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Rejuvenating Subventricular Zone Neurogenesis in the Aging Brain

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Abstract

Neural stem cells exist in specialized regions of the brain and have the capacity to give rise to neurons and glia over the lifespan. The process of giving rise to new neurons, also known as neurogenesis, is thought to be important in cognition and certain types of brain repair. However, during aging, neural stem cell function is reduced resulting in fewer new neurons and declines in learning, memory and repair. Recently, research has approached this problem through the lens of rejuvenation that now has produced several strategies, from dietary to pharmacological interventions, to restore functional neurogenesis that resembles the youthful brain. Here, we outline aging in the subventricular zone neurogenic niche, review the multiple modalities of rejuvenation strategies, and propose next steps for future studies to approach translational outcomes.

Introduction

Adult neurogenesis is the generation of new neurons from neural stem cells (NSCs). NSCs are known for their hallmark characteristics of long-term-self-renewal and differentiation into neurons and glia [1]. While many noncanonical sites of neurogenesis have been observed in the mammalian brain [2], the two main stem cell niches studied are the subventricular zone (SVZ) located along the walls of the lateral ventricles (LV) (Figure 1A, B) and subgranular zone (SGZ) in the hippocampus. The largest pool of NSCs in rodents lies in the SVZ, where the majority of NSCs are quiescent (qNSCs). These qNSCs undergo activation (aNSC) and proliferate to produce transit amplifying cells (TACs). TACs rapidly proliferate and then differentiate into neuroblasts that migrate in chains along the rostral migratory stream (RMS) to the olfactory bulb (OB) and become synaptically integrated into the existing circuitry [3] (Figure 1C). Importantly, the niche is comprised of several distinct

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cell types that lie in a milieu of signals from blood and cerebrospinal fluid (CSF) that together makes up the 'SVZ neurogenic niche.' [4,5] (Figure 1C). Neurogenesis in the SVZ results in the functional integration of neurons in the OB. This has been shown to be important in olfactory behavior such as memory and scent/pheromone discrimination [6,7]. In addition, brain injury, in the form of ischemic stroke, induces NSC proliferation and production of neuroblasts (NBs) [8]. These NBs migrate to the site of injury to differentiate into astrocytes and neurons that synaptically integrate into the peri-infarct cortex [8,9]. Blockade of neuroblast migration results in increased lesion size and worsened behavioral outcomes as SVZ-derived neurons with synaptic function are critical to stroke recovery [9,10]. Additionally, post-stroke neurogenesis is plastic and can be increased and directed by overuse behavior that mimics current human neurorehabilitation therapies [9]. During aging, neurogenesis is reduced, which contributes to declines in olfactory memory and repair [11,12]. In this review, we discuss recent findings of murine SVZ aging and interventions aimed at rejuvenating neurogenesis in the aged brain (Table 1).

Age-Related Changes in the Subventricular Zone Neurogenic Niche

Most studies agree on a dramatic decline of proliferation in the SVZ as evidenced by decreases of up to 71% of BrdU positive cells between young (2-4 months) and old mice (19-25 months) and has been suggested to be due to increasing NSC quiescence [13,14]. Although, a significant decline in frequency of qNSCs, aNSCs, and TACs occurs as early as 7-months [14]. Microglia, the resident macrophages of the brain, have been shown to acquire an activated phenotype and excrete increased levels of pro-inflammatory cytokines in mice as young as 6-months [15] (Figure 2A). The NB population also declines with aging and fewer migrate to the OB [16] (Figure 2B). Furthermore, the number of newborn neurons in the OB is reduced in 2-month vs 24-month old mice [11]. Structurally, the SVZ thins during aging and proliferation becomes restricted to the dorsolateral corner in 19-22-month old mice [16]. This is accompanied by the loss of the ependymal lining and interpolation of astrocytes and microglia into the ependyma [16,17] (Figure 2A). NSCs have an apical astrocytic process that extends through the ependymal layer to contact the CSF in the LV [18] (Figure 1C). During aging the number of NSCs is reduced resulting in less contact with the CSF signaling milieu [19] (Figure 2A). The niche vasculature, which is an important regulator of NSC quiescence and activation, decreases in density and branching (Figure 2A), resulting in reduced blood flow [20].

