Stem cell therapy for traumatic spinal cord injury

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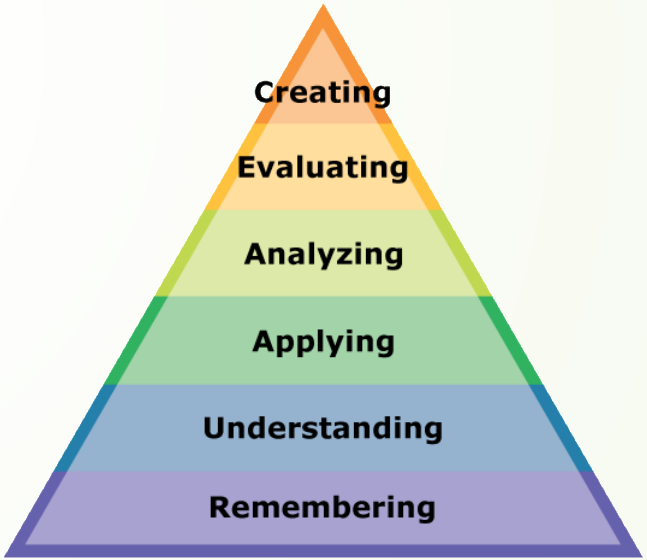
Northwest Regional SCI System Forum
University of Washington
March 28, 2018

Disclosures

None

Objectives

- **Learn**: types of stem cell therapy (SCT) for SCI
- **Understand**: state of research about effectiveness of SCT for SCI
- **Apply and Evaluate**: safety, risks, and potential benefits of participating in a stem cell therapy, clinic, or study



Outline

1. Background and types of stem cells
2. Review of current study results
3. Ethics of stem cell therapy and questions for future studies

ANNALS OF MEDICINE

ONE SMALL STEP

A paraplegic undergoes pioneering surgery.

BY D. T. MAX

When a spinal cord is damaged, location is destiny: the higher the injury, the more severe the effects. The spine has thirty-three vertebrae, which are divided into five regions—the coccygeal, the sacral, the lumbar, the thoracic, and the cervical. The nerve-rich cord traverses nearly the entire length of the spine. The nerves at the bottom of the cord are well buried, and sometimes you can walk away from damage to these areas. In between are insults to the long middle region of the spine, which begins at the shoulders and ends at the midriff. These are the thoracic injuries. Although they don't affect the upper body, they can still take away the ability to walk or feel below the waist, including autonomic function (bowel, bladder, and sexual control). Injuries to the cord in the cervical area—what is called "breaking your neck"—can be lethal or leave you paralyzed and unable to breathe without a ventilator.

Doctors who treat spinal-cord-injury patients use a letter-and-number combination to identify the site of the damage. They talk of C3s (the cord as it passes through the third cervical vertebra) or T8s (the eighth thoracic vertebra). These morbid bingo-like codes help doctors instantly gauge the severity of a patient's injury.

Darek Fidyka, who is forty-one years old, is a T9. He was born and raised in Pradzew, a small farming town in central Poland, not far from Lodz. At 3 A.M. on July 27, 2010, Fidyka and his girlfriend, Justyna, woke up to the sound of someone smashing Fidyka's Volkswagen outside their house, a few miles from Pradzew. They got out of bed, rushed out the door, and found her ex-husband, Jaroslaw, battering the car with a cinder block. They were not completely shocked. The three of them had been friends since their teen years—Fidyka had gone to Justyna and Jaroslaw's wedding—but Jaroslaw eventually became a heavy drinker. He started beating Justyna, and then went to prison for it. Justyna obtained an order of protection, and eventually took up with Darek. He moved into her house. "Our earlier relationships hadn't worked out, so we decided to give it a try," Fidyka recalls. But Jaroslaw, paranoid, believed that his two friends had begun a relationship while he and Justyna were still married.

Outside the house, Fidyka and Justyna tried to calm Jaroslaw down. Though Fidyka was tall and athletic—he was a contractor and a volunteer fireman—Jaroslaw pounced on him. "I didn't expect him to have a knife," Fidyka says. Jaroslaw stabbed him eighteen times. Several of the wounds punctured his lungs, and one nearly cut his spinal cord in half.

As Fidyka lay on the ground, he felt his body change. "I can remember very vividly losing feeling in my legs, bit by bit," he says. "It started in the upper part of the spine and was moving down slowly while I lay waiting for the ambulance to arrive." He adds, "I was aware of everything. I could feel my strength leaking out with every thrust."

Jaroslaw dropped his weapon and ran away. He hanged himself shortly afterward, in a nearby orchard.

Today, Fidyka lives at Akson, a rehabilitation facility in Wroclaw, a city in western Poland. The attack left him paralyzed from the waist down. The Akson facility is affiliated with the city's university hospital—Wroclaw is the former German city of Breslau, long a place of medical excellence—and occupies a two-story building on the town's outskirts. The long, low structure, a former Hare Krishna center, was built on open land, but it is being walled in as Poland prospers and new buildings are constructed. Fidyka lives in a narrow room on the second floor. He has a laptop and a few books; the only picture on the wall is of Pope John Paul II. Justyna left him six months after the knifing.

On the day I [illegible] bowl of clementi[illegible] who lives in Prad[illegible] him. Many night[illegible] a bed on the oth[illegible] Her scuffs are l[illegible] sneakers, which [illegible]

Fidyka spend[illegible] downstairs in an [illegible] to gain back his lo[illegible] him there one sur[illegible] spring, as a physi[illegible] him stretch. Cram[illegible] a problem for the [illegible] part of what ther[illegible] provide artificial [illegible] that are meant to [illegible] lay near two fema[illegible] who had been par[illegible] down after a car [illegible] whose spine had b[illegible] an operation for [illegible] lying face down o[illegible] spist was sitting [illegible] and pulling up [illegible] therapy is not me[illegible] is intimate and s[illegible] tween the well an[illegible] denscored at every[illegible]

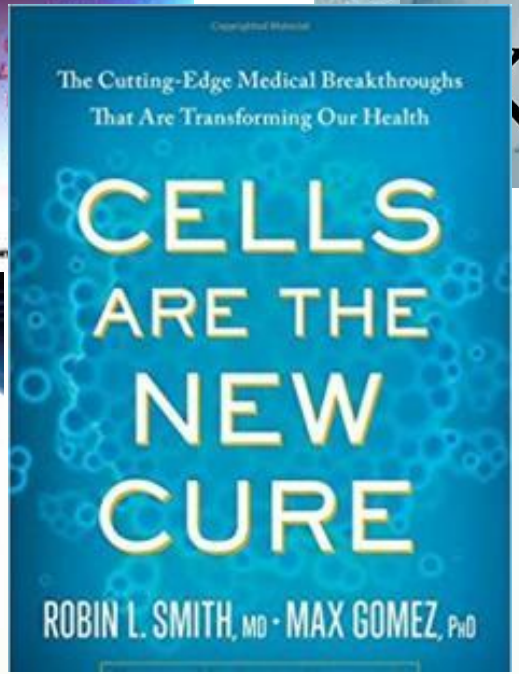
Fidyka looked [illegible] sapped his energy[illegible] When you do ph[illegible] hours a day, five [illegible] hard as athletics. [illegible] Fidyka and his [illegible] Pradzew, about a [illegible] he is depleted.

