CHINASCINET
中國脊髓損傷研究協作組

HONG KONG SPINAL CORD INJURY FUND
香 港 脊 髓 損 傷 基 金

Newsletter
2008 Issue 2

ChinaSCINet and HKSCIFund

In September 2004, the University of Hong Kong Spinal Cord Injury Fund (HKU-SCI Fund) was formed, and the China Spinal Cord Injury Network (ChinaSCINet) was established in partnership with the HKU-SCI Fund. From this collaboration, in June 2006, two non-profit companies, the China Spinal Cord Injury Network (ChinaSCINet) Company Limited and the Hong Kong Spinal Cord Injury Fund (HKSCIFund) Limited (formerly the 'HKU-SCI Fund'), were established. They are dedicated to running the clinical trials and to raising funds for the trials respectively.

The HKSCIFund Ltd. is a registered charitable organization in Hong Kong (Registered Charity Number: 918370). Its function is to support ChinaSCINet.

The China Spinal Cord Injury Network is the largest spinal cord injury clinical trial network in the world, comprising more than 20 leading spinal cord injury centers in Mainland China, Hong Kong and Taiwan. Aiming at accelerating movement of therapies from laboratory to clinic, it has been coordinating and sponsoring a series of clinical studies. In order to facilitate spinal cord injury research, it also organizes ISCITT symposium every one or two years, 1 to 2 workshops every year and other different activities from time to time.

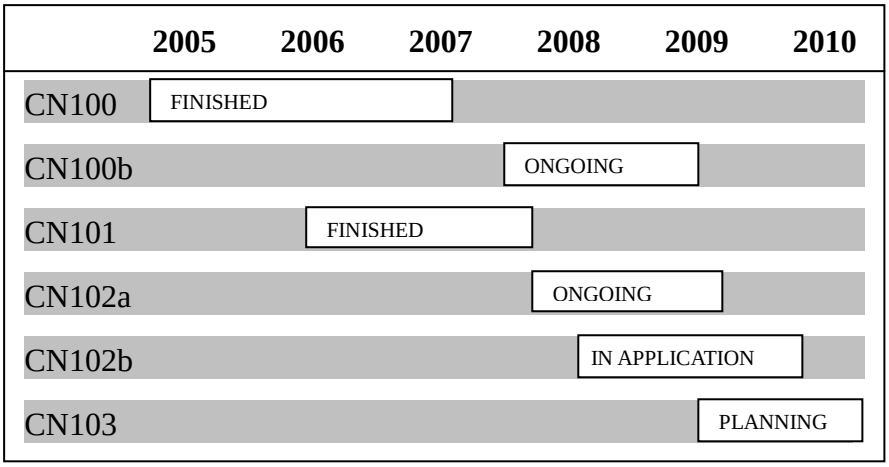
Study Progress

CN100: ChinaSCINet began a multicentre observational study in October 2005 to collect the spinal cord injured patients outcome data from 17 hospitals in Mainland China and Hong Kong. This established a solid foundation for the ChinaSCINet to perform clinical trials to test promising SCI therapies following international standards and guidelines. The study finished by the end of 2007.

CN100b: Started at the end of 2007, this extensional observational trial involves five new centers in Mainland China and Taiwan. It will be completed in the first half of 2009.

CN101: ChinaSCINet completed this Phase 1 clinical trial at the University of Hong Kong and MacLehose Medical Rehabilitation Center in 2007, showing that a 6-week course of oral lithium carbonate does not cause significant adverse event in patients suffering from chronic spinal cord injury.

Intradural Decompression Study: Under the leadership of Prof. Ju Gong, the Fourth Military Medical University and Dr. Zhu Hui, the Kunming Army General Hospital, it is found that intradural spinal cord decompression at 2 to 65 days after injury and intensive rehabilitation markedly improved locomotor recovery in 30 patients with "complete" spinal cord injuries. After the surgery and 3 months of intensive locomotor training, 20% converted from ASIA A to D, 33% recovered from ASIA to ASIA B or C, and 60% regained unassisted locomotion. The study shows that intradural decompression is safe and provides a template for locomotor rehabilitation after spinal cord injury.



CN102a: This Phase 2 double-blind randomized placebo-controlled trial will assess the safety and efficacy of a 6-week course of oral lithium treatment in chronic spinal cord injury. The trial is now being conducted in Beijing. Recent studies suggest that lithium alone may be beneficial for spinal cord injury and this trial will assess whether lithium has any effect on neurological recovery.

