



From the Barn to the Bedside:
The CuRe Trial

Diana L. Farmer, MD, FACS, FRCS

Distinguished Professor and Pearl Stamps Stewart Endowed Chair
Chair, Department of Surgery, UC Davis School of Medicine
Founder and Co-Director, Center for Surgical Bioengineering
Chief of Pediatric Surgery, Shriners Hospitals – Northern California

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Cellular therapy for in utero Repair of Myelomeningocele

CIRM
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Fetal Therapy

Dedicated to Treating Disease Before Birth

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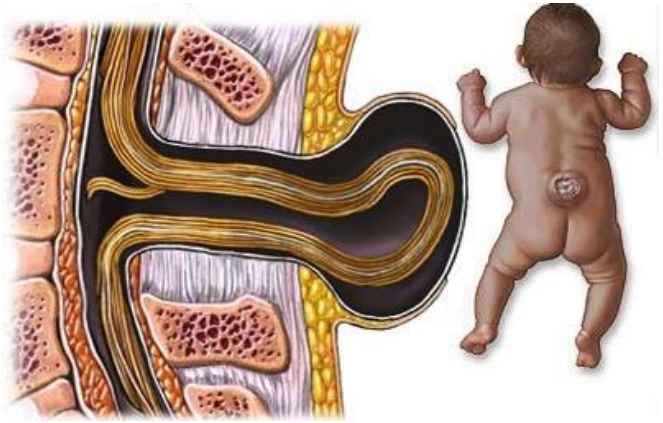
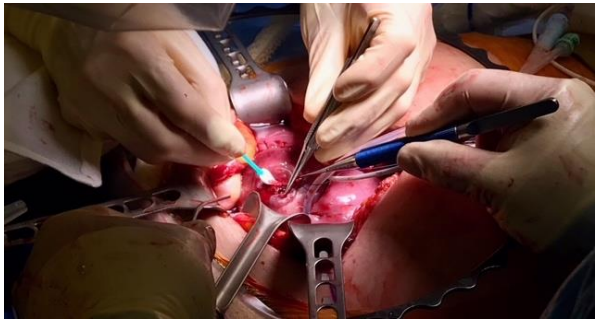
Spina Bifida

(Myelomeningocele, MMC)

- 2nd most common birth defect
- Afflicts **4 children** born in the United States **every day**
- CA prevalence - **2.43** (95% CI 2.38-2.48)
- Lifelong disability: **paralysis**, incontinence, cognitive disability
- $200 million annual cost for children with MMC in the US





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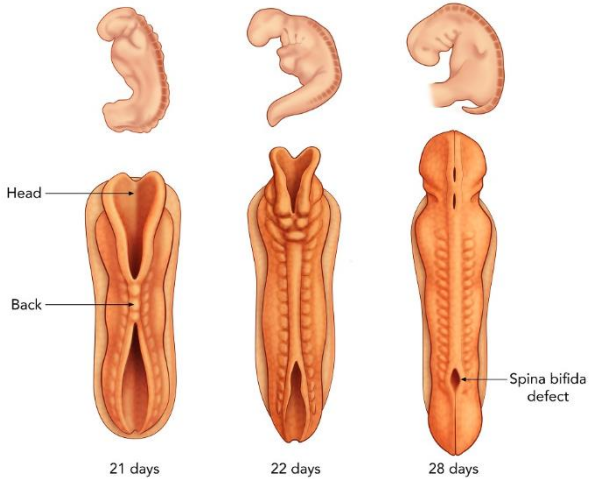
Two-hit Hypothesis

- **Primary defect in neurulation**



- **Secondary intrauterine damage**
  - Mechanical trauma to exposed spinal cord
  - Amniotic fluid toxicity

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NIH-sponsored Clinical Trial

- Randomized Clinical Trial started March 2002
- Prenatal Surgery versus Postnatal Surgery
- 200 women planned enrollment
- Decreased need for VP shunt (40% vs. 82%)
- Improved motor function at 30 months of age
- However, 58% of children still with disabling lower extremity paralysis

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MOMS
Management of Myelomeningocele Study

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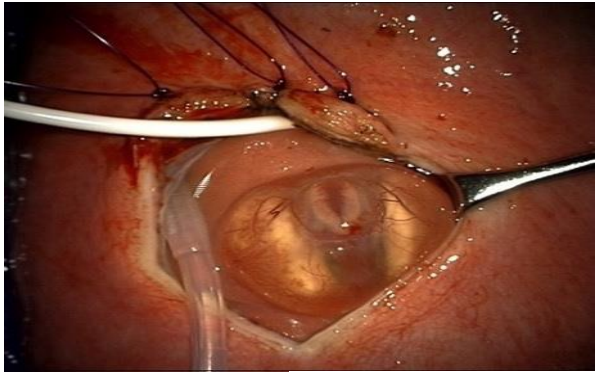
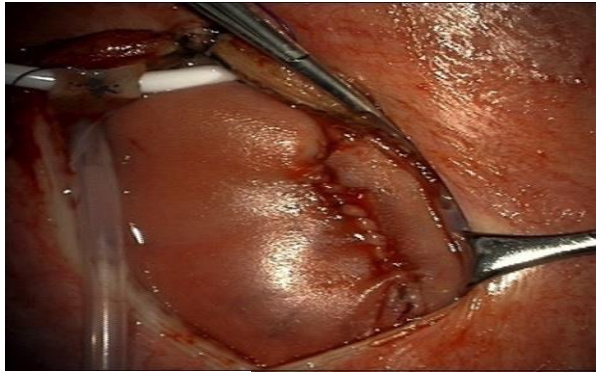
Fetal Treatment of Spina Bifida





The NEW ENGLAND JOURNAL of MEDICINE

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*

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How can we do it better?

- **We hypothesize that we can further improve distal neurological function and repair the damaged spinal cord by incorporating biologically active STEM CELLS:**
  - Neural tissue replacement?
  - Neuronal rescue / protection?

