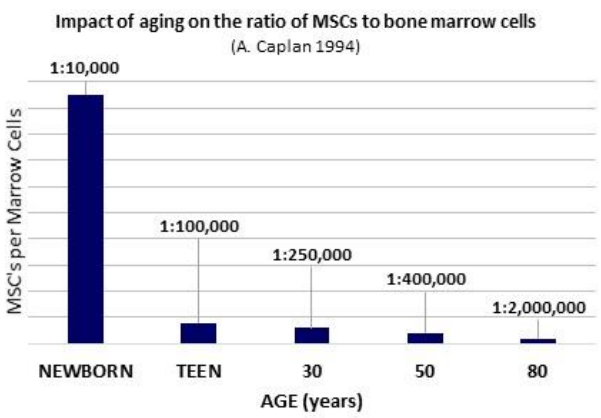
With the increase in advertisements, and social media, people are relating regenerative medicine therapies to "stem cell" treatments. Typically, when discussing regenerative medicine, the first question we are asked is "what is the stem cell count". Regenerative medicine is much more than just stem cells, whose outcome is very dependent on the age of the patient they are being harvested from, (Figure 1) which is why often taking your own stem cells is not effective.

Figure 1



One of the most valuable aspects of a science-driven approach to regenerative medicine is that our understanding evolves with the science. We once bought into the same "stem cell-based therapy" model that everyone else touts, but as scientists scrutinized the data, they came to embrace a view shared by hundreds of other leading regenerative medicine researchers – including the father of the mesenchymal stem cell, Dr. Arnold Caplan.

In June 2017 Dr. Caplan published an article: *Mesenchymal Stem Cells: Time to Change the Name*. In this article Dr. Caplan refers to these cells as "medicinal signaling cells", capable of releasing paracrine effectors which thereby influence the body via immunomodulatory and trophic mechanisms. These bioactive factors recruit the patient's stem cells, which reside throughout all the tissues of our bodies, and affect the phenotypic and physiological expression of our immune system. So, if these bioactive factors are so effective, why is so much attention paid to stem cells. The answer lies in the fact that the old textbooks remain on the shelves and those who have read them continue to preach their teachings. In addition, alternative therapeutic options have only recently become available on the marketplace. One of these options is the exosome. Older cells are less robust in the production of growth factors, micro RNA and messenger RNA and are frequently limited in total number.

Exosomes, measuring 40 to 100 nm are lipid membrane packets formed by a two-step budding process. Formed by inward budding of membranous vesicles in a multi-vesicular body, they fuse with the plasma membrane to release these ultra-tiny vesicles. Exosomes contain transmembrane proteins from their parent cells, which are important in regulating uptake by other cells. By conserving these transmembrane proteins, it has been shown that uptake is facilitated by other cells to a much greater degree than if the cargo was simply released into the extracellular environment.

Exosomes are important in autocrine signaling (local between same cells), paracrine signaling (local between different cells) and endocrine signaling (between distant cells). Commercially, at present, exosomes are only available from placental tissues whose MSCs secrete a cargo rich in growth and immunomodulatory substances. Of course, any resident stem cells whom traffic to the areas of concern, will then secrete exosomes specific to themselves and will be modified by their own local extracellular microenvironment. This information includes messenger RNAs, micro RNAs, and various proteins. The intrinsic durability of the exosome makes them uniquely durable and naturally biocompatible. Additionally, the wide spectrum of proteins and messenger RNA contained within exosomes allows for a vastly greater capacity of information compared with single molecule messengers like hormones, growth factors and cytokines. Finally, the transmembrane protein receptors allow exosomes to traffic or home to areas of injury and inflammation while facilitating uptake by numerous cells.

Unlike MSCs, exosomes demonstrate a number of advantages distinct from their parent cells. They can travel systemically without the risk of clumping (as is seen with large peripheral intravascular doses of MSCs). As much smaller particles, exosomes do not demonstrate a first pass effect into the lungs when administered intravascularly. Exosomes can cross the blood-brain barrier easily without utilizing diuretics such as Mannitol. While allogeneic MSCs may be perceived as foreign by the innate and adaptive immune system and quickly whisked away, exosomes are able to evade the immune response. Exosomes from healthy stromal cells do not contain DNA, so that there is no risk of malignant transformation. Alternatively, autologous MSCs are of the same age as the donor patient and are therefore limited by the inherent age of the individual. Older cells are less robust in the production of growth factors, micro RNA and messenger RNA and are frequently limited in total number.

Exosomes derived from MSCs provide many therapeutic benefits including regenerative and immunomodulatory capabilities which dictate their indications. The trophic effects of exosomes require an understanding of the patient's own stem cells in which they act upon. Stem cells lie dormant within niches throughout our bodies. This population of cells are partially undifferentiated and once activated can proliferate and migrate to sites of injury where they acquire a mature phenotype in order to facilitate repair and remodeling.