CN102b: This will be a dose-escalating trial to assess the feasibility, safety and possible efficacy of transplanting cord blood mononuclear cells into chronic spinal cord injury patients. After solving various problems related to the therapy, such as the cell transplant method, cell processing and transport, and blood typing and matching, the application for conducting this trial has been submitted for regulatory approval.

CN103: This multi-center trial will assess the efficacy of combination therapy with umbilical cord blood transplant and oral lithium in the patients with chronic spinal cord injuries. ChinaSCINet plans to start this milestone clinical trial in Mainland China, Hong Kong and Taiwan simultaneously in 2010. We hoped that the combination therapy would benefit the patients suffering from chronic spinal cord injury.

The combination therapy mentioned above aims to overcome two of the three main obstacles to spinal cord regeneration, inhospitable environment and lack of sustained growth factor support that may prevent neuroregeneration in the central nervous system. ChinaSCINet will address the remaining third obstacle, growth inhibitors in the spinal cord, by adding inhibitor blockers to the combination therapy. These new trials will be planned after CN103.

In addition to these planned trials, ChinaSCINet is actively discussing and developing several other therapies for spinal cord injuries, including intradural decompression, different kinds of stem cell transplants (such as mesenchymal stme cells), and several growth inhibitor blockers, such as chondroitinase, cethrin, nogo receptor protein, and decorin. The goal would be to add test these additional therapies in patients to have participated in the clinical trials to date. We are committed to designing clinical trials for people who have participated in our clinical trials to date.

Training Workshops & Open House

Training has been a primary mission of ChinaSCINet since it was established in 2004. ChinaSCINet holds

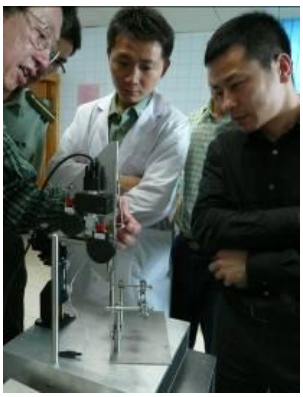
training workshops twice per year. We have conducted over a dozen training workshops in standardized neurological examinations, double-blind randomized clinical trials and preclinical studies since establishment. ChinaSCINet organizes the International Spinal Cord Injury Treatments & Trials (ISCITT) Symposium every one or two years, to showcase the achievements and discuss the problems in preclinical studies and clinical trials of spinal cord injuries.

In May 2008, we held a Spinal Cord Injury Impactor Workshop and an Open House (for people and families with spinal cord injury) in Xi'an. We held the 3rd ISCITT symposium on October 30 to November 1, 2008 in Beijing.

- **The 21st Chinese Spinal Cord Injury (CSCI) Academic Annual Meeting & the 3rd International Spinal Cord Injury Treatments and Trials Symposium (ISCITT), October 30 –November 1, 2008**

The 21st CSCI and 3rd ISCITT were held in Beijing from October 30 to November 1, 2008. The symposium had attracted nearly 500 participants. Speakers including spinal surgeons and researchers from China, other parts of Asia and the United States introduced their researches in the treatment and care for spinal cord injuries. New therapies discussed include: intradural decompression, transplantation of Schwann cells, olfactory ensheathing cells, neural stem cells, bone marrow mesenchymal stem cells, new-born rat blood cells, and GRP-derived astrocytes, use of drug therapies such as methylpredinisolone, lithium, 4-aminoprimidine, self-assembling polypeptide (SAP), Decorin, and Scirr10. The meeting was successful with overwhelmingly positive responses from participants.

- **Spinal Cord Injury Research Method Workshop, May 9-13, 2008**



ChinaSCINet, HKU-SCIF, Institute of Neuroscience of the Fourth Military Medical University, W.M. Keck Center for Collaborative Neuroscience offered an intensive five-day training workshop on spinal cord injury research method.

This workshop includes lectures, demonstrations, and hands-on experience in all facets of spinal cord research. Featured is the MASCIS Impactor, rat model of spinal cord contusion that has been adopted by the majority of the world's leading spinal cord research laboratories. The workshop covered anesthesia, surgery, spinal cord contusion, locomotor scoring (BBB), animal care, and other outcome measures. Cell transplantation at the spinal cord was also covered.

