



# SERENDIPITY AND THE SCIENTIFIC JOURNEY FROM SINGAPORE TO STEM CELLS

UNIVERSITY OF ALABAMA AT BIRMINGHAM  
WOMEN IN SURGERY

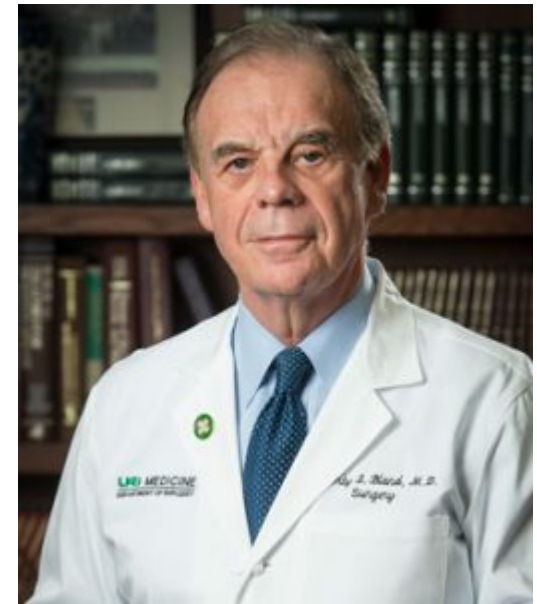
APRIL 2, 2019

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# Surgical Science and Regenerative Medicine: More than just Cells

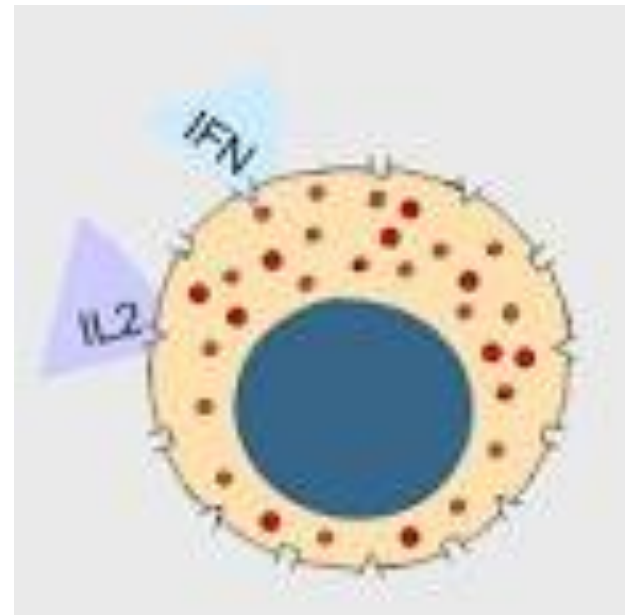
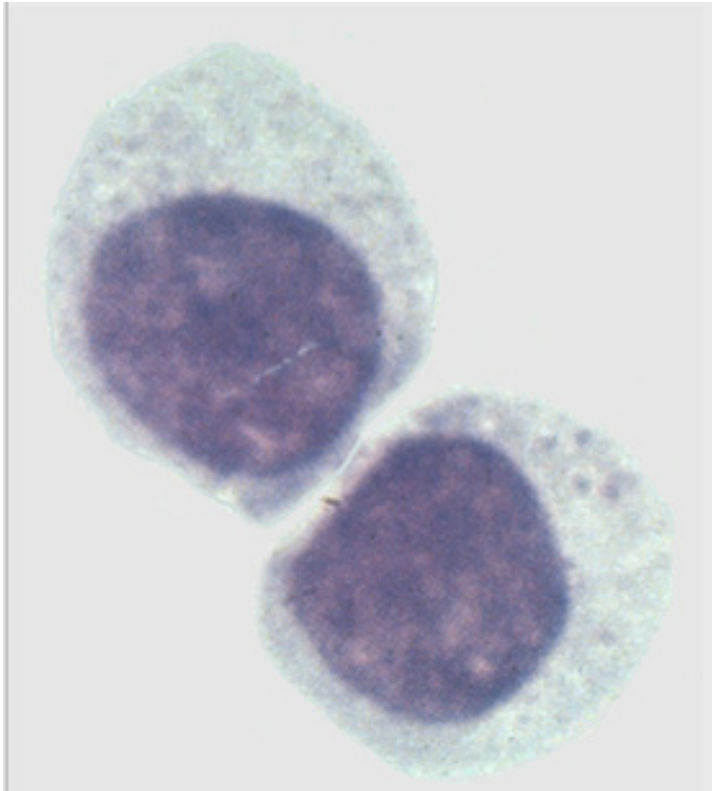


## Luce ( Not Loose) Scholarship

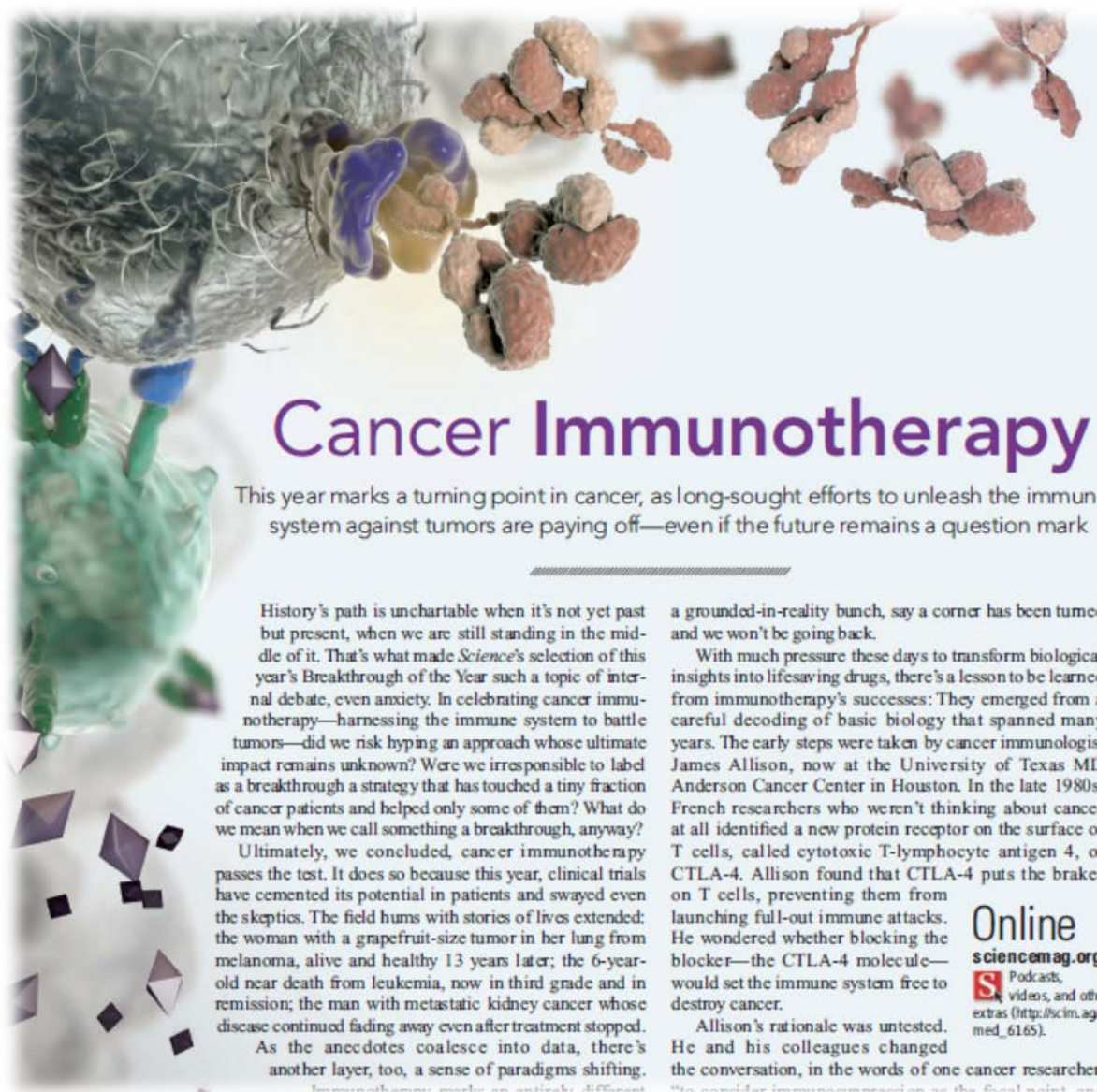




# Early Cell Therapy: Investigating New treatments for Cancer



IL-2 & LAK Cells



# Cancer Immunotherapy

This year marks a turning point in cancer, as long-sought efforts to unleash the immune system against tumors are paying off—even if the future remains a question mark

History's path is unchartable when it's not yet past but present, when we are still standing in the middle of it. That's what made *Science's* selection of this year's Breakthrough of the Year such a topic of internal debate, even anxiety. In celebrating cancer immunotherapy—harnessing the immune system to battle tumors—did we risk hyping an approach whose ultimate impact remains unknown? Were we irresponsible to label as a breakthrough a strategy that has touched a tiny fraction of cancer patients and helped only some of them? What do we mean when we call something a breakthrough, anyway?

Ultimately, we concluded, cancer immunotherapy passes the test. It does so because this year, clinical trials have cemented its potential in patients and swayed even the skeptics. The field hums with stories of lives extended: the woman with a grapefruit-size tumor in her lung from melanoma, alive and healthy 13 years later; the 6-year-old near death from leukemia, now in third grade and in remission; the man with metastatic kidney cancer whose disease continued fading away even after treatment stopped.

As the anecdotes coalesce into data, there's another layer, too, a sense of paradigms shifting.

Immunotherapy marks an entirely different

a grounded-in-reality bunch, say a corner has been turned and we won't be going back.

With much pressure these days to transform biological insights into lifesaving drugs, there's a lesson to be learned from immunotherapy's successes: They emerged from a careful decoding of basic biology that spanned many years. The early steps were taken by cancer immunologist James Allison, now at the University of Texas MD Anderson Cancer Center in Houston. In the late 1980s, French researchers who weren't thinking about cancer at all identified a new protein receptor on the surface of T cells, called cytotoxic T-lymphocyte antigen 4, or CTLA-4. Allison found that CTLA-4 puts the brakes on T cells, preventing them from launching full-out immune attacks. He wondered whether blocking the blocker—the CTLA-4 molecule—would set the immune system free to destroy cancer.

Allison's rationale was untested. He and his colleagues changed the conversation, in the words of one cancer researcher, "to consider immunosuppression as the focal point, and

Online  
[sciencemag.org](http://sciencemag.org)

Podcasts,  
videos, and other  
extras ([http://scim.ag/med\\_6165](http://scim.ag/med_6165)).









