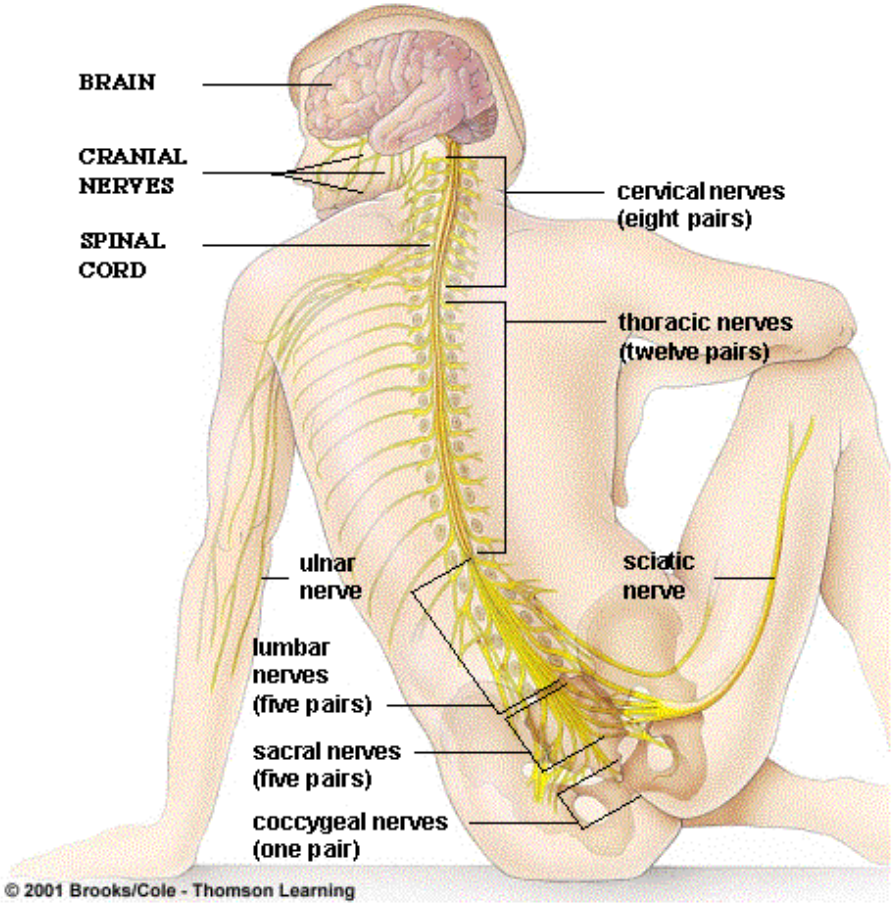
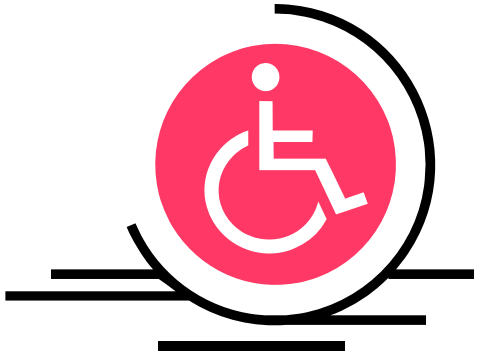
# Modern assessment modalities of spinal cord function

Armin Curt, MD
Chairman and Professor
Spinal Cord Injury Center
University of Zürich

# Spinal cord injury: a neurological disorder



# *The challenge*



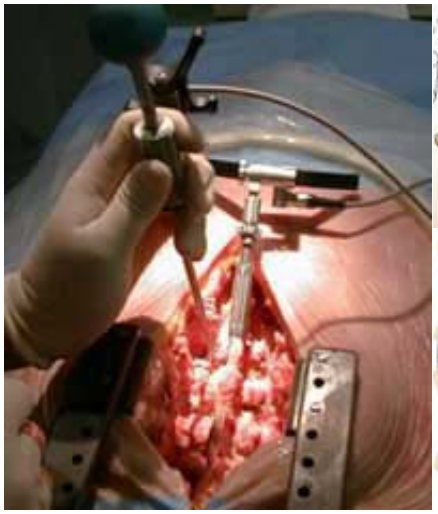
- informed clinical trials in human SCI
- appraisal of pre-clinical studies in SCI
- proof of mechanisms in human SCI

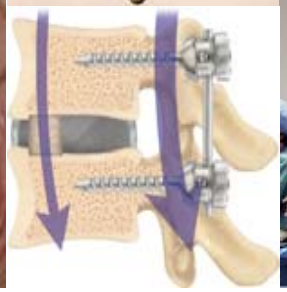
# How to bring preclinical science from bench to bed?






# How to bring preclinical science from bench to bed?



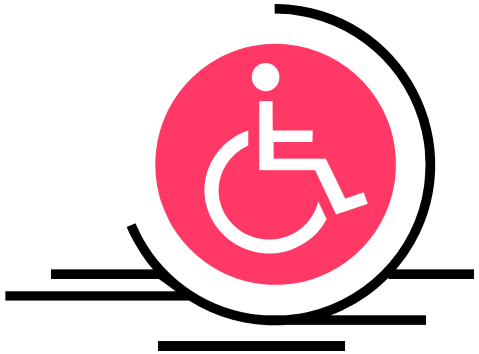






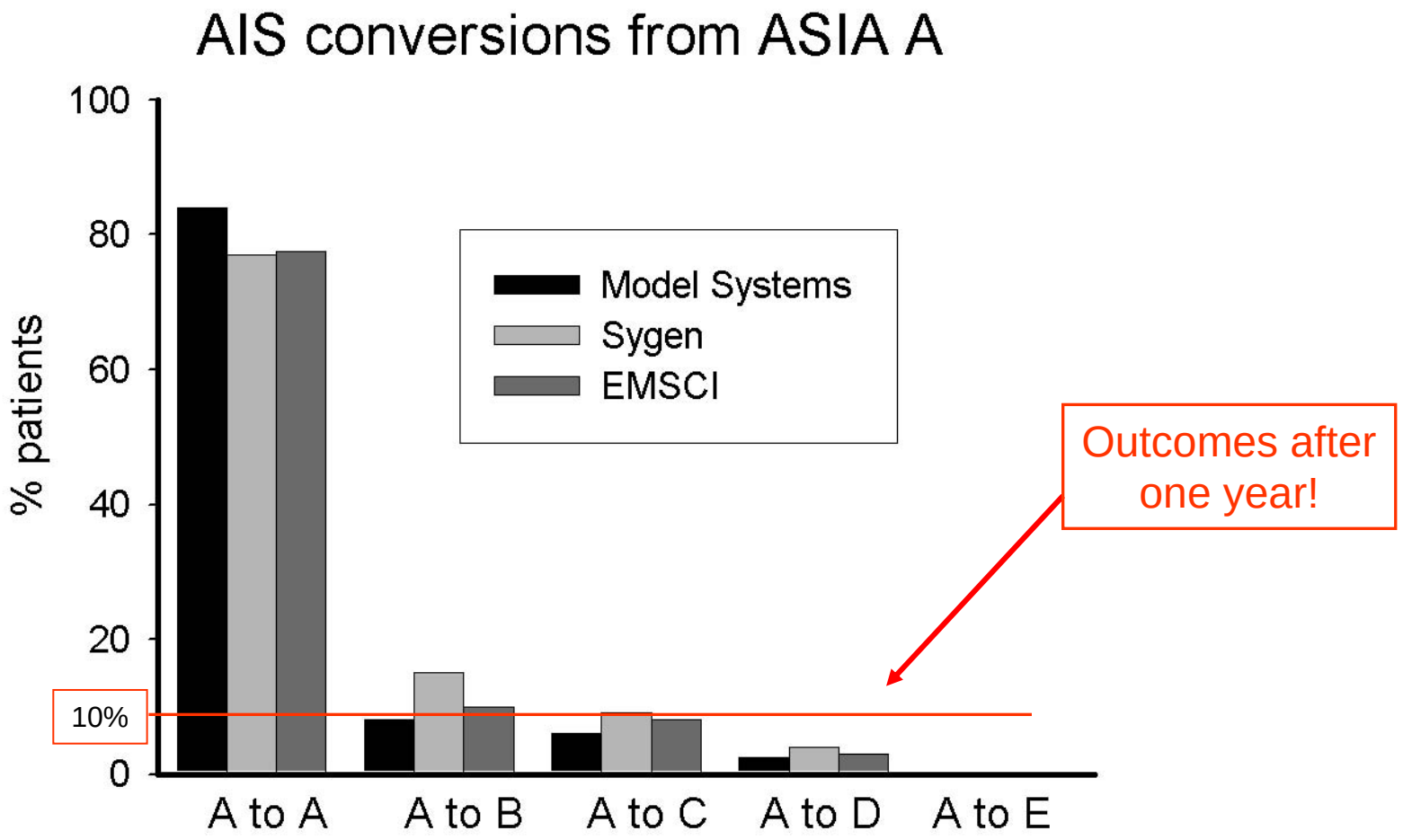


# *The challenge*



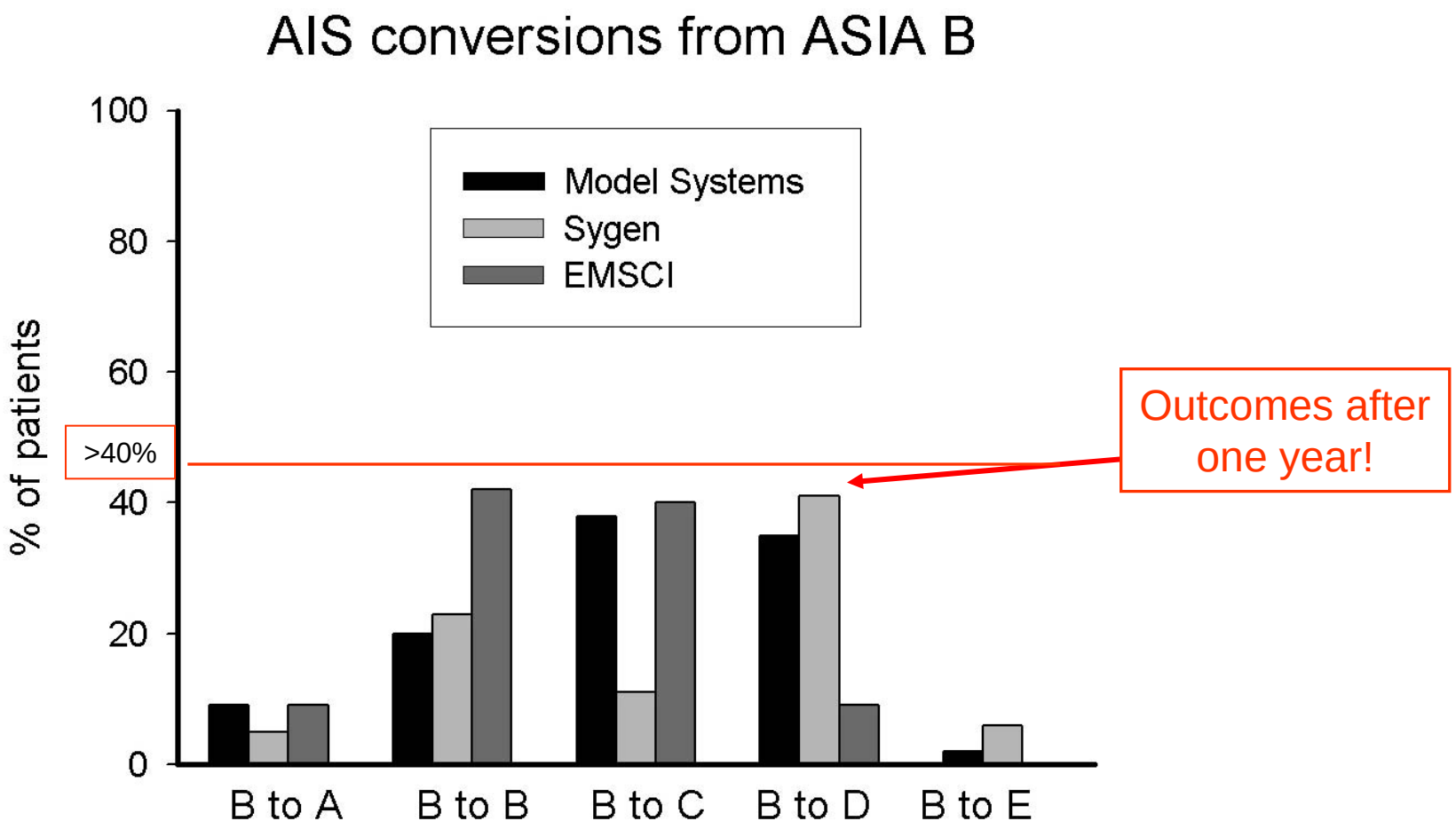
- informed clinical trials in human SCI
- appraisal of pre-clinical studies in SCI
- proof of mechanisms in human SCI

# Conversion rates in complete SCI




Fawcett J et al (2007) Spinal Cord

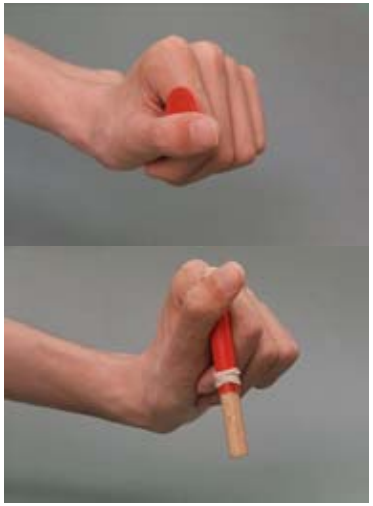
# Conversion rates in complete SCI



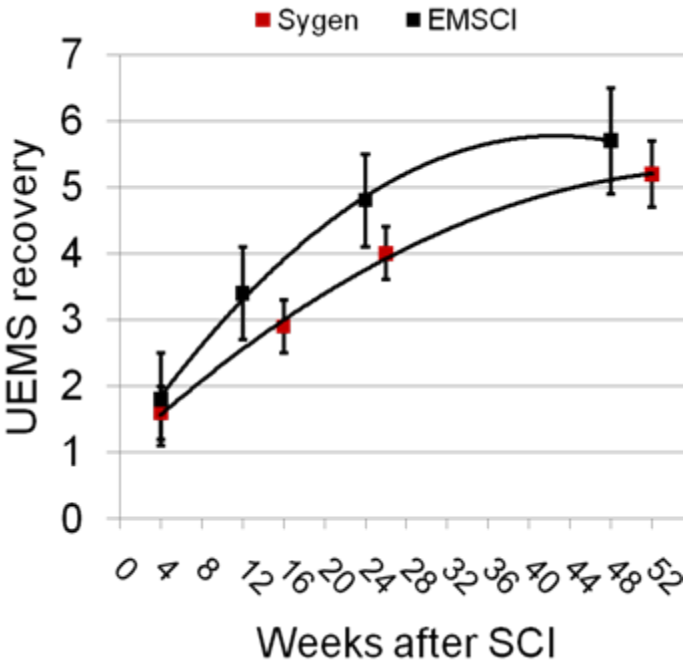

Fawcett J et al (2007) Spinal Cord

Dobkin B et al (2006) Neurology

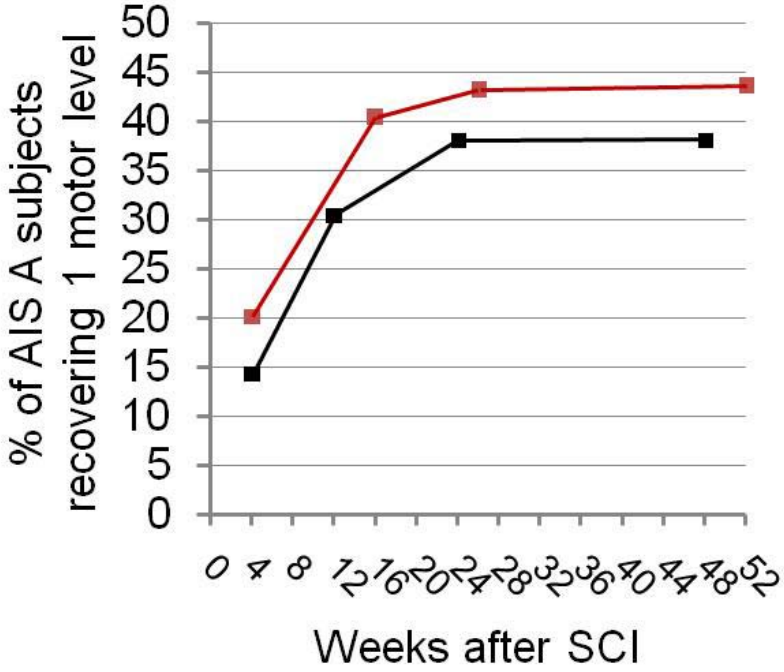
# Segmental motor changes in cervical SCI



Motor scores

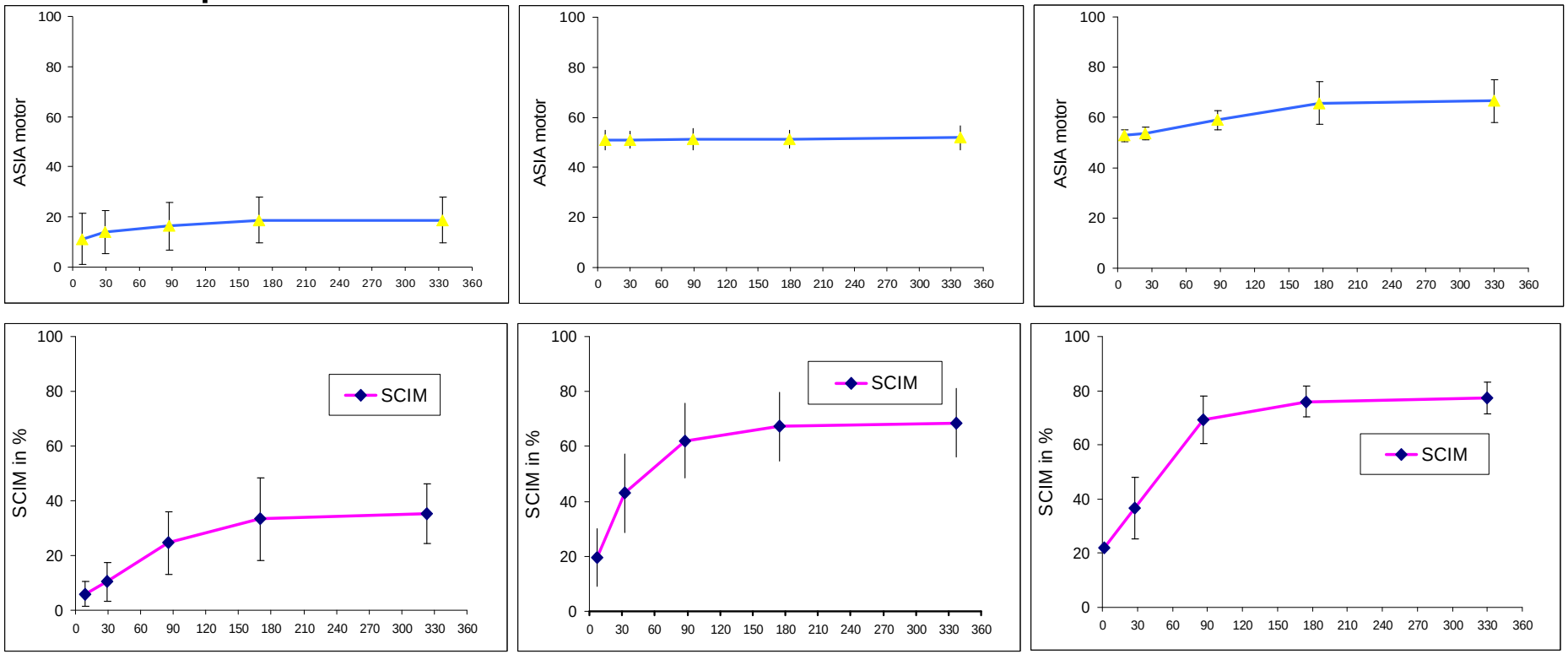



Motor level



# Functional recovery in **complete** SCI

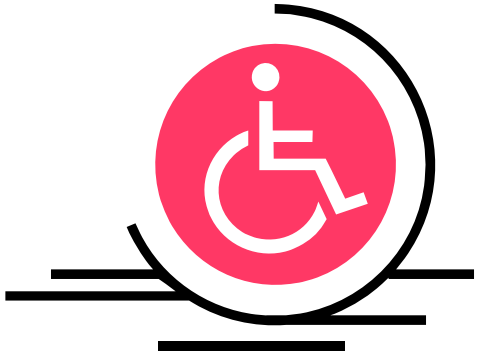
Complete tetra | thoracic | conus/cauda




Curt A, Hedel vH et al.. Recovery from a spinal cord injury: Significance of compensation, neural plasticity and repair. J Neurotrauma 2008

Wirth B, et al.. Changes in activity after a complete spinal cord injury as measured by the Spinal Cord Independence Measure II (SCIM II). Neurorehabil Neural Repair 2007

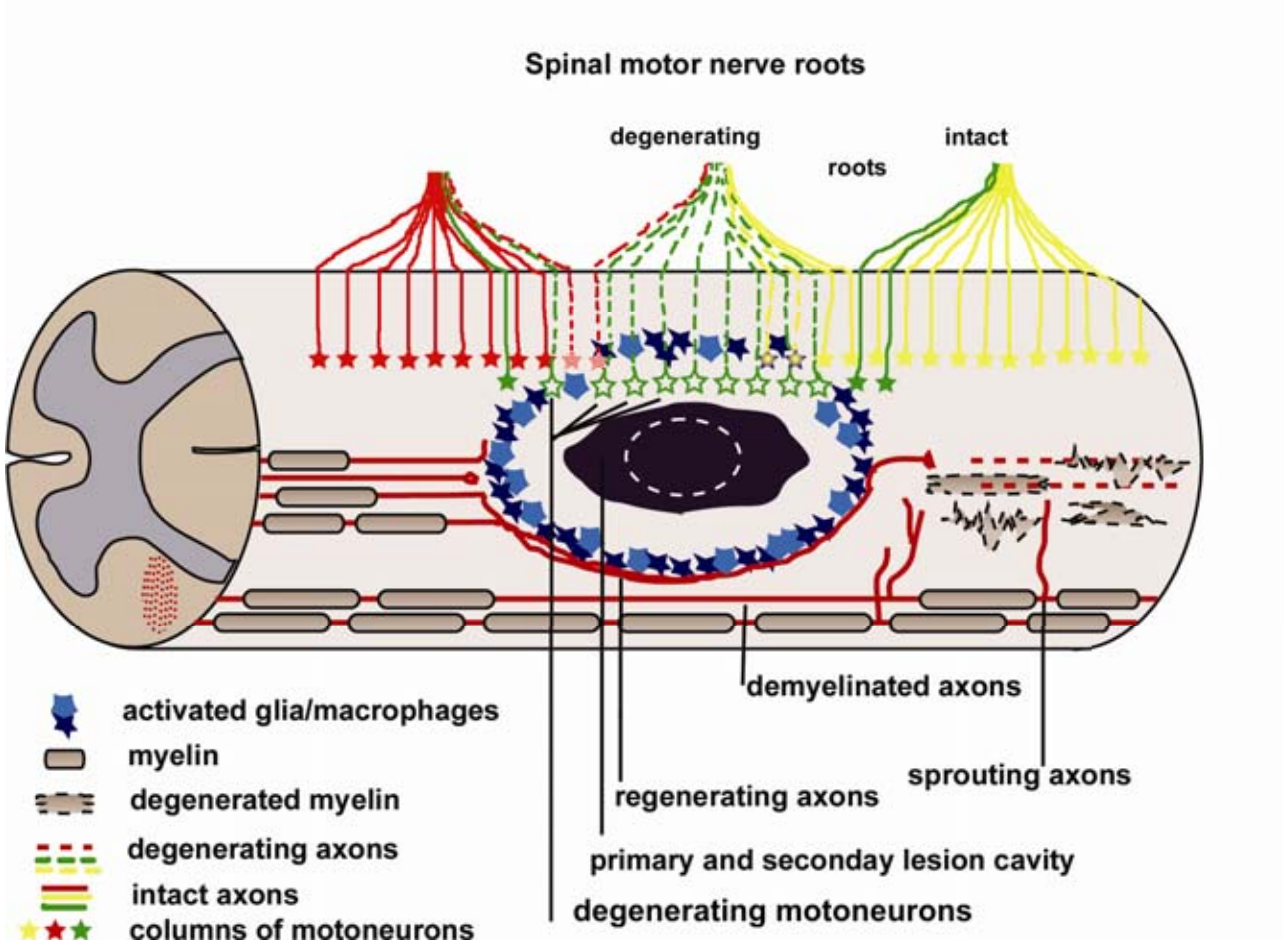
# *The challenge*



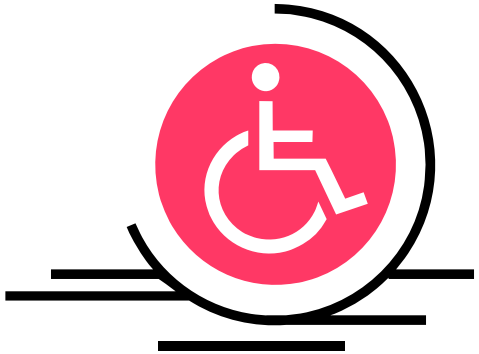
- informed clinical trials in human SCI
- appraisal of pre-clinical studies in SCI
- proof of mechanisms in human SCI

# Similar approaches in stroke and SCI!

from bench to bed



# *The challenge*



- informed clinical trials in human SCI
- appraisal of pre-clinical studies in SCI
- proof of mechanisms in human SCI

# Functional recovery in incomplete spinal cord injury

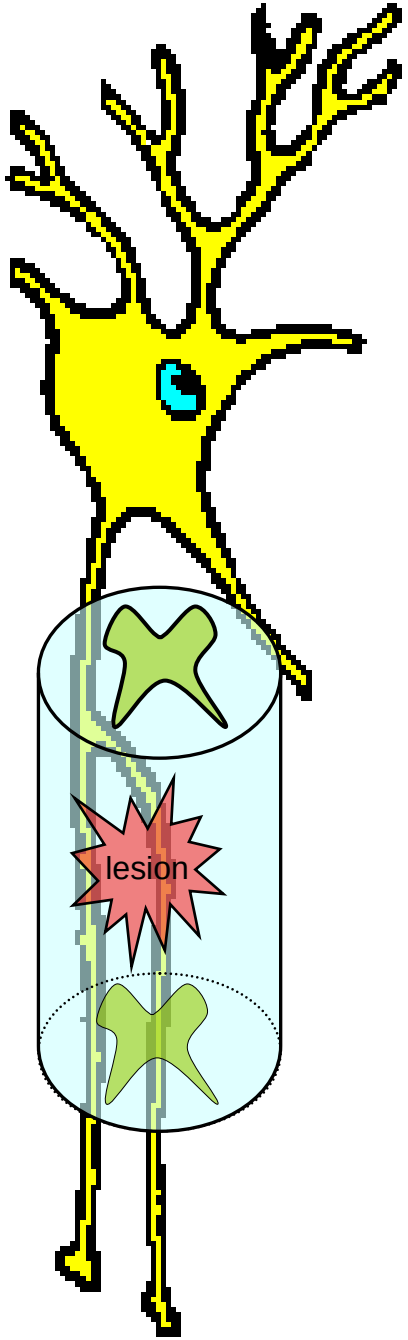
3 weeks after injury

12 weeks after injury

# Outcome measures: high clinical value

- 10-m walk test
- 6-minute walk test
- Timed up and go test
- LEMS (manual muscle testing)
- SCIM III (walking items)
- WISCI II
- Modified Ashworth Test


but no means of mechanisms!!

