The DoW and the Evolution of Cell Therapeutics for Trauma

From Radiation Countermeasures to Regenerative Medicine for Warfighters

Shibani Pati, MD, PhD

Professor, Laboratory Medicine and Surgery
Director Center for Research in Transfusion Medicine and Cell Therapies
Girish N. Vyas Distinguished Professor and Endowed Chair University of California San Francisco

UCSF
University of California
San Francisco

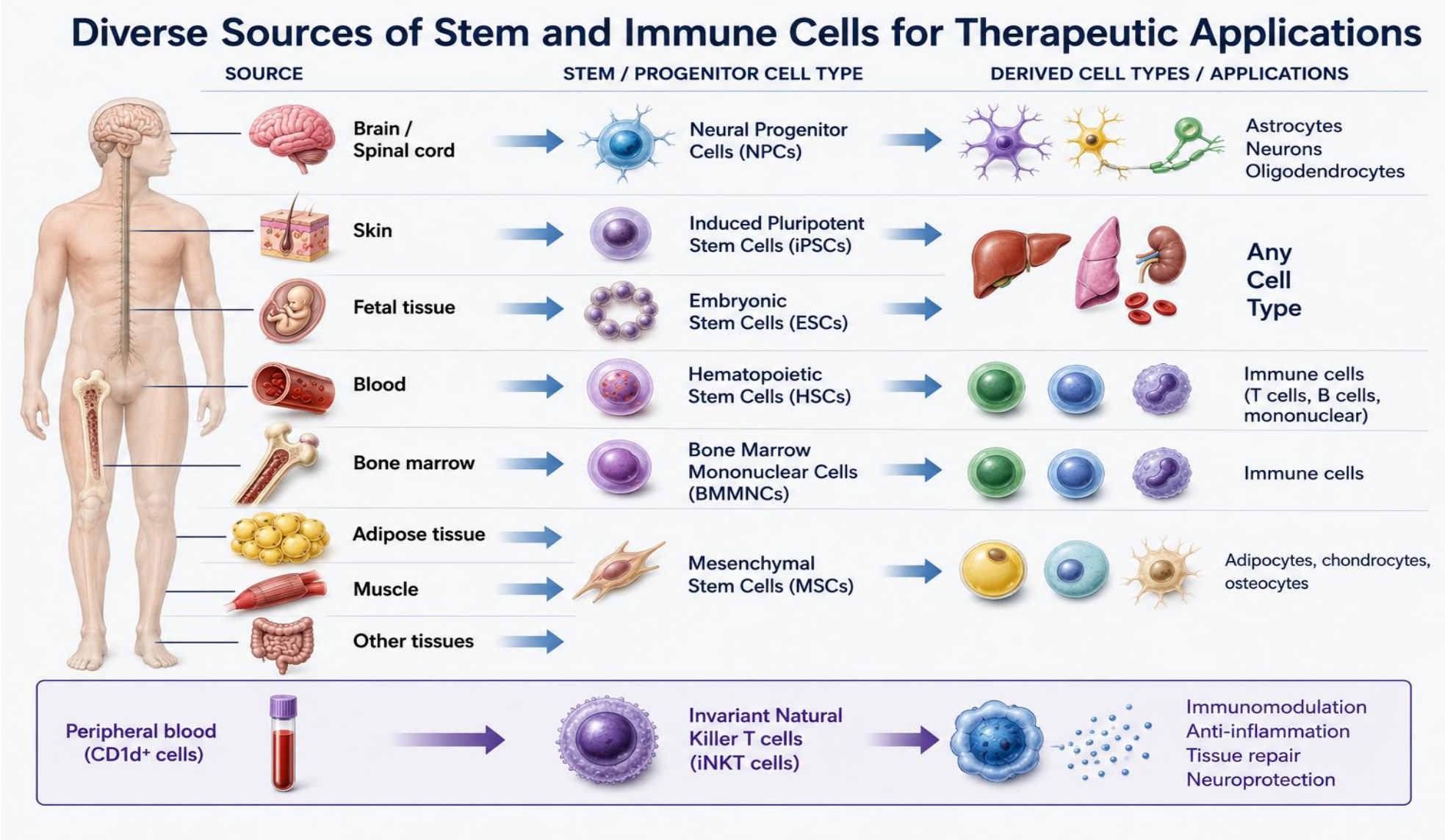
Whole Blood is the first cell therapy to be utilized in the US during the Civil War.

Key Points

- In **1865,** whole blood transfusion was used in the USA during the Civil War.
- Whole blood contains red blood cells, white blood cells, platelets, plasma and bioactive factors.

From the battlefield to the future – cellular therapies have long been a lifeline for the wounded.

Types of Stem Cells and Their Therapeutic Applications



Pati, Holcomb…. Rasmussen et al. Shock 2015

Timeline of DoW Investment in Cell Therapies

1961
AFRRI founded

Focus on protecting Service members from the effects of radiation exposure

1980s
Bone marrow transplantation

Advances in marrow transplantation demonstrate the power of cellular regeneration

2006
Soldier Treatment and Regeneration Program

DoD-led program to advance regenerative medicine solutions for wounded, ill, and injured Service members

2008
Prochymal® for Acute Radiation Syndrome

First MSC therapy advanced for treatment of Acute Radiation Syndrome (ARS)

2008
AFIRM established

AFIRM
ARMED FORCES INSTITUTE OF REGENERATIVE MEDICINE

Formal launch of AFIRM to accelerate regenerative medicine for Service Members

2012–2018
Expansion to trauma, burns, and ARDS

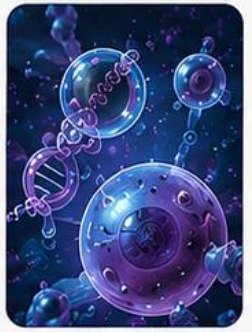
Broadening MSC applications to:

- Trauma
- Burns
- ARDS

2018–2024
Focus on MSC secretome

Deepening understanding of MSC secretome, EVs, and paracrine biology

Today
Next-generation therapies



- EV therapeutics
- Engineered MSCs
- iNKT cells
- Cell-free biologics

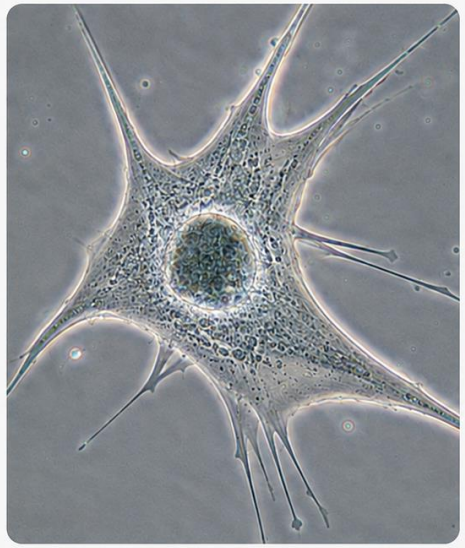
The Turning Point for Cell Therapies: Osiris Prochymal (2007-2008)

First Major DoW Investment and largest in MSCs for ARS which ultimately led to the first approved MSC product in 2024 for Steroid Refractory GvHD in Pediatrics (Mesoblast- Ryoncil)

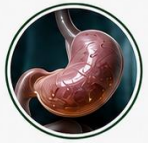
Osiris™
THERAPEUTICS

Prochymal®
(MSCs)

Mesenchymal
Stem Cells



Indication:
Acute Radiation Syndrome (ARS)



Targets
GI injury, epithelial damage, and multi-organ dysfunction

Product
Allogeneic, off-the-shelf, cryopreserved product

Contract
Up to $224.7 Million contract from the DoD

Why MSCs? Broad-spectrum reparative potential, immunomodulation, and logistical advantages for stockpiling and deployment.