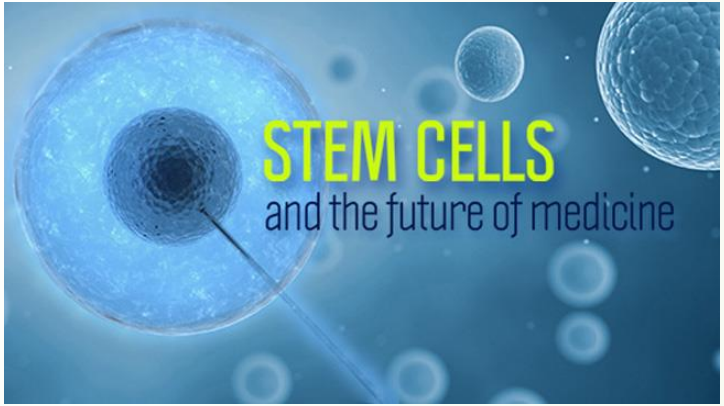
People with a [illegible] can get better wit[illegible] the first few months, it is not unusual for a patient, especially one with partial spinal-cord damage, to regain some strength or sensation in the legs, or some bowel control or sexual function. But after this period the likelihood of improvement drops off radically. Scar

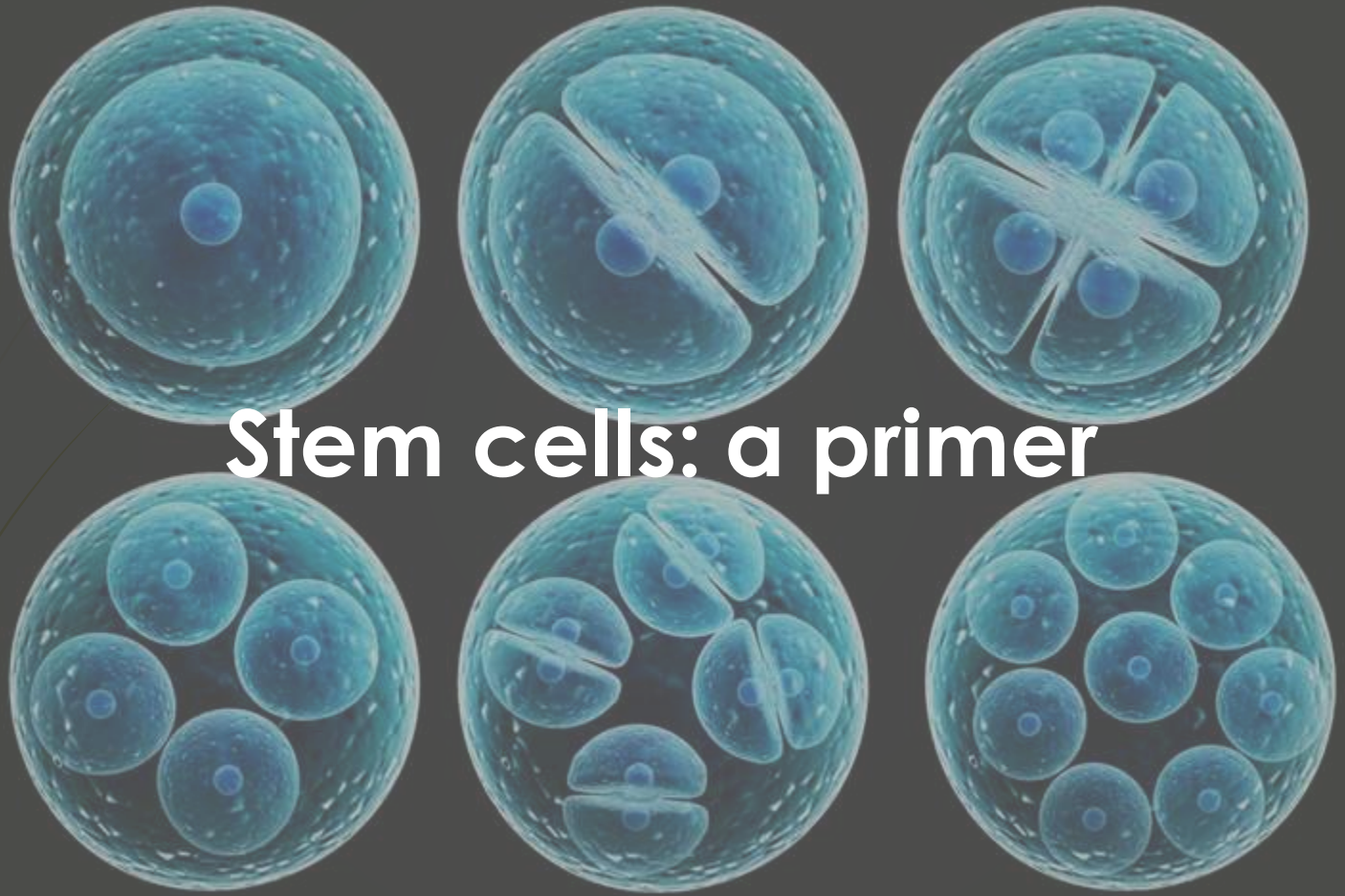
In 2012, Darek Fidyka underwent surgery in which cells from his olfactory nerve were inserted into his damaged spinal cord.

PHOTOGRAPH BY CARLA VAN DE PUTTELAAR

- Ability
- Read
- If auto



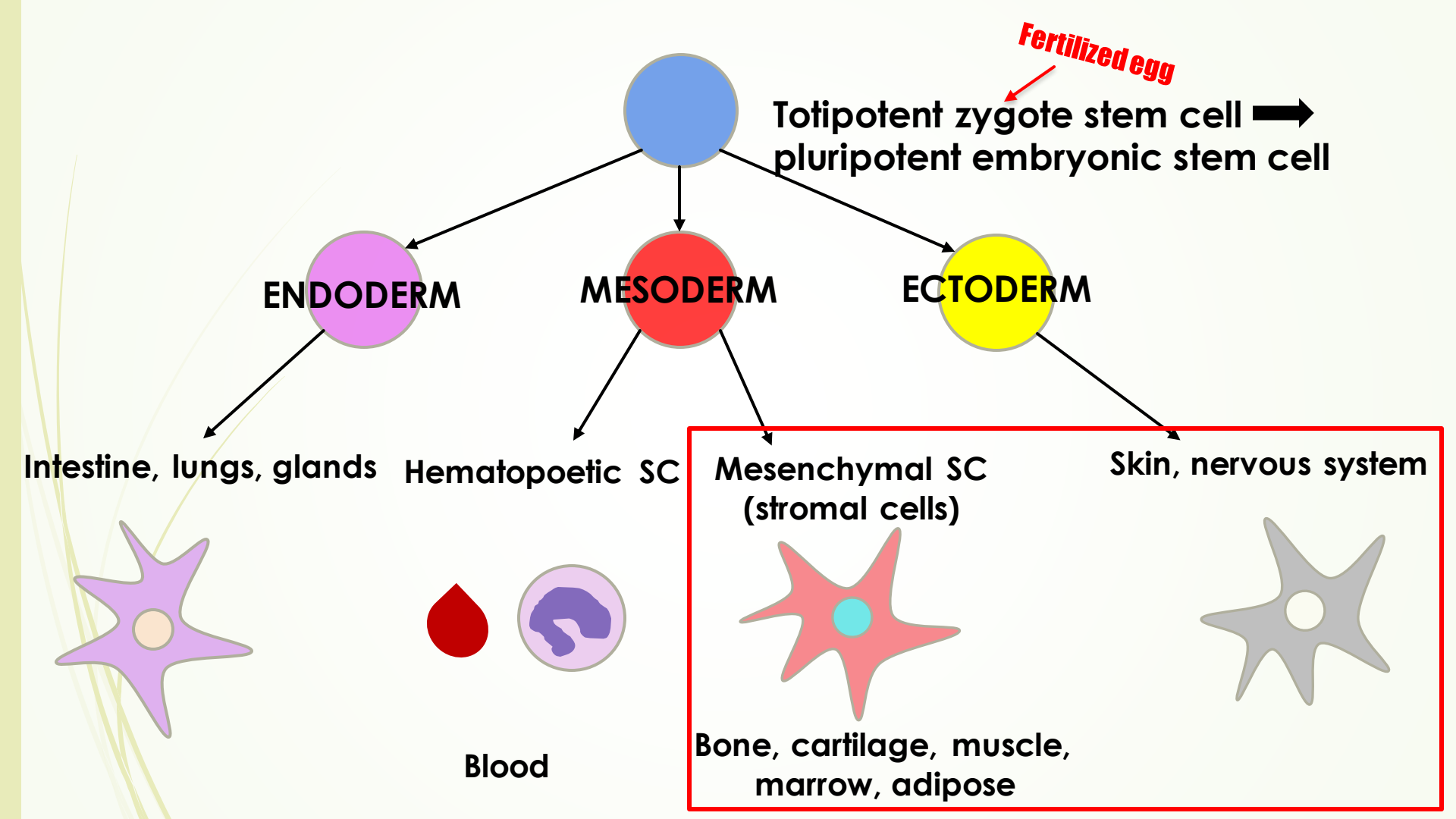




Stem cells: a primer

Where do stem cells come from?

