Title: **Detoxifying & harnessing "inflammo-attraction" to direct therapeutic stem cell migration**

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Abstract:
A transplanted stem cell's engagement with a pathologic niche is the first step in its restoring homeostasis to that site. Inflammatory chemokines are constitutively produced in such a niche; their binding to receptors on the stem cell helps direct that cell's "pathotropism." Neural stem cells (NSCs), which express CXCR4, migrate to sites of CNS injury or degeneration in part because astrocytes and vasculature produce the inflammatory chemokine CXCL12. Binding of CXCL12 to CXCR4 (a G protein-coupled receptor, GPCR) triggers repair processes within the NSC. Although a tool directing NSCs to where needed has been long-sought, one would not inject this chemokine in vivo because undesirable inflammation also follows CXCL12–CXCR4 coupling. Alternatively, we chemically "mutated" CXCL12, creating a CXCR4 agonist that contained a strong pure binding motif linked to a signaling motif devoid of sequences responsible for synthetic functions. This synthetic dual-moity CXCR4 agonist not only elicited more extensive and persistent human NSC migration and distribution than did native CXCL 12, but induced no host inflammation (or other adverse effects); rather, there was predominantly reparative gene expression. When coadministered with transplanted human induced pluripotent stem cell-derived hNSCs in a mouse model of a prototypical neurodegenerative disease, the agonist enhanced migration, dissemination, and integration of donor-derived cells into the diseased cerebral cortex (including as electrophysiologically-active cortical neurons) where their secreted cross-corrective enzyme mediated a therapeutic impact unachieved by cells alone. Such a "designer" cytokine receptor-agonist peptide illustrates that treatments can be controlled and optimized by exploiting fundamental stem cell properties (e.g., "inflammo-attraction").