NHLBI PACT Workshop:
Clinical Application of hESC derived Motor Neuron Progenitors (MotorGraft™) in the Treatment of Infantile Spinal Muscular Atrophy (SMA) Type I

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SMA Type I is characterized by severe, generalized muscle weakness within the first sixth months of life. Infants are never able to sit. The diagnosis of SMA Type I is usually made before 3 months of age and >95 percent die or require full-time respiratory support in infancy.

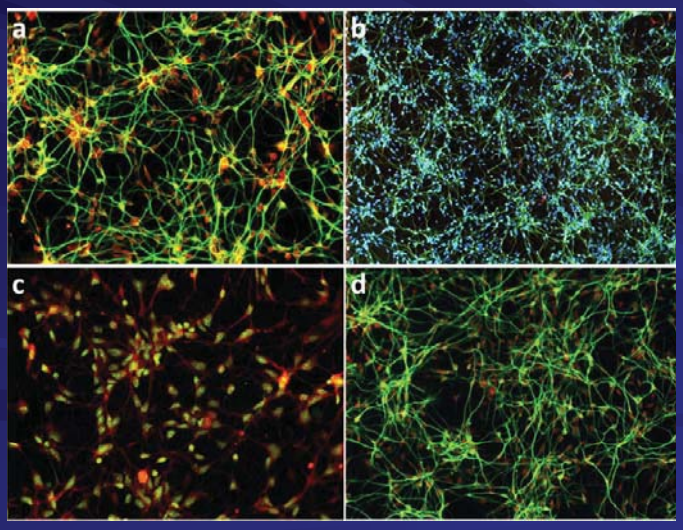
Type I SMA is the most common form, representing 60 to 70% of newly diagnosed cases, with the other forms, Type II and Type III being less severe. To date, there are no existing treatments that can reverse or delay disease progression from motor neuron death.

MotorGraft was developed by California Stem Cell, Inc. (CSC) as a cell therapy for diseases characterized by motor neuron loss, such as SMA Type I, Amyotrophic Lateral Sclerosis (ALS), and spinal cord injury (SCI).

Animal models for diseases of motor neuron loss include:

1. SMNdelta7-/- mouse
   - Best mimics SMA Type I
   - Mice have very short lifespan (~13 days)
2. SOD1 mouse
   - Best mimics familial form of ALS
   - Lifespan is several months
3. SCI models in rat or mouse
   - Best mimics SCI
   - Lifespan can be several years

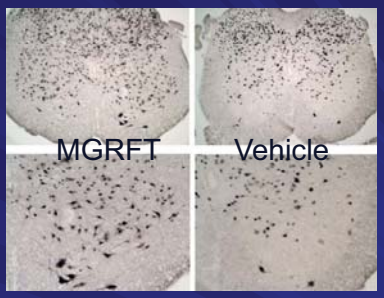
Motorgraft is a high purity motor neuron progenitor cell population derived from human embryonic stem cells from a single donor embryo.



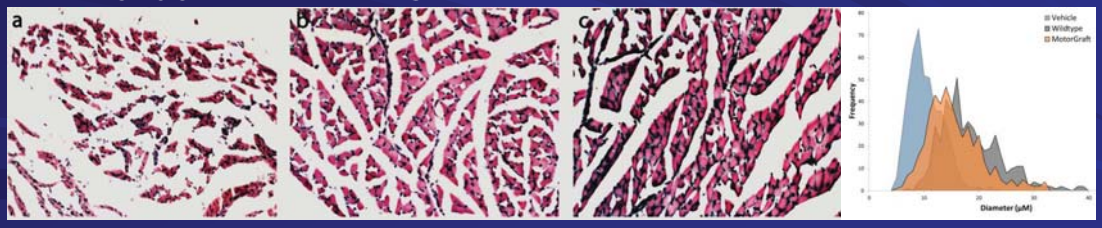
a) TUJ1 (green) and HB9 (red)
b) TUJ1 (green and GFAP (red)
c) HB9 (green) and Islet1 (red)
d) TUJ1 (green) and Islet1 (red)

Transplantation of MotorGraft into the diseased or damaged spinal cord may secrete motor neuron specific factors that delay the loss of host motor neurons

NeuN staining in SOD1 mouse model of ALS demonstrates more endogenous neurons in treated animals