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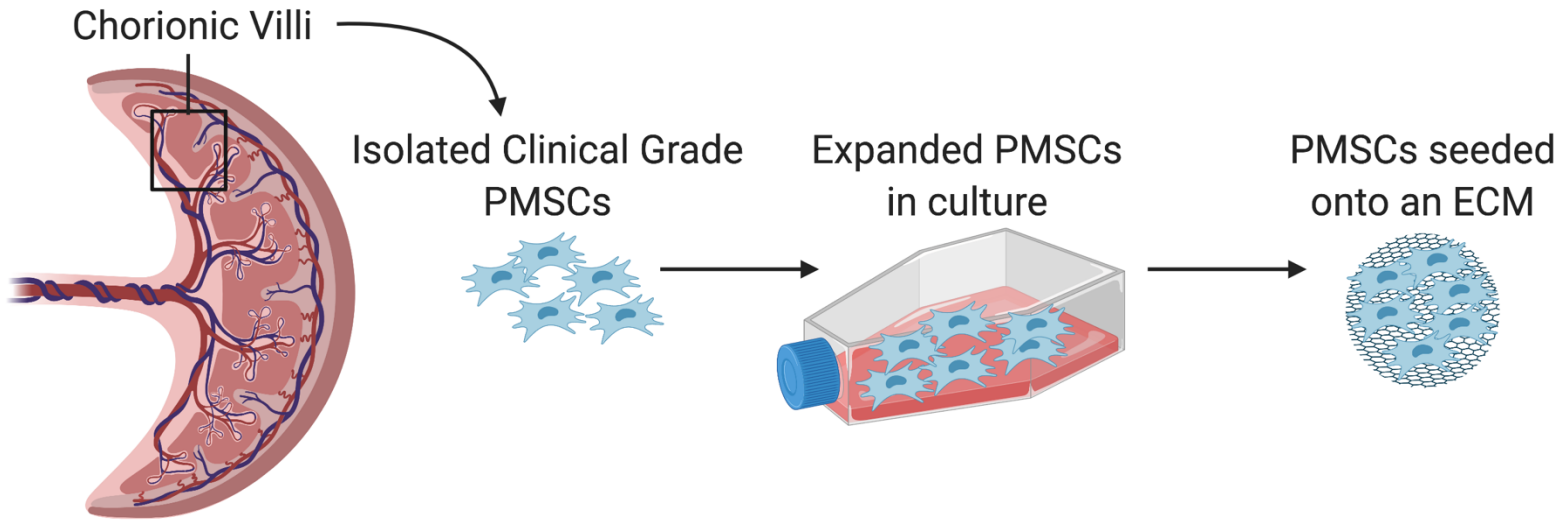
Placental Mesenchymal Stromal Cells (PMSCs)



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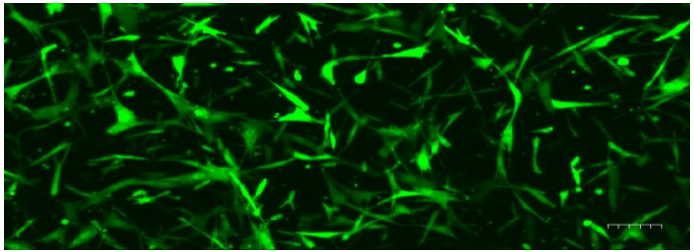
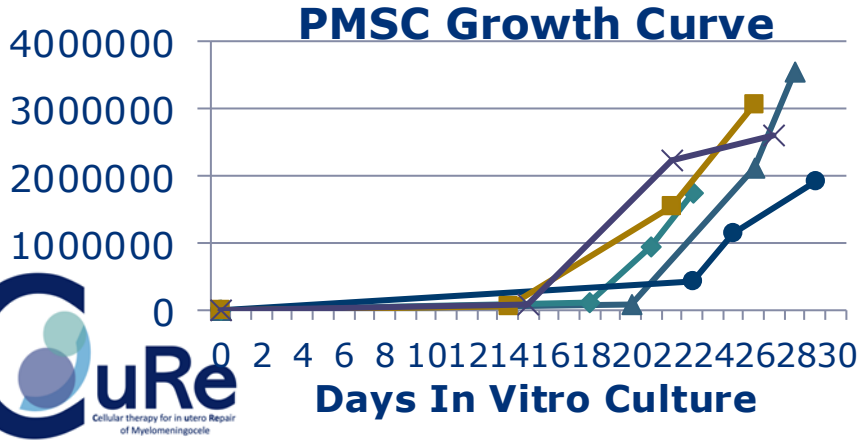
Placenta-derived Mesenchymal Stromal Cells (PMSCs)





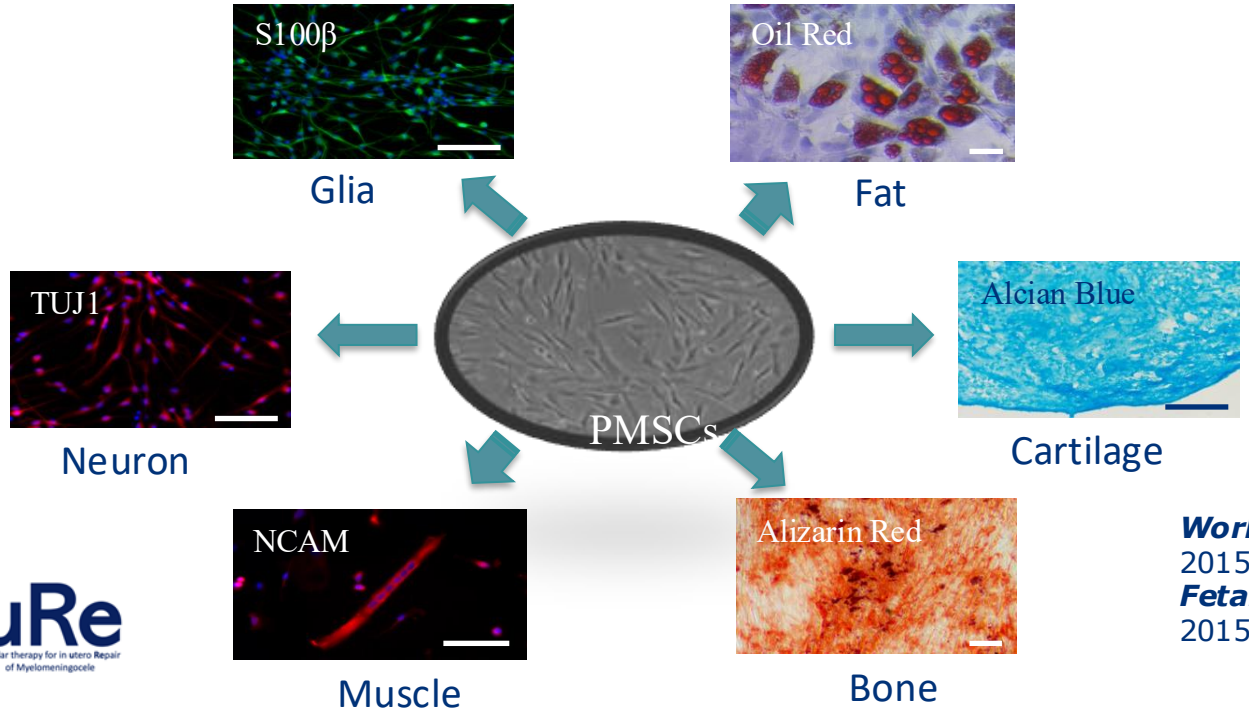
Unique properties

- **Developmentally relevant** fetal cells
- Largely **expandable**- reach a sufficient number within the time window for *in utero* treatment

World Journal of Stem Cells. 2015 Jan; 7(1): 195-207.