Cellular Therapies in Trauma and Critical Care
State of the Science Meeting at Ft. Detrick in 2015

SHOCK, Vol. 44, No. 6, pp. 505–523, 2015

OPEN

Review Article

CELLULAR THERAPIES IN TRAUMA AND CRITICAL CARE MEDICINE: FORGING NEW FRONTIERS

Shibani Pati,*† Marcello Pilia,‡ Juanita M. Grimsley,‡ Alexia T. Karanikas,§ Blessing Oyeniyi,‖ John B. Holcomb,‖ Andrew P. Cap,¶ and Todd E. Rasmussen‡

*Blood Systems Research Institute, San Francisco, California; †University of California San Francisco, San Francisco, California; ‡Combat Casualty Care Research Program, Fort Detrick, Maryland; §Booz Allen Hamilton, Rockville, Maryland; ‖Department of Surgery, University of Texas, Houston, Texas; and ¶United States Army Institute of Surgical Research, Fort Sam Houston, Texas

PERSPECTIVE

Cellular therapies in trauma and critical care medicine: Looking towards the future

Shibani Pati[1,2]*, Todd E. Rasmussen[3]

1 Department of Laboratory Medicine, University of California San Francisco, San Francisco, California, United States of America, **2** Blood Systems Research Institute, San Francisco, California, United States of America, **3** F. Edward Hebert School of Medicine, Uniformed Services University of Health Sciences, Bethesda, Maryland, United States of America

PLOS | MEDICINE 2017

The **2015 Department of War hosted a Cellular Therapies in Trauma and Critical Care Medicine meeting** at **Fort Detrick, Maryland.** It fundamentally changed how the military, academia, industry, regulators, and funding agencies viewed **cellular therapies as a legitimate platform technology for trauma.** The meeting was organized by the **Combat Casualty Care Research Program (CCCRP) under Director Col. Todd Rasmussen**

Pati, Holcomb…. Rasmussen et al. Shock 2015, Pati and Rasmussen Plos Med 2017

The DoW Major Trauma Trials of Cell Therapies in Trauma/TBI- Multiple have been Supported by the DoW

Trial	Cell Product	NCT	Indication	Military Sponsor	Phase
Adult BMMNC	Autologous Bone Marrow Mononuclear Cells	NCT01575470	Severe TBI Ph1 and 2 Phase	**CDMRP/Joint Warfighter/ AFIRM/DoW**	I Acute
Pediatric BMMNC	Autologous Bone Marrow Mononuclear Cells	NCT01851083	Pediatric TBI	**NIH**	I Acute
Pediatric BMMNC II	Autologous Bone Marrow Mononuclear Cells	NCT02525432	Pediatric TBI	NIH	II Acute
SB623	Allogeneic Modified MSCs	NCT02416492	Chronic TBI	SanBio	II Chronic
Hope Biosciences Phase I/IIa	Autologous Adipose MSCs	NCT04063215	Chronic TBI	**Hope Biosciences/DoW**	I/II Chronic
Hope Biosciences Phase II	Autologous Adipose MSCs	NCT05951777	Chronic TBI	**DoW CDMRP**	II Chronic
MATRICS-1	MultiStem® (MAPCs)	NCT04533464	Polytrauma / Hemorrhagic Shock AKI	**MTEC / DoW**	II Acute
AURORA	Allogeneic HB-adMSCs	NCT06654193	Trauma-induced AKI	**AFIRM / MTEC / DoW**	I/II Acute (ClinicalTrials.gov)

Ph 1 BMMNCs- AFIRM/DoW

Focus: TBI and the Need for Novel Therapeutics in both Acute and Chronic Settings

Military:

~528,450 Service Members Diagnosed with Mild to Severe TBI (2000-2025)

~ 70,000 Moderate to Severe TBI since 2000

~ 82% are mild TBI

~15,000-20,000 New TBI Diagnosed/YR

~441, 639 Post-9/11 Veterans in TBI Registry

- Most Common Causes- Blast, Falls, GSW,
MVAs. Training Injuries

Civilians-:

~2.8 million ER visits/yr

~- A Leading Cause of Death in Ages 1-44

~76.5 Billion annual economic cost

https://health.mil/MHSHome/Military-Health-Topics/Centers-of-Excellence/Traumatic-Brain-Injury-Center

Acute TBI

Funded by the DoW

Cox, Hetz, et al 2016
Stem Cells

Treatment of Severe Adult Traumatic Brain Injury Using Bone Marrow Mononuclear Cells

STEM CELLS TRANSLATIONAL AND CLINICAL RESEARCH

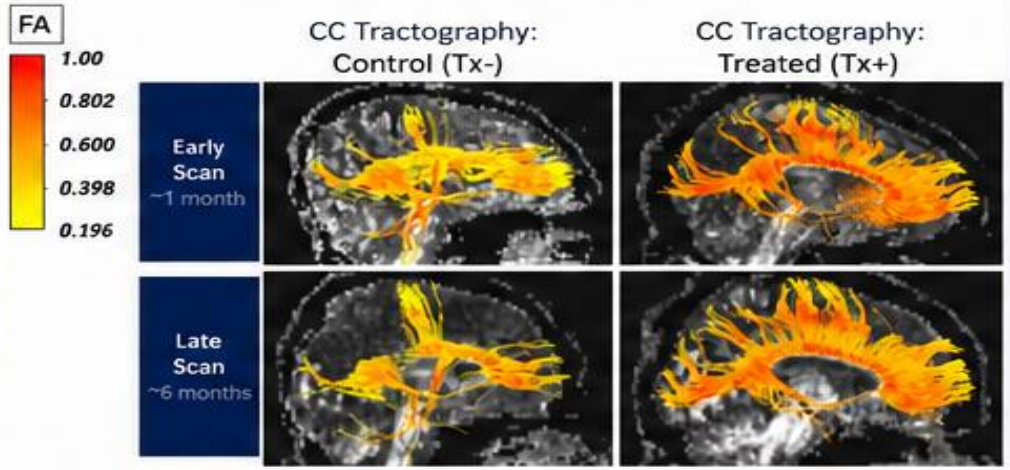
Phase 1 Clinical Trial (DOD-DOW Funded)

