Neurogenic compounds as inducers of brain self-repair

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Chemical approaches using small molecules have yielded exciting results in induction and differentiation of pluripotent stem cells, lineage conversion of somatic cells, and ex vivo as well as in vivo modulation of adult stem cells. The application of small molecules, either as probes to dissect the underlying mechanism of stem cell biology or as key tools to manipulate stem cell fate, will continue to facilitate the progress of future stem cell research and cell-based clinical interventions, combining conventional synthetic pharmacology and stem cell technology. Applications of regenerative therapeutic technologies in the age-related neurodegenerative diseases represent one of the largest future burdens. The definition of mechanisms controlling adult neural stem self-renewal, migration and differentiation will provide new insights and therapeutic targets to pharmacologically induce brain self-repair processes. Deficiencies in neurotrophins are implicated in the pathogenesis of many age-related neurodegenerative disorders, due also to their central role in controlling adult neurogenesis. Central nervous system networks are effectively maintained through aging by neuroprotective, neuroplasticity and neurogenesis signaling mechanisms which are predominantly controlled by neurotrophin receptor signaling. Neurotrophin receptors are single pass receptor tyrosine kinases that form dimeric structures upon ligand binding to initial cellular signaling events that control many protective and plasticity-neurogenesis related pathways. While the therapeutic applications of cognate polypeptide ligands for neurotrophin receptors are limited, the development of nonpeptidergic, small-molecule ligands can overcome these limitations, and productively regulate this important receptor system with beneficial effects. Our group develops blood brain barrier-permeable small molecules, agonists of neurotrophin receptors (microneurotrophins) which induce fetal and adult neural stem cell self-renewal and differentiation, in vitro and in vivo. We are testing our neurogenic microneurotrophins in animal models of Alzheimer's disease, showing decreased hippocampal neurogenesis and deficient memory.