A Failed Future

Roger L. Albin, MD
Jeffrey H. Kordower, PhD

¹GRECC & Neurology Service, VAAAHS, Ann Arbor, MI, USA
²Dept. of Neurology, University of Michigan, Ann Arbor, MI, USA
³University of Michigan Parkinson’s Foundation Research Center of Excellence, Ann Arbor, MI, USA
⁴Michigan Alzheimer Disease Center, Ann Arbor, MI, USA
⁵Dept. of Neurological Sciences, Rush University Medical Center, Chicago, IL, USA
⁶Dept. of Neurosurgery, Rush University Medical Center, Chicago, IL, USA

Address Correspondence to: Roger L. Albin, 5023 BSRB, 109 Zina Pitcher Place, Ann Arbor, MI, USA, 48109-2200, ralbin@med.umich.edu, (ph) 734-764-1347, (fax) 734-763-7686.

Word Count: 1165

Keywords: Huntington disease, Transplant, Grafts, Fetal Tissue

Financial Disclosure/Conflicts of Interest: The authors have no relevant financial disclosures or conflicts of interest.

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/mds.28130

This article is protected by copyright. All rights reserved.
Funding Sources: Supported grants from the Parkinson’s Foundation, Michael J. Fox Foundation, P50NS091856, and R21NS114749 to RLA.
In this issue, Bachoud-Levi et al. describe the results of the Multicentric Intracerebral Grafting in Huntington Disease (MIG-HD) study, a phase II trial of engrafting fetal ganglionic eminence tissue into the striata of subjects with manifest HD. The concept motivating MIG-HD was that fetal ganglionic eminence contains striatal neuron precursors, that engrafted cells would differentiate into striatal projection neurons and reconstitute some of the striatal circuitry degenerating in HD, and that grafting would produce symptomatic improvement. Based on preclinical non-human primate experiments and single-site open label study data, the authors designed an ambitious experiment to assess target engagement, safety, and efficacy.

Prior open-label, single site studies were heterogeneous. Grafting methods differed (tissue blocs versus cell suspensions and varying numbers of grafts), there was variable subject selection and outcome measures, and markedly differing approaches to immunosuppression varying from none to several different regimens. There were no actual controls in any prior study and a number of serious adverse events, notably subdural hematomas (SDHs) requiring evacuation, were reported. Outcomes were highly variable with a small number of reports of that were suggestive, but not definitive, of improvement after grafting. MIG-HD aimed to bring some order to the field with a uniform multi-center study. To address the critical issue of controls, the MIG-HD investigators chose a delayed start design with a substantial run-in period to estimate the rates of decline of all subjects. This approach allowed comparison of grafted and delayed grafted subjects and comparison also of subject clinical trajectories before and
after grafting. Tissue blocs were engrafted, the surgical approach was standardized, standard immunosuppression protocols were employed, and engraftment was measured with PET imaging and cortical evoked potential methods. This complex study had to overcome a number of obstacles and required a significant extension of the study period to accumulate the projected number of subjects.3

Bachoud-Levi et al. provide a clear and comprehensive description of MIG-HD outcomes.2 Neither the primary outcome measure, changes in the Total Motor Score component of the Unified Huntington Disease Rating Scale (UHDRS-TMS), nor any of the numerous secondary/exploratory measures revealed evidence of engrafting benefits. Particularly problematic is the fact that PET studies indicated failure of the transplants to survive, in clear contrast to previous studies that demonstrated graft viability upon post-mortem assessment4,5,6. The hypothesis underlying this major effort could not really be tested. Furthermore, there was immunological evidence of rejection responses in numerous subjects, resulting in a midstream immunosuppression protocol alteration. Out of 53 subjects, there were 10 serious procedure related adverse events, including 1 intracranial empyema, 3 SDHs (2 requiring surgical intervention), 1 putaminal hematoma with significant sequelae, 1 seizure, 1 clinically manifest graft rejection event, and 3 intrastriatal cysts (1 requiring endoscopic surgery with cauterization of ectopic choroid plexus). Intrastriatal cysts occurred previously in grafted HD patients7, likely caused by inadequate tissue dissection/preparation8. Because of SDHs, the grafting procedure was modified after the initial 29 grafting sessions by reducing the number of injection tracks. Due to evidence of graft rejection, the immunosuppression regimen was intensified for the last 20 subjects, although this did not seem to help graft viability.
What can be learned from MIG-HD? With respect to efficacy, the results are clearly negative on all measures. There was no positive evidence of successful engraftment and the significant changes in surgical methods and immunosuppression protocols in mid-trial makes the dataset difficult to interpret. Parallel efficacy and engraftment results were obtained in a single-site German study that mimicked the MIG-HD protocol (N=10). The authors argue that MIG-HD results are informative in terms of other goals of phase II studies – assessing safety and study procedures. The authors argue that MIG-HD results led to a safer surgical approach and demonstrated the need for improved immunosuppression. In light of the present results, this interpretation can only be justified for a devastating and universally fatal disease such as HD.