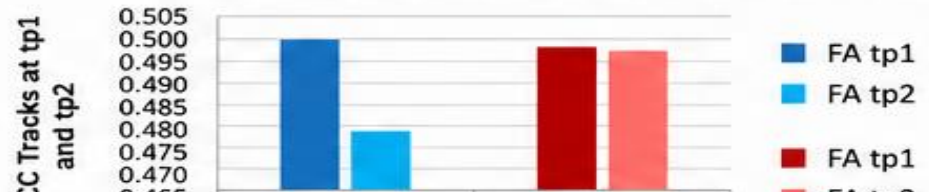
- DOD-DOW Funded (NCT....)
- Phase 1 Dose-Escalation in 25 Patients
  - 5 controls, 5 patients in 3 dose cohorts, 5 more controls
  - Bone marrow harvest, reinfusion within 48 hours of injury

- Key Findings
  - No Serious AEs relating to harvest / infusion
  - Down-Regulation of Key Inflammatory Cytokines
  - TBI caused brain atrophy and chronic inflammation
  - Structural Preservation of Critical Regions, Functional Outcomes

1. STRUCTURAL PRESERVATION (DTI)

Corpus Callosal Fiber Tract Fractional Anisotropy: Structural Preservation via Cellular Therapy

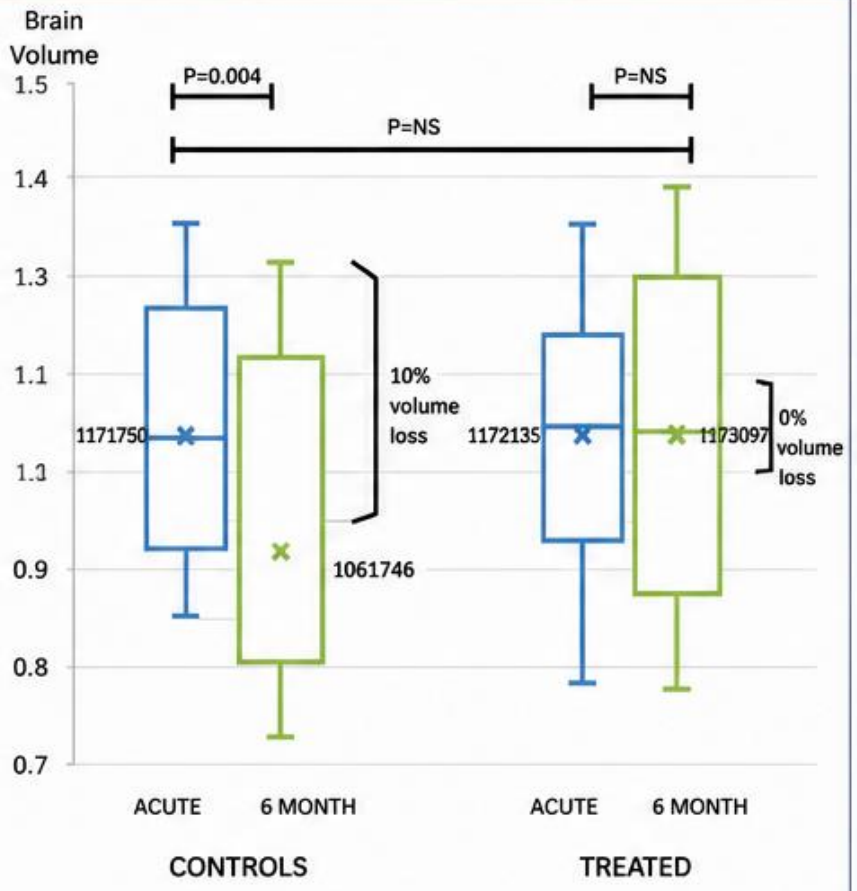




	Tx-	Tx+
FA tp1	0.500	0.498
FA tp2	0.479	0.498

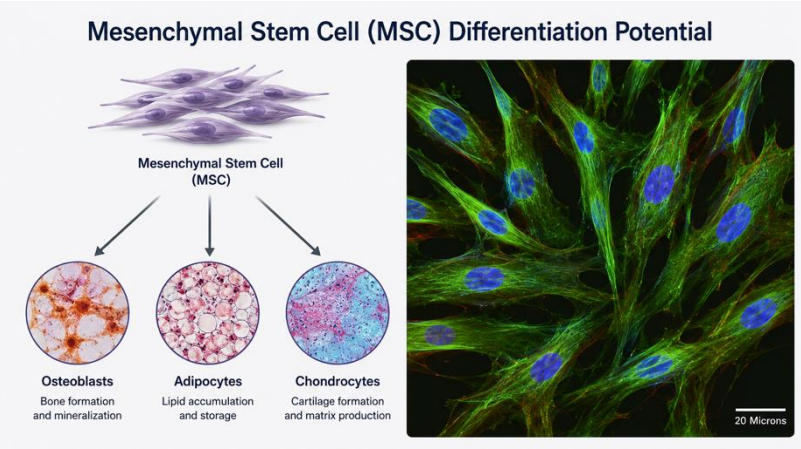
DTI can be used as an imaging endpoint to quantify structural preservation in TBI clinical trials. Moderate to large treatment effect size was demonstrated at the corpus callosum pointing to the feasibility of a Phase 2b trial using BMMNC in TBI.

