A patient's own skin cells may one day treat multiple diseases

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The possibility of developing stem cells from a patient's own skin and using them to treat conditions as diverse as Parkinson's disease, Alzheimer's disease and cancer has generated tremendous excitement in the stem cell research community in recent years. Such therapies would avoid the controversial need for using stem cells derived from human embryos, and in theory, also bypass immunological problems inherent in using cells from one person to treat another.

However, in the nearly five years since the first article describing the development of stem cells derived from adult cells — so-called induced pluripotent stem cells (iPSCs) — unique problems inherent in their use have surfaced and even their immunological safety has been called into question.

According to Paul S. Knoepfler, UC Davis associate professor of cell biology and human anatomy, finding such obstacles in such a new and novel approach is not surprising and should not dissuade investigators from actively pursuing this avenue of research. A roadmap for finding solutions to the problems identified with iPSCs, written by Knoepfler and Bonnie Barrilleaux, a postdoctoral fellow working in Knoepfler's laboratory, is available online and will be published in the Aug. 5 issue of the journal Cell Stem Cell. Their perspective, "Inducing iPSCs to escape the dish," suggests research strategies to advance the field more rapidly toward applications for human diseases.

"iPSCs offer the potential to treat many diseases as an alternative or

adjuvant therapy to drugs or surgery," said Knoepfler, who also is a faculty member of the UC Davis Genome Center and UC Davis Cancer Center. "Problems that have been identified with their use likely can be overcome, allowing iPSCs to jump from the laboratory dish to patients who could benefit from them."

iPSCs were first produced in 2006 from mouse cells and in 2007 from human cells. They have many of the same regenerative properties as human embryonic stem cells, but they are derived in a lab from adult cells, such as skin cells, by inducing or forcing them to express specific genes that are normally dormant in that type of cell. In theory, a person's skin cells could be induced to make neurons that produce the neurotransmitter dopamine, for example, and be delivered to brain regions where it is lacking in patients with Parkinson's disease. Similarly, cells could be induced to regenerate heart muscle and blood vessels after a heart attack, or neurons following a spinal cord injury. Many labs at UC Davis, including the Knoepfler lab, are producing and studying human iPSCs.

One advantage cited for iPSCs over stem cells derived from embryos is that problems of rejection due to immunological differences between the donor (the embryo) and the patient would be eliminated, because the iPSCs would be derived from each individual patient. A recent study using iPSCs in mice found that tissue rejection may, in fact, occur in some cases. However, Knoepfler believes that particular study was conducted in the context of tumors, which tend to be highly immunogenic and not be applicable for human use. While the ability of human iPSCs to escape immune attention must be investigated further, Knoepfler says that iPSCs remain an attractive potential avenue for stem cell-based medicine, in addition to embryonic stem cells.

Another concern with using either iPSCs or embryonic stem cells is that cells with the ability to turn into many different cell types may grow out

of control, producing cancerous tumors. Knoepfler points out those studies involved implanting large numbers of undifferentiated stem cells into mice that were treated with immunosuppressant drugs to reject transplants, making the conditions ideal for cancers to arise. This scenario, he argues, is unlikely to be applicable when treating humans for actual diseases. In such cases, the stem cells would be induced to have a specific function, and the body's natural immune defenses would be present.

The "pluripotent" nature of stem cells, which potentially allow their use to repair almost any tissue, is only beginning to be harnessed for human therapies. Stem cell therapy has already been successfully used for years to treat leukemia and related bone and blood cancers. The use of iPSCs could vastly increase the spectrum of diseases that might be treated with stem cells, without the safety and ethical concerns inherent in using embryonic stem cells.

"Dr. Barrilleaux and I argue for a shift in research priorities," said Knoepfler. "Future studies of iPSCs should increasingly focus on issues most relevant to the eventual clinical use of the cells, offering the fastest pathway to treating patients with this potentially powerful therapeutic tool."

Knoepfler's own research focuses on determining how stem cell behavior is controlled during normal embryonic development as well as during healing and regeneration. He also studies how control systems go awry in developmental disorders and cancer. One key direction for the Knoepfler lab is using leading genomics technology to better understand why stem cells behave the way they do and how to change that behavior for clinical use.

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