It is unlikely that future cell-based therapy experiments will utilize fetal tissues. The implication is that the MIG-HD experience will inform future cell-based therapy experiments based on embryonic stem cells (ESCs) or induced pluripotent stem cells (IPSCs). This interpretation may be generous. Reducing the number of injection tracks may reduce surgical complications but as the goal is to reconstitute striatal circuits, reducing the number of injections may also reduce the probability of a clinical effect. Some current therapeutic gene therapy trials are delivering compounds to the putamen using a posterior to anterior approach. This approach would likely be safer although any clinical trial using this approach for HD cell-based therapy should be preceded and modeled by experiments in nonhuman primates. Whether or not failure of immunosuppression was responsible for engraftment failure is difficult to assess without evidence that engraftment succeeded in at least some subjects. The authors’ interpretation is problematic as intraputamenal solid tissue nigral grafts in Parkinson disease...
patients survive consistently\textsuperscript{11-15}. Ependymal cells, which are notoriously antigenic, may have been included in these tissue preparations. As the authors point out, it’s likely that significant bench research will be needed to clarify the role of immunosuppression and indicate appropriate protocols. As the field moves towards cell-based therapies with individual patient derived iPSCs, immunosuppression may not be required.

One thing that is very clear is that a trial of this kind requires a great deal of effort. The costs of the MIG-HD trial should be measured partly in terms of opportunity costs. These resources, not least of which was the time and effort of numerous talented investigators, could have been devoted to more productive experiments. The MIG-HD results and this additional consideration should prompt re-examination of the rationale for cell-based therapies in HD. HD is a multisystem neurodegeneration. It is true that there is early, preferential loss of striatal projection neurons but many brain regions undergo marked neurodegeneration. In addition, the motor aspects of HD are a lower priority for therapeutic attention as personality and cognitive impairments are the major sources of disability in early to moderately advanced HD. The evidence for striatal circuit reconstitution improving these features is less compelling. There is also experimental evidence that striatal neurodegeneration in HD is partly the consequence of loss of trophic support from neocortical afferents.\textsuperscript{16} Against this background, the idea that focal striatal engraftment will produce marked clinical effects, and they would have to be marked to justify the risks of surgery (and possible immunosuppression), seems naïve.

Scientists and physicians are avid consumers and promoters of novel technologies. Historians of industrial technologies remind us that most efforts to develop novel technologies end in failure.\textsuperscript{1} Biomedical research, as shown by the pitiful success rate of drug candidates
entering clinical trials, is no exception. In pursuit of novel technologies, there is a constant risk that enthusiasm for innovation leads to sterile infatuations with specific approaches. The pursuit of useful therapies for HD has been frustrating. This frustration should not overpower our critical judgment and promote perseverative pursuit of approaches unlikely to succeed.
Authors’ Roles: RLA – initial draft, writing, review, and critique. JHK – writing, review, and critique.

Financial Disclosures: RLA - grant support from the Parkinson’s Foundation, Michael J. Fox Foundation, P50NS091856, R21NS114749, R25 NS089450, and P30AG053760. RLA serves on the DSMBs for the M-STAR (ICON/Biohaven), COMPASS (IQVIA/Biogen), and PASSPORT (IQVIA/Biogen) trials. RLA has been a paid consultant for Takeda and the Michael J. Fox Foundation. JHK has been a paid consultant for Seelos Inc, Inhibikase Inc, Brainstorm Inc, Clintrex Inc., Fuji-Cellular Dynamics, and Abbvie. JHK has received grant support from Biogen Inc, the Michael J. Fox Foundation, and Abbvie.


3) Bachoud-Levi A-C. From open to large-scale randomized cell transplantation trials in Huntington's disease: lessons from the multicentric intracerebral grafting in Huntington's disease trial (MIG-HD) and previous pilot studies. Prog Brain Res 2017; 230:227-261.


This article is protected by copyright. All rights reserved.