A study using RNA-sequencing (RNA-Seq) to profile the aging SVZ revealed reduced expression of genes associated with neurogenesis, proliferation, and cell cycle, which corresponded to an actual dip in TAC proliferation in 18-month old mice [21]. Unexpectedly, these trends were reversed at 22-months along with proliferation in remaining TACs [21]. Surprisingly, no evidence of DNA strand breakage has been found in aged (22-month) NSCs [14], although evidence of mutation accumulation and transcript mutations is yet to be elucidated. More recently, single-cell RNA-sequencing (scRNA-Seq) was employed to profile young (2-months) and old (22-months) NSCs which unexpectedly showed no major differences [14]. However, after deeper sequencing, signatures of inflammation were discovered in niche progenitors, microglia, and endothelial cells in the old (19-months) SVZ compared to young (2-months) controls and were shown to play a causative role in age-

dependent increases in NSC quiescence [14]. The latest SVZ scRNA-Seq analysis has identified an almost exclusive enrichment of clonally expanded T-cells in the aged (3-month vs 28-29-months) SVZ, which express interferon-γ and decrease proliferation of NSCs *in vitro* [22] (Figure 2A).

Strategies to Rejuvenate Neurogenesis in the Aged Subventricular Zone Neurogenic Niche

Factors in Blood Plasma and Cerebrospinal Fluid

Multiple strategies to rejuvenate neurogenesis have come from experiments utilizing blood/plasma exchange between young and aged rodents. Landmark studies utilizing heterochronic parabiosis, where a young and aged mouse are connected surgically to share circulation, showed that young circulating factors can rejuvenate neurogenesis in aged mice as well as old circulating factors that can reduce neurogenesis in young mice [20,23]. The field has since made further progress by identification of circulating rejuvenation factors of NSCs in the SVZ and hippocampus that include GDF11 [20] and TIMP2 [24] as well as the pro-aging factors CCL11 [23], β2-microglobulin [25],TGF-β [26] and recently VCAM1 [27]. The lateral ventricle choroid plexus (LVCP), located within the LVs adjacent to the SVZ, produces CSF that carries signals which influence neurogenesis [28]. During aging (2-months vs 18-months), the LVCP alters the composition of CSF that reduces proliferation of NSCs [28]. Using transcriptome and proteome analysis, BMP5 and IGF1 were discovered to be enriched in the young LVCP and promote NSC proliferation *in vitro* similar to young LVCP conditioned medium [28].

These interventions suggest that the aging niche is highly influenced by extracellular factors and that young homeostatic potential can be reprogrammed through alterations of the systemic milieu. However, the interaction network between these factors is understudied which may limit therapeutic potential of selectively upregulating or inhibiting certain factors to rescue neurogenesis. Future research should modulate factors in combination to study the interactions, as has been recently done with oxytocin and TGF-B to partially rejuvenate hippocampal neurogenesis [29].

Dietary Interventions

The dietary interventions caloric restriction (CR) (10-40% reduction in caloric intake) and the fasting mimicking diet (FMD) (50-90% reduction in caloric intake for 4 days twice a month) are perhaps the most robust, pleiotropic, and conserved methods of longevity extension [30] and rejuvenation [31] (reviewed in [32]). In a mouse model of caloric restriction starting at 14-weeks of age, the number of NB and new neurons in the OB were preserved in the aged (12- to 18-months) and comparable to levels of *ad libitum* fed young (6-months) mice. This preservation of neurogenesis resulted in olfactory memory in aged mice that was similar to young (6-month) mice [33]. Research should follow up this result by testing whether CR started at old ages, as has been tested in humans [34], produces the same magnitude of effect, as well as determining the optimal timing for this intervention. In addition, the FMD, a more compliant diet with similar effects as CR, should also be tested for increases of neurogenesis in the aging SVZ as it has already been shown to increase

neurogenesis and function in the hippocampus in 23-month old mice [31]. The LMN diet, rich in methionine-rich proteins, vitamins, and fish, is neuroprotective during aging [35]. After 5 months of feeding 18-month old mice an LMN diet, it was found that SVZ proliferation was comparable to 4-month old control mice [35].

The two top drugs that have emerged from CR research are rapamycin and metformin, which induce systemic rejuvenation primarily through inhibition of the mTOR and activation of the AMPK (downstream inhibition of mTOR) pathways, respectively [32]. Decreased activation potential of old qNSCs has been shown to be due in-part to faltering proteostasis [36]. A 3 month rapamycin treatment in 22-month old mice was shown to enhance the lysosome-autophagy axis and counteract the lack of qNSC activation [36]. However, other studies suggest that mTOR signaling is a mediator of TAC proliferation since rapamycin treatment decreases the number of TACs in 2-month old mice and mTOR activation decreases with age, concomitant with proliferation [37]. Metformin has been shown to enhance proliferation in the young (3-month) SVZ [38]. Metformin is known to downregulate IGF-1 signaling [39], and a study using NSC specific IGF-1R knockout prevented age-associated reductions in neurogenesis as well as improved olfactory function via increased OB neuron integration [40]. Despite interest in using metformin to ameliorate aging phenotypes, research with this drug in the aging SVZ is lacking. Thus, future research should address the *in vivo* rejuvenation potential of metformin and rapamycin in the aging SVZ, especially as some of these molecules are FDA approved and available to humans.

