Stem Cell Implants:
Emerging Innovation for Stroke Recovery

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Presenter

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- Brandon Lucke-Wold graduated magna cum laude with a BS in Neuroscience and distinction in honors from Baylor University. He completed his MD/PhD, Master's in Clinical and Translational Research, and the Global Health Track at West Virginia University School of Medicine. His research focus was on traumatic brain injury, neurosurgical simulation, and stroke. At West Virginia University, he also served as a health coach for the Diabetes Prevention and Management program in Morgantown and Charleston, WV, which significantly improved health outcomes for participants.
- He has completed neurosurgery residency and is currently a neuroendovascular fellow at University of Florida. He has transitioned to research on treatment of vasospasm by targeting the neuroinflammatory cascade following subarachnoid hemorrhage. He was awarded the Dempsey Cerebrovascular Research Fellowship, other distinguished grants and fellowships addition to multiple research presentation awards.

Disclosures

- Dr. Brandon Lucke-Wold is founder of TauGen Pharmaceuticals and Swiftscience. Dr. Lucke-Wold does not have any relevant financial or non-financial interests to disclose relating to the content of this activity.
- The views expressed in this presentation are those of the author and do not necessarily reflect the official policy or position of the Department of Defense, nor the U. S. Government.
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- Commercial support was not received for this activity.

Learning Objectives

At the conclusion:

1. Review the limited options for intervention and rehabilitation in stroke.
2. Discuss the potential advantages of stem cell therapy and mechanisms of delivery.
3. Summarize the promising initial data showing potential success.

Background

- 795000 strokes occur each year in the United States (87% are ischemic)
- The two primary options are tPA and mechanical thrombectomy
- tPA has a time limitation of 4.5 hours after last known normal
- Mechanical thrombectomy must be performed within 24 hours
- Decompressive hemicraniectomy can be performed as a life saving measure

Key take away: these treatments are primarily damage control measures to prevent worsening

Stem Cell Options

- Relatively new field: first isolated human embryonic stem cells 1998 (Thomson et al)
- Three types being investigated for stroke: neural, bone marrow, and mesenchymal
- Unique ability to self-renew and create functional tissues

Stem cell categories

- Totipotent- ability to form all cell types
- Pluripotent- can be induced to give rise to all cell types
- Multipotent- more specific with adult stem cell and neural stem cell

Bystander effect: implanted cells release chemokines and factors to promote healing and reduce neuroinflammation

Approaches

- Bone marrow and fetal neural stem cells are both being investigated.
- Pre-clinical studies have shown that stem cells promote axonal regrowth and allow the formation of biobridges across viable brain regions
- Functional recovery has been improved across rodent models

Feasibility

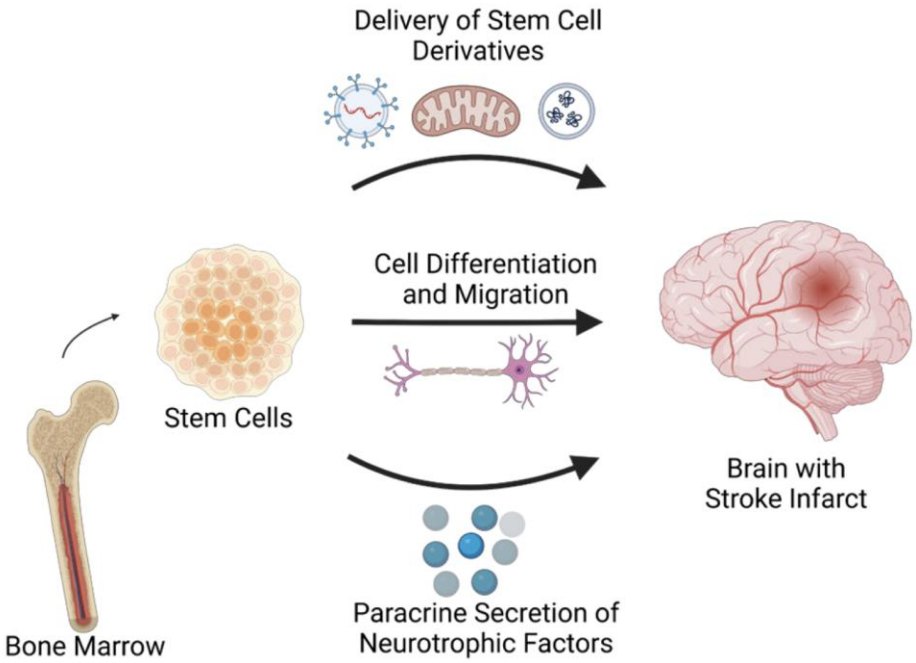

Figure 1: Mechanisms of stem cell therapy include (1) delivery of stem cell derivatives such as extracellular vesicles, mitochondria and exosomes, (2) direct cell differentiation with replacement and induced migration with "biobridges" and (3) paracrine secretion of various neurotrophic factors.