COPYRIGHT TRANSFER AGREEMENT

Date: 5/11/20
Contributor name: Roger L. Albin, MD
Contributor address: 5023 BSRB, 109 Zina Pitcher Place, Ann Arbor, MI, 48109-2200
Manuscript number: MDS-20-0654
Re: Manuscript entitled: A Failed Future (the “Contribution”)
for publication in: Movement Disorders (the “Journal”)

Published by Wiley on behalf of The International Parkinson and Movement Disorder Society (the “Owner”)

Dear Contributor(s):

Thank you for submitting your Contribution for publication. In order to expedite the editing and publishing process and enable the Owner to disseminate your Contribution to the fullest extent, we need to have this Copyright Transfer Agreement executed. If the Contribution is not accepted for publication, or if the Contribution is subsequently rejected, this Agreement shall be null and void. **Publication cannot proceed without a signed copy of this Agreement.**

---

**A. COPYRIGHT**

The Contributor assigns to the Owner, during the full term of copyright and any extensions or renewals, all copyright in and to the Contribution, and all rights therein, including but not limited to the right to reproduce, publish, republish, transmit, sell, transfer, distribute, and otherwise use the Contribution in whole or in part in electronic and print editions of the Journal and in derivative works throughout the world, in all languages and in all media of expression now known or later developed, and to license or permit others to do so.

**B. RETAINED RIGHTS**

Notwithstanding the above, the Contributor or, if applicable, the Contributor’s employer, retains all proprietary rights other than copyright, such as patent rights, in any process, procedure or article of manufacture described in the Contribution. This reservation of rights does not affect or limit the rights assigned to Owner in Section A.

**C. PERMITTED USES BY CONTRIBUTOR**

1. License. The Owner grants to Contributor a non-exclusive, non-transferable and limited license to reproduce and distribute copies of the print or electronic “preprints” of the unpublished Contribution, in the original form submitted to the Journal prior to the peer review process, solely to colleagues within the Contributor’s nonprofit organization or educational institution. The Contributor shall make no more than 100 printed copies of the preprints in any calendar year. Such preprints may be posted as electronic files on the Contributor’s own personal website, on the Contributor’s internal intranet at Contributor’s nonprofit organization or educational institution, or on a secure external website at the Contributor’s nonprofit organization or educational institution, provided that access is limited to employees and/or students at Contributor’s non-profit organization or educational institution. Contributor shall not charge a fee for any
preprints, and Contributor’s use under this Section C shall not be for any commercial purpose, or for any systematic external distribution (e.g., posting on a listserv, public website, database connected to a public access server, or automated delivery system). The license grant in this Section does not apply to for-profit corporations, and any proposed use outside of the scope of this Section C must be pre-approved in writing by the Owner. The rights granted to Contributor under this Section C do not include reproduction, distribution or any other use of rating scales, videos or other audiovisual materials associated with the Contribution.

2. Required Citation. Prior to publication, the Contributor must provide full credit and acknowledgement of the Journal in all preprints in the following format: This is a preprint of an article accepted for publication in [Journal Title], Copyright © [year] The International Parkinson and Movement Disorder Society. After publication, the Contributor must provide a citation to the Journal in all preprints in the following format: This is a preprint of an article that was published in [Journal title]: (Title of Article, Contributor, Journal Title and Volume/Issue, Copyright © [year] The International Parkinson and Movement Disorder Society). An electronic link must be provided to the Journal’s website, located at http://www.interscience.Wiley.com. The Contributor agrees not to update the preprint or replace it with the published version of the Contribution.

3. Accepted Version. Re-use of the accepted and peer-reviewed (but not the final typeset published) version of the Contribution (the “Accepted Version”) is not permitted under this Agreement. There are separate arrangements with certain funding agencies governing reuse of the Accepted Version. Additional terms apply if the Contributor receives or received funding from these agencies. The details of those relationships, and other offerings allowing open web use, are set forth at the following website: http://www.wiley.com/go/funderstatement.

4. Additional Terms for Certain Funders. Certain funders, including the NIH, members of the Research Councils UK (RCUK) and Wellcome Trust require deposit of the Accepted Version in a public repository after an embargo period. Details of funding arrangements are set out at the following website: http://www.wiley.com/go/funderstatement. Additional terms may be applicable. Please contact the production editor for the journal at MDSprod@wiley.com if you have additional funding requirements.

If any Contributor receiving funds from applicable sources does not choose the Owner’s OnlineOpen option, the Contributor will be allowed to self-archive by depositing the Accepted Version in a public repository after the following applicable embargo period has expired, subject to further conditions imposed by the RCUK:

a. 12 months from first publication online of the final published version of the Contribution for research funded by members of the Research Councils UK (RCUK) other than The Economic and Social Research Council (ESRC) and the Arts and Humanities Research Council (AHRC); or

b. 24 months from first publication online of the final published version of the Contribution for research funded by ESRC or AHRC.