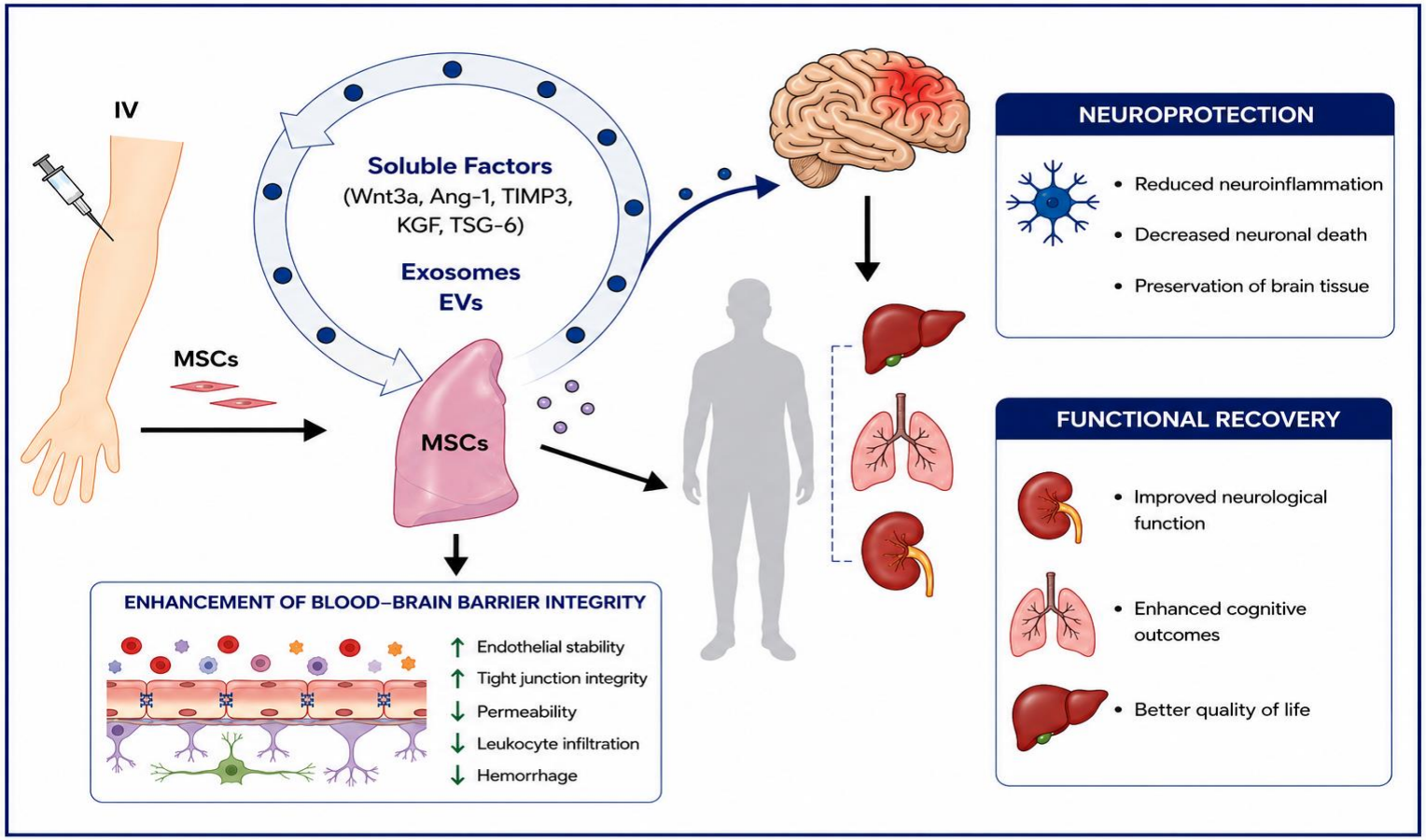
2. BRAIN VOLUME OVER TIME



Controls demonstrated significant brain volume loss over 6 months, whereas treated patients showed structural preservation.

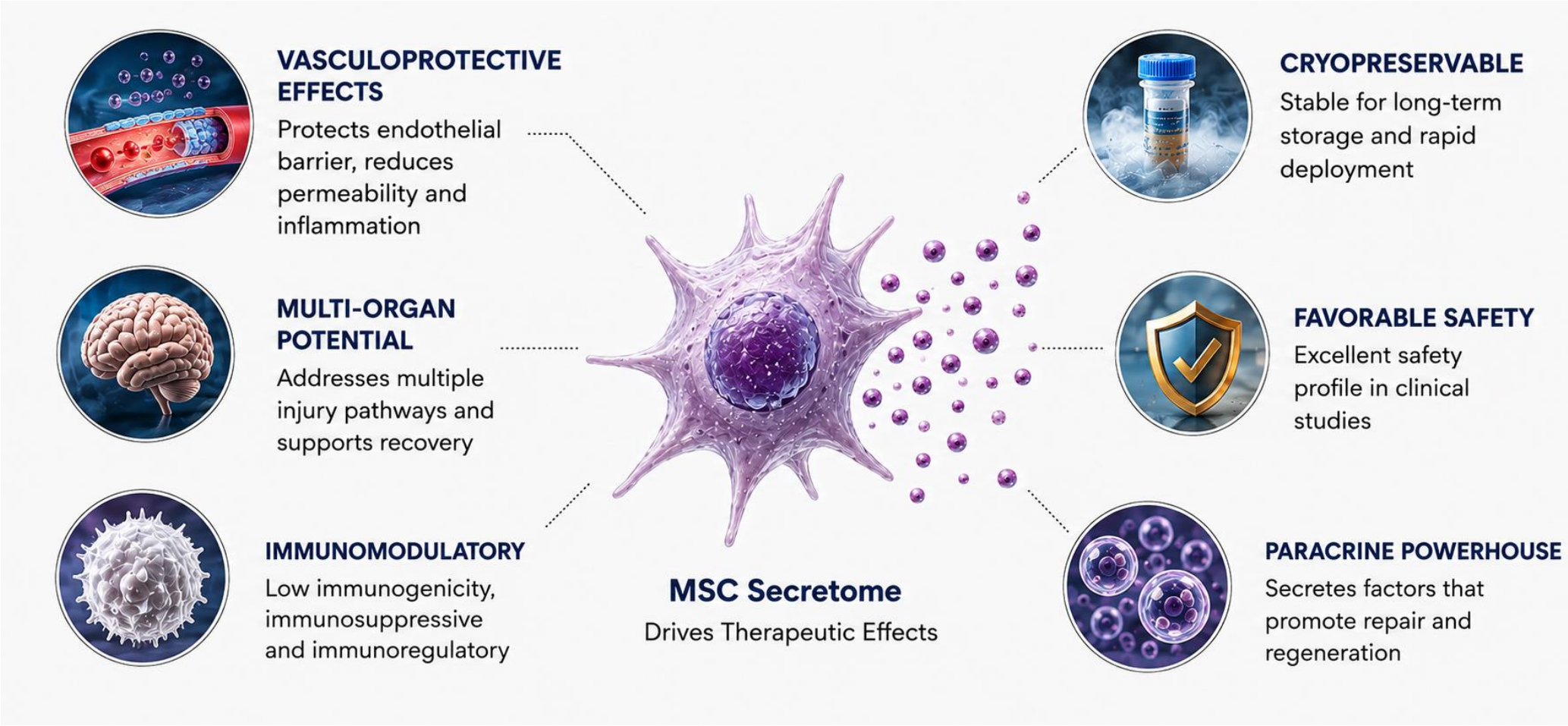
Adult Bone Marrow Mesenchymal Stem Cells. How do they Work? MSCs Secrete Soluble Factors and Extracellular Vesicles that mediate Potent Reparative Effects





Prockop et al. Science 1997.Pittenger et al. Science 1999, Pati et al 2010
Menge… Holcomb… Cox, Pati Sci. Translation Med 2012, Zhao….Pati Stem Cells 2016

Why MSCs were Attractive to the DoW and Warfighter



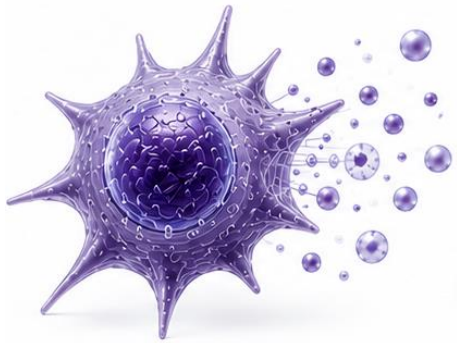
Paradigm shift in thought where cells were viewed as regulators or orchestrators of healing- not tissue replacement

Mouse Models to Humans----- 20+ years

20 Years of Translational Progress: From Cells to Clinical Impact in TBI

A two-decade journey of discovery and development advancing cell-based therapies from bench to bedside for traumatic brain injury.

Late 1990s — **2000–2010** — **2015** — **2025**

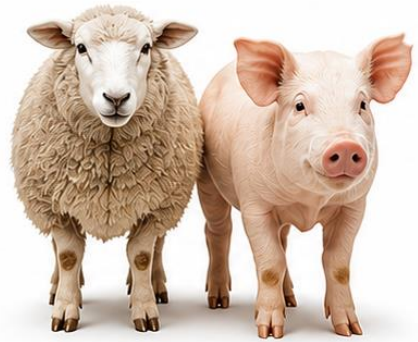


Cells & Secretome

Identification of bioactive factors and mechanisms. In vitro studies demonstrate therapeutic potential for neuroprotection and immunomodulation.