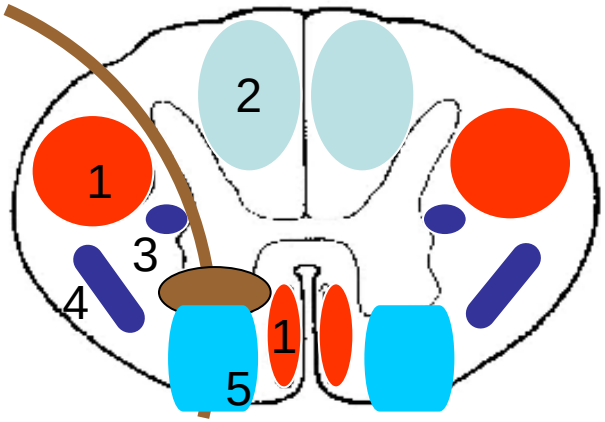



# Is there repair of damaged pathways?

balgrist paraplegiker ZENTRUM

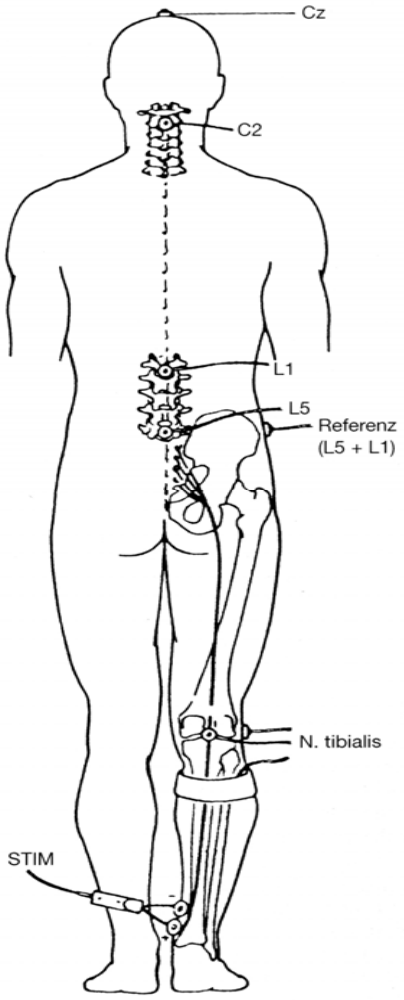
# Nervenbahnen im Rückenmark sind messbar!

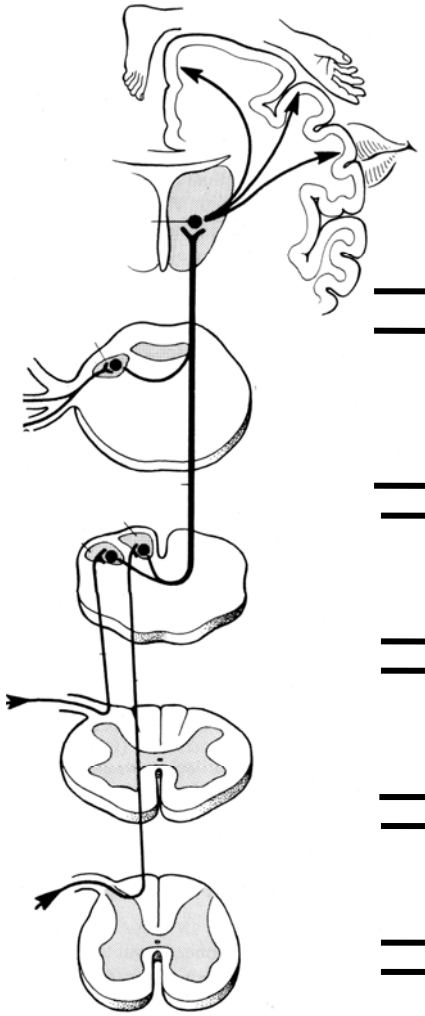


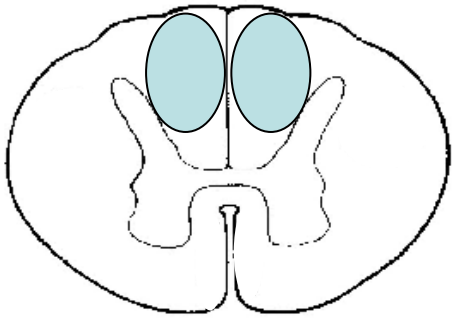


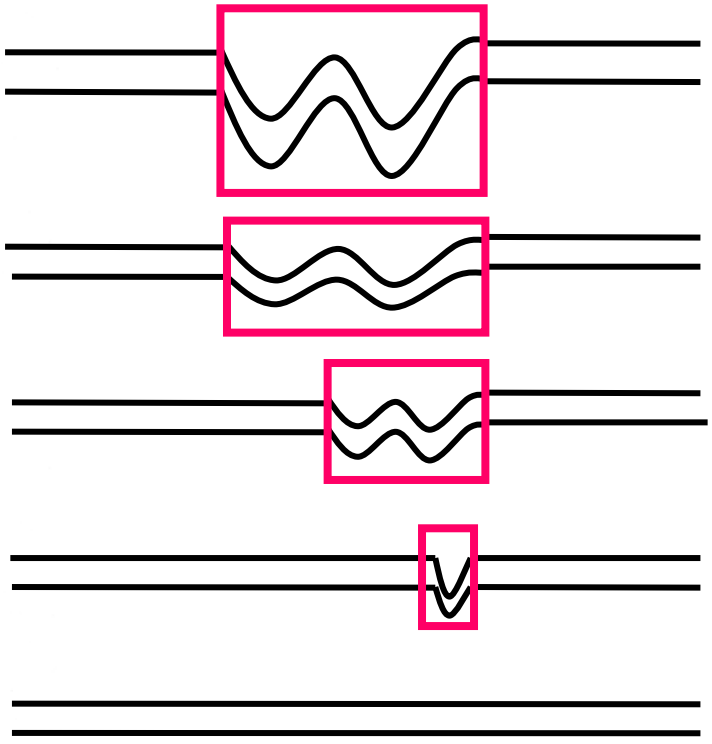

| Nervenbahnen | Methode |
|---|---|
| Motorische Bahnen[1] | MEP |
| Berührungsempfinden[2] | SSEP<br>dSSEP |
| Autonome Bahnen[3] | SSR |
| Schmerz Bahnen[4] | CHEPs<br>(LEP) |
| Gleichgewichts Bahnen[5] | GVS |

# SSEP recordings







normal

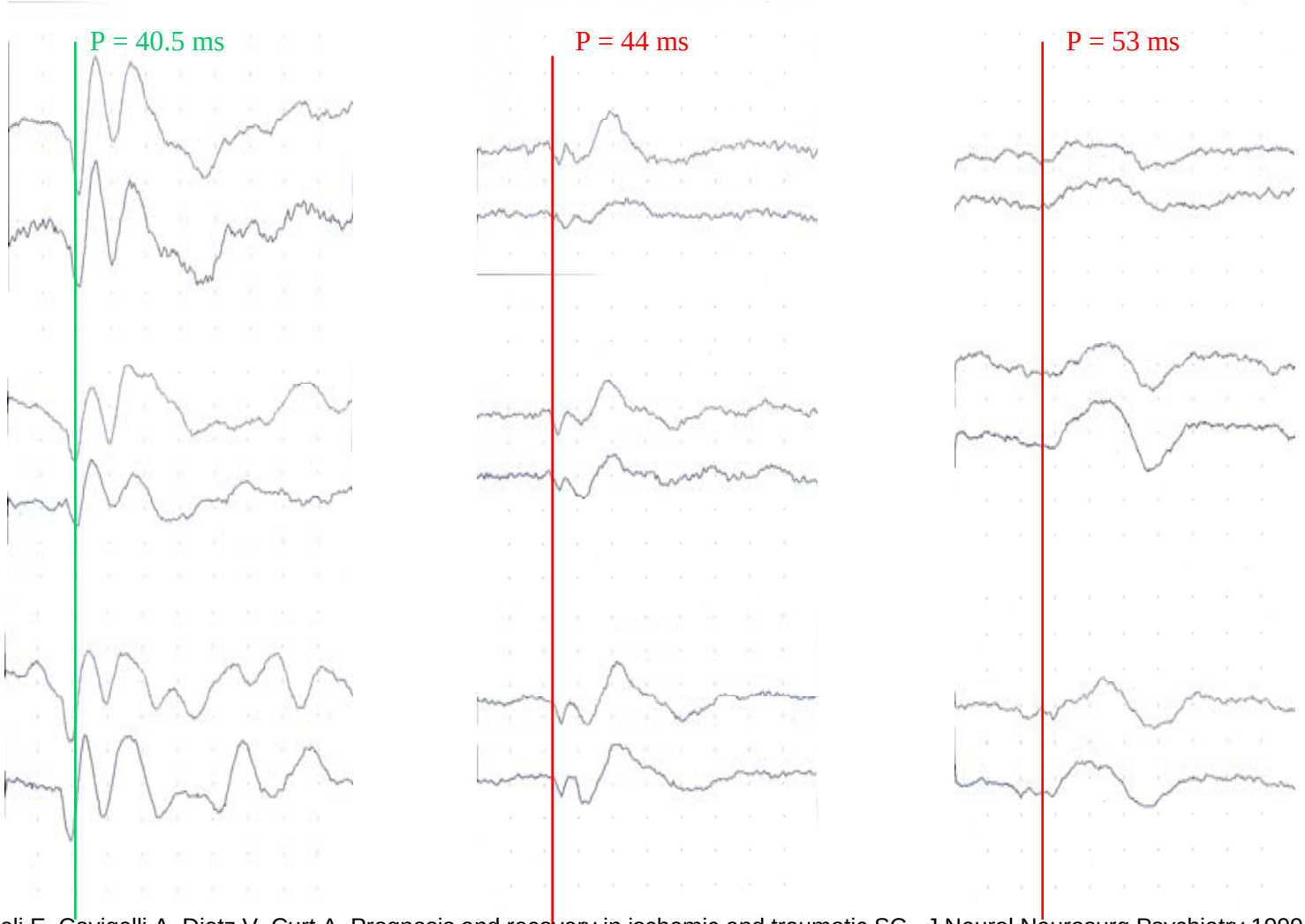
reduced

reduced
slowed

suspected

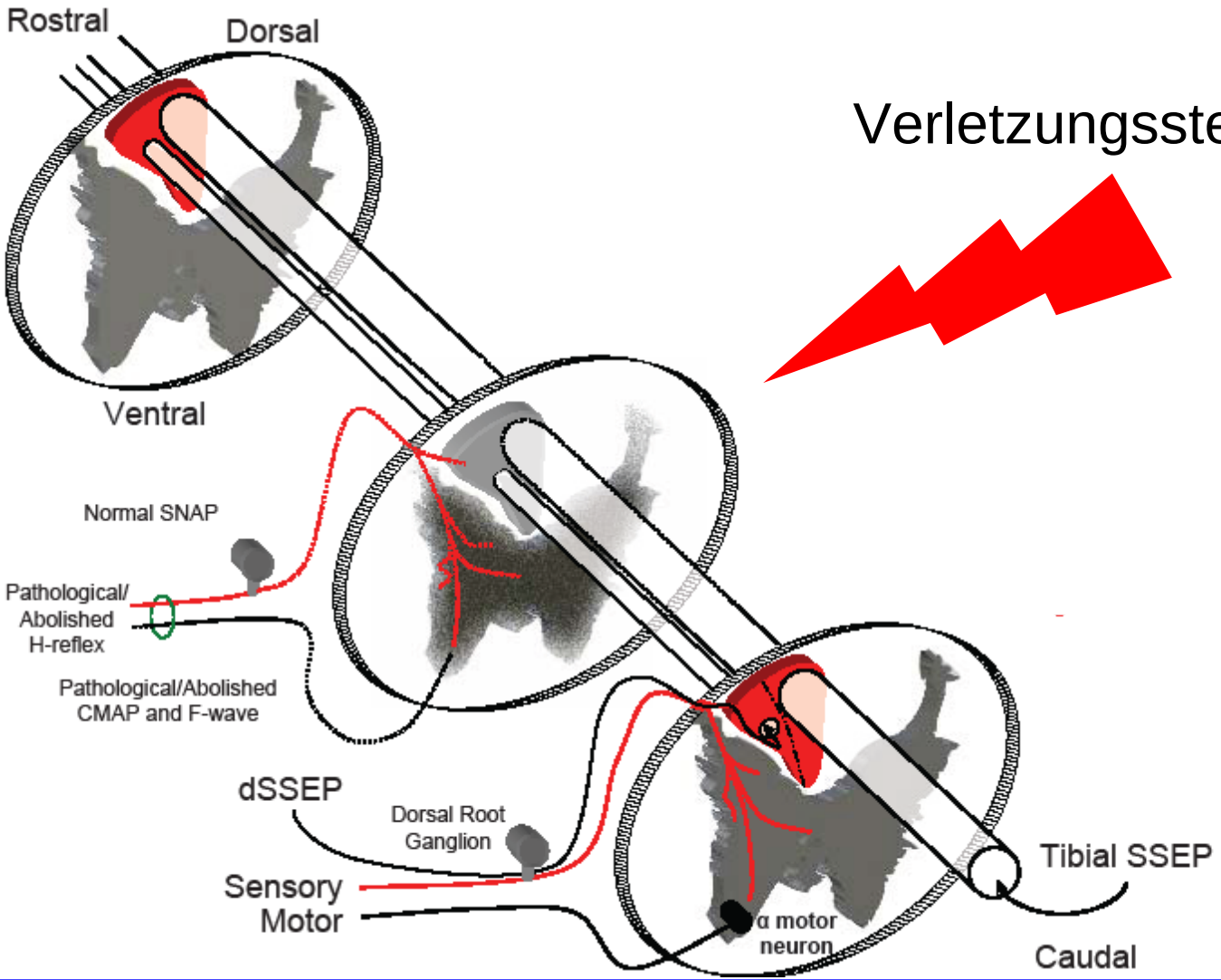
abolished

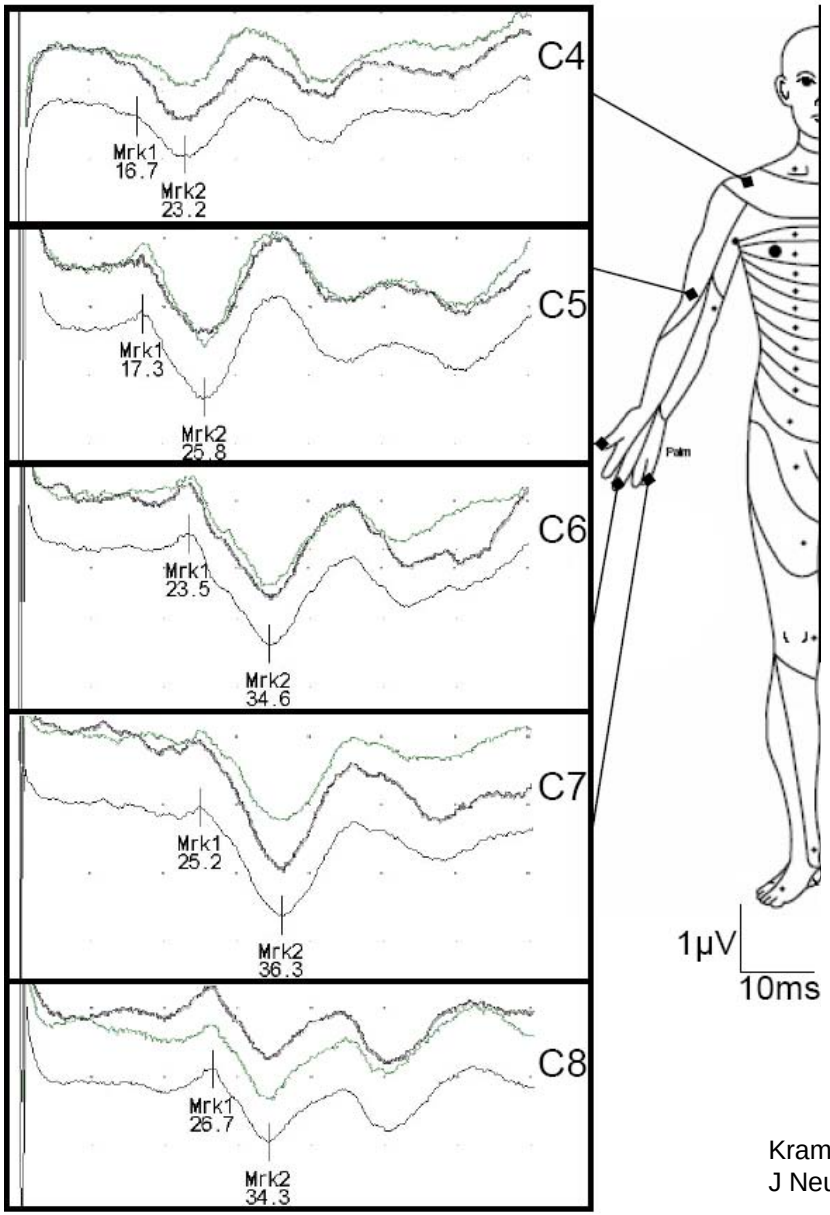
# Follow-up SSEP in ASIA C/D




Iseli E, Cavigelli A, Dietz V, Curt A. Prognosis and recovery in ischemic and traumatic SC. J Neurol Neurosurg Psychiatry 1999

# Segmental Sensory Recovery

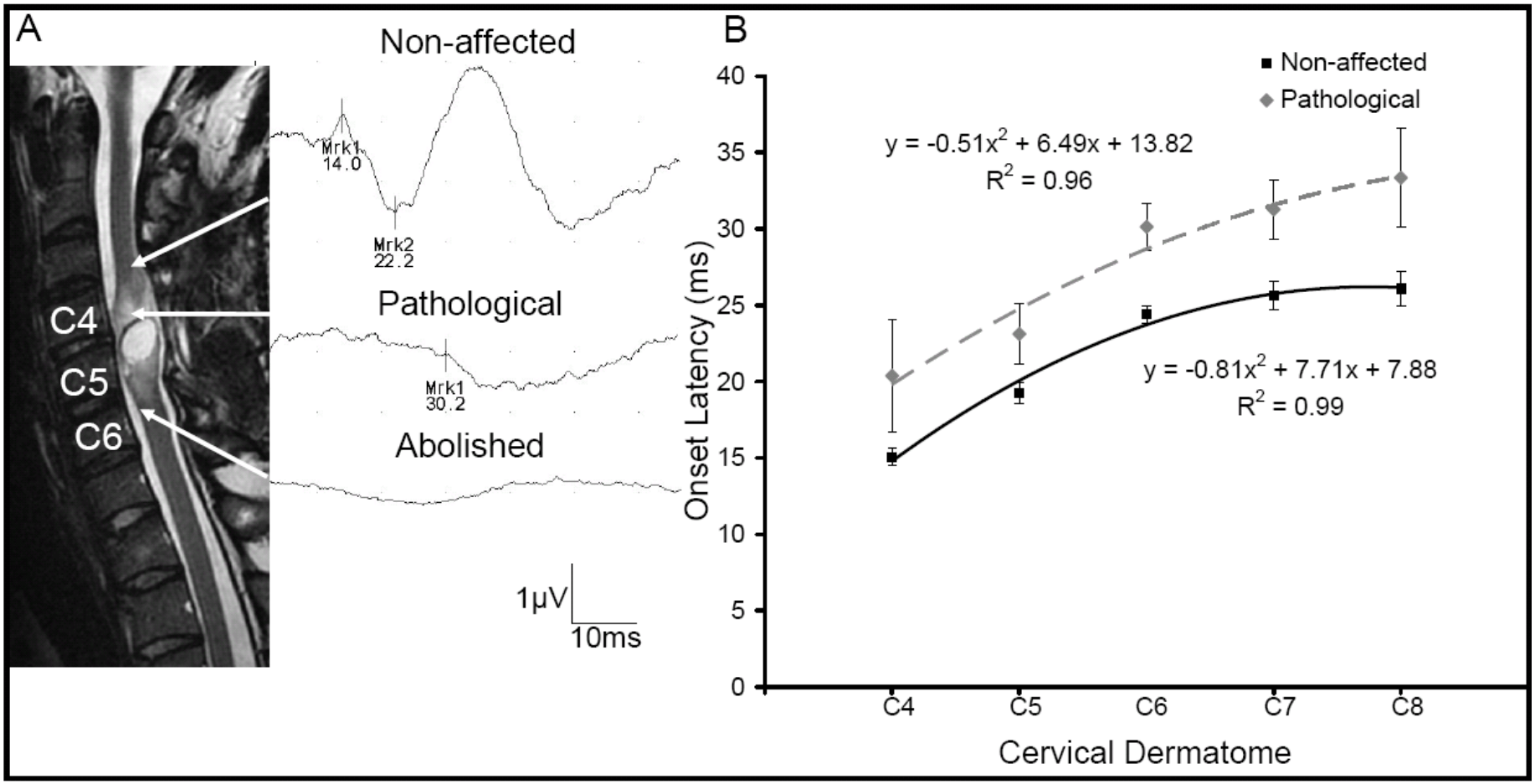





# Dermatomal – SSEP
# Electrical Perception Threshold (EPT)

| Dermatome | Onset Latency (ms) mean ±SD | Inter-peak Interval (ms) mean ±SD | EPT (mA) mean ±SD |
|---|---|---|---|
| C4 | 14.2 ±2.7 | 6.9 ±1.8 | 1.0 ±0.5 |
| C5 | 16.1 ±1.7 | 7.6 ±1.6 | 1.3 ±0.6 |
| C6 | 24.2 ±2.6 | 6.9±2.5 | 0.9 ±0.2 |
| C7 | 24.7 ±1.9 | 9.4±7.0 | 1.0 ±0.3 |
| C8 | 24.7 ±2.2 | 9.0±7.0 | 1.1 ±0.3 |

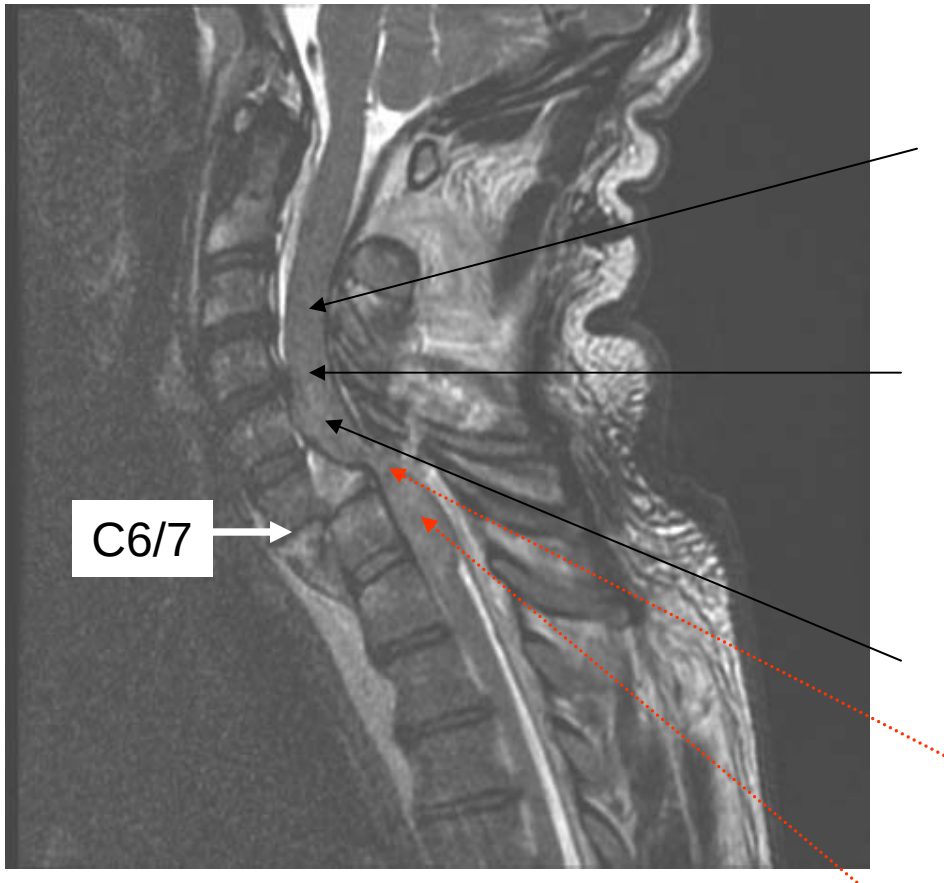
Kramer J, et al.. D-SSEP and EPT for the assessment of posterior cord function in SCI. J Neurotrauma 2008

