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Reaction from StemCells, Inc. to Two Papers in *Stem Cell Reports* on the Efficacy of Human NSCs in Mouse Models of Alzheimer's Disease and Spinal Cord Injury

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The two articles in this issue of *Stem Cell Reports* authored by UCI researchers are based on sponsor-supported collaborations that were conducted in the effort to develop therapies for serious and debilitating neurological disorders that have no effective therapy: specifically, cervical spinal cord injury (SCI) and Alzheimer's disease (AD) (Anderson et al., 2017; Marsh et al., 2017).

As industry sponsor of four separate INDs involving human neural stem cell (HuCNS-SC) transplantation in human subjects (over a course of more than a decade), StemCells, Inc. held as an absolute that all emerging data from preclinical studies were to be carefully analyzed for any safety concerns and potential impact on clinical development. The data from each of the reports published in this issue were carefully reviewed by the company and discussed at length with the respective senior authors. The outcome of the animal study by Anderson et al. (2017) was disclosed to the clinical investigators for the company's Pathway Study and to the U.S. FDA in regulatory filings. The observations of focal cellular clusters from Marsh et al. (2017) had been previously observed and extensively analyzed in other in vivo studies and was also disclosed to the FDA as part of required regulatory filings. After careful analysis, the company reached the conclusion that neither study indicated a safety concern.

We respectfully disagree with several interpretations made by each senior author regarding the analysis of the animal data and their relevance for the clinical studies. Brevity prohibits a point-by-point response to the various results in the two papers, but none of the conclusions reached in either report required alteration to then ongoing clinical testing or informed consent. The paper by Anderson et al. (2017) (1) assumes the animal model of chronic cervical spinal cord injury is predictive of efficacy in the human setting, (2) does not acknowledge that the mild cervical hemi-contusion injury is not validated as a translational model, and (3) fails to emphasize that neither the research nor clinical cell line (when directly compared) achieved evidence of efficacy. The paper by Marsh et al. (2017) confirms that HuCNS-SC was not effective in the specific model of AD, but also raises the possibility that the observations of focal clusters of cells represents a safety concern, despite (1) any adverse clinical, behavioral, or histological observations in the animals and (2) the assessment by an independent veterinary pathologist that the histology was consistent with normal in vivo behavior of neural stem cells and did not represent a concern for neoplasia.

To date, after 10 years of clinical trial experience involving HuCNS-SC transplantation in more than 50 subjects (with clinical follow-up extending to 5 years post transplant), absolutely no safety concerns regarding the HuCNS-SC cells have been identified.

We share the senior authors' frustration regarding the failed cervical SCI and negative AD outcomes of the respective preclinical studies and acknowledge the complexity of successfully translating cellular therapy in human patients for neurological disorders. However, we note that the ultimate test of efficacy resides in the human setting, and the limitations of animal models for predicting efficacy in human neurological disorders are well recognized. Thus, it is important to interpret data derived from animal studies in the larger context of the weak correlation between success in animals and success in humans. Clinical development for a treatment with a strong therapeutic hypothesis is therefore first and foremost based on identifying safety issues in preclinical studies and in the subsequent accrual of human safety profiles. Nonetheless, given the limitations of animal models for predicting efficacy, we have been very reassured by the signals of efficacy, albeit modest, observed in the early human studies conducted to date with HuCNS-SC cells (across multiple cell banks), and that it is these emerging signals that has supported further clinical investigation.

In this spirit, we sincerely hope investigators focused on preclinical studies in cellular therapy continue to push the field forward, but we also acknowledge that no animal model can fully recapitulate the experience of testing

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