concerns notwithstanding, the study by Dimos et al. is a seminal achievement. The authors have created a new platform for studying the biology of normal and diseased human neural cells that is likely to enhance studies of disease pathophysiology and accelerate the development of therapies for many categories of human nervous system disorders.

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