The “other” option for research: Industry

# COMPANY HISTORY

 **New England Nuclear  
Radiopharmaceutical Division**  
Atomlight Place, North Billerica, Mass. 01862  
Telephone (617) 667-9531  
**1956-1981**

 **New England Nuclear  
Radiopharmaceutical Division**  
Atomlight Place, North Billerica, Mass. 01862  
Telephone (617) 667-9531

**A Dupont Company 1981-1984**



**Medical Products 1984-1991**



**1991-1998**



**Dupont Pharmaceutical Co.**

**1998-2001**



**2001-2008**



**2008**







# The Birth of In Utero Stem Cell Therapy



## Surgery on the World Stage





- 3<sup>rd</sup> Edition (2014) : Volume on Surgery

Disease Control  
Priorities in  
Developing Countries

SECOND EDITION

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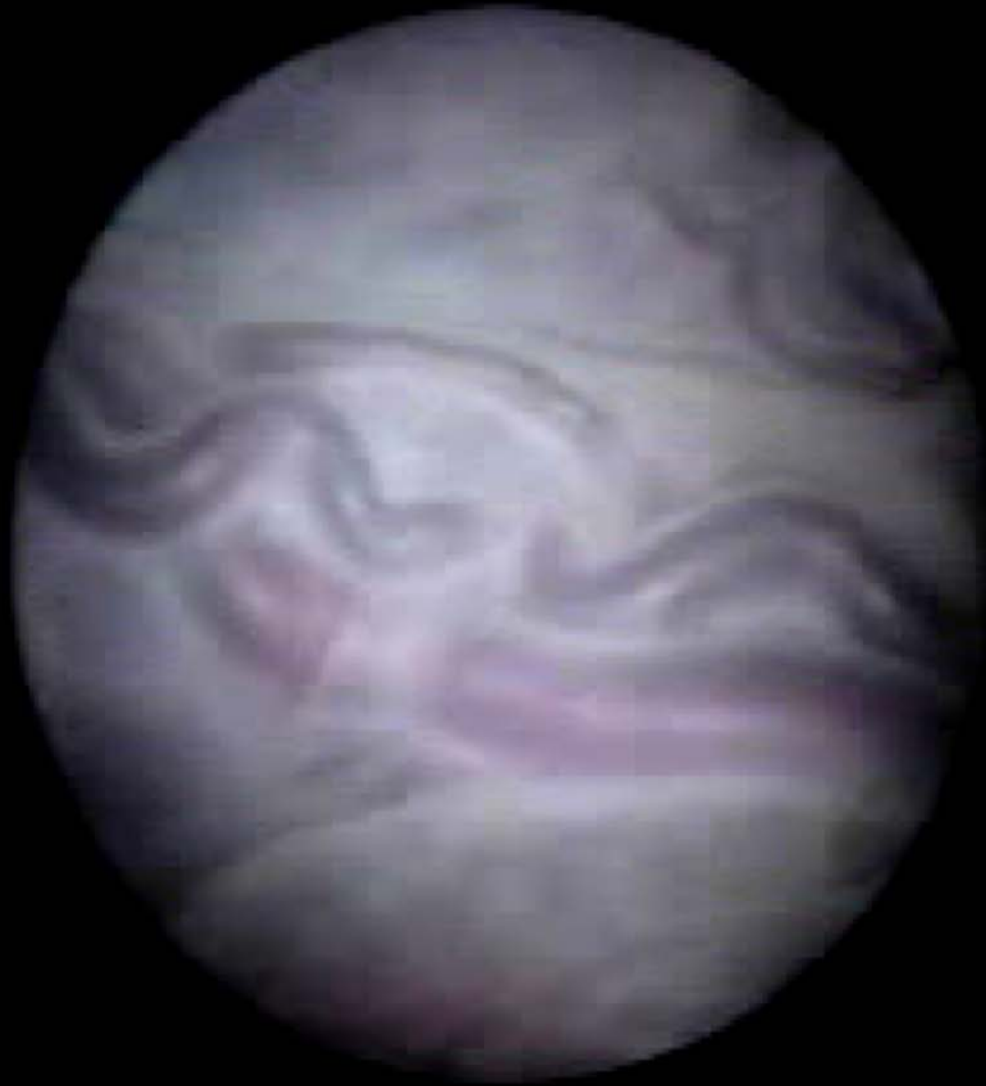
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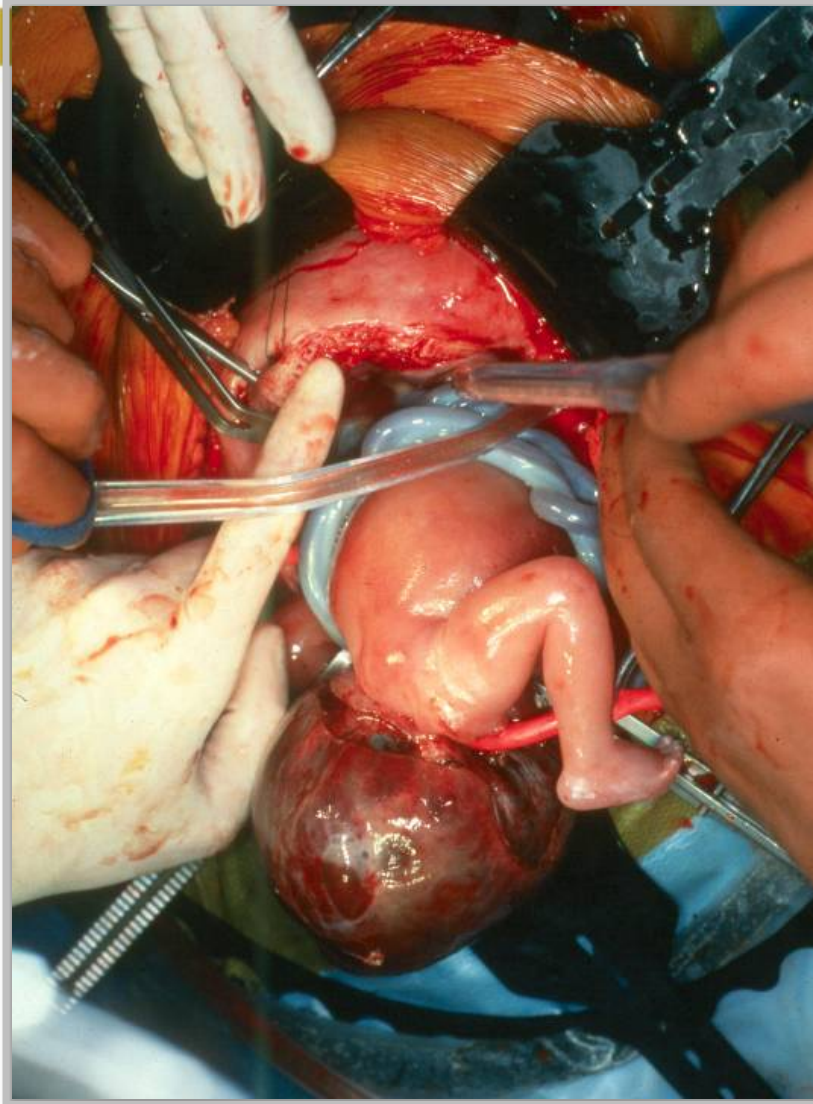
## Curing Myelomeningocele: from Ovine Surgery to Stem Cells



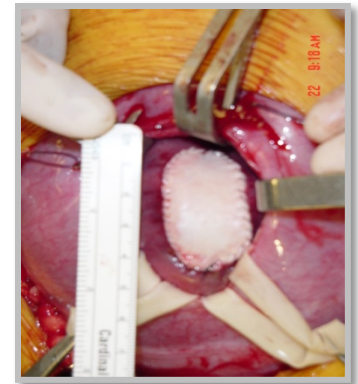
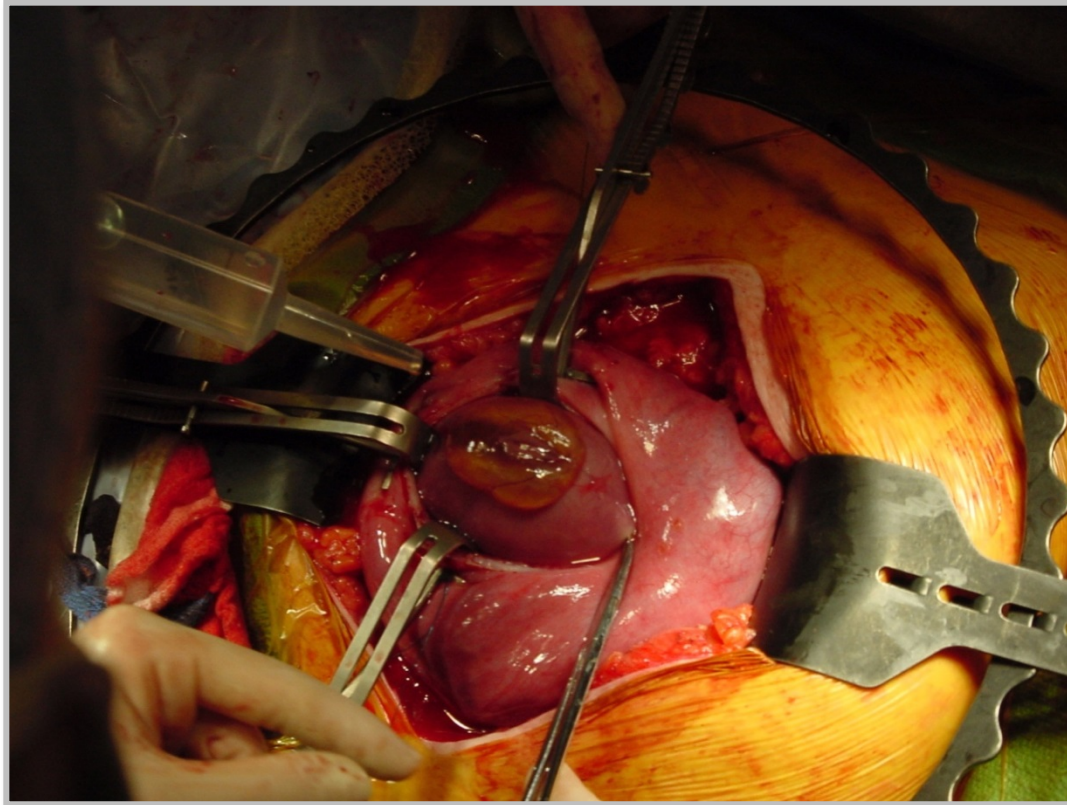