- **Open House – Meeting with Spinal Cord Injured Patients and Families, 10 May, 2008**

Open House is held in different places on an irregular schedule. The investigators of ChinaSCINet meet the patients, their relatives or friends, or any other relevant persons to update and discuss the new

achievements in spinal cord injury studies and the development of this Organization.

This Open House was co-organized by The 2nd Affiliated Hospital of Xi'an Jiaotong University and China Spinal Cord Injury Network. Professors Xijing He, Jianjun Li, Kwok-Fai So and Wise Young talked with more than 60 spinal cord injured patients and their families and friends, answered their questions and gave advice concerning therapies and summarized the status of spinal cord injury research.

Information on Spinal Cord Injury

We will provide a series of information articles in this and upcoming newsletters to raise public awareness.

About Spinal Cord Injury

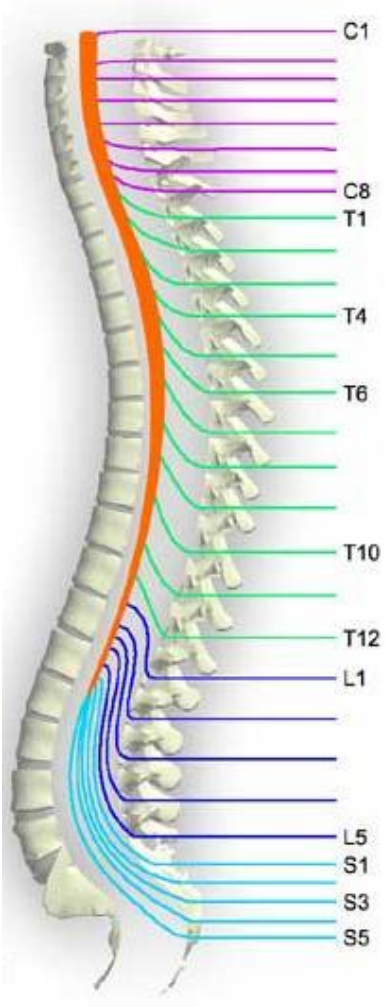
The spinal cord connects the brain to the body. Thus, spinal cord injury (SCI) disconnects the brain from the body, causing not only loss of sensation and voluntary movement below the injury level, but also loss of sexual, bladder, and other functions. In addition, many people suffer from severe pain and spasticity (abnormally increased reflexes or muscle tone) below the injury site, as well as atrophy (degeneration) of muscle and bone below the injury site. Injury to the neck produces paralysis of all four limbs (called tetraplegia or quadriplegia) while injury to the back produces paralysis of the legs (called paraplegia).

Because SCI happen mostly to young people under age 30, it causes more years of disability than other neurological conditions. Recent improvements in emergency and acute care have improved survival and increased the number of people with life-long disabilities from SCI. The societal costs of SCI, in terms of health care costs, disability payments, and lost income, are disproportionately high compared to other medical conditions. About 65 new SCI cases occur per million people in China each year. With a population of 1.3 billion people, China has over 85,000 new cases per year and a population nearly a million people with SCI, more than any other country in the world. By comparison, the United States has only about 12,000 new cases of SCI each year and between 200,000 to 300,000 people with chronic spinal cord injury.

SCI may result from many causes. The most common cause of spinal cord injury is trauma, from automobile accidents, falls, sports, or violence. However, it can also occur as a result of tumors, loss of blood flow, tuberculosis, and other diseases. Automobile account for about half of traumatic SCI, sports accidents and falls about a quarter, and violence the remainder. Some people can get paralyzed without an apparent cause. For example, a condition called transverse myelitis may occur without any trauma, A person may wake up or suddenly become paralyzed.

A traumatic SCI usually begins with a sudden, traumatic blow to the spine that fractures or dislocates

vertebrae. The damage begins at the moment of injury when displaced bone fragments, disc material, or ligaments bruise or tear into spinal cord tissue. Most injuries do not completely severe the spinal cord. Instead, an injury is more likely to cause fractures and dislocation of the vertebrae, which then can compress the spinal cord, crushing and stretching axons or nerve fibers that carry signals up and down the spinal cord, connecting the brain to the body below the injury site. An injury to the spinal cord can damage a few, many, or almost all of these axons. Some injuries will allow almost complete recovery. Others will result in complete paralysis.



