http://www.cell.com/cell-stem-cell/comments/S1934-5909%2811%2900173-1

Frederic Bretzner
Frederic Gilbert, Francoise Baylis, Robert Brownstone
Saturday, June 11, 2011
17:14:42
Affiliation: Dalhousie University, Halifax

Subject selection for first first-in-human hESC-derived GNROPC1 research: A Response to Wirth et al. 2011

Our paper "Target populations for first-in-human embryonic stem cell research in spinal cord injury" (Bretzner et al., 2011) is about the relationship between subject selection and research objectives, and about the ethical obligation to select for trial participation "the least vulnerable population that can usefully answer the research question.".

We argued that the ideal target population for a Phase 1 safety and feasibility trial of hESC-derived GRNOPC1 cells is a chronic complete spinal cord injury (SCI) population, and offered scientific and ethical reasons for this view. We suggested that Geron did not choose this target population, however, because it wanted data on efficacy, and most likely no such data could be obtained in a trial involving chronic complete SCI patients.

Our hypothesis -- that the secondary endpoint of efficacy "explains the choice of subacute complete SCI patients as the target populationC -- is confirmed by authors at Geron in their response to our article (Wirth et al. 2011). These authors maintain that as "risks due to GRNOPC1 injection, immunosuppression, and the GRNOPC1 cells are similar for both groups [patients with chronic complete SCI and patients with subacute complete SCI], the risk-to-benefit ratio, based on the preclinical data, favors treatment of patients with subacute SCI rather than chronic SCI."

In our view, this rationale for choosing subacute complete SCI patients as the target population over chronic complete SCI patients is problematic for several reasons. A first problem concerns the description of research participation as treatment. Treatment is precisely what the enrolled subjects would not be receiving. In fact, it is worrisome that the Geron authors use the term "treatment" in an article explaining that subjects are not at risk of therapeutic misconception. Can there be confidence that similar language would not be used in conversations with prospective trial participants? The use of this language substantiates our concern about the risk of therapeutic misconception (i.e., conflating treatment and research).

Secondly, Wirth et al. explain that considerable efforts are made to ensure that prospective research participants have a complete SCI. As such, there is little likelihood of spontaneous recovery – meaning, there is little likelihood of opportunity costs with trial participation. As noted in our original paper, if this is indeed the case, then, given that the pre-clinical evidence of efficacy of GRNOPC1 transplants in SCI was in rodents with subacute incomplete SCI (Cloutier et al., 2006; Keirstead et al., 2005), there can be no reasonable expectation of efficacy in these patients. How, then, does the "risk-to-benefit ratio based on the preclinical data favor" (p. 477) the use of hESC-derived GRNOPC1 cells in patients with subacute complete SCI?

A third problem is with the authors' narrow understanding of the risks of research participation in terms of potential medical harms, when our paper has much to say about non-medical harms, with particular attention to the risk of exploitation among those who confuse research with therapy. We agree with Wirth et al. that the potential medical harms for both patient populations are the same (and explicitly say this). We disagree with their effort to either ignore the non-medical harms, or to treat these harms as equivalent for both patient populations.

Wirth et al. insist that therapeutic misconception is minimized because of the quality of their consent form. They maintain that no person able "to absorb information and assess it reasonably" would be at risk of therapeutic misconception or misestimation of harms or benefits. In response, it is important to emphasize that informed consent to research participation is a process, not a form; that many people (not just researchers) are involved in this process; and, that the information available to prospective research participants is not limited to the information in the consent form. As well, the informed consent process requires time for reflection and consultation, and time is limited for subacute patients as compared with

chronic complete SCI patients. Moreover, consent processes take place in an historical, social and political context which currently includes considerable hype about the promise of stem cell research – hype that Timothy Atchison, the first person to receive the hESC-derived GNROPC1 injection, is now contributing to with claims that "he is recovering sensation; he can feel it when you lift a bowling ball from his lap" (Geron, 2011). As Atchison and his agent decide how best to tell his story, there can be little doubt that this will influence recruitment. These facts cannot simply be set aside, nor can their importance be minimized.

We stand by our conclusion that a preferable population in which to answer questions about the safety and feasibility of hESC-derived GRNOPC1 cells is a population of chronic complete SCI patients because they are "the least vulnerable population that can usefully answer the research question". Further, we note that recent qualitative research involving SCI patients supports this view: "Although biomedical science is targeting fairly acute time points for stem cell clinical trials for SCI, our findings suggest that this is the time when a person with SCI is most vulnerable, poorly informed about the evolution of the condition and options for intervention and is unlikely, therefore, to be able to make an informed decision about participation" (Illes et al., 2011).

Wirth et al. state that Geron consulted "many expert SCI clinicians" about the design of the clinical protocol, including "Geron's clinical steering committee, independent data monitoring committee, embryonic stem cell research oversight committee, investigators and the FDA". It is noteworthy that they do not mention having consulted people who are living with SCI. This would seem to be an important omission, especially given the data presented by Illes et al. (2011).

We realize that Geron did not merely want to answer questions about safety and feasibility, and that in order to answer questions about efficacy it needed to enrol a different patient population than would have been optimal for a safety and feasibility trial. More generally, along with others, we recognize that first-in-human trials "generally are designed with the secondary goal of evaluating promise of efficacy, and various trial design reforms are intended to enhance the therapeutic benefits of participating in Phase 1 studies" (Anderson and Kimmelman, 2010). Nevertheless, the question remains – should Geron have been required to proceed in a step-wise fashion and first complete research involving chronic complete SCI patients, prior to moving to a trial involving other patient populations?

We thank Wirth et al. for their comments on our paper and especially for putting more information about the Geron trial in the public domain. This can but enrich further discussion about ethical subject selection and hopefully contribute to improved trial designs for future stem cell trials.

References:

Anderson, J.A., and Kimmelman, J. (2010). Kennedy Institute of Ethics Journal 20, 75-98.
Bretzner, F., Gilbert, F., Baylis, F., and Brownstone, R.M. (2011). Cell Stem Cell 8, 468-475.
Cloutier, F., Siegenthaler, M.M., Nistor, G., and Keirstead, H.S. (2006). Regenerative Medicine 1, 469-479.
Geron (2011). (Available at http://www.spinalcordinjury-paralysis.org/research/2011/05/12/geron-stem-cell-trial-enrolls-second-first-hires-a).
Illes, J., Reimer, J.C., and Kwon, B.K. (2011). Stem Cell Reviews.
Keirstead, H.S., Nistor, G., Bernal, G., Totoiu, M., Cloutier, F., Sharp, K., and Steward, O. (2005). J Neurosci 25, 4694-4705.
Wirth, E., 3rd, Lebkowski, J.S., and Lebacqz, K. (2011). Cell Stem Cell 8, 476-478.