Inflammation Amelioration

Multiple lines of evidence now point towards an increased age-dependent inflammatory environment within the SVZ [14,15,22,28,33,41]. Factors contributing to inflammation include the cytokines IFN-α, IFN-β, and IFN-γ related to the interferon response [22,41], CXCL10 [14], TNF-α[15], IL-1 [15,42], and IL-6 [15]. A major source of this inflammation originates from aged microglia and should be a central target for inflammation reduction in future studies [15]. Having identified the neurogenic-inhibiting contribution of aged microglia to NSC proliferation, L'Episcopo and colleagues fed 8-month old mice the anti-inflammatory drug HCT1026. This treatment restored redox/inflammatory balance to the niche, and substantially increased neurogenesis [42]. Acute inhibition of CXCL10, a ligand induced in the interferon response program, increased OB neurogenesis in addition to increasing activation of qNSCs in 22-month old mice [14]. In the CSF-producing choroid plexus of 22-month old mice, expression of type I interferon response is upregulated while type II interferon response expression is downregulated. This is associated with decreased neurogenesis in the SVZ and SGZ as well as a decline in hippocampal function [28,41]. However, inflammation and functional decline were ameliorated by a neutralizing antibody against interferon-α/β receptor in the CSF, which blocks binding of type I interferon cytokines [41].

It is becoming increasingly clear that aberrant inflammation signaling processes that originate from glia play an early [15] and causative role in SVZ niche aging. Thus, future studies must now look towards altered interactions/signaling between glial cells and NSCs

and intrinsic (mutations/epigenetics) modulating glia during early aging to pinpoint key drivers of niche aging.

Cellular Senescence and Senolytics

Cellular senescence research has made strides in the last several decades from identifying key markers of senescent cells (e.g. senescent associated secretory profile, P16, SA-β-galactosidase) (reviewed in [43]), to the negative physiological impact of accumulating senescent cells during aging [44],and finally to the development of novel senescent cell ablation therapies [44,45]. Increase in senescent cell burden in the aging SVZ has been found in 12-18 month old mice [35]. Additionally, senescence-causing $p16^{INK41}$ mRNA expression has been shown to be enriched in the 24-month old murine SVZ [46]. Avoidance of the senescence program was achieved with $p16^{INK41-/-}$ mice aged to 15-19 months that partially rescued OB neurogenesis [46]. A recent study showed that obesity is associated with increased senescence and reduced neuroblasts in the SVZ of middle-aged (10-13 months) mice and clearance of senescent cells partially rescued the number of neural precursors [47]. Thus, removal of senescent cells in elderly mice, especially using treatments such as Dasatinib + Quercetin that have been used in clinical trials [48], appear to be favorable routes to rejuvenate neurogenesis but are in need of further study in aged animals to determine long term effects.

Conclusion

The studies gathered here present compelling evidence that aging of the SVZ niche is not a one-way street. Instead, the aging process is not only delayable through early interventions such as CR, but is also reversible by way of systemic interventions started late in life (Table 1). The possibility of rejuvenation not only sheds light on the mechanisms of NSC aging, but is also an appealing therapeutic avenue for the rapidly increasing elderly human population [49].

Key to developing translational therapies in animal models is whether murine adult neurogenesis is conserved in humans. While there have been a large amount of studies on post-mortem human brains, a definitive answer to this question remains controversial. SVZ neurogenesis appears to be at least robust during human infancy, with evidence of migrating NBs along the RMS to the OB [50]. Once reaching adulthood, the number of NBs sharply decline and new neurons are not added to the OB [50,51]. Although, some still appear to be distributed along the RMS [52] as well as migrating to the neighboring striatum that depletes with aging [53]. In contrast, others have reported continued SVZ neurogenesis in adulthood that is not easily detectable because the RMS path in the adult brain is altered due to an enlarged frontal cortex [54]. Evidence remains on both sides of the aisle for the dentate gyrus (DG) as well. As with the SVZ, some reports indicate that DG neurogenesis primarily occurs during infancy [55], while others have shown that neurogenesis occurs over the lifespan but declines with aging and further with Alzheimer's disease [56]. A meta-analysis of all current studies is needed to reach a consensus. What may underlie the discrepancies between these studies is the detection of proliferation and cell identity within the neurogenic

lineage using either proxy markers from mice, birth dating, or isolation and culture of NSCs [57].