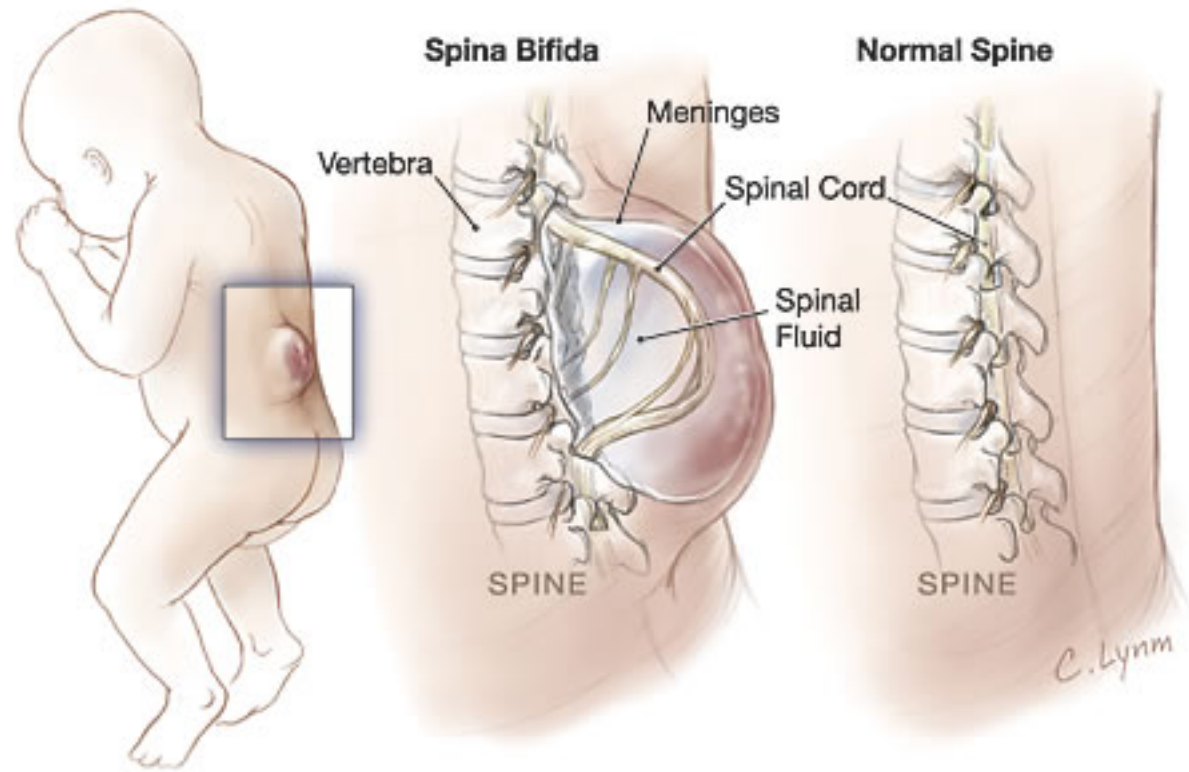




# Myelomeningocele (MMC)



# Spina Bifida or MMC



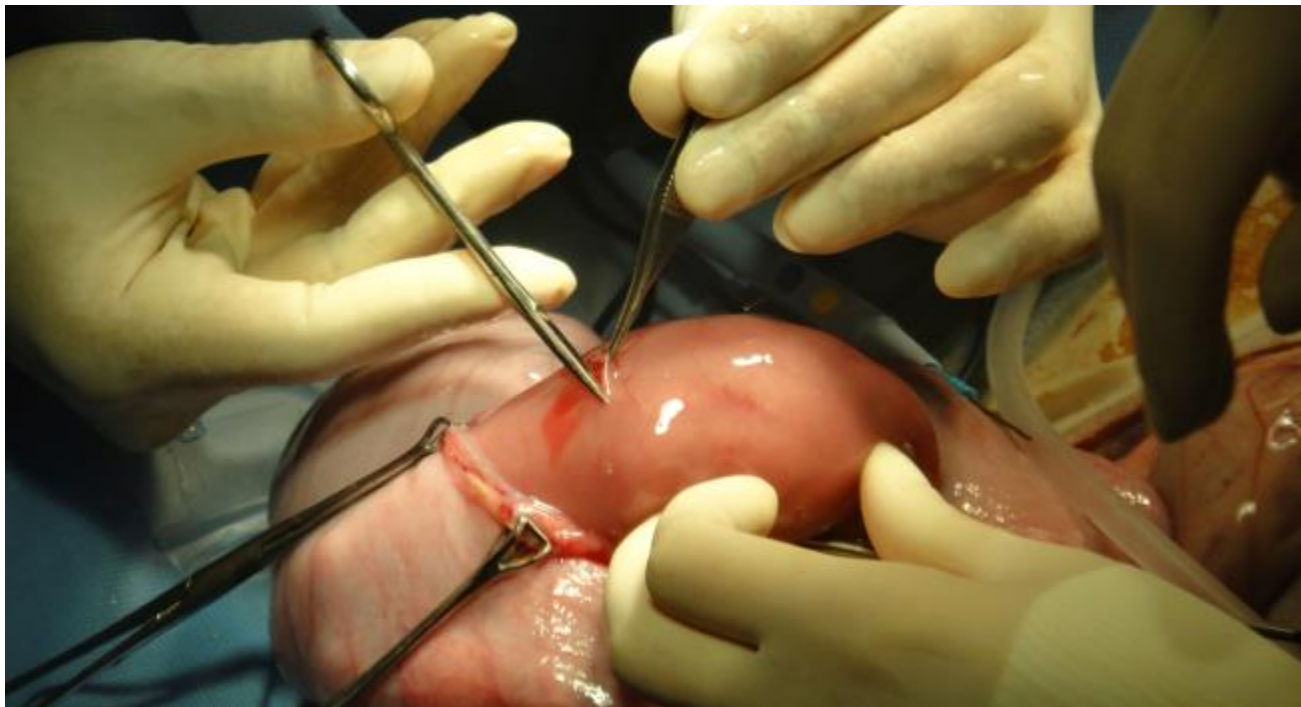
- 4 children born each day in US
- Annual cost of MMC in US is \$500 million



# **Creation of Myelomeningocele In Utero: A Model of Functional Damage From Spinal Cord Exposure in Fetal Sheep**

By Martin Meuli, Claudia Meuli-Simmen, Charles D. Yingling, Grover M. Hutchins, Kathleen McBiles Hoffman,  
Michael R. Harrison, and N. Scott Adzick  
*San Francisco, California and Baltimore, Maryland*

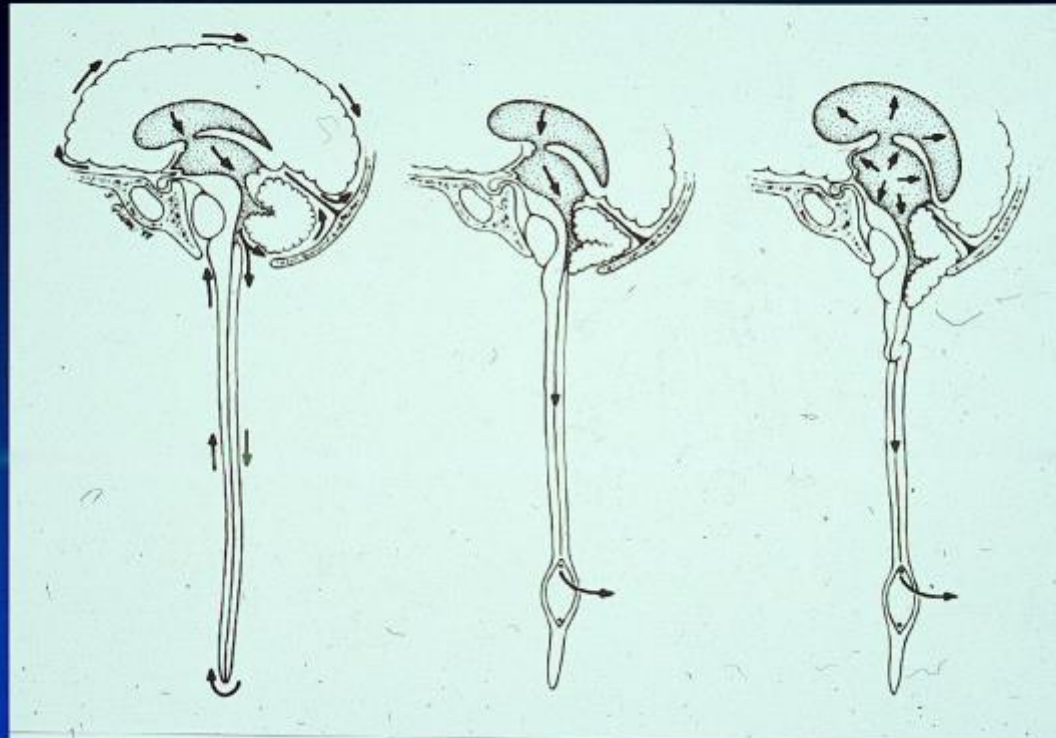
J Pediatric Surgery 1995



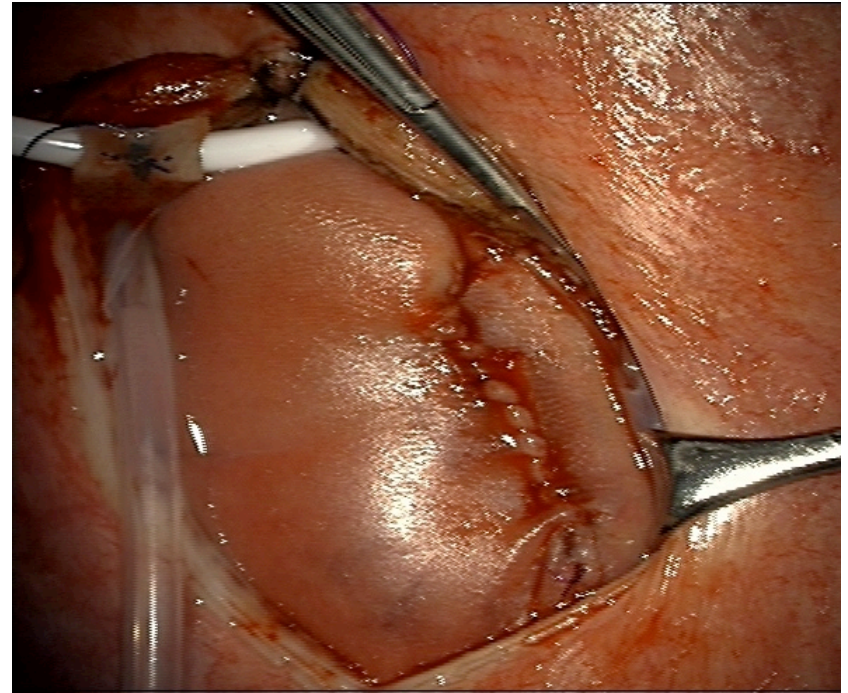
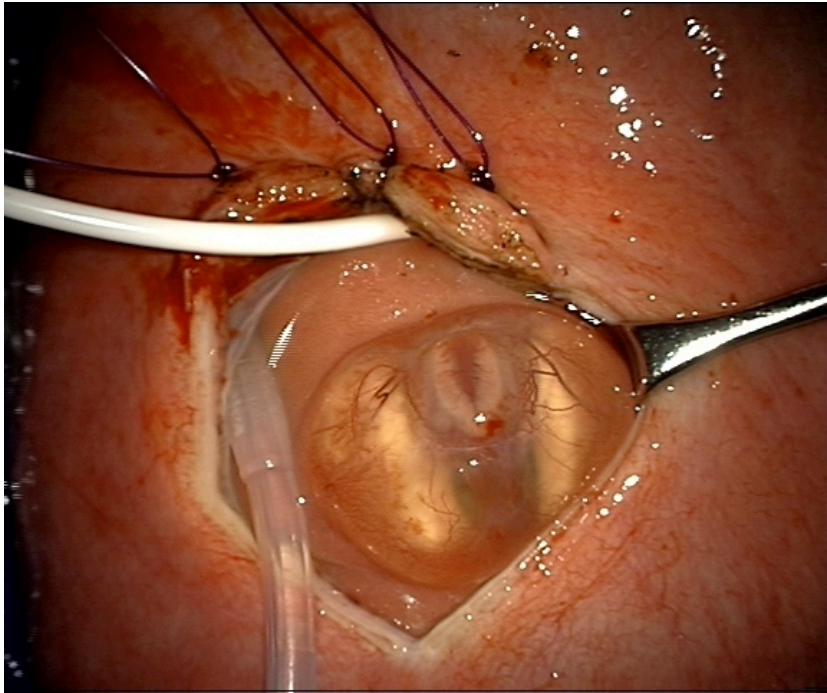
**Hindbrain Herniation develops in surgically created myelomeningocele model but is absent after repair in fetal lambs .**

