The promise of stem cells in Parkinson disease

J. William Langston

Parkinson’s Institute, Sunnyvale, California, USA.

Neurotransplantation as a treatment for Parkinson disease reached the stage of human trials over 15 years ago, but the field, which is still in its infancy, has encountered a number of roadblocks since then, both political and scientific. With hope that stem cells may be used as a new source of dopaminergic neurons to replace the degenerating nerve cells in Parkinson disease looming, it is critical that we learn from the past as we work toward achieving new milestones aimed at making this new therapeutic strategy a reality. One of those milestones, which is a significant translational step in the development of stem cell technology and the subject of a report in this issue of the JCI, involves transplanting new dopaminergic cell lines to a primate model of Parkinson disease (see the related article beginning on page 102).

The possibility of repairing the damaged human brain has been a dream of physicians and scientists for decades. Over time it has become obvious that Parkinson disease is a natural first when it comes to tackling this ambitious feat, primarily because the majority of the signs and symptoms appear to result from the progressive loss of cells in a small area known as the substantia nigra, which sits atop the brain stem. These cells make dopamine, which is delivered to a part of the basal ganglia known as the striatum; when nigral neurons die and striatal dopamine diminishes, the signs and symptoms of Parkinson disease become manifest. Thus, replenishing missing neurons in a limited area of the brain should in theory reverse parkinsonism, making this an attractive approach. But the challenge of actually replacing injured and/or lost neurons in the adult human nervous system has proven to be a daunting task with far more bumps in the road, both political and scientific, than anyone would have anticipated.

Neurotransplantation: trials and tribulations

While stem cell therapy is very much in the forefront when approaches to brain repair and cell replacement therapy are being considered, there is already a substantial body of work in the Parkinson disease field involving neurotransplantation, including the use of both adult adrenomedullary tissue and human fetal mesencephalic tissue (which is rich in dopaminergic [DA] neurons); the lessons learned should not be ignored. While adrenomedullary transplantation proved to be something of a medical fiasco, with little efficacy and unacceptable morbidity and mortality, a number of the early open label trials with human fetal mesencephalic tissue appeared to be very promising. However, due to a ban on the use of federal funds for research utilizing human fetal tissue imposed by then-President Ronald Reagan, little work was done in this area until President Bill Clinton lifted this moratorium on his second day in office. Not long thereafter, 2 large controlled clinical trials aimed at using fetal human mesencephalic tissue transplanted to the striatum to treat Parkinson disease were launched with federal funding. However, to the surprise of many, both trials failed to show a significant clinical benefit based on their primary endpoint variables (1, 2) in spite of substantial evidence of graft survival based on both autopsy (3) and imaging studies. Unfortunately, a substantial subset of patients also developed persistent excessive movements known as dyskinesias (2). Dyskinesias are typically a consequence of long-term l-dopa therapy, but in the patients

Nonstandard abbreviations used: DA, dopaminergic.

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receiving transplants, these movements persisted even after L-dopa was discontinued, raising serious safety concerns.

Why didn’t this approach work? Theories range from poor graft survival to the possibility that low-grade inflammation interfered with graft function. But the reality is that we still don’t know. Why is all this relevant to the use of stem cells to treat Parkinson disease? First, strategies used in fetal cell transplantation are essentially the same as those which will be applied with DA stem cells, but we are now in a quandary regarding this entire approach. A second hurdle relates to the vast technical barriers that are being encountered in the process of learning how to use stem cells to treat any human disease. With regard to Parkinson disease, the first task has been to create authentic DA cell lines that can be used to replace the missing neurons in the nigrostriatal system, and the second to get those cells to persist in vivo without forming tumors. While this has been an intensive area of research, there are only a limited number of successes so far, and these have been achieved primarily in rodents (4–7). For these reasons, the current report by Takagi and colleagues in this issue of the JCI is of great interest (8). These investigators have prepared what appear to be authentic DA neurons and used those cells to reverse parkinsonism in a primate model of the disease (Figure 1). This is important because treatment of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine–induced (MPTP-induced) parkinsonism in primates (the model used here) has proven highly predictive of new symptomatic approaches in the treatment of Parkinson disease. Yet we still have a long way to go.