PMSCs- Multipotency

To replace damaged, diseased, or absent tissues



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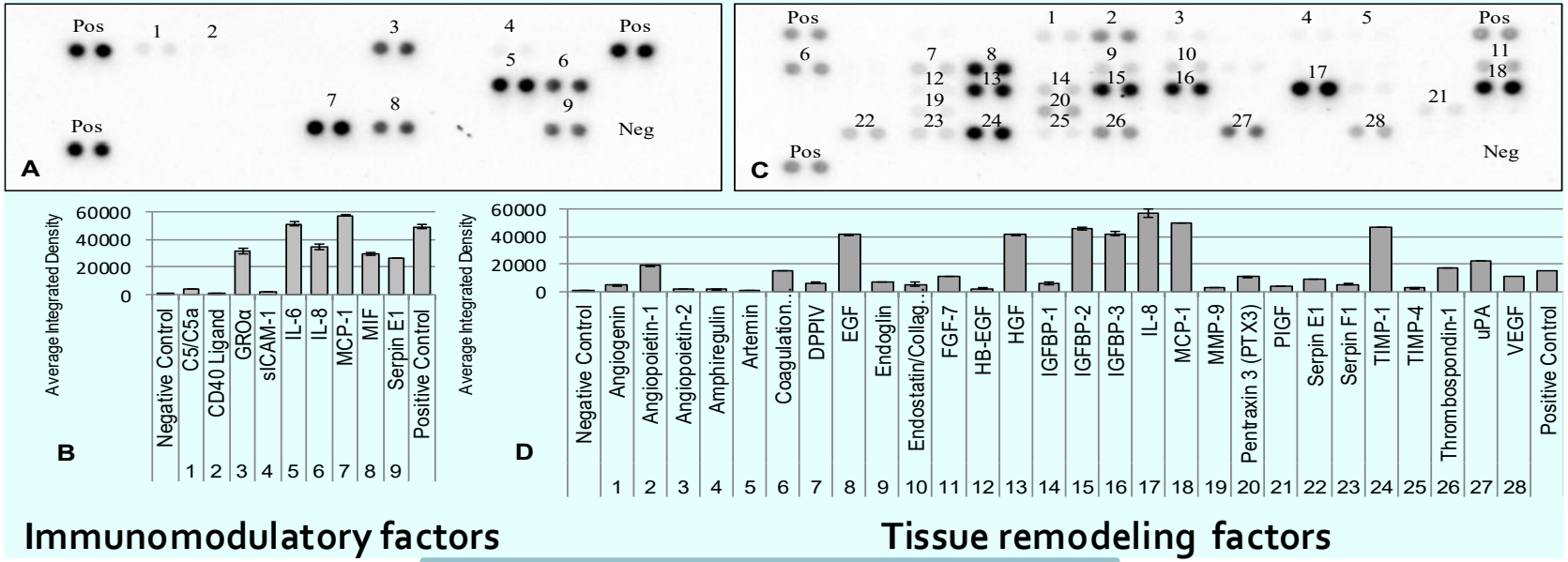
World Journal of Stem Cells. 2015 Jan; 7(1): 195-207.
Fetal Diagnosis and Therapy. 2015. Jul 7. Epub

PMSCs- Paracrine Secretion

To induce healing or regeneration of nearby tissues



Immunomodulatory factors **Tissue remodeling factors**

Human Cytokine Array

World Journal of Stem Cells. 2015 Jan; 7(1): 195-207.
Stem Cells Translational Medicine. 2015 Jun; 4(6):659-69.

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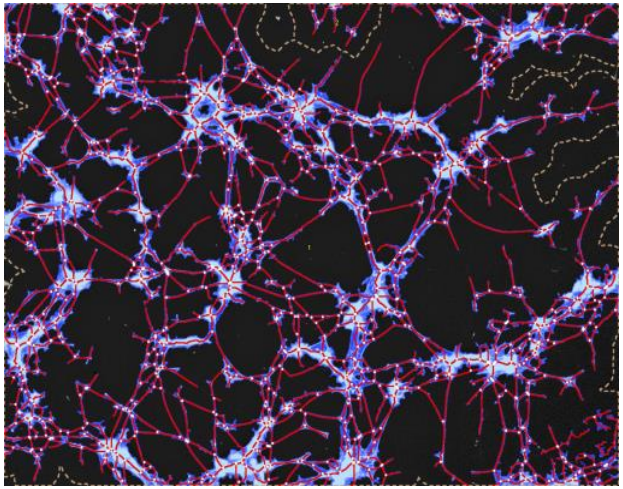
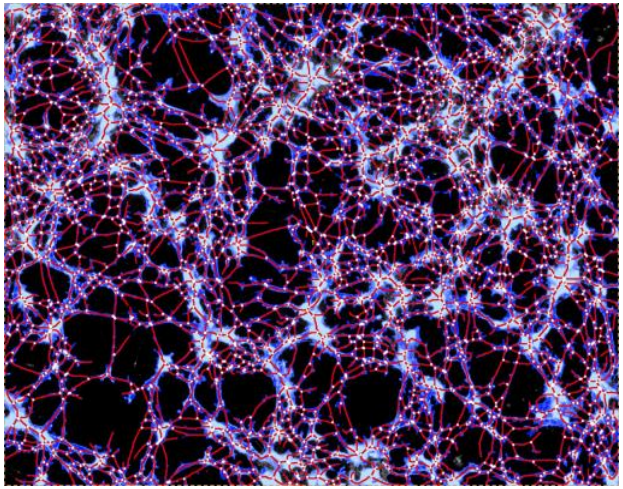
PMSCs- Neuroprotection