By: Paek,BW, Farmer DL, Et al  
J Obstet Gynecol. 2000;183(5):1119-23

### **Etiology of the Chiari II malformation**



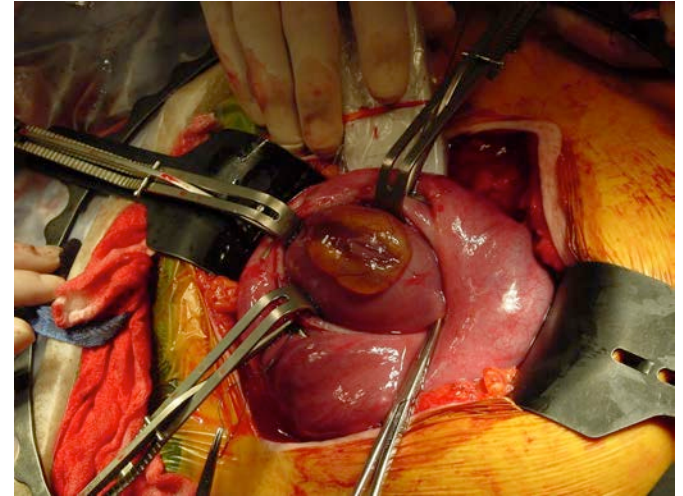
# Fetal Repair of Spina Bifida





# MOMS

Management of Myelomeningocele Study





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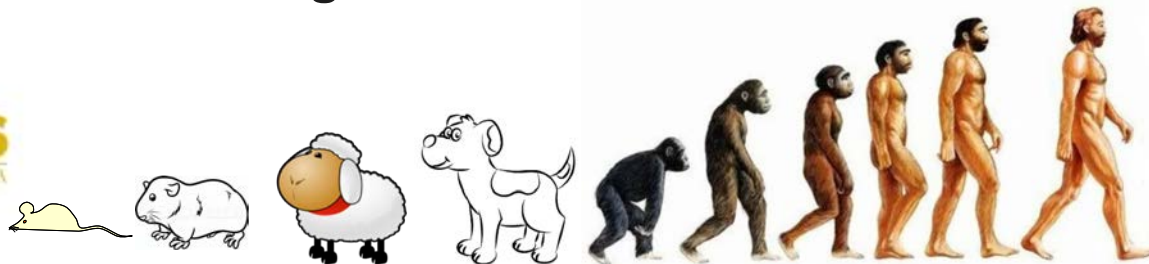
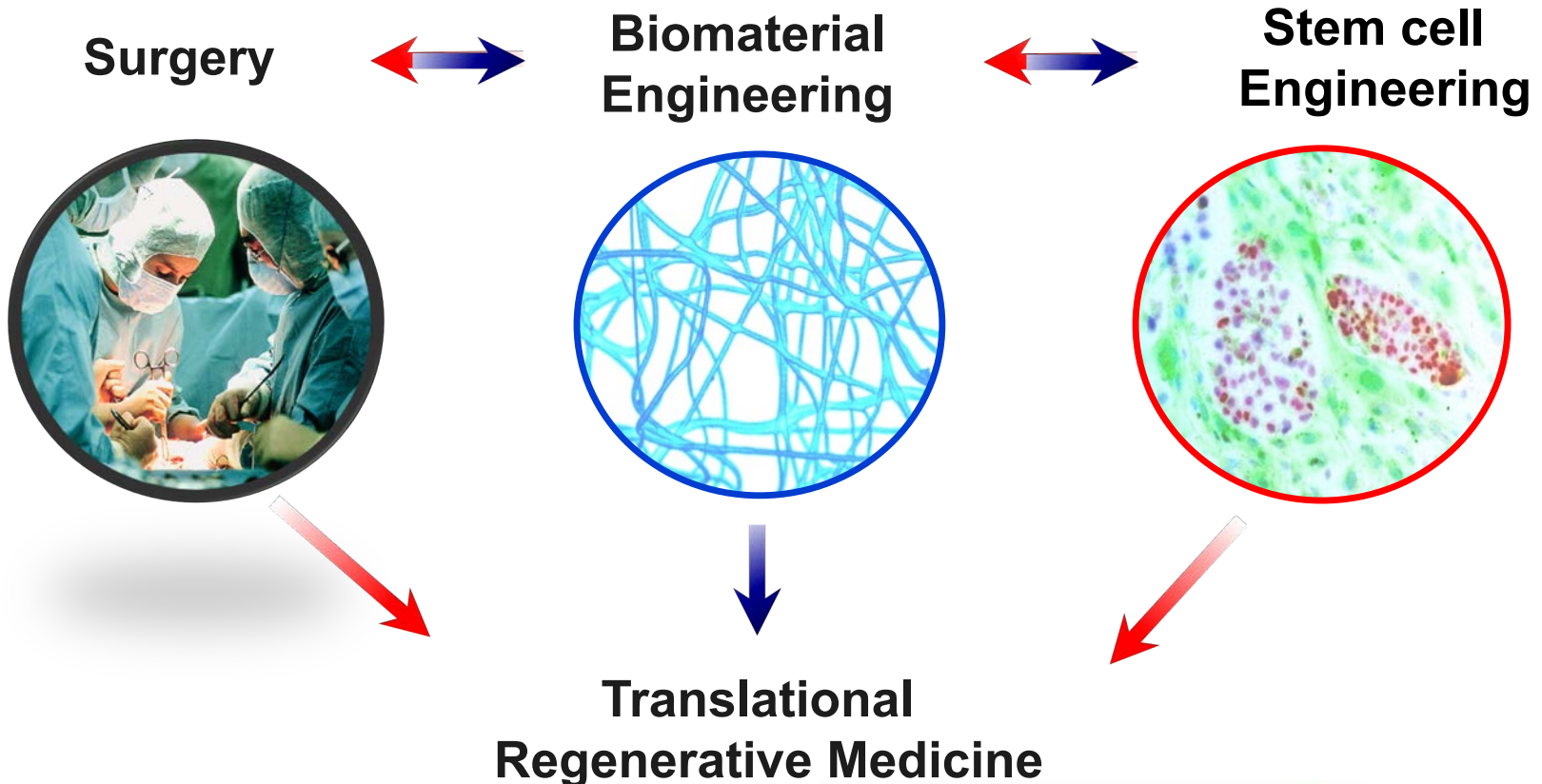
**MOMS**  
Management of Myelomeningocele Study

## A Randomized Trial of Prenatal versus Postnatal Repair of Myelomeningocele

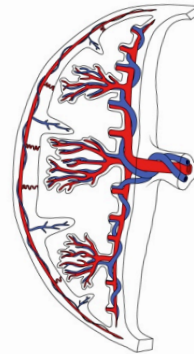
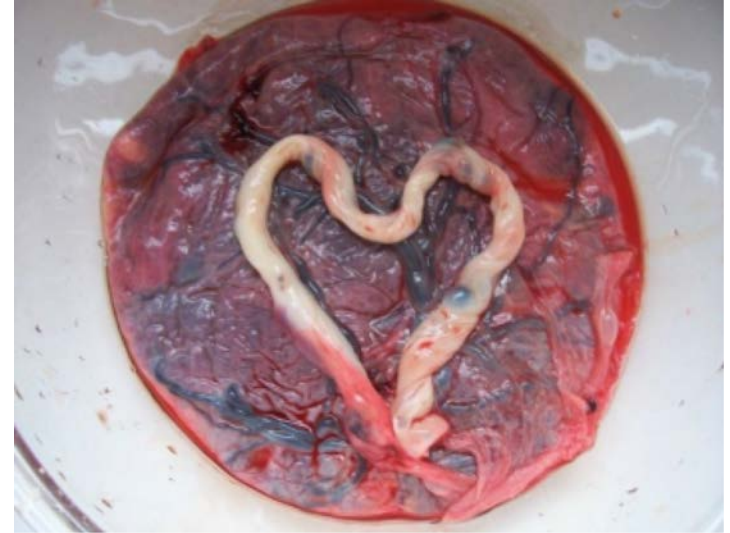
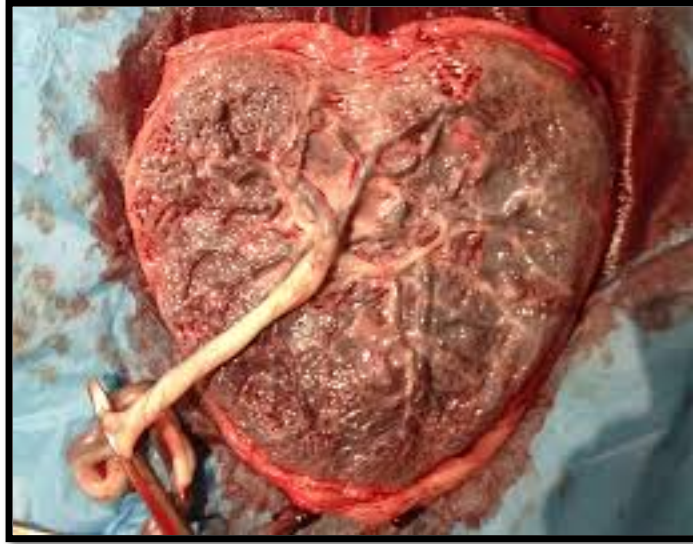
N. Scott Adzick, M.D., Elizabeth A. Thom, Ph.D., Catherine Y. Spong, M.D., John W. Brock III, M.D., Pamela K. Burrows, M.S., Mark P. Johnson, M.D., Lori J. Howell, R.N., M.S., Jody A. Farrell, R.N., M.S.N., Mary E. Dabrowiak, R.N., M.S.N., Leslie N. Sutton, M.D., Nalin Gupta, M.D., Ph.D., Noel B. Tulipan, M.D., Mary E. D'Alton, M.D., and Diana L. Farmer, M.D., for the MOMS Investigators\*

N Engl J Med 2011; 364:993-1004 | [March 17, 2011](#)

# Surgery + Bioengineering



# Placenta



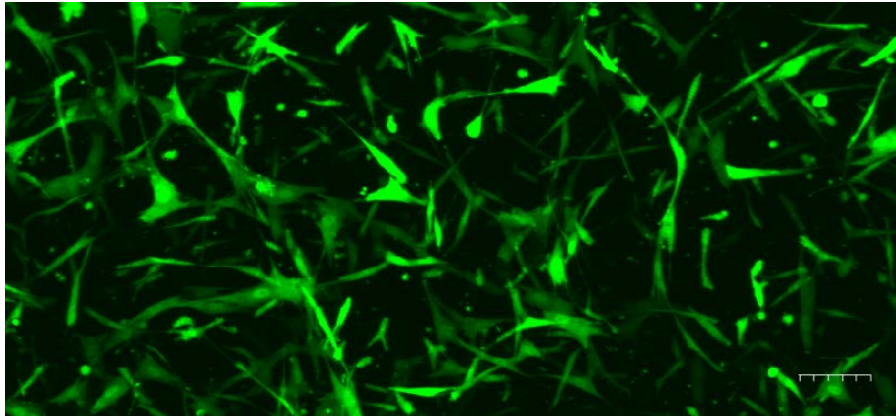
Discarded Placenta  
(Term)