Challenges for the future

While the observations in the current study (8) are encouraging, the number of surviving DA neurons was very low, with only 1% to 3% of the cells surviving—well below the estimated number of DA neurons that survived after fetal cell transplants, where figures hovered around 10%. The explanation may lie in species differences and/or simple volumetric issues; however, based on what we have learned to date in human fetal cell trials, it may be necessary for far more DA neurons to survive, and, of course, the survival must be long lasting, an aspect of therapy that was not assessed in the current study. It is also important to note that, as the authors point out, dyskinesias were not observed in their monkeys. However, the authors do not present evidence that this species develops L-dopa–induced dyskinesias, and much longer-term follow-up may be needed since dyskinesias were typically not seen during the first year in human studies. It is good news that tumors were not observed, but this could also be related to the small number of surviving cells.

Keeping in mind these caveats, clearly the study reported here will advance research aimed at validating the use of stem cells to treat neurodegenerative disease. And
this is most welcome, particularly for
investigators working on strategies for cell
replacement the United States, who must
be feeling something of a déjà vu in face
of yet another presidential moratorium,
this time limiting the number of human
stem cell lines that can be used for research
and treatment. Ironically, this frustration
recently led California voters to approve a
$3 billion initiative to fund stem cell
research, which some have predicted will
lead to a “gold rush” on stem cell research
(9). Regardless of whether or not this
proves to be the case, it can be hoped that
this new initiative will serve as a beacon of
hope for scientists and patients alike as
we press ahead in this challenging area of
science that appears to promise so much
for the treatment of human diseases.

Address correspondence to: J. William
Langston, The Parkinson’s Institute,
1170 Morse Avenue, Sunnyvale, Cali-
ifornia 94089-1605, USA. Phone: (408)
734-2800; Fax: (408) 734-8522; E-mail:
jwlangston@theipi.org.

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Immune complexes as therapy for autoimmunity

Raphael Clynes

Department of Medicine and Microbiology, Columbia University, New York, New York, USA.

For several decades, intravenous Ig has been used as treatment for a variety of
immune-related diseases, including immune thrombocytopenic purpura
(ITP), autoimmune neuropa-thies, systemic lupus erythematosus, myasthe-
nia gravis, Guillain-Barré syndrome, skin blistering syndromes, and Kawas-
ski disease. Despite years of use, its mechanism of immunomodulation
is still unclear. Recent studies using mouse models of ITP and arthritis,
including one reported in this issue of the JCI (see the related article begin-
ning on page 155), now provide some insights into this mechanism and the
rationale for the development of Fcγ receptor–targeted therapeutics.

Fc receptors in the pathogenesis
and treatment of ITP

Intravenous Ig (IVIg) is remarkably
effective in the treatment of immune
thrombocytopenic purpura (ITP), with
improved platelet counts seen in 80% of
treated patients. ITP occurs in patients as
the result of the generation of autoantibodies
that bind to platelet surface antigens. These
opsonized platelets are phagocytosed by
Fc receptor–bearing splenic and hepatic
macrophages (1). In the mouse, macro-
phage-mediated clearance occurs via acti-
vating Fc receptors, with complement-medi-
ated uptake playing little or no role (2, 3).
Thus, blockage of activating Fc receptors
(FcγRs) would be predicted to be an effec-
tive therapy in ITP. Indeed, this has proven
to be a valid approach; antibodies that block
FcγRIII have been shown to be effective in
murine studies (2, 4) as well as in pilot clin-
ical studies (5).

Although activating Fc receptor blockade is
an appealing mechanism, a second, unexpect-
ed FcγR-related pathway is clearly rele-
ant to the therapeutic action of IVIg. It was recently
shown (4) that the protective effect of IVIg is
associated with upregulation of the inhibito-
ry receptor FcγRIIB on splenic macrophages
and is abrogated in mice lacking FcγRIIB.
Curiously, this effect is independent of SHIP
and SHP-1 (6), the 2 downstream inhibi-

tory phosphatases previously assumed to
include cell-associated and soluble host
antigens bound by donor natural antibodies
as well as dimers and aggregated Igs formed
in the IVIg product itself. Using mimetic
modeling studies, Siragam et al. (11) suggest
that the 2 therapeutics IVIg and anti-D have

Nonstandard abbreviations used: FcγR, Fcγ receptor;
IC, immune complex; ITP, immune thrombocytopenic
purpura; IVIg, intravenous Ig.

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commentaries

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