Our review of the rejuvenation literature revealed a lack of reporting in this literature on the possible trade-offs that each rejuvenation strategy may bring. For example, inflammation signaling that appears to be detrimental in the aging niche also plays a crucial role in activation of the innate immune system in response to viral infections [58]. As normal homeostatic regulation of the niche is highly influenced by external signaling factors [5], it is not entirely surprising that this method of signaling also appears to be the mode in which aging phenotypes arise. This signaling interaction in the niche should be a major theme of future research. In conclusion, this review is just a first glimpse into the emerging field of rejuvenation research that is bound to continue to shed light on NSC aging and develop effective strategies to turn back time.

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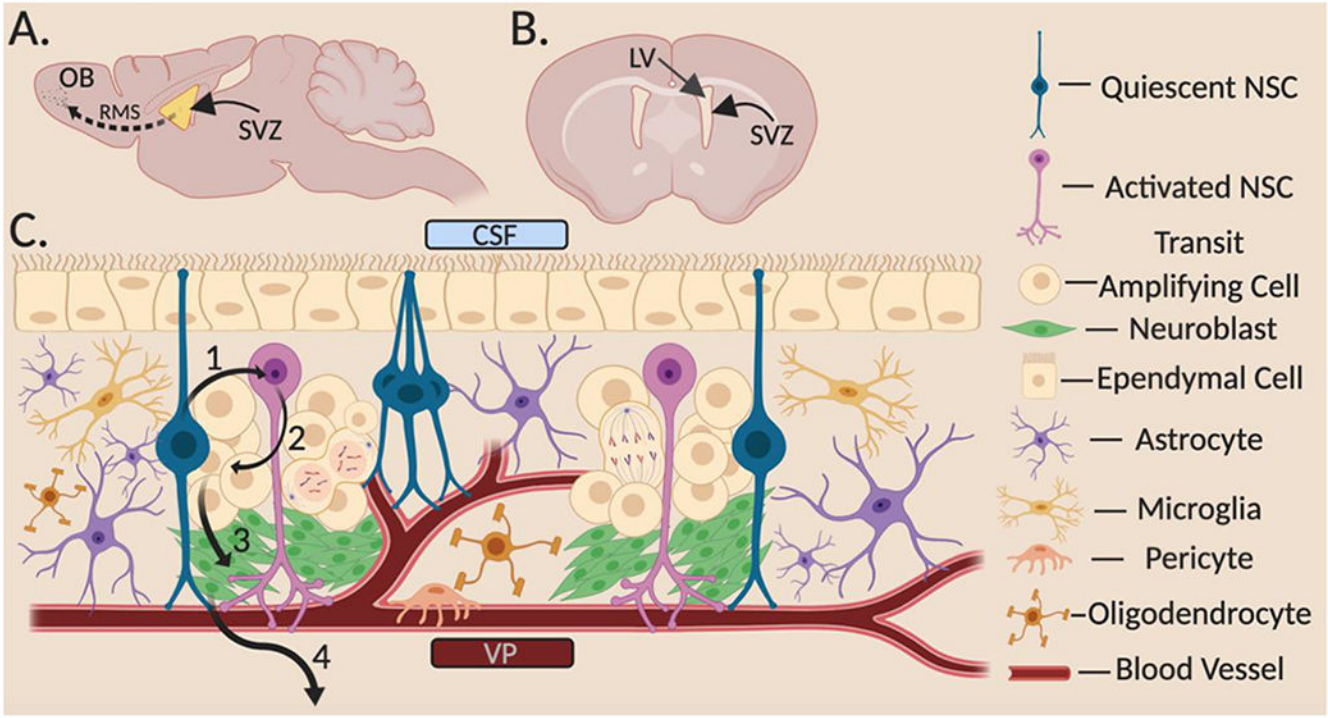

Figure 1).