Donated Placenta  
(8-24 weeks)

Chorionic Villus  
Sampling (CVS)  
procedure  
(10-12 weeks)

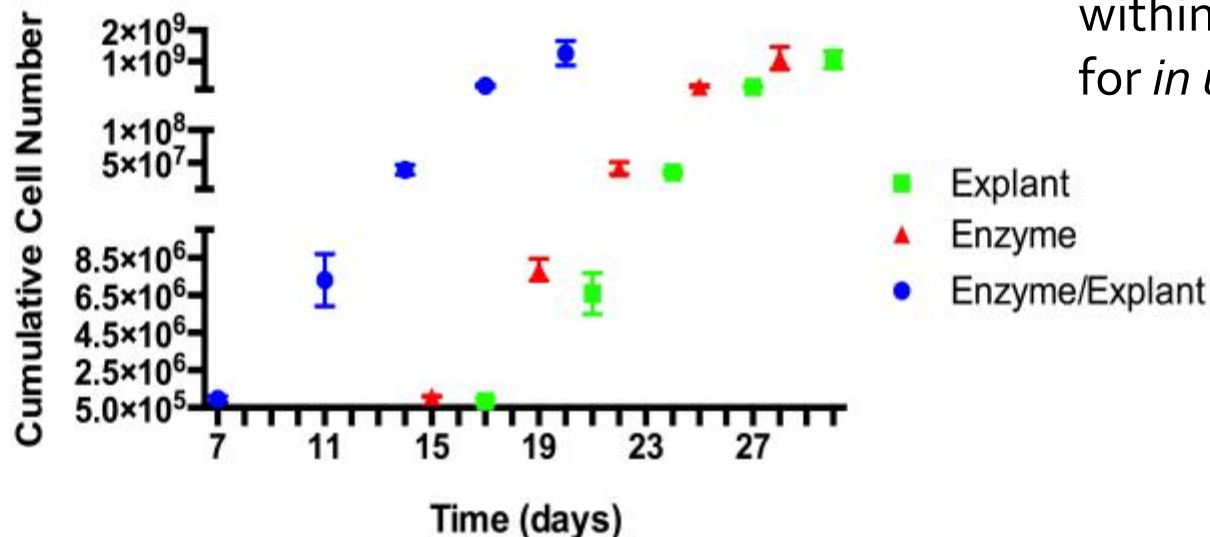
# Placenta-derived Mesenchymal Stromal Cells

## (PMSCs)



## Unique properties

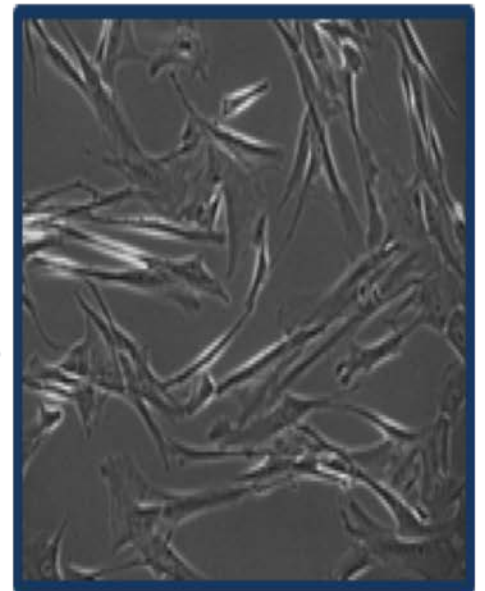
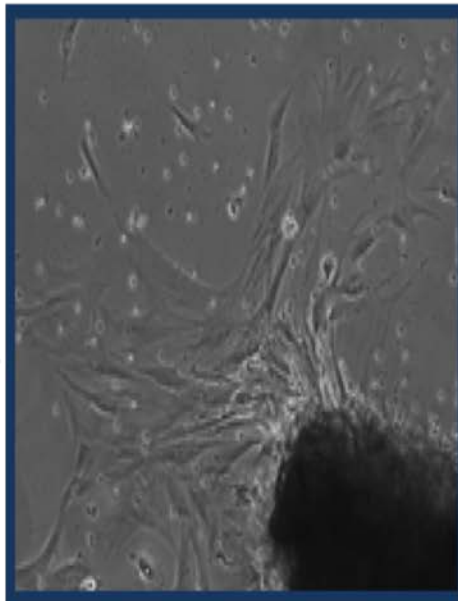
- Fetal origin
- Important **development** related functions
- Largely **expandable**- reach a sufficient number within the time window for *in utero* treatment





