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STEM CELL THERAPIES IN PRECLINICAL MODELS OF STROKE: IS THE AGED BRAIN MICROENVIRONMENT REFRACTORY TO CELL THERAPY?

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Attractive therapeutic strategies to enhance post-stroke recovery of aged brains include methods of cellular therapy that can enhance the endogenous restorative mechanisms of the injured brain. The translational failure of experimental therapies in aged subjects might at least partially be related to the aged brain microenvironment. However, in previous work we have shown that G-CSF alone is effective in improving behavioral recovery after stroke in aged rats. Here, we tested the hypothesis that treating post-stroke aged rats with the combination of bone marrow-derived mononuclear cells (BM MNC) or bone marrow-derived mesenchymal cells BM MSC and G-CSF might improve the long term (56 days) functional outcome. To this end, 1x106 syngeneic BM MSC and BM MNC per kg bodyweight (BW) in combination with G-CSF (50µg/kg, continued for 28 days) were administered via the jugular vein to Sprague-Dawley rats six hours post-stroke. Infarct volume was measured by magnetic resonance imaging 3 and 48 days post-stroke and additionally by immunohistochemistry at day 56. Functional recovery was tested during the entire recovery period. Daily G-CSF treatment led to robust and consistent improvement of neurological function, but did not alter final infarct volumes. The combination of G-CSF and BM MNC, did not further improve post-stroke recovery. The lack of an additional benefit may be due to a hitherto not well investigated interaction between both approaches and, to a minor extent, to the insensitivity of the aged brains to regenerative mechanisms. Also considering recent findings on other tandem approaches involving G-CSF in animal models featuring relevant co-morbidities, we conclude that such combination therapies are not the optimal approach to treat the acutely injured aged brain.