No placenta stem cells



With placenta stem cells

- Increased neuron branching

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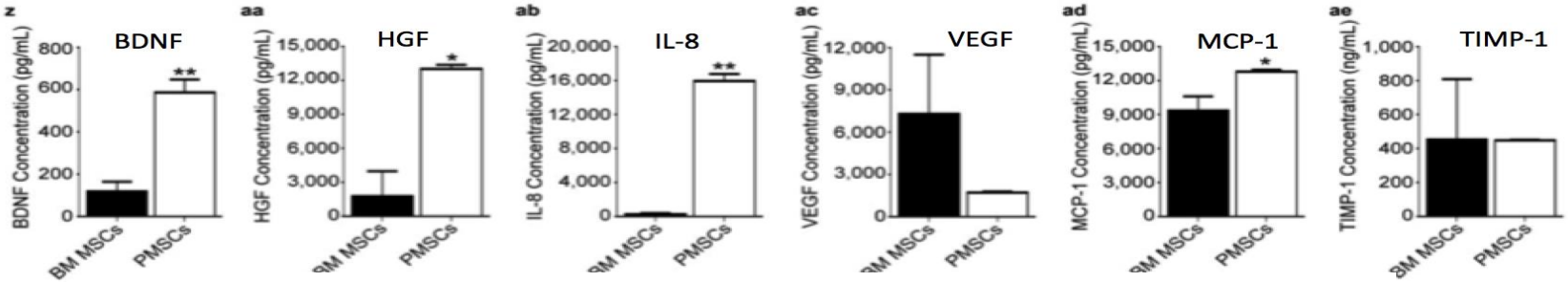
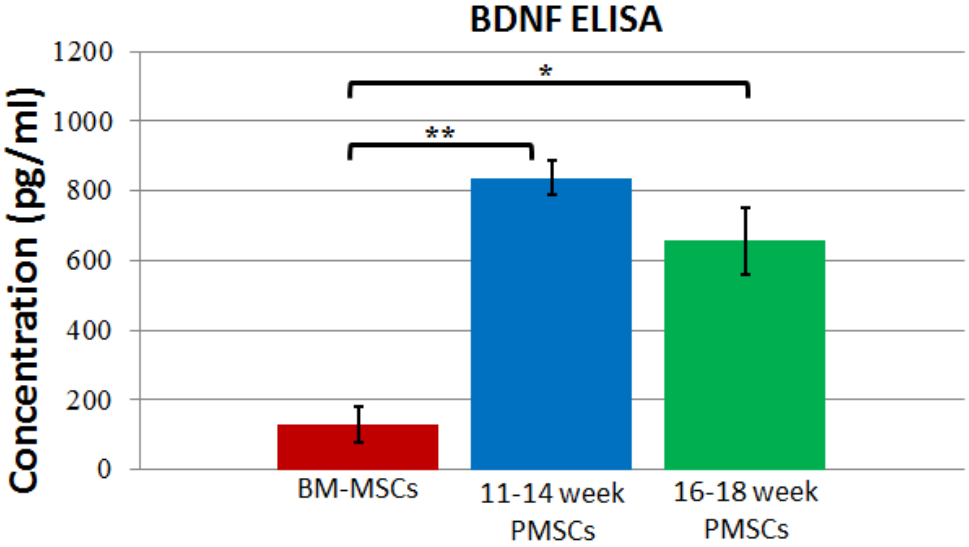
PMSCs- Paracrine Secretion





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

World Journal of Stem Cells. 2015 Jan; 7(1): 195-207.
Stem Cells Translational Medicine. 2015 Jun; 4(6):659-69.

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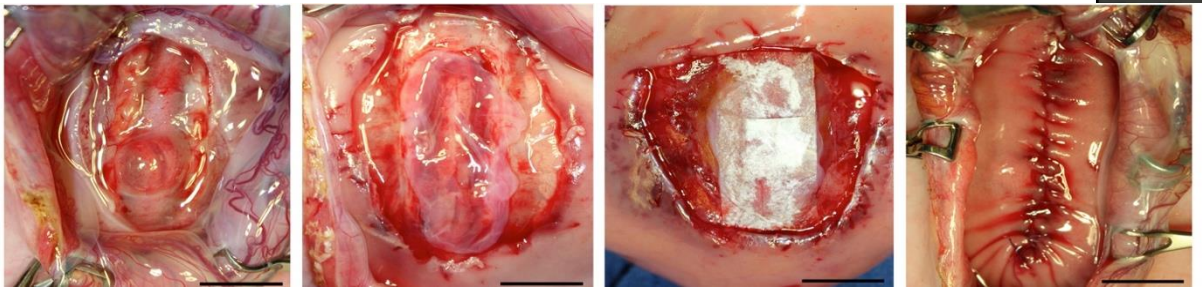
In Utero Stem Cell Treatment of Spina Bifida

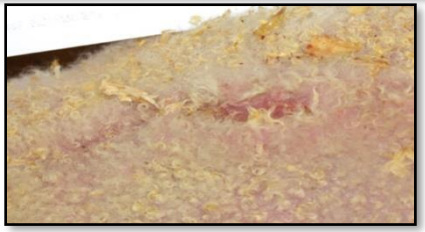
Experimental Set-up:

- Well-established fetal lamb model
- Defect creation: GA-75
- Defect repair: GA-100

- Groups:
  - No repair
  - Skin repair
  - Repair with matrix only
  - Repair with matrix + human PMSCs



Before Repair | Repair w/ Stem Cells | ECM Patch | Skin Closed



Live birth at GA146
Closed skin

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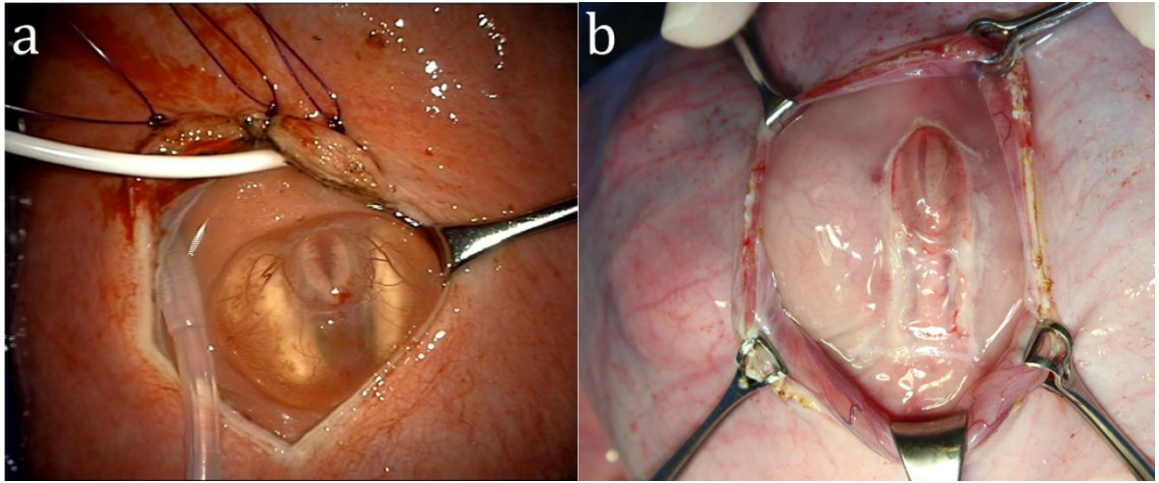
The Journal of Pediatric Surgery. 2014; 49(1):133-7.
Stem Cells Translational Medicine. 2015; 4(6):659-69.
The Journal of Pediatric Surgery. 2015;50(4):617-21.