- Autologous – from self
- Allogenic – from other people

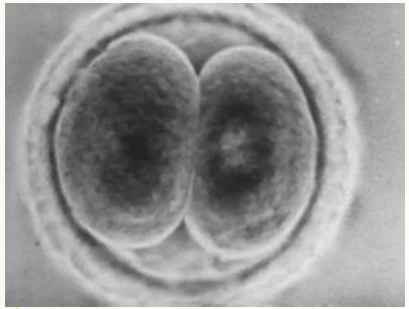

Fertilized egg
Totipotent zygote stem cell
pluripotent embryonic stem cell
ENDODERM
MESODERM
ECTODERM
Intestine, lungs, glands
Hematopoetic SC
Mesenchymal SC
(stromal cells)
Skin, nervous system
Blood
Bone, cartilage, muscle,
marrow, adipose

Potency as it relates to stem cells

Totipotent

Can become anything

Zygote

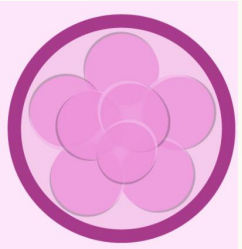


Pluripotent

Can become most things

Induced pluripotent (iPSCs)

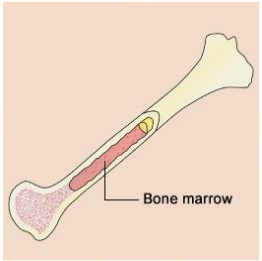
Embryonic



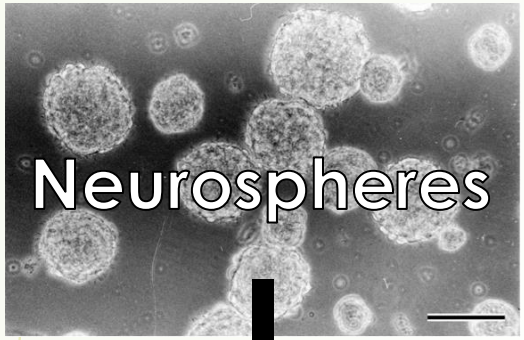
Multipotent

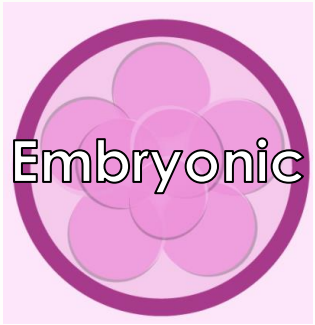
Can become some things

Adult stem cells

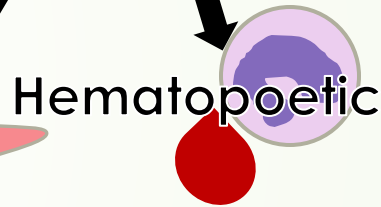


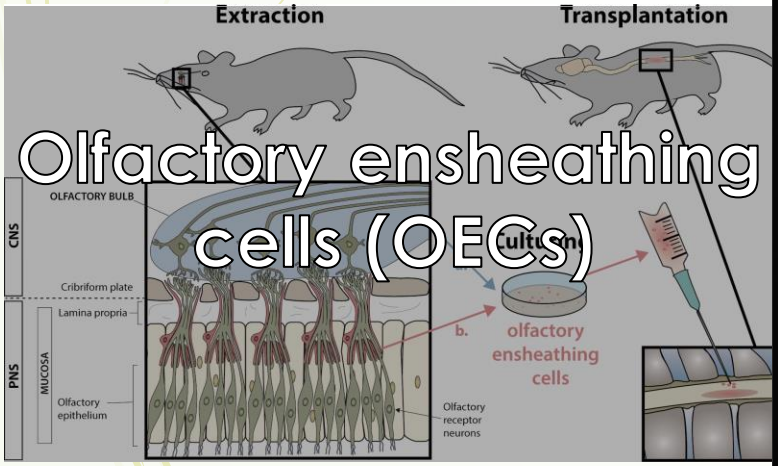
Types of cells used in reviewed studies





Neural stem/progenitor cells (precursor brain cells)



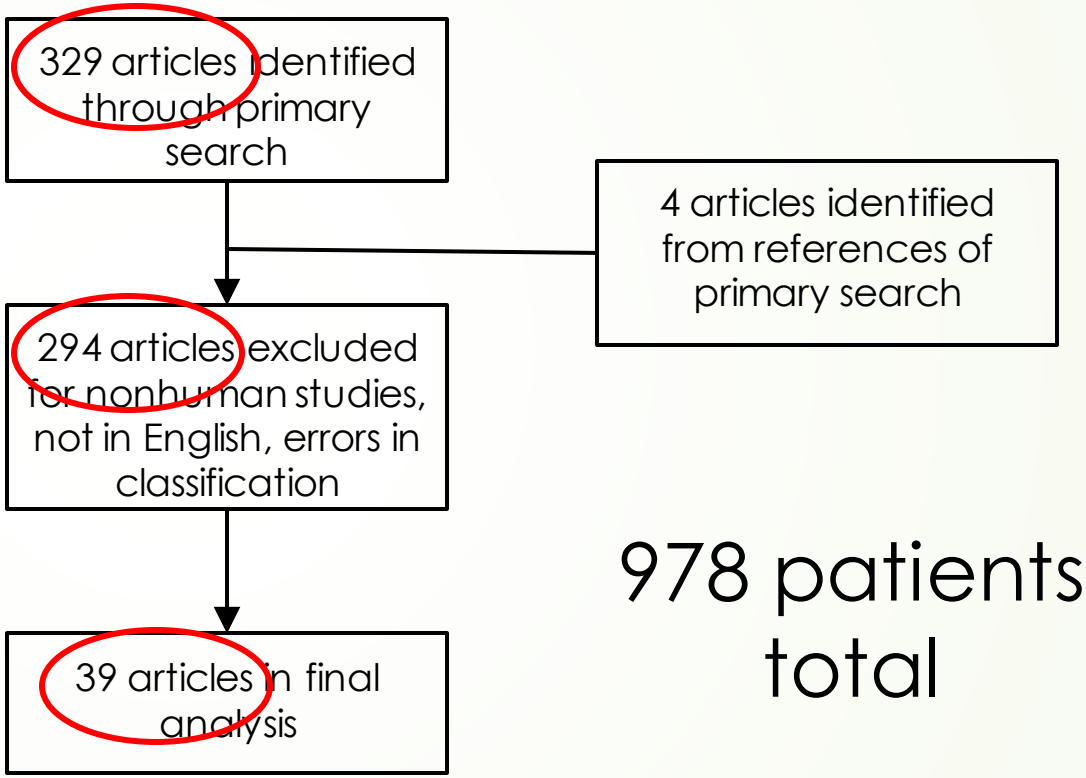


Outline

1. SCI epidemiology and types of stem cells
2. **Review of current study results**
3. Ethics of stem cell therapy and questions for future studies