Source: www.apparelyzed.com

SCI is classified as complete or incomplete. An incomplete injury means that the spinal cord still can convey some messages to or from the brain to the spinal cord below the injury site. People with incomplete injuries retain some voluntary motor or conscious sensory function below the injury. A complete injury is indicated by loss of sensory and motor function below some level of the spinal cord. Because the S4/S5 segment is the lowest spinal cord segment and innervates the anus and the anal sphincter, loss of anal sensation and voluntary anal contraction means "complete" loss of motor and sensory function at the S4/S5 level and is used by the American Spinal Injury Association (ASIA) as the clinical criterion for complete SCI. A person that is "complete" is classified as ASIA A. A person that is sensory "incomplete" with no motor function is ASIA B. A person that is motor incomplete with <50% motor function is ASIA C.

Prevention of further injury (by careful support of the neck and back during transportation), early treatment with steroid drugs to reduce tissue damage, and early surgical decompression of the spinal cord can improve functional recovery. Recent students suggest that patients with even sight preservation of motor and sensory function below the injury site may recover substantially, including walking, especially with intensive rehabilitation and exercise. Therefore, the goal of early treatment is to prevent further injury and the goal of rehabilitation is to maximize recovery. Some recovery is the rule and not the exception in spinal cord injury. However, many people, particularly those with "complete" spinal cord injury, may not recover much function and will require further therapies to regain full function.

Recovery may take years. About 80% of recovery occur during the first year but many people continue to recover function 2 or more years after injury. For example, Christopher Reeve (actor of 'Superman') was injured at C1/2, at the very top of his spinal cord. In the three years that followed his injury, he gradually recovered over 70% of his sensation, so that he could feel light touch in most of his body, including his anus. At 5 years after injury, he discovered that he could move his left index finger and could move his legs slightly. Of course, these are promising and welcome improvements but he needed regenerative therapies to recover more. Some people do not recover very much function below the injury site.

Spontaneous recovery from spinal cord injury likely result from plasticity and redundancy of the spinal cord. One can cut as much as 90% of the spinal cord of an animal but it will recover skilled voluntary activity, including walking, within several weeks. The recovery is very likely to be due to changes in the central nervous system that allows the surviving axons to sprout and to make new connections. The recovery occurs too quickly to be due to regeneration. In order to reconnect, injured spinal axons must

grow across the injury site and then all the way back to their original targets.

Regeneration will be slow. Axons typically grow no faster than hair, probably less than 1 mm per day. Regenerating motor axons must grow from the injury site to the lower spinal cord and sensory axons must grow from the injury site to the brainstem. Depending on the level of injury, the regenerative distance may be a meter or more. The main reason why large mammals did not evolve the ability to regenerate their spinal cords may be because regeneration is too slow to provide sufficient recovery for an animal for recover ability to escape, to catch food, and to procreate. Therefore, the animals evolved exquisite mechanical protection (the spine), redundancy and plasticity so that 10% of the spinal axons is necessary and sufficient for recovery.

Regenerating axons must overcome at least three obstacles. The first obstacle is the injury site, which is surrounded by astrocytes and extracellular molecules that block axonal growth. This can be addressed by building a cellular bridge across the injury site. Second, sustained growth factor support is necessary, including neurotrophin-3 (NT-3), nerve growth factor (NGF), glial-derived neurotrophic factor (GDNF). We recently found that lithium strongly stimulate umbilical cord blood stem cells to proliferate and to produce these three neurotrophic factors. Third, spinal cord contains growth inhibitors, particularly a protein called Nogo and an extracellular protein called chondroitin-6-sulfate-proteoglycan (CSPG). Nogo can be blocked with antibodies or the Nogo receptor. CSPG can be broken down with chondroitinase.

Many cells can serve as a bridge across the injury site. Umbilical cord blood cells are attractive because they are available in sufficient number and diversity, so that they can be immune-matched to the recipient. Cord blood cells are well-behaved, i.e. they do not migrate all over the place and do not produce tumors. Finally, cord blood cells have been transplanted for decades to thousands of people and have a strong safety record. An alternative source of immune-compatible cells are mesenchymal stem cells from the person's own bone marrow. While stem cells are available from embryonic or fetal sources, these are typically not immune-matched to recipient and therefore not suitable as a immune-compatible cell source.