5. Additional Terms for Certain Institutions. Wiley has arrangements with certain educational institutions to permit the deposit of the Accepted Version in the institutional repository after an embargo period. Details of such arrangements are set out at the following website: http://olabout.wiley.com/WileyCDA/Section/id-406074.html. Additional terms may be applicable.

If any Contributor affiliated with these applicable educational institutions does not choose the Owner’s OnlineOpen option, the Contributor will be allowed to self-archive by depositing the Accepted Version in the educational institution’s repository after the following applicable embargo period has expired. See the following website for details: http://olabout.wiley.com/WileyCDA/Section/id-817011.html.

This article is protected by copyright. All rights reserved.
D. CONTRIBUTIONS OWNED BY EMPLOYER

If the Contribution was written by the Contributor in the course of the Contributor’s employment (as a “work-made-for-hire” in the course of employment), the Contribution is owned by the company/institution which must execute this Agreement (in addition to the Contributor’s signature). In such case, the company/institution hereby assigns to the Owner, during the full term of copyright, all copyright in and to the Contribution for the full term of copyright throughout the world as specified in Section A above.

E. GOVERNMENT CONTRACTS

In the case of a Contribution prepared under U.S. Government contract or grant, the U.S. Government may reproduce, without charge, all or portions of the Contribution and may authorize others to do so, for official U.S. Government purposes only, if the U.S. Government contract or grant so requires. (U.S. Government, U.K. Government, and other government employees: see notes at end.)

F. CONTRIBUTOR’S REPRESENTATIONS

The Contributor represents that the Contribution is the Contributor’s original work, all individuals identified as Contributors actually contributed to the Contribution, and all individuals who contributed are included. The Contribution is submitted only to this Journal and has not been published before. (If excerpts from copyrighted works owned by third parties are included, the Contributor will obtain written permission from the copyright owners for all uses as set forth in the Journal’s Instructions for Contributors, and show credit to the sources in the Contribution.) The Contributor also warrants that the Contribution contains no libelous or unlawful statements, does not infringe upon the rights (including without limitation the copyright, patent or trademark rights) or the privacy of others, or contain material or instructions that might cause harm or injury. Upon request, Contributor will provide the data or will cooperating fully in obtaining and providing the data on which the Contribution is based for examination by the editors or their assignees.

G. FINANCIAL DISCLOSURES

The Contributor certifies that his/her financial and material support for this research and work, regardless of date, is clearly identified on Exhibit A to this Agreement. The Contributor has also identified on Exhibit A, all other support unrelated to this research, covering the past year from the date of submission (e.g., grants, advisory boards, employment, consultancies, contracts, honoraria, royalties, expert testimony, partnerships, or stock ownership in medically-related fields).

H. VIDEO AND PHOTOGRAPHY CONSENT

In the event that the Contribution includes, discloses or incorporates any content (including, without limitation, any video clip or photograph) which identifies any individual patient(s) (“patient identifiable content”), the Contributor obtained from such patient(s) written consent to such inclusion, disclosure or incorporation and that this consent fully complies with all legal requirements, including without limitation, all of the requirements of the laws of the jurisdiction(s) to which the patient(s) and the patient(s)’ physician are subject, including the United States Health Insurance Portability and Accountability Act of 1996 (“HIPAA”) if applicable. The Contributor hereby certifies that, if the patient consent form is in a language other than English, such consent form meets all of the requirements set forth in the Instructions to Authors. In addition, the Contributor hereby confirms that he/she obtained from patient(s) written consent to use the patient identifiable content in both print and online (i.e., internet/web-based) publication formats. The Contributor further certifies that the person executing any such patient consent form, to the best of his/her knowledge, had legal capacity under applicable law to execute the form on behalf of the patient.
I. ACKNOWLEDGEMENTS

The Contributor should obtain written permission from all individuals named in the acknowledgement since readers may infer their endorsement of data and conclusions. The Contributor certifies that all individuals named in the acknowledgement section have provided written permission to be named.

J. MISCELLANEOUS

This Agreement may be amended or modified only in a writing executed by both parties. The waiver or failure of any party to exercise any rights under this Agreement shall not be deemed a waiver or other limitation of any other right or any future right. This Agreement shall inure to the benefit of, and shall be binding upon, the parties, their respective successors and permitted assigns. This Agreement may be executed in two (2) or more counterparts, each of which shall be an original and all of which taken together shall constitute one and the same agreement. Executed copies of this Agreement may be delivered by facsimile transmission, pdf/email or other comparable electronic means. If for any reason any provision of this Agreement shall be deemed by a court of competent jurisdiction to be legally invalid or unenforceable, the validity, legality and enforceability of the remainder of this Agreement shall not be affected and such provision shall be deemed modified to the minimum extent necessary to make such provision consistent with applicable law and, in its modified form, such provision shall then be enforceable and enforced. The parties agree to do such further acts and to execute and deliver such additional agreements and instruments from time to time as either may at any time reasonably request in order to assure and confirm unto such requesting party the rights, powers and remedies conferred in the Agreement. This Agreement, including any exhibits attached hereto, contains the entire agreement and understanding of the parties with respect to the subject matter hereof, and supersedes all prior agreements, negotiations, representations and proposals, written and oral, relating thereto.