Search through medical literature

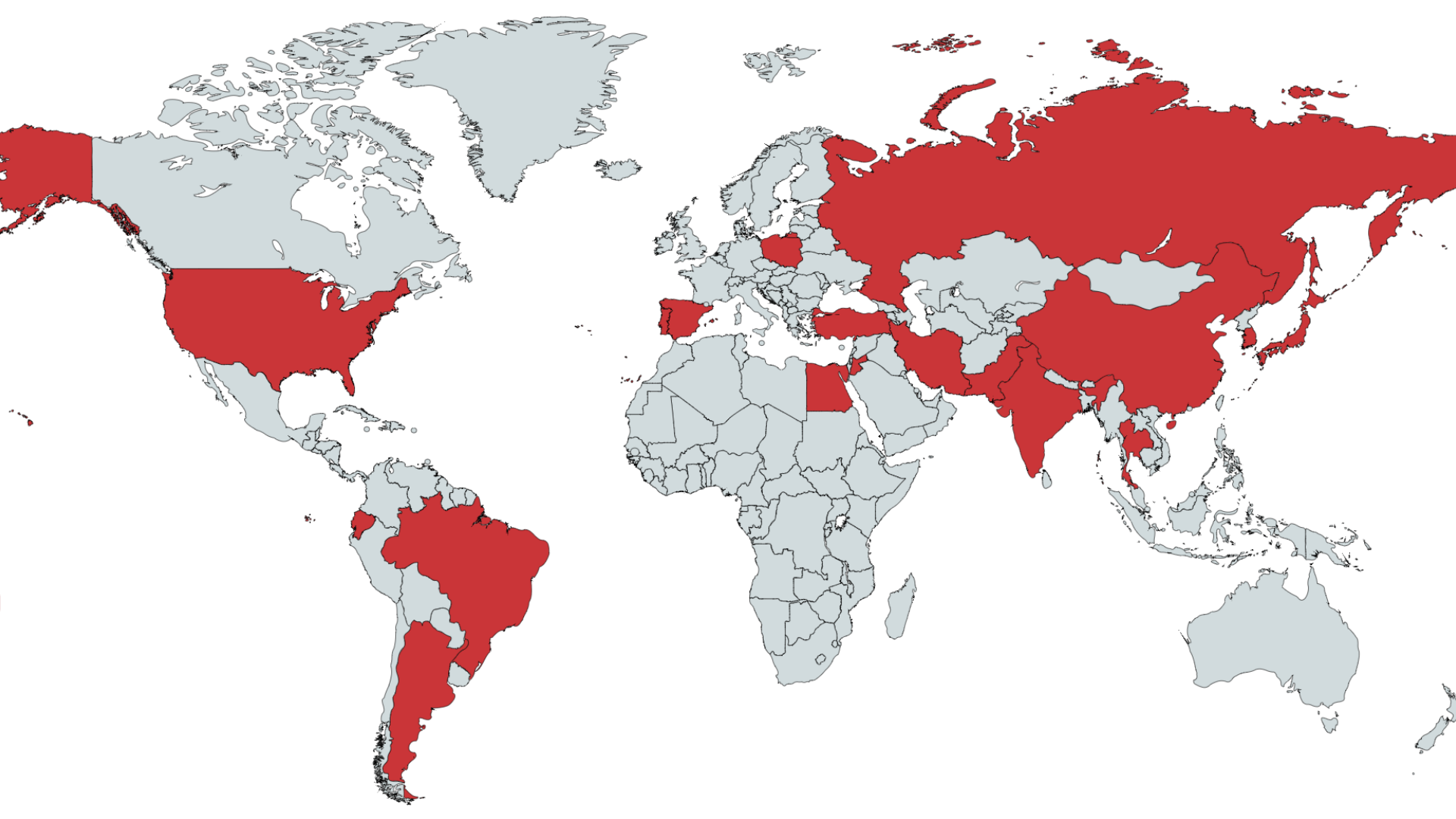
Filter: Humans, English



Not every search result is a good one

Read and analyzed

978 patients total



Variables

- Timing after injury
- Completeness
- Type of cells
- Dose of cells
- Route of administration

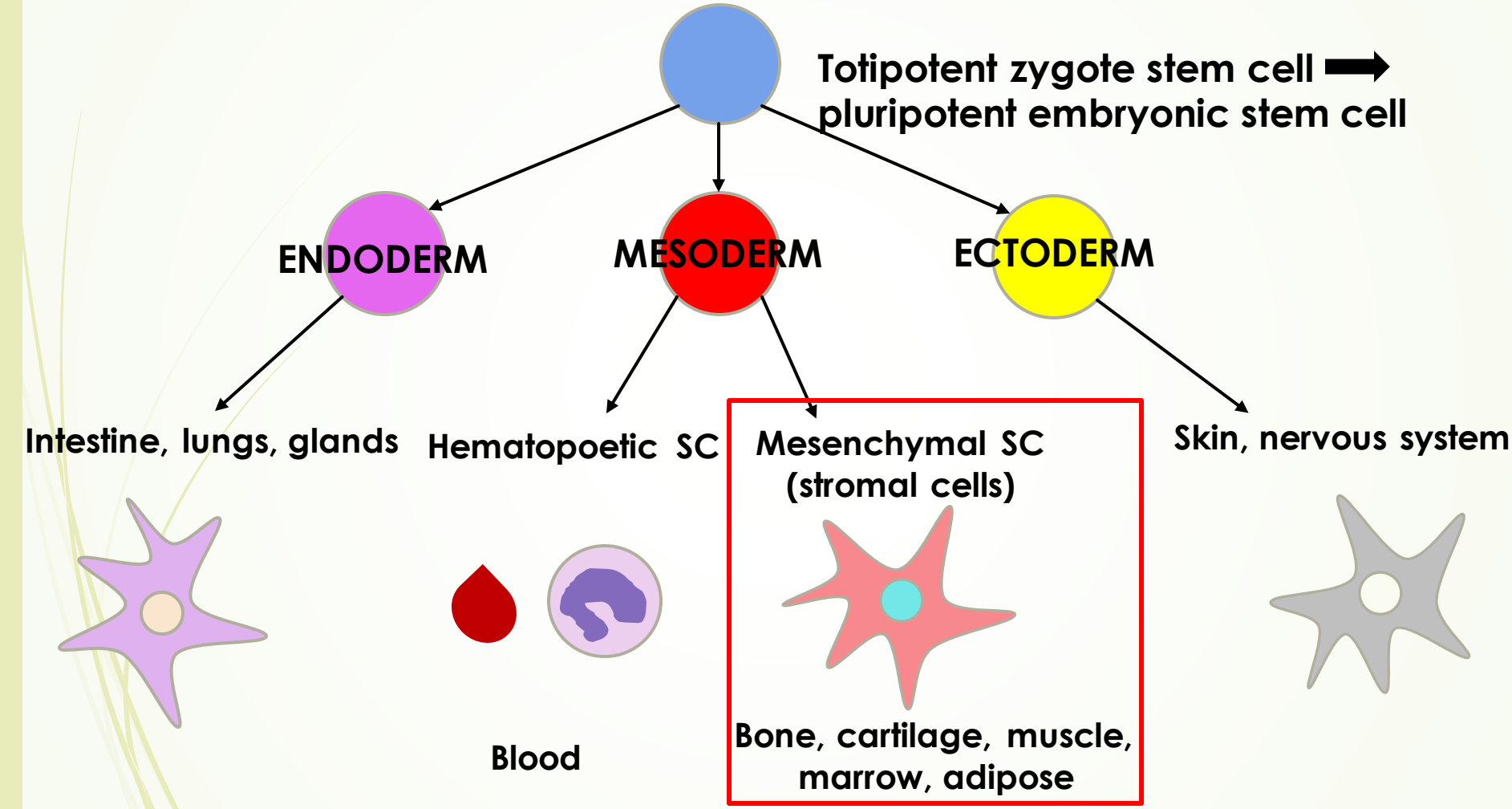
Who were in these studies?