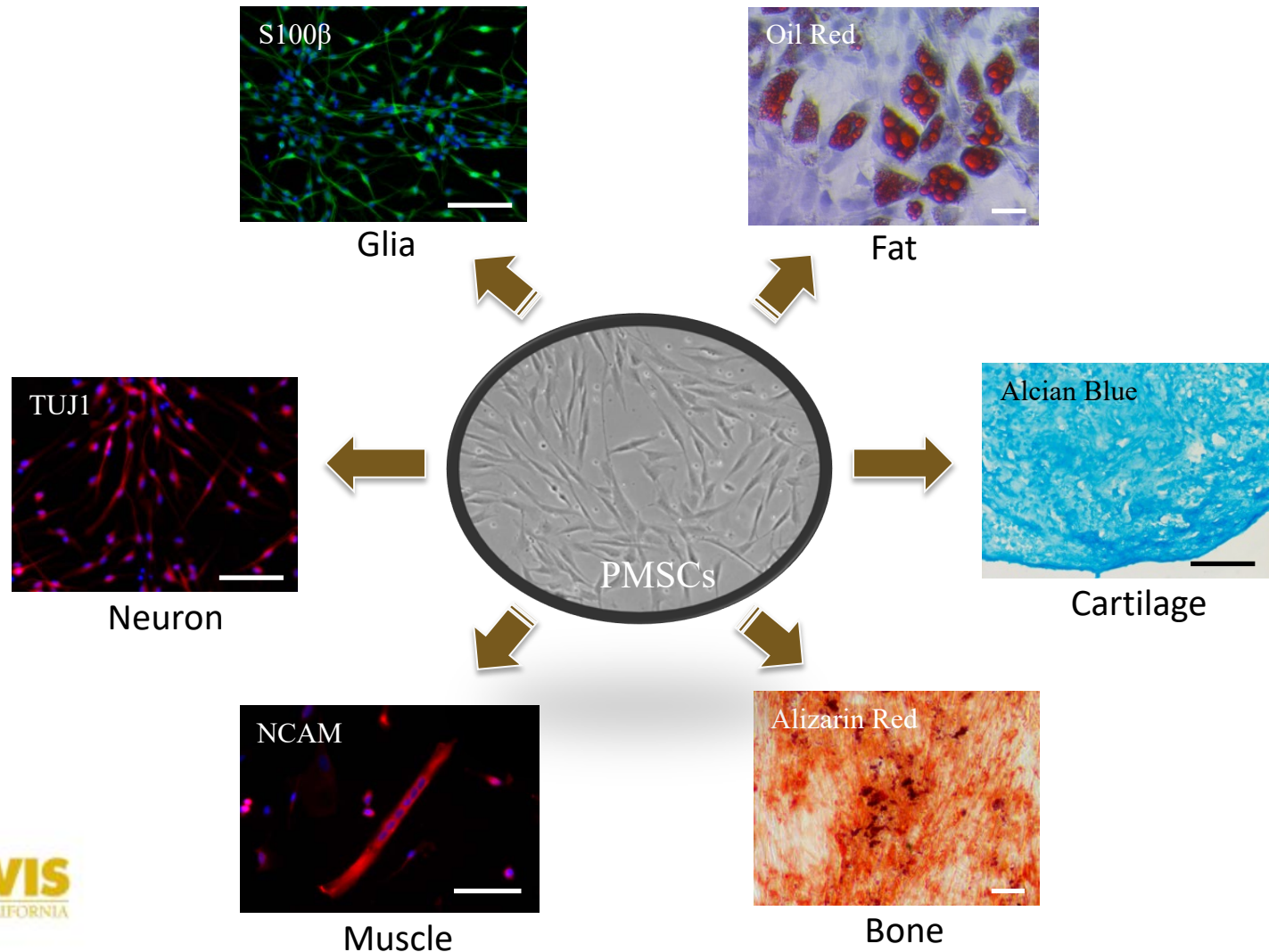
# Placental Tissue

Tissue dissection, plating and migration

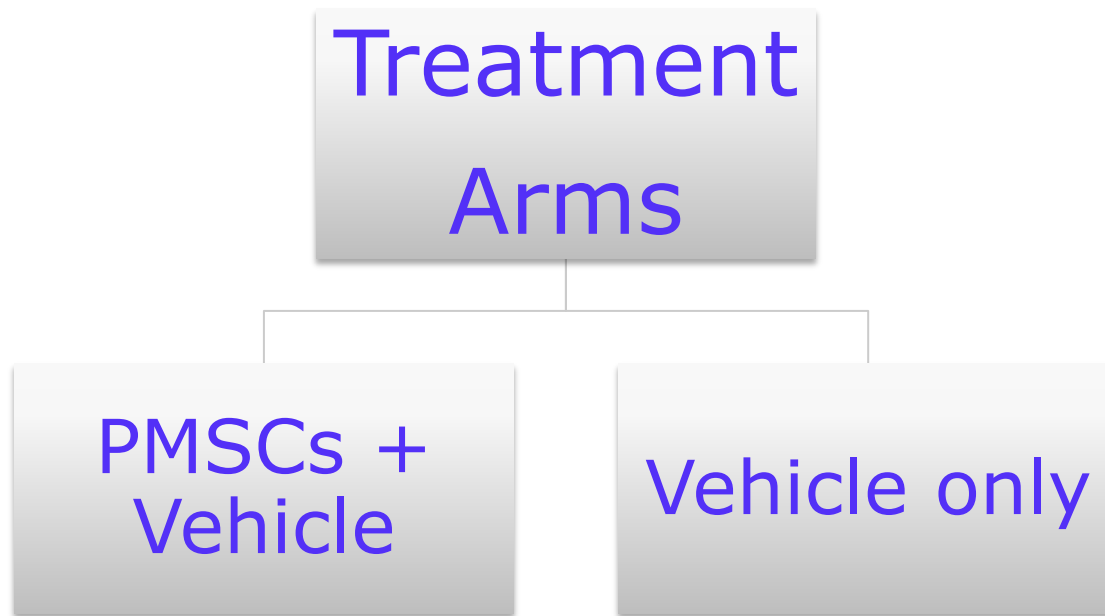


# PMSCs- Multipotency

To replace damaged, diseased, or absent tissues



# MMC Defect Repair



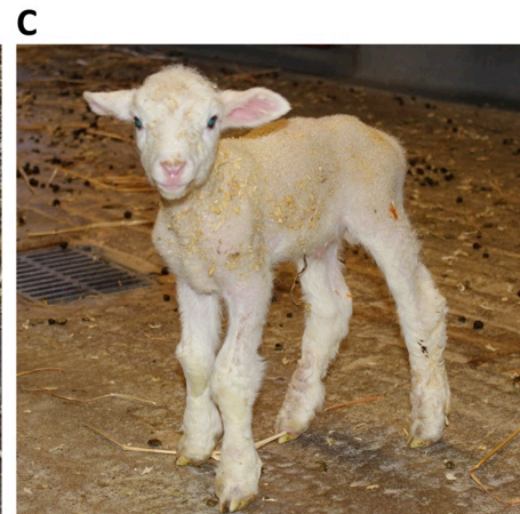
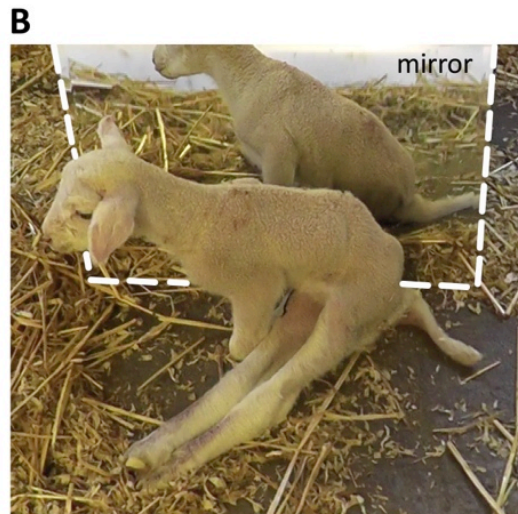
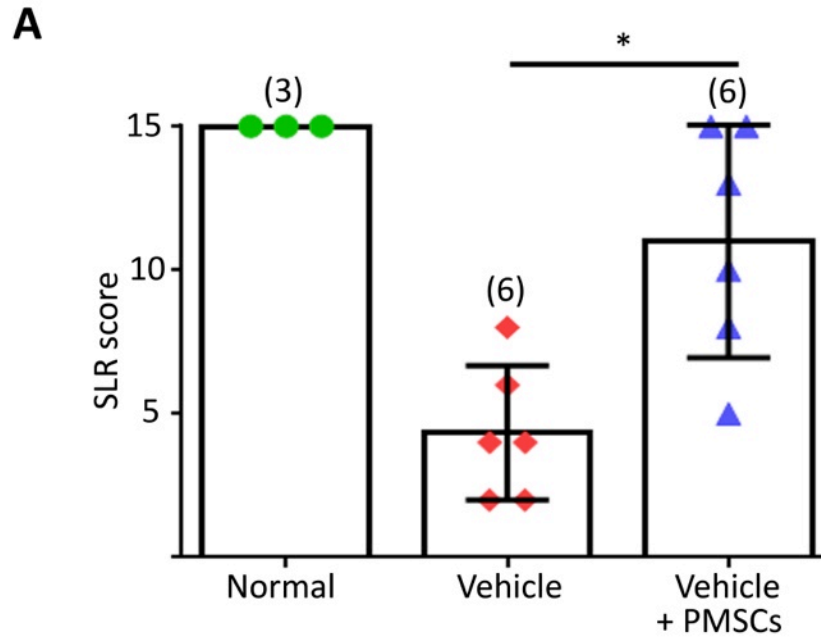
## Representative Behavioral Data

Twin Lambs with Myelomeningocele from the Same Ewe

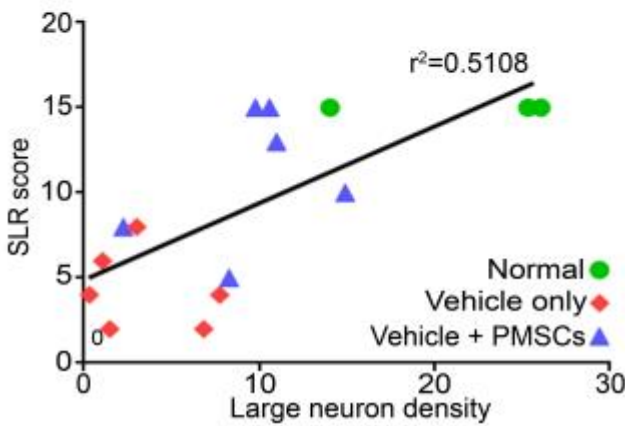
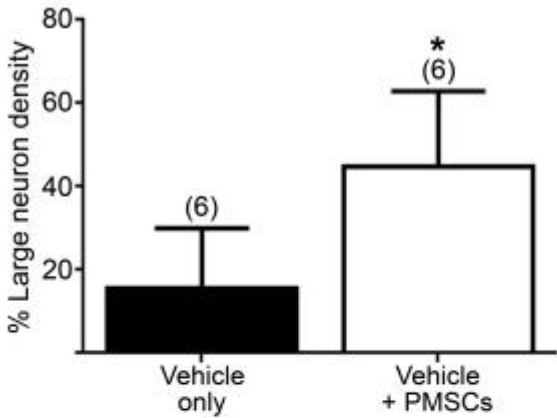
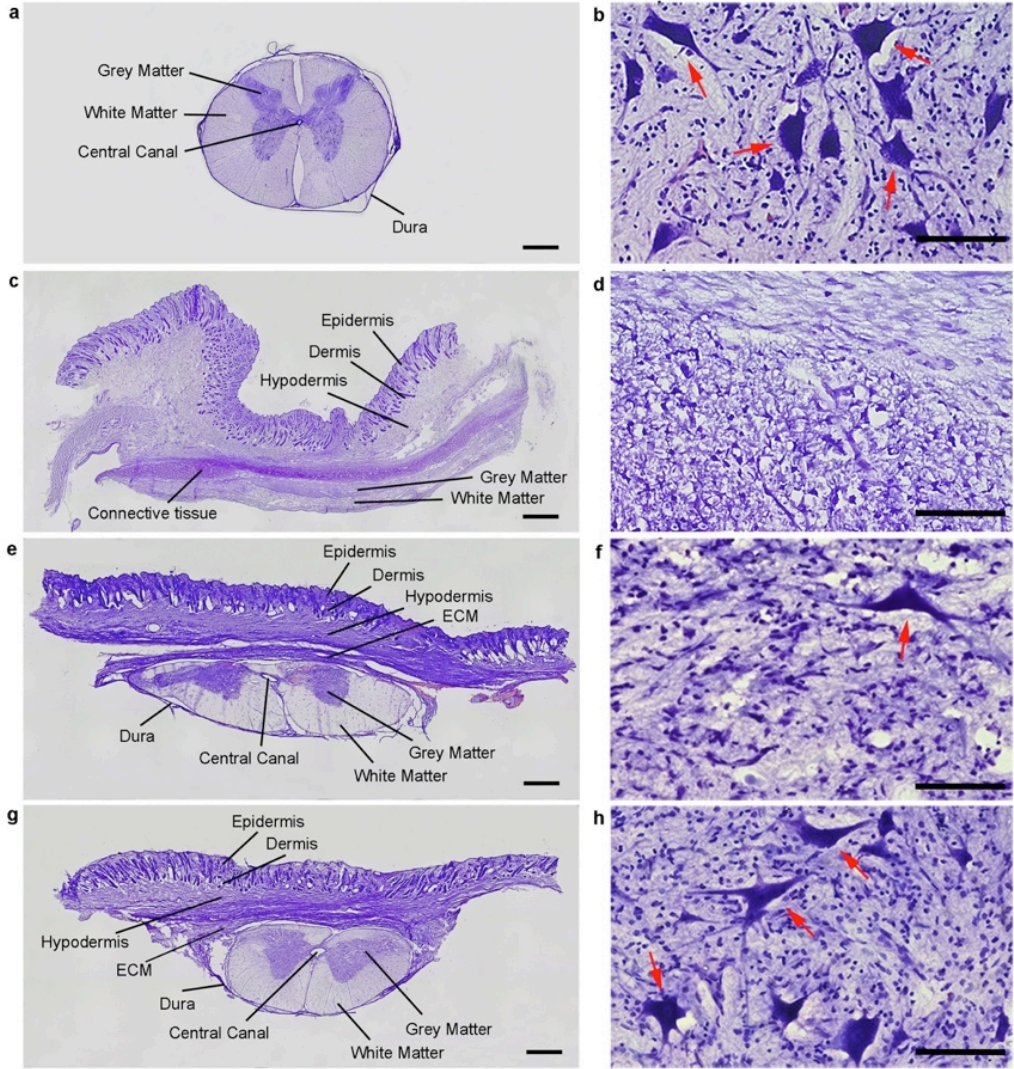
MMC25A: Matrix + C-mpSCs

MMC25B: Matrix only

# In Utero PMSC Treatment Cures MMC Paralysis

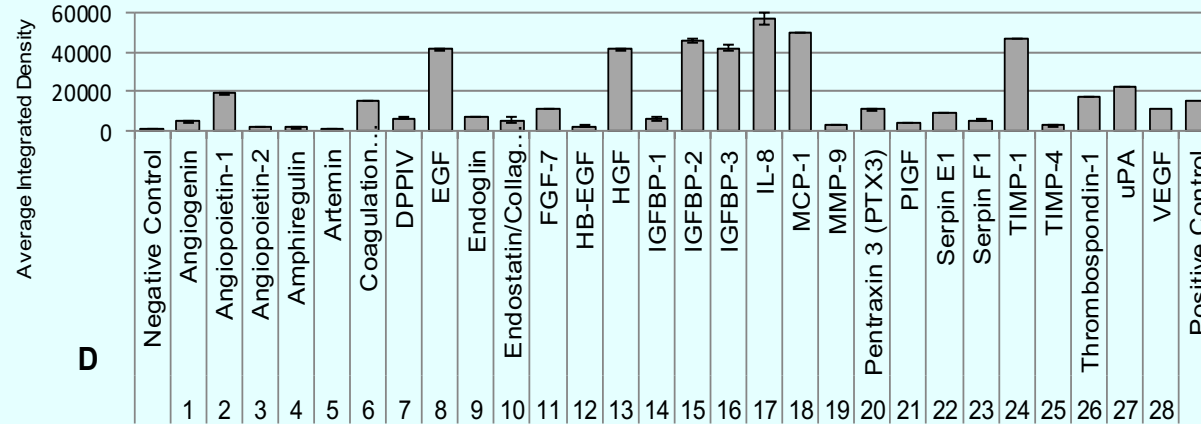
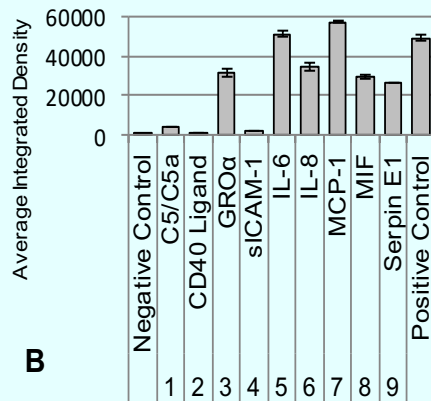
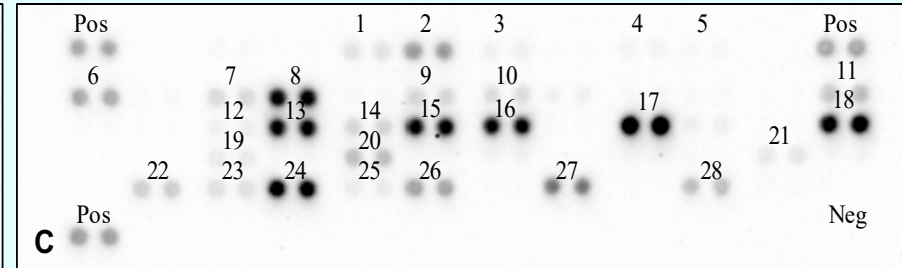
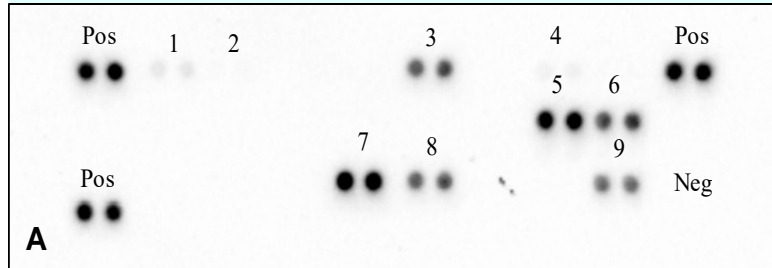