All Contributors must sign below. Contributors must check one box except that NIH grantees should check both Contributor-owned work and the NIH grantee box. If your Contribution was written during the course of employment, your employer must also sign where indicated.

Please send your original completed and signed forms by fax or email a scanned copy to the Journal production editor. For production editor contact details please visit the Journal’s online author guidelines. Do not send in hard copies of these forms.

[ XXX ] Contributor-owned work

Roger L. Albin, MD; Professor of Neurology

Jeffrey H. Kordower, PhD; Professor of Neurological Sciences

This article is protected by copyright. All rights reserved.
[_____] Company/Institution-owned Work (made-for-hire in the Course of employment)

Company or Institution (Employer-for-Hire) Date

__________________________
Authorized signature of Employer Date

__________________________
Contributor’s signature Date

__________________________
Type or print name and title

ATTACH ADDITIONAL SIGNATURE PAGES AS NECESSARY

[_____] U.S. Government work

Note to U.S. Government Employees
A contribution prepared by a U.S. federal government employee as part of the employee's official duties, or which is an official U.S. Government publication, is called a "U.S. Government work", and is in the public domain in the United States. In such case, Paragraph A.1 will not apply but the Contributor must type his/her name (in the Contributor's signature line) above. Contributor acknowledges that the Contribution will be published in the United States and other countries. If the Contribution was not prepared as part of the employee's duties or is not an official U.S. Government publication, it is not a U.S. Government work.

[_____] U.K. Government work (Crown Copyright)

Note to U.K. Government Employees
The rights in a contribution prepared by an employee of a UK government department, agency or other Crown body as part of his/her official duties, or which is an official government publication, belong to the Crown. Contributors must ensure they comply with departmental regulations and submit the appropriate authorisation to publish. If your status as a government employee legally prevents you from signing this Agreement, please contact the Journal production editor.

[_____] Other

Including Other Government work or Non-Governmental Organisation work

Note to Non-U.S., Non-U.K. Government Employees or Non-Governmental Organisation Employees
If your status as a government or non-governmental organisation employee legally prevents you from signing this Agreement, please contact the Journal production editor.
Exhibit A

Financial Disclosure

The Contributor has received financial and material support for this research and work regardless of date from the following sources:

Name: Roger L. Albin, MD
Address: 5023 BSRB, 109 Zina Pitcher Place, Ann Arbor, MI, 48109-2200
Type of support: Parkinson’s Foundation, Michael J. Fox Foundation, P50NS091856, and R21NS114749

This material will be printed with the published article.

In the past year from the date of submission, the Contributor has also received the following support unrelated to this research (e.g., grants, advisory boards, employment, consultancies, contracts, honoraria, royalties, expert testimony, partnerships, or stock ownership in medically-related fields):

Name: Roger L. Albin, MD
Address: 5023 BSRB, 109 Zina Pitcher Place, Ann Arbor, MI, 48109-2200
Type of support: RLA serves on the DSMBs for the M-STAR (ICON/Biohaven), COMPASS (IQVIA/Biogen), and PASSPORT (IQVIA/Biogen) trials. RLA has been a paid consultant for Takeda and the Michael J. Fox Foundation.

This material will be posted on the journal website and may be printed at the Editors’ discretion.

ATTACH ADDITIONAL INFORMATION AS NECESSARY

In the past year from the date of submission, the Contributor has also received the following support unrelated to this research (e.g., grants, advisory boards, employment, consultancies, contracts, honoraria, royalties, expert testimony, partnerships, or stock ownership in medically-related fields):

Name: Jeffrey J. Kordower, PhD
Address: Dept. of Neurological Sciences, Rush University Medical Center, Chicago, IL, USA
Type of support: JHK has been a paid consultant for Seelos Inc, Inhibikase Inc, Brainstorm Inc, Clintrex Inc., Fuji-Cellular Dynamics, and Abbvie. JHK has received grant support from Biogen Inc, the Michael J. Fox Foundation, and Abbvie.

This material will be posted on the journal website and may be printed at the Editors’ discretion.