- Mix of patients with chronic and acute injuries, paraplegia and tetraplegia, complete and incomplete
- Majority of patients had chronic injuries, mix of paraplegia or tetraplegia, and were complete

Cell Types

The majority of studies in this review assessed the effects of autologous MSCs as treatment for SCI.

From self


Totipotent zygote stem cell
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ENDODERM
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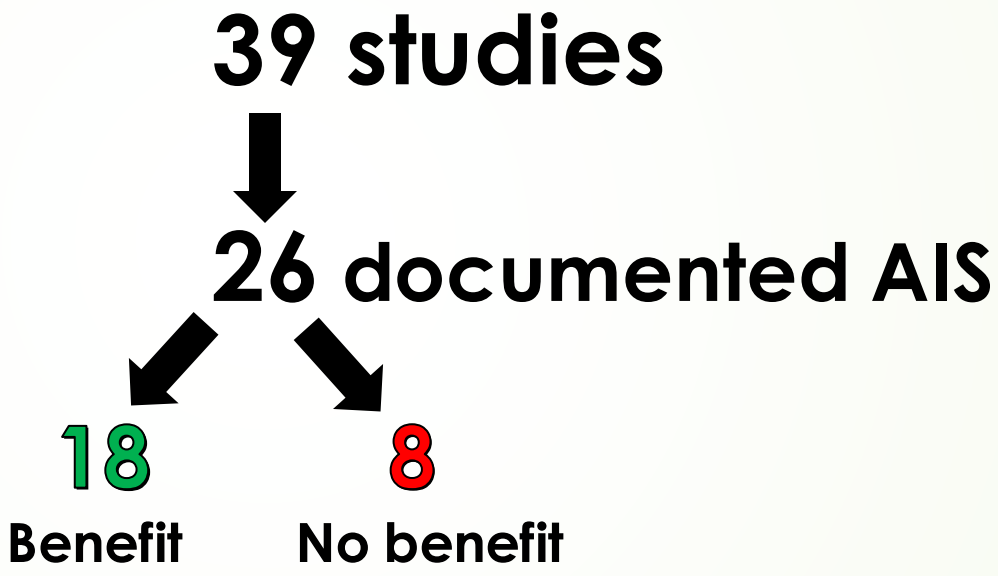
Intestine, lungs, glands
Hematopoetic SC
Mesenchymal SC
(stromal cells)
Skin, nervous system
Blood
Bone, cartilage, muscle,
marrow, adipose

Stem cell therapy: did it help?

Change in AIS (ASIA) classification (A-E)



It helped! What's the problem?

- These studies were all very different
  - different injury levels, completeness, time since injury, cells used, number in study, non-randomized, non-blind
- Although these were in "peer-reviewed" journals, overall they are not very "strong" studies

Archives of
Physical Medicine and Rehabilitation

Late Neurologic Recovery After Traumatic Spinal Cord Injury

Steven Kirshblum, MD, Scott Millis, PhD, William McKinley, MD, David Tulsky, PhD

ABSTRACT. Kirshblum S, Millis S, McKinley W, Tulsky D. Late neurologic recovery after traumatic spinal cord injury. Arch Phys Med Rehabil 2004;85:1811-7.

Objective: To present Model Spinal Cord Injury System (MSCIS) data on late neurologic recovery after 1 year after spinal cord i

Design: L mined by an

Setting: M traumatic SC Center datab

Participants: People with traumatic SCI (N=987) admitted to an MSCIS between 1988 and 1997 with 1- and 5-year follow-up examinations.

Interventions: Not applicable.

Main Outcome Measures: American Spinal Injury Association (ASIA) Impairment Scale (AIS) classification, motor index scores (MIS), motor level, and neurologic level of injury (NLI), measured and compared for changes over time.

Key Words: Neurologic disorders; Recovery of function; Rehabilitation; Spinal cord injuries.

"[Of those with neurologically complete injuries at 1 year], 3.5% improved to AIS B, and up to 1.05% each improved to AIS grades C and D at 5 years post injury"

neurologic (SCI) is ermine the nd chronic tment pro- rehabilita-

tion program.[1] In recent years, our knowledge of the course of neurologic recovery has increased to where it is now possible to predict, within a week of injury, the recovery of arm and leg strength in the early years postinjury.[2,3] The most accurate method used to predict such recovery is to perform a standardized physical examination early after injury, utilizing the *International Standards for Neurologic Classification of Spinal Cord Injury*.[4] This examination makes it possible for clinicians

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Archives of Physical Medicine and Rehabilitation

journal homepage: www.archives-pmr.org

Archives of Physical Medicine and Rehabilitation 2016;97:1647-55

ORIGINAL RESEARCH

Patterns of Sacral Sparing Components on Neurologic Recovery in Newly Injured Persons With Traumatic Spinal Cord Injury

Initial AIS grade	AIS Grade at Discharge (%)				AIS Grade at 1 Year (%)			
	A	B	C	D	A	B	C	D
A	80.2	13.1	6.2	0.5	72.2	10.7	13.9	3.2
B	5.0	53.4	33.9	7.7	10.7	35.7	32.2	21.4
C	1.8	2.0	44.3	51.9	1.8	6.4	19.3	72.5
D	0.4	0	0.6	99.0	0	0	0	100

Study example of "success"

Korean study that used autologous MSCs into the spinal cord or spinal space (via spinal tap):

- Patient 1 (8 months from injury) started at less than antigravity strength in elbow flexors/extensors and wrist extensors and returned to near-full strength in those muscles at 40 months post-treatment
- Patient 2 (38 months from injury) started at antigravity strength in elbow extensors and regained full strength in those muscles at 39 months post-treatment
- Patient 3 (96 months post injury) started at flicker to near-anti-gravity strength in finger muscles and regained full strength in those muscles at 30 months post-treatment

Park 2012

Expected functional outcomes

TABLE 6. Expected Functional Outcomes — **Level C5**

	Expected Functional Outcomes	Equipment	FIM/Assistance Data Exp	Med	IR
Respiratory	Low endurance and vital capacity secondary to paralysis of intercostals; may require assist to clear secretions				
Bowel	Total assist	Padded shower/commode chair or padded transfer tub bench with commode cutout	1	1	1
Bladder	Total assist	Adaptive devices may be indicated (electric leg bag emptier)	1	1	1
Bed Mobility	Some assist	• Full electric hospital bed with Trendelenburg feature with patients control • Side rails			
Bed/Wheelchair Transfers	Total assist	• Transfer board • Power or mechanical lift	1	1	1
Pressure Relief/ Positioning	Independent with equipment	• Power recline and/or tilt wheelchair • Wheelchair pressure-relief cushion • Hand splints • Specialty bed or pressure-relief mattress may be indicated • Postural support devices			
Eating	Total assist for setup, then independent eating with equipment	• Long opponens splint • Adaptive devices as indicated	5	5	2.5–5.5
Dressing	Lower extremity: Total assist Upper extremity: Some assist	• Long opponens splint • Adaptive devices as indicated	1	1	1–4
Grooming	Some to total assist	• Long opponens splints • Adaptive devices as indicated	1–3	1	1–5
Bathing	Total assist	• Padded tub transfer bench or shower/commode chair • Handheld shower	1	1	1–3
Wheelchair Propulsion	Power: Independent Manual: Independent to some assist indoors on noncarpet, level surface; some to total assist outdoors	Power: Power recline and/or tilt with arm drive control Manual: Lightweight rigid or folding frame with handrim modifications	6	6	5–6
Assist Required	• Personal care: 10 hours/day • Homecare: 6 hours/day • Able to instruct in all aspects of care		16*	23*	10–24*

*Hours per day.