The young SVZ Structure and Organization A) Sagittal section of murine brain showing lateral SVZ enface with the rostral migratory stream (RMS). B) Coronal section of murine brain showing the LV adjacent to lateral SVZ. C) Cellular SVZ niche cross section. The SVZ lies between the CSF (top) and VP (bottom). qNSCs make contact through the ependymal layer and receive signals from the CSF. Upon activation, qNSCs transition to aNSCs (1) where they either divide symmetrically or asymmetrically into TACs (2). TACs then produce NBs (3) that then exit the SVZ (4) and migrate along the RMS to the OB where they will terminally differentiation into inhibitory neurons. qNSC, quiescent neural stem cell; aNSC, active neural stem cell; TAC, transit amplifying cell; NB, neuroblast; OB, olfactory bulb; RMS, rostral migratory stream; LV, lateral ventricle; SVZ, subventricular zone; CSF, cerebrospinal fluid; VP, vascular plexus.

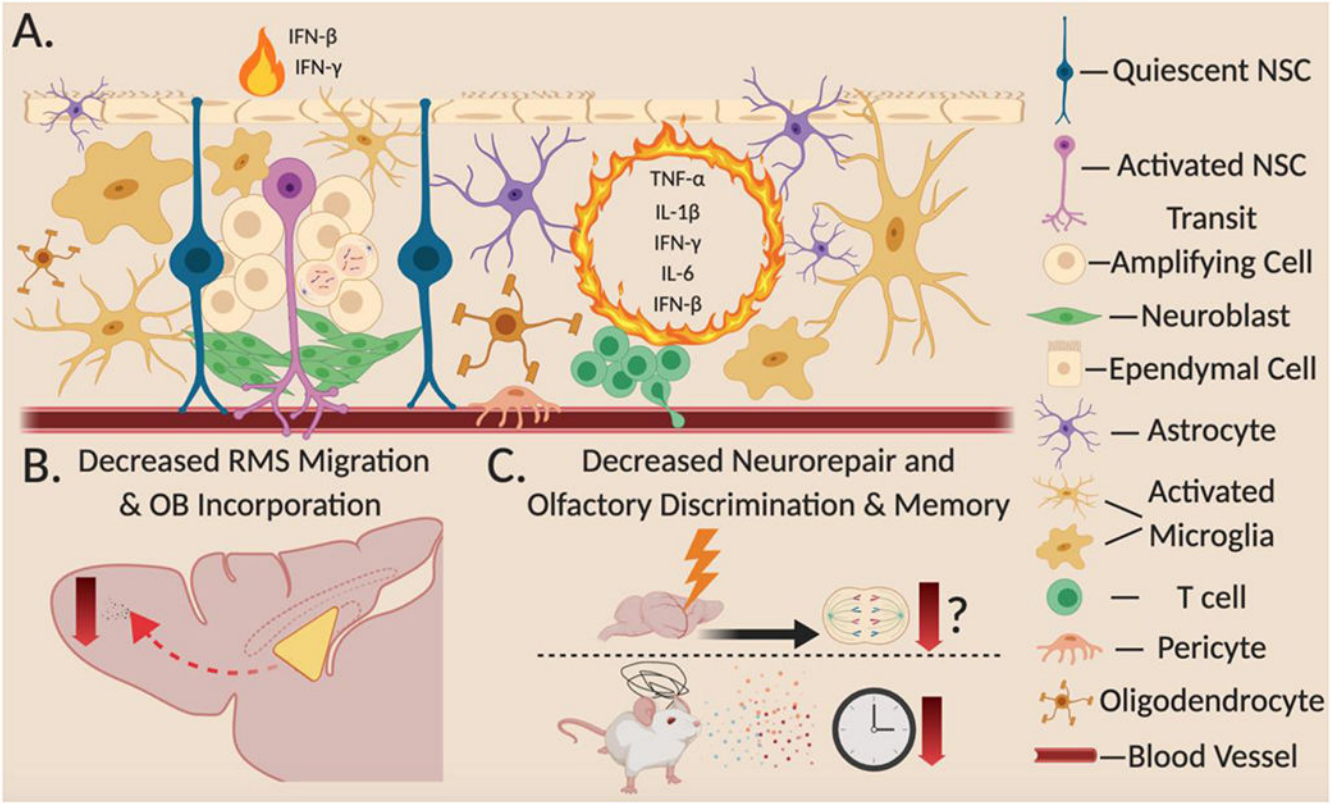

Figure 2).