Routes

- Intravenous
- Intrathecal
- Intraparenchymal
- Intranasal

Ongoing testing

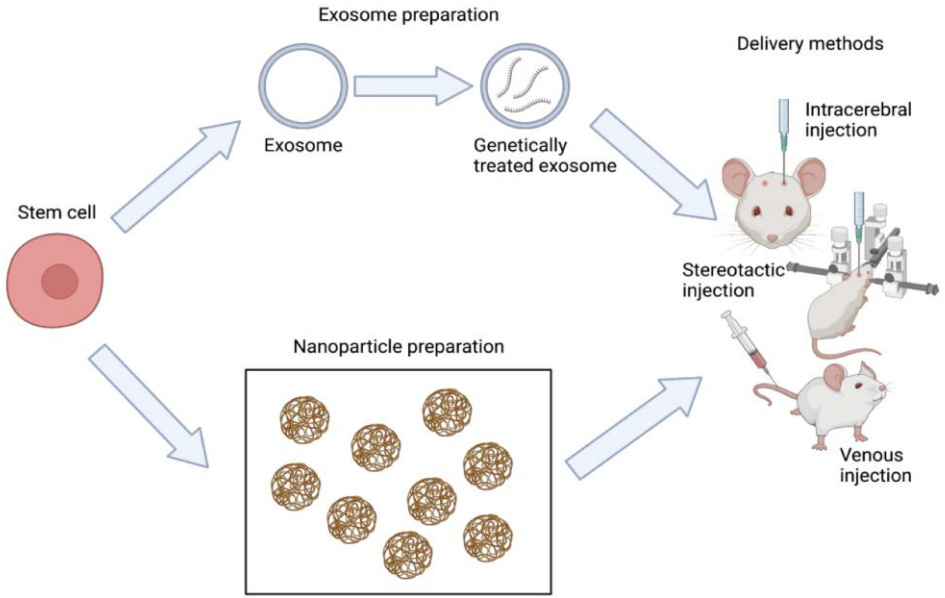

Figure 2: Depiction of two stem cell preparation methods and three delivery routes. The top portion of the figure shows a method which involves genetically treating exosomes from stem cells prior to delivery. The bottom portion depicts packaging the stem cells into nanoparticles and the right-hand side of the figure displays three major modes of delivery used in rodent experiments: intracerebral injection, stereotactic injection and venous injection.

Trials (1 of 2)

Trial/location/acronym	Cell	Route	Setting	Phase	n	Design	Estimated Completion Date
NCT05008588 Indonesia	UC-MSC	IC	acute	1/2	15	RCT-OL	December 2023
NCT04811651 China "UMSIS"	UC-MSC	IV	<6 months	2	200	RCT-B	October 1, 2023
NCT05292625 Vietnam	UC-MSC	IV/IT	<24 months	1/2	48	RCT-B	June 2, 2023
NCT04631406 USA/Canada	NSC	IC	6-60 months	1/2	30	Single Arm	December 31, 2024
NCT05158101 Argentina	UC-MSC	IV	N/A	1	15	Single Arm	February 2026
NCT04280003 Spain "AMASCIS-02"	A-MSC	IV	<4 days	2	30	RCT-B	July 15, 2023
NCT01151124 UK "PISCES"	NSC	IC	6-60 months	1	12	Single Arm	March 2023

Trials (2 of 2)

NCT04434768 Taiwan	UC-MSC	IV/IV+IA	<36 hours	1	14	Single Arm	December 31, 2023
NCT04097652 Taiwan	UC-MSC	IV	4-7 days	1	9	Single Arm	December 31, 2025
NCT03384433 Iran	MSC-CfE	IV	<24 hours	1/2	5	Single Arm	December 17, 2021
NCT04953663 China	BM-MSC	IV	>6 months	1/2	60	RCT-B	January 1, 2023
NCT03545607 USA	APC	IV	18-36 hours	3	300	RCT-B	June 2023
NCT04590118 China	BM-MSC	IV	>6 months	1/2	60	RCT-B	August 1, 2023
NCT02795052 UAE	BM-MSC	IV+IN	>6 months	N/A	500	Single Arm	July 2024
NCT04093336 China	BM-MSC	IV	<7 days	1/2	120	RCT-B	August 31, 2024

USA = United States of America, UAE = United Arab Emirates, UC-MSC = Umbilical Cord Derived Mesenchymal Stem Cells, NSC = Neural Stem Cells, A-MSC = Adipose Derived Mesenchymal Stem Cells, MSC-CfE = Mesenchymal Stem Cell Derived Cell-free Exomes, BM-MSC = Bone Marrow Derived Mesenchymal Stem Cells, APC = Multipotent Adult Progenitor Cells, IC = Intracerebral, IV = Intravenous, IA = Intraarterial, IN = Intranasal, RCT-OL = Open Label Randomized Controlled Trial, RCT-B = Blinded Randomized Controlled Trial

Table 1: Ongoing trials.