TABLE 6. Expected Functional Outcomes — **Level C6**

	Expected Functional Outcomes	Equipment	FIM/Assistance Data Exp	Med	IR
Respiratory	Low endurance and vital capacity secondary to paralysis of intercostals; may require assist to clear secretions				
Bowel	Some to total assist	• Padded tub bench with commode cutout or padded shower/commode chair • Other adaptive devices as indicated	1–2	1	1
Bladder	Some to total assist with equipment; may be independent with leg bag emptying	Adaptive devices as indicated	1–2	1	1
Bed Mobility	Some assist	• Full electric hospital bed • Side rails • Full to king standard bed may be indicated			
Bed/Wheelchair Transfers	Level: Some assist to independent Uneven: Some to total assist	• Transfer board • Mechanical lift	3	1	1–3
Pressure Relief/ Positioning	Independent with equipment and/or adapted techniques	• Power recline wheelchair • Wheelchair pressure relief cushion • Postural support devices • Pressure-relief mattress or overlay may be indicated			
Eating	Independent with or without equipment; except cutting, which is total assist	Adaptive devices as indicated (e.g., u-cuff, tendenosis splint, adapted utensils, plate guard)	5–6	5	4–6
Dressing	Independent upper extremity; some assist to total assist for lower extremities	Adaptive devices as indicated (e.g., button; hook; loops on zippers, pants; socks, velcro on shoes)	1–3	2	1–5
Grooming	Some assist to independent with equipment	Adaptive devices as indicated (e.g., U-cuff, adapted handles)	3–6	4	2–6
Bathing	Upper body: Independent Lower body: Some to total assist	• Padded tub transfer bench or shower/commode chair • Adaptive devices as needed • Handheld shower	1–3	1	1–3
Wheelchair Propulsion	Power: Independent with standard arm drive on all surfaces Manual: Independent indoors; some to total assist outdoors	Manual: Lightweight rigid or folding frame with modified rims Power: May require power recline or standard upright power wheelchair	6	6	4–6
Assist Required	• Personal care: 6 hours/day • Homecare: 4 hours/day		10*	17*	8–24*

*Hours per day.

Spinal Cord Injury CPG 1999

TABLE 6. Expected Functional Outcomes — **Level C5**

	Expected Functional Outcomes	Equipment	FIM/Assistance Data Exp	Med	IR
Eating	Total assist for setup, then independent eating with equipment	• Long opponens splint • Adaptive devices as indicated	5	5	2.5–5.5
Dressing	Lower extremity: Total assist Upper extremity: Some assist	• Long opponens splint • Adaptive devices as indicated	1	1	1–4
Grooming	Some to total assist	• Long opponens splints • Adaptive devices as indicated	1–3	1	1–5
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*Hours per day.

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Eating	Independent with or without equipment; except cutting, which is total assist	Adaptive devices as indicated (e.g., u-cuff, tendenosis splint, adapted utensils, plate guard)	5–6	5	4–6
Dressing	Independent upper extremity; some assist to total assist for lower extremities	Adaptive devices as indicated (e.g., button; hook; loops on zippers, pants; socks, velcro on shoes)	1–3	2	1–5
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Assist Required	• Personal care: 6 hours/day • Homecare: 4 hours/day		10*	17*	8–24*

*Hours per day.

FIM Score	Ability
7	Independent
6	Independent with assistive device
5	Supervision
4	Minimal assistance
3	Moderate assistance
2	Maximal assistance
1	Total assistance

Spinal Cord Injury CPG 1999


SNAKE
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Spinal Cord Reconstruction and Stem Cell Implantati
Spinal Cord Injury in Beijing China

At Beijing Puhua International Hospital, the price for the Spinal Cord Reconstruction
Cell Implantation package starts from $30,780 (4 weeks, non-surgery) and $33,783
(3 weeks, cervical segment).

Package price:
$ 30780
View P

Best Stem Cell Therapy for Spinal Cord Injury in Euro

Are you tired of bad treatments? Would you like to enjoy life like you did? Don't worry we got the right thing for you. You can enjoy walks with your family again for just 7,000 euros.

Package price:
$ 7000
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Choose one this Stem Cell Therapy for Spinal Cord Injury and get on your feet soon! Stem Cell Therapy for Spinal Cord Injury in Asia. You can walk again and enjoy your life for only $9,900.

Package price:
$ 9900
View Package

Stem Cell Therapy in India for Severe Spinal Cord Injury

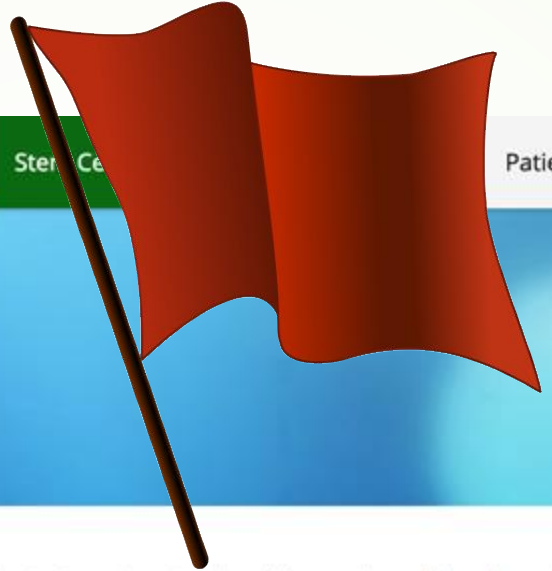
Choose this Reelabs stem cell therapy for severe spinal cord injury and get back on your feet right now! ReeLabs is one of the most reputed centers in India for Stem Cell Therapy treatments especially for severe injuries such as spinal cord and neurological affections.

Stem Cell Therapy for ALS in Vienna Austria

The stem cell therapy for ALS can help patients struggling with the condition to improve their health, by relieving the symptoms and slowing the progression of the disease.

ancells
WER TO CURE

REGENERATION
Center of Thailand



北科生物 Beike Biotechnology

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Beike Stem Cells

Different Types of Stem Cells for Different Purposes

Beike is only using adult stem cells (also called somatic stem cells) in its treatment protocols and does not provide embryonic stem cells. It is important to remember that while embryonic st
not compromise o
about adults stem

22,500 patients with no serious adverse reaction reported.

The adult stem cells provided in our treatment protocols come from two distinct sources: umbilical cord tissue and umbilical cord blood. This allow us to provide our patients with **Umbilical Cord Blood Stem Cells (UCBSC)** and **Umbilical Cord Mesenchymal Stem Cells (UCMSC)** separately or in combination depending on each patient's specific condition and need. Umbilical cord derived stem cells do not draw any concern from the scientific community and have been proven effective for a wide range of conditions.