Many of the anti-fibrotic benefits of MSC exosomes are attributable to several factors. They produce large amounts of TGFß3 which regulates cell adhesion and extracellular matrix formation. In scar repair they increased the ratio of Collagen Type III to Type I. Additionally, MSC exosomes displayed inhibition of granulation tissue leading to fine reticular collagen with fewer fibroblasts. Finally, MSC exosomes prevent apoptosis (cell death) through numerous techniques.

Immune and growth factors present in MSC exosomes.

BMP5	Stimulates Bone Growth
GDF15	Regulates inflammation, apoptosis, cell repair, and growth
OPG	Stimulates Bone Growth/Blocks Osteoclast Precursor Formation
G-CSF	Stimulates Bone Marrow to Procedure Granulocytes and Stem Cells
SCF	Responsible for Stem Cell and Melanocyte Growth
TGFß3	Most Important Anti-Inflammatory Protein. Converts Inflammatory T Cells into Anti-Inflammatory Regulatory T Cells.
VEGF	Stimulates Formation of Blood Vessels
ICAM-1	Binds Inflammatory Ligands on White Cells
IL-1RA	Binds and Sequesters the Inflammatory Cytokine IL-1
IL-6	Responsible for Macrophage Activation
IL-10	Anti-Inflammatory Cytokine responsible for Immunomodulation and Regulatory T Cell Conversion
MCP-1	Recruits Mononuclear Cells to Treatment Area
MIP-1	Also known as CC1-4, Recruits Mononuclear Cells to the Treatment Area
PDGF-BB	Growth Factor Used to Stimulate Healing in Soft and Hard Tissues
TIMP1 & TIMP2	Blocks Cartilage and Extracellular Matrix Degradation, Important for Cartilage Repair
HGF	Involved in Organ Regeneration and Wound Healing
GDNF	Promotes Survival of Neurons
BDNF	Supports Survival of Neurons and Encourage Growth
FGF	Potent Growth Factors Affecting Many Cells
TNFR1	Binds and Inactivates the Inflammatory cytokine TNF-α

Key mRNA present in MSC exosomes.

IL-1RA
TIMP1 & TIMP2 TMFR1 AND TNFR2
Histone Deacetylase mRNAs
GDF11-Potent anti-aging agent
GDF15 – Regulates Inflammation
IGFBP2 - One of six IGF binding proteins that bind IGF-1 and IGF-2
IGFBP3
IGFBP4 - Reportedly anti-tumorigenic effects against prostate cancer, colon cancer, and glioblastoma
IGFBP6 OPG SCFR
TGF-ß1 & TGF-ß3 VEGF
VEGFR-2
BMP4 - Involved in bone and cartilage development, fracture repair, and muscle development
BMP7 - Important in bone homeostasis
PTEN - A potent tumor suppressor gene Numerous Key miRNA

Conditions Treated Include:

- Musculoskeletal – Joints, discs, muscles, bones, ligaments, tendons
- Neurodegenerative – MS, Parkinson's, Alzheimer's, Huntington's, ALS, Cerebellar Ataxia
- CNS Injury/Trauma – CVA, CTE, TBI, SCI, Transverse Myelitis, Cerebellar Ataxia
- Burns/Scars/Ulcers
- Heart Disease – MI, Angina, CHF
- Lung Disease – COPD, Pulmonary Fibrosis, Interstitial Lung Disease
- Liver Disease
- Kidney Disease
- Inflammatory Bowel Disease – UC, Crohn's
- Alopecia

- Neuropathy/CIDP
- Erectile Dysfunction
- Urinary Incontinence
- Peripheral Vascular Disease
- Cerebral Palsy/Seizure Disorders/Autism
- Numerous Aesthetic Applications
- Depression/Bipolar Disorder
- Drug Addiction
- Type II Diabetes Mellitus
- Infertility
- Aging

Due to their size, exosomes allow for easy injection-based therapies. Alone, they can be delivered through needles as small as 30 gauge. Direct delivery is recommended intravenously, intrathecally, and intranasally. When injecting into other areas of the body, it is often prudent to utilize a scaffold to limit traffic out of the injection site. Common scaffolds like PRP and acellular Wharton's Jelly or amniotic fluid serve the dual purpose of cell retention and cell migration as well, without significantly elevating the cost of the procedure. Combining exosomes with these and by utilizing a 22-gauge needle will allow time to inject without compromising safety. Some procedures do not require image guidance and can be accomplished in office. More invasive procedures like intradiscal injections, cervical intrathecal injections, and deep paraspinal injections are best performed utilizing guidance imaging – while joint, tendinous, perineural, and other musculoskeletal indications are well suited for ultrasound guidance.