Results

- Mixed results: some improvements on some measures but not widely replicable
- Most promising has been some extended improvements in mRS at 12 months
- Optimization for acute/subacute settings vs. chronic settings is ongoing
- Trials will help shape appropriate patient selection

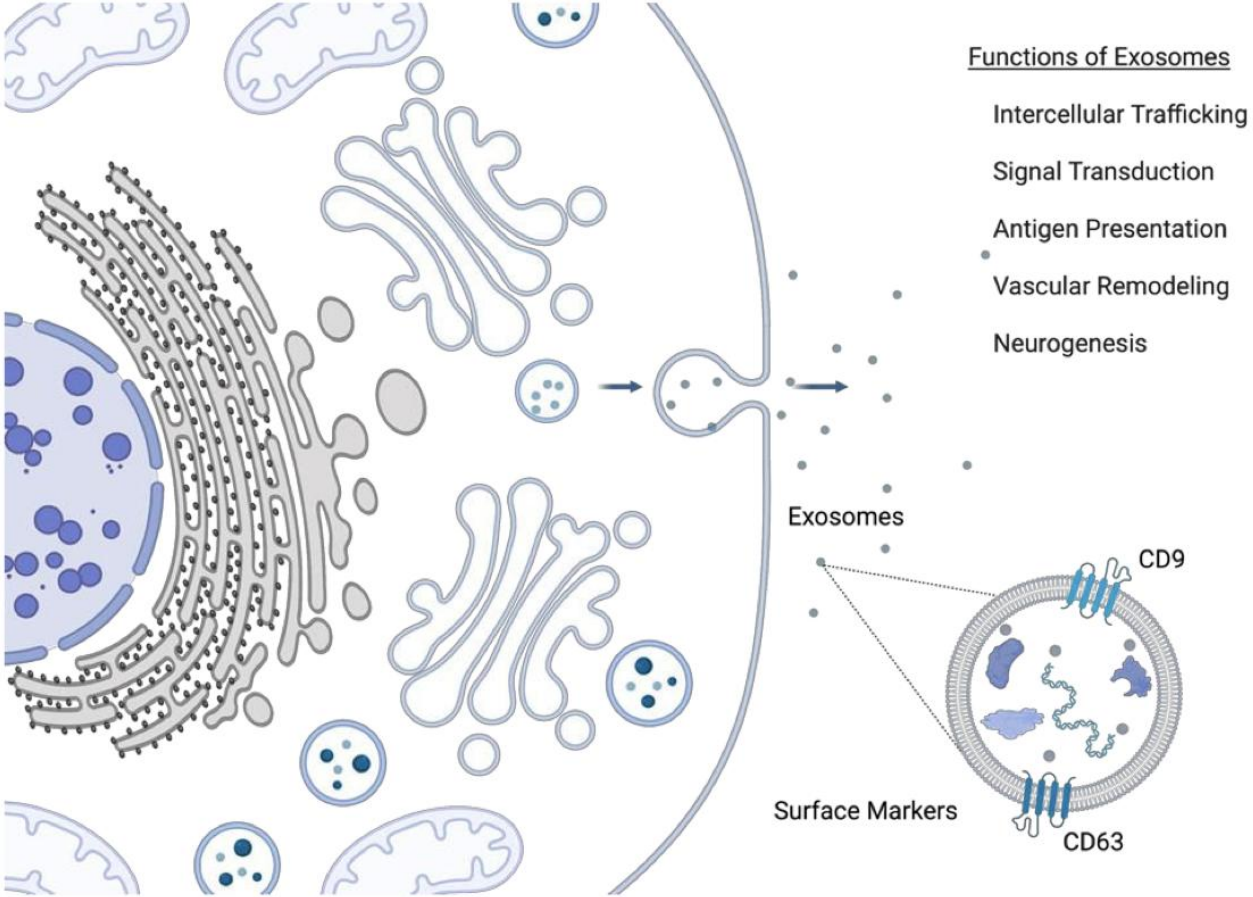

Figure 3: Exosome function and utilization as nanomedicine. Exosomes are nano-sized (30-150 nm) extracellular vesicles that transmit cargo to other cells. Much of the recent research utilizes this function to insert drugs and proteins as a form of regenerative medicine.

Key Takeaways

- Stroke remains a debilitating and costly disease with limited treatment options
- Stem cells have ability to bridge gap in treatment
- In vivo studies have showed value of MSC, BMSC, and NSC
- Intrathecal and intravenous delivery offer promise on original studies
- Exosome and nanoparticle delivery options offer promise

Ongoing work is needed for selection of appropriate patient population and optimization for both the acute and chronic periods post stroke

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Questions?