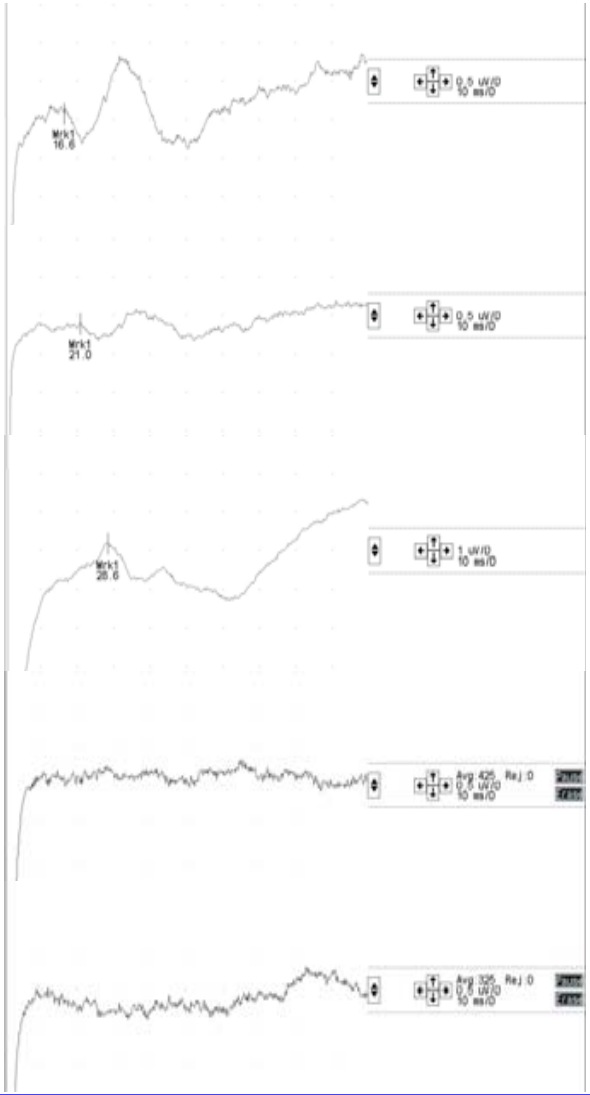



Kramer J, et al.. D-SSEP and EPT for the assessment of posterior cord function in SCI. J Neurotrauma 2008

Pre-surgical MRI

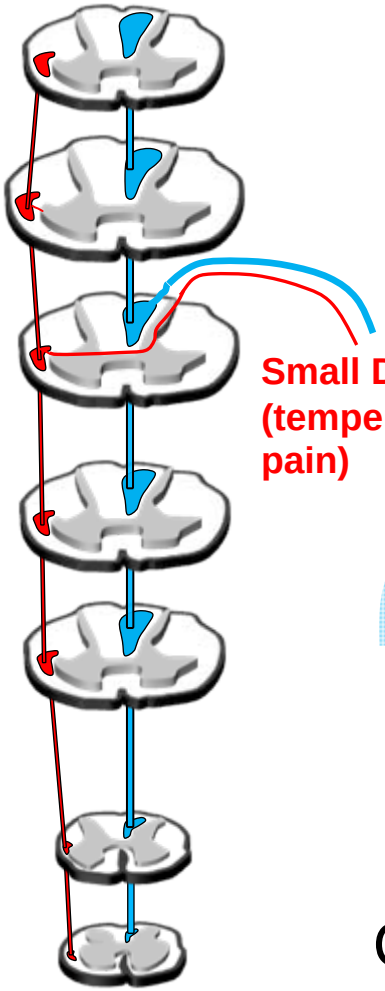
Dermatomal SSEP



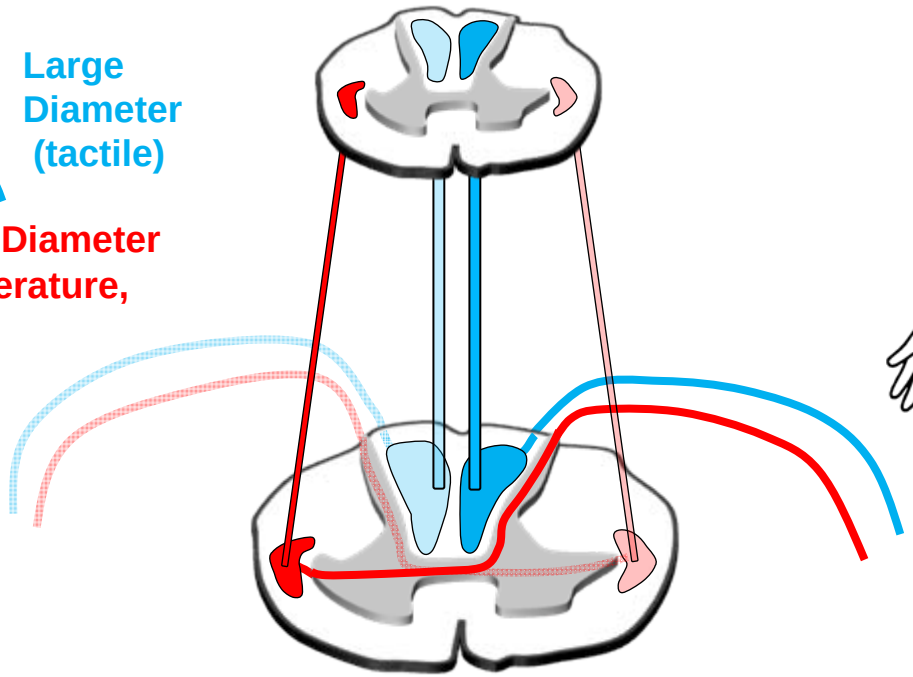

Male 41yrs, fall injury
C6 ASIA A

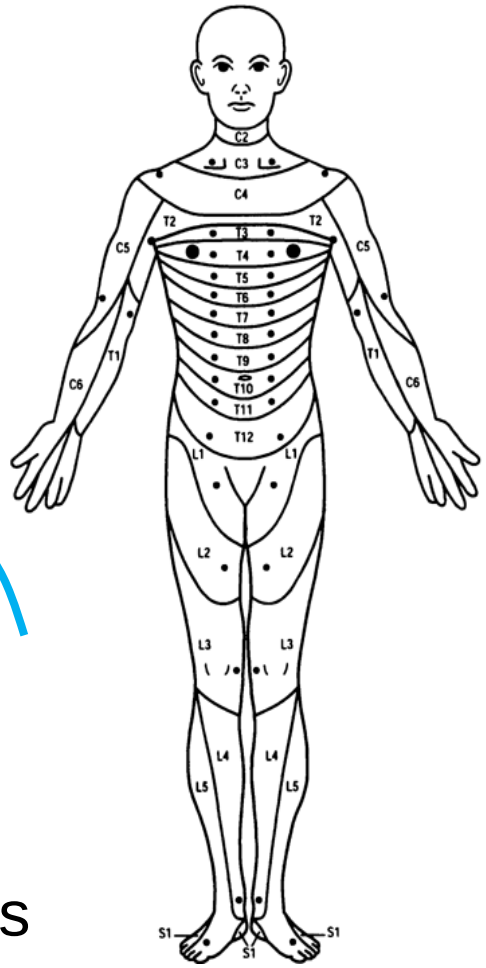
# Segmental Sensory Assessment



Large Diameter (tactile)

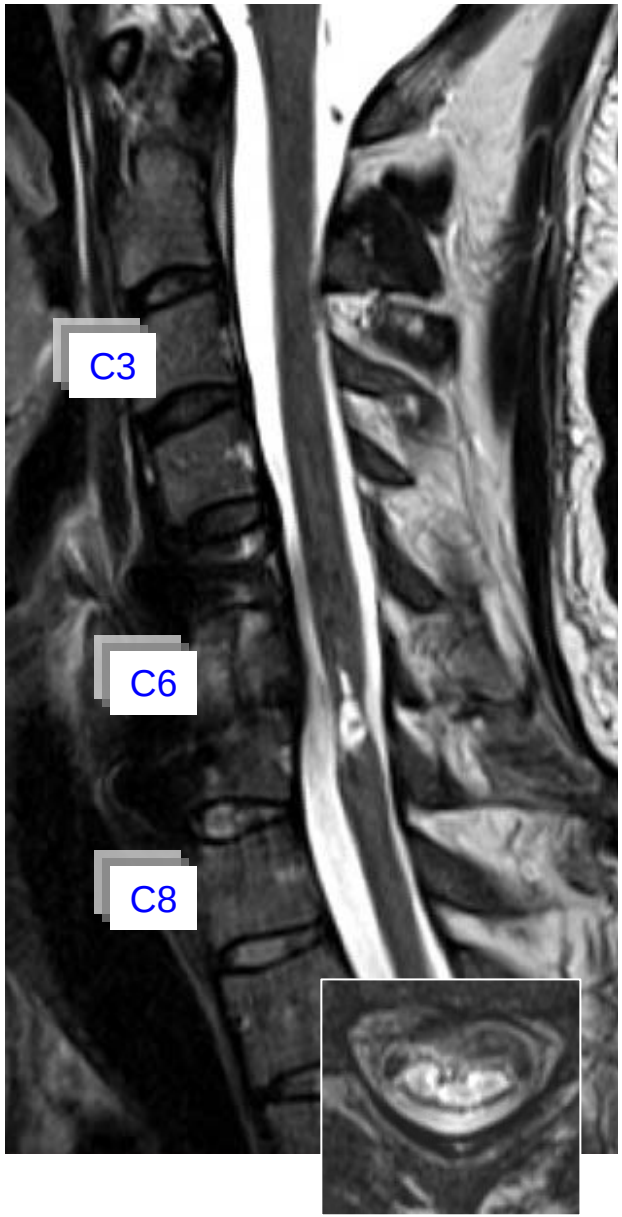
Small Diameter (temperature, pain)



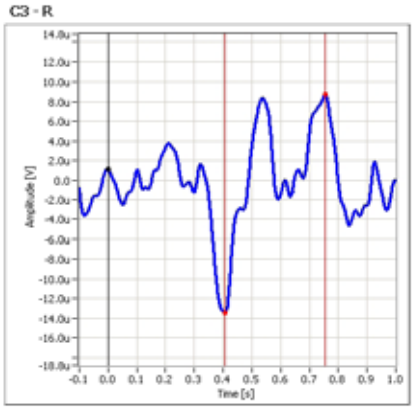



Contact Heat Evoked Potentials

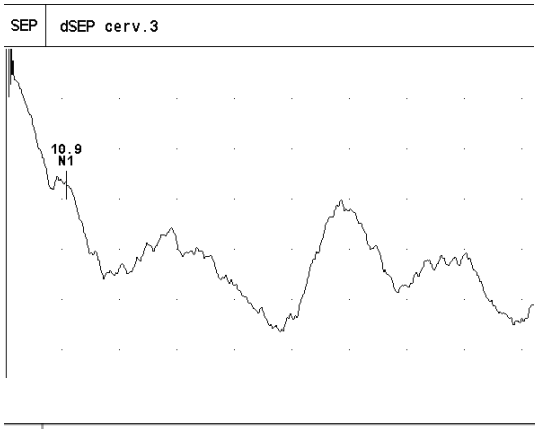
**CHEPS**




C3

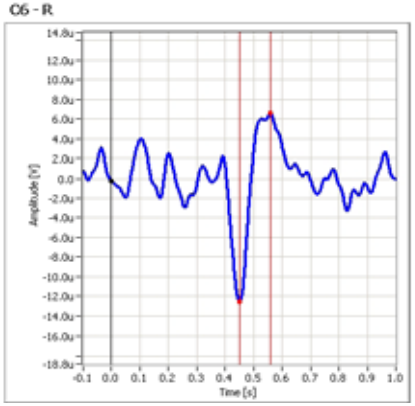



C3



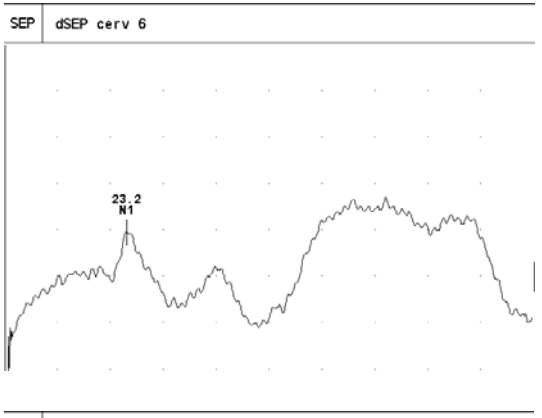

C6

CHEPS



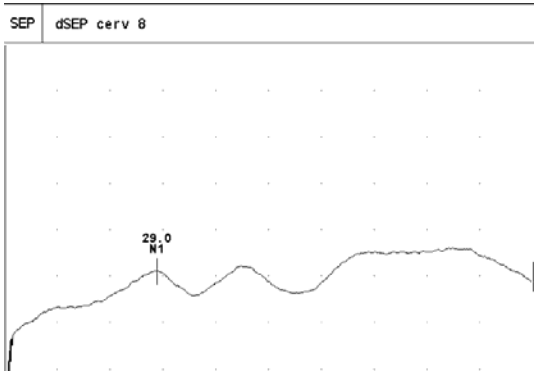

C6

dSSEP



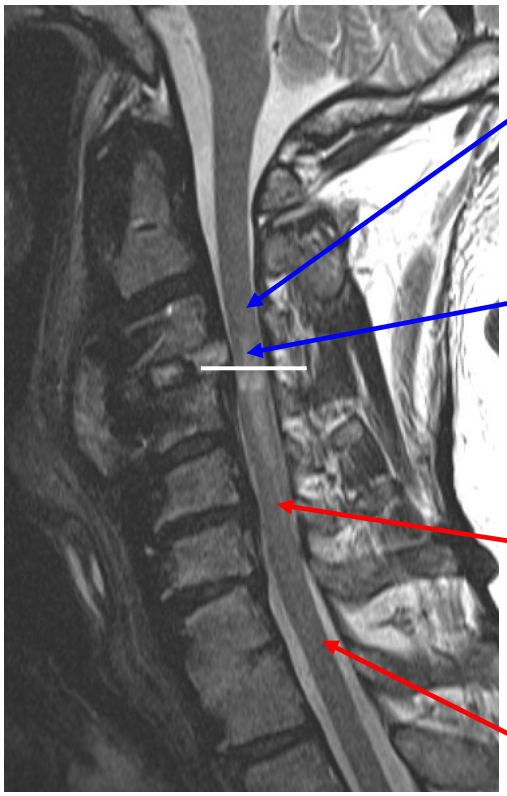

C8

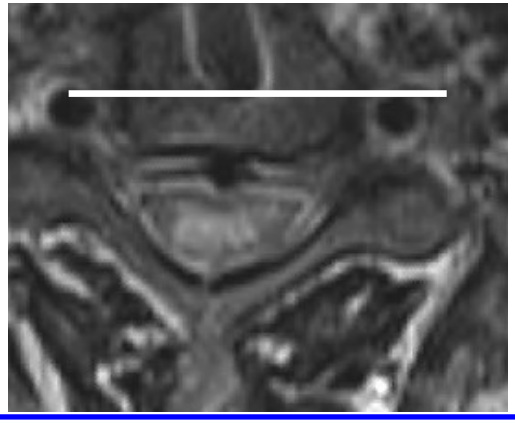

C8



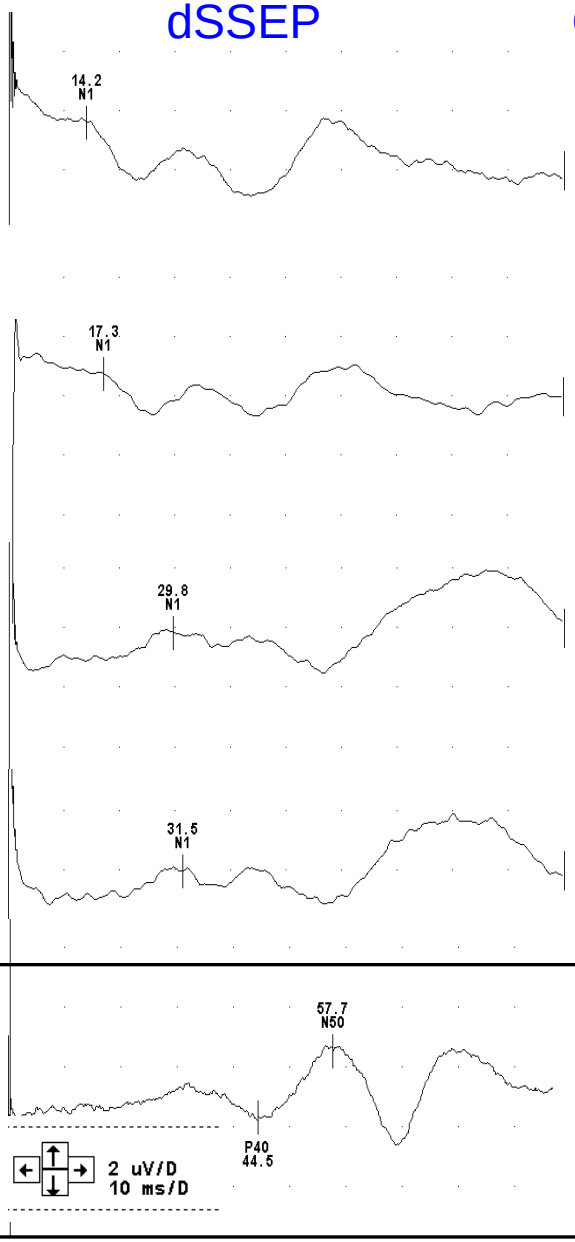

Universität Zürich[UZH]

balgrist paraplegiker ZENTRUM

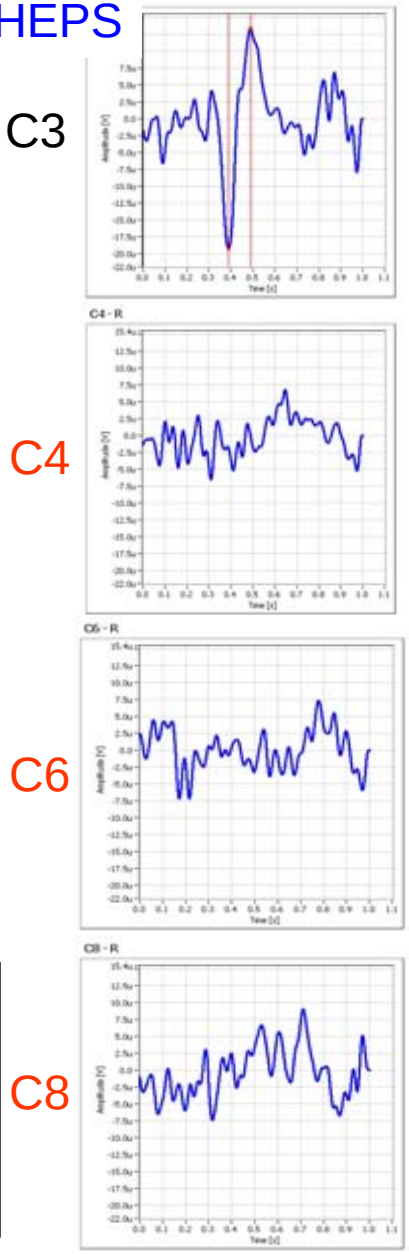

C3
C4
C6
C8



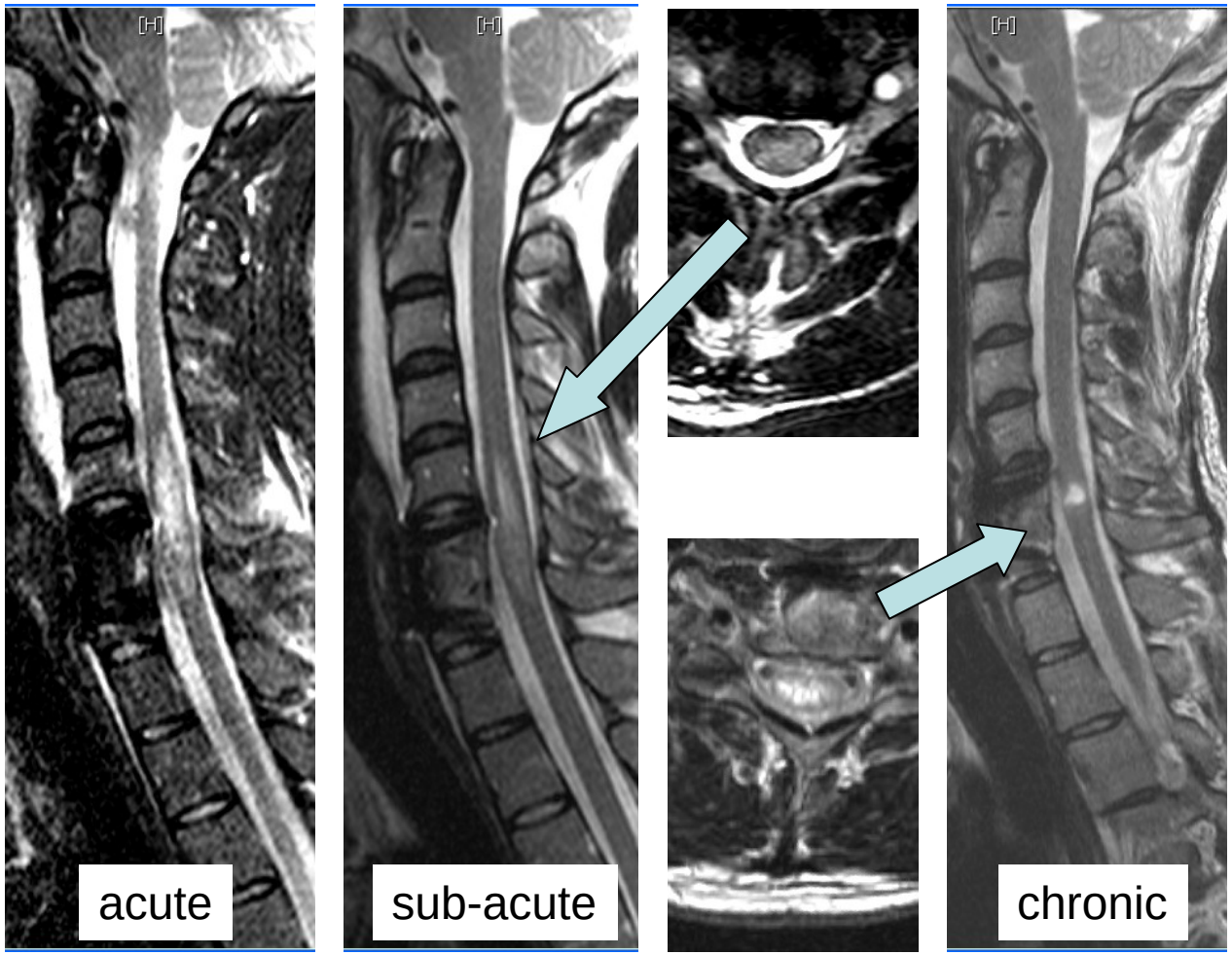
dSSEP


14.2
N1
17.3
N1
29.8
N1
31.5
N1
tibial
57.7
N50
P40
44.5
2 uV/D
10 ms/D

CHEPS

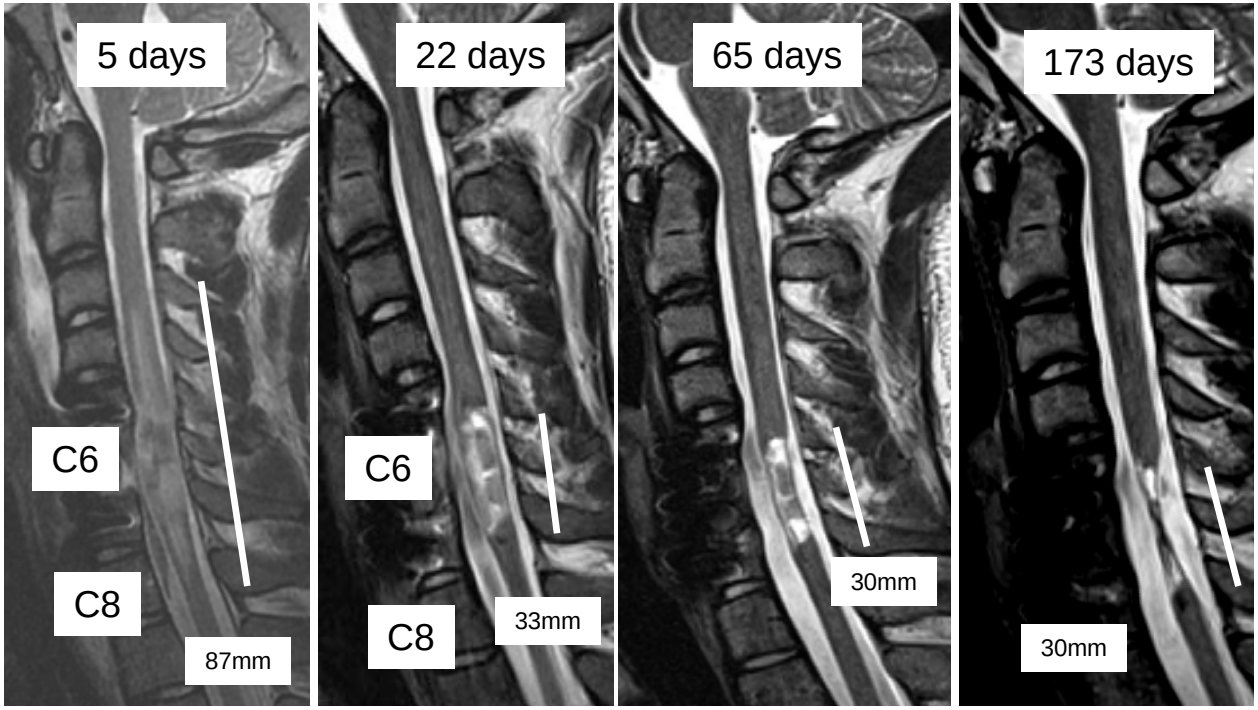

C3
C4
C4 - R
C6
C6 - R
C8
C8 - R

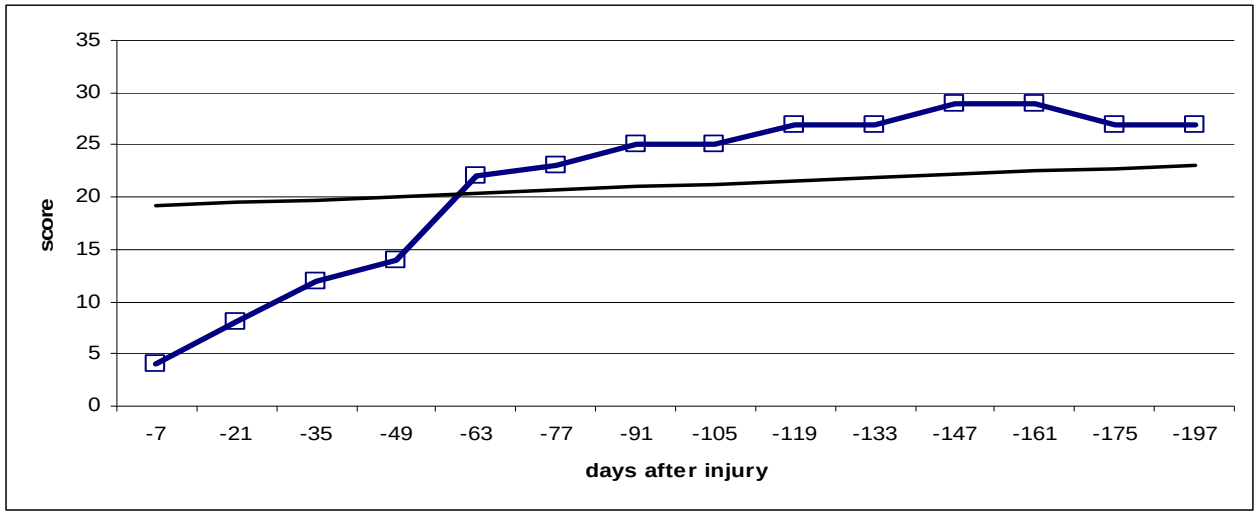
# Neuro-imaging spinal cord




Male 36 yrs
snowboard acc
mild central cord
neuropathic pain

works again as a surgeon!