Age-Related Changes in the SVZ. A) The SVZ becomes thinner and vasculature is reduced in density and branching. The ependymal layer itself thins and experiences cell loss, cilia become unevenly distributed, and inflammation can be detected in the CSF adjacent to the niche. qNSC, aNSC, TAC, NB, and are decreased in frequency while microglia trend in the opposite direction. Furthermore, microglia display activated and ameboid phenotypes that is associated with enrichment of pro-inflammatory cytokines within the SVZ. qNSCS in pinwheel formations are lost while microglia processes and astrocytes infiltrate the thinning ependymal layer. Lastly, T cells can be seen infiltrating the niche and then expand clonally, contributing to niche inflammation though IFN-γ. B). Sagittal view of murine brain depicting disappearance of the RMS due to fewer migrating NBs that results in decreased incorporation of immature neurons into the OB circuitry. C) The main functional outcomes of SVZ aging are decreased repair following brain injury and decreased olfactory discrimination & memory. qNSC, quiescent neural stem cell; aNSC, active neural stem cell; TAC, transit amplifying cell; NB, neuroblast; OB, olfactory bulb; RMS, rostral migratory stream; LV, lateral ventricle; SVZ, subventricular zone; CSF, cerebrospinal fluid; VP, vascular plexus; IFN-α, interferon-alpha; IFN-β, interferon-beta; IFN-γ, interferon-gamma; TNF- α, tumor necrosis factor alpha; IL-1 β, interleukin-1 beta; IL-6, interleukin 6.

Table 1)

Summary of Rejuvenation Interventions. Intervention column list the name of the administered molecule, drug, neutralizing antibody, or diet plan. Age at Intervention column is the age of the mouse or mouse that cells were derived from at the time of the intervention. Result column list the main results from rejuvenation intervention as compared to appropriate controls. *In vivo* or *in vitro* column list if intervention was done on the animal or in cell culture Functional result list results from challenges or behavioral testing related to SVZ neurogenesis. Comparisons column list ages and conditions used in experiments. Reference column list paper intervention was tested in. NSC, neural stem cell; aNSC, active neural stem cell; TAC, transit amplifying cell; NB, neuroblast; OB, olfactory bulb; RMS, rostral migratory stream; LVCP, lateral ventricle chroid plexus; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; TMZ, Temozolomide; SVZ, subventricular zone; LCVPsec, conditioned medium from LVCP explants;

Intervention	Age at Intervention	Result	*in vivo* or *in vitro*	Functional Result	Comparisons	Reference
GDF11	22mo	Increased vascularization in SVZ, Increased NSCs in SVZ	*in vivo*	NA	22mo rGDF11 vs 22mo PBS	Katsimpardi et al., 2014
Heterochronic Parabiosis	21mo	Increased NSCs and oligodendrocyte progenitors in SVZ; Increase proliferation in OB; Increased vascularization in SVZ	*in vivo*	Increased odor sensitivity	2mo vs 21mo; Isochronic and Heterochronic	Katsimpardi et al., 2014
BMP5	2mo	aNSC clone increase 60% of LVCPsec	*in vitro*	NA	2mo LVCPsec vs ligand	Silva-Vargas et al., 2016
IGF1	2mo	aNSC clone increase ~20% of LVCPsec	*in vitro*	NA	2mo LVCPsec vs ligand	Silva-Vargas et al., 2016
Caloric Restriction	14 weeks	Increased NB in SVZ; Increased proliferation in OB; Decreased microglia activation; Decreased inflammation; Decreased senescent cell frequency	*in vivo*	Increased olfactory memory	6mo vs 12-18mo; ad libitum vs caloric restriction	Apple et al., 2019
LMN Diet	18mo	Increased proliferation in SVZ	*in vivo*	NA	4mo vs 18mo; ad libitum vs LMN	Fernandez-Fernandez et al., 2012
Rapamycin	22mo	Increased aNSC frequency in SVZ	*in vivo*	NA	Regular chow vs Rapamycin-containing chow	Leeman et al., 2018
HCT1026	8-10mo	Decreased inflammatory gene expression; Increased proliferation in SVZ; Increased NB frequency, Increased immature neurons in SVZ	*in vivo*	Rescues DAergic neuroprotection from MPTP challenge	No HCT1026 vs HCT1026	L'Episcopo et al., 2013
Anti-CXCL10	22mo	Increased newborn neurons; Increased proliferation in OB	*in vivo*	NA	22mo anti-CXCL10 vs 22mo IgG	Kalamakis et al., 2019
Anti-sFRP5	22mo	Increase aNSC in SVZ	*in vivo*	Increased proliferation after TMZ injury	22mo anti-sFRP5 vs 22mo IgG	Kalamakis et al., 2019