Ovine MMC vs. human MMC

Human

Sheep
(100 days pregnancy)



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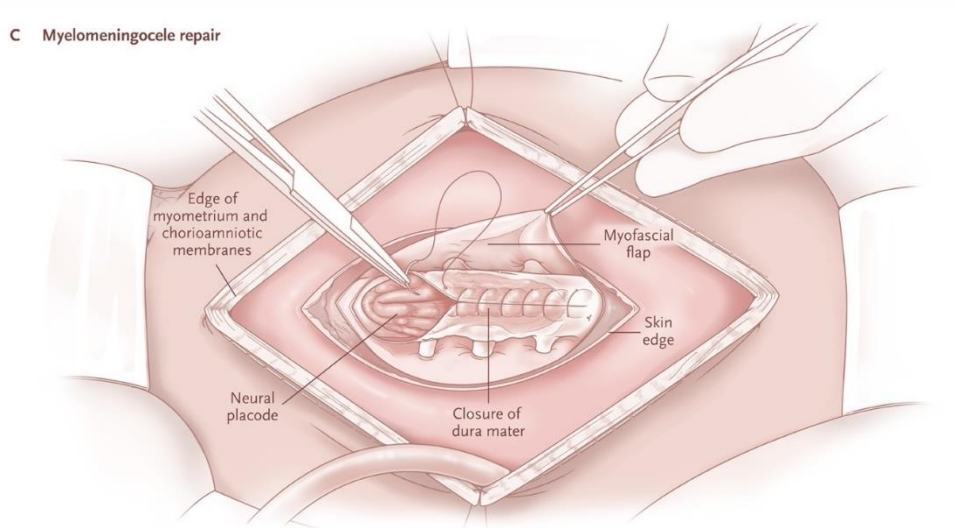
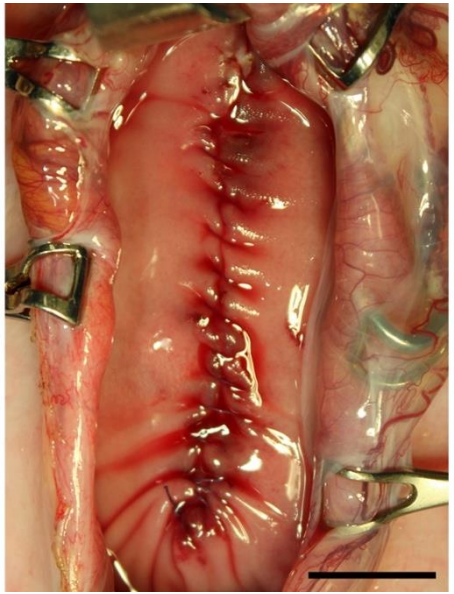
Ovine MMC Repair

Fetal repair by closing dura and skin over the defect





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N Engl J Med 2011; 364:993-1004.

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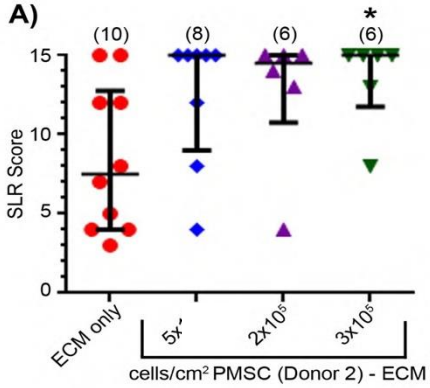
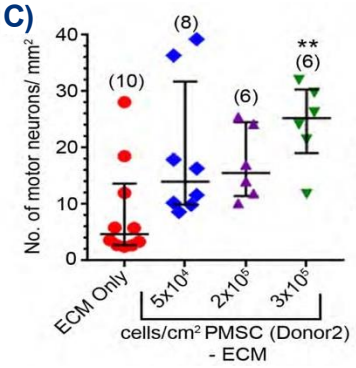
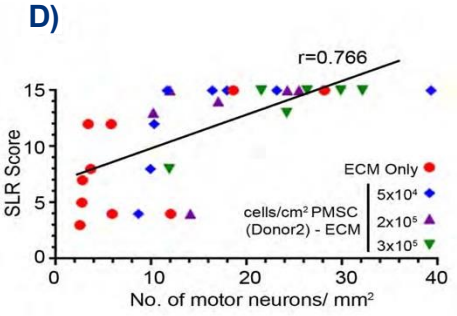
In Utero PMSC Improved Paralysis







Wang, et al., ***Stem Cells Translational Medicine***. 2015
Kabagambe, et al., ***The Journal of Pediatric Surgery***. 2018
Vanover, et al., ***The Journal of Pediatric Surgery***. 2019

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In Utero PMSC Treatment Cures MMC Paralysis

Representative Behavioral Data

Twin Lambs with Myelomeningocele from the Same Ewe

MMC25A: Matrix + C-mpSCs
MMC25B: Matrix only

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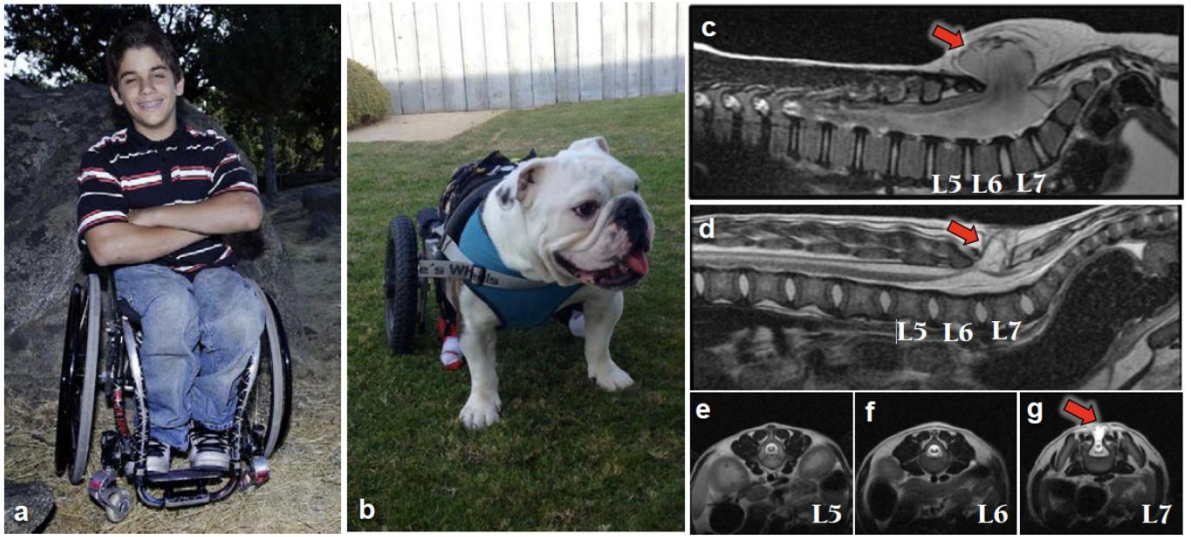
Canine MMC model