# Time course in neuro-imaging and clinical scores

Patient C6 AIS-A with increase in independence (SCIM; open squares) but rather stable ASIA motor scores (solid trend line, total motor score 19 to 23).

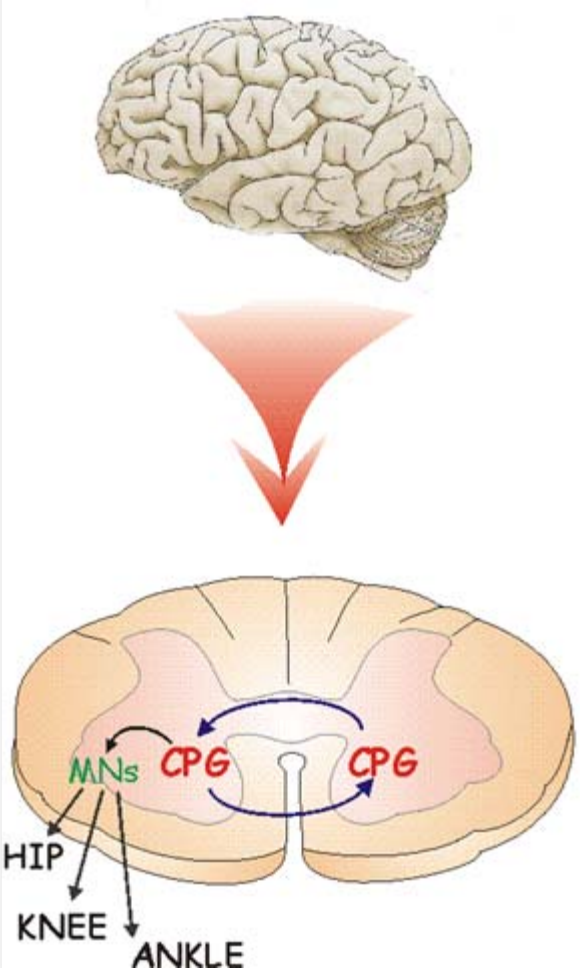
# Assessment of Brain & Spinal Cord

CORTICOL CONTROL

CONDUCTION ↑ ↓

SPINAL CIRCUITS

MOTOR OUTPUTS




Brain control
Preservation - Reorganization

Re-myelination (repair)?
Novel pathways (sprouting)?

Plasticity of neural circuits
- cortical
- spinal

Adaptation of motoneurones and muscle properties

Dexterity & motor skills
Weakness of muscles
Spasticity

# *Thanks for your attention!*

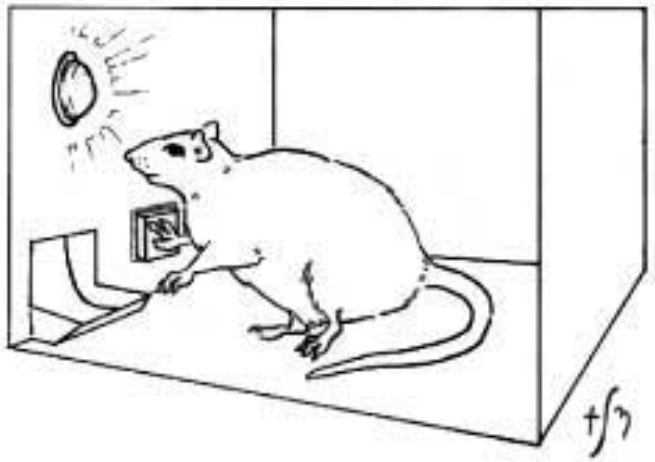
# Appraisal of pre-clinical studies in SCI

effectiveness and clinical relevance in humans

Species specific differences in:

- Rubro – reticulo – vestibulo spinal descending motor projections
- proprio – spinal pathways and influence of CPG on locomotor output
- requirements of neural changes to achieve ADL relevant outcomes

# How to bring preclinical science from bench to bed?



# Clinical SCI networks


European Multicenter study in SCI
EM-SCI

Lead: SCI Centre Balgrist


CHRISTOPHER & DANA REEVE FOUNDATION
TODAY'S CARE. TOMORROW'S CURE.

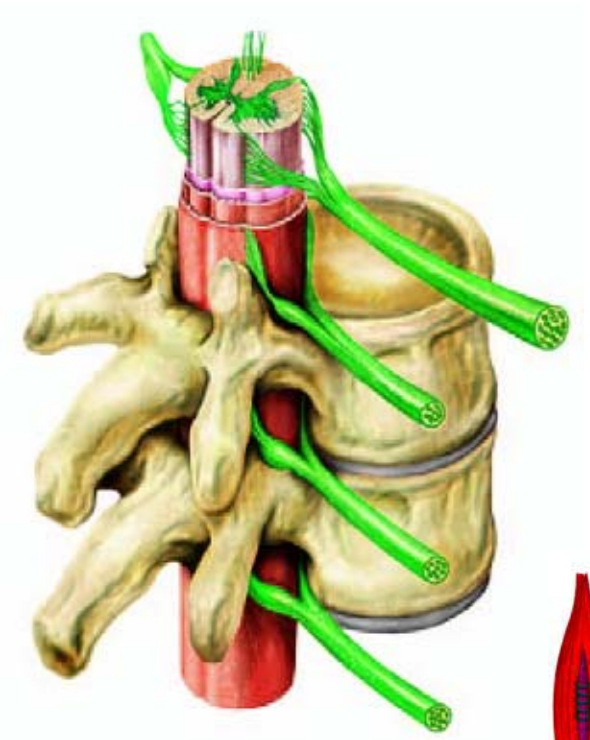
North American Clinical Trial Network in SCI

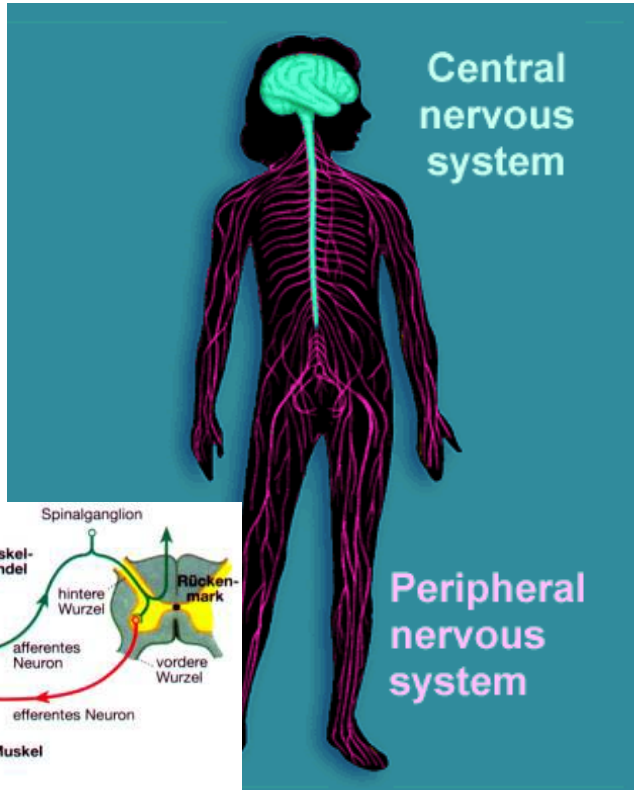

**CANADA'S NEW GOVERNMENT COMMITS NEW FUNDING TO THE RICK HANSEN FOUNDATION IN ITS DRIVE FOR A CURE FOR SPINAL CORD INJURIES**

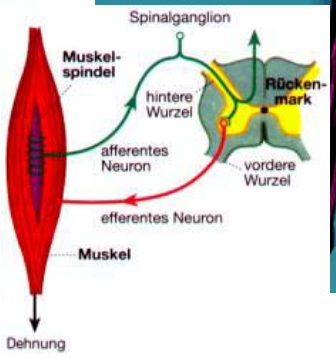
February 02, 2007

# This is not neuro - rehabilitation!


# Spinal cord: not only stupid wires….






Spinal tracts!

Complex network!

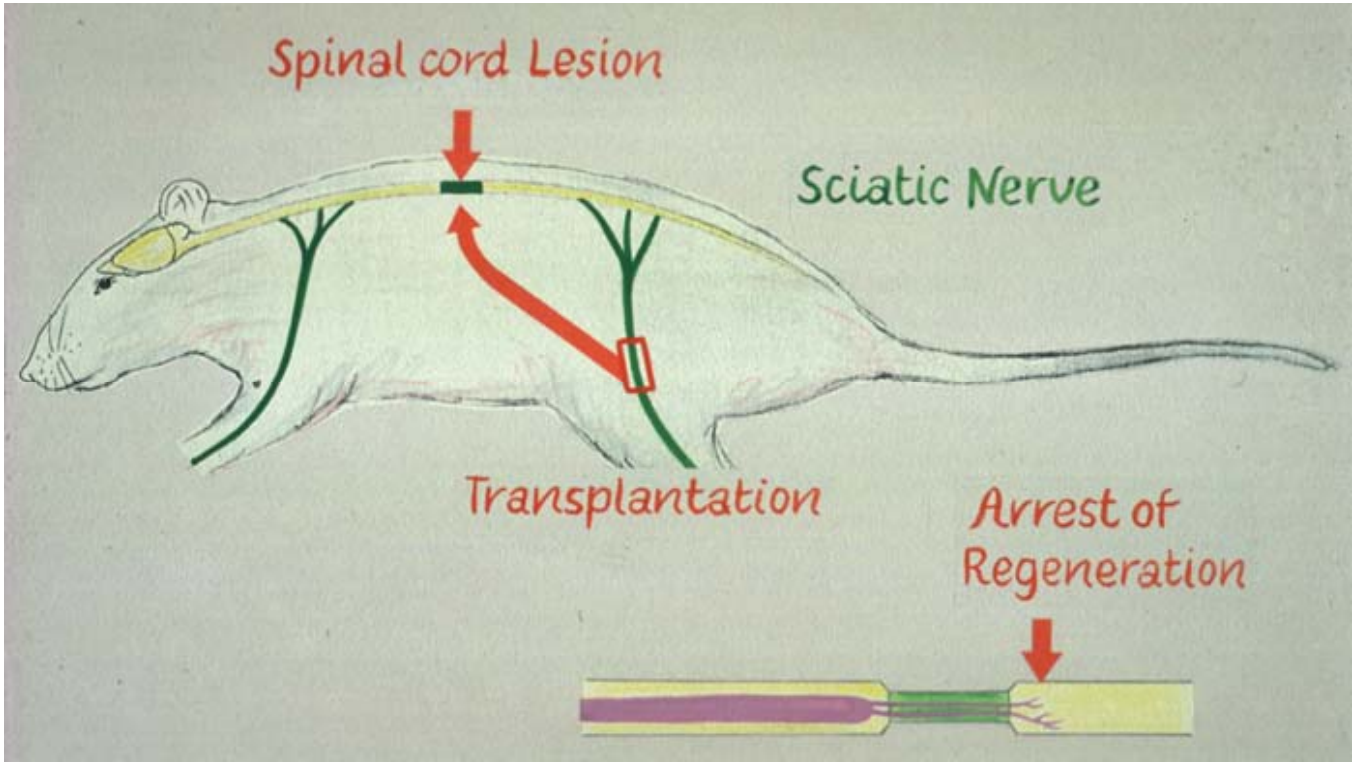
Central pattern generators…

# Moderne Paraplegiologie?

Sir Ludwig Guttmann
Ass.-Arzt Neurochirurgie am
Jüdischen Krankenhaus Breslau
floh 1933 nach London, UK
1944 Aufbau des
weltweit ersten SCI Center

1948
First „sports competitions involving World War II Veterans“ in Stoke Mandeville, England
1960 introduced as Paralympics in Rome

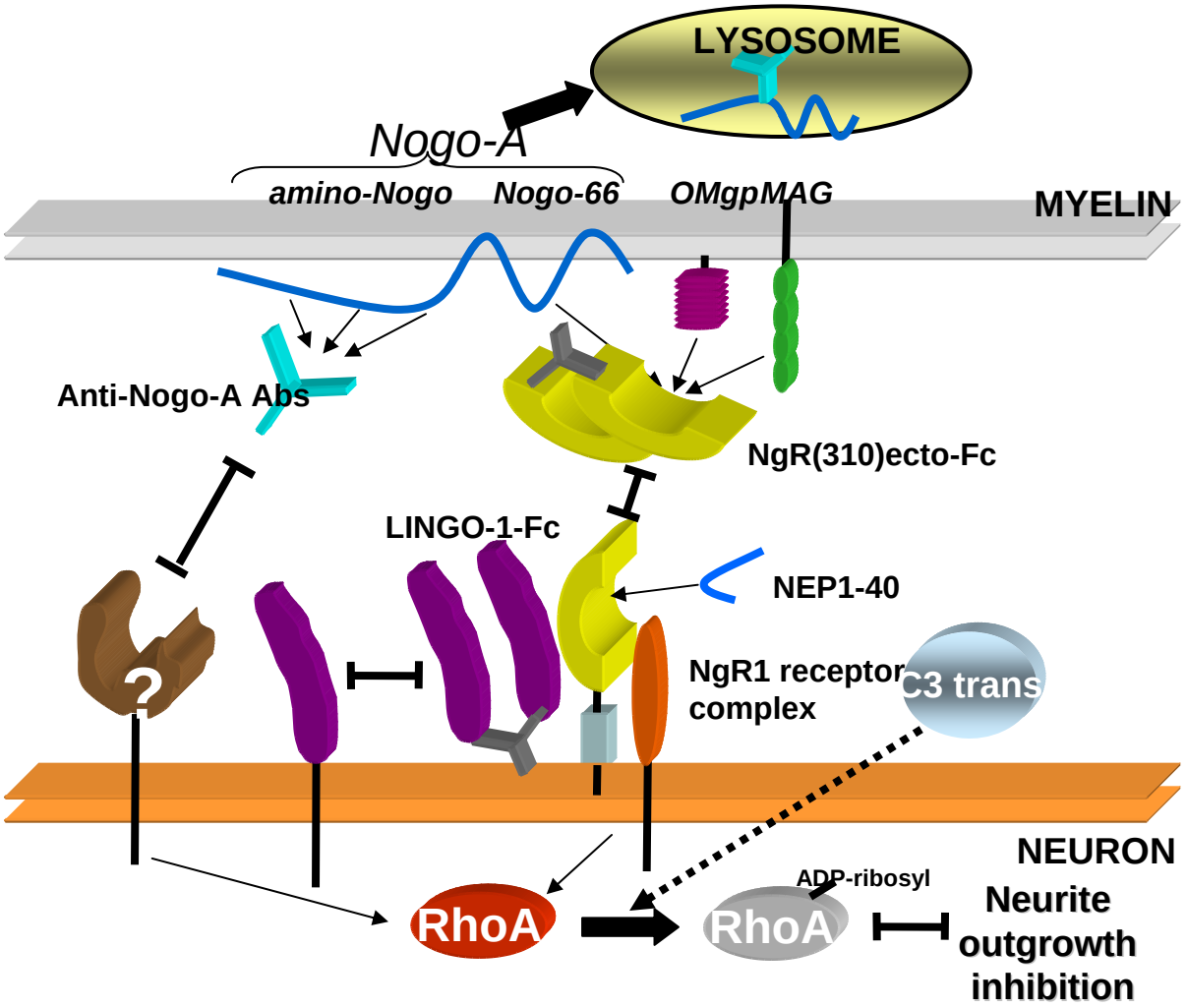
# Poor regenerative/plastic capacity of the adult CNS