Preclinical in Mice

Efficacy demonstrated in murine models of TBI. Reduced neuroinflammation, preserved BBB integrity, and improved functional outcomes.



Large Animal Studies

Validation in clinically relevant models (sheep, pigs). Assessment of safety, dosing, biodistribution, and functional neurological recovery.

Human Clinical Trials

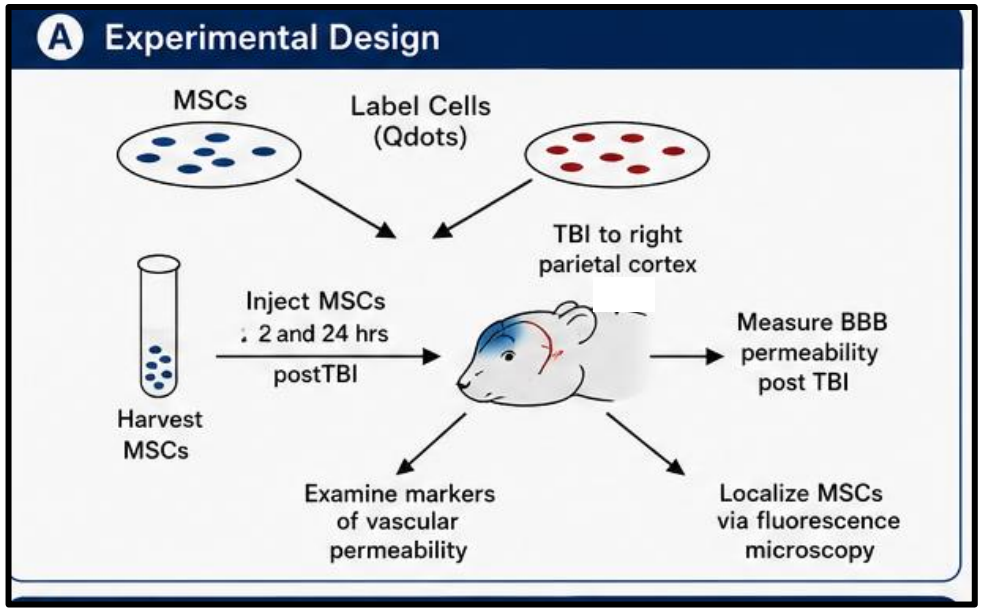
First-in-human clinical trials in TBI patients. Evaluating safety, feasibility, and signals of efficacy to improve neurological recovery and long-term outcomes.

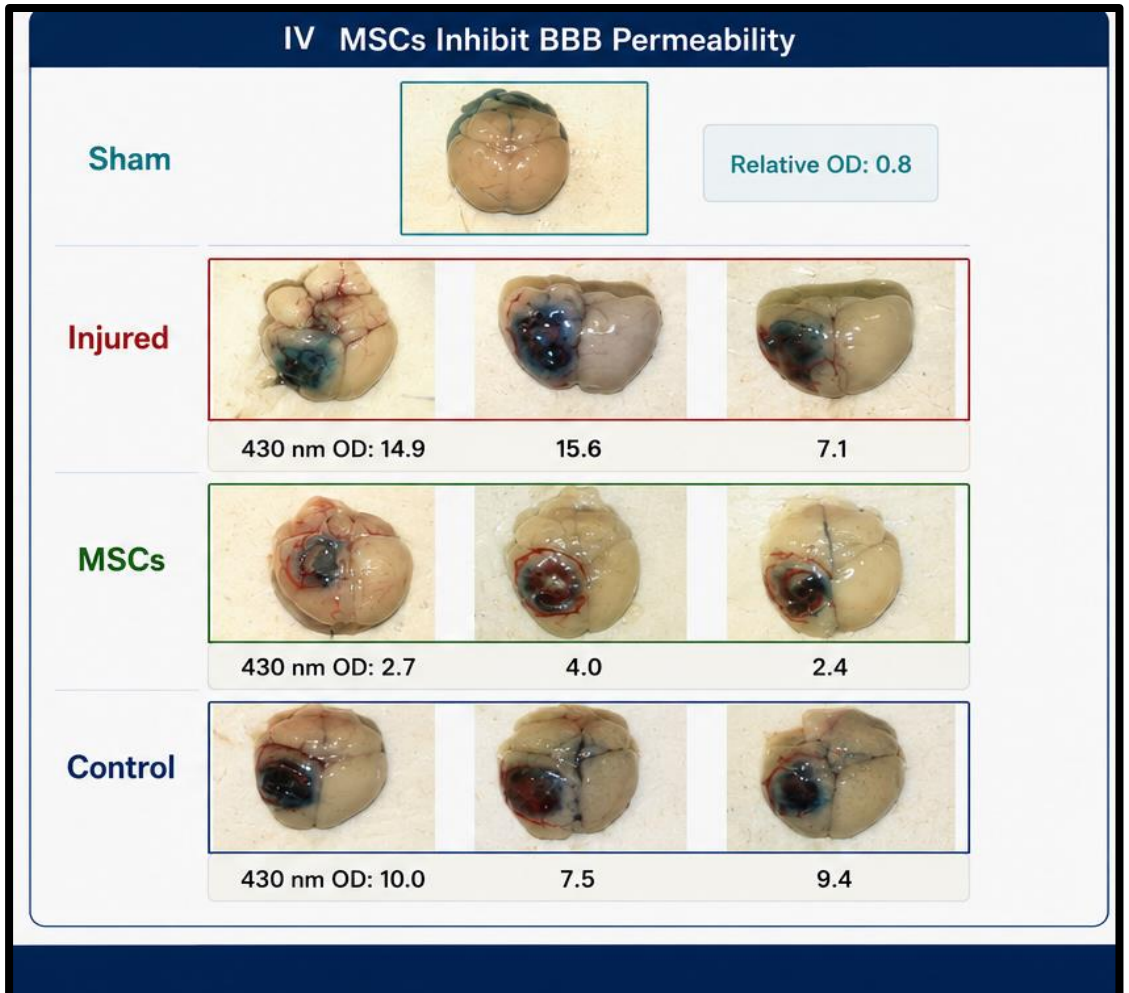
UCSF
University of California
San Francisco

Pre-Clinical Work in Mice that Laid the Foundation

Human Mesenchymal Stem Cells Inhibit Vascular Permeability by Modulating Vascular Endothelial Cadherin/β-Catenin Signaling

Shibani Pati[1], Aarif Y. Khakoo,[2] Jing Zhao,[3] Fernando Jimenez,[4] Michael H. Gerber,[3] Matthew Harting,[4] John B. Redell,[3] Raymond Grill,[5] Yoichi Matsuo,[2] Sushovan Guha,[2] Charles S. Cox, Jr.,[4] Marvin S. Reitz, Jr.,[6] John B. Holcomb,[1] and Pramod K. Dash[3]