# Histopathological Analysis



# PMSCs- Paracrine Secretion

To induce healing or regeneration of nearby tissues

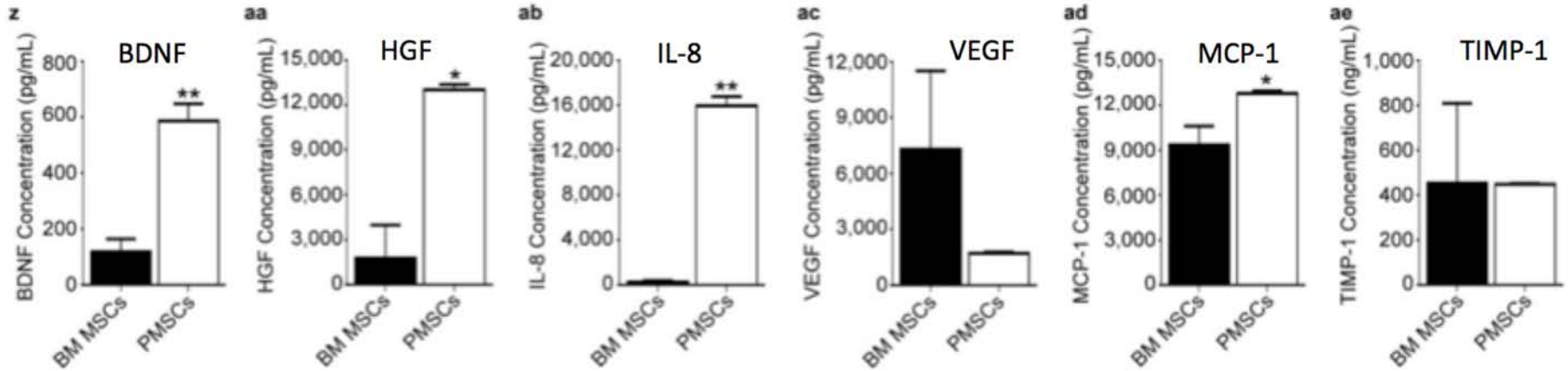


Immunomodulatory factors

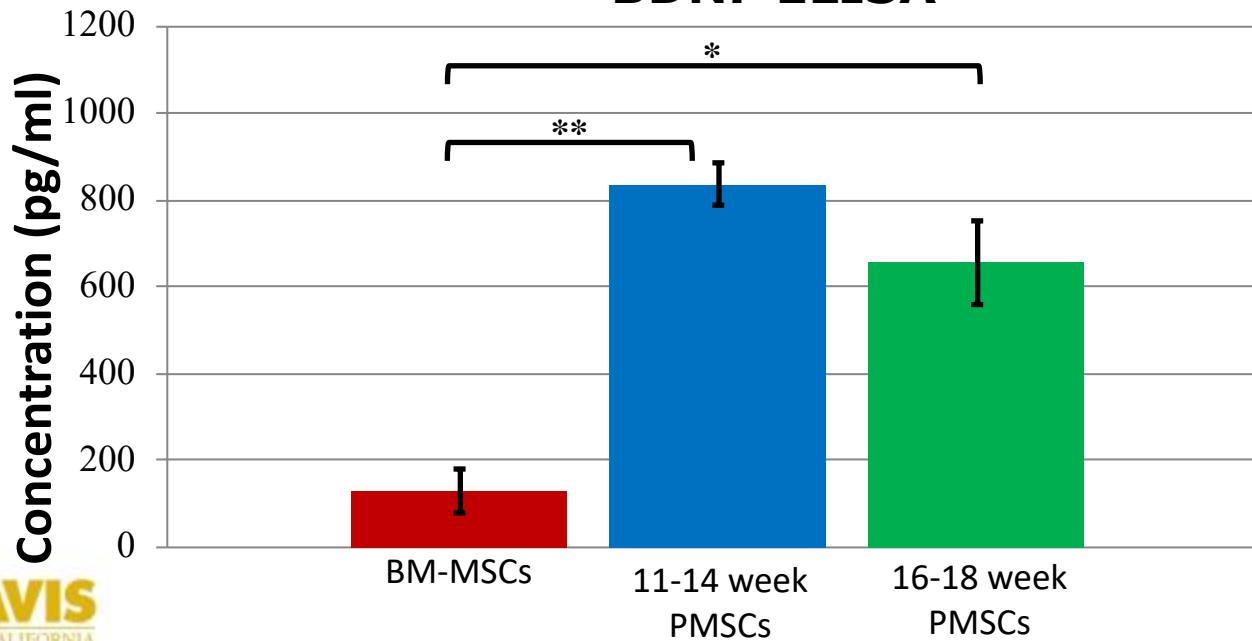
Tissue remodeling factors

Human Cytokine Array

# PMSCs- Paracrine Secretion

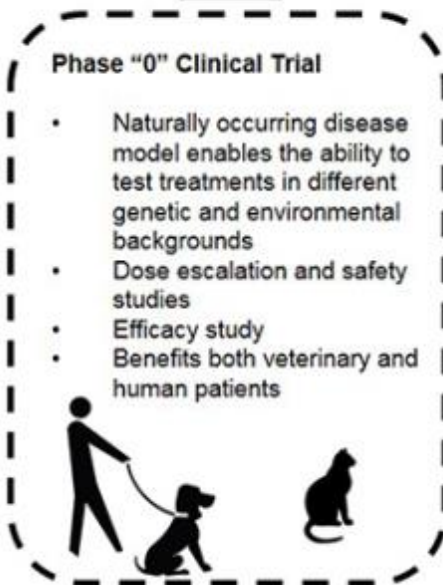
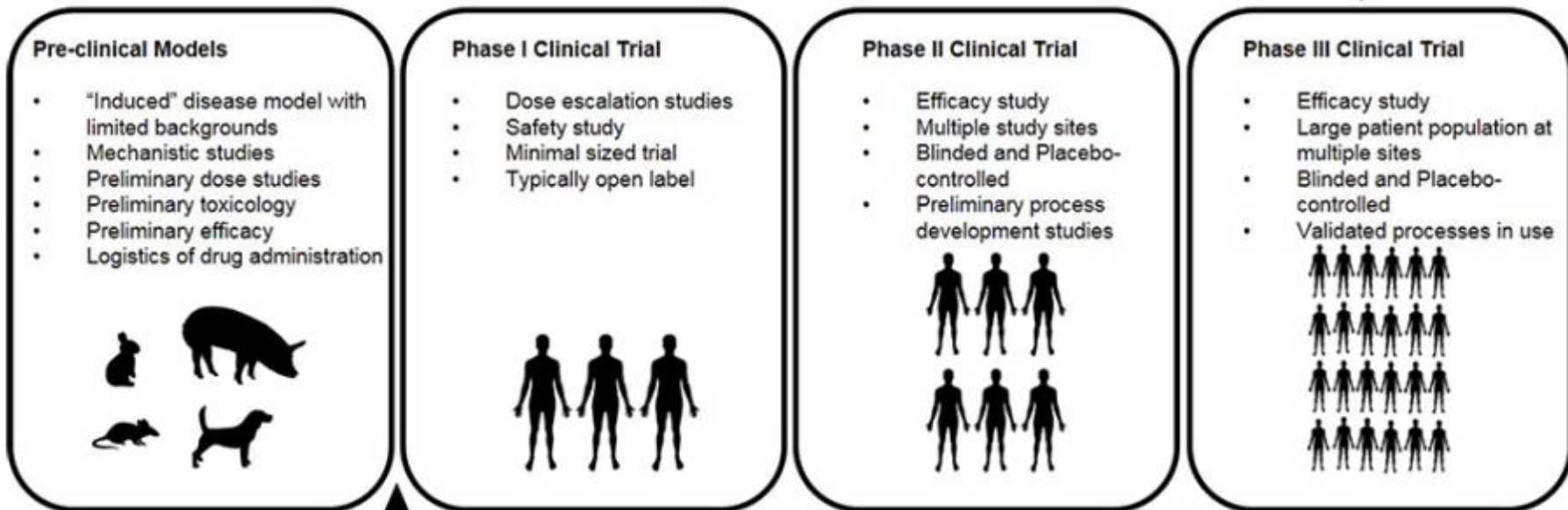


