human subjects, nor become, in the absence of safety concerns, the exclusive factor on which clinical testing is based. In closing, we wish to express our gratitude to the physicians and patients who understand the nature of clinical translation and that human outcomes ultimately determine whether therapeutic testing continues to advance.

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Response to StemCells Inc.

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We welcome the opportunity for further discussion of this data, and in the paragraphs below, we briefly address the comments provided by StemCells Inc. (STEM).

One issue raised is that the data in both papers encompass development of novel therapeutics for conditions with no effective therapy. We agree that the need to move clinical testing forward for conditions in which there are no effective therapeutics cannot be overstated. Cervical spinal cord injury (SCI) and Alzheimer's disease (AD) are both prime examples of this need, although with some critical differences. As many reviews have summarized, risk tolerance in progressing to a clinical trial is inherently different for terminal conditions in comparison with chronic conditions, and different again for chronic conditions involving greater or lesser impacts on the activities of daily living or quality of life. We believe that publication of these studies supports this need by opening further discussion of translational research, including its pitfalls. In the case of cell therapeutics, and as discussed in the primary papers (Anderson et al., 2017; Marsh et al., 2017), we suggest that these include testing of the final clinical product, careful consideration of the tenant of informed consent for the subjects that choose to enroll in a clinical trial of any kind, and the relationship between pre-clinical research and clinical trial success rate.

A parallel issue in the clinical development of a cell therapy for SCI is disclosure of pre-clinical animal study outcomes to clinical investigators for the company's Pathway Study and to the US FDA in regulatory filings. We, of course, agree that full disclosure and open discussion are critical to the integrity of conducting a clinical trial, but we have no direct knowledge of what exactly was disclosed to clinical investigators or in regulatory filings for the "Pathway" cervical SCI trial, or when. In this regard, the timeline as we know is as follows. A preliminary analysis of the findings detailed in the Anderson et al. (2017) was provided to STEM in the form of a Research Performance Progress Report for the associated U01 on July 1, 2014. The failure of the CCL to meet the U01 efficacy milestone in the cervical model was made clear and resulted in early termination of U01 funding. A more complete analysis of these data was submitted to STEM in the form of a set of presentation slides on December 3, 2014. Transplantation of the first patient in the Pathway study was announced December 18, 2014. A face-to-face meeting was held between the SCI team and STEM on January 22, 2015. However, in the absence of further information, this timeline provides rather limited insight. The key issues would seem to be what information was shared and in what form, and whether it can be ethically considered that informed consent was achieved for the subjects enrolling in the trial (Anderson and Cummings, 2016). It is understood that the investment and intellectual property of a sponsor requires

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protection in order to enable the clinical trial enterprise. However, without a standard for such disclosures that includes a process by which it can be assured that all of the data is independently reviewed, including IRB assessment of enrollment parameters and consent documentation, potential concerns remain.

Similarly for the development of this cell therapy for AD, it is noted that focal cellular clusters similar to ones demonstrated in Marsh et al. (2017) had previously been observed and analyzed in other in vivo studies and disclosed to the FDA as part of required regulatory filings. It is certainly reassuring that the FDA was allowed to review such findings. It is, however, disappointing that these findings were not made publicly available to inform the cell transplantation field as a whole, or at least disclosed to the basic scientists who spent years of concerted effort working with these cells. Critically, this type of disclosure again relates to the issue of risk tolerance and pre-clinical study design. Previous trials sponsored by STEM included the indications of neuronal ceroid lipofuscinoses (NCL, or Batten's disease) and Pelizaeus-Merzbacher disease (PMD), both of which exhibit infantile onset and early lethality. In contrast, individuals with AD can live for well over a decade beyond the initial diagnosis, and those with SCI may live a normal lifespan. Thus, the relative risk presented by an unregulated ectopic ventricular growth in the brain or spinal cord is likely to carry a different weight for these conditions. This point raises another issue, however, in the potential for the lack of clear two-way communication between the pharmaceutical industry and their basic science collaborators to contribute to translational failure.