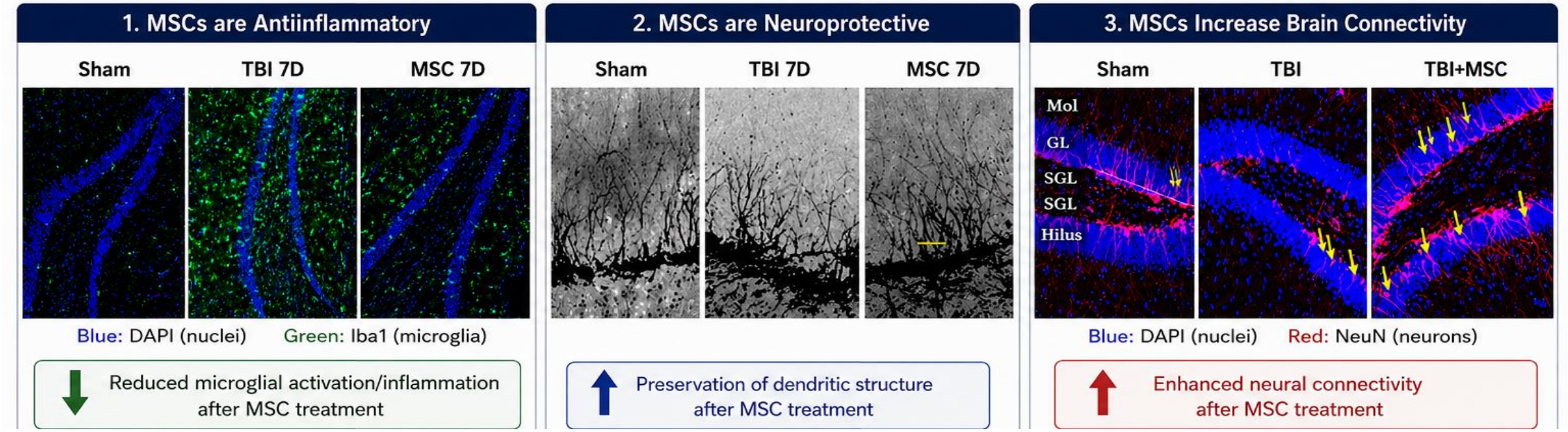




Pati, Holcomb, Cox et al 2011 Stem Cells and Dev.

Functional Effects in TBI: MSCs are Anti-inflammatory, Neuroprotective and enhance Neural Connections

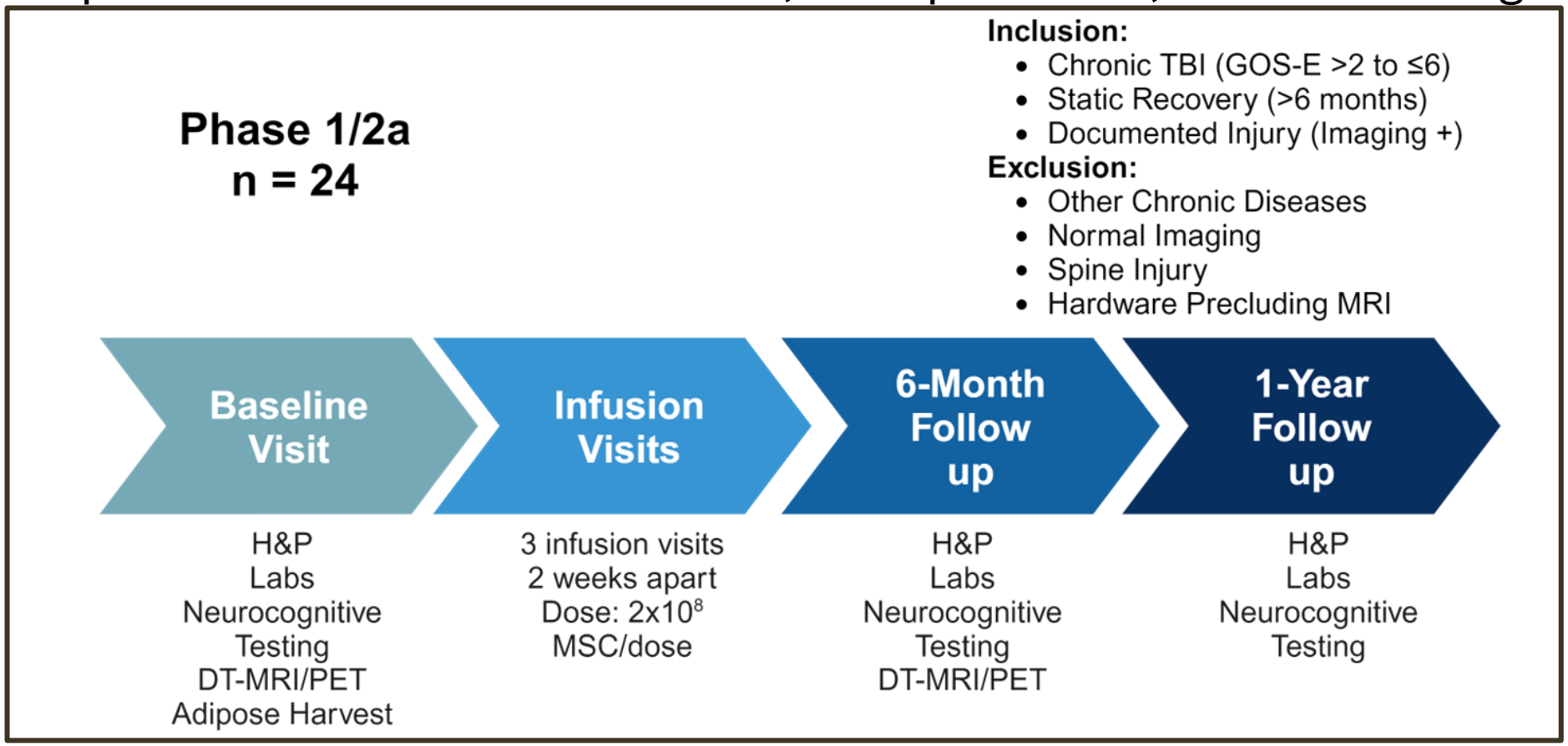
Decreased Inflammation | **Increased Connectivity** | **Increased Neuronal Stem Cell Survival**



Zhao, Holcomb,,, Pati *Stem Cells*, 2016

Clinical Trials for Chronic TBI - Adipose derived MSCs for Chronic TBI (Autologous from Patient's Tissue)- Ph1/2 trial complete, Phase 2 now in Progress –DoW Funded