Neuronal replacement may be necessary for some people, particularly those that have had injuries to their lower spinal cord, may have damaged their lumbosacral motoneurons responsible for activating leg muscle. To restore function to such people, neuronal replacement may be necessary. At present, two sources of neurons may be suitable for transplantation: neural stem cells harvested from adult or fetal brain or differentiated from embryonic stem cells. While aborted fetuses have neural stem cells, they are not usually cannot be matched immunologically with the recipient and therefore will be rejected if transplanted into the spinal cord.

Clinical trials determine the safety and efficacy of therapies. To rule out the possibility that any observed recovery could have been spontaneous, clinical trials must have "control" groups of patients who did not receive the experimental therapy. To avoid bias, treatments are randomized and double-blinded so that neither the patients nor the doctors know who is receiving the experimental therapy or the control therapy.

Because the therapies have not proven to be effective, it is inappropriate for people to pay for experimental therapies in clinical trials. Funds must be raised for the clinical trials. Companies may provide funding for clinical trials, as long as the trials are well-designed, approved, and monitored by third-party groups.

Once clinical trials have established the safety and efficacy of a therapy, regulatory authorities such as the U.S. Food and Drug Administration (FDA) or the China State Food will approve the therapy. The therapy will be widely available to everybody who needs it. People or medical insurance can then pay for the therapy. However, clinical trials have one additional important purpose, to determine when a therapy does not work. Several clinics have been offering unproven therapies to people with spinal cord injury. For example, one clinic is telling patients that umbilical cord blood cells are beneficial for spinal cord injury and charging people US$20,000 or more for the treatment but not doing rigorous clinical trials to prove that it is safe or effective.

If ChinaSCINet clinical trials show that a therapy is unsafe or ineffective, we will recommend that the therapy not be used. Showing that a therapy is ineffective is an important goal of clinical trials, to prevent the waste of time and money on ineffective therapies. Because many leading centers are testing therapies together, ChinaSCINet trials gives added credibility to claims of safety and efficacy, as well as ineffectiveness of therapies.

In summary, SCI produces paralysis and sensory loss, as well as impaired sexual, bladder, and bowel function, and it causes pain and spasticity. Occurring mostly in young people, SCI causes life-long disabilities. China has over 85,000 new cases of SCI per year and nearly a million people with chronic SCI. Trauma is the most frequent cause but SCI may also result from tumors, infections, ischemia, and other causes. Recovery depends on injury severity, takes a long time, and results from plasticity and redundancy of the spinal cord. Regeneration requires a bridge across the injury site, sustained growth factor support, and blockade of growth inhibitors. Cord blood cells are attractive for transplantation because they can be immune-matched and they have a good safety record. Stem cells from one's own bone marrow is another option. Fetal and embryonic stem cells are not available in sufficient number and diversity as an immune-matchable source. Clinical trials are important not only for showing that an experimental therapy is safe and effective but also for identifying therapies that are not. Clinical trial design must not only be scientifically but ethically rigorous.

"Nothing is impossible". This was the philosophy of Christopher Reeve (1952-2004), one of the world's most recognisable and tireless advocates of SCI research and treatment.

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Forthcoming Event

HKSCIFund will have a documentary programme on TVB Jade to raise the public awareness on the spinal cord injury.

16 December 2008	HKSCIFund Documentary Programme on TVB Jade from 11:00pm to 11:30pm (will be re-run at www.tvb.com from 1 January to 31 January 2009)

Support Us

Our target is to raise US$2 million per year to support the ChinaSCINet's activities and to fund its on-going and future clinical trials. We are seeking your help to support our clinical trials and activities, to bring hope to the spinal cord injured patients and families.

Donation methods:

- Deposit to the HKSCIFund's Hang Seng Bank account: **773-515747-668**
- Send crossed cheque payable to the '**Hong Kong Spinal Cord Injury Fund Limited'** (Address: Room 803, Asia Orient Tower, 33 Lockhart Road, Wanchai, Hong Kong)
- Online donation (**www.hkscifund.org**)
- Donation Hotline: **(852) 2866-0809**

Tax-deductible receipts will be issued for donations over HK$100.

"The establishment of China Spinal Cord Injury Network is to bring promising therapies for spinal cord injury from laboratory to people"

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