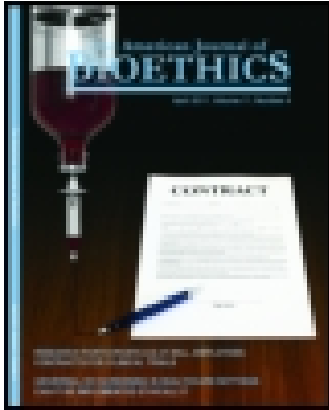


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# Unintended Benefits Arising from Cell-Based Interventions for Neurological Conditions

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The bedrock of assessing any new technology is risk-benefit analysis. Duggan and colleagues (2009) take a reasoned approach to the subject of unintended risks relating to changes in cognition, mood, and behavior as a result of cell-based interventions (CBIs), but mention the potential benefits only in passing. If, as the authors surmise, changes in behavior can be construed as unintended risks, there is also every reason to assume that changes in behavior may also represent unintended benefits. Both benefits and risks merit consideration when assessing the ethical consequences of testing CBIs.

The most important unintended benefits that might accrue from the testing of CBIs would be to test the hypothesis that changing the cellular milieu of the human brain will change its circuitry and ultimately behavior. This *cellular modification of behavior hypothesis* is an *implicit* linchpin in the field of CBIs, and provides the intellectual framework for both experimental and translational work in the field and indeed much of the field of neurobiology. There exists a large body of experimental literature which supports the cellular modification of behavior hypothesis in experimental animals (Gage 2000), although the analysis is biased towards data that yield positive results; in truth, there is no shortage of conflicting data. However, with the exception of limited pioneering studies (Winner et al. 2009), there has been little human data to support or refute this assertion. One potential unintended benefit of CBIs would be to test the cellular modification of behavior hypothesis in the human brain.

Duggan and colleagues (2009) cite (and largely dismiss) concerns about enhancement as a consequence of CBIs. They distinguish between two consequences of CBI-based treatment: 1) enhancing brain function beyond what is expected to achieve a given therapeutic endpoint; and 2) the use of CBIs to explicitly produce an enhancement. The authors caution that concerns about the latter objective should not deter us from pursuing the first.

One need not posit any form of enhancement for the cellular modification of behavior hypothesis to receive support from CBIs. Indeed, the essential *therapeutic* goal of any such intervention is to modify behavior; success in that regard would go some distance in validating the cellular modification of behavior hypothesis. However, evidence of enhancement would provide much stronger support for the

hypothesis, and moreover would be of widespread scientific interest.

The issue is perhaps best illustrated by using the example of cognitive enhancement. (Greely et al. 2008) have recently outlined a series of steps which would allow for prudent and responsible development of cognitive enhancers; CBIs would seem an unlikely technological means towards this end. That being said, the bulk of neurobiological opinion would suggest that cognitive abilities derive from the network properties of neurons (Hagmann et al. 2008), and that given appropriate conditions for externally derived cells to establish connections with existing neurons in the brain, changes in cognitive ability (or any other brain function) would be remarkable but hardly unexpected.

Perhaps more surprising is the paucity of evidence that CBIs alter cognitive abilities *in vivo*. While a sizeable body of data derived from experiments in transgenic animals demonstrates that manipulation of the molecular physiology of the brain may enhance cognitive abilities (Lee and Silva, 2009), there are far fewer studies that have demonstrated effects of CBIs upon enhanced cognition (Bakshi et al. 2006; Gao et al. 2006; Pizzo et al. 2006). Thus, any enhancement of cognitive ability that arises as a result of CBIs would represent a scientific breakthrough of substantial interest.

It is not just the mere fact of enhancement by CBIs that would be of interest but even more so the details of the cellular changes that produce enhancement that would be revealing. The specific anatomical loci in which CBIs produce enhancement as well as the molecular phenotype of the cells utilized are likely to be crucial to the specific cognitive changes observed. Finally, the impressive cognitive endowment of humans coupled with their ability to communicate opens avenues for probing subtleties of cognitive function rarely revealed in experiments with laboratory animals.

Similar arguments can be made for other important behavioral variables. For these reasons, Duggan and colleagues (2009) call for inclusion of unintended outcomes in the informed consent process is timely. Unintended benefits may or may not accrue to the test subject. However, it is a near certainty that such information would be of both widespread scientific interest and of general utility to

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others. As such, it would satisfy the *Common Rule's* admonition not only to minimize risks but to insure that "risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of knowledge that may reasonably be expected to result" (45 CFR 46.11(a)(1,2)). Offering realistic assessments of *both* risks and rewards will allow individuals to make decisions with the best knowledge available. ■

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