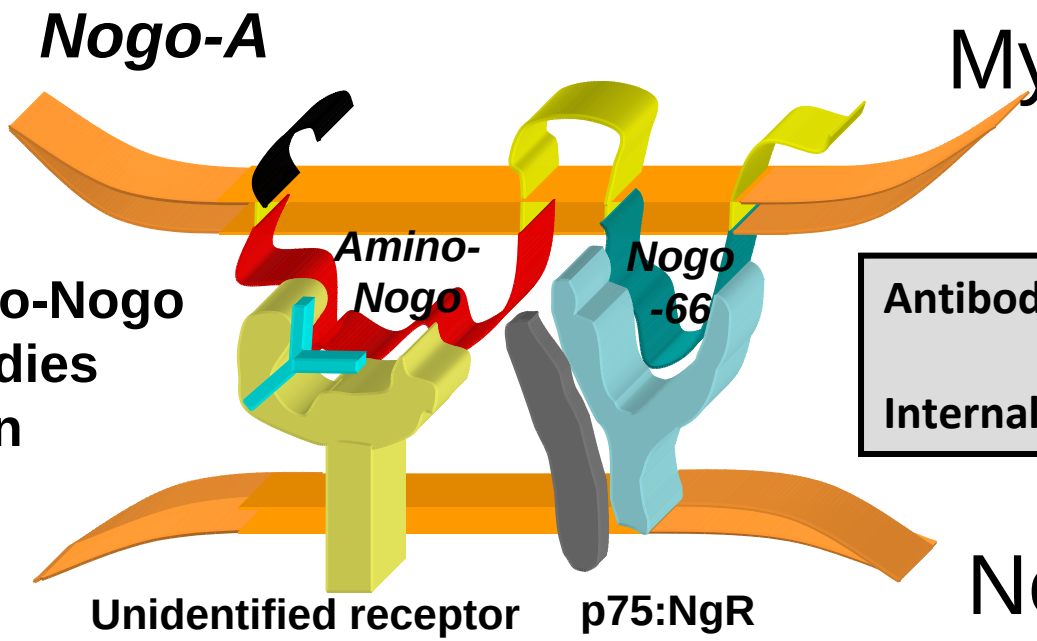

PNS environment allows spinal nerve regeneration
**Albert Aguayo 1982**

- Axonal regeneration and plasticity is restricted in CNS but not PNS

# Multiple inhibitors block neurite outgrowth



# Nogo-A antibody to block neurite outgrowth inhibition




**Blocking Amino-Nogo with antibodies results in**

**Antibody & Nogo-A complex**

**Internalised in vivo**

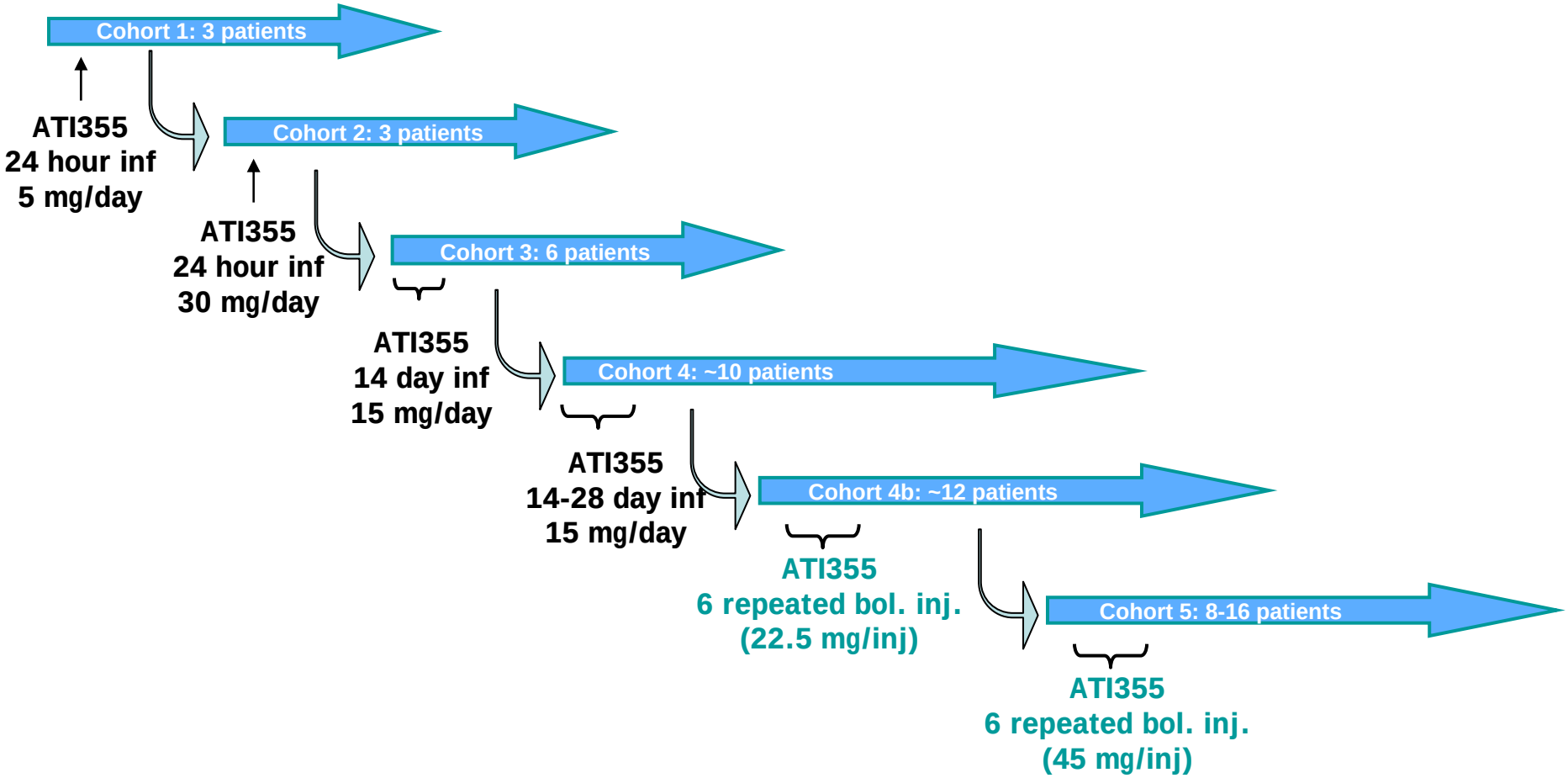
**Neurite outgrowth**

**Nerve fiber growth**

**Plasticity**

**Improved functional recovery**

# *First-in-man* study: cohort design

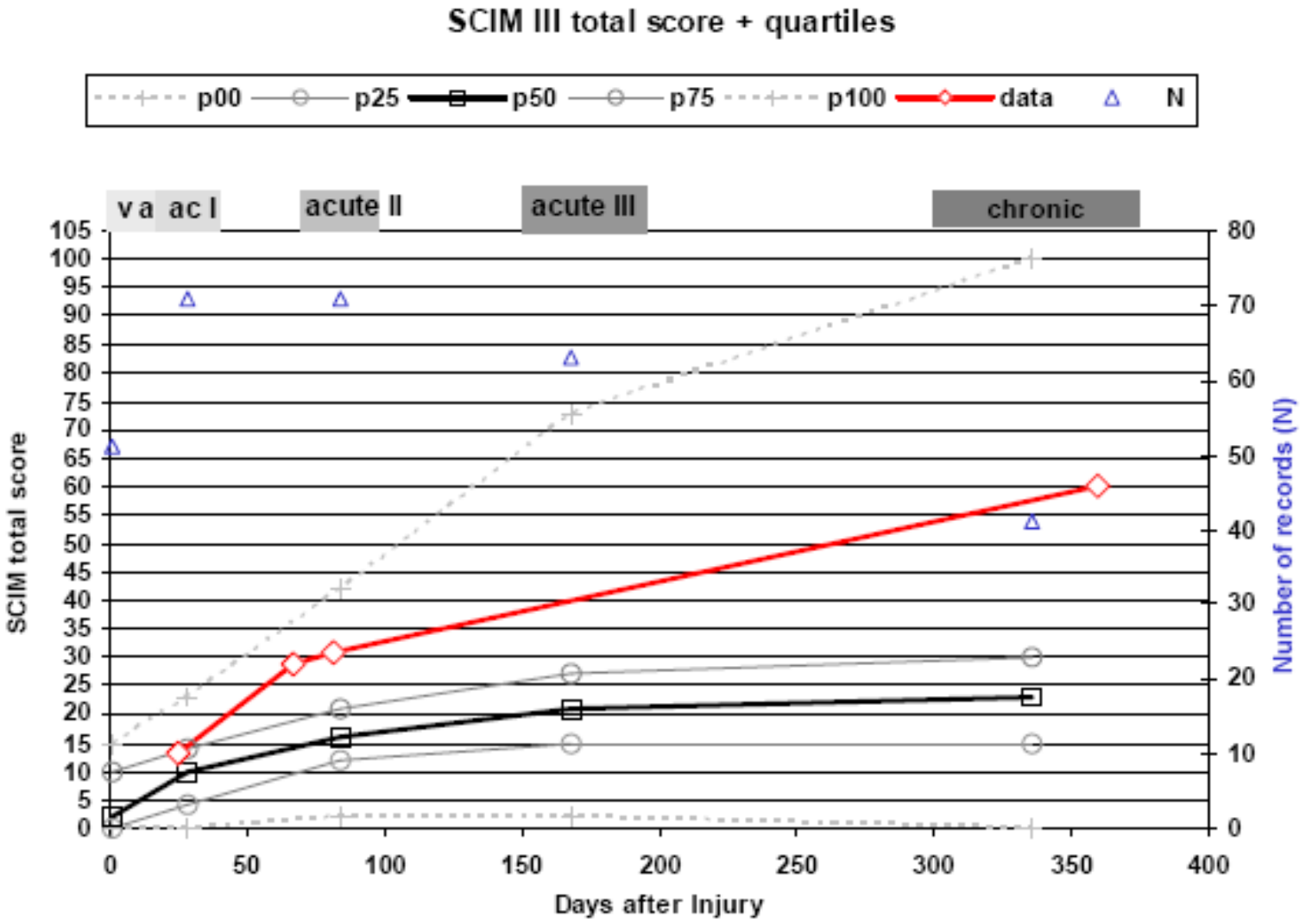


# *First-in-man* study: trial allocation

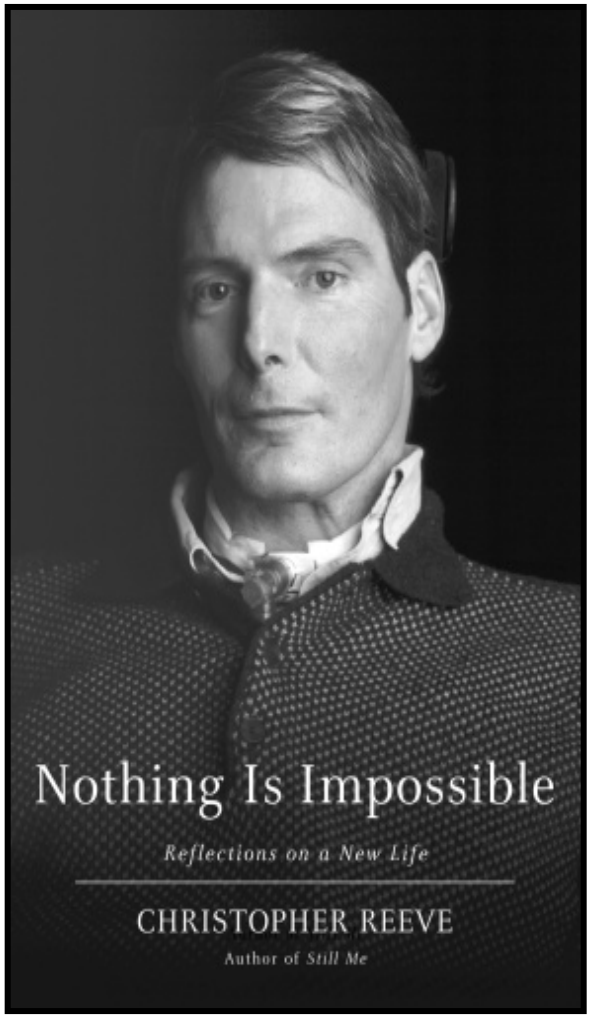
| **Country** | **Number of sites** | **No. of patients screened** | **No. of patients entered** |
|---|---|---|---|
| Switzerland | 1 | 7 | 6 |
| Germany | 9 | 48 | 43 |
| Canada | 3 | 6 | 5 |
| Spain | 2 | 0 | 0 |
| US | 1 | 0 | 0 |
| **Global** | **13** | **60** | **51** |

# C4 AIS - A

matched control values
based on EM-SCI



# Experimentelle Therapien mit Zellimplantationen





Dr. Huang, Bejing China
OEC transplantation in SCI

www.stemcellchina.com

offers solutions for everything!!!

# American Academy of Neurology April 3, 2008

Patients with spinal cord injury, amyotrophic lateral sclerosis (ALS), or other CNS disorders (MS, stroke) have been queuing up at clinics in China or other countries, where **some pay up to $60,000 for cell transplants** administered by epidural or intravenous injections or sometimes transplants to the frontal lobe of the brain.

Dr. Dobkin, Dr. Guest, and Armin Curt, MD (professor and associate director of ICORD) examined seven of Dr. Huang's patients with chronic SCI before and up to one year after OEC cell transplantation…
. …they reported no clinically useful sensorimotor, disability, or autonomic improvements….but reported complications…

Dr. Hongyun was quoted as calling Dr. Dobkin's paper rubbish and a vicious attack that he would not discuss

Dobkin BH, Curt A, Guest J.
Cellular transplants in China: observational study from the largest human experiment in chronic spinal cord injury. NNR 2006;20:5-13.

ChinaStemCellNews
Bringing the Latest Research and Treatments to You.

Behandelte Krankheiten

- ALS
- Alzheimer
- Arthrose
- Diabetes
- Zerebrale Kinderlähmung
- Kardiovaskuläre Erkrankungen
- Multiple Sklerose
- Parkinson-Krankheit
- Schlaganfall
- Verletzungen des Rückenmarks

Prof. W Young
Rutgers University
New York

Dr. Sean Hu said Beike Biotech has treated 2,500 patients since 2001

*"We have embarked on one of the most ambitious journeys in human history: to achieve something that was deemed impossible by many generations of scientists and clinicians."*

– Dr. Wise Young, Founding Director

Universität Zürich[UZH]

balgrist paraplegiker ZENTRUM

ChinaStemCellNews
Bringing the Latest Research and Treatments to You.

Shenzhen Beike Biotechnology Center, China

Dr. Sean Hu said Beike Biotech has treated >2,500 patients since 2001

*"We have embarked on one of the most ambitious journeys in human history: to achieve something that was deemed impossible by many generations of scientists and clinicians."*

– Dr. Wise Young, Founding Director

Universität Zürich[UZH]

balgrist paraplegiker ZENTRUM

# China ist fast überall!!

30 August 1971
Autounfall, Tetra

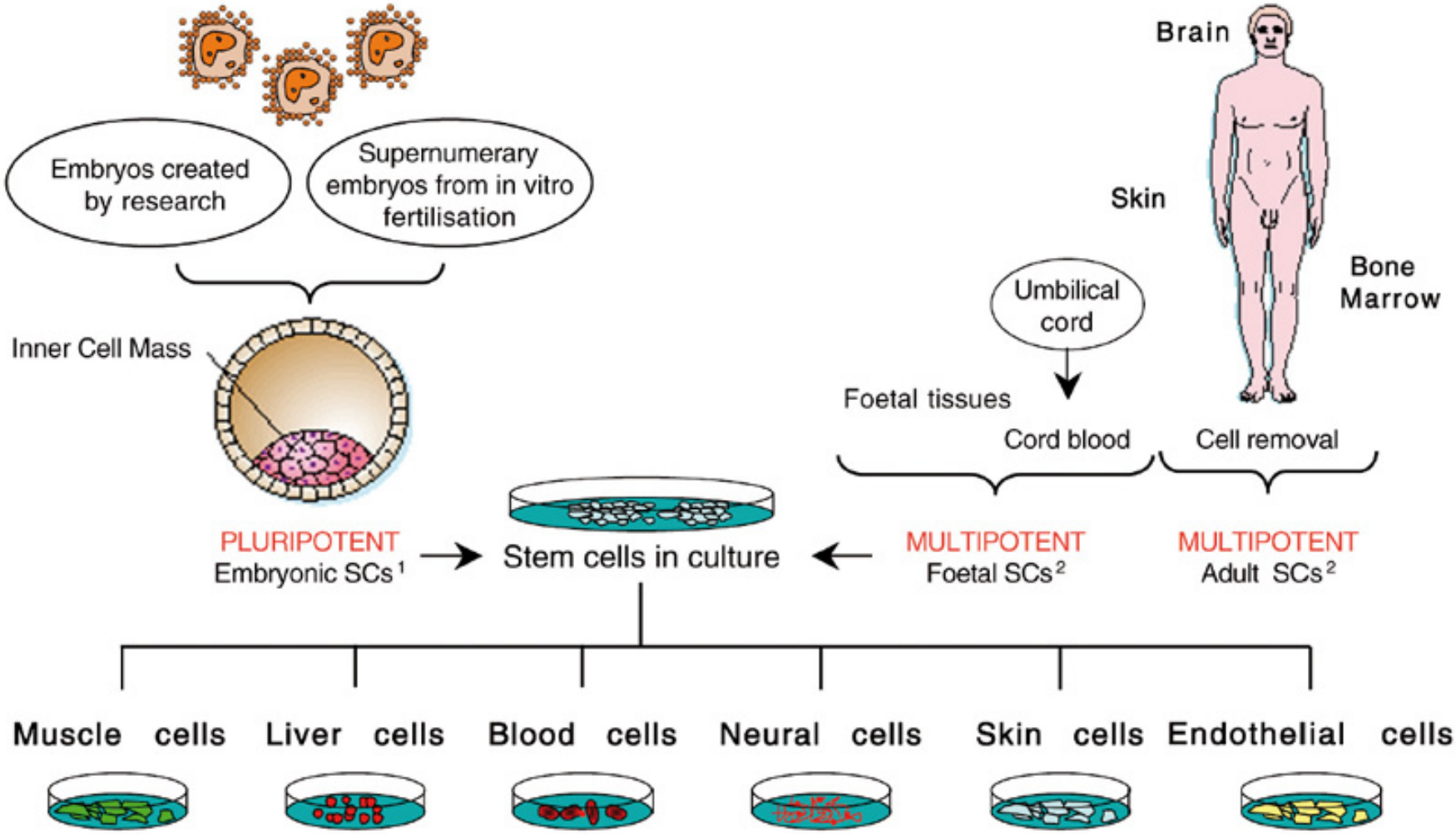
**My First Treatment**
December 2008 at the XCell-Center in Cologne, Germany. After that treatment, I did my best to exercise; a combination of physical therapy and swimming pool exercises. However, the recovery was slow because I had spasms. Because of these spasms, improvement was not as expected.

**My Second Treatm**
In Jun via lumbar puncture.
Afterwards exercise. Spasms significantly decreased and visible.

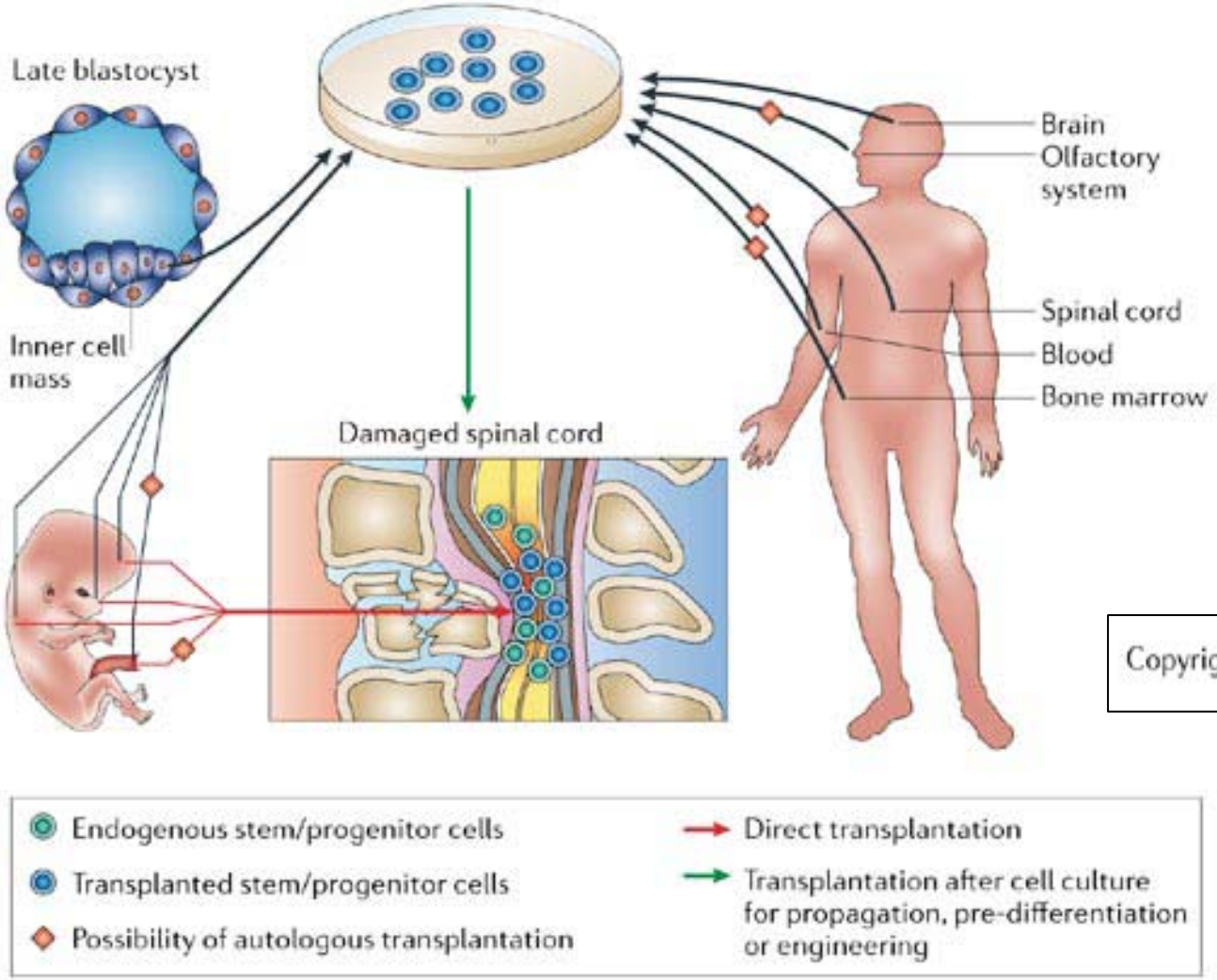
Keine seriös kontrollierte Studien!!

**My Third Treatment**
My third stem cell treatment was performed in January 2010. The doctor told me that I must consistently work on my physical therapy and that any results can be expected in the following 3 to 6 months. I hope that further progress will be obvious. I do not want to regret.

# Stammzellen



# Stammzellen in „spinal cord injury“



# First US stem cell trial acute SCI

**12.10.10 Embryonic stem-cells used on human in trial first for spinal injuries**

**Geron (US company)**
the patient was enrolled at Shepherd Centre, Atlanta
acute SCI < 2 weeks, T3-T10,

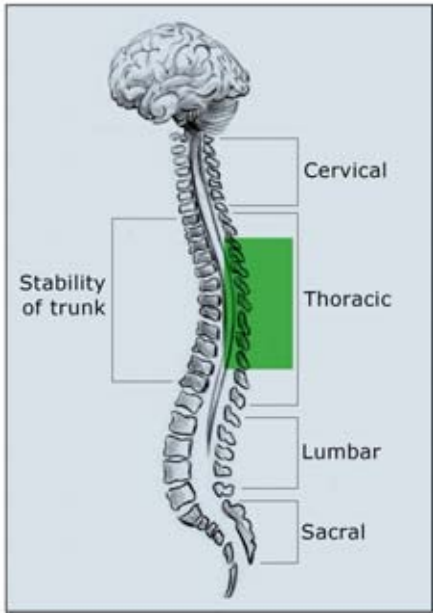
about 10 patients

GRNOPC1 - contains oligodendrocyte progenitor cells. Those progenitor cells turn into oligodendrocytes, a type of cell that produces myelin

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

*GRNOPC1 Phase 1 Multi-Center Spinal Cord Injury Trial*

- **Open Label Trial**
- **Subacute, Functionally Complete Spinal Cord Injury with a Neurological Level of T3 to T10**
- **2x10⁶ Cells**
- **Transplant 7-14 Days Post Injury**
- **Temporary Immunosuppression with Low Dose Tacrolimus**
- **Primary Endpoint: Safety**
  - *Neurological*
  - *Overall*
- **Secondary Endpoint: Efficacy**
  - *ASIA Sensory Score*
  - *Lower Extremity Motor Score*



# First European Hu-CNS SC trial

**Human Neuronal stem cells**
**first trial in human SCI**

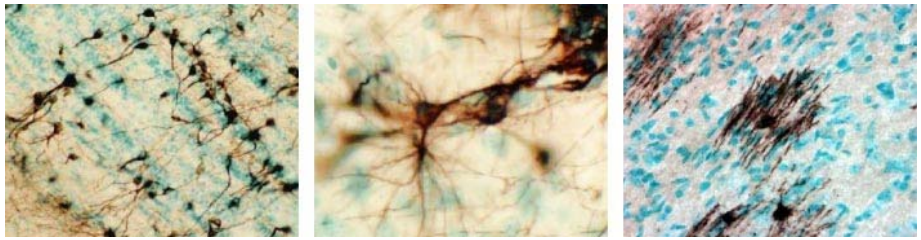
**StemCells Inc. (Palo Alto, US)**
*spin off Stanford Uni (I Weissman)*

European referral study
Spinal Cord Injury Center Balgrist
Study and lead center

target:
sub-acute / chronic SCI
4-12 mts after injury
T2 - T10
implantation of SC into spinal cord
12 patient AIS A-C

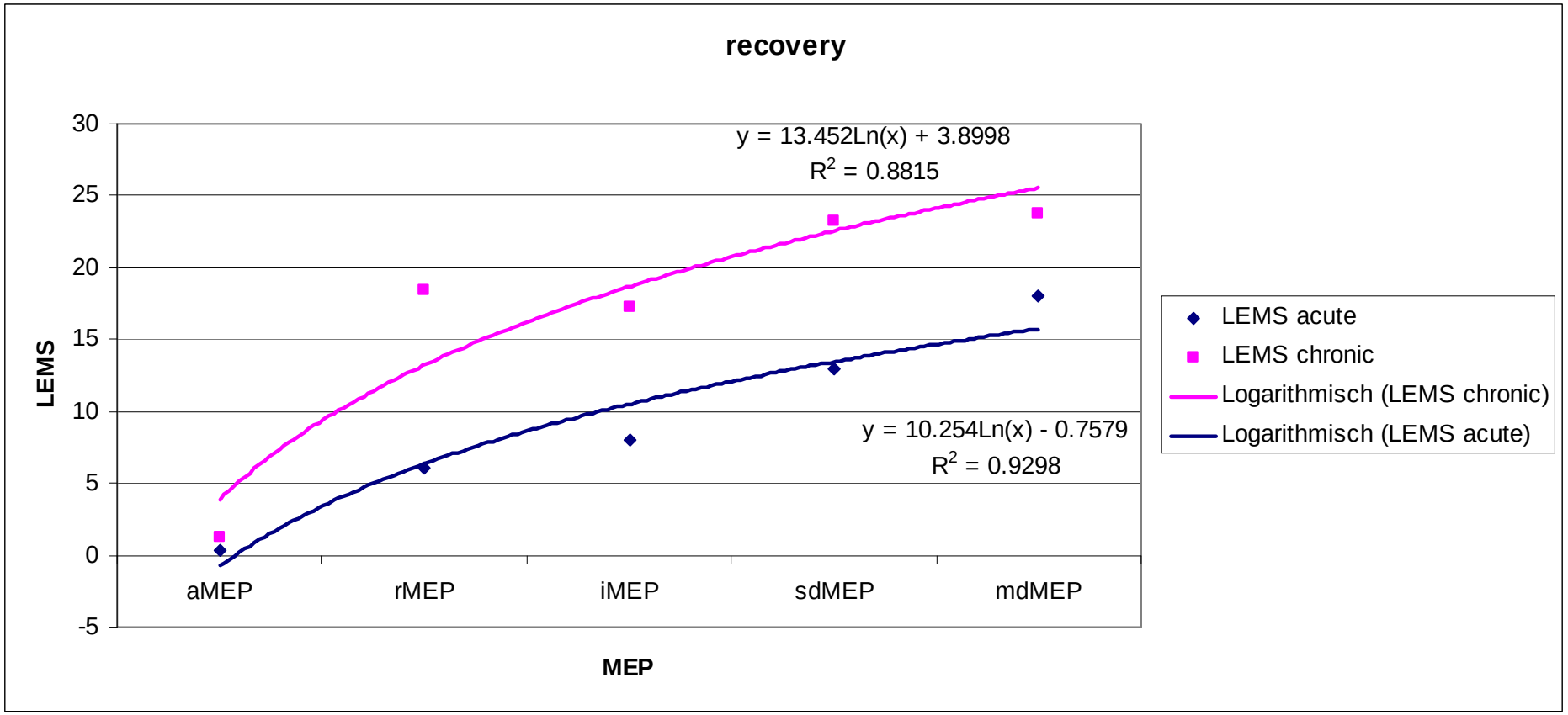
HuCNS-SC product is a highly purified population of human neural stem cells that are grown in suspension (neurospheres) that can be expanded for a number of generations (cell bank)

they retain their potential to, at a single cell level, self-renew and differentiate into the three major cell types of the CNS:
neurons - astrocytes - oligodendrocytes.