- Post-birth repair model for moms who don't qualify for fetal surgery
- Animal model test stem cell treatment for post birth repair
- English bulldogs prone to naturally occurring spina bifida



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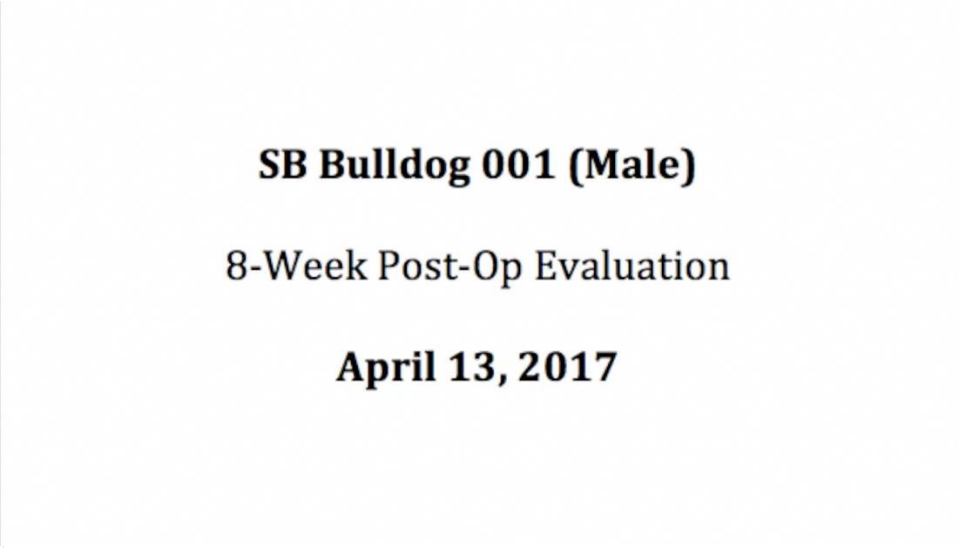
Canine MMC model

SB Bulldog 001
(Male)

Pre-Op Evaluation

February 14, 2017



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Grant Award Details

Placental Stem Cells for the In Utero Treatment of Spina Bifida

Grant Type:	Preclinical Development Awards
Grant Number:	PC1-08103
Project Objective:	Development of placental stem cells as a candidate for the in utero treatment of spina bifida.
Investigator:	**Name:** Diana Farmer **Institution:** University of California, Davis **Type:** PI
	Name: Aijun Wang **Institution:** University of California, Davis **Type:** Co-PI
Disease Focus:	Neurological Disorders, Pediatrics, Spina Bifida
Human Stem Cell Use:	Adult Stem Cell
Cell Line Generation:	Adult Stem Cell
Award Value:	$2,182,146
Status:	Active

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Promising Approach to Curing Spina Bifida Gets $5.6 Million from Stem Cell Agency

NOVEMBER 15, 2018 / KEVIN MCCORMACK / 1 COMMENT

Every day in the U.S. four children are born with spina bifida. It is the most common cause of lifelong paralysis and also frequently leads to other serious health problems affecting the bowel and bladder. The impact on families is enormous. A new approach to repairing the defect that causes spina bifida was today awarded $5.66 million by the Board of the California Institute for Regenerative Medicine (CIRM).

In spina bifida the spinal cord doesn't form properly, in many cases leaving a section of it open, exposing tissues and nerves. The current standard of care is surgery, but even this leaves almost 60% of children unable to walk independently. Diana Farmer MD, and Aijun Wang PhD at U.C. Davis will use mesenchymal stem cells, taken from a donor placenta, and place them on a form of synthetic scaffold over the injury site in the womb. Tests in animals show this approach was able to repair the defect and prevent paralysis.

Ovine Efficacy Study

- **Lambs delivered at 141 days gestation by Cesarean Section**
- **Functional assessments occurred postnatally at:**
  - 2-4 hrs
  - 24 hrs
  - 48 hrs

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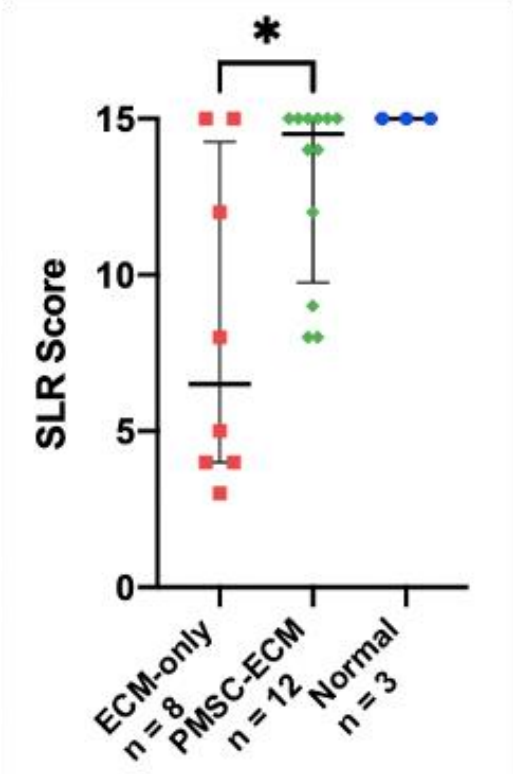
Motor function results



PMSC-ECM treated lamb

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IND Submission

- Clinical protocol finalized and IND submitted (June 2020)
- FDA Approved (August 2020)
- Funding Secured, CIRM CLIN2 (October 2020)

State stem cell agency funds clinical trial for spina bifida treatment

First human clinical trial combines surgery and cellular therapy

(SACRAMENTO) — California's stem cell agency (CIRM) today awarded a $9 million grant to Diana Farmer and Aijun Wang to help launch the world's first human clinical trial using stem cells to treat spina bifida, a birth defect that occurs when the spine and spinal cord don't form properly.