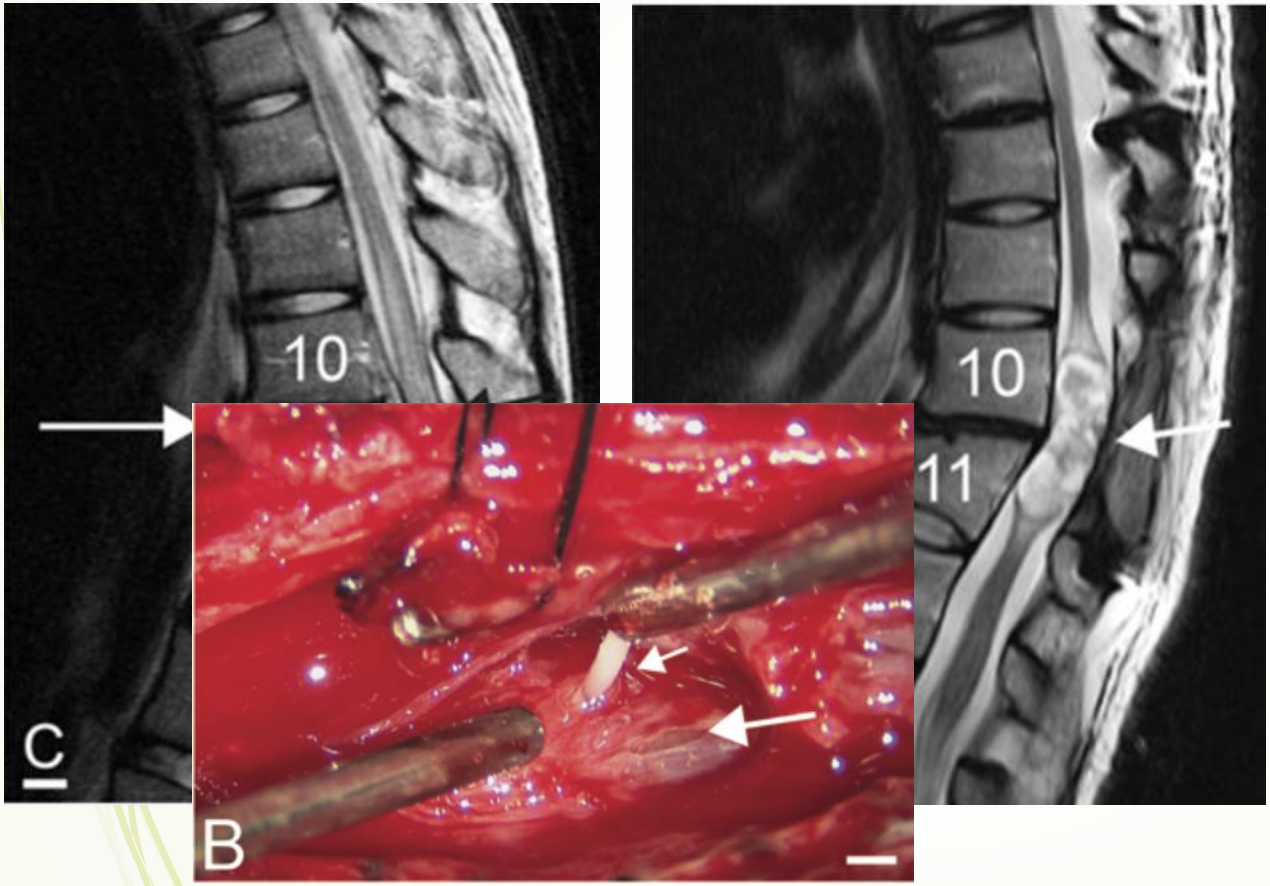
TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER D--DRUGS FOR HUMAN USE

An adverse event or suspected adverse reaction is considered "serious" if […] it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

US FDA Code of Federal Regulations

Dr. Geeta Shroff

Risks



- 18 year old woman at time of injury
- 3 years later underwent olfactory (nasal cell) transplant
- 8 years later had back pain

What is this?

Dlouhy 2014

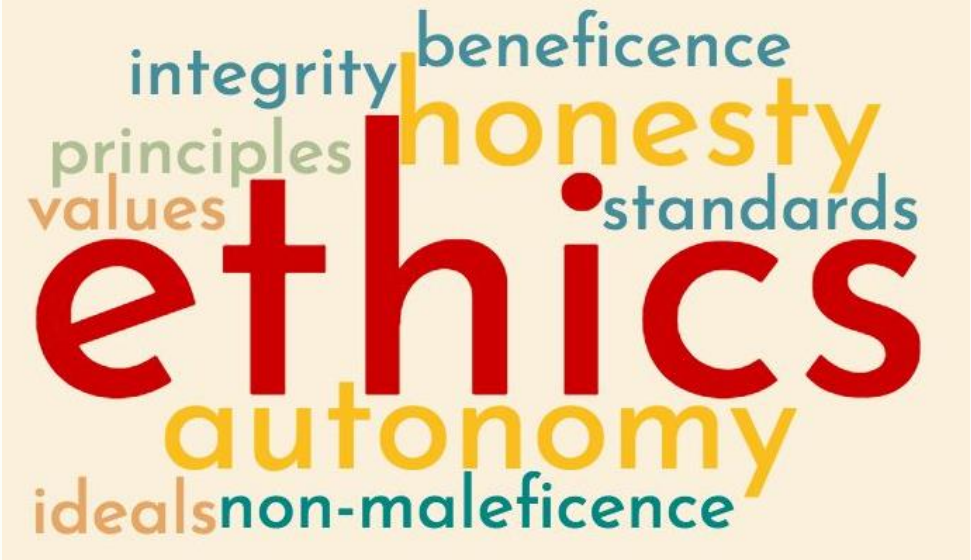
Why aren't there more stem cell trials for SCI?

- Lack of standardization (type of stem cell, dose, route)
- Difficult to randomize and/or control, small study sizes
- FDA approval (usually lacking or slow)
- Expensive (cost of treatment, travel, sick time)
- Unclear level of risk

Outline

1. SCI epidemiology and types of stem cells
2. Review of current study results
3. **Ethics of stem cell therapy and questions for future studies**

What's ethics got to do with it?



Excerpt from one paper…

The first consent should be obtained before operation shortly after the injury occurs, but in this case the patient was sedated and his family was upset,

Saito 2008

Medical Vulnerability

"Social groups who have an increased relative risk or susceptibility to adverse health outcomes"

Flaskerud 1998

Balance in reporting: is it #fakenews?