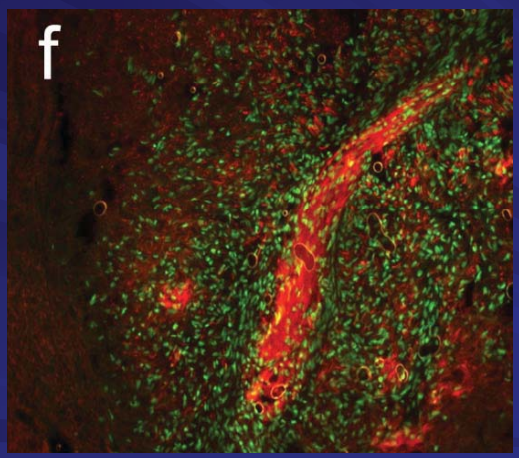


Vehicle MGRFT WT



Muscle fiber diameter is significantly improved in treated SMNdelta7-/- mice, demonstrating fiber diameter distribution more comparable to WT

Transplantation of MotorGraft into the diseased or damaged spinal cord may replace dying or dead motor neurons. In the latter instance, axonal growth from transplanted cells to the periphery would ultimately restore lost muscle function.



Human nuclei (green) and TUJ1 (red) in the rat spinal cord demonstrating the potential of axonal growth

To test or not to test in infants?

Should the first-in-human clinical trial be conducted in adults?

SMA Type I is a pediatric disease; it is not nor will it ever become an adult disease. Unlike other diseases which share similar if not identical presentations in children and adults, an adult phase 1 clinical trial of an SMA Type I cell therapy may not have sufficient predictive relevance to a follow-on safety/efficacy evaluation in children.

If first-in-human trials of Motorgraft must be conducted in adults, three outcome scenarios can be envisioned:

The first scenario, although unlikely, is that a safety issue comes to light in the adult trial. Even if the event can be pinned to the etiology and the course of the disease in adults, there is concern that regulators, or even our on research committee, in light of these findings, may stall or even prevent follow-on studies in children. In this case, risk/benefit in children may never be directly investigated.

A second scenario is that no safety issues are found in the adult population, but there are also no indications of preliminary benefit. There is concern here too that regulators, in light of these non-findings, may not allow follow-on studies in children until more robust translational studies are carried out. In this scenario as well then, risk/benefit in children may never be directly investigated.

A third more probable scenario is that no safety issues are found in the adult population, and some preliminary functional benefit is discovered. Given the high cost and time that will be required to reach this milestone, our research team might very well decide to continue the adult trials and put the pediatric clinical testing on the “back burner” or even abandon the studies altogether.

It just might be then that the “first in human adult” ethic has a built in de facto bias against conducting follow-on pediatric trails.

As a consequence, promising cell therapies may never be tested in children.

Or these therapies may move off-shore to a more “pediatric-friendly” regulatory environment.

A couple of thoughts on
the changing regulatory playing field:

The novelty of cell therapy means there will be a steep learning curve for both the scientific and regulatory communities. Mature therapeutic modalities, on the other hand, have regulatory guidance for both pre-clinical and clinical trial protocol development.

As one example, following a recent report in the scientific literature that nude rats are more susceptible to hESC induction of teratomas, the FDA began advising researchers to switch from using nude mice to nude rats in their pivotal pre-clinical safety study.

Making an investment in a several million dollar pre-clinical study, therefore, carries the unknown risk that a better animal model may at any time "rear its ugly head!" After starting a pre-clinical study, or worse, after completing an animal study, the researchers may come to find out that the model has been superceded by a more "robust" model. These possibilities can be strong financial deterrents to those wishing to investigate novel cell therapies. What if the best model turns out to be dogs? Or primates? Oh.my gosh!

The FDA does encourage frequent discussions on matters such as these, and there is no blame to levy on them. But perhaps some ground rule agreements could be pursued prior to a "betting the farm" study!

In discussions with others in the field, it became obvious that FDA has been recommending increased number of animals per sex per group for the pivotal rodent safety trial, in some cases three to five-fold over what was accepted just a few years back. In fact, rodent vendors, although elated by the new standards, can't even meet these new demands for nude rats without the sponsor accepting a staggered study design.

Summary

The proposed hESC derived therapy for SMA Type I illustrates:

1) The difficulties in meeting the regulatory requirements for high-risk 'first-in-human' pediatric treatments, such as finding a similar adult patient population. This may inadvertently stall product development in the 'target' pediatric population or even steer the investigational direction away from children,

2) The need for agreement on animal model standards for pre-clinical safety and efficacy evaluations,

3) The need for a pre-determined investigational strategy approved and "inked" by the regulatory bodies and

4) Finally, the ever increasing costs of translational research.