## BDNF ELISA



\*\*  $P < 0.01$ ;  
\*  $P < 0.05$



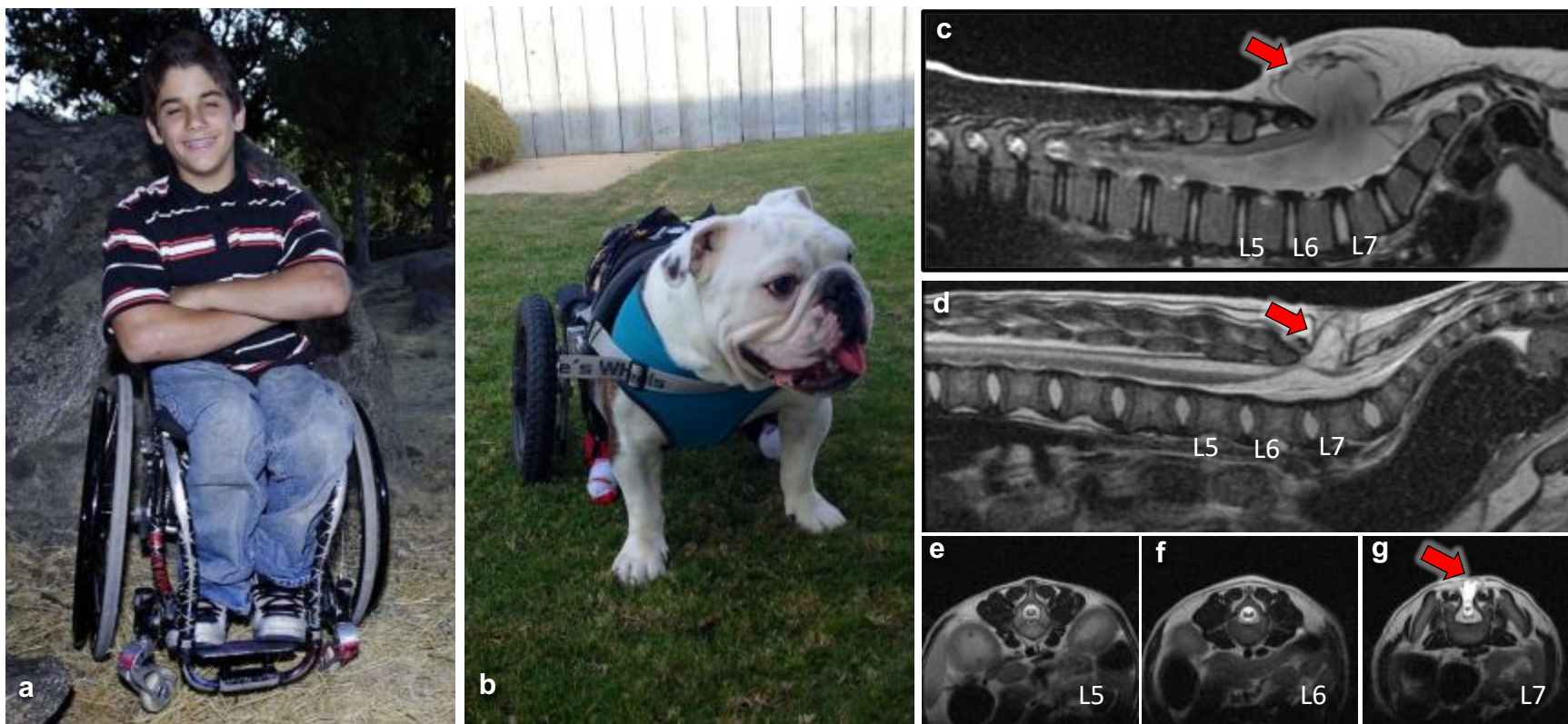


A "paradigm shift" for clinical translation





# A Comparison of Human and Canine Spina Bifida

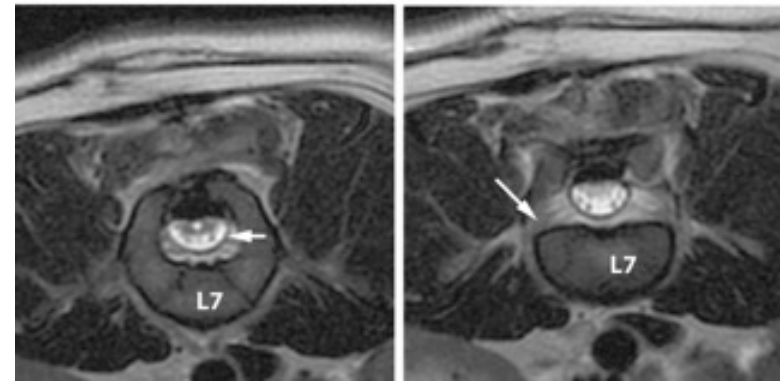
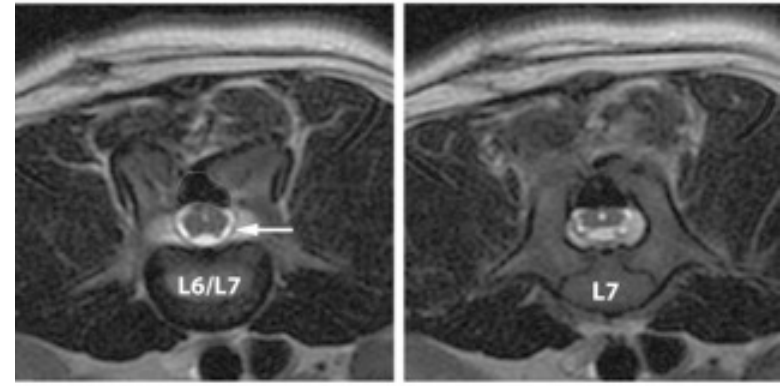
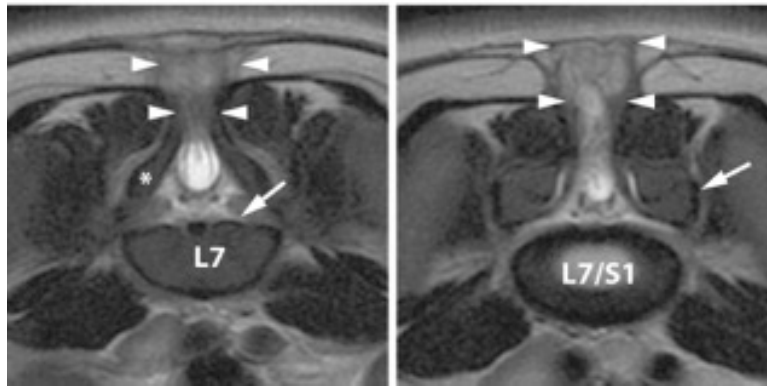
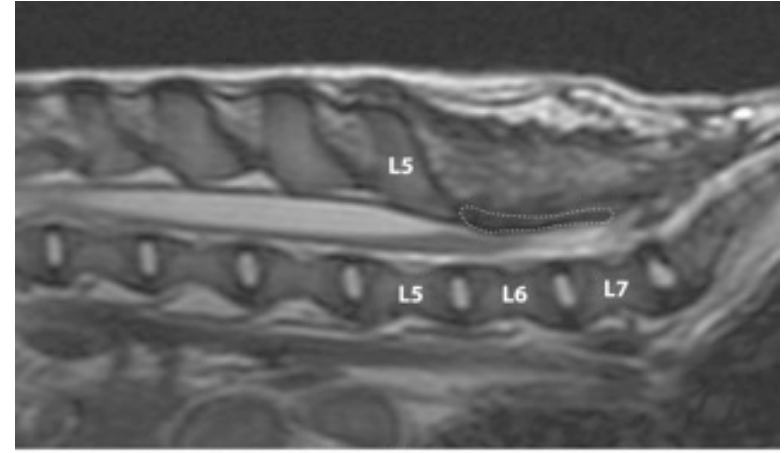
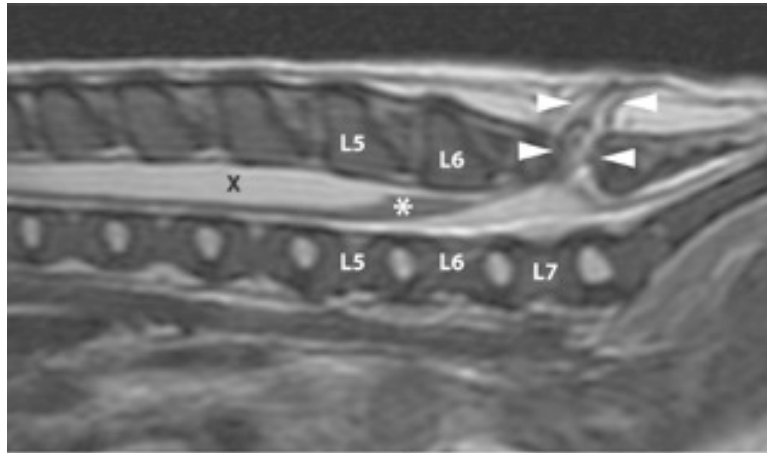


Humans and canines affected by SB share the same clinical symptoms including lower extremity/hind limb paralysis and bladder/bowel incontinence (a-b). Comparison of magnetic resonance imaging (MRI) also demonstrates similarities between human (c) and canine (d-g) SB lesions. These similarities include congenital absence of the lumbar spinous process and herniation of the spinal cord and meninges (indicated by red arrows in c, d, g). MR imaging sagittal sections (c, d); transverse sections (e-g). Image (c) was from a 3-year old human SB patient. Case courtesy of Dr. Mahmoud Yacout Alabd, Radiopaedia.org, rID: 39982. Images (d-g) were obtained from a 9-week old canine SB patient at the UC Davis Veterinary Medicine Teaching Hospital (VMTH).



# MRI

## Pre-operative vs. 8w post-operative



Preoperative sagittal (A) and transverse (B and C) T2W MR images versus 8w post-operative sagittal (D) and transverse (E-H) T2W MR images of an English bulldog SB puppy.

# Pre-treatment (9 weeks old)



**SB Bulldog 001  
(Male)**

Pre-Op Evaluation

**February 14, 2017**

# 8 weeks Post-Op (17 weeks old)

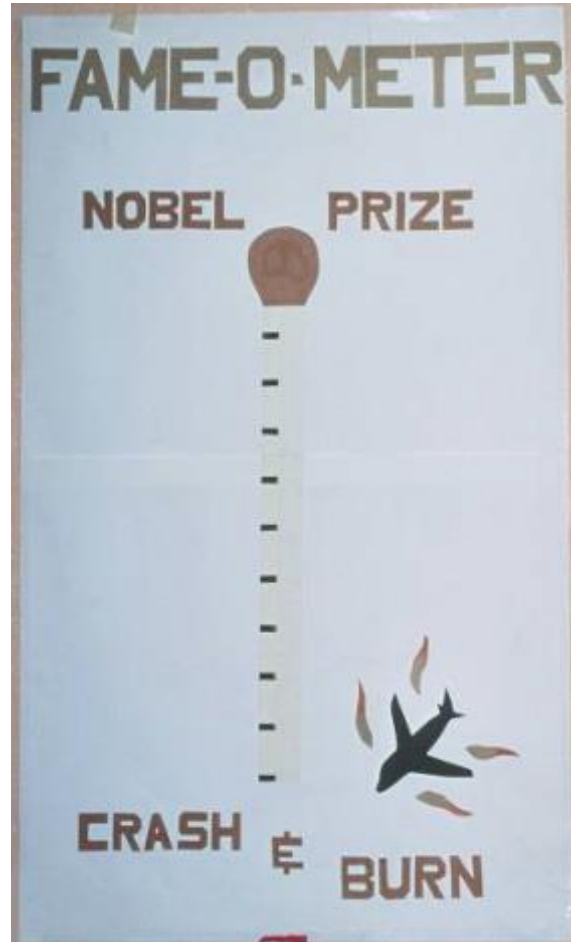


**SB Bulldog 001 (Male)**

8-Week Post-Op Evaluation

**April 13, 2017**

# FAME-O-METER





# Acknowledgements

## Surgical Bioengineering Lab




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for Children®



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- Erin Brown, MD
- Ben Keller, MD
- James Becker, MD
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- Zoe Saenz, BS
- Volodymyr Ryzhuk, MA



**Cell and Tissue Engineering Lab**  
*"Transform cells, repair tissues"*



**BRAIN AND SPINAL INJURY CENTER**  
San Francisco General Hospital  
University of California at San Francisco



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**“The future belongs to those who believe in the beauty  
of their dreams.”**

***Eleanor Roosevelt***

