

## Summary of Visit to the Lab of Dr. Stephen Davies – July 25, 2008

On Friday, July 25<sup>th</sup>, my husband, Colin and I accepted a standing invitation to visit the lab of Dr. Stephen Davies at the University of Colorado-Denver. We have gotten to know Stephen quite well over the past few years due to his gracious participation in Working 2 Walk. Each spring in Washington, DC, he has presented his research to the W2W attendees, spoke during a Congressional briefing on Capitol Hill, and visited with Senators and Congressmen on the topic of “Rapid Advancements in Paralysis Research”. Based on this and other reports regarding the research being conducted in Stephen’s lab, we knew we would not be disappointed during our visit to Denver.

At 9:15 AM, Stephen and his wife and research partner, Dr. Jeannette Davies, met us at our hotel and escorted us the University of Colorado Anschutz Medical Center in Aurora. Arriving at the medical center, Jeannette gave us a quick campus tour before we met up with Stephen at his 9<sup>th</sup> floor lab in one of the research buildings. Stephen’s office is a modestly sized corner office with breathtaking views of the Rocky Mountains and the city of Denver. It was here where we spent the majority of the next 8 hours (it seemed more like 20 minutes).

We discussed many topics including basic spinal cord anatomy, the injury process from acute to chronic, past research in the field and how it has led to new discoveries, published and unpublished data, plans for continued studies in acute and chronic injuries, and progression of clinical trials. To better understand the science underlying the new therapies being developed by the Davies research lab, here is a quick overview of some spinal cord anatomy and concepts in SCI repair that pertain to regenerating new functional connections.

### Overview

Nerve fibers in the spinal cord are actually called axons. Sensory axons relaying sensory information to the brain ascend the spinal cord and motor axons that control movement descend the cord. These different types of axons are segregated within different white matter tracts that run up and down the spinal cord and surround the central gray matter where neurons of the spinal cord reside. Most axons within the spinal cord white matter pathways make their connections by sending out side branches called collaterals that make connections with neurons in the central gray matter. Some axons have *ends* that actually do not connect to anything and these axons (e.g cortico-spinal tract axons that control fine hand movement) make all their connections in the spinal cord by sending out collaterals.

After traumatic injury to the spinal cord, the body rushes to repair the injury. However, if the injury is sufficiently large, instead of repairing it the body forms scar tissue as a means of preventing infection. Scar tissue in the injured spinal cord contains cells that invade the injury site from outside the spinal cord such as fibroblasts and Schwann cells, and also cells from the spinal cord such as astrocytes, which together with the molecules they can secrete (e.g. CSPGs), form an inhibitory environment across which axons are unable to grow. The cut ends of the axons try to regenerate, but often wind up growing in the shape of a fish hook and stopping. They are therefore unable to re-connect with their former targets beyond the injury site to form new functional connections. The malformed ends are called dystrophic endings and they are thought to persist at sites of spinal cord

injury for many years. In attempting to regenerate, the cut ends of axons at a site of injury must therefore first grow through or around inhibitory scar tissue and then re-enter and grow within white matter pathways that are full of myelin associated inhibitors. Having grown within white matter they must then send out collaterals which must be able to enter gray matter, that is also full of axon growth inhibitory CSPGs (many of the same ones that are found in the scar), whose function in gray matter is to stabilize existing connections. New collateral formation by spared axons that have survived after an SCI, is also a very important component of recovery of function and these collaterals must also negotiate the same gambit of inhibitors near sites of injury and within white and gray matter tissues of the injured spinal cord.

### **New SCI Therapies**

There are two complementary therapies for promoting SCI repair that are being developed in the Davies lab. One line of research focuses on overcoming scar tissue and the inhibitors within the environment of the injured spinal cord with a molecule called Decorin. The other line of research is focused on making the right kinds of support cells with stem cell technology for bridging spinal cord injuries.

