MARROW CELLUTIONS AND MATRIX
The Power of Synergy

Bone marrow cells reside deep inside bone cavities in the most protected part of the body and are redundant throughout the organism. This preferential status reflects the primary role these cells play in the survival of the organism. Stem cells from marrow naturally home to, thrive and proliferate in hypoxic tissue.[10] In response to trauma, which creates a hypoxic environment, marrow cells mobilize into the vasculature from the medullary space where the cells aggregate themselves into the recently created hypoxic damaged tissue.[3-10] Once resident, marrow stem cells are capable of functioning in the hostile hypoxic environment to orchestrate the tissue regeneration process.[10]

By capturing all of the nucleated cells through a proper marrow aspiration, you are maintaining the same relative proportion of cells that naturally aggregates at the defect site. The following quote captures the essence of this insight "These data demonstrate that removing BMSC's (bone marrow stem cells) from their normal environment of complimentary cells reduces their osteoblastic capacity and that to achieve their maximal differentiation, BMSC's require direct physical contact with accessory cells." [2]

Consequently, the potential of marrow-sourced nucleated cells should be thought of as a group of different cells that is able to:

+ Home to and self organize at the defect site
+ Release the appropriate levels of various growth factors to influence the function and cytokine production of resident cells based on the stage of the healing cascade and
+ Cooperate with and influence resident cells to accomplish the steps of the healing cascade that culminates in repair. [1,10, 19-38]

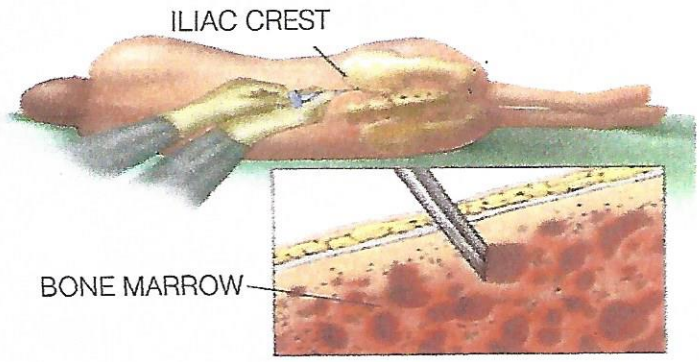
Each nucleated cell type contributes to the process of tissue repair.[2] For example, granulocytes in the area of bone regeneration release large amounts of VEFG which up regulates the production of BMP-2 and BMP-6 by sub-populations of CD-34 + cells.[37,38]

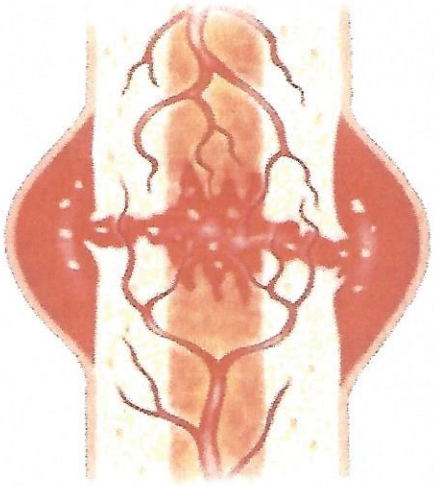
Properly aspirating marrow, and appropriately administering the cells is significantly enhancing and exactly mimicking the body's natural healing process.[10] This simple explanation is fundamental to the use of marrow cells in damaged tissue. In the case of bone grafting, the cells need to be combined with a functional bone matrix. In the case of osteonecrosis or heart disease and limb ischemia, the ischemic bone or muscle serves as the scaffold and the cells are directly injected to the site.[14,16,30] Trauma that does not heal is often the result of an inadequate number of mobilized marrow cells at the site of the defect.[11,12]

Autograft exactly mimics and supplements the natural process in that resident in the harvested bone are the living cells of the marrow that are cut from one part of the body and transplanted to another. Autograft is especially suited for bone repair as the bone from the autograft serves as an appropriate scaffold for the transplanted cells.

A marrow aspirate that is efficient at capturing nucleated cells has the same number and types of nucleated cells as autograft. In fact, by collagenase digesting human autograft and counting the cells, Muechler et al demonstrated that autograft has approximately the number of nucleated cells per CC and cfu-f as the marrow cellution needle aspirate.[29,42] By combining the nucleated cell rich fraction with a functioning matrix, you create the same treating composition, (types and ratio of cells) as is contained in autograft without donor site morbidity.

By examining all of the cellular components of autograft, we see that those same cells are contained in marrow aspirate.[29] When we look at the role of those different cells in bone formation, we see that each of the cellular components of autograft, and thus by extension, marrow, play a positive role in the micro-environment of bone formation. For example, T-cells and other lymphocytes improve the mobility and functionality of EPC's[39, 40] In addition; some of the most potent stem cells reside in the deeper granulocytic layer.[28] This is likely because cycling progenitor cells increase the density of their nucleus just before going through mitosis. So, capturing all of the nucleated cells, similar to autograft, is the optimal strategy. A review of the literature demonstrates similar clinical outcomes to autograft when using high concentrations of nucleated cells from marrow as measured by cfu-f. For example, Hernigou et al in non-union, Gan et al in multilevel lumbar spine fusion, Jager et al in orthopedic bone defects, Gangji et al and Herigou et al in osteonecrosis, Velardi et al for pediatric skull defects, and Sauerbier et al for sinus lift augmentation.[13-18,35]





Reliable new bone formation requires all of the nucleated cells contained in living bone, i.e., the monocytes (density range of 1.04-1.06) and granulocytes (density range 1.06-1.08)

Each cell in a different micro-environment can provide a different function; for example, granulocytes are inflammatory in the micro-environment of infection compared to pro-regeneration in the micro-environment of building new bone or tissue.[1, 41] Just because a cell has what could be construed to be a negative impact such as pro-inflammatory in a different micro-environment (i.e., granulocytes in an area of infection), does not mean that cell will have that impact in another micro-environment such as tissue repair. Recent insights have focused on the role that marrow stem cells play in regulating other cells during the immune reparative processes at the sight of trauma.[43]

Aspirating high quality marrow and combining it with a functioning matrix for transplantation into a bone defect is exactly mimicking and supplementing the body's natural response to that surgical trauma site. Clinical results are positively correlated to the number of cfu-f contained in the graft.[15-18,35]

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