# Reliable recovery profiles

## Beinfunktion (Lower extremities motor scores (LEMS)



# Rehabilitation Innovation Technology Zürich

Netzwerk: klinische Rehabilitation
biologische Forschung und
technische Innovationen (Uni & ETH Zürich)

Geh-roboter (Lokomat$^{R}$)

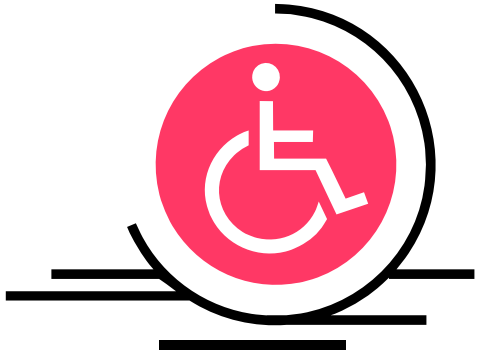
Arm-roboter (Armeo-power$^{R}$)

Universität Zürich$^{UZH}$

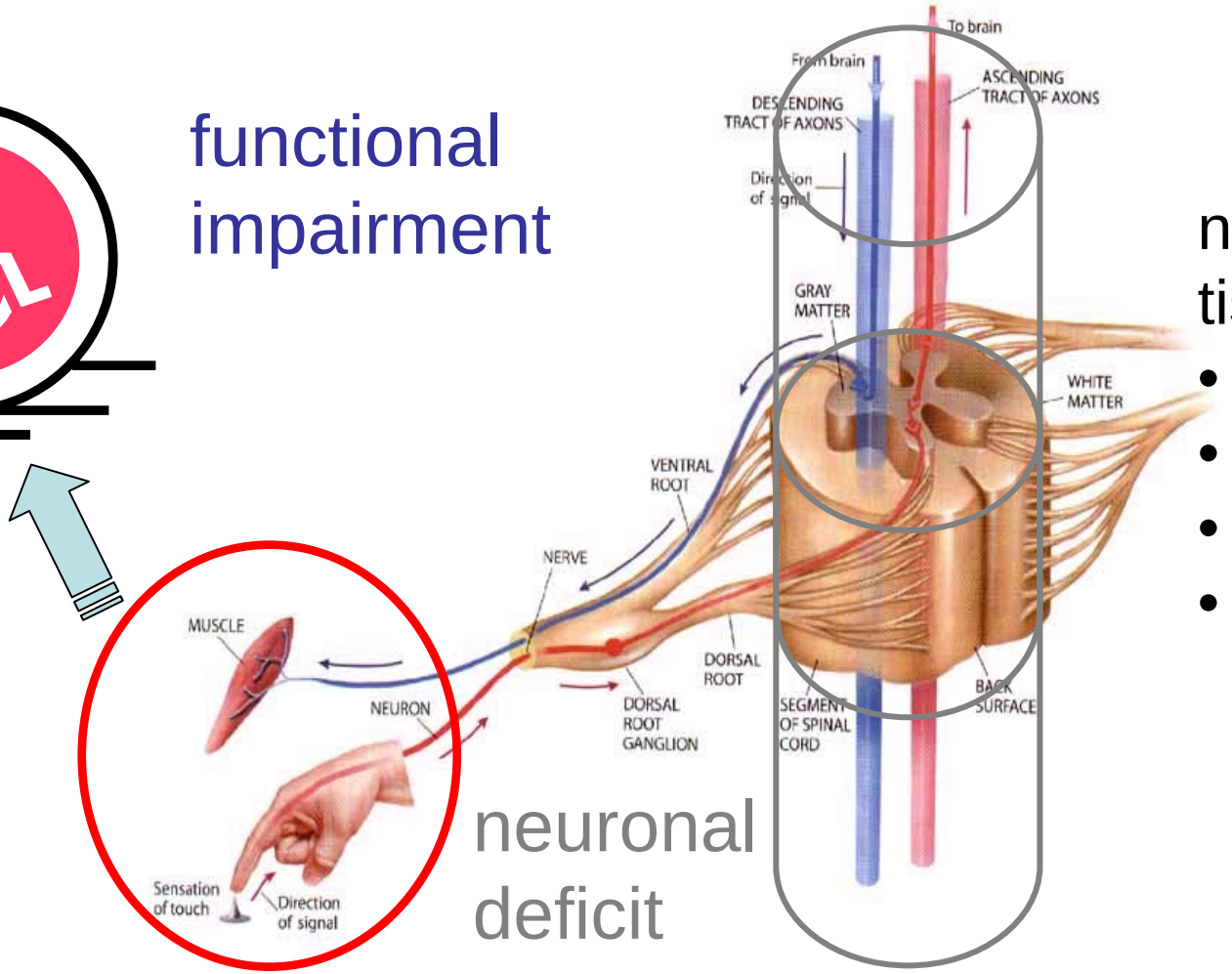
balgrist paraplegiker ZENTRUM

# “bridging preclinical and clinical research”

# Proof of mechanism and concept



functional impairment

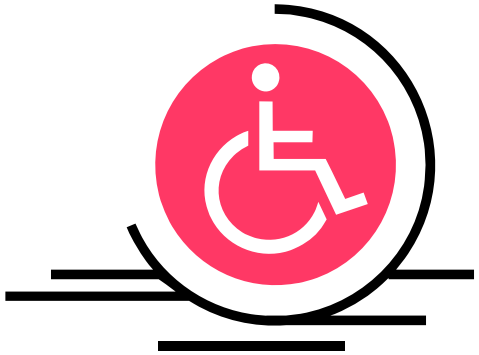



neuronal deficit

neuronal tissue

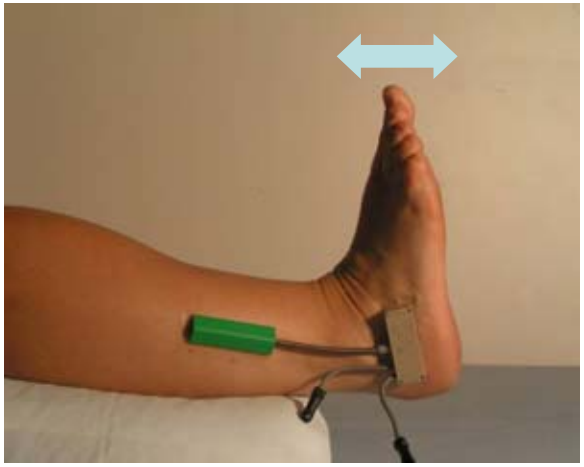
- structure
- imaging
- markers
- responses

# *The challenge*

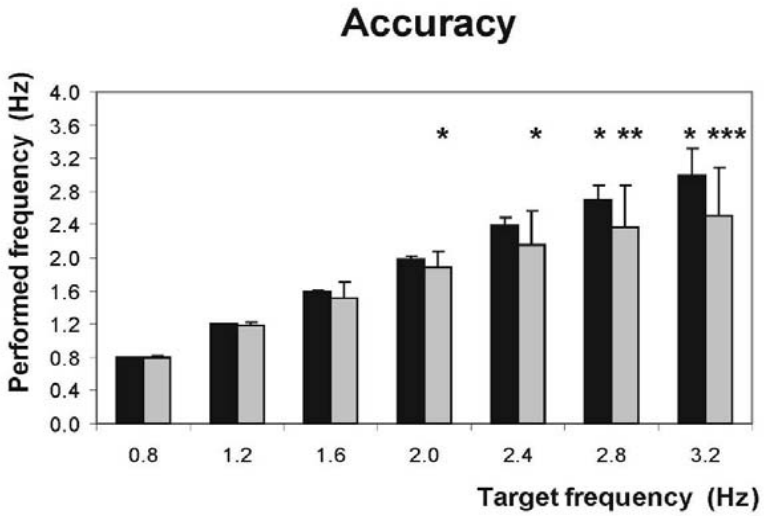


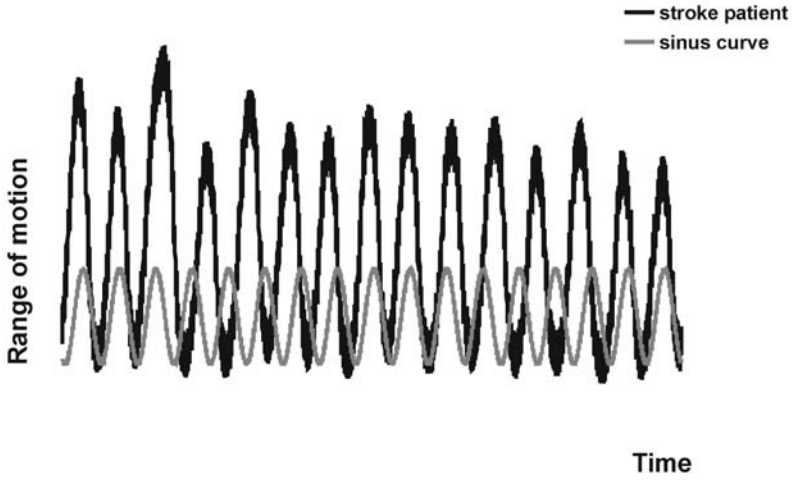
- informed clinical trials in human SCI
- appraisal of pre-clinical studies in SCI
- proof of mechanisms in human SCI
- successful phase I study – **next phase soon!!**

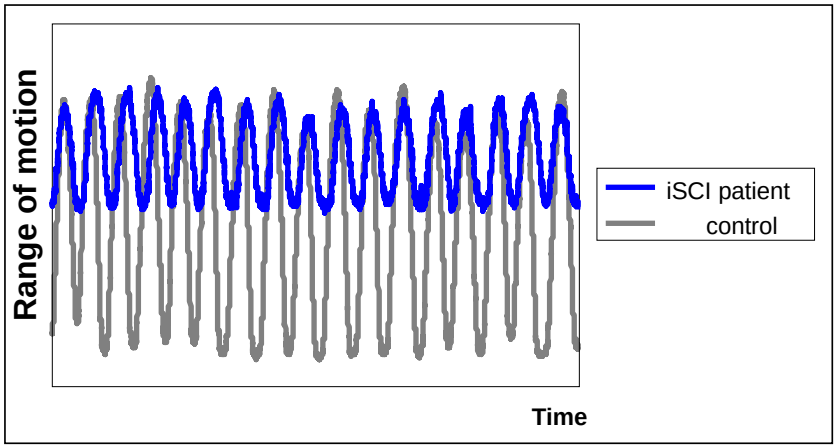
# Dexterity in iSCI



Accuracy



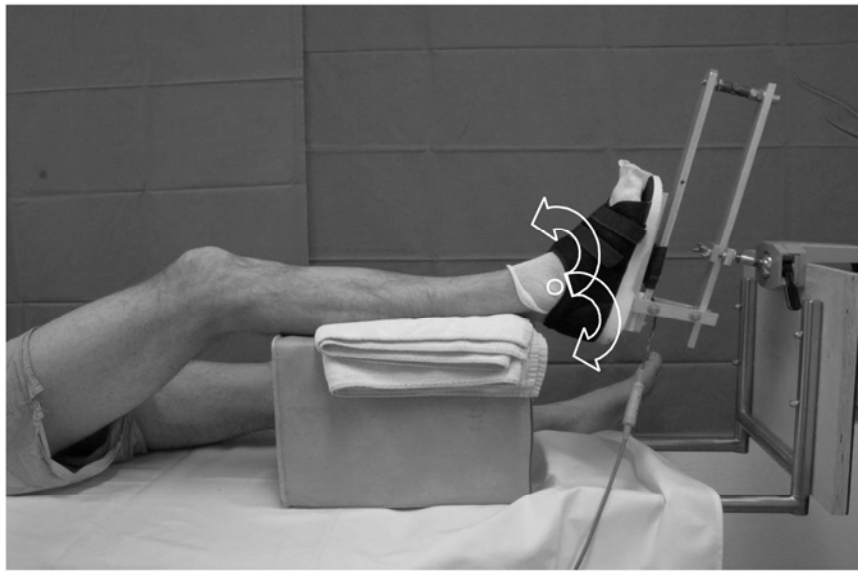



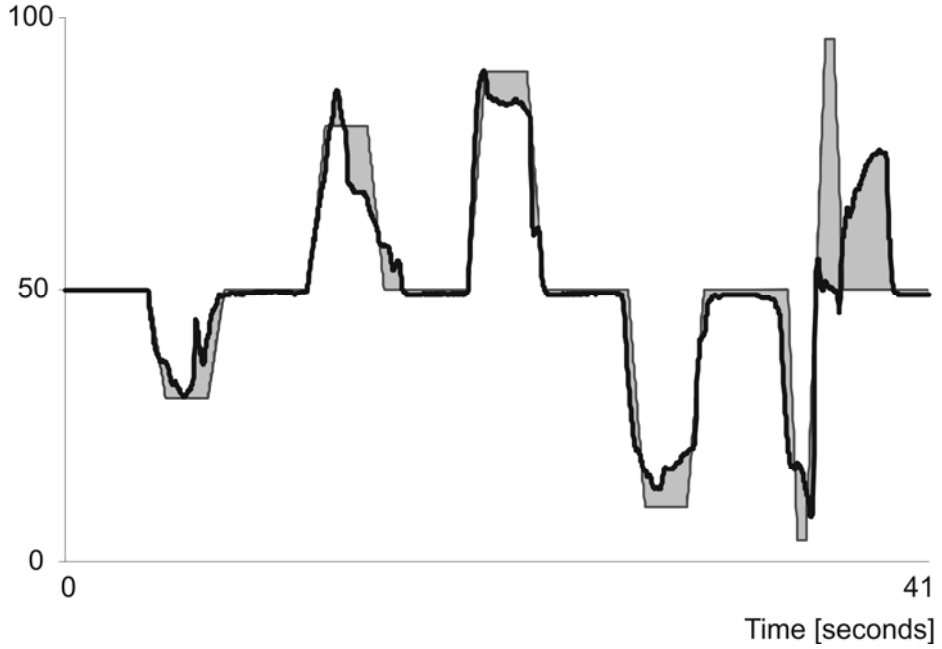

Wirth et al, J Neurol 2008

# Dexterity in iSCI

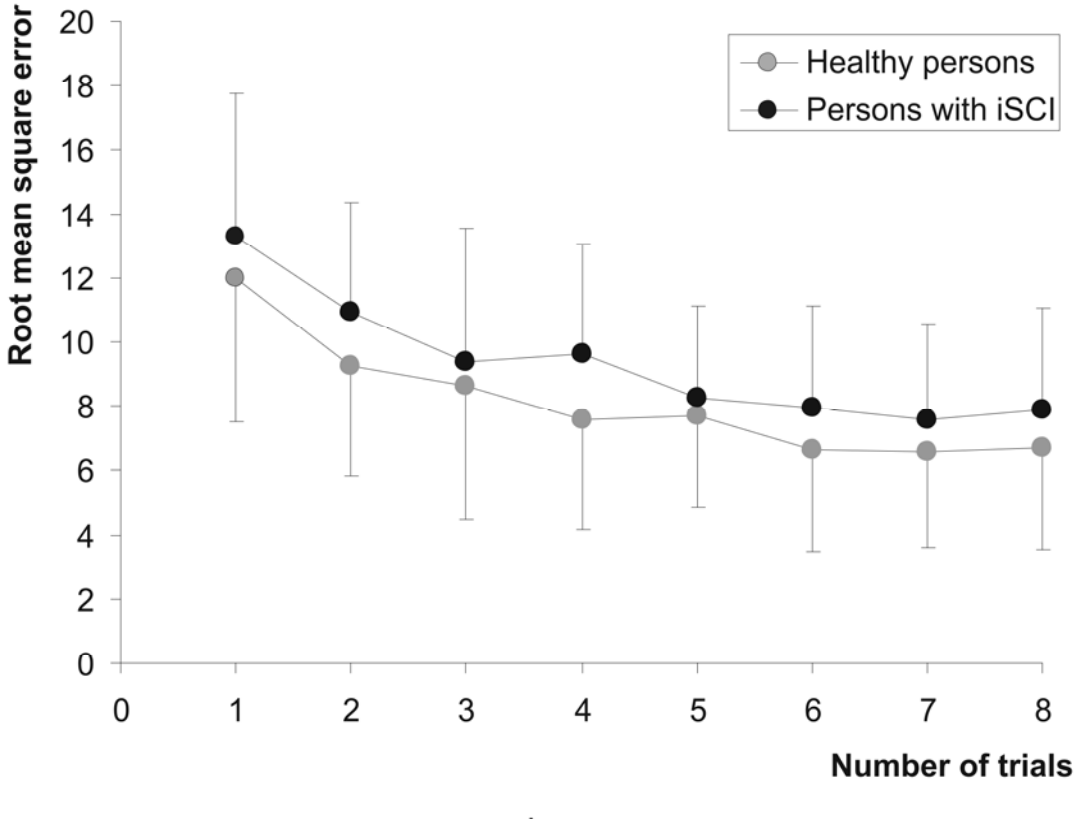
A

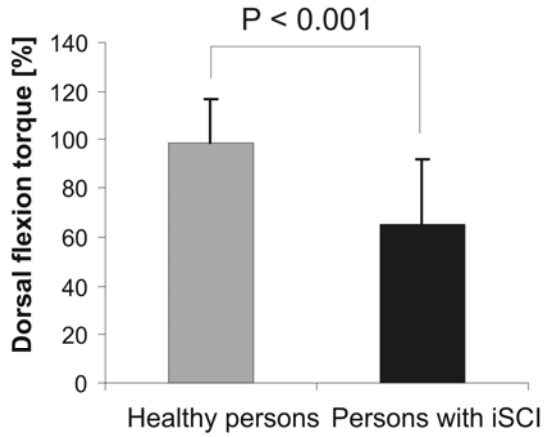


B

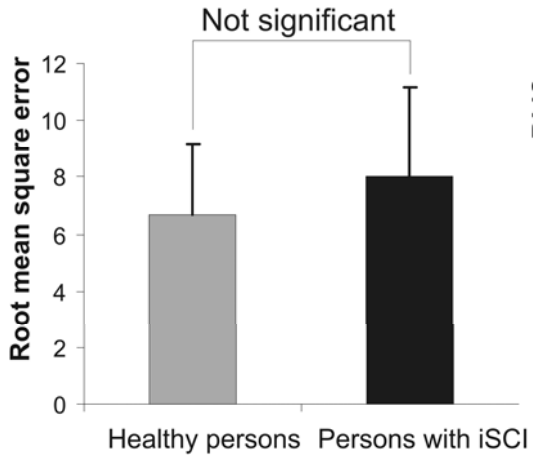


# Dexterity in iSCI

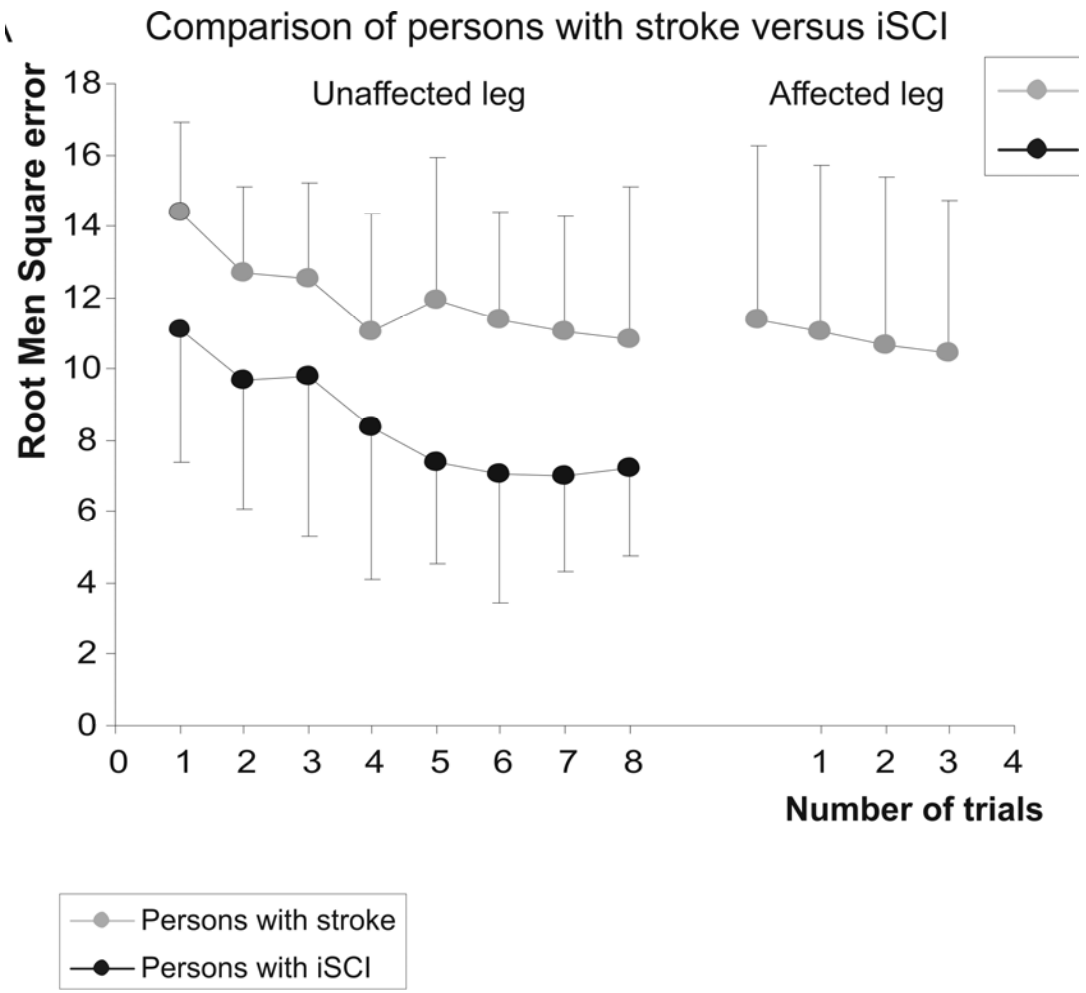


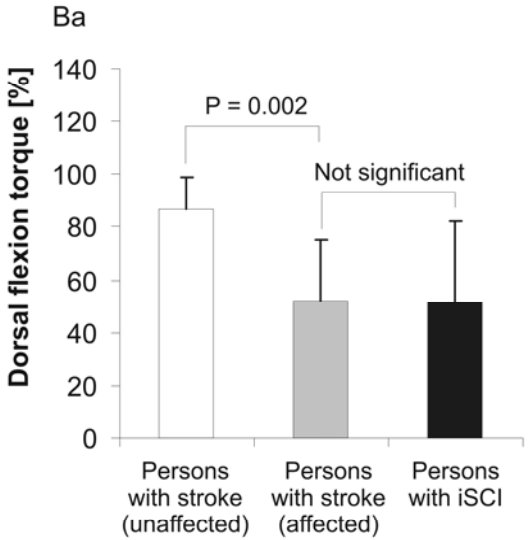



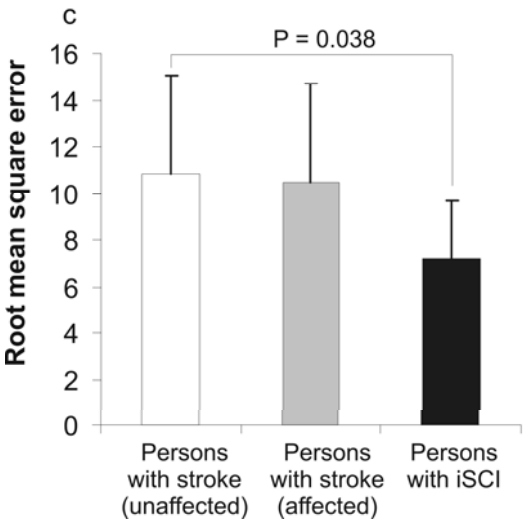

c



# Dexterity in iSCI

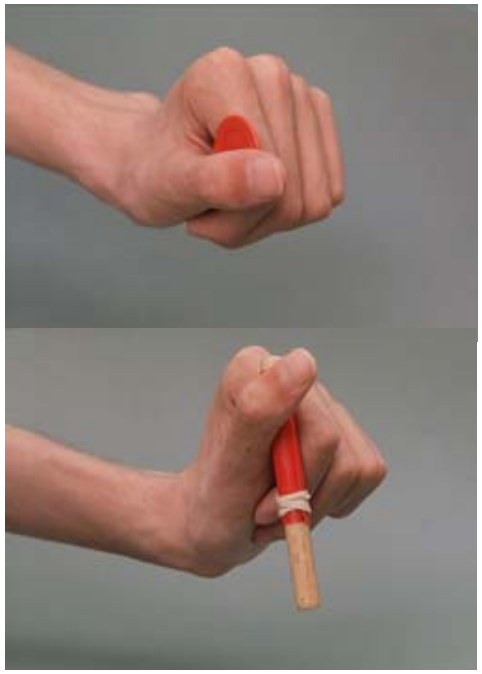


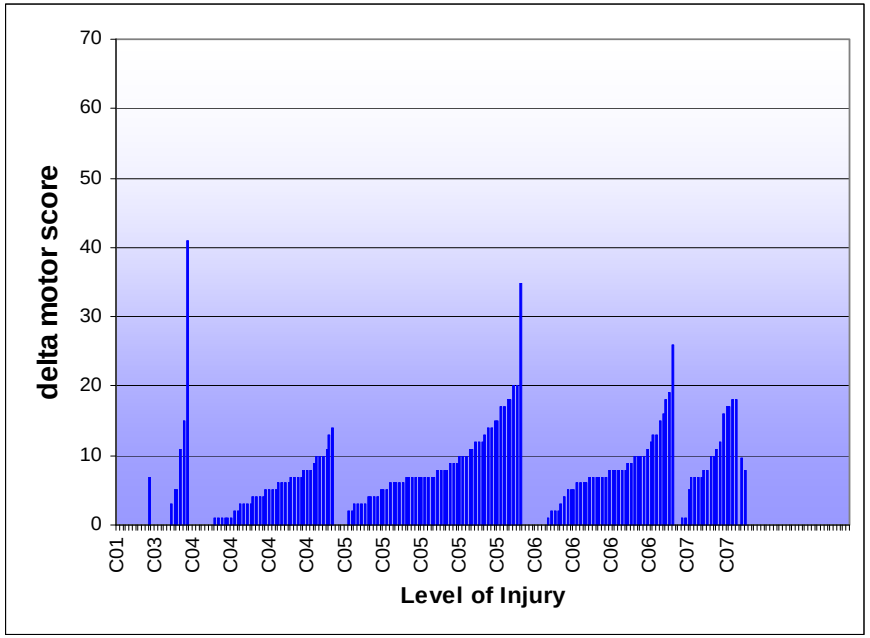



# Informed clinical trials in human SCI

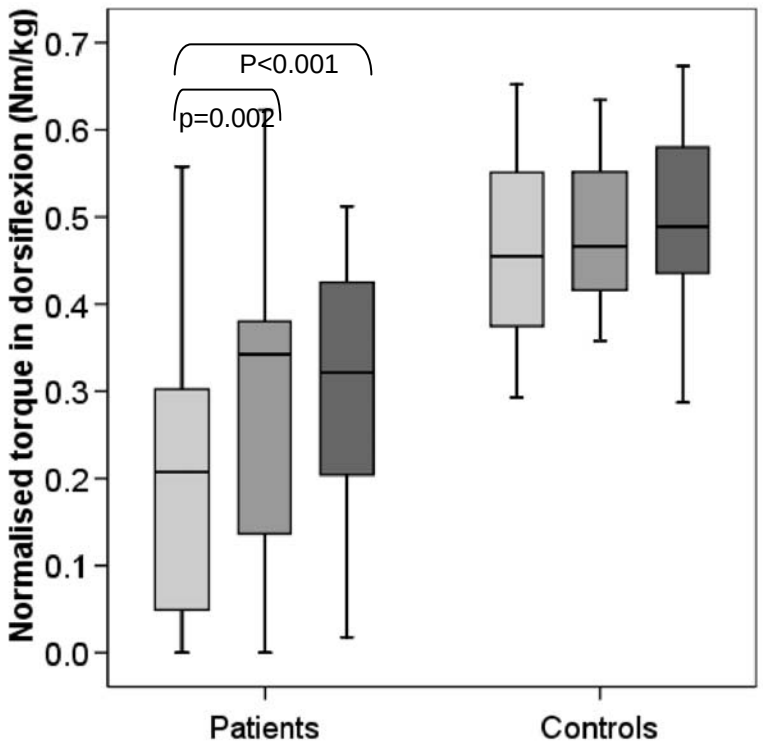
## Upper limb function

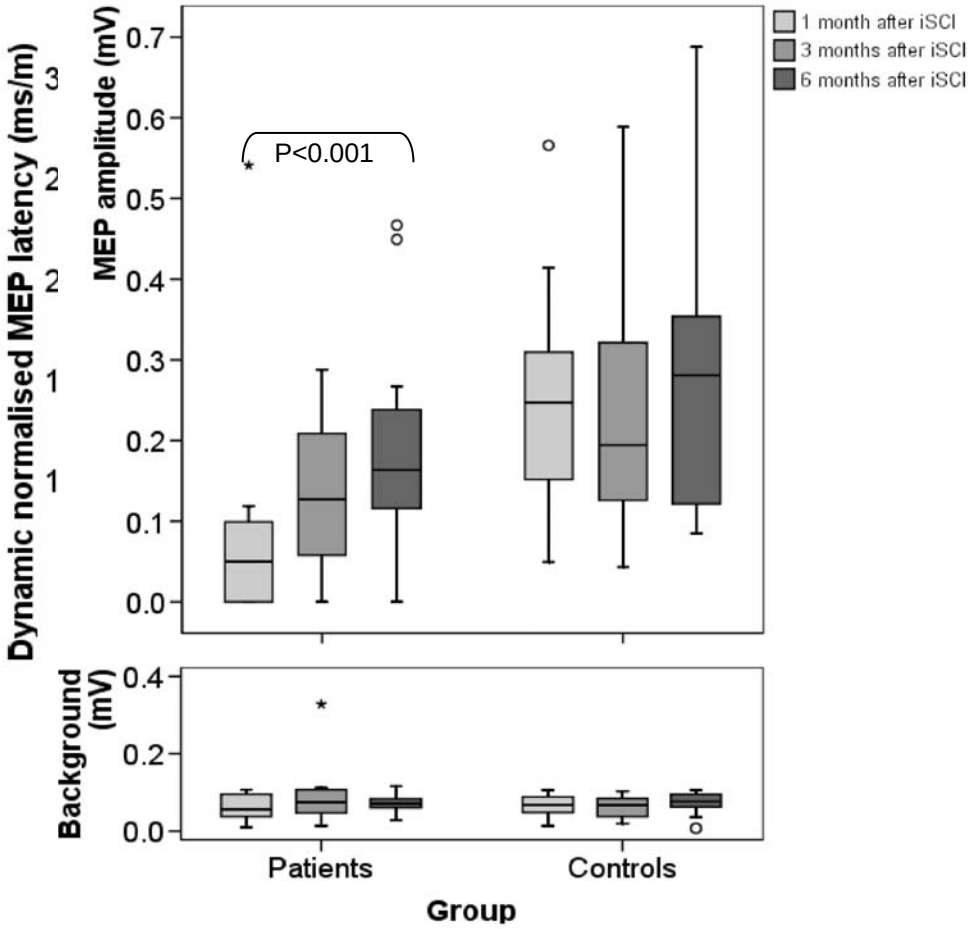





Sygen control data (n=195 tetraplegic patients)