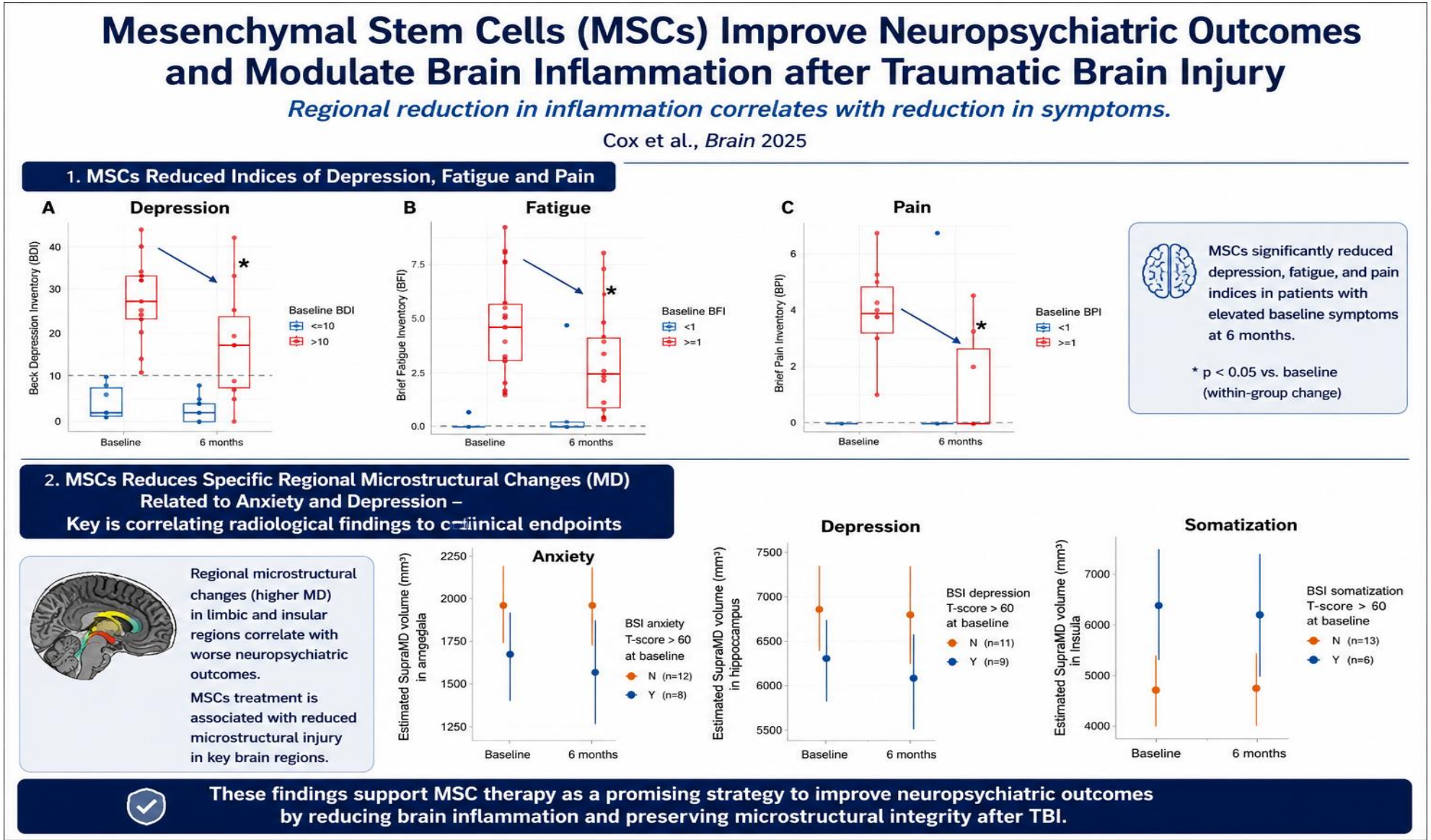
Novel aspects: Fresh/never frozen cells, multiple doses, advanced imaging.



Cox et al Brain.

Phase1-2a Trial found MSCs decrease Depression, Fatigue, Pain, and Anxiety by 6 Months

Cox et al Brain. 2024



Functional Outcomes Improve with Treatment Baseline vs. 6 months post MSC treatment

JOURNAL ARTICLE ACCEPTED MANUSCRIPT

Autologous adipose-derived mesenchymal stromal cells for chronic traumatic brain injury

Get access >

Charles S Cox, Jr ✉, Janet R Ashley, Jenifer Juranek, Linda Ewing-Cobbs, Alan R Prossin, Claudia Pedroza, Bingrui Chen, Steven Kosmach, Maria Carmen Duron, Michael C Scott, Joana Bianchi, Aidan Collier, Scott D Olson, Jacob B Schriner, Sean I Savitz

Brain, awag165, https://doi.org/10.1093/brain/awag165

Human Studies Validate Findings from Animal Models.

Functional Outcomes
Disability Rating Scale-Improved

TBI Quality of Life
Cognition Improved
Communication Improved
Comprehension Improved
Independence Improved
Mobility Improved

Brief Symptom Inventory
Depression Improved
Anxiety Improved

From Living Cells to Dried Therapeutics

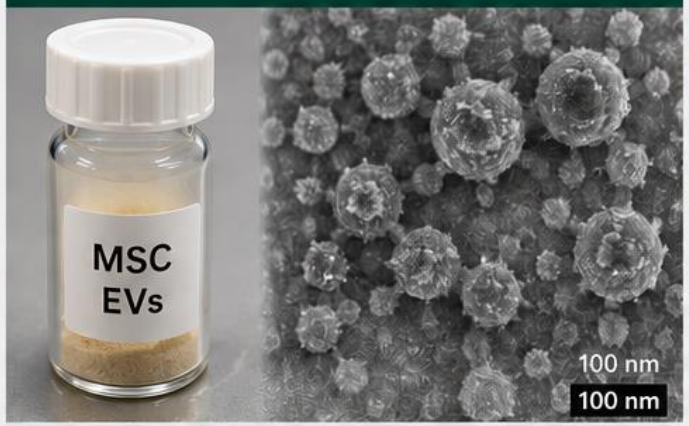
Innovative, Stable, and Deployable Solutions for Battlefield and Remote Environments

Project supported by AFIRM
Advanced Functional Innovative Research in Medicine

Dried MSCs from Live Cells

- Derived from clinical-grade MSCs
- Lyophilized for stability and rapid reconstitution
- Retains viability, potency, and immunomodulatory function

Dried Extracellular Vesicles from MSCs



- Purified MSC-derived extracellular vesicles
- Lyophilized to preserve bioactivity
- Potent modulators of inflammation and tissue repair

Dried Conditioned Media (CM) from MSCs

- Concentrated MSC secretome
- Lyophilized for long-term stability
- Supports immunomodulation, angiogenesis, and tissue regeneration

Room temperature stable | Rapid reconstitution for immediate use | Lightweight, portable, and easy to deploy

Project Supported by AFIRM with Industry Partners

UCSF University of California San Francisco

hope BIOSCIENCES

DesiCorp

Advanced Cellular Therapeutics – Ready When and Where They Are Needed Most

Don’t forget the healing power of blood!
A Dried Platelet Derived Biologic (FPH) Improves Outcomes in TBI

Funded by Combat Casualty Care - DoW

ORIGINAL RESEARCH

VASCULAR BIOLOGY

A dried platelet–derived biologic for blood-brain barrier repair and hemorrhage control after TBI in mice