#### *Decorin*

Decorin is a naturally occurring suppressor of scar formation that is found throughout the body, including the spinal cord. Unfortunately decorin production by the spinal cord is normally shut down after severe spinal cord injury. Stephen's lab has previously shown that infusion of decorin can suppress scar formation and its associated CSPG inhibitors by up to 90% in acute SCI. This allowed sensory axons to cross injury sites in just 4 days. Decorin also has the ability to make the injured spinal cord make an enzyme called Plasmin that has the ability to breakdown scar tissue and activate growth factors called neurotrophins. The concept of being able to breakdown scar tissue is particularly relevant to chronic SCI where there are indications that scarring may extend within pathways beyond sites of injury. A newly published study from the Davies lab, however, shows that in addition to being able to "lower the hurdle" presented by scar tissue within the injured cord, decorin can also effectively de-sensitize axons to the effects of both the CSPGs (found in the scar and in gray matter) and to the myelin associated inhibitors found in white matter pathways. Treating adult sensory neurons with decorin in tissue culture resulted in a more than 14 fold increase in axon growth, despite the presence of very high levels of inhibitory CSPGs. This result has very important implications for not only promoting the growth of axons across scar tissue but also in promoting the growth of axons and collaterals within white and gray matter beyond injury sites in both the acute and chronically injured spinal cord.

As Decorin is normally made by the body it is easily tolerated, even at high doses. Stephen's technique is to deliver the molecule to the injury site using a mini-pump infusion system adapted for use with rat spinal cord. Stephen mentioned that there is a similar infusion system already FDA approved for human spinal cords that could be used to deliver decorin. Importantly Good Manufacturing Practices (GMP) grade Decorin that would be suitable for use in humans has already been developed.

### **Glial restricted precursor derived astrocytes (GDAs)**

It is estimated that the vast majority (70%) of cells within the human spinal cord are support cells called astrocytes (star cells). Amongst the many functions that have been

attributed to astrocytes in the nervous system, they are thought to be able to support the growth of axons away from sites of injury and stabilize the axon connections to neurons in gray matter. They are also known however to form inhibitory scar tissue and be involved in neuropathic pain after an SCI. At present relatively little is known about the existence of different types of astrocytes, and whether these different astrocytic functions in the injured spinal cord are in fact carried out by different types of astrocytes. Using a novel stem cell technology Stephen and his colleagues have discovered that two distinct types of astrocytes can be made from stem cell-like cells called glial restricted precursors. One type of astrocyte can promote robust axon regeneration (~40% in just 8 days) and equally robust functional recovery when transplanted into acute spinal cord injured rats. The other type of astrocyte closely resembles the astrocytes found in spinal scar tissue and therefore actually inhibits axon growth and can cause pain, We saw evidence that spinal cord injured rats transplanted with the right type of astrocytes, improved from between 6 to 8 mistakes per walk across a ladder at day 3 to only 1 to 2 mistakes (close to normal) by day 28 after injury. Untreated rats showed no recovery at all. So far 36 out of 36 rats that received scissor cuts to the spinal cord and transplants of the good astrocytes have shown this very consistent level of recovery, indicating a robust process. Stephen's lab is busy developing the human form of the good astrocytes (called GDAs BMP) and the early indications are very promising.

The results of the effects of decorin and the astrocyte transplants are displayed on posters in the lab, but, the work is ongoing; day we were there, we observed through the microscope a breakthrough in the delivery of Decorin that had been 2 years in process. We observed the results moments after Stephen himself did. It was an amazing experience.

#### **Current plans:**

\*continue chronic studies; 45 rats are currently reaching appropriate chronic stages for testing with decorin and GDA cells.

\*prove safety of Decorin in large animal model; currently no safety issues with Decorin have been reported at any dosage.

\*planning to conduct human clinical trials in the US and exploring options in other countries.

Colin and I want to extend our thanks to Stephen, Jeanette, and the rest of the research team for being such gracious hosts. Their enthusiasm and excitement over the results being produced by their lab is tremendous. Stephen is confident there will be effective curative therapies for both chronic and acute therapies in my lifetime (and hopefully within the next 5 years if not sooner). I am 44 years old.

His lab currently operates on a \$500,000 annual budget. I asked Stephen, "what if you had double that amount to work with?" He said, we could work twice as fast, except for a few experiments that simply take time. Already, his lab is working at lightning speed.

Susan & Colin Maus