The company also comments on assumptions made in both the SCI and AD papers, specifically regarding the predictive nature and validity of animal models, and the overall interpretation of the data with regard to safety and efficacy. It is of course true that the predictability of animal models for most neurological conditions is largely unclear. As discussed in Anderson et al. (2017), one reason for this is the general lack of success in clinical trials focusing on neurological disease and neurotrauma. Without published examples of successful bench-to-bedside translation in the form of clinical trial results, which have been broadly lacking, or definitive mechanistic studies of the basic biology underlying these conditions (Südhof, 2017), animal models remain the best option for pre-clinical research. They are, however, largely unproven.

All pre-clinical models therefore have flaws, but the thoracic SCI pre-clinical animal work appears to have been predictive for the thoracic SCI Zurich phase I/II clinical study (although clinical data in the thoracic study remain unpublished, despite the requirement to publish results within one year of a study's closure). Of additional note, the cervical SCI pre-clinical animal models utilized in Anderson et al. (2017) were subject to peer review as a part of two major funded grant applications, one to CIRM and one to NIH, in which STEM actively participated and was represented by co-principal investigator status. It therefore remains that a fair interpretation of this data is that these observations derive from variation between cell lines and/or in cell manufacture/processing, and not in the model itself or in the experimental execution of the model. For clarity, we note that in the direct comparison data for the RCL and CCL, the RCL exhibited significant increase in Aa step pattern versus both the CCL and hFb control cells, but not versus vehicle. Regardless of how one views this data, the point remains that either the Pathway Study went forward in the absence of in vivo efficacy testing, or with cells that failed to yield pre-clinical efficacy; moreover, subjects enrolling in this trial may have been influenced by published pre-clinical data and publically released clinical data from thoracic SCI in making their decision to participate (Anderson and Cummings, 2016).

In parallel, we would question the blanket conclusion that the observed cell clusters in the AD study led to no adverse histological findings. As detailed in the discussion of the Marsh et al. (2017) paper, differing conclusions regarding the potential risk of these ectopic cell clusters were reached by the STEM-sponsored veterinary pathologist and a practicing board-certified human neuropathologist (ESM). Importantly, the sponsor expressed no questions regarding the validity of the histological results and the figures depicted in the manuscript. Rather, it is the interpretation of those findings that has been questioned. Thus, there is clearly a difference of professional opinion about the risk such ectopic cell clusters might present to a patient. We would therefore refer the reader to Figure 3 and Movie S2 in Marsh et al. (2017) to form their own opinions about these ectopic cell clusters and whether the images depict signs of host tissue infiltration/invasion.

In sum, we agree that the ultimate test of efficacy resides in the human setting. However, we re-emphasize that although the prevailing view of evidentiary standards for drug testing and approval holds mechanism of action to be subsidiary to demonstration of safety and clinical efficacy, the failure (or disincentive) to understand mechanisms of action, and thus to enable derivation of surrogate measures that can accurately inform pre-clinical comparability and potency studies, may be an alternative reason for failure in translational medicine and clinical trials. Furthermore, lack of transparency between study sponsors and basic scientists may be critical. In this case, in addition to failing to communicate previous observations of cell clusters after transplantation, communication between

the sponsor and basic scientists was dramatically different for the thoracic and cervical SCI indications. Leading up to the thoracic SCI trial, the basic scientists were involved in pre-clinical meetings with regulatory agencies, and our input was sought regarding clinical trial design. This was not the case for cervical SCI, and the basic science investigators were neither involved in nor aware of communication between the sponsor and the FDA. Perhaps increased transparency and the inclusion of basic scientists in clinical trial planning teams is an approach that could accelerate translational success. The combined experience of both the SCI and AD pre-clinical teams suggests that although blaming the "model" is in vogue, it is not the model that failed in these two cases.

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