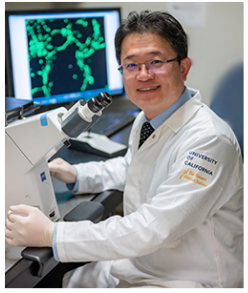
Diana Farmer

Farmer, professor and chair of surgery at UC Davis Health, in collaboration with Wang, recently received approval from the U.S. Food and Drug Administration (FDA) for their groundbreaking treatment that combines fetal surgery with a special stem cell therapy.

Now, with the generous CIRM funding, the team will be able to launch their one-of-a-kind treatment in the coming months. It will be delivered while the baby is still in the mother's womb (in utero). The complex procedure, with its unique use of a stem cell "patch," could improve outcomes for children who are born with the severe form of spina bifida known as myelomeningocele.

Farmer and Wang will generate a type of stem cells -- mesenchymal stem cells -- from placental tissue. The cells are known to be among the most promising type of cells in regenerative medicine.

"This is truly an historic opportunity," said Jan Nolta, director of the UC Davis Stem Cell Program and the university's Institute for Regenerative Cures. "Drs. Farmer and Wang will be using stem cells that are known to be safe and helpful in repairing damaged tissues. We often call them the 'paramedics' of the body because they produce healing factors, which are crucial for treating something like spina bifida."


Aijun Wang

Wang, an associate professor of surgery and biomedical engineering, and co-director of UC Davis' surgical bioengineering laboratory, is a leader in developing cellular therapies that promote tissue regeneration. He and Farmer hope to successfully repair the spina bifida birth defect that occurs when the protective tissue around a baby's developing spinal cord fails to fully close before birth.

Without treatment, an exposed spinal cord causes severe neurological damage. The resulting problems can be a range of lifelong cognitive, mobility, urinary and bowel disabilities. The birth defect affects approximately 1,500 to 2,000 children each year in the U.S.

Farmer has been working for years to gain approval and funding for a human clinical trial to address spina bifida. She launched the UC Davis Children's Hospital Fetal Care and Treatment Center (with pediatric surgeon Shinjiro Hirose) and UC Davis Children's Surgery Center several years ago. The new CIRM grant complements previous funding from the agency. The earlier grant enabled Farmer and Wang to manufacture and evaluate their specialized stem cells for safety and efficacy.

The UC Davis Health team is preparing to recruit pregnant women whose babies have been diagnosed with spina bifida to test the combined surgery and stem cell procedure. The clinical trial is expected to begin in early 2021.

Clinical trial participants will be treated at the centers Farmer helped establish. UC Davis Children's Hospital and Shriners Hospitals for Children — Northern California will provide the follow-up care.

All News Releases»

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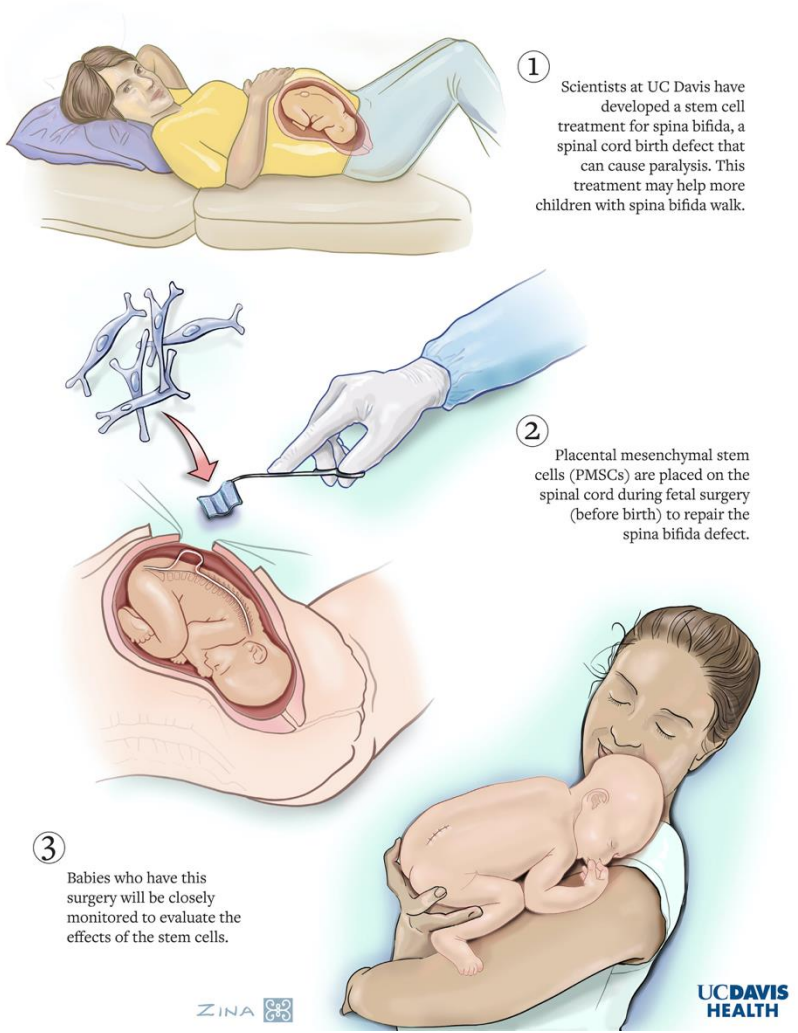
CALIFORNIA'S STEM CELL AGENCY

The CuRe Trial:
Cellular Therapy for in **u**tero **Re**pair of Myelomeningocele



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The CuRe Trial: Cellular therapy for in utero repair of myelomeningocele

- Phase 1/2a prospective study to determine:

Safety

Preliminary Efficacy

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Fetal Care and Treatment Center

916-794-2229
FCTC@ucdavis.edu

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The CuRe Trial: Cellular therapy for in utero repair of myelomeningocele

- 35 patients prenatally diagnosed with an MMC lesion and eligible for standard fetal surgical repair
- Phase 1: First 6 patients
  - February 2021–December 2022
- Phase 2a: 29 additional patients
  - January 2023–February 2024