# CST conductivity during recovery

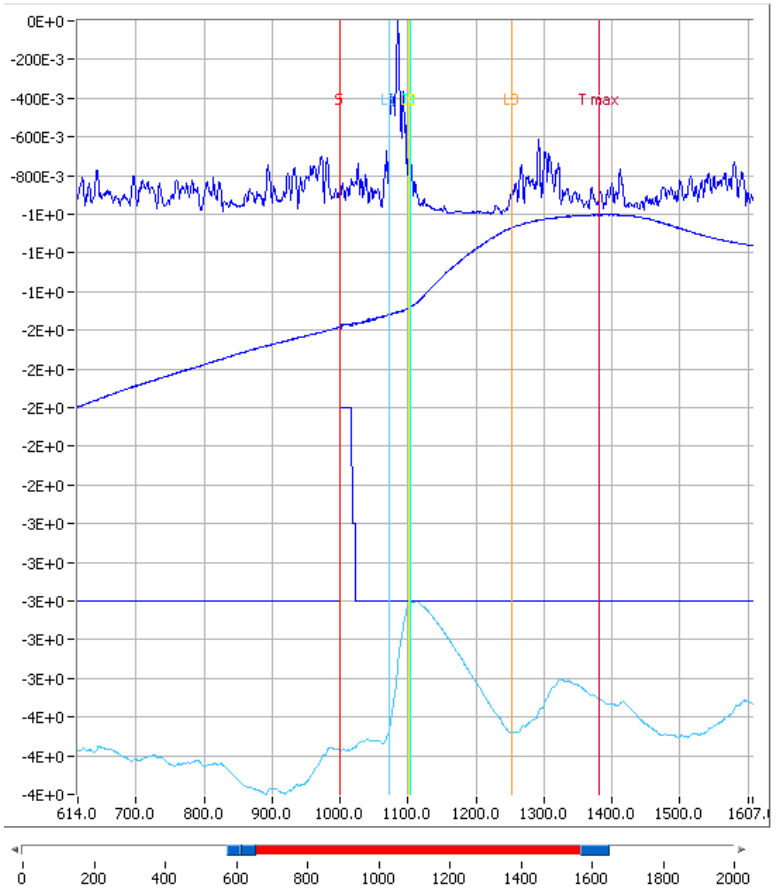



Follow up study in acute iSCI

Wirth B, Hedel vH, Curt A. Changes in corticospinal function and ankle motor control during recovery from incomplete SCI. J Neurotrauma 2008

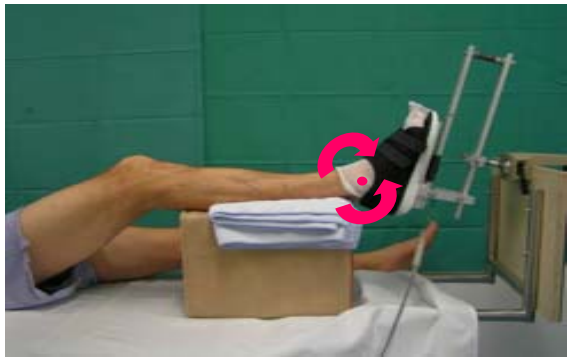
# Motor evoked potentials




EMG recordings
MEP – silent period

Torque performance

TMS trigger



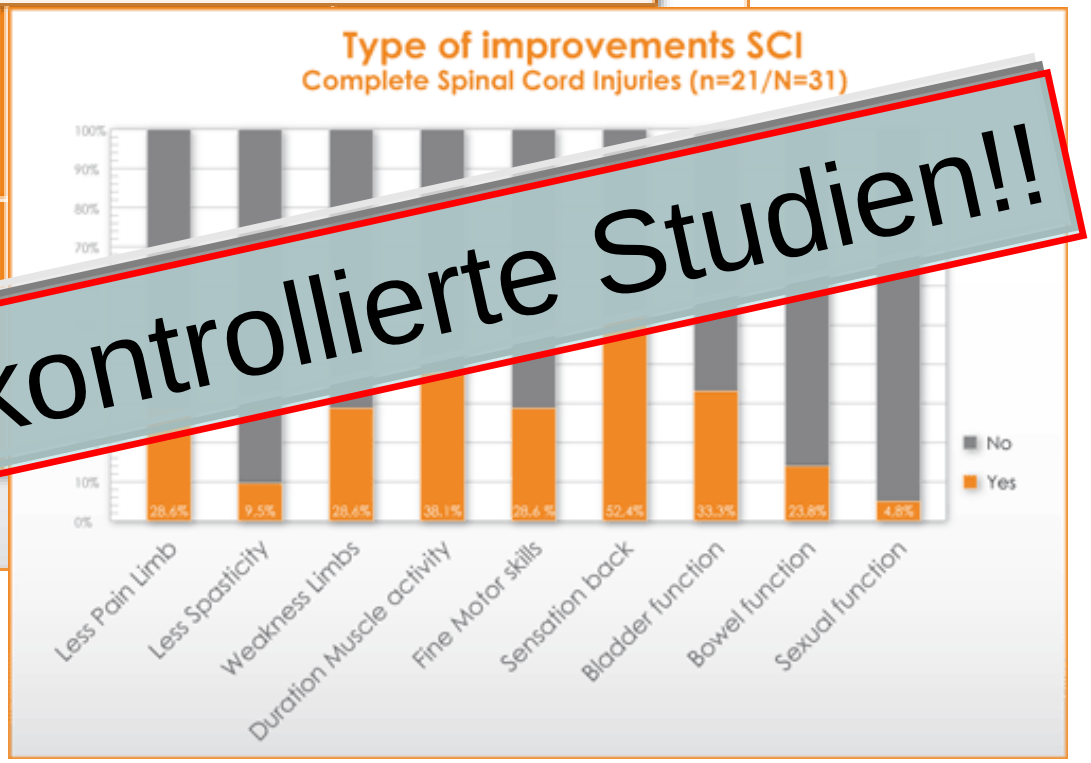
Diehl P, Kliesch U, Dietz V, Curt A. Impaired facilitation of motor evoked potentials in incomplete spinal cord injury. J Neurology 2006

# SCI – Results of Stem Cell Treatment

## Efficacy by Complete or Incomplete Spinal Cord Injury (N=85)

Table: Improvements type of Spinal Cord Injury
(complete or incomplete lesion / N=85)

| | Improvements Counts (%) |
|---|---|
| Complete SCI Injury | 21 (67,7%) |
| Incomplete SCI Injury | 30 |




**Keine seriös kontrollierte Studien!!**

Deda H, Inci MC, Kurekci AE, Kayihan K, Ozgun E, Ustunsoy GE, Kocabay S.
Treatment of chronic spinal cord injured patients with autologous bone marrow-derived hematopoietic stem cell transplantation: 1-year follow-up. Cytotherapy. 2008;10(6):565-574.

# Novartis SCI trials

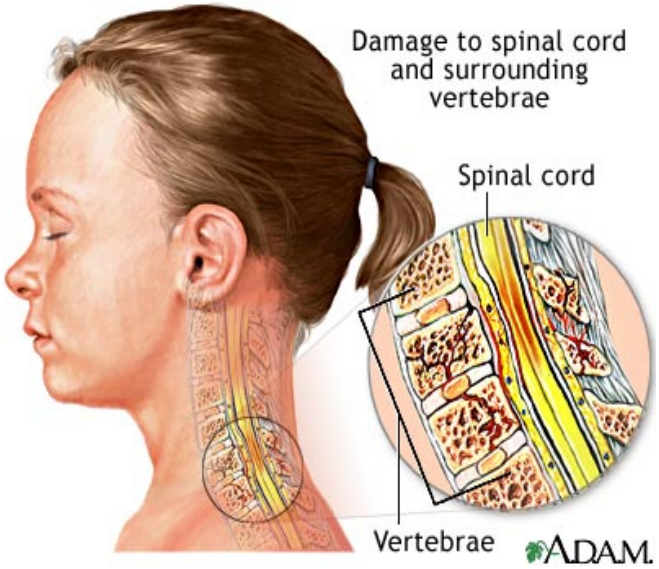
# ATI355

# Anti-Nogo-A Antibody in Spinal Cord Injury

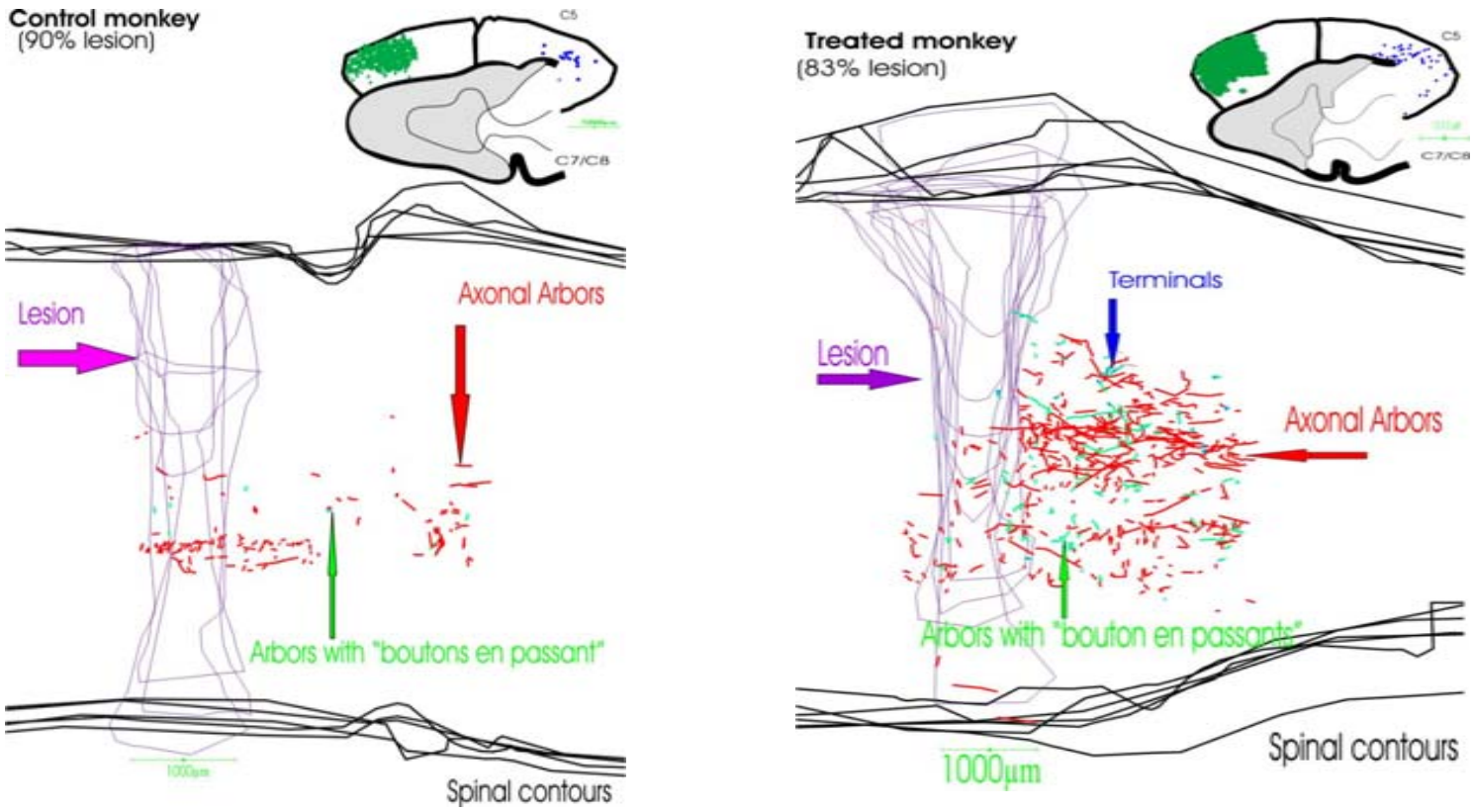
## sPoC Proposal for ATI355A

**Nogo-A neutralization: facilitation of central nervous system regeneration/plasticity after injury**

**DA Neuroscience / Neurodegeneration FIP**



# Human anti-Nogo-A Ab enhances axonal regeneration in macaque monkey model of SCI



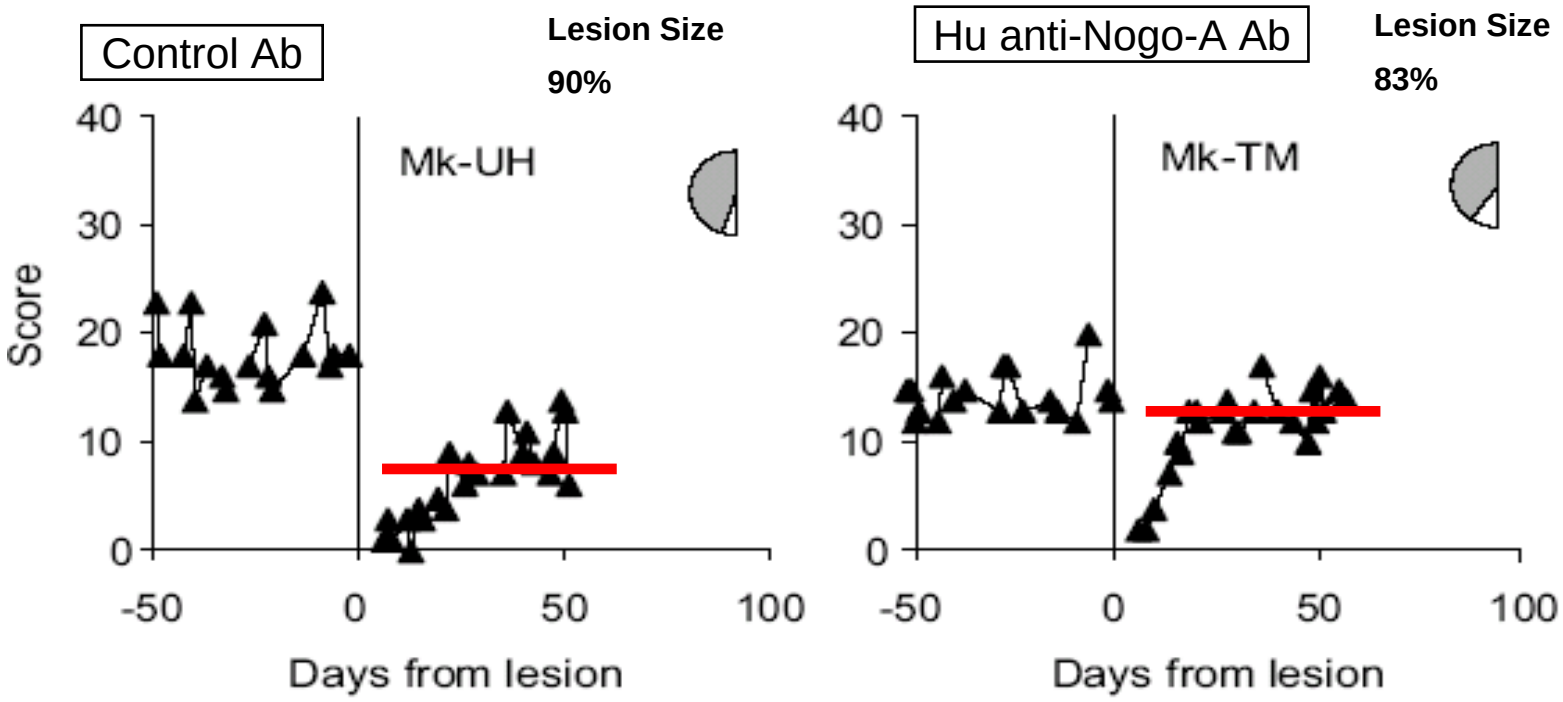

Intrathecal treatment with human anti-Nogo-A Ab increases

- axonal arborization
- boutons caudal to the lesion site

Freund et al 2006 Nat Med

# Human anti-Nogo-A Ab improves functional recovery in macaque monkey model of SCI

- Anatomical regeneration correlates with faster and increased recovery in food pellet grasping score in modified Brinkmann Board test



# Principles in SCI rehabilitation

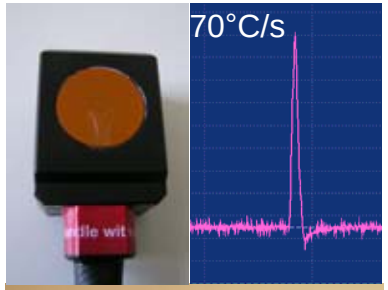
## Sir Ludwig Guttmann

Stoke Mandeville 1944

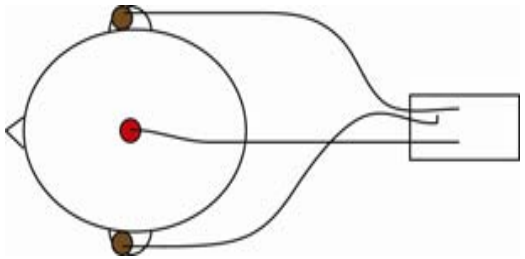
Spinal cord injuries: comprehensive management and research

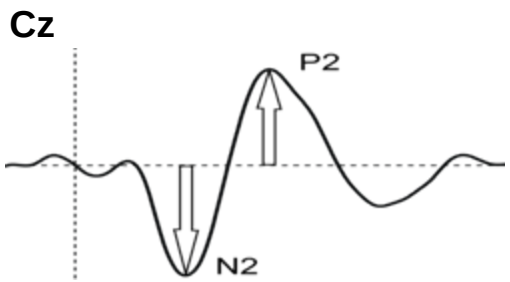
(1976)

# setup bedside test
# CHEPs

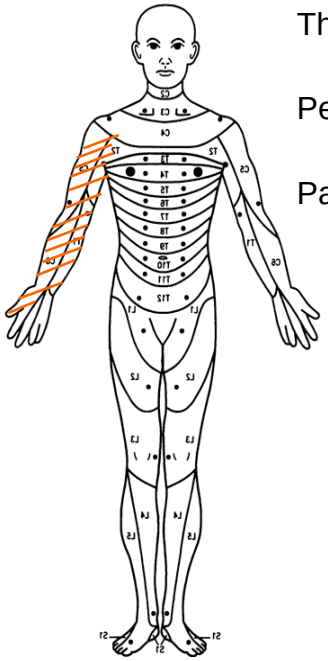



Evoked potential






Sensation to heat / QST

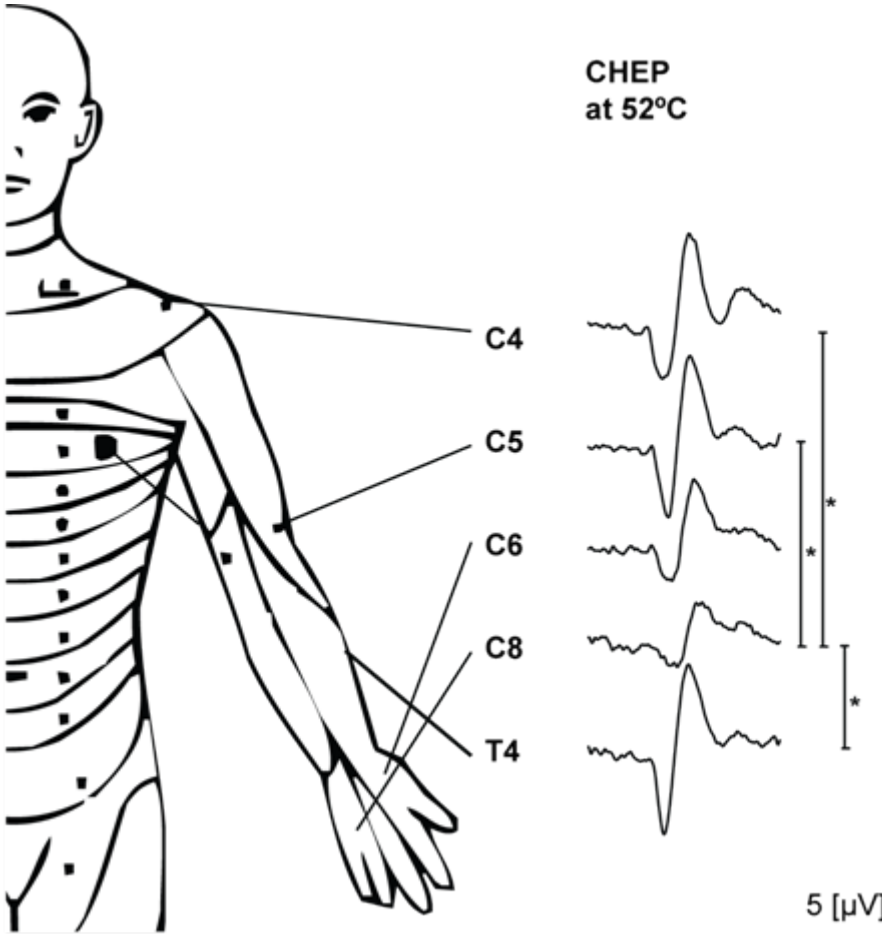


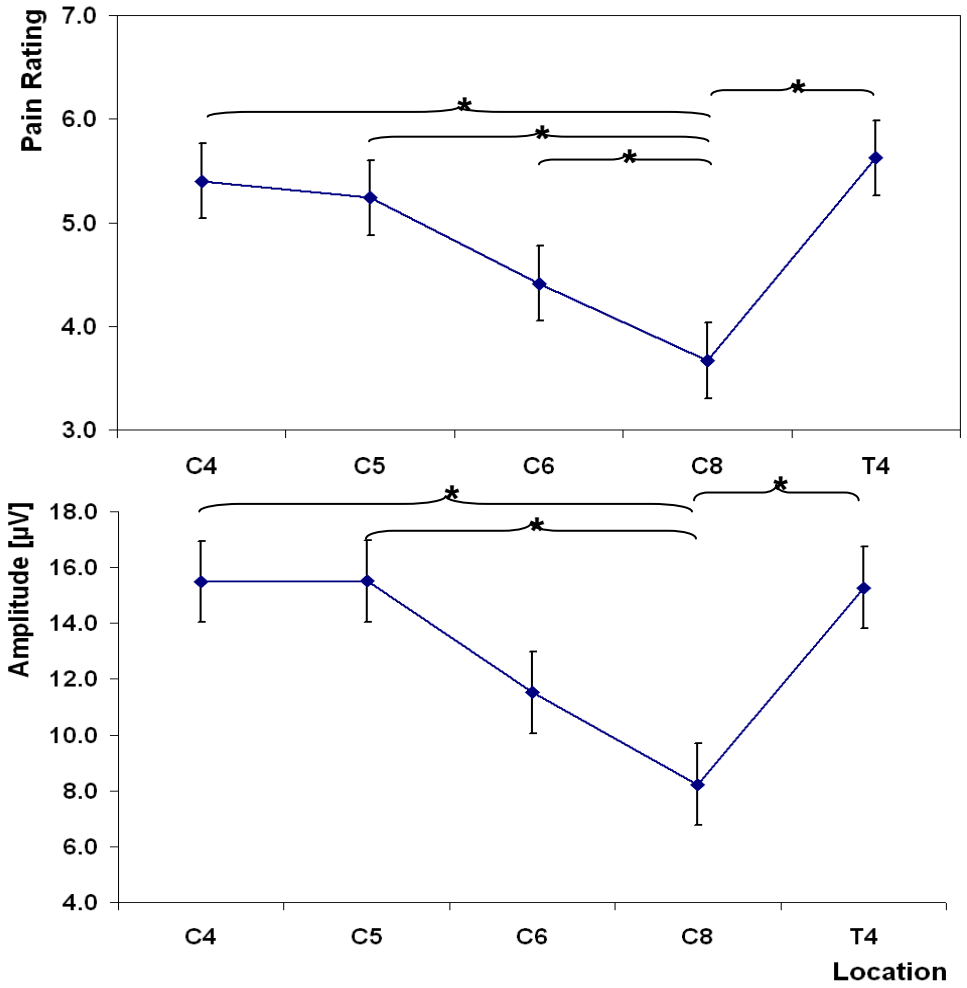
Thermal stimulation

Perception threshold

Pain threshold

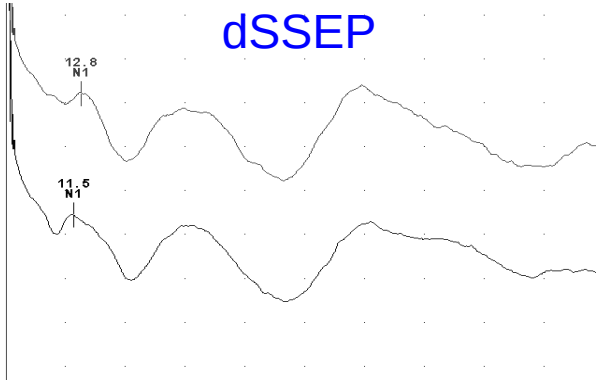
# Pain Rating & amplitudes - 52 °



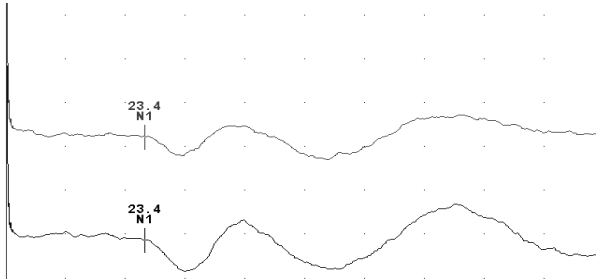




## dSSEP

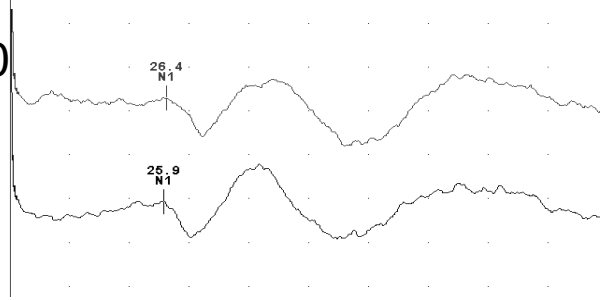
C3




T7




T10



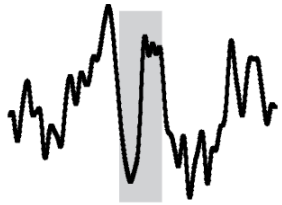

LEMS = 0

## CHEPS

**C3 right**

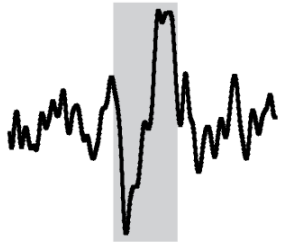
35°C 54°C

Perception thr. Pain thr.