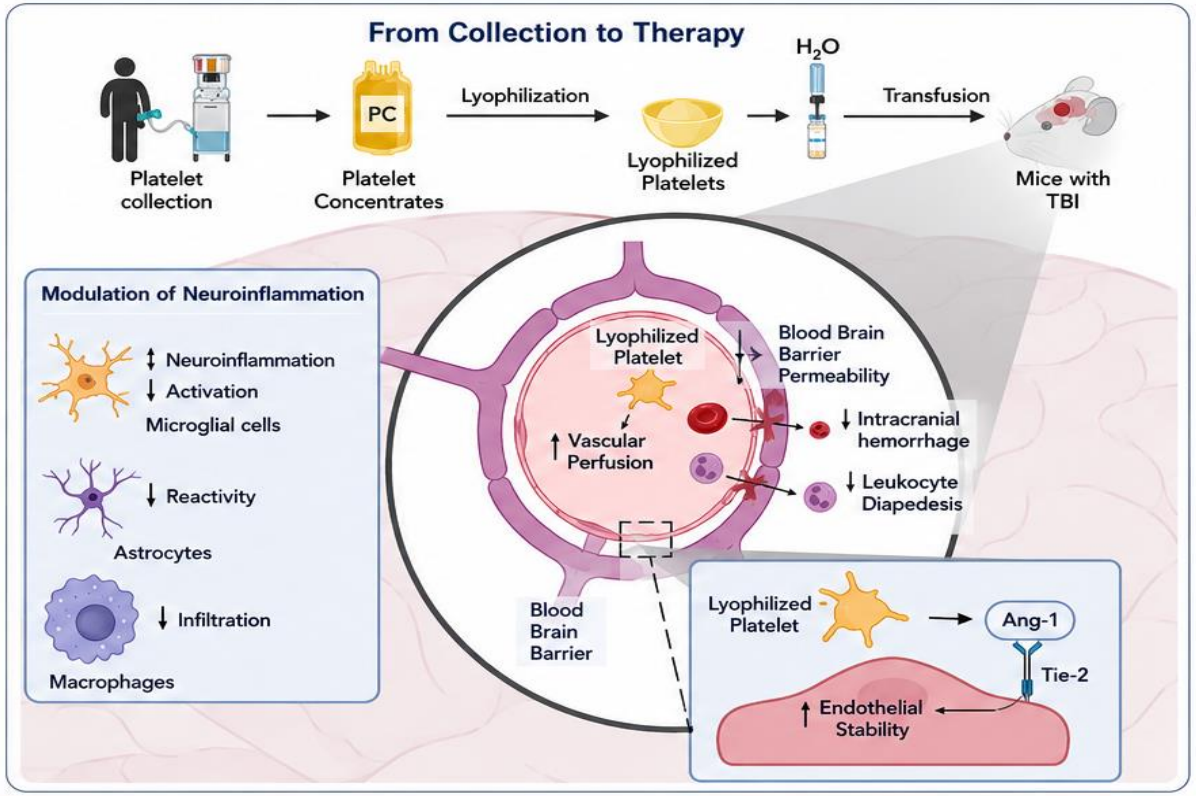
Alpa Trivedi,[1] Byron Miyazawa,[1] Haoqian Zhang,[1] Longhui Qiu,[2] Daniel Potter,[1] Austin Edwards,[3] Lindsay Vivona,[1] Maximillian Lin,[1] Callie Keane,[1] Huimin Geng,[1] Simon J. Cleary,[2] Alison Nair,[4] Michael Fitzpatrick,[5] Mark R. Looney,[1,2] and Shibani Pati[1,6]

COMMENTARY

Comment on Trivedi et al, page 3231

From bench to broken brains: freeze-dried platelets

Moritz Stolla | Bloodworks Northwest Research Institute and University of Washington



Dried platelets enhance vascular repair, reinforce blood-brain barrier integrity, and reduce inflammation and hemorrhage after TBI.
Combining blood-based therapies like dried platelets with cell therapies (e.g., MSCs) offers a powerful strategy to target the multifaceted pathophysiology of TBI.

Pati Blood 2026, Stolla Blood 2026 ***Cellphire- source of FPH***

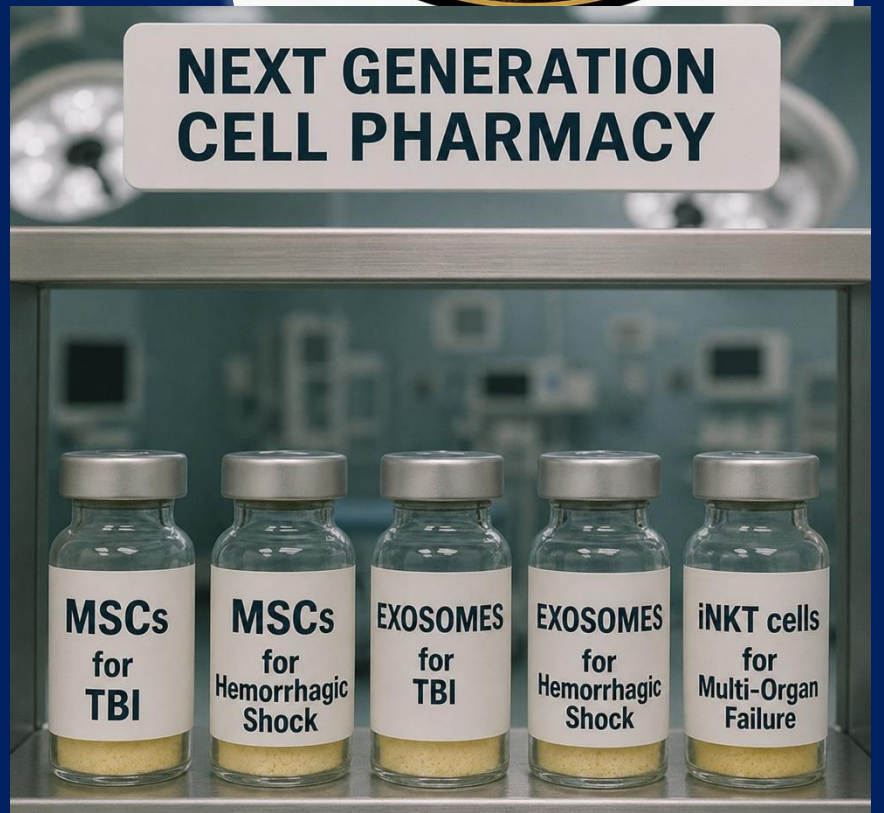
The Future of Battlefield to Role 3 Care and Beyond

What do we need for our warfighters?

- Novel Therapies that can be utilized in remote or austere settings such as dried, disease-condition-specific therapeutics
-Next Generation Cell Pharmacy
-Immunomodulatory therapies for PCC to prevent multi-organ failure- i.e. iNKT cells

What do we need to make this happen?

-Funding for research, Phase 2 and 3 trials
-Large industry and VC interest
-Industry-Academia Multidisciplinary Teaming
--Regulatory Agency Support



Cellular Therapies and Transfusion Medicine in Trauma and Critical Care Medicine

7th iteration 14th year- supported by the Office of the ASDHA, USU, AFIRM and UCSF. Includes a focused Military Health Session

Thank You!

DoW
Hon. Keith Bass
Dr. Terry Rauch
Dr. John Holcomb
Dr. Therese West
Combat Casualty Care