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Stem Cell Transfer

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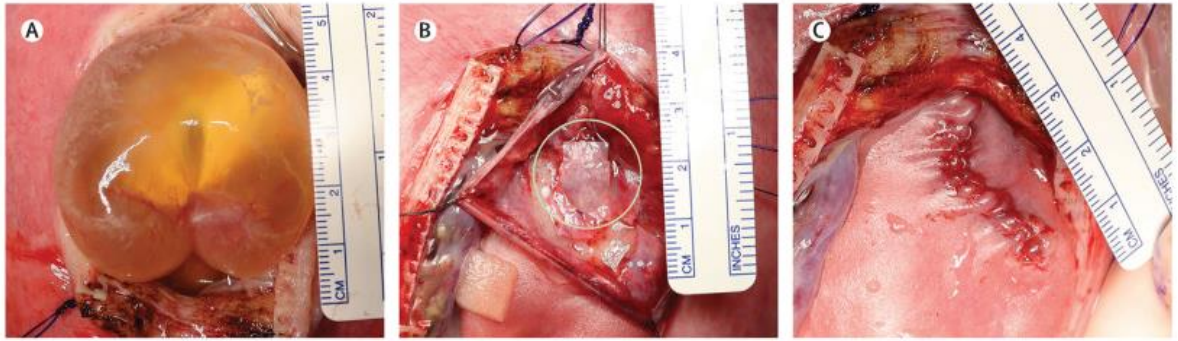

Figure 2 Intraoperative steps of in-utero myelomeningocele repair using PMSC-ECM

THE LANCET

Feasibility and safety of cellular therapy for in-utero repair of myelomeningocele (CuRe Trial): a first-in-human, phase 1, single-arm study

Prof Diana L Farmer, MD [a,b,c,d] · Priyadarsini Kumar, PhD [b,c] · Elizabeth Reynolds, MD [a,b] · Su Yeon Lee, MD [a,b] · Amy B Powne, MSN [a,d] · Christopher D Pivetti, MS [b] · Prof Marike Zwienenberg, MD [d,e] · Amelia S McLennan, MD [d,f] · Prof Jan A Nolta, PhD [g] · Erin G Brown, MD [a,d] · Payam Saadai, MD [a,d] · Prof Shinjiro Hirose, MD [a,d] · Prof Aijun Wang, PhD [b,c,h] Show less

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Acknowledgements

UC Davis Center for Surgical Bioengineering:
Dr. Aijun Wang (PhD)
Dr. Jan Nolta (PhD)
Gerhard Bauer (GMP Facility Director)
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Alicia Hyllen (Junior Specialist)
Meiby Ramos (Junior Specialist)
Bill Gruenloh (Regulatory Director)
Dr. Sarah Strokes (Surgical Resident)
Dr. Jordan Jackson (Surgical Resident)
Dr. Christina Theodorou (Surgical Resident)
Dr. Edwin Kulubya (Surgical Resident)
Dr. Dake Hao (Postdoctoral Scholar)
Dr. Kewa Gao (Postdoctoral Scholar)
Dr. Chaoxing Zhang (Postdoctoral Scholar)
Lalitha Ramasubramanian (PhD Candidate)
Kaitlin Clark (PhD Candidate)
Leora Goldbloom-Helzner (PhD Student)
Siqi He (Visiting PhD Student)
Hengyue Song (Visiting PhD Student)
Lu Lu (Visiting PhD student)
Zachary Paxton (Junior Specialist)
Nora Lelivelt (Junior Specialist)
Natalie Tobin (Junior Specialist)

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Acknowledgements

UC Davis Fetal Care & Treatment Center Team:
Dr. Shinjiro Hirose (Medical Director)
Dr. Diana Farmer (Fetal Surgeon, Surgeon-in-Chief, Chair)
Dr. Payam Saadai (Fetal Surgeon)
Dr. Erin Brown (Fetal Surgeon)
Amy B Powne (Nurse Practice Manager)
Kristi Ortiz (Lead MOSC)
Lindsay Macias (Social Worker)
Amber Lindgren (Nurse Coordinator)
Dr. Herman Hedriana (MFM Chief)
Dr. Amelia McLennan (MFM & Fetal Interventionalist)
Nia Nutt (Sonographer)
Debby Johnson (Sonographer)
Dr. Sherzana Sunderji (Director of Fetal Cardiology)
Dr. Jay Yeh (Fetal Cardiology)
Yoni Dayan (Fetal Cardiology)
Ashley Sabre (Fetal Cardiology Nurse Coordinator)
Dina Taylor-Schmidt (Principal Fetal Echo Sonographer)
UC Davis Fetal Operative Team:
Aida Benitez (CN3)
Amanda Sherwood (CN2)
Allison Horsley (CN2)
Andrew OBrien (CN2)
Frances Villote (CN2)
Tatyana Kolpakchi (CN2)
Alex Poshelyuznyy (Equipment Specialist)
Saul Gonzalez-Gudino (Equipment Specialist)
Cindy Lomperski (Anesthesia Technician)
Angela Chavez (AN1)
Kimberly Schaeffer (AN1)
UC Davis Pediatric and OB Anesthesia

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Acknowledgements

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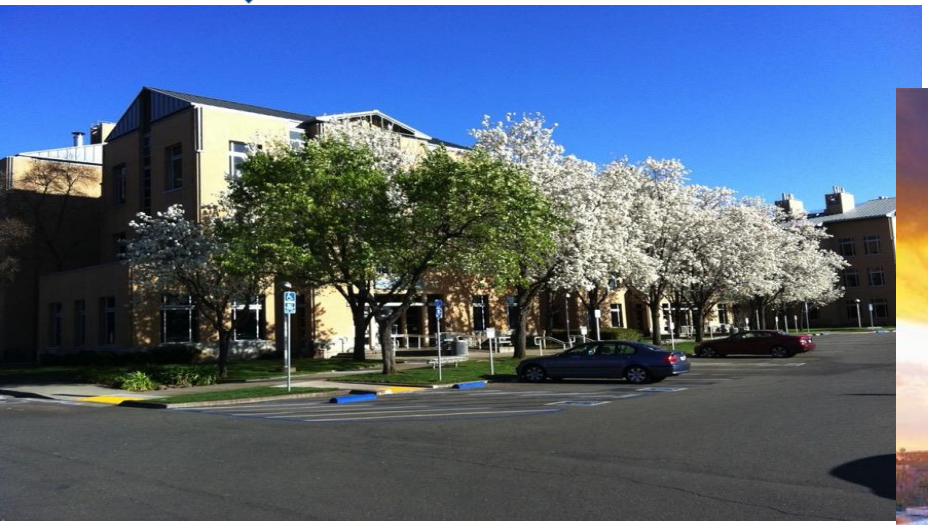

Thank You!

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Representative Behavioral Data

Twin Lambs with Myelomeningocele from the Same Ewe

MMC25A: Matrix + C-mpSCs
MMC25B: Matrix only

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UC DAVIS CHILDREN'S HOSPITAL

SB Bulldog 001
(Male)

Pre-Op Evaluation

February 14, 2017