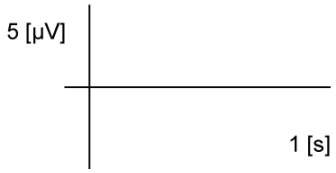
**T7 right**

35°C 54°C



**T10 right**

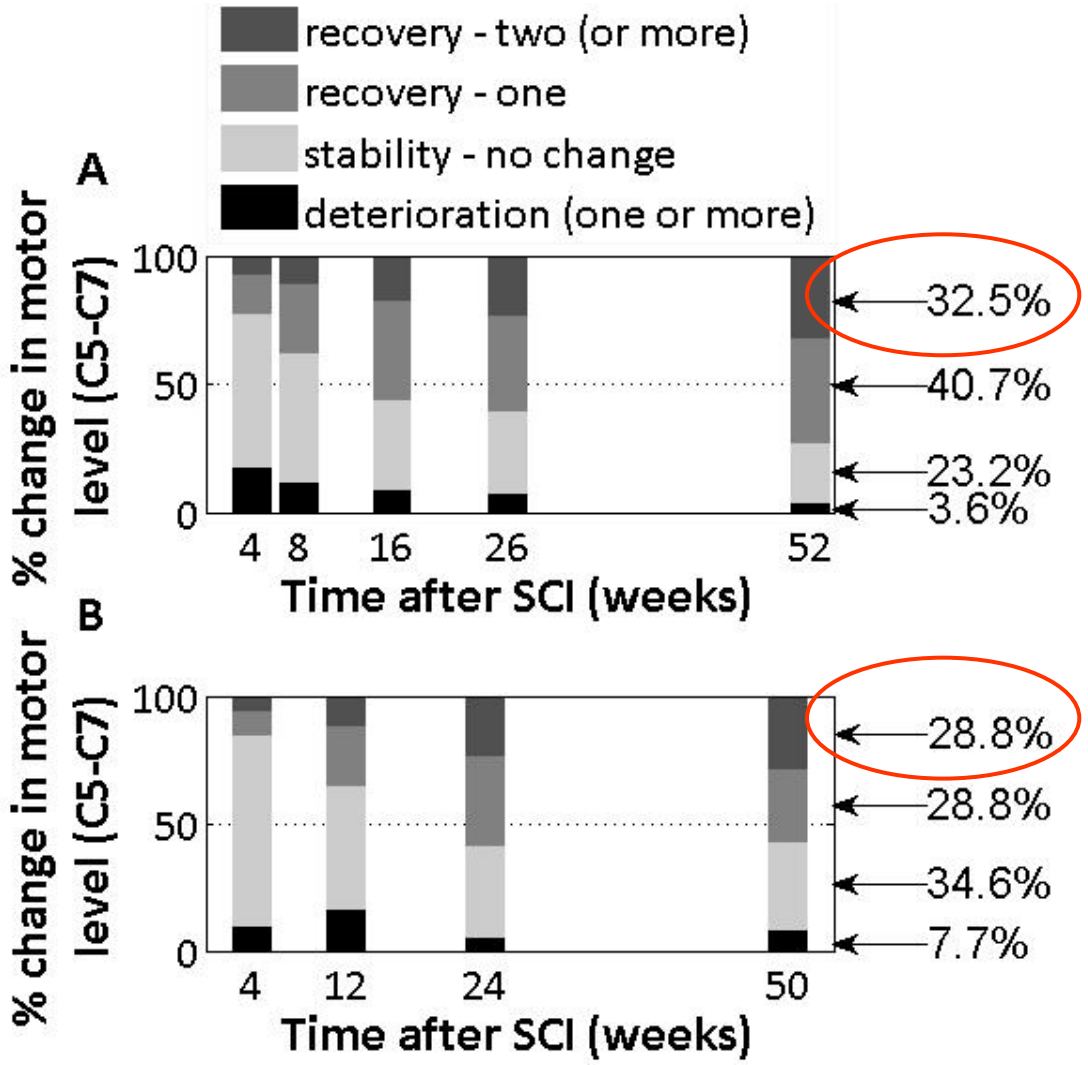
35°C 54°C



# *First-in-man* study (CATI355A2102)

A multi-center, open-label, cohort study to assess feasibility, acute safety, tolerability and pharmacokinetics of 4 dose regimens of continuous intrathecal ATI355 infusion and two regimen of repeated intrathecal bolus injections in acute spinal cord injury paraplegic & tetraplegic patients

# Motor level changes in cervical SCI



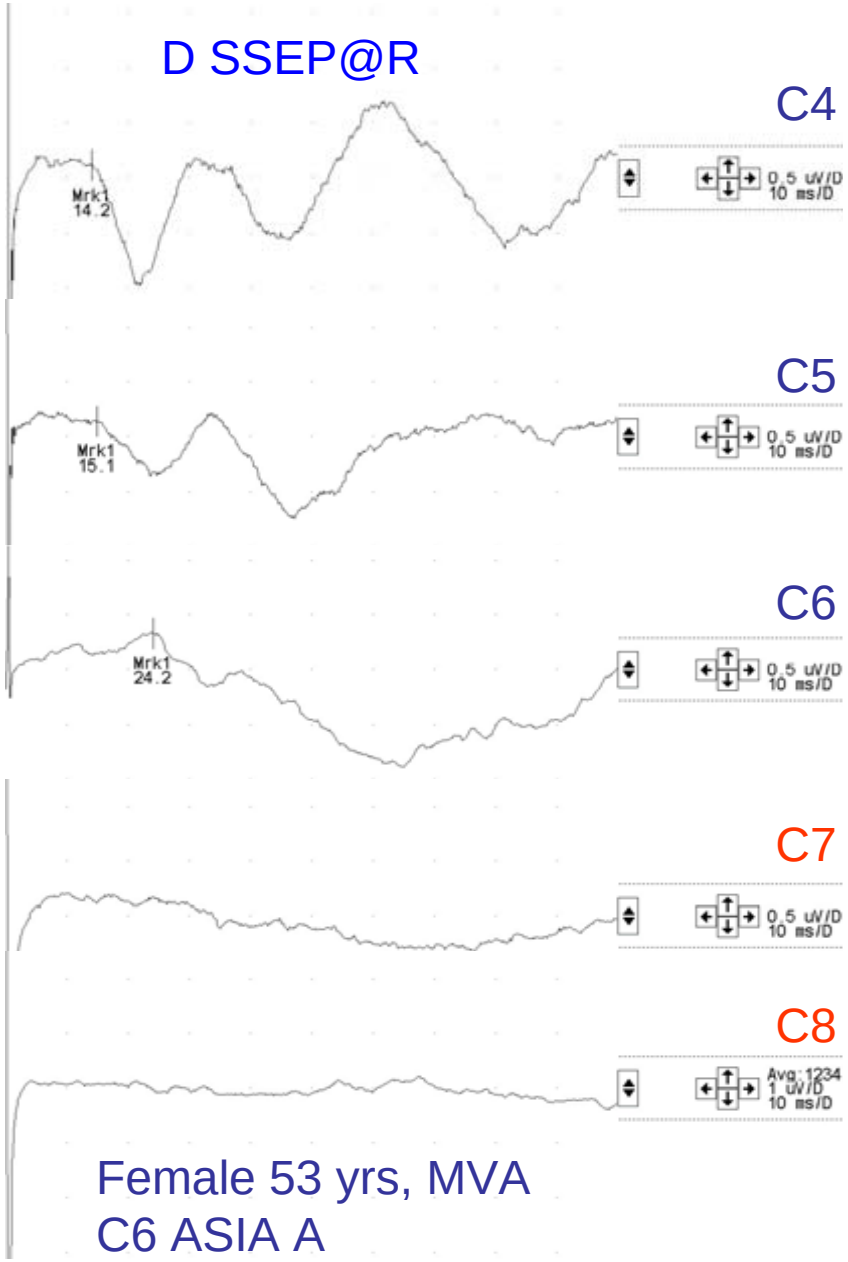

EMSCI

Sygen

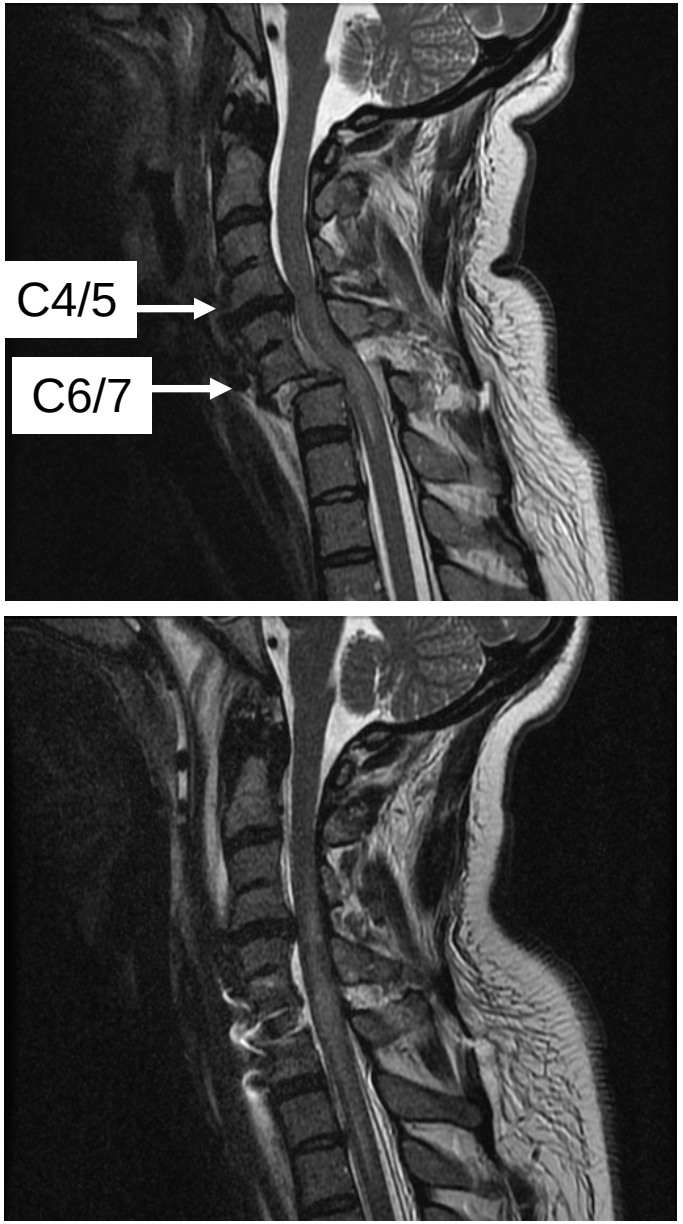
# *First-in-man* study: Objectives

- Primary objectives
  - feasibility, acute safety and tolerability of a continuous intrathecal (i.t.) infusion of 4 dose regimens of ATI355 and of two regimen of repeated intrathecal bolus injections
  - Serum pharmacokinetics (PK) and cerebrospinal fluid (CSF) concentrations of ATI355
- Secondary objectives
  - To explore the immunogenicity of ATI355 in acute SCI patients
  - To investigate an early potential signal of efficacy (ASIA protocol) and/or pharmacodynamic changes (Somatosensory Evoked Potential (SSEP))

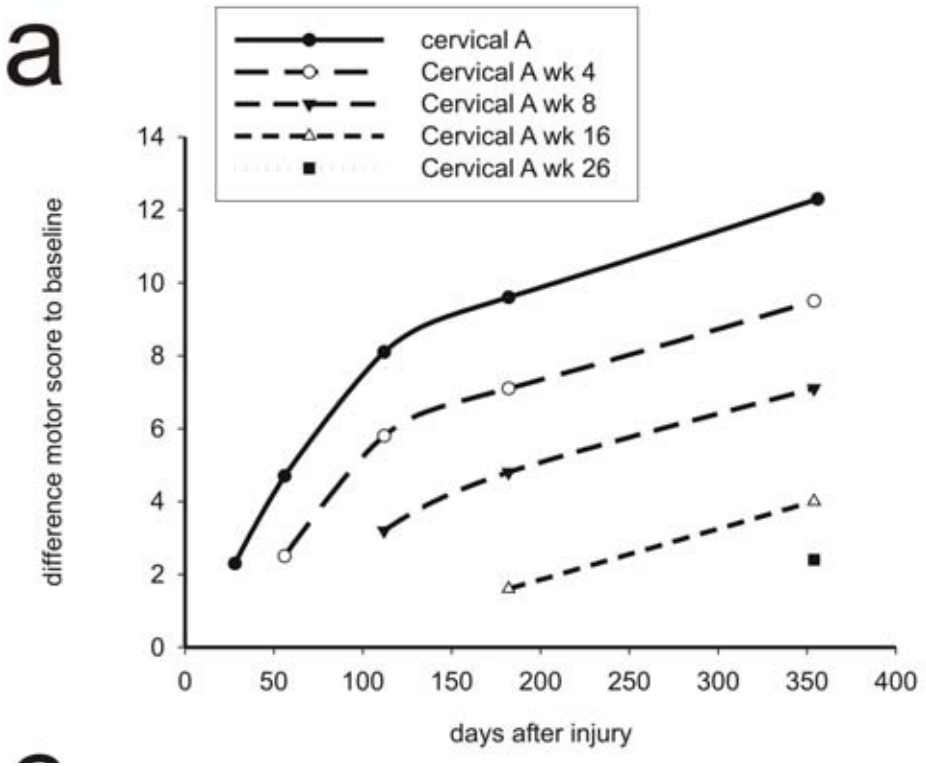
D SSEP@R

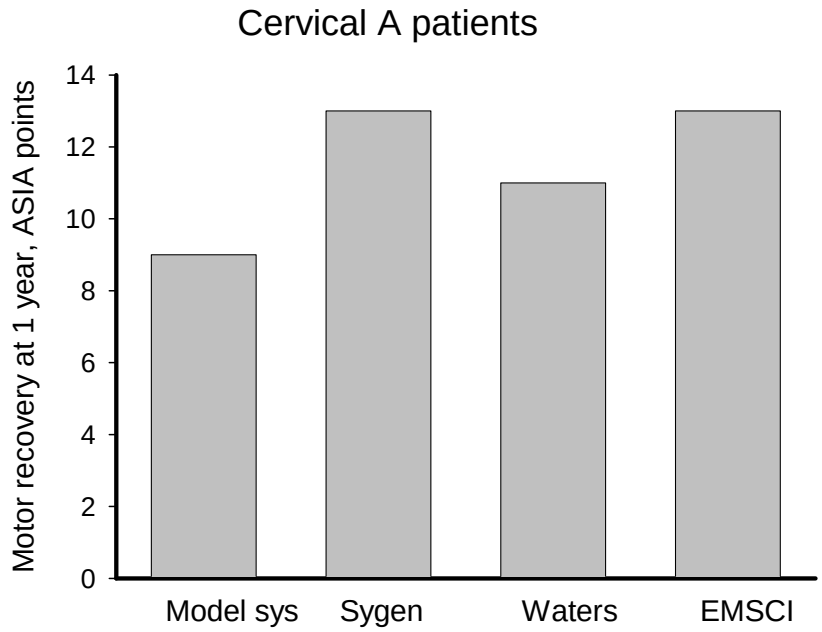



Female 53 yrs, MVA
C6 ASIA A



# Effect size matters




Data analysis based on Sygen samples

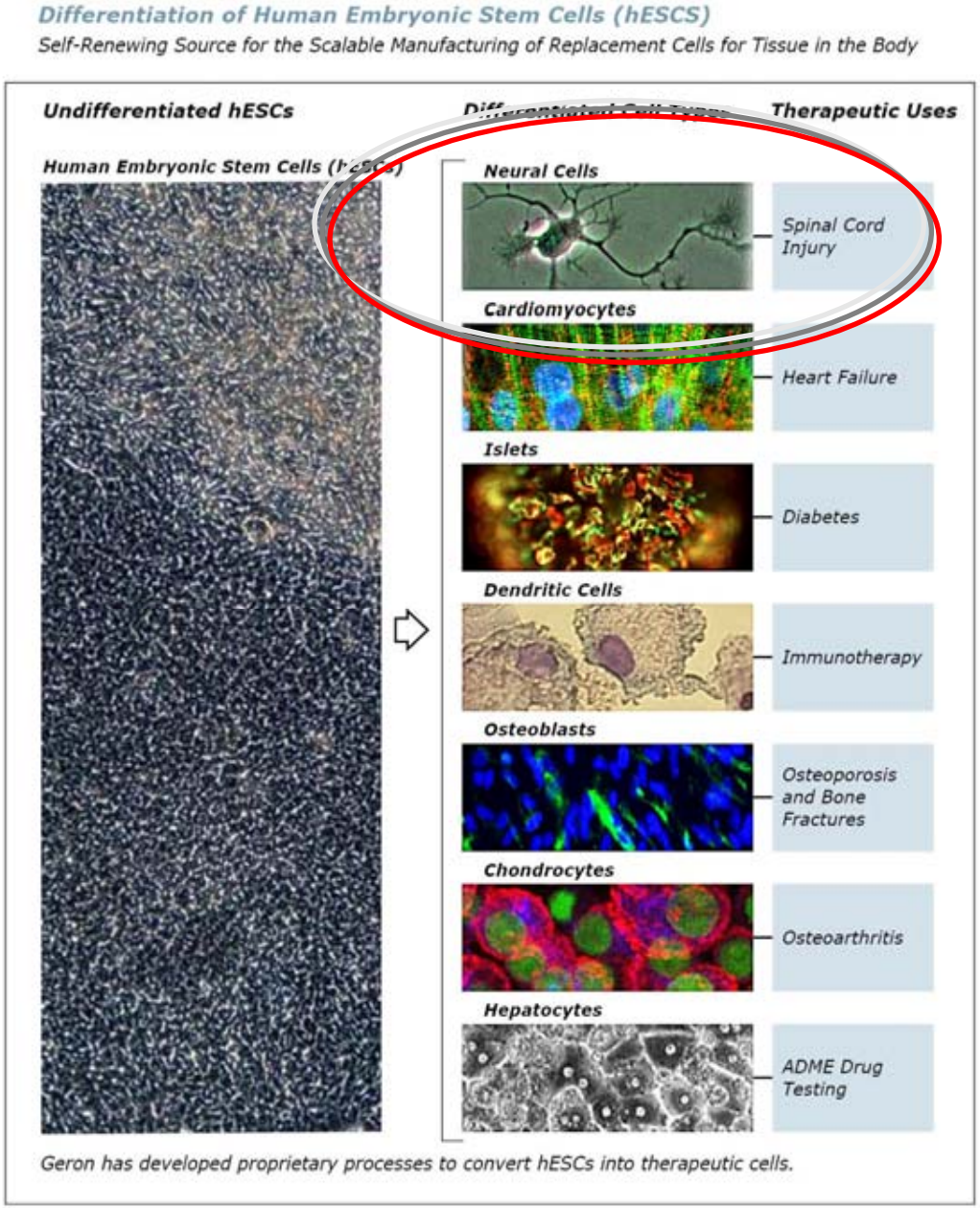
# Stammzellen

## 12.10.10 Embryonic stem-cells used on human in trial first for spinal injuries

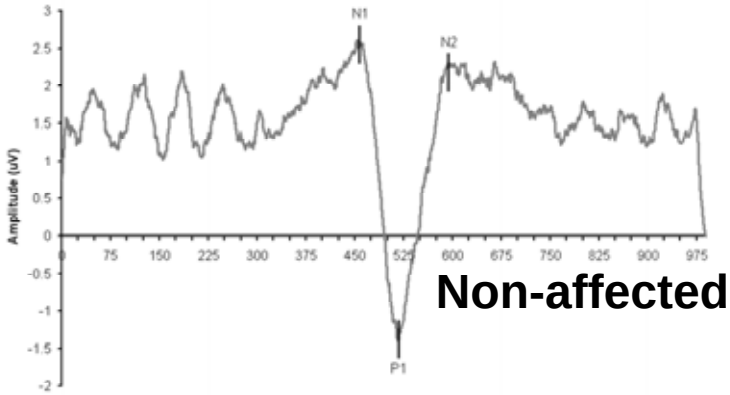
**Geron (US company)**
the patient was enrolled at Shepherd Centre, Atlanta
acute SCI < 2 weeks, T3-T10,

about 10 patients

GRNOPC1 - contains oligodendrocyte progenitor cells. Those progenitor cells turn into oligodendrocytes, a type of cell that produces myelin

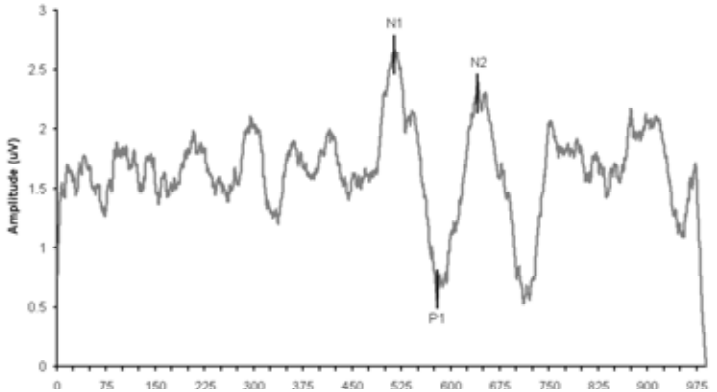


# CHEPs in SCI



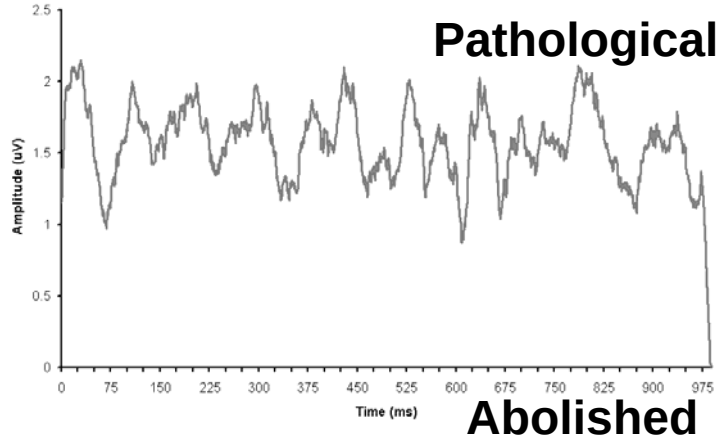

C4

**Non-affected**




C5

**Pathological**




**Abolished** C6