On SCI Advocacy websites that mentioned stem cells…

Positive:negative statem

10:1

Ethics-related information comprised **20%** of total content

Parke 2010

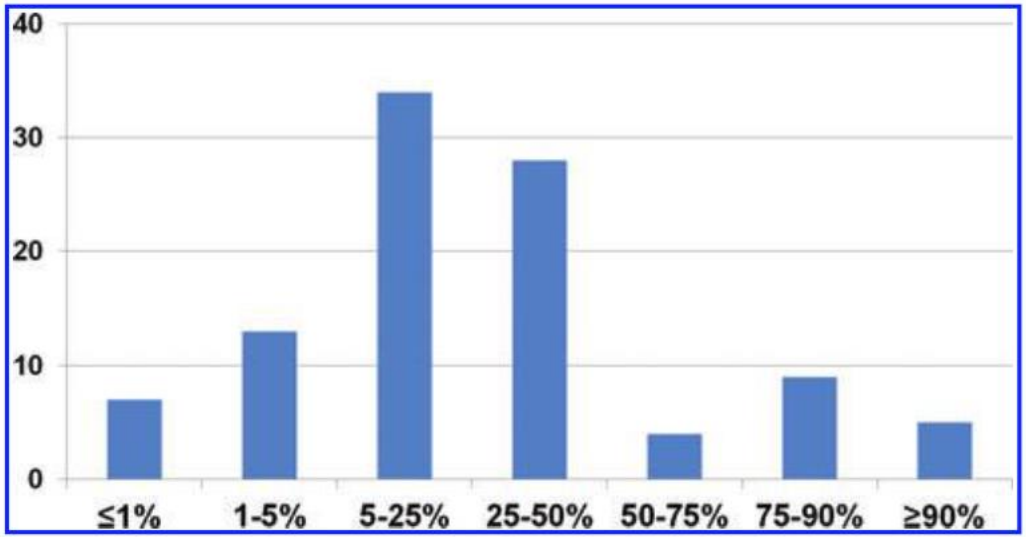
Risks of social media

Most SCI tweets pertaining to stem cell therapy

neutral or **positive**

Robillard 2015

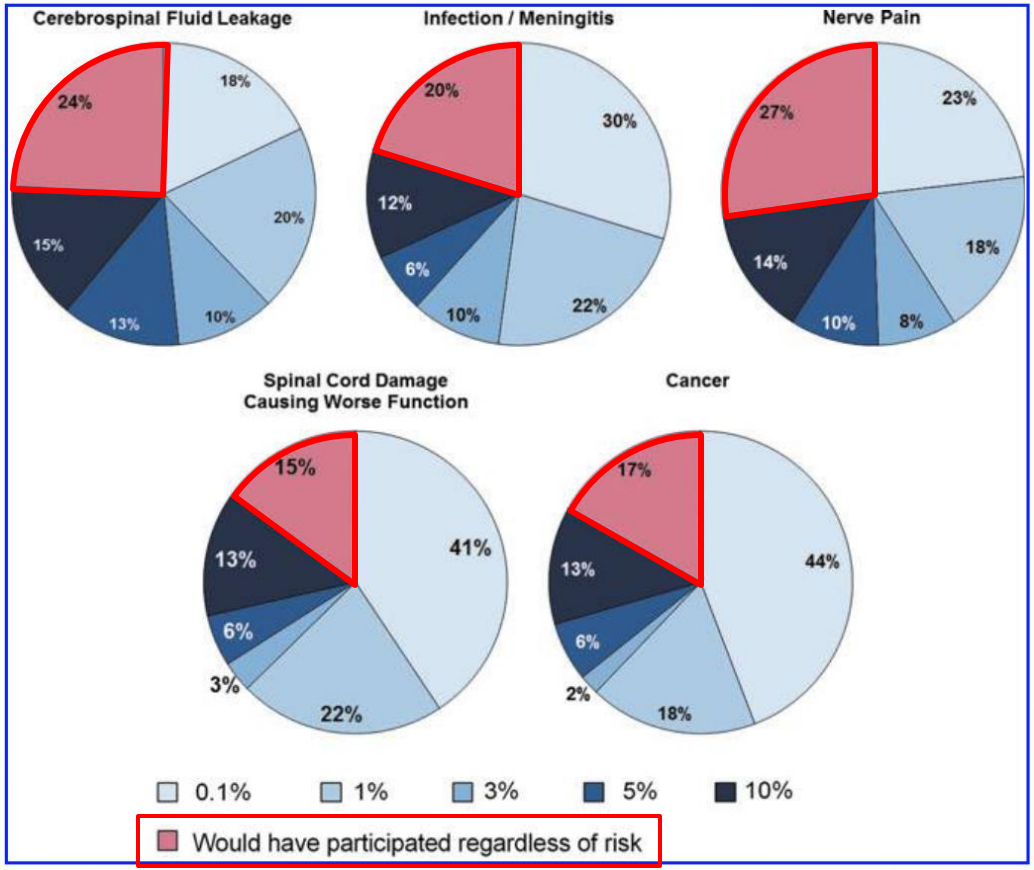
“What would you want your chances to be for getting some functional recovery back?”



Minimum chance of functional recovery required for entering a SCT research trial

Kwon 2012

Risk-taking



Kwon 2012

The literature supports that:

- Majority of stem cell therapy information is neutral or positive, both on websites and social media
- Majority of respondents (8 of 10) would be satisfied with 1-50% chance of functional recovery from SCT
- Up to 25% of respondents willing to participate in SCT regardless of risk

Questions About Experimental Treatments for Spinal Cord Injury.

Were assessments of lesions, interventions, and other evaluations performed in a blinded fashion by multiple observers?

Were animals showing a rate of recovery that was too rapid for regeneration (or even rescue) or were lesions that were incorrectly staged eliminated from the data set?

Were observation periods carried out for at least 4 months after the intervention?

Were the longitudinal fibers of the cord traced both before and after a lesion to distinguish preexisting (unsevered) tracts versus recreated or reclaimed tracts?

Were the tracts or cells that were credited with recovery then removed experimentally to show that their elimination returned the animal to the pretreatment state? Was there plausible molecular, cellular, and histologic evidence of a sufficiently robust regenerative process?

Were measures of open-field behavior analyzed with appropriate statistical rigor and an appreciation for the pitfalls of that type of assessment?

Were approaches other than open-field testing used to evaluate spinal function?

Were improvements in cortically recorded motor and sensory evoked potentials documented?

Are the results reproducible?

If transplanted cells are required, can they be isolated, characterized, and safely scaled up within a timeframe that can produce an effect on a freshly injured human spinal cord?

Questions when reviewing future studies

Were assessments performed in a blinded manner?

Were participants followed and observed for at least 4 months after the treatment?

Are the results reproducible?

Snyder 2012

Essential questions to ask a stem cell clinic

- Is the treatment FDA-approved, and if not, why not?
- Will this affect whether I can get into another clinical trial?
- What benefits can I expect?
- How will this be measured, and how long will it take?

From the Christopher and Dana Reeve Foundation

Essential questions to ask a stem cell clinic

- What other medications or special care might I need?
- How is this stem cell procedure done?
- What is the source of the stem cells?
- How are the stem cells identified, isolated, and grown?

From the Christopher and Dana Reeve Foundation

Essential questions to ask a stem cell clinic

- Are the cells differentiated into specialized cells before therapy?
- How do I know if the cells are delivered to the right part of my body?
- If the cells are not my own, how will my immune system be prevented from reacting to the transplanted cells?
- What do the cells actually do, and is there scientific evidence that this procedure could work for my disease or condition? Where is this published?

From the Christopher and Dana Reeve Foundation

On the horizon…

Hospital Sao Rafael – autologous MSCs
Ferrer – allogenic MSCs
Sun Yat Sen – umbilical MSCs
Beijing – MSCs or NSCs on collagen scaffold
Miami – autologous Schwann
Da Nang – autologous mononuclear
Sci star – oligodendrocyte progenitor
UCSD – neural stem
BioArctic – FGF1 and peripheral nerve

Excerpted from SCOPE 2017

Non-SCT

SPRING trial	VX-201/Cethrin
Eusol	rFGF
Rick Hansen	Minocycline
RISCIS	Riluzole
Kringle	Hepatocyte GF
OSU	Glyburide
Kessler	Dalfampyridine
Others	Hypothermia, HBO, AIH, BP

Excerpted from SCOPE 2017

I’m interested in learning more… what do I do next?

Closerlookatstemcells.org

How do I learn more about clinical trials?

NIH Clinical Center
America's Research Hospital

Find NIH Clinical Center Trials

The National Institutes of Health (NIH) Clinical Center Search the Studies site is a registry of publicly supported clinical studies conducted mostly in Bethesda, MD.

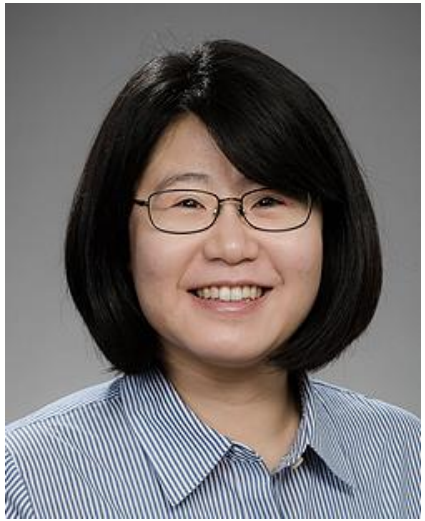
Keyword: Enter Diagnosis or Keyword

Search ?

Take-home points

- Stem cell therapy for spinal cord injury has shown some benefit, but is not without risks of its own; additionally, **"benefits" are not guaranteed**
- If you are considering stem cell therapy: Do your homework!
- Beware of anecdotal evidence or testimonials
- If it sounds too good to be true, it probably is

Acknowledgements



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